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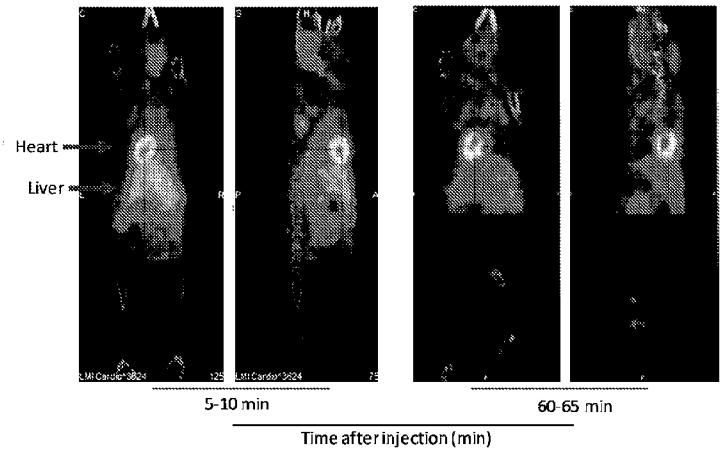
Figure 15



(57) Abstract: The present invention provides compounds with imaging moieties for imaging a subject. The present invention also relates to systems, compositions, and methods for the synthesis and use of imaging agents, or precursors thereof. An imaging agent precursor may be converted to an imaging agent using the methods described herein. In some cases, a composition or plurality of imaging agents is enriched in 18 F. In some cases, an imaging agent may be used to image an area of interest in a subject, including, but not limited to, the heart, cardiovascular system, cardiac vessels, brain, and other organs.

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COMPOSITIONS, METHODS, AND SYSTEMS FOR THE SYNTHESIS AND USE OF IMAGING AGENTS

Related Applications

The present application claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent applications, U.S.S.N. 61/682,185, filed August 10, 2012, and U.S.S.N. 61/794,277, filed March 15, 2013, each of which is incorporated herein by reference.

Field of the Invention

The present invention relates to compounds useful as imaging agents, compositions thereof, methods for the synthesis and use thereof, and precursors thereto.

Background of the Invention

Mitochondria are membrane-enclosed organelles distributed through the cytosol of most eukaryotic cells. Mitochondria are especially concentrated in myocardial tissue.

Mitochondrial complex 1 ("MC-1") is a membrane-bound protein complex of 46 dissimilar subunits. This enzyme complex is one of three energy-transducing complexes that constitute the respiratory chain in mammalian mitochondria. This NADH-ubiquinone oxidoreductase is the point of entry for the majority of electrons that traverse the respiratory chain, eventually resulting in the reduction of oxygen to water (*Q. Rev. Biophys.* 1992, *25*, 253-324). Examples of inhibitors of MC-1 include deguelin, piericidin A, ubicidin-3, rolliniastatin-1, rolliniastatin-2 (bullatacin), capsaicin, pyridaben, fenpyroximate, amytal, MPP+, quinolines, and quinolones (*BBA* 1998, *1364*, 222-235). Studies have shown that interrupting the normal function of mitochondria could advantageously concentrate certain compounds in the mitochondria, and hence in the mitochondria-rich myocardial tissue. Compounds that include an imaging moiety (*e.g.*, ^{18}F) can be useful in determining such a build-up of compounds, thereby providing valuable diagnostic markers for myocardial perfusion imaging. In addition, such compounds may find application for the diagnosis of coronary artery disease (CAD).

CAD is a major cause of death in modern industrialized countries, and it has been found previously that assessments of regional myocardial perfusion at rest and during stress (exercise or pharmacologic coronary vasodilation) are valuable for noninvasive diagnosis of CAD. While myocardial perfusion imaging (MPI) with Positron Emission Tomography (PET) has been shown to be superior in some embodiments as compared to single photon

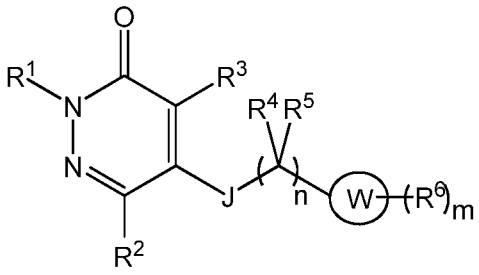
emission computed tomography (SPECT), widespread clinical use of PET MPI has been limited by the previously available PET myocardial perfusion tracers.

Several PET blood flow tracers, such as rubidium-82 (^{82}Rb) chloride, nitrogen-13 (^{13}N) ammonia, and oxygen-15 (^{15}O) water, have been developed and validated for assessment of myocardial perfusion. ^{13}N and ^{15}O are cyclotron-produced isotopes with short half-lives. Therefore, their use is limited to facilities with an on-site cyclotron. Although ^{82}Rb is a generator-produced tracer, its short half-life, the high cost of the generator, and the inability to perform studies in conjunction with treadmill exercise have made this tracer impractical for widespread use. Tracers that comprise ^{18}F have, however, found application as imaging agents.

Summary of the Invention

The present invention provides, in a broad sense, compounds, and compositions thereof, that are useful as imaging agents or imaging agent precursors, kits thereof, methods of use thereof, and methods of synthesizing the provided compounds.

In some embodiments, a compound is provided comprising the structure:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –NO_2, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –

CN, $-NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

W is heteroaryl, naphthyl, heterocyclyl or aryl;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, -OH, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, -CN, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and an imaging moiety;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and an imaging moiety; and

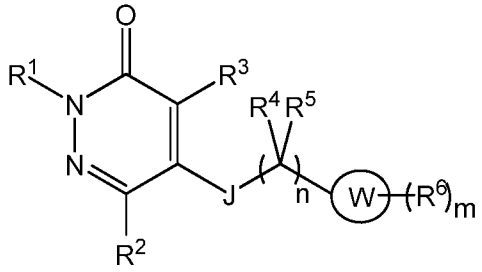
each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound; and

provided that when W is aryl, a) R^3 is not halo, alkyl or haloalkyl, or b) at least one R^6 is selected from the group consisting of alkynyl optionally substituted, alkenyl optionally substituted, alkyl substituted with -CN, alkyl substituted with $-C(=O)OR^8$, alkyl substituted

with –C(=O)R^8, alkyl substituted with –N(R^7)$_2$, –CN, –NO_2, –N(R^7)$_2$, –C(=O)OR^8, –OC(=O)R^8, –C(=O)R^8, –C(=O)N(R^7)$_2$, and –N(R^7)C(=O)R^8.

In some embodiments, a compound is provided comprising the structure:



(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –NO_2, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, –NO_2, and an imaging moiety;

J is selected from the group consisting of N(R^7), S, O, C(=O), C(=O)O, OC(=O), C(=O)N(R^7), N(R^7)C(=O), CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

W is heteroaryl, naphthyl, or heterocyclyl;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –N(R^7)$_2$, –NO_2, –

OH, –C(=O)R^8, –C(=O)OR^8, –OC(=O)R^8, –C(=O)N(R^7)$_2$, –N(R^7)C(=O)R^8, –CN, –Si(R^9)$_3$, –B($R^{9'}$)$_3$, –OR^8, and an imaging moiety;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

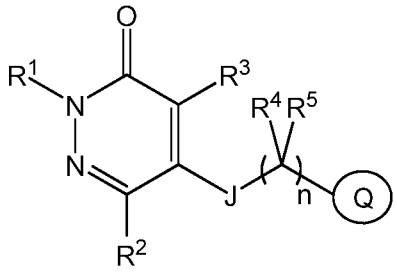
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound.

In some embodiments, a compound is provided comprising the structure:



(III)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –NO_2, and an imaging moiety;

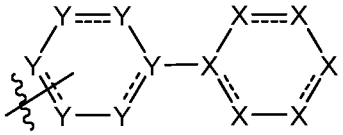
R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

Q has the structure:



wherein each Y and each X is independently selected from the group consisting of C, $C(R^6)$, $C(R^6)_2$, N, NR^7, O, and S, provided at least one Y is not C or $C(R^6)$, optionally, wherein one X and/or one Y is absent;

each ------ is independently a single or double bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–N(R^7)_2$, $–NO_2$, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, $–Si(R^9)_3$, $–B(R^{9'})_3$, $–OR^8$, and an imaging moiety;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

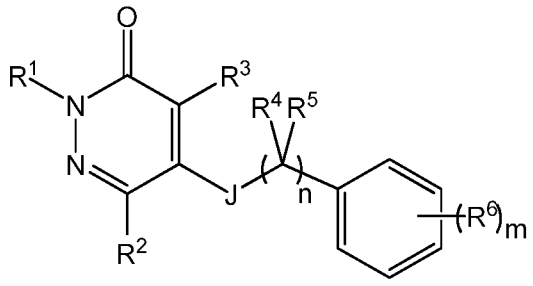
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound.

In some embodiments, a compound is provided comprising the structure:



(IV)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–NO_2$, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, unsubstituted alkyl or alkyl optionally substituted with a moiety other than a halogen, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, –CN, and $–NO_2$;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted,

heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and an imaging moiety;

m is 0, 1, 2, 3, 4, or 5;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

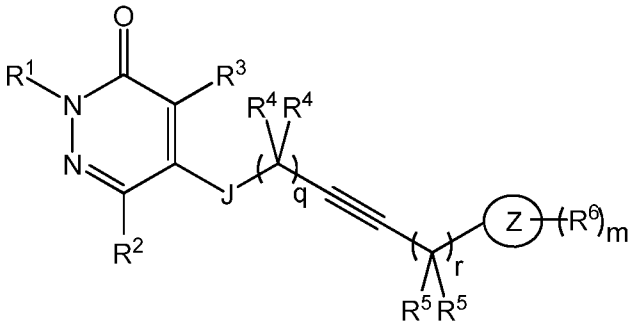
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and an imaging moiety; and

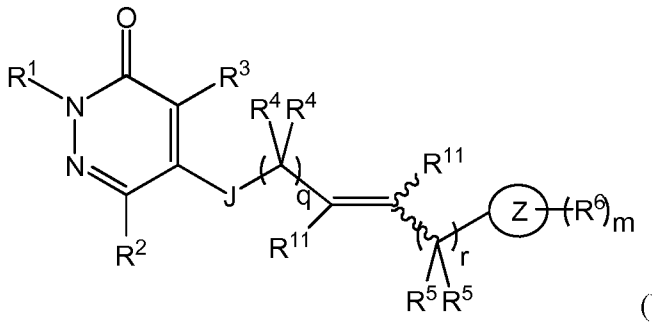
each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound.

In some embodiments, a compound is provided comprising the structure



: (V) or



(VI),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $-NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

each R^4, R^5, and R^{11} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 or any two of R^5 are joined together to form a ring;

q, and r are each independently 0, 1, 2, or 3;

Z is selected from the group consisting of aryl, heteroaryl, heterocyclyl, and a bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, –OH, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, –CN, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and an imaging moiety;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

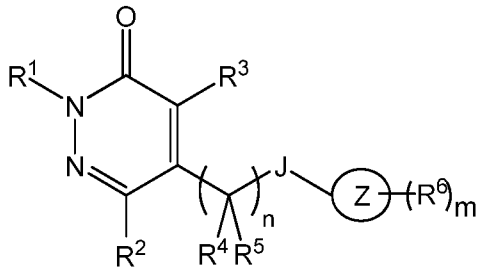
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound.

In some embodiments, a compound is provided comprising the structure:



(VII)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, $–NO_2$, haloalkyl, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally

substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, and $–CH_2O$;

each R^4 and R^5 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 1, 2, or 3;

Z is selected from the group consisting of aryl, heteroaryl, heterocyclyl, and a bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–N(R^7)_2$, $–NO_2$, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, $–Si(R^9)_3$, $–B(R^{9'})_3$, $–OR^8$, and an imaging moiety;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

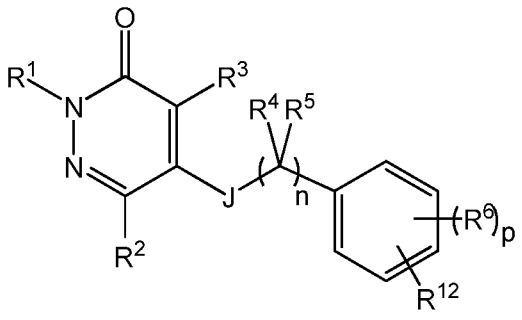
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound.

In some embodiments, a compound is provided comprising the structure:



(VIII)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $-NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, –OH, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, –CN, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and an imaging moiety;

p is 0, 1, 2, 3, or 4;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring; and

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

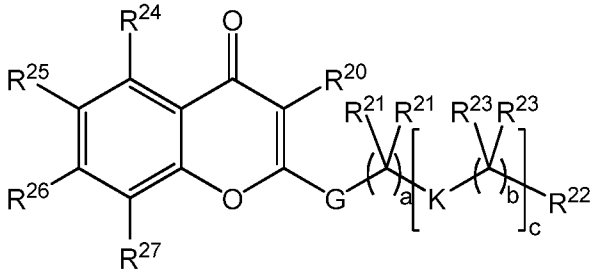
R^{12} is selected from the group consisting of alkynyl optionally substituted, alkenyl optionally substituted, alkyl substituted with –CN, alkyl substituted with $–C(=O)OR^8$, alkyl substituted with $–C(=O)R^8$, alkyl substituted with $–N(R^7)_2$, –CN, $–NO_2$, $–N(R^7)_2$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)R^8$, $–C(=O)N(R^7)_2$, and $–N(R^7)C(=O)R^8$;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound.

In some embodiments, a compound is provided comprising the structure:



(IX)

or a pharmaceutically acceptable salt thereof, wherein:

R^{20} is selected from the group consisting of hydrogen, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, and $–NO_2$;

each R^{21} and R^{23} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted,

alkoxyalkyl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally any two R^{21} or any two R^{23} may be joined together to form a ring;

R^{22} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, $-OR^{28}$, $-Si(R^9)_3$, $-B(R^{9'})_3$, and an imaging moiety;

R^{24}, R^{25}, R^{26}, and R^{27} are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, and an imaging moiety;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring; and

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and an imaging moiety;

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

R^{28} is selected from the group consisting of hydrogen, alkyl optionally substituted, and heteroalkyl optionally substituted;

G is O, S, or NR^{28};

a is 0, 1, 2, 3, or 4;

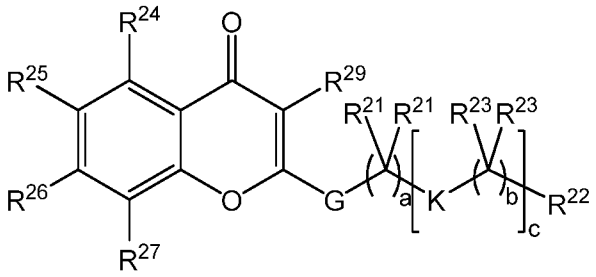
each K is independently arylene, heteroarylene, alkenylene, or alkynylene, each optionally substituted;

each b is independently 0, 1, 2, 3, or 4; and

c is 1 or 2,

provided at least one imaging moiety is present in the compound.

In some embodiments, a compound is provided comprising the structure:



(X)

or a pharmaceutically acceptable salt thereof, wherein:

each R^{21} and R^{23} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally any two R^{21} or any two R^{23} may be joined together to form a ring;

R^{22} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, $-OR^{28}$, $-Si(R^9)_3$, $-B(R^{9'})_3$, and an imaging moiety;

R^{24}, R^{25}, R^{26}, and R^{27} are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, and an imaging moiety;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring; and

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and an imaging moiety;

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

R^{28} is selected from the group consisting of hydrogen, alkyl optionally substituted, and heteroalkyl optionally substituted;

R^{29} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and an imaging moiety;

G is O, S, or NR^{28};

a is 0, 1, 2, 3, or 4;

each K is independently arylene, heteroarylene, alkenylene, or alkynylene, each optionally substituted, provided at least one K is alkenylene, or alkynylene;

each b is independently 0, 1, 2, 3, or 4; and

c is 1 or 2,

provided at least one imaging moiety is present in the compound.

In some embodiments, the compounds provided above are imaging agents. In some embodiments, a pharmaceutical composition is provided comprising a compound described above and optionally a pharmaceutically acceptable excipient. In some embodiments, a sterile aqueous solution is provided comprising a compound as described above. In some embodiments, use of a compound as described above as an imaging agent is provided. In some embodiments, use of a compound as described above in myocardial perfusion imaging is provided. In some embodiments, use of a compound as described above in the manufacture of a medicament for detecting, imaging or monitoring myocardial perfusion is provided. In some embodiments, a method of imaging a portion of a subject is provided comprising administering to the subject a compound as described above and acquiring at least one image of a portion of the subject. In some embodiments, a method of imaging a portion of a subject is provided comprising administering to a subject a compound as described above, detecting radiation emitted by the compound, and forming an image therefrom. In some embodiments, a diagnostic kit is provided comprising one or more vials containing a precursor to a compound as described above and optionally other components. In some embodiments, a method of imaging myocardial perfusion is provided comprising administering to a patient a compound as described above and scanning the patient using diagnostic imaging. In some embodiments, a method of detecting myocardial perfusion is provided comprising administering to a patient a compound as described above and scanning the patient using diagnostic imaging. In some embodiments, a method of monitoring

myocardial perfusion is provided comprising administering to a patient a compound as described above and scanning the patient using diagnostic imaging. In some embodiments, precursors to the compounds described above are provided. In some embodiments, the at least one imaging agent is replaced with at least one leaving group.

In some embodiments, a cassette for the preparation of an imaging agent is provided comprising the components arranged as shown in Figure 17.

In some embodiments, an apparatus for synthesizing an imaging agent comprising a linear arrangement of a plurality of stopcock manifolds arranged in the order:

1) luer connections (2) to gas inlet and $[^{18}O]H_2O$ recovery;
2) anion exchange cartridge – column eluting solution;
3) spike connection for acetonitrile;
4) empty syringe;
5) reservoir with solution of imaging agent precursor;
6) reaction vessel;
7) outlet to HPLC;
8) syringe with solution of a stabilizing agent;
9) inlet from HPLC;
10) ethanol reservoir;
11) syringe with solution of a stabilizing agent;
12) syringe with water;
13) final product vial;
14) empty syringe; and
15) reaction vessel and exhaust.

In some embodiments, an apparatus for synthesizing an imaging agent comprising a linear arrangement of a plurality of stopcock manifolds arranged in the order:

1) luer connections (2) to gas inlet and $[^{18}O]H_2O$ recovery;
2) anion exchange cartridge – column eluting solution;
3) reservoir with solution of imaging agent precursor;
4) empty syringe;
5) spike connection for acetonitrile;
6) reaction vessel;
7) outlet to HPLC;
8) syringe with solution of a stabilizing agent;
9) inlet from HPLC;

10) ethanol reservoir;
11) syringe with solution of a stabilizing agent;
12) syringe with water;
13) final product vial;
14) empty syringe; and
15) reaction vessel and exhaust.

In some embodiments, an apparatus for synthesizing an imaging agent comprising a linear arrangement of a plurality of stopcock manifolds arranged in the order:

1) luer connections (2) to gas inlet and $[^{18}O]H_2O$ recovery;
2) anion exchange cartridge – column eluting solution;
3) reservoir with solution of imaging agent precursor;
4) empty syringe;
5) spike connection for acetonitrile;
6) reaction vessel;
7) outlet to HPLC;
8) syringe with solution of a stabilizing agent;
9) inlet from HPLC;
10) ethanol reservoir;
11) final product vial;
12) syringe with water;
13) syringe with solution of a stabilizing agent
14) empty syringe; and
15) reaction vessel and exhaust.

In some embodiments, an apparatus for synthesizing an imaging agent comprising a linear arrangement of a plurality of stopcock manifolds arranged in the order:

1) luer connections (2) to gas inlet and $[^{18}O]H_2O$ recovery;
2) anion exchange cartridge – column eluting solution;
3) spike connection for acetonitrile;
4) empty syringe;
5) reservoir with solution of imaging agent precursor;
6) reaction vessel;
7) outlet to HPLC;
8) syringe with solution of a stabilizing agent;
9) inlet from HPLC;

10) ethanol reservoir;
11) final product vial;
12) syringe with water;
13) syringe with solution of a stabilizing agent;
14) empty syringe; and
15) reaction vessel and exhaust.

Brief Description of the Drawings

Figures 1-15 show representative images of non-limiting compounds in rat.

Figure 16 shows a flow chart describing a method for synthesizing an imaging agent, according to some embodiments.

Figure 17 shows a schematic representation of a cassette, with associated columns and reagents for synthesizing an imaging agent using an automated synthesis module, according to some embodiments.

Other aspects, embodiments, and features of the invention will become apparent from the following detailed description when considered in conjunction with the accompanying drawings. The accompanying figures are schematic and are not intended to be drawn to scale. For purposes of clarity, not every component is labeled in every figure, nor is every component of each embodiment of the invention shown where illustration is not necessary to allow those of ordinary skill in the art to understand the invention. All patent applications and patents incorporated herein by reference are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

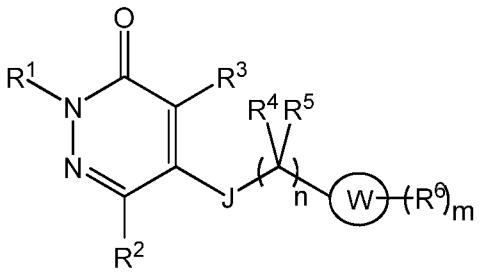
Detailed Description of Certain Embodiments of the Invention

The present invention provides compounds, compositions thereof, systems comprising such compounds, reagents, cassettes, methods, kits, and apparatuses for the synthesis and/or use of the compounds as imaging agents and precursors thereof. The imaging agents of the present invention may be used to image an area of interest in a subject, including, but not limited to, the heart, a portion of the heart, the cardiovascular system, cardiac vessels, brain, and other organs. In some embodiments, the imaging agent comprises an imaging moiety, wherein the imaging moiety is selected from the group consisting of ^{11}C, ^{13}N, ^{18}F, ^{76}Br, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{99m}Tc, ^{95}Tc, ^{111}In, ^{62}Cu, ^{64}Cu, ^{67}Ga, and ^{68}Ga. In certain embodiments, the imaging agent comprises ^{18}F as the imaging moiety. In certain embodiments, the area of the subject being imaged is imaged by positron emission tomography (PET).

In some embodiments, the present invention provides methods of imaging, including methods of imaging of a subject that includes administering a composition or formulation (*e.g.*, that comprises an imaging agent as described herein) to the subject by injection, infusion, or any other known method of administration, and imaging a region of the subject that is of interest. Regions of interest may include, but are not limited to, the heart, cardiovascular system, cardiac vessels, blood vessels (*e.g.*, arteries, veins), brain, and other organs. Regions of interest may also include tumors or regions of the subject's body that may include a tumor. A parameter of interest, such as blood flow, cardiac wall motion, or perfusion, can be imaged and detected using methods and/or systems described herein. An event of interest can be imaged and detected and/or other information may be determined using methods and/or systems of the disclosure. In some embodiments, methods for evaluating perfusion, including myocardial perfusion, are provided.

Imaging Agents

In one aspect, the invention provides compounds useful as imaging agents for imaging an area of interest of a subject. In some embodiments, the imaging agent comprises an imaging moiety, wherein the imaging moiety is selected from the group consisting of ^{11}C, ^{13}N, ^{18}F, ^{76}Br, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{99m}Tc, ^{95}Tc, ^{111}In, ^{62}Cu, ^{64}Cu, ^{67}Ga, and ^{68}Ga. In certain embodiments, the imaging agent is labeled with ^{18}F and is useful in PET imaging. In some embodiments, a compound is provided comprising the structure:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –

NO_2, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

W is heteroaryl, naphthyl, heterocyclyl or aryl;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–N(R^7)_2$, $–NO_2$, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, $–Si(R^9)_3$, $–B(R^{9'})_3$, $–OR^8$, and an imaging moiety;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

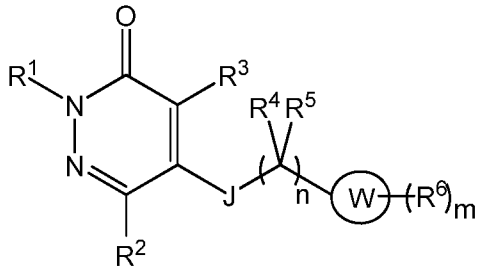
each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound; and

provided that when W is aryl, a) R^3 is not halo, alkyl, or haloalkyl, or b) at least one R^6 is selected from the group consisting of alkynyl optionally substituted, alkenyl optionally substituted, alkyl substituted with –CN, alkyl substituted with $–C(=O)OR^8$, alkyl substituted with $–C(=O)R^8$, alkyl substituted with $–N(R^7)_2$, –CN, $–NO_2$, $–N(R^7)_2$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)R^8$, $–C(=O)N(R^7)_2$, and $–N(R^7)C(=O)R^8$.

In some embodiments, a compound is provided comprising the structure:



(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–NO_2$, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

W is heteroaryl, naphthyl, or heterocyclyl;

each R^6 is independently selected from the group consisting of hydrogen, alkyl

optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, –OH, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, –CN, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and an imaging moiety;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

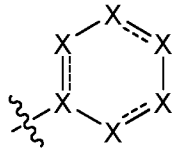
each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

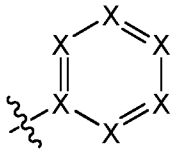
provided that at least one imaging moiety is present in the compound.

In some embodiments, for a compound of Formula (I), W is aryl. In some embodiments, for a compound of Formula (I), W is a 5-membered or 6-membered aryl group.

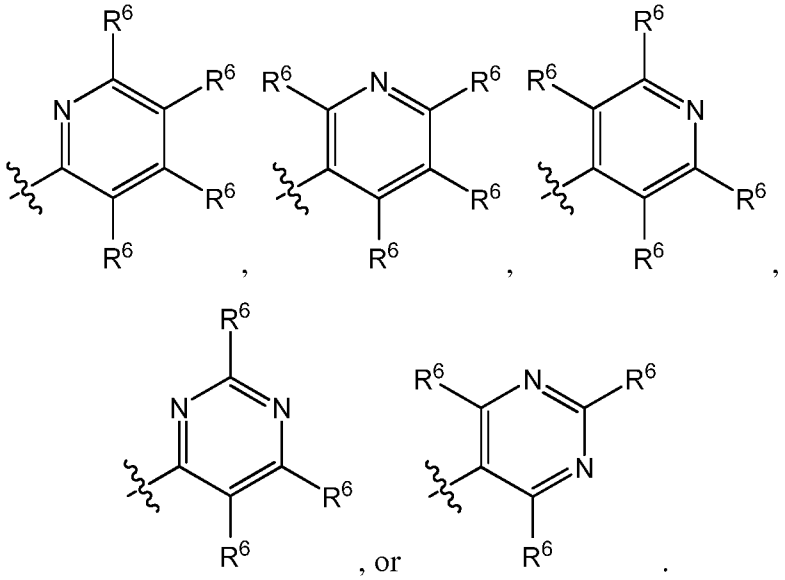
The following description of W groups may be used in connection with a compound of Formula (I) or (II), or as noted herein. In some embodiments, W is heteroaryl. In some embodiments, W is five-membered heteroaryl. In some embodiments, W is six-membered heteroaryl. In some embodiments, W is moncyclic heteroaryl. In some embodiments, W is bicyclic heteroaryl. In some embodiments, W is tricyclic heteroaryl. In some embodiments, W is naphthyl. In some embodiments, W is heterocyclyl. In some embodiments, W is:



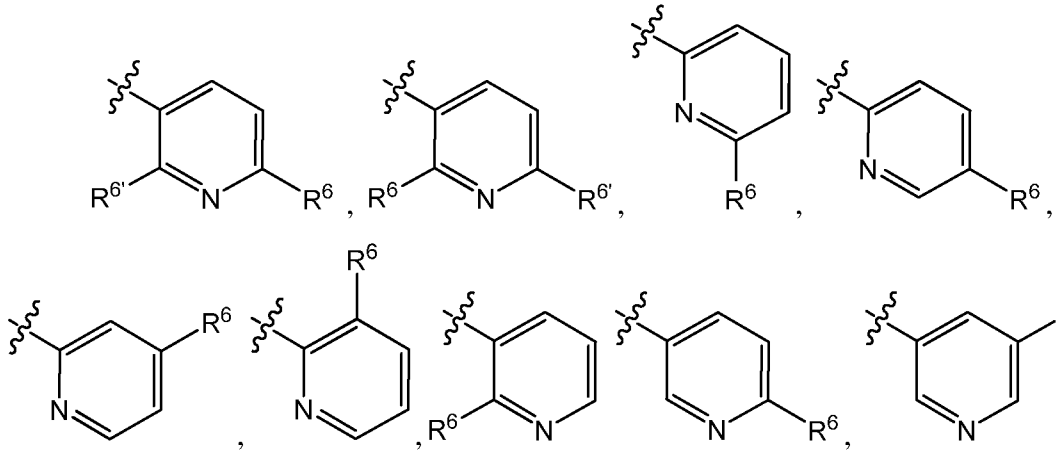
wherein each X is independently selected from the group consisting of C, $C(R^6)$, $C(R^6)_2$, N, NR^7, O, and S; and wherein each ------ is independently a single or double bond, provided at least one X is not C or $C(R^6)$. In some embodiments, at least one X is N. In some embodiments, at least one X is $N(R^7)$. In some embodiments, at least one X is O. In some embodiments, at least one X is S. In some embodiments, W is:

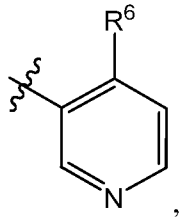


wherein each X is independently C, $C(R^6)$ or N, provided at least one X is not C or $C(R^6)$. In some embodiments, W is:

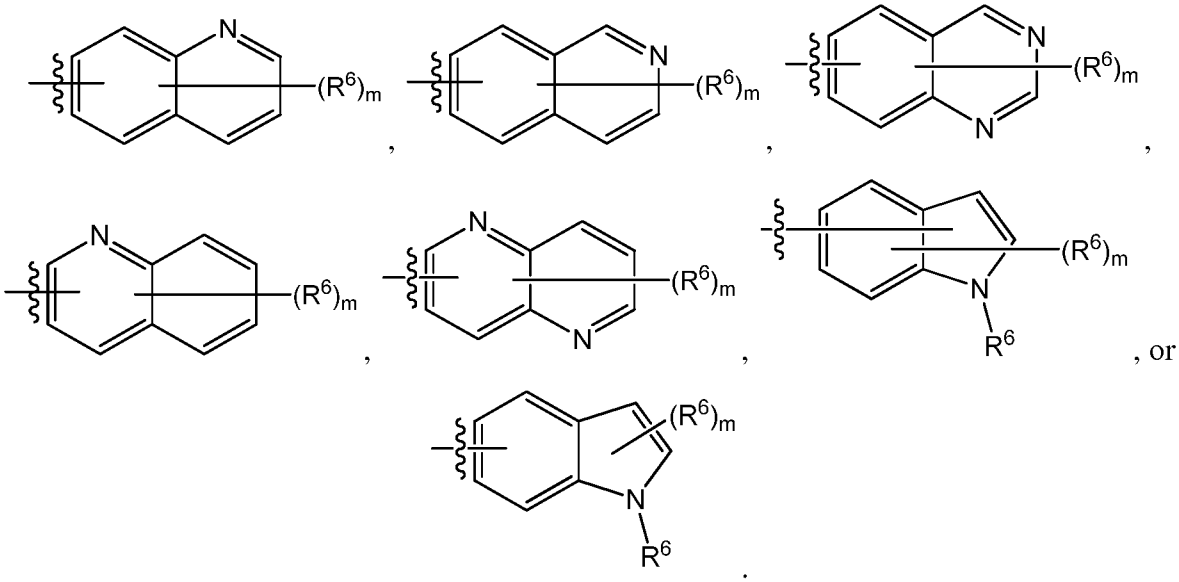


In some embodiments, W is:

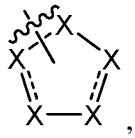




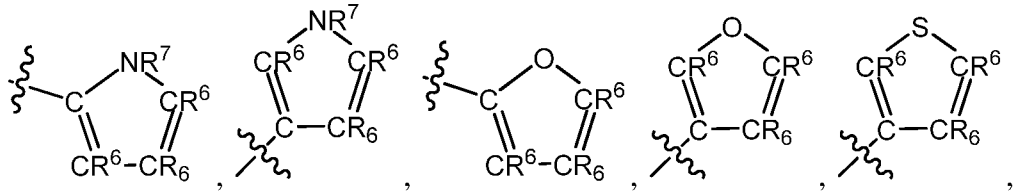
wherein $R^{6'}$ is halo or hydrogen. In some embodiments, $R^{6'}$ is fluoro, chloro, bromo, or hydrogen. In some embodiments, R^6 is $-O(CH_2)_jI_m$, wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6. In some embodiments, R^6 is $-(CH_2)_jO(CH_2)_jI_m$ I_m is an imaging moiety and wherein each j is independently 1, 2, 3, 4, 5, or 6. In some cases, I_m is ^{18}F. In some embodiments, W is:

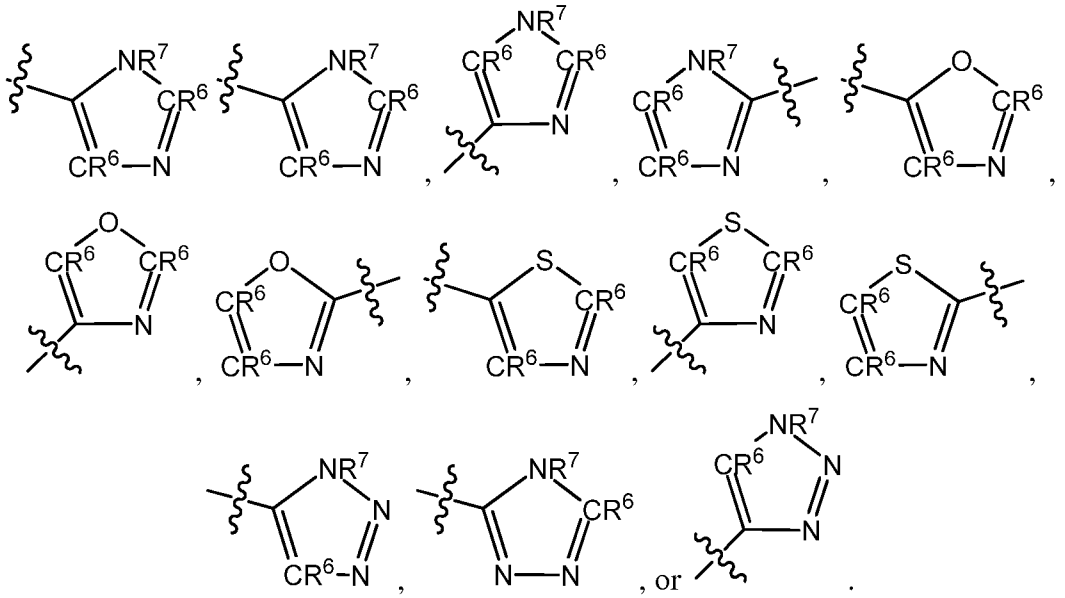


In some embodiments, W is:



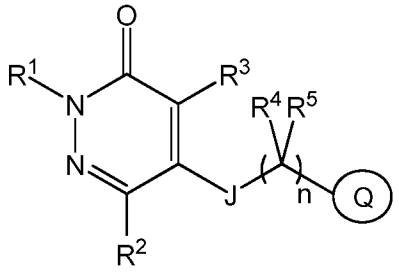
wherein each X is independently selected from the group consisting of C, $C(R^6)$, $C(R^6)_2$, N, NR^7, O, and S; and each ------ is independently a single or double bond, provided at least one X is not C or $C(R^6)$. In some embodiments, W is selected from the group consisting of:





For a compound of Formula (I) or (II), each of the W groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, J, m, and n, or combinations thereof, as described herein.

In some embodiments, a compound is provided comprising the structure:



(III)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and an imaging moiety;

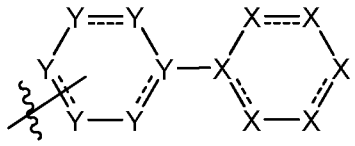
R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $-NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

Q has the structure:



each Y and each X is independently selected from the group consisting of C, $C(R^6)$, $C(R^6)_2$, N, NR^7, O, and S, provided at least one Y is not C or $C(R^6)$, and optionally, wherein one Y and/or one X may be absent;

each ------ is independently a single or double bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, –OH, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, –CN, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and an imaging moiety;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

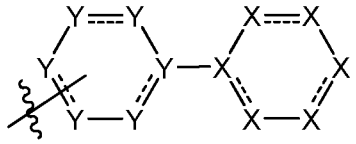
each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally

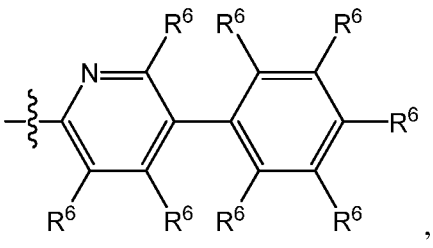
substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound.

The following description of Q groups may be used in connection with a compound of Formula (III), or as noted herein. In some embodiments, Q has the structure:



wherein each Y and each X is independently selected from the group consisting of C, $C(R^6)$, $C(R^6)_2$, N, NR^7, O, and S, provided at least one Y is not C or $C(R^6)$. In some embodiments, one Y and/or one X may be absent. In some embodiments, one Y is absent. In some embodiments, one X is absent. In some embodiments, one Y and one X are absent. In some embodiments, one Y is absent and one Y is N. In some embodiments, one Y is absent and one Y is NR^7. In some embodiments, one Y is absent and one Y is O. In some embodiments, one Y is absent and one Y is S. In some embodiments, one X is absent and one X is N. In some embodiments, one X is absent and one X is NR^7. In some embodiments, one X is absent and one X is O. In some embodiments, one X is absent and one X is S. In some embodiments, for Q, at least one Y is NR^7. In some embodiments, for Q, at least one of each of X and Y is NR^7. In some embodiments, for Q, at least one Y is N. In some embodiments, for Q, at least one of each of X and Y is N. In some embodiments, for Q, at least one Y is O. In some embodiments, for Q, at least one Y is S. In some embodiments, for Q, each X is C or $C(R^6)$. In some embodiments, for Q, at least one X is not C or $C(R^6)$. In some embodiments, for Q, at least two Y are not C or $C(R^6)$. In some embodiments, for Q, at least one of each of X and Y is not C or $C(R^6)$. In some embodiments, for Q, at least two X are not C or $C(R^6)$. In some embodiments, Q is: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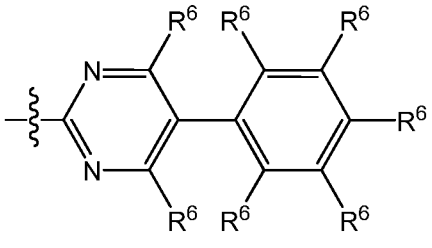
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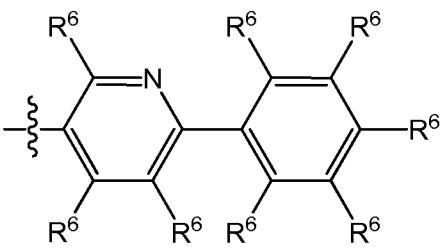
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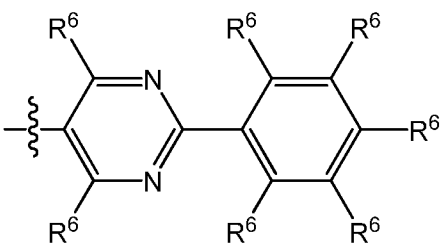
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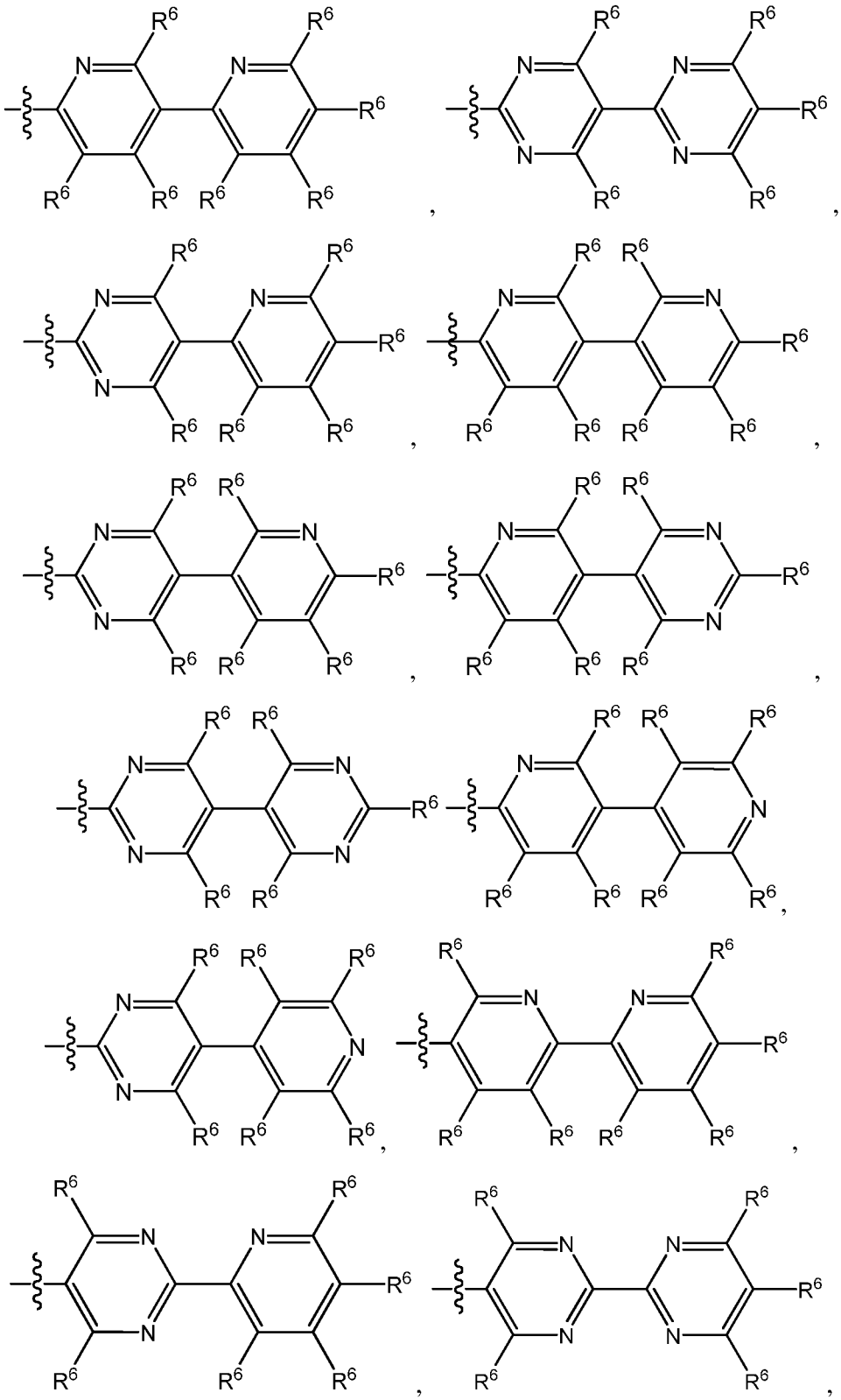
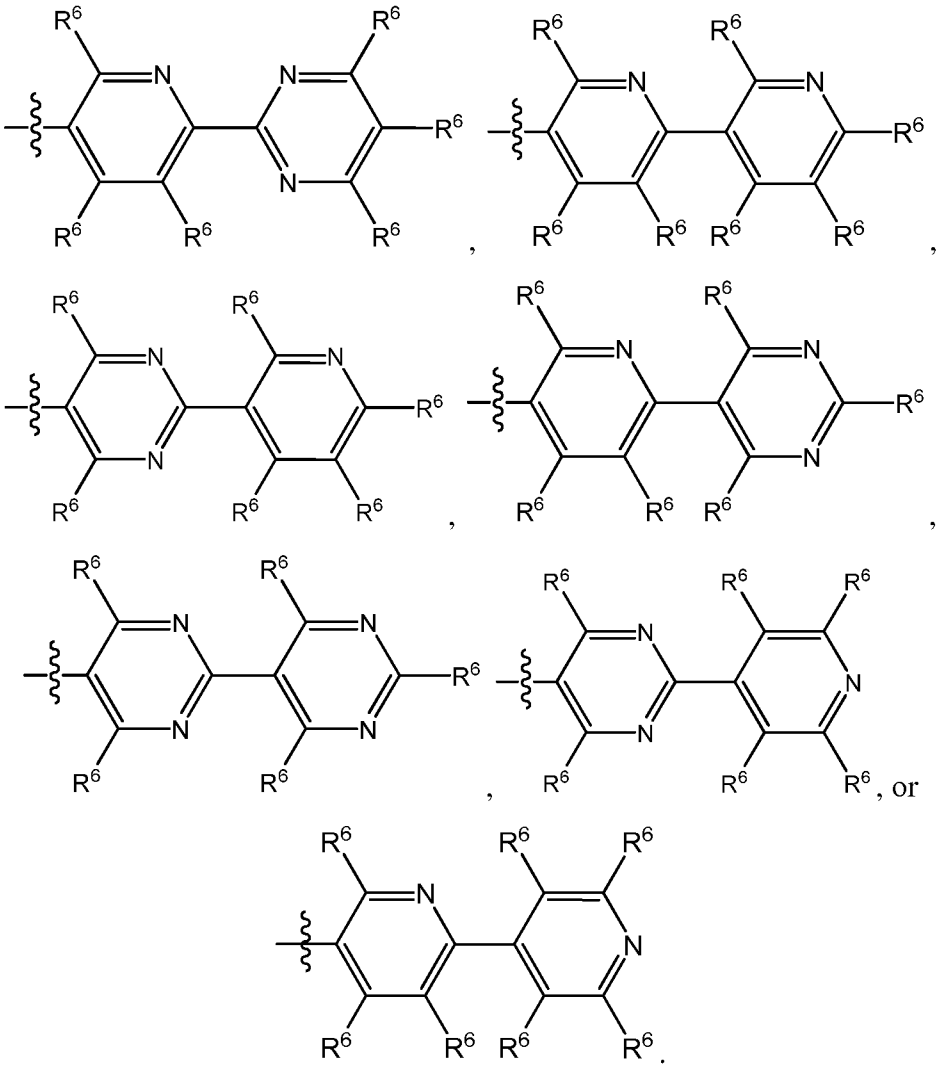
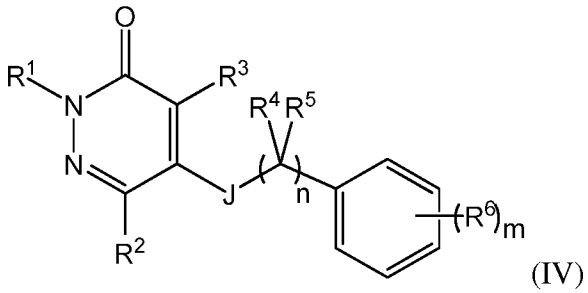




For a compound of Formula (III), each of the Q groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, J, and n, or combinations thereof, as described herein.

In some embodiments, a compound is provided comprising the structure:



(IV)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging

moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, unsubstituted alkyl or alkyl optionally substituted with a moiety other than a halogen, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, –CN, and $–NO_2$;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–N(R^7)_2$, $–NO_2$, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, $–Si(R^9)_3$, $–B(R^{9'})_3$, $–OR^8$, and an imaging moiety;

m is 0, 1, 2, 3, 4, or 5;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

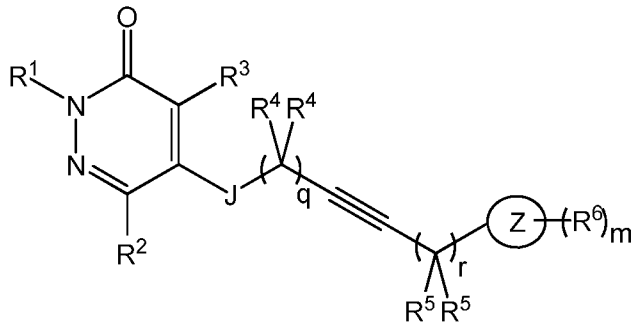
each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and an imaging moiety;

and

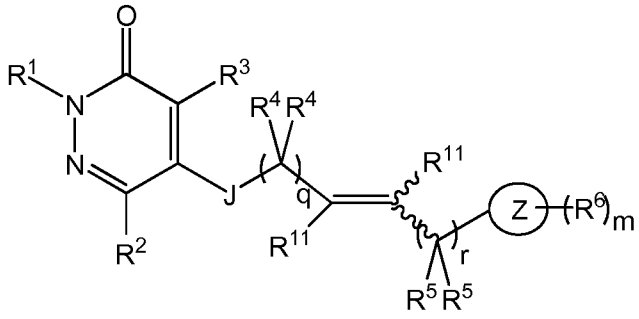
each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound.

In some embodiments, a compound is provided comprising the structure:



(V) or



(VI),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $-NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), C(=O)$N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

each R^4, R^5, and R^{11} is independently selected from the group consisting of hydrogen,

alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 or any two of R^5 are joined together to form a ring;

q, and r are each independently 0, 1, 2, or 3;

Z is selected from the group consisting of aryl, heteroaryl, heterocyclyl, and a bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and an imaging moiety;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

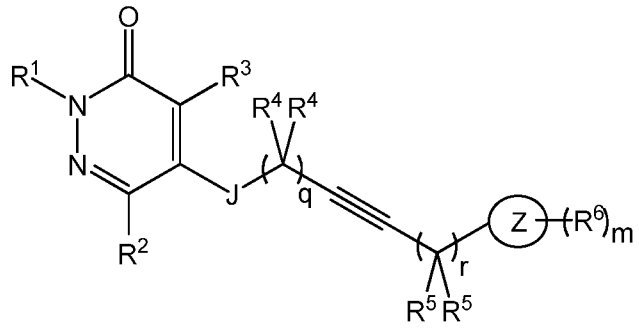
each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and an imaging moiety; and

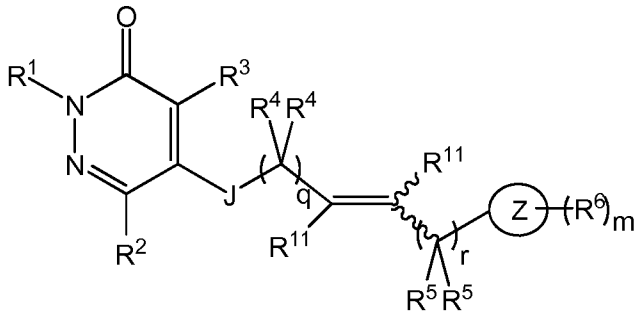
each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound. In some embodiments, In some embodiments, a compound is provided comprising the structure:



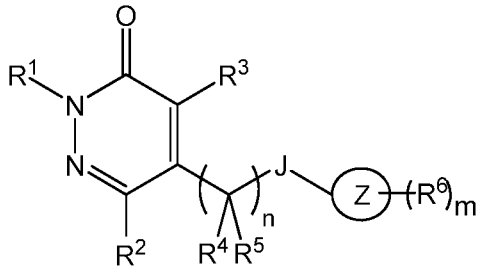
(V).

In some embodiments, a compound is provided comprising the structure:



(VI),

In some embodiments, a compound is provided comprising the structure:



(VII)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, $–NO_2$, haloalkyl, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O),

$C(=O)N(R^7)_2$, $N(R^7)C(=O)$, and $-CH_2O$;

each R^4 and R^5 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 or any two of R^5 are joined together to form a ring;

n is 1, 2, or 3;

Z is selected from the group consisting of aryl, heteroaryl, heterocyclyl, and a bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and an imaging moiety;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

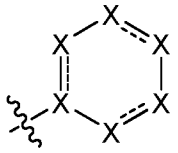
each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

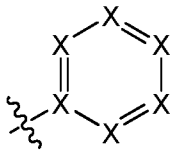
provided that at least one imaging moiety is present in the compound.

The following description of Z groups may be used in connection with a compound of Formula (V), (VI), or (VII). In some embodiments, Z is aryl. In some embodiments, Z is phenyl. In some embodiments, Z is naphthyl. In some embodiments, Z is heteroaryl. In some embodiments, Z is five-membered heteroaryl. In some embodiments, Z is six-membered heteroaryl. In some embodiments, Z is moncyclic heteroaryl. In some

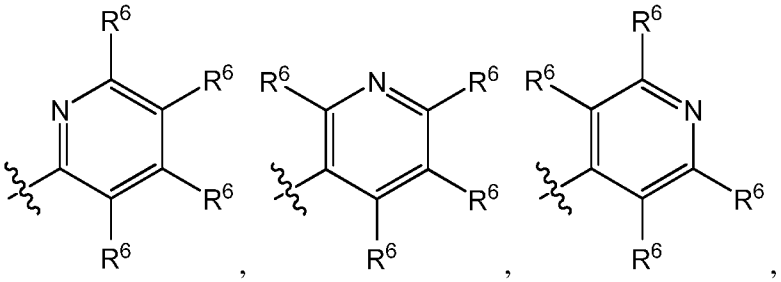
embodiments, Z is bicyclic heteroaryl. In some embodiments, Z is tricyclic heteroaryl. In some embodiments, Z is heterocyclyl. In some embodiments, Z is:



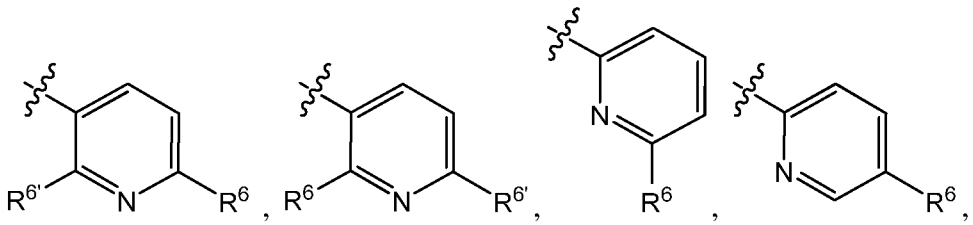
wherein each X is independently selected from the group consisting of C, $C(R^6)$, $C(R^6)_2$, N, NR^7, O, and S; and wherein each ------ is independently a single or double bond. In some embodiments, at least one X is not C or $C(R^6)$. In some embodiments, at least one X is N. In some embodiments, at least one X is $N(R^7)$. In some embodiments, at least one X is O. In some embodiments, at least one X is S. In some embodiments, Z is:



wherein each X is independently C, $C(R^6)$, or N. In some embodiments, at least one X is not C or $C(R^6)$. In some embodiments, at least one X is N. In some embodiments, Z is:


, or .

In some embodiments, Z is: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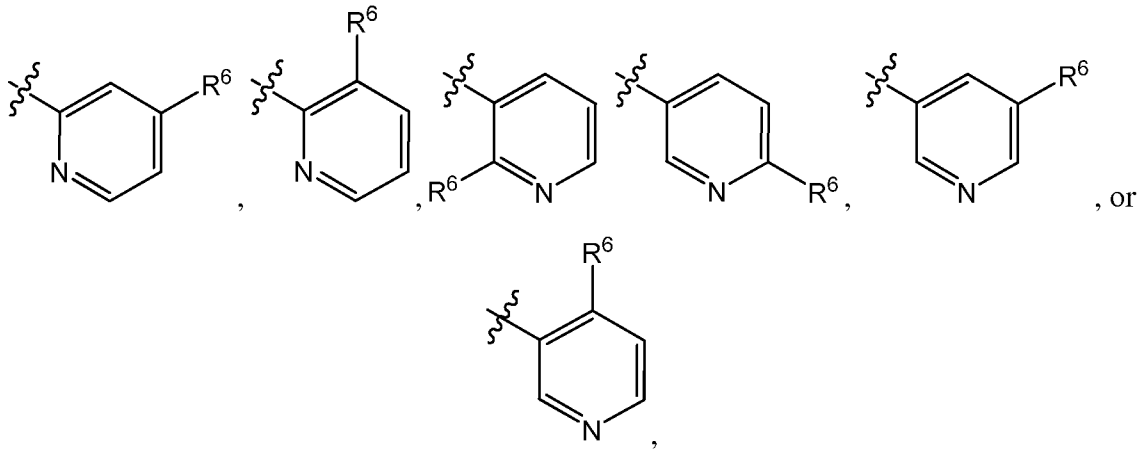
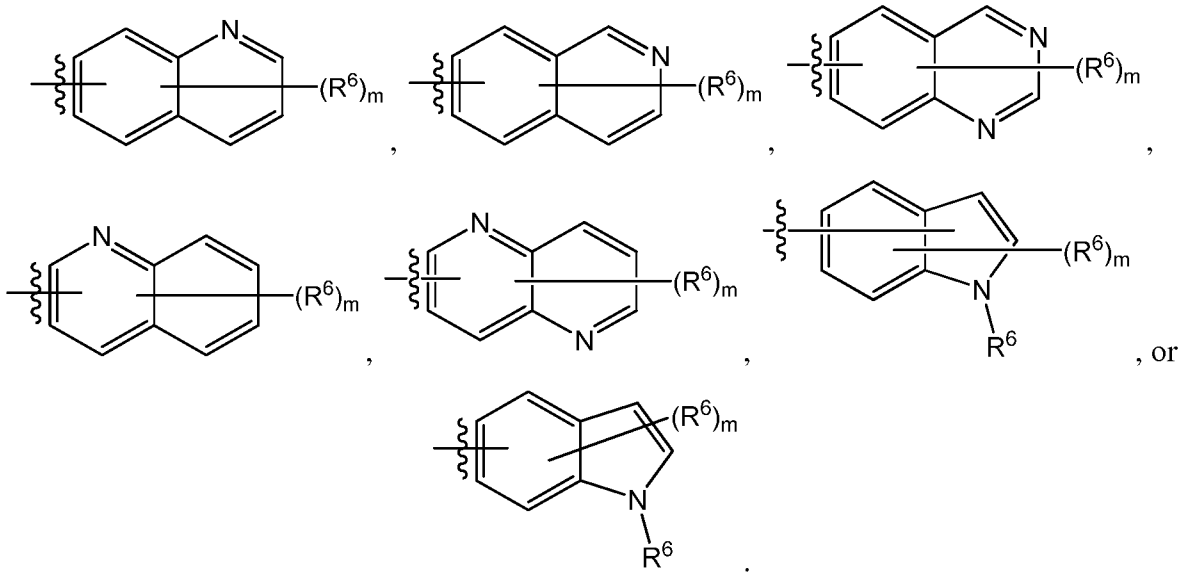
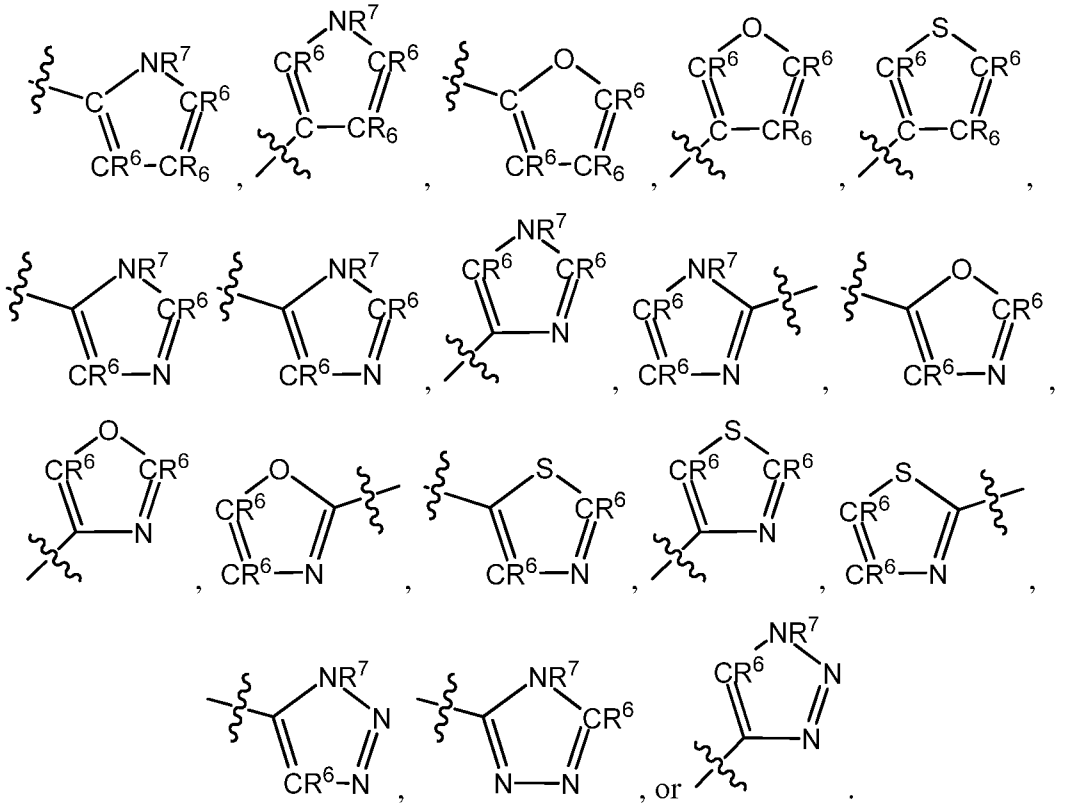


wherein $R^{6'}$ is halo or hydrogen. In some embodiments, $R^{6'}$ is fluoro, chloro, bromo, or hydrogen. In some embodiments, R^6 is $-O(CH_2)_jI_m$; wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6. In some embodiments, R^6 is $-(CH_2)_jO(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6. In some embodiments, Z is:

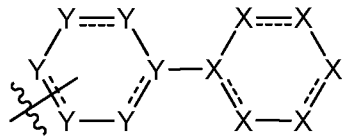


In some embodiments, Z is:

each X is independently selected from the group consisting of C, $C(R^6)$, $C(R^6)_2$, N, NR^7, O, and S; and each ------ is independently a single or double bond. In some embodiments, at least one X is not C or $C(R^6)$. In some embodiments, at least one X is N. In some embodiments, at least one X is $N(R^7)$. In some embodiments, at least one X is O. In some embodiments, at least one X is S. In some embodiments, Z is selected from the group consisting of:

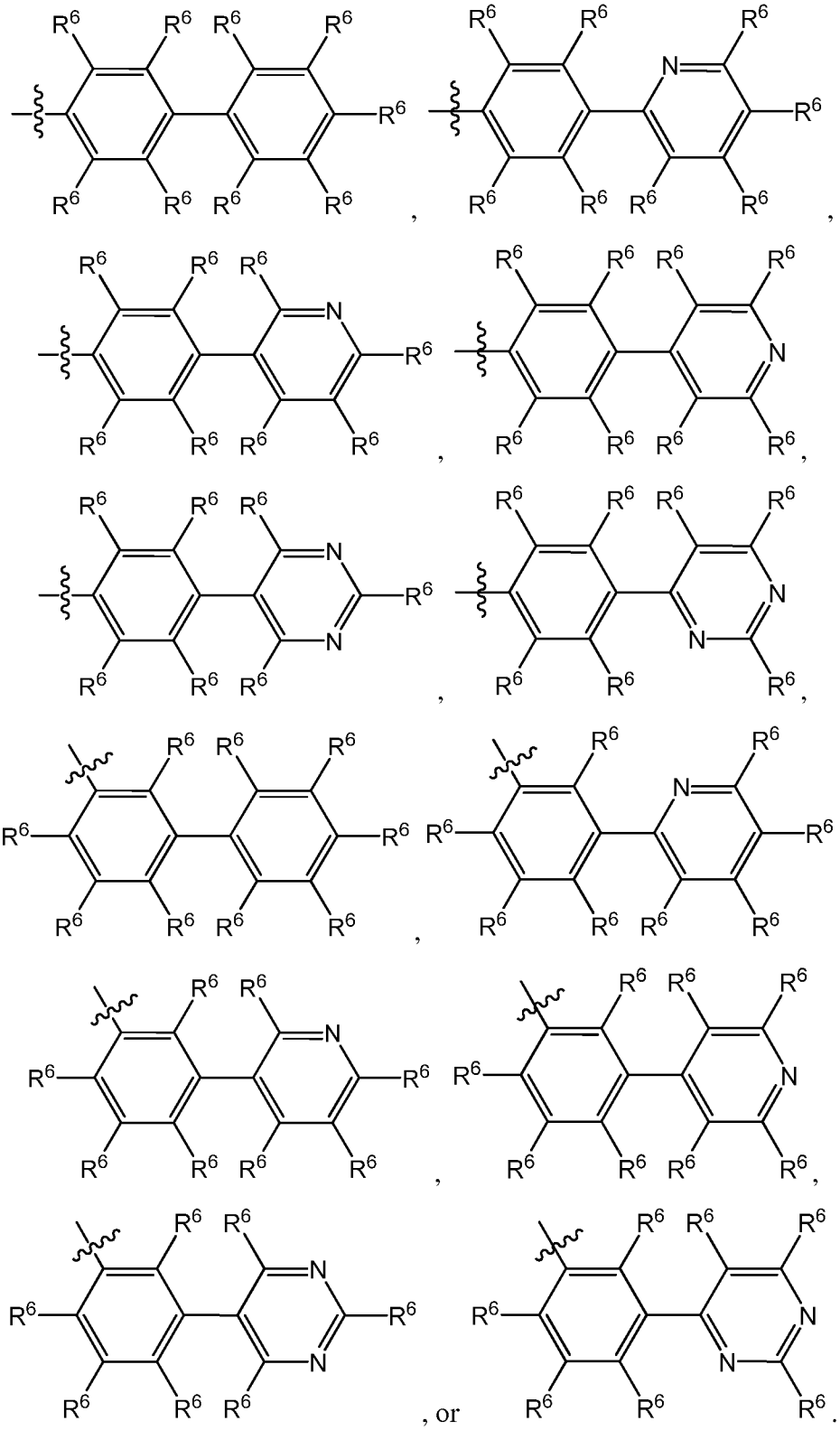


In some embodiments, Z is:

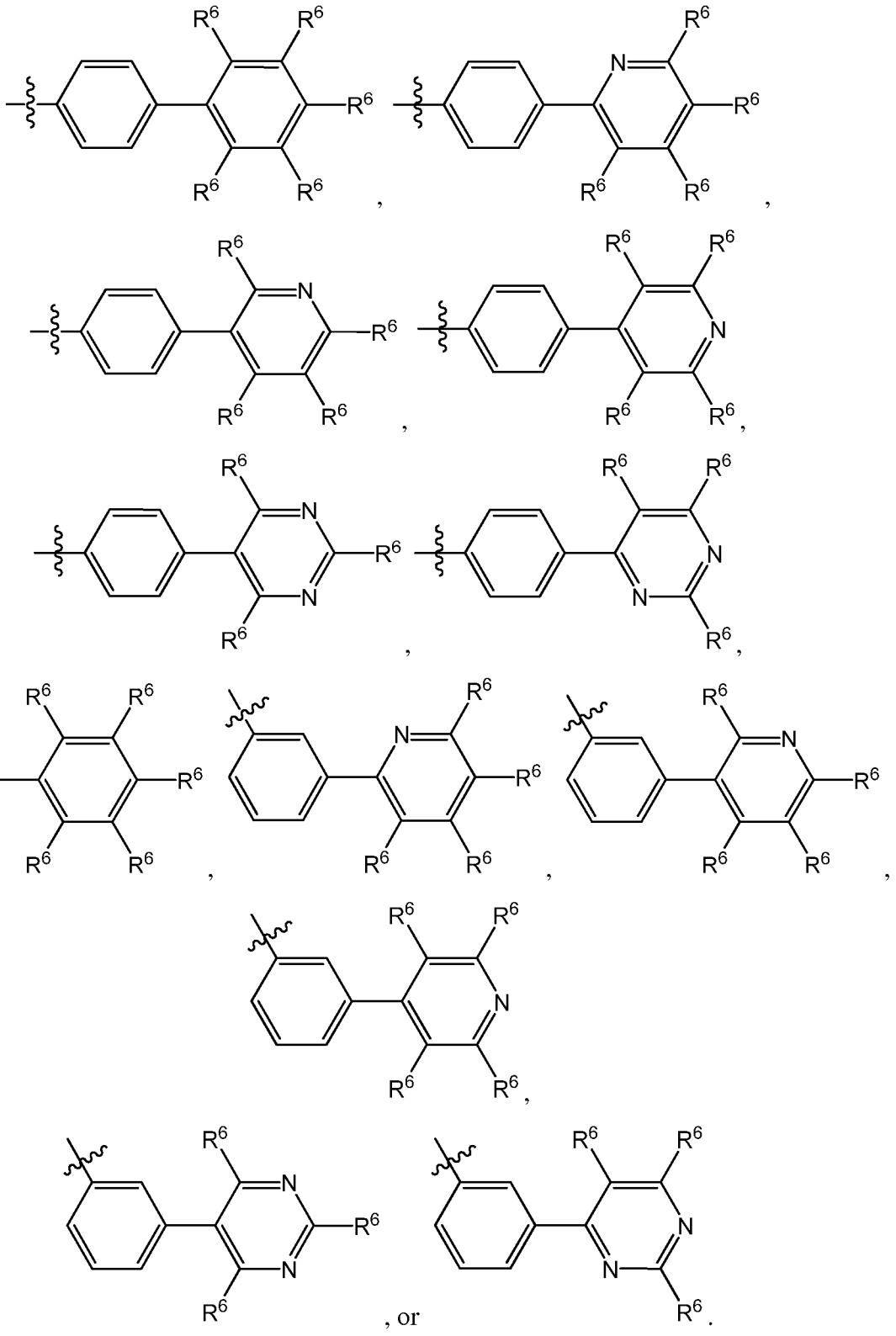


each Y is independently selected from the group consisting of C, $C(R^6)$, $C(R^6)_2$, N, NR^7, O, and S; and each ====== is independently a single or double bond, optionally, wherein one X and/or one Y is absent. In some embodiments, one Y and/or one X may be absent. In some embodiments, one Y is absent. In some embodiments, one X is absent. In some embodiments, one Y and one X are absent. In some embodiments, one Y is absent and one Y is N. In some embodiments, one Y is absent and one Y is NR^7. In some embodiments, one Y is absent and one Y is O. In some embodiments, one Y is absent and one Y is S. In some embodiments, one X is absent and one X is N. In some embodiments, one X is absent and one X is NR^7. In some embodiments, one X is absent and one X is O. In some embodiments, one X is absent and one X is S. In some embodiments, for Z, at least one Y is NR^7. In some embodiments, for Z, at least one of each of X and Y is NR^7. In some embodiments, for Z, at least one Y is N. In some embodiments, for Z, at least one of each of X and Y is N. In some embodiments, for Z, at least one Y is O. In some embodiments, for Z, at least one Y is S. In some embodiments, for Z, each X is C or $C(R^6)$. In some embodiments, for Z, at least one X

is not C or C(R^6). In some embodiments, for Z, at least two Y are not C or C(R^6). In some embodiments, for Z, at least one of each of X and Y is not C or C(R^6). In some embodiments, for Z, at least two X are not C or C(R^6). In some embodiments, Z is:

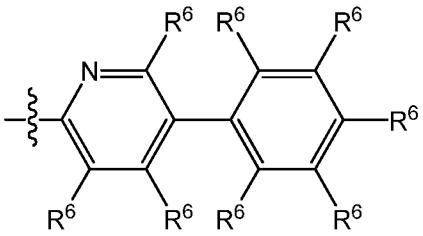


In some embodiments, Z is:



, or

In some embodiments, Z is: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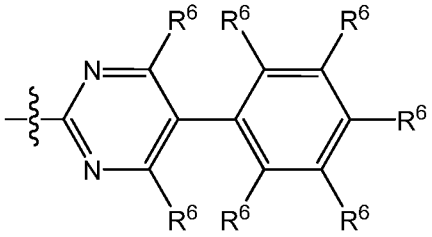
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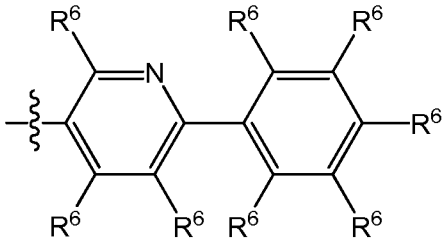
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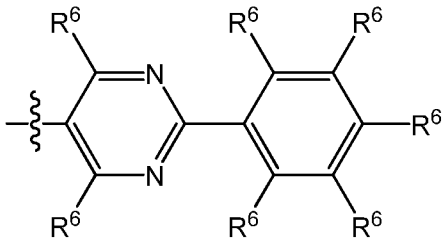
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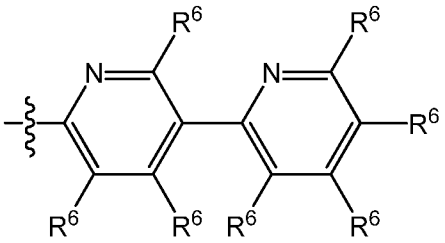
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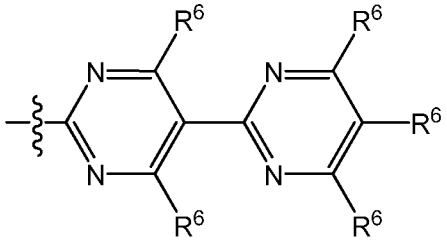
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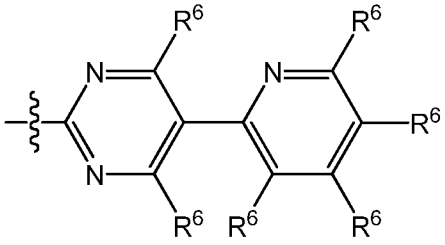
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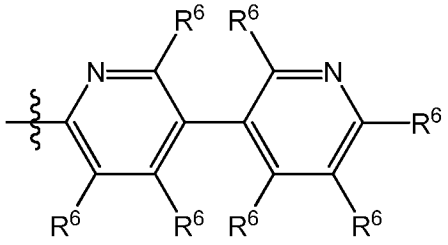
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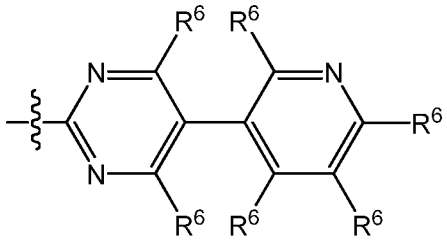
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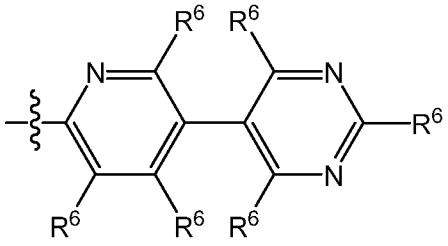
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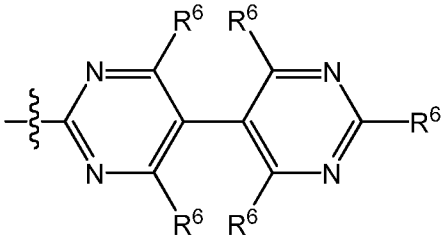
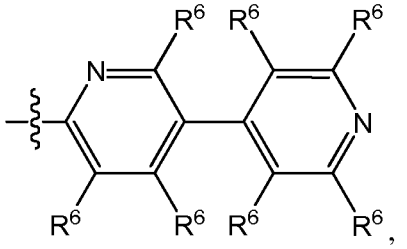
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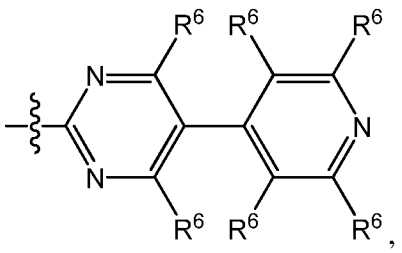
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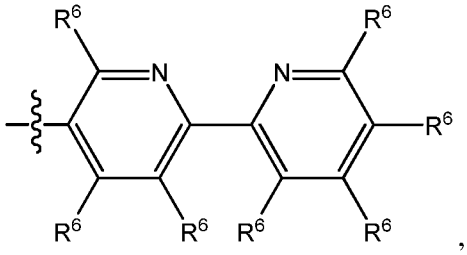
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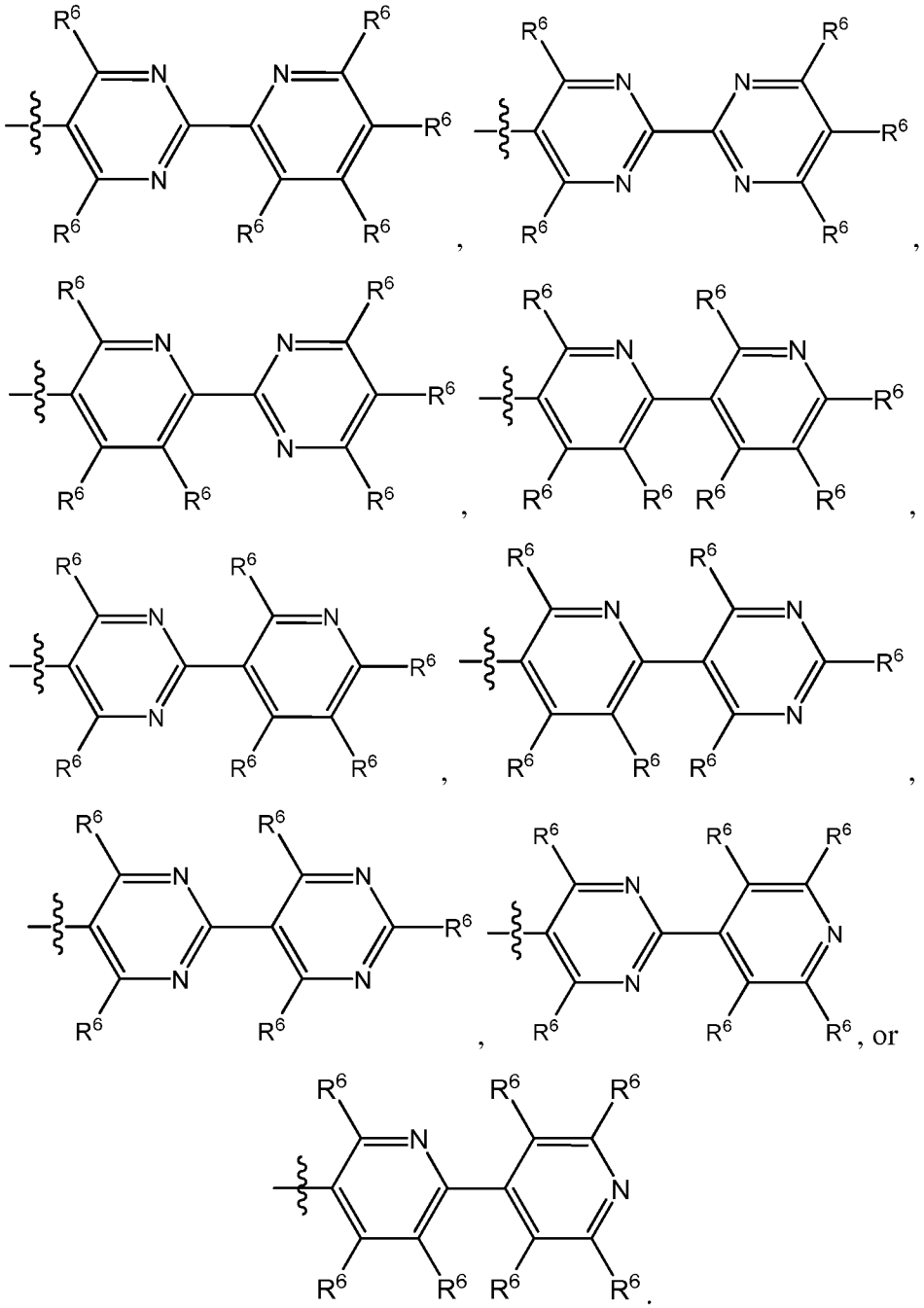
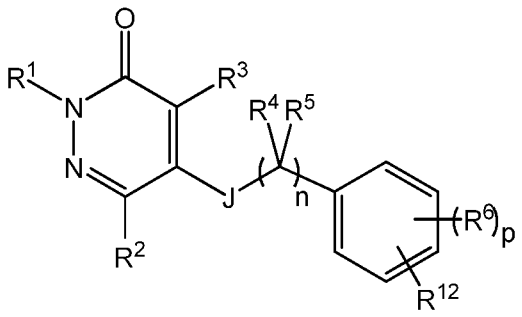


For a compound of Formula (V) or (VI), each of the Z groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{11}, J, m, q, and r, or combinations thereof, as described herein. For a compound of Formula (VII), each of the Z groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, J, n, and m, or combinations thereof, as described herein.

In some embodiments, a compound is provided comprising the structure:



(VIII)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $-NO_2$, and an imaging moiety;

J is selected from the group consisting of consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, –OH, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, –CN, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and an imaging moiety;

p is 0, 1, 2, 3, or 4;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

R^{12} is selected from the group consisting of alkynyl optionally substituted, alkenyl optionally substituted, alkyl substituted with –CN, alkyl substituted with $–C(=O)OR^8$, alkyl substituted with $–C(=O)R^8$, alkyl substituted with $–N(R^7)_2$, –CN, $–NO_2$, $–N(R^7)_2$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)R^8$, $–C(=O)N(R^7)_2$, and $–N(R^7)C(=O)R^8$;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound.

The following description of R^1 groups may be used in connection with a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII). In some embodiments, R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety. In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is alkyl optionally substituted. In some embodiments, R^1 is unsubstituted alkyl. In some embodiments, R^1 is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, or t-butyl. In some embodiments, R^1 is t-butyl. In some embodiments, R^1 is heteroalkyl optionally substituted. In some embodiments, R^1 is unsubstituted heteroalkyl. In some embodiments, R^1 is $–[C(R')_2]_jOH$, wherein j is 1, 2, 3, 4, 5, or 6, and each R' is the same or different and is hydrogen or alkyl optionally substituted. In some embodiments, R^1 is $-C(CH_3)_2CH_2OH$. In some embodiments, R^1 is alkoxy optionally substituted. In some embodiments, R^1 is alkoxyalkyl optionally substituted. In some embodiments, R^1 is aryl optionally substituted. In some embodiments, R^1 is unsubstituted aryl. In some embodiments, R^1 is phenyl optionally substituted. In some

embodiments, R^1 is unsubstituted phenyl. In some embodiments, R^1 is cycloalkyl optionally substituted. In some embodiments, R^1 is unsubstituted cycloalkyl. In some embodiments, R^1 is cyclohexyl optionally substituted. In some embodiments, R^1 is unsubstituted cyclohexyl. In some embodiments, R^1 is cyclopentyl optionally substituted. In some embodiments, R^1 is unsubstituted cyclopentyl. For a compound of Formula (I) or (II) each of the R^1 groups described herein may be combined with any R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, J, W, m, and n, or combinations thereof, as described herein. For a compound of Formula (III), each of the R^1 groups described herein may be combined with any R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, J, Q, and n, or combinations thereof, as described herein. For a compound of Formula (IV), each of the R^1 groups described herein may be combined with any R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, J, m, and n, or combinations thereof, as described herein. For a compound of Formula (V) or (VI), each of the R^1 groups described herein may be combined with any R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R11, J, Z, m, q, and r, or combinations thereof, as described herein. For a compound of Formula (VII), each of the R^1 groups described herein may be combined with any R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, J, Z, n, and m, or combinations thereof, as described herein. For a compound of Formula (VIII), each of the R^1 groups described herein may be combined with any R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R12, J, p, and n, or combinations thereof, as described herein.

The following description of R^2 groups may be used in connection with a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII). In some embodiments, R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and an imaging moiety. In some embodiments, R^2 is hydrogen. In some embodiments, R^2 is alkyl optionally substituted. In some embodiments, R^2 is unsubstituted alkyl. In some embodiments, R^2 is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, or t-butyl. In some embodiments, R^2 is aryl optionally substituted. In some embodiments, R^2 is unsubstituted aryl. In some embodiments, R^2 is phenyl optionally substituted. In some embodiments, R^2 is unsubstituted phenyl. In some embodiments, R^2 is cycloalkyl optionally substituted. In some embodiments, R^2 is unsubstituted cycloalkyl. In some embodiments, R^2 is cyclohexyl optionally substituted. In some embodiments, R^2 is unsubstituted cyclohexyl. Each of the R^2 groups described herein may be combined with any R^1, R^3, R^4, R^5, R^6, R^{12}, J, Q, W, and/or m, or combinations thereof, as described herein. For a compound of Formula (I) or (II), each of the R^2 groups described herein may be combined with any R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$,

J, W, m, and n, or combinations thereof, as described herein. For a compound of Formula (III), each of the R^2 groups described herein may be combined with any R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, J, Q, and n, or combinations thereof, as described herein. For a compound of Formula (IV), each of the R^2 groups described herein may be combined with any R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, J, m, and n, or combinations thereof, as described herein. For a compound of Formula (V) or (VI), each of the R^2 groups described herein may be combined with any R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R11, J, Z, m, q, and r, or combinations thereof, as described herein. For a compound of Formula (VII), each of the R^2 groups described herein may be combined with any R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, J, Z, n, and m, or combinations thereof, as described herein. For a compound of Formula (VIII), each of the R^2 groups described herein may be combined with any R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R^{12}, J, p, and n, or combinations thereof, as described herein.

The following description of R^3 groups may be used in connection with a compound of Formula (I), (II), (IV), (V), (VI), (VII), or (VIII). In some embodiments, R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and an imaging moiety. In some embodiments, R^3 is H. In some embodiments, R^3 is alkyl optionally substituted. In some embodiments, R^3 is alkyl optionally substituted with a moiety other than a halogen. In some embodiments, R^3 is unsubstituted alkyl. In some embodiments, R^3 is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, or t-butyl. In some embodiments, R^3 is methyl. In some embodiments, R^3 is i-propyl. In some embodiments, R^3 is –CN. In some embodiments, R^3 is $–NO_2$. In some embodiments, R^3 is heteroalkyl optionally substituted. In some embodiments, R^3 is unsubstituted heteroalkyl. In some embodiments, R^3 is aryl optionally substituted. In some embodiments, R^3 is unsubstituted aryl. In some embodiments, R^3 is phenyl optionally substituted. In some embodiments, R^3 is unsubstituted phenyl. In some embodiments, R^3 is halo. In some embodiments, R^3 is F. In some embodiments, R^3 is ^{18}F. In some embodiments, R^3 is Cl. In some embodiments, R^3 is Br. In some embodiments, R^3 is I. In some embodiments, R^3 is not halo. In some embodiments, R^3 is not halo, haloalkyl optionally substituted, or an imaging moiety. In some embodiments, R^3 is not haloalkyl optionally substituted. In some embodiments, R^3 is an imaging moiety. In some embodiments R^3 is not an imaging moiety. Each of the R^3 groups described herein may be combined with any R^1, R^2, R^4, R^5, R^6, R^{12}, J, Q, W, and/or m, or combinations thereof, as described herein. For a compound of Formula (I) or (II), each of the R^3 groups described

herein may be combined with any R^1, R^2, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, J, W, m, and n, or combinations thereof, as described herein. For a compound of Formula (IV), each of the R^3 groups described herein may be combined with any R^1, R^2, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, J, m, and n, or combinations thereof, as described herein. For a compound of Formula (V) or (VI), each of the R^3 groups described herein may be combined with any R^1, R^2, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R^{11}, J, Z, m, q, and r, or combinations thereof, as described herein. For a compound of Formula (VII), each of the R^3 groups described herein may be combined with any R^1, R^2, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, J, Z, n, and m, or combinations thereof, as described herein. For a compound of Formula (VIII), each of the R^3 groups described herein may be combined with any R^1, R^2, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R^{12}, J, p, and n, or combinations thereof, as described herein.

The following description of R^3 groups may be used in connection with a compound of Formula (III). In some embodiments, R^3 is selected from the group consisting of hydrogen, unsubstituted alkyl or alkyl optionally substituted with a moiety other than a halogen, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, –CN, and $–NO_2$. In some embodiments, R^3 is alkyl optionally substituted with a moiety other than a halogen. In some embodiments, R^3 is unsubstituted alkyl. In some embodiments, R^3 is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, or t-butyl. In some embodiments, R^3 is methyl. In some embodiments, R^3 is i-propyl. In some embodiments, R^3 is –CN. In some embodiments, R^3 is $–NO_2$. In some embodiments, R^3 is heteroalkyl optionally substituted. In some embodiments, R^3 is unsubstituted heteroalkyl. In some embodiments, R^3 is aryl optionally substituted. In some embodiments, R^3 is unsubstituted aryl. In some embodiments, R^3 is phenyl optionally substituted. In some embodiments, R^3 is unsubstituted phenyl. For a compound of Formula (III), each of the R^3 groups described herein may be combined with any R^1, R^2, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, J, Q, and n, or combinations thereof, as described herein.

The following description of R^4 and R^5 groups may be used in connection with a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII). In some embodiments, R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring. In some embodiments, any two of R^4 and R^5 may be joined together to form a ring. In some cases, the ring formed may comprise a total of 4, 5, 6, 7, 8, or more, atoms. In some cases, the ring comprises 5 or 6 atoms. In some embodiments, each of R^4

and R^5 is H. In some embodiments, at least one R^4 and R^5 is ^2H. In some embodiments, each of R^4 and R^5 is ^2H. In some embodiments, each of R^4 and R^5 is H or alkyl optionally substituted. In some embodiments, each of R^4 and R^5 is H or unsubstituted alkyl. In some embodiments, at least one R^4 or R^5 is not H. For a compound of Formula (I) or (II), each of the R^4 and/or R^5 groups described herein may be combined with any R^1, R^2, R^3, R^6, R^7, R^8, R^9, $R^{9'}$, J, W, m, and n, or combinations thereof, as described herein. For a compound of Formula (III), each of the R^4 and/or R^5 groups described herein may be combined with any R^1, R^2, R^3, R^6, R^7, R^8, R^9, $R^{9'}$, J, Q, and n, or combinations thereof, as described herein. For a compound of Formula (IV), each of the R^4 and/or R^5 groups described herein may be combined with any R^1, R^2, R^3, R^6, R^7, R^8, R^9, $R^{9'}$, J, m, and n, or combinations thereof, as described herein. For a compound of Formula (V) or (VI), each of the R^4 and/or R^5 groups described herein may be combined with any R^1, R^2, R^3, R^6, R^7, R^8, R^9, $R^{9'}$, R^{11}, J, Z, m, q, and r, or combinations thereof, as described herein. For a compound of Formula (VII), each of the R^4 and/or R^5 groups described herein may be combined with any R^1, R^2, R^3, R^6, R^7, R^8, R^9, $R^{9'}$, J, Z, n, and m, or combinations thereof, as described herein. For a compound of Formula (VIII), each of the R^4 and/or R^5 groups described herein may be combined with any R^1, R^2, R^3, R^6, R^7, R^8, R^9, $R^{9'}$, R^{12}, J, p, and n, or combinations thereof, as described herein.

The following description of R^4, R^5, and R^{11} groups may be used in connection with a compound of Formula (VI). In some embodiments, R^4, R^5, and R^{11} are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4, R^5, and R^{11} are joined together to form a ring. In some embodiments, any two of R^4, R^5, and R^{11} may be joined together to form a ring. In some cases, the ring formed may comprise a total of 4, 5, 6, 7, 8, or more, atoms. In some cases, the ring comprises 5 or 6 atoms. In some embodiments, each of R^4, R^5, and R^{11} is H. In some embodiments, at least one R^4, R^5, and R^{11} is ^2H. In some embodiments, each of R^4, R^5, and R^{11} is ^2H. In some embodiments, each of R^4, R^5, and R^{11} is H or alkyl optionally substituted. In some embodiments, each of R^4, R^5, and R^{11} is H or unsubstituted alkyl. In some embodiments, at least one R^4, R^5, and R^{11} is not H. For a compound of Formula (VI), each of the R^4, R^5, and/or R^{11} groups described herein may be combined with any R^1, R^2, R^3, R^6, R^7, R^8, R^9, $R^{9'}$, J, Z, m, q, and r, or combinations thereof, as described herein.

The following description of R^{12} groups may be used in connection with a compound of Formula (VIII). In some embodiments, R^{12} is selected from the group consisting of alkynyl optionally substituted, alkenyl optionally substituted, alkyl substituted with –CN, alkyl substituted with $–C(=O)OR^8$, alkyl substituted with $–C(=O)R^8$, alkyl substituted with –

$N(R^7)_2$, –CN, $–NO_2$, $–N(R^7)_2$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)R^8$, $–C(=O)N(R^7)_2$, and $–N(R^7)C(=O)R^8$, wherein each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring; and each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety. In some embodiments, any two of R^7 may be joined together to form a ring. In some cases, the ring formed may comprise a total of 4, 5, 6, 7, 8, or more, atoms. In some cases, the ring comprises 5 or 6 atoms. In some embodiments, R^{12} is alkynyl optionally substituted. In some embodiments, R^{12} is unsubstituted alkynyl. In some embodiments, R^{12} is alkenyl optionally substituted. In some embodiments, R^{12} is unsubstituted alkenyl. In some embodiments, R^{12} is alkyl substituted with $–C(=O)OR^8$. In some embodiments, R^{12} is alkyl substituted with $–C(=O)R^8$. In some embodiments, R^{12} is alkyl substituted with $–N(R^7)_2$. In some embodiments, R^{12} is –CN. In some embodiments, R^{12} is $–NO_2$. In some embodiments, R^{12} is $–N(R^7)_2$. In some embodiments, R^{12} is $–C(=O)OR^8$. In some embodiments, R^{12} is $–OC(=O)R^8$. In some embodiments, R^{12} is $–C(=O)R^8$. In some embodiments, R^{12} is $–C(=O)N(R^7)_2$. In some embodiments, R^{12} is $–N(R^7)C(=O)R^8$. In some embodiments, R^{12} is $–NO_2$, $–C(=O)(CH_2)_uI_m$, $–C(=O)O(CH_2)_uI_m$, $–C\equiv C(CH_2)_uI_m$, or $–Si(alkyl)_2I_m$, wherein I_m is an imaging moiety and u is 1, 2, 3, 4, 5, or 6. For a compound of Formula (VIII), each of the R^{12} groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, J, p, and n, or combinations thereof, as described herein.

The following description of J groups may be used in connection with a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII). In some embodiments, J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond, wherein each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring. In some embodiments, any two of R^7 may be joined together to form

a ring. In some cases, the ring formed may comprise a total of 4, 5, 6, 7, 8, or more, atoms. In some cases, the ring comprises 5 or 6 atoms. In some embodiments, J is a bond. In some embodiments, J is O. In some embodiments, J is S. In some embodiments, J is $N(R^7)$. In some embodiments, J is C(=O). In some embodiments, J is C(=O)O. In some embodiments, J is OC(=O). In some embodiments, J is $-CH_2O$. In some embodiments, J is $N(R^7)$ or $C(=O)N(R^7)$ and any two R^7 are joined together to form a ring. In some cases, the ring formed may comprise a total of 4, 5, 6, 7, 8, or more, atoms. In some cases, the ring comprises 5 or 6 atoms. For a compound of Formula (I) or (II), each of the J groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, W, m, and n, or combinations thereof, as described herein. For a compound of Formula (III), each of the J groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, Q, and n, or combinations thereof, as described herein. For a compound of Formula (IV), each of the J groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, m, and n, or combinations thereof, as described herein. For a compound of Formula (V) or (VI), each of the J groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R11, Z, m, q, and r, or combinations thereof, as described herein. For a compound of Formula (VIII), each of the J groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R^{12}, p, and n, or combinations thereof, as described herein.

The following description of J and n groups may be used in connection with a compound of Formula (I), (II), (III), (IV), or (VIII). In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, J is O and n is 0. In some embodiments, J is O, and n is 1. In some embodiments, J is O, and n is 2. In some embodiments, J is O and n is 3. In some embodiments, J is S and n is 0. In some embodiments, J is S, and n is 1. In some embodiments, J is S, and n is 2. In some embodiments, J is S and n is 3. Each of the J groups and/or n groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^{12}, Q, W, and/or m, or combinations thereof, as described herein. For a compound of Formula (I) or (II), each of the J and/or n groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, W, and m, or combinations thereof, as described herein. For a compound of Formula (III), each of the J and/or n groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, and Q, or combinations thereof, as described herein. For a compound of Formula (IV), each of the J and/or n groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, and m, or combinations thereof,

as described herein. For a compound of Formula (VIII), each of the J and/or n groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R^{12}, and p, or combinations thereof, as described herein.

The following description of J, q, and/or r groups may be used in connection with a compound of Formula (V) or (VI). In some embodiments, q is 0. In some embodiments, q is 1. In some embodiments, q is 2. In some embodiments, q is 3. In some embodiments, r is 0. In some embodiments, r is 1. In some embodiments, r is 2. In some embodiments, r is 3. In some embodiments, q and r are each 0. In some embodiments, q and r are each 1. In some embodiments, J is O and q and r are each 0. In some embodiments, J is O and q and r are each 1. In some embodiments, J is O and q and r are each 2. In some embodiments, J is O and q and r are each 3. In some embodiments, J is S and q and r are each 0. In some embodiments, J is S and q and r are each 1. In some embodiments, J is S and q and r are each 2. In some embodiments, J is S and q and r are each 3. In some embodiments, J is O, q is 0, and r is 0, 1, 2, or 3. In some embodiments, J is O, q is 1, and r is 0, 1, 2, or 3. In some embodiments, J is O, q is 2, and r is 0, 1, 2, or 3. In some embodiments, J is O, q is 3, and r is 0, 1, 2, or 3. For a compound of Formula (V) or (VI), each of the J, q, and/or r groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R11, Z, and m, or combinations thereof, as described herein.

The following description of J and n groups may be used in connection with a compound of Formula (VII). In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, J is O, and n is 1. In some embodiments, J is O, and n is 2. In some embodiments, J is O and n is 3. In some embodiments, J is S, and n is 1. In some embodiments, J is S, and n is 2. In some embodiments, J is S and n is 3. For a compound of Formula (VII), each of the J and/or n groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, Z, and m, or combinations thereof, as described herein.

In some embodiments, for a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII) or (VIII), the compound comprises a single imaging moiety. In some embodiments, for a compound of Formula (I), (II), (III), (IV) or (VII), the at least one imaging moiety is present in R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, or R^9. In some embodiments, for a compound of Formula (VIII), the at least one imaging moiety is present in R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9 or R^{12}. In some embodiments, for a compound of Formula (V) or (VI), the at least one imaging moiety is present in R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 or R^{11}. In some embodiments, for a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII) or (VIII), the at least one imaging moiety is

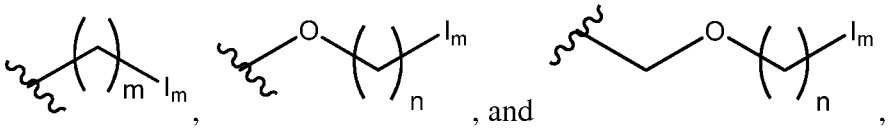
present in R^1, R^2, R^3, R^4, R^5, or R^6. In some embodiments, for a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII), the at least one imaging moiety is present in R^6. As will be understood by those of ordinary skill in the art, when referring to an imaging moiety, the imaging moiety "is present" in a group in embodiments wherein 1) the imaging moiety is the group (*e.g.*, R^6 is an imaging moiety) or b) the group comprises the imaging moiety (*e.g.*, R^6 is substituted with an imaging moiety). In some embodiments, for a compound of Formula (I), (II), (III), (IV), (V), (VI) or (VII), R^1, R^2, R^3, R^4, R^5, or R^6 comprises the at least one imaging moiety. In some embodiments, for a compound of Formula (VIII), R^1, R^2, R^3, R^4, R^5, R^6, or R^{12} comprises the at least one imaging moiety. In some embodiments, for a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII), at least one R^6 is substituted with the at least one imaging moiety. In some embodiments, for a compound of Formula (I), (II), (IV), or (VII), R^1, R^2, R^3, R^4, R^5, or R^6 is the at least one imaging moiety. In some embodiments, for a compound of Formula (III), R^1, R^2, R^4, R^5, or R^6 is the at least one imaging moiety. In some embodiments, for a compound of Formula (V) or (VI), R^1, R^2, R^3, R^4, R^5, R^6, or R^{11} is the at least one imaging moiety. In some embodiments, for a compound of Formula (VIII), R^1, R^3, R^4, R^5, R^6, or R^{12} is the at least one imaging moiety. In some embodiments, for a compound of Formula (I), (II), (IV), or (VII), R^1, R^2, R^3, R^4, R^5, or R^6 is not an imaging moiety. In some embodiments, for a compound of Formula (III), R^1, R^2, R^4, R^5, or R^6 is not an imaging moiety. In some embodiments, for a compound of Formula (V) or (VI), R^1, R^2, R^3, R^4, R^5, R^6, or R^{11} is not an imaging moiety. In some embodiments, for a compound of Formula (VIII), R^1, R^3, R^4, R^5, R^6, or R^{12} is not an imaging moiety. In some embodiments, for a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII), at least one R^6 is an imaging moiety. For a compound of Formula (I) or (II), each of the placements of the imaging moieties described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, J, W, m, and n, or combinations thereof, as described herein. For a compound of Formula (III), each of the placements of the imaging moieties described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, Q, J, and n, or combinations thereof, as described herein. For a compound of Formula (IV), each of the placements of the imaging moieties described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, J, n, and m, or combinations thereof, as described herein. For a compound of Formula (V) or (VI), each of the placements of the imaging moieties described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R11, J, Z, m, q, and r, or combinations thereof, as described herein. For a compound of Formula (VII), each of the placements of the imaging moieties described herein may be combined with any R^1, R^2,

R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, J, Z, n, and m, or combinations thereof, as described herein. For a compound of Formula (VIII), each of the placements of the imaging moieties described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R12, J, p, and n, or combinations thereof, as described herein.

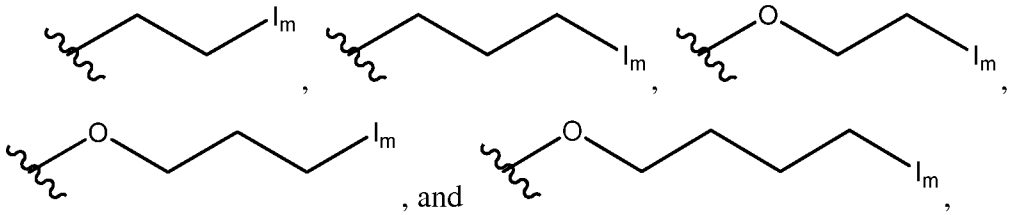
The following description of the imaging moiety may be used in connection with a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII). In some embodiments, the at least one imaging moiety is selected from the group consisting of ^{11}C, ^{13}N, ^{18}F, ^{76}Br, ^{89}Zr, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{99m}Tc, ^{95}Tc, ^{111}In, ^{62}Cu, ^{64}Cu, ^{67}Ga, and ^{68}Ga. In some embodiments, the at least one imaging moiety is ^{18}F. Imaging moieties are described in more detail herein.

The following description of R^6 groups may be used in connection with a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII). In some embodiments, for a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII), all but one R^6 is H. That is, all R^6 are H and one R^6 is not H. In some cases, the one R^6 which is not H is substituted with the at least one imaging moiety. In some cases, the one R^6 which is not H is the at least one imaging moiety. In some embodiments, for a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII), at least one R^6 is alkyl optionally substituted, alkoxy optionally substituted, or alkoxyalkyl optionally substituted, each substituted with an imaging moiety. In some embodiments, for a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII), at least one R^6 is $-(CH_2)_jI_m$; wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6. In some cases, at least one R^6 is $-(CH_2)I_m$, $-(CH_2)_2I_m$, $-(CH_2)_3I_m$, $-(CH_2)_4I_m$, $-(CH_2)_5I_m$, $-(CH_2)_6I_m$, $-(CH_2)_7I_m$, $-(CH_2)_8I_m$, $-(CH_2)_9I_m$, or $-(CH_2)_{10}I_m$. In some cases, at least one R^6 is $-(CH_2)^{18}F$, $-(CH_2)_2{}^{18}F$, $-(CH_2)_3{}^{18}F$, $-(CH_2)_4{}^{18}F$, $-(CH_2)_5{}^{18}F$, $-(CH_2)_6{}^{18}F$, $-(CH_2)_7{}^{18}F$, $-(CH_2)_8{}^{18}F$, $-(CH_2)_9{}^{18}F$, or $-(CH_2)_{10}{}^{18}F$. In some embodiments, at least one R^6 is $-O(CH_2)_jI_m$; wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6. In some cases, at least one R^6 is $-O(CH_2)_5I_m$, $-O(CH_2)_6I_m$, $-O(CH_2)_7I_m$, $-O(CH_2)_8I_m$, $-O(CH_2)_9I_m$, or $-O(CH_2)_{10}I_m$. In some cases, at least one R^6 is $-O(CH_2)^{18}F$, $-O(CH_2)_2{}^{18}F$, $-O(CH_2)_3{}^{18}F$, $-O(CH_2)_4{}^{18}F$, $-O(CH_2)_5{}^{18}F$, $-O(CH_2)_6{}^{18}F$, $-O(CH_2)_7{}^{18}F$, $-O(CH_2)_8{}^{18}F$, $-O(CH_2)_9{}^{18}F$, or $-O(CH_2)_{10}{}^{18}F$. In some embodiments, at least one R^6 is $-(CH_2)_jO(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6. In some embodiments, at least one R^6 is $-(CH_2)O(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6. In some cases, at least one R^6 is $-CH_2O(CH_2)\ I_m$, $-CH_2O(CH_2)_2I_m$, $-CH_2O(CH_2)_3I_m$, $-CH_2O(CH_2)_4I_m$, $-CH_2O(CH_2)_5I_m$, $-CH_2O(CH_2)_6I_m$, $-CH_2O(CH_2)_7I_m$, $-CH_2O(CH_2)_8I_m$, $-CH_2O(CH_2)_9I_m$, or $-CH_2O(CH_2)_{10}I_m$. In some cases, at least one R^6 is $-CH_2O(CH_2)^{18}F$, $-CH_2O(CH_2)_2{}^{18}F$, $-CH_2O(CH_2)_3{}^{18}F$, $-CH_2O(CH_2)_4{}^{18}F$, $-CH_2O(CH_2)_5{}^{18}F$, $-CH_2O(CH_2)_6{}^{18}F$, –

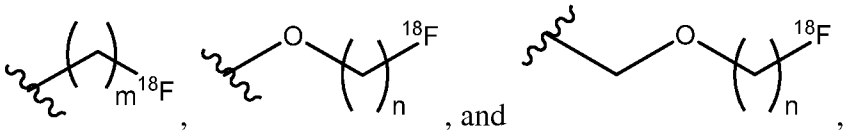
$CH_2O(CH_2)_7{}^{18}F$, $-CH_2O(CH_2)_8{}^{18}F$, $-CH_2O(CH_2)_9{}^{18}F$, or $-CH_2O(CH_2)_{10}{}^{18}F$. In some embodiments, at least one R^6 is $-C\equiv C-(CH_2)_jI_m$; wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6. In some embodiments, at least one R^6 is $-[(CH_2)_jO]_j(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6. In some embodiments, at least one R^6 is $-O[(CH_2)_jO]_j(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6. In some embodiments, at least one R^6 is optionally substituted alkyl substituted with an imaging moiety. In some embodiments, at least one R^6 is $-C(=O)O(CH_2)_jI_m$; wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6. In some embodiments, at least one R^6 is $-C(=O)(CH_2)_jI_m$; wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6. In some embodiments, at least one R^6 is $-(CH_2)_jNH(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6. In some embodiments, at least one R^6 is $Si(R^9)_2I_m$, wherein each R^9 is alkyl optionally substituted and wherein I_m is an imaging moiety. In some embodiments, at least one R^6 is $B(R^{9'})_2I_m$, wherein each $R^{9'}$ is alkyl optionally substituted and wherein I_m is an imaging moiety. In some embodiments, at least one R^6 is selected from the group consisting of $-C\equiv C-CH_2CH_2CH_2I_m$, $-C\equiv C-CH_2CH_2I_m$, $-C\equiv C-CH_2I_m$, $-CH_2I_m$, $-(CH_2)_2I_m$, $-(CH_2)_3I_m$, $-(CH_2)_4I_m$, $-(CH_2)_5I_m$, $-(CH_2)_6I_m$, $-OCH_2I_m$, $-O(CH_2)_2I_m$, $-O(CH_2)_3I_m$, $-O(CH_2)_4I_m$, $-O(CH_2)_5I_m$, $-O(CH_2)_6I_m$, $-CH_2O(CH_2)_2I_m$, $-CH(CH_3)O(CH_2)_2I_m$, $-CH_2O(CH_2)_3I_m$, $-CD_2O(CH_2)_2I_m$, $-(CH_2)_2O(CH_2)_2I_m$, $-CHBrC(CH_3)_2I_m$, $-CHClC(CH_3)_2I_m$, $-CHFC(CH_3)_2I_m$, $-C(=O)OCH_2I_m$, $-C(=O)O(CH_2)_2I_m$, $-C(=O)O(CH_2)_3I_m$, $-CH_2NH(CH_2)_2I_m$, $-CH_2NHCH_2I_m$, $-CH_2O(CH_2)_2O(CH_2)_2I_m$, $-CH_2O(CH_2)_2O(CH_2)_3I_m$, $-O(CH_2)_2O(CH_2)_2I_m$, $-C(=O)(CH_2)_2I_m$, and $-C(=O)(CH_2)_3I_m$. In some embodiments, I_m is ^{18}F. In some embodiments, at least one R^6 is selected from the group consisting of:



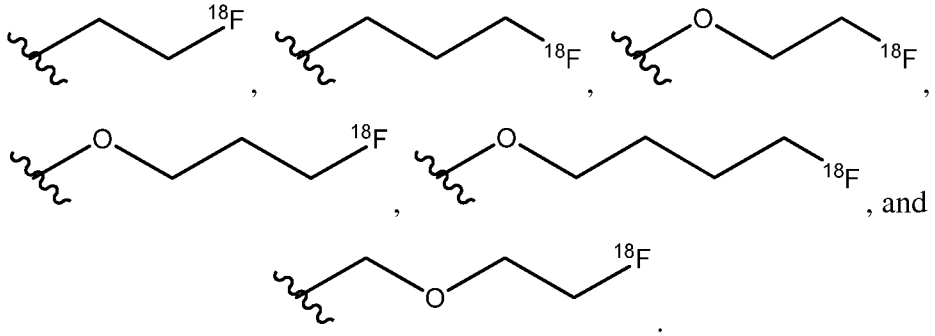
wherein m and n is an integer between 1 and 6, inclusive, and I_m is an imaging moiety. In some embodiments, at least one R^6 is selected from the group consisting of:



wherein I_m is an imaging moiety. In some embodiments, at least one R^6 is selected from the group consisting of:

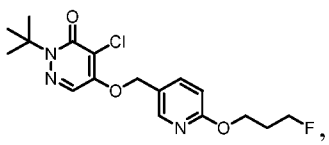
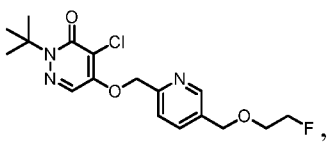
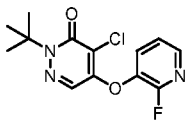
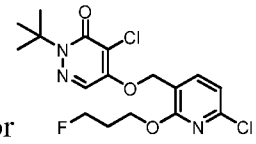


wherein m and n is an integer between 1 and 6, inclusive. In some embodiments, at least one R^6 is selected from the group consisting of:

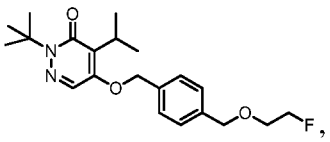


In some embodiments, for a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII), at least one R^6 is optionally substituted with at least one ^2H. In some embodiments, at least one R^6 is $Si(R^9)_3$. In some embodiments, at least one R^6 is $B(R^{9'})_3$. In some embodiments, at least one R^6 is $-NO_2$. In some embodiments, at least one R^6 is halo. In some embodiments, at least one R^6 is Cl. In some embodiments, at least one R^6 is Br. In some embodiments, at least one R^6 is F. For a compound of Formula (I) or (II), each of the R^6 groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, $R^{9'}$, J, W, m, and n, or combinations thereof, as described herein. For a compound of Formula (III), each of the R^6 groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, $R^{9'}$, Q, J, and n, or combinations thereof, as described herein. For a compound of Formula (IV), each of the R^6 groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, $R^{9'}$, J, m, and n, or combinations thereof, as described herein. For a compound of Formula (V) or (VI), each of the R^6 groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, $R^{9'}$, R^{11}, J, Z, m, q, and r, or combinations thereof, as described herein. For a compound of Formula (VII), each of the R^6 groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, $R^{9'}$, J, Z, n, and m, or combinations thereof, as described herein. For a compound of Formula (VIII), each of the R^6 groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, $R^{9'}$, R^{12}, J, p, and n, or combinations thereof, as described herein.

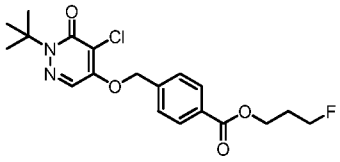
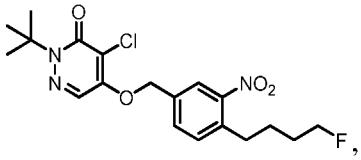
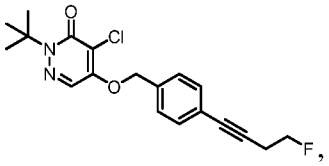
In some embodiments, a compound of Formula (II) is selected from the group consisting of:

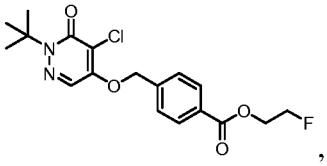
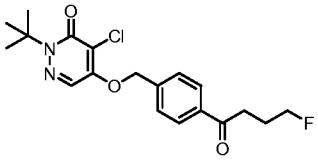
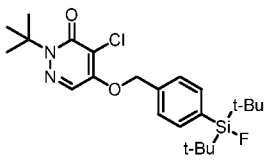
 ,  ,  , or 

or a pharmaceutically acceptable salt thereof, wherein F is optionally ^{18}F. In some embodiments, a compound of Formula (IV) is of the formula:

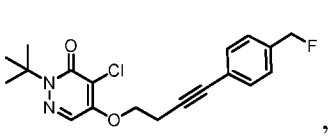
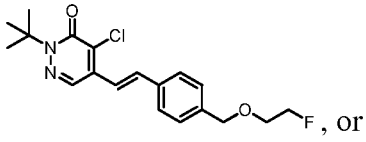
 ,

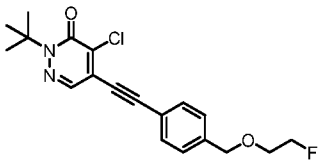
or a pharmaceutically acceptable salt thereof, wherein F is optionally ^{18}F. In some embodiments, a compound of Formula (VIII) is of the formula:

 ,  ,  ,

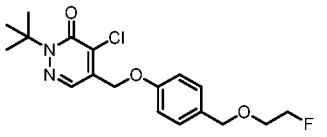
 ,  , or 

or a pharmaceutically acceptable salt thereof, wherein F is optionally ^{18}F. In some embodiments, a compound of Formula (V) or (VI) is selected from the group consisting of:

 ,  , or

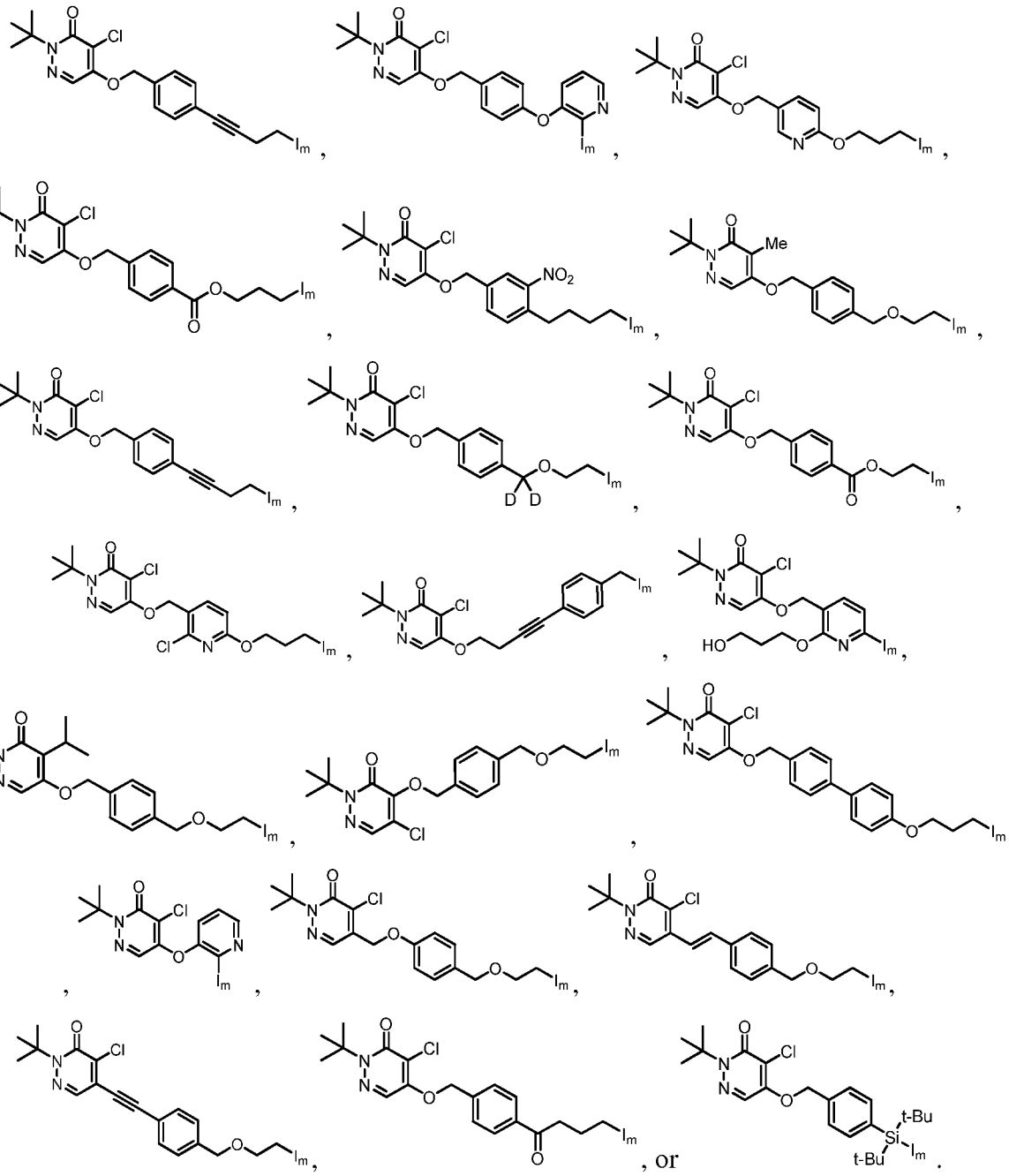


or a pharmaceutically acceptable salt thereof, wherein F is optionally ^{18}F. In some embodiments, a compound of Formula (VII) is of the formula:

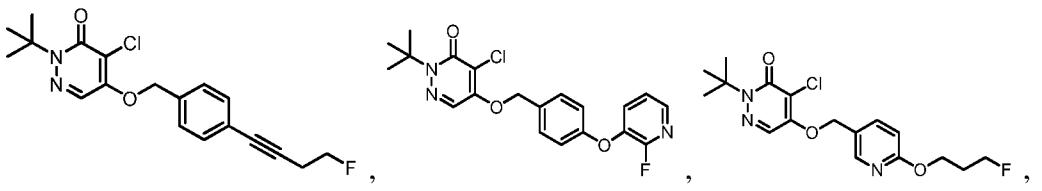


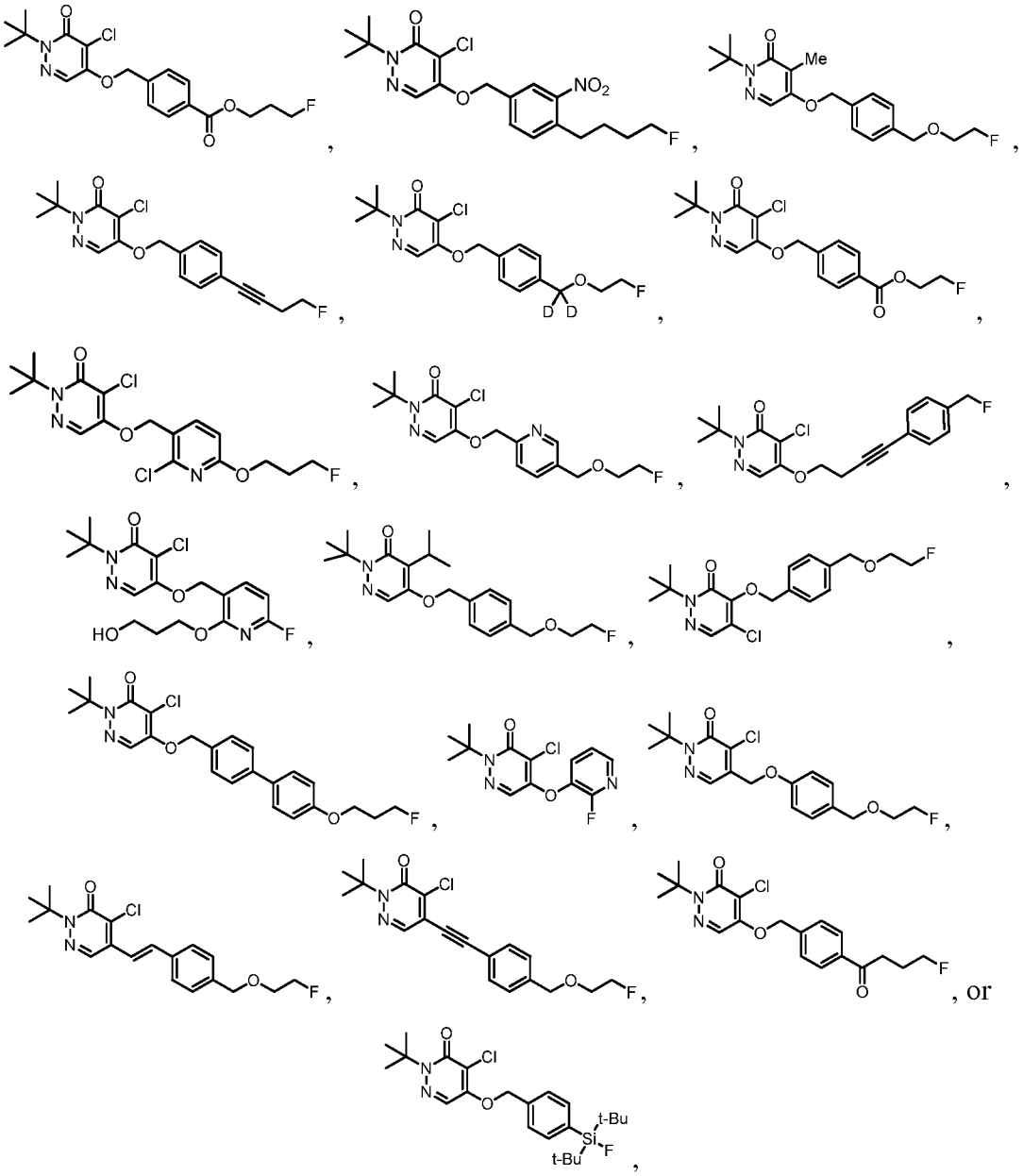
or a pharmaceutically acceptable salt thereof, wherein F is optionally ^{18}F.

In some embodiments, the compound is selected from the group consisting of:



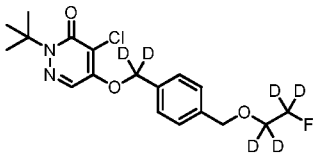
or a pharmaceutically acceptable salt thereof, wherein I_m is an imaging moiety. In some embodiments, the I_m is ^{18}F. In some embodiments, the compound is selected from the group consisting of:



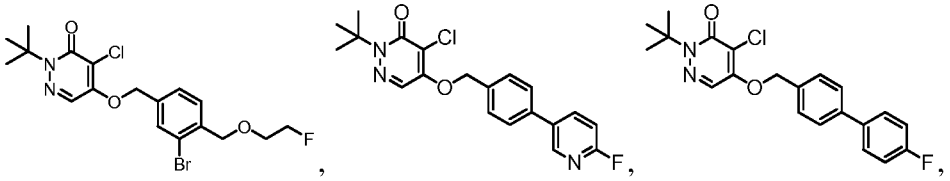


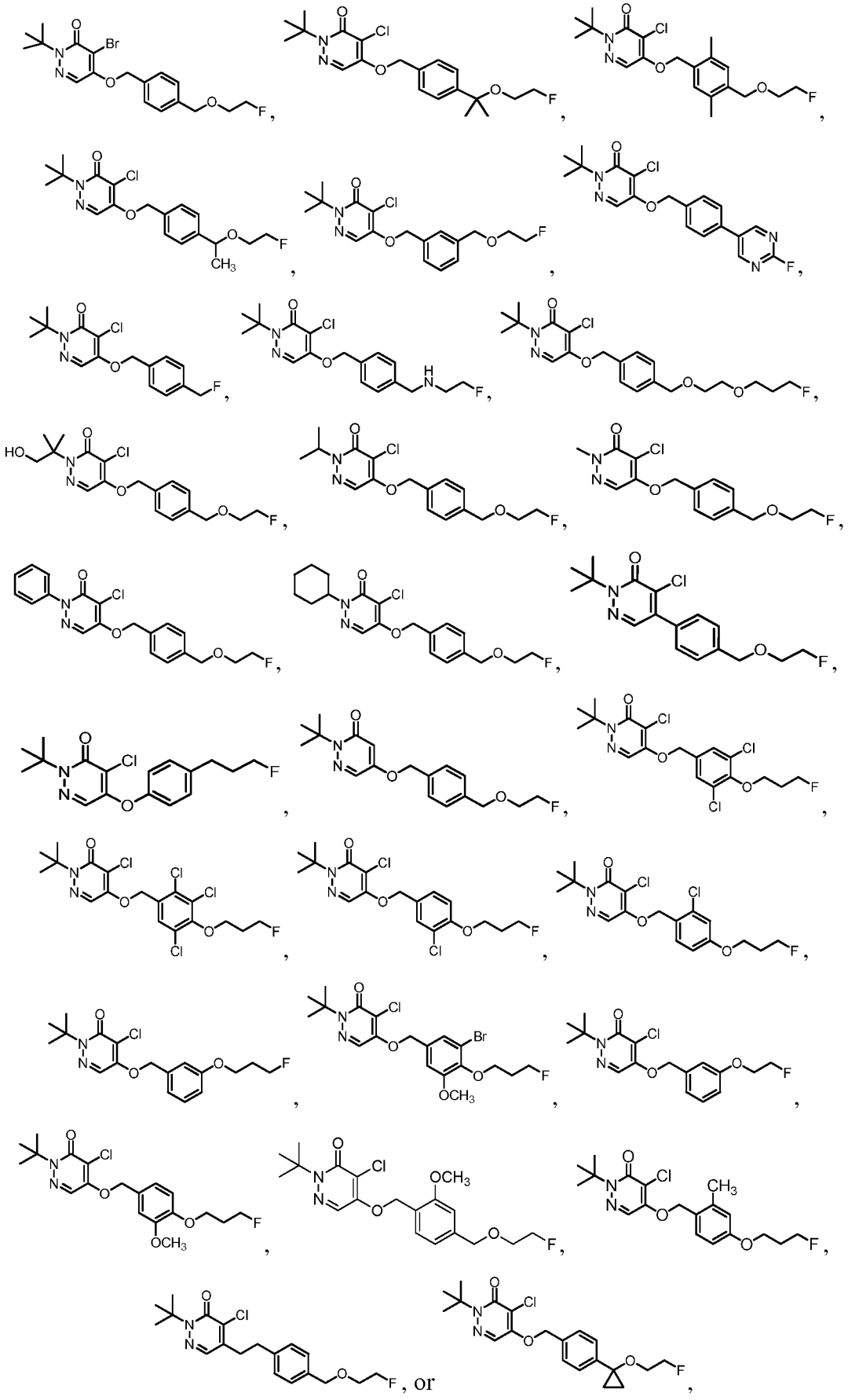
or a pharmaceutically acceptable salt thereof. In some embodiments, each F is ^{18}F.

In some embodiments, the compound is:



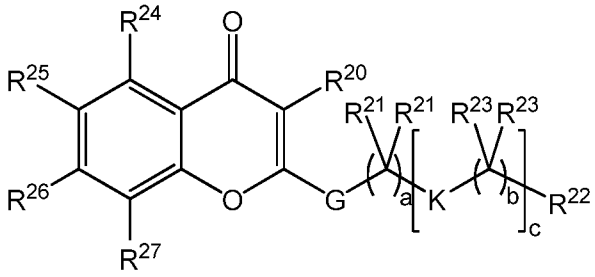
In some embodiments, the compound is selected from the group consisting of:





or a pharmaceutically acceptable salt thereof. In some embodiments, each F is ^{18}F.

In some embodiments, a compound is provided comprising the structure:



(IX)

or a pharmaceutically acceptable salt thereof, wherein:

R^{20} is selected from the group consisting of hydrogen, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, and $–NO_2$;

each R^{21} and R^{23} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally any two R^{21} or any two R^{23} may be joined together to form a ring;

R^{22} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, $–OR^{28}$, $–Si(R^9)_3$, $–B(R^{9'})_3$, and an imaging moiety;

R^{24}, R^{25}, R^{26}, and R^{27} are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–NO_2$, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, and an imaging moiety;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and an imaging moiety;

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety;

R^{28} is selected from the group consisting of hydrogen, alkyl optionally substituted, and heteroalkyl optionally substituted;

G is O, S, or NR^{28};

a is 0, 1, 2, 3, or 4;

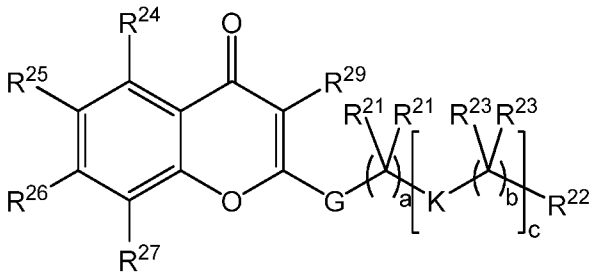
each K is independently arylene, heteroarylene, alkenylene, or alkynylene, each optionally substituted;

each b is independently 0, 1, 2, 3, or 4; and

c is 1 or 2,

provided at least one imaging moiety is present in the compound.

In some embodiments, a compound is provided comprising the structure:



(X)

or a pharmaceutically acceptable salt thereof, wherein:

each R^{21} and R^{23} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally any two R^{21} or any two R^{23} may be joined together to form a ring;

R^{22} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, $-OR^{28}$, $-Si(R^9)_3$, $-B(R^{9'})_3$, and an imaging moiety;

R^{24}, R^{25}, R^{26}, and R^{27} are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –

NO_2, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, and an imaging moiety;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and an imaging moiety;

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety;

R^{28} is selected from the group consisting of hydrogen, alkyl optionally substituted, and heteroalkyl optionally substituted;

R^{29} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, alkoxy optionally substituted , alkoxyalkyl optionally substituted , –CN, $–NO_2$, and an imaging moiety;

G is O, S, or NR^{28};

a is 0, 1, 2, 3, or 4;

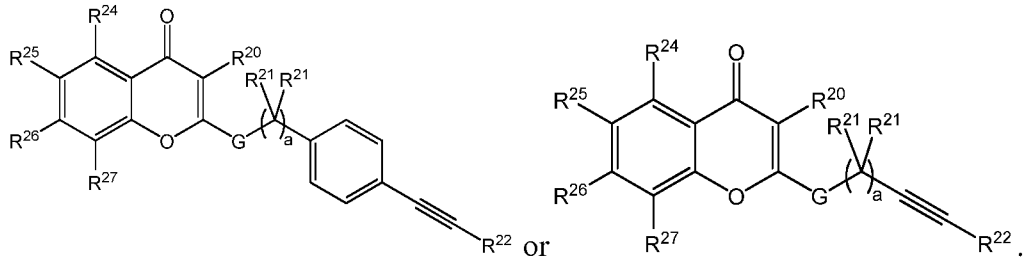
each K is independently arylene, heteroarylene, alkenylene, or alkynylene, each optionally substituted, provided at least one K is alkenylene or alkynylene;

each b is independently 0, 1, 2, 3, or 4; and

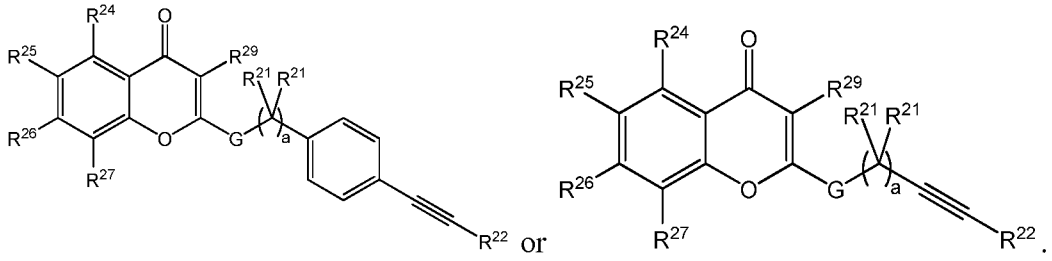
c is 1 or 2,

provided at least one imaging moiety is present in the compound.

In some embodiments, a compound of Formula (IX) comprises the structure:



In some embodiments, a compound of Formula (X) comprises the structure:



The following description of R^{20} groups may be used in connection with a compound of Formula (IX). In some embodiments, R^{20} is selected from the group consisting of hydrogen, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, and $–NO_2$. In some embodiments, R^{20} is hydrogen. In some embodiments, R^{20} is heteroalkyl optionally substituted. In some embodiments, R^{20} is alkoxy optionally substituted. In some embodiments, R^{20} is alkoxyalkyl optionally substituted. In some embodiments, R^{20} is halo. In some embodiments, R^{20} is F. In some embodiments, R^{20} is Cl. In some embodiments, R^{20} is Br. In some embodiments, R^{20} is I. In some embodiments, R^{20} is haloalkyl. In some embodiments, R^{20} is aryl optionally substituted. In some embodiments, R^{20} is unsubstituted aryl. In some embodiments, R^{20} is phenyl optionally substituted. In some embodiments, R^{20} is unsubstituted phenyl. In some embodiments, R^{20} is cycloalkyl optionally substituted. For a compound of Formula (IX), each of the R^{20} groups described herein may be combined with any R^7, R^8, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, G, a, K, b, and c, or combinations thereof, as described herein.

The following description of R^{29} groups may be used in connection with a compound of Formula (X). In some embodiments, R^{29} is selected from the group consisting of R^{29} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and an imaging moiety. In some embodiments, R^{29} is hydrogen. In some embodiments, R^{29} is alkyl optionally substituted. In some embodiments, R^{29} is

unsubstituted alkyl. In some embodiments, R^{29} is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, or t-butyl. In some embodiments, R^{29} is methyl. In some embodiments, R^{29} is heteroalkyl optionally substituted. In some embodiments, R^{29} is alkoxy optionally substituted. In some embodiments, R^{29} is alkoxyalkyl optionally substituted. In some embodiments, R^{29} is halo. In some embodiments, R^{29} is F. In some embodiments, R^{29} is Cl. In some embodiments, R^{29} is Br. In some embodiments, R^{29} is I. In some embodiments, R^{29} is haloalkyl. In some embodiments, R^{29} is aryl optionally substituted. In some embodiments, R^{29} is unsubstituted aryl. In some embodiments, R^{29} is phenyl optionally substituted. In some embodiments, R^{29} is unsubstituted phenyl. In some embodiments, R^{29} is cycloalkyl optionally substituted. In some embodiments, R^{29} is –CN. In some embodiments, R^{29} is $-NO_2$. In some embodiments, R^{29} is an imaging moiety For a compound of Formula (X), each of the R^{29} groups described herein may be combined with any R^7, R^8, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, G, a, K, b, and c, or combinations thereof, as described herein.

The following description of R^{21} and R^{23} groups may be used in connection with a compound of Formula (IX) or (X). In some embodiments, R^{21} and R^{23} are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally any two R^{21} or any two R^{23} may be joined together to form a ring. In some embodiments, any two of R^{21} and R^{23} may be joined together to form a ring. In some cases, the ring formed may comprise a total of 4, 5, 6, 7, 8, or more, atoms. In some cases, the ring comprises 5 or 6 atoms. In some embodiments, each of R^{21} and R^{23} is H. In some embodiments, at least one R^{21} and R^{23} is ^2H. In some embodiments, each of R^{21} and R^{23} is ^2H. In some embodiments, each of R^{21} and R^{23} is H or alkyl optionally substituted. In some embodiments, each of R^{21} and R^{23} is H or unsubstituted alkyl. In some embodiments, at least one R^{21} and R^{23} is not H. In some embodiments, at least one R^{21} or R^{23} is an imaging moiety. For a compound of Formula (IX), each of the R^{21} and/or R^{23} groups described herein may be combined with any R^7, R^8, R^{20}, R^{22}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, G, a, K, b, and c, or combinations thereof, as described herein. For a compound of Formula (X), each of the R^{21} and/or R^{23} groups described herein may be combined with any R^7, R^8, R^{22}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, G, a, K, b, and c, or combinations thereof, as described herein.

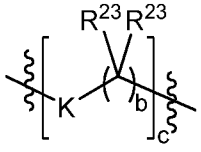
The following description of R^{24}, R^{25}, R^{26}, and R^{27} groups may be used in connection with a compound of Formula (IX) or (X). In some embodiments, R^{24}, R^{25}, R^{26}, and R^{27} are each independently selected from the group consisting of hydrogen, alkyl optionally

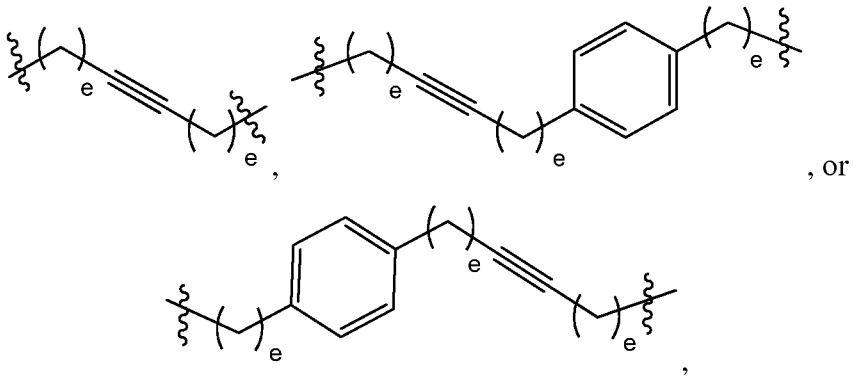
substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, and an imaging moiety. In some embodiments, each of R^{24}, R^{25}, R^{26}, and R^{27} are H. In some embodiments, at least one R^{24}, R^{25}, R^{26}, and R^{27} is not H. In some embodiments, each of R^{24}, R^{25}, R^{26}, and R^{27} is H or alkyl optionally substituted. In some embodiments, each of R^{24}, R^{25}, R^{26}, and R^{27} is H or unsubstituted alkyl. For a compound of Formula (IX), each of the R^{24}, R^{25}, R^{26}, and R^{27} groups described herein may be combined with any R^7, R^8, R^{20}, R^{21}, R^{22}, R^{23}, R^{28}, G, a, K, b, and c, or combinations thereof, as described herein. For a compound of Formula (X), each of the R^{24}, R^{25}, R^{26}, and R^{27} groups described herein may be combined with any R^7, R^8, R^{21}, R^{22}, R^{23}, R^{28}, R^{29}, G, a, K, b, and c, or combinations thereof, as described herein.

The following description of G groups may be used in connection with a compound of Formula (IX) or (X). In some embodiments, G is O, S, or NR^{28}. In some embodiments, G is O. In some embodiments, G is S. In some embodiments, G is NR^{28}, wherein R^{28} is selected from the group consisting of hydrogen, alkyl optionally substituted, and heteroalkyl optionally substituted. In some embodiments, G is NH. In some embodiments, G is NR^{28}, wherein R^{28} is H or alkyl optionally substituted. In some embodiments, G is NR^{28}, wherein R^{28} is alkyl optionally substituted. In some embodiments, G is NR^{28}, wherein R^{28} is unsubstituted alkyl. For a compound of Formula (IX), each of the G groups described herein may be combined with any R^7, R^8, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, a, K, b, and c, or combinations thereof, as described herein. For a compound of Formula (X), each of the G groups described herein may be combined with any R^7, R^8, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, a, K, b, and c, or combinations thereof, as described herein.

The following description of a, b, and c variables may be used in connection with a compound of Formula (IX) or (X). In some embodiments, a is 0. In some embodiments, wherein a is 1. In some embodiments, a is 2. In some embodiments, a is 3. In some embodiments, a is 4. In some embodiments, b is 0. In some embodiments, wherein b is 1. In some embodiments, b is 2. In some embodiments, b is 3. In some embodiments, b is 4. In some embodiments, c is 1. In some embodiments, c is 2. In some embodiments, a is 1, b is 1, and c is 1. In some embodiments, a is 2, b is 2, and c is 1. In some embodiments, a is 2, b is 2, and c is 2. For a compound of Formula (IX), each of the a, b, and c variables described herein may be combined with any R^7, R^8, R^{20}, R^{21}, R^{22}, R^{23}, R^{24},

R^{25}, R^{26}, R^{27}, R^{28}, G, and K, or combinations thereof, as described herein. For a compound of Formula (X), each of the a, b, and c variables described herein may be combined with any R^7, R^8, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, G, and K, or combinations thereof, as described herein.

The following description of groups may be used in connection with a compound of Formula (IX) or (X). In some embodiments, at least one K is alkynylene. In some embodiments, at least one K is alkenylene. In some embodiments,  has the structure:



, or

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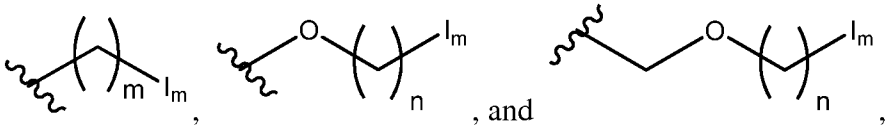
wherein each e is independently 1, 2, 3, or 4. In some embodiments, each e is 1. For a compound of Formula (IX), each of the above groups may be combined with any R^7, R^8, R^{20}, R^{21}, R^{22}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, G, and a, or combinations thereof, as described herein. For a compound of Formula (X), each of the above groups may be combined with any R^7, R^8, R^{21}, R^{22}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, G, and a, or combinations thereof, as described herein.

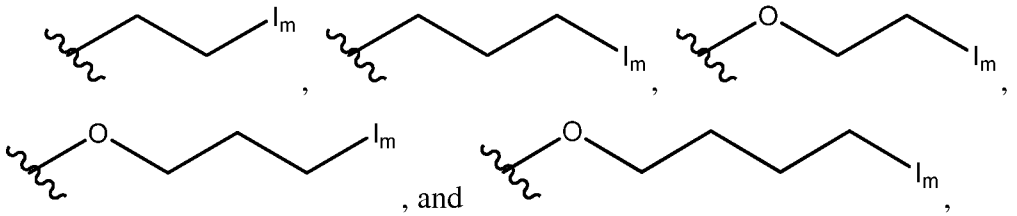
The following description of R^{22} groups may be used in connection with a compound of Formula (IX) or (X). In some embodiments, R^{22} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, $-OR^{28}$, and an imaging moiety. In some embodiments, R^{22} is $-Si(R^9)_3$ or $-B(R^{9'})_3$. In some embodiments, R^{22} is hydrogen. In some embodiments, R^{22} is alkyl optionally substituted. In some embodiments, R^{22} is unsubstituted alkyl. In some embodiments, R^{22} is heteroalkyl optionally substituted. In some embodiments, R^{22} is unsubstituted heteroalkyl. In some embodiments, R^{22} is alkoxyalkyl optionally substituted. In some embodiments, R^{22} is unsubstituted alkoxyalkyl. In some embodiments, R^{22} is halo. In some embodiments, R^{22} is F. In some embodiments, R^{22} is Cl. In some embodiments, R^{22} is Br. In some embodiments, R^{22} is I. In some embodiments, R^{22}

is haloalkyl. In some embodiments, R^{22} is $-OR^{28}$, wherein R^{28} is selected from the group consisting of hydrogen, alkyl optionally substituted, and heteroalkyl optionally substituted. In some embodiments, R^{22} is OH. In some embodiments, R^{22} is OR^{28}, wherein R^{28} is H or alkyl optionally substituted. In some embodiments, R^{22} is OR^{28}, wherein R^{28} is alkyl optionally substituted. In some embodiments, R^{22} is OR^{28}, wherein R^{28} is unsubstituted alkyl. In some embodiments, R^{22} is an imaging moiety. In some embodiments, R^{22} is substituted with an imaging moiety. In some embodiments, R^{22} is alkyl optionally substituted, alkoxy optionally substituted, or alkoxyalkyl optionally substituted, each substituted with an imaging moiety. In some embodiments, R^{22} is $-(CH_2)_jI_m$; wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6. In some cases, R^{22} is $-(CH_2)I_m$, $-(CH_2)_2I_m$, $-(CH_2)_3I_m$, $-(CH_2)_4I_m$, $-(CH_2)_5I_m$, $-(CH_2)_6I_m$, $-(CH_2)_7I_m$, $-(CH_2)_8I_m$, $-(CH_2)_9I_m$, or $-(CH_2)_{10}I_m$. In some cases, R^{22} is $-(CH_2)^{18}F$, $-(CH_2)_2{}^{18}F$, $-(CH_2)_3{}^{18}F$, $-(CH_2)_4{}^{18}F$, $-(CH_2)_5{}^{18}F$, $-(CH_2)_6{}^{18}F$, $-(CH_2)_7{}^{18}F$, $-(CH_2)_8{}^{18}F$, $-(CH_2)_9{}^{18}F$, or $-(CH_2)_{10}{}^{18}F$. In some embodiments, R^{22} is $-O(CH_2)_jI_m$; wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6. In some cases, R^{22} is $-O(CH_2)I_m$, $-O(CH_2)_2I_m$, $-O(CH_2)_3I_m$, $-O(CH_2)_4I_m$, $-O(CH_2)_5I_m$, $-O(CH_2)_6I_m$, $-O(CH_2)_7I_m$, $-O(CH_2)_8I_m$, $-O(CH_2)_9I_m$, or $-O(CH_2)_{10}I_m$. In some cases, R^{22} is $-O(CH_2)^{18}F$, $-O(CH_2)_2{}^{18}F$, $-O(CH_2)_3{}^{18}F$, $-O(CH_2)_4{}^{18}F$, $-O(CH_2)_5{}^{18}F$, $-O(CH_2)_6{}^{18}F$, $-O(CH_2)_7{}^{18}F$, $-O(CH_2)_8{}^{18}F$, $-O(CH_2)_9{}^{18}F$, or $-O(CH_2)_{10}{}^{18}F$. In some embodiments, R^{22} is $-(CH_2)_jO(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6. In some embodiments, R^{22} is $-(CH_2)O(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6. In some cases, R^{22} is $-CH_2O(CH_2)I_m$, $-CH_2O(CH_2)_2I_m$, $-CH_2O(CH_2)_3I_m$, $-CH_2O(CH_2)_4I_m$, $-CH_2O(CH_2)_5I_m$, $-CH_2O(CH_2)_6I_m$, $-CH_2O(CH_2)_7I_m$, $-CH_2O(CH_2)_8I_m$, $-CH_2O(CH_2)_9I_m$, or $-CH_2O(CH_2)_{10}I_m$. In some cases, R^{22} is $-CH_2O(CH_2)\,{}^{18}F$, $-CH_2O(CH_2)_2{}^{18}F$, $-CH_2O(CH_2)_3{}^{18}F$, $-CH_2O(CH_2)_4{}^{18}F$, $-CH_2O(CH_2)_5{}^{18}F$, $-CH_2O(CH_2)_6{}^{18}F$, $-CH_2O(CH_2)_7{}^{18}F$, $-CH_2O(CH_2)_8{}^{18}F$, $-CH_2O(CH_2)_9{}^{18}F$, or $-CH_2O(CH_2)_{10}{}^{18}F$. In some embodiments, R^{22} is $-C\equiv C-(CH_2)jI_m$; wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6. In some embodiments, R^{22} is $-[(CH_2)_jO]_j(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6. In some embodiments, R^{22} is $-O[(CH_2)_jO]_j(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6. In some embodiments, R^{22} is optionally substituted alkyl substituted with an imaging moiety. In some embodiments, R^{22} is $-C(=O)O(CH_2)_jI_m$; wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6. In some embodiments, R^{22} is $-C(=O)(CH_2)_jI_m$; wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6. In some embodiments, R^{22} is $-(CH_2)_jNH(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6.

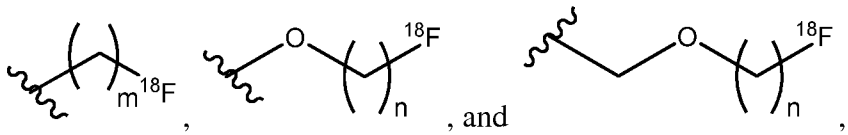
In some embodiments, R^{22} is $Si(R^9)_2I_m$, wherein each R^9 is alkyl optionally substituted and wherein I_m is an imaging moiety. In some embodiments, R^{22} is $B(R^{9'})_2I_m$, wherein each $R^{9'}$ is alkyl optionally substituted and wherein I_m is an imaging moiety. In some embodiments, R^{22} is selected from the group consisting of $–C\equiv C–CH_2CH_2CH_2I_m$, $–C\equiv C–CH_2CH_2I_m$, $–C\equiv C–CH_2I_m$, $–CH_2I_m$, $–(CH_2)_2I_m$, $–(CH_2)_3I_m$, $–(CH_2)_4I_m$, $–(CH_2)_5I_m$, $–(CH_2)_6I_m$, $–OCH_2I_m$, $–O(CH_2)_2I_m$, $–O(CH_2)_3I_m$, $–O(CH_2)_4I_m$, $–O(CH_2)_5I_m$, $–O(CH_2)_6I_m$, $–CH_2O(CH_2)_2I_m$, $–CH(CH_3)O(CH_2)_2I_m$, $–CH_2O(CH_2)_3I_m$, $–CD_2O(CH_2)_2I_m$, $–(CH_2)_2O(CH_2)_2I_m$, $–CHBrC(CH_3)_2I_m$, $–CHClC(CH_3)_2I_m$, $–CHFC(CH_3)_2I_m$, $–C(=O)OCH_2I_m$, $–C(=O)O(CH_2)_2I_m$, $–C(=O)O(CH_2)_3I_m$, $–CH_2NH(CH_2)_2I_m$, $–CH_2NHCH_2I_m$, $–CH_2O(CH_2)_2O(CH_2)_2I_m$, $–CH_2O(CH_2)_2O(CH_2)_3I_m$, $–O(CH_2)_2O(CH_2)_2I_m$, $–C(=O)(CH_2)_2I_m$, and $–C(=O)(CH_2)_3I_m$. In some embodiments, wherein I_m is ^{18}F. In some embodiments, R^{22} is selected from the group consisting of:



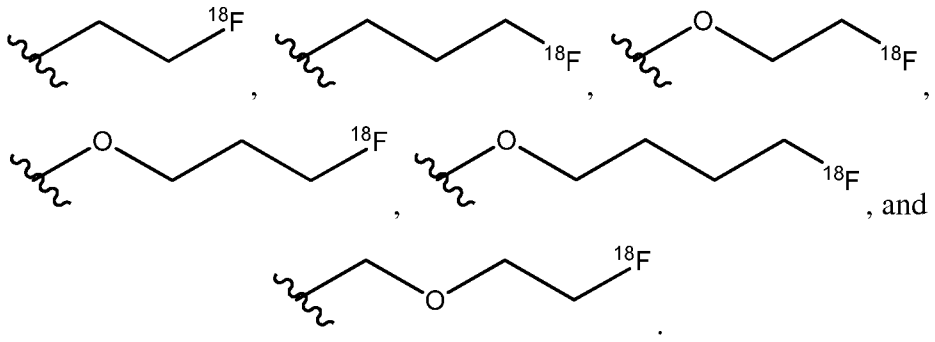
wherein m and n is an integer between 1 and 6, inclusive, and I_m is an imaging moiety. In some embodiments, R^{22} is selected from the group consisting of:



wherein I_m is an imaging moiety. In some embodiments, R^{22} is selected from the group consisting of:



wherein m and n is an integer between 1 and 6, inclusive. In some embodiments, R^{22} is selected from the group consisting of:



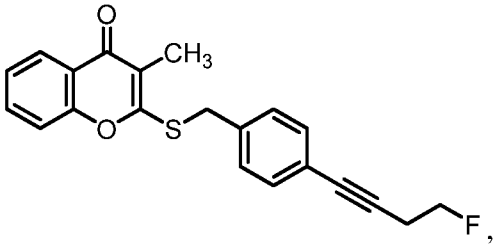
For a compound of Formula (IX), each of the R^{22} groups described herein may be combined with any R^7, R^8, R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, G, a, K, b, and c, or combinations thereof, as described herein. For a compound of Formula (X), each of the R^{22} groups described herein may be combined with any R^7, R^8, R^{21}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, G, a, K, b, and c, or combinations thereof, as described herein.

In some embodiments, for a compound of Formula (IX), the at least one imaging moiety is present in R^7, R^8, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, or R^{28}. In some embodiments, a compound of Formula (X) or (IX) comprises a single imaging moiety. In some embodiments, for a compound of Formula (X), the at least one imaging moiety is present in R^7, R^8, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, or R^{29}. In some embodiments, for a compound of Formula (X) or (IX), the at least one imaging moiety is present in R^{22}. As noted above, as will be understood by those of ordinary skill in the art, when referring to an imaging moiety, the imaging moiety "is present" in a group in embodiments wherein 1) the imaging moiety is the group (*e.g.*, R^{22} is an imaging moiety) or b) the group comprises the imaging moiety (*e.g.,* R^{22} is substituted with an imaging moiety). In some embodiments, for a compound of Formula (IX), R^7, R^8, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, or R^{28} comprises the at least one imaging moiety. In some embodiments, for a compound of Formula (X), R^7, R^8, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, or R^{29} comprises the at least one imaging moiety. In some embodiments, for a compound of Formula (IX), R^7, R^8, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, is the at least one imaging moiety. In some embodiments, for a compound of Formula (X) R^7, R^8, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, or R^{29} is the at least one imaging moiety. For a compound of Formula (IX), each of the above placements of the imaging moieties may be combined with any R^7, R^8, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, G, a, K, b, and c, or combinations thereof, as described herein. For a compound of Formula (X), each of the above placements of the imaging moieties may be combined with any R^7, R^8, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, G, a, K, b, and c, or combinations thereof, as described herein.

The following description of the imaging moiety may be used in connection with a

compound of Formula (IX) and (X). In some embodiments, the at least one imaging moiety is selected from the group consisting of ^{11}C, ^{13}N, ^{18}F, ^{76}Br, ^{89}Zr, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{99m}Tc, ^{95}Tc, ^{111}In, ^{62}Cu, ^{64}Cu, ^{67}Ga, and ^{68}Ga. In some embodiments, the at least one imaging moiety is ^{18}F. Imaging moieties are described in more detail herein.

In some embodiments, a compound of Formula (IX) is selected from the group consisting of: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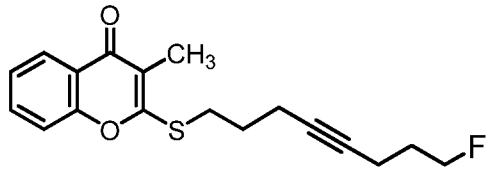
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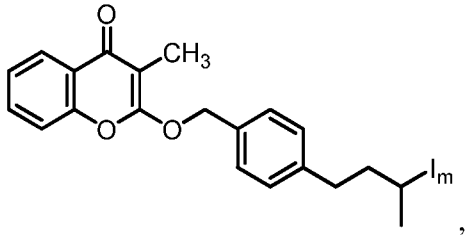
or a pharmaceutically acceptable salt thereof, wherein F is optionally ^{18}F.

In some embodiments, a compound is selected from the group consisting of: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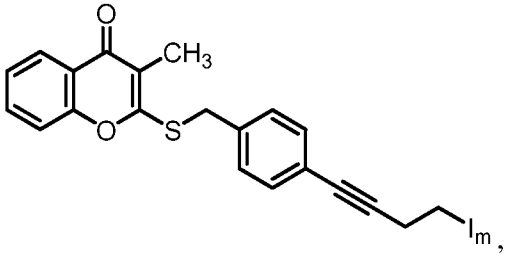
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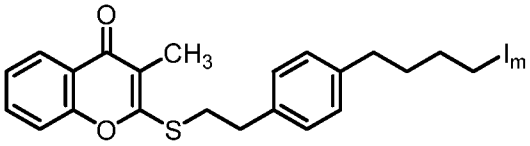
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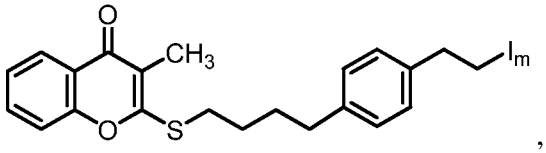
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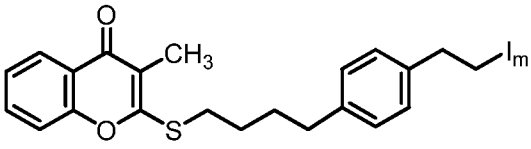
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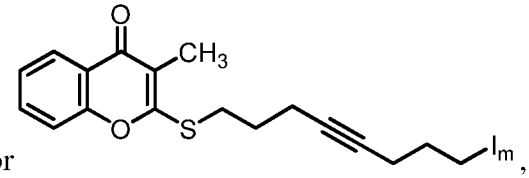
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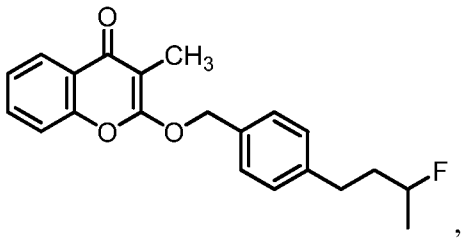
or a pharmaceutically acceptable salt thereof, wherein I_m is an imaging moiety. In some embodiments, I_m is ^{18}F. In some embodiments, a compound is selected from the group consisting of: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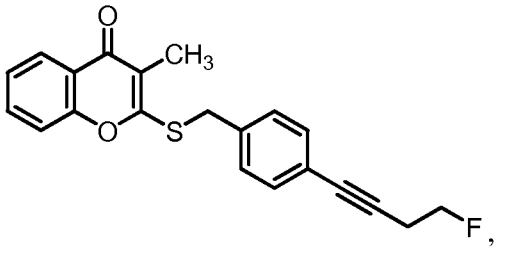
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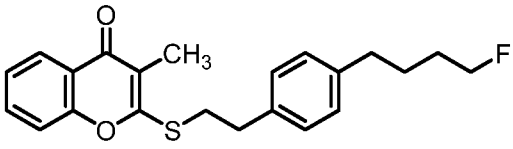
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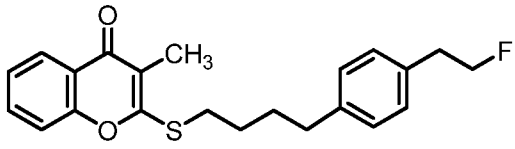
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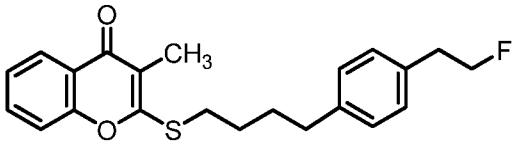
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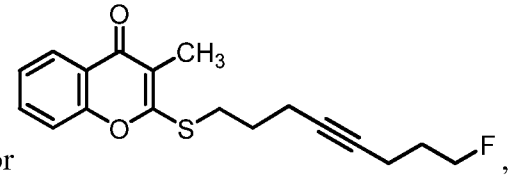
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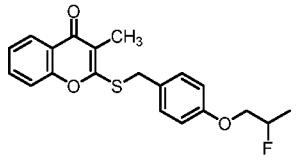
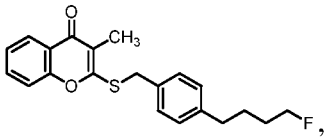
or a pharmaceutically acceptable salt thereof. In some embodiments, each F is ^{18}F. In some embodiments, a compound is:



or a pharmaceutically acceptable salt thereof. In some embodiments, each F is ^{18}F.

In some embodiments, a compound is selected from the group consisting of: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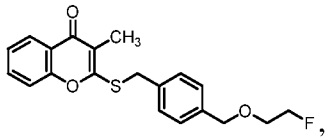
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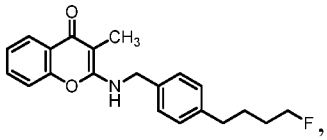
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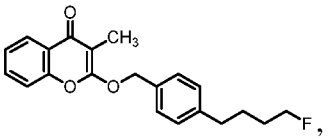
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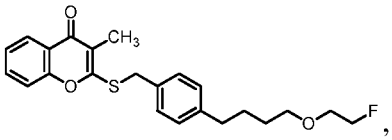
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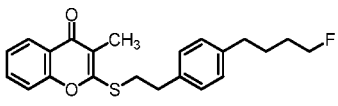
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or a pharmaceutically acceptable salt thereof. In some embodiments, each F is ^{18}F.

It should be understood, that any hydrogen molecule of a structure described herein may, in some embodiments, may be optionally substituted and/or enriched in ^{2}H. In some cases, at least one ^{2}H has been substituted for a ^{1}H.

As used herein, the term "imaging agent" refers to any chemical compound that includes an imaging moiety. Typically, the imaging agent may be administered to a subject in order to provide information relating to at least a portion of the subject (*e.g.*, human). In some cases, an imaging agent may be used to highlight a specific area of a subject, rendering organs, blood vessels, tissues, and/or other portions more detectable and/or more clearly imaged. By increasing the detectability and/or image quality of the object being studied, the presence and extent of disease and/or injury can be determined. An "imaging moiety" refers to an atom or group of atoms that is capable of producing a detectable signal itself (*e.g.*, radioisotopes), or upon exposure to an external source of energy (*e.g.*, electromagnetic radiation, ultrasound, and the like). In certain cases, the imaging moiety may alter its local

chemical and/or magnetic and/or electronic environment. Non-limiting examples of imaging moieties include ^{11}C, ^{13}N, ^{18}F, ^{76}Br, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{99m}Tc, ^{95}Tc, ^{111}In, ^{62}Cu, ^{64}Cu, ^{67}Ga, ^{68}Ga, and ^{89}Zr. In some embodiments, the imaging moiety is associated with a group comprising the structure $-B(R^{9'})_2I_m$ or $-Si(R^9)_2I_m$, wherein I_m is an imaging moiety, optionally ^{18}F. In some embodiments, the imaging moiety is directly associated (*i.e.*, through a covalent bond) with a compound as described herein (*e.g.*, in the case of ^{18}F, ^{76}Br, ^{124}I, or ^{131}I). In some embodiments, the imaging moiety is associated with the compound through non-covalent interactions (*e.g.*, electrostatic interactions). In some embodiments, the imaging moiety is associated with the compound through a chelator (*e.g.*, in the case of ^{64}Cu, ^{89}Zr, ^{99m}Tc, and ^{111}In). Chelators are described in more detail herein. In some embodiments, the imaging moiety is selected from the group consisting of ^{18}F, ^{76}Br, ^{124}I, ^{131}I, ^{64}Cu, ^{89}Zr, ^{99m}Tc, and ^{111}In. In certain embodiments, the imaging moiety is ^{18}F. In certain embodiments, the imaging moiety is ^{76}Br. In certain embodiments, the imaging moiety is ^{124}I. In certain embodiments, the imaging moiety is ^{131}I. In some cases, the imaging moiety is ^{18}F, ^{76}Br, or ^{124}I. In some cases, the imaging moiety is ^{18}F or ^{76}Br. In some cases, an imaging agent comprises a single imaging moiety. In some cases, an imaging agent comprises more than one imaging moiety (*e.g.*, two imaging moieties). As used herein, the term "imaging agent" encompasses contrast agents. In some embodiments, an imaging agent is a contrast agent. The term "contrast agent" refers to a type of imaging agent comprising an imaging moiety that produces a detectable signal in response to an external source of energy. In certain cases, the contrast agent may comprise an imaging moiety that absorbs and/or reflects and/or transmits the external source of energy.

In some embodiments, a composition comprising a compound of the invention or a plurality of compounds is enriched with compounds including an isotope such as a radioisotope. In such a case, the plurality or composition may be referred to as being "isotopically enriched." An "isotopically enriched" composition refers to a composition comprising a percentage of one or more isotopes of an element that is greater than the percentage of that isotope that occurs naturally. For example, a composition that is isotopically enriched with a fluoride species may be "isotopically enriched" with fluorine-18 (^{18}F). Thus, with regard to a plurality of compounds, when a particular atomic position is designated as ^{18}F, it is to be understood that the abundance (or frequency) of ^{18}F at that position (in the plurality) is greater than the natural abundance (or frequency) of ^{18}F, which is essentially zero.

In some embodiments, an atom designated as being enriched may have a minimum isotopic enrichment factor of about 0.001% (*i.e.*, about 1 out of 10^5 atoms is the desired isotope of the atom), about 0.002%, about 0.003%, about 0.004%, about 0.005%, about 0.006%, about 0.007%, about 0.008%, about 0.009%, about 0.01%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.75%, about 1%, about 2%, about 3%, about 4%, about 5%, about 10%, about 15%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, or greater. The minimum isotopic enrichment factor, in some instances, may range from about 0.001% to about 1%. For example, in embodiments wherein the imaging moiety is fluorine, a fluorine designated as ^{18}F may have a minimum isotopic enrichment factor of about 0.001% (*i.e.*, about 1 out of 10^5 fluorine species is ^{18}F), about 0.002%, about 0.003%, about 0.004%, about 0.005%, about 0.006%, about 0.007%, about 0.008%, about 0.009%, about 0.01%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.75%, about 1%, about 2%, about 3%, about 4%, about 5%, about 10%, about 15%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, or greater. The isotopic enrichment of a composition or plurality of compounds provided herein can be determined using conventional analytical methods known to one of ordinary skill in the art, including, for example, mass spectrometry and HPLC.

In some embodiments, compositions, methods, uses, and/or systems described herein include or use compounds described herein. In some embodiments, the compounds are imaging agents. In some embodiments, the compounds are contrast agents. In some embodiments, the compounds are precursor to imaging agents or contrast agents.

Chelators

In some cases, an imaging moiety may be associated with a compound as described herein via association with a chelator (*e.g.*, in embodiments where the imaging moiety is ^{64}Cu, ^{68}Ga, ^{89}Zr, ^{99m}Tc, ^{111}In). The chelator is typically covalently attached to the compound. However, in certain embodiments, the chelator may be associated with the compound through non-covalent interactions. The term chelator is given its ordinary meaning in the art and generally refers to a chemical moiety capable of complexing an imaging moiety (*e.g.*, a metal ion and/or radionuclide), wherein the complex is stable under physiological conditions. For example, generally, the imaging moiety remains complexed with the chelator *in vivo*. In some embodiments, the chelator is the moiety or group on a compound that binds to an imaging moiety through one or more donor atoms and/or groups. The chelator may be any

chelator known in the art for complexing a medically useful metal ion or radionuclide. In some embodiments, the chelator comprises one, two, three, four, five, six, seven, eight, nine, or ten donor atoms and/or groups. In embodiments where the chelator comprises more than one donor atom and/or group, the donor atoms/groups may be the same or different. The chelator may be monodentate, bidentate, tridentate, tetradentate, pentadentate, or more. Non-limiting examples of donor atoms/groups include –OH, $–O^-$, –COOR', $–COO^-$, $–N(R')_2$, $=N^-$, –SR', $–S^-$, $–OPO_3^-$, or $–OPO_3R'$, wherein each R' can be the same or different and is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkylaryl, alkylcarbonyl, aryl, arylalkyl, alkylarylalkyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, heteroalkyl, heterocyclyl, heterocyclylalkyl, each optionally substituted. In some cases, the chelator may be a macrocycle. Non-limiting examples of chelators are described in International PCT Publication No. WO2011/005322 and U.S. Patent No. 6,511,648, each of which is incorporated herein by reference for all purposes. In some embodiments, the chelator comprises diaminodithiol, mercaptoacetyltriglycine, monoaminomonoamide, picolylamine monoacetic acid, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, bis(thiosemicarbazone), propyleneamine oxime, ethylenediaminetetraacetic acid, or diethylenetriaminepentaacetic acid. In some embodiments, the chelator comprises a metal atom (*e.g.*, Al), wherein an imaging moiety (*e.g.*, ^{18}F) associates with the metal atom.

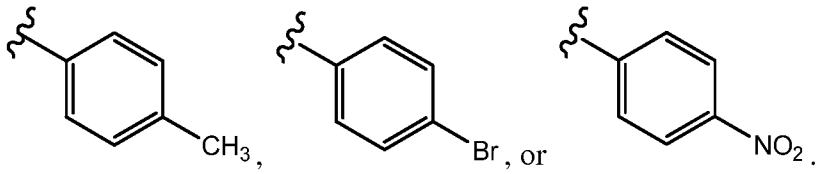
In some cases, an imaging moiety associated with a chelator may be further associated with one or more ancillary or co-ligands. "Ancillary" or "co-ligands" may be ligands which serve to complete the coordination sphere of the imaging moiety together with the chelator. In some embodiments, the imaging moiety coordination sphere may comprise one or more bonding atoms and/or groups from the chelators and optionally, one or more ancillary and/or co-ligands. Ancillary or co-ligands useful in the preparation of radiopharmaceuticals and in diagnostic kits useful for the preparation of said radiopharmaceuticals may be comprised of one or more oxygen, nitrogen, carbon, sulfur, phosphorus, arsenic, selenium, and tellurium donor atoms. Conditions for effecting association of an imaging moiety with a chelator will depend on the type of chelator being used and are well known in the art.

Imaging Agent Precursors

In another aspect of the invention, imaging agent precursors useful in the preparation of imaging agents as described herein are provided. In certain embodiments, an imaging agent precursor comprises a leaving group (*e.g.*, a sulfonate, halide) that can be replaced with a nucleophile in a substitution reaction to form an imaging agent. The imaging agent

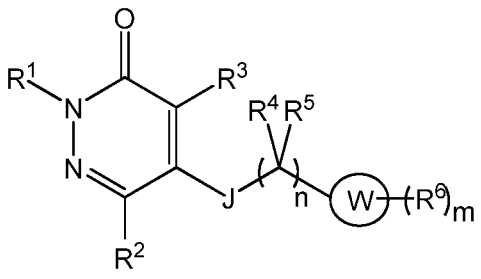
precursor may also include functional groups that are optionally protected. In some embodiments, an imaging agent precursor has a substantially similar structure as an imaging agent described above (*e.g.*, a compound comprising at least one imaging moiety), except that the imaging moiety or the substituent which includes the imaging moiety instead includes a leaving group. In certain embodiments, an imaging agent precursor has a substantially similar structure as an imaging agent described above, except that the chelator group is not yet associated with an imaging moiety.

As used herein, the term "leaving group" is given its ordinary meaning in the art of synthetic organic chemistry and refers to an atom or a group capable of being displaced by a nucleophile. Examples of suitable leaving groups include, but are not limited to, halides (such as chloride, bromide, or iodide), alkoxycarbonyloxy, aryloxycarbonyloxy, alkanesulfonyloxy, arenesulfonyloxy, alkyl-carbonyloxy (*e.g.*, acetoxy), arylcarbonyloxy, aryloxy, methoxy, N,O-dimethylhydroxylamino, pixyl, haloformates, $-NO_2$, trialkylammonium, and aryliodonium salts. In some embodiments, the leaving group is a sulfonic acid ester. In some embodiments, the sulfonic acid ester comprises the formula $-OSO_2R'$ wherein R' is selected from the group consisting alkyl optionally, alkenyl optionally substituted, heteroalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, arylalkyl optionally substituted, and heterarylalkyl optionally substituted. In some embodiments, R' is substituted or unsubstituted C_1-C_6 alkyl. In some embodiments, R' is methyl. In some embodiments, R' is $-CF_3$. In some embodiments, R' is substituted or unsubstituted aryl. In some embodiments, R' is substituted or unsubstituted phenyl. In some embodiments R' is:



In some cases, the leaving group is toluenesulfonate (tosylate, Ts), methanesulfonate (mesylate, Ms), *p*-bromobenzenesulfonyl (brosylate, Bs), or trifluoromethanesulfonate (triflate, Tf). In some cases, the leaving group is a brosylate (*p*-bromobenzenesulfonyl). In some cases, the leaving group is a nosylate (2-nitrobenzenesulfonyl). In some embodiments, the leaving group is a sulfonate-containing group. In some embodiments, the leaving group is a tosylate group. The leaving group may also be a phosphineoxide (*e.g.*, formed during a Mitsunobu reaction) or an internal leaving group such as an epoxide or cyclic sulfate.

In some embodiments, a compound is provided comprising the structure:



(XI)

or a salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and a leaving group;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, -NO_2, and a leaving group;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, –NO_2, and a leaving group;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and a leaving group, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

W is heteroaryl, naphthyl, heterocyclyl, or aryl;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–N(R^7)_2$, $–NO_2$, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, $–Si(R^9)_3$, $–B(R^{9'})_3$, $–OR^8$, and a leaving group;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl

optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

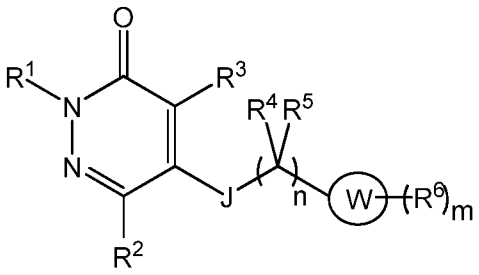
each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and a leaving group; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and leaving group,

provided that at least one leaving group is present in the compound; and

provided that when W is aryl, a) R^3 is not halo, alkyl or haloalkyl, or b) at least one R^6 is selected from the group consisting of alkynyl optionally substituted, alkenyl optionally substituted, alkyl substituted with –CN, alkyl substituted with $–C(=O)OR^8$, alkyl substituted with $–C(=O)R^8$, alkyl substituted with $–N(R^7)_2$, –CN, $–NO_2$, $–N(R^7)_2$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)R^8$, $–C(=O)N(R^7)_2$, and $–N(R^7)C(=O)R^8$.

In some embodiments, a compound is provided comprising the structure:



(XII)

or a salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and a leaving group;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–NO_2$, and a leaving group;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally

substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and a leaving group;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and a leaving group, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

W is heteroaryl, naphthyl, or heterocyclyl;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–N(R^7)_2$, $–NO_2$, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, $–Si(R^9)_3$, $–B(R^{9'})_3$, $–OR^8$, and a leaving group;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring;

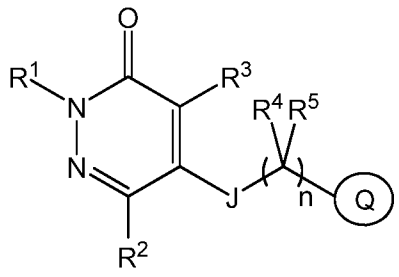
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and a leaving group; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group,

provided that at least one leaving group is present in the compound.

In some embodiments, a compound is provided comprising the structure:



(XIII)

or a salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and a leaving group;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and a leaving group;

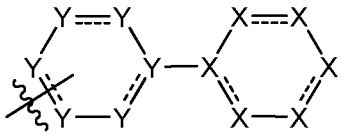
R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and a leaving group;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and a leaving group, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

Q has the structure:



each Y and each X is independently selected from the group consisting of C, $C(R^6)$, $C(R^6)_2$, N, NR^7, O, and S, provided at least one Y is not C or $C(R^6)$;

each ------ is independently a single or double bond.

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally

substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and a leaving group;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring;

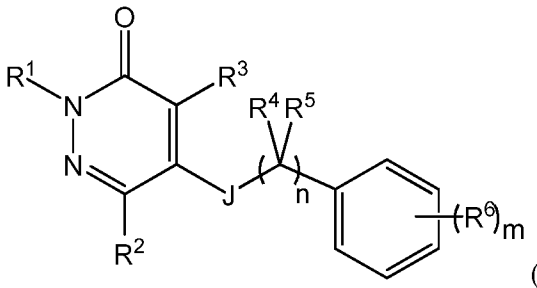
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and a leaving group; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group,

provided that at least one leaving group is present in the compound.

In some embodiments, a compound is provided comprising the structure:



(XIV)

or a salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and a leaving group;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and a leaving group;

R^3 is selected from the group consisting of hydrogen, unsubstituted alkyl or alkyl optionally substituted with a moiety other than a halogen, heteroalkyl optionally substituted,

alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, –CN, and $–NO_2$;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and a leaving group, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–N(R^7)_2$, $–NO_2$, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, $–Si(R^9)_3$, $–B(R^{9'})_3$, $–OR^8$, and a leaving group;

m is 0, 1, 2, 3, 4, or 5;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring;

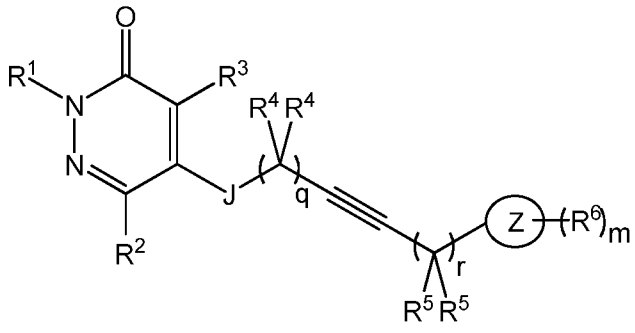
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and a leaving group; and

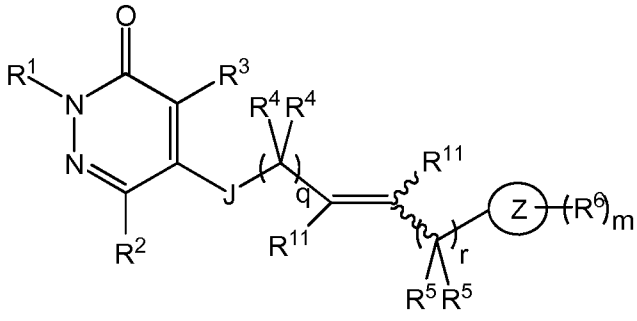
each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group,

provided that at least one leaving group is present in the compound.

In some embodiments, a compound is provided comprising the structure:



(XV) or



(XVI),

or a salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and a leaving group;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and a leaving group;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $-NO_2$, and a leaving group;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

each R^4, R^5, and R^{11} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, and a leaving group, or optionally any two of R^4 or any two of R^5 are joined together to form a ring;

q, and r are each independently 0, 1, 2, or 3;

Z is selected from the group consisting of aryl, heteroaryl, heterocyclyl, and a bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl

optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, –OH, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, –CN, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and a leaving group;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring;

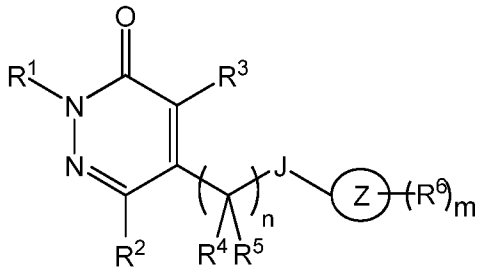
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and a leaving group; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group,

provided that at least one leaving group is present in the compound.

In some embodiments, a compound is provided comprising the structure:



(XVII)

or a salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and a leaving group;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, $-NO_2$,

haloalkyl, and a leaving group;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and a leaving group;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, and $–CH_2O$;

each R^4 and R^5 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, and a leaving group, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 1, 2, or 3;

Z is selected from the group consisting of aryl, heteroaryl, heterocyclyl, and a bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–N(R^7)_2$, $–NO_2$, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, $–Si(R^9)_3$, $–B(R^{9'})_3$, $–OR^8$, and a leaving group;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring;

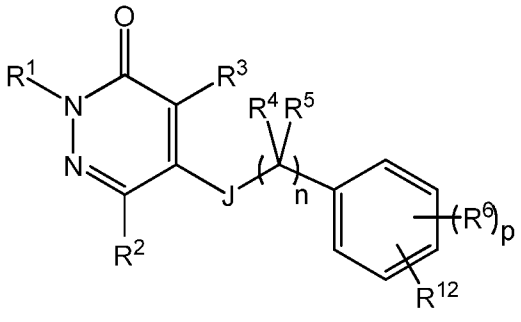
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and a leaving group; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group,

provided that at least one leaving group is present in the compound.

In some embodiments, a compound is provided comprising the structure:



(XVIII)

or a salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and a leaving group;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and a leaving group;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-CN$, $-NO_2$, and a leaving group;

J is selected from the group consisting of consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and a leaving group, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and a leaving group;

p is 0, 1, 2, 3, or 4;

each R^7 is independently selected from the group consisting of hydrogen, alkyl

optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring; and

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

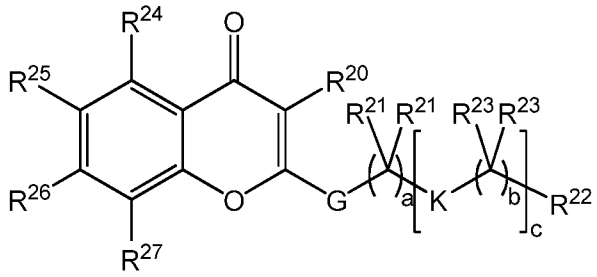
each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and a leaving group;

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group; and

R^{12} is selected from the group consisting of alkynyl optionally substituted, alkenyl optionally substituted, alkyl substituted with –CN, alkyl substituted with $–C(=O)OR^8$, alkyl substituted with $–C(=O)R^8$, alkyl substituted with $–N(R^7)_2$, –CN, $–NO_2$, $–N(R^7)_2$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)R^8$, $–C(=O)N(R^7)_2$, and $–N(R^7)C(=O)R^8$,

provided that at least one leaving group is present in the compound.

In some embodiments, a compound is provided comprising the structure:



(XIX)

or a salt thereof, wherein:

R^{20} is selected from the group consisting of hydrogen, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, and $–NO_2$;

each R^{21} and R^{23} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, and a leaving group, or optionally any two R^{21} or any two R^{23} may be joined together to form a ring;

R^{22} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, $–OR^{28}$, $–Si(R^9)_3$, $–B(R^{9'})_3$, and a leaving group;

R^{24}, R^{25}, R^{26}, and R^{27} are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, –OH, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, –CN, and a leaving group;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring; and

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and a leaving group;

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group;

R^{28} is selected from the group consisting of hydrogen, alkyl optionally substituted, and heteroalkyl optionally substituted;

G is O, S, or NR^{28};

a is 0, 1, 2, 3, or 4;

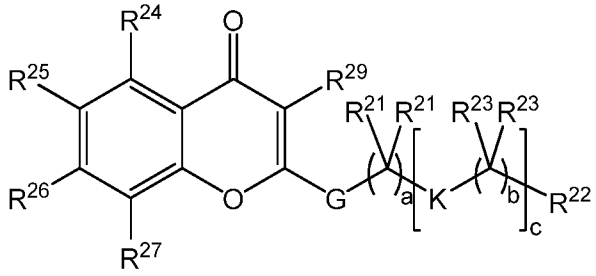
each K is independently arylene, heteroarylene, alkenylene, or alkynylene, each optionally substituted;

each b is independently 0, 1, 2, 3, or 4; and

c is 1 or 2,

provided at least one leaving group is present in the compound.

In some embodiments, a compound is provided comprising the structure:



(XX)

or a salt thereof, wherein:

each R^{21} and R^{23} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, and a leaving group, or optionally any two R^{21} or any two R^{23} may be joined together to form a ring;

R^{22} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, $-OR^{28}$, $-Si(R^9)_3$, $-B(R^{9'})_3$, and a leaving group;

R^{24}, R^{25}, R^{26}, and R^{27} are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, and a leaving group;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring; and

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halo, and a leaving group;

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group;

R^{28} is selected from the group consisting of hydrogen, alkyl optionally substituted, and heteroalkyl optionally substituted;

R^{29} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and a leaving group;

G is O, S, or NR^{28};

a is 0, 1, 2, 3, or 4;

each K is independently arylene, heteroarylene, alkenylene, or alkynylene, each optionally substituted, provided at least one K is alkenylene, or alkynylene;

each b is independently 0, 1, 2, 3, or 4; and

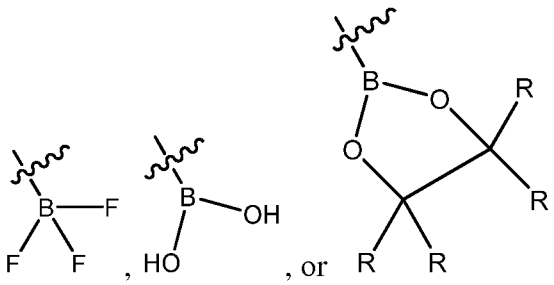
c is 1 or 2,

provided at least one leaving group is present in the compound.

In each of the above compounds comprising Formula (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), (XIX), or (XX), each group and/or variable may optionally be selected from the groups and/or variables provided above for the corresponding imaging agents having Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), or (X), respectively, wherein each imaging moiety in the groups provided for a compound comprising Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), or (X) is replaced with a leaving group.

The following description of R^6 groups may be used in connection with a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII). In some embodiments, for a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII), all but one R^6 is H. That is, all R^6 are H and one R^6 is not H. In some cases, the one R^6 which is not H is substituted with the at least one leaving group. In some cases, the one R^6 which is not H is the at least one leaving group. In some embodiments, for a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII), at least one R^6 is alkyl optionally substituted, alkoxy optionally substituted, or alkoxyalkyl optionally substituted, each substituted with a leaving group. In some embodiments, for a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII), at least one R^6 is $–(CH_2)_jL_G$; wherein L_G is a leaving group and j is 1, 2, 3, 4, 5, or 6. In some cases, at least one R^6 is $–(CH_2)L_G$, $–(CH_2)_2L_G$, $–(CH_2)_3L_G$, $–(CH_2)_4L_G$, $–(CH_2)_5L_G$, $–(CH_2)_6L_G$, $–(CH_2)_7L_G$, $–(CH_2)_8L_G$, $–(CH_2)_9L_G$, or $–(CH_2)_{10}L_G$. In some embodiments, at least one R^6 is $–O(CH_2)_jL_G$; wherein L_G is a leaving group and j is 1, 2, 3, 4, 5, or 6. In some cases, at least one R^6 is $–O(CH_2)_5L_G$, $–O(CH_2)_6L_G$, $–O(CH_2)_7L_G$, $–O(CH_2)_8L_G$, $–O(CH_2)_9L_G$, or $–O(CH_2)_{10}L_G$. In some embodiments, at least one R^6 is $–(CH_2)_jO(CH_2)_jL_G$; wherein L_G is a leaving group and each j is independently 1, 2, 3, 4, 5, or 6. In some embodiments, at least

one R^6 is $-(CH_2)O(CH_2)_jL_G$; wherein L_G is a leaving group and each j is independently 1, 2, 3, 4, 5, or 6. In some cases, at least one R^6 is $-CH_2O(CH_2)L_G$, $-CH_2O(CH_2)_2L_G$, $-CH_2O(CH_2)_3L_G$, $-CH_2O(CH_2)_4L_G$, $-CH_2O(CH_2)_5L_G$, $-CH_2O(CH_2)_6L_G$, $-CH_2O(CH_2)_7L_G$, $-CH_2O(CH_2)_8L_G$, $-CH_2O(CH_2)_9L_G$, or $-CH_2O(CH_2)_{10}L_G$. In some embodiments, at least one R^6 is $-C\equiv C-(CH_2)_jL_G$; wherein L_G is a leaving group and j is 1, 2, 3, 4, 5, or 6. In some embodiments, at least one R^6 is $-[(CH_2)_jO]_j(CH_2)_jL_G$; wherein L_G is a leaving group and each j is independently 1, 2, 3, 4, 5, or 6. In some embodiments, at least one R^6 is $-O[(CH_2)_jO]_j(CH_2)_jL_G$; wherein L_G is a leaving group and each j is independently 1, 2, 3, 4, 5, or 6. In some embodiments, at least one R^6 is optionally substituted alkyl substituted with a leaving group. In some embodiments, at least one R^6 is $-C(=O)O(CH_2)_jL_G$; wherein L_G is a leaving group and j is 1, 2, 3, 4, 5, or 6. In some embodiments, at least one R^6 is $-C(=O)(CH_2)_jL_G$; wherein L_G is a leaving group and j is 1, 2, 3, 4, 5, or 6. In some embodiments, at least one R^6 is $-(CH_2)_jNH(CH_2)_jL_G$; wherein L_G is a leaving group and each j is independently 1, 2, 3, 4, 5, or 6. In some embodiments, at least one R^6 is $Si(R^9)_2L_G$, wherein each R^9 is alkyl optionally substituted and wherein L_G is a leaving group. In some embodiments, at least one R^6 is $B(R^{9'})_2L_G$, wherein each $R^{9'}$ is alkyl optionally substituted and wherein L_G is a leaving group, or optionally, two $R^{9'}$ join together to form a ring which is a portion of leaving, or optionally, one $R^{9'}$ is absent, for example:



(e.g., wherein each R is alkyl or aryl),

In some embodiments, at least one R^6 is selected from the group consisting of $-C\equiv C-CH_2CH_2CH_2L_G$, $-C\equiv C-CH_2CH_2L_G$, $-C\equiv C-CH_2L_G$, $-CH_2L_G$, $-(CH_2)_2L_G$, $-(CH_2)_3L_G$, $-(CH_2)_4L_G$, $-(CH_2)_5L_G$, $-(CH_2)_6L_G$, $-OCH_2L_G$, $-O(CH_2)_2L_G$, $-O(CH_2)_3L_G$, $-O(CH_2)_4L_G$, $-O(CH_2)_5L_G$, $-O(CH_2)_6L_G$, $-CH_2O(CH_2)_2L_G$, $-CH(CH_3)O(CH_2)_2L_G$, $-CH_2O(CH_2)_3L_G$, $-CD_2O(CH_2)_2L_G$, $-(CH_2)_2O(CH_2)_2L_G$, $-CHBrC(CH_3)_2L_G$, $-CHClC(CH_3)_2L_G$, $-CHFC(CH_3)_2L_G$, $-C(=O)OCH_2L_G$, $-C(=O)O(CH_2)_2L_G$, $-C(=O)O(CH_2)_3L_G$, $-CH_2NH(CH_2)_2L_G$, $-CH_2NHCH_2L_G$, $-CH_2O(CH_2)_2O(CH_2)_2L_G$, $-CH_2O(CH_2)_2O(CH_2)_3L_G$, $-O(CH_2)_2O(CH_2)_2L_G$, $-C(=O)(CH_2)_2L_G$, and $-C(=O)(CH_2)_3L_G$. For a compound of Formula (XI) or (XII), each of the R^6 groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, $R^{9'}$, J, W, m, and n, or combinations thereof, as described herein. For a

compound of Formula (XIII), each of the R^6 groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, $R^{9'}$, Q, J, and n, or combinations thereof, as described herein. For a compound of Formula (XIV), each of the R^6 groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, $R^{9'}$, J, m, and n, or combinations thereof, as described herein. For a compound of Formula (XV) or (XVI), each of the R^6 groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, $R^{9'}$, R11, J, Z, m, q, and r, or combinations thereof, as described herein. For a compound of Formula (XVII), each of the R^6 groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, $R^{9'}$, J, Z, n, and m, or combinations thereof, as described herein. For a compound of Formula (XVIII), each of the R^6 groups described herein may be combined with any R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, $R^{9'}$, R^{12}, J, p, and n, or combinations thereof, as described herein.

The following description of R^{22} groups may be used in connection with a compound of Formula (XIX) or (XX). In some embodiments, R^{22} is a leaving group. In some embodiments, R^{22} is substituted with a leaving group. In some embodiments, R^{22} is alkyl optionally substituted, alkoxy optionally substituted, or alkoxyalkyl optionally substituted, each substituted with a leaving group. In some embodiments, R^{22} is $-Si(R^9)_3$ or $-B(R^{9'})_3$. In some embodiments, R^{22} is $-(CH_2)_jL_G$; wherein L_G is a leaving group and j is 1, 2, 3, 4, 5, or 6. In some cases, R^{22} is $-(CH_2)L_G$, $-(CH_2)_2L_G$, $-(CH_2)_3L_G$, $-(CH_2)_4L_G$, $-(CH_2)_5L_G$, $-(CH_2)_6L_G$, $-(CH_2)_7L_G$, $-(CH_2)_8L_G$, $-(CH_2)_9L_G$, or $-(CH_2)_{10}L_G$. In some embodiments, R^{22} is $-O(CH_2)_jL_G$; wherein L_G is a leaving group and j is 1, 2, 3, 4, 5, or 6. In some cases, R^{22} is $-O(CH_2)L_G$, $-O(CH_2)_2L_G$, $-O(CH_2)_3L_G$, $-O(CH_2)_4L_G$, $-O(CH_2)_5L_G$, $-O(CH_2)_6L_G$, $-O(CH_2)_7L_G$, $-O(CH_2)_8L_G$, $-O(CH_2)_9L_G$, or $-O(CH_2)_{10}L_G$. In some embodiments, R^{22} is $-(CH_2)_jO(CH_2)_jL_G$; wherein L_G is a leaving group and each j is independently 1, 2, 3, 4, 5, or 6. In some embodiments, R^{22} is $-(CH_2)O(CH_2)_jL_G$; wherein L_G is a leaving group and each j is independently 1, 2, 3, 4, 5, or 6. In some cases, R^{22} is $-CH_2O(CH_2)L_G$, $-CH_2O(CH_2)_2L_G$, $-CH_2O(CH_2)_3L_G$, $-CH_2O(CH_2)_4L_G$, $-CH_2O(CH_2)_5L_G$, $-CH_2O(CH_2)_6L_G$, $-CH_2O(CH_2)_7L_G$, $-CH_2O(CH_2)_8L_G$, $-CH_2O(CH_2)_9L_G$, or $-CH_2O(CH_2)_{10}L_G$. In some embodiments, R^{22} is $-C\equiv C-(CH_2)_jL_G$; wherein L_G is a leaving group and j is 1, 2, 3, 4, 5, or 6. In some embodiments, R^{22} is $-[(CH_2)_jO]_j(CH_2)_jL_G$; wherein L_G is a leaving group and each j is independently 1, 2, 3, 4, 5, or 6. In some embodiments, R^{22} is $-O[(CH_2)_jO]_j(CH_2)_jL_G$; wherein L_G is a leaving group and each j is independently 1, 2, 3, 4, 5, or 6. In some embodiments, R^{22} is optionally substituted alkyl substituted with a leaving group. In some embodiments, R^{22} is $-C(=O)O(CH_2)_jL_G$; wherein L_G is a leaving group and j is 1, 2, 3, 4, 5, or 6. In some

embodiments, R^{22} is $-C(=O)(CH_2)_jL_G$; wherein L_G is a leaving group and j is 1, 2, 3, 4, 5, or 6. In some embodiments, R^{22} is $-(CH_2)_jNH(CH_2)_jL_G$; wherein L_G is a leaving group and each j is independently 1, 2, 3, 4, 5, or 6. In some embodiments, R^{22} is $Si(R^9)_2L_G$, wherein each R^9 is alkyl optionally substituted and wherein L_G is a leaving group. In some embodiments, R^{22} is $B(R^{9'})_2L_G$, wherein each $R^{9'}$ is alkyl optionally substituted and wherein L_G is a leaving group. In some embodiments, R^{22} is selected from the group consisting of $-C\equiv C-CH_2CH_2CH_2L_G$, $-C\equiv C-CH_2CH_2L_G$, $-C\equiv C-CH_2L_G$, $-CH_2L_G$, $-(CH_2)_2L_G$, $-(CH_2)_3L_G$, $-(CH_2)_4L_G$, $-(CH_2)_5L_G$, $-(CH_2)_6L_G$, $-OCH_2L_G$, $-O(CH_2)_2L_G$, $-O(CH_2)_3L_G$, $-O(CH_2)_4L_G$, $-O(CH_2)_5L_G$, $-O(CH_2)_6L_G$, $-CH_2O(CH_2)_2L_G$, $-CH(CH_3)O(CH_2)_2L_G$, $-CH_2O(CH_2)_3L_G$, $-CD_2O(CH_2)_2L_G$, $-(CH_2)_2O(CH_2)_2L_G$, $-CHBrC(CH_3)_2L_G$, $-CHClC(CH_3)_2L_G$, $-CHFC(CH_3)_2L_G$, $-C(=O)OCH_2L_G$, $-C(=O)O(CH_2)_2L_G$, $-C(=O)O(CH_2)_3L_G$, $-CH_2NH(CH_2)_2L_G$, $-CH_2NHCH_2L_G$, $-CH_2O(CH_2)_2O(CH_2)_2L_G$, $-CH_2O(CH_2)_2O(CH_2)_3L_G$, $-O(CH_2)_2O(CH_2)_2L_G$, $-C(=O)(CH_2)_2L_G$, and $-C(=O)(CH_2)_3L_G$. For a compound of Formula (XIX), each of the R^{22} groups described herein may be combined with any R^7, R^8, R^{20}, R^{21}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, G, a, K, b, and c, or combinations thereof, as described herein. For a compound of Formula (XX), each of the R^{22} groups described herein may be combined with any R^7, R^8, R^{21}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, G, a, K, b, and c, or combinations thereof, as described herein.

As described in more detail herein, in some embodiments, a diagnostic kit is provided comprising one or more vials containing a compound as described in this section or a salt thereof (*e.g.*, a compound comprising Formula (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), (XIX), or (XX)), and optionally other components. In some embodiments, the diagnostic kit is for the preparation of diagnostic agents for imaging, detecting, and/or monitoring myocardial perfusion in a subject. In some embodiments, said other components are selected from the group consisting of ancillary ligands, reducing agents, transfer ligands, buffers, lyophilization aids, stabilization aids, solubilization aids, and bacteriostats.

As described in more detail herein, in some embodiments, methods for forming an imaging agent are provided, the method comprising reacting a compound as described in this section or a salt thereof (*e.g.*, a compound comprising Formula (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), (XIX), or (XX)) with an ^{18}F-containing species to produce an imaging agent comprising ^{18}F (*e.g.*, a compound comprising Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), or (X, respectively).

Salts

In some embodiments, the imaging agents and precursors described herein may be salts. In some cases, the salt is a pharmaceutically acceptable salt. However, in the case of imaging agent precursors, the salt may not necessarily be a pharmaceutically acceptable salt. Those of ordinary skill in the art will be aware of suitable counter anions for forming a salt of the imaging agents and imaging agent precursors described herein. In addition, those of ordinary skill in the art will be aware that the counter anion $X^{\ominus}$ may have a charge of less than -1 (*e.g.*, -2, -3), and in such embodiments, each counter anion $X^{\ominus}$ may be associated with more than one molecule of the compound. In some embodiments, the counter ion is a halide, phosphate, hydrogen phosphate, dihydrogen phosphate, hydrogen sulfate, sulfate, trifluoroacetate, toluenesulfonate, acetate, formate, citrate, ascorbate, mesylate (methanesulfonate), triflate (trifluoromethanesulfonate), tartrate, lactate, or benzoate. Additional non-limiting examples of suitable counter anions include the conjugate base of inorganic acids (*e.g.*, chloride, bromide, iodide, fluoride, nitrate, sulfate, phosphate) or from the conjugate base of organic acids (*e.g.*, carboxylate, acetate, benzoate, tartrate, adipate, lactate, formate, maleate, glutamate, ascorbate, citrate, gluconate, oxalate, succinate, pamoate, salicylate, isethionate, succinamate, mono-diglycollate, di-isobutyrate, glucoheptonate). Still yet other non-limiting examples of salts include adipate, alginate, aminosalicylate, anhydromethylenecitrate, arecoline, aspartate, bisulfate, camphorate, digluconate, dihydrobromide, disuccinate, glycerophosphate, hemisulfate, fluoride, iodide, methylenebis(salicylate), napadisylate, oxalate, pectinate, persulfate, phenylethylbarbiturate, picrate, propionate, thiocyanate, tosylate, undecanoate, acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edentate, camyslate, carbonate, chloride, citrate, dihydrochloride, edentate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, bromide, chloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, and triethiodide (see Berge *et al.*, *Journal of Pharmaceutical Sciences*, 66(1), 1977, 1-19).

Methods of Synthesizing Imaging Agents

In other aspects, methods are provided for synthesizing imaging agents. The methods

described herein may be used for the synthesis of a variety of imaging agents as described herein from imaging agent precursors as described herein. Generally, an imaging agent may be synthesized by reacting an imaging agent precursor with a reactant comprising the imaging moiety. In some cases, the reaction involves the formation of a covalent bond between the imaging agent precursor and the imaging moiety of the reactant. In other cases, however, the reaction involves non-covalent association of an imaging moiety with an imaging agent precursor (*e.g.*, via chelation). The following sections provide a number of non-limiting embodiments for forming an imaging agent from an imaging agent precursor. Those of ordinary skill in the art will be aware of other suitable methods and techniques for forming an imaging agent from an imaging agent precursor. In addition, other steps which may be conducted in connection with the synthesis of an imaging agent (*e.g.*, formulation, purification) are also described.

In some cases, the imaging agent is formed by reacting an imaging agent precursor with an imaging moiety. In certain embodiments, a method involves reacting an imaging agent precursor comprising a leaving group with a source of an imaging moiety (*e.g.*, a fluoride species). For example, the imaging moiety replaces the leaving group via a substitution reaction, such as an S_N2 or S_N1 reaction. That is, during the reaction an imaging moiety replaces the leaving group, thereby producing the imaging agent.

The methods described herein may be used for the synthesis of a wide variety of imaging agents from an imaging agent precursor. Generally, the imaging agent precursor may include at least one leaving group that may be displaced by an imaging moiety, such as an ^{18}F species. Imaging agent precursors may be synthesized using methods known to those of ordinary skill in the art.

A. General Reaction Conditions

The synthetic methods described herein may be carried out in any suitable solvent, including, but not limited to, non-halogenated hydrocarbon solvents (*e.g.*, pentane, hexane, heptane, cyclohexane), halogenated hydrocarbon solvents (*e.g.*, dichloromethane, chloroform, fluorobenzene, trifluoromethylbenzene), aromatic hydrocarbon solvents (*e.g.*, toluene, benzene, xylene), ester solvents (*e.g.*, ethyl acetate), ether solvents (*e.g.*, tetrahydrofuran, dioxane, diethyl ether, dimethoxyethane.), and alcohol solvents (*e.g.*, ethanol, methanol, propanol, isopropanol, *tert*-butanol). In certain embodiments, a protic solvent is used. In other embodiments, an aprotic solvent is used. Non-limiting examples of solvents useful in the synthetic methods include acetone, acetic acid, formic acid, dimethyl sulfoxide, dimethyl

formamide, acetonitrile, *p*-cresol, glycol, petroleum ether, carbon tetrachloride, hexamethyl-phosphoric triamide, triethylamine, picoline, and pyridine.

The methods may be carried out at any suitable temperature. In some cases, the method is carried out at about room temperature (*e.g.*, about 20 ºC, between about 20 ºC and about 25 ºC, about 25 ºC, or the like). In some cases, however, the method is carried out at a temperature below or above room temperature, for example, at about -78 ºC at about -70 ºC, about -50 ºC, about -30 ºC, about -10 ºC, about -0 ºC, about 10 ºC, about 30 ºC, about 40 ºC, about 50 ºC, about 60 ºC, about 70 ºC, about 80 ºC, about 90 ºC, about 100 ºC , about 120 ºC, about 140 ºC, or the like. In some embodiments, the method is carried out at temperatures above room temperature, for example, between about 25 °C and about 120 °C, or between about 25 °C and about 100 °C, or between about 40 °C and about 120 °C, or between about 80 °C and about 120 °C. The temperature may be maintained by reflux of the solution. In some cases, the method is carried out at temperatures between about -78 ºC and about 25 ºC, or between about 0 ºC and about 25 ºC.

The methods described herein may be carried out at any suitable pH, for example, equal to or less than about 13, equal to or less than about 12, equal to or less than about 11, equal to or less than about 10, equal to or less than about 9, equal to or less than about 8, equal to or less than about 7, or equal to or less than about 6. In some cases, the pH may be greater than or equal to 1, greater than or equal to 2, greater than or equal to 3, greater than or equal to 4, greater than or equal to 5, greater than or equal to 6, greater than or equal to 7, or greater than or equal to 8. In some cases, the pH may be between about 2 and about 12, or between about 3 and about 11, or between about 4 and about 10, or between about 5 and about 9, or between about 6 and about 8, or about 7.

The percent yield of a product may be greater than about 60%, greater than about 70%, greater than about 75%, greater than about 80%, greater than about 85%, greater than about 90%, greater than about 92%, greater than about 95%, greater than about 96%, greater than about 97%, greater than about 98%, greater than about 99%, or greater.

B1. Halogenation

In some embodiments, an imaging agent is formed by reacting an imaging agent precursor with an imaging moiety. In certain embodiments, an imaging agent precursor comprises at least one leaving group that is susceptible to being displaced by an imaging moiety, such as, for example, a halogen (*e.g.*, ^{18}F, ^{76}Br, ^{124}I, ^{131}I). Thus, in certain embodiments, the methods described herein involve reacting an imaging agent precursor

comprising a leaving group with a source of an imaging moiety.

In some embodiments, a halide displaces a leaving group on a provided imaging agent precursor via a substitution reaction, such as an S_N2 or S_N1 reaction, thereby producing an imaging agent. For example, a halide such as fluoride may displace a sulfonate leaving group of the imaging agent precursor to yield a fluorinated imaging agent. In certain embodiments, a substitution reaction is a one-step procedure which does not require a subsequent deprotection step. That is, the substitution step is performed on a fully deprotected imaging agent precursor. In certain embodiments, a substitution reaction provided by the present invention produces a fluorinated imaging agent (*e.g.*, an imaging agent comprising ^{18}F).

In some embodiments, a provided imaging agent is synthesized via an aryl or heteroaryl halogenation reaction (*e.g.*, aryl fluorination, aryl bromination, aryl iodination). Many techniques for synthesizing aryl or heteroaryl halides are known in the art. For example, in certain embodiments, an imaging agent comprising an ^{124}I, ^{131}I, or ^{76}Br imaging moiety is synthesized via a Sandmeyer reaction from an aryl diazonium imaging agent precursor, with or without the use of copper(I) catalysis (see, for example, Beletskaya *et al.*, *Synthesis*, 2007, 2534-2538; Hubbard *et al.*, *J. Org. Chem.*, 2008, 73, 316-319; Filimonov *et al.*, *Org. Lett.*, 2008, 10, 3961-3964; Krasnokutskaya *et al.*, *Synthesis*, 2007, 81-84). In other embodiments, an imaging agent comprising an ^{18}F imaging moiety is synthesized via a related Balz-Schiemann reaction from a diazonium imaging agent precursor. In certain embodiments, an imaging agent comprising a ^{124}I or ^{131}I imaging moiety is synthesized via an "aromatic Finkelstein" reaction from an aryl bromide imaging agent precursor (see, for example, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, 124, 14844-14845). In other embodiments, an imaging agent comprising an ^{124}I, ^{131}I, or ^{76}Br imaging moiety is synthesized by allowing a boronic acid or ester imaging agent precursor to react with the appropriate N-halosuccinimide reagent (Thiebes *et al.*, *Synlett*, 1998, 141-142) or copper bromide reagent (see, for example, Murphy *et al.*, *J. Am. Chem. Soc.*, 2007, 129, 15434-15435; Thompson *et al.*, *Synthesis*, 2005, 547-550). In some embodiments, an imaging agent comprising a ^{76}Br imaging moiety is synthesized via an organotrifluoroborate imaging agent precursor (see, for example, G. W. Kabalka, A. R. Mereddy, *Organometallics*, 2004, 23, 4519-4521). One of ordinary skill in the art will appreciate that there are many other conditions under which activated or deactivated arenes may be halogenated (see, for example, Kraszkiewicz *et al.*, *Synthesis*, 2006, 1195-1199; Ganguly *et al.*, *Synthesis*, 2010, 1467-1472; Iskra *et al.*, *Synthesis*, 2004, 1869-1873; Castanet *et al.*, *Tetrahedron Lett.*, 2002, 43, 5047-5048; Prakash *et al.*, J. Am. Chem. Soc., 2004, 126, 15570-15776; Lulinski *et al.*, *Synthesis*,

2004, 441-445; Ganguly *et al.*, *Synthesis*, 2005, 1103-1108; Rajesh *et al.*, *Org. Chem.*, 2007, 72, 5867-5869; Kumar *et al.*, *Synthesis*, 2010, 1629-1632; Zhou *et al.*, *Synthesis*, 2011, 207-209; Menzel *et al.*, *J. Org. Chem.*, 2006, 71, 2188-2191), and such a reaction may be employed in certain embodiments to synthesize imaging agents described herein. One of ordinary skill in the art will also appreciate that many of the aryl halogenation reactions described herein will also be effective for generating a haloalkene- or haloalkyne-containing imaging agent, as well as haloheteroaryl-containing imaging agents.

In some embodiments, an imaging agent comprising an ^{18}F imaging moiety is synthesized via an aryl fluorination. See, for example, Furuya *et al.*, *Synthesis,* 2010(11): 1804–1821 (2010), for an informative review of aryl fluorination reactions. For example, in certain embodiments, an imaging agent comprising an ^{18}F imaging moiety is synthesized via a nucleophilic fluorination reaction. Examples of nucleophilic fluorination reactions include, but are not limited to, the Halex process (Adams *et al.*, *Chem Soc Rev* 1999;28:225; Horwitz *et al.*, *J. Org. Chem* 1961;26:3392; Barlin *et al.*, *J. Chem. Soc., Perkin Trans* 1 1972:1269; Pike *et al.*, *J. Chem. Soc., Chem Commun* 1995:2215; Shah *et al.*, *J. Chem. Soc., Perkin Trans 1* 1998:2043; Ermert *et al.*, *J Labelled Compd Radiopharm* 2004;47:429), fluorodenitration (Adams *et al.*, *Chem Soc Rev* 1999;28:225; Adams *et al.*, *J. Fluorine Chem* 1998;92:127), displacement of ammonium with fluoride (Angelini *et al.*, *J. Fluorine Chem* 1985;27:177), and fluorination of diaryliodonium salts (Zhdankin *et al.*, *Chem Rev* 2008;108:5299; Beringer *et al.*, *J. Am. Chem Soc* 1953;75:2708; Ross *et al.*, *J. Am. Chem Soc* 2007;129:8018). Trialkylammonium fluoride reagents may also be employed in nucleophilic fluorination reactions (Sun *et al.*, *Angew. Chem., Int. Ed* 2006;45:2720; Grushin *et al.*, *Organometallics* 2008;27:4825). In certain embodiments, a nucleophilic fluorination reaction is Palladium catalyzed (see, for example, Grushin *et al.*, *Organometallics* 2008;27:4825; Watson *et al.*, *Science* 2009;325:1661). In other embodiments, an imaging agent comprising an ^{18}F imaging moiety is synthesized via an electrophilic fluorination reaction. Examples of electrophilic fluorination reactions include, but are not limited to, fluorination of aryl Grignard reagents (Anbarasan P, Neumann H, Beller M. *Angew Chem, Int Ed.* 2010;49:2219), fluorination of arylmagnesium reagents (Yamada S, Gavryushin A, Knochel P. *Angew Chem, Int Ed.* 2010;49:2215), fluorination of organometallic reagents such as arylzinc halides, arylsilanes, arylstannanes, arylgermaniums, arylboronic ester, or arylboronic acids (Bryce *et al.*, *J. Chem. Soc, Chem Commun* 1986:1623; Tius *et al.*, Synth Commun 1992;22:1461; Cazorla *et al.*, *Tetrahedron Lett* 2009;50:3936), fluorination of arylsilanes (Lothian *et al.*, *Synlett* 1993:753), and fluorodestannylation reactions (Lothian *et*

al., *Synlett* 1993:753; Namavari *et al.*, *Appl Radiat Isot* 1992;43:989.). In some embodiments, an electrophilic fluorination reaction employs stoichiometric or catalytic palladium (see, for example, Furuya *et al.*, *Angew Chem, Int Ed* 2008;47:5993) or silver (see, for example, Furuya *et al.*, *J. Am. Chem Soc* 2009;131:1662; Furuya *et al.*, *Org Lett* 2009;11:2860).

B2. Fluorination

It should be understood, that while the following section focuses on fluorination reactions, this is by no means limiting, and the teachings of this section may be applied to other halogenation reactions.

In some embodiments, a method for synthesizing an imaging agent comprises contacting an imaging agent precursor of the invention with a fluoride species resulting in the fluoride species replacing the leaving group of the precursor to produce an imaging agent. In some embodiments, an inventive method employs a reaction described herein, such as in the description of halogenation reactions above.

In certain embodiments, a method for synthesizing an imaging agent involves a nucleophilic fluorination reaction. It will be understood that the discussion of nucleophilic fluorination is exemplary of the methods described herein and is not limiting. In certain embodiments, an imaging agent precursor comprising a leaving group is reacted in the presence of a fluoride species, whereby S_N2 or S_N1 displacement of the leaving group by the fluoride species produces an imaging agent. In some embodiments, for a composition, a fluoride species is isotopically enriched with ^{18}F.

Those of ordinary skill in the art will be aware of suitable conditions for fluorinating a compound. For example, see International Patent Application PCT/US2011/024109, filed February 8, 2011, to Cesati *et al.*, and Intenational Patent Application No. PCT/US2005/004687, filed Feb. 11, 2005, to Casebier *et al.*, each incorporated by reference herein for all purposes. In some cases, the source of fluorine is a fluoride salt (*e.g.*, KF, NaF, tetralkylammonium fluoride).

In some embodiments, a fluorinating agent for use in a provided method is a source of fluoride. In certain embodiments, a fluorinating agent for use in a provided method is NaF or KF. In certain embodiments, a fluorinating agent for use in a provided method is isotopically enriched with ^{18}F. In certain embodiments, suitable conditions for a fluorination reaction according to the present invention comprise the presence of an ammonium salt or a bicarbonate salt.

The fluorine source may comprise or be associated with or may be used in connection with another reagent. In some embodiments, an additional reagent may be capable of enhancing the reactivity of the fluorine species or otherwise facilitating conversion of the precursor to the imaging agent. For example, in certain embodiments, an additional reagent is used in combination with a multidentate ligand, such as a crown ether or a cryptand that is capable of chelating a metal ion. In certain embodiments, a multidentate ligand is, for example, 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]-hexacosane (*i.e.*, Kryptofix® 222). In certain embodiments, when KF is a fluorine source, cryptands having a high affinity for potassium are useful as they chelate potassium and thereby increase the reactivity of the fluoride ion. In some embodiments, cryptands having an affinity for potassium near that of Kryptofix® 222 (*e.g.*, 75%, 80%, 85%, 90%, 95%, or more of the Kryptofix® 222's affinity for potassium) are used. The reaction conditions may comprise one or more solvents.

In some embodiments, the fluorination occurs in the presence of K_2CO_3 and Kryptofix® 222 (or any another cryptand having affinity for the cation of interest, including for example potassium, near that of Kryptofix® 222) in MeCN (acetonitrile) alone or in combination with another solvent. In some embodiments, the molar ratio of K_2CO_3 to imaging agent precursor ranges from about 0.25:1 to about 5:1, for example 0.5:1 to 1:1.

In some embodiments, fluorination occurs in the presence of tetraalkylammonium carbonate or tetraalkylammonium bicarbonate in MeCN as the solvent. In some embodiments, the molar ratio of tetraalkylammonium carbonate or bicarbonate to imaging agent precursor is less than about 2:1. Other molar ratios are provided herein.

In certain embodiments, the synthetic methods described herein involve a single-step preparation of imaging agents of the invention. In certain embodiments, a single–step method involves fluorination of a precursor in the presence of, for example, K_2CO_3/Kryptofix® 222 (or other suitable alternatives to Kryptofix® 222) or tetraalkylammonium carbonate or bicarbonate (*e.g.*, in MeCN alone or in an MeCN mixture). In certain embodiments, single-step preparation methods are particularly suitable when particular salt forms of the imaging agent precursors of the invention are used, such as halide, acetate, formate, citric, ascorbate, trifluoroacetate, tolunesulfonate, benzoate, acetate, phosphate, sulfate, tosylate, and mesylate.

In some embodiments, one or more reagents are used in a reaction mixture comprising an imaging agent precursor and a fluoride species. A "reagent," also referred to as an "additive," is used herein to mean any chemical compound added to a reaction mixture. A reagent may be consumed or not consumed during the reaction. A reagent may be a

stoichiometric or catalytic reagent. Exemplary reagents include catalysts, salts, oxidants, reductants, chelating agents, bases, acids, metals, phase transfer reagents, and others as would be appreciated by one of skill in the art.

A reagent may, in some embodiments, facilitate reaction between an imaging agent precursor and a fluoride species and/or may aid in stabilizing a resultant imaging agent. For example, in certain embodiments, a fluoride species may have relatively low reactivity (*e.g.*, nucleophilicity), and addition of certain reagents may enhance the reactivity of the fluoride species. As an illustrative embodiment, a fluorine species may be a negatively charged fluoride ion (*e.g.*, an isotopically enriched ^{18}F ion), and a reagent may be used to bind to any positively charged counter ions present within the reaction mixture, thereby enhancing the reactivity of the fluoride ion. An example of such a reagent is a cryptand such as, but not limited to, Kryptofix® (*e.g.*, Kryptofix® 222). In some embodiments, a reagent decreases the rate of undesired side reactions.

In some embodiments, a reagent may be combined with a fluoride species prior to its contact with an imaging agent precursor. For example, in certain embodiments, a solution comprising a fluoride species and a reagent is prepared, and the solution is added to an imaging agent precursor. In other embodiments, a solid comprising a fluoride species and a reagent is prepared, and the solid is contacted with an imaging agent precursor in solution. In certain embodiments, a fluoride species is adsorbed onto a solid support (*e.g.*, an anion exchange column), and a solution comprising the reagent is used to elute the fluoride species from the solid support. The eluted solution is then contacted with the imaging agent precursor, or is concentrated to produce a solid, which is then contacted with the imaging agent precursor in solution.

In some embodiments, a provided reagent is a bicarbonate salt. As used herein, the term "bicarbonate salt" refers to a salt comprising a bicarbonate or hydrogen carbonate ion (HCO_3^- ion). In some embodiments, a bicarbonate salt is a metal bicarbonate, such as sodium bicarbonate, calcium bicarbonate, potassium bicarbonate, and magnesium bicarbonate. In certain embodiments, a bicarbonate salt is potassium bicarbonate ($KHCO_3$). In some embodiments, a bicarbonate salt comprises a non-metal counter ion, such as ammonium bicarbonate. For example, a bicarbonate salt may be a tetraalkylammonium bicarbonate salt having the formula, R_4NHCO_3, wherein R is alkyl. In some embodiments, R may be lower alkyl, such as methyl, ethyl, propyl, butyl, pentyl, hexyl, or the like. In certain embodiments, the ammonium salt is Et_4NHCO_3. In other embodiments, the salt is Me_4NHCO_3, *i*-Pr_4NHCO_3, *n*-Pr_4NHCO_3, *n*-Bu_4NHCO_3, *i*-Bu_4NHCO_3, or *t*-Bu_4NHCO_3.

In some embodiments, a provided reagent is a carbonate salt. As used herein, the term "carbonate salt" refers to a salt comprising a carbonate ion (CO_3^{-2} ion). In some embodiments, a carbonate salt is a metal carbonate, such as sodium carbonate, calcium carbonate, potassium carbonate, and magnesium carbonate. In certain embodiments, a carbonate salt is potassium carbonate (K_2CO_3). In some embodiments, a carbonate salt comprises a non-metal counter ion, such as ammonium carbonate. For example, a carbonate salt may be a tetraalkylammonium carbonate salt having the formula, $(R_4N)_2CO_3$, wherein R is alkyl. In some embodiments, R may be a lower alkyl, such as methyl, ethyl, propyl, butyl, pentyl, hexyl, or the like. In certain embodiments, the ammonium salt is $(Et_4N)_2CO_3$. In other embodiments, the salt is $(Me_4N)_2CO_3$, $(i\text{-}Pr_4N)_2CO_3$, $(n\text{-}Pr_4N)_2CO_3$, $(n\text{-}Bu_4N)_2CO_3$, $(i\text{-}Bu_4N)_2CO_3$, or $(t\text{-}Bu_4N)_2CO_3$.

Without wishing to be bound by any particular theory, use of bicarbonate, carbonate, and/or ammonium salt(s) may aid in decreasing the rate of competing reactions such as hydrolysis during nucleophilic fluorination of an imaging agent precursor.

In some embodiments, a reagent is a salt comprising a cation that forms a weakly coordinating salt with a fluoride species. As used herein, a "cation that forms a weakly coordinating salt with a fluoride species" refers to a cation that renders a fluoride species reactive in the context of a fluorination reaction. For example, a cation may not strongly bind to the fluoride species, allowing the fluoride species to act as a nucleophile during a nucleophilic fluorination reaction. Those of ordinary skill the art would be able to select an appropriate cation that would be suitable as a weakly coordinating counter ion for a fluoride species. For example, a cation may be have a relatively large atomic radius and/or may be a weak Lewis base. In some cases, a cation may be selected to be lipophilic. In some cases, a cation may comprise one or more alkyl groups. Examples of weakly coordinating cations include cesium ions, ammonium ions, weakly coordinating salts of hexamethylpiperidindium, $S(NMe_2)_3$, $P(NMe_2)_4$, tetraaalkylphosphonium salts, tetraarylphosphonium salts, (*e.g.*, tetraphenylphosphonium), hexakis(dimethylamino)diphosphazenium, and tris(dimethylamino)sulfonium.

In some embodiments, a provided reagent is an ammonium salt, *i.e.*, a salt comprising a substituted or unsubstituted ammonium ion. In some embodiments, an ammonium ion is a weakly coordinating cation. In some embodiments, an ammonium salt has the formula, R_4NX, where each R can be the same or different and is alkyl, heteroalkyl, aryl, heteroaryl, or heterocyclic, each optionally substituted, and X is a negatively charged counter ion. In some cases, R is alkyl, heteroalkyl, aryl, heteroaryl, or heterocyclic, each optionally substituted. In

some embodiments, ammonium salt may include a range of negatively charged counter ions, including halides, carbonates, and bicarbonates. Examples of ammonium salts include, but are not limited to, ammonium bicarbonate salts, ammonium hydroxide salts, ammonium acetate salts, ammonium lactate salts, ammonium trifluoroacetate salts, ammonium methanesulfonate salts, ammonium p-toluenesulfonate salts, ammonium nitrate salts, ammonium halide salts (*e.g.*, ammonium iodide salts), and ammonium bisulfate salts.

In one set of embodiments, an ammonium salt is a tetraalkylammonium salt, such as a tetraalkylammonium bicarbonate salt. For example, an ammonium salt may have the formula, R_4NHCO_3, wherein each R is independently alkyl. In some cases, R is optionally substituted. In some embodiments, the alkyl group is a lower C_1-C_6 alkyl group. In some embodiments, an tetraalkylammonium salt is a basic tetraalkylammonium salt.

In some embodiments, a salt (*e.g.*, bicarbonate salt and/or ammonium salt) may be utilized in the reaction such that the molar ratio of the salt to the imaging agent precursor is less than or equal to about 2:1. In some cases, the molar ratio is less than or equal to about 2:1, less than or equal to about 1.9:1, less than or equal to about 1.8:1, less than or equal to about 1.7:1, less than or equal to about 1.6:1, less than or equal to about 1.5:1, less than or equal to about 1.4:1, or less than or equal to about 1.3:1, or less than or equal to about 1.25:1, or less than or equal to about 1.2:1, or less than or equal to about 1.1:1, or less than or equal to about 1:1, or less than or equal to about 0.75:1, or less than or equal to about 0.5:1, or less than or equal to about 0.25:1, or less than or equal to about 0.1:1, or less than or equal to about 0.05:1. In some cases, the ratio is greater than about 0.05:1, greater than about 0.01:1, or greater than about 0.25:1. In some embodiments, the molar ratio of salt additive to imaging agent precursor is between about 0.5:1 to about 1:1, or about 0.25:1 to about 1:1, or about 0.25:1 to about 0.75:1, about 1.49:1 to about 0.05:1, or between about 1.4:1 to about 0.25:1, or between about 0.25:1 and about 1.4:1, or between about 0.25:1 and about 1.25:1.

In some embodiments, a reagent is used in combination with a species capable of enhancing the reactivity of the fluoride species or otherwise facilitating conversion of the imaging agent precursor to the imaging agent. For example, a species may be a compound capable of chelating one or more ions (*e.g.*, metal ions) that may be present within the reaction mixture. Without wishing to be bound by theory, a species may be used to chelate a counter ion to a fluoride species, such as a potassium ion, thereby increasing the reactivity (*e.g.*, nucleophilicity) of the fluoride species. In certain embodiments, a reagent is used in combination with a multidentate ligand, such as a crown ether or a cryptand that is capable of chelating a metal ion. The multidentate ligand (*e.g.*, cryptand) may be selected based on the

metal ion to be chelated. A multidentate ligand may be, for example, 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]-hexacosane (*e.g.*, Kryptofix® 222). Other cryptands will be known to those of ordinary skill in the art. Some embodiments involve use of a carbonate salt in combination with 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]-hexacosane. In a specific embodiment, K_2CO_3 and/or $KHCO_3$ is used in combination with 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]-hexacosane.

In another set of embodiments, it may be advantageous to utilize the methods described herein in the absence of a cryptand. The term "cryptand" is given its ordinary meaning in the art and refers to a bi- or a polycyclic multidentate ligand for a cation. For example, inventive methods may be carried out using an ammonium salt, in the absence of a cryptand (*e.g.*, 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]-hexacosane). In some embodiments, cryptands may increase the pH of the reaction solution, which in the presence of another reagent (*e.g.,* carbonate salt) may adversely affect the yield and/or purity of the fluorination reaction. Accordingly, in certain embodiments, carrying out the fluorination reaction, in the absence of a cryptand, and optionally in the presence of another reagent (*e.g.*, ammonium and/or bicarbonate salt) may increase the yield and/or purity of the reaction.

In another set of embodiments, a method according to the present invention is performed in the absence of a carbonate salt.

Those of ordinary skill in the art will be able to select and/or determine an appropriate set of reaction conditions (*e.g.*, concentration, temperature, pressure, reaction time, solvents) suitable for use in a particular application. In some embodiments, an imaging agent may be further processed using one or more purification techniques, and may optionally be combined with additional components, such as a stabilizing agent.

In some embodiments, an imaging agent is formed as a salt (*e.g.*, a pharmaceutically acceptable salt). Pharmaceutically acceptable excipients and other aspects of pharmaceutically acceptable compositions are described herein.

Those of ordinary skill in the art would be able to select a source of a fluoride species suitable for use in the methods described herein. The term "fluoride species" as used herein refers to a fluoride atom or group of atoms comprising at least one fluoride atom, wherein the fluoride atom is capable of reacting with another compound (*e.g.*, an imaging agent precursor). In some embodiments, an isotopically-enriched ^{18}F species may be produced by the nuclear reaction $^{18}O(p,n)^{18}F$ from proton bombardment of $[^{18}O]H_2O$ in a cyclotron. In certain embodiments, a method may involve treating a solution of the ^{18}F species to remove any impurities, such as unreacted $[^{18}O]H_2O$. For example, a solution of the ^{18}F species may

be filtered through an anion exchange column, where the ^{18}F species is retained on the cationic resin matrix while the $[^{18}O]H_2O$ is eluted. The ^{18}F species is then removed by washing the anion exchange column with various mixtures of solvents and optional reagents (*e.g.*, salt), forming an ^{18}F-containing solution. In some embodiments, an anion exchange column is washed with an aqueous solution of a salt, such as K_2CO_3 or Et_4NHCO_3. In other embodiments, a column is washed (*e.g.*, with aqueous K_2CO_3), and the resulting solution diluted (*e.g.*, with MeCN) and/or concentrated (*e.g.*, to dryness using elevated temperature and/or reduced pressure). Anhydrous $[^{18}F]KF$ and/or $[^{18}F]Et_4NF$ may be obtained and reacted with a compound or a salt thereof.

In some embodiments, a ^{18}F-containing solution is combined with additional components prior to reaction with an imaging agent precursor. For example, one or more solvents may be added to dilute a ^{18}F-containing solution to a desired concentration. In certain embodiments, a ^{18}F-containing solution is diluted with acetonitrile (MeCN). In certain embodiments, a ^{18}F-containing solution is diluted with acetonitrile (MeCN) and *t*-BuOH.

In some embodiments, a ^{18}F-containing solution may be concentrated to dryness by exposure to elevated temperature and/or reduced pressure to form an anhydrous ^{18}F-containing solid. In some embodiments, a ^{18}F-containing solid may further comprise one or more reagents (*e.g.*, salts). The chemical composition of a ^{18}F-containing solid may depend on the number and kind of reagents used in preparation of the ^{18}F-containing solution. For example, a solution of potassium carbonate may be used to elute a ^{18}F species from the anion exchange column, thereby resulting in an ^{18}F-containing solid comprising $[^{18}F]KF$. In another example, a solution of tetraethylammonium bicarbonate is used to elute a ^{18}F species from the anion exchange column, thereby resulting in an ^{18}F-containing solid comprising $[^{18}F]Et_4NF$.

In some embodiments, a solution comprising a ^{18}F species is heated to a temperature ranging from room temperature to about 200 °C. For example, a solution comprising a $[^{18}F]$-fluoride may be heated to elevated temperatures to encourage evaporation of the solvent (*e.g.*, to about 110 °C). In some embodiments, a solution is heated to a temperature ranging from about 90-120 °C or from about 100-150 °C. In some embodiments, a solution is heated to about 75 °C, about 85 °C, about 95 °C, about 105 °C, about 115 °C, about 125 °C, or greater. In some embodiments, a solution is placed under a reduced pressure of about 100 mm Hg, about 125 mm Hg, about 150 mm Hg, about 175 mm Hg, about 200 mm Hg, about 225 mm Hg, about 250 mm Hg, about 275 mm Hg, about 300 mm Hg, about 325 mm Hg, about 350

mm Hg, about 375 mm Hg, about 400 mm Hg, or greater. In some embodiments, a solution is placed under a reduced pressure of about 100 mbar, about 125 mbar, about 150 mbar, about 175 mbar, about 200 mbar, about 225 mbar, about 250 mbar, about 275 mbar, about 280 mbar, about 300 mbar, about 325 mbar, about 350 mbar, about 375 mbar, about 400 mbar, about 450 mbar, about 500 mbar, or greater. Those of ordinary skill in the art would be able to select and/or determine conditions suitable for a particular process. In some embodiments, a solution is concentrated to dryness at about 150 mm Hg and about 115 °C. In some embodiments, a solution is concentrated to dryness at about 375 mm Hg and about 115 °C. In some embodiments, a solution is concentrated to dryness at about 400 mbar and about 110-150 °C. In some embodiments, a solution is concentrated to dryness at about 280 mbar and about 95-115 °C.

In certain embodiments, a fluoride species and/or a reagent, if present, is then contacted with an imaging agent precursor under conditions that result in conversion of the imaging agent precursor to the imaging agent product via nucleophilic fluorination. Those of ordinary skill in the art would be able to select conditions suitable for use in a particular reaction. For example, in certain embodiments, the ratio of fluoride species to imaging agent precursor may be selected to be about 1:10,000 or more, about 1:5000 or more, about 1:3000 or more, about 1:2000 or more, about 1:1000 or more, about 1:500 or more, about 1:100 or more, about 1:50 or more, about 1:10 or more, about 1:5 or more, or, in some cases, about 1:1 or more. In some embodiments, a fluoride species may be present at about 10 mol %, or about 5 mol%, or about 3 mol%, or about 2 mol%, or about 1 mol% or about 0.5 mol%, or about 0.1 mol%, or about 0.05 mol%, or about 0.01 mol% relative to the amount of imaging agent precursor. In some embodiments, a fluoride species is isotopically enriched with ^{18}F. For example, in some embodiments, the ratio of ^{18}F species to imaging agent precursor may be selected to be about 1:1,000,000 or more, or about 1:500,000 or more, or about 1:250,000 or more, or about 1:100,000 or more, or about 1:50,000 or more, or about 1:25,000 or more, or about 1:10,000 or more, about 1:5000 or more, about 1:3000 or more, about 1:2000 or more, about 1:1000 or more, about 1:500 or more, about 1:100 or more, about 1:50 or more, about 1:10 or more, about 1:5 or more, or, in some cases, about 1:1 or more.

In some embodiments, a nucleophilic fluorination reaction is carried out in the presence of one or more solvents, for example, an organic solvent, a non-organic solvent (*e.g.*, an aqueous solvent), or a combination thereof. In some embodiments, the solvent is a polar solvent or a non-polar solvent. In some embodiments, the solvent is an aqueous solution, such as water. In some embodiments, the solvent comprises at least about 0.001%

water, at least about 0.01% water, at least about 0.1% water, at least about 1% water, at least about 5%, at least about 10%, at least about 20% water, at least about 30% water, at least about 40% water, at least about 50% water, or greater. In some embodiments, the solvent may comprise between about 0.1% and about 100% water, about 1% to about 90%, about 1% to about 70%, about 1% to about 50%, or about 10% to about 50%. In some embodiments, the solvent comprises no more than about 10% water, about 5% water, about 4% water, about 3% water, about 2% water, about 1% water, or about 0.5% water. In some embodiments, the solvent comprises between about 0.01% water and about 5% water, or between about 0.01% water and about 2% water, or between about 0.1% water and about 0.2% water.

Other examples of solvents useful in the methods include, but are not limited to, non-halogenated hydrocarbon solvents (*e.g.*, pentane, hexane, heptane, cyclohexane), halogenated hydrocarbon solvents (*e.g.*, dichloromethane, chloroform, fluorobenzene, trifluoromethylbenzene), aromatic hydrocarbon solvents (*e.g.*, toluene, benzene, xylene), ester solvents (*e.g.*, ethyl acetate), ether solvents (*e.g.*, tetrahydrofuran, dioxane, diethyl ether, dimethoxyethane), and alcohol solvents (*e.g.*, ethanol, methanol, propanol, isopropanol, *tert*-butanol). Other non-limiting examples of solvents include acetone, acetic acid, formic acid, dimethyl sulfoxide, dimethyl formamide, acetonitrile, *p*-cresol, glycol, petroleum ether, carbon tetrachloride, hexamethyl-phosphoric triamide, triethylamine, picoline, and pyridine. In some embodiments, a provided reaction is carried out in a polar solvent, such as acetonitrile. In some embodiments, a solvent may be selected so as to reduce and/or minimize the formation of side products. In certain embodiments, a fluorination reaction is carried out in MeCN as solvent. In certain embodiments, a fluorination reaction is carried out in *t*-BuOH as solvent. In certain embodiments, a fluorination reaction is carried out in a mixture of MeCN and *t*-BuOH as solvent. In certain embodiments, a fluorination reaction is carried out in DMF as solvent. In certain embodiments, a fluorination reaction is carried out in DMSO as solvent. In certain embodiments, a fluorination reaction is carried out in THF as solvent.

In certain embodiments, an anhydrous ^{18}F-containing solid, optionally comprising a reagent, may be contacted with a solution of an imaging agent precursor (*e.g.*, a tosylate precursor), and the resulting solution is heated to an elevated temperature for a select period of time. A solution may be, for example, an acetonitrile solution. In other embodiments, a solution of an ^{18}F species and reagent, if present, is contacted with a solid imaging agent precursor or a solution of an imaging agent precursor.

Some embodiments involve contacting an imaging agent precursor with a fluoride species in a solution having a pH below about 13, below about 12, or below about 11. In some cases, a solution has a pH between about 8 and about 9, or between about 8 and about 10, or between about 7 and about 8. In certain embodiments, a pH range for the fluorination reaction is greater than about 6, or greater than about 7, or between and including 7-13, between and including 6-12, between and including 7-12, between and including 8-12, between and including 9-12, and between and including 10-12.

In some cases, a solution comprising a ^{18}F species, imaging agent precursor, and, optionally, a reagent, is heated to an elevated temperature for a period of time. For example, a solution may be heated to about 50 °C, about 60 °C, about 70 °C, about 80 °C, about 90 °C, about 100 °C, about 110 °C, about 120 °C, about 150 °C, about 170 °C, about 200 °C, about 225 °C, about 250 °C, or greater, for a period of about 5 minutes or less, about 10 minutes or less, about 20 minutes or less, about 30 minutes or less. It should be understood that other temperatures and reaction times may be used. In some embodiments, upon completion of the reaction, the reaction mixture is cooled (*e.g.*, to room temperature) and optionally diluted with a solvent, such as water, or mixtures of solvents, such as water/acetonitrile. In some embodiments, a reaction mixture is heated to elevated temperatures to encourage evaporation of the solvent (*e.g.*, to about 95 °C). In some embodiments, a solution is heated to a temperature ranging from about 55-125 °C. In some cases, a solution is heated to about 65 °C, about 75 °C, about 85 °C, about 95 °C, about 105 °C, about 115 °C, or greater. In some cases, a solution is placed under a reduced pressure of about 100 mm Hg, about 125 mm Hg, about 150 mm Hg, about 175 mm Hg, about 200 mm Hg, about 225 mm Hg, about 250 mm Hg, about 275 mm Hg, about 300 mm Hg, about 325 mm Hg, about 350 mm Hg, about 375 mm Hg, about 400 mm Hg, or greater. In some cases, a solution is placed under a reduced pressure of about 100 mbar, about 125 mbar, about 150 mbar, about 175 mbar, about 200 mbar, about 225 mbar, about 250 mbar, about 275 mbar, about 280 mbar, about 300 mbar, about 325 mbar, about 350 mbar, about 375 mbar, about 400 mbar, about 450 mbar, about 500 mbar, or greater. Those of ordinary skill in the art would be able to select and/or determine conditions suitable for a particular process. In some embodiments, a solution is concentrated to dryness under a flow of inert gas at about 95 °C.

In some embodiments, upon completion of a fluorination reaction, the resulting imaging agent is optionally subjected to one or more purification steps. In some embodiments, an imaging agent may be reconstituted in a solvent prior to purification (*e.g.*, by chromatography such as HPLC). In some cases, an imaging agent is dissolved in water,

acetonitrile, or combinations thereof. In some embodiments, following formation of a solution comprising an imaging agent and a solvent and prior to purification (*e.g.*, by HPLC), the solution is heated. In a particular embodiment, an imaging agent is reconstituted in a water/acetonitrile mixture and heated (*e.g.,* to a temperature of about 90-100 ºC) for about 1 minute, about 3 minutes, about 5 minutes, about 10 minutes, about 20 minutes, about 30 minutes, or more. Following heating of the mixture, the solution may be optionally cooled prior to purification.

C. Purification and Formulation

In some cases, the synthesis, purification, and/or formulation of an imaging agent is performed using an automated reaction system optionally comprising a cassette, wherein the cassette comprises a synthesis module, a purification module, and/or a formulation module. Automated reaction systems and cassettes are described herein.

Purification and isolation may be performed using methods known to those skilled in the art, including separation techniques like chromatography, or combinations of various separation techniques known in the art, for example, extractions, distillation, and crystallization. In one embodiment, high performance liquid chromatography (HPLC) is used with a solvent, or mixture of solvents, as the eluent, to recover the product. In some cases, the eluent includes a mixture of water and acetonitrile, such as a 20:80 water:acetonitrile mixture. The content of water in the eluent may vary from, for example, about 1% to about 30%. In some cases, HPLC purification may be performed using a C-18 column. The product may be analyzed (*e.g.*, by HPLC) to determine yield (*e.g.*, radiochemical yield) and/or radiochemical purity. The radiochemical purity may be greater than about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 97%, about 98%, about 99%, or more. The percent yield of a product may be greater than 10%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than about 60%, greater than about 70%, greater than about 75%, greater than about 80%, greater than about 85%, greater than about 90%, greater than about 92%, greater than about 95%, greater than about 96%, greater than about 97%, greater than about 98%, greater than about 99%, or greater. In some embodiments, the radiochemical yield ranges from 15-50%.

The product may be further processed using additional purification techniques, such as filtration. In some cases, the imaging agent is purified using HPLC, to produce a solution of HPLC mobile phase and the imaging agent. The HPLC mobile phase may be subsequently exchanged for a solution of ascorbic acid or a salt thereof, and ethanol solution, by filtration

through a C-18 resin (*e.g.*, C18 Sep-Pak® cartridge). In some embodiments, the solution of the HPLC mobile phase and the imaging agent is filtered through a C-18 resin, where the imaging agent remains on the resin and the other components, such as acetonitrile and/or other solvents or components, are removed via elution. The C-18 resin may be further washed with a solution of ascorbic acid or a salt thereof, and the filtrate discarded. To recover the purified imaging agent, the C-18 resin is washed with a solvent, such as ethanol, and the resulting solution is optionally further diluted with an ascorbic acid solution or a salt thereof, as described herein.

Optionally, the recovered product is combined with one or more stabilizing agents, such as ascorbic acid or a salt thereof. For example, a solution comprising the purified imaging agent may be further diluted with a solution of ascorbic acid or a salt thereof. As described herein, a formulation may be prepared via an automated reaction system comprising a cassette.

In some cases, a solution comprising the imaging agent product may be sterile filtered (*e.g.*, using a 13 mm diameter, Millipore, Millex PVDF 0.22 μm sterilizing filter) into a sterile product vial. The sterile product vial may be a commercially available, pre-sterilized unit that is not opened during the production process, as any imaging agents (or other components) may be aseptically inserted through the septum prior to use. Those of ordinary skill in the art would be able to select suitable vials and production components, including commercially available, pre-sterilized units comprising a 0.22 μm pore size membrane venting filter and quality control sampling syringes.

Following aseptic filtration, individual doses may be filled in syringes, labeled, and shipped to a clinical site. Dosing administration techniques, kits, cassettes, methods and systems (*e.g.*, automated reaction systems) for synthesis of the imaging agent, and testing procedures are described herein. In some embodiments, the product is dispensed into a 3 or 5 mL syringe and labeled for distribution. Labels may be prepared at a radiopharmacy and applied to a syringe shield and shipping container. Additional labels may be provided in the shipping container for inclusion in clinical site records.

Uses of Imaging Agents

In another aspect, methods of imaging using the imaging agents described herein are provided. Such methods of imaging a subject include administering a composition or formulation that includes an imaging agent as described herein to the subject by injection, infusion, or any other known method of administration, and imaging a region of interest of

the subject. Regions of interest may include, but are not limited to, the heart, a portion of the heart, the cardiovascular system, cardiac vessels, blood vessels (*e.g.*, arteries and/or veins), brain, pancreas, adrenal glands, other organs, and tumors.

In some embodiments, the methods of imaging comprise (a) administering to a subject a composition that includes a compound as described herein comprising at least one imaging moiety (*e.g.*, an imaging agent), and (b) acquiring at least one image of at least a portion of the subject. In some cases, the step of acquiring employs positron emission tomography (PET) for visualizing the distribution of the imaging agent within at least a portion of the subject. As will be understood by those of ordinary skill in the art, imaging using methods of this disclosure may include full body imaging of a subject, or imaging of a specific body region, organ, or tissue of the subject that is of interest. For example, if a subject is known to have, or is suspected of having myocardial ischemia, methods of this disclosure may be used to image the heart of the subject. In some embodiments, imaging may be limited to the heart or may include the heart and its associated vasculature.

In some embodiments of the invention, methods of diagnosing or assisting in diagnosing a disease or condition, assessing efficacy of treatment of a disease or condition, or imaging in a subject with a known or suspected cardiovascular disease or condition are provided. A cardiovascular disease can be any disease of the heart or other organ or tissue nourished by the vascular system. The vascular system includes coronary arteries, and all peripheral arteries supplying nourishment to the peripheral vascular system and the brain, as well as veins, arterioles, venules, and capillaries. Examples of cardiovascular diseases include diseases of the heart, such as coronary artery disease, myocardial infarction, myocardial ischemia, angina pectoris, congestive heart failure, cardiomyopathy (congenital or acquired), arrhythmia, or valvular heart disease. In some embodiments, the methods disclosed herein are useful for monitoring and measuring coronary artery disease and/or myocardial perfusion. For example, a method described herein can determine the presence or absence of coronary artery disease and/or the presence or absence of myocardial infarct. Conditions of the heart may include damage, not brought on by disease but resulting from injury – *e.g.*, traumatic injury, surgical injury. In some cases, methods of the invention may include determining a parameter of, or the presence or absence of, myocardial ischemia, rest (R) and/or stress (S) myocardial blood flows (MBFs), coronary flow reserve (CFR), coronary artery disease (CAD), left ventricular ejection fraction (LVEF), end-systolic volume (ESV), end-diastolic volume (EDV), and the like.

Without wishing to be bound by any particular theory, an imaging agent as described herein is thought to bind to the mitochondrial complex I of the electron transport chain with high affinity. In some embodiments, the imaging agent shows selective uptake to the heart due to the high density of mitochondria in the myocardium. Regions of interest may include, but are not limited to, the heart, cardiovascular system, cardiac vessels, blood vessels (*e.g.*, arteries, veins) brain, and other organs. A parameter of interest, such as blood flow, cardiac wall motion, *etc.*, can be imaged and detected using methods and/or systems of the invention. In some aspects of the invention, methods for evaluating perfusion, including myocardial perfusion, are provided.

In some embodiments, a method of imaging a portion of a subject comprises administering to the subject a compound (*e.g.*, an imaging agent) as described herein and acquiring at least one image of a portion of the subject. In some embodiments, a method of imaging a portion of a subject comprises administering to a subject a compound as described herein (*e.g.*, an imaging agent); detecting radiation emitted by the compound; and forming an image therefrom. In some embodiments, an effective amount of the compound is administered to the subject.

In some cases, a subject to whom a method of the invention is applied, may have signs or symptoms suggestive of myocardial ischemia or myocardial infarction. In some cases methods of the invention can be used to identify early or pre-disease conditions that indicate that a subject is at increased risk of a disease. In some instances, methods of the invention can be used to determine a subject's risk of future cardiac events such as myocardial infarction or cardiac death. Imaging methods of the invention can be used to detect myocardial ischemia in subjects already diagnosed as having a myocardial ischemia disorder or condition, or in subjects that have no history or diagnosis of such a condition. In other instances, methods of the invention can be used to obtain measurements that provide a diagnosis or aid in providing a diagnosis of a myocardial ischemia disorder or condition. In some instances, a subject may already be undergoing drug therapy for a disorder or condition associated with myocardial ischemia, while in other instances a subject may not be undergoing therapy for myocardial ischemia. In some embodiments, methods of the invention can be used to assess efficacy of a treatment for a disease or condition. For example, the heart can be visualized using imaging agents of the invention before, during, and/or after treatment of a condition affecting the heart of a subject. Such visualization may be used to assess a disease or condition and aid in the selection of a treatment regimen, *e.g.*, therapy, surgery, or medications, for the subject.

A PET imaging agent may have a high first-pass extraction fraction and can track regional myocardial blood flow over a wide range. These features may permit detection of milder decreases in coronary flow reserve and accurate estimation of absolute myocardial blood flow (MBF). PET imaging agents of the invention provide these and other features and are also available as a unit dose from regional PET radiopharmacies, obviating the need for on-site cyclotrons or costly Rb-82 generators.

In some embodiments of the invention, a compound as described herein (*e.g.*, comprising at least one imaging moiety) is used as an imaging agent in combination with positron emission tomography (PET) or with other imaging methods including, but not limited to SPECT imaging. In some embodiments of the invention, a compound as described herein comprising at least one imaging moiety is administered to a subject and imaged in the subject using PET. As will be known to those of ordinary skill in the art, PET is a non-invasive technique that allows serial images and measurements to be obtained in a single subject over a time period. PET imaging used in methods of the invention may be carried out using known systems, methods, and/or devices. In some embodiments of the invention, PET imaging is conducted using a cardiac imaging system. A cardiac imaging system may include PET imaging functionality and a control unit configured to drive the imaging functionality to perform a PET imaging procedure on a portion of the subject before, during, and/or after administration of the imaging agent to the subject. In some cases, the control unit is configured to drive the imaging functionality to perform a PET imaging procedure. The control unit may comprise a computer system and/or software. In such a case, the computer system may be programmed or configured to execute the required methods for acquiring and/or analyzing the images. Further, the system may include a data storage device that is readable by a machine, embodying a set of instructions executable by the machine to perform the required methods of acquiring and/or analyzing the images.

The useful dosage of the imaging agent to be administered and the particular mode of administration will vary depending upon such factors as age, weight, and particular region to be imaged, as well as the particular imaging agent used, the diagnostic use contemplated, and the form of the formulation, for example, suspension, emulsion, microsphere, liposome, or the like, as described herein, and as will be readily apparent to those skilled in the art.

In some embodiments, an imaging agent is administered at a low dosage and the dosage increased until the desirable diagnostic effect is achieved. In one embodiment, the above-described imaging agents may be administered by intravenous injection, usually in a saline solution, at a dose of about 0.1 to about 100 mCi (and all combinations and

subcombinations of dosage ranges and specific dosages therein), or between about 0.5 and about 50 mCi, or between about 0.1 mCi and about 30 mCi, or between 0.5 mCi and about 20 mCi. In some embodiments, the dosage range is per 70 kg body weight. For use as nuclear medicine imaging agents, the imaging agent dosages, administered by intravenous injection, may range from about 0.1 pmol/kg to about 1000 pmol/kg (and all combinations and subcombinations of dosage ranges and specific dosages therein), and in some embodiments, less than 150 pmol/kg.

Imaging systems and components thereof will be known to those of ordinary skill in the art. Many imaging systems and components (*e.g.*, cameras, software for analyzing the images, *etc.*) are known and commercially available, for example, a Siemens Biograph-64 scanner. Any technique, software, or equipment that reduces or eliminates motion in static perfusion images may be used in methods of the invention, because spatial blurring and artifacts can be caused by patient motion during image acquisition. In some embodiments of the invention, images may be acquired in list mode, and may be static, dynamic, or gated images. An appropriate period of time for acquiring images can be determined by one of ordinary skill in the art, and may vary depending on the cardiac imaging system, the imaging agent (*e.g.*, amount administered, composition of the imaging agent, subject parameters, area of interest). As used herein a "period of acquiring images" or an "image acquisition period" may be a period of obtaining a single continuous image, or may be a period during which one or more individual discrete images are obtained. Thus, a period of image acquisition can be a period during which one or more images of one or more regions of a subject are acquired.

In some embodiments of the invention, a period of image acquisition after administration of an imaging agent of the invention to a subject may be between about 30 seconds and about 60 minutes, between about 1 minute and about 30 minutes, between about 5 minutes and about 20 minutes, or at least about 1 minute, about 3 minutes, about 5 minutes, about 6 minutes, about 7 minutes, about 8 minutes, about 9 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, 4 about 5 minutes, about 60 minutes, or greater. For example, in a rest/stress imaging protocol there would be at least two periods of image acquisition with at least one corresponding to the rest segment and at least one corresponding to the stress segment. In some embodiments, imaging may be continuous over the imaging period of time, or images may be acquired at intervals such as in periodic or gated imaging.

In some aspects of the invention, gated acquisition is used to acquire images from a subject to whom an imaging agent has been administered. Gated imaging can be used in

various aspects of the invention, and for example, may provide images of a beating heart of a subject and may be used to attain a functional evaluation of how well a heart is beating. Gated imaging can be performed by acquiring separate images from the subject at specific intervals during a period of image acquisition. A non-limiting example of gated imaging is a case when a period of image acquisition is about 10 minutes long, and images are acquired at repeated intervals during the 10 minute period. The frequency of acquisition of images during the period can be set by the operator, for example, the frequency can be at least every about 1 msec, about 5 msec, about 10 msec, about 20 msec, about 50 msec, about 100 msec, about 125 msec, about 250 msec, or more. The length of the interval is set by the operator to be triggered by an event, such as a cardiac R wave, with the length of the interval is defined by the number of time bins desired per R wave to R wave interval. Those of skill in the art will be familiar with the concept and methods of gated image acquisition and can use known methods to obtain gated images using an imaging agent.

Image acquisition in gated imaging can be triggered at specific intervals, for example, image acquisition can be triggered using an EKG of the heart. In a non-limiting example, an R wave-gated scanner may trigger acquisition of an image and the mean length of time between one R wave of a heart and the next can be stored. The number of images to collect can then be determined. For example, a first image can be acquired at 125 msec, a second image can be acquired at 250 msec, a third image can be acquired at 375 msec, *etc.* – thus images in that R interval may be acquired at 125 msec intervals. When the next R interval begins, the collection of images resets and image data is then acquired into the "first" image at 125 msec from that R interval start time, and then into the "second" image collected 250 msec from that R interval start time, *etc.* Thus, within each R interval image acquisition is added into the initial image of the series and incremented into successive images in the series so that a sequence of images can be collected at a desired frequency with the zero time being reset at the start of each R interval. Acquired gated images can be used to provide an image of heart motion and can provide information on heart wall thickness, whether or not one or more sections of the heart are not moving or beating (*e.g.,* a wall motion defect). Use of gated imaging may provide data with which to judge perfusion of the heart, such as ejection fraction, and to visualize and identify reduced, absent, paradoxical or asynchronous wall motion. Use of gated imaging may also provide data with which to improve assessment of myocardial perfusion, judge cardiac function and to visualize and identify asynchronous wall motion.

In some cases, PET imaging may be used to assess myocardial viability via the ability of this technique to demonstrate metabolic consequences of myocardial ischemia. Using PET imaging, myocardial segments that are likely to improve after revascularization can be identified. In some cases, PET imaging may be used in the detection of coronary artery disease and can also serve as an alternative test for subjects who cannot undergo treadmill exercise stress testing. In some embodiments, a stress test method (*e.g.*, pharmacological stress, exercise stress) may be employed with PET using methods of the invention to qualitatively or quantitatively assess one or more parameters of cardiac function during infusion of the imaging agent. Agents for, and methods of, inducing stress, for example, using exercise or pharmacological stress are well known in the art. Suitable induction of stress can be carried out using established, known agents and methods. Functions usefully measured using methods of the invention include, but are not limited to, in various embodiments, imaging of myocardial perfusion, imaging, or measurement of ventricular function, and measuring coronary blood flow velocity.

In some cases, methods for imaging the heart of a subject may include administering a first dose of an imaging agent to the subject while the subject is at rest, acquiring at least one first image of the heart, followed by subjecting the subject to stress (*e.g.*, exercise stress or pharmacological stress) and administering a second dose of the imaging agent to the subject during the period of stress, and acquiring at least one other image of the heart.

In some embodiments, the dose of the imaging agent to be used during exercise-induced stress in a rest/stress protocol is greater than that necessary for pharmacologically-induced stress with the ratio of exercise-induced stress dose to pharmacologically-induced stress dose being greater than or equal to about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, or greater. With respect to pharmacological stress, in some embodiments of the invention that involve rest/stress imaging methods, the dose of the imaging agent administered for imaging during the pharmacological stress is a minimum of two times the dose of the imaging agent administered for imaging at rest. With respect to exercise stress, in some embodiments of the invention that involve rest/stress imaging methods, the dose of the imaging agent administered for imaging during the exercise-induced stress is a minimum of three times the dose of the imaging agent administered for imaging at rest. In some embodiments of the invention, for imaging first at rest followed by imaging with stress, the dose of the imaging agent administered at rest will be lower than the dose of the imaging agent administered at stress. In some cases, imaging methods of the invention may be completed in a single day (*e.g.*, less than about 24 hours, less than about 12 hours,

less than about 6 hours, less than about 4 hours, less than about 2 hours, less than about 1 hour), as described herein. In other cases, methods may be completed in longer periods of time, *e.g.,* over more than about 24 hours, about 36 hours, or about 48 hours.

For stress testing in methods, a subject may be subjected to stress using procedures known to those of ordinary skill in the art. In some cases, the subject may be subjected to stress using procedures including exercise stress and/or pharmacological stress. Pharmacological stress may be induced by administering to the subject a pharmacological agent such as a vasodilator. Examples of useful pharmacological stress agents, include, but are not limited to adenosine, dobutamine, dipyridamole, regadenoson, binodeneson, apadeneson, and other adenosine A2a receptor agonists. Dosing and administration of pharmacological stress inducing agents, such as vasodilators, are well known in the art and can be determined for use in conjunction with methods and systems of the invention. Exercise stress may be induced using a treadmill, exercise bicycle, hand crank, or other equipment suitable to increase a subject's heart rate through increased exertion.

An imaging agent may be provided in any suitable form, for example, in a pharmaceutically acceptable form. In some cases, an imaging agent is included in a pharmaceutically acceptable composition. In some embodiments, an imaging agent is provided as a composition comprising ethanol, sodium ascorbate, and water. In some cases, the composition comprises less than 20 weight% ethanol, less than 15 weight% ethanol, less than 10 weight% ethanol, less than 8 weight% ethanol, less than 6 weight% ethanol, less than 5 weight% ethanol, less than 4 weight% ethanol, less than 3 weight% ethanol, or less ethanol. In some cases, the composition comprises less than 100 mg/mL, less than 75 mg/mL, less than 60 mg/mL, less than 50 mg/mL, less than 40 mg/mL, less than 30 mg/mL, or less sodium ascorbate in water. In some embodiments, the composition comprises about 20 mg/mL, about 30 mg/mL, about 40 mg/mL, about 50 mg/mL, about 60 mg/mL, about 70 mg/mL, about 80 mg/mL, about 90 mg/mL, about 100 mg/mL, about 110 mg/mL, about 120 mg/mL, about 130 mg/mL, about 140 mg/mL, about 150 mg/mL, about 160 mg/mL, about 170 mg/mL, about 180 mg/mL, about 190 mg/mL, or about 200 mg/mL. In a particular non-limiting embodiment, an imaging agent is provided as a solution in water comprising less than 4% ethanol and less than about 50 mg/mL sodium ascorbate in water.

In some embodiments, the pH of the composition is between about 1.5 and about 8, or between about 1.5 and about 7, or between about 1.5 and 6, or between about 1.5 and 5, or between 1.5 and 4, or between 2 and 7, or between 3 and 7, or between 4 and 7, or between 5 and 7, or between 5 and 6, or between 5.5 and 6. In some embodiments, the pH is about 5.8.

In some embodiments, the pH of the composition is about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, or about 3.5. In some embodiments, the pH of the composition is between about 1.5 and about 1.6. In some embodiments, the pH of the composition is between about 1.5 and about 1.9. In some embodiments, the pH of the composition is between about 2.1 and about 3.5. In some embodiements, the pH of the composition is between about 2.4 and about 3.5. In some embodiments, the pH of the composition is between about 2.5 and about 3.5. In some embodiments, the pH of the composition is between 2.1 and about 2.3.

An imaging agent may be provided as composition for injection, which may be prepared in an injection syringe. For example, the imaging agent may be prepared by a radiopharmacy (*e.g.*, using the methods described herein) and/or a PET manufacturing center and provided to a health-care professional for administration. In some aspects of the invention, the imaging agent is provided, for example, in a syringe or other container, with ≤ 50 mg/mL sodium ascorbate in water, ≤ 4 weight% ethanol, and about 1 to 14 mCi of the imaging agent.

In some embodiments, a dose of an imaging agent may be diluted with saline (*e.g.*, as described herein), if needed to obtain a practical dose volume. For example, if the activity concentration of an imaging agent is so high that only 0.1 mL is need for an appropriate dose for a subject, the solution can be diluted, *e.g.*, with sterile saline, so the syringe contains 0.5 ml to 4 or more mL of an imaging agent solution for administration. In some embodiments of the invention, an injection volume for an imaging agent is between 0.5 and 5 mL, 1 and 4 mL, 2 and 3 mL, at least 0.5 mL, 1 mL, 2 mL, 3 mL, 4 mL, 5 mL, 6 mL, 7 mL, 8 mL, 9 mL, 10 mL, or more. Those of skill in the art will recognize how to dilute an imaging agent to produce a sufficient dose volume for administration. In some embodiments, an imaging agent is provided in a container such as a vial, bottle, or syringe, and may be transferred, as necessary, into a suitable container, such as a syringe for administration.

Syringes that include an adsorbent plunger tip may result in 10 to 25% of an imaging agent activity remaining in the syringe after injection. Syringes lacking an adsorbent plunger tip may be used, such as a 3 or 5 mL NORM-JECT (Henke Sass Wolf, Dudley, MA) or other equivalent syringe lacking an adsorbent plunger tip. Reduction of adsorption in the syringe can increase the amount of an imaging agent that is transferred from the syringe and administered to the subject in methods of the invention. A syringe used in methods of the invention may comprise an imaging agent, and be a non-adsorbing, or reduced adsorbent

syringe. In some embodiments a non-adsorbent or reduced-adsorbent syringe is a syringe that has been coated or treated to reduce adsorption of the imaging agent. In some embodiments, a non-adsorbent or reduced-adsorbent syringe is a syringe that lacks an adsorbent plunger tip. In some embodiments, a syringe used in conjunction with the invention 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 it contains. In certain aspects of the invention, a syringe that contains an imaging agent does not include a rubber or latex tip on the plunger. In some cases a syringe used in methods of the invention, includes 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 an imaging agent that the syringe contains. A syringe of the invention may also comprise sodium ascorbate, ethanol, and water, and certain embodiments of the invention include a syringe containing an imaging agent in a solution comprising less than 4 weight% ethanol and less than about 50 mg/mL sodium ascorbate in water. A syringe of the invention may be a syringe that is latex free, rubber free, and/or lubricant free. A syringe of the invention may contain an imaging agent in an amount between about 1.5 and about 14 mCi. A syringe of the invention may contain about 20 mCi or less of an imaging agent.

Components of a composition comprising an imaging agent may be selected depending on the mode of administration to the subject. Various modes of administration that effectively deliver imaging agents of the invention to a desired tissue, cell, organ, or bodily fluid will be known to one of ordinary skill in the art. In some embodiments, the imaging agent is administered intravenously (*e.g.*, intravenous bolus injection) using methods known to those of ordinary skill in the art. As used herein, a dose that is "administered to a subject" means an amount of the imaging agent that enters the body of the subject. In some embodiments, due to factors such as partial retention of an imaging agent in a syringe, tubing, needles, catheter, or other equipment used to administer the imaging agent to a subject, the amount of an imaging agent that is measured or determined to be in the a syringe or other equipment prepared for administration may be more than the amount in the dose that is administered to the subject. In some embodiments, an injection of an imaging agent is followed by a flushing injection of normal saline, into the subject, using the same tubing, needle, port, *etc.*, used for administration of an imaging agent. Flushing may be performed immediately following administration of an imaging agent, or up to 1 min, 2 min, 3 min, 5 min, or more, after the administration. The volume of saline or other agent for flushing may be up to 5 mL, 6 mL, 7 mL, 8 mL, 9 mL, 10 mL, 15 mL, 20 mL, or more. As will be

understood by those of ordinary skill in the art, in embodiments where an imaging agent is administered using a syringe or other container, the true amount of the imaging agent administered to the subject may be corrected for any imaging agent that remains in the container. For example, the amount of radioactivity remaining in the container, and tubing and needle or delivery instrument that carried the imaging agent from the container and into the subject can be determined after the imaging agent has been administered to the subject and the difference between the starting amount of radioactivity and the amount remaining after administration indicates the amount that was delivered into the subject. In some cases, the container or injection device (*e.g.*, catheter, syringe) may be rinsed with a solution (*e.g.*, saline solution) following administration of the imaging agent.

In some embodiments of the invention, the total amount of an imaging agent administered to a subject over a given period of time, *e.g.*, in one session, is less than or equal to about 50 mCi, less than or equal to 40 mCi, less than or equal to 30 mCi, less than or equal to 20 mCi, less than or equal to 18 mCi, less than or equal to 16 mCi, less than or equal to 15 mCi, less than or equal to 14 mCi, less than or equal to 13 mCi, less than or equal to 12 mCi, less than or equal to 10 mCi, less than or equal to 8 mCi, less than or equal to 6 mCi, less than or equal to 4 mCi, less than or equal to 2 mCi, less than or equal to 1 mCi, less than or equal to 0.5 mCi. The total amount administered may be determined based on a single dose or multiple doses administered to a subject within a given time period of up to 1 minute, 10 minutes, 30 minutes, 1 hour, 2 hours, 6 hours, 12 hours, 24 hours, 48 hours, or more.

Based on radiation dose studies, the desirable maximum dose administered to a subject may be based on determining the amount of an imaging agent which limits the radiation dose to about 5 rem to the critical organ and/or about 1 rem effective dose (ED) or lower, as will be understood by those of ordinary skill in the art. In some embodiments, the desirable maximum dose or total amount of an imaging agent administered is less than or equal to about 25 mCi, or less than or equal to about 14 mCi over a period of time of up to 30 min, 1 hour, 2 hours, 6 hours, 12 hours, 24 hours, 48 hours, or more. In some embodiments, the maximum dose of an imaging agent administered to a subject may be less than 3.5 μg per 50 kg of body weight per day. That is, in some embodiments of the invention, the maximum dose of an imaging agent administered to a subject may be less than about 0.07 μg of an imaging agent per kg of body weight per day.

Exemplary Cassettes and Reaction Systems

In some embodiments, systems, methods, kits, and cassettes are provided for the synthesis of an imaging agent as described herein. In some embodiments, an imaging agent may be prepared using an automated reaction system comprising a disposable or single use cassette. The cassette may comprise all the non-radioactive reagents, solvents, tubing, valves, reaction vessels, and other apparatus and/or components necessary to carry out the preparation of a given batch of imaging agent. The cassette allows the reaction system to have the flexibility to make a variety of different imaging agents with minimal risk of cross-contamination, by simply changing the cassette. By the term "cassette" is meant a piece of apparatus designed to fit removably and interchangeably onto automated reaction systems, in such a way that mechanical movement of moving parts of the automated reaction system controls the operation of the cassette from outside the cassette, *i.e.*, externally. In certain embodiments, a cassette comprises a linear arrangement of valves, each linked to a port where various reagents, cartridges, syringes, and/or vials can be attached, by either needle puncture of a septum-sealed vial, or by gas-tight, marrying joints. Each valve may have a male-female joint which interfaces with a corresponding moving arm of the automated synthesizer. External rotation of the arm can control the opening or closing of the valve when the cassette is attached to the automated reaction system. Additional moving parts of the automated reaction system are designed to clip onto syringe plunger tips, and thus raise or depress syringe barrels. An automated reaction system may further include a controller and one or more controllable valves in electrical communication with the controller. An automated reaction system may also include additional vessels, valves, sensors, heaters, pressurizing elements, *etc.*, in electrical communication with the controller. An automated reaction system may be operated by a controller using suitable software for control of valve openings and closings, heating, cooling, pressure levels, fluid movement, flow rate, *etc.* The automated reaction system may optionally include a computer operating system, software, controls, *etc.*, or other component. In addition, the automated reaction system may comprise a mount for the cassette. In some embodiments, a cassette of the present invention comprises one or more syringes for introducing one or more reagents. In addition, in some embodiments, improved methods employed in combination with cassettes and automated reactions systems are provided. Use of the cassettes and/or improved methods can result in improved liquid handling efficiency, resulting in increased imaging agent recovery (*e.g.*, via reduced retention of the imaging agent in the cassette), as described herein.

Examples of automated reaction systems (*e.g.*, a nucleophilic reaction system),

include, but are not limited to, the Explora GN or RN synthesis system (Siemens Medical Solutions USA, Inc.), Tracerlab-MX synthesis system (GE Healthcare), Eckert & Zeigler Modular-Lab Synthesis system, NEPTIS® synthesis system, *etc.*, which are commonly available at PET manufacturing facilities.

The automated reaction systems may carry out numerous steps, as outlined in Figure 16, including, but not limited to, preparation of the ^{18}F fluoride species, providing an imaging agent precursor, optionally in a solution (*e.g.*, an imaging agent precursor in acetonitrile), a radiolabeling reaction (*e.g.*, reaction of the ^{18}F species and the imaging agent precursor to form the imaging agent) optionally in a synthesis module, purification (*e.g.*, by preparative HPLC), solvent exchange (*e.g.*, by Sep-Pak), aseptic filtration, and release into a container. For example, see Example 68.

In some embodiments, the automated reaction system may make use of a cassette comprising a reaction module in fluid connection with a purification module and/or a formulation module. Figure 17 shows a schematic representation of a cassette in connection with exemplary reaction systems for synthesizing an imaging agent comprising a reaction module, a purification module, and/or a formulation module, according to some embodiments.

In some embodiments, the reaction module may include a reaction chamber in which conversion of the imaging agent precursor to the imaging agent is performed. The reaction module may include a source of a fluoride species (*e.g.*, ^{18}F), a source of the imaging agent precursor, a source of an additive (*e.g.*, salt additive), and other sources of additional components such as solvents, each of which may optionally be fluidly connected to the reaction chamber. In some embodiments, one or more reagents are provided via a syringe as opposed to vials or reservoirs as previously reported. The reaction module may also comprise an anion exchange column for purification of the fluoride species, prior to introduction into the reaction chamber.

Upon reaction, the resulting imaging agent product is transferred from the reaction module to the purification module for further processing, treatment, and/or purification. The purification module may include, for example, a column (*e.g.*, an HPLC column) fluidly connected to one or more sources of solvents to be used as eluents. The purification module may further comprise a source of a stabilizing agent (*e.g.*, ascorbic acid or a salt thereof), which may be added to the imaging agent upon purification (*e.g.*, by HPLC). The purified imaging agent is then transferred to the formulation module, where further purification and

formulation may be performed. The formulation module may include a filter for aseptic filtration and/or a C-18 column for solvent exchange.

In some embodiments, a cassette comprises a reaction module and a formulation module. A reaction module of the invention may include a source of ^{18}F, a filter to remove unreacted [^{18}O]H_2O, a source of an ammonium salt, a source for a diluent for the ^{18}F, a source for an imaging agent precursor, a source for an H_2O diluent for the imaging agent precursor, a reaction vessel for reacting the ^{18}F and the imaging agent precursor, a solid phase extraction column (*e.g.*, a C-18 column, or other suitable column) in fluid communication with the reaction vessel. The solid phase extraction column includes a solid sorbent to adsorb the radiolabeled imaging agent product on the sorbent. At least a portion of the residual reaction impurities pass through solid phase extraction column without adsorbing on the sorbent. The reaction module also includes a source of wash solutions in fluid communication with the solid phase extraction column for providing wash solutions to elute the remaining impurities on the sorbent, and includes a source of an eluent (*e.g.*, as H_2O/MeCN, or other suitable eluent) in fluid communication with the solid phase extraction column for eluting the radiolabeled imaging agent product off the sorbent. The reaction module may also include a source of a diluent for the eluted radiolabeled imaging agent.

A formulation module of an apparatus of the invention may be in fluid communication with a reaction module and may include a solid phase extraction cartridge that includes a solid sorbent (*e.g.*, C-18, or other suitable sorbent) to adsorb the diluted radiolabeled imaging agent, a source of wash solutions (*e.g.*, comprising ascorbic acid, a salt thereof, or other suitable wash solution) in fluid communication with the solid phase extraction cartridge for providing wash solutions to wash off any remaining impurities on the sorbent, and a source of eluting fluid (*e.g.*, ethanol, or other suitable eluting fluid) in fluid communication with the solid phase extraction cartridge for eluting the radiolabeled imaging agent product off the sorbent. In some embodiments, the wash solution(s) is provided in a syringe which may provide certain advantages, as described herein. The formulation module may also include a source of a diluent (*e.g.*, comprising ascorbic acid, a salt thereof, or other suitable diluent), for diluting the eluted radiolabeled imaging agent. The formulation module may also be in fluid communication with a sterilizing filter (*e.g.*, a Sartorius Minisart RC15 sterilizing filter, or other suitable sterilizing filter).

In a particular embodiment, a cassette is provided for use with an automated synthesis module, for example, a GE TracerLab MX synthesis module. In one embodiment, a cassette comprises a disposable sterilized assembly of molded stopcock manifolds specifically designed

for use with the automated synthesis module (*e.g.*, GE TracerLab MX synthesis module). Individual manifolds are connected in a linear or non-linear fashion to form a directional array that dictates the flow path of reagents used in the preparation of an imaging agent. In some embodiments, the main body of the cassette contains at least one manifold comprising a plurality of manifold positions (*e.g.,* stockcocks). For example, the main body may comprise at least one, two, three, four or more, manifolds. The cassette may comprise between 1 to 20 manifold positions, between 1 to 15 manifold positions, between 5 and 20 manifold positions, between 5 and 15 manifold positions. Each of the manifolds may or may not be symmetrical. In one embodiment, the main body of the cassette contains three plastic manifolds each fitted with five standard molded stopcocks, thereby having a total of 15 total manifold positions. Individual stopcocks are adapted with luer fittings to accommodate solvents, reagents, syringes, tubing required for gas and liquid handling, *etc*. The stopcocks are adapted for solvents and reagents and may be fitted with plastic spikes upon which inverted punch vials are located, while those featuring tubing and syringes are fitted with male luer connections according to function. In some embodiments, the cassette comprises a linear arrangement of a plurality of stopcock manifolds connected to one or more of the components selected from the group consisting of a gas inlet, anion exchange cartridge, C-18 cartridge, syringe, solvent reservoir, reaction vessel, HPLC system, collection vessel, reservoirs for solutions of ascorbic acid or salt thereof, and exhaust outlet. In some embodiments, the reservoirs for solutions of ascorbic acid or salt thereof comprise a syringe. In some cases, the cassette further comprises tubing. In some cases, the cassette further comprises an imaging agent synthesis module, wherein the apparatus is fluidically connected to the cassette. In some cases, the apparatus is capable carrying out the method of synthesizing an imaging agent as described herein.

In some embodiments, the cassette configuration provided for the preparation of an imaging agent is depicted in Figure 17. In some embodiments, the cassette configuration comprises a linear arrangement of a plurality of stopcock manifolds arranged in the order:

1) luer connections (2) to gas inlet and [^{18}O]H_2O recovery;
2) anion exchange cartridge – column eluting solution (optionally 1 mL punch vial);
3) spike connection for acetonitrile (optionally 10 mL punch vial);
4) empty syringe (optionally 30 mL);
5) reservoir with solution of imaging agent precursor (optionally 10 mL punch vial);
6) reaction vessel;
7) outlet to HPLC;

8) syringe (optionally 20 mL) with solution of ascorbic acid or salt thereof (*e.g.*, at pH 2);
9) inlet from HPLC;
10) ethanol reservoir (optionally 3 mL syringe);
11) syringe (optionally 10 mL) with solution of ascorbic acid or salt thereof (*e.g.*, at pH 5.8);
12) syringe (optionally 5 mL) with water;
13) final product vial;
14) empty syringe (optionally 30 mL); and
15) reaction vessel and exhaust.

In some embodiments, the linear arrangement disclosed above can be changed to switch the reagent at position 3 with the reagent at position 5 and/or to switch the reagent at position 11 with the reagent at position 13.

The cassettes and corresponding methods described herein provide unexpected results as compared to previously described cassettes and methods. In some cases, the use of syringes as reservoirs for reagents (*e.g.*, ascorbic acid or salt thereof) results in overall reduced production cost and improved liquid handling efficiency during the manufacture of an imaging agent. In addition, a variation in the configuration of the placement of the components of the cassette also results in improved liquid handling efficiency as well as increased drug product recovery during the manufacture of an imaging agent. This may be due to reduced exposure to the plastic manifold which can result in less adsorption of the imaging agent during the delivery process. In some cases, the variation of the cassette comprises repositioning one of the reagents (*e.g.*, to position 11) and the final product vial (*e.g.*, to position 13). In some embodiments, improved methods of use of the cassettes are provided. In some embodiments, computer control of the cassettes is employed to execute a unique sequence of mechanical events dictated by the individual tracers. In some cases, a discrete sequence file is employed to describe the essential synthetic parameters (*e.g.* reaction time and temperature) and to adapt the preferred reagent and cassette configuration for the selected imaging agent. In some embodiments, sequence modifications as compared to previously described methods may be incorporated based upon the novel reagent containers (*e.g.*, syringes) and cassette configurations as described herein. For example, in some embodiments, unique programming sequences are employed to add nitrogen gas into the syringe containers thereby providing for complete reagent transfer. Additionally, for example, in some embodiments, overall sequence timing is

modified as compared to previously described methods to provide shorter sequence durations (*e.g.*, such that preparatory occurs in a parallel fashion rather than as a linear series).

Exemplary Kits

In some embodiments, systems, methods, kits, and cassettes kits for the preparation of an imaging agent are provided for detecting, imaging, and/or monitoring myocardial perfusion. In some embodiments, kits for the administration of an imaging agent are provided. Kits of the invention may include, for example, a container comprising an imaging agent or an imaging agent precursor, and instructions for use. Kits may include a sterile, non-pyrogenic, formulation comprising a predetermined amount of an imaging agent or precursor thereof and optionally other components. In some aspects of the invention, a kit may include one or more syringes that contain an imaging agent or precursor thereof to be prepared for administration to a subject. A container that may be used in conjunction with an imaging agent (*e.g.,* to deliver and/or administer an imaging agent to a subject) may be a syringe, bottle, vial, tubes, *etc.* Exemplary syringes that may be included in a kit of the invention are syringes lacking an adsorbent plunger tip, such as a 3 or 5 mL NORM-JECT (Henke Sass Wolf, Dudley, MA), or other equivalent syringe lacking an adsorbent plunger tip. An imaging agent or precursor thereof may be provided in a kit and additional preparations before use may optionally include diluting the imaging agent to a usable concentration. Instructions in a kit of the invention may relate to methods for preparing the imaging agent, methods of diluting the imaging agent, methods of administering the imaging agent to a subject for diagnostic imaging, or other instructions for use.

In some cases, a kit can also include one or more vials containing a diluent for preparing an imaging agent composition for administration to a subject (*e.g.*, human). A diluent vial may contain a diluent such as physiological saline, water, buffered solution, *etc.* for diluting an imaging agent. For example, the imaging agent may be packaged in a kit in a ready-to-inject formulation, or may require some reconstitution or dilution whereby a final composition/formulation for injection or infusion is prepared.

Instructions in a kit of the invention may also include instructions for administering the imaging agent to a subject and may include information on dosing, timing, stress induction, *etc.* For example, a kit may include an imaging agent or precursor thereof described herein, along with instructions describing the intended application and the proper administration of the agent. As used herein, “instructions" can define a component of instruction and/or promotion, and typically involve written instructions on or associated with

packaging of the invention. Instructions also can include any oral or electronic instructions provided in any manner such that a user will clearly recognize that the instructions are to be associated with the kit, for example, audiovisual (*e.g.*, videotape, DVD, *etc.*), Internet, and/or web-based communications, *etc.* The written instructions may be in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which instructions can also reflect approval by the agency of manufacture, use or sale for human administration. In some cases, the instructions can include instructions for mixing a particular amount of the diluent with a particular amount of a concentrated solution of the imaging agent or precursor thereof or a solid preparation of the imaging agent, or precursor thereof whereby a final formulation for injection or infusion is prepared for example, such that the resulting solution is at a suitable concentration for administration to a subject (*e.g.*, at a concentration as described herein). A kit may include a whole treatment regimen of the inventive compound (*e.g.*, a rest dose and a stress dose).

The kit may contain any one or more of the components described herein in one or more containers. As an example, in one embodiment, the kit may include instructions for mixing one or more components of the kit and/or isolating and mixing a sample and applying to a subject. The kit may include a container housing an agent described herein. The agent may be in the form of a liquid, gel or solid (powder). The agent may be prepared sterilely, packaged in syringe and shipped refrigerated. Alternatively it may be housed in a vial or other container for storage. A second container may have other agents prepared sterilely. Alternatively the kit may include an active agent premixed and shipped in a syringe, vial, tube, or other container. The kit may have one or more or all of the components required to administer the agents to a patient, such as a syringe, topical application devices, or iv needle tubing and bag.

It also will be understood that containers containing the components of a kit of the invention, whether the container is a bottle, a vial (*e.g.,* with a septum), an ampoule, an infusion bag, or the like, can include additional indicia such as conventional markings that change color when the preparation has been autoclaved or otherwise sterilized. A kit of the invention may further include other components, such as syringes, labels, vials, tubing, catheters, needles, ports, and the like. In some aspect of the invention, a kit may include one or more syringes containing the imaging agent sufficient for administration.

Buffers useful in the preparation of imaging agents or precursor thereof and kits include, for example, phosphate, citrate, sulfosalicylate, and acetate buffers. A more complete list can be found in the United States Pharmacopoeia. Lyophilization aids useful in

the preparation of imaging agents and kits include, for example, mannitol, lactose, sorbitol, dextran, FICOLL® polymer, and polyvinylpyrrolidine (PVP). Stabilization aids useful in the preparation of imaging agents and kits include, for example, ascorbic acid, cysteine, monothioglycerol, sodium bisulfite, sodium metabisulfite, gentisic acid, and inositol. Solubilization aids useful in the preparation of imaging agents and kits include, for example, ethanol, glycerin, polyethylene glycol, propylene glycol, polyoxyethylene sorbitan monooleate, sorbitan monoloeate, polysorbates, poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) block copolymers ("Pluronics") and lecithin. In certain embodiments, the solubilizing aids are polyethylene glycol, cyclodextrins, and Pluronics. Bacteriostats useful in the preparation of imaging agents and kits include, for example, benzyl alcohol, benzalkonium chloride, chlorbutanol, and methyl, propyl, or butyl paraben.

Pharmaceutical Compositions

Once a compound as described herein (*e.g.*, an imaging agent) has been prepared or obtained, it may be combined with one or more pharmaceutically acceptable excipients to form a pharmaceutical composition that is suitable for administration to a subject, including a human. As would be appreciated by one of skill in this art, the excipients may be chosen, for example, based on the route of administration as described below, the imaging agent being delivered, time course of delivery of the agent, and/or the health/condition of the subject. The pharmaceutical composition may be a solid or liquid.

Pharmaceutical compositions of the present invention and for use in accordance with the present invention may include a pharmaceutically acceptable excipient or carrier. As used herein, the term "pharmaceutically acceptable excipient" or "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose, and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; detergents such as Tween 80; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as

sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

Pharmaceutically acceptable excipients include any and all solvents, diluents or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. General considerations in formulation and/or manufacture of pharmaceutical compositions agents can be found, for example, in *Remington's Pharmaceutical Sciences*, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and *Remington: The Science and Practice of Pharmacy*, 21st Edition (Lippincott Williams & Wilkins, 2005).

Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the compound of the present invention (the "active ingredient") into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single– or multi–dose unit.

Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one–half or one–third of such a dosage.

Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and combinations thereof.

Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium iodide, sodium metabisulfite, sodium nitrite, sodium sulfite, and sodium thiosulfate.

Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (*e.g.*, sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (*e.g.*, citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorohexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta–carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In

certain embodiments, the preservative is an anti–oxidant. In other embodiments, the preservative is a chelating agent.

Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D–gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen–free water, isotonic saline, Ringer's solution, ethyl alcohol, *etc.*, and combinations thereof.

Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3–butylene glycol, dimethylformamide, oils (*e.g.*, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the conjugates of the invention are mixed with solubilizing agents such as Cremophor, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and combinations thereof.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3–butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including

synthetic mono– or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulations can be sterilized, for example, by filtration through a bacterial–retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices such as those described in U.S. Patents 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which deliver liquid vaccines to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Patents 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes can be used in the classical Mantoux method of intradermal administration.

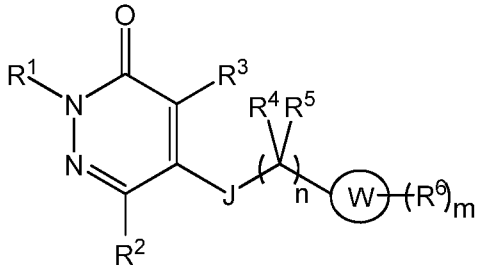
Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

The pharmaceutical compositions of this invention can be administered to humans and/or to other animals parenterally (*e.g.*, by intravenous, intramuscular, subcutaneous, or intraperitoneal injection). The mode of administration will vary depending on the intended use, as is well known in the art.

Further embodiments

Certain embodiments are further contemplated herein.

Embodiment 1. In embodiment 1, provided is a compound comprising the structure:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $-NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

W is heteroaryl, naphthyl, heterocyclyl, or aryl;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, –

OH, –C(=O)R^8, –C(=O)OR^8, –OC(=O)R^8, –C(=O)N(R^7)$_2$, –N(R^7)C(=O)R^8, –CN, –Si(R^9)$_3$, -B($R^{9'}$)$_3$, –OR^8, and an imaging moiety;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

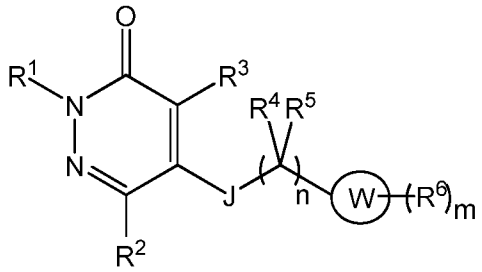
each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound; and

provided that when W is aryl, a) R^3 is not halo, alkyl or haloalkyl, or b) at least one R^6 is selected from the group consisting of alkynyl optionally substituted, alkenyl optionally substituted, alkyl substituted with –CN, alkyl substituted with –C(=O)OR^8, alkyl substituted with –C(=O)R^8, alkyl substituted with –N(R^7)$_2$, –CN, –NO_2, –N(R^7)$_2$, –C(=O)OR^8, –OC(=O)R^8, –C(=O)R^8, –C(=O)N(R^7)$_2$, and –N(R^7)C(=O)R^8.

Embodiment 2. The compound of embodiment 1, wherein the compound comprises the structure:



(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted,

heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–NO_2$, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

W is heteroaryl, naphthyl, or heterocyclyl;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–N(R^7)_2$, $–NO_2$, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, $–Si(R^9)_3$, $-B(R^{9'})_3$, $–OR^8$, and an imaging moiety;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging

moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

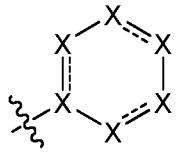
provided that at least one imaging moiety is present in the compound.

Embodiment 3. The compound of embodiment 1 or 2, wherein W is heteroaryl.

Embodiment 4. The compound of embodiment 1 or 2, wherein W is naphthyl.

Embodiment 5. The compound of embodiment 1 or 2, wherein W is heterocyclyl.

Embodiment 6. The compound of embodiment 1 or 2, wherein W is:

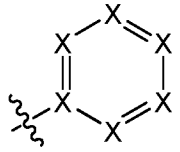


wherein each X is independently selected from the group consisting of C, $C(R^6)$, $C(R^6)_2$, N, NR^7, O, and S; and

wherein each ------ is independently a single or double bond,

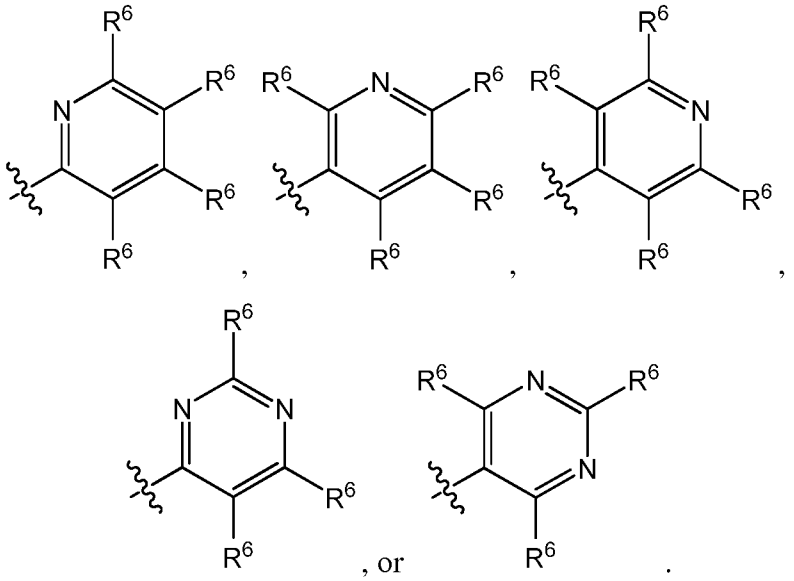
provided at least one X is not C or $C(R^6)$.

Embodiment 7. The compound of embodiment 1 or 2, wherein W is:

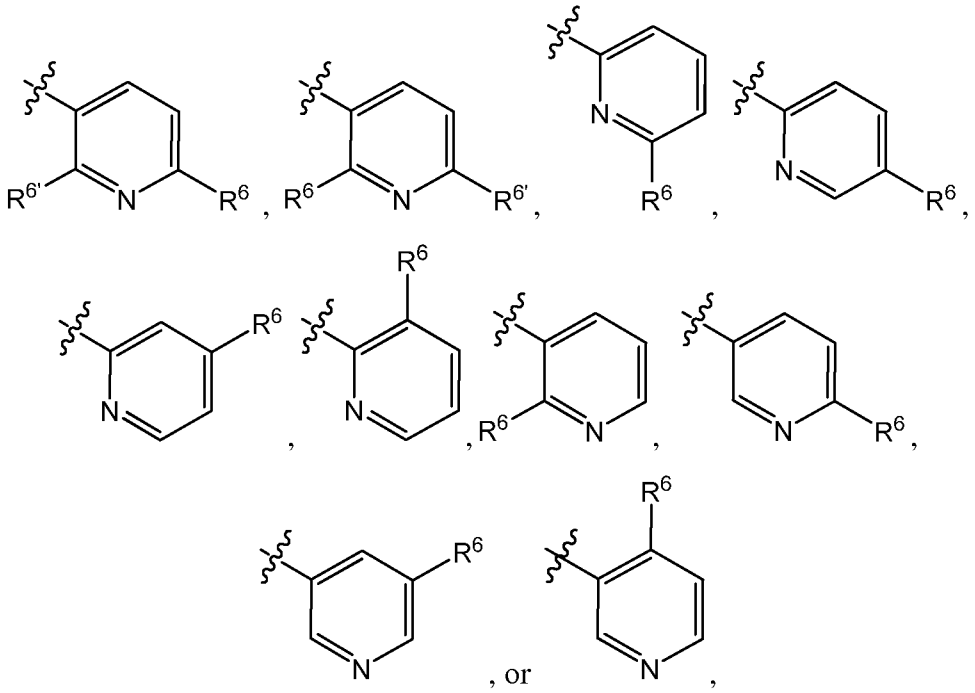


wherein each X is independently C, $C(R^6)$ or N, provided at least one X is not C or $C(R^6)$.

Embodiment 8. The compound of embodiment 1 or 2, wherein W is:



Embodiment 9. The compound of embodiment 1 or 2, wherein W is:



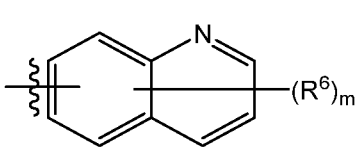
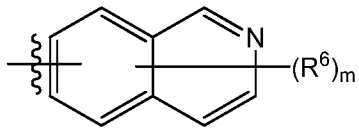
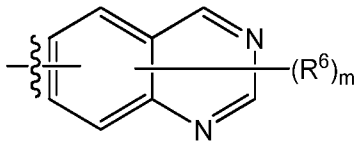
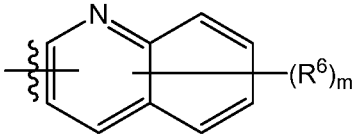
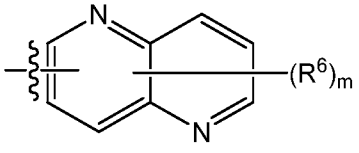
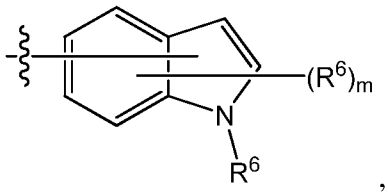
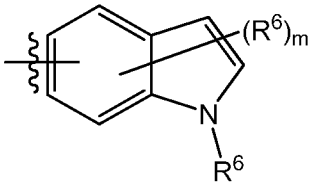
wherein $R^{6'}$ is halo or hydrogen; and optionally, wherein $R^{6'}$ is fluoro, chloro, bromo, or hydrogen.

Embodiment 10. The compound of embodiment 9, wherein R^6 is $-O(CH_2)_jI_m$; wherein j is 1, 2, 3, 4, 5, or 6; and optionally, wherein I_m is ^{18}F.

Embodiment 11. The compound of embodiment 9, wherein R^6 is $-(CH_2)_jO(CH_2)_jI_m$;

wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6; and optionally, wherein I_m is ^{18}F.

Embodiment 12. The compound of embodiment 1 or 2, wherein W is:

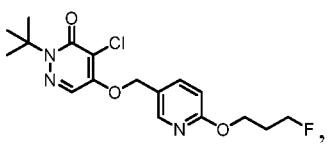
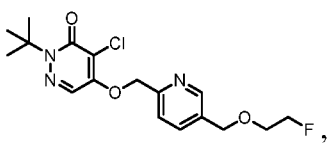
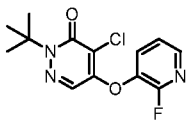
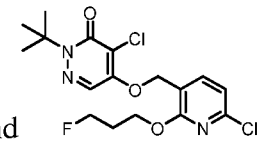
Embodiment 13. The compound of embodiment 1 or 2, wherein W is:

each X is independently selected from the group consisting of C, $C(R^6)$, $C(R^6)_2$, N, NR^7, O, and S; and

each ------ is independently a single or double bond,

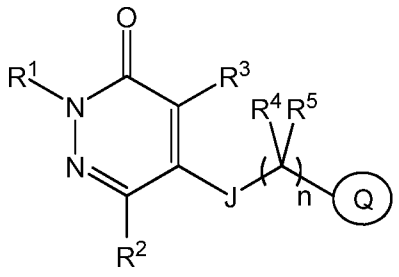
provided at least one X is not C or $C(R^6)$.

Embodiment 14. The compound of embodiment 1 or 2, wherein the compound is selected from the group consisting of:

or a pharmaceutically acceptable salt thereof, wherein F is optionally ^{18}F.

Embodiment 15. The compound of embodiment 1 or 2, wherein the compound comprises the structure:



(III)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and an imaging moiety;

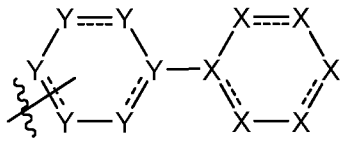
R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

Q has the structure:



each Y and each X is independently selected from the group consisting of C, $C(R^6)$, $C(R^6)_2$, N, NR^7, O, and S, provided at least one Y is not C or $C(R^6)$, optionally, wherein one X and/or one Y is absent;

each ------ is independently a single or double bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl

optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, –OH, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, –CN, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and an imaging moiety;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and an imaging moiety; and

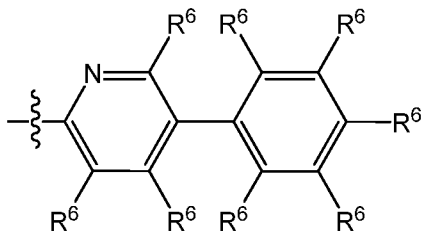
each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound.

Embodiment 16. The compound of embodiment 15, wherein each Y and each X is independently selected from the group consisting of C, $C(R^6)$, $C(R^6)_2$, N, NR^7, O, and S, provided at least one Y is not C or $C(R^6)$.

Embodiment 17. The compound of embodiment 15, wherein one Y is absent or one X is absent.

Embodiment 18. The compound of embodiment 15, wherein Q is: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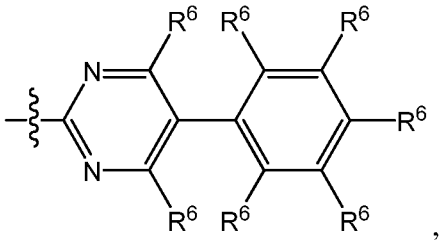
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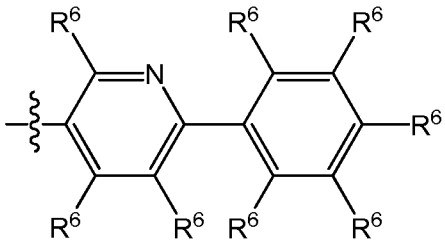
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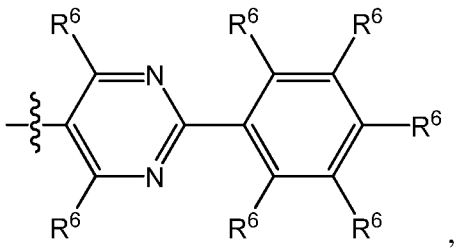
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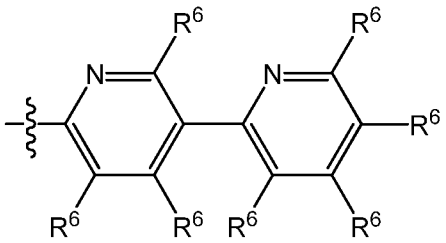
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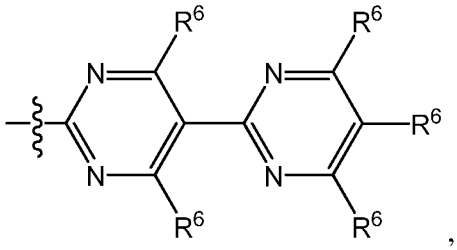
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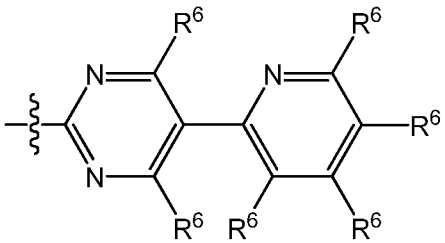
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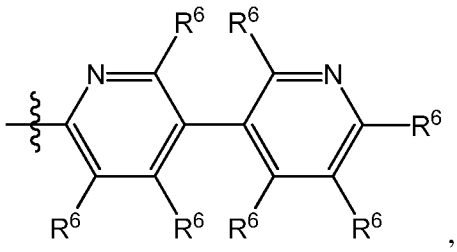
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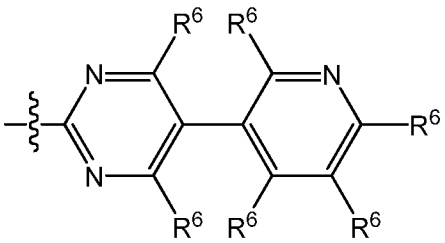
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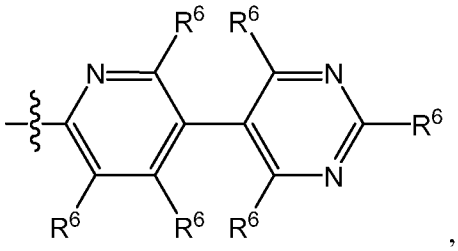
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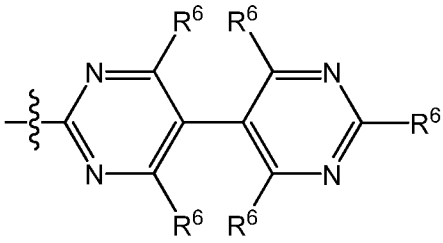
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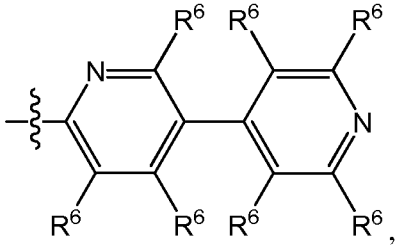
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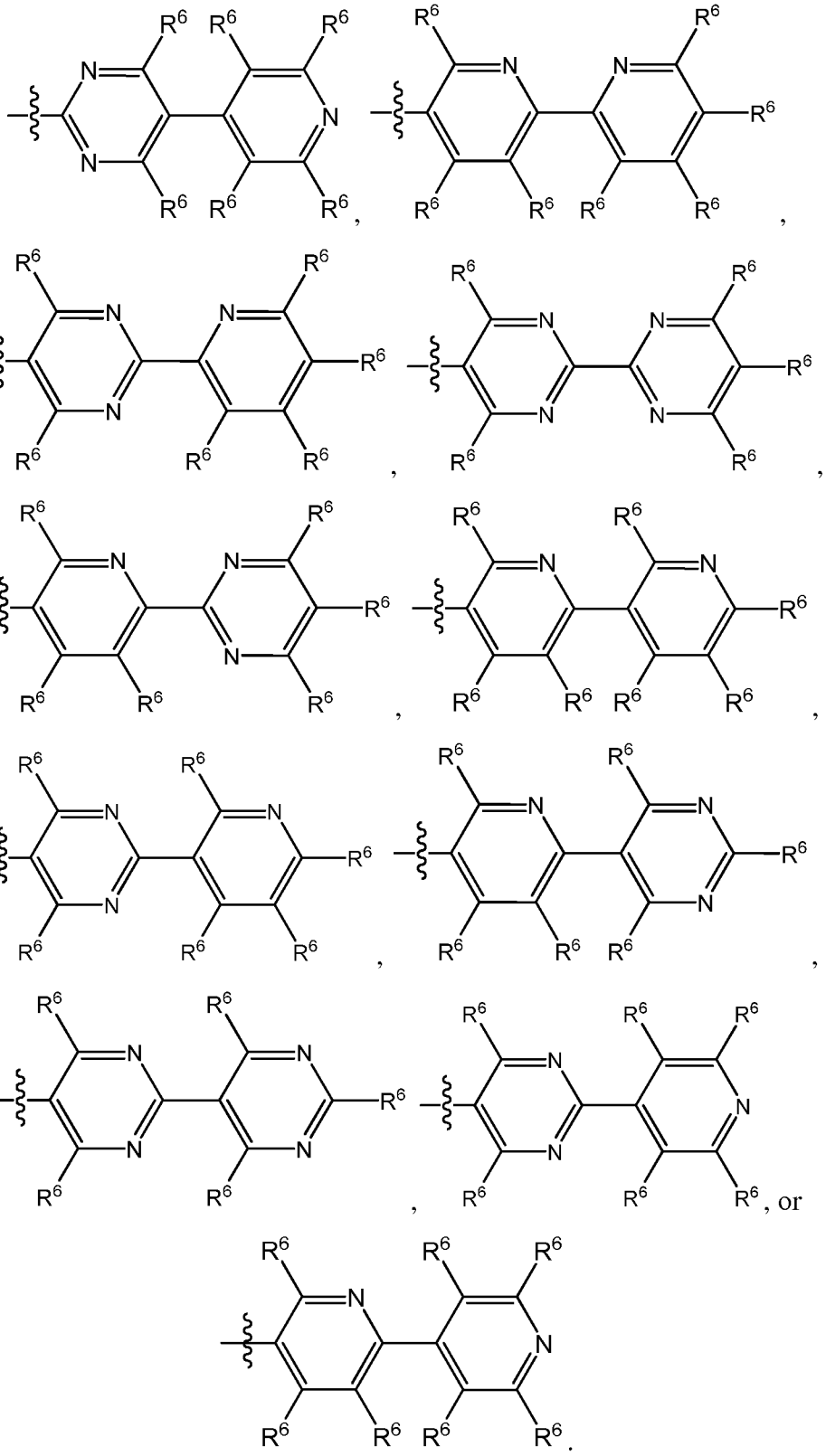


Embodiment 19. The compound of any one of embodiments 1-13 and 15-18, wherein

the at least one imaging moiety is present in R^1, R^2, R^3, R^4, R^5, or R^6.

Embodiment 20. The compound of any one of embodiments 1-13 and 15-19, wherein R^1 is alkyl optionally substituted.

Embodiment 21. The compound of any one of embodiments 1-13 and 15-19, wherein R^1 is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, or t-butyl.

Embodiment 22. The compound of any one of embodiments 1-13 and 15-19, wherein R^1 is-$C(CH_3)_2CH_2OH$.

Embodiment 23. The compound of any one of embodiments 1-13 and 15-19, wherein R^1 is t-butyl.

Embodiment 24. The compound of any one of embodiments 1-13 and 15-19, wherein R^1 is aryl optionally substituted.

Embodiment 25. The compound of any one of embodiments 1-13 and 15-19, wherein R^1 is phenyl optionally substituted.

Embodiment 26. The compound of any one of embodiments 1-13 and 15-19, wherein R^1 is unsubstituted phenyl.

Embodiment 27. The compound of any one of embodiments 1-13 and 15-19, wherein R^1 is cycloalkyl optionally substituted.

Embodiment 28. The compound of any one of embodiments 1-13 and 15-19, wherein R^1 is cyclohexyl optionally substituted.

Embodiment 29. The compound of any one of embodiments 1-13 and 15-28, wherein R^2 is H.

Embodiment 30. The compound of any one of embodiments 1-13 and 15-29, wherein J is a bond.

Embodiment 31. The compound of any one of embodiments 1-13 and 15-29, wherein J is O.

Embodiment 32. The compound of any one of embodiments 1-13 and 15-29, wherein J is S.

Embodiment 33. The compound of any one of embodiments 1-13 and 15-32, wherein n is 0.

Embodiment 34. The compound of any one of embodiments 1-13 and 15-32, wherein n is 1.

Embodiment 35. The compound of any one of embodiments 1-13 and 15-32, wherein n is 2.

Embodiment 36. The compound of any one of embodiments 1-13 and 15-32, wherein n is 3.

Embodiment 37. The compound of any one of embodiments 1-13 and 15-36, wherein each of R^4 and R^5 is H.

Embodiment 38. The compound of any one of embodiments 1-13 and 15-36, wherein at least one R^4 and R^5 is ^2H, and optionally, wherein each of R^4 and R^5 is ^2H.

Embodiment 39. The compound of any one of embodiments 1-13 and 15-38, wherein R^3 is halo.

Embodiment 40. The compound of any one of embodiments 1-13 and 15-38, wherein R^3 is Cl.

Embodiment 41. The compound of any one of embodiments 1-13 and 15-38, wherein R^3 is Br.

Embodiment 42. The compound of any one of embodiments 1-13 and 15-38, wherein R^3 is H.

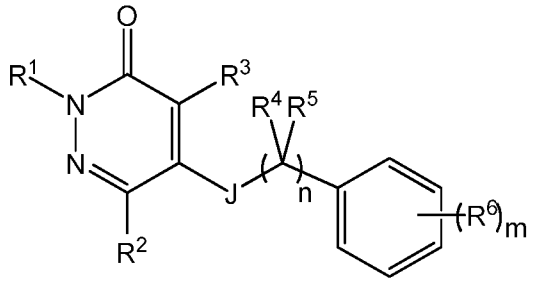
Embodiment 43. The compound of any one of embodiments 1-13 and 15-38, wherein R^3 is alkyl optionally substituted.

Embodiment 44. The compound of any one of embodiments 1-13 and 15-38, wherein R^3 is unsubstituted alkyl.

Embodiment 45. The compound of any one of embodiments 1-13 and 15-38, wherein R^3 is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, or t-butyl.

Embodiment 46. The compound of any one of embodiments 1-13 and 15-38, wherein R^3 is methyl.

Embodiment 47. The compound of embodiment 1, wherein the compound comprises the structure:



(IV)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, unsubstituted alkyl or alkyl optionally substituted with a moiety other than a halogen, heteroalkyl optionally substituted,

alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, –CN, and $–NO_2$;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–N(R^7)_2$, $–NO_2$, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, $–Si(R^9)_3$, $–B(R^{9'})_3$, $–OR^8$, and an imaging moiety;

m is 0, 1, 2, 3, 4, or 5;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound.

Embodiment 48. The compound of embodiment 47, wherein R^3 is alkyl optionally substituted.

Embodiment 49. The compound of embodiment 47, wherein R^3 is unsubstituted alkyl.

Embodiment 50. The compound of embodiment 47, wherein R^3 is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, or t-butyl.

Embodiment 51. The compound of embodiment 47, wherein R^3 is methyl.

Embodiment 52. The compound of any one of embodiments 47-51, wherein the at least one imaging moiety is present in R^1, R^2, R^3, R^4, R^5, or R^6.

Embodiment 53. The compound of any one of embodiments 47-52, wherein R^1 is alkyl optionally substituted.

Embodiment 54. The compound of any one of embodiments 47-52, wherein R^1 is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, or t-butyl.

Embodiment 55. The compound of any one of embodiments 47-52, wherein R^1 is $-C(CH_3)_2CH_2OH$.

Embodiment 56. The compound of any one of embodiments 47-52, wherein R^1 is t-butyl.

Embodiment 57. The compound of any one of embodiments 47-52, wherein R^1 is aryl optionally substituted.

Embodiment 58. The compound of any one of embodiments 47-52, wherein R^1 is phenyl optionally substituted.

Embodiment 59. The compound of any one of embodiments 47-52, wherein R^1 is unsubstituted phenyl.

Embodiment 60. The compound of any one of embodiments 47-52, wherein R^1 is cycloalkyl optionally substituted.

Embodiment 61. The compound of any one of embodiments 47-52, wherein R^1 is cyclohexyl optionally substituted.

Embodiment 62. The compound of any one of embodiments 47-61, wherein R^2 is H.

Embodiment 63. The compound of any one of embodiments 47-62, wherein J is a bond.

Embodiment 64. The compound of any one of embodiments 47-62, wherein J is O.

Embodiment 65. The compound of any one of embodiments 47-62, wherein J is S.

Embodiment 66. The compound of any one of embodiments 47-65, wherein n is 0.

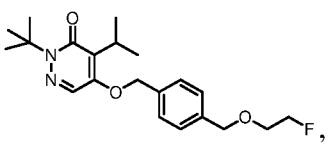
Embodiment 67. The compound of any one of embodiments 47-65, wherein n is 1.

Embodiment 68. The compound of any one of embodiments 47-65, wherein n is 2.

Embodiment 69. The compound of any one of embodiments 47-68, wherein each of R^4 and R^5 is H.

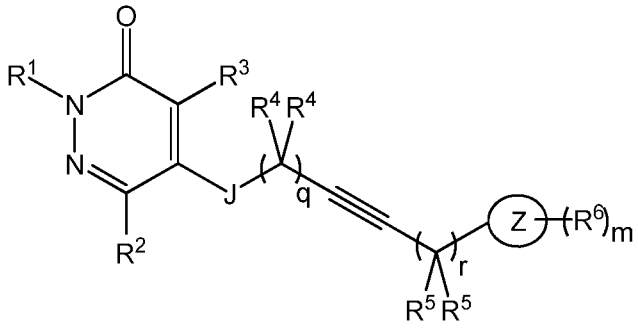
Embodiment 70. The compound of any one of embodiments 47-68, wherein at least one R^4 and R^5 is ^2H, and optionally, wherein each of R^4 and R^5 is ^2H.

Embodiment 71. The compound of embodiment 47, wherein the compound is of the formula:

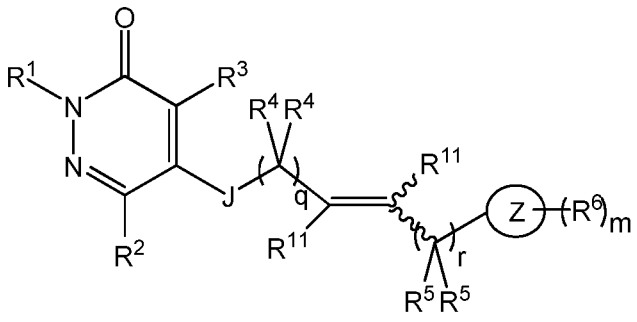


or a pharmaceutically acceptable salt thereof, wherein F is optionally ^{18}F.

Embodiment 72. In embodiment 72, provided is a compound comprising the structure:



(V) or



(VI),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $-NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

each R^4, R^5, and R^{11} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 or any two of R^5 are joined together to form a ring;

q, and r are each independently 0, 1, 2, or 3;

Z is selected from the group consisting of aryl, heteroaryl, heterocyclyl, and a bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and an imaging moiety;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

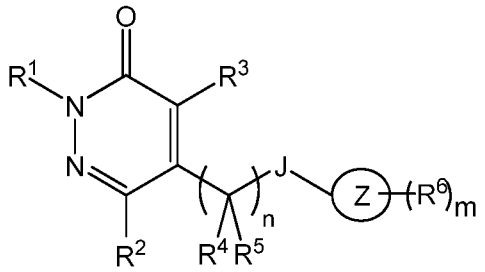
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound.

Embodiment 73. In embodiment 73, provided is a compound comprising the structure:



(VII)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted,

heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, $–NO_2$, haloalkyl, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)_2$, $N(R^7)C(=O)$, and $–CH_2O$;

each R^4 and R^5 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 or any two of R^5 are joined together to form a ring;

n is 1, 2, or 3;

Z is selected from the group consisting of aryl, heteroaryl, heterocyclyl, and a bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–N(R^7)_2$, $–NO_2$, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, $–Si(R^9)_3$, $–B(R^{9'})_3$, $–OR^8$, and an imaging moiety;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging

moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound.

Embodiment 74. The compound of embodiment 72 or 73, wherein Z is aryl.

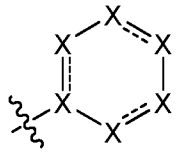
Embodiment 75. The compound of embodiment 72 or 73, wherein Z is phenyl.

Embodiment 76. The compound of embodiment 72 or 73, wherein Z is naphthyl.

Embodiment 77. The compound of embodiment 72 or 73, wherein Z is heteroaryl.

Embodiment 78. The compound of embodiment 72 or 73, wherein Z is heterocyclyl.

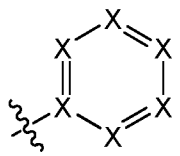
Embodiment 79. The compound of embodiment 72 or 73, wherein Z is:



wherein each X is independently selected from the group consisting of C, $C(R^6)$, $C(R^6)_2$, N, NR^7, O, and S; and

wherein each ------ is independently a single or double bond.

Embodiment 80. The compound of embodiment 72 or 73, wherein Z is:

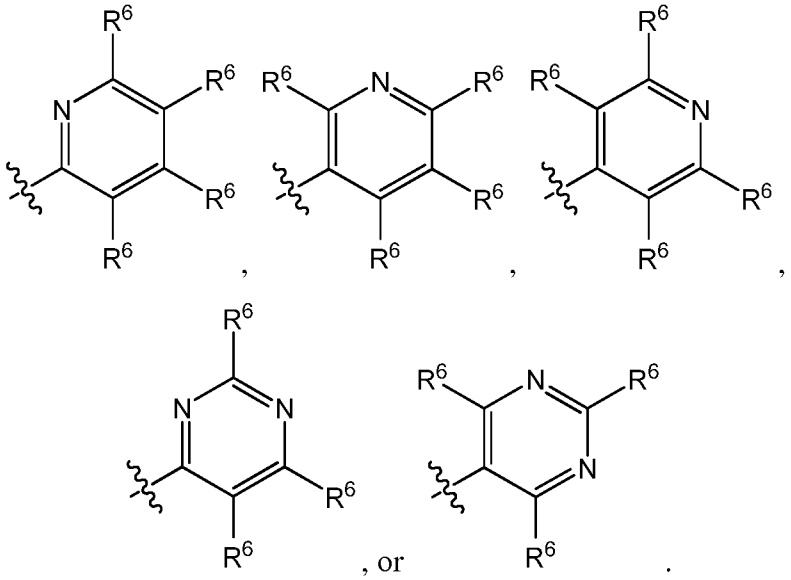


wherein each X is independently C, $C(R^6)$ or N.

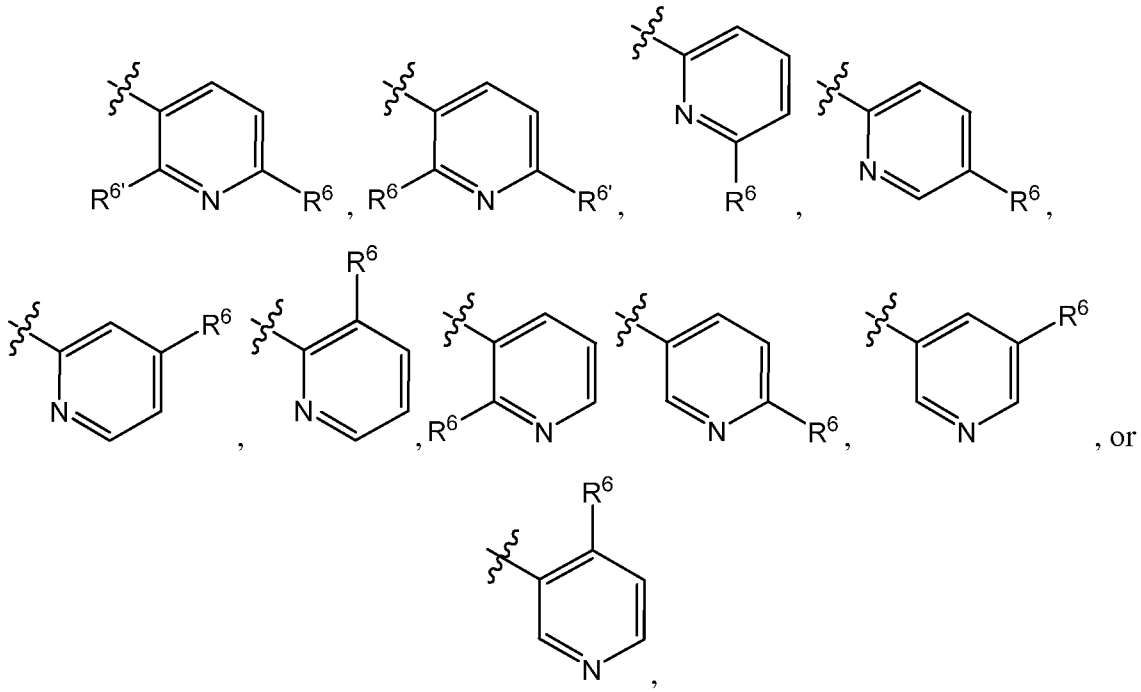
Embodiment 81. The compound of embodiment 79 or 80, wherein at least one X is not

C or C(R^6).

Embodiment 82. The compound of embodiment 72, 73, or 80, wherein Z is:



Embodiment 83. The compound of embodiment 72, 73, or 80, wherein Z is:



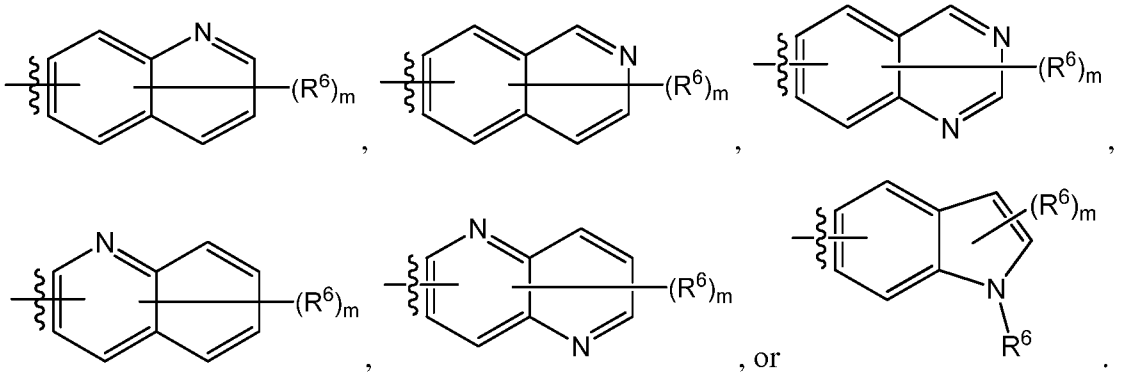
wherein $R^{6'}$ is halo or hydrogen.

Embodiment 84. The compound of embodiment 83, wherein $R^{6'}$ is fluoro, chloro, bromo, or hydrogen.

Embodiment 85. The compound of embodiment 83, wherein R^6 is $-O(CH_2)_jI_m$; wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6.

Embodiment 86. The compound of embodiment 83, wherein R^6 is $-(CH_2)_jO(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6.

Embodiment 87. The compound of embodiment 72 or 73, wherein Z is:



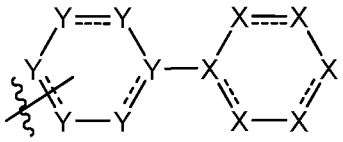
Embodiment 88. The compound of embodiment 72 or 73, wherein Z is:

each X is independently selected from the group consisting of C, $C(R^6)$, $C(R^6)_2$, N, NR^7, O, and S; and

each ------ is independently a single or double bond.

Embodiment 89. The compound of embodiment 88, wherein at least one X is not C or $C(R^6)$.

Embodiment 90. The compound of embodiment 72 or 73, wherein Z has the structure:



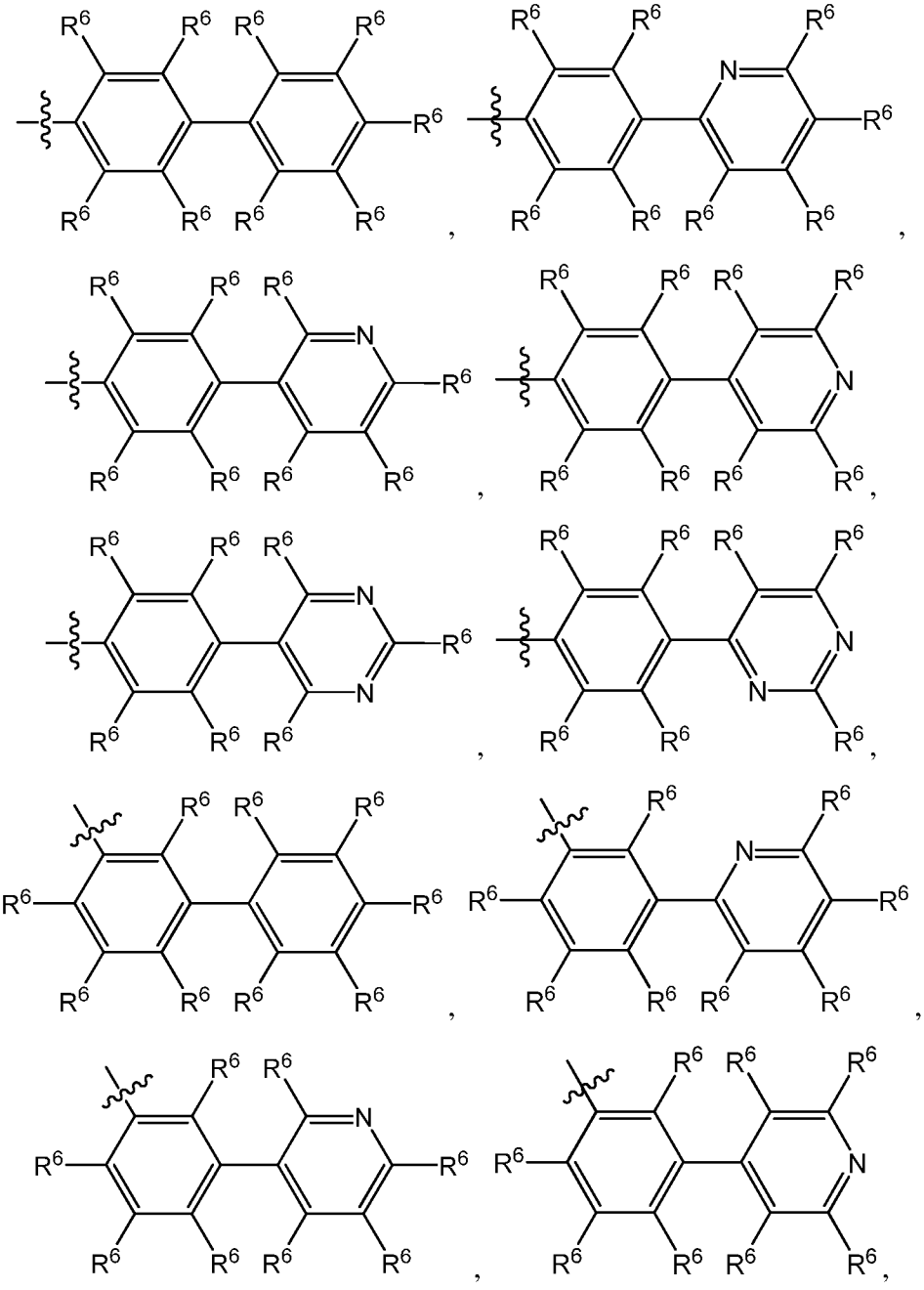
each Y and each X is independently selected from the group consisting of C, $C(R^6)$, $C(R^6)_2$, N, NR^7, O, and S;

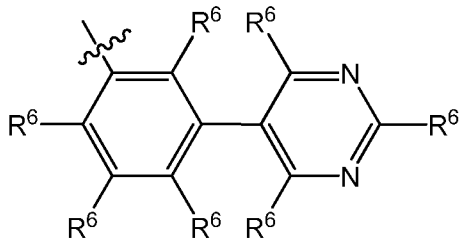
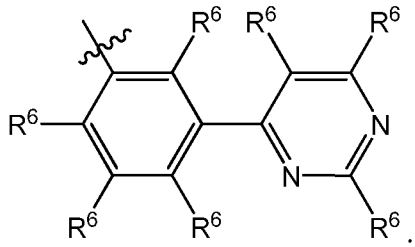
each ------ is independently a single or double bond.

Embodiment 91. The compound of embodiment 90, wherein at least one Y is not C or C(R^6).

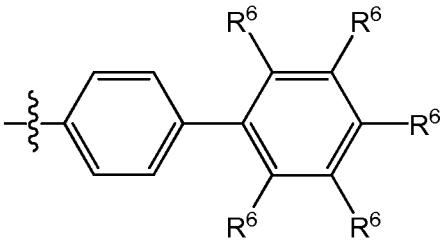
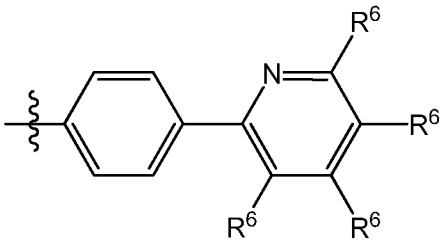
Embodiment 92. The compound of embodiment 90 or 91, wherein at least one X is not C or C(R^6).

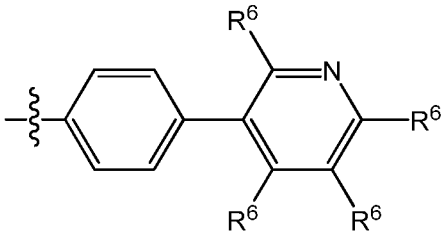
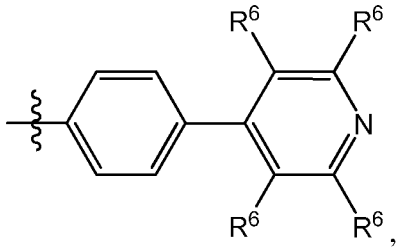
Embodiment 93. The compound of embodiment 72, 73, or 90, wherein Z is:

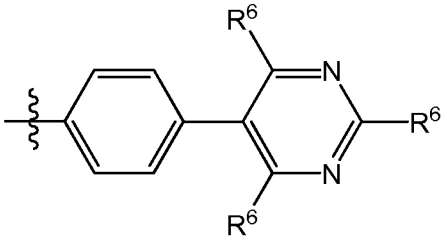
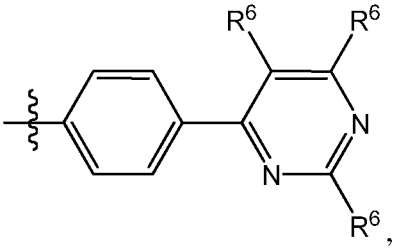


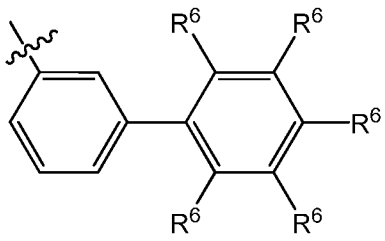
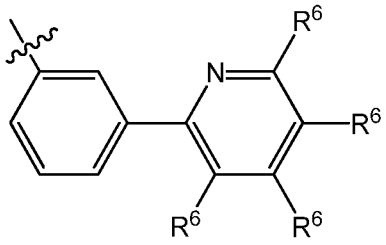

, or  .

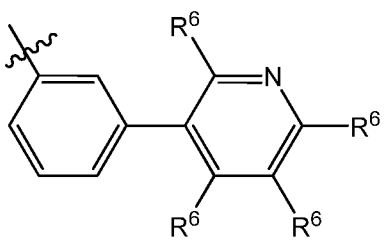
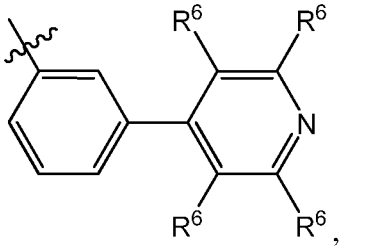
Embodiment 94. The compound of embodiment 72, 73, or 90, wherein Z is:

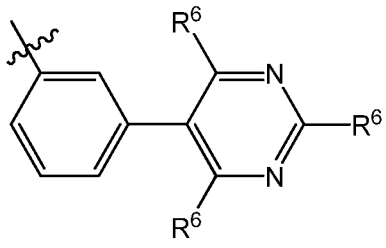

,  ,


,  ,


,  ,


,  ,


,  ,



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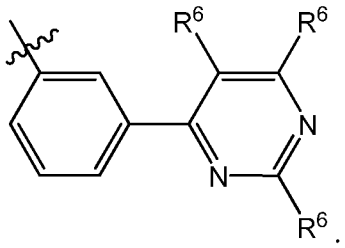


.

Embodiment 95. The compound of any one of embodiments 73 or 72-94, wherein J is a bond.

Embodiment 96. The compound of any one of embodiments 73 or 72-94, wherein J is O.

Embodiment 97. The compound of any one of embodiments 73 or 72-94, wherein J is S.

Embodiment 98. The compound of any one of embodiments 72-97, wherein q is 0.

Embodiment 99. The compound of any one of embodiments 72-97, wherein q is 1.

Embodiment 100. The compound of any one of embodiments 72-97, wherein q is 2.

Embodiment 101. The compound of any one of embodiments 72-100, wherein r is 0.

Embodiment 102. The compound of any one of embodiments 72-100, wherein r is 1.

Embodiment 103. The compound of any one of embodiments 72-100, wherein r is 2.

Embodiment 104. The compound of any one of embodiments 72-97, wherein q and r are each 0.

Embodiment 105. The compound of any one of embodiments 72-97, wherein q and r are each 1.

Embodiment 106. The compound of any one of embodiments 73 or 74-83, wherein n is 0.

Embodiment 107. The compound of any one of embodiments 73 or 74-83, wherein n is 1.

Embodiment 108. The compound of any one of embodiments 73 or 74-83, wherein n is 2.

Embodiment 109. The compound of any one of embodiments 72-91, or 107-108, wherein each R^4 and R^5 is H.

Embodiment 110. The compound of any one of embodiments 72-109, wherein each R^{11} is H.

Embodiment 111. The compound of any one of embodiments 73 or 72-110, wherein the at least one imaging moiety is present in R^1, R^2, R^3, R^4, R^5, R^6, or R^{11}.

Embodiment 112. The compound of any one of embodiments 73 or 72-111, wherein R^1 is alkyl optionally substituted.

Embodiment 113. The compound of any one of embodiments 73 or 72-111, wherein R^1 is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, or t-butyl.

Embodiment 114. The compound of any one of embodiments 73 or 72-111, wherein R^1 is $-C(CH_3)_2CH_2OH$.

Embodiment 115. The compound of any one of embodiments 73 or 72-111, wherein R^1 is t-butyl.

Embodiment 116. The compound of any one of embodiments 73 or 72-111, wherein R^1 is aryl optionally substituted.

Embodiment 117. The compound of any one of embodiments 73 or 72-111, wherein R^1 is phenyl optionally substituted.

Embodiment 118. The compound of any one of embodiments 73 or 72-111, wherein R^1 is

unsubstituted phenyl.

Embodiment 119. The compound of any one of embodiments 73 or 72-111, wherein R^1 is cycloalkyl optionally substituted.

Embodiment 120. The compound of any one of embodiments 73 or 72-111, wherein R^1 is cyclohexyl optionally substituted.

Embodiment 121. The compound of any one of embodiments 73 or 72-120, wherein R^2 is H.

Embodiment 122. The compound of any one of embodiments 73 or 72-121, wherein R^3 is halo.

Embodiment 123. The compound of any one of embodiments 73 or 72-121, wherein R^3 is Cl.

Embodiment 124. The compound of any one of embodiments 73 or 72-121, wherein R^3 is Br.

Embodiment 125. The compound of any one of embodiments 73 or 72-121, wherein R^3 is H.

Embodiment 126. The compound of any one of embodiments 73 or 72-121, wherein R^3 is alkyl optionally substituted.

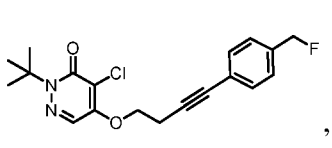
Embodiment 127. The compound of any one of embodiments 73 or 72-121, wherein R^3 is unsubstituted alkyl.

Embodiment 128. The compound of any one of embodiments 73 or 72-121, wherein R^3 is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, or t-butyl.

Embodiment 129. The compound of any one of embodiments 73 or 72-121, wherein R^3 is

methyl.

Embodiment 130. The compound of embodiment 72, wherein the compound is selected from the group consisting of: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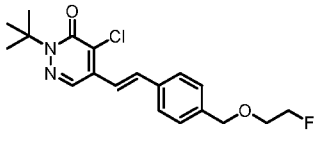
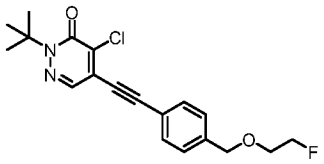
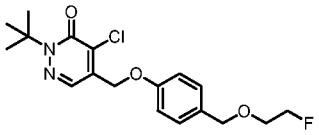

, or



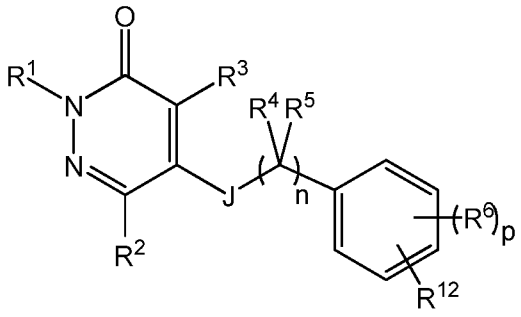
or a pharmaceutically acceptable salt thereof, wherein F is optionally ^{18}F.

Embodiment 131. The compound of embodiment 73, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof, wherein F is optionally ^{18}F.

Embodiment 132. The compound of embodiment 1, wherein the compound comprises the structure:


(VIII)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted,

heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –NO_2, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, –NO_2, and an imaging moiety;

J is selected from the group consisting of consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–N(R^7)_2$, –NO_2, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, $–Si(R^9)_3$, $–B(R^{9'})_3$, $–OR^8$, and an imaging moiety;

p is 0, 1, 2, 3, or 4;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring; and

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

R^{12} is selected from the group consisting of alkynyl optionally substituted, alkenyl optionally substituted, alkyl substituted with –CN, alkyl substituted with $–C(=O)OR^8$, alkyl substituted with $–C(=O)R^8$, alkyl substituted with $–N(R^7)_2$, –CN, –NO_2, $–N(R^7)_2$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)R^8$, $–C(=O)N(R^7)_2$, and $–N(R^7)C(=O)R^8$;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound.

Embodiment 133. The compound of embodiment 132, wherein R^{12} is $–NO_2$, $–C(=O)(CH_2)_uI_m$, $–C(=O)O(CH_2)_uI_m$, $–C\equiv C(CH_2)_uI_m$, or $–Si(alkyl)_2I_m$; wherein I_m is an imaging moiety and u is 1, 2, 3, 4, 5, or 6.

Embodiment 134. The compound of any one of embodiments 132-133, wherein the at least one imaging moiety is present in R^1, R^2, R^3, R^4, R^5, R^6, or R^{12}.

Embodiment 135. The compound of any one of embodiments 132-133, wherein the at least one imaging moiety is present in R^1, R^3, R^4, R^5, R^6, or R^{12}.

Embodiment 136. The compound of any one of embodiments 132-134, wherein R^1 is alkyl optionally substituted.

Embodiment 137. The compound of any one of embodiments 132-134, wherein R^1 is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, or t-butyl.

Embodiment 138. The compound of any one of embodiments 132-134, wherein R^1 is $–C(CH_3)_2CH_2OH$.

Embodiment 139. The compound of any one of embodiments 132-134, wherein R^1 is t-butyl.

Embodiment 140. The compound of any one of embodiments 132-134, wherein R^1 is aryl optionally substituted.

Embodiment 141. The compound of any one of embodiments 132-134, wherein R^1 is

phenyl optionally substituted.

Embodiment 142. The compound of any one of embodiments 132-134, wherein R^1 is unsubstituted phenyl.

Embodiment 143. The compound of any one of embodiments 132-134, wherein R^1 is cycloalkyl optionally substituted.

Embodiment 144. The compound of any one of embodiments 132-134, wherein R^1 is cyclohexyl optionally substituted.

Embodiment 145. The compound of any one of embodiments 132-144, wherein R^2 is H.

Embodiment 146. The compound of any one of embodiments 132-145, wherein J is a bond.

Embodiment 147. The compound of any one of embodiments 132-145, wherein J is O.

Embodiment 148. The compound of any one of embodiments 132-145, wherein J is S.

Embodiment 149. The compound of any one of embodiments 132-148, wherein n is 0.

Embodiment 150. The compound of any one of embodiments 132-148, wherein n is 1.

Embodiment 151. The compound of any one of embodiments 132-148, wherein n is 2.

Embodiment 152. The compound of any one of embodiments 132-151, wherein each of R^4 and R^5 is H.

Embodiment 153. The compound of any one of embodiments 132-151, wherein at least one R^4 and R^5 is ^2H, and optionally, wherein each of R^4 and R^5 is ^2H.

Embodiment 154. The compound of any one of embodiments 132-153, wherein R^3 is halo.

Embodiment 155. The compound of any one of embodiments 132-153, wherein R^3 is Cl.

Embodiment 156. The compound of any one of embodiments 132-153, wherein R^3 is Br.

Embodiment 157. The compound of any one of embodiments 132-153, wherein R^3 is H.

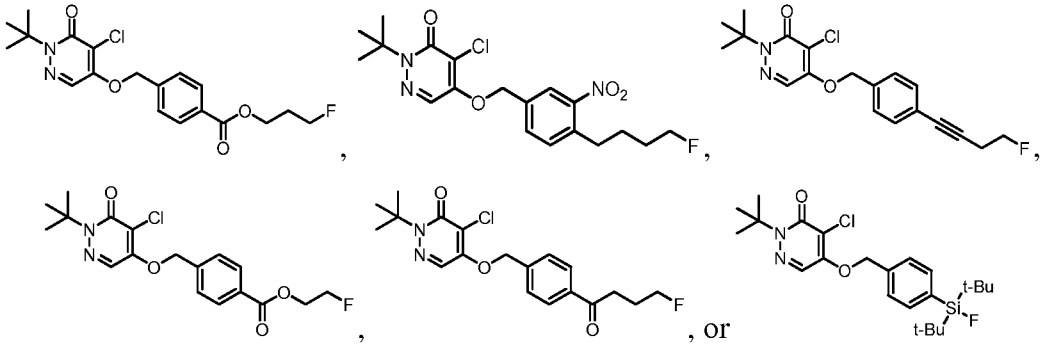
Embodiment 158. The compound of any one of embodiments 132-153, wherein R^3 is alkyl optionally substituted.

Embodiment 159. The compound of any one of embodiments 132-153, wherein R^3 is unsubstituted alkyl.

Embodiment 160. The compound of any one of embodiments 132-153, wherein R^3 is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, or t-butyl.

Embodiment 161. The compound of any one of embodiments 132-153, wherein R^3 is methyl.

Embodiment 162. The compound of embodiment 132, wherein the compound is selected from the group consisting of:



or a pharmaceutically acceptable salt thereof, wherein F is optionally ^{18}F.

Embodiment 163. The compound of any one of embodiments 1 -13, 15-70, 72-124, and 132-161, wherein the at least one imaging moiety is present in R^6.

Embodiment 164. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-

161, and 163, wherein at least one R^6 is substituted with the at least one imaging moiety.

Embodiment 165. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-164, wherein the at least one imaging moiety is selected from the group consisting of ^{11}C, ^{13}N, ^{18}F, ^{76}Br, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{99m}Tc, ^{95}Tc, ^{111}In, ^{62}Cu, ^{64}Cu, ^{67}Ga, and ^{68}Ga.

Embodiment 166. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-165, wherein the at least one imaging moiety is ^{18}F.

Embodiment 167. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-165, wherein the at least one imaging moiety is associated with a group comprising the structure $-B(R^{9'})_2(I_m)$, wherein I_m is an imaging moiety, optionally ^{18}F.

Embodiment 168. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-165, wherein the at least one imaging moiety is associated with a group comprising the structure $-Si(R^9)_2(I_m)$, wherein I_m is an imaging moiety, optionally ^{18}F.

Embodiment 169. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-168, wherein all but one R^6 is H.

Embodiment 170. The compound of embodiment 169, wherein one R^6 is substituted with the at least one imaging moiety.

Embodiment 171. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-166, wherein at least one R^6 is alkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, each substituted with an imaging moiety.

Embodiment 172. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-166, wherein at least one R^6 is $-O(CH_2)_jI_m$; wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6.

Embodiment 173. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-166, wherein at least one R^6 is $-(CH_2)_jO(CH_2)_jI_m$; wherein I_m is an imaging

moiety and each j is independently 1, 2, 3, 4, 5, or 6.

Embodiment 174. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-166, wherein at least one R^6 is $–C\equiv C–(CH_2)_jI_m$; wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6.

Embodiment 175. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-166, wherein at least one R^6 is $–[(CH_2)_jO]_j(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6.

Embodiment 176. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-166, wherein at least one R^6 is $–O[(CH_2)_jO]_j(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6.

Embodiment 177. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-166, wherein at least one R^6 is optionally substituted alkyl substituted with an imaging moiety.

Embodiment 178. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-166, wherein at least one R^6 is $–C(=O)O(CH_2)_jI_m$; wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6.

Embodiment 179. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-166, wherein at least one R^6 is $–C(=O)(CH_2)_jI_m$; wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6.

Embodiment 180. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-166, wherein at least one R^6 is $–(CH_2)_jNH(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6.

Embodiment 181. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-166, wherein at least one R^6 is $Si(R^9)_2\ I_m$, wherein each R^9 is alkyl optionally substituted and wherein I_m is an imaging moiety.

Embodiment 182. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-166, wherein the at least one imaging moiety is associated with a group comprising the structure $–B(R^{9'})_2(I_m)$, wherein I_m is an imaging moiety, optionally ^{18}F.

Embodiment 183. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-166, wherein at least one R^6 is selected from the group consisting of $–C\equiv C–CH_2CH_2CH_2I_m$, $–C\equiv C–CH_2CH_2I_m$, $–C\equiv C–CH_2I_m$, $–CH_2I_m$, $–(CH_2)_2I_m$, $–(CH_2)_3I_m$, $–(CH_2)_4I_m$, $–(CH_2)_5I_m$, $–(CH_2)_6I_m$, $–OCH_2I_m$, $–O(CH_2)_2I_m$, $–O(CH_2)_3I_m$, $–O(CH_2)_4I_m$, $–O(CH_2)_5I_m$, $–O(CH_2)_6I_m$, $–CH_2O(CH_2)_2I_m$, $–CH(CH_3)O(CH_2)_2I_m$, $–CH_2O(CH_2)_3I_m$, $–CD_2O(CH_2)_2I_m$, $–(CH_2)_2O(CH_2)_2I_m$, $–CHBrC(CH_3)_2I_m$, $–CHClC(CH_3)_2I_m$, $–CHFC(CH_3)_2I_m$, $–C(=O)OCH_2I_m$, $–C(=O)O(CH_2)_2I_m$, $–C(=O)O(CH_2)_3I_m$, $–CH_2NH(CH_2)_2I_m$, $–CH_2NHCH_2I_m$, $–CH_2O(CH_2)_2O(CH_2)_2I_m$, $–CH_2O(CH_2)_2O(CH_2)_3I_m$, $–O(CH_2)_2O(CH_2)_2I_m$, $–C(=O)(CH_2)_2I_m$, and $–C(=O)(CH_2)_3I_m$; optionally, wherein I_m is ^{18}F.

Embodiment 184. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-166, wherein at least one R^6 is an imaging moiety, optionally, wherein the imaging moiety is ^{18}F.

Embodiment 185. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-166, wherein at least one R^6 is optionally substituted with at least one ^2H.

Embodiment 186. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-166, wherein at least one R^6 is $–Si(R^9)_3$.

Embodiment 187. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-166, wherein at least one R^6 is $–B(R^{9'})_3$.

Embodiment 188. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-187, wherein at least one R^6 is $–NO_2$.

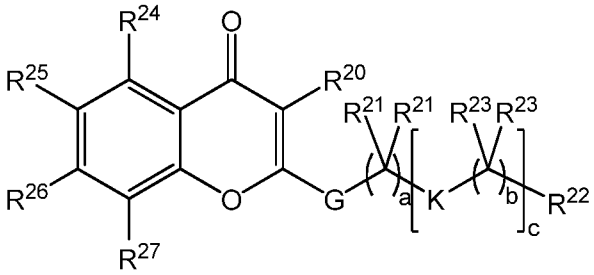
Embodiment 189. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-187, wherein at least one R^6 is halo.

Embodiment 190. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-187, wherein at least one R^6 is Cl.

Embodiment 191. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-187, wherein at least one R^6 is Br.

Embodiment 192. The compound of any one of embodiments 1 -13, 15-70, 72-124, 132-161, and 163-187, wherein at least one R^6 is F.

Embodiment 193. In embodiment 193, provided is a compound comprising the formula:



(IX)

or a pharmaceutically acceptable salt thereof, wherein:

R^{20} is selected from the group consisting of hydrogen, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, and $–NO_2$;

each R^{21} and R^{23} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally any two R^{21} or any two R^{23} may be joined together to form a ring;

R^{22} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, $–OR^{28}$, $–Si(R^9)_3$, $–B(R^{9'})_3$, and an imaging moiety;

R^{24}, R^{25}, R^{26}, and R^{27} are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –

NO_2, –OH, –C(=O)R^8, –C(=O)OR^8, –OC(=O)R^8, –C(=O)N(R^7)$_2$, –N(R^7)C(=O)R^8, –CN, and an imaging moiety;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring; and

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and an imaging moiety;

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety;

R^{28} is selected from the group consisting of hydrogen, alkyl optionally substituted, and heteroalkyl optionally substituted;

G is O, S, or NR^{28};

a is 0, 1, 2, 3, or 4;

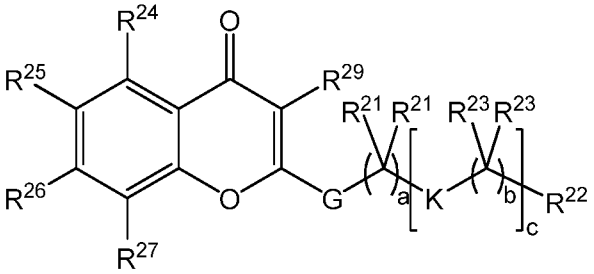
each K is independently arylene, heteroarylene, alkenylene, or alkynylene, each optionally substituted;

each b is independently 0, 1, 2, 3, or 4; and

c is 1 or 2,

provided at least one imaging moiety is present in the compound.

Embodiment 194. In embodiment 194, provided is a compound comprising the formula:



(X)

or a pharmaceutically acceptable salt thereof, wherein:

each R^{21} and R^{23} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally any two R^{21} or any two R^{23} may be joined together to form a ring;

R^{22} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, $-OR^{28}$, $-Si(R^9)_3$, $-B(R^{9'})_3$, and an imaging moiety;

R^{24}, R^{25}, R^{26}, and R^{27} are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, and an imaging moiety;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and an imaging moiety;

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety;

R^{28} is selected from the group consisting of hydrogen, alkyl optionally substituted, and heteroalkyl optionally substituted;

R^{29} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, optionally substituted alkoxy, optionally substituted alkoxyalkyl, halo, haloalkyl, $-CN$, $-NO_2$, and an imaging moiety;

G is O, S, or NR^{28};

a is 0, 1, 2, 3, or 4;

each K is independently arylene, heteroarylene, alkenylene, or alkynylene, each optionally substituted, provided at least one K is alkenylene, or alkynylene;

each b is independently 0, 1, 2, 3, or 4; and

c is 1 or 2,

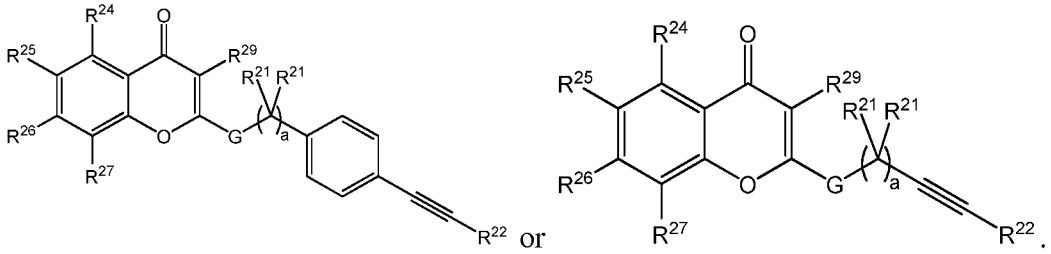
provided at least one imaging moiety is present in the compound.

Embodiment 195. The compound of embodiment 193, wherein R^{29} is alkyl optionally substituted.

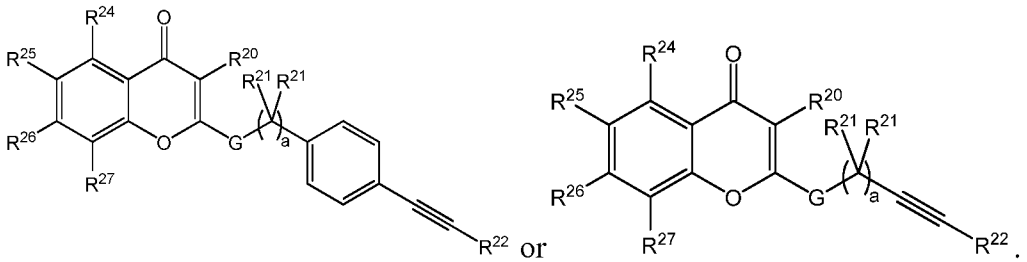
Embodiment 196. The compound of embodiment 193, wherein R^{29} is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, or t-butyl.

Embodiment 197. The compound of embodiment 193, wherein R^{29} is methyl.

Embodiment 198. The compound of embodiment 194, wherein the compound comprises the structure:



Embodiment 199. The compound of embodiment 193, wherein the compound comprises the structure:



Embodiment 200. The compound of any one of embodiments 193-199, wherein each of R^{24}, R^{25}, R^{26}, and R^{27} are H.

Embodiment 201. The compound of any one of embodiments 193-200, wherein G is O.

Embodiment 202. The compound of any one of embodiments 193-200, wherein G is S.

Embodiment 203. The compound of any one of embodiments 193-200, wherein G is NR^{28}.

Embodiment 204. The compound of any one of embodiments 193-200, wherein G is NH.

Embodiment 205. The compound of any one of embodiments 193-204, wherein a is 0.

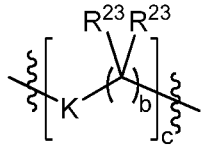
Embodiment 206. The compound of any one of embodiments 193-204, wherein a is 1.

Embodiment 207. The compound of any one of embodiments 193-204, wherein a is 2.

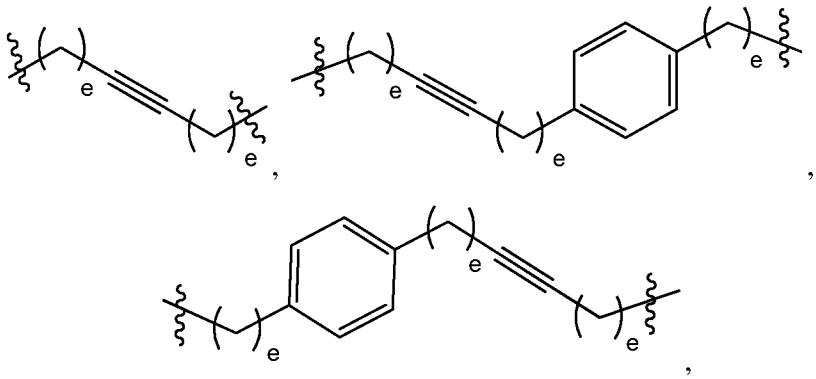
Embodiment 208. The compound of any one of embodiments 193-204, wherein a is 3.

Embodiment 209. The compound of any one of embodiments 193-204, wherein a is 4.

Embodiment 210. The compound of any one of embodiments 193-197 or 200-209, wherein at least one K is alkynylene.

Embodiment 211. The compound of any one of embodiments 193-197 or 200-209, wherein 

has the structure:



, or

,

wherein each e is independently 1, 2, 3, or 4.

Embodiment 212. The compound of any one of embodiments 193-211, wherein each R^{21} is H.

Embodiment 213. The compound of any one of embodiments 193-212, wherein R^{22} is $-O(CH_2)_jI_m$; wherein I_m is an imaging moiety and j is 1, 2, 3, 4, 5, or 6.

Embodiment 214. The compound of any one of embodiments 193-212, wherein R^{22} is $-(CH_2)_jO(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6.

Embodiment 215. The compound of any one of embodiments 193-212, wherein R^{22} is $-[(CH_2)_jO]_j(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6.

Embodiment 216. The compound of any one of embodiments 193-212, wherein R^{22} is $-O[(CH_2)_jO]_j(CH_2)_jI_m$; wherein I_m is an imaging moiety and each j is independently 1, 2, 3, 4, 5, or 6.

Embodiment 217. The compound of any one of embodiments 193-212, wherein R^{22} is optionally substituted alkyl substituted with an imaging moiety.

Embodiment 218. The compound of any one of embodiments 193-212, wherein the at least one imaging moiety is present in R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, or R^{27}.

Embodiment 219. The compound of any one of embodiments 193-212, wherein the at least one imaging moiety is present in R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27} or R^{29}.

Embodiment 220. The compound of any one of embodiments 193-212, wherein the at least one imaging moiety is present in R^{21}, R^{22}, or R^{23}.

Embodiment 221. The compound of any one of embodiments 193-212, wherein the at least one imaging moiety is present in R^{22}.

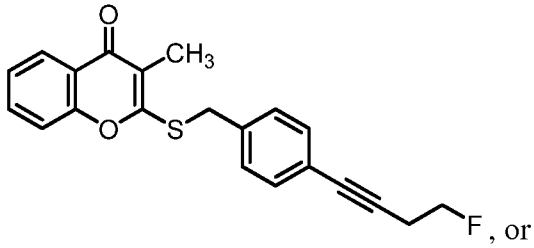
Embodiment 222. The compound of any one of embodiments 193-212, wherein R^{22} comprises the at least one imaging moiety.

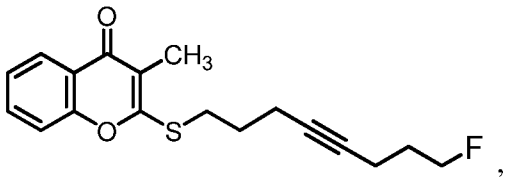
Embodiment 223. The compound of any one of embodiments 193-212, wherein R^{22} is an imaging moiety.

Embodiment 224. The compound of any one of embodiments 193-223, wherein the at least one imaging moiety is selected from the group consisting of ^{11}C, ^{13}N, ^{18}F, ^{76}Br, ^{89}Zr, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{99m}Tc, ^{95}Tc, ^{111}In, ^{62}Cu, ^{64}Cu, ^{67}Ga, and ^{68}Ga.

Embodiment 225. The compound of any one of embodiments 193-224, wherein the at least one imaging moiety is ^{18}F.

Embodiment 226. The compound of embodiment 194, wherein the compound is selected from the group consisting of:

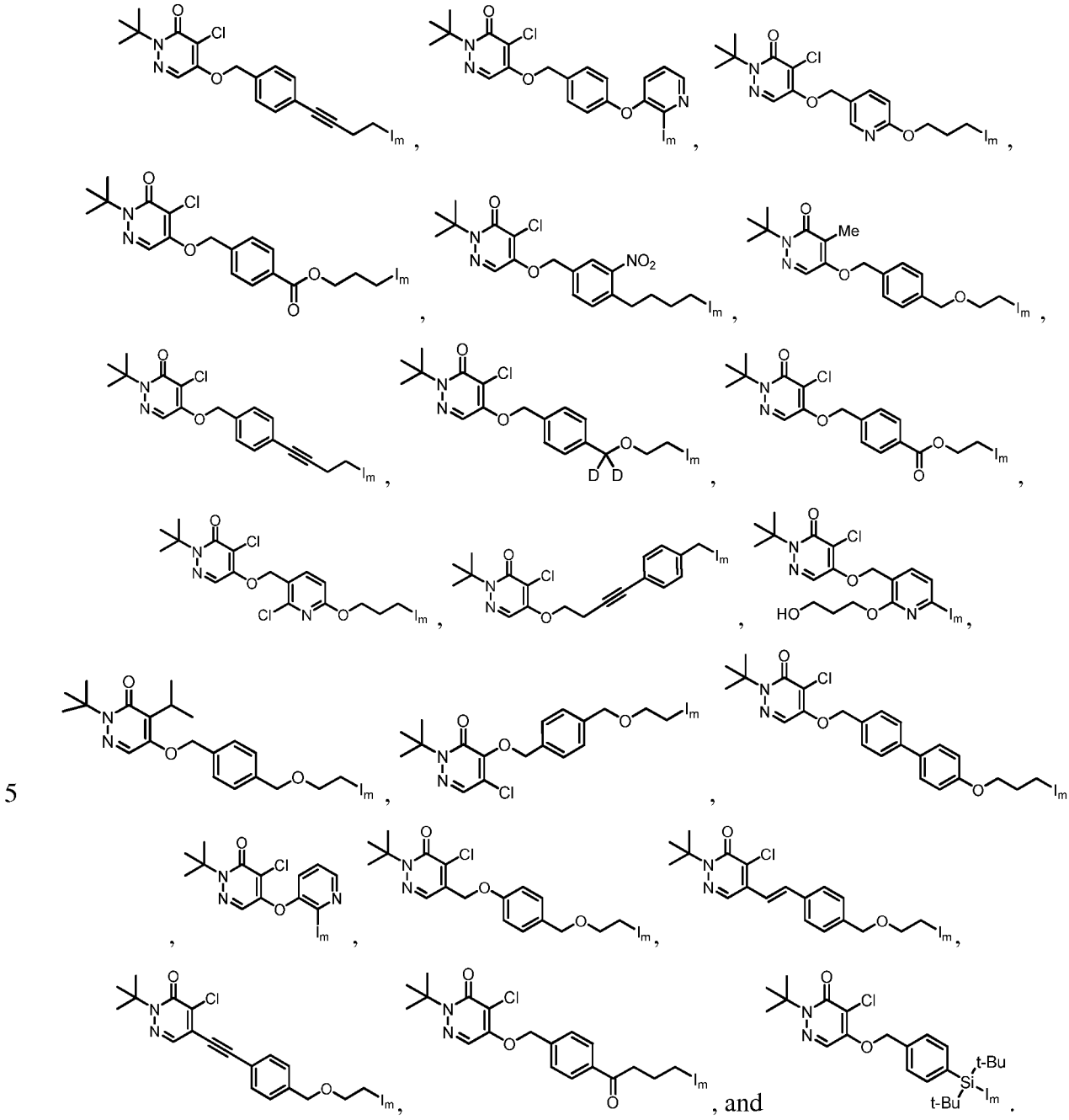


, or


,

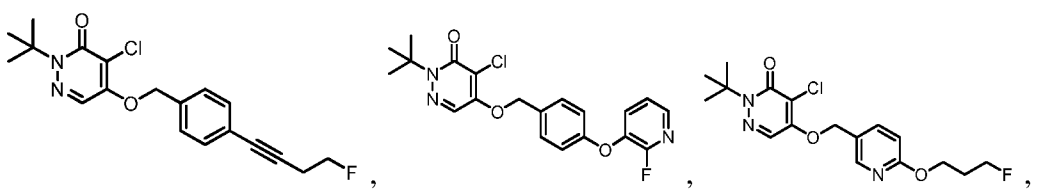
or a pharmaceutically acceptable salt thereof, wherein F is optionally ^{18}F.

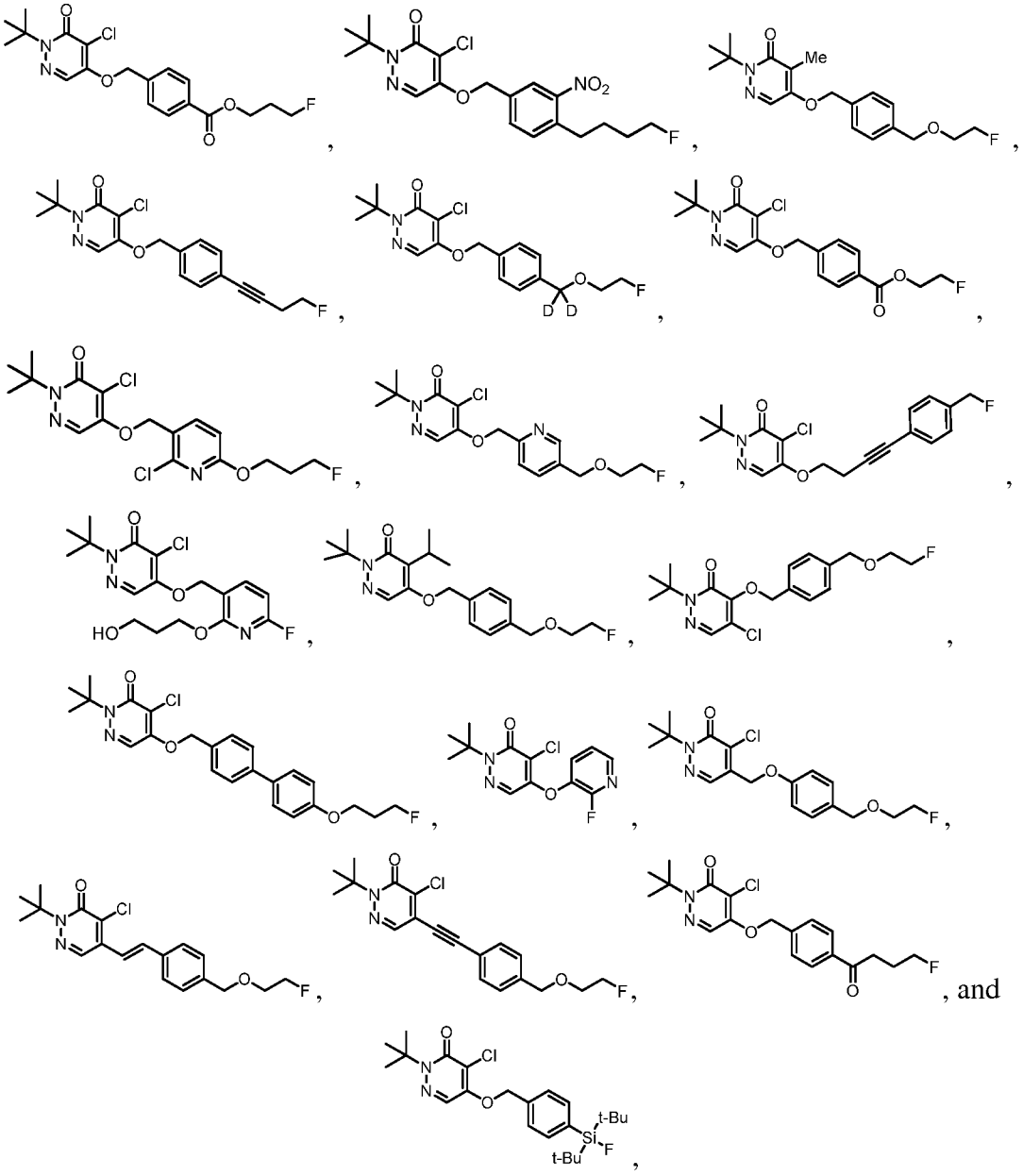
Embodiment 227. In embodiment 227, provided is a compound is selected from the group consisting of:



or a pharmaceutically acceptable salt thereof, wherein I_m is an imaging moiety.

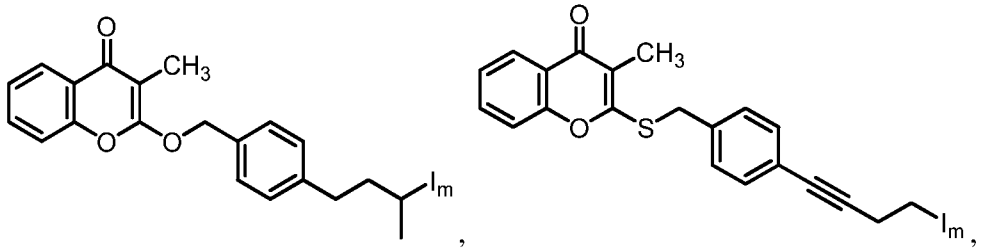
Embodiment 228. The compound of embodiment 227, wherein the compound is selected from the group consisting of:

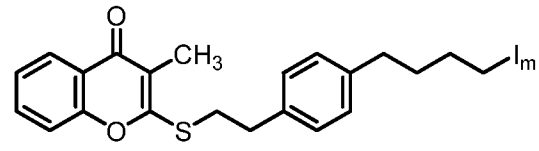




or a pharmaceutically acceptable salt thereof, wherein each F is optionally ^{18}F.

Embodiment 229. In embodiment 229, provided is a compound selected from the group consisting of:

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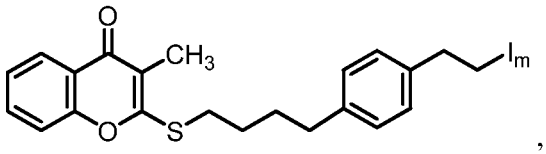
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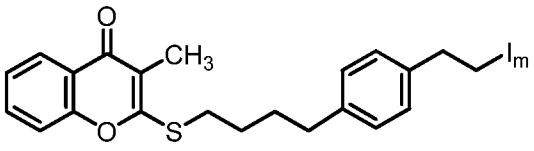
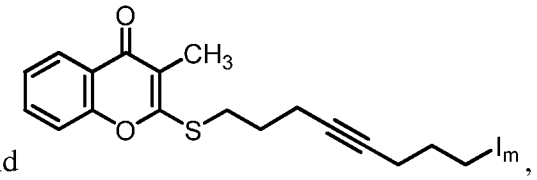
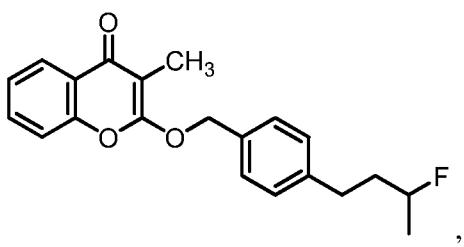

, and

,

or a pharmaceutically acceptable salt thereof, wherein I_m is an imaging moiety.

Embodiment 230. The compound of embodiment 229, wherein the compound is selected from the group consisting of: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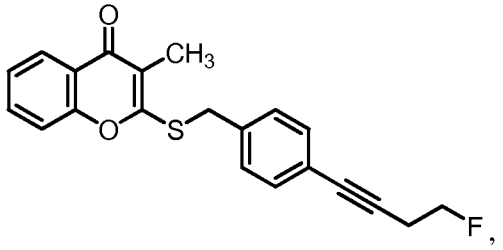
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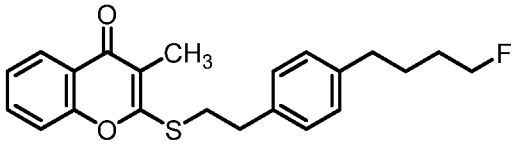
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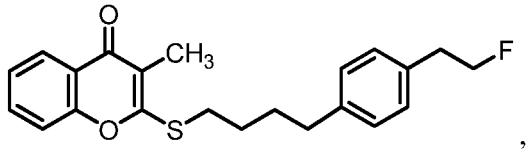
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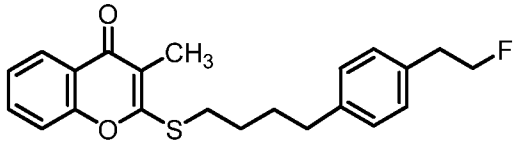
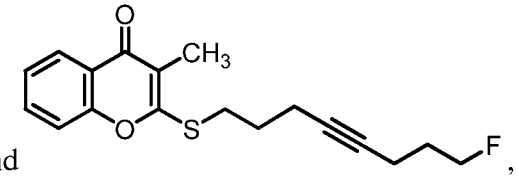

, and

,

or a pharmaceutically acceptable salt thereof, wherein each F is optionally ^{18}F.

Embodiment 231. In embodiment 231, provided is a pharmaceutical composition comprising a compound or a salt thereof of any preceding embodiment, and optionally a pharmaceutically acceptable excipient.

Embodiment 232. In embodiment 232, provided is a sterile aqueous solution comprising a compound or a salt thereof of any preceding embodiment.

Embodiment 233. Use of a compound or a salt thereof of any preceding embodiment as an imaging agent.

Embodiment 234. Use of a compound or a salt thereof of any preceding embodiment in myocardial perfusion imaging.

Embodiment 235. Use of a compound or salt thereof of any preceding embodiment in the manufacture of a medicament for detecting, imaging or monitoring myocardial perfusion.

Embodiment 236. In embodiment 236, provided is a method of imaging a portion of a subject, comprising:

administering to the subject a compound or a salt thereof of any preceding embodiment, or a composition of embodiment 231, or a sterile aqueous solution of embodiment 232; and

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

Embodiment 237. In embodiment 237, provided is a method of imaging a portion of a subject, comprising:

administering to a subject a compound or a salt thereof of any preceding embodiment or a salt thereof, or a pharmaceutical composition of embodiment 231, or a sterile aqueous solution of embodiment 232;

detecting radiation emitted by the compound; and

forming an image therefrom.

Embodiment 238. The method of embodiment 237, wherein the portion of the subject imaged is a portion of the heart.

Embodiment 239. In embodiment 239, provided is a diagnostic kit comprising one or more vials containing a precursor to a compound or a salt thereof of any preceding embodiment; and optionally other components.

Embodiment 240. The diagnostic kit of embodiment 239, wherein the diagnostic kit is for the preparation of diagnostic agents for imaging, detecting, and/or monitoring myocardial perfusion in a subject.

Embodiment 241. The diagnostic kit of embodiment 239 or 240, wherein said other components are selected from the group consisting of ancillary ligands, reducing agents, transfer ligands, buffers, lyophilization aids, stabilization aids, solubilization aids, and bacteriostats.

Embodiment 242. In embodiment 242, provided is a method of imaging myocardial perfusion, comprising:

administering to a patient a compound or a salt thereof of any preceding embodiment, or a pharmaceutical composition of embodiment 231, or a sterile aqueous solution of embodiment 232; and

scanning the patient using diagnostic imaging.

Embodiment 243. In embodiment 243, provided is a method of detecting myocardial perfusion, comprising:

administering to a patient a compound or a salt thereof of any preceding embodiment, or a pharmaceutical composition of embodiment 231, or a sterile aqueous solution of embodiment 232; and

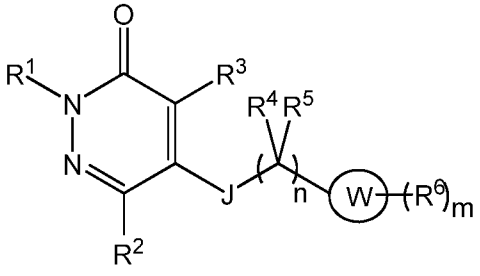
scanning the patient using diagnostic imaging.

Embodiment 244. In embodiment 244, provided is a method of monitoring myocardial perfusion, comprising:

administering to a patient a compound or a salt thereof of any preceding embodiment, or a pharmaceutical composition of embodiment 231, or a sterile aqueous solution of embodiment 232; and

scanning the patient using diagnostic imaging.

Embodiment 245. In embodiment 245, provided is a compound comprising the structure:



(XI)

or a salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and a leaving group;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and a leaving group;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $-NO_2$, and a leaving group;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and a leaving group, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

W is heteroaryl, naphthyl, heterocyclyl or aryl;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, –OH, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, –CN, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and a leaving group;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

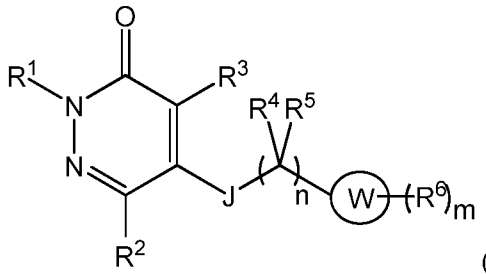
each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and a leaving group; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group,

provided that at least one leaving group is present in the compound; and

provided that when W is aryl, a) R^3 is not halo, alkyl or haloalkyl, or b) at least one R^6 is selected from the group consisting of alkynyl optionally substituted, alkenyl optionally substituted, alkyl substituted with –CN, alkyl substituted with $–C(=O)OR^8$, alkyl substituted with $–C(=O)R^8$, alkyl substituted with $–N(R^7)_2$, –CN, $–NO_2$, $–N(R^7)_2$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)R^8$, $–C(=O)N(R^7)_2$, and $–N(R^7)C(=O)R^8$.

Embodiment 246. The compound of embodiment 245, wherein the compound comprises the structure:



(XII)

or a salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and a leaving group;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–NO_2$, and a leaving group;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and a leaving group;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and a leaving group, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

W is heteroaryl, naphthyl, or heterocyclyl;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and a leaving group;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring; and

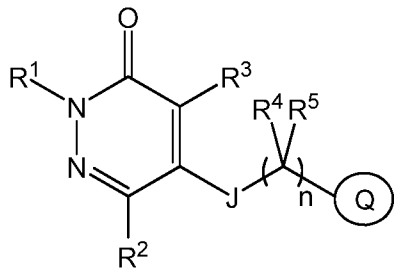
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and a leaving group; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group,

provided that at least one leaving group is present in the compound.

Embodiment 247. The compound of embodiment 245, wherein the compound comprises the structure:



(XIII)

or a salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and a leaving group;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–NO_2$, and a leaving group;

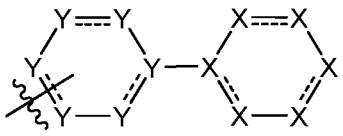
R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and a leaving group;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and a leaving group, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

Q has the structure:



each Y and each X is independently selected from the group consisting of C, $C(R^6)$, $C(R^6)_2$, N, NR^7, O, and S, provided at least one Y is not C or $C(R^6)$;

each ------ is independently a single or double bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally

substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and a leaving group;

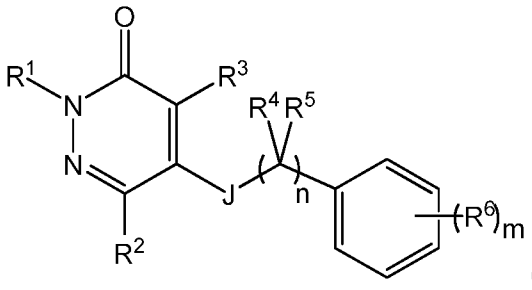
each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring; each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and a leaving group; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group,

provided that at least one leaving group is present in the compound.

Embodiment 248. The compound of embodiment 245, wherein the compound comprises the structure:



(XIV)

or a salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and a leaving group;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –

NO_2, and a leaving group;

R^3 is selected from the group consisting of hydrogen, unsubstituted alkyl or alkyl optionally substituted with a moiety other than a halogen, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, –CN, and $–NO_2$;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and a leaving group, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–N(R^7)_2$, $–NO_2$, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, $–Si(R^9)_3$, $–B(R^{9'})_3$, $–OR^8$, and a leaving group;

m is 0, 1, 2, 3, 4, or 5;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring; and

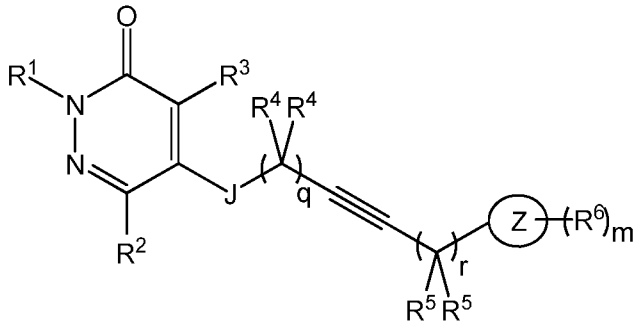
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and a leaving group; and

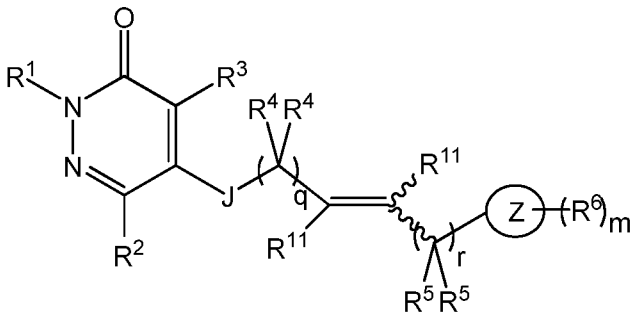
each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group,

provided that at least one leaving group is present in the compound.

Embodiment 249. In embodiment 249, provided is a compound comprising the structure:



(XV) or



(XVI),

or a salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and a leaving group;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and a leaving group;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $-NO_2$, and a leaving group;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

each R^4, R^5, and R^{11} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, and a leaving group, or optionally any two of R^4 or any two of R^5 are joined together to form a ring;

q, and r are each independently 0, 1, 2, or 3;

Z is selected from the group consisting of aryl, heteroaryl, heterocyclyl, and a bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl

optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, –OH, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, –CN, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and a leaving group;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring;

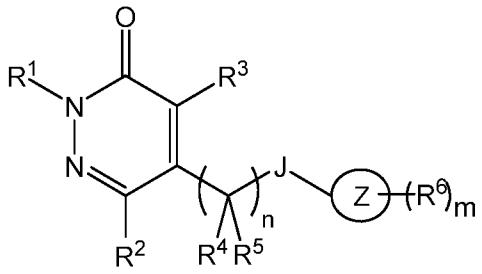
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and a leaving group; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group,

provided that at least one leaving group is present in the compound.

Embodiment 250. In embodiment 250, provided is a compound comprising the structure:



(XVII)

or a salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and a leaving group;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted,

heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, $–NO_2$, haloalkyl, and a leaving group;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and a leaving group;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)_2$, $N(R^7)C(=O)$, and $–CH_2O$;

each R^4 and R^5 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, and a leaving group, or optionally any two of R^4 or any two of R^5 are joined together to form a ring;

n is 1, 2, or 3;

Z is selected from the group consisting of aryl, heteroaryl, heterocyclyl, and a bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–N(R^7)_2$, $–NO_2$, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, $–Si(R^9)_3$, $–B(R^{9'})_3$, $–OR^8$, and a leaving group;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring; and

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

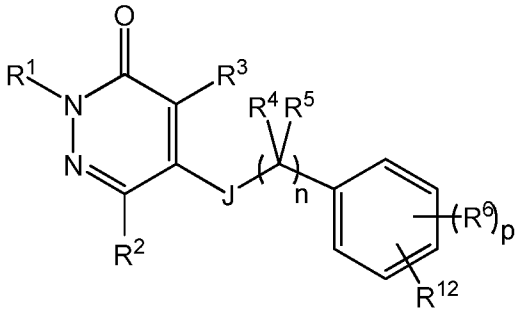
each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and a leaving group; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally

substituted , aryl optionally substituted, and a leaving group,

provided that at least one leaving group is present in the compound.

Embodiment 251. The compound of embodiment 245, wherein the compound comprises the structure:



(XVIII)

or a salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and a leaving group;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, and a leaving group;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and a leaving group;

J is selected from the group consisting of consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and a leaving group, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl

optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and a leaving group;

p is 0, 1, 2, 3, or 4;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

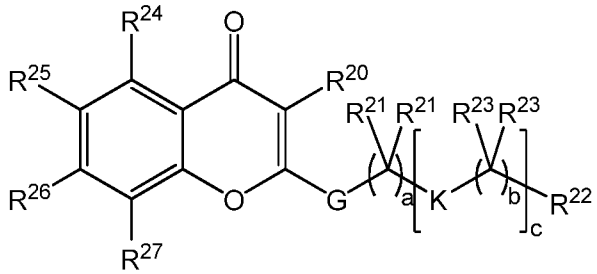
R^{12} is selected from the group consisting of alkynyl optionally substituted, alkenyl optionally substituted, alkyl substituted with $-CN$, alkyl substituted with $-C(=O)OR^8$, alkyl substituted with $-C(=O)R^8$, alkyl substituted with $-N(R^7)_2$, $-CN$, $-NO_2$, $-N(R^7)_2$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)R^8$, $-C(=O)N(R^7)_2$, and $-N(R^7)C(=O)R^8$;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and a leaving group; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group,

provided that at least one leaving group is present in the compound.

Embodiment 252. In embodiment 252, provided is a compound comprising the formula:



(XIX)

or a salt thereof, wherein:

R^{20} is selected from the group consisting of hydrogen, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-CN$, and $-NO_2$;

each R^{21} and R^{23} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, and a leaving group, or optionally any two R^{21} or any two R^{23} may be joined together to form a ring;

R^{22} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, $-OR^{28}$, $-Si(R^9)_3$, $-B(R^{9'})_3$, and a leaving group;

R^{24}, R^{25}, R^{26}, and R^{27} are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, and a leaving group;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring; each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and a leaving group;

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group;

R^{28} is selected from the group consisting of hydrogen, alkyl optionally substituted, and heteroalkyl optionally substituted;

G is O, S, or NR^{28};

a is 0, 1, 2, 3, or 4;

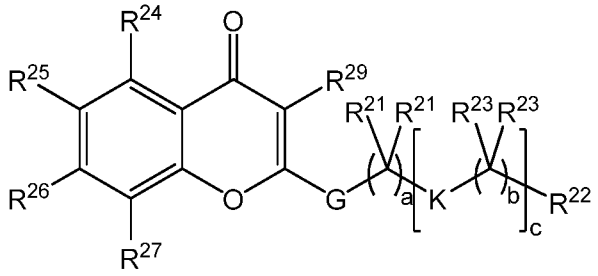
each K is independently arylene, heteroarylene, alkenylene, or alkynylene, each optionally substituted;

each b is independently 0, 1, 2, 3, or 4; and

c is 1 or 2,

provided at least one leaving group is present in the compound.

Embodiment 253. In embodiment 253, provided is a compound comprising the formula:



(XX)

or a salt thereof, wherein:

each R^{21} and R^{23} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, and a leaving group, or optionally any two R^{21} or any two R^{23} may be joined together to form a ring; R^{22} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, $-OR^{28}$, $-Si(R^9)_3$, $-B(R^{9'})_3$, and a leaving group;

R^{24}, R^{25}, R^{26}, and R^{27} are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, and a leaving group;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and a leaving group;

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group;

R^{28} is selected from the group consisting of hydrogen, alkyl optionally substituted, and heteroalkyl optionally substituted;

R^{29} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –C, $–NO_2$, and a leaving group;

G is O, S, or NR^{28};

a is 0, 1, 2, 3, or 4;

each K is independently arylene, heteroarylene, alkenylene, or alkynylene, each optionally substituted, provided at least one K is alkenylene, or alkynylene;

each b is independently 0, 1, 2, 3, or 4; and

c is 1 or 2,

provided at least one leaving group is present in the compound.

Embodiment 254. In embodiment 254, provided is a diagnostic kit comprising one or more vials containing a compound of any one of embodiments 245-253 or a salt thereof; and optionally other components.

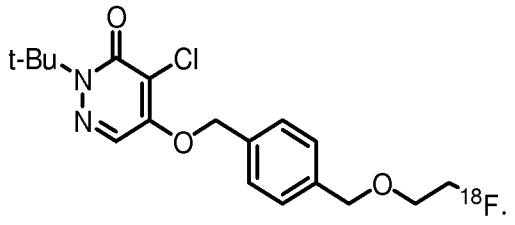
Embodiment 255. The diagnostic kit of embodiment 254, wherein the diagnostic kit is for the preparation of diagnostic agents for imaging, detecting, and/or monitoring myocardial perfusion in a subject.

Embodiment 256. The diagnostic kit of embodiment 254 or 255, wherein said other components are selected from the group consisting of ancillary ligands, reducing agents, transfer ligands, buffers, lyophilization aids, stabilization aids, solubilization aids, and bacteriostats.

Embodiment 257. In embodiment 257, provided is a method for forming an imaging agent, comprising reacting a compound of any one of embodiments 245-253 or a salt thereof with an ^{18}F-containing species to produce a imaging agent comprising ^{18}F.

Embodiment 258. In embodiment 258, provided is a cassette for the preparation of an imaging agent comprising the components arranged as shown in Figure 17.

Embodiment 259. The cassette as in embodiment 258, wherein the imaging agent has the formula:



Embodiment 260. In embodiment 260, provided is an apparatus for synthesizing an imaging agent comprising a linear arrangement of a plurality of stopcock manifolds arranged in the order:

1) luer connections (2) to gas inlet and [18O]H2O recovery;
2) anion exchange cartridge – column eluting solution;
3) spike connection for acetonitrile;
4) empty syringe;
5) reservoir with solution of imaging agent precursor;
6) reaction vessel;
7) outlet to HPLC;
8) syringe with solution of a stabilizing agent;
9) inlet from HPLC;
10) ethanol reservoir;
11) syringe with solution of a stabilizing agent;
12) syringe with water;
13) final product vial;
14) empty syringe; and
15) reaction vessel and exhaust.

Embodiment 261. In embodiment 261, provided is an apparatus for synthesizing an imaging agent comprising a linear arrangement of a plurality of stopcock manifolds arranged in the order:

1) luer connections (2) to gas inlet and [18O]H2O recovery;
2) anion exchange cartridge – column eluting solution;
3) reservoir with solution of imaging agent precursor;

4) empty syringe;
5) spike connection for acetonitrile;
6) reaction vessel;
7) outlet to HPLC;
8) syringe with solution of a stabilizing agent;
9) inlet from HPLC;
10) ethanol reservoir;
11) syringe with solution of a stabilizing agent;
12) syringe with water;
13) final product vial;
14) empty syringe; and
15) reaction vessel and exhaust.

Embodiment 262. In embodiment 262, provided is an apparatus for synthesizing an imaging agent comprising a linear arrangement of a plurality of stopcock manifolds arranged in the order:

1) luer connections (2) to gas inlet and [18O]H2O recovery;
2) anion exchange cartridge – column eluting solution;
3) reservoir with solution of imaging agent precursor;
4) empty syringe;
5) spike connection for acetonitrile;
6) reaction vessel;
7) outlet to HPLC;
8) syringe with solution of a stabilizing agent;
9) inlet from HPLC;
10) ethanol reservoir;
11) final product vial;
12) syringe with water;
13) syringe with solution of a stabilizing agent
14) empty syringe; and
15) reaction vessel and exhaust.

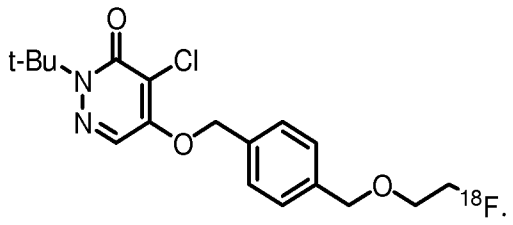
Embodiment 263. In embodiment 263, provided is an apparatus for synthesizing an imaging agent comprising a linear arrangement of a plurality of stopcock manifolds arranged in the order:

1) luer connections (2) to gas inlet and [18O]H2O recovery;
2) anion exchange cartridge – column eluting solution;
3) spike connection for acetonitrile;
4) empty syringe;
5) reservoir with solution of imaging agent precursor;
6) reaction vessel;
7) outlet to HPLC;
8) syringe with solution of a stabilizing agent;
9) inlet from HPLC;
10) ethanol reservoir;
11) final product vial;
12) syringe with water;
13) syringe with solution of a stabilizing agent;
14) empty syringe; and
15) reaction vessel and exhaust.

Embodiment 264. The apparatus of any one of embodiments 260-263, further comprising tubing.

Embodiment 265. The apparatus of any one of embodiments 260-264, further comprising an imaging agent synthesis module, wherein the apparatus is fluidically connected to the apparatus.

Embodiment 266. The apparatus of any one of embodiments 260-265, wherein the apparatus is capable of preparing an imaging agent comprising the formula:



Embodiment 267. The apparatus of any one of embodiments 260-266, wherein the solution of a stabilizing agent comprises a solution comprising ascorbic acid or a salt thereof.

Embodiment 268. The apparatus of any one of embodiments 267, wherein the syringe with solution of ascorbic acid or salt thereof at position 8 comprises a solution of ascorbic acid at pH 2.

Embodiment 269. The apparatus of any one of embodiments 260-268, wherein the syringe with solution of ascorbic acid or salt thereof at position 11 comprises a solution of ascorbic acid at pH 5.8.

Definitions

For convenience, certain terms employed in the specification, examples, and appended claims are listed here.

Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito: 1999, the entire contents of which are incorporated herein by reference.

Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

Isomeric mixtures containing any of a variety of isomer ratios may be utilized in accordance with the present invention. For example, where only two isomers are combined, mixtures containing 50:50, 60:40, 70:30, 80:20, 90:10, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0 isomer ratios are all contemplated by the present invention. Those of ordinary skill in the art will readily appreciate that analogous ratios are contemplated for more complex isomer

mixtures.

If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

The term "aliphatic," as used herein, includes both saturated and unsaturated, nonaromatic, straight chain (i.e., unbranched), branched, acyclic, and cyclic (i.e., carbocyclic) hydrocarbons, which are optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, "aliphatic" is intended herein to include, but is not limited to, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties. Thus, as used herein, the term "alkyl" includes straight, branched and cyclic alkyl groups. An analogous convention applies to other generic terms such as "alkenyl", "alkynyl", and the like. Furthermore, as used herein, the terms "alkyl", "alkenyl", "alkynyl", and the like encompass both substituted and unsubstituted groups. In certain embodiments, as used herein, "aliphatic" is used to indicate those aliphatic groups (cyclic, acyclic, substituted, unsubstituted, branched or unbranched) having 1–20 carbon atoms. Aliphatic group substituents include, but are not limited to, any of the substituents described herein, that result in the formation of a stable moiety (*e.g.*, aliphatic, alkyl, alkenyl, alkynyl, heteroaliphatic, heterocyclic, aryl, heteroaryl, acyl, oxo, imino, thiooxo, cyano, isocyano, amino, azido, nitro, hydroxyl, thiol, halo, aliphaticamino, heteroaliphaticamino, alkylamino, heteroalkylamino, arylamino, heteroarylamino, alkylaryl, arylalkyl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, acyloxy, and the like, each of which may or may not be further substituted).

As used herein, the term "alkyl" is given its ordinary meaning in the art and refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In some cases, the alkyl group may be a lower alkyl group, *i.e.*, an alkyl group having 1 to 10 carbon atoms (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, or decyl). In some embodiments, a straight chain or

branched chain alkyl may have 30 or fewer carbon atoms in its backbone, and, in some cases, 20 or fewer. In some embodiments, a straight chain or branched chain alkyl may have 12 or fewer carbon atoms in its backbone (*e.g.*, C_1-C_{12} for straight chain, C_3-C_{12} for branched chain), 6 or fewer, or 4 or fewer. Likewise, cycloalkyls may have from 3-10 carbon atoms in their ring structure, or 5, 6 or 7 carbons in the ring structure. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, *t*-butyl, cyclobutyl, hexyl, and cyclochexyl.

The term "alkylene" as used herein refers to a bivalent alkyl group. An "alkylene" group is a polymethylene group, *i.e.*, $-(CH_2)_z-$, wherein z is a positive integer, *e.g.*, from 1 to 20, from 1 to 10, from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described herein for a substituted aliphatic group.

Generally, the suffix "-ene" is used to describe a bivalent group. Thus, any of the terms defined herein can be modified with the suffix "-ene" to describe a bivalent version of that moiety. For example, a bivalent carbocycle is "carbocyclylene", a bivalent aryl ring is "arylene", a bivalent benzene ring is "phenylene", a bivalent heterocycle is "heterocyclylene", a bivalent heteroaryl ring is "heteroarylene", a bivalent alkyl chain is "alkylene", a bivalent alkenyl chain is "alkenylene", a bivalent alkynyl chain is "alkynylene", a bivalent heteroalkyl chain is "heteroalkylene", a bivalent heteroalkenyl chain is "heteroalkenylene", a bivalent heteroalkynyl chain is "heteroalkynylene",and so forth.

The terms "alkenyl" and "alkynyl" are given their ordinary meaning in the art and refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

In certain embodiments, the alkyl, alkenyl and alkynyl groups employed in the invention contain 1-20 aliphatic carbon atoms. In certain other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-8 aliphatic carbon atoms. In still other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-6 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-4 carbon atoms. Illustrative aliphatic groups thus include, but are not limited to, for example, methyl, ethyl, *n*-propyl, isopropyl, allyl, *n*-butyl, sec-butyl, isobutyl, *t*-butyl, *n*-pentyl, sec-pentyl, isopentyl, *t*-pentyl, *n*-hexyl, sec-hexyl, moieties and the like, which again, may bear

one or more substituents. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-l-yl, and the like. Representative alkynyl groups include, but are not limited to, ethynyl, 2-propynyl (propargyl), 1-propynyl and the like.

The term "cycloalkyl," as used herein, refers specifically to groups having three to ten, preferably three to seven carbon atoms. Suitable cycloalkyls include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like, which, as in the case of other aliphatic, heteroaliphatic, or hetercyclic moieties, may optionally be substituted with substituents including, but not limited to aliphatic; heteroaliphatic; aryl; heteroaryl; arylalkyl; heteroarylalkyl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; -F; -Cl; -Br; -I; -OH; $-NO_2$; -CN; $-CF_3$; $-CH_2CF_3$; $-CHCl_2$; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NH_2$; $-CH_2SO_2CH_3$; $-C(O)R_x$; $-CO_2(R_x)$; $-CON(R_x)_2$; $-OC(O)R_x$; $-OCO_2R_x$; $-OCON(R_x)_2$; $-N(R_x)_2$; $-S(O)_2R_x$; $-NR_x(CO)R_x$, wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, heteroaliphatic, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein any of the aliphatic, heteroaliphatic, arylalkyl, or heteroarylalkyl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples of generally applicable substitutents are illustrated by the specific embodiments shown in the Examples that are described herein.

The term "heteroaliphatic," as used herein, refers to an aliphatic moiety, as defined herein, which includes both saturated and unsaturated, nonaromatic, straight chain (i.e., unbranched), branched, acyclic, cyclic (i.e., heterocyclic), or polycyclic hydrocarbons, which are optionally substituted with one or more functional groups, and that contain one or more oxygen, sulfur, nitrogen, phosphorus, or silicon atoms, *e.g.*, in place of carbon atoms. In certain embodiments, heteroaliphatic moieties are substituted by independent replacement of one or more of the hydrogen atoms thereon with one or more substituents. As will be appreciated by one of ordinary skill in the art, "heteroaliphatic" is intended herein to include, but is not limited to, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, and heterocycloalkynyl moieties. Thus, the term "heteroaliphatic" includes the terms "heteroalkyl," "heteroalkenyl", "heteroalkynyl", and the like. Furthermore, as used herein, the terms "heteroalkyl", "heteroalkenyl", "heteroalkynyl", and the like encompass both substituted and unsubstituted groups. In certain embodiments, as used herein, "heteroaliphatic" is used to indicate those heteroaliphatic groups (cyclic, acyclic,

substituted, unsubstituted, branched or unbranched) having 1–20 carbon atoms. Heteroaliphatic group substituents include, but are not limited to, any of the substituents described herein, that result in the formation of a stable moiety (*e.g.*, aliphatic, alkyl, alkenyl, alkynyl, heteroaliphatic, heterocyclic, aryl, heteroaryl, acyl, sulfinyl, sulfonyl, oxo, imino, thiooxo, cyano, isocyano, amino, azido, nitro, hydroxyl, thiol, halo, aliphaticamino, heteroaliphaticamino, alkylamino, heteroalkylamino, arylamino, heteroarylamino, alkylaryl, arylalkyl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, acyloxy, and the like, each of which may or may not be further substituted).

The term "heteroalkyl" is given its ordinary meaning in the art and refers to an alkyl group as described herein in which one or more carbon atoms is replaced by a heteroatom. Suitable heteroatoms include oxygen, sulfur, nitrogen, phosphorus, and the like. Examples of heteroalkyl groups include, but are not limited to, alkoxy, alkoxyalkyl, amino, thioester, poly(ethylene glycol), and alkyl-substituted amino.

The terms "heteroalkenyl" and "heteroalkynyl" are given their ordinary meaning in the art and refer to unsaturated aliphatic groups analogous in length and possible substitution to the heteroalkyls described above, but that contain at least one double or triple bond respectively.

Some examples of substituents of the above-described aliphatic (and other) moieties of compounds of the invention include, but are not limited to aliphatic; heteroaliphatic; aryl; heteroaryl; alkylaryl; alkylheteroaryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; C1; Br; I; -OH; $-NO_2$; -CN; $-CF_3$; $-CHF_2$; $-CH_2F$; $-CH_2CF_3$; $-CHC1_2$; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NH_2$; $-CH_2SO_2CH_3$; $-C(O)R_x$; $-CO_2(R_x)$; $-CON(R_x)_2$; $-OC(O)R_x$; $-OCO_2R_x$; $-OCON(R_x)_2$; $-N(R_x)_2$; $-S(O)_2R_x$; $-NR_x(CO)R_x$ wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, alycyclic, heteroaliphatic, heterocyclic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, wherein any of the aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

The term "aryl" is given its ordinary meaning in the art and refers to aromatic carbocyclic groups, optionally substituted, having a single ring (*e.g.*, phenyl), multiple rings (*e.g.*, biphenyl), or multiple fused rings in which at least one is aromatic (*e.g.*, 1,2,3,4-

tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl). That is, at least one ring may have a conjugated pi electron system, while other, adjoining rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls. The aryl group may be optionally substituted, as described herein. Substituents include, but are not limited to, any of the previously mentioned substitutents, *i.e.*, the substituents recited for aliphatic moieties, or for other moieties as disclosed herein, resulting in the formation of a stable compound. In some cases, an aryl group is a stable mono- or polycyclic unsaturated moiety having preferably 3-14 carbon atoms, each of which may be substituted or unsubstituted. "Carbocyclic aryl groups" refer to aryl groups wherein the ring atoms on the aromatic ring are carbon atoms. Carbocyclic aryl groups include monocyclic carbocyclic aryl groups and polycyclic or fused compounds (*e.g.*, two or more adjacent ring atoms are common to two adjoining rings) such as naphthyl groups.

The terms "heteroaryl" is given its ordinary meaning in the art and refers to aryl groups comprising at least one heteroatom as a ring atom. A "heteroaryl" is a stable heterocyclic or polyheterocyclic unsaturated moiety having preferably 3-14 carbon atoms, each of which may be substituted or unsubstituted. Substituents include, but are not limited to, any of the previously mentioned substitutents, *i.e.*, the substituets recited for aliphatic moieties, or for other moieties as disclosed herein, resulting in the formation of a stable compound. In some cases, a heteroaryl is a cyclic aromatic radical having from five to ten ring atoms of which one ring atom is selected from S, O, and N; zero, one, or two ring atoms are additional heteroatoms independently selected from S, O, and N; and the remaining ring atoms are carbon, the radical being joined to the rest of the molecule via any of the ring atoms, such as, for example, pyridyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl,oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, and the like.

It will also be appreciated that aryl and heteroaryl moieties, as defined herein may be attached via an alkyl or heteroalkyl moiety and thus also include –(alkyl)aryl, -(heteroalkyl)aryl, -(heteroalkyl)heteroaryl, and –(heteroalkyl)heteroaryl moieties. Thus, as used herein, the phrases "aryl or heteroaryl moieties" and "aryl, heteroaryl, –(alkyl)aryl, -(heteroalkyl)aryl, -(heteroalkyl)heteroaryl, and -(heteroalkyl)heteroaryl" are interchangeable. Substituents include, but are not limited to, any of the previously mentioned substituents, *i.e.*, the substituents recited for aliphatic moieties, or for other moieties as disclosed herein, resulting in the formation of a stable compound.

It will be appreciated that aryl and heteroaryl groups (including bicyclic aryl groups) can be unsubstituted or substituted, wherein substitution includes replacement of one or more of the hydrogen atoms thereon independently with any one or more of the following moieties including, but not limited to: aliphatic; alicyclic; heteroaliphatic; heterocyclic; aromatic; heteroaromatic; aryl; heteroaryl; alkylaryl; heteroalkylaryl; alkylheteroaryl; heteroalkylheteroaryl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; C1; Br; I; -OH; $-NO_2$; -CN; $-CF_3$; $-CH_2F$; $-CHF_2$; $-CH_2CF_3$; $-CHC1_2$; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NH_2$; $-CH_2SO_2CH_3$; $-C(O)R_x$; $-CO_2(R_x)$; $-CON(R_x)_2$; $-OC(O)R_x$; $-OCO_2R_x$; $-OCON(R_x)_2$; $-N(R_x)_2$; $-S(O)R_x$; $-S(O)_2R_x$; $-NR_x(CO)R_x$ wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, alicyclic, heteroaliphatic, heterocyclic, aromatic, heteroaromatic, aryl, heteroaryl, alkylaryl, alkylheteroaryl, heteroalkylaryl or heteroalkylheteroaryl, wherein any of the aliphatic, alicyclic, heteroaliphatic, heterocyclic, alkylaryl, or alkylheteroaryl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, saturated or unsaturated, and wherein any of the aromatic, heteroaromatic, aryl, heteroaryl, -(alkyl)aryl or -(alkyl)heteroaryl substituents described above and herein may be substituted or unsubstituted. Additionally, it will be appreciated, that any two adjacent groups taken together may represent a 4, 5, 6, or 7-membered substituted or unsubstituted alicyclic or heterocyclic moiety. Additional examples of generally applicable substituents are illustrated by the specific embodiments described herein.

The term "heterocycle" is given its ordinary meaning in the art and refers to cyclic groups containing at least one heteroatom as a ring atom, in some cases, 1 to 3 heteroatoms as ring atoms, with the remainder of the ring atoms being carbon atoms. Suitable heteroatoms include oxygen, sulfur, nitrogen, phosphorus, and the like. In some cases, the heterocycle may be 3- to 10-membered ring structures or 3- to 7-membered rings, whose ring structures include one to four heteroatoms.

The term "heterocycle" may include heteroaryl groups, saturated heterocycles (*e.g.*, cycloheteroalkyl) groups, or combinations thereof. The heterocycle may be a saturated molecule, or may comprise one or more double bonds. In some cases, the heterocycle is a nitrogen heterocycle, wherein at least one ring comprises at least one nitrogen ring atom. The heterocycles may be fused to other rings to form a polycylic heterocycle. The heterocycle may also be fused to a spirocyclic group. In some cases, the heterocycle may be attached to a compound via a nitrogen or a carbon atom in the ring.

Heterocycles include, for example, thiophene, benzothiophene, thianthrene, furan, tetrahydrofuran, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, dihydropyrrole, pyrrolidine, imidazole, pyrazole, pyrazine, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, triazole, tetrazole, oxazole, isoxazole, thiazole, isothiazole, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, oxazine, piperidine, homopiperidine (hexamnethyleneimine), piperazine (*e.g.*, N-methyl piperazine), morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, other saturated and/or unsaturated derivatives thereof, and the like. The heterocyclic ring can be optionally substituted at one or more positions with such substituents as described herein. In some cases, the heterocycle may be bonded to a compound via a heteroatom ring atom (*e.g.*, nitrogen). In some cases, the heterocycle may be bonded to a compound via a carbon ring atom. In some cases, the heterocycle is pyridine, imidazole, pyrazine, pyrimidine, pyridazine, acridine, acridin-9-amine, bipyridine, naphthyridine, quinoline, benzoquinoline, benzoisoquinoline, phenanthridine-1,9-diamine, or the like.

The terms "halo" and "halogen" as used herein refer to an atom selected from the group consisting of fluorine, chlorine, bromine, and iodine.

The term "haloalkyl" denotes an alkyl group, as defined above, having one, two, or three halogen atoms attached thereto and is exemplified by such groups as chloromethyl, bromoethyl, trifluoromethyl, and the like.

The term "amino," as used herein, refers to a primary ($-NH_2$), secondary ($-NHR_x$), tertiary ($-NR_xR_y$), or quaternary ($-N^+R_xR_yR_z$) amine, where R_x, R_y, and R_z are independently an aliphatic, alicyclic, heteroaliphatic, heterocyclic, aryl, or heteroaryl moiety, as defined herein. Examples of amino groups include, but are not limited to, methylamino, dimethylamino, ethylamino, diethylamino, methylethylamino, iso-propylamino, piperidino, trimethylamino, and propylamino.

The term "alkyne" is given its ordinary meaning in the art and refers to branched or unbranched unsaturated hydrocarbon groups containing at least one triple bond. Non-limiting examples of alkynes include acetylene, propyne, 1-butyne, 2-butyne, and the like. The alkyne group may be substituted and/or have one or more hydrogen atoms replaced with a functional group, such as a hydroxyl, halogen, alkoxy, and/or aryl group.

The term "alkoxy" (or "alkyloxy"), or "thioalkyl" as used herein refers to an alkyl group, as previously defined, attached to the parent molecular moiety through an oxygen atom or through a sulfur atom. In certain embodiments, the alkyl group contains 1-20 aliphatic carbon atoms. In certain other embodiments, the alkyl group contains 1-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-8 aliphatic carbon atoms. In still other embodiments, the alkyl group contains 1-6 aliphatic carbon atoms. In yet other embodiments, the alkyl group contains 1-4 aliphatic carbon atoms. Examples of alkoxy, include but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, *t*-butoxy, neopentoxy and *n*-hexoxy. Examples of thioalkyl include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, *n*-butylthio, and the like.

The term "aryloxy" refers to the group, -O-aryl.

The term "acyloxy" refers to the group, -O-acyl.

The term "alkoxyalkyl" refers to an alkyl group substituted with at least one alkoxy group (*e.g.*, one, two, three, or more, alkoxy groups). For example, an alkoxyalkyl group may be -(C_{1-6}-alkyl)-O-(C_{1-6}-alkyl), optionally substituted. In some cases, the alkoxyalkyl group may be optionally substituted with another alkyoxyalkyl group (*e.g.*, -(C_{1-6}-alkyl)-O-(C_{1-6}-alkyl)-O-(C_{1-6}-alkyl) , optionally substituted.

It will be appreciated that the above groups and/or compounds, as described herein, may be optionally substituted with any number of substituents or functional moieties. That is, any of the above groups may be optionally substituted. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds, "permissible" being in the context of the chemical rules of valence known to those of ordinary skill in the art. In general, the term "substituted" whether preceeded by the term "optionally" or not, and substituents contained in formulas of this invention, refer to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. It will be understood that "substituted" also includes that the substitution results in a stable compound, *e.g.*, which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, *etc.* In some cases, "substituted" may generally refer to replacement of a hydrogen with a substituent as described herein. However, "substituted," as used herein, does not encompass replacement and/or alteration of a key functional group by which a molecule is identified, *e.g.*, such that

the "substituted" functional group becomes, through substitution, a different functional group. For example, a "substituted phenyl group" must still comprise the phenyl moiety and cannot be modified by substitution, in this definition, to become, *e.g.*, a pyridine ring. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valencies of the heteroatoms. Furthermore, this invention is not intended to be limited in any manner by the permissible substituents of organic compounds. Combinations of substituents and variables envisioned by this invention are preferably those that result in the formation of stable compounds useful for the formation of an imaging agent or an imaging agent precursor. The term "stable," as used herein, preferably refers to compounds which possess stability sufficient to allow manufacture and which maintain the integrity of the compound for a sufficient period of time to be detected and preferably for a sufficient period of time to be useful for the purposes detailed herein.

Examples of substituents include, but are not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, $-CF_3$, -CN, aryl, aryloxy, perhaloalkoxy, aralkoxy, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroaralkoxy, azido, amino, halide, alkylthio, oxo, acylalkyl, carboxy esters, -carboxamido, acyloxy, aminoalkyl, alkylaminoaryl, alkylaryl, alkylaminoalkyl, alkoxyaryl, arylamino, aralkylamino, alkylsulfonyl, -carboxamidoalkylaryl, -carboxamidoaryl, hydroxyalkyl, haloalkyl, alkylaminoalkylcarboxy-, aminocarboxamidoalkyl-, cyano, alkoxyalkyl, perhaloalkyl, arylalkyloxyalkyl, and the like. In some embodiments, a substituent may also be an imaging moiety (*e.g.*, ^{18}F) or a group for associating an imaging moiety (*e.g.*, a chelator). Nitrogen-protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference. For example, nitrogen protecting groups include, but are not limited to, carbamates (including methyl, ethyl and substituted ethyl carbamates (*e.g.,* Troc), to name a few), amides, cyclic imide derivatives, N-alkyl and N-aryl amines, imine derivatives, and enamine derivatives, to name a few. In some embodiments,

the nitrogen-protecting group is carbobenzyloxy (Cbz), *p*-methoxybenzyl carbonyl (MeOZ), *t*-butyloxycarbonyl (Boc), 9-fluorenylmethyloxycarbonyl (Fmoc), acetyl (Ac), benzoyl (Bz), benzyl (Bn), *p*-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMPM), *p*-methoxyphenyl (PMP), or *p*-toluenesulfonyloxy (Ts).

Nitrogen-protecting groups such as amide groups include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3–phenylpropanamide, picolinamide, 3–pyridylcarboxamide, *N*–benzoylphenylalanyl derivative, benzamide, *p*–phenylbenzamide, *o*–nitrophenylacetamide, *o*–nitrophenoxyacetamide, acetoacetamide, (*N'*–dithiobenzyloxyacylamino)acetamide, 3–(*p*–hydroxyphenyl)propanamide, 3–(*o*–nitrophenyl)propanamide, 2–methyl–2–(*o*–nitrophenoxy)propanamide, 2–methyl–2–(*o*–phenylazophenoxy)propanamide, 4–chlorobutanamide, 3–methyl–3–nitrobutanamide, *o*–nitrocinnamide, *N*–acetylmethionine derivative, *o*–nitrobenzamide, and *o*–(benzoyloxymethyl)benzamide.

Nitrogen-protecting groups such as carbamate groups include, but are not limited to, methyl carbamate, ethyl carbamante, 9–fluorenylmethyl carbamate (Fmoc), 9–(2–sulfo)fluorenylmethyl carbamate, 9–(2,7–dibromo)fluoroenylmethyl carbamate, 2,7–di–*t*–butyl–[9–(10,10–dioxo–10,10,10,10–tetrahydrothioxanthyl)]methyl carbamate (DBD–Tmoc), 4–methoxyphenacyl carbamate (Phenoc), 2,2,2–trichloroethyl carbamate (Troc), 2–trimethylsilylethyl carbamate (Teoc), 2–phenylethyl carbamate (hZ), 1–(1–adamantyl)–1–methylethyl carbamate (Adpoc), 1,1–dimethyl–2–haloethyl carbamate, 1,1–dimethyl–2,2–dibromoethyl carbamate (DB–*t*–Boc), 1,1–dimethyl–2,2,2–trichloroethyl carbamate (TCBoc), 1–methyl–1–(4–biphenylyl)ethyl carbamate (Bpoc), 1–(3,5–di–*t*–butylphenyl)–1–methylethyl carbamate (*t*–Bumeoc), 2–(2'– and 4'–pyridyl)ethyl carbamate (Pyoc), 2–(*N,N*–dicyclohexylcarboxamido)ethyl carbamate, *t*–butyl carbamate (Boc), 1–adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1–isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4–nitrocinnamyl carbamate (Noc), 8–quinolyl carbamate, *N*–hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), *p*–methoxybenzyl carbamate (Moz), *p*–nitrobenzyl carbamate, *p*–bromobenzyl carbamate, *p*–chlorobenzyl carbamate, 2,4–dichlorobenzyl carbamate, 4–methylsulfinylbenzyl carbamate (Msz), 9–anthrylmethyl carbamate, diphenylmethyl carbamate, 2–methylthioethyl carbamate, 2–methylsulfonylethyl carbamate, 2–(*p*–toluenesulfonyl)ethyl carbamate, [2–(1,3–dithianyl)]methyl carbamate (Dmoc), 4–methylthiophenyl carbamate (Mtpc), 2,4–dimethylthiophenyl carbamate (Bmpc), 2–phosphonioethyl carbamate (Peoc), 2–triphenylphosphonioisopropyl carbamate (Ppoc), 1,1–dimethyl–2–cyanoethyl carbamate, *m*–

chloro–*p*–acyloxybenzyl carbamate, *p*–(dihydroxyboryl)benzyl carbamate, 5–benzisoxazolylmethyl carbamate, 2–(trifluoromethyl)–6–chromonylmethyl carbamate (Tcroc), *m*–nitrophenyl carbamate, 3,5–dimethoxybenzyl carbamate, *o*–nitrobenzyl carbamate, 3,4–dimethoxy–6–nitrobenzyl carbamate, phenyl(*o*–nitrophenyl)methyl carbamate, *t*–amyl carbamate, *S*–benzyl thiocarbamate, *p*–cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*–decyloxybenzyl carbamate, 2,2–dimethoxyacylvinyl carbamate, *o*–(*N,N*–dimethylcarboxamido)benzyl carbamate, 1,1–dimethyl–3–(*N,N*–dimethylcarboxamido)propyl carbamate, 1,1–dimethylpropynyl carbamate, di(2–pyridyl)methyl carbamate, 2–furanylmethyl carbamate, 2–iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, *p*–(*p'*–methoxyphenylazo)benzyl carbamate, 1–methylcyclobutyl carbamate, 1–methylcyclohexyl carbamate, 1–methyl–1–cyclopropylmethyl carbamate, 1–methyl–1–(3,5–dimethoxyphenyl)ethyl carbamate, 1–methyl–1–(*p*–phenylazophenyl)ethyl carbamate, 1–methyl–1–phenylethyl carbamate, 1–methyl–1–(4–pyridyl)ethyl carbamate, phenyl carbamate, *p*–(phenylazo)benzyl carbamate, 2,4,6–tri–*t*–butylphenyl carbamate, 4–(trimethylammonium)benzyl carbamate, and 2,4,6–trimethylbenzyl carbamate.

Nitrogen-protecting groups such as sulfonamide groups include, but are not limited to, *p*–toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6,–trimethyl–4–methoxybenzenesulfonamide (Mtr), 2,4,6–trimethoxybenzenesulfonamide (Mtb), 2,6–dimethyl–4–methoxybenzenesulfonamide (Pme), 2,3,5,6–tetramethyl–4–methoxybenzenesulfonamide (Mte), 4–methoxybenzenesulfonamide (Mbs), 2,4,6–trimethylbenzenesulfonamide (Mts), 2,6–dimethoxy–4–methylbenzenesulfonamide (iMds), 2,2,5,7,8–pentamethylchroman–6–sulfonamide (Pmc), methanesulfonamide (Ms), β–trimethylsilylethanesulfonamide (SES), 9–anthracenesulfonamide, 4–(4',8'–dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

Other nitrogen-protecting groups include, but are not limited to, phenothiazinyl–(10)–acyl derivative, *N'*–*p*–toluenesulfonylaminoacyl derivative, *N'*–phenylaminothioacyl derivative, *N*–benzoylphenylalanyl derivative, *N*–acetylmethionine derivative, 4,5–diphenyl–3–oxazolin–2–one, *N*–phthalimide, *N*–dithiasuccinimide (Dts), *N*–2,3–diphenylmaleimide, *N*–2,5–dimethylpyrrole, *N*–1,1,4,4–tetramethyldisilylazacyclopentane adduct (STABASE), 5–substituted 1,3–dimethyl–1,3,5–triazacyclohexan–2–one, 5–substituted 1,3–dibenzyl–1,3,5–triazacyclohexan–2–one, 1–substituted 3,5–dinitro–4–pyridone, *N*–methylamine, *N*–allylamine, *N*–[2–(trimethylsilyl)ethoxy]methylamine (SEM), *N*–3–acetoxypropylamine, *N*–

(1–isopropyl–4–nitro–2–oxo–3–pyroolin–3–yl)amine, quaternary ammonium salts, *N*–benzylamine, *N*–di(4–methoxyphenyl)methylamine, *N*–5–dibenzosuberylamine, *N*–triphenylmethylamine (Tr), *N*–[(4–methoxyphenyl)diphenylmethyl]amine (MMTr), *N*–9–phenylfluorenylamine (PhF), *N*–2,7–dichloro–9–fluorenylmethyleneamine, *N*–ferrocenylmethylamino (Fcm), *N*–2–picolylamino *N'*–oxide, *N*–1,1–dimethylthiomethyleneamine, *N*–benzylideneamine, *N*–*p*–methoxybenzylideneamine, *N*–diphenylmethyleneamine, *N*–[(2–pyridyl)mesityl]methyleneamine, *N*–(*N',N'*–dimethylaminomethylene)amine, *N,N'*–isopropylidenediamine, *N*–*p*–nitrobenzylideneamine, *N*–salicylideneamine, *N*–5–chlorosalicylideneamine, *N*–(5–chloro–2–hydroxyphenyl)phenylmethyleneamine, *N*–cyclohexylideneamine, *N*–(5,5–dimethyl–3–oxo–1–cyclohexenyl)amine, *N*–borane derivative, *N*–diphenylborinic acid derivative, *N*–[phenyl(pentaacylchromium– or tungsten)acyl]amine, *N*–copper chelate, *N*–zinc chelate, *N*–nitroamine, *N*–nitrosoamine, amine *N*–oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*–nitrobenzenesulfenamide (Nps), 2,4–dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2–nitro–4–methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3–nitropyridinesulfenamide (Npys).

As used herein, the term "determining" generally refers to the analysis of a species or signal, for example, quantitatively or qualitatively, and/or the detection of the presence or absence of the species or signals.

The term "diagnostic imaging," as used herein, refers to a procedure used to detect an imaging agent.

The term "diagnosis" as used herein encompasses identification, confirmation, and/or characterization of a condition, a disease, and/or a disorder.

A "diagnostic kit" or "kit" comprises a collection of components, termed the formulation, in one or more vials which are used by the practicing end user in a clinical or pharmacy setting to synthesize diagnostic radiopharmaceuticals. For example, the kit may be used by the practicing end user in a clinical or pharmacy setting to synthesize and/or use diagnostic radiopharmaceuticals. In some embodiments, the kit may provide all the requisite components to synthesize and use the diagnostic pharmaceutical except those that are commonly available to the practicing end user, such as water or saline for injection and/or the radioisotope (*e.g.*, ^{18}F), equipment for processing the kit during the synthesis and manipulation of the radiopharmaceutical, if required, equipment necessary for administering

the radiopharmaceutical to the subject such as syringes, shielding, imaging equipment, and the like. In some embodiments, imaging agents may be provided to the end user in their final form in a formulation contained typically in one vial or syringe, as either a lyophilized solid or an aqueous solution.

As used herein, a "portion of a subject" refers to a particular region of a subject, location of the subject. For example, a portion of a subject may be the brain, heart, vasculature, cardiac vessels, tumor, *etc.*, of a subject.

As used herein a "session" of testing may be a single testing protocol that a subject undergoes.

As used herein, the term "subject" refers to a human or non-human mammal or animal. Non-human mammals include livestock animals, companion animals, laboratory animals, and non-human primates. Non-human subjects also specifically include, without limitation, horses, cows, pigs, goats, dogs, cats, mice, rats, guinea pigs, gerbils, hamsters, mink, and rabbits. In some embodiments of the invention, a subject is referred to as a "patient." In some embodiments, a patient or subject may be under the care of a physician or other health care worker, including, but not limited to, someone who has consulted with, received advice from or received a prescription or other recommendation from a physician or other health care worker.

Any of the compounds described herein may be in a variety of forms, such as, but not limited to, salts, solvates, hydrates, tautomers, and isomers.

In certain embodiments, the imaging agent is a pharmaceutically acceptable salt of the imaging agent. The term "pharmaceutically acceptable salt" as used herein refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.,* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, *66*, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate,

alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counter ions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

In certain embodiments, the compound is in the form of a hydrate or solvate. The term "hydrate" as used herein refers to a compound non–covalently associated with one or more molecules of water. Likewise, the term "solvate" refers to a compound non–covalently associated with one or more molecules of an organic solvent.

In certain embodiments, the compound described herein may exist in various tautomeric forms. The term "tautomer" as used herein includes two or more interconvertable compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (*e.g.,* a single bond to a double bond, a triple bond to a single bond, or *vice versa*). The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Tautomerizations (*i.e.,* the reaction providing a tautomeric pair) may be catalyzed by acid or base. Exemplary tautomerizations include keto–to–enol; amide–to–imide; lactam–to–lactim; enamine–to–imine; and enamine–to–(a different) enamine tautomerizations.

In certain embodiments, the compounds described herein may exist in various isomeric forms. The term "isomer" as used herein includes any and all geometric isomers and stereoisomers (*e.g.,* enantiomers, diasteromers, *etc.*). For example, "isomer" includes *cis*– and *trans*–isomers, *E*– and *Z*– isomers, *R*– and *S*–enantiomers, diastereomers, (D)–isomers, (L)–isomers, racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. For instance, an isomer/enantiomer may, in some embodiments, be provided substantially free of the corresponding enantiomer, and may also be referred to

as "optically enriched." "Optically–enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments the compound of the present invention is made up of at least about 90% by weight of a preferred enantiomer. In other embodiments the compound is made up of at least about 95%, 98%, or 99% by weight of a preferred enantiomer. Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses. See, for example, Jacques, *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, S.H., *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

These and other aspects of the present invention will be further appreciated upon consideration of the following Examples, which are intended to illustrate certain particular embodiments of the invention but are not intended to limit its scope, as defined by the claims.

Examples

General Experimental Protocols

Method A:

A cooled (0 ºC) aqueous solution of mucochloric acid was treated with sodium carbonate in one portion then stirred until complete dissolution was observed. The resulting mixture was then treated with the substituted hydrazine, and stirred 2.5-5 h while slowly warming to ambient temperature. The newly formed precipitate was then collected, exhaustively washed with water, partially dried on the funnel then dissolved in acetic acid and heated to reflux. After 30 min, the solution was cooled to ambient temperature and all volatiles removed in vacuo. The crude pyridazinone was then dissolved in an appropriate organic solvent, washed with aqueous base, dried, filtered and concentrated in vacuo. The crude material thus obtained was typically used without additional purification, but alternatively may be further purified by chromatography on silica.

Method B:

A solution of the substituted pyridazinone and either a benzylic alcohol or benzylic bromide in dimethylformamide was treated with cesium carbonate then optionally heated to 55-80 °C. After cooling to ambient temperature, the crude product was isolated as a solution

in ethyl acetate, washed with water and aqueous sodium chloride then dried, filtered and concentrated. Subsequent purification by chromatography on silica afforded the title compound.

Method C:

A dichloromethane solution of the benzylic alcohol was treated with phosphorous tribromide at ambient temperature. After 1-3 h, the resulting mixture was diluted with water and the layers separated. The aqueous layer was washed with additional dichloromethane, and the combined extracts dried, filtered and concentrated. The crude material thus obtained was typically used without additional purification, but alternatively may be further purified by chromatography on silica.

Method D:

A dichloromethane solution of the alcohol, *p*-toluenesulfonyl chloride, 4-dimethylaminopyridine, and a base was prepared at ambient temperature. After 1-3 h, the resulting mixture was diluted with water and the layers separated. The aqueous layer was washed with additional dichloromethane, and the combined extracts further washed with aqueous sodium chloride then dried, filtered, and concentrated. Subsequent purification by chromatography on silica afforded the title compound.

Method E:

A suspension of potassium *tert*-butoxide in 2-fluoroethanol was heated to 60 °C, maintained 20 min then treated with a solution of the benzylic halide in tetrahydrofuran. The resulting mixture was heated to reflux, maintained 2-24 h then cooled to ambient temperature and treated with water. The aqueous layer was separated then extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. Subsequent purification by chromatography on silica afforded the title compound.

Method F:

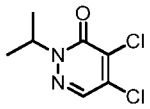
A suspension of the phenol, 3-fluoropropyl *p*-toluenesulfonate, and cesium carbonate in dimethylformamide was heated to 60-65 °C and maintained overnight. After cooling to ambient temperature, the resulting mixture was treated with water, and the aqueous layer

extracted with ethyl acetate. The combined organic layers were washed with water, saturated aqueous sodium chloride, dried over sodium sulfate, filtered and concentrated in vacuo.

Example 1

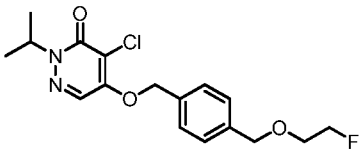
Preparation of 4-chloro-5-((4-((2-fluoroethoxy)methyl)benzyl)oxy)-2-isopropylpyridazin-3(2*H*)-one

Part A – Preparation of 4,5-dichloro-2-isopropylpyridazin-3(2*H*)-one



Prepared according to General Method A, using mucochloric acid (1.07 g, 6.33 mmol), sodium carbonate (0.336 g, 3.17 mmol), and isopropylhydrazine hydrochloride (0.700 g, 6.33 mmol). Isolated yield – 0.629 g; 47.9%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.82 (s, 1H), 5.27 (m, 1H), 1.37 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.3, 135.9, 135.3, 133.8, 51.4, 20.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_7H_8{}^{35}Cl_2N_2O$: 207.0086, found 207.0085.

Part B – Preparation of 4-chloro-5-((4-((2-fluoroethoxy)methyl)benzyl)oxy)-2-isopropylpyridazin-3*(2H)*-one



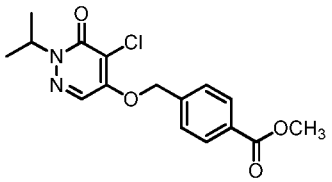
Prepared according to General Method B, using the product of Example 1A (45.5 mg, 0.220 mmol), (4-((2-fluoroethoxy)methyl)phenyl)methanol (41 mg, 0.22 mmol; e.g., see Radeke, H.; Hanson, K.; Yalamanchili, P.; Hayes, M.; Zhang, Z.-Q.; Azure, M.; Yu, M.; Guaraldi, M.; Kagan, M.; Robinson, S.; Casebier, D. Synthesis and Biological evaluation of the mitochondrial complex I inhibitor 2-[4-(4-fluorobutyl)benzylsulfanyl]-3-methylchromene-4-one as a potential cardiac positron emission tomography tracer. J. Med.Chem. 2007, 50, 4304-4315.), and cesium carbonate (0.215 g, 0.661 mmol) in dimethylformamide (2.20 mL) at 55 °C. Isolated yield – 49 mg; 63%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.66 (s, 1H), 7.41 (d, J = 7.5 Hz, 2H), 7.37 (d, J = 8.6 Hz, 2H), 5.17 (s, 2H), 4.68 (m, 1H), 4.62 (s, 2H), 4.53 (m, 1H), 3.80 (m, 1H), 3.71 (m, 1H), 3.54-3.45 (m, 1H), 1.27 (d, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.3, 154.2, 138.3, 135.4, 129.3, 128.1,

127.4, 125.8, 83.1 (d, J_{CF} = 165 Hz), 73.0, 70.8, 69.4 (d, J_{CF} = 22.5 Hz), 65.0, 19.5; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{17}H_{20}{}^{35}ClFN_2O_3$: 355.1219, found 355.1217.

Example 2

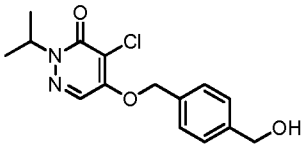
Preparation of 2-((4-(((5-chloro-1-isopropyl-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl) benzyl)oxy)ethyl-4-methylbenzenesulfonate

Part A – Preparation of methyl 4-(((5-chloro-1-isopropyl-6-oxo-1,6-dihydropyridazin-4-yl)oxy) methyl)benzoate



Prepared according to General Method B, using the product of Example 1A (0.629 g, 3.01 mmol), 4-hydroxymethyl benzoate (0.550 g, 3.31 mmol), and cesium carbonate (1.57 g, 4.82 mmol) in dimethylformamide (30.0 mL) at 60 °C. Isolated yield – 0.604 g; 59.6%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.08 (d, *J* = 8.5 Hz, 2H), 7.82 (s, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 5.39 (s, 2H), 5.30 (m, 1H), 3.90 (s, 3H), 1.33 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.5, 158.3, 153.6, 139.7, 130.5, 130.2, 129.7, 126.7,117.5, 71.2, 52.0, 50.7, 20.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{16}H_{17}{}^{35}ClN_2O_4$: 337.0950, found 337.0948.

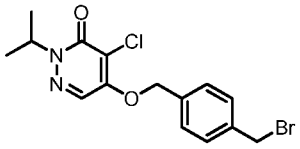
Part B – Preparation of 4-chloro-5-((4-(hydroxymethyl)benzyl)oxy)-2-isopropylpyridazin-3(2*H*)-one



To a solution of the product of Example 2A (0.604 g, 1.79 mmol), in tetrahydrofuran at 0 °C was added lithium aluminum hydride (0.9 mL, 0.9 mmol, 1 M solution in tetrahydrofuran) dropwise. The resulting mixture was stirred 3 h then treated with water (20 mL). The aqueous layer was separated and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride (50 mL), dried over sodium sulfate, filtered and concentrated to yield an orange solid (0.186 g). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.82 (s, 1H), 7.41 (br s, 4H), 5.32 (s, 2H), 5.28 (m, 1H), 4.72 (s, 2H),

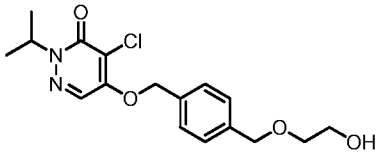
1.28 (d, J = 6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.5, 153.8, 141.8, 134.0, 127.5, 127.4, 127.0, 117.4, 71.8, 64.8, 50.7, 20.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{15}H_{17}{}^{35}ClN_2O_3$: 309.1000, found 309.1001.

Part C – Preparation of 5-((4-(bromomethyl)benzyl)oxy)-4-chloro-2-isopropylpyridazin-3(2*H*)-one



Prepared according to General Method C, using the product of Example 2B (0.186 g, 0.602 mmol) and phosphorous tribromide (0.3 mL, 0.3 mmol, 1 M in dichloromethane).Isolated yield – 0.128 g; 57.2%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.07 (s, 1H), 7.34 (m, 4H), 5.23 (s, 2H), 5.21 (m, 1H), 4.41 (s, 2H), 1.24 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$,75 MHz): δ 158.4, 153.7, 138.5, 135.0, 129.6, 127.5, 126.9, 117.2, 71.5, 50.7, 32.8, 21.0; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{15}H_{16}{}^{79}Br^{35}ClN_2O_2$: 371.0156, found 371.0155.

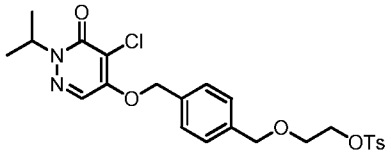
Part D – Preparation of 4-chloro-5-((4-((2-hydroxyethoxy)methyl)benzyl)oxy)-2-isopropylpyridazin-3(2*H*)-one



A suspension of potassium *tert*-butoxide (48 mg, 0.43 mmol) in ethylene glycol (0.685 mL) was heated to 60 °C for 30 min. The product of Example 2C (0.691 g, 1.86 mmol), dissolved in tetrahydrofuran (21.0 mL) was added dropwise. After completion of the addition, the reaction mixture was heated at reflux. After 6 h the reaction mixture was cooled and quenched with water (10 mL). The aqueous layer was separated then extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was then purified by silica gel chromatography (80-100% diethyl ether in hexanes) to afford the desired product as a white solid (2.8 mg, <1% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.76 (br s, 1H), 7.31 (s, 4H), 5.23 (s, 2H), 5.19 (m, 1H), 4.48 (s, 2H), 3.67 (m, 2H), 3.52 (m, 2H), 1.23 (d, J = 6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.4, 153.8, 138.9, 134.2, 128.2, 127.3, 127.0, 117.2, 72.7, 71.8, 71.7,

61.8, 50.7, 20.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{17}H_{21}{}^{35}ClN_2O_4$: 353.1263, found 353.1267.

Part E – Preparation of 2-((4-(((5-chloro-1-isopropyl-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzyl)oxy)ethyl-4-methylbenzenesulfonate

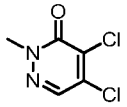


Prepared according to General Method D, using the product of Example 2D (85.6 mg, 0.243 mmol), *p*-toluenesulfonyl chloride (55.6 mg, 0.292 mmol), 4-dimethylaminopyridine (35.6 mg, 0.291 mmol), and diisopropylethylamine (0.051 mL, 0.292 mmol). Isolated yield – 53 mg; 43%. ^1H ($CDCl_3$, 300 MHz): δ 7.82 (s, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H),7.33 – 7.27 (m, 4H), 5.31 (s, 2H), 5.28 (m, 1H), 4.51 (s, 2H), 4.20 (m, 2H), 3.69 (m, 2H), 2.44 (s, 3H), 1.33 (d, J = 6.7 Hz, 6H); ^{13}C ($CDCl_3$, 75 MHz): δ 158.4, 153.7, 144.8, 138.5, 134.3, 133.0, 129.8, 128.1, 128.0, 127.3, 127.0, 117.4, 72.7, 71.8, 69.2, 67.8, 50.7, 21.7, 20.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{24}H_{27}{}^{35}ClN_2O_6S$: 507.1351, found 507.1349.

Example 3

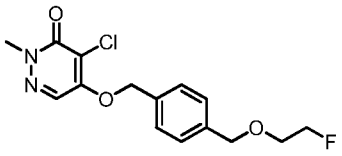
Preparation of 4-chloro-5-((4-((2-fluoroethoxy) methyl) benzyl)oxy)-2-methylpyridazin-3*(2H)*-one

Part A – Preparation of 4,5-dichloro-2-methylpyridazin-3(2*H*)-one



Prepared according to General Method A, using mucochloric acid (2.03 g, 12.1 mmol), sodium carbonate (0.640 g, 6.03 mmol), and methyl hydrazine (0.555 g, 12.1 mmol). Isolated yield – 0.840 g; 38.8%. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.70 (s, 1H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.8, 136.5, 135.3, 134.0, 41.0; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_5H_4{}^{35}Cl_2N_2O$: 178.9773, found 178.9773.

Part B – Preparation of 4-chloro-5-((4-((2-fluoroethoxy)methyl)benzyl)oxy)-2-methylpyridazin- 3*(2H)*-one

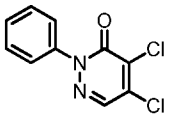


Prepared according to General Method B, using the product of Example 3A (47 mg, 0.26 mmol), (4-((2-fluoroethoxy)methyl)phenyl)methanol (0.141 g, 0.770 mmol), and cesium carbonate (0.251 g, 0.770 mmol) in dimethylformamide (2.50 mL) at 80 °C. Isolated yield – 38 mg; 45%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.67 (s, 1H), 7.33 (s, 4H), 5.25 (br s, 2H), 4.61 (m, 1H), 4.54 (s, 2H), 4.45 (m, 1H), 3.72 (m, 1H), 3.71 (s, 3H), 3.63 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 154.4, 138.8, 134.1, 128.2, 127.3, 127.2, 117.7, 83.1 (d, J_{CF} = 165 Hz), 72.9, 72.0, 69.4 (d, J_{CF} = 22.5 Hz), 40.7; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{15}H_{16}{}^{35}ClFN_2O_3$: 395.1532, found 395.1522.

Example 4

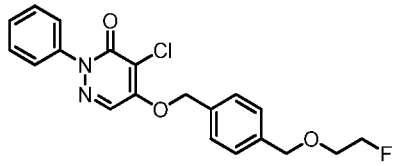
Preparation of 4-chloro-5-((4-((2-fluoroethoxy)methyl)benzyl)oxy)-2-phenylpyridazin-3*(2H)*-one

Part A – Preparation of 4,5-dichloro-2-phenylpyridrazin-3(2*H*)-one



Prepared according to General Method A, using mucochloric acid (0.985 g, 5.83 mmol), sodium carbonate (0.309 g, 2.91 mmol), and phenyl hydrazine hydrochloride (0.843 g, 5.83 mmol). Isolated yield – 1.31 g; 93.2%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.91 (s, 1H), 7.59 – 7.54 (m, 2H), 7.48 – 7.39 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.1, 140.9, 136.4, 136.1, 135.3, 128.9, 128.8, 125.2; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{10}H_6{}^{35}Cl_2N_2O$: 240.9930, found 240.9932.

Part B – Preparation of 4-chloro-5-((4-((2-fluoroethoxy)methyl)benzyl)oxy)-2-phenylpyridazin- 3*(2H)*-one

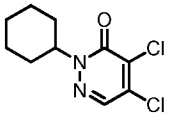


Prepared according to General Method B, using the product of Example 4A (0.070 g, 0.290 mmol), (4-((2-fluoroethoxy)methyl)phenyl)methanol (0.160 g, 0.870 mmol), and cesium carbonate (0.283 g, 0.870 mmol) in dimethylformamide (2.90 mL) at 80 °C. Isolated yield – 45 mg; 40%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.84 (s, 1H), 7.49 – 7.30 (m, 9H), 5.31 (s, 2H), 4.59 (m, 1H), 4.54 (s, 2H), 4.44 (m, 1H), 3.71 (m, 1H), 3.61 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.3, 154.0, 141.2, 138.9, 134.0, 128.8, 128.3, 128.2, 128.0, 127.4, 127.1, 125.3, 81.6 (d, J_{CF} = 60 Hz), 73.1, 72.1, 69.5 (d, J_{CF} = 15 Hz); HRMS-TOF *(m / z)*: [M + H]$^+$ HRMS: Calcd. for $C_{20}H_{18}{}^{35}ClFN_2O_3$: 327.0906, found 327.0901.

Example 5

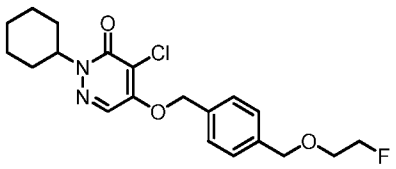
Preparation of 4-chloro-2-cyclohexyl-5-((4-((2-fluoroethoxy)methyl)benzyl)oxy)pyridazin-3*(2H)*-one

Part A – Preparation of 4,5-dichloro-2-cyclohexylpyridrazin-3(2*H*)-one



Prepared according to General Method A, using mucochloric acid (0.443 g, 2.62 mmol), sodium carbonate (0.138 g, 1.31 mmol), and cyclohexyl hydrazine hydrochloride (0.403 g, 2.62 mmol). Isolated yield – 0.440 g; 67.9%. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.74 (s, 1H), 4.77 (tt, *J*=11.6, 3.6 Hz, 1H), 1.79 (m, 4H), 1.68 – 1.56 (m, 3H), 1.44 – 1.30 (m, 2H), 1.21 – 1.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 156.3, 135.7, 135.1, 133.6, 58.5, 31.1, 25.4, 25.2; HRMS-TOF *(m / z)*: [M + H]$^+$ HRMS: Calcd. for $C_{10}H_{12}{}^{35}Cl_2N_2O$: 247.0399, found 247.0399.

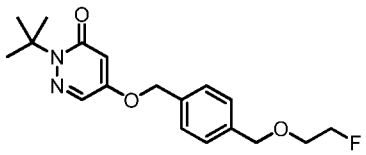
Part B – Preparation of 4-chloro-2-cyclohexyl-5-((4-((2-fluoroethoxy)methyl)benzyl)oxy) pyridazin-3*(2H)*-one



Prepared according to General Method B, using the product of Example 5A (31 mg, 0.13 mmol), (4-((2-fluoroethoxy)methyl)phenyl)methanol (29 mg, 0.16 mmol), and cesium carbonate (0.123 g, 0.380 mmol) in dimethylformamide (1.26 mL) at 55 °C. Isolated yield – 25 mg; 49%. HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{20}H_{24}{}^{35}ClN_2O_3$: 389.1063, found 389.1054.

Example 6

Preparation of 2-(*tert*-butyl)-5-((4-((2-fluoroethoxy)methyl)benzyl)oxy)pyridazin-3(2*H*)-one

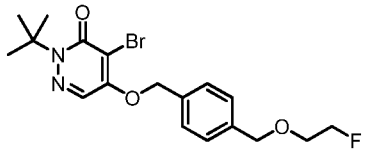


2-(*tert*-Butyl)-4-chloro-5-((4-((2-fluoroethoxy)methyl)benzyl)oxy)pyridazin-3(2*H*)-one (0.184 g, 0.50 mmol; e.g., see Purohit, A.; Radeke, H. S.; Azure, M.; Hanson, K.; Benetti, R.; Su, F.; Yalamanchili, P.; Yu, M.; Hayes, M.; Guaraldi, M.; Kagan, M.; Robinson, S.; Casebier, D. Synthesis and Biological Evaluation of Pyridazinone Analogs as Potential Cardiac Positron Emission Tomography Tracers J. Med. Chem. 2008, 51, 2954) was suspended in dry toluene (5.00 mL), successively treated with tributyltin hydride (0.161 g, 0.60 mmol) and 2,2′-azobis(2-methylpropionitrile) (0.004 mg, 0.025 mmol), then heated to reflux and maintained 20 h. After cooling to ambient temperature, all volatiles were removed in vacuo, and the residue directly purified by chromatography on silica (30 x 190 mm) using a step gradient from 3:1 hexanes/ethyl acetate (400 mL) to 2:1 hexanes/ethyl acetate (500 mL). The main product peak eluting 550-750 mL was collected, pooled and concentrated in vacuo to a colorless oil (0.101 g, 0.302 mmol; 60.3%). ^{1}H NMR: (600 MHz, DMSO-d_6) δ 7.72 (1H, d, J = 2.9 Hz), 7.43 (2H, AB, J_{AB} = 8.1 Hz), 7.37 (2H, AB, J_{AB} = 8.1 Hz), 6.26 (1H, d, J = 2.9 Hz), 5.11 (s, 2H), 4.63 – 4.58 (1H, m), 4.54 (2H, s), 4.53 – 4.49 (1H, m), 3.73 – 3.68 (1H, m), 3.68 – 3.63 (1H, m), 1.55 (9H, s). ^{13}C NMR: (151 MHz, DMSO-d_6) δ 161.5, 158.4, 138.4, 134.4, 130.2, 128.1, 127.6, 105.5, 82.9 (d, J_{CF} = 166 Hz), 71.6, 69.8, 69.0 (d,

J_{CF} = 19.0 Hz), 63.6, 27.6. HRMS Calcd. for $C_{18}H_{23}FN_2O_3$ (M+H): 335.1766; found: 335.1766. TLC: R_f 0.38 (silica gel, 1:1 hexanes/ethyl acetate, CAM).

Example 7

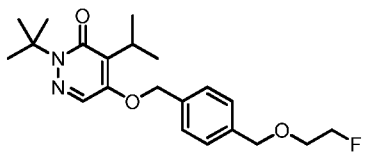
Preparation of 4-bromo-2-(*tert*-butyl)-5-((4-((2-fluoroethoxy)methyl)benzyl)oxy)pyridazin-3(2*H*)-one



Prepared according to General Method B, using 4,5-dibromo-2-(*tert*-butyl)pyridazin-3(2*H*)-one (0.310 g, 1.00 mmol; e.g., see Taniguchi M.; Ochiai Y.; Hirose M.; Hirata K.; Baba M. (Nissan Chemical Industries) Benzylthio pyridazinone derivatives, preparation thereof, and insecticidal acaricidal, fungicidal compositions. US Pat. Appl. 4,877,787, October 31, 1989), (4-((2-fluoroethoxy)methyl)phenyl)methanol (92.1 mg, 0.500 mmol), and cesium carbonate (0.326 g, 1.00 mmol) in dimethylformamide (2.50 mL) at 65 °C. Isolated yield – 0.121 g; 58.5%. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.62 (1H, s), 7.41 (4H, s), 5.32 (2H, s), 4.73 – 4.64 (1H, m), 4.61 (2H, s), 4.57 – 4.48 (1H, m), 3.85 – 3.75 (1H, m), 3.75 – 3.65 (1H, m), 1.63 (9H, s). ^{13}C NMR: (75 MHz, $CDCl_3$) δ 159.3, 155.8, 138.8, 134.6, 128.4, 127.4, 124.8, 110.5, 83.3 (d, J_{CF} = 169 Hz), 73.2, 71.8, 69.7 (d, J_{CF} = 19.6 Hz), 66.7, 28.1. HRMS Calcd. for $C_{18}H_{22}{}^{79}BrFN_2O_3$ (M+H): 413.0871; found: 413.0876. TLC: *R* 0.31 (silica gel, 7:3 hexanes/ethyl acetate, CAM).

Example 8

Preparation of 4-chloro-2-cyclohexyl-5-((4-((2-fluoroethoxy)methyl)benzyl)oxy)pyridazin-3*(2H)*-one



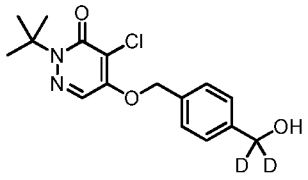
To a cooled (0 °C) solution of isopropyl magnesium bromide (0.087 mL, 2 M solution in tetrahydrofuran) was added 2-(*tert*-butyl)-4-chloro-5-((4-((2-fluoroethoxy)methyl)benzyl)oxy)-4-pyridazin-3(2*H*)-one (32 mg, 0.087 mmol) dissolved in tetrahydrofuran (0.783 mL). The reaction was stirred at 0 °C for 2 h then treated with additional equivalents of isopropyl magnesium bromide (0.261 mL, 2M solution in

tetrahydrofuran). After 24 h, the reaction was quenched with water (0.5 mL) and diluted with ethyl acetate (20 mL). The organic layer was separated, washed with saturated aqueous sodium chloride (3 x 50 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was then purified using silica gel chromatography 3:1 hexanes/ethyl acetate to afford the desired product as a clear oil (12.0 mg, 36.6% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.67 (s, 1H), 7.41 (d, J = 7.5 Hz, 2H), 7.37 (d, J = 8.7 Hz, 2H), 5.17 (s, 2H), 4.68 (m, 1H), 4.62 (s, 2H), 4.53 (m, 1H), 3.80 (m, 1H), 3.71 (m, 1H), 3.50 (m, 1H), 1.62 (s, 9H), 1.27 (d, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.3, 154.2, 138.3, 135.4, 129.3, 128.1, 127.4, 125.8, 83.1 (d, J_{CF} = 165 Hz), 73.0, 70.8, 69.4 (d, J_{CF} = 22.5 Hz), 65.0, 28.1, 24.6, 19.5; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{21}H_{29}FN_2O_3$: 377.2235, found 377.2231.

Example 9

Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-((2-fluoroethoxy)-d_2-methyl)benzyl)oxy)pyridazin-3(2*H*)-one

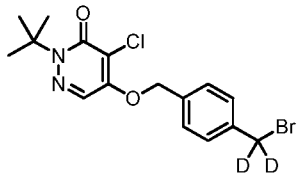
Part A – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(d_2-hydroxymethyl)benzyl)oxy)pyridazin-3(2*H*)-one



To a solution of methyl 4-(((1-*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzoate (1.50 g, 4.28 mmol; e.g., see Cesati, R; Cheesman, E. H.; Lazewatsky, J.; Radeke, S.; Castner, J. F.; Mongeau, E.; Zdankiewicz, D. D.; Siegler, R. W.; Devine, M. Methods and apparatus for synthesizing imaging agents, and intermediates thereof PCT Int. Appl. (2011), WO 2011/097649, August 8, 2011) in tetrahydrofuran (42.8 mL) at 0 °C was added lithium aluminum deuteride (2.14 mL, 2.14 mmol, 1 M solution in tetrahydrofuran) dropwise. The resulting mixture was stirred for 2 h then treated with water (20 mL). The aqueous layer was separated and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered and concentrated to yield a white solid (1.36 g, 97.8% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.64 (s, 1H), 7.35 (br s, 4H), 5.24 (s, 2H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz, *partial*): δ 159.0, 153.7, 141.5, 134.3, 127.5, 127.3, 125.1, 118.4, 71.7,

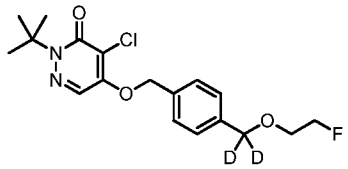
64.4, 27.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{16}H_{17}D_2{}^{35}ClN_2O_3$: 325.1283, found 325.1284.

Part B – Preparation 5-((4-(bromo-d_2-methyl)benzyl)oxy)-2-(*tert*-butyl)-4-chloropyridazin-3(2*H*)-one



Prepared according to General Method C, using the product of Example 9A (0.882 g, 2.72 mmol) and phosphorous tribromide (1.36 mL, 1.36 mmol, 1 M in dichloromethane). Isolated yield – 0.981 g; 93.0%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.64 (s, 1H), 7.37 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 5.23 (s, 2H), 1.59 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz, *partial*): δ 159.0, 153.6, 138.3, 135.1, 129.6, 127.5, 125.0, 118.4, 71.4, 66.5, 27.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{16}H_{16}D_2{}^{79}Br^{35}ClN_2O_2$: 387.0438, found 387.0439.

Part C – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-((2-fluoroethoxy)-d_2-methyl)benzyl)oxy)pyridazin-3(2*H*)-one

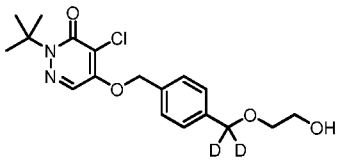


Prepared according to General Method E, using potassium *tert*-butoxide (25.3 mg, 0.225 mmol), 2-fluoroethanol (14.5 mg, 0.226 mmol) and the product of Example 9B (0.105 g, 0.271 mmol). Isolated yield – 7.5 mg; 9.8%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74 (s, 1H), 7.33 (s, 4H), 5.24 (s, 2H), 4.60 (m, 1H), 4.45 (s, 1H), 3.72 (m, 1H), 3.63 (m, 1H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz, *partial*): δ 159.0, 153.7, 138.6, 134.4, 128.3, 127.3, 125.1, 118.4, 83.1 (d, J_{CF} = 165 Hz), 71.7, 69.4 (d, J_{CF} = 15 Hz), 66.4, 27.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{18}H_{20}D_2{}^{35}ClFN_2O_3$: 371.1501, found 371.1507.

Example 10

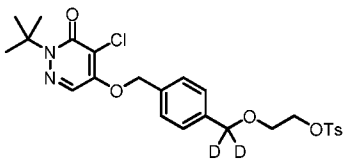
Preparation of 2-((4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)-d_2-methyl) benzyl)oxy)ethyl-4-methylbenzenesulfonate

Part A – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-((2-hydroxyethoxy)-d_2-methyl)benzyl) oxy) pyridazin-3(2*H*)-one



A suspension of potassium *tert*-butoxide (0.174 g, 1.55 mmol) in ethylene glycol (0.685 mL) was heated to 60 °C for 20 min then treated with a solution of the product of Example 9B (0.720 g, 1.86 mmol) in tetrahydrofuran (21 mL). The resulting mixture was heated to reflux, maintained 16 h then cooled to ambient temperature and treated with water (15 mL). The aqueous layer was separated then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was then purified using silica gel chromatography (20-50% ethyl acetate in hexanes) to afford the desired product as a yellow oil (0.144 g, 25.2% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 (s, 1H), 7.33 (s, 4H), 5.24 (s, 2H), 3.71 (m, 2H), 3.54 (m, 2H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz, *partial*): δ 159.0, 153.6, 138.6, 134.4, 128.3, 127.2, 125.0, 118.3, 71.6, 71.5, 66.4, 61.9, 27.8; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{18}H_{21}D_2{}^{35}ClN_2O_4$: 369.1545, found 369.1548.

Part B – Preparation of 2-((4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)-d_2- methyl)benzyl)oxy)ethyl-4-methylbenzenesulfonate



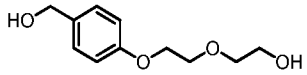
Prepared according to General Method D, using the product of Example 10A (78.2 mg, 0.213 mmol), *p*-toluenesulfonyl chloride (48.6 mg, 0.255 mmol), 4-dimethylaminopyridine (31.2 mg, 0.255 mmol), and diisopropylethylamine (0.044 mL, 0.255 mmol). Isolated yield – 32.8 mg; 29.4%. ^{1}H ($CDCl_3$, 600 MHz): δ 7.72 (d, J = 8.4 Hz, 2H), 7.65 (s, 1H), 7.31 (d, J = 8.3 Hz, 2H), 7.26 – 7.19 (m, 4H), 5.23 (s, 2H), 4.13 (m, 2H), 3.62 (m, 2H), 2.37 (s, 3H), 1.51 (s, 9H); ^{13}C ($CDCl_3$, 150 MHz, *partial*): δ 159.0, 153.6, 144.8,

138.3, 134.4, 133.0, 129.8, 128.2, 128.0, 127.2, 125.0, 118.3, 71.6, 69.2, 67.7, 66.4, 27.8, 21.6; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{25}H_{27}D_2{}^{35}ClN_2O_6S$: 523.1633, found 523.1629.

Example 11

Preparation of 2-(2-(4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)phenoxy)ethoxy)ethyl-4-methylbenzenesulfonate

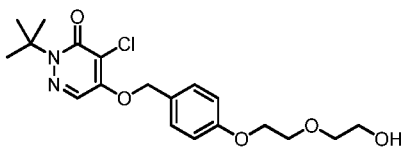
Part A – Preparation of 2-(2-(4-(hydroxymethyl)phenoxy)ethoxy)ethanol



A suspension of potassium iodide (1.10 g, 6.58 mmol), methyl-4-hydroxybenzoate (2.00 g, 13.1 mmol), cesium carbonate (8.53 g, 26.2 mmol), and 2-(2-chloroethoxy)ethanol (3.60 mL, 34.0 mmol) in cyclohexanone (40.0 mL) was heated to reflux and maintained 24 h. After cooling to ambient temperature, the solids were removed by filtration and the resulting filtrate concentrated to an orange oil that was directly used in the subsequent reduction without further purification.

A tetrahydrofuran solution (35.0 mL) of the crude ester was cooled to 0 °C then treated with lithium aluminum hydride (9.12 mL, 9.12 mmol, 1 M tetrahydrofuran solution). Upon complete addition, the resulting mixture was warmed to ambient temperature and stirred overnight then treated with water (20 mL). The layers were then separated and the aqueous layer extracted with ethyl acetate (2 x 50 mL). The combined organic layers were then dried over sodium sulfate, filtered and concentrated to a yellow oil (0.789 g, 28.4% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.21 (m, 2H), 6.83 (m, 2H), 4.55 (s, 2H), 4.07 (m, 2H), 3.80 (m, 2H), 3.70 (m, 2H), 2.60 (m, 2H).

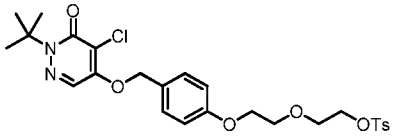
Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(2-(2-hydroxyethoxy)ethoxy)benzyl)oxy)pyridazin-3(2*H*)-one



A solution of 2-(*tert*-butyl)-4-chloro-5-hydroxypyridrazin-3(2*H*)-one[4] (0.375 g, 1.85 mmol) in tetrahydrofuran (15.4 mL) was successively treated with the product of Example 11A, (0.327 g, 1.54 mmol), triphenylphosphine (0.609 g, 2.32 mmol), and

diethylazodicarboxylate (0.404 g, 2.32 mmol) at ambient temperature. After 1 h, all volatiles were removed in vacuo and the residue directly purified by silica gel chromatography using 4:1 diethyl ether/ethyl acetate to afford the desired product (20 mg, 3% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (s, 1H), 7.31 (m, 2H), 6.96 (m, 2H), 5.25 (s, 2H), 4.16 (m, 2H), 3.88 (m, 2H), 3.76 (m, 2H), 3.68 (m, 2H), 1.63 (s, 9H).

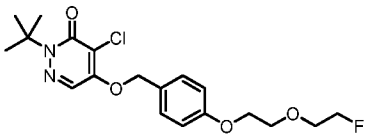
Part C – Preparation of 2-(2-(4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy) methyl) phenoxy)ethoxy)ethyl-4-methylbenzenesulfonate



Prepared according to General Method D, using the product of Example 11B, (19.7 mg, 0.0495 mmol), *p*-toluenesulfonyl chloride (11.3 mg, 0.0594 mmol), 4-dimethylaminopyridine (7.26 mg, 0.0594 mmol), and diisopropylethylamine (0.010 mL, 0.0594 mmol). Isolated yield – 5.2 mg; 19%. ^{1}H ($CDCl_3$, 300 MHz): δ 7.72 (d, J = 8.3 Hz, 2H), 7.66 (s, 1H), 7.28 – 7.19 (m, 4H), 6.85 (m, 2H), 5.18 (s, 2H), 4.14 (m, 2H), 3.99 (m, 2H), 3.74 – 3.68 (m, 4H), 2.34 (s, 3H), 1.56 (s, 9H).

Example 12

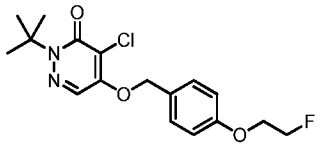
Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(2-(2-fluoroethoxy)ethoxy)benzyl)oxy)pyridazin-3(2*H*)-one



A solution of the product of Example 11C (1.90 mg, 0.0034 mmol), tetraethylammonium fluoride (0.85 mg, 0.0046 mmol), and tetraethylammonium bicarbonate (0.88 mg, 0.0046 mmol) in acetonitrile (0.70 mL) was heated to 90 °C and maintained 10 min. After cooling to ambient temperature, all volatiles were removed in vacuo and the residue directly purified by preparative thin layer chromatography using 4:1 hexanes/ethyl acetate to afford the desired product (0.2 mg, 15% yield). API-ES [M+Na] 421.1.

Example 13

Preparation of 2-(*tert*-butyl-4-chloro-5-((4-(2-fluoroethoxy)benzyl)oxy)pyridazin-3(2*H*)-one

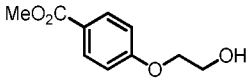


Prepared according to General Method B, using of 2-(*tert*-butyl)-4,5-dichloropyridrazin-3(2*H*)-one[3] (68 mg, 0.31 mmol), (4-(2-fluoroethoxy)phenyl)methanol (53 mg, 0.31 mmol, e.g., see Zhou, D.; Chu, W.; Rothfuss, J.; Zeng, C.; Xu, J.; Jones, L.; Welch, M. J.; Mach, R. H. Synthesis, radiolebeling and in vivo evaluation of an 18F-labeled isatin analog for imaging caspase-3 activation in apoptosis Bioorg. Med. Chem. Lett. 2006, 16, 5041-5045), and cesium carbonate (0.303 g, 0.930 mmol) in dimethylformamide (3.10 mL) at 50 °C. Isolated yield – 25 mg; 23%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (s, 1H), 7.33 (m, 2H), 6.95 (m, 2H), 5.25 (s, 2H), 4.84 (m, 1H), 4.68 (m, 1H), 4.29 (m, 1H), 4.16(m, 1H), 1.57 (s, 9H).

Example 14

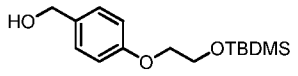
Preparation of 2-(4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)phenoxy)ethyl-4-methylbenzenesulfonate

Part A – Preparation of methyl 4-(2-hydroxyethoxy)benzoate



A suspension of methyl 4-hydroxybenzoate (1.52 g, 1.00 mmol), 1-bromoethanol (1.05 mL, 1.5 mmol), and cesium carbonate (8.13 g, 2.5 mmol) in dimethylformamide (100 mL) was heated to 65 °C and maintained overnight. After cooling to ambient temperature, the resulting mixture was diluted with water (250 mL) then extracted with ethyl acetate (3 x 250 mL). The combined organic layers were washed with water and saturated aqueous sodium chloride then dried over sodium sulfate, filtered and concentrated to a yellow oil (1.83 g, 93.3% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.92 (m, 2H), 6.86 (m, 2H), 4.45 (s, 3H), 4.08 (m, 2H), 3.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.8, 162.4, 131.6, 123.1, 114.2, 69.4, 61.3, 51.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{10}H_{12}O_4$: 197.0808, found 197.0811.

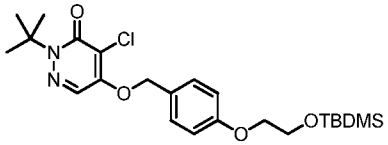
Part B – Preparation of (4-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)phenyl)methanol



A solution of the product of Example 14A (1.00 g, 5.07 mmol), in dimethylformamide (50.0 mL) was successively treated with *tert*-butyldimethylsilyl chloride (1.14 g, 7.61 mmol) and imidazole (0.518 g, 7.61 mmol) at ambient temperature. After 1 h, the solution was diluted with 0.1 N hydrochloric acid (30 mL) then extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo to obtain a crude oil, which was used without further purification in the subsequent step.

The crude silyl ether (0.965 g, 3.11 mmol) was dissolved in tetrahydrofuran (31.1 mL), cooled to 0 °C then treated with lithium aluminum hydride (1.55 mL, 1.55 mmol, 1 M solution of lithium aluminum hydride in tetrahydrofuran) and warmed to ambient temperature. After 4 h, the resulting mixture was treated with water (10 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers dried over sodium sulfate, filtered then concentrated in vacuo to afford an oil (0.779 g, 54.4% yield). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.14 (m, 2H), 6.80 (m, 2H), 4.96 (t, J = 5.7 Hz, 1H), 4.35 (d, J = 5.6 Hz, 2H), 3.95-3.83 (m, 4H), 0.80 (s, 9H), 0.01 (s, 6H).

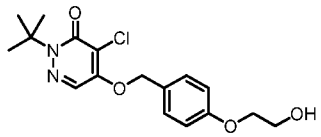
Part C – Preparation of 2-(*tert*-butyl)-5-((4-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)benzyl)oxy)-4-chloropyridazin-3(2*H*)-one



A solution of 2-(*tert*-butyl)-4-chloro-5-hydroxypyridrazin-3(2*H*)-one (0.465 g, 2.29 mmol) in tetrahydrofuran (27.6 mL) was successively treated was added the product of Example 14B (0.779 g, 2.76 mmol), triphenylphosphine (0.905 g, 3.45 mmol), and diisopropylazodicarboxylate (0.686 mL, 3.45 mmol) at ambient temperature. After 20 min, the resulting mixture was treated with water (5 mL), the aqueous layer separated then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was then purified using silica gel chromatography (20-50% ethyl acetate in hexanes) to afford the desired product as a clear oil (0.359 g, 33.6% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.63 (s, 1H), 7.23 (m, 2H), 6.86 (m, 2H), 5.15 (s, 2H), 4.01 (m, 2H), 3.87 (m, 2H), 1.53(s, 9H), 0.82 (s,

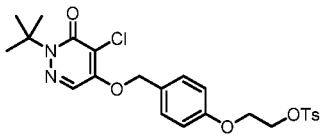
9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz, *partial*): δ 159.1, 153.7, 129.0, 127.4, 125.3, 118.4, 115.0, 71.8, 69.9, 66.4, 61.4, 27.9, 26.6, -3.6; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{23}H_{35}{}^{35}ClN_2O_4Si$:467.2127, found 467.2128.

Part D – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(2-hydroxyethoxy)benzyl)oxy)pyridazin-3(2*H*)-one



A solution of the product of Example 14C (0.240 g, 0.513 mmol) in tetrahydrofuran (5.13 mL) was treated with tetrabutylammonium fluoride (1.03 mL, 1.03 mmol, 1 M solution in tetrahydrofuran) dropwise at ambient temperature. After 40 min, the resulting mixture was diluted with water (5 mL) the aqueous layer was separated then extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford an off white solid (0.157 g, 86.7% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.62 (s, 1H), 7.27 (m, 2H), 7.89 (m, 2H), 5.18 (s, 2H), 4.03 (m, 2H), 3.90 (m, 2H), 1.57 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz, *partial*): δ 159.1, 153.8, 129.0, 127.4, 125.3, 118.4, 115.0, 71.7, 69.3, 66.4, 61.4, 27.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{17}H_{21}{}^{35}ClN_2O_4$: 375.1082, found 375.1079.

Part E – Preparation of 2-(4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)phenoxy)ethyl-4-methylbenzenesulfonate

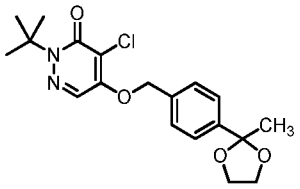


Prepared according to General Method D, using the product of Example 14D (0.157 g, 0.446 mmol), *p*-toluenesulfonyl chloride (0.102 g, 0.536 mmol), 4-dimethylaminopyridine (81.9 mg, 0.67 mmol), and triethylamine (0.075 mL, 0.536 mmol). Isolated yield – 0.120 g; 53.1%. ^{1}H ($CDCl_3$, 600 MHz): δ 7.74 (d, J = 8.3 Hz, 2H), 7.64 (s, 1H), 7.28 – 7.19 (m, 4H), 6.75 (m, 2H), 5.16 (s, 2H), 4.30 (m, 2H), 4.09 (m, 2H), 2.38 (s, 3H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 159.0, 158.5, 153.7, 145.0, 132.9, 129.9, 128.9, 128.0, 127.7, 125.2, 118.4, 115.0, 71.7, 67.9, 66.4, 65.6, 27.9, 21.6; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{24}H_{27}{}^{35}ClN_2O_6S$: 507.1351, found 507.1365.

Example 15

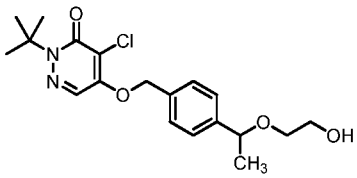
Preparation of 2-(1-(4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl) phenyl)ethoxy)ethyl 4-methylbenzenesulfonate

Part A – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(2-methyl-1,3-dioxolan-2-yl)benzyl)oxy) pyridazin-3(2*H*)-one



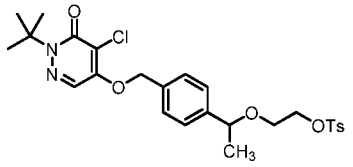
A solution of 2-(*tert*-butyl)-4,5-dichloro-2-hydropyridazin-3-one (1.66 g, 7.50 mmol) and (4-(2-methyl-1,3-dioxolan-2-yl)phenyl)methanol (0.971 g, 5.00 mmol; e.g., see Takebayashi, S.; Dabral, N.; Miskolzie, M.; Bergens, S. H. J. Am. Chem. Soc., 2011 , 133, 25, 9666 – 9669) in dry dimethylformamide (50.0 mL) was treated with cesium carbonate (3.26 g, 10.0 mmol) in one portion at ambient temperature. The resulting suspension was then immersed in a pre-heated oil bath, and maintained at 65 °C, with vigorous stirring, 4 h. After cooling to ambient temperature, the suspension was maintained an additional 12 h, then partitioned between ethyl acetate and water (50 mL each), with transfer to a separatory funnel. The layers were then separated, and the aqueous layer washed with ethyl acetate (2 x 50 mL). The combined ethyl acetate washes were further washed with saturated aqueous sodium chloride (5 x 50 mL), then dried over magnesium sulfate, filtered and concentrated in vacuo to a yellow solid. The crude material was then purified by chromatography on silica (40 x 220 mm) using 7:3 pentane/ethyl acetate. The main product peak eluting 400-700 mL was collected, pooled and concentrated in vacuo to a white solid. The purified material was then recrystallized from hot ethyl acetate/pentane to afford colorless needles (1.33 g, 3.51 mmol; 70.1%). ^{1}H NMR: (300 MHz, DMSO-d_6) δ 8.27 (1H, s), 7.52 – 7.36 (4H, m), 5.44 (2H, s), 4.07 – 3.93 (2H, m), 3.76 – 3.60 (2H, m), 1.57 (9H, s), 1.55 (3H, s). ^{13}C NMR: (75 MHz, DMSO-d_6) δ 157.8, 153.9, 143.6, 134.9, 127.7, 126.2, 125.4, 115.5, 107.9, 71.2, 65.4, 64.1, 27.5, 27.2. HRMS Calcd. for $C_{19}H_{23}{}^{35}ClN_2O_4$ (M+H): 379.1419; found: 379.1416. TLC: R_f 0.39 (silica gel, 7:3 pentane/ethyl acetate, uv).

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(1-(2-hydroxyethoxy)ethyl)benzyl)oxy)pyridazin-3(2*H*)-one



A 25 mL flame-dried round bottom flask was charged with zirconium chloride (0.233 g, 1.00 mmol) and dry tetrahydrofuran (3.00 mL) at ambient temperature. The resulting solution was then treated with sodium borohydride (75.7 mg, 2.00 mmol), in one portion, followed by the product of Example 15A (1.00 mmol; 2.00 mL of a 0.5 M solution in tetrahydrofuran), dropwise over 3 min at ambient temperature. After 1.5 h, excess sodium borohydride was then consumed by the dropwise addition of water and the resulting solution partitioned between ethyl acetate and water (25 mL each) with transfer to a separatory funnel. The layers were then separated, and the aqueous layer washed with ethyl acetate (2 x 25 mL). The combined ethyl acetate washes were then dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material thus obtained was then purified by chromatography on silica (30 x 170 mm) using 1:1 pentane/ethyl acetate. The main product peak eluting 250-460 mL was collected, pooled and concentrated in vacuo to a colorless oil (0.289 g, 0.758 mmol; 75.8%). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.74 (1H, s), 7.45 – 7.29 (4H, m), 5.29 (2H, s), 4.47 (1H, q, J = 6.5 Hz), 3.79 – 3.63 (2H, m), 3.52 – 3.35 (2H, m), 1.63 (9H, s), 1.46 (3H, d, J = 6.5 Hz). ^{13}C NMR: (75 MHz, $CDCl_3$) δ 159.0, 153.7, 144.3, 134.1, 127.4, 126.7, 125.1, 118.3, 78.1, 71.7, 69.8, 66.4, 62.0, 27.9, 23.9. HRMS Calcd. for $C_{19}H_{25}{}^{35}ClN_2O_4$ (M+H): 381.1576; found: 381.1574.

Part C – Preparation of 2-(1-(4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)phenyl)ethoxy)ethyl 4-methylbenzenesulfonate

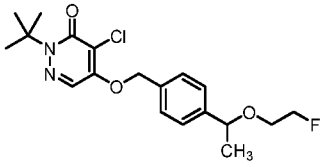


A solution of the product of Example 15B (95.2 mg, 0.250 mmol) in dry pyridine (0.50 mL) was cooled to 0 °C then treated with *p*-toluenesulfonyl chloride (95.3 mg, 0.50 mmol) in one portion. After 0.25 h, the resulting solution was then warmed to ambient temperature and maintained 3.25 h, when additional *p*-toluenesulfonyl chloride (95.3 mg, 0.50 mmol) was added. After 0.75 h, the resulting solution was diluted with ethyl acetate

(150 mL) and water (50 mL), with transfer to a separatory funnel. The layers were then separated and the ethyl acetate layer successively washed with 0.1 M hydrochloric acid and saturated aqueous sodium bicarbonate (3 x 50 mL each), then dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material thus obtained was then purified by chromatography on silica (30 x 175 mm) using 3:2 pentane/ethyl acetate. The main product peak eluting 150-250 mL was collected, pooled and concentrated in vacuo to a colorless oil (62.1 mg, 0.116 mmol; 46.4%). ^{1}H NMR: (300 MHz, DMSO-d_6) δ 8.28 (1H, s), 7.82 – 7.71 (2H, AA'BB', J_{AB} = 8.3 Hz, $J_{AA'}$ = 2.0 Hz), 7.45 (2H, AB, d, J_{AB} = 8.6 Hz), 7.42 (2H, AB, J_{AB} = 8.1 Hz), 7.28 (2H, AB, J_{AB} = 8.1 Hz), 5.44 (2H, s), 4.42 (1H, q, J = 6.4 Hz), 4.11 (2H, ABdd, J_{AB} = 11.2 Hz, J_{dd} = 5.7, 3.0 Hz), 3.40 (2H, ABdd, J_{AB} = 11.9 Hz, J_{dd} = 5.6, 3.0 Hz), 2.41 (3H, s), 1.57 (9H, s), 1.27 (3H, d, J = 6.4 Hz). ^{13}C NMR: (75 MHz, DMSO-d_6) δ 157.8, 153.9, 144.8, 143.6, 134.5, 132.5, 130.1, 127.9, 127.6, 126.2, 126.2, 115.5, 76.7, 71.3, 70.1, 65.5, 65.4, 27.5, 23.4, 21.0. HRMS Calcd. for $C_{26}H_{31}{}^{35}ClN_2O_6S$ (M+H): 535.1644; found: 535.1657. TLC: R_f 0.58 (silica gel, 1:1 pentane/ethyl acetate, uv).

Example 16

Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(1-(2-fluoroethoxy)ethyl)benzyl)oxy)pyridazin-3(2*H*)-one

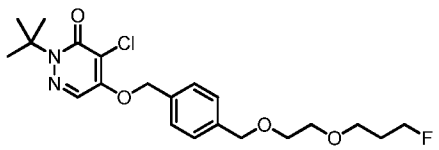


A solution of the product of Example 15C (79.7 mg, 0.150 mmol) and 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (113 mg, 0.200 mmol) in dry acetonitrile (1.50 mL) was treated with potassium fluoride (17.4 mg, 0.300 mmol) in one portion at ambient temperature. The resulting suspension was then immersed in a pre-heated oil bath, and maintained at 90 °C for 0.25 h. After cooling to ambient temperature, all volatiles were removed in vacuo, and the residue directly purified by chromatography on silica (30 x 160 mm) using 1:1 pentane/diethyl ether. The main product peak eluting 140-220 mL was collected, pooled and concentrated in vacuo to a colorless oil (42.6 mg, 0.111 mmol; 74.2%). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.74 (1H, s), 7.45 – 7.30 (4H, m), 5.29 (2H, s), 4.53 (2H, ddd, J = 47.7, 4.7, 3.7 Hz), 4.51 (1H, q, J = 6.5 Hz), 3.69 – 3.53 (1H, m), 3.59 – 3.44 (1H, m), 1.63 (9H, s), 1.47 (3H, d, J = 6.5 Hz). ^{13}C NMR: (75 MHz, $CDCl_3$) δ 159.0, 153.7, 144.2, 134.1, 127.4, 126.7, 125.1, 118.3, 83.1 (d, J_{CF} = 169 Hz), 78.1, 71.7, 67.7 (d, J_{CF} =

19.8 Hz), 66.4, 27.8, 24.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ -223.2 (tt, J = 47.8, 29.6 Hz). HRMS Calcd. for $C_{19}H_{24}{}^{35}ClFN_2O_3$ (M+H): 383.1532; found: 383.1531. TLC: R_f 0.40 (silica gel, 1:1 pentane/diethyl ether, uv).

Example 17

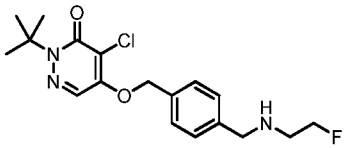
Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-((2-fluoropropoxy)ethoxy)methyl)benzyl) oxy)pyridazin-3(2*H*)-one



A suspension of potassium *tert*-butoxide (0.174 g, 1.55 mmol), 3-fluoropropyl *p*-toluenesulfonate (0.152 g, 0.654 mmol), and 2-(*tert*-butyl)-4-chloro-5-((4-((2-fluoroethoxy) methyl)benzyl)oxy)-4-pyridazin-3(2*H*)-one (0.200 g, 0.59 mmol) in tetrahydrofuran (5.90 mL) was heated to reflux and maintained overnight. After cooling to ambient temperature, the resulting mixture was treated with water (15 mL), the aqueous layer separated then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was then purified by preparative thin layer chromatography on silica using 4:1 hexanes/ethyl acetate to afford the desired product as a yellow oil (0.8 mg, 1% yield). API-ES *(m / z)*: [M+H] 427.2.

Example 18

Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(((2-fluoroethyl)amino)methyl)benzyl)oxy)pyridazin-3(2*H*)-one

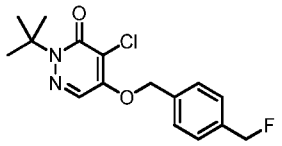


A solution of 5-((4-(bromomethyl)benzyl)oxy)-2-(*tert*-butyl)-4-chloropyridazin-3(2*H*)-one[3] (0.200 g, 0.521 mmol) in dimethylformamide (5.20 mL) was successively treated with 2-fluoroethylamine hydrochloride (62.2 mg, 0.625 mmol) and diisopropylethylamine (0.136 mL, 0.782 mmol) at ambient temperature. After 2 d, the resulting mixture was diluted with water (50 mL), the aqueous layer separated then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was then purified using silica gel chromatography (50-80% ethyl acetate in hexanes) to afford the desired product as a clear oil (17.2 mg, 9.0% yield). ^{1}H

NMR ($CDCl_3$, 600 MHz): δ 7.64 (s, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 5.22 (s, 2H), 4.65 (m, 1H), 4.50 (m, 1H), 3.90 (s, 2H), 2.97 (m, 1H), 2.88 (m, 1H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 158.0, 152.7, 138.1, 133.1, 128.0, 126.9, 126.4, 117.3, 81.8 (d, J_{CF} = 165 Hz), 70.7, 65.4, 51.8, 47.4 (d, J_{CF} = 22.5 Hz), 26.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{18}H_{23}{}^{35}ClFN_3O_2$: 368.1536, found 368.1533.

Example 19

Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(fluoromethyl)benzyl)oxy)pyridazin-3(2*H*)-one

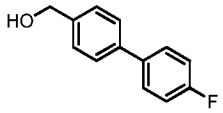


A solution of 5-((4-(bromomethyl)benzyl)oxy)-2-(*tert*-butyl)-4-chloropyridazin-3(2*H*)-one[3] (0.110 g, 0.285 mmol) in dry acetonitrile (2.85 mL) was treated with silver fluoride (72.4 mg, 0.570 mmol) in one portion at ambient temperature. After 0.25 h, the resulting suspension was then immersed in a pre-heated oil bath, and maintained at 65 °C for 0.75 h, when additional silver fluoride (72.4 mg, 0.570 mmol) was added. After 1 h, the resulting suspension was cooled to ambient temperature, all volatiles removed in vacuo, and the residue directly purified by chromatography on silica (25 x 185 mm) using 4:1 hexanes/ethyl acetate. The main product peak eluting 280-420 mL was collected, pooled and concentrated in vacuo to a white solid (64.6 mg, 0.199 mmol; 69.8%). ^1H NMR: (300 MHz, DMSO-d_6) δ 8.25 (1H, s), 7.56 – 7.42 (4H, m), 5.48 (2H, d, J = 1.4 Hz), 5.43 (2H, d, J = 47.7 Hz), 1.57 (9H, s). ^{13}C NMR: (75 MHz, DMSO-d_6) δ 157.8, 153.8, 136.4 (d, J_{CF} = 16.7 Hz), 135.9 (d, J_{CF} = 3.1 Hz), 128.1 (d, J_{CF} = 5.7 Hz), 127.9 (d, J_{CF} = 1.4 Hz), 126.1, 115.6, 83.8 (d, J_{CF} = 162 Hz), 71.1, 65.4, 27.4. ^{19}F NMR: (282 MHz, DMSO-d_6) δ -205.4 (t, J = 47.7 Hz). HRMS Calcd. for $C_{16}H_{18}{}^{35}ClFN_2O_2$ (M+H): 325.1114; found: 325.1117. TLC: R_f 0.24 (silica gel, 4:1 hexanes/ethyl acetate, uv).

Example 20

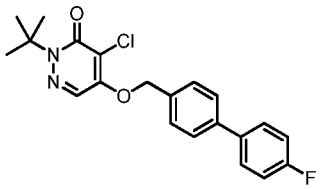
Preparation of 2-(*tert*-butyl)-4-chloro-5-((4'-fluoro-[1,1'-biphenyl]-4-yl)methoxy)pyridazin-3(2*H*)-one

Part A – Preparation of (4'-fluoro-[1,1'-biphenyl]-4-yl)methanol



A solution of 4-(4-fluorophenyl)benzoic acid (0.500 g, 2.31 mmol) in tetrahydrofuran (23.1 mL) was cooled to 0 °C, treated with lithium aluminum hydride (1.15 mL, 1.15 mmol, 1 M solution in tetrahydrofuran) then warmed to ambient temperature and stirred overnight. The resulting mixture was then treated with water (20 mL), the aqueous layer separated then extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered and concentrated to a white solid (0.290 g, 62.1% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48-7.44 (m, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 7.04 (m, 2H), 4.67 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.5 (d, J_{CF} = 240 Hz), 138.9, 138.7, 136.0 (d, J_{CF} = 7.5 Hz), 127.7 (d, J_{CF} = 7.5 Hz), 126.5, 126.2, 114.6 (d, J_{CF} = 22.5 Hz), 64.0; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{13}H_{11}FO$: 203.0867, found 203.0868.

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4'-fluoro-[1,1'-biphenyl]-4-yl)methoxy)pyridazin-3(2*H*)-one



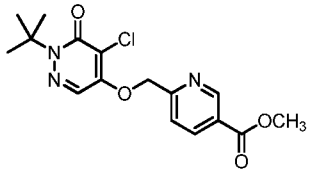
Prepared according to General Method B, using 2-(*tert*-butyl)-4,5-dichloropyridrazin-3(2*H*)-one (0.288 g, 1.30 mmol), the product of Example 20A, (0.290 g, 1.43 mmol), and cesium carbonate (0.680 g, 2.09 mmol) in dimethylformamide (13.0 mL) at 60 °C. Isolated yield – 0.144 g; 28.6%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.68 (s, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.53-7.45 (m, 2H), 7.40 (d, J = 8.5 Hz, 2H), 7.06 (m, 2H), 5.28 (s, 2H), 1.54 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.7 (d, J_{CF} = 247.5 Hz), 159.0, 153.7, 140.8, 136.5 (d, J_{CF} = 7.5 Hz), 133.9, 128.7 (d, J_{CF} = 7.5 Hz), 127.7, 127.6, 125.1, 118.4, 115.8 (d, J_{CF} = 22.5 Hz), 71.6,

66.4, 27.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{21}H_{20}{}^{35}ClFN_2O_2$: 387.1270, found 387.1268.

Example 21

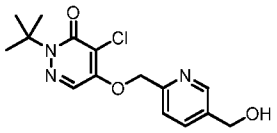
Preparation of 2-(*tert*-butyl)-4-chloro-5-((5-((2-fluoroethoxy)methyl)pyridin-2-yl)methoxy)pyridazin-3(2*H*)-one

Part A – Preparation of methyl 6-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-ol)oxy)methyl)nicotinate



Prepared according to General Method B, using 2-(*tert*-butyl)-4-chloro-5-hydroxypyridrazin-3(2*H*)-one (0.917 g, 4.54 mmol), methyl 6-(bromomethyl)nicotinate (0.994 g, 4.32 mmol), and cesium carbonate (2.25 g, 6.91 mmol) in dimethylformamide (21.0 mL) at 60 °C. Isolated yield – 0.666 g; 41.7%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.22 (d, *J* = 1.3 Hz, 1H), 8.41(dd, *J* = 8.1, 2.1 Hz, 1H), 7.79 (s, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 5.48 (s, 2H), 3.99 (s, 3H), 1.66 (s, 9H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 165.2, 159.1, 158.9, 153.3, 150.4, 138.6, 125.9, 124.7, 120.8, 118.5, 70.7, 66.7, 52.6, 27.8; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{16}H_{18}{}^{35}ClN_3O_4$: 352.1059, found 352.1059.

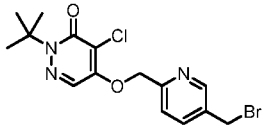
Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((5-(hydroxymethyl)pyridin-2-yl)methoxy)pyridazin-3(2*H*)-one



A solution of the product of Example 21A (0.333 g, 0.945 mmol) in tetrahydrofuran (9.45 mL) was cooled to 0 °C, treated with lithium aluminum hydride (0.472 mL, 0.5 mmol, 1M solution in tetrahydrofuran) then warmed to ambient temperature. After 4 h, the resulting mixture was treated with water (10 mL), the aqueous layer separated then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered and concentrated to a yellow oil (0.290 g, 94.8% yield). ^{1}H NMR (DMSO-d_6, 600 MHz): δ 8.59 (d, 1H, *J* = 1.4 Hz), 8.32 (s, 1H), 7.87

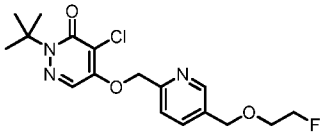
(dd, J = 7.9, 2.2 Hz, 1H), 7.57 (m, 1H), 5.58 (s, 2H), 5.39 (t, J = 5.74 Hz, 1H), 4.61 (d, J = 5.6 Hz, 2H), 1.64 (s, 9H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 157.8, 153.9, 153.4, 147.8, 137.4, 135.5, 126.3, 121.6, 115.5, 71.8, 64.8, 50.7, 20.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{15}H_{18}{}^{35}ClN_3O_3$: 324.1109, found 324.111.

Part C – Preparation of 5-((5-(bromomethyl) pyridin-2-yl) methoxy)-2-(*tert*-butyl)-4-chloro pyridazin-3(*2H*)-one



Prepared according to General Method C, using product of Example 21B (0.289 g, 0.891 mmol) and phosphorous tribromide (0.446 mL, 0.446 mmol, 1 M in dichloromethane). Isolated yield – 0.212 g; 61.5%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.73 (d, J = 1.4 Hz, 1H), 8.31 (s, 1H), 8.03 (dd, J = 8.1, 2.3 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 5.60 (s, 2H), 4.83 (s, 2H), 1.64 (s, 9H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 157.8, 154.8, 153.8, 149.6, 138.0, 133.8, 126.3, 121.8, 115.6, 71.8, 66.4, 30.4, 27.5. HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{15}H_{17}{}^{79}Br^{35}ClN_3O_2$: 386.0265, found 386.0267.

Part D – Preparation of 2-(*tert*-butyl)-4-chloro-5-((5-((2-fluoroethoxy)methyl)pyridin-2-yl)methoxy)pyridazin-3(2*H*)-one

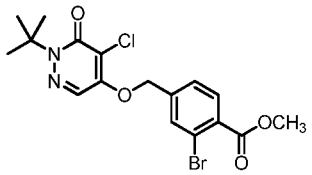


Prepared according to General Method A, using potassium *tert*-butoxide (25.9 mg, 0.231 mmol), 2-fluoroethanol (14.8 mg, 0.231 mmol) and the product of Example 21C (0.100 g, 0.260 mmol). Isolated yield – 23.8 mg; 27.9%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.51 (d, J = 1.5 Hz, 1H), 7.73 (s, 1H), 7.72 (dd, J = 7.3, 2.17 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 5.34 (s, 2H), 4.47 (m, 1H), 4.45 (s, 2H), 4.46 (m, 1H), 3.77 (m, 1H), 3.67 (m, 1H), 1.48 (s, 9H); HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{17}H_{21}{}^{35}ClFN_3O_3$: 370.1328, found 370.1328.

Example 22

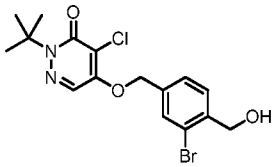
Preparation of 5-((3-bromo-4-((2-fluoroethoxy)methyl)benzyl)oxy)-2-(*tert*-butyl)-4-chloropyridazin-3(2*H*)-one

Part A – Preparation of methyl 2-bromo-4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzoate



Prepared according to General Method B, using 2-(*tert*-butyl)-4-chloro-5-hydroxypyridrazin-3(2*H*)-one (0.750 g, 3.70 mmol), methyl 2-bromo-4-bromomethyl benzoate (1.09 g, 3.52 mmol), and cesium carbonate (1.37 g, 4.22 mmol) in dimethylformamide (35.0 mL) at 70 °C. Isolated yield – 0.695 g; 46.0%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.84 (m, 1H), 7.73 (m, 1H), 7.69 (s, 1H), 7.44 (m, 1H), 5.32 (s, 2H), 3.93 (s, 3H), 1.64 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.2, 158.9, 153.3,139.9, 132.4, 132.3, 131.9, 125.4, 124.7, 122.3, 118.7, 70.2, 66.6, 52.6, 27.8; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{17}H_{18}{}^{79}Br^{35}ClN_2O_4$: 429.0211, found 429.0209.

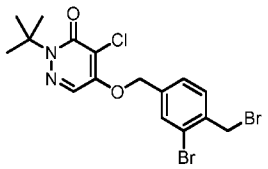
Part B – Preparation of 5-((3-bromo-4-(hydroxymethyl) benzyl) oxy)-2-(*tert*-butyl)-4-chloropyridazin-3(2*H*)-one



A solution of the product of Example 22A (0.300 g, 0.697 mmol), in tetrahydrofuran (2.50 mL) was cooled -20 °C, treated with diisobutylaluminum hydride (1.57 mL, 1.57 mmol, 1 M solution in dichloromethane) the warmed to ambient temperature and stirred overnight. The resulting mixture was treated with water (10 mL), the aqueous layer separated then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was then purified by silica gel chromatography (0-50% ethyl acetate in hexanes) to afford the desired product as a yellow oil (0.109 g, 38.9% yield). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.59 (d, J = 1.4 Hz, 1H), 8.32 (s, 1H), 7.87 (dd, J = 7.9, 2.2 Hz, 1H), 7.57 (m, 1H), 5.58 (s, 2H), 5.39 (t, J = 5.7

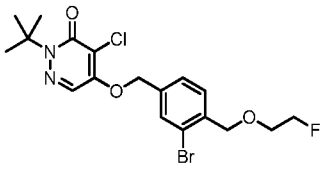
Hz, 1H), 4.61 (d, *J* =5.6 Hz, 2H), 1.64 (s, 9H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 159.0, 153.4, 140.4, 136.0, 131.0, 129.2, 126.1, 124.9, 122.8, 118.5, 70.7, 66.6, 64.7, 27.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{16}H_{18}{}^{79}Br^{35}ClN_2O_3$: 401.0262, found 401.0266.

Part C – Preparation of 5-((3-bromo-4-(bromomethyl)benzyl)oxy)-2-(*tert*-butyl)-4-chloropyridazin-3(2*H*)-one



Prepared according to General Method C, using the product of Example 22B (0.109 g, 0.270 mmol) and phosphorous tribromide (0.135 mL, 0.135 mmol, 1 M in dichloromethane). Isolated yield – 87.1 mg; 69.4%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.69 (s, 1H), 7.64 (d, *J* = 1.4 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.36 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.27 (s, 2H), 4.60 (s, 2H), 1.64 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 153.3, 137.6, 137.2, 131.7, 131.6, 126.4, 124.9, 124.8 118.6, 70.4, 66.6, 32.6, 27.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{16}H_{17}{}^{79}Br_2{}^{35}ClN_2O_2$: 464.9397, found 464.9400.

Part D – Preparation of 2-(*tert*-butyl)-4-chloro-5-((5-((2-fluoroethoxy)methyl)pyridin-2-yl)methoxy)pyridazin-3(2*H*)-one

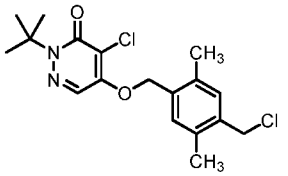


Prepared according to General Method E, using potassium *tert*-butoxide (9.5 mg, 0.084 mmol), 2-fluoroethanol (5.4 mg, 0.084 mmol) and the product of Example 22C (43.5 mg, 0.0940 mmol). Isolated yield – 3.0 mg; 8.0%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.69 (s, 1H), 7.61 (d, 1H, *J* =1.4 Hz), 7.57 (d, *J* = 8.0 Hz, 1H), 7.38 (dd, *J* = 6.3, 1.6 Hz, 1H), 5.27 (s, 2H), 4.72 (m, 1H), 4.66 (s, 2H), 4.56 (m, 1H), 3.89 (m, 1H), 3.79 (m, 1H), 1.64 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 153.4, 138.0, 136.0, 131.0, 129.4, 126.1, 124.9, 122.9, 118.6, 83.0 (d, J_{CF} = 165 Hz), 72.3, 70.7, 70.1 (d, J_{CF} = 15 Hz), 66.5, 27.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{18}H_{21}{}^{79}Br^{35}ClFN_2O_3$: 447.0481, found 447.0471.

Example 23

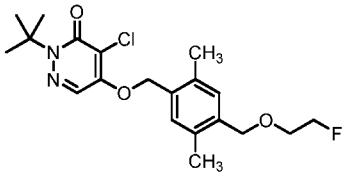
Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-((2-fluoroethoxy)methyl)-2,5-dimethylbenzyl)oxy)pyridazin-3(2*H*)-one

Part A – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(chloromethyl)-2,5-dimethylbenzyl)oxy)pyridazin-3(2*H*)-one



Prepared according to General Method B, using 2-(*tert*-butyl)-4-chloro-5-hydroxypyridrazin-3(2*H*)-one (0.500 g, 2.47 mmol), 2, 5-bis(chloromethyl)-p-xylene (1.00 g, 5.00 mmol), and cesium carbonate (2.60 g, 8.00 mmol) in dimethylformamide (25.0 mL) at ambient temperature. Isolated yield – 0.410 g; 44.9%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.68 (s, 1H), 7.13 (m, 2H), 5.17 (s, 2H), 4.51 (s, 2H), 2.34 (s, 3H), 2.28 (s, 3H), 1.58 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 153.7, 136.2, 135.1, 134.5, 133.3, 132.2, 130.7, 125.0, 118.3, 70.3, 66.4, 44.2, 27.9, 18.4, 18.3; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{18}H_{22}{}^{35}Cl_2N_2O_2$: 369.1131, found 369.1134.

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-((2-fluoroethoxy)methyl)-2,5-dimethylbenzyl)oxy)pyridazin-3(2*H*)-one

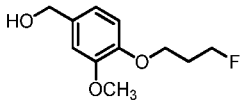


Prepared according to General Method E, using potassium *tert*-butoxide (38.0 mg, 0.339 mmol), 2-fluoroethanol (14.5 mg, 0.226 mmol) and the product of Example 23A (0.100 g, 0.271 mmol). Isolated yield – 18.3 mg; 20.4%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.69 (s, 1H), 7.61 (d, J = 14.9 Hz, 1H), 7.57 (d, J = 12.6 Hz, 1H), 5.18 (s, 2H), 4.49 (m, 1H), 4.46 (s, 2H), 4.44 (m, 1H), 3.73 (m, 1H), 3.64 (m, 1H), 2.28 (s, 3H), 2.25 (3H, s), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.1, 152.8, 135.6, 133.5, 133.1, 131.2, 130.1, 129.5, 124.1, 117.2, 82.1 (d, J_{CF} = 165 Hz), 70.4, 69.5, 68.6(d, J_{CF} = 22.5 Hz), 65.4, 26.9, 17.4, 17.3; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{20}H_{26}{}^{35}ClFN_2O_3$: 397.1689, found 397.1687.

Example 24

Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(3-fluoropropoxy)-3-methoxybenzyl)oxy)pyridazin-3(*2H*)-one

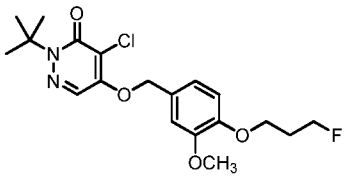
Part A – Preparation of (4-(3-fluoropropoxy)-3-methoxphenyl)methanol



Prepared according to General Method F, using 4-hydroxy-3-methoxybenzaldehyde (0.688 g, 4.52 mmol), 3-fluoropropyl *p*-toluenesulfonate (1.00 g, 4.30 mmol), and cesium carbonate (2.24 mg, 6.89 mmol) in dimethylformamide (43.0 mL) at 60 °C. Isolated yield – 0.517 g; 56.1%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.78 (s, 1H), 7.37 (dd, *J* = 8.1, 1.9Hz, 1H), 7.35 (m, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 4.68 (t, *J* = 5.7 Hz, 1H), 4.53 (t, *J* = 5.7 Hz, 1H), 4.18 (t, *J* = 6.3 Hz, 2H), 3.12 (s, 3H), 2.24 (m, 1H), 2.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.8, 153.8, 150.0, 130.3, 126.7, 111.7, 109.5, 80.5 (d, J_{CF} = 165 Hz), 64.8 (d, J_{CF} = 7.5 Hz), 56.0, 30.2 (d, J_{CF} = 22.5 Hz).

A solution of the crude 4-(3-fluoropropoxy)-3-methoxybenzaldehyde (0.839 g, 3.90 mmol) in ethanol (39.0 mL) was treated sodium borohydride (0.112 g, 2.90 mmol) in one portion at ambient temperature. The resulting mixture was stirred overnight, then treated with water (50 mL) and concentrated in vacuo to remove the ethanol. The resulting aqueous solution was extracted with ethyl acetate (3 x 150 mL), and the combined organic layers dried over sodium sulfate, filtered and concentrated to afford the desired product (0.807 g, 96.6% yield). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6. 87 (br s, 1H), 6.81 (br s, 2H), 4.68 (m, 1H), 4.56 (s, 2H), 4.52 (m, 1H), 4.08 (t, *J* = 6.3 Hz, 2H), 3.81 (s, 3H), 2.19 (m, 1H), 2.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 149.7, 147.8, 121.5, 119.5, 113.4, 111.8, 81.9 (d, J_{CF} = 157.5 Hz), 65.3. 65.0 (d, J_{CF} = 7.5 Hz), 56.0, 30.5 (d, J_{CF} = 22.5 Hz); HRMS-TOF *(m / z)*: [M + Na]$^+$ HRMS: Calcd. for $C_{11}H_{15}FO_3$: 237.0897, found 237.0898.

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(3-fluoropropoxy)-3-methoxybenzyl)oxy)pyridazin-3(*2H*)-one

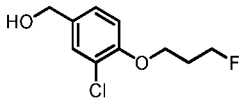


A solution of 2-(*tert*-butyl)-4-chloro-5-hydroxypyridrazin-3(2*H*)-one (0.200 g, 0.990 mmol) in tetrahydrofuran (8.24 mL) was successively treated with the product of Example 24A (0.254 g, 1.19 mmol), triphenylphosphine (0.388 g, 1.48 mmol), and diisopropylazodicarboxylate (0.291 mL, 1.48 mmol) at ambient temperature. The resulting mixture was stirred overnight then concentrated in vacuo to a yellow oil. The crude material was then purified by preparative thin layer chromatography on silica using 98:2 hexanes/diethyl ether to afford the desired product (12.6 mg, 3.2% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 (s, 1H), 6.86 (m, 3H), 5.18 (s, 2H), 4.68 (t, J = 5.7 Hz, 1H), 4.52 (t, J = 5.7 Hz, 1H), 4.09 (t, J = 6.3 Hz, 2H), 3.08 (s, 3H), 2.24 – 2.07 (m, 2H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz, *partial*): δ 159.0, 153.8, 150.0, 148.7, 127.8, 125.3, 120.0, 113.2, 110.9, 80.7 (d, J_{CF} = 165 Hz), 72.0, 66.4, 64.9 (d, J_{CF} = 7.5 Hz), 56.0, 30.4 (d, J_{CF} = 22.5 Hz), 27.9; HRMS-TOF *(m / z)*: $[M + H]^+$ Calcd. for $C_{19}H_{24}{}^{35}ClFN_2O_4$: 399.1481, found 399.1484.

Example 25

Preparation of 2-(*tert*-butyl)-4-chloro-5-((3-chloro-4-(3-fluoropropoxy)benzyl)oxy)pyridazin-3(2*H*)-one

Part A – Preparation of (3-chloro-4-(3-fluoropropoxy)phenyl)methanol

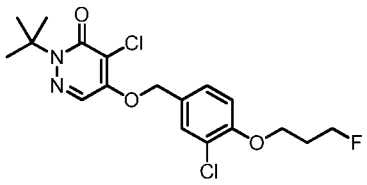


Prepared according to General Method F, using 3-chloro-4-hydroxybenzaldehyde (0.300 g, 1.92 mmol), 3-fluoropropyl *p*-toluenesulfonate (424 g, 1.83 mmol), and cesium carbonate (0.951 g, 2.93 mmol) in dimethylformamide (19.0 mL) at 65 °C. Isolated yield – 0.262 g; 66.1%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.89 (s, 1H), 7.93 (d, J = 2.1 Hz, 1H), 7.78 (dd, J = 8.5, 2.1 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 4.80 (t, J = 5.7 Hz, 1H), 4.64 (t, J = 5.7 Hz, 1H), 4.28 (t, J = 6.0 Hz, 2H), 2.33 (m, 1H), 2.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.6, 159.1, 131.3, 130.4, 130.4, 124.0, 112.6, 80.2 (d, J_{CF} = 165 Hz), 64.9 (d, J_{CF} = 7.5 Hz), 30.2(d, J_{CF} = 22.5 Hz).

A solution of the crude 3-chloro-4-(3-fluoropropoxy)benzaldehyde (0.262 g, 1.21 mmol) in ethanol (8.95 mL) was treated with sodium borohydride (25.4 mg, 0.671 mmol) in one portion at ambient temperature. The resulting mixture was stirred overnight, then treated with water (10 mL) and concentrated in vacuo to remove the ethanol. The resulting aqueous solution was extracted with ethyl acetate (3 x 50 mL), and the combined organic layers dried

over sodium sulfate, filtered and concentrated to afford the desired product as a white solid (0.242 g, 91.5% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32 (d, J = 2.1 Hz, 1H), 7.13 (dd, J = 8.4, 2.2 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 4.71 (t, J = 5.6 Hz, 1H), 4.57 (t, J = 5.6 Hz, 1H), 4.54 (s, 2H), 4.09 (t, J = 6.0 Hz, 2H), 2.19 (m, 1H), 2.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.7, 134.4, 129.2, 126.5, 123.1, 113.5, 80.6 (d, J_{CF} = 165 Hz), 64.8 (d, J_{CF} = 7.5 Hz), 64.4, 30.4 (d, J_{CF} = 22.5 Hz); HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{10}H_{12}{}^{35}ClFO_2$: 217.0437, found 217.0442.

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((3-chloro-4-(3-fluoropropoxy)benzyl)oxy)pyridazin-3(*2H*)-one

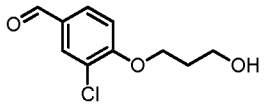


A solution of 2-(*tert*-butyl)-4-chloro-5-hydroxypyridrazin-3(2*H*)-one (0.186 g, 0.920 mmol) in THF (7.60 mL) was successively treated with the product of Example 25A (0.242 g, 1.10 mmol), triphenylphosphine (0.362 g, 1.38 mmol), and diisopropylazodicarboxylate (0.362 g, 1.38 mmol) at ambient temperature. The resulting mixture was stirred overnight then concentrated in vacuo to a yellow oil. The crude material was then purified by silica gel chromatography using 4:1 dichloromethane/methanol to afford the desired product as a white solid (53.8 mg, 14.5% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 (s, 1H), 7.36 (d, J = 2.2 Hz, 1H), 7.20 (dd, J = 2.3, 4.8 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 5.14 (s, 2H), 4.70 (t, J = 5.8 Hz, 1H), 4.54 (t, J = 5.8 Hz, 1H), 4.10 (t, J = 6.0 Hz, 2H), 2.16 (m,1H), 2.11 (m, 1H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 154.6, 153.5, 129.4, 128.1, 127.0, 125.1, 123.45, 118.4, 113.5, 80.4 (d, J_{CF} = 165 Hz), 71.0, 66.4, 64.7 (d, J_{CF} = 7.5 Hz), 30.3 (d, J_{CF} = 22.5 Hz), 27.8; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{18}H_{21}ClFN_2O_3$: 403.0986, found 403.0985.

Example 26

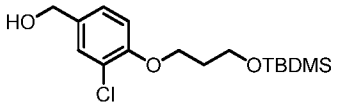
Preparation of 3-(4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)-2-chlorophenoxy)propyl 4-methylbenzenesulfonate

Part A – Preparation of 3-chloro-4-(3-hydroxypropoxy)benzaldehyde



A suspension of 3-chloro-4-hydroxybenzaldehyde (0.500 g, 3.20 mmol), 1-bromopropanol (0.271 mL, 3.0 mmol), and cesium carbonate (2.44 g, 7.50 mmol) in dimethylformamide (32.0 mL) was heated to 60 °C and maintained overnight. After cooling to ambient temperature, the resulting mixture was diluted with water (150 mL) and the aqueous layer was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with water, saturated aqueous sodium chloride, dried over sodium sulfate, filtered and concentrated to a yellow oil (0.322 g, 46.9% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.77 (s, 1H), 7.83 (d, J = 2.1 Hz, 1H), 7.68 (dd, J = 8.5, 2.0 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 4.22 (t, J = 5.9 Hz, 2H), 4.15 (t, J = 5.7 Hz, 2H), 2.11 – 2.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.8, 159.1, 131.2, 130.6, 130.3, 123.8, 112.4, 67.2, 60.0, 31.6.

Part B – Preparation of 4-(3-((*tert*-butyldimethylsilyl)oxy)propoxy)-3-chlorophenyl)methanol

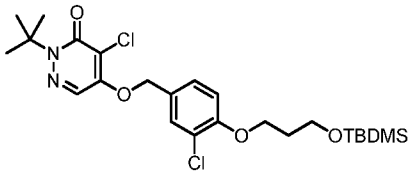


A solution of the product of Example 26A (0.312 g, 1.45 mmol), in dimethylformamide (14.5 mL) was successively treated with *tert*-butyldimethylsilyl chloride (0.329 g, 2.18 mmol) and imidazole (0.149 g, 2.18 mmol) at ambient temperature then stirred overnight. The resulting mixture was diluted with 0.1 N hydrochloric acid (30 mL) then extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was then purified by silica gel chromatography (0-50% ethyl acetate in hexanes) to afford the desired product as a clear oil (0.167 g, 35.0 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.81 (s, 1H), 7.87 (d, J = 2.1 Hz, 1H), 7.72 (dd, J = 8.5, 2.1 Hz, 1H), 7.03 (d, J = 8.6 Hz, 1H), 4.20 (t, J = 6.1 Hz, 2H), 3.81 (t, J = 5.8 Hz, 2H), 2.07 – 1.99 (m, 2H), 0.84 (s, 9H), 0.01(s, 6H); ^{13}C NMR ($CDCl_3$,75 MHz): δ 189.7, 159.4, 131.2, 130.5,

130.1, 124.0, 112.5, 65.9,65.8, 59.0, 32.0, 25.9, 18.3, -5.5; HRMS-TOF *(m / z)*: $[M + H]^+$ for $C_{16}H_{25}ClO_3Si$: 329.1334, found 329.1329.

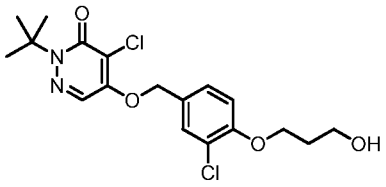
A solution of the silyl ether (0.176 g, 0.536 mmol) in ethanol (6.00 mL) was treated with sodium borohydride (15.2 mg, 0.402 mmol) in one portion at ambient temperature then stirred overnight. The resulting mixture was then diluted with water (10 mL) and concentrated in vacuo to remove the ethanol. The resulting aqueous solution was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers dried over sodium sulfate, filtered and concentrated to afford the desired product as an oil (0.164 g, 92.5% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34 (d, J= 2.2 Hz, 1H), 7.16 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 4.57 (s, 2H), 4.09 (t, *J* = 6.1 Hz, 2H), 3.80 (t, *J* = 5.9 Hz, 2H), 2.03 – 1.95 (m, 2H), 0.84 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.1, 133.7, 129.2, 126.5, 123.0, 113.2, 65.6, 64.5, 59.3, 32.2, 25.9, 18.5, -5.4; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{16}H_{27}{}^{35}ClO_3Si$: 331.1491, found 331.1493.

Part C – Preparation of 2-(*tert*-butyl)-5-((4-(3-((*tert*-butyldimethylsilyl)oxy)propoxy)-3-chlorobenzyl)oxy)-4-chloropyridazin-3(2*H*)-one



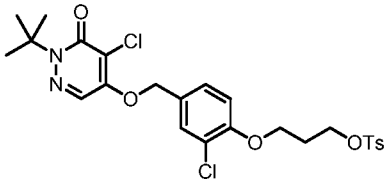
A solution of 2-(*tert*-butyl)-4-chloro-5-hydroxypyridazin-3(2*H*)-one (82.8 mg, 0.410 mmol) in tetrahydrofuran (4.90 mL) was successively treated with the product of Example 27B (0.162 g, 0.490 mmol), triphenylphosphine (0.161 g, 0.615 mmol), and diethylazodicarboxylate (0.107 g, 0.615 mmol) at ambient temperature. After 20 min, the resulting mixture was diluted with water (5 mL), the aqueous layer separated then extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was then purified by silica gel chromatography (0-10% gradient ethyl acetate in hexanes) to afford the desired product as a clear oil (0.127 g, 60.1% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.67 (s, 1H), 7.37 (d, *J* = 2.2 Hz, 1H), 7.21 (dd, *J* = 2.3, 8.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 5.17 (s, 2H), 4.11 (t, *J* = 6.1 Hz, 2H), 3.80 (t, *J* = 5.9 Hz, 2H), 2.04 – 1.96 (m, 2H), 1.60 (s, 9H), 0.84 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 155.0, 153.6, 129.3, 127.6, 127.0, 125.1, 123.3, 118.5, 113.3, 71.1, 66.4, 65.6, 59.2, 32.2, 27.9, 25.9, 18.3, -5.4.

Part D – Preparation of 2-(*tert*-butyl)-4-chloro-5-((3-chloro-4-(3-hydroxypropoxy)benzyl)oxy)pyridazin-3(2*H*)-one



A solution of the product of Example 27C (0.127 g, 0.246 mmol), in tetrahydrofuran (2.5 mL) was treated with tetrabutylammonium fluoride (0.49 mL, 0.49 mmol, of a 1 M solution in tetrahydrofuran) at ambient temperature. After 40 min, the resulting mixture was diluted with water (5 mL), the aqueous layer separated then extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was then purified by silica gel chromatography (0-80% ethyl acetate in hexanes) to afford the desired product (71.6 mg, 72.5% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.63 (s, 1H), 7.36 (d, *J* = 2.2 Hz, 1H), 7.21 (dd, *J* = 8.5, 3.0 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 5.14 (s, 2H), 4.15 (t, *J* = 5.8 Hz, 2H), 3.84 (t, *J* = 5.7 Hz, 2H), 2.08-1.99 (m, 2H), 1.57 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 154.6, 153.5, 129.3, 128.1, 127.0, 125.1, 123.3, 118.6, 113.3, 71.0, 67.4, 66.5, 60.5, 31.7, 27.9; HRMS-TOF *(m / z)*: [M + H]$^+$ for $C_{18}H_{22}{}^{35}Cl_2N_2O_4$: 401.1029, found 401.1023.

Part E – Preparation of 3-(4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)-2-chlorophenoxy)propyl 4-methylbenzenesulfonate

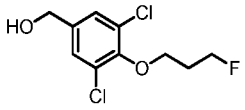


Prepared according to General Method D, using the product of Example 27D (35.8 mg, 0.089 mmol), *p*-toluenesulfonyl chloride (20.5 mg, 0.107 mmol), 4-dimethylaminopyridine (16.3 mg, 0.13 mmol), and diisopropylethylamine (0.015 mL, 0.107 mmol). Isolated yield – 29.8 mg; 60.3%. ^{1}H ($CDCl_3$, 300 MHz): δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.65 (s, 1H), 7.31 (d, *J* = 2.2 Hz, 2H), 7.17 (m, 1H), 7.15 (d, *J* = 8.3 Hz, 2H), 5.13 (s, 2H), 4.22 (t, *J* = 5.9 Hz, 2H), 3.95 (t, *J* = 5.7 Hz, 2H), 2.27 (s, 3H), 2.14-2.07 (m, 2H), 1.57 (s, 9H); ^{13}C ($CDCl_3$, 75MHz): δ 159.0, 154.4, 153.5, 144.8, 132.7, 129.8, 129.4, 128.1, 127.8, 127.0, 125.0, 123.5, 118.3, 113.28, 71.0, 66.7, 66.5, 64.2, 28.8, 27.9, 21.6; HRMS-TOF *(m / z)*: [M + H]$^+$ HRMS: Calcd. for $C_{25}H_{28}{}^{35}Cl_2N_2O_6S$: 555.1118, found 555.1138.

Example 27

Preparation of 2-(*tert*-butyl)-4-chloro-5-((3, 5-dichloro-4-(3-fluoropropoxy)benzyl)oxy)pyridazin-3(*2H*)-one

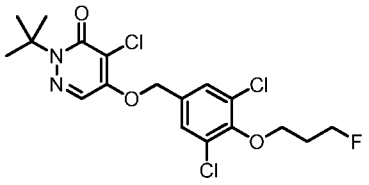
Part A – Preparation of (3,5-dichloro-4-(3-fluoropropoxy)phenyl)methanol



Prepared according to General Method F, using 3,5-dichloro-4-hydroxybenzaldehyde (0.860 g, 4.50 mmol), 3-fluoropropyl *p*-toluenesulfonate (1.00 g, 4.29 mmol), and cesium carbonate (2.49 g, 7.64 mmol) in dimethylformamide (45.0 mL) at 65 °C. ^{1}HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{10}H_9Cl_2FO_2$: 251.0036, found 251.0038.

A solution of the crude aldehyde (1.32 g, 5.26 mmol) in ethanol (5.26 mL) was treated with sodium borohydride (0.149 g, 3.94 mmol) in one portion at ambient temperature. After 3 d, the resulting mixture was diluted with water (20 mL) and concentrated in vacuo to remove the ethanol. The resulting aqueous solution was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers dried over sodium sulfate, filtered and concentrated to afford the desired product as a clear oil (1.21 g, 90.9% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24 (s, 2H), 4.76 (t, *J* = 5.8 Hz, 1H), 4.61 (t, *J* = 5.8 Hz, 1H), 4.56 (s, 2H), 4.07 (t, *J* = 6.0 Hz, 2H), 2.20 (m, 1H), 2.13 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.4, 138.3, 129.5, 127.2, 81.4(d, J_{CF} = 165 Hz), 69.2 (d, J_{CF} = 7.5 Hz), 63.7, 31.2 (d, J_{CF} = 22.5 Hz).

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((3,5-dichloro-4-(3-fluoropropoxy)benzyl)oxy) pyridazin-3(2*H*)-one

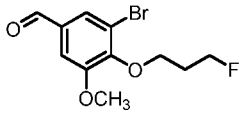


Prepared according to General Method B, using 2-(*tert*-butyl)-4,5-dichloropyridrazin-3(*2H*)-one (0.195 g, 0.872 mmol), the product of Example 27A (0.138 g, 0.545 mmol), and cesium carbonate (0.213 g, 0.654 mmol) in dimethylformamide (8.50 mL) at 65 °C. Isolated yield – 0.192 g; 80.5% ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61 (s, 1H), 7.29 (s, 2H), 5.12 (s, 2H), 4.76 (t, *J* = 5.8 Hz, 1H), 4.58 (t, *J* = 5.8 Hz, 1H), 4.10 (t, *J* = 6.0 Hz, 2H), 2.20 (m, 1H), 2.14 (m, 1H), 1.57 (s, 9H); HRMS: Calcd. for $C_{18}H_{20}{}^{35}Cl_3FN_2O_3$: 437.0596, found 437.0609.

Example 28

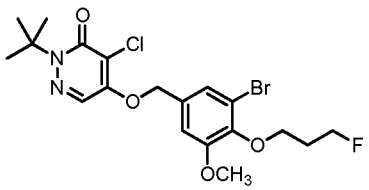
Preparation of 5-((3-bromo-4-(3-fluoropropoxy)-5-methoxybenzyl)oxy)-2-(*tert*-butyl)-4-chloropyridazin-3(2*H*)-one

Part A – Preparation of 3-bromo-4-(3-fluoropropoxy)-5-methoxybenzaldehyde



3-Bromo-4-hydroxy-5-methoxybenzaldehyde (0.578 g, 2.50 mmol), triphenylphosphine (0.820 g, 3.13 mmol) and 3-fluoropropan-1-ol (0.244 mL, 3.25 mmol) were combined in dry tetrahydrofuran (12.5 mL), then cooled to 0 °C and treated with diethyl azodicarboxylate (0.472 mL, 3.00 mmol) dropwise over 0.25 h. After 0.25 h, the resulting solution was warmed to ambient temperature and maintained an additional 0.25 h. All volatiles were then removed in vacuo and the residue directly purified by chromatography on silica (50 x 155 mm) using 3:1 pentane/diethyl ether. The main product peak eluting 700 – 1200 mL was collected, pooled and concentrated in vacuo to a colorless oil (0.555 g, 1.91 mmol; 76.3%). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 9.84 (1H, s), 7.65 (1H, d, J = 1.8 Hz), 7.38 (1H, d, J = 1.8 Hz), 4.75 (2H, dt, J = 47.0, 5.8 Hz), 4.24 (2H, t, J = 6.0 Hz), 3.92 (3H, s), 2.19 (2H, dtt, J = 25.7, 5.9, 5.9 Hz). ^{13}C NMR: (75 MHz, $CDCl_3$) δ 189.8, 154.1, 150.8, 133.0, 128.8, 118.0, 110.0, 80.8 (d, J_{CF} = 164 Hz), 69.2 (d J_{CF} = 5.4 Hz), 56.2, 31.3 (d, J_{CF} = 20.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -222.0 (tt, J = 46.9, 25.7 Hz). HRMS Calcd. for $C_{11}H_{12}{}^{79}BrFO_3$ (M+H): 291.0027; found: 291.0030. TLC: R_f 0.26 (silica gel, 3:1 pentane/diethyl ether, $KMnO_4$).

Part B – Preparation of 5-((3-bromo-4-(3-fluoropropoxy)-5-methoxybenzyl)oxy)-2-(*tert*-butyl)-4-chloropyridazin-3(2*H*)-one



A solution of the product of part A (0.146 g, 0.500 mmol) in wet methanol (5.00 mL) was cooled to 0 °C then treated with sodium borohydride (37.8 mg, 1.00 mmol) in one portion. After 0.25 h, excess sodium borohydride was consumed by the dropwise addition of

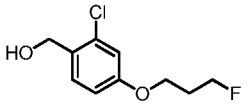
saturated aqueous ammonium chloride (2 mL), and the resulting solution warmed to ambient temperature. After 0.5 h, the resulting mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate (25 mL each), with transfer to a separatory funnel, and the layers separated. The aqueous layer was then washed with ethyl acetate (2 x 25 mL), and the combined ethyl acetate washes dried over magnesium sulfate, filtered and concentrated in vacuo to a colorless oil.

The crude oil thus obtained was dissolved in dry dimethylformamide (5.00 mL) then successively treated with 2-(*tert*-butyl)-4,5-dichloro-2-hydropyridazin-3-one[3] (0.166 g, 0.750 mmol) and cesium carbonate (0.326 , 1.00 mmol) in one portion at ambient temperature. The resulting suspension was then immersed in a pre-heated oil bath, and maintained at 65 °C, with vigorous stirring, 21 h. After cooling to ambient temperature, the suspension was partitioned between ethyl acetate and water (20 mL each), with transfer to a separatory funnel, and the layers separated. The aqueous layer was then washed with ethyl acetate (2 x 20 mL) and the combined ethyl acetate washes dried over magnesium sulfate, filtered and concentrated in vacuo to an amber oil. The crude material was then purified by chromatography on silica (30 x 180 mm) using 7:3 pentane/ethyl acetate. The main product peak eluting 200 – 350 mL was collected, pooled and concentrated in vacuo to a white solid (0.191 g, 0.400 mmol; 79.9%). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.71 (1H, s), 7.15 (1H, d, J = 1.9 Hz), 6.92 (1H, d, J = 2.0 Hz), 5.21 (2H, s), 4.74 (2H, dt, J = 47.1, 5.9 Hz), 4.13 (2H, t, J = 6.0 Hz), 3.86 (3H, s), 2.17 (2H, dtt, J = 25.5, 6.0, 6.0 Hz), 1.64 (9H, s). ^{13}C NMR: (75 MHz, $CDCl_3$) δ 158.9, 154.1, 153.4, 145.8, 131.9, 125.0, 123.2, 118.6, 118.0, 110.2, 81.0 (d, J_{CF} = 164 Hz), 71.0, 68.9 (d, J_{CF} = 5.5 Hz), 66.5, 56.1, 31.3 (d, J_{CF} = 20.2 Hz), 27.8. HRMS Calcd. for $C_{19}H_{23}{}^{79}Br^{35}ClN_2O_4$ (M+H): 477.0587; found: 477.0589. TLC: R_f 0.15 (silica gel, 4:1 pentane/ethyl acetate, CAM).

Example 29

Preparation of 2-(*tert*-butyl)-4-chloro-5-((2-chloro-4-(3-fluoropropoxy)benzyl)oxy)pyridazin-3(2*H*)-one

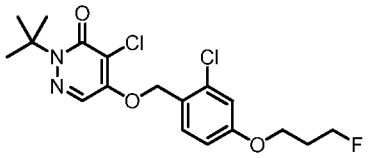
Part A – Preparation of (2-chloro-4-(3-fluoropropoxy)phenyl)methanol



Prepared according to General Method F, using methyl 2-chloro-4-hydroxybenzoate (0.354 g, 2.26 mmol), 3-fluoropropyl *p*-toluenesulfonate (0.500 g, 2.15 mmol), and cesium carbonate (1.12 g, 3.44 mmol) in dimethylformamide (22.6 mL) at 60 °C. Isolated yield – 0.510 g). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.81 (d, *J* = 8.9 Hz, 1H), 6.90 (d, *J* = 2.5 Hz, 1H), 6.75 (dd, *J* = 8.8, 2.5 Hz, 1H), 4.64 (t, *J* = 5.7 Hz, 1H), 4.49 (t, *J* = 5.8 Hz, 1H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.82 (s, 3H), 2.16 (m, 1H), 2.09 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.5, 161.7, 135.9, 133.4, 121.8, 117.0, 112.9, 80.3 (d, J_{CF} = 165 Hz), 64.1 (d, J_{CF} = 7.5 Hz), 52.1, 30.2 (d, J_{CF} = 22.5 Hz).

A solution of the alcohol (0.510 g, 2.35 mmol) in ethanol (23.5 mL) was treated with sodium borohydride (66.7 mg, 1.76 mmol) in one portion at ambient temperature then stirred overnight. The resulting mixture was diluted with water (20 mL) and concentrated in vacuo to remove the ethanol. The resulting aqueous solution was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers dried over sodium sulfate, filtered and concentrated to afford the desired product as a clear oil (0.388 g, 78.5% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.80 (d, *J* = 8.8 Hz, 1H), 6.90 (d, *J* = 2.6 Hz, 1H), 6.75 (dd, *J* = 8.8, 2.5 Hz, 1H), 4.64 (t, *J* = 6.4 Hz, 1H), 4.65 (s, 2H), 4.49 (t, *J* = 5.8 Hz, 1H), 4.07 (t, *J* = 6.2 Hz, 2H), 2.16 (m, 1H), 2.09 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 135.8, 133.3, 130.1, 117.0, 112.8, 80.3 (d, J_{CF} = 165 Hz), 64.1 (d, J_{CF} = 7.5 Hz), 61.1, 30.2 (d, J_{CF} = 22.5 Hz); ^{1}HRMS-TOF *(m / z)*: $[M - H]^+$ HRMS: Calcd. for $C_{10}H_{12}{}^{35}ClFO_2$: 217.0437, found 217.0453.

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((2-chloro-4-(3-fluoropropoxy) benzyl) oxy) pyridazin-3 (*2H*)-one.



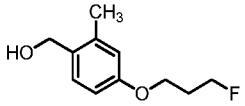
Prepared according to General Method B, using 2-(*tert*-butyl)-4,5-dichloropyridrazin-3(*2H*)-one (0.358 g, 1.62 mmol), the product of Example 29A, (0.388 g, 1.78 mmol), and cesium carbonate (0.845 g, 2.59 mmol) in dimethylformamide (16.2 mL) at 60 °C. Isolated yield – 0.251 g; 38.4% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.67 (s, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 6.91 (d, *J* = 2.5 Hz, 1H), 6.79 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.26 (s, 2H), 4.65 (t, *J* = 5.7 Hz, 1H), 4.49 (t, *J* = 5.7 Hz, 1H), 4.04 (t, *J* = 6.3 Hz, 2H), 2.15 (m, 1H), 2.06 (m, 1H), 1.57 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.7, 153.6, 133.7, 130.1, 125.2, 124.7, 118.5, 115.8,

113.7, 80.3 (d, J_{CF} = 165 Hz), 68.9, 66.4, 64.0 (d, J_{CF} = 7.5 Hz), 30.4, 30.1, 27.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{18}H_{21}{}^{35}Cl_2FN_2O_3$: 403.0986, found 403.0994.

Example 30

Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(3-fluoropropoxy)-2-methylbenzyl)oxy)pyridazin-3(2*H*)-one

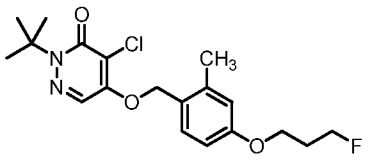
Part A – Preparation of (4-(3-fluoropropoxy)-2-methylphenyl)methanol



Prepared according to General Method F, using 4-hydroxy-2-methylbenzaldehyde (0.614 g, 4.50 mmol), 3-fluoropropyl *p*-toluenesulfonate (1.00 g, 4.29 mmol), and cesium carbonate (2.49 g, 7.64 mmol) in dimethylformamide (45.0 mL) at 60 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.13 (s, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 6.86 (dd, *J* = 8.6, 4.6 Hz, 1H), 6.77 (d, *J* = 2.3 Hz, 1H), 4.75 (t, *J* = 5.7 Hz, 1H), 4.59 (t, *J* = 5.7 Hz, 1H), 4.18 (t, *J* = 6.1 Hz, 2H), 2.66 (s, 3H), 2.27 (m, 1H), 2.15 (m, 1H); HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{11}H_{13}FO_2$: 197.0976, found 197.0972.

A cooled (0 °C) solution of 4-(3-fluoropropoxy)-2-methylbenzaldehyde (0.840 g, 4.28 mmol) in tetrahydrofuran (42.8 mL) was treated with lithium aluminum hydride (2.14 mL, 2.14 mmol, of 1 M tetrahydrofuran solution) then warmed to ambient temperature. The resulting mixture was stirred overnight then diluted with water (20 mL). The aqueous layer was then separated and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to a dark orange oil (0.800 g, 94.3% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24 (m, 1H), 6.73 (m, 2H), 4.72 (t, *J* = 5.8 Hz, 1H), 4.63 (s, 2H), 4.56 (t, *J* = 5.8 Hz, 1H), 4.09 (t, *J* = 6.0 Hz, 2H), 2.36 (s, 3H), 2.20 (m, 1H), 2.10 (m, 1H).

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(3-fluoropropoxy)-2-methylbenzyl) oxy) pyridazin-3 (2*H*)-one.

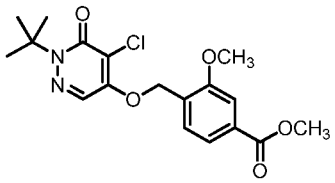


Prepared according to General Method B, using 2-(*tert*-butyl)-4,5-dichloropyridrazin-3(*2H*)-one (0.480 g, 2.37 mmol), the product of Example 30A, (0.940 g, 4.74 mmol), and cesium carbonate (1.70 g, 5.28 mmol) in dimethylformamide (24.0 mL) at 65 °C overnight. Isolated yield – 38.6 mg; 4.3% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50 (s, 1H), 7.19 (m, 1H), 6.66 (m, 2H), 5.09 (s, 2H), 4.64 (m, 1H), 4.48 (m, 1H), 4.02 (t, *J* = 6.2 Hz, 2H), 2.27 (s, 3H), 2.14 (m, 1H), 2.03 (m, 1H), 1.57 (s, 9H); HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{19}H_{24}{}^{35}ClFN_2O_3$: 386.1532, found 383.1537.

Example 31

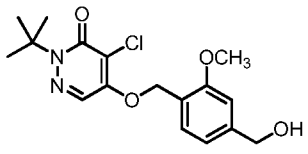
Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-((2-fluoroethoxy)methyl)-2-methoybenzyl)oxy)pyridazin-3(*2H*)-one

Part A – Preparation of methyl 4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)-3-methoxybenzoate



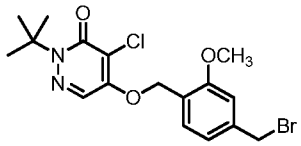
Prepared according to General Method B, using 2-(*tert*-butyl)-4-chloro-5-hydroxypyridrazin-3(*2H*)-one (0.617 g, 3.05 mmol), methyl 4-(bromomethyl)-3-methoxybenzoate (0.750 g, 2.91 mmol), and cesium carbonate (1.51 g, 4.64 mmol) in dimethylformamide (15.0 mL) at ambient temperature. Isolated yield – 1.11 g; >98%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 (s, 1H), 7.63 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.51 (d, *J* = 1.4 Hz, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 5.30 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 1.57 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.6, 159.0, 156.3, 153.7, 131.6, 128.4, 127.7, 125.0, 122.4, 118.2, 111.1, 66.7, 66.4, 55.7, 52.3, 27.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{18}H_{21}{}^{35}ClN_2O_5$: 381.1212, found 381.1206.

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(hydroxymethyl)-2-methoxybenzyl)oxy)pyridazin-3(*2H*)-one



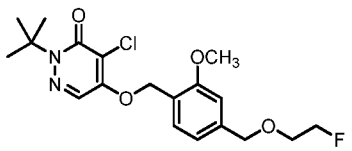
A solution of the product of Example 31A (1.11 g, 2.92 mmol), in tetrahydrofuran (29.0 mL) at 0 °C was treated with lithium aluminum hydride (1.46 mL, 1.46 mmol, 1 M solution in tetrahydrofuran) then warmed to ambient temperature. The resulting mixture was stirred overnight then diluted with water (50 mL). The aqueous layer was separated then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to an amorphous orange solid (0.890 g, 86.4% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.68 (s, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.89 (m, 2H), 5.27 (s, 2H), 4.64 (s, 2H), 3.85 (s, 3H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 156.9, 153.9, 143.2, 128.7, 125.4, 122.5, 119.1, 118.0, 109.1, 67.0, 66.3, 65.1, 55.5, 27.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{17}H_{21}{}^{35}ClN_2O_4$: 353.1263, found 353.1257.

Part C – Preparation of 5-((4-(bromomethyl)-2-methoxybenzyl)oxy)-2-(*tert*-butyl)-4-chloropyridazin-3(2*H*)-one



Prepared according to General Method C, using the product of Example 31B (0.448 g, 1.26 mmol) and phosphorous tribromide (0.631 mL, 0.63 mmol, 1 M in dichloromethane). Isolated yield – 0.429 g; 81.9%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.67 (s, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 6.98 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.88 (d, *J* = 1.5 Hz, 1H), 5.25 (s, 2H), 4.42 (s, 2H), 3.82 (s, 3H), 1.57 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 156.7, 153.8, 139.6, 128.7, 125.2, 123.7, 121.5, 118.1, 111.1, 66.8, 66.3, 55.6, 33.1, 27.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{17}H_{20}{}^{79}Br^{35}ClN_2O_3$: 415.0419, found 415.0416.

Part D – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-((2-fluoroethoxy)methyl)-2-methoxybenzyl)oxy)pyridazin-3(2*H*)-one



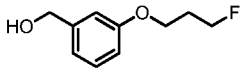
Prepared according to General Method E, using potassium *tert*-butoxide (38 mg, 0.340 mmol), 2-fluoroethanol (14.5 mg, 0.226 mmol) and the product of Example 31C (0.112 g, 0.271 mmol). Isolated yield – 2.3 mg; 2.6%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.68 (s, 1H),

7.30 (d, J = 7.5 Hz, 1H), 6.9 (s, 1H), 6.88 (d, J = 8.0 Hz, 1H), 5.27 (s, 2H), 4.62 (m, 1H), 4.53 (s, 2H), 4.46 (m, 1H), 3.82 (s, 3H), 3.73 (m, 1H), 3.63 (m, 1H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.1, 155.8, 152.9, 139.1, 127.5, 124.3, 121.7, 119.0, 117.0, 108.6, 82.1 (d, J_{CF} = 165 Hz), 72.0, 68.5 (d, J_{CF} = 22.5 Hz), 65.9, 65.3, 54.5, 26.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{19}H_{24}{}^{35}ClFN_2O_3$: 399.1481, found 399.1479.

Example 32

Preparation of 2-(*tert*-butyl)-4-chloro-5-((3-(3-fluoropropoxy)benzyl)oxy)pyridazin-3(*2H*)-one

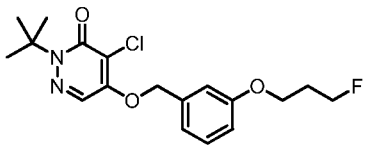
Part A – Preparation of (3-(3-fluoropropoxy)phenyl)methanol



Prepared according to General Method F, using 3-hydroxybenzaldehyde (0.552 g, 4.52 mmol), 3-fluoropropyl *p*-toluenesulfonate (0.998 g, 4.30 mmol), and cesium carbonate (2.24 g, 6.90 mmol) in dimethylformamide (45.2 mL) at 60 °C. Isolated yield – 0.700 g; 89.4%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.91 (s, 1H), 7.40 – 7.37 (m, 2H), 7.34 (m, 1H), 7.11 (m, 1H), 4.66 (t, J= 5.8 Hz, 1H), 4.52 (t, J= 5.7 Hz, 1H), 4.10 (t, J= 6.1 Hz, 2H), 2.17 (m, 1H), 2.09 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 192.0, 159.4, 137.9, 130.1, 123.6, 121.8, 113.0, 80.5 (d, J_{CF} = 165 Hz), 63.9 (d, J_{CF} = 7.5 Hz), 30.3 (d, J_{CF} = 22.5 Hz). ^{1}HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{10}H_{11}FO_2$: 183.0816, found 183.0827.

A cooled (0 °C) solution of 3-(3-fluoropropoxy) benzaldehyde (0.700 g, 3.82 mmol) dissolved in ethanol (38 mL) was treated with sodium borohydride (72.3 mg, 1.91 mmol) then warmed to ambient temperature. After 2 h, the resulting mixture was diluted with water (20 mL) and concentrated in vacuo to remove the ethanol. The resulting aqueous solution was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers dried over sodium sulfate, filtered and concentrated to afford the desired product as a yellow oil (0.625 g, 88.8% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20 (m, 1H), 6.87 (m, 2H), 6.76 (dd, J = 8.3, 2.1 Hz, 1H), 4.65 (t, J = 5.8 Hz, 1H), 4.60 (s, 2H), 4.50 (t, J = 5.8 Hz, 1H),4.04 (t, J = 6.1 Hz, 2H), 2.14 (m, 1H), 2.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 142.6, 129.6, 119.3, 113.8, 113.0, 80.7 (d, J_{CF} = 165 Hz), 65.2, 63.5 (d, J_{CF} = 7.5 Hz), 30.6 (d, J_{CF} = 22.5 Hz). ^{1}HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{10}H_{13}FO_2$: 185.0972, found 186.0967.

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((3-(3-fluoropropoxy)benzyl)oxy)pyridazin-3(2*H*)-one

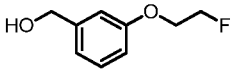


Prepared according to General Method B, using of 2-(*tert*-butyl)-4,5-dichloropyridrazin-3(2*H*)-one (0.339 g, 1.53 mmol), the product of Example 32A (0.313 g, 1.69 mmol), and cesium carbonate (0.798 g, 2.45 mmol) in dimethylformamide (17.0 mL) at 60 °C. Isolated yield – 0.122 g, 21.6% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.63 (s, 1H), 7.25 (m, 1H), 6.92 – 6.81 (m, 3H), 5.21 (s, 2H), 4.66 (t, J = 5.8 Hz, 1H), 4.50 (t, J = 5.8 Hz, 1H), 4.04 (t, J = 6.1 Hz, 2H), 2.15 (m, 1H), 2.07 (m, 1H), 1.57 (s, 9H); ($CDCl_3$, 75 MHz): δ 159.3, 159.0, 153.7, 136.5, 130.1, 125.1, 119.3, 118.4, 114.7, 113.9, 80.6 (d, J_{CF} = 165 Hz), 71.7, 66.4, 63.6 (d, J_{CF} = 7.5 Hz), 30.4 (d, J_{CF} = 22.5 Hz), 27.9; HRMS-TOF *(m / z)*: [M + H]$^+$ HRMS: Calcd. for $C_{18}H_{22}{}^{35}ClFN_2O_3$: 369.1376, found 369.1379.

Example 33

Preparation of 2-(*tert*-butyl)-4-chloro-5-((3-(2-fluoroethoxy)benzyl)oxy)pyridazin-3(2*H*)-one

Part A – Preparation of (3-(2-fluoroethoxy)phenyl)methanol

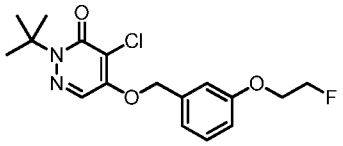


A suspension of 3-hydroxybenzaldehyde (1.02 g, 8.33 mmol), 1-bromo-2-fluoroethane (1.00 g, 7.93 mmol), and cesium carbonate (4.13 g, 12.7 mmol) in dimethylformamide (83.0 mL) was heated to 60 °C and maintained overnight. After cooling to ambient temperature, the resulting mixture was diluted with water (100 mL), and the aqueous layer extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with water (150 mL) and saturated aqueous sodium chloride (150 mL) then dried over sodium sulfate, filtered and concentrated to an orange oil (1.34 g). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.91 (s, 1H), 7.44 – 7.33 (m, 3H), 7.19 – 7.13(m, 1H), 4.79 (m, 1H), 4.63 (m, 1H), 4.26 (m, 1H), 4.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 192.0, 159.0, 137.9, 130.2, 124.1, 122.2, 112.7, 81.9 (d, J_{CF} = 165 Hz), 67.4 (d, J_{CF} = 22.5 Hz); ^{1}HRMS-TOF *(m / z)*: [M + H]$^+$ HRMS: Calcd. for $C_9H_9FO_2$: 169.0659, found 169.0660.

A cooled (0 °C) solution of the aldehyde (1.34 g) in ethanol (39.5 mL) was treated with sodium borohydride (0.150 g, 3.97 mmol) in one portion then warmed to ambient

temperature. After 2 h, the resulting mixture was diluted with water (20 mL) and concentrated in vacuo to remove the ethanol. The resulting aqueous solution was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers dried over sodium sulfate, filtered and concentrated to afford the desired product as a yellow oil (1.28 g, 94.8% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20 (m, 1H), 6.89 (m, 2H), 6.78 (m, 1H), 4.75 (m, 1H), 4.60 (s, 2H), 4.59 (m, 1H), 4.20 (m, 1H), 4.10 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.7, 142.7, 129.7, 119.7, 114.0, 113.0, 81.9 (d, J_{CF} = 165 Hz), 67.2 (d, J_{CF} = 22.5 Hz), 65.2; ^{1}HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_9H_{11}FO_2$: 171.0816, found 171.0815.

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((3-(2-fluoroethoxy)benzyl)oxy)pyridazin-3(*2H*)-one

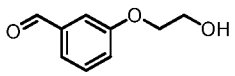


Prepared according to General Method B, using 2-(*tert*-butyl)-4,5-dichloropyridrazin-3(*2H*)-one (0.587 g, 2.66 mmol), the product of Example 33A, (0.500 g, 2.92 mmol), and cesium carbonate (1.38 g, 4.25 mmol) in dimethylformamide (26.6 mL) at 60 °C. Isolated yield – 20 mg, 2.1% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.63 (s, 1H), 7.26 (m, 1H), 6.95 – 6.84 (m, 3H), 5.22 (s, 2H), 4.78 (m, 1H), 4.62 (m, 1H), 4.21 (m, 1H), 4.11 (m, 1H), 1.56 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 158.9, 153.6, 136.6, 130.2, 125.1, 119.3, 114.9, 114.8, 113.2, 81.9 (d, J_{CF} = 7.5 Hz), 71.6, 67.2 (d, J_{CF} = 22.5 Hz), 66.4, 27.9. HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{17}H_{20}{}^{35}ClFN_2O_3$: 355.1219, found 355.1218.

Example 34

Preparation of 2-(3-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)phenoxy)ethyl 4-methylbenzenesulfonate

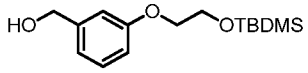
Part A – Preparation of 3-(2-hydroxyethoxy)benzaldehyde



A suspension of 3-hydroxybenzaldehyde (1.02 g, 8.33 mmol), 1-bromoethanol (0.991 g, 7.93 mmol), and cesium carbonate (4.13 g, 12.7 mmol) in dimethylformamide (20.0 mL) was heated to 60 °C and maintained overnight. After cooling to ambient temperature, the resulting mixture was diluted with water (50 mL), and the aqueous layer extracted with ethyl

acetate (3 x 50 mL). The combined organic layers were washed with water (150 mL) and saturated aqueous sodium chloride then dried over sodium sulfate, filtered and concentrated to yield a yellow oil. The crude material was then purified by silica gel chromatography 4:1 hexanes/ethyl acetate to afford the desired product as a white solid (1.38 g, >98% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.98 (s, 1H), 7.48 – 7.41(m, 3H), 7.23 – 7.19 (m, 1H), 4.16 (m, 2H), 4.00 (m, 2H); HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_9H_{10}O_3$: 167.0703, found 167.0696.

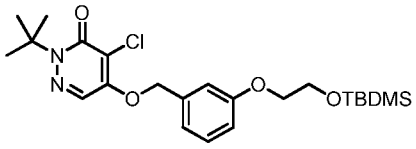
Part B – Preparation of (3-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)phenyl)methanol



A solution of the product of Example 34A (1.38 g), in dimethylformamide (8.3 mL) was successively treated with *tert*-butyldimethylsilyl chloride (1.88 g, 12.5 mmol) and imidazole (0.850 g, 12.5 mmol) then stirred at ambient temperature overnight. The resulting mixture was then diluted with water (50 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo to a yellow oil (0.597 g, 26.8% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.87 (s, 1H), 7.35 – 7.29 (m, 3H), 7.11 – 7.08 (m, 1H), 4.00 (m, 2H), 3.89 (m, 2H), 0.84 (s, 9H), 0.01(s, 6H); ^{13}C NMR ($CDCl_3$,75 MHz): δ 189.7, 159.4, 137.8, 130.0, 123.5, 122.0, 113.0, 69.6, 61.9, 25.6, 18.4, -5.2; HRMS-TOF *(m / z)*: $[M + H]^+$ for $C_{15}H_{24}O_3Si$: 281.1567, found 281.1563.

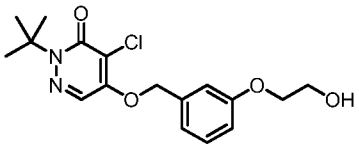
A solution of the silyl ether (0.597 g, 2.13 mmol) in ethanol (21.0 mL) was treated with sodium borohydride (60.4 mg, 1.60 mmol) in one portion at ambient temperature. After 3 h, the resulting mixture was diluted with water (10 mL) and concentrated in vacuo to remove the ethanol. The resulting aqueous solution was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers dried over sodium sulfate, filtered and concentrated to afford the desired product as a milky white oil (0.600 g, >98% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.16 (m, 1H), 6.84 (m, 2H), 6.74 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.57 (s, 2H), 3.94 (m, 2H), 3.87 (m, 2H), 0.81 (s, 9H), 0.01(s, 6H); ^{13}C NMR ($CDCl_3$,75 MHz): δ 159.3, 142.5, 129.6, 119.1, 114.0, 113.0, 69.3, 65.3, 62.0, 25.6, 18.4, -5.2; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{15}H_{26}O_3Si$: 283.1724, found 283.1717.

Part C – Preparation of 2-(*tert*-butyl)-5-((3-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)benzyl)oxy)-4-chloropyridazin-3(2*H*)-one



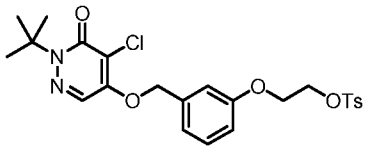
Prepared according to General Method B, using 2-(*tert*-butyl)-4,5-dichloropyridrazin-3(2*H*)-one (0.711 g, 3.19 mmol), the product of Example 34B (0.600 g, 2.13 mmol), and cesium carbonate (0.834 g, 2.56 mmol) in dimethylformamide (32.0 mL) at 60 °C. Isolated yield – 0.159 g, 16.0% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.62 (s, 1H), 7.21(m, 1H), 6.82 – 6.79 (m, 3H), 5.19 (s, 2H), 3.95 (m, 2H), 3.88 (m, 2H), 1.53(s, 9H), 0.80 (s, 9H), -0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.5, 159.0, 153.7, 136.5, 130.0, 125.1, 119.1, 118.2, 114.8, 113.2, 71.7, 69.4, 66.4, 62.0, 27.9, 25.9, 18.4, -5.2; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{23}H_{35}{}^{35}ClN_2O_4Si$: 467.2127, found 467.2129.

Part D – Preparation of 2-(*tert*-butyl)-4-chloro-5-((3-(2-hydroxyethoxy)benzyl)oxy)pyridazin-3(2*H*)-one



A solution of the product of Example 34C (0.140 g, 0.300 mmol), in tetrahydrofuran (3.0 mL) was treated with tetrabutylammonium fluoride (0.60 mL, 0.60 mmol, of 1 M solution in tetrahydrofuran) at ambient temperature. After 1 h, the resulting mixture was diluted with water (10 mL), the aqueous layer separated then extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was then purified by silica gel chromatography (20-50% ethyl acetate in hexanes) to afford the desired product (0.105 g, >98% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.57 (s, 1H), 7.16 (m, 1H), 6.83 (m, 2H), 6.76 (dd, J = 7.5, 2.0 Hz, 1H), 5.13 (s, 2H), 3.95 (m, 2H), 3.82 (m, 2H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 159.0, 153.6, 136.5, 130.0, 125.0, 119.3, 118.2, 114.6. 113.1, 71.5, 69.2, 66.4, 61.2, 27.8; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{17}H_{21}{}^{35}ClN_2O_4$: 353.1263, found 353.1259.

Part E – Preparation of 2-(3-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)phenoxy)ethyl 4-methylbenzenesulfonate

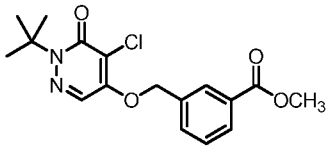


Prepared according to General Method D, using the product of Example 34D (52.4 mg, 0.149 mmol), *p*-toluenesulfonyl chloride (34.1 mg, 0.179 mmol), 4-dimethylaminopyridine (22.0 mg, 0.179 mmol), and diisopropylethylamine (0.032 mL, 0.179 mmol). Isolated yield – 48.5 mg, 64.2% yield. ^{1}H ($CDCl_3$, 300 MHz): δ 7.75 (d, *J* = 8.4 Hz, 2H),7.63 (s, 1H), 7.29 – 7.20 (m, 3H), 6.92 (d, *J* =7.1 Hz, 1H), 6.79 (m, 1H), 6.72 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.19 (s, 2H), 4.30 (m, 2H), 4.09 (m, 2H), 2.38 (s, 3H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.0, 157.5, 152.6, 144.0, 135.6, 131.8, 129.1, 128.9, 127.0, 124.0, 118.8, 117.3, 113.8, 112.1, 70.5, 66.9, 65.4, 64.5, 26.8, 20.6. HRMS-TOF *(m / z)*: [M + H]$^+$ HRMS: Calcd. for $C_{24}H_{27}{}^{35}ClN_2O_6S$: 507.1351, found 507.1354.

Example 35

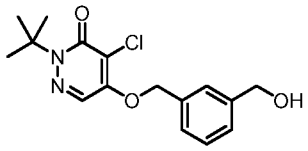
Preparation of 2-(*tert*-butyl)-4-chloro-5-((3-((2-fluoroethoxy)methyl)benzyl)oxy)pyridazin-3(*2H*)-one

Part A – Preparation of methyl 3-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methylbenzoate



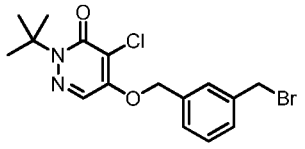
Prepared according to General Method B, using 2-(*tert*-butyl)-4-chloro-5-hydroxypyridrazin-3(*2H*)-one (0.750 g, 3.70 mmol), methyl 4-(bromomethyl)benzoate (0.806 g, 3.52 mmol), and cesium carbonate (1.45 g, 4.45 mmol) in dimethylformamide (7.5 mL) at ambient temperature. Isolated yield – 0.643 g, 52.1% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.01 – 7.96 (m, 2H), 7.65 (s, 1H), 7.59 – 7.41 (m, 2H), 5.27 (s, 2H), 3.86 (s, 3H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.5, 159.0, 153.5, 135.4, 131.5, 130.9, 129.2, 128.2, 127.8, 125.0, 118.6, 71.4, 66.5, 52.3, 27.9.

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((3-(hydroxymethyl)benzyl)oxy)pyridazin-3 (2*H*)-one



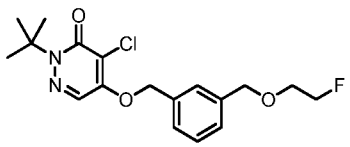
A cooled (0 °C) solution of the product of Example 35A (0.643 g, 1.83 mmol), in tetrahydrofuran (6.5 mL) was treated with lithium diisobutylaluminum hydride (2.25 mL, 2.25 mmol, 1 M solution in hexanes) then warmed to ambient temperature and stirred overnight. The resulting solution was diluted with water (50 mL), the aqueous layer was separated then extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was then purified by silica gel chromatography (5-50% ethyl acetate in hexanes) to afford the desired product as a white solid (0.403 g, 68.2% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74 (s, 1H), 7.45 – 7.28 (m, 4H), 5.34 (s, 2H), 4.76 (s, 2H), 1.65 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 153.7, 141.8, 135.3, 129.2, 127.3, 126.3, 125.5, 125.1, 118.4, 71.8, 66.4, 64.9, 27.9; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{16}H_{19}{}^{35}ClN_2O_3$: 323.1157, found 323.1154.

Part C – Preparation of 5-((3-(bromomethyl) benzyl) oxy)-2-(*tert*-butyl)-4-chloropyridazin-3(2*H*)-one



Prepared according to General Method C, using the product of Example 35B (0.190 g, 0.590 mmol) and phosphorous tribromide (0.280 mL, 0.29 mmol, 1 M in dichloromethane) dropwise. Isolated yield – 0.203 g, 89.2% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.64 (s, 1H), 7.37 – 7.28 (m, 4H), 5.23 (s, 2H), 4.43 (s, 2H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ159.0, 153.6, 138.7, 135.6, 129.3, 129.2, 127.6, 127.1, 125.1, 118.5, 71.5, 66.5, 32.8, 27.9; HRMS-TOF *(m / z)*: $[M + H]^+$ for $C_{16}H_{18}{}^{79}Br^{35}ClN_2O_2$: 385.0313, found 385.0316.

Part D – Preparation of 2-(*tert*-butyl)-4-chloro-5-((3-((2-fluoroethoxy)methyl)benzyl)oxy)pyridazin-3(2*H*)-one

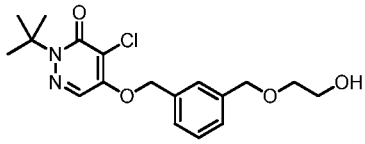


Prepared according to General Method E, using potassium *tert*-butoxide (25.9 mg, 0.231 mmol), 2-fluoroethanol (14.8 mg, 0.231 mmol) and the product of Example 35C (0.100 g, 0.260 mmol). Isolated yield – 2.3 mg; 2.7%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 (s, 1H), 7.37 – 7.30 (m, 4H), 5.25 (s, 2H), 4.62 (m, 1H), 4.55 (s, 2H), 4.46 (m, 1H), 3.73 (m, 1H), 3.64 (m, 1H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 153.7, 138.8, 135.2, 129.1, 128.0, 126.5, 126.2, 125.1, 118.4, 83.0 (d, J_{CF} = 165 Hz), 73.0, 71.8, 69.7 (d, J_{CF} = 22.5 Hz), 66.4, 28.9; HRMS-TOF *(m / z)*: $[M + H]^+$ for $C_{18}H_{22}{}^{35}ClFN_2O_3$: 369.1376, found 369.1373.

Example 36

Preparation of 2-((3-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzyl)oxy)ethyl 4-methylbenzenesulfonate

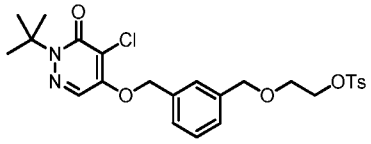
Part A – Preparation of 2-(*tert*-butyl)-4-chloro-5-((3-((2-hydroxyethoxy)methyl)benzyl)oxy)pyridazin-3(2*H*)-one



A suspension of potassium *tert*-butoxide (25.3 mg, 0.226 mmol) and ethylene glycol (111 mg, 1.79 mmol) were heated to 60 °C and maintained 20 min. The product of Example 35C (0.104 g, 0.271 mmol), dissolved in tetrahydrofuran (3 mL) was added dropwise. After completion of the addition, the reaction mixture was heated at reflux, maintained overnight, then cooled and quenched with water (15 mL). The aqueous layer was separated then extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was then purified by silica gel chromatography using 4:1 hexanes/ethyl acetate to afford the desired product as a clear oil (60.2 mg, 60.6% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.73 (s, 1H), 7.44 – 7.29 (m, 4H), 5.32 (s, 2H), 4.59 (s, 2H), 3.78 (m, 2H), 3.62 (m, 2H), 1.63 (s, 9H); ^{13}C NMR ($CDCl_3$,

75 MHz): δ 159.1, 153.7, 139.0, 135.2, 129.2, 128.1, 126.5, 126.2, 125.1, 118.4, 72.9, 71.8, 71.6, 66.4, 61.9, 27.9.

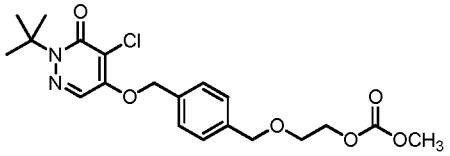
Part B – Preparation of 2-((3-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)ethyl)benzyl)oxy)ethyl 4-methylbenzenesulfonate



Prepared according to General Method D, using the product of Example 36A (50.2 mg, 0.137 mmol), *p*-toluenesulfonyl chloride (31.3 mg, 0.165 mmol), 4-dimethylaminopyridine (21.0 mg, 0.165 mmol), and diisopropylethylamine (0.016 mL, 0.165 mmol). Isolated yield – 21.2 mg; 29.7%. ^{1}H ($CDCl_3$, 300 MHz): δ 7.73 (d, J = 8.4 Hz, 2H), 7.66 (s, 1H), 7.34 – 7.19 (m, 6H), 5.23 (s, 2H), 4.45 (s, 2H), 4.06 (m, 2H), 3.62 (m, 2H), 2.38 (s, 3H), 1.56 (s, 9H); ^{13}C ($CDCl_3$, 75 MHz): δ 159.0, 153.7, 144.9, 138.6, 135.2, 133.0, 129.8, 129.1, 127.9, 127.8, 126.5, 126.1, 125.1, 118.3, 72.8, 71.8, 69.2, 67.8, 66.4, 27.9, 21.6; HRMS-TOF *(m / z)*: $[M + H]^+$ for $C_{25}H_{29}{}^{35}ClN_2O_6S$: 521.1508, found 521.1500.

Example 37

Preparation of 2-((4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzyl)oxy)ethyl methyl carbonate

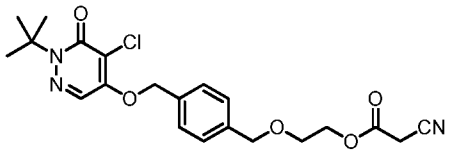


A solution of 2-(*tert*-butyl)-4-chloro-5-((4-((2-hydroxyethoxy) methyl)benzyl) oxy) pyridazin-3(2*H*)-one (0.147 g, 0.400 mmol; e.g., see Casebier, David S.; Robinson, Simon P.; Purohit, Ajay; Radeke, Heike S.; Azure, Michael T.; Dischino, Douglas D. (Bristol-Myers Squibb) Preparation of contrast agents for myocardial perfusion imaging comprising an imaging moiety and deguelin, pyridaben, pyrimidifen, tebufenpyrad, fenazaquin, and analogs thereof. PCT Int. Appl. WO 2005/079391. September 1, 2005) in pyridine (2.00 mL) was cooled to 0 °C then treated with methyl chloroformate (34 μL, 0.44 mmol) in one portion. After 1.25 h, additional methyl chloroformate (34 μL, 0.44 mmol) was added. After an additional 1.5 h, a final addition of methyl chloroformate (34 μL, 0.44 mmol) was performed. After 0.25 h, the solution was diluted with ethyl acetate, with transfer to a separatory funnel,

then washed with a 5% aqueous solution of $CuSO_4$, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material thus obtained was then purified by chromatography on silica (30 x 175 mm) using 3:2 pentane/ethyl acetate. The main product peak eluting 175 – 280 mL was collected, pooled and concentrated in vacuo to a colorless oil (0.144 g, 0.339 mmol; 84.7%). ^{1}H NMR: (300 MHz, DMSO-d_6) δ 8.26 (1H, s), 7.45 (2H, AB, J_{AB} = 8.2 Hz), 7.37 (2H, AB, J_{AB} = 8.4 Hz), 5.45 (2H, s), 4.52 (2H, s), 4.29 – 4.19 (2H, m), 3.69 (3H, s), 3.68 – 3.60 (2H, m), 1.57 (9H, s). ^{13}C NMR: (75 MHz, DMSO-d_6) δ 157.8, 155.2, 153.8, 138.6, 134.6, 127.8, 127.7, 126.2, 115.6, 71.5, 71.3, 67.5, 66.7, 65.4, 54.6, 27.4. HRMS Calcd. for $C_{20}H_{25}{}^{35}ClN_2O_6$ (M+H): 425.1474; found: 425.1470. TLC: R_f 0.50 (silica gel, 1:1 pentane/ethyl acetate, CAM).

Example 38

Preparation of 2-((4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzyl)oxy)ethyl 2-cyanoacetate

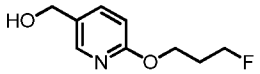


A solution of 2-(*tert*-butyl)-4-chloro-5-((4-((2-hydroxyethoxy) methyl) benzyl) oxy) pyridazin-3(2*H*)-one[6] (0.183 g, 0.500 mmol) and cyanoacetic acid (85.1 mg, 1.00 mmol) in dry dichloromethane (2.50 mL) was treated with *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.191 g, 1.00 mmol) in one portion at ambient temperature. After 0.25 h, all volatiles were removed in vacuo, and the residue directly purified by chromatography on silica (30 x 180 mm) using 1:1 pentane/ethyl acetate. The main product peak eluting 175 – 325 mL was collected, pooled and concentrated in vacuo to a colorless oil (0.206 g, 0.476 mmol; 95.1%). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.72 (1H, s), 7.43 – 7.37 (4H, m), 5.31 (2H, s), 4.57 (2H, s), 4.41 – 4.38 (2H, m), 3.75 – 3.72 (2H, m), 3.49 (2H, s), 1.63 (9H, s). ^{13}C NMR: (75 MHz, $CDCl_3$) δ 162.9, 159.0, 153.6, 138.3, 134.5, 128.2, 127.3, 125.0, 118.3, 112.8, 72.8, 71.6, 67.5, 66.4, 65.8, 27.8, 24.7. HRMS Calcd. for $C_{21}H_{24}{}^{35}ClN_3O_5$ (M+H): 434.1477; found: 434.1474. TLC: R_f 0.41 (silica gel, 1:1 pentane/ethyl acetate, uv).

Example 39

Preparation of 2-(*tert*-butyl)-4-chloro-5-((6-(3-fluoropropoxy)pyridine-3-yl)methoxy)pyridazin-3(2*H*)-one

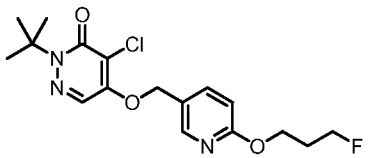
Part A – Preparation of (6-(3-fluoropropoxy)pyridine-3-yl)methanol



A suspension of sodium hydride (26.4 mg, 1.10 mmol) and 3-fluoropropanol (78.0 mg, 1.00 mmol) in dimethylformamide (1.0 mL) was maintained at ambient temperature for 25 min then treated with a solution of methyl 6-bromonicotinate (0.216 g, 1.00 mmol) in dimethylformamide (0.5 mL). After 1 h, the resulting mixture was diluted with water (2 mL), the aqueous layer separated then extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo to a yellow oil.

A solution of methyl 6-(3-fluoropropoxy) nicotinate in tetrahydrofuran was added dropwise to a cooled (0 °C) solution of lithium aluminum hydride (0.14 mL, 0.14 mmol, 1 M in tetrahydrofuran) and the resulting mixture warmed to ambient temperature. After 2 h, the solution was diluted with water, the aqueous layer separated then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The crude material was then purified by silica gel chromatography (0-60% ethyl acetate in hexanes) to afford the desired product as a yellow oil (22.3 mg, 12.0% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06 – 7.99 (m, 1H), 7.55 (dd, J = 2.4, 8.4 Hz,1H), 6.66 (d, J = 8.5 Hz, 1H), 4.63 (t, J = 5.9 Hz, 1H), 4.54 (s, 2H), 4.47 (t, J = 5.9 Hz, 1H), 4.30 (t, J = 6.2 Hz, 2H), 2.18-2.01 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 144.7, 137.4, 128.1, 109.9, 79.9 (d, J_{CF} = 165 Hz), 61.4, 60.8, (d, J_{CF} = 7.5 Hz), 29.2 (d, J_{CF} = 22.5 Hz).

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((6-(3-fluoropropoxy)pyridine-3-yl)methoxy)pyridazin-3(2*H*)-one

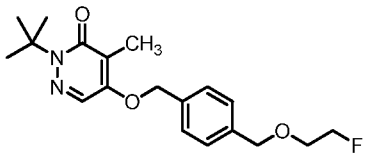


Prepared according to General Method B, using 2-(*tert*-butyl)-4-chloro-5-hydroxypyridrazin-3(2*H*)-one (22.3 mg, 0.100 mmol), the product of Example 39A (18.7 mg, 0.100 mmol), and cesium carbonate (52.5, 0.161 mmol) in dimethylformamide (1.0 mL) at ambient temperature. Isolated yield – 15.3 mg; 41.4%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.12

(d, J = 1.9 Hz, 1H), 7.69 (s, 1H), 7.60 (dd, J = 2.5, 8.5 Hz, 1H), 6.73 (d, J = 8.7 Hz, 1H), 5.15 (s, 2H), 4.64 (t, J = 5.8 Hz, 1H), 4.48 (t, J = 5.8 Hz, 1H), 4.39 (t, J = 6.2 Hz, 2H), 2.19-2.02 (m, 2H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.1, 157.9, 152.4, 145.3, 137.5, 124.1, 122.3, 117.7, 110.5, 79.8 (d, J_{CF} = 165 Hz), 68.5, 65.4, 61.0 (d, J_{CF} = 7.5 Hz), 29.1 (d, J_{CF} = 22.5 Hz), 26.8; HRMS Calcd. for $C_{17}H_{21}{}^{35}ClFN_3O_5$ (M+H): 370.1328; found: 370.1331.

Example 40

Preparation of 2-(*tert*-butyl)-5-((4-((2-fluoroethoxy)benzyl)oxy)-4-methylpyridazin-3(2*H*)-one

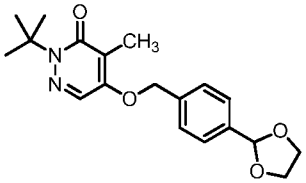


Prepared according to General Method B, using 2-(*tert*-butyl)-5-chloro-4-methylpyridrazin-3(*2H*)-one[6] (0.100 g, 0.500 mmol), (4-((2-fluoroethoxy)methyl)phenyl)methanol (0.110 g, 0.600 mmol), and cesium carbonate (0.261 g, 0.800 mmol) in dimethylformamide (5.0 mL) at 65 °C. Isolated yield – 49 mg; 28.1%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61 (s, 1H), 7.30 (br s, 4H), 5.10 (s, 2H), 4.59 (m, 1H), 4.53 (s, 2H), 4.43 (m, 1H), 3.71 (m, 1H), 3.61 (m, 1H), 1.98 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 153.3, 137.2, 134.3, 127.0, 126.2, 124.5, 120.1, 82.0 (d, J_{CF} = 165 Hz), 71.9, 69.8, 68.4 (d, J_{CF} = 22.5 Hz), 63.9, 27.0, 7.7; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{19}H_{25}FN_2O_3$: 349.1922, found 349.1916.

Example 41

Preparation of 2-((4-(((1-(*tert*-butyl)-5-methyl-6-oxo-1,6-dihydropyridazin-4yl)-oxy)methyl)benzyl)oxy)ethyl 4-methylbenzenesulfonate

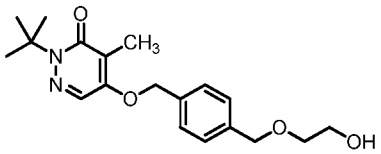
Part A – Preparation of 5-((4-(1,3-dioxolan-2-yl)benzyl)oxy)-2-(*tert*-butyl)-4-methylpyridazin-3(2*H*)-one



Prepared according to General Method B, using 2-(*tert*-butyl)-5-chloro-4-methylpyridrazin-3(*2H*)-one (0.200 g, 1.00 mmol), (4-(1,3-dioxolan-2-yl)phenyl)methanol

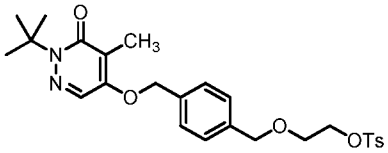
(0.150 g, 0.830 mmol), and cesium carbonate (0.540 g, 1.66 mmol) in dimethylformamide (10.0 mL) at 60 °C. Isolated yield – 56.5 mg; 19.8%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.67 (s, 1H), 7.51 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 5.81 (s, 1H), 5.20 (s, 2H), 4.26 – 3.84 (m, 4H), 2.05 (s, 3H), 1.57 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.1, 154.3, 138.2, 136.8, 127.0, 126.9, 125.5, 121.1, 103.3, 70.6, 65.3, 64.9, 28.0, 8.7; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{19}H_{24}N_2O_4$: 345.1809, found 345.1806.

Part B – Preparation of 2-(*tert*-butyl)-5-((4-((2-hydroxyethoxy)methyl)benzyl)oxy)-4-methylpyridazin-3(2*H*)-one



A solution of the product of Example 41A (55.7 mg, 0.162 mmol) in tetrahydrofuran (0.8 mL) was added dropwise to a suspension of zirconium chloride (37.8 mg, 0.162 mmol) and sodium borohydride (12.3 mg, 0.324 mmol) in tetrahydrofuran (0.80 mL) at ambient temperature. After 2 h, the resulting mixture was diluted with water (5 mL), the aqueous layer separated then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to a clear oil (50.6 mg, 90.2% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.62 (s, 1H), 7.30 (br s, 4H), 5.10 (s, 2H), 4.50 (s, 2H), 3.70 (m, 2H), 3.54 (dd, J = 3.9, 5.3 Hz, 2H), 1.98 (s, 3H), 1.55 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.1, 153.4, 137.4, 134.3, 127.1, 126.8, 126.2, 119.3, 71.8, 70.5, 69.8, 63.9, 60.8, 27.0, 7.7; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{19}H_{26}N_2O_4$: 347.1965, found 347.1960.

Part C – Preparation of 2-((4-(((1-(*tert*-butyl)-5-methyl-6-oxo-1,6-dihydropyridazin-4yl)-oxy)methyl)benzyl)oxy)ethyl 4-methylbenzenesulfonate



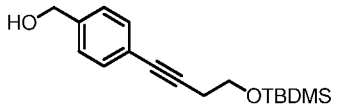
Prepared according to General Procedure D, using the product of Example 41B (46.8 mg, 0.135 mmol), *p*-toluenesulfonyl chloride (30.9 mg, 0.162 mmol), 4-dimethylaminopyridine (5.4 mg, 0.54 mmol), and diisopropylethylamine (0.026 mL, 0.189 mmol). Isolated yield – 42.6 mg; 63.0%. ^{1}H ($CDCl_3$, 300 MHz): δ 7.80 (d, 2H, J = 8.33 Hz), 7.69 (s, 1H), 7.33 (m, 6H), 5.18 (s, 2H), 4.50 (s, 2H), 4.21 (m, 2H), 3.69 (m, 2H), 2.43 (s,

3H), 2.05 (s, 3H), 1.63 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 154.3, 144.7, 138.0, 135.3, 133.0, 129.7, 128.0, 127.9, 127.2, 125.5, 121.2, 72.8, 70.8, 69.1, 67.7, 64.9, 28.0, 21.6, 8.7.

Example 43

Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(4-fluorobut-1-yn-1-yl)benzyl)oxy)pyridazin-3*(2H)*-one

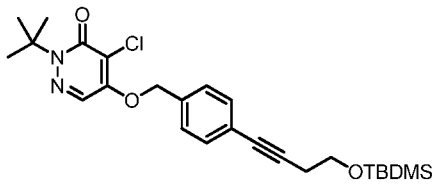
Part A – Preparation of (4-(4-((*tert*-butyldimethylsilyl)oxy)but-1-yn-1-yl)phenyl)methanol



A solution of methyl 4-(4-hydroxybut-1-yn-1-yl)benzoate (0.771 g, 3.77 mmol),[1] in dimethylformamide (37.0 mL) was successively treated with *tert*-butylchlorodimethylsilane (0.848 g, 5.63 mmol), and imidazole (0.386 g, 5.67 mmol) at ambient temperature. After 2 h, the resulting mixture was diluted with water (150 mL), the aqueous layer separated then extracted with ethyl acetate (3 x 200 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to yield to a yellow oil (1.50 g).

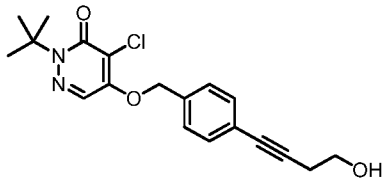
The crude silyl ether was dissolved in tetrahydrofuran (47.0 mL) then cooled to 0 °C and treated with lithium aluminum hydride (4.71 mL, 4.71 mmol, 1 M in tetrahydrofuran). The resulting solution then warmed slowly to ambient temperature and, after 2 h, was diluted with water (20 mL). The aqueous layer was separated then extracted with ethyl acetate (3 x 50 mL) and the combined organic layers washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo (1.22 g, >98% crude yield). ^{1}H ($CDCl_3$, 300 MHz): δ 7.29 (d, J = 8.28 Hz, 2H), 7.18 (d, J = 8.47 Hz, 2H), 4.58 (s, 2H), 3.72 (t, J = 7.05 Hz, 2H), 2.53 (t, J = 7.03 Hz, 2H), 0.82 (s, 6H); 0.01 (s, 9H); HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{17}H_{26}O_2Si$: 291.1775, found 291.1763.

Part B – Preparation of 2-(*tert*-butyl)-5-((4-(4-((*tert*-butyldimethylsilyl)oxy)but-1-yn-1-yl)benzyl)oxy)-4-chloropyridazinone-3(2*H*)-one



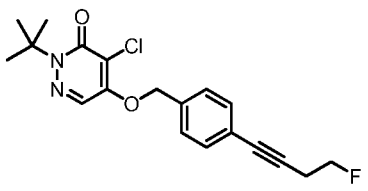
Prepared according to General Method B, using 2-(*tert*-butyl)-4,5-dichloropyridrazin-3(*2H*)-one (0.318 g, 1.45 mmol), the product of Example 43A (0.500 g, 1.73 mmol), and cesium carbonate (0.750 g, 2.31 mmol) in dimethylformamide (14.5 mL) at 60 °C. Isolated yield – 0.242 g; 35.1%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ δ 7.58 (s, 1H), 7.33 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 5.19 (s, 2H), 3.72 (t, J = 7.0 Hz, 2H), 2.53 (t, J = 6.9 Hz, 2H), 1.44 (s, 9H), 0.82 (s, 9H), 0.20 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz, *partial*): δ 159.0, 153.5, 134.2, 132.1, 127.1, 126.8, 125.1, 124.4, 118.4, 88.3, 80.9, 71.5, 66.4, 61.8, 27.8, 25.8, 23.8, -5.2; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{25}H_{35}{}^{35}ClN_2O_3Si$: 475.2178, found 475.2162.

Part C – Preparation of 2-(*tert*-butyl)- 4-chloro-5-((4-(4-hydroxybut-1-yn-1-yl)benzyl)oxy)pyridazinone-3(2*H*)-one



A solution of the product of Example 43B (0.242 g, 0.510 mmol) dissolved in tetrahydrofuran (10.0 mL) was treated with a solution of tetrabutylammonium fluoride (1.02 mL, 1.02 mmol, 1 M in tetrahydrofuran) at ambient temperature. After 2 h, the resulting mixture was concentrated in vacuo and the residue directly purified by silica gel chromatography (0-60% ethyl acetate in hexanes) to afford the desired product as an oil (0.120 g, 65.2% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.68 (s, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 5.29 (s, 2H), 3.82 (m, 4H), 1.63 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 153.5, 134.5, 132.2, 126.9, 125.0, 123.9, 118.4, 87.4, 81.8, 71.4, 66.4, 61.1, 27.8, 23.8; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{19}H_{21}{}^{35}ClN_2O_3$: 361.1313, found 361.1309.

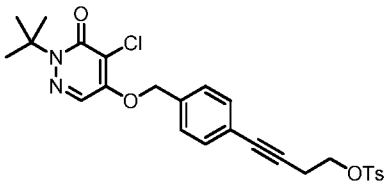
Part D – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(4-fluorobut-1-yn-1-yl)benzyl)oxy)pyridazin-3*(2H)*-one



A cooled (0 °C) solution of the product of Example 43C (0.050 g, 0.138 mmol) in dichloromethane (0.10 mL) was treated with Deoxofluor (0.152 mmol, 33.7 mg, 50% in toluene) then maintained 1.5 h. The resulting mixture was diluted with water (1 mL), the aqueous layer separated then extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was then purified by preparative thin layer chromatography on silica using 3:2 hexanes/ethyl acetate to afford the desired product (11.5 mg, 23.0% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61 (s, 1H), 7.38 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 5.22 (s, 2H), 4.59 (t, J = 6.6 Hz, 1H), 4.44 (t, J = 6.6 Hz, 1H), 2.78 (dt, J = 19.6, 6.6 Hz, 2H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 157.9, 152.5, 133.6, 131.2, 125.8, 124.0, 122.8, 117.4, 84.4 (d, J_{CF} = 15 Hz), 80.3 (d, J_{CF} = 165 Hz), 80.6, 70.4, 65.4, 26.8, 20.6 (d, J_{CF} = 22.5 Hz); HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{19}H_{20}{}^{35}ClFN_2O_2$: 363.1270, found 363.1270.

Example 44

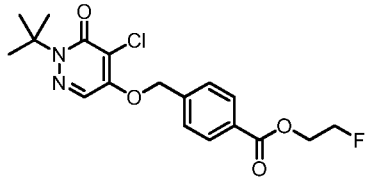
Preparation of 4-(4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)-oxy)methyl)benzyl)but-3-yn-1-yl 4-methylbenzenesulfonate



Prepared according to General Method D, using the product of Example 43C (77.4 mg, 0.215 mmol), *p*-toluenesulfonyl chloride (49.2 mg, 0.258 mmol), 4-dimethylaminopyridine (1.1 mg, 0.0086 mmol), and triethylamine (0.042 mL, 0.30 mmol). Isolated yield – 42.2 mg; 38.1%. ^{1}H ($CDCl_3$, 300 MHz): δ 7.75 (d, J = 8.3 Hz, 2H), 7.61 (s, 1H), 7.36 – 7.21 (m, 6H), 5.22 (s, 2H), 4.12 (t, J = 6.9 Hz, 2H), 2.72 (t, J = 6.9 Hz, 2H), 2.35 (s, 3H), 1.56 (s, 9H); ^{13}C ($CDCl_3$, 75 MHz): δ 158.9, 153.5, 144.9, 134.7, 132.9, 132.1, 129.8, 127.9, 126.8, 125.0, 123.5, 118.4, 84.8, 82.0, 71.4, 67.6, 66.4, 27.8, 21.6, 20.4; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{26}H_{27}{}^{35}ClN_2O_6S$: 515.1402, found 515.1409.

Example 45

Preparation of 2-fluoroethyl 4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzoate

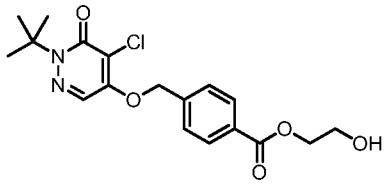


A suspension of 2-fluoroethanol (2 mL) and potassium *tert*-butoxide (0.0300 g, 0.267 mmol) was heated to 60 °C, maintained 20 min then treated with a solution of methyl 4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzoate (93.5 mg, 0.267 mmol)[4] in tetrahydrofuran (0.70 mL). The resulting mixture was stirred overnight then cooled to ambient temperature and diluted with water (5 mL). The aqueous layer was separated, extracted with ethyl acetate (3 x 20 mL), and the combined organic layers washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was then purified by silica gel chromatography (0-80% diethyl ether in hexanes) to afford the desired product as a white solid (11.7 mg, 11.4% yield). ^{1}H ($CDCl_3$, 300 MHz): δ 8.17 – 8.08 (m, 2H), 7.70 (s, 1H), 7.51 (d, J = 8.0 Hz, 2H), 5.38 (s, 2H), 4.81 (m, 1H), 4.61-4.67 (m, 2H), 4.53 (m, 1H), 1.63 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.7, 157.9, 152.3, 139.1, 129.4, 129.0, 125.7, 123.8, 117.5, 80.2 (d, J_{CF} = 165 Hz), 70.1, 65.4 (d, J_{CF} = 22.5 Hz), 62.8, 20.0.

Example 46

Preparation of 2-(tosyloxy)ethyl 4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzoate

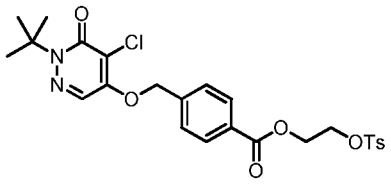
Part A – Preparation of 2-hydroxyethyl 4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzoate



A suspension of ethylene glycol (15 mL) and potassium *tert*-butoxide (0.224 g, 2.00 mmol) was heated to 60 °C, maintained 20 min then treated with a solution of methyl 4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzoate (0.773 g, 2.20

mmol) in tetrahydrofuran (5.0 mL). After 1.5 h, the resulting mixture was cooled to ambient temperature and diluted with water (50 mL). The aqueous layer was separated then extracted with toluene (3 x 100 mL), and the combined organic layers were washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated. The crude material was then purified by silica gel chromatography (40-60% ethyl acetate in hexanes) to afford the desired product as a white solid (47.7 mg, 5.3% yield). ^{1}H ($CDCl_3$, 300 MHz): δ 8.11 (d, J = 8.4 Hz, 2H), 7.71 (s, 1H), 7.49 (d, J = 8.5 Hz, 2H), 5.37 (s, 2H), 4.59 – 4.34 (m, 2H), 4.04 – 3.86 (m, 2H), 1.63 (s, 9H); HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{18}H_{21}{}^{35}ClN_2O_5$: 381.1212, found 384.1206.

Part B – Preparation of 2-(tosyloxy) ethyl 4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzoate

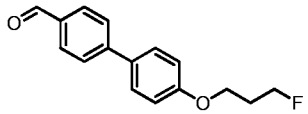


Prepared according the General Method D, using the product of Example 46A (47.1 mg, 0.124 mmol), *p*-toluenesulfonyl chloride (28.3 mg, 0.148 mmol), 4-dimethylaminopyridine (0.60 mg, 0.0049 mmol), and triethylamine (0.024 mL, 1.4 mmol). Isolated yield – 33.6 mg; 50.6%. ^{1}H ($CDCl_3$, 300 MHz): δ 8.07 – 7.96 (m, 2H), 7.78 (s, 1H), 7.71 (m, 2H), 7.49 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 5.37 (s, 2H), 4.54 – 4.46 (m, 2H), 4.41 – 4.32 (m, 2H), 2.40 (s, 3H), 1.64 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.4, 158.9, 153.4, 145.0, 140.2, 132.8,130.4, 129.9, 129.7, 127.9, 127.5, 126.7, 118.5, 71.0, 67.5, 66.6, 62.2, 27.8, 21.6; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{25}H_{27}{}^{35}ClN_2O_7S$: 535.1300, found 535.1290.

Example 47

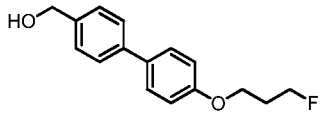
Preparation of 2-(*tert*-butyl)-4-chloro-5-((4'-(3-fluoropropoxy)-[1,1'-biphenyl]-4-yl)methoxy)pyridazin-3(2*H*)-one

Part A – Preparation of 4'-(3-fluoropropoxy)-[1,1'-biphenyl]-4-carbaldehyde



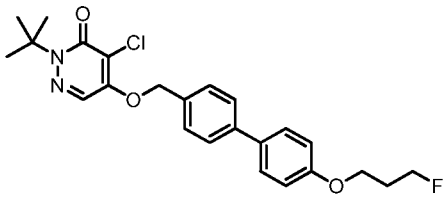
Prepared according to General Method F, using 4'-hydroxy-[1,1'biphenyl]-4-carbaldehyde (0.500 g, 2.52 mmol), 3-fluoropropyl p-toluenesulfonate (0.557 g, 2.40 mmol), and cesium carbonate (1.25 g, 3.84 mmol) in dimethylformamide (25.2 mL) was at ambient temperature. The crude material was further purified by silica gel chromatography (0-60% ethyl acetate in hexanes) to afford the desired product as a white solid (0.380 g, 61.3% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.03 (s, 1H), 7.97 – 7.87 (m, 2H), 7.75 – 7.68 (m, 2H), 7.63 – 7.53 (m, 2H), 7.06 – 6.96 (m, 2H), 4.75 (t, J = 5.7 Hz, 1H), 4.59 (t, J = 5.7 Hz, 1H), 4.16 (t, J = 6.1 Hz, 2H), 2.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz, $CDCl_3$) δ 191.8, 159.3, 146.7, 134.7, 132.2, 130.2, 128.5, 127.0, 115.0, 80.6 (d, J_{CF} = 165 Hz), 63.7 (d, J_{CF} = 7.5 Hz), 30.4 (d, J_{CF} = 22.5 Hz); HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{16}H_{15}FO_2$: 259.1129, found 259.1131.

Part B – Preparation of 4'-(3-fluoropropoxy)-[1,1'-biphenyl]-4-yl)methanol



A cooled (0 °C) solution of the product of Example 47A (0.190 g, 0.730 mmol) dissolved in tetrahydrofuran (7.3 mL) was treated with a solution of lithium aluminum hydride (0.40 mL, 0.40 mmol, 1 M in tetrahydrofuran) then warmed to ambient temperature. After 2 h, the resulting mixture was diluted with water (10 mL), the aqueous layer separated then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated to a white solid (0.170 g, 89.5% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.60 – 7.47 (m, 4H), 7.42 (d, J = 8.4 Hz, 2H), 7.03 – 6.88 (m, 2H), 4.83 – 4.63 (m, 3H), 4.59 (t, J = 5.7 Hz, 1H), 4.15 (t, J = 6.1 Hz, 2H), 2.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 140.2, 139.2, 133.5, 128.1, 127.4, 126.8, 114.8, 80.7 (d, J_{CF} = 165 Hz), 65.1, 63.7 (d, J_{CF} = 7.5 Hz), 30.4 (d, J_{CF} = 22.5 Hz); HRMS-TOF *(m / z)*: $[M + Na]^+$ HRMS: Calcd. for $C_{16}H_{17}FO_2$: 261.1285, found 261.1282.

Part C – Preparation of 2-(tert-butyl)-4-chloro-5-((4'-(3-fluoropropoxy)-[1,1'-biphenyl]-4-yl)methoxy)pyridazin-3(2*H*)-one

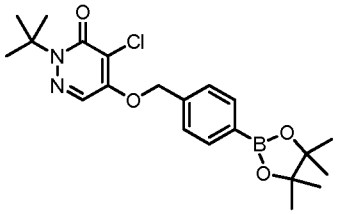


Prepared according to General Procedure B, using 2-(*tert*-butyl)-4,5-dichloropyridrazin-3(2*H*)-one (0.120 g, 0.540 mmol), the product of Example 47B (0.170 g, 0.650 mmol), and cesium carbonate (0.265 g, 0.816 mmol) in dimethylformamide (6.5 mL) at 65 °C. Isolated yield – 12.7 mg; 5.3%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.53 (s, 1H), 7.49 – 7.38 (m, 6H), 6.94 – 6.85 (m, 2H), 5.53 (s, 2H), 4.67 (t, J = 5.7 Hz, 1H), 4.51 (t, J = 5.7 Hz, 1H), 4.07 (t, J = 6.1 Hz, 2H), 2.12 (m, 2H), 1.57 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.7, 158.4, 150.5, 140.8, 134.9, 133.3, 129.0, 128.1, 126.6, 124.5, 114.8, 80.7 (d, J_{CF} = 165 Hz), 73.4, 65.7, 63.6 (d, J_{CF} = 22.5 Hz), 30.5 (d, J_{CF} = 7.5 Hz), 27.8; HRMS-TOF *(m / z)*: [M + Na]$^+$ HRMS: Calcd. for $C_{24}H_{26}{}^{35}ClFN_2O_3$: 445.1689, found 445.1684.

Example 48

Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(2-fluoropyrimidin-5-yl)-benzyl)oxy)pyridazin-3(2*H*) one

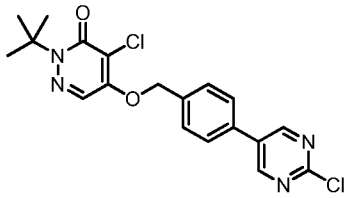
Part A – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(4, 4, 5, 5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)oxy)pyridazin-3(2*H*)-one



A solution of 2-(*tert*-butyl)-4-chloro-5-hydroxypyridrazin-3(2*H*)-one (0.537 g, 2.65 mmol) in tetrahydrofuran (22.1 mL) was successively treated with (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (0.745 g, 3.18 mmol), triphenylphosphine (1.04 g, 3.97 mmol), and diisopropylazodicarboxylate (0.782 mL, 3.97 mmol) at ambient temperature. After 45 min, the resulting mixture was diluted with water (20 mL), the aqueous layer separated then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was suspended in diethyl ether, stirred 3 h then collected by filtration and purified by silica gel chromatography using 4:1 hexane/ethyl acetate to afford the desired product as a white solid (0.347 g, 31.3% yield).^{1}H NMR (300 MHz, DMSO-d6): δ 8.22 (s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 5.49 (s, 2H), 1.57 (s, 9H), 1.30 (s, 12H); ^{13}C NMR (75 MHz, DMSO-d6, *partial*): δ 157.7, 153.5, 138.6, 134.7 , 126.9, 125.1, 115.6, 83.7, 71.1, 65.3, 27.4,

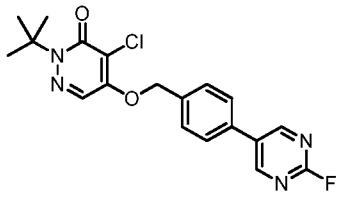
24.6; HRMS-TOF *(m / z)*: $[M + Na]^+$ HRMS: Calcd. for $C_{21}H_{28}B^{35}ClN_2O_4$: 419.1907, found 419.1903.

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(2-chloropyrimidin-5-yl)benzyl)oxy)pyridazin-3(2*H*)-one



2-Chloro-5-bromopyrimidine (41.3 mg, 0.215 mmol) and tetrakis(triphenylphosphine) palladium (0) (7.0 mg, 2.5 mol %) were dissolved in 1,2-dimethoxyethane (1.0 mL) at ambient temperature, maintained 15 min then successively treated with the product of Example 48A (0.090 g, 0.215 mmol) as a solution in 1,2-dimethoxyethane (1.2 mL) and aqueous potassium carbonate (0.43 mL, 0.43 mmol). The resulting mixture was warmed to 80 °C, maintained 1.5 h then cooled to ambient temperature and diluted with water (2 mL). The aqueous layer was separated then extracted with ethyl acetate (3 x 10 mL), and the combined organic layers dried over sodium sulfate, filtered and concentrated to a light yellow solid (59.0 mg, 67.7% yield). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.26 (s, 2H), 8.40 (s, 1H), 8.01 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H), 5.65 (s, 2H), 1.69 (s, 9H);^{13}C NMR (75 MHz, DMSO-d_6): δ 159.0, 158.0, 157.7, 153.7, 136.5, 132.6, 131.7, 128.5, 127.3, 126.1, 115.7, 70.9, 65.4, 27.5

Part C – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(2-fluoropyrimidin-5-yl)benzyl)oxy)pyridazin-3(2*H*)-one



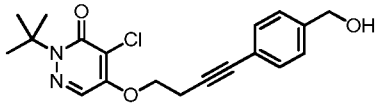
A solution of the product of Example 48B (97.0 mg, 0.024 mmol), in dimethyl sulfoxide (0.25 mL) was treated with potassium fluoride (1.43 mg, 0.024 mmol) and Kryptofix™ (18 mg, 0.48 mmol) then heated to 80 °C and maintained 10 min. The resulting mixture was cooled to ambient temperature then diluted with 1 mL of dichloromethane and directly purified by preparative thin layer chromatography on silica using 4:1 hexanes/ethyl acetate to afford the desired product as a white solid (1.3 mg, 13.9% yield). ^{1}H NMR

(DMSO-d_6, 600 MHz): δ 9.22 (d, J = 1.6 Hz, 2H), 8.35 (s, 1H), 7.96 – 7.90 (m, 2H), 7.69 (d, J = 8.3 Hz, 2H), 5.81 (s, 2H), 1.64 (s, 9H); ^{13}C NMR (DMSO-d_6, 150 MHz, *partial*): δ 159.3 (d, J_{CF} = 15 Hz), 136.2, 129.5, 128.5, 127.2, 126.1, 71.0, 65.4, 27.4; ^{19}F NMR (DMSO-d_6, 262 MHz): δ -49.19 (br s, 1H).

Example 49

Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(4-(fluoromethyl)phenyl)but-3-yn-1-yl)oxy)pyridazin-3(2*H*)-one

Part A – Preparation of 2-(tert-butyl)-4-chloro-5-((4-(4-hydroxymethyl)phenyl)but-3-yn-1-yl)oxy)pyridazin-3(2*H*)-one

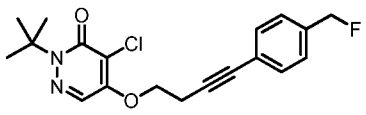


2-(*tert*-Butyl)-4-chloro-5-hydroxypyridrazin-3(*2H*)-one (62.0 mg, 0.368 mmol), triphenylphosphine (0.145 g, 0.552 mmol) and methyl 4-(4-hydroxybut-1-yn-1-yl) benzoate (74.4 mg, 0.442 mmol)[1] were combined in dry tetrahydrofuran (3.7 mL), then cooled to 0 °C and treated with diethyl azodicarboxylate (0.109 mL,0.552 mmol). The resulting mixture warmed slowly to ambient temperature, and after 1.5 h was diluted with water (10 mL). The aqueous layer was separated then extracted with ethyl acetate (3 x 20 mL), and the combined organic layers dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was purified by silica gel chromatography (0-80% ethyl acetate in hexanes) to afford the desired product (40 mg).

A cooled (0 °C) solution of the ester (40.0 mg, 0.103 mmol) in tetrahydrofuran (1.0 mL) was treated with a solution of lithium aluminum hydride (0.05 mL, 0.05 mmol, 1 M in tetrahydrofuran) then warmed to ambient temperature. After 2 h, the resulting mixture was diluted with water (2 mL), the aqueous layer separated then extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was purified by silica gel chromatography (0-20% ethyl acetate in hexanes) to afford the desired product (31.5 mg, 23.7% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (s, 1H), 7.33 – 7.28 (m, 2H), 7.24 – 7.18 (m, 2H), 4.61 (s, 2H), 4.35 (t, J = 6.8 Hz, 2H), 2.89 (t, J = 6.88 Hz, 2H); 1.57 (s, 9H);^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 153.6, 141.0, 131.7, 126.7, 125.1, 122.0, 118.3, 84.2, 82.8, 68.4, 66.4, 64.8, 27.8, 20.8;

HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{19}H_{21}{}^{35}ClN_2O_3$: 361.1313, found 361.1315.

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(4-(fluoromethyl)phenyl)but-3-yn-1-yl)oxy)pyridazin-3(2*H*)-one

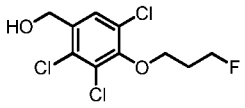


A cooled (0 °C) solution of the product of Example 49A (31.8 mg, 0.088 mmol) in dichloromethane (1.0 mL) was treated with Deoxofluor (21.3 mg, 0.096 mmol; 50% in toluene) and maintained 1.5 h. The resulting mixture was diluted with water (1 mL), the aqueous layer separated then extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was then purified by preparative thin layer chromatography on silica using 4:1 hexanes/ethyl acetate to afford the desired product (11.5 mg, 36.0% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71 (s, 1H), 7.37 – 7.29 (m, 2H), 7.26 – 7.19 (m, 2H), 5.37 (s, 1H), 5.21 (s, 1H), 4.35 (t, J = 6.8 Hz, 2H), 2.90 (t, J = 6.8 Hz, 2H), 1.57 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 153.6, 136.2 (d, J_{CF} = 22.5 Hz), 131.8, 127.2 (d, J_{CF} = 7.5 Hz), 125.1, 123.3, 118.3, 84.0 (d, J_{CF} = 165 Hz), 84.8, 82.5, 68.3, 66.4, 27.8, 20.8; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{19}H_{20}{}^{35}ClFN_2O_3$: 363.1270, found 363.1268.

Example 50

Preparation of 2-(*tert*-butyl)-4-chloro-5-((2,3,5-dichloro-4-(3-fluoropropoxy)benzyl)oxy)pyridazin-3(2*H*)-one

Part A – Preparation of (2,3,5-dichloro-4-(3-fluoropropoxy)phenyl)methanol

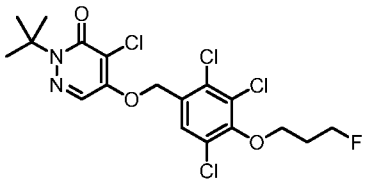


Prepared according to General Method F, using 2,3,5-dichloro-4-hydroxymethylbenzoate (1.00 g, 4.52 mmol), 3-fluoropropyl *p*-toluenesulfonate (1.26 g, 5.42 mmol), and cesium carbonate (2.35 g, 7.23 mmol) in dimethylformamide (45.0 mL) at 65 °C. Isolated yield – 0.650 g; 50.4%.

A solution of the crude ester (63.0 mg, 0.200 mmol) dissolved in ethanol (2.0 mL) was treated with sodium borohydride (5.7 mg, 0.15 mmol) in one portion at ambient

temperature. The resulting mixture was stirred 2 d then diluted with water (20 mL) and concentrated in vacuo to remove the ethanol. The resulting aqueous solution was extracted with ethyl acetate (3 x 100 mL) and the combined organic layers dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was purified by silica gel chromatography using 4:1 hexanes/ethyl acetate to afford the desired product (52.7 mg, 91.6% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42 (s, 1H), 4.75 (t, J = 5.8 Hz, 1H), 4.66 (s, 2H), 4.59 (t, J = 5.8 Hz, 1H), 4.07 (t, J = 6.0 Hz, 2H), 2.16 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 151.3, 136.3, 129.8, 129.0, 127.7, 127.0, 80.6 (d, J_{CF} = 165 Hz), 69.3 (d, J_{CF} = 7.5 Hz), 62.3, 31.1 (d, J_{CF} = 22.5 Hz).

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((2,3,5-dichloro-4-(3-fluoropropoxy)benzyl)oxy)pyridazin-3(2*H*)-one

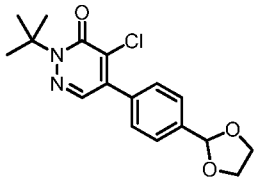


Prepared according to General Method B, using 2-(*tert*-butyl)-4,5-dichloropyridrazin-3(2*H*)-one (39.2 mg, 0.178 mmol), the product of Example 50A (61.2 mg, 0.213 mmol), and cesium carbonate (92.5 mg, 0.284 mmol) in dimethylformamide (1.7 mL) at 65 °C. Isolated yield – 23.0 mg; 27.4%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.89 – 7.68 (br s, 1H), 7.67 – 7.41 (br s, 1H), 5.32 (s, 2H), 4.93 – 4.74 (m, 1H), 4.75 – 4.54 (m, 1H), 4.19 (m, 2H), 2.41 – 2.11 (m, 2H),1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.8, 153.1, 152.5, 130.7, 130.0, 129.6, 128.2, 127.4, 124.7, 118.7, 80.4 (d, J_{CF} = 165 Hz), 69.4 (d, J_{CF} = 7.5 Hz), 68.6, 66.6, 31.1 (d, J_{CF} = 22.5 Hz), 27.8; HRMS: Calcd. for $C_{18}H_{19}{}^{35}Cl_4FN_2O_3$: 471.0207, found 471.0206.

Example 51

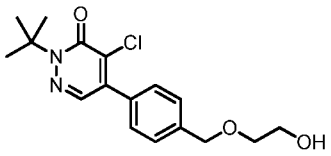
Preparation of 2-(*tert*-butyl)-4-chloro-5-(4-((2-fluoroethoxy)methyl)phenyl)pyridazin-3(2*H*)-one

Part A – Preparation of 5-((4-(1,3-dioxolan-2-yl)phenyl)-2-(*tert*-butyl)-4-chloropyridazin-3(2*H*)-one



A cooled (0 °C) solution of 2-(*tert*-butyl)-4,5-dichloropyridrazin-3(2*H*)-one (3.00 g, 13.6 mmol) in diethyl ether (6.5 mL) was treated with (4-(1,3-dioxolan)-2-yl)phenyl)magnesium bromide solution (27.3 mL, 13.6 mmol, 0.5 M in tetrahydrofuran) and maintained 30 min. The resulting mixture was diluted with water (20 mL), the aqueous layer separated then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was then purified by silica gel purification (0-30% ethyl acetate in hexanes) to afford the desired product as a white solid (2.87 g, 63.0% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (s, 1H), 7.59 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 5.91 (s, 1H), 4.25 – 3.94 (m, 4H), 1.68 (s, 9H).

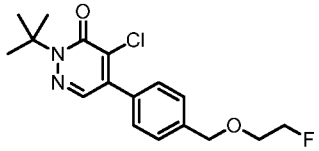
Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(2-hydroxyethoxy)methyl)phenyl)pyridazin-3(2*H*)-one



A solution of the product of Example 51A (0.342 g, 1.02 mmol) in tetrahydrofuran (2.0 mL) was added dropwise to a suspension of zirconium chloride (0.238 g, 1.02 mmol) and sodium borohydride (77.3 mg, 2.04 mmol) in tetrahydrofuran (3.1 mL) at ambient temperature. After 3 h, the resulting mixture was diluted with water (10 mL), the aqueous layer separated then extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to a clear oil (0.322 g, 93.7% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (s, 1H), 7.36 (br s, 4H), 4.54 (s, 2H), 3.70 (m, 2H), 3.56 (m, 2H), 1.59 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): 159.6, 153.2, 139.0, 135.1, 134.9, 131.0,

129.8, 127.2, 72.9, 71.4, 66.0, 61.9, 27.8; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{17}H_{21}{}^{35}ClFN_2O_3$: 337.1313, found 337.1311.

Part C – Preparation of 2-(*tert*-butyl)-4-chloro-5-(4-((2-fluoroethoxy)methyl)phenyl)pyridazin-3(2*H*)-one

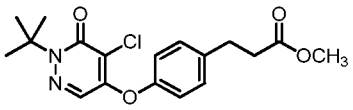


A cooled (0 ºC) solution of the product of Example 51B (0.100 g, 0.297 mmol) in dichloromethane (3.0 mL) was treated with Deoxofluor (72.3 mg, 0.326 mmol; 50% in toluene) and maintained 2 h. The resulting mixture was diluted with water (10 mL), the aqueous layer separated then extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was then purified by preparative thin layer chromatography on silica using 4:1 hexanes/ethyl acetate to afford the desired product as a white solid (19.7 mg, 19.6% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (s, 1H), 7.36 (s, 4H), 4.60 (m, 1H), 4.57 (s, 2H), 4.46 – 4.39 (m, 1H), 3.75 – 3.68 (m, 1H), 3.65 – 3.58 (m, 1H), 1.58 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.6, 153.1, 138.8, 135.1, 134.9, 131.0, 129.8, 127.2, 83.0 (d, J_{CF} = 165 Hz), 72.9, 69.2 (d, J_{CF} = 22.5 Hz), 66.0, 27.8; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{17}H_{20}{}^{35}ClFN_2O_2$: 339.1270, found 339.1268.

Example 52

Preparation of 2-(*tert*-butyl)-4-chloro-5-(4-(3-fluoropropyl)phenoxy)pyridazin-3(2*H*)-one

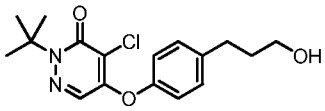
Part A – Preparation of methyl 3-(4-((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)phenyl)propanoate



Prepared according to General Method B, using 2-(*tert*-butyl)-4,5-dichloropyridrazin-3(2*H*)-one (0.750 g, 3.39 mmol), methyl 3-(4-hydroxyphenyl)propionate (0.734 g, 4.07 mmol), and cesium carbonate (1.76 g, 5.43 mmol) in dimethylformamide (34.0 mL) at room temperature overnight. Isolated yield – 0.960 g; 77.6%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40 (s, 1H), 7.25 (d, J = 7.8 Hz, 2H), 7.05 – 6.99 (m, 2H), 3.68 (s, 3H), 2.97 (m, 2H), 2.64 (m,

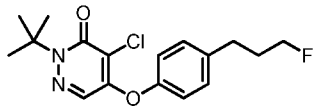
2H), 1.64 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.9, 158.9, 152.9, 152.2, 138.2, 130.1, 127.0, 120.2, 119.8, 66.4, 51.6, 35.5, 30.1, 27.8; HRMS: Calcd. for $C_{18}H_{21}{}^{35}ClN_2O_4$: 365.1263, found 365.1259.

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-(4-(3-hydroxypropyl)phenoxy)pyridazin-3(2*H*)-one



A cooled (0 °C) solution of the product of Example 52A (0.473 g, 1.30 mmol) in tetrahydrofuran (13 mL) was treated with lithium aluminum hydride (0.65 mL, 0.65 mmol, 1 M in tetrahydrofuran) then warmed to ambient temperature. After 1 h, the resulting mixture was diluted with water (10 mL), the aqueous layer separated then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated to a light yellow solid (0.384 g, 87.7%). ^{1}H ($CDCl_3$, 600 MHz): δ 7.40 (s, 1H), 7.25 (d, J = 7.7 Hz, 2H), 7.05 – 6.98 (m, 2H), 3.75 – 3.65 (m, 2H), 2.79 – 2.68 (m, 2H), 1.97 – 1.82 (m, 2H), 1.65 (s, 9H); ^{13}C NMR ($CDCl_3$,150 MHz) δ 158.9, 153.0, 151.9, 139.6, 130.1, 127.0, 120.0, 119.7, 66.4, 61.9, 34.1, 31.3, 27.8; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{17}H_{21}{}^{35}ClN_2O_3$: 337.1313, found 337.1319.

Part C – Preparation of 2-(*tert*-butyl)-4-chloro-5-(4-(3-fluoropropyl)phenoxy)pyridazin-3(2*H*)-one



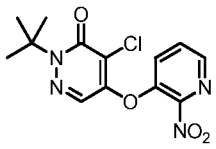
A cooled (0 °C) solution of the product of Example 52B (50.0 mg, 0.149 mmol) in dichloromethane (0.1 mL) was treated with Deoxofluor (36.0 mg, 0.164 mmol; 50% in toluene) and maintained 1.5 h. The resulting mixture was diluted with water (1 mL), the aqueous layer separated then extracted with dichloromethane (2 x 10 mL). The combined organic portions were dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was then purified by silica gel chromatography (0-50% ethyl acetate in hexanes) to afford the desired product as a yellow oil (5.6 mg, 11.1% yield). ^{1}H NMR ($CDCl_3$, 600 MHz, *contains small amount of alcohol starting material*): δ 7.34 (s, 1H), 7.18 (d, J = 8.0 Hz, 2H), 6.96 (m, 2H), 4.48 (t, J = 5.8 Hz, 1H), 4.32 (t, J = 5.8 Hz, 1H), 3.47 (t, J

= 6.3 Hz, 2H), 2.02 (m, 2H), 1.58 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz, *contains small amount of alcohol starting material*): δ 157.9, 151.9, 151.1, 137.8, 129.3 (129.2), 126.0, 118.8, 81.8 (d, J_{CF} = 165 Hz), 65.4, 42.9, 31.1 (d, J_{CF} = 22.5 Hz), 29.7 (d, J_{CF} = 7.5 Hz), 26.84; HRMS-TOF *(m / z)*: $[M + H]^+$ HRMS: Calcd. for $C_{17}H_{20}{}^{35}ClFN_2O_2$: 339.1270, found 339.1268.

Example 53

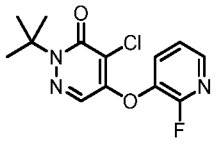
Preparation of 2-(*tert*-butyl)-4-chloro-5-((2-fluoropyridin-3-yl)oxy)pyridazin-3(2*H*)-one

Part A – Preparation of 2-(*tert*-butyl)-4-chloro-5-((2-nitropyridin-3-yl)oxy)pyridazin-3(2*H*)-one



Prepared according to General Method B, using 2-(*tert*-butyl)-4,5-dichloropyridrazin-3(2*H*)-one (0.221 g, 1.00 mmol), 2-nitropyridin-3-ol (0.140 g, 1.00 mmol), and cesium carbonate (0.170 g, 0.52 mmol) in dimethylformamide (2.0 mL) at 80 °C. Isolated yield – 0.120 g; 37.0%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.52 (dd, J = 4.5, 1.3 Hz, 1H), 8.22 (dd, J = 8.4, 1.3 Hz, 1H), 8.00 (s, 1H), 7.92 (dd, J = 8.4, 4.5 Hz, 1H), 1.60 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.62, 151.15, 144.95, 142.38, 138.09, 132.05, 130.95, 128.14, 121.01, 65.99, 27.33. HRMS Calcd. for $C_{13}H_{13}{}^{35}ClN_4O_4$ (M+H): 325.0698; found: 325.0697.

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((2-fluoropyridin-3-yl)oxy)pyridazin-3(2*H*)-one

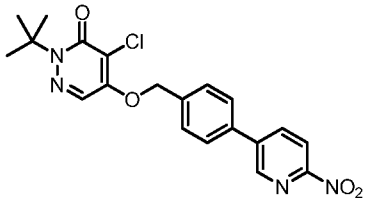


A solution of the product of Example 53A (35.7 mg, 0.110 mmol), potassium fluoride (9.0 mg, 0.15mmol), and Kryptofix™ (60.2 mg, 0.16 mmol) in dimethylsulfoxide (2.5mL) was heated to 125 °C and maintained 30 min. The resulting mixture was then cooled to ambient temperature and diluted with ethyl acetate (40 mL). The organic layer was separated then washed with water (2 x 50 mL) and saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was then purified by silica gel chromatography (10-40% ethyl acetate in hexanes) to afford the desired product

as colorless oil (25.0 mg, 76.3% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.14 (dt, J = 4.8, 1.6 Hz, 1H), 8.00 (ddd, J = 10.2, 7.9, 1.6 Hz, 1H), 7.93 (s, 1H), 7.45 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 1.60 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.63, 151.52, 143.31(d, J_{CF} = 13.5 Hz), 136.40, 136.04, 131.60 (d, J_{CF} = 3.0 Hz), 127.70, 123.54 (d, J_{CF} = 4.5 Hz), 120.18, 65.94, 27.34; ^{19}F NMR (282 MHz, DMSO-d6): δ -83.96 (d, J = 10.2 Hz). HRMS Calcd. for $C_{13}H_{13}{}^{35}ClFN_3O_2$ (M+H): 298.0753; found: 298.0753.

Example 54

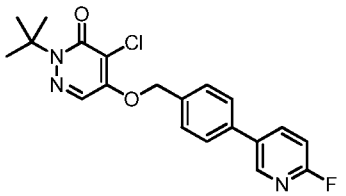
Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(6-nitropyridin-3-yl)benzyl)oxy)pyridazin-3(2*H*)-one



A solution of 5-bromo-2-nitropyridine (50.7 mg, 0.250 mmol) and tetrakis (triphenylphosphine) palladium (0) (6.7 mg; 2.3 mol %) in dimethoxyethane (1.5 mL), was successively treated with the product of Example 48A (0.105 g, 0.250 mmol) as a solution in 1.5 mL dimethoxyethane, and aqueous potassium carbonate (0.50 mmol; 0.50 mL) at ambient temperature. The resulting mixture was heated to 80 °C, maintained 2 h then cooled back to ambient temperature and diluted with ethyl acetate (50 mL). The organic layer was separated, washed with water (2 x 50 mL) and saturated aqueous sodium chloride then dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was then purified by silica gel chromatography (20-50% ethyl acetate in hexanes) to afford the desired product as a faint yellow solid (75.0 mg, 72.3% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.46 (dd, J = 2.7, 0.7 Hz, 1H), 8.68 (dd, J = 8.8, 2.7 Hz, 1H), 8.36 – 8.23 (m, 4H), 7.71 – 7.61 (m, 2H), 5.57 (s, 2H), 1.58 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.45 , 157.79, 153.78, 144.87, 143.15, 138.17, 136.64, 132.71, 128.22, 127.89, 126.17, 120.68, 115.73, 70.90, 65.43, 27.46 . HRMS Calcd. for $C_{20}H_{19}{}^{35}ClN_4O_4$ (M+H): 415.1168; found: 415.1168.

Example 55

Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(6-fluoropyridin-3-yl)benzyl)oxy)pyridazin-3(2*H*)-one

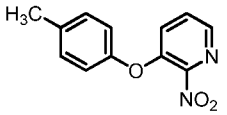


A solution of 5-bromo-2-fluoropyridine (37.0 mg, 0.210 mmol) and tetrakis (triphenyl- phosphine) palladium (0) (9.0 mg; 3.9 mol %) in dimethoxyethane (1.0 mL) was successively treated with the product of Example 48A (85.0 mg, 0.200 mmol) as a solution in 1.0 mL dimethoxyethane, and aqueous potassium carbonate (0.50 mmol; 0.50 mL) at ambient temperature. The resulting mixture was heated to 80 °C, maintained 2 h then cooled back to ambient temperature and diluted with ethyl acetate (50 mL). The organic layer was separated, washed with water (2 x 50 mL) and saturated aqueous sodium chloride then dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was then purified by silica gel chromatography (20-50% ethyl acetate in hexanes) to afford the desired product as white solid (50.0 mg, 64.5% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.58 (dt, J = 2.6, 0.8 Hz, 1H), 8.38 – 8.24 (m, 2H), 7.87 – 7.74 (m, 2H), 7.65 – 7.54 (m, 2H), 7.30 (ddd, J = 8.6, 2.9, 0.7 Hz, 1H), 5.52 (s, 2H), 1.58 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.79, 153.82, 145.45 (d, J_{CF} = 15.0 Hz), 140.34 (d, J_{CF} = 8.3 Hz), 136.01, 135.39, 133.62 (d, J_{CF} = 4.5 Hz), 128.52, 127.17, 126.18, 115.67, 109.89, 109.39, 71.03, 65.40, 27.47; ^{19}F NMR (282 MHz, DMSO-d_6): δ -70.87 (dd, J = 8.0, 2.8 Hz). HRMS Calcd. for $C_{20}H_{19}{}^{35}ClFN_3O_2$ (M+H): 388.1223; found: 388.1217.

Example 56

Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-((2-fluoropyridin-3-yl)oxy)benzyl)oxy)pyridazin-3(2*H*)-one

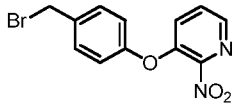
Part A – Preparation of 2-nitro-3-(p-tolyoxy)pyridine



A suspension of *p*-cresol (0.325 g, 3.00 mmol), 3-bromo-2-nitropyridine (0.404 g, 2.00 mmol), and potassium carbonate (0.345 g, 2.50 mmol) in acetonitrile (2.0 mL) was

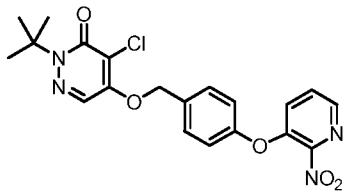
heated at 70 °C and maintained 16 h. The resulting mixture was cooled to room temperature and diluted with ethyl acetate (100 mL) then washed with water (2 x 100 mL) and saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was then purified by silica gel chromatography (0-20% ethyl acetate in hexanes) to obtain the desired product (46.0 mg, 10.0% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (dd, J = 4.4, 1.5 Hz, 1H), 7.48 (dd, J = 8.4, 4.4 Hz, 1H), 7.41 (dd, J = 8.4, 1.5 Hz, 1H), 7.31 – 7.19 (m, 2H), 7.05 – 6.95 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, *partial*): δ 152.16, 146.82, 141.31, 135.46, 130.85, 128.53, 128.07, 119.74, 20.78.

Part B – Preparation of 3-(4-(bromomethyl)phenoxy)-2-nitropyridine



A solution of the product of Example 56A (0.039 g, 0.170 mmol), *N*-bromosuccinimide (35.0 mg, 0.200 mmol), and benzoyl peroxide (1 mg) in 1,2-dichloroethane (4.0 mL) was heated to reflux and maintained 2 h. The resulting mixture was cooled to room temperature and diluted with dichloromethane (20 mL), the organic layer separated then washed with water (2 x 20 mL) and saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated. The crude yellow oil was then purified by silica gel chromatography (10-40% ethyl acetate in hexanes) to obtain the desired product as a faint yellow oil (45.0 mg, 85.6% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (dd, J = 4.3, 1.6 Hz, 1H), 7.59 – 7.43 (m, 4H), 7.12 – 7.02 (m, 2H), 4.52 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, *partial*) δ 154.79, 145.77, 142.31, 135.07, 131.13, 129.28, 128.74, 119.64, 32.33.

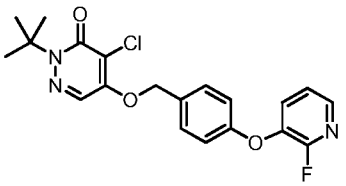
Part C – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-((2-nitropyridin-3-yl)oxy)benzyl)oxy)pyridazin-3(*2H*)-one



Prepared according to General Method B, using 2-(*tert*-butyl)-4-chloro-5-pyridrazin-3(*2H*)-one (21.0 mg, 0.100 mmol), the product of Example 56B (31.0 mg, 0.100 mmol), and cesium carbonate (33.0 mg, 0.100 mmol) in dimethylformamide (1.0 mL) at 80 °C. Isolated yield – 20.0 mg; 46.4%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (dd, J = 4.3, 1.7 Hz, 1H), 7.68

(s, 1H), 7.54 – 7.34 (m, 4H), 7.04 (d, J = 8.7 Hz, 2H), 5.23 (s, 2H), 1.57 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, *partial*): δ 158.95, 155.27, 153.50, 145.64, 142.47, 131.98, 129.45, 129.39, 128.79, 124.98, 119.72, 118.54, 71.17, 66.53, 27.86. HRMS Calcd. for $C_{20}H_{19}{}^{35}ClN_4O_5$ (M+H): 431.1117; found: 431.1110.

Part D – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-((2-fluoropyridin-3-yl)oxy)benzyl)oxy)pyridazin-3(*2H*)-one

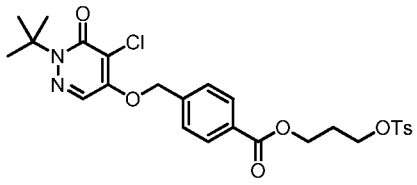


A solution of the product of Example 56C (12.0 mg, 0.030 mmol), potassium fluoride (3.5 mg, 0.06 mmol), and Kryptofix™ (26.0 mg, 0.070 mmol) in dimethylsulfoxide (2.0 mL) was heated to 125 °C and maintained 30 min. The resulting mixture was cooled to room temperature and diluted with ethyl acetate (40 mL) then washed with water (2 x 40 mL) and saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated. The crude material was then purified by preparative thin layer chromatography on silica (1% methanol in dichloromethane) to obtain the desired product (9.0 mg, 74.3% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, J = 4.7 Hz, 1H), 7.67 (s, 1H), 7.47 – 7.30 (m, 3H), 7.12 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 7.02 – 6.90 (m, 2H), 5.21 (s, 2H), 1.57 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.00, 156.99, 156.75, 153.80, 153.60, 141.76 (d, J_{CF} = 13.5 Hz), 130.60 (d, J_{CF} = 3.8 Hz), 130.46, 129.12, 125.09, 122.19, 118.50, 118.03, 71.37, 66.47, 27.87; ^{19}F NMR (282 MHz, $CDCl_3$): δ -81.30 (d, J = 9.8 Hz). HRMS Calcd. for $C_{20}H_{19}{}^{35}ClFN_3O_3$ (M+H): 404.1172; found: 404.1176.

Example 57

Preparation of 3-fluoropropyl 4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzoate

Part A – Preparation of 3-(tosyloxy) propyl 4-(((1-(tert-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl) benzoate

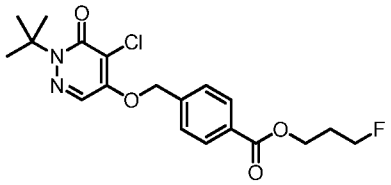


A solution of methyl 4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzoate[3] (0.702 g, 2.00 mmol) in tetrahydrofuran/water (10.0 mL; 4:1 v/v) was cooled to 0 °C and treated with lithium hydroxide hydrate (0.252 g, 6.00 mmol) in one portion. After 0.25 h, the now opaque solution was warmed to ambient temperature and maintained 16 h. The resulting solution was then diluted with water (50 mL), with transfer to a separatory funnel, washed with diethyl ether (3 x 50 mL), and acidified with 1 M hydrochloric acid. The now acidic solution was further washed with warm ethyl acetate (3 x 50 mL) and the combined ethyl acetate washes dried over magnesium sulfate, filtered and concentrated in vacuo to a white powder. Subsequent recrystallization from hot ethyl acetate/pentane afforded the purified 4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzoic acid as colorless needles.

The intermediate acid thus obtained was dissolved in dry dimethylformamide (20.0 mL) then successively treated with propane-1,3-diyl bis(4-methylbenzenesulfonate) (1.15 g, 3.00 mmol) and potassium carbonate (0.415 g, 3.00 mmol) in one portion at ambient temperature. After 5 h, the resulting suspension was partitioned between ethyl acetate and water (50 mL each), with transfer to a separatory funnel, and the layers separated. The aqueous layer was then washed with ethyl acetate (2 x 50 mL) and the combined ethyl acetate washes dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was then purified by chromatography on silica using a step gradient from 7:3 pentane/ethyl acetate (500 mL) to 3:2 pentane/ethyl acetate (1000 mL). The main product peak eluting 1075-1275 mL was collected, pooled and concentrated in vacuo to a colorless oil (0.566 g, 1.03 mmol; 51.6%). ^{1}H NMR: (300 MHz, DMSO-d_6) δ 8.25 (1H, s), 7.89 (2H, AA'BB', J_{AB} = 8.3 Hz, $J_{AA'}$ = 2.0 Hz), 7.75 (2H, AA'BB', J_{AB} = 8.3 Hz, $J_{AA'}$ = 2.0 Hz), 7.57 (2H, d, J = 8.6 Hz), 7.35 (2H, d, J = 7.9 Hz), 5.57 (2H, s), 4.23 (2H, d, J = 5.9 Hz), 4.18 (2H, t, J = 5.7

Hz), 2.27 (3H, s), 2.04 (2H, tt, J = 5.9, 5.9 Hz), 1.57 (9H, s). ^{13}C NMR: (75 MHz, DMSO-d_6) δ 165.0, 157.7, 153.7, 144.8, 140.8, 132.0, 130.0, 129.5, 129.4, 127.5, 126.1, 115.8, 70.7, 67.5, 65.4, 60.5, 27.5, 27.4, 20.9. HRMS Calcd. for $C_{26}H_{29}{}^{35}ClN_2O_7S$ (M+H): 549.1457; found: 549.1467. TLC: R_f 0.33 (silica gel, 1:1 pentane/ethyl acetate, uv).

Part B – Preparation of 3-fluoropropyl 4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzoate



A solution of methyl 4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzoate[3] (0.702 g, 2.00 mmol) in tetrahydrofuran/water (10.0 mL; 4:1 v/v) was cooled to 0 °C and treated with lithium hydroxide hydrate (0.252 g, 6.00 mmol) in one portion. After 0.25 h, the now opaque solution was warmed to ambient temperature and maintained 16 h. The resulting solution was then diluted with water (50 mL), with transfer to a separatory funnel, washed with diethyl ether (3 x 50 mL), and acidified with 1 M hydrochloric acid. The now acidic solution was further washed with warm ethyl acetate (3 x 50 mL) and the combined ethyl acetate washes dried over magnesium sulfate, filtered and concentrated in vacuo to a white powder.

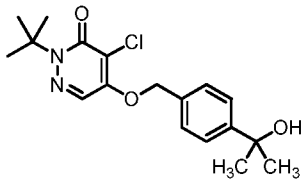
The intermediate acid thus obtained was dissolved in dry dimethylformamide (5.00 mL) then successively treated with 3-fluoropropyl 4-methylbenzenesulfonate (0.697 g, 3.00 mmol) and potassium carbonate (0.415 g, 3.00 mmol) in one portion at ambient temperature. After 0.25 h, the resulting solution was warmed to 55 °C, maintained 1.5 h, then cooled to ambient temperature and diluted with ethyl acetate (150 mL each) with transfer to a separatory funnel. The ethyl acetate solution thus obtained was then washed with saturated aqueous sodium chloride (5 x 50 mL), dried over magnesium sulfate, filtered and concentrated in vacuo to an amber oil. The crude material was then purified by chromatography on silica (30 x 200 mm) using 3:1 pentane/ethyl acetate. The main product peak eluting 300-560 mL was collected, pooled and concentrated in vacuo to a white solid (0.680 g, 1.71 mmol; 85.7%). ^{1}H NMR: (300 MHz, DMSO-d_6) δ 8.23 (1H, s), 8.03 (2H, AA'BB', J_{AB} = 8.5 Hz, $J_{AA'}$ = 1.9 Hz), 7.60 (2H, AA'BB', J_{AB} = 8.7 Hz, $J_{BB'}$ = 1.9 Hz), 5.56 (2H, s), 4.61 (2H, dt, J = 47.2, 5.9 Hz), 4.38 (2H, t, J = 6.3 Hz), 2.11 (2H, dtt, J = 25.9, 6.1, 6.1 Hz) 1.57 (9H, s). ^{19}F NMR: (282 MHz, DMSO-d_6) δ -220.4 (1F, tt, J = 47.1, 25.8 Hz).

^{13}C NMR: (75 MHz, DMSO-d_6) δ 165.3, 157.7, 153.7, 140.8, 129.6, 129.5, 127.5, 126.1, 115.8, 80.9 (d, J = 161.9 Hz), 70.7, 65.4, 61.0 (d, J = 5.6 Hz), 29.2 (d, J = 19.6 Hz), 27.4. HRMS Calcd. for $C_{19}H_{22}{}^{35}ClFN_2O_4$ (M+H): 397.1325; found: 397.1330. TLC: R_f 0.24 (silica gel, 3:1 pentane/ethyl acetate, uv).

Example 58

Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(2-(2-fluoroethoxy)propan-2-yl)benzyl)oxy) pyridazin-3(*2H*)-one

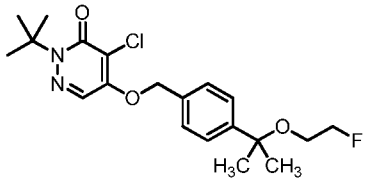
Part A – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(2-hydroxypropan-2-yl)benzyl)oxy)pyridazin-3(*2H*)-one



A solution of 2-(*tert*-butyl)-4,5-dichloropyridazin-3(2H)-one (0.995 g, 4.50 mmol) and 2-(4-(hydroxymethyl)phenyl)propan-2-ol (0.499 g, 3.00 mmol; e.g., see Machacek, Michelle R.; Haidle, Andrew; Zabierek, Anna A.; Konrad, Kaleen M.; Altman, Michael D. (Merck & Co., Inc.) Preparation of thiazolecarboxamides as inhibitors of Janus kinases. PCT Int. Appl. WO 2010/011375. January 28, 2010) in dry dimethylformamide (15.0 mL) was treated with cesium carbonate (1.96 g, 6.00 mmol) in one portion at ambient temperature. The resulting suspension was then immersed in a pre-heated oil bath and maintained 2.5 h at 80 °C. Left unattended, the suspension was cooled to ambient temperature and maintained 20 h. The resulting suspension was then partitioned between ethyl acetate (150 mL) and water (25 mL), with transfer to a separatory funnel, and the layers separated. The ethyl acetate layer was then washed with saturated aqueous sodium chloride (5 x 25 mL), dried over magnesium sulfate, filtered and concentrated in vacuo to an amber oil. The crude material was then purified by chromatography on silica (40 x 170 mm) using 3:2 hexanes/ethyl acetate. The main product peak eluting 400-700 mL was collected, pooled and concentrated in vacuo to a white solid. Subsequent recrystallization from hot ethyl acetate/pentane afford the desired product as colorless needles (0.682 g, 1.95 mmol; 64.9%). ^{1}H NMR: (300 MHz, DMSO-d_6) δ 8.26 (s, 1H), 7.51 (2H, AB, J_{AB} = 8.3 Hz), 7.39 (2H, AB, J_{AB} = 8.3 Hz), 5.42 (s, 2H), 5.01 (s, 1H), 1.57 (s, 9H), 1.42 (s, 6H). ^{13}C NMR: (75 MHz, DMSO-d_6) δ 157.8, 153.9, 151.0, 132.8, 127.4, 126.2, 124.8, 115.5, 71.4, 70.5, 65.3, 31.8, 27.4. HRMS Calcd. for

$C_{18}H_{23}{}^{35}ClN_2O_3$ (M+H): 351.1470; found: 351.1474. TLC: R_f 0.16 (silica gel, 7:3 hexanes/ethyl acetate, CAM).

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(2-(2-fluoroethoxy)propan-2-yl)benzyl)oxy)pyridazin-3(2*H*)-one

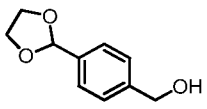


A solution of the product of part A (0.105 g, 0.300 mmol) in 2-fluoroethanol (1.75 mL) was treated with 11.4 mg *p*-toluenesulfonic acid hydrate (0.06 mmol; 20 mol %) in one portion at ambient temperature. After 24 h, all volatiles were removed in vacuo, and the residue directly purified by chromatography on silica (30 x 185 mm) using 4:1 hexanes/ethyl acetate. The main product peak eluting 360-450 mL was collected, pooled and concentrated in vacuo to a colorless oil (81.2 mg, 0.205 mmol; 68.3%). ^{1}H NMR: (300 MHz, DMSO-d_6) δ 8.28 (1H, s), 7.55 – 7.39 (4H, m), 5.44 (2H, s), 4.62 – 4.52 (1H, m), 4.47 – 4.36 (1H, m), 3.46 – 3.34 (1H, m), 3.36 – 3.25 (1H, m), 1.58 (9H, s), 1.49 (6H, s). ^{19}F NMR: (282 MHz, DMSO-d_6) δ -222.01 (1F, tt, J = 47.8, 30.6 Hz). ^{13}C NMR: (75 MHz, DMSO-d_6) δ 157.8, 153.9, 146.3, 133.9, 127.7, 126.1, 125.8, 115.5, 83.17 (d, J = 166.3 Hz), 76.3, 71.2, 65.3, 61.89 (d, J = 19.2 Hz), 28.0, 27.4. HRMS Calcd. for $C_{20}H_{26}{}^{35}ClFN_2O_3$ (M+H): 397.1689; found: 397.1695.TLC: R_f 0.51 (silica gel, 3:2 hexanes/ethyl acetate, uv).

Example 59

Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-((2-fluoroethoxy)methyl)phenyl)ethynyl)pyridazin-3(2*H*)-one

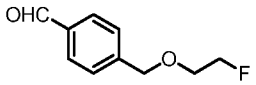
Part A – Preparation of (4-(1,3-dioxolan-2-yl)phenyl)methanol



Methyl 4-formylbenzoate (4.92 g, 30.0 mmol) was dissolved in dry toluene (50.0 mL), successively treated with ethylene glycol (1.84 mL, 33.0 mmol) and p-toluenesulfonic acid (57.1 mg, 0.300 mmol), then heated to reflux under Dean-Stark conditions; acetal formation was complete within 1 h. The solution was then cooled to 22 °C and directly treated with sodium bis(2-methoxyethoxy)aluminum hydride (45.0 mmol; 12.7 mL of a 70.3

wt. % solution in toluene) at a rate of 0.5 mL/min using a syringe pump. Upon completion of the addition, the resulting solution was cooled to 0 °C, carefully treated with a saturated aqueous solution of potassium sodium tartrate (100 mL) then vigorously stirred 1 h; steady formation of a clear solution was observed. The resulting biphase was then diluted with ethyl acetate (50 mL), with transfer to a conical funnel, and the layers separated. The aqueous layer was then washed with ethyl acetate (3 x 50 mL) and the combined ethyl acetate and toluene solutions dried over magnesium sulfate, filtered and concentrated in vacuo to a colorless oil. The crude product was then purified by chromatography on silica (50 x 135 mm) using 1:1 pentane/ethyl acetate. The main product peak eluting 425-725 mL was collected, pooled and concentrated in vacuo to a colorless oil, which solidified in the freezer (4.50 g, 83.2% over two steps). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.48 (2H, AB, J_{AB} = 8.1 Hz), 7.39 (2H, AB, J_{AB} = 8.3 Hz), 5.82 (1H, s), 4.71 (2H, d, J = 6.0 Hz), 4.08 (4H, AA'BB', $J_{AA'}$ = $J_{BB'}$ = 7.2 Hz, J_{AB} = -7.5 Hz, $J_{AB'}$ = 6.4 Hz), 1.63 (1H, t, J = 6.0 Hz). ^{13}C NMR: (75 MHz, $CDCl_3$) δ 142.0, 137.2, 126.8, 126.6, 103.5, 65.3, 64.9.

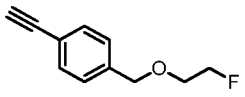
Part B – Preparation of 4-((2-fluoroethoxy)methyl)benzaldehyde



A solution of the product of Example 59A (1.80 g, 10.0 mmol) in dry acetonitrile (50.0 mL) was successively treated with 1-bromo-2-fluoroethane (3.73 mL, 50.0 mmol) and powdered potassium hydroxide (5.61 g, 0.100 mol) in one portion at ambient temperature. After 0.5 h, the resulting suspension was warmed to 80 °C then maintained 2.5 h. After cooling to ambient temperature, the suspension was diluted with water (100 mL), with transfer to a separatory funnel then washed with ethyl acetate (3 x 100 mL). The combined ethyl acetate washes were dried over magnesium sulfate, filtered and concentrated in vacuo to a colorless that was directly purified by chromatography on silica (50 x 195 mm) using 1:1 pentane/diethyl ether to afford 2-(4-((2-fluoroethoxy)methyl)phenyl)-1,3-dioxolane as a colorless oil (2.04 g, 9.02 mmol; 90.2%). The purified acetal (0.423 g, 2.00 mmol) was then dissolved in wet acetone (8.00 mL) and directly treated with dilute hydrochloric acid (2.00 mmol; 2.00 mL of a 1.0 N solution in water) at ambient temperature. After stirring 18 h, the resulting mixture was partitioned between diethyl ether and saturated aqueous sodium bicarbonate (50 mL each), with transfer to a conical funnel, and the layers separated. The aqueous layer was then washed with diethyl ether (2 x 50 mL) and the combined ethereal solutions dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by

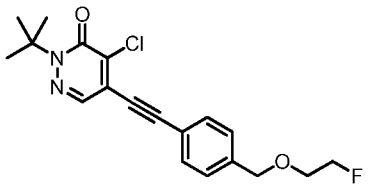
bulb-to-bulb distillation under reduced pressure afforded the title compound as a colorless oil (0.340 g, 1.87 mmol; 93.4%).

Part C – Preparation of 1-ethynyl-4-((2-fluoroethoxy)methyl)benzene



Carbontetrabromide (1.06 g, 3.20 mmol), zinc dust (0.210 g, 3.20 mmol) and triphenylphosphine (0.840 g, 3.20 mmol) were added to a solution of the product of Example 59B (0.290 g, 1.60 mmol) in dichloromethane (10.0 mL) at ambient temperature. The crude dibromo intermediate was isolated using standard workup procedures, dissolved in dry tetrahydrofuran (8.00 mL) then cooled to -78 °C and treated with a solution of n-butyllithium in tetrahydrofuran (2.00 mL). The resulting mixture was then warmed to ambient temperature, treated with water and extracted with ethyl acetate. The ethyl acetate solution was washed with water and saturated aqueous sodium chloride then dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material thus obtained was then purified by chromatography on silica (12 g) using 9:1 hexanes/ethyl acetate, to afford the title compound (0.190 g, 66.6%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.50 – 7.44 (m, 2H), 7.38 – 7.32 (m, 2H), 4.67 – 4.63 (m, 1H), 4.55 (s, 2H), 4.51 – 4.47 (m, 1H), 4.16 (s, 1H), 3.76 – 3.72 (m, 1H), 3.66 – 3.62 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 139.19, 131.60, 127.51, 120.72, 83.68 (d, J = 51.8 Hz), 81.82, 80.62, 71.41, 69.10 (d, J = 18.8 Hz).

Part D – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-((2-fluoroethoxy)methyl)phenyl)ethynyl) pyridazin-3(2*H*)-one



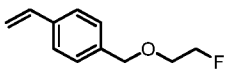
A solution of 1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl trifluoromethane sulfonate (0.175 g, 0.523 mmol), the product of Example 59C (95.0 mg, 0.533 mmol), trans-dichloro(triphenylphosphine)palladium (II) (11.0 mg, 0.0157 mmol; 3.0 mol%), copper(I) iodide (30.0 mg, 0.158 mmol), n-tetrabutylammonium iodide (0.576 g, 1.55 mmol) and triethylamine (220 μL, 1.58 mmol) in anhydrous tetrahydrofuran (5.00 mL) was stirred 2 h at ambient temperature then diluted with ethyl acetate, and filtered through Celite with transfer to a separatory funnel. The ethyl acetate solution was then washed with water

and saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material thus obtained was then purified by chromatography on silica (4 g) using 3:1 hexanes/ethyl acetate, to afford the title compound (90.0 mg, 46.5%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.66 – 7.63 (m, 2H), 7.48 – 7.45 (m, 2H), 4.68 – 4.66 (m, 1H), 4.61 (s, 2H), 4.52 – 4.50 (m, 1H), 3.79 – 3.76 (m, 1H), 3.69-3.66 (m, 1H), 1.60 (s, 9H).^{13}C NMR (75 MHz, DMSO-d_6) δ 155.85, 141.13, 136.51, 134.28, 131.97, 127.71, 124.57, 119.20, 102.11, 84.02, 81.58 (d, J = 36.0 Hz), 71.33, 69.25 (d, J = 19.5 Hz), 65.89, 27.30. ^{19}F NMR (282 MHz, DMSO-d_6) δ -221.61 (tt, J = 48.0, 31.1 Hz). HRMS Calcd. for $C_{19}H_{20}{}^{35}ClFN_2O_2$ (M+H): 363.1270; found: 363.1266.

Example 60

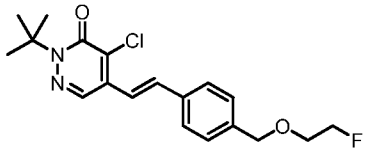
Preparation of (*E*)-2-(*tert*-butyl)-4-chloro-5-(4-((2-fluoroethoxy)methyl)styryl)pyridazin-3(2*H*)-one

Part A – Preparation of 1-((2-fluoroethoxy)methyl)-4-vinylbenzene



A suspension of methyltriphenylphosphonium bromide (0.260 g, 0.728 mmol) and sodium hydride (80.0 mg, 3.33 mmol) in dry tetrahydrofuran (2.50 mL) was cooled to 0 °C then treated with the product of Example 59A (0.110 g, 0.604 mmol). The resulting mixture then warmed slowly to ambient temperature as the ice melted. After 2 h total, the suspension was diluted with diethyl ether with transfer to a separatory funnel then washed with water and saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material thus obtained was then purified by chromatography on silica (4 g) using 9:1 hexanes/ethyl acetate, to afford the title compound (40.0 mg, 36.7%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 2H), 7.24 (d, J = 8.2 Hz, 2H), 6.64 (dd, J = 17.6, 10.9 Hz, 1H), 5.67 (dd, J = 17.6, 1.0 Hz, 1H), 5.17 (dd, J = 10.9, 0.9 Hz, 1H), 4.64 – 4.56 (m, 1H), 4.52 (s, 2H), 4.47 – 4.38 (m, 1H), 3.75 – 3.65 (m, 1H), 3.64 – 3.55 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -223.12 (tt, J = 48.0, 31.1 Hz).

Part B – Preparation of (*E*)-2-(*tert*-butyl)-4-chloro-5-(4-((2-fluoroethoxy)methyl)styryl)pyridazin-3(2*H*)-one

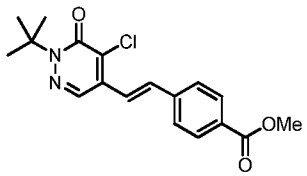


A solution of 1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl trifluoromethane sulfonate (0.180 g, 0.538 mmol), the product of Example 60A (0.140 g, 0.777 mmol), trans-dichlorobis(tri-*o*-tolylphosphine)palladium (II) (40.0 mg, 0.057 mmol; 7.3 mol %) and triethylamine (120 μL, 0.860 mmol) in dry dimethylformamide (5.00 mL) was warmed to 110°C and maintained 2 h. After cooling to ambient temperature, the resulting mixture was diluted with ethyl acetate, and filtered through Celite with transfer to a separatory funnel. The ethyl acetate solution was then washed with water and saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material thus obtained was then purified by chromatography on silica (4 g) using 4:1 hexanes/ethyl acetate, to afford the title compound (50.0 mg, 25.5%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.60-7.57 (m, 2H), 7.44 – 7.41 (m, 2H), 7.29 (d, J = 6.0 Hz, 1H), 4.72 – 4.69 (m, 1H), 4.65 (s, 2H), 4.56 – 4.53 (m, 1H), 3.84 – 3.81 (m, 1H), 3.74 – 3.71 (m, 1H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.59, 139.74, 136.58, 135.09, 134.98, 132.73, 130.83, 128.16, 127.58, 120.07, 83.08 (d, J = 168.0 Hz), 72.87, 69.42 (d, J = 19.5 Hz), 66.08, 27.85.^{19}F NMR (282 MHz, DMSO) δ -223.04(tt, J = 47.9, 28.2 Hz). HRMS Calcd. for $C_{19}H_{22}{}^{35}ClFN_2O_2$ (M+H): 365.1427; found: 365.1421.

Example 61

Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-((2-fluoroethoxy)methyl)phenyl)ethynyl)pyridazin-3(2*H*)-one

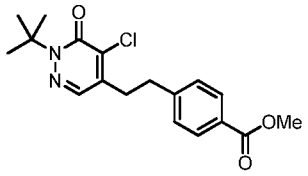
Part A – Preparation of (*E*)-methyl 4-(2-(1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)vinyl)benzoate



A solution of 1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl trifluoromethane sulfonate (0.400 g, 1.20 mmol), methyl 4-vinylbenzoate (0.210 g, 1.29

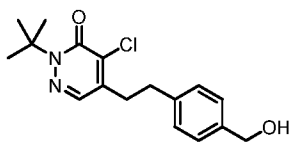
mmol), trans-dichlorobis(tri-*o*-tolylphosphine)palladium (II)(40.0 mg, 0.057 mmol; 4.8 mol %) and triethylamine (80.0 μL, 0.574 mmol) in dry dimethylformamide (2.00 mL) was warmed to 110°C and maintained 2 h. After cooling to ambient temperature, the resulting mixture was diluted with ethyl acetate, and filtered through Celite with transfer to a separatory funnel. The ethyl acetate solution was then washed with water with and saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material thus obtained was then purified by chromatography on silica (12 g) using 4:1 hexanes/ethyl acetate, to afford the title compound (80.0 mg, 19.2%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 – 8.08 (m, 2H), 8.03 (s, 1H), 7.68 – 7.62 (m, 2H), 7.48 – 7.32 (m, 2H), 3.96 (s, 3H), 1.70 (s, 9H).

Part B – Preparation of methyl 4-(2-(1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)ethyl)benzoate



A solution of the product of Example 61A (50.0 mg, 0.144 mmol) in 2:1 methanol/dichloromethane (15.0 mL) was treated with platinum(II) oxide (20.0 mg, 0.088 mmol) in one portion at ambient temperature. The resulting suspension was stirred under a hydrogen atmosphere then filtered through a mixture of Celite and silica gel and the resulting filtrate concentrated in vacuo. The crude material thus obtained was then purified by chromatography on silica (4 g) using 4:1 hexanes/ethyl acetate, to afford the title compound (30.0 mg, 59.7%).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, 2H, J = 8.3 Hz), 7.47 (s, 1H), 7.28 (d, 2H, J = 8.2 Hz), 3.93 (s, 3H), 3.00 – 2.94 (m, 4H), 1.66 (s, 9H).

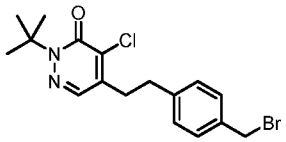
Part C – Preparation of 2-(*tert*-butyl)-4-chloro-5-(4-(hydroxymethyl)phenethyl)pyridazin-3(2*H*)-one



A solution of the product of Example 61B (30.0 mg, 0.086 mmol) in tetrahydrofuran (2.00 mL) was cooled to 0 °C then treated with lithium aluminum hydride (0.4 mL, 0.4 mmol of a 1 M solution in tetrahydrofuran) and warmed to ambient temperature. After 1 h, the

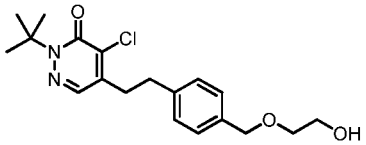
resulting mixture was diluted with water (20 mL), the aqueous layer separated then washed with dichloromethane (3 x 20 mL). The combined organic washes were further washed with saturated aqueous sodium chloride then dried over magnesium sulfate, filtered and concentrated to in vacuo to yield the title compound (20.0 mg) that was used without additional purification in the subsequent reaction.

Part D – Preparation of 5-(4-(bromomethyl)phenethyl)-2-(*tert*-butyl)-4-chloropyridazin-3(2*H*)-one



A solution of the product of Example 61C (20.0 mg, 0.062 mmol) in dichloromethane (1.00 mL) was directly treated with phosphorous tribromide (0.030 mmol; 30 μL of a 1 M solution in dichloromethane) then stirred 1 h at ambient temperature. The resulting mixture was then diluted with dichloromethane (20 mL), with transfer to a separatory funnel, and washed with water and saturated aqueous sodium chloride, dried over magnesium sulfate, filtered, and concentrated in vacuo to yield the title compound (20.0 mg) that was used without additional purification in the subsequent reaction.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.33 – 7.28 (m, 2H), 7.23 – 7.17 (m, 2H), 4.56 (s, 2H), 3.80 – 3.74 (m, 2H), 3.63 – 3.57 (m, 2H), 2.93 (s, 4H), 1.67 (s, 9H).

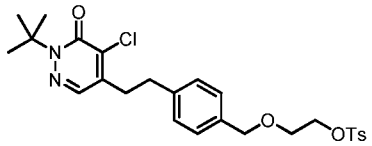
Part E – Preparation of 2-(*tert*-butyl)-4-chloro-5-(4-((2-hydroxyethoxy)methyl)phenethyl) pyridazin -3(2*H*)-one



A suspension of sodium hydride (0.20 mmol; 8.0 mg of a 60% dispersion in mineral oil) and ethylene glycol (10.0 μL, 0.18 mmol), was treated with a solution of the product of Example 61D (20.0 mg, 0.052 mmol) in dry tetrahydrofuran (2.00 mL) and the resulting mixture heated to reflux. After 4 h, the reaction mixture was cooled to ambient temperature, diluted with diethylether (20 mL) then transferred to a separatory funnel, washed with water and saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material thus obtained was then purified by chromatography on silica (4 g) using 7:3 hexanes/ethyl acetate, to afford the title compound

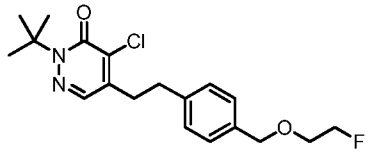
(5.5 mg, 29.0%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.32 – 7.28 (m, 2H), 7.22 – 7.18 (m, 2H), 4.57 (s, 2H), 3.80 – 3.76 (m, 2H), 3.63 – 3.59 (m, 2H), 2.93 (s, 4H), 1.67 (s, 9H).

Part F – Preparation of 2-((4-(2-(1-(tert-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)ethyl)benzyl) oxy)ethyl 4-methylbenzenesulfonate



Prepared according the General Method D, using the product of Example 61E (5.5 mg, 0.015 mmol), *p*-toluenesulfonyl chloride (8.0 mg, 0.042 mmol), 4-dimethylaminopyridine (one crystal), and triethylamine (0.010 mL, 0.072 mmol). Isolated yield – 5.0 mg; 64.2%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 – 7.79 (m, 2H), 7.50 (s, 1H), 7.39 – 7.30 (m, 2H), 7.25 – 7.17 (m, 4H), 4.49 (s, 2H), 4.27 – 4.17 (m, 2H), 3.73 – 3.63 (m, 2H), 2.93 (s, 4H), 2.46 (s, 3H), 1.67 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.53, 144.74, 140.72, 139.49, 135.95, 135.18, 134.90, 133.11, 129.78, 128.35, 128.05, 127.96, 72.96, 69.21, 67.52, 66.26, 33.56, 32.69, 27.77, 21.63.

Part G – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-((2-fluoroethoxy)methyl)phenyl)ethynyl)pyridazin-3(*2H*)-one



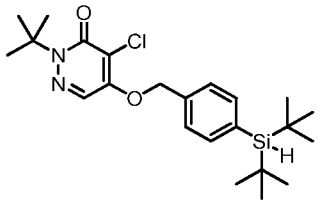
A solution of the product of Example 59C (40.0 mg, 0.110 mmol) in 1:1 ethyl acetate/hexanes (10.0 mL) was treated with 5% palladium on calcium carbonate, poisoned with lead (20.0 mg, 0.094 mmol) in one portion at ambient temperature. The resulting suspension was stirred under a hydrogen atmosphere then filtered through a mixture of Celite and silica gel and the resulting filtrate concentrated in vacuo. The crude material thus obtained was then purified by chromatography on silica (4 g) using 4:1 hexanes/ethyl acetate, to afford the title compound (20.0 mg, 49.6%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.29 – 7.22 (m, 4H), 4.65 – 4.62 (m, 1H), 4.50(s, 2H), 4.49 – 4.46 (m, 1H), 3.72 – 3.69 (m, 1H), 3.62 – 3.59 (m, 1H), 2.91 – 2.89 (m, 4H), 1.58 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.34, 141.37, 139.41, 136.10, 135.56, 133.71, 128.15, 127.71, 82.95 (d, J = 164 Hz), 71.78, 68.82 (d, J = 18.8 Hz), 65.27, 32.62, 31.78, 27.34. ^{19}F NMR (282 MHz, DMSO) δ -

221.51(tt, J = 48.0, 31.1 Hz). HRMS Calcd. for $C_{19}H_{24}{}^{35}ClFN_2O_2$ (M+H): 367.1583; found: 367.1580.

Example 62

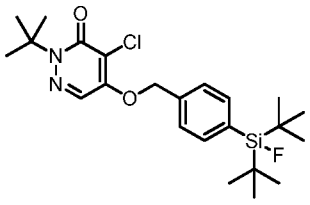
Preparation of Silyl Derivatives

Part A – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(di-*tert*-butylsilyl)benzyl)oxy)pyridazin-3(2*H*)-one



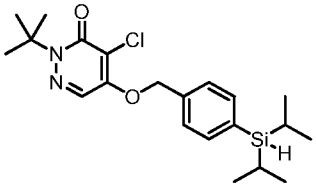
A solution of 2-(*tert*-butyl)-4-chloro-5-hydroxypyridrazin-3(*2H*)-one (0.476 g, 2.36 mmol) in tetrahydrofuran (23.6 mL) was successively treated with (4-(di-*tert*-butylsilyl) phenyl) methanol (0.706 g, 2.82 mmol; e.g., see James, D.; Escudier, J.-M.; Amigues, E.; Schulz, J.; Virty, C.; Bordenave, T.; Szlosek-pinaud, M.; Fouquet, E. A "click chemistry" approach to the efficient synthesis of modified nucleosides and oligonucleotides for PET imaging. Tetrahedron Lett., 2010, 51, 1230-1232), triphenylphosphine (0.929 g, 3.54 mmol), and diethylazodicarboxylate (0.617 g, 3.54 mmol) at ambient temperature. After 90 min, the resulting mixture was diluted with water (50 mL), with transfer to a separatory funnel and the aqueous layer separated then washed with ethyl acetate (3 x 100 mL). The combined organic washes were dried over sodium sulfate, filtered, and concentrated in vacuo to an orange oil. The crude material was then triturated with diethyl ether for 2 h and the resulting suspension filtered to remove the suspended triphenylphosphine oxide. The filtrate was purified by chromatography on silica using a 0-50% ethyl acetate in hexanes gradient to afford the title compound as a white solid (0.227 g, 22.1%). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.64 (d, 2H, J = 8.12 Hz), 7.40 (d, 2H, J = 8.12 Hz), 5.34 (s, 2H), 3.90 (s, 1H), 1.55 (s, 9H), 1.07 (s, 18H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 159.04, 153.78, 136.49, 136.29, 135.43, 126.03, 125.18, 98.55, 71.91, 66.38, 28.87, 27.87, 18.99. HRMS Calcd. for $C_{23}H_{35}{}^{35}ClN_2O_2Si$ (M+Na): 429.1736; found: 429.1729.

Part B – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(di-*tert*-butylfluorosilyl)benzyl)oxy)pyridazin-3(2*H*)-one



A solution of the product of Example 62A (5.0 mg, 0.011 mmol) in dimethylsulfoxide (0.3 mL) was added to a mixture of 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (8.7 mg, 0.023 mmol) and potassium fluoride (0.6 mg, 0.011 mmol) then warmed to 35 ºC. After 10 min, the resulting mixture was cooled to ambient temperature then diluted with water (0.5 mL) with transfer to a separatory funnel. The aqueous layer was then washed with ethyl acetate (3 x 2 mL) and the combined washes dried over sodium sulfate, filtered and concentrated in vacuo to an oil. The crude material thus obtained was then purified by preparative thin-layer chromatography on silica using 4:1 hexanes/ethyl acetate to afford the title compound as a white solid (3.2 mg, 70.6%; *e.g.*, see Mu L.; Hoehne, A.; Schubiger, P. A.; Ametamey, S. M.; Graham, K.; Cyr, J. E.; Dinkelborg, L.; Stellfeld, T.; Srinivasan, A.; Voigtmann, U.; Klar, U. Silicon-based Building blocks for one step 18F-radiolabeling of peptides for PET imaging. Angew. Chem. Int. Ed. 2008, 47, 4922-4925). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.72 – 7.59 (m, 3H), 7.33 (d, 2H, J = 8.14 Hz), 5.24 (s, 2H), 1.57 (s, 9H), 0.97 (s, 18H).^{13}C NMR (75 MHz, $CDCl_3$, *partial*) δ 158.03, 152.73, 135.12, 133.66 (d, J = 4.5 Hz), 125.09, 124.12, 98.97, 70.79, 65.43, 26.87, 26.29, 19.23 (d, J = 12.0 Hz).^{19}F NMR: (282 MHz, $CDCl_3$) δ -188.74 (1F, s). HRMS Calcd. for $C_{23}H_{34}{}^{35}ClFN_2O_2Si$ (M+H): 453.2135; found: 453.2139.

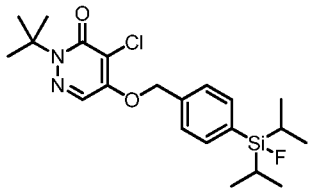
Part C – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(diisopropylsilyl)benzyl)oxy)pyridazin-3(2*H*)-one



A solution of 2-(*tert*-butyl)-4-chloro-5-hydroxypyridrazin-3(2*H*)-one (0.476 g, 2.36 mmol) in tetrahydrofuran (23.6 mL) was successively treated with (4-(diisopropylsilyl) phenyl) methanol (0.627 g, 2.82 mmol; *e.g.*, see James, D.; Escudier, J.-M.; Amigues, E.; Schulz, J.; Virty, C.; Bordenave, T.; Szlosek-pinaud, M.; Fouquet, E. A "click chemistry"

approach to the efficient synthesis of modified nucleosides and oligonucleotides for PET imaging. Tetrahedron Lett., 2010, 51, 1230-1232), triphenylphosphine (0.929 g, 3.54 mmol), and diethylazodicarboxylate (0.617 g, 3.54 mmol) at ambient temperature. After 2 h, the resulting mixture was diluted with water (50 mL), with transfer to a separatory funnel and the aqueous layer separated then washed with ethyl acetate (3 x 100 mL). The combined organic washes were dried over sodium sulfate, filtered, and concentrated in vacuo to an oil. The crude material was then triturated with diethyl ether for 2 h and the resulting suspension filtered to remove the suspended triphenylphosphine oxide. The filtrate was purified by chromatography on silica using a 0-50% ethyl acetate in hexanes gradient to afford the title compound as a white solid (0.259 g, 27.0% yield). ^{1}H NMR: (300 MHz, $CDCl_3$) δ7.55 (s, 1H), 7.38 (d, 2H, J = 8.03 Hz), 7.19 (d, 2H, J = 8.12 Hz), 5.12 (s, 2H), 3.77 (m, 1H), 1.46 (s, 9H), 1.05 (m, 2H), 0.87 (dd, J = 6.0 Hz, 6H), 0.82 (dd, J = 6.0 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 159.03, 153.76, 136.01, 135.63, 135.21, 126.18, 125.14, 71.90, 66.39, 27.87, 18.61, 18.45, 10.65. HRMS Calcd. for $C_{21}H_{31}{}^{35}ClN_2O_2Si$ (M+H): 407.1916; found: 407.1922.

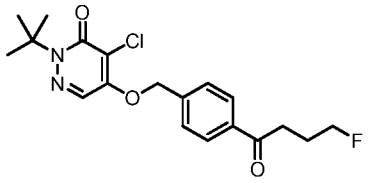
Part D – Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(diisopropylfluorosilyl)benzyl)oxy)pyridazin-3(2*H*)-one



A solution of the product of Example 62C (5.0 mg, 0.011 mmol) in tetrahydrofuran (0.3 mL) was added to a solution of tetrabutylammonium fluoride (0.011 mmol; 0.011 mL of a 1 M solution in tetrahydrofuran at -78 °C. After 6 h, the resulting mixture was warmed to -20 °C and maintained an additional 20 h. After warming to ambient temperature, the crude mixture was directly purified by preparative thin-layer chromatography on silica using 9:1 hexanes/ethyl acetate to afford the title compound as a colorless oil (4.2 mg, 82.4%). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.58 – 7.49 (m, 2H), 7.37 (d, 2H, J = 7.84 Hz), 5.24 (s, 2H), 1.57 (s, 9H), 1.16-1.25 (m, 2H), 0.96-0.94 (m, 12H).^{13}C NMR (75 MHz, $CDCl_3$, *partial*) δ 159.01, 153.70, 136.53, 134.43 (d, J = 3.7 Hz), 126.29, 125.08, 71.76, 66.43, 27.87, 16.65, 16.62, 12.30 (d, J = 12.7 Hz).^{19}F NMR: (282 MHz, $CDCl_3$) δ -187.01 (t, J = 5.6 Hz).

Example 63

Preparation of 2-(*tert*-butyl)-4-chloro-5-((4-(4-fluorobutanoyl)benzyl)oxy)pyridazin-3(2*H*)-one



A solution of the product of Example 43D in 1,4-dioxane is treated with [(IPr)AuCl] (*e.g.*, see Marion, N.; Ramon, R.; Nolan, S. P. [(NHC)AuI]-Catalyzed Acid Free Hydration of Alkynes at Part-Per-Million Catalyst Loadings. J. Am. Chem. Soc. 2009, 131, 448-449) and silver hexafluoroantiminate at ambient temperature. After 1 min, water is added and the resulting mixture warmed to 120 °C and maintained overnight. After cooling to ambient temperature, all volatile materials are removed in vacuo and the residue purified by chromatography on silica to afford the title compound.

Example 64

Part A – Preparation of submitochondrial particles from bovine heart

Bovine heart mitochondria were prepared as described by Lester *et al.* (*e.g.*, see Lester R. L.; Smith A. L. Studies on the electron transport system. 28. The mode of reduction of tetrazolium salts by beef heart mitochondria; role of coenzyme Q and other lipids. Biochim Biophys. Acta. 1961, 47, 475-96). In brief, bovine heart was minced and 200 g of ground heart tissue was suspended in 400 mL of 0.25 M sucrose, 0.01 M Tris-Cl, 1 mM Tris-succinate, and 0.2 mM ethylenediamine tetra-acetic acid (EDTA) and homogenized in a Waring blender. The homogenate was centrifuged for 20 min at 1,200 x g and the supernatant was centrifuged for 15 min at 26,000 x g resulting in a mitochondrial pellet. The protein concentration of the mitochondrial samples as measured by BioRad Protein Assay Kit (BioRad Life Science Research, Hercules, CA) was adjusted to 20 mg/mL using 0.25 M sucrose, 10 mM Tris-acetate pH 7.5, 1.5 mM adenosine triphosphate (ATP), and 10 mM magnesium chloride. The samples were stored at -80 °C.

Bovine submitochondrial particles (SMPs) were prepared from mitochondria as described by Matsuno-Yagi *et al.* (*e.g.*, see Matsuno-Yagi, A.; Hatefi, Y. Studies on the mechanism of oxidative phosphorylation. Catalytic site cooperativity in ATP synthesis. J. Biol. Chem. 1985, 260, 11424-7). In brief, isolated bovine heart mitochondria were sonicated in batches of 15 mL for 1 minute with a digital Branson sonifier (Branson,

Danbury, CT) at 70% maximum output in an ice bath. The sonicated suspension was centrifuged at 16,000 x g for 10 min, and the supernatant was centrifuged at 150,000 x g for 45 min at 4 ºC. The submitochondrial pellet was resuspended in buffer containing 0.25 M Sucrose, 10 mM Tris-acetate, pH 7.5. The protein concentration was determined using the BioRad Protein Assay Kit (BioRad Life Science Research, Hercules CA), and the samples were stored at -80 °C, at a concentration of 20 mg/mL.

Part B – Submitochondrial particle (SMP) catalytic activity and compound inhibition assay

The procedure for determining catalytic activity of submitochondrial particles was adapted from Satoh et al. (e.g., see Satoh T, Miyoshi H, Sakamoto K, Iwamura H. Comparison of the inhibitory action of synthetic capsaicin analogues with various NADH-ubiquinone oxidoreductases. Biochim Biophys Acta. 1996, 1273, 21-30). NADH-DB reductase activity was measured using a stirred cuvette in a spectrophotometer (Hewlett-Packard, Houston TX) at 37 °C, as the rate of NADH oxidation at 340 nm ($\varepsilon = 5.4\ mM^{-1}$ X cm^{-1}) for 120 seconds. The final volume of the reaction was 2.5 mL, containing 50 mM K_2HPO_4 (pH 7.4), 0.4 µM Antimycin A, and 2 mM potassium cyanide. The final SMP concentration was 45 µg/mL. The enzyme reaction was initiated by the addition of 100 µM decyl ubiquinone and 50 µM NADH. Inhibitors at varying concentrations were pre-incubated with the reaction mixture containing SMPs for 4 min prior to initiation of the reaction. The IC_{50} value was determined as the concentration of the inhibitor required for 50% inhibition of the NADH oxidation. The IC_{50} value was calculated using GraphPad Prism Version 4 (GraphPad, San Diego, CA).

Table 1: MC1 inhibition data

Example	*IC_{50} (nM)*	*Example*	*IC_{50} (nM)*
flurpiridaz	<100	38	≤1000
1	>1000	39	<100
3	>1000	40	<100
4	>1000	43	<100
5	>1000	45	<100
6	>1000	47	>1000
7	<100	49	>1000
8	>1000	50	<100
9	<100	51	>1000

Example	IC_{50} (nM)	Example	IC_{50} (nM)
12	≤1000	52	>1000
16	≤1000	54	<100
17	≤1000	55	<100
18	≤1000	60	>4000
19	≤1000	61	≤1000
20	<100	48B	<100
21	≤1000	48C	≤1000
22	<100	53A	>1000
23	≤1000	53B	>1000
25	<100	56C	<100
27	<100	56D	<100
28	≤1000	57B	<100
29	<100	58A	≤1000
31	>1000	58B	≤1000
32	<100	59D	>4000
33	≤1000	62A	>1000
35	≤1000	62B	≤1000
36	≤1000	62C	≤1000
37	<100	62D	>1000

Example 65

Preparation of imaging agents using a custom robotic device

Part A – Preparation of [^{18}F]fluoride

[^{18}F]Fluoride was produced by proton bombardment of [^{18}O]H_2O in a cyclotron; the nuclear chemical transformation is shown below and may be summarized as $^{18}O(p,n)^{18}F$. For purposes of the bombardment, the chemical form of the ^{18}O is $H_2{}^{18}O$. The chemical form of the resulting ^{18}F is fluoride ion.

$$^{18}O + \text{proton} \rightarrow {}^{18}F + \text{neutron}$$

According to established industry procedures, [^{18}O]H_2O (2-3 mL) housed within a tantalum target body using Havar® foil, was bombarded with 11 MeV protons (nominal energy); where the proton threshold energy for the reaction is 2.57 MeV and the energy of maximum cross section is 5 MeV. Target volume, bombardment time and proton energy each may be adjusted to manage the quantity of [^{18}F]fluoride produced.

Part B – Preparation of imaging agents using a custom robotic device

[^{18}F]Fluoride prepared according to Example 65A was applied to a previously activated MP1 anion exchange resin (BioRad) contained within a small volume plastic housing. The loaded cartridge was then placed into an elution loop located within a custom designed robotic radiosynthesis system and introduced when needed using one of the following methods.

Method A: [^{18}F]Fluoride (1 Ci) was transferred from the resin to a glass vessel using an aqueous solution of tetraethylammonium bicarbonate (1.1 – 1.3 molar equivalents). The resulting mixture was then concentrated to dryness at elevated temperature (120 °C) and reduced pressure. Anhydrous acetonitrile was then added to the concentrated solution and all volatiles removed once again using elevated temperature (70 °C) and reduced pressure.

Method B: [^{18}F]Fluoride (1 Ci) was transferred from the resin to a glass vessel using an aqueous solution of potassium bicarbonate (3 molar equivalents). The resulting mixture was then concentrated to dryness at elevated temperature (120 °C) and reduced pressure. A solution of Kryptofix^{TM} (4 molar equivalents) in anhydrous acetonitrile was then added to the concentrated solution and all volatiles removed once again using elevated temperature (70 °C) and reduced pressure.

A solution of the desired precursor (5 – 10 μmol) in anhydrous acetonitrile was then added to the glass reaction vessel in order to solvate both [^{18}F]fluoride and the remaining reaction components. The resulting solution was then transferred to a new glass vessel, heated to 90 °C and maintained 10 min. After cooling to ambient temperature, the solution was diluted with water and directly purified by HPLC using a Waters Xterra C18 column (250 x 10 mm; 10μ) in combination with various mixtures of water/acetonitrile for proper purification; both uv (220 nm) and radiation (NaI) detectors were utilized to determine the optimal peak collection window. The purified product thus obtained was concentrated in vacuo then formulated in saline containing ≤10% ethanol. During routine preparation, ~50 mCi of the fluorinated product was prepared within 75 min.

Table 2: Synthetic parameters using a custom robotic device

Precursor	Example	Base	K_{222}	RCY	RCP
36	65A	Et_4NHCO_3	No	5%	99%
36	65A	$KHCO_3$	Yes	6%	99%
11	65B	Et_4NHCO_3	No	1%	Low
26	65C	$KHCO_3$	Yes	7%	99%
14	65D	$KHCO_3$	Yes	13%	Low

Example 66

Part A – Preparation of imaging agents using the Explora RN chemistry module

[^{18}F]fluoride (1 Ci) produced according to Example 65A was transferred from cyclotron to the synthesis module then filtered through an anion exchange column (QMA, Waters, Inc.) to remove unreacted [^{18}O]H_2O; [^{18}F]fluoride was retained within the cationic resin matrix. The column was then washed with aqueous tetraethylammonium bicarbonate (1 molar equivalent) with transfer to the reaction vessel. The resulting solution was diluted with acetonitrile then concentrated to dryness; 150 mm Hg at 115 °C for 4 min. The mixture of anhydrous [^{18}F]tetraethylammonium fluoride and tetraethylammonium bicarbonate thus obtained was treated with an acetonitrile solution of the required precursor (1 molar equivalent) then warmed to 90 °C and maintained 20 min.

Alternatively, [^{18}F]fluoride (1 Ci) produced according to Example 65A was transferred from cyclotron to the synthesis module then filtered through an anion exchange column (QMA, Waters, Inc.) to remove unreacted [^{18}O]H_2O; [^{18}F]fluoride was retained within the cationic resin matrix. The column was then washed with aqueous potassium carbonate (1 molar equivalent) with transfer to the reaction vessel. The resulting solution was treated with an acetonitrile solution of Kryptofix^{TM} (2 molar equivalents) then concentrated to dryness; 150 mm Hg at 115 °C for 4 min. The mixture of anhydrous [^{18}F]potassium fluoride, potassium carbonate and Kryptofix^{TM} thus obtained was treated with the required precursor (1 molar equivalent; 10-50% dimethyl sulfoxide in acetonitrile) then warmed to 90-125°C and maintained 10 min.

Alternatively, [^{18}F]fluoride (1 Ci) produced according to Example 65A was transferred from cyclotron to the synthesis module then filtered through a previously activated MP1 anion exchange resin (BioRad) to remove unreacted [^{18}O]H_2O; [^{18}F]fluoride was retained within the cationic resin matrix. The loaded cartridge was then placed into an elution loop located within a custom designed robotic radiosynthesis system then washed

with aqueous tetraethylammonium bicarbonate (1 molar equivalent) with transfer to the reaction vessel. The solution was concentrated to dryness at 280 mbar, 95-115 °C, 4 min then treated with an acetonitrile solution of the required precursor (1 molar equivalent), warmed to 90 °C and maintained 10 min.

After cooling the crude reaction mixtures to 35 °C, the resulting solution was diluted with water then directly purified by HPLC on a Waters Xterra MS C18 column (10 μ; 10 x 250 mm) using a water/acetonitrile eluent. The main product peak was collected, diluted with ascorbic acid then formulated in 5% ethanol in ascorbic acid. During routine preparation, ~250 mCi of the fluorinated product was prepared.

Table 3: Synthetic parameters using the Explora RN chemistry module

Precursor	*Example*	*RCY*	*RCP*
10	66A	15%	99%
36	66B	4%[a]	99%
34	66C	13%	99%
15	66D	29%	99%
2	66E	33%	99%
41	66F	35%	99%
46	66G	6%	99%
57A	66H	19%	99%
44	66I	5%	99%
48B	66J	9%	99%
61F	66K	20%	99%
62A	66L	14%[a]	99%
56C	66M	39%	99%

[a]Combination of Kryptofix™ and potassium carbonate was utilized.

Part B – Preparation of imaging agents using the GE TracerLab MX Chemistry Module

Figure 17 depicts a schematic representation of the preferred cassette configuration used during the preparation of imaging agents on the GE TracerLab MX chemistry module.

The product of Example 65A was transferred from cyclotron to the synthesis module then filtered through an anion exchange column to remove unreacted [^{18}O]H_2O; [^{18}F]fluoride was retained within the cationic resin matrix. The column was then washed with tetraethylammonium bicarbonate (28.8 μmol; 0.500 mL of a 57.5 mM solution in water) with transfer to the reaction vessel. The resulting solution was diluted with acetonitrile then

concentrated to dryness. Additional acetonitrile was then added and the drying process repeated several times. The mixture of anhydrous tetraethylammonium fluoride and tetraethylammonium bicarbonate thus obtained was treated with the precursor compound (23.0 μmol; 2.00 mL of a 11.5 mM solution in acetonitrile) then warmed to 90 °C and maintained 10 min. The resulting solution was then diluted with water and directly purified by HPLC on a Waters Xterra MS C18 column using a water/acetonitrile eluent. The main product peak was collected, diluted with ascorbic acid then filtered through a C18 Sep-Pak® cartridge to remove acetonitrile; the fluorinated compound was retained within the C18 resin matrix and the filtrate discarded. The loaded cartridge was successively washed with ascorbic acid, the filtrate discarded, then absolute ethanol, and the filtrate collected. The ethanol concentrate of the imaging agent thus obtained was further diluted with ascorbic acid then automatically delivered to the final product vial through a 0.22 μm sterilizing filter.

2-(*tert*-Butyl)-4-chloro-5-((4-((2-fluoroethoxy)methyl)benzyl)oxy)pyridazin-3(2*H*)-one may be prepared from 2-((4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzyl)oxy)ethyl 4-methylbenzenesulfonate in 52% radiochemical yield using the method described herein. An average decrease in drug product retention of 1.5% was observed using the revised cassette configuration described herein.

Part C – Preparation of imaging agents using the ORA NEPTIS Chemistry Module

Figure 17 depicts a schematic representation of the preferred cassette configuration used during the preparation of imaging agents on the ORA NEPTIS chemistry module.

The product of Example 65A was transferred from cyclotron to the synthesis module then filtered through an anion exchange column to remove unreacted [^{18}O]H_2O; [^{18}F]fluoride was retained within the cationic resin matrix. The column was then washed with tetraethylammonium bicarbonate (28.8 μmol; 0.500 mL of a 57.5 mM solution in water) with transfer to the reaction vessel. The resulting solution was diluted with acetonitrile then concentrated to dryness. Additional acetonitrile was then added and the drying process repeated several times. The mixture of anhydrous tetraethylammonium fluoride and tetraethylammonium bicarbonate thus obtained was treated with the precursor compound (23.0 μmol; 2.00 mL of a 11.5 mM solution in acetonitrile) then warmed to 90 °C and maintained 10 min. The resulting solution was then diluted with water and directly purified by HPLC on a Waters Xterra MS C18 column using a water/acetonitrile eluent. The main product peak was collected, diluted with ascorbic acid then filtered through a C18 Sep-Pak® cartridge to remove acetonitrile; the fluorinated compound was retained within the C18 resin

matrix and the filtrate discarded. The loaded cartridge was successively washed with ascorbic acid, the filtrate discarded, then absolute ethanol, and the filtrate collected. The ethanol concentrate of the imaging agent thus obtained was further diluted with ascorbic acid then automatically delivered to the final product vial through a 0.22 μm sterilizing filter.

2-(*tert*-Butyl)-4-chloro-5-((4-((2-fluoroethoxy)methyl)benzyl)oxy)pyridazin-3(2*H*)-one may be prepared from 2-((4-(((1-(*tert*-butyl)-5-chloro-6-oxo-1,6-dihydropyridazin-4-yl)oxy)methyl)benzyl)oxy)ethyl 4-methylbenzenesulfonate in 48% radiochemical yield using the method described herein.

Example 67

Tissue distribution and imaging in rats

Part A – Tissue distribution

Anesthetized (sodium pentobarbital at 50 mg/kg, ip or isoflurane gas inhalation) Male Sprague Dawley rats (250-350 g) received an iv injection of the imaging agent (~15 μCi) via the tail vein. At 15 or 60 min post injection, the animals were euthanized and the required tissue samples harvested. All samples were then weighed and counted for radioactivity (Wallac Wizard 1480 or Packard Cobra II Autogamma); regional tissue uptake of the imaging agent was thus expressed as a percentage of the total injected dose per gram of tissue (%ID/g).

The generic structure depicted below highlights specific structural features evaluated during distribution experiments. Tables 4 – 6 summarize results from select studies.

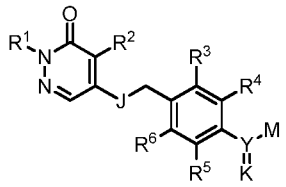


Table 4: Structure correlation table

Example	R^1	R^2	R^3	R^4	R^5	R^6	J	K	M	Y
67A	t-Bu	Cl	H	$CH_2O(CH_2)_2F$	H	H	O	N/A	N/A	H
67B	t-Bu	Cl	H	H	H	H	O	N/A	$(CH_2)_2O(CH_2)_2F$	O
67C	t-Bu	Cl	H	Cl	H	H	O	N/A	$(CH_2)_3F$	O
67D	t-Bu	Cl	H	H	H	H	O	N/A	$(CH_2)_2F$	O
67E	t-Bu	Cl	H	H	H	H	O	D,D	$O(CH_2)_2F$	C
67F	t-Bu	Cl	H	$O(CH_2)_2F$	H	H	O	N/A	N/A	H
67G	t-Bu	Cl	H	H	H	H	O	CH_3,H	$O(CH_2)_2F$	C
67H	i-Pr	Cl	H	H	H	H	O	H,H	$O(CH_2)_2F$	C
67I	t-Bu	CH_3	H	H	H	H	O	H,H	$O(CH_2)_2F$	C
67J	t-Bu	Cl	H	H	H	H	O	O	$O(CH_2)_2F$	C
67K	t-Bu	Cl	H	H	H	H	O	N/A	$C\equiv C(CH_2)_2F$	bond
67L	t-Bu	Cl	H	H	H	H	O	N/A	2-fluoropyrimidin-5-yl	bond
67M	t-Bu	Cl	H	H	H	H	CH_2	H,H	$O(CH_2)_2F$	C
67N	t-Bu	Cl	H	H	H	H	O	t-Bu,t-Bu	F	Si
67O	t-Bu	Cl	H	H	H	H	O	N/A	2-fluoropyridin-3-yl	O

Table 5: Summary of imaging agent distribution at 15 min (%ID/g ± SEM)

Example	Blood	Liver	Heart	Lung	Spleen
67A	0.03±0.01	0.08±0.03	0.65±0.36	0.07±0.01	0.05±0.01
67B	0.49±0.02	2.33±0.09	1.66±0.06	0.49±0.04	0.41±0.01
67C	0.26±0.05	2.67±0.17	4.21±0.29	0.50±0.08	0.37±0.05
67D	1.11	3.61	3.63	1.00	0.37
67E	0.17±0.02	0.66±0.09	4.80±0.27	0.39±0.05	0.36±0.08
67F	0.32±0.05	0.40±0.04	1.92±0.15	0.41±0.03	0.28±0.01
67G	0.50±0.18	0.33±0.10	2.19±0.36	0.46±0.12	0.32±0.11
67H	0.45±0.02	0.46±0.01	1.14±0.09	0.41±0.01	0.34±0.03
67I	0.11±0.02	0.33±0.02	2.34±0.57	0.19±0.03	0.18±0.01
67J	0.50±0.02	0.32±0.01	1.19±0.25	0.39±0.02	0.34±0.01
67K	0.07±0.03	0.99±0.06	2.68±0.35	0.37±0.15	0.31±0.09
67L	0.14±0.01	1.71±0.36	1.19±0.18	0.29±0.03	0.18±0.01
67M	0.53±0.13	0.96±0.10	2.54±0.20	0.97±0.13	0.35±0.05
67N	0.22±0.04	4.91±0.49	0.65±0.09	1.31±0.24	3.47±0.80
67O	0.07±0.03	0.99±0.06	2.68±0.35	0.37±0.15	0.31±0.09
Example	**Pancreas**	**Kidney**	**Brain**	**Femur**	**Muscle**
67A	0.15±0.05	0.38±0.08	0.14±0.05	0.06±0.02	0.09±0.04
67B	N/A	2.25±0.05	0.37±0.02	0.80±0.12	0.19±0.00
67C	N/A	3.04±0.21	0.42±0.01	0.33±0.01	0.24±0.04
67D	N/A	3.81	0.74	0.21	0.14
67E	0.82±0.07	2.61±0.18	0.97±0.11	0.50±0.04	0.77±0.09
67F	0.52±0.04	1.04±0.10	0.50±0.04	0.44±0.04	0.60±0.06
67G	0.41±0.03	0.88±0.05	0.59±0.03	0.40±0.05	0.35±0.04
67H	0.44±0.03	0.78±0.01	0.43±0.05	0.36±0.04	0.38±0.02
67I	0.43±0.10	1.13±0.11	0.49±0.10	0.28±0.04	0.28±0.13
67J	0.23±0.02	0.39±0.01	0.36±0.01	0.28±0.02	0.38±0.04
67K	0.55±0.10	1.35±0.14	0.36±0.04	0.27±0.02	0.28±0.02
67L	0.36±0.06	0.65±0.07	0.30±0.05	0.31±0.01	0.27±0.02
67M	N/A	0.79±0.07	0.55±0.31	0.52±0.19	0.24±0.04
67N	N/A	0.51±0.09	0.03±0.00	0.14±0.02	0.06±0.00
67O	0.55±0.10	1.35±0.14	0.36±0.04	0.27±0.02	0.28±0.02

Table 6: Summary of imaging agent distribution at 60 min (%ID/g ± SEM)

Example	Blood	Liver	Heart	Lung	Spleen
67A	0.11±0.02	0.11±0.02	0.84±0.22	0.11±0.02	0.09±0.02
67B	0.26±0.04	1.34±0.22	1.58±0.13	0.27±0.03	0.20±0.04
67C	0.20±0.07	0.65±0.12	4.54±0.29	0.61±0.32	0.18±0.02
67D	1.00	1.49	4.66	0.96	0.23
67E	0.26±0.03	0.53±0.06	3.61±0.45	0.34±0.03	0.25±0.01
67F	0.48±0.01	0.39±0.04	0.87±0.02	0.44±0.03	0.31±0.01
67G	0.47±0.04	0.32±0.03	0.98±0.16	0.38±0.03	0.28±0.03
67H	0.55±0.02	0.40±0.02	0.55±0.03	0.42±0.01	0.35±0.02
67I	0.16±0.01	0.30±0.01	1.78±0.15	0.19±0.01	0.13±0.00
67J	0.58±0.04	0.35±0.02	0.50±0.03	0.42±0.02	0.37±0.02
67K	0.03±0.00	0.83±0.17	2.46±0.27	0.15±0.03	0.11±0.02
67L	0.10±0.02	2.06±0.27	0.62±0.12	0.21±0.02	0.11±0.02
67M	0.73±0.16	0.43±0.04	0.55±0.06	1.03±0.22	0.26±0.03
67O	0.03±0.00	0.83±0.17	2.46±0.27	0.15±0.03	0.11±0.02
Example	**Pancreas**	**Kidney**	**Brain**	**Femur**	**Muscle**
67A	0.13±0.03	0.23±0.03	0.14±0.03	0.17±0.04	0.18±0.04
67B	N/A	1.17±0.20	0.30±0.02	0.78±0.22	0.15±0.04
67C	N/A	1.77±0.25	0.44±0.03	0.84±0.07	0.26±0.02
67D	N/A	1.71	0.69	0.26	0.18
67E	0.43±0.05	0.98±0.04	0.62±0.04	0.69±0.05	0.69±0.17
67F	0.48±0.01	0.60±0.03	0.38±0.01	0.57±0.04	0.43±0.07
67G	0.26±0.01	0.44±0.02	0.39±0.05	0.58±0.06	0.33±0.01
67H	0.32±0.02	0.49±0.03	0.43±0.02	0.71±0.06	0.31±0.02
67I	0.23±0.02	0.48±0.04	0.36±0.01	0.31±0.02	0.35±0.09
67J	0.23±0.03	0.42±0.02	0.43±0.02	0.40±0.03	0.31±0.02
67K	0.38±0.02	0.83±0.08	0.36±0.03	0.37±0.05	0.39±0.04
67L	0.33±0.08	0.40±0.08	0.22±0.03	0.78±0.15	0.20±0.06
67M	N/A	0.43±0.04	2.33±0.12	0.43±0.03	0.31±0.04
67O	0.38±0.02	0.83±0.08	0.36±0.03	0.37±0.05	0.39±0.04

Part B – PET imaging and data reconstruction

PET imaging was performed in Male Sprague Dawley rats anesthetized as outlined above. The animal was then positioned in a microPET camera (Focus220, CTI Molecular Imaging or Philips MOSAIC HP) and injected with the imaging agent (~1 mCi) via a tail vein catheter. Image acquisition was initiated immediately following injection and was terminated at 60 min. Following acquisition, the images were reconstructed in a matrix of 256 x 256 or 128 x 128 pixels (microPET Manager and ASIPro or PETview, respectively) and decay corrected. Serial tomographic images were thus generated using 5 or 10 min intervals.

Figure 1 shows representative images of [^{18}F]67A in rat.
Figure 2 shows representative images of [^{18}F]67B in rat.
Figure 3 shows representative images of [^{18}F]67C in rat.
Figure 4 shows representative images of [^{18}F]67D in rat.
Figure 5 shows representative images of [^{18}F]67E in rat.
Figure 6 shows representative images of [^{18}F]67F in rat.
Figure 7 shows representative images of [^{18}F]67G in rat.
Figure 8 shows representative images of [^{18}F]67H in rat.
Figure 9 shows representative images of [^{18}F]67I in rat.
Figure 10 shows representative images of [^{18}F]67J in rat.
Figure 11 shows representative images of [^{18}F]67K in rat.
Figure 12 shows representative images of [^{18}F]67L in rat.
Figure 13 shows representative images of [^{18}F]67M in rat.
Figure 14 shows representative images of [^{18}F]67N in rat.
Figure 15 shows representative images of [^{18}F]67O in rat.

Example 68

Metabolic profiling of imaging agents

Part A – Hepatocyte Preparation

Cryopreserved hepatocytes were purchased from Celsis/In Vitro Technologies, Inc. (Baltimore, MD) and stored at -150 °C prior to use. Multiple lots of hepatocytes for human (mixed sexes 5-donor pool), primate (male, rhesus monkey), dog (male, beagle),

rabbit (male, New Zealand white) and rat (male, Sprague-Dawley) were used. On the day of the study, hepatocytes in cryopreserved vials were vented to release any liquid N_2 then placed into a 37 °C water bath for 75-90 seconds to thaw. The hepatocytes were transferred into pre-warmed KHB and centrifuged for 5 min at 50 x *g*. The supernatant was discarded and the hepatocytes re-suspended in KHB at a concentration of $1x10^6$ cells/mL. Cell viability was confirmed by Trypan blue exclusion.

Part B – Hepatocyte Incubation

Test compounds were incubated in hepatocytes ($1x10^6$ cells/mL; 0.5 mL) were incubated for 0, 15, 30, 60 or 180 min at 37°C/5% CO_2 then transferred directly into acetonitrile (1.0 mL), vortexed for 30 s and centrifuged at 2500 x *g* for 20 min. The supernatant was then transferred to a new centrifuge tube, acetonitrile evaporated under a stream of nitrogen in a heating block at 37°C and, following re-constitution in water, assayed by HPLC with radiodetection.

Part C – HPLC Analysis

Extracted samples and standards were analyzed on an Agilent 1100 HPLC (Agilent Technologies, Burlington, MA) using a Phenomenex Luna C18 column (5 µ; 4.6 x 150 mm), maintained at ambient temperature (25 °C), and a flow rate of 1.0 mL/min. Mobile phase A contained 0.1% formic acid in water, and mobile phase B contained 0.1% formic acid in acetonitrile. A linear gradient from 5 to 90% B over 15 min was used for elution. A 5 min post-time of 5% B was used to re-equilibrate the column. Radioactive products were recorded using in-line γ- or β-flow detectors (INUS, Tampa, FL).

Imaging Agent	*% Parent Remaining*
35	30
25	71
9	73
16	20
1	20
45	19
40	34
57B	31
43	63
48C	95

Imaging Agent	% Parent Remaining
61G	6
62B	98

It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

While several embodiments of the present invention have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the present invention. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the teachings of the present invention is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, the invention may be practiced otherwise than as specifically described and claimed. The present invention is directed to each individual feature, system, article, material, kit, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the scope of the present invention.

The indefinite articles "a" and "an," as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to mean "at least one."

The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified unless clearly indicated to the contrary. Thus, as a non-limiting example, a reference to "A and/or B," when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A without B (optionally including elements other than B); in another embodiment, to B without A (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); *etc.*

As used herein in the specification and in the claims, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of" or "exactly one of," or, when used in the claims, "consisting of," will refer to the inclusion of exactly one element or a list of elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e. "one or the other but not both") when preceded by terms of exclusivity, such as "either," "one of," "only one of," or "exactly one of." "Consisting essentially of," when used in the claims, shall have its ordinary meaning as used in the field of patent law.

As used herein in the specification and in the claims, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus,

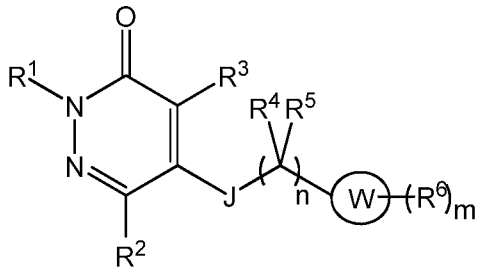
as a non-limiting example, "at least one of A and B" (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); *etc.*

In the claims, as well as in the specification above, all transitional phrases such as "comprising," "including," "carrying," "having," "containing," "involving," "holding," and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases "consisting of" and "consisting essentially of" shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

What is claimed:

Claims

1. A compound comprising the structure:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–NO_2$, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

W is heteroaryl, naphthyl, heterocyclyl, or aryl;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally

substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and an imaging moiety;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

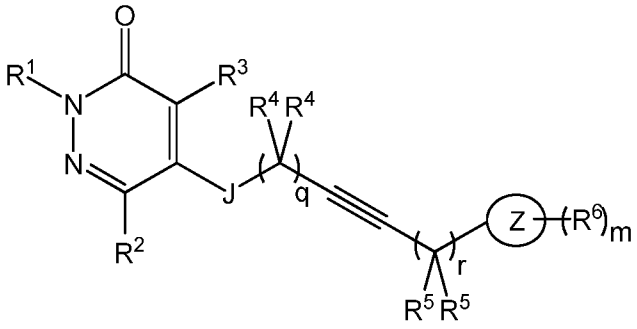
each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

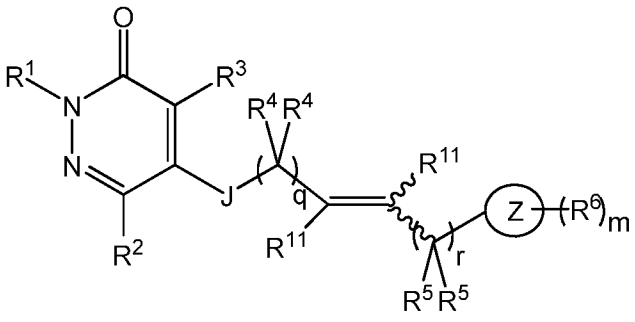
provided that at least one imaging moiety is present in the compound; and

provided that when W is aryl, a) R^3 is not halo, alkyl or haloalkyl, or b) at least one R^6 is selected from the group consisting of alkynyl optionally substituted, alkenyl optionally substituted, alkyl substituted with –CN, alkyl substituted with $-C(=O)OR^8$, alkyl substituted with $-C(=O)R^8$, alkyl substituted with $-N(R^7)_2$, –CN, $-NO_2$, $-N(R^7)_2$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)R^8$, $-C(=O)N(R^7)_2$, and $-N(R^7)C(=O)R^8$.

2. A compound comprising the structure:



(V) or



(VI),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–NO_2$, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

each R^4, R^5, and R^{11} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of

R^4 or any two of R^5 are joined together to form a ring;

q, and r are each independently 0, 1, 2, or 3;

Z is selected from the group consisting of aryl, heteroaryl, heterocyclyl, and a bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and an imaging moiety;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

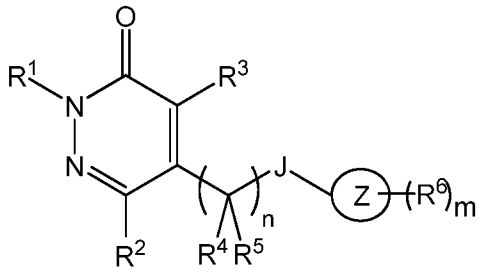
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound.

3. A compound comprising the structure:



(VII)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and an imaging moiety;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, $–NO_2$, haloalkyl, and an imaging moiety;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and an imaging moiety;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)_2$, $N(R^7)C(=O)$, and $–CH_2O$;

each R^4 and R^5 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, and an imaging moiety, or optionally any two of R^4 or any two of R^5 are joined together to form a ring;

n is 1, 2, or 3;

Z is selected from the group consisting of aryl, heteroaryl, heterocyclyl, and a bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl

optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and an imaging moiety;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

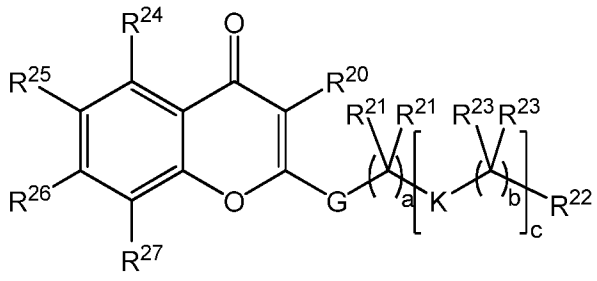
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and an imaging moiety; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety,

provided that at least one imaging moiety is present in the compound.

4. A compound comprising the formula:



(IX)

or a pharmaceutically acceptable salt thereof, wherein:

R^{20} is selected from the group consisting of hydrogen, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, and $–NO_2$;

each R^{21} and R^{23} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally any two R^{21} or any two R^{23} may be joined together to form a ring;

R^{22} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, $-OR^{28}$, $-Si(R^9)_3$, $-B(R^{9'})_3$, and an imaging moiety;

R^{24}, R^{25}, R^{26}, and R^{27} are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, and an imaging moiety;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring; and

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and an imaging moiety;

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety;

R^{28} is selected from the group consisting of hydrogen, alkyl optionally substituted, and heteroalkyl optionally substituted;

G is O, S, or NR^{28};

a is 0, 1, 2, 3, or 4;

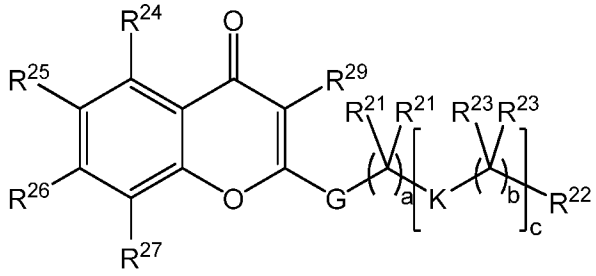
each K is independently arylene, heteroarylene, alkenylene, or alkynylene, each optionally substituted;

each b is independently 0, 1, 2, 3, or 4; and

c is 1 or 2,

provided at least one imaging moiety is present in the compound.

5. A compound comprising the formula:



(X)

or a pharmaceutically acceptable salt thereof, wherein:

each R^{21} and R^{23} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally any two R^{21} or any two R^{23} may be joined together to form a ring;

R^{22} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, $–OR^{28}$, $–Si(R^{9})_3$, $–B(R^{9'})_3$, and an imaging moiety;

R^{24}, R^{25}, R^{26}, and R^{27} are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–NO_2$, –OH, $–C(=O)R^{8}$, $–C(=O)OR^{8}$, $–OC(=O)R^{8}$, $–C(=O)N(R^{7})_2$, $–N(R^{7})C(=O)R^{8}$, –CN, and an imaging moiety;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and an imaging moiety, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and an imaging moiety;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and an imaging moiety;

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and an imaging moiety;

R^{28} is selected from the group consisting of hydrogen, alkyl optionally substituted, and heteroalkyl optionally substituted;

R^{29} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, optionally substituted alkoxy, optionally substituted alkoxyalkyl, halo, haloalkyl, –CN, $–NO_2$, and an imaging moiety;

G is O, S, or NR^{28};

a is 0, 1, 2, 3, or 4;

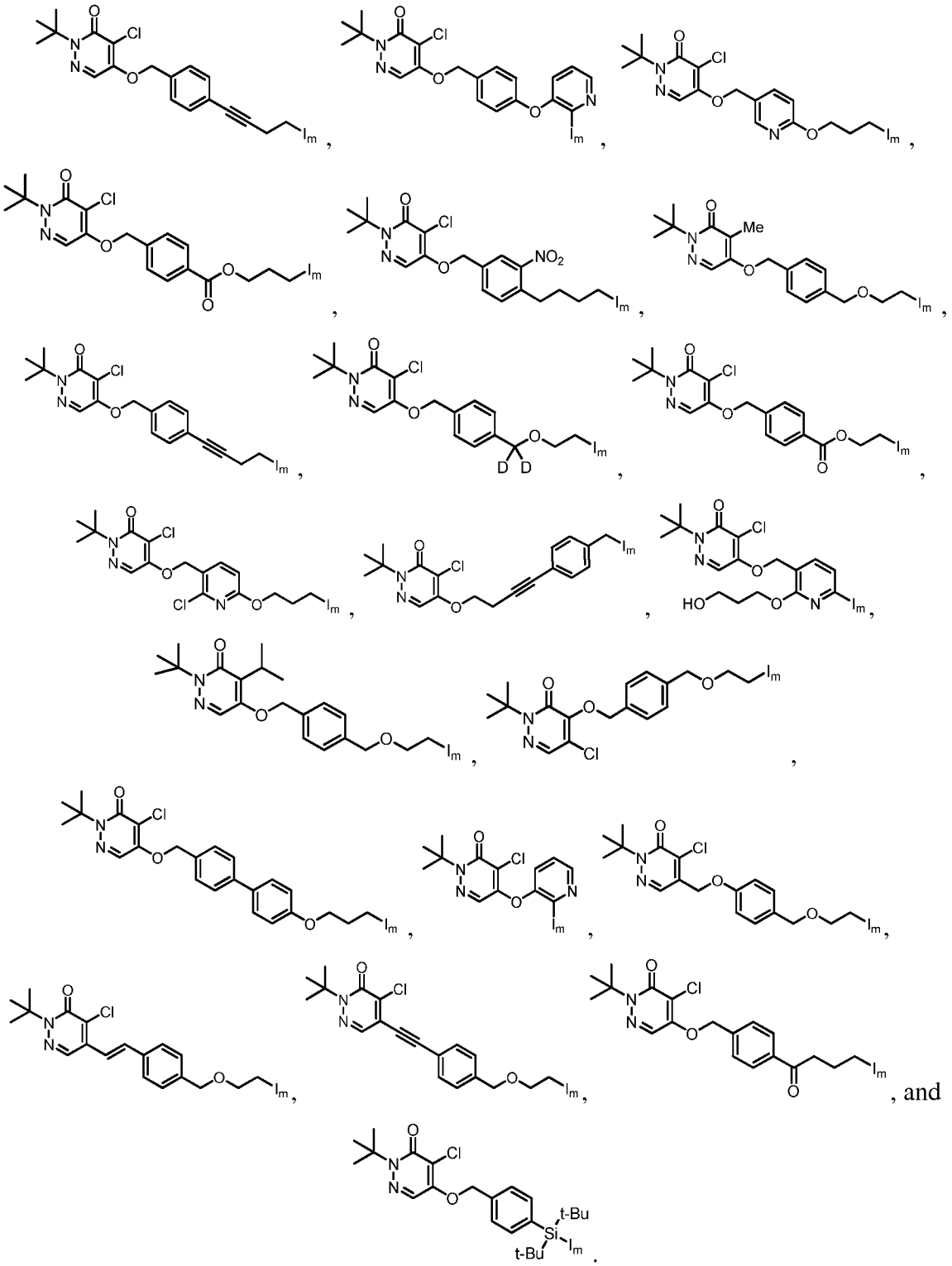
each K is independently arylene, heteroarylene, alkenylene, or alkynylene, each optionally substituted, provided at least one K is alkenylene, or alkynylene;

each b is independently 0, 1, 2, 3, or 4; and

c is 1 or 2,

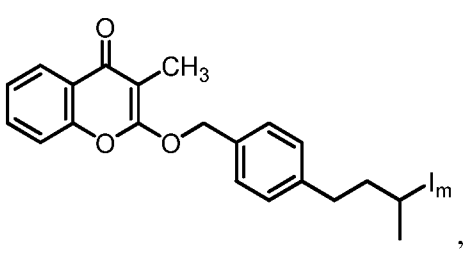
provided at least one imaging moiety is present in the compound.

6. A compound, wherein the compound is selected from the group consisting of:



or a pharmaceutically acceptable salt thereof, wherein I_m is an imaging moiety.

7. A compound, wherein the compound is selected from the group consisting of:



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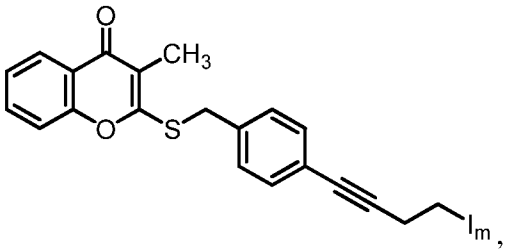

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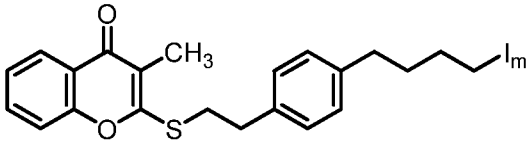

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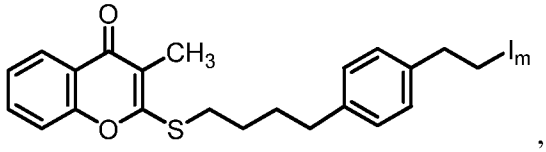

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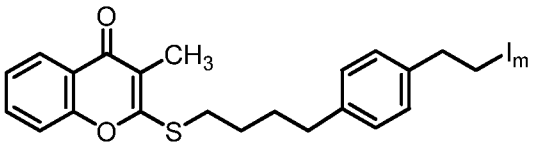
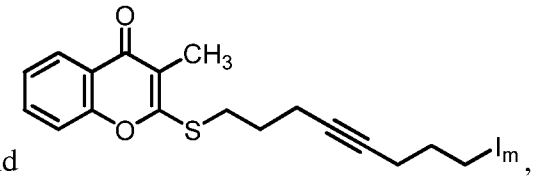


, and



,

or a pharmaceutically acceptable salt thereof, wherein I_m is an imaging moiety.

8. A pharmaceutical composition comprising a compound or a salt thereof of any preceding claim, and optionally a pharmaceutically acceptable excipient.

9. A sterile aqueous solution comprising a compound or a salt thereof of any preceding claim.

10. Use of a compound or a salt thereof of any preceding claim as an imaging agent.

11. Use of a compound or a salt thereof of any preceding claim in myocardial perfusion imaging.

12. Use of a compound or salt thereof of any preceding claim in the manufacture of a medicament for detecting, imaging or monitoring myocardial perfusion.

13. A method of imaging a portion of a subject, comprising:

administering to the subject a compound or a salt thereof of any preceding claim, or a composition of claim 8, or a sterile aqueous solution of claim 9; and

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

14. A method of imaging a portion of a subject, comprising:

administering to a subject a compound or a salt thereof of any preceding claim or a salt thereof, or a pharmaceutical composition of claim 8, or a sterile aqueous solution of claim 9;

detecting radiation emitted by the compound; and

forming an image therefrom.

15. A diagnostic kit comprising one or more vials containing a precursor to a compound or a salt thereof of any preceding claim; and optionally other components.

16. A method of imaging myocardial perfusion, comprising:

administering to a patient a compound or a salt thereof of any preceding claim, or a pharmaceutical composition of claim 8, or a sterile aqueous solution of claim 9; and

scanning the patient using diagnostic imaging.

17. A method of detecting myocardial perfusion, comprising:

administering to a patient a compound or a salt thereof of any preceding claim, or a pharmaceutical composition of claim 8, or a sterile aqueous solution of claim 9; and

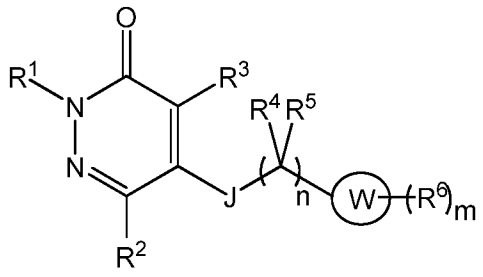
scanning the patient using diagnostic imaging.

18. A method of monitoring myocardial perfusion, comprising:

administering to a patient a compound or a salt thereof of any preceding claim, or a pharmaceutical composition of claim 8, or a sterile aqueous solution of claim 9; and

scanning the patient using diagnostic imaging.

19. A compound comprising the structure:



(XI)

or a salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and a leaving group;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–NO_2$, and a leaving group;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and a leaving group;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, and a leaving group, or optionally any two of R^4 and R^5 are joined together to form a ring;

n is 0, 1, 2, or 3;

W is heteroaryl, naphthyl, heterocyclyl or aryl;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl

optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-N(R^7)_2$, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, $-Si(R^9)_3$, $-B(R^{9'})_3$, $-OR^8$, and a leaving group;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

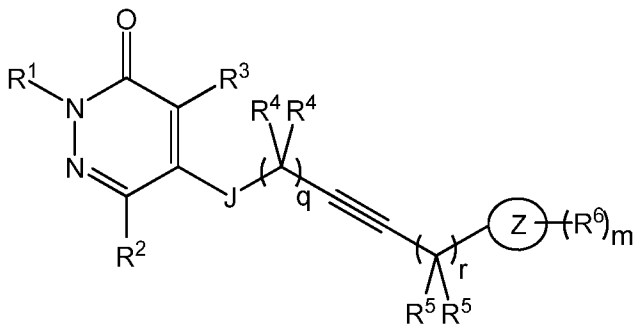
each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and a leaving group; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group,

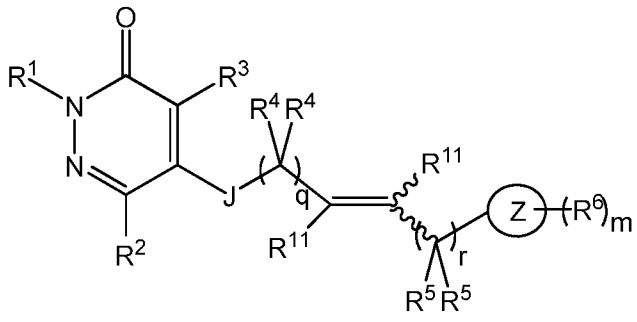
provided that at least one leaving group is present in the compound; and

provided that when W is aryl, a) R^3 is not halo, alkyl or haloalkyl, or b) at least one R^6 is selected from the group consisting of alkynyl optionally substituted, alkenyl optionally substituted, alkyl substituted with $-CN$, alkyl substituted with $-C(=O)OR^8$, alkyl substituted with $-C(=O)R^8$, alkyl substituted with $-N(R^7)_2$, $-CN$, $-NO_2$, $-N(R^7)_2$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)R^8$, $-C(=O)N(R^7)_2$, and $-N(R^7)C(=O)R^8$.

20. A compound comprising the structure:



(XV) or



(XVI),

or a salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and a leaving group;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–NO_2$, and a leaving group;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and a leaving group;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)$, $N(R^7)C(=O)$, CH_2O, and a bond;

each R^4, R^5, and R^{11} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, and a leaving group, or optionally any two of R^4 or any two of R^5 are joined together to form a ring;

q, and r are each independently 0, 1, 2, or 3;

Z is selected from the group consisting of aryl, heteroaryl, heterocyclyl, and a bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–N(R^7)_2$, $–NO_2$,

–OH, –C(=O)R^8, –C(=O)OR^8, –OC(=O)R^8, –C(=O)N(R^7)$_2$, –N(R^7)C(=O)R^8, –CN, –Si(R^9)$_3$, –B($R^{9'}$)$_3$, –OR^8, and a leaving group;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring;

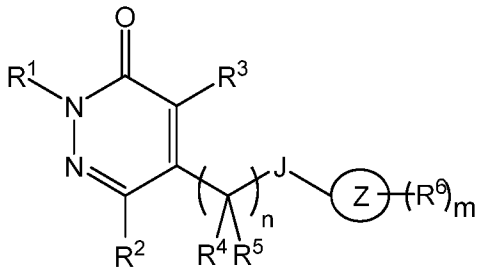
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and a leaving group; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group,

provided that at least one leaving group is present in the compound.

21. A compound comprising the structure:



(XVII)

or a salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, and a leaving group;

R^2 is selected from the group consisting of hydrogen, alkyl optionally substituted,

heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, $–NO_2$, haloalkyl, and a leaving group;

R^3 is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, $–NO_2$, and a leaving group;

J is selected from the group consisting of $N(R^7)$, S, O, C(=O), C(=O)O, OC(=O), $C(=O)N(R^7)_2$, $N(R^7)C(=O)$, and $–CH_2O$;

each R^4 and R^5 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, and a leaving group, or optionally any two of R^4 or any two of R^5 are joined together to form a ring;

n is 1, 2, or 3;

Z is selected from the group consisting of aryl, heteroaryl, heterocyclyl, and a bond;

each R^6 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–N(R^7)_2$, $–NO_2$, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, $–Si(R^9)_3$, $–B(R^{9'})_3$, $–OR^8$, and a leaving group;

m is 0, 1, 2, 3, 4, 5, 6, or 7;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring; and

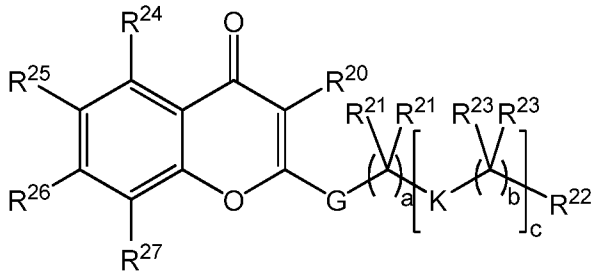
each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and a leaving group; and

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group,

provided that at least one leaving group is present in the compound.

22. A compound comprising the formula:



(XIX)

or a salt thereof, wherein:

R^{20} is selected from the group consisting of hydrogen, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –CN, and $–NO_2$;

each R^{21} and R^{23} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, and a leaving group, or optionally any two R^{21} or any two R^{23} may be joined together to form a ring;

R^{22} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, $–OR^{28}$, $–Si(R^9)_3$, $–B(R^{9'})_3$, and a leaving group;

R^{24}, R^{25}, R^{26}, and R^{27} are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $–NO_2$, –OH, $–C(=O)R^8$, $–C(=O)OR^8$, $–OC(=O)R^8$, $–C(=O)N(R^7)_2$, $–N(R^7)C(=O)R^8$, –CN, and a leaving group;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and a leaving group;

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group;

R^{28} is selected from the group consisting of hydrogen, alkyl optionally substituted, and heteroalkyl optionally substituted;

G is O, S, or NR^{28};

a is 0, 1, 2, 3, or 4;

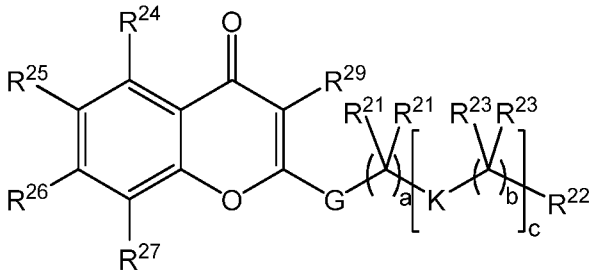
each K is independently arylene, heteroarylene, alkenylene, or alkynylene, each optionally substituted;

each b is independently 0, 1, 2, 3, or 4; and

c is 1 or 2,

provided at least one leaving group is present in the compound.

23. A compound comprising the formula:



(XX)

or a salt thereof, wherein:

each R^{21} and R^{23} is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, and a leaving group, or optionally any two R^{21} or any two R^{23} may be joined together to form a ring;

R^{22} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, halo, haloalkyl, $-OR^{28}$, $-Si(R^9)_3$, $-B(R^{9'})_3$, and a leaving group;

R^{24}, R^{25}, R^{26}, and R^{27} are each independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, aryloxy optionally substituted, heteroaryloxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, $-NO_2$, $-OH$, $-C(=O)R^8$, $-C(=O)OR^8$, $-OC(=O)R^8$, $-C(=O)N(R^7)_2$, $-N(R^7)C(=O)R^8$, $-CN$, and a leaving group;

each R^7 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, alkenyl optionally substituted, alkynyl optionally substituted, heteroalkyl optionally substituted, alkoxy optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, and a leaving group, or optionally, any two R^7 may be joined together to form a ring;

each R^8 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, alkoxyalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, haloalkyl, and a leaving group;

each R^9 is independently selected from the group consisting of hydrogen, alkyl optionally substituted, aryl optionally substituted, haloalkyl, halogen, and a leaving group;

each $R^{9'}$ is independently selected from the group consisting of halo, alkyl optionally substituted , aryl optionally substituted, and a leaving group;

R^{28} is selected from the group consisting of hydrogen, alkyl optionally substituted, and heteroalkyl optionally substituted;

R^{29} is selected from the group consisting of hydrogen, alkyl optionally substituted, heteroalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, halo, haloalkyl, –C, $–NO_2$, and a leaving group;

G is O, S, or NR^{28};

a is 0, 1, 2, 3, or 4;

each K is independently arylene, heteroarylene, alkenylene, or alkynylene, each optionally substituted, provided at least one K is alkenylene, or alkynylene;

each b is independently 0, 1, 2, 3, or 4; and

c is 1 or 2,

provided at least one leaving group is present in the compound.

24. A diagnostic kit comprising one or more vials containing a compound of any one of claims 19-23 or a salt thereof; and optionally other components.

25. A method for forming an imaging agent, comprising reacting a compound of any one of claims 19-23 or a salt thereof with an ^{18}F-containing species to produce a imaging agent comprising ^{18}F.

26. A cassette for the preparation of an imaging agent comprising the components arranged as shown in Figure 17.

27. An apparatus for synthesizing an imaging agent comprising a linear arrangement of a plurality of stopcock manifolds arranged in the order:

1) luer connections (2) to gas inlet and [18O]H2O recovery;
2) anion exchange cartridge – column eluting solution;
3) spike connection for acetonitrile;
4) empty syringe;
5) reservoir with solution of imaging agent precursor;
6) reaction vessel;
7) outlet to HPLC;

8) syringe with solution of a stabilizing agent;
9) inlet from HPLC;
10) ethanol reservoir;
11) syringe with solution of a stabilizing agent;
12) syringe with water;
13) final product vial;
14) empty syringe; and
15) reaction vessel and exhaust.

28. An apparatus for synthesizing an imaging agent comprising a linear arrangement of a plurality of stopcock manifolds arranged in the order:

1) luer connections (2) to gas inlet and [18O]H2O recovery;
2) anion exchange cartridge – column eluting solution;
3) reservoir with solution of imaging agent precursor;
4) empty syringe;
5) spike connection for acetonitrile;
6) reaction vessel;
7) outlet to HPLC;
8) syringe with solution of a stabilizing agent;
9) inlet from HPLC;
10) ethanol reservoir;
11) syringe with solution of a stabilizing agent;
12) syringe with water;
13) final product vial;
14) empty syringe; and
15) reaction vessel and exhaust.

29. An apparatus for synthesizing an imaging agent comprising a linear arrangement of a plurality of stopcock manifolds arranged in the order:

1) luer connections (2) to gas inlet and [18O]H2O recovery;
2) anion exchange cartridge – column eluting solution;

3) reservoir with solution of imaging agent precursor;
4) empty syringe;
5) spike connection for acetonitrile;
6) reaction vessel;
7) outlet to HPLC;
8) syringe with solution of a stabilizing agent;
9) inlet from HPLC;
10) ethanol reservoir;
11) final product vial;
12) syringe with water;
13) syringe with solution of a stabilizing agent
14) empty syringe; and
15) reaction vessel and exhaust.

30. An apparatus for synthesizing an imaging agent comprising a linear arrangement of a plurality of stopcock manifolds arranged in the order:

1) luer connections (2) to gas inlet and [18O]H2O recovery;
2) anion exchange cartridge – column eluting solution;
3) spike connection for acetonitrile;
4) empty syringe;
5) reservoir with solution of imaging agent precursor;
6) reaction vessel;
7) outlet to HPLC;
8) syringe with solution of a stabilizing agent;
9) inlet from HPLC;
10) ethanol reservoir;
11) final product vial;
12) syringe with water;
13) syringe with solution of a stabilizing agent;
14) empty syringe; and
15) reaction vessel and exhaust.

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AS FILED BY APPLICANT

Figure 1

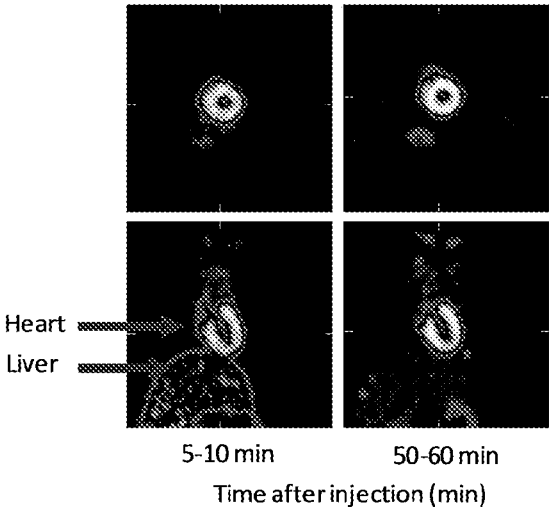


Figure 2

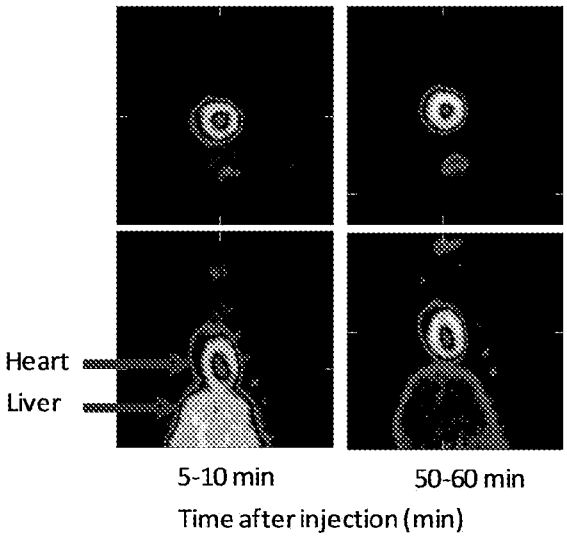


Figure 3

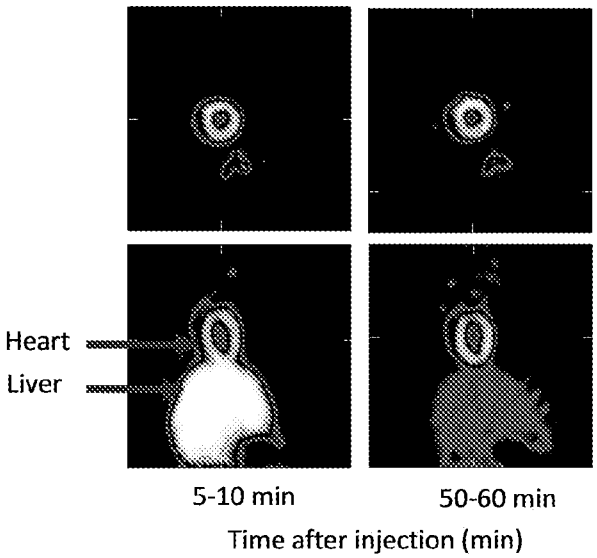


Figure 4

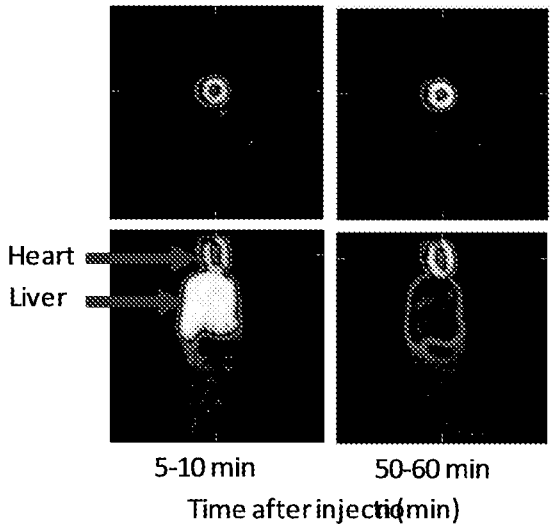
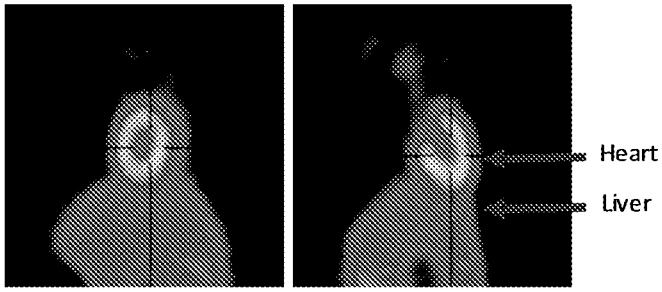


Figure 5



60-65 min after injection

Figure 6

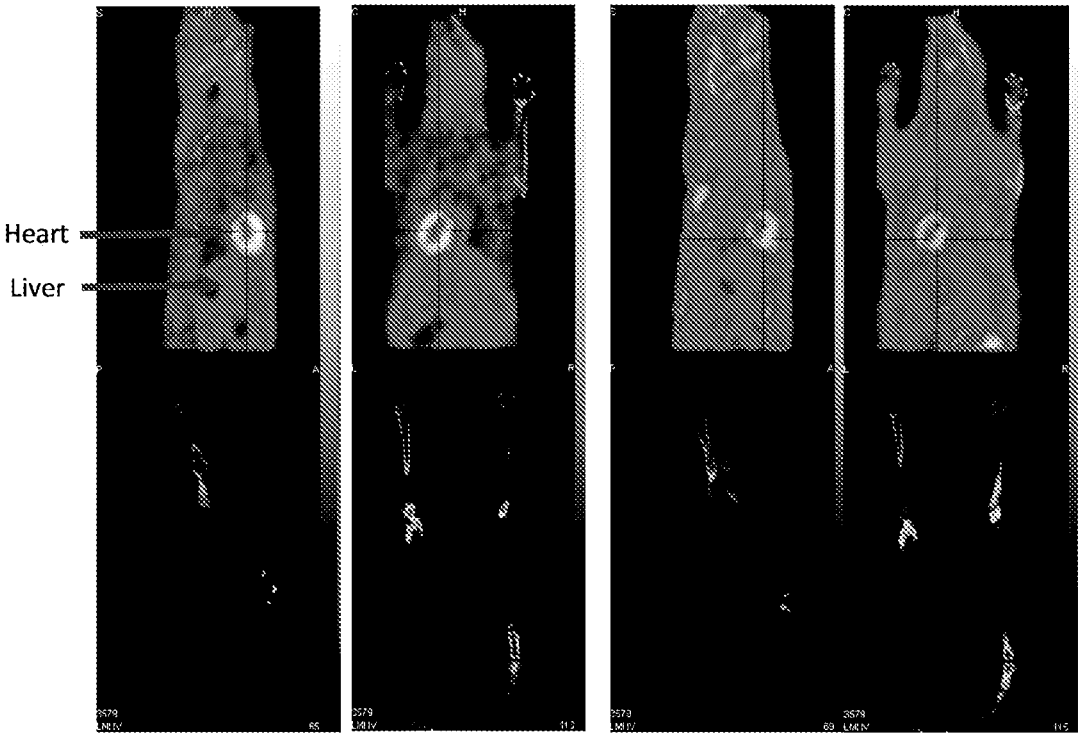


Figure 7

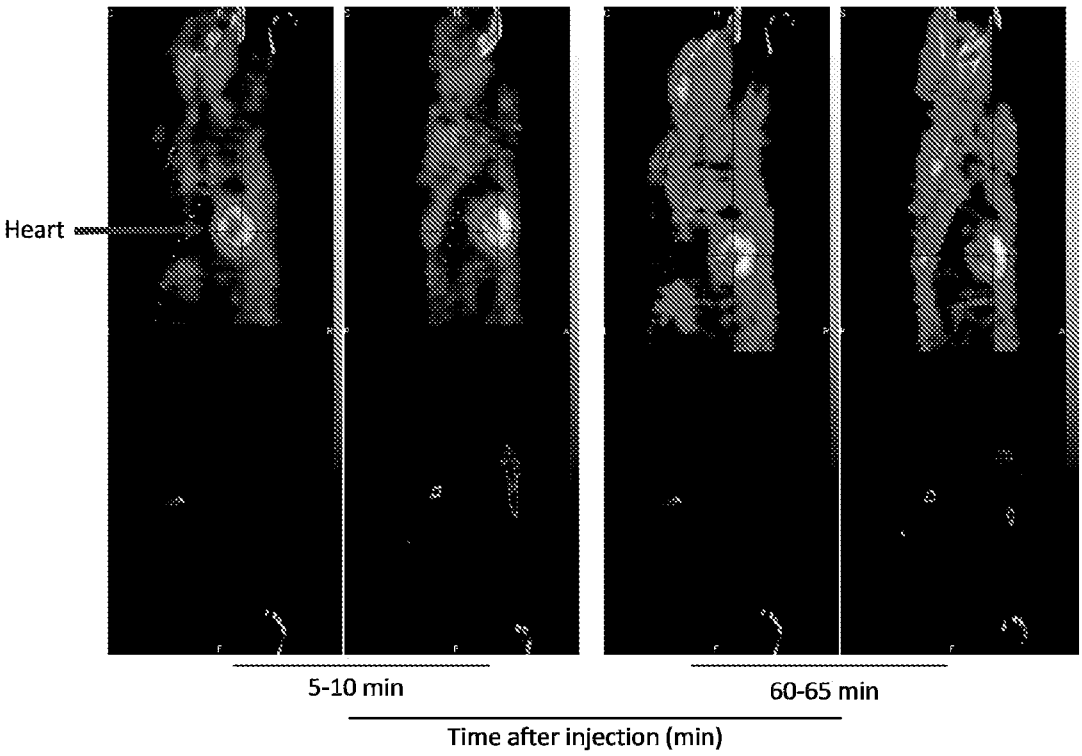


Figure 8

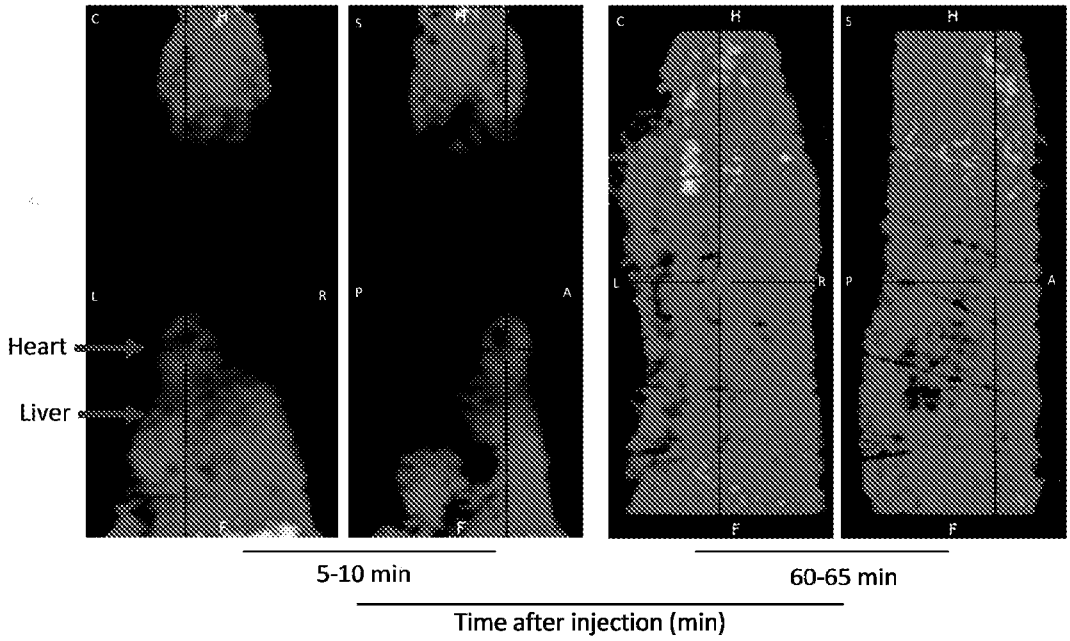


Figure 9

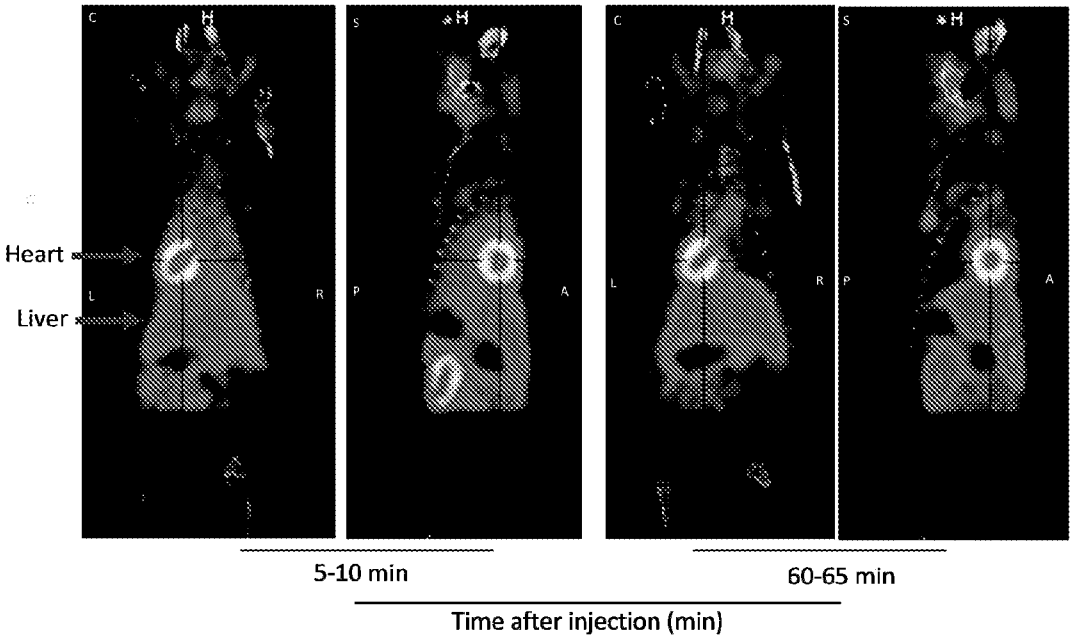


Figure 10

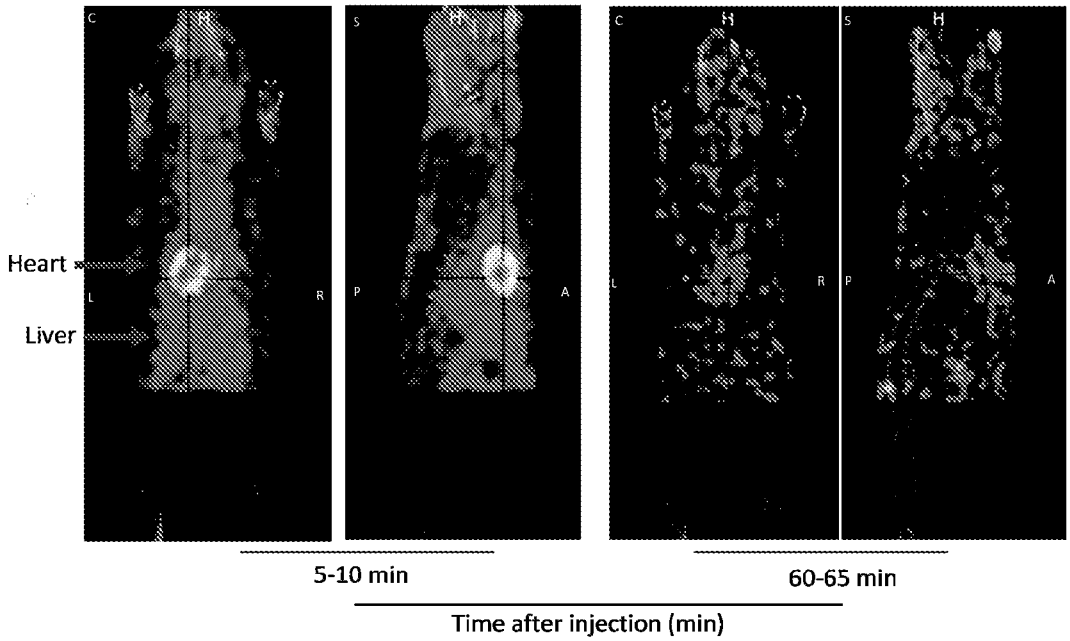


Figure 11

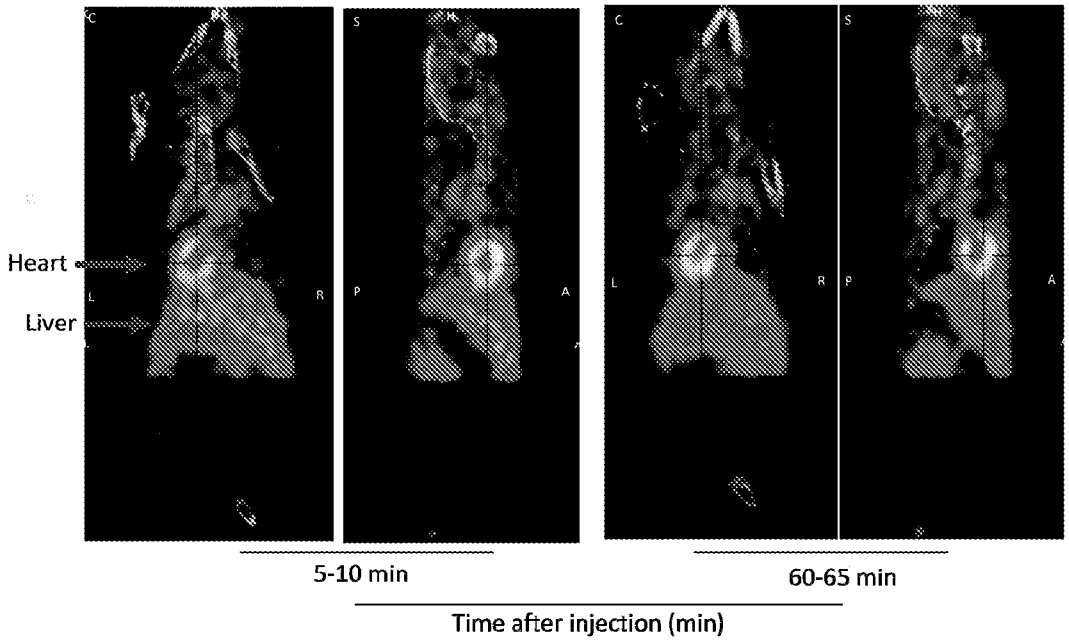


Figure 12

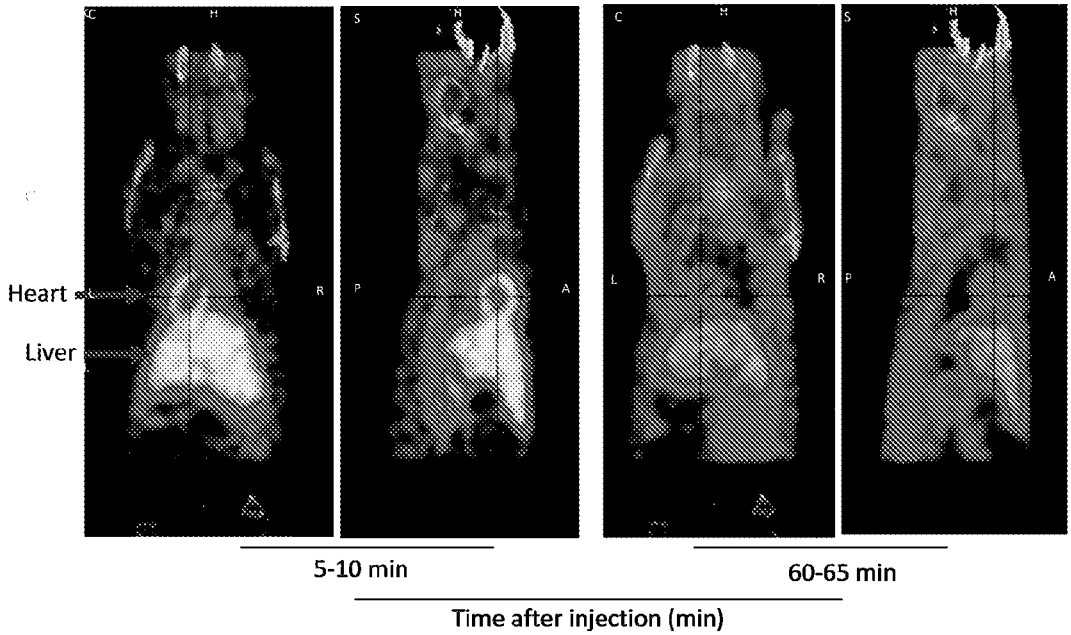


Figure 13

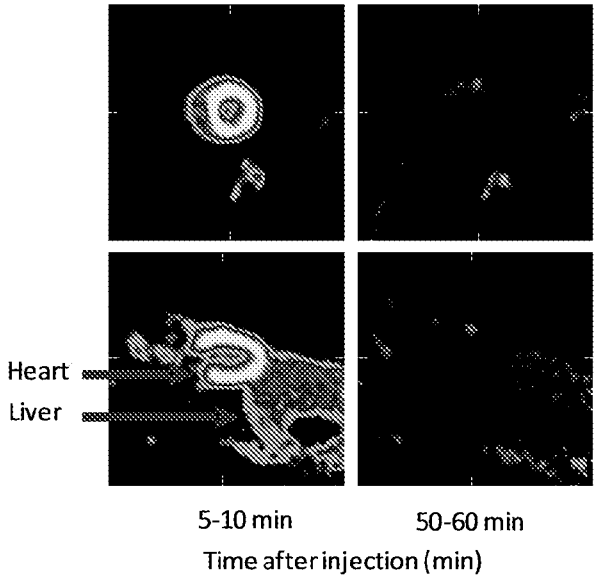


Figure 14

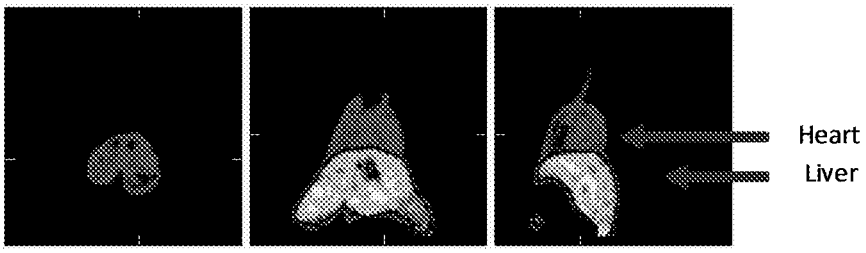


Figure 15

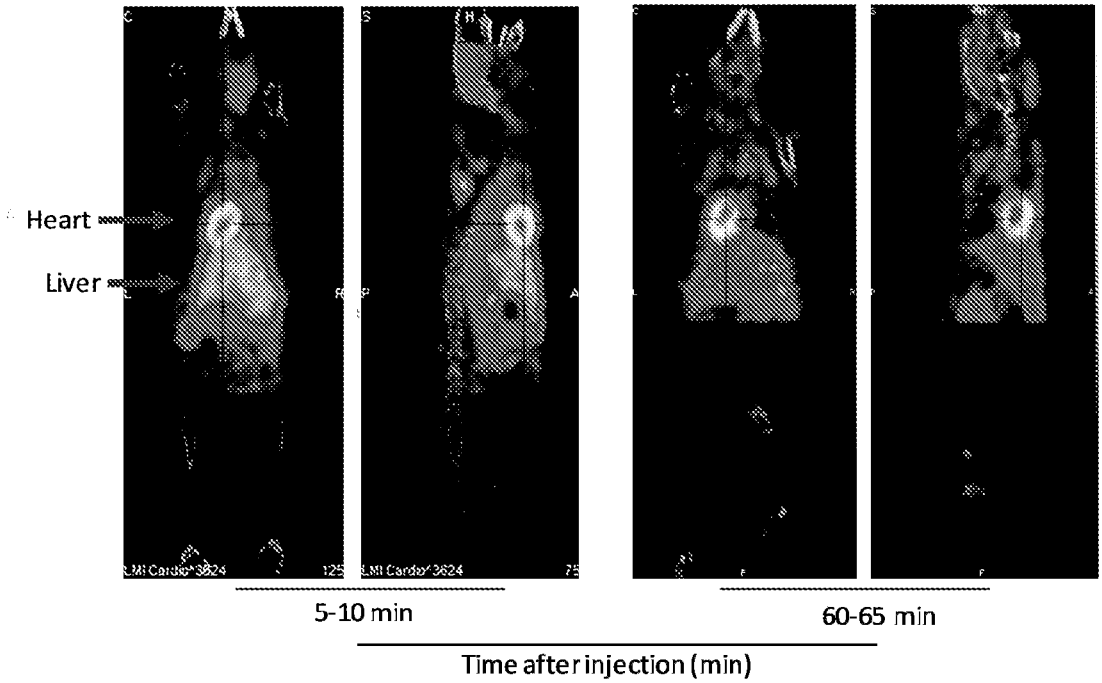


Figure 16

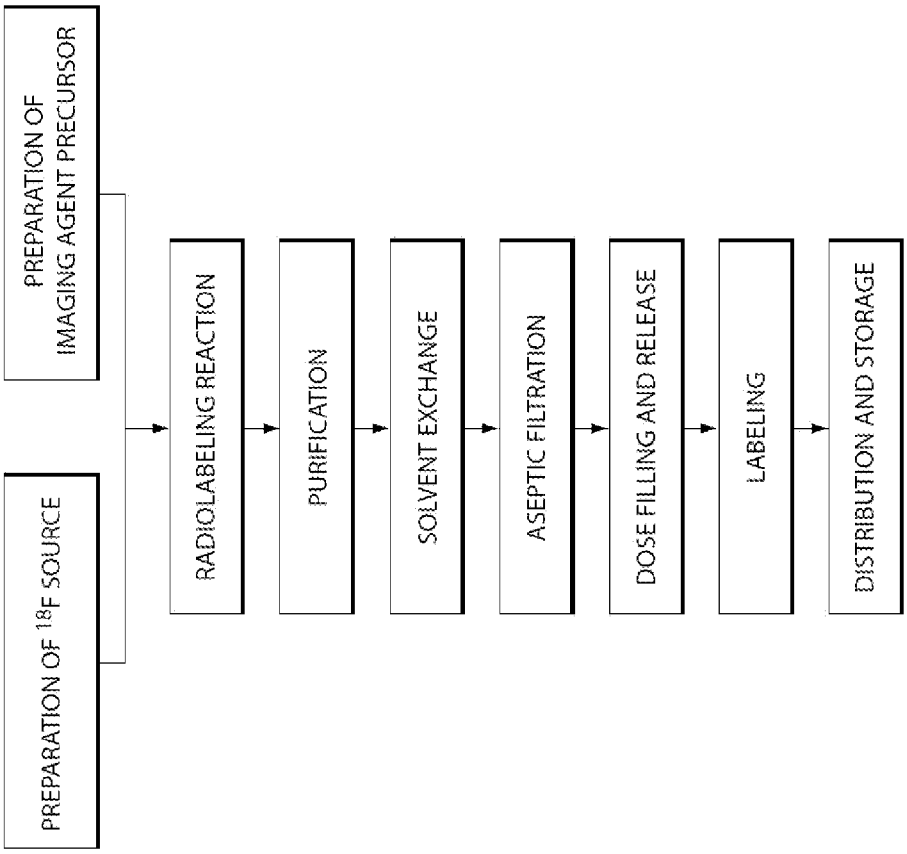
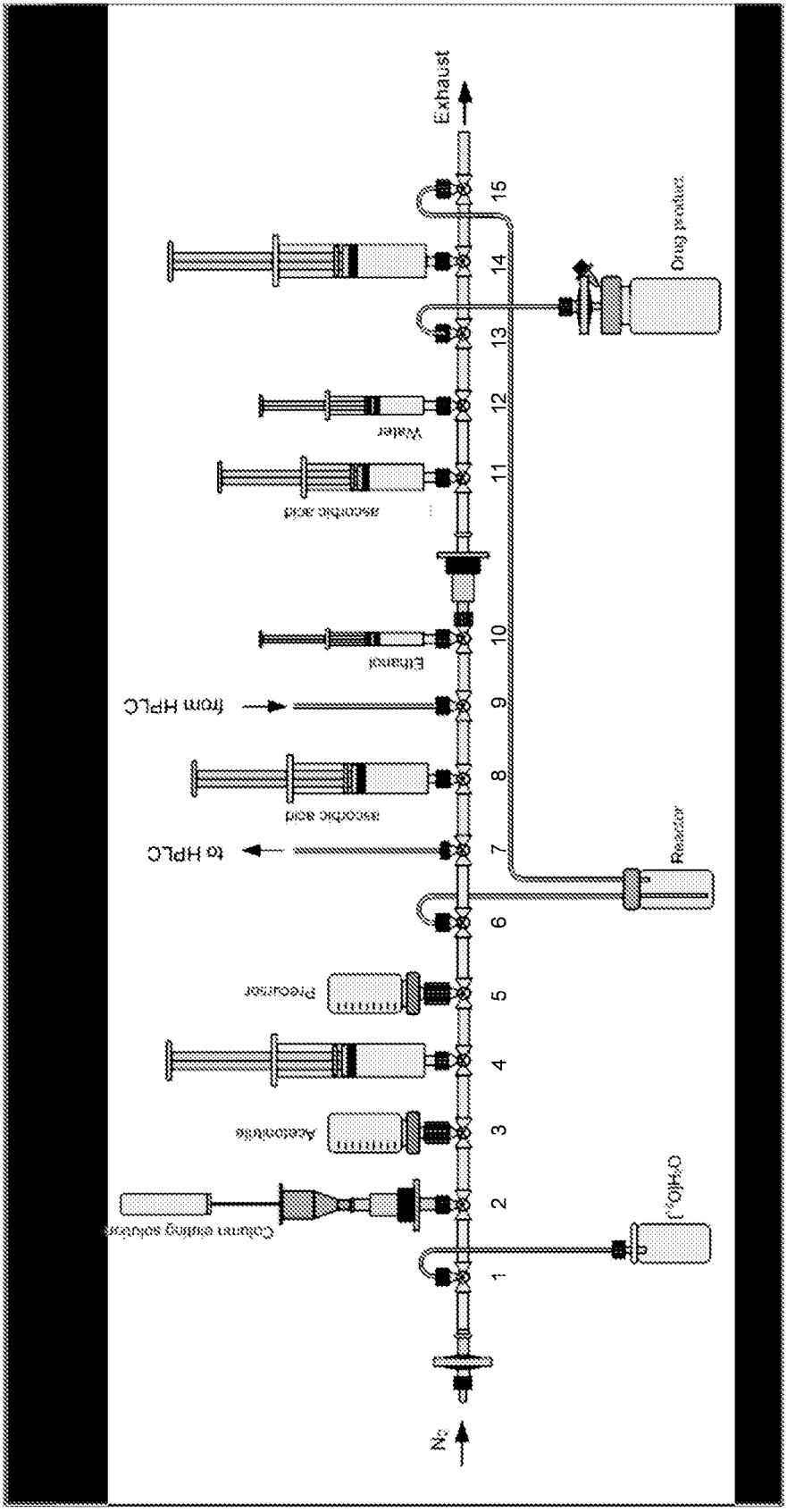

PREPARATION OF ^{18}F SOURCE
PREPARATION OF IMAGING AGENT PRECURSOR
RADIOLABELING REACTION
PURIFICATION
SOLVENT EXCHANGE
ASEPTIC FILTRATION
DOSE FILLING AND RELEASE
LABELING
DISTRIBUTION AND STORAGE

Figure 17


Exhaust
Drug product
Water
ascorbic acid
Ethanol
from HPLC
ascorbic acid
to HPLC
Reactor
Precursor
Acetonitrile
Column eluting solvent
N2

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 February 2014 (13.02.2014)

WIPO | PCT

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C07D 311/42 (2006.01) *A61K 49/00* (2006.01)

(21) International Application Number:
PCT/US2013/054268

(22) International Filing Date:
9 August 2013 (09.08.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/682,185 10 August 2012 (10.08.2012) US
61/794,277 15 March 2013 (15.03.2013) US

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(72) Inventors: **CESATI, Richard, R.**; 63 Nashua Road, Pepperell, MA 01463 (US). **RADEKE, Heike, S.**; 15 Seaver Farm Lane, South Grafton, MA 01560 (US). **PANDEY, Suresh, K.**; 708 Wellman Avenue, North Chelmsford, MA 01863 (US). **PUROHIT, Ajay**; 33 Country Village Lane, Sudbury, MA 01776-1638 (US). **ROBINSON, Simon, P.**; 22 Kettell Plain Road, Stow, MA 01775 (US).

(74) Agent: **BAKER, C., Hunter**; Wolf, Greenfield & Sacks, P.C, 600 Atlantic Avenue, Boston, MA 02210-2206 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

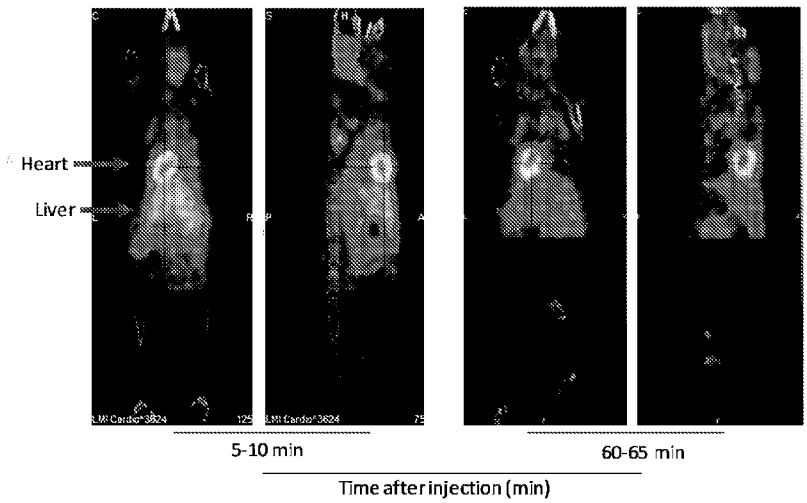
— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
30 May 2014

(54) Title: COMPOSITIONS, METHODS, AND SYSTEMS FOR THE SYNTHESIS AND USE OF IMAGING AGENTS

Figure 15



(57) Abstract: The present invention provides compounds with imaging moieties for imaging a subject. The present invention also relates to systems, compositions, and methods for the synthesis and use of imaging agents, or precursors thereof. An imaging agent precursor may be converted to an imaging agent using the methods described herein. In some cases, a composition or plurality of imaging agents is enriched in 18 F. In some cases, an imaging agent may be used to image an area of interest in a subject, including, but not limited to, the heart, cardiovascular system, cardiac vessels, brain, and other organs.

WO 2014/026079 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/054268

A. CLASSIFICATION OF SUBJECT MATTER

C07D 237/16(2006.01)i, C07D 311/42(2006.01)i, A61K 49/06(2006.01)i, A61K 49/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 237/16; C07D 451/02; A61K 51/00; A61B 5/055; C07D 255/02; C07D 277/84; A61K 51/02; C07D 225/00; C07D 311/42; A61K 49/06; A61K 49/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: imaging agent

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2007-0258887 A1 (TAMAGNAN, G. D. et al.) 08 November 2007 See the whole document.	1-12,15,19-25,27-30
A	WO 95-11901 A1 (THE GENERAL HOSPITAL CORPORATION et al.) 04 May 1995 See the whole document.	1-12,15,19-25,27-30
A	US 05417959 A (WALLACE, R. A.) 23 May 1995 See the whole document.	1-12,15,19-25,27-30
A	US 2010-0322855 A1 (CHONG, H. -S.) 23 December 2010 See the whole document.	1-12,15,19-25,27-30

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 March 2014 (31.03.2014)	**01 April 2014 (01.04.2014)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
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Republic of Korea
Facsimile No. +82-42-472-7140

Authorized officer
YOO, Jun Seok
Telephone No. +82-42-481-5782

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/054268

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13-14,16-18
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 13-14 and 16-18 are directed to treatment methods of the human body by therapy, as well as diagnostic methods, and thus relate to a subject matter which this International Searching Authority is not required to search under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT.

2. ☒ Claims Nos.: 26
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The claim relys on reference to drawing instead of definite structure expressly stated in the claim.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Class I: The compound of formulae I, XI, and its use etc.(claims 1, 6(partial), 8-12(partial), 15(partial), 19, 24-30(partial))

Class II: The compound of formulae V, VI, XV, XVI, and its use etc.(claims 2, 6(partial), 8-12(partial), 15(partial), 20, 24-30
(partial))

Class III: The compound of formulae VII, XVII, and its use etc.(claims 3, 6(partial), 8-12(partial), 15(partial), 21, 24-30
(partial))

Class IV: The compound of formulae IX, X, XIX, XX, and its use etc.(claims 4-5, 7, 8-12(partial), 15(partial), 22-23, 24-30
(partial))

1. ☒ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☒ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2013/054268

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(19)中华人民共和国国家知识产权局

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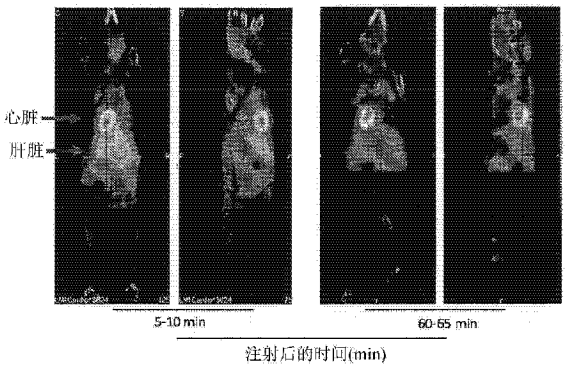
(54)发明名称

用于合成和使用造影剂的组合物、方法以及系统

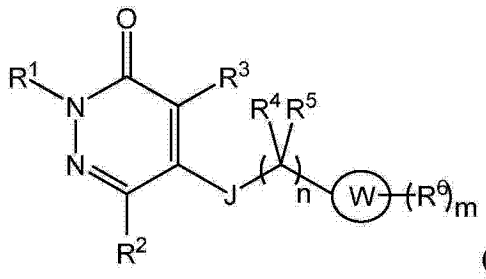
(57)摘要

本发明提供用于对个体进行造影的具有造影部分的化合物。本发明还涉及用于合成和使用造影剂或其前驱体的系统、组合物以及方法。造影剂前驱体可使用本文所述的方法转化成造影剂。在一些情况下，组合物或多种造影剂富集 ^{18}F。在一些情况下，造影剂可用于对个体的相关区域进行造影，所述相关区域包括（但不限于）心脏、心血管系统、心血管、脑以及其它器官。



CN 104718193 A

1. 一种化合物，其包含以下结构：



(I)

或其医药学上可接受的盐，其中：

R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及造影部分；

R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及造影部分；

J选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O以及键；

R^4和R^5各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地R^4和R^5中的任何两者相连以形成环；

n为0、1、2或3；

W为杂芳基、萘基、杂环基或芳基；

每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、-C(=O)R^8、-C(=O)OR^8、-OC(=O)R^8、-C(=O)$N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

m为0、1、2、3、4、5、6或7；

每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个R^7可相连以形成环；

每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

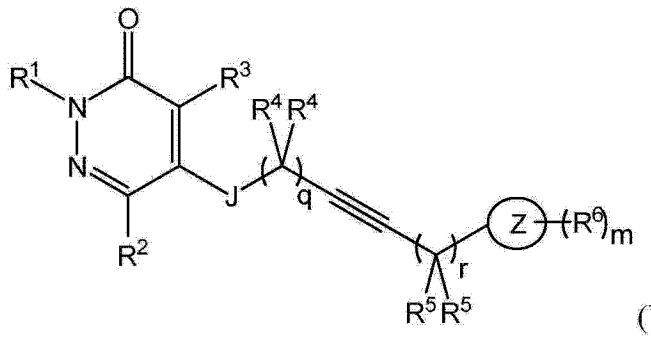
每个R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及造影部分；且

每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

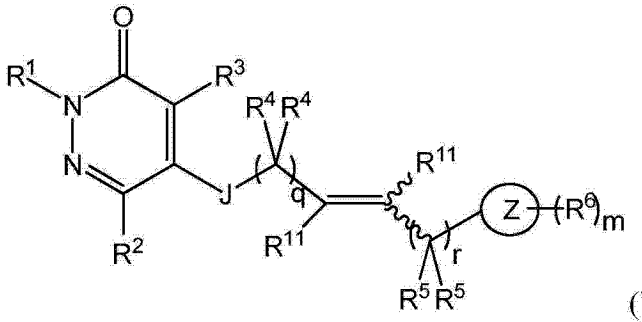
其限制条件为在所述化合物中存在至少一个造影部分；且

其限制条件为当 W 为芳基时，a) R^3 不为卤基、烷基或卤烷基，或 b) 至少一个 R^6 选自由以下各项组成的群组：任选地经取代的炔基、任选地经取代的烯基、经 -CN 取代的烷基、经 $-C(=O)OR^8$ 取代的烷基、经 $-C(=O)R^8$ 取代的烷基、经 $-N(R^7)_2$ 取代的烷基、-CN、$-NO_2$、$-N(R^7)_2$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)R^8$、$-C(=O)N(R^7)_2$ 以及 $-N(R^7)C(=O)R^8$。

2. 一种化合物，其包含以下结构：



(V)或



(VI)，

或其医药学上可接受的盐，其中：

R^1 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

R^2 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$ 以及造影部分；

R^3 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$ 以及造影部分；

J 选自由以下各项组成的群组：$N(R^7)$、S、O、$C(=O)$、$C(=O)O$、$OC(=O)$、$C(=O)N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及键；

每个 R^4、R^5 和 R^{11} 独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地任何两个 R^4 或任何两个 R^5 相连以形成环；

q 和 r 各自独立地为 0、1、2 或 3；

Z 选自由以下各项组成的群组：芳基、杂芳基、杂环基以及键；

每个 R^6 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$ 以及造影部分；

m 为 0、1、2、3、4、5、6 或 7；

每个 R^7 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7 可相连以形成环；

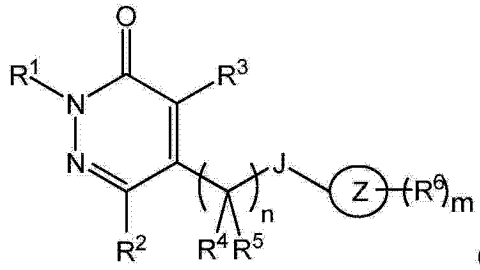
每个 R^8 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

每个 R^9 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及造影部分；且

每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

其限制条件为在所述化合物中存在至少一个造影部分。

3. 一种化合物，其包含以下结构：



(VII)

或其医药学上可接受的盐，其中：

R^1 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

R^2 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、$-NO_2$、卤烷基以及造影部分；

R^3 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$ 以及造影部分；

J 选自由以下各项组成的群组：$N(R^7)$、S、O、$C(=O)$、$C(=O)O$、$OC(=O)$、$C(=O)N(R^7)_2$、$N(R^7)C(=O)$ 以及 $-CH_2O$；

每个 R^4和 R^5独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地任何两个 R^4或任何两个 R^5相连以形成环；

n 为 1、2 或 3；

Z 选自由以下各项组成的群组：芳基、杂芳基、杂环基以及键；

每个 R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

m 为 0、1、2、3、4、5、6 或 7；

每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7可相连以形成环；

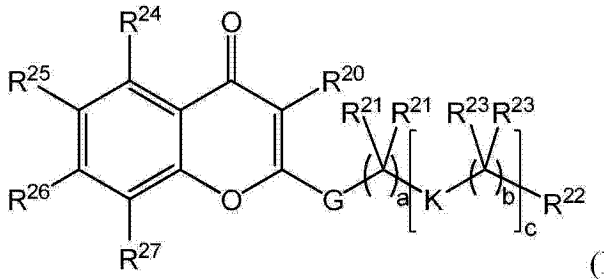
每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

每个 R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及造影部分；且

每个 $R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

其限制条件为在所述化合物中存在至少一个造影部分。

4. 一种化合物，其包含下式：



(IX)

或其医药学上可接受的盐，其中：

R^{20}选自由以下各项组成的群组：氢、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN 以及 $-NO_2$；

每个 R^{21}和 R^{23}独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、卤基、卤烷基以及造影部分，或任选地任何两个 R^{21}或任何两个 R^{23}可相连以形成环；

R^{22}选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、卤基、卤烷基、$-OR^{28}$、$-Si(R^9)_3$、$-B(R^{9'})_3$以及造影部分；

R^{24}、R^{25}、R^{26}和 R^{27}各自独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN 以及造影部分；

每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7可相连以形成环；且

每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

每个 R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及造影部分；

每个 $R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

R^{28}选自由以下各项组成的群组：氢、任选地经取代的烷基和任选地经取代的杂烷基；

G 为 O、S 或 NR^{28}；

a 为 0、1、2、3 或 4；

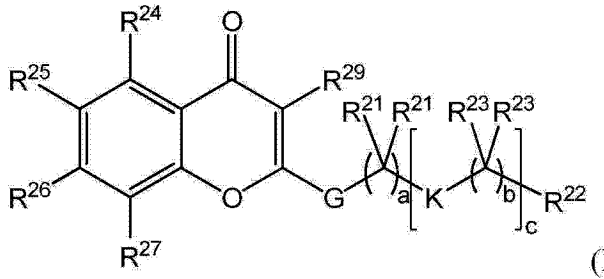
每个 K 独立地为各自任选地经取代的亚芳基、亚杂芳基、亚烯基或亚炔基；

每个 b 独立地为 0、1、2、3 或 4；且

c 为 1 或 2，

其限制条件为在所述化合物中存在至少一个造影部分。

5. 一种化合物，其包含下式：



(X)

或其医药学上可接受的盐，其中：

每个 R^{21}和 R^{23}独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、卤基、卤烷基以及造影部分，或任选地任何两个 R^{21}或任何两个 R^{23}可相连以形成环；

R^{22}选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、卤基、卤烷基、$-OR^{28}$、$-Si(R^9)_3$、$-B(R^{9'})_3$以及造影部分；

R^{24}、R^{25}、R^{26}和 R^{27}各自独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选

地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN 以及造影部分；

每个 R^7 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7 可相连以形成环；

每个 R^8 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

每个 R^9 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及造影部分；

每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

R^{28} 选自由以下各项组成的群组：氢、任选地经取代的烷基和任选地经取代的杂烷基；

R^{29} 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的芳基、任选地经取代的杂芳基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、卤基、卤烷基、-CN、$-NO_2$ 以及造影部分；

G 为 O、S 或 NR^{28}；

a 为 0、1、2、3 或 4；

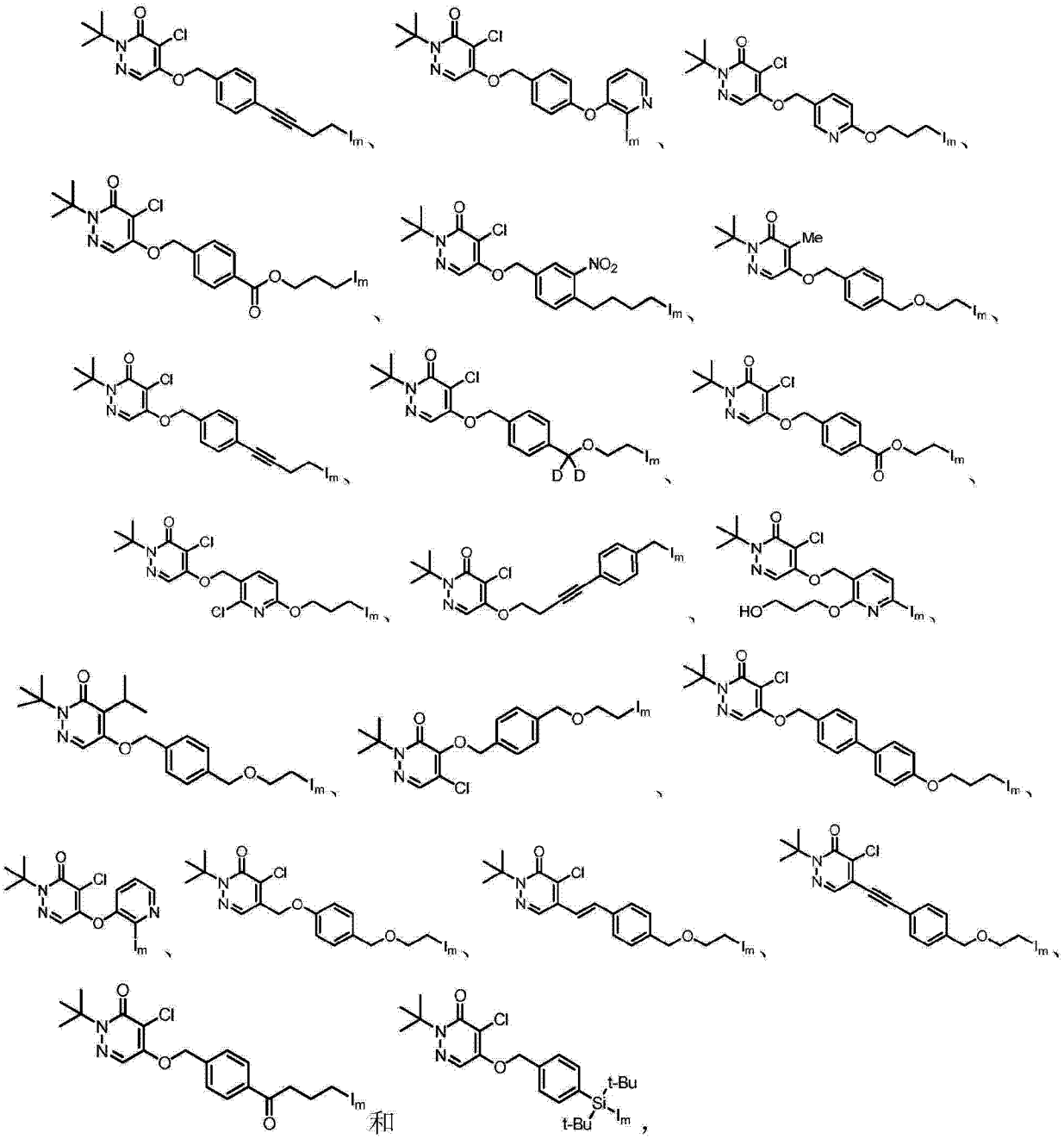
每个 K 独立地为各自任选地经取代的亚芳基、亚杂芳基、亚烯基或亚炔基，其限制条件为至少一个 K 为亚烯基或亚炔基；

每个 b 独立地为 0、1、2、3 或 4；且

c 为 1 或 2，

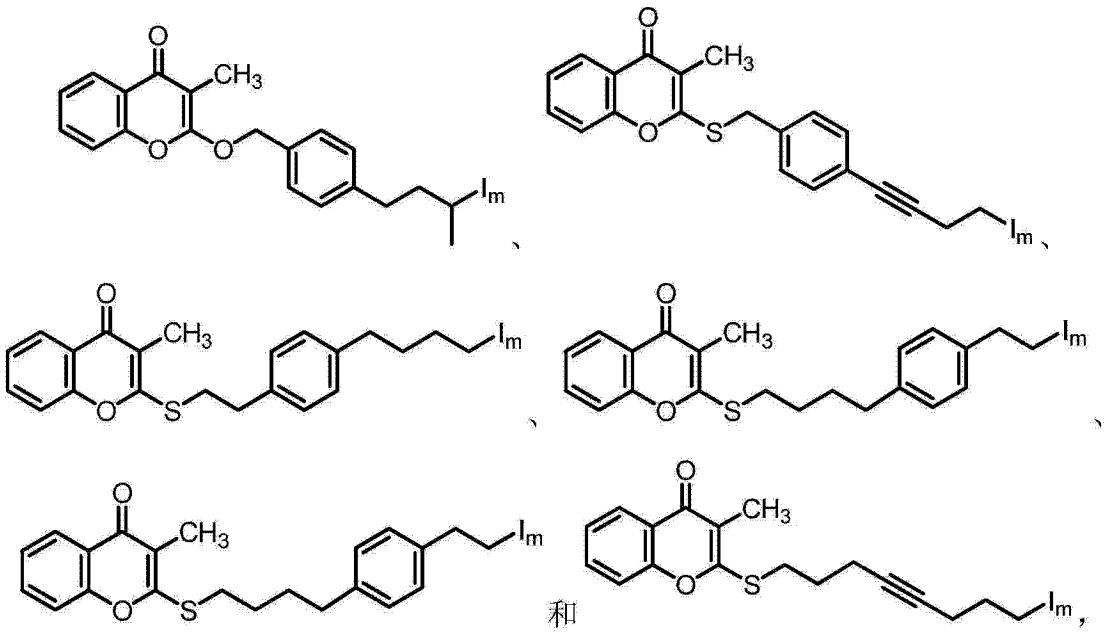
其限制条件为在所述化合物中存在至少一个造影部分。

6. 一种化合物，其中所述化合物选自由以下各项组成的群组：



或其医药学上可接受的盐，其中 I_m 为造影部分。

7. 一种化合物，其中所述化合物选自由以下各项组成的群组：



或其医药学上可接受的盐，其中 I_m 为造影部分。

8. 一种医药组合物，其包含根据任一前述权利要求所述的化合物或其盐，和任选的医药学上可接受的赋形剂。

9. 一种无菌水溶液，其包含根据任一前述权利要求所述的化合物或其盐。

10. 一种根据任一前述权利要求所述的化合物或其盐的用途，其用作造影剂。

11. 一种根据任一前述权利要求所述的化合物或其盐的用途，其用于心肌灌注造影。

12. 一种根据任一前述权利要求所述的化合物或其盐的用途，其用于制造供检测、造影或监控心肌灌注用的药剂。

13. 一种对个体的一部分进行造影的方法，其包含：

向所述个体投予根据任一前述权利要求所述的化合物或其盐或根据权利要求 8 所述的组合物或根据权利要求 9 所述的无菌水溶液；且

撷取所述个体的一部分的至少一个图像。

14. 一种对个体的一部分进行造影的方法，其包含：

向个体投予根据任一前述权利要求所述的化合物或其盐或根据权利要求 8 所述的医药组合物或根据权利要求 9 所述的无菌水溶液；

检测由所述化合物所放出的辐射；且

自其形成图像。

15. 一种诊断试剂盒，其包含一或多个含有根据任一前述权利要求所述的化合物或其盐的前驱体和任选的其它组分的小瓶。

16. 一种对心肌灌注进行造影的方法，其包含：

向患者投予根据任一前述权利要求所述的化合物或其盐或根据权利要求 8 所述的医药组合物或根据权利要求 9 所述的无菌水溶液；且

使用诊断造影扫描所述患者。

17. 一种检测心肌灌注的方法，其包含：

向患者投予根据任一前述权利要求所述的化合物或其盐或根据权利要求 8 所述的医

药组合物或根据权利要求 9 所述的无菌水溶液；且

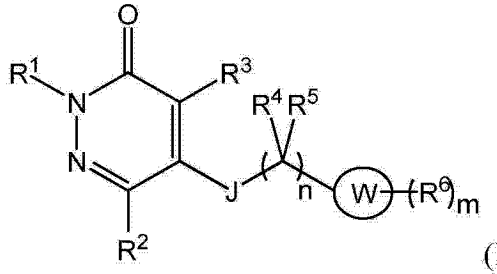
使用诊断造影扫描所述患者。

18. 一种监控心肌灌注的方法，其包含：

向患者投予根据任一前述权利要求所述的化合物或其盐或根据权利要求 8 所述的医药组合物或根据权利要求 9 所述的无菌水溶液；且

使用诊断造影扫描所述患者。

19. 一种化合物，其包含以下结构：



(XI)

或其盐；其中

R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及离去基；

R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及离去基；

R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及离去基；

J 选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)$C(=O)、CH_2O 以及键；

R^4和 R^5各自独立地选自由氢、任选地经取代的烷基以及离去基组成的群组，或任选地 R^4和 R^5中的任何两者相连以形成环；

n 为 0、1、2 或 3；

W 为杂芳基、萘基、杂环基或芳基；

每个 R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及离去基；

m 为 0、1、2、3、4、5、6 或 7；

每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，

或任选地任何两个 R^7 可相连以形成环；

每个 R^8 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

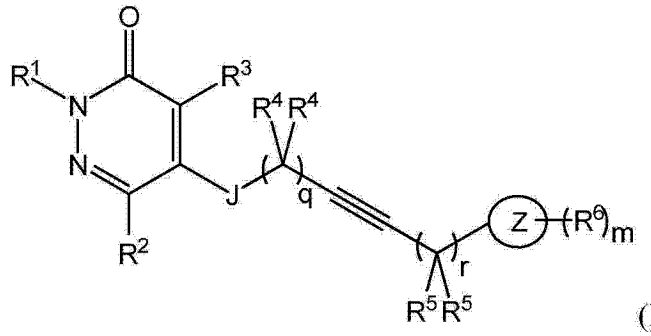
每个 R^9 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及离去基；且

每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基，

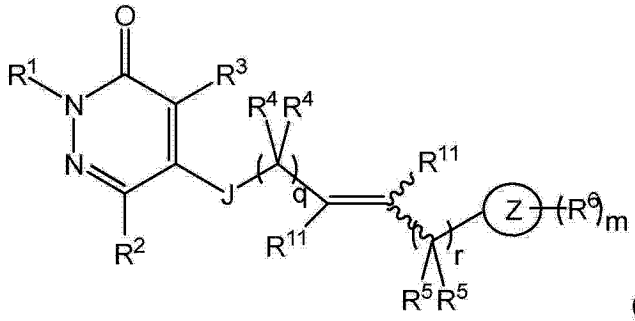
其限制条件为在所述化合物中存在至少一个离去基；且

其限制条件为当 W 为芳基时，a) R^3 不为卤基、烷基或卤烷基，或 b) 至少一个 R^6 选自由以下各项组成的群组：任选地经取代的炔基、任选地经取代的烯基、经 -CN 取代的烷基、经 $-C(=O)OR^8$ 取代的烷基、经 $-C(=O)R^8$ 取代的烷基、经 $-N(R^7)_2$ 取代的烷基、-CN、$-NO_2$、$-N(R^7)_2$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)R^8$、$-C(=O)N(R^7)_2$ 以及 $-N(R^7)C(=O)R^8$。

20. 一种化合物，其包含以下结构：



(XV)或



(XVI)，

或其盐；其中

R^1 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及离去基；

R^2 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$ 以及离去基；

R^3 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的

杂芳基、卤基、卤烷基、-CN、$-NO_2$以及离去基；

J选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O以及键；

每个R^4、R^5和R^{11}独立地选自由氢、任选地经取代的烷基以及离去基组成的群组，或任选地任何两个R^4或任何两个R^5相连以形成环；

q和r各自独立地为0、1、2或3；

Z选自由以下各项组成的群组：芳基、杂芳基、杂环基以及键；

每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、-C(=O)R^8、-C(=O)OR^8、-OC(=O)R^8、-C(=O)$N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及离去基；

m为0、1、2、3、4、5、6或7；

每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个R^7可相连以形成环；

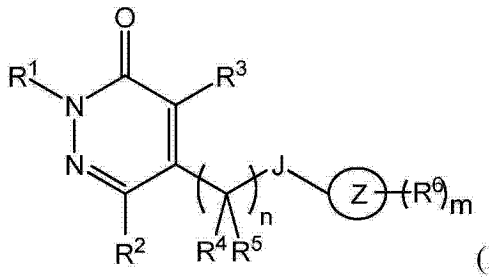
每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

每个R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及离去基；且

每个$R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基，

其限制条件为在所述化合物中存在至少一个离去基。

21.一种化合物，其包含以下结构：



(XVII)

或其盐；其中

R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及离去基；

R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的

杂芳基、卤基、$-NO_2$、卤烷基以及离去基；

R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及离去基；

J 选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)_2$、$N(R^7)C(=O)$ 以及 $-CH_2O$；

每个 R^4和 R^5独立地选自由氢、任选地经取代的烷基以及离去基组成的群组，或任选地任何两个 R^4或任何两个 R^5相连以形成环；

n 为 1、2 或 3；

Z 选自由以下各项组成的群组：芳基、杂芳基、杂环基以及键；

每个 R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、-C(=O)R^8、-C(=O)OR^8、-OC(=O)R^8、-C(=O)$N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及离去基；

m 为 0、1、2、3、4、5、6 或 7；

每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个 R^7可相连以形成环；且

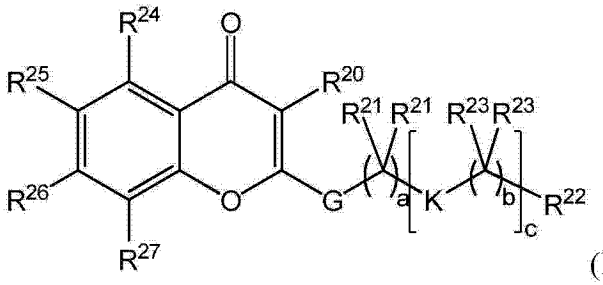
每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

每个 R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及离去基；且

每个 $R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基，

其限制条件为在所述化合物中存在至少一个离去基。

22. 一种化合物，其包含下式：



(XIX)

或其盐；其中

R^{20}选自由以下各项组成的群组：氢、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷

基、-CN 以及 $-NO_2$；

每个 R^{21}和 R^{23}独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、卤基、卤烷基以及离去基，或任选地任何两个 R^{21}或任何两个 R^{23}可相连以形成环；

R^{22}选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、卤基、卤烷基、$-OR^{28}$、$-Si(R^9)_3$、$-B(R^{9'})_3$以及离去基；

R^{24}、R^{25}、R^{26}和 R^{27}各自独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN 以及离去基；

每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个 R^7可相连以形成环；

每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

每个 R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及离去基；

每个 $R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基；

R^{28}选自由以下各项组成的群组：氢、任选地经取代的烷基和任选地经取代的杂烷基；

G 为 O、S 或 NR^{28}；

a 为 0、1、2、3 或 4；

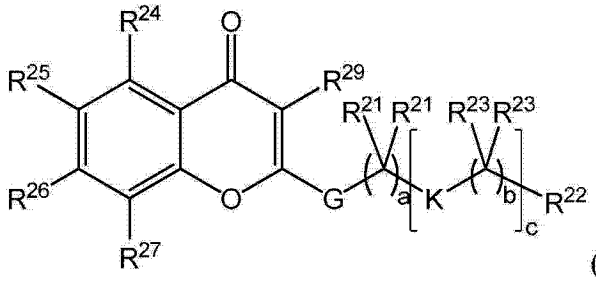
每个 K 独立地为各自任选地经取代的亚芳基、亚杂芳基、亚烯基或亚炔基；

每个 b 独立地为 0、1、2、3 或 4；且

c 为 1 或 2，

其限制条件为在所述化合物中存在至少一个离去基。

23. 一种化合物，其包含下式：



(XX)

或其盐；其中

每个 R^{21}和 R^{23}独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、卤基、卤烷基以及离

去基，或任选地任何两个 R^{21} 或任何两个 R^{23} 可相连以形成环；

R^{22} 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、卤基、卤烷基、$-OR^{28}$、$-Si(R^{9})_3$、$-B(R^{9'})_3$ 以及离去基；

R^{24}、R^{25}、R^{26} 和 R^{27} 各自独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$、-OH、$-C(=O)R^{8}$、$-C(=O)OR^{8}$、$-OC(=O)R^{8}$、$-C(=O)N(R^{7})_2$、$-N(R^{7})C(=O)R^{8}$、-CN 以及离去基；

每个 R^{7} 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个 R^{7} 可相连以形成环；

每个 R^{8} 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

每个 R^{9} 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及离去基；

每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基；

R^{28} 选自由以下各项组成的群组：氢、任选地经取代的烷基和任选地经取代的杂烷基；

R^{29} 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-C、$-NO_2$ 以及离去基；

G 为 O、S 或 NR^{28}；

a 为 0、1、2、3 或 4；

每个 K 独立地为各自任选地经取代的亚芳基、亚杂芳基、亚烯基或亚炔基，其限制条件为至少一个 K 为亚烯基或亚炔基；

每个 b 独立地为 0、1、2、3 或 4；且

c 为 1 或 2，

其限制条件为在所述化合物中存在至少一个离去基。

24. 一种诊断试剂盒，其包含一或多个含有根据权利要求 19 到 23 中任一权利要求所述的化合物或其盐和任选的其它组分的小瓶。

25. 一种用于形成造影剂的方法，其包含使根据权利要求 19 到 23 中任一权利要求所述的化合物或其盐与含 ^{18}F 物质反应以产生包含 ^{18}F 的造影剂。

26. 一种用于制备造影剂的卡匣，其包含如图 17 所示而排列的组件。

27. 一种用于合成造影剂的装置，其包含多个按以下顺序排列的旋塞阀歧管的线性排列：

1) 与气体入口和 $[^{18}O]H_2O$ 回收连接的鲁尔 (luer) 接头 (2)；

2) 阴离子交换滤筒 - 管柱溶离溶液；

3) 用于乙腈的针接头；

4) 空注射器；

5) 具有造影剂前驱体的溶液的储集器；

6) 反应容器；

7) 通向 HPLC 的出口；

8) 具有稳定剂的溶液的注射器；

9) 来自 HPLC 的入口；

10) 乙醇储集器；

11) 具有稳定剂的溶液的注射器；

12) 具有水的注射器；

13) 最终产物小瓶；

14) 空注射器；和

15) 反应容器和排气口。

28. 一种用于合成造影剂的装置，其包含多个按以下顺序排列的旋塞阀歧管的线性排列：

1) 与气体入口和 $[^{18}O]H_2O$ 回收连接的鲁尔接头 (2)；

2) 阴离子交换滤筒 - 管柱溶离溶液；

3) 具有造影剂前驱体的溶液的储集器；

4) 空注射器；

5) 用于乙腈的针接头；

6) 反应容器；

7) 通向 HPLC 的出口；

8) 具有稳定剂的溶液的注射器；

9) 来自 HPLC 的入口；

10) 乙醇储集器；

11) 具有稳定剂的溶液的注射器；

12) 具有水的注射器；

13) 最终产物小瓶；

14) 空注射器；和

15) 反应容器和排气口。

29. 一种用于合成造影剂的装置，其包含多个按以下顺序排列的旋塞阀歧管的线性排列：

1) 与气体入口和 $[^{18}O]H_2O$ 回收连接的鲁尔接头 (2)；

2) 阴离子交换滤筒 - 管柱溶离溶液；

3) 具有造影剂前驱体的溶液的储集器；

4) 空注射器；

5) 用于乙腈的针接头；

6) 反应容器；

7) 通向 HPLC 的出口；

8) 具有稳定剂的溶液的注射器；

9) 来自 HPLC 的入口；

10) 乙醇储集器；

11) 最终产物小瓶；

12) 具有水的注射器；

13) 具有稳定剂的溶液的注射器；

14) 空注射器；和

15) 反应容器和排气口。

30. 一种用于合成造影剂的装置，其包含多个按以下顺序排列的旋塞阀歧管的线性排列：

1) 与气体入口和 $[^{18}O]H_2O$ 回收连接的鲁尔接头 (2)；

2) 阴离子交换滤筒 - 管柱溶离溶液；

3) 用于乙腈的针接头；

4) 空注射器；

5) 具有造影剂前驱体的溶液的储集器；

6) 反应容器；

7) 通向 HPLC 的出口；

8) 具有稳定剂的溶液的注射器；

9) 来自 HPLC 的入口；

10) 乙醇储集器；

11) 最终产物小瓶；

12) 具有水的注射器；

13) 具有稳定剂的溶液的注射器；

14) 空注射器；和

15) 反应容器和排气口。

用于合成和使用造影剂的组合物、方法以及系统

[0001] 相关申请案

[0002] 本申请案根据 35 U.S.C. §119(e) 的规定要求 2012 年 8 月 10 申请的美国临时专利申请案 U.S.S.N.61/682,185 和 2013 年 3 月 15 日申请的美国临时专利申请案 U.S.S.N.61/794,277 的优先权，所述申请案中的每一者以引用的方式并入本文中。

技术领域

[0003] 本发明涉及适用作造影剂的化合物、其组合物、其合成和使用方法以及其前驱体。

背景技术

[0004] 粒线体为分散在大多数真核细胞的胞溶质中的膜封闭型胞器。粒线体尤其浓缩在心肌组织中。

[0005] 粒线体复合物 1(“MC-1”) 为 46 个不同次单位的膜结合蛋白复合物。这种酶复合物为构成哺乳动物粒线体中的呼吸链的三种能量转换复合物之一。这种 NADH- 泛醌氧化还原酶为穿过呼吸链，最后促使氧气还原成水的大部分电子的进入点 (生物物理学评论季刊 (Q.Rev.Biophys.)1992,25,253-324)。MC-1 的抑制剂的实例包括鱼藤素 (deguelin)、杀粉蝶菌素 A(piericidin A)、必西啶 -3(ubicidin-3)、罗林素 -1(rolliniastatin-1)、罗林素 -2(布拉他辛 (bullatacin))、辣椒碱 (capsaicin)、比达本 (pyridaben)、芬普螨 (fenpyroximate)、安密妥 (amytal)、MPP+、喹啉以及喹诺酮 (BBA 1998,1364,222-235)。研究已显示，中断粒线体的正常功能可在粒线体中，且因此在富含粒线体的心肌组织中有利地浓缩某些化合物。包括造影部分 (例如 ^{18}F) 的化合物可适用于测定化合物的这类积聚，从而提供用于心肌灌注造影的有价值的诊断标记。另外，这类化合物可用于诊断冠状动脉疾病 (CAD)。

[0006] CAD 为现代工业化国家中的主要死亡原因，并且先前已发现，在休息时和在压力期间 (运动或药物冠状动脉扩张) 的区域心肌灌注评估对非侵袭性诊断 CAD 来说是重要的。虽然在一些实施例中，用正电子发射断层摄影法 (Positron Emission Tomography ;PET) 进行心肌灌注造影 (myocardial perfusion imaging ;MPI) 相比于单光子发射电脑断层摄影术 (single photon emission computed tomography ;SPECT) 已显示为优越的，但 PET MPI 的广泛临床用途已受到先前可用的 PET 心肌灌注示踪剂的限制。

[0007] 已发展若干种 PET 血流示踪剂，如氯化铷 -82(^{82}Rb)、氨氮 -13(^{13}N) 以及水的氧 -15(^{15}O)，并且经验证用于评估心肌灌注。^{13}N 和 ^{15}O 为具有短半衰期的回旋加速器产生的同位素。因此，其用途限于具有现场回旋加速器的设施。尽管 ^{82}Rb 为一种产生剂产生的示踪剂，但其短半衰期、产生剂的高成本以及不能联合踏车运动进行研究已使得这种示踪剂于广泛使用为不实际的。然而，包含 ^{18}F 的示踪剂已用作造影剂。

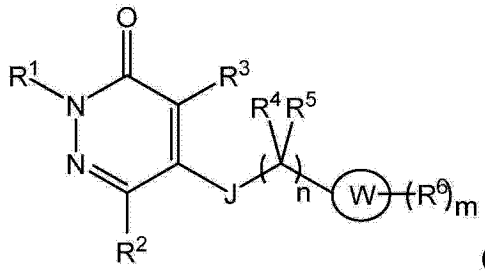
发明内容

[0008] 在广义上，本发明提供适用作造影剂或造影剂前驱体的化合物和其组合物、其试

剂盒、其使用方法以及合成所提供的化合物的方法。

[0009] 在一些实施例中，提供包含以下结构的化合物：

[0010]



(I)

[0011] 或其医药学上可接受的盐，其中：

[0012] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0013] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及造影部分；

[0014] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及造影部分；

[0015] J选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O以及一键；

[0016] R^4和R^5各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地R^4和R^5中的任何两者相连以形成环；

[0017] n为0、1、2或3；

[0018] W为杂芳基、萘基、杂环基或芳基；

[0019] 每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

[0020] m为0、1、2、3、4、5、6或7；

[0021] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个R^7可相连以形成环；

[0022] 每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

[0023] 每个R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及造影部分；和

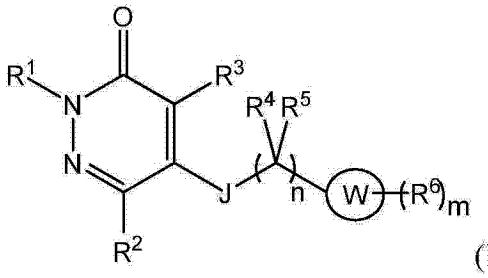
[0024] 每个$R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[0025] 其限制条件为在所述化合物中存在至少一个造影部分；和

[0026] 其限制条件为当W为芳基时，a)R^3不为卤基、烷基或卤烷基，或b)至少一个R^6选自由以下各项组成的群组：任选地经取代的炔基、任选地经取代的烯基、任选地经-CN取代的烷基、任选地经$-C(=O)OR^8$取代的烷基、任选地经$-C(=O)R^8$取代的烷基、任选地经$-N(R^7)_2$取代的烷基、-CN、$-NO_2$、$-N(R^7)_2$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)R^8$、$-C(=O)N(R^7)_2$以及$-N(R^7)C(=O)R^8$。

[0027] 在一些实施例中，提供包含以下结构的化合物：

[0028]



(II)

[0029] 或其医药学上可接受的盐，其中：

[0030] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0031] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及造影部分；

[0032] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及造影部分；

[0033] J选自由以下各项组成的群组：$N(R^7)$、S、O、$C(=O)$、$C(=O)O$、$OC(=O)$、$C(=O)N(R^7)$、$N(R^7)C(=O)$、CH_2O以及一键；

[0034] R^4和R^5各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地R^4和R^5中的任何两者相连以形成环；

[0035] n为0、1、2或3；

[0036] W为杂芳基、萘基或杂环基；

[0037] 每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影

部分；

[0038] m 为 0、1、2、3、4、5、6 或 7；

[0039] 每个 R^7 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7 可相连以形成环；

[0040] 每个 R^8 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

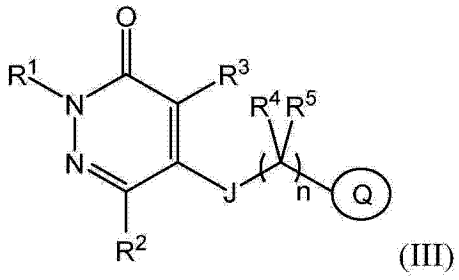
[0041] 每个 R^9 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及造影部分；和

[0042] 每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[0043] 其限制条件为在所述化合物中存在至少一个造影部分。

[0044] 在一些实施例中，提供包含以下结构的化合物：

[0045]



(III)

[0046] 或其医药学上可接受的盐，其中：

[0047] R^1 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0048] R^2 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$ 以及造影部分；

[0049] R^3 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$ 以及造影部分；

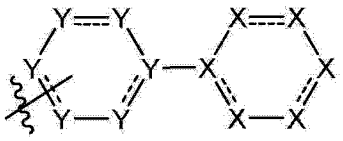
[0050] J 选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键；

[0051] R^4 和 R^5 各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地 R^4 和 R^5 中的任何两者相连以形成环；

[0052] n 为 0、1、2 或 3；

[0053] Q 具有以下结构：

[0054]



[0055] 其中每个 Y 和每个 X 独立地选自由 C、$C(R^6)$、$C(R^6)_2$、N、NR^7、O 以及 S 组成的群组，其限制条件为至少一个 Y 不为 C 或 $C(R^6)$，任选地其中缺少一个 X 和 / 或一个 Y；

[0056] 每个------独立地为单键或双键；

[0057] 每个 R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

[0058] 每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7可相连以形成环；

[0059] 每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

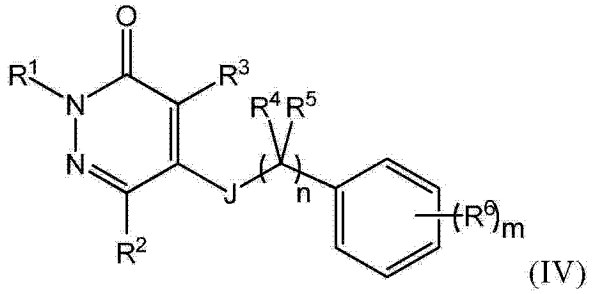
[0060] 每个 R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及造影部分；和

[0061] 每个 $R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[0062] 其限制条件为在所述化合物中存在至少一个造影部分。

[0063] 在一些实施例中，提供包含以下结构的化合物：

[0064]



(IV)

[0065] 或其医药学上可接受的盐，其中：

[0066] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0067] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经

取代的杂芳基、卤基、卤烷基、$-NO_2$以及造影部分；

[0068] R^3选自由以下各项组成的群组：氢、未经取代的烷基或任选地经除卤素以外的部分取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、-CN 以及 $-NO_2$；

[0069] J 选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键；

[0070] R^4和 R^5各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地 R^4和 R^5中的任何两者相连以形成环；

[0071] n 为 0、1、2 或 3；

[0072] 每个 R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、-C(=O)R^8、-C(=O)OR^8、-OC(=O)R^8、-C(=O)$N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

[0073] m 为 0、1、2、3、4 或 5；

[0074] 每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7可相连以形成环；

[0075] 每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

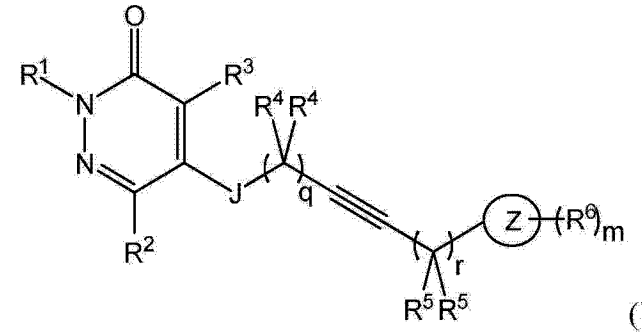
[0076] 每个 R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及造影部分；和

[0077] 每个 $R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

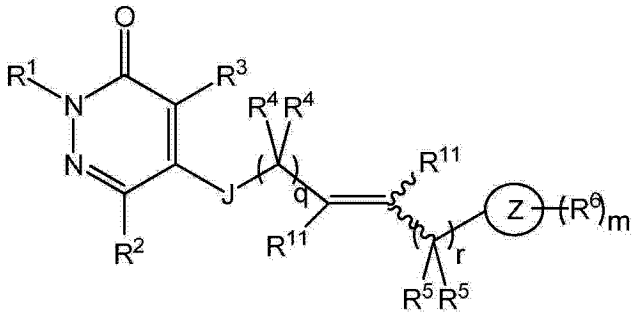
[0078] 其限制条件为在所述化合物中存在至少一个造影部分。

[0079] 在一些实施例中，提供包含以下结构的化合物：

[0080]



(V)或



(VI)，

[0081] 或其医药学上可接受的盐，其中：

[0082] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0083] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及造影部分；

[0084] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及造影部分；

[0085] J选自由以下各项组成的群组：$N(R^7)$、S、O、$C(=O)$、$C(=O)O$、$OC(=O)$、$C(=O)N(R^7)$、$N(R^7)C(=O)$、CH_2O以及一键；

[0086] 每个R^4、R^5以及R^{11}独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地任何两个R^4或任何两个R^5相连以形成环；

[0087] q和r各自独立地为0、1、2或3；

[0088] Z选自由以下各项组成的群组：芳基、杂芳基、杂环基及一键；

[0089] 每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

[0090] m为0、1、2、3、4、5、6或7；

[0091] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地

经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7 可相连以形成环；

[0092] 每个 R^8 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

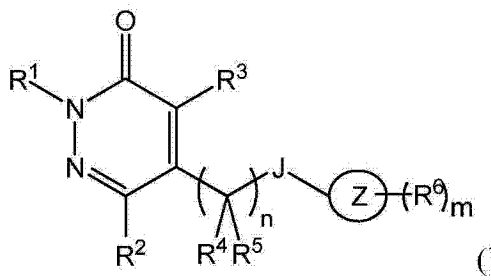
[0093] 每个 R^9 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及造影部分；和

[0094] 每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[0095] 其限制条件为在所述化合物中存在至少一个造影部分。

[0096] 在一些实施例中，提供包含以下结构的化合物：

[0097]



(VII)

[0098] 或其医药学上可接受的盐，其中：

[0099] R^1 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0100] R^2 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、$-NO_2$、卤烷基以及造影部分；

[0101] R^3 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$ 以及造影部分；

[0102] J 选自由以下各项组成的群组：$N(R^7)$、S、O、$C(=O)$、$C(=O)O$、$OC(=O)$、$C(=O)N(R^7)$、$N(R^7)C(=O)$ 以及 $-CH_2O$；

[0103] 每个 R^4 和 R^5 独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地 R^4 和 R^5 中的任何两者相连以形成环；

[0104] n 为 1、2 或 3；

[0105] Z 选自由以下各项组成的群组：芳基、杂芳基、杂环基及一键；

[0106] 每个 R^6 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$ 以及造影

部分；

[0107] m 为 0、1、2、3、4、5、6 或 7；

[0108] 每个 R^7 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7 可相连以形成环；

[0109] 每个 R^8 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

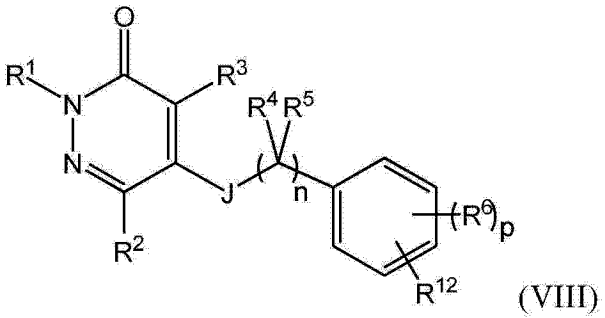
[0110] 每个 R^9 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及造影部分；和

[0111] 每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[0112] 其限制条件为在所述化合物中存在至少一个造影部分。

[0113] 在一些实施例中，提供包含以下结构的化合物：

[0114]



(VIII)

[0115] 或其医药学上可接受的盐，其中：

[0116] R^1 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0117] R^2 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$ 以及造影部分；

[0118] R^3 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$ 以及造影部分；

[0119] J 选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键；

[0120] R^4 和 R^5 各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地 R^4 和 R^5 中的任何两者相连以形成环；

[0121] n 为 0、1、2 或 3；

[0122] 每个 R^6 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经

取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

[0123] p 为 0、1、2、3 或 4；

[0124] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个R^7可相连以形成环；和

[0125] 每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

[0126] R^{12}选自由以下各项组成的群组：任选地经取代的炔基、任选地经取代的烯基、经 -CN 取代的烷基、经$-C(=O)OR^8$取代的烷基、经$-C(=O)R^8$取代的烷基、经$-N(R^7)_2$取代的烷基、-CN、$-NO_2$、$-N(R^7)_2$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)R^8$、$-C(=O)N(R^7)_2$以及$-N(R^7)C(=O)R^8$；

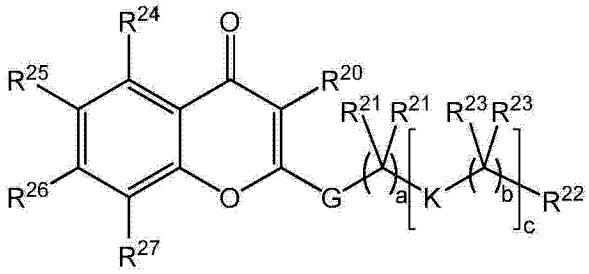
[0127] 每个R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及造影部分；和

[0128] 每个$R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[0129] 其限制条件为在所述化合物中存在至少一个造影部分。

[0130] 在一些实施例中，提供包含以下结构的化合物：

[0131]



(IX)

[0132] 或其医药学上可接受的盐，其中：

[0133] R^{20}选自由以下各项组成的群组：氢、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN 以及$-NO_2$；

[0134] 每个R^{21}和R^{23}独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、卤基、卤烷基以及造影部分，或任选地任何两个R^{21}或任何两个R^{23}可相连以形成环；

[0135] R^{22}选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷

基、任选地经取代的烷氧基烷基、卤基、卤烷基、$-OR^{28}$、$-Si(R^9)_3$、$-B(R^{9'})_3$以及造影部分；

[0136] R^{24}、R^{25}、R^{26}以及R^{27}各自独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$、$-OH$、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、$-CN$以及造影部分；

[0137] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个R^7可相连以形成环；和

[0138] 每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

[0139] 每个R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及造影部分；

[0140] 每个$R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[0141] R^{28}选自由以下各项组成的群组：氢、任选地经取代的烷基以及任选地经取代的杂烷基；

[0142] G为O、S或NR^{28}；

[0143] a为0、1、2、3或4；

[0144] 每个K独立地为各自任选地经取代的亚芳基、亚杂芳基、亚烯基或亚炔基；

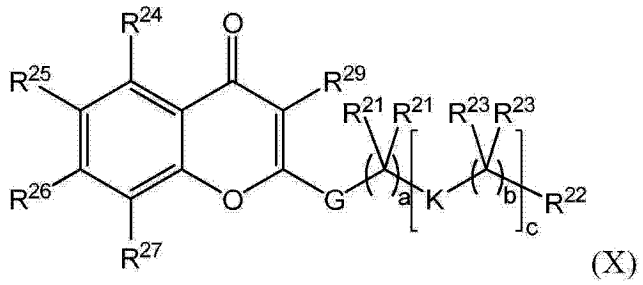
[0145] 每个b独立地为0、1、2、3或4；和

[0146] c为1或2，

[0147] 其限制条件为在所述化合物中存在至少一个造影部分。

[0148] 在一些实施例中，提供包含以下结构的化合物：

[0149]



(X)

[0150] 或其医药学上可接受的盐，其中：

[0151] 每个R^{21}和R^{23}独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、卤基、卤烷基以及造影部分，或任选地任何两个R^{21}或任何两个R^{23}可相连以形成环；

[0152] R^{22}选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、卤基、卤烷基、$-OR^{28}$、$-Si(R^9)_3$、$-B(R^{9'})_3$以及造影部分；

[0153] R^{24}、R^{25}、R^{26}以及 R^{27}各自独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN 以及造影部分；

[0154] 每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7可相连以形成环；和

[0155] 每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

[0156] 每个 R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及造影部分；

[0157] 每个 $R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[0158] R^{28}选自由以下各项组成的群组：氢、任选地经取代的烷基以及任选地经取代的杂烷基；

[0159] R^{29}选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及造影部分；

[0160] G 为 O、S 或 NR^{28}；

[0161] a 为 0、1、2、3 或 4；

[0162] 每个 K 独立地为各自任选地经取代的亚芳基、亚杂芳基、亚烯基或亚炔基，其限制条件为至少一个 K 为亚烯基或亚炔基；

[0163] 每个 b 独立地为 0、1、2、3 或 4；和

[0164] c 为 1 或 2，

[0165] 其限制条件为在所述化合物中存在至少一个造影部分。

[0166] 在一些实施例中，以上所提供的化合物为造影剂。在一些实施例中，提供一种医药组合物，其包含上述化合物和任选的医药学上可接受的赋形剂。在一些实施例中，提供一种包含如上所述的化合物的无菌水溶液。在一些实施例中，提供如上所述的化合物作为造影剂的用途。在一些实施例中，提供如上所述的化合物在心肌灌注造影中的用途。在一些实施例中，提供如上所述的化合物在制造用于检测、造影或监控心肌灌注的药剂中的用途。在一些实施例中，提供一种对个体的一部分进行造影的方法，所述方法包含向个体投予如上所述的化合物且获得所述个体的一部分的至少一个图像。在一些实施例中，提供一种对个体的一部分进行造影的方法，所述方法包含向个体投予如上所述的化合物，检测由所述化合物所放出的辐射和自其形成的图像。在一些实施例中，提供一种诊断试剂盒，其包含一或多个含有如上所述的化合物的前驱体和任选的其它组分的小瓶。在一些实施例中，提供一种心肌灌注的造影方法，所述方法包含向患者投予如上所述的化合物且使用诊断造影扫描患者。在一些实施例中，提供一种心肌灌注的检测方法，所述方法包含向患者投予如上所述

的化合物且使用诊断造影扫描患者。在一些实施例中，提供一种心肌灌注的监控方法，所述方法包含向患者投予如上所述的化合物且使用诊断造影扫描患者。在一些实施例中，提供上述化合物的前驱体。在一些实施例中，至少一种造影剂经至少一个离去基置换。

[0167] 在一些实施例中，提供一种用于制备造影剂的卡匣，其包含如图 17 所示而排列的组件。

[0168] 在一些实施例中，用于合成造影剂的装置包含多个按以下顺序排列的旋塞阀歧管的线性排列：

[0169] 1) 与气体入口和 $[^{18}O]H_2O$ 回收连接的鲁尔 (luer) 接头 (2)；

[0170] 2) 阴离子交换滤筒 - 管柱溶离溶液；

[0171] 3) 用于乙腈的针接头；

[0172] 4) 空注射器；

[0173] 5) 具有造影剂前驱体的溶液的储集器；

[0174] 6) 反应容器；

[0175] 7) 通向 HPLC 的出口；

[0176] 8) 具有稳定剂的溶液的注射器；

[0177] 9) 来自 HPLC 的入口；

[0178] 10) 乙醇储集器；

[0179] 11) 具有稳定剂的溶液的注射器；

[0180] 12) 具有水的注射器；

[0181] 13) 最终产物小瓶；

[0182] 14) 空注射器；和

[0183] 15) 反应容器和排气口。

[0184] 在一些实施例中，用于合成造影剂的装置包含多个按以下顺序排列的旋塞阀歧管的线性排列：

[0185] 1) 与气体入口和 $[^{18}O]H_2O$ 回收连接的鲁尔接头 2；

[0186] 2) 阴离子交换滤筒 - 管柱溶离溶液；

[0187] 3) 具有造影剂前驱体的溶液的储集器；

[0188] 4) 空注射器；

[0189] 5) 用于乙腈的针接头；

[0190] 6) 反应容器；

[0191] 7) 通向 HPLC 的出口；

[0192] 8) 具有稳定剂的溶液的注射器；

[0193] 9) 来自 HPLC 的入口；

[0194] 10) 乙醇储集器；

[0195] 11) 具有稳定剂的溶液的注射器；

[0196] 12) 具有水的注射器；

[0197] 13) 最终产物小瓶；

[0198] 14) 空注射器；和

[0199] 15) 反应容器及排气口。

[0200] 在一些实施例中，用于合成造影剂的装置包含多个按以下顺序排列的旋塞阀歧管的线性排列：

[0201] 1）与气体入口和 $[^{18}O]H_2O$ 回收连接的鲁尔接头 2；

[0202] 2）阴离子交换滤筒 - 管柱溶离溶液；

[0203] 3）具有造影剂前驱体的溶液的储集器；

[0204] 4）空注射器；

[0205] 5）用于乙腈的针接头；

[0206] 6）反应容器；

[0207] 7）通向 HPLC 的出口；

[0208] 8）具有稳定剂的溶液的注射器；

[0209] 9）来自 HPLC 的入口；

[0210] 10）乙醇储集器；

[0211] 11）最终产物小瓶；

[0212] 12）具有水的注射器；

[0213] 13）具有稳定剂的溶液的注射器；

[0214] 14）空注射器；和

[0215] 15）反应容器和排气口。

[0216] 在一些实施例中，用于合成造影剂的装置包含多个按以下顺序排列的旋塞阀歧管的线性排列：

[0217] 1）与气体入口和 $[^{18}O]H_2O$ 回收连接的鲁尔接头 2；

[0218] 2）阴离子交换滤筒 - 管柱溶离溶液；

[0219] 3）用于乙腈的针接头；

[0220] 4）空注射器；

[0221] 5）具有造影剂前驱体的溶液的储集器；

[0222] 6）反应容器；

[0223] 7）通向 HPLC 的出口；

[0224] 8）具有稳定剂的溶液的注射器；

[0225] 9）来自 HPLC 的入口；

[0226] 10）乙醇储集器；

[0227] 11）最终产物小瓶；

[0228] 12）具有水的注射器；

[0229] 13）具有稳定剂的溶液的注射器；

[0230] 14）空注射器；和

[0231] 15）反应容器和排气口。

附图说明

[0232] 图 1-15 显示非限制性化合物在大鼠中的代表性图像。

[0233] 图 16 显示描述根据一些实施例的用于合成造影剂的方法的流程图。

[0234] 图 17 显示根据一些实施例的卡匣的示意图，所述卡匣具有用于合成造影剂的相

关管柱和试剂，使用自动化合成模块。

[0235] 当结合附图考虑时，本发明的其它方面、实施例以及特征由以上实施方式将变得显而易知。附图具示意性且不欲按比例绘制。出于清楚了解的目的，并非每一组件均标示在每一图中，亦非均显示本发明的每个实施例的每一组件，未标示的组件的说明并非为所属领域的技术人员了解本发明所必需的。所有以引用的方式并入本文中的专利申请案和专利均以其全文引用的方式并入。在出现矛盾的情况下，将以本说明书（包括定义）为准。

具体实施方式

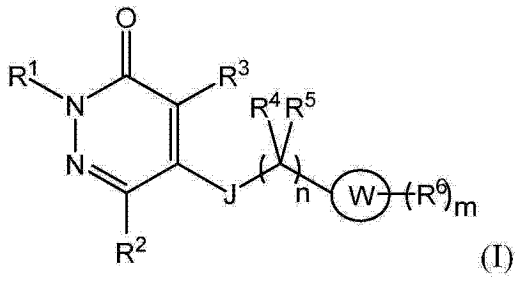
[0236] 本发明提供化合物、其组合物、包含所述化合物的系统、用于合成所述化合物和/或使用所述化合物作为造影剂和其前驱体的试剂、卡匣、方法、试剂盒以及装置。本发明的造影剂可用于对个体的相关区域进行造影，所述相关区域包括（但不限于）心脏、心脏的一部分、心血管系统、心血管、脑以及其它器官。在一些实施例中，造影剂包含造影部分，其中造影部分选自由以下各项组成的群组：^{11}C、^{13}N、^{18}F、^{76}Br、^{123}I、^{124}I、^{125}I、^{131}I、^{99m}Tc、^{95}Tc、^{111}In、^{62}Cu、^{64}Cu、^{67}Ga 以及 ^{68}Ga。在某些实施例中，造影剂包含 ^{18}F 作为造影部分。在某些实施例中，待造影的个体区域通过正电子发射断层摄影法 (PET) 造影。

[0237] 在一些实施例中，本发明提供造影方法，包括个体的造影方法，其包括通过注射、输注或任何其它已知的投药方法向个体投予组合物或配方（例如包含如本文所述的造影剂者），且对所述个体的相关区域进行造影。相关区域可包括（但不限于）心脏、心血管系统、心血管、血管（例如动脉、静脉）、脑以及其它器官。相关区域亦可包括肿瘤或可包括肿瘤的个体身体的区域。可使用本文所述的方法和/或系统对如血流量、心壁运动或灌注的相关参数进行造影和检测。相关事件可经造影以及检测和/或其它信息可使用本揭示案的方法和/或系统来测定。在一些实施例中，提供用于评估灌注（包括心肌灌注）的方法。

[0238] 造影剂

[0239] 在一个方面中，本发明提供适用作用于对个体的相关区域进行造影的造影剂的化合物。在一些实施例中，造影剂包含造影部分，其中造影部分选自由以下各项组成的群组：^{11}C、^{13}N、^{18}F、^{76}Br、^{123}I、^{124}I、^{125}I、^{131}I、^{99m}Tc、^{95}Tc、^{111}In、^{62}Cu、^{64}Cu、^{67}Ga 以及 ^{68}Ga。在某些实施例中，造影剂用 ^{18}F 标记且适用于 PET 造影。在一些实施例中，提供包含以下结构的化合物：

[0240]



(I)

[0241] 或其医药学上可接受的盐，其中：

[0242] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0243] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷

基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及造影部分；

[0244] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及造影部分；

[0245] J选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O以及一键；

[0246] R^4和R^5各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地R^4和R^5中的任何两者相连以形成环；

[0247] n为0、1、2或3；

[0248] W为杂芳基、萘基、杂环基或芳基；

[0249] 每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、-C(=O)R^8、-C(=O)OR^8、-OC(=O)R^8、-C(=O)$N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

[0250] m为0、1、2、3、4、5、6或7；

[0251] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个R^7可相连以形成环；

[0252] 每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

[0253] 每个R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及造影部分；和

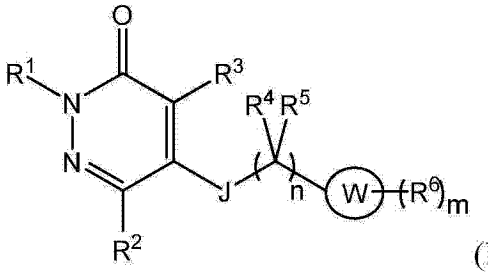
[0254] 每个$R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[0255] 其限制条件为在所述化合物中存在至少一个造影部分；和

[0256] 其限制条件为当W为芳基时，a)R^3不为卤基、烷基或卤烷基，或b)至少一个R^6选自由以下各项组成的群组：任选地经取代的炔基、任选地经取代的烯基、经-CN取代的烷基、经$-C(=O)OR^8$取代的烷基、经$-C(=O)R^8$取代的烷基、经$-N(R^7)_2$取代的烷基、-CN、$-NO_2$、$-N(R^7)_2$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)R^8$、$-C(=O)N(R^7)_2$以及$-N(R^7)C(=O)R^8$。

[0257] 在一些实施例中，提供包含以下结构的化合物：

[0258]



(II)

[0259] 或其医药学上可接受的盐，其中：

[0260] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0261] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及造影部分；

[0262] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及造影部分；

[0263] J选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O以及一键；

[0264] R^4和R^5各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地R^4和R^5中的任何两者相连以形成环；

[0265] n为0、1、2或3；

[0266] W为杂芳基、萘基或杂环基；

[0267] 每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、-C(=O)R^8、-C(=O)OR^8、-OC(=O)R^8、-C(=O)$N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

[0268] m为0、1、2、3、4、5、6或7；

[0269] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个R^7可相连以形成环；

[0270] 每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

[0271] 每个R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及造影部分；和

[0272] 每个$R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地

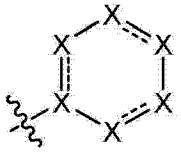
经取代的芳基以及造影部分；

[0273] 其限制条件为在所述化合物中存在至少一个造影部分。

[0274] 在一些实施例中，关于式 (I) 化合物，W 为芳基。在一些实施例中，关于式 (I) 化合物，W 为 5 元或 6 元芳基。

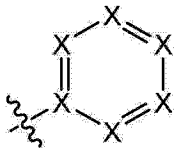
[0275] W 基团的以下描述可联合式 (I) 或 (II) 化合物使用，或如在此所指出。在一些实施例中，W 为杂芳基。在一些实施例中，W 为五元杂芳基。在一些实施例中，W 为六元杂芳基。在一些实施例中，W 为单环杂芳基。在一些实施例中，W 为双环杂芳基。在一些实施例中，W 为三环杂芳基。在一些实施例中，W 为萘基。在一些实施例中，W 为杂环基。在一些实施例中，W 为：

[0276]



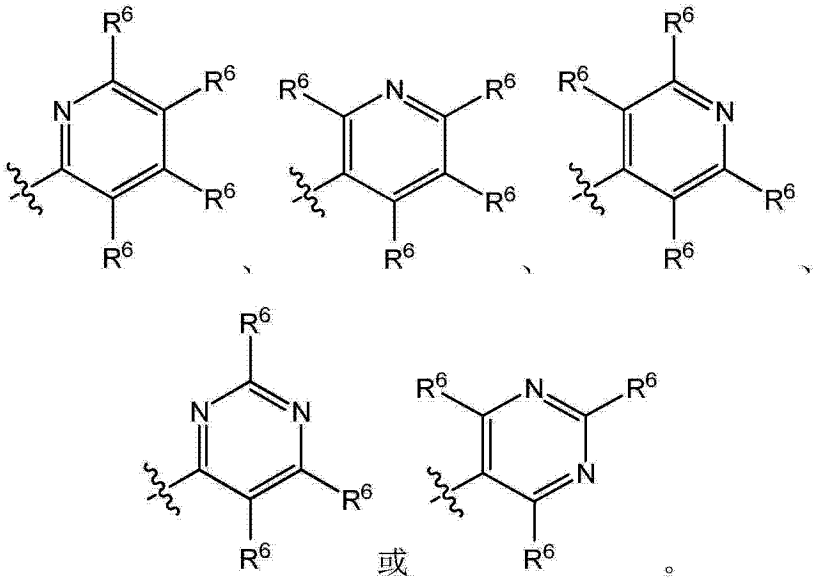
[0277] 其中每个 X 独立地选自由 C、$C(R^6)$、$C(R^6)_2$、N、NR^7、O 以及 S 组成的群组；且其中每个 ------ 独立地为单键或双键，其限制条件为至少一个 X 不为 C 或 $C(R^6)$。在一些实施例中，至少一个 X 为 N。在一些实施例中，至少一个 X 为 $N(R^7)$。在一些实施例中，至少一个 X 为 O。在一些实施例中，至少一个 X 为 S。在一些实施例中，W 为：

[0278]



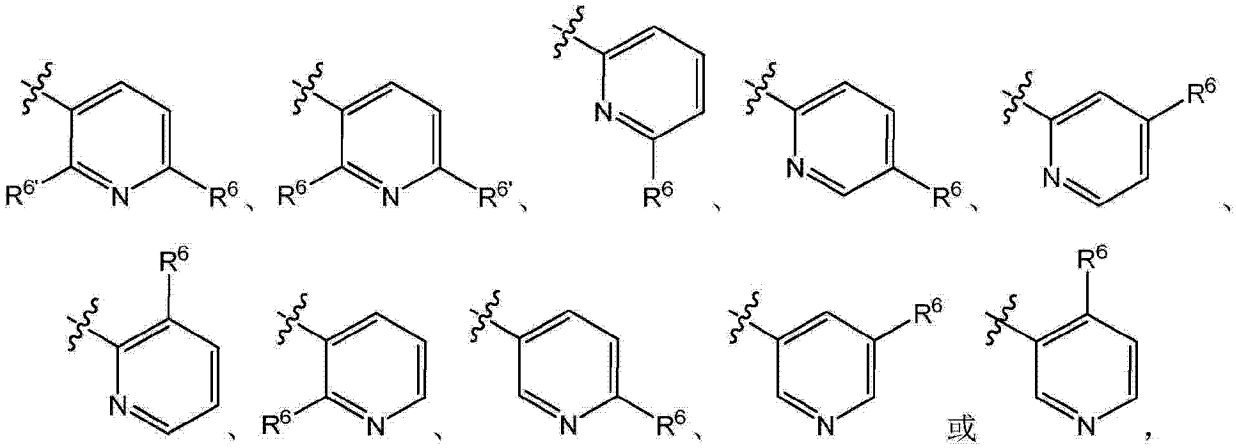
[0279] 其中每个 X 独立地为 C、$C(R^6)$ 或 N，其限制条件为至少一个 X 不为 C 或 $C(R^6)$。在一些实施例中，W 为：

[0280]



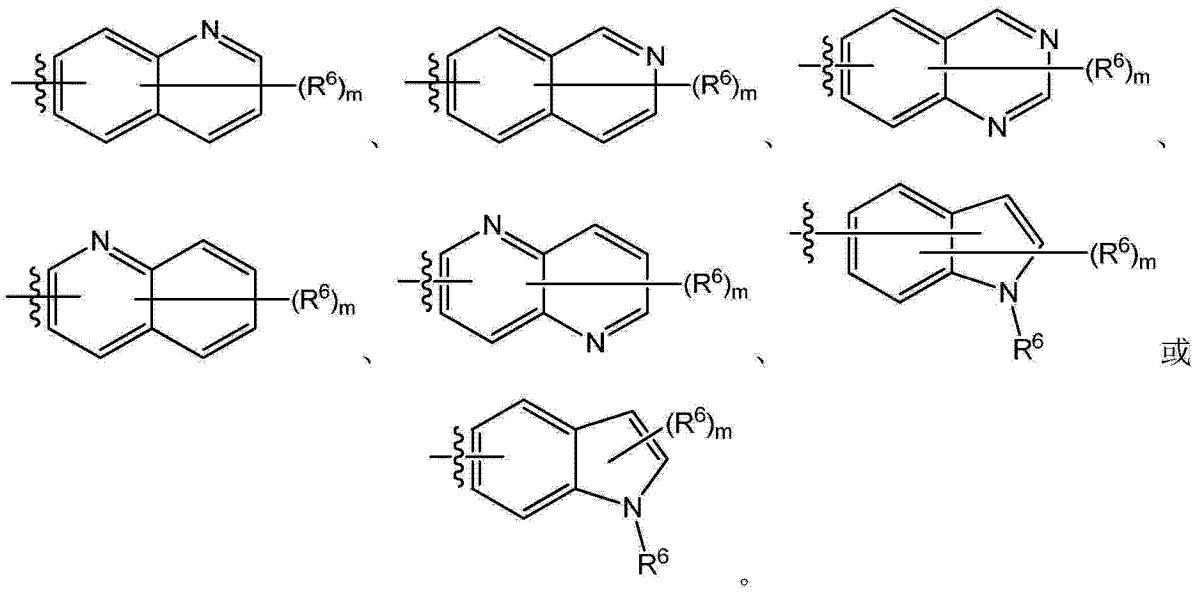
[0281] 在一些实施例中，W 为：

[0282]



[0283] 其中 $R^{6'}$ 为卤基或氢。在一些实施例中，$R^{6'}$ 为氟、氯、溴或氢。在一些实施例中，R^6 为 $-O(CH_2)_jI_m$，其中 I_m 为造影部分且 j 为 1、2、3、4、5 或 6。在一些实施例中，R^6 为 $-(CH_2)_jO(CH_2)_jI_m$，I_m 为造影部分且其中每个 j 独立地为 1、2、3、4、5 或 6。在一些情况下，I_m 为 ^{18}F。在一些实施例中，W 为：

[0284]

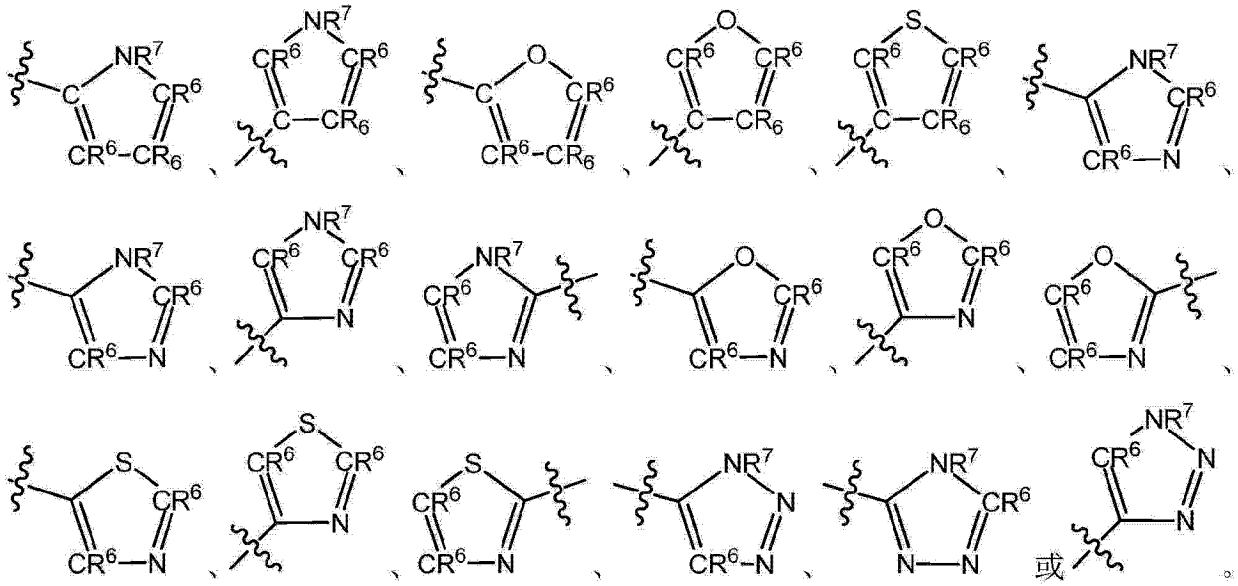


[0285] 在一些实施例中，W 为：

[0286]

[0287] 其中每个 X 独立地选自由 C、$C(R^6)$、$C(R^6)_2$、N、NR^7、O 以及 S 组成的群组；且每个 ------ 独立地为单键或双键，其限制条件为至少一个 X 不为 C 或 $C(R^6)$。在一些实施例中，W 选自由以下各项组成的群组：

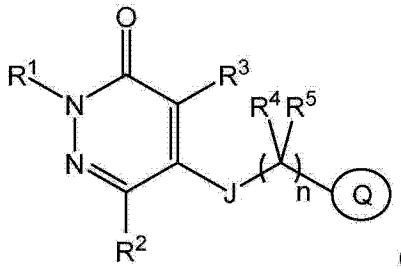
[0288]



[0289] 关于式 (I) 或 (II) 化合物，本文所述的 W 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、J、m 以及 n 或其组合中的任一者组合。

[0290] 在一些实施例中，提供包含以下结构的化合物：

[0291]



(III)

[0292] 或其医药学上可接受的盐，其中：

[0293] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0294] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及造影部分；

[0295] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及造影部分；

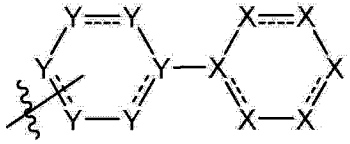
[0296] J 选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键；

[0297] R^4和 R^5各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地 R^4和 R^5中的任何两者相连以形成环；

[0298] n 为 0、1、2 或 3；

[0299] Q 具有以下结构：

[0300]



[0301] 每个 Y 及每个 X 独立地选自由 C、C(R^6)、C(R^6)$_2$、N、NR^7、O 以及 S 组成的群组，其限制条件为至少一个 Y 不为 C 或 C(R^6)，且任选地其中可缺少一个 Y 和 / 或一个 X；

[0302] 每个═══独立地为单键或双键；

[0303] 每个 R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$及造影部分；

[0304] 每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7可相连以形成环；

[0305] 每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

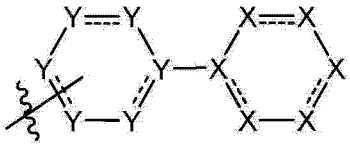
[0306] 每个 R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及造影部分；和

[0307] 每个 $R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[0308] 其限制条件为在所述化合物中存在至少一个造影部分。

[0309] Q 基团的以下描述可联合式 (III) 化合物使用，或如在本文中所指出。在一些实施例中，Q 具有以下结构：

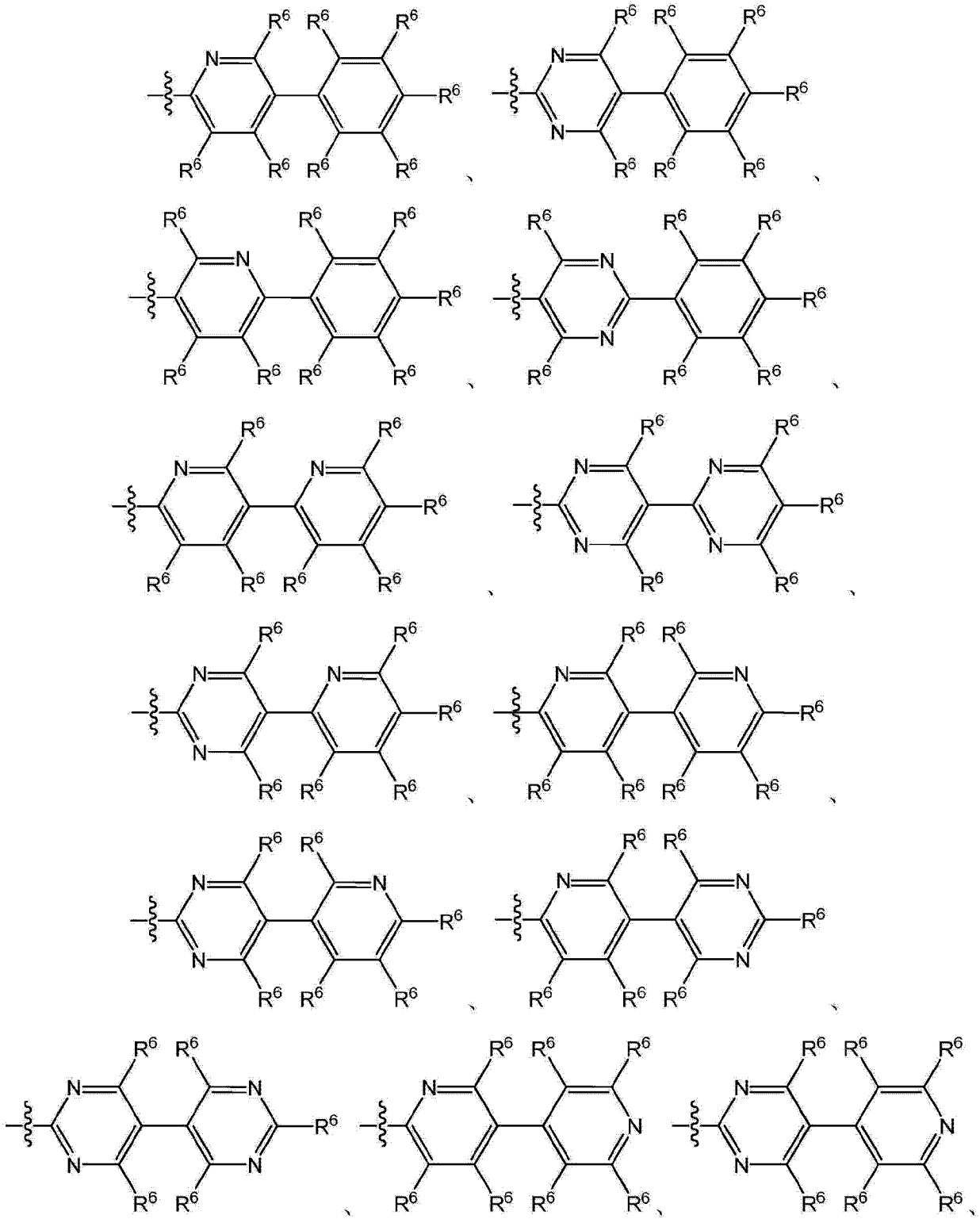
[0310]



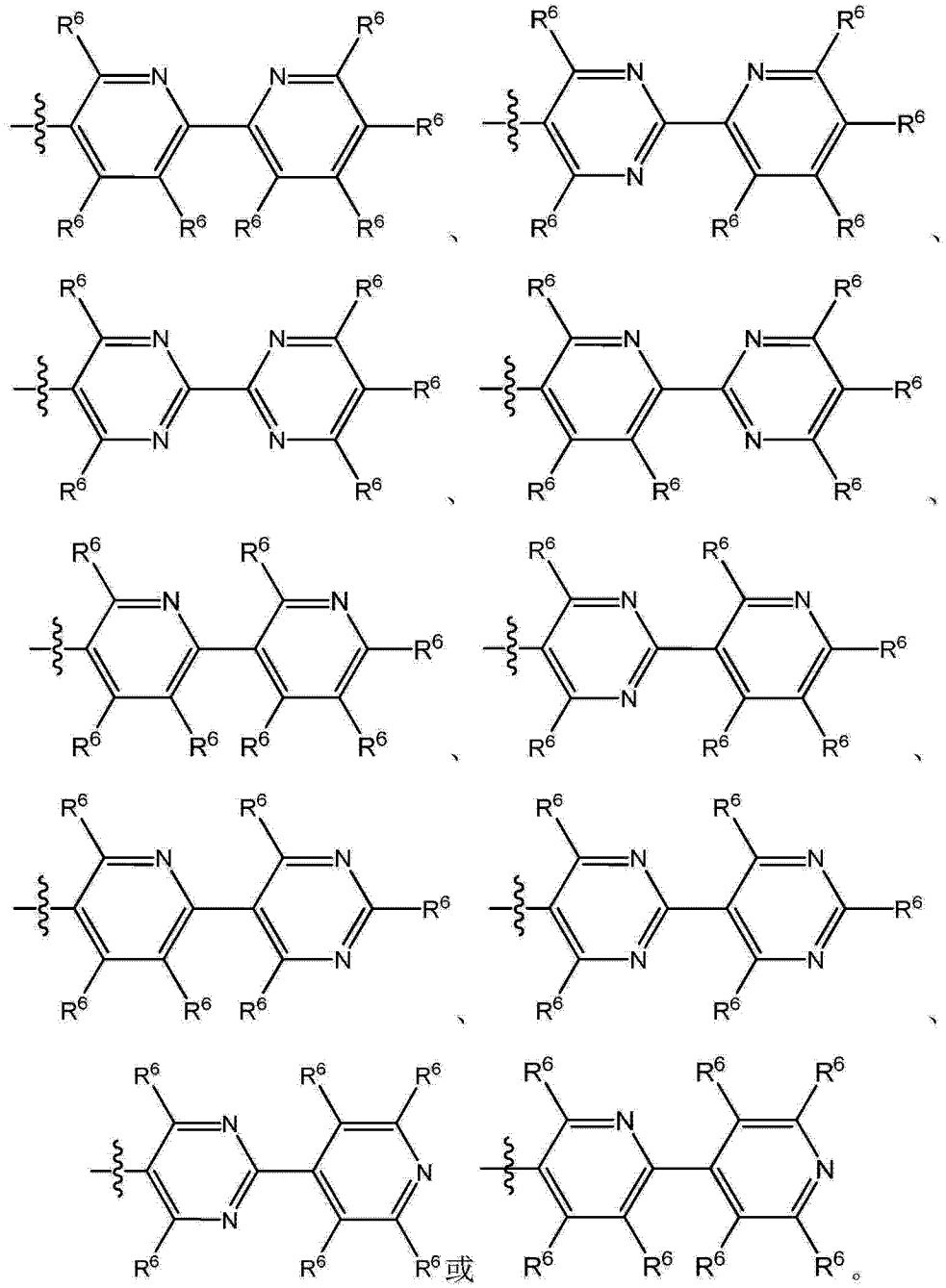
[0311] 其中每个 Y 和每个 X 独立地选自由 C、C(R^6)、C(R^6)$_2$、N、NR^7、O 及 S 组成的群组，其限制条件为至少一个 Y 不为 C 或 C(R^6)。在一些实施例中，可缺少一个 Y 和 / 或一个 X。在一些实施例中，缺少一个 Y。在一些实施例中，缺少一个 X。在一些实施例中，缺少一个 Y 和 / 或一个 X。在一些实施例中，缺少一个 Y 且一个 Y 为 N。在一些实施例中，缺少一个 Y 且一个 Y 为 NR^7。在一些实施例中，缺少一个 Y 且一个 Y 为 O。在一些实施例中，缺少一个 Y 且一个 Y 为 S。在一些实施例中，缺少一个 X 且一个 X 为 N。在一些实施例中，缺少一个 X 且一个 X 为 NR^7。在一些实施例中，缺少一个 X 且一个 X 为 O。在一些实施例中，缺少一个 X 且一

个 X 为 S。在一些实施例中，关于 Q，至少一个 Y 为 NR^7。在一些实施例中，关于 Q，X 和 Y 各自至少一个为 NR^7。在一些实施例中，关于 Q，至少一个 Y 为 N。在一些实施例中，关于 Q，X 和 Y 各自至少一个为 N。在一些实施例中，关于 Q，至少一个 Y 为 O。在一些实施例中，关于 Q，至少一个 Y 为 S。在一些实施例中，关于 Q，每个 X 为 C 或 $C(R^6)$。在一些实施例中，关于 Q，至少一个 X 不为 C 或 $C(R^6)$。在一些实施例中，关于 Q，至少两个 Y 不为 C 或 $C(R^6)$。在一些实施例中，关于 Q，X 和 Y 各自至少一个不为 C 或 $C(R^6)$。在一些实施例中，关于 Q，至少两个 X 不为 C 或 $C(R^6)$。在一些实施例中，Q 为：

[0312]



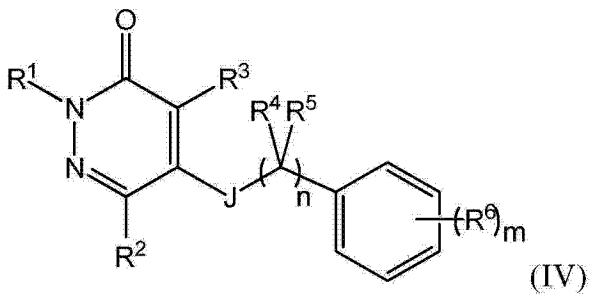
[0313]



[0314] 关于式（III）化合物，本文所述的 Q 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、J 以及 n 或其组合中的任一者组合。

[0315] 在一些实施例中，提供包含以下结构的化合物：

[0316]



(IV)

[0317] 或其医药学上可接受的盐，其中：

[0318] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0319] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及造影部分；

[0320] R^3选自由以下各项组成的群组：氢、未经取代的烷基或任选地经除卤素以外的部分取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、-CN 以及 $-NO_2$；

[0321] J 选自由以下各项组成的群组：$N(R^7)$、S、O、$C(=O)$、$C(=O)O$、$OC(=O)$、$C(=O)N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键；

[0322] R^4和 R^5各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地 R^4和 R^5中的任何两者相连以形成环；

[0323] n 为 0、1、2 或 3；

[0324] 每个 R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

[0325] m 为 0、1、2、3、4 或 5；

[0326] 每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7可相连以形成环；

[0327] 每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

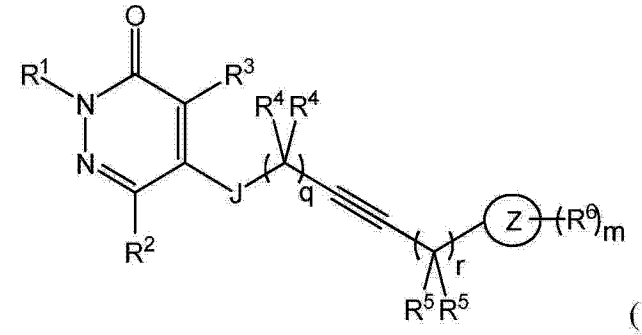
[0328] 每个 R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及造影部分；和

[0329] 每个 $R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

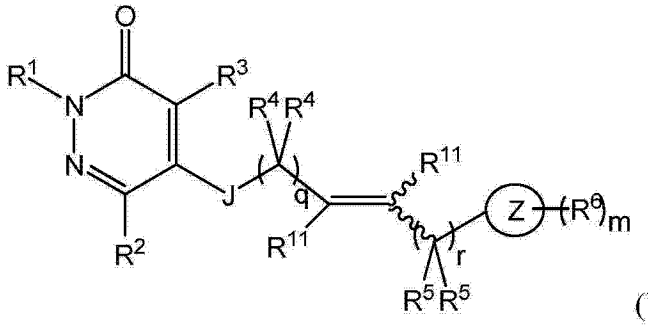
[0330] 其限制条件为在所述化合物中存在至少一个造影部分。

[0331] 在一些实施例中，提供包含以下结构的化合物：

[0332]



(V)或



(VI)，

[0333] 或其医药学上可接受的盐，其中：

[0334] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0335] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及造影部分；

[0336] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及造影部分；

[0337] J选自由以下各项组成的群组：$N(R^7)$、S、O、$C(=O)$、$C(=O)O$、$OC(=O)$、$C(=O)N(R^7)$、$N(R^7)C(=O)$、CH_2O以及一键；

[0338] 每个R^4、R^5以及R^{11}独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地任何两个R^4或任何两个R^5相连以形成环；

[0339] q和r各自独立地为0、1、2或3；

[0340] Z选自由以下各项组成的群组：芳基、杂芳基、杂环基以及一键；

[0341] 每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

[0342] m为0、1、2、3、4、5、6或7；

[0343] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取

代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7 可相连以形成环；

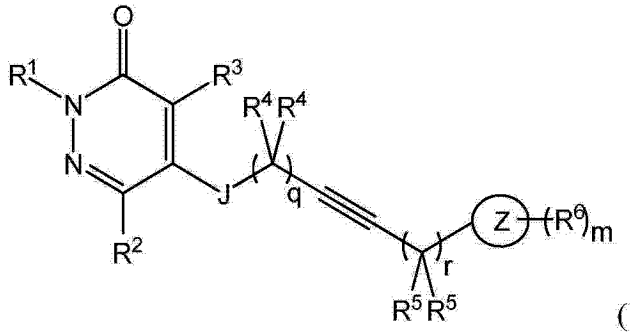
[0344] 每个 R^8 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

[0345] 每个 R^9 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及造影部分；和

[0346] 每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[0347] 其限制条件为在所述化合物中存在至少一个造影部分。在一些实施例中，提供包含以下结构的化合物：

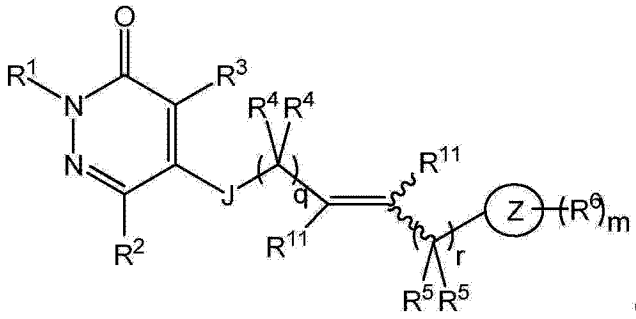
[0348]



(V)。

[0349] 在一些实施例中，提供包含以下结构的化合物：

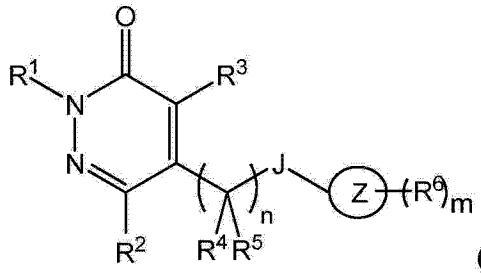
[0350]



(VI)。

[0351] 在一些实施例中，提供包含以下结构的化合物：

[0352]



(VII)

[0353] 或其医药学上可接受的盐，其中：

[0354] R^1 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷

基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0355] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、$-NO_2$、卤烷基以及造影部分；

[0356] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及造影部分；

[0357] J选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)_2$、$N(R^7)C(=O)$以及$-CH_2O$；

[0358] 每个R^4和R^5独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地任何两个R^4或任何两个R^5相连以形成环；

[0359] n为1、2或3；

[0360] Z选自由以下各项组成的群组：芳基、杂芳基、杂环基以及一键；

[0361] 每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、-C(=O)R^8、-C(=O)OR^8、-OC(=O)R^8、-C(=O)$N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

[0362] m为0、1、2、3、4、5、6或7；

[0363] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个R^7可相连以形成环；

[0364] 每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

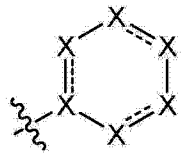
[0365] 每个R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及造影部分；和

[0366] 每个$R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[0367] 其限制条件为在所述化合物中存在至少一个造影部分。

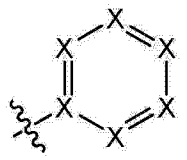
[0368] Z基团的以下描述可联合式(V)、(VI)或(VII)化合物使用。在一些实施例中，Z为芳基。在一些实施例中，Z为苯基。在一些实施例中，Z为萘基。在一些实施例中，Z为杂芳基。在一些实施例中，Z为五元杂芳基。在一些实施例中，Z为六元杂芳基。在一些实施例中，Z为单环杂芳基。在一些实施例中，Z为双环杂芳基。在一些实施例中，Z为三环杂芳基。在一些实施例中，Z为杂环基。在一些实施例中，Z为：

[0369]



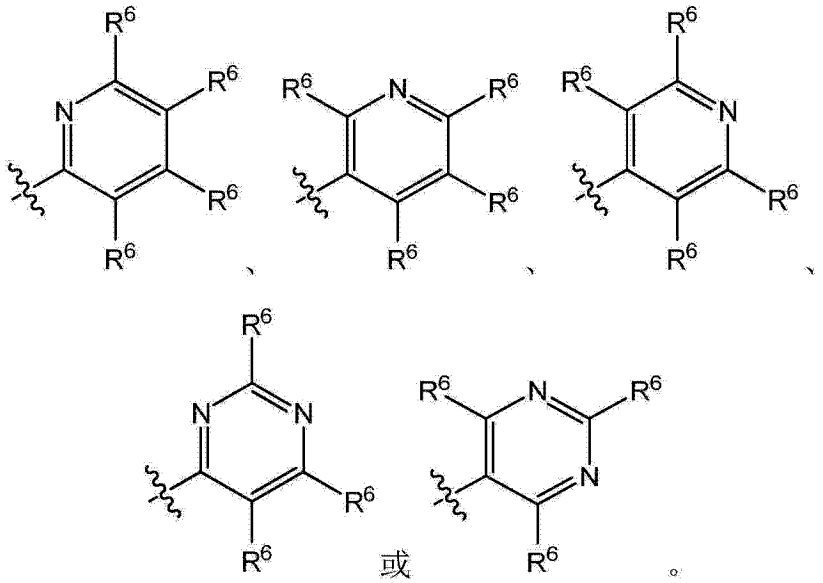
[0370] 其中每个 X 独立地选自由 C、$C(R^6)$、$C(R^6)_2$、N、NR^7、O 以及 S 组成的群组；且其中每个------独立地为单键或双键。在一些实施例中，至少一个 X 不为 C 或 $C(R^6)$。在一些实施例中，至少一个 X 为 N。在一些实施例中，至少一个 X 为 $N(R^7)$。在一些实施例中，至少一个 X 为 O。在一些实施例中，至少一个 X 为 S。在一些实施例中，Z 为：

[0371]



[0372] 其中每个 X 独立地为 C、$C(R^6)$ 或 N。在一些实施例中，至少一个 X 不为 C 或 $C(R^6)$。在一些实施例中，至少一个 X 为 N。在一些实施例中，Z 为：

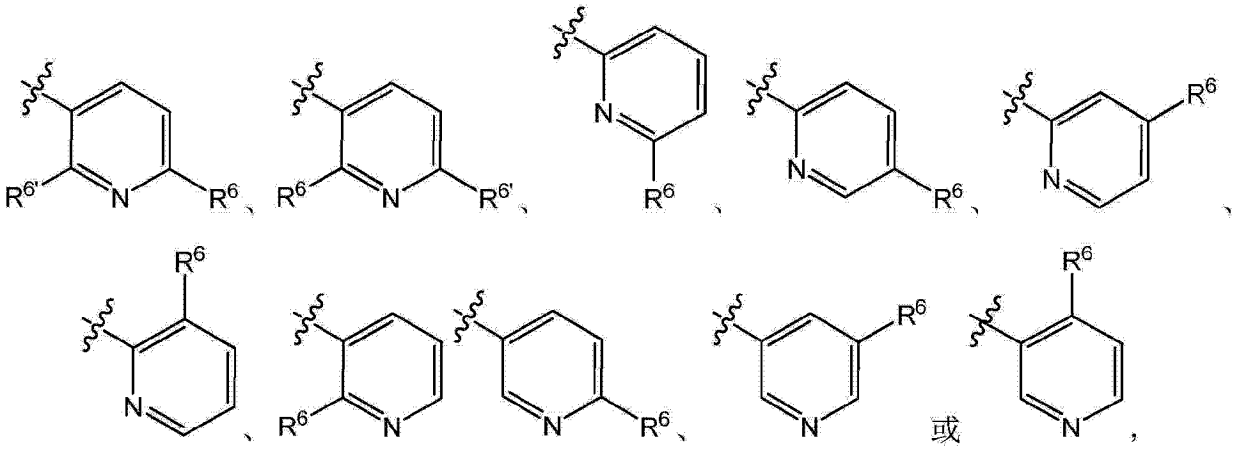
[0373]



或 。

[0374] 在一些实施例中，Z 为：

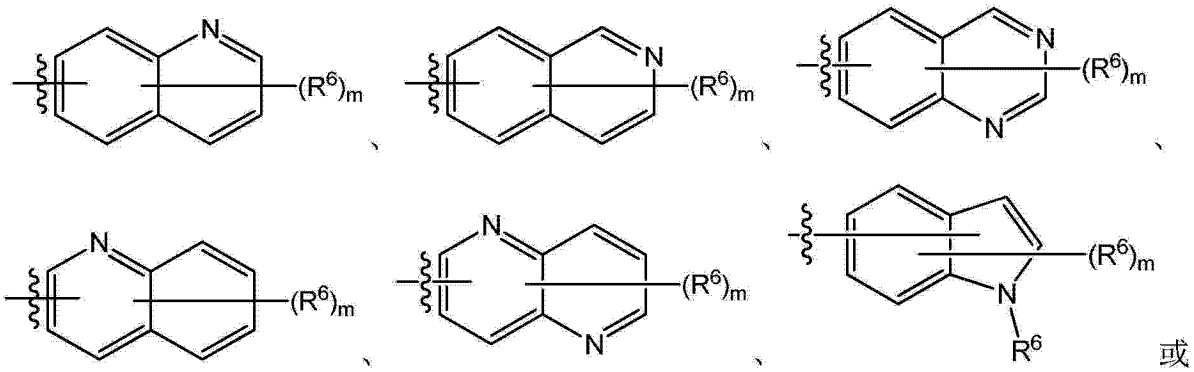
[0375]



或 ，

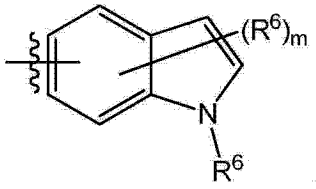
[0376] 其中 $R^{6'}$ 为卤基或氢。在一些实施例中，$R^{6'}$ 为氟、氯、溴或氢。在一些实施例中，R^6 为 $-O(CH_2)_jI_m$；其中 I_m 为造影部分且 j 为 1、2、3、4、5 或 6。在一些实施例中，R^6 为 $-(CH_2)_jO(CH_2)_jI_m$，其中 I_m 为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。在一些实施例中，Z 为：

[0377]



或

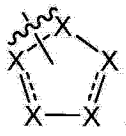
[0378]



。

[0379] 在一些实施例中，Z 为：

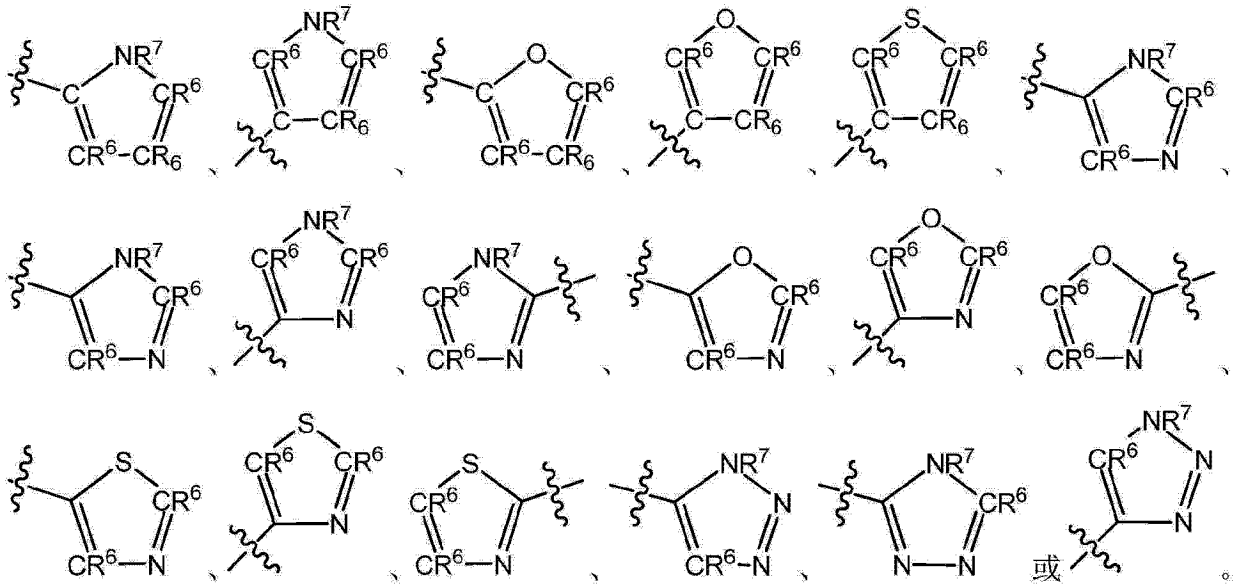
[0380]



，

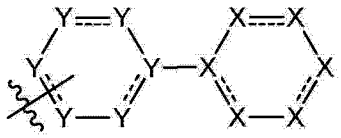
[0381] 每个 X 独立地选自由 C、$C(R^6)$、$C(R^6)_2$、N、NR^7、O 以及 S 组成的群组；且每个 ------ 独立地为单键或双键。在一些实施例中，至少一个 X 不为 C 或 $C(R^6)$。在一些实施例中，至少一个 X 为 N。在一些实施例中，至少一个 X 为 $N(R^7)$。在一些实施例中，至少一个 X 为 O。在一些实施例中，至少一个 X 为 S。在一些实施例中，Z 选自由以下各项组成的群组：

[0382]



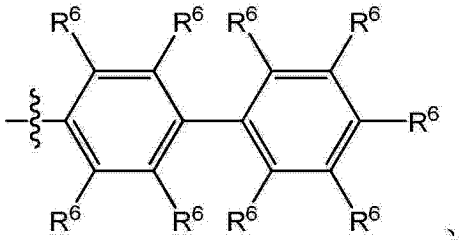
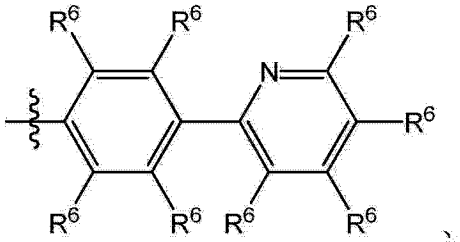
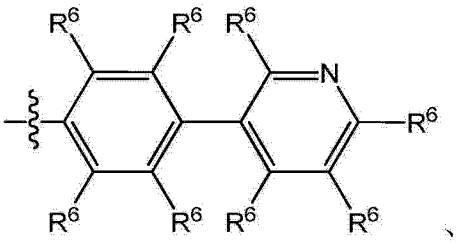
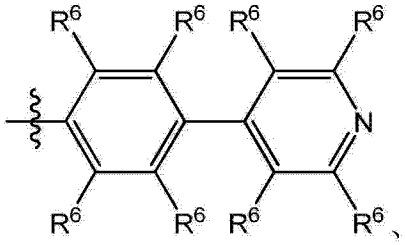
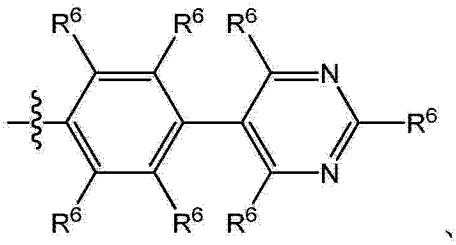
[0383] 在一些实施例中，Z 为：

[0384]



[0385] 每个 Y 独立地选自由 C、$C(R^6)$、$C(R^6)_2$、N、NR^7、O 以及 S 组成的群组；且每个 ------ 独立地为单键或双键，任选地其中缺少一个 X 和 / 或一个 Y。在一些实施例中，可缺少一个 Y 和 / 或一个 X。在一些实施例中，缺少一个 Y。在一些实施例中，缺少一个 X。在一些实施例中，缺少一个 Y 和一个 X。在一些实施例中，缺少一个 Y 且一个 Y 为 N。在一些实施例中，缺少一个 Y 且一个 Y 为 NR^7。在一些实施例中，缺少一个 Y 且一个 Y 为 O。在一些实施例中，缺少一个 Y 且一个 Y 为 S。在一些实施例中，缺少一个 X 且一个 X 为 N。在一些实施例中，缺少一个 X 且一个 X 为 NR^7。在一些实施例中，缺少一个 X 且一个 X 为 O。在一些实施例中，缺少一个 X 且一个 X 为 S。在一些实施例中，关于 Z，至少一个 Y 为 NR^7。在一些实施例中，关于 Z，X 和 Y 各自至少一个为 NR^7。在一些实施例中，关于 Z，至少一个 Y 为 N。在一些实施例中，关于 Z，X 和 Y 各自至少一个为 N。在一些实施例中，关于 Z，至少一个 Y 为 O。在一些实施例中，关于 Z，至少一个 Y 为 S。在一些实施例中，关于 Z，每个 X 为 C 或 $C(R^6)$。在一些实施例中，关于 Z，至少一个 X 不为 C 或 $C(R^6)$。在一些实施例中，关于 Z，至少两个 Y 不为 C 或 $C(R^6)$。在一些实施例中，关于 Z，X 和 Y 各自至少一个不为 C 或 $C(R^6)$。在一些实施例中，关于 Z，至少两个 X 不为 C 或 $C(R^6)$。在一些实施例中，Z 为：

[0386]


、

、

、

、

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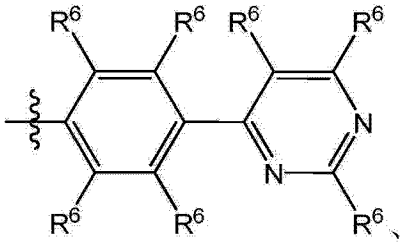
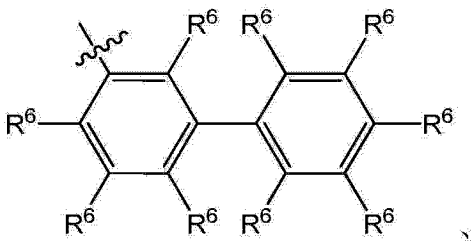
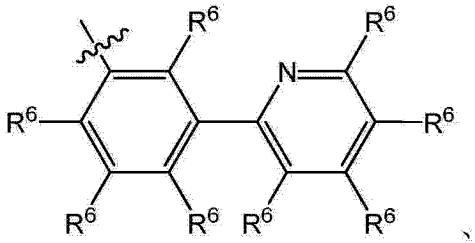
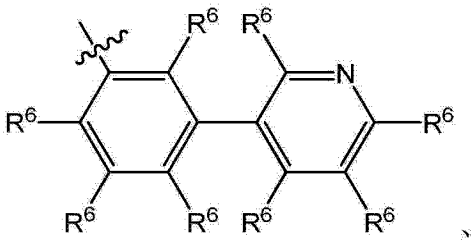
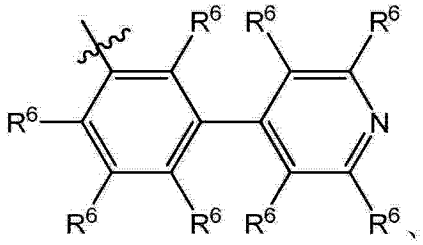

、

、

、

[0387]


、

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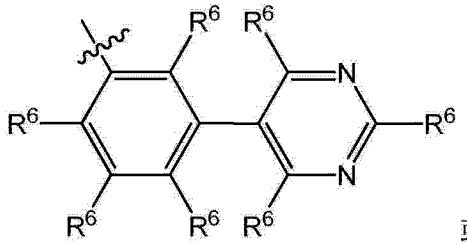
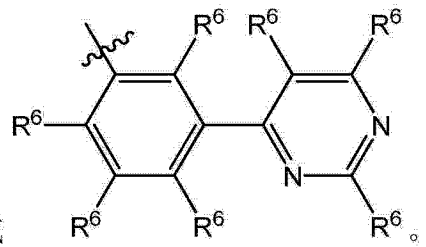
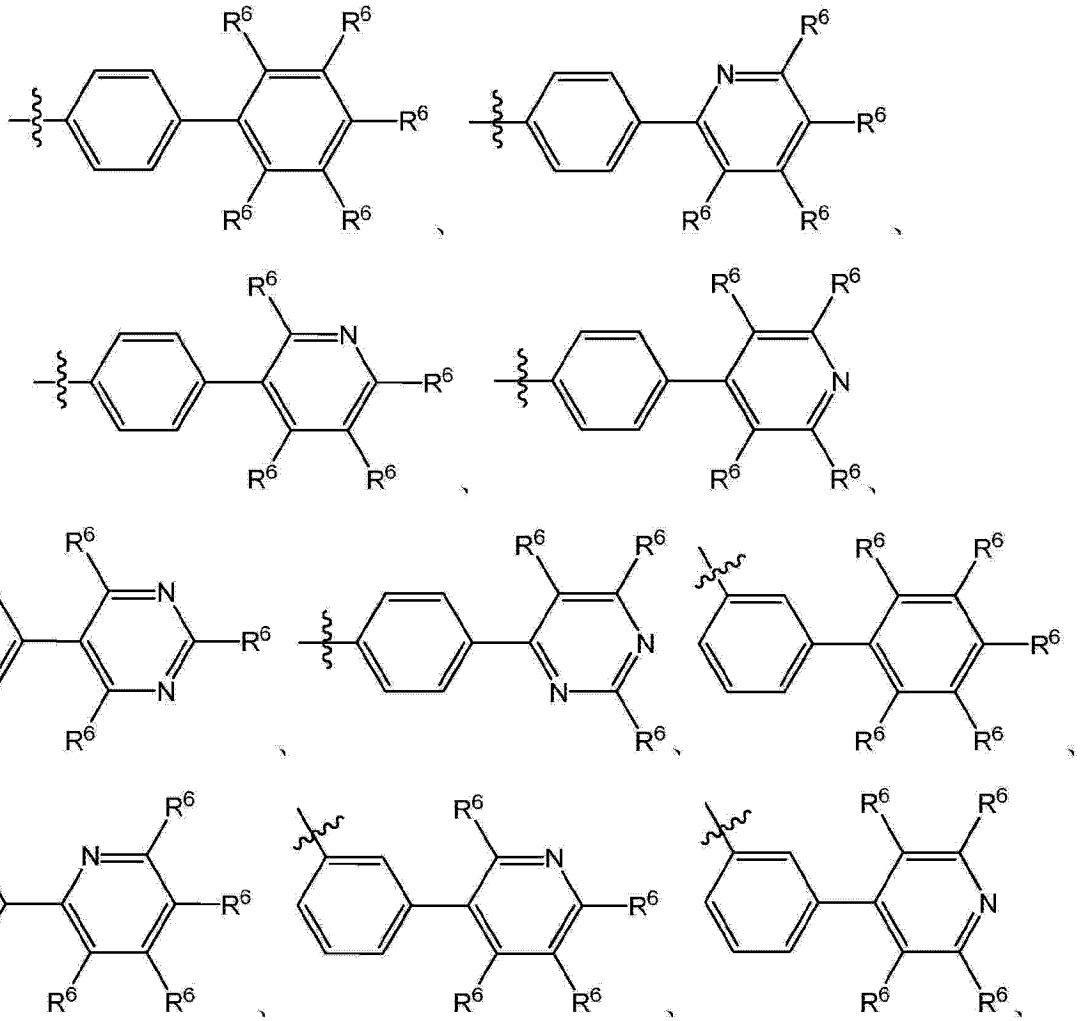
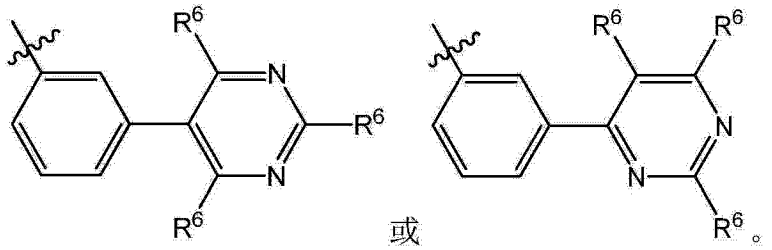

或

。

[0388] 在一些实施例中，Z 为：

[0389]

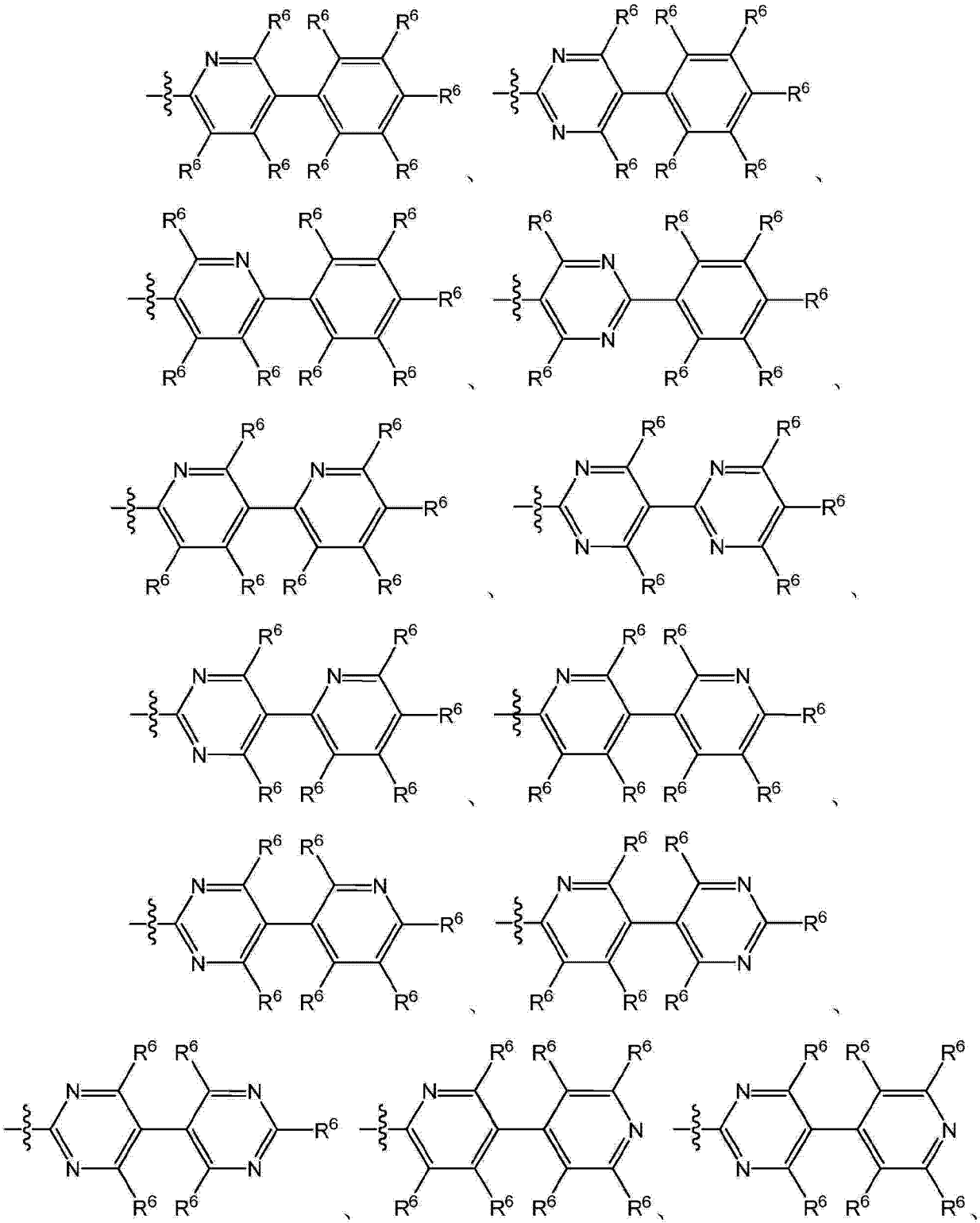


[0390]

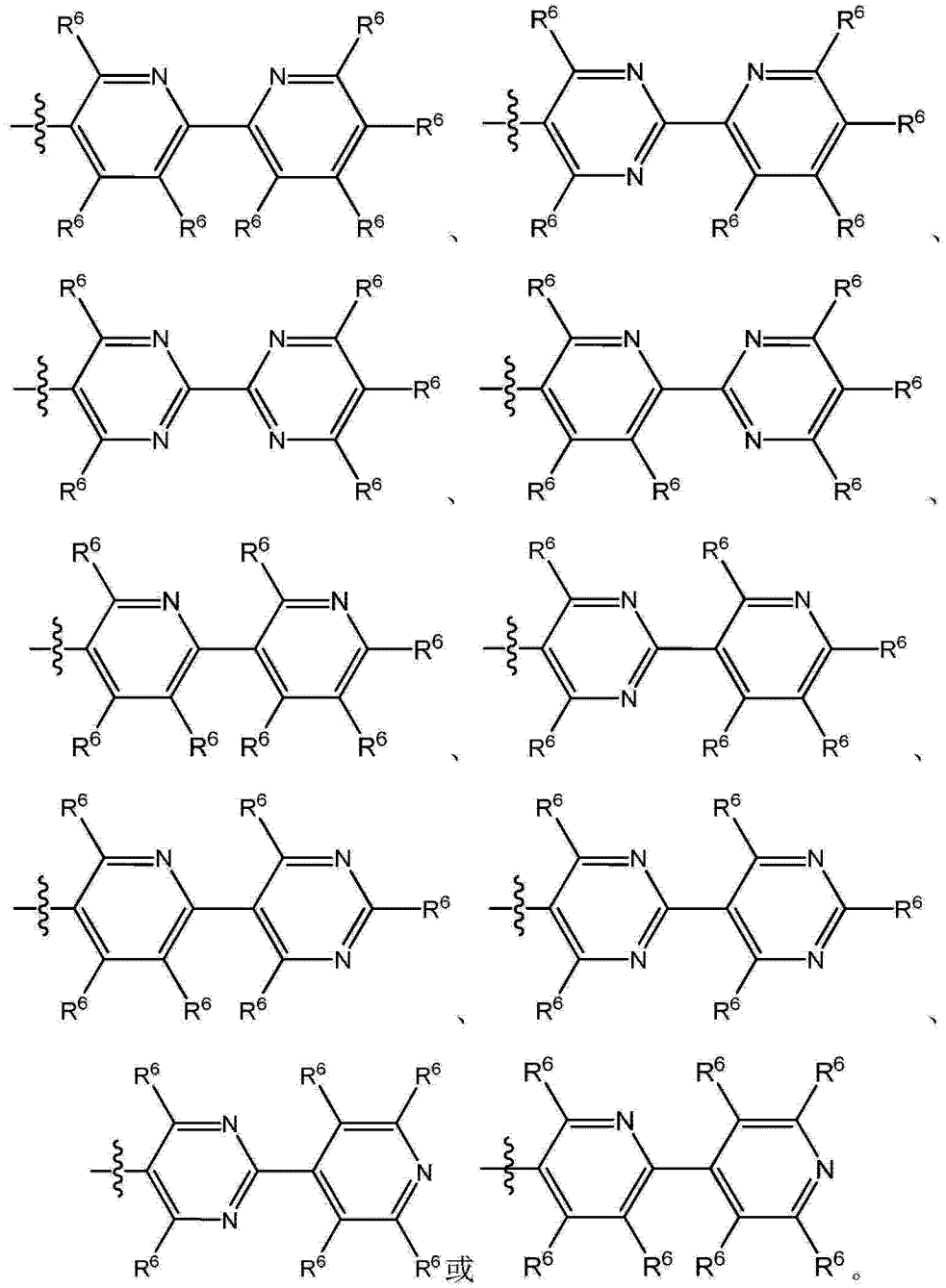


[0391] 在一些实施例中，Z 为：

[0392]



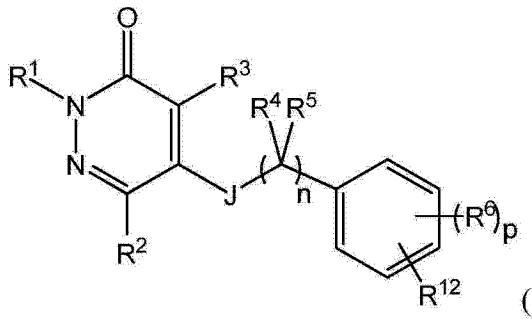
[0393]



[0394] 关于式 (V) 或 (VI) 化合物，本文所述的 Z 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、R^{11}、J、m、q 以及 r 或其组合中的任一者组合。关于式 (VII) 化合物，本文所述的 Z 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、J、n 以及 m 或其组合中的任一者组合。

[0395] 在一些实施例中，提供包含以下结构的化合物：

[0396]



(VIII)

[0397] 或其医药学上可接受的盐，其中：

[0398] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0399] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及造影部分；

[0400] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及造影部分；

[0401] J选自由以下各项组成的群组：$N(R^7)$、S、O、$C(=O)$、$C(=O)O$、$OC(=O)$、$C(=O)N(R^7)$、$N(R^7)C(=O)$、CH_2O以及一键；

[0402] R^4和R^5各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地R^4和R^5中的任何两者相连以形成环；

[0403] n为0、1、2或3；

[0404] 每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

[0405] p为0、1、2、3或4；

[0406] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个R^7可相连以形成环；

[0407] 每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

[0408] R^{12}选自由以下各项组成的群组：任选地经取代的炔基、任选地经取代的烯基、经-CN取代的烷基、经$-C(=O)OR^8$取代的烷基、经$-C(=O)R^8$取代的烷基、经$-N(R^7)_2$取代的烷基、-CN、$-NO_2$、$-N(R^7)_2$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)R^8$、$-C(=O)N(R^7)_2$以

及 $-N(R^7)C(=O)R^8$；

[0409] 每个 R^9 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及造影部分；和

[0410] 每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[0411] 其限制条件为在所述化合物中存在至少一个造影部分。

[0412] R^1 基团的以下描述可联合式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物使用。在一些实施例中，R^1 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分。在一些实施例中，R^1 为氢。在一些实施例中，R^1 为任选地经取代的烷基。在一些实施例中，R^1 为未经取代的烷基。在一些实施例中，R^1 为甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。在一些实施例中，R^1 为叔丁基。在一些实施例中，R^1 为任选地经取代的杂烷基。在一些实施例中，R^1 为未经取代的杂烷基。在一些实施例中，R^1 为 $-[C(R')_2]_jOH$，其中 j 为 1、2、3、4、5 或 6，且每个 R' 相同或不同且为氢或任选地经取代的烷基。在一些实施例中，R^1 为 $-C(CH_3)_2CH_2OH$。在一些实施例中，R^1 为任选地经取代的烷氧基。在一些实施例中，R^1 为任选地经取代的烷氧基烷基。在一些实施例中，R^1 为任选地经取代的芳基。在一些实施例中，R^1 为未经取代的芳基。在一些实施例中，R^1 为任选地经取代的苯基。在一些实施例中，R^1 为未经取代的苯基。在一些实施例中，R^1 为任选地经取代的环烷基。在一些实施例中，R^1 为未经取代的环烷基。在一些实施例中，R^1 为任选地经取代的环己基。在一些实施例中，R^1 为未经取代的环己基。在一些实施例中，R^1 为任选地经取代的环戊基。在一些实施例中，R^1 为未经取代的环戊基。关于式 (I) 或 (II) 化合物，本文所述的 R^1 基团中的每一者可与如本文所述的 R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、J、W、m 以及 n 或其组合中的任一者组合。关于式 (III) 化合物，本文所述的 R^1 基团中的每一者可与如本文所述的 R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、J、Q 以及 n 或其组合中的任一者组合。关于式 (IV) 化合物，本文所述的 R^1 基团中的每一者可与如本文所述的 R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、J、m 以及 n 或其组合中的任一者组合。关于式 (V) 或 (VI) 化合物，本文所述的 R^1 基团中的每一者可与如本文所述的 R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、R^{11}、J、Z、m、q 以及 r 或其组合中的任一者组合。关于式 (VII) 化合物，本文所述的 R^1 基团中的每一者可与如本文所述的 R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、J、Z、n 以及 m 或其组合中的任一者组合。关于式 (VIII) 化合物，本文所述的 R^1 基团中的每一者可与如本文所述的 R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、R^{12}、J、p 以及 n 或其组合中的任一者组合。

[0413] R^2 基团的以下描述可联合式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物使用。在一些实施例中，R^2 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$ 以及造影部分。在一些实施例中，R^2 为氢。在一些实施例中，R^2 为任选地经取代的烷基。在一些实施例中，R^2 为未经取代的烷基。在一些实施例中，R^2 为甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。在一些实施例中，R^2 为任选地经取代的芳基。在一些实施例中，R^2 为未经取代的芳基。在一些实施例中，R^2 为任选地经取代的苯基。在一些实施例中，R^2 为未经取代的苯基。在一些实施例

中，R^2为任选地经取代的环烷基。在一些实施例中，R^2为未经取代的环烷基。在一些实施例中，R^2为任选地经取代的环己基。在一些实施例中，R^2为未经取代的环己基。本文所述的R^2基团中的每一者可与如本文所述的R^1、R^3、R^4、R^5、R^6、R^{12}、J、Q、W 和 / 或 m 或其组合中的任一者组合。关于式 (I) 或 (II) 化合物，本文所述的R^2基团中的每一者可与如本文所述的R^1、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、J、W、m 以及 n 或其组合中的任一者组合。关于式 (III) 化合物，本文所述的R^2基团中的每一者可与如本文所述的R^1、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、J、Q 以及 n 或其组合中的任一者组合。关于式 (IV) 化合物，本文所述的R^2基团中的每一者可与如本文所述的R^1、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、J、m 以及 n 或其组合中的任一者组合。关于式 (V) 或 (VI) 化合物，本文所述的R^2基团中的每一者可与如本文所述的R^1、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、R^{11}、J、Z、m、q 以及 r 或其组合中的任一者组合。关于式 (VII) 化合物，本文所述的R^2基团中的每一者可与如本文所述的R^1、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、J、Z、n 以及 m 或其组合中的任一者组合。关于式 (VIII) 化合物，本文所述的R^2基团中的每一者可与如本文所述的R^1、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、R^{12}、J、p 以及 n 或其组合中的任一者组合。

[0414] R^3基团的以下描述可联合式 (I)、(II)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物使用。在一些实施例中，R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及造影部分。在一些实施例中，R^3为 H。在一些实施例中，R^3为任选地经取代的烷基。在一些实施例中，R^3为任选地经除卤素以外的部分取代的烷基。在一些实施例中，R^3为未经取代的烷基。在一些实施例中，R^3为甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。在一些实施例中，R^3为甲基。在一些实施例中，R^3为异丙基。在一些实施例中，R^3为 -CN。在一些实施例中，R^3为 $-NO_2$。在一些实施例中，R^3为任选地经取代的杂烷基。在一些实施例中，R^3为未经取代的杂烷基。在一些实施例中，R^3为任选地经取代的芳基。在一些实施例中，R^3为未经取代的芳基。在一些实施例中，R^3为任选地经取代的苯基。在一些实施例中，R^3为未经取代的苯基。在一些实施例中，R^3为卤基。在一些实施例中，R^3为 F。在一些实施例中，R^3为 ^{18}F。在一些实施例中，R^3为 Cl。在一些实施例中，R^3为 Br。在一些实施例中，R^3为 I。在一些实施例中，R^3不为卤基。在一些实施例中，R^3不为卤基、任选地经取代的卤烷基或造影部分。在一些实施例中，R^3不为任选地经取代的卤烷基。在一些实施例中，R^3为造影部分。在一些实施例中，R^3不为造影部分。本文所述的R^3基团中的每一者可与如本文所述的R^1、R^2、R^4、R^5、R^6、R^{12}、J、Q、W 和 / 或 m 或其组合中的任一者组合。关于式 (I) 或 (II) 化合物，本文所述的R^3基团中的每一者可与如本文所述的R^1、R^2、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、J、W、m 以及 n 或其组合中的任一者组合。关于式 (IV) 化合物，本文所述的R^3基团中的每一者可与如本文所述的R^1、R^2、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、J、m 以及 n 或其组合中的任一者组合。关于式 (V) 或 (VI) 化合物，本文所述的R^3基团中的每一者可与如本文所述的R^1、R^2、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、R^{11}、J、Z、m、q 以及 r 或其组合中的任一者组合。关于式 (VII) 化合物，本文所述的R^3基团中的每一者可与如本文所述的R^1、R^2、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、J、Z、n 以及 m 或其组合中的任一者组合。关于式 (VIII) 化合物，本文所述的R^3基团中的每一者可与如本文所述的R^1、R^2、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、R^{12}、J、p 以及 n 或其组合中的任一者组合。

[0415] R^3基团的以下描述可联合式 (III) 化合物使用。在一些实施例中，R^3选自由以

下各项组成的群组：氢、未经取代的烷基或任选地经除卤素以外的部分取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、-CN 以及 $-NO_2$。在一些实施例中，R^3为任选地经除卤素以外的基团取代的烷基。在一些实施例中，R^3为未经取代的烷基。在一些实施例中，R^3为甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。在一些实施例中，R^3为甲基。在一些实施例中，R^3为异丙基。在一些实施例中，R^3为 -CN。在一些实施例中，R^3为 $-NO_2$。在一些实施例中，R^3为任选地经取代的杂烷基。在一些实施例中，R^3为未经取代的杂烷基。在一些实施例中，R^3为任选地经取代的芳基。在一些实施例中，R^3为未经取代的芳基。在一些实施例中，R^3为任选地经取代的苯基。在一些实施例中，R^3为未经取代的苯基。关于式 (III) 化合物，本文所述的 R^3基团中的每一者可与如本文所述的 R^1、R^2、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、J、Q 以及 n 或其组合中的任一者组合。

[0416] R^4和 R^5基团的以下描述可联合式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物使用。在一些实施例中，R^4和 R^5各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地 R^4和 R^5中的任何两者相连以形成环。在一些实施例中，R^4和 R^5中的任何两者可相连以形成环。在一些情况下，所形成的环可包含总计 4、5、6、7、8 或 8 个以上原子。在一些情况下，所述环包含 5 或 6 个原子。在一些实施例中，R^4和 R^5中的每一者为 H。在一些实施例中，至少一个 R^4和 R^5为 ^2H。在一些实施例中，R^4和 R^5中的每一者为 ^2H。在一些实施例中，R^4和 R^5中的每一者为 H 或任选地经取代的烷基。在一些实施例中，R^4和 R^5中的每一者为 H 或未经取代的烷基。在一些实施例中，至少一个 R^4或 R^5不为 H。关于式 (I) 或 (II) 化合物，本文所述的 R^4和 / 或 R^5基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^6、R^7、R^8、R^9、$R^{9'}$、J、W、m 以及 n 或其组合中的任一者组合。关于式 (III) 化合物，本文所述的 R^4和 / 或 R^5基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^6、R^7、R^8、R^9、$R^{9'}$、J、Q 以及 n 或其组合中的任一者组合。关于式 (IV) 化合物，本文所述的 R^4和 / 或 R^5基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^6、R^7、R^8、R^9、$R^{9'}$、J、m 以及 n 或其组合中的任一者组合。关于式 (V) 或 (VI) 化合物，本文所述的 R^4和 / 或 R^5基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^6、R^7、R^8、R^9、$R^{9'}$、R^{11}、J、Z、m、q 以及 r 或其组合中的任一者组合。关于式 (VII) 化合物，本文所述的 R^4和 / 或 R^5基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^6、R^7、R^8、R^9、$R^{9'}$、J、Z、n 以及 m 或其组合中的任一者组合。关于式 (VIII) 化合物，本文所述的 R^4和 / 或 R^5基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^6、R^7、R^8、R^9、$R^{9'}$、R^{12}、J、p 以及 n 或其组合中的任一者组合。

[0417] R^4、R^5和 R^{11}基团的以下描述可联合式 (VI) 化合物使用。在一些实施例中，R^4、R^5和 R^{11}各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地 R^4、R^5及 R^{11}中的任何两者相连以形成环。在一些实施例中，R^4、R^5及 R^{11}中的任何两者可相连以形成环。在一些情况下，所形成的环可包含总计 4、5、6、7、8 或 8 个以上原子。在一些情况下，所述环包含 5 或 6 个原子。在一些实施例中，R^4、R^5和 R^{11}中的每一者为 H。在一些实施例中，至少一个 R^4、R^5和 R^{11}为 ^2H。在一些实施例中，R^4、R^5和 R^{11}中的每一者为 ^2H。在一些实施例中，R^4、R^5和 R^{11}中的每一者为 H 或任选地经取代的烷基。在一些实施例中，R^4、R^5和 R^{11}中的每一者为 H 或未经取代的烷基。在一些实施例中，至少一个 R^4、R^5和 R^{11}不为 H。关于式 (VI) 化合物，本文所述的 R^4、R^5和 / 或 R^{11}基团中的每一者可与如本文所述的 R^1、R^2、R^3、

R^6、R^7、R^8、R^9、$R^{9'}$、J、Z、m、q 以及 r 或其组合中的每一者组合。

[0418] R^{12}基团的以下描述可联合式 (VIII) 化合物使用。在一些实施例中，R^{12}选自由以下各项组成的群组：任选地经取代的炔基、任选地经取代的烯基、经 -CN 取代的烷基、经 $-C(=O)OR^8$取代的烷基、经 $-C(=O)R^8$取代的烷基、经 $-N(R^7)_2$取代的烷基、-CN、$-NO_2$、$-N(R^7)_2$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)R^8$、$-C(=O)N(R^7)_2$以及 $-N(R^7)C(=O)R^8$，其中每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7可相连以形成环；且每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分。在一些实施例中，任何两个 R^7可相连以形成环。在一些情况下，所形成的环可包含总计 4、5、6、7、8 或 8 个以上原子。在一些情况下，所述环包含 5 或 6 个原子。在一些实施例中，R^{12}为任选地经取代的炔基。在一些实施例中，R^{12}为未经取代的炔基。在一些实施例中，R^{12}为任选地经取代的烯基。在一些实施例中，R^{12}为未经取代的烯基。在一些实施例中，R^{12}为经 $-C(=O)OR^8$取代的烷基。在一些实施例中，R^{12}为经 $-C(=O)R^8$取代的烷基。在一些实施例中，R^{12}为经 $-N(R^7)_2$取代的烷基。在一些实施例中，R^{12}为 -CN。在一些实施例中，R^{12}为 $-NO_2$。在一些实施例中，R^{12}为 $-N(R^7)_2$。在一些实施例中，R^{12}为 $-C(=O)OR^8$。在一些实施例中，R^{12}为 $-OC(=O)R^8$。在一些实施例中，R^{12}为 $-C(=O)R^8$。在一些实施例中，R^{12}为 $-C(=O)N(R^7)_2$。在一些实施例中，R^{12}为 $-N(R^7)C(=O)R^8$。在一些实施例中，R^{12}为 $-NO_2$、$-C(=O)(CH_2)_uI_m$、$-C(=O)O(CH_2)_uI_m$、$-C\equiv C(CH_2)_uI_m$或 $-Si(烷基)_2I_m$，其中 I_m为造影部分且 u 为 1、2、3、4、5 或 6。关于式 (VIII) 化合物，本文所述的 R^{12}基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、J、p 以及 n 或其组合中的任一者组合。

[0419] J 基团的以下描述可联合式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物使用。在一些实施例中，J 选自由以下各项组成的群组：$N(R^7)$、S、O、$C(=O)$、$C(=O)O$、$OC(=O)$、$C(=O)N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键，其中每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7可相连以形成环。在一些实施例中，任何两个 R^7可相连以形成环。在一些情况下，所形成的环可包含总计 4、5、6、7、8 或 8 个以上原子。在一些情况下，所述环包含 5 或 6 个原子。在一些实施例中，J 为键。在一些实施例中，J 为 O。在一些实施例中，J 为 S。在一些实施例中，J 为 $N(R^7)$。在一些实施例中，J 为 $C(=O)$。在一些实施例中，J 为 $C(=O)O$。在一些实施例中，J 为 $OC(=O)$。在一些实施例中，J 为 $-CH_2O$。在一些实施例中，J 为 $N(R^7)$ 或 $C(=O)N(R^7)$ 且任何两个 R^7相连以形成环。在一些情况下，所形成的环可包含总计 4、5、6、7、8 或 8 个以上原子。在一些情况下，所述环包含 5 或 6 个原子。关于式 (I) 或 (II) 化合物，本文所述的 J 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、W、m 以及 n 或其组合中的任一者组合。关于式 (III) 化合物，本文所述的 J 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、Q 以及 n 或其组合中的任一者组合。关于式 (IV) 化

合物，本文所述的 J 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、m 以及 n 或其组合中的任一者组合。关于式 (V) 或 (VI) 化合物，本文所述的 J 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、R^{11}、Z、m、q 以及 r 或其组合中的任一者组合。关于式 (VIII) 化合物，本文所述的 J 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、R^{12}、p 以及 n 或其组合中的任一者组合。

[0420] J 和 n 基团的以下描述可联合式 (I)、(II)、(III)、(IV) 或 (VIII) 化合物使用。在一些实施例中，n 为 0。在一些实施例中，n 为 1。在一些实施例中，n 为 2。在一些实施例中，n 为 3。在一些实施例中，J 为 O 且 n 为 0。在一些实施例中，J 为 O 且 n 为 1。在一些实施例中，J 为 O 且 n 为 2。在一些实施例中，J 为 O 且 n 为 3。在一些实施例中，J 为 S 且 n 为 0。在一些实施例中，J 为 S 且 n 为 1。在一些实施例中，J 为 S 且 n 为 2。在一些实施例中，J 为 S 且 n 为 3。本文所述的 J 基团和 / 或 n 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^{12}、Q、W 和 / 或 m 或其组合中的任一者组合。关于式 (I) 或 (II) 化合物，本文所述的 J 和 / 或 n 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、W 以及 m 或其组合中的任一者组合。关于式 (III) 化合物，本文所述的 J 和 / 或 n 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$ 以及 Q 或其组合中的任一者组合。关于式 (IV) 化合物，本文所述的 J 和 / 或 n 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$ 以及 m 或其组合中的任一者组合。关于式 (VIII) 化合物，本文所述的 J 和 / 或 n 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、R^{12} 以及 p 或其组合中的任一者组合。

[0421] J、q 和 / 或 r 基团的以下描述可联合式 (V) 或 (VI) 化合物使用。在一些实施例中，q 为 0。在一些实施例中，q 为 1。在一些实施例中，q 为 2。在一些实施例中，q 为 3。在一些实施例中，r 为 0。在一些实施例中，r 为 1。在一些实施例中，r 为 2。在一些实施例中，r 为 3。在一些实施例中，q 和 r 各自为 0。在一些实施例中，q 和 r 各自为 1。在一些实施例中，J 为 O 且 q 和 r 各自为 0。在一些实施例中，J 为 O 且 q 和 r 各自为 1。在一些实施例中，J 为 O 且 q 和 r 各自为 2。在一些实施例中，J 为 O 且 q 和 r 各自为 3。在一些实施例中，J 为 S 且 q 和 r 各自为 0。在一些实施例中，J 为 S 且 q 和 r 各自为 1。在一些实施例中，J 为 S 且 q 和 r 各自为 2。在一些实施例中，J 为 S 且 q 和 r 各自为 3。在一些实施例中，J 为 O，q 为 0 且 r 为 0、1、2 或 3。在一些实施例中，J 为 O，q 为 1 且 r 为 0、1、2 或 3。在一些实施例中，J 为 O，q 为 2 且 r 为 0、1、2 或 3。在一些实施例中，J 为 O，q 为 3 且 r 为 0、1、2 或 3。关于式 (V) 或 (VI) 化合物，本文所述的 J、q 和 / 或 r 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、R^{11}、Z 以及 m 或其组合中的任一者组合。

[0422] J 和 n 基团的以下描述可联合式 (VII) 化合物使用。在一些实施例中，n 为 1。在一些实施例中，n 为 2。在一些实施例中，n 为 3。在一些实施例中，J 为 O 且 n 为 1。在一些实施例中，J 为 O 且 n 为 2。在一些实施例中，J 为 O 且 n 为 3。在一些实施例中，J 为 S 且 n 为 1。在一些实施例中，J 为 S 且 n 为 2。在一些实施例中，J 为 S 且 n 为 3。关于式 (VII) 化合物，本文所述的 J 和 / 或 n 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、Z 以及 m 或其组合中的任一者组合。

[0423] 在一些实施例中，关于式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物，所述化合物包含单个造影部分。在一些实施例中，关于式 (I)、(II)、(III)、(IV) 或

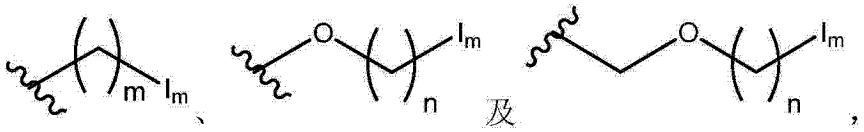
(VII) 化合物，至少一个造影部分存在于 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8或 R^9中。在一些实施例中，关于式 (VIII) 化合物，至少一个造影部分存在于 R^1、R^3、R^4、R^5、R^6、R^7、R^8、R^9或 R^{12}中。在一些实施例中，关于式 (V) 或 (VI) 化合物，至少一个造影部分存在于 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9或 R^{11}中。在一些实施例中，关于式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物，至少一个造影部分存在于 R^1、R^2、R^3、R^4、R^5或 R^6中。在一些实施例中，关于式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物，至少一个造影部分存在于 R^6中。如所属领域的技术人员所了解，当提及造影部分时，所述造影部分“存在于”实施例中的基团中，其中 1) 造影部分为基团 (例如 R^6为造影部分) 或 b) 基团包含造影部分 (例如 R^6经造影部分取代)。在一些实施例中，关于式 (I)、(II)、(III)、(IV)、(V)、(VI) 或 (VII) 化合物，R^1、R^2、R^3、R^4、R^5或 R^6包含至少一个造影部分。在一些实施例中，关于式 (VIII) 化合物，R^1、R^2、R^3、R^4、R^5、R^6或 R^{12}包含至少一个造影部分。在一些实施例中，关于式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物，至少一个 R^6经至少一个造影部分取代。在一些实施例中，关于式 (I)、(II)、(IV) 或 (VII) 化合物，R^1、R^2、R^3、R^4、R^5或 R^6为至少一个造影部分。在一些实施例中，关于式 (III) 化合物，R^1、R^2、R^4、R^5或 R^6为至少一个造影部分。在一些实施例中，关于式 (V) 或 (VI) 化合物，R^1、R^2、R^3、R^4、R^5、R^6或 R^{11}为至少一个造影部分。在一些实施例中，关于式 (VIII) 化合物，R^1、R^3、R^4、R^5、R^6或 R^{12}为至少一个造影部分。在一些实施例中，关于式 (I)、(II)、(IV) 或 (VII) 化合物，R^1、R^2、R^3、R^4、R^5或 R^6不为造影部分。在一些实施例中，关于式 (III) 化合物，R^1、R^2、R^4、R^5或 R^6不为造影部分。在一些实施例中，关于式 (V) 或 (VI) 化合物，R^1、R^2、R^3、R^4、R^5、R^6或 R^{11}不为造影部分。在一些实施例中，关于式 (VIII) 化合物，R^1、R^3、R^4、R^5、R^6或 R^{12}不为造影部分。在一些实施例中，关于式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物，至少一个 R^6为造影部分。关于式 (I) 或 (II) 化合物，本文所述的造影部分的置放中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、J、W、m 以及 n 或其组合中的任一者组合。关于式 (III) 化合物，本文所述的造影部分的置放中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、Q、J 以及 n 或其组合中的任一者组合。关于式 (IV) 化合物，本文所述的造影部分的置放中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、J、n 以及 m 或其组合中的任一者组合。关于式 (V) 或 (VI) 化合物，本文所述的造影部分的置放中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、R^{11}、J、Z、m、q 以及 r 或其组合中的任一者组合。关于式 (VII) 化合物，本文所述的造影部分的置放中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、J、Z、n 以及 m 或其组合中的任一者组合。关于式 (VIII) 化合物，本文所述的造影部分的置放中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9、$R^{9'}$、R^{12}、J、p 以及 n 或其组合中的任一者组合。

[0424] 造影部分的以下描述可联合式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物使用。在一些实施例中，至少一个造影部分选自由以下各项组成的群组：^{11}C、^{13}N、^{18}F、^{76}Br、^{89}Zr、^{123}I、^{124}I、^{125}I、^{131}I、^{99m}Tc、^{95}Tc、^{111}In、^{62}Cu、^{64}Cu、^{67}Ga 以及 ^{68}Ga。在一些实施例中，至少一个造影部分为 ^{18}F。本文中将较详细描述造影部分。

[0425] R^6基团的以下描述可联合式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物使用。在一些实施例中，关于式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物，除一个 R^6以外所有 R^6均为 H。即，所有 R^6为 H 且一个 R^6不为 H。在一些情况下，

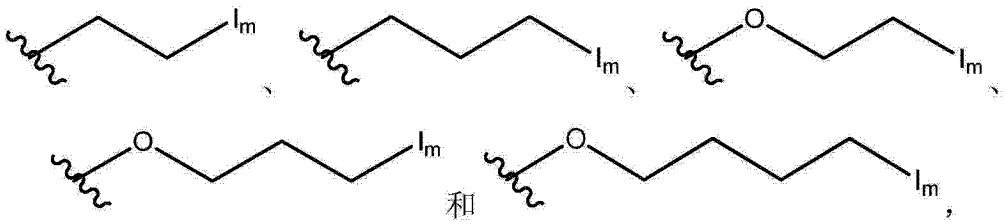
不为 H 的一个 R^6 经至少一个造影部分取代。在一些情况下，不为 H 的一个 R^6 为至少一个造影部分。在一些实施例中，关于式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物，至少一个 R^6 为各自经造影部分取代的任选地经取代的烷基、任选地经取代的烷氧基或任选地经取代的烷氧基烷基。在一些实施例中，关于式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物，至少一个 R^6 为 $-(CH_2)_jI_m$；其中 I_m 为造影部分且 j 为 1、2、3、4、5 或 6。在一些情况下，至少一个 R^6 为 $-(CH_2)I_m$、$-(CH_2)_2I_m$、$-(CH_2)_3I_m$、$-(CH_2)_4I_m$、$-(CH_2)_5I_m$、$-(CH_2)_6I_m$、$-(CH_2)_7I_m$、$-(CH_2)_8I_m$、$-(CH_2)_9I_m$ 或 $-(CH_2)_{10}I_m$。在一些情况下，至少一个 R^6 为 $-(CH_2)^{18}F$、$-(CH_2)_2{}^{18}F$、$-(CH_2)_3{}^{18}F$、$-(CH_2)_4{}^{18}F$、$-(CH_2)_5{}^{18}F$、$-(CH_2)_6{}^{18}F$、$-(CH_2)_7{}^{18}F$、$-(CH_2)_8{}^{18}F$、$-(CH_2)_9{}^{18}F$ 或 $-(CH_2)_{10}{}^{18}F$。在一些实施例中，至少一个 R^6 为 $-O(CH_2)_jI_m$；其中 I_m 为造影部分且 j 为 1、2、3、4、5 或 6。在一些情况下，至少一个 R^6 为 $-O(CH_2)_5I_m$、$-O(CH_2)_6I_m$、$-O(CH_2)_7I_m$、$-O(CH_2)_8I_m$、$-O(CH_2)_9I_m$ 或 $-O(CH_2)_{10}I_m$。在一些情况下，至少一个 R^6 为 $-O(CH_2)^{18}F$、$-O(CH_2)_2{}^{18}F$、$-O(CH_2)_3{}^{18}F$、$-O(CH_2)_4{}^{18}F$、$-O(CH_2)_5{}^{18}F$、$-O(CH_2)_6{}^{18}F$、$-O(CH_2)_7{}^{18}F$、$-O(CH_2)_8{}^{18}F$、$-O(CH_2)_9{}^{18}F$ 或 $-O(CH_2)_{10}{}^{18}F$。在一些实施例中，至少一个 R^6 为 $-(CH_2)_jO(CH_2)_jI_m$；其中 I_m 为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。在一些实施例中，至少一个 R^6 为 $-(CH_2)O(CH_2)_jI_m$；其中 I_m 为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。在一些情况下，至少一个 R^6 为 $-CH_2O(CH_2)I_m$、$-CH_2O(CH_2)_2I_m$、$-CH_2O(CH_2)_3I_m$、$-CH_2O(CH_2)_4I_m$、$-CH_2O(CH_2)_5I_m$、$-CH_2O(CH_2)_6I_m$、$-CH_2O(CH_2)_7I_m$、$-CH_2O(CH_2)_8I_m$、$-CH_2O(CH_2)_9I_m$ 或 $-CH_2O(CH_2)_{10}I_m$。在一些情况下，至少一个 R^6 为 $-CH_2O(CH_2)^{18}F$、$-CH_2O(CH_2)_2{}^{18}F$、$-CH_2O(CH_2)_3{}^{18}F$、$-CH_2O(CH_2)_4{}^{18}F$、$-CH_2O(CH_2)_5{}^{18}F$、$-CH_2O(CH_2)_6{}^{18}F$、$-CH_2O(CH_2)_7{}^{18}F$、$-CH_2O(CH_2)_8{}^{18}F$、$-CH_2O(CH_2)_9{}^{18}F$ 或 $-CH_2O(CH_2)_{10}{}^{18}F$。在一些实施例中，至少一个 R^6 为 $-C\equiv C-(CH_2)_jI_m$；其中 I_m 为造影部分且 j 为 1、2、3、4、5 或 6。在一些实施例中，至少一个 R^6 为 $-[(CH_2)_jO]_j(CH_2)_jI_m$；其中 I_m 为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。在一些实施例中，至少一个 R^6 为 $-O[(CH_2)_jO]_j(CH_2)_jI_m$；其中 I_m 为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。在一些实施例中，至少一个 R^6 为经造影部分取代的任选地经取代的烷基。在一些实施例中，至少一个 R^6 为 $-C(=O)O(CH_2)_jI_m$；其中 I_m 为造影部分且 j 为 1、2、3、4、5 或 6。在一些实施例中，至少一个 R^6 为 $-C(=O)(CH_2)_jI_m$；其中 I_m 为造影部分且 j 为 1、2、3、4、5 或 6。在一些实施例中，至少一个 R^6 为 $-(CH_2)_jNH(CH_2)_jI_m$；其中 I_m 为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。在一些实施例中，至少一个 R^6 为 $Si(R^9)_2I_m$，其中每个 R^9 为任选地经取代的烷基且其中 I_m 为造影部分。在一些实施例中，至少一个 R^6 为 $B(R^{9'})_2I_m$，其中每个 $R^{9'}$ 为任选地经取代的烷基且其中 I_m 为造影部分。在一些实施例中，至少一个 R^6 选自由以下各项组成的群组：$-C\equiv C-CH_2CH_2CH_2I_m$、$-C\equiv C-CH_2CH_2I_m$、$-C\equiv C-CH_2I_m$、$-CH_2I_m$、$-(CH_2)_2I_m$、$-(CH_2)_3I_m$、$-(CH_2)_4I_m$、$-(CH_2)_5I_m$、$-(CH_2)_6I_m$、$-OCH_2I_m$、$-O(CH_2)_2I_m$、$-O(CH_2)_3I_m$、$-O(CH_2)_4I_m$、$-O(CH_2)_5I_m$、$-O(CH_2)_6I_m$、$-CH_2O(CH_2)_2I_m$、$-CH(CH_3)O(CH_2)_2I_m$、$-CH_2O(CH_2)_3I_m$、$-CD_2O(CH_2)_2I_m$、$-(CH_2)_2O(CH_2)_2I_m$、$-CHBrC(CH_3)_2I_m$、$-CHClC(CH_3)_2I_m$、$-CHFC(CH_3)_2I_m$、$-C(=O)OCH_2I_m$、$-C(=O)O(CH_2)_2I_m$、$-C(=O)O(CH_2)_3I_m$、$-CH_2NH(CH_2)_2I_m$、$-CH_2NHCH_2I_m$、$-CH_2O(CH_2)_2O(CH_2)_2I_m$、$-CH_2O(CH_2)_2O(CH_2)_3I_m$、$-O(CH_2)_2O(CH_2)_2I_m$、$-C(=O)(CH_2)_2I_m$ 以及 $-C(=O)(CH_2)_3I_m$。在一些实施例中，I_m 为 ^{18}F。在一些实施例中，至少一个 R^6 选自由以下各项组成的群组：

[0426]



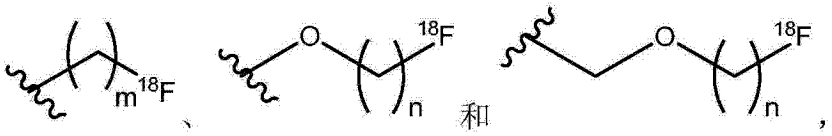
[0427] 其中 m 和 n 为介于 1 与 6 之间（包括 1 和 6）的整数，且 I_m 为造影部分。在一些实施例中，至少一个 R^6 选自由以下各项组成的群组：

[0428]



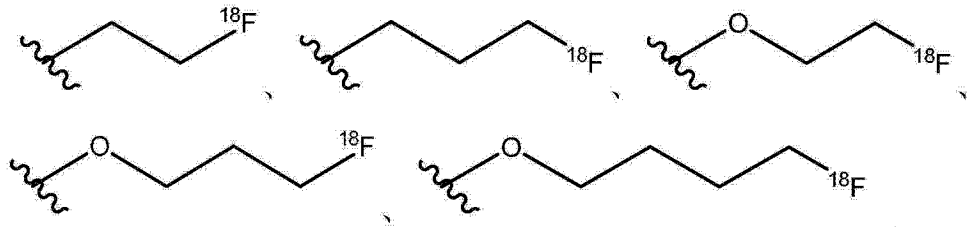
[0429] 其中 I_m 为造影部分。在一些实施例中，至少一个 R^6 选自由以下各项组成的群组：

[0430]

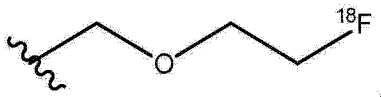


[0431] 其中 m 和 n 为介于 1 与 6 之间（包括 1 及 6）的整数。在一些实施例中，至少一个 R^6 选自由以下各项组成的群组：

[0432]



[0433] 以及

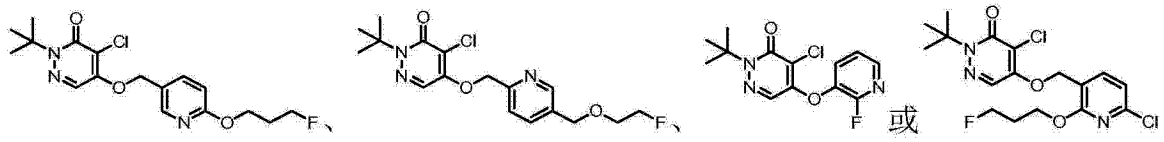


。

[0434] 在一些实施例中，关于式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物，至少一个 R^6 任选地经至少一个 ^2H 取代。在一些实施例中，至少一个 R^6 为 $Si(R^9)_3$。在一些实施例中，至少一个 R^6 为 $B(R^{9'})_3$。在一些实施例中，至少一个 R^6 为 $-NO_2$。在一些实施例中，至少一个 R^6 为卤基。在一些实施例中，至少一个 R^6 为 Cl。在一些实施例中，至少一个 R^6 为 Br。在一些实施例中，至少一个 R^6 为 F。关于式 (I) 或 (II) 化合物，本文所述的 R^6 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^7、R^8、R^9、$R^{9'}$、J、W、m 以及 n 或其组合中的任一者组合。关于式 (III) 化合物，本文所述的 R^6 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^7、R^8、R^9、$R^{9'}$、Q、J 以及 n 或其组合中的任一者组合。关于式 (IV) 化合物，本文所述的 R^6 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^7、R^8、R^9、$R^{9'}$、J、m 以及 n 或其组合中的任一者组合。关于式 (V) 或 (VI) 化合物，本文所述的 R^6 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^7、R^8、R^9、$R^{9'}$、R^{11}、J、Z、m、q 以及 r 或其组合中的任一者组合。关于式 (VII) 化合物，本文所述的 R^6 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^7、R^8、R^9、$R^{9'}$、J、Z、n 以及 m、或其组合中的任一者组合。关于式 (VIII) 化合物，本文所述的 R^6 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^7、R^8、R^9、$R^{9'}$、R^{12}、J、p 以及 n、或其组合中的任一者组合。

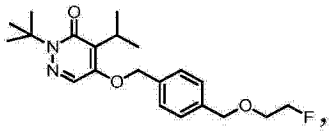
[0435] 在一些实施例中，式 (II) 化合物选自由以下各项组成的群组 ：

[0436]



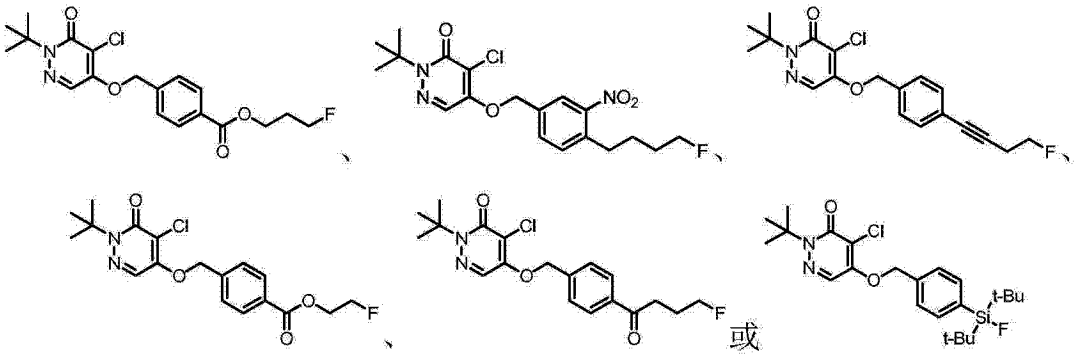
[0437] 或其医药学上可接受的盐，其中 F 任选地为 ^{18}F。在一些实施例中，式 (IV) 化合物具有下式 ：

[0438]



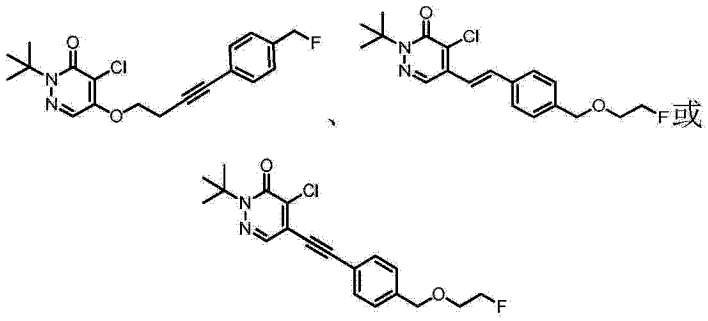
[0439] 或其医药学上可接受的盐，其中 F 任选地为 ^{18}F。在一些实施例中，式 (VIII) 化合物具有下式 ：

[0440]



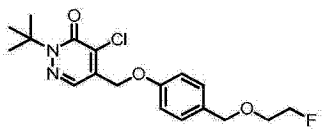
[0441] 或其医药学上可接受的盐，其中 F 任选地为 ^{18}F。在一些实施例中，式 (V) 或 (VI) 化合物选自由以下各项组成的群组 ：

[0442]



[0443] 或其医药学上可接受的盐，其中 F 任选地为 ^{18}F。在一些实施例中，式 (VII) 化合物具有下式 ：

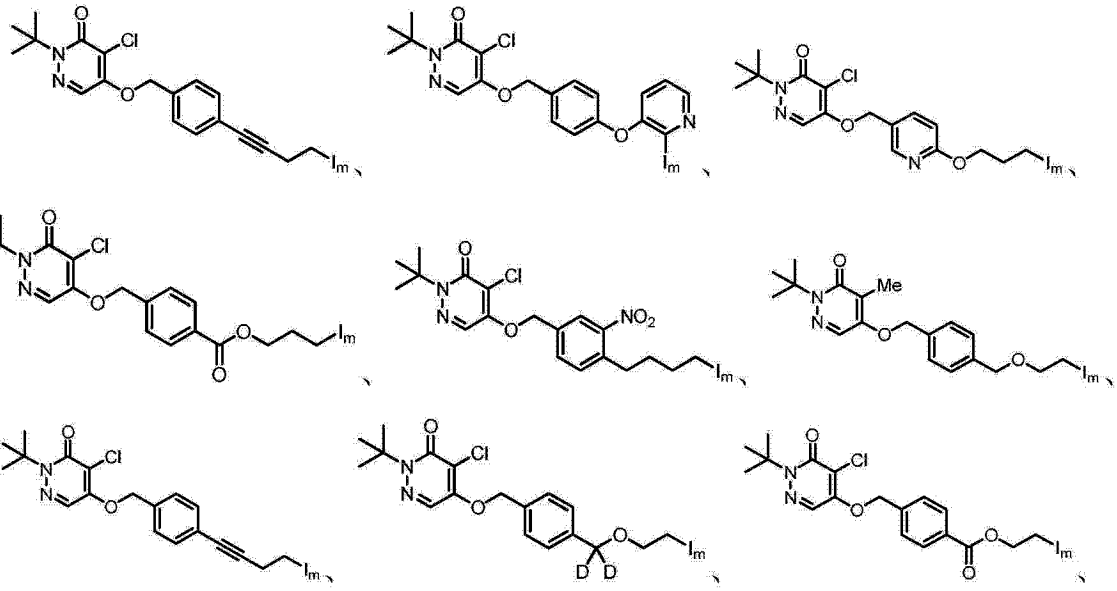
[0444]



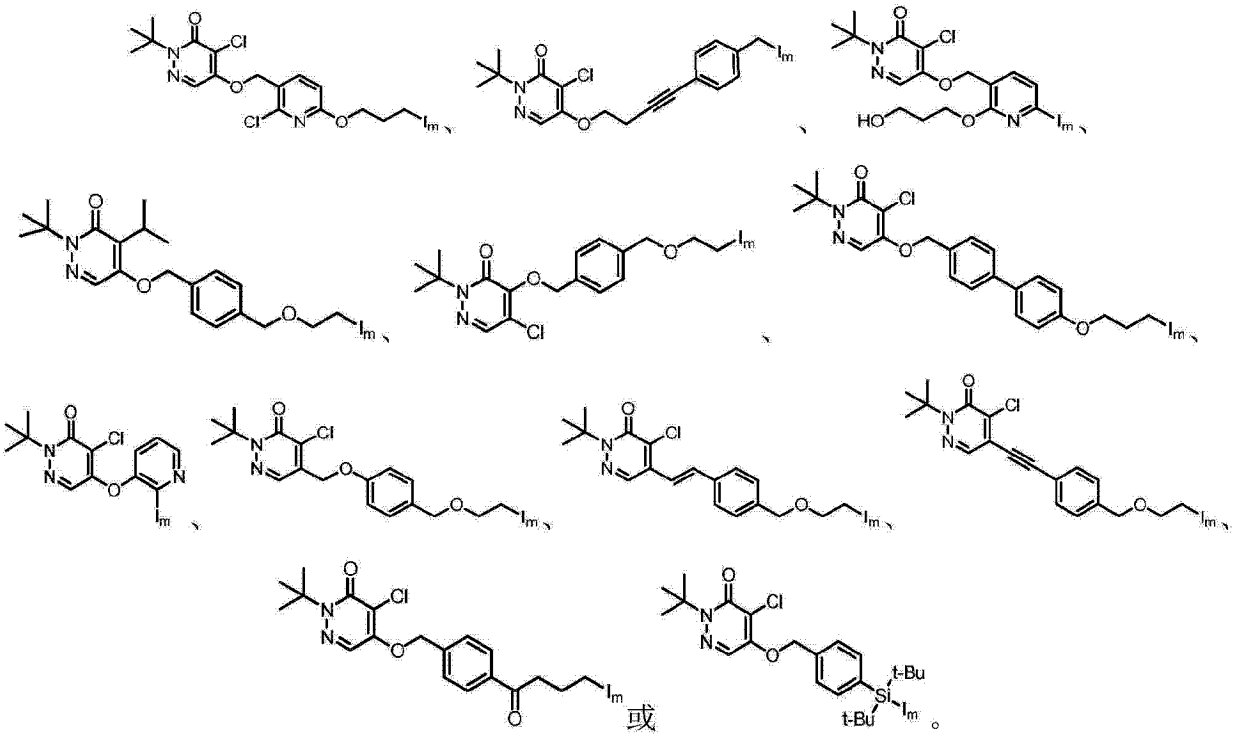
[0445] 或其医药学上可接受的盐，其中 F 任选地为 ^{18}F。

[0446] 在一些实施例中，所述化合物选自由以下各项组成的群组：

[0447]

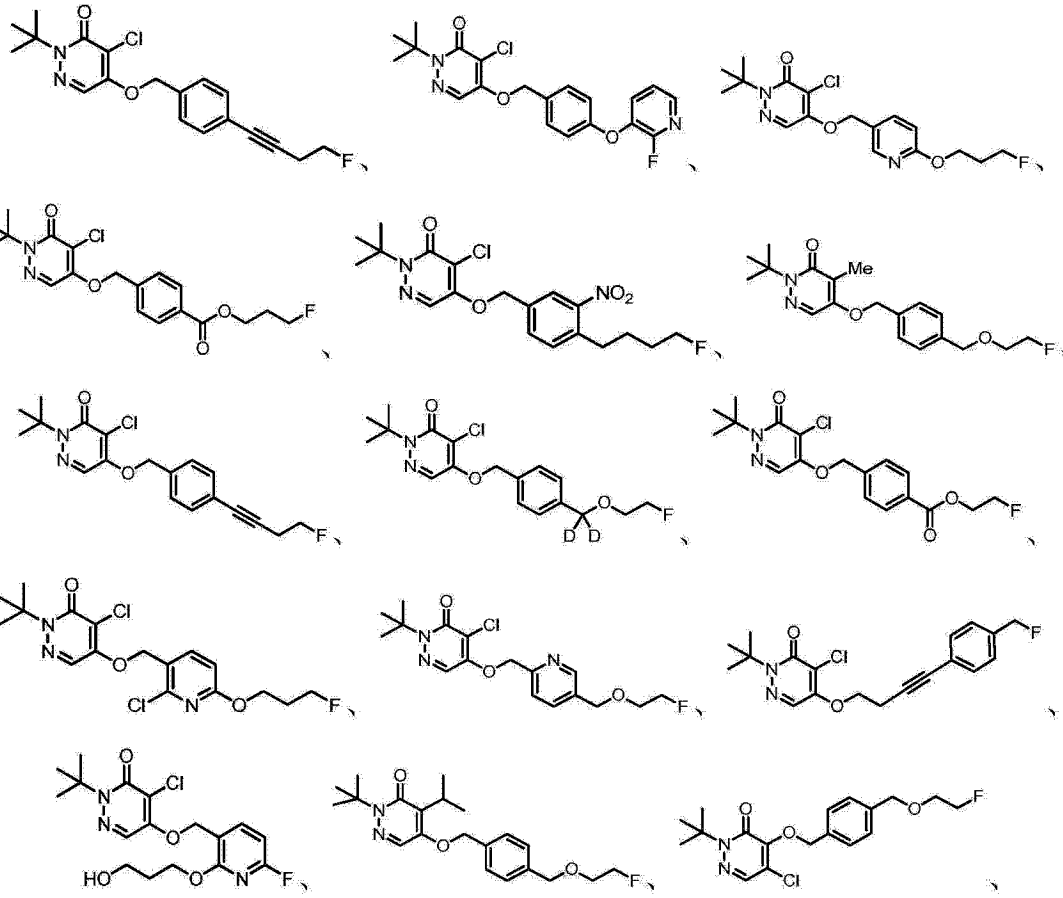


[0448]

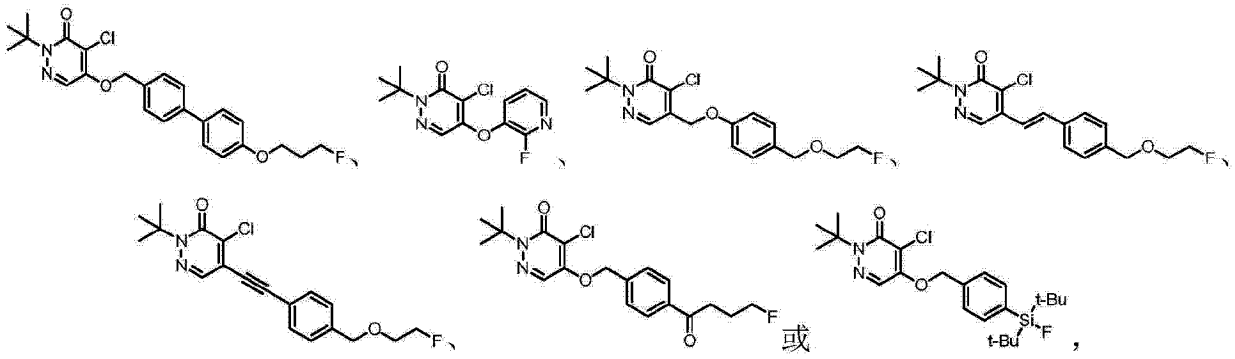


[0449] 或其医药学上可接受的盐，其中 I_m 为造影部分。在一些实施例中，I_m 为 ^{18}F。在一些实施例中，所述化合物选自由以下各项组成的群组：

[0450]



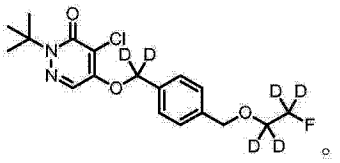
[0451]



[0452] 或其医药学上可接受的盐。在一些实施例中，每个 F 为 ^{18}F。

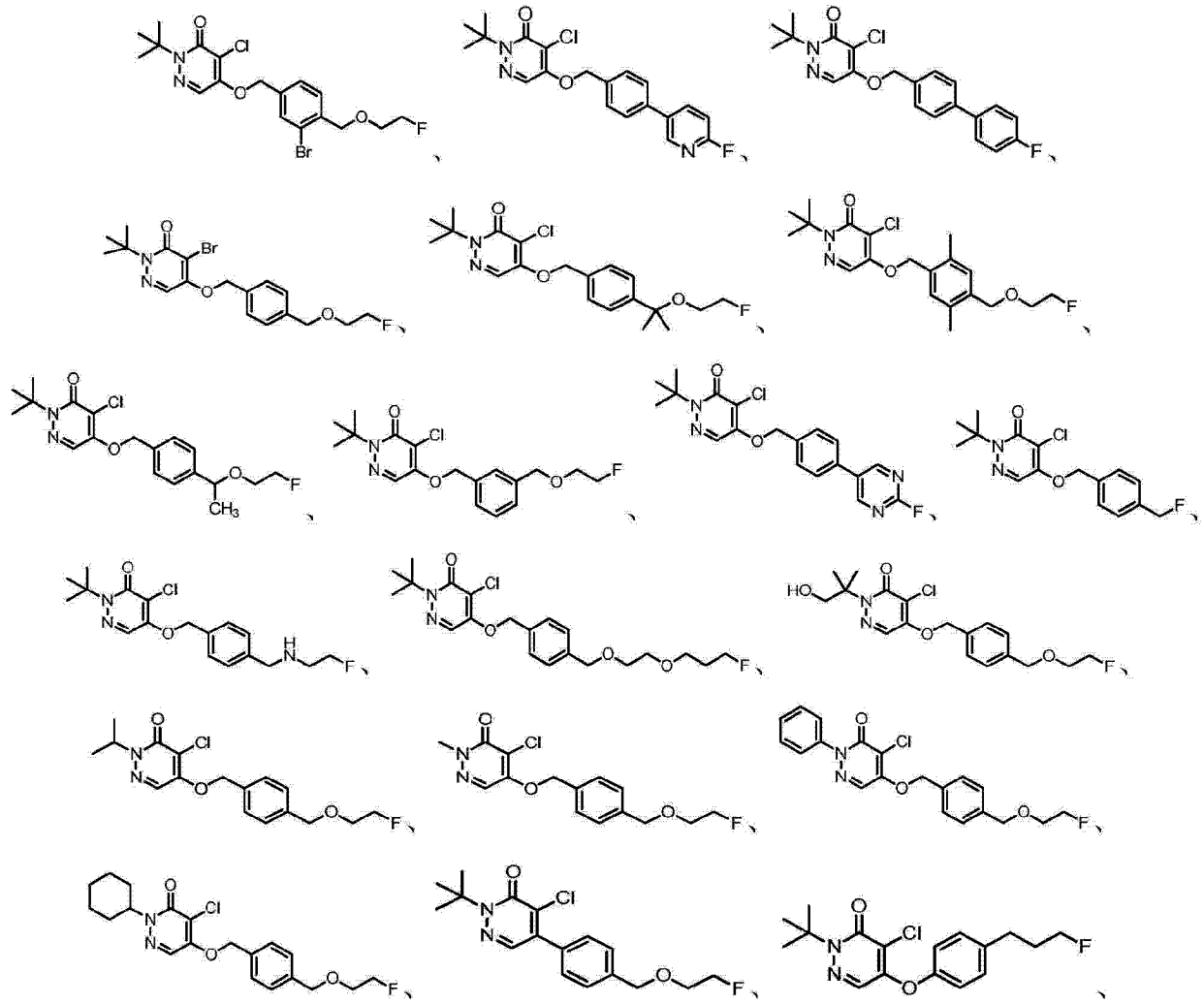
[0453] 在一些实施例中，所述化合物为：

[0454]

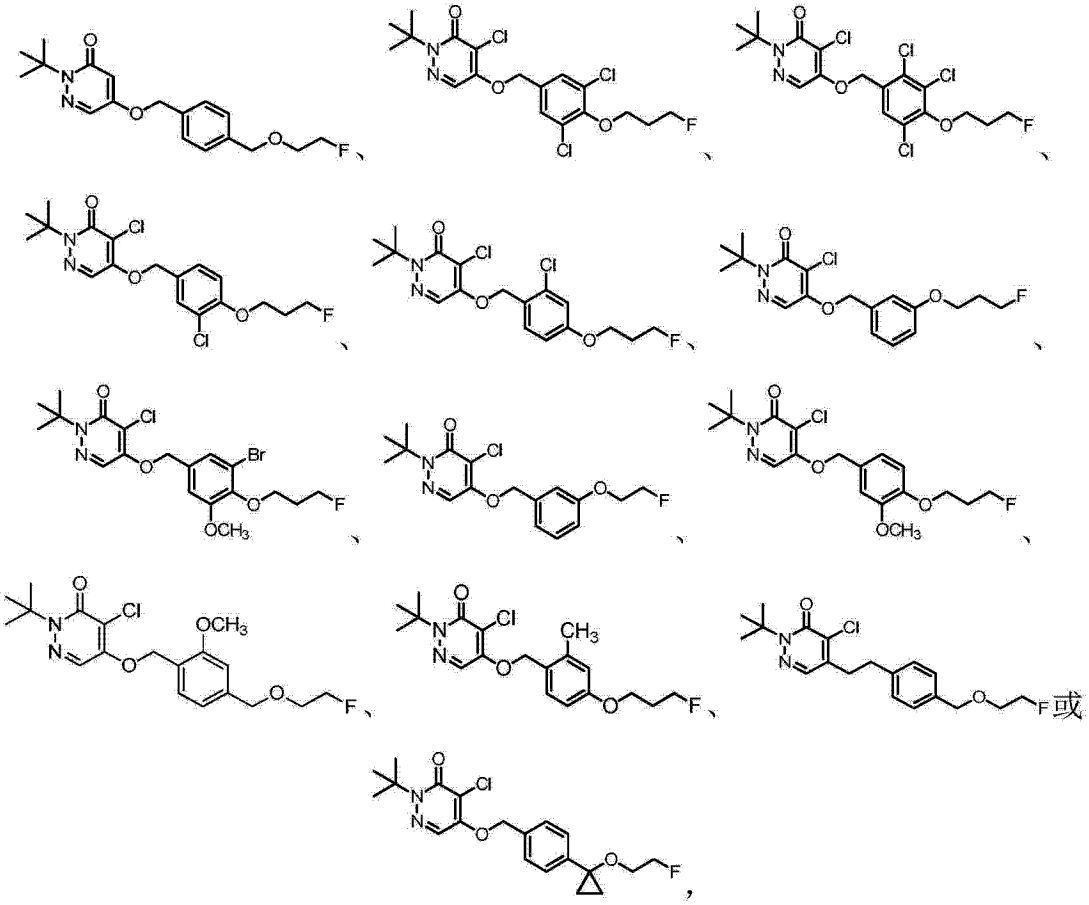


[0455] 在一些实施例中，所述化合物选自由以下各项组成的群组：

[0456]

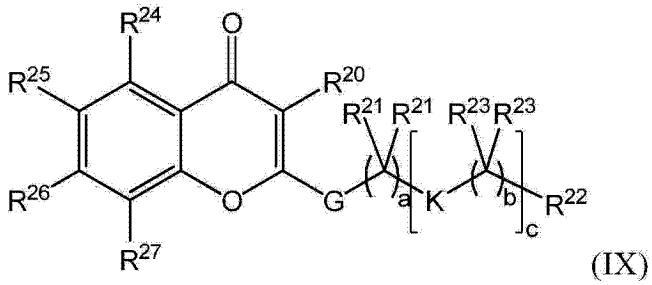


[0457]



或其医药学上可接受的盐。在一些实施例中，每个 F 为 ^{18}F。

在一些实施例中，提供包含以下结构的化合物：



(IX)

或其医药学上可接受的盐，其中：

R^{20}选自由以下各项组成的群组：氢、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN 以及 $-NO_2$；

每个 R^{21}和 R^{23}独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、卤基、卤烷基以及造影部分，或任选地任何两个 R^{21}或任何两个 R^{23}可相连以形成环；

R^{22}选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、卤基、卤烷基、$-OR^{28}$、$-Si(R^9)_3$、$-B(R^{9'})_3$以及造影部分；

R^{24}、R^{25}、R^{26}以及 R^{27}各自独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取

代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN 以及造影部分；

[0466] 每个 R^7 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7 可相连以形成环；

[0467] 每个 R^8 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

[0468] 每个 R^9 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及造影部分；

[0469] 每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[0470] R^{28} 选自由以下各项组成的群组：氢、任选地经取代的烷基以及任选地经取代的杂烷基；

[0471] G 为 O、S 或 NR^{28}；

[0472] a 为 0、1、2、3 或 4；

[0473] 每个 K 独立地为各自任选地经取代的亚芳基、亚杂芳基、亚烯基或亚炔基；

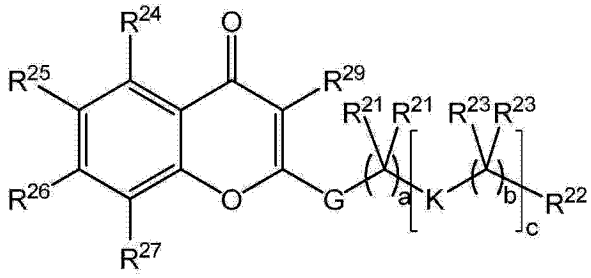
[0474] 每个 b 独立地为 0、1、2、3 或 4；和

[0475] c 为 1 或 2，

[0476] 其限制条件为在所述化合物中存在至少一个造影部分。

[0477] 在一些实施例中，提供包含以下结构的化合物：

[0478]



(X)

[0479] 或其医药学上可接受的盐，其中：

[0480] 每个 R^{21} 和 R^{23} 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、卤基、卤烷基以及造影部分，或任选地任何两个 R^{21} 或任何两个 R^{23} 可相连以形成环；

[0481] R^{22} 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、卤基、卤烷基、$-OR^{28}$、$-Si(R^9)_3$、$-B(R^{9'})_3$ 以及造影部分；

[0482] R^{24}、R^{25}、R^{26} 以及 R^{27} 各自独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基

烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN 以及造影部分；

[0483] 每个 R^7 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7 可相连以形成环；

[0484] 每个 R^8 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

[0485] 每个 R^9 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及造影部分；

[0486] 每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[0487] R^{28} 选自由以下各项组成的群组：氢、任选地经取代的烷基以及任选地经取代的杂烷基；

[0488] R^{29} 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、-CN、$-NO_2$ 以及造影部分；

[0489] G 为 O、S 或 NR^{28}；

[0490] a 为 0、1、2、3 或 4；

[0491] 每个 K 独立地为各自任选地经取代的亚芳基、亚杂芳基、亚烯基或亚炔基，其限制条件为至少一个 K 为亚烯基或亚炔基；

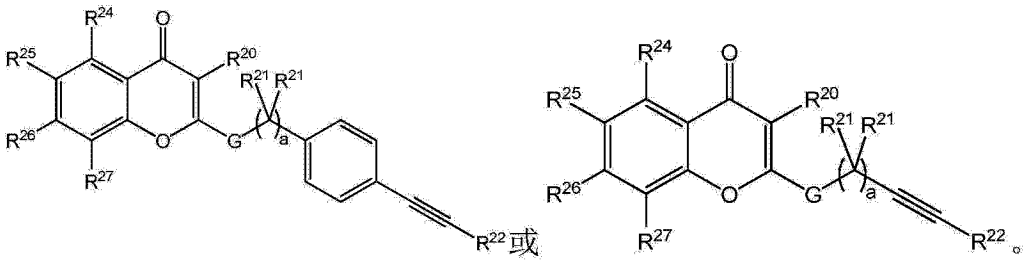
[0492] 每个 b 独立地为 0、1、2、3 或 4；和

[0493] c 为 1 或 2，

[0494] 其限制条件为在所述化合物中存在至少一个造影部分。

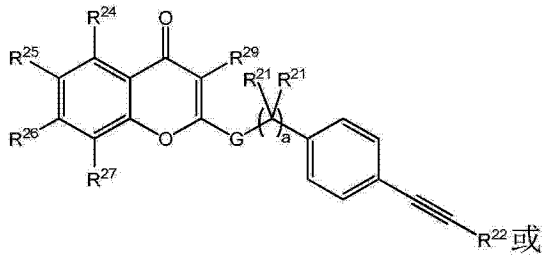
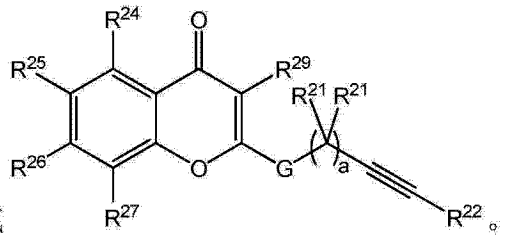
[0495] 在一些实施例中，式 (IX) 化合物包含以下结构：

[0496]



[0497] 在一些实施例中，式 (X) 化合物包含以下结构：

[0498]


或

。

[0499] R^{20}基团的以下描述可联合式 (IX) 化合物使用。在一些实施例中，R^{20}选自由以下各项组成的群组：氢、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN 以及 $-NO_2$。在一些实施例中，R^{20}为氢。在一些实施例中，R^{20}为任选地经取代的杂烷基。在一些实施例中，R^{20}为任选地经取代的烷氧基。在一些实施例中，R^{20}为任选地经取代的烷氧基烷基。在一些实施例中，R^{20}为卤基。在一些实施例中，R^{20}为 F。在一些实施例中，R^{20}为 Cl。在一些实施例中，R^{20}为 Br。在一些实施例中，R^{20}为 I。在一些实施例中，R^{20}为卤烷基。在一些实施例中，R^{20}为任选地经取代的芳基。在一些实施例中，R^{20}为未经取代的芳基。在一些实施例中，R^{20}为任选地经取代的苯基。在一些实施例中，R^{20}为未经取代的苯基。在一些实施例中，R^{20}为任选地经取代的环烷基。关于式 (IX) 化合物，本文所述的 R^{20}基团中的每一者可与如本文所述的 R^7、R^8、R^{21}、R^{22}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}、G、a、K、b 以及 c 或其组合中的任一者组合。

[0500] R^{29}基团的以下描述可联合式 (X) 化合物使用。在一些实施例中，R^{29}选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及造影部分。在一些实施例中，R^{29}为氢。在一些实施例中，R^{29}为任选地经取代的烷基。在一些实施例中，R^{29}为未经取代的烷基。在一些实施例中，R^{29}为甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。在一些实施例中，R^{29}为甲基。在一些实施例中，R^{29}为任选地经取代的杂烷基。在一些实施例中，R^{29}为任选地经取代的烷氧基。在一些实施例中，R^{29}为任选地经取代的烷氧基烷基。在一些实施例中，R^{29}为卤基。在一些实施例中，R^{29}为 F。在一些实施例中，R^{29}为 Cl。在一些实施例中，R^{29}为 Br。在一些实施例中，R^{29}为 I。在一些实施例中，R^{29}为卤烷基。在一些实施例中，R^{29}为任选地经取代的芳基。在一些实施例中，R^{29}为未经取代的芳基。在一些实施例中，R^{29}为任选地经取代的苯基。在一些实施例中，R^{29}为未经取代的苯基。在一些实施例中，R^{29}为任选地经取代的环烷基。在一些实施例中，R^{29}为 -CN。在一些实施例中，R^{29}为 $-NO_2$。在一些实施例中，R^{29}为造影部分。关于式 (X) 化合物，本文所述的 R^{29}基团中的每一者可与如本文所述的 R^7、R^8、R^{21}、R^{22}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}、G、a、K、b 以及 c 或其组合中的任一者组合。

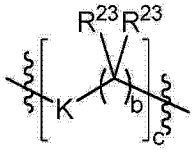
[0501] R^{21}和 R^{23}基团的以下描述可联合式 (IX) 或 (X) 化合物使用。在一些实施例中，R^{21}和 R^{23}各自独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、卤基、卤烷基以及造影部分，或任选地任何两个 R^{21}或任何两个 R^{23}可相连以形成环。在一些实施例中，R^{21}和 R^{23}中的任何两者可相连以形成环。在一些情况下，所形成的环可包含总计 4、5、6、7、8 或 8 个以上原子。在一些情况下，所述环包含 5 或 6 个原子。在一些实施例中，R^{21}和 R^{23}中的每一者为 H。在一些实施例中，至少一个 R^{21}和 R^{23}为 ^2H。在一些实施例中，R^{21}和 R^{23}中的每一者为 ^2H。在

一些实施例中，R^{21}和 R^{23}中的每一者为 H 或任选地经取代的烷基。在一些实施例中，R^{21}和 R^{23}中的每一者为 H 或未经取代的烷基。在一些实施例中，至少一个 R^{21}和 R^{23}不为 H。在一些实施例中，至少一个 R^{21}或 R^{23}为造影部分。关于式 (IX) 化合物，本文所述的 R^{21}和 / 或 R^{23}基团中的每一者可与如本文所述的 R^{7}、R^{8}、R^{20}、R^{22}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}、G、a、K、b 以及 c 或其组合中的任一者组合。关于式 (X) 化合物，本文所述的 R^{21}和 / 或 R^{23}基团中的每一者可与如本文所述的 R^{7}、R^{8}、R^{22}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}、R^{29}、G、a、K、b 以及 c 或其组合中的任一者组合。

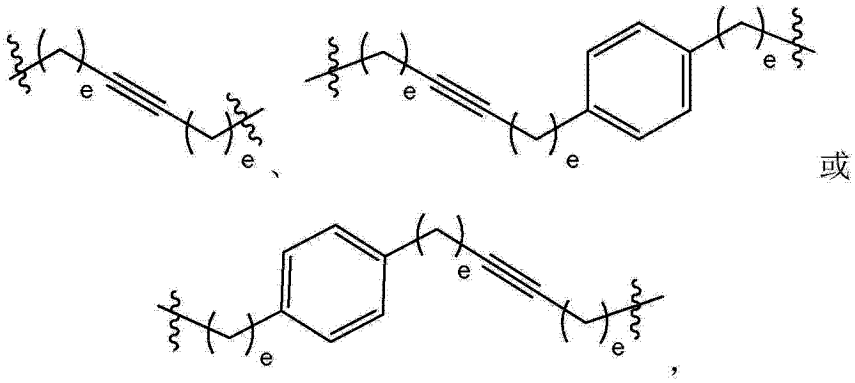
[0502] R^{24}、R^{25}、R^{26}以及 R^{27}基团的以下描述可联合式 (IX) 或 (X) 化合物使用。在一些实施例中，R^{24}、R^{25}、R^{26}以及 R^{27}各自独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN 以及造影部分。在一些实施例中，R^{24}、R^{25}、R^{26}以及 R^{27}中的每一者为 H。在一些实施例中，至少一个 R^{24}、R^{25}、R^{26}以及 R^{27}不为 H。在一些实施例中，R^{24}、R^{25}、R^{26}以及 R^{27}中的每一者为 H 或任选地经取代的烷基。在一些实施例中，R^{24}、R^{25}、R^{26}以及 R^{27}中的每一者为 H 或未经取代的烷基。关于式 (IX) 化合物，本文所述的 R^{24}、R^{25}、R^{26}以及 R^{27}基团中的每一者可与如本文所述的 R^{7}、R^{8}、R^{20}、R^{21}、R^{22}、R^{23}、R^{28}、G、a、K、b 以及 c 或其组合中的任一者组合。关于式 (X) 化合物，本文所述的 R^{24}、R^{25}、R^{26}以及 R^{27}基团中的每一者可与如本文所述的 R^{7}、R^{8}、R^{21}、R^{22}、R^{23}、R^{28}、R^{29}、G、a、K、b 以及 c 或其组合中的任一者组合。

[0503] G 基团的以下描述可联合式 (IX) 或 (X) 化合物使用。在一些实施例中，G 为 O、S 或 NR^{28}。在一些实施例中，G 为 O。在一些实施例中，G 为 S。在一些实施例中，G 为 NR^{28}，其中 R^{28}选自由氢、任选地经取代的烷基以及任选地经取代的杂烷基组成的群。在一些实施例中，G 为 NH。在一些实施例中，G 为 NR^{28}，其中 R^{28}为 H 或任选地经取代的烷基。在一些实施例中，G 为 NR^{28}，其中 R^{28}为任选地经取代的烷基。在一些实施例中，G 为 NR^{28}，其中 R^{28}为未经取代的烷基。关于式 (IX) 化合物，本文所述的 G 基团中的每一者可与如本文所述的 R^{7}、R^{8}、R^{20}、R^{21}、R^{22}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}、a、K、b 以及 c 或其组合中的任一者组合。关于式 (X) 化合物，本文所述的 G 基团中的每一者可与如本文所述的 R^{7}、R^{8}、R^{21}、R^{22}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}、R^{29}、a、K、b 以及 c 或其组合中的任一者组合。

[0504] a、b 以及 c 变量的以下描述可与式 (IX) 或 (X) 化合物联合使用。在一些实施例中，a 为 0。在一些实施例中，其中 a 为 1。在一些实施例中，a 为 2。在一些实施例中，a 为 3。在一些实施例中，a 为 4。在一些实施例中，b 为 0。在一些实施例中，其中 b 为 1。在一些实施例中，b 为 2。在一些实施例中，b 为 3。在一些实施例中，b 为 4。在一些实施例中，c 为 1。在一些实施例中，c 为 2。在一些实施例中，a 为 1，b 为 1，且 c 为 1。在一些实施例中，a 为 2，b 为 2，且 c 为 1。在一些实施例中，a 为 2，b 为 2，且 c 为 2。关于式 (IX) 化合物，本文所述的 a、b 及 c 变量中的每一者可与如本文所述的 R^{7}、R^{8}、R^{20}、R^{21}、R^{22}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}、G 以及 K 或其组合中的任一者组合。关于式 (X) 化合物，本文所述的 a、b 以及 c 变量中的每一者可与如本文所述的 R^{7}、R^{8}、R^{21}、R^{22}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}、R^{29}、G 以及 K 或其组合中的任一者组合。

[0505] 基团的以下描述可联合式 (IX) 或 (X) 化合物使用。在一些实施例中，至少一个 K 为亚炔基。在一些实施例中，至少一个 K 为亚烯基。在一些实施例中，  具有以下结构：

[0506]

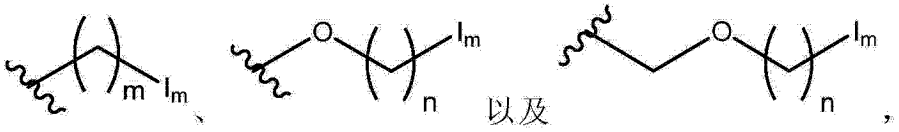


[0507] 其中每个 e 独立地为 1、2、3 或 4。在一些实施例中，每个 e 为 1。关于式 (IX) 化合物，以上基团中的每一者可与如本文所述的 R^7、R^8、R^{20}、R^{21}、R^{22}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}、G 以及 a 或其组合中的任一者组合。关于式 (X) 化合物，以上基团中的每一者可与如本文所述的 R^7、R^8、R^{21}、R^{22}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}、R^{29}、G 以及 a 或其组合中的任一者组合。

[0508] R^{22}基团的以下描述可与式 (IX) 或 (X) 化合物联合使用。在一些实施例中，R^{22} 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、卤基、卤烷基、$-OR^{28}$及造影部分。在一些实施例中，R^{22}为 $-Si(R^9)_3$ 或 $-B(R^{9'})_3$。在一些实施例中，R^{22}为氢。在一些实施例中，R^{22}为任选地经取代的烷基。在一些实施例中，R^{22}为未经取代的烷基。在一些实施例中，R^{22}为任选地经取代的杂烷基。在一些实施例中，R^{22}为未经取代的杂烷基。在一些实施例中，R^{22}为任选地经取代的烷氧基烷基。在一些实施例中，R^{22}为未经取代的烷氧基烷基。在一些实施例中，R^{22}为卤基。在一些实施例中，R^{22}为 F。在一些实施例中，R^{22}为 Cl。在一些实施例中，R^{22}为 Br。在一些实施例中，R^{22}为 I。在一些实施例中，R^{22}为卤烷基。在一些实施例中，R^{22}为 $-OR^{28}$，其中 R^{28}选自由氢、任选地经取代的烷基以及任选地经取代的杂烷基组成的群。在一些实施例中，R^{22}为 OH。在一些实施例中，R^{22}为 OR^{28}，其中 R^{28}为 H 或任选地经取代的烷基。在一些实施例中，R^{22}为 OR^{28}，其中 R^{28}为任选地经取代的烷基。在一些实施例中，R^{22}为 OR^{28}，其中 R^{28}为未经取代的烷基。在一些实施例中，R^{22}为造影部分。在一些实施例中，R^{22}经造影部分取代。在一些实施例中，R^{22}为各自经造影部分取代的任选地经取代的烷基、任选地经取代的烷氧基或任选地经取代的烷氧基烷基。在一些实施例中，R^{22}为 $-(CH_2)_jI_m$；其中 I_m为造影部分且 j 为 1、2、3、4、5 或 6。在一些情况下，R^{22}为 $-(CH_2)I_m$、$-(CH_2)_2I_m$、$-(CH_2)_3I_m$、$-(CH_2)_4I_m$、$-(CH_2)_5I_m$、$-(CH_2)_6I_m$、$-(CH_2)_7I_m$、$-(CH_2)_8I_m$、$-(CH_2)_9I_m$或 $-(CH_2)_{10}I_m$。在一些情况下，R^{22}为 $-(CH_2)^{18}F$、$-(CH_2)_2{}^{18}F$、$-(CH_2)_3{}^{18}F$、$-(CH_2)_4{}^{18}F$、$-(CH_2)_5{}^{18}F$、$-(CH_2)_6{}^{18}F$、$-(CH_2)_7{}^{18}F$、$-(CH_2)_8{}^{18}F$、$-(CH_2)_9{}^{18}F$ 或 $-(CH_2)_{10}{}^{18}F$。在一些实施例中，R^{22}为 $-O(CH_2)_jI_m$；其中 I_m为造影部分且 j 为 1、2、3、4、5 或 6。在一些情况下，R^{22}为 $-O(CH_2)I_m$、$-O(CH_2)_2I_m$、$-O(CH_2)_3I_m$、$-O(CH_2)_4I_m$、$-O(CH_2)_5I_m$、$-O(CH_2)_6I_m$、$-O(CH_2)_7I_m$、-

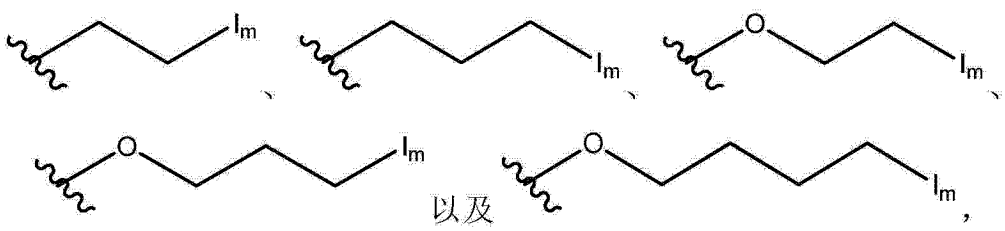
$O(CH_2)_8I_m$、$-O(CH_2)_9I_m$或 $-O(CH_2)_{10}I_m$。在一些情况下，R^{22}为 $-O(CH_2)^{18}F$、$-O(CH_2)_2{}^{18}F$、$-O(CH_2)_3{}^{18}F$、$-O(CH_2)_4{}^{18}F$、$-O(CH_2)_5{}^{18}F$、$-O(CH_2)_6{}^{18}F$、$-O(CH_2)_7{}^{18}F$、$-O(CH_2)_8{}^{18}F$、$-O(CH_2)_9{}^{18}F$ 或 $-O(CH_2)_{10}{}^{18}F$。在一些实施例中，R^{22}为 $-(CH_2)_jO(CH_2)_jI_m$；其中 I_m为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。在一些实施例中，R^{22}为 $-(CH_2)O(CH_2)_jI_m$；其中 I_m为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。在一些情况下，R^{22}为 $-CH_2O(CH_2)I_m$、$-CH_2O(CH_2)_2I_m$、$-CH_2O(CH_2)_3I_m$、$-CH_2O(CH_2)_4I_m$、$-CH_2O(CH_2)_5I_m$、$-CH_2O(CH_2)_6I_m$、$-CH_2O(CH_2)_7I_m$、$-CH_2O(CH_2)_8I_m$、$-CH_2O(CH_2)_9I_m$或 $-CH_2O(CH_2)_{10}I_m$。在一些情况下，R^{22}为 $-CH_2O(CH_2)^{18}F$、$-CH_2O(CH_2)_2{}^{18}F$、$-CH_2O(CH_2)_3{}^{18}F$、$-CH_2O(CH_2)_4{}^{18}F$、$-CH_2O(CH_2)_5{}^{18}F$、$-CH_2O(CH_2)_6{}^{18}F$、$-CH_2O(CH_2)_7{}^{18}F$、$-CH_2O(CH_2)_8{}^{18}F$、$-CH_2O(CH_2)_9{}^{18}F$ 或 $-CH_2O(CH_2)_{10}{}^{18}F$。在一些实施例中，$R^{22}$为 $-C\equiv C-(CH_2)_jI_m$；其中 I_m为造影部分且 j 为 1、2、3、4、5 或 6。在一些实施例中，R^{22}为 $-[(CH_2)_jO]_j(CH_2)_jI_m$；其中 I_m为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。在一些实施例中，R^{22}为 $-O[(CH_2)_jO]_j(CH_2)_jI_m$；其中 I_m为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。在一些实施例中，R^{22}为经造影部分取代的任选地经取代的烷基。在一些实施例中，R^{22}为 $-C(=O)O(CH_2)_jI_m$；其中 I_m为造影部分且 j 为 1、2、3、4、5 或 6。在一些实施例中，R^{22}为 $-C(=O)(CH_2)_jI_m$；其中 I_m为造影部分且 j 为 1、2、3、4、5 或 6。在一些实施例中，R^{22}为 $-(CH_2)_jNH(CH_2)_jI_m$；其中 I_m为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。在一些实施例中，R^{22}为 $Si(R^9)_2I_m$，其中每个 R^9为任选地经取代的烷基且其中 I_m为造影部分。在一些实施例中，R^{22}为 $B(R^{9'})_2I_m$，其中每个 $R^{9'}$为任选地经取代的烷基且其中 I_m为造影部分。在一些实施例中，R^{22}选自由以下各项组成的群组：$-C\equiv C-CH_2CH_2CH_2I_m$、$-C\equiv C-CH_2CH_2I_m$、$-C\equiv C-CH_2I_m$、$-CH_2I_m$、$-(CH_2)_2I_m$、$-(CH_2)_3I_m$、$-(CH_2)_4I_m$、$-(CH_2)_5I_m$、$-(CH_2)_6I_m$、$-OCH_2I_m$、$-O(CH_2)_2I_m$、$-O(CH_2)_3I_m$、$-O(CH_2)_4I_m$、$-O(CH_2)_5I_m$、$-O(CH_2)_6I_m$、$-CH_2O(CH_2)_2I_m$、$-CH(CH_3)O(CH_2)_2I_m$、$-CH_2O(CH_2)_3I_m$、$-CD_2O(CH_2)_2I_m$、$-(CH_2)_2O(CH_2)_2I_m$、$-CHBrC(CH_3)_2I_m$、$-CHClC(CH_3)_2I_m$、$-CHFC(CH_3)_2I_m$、$-C(=O)OCH_2I_m$、$-C(=O)O(CH_2)_2I_m$、$-C(=O)O(CH_2)_3I_m$、$-CH_2NH(CH_2)_2I_m$、$-CH_2NHCH_2I_m$、$-CH_2O(CH_2)_2O(CH_2)_2I_m$、$-CH_2O(CH_2)_2O(CH_2)_3I_m$、$-O(CH_2)_2O(CH_2)_2I_m$、$-C(=O)(CH_2)_2I_m$以及 $-C(=O)(CH_2)_3I_m$。在一些实施例中，其中 I_m为 ^{18}F。在一些实施例中，R^{22}选自由以下各项组成的群组：

[0509]



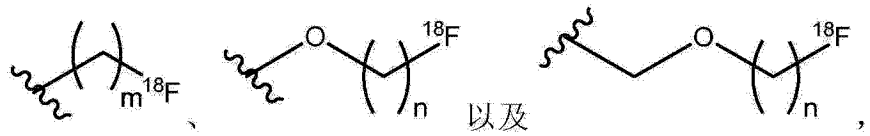
[0510] 其中 m 和 n 为介于 1 与 6 之间（包括 1 及 6）的整数，且 I_m为造影部分。在一些实施例中，R^{22}选自由以下各项组成的群组：

[0511]



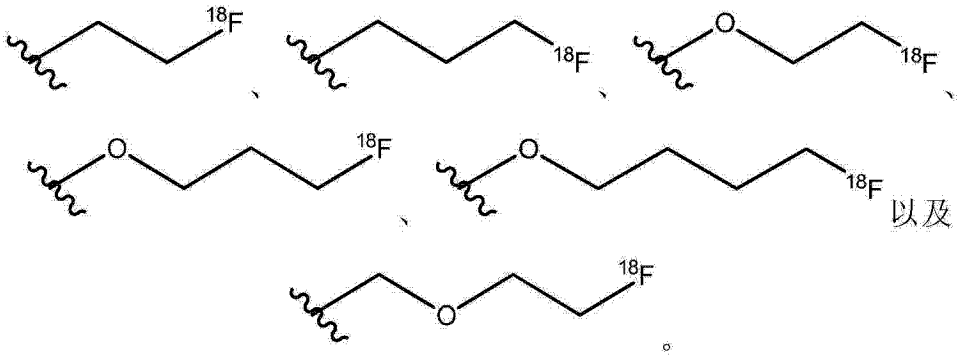
[0512] 其中 I_m为造影部分。在一些实施例中，R^{22}选自由以下各项组成的群组：

[0513]



[0514] 其中 m 和 n 为介于 1 与 6 之间（包括 1 和 6）的整数。在一些实施例中，R^{22}选自由以下各项组成的群组：

[0515]



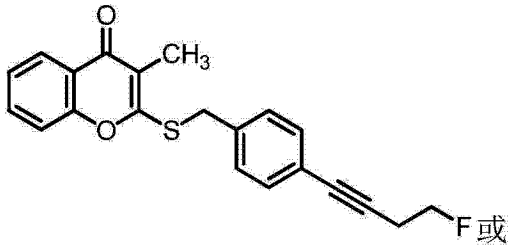
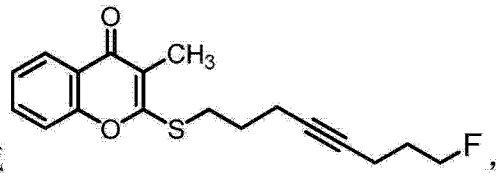
[0516] 关于式 (IX) 化合物，本文所述的 R^{22}基团中的每一者可与如本文所述的 R^{7}、R^{8}、R^{20}、R^{21}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}、G、a、K、b 以及 c 或其组合中的任一者组合。关于式 (X) 化合物，本文所述的 R^{22}基团中的每一者可与如本文所述的 R^{7}、R^{8}、R^{21}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}、R^{29}、G、a、K、b 以及 c、或其组合中的任一者组合。

[0517] 在一些实施例中，关于式 (IX) 化合物，至少一个造影部分存在于 R^{7}、R^{8}、R^{20}、R^{21}、R^{22}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}或 R^{28}中。在一些实施例中，式 (X) 或 (IX) 化合物包含单个造影部分。在一些实施例中，关于式 (X) 化合物，至少一个造影部分存在于 R^{7}、R^{8}、R^{21}、R^{22}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}或 R^{29}中。在一些实施例中，关于式 (X) 或 (IX) 化合物，至少一个造影部分存在于 R^{22}中。如上所指出，如所属领域的技术人员所了解，当提及造影部分时，所述造影部分“存在于”实施例中的基团中，其中 1) 造影部分为基团（例如 R^{22}为造影部分）或 b) 基团包含造影部分（例如 R^{22}经造影部分取代）。在一些实施例中，关于式 (IX) 化合物，R^{7}、R^{8}、R^{20}、R^{21}、R^{22}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}或 R^{28}包含至少一个造影部分。在一些实施例中，关于式 (X) 化合物，R^{7}、R^{8}、R^{21}、R^{22}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}或 R^{29}包含至少一个造影部分。在一些实施例中，关于式 (IX) 化合物，R^{7}、R^{8}、R^{21}、R^{22}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}为至少一个造影部分。在一些实施例中，关于式 (X) 化合物，R^{7}、R^{8}、R^{21}、R^{22}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}或 R^{29}为至少一个造影部分。关于式 (IX) 化合物，造影部分的上述置放中的每一者可与如本文所述的 R^{7}、R^{8}、R^{20}、R^{21}、R^{22}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}、G、a、K、b 以及 c、或其组合中的任一者组合。关于式 (X) 化合物，造影部分的上述置放中的每一者可与如本文所述的 R^{7}、R^{8}、R^{21}、R^{22}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}、R^{29}、G、a、K、b 以及 c、或其组合中的任一者组合。

[0518] 造影部分的以下描述可联合式 (IX) 及 (X) 化合物使用。在一些实施例中，至少一个造影部分选自由以下各项组成的群组：^{11}C、^{13}N、^{18}F、^{76}Br、^{89}Zr、^{123}I、^{124}I、^{125}I、^{131}I、^{99m}Tc、^{95}Tc、^{111}In、^{62}Cu、^{64}Cu、^{67}Ga 以及 ^{68}Ga。在一些实施例中，至少一个造影部分为 ^{18}F。本文中较详细描述造影部分。

[0519] 在一些实施例中，式 (IX) 化合物选自由以下各项组成的群组：

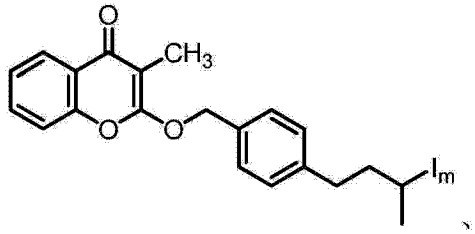
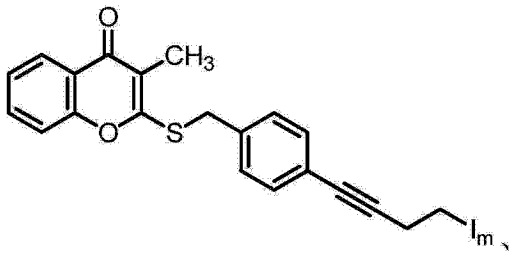
[0520]


或

，

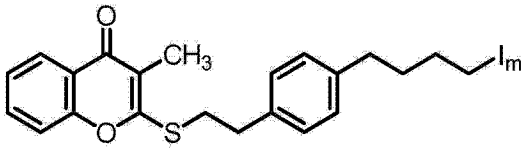
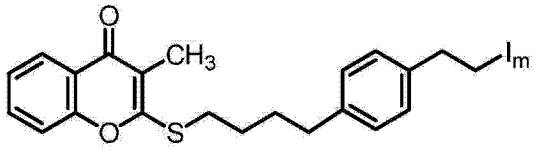
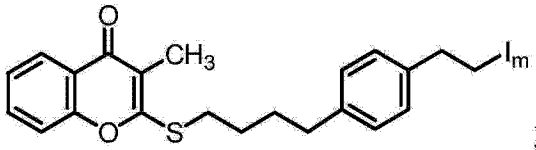
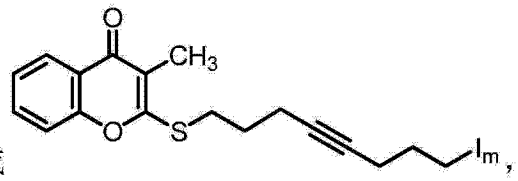
[0521] 或其医药学上可接受的盐，其中 F 任选地为 ^{18}F。

[0522] 在一些实施例中，化合物选自由以下各项组成的群组：

[0523]

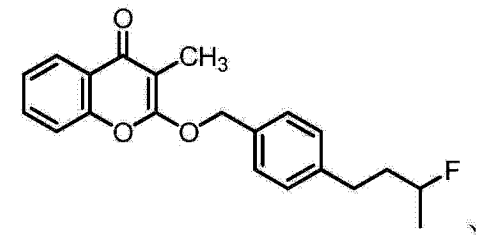

、

、

[0524]


、

、


或
，

[0525] 或其医药学上可接受的盐，其中 I_m 为造影部分。在一些实施例中，I_m 为 ^{18}F。在一些实施例中，化合物选自由以下各项组成的群组：

[0526]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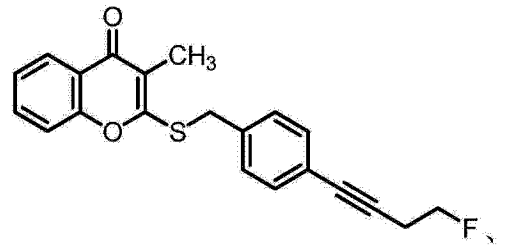
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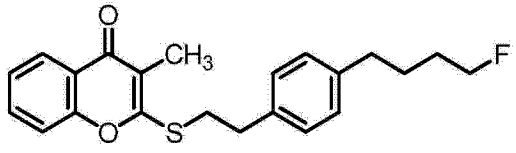
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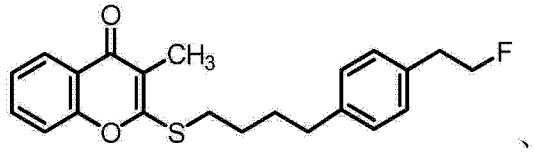
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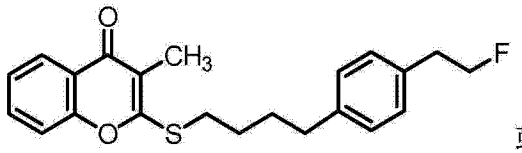
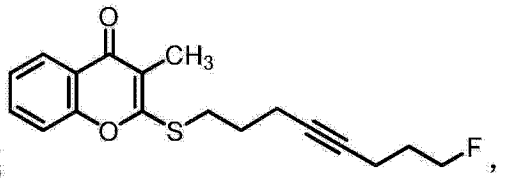
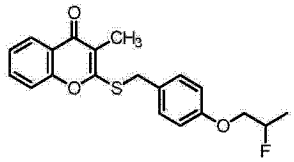

或

，

[0527] 或其医药学上可接受的盐。在一些实施例中，每个 F 为 ^{18}F。在一些实施例中，化合物为：

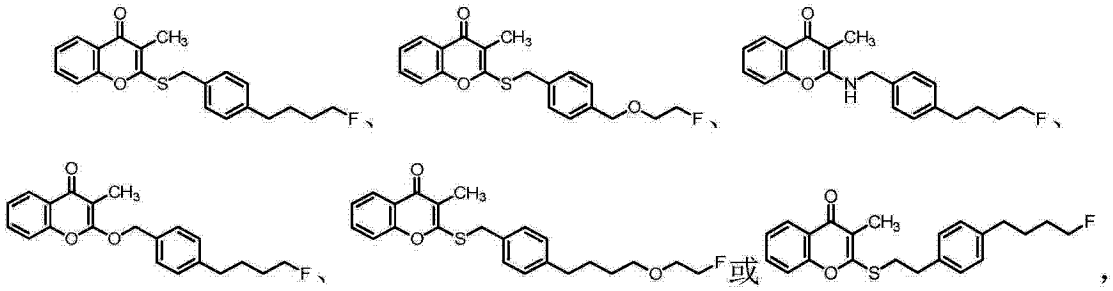
[0528]



[0529] 或其医药学上可接受的盐。在一些实施例中，每个 F 为 ^{18}F。

[0530] 在一些实施例中，化合物选自由以下各项组成的群组：

[0531]



[0532] 或其医药学上可接受的盐。在一些实施例中，每个 F 为 ^{18}F。

[0533] 应了解，本文所述的结构的任何氢分子在一些实施例中可任选地经 ^{2}H 取代和 / 或增浓。在一些情况下，至少一个 ^{2}H 已经取代为 ^{1}H。

[0534] 如本文所用，术语“造影剂”指包括造影部分的任何化合物。通常可向个体投予造影剂以提供关于个体（例如人类）的至少一部分的信息。在一些情况下，造影剂可用于突出显示个体的特定区域，使得器官、血管、组织和 / 或其它部分更可检测和 / 或造影更清楚。通过提高待研究物体的检测能力和 / 或图像品质，可测定疾病和 / 或损伤的存在和程度。“造影部分”指本身（例如放射性同位素）或在暴露于外部能源（例如电磁辐射、超音波等）时能够产生可检测信号的原子或原子团。在某些情况下，造影部分可更改其局部的化学和 / 或磁和 / 或电子环境。造影部分的非限制性实例包括 ^{11}C、^{13}N、^{18}F、^{76}Br、^{123}I、^{124}I、^{125}I、^{131}I、^{99m}Tc、^{95}Tc、^{111}In、^{62}Cu、^{64}Cu、^{67}Ga、^{68}Ga 以及 ^{89}Zr。在一些实施例中，造影部分与包含结构 $-B(R^{9'})_2I_m$ 或 $-Si(R^{9})_2I_m$ 的基团相连，其中 I_m 为造影部分，任选地为 ^{18}F。在一些实施例中，造影部分与本文所述的化合物直接相连（例如通过共价键）（例如在 ^{18}F、^{76}Br、^{124}I 或 ^{131}I 的情况下）。在一些实施例中，造影部分通过非共价相互作用（例如静电相互作用）与化合物相连。在一些实施例中，造影部分通过螯合剂与化合物相连（例如在 ^{64}Cu、^{89}Zr、^{99m}Tc 以及 ^{111}In 的情况下）。本文中较详细描述螯合剂。在一些实施例中，造影部分选自由以下各项组成的群组：^{18}F、^{76}Br、^{124}I、^{131}I、^{64}Cu、^{89}Zr、^{99m}Tc 以及 ^{111}In。在某些实施例中，造影部分为 ^{18}F。在某些实施例中，造影部分为 ^{76}Br。在某些实施例中，造影部分为 ^{124}I。在某些实施例中，造影部分为 ^{131}I。在一些情况下，造影部分为 ^{18}F、^{76}Br 或 ^{124}I。在一些情况下，造影部分为 ^{18}F 或 ^{76}Br。在一些情况下，造影剂包含单个造影部分。在一些情况下，造影剂包含一个以上造影部分（例如两个造影部分）。如本文所用，术语“造影剂”涵盖对比剂。在一些实施例中，造影剂为对比剂。术语“对比剂”指包含响应外部能源产生可检测信号的造影部分的一类造影剂。在某些情况下，对比剂可包含吸收和 / 或反射和 / 或透射外部能源的造影

部分。

[0535] 在一些实施例中，包含本发明化合物的组合物或多个化合物用包括同位素（如放射性同位素）的化合物增浓。在这种情况下，所述多个化合物或组合物可称为“同位素增浓”。“同位素增浓”组合物指一种元素的一或多种同位素的百分比大于天然存在的同位素的百分比的组合物。例如，用氟物质同位素增浓的组合物可用氟 -18(^{18}F) “同位素增浓”。因此，关于多个化合物，当特定原子位置指定为 ^{18}F 时，应了解，在这一位置处（在所述多个化合物中）的 ^{18}F 的丰度（或频率）大于 ^{18}F 的基本上为零的天然丰度（或频率）。

[0536] 在一些实施例中，指定为待增浓的原子的最小同位素增浓因素可为约 0.001％（即 10^5个原子中约 1 个为原子的所需同位素）、约 0.002％、约 0.003％、约 0.004％、约 0.005％、约 0.006％、约 0.007％、约 0.008％、约 0.009％、约 0.01％、约 0.05％、约 0.1％、约 0.2％、约 0.3％、约 0.4％、约 0.5％、约 0.75％、约 1％、约 2％、约 3％、约 4％、约 5％、约 10％、约 15％、约 20％、约 30％、约 40％、约 50％、约 60％、约 70％、约 80％、约 90％、约 95％或 95％以上。最小同位素增浓因素在一些情况下可在约 0.001％至约 1％的范围内。例如，在造影部分为氟的实施例中，指定为 ^{18}F 的氟的最小同位素增浓因素可为约 0.001％（即 10^5个氟物质中约 1 个为 ^{18}F）、约 0.002％、约 0.003％、约 0.004％、约 0.005％、约 0.006％、约 0.007％、约 0.008％、约 0.009％、约 0.01％、约 0.05％、约 0.1％、约 0.2％、约 0.3％、约 0.4％、约 0.5％、约 0.75％、约 1％、约 2％、约 3％、约 4％、约 5％、约 10％、约 15％、约 20％、约 30％、约 40％、约 50％、约 60％、约 70％、约 80％、约 90％、约 95％或 95％以上。本文所提供的组合物或多个化合物的同位素增浓可使用所属领域的技术人员所已知的常规分析方法（包括例如质谱法和 HPLC）来测定。

[0537] 在一些实施例中，本文所述的组合物、方法、用途和 / 或系统包括或使用本文所述的化合物。在一些实施例中，所述化合物为造影剂。在一些实施例中，所述化合物为对比剂。在一些实施例中，所述化合物为造影剂或对比剂的前驱体。

[0538] 螯合剂

[0539] 在一些情况下，造影部分可通过与螯合剂缔合而与如本文所述的化合物缔合（例如在造影部分为 ^{64}Cu、^{68}Ga、^{89}Zr、^{99m}Tc、^{111}In 的实施例中）。螯合剂通常共价连接到化合物。然而，在某些实施例中，螯合剂可通过非共价相互作用与化合物缔合。术语螯合剂在本领域中具有其一般含义且一般指能够错合造影部分（例如金属离子和 / 或放射性核种）的化学部分，其中所述错合物在生理条件下稳定。例如，造影部分通常将与螯合剂的错合物截留在活体内。在一些实施例中，螯合剂为通过一或多个施体原子和 / 或基团与造影部分结合的化合物上的部分或基团。螯合剂可为本领域中已知用于错合医学上有用的金属离子或放射性核种的任何螯合剂。在一些实施例中，螯合剂包含一、二、三、四、五、六、七、八、九或十个施体原子和 / 或基团。在螯合剂包含一个以上施体原子和 / 或基团的实施例中，施体原子 / 基团可相同或不同。螯合剂可为单齿、双齿、三齿、四齿、五齿或五齿以上。施体原子 / 基团的非限制性实例包括 -OH、$-O^-$、-COOR’、$-COO^-$、$-N(R')_2$、$=N^-$、-SR’、$-S^-$、$-OPO_3^-$或 $-OPO_3R'$，其中每个 R’ 可相同或不同且为氢、各自任选地经取代的烷基、烯基、炔基、环烷基、烷芳基、烷羰基、芳基、芳烷基、烷芳烷基、烷氧基、烷氧基烷基、烷氧基羰基、杂烷基、杂环基、杂环基烷基。在一些情况下，螯合剂可为大环。螯合剂的非限制性实例描述在国际 PCT 公开案第 WO2011/005322 号和美国专利第 6,511,648 号中，所述专利中的每一者出于所有目的以引

用的方式并入本文中。在一些实施例中，螯合剂包含二氨基二硫醇、巯基乙酰基三甘氨酸、单氨基单酰胺、吡啶甲基氨单乙酸、1,4,7,10- 四氮杂环十二烷 -1,4,7,10- 四乙酸、双（硫缩氨基脲）、丙烯氨肟、乙二氨四乙酸或二亚乙三氨五乙酸。在一些实施例中，螯合剂包含金属原子（例如 Al），其中造影部分（例如 ^{18}F）与金属原子缔合。

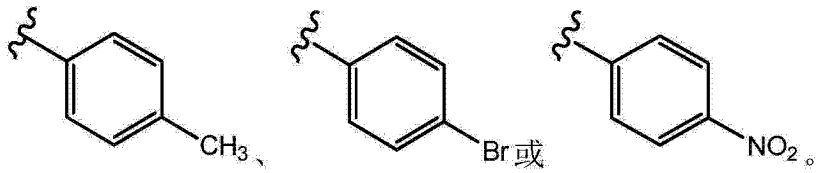
[0540] 在一些情况下，与螯合剂缔合的造影部分可进一步与一或多个辅助物或辅配位体缔合。“辅助物”或“辅配位体”可为用于完成造影部分以及螯合剂的配位层的配位体。在一些实施例中，造影部分配位层可包含一或多个来自螯合剂的键结原子和 / 或基团且任选地一或多个辅助物和 / 或辅配位体。适用于制备放射性药物及适用于制备所述放射性药物的诊断试剂盒的辅助物或辅配位体可包含一或多个氧、氮、碳、硫、磷、砷、硒及碲施体原子。实现造影部分与螯合剂的缔合的条件将视待使用的螯合剂类型而定且在本领域中为众所周知的。

[0541] 造影剂前驱体

[0542] 在本发明的另一方面中，提供适用于制备如本文所述的造影剂的造影剂前驱体。在某些实施例中，造影剂前驱体包含可在取代反应中经亲核试剂置换以形成造影剂的离去基（例如磺酸酯、卤化物）。造影剂前驱体还可包括任选地保护的官能基。在一些实施例中，造影剂前驱体具有与上述造影剂（例如包含至少一个造影部分的化合物）实质上类似的结构，但其中造影部分或取代基包括造影部分而非包括离去基。在某些实施例中，造影剂前驱体具有与上述造影剂实质上类似的结构，但其中螯合剂基团不与造影部分缔合。

[0543] 如本文所用，术语“离去基”具有其在合成有机化学技术中的一般含义且指能够经亲核试剂置换的原子或基团。适合的离去基的实例包括（但不限于）卤化物（如氯化物、溴化物或碘化物）、烷氧基羰氧基、芳氧基羰氧基、烷磺酰基氧基、芳烃磺酰基氧基、烷基 - 羰氧基（例如乙酰氧基）、芳基羰氧基、芳氧基、甲氧基、N,O- 二甲基羟氨基、9- 苯基呫吨 (pixyl)、卤甲酸盐、$-NO_2$、三烷基铵以及芳基鎓盐。在一些实施例中，离去基为磺酸酯。在一些实施例中，磺酸酯包含式 $-OSO_2R'$，其中 R’ 选自由以下各项组成的群组：任选地经取代的烷基、任选地经取代的烯基、任选地经取代的杂烷基、任选地经取代的芳基、任选地经取代的杂芳基、任选地经取代的芳烷基以及任选地经取代的杂芳烷基。在一些实施例中，R’ 为经取代或未经取代的 C_1-C_6 烷基。在一些实施例中，R’ 为甲基。在一些实施例中，R’ 为 $-CF_3$。在一些实施例中，R’ 为经取代或未经取代的芳基。在一些实施例中，R’ 为经取代或未经取代的苯基。在一些实施例中，R’ 为

[0544]

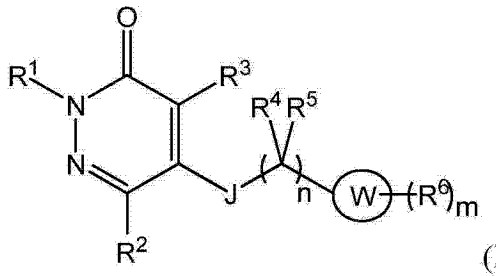


[0545] 在一些情况下，离去基为甲苯磺酸酯基 (toluenesulfonate)（甲苯磺酸酯基 (tosylate)，Ts）、甲烷磺酸酯基（甲磺酸盐，Ms）、对溴苯磺酰基（溴苯磺酸酯基，Bs）或三氟甲烷磺酸酯基（三氟甲磺酸酯基，Tf）。在一些情况下，离去基为溴苯磺酸酯基（对溴苯磺酰基）。在一些情况下，离去基为硝基苯磺酸酯基 (2- 硝基苯磺酰基）。在一些实施例中，离去基为含磺酸酯的基团。在一些实施例中，离去基为甲苯磺酸酯基。离去基亦可为氧化

膦（例如在光延反应(Mitsunobu reaction)期间形成）或内部离去基，如环氧化物或环状硫酸酯。

[0546] 在一些实施例中，提供包含以下结构的化合物：

[0547]



(XI)

[0548] 或其盐；其中

[0549] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及离去基；

[0550] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及离去基；

[0551] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及离去基；

[0552] J选自由以下各项组成的群组：$N(R^7)$、S、O、$C(=O)$、$C(=O)O$、$OC(=O)$、$C(=O)N(R^7)$、$N(R^7)C(=O)$、CH_2O以及一键；

[0553] R^4和R^5各自独立地选自由氢、任选地经取代的烷基以及离去基组成的群组，或任选地R^4和R^5中的任何两者相连以形成环；

[0554] n为0、1、2或3；

[0555] W为杂芳基、萘基、杂环基或芳基；

[0556] 每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及离去基；

[0557] m为0、1、2、3、4、5、6或7；

[0558] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个R^7可相连以形成环；

[0559] 每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、

卤烷基以及离去基；

[0560] 每个 R^9 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及离去基；和

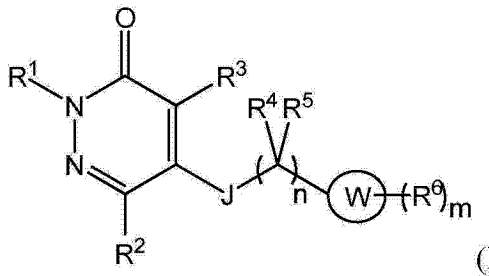
[0561] 每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基，

[0562] 其限制条件为在所述化合物中存在至少一个离去基；和

[0563] 其限制条件为当 W 为芳基时，a) R^3 不为卤基、烷基或卤烷基，或 b) 至少一个 R^6 选自由以下各项组成的群组：任选地经取代的炔基、任选地经取代的烯基、经 -CN 取代的烷基、经 $-C(=O)OR^8$ 取代的烷基、经 $-C(=O)R^8$ 取代的烷基、经 $-N(R^7)_2$ 取代的烷基、-CN、$-NO_2$、$-N(R^7)_2$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)R^8$、$-C(=O)N(R^7)_2$ 以及 $-N(R^7)C(=O)R^8$。

[0564] 在一些实施例中，提供包含以下结构的化合物：

[0565]



(XII)

[0566] 或其盐；其中

[0567] R^1 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及离去基；

[0568] R^2 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$ 以及离去基；

[0569] R^3 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$ 以及离去基；

[0570] J 选自由以下各项组成的群组：$N(R^7)$、S、O、$C(=O)$、$C(=O)O$、$OC(=O)$、$C(=O)N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键；

[0571] R^4 和 R^5 各自独立地选自由氢、任选地经取代的烷基以及离去基组成的群组，或任选地 R^4 和 R^5 中的任何两者相连以形成环；

[0572] n 为 0、1、2 或 3；

[0573] W 为杂芳基、萘基或杂环基；

[0574] 每个 R^6 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)$

OR^8、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及离去基；

[0575] m 为 0、1、2、3、4、5、6 或 7；

[0576] 每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个 R^7可相连以形成环；

[0577] 每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

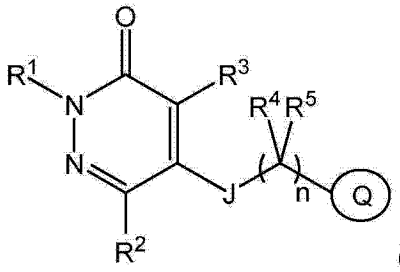
[0578] 每个 R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及离去基；和

[0579] 每个 $R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基，

[0580] 其限制条件为在所述化合物中存在至少一个离去基。

[0581] 在一些实施例中，提供包含以下结构的化合物：

[0582]



(XIII)

[0583] 或其盐；其中

[0584] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及离去基；

[0585] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及离去基；

[0586] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及离去基；

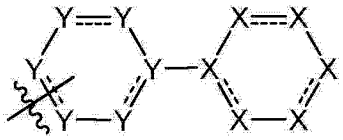
[0587] J 选自由以下各项组成的群组：$N(R^7)$、S、O、$C(=O)$、$C(=O)O$、$OC(=O)$、$C(=O)N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键；

[0588] R^4和 R^5各自独立地选自由氢、任选地经取代的烷基以及离去基组成的群组，或任选地 R^4和 R^5中的任何两者相连以形成环；

[0589] n 为 0、1、2 或 3；

[0590] Q 具有以下结构：

[0591]



[0592] 每个 Y 和每个 X 独立地选自由 C、$C(R^6)$、$C(R^6)_2$、N、NR^7、O 以及 S 组成的群组，其限制条件为至少一个 Y 不为 C 或 $C(R^6)$；

[0593] 每个 ------ 独立地为单键或双键。

[0594] 每个 R^6 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$ 以及离去基；

[0595] 每个 R^7 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个 R^7 可相连以形成环；

[0596] 每个 R^8 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

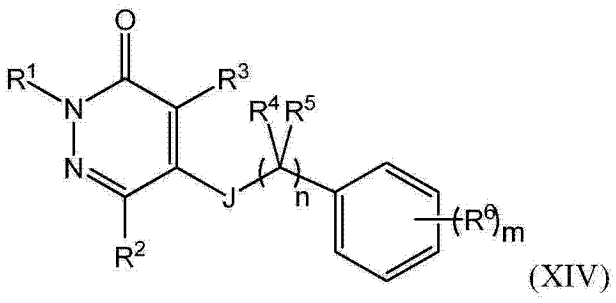
[0597] 每个 R^9 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及离去基；和

[0598] 每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基，

[0599] 其限制条件为在所述化合物中存在至少一个离去基。

[0600] 在一些实施例中，提供包含以下结构的化合物：

[0601]



(XIV)

[0602] 或其盐；其中

[0603] R^1 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及离去基；

[0604] R^2 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷

基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及离去基；

[0605] R^3选自由以下各项组成的群组：氢、未经取代的烷基或任选地经除卤素以外的部分取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、-CN 以及 $-NO_2$；

[0606] J 选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键；

[0607] R^4和 R^5各自独立地选自由氢、任选地经取代的烷基以及离去基组成的群组，或任选地 R^4和 R^5中的任何两者相连以形成环；

[0608] n 为 0、1、2 或 3；

[0609] 每个 R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及离去基；

[0610] m 为 0、1、2、3、4 或 5；

[0611] 每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个 R^7可相连以形成环；

[0612] 每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

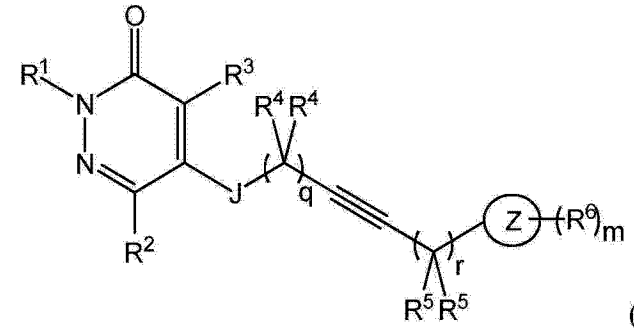
[0613] 每个 R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及离去基；和

[0614] 每个 $R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基，

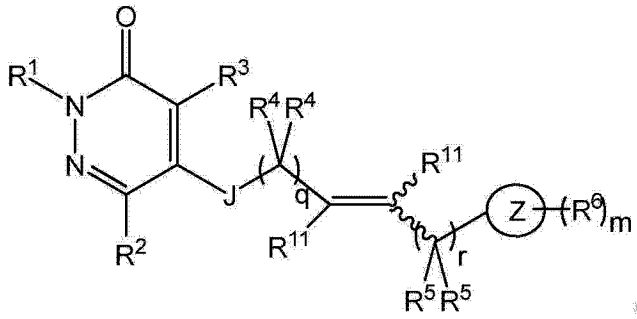
[0615] 其限制条件为在所述化合物中存在至少一个离去基。

[0616] 在一些实施例中，提供包含以下结构的化合物：

[0617]



(XV)或



(XVI)，

[0618] 或其盐；其中

[0619] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及离去基；

[0620] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及离去基；

[0621] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及离去基；

[0622] J选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O以及一键；

[0623] 每个R^4、R^5和R^{11}独立地选自由氢、任选地经取代的烷基以及离去基组成的群组，或任选地任何两个R^4或任何两个R^5相连以形成环；

[0624] q和r各自独立地为0、1、2或3；

[0625] Z选自由以下各项组成的群组：芳基、杂芳基、杂环基以及一键；

[0626] 每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及离去基；

[0627] m为0、1、2、3、4、5、6或7；

[0628] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取

代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基及离去基，或任选地任何两个 R^7 可相连以形成环；

[0629] 每个 R^8 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

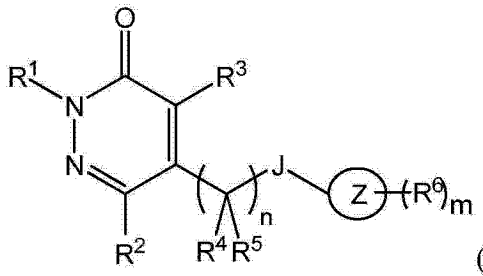
[0630] 每个 R^9 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及离去基；和

[0631] 每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基，

[0632] 其限制条件为在所述化合物中存在至少一个离去基。

[0633] 在一些实施例中，提供包含以下结构的化合物：

[0634]



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[0635] 或其盐；其中

[0636] R^1 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及离去基；

[0637] R^2 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、$-NO_2$、卤烷基以及离去基；

[0638] R^3 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$ 以及离去基；

[0639] J 选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$ 以及 $-CH_2O$；

[0640] 每个 R^4 和 R^5 独立地选自由氢、任选地经取代的烷基以及离去基组成的群组，或任选地 R^4 和 R^5 中的任何两者相连以形成环；

[0641] n 为 1、2 或 3；

[0642] Z 选自由以下各项组成的群组：芳基、杂芳基、杂环基以及一键；

[0643] 每个 R^6 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、-C(=O)

OR^8、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及离去基；

[0644] m 为 0、1、2、3、4、5、6 或 7；

[0645] 每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个 R^7可相连以形成环；

[0646] 每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

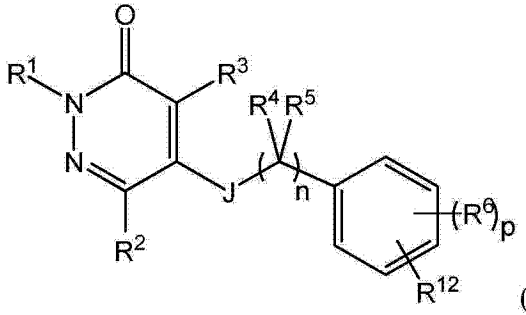
[0647] 每个 R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及离去基；和

[0648] 每个 $R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基，

[0649] 其限制条件为在所述化合物中存在至少一个离去基。

[0650] 在一些实施例中，提供包含以下结构的化合物：

[0651]



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[0652] 或其盐；其中

[0653] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及离去基；

[0654] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及离去基；

[0655] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及离去基；

[0656] J 选自由以下各项组成的群组：$N(R^7)$、S、O、$C(=O)$、$C(=O)O$、$OC(=O)$、$C(=O)N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键；

[0657] R^4和 R^5各自独立地选自由氢、任选地经取代的烷基以及离去基组成的群组，或任选地 R^4和 R^5中的任何两者相连以形成环；

[0658] n 为 0、1、2 或 3；

[0659] 每个 R^6 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$ 以及离去基；

[0660] p 为 0、1、2、3 或 4；

[0661] 每个 R^7 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个 R^7 可相连以形成环；和

[0662] 每个 R^8 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

[0663] 每个 R^9 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及离去基；

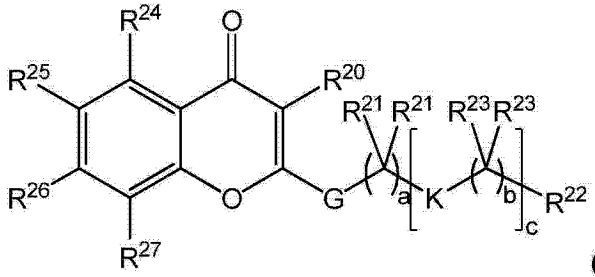
[0664] 每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基；和

[0665] R^{12} 选自由以下各项组成的群组：任选地经取代的炔基、任选地经取代的烯基、经 -CN 取代的烷基、经 $-C(=O)OR^8$ 取代的烷基、经 $-C(=O)R^8$ 取代的烷基、经 $-N(R^7)_2$ 取代的烷基、-CN、$-NO_2$、$-N(R^7)_2$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)R^8$、$-C(=O)N(R^7)_2$ 以及 $-N(R^7)C(=O)R^8$，

[0666] 其限制条件为在所述化合物中存在至少一个离去基。

[0667] 在一些实施例中，提供包含以下结构的化合物：

[0668]



(XIX)

[0669] 或其盐；其中

[0670] R^{20} 选自由以下各项组成的群组：氢、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN 以及 $-NO_2$；

[0671] 每个 R^{21} 和 R^{23} 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、卤基、卤烷基以及离去基，或任选地任何两个 R^{21} 或任何两个 R^{23} 可相连以形成环；

[0672] R^{22} 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷

基、任选地经取代的烷氧基烷基、卤基、卤烷基、$-OR^{28}$、$-Si(R^9)_3$、$-B(R^{9'})_3$以及离去基；

[0673] R^{24}、R^{25}、R^{26}以及R^{27}各自独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN以及离去基；

[0674] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个R^7可相连以形成环；和

[0675] 每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

[0676] 每个R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及离去基；

[0677] 每个$R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基；

[0678] R^{28}选自由以下各项组成的群组：氢、任选地经取代的烷基以及任选地经取代的杂烷基；

[0679] G为O、S或NR^{28}；

[0680] a为0、1、2、3或4；

[0681] 每个K独立地为各自任选地经取代的亚芳基、亚杂芳基、亚烯基或亚炔基；

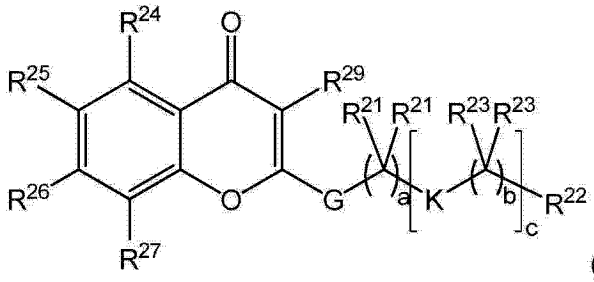
[0682] 每个b独立地为0、1、2、3或4；和

[0683] c为1或2，

[0684] 其限制条件为在所述化合物中存在至少一个离去基。

[0685] 在一些实施例中，提供包含以下结构的化合物：

[0686]



(XX)

[0687] 或其盐；其中

[0688] 每个R^{21}和R^{23}独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、卤基、卤烷基以及离去基，或任选地任何两个R^{21}或任何两个R^{23}可相连以形成环；

[0689] R^{22}选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、卤基、卤烷基、$-OR^{28}$、$-Si(R^9)_3$、$-B(R^{9'})_3$以及离去基；

[0690] R^{24}、R^{25}、R^{26}以及 R^{27}各自独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$、-OH、-C(=O)R^8、-C(=O)OR^8、-OC(=O)R^8、-C(=O)N$(R^7)_2$、-N(R^7)C(=O)R^8、-CN 以及离去基；

[0691] 每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个 R^7可相连以形成环；和

[0692] 每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

[0693] 每个 R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤基以及离去基；

[0694] 每个 $R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基；

[0695] R^{28}选自由以下各项组成的群组：氢、任选地经取代的烷基以及任选地经取代的杂烷基；

[0696] R^{29}选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及离去基；

[0697] G 为 O、S 或 NR^{28}；

[0698] a 为 0、1、2、3 或 4；

[0699] 每个 K 独立地为各自任选地经取代的亚芳基、亚杂芳基、亚烯基或亚炔基，其限制条件为至少一个 K 为亚烯基或亚炔基；

[0700] 每个 b 独立地为 0、1、2、3 或 4；和

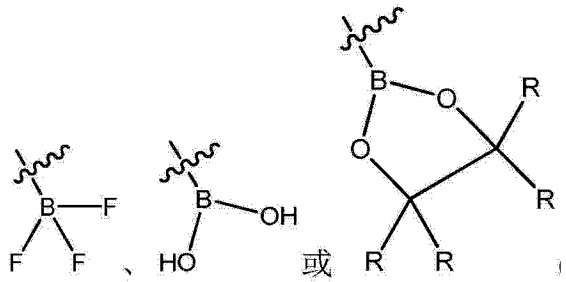
[0701] c 为 1 或 2，

[0702] 其限制条件为在所述化合物中存在至少一个离去基。

[0703] 在包含式 (XI)、(XII)、(XIII)、(XIV)、(XV)、(XVI)、(XVII)、(XVIII)、(XIX) 或 (XX) 的以上化合物中的每一者中，每个基团和 / 或变量可任选地选自以上为具有式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII)、(VIII)、(IX) 或 (X) 的相应造影剂所提供的基团和 / 或变量，其中为包含式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII)、(VIII)、(IX) 或 (X) 的化合物所提供的基团中的每个造影部分经离去基置换。

[0704] R^6基团的以下描述可联合式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物使用。在一些实施例中，关于式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物，除一个 R^6以外所有 R^6均为 H。即，所有 R^6为 H 且一个 R^6不为 H。在一些情况下，不为 H 的一个 R^6经至少一个离去基取代。在一些情况下，不为 H 的一个 R^6为至少一个离去基。在一些实施例中，关于式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII) 或 (VIII) 化合物，至少一个 R^6为各自经离去基取代的任选地经取代的烷基、任选地经取代的烷氧基或任选地经取代的烷氧基烷基。在一些实施例中，关于式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII)

或 (VIII) 化合物，至少一个 R^6 为 $-(CH_2)_jL_G$；其中 L_G 为离去基且 j 为 1、2、3、4、5 或 6。在一些情况下，至少一个 R^6 为 $-(CH_2)L_G$、$-(CH_2)_2L_G$、$-(CH_2)_3L_G$、$-(CH_2)_4L_G$、$-(CH_2)_5L_G$、$-(CH_2)_6L_G$、$-(CH_2)_7L_G$、$-(CH_2)_8L_G$、$-(CH_2)_9L_G$ 或 $-(CH_2)_{10}L_G$。在一些实施例中，至少一个 R^6 为 $-O(CH_2)_jL_G$；其中 L_G 为离去基且 j 为 1、2、3、4、5 或 6。在一些情况下，至少一个 R^6 为 $-O(CH_2)_5L_G$、$-O(CH_2)_6L_G$、$-O(CH_2)_7L_G$、$-O(CH_2)_8L_G$、$-O(CH_2)_9L_G$ 或 $-O(CH_2)_{10}L_G$。在一些实施例中，至少一个 R^6 为 $-(CH_2)_jO(CH_2)_jL_G$；其中 L_G 为离去基且每个 j 独立地为 1、2、3、4、5 或 6。在一些实施例中，至少一个 R^6 为 $-(CH_2)O(CH_2)_jL_G$；其中 L_G 为离去基且每个 j 独立地为 1、2、3、4、5 或 6。在一些情况下，至少一个 R^6 为 $-CH_2O(CH_2)L_G$、$-CH_2O(CH_2)_2L_G$、$-CH_2O(CH_2)_3L_G$、$-CH_2O(CH_2)_4L_G$、$-CH_2O(CH_2)_5L_G$、$-CH_2O(CH_2)_6L_G$、$-CH_2O(CH_2)_7L_G$、$-CH_2O(CH_2)_8L_G$、$-CH_2O(CH_2)_9L_G$ 或 $-CH_2O(CH_2)_{10}L_G$。在一些实施例中，至少一个 R^6 为 $-C\equiv C-(CH_2)_jL_G$；其中 L_G 为离去基且 j 为 1、2、3、4、5 或 6。在一些实施例中，至少一个 R^6 为 $-[(CH_2)_jO]_j(CH_2)_jL_G$；其中 L_G 为离去基且每个 j 独立地为 1、2、3、4、5 或 6。在一些实施例中，至少一个 R^6 为 $-O[(CH_2)_jO]_j(CH_2)_jL_G$；其中 L_G 为离去基且每个 j 独立地为 1、2、3、4、5 或 6。在一些实施例中，至少一个 R^6 为经离去基取代的任选地经取代的烷基。在一些实施例中，至少一个 R^6 为 $-C(=O)O(CH_2)_jL_G$；其中 L_G 为离去基且 j 为 1、2、3、4、5 或 6。在一些实施例中，至少一个 R^6 为 $-C(=O)(CH_2)_jL_G$；其中 L_G 为离去基且 j 为 1、2、3、4、5 或 6。在一些实施例中，至少一个 R^6 为 $-(CH_2)_jNH(CH_2)_jL_G$；其中 L_G 为离去基且每个 j 独立地为 1、2、3、4、5 或 6。在一些实施例中，至少一个 R^6 为 $Si(R^9)_2L_G$，其中每个 R^9 为任选地经取代的烷基且其中 L_G 为离去基。在一些实施例中，至少一个 R^6 为 $B(R^{9'})_2L_G$，其中每个 $R^{9'}$ 为任选地经取代的烷基且其中 L_G 为离去基；或任选地两个 $R^{9'}$ 相连以形成环，其为离去基的一部分；或任选地缺少一个 $R^{9'}$，例如：

[0705] 

（例如其中每个 R 为烷基或芳基）。

[0706] 在一些实施例中，至少一个 R^6 选自由以下各项组成的群组：$-C\equiv C-CH_2CH_2CH_2L_G$、$-C\equiv C-CH_2CH_2L_G$、$-C\equiv C-CH_2L_G$、$-CH_2L_G$、$-(CH_2)_2L_G$、$-(CH_2)_3L_G$、$-(CH_2)_4L_G$、$-(CH_2)_5L_G$、$-(CH_2)_6L_G$、$-OCH_2L_G$、$-O(CH_2)_2L_G$、$-O(CH_2)_3L_G$、$-O(CH_2)_4L_G$、$-O(CH_2)_5L_G$、$-O(CH_2)_6L_G$、$-CH_2O(CH_2)_2L_G$、$-CH(CH_3)O(CH_2)_2L_G$、$-CH_2O(CH_2)_3L_G$、$-CD_2O(CH_2)_2L_G$、$-(CH_2)_2O(CH_2)_2L_G$、$-CHBrC(CH_3)_2L_G$、$-CHClC(CH_3)_2L_G$、$-CHFC(CH_3)_2L_G$、$-C(=O)OCH_2L_G$、$-C(=O)O(CH_2)_2L_G$、$-C(=O)O(CH_2)_3L_G$、$-CH_2NH(CH_2)_2L_G$、$-CH_2NHCH_2L_G$、$-CH_2O(CH_2)_2O(CH_2)_2L_G$、$-CH_2O(CH_2)_2O(CH_2)_3L_G$、$-O(CH_2)_2O(CH_2)_2L_G$、$-C(=O)(CH_2)_2L_G$ 及 $-C(=O)(CH_2)_3L_G$。关于式 (XI) 或 (XII) 化合物，本文所述的 R^6 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^7、R^8、R^9、$R^{9'}$、J、W、m 以及 n 或其组合中的任一者组合。关于式 (XIII) 化合物，本文所述的 R^6 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^7、R^8、R^9、$R^{9'}$、Q、J 以及 n 或其组合中的任一者组合。关于式 (XIV) 化合物，本文所述的 R^6 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^7、R^8、R^9、$R^{9'}$、J、m 以及 n 或其组合中的任一者组合。关于式 (XV) 或 (XVI) 化合物，本文所述的 R^6 基团中的每一者可与如本文所述的 R^1、R^2、R^3、R^4、R^5、R^7、R^8、R^9、$R^{9'}$、R^{11}、J、Z、m、q 以及 r 或其组合中的任一者组合。关于式 (XVII) 化合物，本

文所述的R^6基团中的每一者可与如本文所述的R^1、R^2、R^3、R^4、R^5、R^7、R^8、R^9、$R^{9'}$、J、Z、n 以及 m 或其组合中的任一者组合。关于式 (XVIII) 化合物，本文所述的R^6基团中的每一者可与如本文所述的R^1、R^2、R^3、R^4、R^5、R^7、R^8、R^9、$R^{9'}$、R^{12}、J、p 以及 n 或其组合中的任一者组合或其组合。

[0707] R^{22}基团的以下描述可与式 (XIX) 或 (XX) 化合物联合使用。在一些实施例中，R^{22}为离去基。在一些实施例中，R^{22}经离去基取代。在一些实施例中，R^{22}为各自经离去基取代的任选地经取代的烷基、任选地经取代的烷氧基或任选地经取代的烷氧基烷基。在一些实施例中，R^{22}为 $-Si(R^9)_3$或 $-B(R^{9'})_3$。在一些实施例中，R^{22}为 $-(CH_2)_jL_G$；其中 L_G为离去基且 j 为 1、2、3、4、5 或 6。在一些情况下，R^{22}为 $-(CH_2)L_G$、$-(CH_2)_2L_G$、$-(CH_2)_3L_G$、$-(CH_2)_4L_G$、$-(CH_2)_5L_G$、$-(CH_2)_6L_G$、$-(CH_2)_7L_G$、$-(CH_2)_8L_G$、$-(CH_2)_9L_G$或 $-(CH_2)_{10}L_G$。在一些实施例中，R^{22}为 $-O(CH_2)_jL_G$；其中 L_G为离去基且 j 为 1、2、3、4、5 或 6。在一些情况下，R^{22}为 $-O(CH_2)L_G$、$-O(CH_2)_2L_G$、$-O(CH_2)_3L_G$、$-O(CH_2)_4L_G$、$-O(CH_2)_5L_G$、$-O(CH_2)_6L_G$、$-O(CH_2)_7L_G$、$-O(CH_2)_8L_G$、$-O(CH_2)_9L_G$或 $-O(CH_2)_{10}L_G$。在一些实施例中，R^{22}为 $-(CH_2)_jO(CH_2)_jL_G$；其中 L_G为离去基且每个 j 独立地为 1、2、3、4、5 或 6。在一些实施例中，R^{22}为 $-(CH_2)O(CH_2)_jL_G$；其中 L_G为离去基且每个 j 独立地为 1、2、3、4、5 或 6。在一些情况下，R^{22}为 $-CH_2O(CH_2)L_G$、$-CH_2O(CH_2)_2L_G$、$-CH_2O(CH_2)_3L_G$、$-CH_2O(CH_2)_4L_G$、$-CH_2O(CH_2)_5L_G$、$-CH_2O(CH_2)_6L_G$、$-CH_2O(CH_2)_7L_G$、$-CH_2O(CH_2)_8L_G$、$-CH_2O(CH_2)_9L_G$或 $-CH_2O(CH_2)_{10}L_G$。在一些实施例中，R^{22}为 $-C\equiv C-(CH_2)_jL_G$；其中 L_G为离去基且 j 为 1、2、3、4、5 或 6。在一些实施例中，R^{22}为 $-[(CH_2)_jO]_j(CH_2)_jL_G$；其中 L_G为离去基且每个 j 独立地为 1、2、3、4、5 或 6。在一些实施例中，R^{22}为 $-O[(CH_2)_jO]_j(CH_2)_jL_G$；其中 L_G为离去基且每个 j 独立地为 1、2、3、4、5 或 6。在一些实施例中，R^{22}为经离去基取代的任选地经取代的烷基。在一些实施例中，R^{22}为 $-C(=O)O(CH_2)_jL_G$；其中 L_G为离去基且 j 为 1、2、3、4、5 或 6。在一些实施例中，R^{22}为 $-C(=O)(CH_2)_jL_G$；其中 L_G为离去基且 j 为 1、2、3、4、5 或 6。在一些实施例中，R^{22}为 $-(CH_2)_jNH(CH_2)_jL_G$；其中 L_G为离去基且每个 j 独立地为 1、2、3、4、5 或 6。在一些实施例中，R^{22}为 $Si(R^9)_2L_G$，其中每个 R^9为任选地经取代的烷基且其中 L_G为离去基。在一些实施例中，R^{22}为 $B(R^{9'})_2L_G$，其中每个 $R^{9'}$为任选地经取代的烷基且其中 L_G为离去基。在一些实施例中，R^{22}选自由以下各项组成的群组：$-C\equiv C-CH_2CH_2CH_2L_G$、$-C\equiv C-CH_2CH_2L_G$、$-C\equiv C-CH_2L_G$、$-CH_2L_G$、$-(CH_2)_2L_G$、$-(CH_2)_3L_G$、$-(CH_2)_4L_G$、$-(CH_2)_5L_G$、$-(CH_2)_6L_G$、$-OCH_2L_G$、$-O(CH_2)_2L_G$、$-O(CH_2)_3L_G$、$-O(CH_2)_4L_G$、$-O(CH_2)_5L_G$、$-O(CH_2)_6L_G$、$-CH_2O(CH_2)_2L_G$、$-CH(CH_3)O(CH_2)_2L_G$、$-CH_2O(CH_2)_3L_G$、$-CD_2O(CH_2)_2L_G$、$-(CH_2)_2O(CH_2)_2L_G$、$-CHBrC(CH_3)_2L_G$、$-CHClC(CH_3)_2L_G$、$-CHFC(CH_3)_2L_G$、$-C(=O)OCH_2L_G$、$-C(=O)O(CH_2)_2L_G$、$-C(=O)O(CH_2)_3L_G$、$-CH_2NH(CH_2)_2L_G$、$-CH_2NHCH_2L_G$、$-CH_2O(CH_2)_2O(CH_2)_2L_G$、$-CH_2O(CH_2)_2O(CH_2)_3L_G$、$-O(CH_2)_2O(CH_2)_2L_G$、$-C(=O)(CH_2)_2L_G$以及 $-C(=O)(CH_2)_3L_G$。关于式 (XIX) 化合物，本文所述的R^{22}基团中的每一者可与如本文所述的R^7、R^8、R^{20}、R^{21}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}、G、a、K、b 以及 c 或其组合中的任一者组合。关于式 (XX) 化合物，本文所述的R^{22}基团中的每一者可与如本文所述的R^7、R^8、R^{21}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27}、R^{28}、R^{29}、G、a、K、b 以及 c 或其组合中的任一者组合。

[0708] 如本文中较详细所述，提供一种诊断试剂盒，其包含一或多个含有如此部分中所述的化合物或其盐（例如包含式 (XI)、(XII)、(XIII)、(XIV)、(XV)、(XVI)、(XVII)、(XVIII)、(XIX) 或 (XX) 的化合物）以及任选的其它组分的小瓶。在一些实施例中，所述诊断试剂盒用于制备用于造影、检测和/或监控个体的心肌灌注的诊断剂。在一些实施例中，所述其它组分选自由以下各项组成的群组：辅助配位体、还原剂、转移配位体、缓冲液、冻干

助剂、稳定化助剂、增溶助剂以及抑菌剂。

[0709] 如本文中较详细所述，在一些实施例中，提供用于形成造影剂的方法，所述方法包含使如本部分中所述的化合物或其盐（例如包含式 (XI)、(XII)、(XIII)、(XIV)、(XV)、(XVI)、(XVII)、(XVIII)、(XIX) 或 (XX) 的化合物）与含 ^{18}F 物质反应，产生包含 ^{18}F 的造影剂（例如分别包含式 (I)、(II)、(III)、(IV)、(V)、(VI)、(VII)、(VIII)、(IX) 或 (X) 的化合物）。

[0710] 盐

[0711] 在一些实施例中，本文所述的造影剂和前驱体可为盐。在一些情况下，所述盐为医药学上可接受的盐。然而，在造影剂前驱体的情况下，所述盐可不必为医药学上可接受的盐。所属领域的技术人员应了解用于形成本文所述的造影剂和造影剂前驱体的盐的适合的相对阴离子。另外，所属领域的技术人员应了解，相对阴离子 $X^{\ominus}$ 的电荷可小于 -1（例如 -2、-3），且在所述实施例中，每个相对阴离子 $X^{\ominus}$ 可与一个以上化合物分子缔合。在一些实施例中，相对离子为卤离子、磷酸根、磷酸氢根、磷酸二氢根、硫酸氢根、硫酸根、三氟乙酸根、甲苯磺酸根、乙酸根、甲酸根、柠檬酸根、抗坏血酸根、甲磺酸根（甲烷磺酸根）、三氟甲磺酸根（三氟甲烷磺酸根）、酒石酸根、乳酸根或苯甲酸根。适合的相对阴离子的其它非限制性实例包括无机酸的共轭碱（例如氯离子、溴离子、碘离子、氟离子、硝酸根、硫酸根、磷酸根）或有机酸的共轭碱（例如羧酸根、乙酸根、苯甲酸根、酒石酸根、己二酸根、乳酸根、甲酸根、顺丁烯二酸根、谷氨酸根、抗坏血酸根、柠檬酸根、葡糖酸根、乙二酸根、丁二酸根、双羟萘酸根、水杨酸根、羟乙基磺酸根、丁二酰胺酸根、单二乙醇酸根、二异丁酸根、葡糖庚酸根）。盐的其它非限制性实例包括己二酸盐、海藻酸盐、氨基水杨酸盐、无水亚甲基柠檬酸盐 (anhydromethylenecitrate)、槟榔碱 (arecoline)、天冬氨酸盐、硫酸氢盐、樟脑酸盐、二葡糖酸盐、二氢溴化物、丁二酸氢盐、甘油磷酸盐、半硫酸盐、氟化物、碘化物、亚甲基双（水杨酸盐）、萘二磺酸盐、乙二酸盐、果胶酸盐、过硫酸盐、苯乙基巴比妥酸盐、苦味酸盐、丙酸盐、硫氰酸盐、甲苯磺酸盐、十一烷酸盐、乙酸盐、苯磺酸盐、苯甲酸盐、碳酸氢盐、酒石酸氢盐、溴化物、依地酸钙 (calcium edentate)、樟脑磺酸盐 (camsylate)、碳酸盐、氯化物、柠檬酸盐、二盐酸盐、依地酸盐、乙二磺酸盐、依托酸盐 (estolate)、乙磺酸盐、反丁烯二酸盐、葡庚糖酸盐、葡糖酸盐、谷氨酸盐、乙内酰胺苯肿酸盐、己基间苯二酚盐 (hexylresorcinate)、海卓氨 (hydrabamine)、溴化物、氯化物、羟基萘甲酸盐、碘化物、羟乙基磺酸盐、乳酸盐、乳糖酸盐、苹果酸盐、顺丁烯二酸盐、杏仁酸盐、甲磺酸盐、粘液酸盐、萘磺酸盐、硝酸盐、双羟萘酸盐（恩波酸盐 (embonate)）、泛酸盐、磷酸盐 / 二磷酸盐、聚半乳糖醛酸盐、水杨酸盐、硬脂酸盐、次乙酸盐、丁二酸盐、硫酸盐、丹宁酸盐 (tannate)、酒石酸盐、8- 氯茶碱盐 (teoclate) 及三乙基碘 (triethiodide)（参见贝格 (Berge) 等人，医药科学杂志 (Journal of Pharmaceutical Sciences)，66(1)，1977，1-19）。

[0712] 合成造影剂的方法

[0713] 在其它方面中，提供合成造影剂的方法。本文所述的方法可用于自如本文所述的造影剂前驱体合成如本文所述的各种造影剂。一般说来，造影剂可通过造影剂前驱体与包含造影部分的反应物反应来合成。在一些情况下，所述反应涉及在造影剂前驱体与反应物的造影部分之间形成共价键。在其它情况下，然而，所述反应涉及造影部分与造影剂前驱体的非共价缔合（例如通过螯合）。以下部分提供多个用于自造影剂前驱体形成造影剂的非

限制性实施例。所属领域的技术人员应了解用于自造影剂前驱体形成造影剂的其它适合方法和技术。另外，还描述可与造影剂的合成联合执行的其它步骤（例如调配、纯化）。

[0714] 在一些情况下，造影剂通过造影剂前驱体与造影部分反应来形成。在某些实施例中，方法涉及包含离去基的造影剂前驱体与造影部分源（例如氟物质）反应。例如，造影部分通过如 S_N2 或 S_N1 反应的取代反应置换离去基。即，在所述反应期间，造影部分置换离去基，从而产生造影剂。

[0715] 本文所述的方法可用于自造影剂前驱体合成各种各样的造影剂。一般说来，造影剂前驱体可包括至少一个可经造影部分置换的离去基，如 ^{18}F 物质。造影剂前驱体可使用所属领域的技术人员已知的方法来合成。

[0716] A. 一般反应条件

[0717] 本文所述的合成方法可在任何适合溶剂中进行，所述溶剂包括（但不限于）非卤化烃溶剂（例如戊烷、己烷、庚烷、环己烷）、卤化烃溶剂（例如二氯甲烷、氯仿、氟苯、三氟甲苯）、芳香族烃溶剂（例如甲苯、苯、二甲苯）、酯溶剂（例如乙酸乙酯）、醚溶剂（例如四氢呋喃、二噁烷、乙醚、二甲氧乙烷）以及醇溶剂（例如乙醇、甲醇、丙醇、异丙醇、叔丁醇）。在某些实施例中，使用质子性溶剂。在其它实施例中，使用非质子性溶剂。适用于所述合成方法的溶剂的非限制性实例包括丙酮、乙酸、甲酸、二甲亚砜、二甲基甲酰胺、乙腈、对甲酚、乙二醇、石油醚、四氯化碳、六甲基－磷酰三酰胺、三乙氨、甲基吡啶以及吡啶。

[0718] 所述方法可在任何适合温度下进行。在一些情况下，所述方法在约室温（例如约 20℃、介于约 20℃与约 25℃之间、约 25℃或其类似温度）下进行。在一些情况下，然而，所述方法在低于或高于室温的温度下进行，例如在约 -78℃下、在约 -70℃、约 -50℃、约 -30℃、约 -10℃、约 -0℃、约 10℃、约 30℃、约 40℃、约 50℃、约 60℃、约 70℃、约 80℃、约 90℃、约 100℃、约 120℃、约 140℃或其类似温度下。在一些实施例中，所述方法在高于室温的温度下进行，例如介于约 25℃与约 120℃之间，或介于约 25℃与约 100℃之间，或介于约 40℃与约 120℃之间，或介于约 80℃与约 120℃之间。可通过溶液回流来维持温度。在一些情况下，所述方法介于约 -78℃与约 25℃之间或介于约 0℃与约 25℃之间的温度下进行。

[0719] 本文所述的方法可在任何适合 pH 值下进行，例如等于或小于约 13、等于或小于约 12、等于或小于约 11、等于或小于约 10、等于或小于约 9、等于或小于约 8、等于或小于约 7 或等于或小于约 6。在一些情况下，pH 值可大于或等于 1、大于或等于 2、大于或等于 3、大于或等于 4、大于或等于 5、大于或等于 6、大于或等于 7 或大于或等于 8。在一些情况下，pH 值可介于约 2 与约 12 之间，或介于约 3 与约 11 之间，或介于约 4 与约 10 之间，或介于约 5 与约 9 之间，或介于约 6 与约 8 之间，或为约 7。

[0720] 产物的产率百分比可大于约 60％、大于约 70％、大于约 75％、大于约 80％、大于约 85％、大于约 90％、大于约 92％、大于约 95％、大于约 96％、大于约 97％、大于约 98％、大于约 99％或 99％以上。

[0721] B1. 卤化

[0722] 在一些实施例中，造影剂通过造影剂前驱体与造影部分反应来形成。在某些实施例中，造影剂前驱体包含至少一个易经造影部分置换的离去基，如卤素（例如 ^{18}F、^{76}Br、^{124}I、^{131}I）。因此，在某些实施例中，本文所述的方法涉及包含离去基的造影剂前驱体与造影部分源反应。

[0723] 在一些实施例中，卤化物通过如 S_N2 或 S_N1 反应的取代反应置换所提供的造影剂前驱体上的离去基，从而产生造影剂。例如，如氟化物的卤化物可置换造影剂前驱体的磺酸酯基离去基，得到氟化造影剂。在某些实施例中，取代反应为不需要后续脱除保护基步骤的一步式程序。即，对完全脱除保护基的造影剂前驱体进行取代步骤。在某些实施例中，本发明所提供的取代反应产生氟化造影剂（例如包含 ^{18}F 的造影剂）。

[0724] 在一些实施例中，所提供的造影剂通过芳基或杂芳基卤化反应（例如芳基氟化、芳基溴化、芳基碘化）合成。用于合成芳基或杂芳基卤化物的许多技术在本领域中为已知的。例如，在某些实施例中，包含 ^{124}I、^{131}I 或 ^{76}Br 造影部分的造影剂在使用或不使用铜(I)催化的情况下，通过桑德迈尔反应(Sandmeyer reaction)由芳基重氮盐造影剂前驱体合成（参见例如贝利斯卡(Beletskaya)等人，合成学(Synthesis)，2007，2534-2538；胡巴德(Hubbard)等人，有机化学杂志(J.Org.Chem.)，2008，73，316-319；菲利莫诺(Filimonov)等人，有机化学通讯(Org.Lett.)，2008，10，3961-3964；库拉诺卡亚(Krasnokutskaya)等人，合成学，2007，81-84)。在其它实施例中，包含 ^{18}F 造影部分的造影剂通过相关巴尔茨-席曼反应(Balz-Schiemann reaction)由重氮盐造影剂前驱体合成。在某些实施例中，包含 ^{124}I 或 ^{131}I 造影部分的造影剂通过“芳香族芬克尔斯坦(aromatic Finkelstein)”反应由芳基溴造影剂前驱体合成（参见例如A.克拉帕斯(A.Klapars)，S.L.布克沃德(S.L.Buchwald)，美国化学会志(J.Am.Chem.Soc.)，2002，124，14844-14845)。在其它实施例中，包含 ^{124}I、^{131}I 或 ^{76}Br 造影部分的造影剂通过使硼酸或硼酸酯造影剂前驱体与适当的N-卤基丁二酰亚胺试剂（赛贝斯(Thiebes)等人，Synlett，1998，141-142）或溴化铜试剂（参见例如穆菲(Murphy)等人，美国化学会志，2007，129，15434-15435；汤普森(Thompson)等人，合成学，2005，547-550）反应来合成。在一些实施例中，包含 ^{76}Br 造影部分的造影剂通过有机三氟硼酸盐造影剂前驱体合成（参见例如G.W.卡巴尔卡(G.W.Kabalka)，A.R.麦瑞迪(A.R.Mereddy)，金属有机化学(Organometallics)，2004，23，4519-4521)。所属领域的技术人员应了解，可在许多其它条件下卤化活化或去活化的芳烃（参见例如库拉茨维茨(Kraszkiewicz)等人，合成学，2006，1195-1199；冈谷利(Ganguly)等人，合成学，2010，1467-1472；艾斯克拉(Iskra)等人，合成学，2004，1869-1873；卡斯奈特(Castanet)等人，四面体通讯(Tetrahedron Lett.)，2002，43，5047-5048；普拉卡什(Prakash)等人，美国化学会志，2004，126，15570-15776；鲁林斯基(Lulinski)等人，合成学，2004，441-445；冈谷利等人，合成学，2005，1103-1108；纳杰什(Rajesh)等人，有机化学(Org.Chem.)，2007，72，5867-5869；库玛(Kumar)等人，合成学，2010，1629-1632；周(Zhou)等人，合成学，2011，207-209；蒙泽尔(Menzel)等人，有机化学杂志，2006，71，2188-2191)，且这类反应可用于某些实施例中以合成本文所述的造影剂。所属领域的技术人员还应了解，本文所述的许多芳基卤化反应还将有效产生含有卤基烯烃或卤基炔烃的造影剂以及含有卤基杂芳基的造影剂。

[0725] 在一些实施例中，包含 ^{18}F 造影部分的造影剂通过芳基氟化合成。参见例如古谷(Furuya)等人，合成学，2010(11)：1804-1821(2010)，用于芳基氟化反应的信息回顾。例如，在某些实施例中，包含 ^{18}F 造影部分的造影剂通过亲核氟化反应合成。亲核氟化反应的实例包括（但不限于）哈莱克斯过程(Halex process)(Adams等人，化学学会评论

(Chem Soc Rev)1999 ;28:225 ;霍维茨 (Horwitz) 等人 , 有机化学杂志 1961 ;26:3392 ;巴林 (Barlin) 等人 , 精细与化学专用品 (J.Chem.Soc.,Perkin Trans)1 1972:1269 ;匹克 (Pike) 等人 , 有机化学杂志化学通讯 (J.Chem.Soc.,Chem Commun)1995:2215 ;沙哈 (Shah) 等人 , 精细与化学专用品 11998:2043 ;艾默特 (Ermert) 等人 , 标记化合物放射性药物 (J Labelled Compd Radiopharm)2004 ;47:429) ;氟化脱硝 (阿达姆斯 (Adams) 等人 , 化学学会评论 1999 ;28:225 ;阿达姆斯等人 , 氟化学杂志 (J.Fluorine Chem)1998 ;92:127) ;用氟化物置换铵 (安吉利尼 (Angelini) 等人 , 氟化学杂志 1985 ;27:177) 以及二芳基鿭盐的氟化 (杰达金 (Zhdankin) 等人 , 化学会志 (Chem Rev)2008 ;108:5299 ;贝林格 (Beringer) 等人 , 美国化学会志 (J.Am.Chem Soc)1953 ;75:2708 ;罗斯 (Ross) 等人 , 美国化学会志 2007 ;129:8018)。氟化三烷基铵试剂也可用于亲核氟化反应 (孙 (Sun) 等人 , 德国应用化学 (Angew.Chem.,Int.Ed)2006 ;45:2720 ;古鲁辛 (Grushin) 等人 , 金属有机化学 2008 ;27:4825)。在某些实施例中 , 亲核氟化反应经钯催化 (参见例如古鲁辛等人 , 金属有机化学 2008 ;27:4825 ;沃特逊 (Watson) 等人 , 科学 (Science)2009 ;325:1661)。在其它实施例中 , 包含 ^{18}F 造影部分的造影剂通过亲电子氟化反应合成。亲电子氟化反应的实例包括 (但不限于) 芳基格林纳 (Grignard) 试剂的氟化 (安巴拉桑 (Anbarasan P), 纽尔曼 (Neumann H), 贝勒 (Beller M). 德国应用化学 2010 ;49:2219) ;芳基镁试剂的氟化 (山田 (Yamada S), 加夫罗辛 (Gavryushin A), 诺切尔 (Knochel P.) 德国应用化学 2010 ;49:2215) ;有机金属试剂的氟化 , 所述有机金属试剂如芳基锌卤化物、芳基硅烷、芳基锡烷、芳基锗、芳基硼酸酯或芳基硼酸 (布瑞斯 (Bryce) 等人 , 有机化学杂志化学通讯 1986:1623 ;迪鲁斯 (Tius) 等人 , 合成通讯 (Synth Commun)1992 ;22:1461 ;卡佐拉 (Cazorla) 等人 , 四面体通讯 2009 ;50:3936) ;芳基硅烷的氟化 (洛塞安 (Lothian) 等人 , Synlett 1993:753) 以及氟化脱锡烷化反应 (洛塞安等人 , Synlett 1993:753 ;纳玛瓦瑞 (Namavari) 等人 , 应用放射同位素 (Appl Radiat Isot)1992 ;43:989)。在一些实施例中 , 亲电子氟化反应采用化学计量或催化量的钯 (参见例如古谷等人 , 德国应用化学 2008 ;47:5993) 或银 (参见例如古谷等人 , 美国化学会志 2009 ;131:1662 ;古谷等人 , 有机四面体 (Org Lett)2009 ;11:2860)。

[0726] B2. 氟化

[0727] 应了解 , 虽然以下部分聚焦于氟化反应 , 但这绝非限制性的 , 且这部分的教示内容可适用于其它卤化反应。

[0728] 在一些实施例中 , 用于合成造影剂的方法包含使本发明的造影剂前驱体与氟物质接触 , 促使氟物质置换前驱体的离去基 , 从而产生造影剂。在一些实施例中 , 本发明方法采用本文 , 如在上文卤化反应的描述中所述的反应。

[0729] 在某些实施例中 , 用于合成造影剂的方法涉及亲核氟化反应。应了解 , 亲核氟化的论述为本文所述方法的例示且并非限制性的。在某些实施例中 , 包含离去基的造影剂前驱体在氟物质存在下反应 , 由此 , 离去基经氟物质 S_N2 或 S_N1 置换 , 产生造影剂。在一些实施例中 , 关于组合物 , 氟物质用 ^{18}F 同位素增浓。

[0730] 所属领域的技术人员应了解用于对化合物进行氟化的适合条件。例如 , 参见切萨迪 (Cesati) 等人于 2011 年 2 月 8 日申请的国际专利申请案 PCT/US2011/024109 和卡斯贝尔 (Casebier) 等人于 2005 年 2 月 11 日申请的国际专利申请案第 PCT/US2005/004687 号 , 每个申请案出于所有目的以引用的方式并入本文中。在一些情况下 , 氟源为氟盐 (例如 KF、

NaF、氟化四烷基铵）。

[0731] 在一些实施例中，适用于所提供的方法的氟化剂为氟源。在某些实施例中，适用于所提供的方法的氟化剂为 NaF 或 KF。在某些实施例中，适用于所提供的方法的氟化剂用 ^{18}F 同位素增浓。在某些实施例中，根据本发明氟化反应的适合条件包含存在铵盐或碳酸氢盐。

[0732] 氟源可包含另一试剂或与另一试剂缔合或可与另一试剂联合使用。在一些实施例中，其它试剂能够增强氟物质的反应性或以其它方式促进前驱体转化成造影剂。例如，在某些实施例中，其它试剂与多齿配位体组合使用，所述多齿配位体如能够螯合金属离子的冠醚或穴状配位子。在某些实施例中，多齿配位体为例如 4,7,13,16,21,24-六氧杂-1,10-二氮杂双环 [8.8.8]-二十六烷（即 Kryptofix® 222）。在某些实施例中，当 KF 为氟源时，对钾具有高亲和力的穴状配位子由于其螯合钾且从而提高氟离子的反应性而为适用的。在一些实施例中，使用对钾的亲和力接近Kryptofix® 222（例如为 Kryptofix® 222 对钾的亲和力的 75%、80%、85%、90%、95%或 95%以上）的穴状配位子。反应条件可包含一或多种溶剂。

[0733] 在一些实施例中，在 K_2CO_3和 Kryptofix® 222（或对相关阳离子（包括例如钾）的亲和力接近 Kryptofix® 222 的任何其它穴状配位子）存在下，在单独或与另一溶剂组合的 MeCN（乙腈）中发生氟化。在一些实施例中，K_2CO_3与造影剂前驱体的摩尔比在约 0.25:1 至约 5:1 的范围内，例如 0.5:1 至 1:1。

[0734] 在一些实施例中，在碳酸四烷基铵或碳酸氢四烷基铵存在下，在作为溶剂的 MeCN 中发生氟化。在一些实施例中，碳酸四烷基铵或碳酸氢四烷基铵与造影剂前驱体的摩尔比小于约 2:1。本文中提供其它摩尔比。

[0735] 在某些实施例中，本文所述的合成方法涉及单步制备本发明的造影剂。在某些实施例中，单步法涉及在例如 K_2CO_3/Kryptofix® 222（或Kryptofix® 222 的其它适合替代物）或碳酸四烷基铵或碳酸氢四烷基铵存在下（例如在单独 MeCN 中或在 MeCN 混合物中）氟化前驱体。在某些实施例中，单步制备方法在使用本发明的造影剂前驱体的特定盐形式时尤其适合，所述盐形式如卤化物、乙酸盐、甲酸盐、柠檬酸盐、抗坏血酸盐、三氟乙酸盐、甲苯磺酸盐 (toluenesulfonate)、苯甲酸盐、乙酸盐、磷酸盐、硫酸盐、甲苯磺酸盐 (tosylate) 以及甲磺酸盐。

[0736] 在一些实施例中，用于反应混合物中的一或多种试剂包含造影剂前驱体和氟物质。“试剂”也称为“添加剂”，在本文中用于意指添加到反应混合物中的任何化合物。在反应期间可消耗或不消耗试剂。试剂可为化学计量或催化量的试剂。例示性试剂包括催化剂、盐、氧化剂、还原剂、螯合剂、碱、酸、金属、相转移试剂以及如所属领域的技术人员应了解的其它试剂。

[0737] 在一些实施例中，试剂可促进造影剂前驱体与氟物质之间的反应和 / 或可有助于稳定所得造影剂。例如，在某些实施例中，氟物质可具有相对低的反应性（例如亲核性），且添加某些试剂可增强氟物质反应性。作为一个说明性实施例，氟物质可为带负电氟离子（例如同位素增浓的 ^{18}F 离子），且试剂可用于结合于反应混合物内存在的任何带正电相对离子，由此提高氟离子反应性。此类试剂的实例为穴状配位子，如（但不限于）Kryptofix®

(例如Kryptofix® 222)。在一些实施例中,试剂降低不当副反应的速率。

[0738] 在一些实施例中,试剂在其与造影剂前驱体接触之前可与氟物质合并。例如,在某些实施例中,制备包含氟物质及试剂的溶液,且将所述溶液添加到造影剂前驱体中。在其它实施例中,制备包含氟物质和试剂的固体,且使所述固体与造影剂前驱体在溶液中接触。在某些实施例中,使氟物质吸附于固体支撑物(例如阴离子交换管柱)上,且包含试剂的溶液用于自固体支撑物溶离氟物质。随后使溶离溶液与造影剂前驱体接触,或浓缩以产生固体,随后使其与造影剂前驱体在溶液中接触。

[0739] 在一些实施例中,所提供的试剂为碳酸氢盐。如本文所用,术语"碳酸氢盐"指包含碳酸氢根(bicarbonate/hydrogen carbonate)离子(HCO_3^-离子)的盐。在一些实施例中,碳酸氢盐为金属碳酸氢盐,如碳酸氢钠、碳酸氢钙、碳酸氢钾以及碳酸氢镁。在某些实施例中,碳酸氢盐为碳酸氢钾($KHCO_3$)。在一些实施例中,碳酸氢盐包含非金属相对离子,如碳酸氢铵。例如,碳酸氢盐可为具有式R_4NHCO_3的碳酸氢四烷基铵,其中R为烷基。在一些实施例中,R可为低碳烷基,如甲基、乙基、丙基、丁基、戊基、己基或其类似基团。在某些实施例中,铵盐为Et_4NHCO_3。在其它实施例中,所述盐为Me_4NHCO_3、i-Pr_4NHCO_3、n-Pr_4NHCO_3、n-Bu_4NHCO_3、i-Bu_4NHCO_3或t-Bu_4NHCO_3。

[0740] 在一些实施例中,所提供的试剂为碳酸盐。如本文所用,术语"碳酸盐"指包含碳酸根离子(CO_3^{-2}离子)的盐。在一些实施例中,碳酸盐为金属碳酸盐,如碳酸钠、碳酸钙、碳酸钾以及碳酸镁。在某些实施例中,碳酸盐为碳酸钾(K_2CO_3)。在一些实施例中,碳酸盐包含非金属相对离子,如碳酸铵。例如,碳酸盐可为具有式$(R_4N)_2CO_3$的碳酸四烷基铵,其中R为烷基。在一些实施例中,R可为低碳烷基,如甲基、乙基、丙基、丁基、戊基、己基或其类似基团。在某些实施例中,铵盐为$(Et_4N)_2CO_3$。在其它实施例中,所述盐为$(Me_4N)_2CO_3$、$(i\text{-}Pr_4N)_2CO_3$、$(n\text{-}Pr_4N)_2CO_3$、$(n\text{-}Bu_4N)_2CO_3$、$(i\text{-}Bu_4N)_2CO_3$或$(t\text{-}Bu_4N)_2CO_3$。

[0741] 不希望受任何特定理论限制,使用碳酸氢盐、碳酸盐和/或铵盐可有助于在造影剂前驱体的亲核氟化期间降低竞争反应(如水解)的速率。

[0742] 在一些实施例中,试剂为包含与氟物质形成弱配位盐的阳离子的盐。如本文所用,"与氟物质形成弱配位盐的阳离子"指在氟化反应的情况下使氟物质具反应性的阳离子。例如,阳离子可并不强烈地结合氟物质,使氟物质在亲核氟化反应期间起亲核试剂的作用。所属领域的技术人员能够选择适用作氟物质的弱配位相对离子的适当阳离子。例如,阳离子可具有相对大的原子半径和/或可为弱路易斯碱(Lewis base)。在一些情况下,可选择亲脂性阳离子。在一些情况下,阳离子可包含一或多个烷基。弱配位阳离子的实例包括铯离子、铵离子、六甲基哌啶的弱配位盐、$S(NMe_2)_3$、$P(NMe_2)_4$、四烷基鏻盐、四芳基鏻盐(例如四苯基鏻)、六(二甲氨基)二膦腈鎓盐以及参(二甲氨基)锍。

[0743] 在一些实施例中,所提供的试剂为铵盐,即包含经取代或未经取代的铵离子的盐。在一些实施例中,铵离子为弱配位阳离子。在一些实施例中,铵盐具有式R_4NX,其中每个R可相同或不同且为各自任选地经取代的烷基、杂烷基、芳基、杂芳基或杂环,且X为带负电的相对离子。在一些情况下,R为各自任选地经取代的烷基、杂烷基、芳基、杂芳基或杂环。在一些实施例中,铵盐可包括一系列带负电的相对离子,包括卤离子、碳酸根和碳酸氢根。铵盐的实例包括(但不限于)碳酸氢铵盐、氢氧化铵盐、乙酸铵盐、乳酸铵盐、三氟乙酸铵盐、甲烷磺酸铵盐、对甲苯磺酸铵盐、硝酸铵盐、卤化铵盐(例如碘化铵盐)以及硫酸氢铵盐。

[0744] 在一组实施例中，铵盐为四烷基铵盐，如碳酸氢四烷基铵盐。例如，铵盐可具有式 R_4NHCO_3，其中每个 R 独立地为烷基。在一些情况下，R 任选地经取代。在一些实施例中，烷基为低碳 C_1-C_6烷基。在一些实施例中，四烷基铵盐为碱性四烷基铵盐。

[0745] 在一些实施例中，在所述反应中可采用盐（例如碳酸氢盐和 / 或铵盐）以使得盐与造影剂前驱体的摩尔比小于或等于约 2:1。在一些情况下，所述摩尔比小于或等于约 2:1、小于或等于约 1.9:1、小于或等于约 1.8:1、小于或等于约 1.7:1、小于或等于约 1.6:1、小于或等于约 1.5:1、小于或等于约 1.4:1、或小于或等于约 1.3:1、或小于或等于约 1.25:1、或小于或等于约 1.2:1、或小于或等于约 1.1:1、或小于或等于约 1:1、或小于或等于约 0.75:1、或小于或等于约 0.5:1、或小于或等于约 0.25:1、或小于或等于约 0.1:1、或小于或等于约 0.05:1。在一些情况下，所述比率大于约 0.05:1、大于约 0.01:1 或大于约 0.25:1。在一些实施例中，盐添加剂与造影剂前驱体的摩尔比介于约 0.5:1 至约 1:1 之间、或约 0.25:1 至约 1:1、或约 0.25:1 至约 0.75:1、约 1.49:1 至约 0.05:1、或介于约 1.4:1 至约 0.25:1 之间、或介于约 0.25:1 与约 1.4:1 之间、或介于约 0.25:1 与约 1.25:1 之间。

[0746] 在一些实施例中，试剂系与能够增强氟物质的反应性或以其它方式促进造影剂前驱体转化成造影剂的物质组合使用。例如，物质可为能够螯合一或多个可存在于反应混合物内的离子（例如金属离子）的化合物。不希望受理论限制，物质可用于螯合氟物质的相对离子，如钾离子，由此提高氟物质的反应性（例如亲核性）。在某些实施例中，试剂与多齿配位体组合使用，所述多齿配位体如能够螯合金属离子的冠醚或穴状配位子。多齿配位体（例如穴状配位子）可基于待螯合的金属离子来选择。多齿配位体可为例如 4,7,13,16,21,24- 六氧杂 -1,10- 二氮杂双环 [8.8.8]- 二十六烷（即 Kryptofix® 222）。其它穴状配位子对所属领域的技术人员应为已知的。一些实施例涉及与 4,7,13,16,21,24- 六氧杂 -1,10- 二氮杂双环 [8.8.8]- 二十六烷组合使用碳酸盐。在特定实施例中，与 4,7,13,16,21,24- 六氧杂 -1,10- 二氮杂双环 [8.8.8]- 二十六烷组合使用 K_2CO_3和 / 或 $KHCO_3$。

[0747] 在另一组实施例中，宜在缺少穴状配位子的情况下采用本文所述的方法。术语“穴状配位子”具有其在本领域中的一般含义且指阳离子的双环或多环多齿配位体。例如，在缺少穴状配位子（例如 4,7,13,16,21,24- 六氧杂 -1,10- 二氮杂双环 [8.8.8]- 二十六烷）的情况下，本发明方法可使用铵盐进行。在一些实施例中，穴状配位子可增加反应溶液的 pH 值，这在其它试剂（例如碳酸盐）存在下可不利地影响氟化反应的产率和 / 或纯度。因此，在某些实施例中，在缺少穴状配位子的情况下和任选地在其它试剂（例如铵和 / 或碳酸氢盐）存在下进行氟化反应可增加所述反应的产率和 / 或纯度。

[0748] 在另一组实施例中，根据本发明的方法在缺少碳酸盐的情况下进行。

[0749] 所属领域的技术人员将能够选择和 / 或确定适用于特定应用中的适当反应条件组（例如浓度、温度、压力、反应时间、溶剂）。在一些实施例中，造影剂可使用一或多种纯化技术进一步加工，且可任选地与如稳定剂的其它组分合并。

[0750] 在一些实施例中，以盐（例如医药学上可接受的盐）的形式形成造影剂。本文中描述医药学上可接受的赋形剂及医药学上可接受的组合物的其它方面。

[0751] 所属领域的技术人员应能够选择适用于本文所述的方法的氟物质源。如本文所用的术语“氟物质”指氟原子或包含至少一个氟原子的原子团，其中氟原子能够与另一化合物

（例如造影剂前驱体）反应。在一些实施例中，同位素增浓的 ^{18}F 物质可通过在回旋加速器中质子轰击 $[^{18}O]H_2O$ 的核反应 $^{18}O(p,n)^{18}F$ 来产生。在某些实施例中，方法可涉及处理 ^{18}F 物质的溶液以移除任何杂质，如未反应的 $[^{18}O]H_2O$。例如，^{18}F 物质的溶液可通过阴离子交换管柱过滤，其中 ^{18}F 物质截留于阳离子树脂基质上，而 $[^{18}O]H_2O$ 经溶离。随后用溶剂与任选的试剂（例如盐）的各种混合物洗涤阴离子交换管柱来移除 ^{18}F 物质，形成含 ^{18}F 溶液。在一些实施例中，用盐的水溶液洗涤阴离子交换管柱，如 K_2CO_3 或 Et_4NHCO_3。在其它实施例中，洗涤管柱（例如用 K_2CO_3 水溶液），且稀释所得溶液（例如用 MeCN）和 / 或浓缩（例如使用高温和 / 或减压达到干燥）。可获得无水 $[^{18}F]KF$ 和 / 或 $[^{18}F]Et_4NF$ 且使其与化合物或其盐反应。

[0752] 在一些实施例中，将含 ^{18}F 溶液在与造影剂前驱体反应之前与其它组分合并。例如，可添加一或多种溶剂以稀释含 ^{18}F 溶液达到所需浓度。在某些实施例中，用乙腈 (MeCN) 稀释含 ^{18}F 溶液。在某些实施例中，用乙腈 (MeCN) 及 t-BuOH 稀释含 ^{18}F 溶液。

[0753] 在一些实施例中，可通过暴露于高温和 / 或减压使含 ^{18}F 溶液浓缩达到干燥，形成含 ^{18}F 的无水固体。在一些实施例中，含 ^{18}F 固体可进一步包含一或多种试剂（例如盐）。含 ^{18}F 固体的化学组成可视用于制备含 ^{18}F 溶液的试剂的数目和种类而定。例如，可使用碳酸钾溶液自阴离子交换管柱溶离 ^{18}F 物质，从而产生包含 $[^{18}F]KF$ 的含 ^{18}F 固体。在其它实例中，可使用碳酸氢四乙铵溶液自阴离子交换管柱溶离 ^{18}F 物质，从而产生包含 $[^{18}F]Et_4NF$ 的含 ^{18}F 固体。

[0754] 在一些实施例中，加热包含 ^{18}F 物质的溶液到在室温热到约 200℃范围内的温度下。例如，可加热包含 $[^{18}F]$- 氟化物的溶液到高温以促进溶剂蒸发（例如至约 110℃）。在一些实施例中，加热溶液到在约 90-120℃或约 100-150℃范围内的温度下。在一些实施例中，加热溶液到约 75℃、约 85℃、约 95℃、约 105℃、约 115℃、约 125℃或 125℃以上。在一些实施例中，将溶液置于以下减压下：约 100mm Hg、约 125mm Hg、约 150mm Hg、约 175mm Hg、约 200mm Hg、约 225mm Hg、约 250mm Hg、约 275mm Hg、约 300mm Hg、约 325mm Hg、约 350mm Hg、约 375mm Hg、约 400mm Hg 或 400mm Hg 以上。在一些实施例中，将溶液置于以下减压下：约 100 毫巴、约 125 毫巴、约 150 毫巴、约 175 毫巴、约 200 毫巴、约 225 毫巴、约 250 毫巴、约 275 毫巴、约 280 毫巴、约 300 毫巴、约 325 毫巴、约 350 毫巴、约 375 毫巴、约 400 毫巴、约 450 毫巴、约 500 毫巴或 500 毫巴以上。所属领域的技术人员将能够选择和 / 或确定适用于特定方法的条件。在一些实施例中，在约 150mm Hg 和约 115℃下浓缩溶液达到干燥。在一些实施例中，在约 375mm Hg 和约 115℃下浓缩溶液达到干燥。在一些实施例中，在约 400 毫巴和约 110-150℃下浓缩溶液达到干燥。在一些实施例中，在约 280 毫巴及约 95-115℃下浓缩溶液达到干燥。

[0755] 在某些实施例中，氟物质和 / 或试剂如果存在，则随后将其在一定条件下与造影剂前驱体接触，使得造影剂前驱体通过亲核氟化转化成造影剂产物。所属领域的技术人员将能够选择适用于特定反应的条件。例如，在某些实施例中，氟物质与造影剂前驱体的比率可选择为约 1:10,000 或 1:10,000 以上、约 1:5000 或 1:5000 以上、约 1:3000 或 1:3000 以上、约 1:2000 或 1:2000 以上、约 1:1000 或 1:1000 以上、约 1:500 或 1:500 以上、约 1:100 或 1:100 以上、约 1:50 或 1:50 以上、约 1:10 或 1:10 以上、约 1:5 或 1:5 以上，或在一些情况下，约 1:1 或 1:1 以上。在一些实施例中，相对于造影剂前驱体的量，氟物质可以约 10mol%、

或约 5mol％、或约 3mol％、或约 2mol％、或约 1mol％或约 0.5mol％、或约 0.1mol％、或约 0.05mol％、或约 0.01mol％存在。在一些实施例中，氟物质用 ^{18}F 同位素增浓。例如，在一些实施例中，^{18}F 物质与造影剂前驱体的比率可选择为约 1:1,000,000 或 1:1,000,000 以上，或约 1:500,000 或 1:500,000 以上、或约 1:250,000 或 1:250,000 以上、或约 1:100,000 或 1:100,000 以上、或约 1:50,000 或 1:50,000 以上、或约 1:25,000 或 1:25,000 以上、或约 1:10,000 或 1:10,000 以上、约 1:5000 或 1:5000 以上、约 1:3000 或 1:3000 以上、约 1:2000 或 1:2000 以上、约 1:1000 或 1:1000 以上、约 1:500 或 1:500 以上、约 1:100 或 1:100 以上、约 1:50 或 1:50 以上、约 1:10 或 1:10 以上、约 1:5 或 1:5 以上，或在一些情况下，约 1:1 或 1:1 以上。

[0756] 在一些实施例中，亲核氟化反应在一或多种溶剂（例如有机溶剂、非有机溶剂（例如水溶剂）或其组合）存在下进行。在一些实施例中，溶剂为极性溶剂或非极性溶剂。在一些实施例中，溶剂为水溶液，如水。在一些实施例中，溶剂包含至少约 0.001％水、至少约 0.01％水、至少约 0.1％水、至少约 1％水、至少约 5％、至少约 10％、至少约 20％水、至少约 30％水、至少约 40％水、至少约 50％水或 50％以上的水。在一些实施例中，溶剂可包含介于约 0.1％与约 100％之间、约 1％至约 90％、约 1％至约 70％、约 1％至约 50％，或约 10％至约 50％的水。在一些实施例中，溶剂包含不超过约 10％水、约 5％水、约 4％水、约 3％水、约 2％水、约 1％水或约 0.5％水。在一些实施例中，溶剂包含介于约 0.01％与约 5％之间的水，或介于约 0.01％与约 2％之间的水，或介于约 0.1％与约 0.2％之间的水。

[0757] 适用于所述方法的溶剂的其它实例包括（但不限于）非卤化烃溶剂（例如戊烷、己烷、庚烷、环己烷）、卤化烃溶剂（例如二氯甲烷、氯仿、氟苯、三氟甲苯）、芳香族烃溶剂（例如甲苯、苯、二甲苯）、酯溶剂（例如乙酸乙酯）、醚溶剂（例如四氢呋喃、二噁烷、乙醚、二甲氧乙烷）以及醇溶剂（例如乙醇、甲醇、丙醇、异丙醇、叔丁醇）。溶剂的其它非限制性实例包括丙酮、乙酸、甲酸、二甲亚砜、二甲基甲酰胺、乙腈、对甲酚、乙二醇、石油醚、四氯化碳、六甲基－磷酸三酰胺、三乙氨、甲基吡啶以及吡啶。在一些实施例中，所提供的反应在如乙腈的极性溶剂中进行。在一些实施例中，可选择溶剂以便减少副产物的形成和／或使其降到最低程度。在某些实施例中，氟化反应在作为溶剂的 MeCN 中进行。在某些实施例中，氟化反应在作为溶剂的 t-BuOH 中进行。在某些实施例中，氟化反应作为溶剂的 MeCN 与 t-BuOH 的混合物中进行。在某些实施例中，氟化反应在作为溶剂的 DMF 中进行。在某些实施例中，氟化反应在作为溶剂的 DMSO 中进行。在某些实施例中，氟化反应在作为溶剂的 THF 中进行。

[0758] 在某些实施例中，可使任选地包含试剂的含 ^{18}F 的无水固体与造影剂前驱体（例如甲苯磺酸盐前驱体）溶液接触，且加热所得溶液到高温维持所选时段。溶液可为例如乙腈溶液。在其它实施例中，^{18}F 物质与试剂的溶液如果存在，则使其与固体造影剂前驱体或造影剂前驱体的溶液接触。

[0759] 一些实施例涉及造影剂前驱体与氟物质在 pH 值低于约 13、低于约 12 或低于约 11 的溶液中接触。在一些情况下，溶液的 pH 值介于约 8 与约 9 之间、或介于约 8 与约 10 之间、或介于约 7 与约 8 之间。在某些实施例中，氟化反应的 pH 值范围大于约 6、或大于约 7、或介于 7-13 之间且包括 7 和 13、介于 6-12 之间且包括 6 和 12、介于 7-12 之间且包括 7 和 12、介于 8-12 之间且包括 8 和 12、介于 9-12 之间且包括 9 和 12 及介于 10-12 之间且包括

10 和 12。

[0760] 在一些情况下，将包含 ^{18}F 物质、造影剂前驱体和任选的试剂的溶液加热到高温，维持一段时间。例如，可加热溶液到约 50℃、约 60℃、约 70℃、约 80℃、约 90℃、约 100℃、约 110℃、约 120℃、约 150℃、约 170℃、约 200℃、约 225℃、约 250℃或 250℃以上，维持约 5 分钟或 5 分钟以下、约 10 分钟或 10 分钟以下、约 20 分钟或 20 分钟以下、约 30 分钟或 30 分钟以下的时段。应了解，可使用其它温度和反应时间。在一些实施例中，当反应完成时，冷却反应混合物（例如达到室温）且任选地用溶剂（如水）或溶剂混合物（如水 / 乙腈）稀释。在一些实施例中，加热反应混合物到高温以促进溶剂蒸发（例如达到约 95℃）。在一些实施例中，加热溶液到在约 55-125℃范围内的温度下。在一些情况下，加热溶液到约 65℃、约 75℃、约 85℃、约 95℃、约 105℃、约 115℃或 115℃以上。在一些情况下，将溶液置于以下减压下：约 100mm Hg、约 125mm Hg、约 150mm Hg、约 175mm Hg、约 200mm Hg、约 225mm Hg、约 250mm Hg、约 275mm Hg、约 300mm Hg、约 325mm Hg、约 350mm Hg、约 375mm Hg、约 400mm Hg 或 400mm Hg 以上。在一些情况下，将溶液置于以下减压下：约 100 毫巴、约 125 毫巴、约 150 毫巴、约 175 毫巴、约 200 毫巴、约 225 毫巴、约 250 毫巴、约 275 毫巴、约 280 毫巴、约 300 毫巴、约 325 毫巴、约 350 毫巴、约 375 毫巴、约 400 毫巴、约 450 毫巴、约 500 毫巴或 500 毫巴以上。所属领域的技术人员将能够选择和 / 或确定适用于特定方法的条件。在一些实施例中，在惰性气体流下在约 95℃下浓缩溶液达到干燥。

[0761] 在一些实施例中，当氟化反应完成时，使所得造影剂任选地经历一或多个纯化步骤。在一些实施例中，在纯化（例如通过色谱，如 HPLC）之前，可在溶剂中复原造影剂。在一些情况下，将造影剂溶解于水、乙腈或其组合中。在一些实施例中，在包含造影剂和溶剂的溶液形成之后且在纯化（例如通过 HPLC）之前，加热溶液。在特定实施例中，在水 / 乙腈混合物中复原造影剂且加热（例如达到约 90-100℃的温度）维持约 1 分钟、约 3 分钟、约 5 分钟、约 10 分钟、约 20 分钟、约 30 分钟或 30 分钟以上。在加热混合物之后，可在纯化之前任选地冷却溶液。

[0762] C. 纯化和调配

[0763] 在一些情况下，造影剂的合成、纯化和 / 或调配使用任选地包含卡匣的自动化反应系统进行，其中所述卡匣包含合成模块、纯化模块和 / 或调配模块。本文描述自动化反应系统及卡匣。

[0764] 纯化和分离可使用所属领域的技术人员已知的方法进行，包括分离技术，如色谱，或本领域中已知的各种分离技术（例如萃取、蒸馏以及结晶）的组合。在一个实施例中，以溶剂或溶剂混合物作为溶离剂来使用高效液相色谱 (HPLC) 以回收产物。在一些情况下，溶离剂包括水与乙腈的混合物，如 20:80 水：乙腈混合物。溶离剂中的水含量可自例如约 1％至约 30％变化。在一些情况下，HPLC 纯化可使用 C-18 管柱进行。可分析（例如通过 HPLC）产物以测定产率（例如放射化学产率）和 / 或放射化学纯度。放射化学纯度可大于约 50％、约 60％、约 70％、约 80％、约 90％、约 95％、约 97％、约 98％、约 99％或 99％以上。产物的产率百分比可大于 10％、大于 20％、大于 30％、大于 40％、大于 50％、大于约 60％、大于约 70％、大于约 75％、大于约 80％、大于约 85％、大于约 90％、大于约 92％、大于约 95％、大于约 96％、大于约 97％、大于约 98％、大于约 99％或 99％以上。在一些实施例中，放射化学产率在 15-50％的范围内。

[0765] 产物可使用如过滤的其它纯化技术进一步加工。在一些情况下，使用 HPLC 纯化造影剂，产生 HPLC 移动相与造影剂的溶液。可随后通过 C-18 树脂（例如 C18 Sep-Pak® 滤筒）过滤将 HPLC 移动相交换为抗坏血酸或其盐的溶液和乙醇溶液。在一些实施例中，通过 C-18 树脂过滤 HPLC 移动相与造影剂的溶液，其中造影剂保留于树脂上且其它组分（如乙腈和 / 或其它溶剂或组分）通过溶离移除。C-18 树脂可用抗坏血酸或其盐的溶液进一步洗涤，且丢弃滤液。为回收纯化的造影剂，用如乙醇的溶剂洗涤 C-18 树脂，且用如本文所述的抗坏血酸溶液或其盐任选地进一步稀释所得溶液。

[0766] 任选地将回收产物与一或多种如抗坏血酸或其盐的稳定剂合并。例如，可用抗坏血酸或其盐的溶液进一步稀释包含纯化造影剂的溶液。如本文所述，可通过包含卡匣的自动化反应系统制备配方。

[0767] 在一些情况下，包含造影剂产物的溶液可经无菌过滤（例如使用 13mm 直径的 Millipore, Millex PVDF 0.22μm 灭菌过滤器）至无菌产物小瓶中。无菌产物小瓶可为市售预灭菌单元，因为任何造影剂（或其它组分）均可在使用之前通过隔膜来无菌插入，所以其在生产过程期间不打开。所属领域的技术人员将能够选择适合小瓶和生产组件，包括市售预灭菌单元，其包含 0.22μm 孔径膜排气过滤器和品质控制取样注射器。

[0768] 在无菌过滤之后，可以个别剂量填充注射器，加以标记，并且装运到临床地点。本文描述给药投予技术、用于合成造影剂的试剂盒、卡匣、方法和系统（例如自动化反应系统）以及测试程序。在一些实施例中，将产物分配到 3 或 5mL 注射器中且经标记以便分配。标签可以放射药剂学制备且施加于注射器护罩 (syringe shield) 和装运容器中。可在装运容器中提供其它标签以便包括于临床地点记录中。

[0769] 造影剂用途

[0770] 在另一方面中，提供使用本文所述的造影剂造影的方法。对个体进行造影的所述方法包括通过注射、输注或任何其它已知的投药方法向个体投予包括如本文所述的造影剂的组合物或配方，且对所述个体的相关区域进行造影。相关区域可包括（但不限于）心脏、心脏的一部分、心血管系统、心血管、血管（例如动脉和 / 或静脉）、脑、胰腺、肾上腺、其它器官以及肿瘤。

[0771] 在一些实施例中，造影方法包含 (a) 向个体投予包括包含至少一个造影部分（例如造影剂）的如本文所述的化合物的组合物，及 (b) 获得所述个体至少一部分的至少一个图像。在一些情况下，撷取步骤采用正电子发射断层摄影法 (PET) 以便观测个体的至少一部分内的造影剂分布。如所属领域的技术人员应了解，使用本揭示案方法的造影可包括个体的完整身体造影，或相关个体的特定身体区域、器官或组织的造影。例如，如果个体已知患有或怀疑患有心肌缺血，则本揭示案方法可用于对个体的心脏进行造影。在一些实施例中，造影可限于心脏或可包括心脏和其相关血管结构。

[0772] 在本发明的一些实施例中，提供诊断或帮助诊断已知患有或怀疑患有心血管疾病或病状的个体的疾病或病状，分析疾病或病状的治疗功效或造影的方法。心血管疾病可为由血管系统滋养的心脏或其它器官或组织的任何疾病。血管系统包括冠状动脉以及向周边血管系统和脑供应营养的所有周边动脉以及静脉、小动脉、小静脉和毛细管。心血管疾病的实例包括心脏疾病，如冠状动脉疾病、心肌梗塞、心肌缺血、心绞痛、充血性心脏衰竭、心肌症（先天性或后天性）、心律不整或心脏瓣膜病。在一些实施例中，本文中所揭示的方法

适用于监控及测量冠状动脉疾病和 / 或心肌灌注。例如，本文所述的方法可确定冠状动脉疾病的存在或不存在和 / 或心肌梗塞的存在或不存在。心脏病状可包括并非由疾病引起而是由损伤（例如创伤性损伤、手术性损伤）导致的伤害。在一些情况下，本发明方法可包括测定以下每个项的参数或存在或不存在：心肌缺血、休息 (R) 和 / 或压力 (S) 心肌血流量 (MBF)、冠状动脉血流储备 (CFR)、冠状动脉疾病 (CAD)、左心室射血分数 (LVEF)、收缩末期容积 (ESV)、心舒末期容积 (EDV) 等。

[0773] 不希望受任何特定理论限制，本文所述的造影剂据认为用高亲和力结合电子传递链的粒线体复合物 I。在一些实施例中，由于粒线体在心肌中的高密度，故造影剂显示选择性吸收到心脏。相关区域可包括（但不限于）心脏、心血管系统、心血管、血管（例如动脉、静脉）、脑以及其它器官。可使用本发明的方法和 / 或系统对如血流量、心壁运动等的相关参数进行造影和检测。在本发明的一些方面中，提供用于评估灌注（包括心肌灌注）的方法。

[0774] 在一些实施例中，对个体的一部分进行造影的方法包含向个体投予如本文所述的化合物（例如造影剂）且撷取所述个体的一部分的至少一个图像。在一些实施例中，对个体的一部分进行造影的方法包含向个体投予如本文所述的化合物（例如造影剂）；检测由所述化合物所放出的辐射；和自其形成图像。在一些实施例中，向所述个体投予有效量的化合物。

[0775] 在一些情况下，施加本发明方法的个体可具有暗示心肌缺血或心肌梗塞的迹象或症状。在一些情况下，本发明方法可用于鉴别表明个体处于升高的疾病风险的早期或疾病前期 (pre-disease) 病状。在一些情况下，本发明方法可用于测定个体的未来心脏事件（如心肌梗塞或心源性死亡）的风险。本发明的造影方法可用于检测已诊断为患有心肌缺血病症或病状的个体或无这类病状的病史或诊断的个体中的心肌缺血。在其它情况中，本发明方法可用于获得提供心肌缺血病症或病状的诊断或有助于提供所述诊断的测量结果。在一些情况下，个体可已经历用于与心肌缺血相关的病症或病状的药物疗法，而在其它情况中，个体可不经历用于心肌缺血的疗法。在一些实施例中，本发明方法可用于分析疾病或病状的治疗功效。例如，可使用本发明的造影剂在影响个体心脏的病状的治疗之前、期间和 / 或之后观测心脏。所述观测可用于分析个体的疾病或病状且有助于选择治疗方案，例如疗法、外科手术或药物。

[0776] PET 造影剂可具有高初次通过萃取分数且可追踪较宽范围内的区域心肌血流量。这些特征可允许检测冠状动脉血流储备的较轻微的降低且精确评估绝对心肌血流量 (MBF)。本发明的 PET 造影剂提供这些和其它特征且也可用作区域 PET 放射药剂学的单位剂量，避免现场回旋加速器或高价 Rb-82 产生剂的需要。

[0777] 在本发明的一些实施例中，与正电子发射断层摄影法 (PET) 或与其它造影方法（包括（但不限于）SPECT 造影）组合使用如本文所述的化合物（例如包含至少一个造影部分）作为造影剂。在本发明的一些实施例中，向个体投予包含至少一个造影部分的如本文所述的化合物且使用 PET 在所述个体中造影。如所属领域的技术人员已知，PET 为非侵袭性技术，其允许历经一定时段获得单一个体的连续图像和测量值。本发明方法中所用的 PET 造影可使用已知系统、方法和 / 或器件进行。在本发明的一些实施例中，使用心脏造影系统进行 PET 造影。心脏造影系统可包括 PET 造影官能团和控制单元，所述控制单元经配置以

在向个体投予造影剂之前、期间和/或之后驱动造影官能团而对个体的一部分进行 PET 造影程序。在一些情况下，控制单元经配置以驱动造影官能团，从而进行 PET 造影程序。控制单元可包含电脑系统和/或软件。在这种情况下，电脑系统可经程式化或配置以执行撷取和/或分析图像的所需方法。此外，系统可包括可由机器读取的资料储存器件，其包含可由机器执行的指令集以进行撷取和/或分析图像的所需方法。

[0778] 造影剂的适用投予剂量和特定投药模式将视如以下的因素而变：年龄、体重和待造影的特定区域，以及所用特定造影剂、所涵盖的诊断用途，以及配方形式，例如悬浮液、乳液、微球体、脂质体或其如本文所述的类似因素，且对于所属领域的技术人员将显而易知。

[0779] 在一些实施例中，以低剂量投予造影剂且增加剂量直到达成合意的诊断效果。在一个实施例中，上述造影剂可通过静脉内注射，通常以生理食盐水溶液形式按以下剂量投予：约 0.1 至约 100mCi（及在其中的剂量范围和特定剂量的所有组合和再组合）、或介于约 0.5 与约 50mCi 之间、或介于约 0.1mCi 与约 30mCi 之间、或介于 0.5mCi 与约 20mCi 之间。在一些实施例中，剂量范围为每 70kg 体重。关于作为核医学造影剂的用途，通过静脉注射投予的造影剂剂量可在约 0.1pmol/kg 至约 1000pmol/kg 的范围内（以及在其中的剂量范围和特定剂量的所有组合和再组合），且在一些实施例中，小于 150pmol/kg。

[0780] 造影系统和其组件对所属领域的技术人员将为已知的。许多造影系统及组件（例如用于分析图像的摄影机、软件等）为已知的且可商购，例如 Siemens Biograph-64 扫描器。减少或消除静态灌注图像中的运动的任何技术、软件或设备可用于本发明方法中，因为在图像撷取期间可由患者运动造成空间模糊和假影。在本发明的一些实施例中，图像可以清单模式撷取且可为静态、动态或闸控图像。撷取图像的适当时段可由所属领域的技术人员确定，且可视心脏造影系统、造影剂（例如投予量、造影剂组成、个体参数、相关区域）而变。如本文中所用，“撷取图像的时段”或“图像撷取时段”可为获得单一连续图像的时段，或可为获得一或多个个别离散图像的时段。因此，图像撷取时段可为撷取个体的一或多个区域的一或多个图像的时段。

[0781] 在本发明的一些实施例中，在向个体投予本发明造影剂之后的图像撷取时段可介于约 30 秒与约 60 分钟之间、介于约 1 分钟与约 30 分钟之间、介于约 5 分钟与约 20 分钟之间、或至少约 1 分钟、约 3 分钟、约 5 分钟、约 6 分钟、约 7 分钟、约 8 分钟、约 9 分钟、约 10 分钟、约 15 分钟、约 20 分钟、约 30 分钟、4 约 5 分钟、约 60 分钟或 60 分钟以上。例如，在休息/压力造影方案中，应存在至少两个图像撷取时段，其中至少一个对应于休息片段且至少一个对应于压力片段。在一些实施例中，造影可在造影时段期间连续进行，或图像可以一定间隔撷取，如在周期性或闸控造影中。

[0782] 在本发明的一些方面中，闸控撷取用于从已投予造影剂的个体撷取图像。闸控造影可用于本发明的每个方面中，且例如，可提供个体的心脏搏动的图像且可用于实现心跳如何的功能性评估。闸控造影可通过在图像撷取时段内以特定间隔自个体撷取分离图像而进行。闸控造影的非限制性实例为当图像撷取时段为约 10 分钟长且在 10 分钟时段内以重复间隔撷取图像时的情况。在所述时段内的图像撷取频率可由操作者设定，例如频率可为至少每约 1msec、约 5msec、约 10msec、约 20msec、约 50msec、约 100msec、约 125msec、约 250msec 或 250msec 以上。间隔长度由经事件（如心脏的 R 波）触发的操作者设定，其中间隔长度由每 R 波至 R 波间隔所需的时间点数定义。所属领域的技术人员应熟悉闸控图像撷

取的概念和方法且可使用已知方法使用造影剂来获得闸控图像。

[0783] 闸控图像中的图像撷取可以特定间隔触发，例如，图像撷取可使用心脏的 EKG 触发。在非限制性实例中，R 波闸控扫描器可触发图像的撷取且可储存在心脏的一个 R 波与下一个之间的平均时长。随后可确定待收集的图像数目。例如，第一图像可在 125msec 时撷取，第二图像可在 250msec 时撷取，第三图像可在 375msec 时撷取等，因此在所述 R 间隔中的图像可以 125msec 间隔撷取。当下一个 R 间隔开始时，重设图像的收集且随后在距所述 R 间隔开始时间 125msec 时撷取影响资料为“第一”图像，且随后为在距所述 R 间隔开始时间 250msec 时收集的“第二”图像等。因此，在每个 R 间隔内，将图像撷取添加为系列的初始图像且累加成系列中的连续图像，以便在每个 R 间隔开始时重设零时的情况下，可以所需频率收集一连串图像。撷取的闸控图像可用于提供心脏运动的图像且可提供关于心壁厚度的信息，无论心脏的一或多个区是否无移动或搏动（例如壁运动缺陷）。使用闸控造影可提供用于判定心脏灌注（如射血分数）和观测且鉴别壁运动减少、缺少、反常或非同步的资料。使用闸控造影亦可提供用于改善心肌灌注的评估、判定心脏功能以及观测且鉴别非同步壁运动的资料。

[0784] 在一些情况下，PET 造影可用于分析心肌生存力，通过此技术的能力说明心肌缺血的代谢结果。使用 PET 造影，可鉴别可能在血管再造之后改善的心肌片段。在一些情况下，PET 造影可用于检测冠状动脉疾病且亦可充当不能经受踏车运动压力试验的个体的替代试验。在一些实施例中，可用 PET 使用本发明方法采用压力试验方法（例如药物压力、运动压力）以定性或定量分析造影剂输注期间心脏功能的一或多个参数。例如使用运动或药物压力来诱导压力的试剂和方法在本领域中为众所周知的。适合的压力诱导可使用已建立的已知试剂和方法进行。适用于使用本发明方法测量的功能在每个实施例中包括（但不限于）心肌灌注的造影、造影或测量心室功能以及测量冠状动脉血流速度。

[0785] 在一些情况下，个体心脏的造影方法可包括在个体休息时向所述个体投予第一剂量的造影剂，撷取心脏的至少一个第一图像，继的以使个体经受压力（例如运动压力或药物压力）且在压力期间向个体投予第二剂量的造影剂，且撷取心脏的至少一个其它图像。

[0786] 在一些实施例中，在休息 / 压力方案中在运动诱导压力期间所用的造影剂剂量大于药物诱导压力所需的剂量，其中运动诱导的压力剂量与药物诱导的压力剂量的比率大于或等于约 1.2、约 1.3、约 1.4、约 1.5、约 1.6、约 1.7、约 1.8、约 1.9 或 1.9 以上。关于药物压力，在涉及休息 / 压力造影方法的本发明的一些实施例中，在药物压力期间用于造影所投予的造影剂的剂量为用于休息时造影所投予的造影剂的剂量的最少两倍。关于运动压力，在涉及休息 / 压力造影方法的本发明的一些实施例中，在运动诱导的压力期间用于造影所投予的造影剂的剂量为用于休息时造影所投予的造影剂的剂量的最少三倍。在本发明的一些实施例中，关于首先休息造影继之以压力造影，在休息时所投予的造影剂的剂量将低于在压力时所投予的造影剂的剂量。在一些情况下，如本文所述，本发明的造影方法可在单日（例如不到约 24 小时、不到约 12 小时、不到约 6 小时、不到约 4 小时、不到约 2 小时、不到约 1 小时）内完成。在其它情况下，方法可在较长时段内完成，例如在超过约 24 小时、约 36 小时或约 48 小时内。

[0787] 关于方法中的压力试验，可使用所属领域的技术人员已知的程序使个体经受压力。在一些情况下，可使用包括运动压力和 / 或药物压力的程序使个体经受压力。药物压

力可通过向个体投予如血管舒张剂的药剂来诱导。适用药物压力试剂的实例包括（但不限于）腺苷、多巴酚丁氨(dobutamine)、双嘧达莫(dipyridamole)、瑞加德松(regadenoson)、必诺德松(binodeneson)、阿帕德松(apadeneson)以及其它腺苷A2a受体促效剂。如血管舒张剂的药物压力诱导试剂的给药和投药在本领域中为众所周知的且可测定以与本发明的方法和系统联合使用。运动压力可使用踏车、运动型脚踏车、手摇曲柄或适于通过加紧努力提高个体的心跳速率的其它设备来诱导。

[0788] 可以任何适合形式提供造影剂，例如以医药学上可接受的形式。在一些情况下，造影剂包括在医药学上可接受的组合物中。在一些实施例中，以包含乙醇、抗坏血酸钠和水的组合物形式提供造影剂。在一些情况下，组合物包含小于20重量％乙醇、小于15重量％乙醇、小于10重量％乙醇、小于8重量％乙醇、小于6重量％乙醇、小于5重量％乙醇、小于4重量％乙醇、小于3重量％乙醇或小于3重量％以下的乙醇。在一些情况下，组合物包含小于100mg/mL、小于75mg/mL、小于60mg/mL、小于50mg/mL、小于40mg/mL、小于30mg/mL或小于30mg/mL以下的抗坏血酸钠水溶液。在一些实施例中，组合物包含约20mg/mL、约30mg/mL、约40mg/mL、约50mg/mL、约60mg/mL、约70mg/mL、约80mg/mL、约90mg/mL、约100mg/mL、约110mg/mL、约120mg/mL、约130mg/mL、约140mg/mL、约150mg/mL、约160mg/mL、约170mg/mL、约180mg/mL、约190mg/mL或约200mg/mL。在特定非限制性实施例中，以包含小于4％乙醇和小于约50mg/mL抗坏血酸钠于水中的水溶液形式提供造影剂。

[0789] 在一些实施例中，组合物的pH值介于约1.5与约8之间、或介于约1.5与约7之间、或介于约1.5与6之间、或介于约1.5与5之间、或介于1.5与4之间、或介于2与7之间、或介于3与7之间、或介于4与7之间、或介于5与7之间、或介于5与6之间、或介于5.5与6之间。在一些实施例中，pH值为约5.8。在一些实施例中，组合物的pH值为约1.5、约1.6、约1.7、约1.8、约1.9、约2.0、约2.1、约2.2、约2.3、约2.4、约2.5、约2.6、约2.7、约2.8、约2.9、约3.0、约3.1、约3.2、约3.3、约3.4或约3.5。在一些实施例中，组合物的pH值介于约1.5与约1.6之间。在一些实施例中，组合物的pH值介于约1.5与约1.9之间。在一些实施例中，组合物的pH值介于约2.1与约3.5之间。在一些实施例中，组合物的pH值介于约2.4与约3.5之间。在一些实施例中，组合物的pH值介于约2.5与约3.5之间。在一些实施例中，组合物的pH值介于约2.1与约2.3之间。

[0790] 可以用于注射的组合物形式提供造影剂，其可在注射器中制备。例如，造影剂可通过放射药剂学（例如使用本文所述的方法）和/或PET制造中心制备且提供给健康照护专业人员用于投药。在本发明的一些方面中，例如在注射器或其它容器中提供造影剂，其具有≤50mg/mL抗坏血酸钠水溶液、≤4重量％乙醇及约1mCi至14mCi的造影剂。

[0791] 在一些实施例中，如果需要获得实际剂量体积，则造影剂的剂量可用生理食盐水（例如如本文所述）稀释。例如，如果造影剂的活性浓度太高以致个体的适当剂量仅需0.1mL，则可用例如无菌生理食盐水稀释溶液，故注射器含有0.5ml至4ml或4ml以上造影剂溶液用于投药。在本发明的一些实施例中，造影剂的注射体积介于0.5mL与5mL、1mL与4mL、2mL与3mL之间、至少0.5mL、1mL、2mL、3mL、4mL、5mL、6mL、7mL、8mL、9mL、10mL或10mL以上。所属领域的技术人员应了解如何稀释造影剂以产生足够剂量的投药体积。在一些实施例中，造影剂提供于如小瓶、瓶或注射器的容器中，且可视需要转移到如投药用注射器的适合容器中。

[0792] 包括吸附性柱塞尖端的注射器可导致在注射之后 10％至 25％的造影剂活性保留在注射器中。可使用缺少吸附性柱塞尖端的注射器，如 3mL 或 5mL NORM-JECT（马萨诸塞州达德利的汉克舍斯沃尔夫公司 (Henke Sass Wolf,Dudley,MA)）或缺少吸附性柱塞尖端的其它等效注射器。在本发明的方法中，降低注射器中的吸附可增加自注射器转移且投予至个体的造影剂的量。本发明方法中所用的注射器可包含造影剂且为非吸附性或吸附性降低的注射器。在一些实施例中，非吸附性或吸附性降低的注射器为已经涂布或处理以降低造影剂的吸附的注射器。在一些实施例中，非吸附性或吸附性降低的注射器为缺少吸附性柱塞尖端的注射器。在一些实施例中，与本发明联合使用的注射器吸附其所含有的造影剂的小于 20％、19％、18％、17％、16％、15％、14％、13％、12％、11％、10％、9％、8％、7％、6％、5％、4％、3％、2％、1％或 0.5％。在本发明的某些方面中，含有造影剂的注射器在柱塞上不包括橡胶或乳胶尖端。在一些情况下，本发明方法中所用的注射器包括柱塞，其吸附注射器所含造影剂的小于 20％、19％、18％、17％、16％、15％、14％、13％、12％、11％、10％、9％、8％、7％、6％、5％、4％、3％、2％、1％或 0.5％。本发明的注射器亦可包含抗坏血酸钠、乙醇和水，且本发明的某些实施例包括含有造影剂溶液的注射器，所述溶液包含小于 4 重量％乙醇和小于约 50mg/mL 抗坏血酸钠水溶液。本发明的注射器可为无乳胶、无橡胶和 / 或无润滑剂的注射器。本发明的注射器可以介于约 1.5mCi 与约 14mCi 之间的量含有造影剂。本发明的注射器可含有约 20mCi 或 20mCi 以下的造影剂。

[0793] 可视向个体投药的模式而定选择包含造影剂的组合物的组分。将本发明的造影剂有效地传递到所需组织、细胞、器官或体液的各种投药模式将为所属领域的技术人员所已知。在一些实施例中，使用所属领域的技术人员已知的方法静脉内投予（例如静脉内快速注射）造影剂。如本文中所用，“向个体投予”的剂量意指进入个体身体的造影剂的量。在一些实施例中，由于如造影剂在注射器、管、针、导管或用于向个体投予造影剂的其它设备中的部分滞留的因素，所测量或测定的用于准备投药用的注射器或其它设备中的造影剂的量可大于向个体投予的剂量中的量。在一些实施例中，使用用于投予造影剂的相同管、针、孔等相继注射造影剂、冲刷注射生理食盐水到个体中。冲刷可在投予造影剂之后立即进行，或在投药之后至多 1 分钟、2 分钟、3 分钟、5 分钟或 5 分钟以上。用于冲刷的生理食盐水或其它试剂的体积可为至多 5mL、6mL、7mL、8mL、9mL、10mL、15mL、20mL 或 20mL 以上。如所属领域的技术人员将了解，在使用注射器或其它容器投予造影剂的实施例中，可对向个体投予的造影剂的真实量关于保留在容器中的任何造影剂进行校正。例如，保留于容器，以及自容器输送造影剂和输入个体的管和针或传递仪器中的放射性的量可在已向个体投予造影剂之后测定，且放射性的起始量与投药后保留量之间的差表示传递至个体中的量。在一些情况下，容器或注射器件（例如导管、注射器）可在投予造影剂之后用溶液（例如生理食盐水溶液）冲洗。

[0794] 在本发明的一些实施例中，在给定时段内（例如在一个时段内）向个体投予的造影剂的总量为小于或等于小于或等于约 50mCi、小于或等于 40mCi、小于或等于 30mCi、小于或等于 20mCi、小于或等于 18mCi、小于或等于 16mCi、小于或等于 15mCi、小于或等于 14mCi、小于或等于 13mCi、小于或等于 12mCi、小于或等于 10mCi、小于或等于 8mCi、小于或等于 6mCi、小于或等于 4mCi、小于或等于 2mCi、小于或等于 1mCi、小于或等于 0.5mCi。可基于向个体投予的单次剂量或多次剂测量定在给定时段内所投予的总量，所述给定时段为至多 1

分钟、10 分钟、30 分钟、1 小时、2 小时、6 小时、12 小时、24 小时、48 小时或 48 小时以上。

[0795] 如所属领域的技术人员所了解，基于辐射剂量研究，可基于限制关健器官的辐射剂量到约 5 雷姆 (rem) 和 / 或约 1 雷姆有效剂量 (ED) 或 1 雷姆以下的造影剂的量来测定向个体投予的合意的最大剂量。在一些实施例中，在至多 30 分钟、1 小时、2 小时、6 小时、12 小时、24 小时、48 小时或 48 小时以上的时段内所投予的造影剂的合意的最大剂量或总量为小于或等于约 25mCi 或小于或等于约 14mCi。在一些实施例中，向个体投予的造影剂的最大剂量可为每 50kg 体重每天小于 3.5μg。即，在本发明的一些实施例中，向个体投予的造影剂的最大剂量可为每公斤体重每天小于约 0.07μg 造影剂。

[0796] 例示性卡匣和反应系统

[0797] 在一些实施例中，提供用于合成如本文所述的造影剂的系统、方法、试剂盒以及卡匣。在一些实施例中，可使用包含抛弃式或单次使用式卡匣的自动化反应系统制备造影剂。所述卡匣可包含所有非放射性试剂、溶剂、管、阀、反应容器，以及制备给定造影剂批料所需的其它装置和 / 或组件。通过简单改变所述卡匣，所述卡匣使得反应系统具有制造多种不同造影剂的灵活性与最小的交叉污染风险。术语“卡匣”意指一件装置，其经设计可以自动化反应系统的可动部分的机械运动自卡匣外（即外部）控制卡匣操作的方式可卸除且可互换地装配于自动化反应系统上。在某些实施例中，卡匣包含线性阀排列，其各自连接到可通过针刺膈膜密封小瓶或者通过气密性对插接头 (marrying joint) 连接各种试剂、滤筒、注射器和 / 或小瓶的孔。每个阀可具有凸 - 凹接头 (male-female joint)，其与自动化合成器的相应移动臂连接。当卡匣连接到自动化反应系统时，臂的外旋转可控制阀打开或关闭。自动化反应系统的其它可动部分经设计可夹于注射器柱塞尖端上，且从而提高或压低注射器筒。自动化反应系统可进一步包括控制器和一或多个与控制器电通信的可控阀。自动化反应系统也可包括其它容器、阀、感测器、加热器、加压元件等与控制器电通信。自动化反应系统可由使用适用于控制阀打开和关闭、加热、冷却、压力位准、流体运动、流速等的软件的控制器操作。自动化反应系统可任选地包括电脑操作系统、软件、控制器等，或其它组件。另外，自动化反应系统可包含卡匣座架。在一些实施例中，本发明的卡匣包含一或多个用于引入一或多种试剂的注射器。另外，在一些实施例中，改善与卡匣和自动化反应系统组合使用的方法。如本文所述，使用卡匣和 / 或改善的方法可改善液体处理效率，提高造影剂回收率（例如通过减少造影剂在卡匣中的滞留）。

[0798] 自动化反应系统（例如亲核反应系统）的实例包括（但不限于）Explora GN 或 RN 合成系统（美国西门子公司 (Siemens Medical Solutions USA, Inc.)）、Tracerlab-MX 合成系统（通用公司 (GE Healthcare)）、Eckert&Zeigler Modular-Lab 合成系统、NEPTIS® 合成系统等，所述反应系统为 PET 制造设施中普遍可得。

[0799] 自动化反应系统可进行如图 16 中所概述的多个步骤，其包括（但不限于）制备 ^{18}F 氟物质、任选地以溶液形式提供造影剂前驱体（例如造影剂前驱体于乙腈中）、任选地在合成模块中的放射性标记反应（例如 ^{18}F 物质与造影剂前驱体反应以形成造影剂）、纯化（例如通过制备型 HPLC）、溶剂交换（例如通过 Sep-Pak）、无菌过滤和释放到容器中。例如，参见实例 68。

[0800] 在一些实施例中，自动化反应系统可利用包含反应模块与纯化模块和 / 或调配模块流体连接的卡匣。图 17 显示根据一些实施例的与用于合成造影剂的例示性反应系统相

连的卡匣的示意图，其包含反应模块、纯化模块和 / 或调配模块。

[0801] 在一些实施例中，反应模块可包括反应室，在其中进行造影剂前驱体到造影剂的转化。反应模块可包括氟物质源（例如 ^{18}F）、造影剂前驱体源、添加剂源（例如盐添加剂）以及其它组分（如溶剂）的其它来源，所述来源中的每一者可任选地流体连接到反应室。在一些实施例中，通过与先前报导的小瓶或储集器相对的注射器提供一或多种试剂。反应模块也可包含阴离子交换管柱以便在将氟物质纯化后引入反应室中。

[0802] 反应时，将所得造影剂产物自反应模块转移到纯化模块以便进一步加工、处理和 / 或纯化。纯化模块可包括例如与一或多种用作溶离剂的溶剂源流体连接的管柱（例如 HPLC 管柱）。纯化模块可进一步包含稳定剂源（例如抗坏血酸或其盐），在纯化（例如通过 HPLC）时可将其添加到造影剂中。随后将纯化造影剂转移到调配模块中，其中可进行进一步纯化和调配。调配模块可包括用于无菌过滤的过滤器和 / 或用于溶剂交换的 C-18 管柱。

[0803] 在一些实施例中，卡匣包含反应模块和调配模块。本发明的反应模块可包括 ^{18}F 源、移除未反应的 $[^{18}O]H_2O$ 的过滤器、铵盐源、^{18}F 的稀释剂源、造影剂前驱体源、造影剂前驱体的 H_2O 稀释剂源、^{18}F 与造影剂前驱体反应的反应容器、与反应容器流体连通的固相萃取管柱（例如 C-18 管柱或其它适合管柱）。固相萃取管柱包括将放射性标记的造影剂产物吸附到吸附剂上的固体吸附剂。至少一部分残留反应杂质通过固相萃取管柱而未吸附在吸附剂上。反应模块还包括与固相萃取管柱流体连通的洗涤溶液源以便提供溶离吸附剂上剩余杂质的洗涤溶液；且包括与固相萃取管柱流体连通的溶离剂源（例如 H_2O/MeCN 或其它适合溶离剂）以便将放射性标记的造影剂产物溶离出吸附剂。反应模块还可包括经溶离的放射性标记造影剂的稀释剂源。

[0804] 本发明的装置的调配模块可与反应模块流体连通且可包括固相萃取滤筒，其包括固体吸附剂（例如 C-18 或其它适合吸附剂）以吸附稀释的放射性标记造影剂、与固相萃取滤筒流体连通的洗涤溶液源（例如包含抗坏血酸、其盐或其它适合洗涤溶液）以便提供洗涤溶液以洗掉吸附剂上的任何剩余杂质，以及与固相萃取滤筒流体连通的溶离流体源（例如乙醇或其它适合溶离流体）以便将放射性标记的造影剂产物溶离出吸附剂。在一些实施例中，如本文所述，在注射器中提供洗涤溶液，其可提供某些优点。调配模块也可包括稀释剂源（例如包含抗坏血酸、其盐或其它适合稀释剂）以便稀释经溶离的放射性标记造影剂。调配模块也可与灭菌过滤器（例如 Sartorius Minisart RC15 灭菌过滤器或其它适合灭菌过滤器）流体连通。

[0805] 在特定实施例中，提供卡匣用于自动化合成模块，例如 GE TracerLab MX 合成模块。在一个实施例中，卡匣包含经特定设计用于自动化合成模块（例如 GE TracerLab MX 合成模块）的模制旋塞阀歧管的抛弃式灭菌组合件。个别歧管以线性或非线性方式连接，形成规定造影剂制备中所用的试剂流动路径的定向阵列。在一些实施例中，卡匣主体含有至少一个包含多个歧管位置（例如旋塞阀）的歧管。例如，主体可包含至少一、二、三、四根或四根以上歧管。卡匣可包含介于 1 个与 20 个之间的歧管位置、介于 1 个与 15 个之间的歧管位置、介于 5 个与 20 个之间的歧管位置、介于 5 个与 15 个之间的歧管位置。每个歧管可能或可能不对称。在一个实施例中，卡匣主体含有三根塑料歧管，其各自配备五个标准模制旋塞阀，从而具有总共 15 个总歧管位置。以鲁尔配件改适个别旋塞阀以容纳溶剂、试剂、注射器、气体以及液体处理所需的管等。旋塞阀适用于溶剂和试剂且可配备塑料针，其

上定位倒置冲压小瓶 (punch vial)，而这些特征化管 (featuring tubing) 和注射器根据功能配备凸鲁尔连接。在一些实施例中，卡匣包含与选自由以下各项组成的群组的组件中的一或多者连接的多个旋塞阀歧管的线性排列：气体入口、阴离子交换滤筒、C-18 滤筒、注射器、溶剂储集器、反应容器、HPLC 系统、收集容器、抗坏血酸或其盐的溶液的储集器以及排气出口。在一些实施例中，抗坏血酸或其盐的溶液的储集器包含注射器。在一些情况下，卡匣进一步包含管。在一些情况下，卡匣进一步包含造影剂合成模块，其中装置与卡匣流体连接。在一些情况下，装置能够执行如本文所述的造影剂的合成方法。

[0806] 在一些实施例中，用于制备造影剂所提供的卡匣配置描绘在图 17 中。在一些实施例中，卡匣配置包含多个按以下顺序排列的旋塞阀歧管的线性排列：

[0807] 1) 与气体入口和 $[^{18}O]H_2O$ 回收连接的鲁尔接头 2；

[0808] 2) 阴离子交换滤筒 - 管柱溶离溶液（任选地选用 1mL 冲压小瓶）；

[0809] 3) 乙腈的针接头（任选地选用 10mL 冲压小瓶）；

[0810] 4) 空注射器（任选地选用 30mL）；

[0811] 5) 具有造影剂前驱体溶液的储集器（任选地选用 10mL 冲压小瓶）；

[0812] 6) 反应容器；

[0813] 7) 通向 HPLC 的出口；

[0814] 8) 具有抗坏血酸或其盐的溶液（例如 pH 为 2) 的注射器（任选地选用 20mL）；

[0815] 9) 来自 HPLC 的入口；

[0816] 10) 乙醇储集器（任选地选用 3mL 注射器）；

[0817] 11) 具有抗坏血酸或其盐的溶液（例如 pH 为 5.8) 的注射器（任选地选用 10mL）；

[0818] 12) 具有水的注射器（任选地选用 5mL）；

[0819] 13) 最终产物小瓶；

[0820] 14) 空注射器（任选地选用 30mL）；和

[0821] 15) 反应容器和排气口。

[0822] 在一些实施例中，可改变以上所揭示的线性排列以便在位置 3 处的试剂与在位置 5 处的试剂转换和 / 或在位置 11 处的试剂与在位置 13 处的试剂转换。

[0823] 本文所述的卡匣及相应方法相比于上述卡匣和方法提供出乎意外的结果。在一些情况下，使用注射器作为试剂（例如抗坏血酸或其盐）的储集器在造影剂制造期间总体上降低生产成本且改善液体处理效率。另外，卡匣组件置放配置的变化还在造影剂制造期间改善液体处理效率以及提高药品回收率。此可能是由于减少了暴露于塑料歧管，这可使得在传递过程期间造影剂的吸附减少。在一些情况下，卡匣变化包含重新定位试剂（例如至位置 11) 和最终产物小瓶（例如到位置 13) 中的一者。在一些实施例中，提供经改善的卡匣使用方法。在一些实施例中，采用电脑控制卡匣以执行由个别示踪剂所规定的机械式事件的独特顺序。在一些情况下，采用离散的顺序档案来描述基本合成参数（例如反应时间和温度）且改适所选造影剂的较佳试剂和卡匣配置。在一些实施例中，可基于如本文所述的新颖试剂容器（例如注射器）和卡匣配置，相比于上述方法进行顺序修改。例如，在一些实施例中，采用独特的程式顺序将氮气添加到注射器容器中，从而完成试剂转移。另外，例如，在一些实施例中，相比于上述方法修改总体顺序定时，提供较短的顺序持续时间（例如使得制备以平行方式而非线性系列发生）。

[0824] 例示性试剂盒

[0825] 在一些实施例中，提供用于制备造影剂的系统、方法、试剂盒以及卡匣试剂盒用于检测、造影和/或监控心肌灌注。在一些实施例中，提供用于投予造影剂的试剂盒。本发明的试剂盒可包括例如包含造影剂或造影剂前驱体和使用说明书的容器。试剂盒可包括无菌非热解配方，其包含预定量的造影剂或其前驱体及任选的其它组分。在本发明的一些方面中，试剂盒可包括一或多个含有制备用于向个体投予的造影剂和其前驱体的注射器。可与造影剂联合使用（例如向个体传递和/或投予造影剂）的容器可为注射器、瓶、小瓶、管等。可包括在本发明试剂盒中的例示性注射器为缺少吸附性柱塞尖端的注射器，如 3mL 或 5mL NORM-JECT（马萨诸塞州达德利的汉克舍斯沃尔夫公司）或缺少吸附性柱塞尖端的其它等效注射器。可在试剂盒中提供造影剂或其前驱体且使用前的其它准备可任选地包括稀释造影剂到可用浓度。本发明试剂盒中的说明书可关于造影剂的制备方法、造影剂的稀释方法、向个体投予造影剂以便诊断造影的方法或其它使用说明。

[0826] 在一些情况下，试剂盒还可包括一或多个含有用于制备向个体（例如人类）投予的造影剂组合物的稀释剂的小瓶。稀释剂小瓶可含有用于稀释造影剂的稀释剂，如生理食盐水、水、缓冲溶液等。例如，造影剂可以即可注射配方形式封装在试剂盒中，或可需要一些复原或稀释藉以制备用于注射或输注的最终组合物/配方。

[0827] 本发明试剂盒中的说明书还可包括向个体投予造影剂的说明且可包括关于给药、时间、压力诱导等的信息。例如，试剂盒可包括本文所述的造影剂或其前驱体，以及描述预期应用和正确投予试剂的说明书。如本文所用，“说明书”可定义说明和/或推广的组分，且通常涉及本发明的包装上或附于本发明的包装上的书面说明书。说明书还可包括以使用者将清楚了解说明书系与试剂盒相关的任何方式提供的任何口头或电子说明书，例如视听（例如录影带、DVD 等）、互联网和/或基于网络的通信等。书面说明书可呈由调控药物或生物产品的制造、使用或销售的政府机构规定的形式，所述说明书也可反映由制造、使用或销售机构批准用于人类投药。在一些情况下，说明书可包括混合特定量稀释剂与特定量造影剂或其前驱体的浓溶液或造影剂或其前驱体的固体制剂，由此制备用于注射或输注的最终配方的说明书，例如因此所得溶液为用于向个体投药的适合浓度（例如以如本文所述的浓度）。试剂盒可包括本发明化合物的整个治疗方案（例如休息剂量和压力剂量）。

[0828] 试剂盒可在一或多个容器中含有任一或多种本文所述的组分。例如，在一个实施例中，试剂盒可包括混合试剂盒的一或多种组分和/或分离和混合样品以及施用于个体的说明书。试剂盒可包括容纳本文所述的试剂的容器。试剂可呈液体、凝胶或固体（粉末）形式。试剂可无菌制备，封装在注射器中且装运冷冻。或者，可将其容纳于小瓶或其它容器中供储存。第二容器可具有无菌制备的其它试剂。或者，试剂盒可包括活性剂预混物且在注射器、小瓶、管或其它容器中装运。试剂盒可具有向患者投予试剂所需的一或多个或所有组件，如注射器、局部施用器件或静脉内针管以及袋。

[0829] 还应了解，含有本发明试剂盒的组分的容器，无论所述容器为瓶、小瓶（例如具有隔膜）、安瓿、输注袋或其类似物，均可包括其它标志，如当制剂已经热压处理或以其它方式灭菌时变色的常规标记。本发明的试剂盒可进一步包括其它组件，如注射器、标签、小瓶、管、导管、针、孔以等。在本发明的一些方面中，试剂盒可包括一或多个含有足以投药的造影剂的注射器。

[0830] 适用于制备造影剂或其前驱体和试剂盒的缓冲液包括例如磷酸盐、柠檬酸盐、磺基水杨酸盐以及乙酸盐缓冲液。较完全清单可见于美国药典(United States Pharmacopoeia)。适用于制备造影剂和试剂盒的冻干助剂包括例如甘露糖醇、乳糖、山梨糖醇、聚葡萄糖、FICOLL®聚合物以及聚乙烯吡咯啶(PVP)。适用于制备造影剂和试剂盒的稳定化助剂包括例如抗坏血酸、半胱氨酸、单硫甘油、亚硫酸氢钠、偏亚硫酸氢钠、龙胆酸以及肌醇。适用于制备造影剂和试剂盒的增溶助剂包括例如乙醇、甘油、聚乙二醇、丙二醇、聚氧化乙烯脱水山梨糖醇单油酸酯、脱水山梨糖醇单油酸酯、聚山梨醇酯、聚(氧化乙烯)-聚(氧化丙烯)-聚(氧化乙烯)嵌段共聚物(“Pluronics”)以及卵磷脂。在某些实施例中,增溶助剂为聚乙二醇、环糊精以及Pluronics。适用于制备造影剂和试剂盒的抑菌剂包括例如苯甲醇、氯化苯甲烃铵、氯丁醇以及对羟基苯甲酸甲酯、对羟基苯甲酸丙酯或对羟基苯甲酸丁酯。

[0831] 医药组合物

[0832] 当已制备或获得如本文所述的化合物(例如造影剂)时,可将其与一或多种医药学上可接受的赋形剂组合,从而形成适合于向包括人类的个体投药的医药组合物。如所属领域的技术人员将了解,可例如基于如下所述的投药途径、所传递的造影剂、试剂传递时程和/或个体的健康/状况来选择赋形剂。医药组合物可为固体或液体。

[0833] 本发明的医药组合物和根据本发明使用的医药组合物可包括医药学上可接受的赋形剂或载剂。如本文所用,术语“医药学上可接受的赋形剂”或“医药学上可接受的载剂”意指任何类型的无毒性惰性固体、半固体或液体填充剂、稀释剂、囊封材料或调配助剂。可用作医药学上可接受的载剂的材料的一些实例为糖,如乳糖、葡萄糖和蔗糖;淀粉,如玉米淀粉和马铃薯淀粉;纤维素和其衍生物,如羧甲基纤维素钠、乙基纤维素和乙酸纤维素;粉末状黄蓍;麦芽;明胶;滑石;赋形剂,如可可脂和栓剂蜡;油,如花生油、棉籽油、红花油、芝麻油、橄榄油、玉米油和大豆油;二醇,如丙二醇;酯,如油酸乙酯和月桂酸乙酯;琼脂;清洁剂,如Tween 80;缓冲剂,如氢氧化镁和氢氧化铝;海藻酸;无热原质水;等张生理食盐水;林格氏溶液(Ringer's solution);乙醇;和磷酸盐缓冲溶液,以及其它无毒相容润滑剂,如月桂基硫酸钠和硬脂酸镁,以及着色剂、脱模剂、涂布剂、甜味剂、调味剂和芳香剂、防腐剂和抗氧化剂也可根据调配者的判断存在于组合物中。

[0834] 医药学上可接受的赋形剂包括如适于所需特定剂型的任何和所有溶剂、稀释剂或其它液体媒剂、分散或悬浮助剂、表面活性剂、等张剂、增稠或乳化剂、防腐剂、固体粘合剂、润滑剂等。调配和/或制造医药组合物试剂的总体考虑可见于例如雷明顿医药科学(Remington's Pharmaceutical Sciences),第十六版,E.W.马丁(E.W.Martin)(宾夕法尼亚州伊斯顿的麦克出版公司(Mack Publishing Co.,Easton,Pa.),1980)和雷明顿:药学技术与实践(Remington:The Science and Practice of Pharmacy),第21版(威廉姆斯和威尔金斯公司(Lippincott Williams&Wilkins),2005)中。

[0835] 本文所述的医药组合物可通过药物技术中已知的任何方法制备。一般说来,所述制备方法包括以下步骤:使得本发明的化合物(“活性成分”)与载剂和/或一或多种其它配合剂缔合,且随后必要和/或需要时将产物成形和/或封装为所需单次或多次剂量单位。

[0836] 医药组合物可以单次单位剂量和/或多个单次单位剂量形式批量制备、封装和/或销售。如本文中所用,“单位剂量”为包含预定量活性成分的医药组合物的离散量。活性

成分的量一般等于向个体投予的活性成分的剂量和 / 或此剂量的适宜分数，如此剂量的二分之一或三分之一。

[0837] 本发明的医药组合物中活性成分、医药学上可接受的赋形剂和 / 或任何其它成分的相对量将视所治疗的个体的身分、体型和 / 或状况而变且进一步视组合物的投予途径而变。例如，组合物可包含介于 0.1％与 100％ (w/w) 之间的活性成分。

[0838] 制造所提供的医药组合物中所用的医药学上可接受的赋形剂包括惰性稀释剂、分散剂和 / 或成粒剂、表面活性剂和 / 或乳化剂、崩解剂、粘合剂、防腐剂、缓冲剂、润滑剂和 / 或油。赋形剂 (如可可脂和栓剂蜡)、着色剂、涂布剂、甜味剂、调味剂和芳香剂芳香剂也可存在于组合物中。

[0839] 例示性稀释剂包括碳酸钙、碳酸钠、磷酸钙、磷酸二钙、硫酸钙、磷酸氢钙、磷酸钠乳糖、蔗糖、纤维素、微晶纤维素、高岭土、甘露糖醇、山梨糖醇、肌醇、氯化钠、干燥淀粉、玉米淀粉、粉糖以及其组合。

[0840] 例示性防腐剂包括抗氧化剂、螯合剂、抗微生物防腐剂、抗真菌防腐剂、醇防腐剂、酸性防腐剂以及其它防腐剂。

[0841] 例示性抗氧化剂包括 α 生育酚、抗坏血酸、抗坏血酸棕榈酸酯、丁基化羟基甲氧苯、丁基化羟基甲苯、单硫甘油、偏亚硫酸氢钾、丙酸、没食子酸丙酯、抗坏血酸钠、亚硫酸氢钠、碘化钠、偏亚硫酸氢钠、亚硝酸钠、亚硫酸钠以及硫代硫酸钠。

[0842] 例示性螯合剂包括乙二氨四乙酸 (EDTA) 以及其盐和水合物 (例如依地酸钠、依地酸二钠、依地酸三钠、依地酸钙二钠、依地酸二钾等)、柠檬酸以及其盐和水合物 (例如单水合柠檬酸)、反丁烯二酸以及其盐和水合物、苹果酸以及其盐和水合物、磷酸以及其盐和水合物，和酒石酸以及其盐和水合物。例示性抗微生物防腐剂包括氯化苯甲烃铵、苄索氯铵 (benzethonium chloride)、苯甲醇、溴硝丙二醇、西曲溴铵 (cetrimide)、氯化十六烷基吡锭 (cetylpyridinium chloride)、氯己定 (chlorohexidine)、氯丁醇、氯甲酚、氯二甲苯酚、甲酚、乙醇、甘油、海克替啶 (hexetidine)、咪唑啶基脲 (imidurea)、酚、苯氧乙醇、苯乙醇、硝酸苯汞、丙二醇以及硫柳汞。

[0843] 例示性抗真菌防腐剂包括对羟基苯甲酸丁酯、对羟基苯甲酸甲酯、对羟基苯甲酸乙酯、对羟基苯甲酸丙酯、苯甲酸、羟基苯甲酸、苯甲酸钾、山梨酸钾、苯甲酸钠、丙酸钠以及山梨酸。

[0844] 例示性醇防腐剂包括乙醇、聚乙二醇、酚、酚系化合物、双酚、氯丁醇、羟基苯甲酸酯以及苯乙醇。

[0845] 例示性酸性防腐剂包括维生素 A、维生素 C、维生素 E、β 胡萝卜素、柠檬酸、乙酸、去氢乙酸、抗坏血酸、山梨酸以及植酸。

[0846] 其它防腐剂包括生育酚、乙酸生育酚、甲磺酸去铁胺 (deteroxime mesylate)、西曲溴铵、丁基化羟基甲氧苯 (BHA)、丁基化羟基甲苯 (BHT)、乙二胺、月桂基硫酸钠 (SLS)、月桂基乙醚硫酸钠 (SLES)、亚硫酸氢钠、偏亚硫酸氢钠、亚硫酸钾、偏亚硫酸氢盐、Glydant Plus、Phenonip、对羟基苯甲酸甲酯、Germall 115、Germaben II、Neolone、Kathon 以及 Euxyl。在某些实施例中，防腐剂为抗氧化剂。在其它实施例中，防腐剂为螯合剂。

[0847] 例示性缓冲剂包括柠檬酸盐缓冲溶液、乙酸盐缓冲溶液、磷酸盐缓冲溶液、氯化铵、碳酸钙、氯化钙、柠檬酸钙、葡乳醛酸钙 (calcium glubionate)、葡庚糖酸钙、葡萄糖酸

钙、D- 葡萄糖酸、甘油磷酸钙、乳酸钙、丙酸、乙酰丙酸钙、戊酸、磷酸氢二钙、磷酸、磷酸三钙、磷酸氢氧化钙、乙酸钾、氯化钾、葡糖酸钾、钾混合物、磷酸氢二钾、磷酸二氢钾、磷酸钾混合物、乙酸钠、碳酸氢钠、氯化钠、柠檬酸钠、乳酸钠、磷酸二钠、磷酸二氢钠、磷酸钠混合物、缓血酸胺、氢氧化镁、氢氧化铝、海藻酸、无热原质水、等张生理食盐水、林格氏溶液、乙醇等以及其组合。

[0848] 供经口和非经肠投予的液体剂型包括医药学上可接受的乳液、微乳液、溶液、悬浮液、糖浆以及酏剂。除活性成分外，液体剂型可包含本领域中常用的惰性稀释剂，如水或其它溶剂；增溶剂以及乳化剂，如乙醇、异丙醇、碳酸乙酯、乙酸乙酯、苯甲醇、苯甲酸苯甲酯、丙二醇、1,3- 丁二醇、二甲基甲酰胺、油（例如棉籽油、花生油、玉米油、胚芽油、橄榄油、蓖麻油以及芝麻油）、甘油、四氢糠醇、聚乙二醇以及脱水山梨糖醇的脂肪酸酯和其混合物。除惰性稀释剂以外，口服组合物可包括佐剂，如湿润剂、乳化剂和悬浮剂、甜味剂、调味剂和芳香剂。在非经肠投予的某些实施例中，将本发明的结合物与如十六醇聚氧乙烯醚(Cremophor)、醇、油、改质油、二醇、聚山梨醇酯、环糊精、聚合物以及其组合的增溶剂混合。

[0849] 可根据已知技术使用适合分散剂或湿润剂和悬浮剂来调配例如无菌可注射水性或油性悬浮液的可注射制剂。无菌可注射制剂可为于无毒非经肠可接受的稀释剂或溶剂中的无菌可注射溶液、悬浮液或乳液，例如于 1,3- 丁二醇中的溶液。在可接受的媒剂和溶剂中，可采用水、林格氏溶液、U.S.P. 以及等张氯化钠溶液。此外，无菌不挥发性油习用作溶剂或悬浮介质。为此，可采用任何温和非挥发性油，包括合成单酸甘油酯或二酸甘油酯。此外，在注射剂的制备中使用脂肪酸，例如油酸。

[0850] 可注射配方可例如通过经细菌截留过滤器过滤或通过以无菌固体组合物形式并入灭菌剂来灭菌，所述无菌固体组合物在使用前可溶解或分散于无菌水或其它无菌可注射介质中。

[0851] 适用于传递本文所述的皮内医药组合物的适合器件包括短针器件，如以下中所述者：美国专利 4,886,499；5,190,521；5,328,483；5,527,288；4,270,537；5,015,235；5,141,496 及 5,417,662。皮内组合物可通过限制针在皮肤内的有效刺入长度的器件（如 PCT 公开案 WO 99/34850 中所述者和其功能等效物）投予。射流注射器件为适合的，其通过液体射流注射器和 / 或通过刺穿角质层且产生到达真皮的射流的针来传递液体疫苗到真皮。射流注射器件描述于例如美国专利 5,480,381；5,599,302；5,334,144；5,993,412；5,649,912；5,569,189；5,704,911；5,383,851；5,893,397；5,466,220；5,339,163；5,312,335；5,503,627；5,064,413；5,520,639；4,596,556；4,790,824；4,941,880；4,940,460；和 PCT 公开案 WO97/37705 以及 WO 97/13537 中。使用压缩气体来加速粉末形式疫苗穿过皮肤外层达到真皮的弹道粉末 / 粒子传递器件为适合的。或者或另外，在皮内投药的传统曼托法 (Mantoux method) 中可使用常规注射器。

[0852] 尽管本文所提供的医药组合物的描述主要针对适合向人类投予的医药组合物，但所属领域的技术人员应了解，所述组合物一般适合向所有类别的动物投予。充分了解修改适用于向人类投予的医药组合物以使得组合物适用于向各种动物投予，且一般熟练兽医药理学家可用一般实验来设计和 / 或进行这种修改。

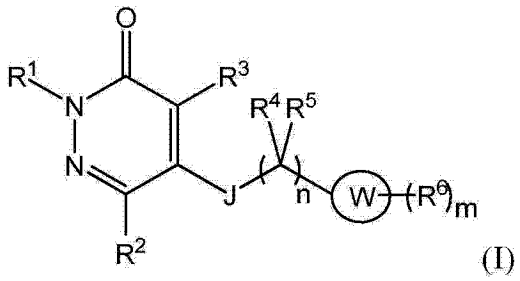
[0853] 本发明的医药组合物可非经肠（例如通过静脉内、肌肉内、皮下或腹膜内注射）向人类和 / 或其它动物投予。投药模式将视预期用途而变，如本领域中所众所周知。

[0854] 其它实施例

[0855] 在本文中进一步涵盖某些实施例。

[0856] 实施例 1. 在实施例 1 中，提供包含以下结构的化合物：

[0857]



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[0858] 或其医药学上可接受的盐，其中：

[0859] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0860] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及造影部分；

[0861] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及造影部分；

[0862] J 选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键；

[0863] R^4和 R^5各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地 R^4和 R^5中的任何两者相连以形成环；

[0864] n 为 0、1、2 或 3；

[0865] W 为杂芳基、萘基、杂环基或芳基；

[0866] 每个 R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

[0867] m 为 0、1、2、3、4、5、6 或 7；

[0868] 每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7可相连以形成环；

[0869] 每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、

卤烷基以及造影部分；

[0870] 每个 R^9 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及造影部分；和

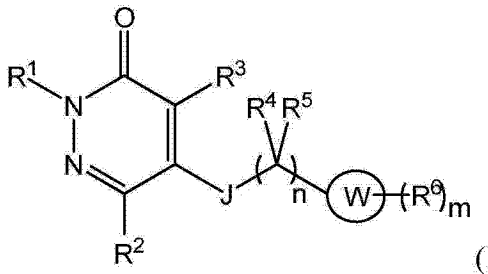
[0871] 每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[0872] 其限制条件为在所述化合物中存在至少一个造影部分；和

[0873] 其限制条件为当 W 为芳基时，a) R^3 不为卤基、烷基或卤烷基，或 b) 至少一个 R^6 选自由以下各项组成的群组：任选地经取代的炔基、任选地经取代的烯基、任选地经 -CN 取代的烷基、任选地经 $-C(=O)OR^8$ 取代的烷基、任选地经 $-C(=O)R^8$ 取代的烷基、任选地经 $-N(R^7)_2$ 取代的烷基、-CN、$-NO_2$、$-N(R^7)_2$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)R^8$、$-C(=O)N(R^7)_2$ 以及 $-N(R^7)C(=O)R^8$。

[0874] 实施例 2. 如实施例 1 的化合物，其中所述化合物包含以下结构：

[0875]



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[0876] 或其医药学上可接受的盐，其中：

[0877] R^1 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0878] R^2 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$ 以及造影部分；

[0879] R^3 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$ 以及造影部分；

[0880] J 选自由以下各项组成的群组：$N(R^7)$、S、O、$C(=O)$、$C(=O)O$、$OC(=O)$、$C(=O)N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键；

[0881] R^4 和 R^5 各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地 R^4 和 R^5 中的任何两者相连以形成环；

[0882] n 为 0、1、2 或 3；

[0883] W 为杂芳基、萘基或杂环基；

[0884] 每个 R^6 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)$

OR^8、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

[0885] m为0、1、2、3、4、5、6或7；

[0886] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个R^7可相连以形成环；

[0887] 每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

[0888] 每个R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及造影部分；和

[0889] 每个$R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[0890] 其限制条件为在所述化合物中存在至少一个造影部分。

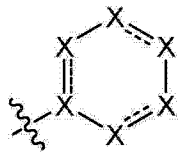
[0891] 实施例3. 如实施例1或2的化合物，其中W为杂芳基。

[0892] 实施例4. 如实施例1或2的化合物，其中W为萘基。

[0893] 实施例5. 如实施例1或2的化合物，其中W为杂环基。

[0894] 实施例6. 如实施例1或2的化合物，其中W为：

[0895]



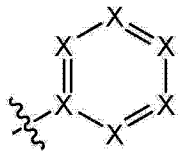
[0896] 其中每个X独立地选自由C、$C(R^6)$、$C(R^6)_2$、N、NR^7、O以及S组成的群组；和

[0897] 其中每个------独立地为单键或双键，

[0898] 其限制条件为至少一个X不为C或$C(R^6)$。

[0899] 实施例7. 如实施例1或2的化合物，其中W为：

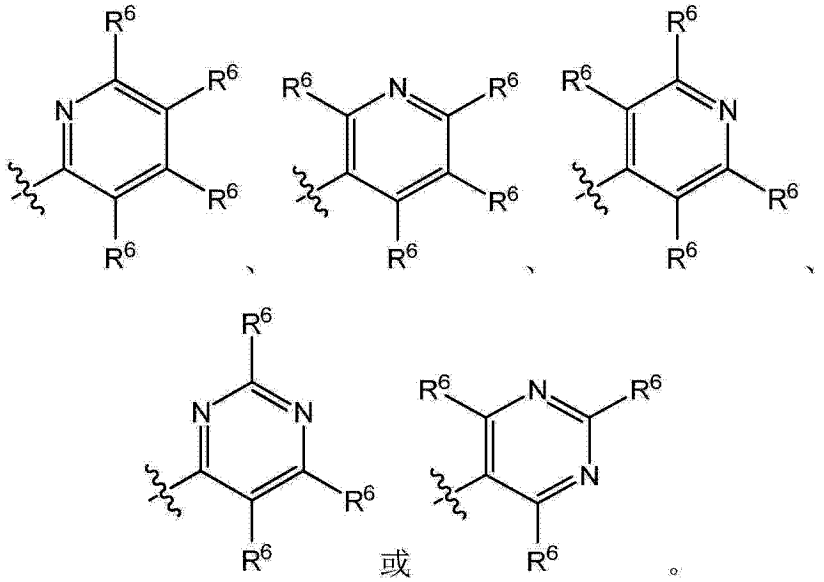
[0900]



[0901] 其中每个X独立地为C、$C(R^6)$或N，其限制条件为至少一个X不为C或$C(R^6)$。

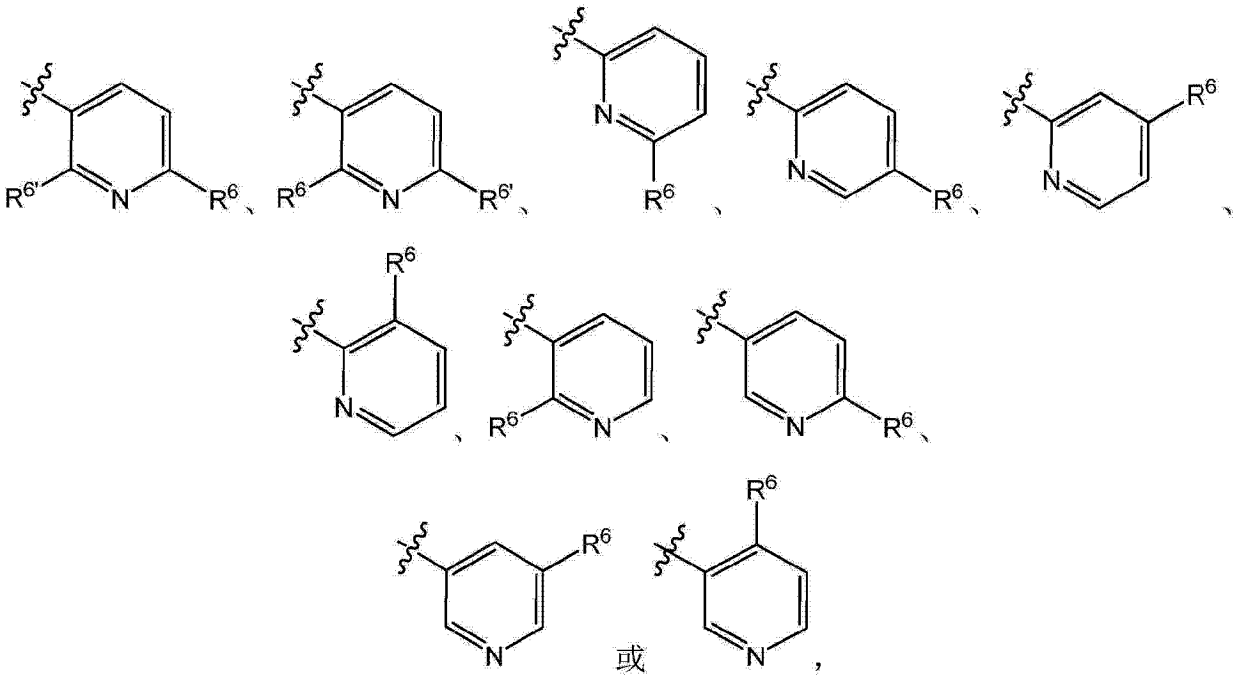
[0902] 实施例8. 如实施例1或2的化合物，其中W为：

[0903]



[0904] 实施例 9. 如实施例 1 或 2 的化合物，其中 W 为：

[0905]



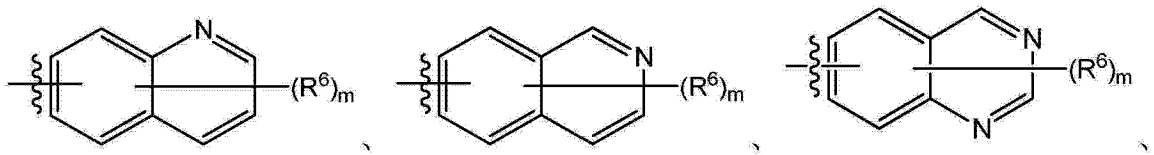
[0906] 其中 $R^{6'}$ 为卤基或氢；且任选地，其中 $R^{6'}$ 为氟、氯、溴或氢。

[0907] 实施例 10. 如实施例 9 的化合物，其中 R^6 为 $-O(CH_2)_jI_m$；其中 j 为 1、2、3、4、5 或 6；且情况，其中 I_m 为 ^{18}F。

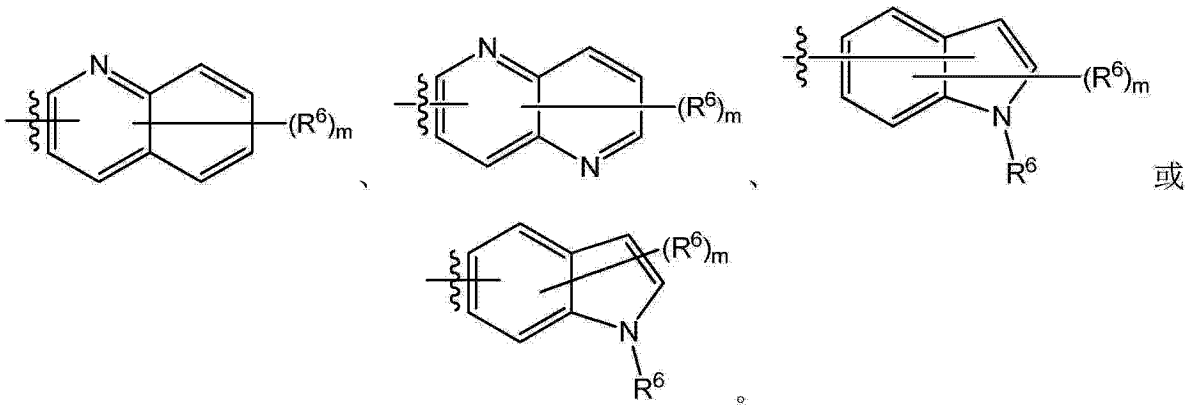
[0908] 实施例 11. 如实施例 9 的化合物，其中 R^6 为 $-(CH_2)_jO(CH_2)_jI_m$；其中 I_m 为造影部分且每个 j 独立地为 1、2、3、4、5 或 6；且任选地，其中 I_m 为 ^{18}F。

[0909] 实施例 12. 如实施例 1 或 2 的化合物，其中 W 为：

[0910]

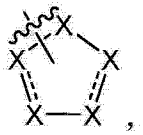


[0911]



[0912] 实施例 13. 如实施例 1 或 2 的化合物，其中 W 为：

[0913]



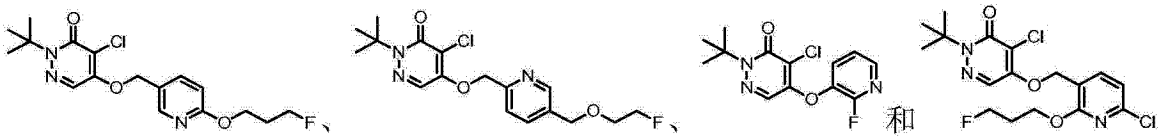
[0914] 每个 X 独立地选自由 C、$C(R^6)$、$C(R^6)_2$、N、NR^7、O 以及 S 组成的群组；和

[0915] 每个------独立地为单键或双键，

[0916] 其限制条件为至少一个 X 不为 C 或 $C(R^6)$。

[0917] 实施例 14. 如实施例 1 或 2 的化合物，其中所述化合物选自由以下各项组成的群组：

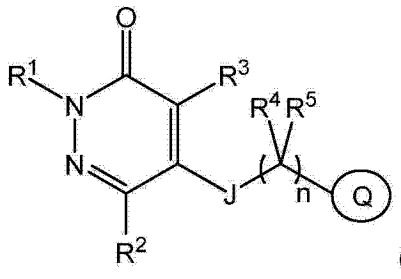
[0918]



[0919] 或其医药学上可接受的盐，其中 F 任选地为 ^{18}F。

[0920] 实施例 15. 如实施例 1 或 2 的化合物，其中所述化合物包含以下结构：

[0921]



(III)

[0922] 或其医药学上可接受的盐，其中：

[0923] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0924] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经

取代的杂芳基、卤基、卤烷基、$-NO_2$以及造影部分；

[0925] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及造影部分；

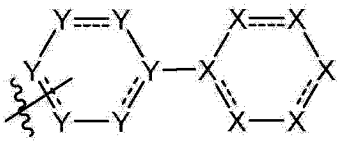
[0926] J 选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键；

[0927] R^4和 R^5各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地 R^4和 R^5中的任何两者相连以形成环；

[0928] n 为 0、1、2 或 3；

[0929] Q 具有以下结构：

[0930]



[0931] 每个 Y 和每个 X 独立地选自由 C、$C(R^6)$、$C(R^6)_2$、N、NR^7、O 及 S 组成的群组，其限制条件为至少一个 Y 不为 C 或 $C(R^6)$，任选地其中缺少一个 X 和 / 或一个 Y；

[0932] 每个═══独立地为单键或双键；

[0933] 每个 R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、-C(=O)R^8、-C(=O)OR^8、-OC(=O)R^8、-C(=O)$N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

[0934] 每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7可相连以形成环；

[0935] 每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

[0936] 每个 R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及造影部分；和

[0937] 每个 $R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

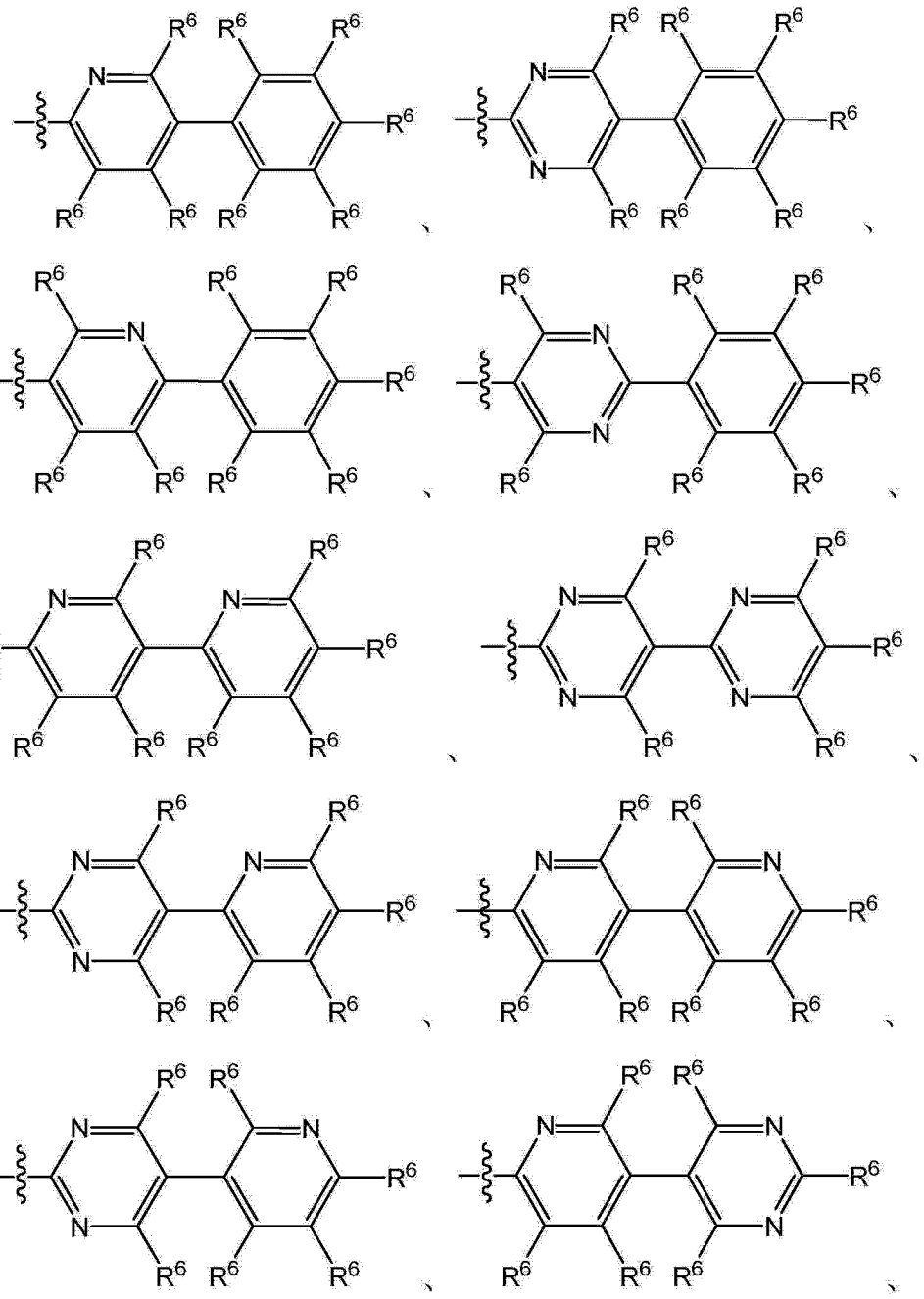
[0938] 其限制条件为在所述化合物中存在至少一个造影部分。

[0939] 实施例 16. 如实施例 15 的化合物，其中每个 Y 和每个 X 独立地选自由 C、$C(R^6)$、$C(R^6)_2$、N、NR^7、O 及 S 组成的群组，其限制条件为至少一个 Y 不为 C 或 $C(R^6)$。

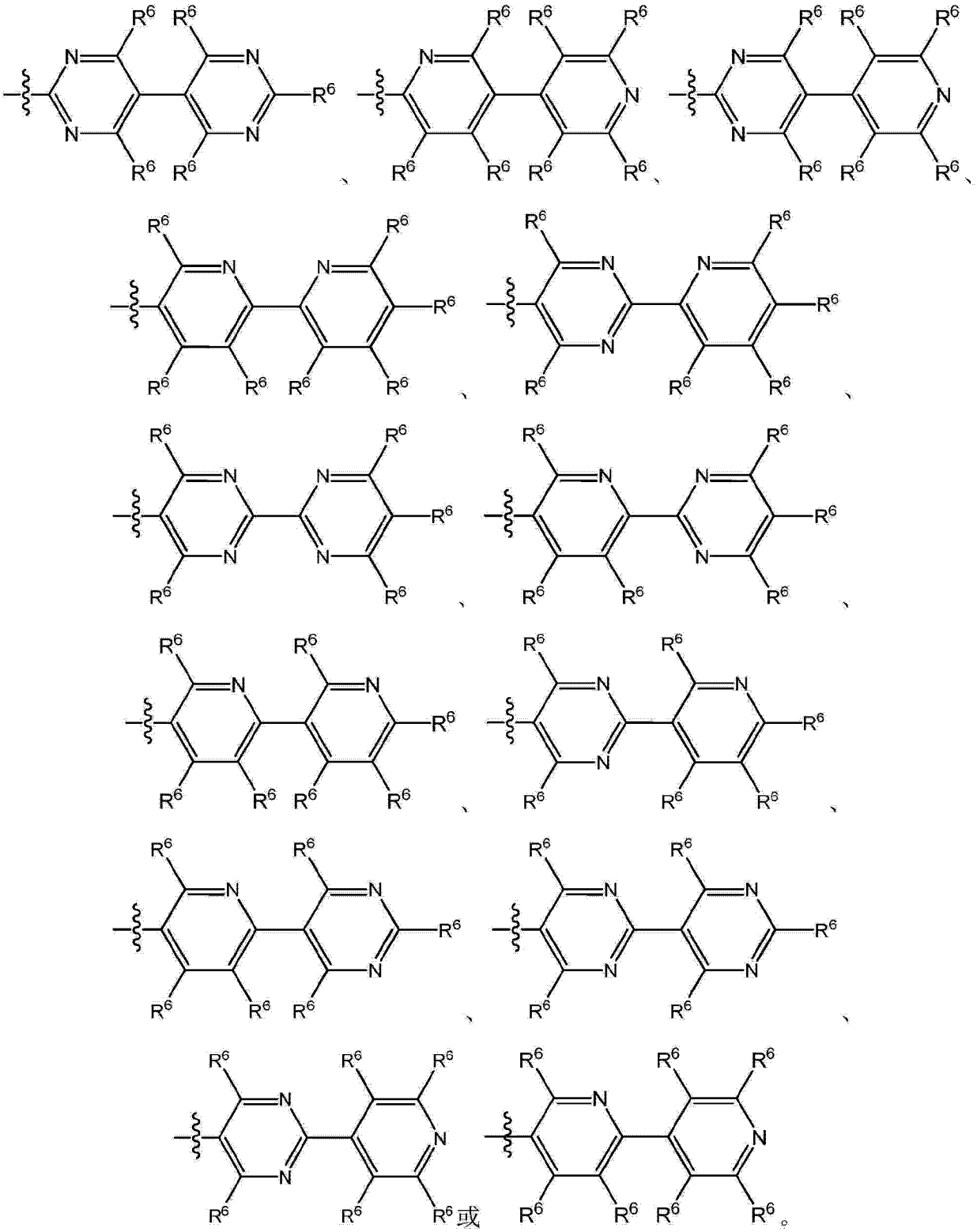
[0940] 实施例 17. 如实施例 15 的化合物，其中缺少一个 Y 或缺少一个 X。

[0941] 实施例 18. 如实施例 15 的化合物，其中 Q 为：

[0942]



[0943]



[0944] 实施例 19. 如实施例 1 至 13 和 15 至 18 中任一项的化合物，其中至少一个造影部分存在于 R^1、R^2、R^3、R^4、R^5或 R^6中。

[0945] 实施例 20. 如实施例 1 至 13 和 15 至 19 中任一项的化合物，其中 R^1为任选地经取代的烷基。

[0946] 实施例 21. 如实施例 1 至 13 和 15 至 19 中任一项的化合物，其中 R^1为甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。

[0947] 实施例22. 如实施例1至13和15至19中任一项的化合物，其中R^1为$-C(CH_3)_2CH_2OH$。

[0948] 实施例23. 如实施例1至13和15至19中任一项的化合物，其中R^1为叔丁基。

[0949] 实施例24. 如实施例1至13和15至19中任一项的化合物，其中R^1为任选地经取代的芳基。

[0950] 实施例25. 如实施例1至13和15至19中任一项的化合物，其中R^1为任选地经取代的苯基。

[0951] 实施例26. 如实施例1至13和15至19中任一项的化合物，其中R^1为未经取代的苯基。

[0952] 实施例27. 如实施例1至13和15至19中任一项的化合物，其中R^1为任选地经取代的环烷基。

[0953] 实施例28. 如实施例1至13和15至19中任一项的化合物，其中R^1为任选地经取代的环己基。

[0954] 实施例29. 如实施例1至13和15至28中任一项的化合物，其中R^2为H。

[0955] 实施例30. 如实施例1至13和15至29中任一项的化合物，其中J为键。

[0956] 实施例31. 如实施例1至13和15至29中任一项的化合物，其中J为O。

[0957] 实施例32. 如实施例1至13和15至29中任一项的化合物，其中J为S。

[0958] 实施例33. 如实施例1至13和15至32中任一项的化合物，其中n为0。

[0959] 实施例34. 如实施例1至13和15至32中任一项的化合物，其中n为1。

[0960] 实施例35. 如实施例1至13和15至32中任一项的化合物，其中n为2。

[0961] 实施例36. 如实施例1至13和15至32中任一项的化合物，其中n为3。

[0962] 实施例37. 如实施例1至13和15至36中任一项的化合物，其中R^4和R^5中的每一者为H。

[0963] 实施例38. 如实施例1至13和15至36中任一项的化合物，其中至少一个R^4和R^5为^2H，且任选地其中R^4和R^5中的每一者为^2H。

[0964] 实施例39. 如实施例1至13和15至38中任一项的化合物，其中R^3为卤基。

[0965] 实施例40. 如实施例1至13和15至38中任一项的化合物，其中R^3为Cl。

[0966] 实施例41. 如实施例1至13和15至38中任一项的化合物，其中R^3为Br。

[0967] 实施例42. 如实施例1至13和15至38中任一项的化合物，其中R^3为H。

[0968] 实施例43. 如实施例1至13和15至38中任一项的化合物，其中R^3为任选地经取代的烷基。

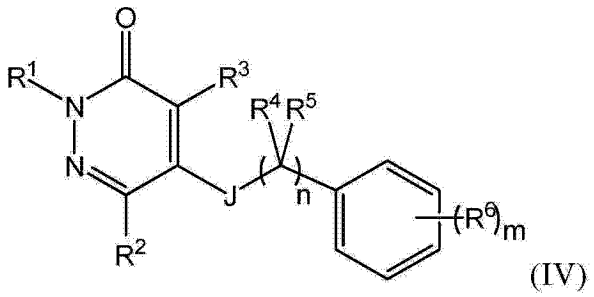
[0969] 实施例44. 如实施例1至13和15至38中任一项的化合物，其中R^3为未经取代的烷基。

[0970] 实施例45. 如实施例1至13和15至38中任一项的化合物，其中R^3为甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。

[0971] 实施例46. 如实施例1至13和15至38中任一项的化合物，其中R^3为甲基。

[0972] 实施例47. 如实施例1化合物，其中所述化合物包含以下结构：

[0973]



(IV)

[0974] 或其医药学上可接受的盐，其中：

[0975] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[0976] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及造影部分；

[0977] R^3选自由以下各项组成的群组：氢、未经取代的烷基或任选地经除卤素以外的部分取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、-CN 以及 $-NO_2$；

[0978] J 选自由以下各项组成的群组：$N(R^7)$、S、O、$C(=O)$、$C(=O)O$、$OC(=O)$、$C(=O)N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键；

[0979] R^4和 R^5各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地 R^4和 R^5中的任何两者相连以形成环；

[0980] n 为 0、1、2 或 3；

[0981] 每个 R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

[0982] m 为 0、1、2、3、4 或 5；

[0983] 每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7可相连以形成环；

[0984] 每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

[0985] 每个 R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及造影部分；和

[0986] 每个 $R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地

经取代的芳基以及造影部分；

[0987] 其限制条件为在所述化合物中存在至少一个造影部分。

[0988] 实施例 48. 如实施例 47 的化合物，其中 R^3为任选地经取代的烷基。

[0989] 实施例 49. 如实施例 47 的化合物，其中 R^3为未经取代的烷基。

[0990] 实施例 50. 如实施例 47 的化合物，其中 R^3为甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。

[0991] 实施例 51. 如实施例 47 的化合物，其中 R^3为甲基。

[0992] 实施例 52. 如实施例 47 至 51 中任一项的化合物，其中至少一个造影部分存在于 R^1、R^2、R^3、R^4、R^5或 R^6中。

[0993] 实施例 53. 如实施例 47 至 52 中任一项的化合物，其中 R^1为任选地经取代的烷基。

[0994] 实施例 54. 如实施例 47 至 52 中任一项的化合物，其中 R^1为甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。

[0995] 实施例 55. 如实施例 47 至 52 中任一项的化合物，其中 R^1为 $-C(CH_3)_2CH_2OH$。

[0996] 实施例 56. 如实施例 47 至 52 中任一项的化合物，其中 R^1为叔丁基。

[0997] 实施例 57. 如实施例 47 至 52 中任一项的化合物，其中 R^1为任选地经取代的芳基。

[0998] 实施例 58. 如实施例 47 至 52 中任一项的化合物，其中 R^1为任选地经取代的苯基。

[0999] 实施例 59. 如实施例 47 至 52 中任一项的化合物，其中 R^1为未经取代的苯基。

[1000] 实施例 60. 如实施例 47 至 52 中任一项的化合物，其中 R^1为任选地经取代的环烷基。

[1001] 实施例 61. 如实施例 47 至 52 中任一项的化合物，其中 R^1为任选地经取代的环己基。

[1002] 实施例 62. 如实施例 47 至 61 中任一项的化合物，其中 R^2为 H。

[1003] 实施例 63. 如实施例 47 至 62 中任一项的化合物，其中 J 为键。

[1004] 实施例 64. 如实施例 47 至 62 中任一项的化合物，其中 J 为 O。

[1005] 实施例 65. 如实施例 47 至 62 中任一项的化合物，其中 J 为 S。

[1006] 实施例 66. 如实施例 47 至 65 中任一项的化合物，其中 n 为 0。

[1007] 实施例 67. 如实施例 47 至 65 中任一项的化合物，其中 n 为 1。

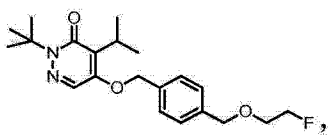
[1008] 实施例 68. 如实施例 47 至 65 中任一项的化合物，其中 n 为 2。

[1009] 实施例 69. 如实施例 47 至 68 中任一项的化合物，其中 R^4和 R^5中的每一者为 H。

[1010] 实施例 70. 如实施例 47 至 68 中任一项的化合物，其中至少一个 R^4和 R^5为 ^2H，且任选地，其中 R^4和 R^5中的每一者为 ^2H。

[1011] 实施例 71. 如实施例 47 的化合物，其中所述化合物具有下式：

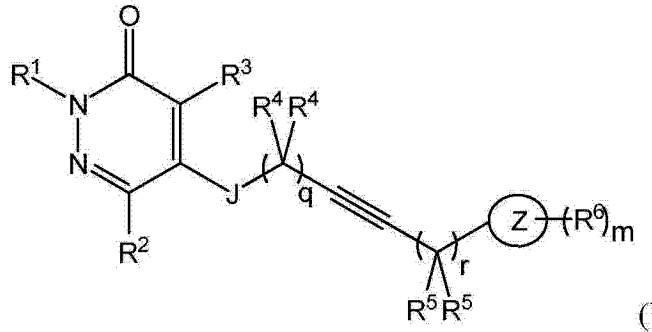
[1012]



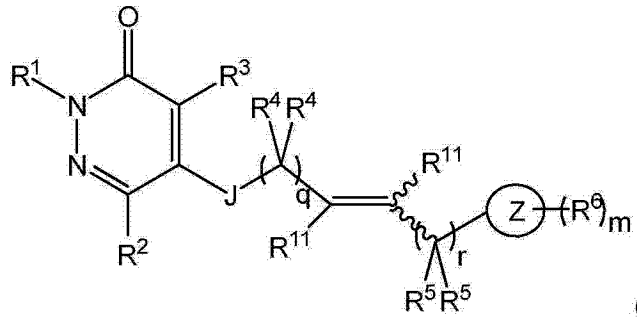
[1013] 或其医药学上可接受的盐，其中 F 任选地为 ^{18}F。

[1014] 实施例 72. 在实施例 72 中，提供包含以下结构的化合物：

[1015]



(V)或



(VI)，

[1016] 或其医药学上可接受的盐，其中：

[1017] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[1018] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及造影部分；

[1019] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及造影部分；

[1020] J选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O以及一键；

[1021] 每个R^4、R^5和R^{11}独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地任何两个R^4或任何两个R^5相连以形成环；

[1022] q以及r各自独立地为0、1、2或3；

[1023] Z选自由以下各项组成的群组：芳基、杂芳基、杂环基以及一键；

[1024] 每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

[1025] m为0、1、2、3、4、5、6或7；

[1026] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取

代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7 可相连以形成环；

[1027] 每个 R^8 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

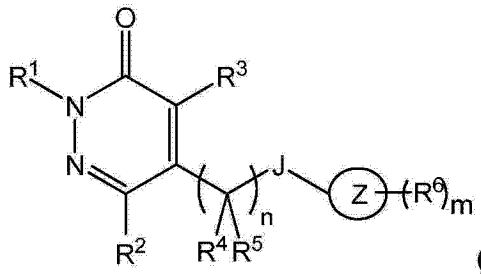
[1028] 每个 R^9 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及造影部分；和

[1029] 每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[1030] 其限制条件为在所述化合物中存在至少一个造影部分。

[1031] 实施例 73. 在实施例 73 中，提供包含以下结构的化合物：

[1032]



(VII)

[1033] 或其医药学上可接受的盐，其中：

[1034] R^1 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[1035] R^2 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、$-NO_2$、卤烷基以及造影部分；

[1036] R^3 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$ 以及造影部分；

[1037] J 选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)_2$、$N(R^7)C(=O)$ 以及 $-CH_2O$；

[1038] 每个 R^4 和 R^5 独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组，或任选地任何两个 R^4 或任何两个 R^5 相连以形成环；

[1039] n 为 1、2 或 3；

[1040] Z 选自由以下各项组成的群组：芳基、杂芳基、杂环基以及一键；

[1041] 每个 R^6 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、-C(=O)

OR^8、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分；

[1042] m 为 0、1、2、3、4、5、6 或 7；

[1043] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个R^7可相连以形成环；

[1044] 每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

[1045] 每个R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及造影部分；和

[1046] 每个$R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[1047] 其限制条件为在所述化合物中存在至少一个造影部分。

[1048] 实施例 74. 如实施例 72 或 73 的化合物，其中 Z 为芳基。

[1049] 实施例 75. 如实施例 72 或 73 的化合物，其中 Z 为苯基。

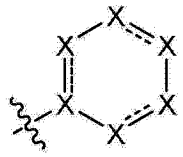
[1050] 实施例 76. 如实施例 72 或 73 的化合物，其中 Z 为萘基。

[1051] 实施例 77. 如实施例 72 或 73 的化合物，其中 Z 为杂芳基。

[1052] 实施例 78. 如实施例 72 或 73 的化合物，其中 Z 为杂环基。

[1053] 实施例 79. 如实施例 72 或 73 的化合物，其中 Z 为：

[1054]

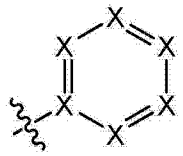


[1055] 其中每个 X 独立地选自由 C、$C(R^6)$、$C(R^6)_2$、N、NR^7、O 以及 S 组成的群组；和

[1056] 其中每个------独立地为单键或双键。

[1057] 实施例 80. 如实施例 72 或 73 的化合物，其中 Z 为：

[1058]

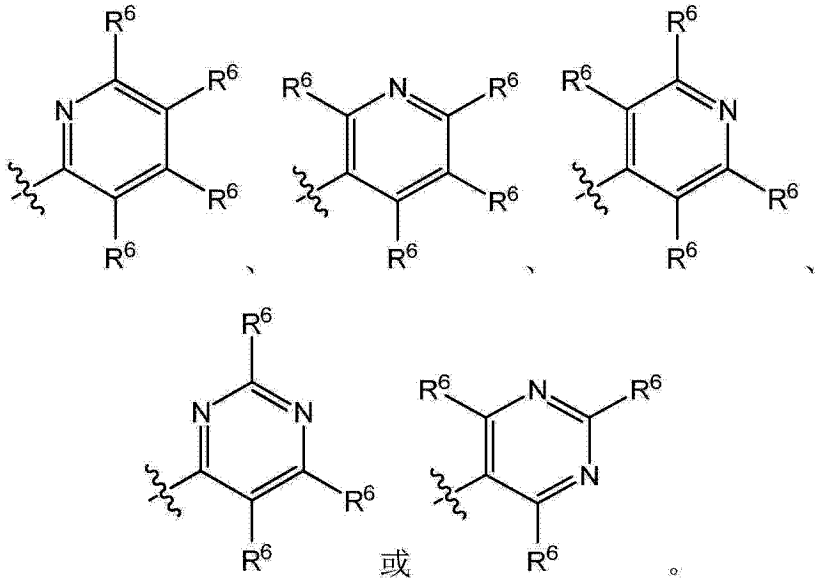


[1059] 其中每个 X 独立地为 C、$C(R^6)$ 或 N。

[1060] 实施例 81. 如实施例 79 或 80 的化合物，其中至少一个 X 不为 C 或 $C(R^6)$。

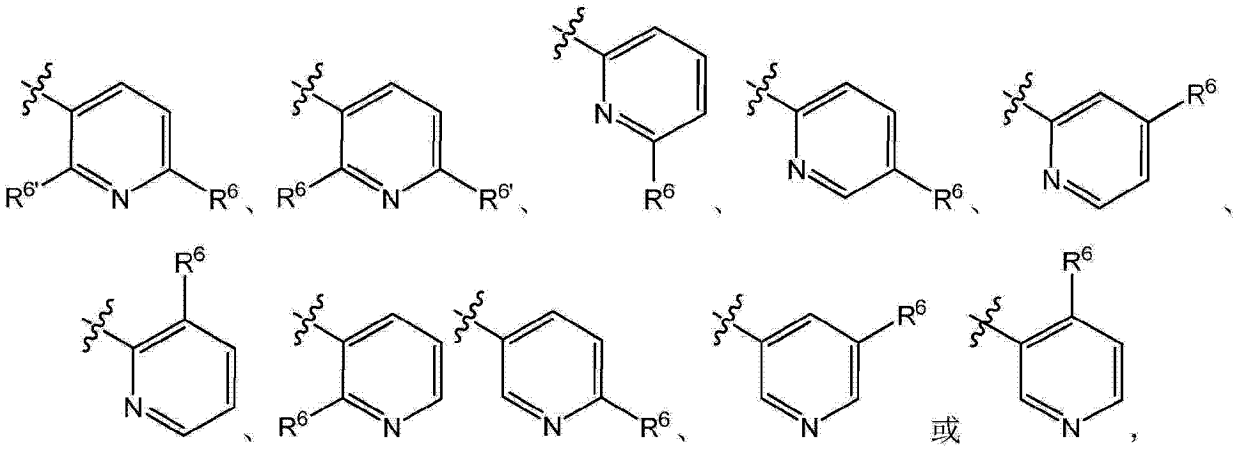
[1061] 实施例 82. 如实施例 72、73 或 80 的化合物，其中 Z 为：

[1062]



[1063] 实施例 83. 如实施例 72、73 或 80 的化合物，其中 Z 为：

[1064]



[1065] 其中 $R^{6'}$ 为卤基或氢。

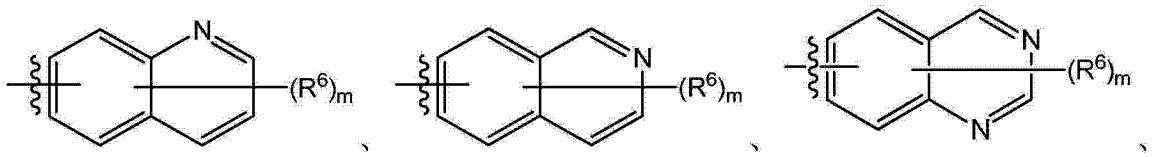
[1066] 实施例 84. 如实施例 83 的化合物，其中 $R^{6'}$ 为氟、氯、溴或氢。

[1067] 实施例 85. 如实施例 83 的化合物，其中 R^6 为 $-O(CH_2)_jI_m$；其中 I_m 为造影部分且 j 为 1、2、3、4、5 或 6。

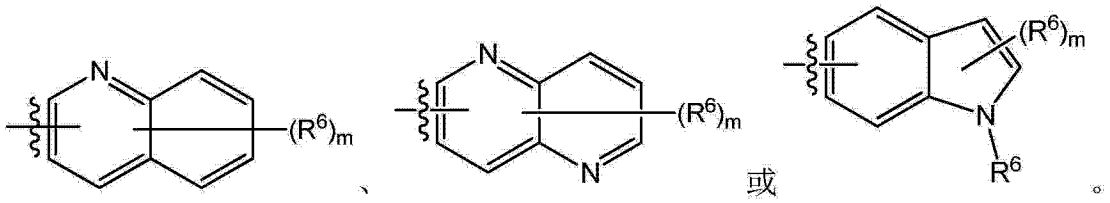
[1068] 实施例 86. 如实施例 83 的化合物，其中 R^6 为 $-(CH_2)_jO(CH_2)_jI_m$；其中 I_m 为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。

[1069] 实施例 87. 如实施例 72 或 73 的化合物，其中 Z 为：

[1070]

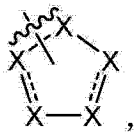


[1071]



[1072] 实施例 88. 如实施例 72 或 73 的化合物，其中 Z 为：

[1073]



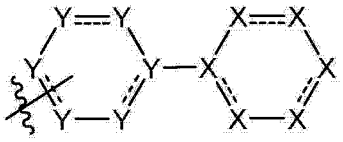
[1074] 每个 X 独立地选自由 C、$C(R^6)$、$C(R^6)_2$、N、NR^7、O 及 S 组成的群组；和

[1075] 每个------独立地为单键或双键。

[1076] 实施例 89. 如实施例 88 的化合物，其中至少一个 X 不为 C 或 $C(R^6)$。

[1077] 实施例 90. 如实施例 72 或 73 的化合物，其中 Z 具有以下结构：

[1078]



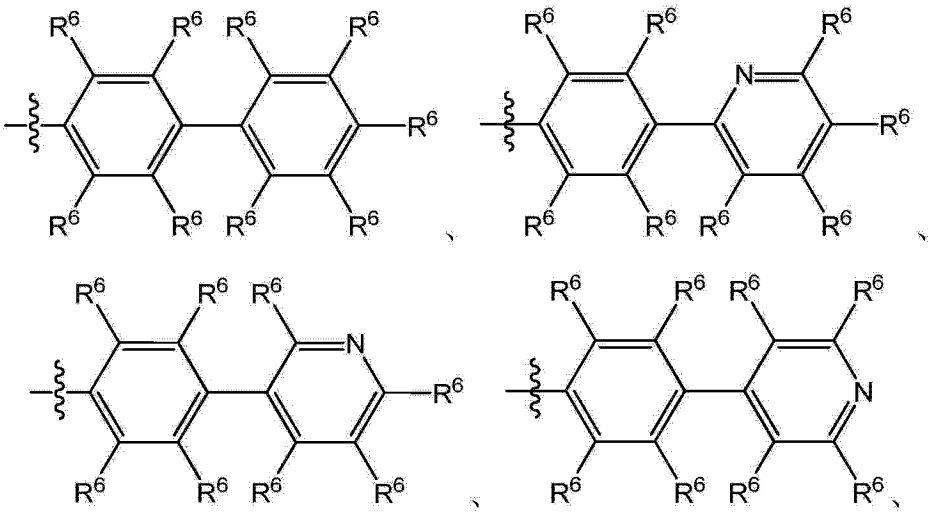
[1079] 每个 Y 及每个 X 独立地选自由 C、$C(R^6)$、$C(R^6)_2$、N、NR^7、O 以及 S 组成的群组；每个------独立地为单键或双键。

[1080] 实施例 91. 如实施例 90 的化合物，其中至少一个 Y 不为 C 或 $C(R^6)$。

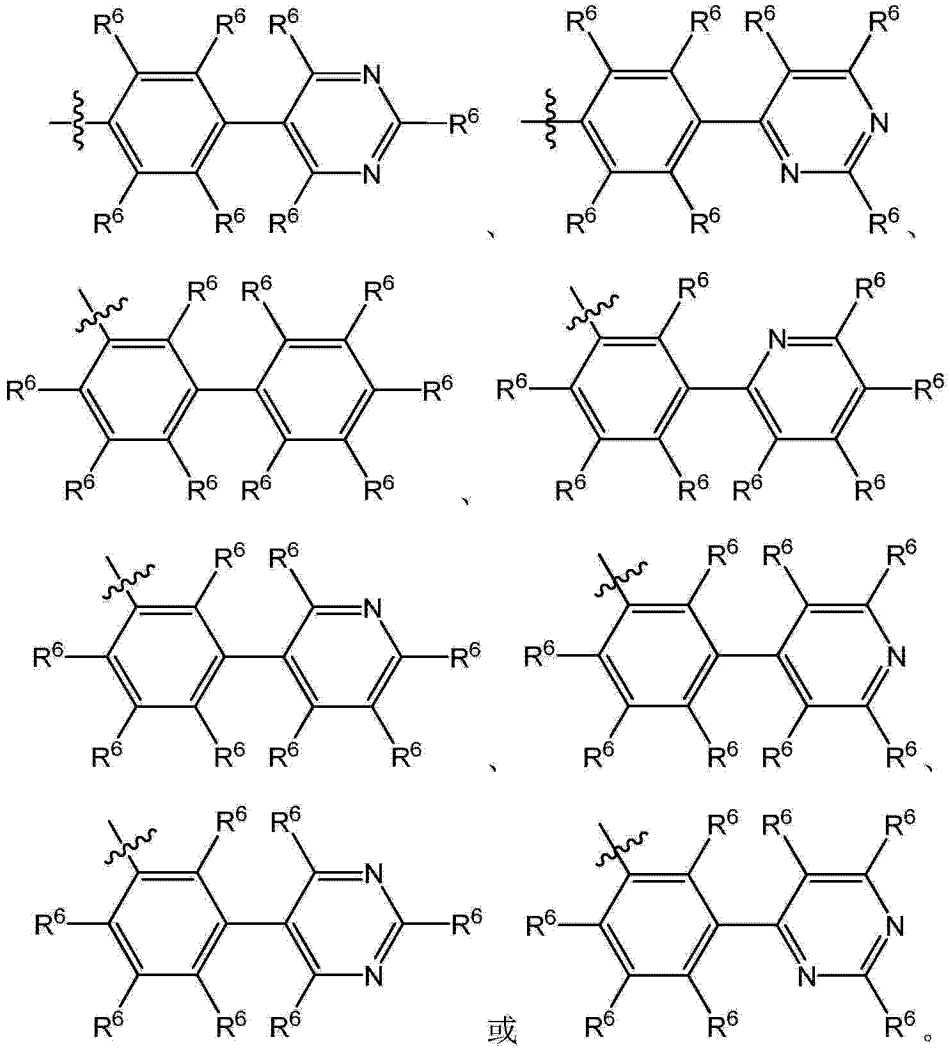
[1081] 实施例 92. 如实施例 90 或 91 的化合物，其中至少一个 X 不为 C 或 $C(R^6)$。

[1082] 实施例 93. 如实施例 72、73 或 90 的化合物，其中 Z 为：

[1083]

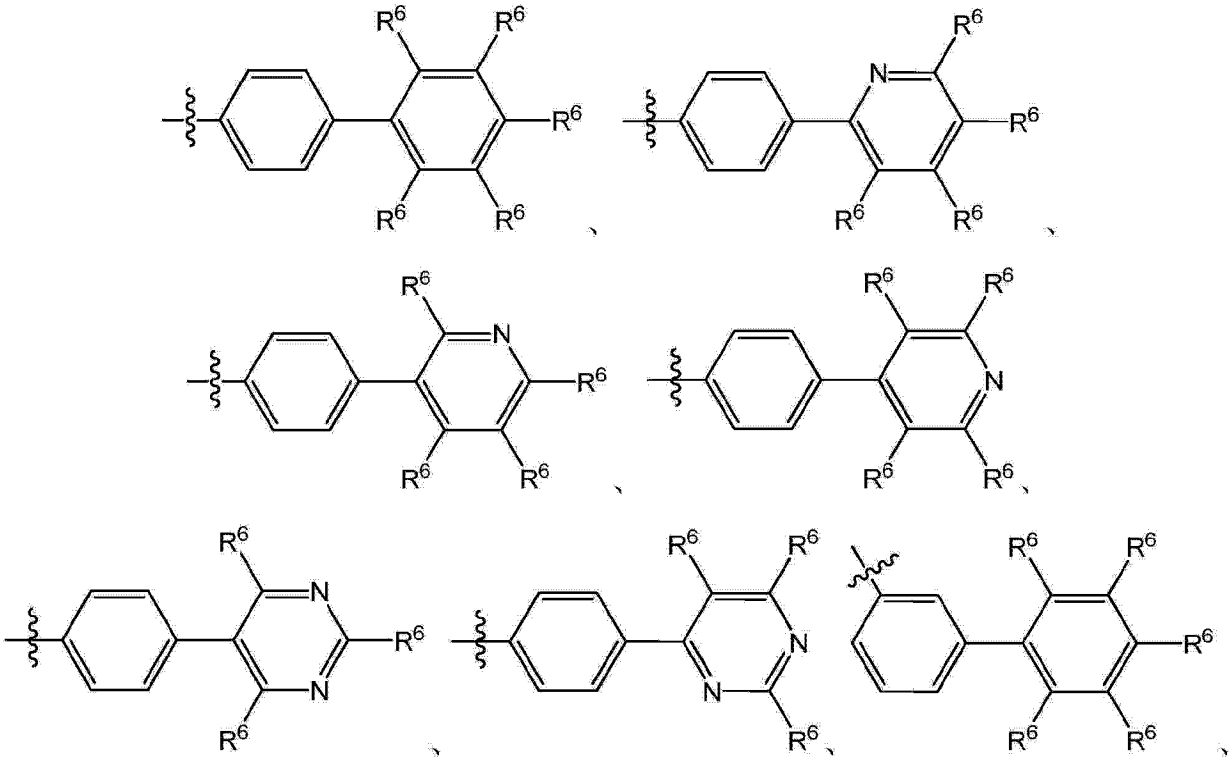


[1084]

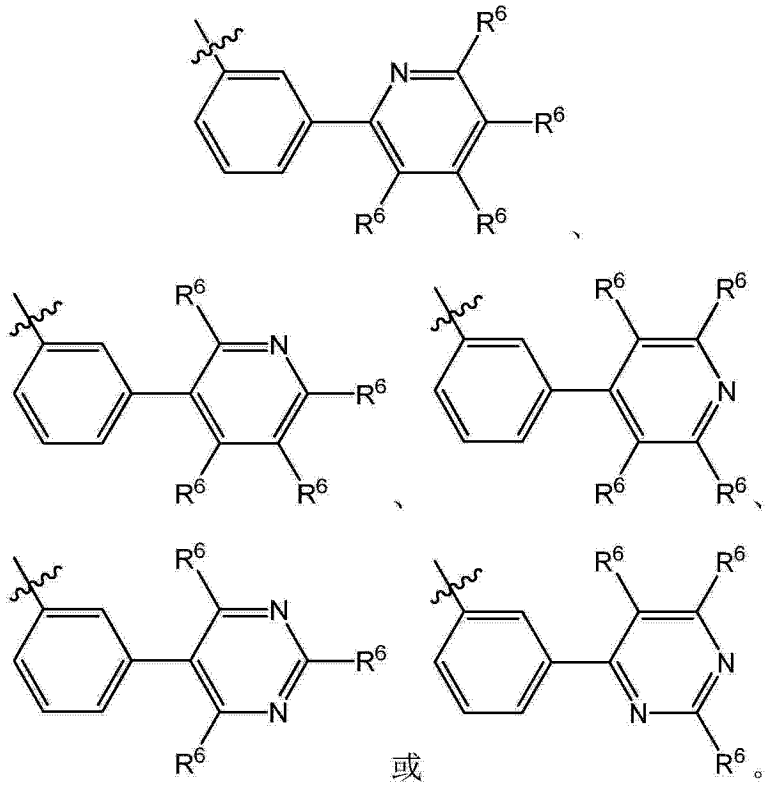


[1085] 实施例 94. 如实施例 72、73 或 90 的化合物，其中 Z 为：

[1086]



[1087]



[1088] 实施例 95. 如实施例 73 或 72 至 94 中任一项的化合物，其中 J 为键。

[1089] 实施例 96. 如实施例 73 或 72 至 94 中任一项的化合物，其中 J 为 O。

[1090] 实施例 97. 如实施例 73 或 72 至 94 中任一项的化合物，其中 J 为 S。

[1091] 实施例 98. 如实施例 72 至 97 中任一项的化合物，其中 q 为 0。

[1092] 实施例 99. 如实施例 72 至 97 中任一项的化合物，其中 q 为 1。

[1093] 实施例 100. 如实施例 72 至 97 中任一项的化合物，其中 q 为 2。

[1094] 实施例 101. 如实施例 72 至 100 中任一项的化合物，其中 r 为 0。

[1095] 实施例 102. 如实施例 72 至 100 中任一项的化合物，其中 r 为 1。

[1096] 实施例 103. 如实施例 72 至 100 中任一项的化合物，其中 r 为 2。

[1097] 实施例 104. 如实施例 72 至 97 中任一项的化合物，其中 q 和 r 各自为 0。

[1098] 实施例 105. 如实施例 72 至 97 中任一项的化合物，其中 q 和 r 各自为 1。

[1099] 实施例 106. 如实施例 73 或 74 至 83 中任一项的化合物，其中 n 为 0。

[1100] 实施例 107. 如实施例 73 或 74 至 83 中任一项的化合物，其中 n 为 1。

[1101] 实施例 108. 如实施例 73 或 74 至 83 中任一项的化合物，其中 n 为 2。

[1102] 实施例 109. 如实施例 72 至 91 或 107 至 108 中任一项的化合物，其中 R^4和 R^5中的每一者为 H。

[1103] 实施例 110. 如实施例 72 至 109 中任一项的化合物，其中每个 R^{11}为 H。

[1104] 实施例 111. 如实施例 73 或 72 至 110 中任一项的化合物，其中至少一个造影部分存在于 R^1、R^2、R^3、R^4、R^5、R^6或 R^{11}中。

[1105] 实施例 112. 如实施例 73 或 72 至 111 中任一项的化合物，其中 R^1为任选地经取代的烷基。

[1106] 实施例 113. 如实施例 73 或 72 至 111 中任一项的化合物，其中 R^1为甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。

[1107] 实施例 114. 如实施例 73 或 72 至 111 中任一项的化合物，其中 R^1为 $-C(CH_3)_2CH_2OH$。

[1108] 实施例 115. 如实施例 73 或 72 至 111 中任一项的化合物，其中 R^1为叔丁基。

[1109] 实施例 116. 如实施例 73 或 72 至 111 中任一项的化合物，其中 R^1为任选地经取代的芳基。

[1110] 实施例 117. 如实施例 73 或 72 至 111 中任一项的化合物，其中 R^1为任选地经取代的苯基。

[1111] 实施例 118. 如实施例 73 或 72 至 111 中任一项的化合物，其中 R^1为未经取代的苯基。

[1112] 实施例 119. 如实施例 73 或 72 至 111 中任一项的化合物，其中 R^1为任选地经取代的环烷基。

[1113] 实施例 120. 如实施例 73 或 72 至 111 中任一项的化合物，其中 R^1为任选地经取代的环己基。

[1114] 实施例 121. 如实施例 73 或 72 至 120 中任一项的化合物，其中 R^2为 H。

[1115] 实施例 122. 如实施例 73 或 72 至 121 中任一项的化合物，其中 R^3为卤基。

[1116] 实施例 123. 如实施例 73 或 72 至 121 中任一项的化合物，其中 R^3为 Cl。

[1117] 实施例 124. 如实施例 73 或 72 至 121 中任一项的化合物，其中 R^3为 Br。

[1118] 实施例 125. 如实施例 73 或 72 至 121 中任一项的化合物，其中 R^3为 H。

[1119] 实施例 126. 如实施例 73 或 72 至 121 中任一项的化合物，其中 R^3为任选地经取代的烷基。

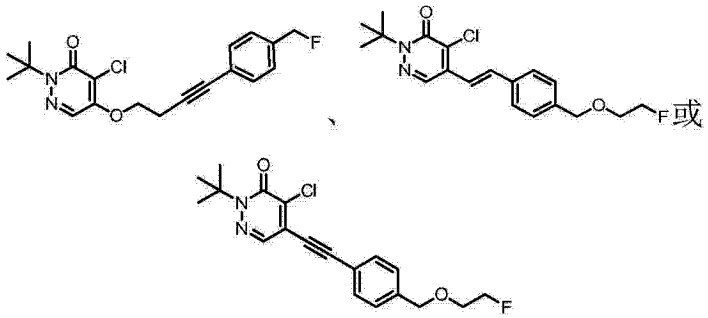
[1120] 实施例 127. 如实施例 73 或 72 至 121 中任一项的化合物，其中 R^3为未经取代的烷基。

[1121] 实施例 128. 如实施例 73 或 72 至 121 中任一项的化合物，其中 R^3为甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。

[1122] 实施例 129. 如实施例 73 或 72 至 121 中任一项的化合物，其中 R^3为甲基。

[1123] 实施例 130. 如实施例 72 的化合物，其中所述化合物选自由以下各项组成的群组：

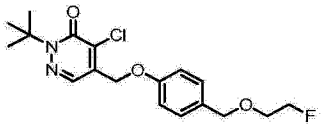
[1124]



[1125] 或其医药学上可接受的盐，其中 F 任选地为 ^{18}F。

[1126] 实施例 131. 如实施例 73 的化合物，其中所述化合物具有下式：

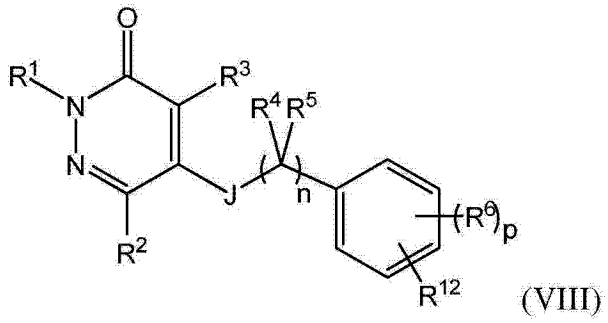
[1127]



[1128] 或其医药学上可接受的盐，其中 F 任选地为 ^{18}F。

[1129] 实施例 132. 如实施例 1 的化合物，其中所述化合物包含以下结构：

[1130]



[1131] 或其医药学上可接受的盐，其中：

[1132] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及造影部分；

[1133] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及造影部分；

[1134] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及造影部分；

[1135] J 选自由以下各项组成的群组 :$N(R^7)$、S、O、C(= O)、C(= O)O、OC(= O)、C(= O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键 ;

[1136] R^4和 R^5各自独立地选自由氢、任选地经取代的烷基以及造影部分组成的群组,或任选地 R^4和 R^5中的任何两者相连以形成环 ;

[1137] n 为 0、1、2 或 3 ;

[1138] 每个 R^6独立地选自由以下各项组成的群组 :氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、-C(= O)R^8、-C(= O)OR^8、-OC(= O)R^8、-C(= O)$N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及造影部分 ;

[1139] p 为 0、1、2、3 或 4 ;

[1140] 每个 R^7独立地选自由以下各项组成的群组 :氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分,或任选地任何两个 R^7可相连以形成环 ;和

[1141] 每个 R^8独立地选自由以下各项组成的群组 :氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分 ;

[1142] R^{12}选自由以下各项组成的群组 :任选地经取代的炔基、任选地经取代的烯基、经 -CN 取代的烷基、经 -C(= O)OR^8取代的烷基、经 -C(= O)R^8取代的烷基、经 $-N(R^7)_2$取代的烷基、-CN、$-NO_2$、$-N(R^7)_2$、-C(= O)OR^8、-OC(= O)R^8、-C(= O)R^8、-C(= O)$N(R^7)_2$以及 $-N(R^7)C(=O)R^8$;

[1143] 每个 R^9独立地选自由以下各项组成的群组 :氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及造影部分 ;和

[1144] 每个 $R^{9'}$独立地选自由以下各项组成的群组 :卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分 ;

[1145] 其限制条件为在所述化合物中存在至少一个造影部分。

[1146] 实施例 133. 如实施例 132 的化合物,其中 R^{12}为 $-NO_2$、$-C(=O)(CH_2)_uI_m$、$-C(=O)O(CH_2)_uI_m$、$-C\equiv C(CH_2)_uI_m$或 -Si(烷基 $)_2I_m$;其中 I_m为造影部分且 u 为 1、2、3、4、5 或 6。

[1147] 实施例 134. 如实施例 132 至 133 中任一项的化合物,其中至少一个造影部分存在于 R^1、R^2、R^3、R^4、R^5、R^6或 R^{12}中。

[1148] 实施例 135. 如实施例 132 至 133 中任一项的化合物,其中至少一个造影部分存在于 R^1、R^3、R^4、R^5、R^6或 R^{12}中。

[1149] 实施例 136. 如实施例 132 至 134 中任一项的化合物,其中 R^1为任选地经取代的烷基。

[1150] 实施例 137. 如实施例 132 至 134 中任一项的化合物,其中 R^1为甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。

[1151] 实施例 138. 如实施例 132 至 134 中任一项的化合物,其中 R^1为 $-C(CH_3)_2CH_2OH$。

[1152] 实施例 139. 如实施例 132 至 134 中任一项的化合物，其中 R^1为叔丁基。

[1153] 实施例 140. 如实施例 132 至 134 中任一项的化合物，其中 R^1为任选地经取代的芳基。

[1154] 实施例 141. 如实施例 132 至 134 中任一项的化合物，其中 R^1为任选地经取代的苯基。

[1155] 实施例 142. 如实施例 132 至 134 中任一项的化合物，其中 R^1为未经取代的苯基。

[1156] 实施例 143. 如实施例 132 至 134 中任一项的化合物，其中 R^1为任选地经取代的环烷基。

[1157] 实施例 144. 如实施例 132 至 134 中任一项的化合物，其中 R^1为任选地经取代的环己基。

[1158] 实施例 145. 如实施例 132 至 144 中任一项的化合物，其中 R^2为 H。

[1159] 实施例 146. 如实施例 132 至 145 中任一项的化合物，其中 J 为键。

[1160] 实施例 147. 如实施例 132 至 145 中任一项的化合物，其中 J 为 O。

[1161] 实施例 148. 如实施例 132 至 145 中任一项的化合物，其中 J 为 S。

[1162] 实施例 149. 如实施例 132 至 148 中任一项的化合物，其中 n 为 0。

[1163] 实施例 150. 如实施例 132 至 148 中任一项的化合物，其中 n 为 1。

[1164] 实施例 151. 如实施例 132 至 148 中任一项的化合物，其中 n 为 2。

[1165] 实施例 152. 如实施例 132 至 151 中任一项的化合物，其中 R^4和 R^5中的每一者为 H。

[1166] 实施例 153. 如实施例 132 至 151 中任一项的化合物，其中至少一个 R^4和 R^5为 ^2H，且任选地，其中 R^4和 R^5中的每一者为 ^2H。

[1167] 实施例 154. 如实施例 132 至 153 中任一项的化合物，其中 R^3为卤基。

[1168] 实施例 155. 如实施例 132 至 153 中任一项的化合物，其中 R^3为 Cl。

[1169] 实施例 156. 如实施例 132 至 153 中任一项的化合物，其中 R^3为 Br。

[1170] 实施例 157. 如实施例 132 至 153 中任一项的化合物，其中 R^3为 H。

[1171] 实施例 158. 如实施例 132 至 153 中任一项的化合物，其中 R^3为任选地经取代的烷基。

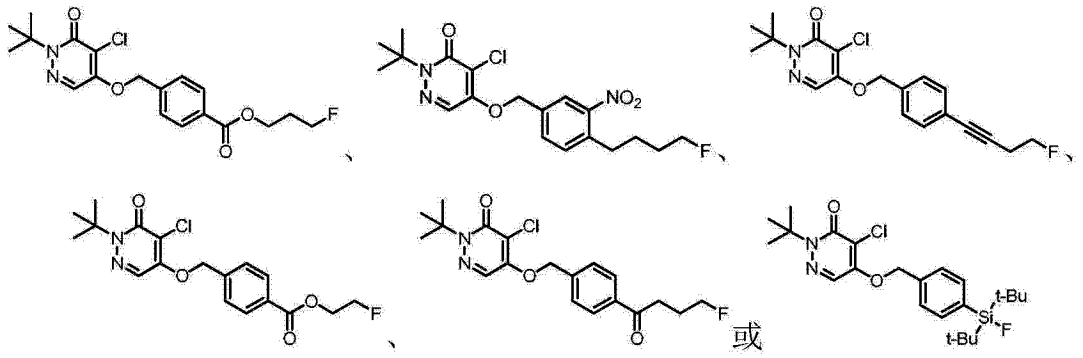
[1172] 实施例 159. 如实施例 132 至 153 中任一项的化合物，其中 R^3为未经取代的烷基。

[1173] 实施例 160. 如实施例 132 至 153 中任一项的化合物，其中 R^3为甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。

[1174] 实施例 161. 如实施例 132 至 153 中任一项的化合物，其中 R^3为甲基。

[1175] 实施例 162. 如实施例 132 的化合物，其中所述化合物选自由以下各项组成的群组：

[1176]



[1177] 或其医药学上可接受的盐，其中 F 任选地为 ^{18}F。

[1178] 实施例 163. 如实施例 1 至 13、15 至 70、72 至 124 及 132 至 161 中任一项的化合物，其中至少一个造影部分存在于 R^6 中。

[1179] 实施例 164. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 中任一项的化合物，其中至少一个 R^6 经至少一个造影部分取代。

[1180] 实施例 165. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 164 中任一项的化合物，其中至少一个造影部分选自由以下各项组成的群组：^{11}C、^{13}N、^{18}F、^{76}Br、^{123}I、^{124}I、^{125}I、^{131}I、^{99m}Tc、^{95}Tc、^{111}In、^{62}Cu、^{64}Cu、^{67}Ga 以及 ^{68}Ga。

[1181] 实施例 166. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 165 中任一项的化合物，其中至少一个造影部分为 ^{18}F。

[1182] 实施例 167. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 165 中任一项的化合物，其中至少一个造影部分与包含结构 $-B(R^{9'})_2(I_m)$ 的基团缔合，其中 I_m 为造影部分，任选地为 ^{18}F。

[1183] 实施例 168. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 165 中任一项的化合物，其中至少一个造影部分与包含结构 $-Si(R^9)_2(I_m)$ 的基团缔合，其中 I_m 为造影部分，任选地为 ^{18}F。

[1184] 实施例 169. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 168 中任一项的化合物，其中除一个 R^6 以外所有 R^6 均为 H。

[1185] 实施例 170. 如实施例 169 的化合物，其中一个 R^6 经至少一个造影部分取代。

[1186] 实施例 171. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 166 中任一项的化合物，其中至少一个 R^6 为各自经造影部分取代的任选地经取代的烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基。

[1187] 实施例 172. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 166 中任一项的化合物，其中至少一个 R^6 为 $-O(CH_2)_jI_m$；其中 I_m 为造影部分且 j 为 1、2、3、4、5 或 6。

[1188] 实施例 173. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 166 中任一项的化合物，其中至少一个 R^6 为 $-(CH_2)_jO(CH_2)_jI_m$；其中 I_m 为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。

[1189] 实施例 174. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 166 中任一项的化合物，其中至少一个 R^6 为 $-C\equiv C-(CH_2)_jI_m$；其中 I_m 为造影部分且 j 为 1、2、3、4、5 或 6。

[1190] 实施例 175. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 166 中任一项的化合物，其中至少一个 R^6 为 $-[(CH_2)_jO]_j(CH_2)_jI_m$；其中 I_m 为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。

[1191] 实施例 176. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 166 中任一项的化合物，其中至少一个 R^6 为 $-O[(CH_2)_jO]_j(CH_2)_jI_m$；其中 I_m 为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。

[1192] 实施例 177. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 166 中任一项的化合物，其中至少一个 R^6 为经造影部分取代的任选地经取代的烷基。

[1193] 实施例 178. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 166 中任一项的化合物，其中至少一个 R^6 为 $-C(=O)O(CH_2)_jI_m$；其中 I_m 为造影部分且 j 为 1、2、3、4、5 或 6。

[1194] 实施例 179. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 166 中任一项的化合物，其中至少一个 R^6 为 $-C(=O)(CH_2)_jI_m$；其中 I_m 为造影部分且 j 为 1、2、3、4、5 或 6。

[1195] 实施例 180. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 166 中任一项的化合物，其中至少一个 R^6 为 $-(CH_2)_jNH(CH_2)_jI_m$；其中 I_m 为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。

[1196] 实施例 181. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 166 中任一项的化合物，其中至少一个 R^6 为 $Si(R^9)_2I_m$，其中每个 R^9 为任选地经取代的烷基且其中 I_m 为造影部分。

[1197] 实施例 182. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 166 中任一项的化合物，其中至少一个造影部分与包含结构 $-B(R^{9'})_2(I_m)$ 的基团缔合，其中 I_m 为造影部分，任选地为 ^{18}F。

[1198] 实施例 183. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 166 中任一项的化合物，其中至少一个 R^6 选自由以下各项组成的群组：$-C\equiv C-CH_2CH_2CH_2I_m$、$-C\equiv C-CH_2CH_2I_m$、$-C\equiv C-CH_2I_m$、$-CH_2I_m$、$-(CH_2)_2I_m$、$-(CH_2)_3I_m$、$-(CH_2)_4I_m$、$-(CH_2)_5I_m$、$-(CH_2)_6I_m$、$-OCH_2I_m$、$-O(CH_2)_2I_m$、$-O(CH_2)_3I_m$、$-O(CH_2)_4I_m$、$-O(CH_2)_5I_m$、$-O(CH_2)_6I_m$、$-CH_2O(CH_2)_2I_m$、$-CH(CH_3)O(CH_2)_2I_m$、$-CH_2O(CH_2)_3I_m$、$-CD_2O(CH_2)_2I_m$、$-(CH_2)_2O(CH_2)_2I_m$、$-CHBrC(CH_3)_2I_m$、$-CHClC(CH_3)_2I_m$、$-CHFC(CH_3)_2I_m$、$-C(=O)OCH_2I_m$、$-C(=O)O(CH_2)_2I_m$、$-C(=O)O(CH_2)_3I_m$、$-CH_2NH(CH_2)_2I_m$、$-CH_2NHCH_2I_m$、$-CH_2O(CH_2)_2O(CH_2)_2I_m$、$-CH_2O(CH_2)_2O(CH_2)_3I_m$、$-O(CH_2)_2O(CH_2)_2I_m$、$-C(=O)(CH_2)_2I_m$ 以及 $-C(=O)(CH_2)_3I_m$；任选地，其中 I_m 为 ^{18}F。

[1199] 实施例 184. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 166 中任一项的化合物，其中至少一个 R^6 为造影部分，任选地其中所述造影部分为 ^{18}F。

[1200] 实施例 185. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 166 中任一项的化合物，其中至少一个 R^6 任选地经至少一个 ^2H 取代。

[1201] 实施例 186. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 166 中任一项的化合物，其中至少一个 R^6 为 $-Si(R^9)_3$。

[1202] 实施例 187. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 166 中任一项的化合物，其中至少一个 R^6 为 $-B(R^{9'})_3$。

[1203] 实施例 188. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 187 中任一项的化合物，其中至少一个 R^6 为 $-NO_2$。

[1204] 实施例 189. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 187 中任一项的化合物，其中至少一个 R^6 为卤基。

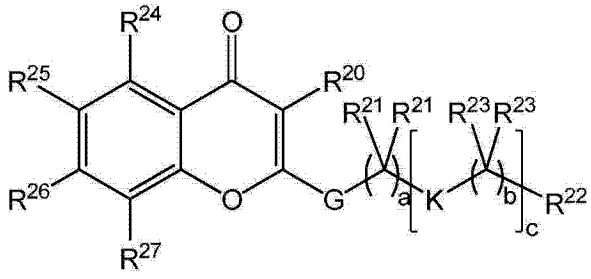
[1205] 实施例 190. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 187 中任一项的化合物，其中至少一个 R^6 为 Cl。

[1206] 实施例 191. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 187 中任一项的化合物，其中至少一个 R^6 为 Br。

[1207] 实施例 192. 如实施例 1 至 13、15 至 70、72 至 124、132 至 161 以及 163 至 187 中任一项的化合物，其中至少一个 R^6 为 F。

[1208] 实施例 193. 在实施例 193 中，提供一种包含下式的化合物：

[1209]



(IX)

[1210] 或其医药学上可接受的盐，其中：

[1211] R^{20} 选自由以下各项组成的群组：氢、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN 以及 $-NO_2$；

[1212] 每个 R^{21} 和 R^{23} 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、卤基、卤烷基以及造影部分，或任选地任何两个 R^{21} 或任何两个 R^{23} 可相连以形成环；

[1213] R^{22} 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、卤基、卤烷基、$-OR^{28}$、$-Si(R^9)_3$、$-B(R^{9'})_3$ 以及造影部分；

[1214] R^{24}、R^{25}、R^{26} 及 R^{27} 各自独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN 以及造影部分；

[1215] 每个 R^7 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个 R^7 可相连以形成环；和

[1216] 每个 R^8 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

[1217] 每个R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及造影部分；

[1218] 每个$R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[1219] R^{28}选自由以下各项组成的群组：氢、任选地经取代的烷基以及任选地经取代的杂烷基；

[1220] G为O、S或NR^{28}；

[1221] a为0、1、2、3或4；

[1222] 每个K独立地为各自任选地经取代的亚芳基、亚杂芳基、亚烯基或亚炔基；

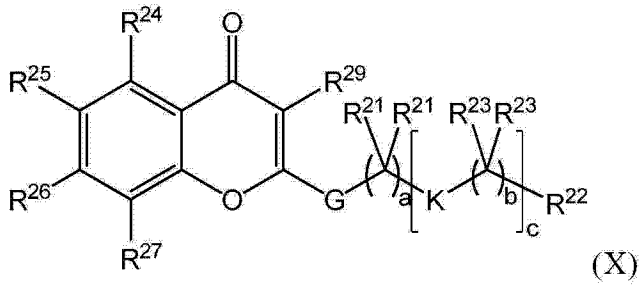
[1223] 每个b独立地为0、1、2、3或4；和

[1224] c为1或2，

[1225] 其限制条件为在所述化合物中存在至少一个造影部分。

[1226] 实施例194. 在实施例194中，提供一种包含下式的化合物：

[1227]



(X)

[1228] 或其医药学上可接受的盐，其中：

[1229] 每个R^{21}和R^{23}独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、卤基、卤烷基以及造影部分，或任选地任何两个R^{21}或任何两个R^{23}可相连以形成环；

[1230] R^{22}选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、卤基、卤烷基、$-OR^{28}$、$-Si(R^9)_3$、$-B(R^{9'})_3$以及造影部分；

[1231] R^{24}、R^{25}、R^{26}及R^{27}各自独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN以及造影部分；

[1232] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及造影部分，或任选地任何两个R^7可相连以形成环；

[1233] 每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及造影部分；

[1234] 每个R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取

代的芳基、卤烷基、卤素以及造影部分；

[1235] 每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及造影部分；

[1236] R^{28} 选自由以下各项组成的群组：氢、任选地经取代的烷基以及任选地经取代的杂烷基；

[1237] R^{29} 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的芳基、任选地经取代的杂芳基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、卤基、卤烷基、-CN、$-NO_2$ 以及造影部分；

[1238] G 为 O、S 或 NR^{28}；

[1239] a 为 0、1、2、3 或 4；

[1240] 每个 K 独立地为各自任选地经取代的亚芳基、亚杂芳基、亚烯基或亚炔基，其限制条件为至少一个 K 为亚烯基或亚炔基；

[1241] 每个 b 独立地为 0、1、2、3 或 4；和

[1242] c 为 1 或 2，

[1243] 其限制条件为在所述化合物中存在至少一个造影部分。

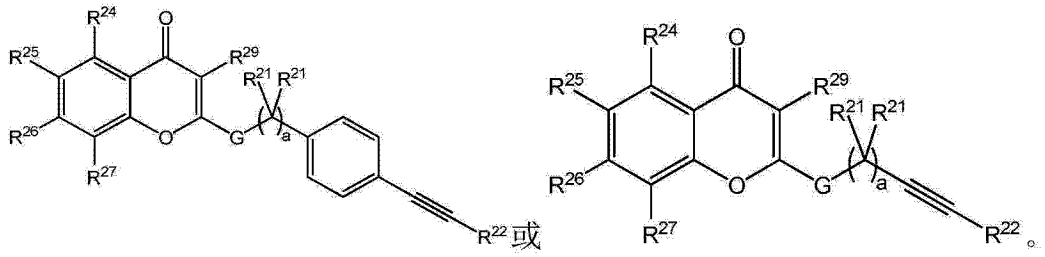
[1244] 实施例 195. 如实施例 193 的化合物，其中 R^{29} 为任选地经取代的烷基。

[1245] 实施例 196. 如实施例 193 的化合物，其中 R^{29} 为甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。

[1246] 实施例 197. 如实施例 193 的化合物，其中 R^{29} 为甲基。

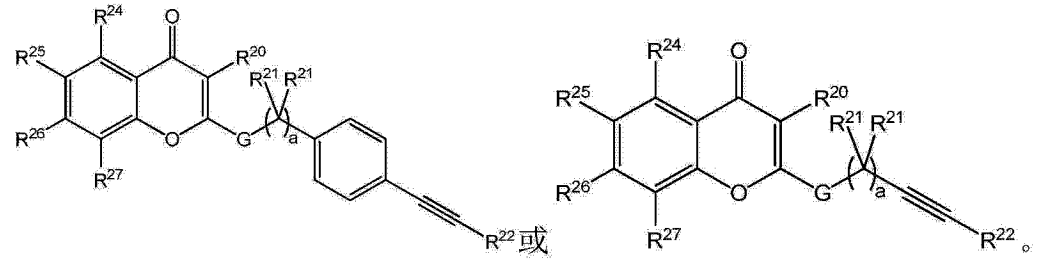
[1247] 实施例 198. 如实施例 194 的化合物，其中所述化合物包含以下结构：

[1248]



[1249] 实施例 199. 如实施例 193 的化合物，其中所述化合物包含以下结构：

[1250]



[1251] 实施例 200. 如实施例 193 至 199 中任一项的化合物，其中 R^{24}、R^{25}、R^{26} 以及 R^{27} 中的每一者为 H。

[1252] 实施例 201. 如实施例 193 至 200 中任一项的化合物，其中 G 为 O。

[1253] 实施例 202. 如实施例 193 至 200 中任一项的化合物，其中 G 为 S。

[1254] 实施例 203. 如实施例 193 至 200 中任一项的化合物，其中 G 为 NR^{28}。

[1255] 实施例 204. 如实施例 193 至 200 中任一项的化合物，其中 G 为 NH。

[1256] 实施例 205. 如实施例 193 至 204 中任一项的化合物，其中 a 为 0。

[1257] 实施例 206. 如实施例 193 至 204 中任一项的化合物，其中 a 为 1。

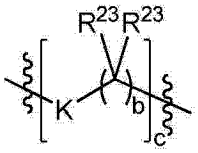
[1258] 实施例 207. 如实施例 193 至 204 中任一项的化合物，其中 a 为 2。

[1259] 实施例 208. 如实施例 193 至 204 中任一项的化合物，其中 a 为 3。

[1260] 实施例 209. 如实施例 193 至 204 中任一项的化合物，其中 a 为 4。

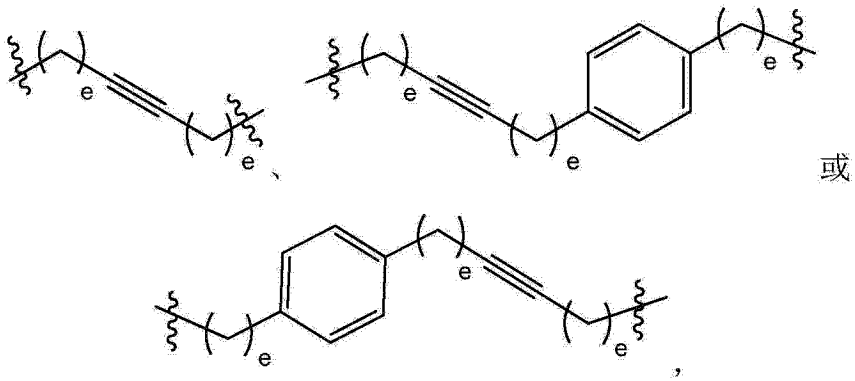
[1261] 实施例 210. 如实施例 193 至 197 或 200 至 209 中任一项的化合物，其中至少一个 K 为亚炔基。

[1262] 实施例 211. 如实施例 193 至 197 或 200 至 209 中任一项的化合物，其中



具有以下结构：

[1263]



[1264] 其中每个 e 独立地为 1、2、3 或 4。

[1265] 实施例 212. 如实施例 193 至 211 中任一项的化合物，其中每个 R^{21} 为 H。

[1266] 实施例 213. 如实施例 193 至 212 中任一项的化合物，其中 R^{22} 为 $-O(CH_2)_jI_m$；其中 I_m 为造影部分且 j 为 1、2、3、4、5 或 6。

[1267] 实施例 214. 如实施例 193 至 212 中任一项的化合物，其中 R^{22} 为 $-(CH_2)_jO(CH_2)_jI_m$；其中 I_m 为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。

[1268] 实施例 215. 如实施例 193 至 212 中任一项的化合物，其中 R^{22} 为 $-[(CH_2)_jO]_j(CH_2)_jI_m$；其中 I_m 为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。

[1269] 实施例 216. 如实施例 193 至 212 中任一项的化合物，其中 R^{22} 为 $-O[(CH_2)_jO]_j(CH_2)_jI_m$；其中 I_m 为造影部分且每个 j 独立地为 1、2、3、4、5 或 6。

[1270] 实施例 217. 如实施例 193 至 212 中任一项的化合物，其中 R^{22} 为经造影部分取代的任选地经取代的烷基。

[1271] 实施例 218. 如实施例 193 至 212 中任一项的化合物，其中至少一个造影部分存在于 R^{21}、R^{22}、R^{23}、R^{24}、R^{25}、R^{26} 或 R^{27} 中。

[1272] 实施例 219. 如实施例 193 至 212 中任一项的化合物，其中至少一个造影部分存在于 R^{21}、R^{22}、R^{23}、R^{24}、R^{25}、R^{26}、R^{27} 或 R^{29} 中。

[1273] 实施例 220. 如实施例 193 至 212 中任一项的化合物，其中至少一个造影部分存在

于 R^{21}、R^{22}或 R^{23}中。

[1274] 实施例 221. 如实施例 193 至 212 中任一项的化合物，其中至少一个造影部分存在于 R^{22}中。

[1275] 实施例 222. 如实施例 193 至 212 中任一项的化合物，其中 R^{22}包含至少一个造影部分。

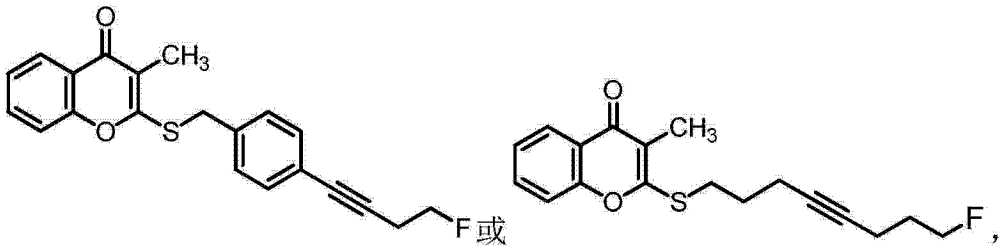
[1276] 实施例 223. 如实施例 193 至 212 中任一项的化合物，其中 R^{22}为造影部分。

[1277] 实施例 224. 如实施例 193 至 223 中任一项的化合物，其中至少一个造影部分选自由以下各项组成的群组：^{11}C、^{13}N、^{18}F、^{76}Br、^{89}Zr、^{123}I、^{124}I、^{125}I、^{131}I、^{99m}Tc、^{95}Tc、^{111}In、^{62}Cu、^{64}Cu、^{67}Ga 以及 ^{68}Ga。

[1278] 实施例 225. 如实施例 193 至 224 中任一项的化合物，其中至少一个造影部分为 ^{18}F。

[1279] 实施例 226. 如实施例 194 的化合物，其中所述化合物选自由以下各项组成的群组：

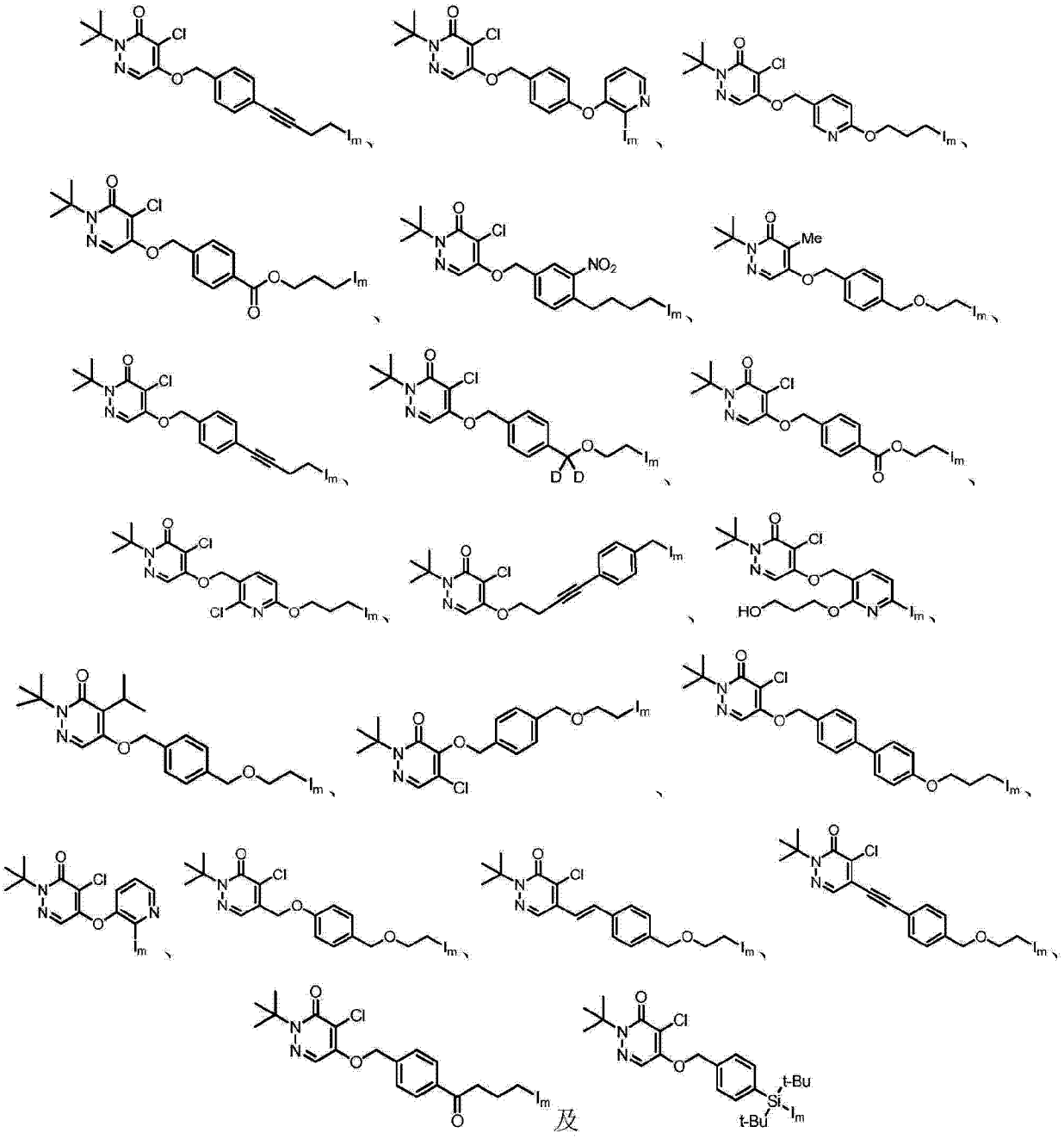
[1280]



[1281] 或其医药学上可接受的盐，其中 F 任选地为 ^{18}F。

[1282] 实施例 227. 在实施例 227 中，提供选自由以下各项组成的群组的化合物：

[1283]

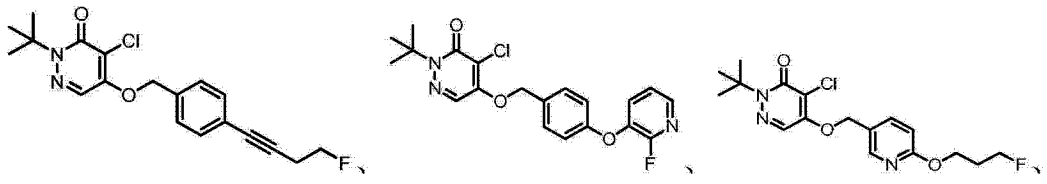


及

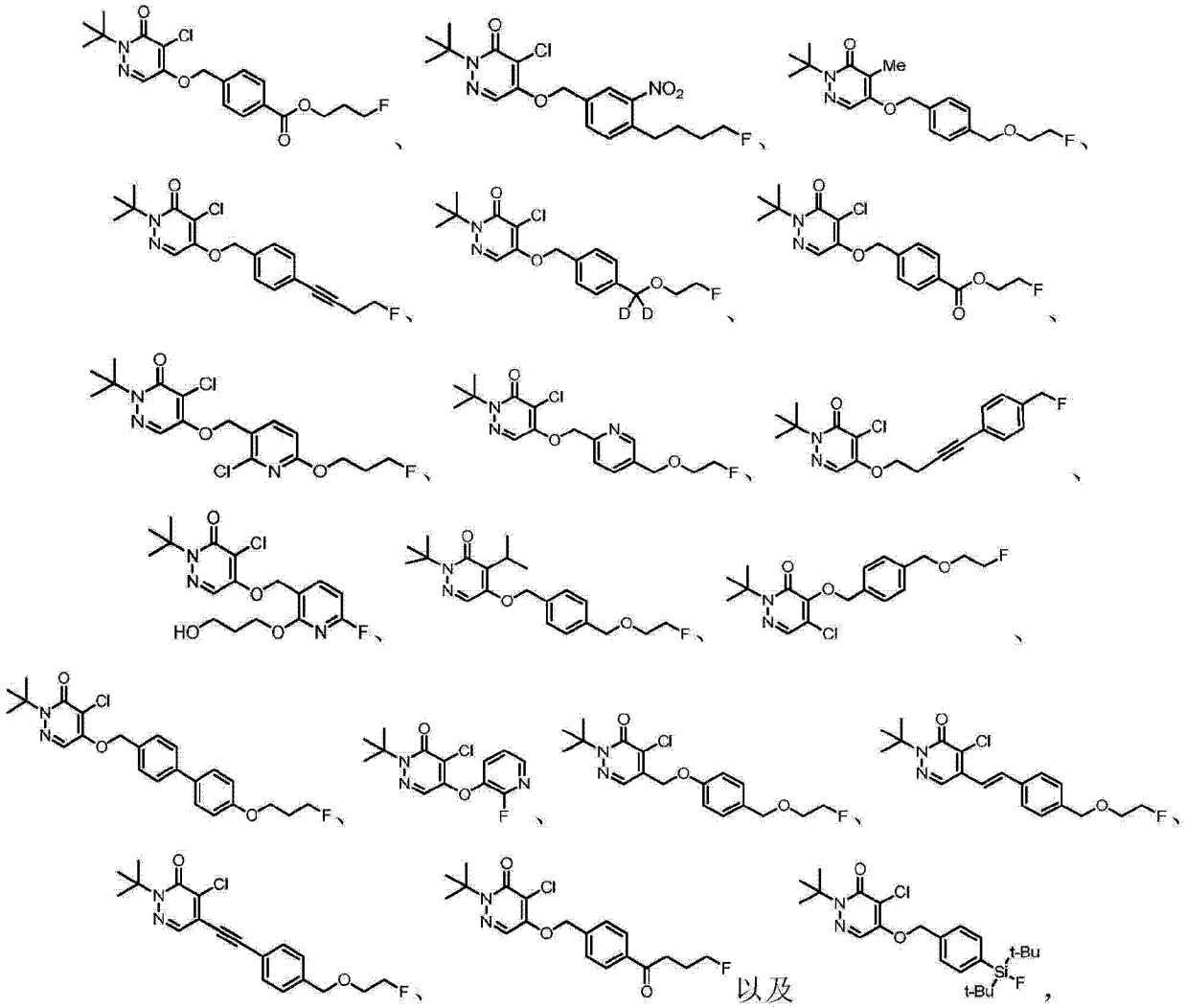
[1284] 或其医药学上可接受的盐，其中 I_m 为造影部分。

[1285] 实施例 228. 如实施例 227 的化合物，其中所述化合物选自由以下各项组成的群组：

[1286]



[1287]

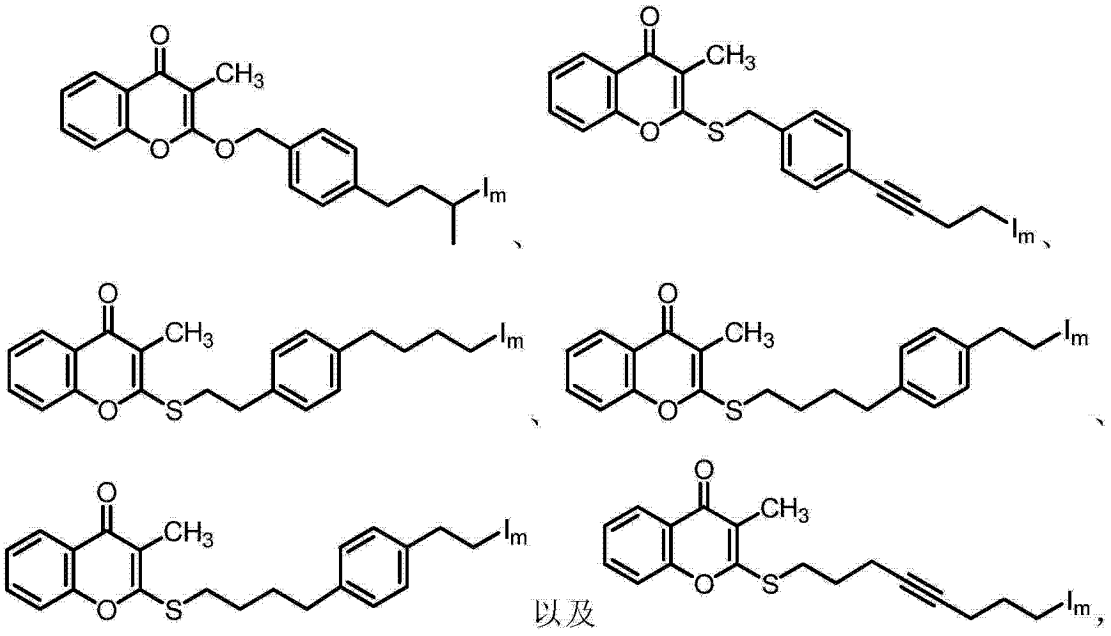


以及

[1288] 或其医药学上可接受的盐，其中每个 F 任选地为 ^{18}F。

[1289] 实施例 229. 在实施例 229 中，提供选自由以下各项组成的群组的化合物：

[1290]

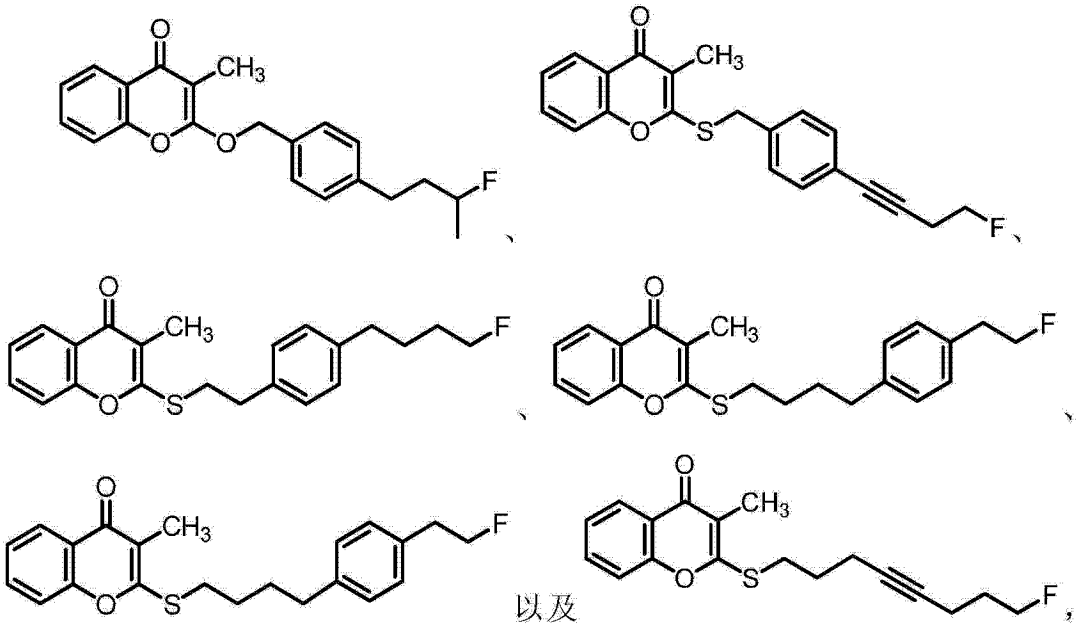


以及

[1291] 或其医药学上可接受的盐，其中 I_m 为造影部分。

[1292] 实施例 230. 如实施例 229 的化合物，其中所述化合物选自由以下各项组成的群组：

[1293]



[1294] 或其医药学上可接受的盐，其中每个 F 任选地为 ^{18}F。

[1295] 实施例 231. 在实施例 231 中，提供一种医药组合物，其包含如任一上述实施例的化合物或其盐，以及任选的医药学上可接受的赋形剂。

[1296] 实施例 232. 在实施例 232 中，提供一种无菌水溶液，其包含如任一上述实施例的化合物或其盐。

[1297] 实施例 233. 一种如任一上述实施例的化合物或其盐的用途，其用作造影剂。

[1298] 实施例 234. 一种如任一上述实施例的化合物或其盐的用途，其用于心肌灌注造影。

[1299] 实施例 235. 一种如任一上述实施例的化合物或其盐的用途，其用于制造供检测、造影或监控心肌灌注用的药剂。

[1300] 实施例 236. 在实施例 236 中，提供一种对个体的一部分进行造影的方法，所述方法包含：

[1301] 向个体投予如任一上述实施例的化合物或其盐或如实施例 231 的组合物或如实施例 232 的无菌水溶液；和

[1302] 撷取所述个体的一部分的至少一个图像。

[1303] 实施例 237. 在实施例 237 中，提供一种对个体的一部分进行造影的方法，所述方法包含：

[1304] 向个体投予如任一上述实施例或其盐的化合物或其盐或如实施例 231 的医药组合物或如实施例 232 的无菌水溶液；

[1305] 检测由所述化合物所放出的辐射；和

[1306] 自其形成图像。

[1307] 实施例 238. 如实施例 237 的方法，其中经造影的所述个体的一部分为心脏的一部

分。

[1308] 实施例 239. 在实施例 239 中，提供一种诊断试剂盒，其包含一或多个含有如任一上述实施例的化合物或其盐之前驱体和任选的其它组分的小瓶。

[1309] 实施例 240. 如实施例 239 的诊断试剂盒，其中所述诊断试剂盒用于制备用于造影、检测和 / 或监控个体的心肌灌注的诊断剂。

[1310] 实施例 241. 如实施例 239 或 240 的诊断试剂盒，其中所述其它组分选自由以下各项组成的群组 ：辅助配位体、还原剂、转移配位体、缓冲液、冻干助剂、稳定化助剂、增溶助剂以及抑菌剂。

[1311] 实施例 242. 在实施例 242 中，提供一种对心肌灌注进行造影的方法，所述方法包含 ：

[1312] 向患者投予如任一上述实施例的化合物或其盐或如实施例 231 的医药组合物或如实施例 232 的无菌水溶液 ；和

[1313] 使用诊断造影扫描所述患者。

[1314] 实施例 243. 在实施例 243 中，提供一种检测心肌灌注的方法，所述方法包含 ：

[1315] 向患者投予如任一上述实施例的化合物或其盐或如实施例 231 的医药组合物或如实施例 232 的无菌水溶液 ；和

[1316] 使用诊断造影扫描所述患者。

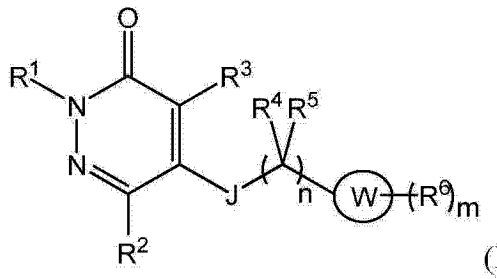
[1317] 实施例 244. 在实施例 244 中，提供一种监控心肌灌注的方法，所述方法包含 ：

[1318] 向患者投予如任一上述实施例的化合物或其盐或如实施例 231 的医药组合物或如实施例 232 的无菌水溶液 ；和

[1319] 使用诊断造影扫描所述患者。

[1320] 实施例 245. 在实施例 245 中，提供一种包含以下结构的化合物 ：

[1321]



(XI)

[1322] 或其盐 ；其中

[1323] R^1选自由以下各项组成的群组 ：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及离去基 ；

[1324] R^2选自由以下各项组成的群组 ：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及离去基 ；

[1325] R^3选自由以下各项组成的群组 ：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及离去基 ；

[1326] J 选自由以下各项组成的群组 :$N(R^7)$、S、O、C(= O)、C(= O)O、OC(= O)、C(= O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键 ;

[1327] R^4和 R^5各自独立地选自由氢、任选地经取代的烷基以及离去基组成的群组,或任选地 R^4和 R^5中的任何两者相连以形成环 ;

[1328] n 为 0、1、2 或 3 ;

[1329] W 为杂芳基、萘基、杂环基或芳基 ;

[1330] 每个 R^6独立地选自由以下各项组成的群组 :氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、-C(= O)R^8、-C(= O)OR^8、-OC(= O)R^8、-C(= O)$N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及离去基 ;

[1331] m 为 0、1、2、3、4、5、6 或 7 ;

[1332] 每个 R^7独立地选自由以下各项组成的群组 :氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基,或任选地任何两个 R^7可相连以形成环 ;

[1333] 每个 R^8独立地选自由以下各项组成的群组 :氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基 ;

[1334] 每个 R^9独立地选自由以下各项组成的群组 :氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及离去基 ;和

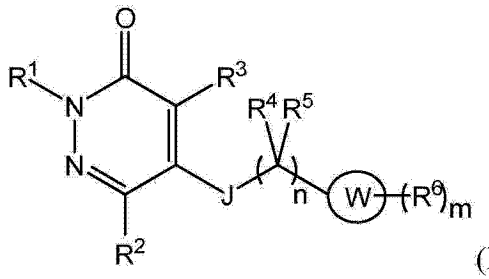
[1335] 每个 $R^{9'}$独立地选自由以下各项组成的群组 :卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基,

[1336] 其限制条件为在所述化合物中存在至少一个离去基 ;和

[1337] 其限制条件为当 W 为芳基时,a)R^3不为卤基、烷基或卤烷基,或 b) 至少一个 R^6选自由以下各项组成的群组 :任选地经取代的炔基、任选地经取代的烯基、任选地经 -CN 取代的烷基、任选地经 -C(= O)OR^8取代的烷基、任选地经 -C(= O)R^8取代的烷基、任选地经 $-N(R^7)_2$取代的烷基、-CN、$-NO_2$、$-N(R^7)_2$、-C(= O)OR^8、-OC(= O)R^8、-C(= O)R^8、-C(= O)$N(R^7)_2$以及 $-N(R^7)C(=O)R^8$。

[1338] 实施例 246. 如实施例 245 化合物,其中所述化合物包含以下结构 :

[1339]



(XII)

[1340] 或其盐 ;其中

[1341] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及离去基；

[1342] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及离去基；

[1343] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及离去基；

[1344] J选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O以及一键；

[1345] R^4和R^5各自独立地选自由氢、任选地经取代的烷基以及离去基组成的群组，或任选地R^4和R^5中的任何两者相连以形成环；

[1346] n为0、1、2或3；

[1347] W为杂芳基、萘基或杂环基；

[1348] 每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、-C(=O)R^8、-C(=O)OR^8、-OC(=O)R^8、-C(=O)$N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及离去基；

[1349] m为0、1、2、3、4、5、6或7；

[1350] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个R^7可相连以形成环；和

[1351] 每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

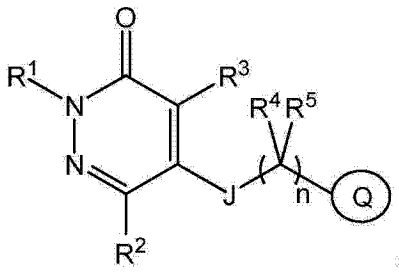
[1352] 每个R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及离去基；和

[1353] 每个$R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基，

[1354] 其限制条件为在所述化合物中存在至少一个离去基。

[1355] 实施例247. 如实施例245的化合物，其中所述化合物包含以下结构：

[1356]



(XIII)

[1357] 或其盐；其中

[1358] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及离去基；

[1359] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及离去基；

[1360] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及离去基；

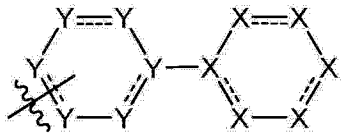
[1361] J选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O以及一键；

[1362] R^4和R^5各自独立地选自由氢、任选地经取代的烷基以及离去基组成的群组，或任选地R^4和R^5中的任何两者相连以形成环；

[1363] n为0、1、2或3；

[1364] Q具有以下结构：

[1365]



[1366] 每个Y和每个X独立地选自由C、$C(R^6)$、$C(R^6)_2$、N、NR^7、O及S组成的群组，其限制条件为至少一个Y不为C或$C(R^6)$；

[1367] 每个------独立地为单键或双键；

[1368] 每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及离去基；

[1369] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个R^7可相连以形成环；

[1370] 每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

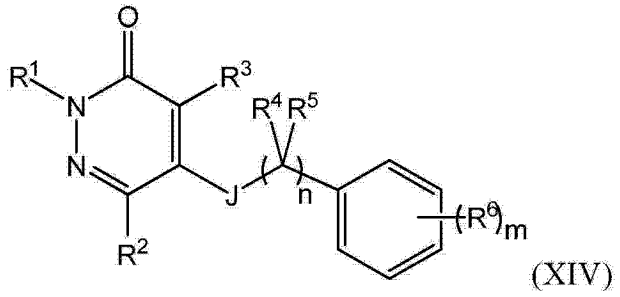
[1371] 每个R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及离去基；和

[1372] 每个$R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基，

[1373] 其限制条件为在所述化合物中存在至少一个离去基。

[1374] 实施例 248. 如实施例 245 的化合物，其中所述化合物包含以下结构：

[1375]



(XIV)

[1376] 或其盐；其中

[1377] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及离去基；

[1378] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及离去基；

[1379] R^3选自由以下各项组成的群组：氢、未经取代的烷基或任选地经除卤素以外的部分取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、-CN 以及 $-NO_2$；

[1380] J 选自由以下各项组成的群组：$N(R^7)$、S、O、$C(=O)$、$C(=O)O$、$OC(=O)$、$C(=O)N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键；

[1381] R^4和 R^5各自独立地选自由氢、任选地经取代的烷基以及离去基组成的群组，或任选地 R^4和 R^5中的任何两者相连以形成环；

[1382] n 为 0、1、2 或 3；

[1383] 每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及离去基；

[1384] m 为 0、1、2、3、4 或 5；

[1385] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取

代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个 R^7 可相连以形成环；和

[1386] 每个 R^8 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

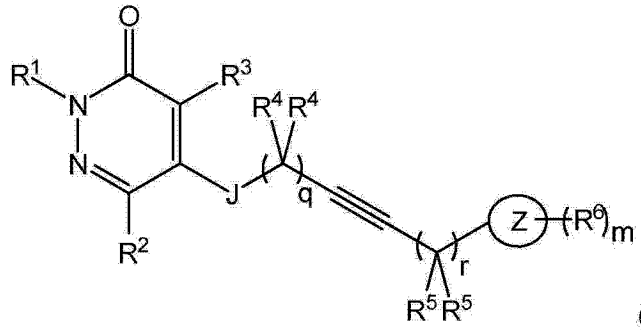
[1387] 每个 R^9 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及离去基；和

[1388] 每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基，

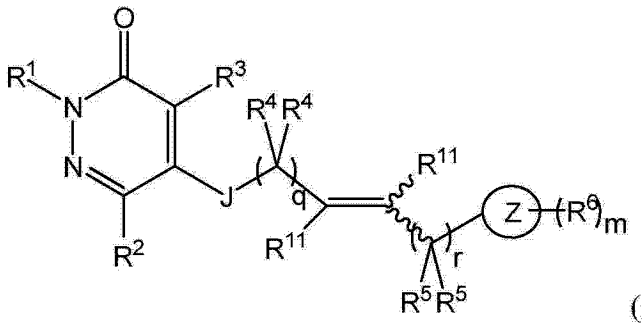
[1389] 其限制条件为在所述化合物中存在至少一个离去基。

[1390] 实施例 249. 在实施例 249 中，提供一种包含以下结构的化合物：

[1391]



(XV)或



(XVI)，

[1392] 或其盐；其中

[1393] R^1 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及离去基；

[1394] R^2 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$ 以及离去基；

[1395] R^3 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-CN$、$-NO_2$ 以及离去基；

[1396] J 选自由以下各项组成的群组：$N(R^7)$、S、O、$C(=O)$、$C(=O)O$、$OC(=O)$、$C(=O)N(R^7)$、$N(R^7)C(=O)$、CH_2O 以及一键；

[1397] 每个 R^4、R^5和 R^{11}独立地选自由氢、任选地经取代的烷基以及离去基组成的群组，或任选地任何两个 R^4或任何两个 R^5相连以形成环；

[1398] q 以及 r 各自独立地为 0、1、2 或 3；

[1399] Z 选自由以下各项组成的群组：芳基、杂芳基、杂环基以及一键；

[1400] 每个 R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及离去基；

[1401] m 为 0、1、2、3、4、5、6 或 7；

[1402] 每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个 R^7可相连以形成环；

[1403] 每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

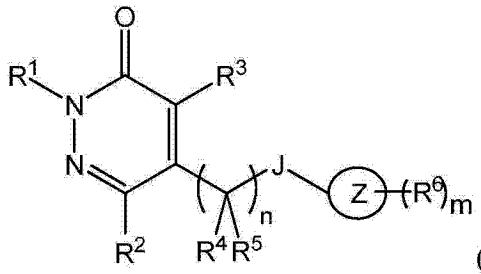
[1404] 每个 R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及离去基；和

[1405] 每个 $R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基，

[1406] 其限制条件为在所述化合物中存在至少一个离去基。

[1407] 实施例 250. 在实施例 250 中，提供一种包含以下结构的化合物：

[1408]



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[1409] 或其盐；其中

[1410] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基以及离去基；

[1411] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、$-NO_2$、卤烷基以及离去基；

[1412] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷

基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及离去基；

[1413] J选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)_2$、$N(R^7)C(=O)$以及$-CH_2O$；

[1414] 每个R^4和R^5独立地选自由氢、任选地经取代的烷基以及离去基组成的群组，或任选地任何两个R^4或任何两个R^5相连以形成环；

[1415] n为1、2或3；

[1416] Z选自由以下各项组成的群组：芳基、杂芳基、杂环基以及一键；

[1417] 每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、-C(=O)R^8、-C(=O)OR^8、-OC(=O)R^8、-C(=O)$N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及离去基；

[1418] m为0、1、2、3、4、5、6或7；

[1419] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个R^7可相连以形成环；和

[1420] 每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

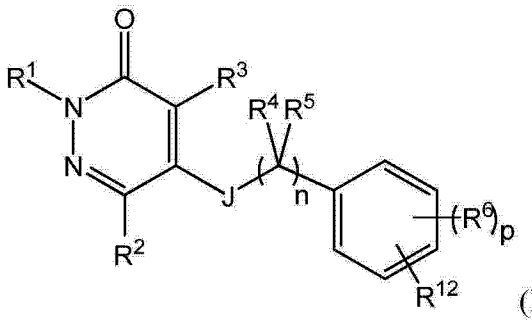
[1421] 每个R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及离去基；和

[1422] 每个$R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基，

[1423] 其限制条件为在所述化合物中存在至少一个离去基。

[1424] 实施例251. 如实施例245的化合物，其中所述化合物包含以下结构：

[1425]



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[1426] 或其盐；其中

[1427] R^1选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经

取代的杂芳基以及离去基；

[1428] R^2选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$以及离去基；

[1429] R^3选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN、$-NO_2$以及离去基；

[1430] J选自由以下各项组成的群组：$N(R^7)$、S、O、C(=O)、C(=O)O、OC(=O)、C(=O)$N(R^7)$、$N(R^7)C(=O)$、CH_2O以及一键；

[1431] R^4和R^5各自独立地选自由氢、任选地经取代的烷基以及离去基组成的群组，或任选地R^4和R^5中的任何两者相连以形成环；

[1432] n为0、1、2或3；

[1433] 每个R^6独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-N(R^7)_2$、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN、$-Si(R^9)_3$、$-B(R^{9'})_3$、$-OR^8$以及离去基；

[1434] p为0、1、2、3或4；

[1435] 每个R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个R^7可相连以形成环；

[1436] 每个R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

[1437] R^{12}选自由以下各项组成的群组：任选地经取代的炔基、任选地经取代的烯基、经-CN取代的烷基、经$-C(=O)OR^8$取代的烷基、经$-C(=O)R^8$取代的烷基、经$-N(R^7)_2$取代的烷基、-CN、$-NO_2$、$-N(R^7)_2$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)R^8$、$-C(=O)N(R^7)_2$以及$-N(R^7)C(=O)R^8$；

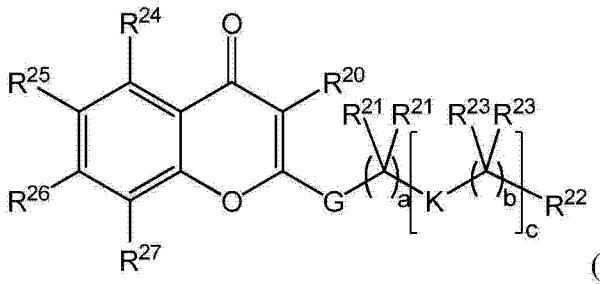
[1438] 每个R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及离去基；和

[1439] 每个$R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基，

[1440] 其限制条件为在所述化合物中存在至少一个离去基。

[1441] 实施例252. 在实施例252中，提供一种包含下式的化合物：

[1442]



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[1443] 或其盐；其中

[1444] R^{20}选自由以下各项组成的群组：氢、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-CN 以及 $-NO_2$；

[1445] 每个 R^{21}和 R^{23}独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、卤基、卤烷基以及离去基，或任选地任何两个 R^{21}或任何两个 R^{23}可相连以形成环；

[1446] R^{22}选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、卤基、卤烷基、$-OR^{28}$、$-Si(R^9)_3$、$-B(R^{9'})_3$以及离去基；

[1447] R^{24}、R^{25}、R^{26}和 R^{27}各自独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$、-OH、$-C(=O)R^8$、$-C(=O)OR^8$、$-OC(=O)R^8$、$-C(=O)N(R^7)_2$、$-N(R^7)C(=O)R^8$、-CN 以及离去基；

[1448] 每个 R^7独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个 R^7可相连以形成环；

[1449] 每个 R^8独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

[1450] 每个 R^9独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及离去基；

[1451] 每个 $R^{9'}$独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基；

[1452] R^{28}选自由以下各项组成的群组：氢、任选地经取代的烷基和任选地经取代的杂烷基；

[1453] G 为 O、S 或 NR^{28}；

[1454] a 为 0、1、2、3 或 4；

[1455] 每个 K 独立地为各自任选地经取代的亚芳基、亚杂芳基、亚烯基或亚炔基；

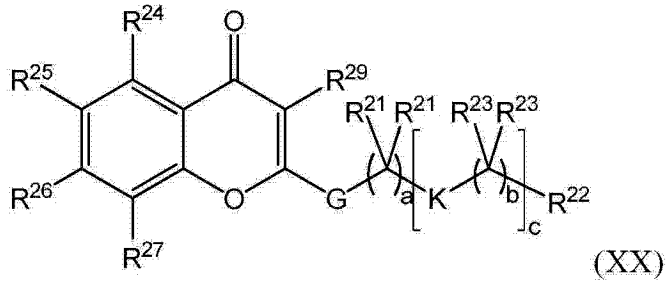
[1456] 每个 b 独立地为 0、1、2、3 或 4；和

[1457] c 为 1 或 2，

[1458] 其限制条件为在所述化合物中存在至少一个离去基。

[1459] 实施例 253. 在实施例 253 中，提供一种包含下式的化合物：

[1460]



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[1461] 或其盐；其中

[1462] 每个 R^{21} 和 R^{23} 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、卤基、卤烷基及离去基，或任选地任何两个 R^{21} 或任何两个 R^{23} 可相连以形成环；R^{22} 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、卤基、卤烷基、$-OR^{28}$、$-Si(R^{9})_3$、$-B(R^{9'})_3$ 以及离去基；

[1463] R^{24}、R^{25}、R^{26} 以及 R^{27} 各自独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的芳氧基、任选地经取代的杂芳氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、$-NO_2$、-OH、$-C(=O)R^{8}$、$-C(=O)OR^{8}$、$-OC(=O)R^{8}$、$-C(=O)N(R^{7})_2$、$-N(R^{7})C(=O)R^{8}$、-CN 以及离去基；

[1464] 每个 R^{7} 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的烯基、任选地经取代的炔基、任选地经取代的杂烷基、任选地经取代的烷氧基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基以及离去基，或任选地任何两个 R^{7} 可相连以形成环；

[1465] 每个 R^{8} 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的烷氧基烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤烷基以及离去基；

[1466] 每个 R^{9} 独立地选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的芳基、卤烷基、卤素以及离去基；

[1467] 每个 $R^{9'}$ 独立地选自由以下各项组成的群组：卤基、任选地经取代的烷基、任选地经取代的芳基以及离去基；

[1468] R^{28} 选自由以下各项组成的群组：氢、任选地经取代的烷基和任选地经取代的杂烷基；

[1469] R^{29} 选自由以下各项组成的群组：氢、任选地经取代的烷基、任选地经取代的杂烷基、任选地经取代的芳基、任选地经取代的杂芳基、卤基、卤烷基、-C、$-NO_2$ 以及离去基；

[1470] G 为 O、S 或 NR^{28}；

[1471] a 为 0、1、2、3 或 4；

[1472] 每个 K 独立地为各自任选地经取代的亚芳基、亚杂芳基、亚烯基或亚炔基，其限制条件为至少一个 K 为亚烯基或亚炔基；

[1473] 每个 b 独立地为 0、1、2、3 或 4；和

[1474] c 为 1 或 2，

[1475] 其限制条件为在所述化合物中存在至少一个离去基。

[1476] 实施例 254. 在实施例 254 中，提供一种诊断试剂盒，其包含一或多个含有如实施例 245 至 253 中任一项的化合物或其盐和任选的其它组分的小瓶。

[1477] 实施例 255. 如实施例 254 的诊断试剂盒，其中所述诊断试剂盒用于制备用于造影、检测和 / 或监控个体的心肌灌注的诊断剂。

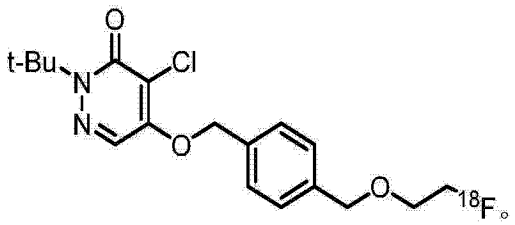
[1478] 实施例 256. 如实施例 254 或 255 的诊断试剂盒，其中所述其它组分选自由以下各项组成的群组：辅助配位体、还原剂、转移配位体、缓冲液、冻干助剂、稳定化助剂、增溶助剂以及抑菌剂。

[1479] 实施例 257. 在实施例 257 中，提供一种用于形成造影剂的方法，所述方法包含如实施例 245 至 253 中任一项的化合物或其盐与含 ^{18}F 物质反应以产生包含 ^{18}F 的造影剂。

[1480] 实施例 258. 在实施例 258 中，提供一种用于制备造影剂的卡匣，其包含如图 17 所示而排列的组件。

[1481] 实施例 259. 如实施例 258 中的卡匣，其中所述造影剂具有下式：

[1482]



[1483] 实施例 260. 在实施例 260 中，提供一种用于合成造影剂的装置，其包含多个按以下顺序排列的旋塞阀歧管的线性排列：

[1484] 1) 与气体入口和 $[^{18}O]H_2O$ 回收连接的鲁尔接头 2；

[1485] 2) 阴离子交换滤筒 - 管柱溶离溶液；

[1486] 3) 用于乙腈的针接头；

[1487] 4) 空注射器；

[1488] 5) 具有造影剂前驱体的溶液的储集器；

[1489] 6) 反应容器；

[1490] 7) 通向 HPLC 的出口；

[1491] 8) 具有稳定剂的溶液的注射器；

[1492] 9) 来自 HPLC 的入口；

[1493] 10) 乙醇储集器；

[1494] 11) 具有稳定剂的溶液的注射器；

[1495] 12) 具有水的注射器；

[1496] 13) 最终产物小瓶；

[1497] 14) 空注射器；和

[1498] 15) 反应容器和排气口。

[1499] 实施例 261. 在实施例 261 中，提供一种用于合成造影剂的装置，其包含多个按以下顺序排列的旋塞阀歧管的线性排列：

[1500] 1) 与气体入口及 $[^{18}O]H_2O$ 回收连接的鲁尔接头 2 ;

[1501] 2) 阴离子交换滤筒 - 管柱溶离溶液 ;

[1502] 3) 具有造影剂前驱体的溶液的储集器 ;

[1503] 4) 空注射器 ;

[1504] 5) 用于乙腈的针接头 ;

[1505] 6) 反应容器 ;

[1506] 7) 通向 HPLC 的出口 ;

[1507] 8) 具有稳定剂的溶液的注射器 ;

[1508] 9) 来自 HPLC 的入口 ;

[1509] 10) 乙醇储集器 ;

[1510] 11) 具有稳定剂的溶液的注射器 ;

[1511] 12) 具有水的注射器 ;

[1512] 13) 最终产物小瓶 ;

[1513] 14) 空注射器 ;和

[1514] 15) 反应容器和排气口。

[1515] 实施例 262. 在实施例 262 中,提供一种用于合成造影剂的装置,其包含多个按以下顺序排列的旋塞阀歧管的线性排列 :

[1516] 1) 与气体入口和 $[^{18}O]H_2O$ 回收连接的鲁尔接头 2 ;

[1517] 2) 阴离子交换滤筒 - 管柱溶离溶液 ;

[1518] 3) 具有造影剂前驱体的溶液的储集器 ;

[1519] 4) 空注射器 ;

[1520] 5) 用于乙腈的针接头 ;

[1521] 6) 反应容器 ;

[1522] 7) 通向 HPLC 的出口 ;

[1523] 8) 具有稳定剂的溶液的注射器 ;

[1524] 9) 来自 HPLC 的入口 ;

[1525] 10) 乙醇储集器 ;

[1526] 11) 最终产物小瓶 ;

[1527] 12) 具有水的注射器 ;

[1528] 13) 具有稳定剂的溶液的注射器 ;

[1529] 14) 空注射器 ;和

[1530] 15) 反应容器和排气口。

[1531] 实施例 263. 在实施例 263 中,提供一种用于合成造影剂的装置,其包含多个按以下顺序排列的旋塞阀歧管的线性排列 :

[1532] 1) 与气体入口和 $[^{18}O]H_2O$ 回收连接的鲁尔接头 2 ;

[1533] 2) 阴离子交换滤筒 - 管柱溶离溶液 ;

[1534] 3) 用于乙腈的针接头 ;

[1535] 4) 空注射器 ;

[1536] 5) 具有造影剂前驱体的溶液的储集器 ;

[1537] 6) 反应容器；

[1538] 7) 通向 HPLC 的出口；

[1539] 8) 具有稳定剂的溶液的注射器；

[1540] 9) 来自 HPLC 的入口；

[1541] 10) 乙醇储集器；

[1542] 11) 最终产物小瓶；

[1543] 12) 具有水的注射器；

[1544] 13) 具有稳定剂的溶液的注射器；

[1545] 14) 空注射器；和

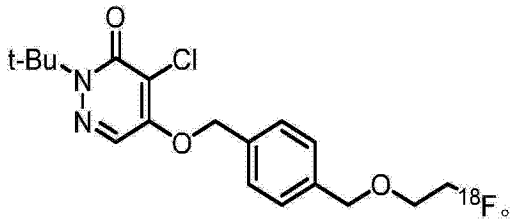
[1546] 15) 反应容器和排气口。

[1547] 实施例 264. 如实施例 260 至 263 中任一项的装置，其进一步包含管。

[1548] 实施例 265. 如实施例 260 至 264 中任一项的装置，其进一步包含造影剂合成模块，其中所述装置流体连接到所述装置。

[1549] 实施例 266. 如实施例 260 至 265 中任一项的装置，其中所述装置能够制备包含下式的造影剂：

[1550]



。

[1551] 实施例 267. 如实施例 260 至 266 中任一项的装置，其中稳定剂溶液包含含有抗坏血酸或其盐的溶液。

[1552] 实施例 268. 如实施例 267 中任一项的装置，其中在位置 8 处的具有抗坏血酸或其盐溶液的注射器包含 pH 值 2 的抗坏血酸溶液。

[1553] 实施例 269. 如实施例 260 至 268 中任一项的装置，其中在位置 11 处的具有抗坏血酸或其盐溶液的注射器包含 pH 值 5.8 的抗坏血酸溶液。

[1554] 定义

[1555] 为方便起见，说明书、实例及随附申请专利范围中所用的某些术语列于此。

[1556] 下文较详细描述特定官能基及化学术语的定义。为达成本发明的目的，根据元素周期表 (Periodic Table of the Elements), CAS 版，化学与物理手册 (Handbook of Chemistry and Physics), 第 75 版封面内页来鉴别化学元素，且特定官能基一般系如其中所述来定义。此外，有机化学以及特定官能部分及反应性的一般原理描述于有机化学 (Organic Chemistry), 汤玛斯·索威尔 (Thomas Sorrell), 大学科学书籍 (University Science Books), 索萨利托 (Sausalito):1999，其全部内容以引用的方式并入本文中。

[1557] 本发明的某些化合物可以特定几何或立体异构形式存在。本发明涵盖属于本发明范畴内的所有所述化合物，其包括顺式异构体及反式异构体、R- 对映异构体以及 S- 对映异构体、非对应异构体、(D)- 异构体、(L)- 异构体、其外消旋混合物以及其其它混合物。如烷基的取代基中可存在其它不对称碳原子。意欲将所有所述异构体以及其混合物包括于本发

明内。

[1558] 可根据本发明采用含有各种异构体比率中任一比率的异构体混合物。例如，在组合仅两种异构体的情形下，含有 50:50、60:40、70:30、80:20、90:10、95:5、96:4、97:3、98:2、99:1 或 100:0 异构体比率的混合物均涵盖于本发明中。所属领域的技术人员易了解，涵盖类似比率的较复杂异构体混合物。

[1559] 例如如果需要本发明化合物的特定对映异构体，则其可通过不对称合成或通过对掌性助剂衍生来制备，其中分离所得非对映异构体混合物且裂解辅助基团以提供纯的所需对映异构体。或者，如果分子含有碱性官能基（如氨基）或酸性官能基（如羧基），则与适当光学活性酸或碱形成非对映异构盐，随后通过本领域中众所周知的分步结晶或色谱方式解析由此形成的非对映异构体，且随后回收纯对映异构体。

[1560] 如本文所用的术语“脂肪族基”包括饱和以及不饱和非芳香族直链（即未分支）、分支链、非环状和环状（即碳环）烃类，其任选地经一或多个官能基取代。如所属领域的技术人员将了解，本文的“脂肪族基”意欲包括（但不限于）烷基、烯基、炔基、环烷基、环烯基以及环炔基部分。因此，如本文所用，术语“烷基”包括直链、分支链和环状烷基。类似规定适用于其它通用术语，如“烯基”、“炔基”等。此外，如本文所用，术语“烷基”、“烯基”、“炔基”等涵盖经取代和未经取代的基团。在某些实施例中，如本文所用，“脂肪族基”用于指示具有 1-20 个碳原子的脂肪族基团（环状、非环状、经取代、未经取代、分支链或未分支）。脂肪族基团取代基包括（但不限于）本文所述的致使形成稳定部分的任何取代基（例如脂肪族基、烷基、烯基、炔基、杂脂肪族基、杂环基、芳基、杂芳基、酰基、侧氧基 (oxo)、亚氨基、硫代侧氧基、氰基、异氰基、氨基、叠氮基、硝基、羟基、硫醇、卤基、脂肪族氨基、杂脂肪族氨基、烷氨基、杂烷基氨基、芳氨基、杂芳基氨基、烷芳基、芳烷基、脂肪族氧基、杂脂肪族氧基、烷氧基、杂烷氧基、芳氧基、杂芳氧基、脂肪族硫氧基、杂脂肪族硫氧基、烷基硫氧基、杂烷基硫氧基、芳基硫氧基、杂芳基硫氧基、酰氧基等，其各自可经进一步取代或可未经进一步取代）。

[1561] 如本文所用，术语“烷基”具有其在本领域中的一般含义且指饱和脂肪族基团的基团，包括直链烷基、分支链烷基、环烷基（脂环）基团、经烷基取代的环烷基以及经环烷基取代的烷基。在一些情况下，烷基可为低碳烷基，即具有 1 至 10 个碳原子的烷基（例如甲基、乙基、丙基、丁基、戊基、己基、庚基、辛基、壬基或癸基）。在一些实施例中，直链或分支链烷基可在其主链中具有 30 个或 30 个以下碳原子，且在一些情况下具有 20 个或 20 个以下碳原子。在一些实施例中，直链或分支链烷基可在其主链中具有 12 个或 12 个以下（例如对于直链为 C_1-C_{12}、对于分支链为 C_3-C_{12}）、6 个或 6 个以下，或 4 个或 4 个以下碳原子。同样地，环烷基可在其环结构中具有 3-10 个碳原子，或在环结构中具有 5、6 或 7 个碳。烷基的实例包括（但不限于）甲基、乙基、丙基、异丙基、环丙基、丁基、异丁基、叔丁基、环丁基、己基以及环己基。

[1562] 如本文所用的术语“亚烷基”指二价烷基。“亚烷基”基团为聚亚甲基，即 $-(CH_2)_z-$，其中 z 为正整数，例如 1 至 20、1 至 10、1 至 6、1 至 4、1 至 3、1 至 2 或 2 至 3。经取代的亚烷基链为一或多个亚甲基氢原子经取代基置换的聚亚甲基。适合取代基包括本文针对经取代的脂肪族基团所述的取代基。

[1563] 一般说来，词首“亚”用于描述二价基团。因此，本文定义的任何术语可经词首“亚”修饰以描述这一部分的二价型式。例如，二价碳环为“亚碳环基”，二价芳基环为“亚芳基”，

二价苯环为“亚苯基”，二价杂环为“亚杂环基”，二价杂芳基环为“亚杂芳基”，二价烷基链为“亚烷基”，二价烯基链为“亚烯基”，二价炔基链为“亚炔基”，二价杂烷基链为“亚杂烷基”，二价杂烯基链为“亚杂烯基”，二价杂炔基链为“亚杂炔基”等。

[1564] 术语“烯基”和“炔基”具有其在本领域中的一般含义且指在长度及可能取代方面与上述烷基类似，但分别含有至少一个双键或三键的不饱和脂肪族基团。

[1565] 在某些实施例中，本发明中所用的烷基、烯基和炔基含有 1-20 个脂肪族碳原子。在某些其它实施例中，本发明中所用的烷基、烯基和炔基含有 1-10 个脂肪族碳原子。在其它实施例中，本发明中所用的烷基、烯基和炔基含有 1-8 个脂肪族碳原子。在其它实施例中，本发明中所用的烷基、烯基和炔基含有 1-6 个脂肪族碳原子。在其它实施例中，本发明中所用的烷基、烯基和炔基含有 1-4 个碳原子。说明性脂肪族基团因此包括（但不限于）例如甲基、乙基、正丙基、异丙基、烯丙基、正丁基、仲丁基、异丁基、叔丁基、正戊基、仲戊基、异戊基、叔戊基、正己基、仲己基部分等，其又可携带一或多个取代基。烯基包括（但不限于）例如乙烯基、丙烯基、丁烯基、1- 甲基 -2- 丁烯 -1- 基等。代表性炔基包括（但不限于）乙炔基、2- 丙炔基（炔丙基）、1- 丙炔基等。

[1566] 如本文所用的术语“环烷基”特定言的指具有三个至十个，较佳三个至七个碳原子的基团。适合环烷基包括（但不限于）环丙基、环丁基、环戊基、环己基、环庚基等，如在其它脂肪族、杂脂肪族或杂环部分的情况下，其可任选地经包括（但不限于）以下的取代基取代：脂肪族基；杂脂肪族基；芳基；杂芳基；芳烷基；杂芳烷基；烷氧基；芳氧基；杂烷氧基；杂芳氧基；烷硫基；芳硫基；杂烷硫基；杂芳硫基；-F；-Cl；-Br；-I；-OH；-NO_2；-CN；-CF_3；-CH_2CF_3；-$CHCl_2$；-CH_2OH；-CH_2CH_2OH；-CH_2NH_2；-$CH_2SO_2CH_3$；-$C(O)R_x$；-$CO_2(R_x)$；-$CON(R_x)_2$；-$OC(O)R_x$；-OCO_2R_x；-$OCON(R_x)_2$；-$N(R_x)_2$；-$S(O)_2R_x$；-$NR_x(CO)R_x$，其中 R_x 每次出现时独立地包括（但不限于）脂肪族基、杂脂肪族基、芳基、杂芳基、芳烷基或杂芳烷基，其中上文及本文所述的脂肪族基、杂脂肪族基、芳烷基或杂芳烷基取代基中的任一者均可经取代或未经取代、分支链或未分支、环状或非环状，且其中上文及本文所述的芳基或杂芳基取代基中的任一者均可经取代或未经取代。一般可适用的取代基的其它实例由本文所述的实例中所示的特定实施例说明。

[1567] 如本文所用的术语“杂脂肪族基”指如本文所定义的脂肪族部分，其包括饱和以及不饱和非芳香族直链（即未分支）、分支链、非环状、环状（即杂环）或多环烃类，其任选地经一或多个官能基取代，且含有一或多个氧、硫、氮、磷或硅原子例如置换碳原子。在某些实施例中，杂脂肪族部分通过其上的一或多个氢原子独立经一或多个取代基置换而经取代。如所属领域的技术人员将了解，本文的“杂脂肪族基”欲包括（但不限于）杂烷基、杂烯基、杂炔基、杂环烷基、杂环烯基及杂环炔基部分。因此，术语“杂脂肪族基”包括术语“杂烷基”、“杂烯基”、“杂炔基”等。此外，如本文所用，术语“杂烷基”、“杂烯基”、“杂炔基”等涵盖经取代和未经取代的基团。在某些实施例中，如本文所用，“杂脂肪族基”用于指示具有 1-20 个碳原子的杂脂肪族基团（环状、非环状、经取代、未经取代、分支链或未分支）。杂脂肪族基团取代基包括（但不限于）本文所述的致使形成稳定部分的任何取代基（例如脂肪族基、烷基、烯基、炔基、杂脂肪族基、杂环基、芳基、杂芳基、酰基、亚磺酰基、磺酰基、侧氧基、亚氨基、硫代侧氧基、氰基、异氰基、氨基、叠氮基、硝基、羟基、硫醇、卤基、脂肪族氨基、杂脂肪族氨基、烷氨基、杂烷基氨基、芳氨基、杂芳基氨基、烷芳基、芳烷基、脂肪族氧基、杂脂肪族氧

基、烷氧基、杂烷氧基、芳氧基、杂芳氧基、脂肪族硫氧基、杂脂肪族硫氧基、烷基硫氧基、杂烷基硫氧基、芳基硫氧基、杂芳基硫氧基、酰氧基等，其各自可经进一步取代或可未经进一步取代）。

[1568] 术语“杂烷基”具有其在本领域中的一般含义且指如本文所述的一或多个碳原子经杂原子置换的烷基。适合杂原子包括氧、硫、氮、磷等。杂烷基的实例包括（但不限于）烷氧基、烷氧基烷基、氨基、硫酯、聚（乙二醇）和经烷基取代的氨基。

[1569] 术语“杂烯基”及“杂炔基”具有其在本领域中的一般含义且指在长度及可能取代方面与上述杂烷基类似，但分别含有至少一个双键或三键的不饱和脂肪族基团。

[1570] 本发明化合物的上述脂肪族（及其它）部分的取代基的一些实例包括（但不限于）脂肪族基；杂脂肪族基；芳基；杂芳基；烷芳基；烷基杂芳基；烷氧基；芳氧基；杂烷氧基；杂芳氧基；烷硫基；芳硫基；杂烷硫基；杂芳硫基；F；Cl；Br；I；-OH；-NO_2；-CN；-CF_3；-CHF_2；-CH_2F；-CH_2CF_3；-$CHCl_2$；-CH_2OH；-CH_2CH_2OH；-CH_2NH_2；-$CH_2SO_2CH_3$；-C(O)R_x；-$CO_2(R_x)$；-$CON(R_x)_2$；-OC(O)R_x；-OCO_2R_x；-$OCON(R_x)_2$；-$N(R_x)_2$；-$S(O)_2R_x$；-$NR_x(CO)R_x$，其中R_x每次出现时独立地包括（但不限于）脂肪族基、脂环基、杂脂肪族基、杂环基、芳基、杂芳基、烷芳基或烷基杂芳基，其中上文和本文所述的脂肪族基、杂脂肪族基、烷芳基或烷基杂芳基取代基中的任一者均可经取代或未经取代、分支链或未分支、环状或非环状，且其中上文和本文所述的芳基或杂芳基取代基中的任一者均可经取代或未经取代。一般可适用的取代基的其它实例由本文所述的实例中所示的特定实施例说明。

[1571] 术语“芳基”具有其在本领域中的一般含义且指任选地经取代的具有单环（例如苯基）、多环（例如联苯）或多个稠环且其中至少一者为芳香族（例如1,2,3,4-四氢萘基、萘基、蒽基或菲基）的芳香族碳环基团。即，至少一个环可具有共轭π电子系统，而其它邻接环可为环烷基、环烯基、环炔基、芳基和/或杂环基。如本文所述，芳基可任选地经取代。取代基包括（但不限于）任何先前提及的取代基，即对于脂肪族部分或对于如本文所揭示的其它部分所述，可形成稳定化合物的取代基。在一些情况下，芳基为较佳具有3-14个碳原子（各自可经取代或未经取代）的稳定的单环或多环不饱和部分。“碳环芳基”指芳香族环上的环原子为碳原子的芳基。碳环芳基包括单环碳环芳基及多环或稠合化合物（例如两个或两个以上邻接环原子为两个邻接环共用），如萘基。

[1572] 术语“杂芳基”具有其在本领域中的一般含义且指包含至少一个杂原子作为环原子的芳基。“杂芳基”为较佳具有3-14个碳原子（各自可经取代或未经取代）的稳定杂环或多杂环不饱和部分。取代基包括（但不限于）任何先前提及的取代基，即对于脂肪族部分或对于如本文所揭示的其它部分所述，可形成稳定化合物的取代基。在一些情况下，杂芳基为具有五个至十个环原子的环状芳香族基团，其中一个环原子选自S、O和N；零、一个或两个环原子为独立地选自S、O和N的其它杂原子；且其余环原子为碳，所述基团通过任何环原子连接到分子的其余部分，如吡啶基、吡嗪基、嘧啶基、吡咯基、吡唑基、咪唑基、噻唑基、噁唑基、异噁唑基、噻二唑基、噁二唑基、噻吩基、呋喃基、喹啉基、异喹啉基等。

[1573] 还应了解，如本文中所定义的芳基和杂芳基部分可通过烷基或杂烷基部分连接，且因此还包括-（烷基）芳基、-（杂烷基）芳基、-（杂烷基）杂芳基以及-（杂烷基）杂芳基部分。因此，如本文所用，片语“芳基或杂芳基部分”与“芳基、杂芳基、-（烷基）芳基、-（杂烷基）芳基、-（杂烷基）杂芳基及-（杂烷基）杂芳基”可互换。取代基包括（但不限于）

任何先前提及的取代基，即对于脂肪族部分或对于如本文所揭示的其它部分所述，可形成稳定化合物的取代基。

[1574] 应了解，芳基和杂芳基（包括双环芳基）可未经取代或经取代，其中取代包括其上的一或多个氢原子独立地经任一或多个以下部分置换：包括（但不限于）脂肪族基；脂环基；杂脂肪族基；杂环基；芳香族基；杂芳香族基；芳基；杂芳基；烷芳基；杂烷基芳基；烷基杂芳基；杂烷基杂芳基；烷氧基；芳氧基；杂烷氧基；杂芳氧基；烷硫基；芳硫基；杂烷硫基；杂芳硫基；F；Cl；Br；I；-OH；$-NO_2$；-CN；$-CF_3$；$-CH_2F$；$-CHF_2$；$-CH_2CF_3$；$-CHCl_2$；$-CH_2OH$；$-CH_2CH_2OH$；$-CH_2NH_2$；$-CH_2SO_2CH_3$；$-C(O)R_x$；$-CO_2(R_x)$；$-CON(R_x)_2$；$-OC(O)R_x$；$-OCO_2R_x$；$-OCON(R_x)_2$；$-N(R_x)_2$；$-S(O)R_x$；$-S(O)_2R_x$；$-NR_x(CO)R_x$，其中 R_x 每次出现时独立地包括（但不限于）脂肪族基、脂环基、杂脂肪族基、杂环基、芳香族基、杂芳香族基、芳基、杂芳基、烷芳基、烷基杂芳基、杂烷基芳基或杂烷基杂芳基，其中上文和本文所述的任何脂肪族基、脂环基、杂脂肪族基、杂环基、烷基芳基或烷基杂芳基取代基均可经取代或未经取代、为分支链或非分支链、饱和或不饱和，且其中上文及本文所述的任何所述芳香族基、杂芳香族基、芳基、杂芳基、-（烷基）芳基或 -（烷基）杂芳基取代基均可经取代或未经取代。另外，应了解，任何两个邻接基团结合以均可表示 4、5、6 或 7 元经取代或未经取代的脂环或杂环部分。一般可适用的取代基的其它实例由本文所述的特定实施例说明。

[1575] 术语“杂环基”具有其在本领域中的一般含义且指含有至少一个杂原子作为环原子，在一些情况下，1 至 3 个杂原子作为环原子，且环原子的其余部分为碳原子的环基。适合杂原子包括氧、硫、氮、磷等。在一些情况下，杂环可为环结构包括一个至四个杂原子的 3 至 10 元环结构或 3 至 7 元环。

[1576] 术语“杂环”可包括杂芳基、饱和杂环基（例如环杂烷基）或其组合。杂环可为饱和分子或可包含一或多个双键。在一些情况下，杂环为氮杂环，其中至少一个环包含至少一个氮环原子。杂环可与其它环稠合形成多环杂环。杂环还可与螺环基团稠合。在一些情况下，杂环可通过环中的氮或碳原子连接到化合物。

[1577] 杂环包括例如噻吩、苯并噻吩、噻嗯、呋喃、四氢呋喃、哌喃、异苯并呋喃、色烯、二苯并哌喃、啡噁噻、吡咯、二氢吡咯、吡咯啶、咪唑、吡唑、吡嗪、异噻唑、异噁唑、吡啶、吡嗪、嘧啶、哒嗪、吲哚嗪、异吲哚、吲哚、吲唑、嘌呤、喹嗪、异喹啉、喹啉、酞嗪、萘啶、喹喏啉、喹唑啉、噌啉、喋啶、咔唑、咔啉、三唑、四唑、噁唑、异噁唑、噻唑、异噻唑、啡啶、吖啶、嘧啶、啡啉、吩嗪、啡砷嗪、啡噻嗪、呋呫、啡噁嗪、吡咯啶、氧杂环戊烷、硫杂环戊烷、噁唑、噁嗪、哌啶、高哌啶（六亚甲基亚胺）、哌嗪（例如 N- 甲基哌嗪）、吗啉、内酯、内酰胺（如氮杂环丁酮和吡咯啶酮）、磺内酰胺、磺内酯、其其它饱和和 / 或不饱和衍生物等。杂环可任选地在一或多个位置经如本文所述的所述取代基取代。在一些情况下，杂环可经杂原子环原子（例如氮）键结于化合物。在一些情况下，杂环可通过碳环原子键结于化合物。在一些情况下，杂环为吡啶、咪唑、吡嗪、嘧啶、哒嗪、吖啶、吖啶 -9- 胺、联吡啶、萘啶、喹啉、苯并喹啉、苯并异喹啉、啡啶 -1,9- 二胺或其类似物。

[1578] 如本文所用的术语“卤基”和“卤素”指选自由氟、氯、溴和碘组成的群的原子。

[1579] 术语“卤烷基”表示连接有一个、两个或三个卤素原子的如上定义的烷基且实例为如氯甲基、溴乙基、三氟甲基等的基团。

[1580] 如本文所用的术语“氨基”指伯（$-NH_2$）、仲（$-NHR_x$）、叔（$-NR_xR_y$）或季（$-N^+R_xR_yR_z$）

氨，其中 R_x、R_y和 R_z独立地为如本文所定义的脂肪族、脂环、杂脂肪族、杂环、芳基或杂芳基部分。氨基的实例包括（但不限于）甲氨基、二甲氨基、乙氨基、二乙氨基、甲基乙氨基、异丙氨基、哌啶基、三甲氨基以及丙氨基。

[1581] 术语“炔烃”具有其在本领域中的一般含义且指含有至少一个三键的分支链或未分支不饱和烃基。炔烃的非限制性实例包括乙炔、丙炔、1- 丁炔、2- 丁炔等。炔烃基团可经取代和 / 或具有一或多个经如羟基、卤素、烷氧基和 / 或芳基的官能基置换的氢原子。

[1582] 如本文所用的术语“烷氧基”（或“烷基氧基”）或“硫烷基”指通过氧原子或通过硫原子连接到母分子部分的如先前定义的烷基。在某些实施例中，烷基含有 1-20 个脂肪族碳原子。在某些其它实施例中，烷基含有 1-10 个脂肪族碳原子。在其它实施例中，本发明中所用的烷基、烯基和炔基含有 1-8 个脂肪族碳原子。在其它实施例中，烷基含有 1-6 个脂肪族碳原子。在其它实施例中，烷基含有 1-4 个脂肪族碳原子。烷氧基的实例包括（但不限于）甲氧基、乙氧基、丙氧基、异丙氧基、正丁氧基、叔丁氧基、新戊氧基以及正己氧基。硫烷基的实例包括（但不限于）甲硫基、乙硫基、丙硫基、异丙硫基、正丁硫基等。

[1583] 术语“芳氧基”指基团 -O- 芳基。

[1584] 术语“酰氧基”指基团 -O- 酰基。

[1585] 术语“烷氧基烷基”指经至少一个烷氧基（例如一个、两个、三个或三个以上烷氧基）取代的烷基。例如，烷氧基烷基可为任选地经取代的 -(C_{1-6}烷基)-O-(C_{1-6}烷基)。在一些情况下，烷氧基烷基可任选地经任选地经取代的其它烷氧基烷基（例如 -(C_{1-6}烷基)-O-(C_{1-6}烷基)-O-(C_{1-6}烷基)）取代。

[1586] 应了解，如本文所述的上述基团和 / 或化合物可任选地经任何数目的取代基或官能部分取代。即，任何上述基团均可任选地经取代。如本文所用，术语“经取代”意欲包括有机化合物的所有可允许取代基，“可允许”为处于所属领域的技术人员已知的化学价态规则的范围中。一般说来，术语“经取代”前无论有或无术语“任选地”，及本发明的式中所含的取代基，均指给定结构中的氢基经特定取代基置换。当任何给定结构中一个以上位置可经一个以上选自特定群组的取代基取代时，在每一位置的取代基可相同或不同。应了解，“经取代”还包括产生稳定化合物，例如不自发经历如重排、环化、消除等的转化的取代。在一些情况下，“经取代”一般可指以如本文所述的取代基置换氢。然而，如本文所用的“经取代”不涵盖藉以鉴别分子的关键官能基的置换和 / 或改变，例如使得“经取代”的官能基通过取代变成不同官能基。例如，“经取代的苯基”必需仍包含苯基部分且不能经取代而改质，在此定义中，改质成例如吡啶环。在一个广泛方面中，可允许取代基包括有机化合物的非环状和环状、分支链和未分支、碳环和杂环、芳香族和非芳香族取代基。说明性取代基包括例如本文所述者。可允许取代基对于适当有机化合物而言可为一或多个且相同或不同。对本发明而言，如氮的杂原子可具有氢取代基和 / 或满足杂原子化合价的本文所述的有机化合物的任何可允许取代基。此外，本发明决不意欲以任何方式受限于有机化合物的可允许取代基。本发明预想的取代基和变量的组合较佳为可形成适用于形成造影剂或造影剂前驱物的稳定化合物的组合。如本文所用的术语“稳定”较佳指化合物具有足够稳定性以允许制造且维持化合物完整性持续足够时段以供检测且较佳持续足够时段以适用于本文详述的目的。

[1587] 取代基的实例包括（但不限于）卤素、叠氮化物、烷基、芳烷基、烯基、炔基、环烷基、羟基、烷氧基、氨基、硝基、硫氢基、亚氨基、酰胺基、膦酸酯、亚膦酸酯、羰基、羧基、硅烷

基、醚、烷硫基、磺酰基、磺酰胺基、酮、醛、酯、杂环基、芳香族或杂芳香族部分、-CF_3、-CN、芳基、芳氧基、全卤烷氧基、芳烷氧基、杂芳基、杂芳氧基、杂芳烷基、杂芳基烷氧基、叠氮基、氨基、卤化物、烷硫基、侧氧基、酰烷基、羧基酯、- 甲酰胺基、酰氧基、氨基烷基、烷氨基芳基、烷芳基、烷氨基烷基、烷氧芳基、芳氨基、芳烷氨基、烷基磺酰基、- 甲酰胺基烷芳基、- 甲酰胺基芳基、羟烷基、卤烷基、烷氨基烷羧基 -、氨基甲酰胺基烷基 -、氰基、烷氧基烷基、全卤烷基、芳基烷氧基烷基等。在一些实施例中，取代基亦可为造影部分（例如 ^{18}F）或用于缔合造影部分的基团（例如螯合剂）。氮保护基为本领域中所众所周知且包括以下中详述者：有机合成中的保护基(Protecting Groups in Organic Synthesis)，T.W. 格林(T.W.Greene)和 P.G.M. 瓦茨 (P.G.M.Wuts)，第 3 版，约翰威利和其子公司 (John Wiley&Sons)，1999，其以引用的方式并入本文中。例如，氮保护基包括（但不限于）例如氨基甲酸酯（包括例如氨基甲酸甲酯、氨基甲酸乙酯和经取代的氨基甲酸乙酯（例如 Troc））、酰胺、环酰亚胺衍生物、N- 烷基和 N- 芳基胺、亚氨衍生物和烯氨衍生物等。在一些实施例中，氮保护基为苯甲氧羰基 (Cbz)、对甲氧基苯甲基羰基 (MeOZ)、叔丁氧基羰基 (Boc)、9- 芴基甲氧基羰基 (Fmoc)、乙酰基 (Ac)、苯甲酰基 (Bz)、苯甲基 (Bn)、对甲氧基苯甲基 (PMB)、3,4- 二甲氧基苯甲基 (DMPM)、对甲氧基苯基 (PMP) 或对甲苯磺酰基氧基 (Ts)。

[1588] 如酰胺基的氮保护基包括（但不限于）甲酰胺、乙酰胺、氯乙酰胺、三氯乙酰胺、三氟乙酰胺、苯基乙酰胺、3- 苯基丙酰胺、吡啶酰胺 (picolinamide)、3- 吡啶基甲酰胺、N- 苯甲酰基苯基丙氨酰基衍生物、苯甲酰胺、对苯基苯甲酰胺、邻硝基苯基乙酰胺、邻硝基苯氧基乙酰胺、乙酰乙酰胺、(N'- 二硫基苯甲氧基酰胺基）乙酰胺、3-（对羟苯基）丙酰胺、3-（邻硝基苯基）丙酰胺、2- 甲基 -2-（邻硝基苯氧基）丙酰胺、2- 甲基 -2-（邻苯基偶氮基苯氧基）丙酰胺、4- 氯丁酰胺、3- 甲基 -3- 硝基丁酰胺、邻硝基肉桂酰胺、N- 乙酰甲硫氨酸衍生物、邻硝基苯甲酰胺及邻（苯甲酰氧基甲基）苯甲酰胺。

[1589] 如氨基甲酸酯基的氮保护基包括（但不限于）氨基甲酸甲酯、氨基甲酸乙酯、氨基甲酸 9- 芴基甲酯 (Fmoc)、氨基甲酸 9-(2- 磺基）芴基甲酯、氨基甲酸 9-(2,7- 二溴）芴基甲酯、氨基甲酸 2,7- 二叔丁基 -[9-(10,10- 二侧氧基 -10,10,10,10- 四氢硫基黄嘌呤酸基）] 甲酯 (DBD-Tmoc)、氨基甲酸 4- 甲氧基苯甲酰甲酯 (Phenoc)、氨基甲酸 2,2,2- 三氯乙酯 (Troc)、氨基甲酸 2- 三甲基硅烷基乙酯 (Teoc)、氨基甲酸 2- 苯基乙酯 (hZ)、氨基甲酸 1-(1- 金刚烷基）-1- 甲基乙酯 (Adpoc)、氨基甲酸 1,1- 二甲基 -2- 卤乙酯、氨基甲酸 1,1- 二甲基 -2,2- 二溴乙酯 (DB-t-BOC)、氨基甲酸 1,1- 二甲基 -2,2,2- 三氯乙酯 (TCBoc)、氨基甲酸 1- 甲基 -1-(4- 联苯基）乙酯 (Bpoc)、氨基甲酸 1-(3,5- 二叔丁基苯基）-1- 甲基乙酯 (t-Bumeoc)、氨基甲酸 2-(2'- 及 4'- 吡啶基）乙酯 (Pyoc)、氨基甲酸 2-(N,N- 二环己基甲酰胺基）乙酯、氨基甲酸叔丁酯 (Boc)、氨基甲酸 1- 金刚烷酯 (Adoc)、氨基甲酸乙烯酯 (Voc)、氨基甲酸烯丙酯 (Alloc)、氨基甲酸 1- 异丙基烯丙酯 (Ipaoc)、氨基甲酸桂皮酯 (Coc)、氨基甲酸 4- 硝基桂皮酯 (Noc)、氨基甲酸 8- 喹啉酯、氨基甲酸 N- 羟基哌啶酯、烷基二硫基氨基甲酸酯、氨基甲酸苯甲酯 (Cbz)、氨基甲酸对甲氧基苯甲酯 (Moz)、氨基甲酸对硝基苯甲酯、氨基甲酸对溴苯甲酯、氨基甲酸对氯苯甲酯、氨基甲酸 2,4- 二氯苯甲酯、氨基甲酸 4- 甲基亚磺酰基苯甲酯 (Msz)、氨基甲酸 9- 蒽基甲酯、氨基甲酸二苯甲酯、氨基甲酸 2- 甲基硫乙酯、氨基甲酸 2- 甲基磺酰基乙酯、氨基甲酸 2-（对甲苯磺酰基）乙酯、氨基甲酸 [2-(1,3- 二噻烷基）] 甲酯 (Dmoc)、氨基甲酸 4- 甲基噻吩酯 (Mtpc)、氨基甲酸 2,4- 二甲

基噻吩酯(Bmpc)、氨基甲酸2-膦基乙酯(2-phosphonioethyl carbamate;Peoc)、氨基甲酸2-三苯基鏻基异丙酯(Ppoc)、氨基甲酸1,1-二甲基-2-氰基乙酯、氨基甲酸间氯-对酰氧基苯甲酯、氨基甲酸对(二羟基氧硼基)苯甲酯、氨基甲酸5-苯并异噁唑基甲酯、氨基甲酸2-(三氟甲基)-6-色酮基甲酯(Tcroc)、氨基甲酸间硝基苯酯、氨基甲酸3,5-二甲氧基苯甲酯、氨基甲酸邻硝基苯甲酯、氨基甲酸3,4-二甲氧基-6-硝基苯甲酯、氨基甲酸苯基(邻硝基苯基)甲酯、氨基甲酸叔戊酯、硫氨基甲酸S-苯甲酯、氨基甲酸对氰基苯甲酯、氨基甲酸环丁酯、氨基甲酸环己酯、氨基甲酸环戊酯、氨基甲酸环丙基甲酯、氨基甲酸对癸氧基苯甲酯、氨基甲酸2,2-二甲氧基酰基乙烯酯、氨基甲酸邻(N,N-二甲基甲酰胺基)苯甲酯、氨基甲酸1,1-二甲基-3-(N,N-二甲基甲酰胺基)丙酯、氨基甲酸1,1-二甲基丙炔酯、氨基甲酸二(2-吡啶基)甲酯、氨基甲酸2-呋喃基甲酯、氨基甲酸2-碘乙酯、氨基甲酸异冰片酯、氨基甲酸异丁酯、氨基甲酸异烟碱酯、氨基甲酸对(对'-甲氧基苯偶氮基)苯甲酯、氨基甲酸1-甲基环丁酯、氨基甲酸1-甲基环己酯、氨基甲酸1-甲基-1-环丙基甲酯、氨基甲酸1-甲基-1-(3,5-二甲氧基苯基)乙酯、氨基甲酸1-甲基-1-(对苯基偶氮基苯基)乙酯、氨基甲酸1-甲基-1-苯乙酯、氨基甲酸1-甲基-1-(4-吡啶基)乙酯、氨基甲酸苯酯、氨基甲酸对(苯偶氮基)苯甲酯、氨基甲酸2,4,6-三叔丁基苯酯、氨基甲酸4-(三甲铵)苯甲酯以及氨基甲酸2,4,6-三甲基苯甲酯。

[1590] 如磺酰胺基的氮保护基包括(但不限于)对甲苯磺酰胺(Ts)、苯磺酰胺、2,3,6-三甲基-4-甲氧基苯磺酰胺(Mtr)、2,4,6-三甲氧基苯磺酰胺(Mtb)、2,6-二甲基-4-甲氧基苯磺酰胺(Pme)、2,3,5,6-四甲基-4-甲氧基苯磺酰胺(Mte)、4-甲氧基苯磺酰胺(Mbs)、2,4,6-三甲基苯磺酰胺(Mts)、2,6-二甲氧基-4-甲基苯磺酰胺(iMds)、2,2,5,7,8-五甲基色满-6-磺酰胺(Pmc)、甲烷磺酰胺(Ms)、β-三甲基硅烷基乙磺酰胺(SES)、9-蒽磺酰胺、4-(4',8'-二甲氧基萘甲基)苯磺酰胺(DNMBS)、苯甲基磺酰胺、三氟甲基磺酰胺以及苯甲酰甲基磺酰胺。

[1591] 其它氮保护基包括(但不限于)啡噻嗪基-(10)-酰基衍生物、N'-对甲苯磺酰基氨酰基衍生物、N'-苯基氨基硫酰基衍生物、N-苯甲酰基苯基丙氨酰基衍生物、N-乙酰甲硫氨酸衍生物、4,5-二苯基-3-噁唑啉-2-酮、N-邻苯二甲酰亚胺、N-二硫杂丁二酰亚胺(Dts)、N-2,3-二苯基顺丁烯二酰亚胺、N-2,5-二甲基吡咯、N-1,1,4,4-四甲基二硅烷基氮杂环戊烷加合物(STABASE)、5-经取代的1,3-二甲基-1,3,5-三氮杂环己烷-2-酮、5-经取代的1,3-二苯甲基-1,3,5-三氮杂环己烷-2-酮、1-经取代的3,5-二硝基-4-吡啶酮、N-甲胺、N-烯丙氨、N-[2-(三甲基硅烷基)乙氧基]甲胺(SEM)、N-3-乙酰氧基丙氨、N-(1-异丙基-4-硝基-2-侧氧基-3-吡咯啉-3-基)氨、四级铵盐、N-苯甲胺、N-二(4-甲氧基苯基)甲胺、N-5-二苯并环庚胺、N-三苯基甲胺(Tr)、N-[(4-甲氧基苯基)二苯甲基]氨(MMTr)、N-9-苯基芴胺(PhF)、N-2,7-二氯-9-芴基亚甲氨、N-二茂铁基甲氨基(Fcm)、N-2-吡啶甲基氨基N'-氧化物、N-1,1-二甲基硫基亚甲氨、N-苯亚甲氨、N-对甲氧基苯亚甲氨、N-二苯基亚甲氨、N-[(2-吡啶基)嫣基]亚甲氨、N-(N',N'-二甲氨基亚甲基)氨、N,N'-亚异丙基二氨、N-对硝基苯亚甲氨、N-亚柳氨、N-5-氯亚柳氨、N-(5-氯-2-羟苯基)苯基亚甲氨、N-亚环己氨、N-(5,5-二甲基-3-侧氧基-1-环己烯基)氨、N-硼烷衍生物、N-二苯基硼酸衍生物、N-[苯基(五酰基铬或钨)酰基]氨、N-铜螯合物、N-锌螯合物、N-硝氨、N-亚硝氨、N-氧化氨、二苯基膦酰胺(Dpp)、二甲基硫基膦酰胺(Mpt)、二苯基

硫基膦酰胺 (Ppt)、磷酰胺二烷酯、磷酰胺二苯甲酯、磷酰胺二苯酯、苯亚磺酰胺、邻硝基苯亚磺酰胺 (Nps)、2,4- 二硝基苯亚磺酰胺、五氯苯亚磺酰胺、2- 硝基 -4- 甲氧基苯亚磺酰胺、三苯甲基亚磺酰胺以及 3- 硝基吡啶亚磺酰胺 (Npys)。

[1592] 如本文所用，术语“测定”一般指分析物质或信号，例如以定量或定性方式，和 / 或检测存在或不存在物质或信号。

[1593] 如本文所用的术语“诊断造影”指用于检测造影剂的程序。

[1594] 如本文所用的术语“诊断”涵盖鉴别、确认和 / 或表征病状、疾病和 / 或病症。

[1595] “诊断试剂盒”或“试剂盒”包含在一或多个小瓶中的一组组分，称为配方，其由实施中的最终使用者在临床或药剂学背景中用于合成诊断性放射性药品。例如，试剂盒可由实施中的最终使用者在临床或药剂学背景中用于合成和 / 或使用诊断性放射性药品。在一些实施例中，试剂盒可提供除实施中的最终使用者通常可得的组分以外的合成和使用诊断性药品的所有必要组分，如注射用水或生理食盐水和 / 或放射性同位素 (例如 ^{18}F)、在合成和操纵放射性药品期间处理试剂盒的设备 (如果需要)、向个体投予放射性药品必需的设备 (如注射器、护罩、造影设备等)。在一些实施例中，造影剂可以在配方中的最终形式提供给最终使用者，所述配方通常以冻干固体或水溶液形式含于一个小瓶或注射器中。

[1596] 如本文所用，“个体的一部分”指个体的特定区域、个体的位置。例如，个体的一部分可为个体的脑、心脏、血管结构、心血管、肿瘤等。

[1597] 如本文所用，测试“时段 (session)”可为个体所经历的单一测试方案。

[1598] 如本文所用，术语“个体”指人类或非人类哺乳动物或动物。非人类哺乳动物包括家畜动物、伴侣动物、实验动物和非人类灵长类动物。非人类个体还特定包括 (不限于) 马、牛、猪、山羊、犬、猫、小鼠、大鼠、天竺鼠、沙鼠、仓鼠、貂以及兔。在本发明的一些实施例中，个体系称作“患者”。在一些实施例中，患者或个体可处于医师或包括 (但不限于) 以下的其它健康照护工作者的照护下 :已向医师或其它健康照护工作者咨询、自其接受建议或接受处方或其它建议的某人。

[1599] 本文所述的任何化合物均可呈多种形式，如 (但不限于) 盐、溶剂合物、水合物、互变异构体以及异构体。

[1600] 在某些实施例中，造影剂为造影剂的医药学上可接受的盐。如本文所用的术语“医药学上可接受的盐”指在正确医学判断的范畴内，适于与人类及低等动物的组织接触使用而无不当毒性、刺激、过敏反应等，且与合理益处 / 风险比相称的盐。医药学上可接受的盐在本领域中为众所周知的。例如，博格 (Berge) 等人于医药科学杂志 (J.Pharmaceutical Sciences),1977,66,1-19(以引用的方式并入本文中) 中详细描述医药学上可接受的盐。本发明化合物的医药学上可接受的盐包括来源于适当无机和有机酸以及碱的盐。医药学上可接受的无毒酸加成盐的实例为氨基与无机酸或有机酸形成的盐，所述无机酸如盐酸、氢溴酸、磷酸、硫酸和高氯酸，所述有机酸如乙酸、草酸、顺丁烯二酸、酒石酸、柠檬酸、丁二酸或丙二酸 ;或通过使用本领域中使用的如离子交换的其它方法形成的盐。其它医药学上可接受的盐包括己二酸盐、海藻酸盐、抗坏血酸盐、天冬氨酸盐、苯磺酸盐、苯甲酸盐、硫酸氢盐、硼酸盐、丁酸盐、樟脑酸盐、樟脑磺酸盐、柠檬酸盐、环戊烷丙酸盐、二葡糖酸盐、十二烷基硫酸盐、乙烷磺酸盐、甲酸盐、反丁烯二酸盐、葡糖庚酸盐、甘油磷酸盐、葡糖酸盐、半硫酸盐、庚酸盐、己酸盐、氢碘酸盐、2- 羟基 - 乙烷磺酸盐、乳糖酸盐、乳酸盐、月桂酸盐、月桂基

硫酸盐、苹果酸盐、顺丁烯二酸盐、丙二酸盐、甲烷磺酸盐、2- 萘磺酸盐、烟碱酸盐、硝酸盐、油酸盐、乙二酸盐、棕榈酸盐、双羟萘酸盐、果胶酸盐、过硫酸盐、3- 苯基丙酸盐、磷酸盐、苦味酸盐、特戊酸盐、丙酸盐、硬脂酸盐、丁二酸盐、硫酸盐、酒石酸盐、硫氰酸盐、对甲苯磺酸盐、十一烷酸盐、戊酸盐等。自适当碱衍生的盐包括碱金属盐、碱土金属盐、铵盐和 $N^+(C_{1-4}$烷基$)_4$盐。代表性碱金属或碱土金属盐包括钠、锂、钾、钙、镁等。其它医药学上可接受的盐适当时包括无毒铵、四级铵和使用相对离子形成的胺阳离子，所述相对离子如卤离子、氢氧根、羧酸根、硫酸根、磷酸根、硝酸根、低碳烷基磺酸根和芳基磺酸根。

[1601] 在某些实施例中，化合物呈水合物或溶剂合物形式。如本文所用的术语“水合物”指与一或多个水分子非共价缔合的化合物。类似地，术语“溶剂合物”指与一或多个有机溶剂分子非共价缔合的化合物。

[1602] 在某些实施例中，本文所述的化合物可以各种互变异构形式存在。如本文所用的术语“互变异构体”包括两种或两种以上因至少一次氢原子形式迁移和至少一次化合价变化（例如单键至双键、三键至单键，或反之亦然）而可相互转化的化合物。互变异构体的确切比率视若干因素而定，包括温度、溶剂和 pH 值。互变异构化（即提供互变异构体对的反应）可由酸或碱催化。例示性互变异构化包括酮至烯醇；酰胺至酰亚胺；内酰胺至内酰亚胺；烯胺至亚胺；和烯胺至（不同）烯胺互变异构化。

[1603] 在某些实施例中，本文所述的化合物可以各种异构形式存在。如本文所用的术语“异构体”包括任何和所有几何异构体和立体异构体（例如对映异构体、非对映异构体等）。例如，“异构体”包括在本发明范畴内的顺式异构体和反式异构体、E- 异构体和 Z- 异构体、R- 对映异构体和 S- 对映异构体、非对映异构体、(D)- 异构体、(L)- 异构体、其外消旋混合物，以及其其它混合物。例如，异构体 / 对映异构体在一些实施例中可以实质上无相应对映异构体的形式提供，且也可称作“光学增浓”。如本文所用的“光学增浓”意指化合物由显著较大比例的一种对映异构体构成。在某些实施例中，本发明化合物由至少约 90 重量％的较佳对映异构体构成。在其它实施例中，化合物由至少约 95 重量％、98 重量％或 99 重量％的较佳对映异构体构成。较佳对映异构体可通过所属领域的技术人员已知的任何方法，包括对掌性高压液相色谱 (HPLC)，以及形成和结晶对掌性盐而从外消旋混合物分离，或通过不对称合成来制备。参见例如雅克 (Jacques) 等人，对映体、消旋体和拆分 (Enantiomers,Racemates and Resolutions)（纽约威利国际科技 (Wiley Interscience,New York),1981）；维能 (Wilen,S.H.) 等人，四面体 (Tetrahedron)33:2725(1977)；艾利尔 (Eliel,E.L.) 含碳化合物的立体化学 (Stereochemistry of Carbon Compounds)（纽约麦格劳 - 希尔公司 (McGraw-Hill,NY),1962)；维能拆分剂和光学拆分表 (Tables of Resolving Agents and Optical Resolutions) 第 268 页（艾利尔编，印地安纳州诺特丹圣母大学出版社 (Univ. of Notre Dame Press,Notre Dame,IN)1972)。

[1604] 考虑以下实例将会进一步理解本发明的这些和其它方面，所述实例意欲说明本发明的某些特定实施例，但不意欲限制其范畴，本发明的范畴由申请专利范围界定。

[1605] 实例

[1606] 一般实验方案

[1607] 方法 A：

[1608] 用碳酸钠一次性处理经冷却（0℃）粘氯酸水溶液，随后搅拌直到观察到完全溶解。随后用经取代的肼处理所得混合物，且搅拌 2.5-5 小时同时缓慢温热到环境温度。随后收集新形成的沉淀，彻底用水洗涤，在漏斗上部分干燥，随后溶解于乙酸中且加热到回流。30 分钟后，冷却溶液至环境温度且在真空中移除所有挥发物。随后将粗哒嗪酮溶解于适当的有机溶剂中，用碱溶液洗涤、干燥、过滤且真空浓缩。由此获得的粗物质通常不经额外纯化即使用，但或者可通过经二氧化硅色谱进一步纯化。

[1609] 方法 B：

[1610] 用碳酸铯处理经取代的哒嗪酮和苯甲醇或溴化苯甲基于二甲基甲酰胺中的溶液，随后任选地加热到 55-80℃。冷却到环境温度后，将粗产物分离为乙酸乙酯溶液，用水和氯化钠水溶液洗涤，随后干燥、过滤且浓缩。随后通过经二氧化硅色谱进行纯化，得到标题化合物。

[1611] 方法 C：

[1612] 在环境温度下，用三溴化磷处理苯甲醇的二氯甲烷溶液。1-3 小时后，用水稀释所得混合物且分离每个层。再用二氯甲烷洗涤水层，且干燥、过滤且浓缩经合并的萃取物。由此获得的粗物质通常不经额外纯化即使用，但或者可通过经二氧化硅色谱进一步纯化。

[1613] 方法 D：

[1614] 在环境温度下制备乙醇、对甲苯磺酰氯、4- 二甲基氨基吡啶和碱的二氯甲烷溶液。1-3 小时后，用水稀释所得混合物且分离每个层。再用二氯甲烷洗涤水层，且用氯化钠水溶液进一步洗涤经合并的萃取物，随后干燥、过滤且浓缩。随后通过经二氧化硅色谱进行纯化，得到标题化合物。

[1615] 方法 E：

[1616] 将叔丁醇钾于 2- 氟乙醇中的悬浮液加热到 60℃，维持 20 分钟，随后用苯甲基卤化物于四氢呋喃中的溶液处理。加热所得混合物至回流，维持 2-24 小时，随后冷却到环境温度且用水处理。分离水层，随后用乙酸乙酯萃取。经硫酸钠干燥经合并的有机层，过滤且真空浓缩。随后通过经二氧化硅色谱进行纯化，得到标题化合物。

[1617] 方法 F：

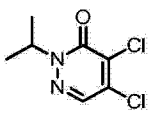
[1618] 将苯酚、对甲苯磺酸 3- 氟丙酯和碳酸铯于二甲基甲酰胺中的悬浮液加热到 60-65℃且维持隔夜。冷却到环境温度后，用水处理所得混合物，且用乙酸乙酯萃取水层。用水、饱和氯化钠水溶液洗涤经合并的有机层，经硫酸钠干燥、过滤且真空浓缩。

[1619] 实例 1

[1620] 制备 4- 氯 -5-((4-((2- 氟乙氧基）甲基）苯甲基）氧基）-2- 异丙基哒嗪 -3(2H)- 酮

[1621] A 部分 - 制备 4,5- 二氯 -2- 异丙基哒嗪 -3(2H)- 酮

[1622]

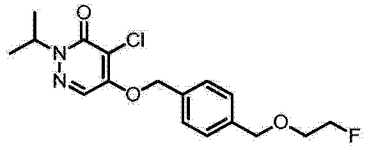


[1623] 根据通用方法 A，使用粘氯酸（1.07g,6.33mmol）、碳酸钠（0.336g,3.17mmol）和盐酸异丙肼（0.700g,6.33mmol）制备。分离产量为 0.629g ;47.9 %。^{1}H NMR($CDCl_3$

,300MHz):δ7.82(s,1H),5.27(m,1H),1.37(d,J = 6.6Hz,6H);^{13}C NMR($CDCl_3$,75MHz):δ156.3,135.9,135.3,133.8,51.4,20.9;HRMS-TOF(m/z):$[M+H]^+$HRMS:$C_7H_8{}^{35}Cl_2N_2O$ 的计算值:207.0086;实验值:207.0085。

[1624] B 部分-制备 4-氯-5-((4-((2-氟乙氧基)甲基)苯甲基)氧基)-2-异丙基哒嗪-3(2H)-酮

[1625]



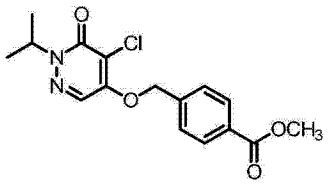
[1626] 根据通用方法 B,使用实例 1A 的产物(45.5mg,0.220mmol)、(4-((2-氟乙氧基)甲基)苯基)甲醇(41mg,0.22mmol;例如参见拉迪克(Radeke,H.);汉森(Hanson,K.);亚拉曼奇尼(Yalamanchili,P.);海耶斯(Hayes,M.);张(Zhang,Z.-Q.);阿祖尔(Azure,M.);于(Yu,M.);加拉德利(Guaraldi,M.);卡甘(Kagan,M.);罗宾逊(Robinson,S.);卡斯贝尔(Casebier,D.)作为潜在心脏正电子发射断层扫描示踪剂的线粒体复合物 I 抑制剂 2-[4-(4-氟丁基)苯甲基硫基]-3-甲基色烯-4-酮的合成和生物评估(Synthesis and Biological evaluation of the mitochondrial complex I inhibitor 2-[4-(4-flurobutyl)benzylsulfanyl]-3-methylchromene-4-one as a potential cardiac positron emission tomography tracer.)医学化学杂志(J.Med.Chem.)2007,50,4304-4315)和碳酸铯(0.215g,0.661mmol)于二甲基甲酰胺(2.20mL)中在 55℃下制备。分离产量为 49mg;63%。^{1}H NMR($CDCl_3$,300MHz):δ7.66(s,1H),7.41(d,J = 7.5Hz,2H),7.37(d,J = 8.6Hz,2H),5.17(s,2H),4.68(m,1H),4.62(s,2H),4.53(m,1H),3.80(m,1H),3.71(m,1H),3.54-3.45(m,1H),1.27(d,J = 7.1Hz,6H);^{13}C NMR($CDCl_3$,75MHz):δ162.3,154.2,138.3,135.4,129.3,128.1,127.4,125.8,83.1(d,J_{CF}= 165Hz),73.0,70.8,69.4(d,J_{CF}= 22.5Hz),65.0,19.5;HRMS-TOF(m/z):$[M+H]^+$HRMS:$C_{17}H_{20}{}^{35}ClFN_2O_3$的计算值:355.1219,实验值:355.1217。

[1627] 实例 2

[1628] 制备 2-((4-(((5-氯-1-异丙基-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯甲基)氧基)乙基-4-甲基苯磺酸酯

[1629] A 部分-制备 4-(((5-氯-1-异丙基-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯甲酸甲酯

[1630]

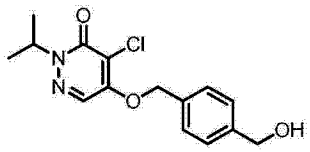


[1631] 根据通用方法 B,使用实例 1A 的产物(0.629g,3.01mmol)、苯甲酸 4-羟甲酯(0.550g,3.31mmol)和碳酸铯(1.57g,4.82mmol)于二甲基甲酰胺(30.0mL)中在 60℃下制备。分离产量为 0.604g;59.6%。^{1}H NMR($CDCl_3$,300MHz):δ8.08(d,J = 8.5Hz,2H),7.82(s,1H),7.50(d,J = 8.5Hz,2H),

5.39(s,2H),5.30(m,1H),3.90(s,3H),1.33(d,J = 6.7Hz,6H);^{13}C NMR($CDCl_3$,75MHz):δ166.5,158.3,153.6,139.7,130.5,130.2,129.7,126.7,117.5,71.2,52.0,50.7,20.9;HRMS-TOF(m/z):[M+H]$^+$HRMS:$C_{16}H_{17}{}^{35}ClN_2O_4$的计算值:337.0950,实验值:337.0948。

[1632] B部分-制备4-氯-5-((4-(羟甲基)苯甲基)氧基)-2-异丙基哒嗪-3(2H)-酮

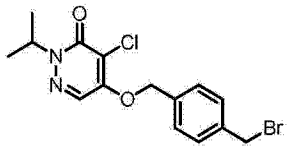
[1633]



[1634] 在0℃下,向实例2A的产物(0.604g,1.79mmol)于四氢呋喃中的溶液中逐滴添加氢化锂铝(0.9mL,0.9mmol,1M四氢呋喃溶液)。搅拌所得混合物3小时,随后用水(20ml)处理。分离水层且用乙酸乙酯(3×50mL)萃取。用饱和氯化钠水溶液(50mL)洗涤经合并的有机层,经硫酸钠干燥,过滤且浓缩,得到橙色固体(0.186g)。^{1}H NMR($CDCl_3$,300MHz):δ7.82(s,1H),7.41(br s,4H),5.32(s,2H),5.28(m,1H),4.72(s,2H),1.28(d,J = 6.7Hz,6H);^{13}C NMR($CDCl_3$,75MHz):δ158.5,153.8,141.8,134.0,127.5,127.4,127.0,117.4,71.8,64.8,50.7,20.9;HRMS-TOF(m/z):[M+H]$^+$HRMS:$C_{15}H_{17}{}^{35}ClN_2O_3$的计算值:309.1000,实验值:309.1001。

[1635] C部分-制备5-((4-(溴甲基)苯甲基)氧基)-4-氯-2-异丙基哒嗪-3(2H)-酮

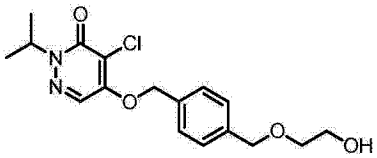
[1636]



[1637] 根据通用方法C,使用实例2B的产物(0.186g,0.602mmol)和三溴化磷(0.3mL,0.3mmol,1M二氯甲烷溶液)制备。分离产量为0.128g;57.2 %。^{1}H NMR($CDCl_3$,300MHz):δ8.07(s,1H),7.34(m,4H),5.23(s,2H),5.21(m,1H),4.41(s,2H),1.24(d,J = 6.6Hz,6H);^{13}C NMR($CDCl_3$,75MHz):δ158.4,153.7,138.5,135.0,129.6,127.5,126.9,117.2,71.5,50.7,32.8,21.0;HRMS-TOF(m/z):[M+H]$^+$HRMS:$C_{15}H_{16}{}^{79}Br^{35}ClN_2O_2$的计算值:371.0156,实验值:371.0155。

[1638] D部分-制备4-氯-5-((4-((2-羟基乙氧基)甲基)苯甲基)氧基)-2-异丙基哒嗪-3(2H)-酮

[1639]

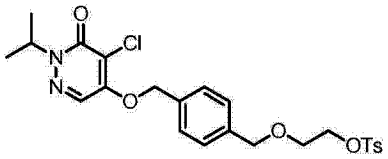


[1640] 将叔丁醇钾(48mg,0.43mmol)于乙二醇(0.685mL)中的悬浮液加热到60℃,维持30分钟。添加逐滴溶解于四氢呋喃(21.0mL)中的实例2C的产物(0.691g,1.86mmol)。添加完成后,加热回流反应混合物。6小时后,冷却反应混合物且用水(10mL)淬灭。分离水层,随后用乙酸乙酯(3×20mL)萃取。经硫酸钠干燥经合并的有机层,过滤且真空浓缩。随后通过硅胶色谱(80-100%乙醚的己烷溶液)纯化粗物质,得到呈白色固体状的所需产物

(2.8mg，产率<1％)。^{1}H NMR($CDCl_3$,300MHz)：δ7.76(br s,1H),7.31(s,4H),5.23(s,2H),5.19(m,1H),4.48(s,2H),3.67(m,2H),3.52(m,2H),1.23(d,J = 6.7Hz,6H)；^{13}C NMR($CDCl_3$,75MHz)：δ158.4,153.8,138.9,134.2,128.2,127.3,127.0,117.2,72.7,71.8,71.7,61.8,50.7,20.9；HRMS-TOF(m/z)：[M+H]$^+$HRMS：$C_{17}H_{21}{}^{35}ClN_2O_4$的计算值：353.1263，实验值：353.1267。

[1641] E部分-制备2-((4-(((5-氯-1-异丙基-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯甲基)氧基)乙基-4-甲基苯磺酸酯

[1642]



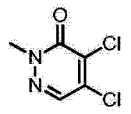
[1643] 根据通用方法D，使用实例2D的产物(85.6mg,0.243mmol)、对甲苯磺酰氯(55.6mg,0.292mmol)、4-二甲基氨基吡啶(35.6mg,0.291mmol)和二异丙基乙氨(0.051mL,0.292mmol)制备。分离产量为53mg；43％。^{1}H($CDCl_3$,300MHz)：δ7.82(s,1H),7.80(d,J = 8.3Hz,2H),7.38(d,J = 8.3Hz,2H),7.33-7.27(m,4H),5.31(s,2H),5.28(m,1H),4.51(s,2H),4.20(m,2H),3.69(m,2H),2.44(s,3H),1.33(d,J = 6.7Hz,6H)；^{13}C($CDCl_3$,75MHz)：δ158.4,153.7,144.8,138.5,134.3,133.0,129.8,128.1,128.0,127.3,127.0,117.4,72.7,71.8,69.2,67.8,50.7,21.7,20.9；HRMS-TOF(m/z)：[M+H]$^+$HRMS：$C_{24}H_{27}{}^{35}ClN_2O_6S$的计算值：507.1351，实验值：507.1349。

[1644] 实例3

[1645] 制备4-氯-5-((4-((2-氟乙氧基)甲基)苯甲基)氧基)-2-甲基哒嗪-3(2H)-酮

[1646] A部分-制备4,5-二氯-2-甲基哒嗪-3(2H)-酮

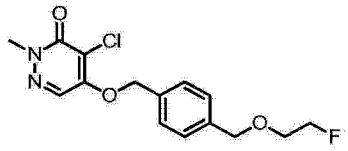
[1647]



[1648] 根据通用方法A，使用粘氯酸(2.03g,12.1mmol)、碳酸钠(0.640g,6.03mmol)和甲肼(0.555g,12.1mmol)制备。分离产量为0.840g；38.8％。^{1}H NMR($CDCl_3$,300MHz)：δ7.70(s,1H),3.75(s,3H)；^{13}C NMR($CDCl_3$,75MHz)：δ156.8,136.5,135.3,134.0,41.0；HRMS-TOF(m/z)：[M+H]$^+$HRMS：$C_5H_4{}^{35}Cl_2N_2O$的计算值：178.9773，实验值：178.9773。

[1649] B部分-制备4-氯-5-((4-((2-氟乙氧基)甲基)苯甲基)氧基)-2-甲基哒嗪-3(2H)-酮

[1650]



[1651] 根据通用方法B，使用实例3A的产物(47mg,0.26mmol)、(4-((2-氟乙氧基)甲基)苯基)甲醇(0.141g,0.770mmol)和碳酸铯(0.251g,0.770mmol)于二甲基甲酰胺(2.50mL)中在80℃下制备。分离产量为38mg；45％。^{1}H NMR($CDCl_3$,300MHz)：δ7.67(s,1H),7.33(s,4H),5.25(br s,2H),4.61(m,1H),4.54(s,2H),4.45(m,1H),3.72(m,1H),3.71

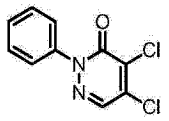
(s,3H),3.63(m,1H);^{13}C NMR($CDCl_3$,75MHz):δ158.9,154.4,138.8,134.1,128.2,127.3,127.2,117.7,83.1(d,J_{CF}= 165Hz),72.9,72.0,69.4(d,J_{CF}= 22.5Hz),40.7;HRMS-TOF(m/z):[M+H]$^+$HRMS:$C_{15}H_{16}{}^{35}ClFN_2O_3$的计算值:395.1532,实验值:395.1522。

[1652] 实例 4

[1653] 制备 4-氯-5-((4-((2-氟乙氧基)甲基)苯甲基)氧基)-2-苯基哒嗪-3(2H)-酮

[1654] A 部分-制备 4,5-二氯-2-苯基哒嗪-3(2H)-酮

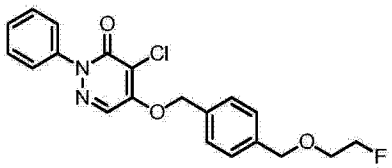
[1655]



[1656] 根据通用方法 A,使用粘氯酸(0.985g,5.83mmol)、碳酸钠(0.309g,2.91mmol)和盐酸苯肼(0.843g,5.83mmol)制备。分离产量为 1.31g;93.2%。^{1}H NMR($CDCl_3$,300MHz):δ7.91(s,1H),7.59-7.54(m,2H),7.48-7.39(m,3H);^{13}C NMR($CDCl_3$,75MHz):δ156.1,140.9,136.4,136.1,135.3,128.9,128.8,125.2;HRMS-TOF(m/z):[M+H]$^+$HRMS:$C_{10}H_6{}^{35}Cl_2N_2O$ 的计算值:240.9930,实验值:240.9932。

[1657] B 部分-制备 4-氯-5-((4-((2-氟乙氧基)甲基)苯甲基)氧基)-2-苯基哒嗪-3(2H)-酮

[1658]



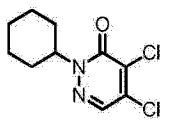
[1659] 根据通用方法 B,使用实例 4A 的产物(0.070g,0.290mmol)、(4-((2-氟乙氧基)甲基)苯基)甲醇(0.160g,0.870mmol)和碳酸铯(0.283g,0.870mmol)于二甲基甲酰胺(2.90mL)中在 80℃下制备。分离产量为 45mg;40%。^{1}H NMR($CDCl_3$,300MHz):δ7.84(s,1H),7.49-7.30(m,9H),5.31(s,2H),4.59(m,1H),4.54(s,2H),4.44(m,1H),3.71(m,1H),3.61(m,1H);^{13}C NMR($CDCl_3$,75MHz):δ158.3,154.0,141.2,138.9,134.0,128.8,128.3,128.2,128.0,127.4,127.1,125.3,81.6(d,J_{CF}= 60Hz),73.1,72.1,69.5(d,J_{CF}= 15Hz);HRMS-TOF(m/z):[M+H]$^+$HRMS:$C_{20}H_{18}{}^{35}ClFN_2O_3$的计算值:327.0906,实验值:327.0901。

[1660] 实例 5

[1661] 制备 4-氯-2-环己基-5-((4-((2-氟乙氧基)甲基)苯甲基)氧基)哒嗪-3(2H)-酮

[1662] A 部分-制备 4,5-二氯-2-环己基哒嗪-3(2H)-酮

[1663]

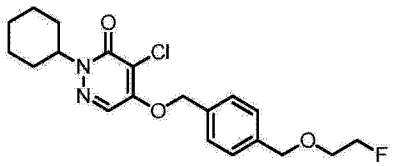


[1664] 根据通用方法 A,使用粘氯酸(0.443g,2.62mmol)、碳酸钠(0.138g,1.31mmol)和盐酸环己基肼(0.403g,2.62mmol)制备。分离产量为 0.440g;67.9 %。^{1}H NMR($CDCl_3$,600MHz):δ7.74(s,1H),4.77(tt,J = 11.6,3.6Hz,1H),

1.79(m,4H),1.68-1.56(m,3H),1.44-1.30(m,2H),1.21-1.06(m,1H);^{13}C NMR(CDCl$_3$,150MHz):δ156.3,135.7,135.1,133.6,58.5,31.1,25.4,25.2;HRMS-TOF(m/z):[M+H]$^+$HRMS:$C_{10}H_{12}{}^{35}Cl_2N_2O$的计算值:247.0399,实验值:247.0399。

[1665] B部分-制备4-氯-2-环己基-5-((4-((2-氟乙氧基)甲基)苯甲基)氧基)哒嗪-3(2H)-酮

[1666]

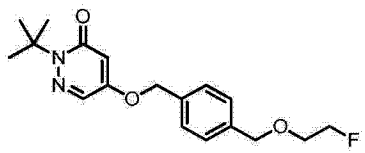


[1667] 根据通用方法B,使用实例5A的产物(31mg,0.13mmol)、(4-((2-氟乙氧基)甲基)苯基)甲醇(29mg,0.16mmol)和碳酸铯(0.123g,0.380mmol)于二甲基甲酰胺(1.26mL)中在55℃下制备。分离产量为25mg;49%。HRMS-TOF(m/z):[M+H]$^+$HRMS:$C_{20}H_{24}{}^{35}ClN_2O_3$的计算值:389.1063,实验值:389.1054。

[1668] 实例6

[1669] 制备2-(叔丁基)-5-((4-((2-氟乙氧基)甲基)苯甲基)氧基)哒嗪-3(2H)-酮

[1670]

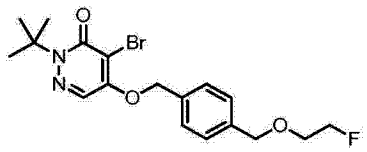


[1671] 使2-(叔丁基)-4-氯-5-((4-((2-氟乙氧基)甲基)苯甲基)氧基)哒嗪-3(2H)-酮(0.184g,0.50mmol;例如参见普罗希特(Purohit,A.);拉迪克S.;阿祖尔;汉森;本尼迪(Benetti,R.);苏(Su,F.);亚拉曼奇尼;于;海耶斯;加拉迪(Guaraldi,M.);卡甘(Kagan,M.);罗宾逊;卡斯贝尔作为潜在心脏正电子发射断层扫描示踪剂的哒嗪酮类似物的合成和生物评估(Synthesis and Biological Evaluation of Pyridazinone Analogs as Potential Cardiac Positron Emission Tomography Tracers)医学化学杂志(J.Med.Chem.)2008,51,2954)悬浮于无水甲苯(5.00mL)中,相继用氢化三丁基锡(0.161g,0.60mmol)和2,2'-偶氮二(2-甲基丙腈)(0.004mg,0.025mmol)处理,随后加热到回流且维持20小时。冷却到环境温度后,在真空中移除所有挥发物,且通过使用从3:1己烷/乙酸乙酯(400mL)到2:1己烷/乙酸乙酯(500mL)的阶段梯度,经二氧化硅(30×190mm)色谱直接纯化残余物。收集在溶离550-750mL时的主要产物峰,合并且真空浓缩成无色油状物(0.101g,0.302mmol;60.3%)。^{1}H NMR:(600MHz,DMSO-d$_6$)δ7.72(1H,d,J=2.9Hz),7.43(2H,AB,J_{AB}=8.1Hz),7.37(2H,AB,J_{AB}=8.1Hz),6.26(1H,d,J=2.9Hz),5.11(s,2H),4.63-4.58(1H,m),4.54(2H,s),4.53-4.49(1H,m),3.73-3.68(1H,m),3.68-3.63(1H,m),1.55(9H,s)。^{13}C NMR:(151MHz,DMSO-d$_6$)δ161.5,158.4,138.4,134.4,130.2,128.1,127.6,105.5,82.9(d,J_{CF}=166Hz),71.6,69.8,69.0(d,J_{CF}=19.0Hz),63.6,27.6。HRMS:$C_{18}H_{23}FN_2O_3$(M+H)的计算值:335.1766;实验值:335.1766。TLC:R_f 0.38(硅胶,1:1己烷/乙酸乙酯,CAM)。

[1672] 实例7

[1673] 制备 4- 溴 -2-(叔丁基)-5-((4-((2- 氟乙氧基) 甲基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

[1674]

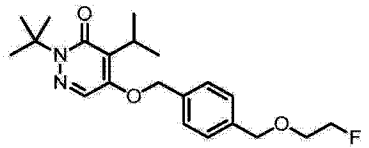


[1675] 根据通用方法B,使用4,5-二溴-2-(叔丁基)哒嗪-3(2H)-酮(0.310g,1.00mmol;例如参见谷口(Taniguchi M.);落合(Ochiai Y.);广濑(Hirose M.);平田(Hirata K.);芭芭(Baba M.)(日产化学公司(Nissan Chemical Industries))苯甲硫基哒嗪酮衍生物,其制备方法和杀螨虫、杀菌组合物(Benzylthio pyridazinone derivatives,preparation thereof,and insecticidal acaricidal,fungicidal compositions).美国专利申请案4,877,787,1989年10月31日)、(4-((2-氟乙氧基)甲基)苯基)甲醇(92.1mg,0.500mmol)和碳酸铯(0.326g,1.00mmol)于二甲基甲酰胺(2.50mL)中在65℃下制备。分离产量为0.121g;58.5%。^{1}H NMR:(300MHz,$CDCl_3$) δ 7.62(1H,s),7.41(4H,s),5.32(2H,s),4.73-4.64(1H,m),4.61(2H,s),4.57-4.48(1H,m),3.85-3.75(1H,m),3.75-3.65(1H,m),1.63(9H,s)。^{13}C NMR:(75MHz,$CDCl_3$) δ 159.3,155.8,138.8,134.6,128.4,127.4,124.8,110.5,83.3(d,J_{CF}= 169Hz),73.2,71.8,69.7(d,J_{CF}= 19.6Hz),66.7,28.1。HRMS:$C_{18}H_{22}{}^{79}BrFN_2O_3$(M+H)的计算值:413.0871;实验值:413.0876。TLC:R 0.31(硅胶,7:3己烷/乙酸乙酯,CAM)。

[1676] 实例 8

[1677] 制备 4- 氯 -2- 环己基 -5-((4-((2- 氟乙氧基) 甲基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

[1678]



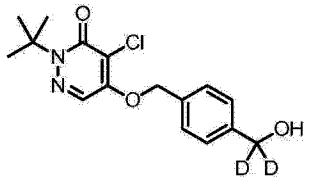
[1679] 向溴化异丙基镁的经冷却(0℃)溶液(0.087mL,2M四氢呋喃溶液)中添加溶解于四氢呋喃(0.783mL)中的2-(叔丁基)-4-氯-5-((4-((2-氟乙氧基)甲基)苯甲基)氧基)-4-哒嗪-3(2H)-酮(32mg,0.087mmol)。在0℃下搅拌反应物2小时,随后用额外当量的溴化异丙基镁(0.261mL,2M四氢呋喃溶液)处理。24小时后,用水(0.5mL)淬灭反应物且用乙酸乙酯(20mL)稀释。分离有机层,用饱和氯化钠水溶液(3×50mL)洗涤,经硫酸镁干燥,过滤且真空浓缩。随后使用硅胶色谱(3:1己烷/乙酸乙酯)纯化粗物质,得到呈透明油状的所需产物(12.0mg,产率36.6%)。^{1}H NMR($CDCl_3$,300MHz):δ 7.67(s,1H),7.41(d,J = 7.5Hz,2H),7.37(d,J = 8.7Hz,2H),5.17(s,2H),4.68(m,1H),4.62(s,2H),4.53(m,1H),3.80(m,1H),3.71(m,1H),3.50(m,1H),1.62(s,9H),1.27(d,J = 7.1Hz,6H);^{13}C NMR($CDCl_3$,75MHz):δ 162.3,154.2,138.3,135.4,129.3,128.1,127.4,125.8,83.1(d,J_{CF}= 165Hz),73.0,70.8,69.4(d,J_{CF}= 22.5Hz),65.0,28.1,24.6,19.5;HRMS-TOF(m/z):$[M+H]^+$HRMS:$C_{21}H_{29}FN_2O_3$的计算值:377.2235,实验值:377.2231。

[1680] 实例 9

[1681] 制备 2-(叔丁基)-4-氯-5-((4-((2-氟乙氧基)-d_2-甲基)苯甲基)氧基)哒嗪-3(2H)-酮

[1682] A 部分-制备 2-(叔丁基)-4-氯-5-((4-(d_2-羟甲基)苯甲基)氧基)哒嗪-3(2H)-酮

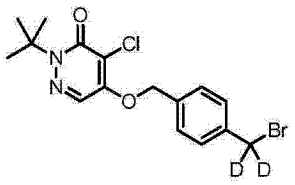
[1683]



[1684] 在 0℃下,向 4-(((1-叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯甲酸甲酯 (1.50g,4.28mmol;例如参见切萨迪 (Cesati,R);切斯曼 (Cheesman,E.H.);拉泽瓦斯基 (Lazewatsky,J.);拉德科 (Radeke,S.);卡斯尼 (Castner,J.F.);蒙格奥 (Mongeau,E.);泽丹维茨 (Zdankiewicz,D.D.);希格勒 (Siegler,R.W.);德维尼 (Devine,M.) 用于合成造影剂和其中间物的方法和装置 (Methods and apparatus for synthesizing imaging agents,and intermediates thereof).PCT 国际申请案 (2011),WO 2011/097649,2011 年 8 月 8 日) 于四氢呋喃 (42.8mL) 中的溶液中逐滴添加氘化锂铝 (2.14mL,2.14mmol,1M 四氢呋喃溶液)。搅拌所得混合物 2 小时,随后用水 (20ml) 处理。分离水层且用乙酸乙酯 (3×50mL) 萃取。用饱和氯化钠水溶液洗涤经合并的有机层,经硫酸钠干燥,过滤且浓缩,得到白色固体 (1.36g,产率 97.8%)。^{1}H NMR($CDCl_3$,300MHz):δ 7.64(s,1H),7.35(br s,4H),5.24(s,2H),1.56(s,9H);^{13}C NMR($CDCl_3$,75MHz, 部分):δ 159.0,153.7,141.5,134.3,127.5,127.3,125.1,118.4,71.7,64.4,27.9;HRMS-TOF(m/z):$[M+H]^+$HRMS:$C_{16}H_{17}D_2{}^{35}ClN_2O_3$的计算值:325.1283,实验值:325.1284。

[1685] B 部分-制备 5-((4-(溴-d_2-甲基)苯甲基)氧基)-2-(叔丁基)-4-氯哒嗪-3(2H)-酮

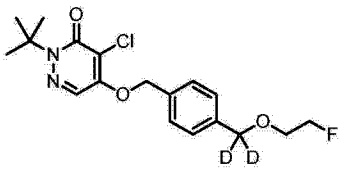
[1686]



[1687] 根据通用方法 C,使用实例 9A 的产物 (0.882g,2.72mmol) 和三溴化磷 (1.36mL,1.36mmol,1M 二氯甲烷溶液) 制备。分离产量为 0.981g;93.0%。^{1}H NMR($CDCl_3$,300MHz):δ 7.64(s,1H),7.37(d,J = 8.5Hz,2H),7.32(d,J = 8.5Hz,2H),5.23(s,2H),1.59(s,9H);^{13}C NMR($CDCl_3$,75MHz, 部分):δ 159.0,153.6,138.3,135.1,129.6,127.5,125.0,118.4,71.4,66.5,27.9;HRMS-TOF(m/z):$[M+H]^+$HRMS:$C_{16}H_{16}D_2{}^{79}Br^{35}ClN_2O_2$的计算值:387.0438,实验值:387.0439。

[1688] C 部分-制备 2-(叔丁基)-4-氯-5-((4-((2-氟乙氧基)-d_2-甲基)苯甲基)氧基)哒嗪-3(2H)-酮

[1689]



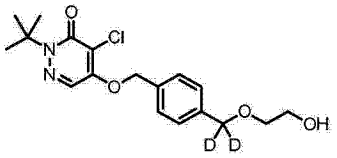
[1690] 根据通用方法E，使用叔丁醇钾(25.3mg，0.225mmol)、2-氟乙醇(14.5mg，0.226mmol)和实例9B的产物(0.105g，0.271mmol)制备。分离产量为7.5mg；9.8%。^{1}H NMR($CDCl_3$，300MHz)：δ 7.74(s，1H)，7.33(s，4H)，5.24(s，2H)，4.60(m，1H)，4.45(s，1H)，3.72(m，1H)，3.63(m，1H)，1.56(s，9H)；^{13}C NMR($CDCl_3$，75MHz，部分)：δ 159.0，153.7，138.6，134.4，128.3，127.3，125.1，118.4，83.1(d，J_{CF}＝165Hz)，71.7，69.4(d，J_{CF}＝15Hz)，66.4，27.9；HRMS-TOF(m/z)：$[M+H]^+$HRMS：$C_{18}H_{20}D_2{}^{35}ClFN_2O_3$的计算值：371.1501，实验值：371.1507。

[1691] 实例10

[1692] 制备2-((4-(((1-(叔丁基)-5-氯-6-侧氧基-1，6-二氢哒嗪-4-基)氧基)-d_2-甲基)苯甲基)氧基)乙基-4-甲基苯磺酸酯

[1693] A部分-制备2-(叔丁基)-4-氯-5-((4-((2-羟基乙氧基)-d_2-甲基)苯甲基)氧基)哒嗪-3(2H)-酮

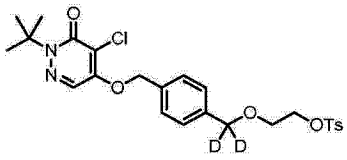
[1694]



[1695] 将叔丁醇钾(0.174g，1.55mmol)于乙二醇(0.685mL)中的悬浮液加热到60℃，维持20分钟，随后用实例9B的产物(0.720g，1.86mmol)于四氢呋喃(21mL)中的溶液处理。加热所得混合物至回流，维持16小时，随后冷却到环境温度且用水(15mL)处理。分离水层，随后用乙酸乙酯(3×50mL)萃取。经硫酸钠干燥经合并的有机层，过滤且真空浓缩。随后使用硅胶色谱(20-50%乙酸乙酯的己烷溶液)纯化粗物质，得到呈黄色油状的所需产物(0.144g，产率25.2%)。^{1}H NMR($CDCl_3$，300MHz)：δ 7.65(s，1H)，7.33(s，4H)，5.24(s，2H)，3.71(m，2H)，3.54(m，2H)，1.56(s，9H)；^{13}C NMR($CDCl_3$，75MHz，部分)：δ 159.0，153.6，138.6，134.4，128.3，127.2，125.0，118.3，71.6，71.5，66.4，61.9，27.8；HRMS-TOF(m/z)：$[M+H]^+$HRMS：$C_{18}H_{21}D_2{}^{35}ClN_2O_4$的计算值：369.1545，实验值：369.1548。

[1696] B部分-制备2-((4-(((1-(叔丁基)-5-氯-6-侧氧基-1，6-二氢哒嗪-4-基)氧基)-d_2-甲基)苯甲基)氧基)乙基-4-甲基苯磺酸酯

[1697]



[1698] 根据通用方法D，使用实例10A的产物(78.2mg，0.213mmol)、对甲苯磺酰氯(48.6mg，0.255mmol)、4-二甲基氨基吡啶(31.2mg，0.255mmol)和二异丙基乙氨(0.044mL，0.255mmol)制备。分离产量为32.8mg；29.4%。^{1}H($CDCl_3$，600MHz)：δ 7.72(d，J＝8.4Hz，2H)，7.65(s，1H)，7.31(d，J＝8.3Hz，2H)，7.26-7.19(m，4H)，5.23(s，2H)，4.13(m，

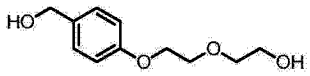
2H), 3.62(m, 2H), 2.37(s, 3H), 1.51(s, 9H) ; $^{13}C(CDCl_3, 150MHz$, 部分): δ 159.0, 153.6, 144.8, 138.3, 134.4, 133.0, 129.8, 128.2, 128.0, 127.2, 125.0, 118.3, 71.6, 69.2, 67.7, 66.4, 27.8, 21.6 ; HRMS-TOF(m/z): $[M+H]^+$ HRMS: $C_{25}H_{27}D_2{}^{35}ClN_2O_6S$ 的计算值: 523.1633, 实验值: 523.1629。

[1699] 实例 11

[1700] 制备 2-(2-(4-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯氧基)乙氧基)乙基-4-甲基苯磺酸酯

[1701] A 部分 - 制备 2-(2-(4-(羟甲基)苯氧基)乙氧基)乙醇

[1702]

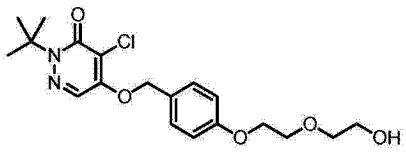


[1703] 将碘化钾 (1.10g, 6.58mmol)、甲基-4-羟基苯甲酸酯 (2.00g, 13.1mmol)、碳酸铯 (8.53g, 26.2mmol) 和 2-(2-氯乙氧基)乙醇 (3.60mL, 34.0mmol) 于环己酮 (40.0mL) 中的悬浮液加热到回流且维持 24 小时。冷却到环境温度后, 通过过滤移除固体且浓缩所得滤液成橙色油状物, 其未经进一步纯化直接用于后续还原。

[1704] 将粗酯的四氢呋喃溶液 (35.0mL) 冷却到 0 ℃, 随后用氢化锂铝 (9.12mL, 9.12mmol, 1M 四氢呋喃溶液) 处理。在添加完成时, 将所得混合物温热到环境温度且搅拌隔夜, 随后用水 (20mL) 处理。随后分离每个层且用乙酸乙酯 (2×50mL) 萃取水层。随后经硫酸钠干燥经合并的有机层, 过滤且浓缩成黄色油状物 (0.789g, 产率 28.4%)。^1H NMR(CDCl$_3$, 300MHz): δ 7.21(m, 2H), 6.83(m, 2H), 4.55(s, 2H), 4.07(m, 2H), 3.80(m, 2H), 3.70(m, 2H), 2.60(m, 2H)。

[1705] B 部分 - 制备 2-(叔丁基)-4-氯-5-((4-(2-(2-羟基乙氧基)乙氧基)苯甲基)氧基)哒嗪-3(2H)-酮

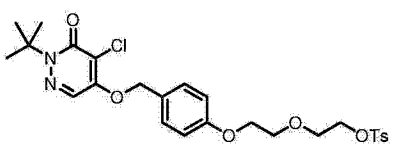
[1706]



[1707] 在环境温度下, 相继用实例 11A 的产物 (0.327g, 1.54mmol)、三苯基膦 (0.609g, 2.32mmol) 和偶氮二甲酸二乙酯 (0.404g, 2.32mmol) 处理 2-(叔丁基)-4-氯-5-羟基哒嗪-3(2H)-酮 [4] (0.375g, 1.85mmol) 于四氢呋喃 (15.4mL) 中的溶液。1 小时后, 在真空中移除所有挥发物且通过硅胶色谱使用 4:1 乙醚 / 乙酸乙酯直接纯化残余物, 得到所需产物 (20mg, 产率 3%)。^1H NMR(CDCl$_3$, 300MHz): δ 7.72(s, 1H), 7.31(m, 2H), 6.96(m, 2H), 5.25(s, 2H), 4.16(m, 2H), 3.88(m, 2H), 3.76(m, 2H), 3.68(m, 2H), 1.63(s, 9H)。

[1708] C 部分 - 制备 2-(2-(4-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯氧基)乙氧基)乙基-4-甲基苯磺酸酯

[1709]

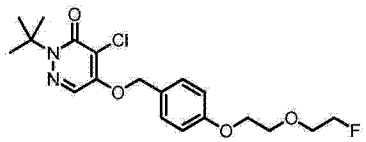


[1710] 根据通用方法D，使用实例11B的产物(19.7mg，0.0495mmol)、对甲苯磺酰氯(11.3mg，0.0594mmol)、4-二甲基氨基吡啶(7.26mg，0.0594mmol)和二异丙基乙氨(0.010mL，0.0594mmol)制备。分离产量为5.2mg；19%。^{1}H($CDCl_3$，300MHz)：δ 7.72(d，J＝8.3Hz，2H)，7.66(s，1H)，7.28-7.19(m，4H)，6.85(m，2H)，5.18(s，2H)，4.14(m，2H)，3.99(m，2H)，3.74-3.68(m，4H)，2.34(s，3H)，1.56(s，9H)。

[1711] 实例12

[1712] 制备2-(叔丁基)-4-氯-5-((4-(2-(2-氟乙氧基)乙氧基)苯甲基)氧基)哒嗪-3(2H)-酮

[1713]

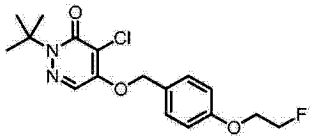


[1714] 将实例11C的产物(1.90mg，0.0034mmol)、氟化四乙铵(0.85mg，0.0046mmol)及碳酸氢四乙铵(0.88mg，0.0046mmol)于乙腈(0.70mL)中的溶液加热到90℃且维持10分钟。冷却到环境温度后，在真空中移除所有挥发物且通过制备型薄层色谱使用4:1己烷/乙酸乙酯直接纯化残余物，得到所需产物(0.2mg，产率15%)。API-ES[M+Na]421.1。

[1715] 实例13

[1716] 制备2-(叔丁基-4-氯-5-((4-(2-氟乙氧基)苯甲基)氧基)哒嗪-3(2H)-酮

[1717]



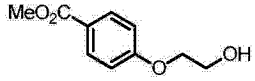
[1718] 根据通用方法B，使用2-(叔丁基)-4，5-二氯哒嗪-3(2H)-酮[3](68mg，0.31mmol)、(4-(2-氟乙氧基)苯基)甲醇(53mg，0.31mmol，例如参见Zhou，D.；Chu，W.；Rothfuss，J.；Zeng，C.；Xu，J.；Jones，L.；Welch，M.J.；Mach，R.H.Synthesis，radiolebeling and in vivo evaluation of an 18F-labeled isatin analog for imaging caspase-3activation in apoptosis Bioorg.Med.Chem.Lett.2006，16，5041-5045)及碳酸铯(0.303g，0.930mmol)于二甲基甲酰胺(3.10mL)中在50℃下制备。分离产量为25mg；23%。^{1}H NMR($CDCl_3$，300MHz)：δ 7.72(s，1H)，7.33(m，2H)，6.95(m，2H)，5.25(s，2H)，4.84(m，1H)，4.68(m，1H)，4.29(m，1H)，4.16(m，1H)，1.57(s，9H)。

[1719] 实例14

[1720] 制备2-(4-(((1-(叔丁基)-5-氯-6-侧氧基-1，6-二氢哒嗪-4-基)氧基)甲基)苯氧基)乙基-4-甲基苯磺酸酯

[1721] A部分-制备4-(2-羟基乙氧基)苯甲酸甲酯

[1722]

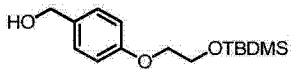


[1723] 将4-羟基苯甲酸甲酯(1.52g，1.00mmol)、1-溴乙醇(1.05mL，1.5mmol)及碳酸铯(8.13g，2.5mmol)于二甲基甲酰胺(100mL)中的悬浮液加热到65℃且维持隔夜。冷却到环

境温度后，用水（250mL）稀释所得混合物，随后用乙酸乙酯（3×250mL）萃取。用水及饱和氯化钠水溶液洗涤经合并的有机层，随后经硫酸钠干燥，过滤且浓缩成黄色油状物（1.83g，产率93.3％）。^{1}H NMR（$CDCl_3$，300MHz）：δ 7.92（m，2H），6.86（m，2H），4.45（s，3H），4.08（m，2H），3.92（m，2H）；^{13}C NMR（$CDCl_3$，75MHz）：δ 166.8，162.4，131.6，123.1，114.2，69.4，61.3，51.9；HRMS-TOF（m/z）：[M+H]$^{+}$HRMS：$C_{10}H_{12}O_4$的计算值：197.0808，实验值：197.0811。

[1724] B 部分－制备（4-（2-（（叔丁基二甲基硅烷基）氧基）乙氧基）苯基）甲醇

[1725]

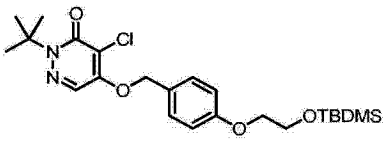


[1726] 在环境温度下，相继用氯化叔丁基二甲基硅烷基（1.14g，7.61mmol）及咪唑（0.518g，7.61mmol）处理实例 14A 的产物（1.00g，5.07mmol）于二甲基甲酰胺（50.0mL）中的溶液。1 小时后，用 0.1N 盐酸（30mL）稀释溶液，随后用乙酸乙酯（3×150mL）萃取。用饱和氯化钠水溶液洗涤经合并的有机层，经硫酸钠干燥，过滤且真空浓缩，获得粗油状物，其无需进一步纯化即可用于后续步骤中。

[1727] 将粗甲硅烷基醚（0.965g，3.11mmol）溶解于四氢呋喃（31.1mL）中，冷却到 0℃，随后用氢化锂铝（1.55mL，1.55mmol，1M 含氢化锂铝的四氢呋喃溶液）处理且温热到环境温度。4 小时后，用水（10mL）处理所得混合物且分离每个层。用乙酸乙酯（3×50mL）萃取水层且经硫酸钠干燥经合并的有机层，过滤，随后真空浓缩，得到油状物（0.779g，产 率 54.4 ％ ）。^{1}H NMR（DMSO-d_6，300MHz）：δ 7.14（m，2H），6.80（m，2H），4.96（t，J ＝ 5.7Hz，1H），4.35（d，J ＝ 5.6Hz，2H），3.95-3.83（m，4H），0.80（s，9H），0.01（s，6H）。

[1728] C 部分－制备 2-（叔丁基）-5-（（4-（2-（（叔丁基二甲基硅烷基）氧基）乙氧基）苯甲基）氧基）-4-氯哒嗪-3（2H）-酮

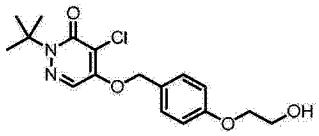
[1729]



[1730] 在环境温度下，相继用实例 14B 的产物（0.779g，2.76mmol）、三苯基膦（0.905g，3.45mmol）及偶氮二甲酸二异丙酯（0.686mL，3.45mmol）处理 2-（叔丁基）-4-氯-5-羟基哒嗪-3（2H）-酮（0.465g，2.29mmol）于四氢呋喃（27.6mL）中的溶液。20 分钟后，用水（5mL）处理所得混合物，分离水层，随后用乙酸乙酯（3×50mL）萃取。经硫酸钠干燥经合并的有机层，过滤且真空浓缩。随后使用硅胶色谱（20-50％乙酸乙酯的己烷溶液）纯化粗物质，得到呈透明油状的所需产物（0.359，产率 33.6％）。^{1}H NMR（$CDCl_3$，300MHz）：δ 7.63（s，1H），7.23（m，2H），6.86（m，2H），5.15（s，2H），4.01（m，2H），3.87（m，2H），1.53（s，9H），0.82（s，9H），0.01（s，6H）；^{13}C NMR（$CDCl_3$，75MHz，部分）：δ 159.1，153.7，129.0，127.4，125.3，118.4，115.0，71.8，69.9，66.4，61.4，27.9，26.6，-3.6；HRMS-TOF（m/z）：[M+H]$^{+}$HRMS：$C_{23}H_{35}{}^{35}ClN_2O_4Si$ 的计算值：467.2127，实验值：467.2128。

[1731] D 部分－制备 2-（叔丁基）-4-氯-5-（（4-（2-羟基乙氧基）苯甲基）氧基）哒嗪-3（2H）-酮

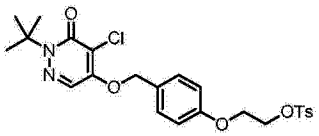
[1732]



[1733] 在环境温度下，用氟化四丁铵 (1.03mL，1.03mmol，1M 四氢呋喃溶液) 逐滴处理实例 14C 的产物 (0.240g，0.513mmol) 于四氢呋喃 (5.13mL) 中的溶液。40 分钟后，用水 (5mL) 稀释所得混合物，分离水层，随后用乙酸乙酯 (3×15mL) 萃取。经硫酸钠干燥经合并的有机层，过滤且浓缩，得到灰白色固体 (0.157g，产率 86.7％)。^{1}H NMR($CDCl_3$，300MHz)：δ 7.62(s，1H)，7.27(m，2H)，7.89(m，2H)，5.18(s，2H)，4.03(m，2H)，3.90(m，2H)，1.57(s，9H) ；^{13}C NMR($CDCl_3$，75MHz，部分)：δ 159.1，153.8，129.0，127.4，125.3，118.4，115.0，71.7，69.3，66.4，61.4，27.9 ；HRMS-TOF(m/z)：[M+H]$^{+}$HRMS：$C_{17}H_{21}{}^{35}ClN_2O_4$ 的计算值 ：375.1082，实验值 ：375.1079。

[1734] E 部分 - 制备 2-(4-(((1-(叔丁基)-5- 氯 -6- 侧氧基 -1，6- 二氢哒嗪 -4- 基) 氧基) 甲基) 苯氧基) 乙基 -4- 甲基苯磺酸酯

[1735]



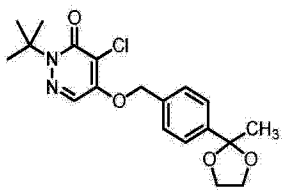
[1736] 根据通用方法 D，使用实例 14D 的产物 (0.157g，0.446mmol)、对甲苯磺酰氯 (0.102g，0.536mmol)、4- 二甲基氨基吡啶 (81.9mg，0.67mmol) 及三乙氨 (0.075mL，0.536mmol) 制备。分离产量为 0.120g ；53.1 ％。^{1}H($CDCl_3$，600MHz)：δ 7.74(d，J = 8.3Hz，2H)，7.64(s，1H)，7.28-7.19(m，4H)，6.75(m，2H)，5.16(s，2H)，4.30(m，2H)，4.09(m，2H)，2.38(s，3H)，1.56(s，9H) ；^{13}C NMR($CDCl_3$，150MHz)：δ 159.0，158.5，153.7，145.0，132.9，129.9，128.9，128.0，127.7，125.2，118.4，115.0，71.7，67.9，66.4，65.6，27.9，21.6 ；HRMS-TOF(m/z)：[M+H]$^{+}$HRMS：$C_{24}H_{27}{}^{35}ClN_2O_6S$ 的计算值 ：507.1351，实验值 ：507.1365。

[1737] 实例 15

[1738] 制备 4- 甲基苯磺酸 2-(1-(4-(((1-(叔丁基)-5- 氯 -6- 侧氧基 -1，6- 二氢哒嗪 -4- 基) 氧基) 甲基) 苯基) 乙氧基) 乙酯

[1739] A 部分 - 制备 2-(叔丁基)-4- 氯 -5-((4-(2- 甲基 -1，3- 二氧杂环戊烷 -2- 基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

[1740]

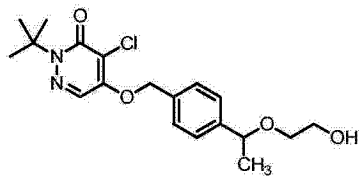


[1741] 在环境温度下，用碳酸铯 (3.26g，10.0mmol) 一次性处理 2-(叔丁基)-4，5- 二氯 -2- 氢哒嗪 -3- 酮 (1.66g，7.50mmol) 及 (4-(2- 甲基 -1，3- 二氧杂环戊烷 -2- 基) 苯基) 甲醇 (0.971g，5.00mmol ；例如参见 Takebayashi，S. ；Dabral，N. ；Miskolzie，M. ；

Bergens, S. H. 美国化学会志 , 2011, 133, 25, 9666-9669) 于无水二甲基甲酰胺 (50.0mL) 中的溶液。随后将所得悬浮液浸于预热油浴中，且在剧烈搅拌下，在 65℃下维持 4 小时。冷却到环境温度后，再维持悬浮液 12 小时，随后分配于乙酸乙酯与水 (每个 50mL) 之间，转移到分液漏斗中。随后分离每个层，且用乙酸乙酯 (2×50mL) 洗涤水层。用饱和氯化钠水溶液 (5×50mL) 进一步洗涤经合并的乙酸乙酯洗涤液，随后经硫酸镁干燥，过滤且真空浓缩成黄色固体。随后通过使用 7:3 戊烷 / 乙酸乙酯经二氧化硅 (40×220mm) 色谱来纯化粗物质。收集在溶离 400-700mL 时的主要产物峰，合并且真空浓缩成白色固体。随后使纯化物质自热乙酸乙酯 / 戊烷再结晶，得到无色针状物 (1.33g, 3.51mmol ;70.1％)。^{1}H NMR: (300MHz, DMSO-d_6) δ 8.27 (1H, s), 7.52-7.36 (4H, m), 5.44 (2H, s), 4.07-3.93 (2H, m), 3.76-3.60 (2H, m), 1.57 (9H, s), 1.55 (3H, s)。^{13}C NMR: (75MHz, DMSO-d_6) δ 157.8, 153.9, 143.6, 134.9, 127.7, 126.2, 125.4, 115.5, 107.9, 71.2, 65.4, 64.1, 27.5, 27.2。HRMS : $C_{19}H_{23}{}^{35}ClN_2O_4$ (M+H) 的计算值 :379.1419 ;实验值 :379.1416。TLC: R_f 0.39 (硅胶，7:3 戊烷 / 乙酸乙酯，uv)。

[1742] B 部分 - 制备 2-(叔丁基)-4- 氯 -5-((4-(1-(2- 羟基乙氧基) 乙基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

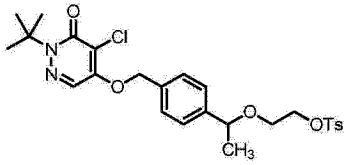
[1743]



[1744] 在环境温度下，将氯化锆 (0.233g, 1.00mmol) 及无水四氢呋喃 (3.00mL) 馈入 25mL 直火干燥的圆底烧瓶中。随后在环境温度下，用硼氢化钠 (75.7mg, 2.00mmol) 一次性处理所得溶液，接着历时 3 分钟逐滴用实例 15A 的产物 (1.00mmol ;2.00mL 0.5M 四氢呋喃溶液) 处理。1.5 小时后，通过逐滴添加水消耗过量硼氢化钠，且将所得溶液分配于乙酸乙酯与水 (每个 25mL) 之间，转移到分液漏斗中。随后分离每个层，且用乙酸乙酯 (2×25mL) 洗涤水层。随后经硫酸镁干燥经合并的乙酸乙酯洗涤液，过滤且真空浓缩。随后通过使用 1:1 戊烷 / 乙酸乙酯经二氧化硅 (30×170mm) 色谱来纯化由此获得的粗物质。收集在溶离 250-460mL 时的主要产物峰，合并且真空浓缩成无色油状物 (0.289g, 0.758mmol ; 75.8％)。^{1}H NMR: (300MHz, $CDCl_3$) δ 7.74 (1H, s), 7.45-7.29 (4H, m), 5.29 (2H, s), 4.47 (1H, q, J = 6.5Hz), 3.79-3.63 (2H, m), 3.52-3.35 (2H, m), 1.63 (9H, s), 1.46 (3H, d, J = 6.5Hz)。^{13}C NMR: (75MHz, $CDCl_3$) δ 159.0, 153.7, 144.3, 134.1, 127.4, 126.7, 125.1, 118.3, 78.1, 71.7, 69.8, 66.4, 62.0, 27.9, 23.9。HRMS : $C_{19}H_{25}{}^{35}ClN_2O_4$ (M+H) 的计算值 :381.1576 ;实验值 : 381.1574。

[1745] C 部分 - 制备 4- 甲基苯磺酸 2-(1-(4-(((1-(叔丁基)-5- 氯 -6- 侧氧基 -1, 6- 二氢哒嗪 -4- 基) 氧基) 甲基) 苯基) 乙氧基) 乙酯

[1746]

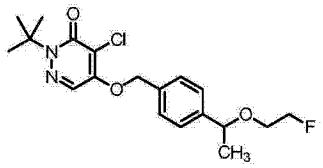


[1747] 将实例 15B 的产物 (95.2mg,0.250mmol) 于无水吡啶 (0.50mL) 中的溶液冷却到 0℃,随后用对甲苯磺酰氯 (95.3mg,0.50mmol) 一次性处理。0.25 小时后,将所得溶液温热到环境温度且维持 3.25 小时,同时再添加对甲苯磺酰氯 (95.3mg,0.50mmol)。0.75 小时后,用乙酸乙酯 (150mL) 及水 (50mL) 稀释所得溶液,转移到分液漏斗中。随后分离每个层且相继用 0.1M 盐酸及饱和碳酸氢钠水溶液 (每个 3×50mL) 洗涤乙酸乙酯层,随后经硫酸镁干燥,过滤且真空浓缩。随后通过使用 3:2 戊烷 / 乙酸乙酯经二氧化硅 (30×175mm) 色谱来纯化由此获得的粗物质。收集在溶离 150-250mL 时的主要产物峰,合并且真空浓缩成无色油状物 (62.1mg,0.116mmol ;46.4%)。^{1}H NMR:(300MHz,DMSO-d_6) δ 8.28(1H,s),7.82-7.71(2H,AA'BB',J_{AB}= 8.3Hz,$J_{AA'}$= 2.0Hz),7.45(2H,AB,d,J_{AB}= 8.6Hz),7.42(2H,AB,J_{AB}= 8.1Hz),7.28(2H,AB,J_{AB}= 8.1Hz),5.44(2H,s),4.42(1H,q,J = 6.4Hz),4.11(2H,ABdd,J_{AB} = 11.2Hz,J_{dd}= 5.7,3.0Hz),3.40(2H,ABdd,J_{AB}= 11.9Hz,J_{dd}= 5.6,3.0Hz),2.41(3H,s),1.57(9H,s),1.27(3H,d,J = 6.4Hz)。^{13}C NMR:(75MHz,DMSO-d_6) δ 157.8,153.9,144.8,143.6,134.5,132.5,130.1,127.9,127.6,126.2,126.2,115.5,76.7,71.3,70.1,65.5,65.4,27.5,23.4,21.0。HRMS :$C_{26}H_{31}{}^{35}ClN_2O_6S$(M+H) 的计算值 :535.1644 ;实验值 :535.1657。TLC :R_f 0.58(硅胶,1:1 戊烷 / 乙酸乙酯,uv)。

[1748] 实例 16

[1749] 制备 2-(叔丁基)-4- 氯 -5-((4-(1-(2- 氟乙氧基) 乙基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

[1750]



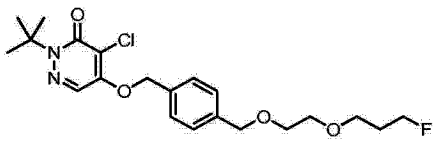
[1751] 在环境温度下,用氟化钾 (17.4mg,0.300mmol) 一次性处理实例 15C 的产物 (79.7mg,0.150mmol) 及 4,7,13,16,21,24- 六氧杂 -1,10- 二氮杂双环 [8.8.8] 二十六烷 (113mg,0.200mmol) 于无水乙腈 (1.50mL) 中的溶液。随后将所得悬浮液浸于预热油浴中,且在 90℃下维持 0.25 小时。冷却到环境温度后,在真空中移除所有挥发物,且通过使用 1:1 戊烷 / 乙醚经二氧化硅 (30×160mm) 色谱直接纯化残余物。收集在溶离 140-220mL 时的主要产物峰,合并且真空浓缩成无色油状物 (42.6mg,0.111mmol ;74.2 %)。^{1}H NMR:(300MHz,$CDCl_3$) δ 7.74(1H,s),7.45-7.30(4H,m),5.29(2H,s),4.53(2H,ddd,J = 47.7,4.7,3.7Hz),4.51(1H,q,J = 6.5Hz),3.69-3.53(1H,m),3.59-3.44(1H,m),1.63(9H,s),1.47(3H,d,J = 6.5Hz)。^{13}C NMR:(75MHz,$CDCl_3$) δ 159.0,153.7,144.2,134.1,127.4,126.7,125.1,118.3,83.1(d,J_{CF}= 169Hz),78.1,71.7,67.7(d,J_{CF}= 19.8Hz),66.4,27.8,24.0。^{19}F NMR(282MHz,$CDCl_3$) δ -223.2(tt,J = 47.8,29.6Hz)。HRMS :$C_{19}H_{24}{}^{35}ClFN_2O_3$(M+H) 的计算值 :383.1532 ;实验值 :383.1531。TLC :R_f 0.40(硅胶,1:1 戊烷

/ 乙醚，uv）。

[1752] 实例 17

[1753] 制备 2-（叔丁基）-4- 氯 -5-((4-((2- 氟丙氧基）乙氧基）甲基）苯甲基）氧基）哒嗪 -3(2H)- 酮

[1754]

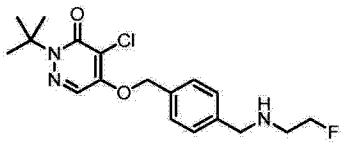


[1755] 将叔丁醇钾 (0.174g,1.55mmol)、对甲苯磺酸 3- 氟丙酯 (0.152g,0.654mmol) 及 2-（叔丁基）-4- 氯 -5-((4-((2- 氟乙氧基）甲基）苯甲基）氧基）-4- 哒嗪 -3(2H)- 酮 (0.200g,0.59mmol) 于四氢呋喃 (5.90mL) 中的悬浮液加热到回流且维持隔夜。冷却到环境温度后，用水 (15mL) 处理所得混合物，分离水层，随后用乙酸乙酯 (3×50mL) 萃取。经硫酸钠干燥经合并的有机层，过滤且真空浓缩。随后通过制备型薄层色谱使用 4:1 己烷 / 乙酸乙酯经二氧化硅纯化粗物质，得到呈黄色油状的所需产物 (0.8mg，产率 1％）。API-ES(m/z)：[M+H]427.2。

[1756] 实例 18

[1757] 制备 2-（叔丁基）-4- 氯 -5-((4-(((2- 氟乙基）氨基）甲基）苯甲基）氧基）哒嗪 -3(2H)- 酮

[1758]

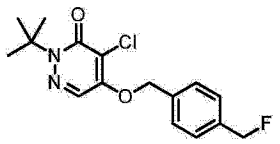


[1759] 在环境温度下，相继用盐酸 2- 氟乙氨 (62.2mg,0.625mmol) 及二异丙基乙氨 (0.136mL,0.782mmol) 处理 5-((4-（溴甲基）苯甲基）氧基）-2-（叔丁基）-4- 氯哒嗪 -3(2H)- 酮 [3](0.200g,0.521mmol) 于二甲基甲酰胺 (5.20mL) 中的溶液。2 天后，用水 (50mL) 稀释所得混合物，分离水层，随后用乙酸乙酯 (3×50mL) 萃取。经硫酸钠干燥经合并的有机层，过滤且真空浓缩。随后使用硅胶色谱 (50-80％乙酸乙酯的己烷溶液）纯化粗物质，得到呈透明油状的所需产物 (17.2mg，产率 9.0％）。^{1}H NMR($CDCl_3$,600MHz)：δ 7.64(s,1H),7.40(d,J = 8.2Hz,2H),7.34(d,J = 8.3Hz,2H),5.22(s,2H),4.65(m,1H),4.50(m,1H),3.90(s,2H),2.97(m,1H),2.88(m,1H),1.56(s,9H)；^{13}C NMR($CDCl_3$,150MHz)：δ 158.0,152.7,138.1,133.1,128.0,126.9,126.4,117.3,81.8(d,J_{CF}= 165Hz),70.7,65.4,51.8,47.4(d,J_{CF}= 22.5Hz),26.9；HRMS-TOF(m/z)：[M+H] $^{+}$HRMS:$C_{18}H_{23}{}^{35}ClFN_3O_2$的计算值：368.1536，实验值：368.1533。

[1760] 实例 19

[1761] 制备 2-（叔丁基）-4- 氯 -5-((4-（氟甲基）苯甲基）氧基）哒嗪 -3(2H)- 酮

[1762]



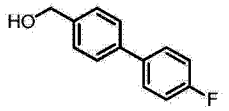
[1763] 在环境温度下，用氟化银 (72.4mg，0.570mmol) 一次性处理 5-((4-(溴甲基)苯甲基)氧基)-2-(叔丁基)-4-氯哒嗪-3(2H)-酮[3](0.110g，0.285mmol) 于无水乙腈 (2.85mL) 中的溶液。0.25 小时后，将所得悬浮液浸于预热油浴中，且在 65℃下维持 0.75 小时，同时添加额外氟化银 (72.4mg，0.570mmol)。1 小时后，将所得悬浮液冷却到环境温度，在真空中移除所有挥发物，且通过使用 4:1 己烷 / 乙酸乙酯经二氧化硅 (25×185mm) 色谱直接纯化残余物。收集在溶离 280-420mL 时的主要产物峰，合并且真空浓缩成白色固体 (64.6mg，0.199mmol ；69.8％)。^{1}H NMR:(300MHz,DMSO-d_6) δ 8.25(1H,s),7.56-7.42(4H,m),5.48(2H,d,J = 1.4Hz),5.43(2H,d,J = 47.7Hz),1.57(9H,s)。^{13}C NMR:(75MHz,DMSO-d_6) δ 157.8,153.8,136.4(d,J_{CF}= 16.7Hz),135.9(d,J_{CF}= 3.1Hz),128.1(d,J_{CF}= 5.7Hz),127.9(d,J_{CF}= 1.4Hz),126.1,115.6,83.8(d,J_{CF}= 162Hz),71.1,65.4,27.4。^{19}F NMR:(282MHz,DMSO-d_6) δ -205.4(t,J = 47.7Hz)。HRMS :$C_{16}H_{18}{}^{35}ClFN_2O_2$(M+H) 的计算值：325.1114 ；实验值 ：325.1117。TLC ：R_f 0.24(硅胶，4:1 己烷 / 乙酸乙酯，uv)。

[1764] 实例 20

[1765] 制备 2-(叔丁基)-4-氯-5-((4'-氟-[1,1'-联二苯]-4-基)甲氧基)哒嗪-3(2H)-酮

[1766] A 部分 - 制备 (4'-氟-[1,1'-联二苯]-4-基) 甲醇

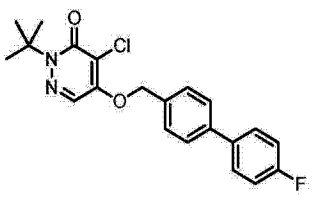
[1767]



[1768] 将 4-(4-氟苯基)苯甲酸 (0.500g，2.31mmol) 于四氢呋喃 (23.1mL) 中的溶液冷却到 0℃，用氢化锂铝 (1.15mL，1.15mmol，1M 四氢呋喃溶液) 处理，随后温热到环境温度且搅拌隔夜。随后用水 (20mL) 处理所得混合物，分离水层，随后用乙酸乙酯 (3×100mL) 萃取。用饱和氯化钠水溶液洗涤经合并的有机层，经硫酸钠干燥，过滤且浓缩成白色固体 (0.290g，产率 62.1％)。^{1}H NMR($CDCl_3$,300MHz)：δ 7.48-7.44(m,2H),7.46(d,J = 8.5Hz,2H),7.36(d,J = 8.5Hz,2H),7.04(m,2H),4.67(s,2H)；^{13}C NMR($CDCl_3$,75MHz)：δ 161.5(d,J_{CF}= 240Hz),138.9,138.7,136.0(d,J_{CF}= 7.5Hz),127.7(d,J_{CF}= 7.5Hz),126.5,126.2,114.6(d,J_{CF}= 22.5Hz),64.0 ；HRMS-TOF(m/z)：$[M+H]^+$HRMS:$C_{13}H_{11}FO$ 的计算值 ：203.0867，实验值 ：203.0868。

[1769] B 部分 - 制备 2-(叔丁基)-4-氯-5-((4'-氟-[1,1'-联二苯]-4-基)甲氧基)哒嗪-3(2H)-酮

[1770]



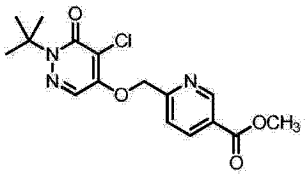
[1771] 根据通用方法B，使用2-(叔丁基)-4,5-二氯哒嗪-3(2H)-酮(0.288g，1.30mmol)、实例20A的产物(0.290g，1.43mmol)及碳酸铯(0.680g，2.09mmol)于二甲基甲酰胺(13.0mL)中在60℃下制备。分离产量为0.144g；28.6%。^{1}H NMR($CDCl_3$，300MHz)：δ 7.68(s,1H)，7.53(d，J = 8.5Hz，2H)，7.53-7.45(m,2H)，7.40(d，J = 8.5Hz，2H)，7.06(m,2H)，5.28(s,2H)，1.54(s,9H)；^{13}C NMR($CDCl_3$，75MHz)：δ 162.7(d，J_{CF} = 247.5Hz)，159.0，153.7，140.8，136.5(d，J_{CF} = 7.5Hz)，133.9，128.7(d，J_{CF} = 7.5Hz)，127.7，127.6，125.1，118.4，115.8(d，J_{CF} = 22.5Hz)，71.6，66.4，27.9；HRMS-TOF(m/z)：[M+H]$^{+}$HRMS：$C_{21}H_{20}{}^{35}ClFN_2O_2$的计算值：387.1270，实验值：387.1268。

[1772] 实例21

[1773] 制备2-(叔丁基)-4-氯-5-((5-((2-氟乙氧基)甲基)吡啶-2-基)甲氧基)哒嗪-3(2H)-酮

[1774] A部分-制备6-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-醇)氧基)甲基)烟碱酸甲酯

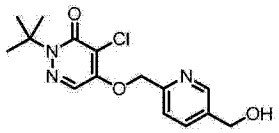
[1775]



[1776] 根据通用方法B，使用2-(叔丁基)-4-氯-5-羟基哒嗪-3(2H)-酮(0.917g，4.54mmol)、6-(溴甲基)烟碱酸甲酯(0.994g，4.32mmol)及碳酸铯(2.25g，6.91mmol)于二甲基甲酰胺(21.0mL)中在60℃下制备。分离产量为0.666g；41.7%。^{1}H NMR($CDCl_3$，300MHz)：δ 9.22(d，J = 1.3Hz，1H)，8.41(dd，J = 8.1，2.1Hz，1H)，7.79(s,1H)，7.69(d，J = 8.2Hz，1H)，5.48(s,2H)，3.99(s,3H)，1.66(s,9H)；^{13}C NMR($CDCl_3$，75MHz)：δ 165.2，159.1，158.9，153.3，150.4，138.6，125.9，124.7，120.8，118.5，70.7，66.7，52.6，27.8；HRMS-TOF(m/z)：[M+H]$^{+}$HRMS：$C_{16}H_{18}{}^{35}ClN_3O_4$的计算值：352.1059，实验值：352.1059。

[1777] B部分-制备2-(叔丁基)-4-氯-5-((5-(羟甲基)吡啶-2-基)甲氧基)哒嗪-3(2H)-酮

[1778]

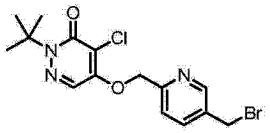


[1779] 将实例21A的产物(0.333g，0.945mmol)于四氢呋喃(9.45mL)中的溶液冷却到0℃，用氢化锂铝(0.472mL，0.5mmol，1M四氢呋喃溶液)处理，随后温热到环境温度。4小时后，用水(10mL)处理所得混合物，分离水层，随后用乙酸乙酯(3×50mL)萃取。用饱和氯化钠水溶液洗涤经合并的有机层，经硫酸钠干燥，过滤且浓缩成黄色油状物(0.290g，产率94.8%)。^{1}H NMR(DMSO-d_6，600MHz)：δ 8.59(d，1H，J = 1.4Hz)，8.32(s,1H)，7.87(dd，J = 7.9，2.2Hz，1H)，7.57(m,1H)，5.58(s,2H)，5.39(t，J = 5.74Hz，1H)，4.61(d，J = 5.6Hz，2H)，1.64(s,9H)；^{13}C NMR(DMSO-d_6，150MHz)：δ 157.8，153.9，153.4，147.8，137.4，135.5，126.3，121.6，115.5，71.8，64.8，50.7，20.9；

HRMS-TOF(m/z):[M+H]$^+$HRMS:$C_{15}H_{18}{}^{35}ClN_3O_3$的计算值:324.1109,实验值:324.111。

[1780] C部分-制备5-((5-(溴甲基)吡啶-2-基)甲氧基)-2-(叔丁基)-4-氯哒嗪-3(2H)-酮

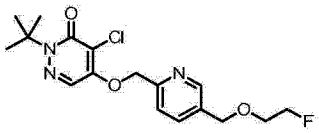
[1781]



[1782] 根据通用方法C,使用实例21B的产物(0.289g,0.891mmol)及三溴化磷(0.446mL,0.446mmol,1M二氯甲烷溶液)制备。分离产量为0.212g;61.5%。^{1}H NMR(DMSO-d_6,300MHz):δ8.73(d,J=1.4Hz,1H),8.31(s,1H),8.03(dd,J=8.1,2.3Hz,1H),7.61(d,J=8.0Hz,1H),5.60(s,2H),4.83(s,2H),1.64(s,9H);^{13}C NMR(DMSO-d_6,75MHz):δ157.8,154.8,153.8,149.6,138.0,133.8,126.3,121.8,115.6,71.8,66.4,30.4,27.5。HRMS-TOF(m/z):[M+H]$^+$HRMS:$C_{15}H_{17}{}^{79}Br^{35}ClN_3O_2$的计算值:386.0265,实验值:386.0267。

[1783] D部分-制备2-(叔丁基)-4-氯-5-((5-((2-氟乙氧基)甲基)吡啶-2-基)甲氧基)哒嗪-3(2H)-酮

[1784]



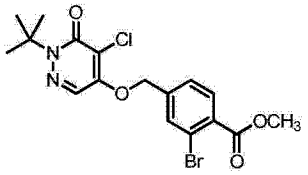
[1785] 根据通用方法A,使用叔丁醇钾(25.9mg,0.231mmol)、2-氟乙醇(14.8mg,0.231mmol)及实例21C的产物(0.100g,0.260mmol)制备。分离产量为23.8mg;27.9%。^{1}H NMR($CDCl_3$,300MHz):δ8.51(d,J=1.5Hz,1H),7.73(s,1H),7.72(dd,J=7.3,2.17Hz,1H),7.47(d,J=8.1Hz,1H),5.34(s,2H),4.47(m,1H),4.45(s,2H),4.46(m,1H),3.77(m,1H),3.67(m,1H),1.48(s,9H);HRMS-TOF(m/z):[M+H]$^+$HRMS:$C_{17}H_{21}{}^{35}ClFN_3O_3$的计算值:370.1328,实验值:370.1328。

[1786] 实例22

[1787] 制备5-((3-溴-4-((2-氟乙氧基)甲基)苯甲基)氧基)-2-(叔丁基)-4-氯哒嗪-3(2H)-酮

[1788] A部分-制备2-溴-4-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯甲酸甲酯

[1789]

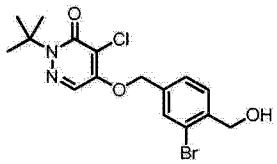


[1790] 根据通用方法B,使用2-(叔丁基)-4-氯-5-羟基哒嗪-3(2H)-酮(0.750g,3.70mmol)、2-溴-4-溴甲基苯甲酸甲酯(1.09g,3.52mmol)及碳酸铯(1.37g,4.22mmol)于二甲基甲酰胺(35.0mL)中在70℃下制备。分离产量为0.695g;46.0%。^{1}H NMR($CDCl_3$,300

MHz)：δ 7.84(m,1H),7.73(m,1H),7.69(s,1H),7.44(m,1H),5.32(s,2H),3.93(s,3H),1.64(s,9H)；^{13}C NMR($CDCl_3$,75MHz)：δ 165.2,158.9,153.3,139.9,132.4,132.3,131.9,125.4,124.7,122.3,118.7,70.2,66.6,52.6,27.8；HRMS-TOF(m/z)：[M+H]$^+$HRMS：$C_{17}H_{18}{}^{79}Br^{35}ClN_2O_4$的计算值：429.0211，实验值：429.0209。

[1791] B部分-制备5-((3-溴-4-(羟甲基)苯甲基)氧基)-2-(叔丁基)-4-氯哒嗪-3(2H)-酮

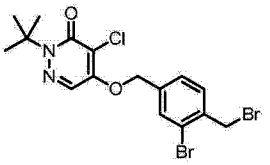
[1792]



[1793] 将实例22A的产物(0.300g,0.697mmol)于四氢呋喃(2.50mL)中的溶液冷却到-20℃，用氢化二异丁基铝(1.57mL,1.57mmol,1M二氯甲烷溶液)处理，随后温热到环境温度且搅拌隔夜。用水(10mL)处理所得混合物，分离水层，随后用乙酸乙酯(3×50mL)萃取。经硫酸钠干燥经合并的有机层，过滤且真空浓缩。随后通过硅胶色谱(0-50％乙酸乙酯的己烷溶液)纯化粗物质，得到呈黄色油状的所需产物(0.109，产率38.9％)。^{1}H NMR(DMSO-d_6,300MHz)：δ 8.59(d,J = 1.4Hz,1H),8.32(s,1H),7.87(dd,J = 7.9,2.2Hz,1H),7.57(m,1H),5.58(s,2H),5.39(t,J = 5.7Hz,1H),4.61(d,J = 5.6Hz,2H),1.64(s,9H)；^{13}C NMR(DMSO-d_6,75MHz)：δ 159.0,153.4,140.4,136.0,131.0,129.2,126.1,124.9,122.8,118.5,70.7,66.6,64.7,27.9；HRMS-TOF(m/z)：[M+H]$^+$HRMS：$C_{16}H_{18}{}^{79}Br^{35}ClN_2O_3$的计算值：401.0262，实验值：401.0266。

[1794] C部分-制备5-((3-溴-4-(溴甲基)苯甲基)氧基)-2-(叔丁基)-4-氯哒嗪-3(2H)-酮

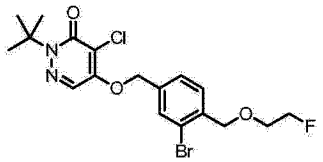
[1795]



[1796] 根据通用方法C，使用实例22B的产物(0.109g,0.270mmol)及三溴化磷(0.135mL,0.135mmol,1M二氯甲烷溶液)制备。分离产量为87.1mg；69.4％。^{1}H NMR($CDCl_3$,300MHz)：δ 7.69(s,1H),7.64(d,J = 1.4Hz,1H),7.51(d,J = 7.9Hz,1H),7.36(dd,J = 7.9,1.7Hz,1H),5.27(s,2H),4.60(s,2H),1.64(s,9H)；^{13}C NMR($CDCl_3$,75MHz)：δ 158.9,153.3,137.6,137.2,131.7,131.6,126.4,124.9,124.8118.6,70.4,66.6,32.6,27.9；HRMS-TOF(m/z)：[M+H]$^+$HRMS：$C_{16}H_{17}{}^{79}Br_2{}^{35}ClN_2O_2$的计算值：464.9397，实验值：464.9400。

[1797] D部分-制备2-(叔丁基)-4-氯-5-((5-((2-氟乙氧基)甲基)吡啶-2-基)甲氧基)哒嗪-3(2H)-酮

[1798]



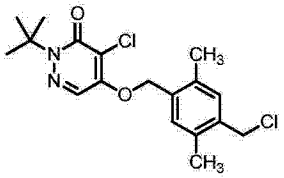
[1799] 根据通用方法E，使用叔丁醇钾(9.5mg,0.084mmol)、2-氟乙醇(5.4mg,0.084mmol)及实例22C的产物(43.5mg,0.0940mmol)制备。分离产量为3.0mg；8.0 %。^{1}H NMR($CDCl_3$,300MHz)：δ 7.69(s,1H),7.61(d,1H,J = 1.4Hz),7.57(d,J = 8.0Hz,1H),7.38(dd,J = 6.3,1.6Hz,1H),5.27(s,2H),4.72(m,1H),4.66(s,2H),4.56(m,1H),3.89(m,1H),3.79(m,1H),1.64(s,9H)；^{13}C NMR($CDCl_3$,75MHz)：δ 159.0,153.4,138.0,136.0,131.0,129.4,126.1,124.9,122.9,118.6,83.0(d,J_{CF}= 165Hz),72.3,70.7,70.1(d,J_{CF}= 15Hz),66.5,27.9；HRMS-TOF(m/z)：[M+H]$^+$HRMS：$C_{18}H_{21}{}^{79}Br{}^{35}ClFN_2O_3$的计算值：447.0481，实验值：447.0471。

[1800] 实例23

[1801] 制备2-(叔丁基)-4-氯-5-((4-((2-氟乙氧基)甲基)-2,5-二甲基苯甲基)氧基)哒嗪-3(2H)-酮

[1802] A部分-制备2-(叔丁基)-4-氯-5-((4-(氯甲基)-2,5-二甲基苯甲基)氧基)哒嗪-3(2H)-酮

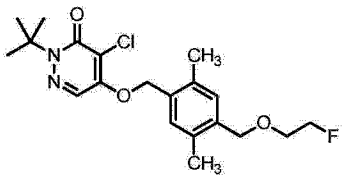
[1803]



[1804] 根据通用方法B，使用2-(叔丁基)-4-氯-5-羟基哒嗪-3(2H)-酮(0.500g,2.47mmol)、2,5-双(氯甲基)-对二甲苯(1.00g,5.00mmol)及碳酸铯(2.60g,8.00mmol)于二甲基甲酰胺(25.0mL)中在环境温度下制备。分离产量为0.410g；44.9 %。^{1}H NMR($CDCl_3$,300MHz)：δ 7.68(s,1H),7.13(m,2H),5.17(s,2H),4.51(s,2H),2.34(s,3H),2.28(s,3H),1.58(s,9H)；^{13}C NMR($CDCl_3$,75MHz)：δ 159.0,153.7,136.2,135.1,134.5,133.3,132.2,130.7,125.0,118.3,70.3,66.4,44.2,27.9,18.4,18.3；HRMS-TOF(m/z)：[M+H]$^+$HRMS：$C_{18}H_{22}{}^{35}Cl_2N_2O_2$的计算值：369.1131，实验值：369.1134。

[1805] B部分-制备2-(叔丁基)-4-氯-5-((4-((2-氟乙氧基)甲基)-2,5-二甲基苯甲基)氧基)哒嗪-3(2H)-酮

[1806]



[1807] 根据通用方法E，使用叔丁醇钾(38.0mg,0.339mmol)、2-氟乙醇(14.5mg,0.226mmol)及实例23A的产物(0.100g,0.271mmol)制备。分离产量为18.3mg；20.4%。

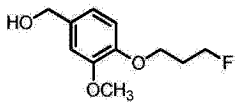
^{1}H NMR($CDCl_3$, 300MHz)：δ 7.69(s, 1H), 7.61(d, J = 14.9Hz, 1H), 7.57(d, J = 12.6Hz, 1H), 5.18(s, 2H), 4.49(m, 1H), 4.46(s, 2H), 4.44(m, 1H), 3.73(m, 1H), 3.64(m, 1H), 2.28(s, 3H), 2.25(3H, s), 1.53(s, 9H)；^{13}C NMR($CDCl_3$, 75MHz)：δ 158.1, 152.8, 135.6, 133.5, 133.1, 131.2, 130.1, 129.5, 124.1, 117.2, 82.1(d, J_{CF}= 165Hz), 70.4, 69.5, 68.6(d, J_{CF}= 22.5Hz), 65.4, 26.9, 17.4, 17.3；HRMS-TOF(m/z)：[M+H]$^+$HRMS：$C_{20}H_{26}{}^{35}ClFN_2O_3$的计算值：397.1689，实验值：397.1687。

[1808] 实例 24

[1809] 制备 2-(叔丁基)-4-氯-5-((4-(3-氟丙氧基)-3-甲氧基苯甲基)氧基)哒嗪-3(2H)-酮

[1810] A 部分-制备 (4-(3-氟丙氧基)-3-甲氧基苯基)甲醇

[1811]

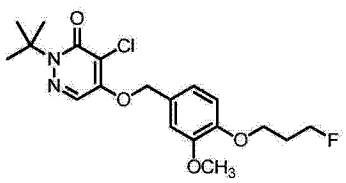


[1812] 根据通用方法 F，使用 4-羟基-3-甲氧基苯甲醛 (0.688g, 4.52mmol)、对甲苯磺酸 3-氟丙酯 (1.00g, 4.30mmol) 及碳酸铯 (2.24mg, 6.89mmol) 于二甲基甲酰胺 (43.0mL) 中在 60℃下制备。分离产量为 0.517g；56.1％。^{1}H NMR($CDCl_3$, 300MHz)：δ 9.78(s, 1H), 7.37(dd, J = 8.1, 1.9Hz, 1H), 7.35(m, 1H), 7.63(d, J = 8.1Hz, 1H), 4.68(t, J = 5.7Hz, 1H), 4.53(t, J = 5.7Hz, 1H), 4.18(t, J = 6.3Hz, 2H), 3.12(s, 3H), 2.24(m, 1H), 2.15(m, 1H)；^{13}C NMR($CDCl_3$, 75MHz)：δ 190.8, 153.8, 150.0, 130.3, 126.7, 111.7, 109.5, 80.5(d, J_{CF}= 165Hz), 64.8(d, J_{CF}= 7.5Hz), 56.0, 30.2(d, J_{CF}= 22.5Hz)。

[1813] 在环境温度下，用硼氢化钠 (0.112g, 2.90mmol) 一次性处理粗 4-(3-氟丙氧基)-3-甲氧基苯甲醛 (0.839g, 3.90mmol) 于乙醇 (39.0mL) 中的溶液。搅拌所得混合物隔夜，随后用水 (50mL) 处理且真空浓缩以移除乙醇。用乙酸乙酯 (3×150mL) 萃取所得水溶液，且经硫酸钠干燥经合并的有机层，过滤且浓缩，得到所需产物 (0.807g，产率 96.6％)。^{1}H NMR($CDCl_3$, 600MHz)：δ 6.87(br s, 1H), 6.81(br s, 2H), 4.68(m, 1H), 4.56(s, 2H), 4.52(m, 1H), 4.08(t, J = 6.3Hz, 2H), 3.81(s, 3H), 2.19(m, 1H), 2.11(m, 1H)；^{13}C NMR($CDCl_3$, 150MHz)：δ 149.7, 147.8, 121.5, 119.5, 113.4, 111.8, 81.9(d, J_{CF}= 157.5Hz), 65.3.65.0(d, J_{CF}= 7.5Hz), 56.0, 30.5(d, J_{CF}= 22.5Hz)；HRMS-TOF(m/z)：[M+Na]$^+$HRMS：$C_{11}H_{15}FO_3$的计算值：237.0897，实验值：237.0898。

[1814] B 部分-制备 2-(叔丁基)-4-氯-5-((4-(3-氟丙氧基)-3-甲氧基苯甲基)氧基)哒嗪-3(2H)-酮

[1815]



[1816] 在环境温度下，相继用实例 24A 的产物 (0.254g, 1.19mmol)、三苯基膦 (0.388g, 1.48mmol) 及偶氮二甲酸二异丙酯 (0.291mL, 1.48mmol) 处理 2-(叔丁基)-4-氯-5-羟基哒嗪-3(2H)-酮 (0.200g, 0.990mmol) 于四氢呋喃 (8.24mL) 中的溶液。搅拌所得混合物隔

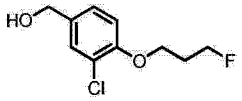
夜，随后真空浓缩成黄色油状物。随后通过制备型薄层色谱使用 98:2 己烷 / 乙醚经二氧化硅纯化粗物质，得到所需产物 (12.6mg，产率 3.2％)。^{1}H NMR($CDCl_3$，300MHz)：δ 7.65(s，1H)，6.86(m，3H)，5.18(s，2H)，4.68(t，J = 5.7Hz，1H)，4.52(t，J = 5.7Hz，1H)，4.09(t，J = 6.3Hz，2H)，3.08(s，3H)，2.24-2.07(m，2H)，1.56(s，9H)；^{13}C NMR($CDCl_3$，75MHz，部分)：δ 159.0，153.8，150.0，148.7，127.8，125.3，120.0，113.2，110.9，80.7(d，J_{CF}= 165Hz)，72.0，66.4，64.9(d，J_{CF}= 7.5Hz)，56.0，30.4(d，J_{CF}= 22.5Hz)，27.9；HRMS-TOF(m/z)：$[M+H]^+$ $C_{19}H_{24}{}^{35}ClFN_2O_4$ 的计算值：399.1481；实验值：399.1484。

[1817] 实例 25

[1818] 制备 2-(叔丁基)-4-氯-5-((3-氯-4-(3-氟丙氧基)苯甲基)氧基)哒嗪-3(2H)-酮

[1819] A 部分 - 制备 (3-氯-4-(3-氟丙氧基)苯基)甲醇

[1820]

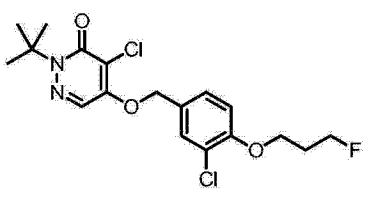


[1821] 根据通用方法 F，使用 3-氯-4-羟基苯甲醛 (0.300g，1.92mmol)、对甲苯磺酸 3-氟丙酯 (424g，1.83mmol) 及碳酸铯 (0.951g，2.93mmol) 于二甲基甲酰胺 (19.0mL) 中在 65℃下制备。分离产量为 0.262g；66.1％。^{1}H NMR($CDCl_3$，300MHz)：δ 9.89(s，1H)，7.93(d，J = 2.1Hz，1H)，7.78(dd，J = 8.5，2.1Hz，1H)，7.06(d，J = 8.5Hz，1H)，4.80(t，J = 5.7Hz，1H)，4.64(t，J = 5.7Hz，1H)，4.28(t，J = 6.0Hz，2H)，2.33(m，1H)，2.22(m，1H)；^{13}C NMR($CDCl_3$，75MHz)：δ 189.6，159.1，131.3，130.4，130.4，124.0，112.6，80.2(d，J_{CF}= 165Hz)，64.9(d，J_{CF}= 7.5Hz)，30.2(d，J_{CF}= 22.5Hz)。

[1822] 在环境温度下，用硼氢化钠 (25.4mg，0.671mmol) 一次性处理粗 3-氯-4-(3-氟丙氧基)苯甲醛 (0.262g，1.21mmol) 于乙醇 (8.95mL) 中的溶液。搅拌所得混合物隔夜，随后用水 (10mL) 处理且真空浓缩以移除乙醇。用乙酸乙酯 (3×50mL) 萃取所得水溶液，且经硫酸钠干燥经合并的有机层，过滤且浓缩，得到呈白色固体状的所需产物 (0.242g，产率 91.5％)。^{1}H NMR($CDCl_3$，300MHz)：δ 7.32(d，J = 2.1Hz，1H)，7.13(dd，J = 8.4，2.2Hz，1H)，6.86(d，J = 8.4Hz，1H)，4.71(t，J = 5.6Hz，1H)，4.57(t，J = 5.6Hz，1H)，4.54(s，2H)，4.09(t，J = 6.0Hz，2H)，2.19(m，1H)，2.11(m，1H)；^{13}C NMR($CDCl_3$，75MHz)：δ 153.7，134.4，129.2，126.5，123.1，113.5，80.6(d，J_{CF}= 165Hz)，64.8(d，J_{CF}= 7.5Hz)，64.4，30.4(d，J_{CF}= 22.5Hz)；HRMS-TOF(m/z)：$[M+H]^+$ HRMS：$C_{10}H_{12}{}^{35}ClFO_2$ 的计算值：217.0437，实验值：217.0442。

[1823] B 部分 - 制备 2-(叔丁基)-4-氯-5-((3-氯-4-(3-氟丙氧基)苯甲基)氧基)哒嗪-3(2H)-酮

[1824]



[1825] 在环境温度下，相继用实例 25A 的产物 (0.242g，1.10mmol)、三苯基膦 (0.362g，

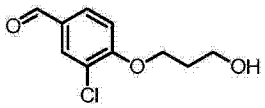
1.38mmol）及偶氮二甲酸二异丙酯（0.362g，1.38mmol）处理2-（叔丁基）-4-氯-5-羟基哒嗪-3(2H)-酮（0.186g，0.920mmol）于THF(7.60mL)中的溶液。搅拌所得混合物隔夜，随后真空浓缩成黄色油状物。随后通过硅胶色谱使用4:1二氯甲烷/甲醇纯化粗物质，得到呈白色固体状的所需产物（53.8mg，产率14.5％）。^{1}H NMR($CDCl_3$，300MHz)：δ7.65(s,1H)，7.36(d,J = 2.2Hz,1H)，7.20(dd,J = 2.3,4.8Hz,1H)，6.89(d,J = 8.5Hz,1H)，5.14(s,2H)，4.70(t,J = 5.8Hz,1H)，4.54(t,J = 5.8Hz,1H)，4.10(t,J = 6.0Hz,2H)，2.16(m,1H)，2.11(m,1H)，1.56(s,9H)；^{13}C NMR($CDCl_3$，75MHz)：δ159.0，154.6，153.5，129.4，128.1，127.0，125.1，123.45，118.4，113.5，80.4(d，J_{CF}= 165Hz)，71.0，66.4，64.7(d，J_{CF}= 7.5Hz)，30.3(d，J_{CF}= 22.5Hz)，27.8；HRMS-TOF(m/z)：[M+H]$^{+}$HRMS：$C_{18}H_{21}ClFN_2O_3$的计算值：403.0986；实验值：403.0985。

[1826] 实例26

[1827] 制备4-甲基苯磺酸3-(4-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基）氧基）甲基)-2-氯苯氧基）丙酯

[1828] A部分－制备3-氯-4-(3-羟基丙氧基）苯甲醛

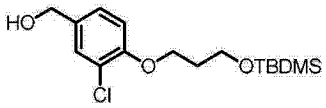
[1829]



[1830] 将3-氯-4-羟基苯甲醛（0.500g，3.20mmol）、1-溴丙醇（0.271mL，3.0mmol）及碳酸铯（2.44g，7.50mmol）于二甲基甲酰胺（32.0mL）中的悬浮液加热到60℃且维持隔夜。冷却到环境温度后，用水（150mL）稀释所得混合物，且用乙酸乙酯（3×150mL）萃取水层。用水、饱和氯化钠水溶液洗涤经合并的有机层，经硫酸钠干燥，过滤且浓缩成黄色油状物（0.322g，产率46.9％）。^{1}H NMR($CDCl_3$，300MHz)：δ9.77(s,1H)，7.83(d,J = 2.1Hz,1H)，7.68(dd,J = 8.5,2.0Hz,1H)，6.98(d,J = 8.5Hz,1H)，4.22(t,J = 5.9Hz,2H)，4.15(t,J = 5.7Hz,2H)，2.11-2.03(m,2H)；^{13}C NMR($CDCl_3$，75MHz)：δ189.8，159.1，131.2，130.6，130.3，123.8，112.4，67.2，60.0，31.6。

[1831] B部分－制备4-(3-((叔丁基二甲基硅烷基）氧基）丙氧基)-3-氯苯基）甲醇

[1832]



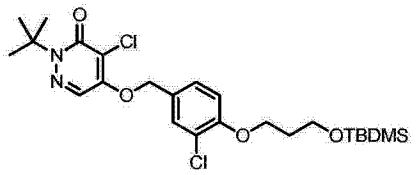
[1833] 在环境温度下，相继用氯化叔丁基二甲基硅烷基（0.329g，2.18mmol）及咪唑（0.149g，2.18mmol）处理实例26A的产物（0.312g，1.45mmol）于二甲基甲酰胺（14.5mL）中的溶液，随后搅拌隔夜。用0.1N盐酸（30mL）稀释所得混合物，随后用乙酸乙酯（2×50mL）萃取。用饱和氯化钠水溶液洗涤经合并的有机层，经硫酸钠干燥，过滤且真空浓缩。随后通过硅胶色谱（0-50％乙酸乙酯的己烷溶液）纯化粗物质，得到呈透明油状的所需产物（0.167g，产率35.0％）。^{1}H NMR($CDCl_3$，300MHz)：δ9.81(s,1H)，7.87(d,J = 2.1Hz,1H)，7.72(dd,J = 8.5,2.1Hz,1H)，7.03(d,J = 8.6Hz,1H)，4.20(t,J = 6.1Hz,2H)，3.81(t,J = 5.8Hz,2H)，2.07-1.99(m,2H)，0.84(s,9H)，0.01(s,6H)；^{13}C NMR($CDCl_3$，75MHz)：δ189.7，159.4，131.2，130.5，130.1，124.0，112.5，65.9，65.8，59.0，32.0，25.9，18.3，-5

.5;HRMS-TOF(m/z):$C_{16}H_{25}ClO_3Si$ 的 $[M+H]^+$:329.1334,实验值:329.1329。

[1834] 在环境温度下,用硼氢化钠(15.2mg,0.402mmol)一次性处理甲硅烷基醚(0.176g,0.536mmol)于乙醇(6.00mL)中的溶液,随后搅拌隔夜。随后用水(10mL)稀释所得混合物且真空浓缩以移除乙醇。用乙酸乙酯(3×50mL)萃取所得水溶液,且经硫酸钠干燥经合并的有机层,过滤且浓缩,得到呈油状的所需产物(0.164g,产率92.5%)。^1H NMR($CDCl_3$,300MHz):δ7.34(d,J = 2.2Hz,1H),7.16(dd,J = 8.3,2.2Hz,1H),6.86(d,J = 8.4Hz,1H),4.57(s,2H),4.09(t,J = 6.1Hz,2H),3.80(t,J = 5.9Hz,2H),2.03-1.95(m,2H),0.84(s,9H),0.01(s,6H);^{13}C NMR($CDCl_3$,75MHz):δ154.1,133.7,129.2,126.5,123.0,113.2,65.6,64.5,59.3,32.2,25.9,18.5,-5.4;HRMS-TOF(m/z):$[M+H]^+$HRMS:$C_{16}H_{27}{}^{35}ClO_3Si$ 的计算值:331.1491,实验值:331.1493。

[1835] C部分-制备2-(叔丁基)-5-((4-(3-((叔丁基二甲基硅烷基)氧基)丙氧基)-3-氯苯甲基)氧基)-4-氯哒嗪-3(2H)-酮

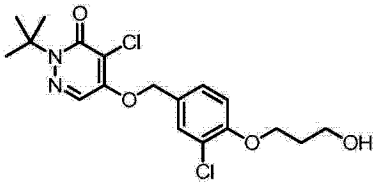
[1836]



[1837] 在环境温度下,相继用实例27B的产物(0.162g,0.490mmol)、三苯基膦(0.161g,0.615mmol)及偶氮二甲酸二乙酯(0.107g,0.615mmol)处理2-(叔丁基)-4-氯-5-羟基哒嗪-3(2H)-酮(82.8mg,0.410mmol)于四氢呋喃(4.90mL)中的溶液。20分钟后,用水(5mL)稀释所得混合物,分离水层,随后用乙酸乙酯(2×50mL)萃取。经硫酸钠干燥经合并的有机层,过滤且真空浓缩。随后通过硅胶色谱(0-10%梯度的乙酸乙酯的己烷溶液)纯化粗物质,得到呈透明油状的所需产物(0.127g,产率60.1%)。^1H NMR($CDCl_3$,300MHz):δ7.67(s,1H),7.37(d,J = 2.2Hz,1H),7.21(dd,J = 2.3,8.5Hz,1H),6.89(d,J = 8.5Hz,1H),5.17(s,2H),4.11(t,J = 6.1Hz,2H),3.80(t,J = 5.9Hz,2H),2.04-1.96(m,2H),1.60(s,9H),0.84(s,9H),0.01(s,6H);^{13}C NMR($CDCl_3$,75MHz):δ159.0,155.0,153.6,129.3,127.6,127.0,125.1,123.3,118.5,113.3,71.1,66.4,65.6,59.2,32.2,27.9,25.9,18.3,-5.4。

[1838] D部分-制备2-(叔丁基)-4-氯-5-((3-氯-4-(3-羟基丙氧基)苯甲基)氧基)哒嗪-3(2H)-酮

[1839]

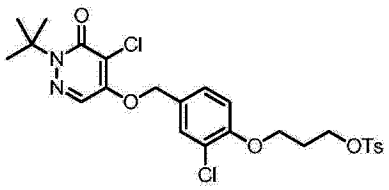


[1840] 在环境温度下,用氟化四丁铵(0.49mL,0.49mmol,1M四氢呋喃溶液)处理实例27C的产物(0.127g,0.246mmol)于四氢呋喃(2.5mL)中的溶液。40分钟后,用水(5mL)稀释所得混合物,分离水层,随后用乙酸乙酯(2×20mL)萃取。经硫酸钠干燥经合并的有机层,过滤且真空浓缩。随后通过硅胶色谱(0-80%乙酸乙酯的己烷溶液)纯化粗物质,得

到所需产物 (71.6mg，产率 72.5％)。^{1}H NMR($CDCl_3$, 300MHz)：δ 7.63(s, 1H), 7.36(d, J＝2.2Hz, 1H), 7.21(dd, J＝8.5, 3.0Hz, 1H), 6.90(d, J＝8.5Hz, 1H), 5.14(s, 2H), 4.15(t, J＝5.8Hz, 2H), 3.84(t, J ＝ 5.7Hz, 2H), 2.08-1.99(m, 2H), 1.57(s, 9H)；^{13}C NMR($CDCl_3$, 75MHz)：δ 159.0, 154.6, 153.5, 129.3, 128.1, 127.0, 125.1, 123.3, 118.6, 113.3, 71.0, 67.4, 66.5, 60.5, 31.7, 27.9；HRMS-TOF(m/z)：$C_{18}H_{22}{}^{35}Cl_2N_2O_4$的 $[M+H]^+$：401.1029，实验值：401.1023。

[1841] E 部分－制备 4-甲基苯磺酸 3-(4-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)-2-氯苯氧基)丙酯

[1842]



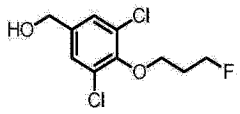
[1843] 根据通用方法 D，使用实例 27D 的产物 (35.8mg，0.089mmol)、对甲苯磺酰氯 (20.5mg，0.107mmol)、4-二甲基氨基吡啶 (16.3mg，0.13mmol) 及二异丙基乙氨 (0.015mL，0.107mmol) 制备。分离产量为 29.8mg；60.3％。^{1}H($CDCl_3$, 300MHz)：δ 7.68(d, J ＝ 8.3Hz, 2H), 7.65(s, 1H), 7.31(d, J ＝ 2.2Hz, 2H), 7.17(m, 1H), 7.15(d, J ＝ 8.3Hz, 2H), 5.13(s, 2H), 4.22(t, J ＝ 5.9Hz, 2H), 3.95(t, J ＝ 5.7Hz, 2H), 2.27(s, 3H), 2.14-2.07(m, 2H), 1.57(s, 9H)；^{13}C($CDCl_3$, 75MHz)：δ 159.0, 154.4, 153.5, 144.8, 132.7, 129.8, 129.4, 128.1, 127.8, 127.0, 125.0, 123.5, 118.3, 113.28, 71.0, 66.7, 66.5, 64.2, 28.8, 27.9, 21.6；HRMS-TOF(m/z)：$[M+H]^+$HRMS：$C_{25}H_{28}{}^{35}Cl_2N_2O_6S$的计算值：555.1118，实验值：555.1138。

[1844] 实例 27

[1845] 制备 2-(叔丁基)-4-氯-5-((3,5-二氯-4-(3-氟丙氧基)苯甲基)氧基)哒嗪-3(2H)-酮

[1846] A 部分－制备 (3,5-二氯-4-(3-氟丙氧基)苯基)甲醇

[1847]



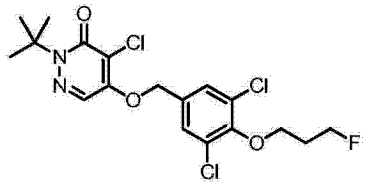
[1848] 根据通用方法 F，使用 3,5-二氯-4-羟基苯甲醛 (0.860g，4.50mmol)、对甲苯磺酸 3-氟丙酯 (1.00g，4.29mmol) 及碳酸铯 (2.49g，7.64mmol) 于二甲基甲酰胺 (45.0mL) 中在 65℃下制备。^{1}HRMS-TOF(m/z)：$[M+H]^+$HRMS：$C_{10}H_9Cl_2FO_2$的计算值：251.0036，实验值：251.0038。

[1849] 在环境温度下，用硼氢化钠 (0.149g，3.94mmol) 一次性处理粗醛 (1.32g，5.26mmol) 于乙醇 (5.26mL) 中的溶液。3 天后，用水 (20mL) 稀释所得混合物且真空浓缩以移除乙醇。用乙酸乙酯 (3×50mL) 萃取所得水溶液，且经硫酸钠干燥经合并的有机层，过滤且浓缩，得到呈透明油状的所需产物 (1.21g，产率 90.9％)。^{1}H NMR($CDCl_3$, 300MHz)：δ 7.24(s, 2H), 4.76(t, J ＝ 5.8Hz, 1H), 4.61(t, J ＝ 5.8Hz, 1H), 4.56(s, 2H), 4.07(t, J ＝ 6.0Hz, 2H), 2.20(m, 1H), 2.13(m, 1H)；^{13}C NMR($CDCl_3$, 75MHz)：δ 150.4, 138.3, 129.5, 127.2

,81.4(d,J_{CF}= 165Hz),69.2(d,J_{CF}= 7.5Hz),63.7,31.2(d,J_{CF}= 22.5Hz)。

[1850] B 部分 - 制备 2-(叔丁基)-4- 氯 -5-((3,5- 二氯 -4-(3- 氟丙氧基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

[1851]



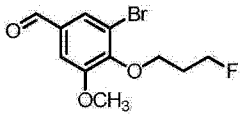
[1852] 根据通用方法 B,使用 2-(叔丁基)-4,5- 二氯哒嗪 -3(2H)- 酮 (0.195g,0.872mmol)、实例 27A 的产物 (0.138g,0.545mmol) 及碳酸铯 (0.213g,0.654mmol) 于二甲基甲酰胺 (8.50mL) 中在 65℃下制备。分离产量为 0.192g ;80.5 %。^{1}H NMR($CDCl_3$,300MHz):δ 7.61(s,1H),7.29(s,2H),5.12(s,2H),4.76(t,J = 5.8Hz,1H),4.58(t,J = 5.8Hz,1H),4.10(t,J = 6.0Hz,2H),2.20(m,1H),2.14(m,1H),1.57(s,9H) ;HRMS:$C_{18}H_{20}{}^{35}Cl_3FN_2O_3$的计算值 :437.0596,实验值 :437.0609。

[1853] 实例 28

[1854] 制备 5-((3- 溴 -4-(3- 氟丙氧基)-5- 甲氧基苯甲基) 氧基)-2-(叔丁基)-4- 氯哒嗪 -3(2H)- 酮

[1855] A 部分 - 制备 3- 溴 -4-(3- 氟丙氧基)-5- 甲氧基苯甲醛

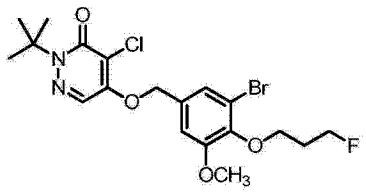
[1856]



[1857] 将 3- 溴 -4- 羟基 -5- 甲氧基苯甲醛 (0.578g,2.50mmol)、三苯基膦 (0.820g,3.13mmol) 及 3- 氟丙 -1- 醇 (0.244mL,3.25mmol) 合并至无水四氢呋喃 (12.5mL) 中,随后冷却到 0℃且历时 0.25 小时用偶氮二甲酸二乙酯 (0.472mL,3.00mmol) 逐滴处理。0.25 小时后,将所得溶液温热到环境温度且再维持 0.25 小时。随后在真空中移除所有挥发物,且通过使用 3:1 戊烷 / 乙醚经二氧化硅 (50×155mm) 色谱直接纯化残余物。收集在溶离 700-1200mL 时的主要产物峰,合并且真空浓缩成无色油状物 (0.555g,1.91mmol ;76.3 %)。^{1}H NMR:(300MHz,$CDCl_3$) δ 9.84(1H,s),7.65(1H,d,J = 1.8Hz),7.38(1H,d,J = 1.8Hz),4.75(2H,dt,J = 47.0,5.8Hz),4.24(2H,t,J = 6.0Hz),3.92(3H,s),2.19(2H,dtt,J = 25.7,5.9,5.9Hz).^{13}C NMR:(75MHz,$CDCl_3$) δ 189.8,154.1,150.8,133.0,128.8,118.0,110.0,80.8(d,J_{CF}= 164Hz),69.2(d J_{CF} = 5.4Hz),56.2,31.3(d,J_{CF}= 20.2Hz)。 ^{19}F NMR(282MHz,$CDCl_3$) δ -222.0(tt,J = 46.9,25.7Hz)。HRMS :$C_{11}H_{12}{}^{79}BrFO_3$(M+H) 的计算值 :291.0027 ;实验值 :291.0030。TLC :R_f 0.26(硅胶,3:1 戊烷 / 乙醚,$KMnO_4$)。

[1858] B 部分 - 制备 5-((3- 溴 -4-(3- 氟丙氧基)-5- 甲氧基苯甲基) 氧基)-2-(叔丁基)-4- 氯哒嗪 -3(2H)- 酮

[1859]



[1860] 将A部分的产物(0.146g,0.500mmol)于湿甲醇(5.00mL)中的溶液冷却到0℃,随后用硼氢化钠(37.8mg,1.00mmol)一次性处理。0.25小时后,通过逐滴添加饱和氯化铵水溶液(2mL)消耗过量的硼氢化钠,且将所得溶液温热到环境温度。0.5小时后,将所得混合物分配于乙酸乙酯与饱和碳酸氢钠水溶液(每个25mL)之间,转移到分液漏斗中,且分离每个层。随后用乙酸乙酯(2×25mL)洗涤水层,且经硫酸镁干燥经合并的乙酸乙酯洗涤液,过滤且真空浓缩成无色油状物。

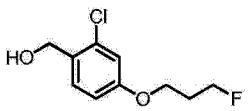
[1861] 在环境温度下,将由此获得的粗油状物溶解于无水二甲基甲酰胺(5.00mL)中,随后相继用2-(叔丁基)-4,5-二氯-2-氢哒嗪-3-酮[3](0.166g,0.750mmol)及碳酸铯(0.326,1.00mmol)一次性处理。随后将所得悬浮液浸于预热油浴中,且在剧烈搅拌下,在65℃下维持21小时。冷却到环境温度后,将悬浮液分配于乙酸乙酯与水(每个20mL)之间,转移到分液漏斗中,且分离每个层。随后用乙酸乙酯(2×20mL)洗涤水层,且经硫酸镁干燥经合并的乙酸乙酯洗涤液,过滤且真空浓缩成琥珀色油状物。随后通过使用7:3戊烷/乙酸乙酯经二氧化硅(30×180mm)色谱来纯化粗物质。收集在溶离200-350mL时的主要产物峰,合并且真空浓缩成白色固体(0.191g,0.400mmol;79.9%)。^{1}H NMR:(300MHz,$CDCl_3$)δ7.71(1H,s),7.15(1H,d,J=1.9Hz),6.92(1H,d,J=2.0Hz),5.21(2H,s),4.74(2H,dt,J=47.1,5.9Hz),4.13(2H,t,J=6.0Hz),3.86(3H,s),2.17(2H,dtt,J=25.5,6.0,6.0Hz),1.64(9H,s)。^{13}C NMR:(75MHz,$CDCl_3$)δ158.9,154.1,153.4,145.8,131.9,125.0,123.2,118.6,118.0,110.2,81.0(d,J_{CF}=164Hz),71.0,68.9(d,J_{CF}=5.5Hz),66.5,56.1,31.3(d,J_{CF}=20.2Hz),27.8。HRMS:$C_{19}H_{23}{}^{79}Br^{35}ClN_2O_4$(M+H)的计算值:477.0587;实验值:477.0589。TLC:R_f 0.15(硅胶,4:1戊烷/乙酸乙酯,CAM)。

[1862] 实例29

[1863] 制备2-(叔丁基)-4-氯-5-((2-氯-4-(3-氟丙氧基)苯甲基)氧基)哒嗪-3(2H)-酮

[1864] A部分-制备(2-氯-4-(3-氟丙氧基)苯基)甲醇

[1865]

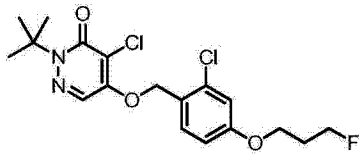


[1866] 根据通用方法F,使用2-氯-4-羟基苯甲酸甲酯(0.354g,2.26mmol)、对甲苯磺酸3-氟丙酯(0.500g,2.15mmol)且碳酸铯(1.12g,3.44mmol)于二甲基甲酰胺(22.6mL)中在60℃下制备。分离产量为0.510g。^{1}H NMR($CDCl_3$,300MHz):δ7.81(d,J=8.9Hz,1H),6.90(d,J=2.5Hz,1H),6.75(dd,J=8.8,2.5Hz,1H),4.64(t,J=5.7Hz,1H),4.49(t,J=5.8Hz,1H),4.07(t,J=6.1Hz,2H),3.82(s,3H),2.16(m,1H),2.09(m,1H);^{13}C NMR($CDCl_3$,75MHz):δ165.5,161.7,135.9,133.4,121.8,117.0,112.9,80.3(d,J_{CF}=165Hz),64.1(d,J_{CF}=7.5Hz),52.1,30.2(d,J_{CF}=22.5Hz)。

[1867] 在环境温度下，用硼氢化钠（66.7mg，1.76mmol）一次性处理醇（0.510g，2.35mmol）于乙醇（23.5mL）中的溶液，随后搅拌隔夜。用水（20mL）稀释所得混合物且真空浓缩以移除乙醇。用乙酸乙酯（3×50mL）萃取所得水溶液，且经硫酸钠干燥经合并的有机层，过滤且浓缩，得到呈透明油状的所需产物（0.388g，产率78.5％）。^{1}H NMR（$CDCl_3$，300MHz）：δ 7.80（d，J ＝ 8.8Hz，1H），6.90（d，J ＝ 2.6Hz，1H），6.75（dd，J ＝ 8.8，2.5Hz，1H），4.64（t，J ＝ 6.4Hz，1H），4.65（s，2H），4.49（t，J ＝ 5.8Hz，1H），4.07（t，J ＝ 6.2Hz，2H），2.16（m，1H），2.09（m，1H）；^{13}C NMR（$CDCl_3$，75MHz）：δ 158.9，135.8，133.3，130.1，117.0，112.8，80.3（d，J_{CF}＝ 165Hz），64.1（d，J_{CF}＝ 7.5Hz），61.1，30.2（d，J_{CF}＝ 22.5Hz）；^{1}HRMS-TOF（m/z）：[M-H]$^{+}$HRMS：$C_{10}H_{12}{}^{35}ClFO_2$的计算值：217.0437，实验值：217.0453。

[1868] B部分－制备2-（叔丁基）-4-氯-5-（（2-氯-4-（3-氟丙氧基）苯甲基）氧基）哒嗪-3（2H）-酮。

[1869]



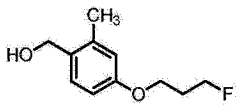
[1870] 根据通用方法B，使用2-（叔丁基）-4，5-二氯哒嗪-3（2H）-酮（0.358g，1.62mmol）、实例29A的产物（0.388g，1.78mmol）及碳酸铯（0.845g，2.59mmol）于二甲基甲酰胺（16.2mL）中在60℃下制备。分离产量为0.251g；产率38.4％。^{1}H NMR（$CDCl_3$，300MHz）：δ 7.67（s，1H），7.35（d，J ＝ 8.6Hz，1H），6.91（d，J ＝ 2.5Hz，1H），6.79（dd，J ＝ 8.7，2.5Hz，1H），5.26（s，2H），4.65（t，J ＝ 5.7Hz，1H），4.49（t，J ＝ 5.7Hz，1H），4.04（t，J ＝ 6.3Hz，2H），2.15（m，1H），2.06（m，1H），1.57（s，9H）；^{13}C NMR（$CDCl_3$，75MHz）：δ 159.7，153.6，133.7，130.1，125.2，124.7，118.5，115.8，113.7，80.3（d，J_{CF}＝ 165Hz），68.9，66.4，64.0（d，J_{CF} ＝ 7.5Hz），30.4，30.1，27.9；HRMS-TOF（m/z）：[M+H]$^{+}$HRMS：$C_{18}H_{21}{}^{35}Cl_2FN_2O_3$的计算值：403.0986，实验值：403.0994。

[1871] 实例30

[1872] 制备2-（叔丁基）-4-氯-5-（（4-（3-氟丙氧基）-2-甲基苯甲基）氧基）哒嗪-3（2H）-酮

[1873] A部分－制备（4-（3-氟丙氧基）-2-甲基苯基）甲醇

[1874]



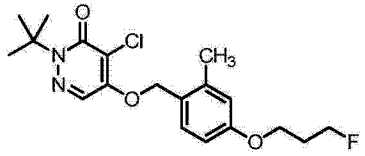
[1875] 根据通用方法F，使用4-羟基-2-甲基苯甲醛（0.614g，4.50mmol）、对甲苯磺酸3-氟丙酯（1.00g，4.29mmol）及碳酸铯（2.49g，7.64mmol）于二甲基甲酰胺（45.0mL）中在60℃下制备。^{1}H NMR（$CDCl_3$，300MHz）：δ 10.13（s，1H），7.77（d，J ＝ 8.6Hz，1H），6.86（dd，J ＝ 8.6，4.6Hz，1H），6.77（d，J ＝ 2.3Hz，1H），4.75（t，J ＝ 5.7Hz，1H），4.59（t，J ＝ 5.7Hz，1H），4.18（t，J ＝ 6.1Hz，2H），2.66（s，3H），2.27（m，1H），2.15（m，1H）；HRMS-TOF（m/z）：[M+H]$^{+}$HRMS：$C_{11}H_{13}FO_2$的计算值：197.0976，实验值：197.0972。

[1876] 用氢化锂铝（2.14mL，2.14mmol，1M四氢呋喃溶液）处理经冷却（0℃）的4-（3-氟

丙氧基)-2-甲基苯甲醛(0.840g,4.28mmol)于四氢呋喃(42.8mL)中的溶液,随后温热到环境温度。搅拌所得混合物隔夜,随后用水(20mL)稀释。随后分离水层,且用乙酸乙酯(3×50mL)萃取。随后经硫酸钠干燥经合并的有机层,过滤且浓缩成暗橙色油状物(0.800g,产率94.3%)。^{1}H NMR($CDCl_3$,300MHz):δ7.24(m,1H),6.73(m,2H),4.72(t,J=5.8Hz,1H),4.63(s,2H),4.56(t,J=5.8Hz,1H),4.09(t,J=6.0Hz,2H),2.36(s,3H),2.20(m,1H),2.10(m,1H)。

[1877] B部分-制备2-(叔丁基)-4-氯-5-((4-(3-氟丙氧基)-2-甲基苯甲基)氧基)哒嗪-3(2H)-酮.

[1878]



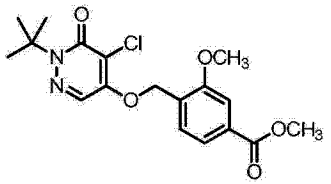
[1879] 根据通用方法B,使用2-(叔丁基)-4,5-二氯哒嗪-3(2H)-酮(0.480g,2.37mmol)、实例30A的产物(0.940g,4.74mmol)及碳酸铯(1.70g,5.28mmol)于二甲基甲酰胺(24.0mL)中在65℃下制备隔夜。分离产量为38.6mg;产率4.3%。^{1}H NMR($CDCl_3$,300MHz):δ7.50(s,1H),7.19(m,1H),6.66(m,2H),5.09(s,2H),4.64(m,1H),4.48(m,1H),4.02(t,J=6.2Hz,2H),2.27(s,3H),2.14(m,1H),2.03(m,1H),1.57(s,9H);HRMS-TOF(m/z):[M+H]$^+$HRMS:$C_{19}H_{24}{}^{35}ClFN_2O_3$的计算值:386.1532,实验值:383.1537。

[1880] 实例31

[1881] 制备2-(叔丁基)-4-氯-5-((4-((2-氟乙氧基)甲基)-2-甲氧基苯甲基)氧基)哒嗪-3(2H)-酮

[1882] A部分-制备4-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)-3-甲氧基苯甲酸甲酯

[1883]

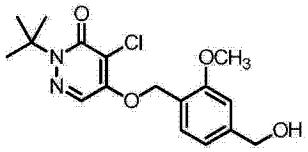


[1884] 根据通用方法B,使用2-(叔丁基)-4-氯-5-羟基哒嗪-3(2H)-酮(0.617g,3.05mmol)、4-(溴甲基)-3-甲氧基苯甲酸甲酯(0.750g,2.91mmol)及碳酸铯(1.51g,4.64mmol)于二甲基甲酰胺(15.0mL)中在环境温度下制备。分离产量为1.11g;>98%。^{1}H NMR($CDCl_3$,300MHz):δ7.65(s,1H),7.63(dd,J=7.9,1.4Hz,1H),7.51(d,J=1.4Hz,1H),7.44(d,J=7.9Hz,1H),5.30(s,2H),3.90(s,3H),3.86(s,3H),1.57(s,9H);^{13}C NMR($CDCl_3$,75MHz):δ166.6,159.0,156.3,153.7,131.6,128.4,127.7,125.0,122.4,118.2,111.1,66.7,66.4,55.7,52.3,27.9;HRMS-TOF(m/z):[M+H]$^+$HRMS:$C_{18}H_{21}{}^{35}ClN_2O_5$的计算值:381.1212,实验值:381.1206。

[1885] B部分-制备2-(叔丁基)-4-氯-5-((4-(羟甲基)-2-甲氧基苯甲基)氧基)哒

嗪 -3(2H)- 酮

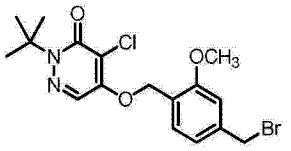
[1886]



[1887] 在 0 ℃下，用氢化锂铝 (1.46mL，1.46mmol，1M 四氢呋喃溶液）处理实例 31A 的产物 (1.11g，2.92mmol) 于四氢呋喃 (29.0mL) 中的溶液，随后温热到环境温度。搅拌所得混合物隔夜，随后用水 (50mL) 稀释。分离水层，随后用乙酸乙酯 (3×50mL) 萃取。随后经硫酸钠干燥经合并的有机层，过滤且浓缩成非晶形橙色固体 (0.890g，产率 86.4 %)。^{1}H NMR($CDCl_3$，300MHz)：δ 7.68(s，1H)，7.31(d，J = 7.5Hz，1H)，7.89(m，2H)，5.27(s，2H)，4.64(s，2H)，3.85(s，3H)，1.56(s，9H) ；^{13}C NMR($CDCl_3$，75MHz)：δ 159.1，156.9，153.9，143.2，128.7，125.4，122.5，119.1，118.0，109.1，67.0，66.3，65.1，55.5，27.9 ；HRMS-TOF(m/z)：[M+H]$^{+}$HRMS：$C_{17}H_{21}{}^{35}ClN_2O_4$的计算值：353.1263，实验值：353.1257。

[1888] C 部分 - 制备 5-((4-(溴甲基)-2- 甲氧基苯甲基) 氧基)-2-(叔丁基)-4- 氯哒嗪 -3(2H)- 酮

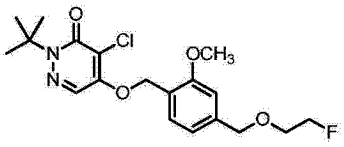
[1889]



[1890] 根据通用方法 C，使用实例 31B 的产物 (0.448g，1.26mmol) 及三溴化磷 (0.631mL，0.63mmol，1M 二氯甲烷溶液）制备。分离产量为 0.429g ；81.9 %。^{1}H NMR($CDCl_3$，300MHz)：δ 7.67(s，1H)，7.32(d，J = 7.7Hz，1H)，6.98(dd，J = 7.7，1.6Hz，1H)，6.88(d，J = 1.5Hz，1H)，5.25(s，2H)，4.42(s，2H)，3.82(s，3H)，1.57(s，9H) ；^{13}C NMR($CDCl_3$，75MHz)：δ 159.1，156.7，153.8，139.6，128.7，125.2，123.7，121.5，118.1，111.1，66.8，66.3，55.6，33.1，27.9 ；HRMS-TOF(m/z)：[M+H]$^{+}$HRMS：$C_{17}H_{20}{}^{79}Br^{35}ClN_2O_3$的计算值：415.0419，实验值：415.0416。

[1891] D 部分 - 制备 2-(叔丁基)-4- 氯 -5-((4-((2- 氟乙氧基) 甲基)-2- 甲氧基苯甲基) 氧基) 哒嗪 -3(2H)- 酮

[1892]



[1893] 根据通用方法 E，使用叔丁醇钾 (38mg，0.340mmol)、2- 氟乙醇 (14.5mg，0.226mmol) 及实例 31C 的产物 (0.112g，0.271mmol) 制备。分离产量为 2.3mg ；2.6 %。^{1}H NMR($CDCl_3$，300MHz)：δ 7.68(s，1H)，7.30(d，J = 7.5Hz，1H)，6.9(s，1H)，6.88(d，J = 8.0Hz，1H)，5.27(s，2H)，4.62(m，1H)，4.53(s，2H)，4.46(m，1H)，3.82(s，3H)，3.73(m，1H)，3.63(m，1H)，1.56(s，9H) ；^{13}C NMR($CDCl_3$，75MHz)：δ 158.1，155.8，152.9，139.1

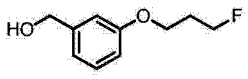
,127.5,124.3,121.7,119.0,117.0,108.6,82.1(d,J_{CF}= 165Hz),72.0,68.5(d,J_{CF}= 22.5Hz),65.9,65.3,54.5,26.9;HRMS-TOF(m/z):[M+H]$^+$HRMS:$C_{19}H_{24}{}^{35}ClFN_2O_3$的计算值:399.1481,实验值:399.1479。

[1894] 实例 32

[1895] 制备 2-(叔丁基)-4-氯-5-((3-(3-氟丙氧基)苯甲基)氧基)哒嗪-3(2H)-酮

[1896] A 部分-制备(3-(3-氟丙氧基)苯基)甲醇

[1897]

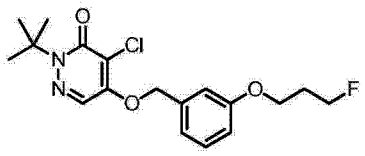


[1898] 根据通用方法 F,使用 3-羟基苯甲醛(0.552g,4.52mmol)、对甲苯磺酸 3-氟丙酯(0.998g,4.30mmol)及碳酸铯(2.24g,6.90mmol)于二甲基甲酰胺(45.2mL)中在 60℃下制备。分离产量为 0.700g;89.4%。^{1}H NMR($CDCl_3$,300MHz):δ9.91(s,1H),7.40-7.37(m,2H),7.34(m,1H),7.11(m,1H),4.66(t,J = 5.8Hz,1H),4.52(t,J = 5.7Hz,1H),4.10(t,J = 6.1Hz,2H),2.17(m,1H),2.09(m,1H);^{13}C NMR($CDCl_3$,75MHz):δ192.0,159.4,137.9,130.1,123.6,121.8,113.0,80.5(d,J_{CF}= 165Hz),63.9(d,J_{CF}= 7.5Hz),30.3(d,J_{CF}= 22.5Hz)。^{1}HRMS-TOF(m/z):[M+H]$^+$HRMS:$C_{10}H_{11}FO_2$的计算值:183.0816,实验值:183.0827。

[1899] 用硼氢化钠(72.3mg,1.91mmol)处理溶解于乙醇(38mL)中的经冷却(0℃)的 3-(3-氟丙氧基)苯甲醛(0.700g,3.82mmol)溶液,随后温热到环境温度。2 小时后,用水(20mL)稀释所得混合物且真空浓缩以移除乙醇。用乙酸乙酯(3×50mL)萃取所得水溶液,且经硫酸钠干燥经合并的有机层,过滤且浓缩,得到呈黄色油状的所需产物(0.625g,产率 88.8%)。^{1}H NMR($CDCl_3$,300MHz):δ7.20(m,1H),6.87(m,2H),6.76(dd,J = 8.3,2.1Hz,1H),4.65(t,J = 5.8Hz,1H),4.60(s,2H),4.50(t,J = 5.8Hz,1H),4.04(t,J = 6.1Hz,2H),2.14(m,1H),2.04(m,1H);^{13}C NMR($CDCl_3$,75MHz):δ159.1,142.6,129.6,119.3,113.8,113.0,80.7(d,J_{CF}= 165Hz),65.2,63.5(d,J_{CF}= 7.5Hz),30.6(d,J_{CF}= 22.5Hz)。^{1}HRMS-TOF(m/z):[M+H]$^+$HRMS:$C_{10}H_{13}FO_2$的计算值:185.0972,实验值:186.0967。

[1900] B 部分-制备 2-(叔丁基)-4-氯-5-((3-(3-氟丙氧基)苯甲基)氧基)哒嗪-3(2H)-酮

[1901]



[1902] 根据通用方法 B,使用 2-(叔丁基)-4,5-二氯哒嗪-3(2H)-酮(0.339g,1.53mmol)、实例 32A 的产物(0.313g,1.69mmol)及碳酸铯(0.798g,2.45mmol)于二甲基甲酰胺(17.0mL)中在 60℃下制备。分离产量为 0.122g,产率 21.6%。^{1}H NMR($CDCl_3$,300MHz):δ7.63(s,1H),7.25(m,1H),6.92-6.81(m,3H),5.21(s,2H),4.66(t,J = 5.8Hz,1H),4.50(t,J = 5.8Hz,1H),4.04(t,J = 6.1Hz,2H),2.15(m,1H),2.07(m,1H),1.57(s,9H);($CDCl_3$,75MHz):δ159.3,159.0,153.7,136.5,130.1,125.1,119.3,118.4,114.7,113.9,80.6(d,J_{CF}= 165Hz),71.7,66.4,63.6(d,J_{CF}= 7.5Hz),30.4(d,J_{CF}= 22.5Hz),27.9;HRMS-TOF(m/z):[M+H]$^+$HRMS:$C_{18}H_{22}{}^{35}ClFN_2O_3$的计算值:369.1376,实验值:

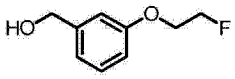
369.1379。

[1903] 实例 33

[1904] 制备 2-(叔丁基)-4-氯-5-((3-(2-氟乙氧基)苯甲基)氧基)哒嗪-3(2H)-酮

[1905] A 部分-制备 (3-(2-氟乙氧基)苯基)甲醇

[1906]

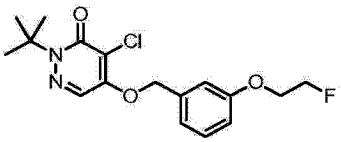


[1907] 将 3-羟基苯甲醛 (1.02g,8.33mmol)、1-溴-2-氟乙烷 (1.00g,7.93mmol) 及碳酸铯 (4.13g,12.7mmol) 于二甲基甲酰胺 (83.0mL) 中的悬浮液加热到 60℃且维持隔夜。冷却到环境温度后,用水 (100mL) 稀释所得混合物,且用乙酸乙酯 (3×150mL) 萃取水层。用水 (150mL) 及饱和氯化钠水溶液 (150mL) 及洗涤经合并的有机层,随后经硫酸钠干燥,过滤且浓缩成橙色油状物 (1.34g)。^{1}H NMR($CDCl_3$,300MHz):δ9.91(s,1H),7.44-7.33(m,3H),7.19-7.13(m,1H),4.79(m,1H),4.63(m,1H),4.26(m,1H),4.17(m,1H);^{13}C NMR($CDCl_3$,75MHz):δ192.0,159.0,137.9,130.2,124.1,122.2,112.7,81.9(d,J_{CF}= 165Hz),67.4(d,J_{CF}= 22.5Hz);^{1}HRMS-TOF(m/z):[M+H]$^{+}$HRMS:$C_9H_9FO_2$的计算值:169.0659,实验值:169.0660。

[1908] 用硼氢化钠 (0.150g,3.97mmol) 一次性处理醛 (1.34g) 于乙醇 (39.5mL) 中的经冷却 (0℃) 的溶液,随后温热到环境温度。2 小时后,用水 (20mL) 稀释所得混合物且真空浓缩以移除乙醇。用乙酸乙酯 (3×50mL) 萃取所得水溶液,且经硫酸钠干燥经合并的有机层,过滤且浓缩,得到呈黄色油状的所需产物 (1.28g,产率 94.8%)。^{1}H NMR($CDCl_3$,300MHz):δ7.20(m,1H),6.89(m,2H),6.78(m,1H),4.75(m,1H),4.60(s,2H),4.59(m,1H),4.20(m,1H),4.10(m,1H);^{13}C NMR($CDCl_3$,75MHz):δ158.7,142.7,129.7,119.7,114.0,113.0,81.9(d,J_{CF}= 165Hz),67.2(d,J_{CF}= 22.5Hz),65.2;^{1}HRMS-TOF(m/z):[M+H]$^{+}$HRMS:$C_9H_{11}FO_2$的计算值:171.0816,实验值:171.0815。

[1909] B 部分-制备 2-(叔丁基)-4-氯-5-((3-(2-氟乙氧基)苯甲基)氧基)哒嗪-3(2H)-酮

[1910]



[1911] 根据通用方法 B,使用 2-(叔丁基)-4,5-二氯哒嗪-3(2H)-酮 (0.587g,2.66mmol)、实例 33A 的产物 (0.500g,2.92mmol) 及碳酸铯 (1.38g,4.25mmol) 于二甲基甲酰胺 (26.6mL) 中在 60℃下制备。分离产量为 20mg,产率 2.1%。^{1}H NMR($CDCl_3$,300MHz):δ7.63(s,1H),7.26(m,1H),6.95-6.84(m,3H),5.22(s,2H),4.78(m,1H),4.62(m,1H),4.21(m,1H),4.11(m,1H),1.56(s,9H)。^{13}C NMR($CDCl_3$,75MHz):δ159.0,158.9,153.6,136.6,130.2,125.1,119.3,114.9,114.8,113.2,81.9(d,J_{CF}= 7.5Hz),71.6,67.2(d,J_{CF}= 22.5Hz),66.4,27.9。HRMS-TOF(m/z):[M+H]$^{+}$HRMS:$C_{17}H_{20}{}^{35}ClFN_2O_3$的计算值:355.1219,实验值:355.1218。

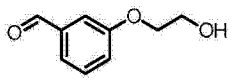
[1912] 实例 34

[1913] 制备 4-甲基苯磺酸 2-(3-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒

嗪 -4- 基）氧基）甲基）苯氧基）乙酯

[1914] A 部分 - 制备 3-(2- 羟基乙氧基）苯甲醛

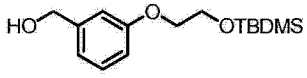
[1915]



[1916] 将 3- 羟基苯甲醛 (1.02g,8.33mmol)、1- 溴乙醇 (0.991g,7.93mmol) 及碳酸铯 (4.13g,12.7mmol) 于二甲基甲酰胺 (20.0mL) 中的悬浮液加热到 60℃且维持隔夜。冷却到环境温度后，用水 (50mL) 稀释所得混合物，且用乙酸乙酯 (3×50mL) 萃取水层。用水 (150mL) 及饱和氯化钠水溶液洗涤经合并的有机层，随后经硫酸钠干燥且浓缩，得到黄色油状物。随后通过硅胶色谱 (4:1 己烷 / 乙酸乙酯）纯化粗物质，得到呈白色固体状的所需产物 (1.38g，产率 >98％）。^{1}H NMR($CDCl_3$,300MHz)：δ 9.98(s,1H),7.48-7.41(m,3H),7.23-7.19(m,1H),4.16(m,2H),4.00(m,2H) ;HRMS-TOF(m/z)：[M+H]$^{+}$HRMS:$C_9H_{10}O_3$的计算值：167.0703，实验值 :167.0696。

[1917] B 部分 - 制备 (3-(2-((叔丁基二甲基硅烷基）氧基）乙氧基）苯基）甲醇

[1918]

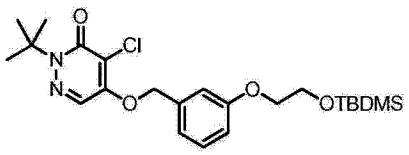


[1919] 相继用氯化叔丁基二甲基硅烷基 (1.88g,12.5mmol) 及咪唑 (0.850g,12.5mmol) 处理实例 34A 的产物 (1.38g) 于二甲基甲酰胺 (8.3mL) 中的溶液，随后在环境温度下搅拌隔夜。随后用水 (50mL) 稀释所得混合物，且用乙酸乙酯 (3×100mL) 萃取。用饱和氯化钠水溶液洗涤经合并的有机层，经硫酸钠干燥，过滤且真空浓缩成黄色油状物 (0.597g，产率 26.8 ％）。^{1}H NMR($CDCl_3$,300MHz)：δ 9.87(s,1H),7.35-7.29(m,3H),7.11-7.08(m,1H),4.00(m,2H),3.89(m,2H),0.84(s,9H),0.01(s,6H) ;^{13}C NMR($CDCl_3$,75MHz)：δ 189.7,159.4,137.8,130.0,123.5,122.0,113.0,69.6,61.9,25.6,18.4,-5.2 ;HRMS-TOF(m/z)：$C_{15}H_{24}O_3Si$ 的 [M+H]$^{+}$:281.1567，实验值 :281.1563。

[1920] 在环境温度下，用硼氢化钠 (60.4mg,1.60mmol) 一次性处理甲硅烷基醚 (0.597g,2.13mmol) 于乙醇 (21.0mL) 中的溶液。3 小时后，用水 (10mL) 稀释所得混合物且真空浓缩以移除乙醇。用乙酸乙酯 (3×50mL) 萃取所得水溶液，且经硫酸钠干燥经合并的有机层，过滤且浓缩，得到呈乳白色油状的所需产物 (0.600g，产率 >98％）。^{1}H NMR($CDCl_3$,300MHz)：δ 7.16(m,1H),6.84(m,2H),6.74(dd,J = 9.0,2.5Hz,1H),4.57(s,2H),3.94(m,2H),3.87(m,2H),0.81(s,9H),0.01(s,6H) ;^{13}C NMR($CDCl_3$,75MHz)：δ 159.3,142.5,129.6,119.1,114.0,113.0,69.3,65.3,62.0,25.6,18.4,-5.2 ;HRMS-TOF(m/z)：[M+H]$^{+}$HRMS:$C_{15}H_{26}O_3Si$ 的计算值 :283.1724，实验值 :283.1717。

[1921] C 部分 - 制备 2-(叔丁基）-5-((3-(2-((叔丁基二甲基硅烷基）氧基）乙氧基）苯甲基）氧基）-4- 氯哒嗪 -3(2H)- 酮

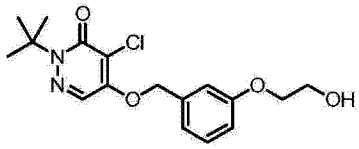
[1922]



[1923] 根据通用方法B，使用2-(叔丁基)-4,5-二氯哒嗪-3(2H)-酮(0.711g，3.19mmol)、实例34B的产物(0.600g,2.13mmol)及碳酸铯(0.834g,2.56mmol)于二甲基甲酰胺(32.0mL)中在60℃下制备。分离产量为0.159g，产率16.0％。^{1}H NMR($CDCl_3$,300MHz)：δ7.62(s,1H),7.21(m,1H),6.82-6.79(m,3H),5.19(s,2H),3.95(m,2H),3.88(m,2H),1.53(s,9H),0.80(s,9H),-0.01(s,6H)；^{13}C NMR($CDCl_3$,75MHz)：δ159.5,159.0,153.7,136.5,130.0,125.1,119.1,118.2,114.8,113.2,71.7,69.4,66.4,62.0,27.9,25.9,18.4,-5.2；HRMS-TOF(m/z)：[M+H]$^{+}$HRMS：$C_{23}H_{35}{}^{35}ClN_2O_4Si$的计算值：467.2127，实验值：467.2129。

[1924] D部分-制备2-(叔丁基)-4-氯-5-((3-(2-羟基乙氧基)苯甲基)氧基)哒嗪-3(2H)-酮

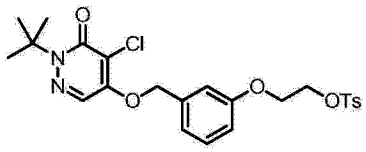
[1925]



[1926] 在环境温度下，用氟化四丁铵(0.60mL,0.60mmol,1M四氢呋喃溶液)处理实例34C的产物(0.140g,0.300mmol)于四氢呋喃(3.0mL)中的溶液。1小时后，用水(10mL)稀释所得混合物，分离水层，随后用乙酸乙酯(2×20mL)萃取。经硫酸钠干燥经合并的有机层，过滤且真空浓缩。随后通过硅胶色谱(20-50％乙酸乙酯的己烷溶液)纯化粗物质，得到所需产物(0.105g，产率>98％)。^{1}H NMR($CDCl_3$,300MHz)：δ7.57(s,1H),7.16(m,1H),6.83(m,2H),6.76(dd,J = 7.5,2.0Hz,1H),5.13(s,2H),3.95(m,2H),3.82(m,2H),1.47(s,9H)；^{13}C NMR($CDCl_3$,75MHz)：δ159.1,159.0,153.6,136.5,130.0,125.0,119.3,118.2,114.6.113.1,71.5,69.2,66.4,61.2,27.8；HRMS-TOF(m/z)：[M+H]$^{+}$HRMS：$C_{17}H_{21}{}^{35}ClN_2O_4$的计算值：353.1263，实验值：353.1259。

[1927] E部分-制备4-甲基苯磺酸2-(3-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯氧基)乙酯

[1928]



[1929] 根据通用方法D，使用实例34D的产物(52.4mg,0.149mmol)、对甲苯磺酰氯(34.1mg,0.179mmol)、4-二甲基氨基吡啶(22.0mg,0.179mmol)及二异丙基乙氨(0.032mL,0.179mmol)制备。分离产量为48.5mg，产率64.2％。^{1}H($CDCl_3$,300MHz)：δ7.75(d,J = 8.4Hz,2H),7.63(s,1H),7.29-7.20(m,3H),6.92(d,J = 7.1Hz,1H),6.79(m,1H),6.72(dd,J = 8.2,2.0Hz,1H),5.19(s,2H),4.30(m,2H),4.09(m,2H),2.38(s,3H),1.56(s,9H)；^{13}C NMR($CDCl_3$,75MHz)：δ158.0,157.5,152.6,144.0,135.6,131.8,129.1,128.9,127.0,124.0,118.8,117.3,113.8,112.1,70.5,66.9,65.4,64.5,26.8,20.6。HRMS-TOF(m/z)：[M+H]$^{+}$HRMS：$C_{24}H_{27}{}^{35}ClN_2O_6S$

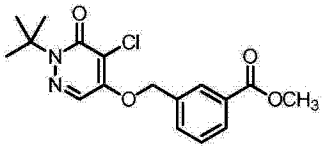
的计算值 :507.1351,实验值 :507.1354。

[1930] 实例 35

[1931] 制备 2-(叔丁基)-4-氯 -5-((3-((2-氟乙氧基)甲基)苯甲基)氧基)哒嗪 -3(2H)-酮

[1932] A 部分 - 制备 3-(((1-(叔丁基)-5-氯 -6-侧氧基 -1,6-二氢哒嗪 -4-基)氧基)甲基苯甲酸甲酯

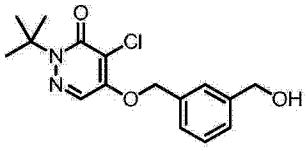
[1933]



[1934] 根据通用方法 B,使用 2-(叔丁基)-4-氯 -5-羟基哒嗪 -3(2H)-酮 (0.750g,3.70mmol)、4-(溴甲基)苯甲酸甲酯 (0.806g,3.52mmol) 及碳酸铯 (1.45g,4.45mmol) 于二甲基甲酰胺 (7.5mL) 中在环境温度下制备。分离产量为 0.643g,产率 52.1 %。^{1}H NMR(CDCl$_3$,300MHz):δ 8.01-7.96(m,2H),7.65(s,1H),7.59-7.41(m,2H),5.27(s,2H),3.86(s,3H),1.56(s,9H) ;^{13}C NMR(CDCl$_3$,75MHz):δ 166.5,159.0,153.5,135.4,131.5,130.9,129.2,128.2,127.8,125.0,118.6,71.4,66.5,52.3,27.9。

[1935] B 部分 - 制备 2-(叔丁基)-4-氯 -5-((3-(羟甲基)苯甲基)氧基)哒嗪 -3(2H)-酮

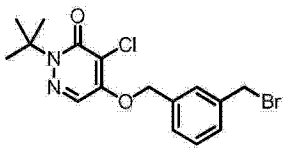
[1936]



[1937] 用氢化锂二异丁基铝 (2.25mL,2.25mmol,1M 己烷溶液) 处理实例 35A 的产物 (0.643g,1.83mmol) 于四氢呋喃 (6.5mL) 中的经冷却 (0 ℃) 溶液,随后温热到环境温度且搅拌隔夜。用水 (50mL) 稀释所得溶液,分离水层,随后用乙酸乙酯 (3×150mL) 萃取。经硫酸钠干燥经合并的有机层,过滤且真空浓缩。随后通过硅胶色谱 (5-50 % 乙酸乙酯的己烷溶液) 纯化粗物质,得到呈白色固体状的所需产物 (0.403g,产率 68.2 %)。^{1}H NMR(CDCl$_3$,300MHz):δ 7.74(s,1H),7.45-7.28(m,4H),5.34(s,2H),4.76(s,2H),1.65(s,9H) ;^{13}C NMR(CDCl$_3$,75MHz):δ 159.0,153.7,141.8,135.3,129.2,127.3,126.3,125.5,125.1,118.4,71.8,66.4,64.9,27.9 ;HRMS-TOF(m/z):[M+H]$^{+}$HRMS:$C_{16}H_{19}{}^{35}ClN_2O_3$的计算值 :323.1157,实验值 :323.1154。

[1938] C 部分 - 制备 5-((3-(溴甲基)苯甲基)氧基)-2-(叔丁基)-4-氯哒嗪 -3(2H)-酮

[1939]

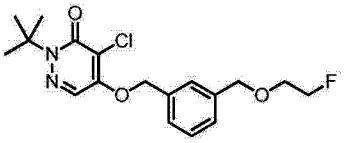


[1940] 根据通用方法 C,逐滴使用实例 35B 的产物 (0.190g,0.590mmol) 及三溴化磷 (0.280mL,0.29mmol,1M 二氯甲烷溶液) 制备

。分离产量为0.203g，产率89.2％。^{1}H NMR($CDCl_3$,300MHz)：δ7.64(s,1H),7.37-7.28(m,4H),5.23(s,2H),4.43(s,2H),1.56(s,9H)；^{13}C NMR($CDCl_3$,75MHz)：δ159.0,153.6,138.7,135.6,129.3,129.2,127.6,127.1,125.1,118.5,71.5,66.5,32.8,27.9；HRMS-TOF(m/z)：$C_{16}H_{18}{}^{79}Br^{35}ClN_2O_2$的$[M+H]^+$：385.0313，实验值：385.0316。

[1941] D部分-制备2-(叔丁基)-4-氯-5-((3-((2-氟乙氧基)甲基)苯甲基)氧基)哒嗪-3(2H)-酮

[1942]



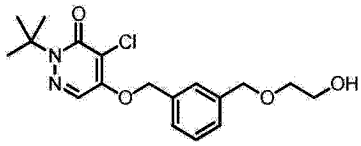
[1943] 根据通用方法E，使用叔丁醇钾(25.9mg,0.231mmol)、2-氟乙醇(14.8mg,0.231mmol)及实例35C的产物(0.100g,0.260mmol)制备。分离产量为2.3mg；2.7％。^{1}H NMR($CDCl_3$,300MHz)：δ7.65(s,1H),7.37-7.30(m,4H),5.25(s,2H),4.62(m,1H),4.55(s,2H),4.46(m,1H),3.73(m,1H),3.64(m,1H),1.56(s,9H)；^{13}C NMR($CDCl_3$,75MHz)：δ159.1,153.7,138.8,135.2,129.1,128.0,126.5,126.2,125.1,118.4,83.0(d,J_{CF}=165Hz),73.0,71.8,69.7(d,J_{CF}= 22.5Hz),66.4,28.9；HRMS-TOF(m/z)：$C_{18}H_{22}{}^{35}ClFN_2O_3$的$[M+H]^+$：369.1376，实验值：369.1373。

[1944] 实例36

[1945] 制备4-甲基苯磺酸2-((3-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯甲基)氧基)乙酯

[1946] A部分-制备2-(叔丁基)-4-氯-5-((3-((2-羟基乙氧基)甲基)苯甲基)氧基)哒嗪-3(2H)-酮

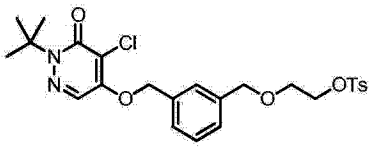
[1947]



[1948] 将叔丁醇钾(25.3mg,0.226mmol)及乙二醇(111mg,1.79mmol)的悬浮液加热到60℃且维持20分钟。添加逐滴溶解于四氢呋喃(3mL)中的实例35C的产物(0.104g,0.271mmol)。添加完成后，加热回流所得混合物，维持隔夜，随后冷却且用水(15mL)淬灭。分离水层，随后用乙酸乙酯(3×25mL)萃取。经硫酸钠干燥经合并的有机层，过滤且真空浓缩。随后通过硅胶色谱使用4:1己烷/乙酸乙酯纯化粗物质，得到呈透明油状的所需产物(60.2mg，产率60.6％)。^{1}H NMR($CDCl_3$,300MHz)：δ7.73(s,1H),7.44-7.29(m,4H),5.32(s,2H),4.59(s,2H),3.78(m,2H),3.62(m,2H),1.63(s,9H)；^{13}C NMR($CDCl_3$,75MHz)：δ159.1,153.7,139.0,135.2,129.2,128.1,126.5,126.2,125.1,118.4,72.9,71.8,71.6,66.4,61.9,27.9。

[1949] B部分-制备4-甲基苯磺酸2-((3-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)乙基)苯甲基)氧基)乙酯

[1950]

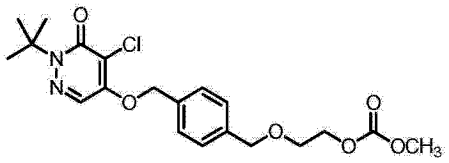


[1951] 根据通用方法D，使用实例36A的产物(50.2mg,0.137mmol)、对甲苯磺酰氯(31.3mg,0.165mmol)、4-二甲基氨基吡啶(21.0mg,0.165mmol)及二异丙基乙氨(0.016mL,0.165mmol)制备。分离产量为21.2mg;29.7%。$^{1}H(CDCl_3,300MHz)$:δ7.73(d,J = 8.4Hz,2H),7.66(s,1H),7.34-7.19(m,6H),5.23(s,2H),4.45(s,2H),4.06(m,2H),3.62(m,2H),2.38(s,3H),1.56(s,9H);$^{13}C(CDCl_3,75MHz)$:δ159.0,153.7,144.9,138.6,135.2,133.0,129.8,129.1,127.9,127.8,126.5,126.1,125.1,118.3,72.8,71.8,69.2,67.8,66.4,27.9,21.6;HRMS-TOF(m/z):$C_{25}H_{29}{}^{35}ClN_2O_6S$ 的$[M+H]^+$:521.1508,实验值:521.1500。

[1952] 实例37

[1953] 制备碳酸2-((4-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯甲基)氧基)乙基甲基酯

[1954]

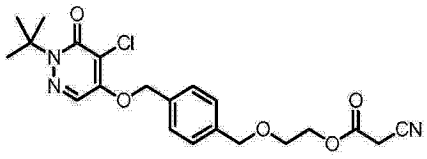


[1955] 将2-(叔丁基)-4-氯-5-((4-((2-羟基乙氧基)甲基)苯甲基)氧基)哒嗪-3(2H)-酮(0.147g,0.400mmol;例如参见卡斯贝尔(Casebier),大卫(David S.);罗宾逊,西蒙(Simon P.);普罗希特(Purohit),阿吉(Ajay);拉德克(Radeke),赫克(Heike S.);阿祖瑞(Azure),迈克尔(Michael T.);迪斯奇诺(Dischino),道格拉斯(Douglas D.)(百时美施贵宝公司(Bristol-Myers Squibb))包含造影部分和鱼藤素、哒螨灵、嘧螨醚、吡螨胺、腈苯唑和其类似物的用于心肌灌注的制备造影剂(Preparation contrast agents for myocardial perfusion imaging comprising an imaging moiety and deguelin,pyridaben,pyrimidifen,tebufenpyrad,fenazaquin,and analogs thereof).PCT国际申请案WO 2005/079391.2005年9月1日)于吡啶(2.00mL)中的溶液冷却到0℃,随后用氯甲酸甲酯(34μL,0.44mmol)一次性处理。1.25小时后,再添加氯甲酸甲酯(34μL,0.44mmol)。再1.5小时后,最后添加氯甲酸甲酯(34μL,0.44mmol)。0.25小时后,用乙酸乙酯稀释溶液,转移到分液漏斗中,随后用5% $CuSO_4$水溶液洗涤,经硫酸镁干燥,过滤且真空浓缩。随后通过使用3:2戊烷/乙酸乙酯经二氧化硅(30×175mm)色谱来纯化由此获得的粗物质。收集在溶离175-280mL时的主要产物峰,合并且真空浓缩成无色油状物(0.144g,0.339mmol;84.7%)。^{1}H NMR:(300MHz,DMSO-d_6)δ8.26(1H,s),7.45(2H,AB,J_{AB} = 8.2Hz),7.37(2H,AB,J_{AB}= 8.4Hz),5.45(2H,s),4.52(2H,s),4.29-4.19(2H,m),3.69(3H,s),3.68-3.60(2H,m),1.57(9H,s)。^{13}C NMR:(75MHz,DMSO-d_6)δ157.8,155.2,153.8,138.6,134.6,127.8,127.7,126.2,115.6,71.5,71.3,67.5,66.7,65.4,54.6,27.4。$C_{20}H_{25}{}^{35}ClN_2O_6$(M+H)的HRMS计算值:425.1474;实验值:425.1470。TLC:R_f 0.50(硅胶,1:1戊烷/乙酸乙酯,CAM)。

[1956] 实例 38

[1957] 制备 2-氰基乙酸 2-((4-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯甲基)氧基)乙酯

[1958]



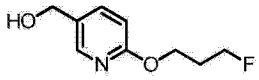
[1959] 在环境温度下,用盐酸 N-(3-二甲基氨基丙基)-N'-乙基碳化二亚氨 (0.191g,1.00mmol) 一次性处理 2-(叔丁基)-4-氯-5-((4-((2-羟基乙氧基)甲基)苯甲基)氧基)哒嗪-3(2H)-酮[6](0.183g,0.500mmol) 和氰基乙酸 (85.1mg,1.00mmol) 于无水二氯甲烷 (2.50mL) 中的溶液。0.25 小时后,在真空中移除所有挥发物,且通过使用 1:1 戊烷/乙酸乙酯经二氧化硅 (30×180mm) 色谱直接纯化残余物。收集在溶离 175-325mL 时的主要产物峰,合并且真空浓缩成无色油状物 (0.206g,0.476mmol ;95.1%)。^{1}H NMR:(300MHz,$CDCl_3$) δ 7.72(1H,s),7.43-7.37(4H,m),5.31(2H,s),4.57(2H,s),4.41-4.38(2H,m),3.75-3.72(2H,m),3.49(2H,s),1.63(9H,s)。^{13}C NMR:(75MHz,$CDCl_3$) δ 162.9,159.0,153.6,138.3,134.5,128.2,127.3,125.0,118.3,112.8,72.8,71.6,67.5,66.4,65.8,27.8,24.7。HRMS :$C_{21}H_{24}{}^{35}ClN_3O_5$(M+H) 的计算值 :434.1477 ;实验值 :434.1474。TLC :R_f 0.41(硅胶,1:1 戊烷/乙酸乙酯,uv)。

[1960] 实例 39

[1961] 制备 2-(叔丁基)-4-氯-5-((6-(3-氟丙氧基)吡啶-3-基)甲氧基)哒嗪-3(2H)-酮

[1962] A 部分-制备 (6-(3-氟丙氧基)吡啶-3-基)甲醇

[1963]

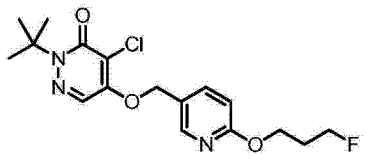


[1964] 将氢化钠 (26.4mg,1.10mmol) 和 3-氟丙醇 (78.0mg,1.00mmol) 于二甲基甲酰胺 (1.0mL) 中的悬浮液在环境温度下维持 25 分钟,随后用 6-溴烟碱酸甲酯 (0.216g,1.00mmol) 于二甲基甲酰胺 (0.5mL) 中的溶液处理。1 小时后,用水 (2mL) 稀释所得混合物,分离水层,随后用乙酸乙酯 (2×10mL) 萃取。经硫酸钠干燥经合并的有机层,且真空浓缩成黄色油状物。

[1965] 逐滴添加 6-(3-氟丙氧基)烟碱酸甲酯于四氢呋喃中的溶液到氢化锂铝 (0.14mL,0.14mmol,1M 四氢呋喃溶液) 的经冷却 (0℃) 溶液中且将所得混合物温热到环境温度。2 小时后,用水稀释溶液,分离水层,随后用乙酸乙酯 (3×10mL) 萃取。经硫酸钠干燥经合并的有机层且真空浓缩。随后通过硅胶色谱 (0-60%乙酸乙酯的己烷溶液) 纯化粗物质,得到呈黄色油状的所需产物 (22.3mg,产率 12.0%)。^{1}H NMR($CDCl_3$,300MHz):δ 8.06-7.99(m,1H),7.55(dd,J = 2.4,8.4Hz,1H),6.66(d,J = 8.5Hz,1H),4.63(t,J = 5.9Hz,1H),4.54(s,2H),4.47(t,J = 5.9Hz,1H),4.30(t,J = 6.2Hz,2H),2.18-2.01(m,2H)。^{13}C NMR(75MHz,$CDCl_3$) δ 162.4,144.7,137.4,128.1,109.9,79.9(d,J_{CF}= 165Hz),61.4,60.8,(d,J_{CF}= 7.5Hz),29.2(d,J_{CF}= 22.5Hz)。

[1966] B 部分 - 制备 2-(叔丁基)-4- 氯 -5-((6-(3- 氟丙氧基) 吡啶 -3- 基) 甲氧基) 哒嗪 -3(2H)- 酮

[1967]

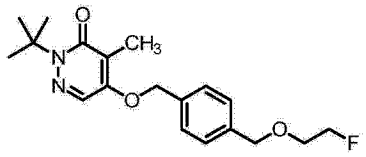


[1968] 根据通用方法 B，使用 2-(叔丁基)-4- 氯 -5- 羟基哒嗪 -3(2H)- 酮 (22.3mg,0.100mmol)、实例 39A 的产物 (18.7mg,0.100mmol) 和碳酸铯 (52.5,0.161mmol) 于二甲基甲酰胺 (1.0mL) 中在环境温度下制备。分离产量为 15.3mg；41.4 %。^{1}H NMR($CDCl_3$,300MHz)：δ 8.12(d,J = 1.9Hz,1H),7.69(s,1H),7.60(dd,J = 2.5,8.5Hz,1H),6.73(d,J = 8.7Hz,1H),5.15(s,2H),4.64(t,J = 5.8Hz,1H),4.48(t,J = 5.8Hz,1H),4.39(t,J = 6.2Hz,2H),2.19-2.02(m,2H),1.56(s,9H)；^{13}C NMR($CDCl_3$,150MHz)：δ 163.1,157.9,152.4,145.3,137.5,124.1,122.3,117.7,110.5,79.8(d,J_{CF}= 165Hz),68.5,65.4,61.0(d,J_{CF}= 7.5Hz),29.1(d,J_{CF}= 22.5Hz),26.8；HRMS：$C_{17}H_{21}{}^{35}ClFN_3O_5$(M+H) 的计算值：370.1328；实验值：370.1331。

[1969] 实例 40

[1970] 制备 2-(叔丁基)-5-((4-((2- 氟乙氧基) 苯甲基) 氧基)-4- 甲基哒嗪 -3(2H)- 酮

[1971]



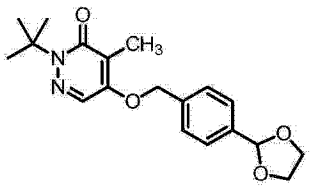
[1972] 根据通用方法 B，使用 2-(叔丁基)-5- 氯 -4- 甲基哒嗪 -3(2H)- 酮 [6](0.100g,0.500mmol)、(4-((2- 氟乙氧基) 甲基) 苯基) 甲醇 (0.110g,0.600mmol) 和碳酸铯 (0.261g,0.800mmol) 于二甲基甲酰胺 (5.0mL) 中在 65℃下制备。分离产量为 49mg；28.1 %。^{1}H NMR($CDCl_3$,300MHz)：δ 7.61(s,1H),7.30(br s,4H),5.10(s,2H),4.59(m,1H),4.53(s,2H),4.43(m,1H),3.71(m,1H),3.61(m,1H),1.98(s,3H),1.55(s,9H)；^{13}C NMR(75MHz,$CDCl_3$) δ 162.1,153.3,137.2,134.3,127.0,126.2,124.5,120.1,82.0(d,J_{CF}= 165Hz),71.9,69.8,68.4(d,J_{CF}= 22.5Hz),63.9,27.0,7.7；HRMS-TOF(m/z)：$[M+H]^+$HRMS：$C_{19}H_{25}FN_2O_3$的计算值：349.1922，实验值：349.1916。

[1973] 实例 41

[1974] 制备 4- 甲基苯磺酸 2-((4-(((1-(叔丁基)-5- 甲基 -6- 侧氧基 -1,6- 二氢哒嗪 -4- 基)- 氧基) 甲基) 苯甲基) 氧基) 乙酯

[1975] A 部分 - 制备 5-((4-(1,3- 二氧杂环戊烷 -2- 基) 苯甲基) 氧基)-2-(叔丁基)-4- 甲基哒嗪 -3(2H)- 酮

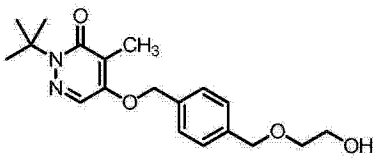
[1976]



[1977] 根据通用方法B，使用2-(叔丁基)-5-氯-4-甲基哒嗪-3(2H)-酮(0.200g,1.00mmol)、(4-(1,3-二氧杂环戊烷-2-基)苯基)甲醇(0.150g,0.830mmol)和碳酸铯(0.540g,1.66mmol)于二甲基甲酰胺(10.0mL)中在60℃下制备。分离产量为56.5mg;19.8%。^{1}H NMR($CDCl_3$,300MHz):δ7.67(s,1H),7.51(d,J = 8.3Hz,2H),7.39(d,J = 8.2Hz,2H),5.81(s,1H),5.20(s,2H),4.26-3.84(m,4H),2.05(s,3H),1.57(s,9H);^{13}C NMR($CDCl_3$,75MHz):δ163.1,154.3,138.2,136.8,127.0,126.9,125.5,121.1,103.3,70.6,65.3,64.9,28.0,8.7;HRMS-TOF(m/z):[M+H]$^{+}$HRMS:$C_{19}H_{24}N_2O_4$的计算值:345.1809,实验值:345.1806。

[1978] B部分-制备2-(叔丁基)-5-((4-((2-羟基乙氧基)甲基)苯甲基)氧基)-4-甲基哒嗪-3(2H)-酮

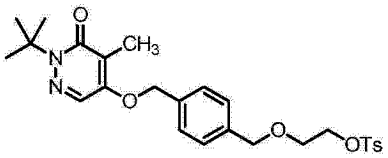
[1979]



[1980] 在环境温度下，逐滴添加实例41A的产物(55.7mg,0.162mmol)于四氢呋喃(0.8mL)中的溶液到氯化锆(37.8mg,0.162mmol)和硼氢化钠(12.3mg,0.324mmol)于四氢呋喃(0.80mL)中的悬浮液中。2小时后，用水(5mL)稀释所得混合物，分离水层，随后用乙酸乙酯(3×10mL)萃取。经硫酸钠干燥经合并的有机层，过滤且浓缩成透明油状物(50.6mg，产率90.2%)。^{1}H NMR($CDCl_3$,300MHz):δ7.62(s,1H),7.30(br s,4H),5.10(s,2H),4.50(s,2H),3.70(m,2H),3.54(dd,J = 3.9,5.3Hz,2H),1.98(s,3H),1.55(s,9H);^{13}C NMR($CDCl_3$,75MHz):δ162.1,153.4,137.4,134.3,127.1,126.8,126.2,119.3,71.8,70.5,69.8,63.9,60.8,27.0,7.7;HRMS-TOF(m/z):[M+H]$^{+}$HRMS:$C_{19}H_{26}N_2O_4$的计算值:347.1965,实验值:347.1960。

[1981] C部分-制备4-甲基苯磺酸2-((4-(((1-(叔丁基)-5-甲基-6-侧氧基-1,6-二氢哒嗪-4-基)-氧基)甲基)苯甲基)氧基)乙酯

[1982]



[1983] 根据通用程序D，使用实例41B的产物(46.8mg,0.135mmol)、对甲苯磺酰氯(30.9mg,0.162mmol)、4-二甲基氨基吡啶(5.4mg,0.54mmol)和二异丙基乙氨(0.026mL,0.189mmol)制备。分离产量为42.6mg;63.0%。^{1}H($CDCl_3$,300MHz):δ7.80(d,2H,J=8.33Hz),7.69(s,1H),7.33(m,6H),5.18(s,2H),4.50(s,2H),4.21(m,2H),3.69(m,2H),2.43(s,3H),2.05(s,3H),1.63(s,9H);^{13}C NMR(75MHz,$CDCl_3$)δ163.1,154.3,144.7,138.0,135.3,13

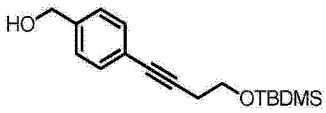
3.0,129.7,128.0,127.9,127.2,125.5,121.2,72.8,70.8,69.1,67.7,64.9,28.0,21.6,8.7。

[1984] 实例 43

[1985] 制备 2-(叔丁基)-4-氯-5-((4-(4-氟丁-1-炔-1-基)苯甲基)氧基)哒嗪-3(2H)-酮

[1986] A 部分-制备 (4-(4-((叔丁基二甲基硅烷基)氧基)丁-1-炔-1-基)苯基)甲醇

[1987]

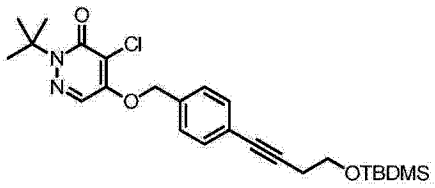


[1988] 在环境温度下,相继用叔丁基氯二甲基硅烷 (0.848g,5.63mmol) 和咪唑 (0.386g,5.67mmol) 处理 4-(4-羟基丁-1-炔-1-基)苯甲酸甲酯 (0.771g,3.77mmol)[1]于二甲基甲酰胺 (37.0mL) 中的溶液。2 小时后,用水 (150mL) 稀释所得混合物,分离水层,随后用乙酸乙酯 (3×200mL) 萃取。经硫酸钠干燥经合并的有机层,过滤且浓缩,得到黄色油状物 (1.50g)。

[1989] 将粗甲硅烷基醚溶解于四氢呋喃 (47.0mL) 中,随后冷却到 0℃且用氢化锂铝 (4.71mL,4.71mmol,1M 四氢呋喃溶液) 处理。随后将所得溶液缓慢温热到环境温度且 2 小时后,用水 (20mL) 稀释。分离水层,随后用乙酸乙酯 (3×50mL) 萃取且用饱和氯化钠水溶液洗涤经合并的有机层,经硫酸钠干燥,过滤且真空浓缩 (1.22g,粗产率 >98 %)。^{1}H(CDCl$_3$,300MHz):δ 7.29(d,J = 8.28Hz,2H),7.18(d,J = 8.47Hz,2H),4.58(s,2H),3.72(t,J = 7.05Hz,2H),2.53(t,J = 7.03Hz,2H),0.82(s,6H);0.01(s,9H);HRMS-TOF(m/z):[M+H]$^+$HRMS:C$_{17}$H$_{26}$O$_2$Si 的计算值:291.1775,实验值:291.1763。

[1990] B 部分-制备 2-(叔丁基)-5-((4-(4-((叔丁基二甲基硅烷基)氧基)丁-1-炔-1-基)苯甲基)氧基)-4-氯哒嗪酮-3(2H)-酮

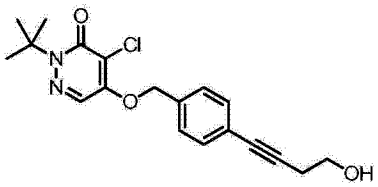
[1991]



[1992] 根据通用方法 B,使用 2-(叔丁基)-4,5-二氯哒嗪-3(2H)-酮 (0.318g,1.45mmol)、实例 43A 的产物 (0.500g,1.73mmol) 和碳酸铯 (0.750g,2.31mmol) 于二甲基甲酰胺 (14.5mL) 中在 60℃下制备。分离产量为 0.242g;35.1%。^{1}H NMR(CDCl$_3$,300MHz):δ 7.58(s,1H),7.33(d,J = 8.3Hz,2H),7.22(d,J = 8.4Hz,2H),5.19(s,2H),3.72(t,J = 7.0Hz,2H),2.53(t,J = 6.9Hz,2H),1.44(s,9H),0.82(s,9H),0.20(s,6H);^{13}C NMR(CDCl$_3$,75MHz,部分):δ 159.0,153.5,134.2,132.1,127.1,126.8,125.1,124.4,118.4,88.3,80.9,71.5,66.4,61.8,27.8,25.8,23.8,-5.2;HRMS-TOF(m/z):[M+H]$^+$HRMS:C$_{25}$H$_{35}$^{35}ClN$_2$O$_3$Si 的计算值:475.2178,实验值:475.2162。

[1993] C 部分 - 制备 2-(叔丁基)-4- 氯 -5-((4-(4- 羟基丁 -1- 炔 -1- 基) 苯甲基) 氧基) 哒嗪酮 -3(2H)- 酮

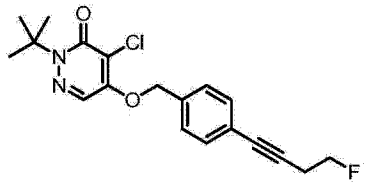
[1994]



[1995] 在环境温度下，用氟化四丁铵溶液 (1.02mL，1.02mmol，1M 四氢呋喃溶液) 处理溶解于四氢呋喃 (10.0mL) 中的实例 43B 的产物 (0.242g，0.510) 的溶液。2 小时后，真空浓缩所得混合物且通过硅胶色谱 (0-60 % 乙酸乙酯的己烷溶液) 直接纯化残余物，得到呈油状的所需产物 (0.120g，产率 65.2 %)。^{1}H NMR(CDCl$_3$，300MHz)：δ 7.68(s，1H)，7.45(d，J = 8.3Hz，2H)，7.34(d，J = 8.4Hz，2H)，5.29(s，2H)，3.82(m，4H)，1.63(s，9H)；^{13}C NMR(CDCl$_3$，75MHz)：δ 158.9，153.5，134.5，132.2，126.9，125.0，123.9，118.4，87.4，81.8，71.4，66.4，61.1，27.8，23.8；HRMS-TOF(m/z)：[M+H]$^+$HRMS：$C_{19}H_{21}{}^{35}ClN_2O_3$ 的计算值：361.1313，实验值：361.1309。

[1996] D 部分 - 制备 2-(叔丁基)-4- 氯 -5-((4-(4- 氟丁 -1- 炔 -1- 基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

[1997]

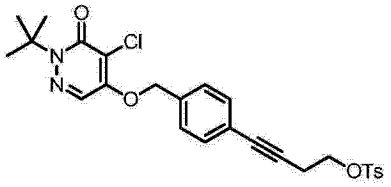


[1998] 用脱氧加氟物 (0.152mmol，33.7mg，50 % 甲苯溶液) 处理实例 43C 的产物 (0.050g，0.138mmol) 于二氯甲烷 (0.10mL) 中的经冷却 (0℃) 溶液，随后维持 1.5 小时。用水 (1mL) 稀释所得混合物，分离水层，随后用二氯甲烷 (3×2mL) 萃取。经硫酸钠干燥经合并的有机层，过滤且真空浓缩。随后通过制备型薄层色谱使用 3:2 己烷 / 乙酸乙酯经二氧化硅纯化粗物质，得到所需产物 (11.5mg，产率 23.0 %)。^{1}H NMR(CDCl$_3$，300MHz)：δ 7.61(s，1H)，7.38(d，J = 8.3Hz，2H)，7.27(d，J = 8.4Hz，2H)，5.22(s，2H)，4.59(t，J = 6.6Hz，1H)，4.44(t，J = 6.6Hz，1H)，2.78(dt，J = 19.6，6.6Hz，2H)，1.56(s，9H)；^{13}C NMR(CDCl$_3$，75MHz)：δ 157.9，152.5，133.6，131.2，125.8，124.0，122.8，117.4，84.4(d，J_{CF}= 15Hz)，80.3(d，J_{CF}= 165Hz)，80.6，70.4，65.4，26.8，20.6(d，J_{CF}= 22.5Hz)；HRMS-TOF(m/z)：[M+H]$^+$HRMS：$C_{19}H_{20}{}^{35}ClFN_2O_2$ 的计算值：363.1270，实验值：363.1270。

[1999] 实例 44

[2000] 制备 4- 甲基苯磺酸 4-(4-(((1-(叔丁基)-5- 氯 -6- 侧氧基 -1，6- 二氢哒嗪 -4- 基)- 氧基) 甲基) 苯甲基) 丁 -3- 炔 -1- 酯

[2001]

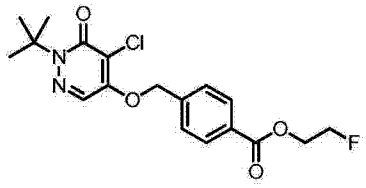


[2002] 根据通用方法D，使用实例43C的产物(77.4mg，0.215mmol)、对甲苯磺酰氯(49.2mg，0.258mmol)、4-二甲基氨基吡啶(1.1mg，0.0086mmol)和三乙氨(0.042mL，0.30mmol)制备。分离产量为42.2mg；38.1％。^{1}H($CDCl_3$，300MHz)：δ7.75(d，J＝8.3Hz，2H)，7.61(s，1H)，7.36-7.21(m，6H)，5.22(s，2H)，4.12(t，J＝6.9Hz，2H)，2.72(t，J＝6.9Hz，2H)，2.35(s，3H)，1.56(s，9H)；^{13}C($CDCl_3$，75MHz)：δ158.9，153.5，144.9，134.7，132.9，132.1，129.8，127.9，126.8，125.0，123.5，118.4，84.8，82.0，71.4，67.6，66.4，27.8，21.6，20.4；HRMS-TOF(m/z)：$[M+H]^+$HRMS：$C_{26}H_{27}{}^{35}ClN_2O_6S$的计算值：515.1402，实验值：515.1409。

[2003] 实例45

[2004] 制备4-(((1-(叔丁基)-5-氯-6-侧氧基-1，6-二氢哒嗪-4-基)氧基)甲基)苯甲酸2-氟乙酯

[2005]



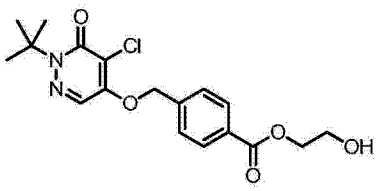
[2006] 将2-氟乙醇(2mL)和叔丁醇钾(0.0300g，0.267mmol)的悬浮液加热到60℃，维持20分钟，随后用4-(((1-(叔丁基)-5-氯-6-侧氧基-1，6-二氢哒嗪-4-基)氧基)甲基)苯甲酸甲酯(93.5mg，0.267mmol)[4]于四氢呋喃(0.70mL)中的溶液处理。搅拌所得混合物隔夜，随后冷却到环境温度且用水(5ml)稀释。分离水层，用乙酸乙酯(3×20mL)萃取且用饱和氯化钠水溶液洗涤经合并的有机层，经硫酸钠干燥，过滤且真空浓缩。随后通过硅胶色谱(0-80％乙醚的己烷溶液)纯化粗物质，得到呈白色固体状的所需产物(11.7mg，产率11.4％)。^{1}H($CDCl_3$，300MHz)：δ8.17-8.08(m，2H)，7.70(s，1H)，7.51(d，J＝8.0Hz，2H)，5.38(s，2H)，4.81(m，1H)，4.61-4.67(m，2H)，4.53(m，1H)，1.63(s，9H)；^{13}C NMR($CDCl_3$，75MHz)：δ164.7，157.9，152.3，139.1，129.4，129.0，125.7，123.8，117.5，80.2(d，J_{CF}＝165Hz)，70.1，65.4(d，J_{CF}＝22.5Hz)，62.8，20.0。

[2007] 实例46

[2008] 制备4-(((1-(叔丁基)-5-氯-6-侧氧基-1，6-二氢哒嗪-4-基)氧基)甲基)苯甲酸2-(甲苯磺酰氧基)乙酯

[2009] A部分-制备4-(((1-(叔丁基)-5-氯-6-侧氧基-1，6-二氢哒嗪-4-基)氧基)甲基)苯甲酸2-羟乙酯

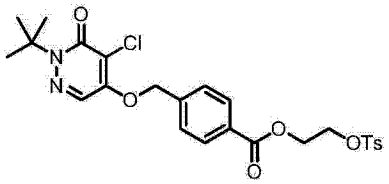
[2010]



[2011] 将乙二醇 (15mL) 和叔丁醇钾 (0.224g,2.00mmol) 的悬浮液加热到 60℃,维持 20 分钟,随后用 4-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯甲酸甲酯 (0.773g,2.20mmol) 于四氢呋喃 (5.0mL) 中的溶液处理。1.5 小时后,将所得混合物冷却到环境温度且用水 (50ml) 稀释。分离水层,随后用甲苯 (3×100mL) 萃取,且用饱和氯化钠水溶液洗涤经合并的有机层,经硫酸钠干燥,过滤且浓缩。随后通过硅胶色谱 (40-60%乙酸乙酯的己烷溶液) 纯化粗物质,得到呈白色固体状的所需产物 (47.7mg,产率 5.3 %)。^{1}H($CDCl_3$,300MHz):δ 8.11(d,J = 8.4Hz,2H),7.71(s,1H),7.49(d,J = 8.5Hz,2H),5.37(s,2H),4.59-4.34(m,2H),4.04-3.86(m,2H),1.63(s,9H);HRMS-TOF(m/z):[M+H]$^{+}$HRMS:$C_{18}H_{21}{}^{35}ClN_2O_5$的计算值:381.1212,实验值:384.1206。

[2012] B 部分-制备 4-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯甲酸 2-(甲苯磺酰氧基)乙酯

[2013]



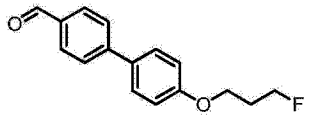
[2014] 根据通用方法 D,使用实例 46A 的产物 (47.1mg,0.124mmol)、对甲苯磺酰氯 (28.3mg,0.148mmol)、4-二甲基氨基吡啶 (0.60mg,0.0049mmol) 和三乙氨 (0.024mL,1.4mmol) 制备。分离产量为 33.6mg;50.6 %。^{1}H($CDCl_3$,300MHz):δ 8.07-7.96(m,2H),7.78(s,1H),7.71(m,2H),7.49(d,J = 8.3Hz,2H),7.29(d,J = 8.0Hz,2H),5.37(s,2H),4.54-4.46(m,2H),4.41-4.32(m,2H),2.40(s,3H),1.64(s,9H);^{13}C NMR($CDCl_3$,75MHz):δ 165.4,158.9,153.4,145.0,140.2,132.8,130.4,129.9,129.7,127.9,127.5,126.7,118.5,71.0,67.5,66.6,62.2,27.8,21.6;HRMS-TOF(m/z):[M+H]$^{+}$HRMS:$C_{25}H_{27}{}^{35}ClN_2O_7S$ 的计算值:535.1300,实验值:535.1290。

[2015] 实例 47

[2016] 制备 2-(叔丁基)-4-氯-5-((4'-(3-氟丙氧基)-[1,1'-联二苯]-4-基)甲氧基)哒嗪-3(2H)-酮

[2017] A 部分-制备 4'-(3-氟丙氧基)-[1,1'-联二苯]-4-甲醛

[2018]

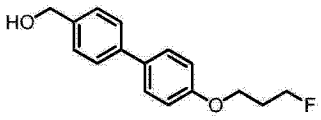


[2019] 根据通用方法 F,使用 4'-羟基-[1,1'-联苯]-4-甲醛 (0.500g,2.52mmol)、对甲苯磺酸 3-氟丙酯 (0.557g,2.40mmol) 和碳酸铯 (1.25g,3.84mmol) 于二甲基甲酰胺 (25.2mL) 中在环境温度下制备。通过硅胶色谱 (0-60%乙酸乙酯的己烷溶液) 进一步纯

化粗物质，得到呈白色固体状的所需产物 (0.380g，产率 61.3％)。^{1}H NMR($CDCl_3$，300MHz)：δ 10.03(s，1H)，7.97-7.87(m，2H)，7.75-7.68(m，2H)，7.63-7.53(m，2H)，7.06-6.96(m，2H)，4.75(t，J = 5.7Hz，1H)，4.59(t，J = 5.7Hz，1H)，4.16(t，J = 6.1Hz，2H)，2.21(m，2H)；^{13}C NMR($CDCl_3$，75MHz，$CDCl_3$) δ 191.8，159.3，146.7，134.7，132.2，130.2，128.5，127.0，115.0，80.6(d，J_{CF}= 165Hz)，63.7(d，J_{CF}= 7.5Hz)，30.4(d，J_{CF}= 22.5Hz)；HRMS-TOF(m/z)：[M+H]$^{+}$HRMS：$C_{16}H_{15}FO_2$的计算值：259.1129，实验值：259.1131。

[2020] B 部分－制备 4'-(3-氟丙氧基)-[1，1'-联二苯]-4-基）甲醇

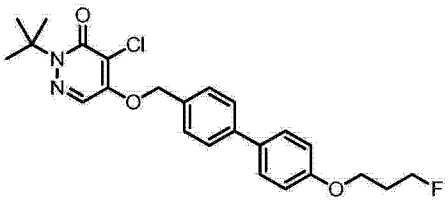
[2021]



[2022] 用氢化锂铝溶液 (0.40mL，0.40mmol，1M 四氢呋喃溶液）处理溶解于四氢呋喃 (7.3mL) 中的实例 47A 的产物 (0.190g，0.730mmol) 的经冷却 (0℃）溶液，随后温热到环境温度。2 小时后，用水 (10mL) 稀释所得混合物，分离水层，随后用乙酸乙酯 (3×50mL) 萃取。经硫酸钠干燥经合并的有机层且浓缩成白色固体 (0.170g，产率 89.5％)。^{1}H NMR($CDCl_3$，300MHz)：δ 7.60-7.47(m，4H)，7.42(d，J = 8.4Hz，2H)，7.03-6.88(m，2H)，4.83-4.63(m，3H)，4.59(t，J = 5.7Hz，1H)，4.15(t，J = 6.1Hz，2H)，2.20(m，2H)；^{13}C NMR(75MHz，$CDCl_3$) δ 158.3，140.2，139.2，133.5，128.1，127.4，126.8，114.8，80.7(d，J_{CF}= 165Hz)，65.1，63.7(d，J_{CF} = 7.5Hz)，30.4(d，J_{CF}= 22.5Hz)；HRMS-TOF(m/z)：[M+Na]$^{+}$HRMS：$C_{16}H_{17}FO_2$的计算值：261.1285，实验值：261.1282。

[2023] C 部分－制备 2-(叔丁基)-4-氯-5-((4'-(3-氟丙氧基)-[1，1'-联二苯]-4-基）甲氧基）哒嗪-3(2H)-酮

[2024]



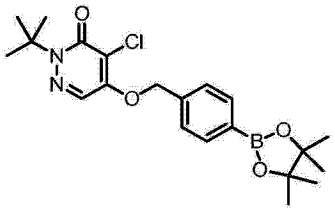
[2025] 根据通用程序 B，使用 2-(叔丁基)-4，5-二氯哒嗪-3(2H)-酮 (0.120g，0.540mmol)、实例 47B 的产物 (0.170g，0.650mmol) 和碳酸铯 (0.265g，0.816mmol) 于二甲基甲酰胺 (6.5mL) 中在 65℃下制备。分离产量为 12.7mg；5.3％。^{1}H NMR($CDCl_3$，300MHz)：δ 7.53(s，1H)，7.49-7.38(m，6H)，6.94-6.85(m，2H)，5.53(s，2H)，4.67(t，J = 5.7Hz，1H)，4.51(t，J = 5.7Hz，1H)，4.07(t，J = 6.1Hz，2H)，2.12(m，2H)，1.57(s，9H)；^{13}C NMR($CDCl_3$，75MHz)：δ 160.7，158.4，150.5，140.8，134.9，133.3，129.0，128.1，126.6，124.5，114.8，80.7(d，J_{CF}= 165Hz)，73.4，65.7，63.6(d，J_{CF}= 22.5Hz)，30.5(d，J_{CF}= 7.5Hz)，27.8；HRMS-TOF(m/z)：[M+Na]$^{+}$HRMS：$C_{24}H_{26}{}^{35}ClFN_2O_3$的计算值：445.1689，实验值：445.1684。

[2026] 实例 48

[2027] 制备 2-(叔丁基)-4-氯-5-((4-(2-氟嘧啶-5-基)-苯甲基）氧基）哒嗪-3(2H)酮

[2028] A 部分 - 制备 2-(叔丁基)-4- 氯 -5-((4-(4,4,5,5- 四甲基 -1,3,2- 二氧杂硼戊环 -2- 基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

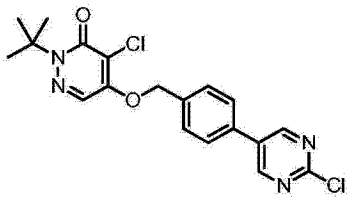
[2029]



[2030] 在环境温度下，相继用 (4-(4,4,5,5- 四甲基 -1,3,2- 二氧杂硼戊环 -2- 基) 苯基) 甲醇 (0.745g,3.18mmol)、三苯基膦 (1.04g,3.97mmol) 和偶氮二甲酸二异丙酯 (0.782mL,3.97mmol) 处理 2-(叔丁基)-4- 氯 -5- 羟基哒嗪 -3(2H)- 酮 (0.537g,2.65mmol) 于四氢呋喃 (22.1mL) 中的溶液。45 分钟后，用水 (20mL) 稀释所得混合物，分离水层，随后用乙酸乙酯 (3×50mL) 萃取。经硫酸钠干燥经合并的有机层，过滤且真空浓缩。使粗物质悬浮于乙醚中，搅拌 3 小时，随后通过过滤收集且通过硅胶色谱使用 4:1 己烷 / 乙酸乙酯纯化，得到呈白色固体状的所需产物 (0.347g，产率 31.3％)。^{1}H NMR(300MHz,DMSO-d6):δ8.22(s,1H),7.73(d,J＝8.0Hz,2H),7.47(d,J＝8.0Hz,2H),5.49(s,2H),1.57(s,9H),1.30(s,12H) ;^{13}C NMR(75MHz,DMSO-d6, 部分):δ157.7,153.5,138.6,134.7,126.9,125.1,115.6,83.7,71.1,65.3,27.4,24.6 ;HRMS-TOF(m/z):[M+Na]$^{+}$HRMS:$C_{21}H_{28}B^{35}ClN_2O_4$的计算值 :419.1907，实验值 :419.1903。

[2031] B 部分 - 制备 2-(叔丁基)-4- 氯 -5-((4-(2- 氯嘧啶 -5- 基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

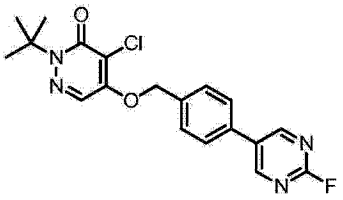
[2032]



[2033] 在环境温度下，将 2- 氯 -5- 溴嘧啶 (41.3mg,0.215mmol) 和四 (三苯基膦) 钯 (0)(7.0mg,2.5mol％) 溶解于 1,2- 二甲氧乙烷 (1.0mL) 中，维持 15 分钟，随后相继用实例 48A 的产物 (0.090g,0.215mmol) 于 1,2- 二甲氧乙烷 (1.2mL) 中的溶液和碳酸钾水溶液 (0.43mL,0.43mmol) 处理。将所得混合物温热到 80℃，维持 1.5 小时，随后冷却到环境温度且用水 (2mL) 稀释。分离水层，随后用乙酸乙酯 (3×10mL) 萃取，且经硫酸钠干燥经合并的有机层，过滤且浓缩成淡黄色固体 (59.0mg，产率 67.7％)。^{1}H NMR(DMSO-d_6,300MHz):δ9.26(s,2H),8.40(s,1H),8.01(d,J＝8.3Hz,2H),7.75(d,J ＝ 8.3Hz,2H),5.65(s,2H),1.69(s,9H) ;^{13}C NMR(75MHz,DMSO-d_6):δ159.0,158.0,157.7,153.7,136.5,132.6,131.7,128.5,127.3,126.1,115.7,70.9,65.4,27.5。

[2034] C 部分 - 制备 2-(叔丁基)-4- 氯 -5-((4-(2- 氟嘧啶 -5- 基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

[2035]



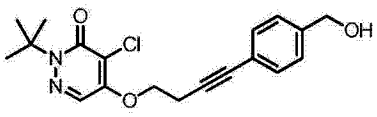
[2036] 用氟化钾 (1.43mg,0.024mmol) 和 Kryptofix™(18mg,0.48mmol) 处理实例 48B 的产物 (97.0mg,0.024mmol) 于二甲亚砜 (0.25mL) 中的溶液,随后加热到 80℃且维持 10 分钟。将所得混合物冷却到环境温度,随后用 1mL 二氯甲烷稀释且通过制备型薄层色谱使用 4:1 己烷 / 乙酸乙酯经二氧化硅直接纯化,得到呈白色固体状的所需产物 (1.3mg,产率 13.9 %)。^{1}H NMR(DMSO-d_6,600MHz):δ 9.22(d,J = 1.6Hz,2H),8.35(s,1H),7.96-7.90(m,2H),7.69(d,J = 8.3Hz,2H),5.81(s,2H),1.64(s,9H);^{13}C NMR(DMSO-d_6,150MHz,部分):δ 159.3(d,J_{CF}= 15Hz),136.2,129.5,128.5,127.2,126.1,71.0,65.4,27.4;^{19}F NMR(DMSO-d_6,262MHz):δ -49.19(br s,1H)。

[2037] 实例 49

[2038] 制备 2-(叔丁基)-4-氯-5-((4-(4-(氟甲基)苯基)丁-3-炔-1-基)氧基)哒嗪-3(2H)-酮

[2039] A 部分 - 制备 2-(叔丁基)-4-氯-5-((4-(4-羟甲基)苯基)丁-3-炔-1-基)氧基)哒嗪-3(2H)-酮

[2040]

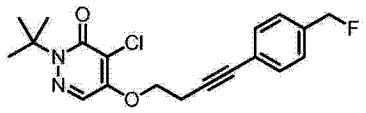


[2041] 将 2-(叔丁基)-4-氯-5-羟基哒嗪-3(2H)-酮 (62.0mg,0.368mmol)、三苯基膦 (0.145g,0.552mmol) 和 4-(4-羟基丁-1-炔-1-基)苯甲酸甲酯 (74.4mg,0.442mmol)[1]并入无水四氢呋喃 (3.7mL) 中,随后冷却到 0℃且用偶氮二甲酸二乙酯 (0.109mL,0.552mmol) 处理。将所得混合物缓慢温热到环境温度,且 1.5 小时后用水 (10mL) 稀释。分离水层,随后用乙酸乙酯 (3×20mL) 萃取,且经硫酸钠干燥经合并的有机层,过滤且真空浓缩。通过硅胶色谱 (0-80%乙酸乙酯的己烷溶液) 纯化粗物质,得到所需产物 (40mg)。

[2042] 用氢化锂铝溶液 (0.05mL,0.05mmol,1M 四氢呋喃溶液) 处理酯 (40.0mg,0.103mmol) 于四氢呋喃 (1.0mL) 中的经冷却 (0℃) 溶液,随后温热到环境温度。2 小时后,用水 (2mL) 稀释所得混合物,分离水层,随后用乙酸乙酯 (3×5mL) 萃取。经硫酸钠干燥经合并的有机层,过滤且真空浓缩。随后通过硅胶色谱 (0-20 % 乙酸乙酯的己烷溶液) 纯化粗物质,得到所需产物 (31.5mg,产率 23.7 %)。^{1}H NMR($CDCl_3$,300MHz):δ 7.72(s,1H),7.33-7.28(m,2H),7.24-7.18(m,2H),4.61(s,2H),4.35(t,J = 6.8Hz,2H),2.89(t,J = 6.88Hz,2H);1.57(s,9H);^{13}C NMR($CDCl_3$,75MHz):δ 159.0,153.6,141.0,131.7,126.7,125.1,122.0,118.3,84.2,82.8,68.4,66.4,64.8,27.8,20.8;HRMS-TOF(m/z):$[M+H]^+$HRMS:$C_{19}H_{21}{}^{35}ClN_2O_3$的计算值:361.1313,实验值:361.1315。

[2043] B 部分 - 制备 2-(叔丁基)-4-氯-5-((4-(4-(氟甲基)苯基)丁-3-炔-1-基)氧基)哒嗪-3(2H)-酮

[2044]



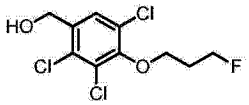
[2045] 用脱氧加氟物 (21.3mg,0.096mmol,50 % 甲苯溶液) 处理实例 49A 的产物 (31.8mg,0.088mmol) 于二氯甲烷 (1.0mL) 中的经冷却 (0℃) 溶液,且维持 1.5 小时。用水 (1mL) 稀释所得混合物,分离水层,随后用二氯甲烷 (3×2mL) 萃取。经硫酸钠干燥经合并的有机层,过滤且真空浓缩。随后通过制备型薄层色谱使用 4:1 己烷 / 乙酸乙酯经二氧化硅纯化粗物质,得到所需产物 (11.5mg,产率 36.0 %)。^{1}H NMR($CDCl_3$,300MHz):δ 7.71(s,1H),7.37-7.29(m,2H),7.26-7.19(m,2H),5.37(s,1H),5.21(s,1H),4.35(t,J = 6.8Hz,2H),2.90(t,J = 6.8Hz,2H),1.57(s,9H) ;^{13}C NMR($CDCl_3$,75MHz):δ 159.0,153.6,136.2(d,J_{CF} = 22.5Hz),131.8,127.2(d,J_{CF} = 7.5Hz),125.1,123.3,118.3,84.0(d,J_{CF} = 165Hz),84.8,82.5,68.3,66.4,27.8,20.8 ;HRMS-TOF(m/z):[M+H]$^{+}$HRMS:$C_{19}H_{20}{}^{35}ClFN_2O_3$的计算值 :363.1270,实验值 :363.1268。

[2046] 实例 50

[2047] 制备 2-(叔丁基)-4- 氯 -5-((2,3,5- 二氯 -4-(3- 氟丙氧基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

[2048] A 部分 - 制备 (2,3,5- 二氯 -4-(3- 氟丙氧基) 苯基) 甲醇

[2049]

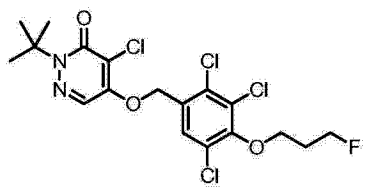


[2050] 根据通用方法 F,使用 2,3,5- 二氯 -4- 羟甲基苯甲酸酯 (1.00g,4.52mmol)、对甲苯磺酸 3- 氟丙酯 (1.26g,5.42mmol) 和碳酸铯 (2.35g,7.23mmol) 于二甲基甲酰胺 (45.0mL) 中在 65℃下制备。分离产量为 0.650g ;50.4%。

[2051] 在环境温度下,用硼氢化钠 (5.7mg,0.15mmol) 一次性处理溶解于乙醇 (2.0mL) 中的粗酯 (63.0mg,0.200mmol) 溶液。搅拌所得混合物 2 天,随后用水 (20mL) 稀释且真空浓缩以移除乙醇。用乙酸乙酯 (3×100mL) 萃取所得水溶液且经硫酸钠干燥经合并的有机层,过滤且真空浓缩。随后通过硅胶色谱使用 4:1 己烷 / 乙酸乙酯纯化粗物质,得到所需产物 (52.7mg,产率 91.6 %)。^{1}H NMR($CDCl_3$,300MHz):δ 7.42(s,1H),4.75(t,J = 5.8Hz,1H),4.66(s,2H),4.59(t,J = 5.8Hz,1H),4.07(t,J = 6.0Hz,2H),2.16(m,2H) ;^{13}C NMR($CDCl_3$,150MHz):δ 151.3,136.3,129.8,129.0,127.7,127.0,80.6(d,J_{CF} = 165Hz),69.3(d,J_{CF} = 7.5Hz),62.3,31.1(d,J_{CF} = 22.5Hz)。

[2052] B 部分 - 制备 2-(叔丁基)-4- 氯 -5-((2,3,5- 二氯 -4-(3- 氟丙氧基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

[2053]



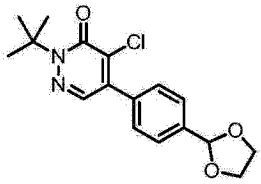
[2054] 根据通用方法B，使用2-(叔丁基)-4,5-二氯哒嗪-3(2H)-酮(39.2mg，0.178mmol)、实例50A的产物(61.2mg,0.213mmol)和碳酸铯(92.5mg,0.284mmol)于二甲基甲酰胺(1.7mL)中在65℃下制备。分离产量为23.0mg;27.4%。^{1}H NMR($CDCl_3$,300MHz):δ7.89-7.68(br s,1H),7.67-7.41(br s,1H),5.32(s,2H),4.93-4.74(m,1H),4.75-4.54(m,1H),4.19(m,2H),2.41-2.11(m,2H),1.56(s,9H);^{13}C NMR($CDCl_3$,75MHz)δ158.8,153.1,152.5,130.7,130.0,129.6,128.2,127.4,124.7,118.7,80.4(d,J_{CF}= 165Hz),69.4(d,J_{CF}= 7.5Hz),68.6,66.6,31.1(d,J_{CF}= 22.5Hz),27.8;HRMS:$C_{18}H_{19}{}^{35}Cl_4FN_2O_3$的计算值:471.0207,实验值:471.0206。

[2055] 实例51

[2056] 制备2-(叔丁基)-4-氯-5-(4-((2-氟乙氧基)甲基)苯基)哒嗪-3(2H)-酮

[2057] A部分-制备5-((4-(1,3-二氧杂环戊烷-2-基)苯基)-2-(叔丁基)-4-氯哒嗪-3(2H)-酮

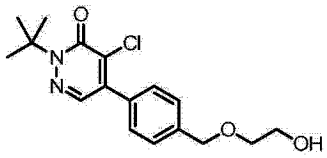
[2058]



[2059] 用溴化(4-(1,3-二氧杂环戊烷)-2-基)苯基)镁溶液(27.3mL,13.6mmol，0.5M四氢呋喃溶液)处理2-(叔丁基)-4,5-二氯哒嗪-3(2H)-酮(3.00g,13.6mmol)于乙醚(6.5mL)中的经冷却(0℃)溶液，且维持30分钟。用水(20mL)稀释所得混合物，分离水层，随后用乙酸乙酯(3×50mL)萃取。经硫酸钠干燥经合并的有机层，过滤且真空浓缩。随后通过硅胶纯化(0-30%乙酸乙酯的己烷溶液)来纯化粗物质，得到呈白色固体状的所需产物(2.87g，产率63.0%)。^{1}H NMR($CDCl_3$,300MHz)δ7.81(s,1H),7.59(d,J=8.1Hz,2H),7.48(d,J=8.4Hz,2H),5.91(s,1H),4.25-3.94(m,4H),1.68(s,9H)。

[2060] B部分-制备2-(叔丁基)-4-氯-5-((4-(2-羟基乙氧基)甲基)苯基)哒嗪-3(2H)-酮

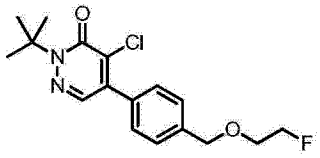
[2061]



[2062] 在环境温度下，逐滴添加实例51A的产物(0.342g,1.02mmol)于四氢呋喃(2.0mL)中的溶液到氯化锆(0.238g,1.02mmol)和硼氢化钠(77.3mg,2.04mmol)于四氢呋喃(3.1mL)中的悬浮液中。3小时后，用水(10mL)稀释所得混合物，分离水层，随后用乙酸乙酯(3×20mL)萃取。经硫酸钠干燥经合并的有机层，过滤且浓缩成透明油状物(0.322g，产率93.7%)。^{1}H NMR($CDCl_3$,300MHz):δ7.72(s,1H),7.36(br s,4H),4.54(s,2H),3.70(m,2H),3.56(m,2H),1.59(s,9H);^{13}C NMR($CDCl_3$,75MHz):159.6,153.2,139.0,135.1,134.9,131.0,129.8,127.2,72.9,71.4,66.0,61.9,27.8;HRMS-TOF(m/z):$[M+H]^+$HRMS:$C_{17}H_{21}{}^{35}ClFN_2O_3$的计算值:337.1313,实验值:337.1311。

[2063] C 部分 - 制备 2-(叔丁基)-4- 氯 -5-(4-((2- 氟乙氧基) 甲基) 苯基) 哒嗪 -3(2H)- 酮

[2064]



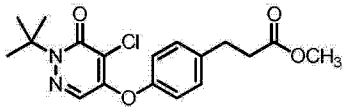
[2065] 用脱氧加氟物 (72.3mg,0.326mmol ;50 % 甲苯溶液) 处理实例 51B 的产物 (0.100g,0.297mmol) 于二氯甲烷 (3.0mL) 中的经冷却 (0℃) 溶液,且维持 2 小时。用水 (10mL) 稀释所得混合物,分离水层,随后用二氯甲烷 (3×10mL) 萃取。经硫酸钠干燥经合并的有机层,过滤且真空浓缩。随后通过制备型薄层色谱使用 4:1 己烷 / 乙酸乙酯经二氧化硅纯化粗物质,得到呈白色固体状的所需产物 (19.7mg,产率 19.6%)。^{1}H NMR($CDCl_3$,300MHz) : δ 7.72(s,1H),7.36(s,4H),4.60(m,1H),4.57(s,2H),4.46-4.39(m,1H),3.75-3.68(m,1 H),3.65-3.58(m,1H),1.58(s,9H) ;^{13}C NMR($CDCl_3$,75MHz) : δ 159.6,153.1,138.8,135.1,1 34.9,131.0,129.8,127.2,83.0(d,J_{CF}= 165Hz),72.9,69.2(d,J_{CF}= 22.5Hz),66.0,27.8 ; HRMS-TOF(m/z) : $[M+H]^+$HRMS:$C_{17}H_{20}{}^{35}ClFN_2O_2$的计算值 :339.1270,实验值 :339.1268。

[2066] 实例 52

[2067] 制备 2-(叔丁基)-4- 氯 -5-(4-(3- 氟丙基) 苯氧基) 哒嗪 -3(2H)- 酮

[2068] A 部分 - 制备 3-(4-((1-(叔丁基)-5- 氯 -6- 侧氧基 -1,6- 二氢哒嗪 -4- 基) 氧基) 苯基) 丙酸甲酯

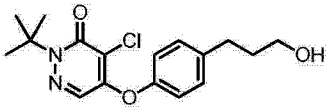
[2069]



[2070] 根据通用方法 B,使用 2-(叔丁基)-4,5- 二氯哒嗪 -3(2H)- 酮 (0.750g, 3.39mmol)、3-(4- 羟苯基) 丙酸甲酯 (0.734g,4.07mmol) 和碳酸铯 (1.76g,5.43mmol) 于二甲基甲酰胺 (34.0mL) 中在室温下制备隔夜。分离产量为 0.960g ;77.6%。^{1}H NMR(CDC l_3,300MHz) : δ 7.40(s,1H),7.25(d,J = 7.8Hz,2H),7.05-6.99(m,2H),3.68(s,3H),2.97(m,2H),2.64(m,2H),1.64(s,9H) ;^{13}C NMR($CDCl_3$,75MHz) δ 172.9,158.9,152.9,152.2,138. 2,130.1,127.0,120.2,119.8,66.4,51.6,35.5,30.1,27.8 ;HRMS :$C_{18}H_{21}{}^{35}ClN_2O_4$的计算值 : 365.1263,实验值 :365.1259。

[2071] B 部分 - 制备 2-(叔丁基)-4- 氯 -5-(4-(3- 羟丙基) 苯氧基) 哒嗪 -3(2H)- 酮

[2072]

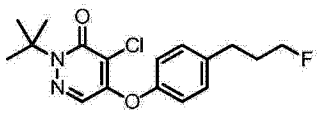


[2073] 用氢化锂铝 (0.65mL,0.65mmol,1M 四氢呋喃溶液) 处理实例 52A 的产物 (0.473g, 1.30mmol) 于四氢呋喃 (13mL) 中的经冷却 (0℃) 溶液,随后温热到环境温度。1 小时后,用水 (10mL) 稀释所得混合物,分离水层,随后用乙酸乙酯 (3×50mL) 萃取。用饱和氯化钠水溶液洗涤经合并的有机层,经硫酸钠干燥,过滤且浓缩成淡黄色固体 (0.384g,87.7%)。

^{1}H($CDCl_3$, 600MHz) : δ 7.40(s, 1H), 7.25(d, J = 7.7Hz, 2H), 7.05-6.98(m, 2H), 3.75-3.65(m, 2H), 2.79-2.68(m, 2H), 1.97-1.82(m, 2H), 1.65(s, 9H) ; ^{13}C NMR($CDCl_3$, 150MHz) δ 158.9, 153.0, 151.9, 139.6, 130.1, 127.0, 120.0, 119.7, 66.4, 61.9, 34.1, 31.3, 27.8 ; HRMS-TOF(m/z) : $[M+H]^+$ HRMS : $C_{17}H_{21}{}^{35}ClN_2O_3$ 的计算值 : 337.1313, 实验值 : 337.1319。

[2074] C 部分 - 制备 2-(叔丁基)-4- 氯 -5-(4-(3- 氟丙基) 苯氧基) 哒嗪 -3(2H)- 酮

[2075]



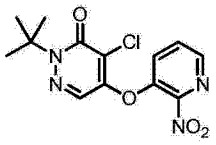
[2076] 用脱氧加氟物 (36.0mg, 0.164mmol ; 50 % 甲苯溶液) 处理实例 52B 的产物 (50.0mg, 0.149mmol) 于二氯甲烷 (0.1mL) 中的经冷却 (0℃) 溶液, 且维持 1.5 小时。用水 (1mL) 稀释所得混合物, 分离水层, 随后用二氯甲烷 (2×10mL) 萃取。经硫酸钠干燥经合并的有机部分, 过滤且真空浓缩。随后通过硅胶色谱 (0-50 % 乙酸乙酯的己烷溶液) 纯化粗物质, 得到呈黄色油状的所需产物 (5.6mg, 产率 11.1 %)。^{1}H NMR($CDCl_3$, 600MHz, 含有少量醇类起始物质) : δ 7.34(s, 1H), 7.18(d, J = 8.0Hz, 2H), 6.96(m, 2H), 4.48(t, J = 5.8Hz, 1H), 4.32(t, J = 5.8Hz, 1H), 3.47(t, J = 6.3Hz, 2H), 2.02(m, 2H), 1.58(s, 9H) ; ^{13}C NMR($CDCl_3$, 150MHz, 含有少量醇类起始物质) : δ 157.9, 151.9, 151.1, 137.8, 129.3(129.2), 126.0, 118.8, 81.8(d, J_{CF} = 165Hz), 65.4, 42.9, 31.1(d, J_{CF} = 22.5Hz), 29.7(d, J_{CF} = 7.5Hz), 26.84 ; HRMS-TOF(m/z) : $[M+H]^+$ HRMS : $C_{17}H_{20}{}^{35}ClFN_2O_2$ 的计算值 : 339.1270, 实验值 : 339.1268。

[2077] 实例 53

[2078] 制备 2-(叔丁基)-4- 氯 -5-((2- 氟吡啶 -3- 基) 氧基) 哒嗪 -3(2H)- 酮

[2079] A 部分 - 制备 2-(叔丁基)-4- 氯 -5-((2- 硝基吡啶 -3- 基) 氧基) 哒嗪 -3(2H)- 酮

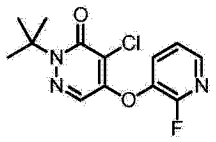
[2080]



[2081] 根据通用方法 B, 使用 2-(叔丁基)-4,5- 二氯哒嗪 -3(2H)- 酮 (0.221g, 1.00mmol)、2- 硝基吡啶 -3- 醇 (0.140g, 1.00mmol) 和碳酸铯 (0.170g, 0.52mmol) 于二甲基甲酰胺 (2.0mL) 中在 80 ℃下制备。分离产量为 0.120g ; 37.0 %。^{1}H NMR(300MHz, DMSO-d_6) : δ 8.52(dd, J = 4.5, 1.3Hz, 1H), 8.22(dd, J = 8.4, 1.3Hz, 1H), 8.00(s, 1H), 7.92(dd, J = 8.4, 4.5Hz, 1H), 1.60(s, 9H) ; ^{13}C NMR(75MHz, DMSO-d_6) : δ 157.62, 151.15, 144.95, 142.38, 138.09, 132.05, 130.95, 128.14, 121.01, 65.99, 27.33。HRMS : $C_{13}H_{13}{}^{35}ClN_4O_4$(M+H) 的计算值 : 325.0698 ; 实验值 : 325.0697。

[2082] B 部分 - 制备 2-(叔丁基)-4- 氯 -5-((2- 氟吡啶 -3- 基) 氧基) 哒嗪 -3(2H)- 酮

[2083]

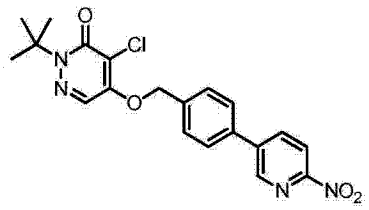


[2084] 将实例53A的产物(35.7mg,0.110mmol)、氟化钾(9.0mg,0.15mmol)和Kryptofix™(60.2mg,0.16mmol)于二甲亚砜(2.5mL)中的溶液加热到125℃且维持30分钟。随后冷却所得混合物至环境温度且用乙酸乙酯(40ml)稀释。分离有机层,随后用水(2×50mL)和饱和氯化钠水溶液洗涤,经硫酸镁干燥,过滤且真空浓缩。随后通过硅胶色谱(10-40%乙酸乙酯的己烷溶液)纯化粗物质,得到呈无色油状的所需产物(25.0mg,产率76.3%)。^{1}H NMR(300MHz,DMSO-d_6):δ8.14(dt,J = 4.8,1.6Hz,1H),8.00(ddd,J = 10.2,7.9,1.6Hz,1H),7.93(s,1H),7.45(ddd,J = 7.9,4.8,0.9Hz,1H),1.60(s,9H);^{13}C NMR(75MHz,DMSO-d_6):δ157.63,151.52,143.31(d,J_{CF}= 13.5Hz),136.40,136.04,131.60(d,J_{CF}= 3.0Hz),127.70,123.54(d,J_{CF}= 4.5Hz),120.18,65.94,27.34;^{19}F NMR(282MHz,DMSO-d6):δ-83.96(d,J = 10.2Hz)。HRMS:$C_{13}H_{13}{}^{35}ClFN_3O_2$(M+H)的计算值:298.0753;实验值:298.0753。

[2085] 实例54

[2086] 制备2-(叔丁基)-4-氯-5-((4-(6-硝基吡啶-3-基)苯甲基)氧基)哒嗪-3(2H)-酮

[2087]

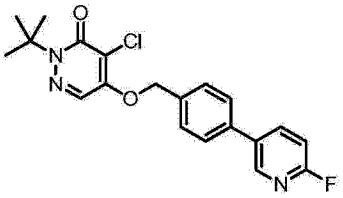


[2088] 在环境温度下,相继用实例48A的产物(0.105g,0.250mmol)于1.5mL二甲氧乙烷中的溶液及碳酸钾水溶液(0.50mmol;0.50mL)处理5-溴-2-硝基吡啶(50.7mg,0.250mmol)和四(三苯基膦)钯(0)(6.7mg;2.3mol%)于二甲氧乙烷(1.5mL)中的溶液。将所得混合物加热到80℃,维持2小时,随后冷却回到环境温度且用乙酸乙酯(50mL)稀释。分离有机层,用水(2×50mL)和饱和氯化钠水溶液洗涤,随后经硫酸镁干燥,过滤且真空浓缩。随后通过硅胶色谱(20-50%乙酸乙酯的己烷溶液)纯化粗物质,得到呈淡黄色固体状的所需产物(75.0mg,产率72.3%)。^{1}H NMR(300MHz,DMSO-d_6):δ9.46(dd,J = 2.7,0.7Hz,1H),8.68(dd,J = 8.8,2.7Hz,1H),8.36-8.23(m,4H),7.71-7.61(m,2H),5.57(s,2H),1.58(s,9H);^{13}C NMR(75MHz,DMSO-d_6):δ160.45,157.79,153.78,144.87,143.15,138.17,136.64,132.71,128.22,127.89,126.17,120.68,115.73,70.90,65.43,27.46。HRMS:$C_{20}H_{19}{}^{35}ClN_4O_4$(M+H)的计算值:415.1168;实验值:415.1168。

[2089] 实例55

[2090] 制备2-(叔丁基)-4-氯-5-((4-(6-氟吡啶-3-基)苯甲基)氧基)哒嗪-3(2H)-酮

[2091]



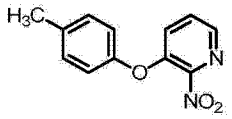
[2092] 在环境温度下，相继用实例 48A 的产物 (85.0mg，0.200mmol) 于 1.0mL 二甲氧乙烷中的溶液和碳酸钾水溶液 (0.50mmol ；0.50mL) 处理 5- 溴 -2- 氟吡啶 (37.0mg，0.210mmol) 和四 (三苯基膦) 钯 (0)(9.0mg ；3.9mol％) 于二甲氧乙烷 (1.0mL) 中的溶液。将所得混合物加热到 80℃，维持 2 小时，随后冷却回到环境温度且用乙酸乙酯 (50mL) 稀释。分离有机层，用水 (2×50mL) 和饱和氯化钠水溶液洗涤，随后经硫酸镁干燥，过滤且真空浓缩。随后通过硅胶色谱 (20-50％乙酸乙酯的己烷溶液) 纯化粗物质，得到呈白色固体状的所需产物 (50.0mg，产率 64.5％)。^{1}H NMR(300MHz，DMSO-d_6)：δ 8.58(dt，J = 2.6，0.8Hz，1H)，8.38-8.24(m，2H)，7.87-7.74(m，2H)，7.65-7.54(m，2H)，7.30(ddd，J = 8.6，2.9，0.7Hz，1H)，5.52(s，2H)，1.58(s，9H) ；^{13}C NMR(75MHz，DMSO-d_6) δ 157.79，153.82，145.45(d，J_{CF}= 15.0Hz)，140.34(d，J_{CF}= 8.3Hz)，136.01，135.39，133.62(d，J_{CF}= 4.5Hz)，128.52，127.17，126.18，115.67，109.89，109.39，71.03，65.40，27.47 ；^{19}F NMR(282MHz，DMSO-d_6)：δ -70.87(dd，J = 8.0，2.8Hz)。HRMS ：$C_{20}H_{19}{}^{35}ClFN_3O_2$(M+H) 的计算值 ：388.1223 ；实验值 ：388.1217。

[2093] 实例 56

[2094] 制备 2-(叔丁基)-4- 氯 -5-((4-((2- 氟吡啶 -3- 基) 氧基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

[2095] A 部分 - 制备 2- 硝基 -3-(对甲苯氧基) 吡啶

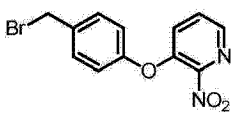
[2096]



[2097] 在 70℃下加热对甲酚 (0.325g，3.00mmol)、3- 溴 -2- 硝基吡啶 (0.404g，2.00mmol) 和碳酸钾 (0.345g，2.50mmol) 于乙腈 (2.0mL) 中的悬浮液且维持 16 小时。将所得混合物冷却到室温且用乙酸乙酯 (100mL) 稀释，随后用水 (2×100mL) 和饱和氯化钠水溶液洗涤，经硫酸镁干燥，过滤且真空浓缩。随后通过硅胶色谱 (0-20％乙酸乙酯的己烷溶液) 纯化粗物质，获得所需产物 (46.0mg，产率 10.0％)。^{1}H NMR(300MHz，$CDCl_3$)：δ 8.22(dd，J = 4.4，1.5Hz，1H)，7.48(dd，J = 8.4，4.4Hz，1H)，7.41(dd，J = 8.4，1.5Hz，1H)，7.31-7.19(m，2H)，7.05-6.95(m，2H)，2.39(s，3H) ；^{13}C NMR(75MHz，$CDCl_3$ 部分)：δ 152.16，146.82，141.31，135.46，130.85，128.53，128.07，119.74，20.78。

[2098] B 部分 - 制备 3-(4-(溴甲基) 苯氧基)-2- 硝基吡啶

[2099]

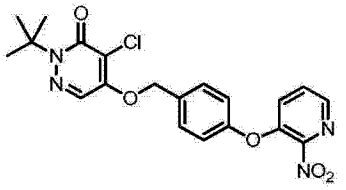


[2100] 将实例 56A 的产物 (0.039g，0.170mmol)、N- 溴代丁二酰亚胺 (35.0mg，0.200mmol)

和过氧化苯甲酰 (1mg) 于 1,2- 二氯乙烷 (4.0mL) 中的溶液加热到回流且维持 2 小时。将所得混合物冷却到室温且用二氯甲烷 (20mL) 稀释，分离有机层，随后用水 (2×20mL) 和饱和氯化钠水溶液洗涤，经硫酸镁干燥，过滤且浓缩。随后通过硅胶色谱 (10-40％乙酸乙酯的己烷溶液）纯化粗黄色油状物，获得呈淡黄色油状的所需产物 (45.0mg，产率 85.6％）。^{1}H NMR(300MHz,$CDCl_3$) δ 8.30(dd,J = 4.3,1.6Hz,1H),7.59-7.43(m,4H),7.12-7.02(m,2H),4.52(s,2H) ;^{13}C NMR(75MHz,$CDCl_3$, 部分) δ 154.79,145.77,142.31,135.07,131.13,129.28,128.74,119.64,32.33。

[2101] C 部分 - 制备 2-(叔丁基)-4- 氯 -5-((4-((2- 硝基吡啶 -3- 基) 氧基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

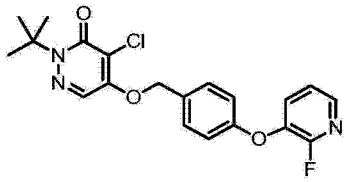
[2102]



[2103] 根据通用方法 B，使用 2-(叔丁基)-4- 氯 -5- 哒嗪 -3(2H)- 酮 (21.0mg，0.100mmol)、实例 56B 的产物 (31.0mg，0.100mmol) 和碳酸铯 (33.0mg，0.100mmol) 于二甲基甲酰胺 (1.0mL) 中在 80 ℃下制备。分离产量为 20.0mg ；46.4 ％。^{1}H NMR(300MHz,$CDCl_3$) : δ 8.22(dd,J = 4.3,1.7Hz,1H),7.68(s,1H),7.54-7.34(m,4H),7.04(d,J = 8.7Hz,2H),5.23(s,2H),1.57(s,9H) ;^{13}C NMR(75MHz,$CDCl_3$, 部分) : δ 158.95,155.27,153.50,145.64,142.47,131.98,129.45,129.39,128.79,124.98,119.72,118.54,71.17,66.53,27.86。HRMS :$C_{20}H_{19}{}^{35}ClN_4O_5$(M+H) 的计算值 ：431.1117 ；实验值 ：431.1110。

[2104] D 部分 - 制备 2-(叔丁基)-4- 氯 -5-((4-((2- 氟吡啶 -3- 基) 氧基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

[2105]



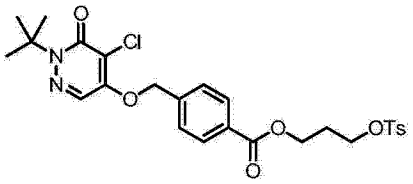
[2106] 将实例 56C 的产物 (12.0mg，0.030mmol)、氟化钾 (3.5mg，0.06mmol) 和 Kryptofix™(26.0mg，0.070mmol) 于二甲亚砜 (2.0mL) 中的溶液加热到 125℃且维持 30 分钟。将所得混合物冷却到室温且用乙酸乙酯 (40mL) 稀释，随后用水 (2×40mL) 和饱和氯化钠水溶液洗涤，经硫酸镁干燥，过滤且浓缩。随后通过制备型薄层色谱经二氧化硅 (1％甲醇的二氯甲烷溶液）纯化粗物质，获得所需产物 (9.0mg，产率 74.3％）。^{1}H NMR(300MHz,$CDCl_3$) : δ 7.94(d,J = 4.7Hz,1H),7.67(s,1H),7.47-7.30(m,3H),7.12(ddd,J = 7.9,4.8,0.9Hz,1H),7.02-6.90(m,2H),5.21(s,2H),1.57(s,9H) ;^{13}C NMR(75MHz,$CDCl_3$) : δ 159.00,156.99,156.75,153.80,153.60,141.76(d,J_{CF} = 13.5Hz),130.60(d,J_{CF} = 3.8Hz),130.46,129.12,125.09,122.19,118.50,118.03,71.37,66.47,27.87 ;^{19}F NMR(282MHz,$CDCl_3$) : δ -81.30(d,J = 9.8Hz)。HRMS :$C_{20}H_{19}{}^{35}ClFN_3O_3$(M+H) 的计算值 ：404.1172 ；实验值 ：404.1176。

[2107] 实例 57

[2108] 制备 4-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯甲酸 3-氟丙酯

[2109] A 部分-制备 4-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯甲酸 3-(甲苯磺酰氧基)丙酯

[2110]

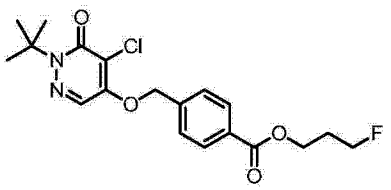


[2111] 将 4-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯甲酸甲酯[3](0.702g,2.00mmol)于四氢呋喃/水(10.0mL;4:1v/v)中的溶液冷却到 0℃且用水合氢氧化锂(0.252g,6.00mmol)一次性处理。0.25 小时后,将当前不透明溶液温热到环境温度且维持 16 小时。随后用水(50mL)稀释所得溶液,转移到分液漏斗中,用乙醚(3×50mL)洗涤且用 1M 盐酸酸化。用温热的乙酸乙酯(3×50mL)进一步洗涤当前酸性溶液,且经硫酸镁干燥经合并的乙酸乙酯洗涤液,过滤且真空浓缩成白色粉末。随后自热乙酸乙酯/戊烷再结晶,得到经纯化的呈无色针状物的 4-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯甲酸。

[2112] 将由此获得的中间物酸溶解于无水二甲基甲酰胺(20.0mL)中,随后在环境温度下,相继用双(4-甲基苯磺酸丙烷-1,3-二酯)(1.15g,3.00mmol)和碳酸钾(0.415g,3.00mmol)一次性处理。5 小时后,将所得悬浮液分配于乙酸乙酯与水(每个 50mL)之间,转移到分液漏斗中,且分离每个层。随后用乙酸乙酯(2×50mL)洗涤水层,且经硫酸镁干燥经合并的乙酸乙酯洗涤液,过滤且真空浓缩。随后通过使用从 7:3 戊烷/乙酸乙酯(500mL)到 3:2 戊烷/乙酸乙酯(1000mL)的阶段梯度经二氧化硅色谱纯化粗物质。收集在溶离 1075-1275mL 时的主要产物峰,合并且真空浓缩成无色油状物(0.566g,1.03mmol;51.6 %)。^{1}H NMR:(300MHz,DMSO-d_6)δ 8.25(1H,s),7.89(2H,AA'BB',J_{AB}= 8.3Hz,$J_{AA'}$= 2.0Hz),7.75(2H,AA'BB',J_{AB}= 8.3Hz,$J_{AA'}$= 2.0Hz),7.57(2H,d,J = 8.6Hz),7.35(2H,d,J = 7.9Hz),5.57(2H,s),4.23(2H,d,J = 5.9Hz),4.18(2H,t,J = 5.7Hz),2.27(3H,s),2.04(2H,tt,J = 5.9,5.9Hz),1.57(9H,s)。^{13}C NMR:(75MHz,DMSO-d_6)δ 165.0,157.7,153.7,144.8,140.8,132.0,130.0,129.5,129.4,127.5,126.1,115.8,70.7,67.5,65.4,60.5,27.5,27.4,20.9。HRMS:$C_{26}H_{29}{}^{35}ClN_2O_7S$(M+H)的计算值:549.1457;实验值:549.1467。TLC:R_f 0.33(硅胶,1:1 戊烷/乙酸乙酯,uv)。

[2113] B 部分-制备 4-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯甲酸 3-氟丙酯

[2114]



[2115] 将4-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯甲酸甲酯[3](0.702g,2.00mmol)于四氢呋喃/水(10.0mL;4:1v/v)中的溶液冷却到0℃且用水合氢氧化锂(0.252g,6.00mmol)一次性处理。0.25小时后,将当前不透明溶液温热到环境温度且维持16小时。随后用水(50mL)稀释所得溶液,转移到分液漏斗中,用乙醚(3×50mL)洗涤且用1M盐酸酸化。用温热的乙酸乙酯(3×50mL)进一步洗涤当前酸性溶液,且经硫酸镁干燥经合并的乙酸乙酯洗涤液,过滤且真空浓缩成白色粉末。

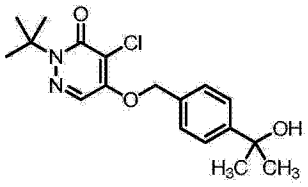
[2116] 将由此获得的中间物酸溶解于无水二甲基甲酰胺(5.00mL)中,随后在环境温度下,相继用4-甲基苯磺酸3-氟丙酯(0.697g,3.00mmol)和碳酸钾(0.415g,3.00mmol)一次性处理。0.25小时后,将所得溶液温热到55℃,维持1.5小时,随后冷却到环境温度且用乙酸乙酯稀释(每个150mL),转移到分液漏斗中。随后用饱和氯化钠水溶液(5×50mL)洗涤由此获得的乙酸乙酯溶液,经硫酸镁干燥,过滤且真空浓缩成琥珀色油状物。随后通过使用3:1戊烷/乙酸乙酯经二氧化硅(30×200mm)色谱纯化粗物质。收集在溶离300-560mL时的主要产物峰,合并且真空浓缩成白色固体(0.680g,1.71mmol;85.7 %)。^{1}H NMR:(300MHz,DMSO-d_6)δ8.23(1H,s),8.03(2H,AA'BB',J_{AB}= 8.5Hz,$J_{AA'}$= 1.9Hz),7.60(2H,AA'BB',J_{AB}= 8.7Hz,$J_{BB'}$= 1.9Hz),5.56(2H,s),4.61(2H,dt,J = 47.2,5.9Hz),4.38(2H,t,J = 6.3Hz),2.11(2H,dtt,J = 25.9,6.1,6.1Hz)1.57(9H,s)。^{19}F NMR:(282MHz,DMSO-d_6)δ-220.4(1F,tt,J = 47.1,25.8Hz)。^{13}C NMR:(75MHz,DMSO-d_6)δ165.3,157.7,153.7,140.8,129.6,129.5,127.5,126.1,115.8,80.9(d,J = 161.9Hz),70.7,65.4,61.0(d,J = 5.6Hz),29.2(d,J = 19.6Hz),27.4。HRMS:$C_{19}H_{22}{}^{35}ClFN_2O_4$(M+H)的计算值:397.1325;实验值:397.1330。TLC:R_f 0.24(硅胶,3:1戊烷/乙酸乙酯,uv)。

[2117] 实例58

[2118] 制备2-(叔丁基)-4-氯-5-((4-(2-(2-氟乙氧基)丙-2-基)苯甲基)氧基)哒嗪-3(2H)-酮

[2119] A部分-制备2-(叔丁基)-4-氯-5-((4-(2-羟基丙-2-基)苯甲基)氧基)哒嗪-3(2H)-酮

[2120]

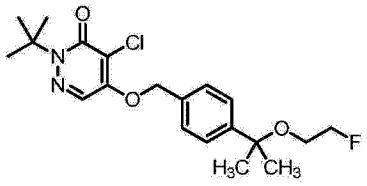


[2121] 在环境温度下,用碳酸铯(1.96g,6.00mmol)一次性处理2-(叔丁基)-4,5-二氯哒嗪-3(2H)-酮(0.995g,4.50mmol)和2-(4-(羟甲基)苯基)丙-2-醇(0.499g,3.00mmol;例如参见麦卡切克(Machacek),迈克尔(Michelle R.);海德尔(Haidle),安德鲁(Andrew);扎别瑞克(Zabierek),安娜(Anna A.);孔纳德(Konrad),卡琳(Kaleen M.);阿尔特曼(Altman),迈克尔(Michael D.)(默克公司(Merck&Co.,Inc.))制备作为双面酶抑制剂的噻唑甲酰胺(Preparation of thiazolecarboxamides as inhibitors of Janus kinases.)PCT国际申请案WO2010/011375.2010年1月28日)于无水二甲基甲酰胺(15.0mL)中的溶液。随后将所得悬浮液浸于预热油浴中,且在80℃下维持2.5小

时。将悬浮液无人照看地冷却到环境温度且维持 20 小时。随后将所得悬浮液分配于乙酸乙酯 (150mL) 与水 (25mL) 之间，转移到分液漏斗中，且分离每个层。随后用饱和氯化钠水溶液 (5×25mL) 洗涤乙酸乙酯层，经硫酸镁干燥，过滤且真空浓缩成琥珀色油状物。随后通过使用 3:2 己烷 / 乙酸乙酯经二氧化硅 (40×170mm) 色谱纯化粗物质。收集在溶离 400-700mL 时的主要产物峰，合并且真空浓缩成白色固体。随后自热乙酸乙酯 / 戊烷再结晶，得到呈无色针状物的所需产物 (0.682g，1.95mmol ；64.9％)。^{1}H NMR:(300MHz,DMSO-d_6) δ 8.26(s,1H),7.51(2H,AB,J_{AB}= 8.3Hz),7.39(2H,AB,J_{AB}= 8.3Hz),5.42(s,2H),5.01(s,1H),1.57(s,9H),1.42(s,6H)。^{13}C NMR:(75MHz,DMSO-d_6) δ 157.8,153.9,151.0,132.8,127.4,126.2,124.8,115.5,71.4,70.5,65.3,31.8,27.4。HRMS :$C_{18}H_{23}{}^{35}ClN_2O_3$(M+H) 的计算值 ：351.1470 ；实验值 ：351.1474。TLC :R_f0.16(硅胶，7:3 己烷 / 乙酸乙酯，CAM)。

[2122] B 部分 - 制备 2-(叔丁基)-4- 氯 -5-((4-(2-(2- 氟乙氧基) 丙 -2- 基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

[2123]



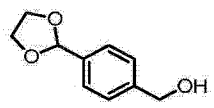
[2124] 在环境温度下，用 11.4mg 水合对甲苯磺酸 (0.06mmol ；20mol％) 一次性处理 A 部分的产物 (0.105g，0.300mmol) 于 2- 氟乙醇 (1.75mL) 中的溶液。24 小时后，在真空中移除所有挥发物，且通过使用 4:1 己烷 / 乙酸乙酯经二氧化硅 (30×185mm) 色谱直接纯化残余物。收集在溶离 360-450mL 时的主要产物峰，合并且真空浓缩成无色油状物 (81.2mg，0.205mmol ；68.3 ％)。^{1}H NMR:(300MHz,DMSO-d_6) δ 8.28(1H,s),7.55-7.39(4H,m),5.44(2H,s),4.62-4.52(1H,m),4.47-4.36(1H,m),3.46-3.34(1H,m),3.36-3.25(1H,m),1.58(9H,s),1.49(6H,s)。^{19}F NMR:(282MHz,DMSO-d_6) δ -222.01(1F,tt,J = 47.8,30.6Hz)。^{13}C NMR:(75MHz,DMSO-d_6) δ 157.8,153.9,146.3,133.9,127.7,126.1,125.8,115.5,83.17(d,J = 166.3Hz),76.3,71.2,65.3,61.89(d,J = 19.2Hz),28.0,27.4。HRMS ：$C_{20}H_{26}{}^{35}ClFN_2O_3$(M+H) 的计算值 ：397.1689 ；实验值 ：397.1695。TLC :R_f 0.51(硅胶，3:2 己烷 / 乙酸乙酯，uv)。

[2125] 实例 59

[2126] 制备 2-(叔丁基)-4- 氯 -5-((4-((2- 氟乙氧基) 甲基) 苯基) 乙炔基) 哒嗪 -3(2H)- 酮

[2127] A 部分 - 制备 (4-(1,3- 二氧杂环戊烷 -2- 基) 苯基) 甲醇

[2128]

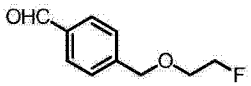


[2129] 将 4- 甲酰基苯甲酸甲酯 (4.92g，30.0mmol) 溶解于无水甲苯 (50.0mL) 中，相继用乙二醇 (1.84mL，33.0mmol) 和对甲苯磺酸 (57.1mg，0.300mmol) 处理，随后在迪恩 - 斯达克 (Dean-Stark) 条件下加热到回流 ；在 1 小时内形成缩醛。随后将溶液冷却到 22℃且使用注射泵用氢化钠双 (2- 甲氧基乙氧基) 铝 (45.0mmol ；12.7mL 70.3 重量％甲苯溶液) 以

0.5mL/min 的速率直接处理。添加完成时，将所得溶液冷却到 0℃，用饱和酒石酸钠钾水溶液 (100mL) 小心处理，随后剧烈搅拌 1 小时；观察到平稳地形成澄清溶液。随后用乙酸乙酯 (50mL) 稀释所得双相，转移到锥形漏斗中，且分离每个层。随后用乙酸乙酯 (3×50mL) 洗涤水层，且经硫酸镁干燥经合并的乙酸乙酯和甲苯溶液，过滤且真空浓缩成无色油状物。随后通过使用 1:1 戊烷 / 乙酸乙酯经二氧化硅 (50×135mm) 色谱纯化粗产物。收集在溶离 425-725mL 时的主要产物峰，合并且真空浓缩成无色油状物，使其在冷冻机中固化 (经两步，4.50g，83.2％)。^{1}H NMR:(600MHz,$CDCl_3$) δ 7.48(2H,AB,J_{AB} = 8.1Hz),7.39(2H,AB,J_{AB} = 8.3Hz),5.82(1H,s),4.71(2H,d,J = 6.0Hz),4.08(4H,AA'BB',$J_{AA'}$ = $J_{BB'}$ = 7.2Hz,J_{AB} = -7.5Hz,$J_{AB'}$ = 6.4Hz),1.63(1H,t,J = 6.0Hz)。^{13}C NMR:(75MHz,$CDCl_3$) δ 142.0,137.2,126.8,126.6,103.5,65.3,64.9。

[2130] B 部分 - 制备 4-((2- 氟乙氧基) 甲基) 苯甲醛

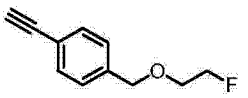
[2131]



[2132] 在环境温度下，相继用 1- 溴 -2- 氟乙烷 (3.73mL,50.0mmol) 和粉末状氢氧化钾 (5.61g,0.100mol) 一次性处理实例 59A 的产物 (1.80g,10.0mmol) 于无水乙腈 (50.0mL) 中的溶液。0.5 小时后，将所得悬浮液温热到 80℃，随后维持 2.5 小时。冷却到环境温度后，用水 (100mL) 稀释悬浮液，转移到分液漏斗中，随后用乙酸乙酯 (3×100mL) 洗涤。经硫酸镁干燥经合并的乙酸乙酯洗涤液，过滤且真空浓缩成无色物，其通过使用 1:1 戊烷 / 乙醚经二氧化硅 (50×195mm) 色谱直接纯化，得到呈无色油状的 2-(4-((2- 氟乙氧基) 甲基) 苯基)-1,3- 二氧戊环 (2.04g,9.02mmol ;90.2％)。随后将经纯化的缩醛 (0.423g,2.00mmol) 在环境温度下溶解于湿丙酮 (8.00mL) 中且用稀盐酸 (2.00mmol ;2.00mL 1.0N 水溶液) 直接处理。搅拌 18 小时后，将所得混合物分配于乙醚与饱和碳酸氢钠水溶液 (每个 50mL) 之间，转移到锥形漏斗中，且分离每个层。随后用乙醚 (2×50mL) 洗涤水层，且经硫酸镁干燥经合并的醚溶液，过滤且真空浓缩。通过在减压下减压蒸馏 (bulb-to-bulb distillation) 纯化，得到呈无色油状的标题化合物 (0.340g,1.87mmol ;93.4％)。

[2133] C 部分 - 制备 1- 乙炔基 -4-((2- 氟乙氧基) 甲基) 苯

[2134]

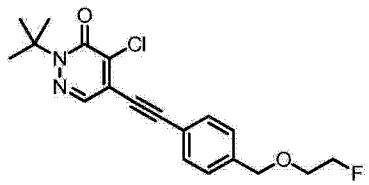


[2135] 在环境温度下，将四溴化碳 (1.06g,3.20mmol)、锌粉 (0.210g,3.20mmol) 和三苯基膦 (0.840g,3.20mmol) 添加到实例 59B 的产物 (0.290g,1.60mmol) 于二氯甲烷 (10.0mL) 中的溶液中。使用标准处理程序分离粗二溴中间物，将其溶解于无水四氢呋喃 (8.00mL) 中，随后冷却到 -78℃且用正丁基锂于四氢呋喃 (2.00mL) 中的溶液处理。随后将所得混合物温热到环境温度，用水处理且用乙酸乙酯萃取。用水和饱和氯化钠水溶液洗涤乙酸乙酯溶液，随后经硫酸镁干燥，过滤且真空浓缩。随后通过使用 9:1 己烷 / 乙酸乙酯经二氧化硅 (12g) 色谱纯化由此获得的粗物质，得到标题化合物 (0.190g,66.6％)。^{1}H NMR(300MHz,DMSO-d_6) δ 7.50-7.44(m,2H),7.38-7.32(m,2H),4.67-4.63(m,1H),4.55(s,2H),4.51-4.47(m,1H),4.16(s,1H),3.76-3.72(m,1H),3.66-3.62(m,1H)。^{13}C

NMR(75MHz,DMSO-d_6) δ 139.19,131.60,127.51,120.72,83.68(d,J = 51.8Hz),81.82,80.62,71.41,69.10(d,J = 18.8Hz)。

[2136] D 部分 - 制备 2-(叔丁基)-4- 氯 -5-((4-((2- 氟乙氧基) 甲基) 苯基) 乙炔基) 哒嗪 -3(2H)- 酮

[2137]



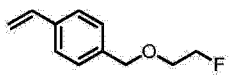
[2138] 在环境温度下,将三氟甲烷磺酸 1-(叔丁基)-5- 氯 -6- 侧氧基 -1,6- 二氢哒嗪 -4- 酯 (0.175g,0.523mmol)、实例 59C 的产物 (95.0mg,0.533mmol)、反式 - 二氯 (三苯基膦) 钯 (II)(11.0mg,0.0157mmol ;3.0mol%)、碘化铜 (I)(30.0mg,0.158mmol)、碘化正四丁铵 (0.576g,1.55mmol) 和三乙氨 (220μL,1.58mmol) 于无水四氢呋喃 (5.00mL) 中的溶液搅拌 2 小时,随后用乙酸乙酯稀释且通过硅藻土过滤,转移到分液漏斗中。随后用水和饱和氯化钠水溶液洗涤乙酸乙酯溶液,经硫酸镁干燥,过滤且真空浓缩。随后通过使用 3:1 己烷 / 乙酸乙酯经二氧化硅 (4g) 色谱纯化由此获得的粗物质,得到标题化合物 (90.0mg,46.5%)。^{1}H NMR(300MHz,DMSO-d_6) δ 8.06(s,1H),7.66-7.63(m,2H),7.48-7.45(m,2H),4.68-4.66(m,1H),4.61(s,2H),4.52-4.50(m,1H),3.79-3.76(m,1H),3.69-3.66(m,1H),1.60(s,9H)。^{13}C NMR(75MHz,DMSO-d_6) δ 155.85,141.13,136.51,134.28,131.97,127.71,124.57,119.20,102.11,84.02,81.58(d,J = 36.0Hz),71.33,69.25(d,J = 19.5Hz),65.89,27.30。^{19}F NMR(282MHz,DMSO-d_6) δ -221.61(tt,J = 48.0,31.1Hz)。HRMS :$C_{19}H_{20}{}^{35}ClFN_2O_2$(M+H) 的计算值 :363.1270 ;实验值 :363.1266。

[2139] 实例 60

[2140] 制备 (E)-2-(叔丁基)-4- 氯 -5-(4-((2- 氟乙氧基) 甲基) 苯乙烯基) 哒嗪 -3(2H)- 酮

[2141] A 部分 - 制备 1-((2- 氟乙氧基) 甲基)-4- 乙烯苯

[2142]

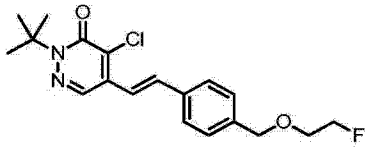


[2143] 将溴化甲基三苯基鏻 (0.260g,0.728mmol) 和氢化钠 (80.0mg,3.33mmol) 于无水四氢呋喃 (2.50mL) 中的悬浮液冷却到 0℃,随后用实例 59A 的产物 (0.110g,0.604mmol) 处理。随后随着冰块融化,将所得混合物缓慢温热到环境温度。2 小时后,用乙醚稀释悬浮液,转移到分液漏斗中,随后用水和饱和氯化钠水溶液洗涤,经硫酸镁干燥,过滤且真空浓缩。随后通过使用 9:1 己烷 / 乙酸乙酯经二氧化硅 (4g) 色谱纯化由此获得的粗物质,得到标题化合物 (40.0mg,36.7%)。^{1}H NMR(300MHz,$CDCl_3$) δ 7.40-7.29(m,2H),7.24(d,J = 8.2Hz,2H),6.64(dd,J = 17.6,10.9Hz,1H),5.67(dd,J = 17.6,1.0Hz,1H),5.17(dd,J = 10.9,0.9Hz,1H),4.64-4.56(m,1H),4.52(s,2H),4.47-4.38(m,1H),3.75-3.65(m,1H),3.64-3.55(m,1H)。^{19}F NMR(282MHz,$CDCl_3$) δ -223.12(tt,J = 48.0,31.1Hz)。

[2144] B 部分 - 制备 (E)-2-(叔丁基)-4- 氯 -5-(4-((2- 氟乙氧基) 甲基) 苯乙烯基)

哒嗪 -3(2H)- 酮

[2145]



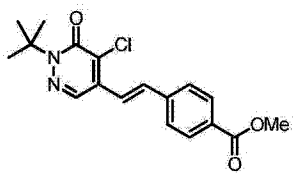
[2146] 将三氟甲烷磺酸 1-(叔丁基)-5- 氯 -6- 侧氧基 -1,6- 二氢哒嗪 -4- 酯 (0.180g,0.538mmol)、实例 60A 的产物 (0.140g,0.777mmol)、反式 - 二氯双 (三邻甲苯基膦) 钯 (II)(40.0mg,0.057mmol ;7.3mol％) 和三乙氨 (120μL,0.860mmol) 于无水二甲基甲酰胺 (5.00mL) 中的溶液温热到 110℃且维持 2 小时。冷却到环境温度后,用乙酸乙酯稀释所得混合物,且通过硅藻土过滤,转移到分液漏斗中。随后用水和饱和氯化钠水溶液洗涤乙酸乙酯溶液,经硫酸镁干燥,过滤且真空浓缩。随后通过使用 4:1 己烷 / 乙酸乙酯经二氧化硅 (4g) 色谱纯化由此获得的粗物质,得到标题化合物 (50.0mg,25.5％)。^{1}H NMR(300MHz,$CDCl_3$) δ 8.04(s,1H),7.60-7.57(m,2H),7.44-7.41(m,2H),7.29(d,J = 6.0Hz,1H),4.72-4.69(m,1H),4.65(s,2H),4.56-4.53(m,1H),3.84-3.81(m,1H),3.74-3.71(m,1H),1.69(s,9H)。^{13}C NMR(75MHz,DMSO-d_6) δ 157.59,139.74,136.58,135.09,134.98,132.73,130.83,128.16,127.58,120.07,83.08(d,J = 168.0Hz),72.87,69.42(d,J = 19.5Hz),66.08,27.85。^{19}F NMR(282MHz,DMSO) δ -223.04(tt,J = 47.9,28.2Hz)。HRMS :$C_{19}H_{22}{}^{35}ClFN_2O_2$(M+H) 的计算值 :365.1427 ;实验值 :365.1421。

[2147] 实例 61

[2148] 制备 2-(叔丁基)-4- 氯 -5-((4-((2- 氟乙氧基) 甲基) 苯基) 乙炔基) 哒嗪 -3(2H)- 酮

[2149] A 部分 - 制备 (E)-4-(2-(1-(叔丁基)-5- 氯 -6- 侧氧基 -1,6- 二氢哒嗪 -4- 基) 乙烯基) 苯甲酸甲酯

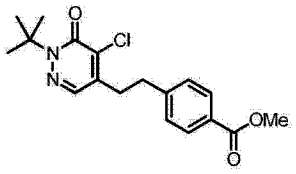
[2150]



[2151] 将三氟甲烷磺酸 1-(叔丁基)-5- 氯 -6- 侧氧基 -1,6- 二氢哒嗪 -4- 酯 (0.400g,1.20mmol)、4- 乙烯基苯甲酸甲酯 (0.210g,1.29mmol)、反式 - 二氯双 (三邻甲苯基膦) 钯 (II)(40.0mg,0.057mmol ;4.8mol％) 和三乙氨 (80.0μL,0.574mmol) 于无水二甲基甲酰胺 (2.00mL) 中的溶液温热到 110℃且维持 2 小时。冷却到环境温度后,用乙酸乙酯稀释所得混合物,且通过硅藻土过滤,转移到分液漏斗中。随后用水和饱和氯化钠水溶液洗涤乙酸乙酯溶液,经硫酸镁干燥,过滤且真空浓缩。随后通过使用 4:1 己烷 / 乙酸乙酯经二氧化硅 (12g) 色谱纯化由此获得的粗物质,得到标题化合物 (80.0mg,19.2％)。^{1}H NMR(300MHz,$CDCl_3$) δ 8.12-8.08(m,2H),8.03(s,1H),7.68-7.62(m,2H),7.48-7.32(m,2H),3.96(s,3H),1.70(s,9H)。

[2152] B 部分 - 制备 4-(2-(1-(叔丁基)-5- 氯 -6- 侧氧基 -1,6- 二氢哒嗪 -4- 基) 乙基) 苯甲酸甲酯

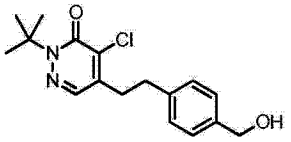
[2153]



[2154] 在环境温度下，用氧化铂 (II)(20.0mg，0.088mmol) 一次性处理实例 61A 的产物 (50.0mg，0.144mmol) 于 2:1 甲醇 / 二氯甲烷 (15.0mL) 中的溶液。在氢大气下搅拌所得悬浮液，随后通过硅藻土与硅胶的混合物过滤且真空浓缩所得滤液。随后通过使用 4:1 己烷 / 乙酸乙酯经二氧化硅 (4g) 色谱纯化由此获得的粗物质，得到标题化合物 (30.0mg，59.7％)。^{1}H NMR(300MHz，$CDCl_3$) δ 8.00(d，2H，J ＝ 8.3Hz)，7.47(s，1H)，7.28(d，2H，J ＝ 8.2Hz)，3.93(s，3H)，3.00-2.94(m，4H)，1.66(s，9H)。

[2155] C 部分 - 制备 2-(叔丁基)-4- 氯 -5-(4-(羟甲基) 苯乙基) 哒嗪 -3(2H)- 酮

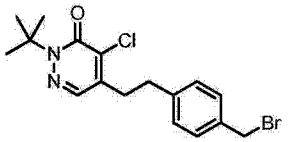
[2156]



[2157] 将实例 61B 的产物 (30.0mg，0.086mmol) 于四氢呋喃 (2.00mL) 中的溶液冷却到 0℃，随后用氢化锂铝 (0.4mL，0.4mmol，1M 四氢呋喃溶液) 处理且温热到环境温度。1 小时后，用水 (20mL) 稀释所得混合物，分离水层，随后用二氯甲烷 (3×20mL) 洗涤。用饱和氯化钠水溶液进一步洗涤经合并的有机洗涤液，随后经硫酸镁干燥，过滤且真空浓缩，得到标题化合物 (20.0mg)，其不经额外纯化即用于后续反应中。

[2158] D 部分 - 制备 5-(4-(溴甲基) 苯乙基)-2-(叔丁基)-4- 氯哒嗪 -3(2H)- 酮

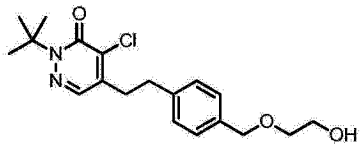
[2159]



[2160] 用三溴化磷 (0.030mmol ;30μL 1M 二氯甲烷溶液) 直接处理实例 61C 的产物 (20.0mg，0.062mmol) 于二氯甲烷 (1.00mL) 中的溶液，随后在环境温度下搅拌 1 小时。随后用二氯甲烷 (20mL) 稀释所得混合物，转移到分液漏斗中，且用水和饱和氯化钠水溶液洗涤，经硫酸镁干燥，过滤且真空浓缩，得到标题化合物 (20.0mg)，其不经额外纯化即用于后续反应中。^{1}H NMR(300MHz，$CDCl_3$) δ 7.49(s，1H)，7.33-7.28(m，2H)，7.23-7.17(m，2H)，4.56(s，2H)，3.80-3.74(m，2H)，3.63-3.57(m，2H)，2.93(s，4H)，1.67(s，9H)。

[2161] E 部分 - 制备 2-(叔丁基)-4- 氯 -5-(4-((2- 羟基乙氧基) 甲基) 苯乙基) 哒嗪 -3(2H)- 酮

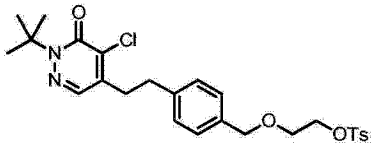
[2162]



[2163] 用实例 61D 的产物 (20.0mg,0.052mmol) 于无水四氢呋喃 (2.00mL) 中的溶液处理氢化钠 (0.20mmol ;8.0mg 60％矿物油分散液) 和乙二醇 (10.0μL,0.18mmol) 的悬浮液，且加热所得混合物到回流。4 小时后，将反应混合物冷却到环境温度，用二乙醚 (20mL) 稀释，随后转移到分液漏斗中，用水和饱和氯化钠水溶液洗涤，经硫酸镁干燥，过滤且真空浓缩。随后通过使用 7:3 己烷 / 乙酸乙酯经二氧化硅 (4g) 色谱纯化由此获得的粗物质，得到标题化合物 (5.5mg,29.0％)。^{1}H NMR(300MHz, $CDCl_3$) δ 7.50(s,1H),7.32-7.28(m,2H),7.22-7.18(m,2H),4.57(s,2H),3.80-3.76(m,2H),3.63-3.59(m,2H),2.93(s,4H),1.67(s,9H)。

[2164] F 部分 - 制备 4- 甲基苯磺酸 2-((4-(2-(1-(叔丁基)-5- 氯 -6- 侧氧基 -1,6- 二氢哒嗪 -4- 基) 乙基) 苯甲基) 氧基) 乙酯

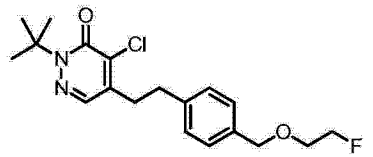
[2165]



[2166] 根据通用方法 D，使用实例 61E 的产物 (5.5mg,0.015mmol)、对甲苯磺酰氯 (8.0mg,0.042mmol)、4- 二甲基氨基吡啶 (一种晶体) 和三乙氨 (0.010mL,0.072mmol) 制备。分离产量为 5.0mg ;64.2％。^{1}H NMR(300MHz, $CDCl_3$) δ 7.87-7.79(m,2H),7.50(s,1H),7.39-7.30(m,2H),7.25-7.17(m,4H),4.49(s,2H),4.27-4.17(m,2H),3.73-3.63(m,2H),2.93(s,4H),2.46(s,3H),1.67(s,9H)。^{13}C NMR(75MHz, $CDCl_3$) δ 157.53,144.74,140.72,139.49,135.95,135.18,134.90,133.11,129.78,128.35,128.05,127.96,72.96,69.21,67.52,66.26,33.56,32.69,27.77,21.63。

[2167] G 部分 - 制备 2-(叔丁基)-4- 氯 -5-((4-((2- 氟乙氧基) 甲基) 苯基) 乙炔基) 哒嗪 -3(2H)- 酮

[2168]



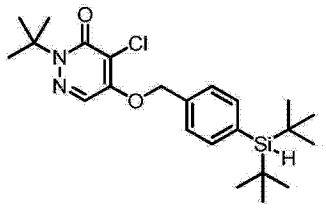
[2169] 在环境温度下，用经铅 (20.0mg,0.094mmol) 毒化的 5％钯 / 碳酸钙一次性处理实例 59C 的产物 (40.0mg,0.110mmol) 于 1:1 乙酸乙酯 / 己烷 (10.0mL) 中的溶液。在氢大气下搅拌所得悬浮液，随后通过硅藻土与硅胶的混合物过滤且真空浓缩所得滤液。随后通过使用 4:1 己烷 / 乙酸乙酯经二氧化硅 (4g) 色谱纯化由此获得的粗物质，得到标题化合物 (20.0mg,49.6％)。^{1}H NMR(300MHz, DMSO-d_6) δ 7.89(s,1H),7.29-7.22(m,4H),4.65-4.62(m,1H),4.50(s,2H),4.49-4.46(m,1H),3.72-3.69(m,1H),3.62-3.59(m,1H),2.91-2.89(m,4H),1.58(s,9H)。^{13}C NMR(75MHz, DMSO-d_6) δ 156.34,141.37,139.41,136.10,135.56,133.71,128.15,127.71,82.95(d,J = 164Hz),71.78,68.82(d,J = 18.8Hz),65.27,32.62,31.78,27.34。^{19}F NMR(282MHz, DMSO) δ -221.51(tt,J = 48.0,31.1Hz)。HRMS :$C_{19}H_{24}{}^{35}ClFN_2O_2$(M+H) 的计算值 :367.1583 ;实验值 :367.1580。

[2170] 实例 62

[2171] 制备硅烷基衍生物

[2172] A 部分 - 制备 2-(叔丁基)-4- 氯 -5-((4-(二叔丁基硅烷基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

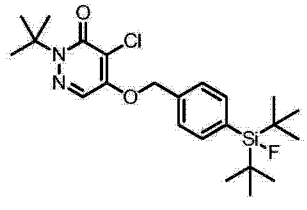
[2173]



[2174] 在环境温度下，相继用 (4-(二叔丁基硅烷基) 苯基) 甲醇 (0.706g,2.82mmol ; 例如参见詹姆斯 (James,D.) ;埃斯库迭尔 (Escudier,J.-M.) ;艾米古斯 (Amigues,E.) ; 舒尔茨 (Schulz,J.) ;维迪 (Virty,C.) ;博德纳维 (Bordenave,T.) ;斯洛斯克 - 皮诺 (Szlosek-pinaud,M.) ;富凯 (Fouquet,E.A) 有效合成用于 PET 造影的经改质的核苷和寡核苷酸的“点击化学”方法 (“click chemistry”approach to the efficient synthesis of modified nucleosides and oligonucleotides for PET imaging.) 四面体通讯 ,2010,51,1230-1232)、三苯基膦 (0.929g,3.54mmol) 和偶氮二甲酸二乙酯 (0.617g, 3.54mmol) 处理 2-(叔丁基)-4- 氯 -5- 羟基哒嗪 -3(2H)- 酮 (0.476g,2.36mmol) 于四氢呋喃 (23.6mL) 中的溶液。90 分钟后，用水 (50mL) 稀释所得混合物，转移到分液漏斗中，且分离水层，随后用乙酸乙酯 (3×100mL) 洗涤。经硫酸钠干燥经合并的有机洗涤液，过滤且真空浓缩成橙色油状物。随后用乙醚湿磨粗物质 2 小时且过滤所得悬浮液以移除悬浮的氧化三苯基膦。通过使用 0-50％乙酸乙酯 / 己烷梯度经二氧化硅色谱纯化滤液，得到呈白色固体状的标题化合物 (0.227g,22.1％)。^{1}H NMR:(300MHz,$CDCl_3$) δ 7.76(s,1H),7.64(d,2H,J ＝ 8.12Hz),7.40(d,2H,J ＝ 8.12Hz),5.34(s,2H),3.90(s,1H),1.55(s,9H),1.07(s,18H) ; ^{13}C NMR:(75MHz,$CDCl_3$) δ 159.04,153.78,136.49,136.29,135.43,126.03,125.18,98.55, 71.91,66.38,28.87,27.87,18.99。HRMS :$C_{23}H_{35}{}^{35}ClN_2O_2Si$(M+Na) 的计算值 :429.1736 ;实验值 :429.1729。

[2175] B 部分 - 制备 2-(叔丁基)-4- 氯 -5-((4-(二叔丁基氟硅烷基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

[2176]

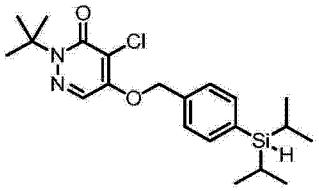


[2177] 将实例 62A 的产物 (5.0mg,0.011mmol) 于二甲亚砜 (0.3mL) 中的溶液添加到 4,7,13,16,21,24- 六氧杂 -1,10- 二氮杂双环 [8.8.8] 二十六烷 (8.7mg,0.023mmol) 和氟化钾 (0.6mg,0.011mmol) 的混合物中，随后温热到 35℃。10 分钟后，将所得混合物冷却到环境温度，随后用水 (0.5mL) 稀释，转移到分液漏斗中。随后用乙酸乙酯 (3×2mL) 洗涤水层，且经硫酸钠干燥经合并的洗涤液，过滤且真空浓缩成油状物。随后通过制备型薄层色谱使用 4:1 己烷 / 乙酸乙酯经二氧化硅纯化由此获得的粗物质，得到呈白色固体状的标题化合物 (3.2mg,70.6％ ;例如参见穆 (Mu L.) ;霍尼 (Hoehne,A.) ;舒比格 (Schubiger,P.

A.）；艾米塔梅（Ametamey,S.M.）；格拉哈姆（Graham,K.）；希尔（Cyr,J.E.）；丁克博格（Dinkelborg,L.）；斯迪菲尔德（Stellfeld,T.）；斯瑞瓦森（Srinivasan,A.）；沃格塔曼（Voigtmann,U.）；克拉尔（Klar,U.）用于PET造影的单步骤18F放射标记的基于硅的构筑嵌段（Silicon-based Building blocks for one step 18F-radiolabeling of peptides for PET imaging.）应用化学国际版（Angew.Chem.Int.Ed.）2008,47,4922-4925）。^{1}H NMR:(300MHz,$CDCl_3$) δ 7.72-7.59(m,3H),7.33(d,2H,J = 8.14Hz),5.24(s,2H),1.57(s,9H),0.97(s,18H)。^{13}C NMR(75MHz,$CDCl_3$,部分）δ 158.03,152.73,135.12,133.66(d,J = 4.5Hz),125.09,124.12,98.97,70.79,65.43,26.87,26.29,19.23(d,J = 12.0Hz)。^{19}F NMR:(282MHz,$CDCl_3$) δ -188.74(1F,s)。HRMS：$C_{23}H_{34}{}^{35}ClFN_2O_2Si$(M+H)的计算值：453.2135；实验值：453.2139。

[2178] C部分-制备2-（叔丁基）-4-氯-5-((4-（二异丙基硅烷基）苯甲基）氧基）哒嗪-3(2H)-酮

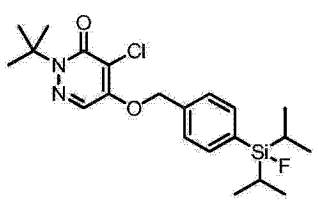
[2179]



[2180] 在环境温度下，相继用（4-（二异丙基硅烷基）苯基）甲醇（0.627g,2.82mmol；例如参见詹姆斯；埃斯库迭尔；艾米古斯；舒尔茨；维迪；博德纳维；斯洛斯克-皮诺；富凯，有效合成用于PET造影的经改质的核苷和寡核苷酸的“点击化学”方法四面体通讯，2010,51,1230-1232）、三苯基膦（0.929g,3.54mmol）和偶氮二甲酸二乙酯（0.617g,3.54mmol）处理2-（叔丁基）-4-氯-5-羟基哒嗪-3(2H)-酮（0.476g,2.36mmol）于四氢呋喃（23.6mL）中的溶液。2小时后，用水（50mL）稀释所得混合物，转移到分液漏斗中，且分离水层，随后用乙酸乙酯（3×100mL）洗涤。经硫酸钠干燥经合并的有机洗涤液，过滤且真空浓缩成油状物。随后用乙醚湿磨粗物质2小时且过滤所得悬浮液以移除悬浮的氧化三苯基膦。通过使用0-50％乙酸乙酯/己烷梯度经二氧化硅色谱纯化滤液，得到呈白色固体状的标题化合物（0.259g，产率27.0％）。^{1}H NMR:(300MHz,$CDCl_3$) δ 7.55(s,1H),7.38(d,2H,J = 8.03Hz),7.19(d,2H,J = 8.12Hz),5.12(s,2H),3.77(m,1H),1.46(s,9H),1.05(m,2H),0.87(dd,J = 6.0Hz,6H),0.82(dd,J = 6.0Hz,6H)。^{13}C NMR(75MHz,$CDCl_3$) δ 159.03,153.76,136.01,135.63,135.21,126.18,125.14,71.90,66.39,27.87,18.61,18.45,10.65。HRMS：$C_{21}H_{31}{}^{35}ClN_2O_2Si$(M+H)的计算值：407.1916；实验值：407.1922。

[2181] D部分-制备2-（叔丁基）-4-氯-5-((4-（二异丙基氟硅烷基）苯甲基）氧基）哒嗪-3(2H)-酮

[2182]



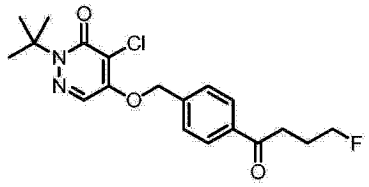
[2183] 在-78℃下，将实例62C的产物（5.0mg,0.011mmol）于四氢呋喃（0.3mL）中的溶

液添加到氟化四丁铵溶液 (0.011mmol ;0.011mL 1M 四氢呋喃溶液) 中。6 小时后,将所得混合物温热到 -20℃且再维持 20 小时。温热到环境温度后,通过制备型薄层色谱使用 9:1 己烷 / 乙酸乙酯经二氧化硅直接纯化粗混合物,得到呈无色油状的标题化合物 (4.2mg, 82.4%)。^{1}H NMR:(300MHz,$CDCl_3$) δ 7.66(s,1H),7.58-7.49(m,2H),7.37(d,2H,J = 7.84Hz),5.24(s,2H),1.57(s,9H),1.16-1.25(m,2H),0.96-0.94(m,12H)。^{13}C NMR(75MHz,$CDCl_3$, 部分) δ 159.01,153.70,136.53,134.43(d,J = 3.7Hz),126.29,125.08,71.76,66.43,27.87,16.65,16.62,12.30(d,J = 12.7Hz)。^{19}F NMR:(282MHz,$CDCl_3$) δ -187.01(t,J = 5.6Hz)。

[2184] 实例 63

[2185] 制备 2-(叔丁基)-4- 氯 -5-((4-(4- 氟丁酰基) 苯甲基) 氧基) 哒嗪 -3(2H)- 酮

[2186]



[2187] 在环境温度下,用 [(IPr)AuCl](例如参见迈瑞恩 (Marion,N.) ;拉蒙 (Ramon,R.) ;诺兰 (Nolan,S.P.) 在百万分之一催化剂负载下的 [(NHC)AuI] 催化的无酸水合 ([(NHC)AuI]-Catalyzed Acid Free Hydration of Alkynes at Part-Per-Million Catalyst Loadings.) 美国化学会志 2009,131,448-449) 和六氟锑酸银处理实例 43D 的产物于 1,4- 二噁烷中的溶液。1 分钟后,添加水且将所得混合物温热到 120℃且维持隔夜。冷却到环境温度后,在真空中移除所有挥发性物质且通过经二氧化硅色谱纯化残余物,得到标题化合物。

[2188] 实例 64

[2189] A 部分 - 由牛心脏制备亚粒线体粒子

[2190] 如李斯特 (Lester) 等人所述来制备牛心脏粒线体 (例如参见李斯特 (Lester R.L.) ;史密斯 (Smith A.L.) 对电子传递系统的研究 .28. 由牛心脏线粒体引起的四唑盐减少的模式 ;辅酶 Q 和其它脂质的作用 (Studies on the electron transport system.28. The mode of reduction of tetrazolium salts by beef heart mitochondria ;role of coenzyme Q and other lipids.) 生物化学和生物物理学报 (Biochim Biophys. Acta.)1961,47,475-96)。简单说来,将牛心脏切碎且使 200g 经研磨的心脏组织悬浮于 400mL 0.25M 蔗糖、0.01M Tris-Cl、1mM Tris- 丁二酸盐和 0.2mM 乙二氨四乙酸 (EDTA) 中且在瓦林掺混机 (Waring blender) 中匀化。使匀浆以 1,200×g 离心 20 分钟,且使上清液以 26,000×g 离心 15 分钟,产生粒线体集结粒。如由 BioRad 蛋白质分析试剂盒 (加利福尼亚洲海克力斯的伯乐生命科学研究中心 (BioRad Life Science Research,Hercules,CA)) 所测量,使用 0.25M 蔗糖、10mM Tris- 乙酸盐 (pH 7.5)、1.5mM 三磷酸腺苷 (ATP) 及 10mM 氯化镁将粒线体样品的蛋白质浓度调整到 20mg/mL。将样品储存在 -80℃下。

[2191] 如松野 - 八木 (Matsuno-Yagi) 等人所述,由粒线体制备牛亚粒线体粒子 (SMP) (例如参见松野 - 八木 ,A. ;海特菲 (Hatefi,Y.) 对氧化磷酸化机制的研究 (Studies on the mechanism of oxidative phosphorylation.)ATP 合成中的催化位点协同性 (Catalytic site cooperativity in ATP synthesis.) 生物化学杂志 (J.Biol.

Chem.)1985,260,11424-7)。简单说来,在冰浴中用70%最大输出量的数字式布兰森超音波仪(digital Branson sonifier;Branson,Danbury,CT)以15mL的批次音波处理经分离的牛心脏粒线体1分钟。在4℃下,使音波处理的悬浮液以16,000×g离心10分钟,且使上清液以150,000×g离心45分钟。使亚粒线体集结粒再悬浮于含有0.25M蔗糖、10mM Tris-乙酸盐(pH 7.5)的缓冲液中。使用BioRad蛋白质分析试剂盒(加利福尼亚洲海克力斯的伯乐生命科学研究中心)测定蛋白质浓度,且将样品以20mg/mL的浓度储存在-80℃下。

[2192] B部分-亚粒线体粒子(SMP)催化活性及化合物抑制分析

[2193] 自萨托(Satoh)等人改编用于测定亚粒线体粒子催化活性的程序(例如参见萨托(Satoh T),三好(Miyoshi H),阪本(Sakamoto K),岩村(Iwamura H.)合成辣椒素与不同NADH泛醌氧化还原酶的抑制作用的比较(Comparison of the inhibitory action of synthetic capsaicin analogues with various NADH-ubiquinone oxidoreductases.)生物化学和生物物理学报1996,1273,21-30)。在37℃下,在分光光度计(Hewlett-Packard,Houston TX)中使用搅拌的比色管测量NADH-DB还原酶活性,作为NADH在340nm($\varepsilon = 5.4mM^{-1}\times cm^{-1}$)下120秒的氧化速率。反应物的最终体积为2.5mL,含有50mM K_2HPO_4(pH 7.4)、0.4μM抗霉素A和2mM氰化钾。最终SMP浓度为45μg/mL。通过添加100μM癸基泛醌和50μM NADH来起始酶反应。在起始反应之前,将不同浓度的抑制剂与含有SMP的反应混合物一起预先培育4分钟。测定IC_{50}值作为50%抑制NADH氧化所需的抑制剂浓度。使用GraphPad Prism第4版(加利福尼亚圣地亚哥的格拉夫派德公司(GraphPad,San Diego,CA))计算IC_{50}值。

[2194] 表1:MC1抑制资料

[2195]

氟吡达(flurpiridaz)	<100	38	≤1000
1	>1000	39	<100
3	>1000	40	<100
4	>1000	43	<100
5	>1000	45	<100
6	>1000	47	>1000
7	<100	49	>1000
8	>1000	50	<100
9	<100	51	>1000
12	≤1000	52	>1000
16	≤1000	54	<100
17	≤1000	55	<100
18	≤1000	60	>4000
19	≤1000	61	≤1000
20	<100	48B	<100

[2196]

21	≤1000	48C	≤1000
22	<100	53A	>1000
23	≤1000	53B	>1000
25	<100	56C	<100
27	<100	56D	<100
28	≤1000	57B	<100
29	<100	58A	≤1000
31	>1000	58B	≤1000
32	<100	59D	>4000
33	≤1000	62A	>1000
35	≤1000	62B	≤1000
36	≤1000	62C	≤1000
37	<100	62D	>1000

[2197] 实例 65

[2198] 使用定制机器人器件制备造影剂

[2199] A 部分 - 制备 [^{18}F] 氟化物

[2200] 通过在回旋加速器中质子轰击 [^{18}O]H_2O 来产生 [^{18}F] 氟化物；核化学转化显示如下且可概括为 $^{18}O(p,n)^{18}F$。为达成轰击的目的，^{18}O 的化学形式为 $H_2{}^{18}O$。所得 ^{18}F 的化学形式为氟离子。

[2201] ^{18}O+ 质子→ ^{18}F+ 中子

[2202] 根据已确立的工业程序，以 11MeV 质子（标称能量）轰击使用Havar®箔包裹于钽目标实体内的 [^{18}O]H_2O(2-3mL)；其中反应的质子临限能量为 2.57MeV 且最大截面的能量为 5MeV。目标体积、轰击时间及质子能量各自可经调整以管理所产生的 [^{18}F] 氟化物的量。

[2203] B 部分 - 使用定制机器人器件制备造影剂

[2204] 将根据实例 65A 制备的 [^{18}F] 氟化物施加于小容积塑料外壳内所容纳的先前经活化的 MP1 阴离子交换树脂 (BioRad) 上。随后将装载滤筒置放在位于定制设计的机器人放射合成系统内的溶离回路中且必要时使用于下方法之一引入。

[2205] 方法 A：使用碳酸氢四乙铵水溶液 (1.1-1.3 摩尔当量）将 [^{18}F] 氟化物 (1Ci) 从树脂转移到玻璃容器中。随后在高温 (120℃）和减压下浓缩所得混合物至干燥。随后将无水乙腈添加到浓缩溶液中，且再次使用高温 (70℃）和减压移除所有挥发物。

[2206] 方法 B：使用碳酸氢钾水溶液 (3 摩尔当量）将 [^{18}F] 氟化物 (1Ci) 自树脂转移到玻璃容器中。随后在高温 (120℃）和减压下浓缩所得混合物至干燥。随后将 Kryptofix™(4 摩尔当量）于无水乙腈中的溶液添加到浓缩溶液中，且再次使用高温 (70℃）和减压移除所有挥发物。

[2207] 随后将所需前驱体 (5-10 μmol) 于无水乙腈中的溶液添加到玻璃反应容器中，以使 [^{18}F] 氟化物和剩余反应组分溶剂化。随后将所得溶液转移到新玻璃容器中，加热到 90℃且维持 10 分钟。冷却到环境温度后，用水稀释溶液且通过 HPLC 使用 Waters Xterra C18 管柱 (250×10mm；10 μ）以及用于适当纯化的各种水 / 乙腈混合物直接纯化；采用 uv(220nm) 检测器与辐射 (NaI) 检测器来确定最佳峰收集窗。真空浓缩由此获得的纯化产物，随后在含有≤ 10％乙醇的生理食盐水中调配。在常规制备期间，在 75 分钟内制备约 50mCi 氟化产

物。

[2208] 表 2 :使用定制机器人器件的合成参数

[2209]

36	65A	Et_4NHCO_3	否	5%	99%
36	65A	$KHCO_3$	是	6%	99%
11	65B	Et_4NHCO_3	否	1%	低
26	65C	$KHCO_3$	是	7%	99%
14	65D	$KHCO_3$	是	13%	低

[2210] 实例 66

[2211] A 部分 - 使用 Explora RN 化学模块制备造影剂

[2212] 将根据实例 65A 产生的 [^{18}F] 氟化物 (1Ci) 自回旋加速器转移到合成模块,随后通过阴离子交换柱 (QMA,Waters,Inc.) 过滤以移除未反应的 [^{18}O]H_2O ;[^{18}F] 氟化物保留在阳离子树脂基体内。随后用碳酸氢四乙铵水溶液 (1 摩尔当量) 洗涤管柱,转移到反应容器中。用乙腈稀释所得溶液,随后在 150mm Hg,115℃下浓缩 4 分钟至干燥。用所需前驱体的乙腈溶液 (1 摩尔当量) 处理由此获得的无水 [^{18}F] 氟化四乙铵与碳酸氢四乙铵的混合物,随后温热到 90℃且维持 20 分钟。

[2213] 或者,将根据实例 65A 产生的 [^{18}F] 氟化物 (1Ci) 从回旋加速器转移到合成模块,随后通过阴离子交换柱 (QMA,Waters,Inc.) 过滤以移除未反应的 [^{18}O]H_2O ;[^{18}F] 氟化物保留在阳离子树脂基体内。随后用碳酸氢钾水溶液 (1 摩尔当量) 洗涤管柱,转移到反应容器中。用 Kryptofix™的乙腈溶液 (2 摩尔当量) 处理所得溶液,随后在 150mm Hg,115℃下浓缩 4 分钟至干燥。用所需前驱体 (1 摩尔当量 ;10-50%二甲亚砜的乙腈溶液) 处理由此获得的无水 [^{18}F] 氟化钾、碳酸钾和 Kryptofix™的混合物,随后温热到 90-125℃且维持 10 分钟。

[2214] 或者,将根据实例 65A 产生的 [^{18}F] 氟化物 (1Ci) 从回旋加速器转移到合成模块,随后通过预先活化的 MP1 阴离子交换树脂 (BioRad) 过滤以移除未反应的 [^{18}O]H_2O ;[^{18}F] 氟化物截留在阳离子树脂基体内。随后将装载滤筒置放在位于定制设计的机器放射合成系统内的溶离回路中,随后用碳酸氢四乙铵水溶液 (1 摩尔当量) 洗涤,转移到反应容器中。在 280 毫巴,95-115℃下,浓缩溶液 4 分钟至干燥,随后用所需前驱体的乙腈溶液 (1 摩尔当量) 处理,温热到 90℃且维持 10 分钟。

[2215] 冷却粗反应混合物到 35℃后,用水稀释所得溶液,随后通过 HPLC 经 Waters Xterra MS C18 管柱 (10μ ;10×250mm) 使用水 / 乙腈溶离剂直接纯化。收集主要产物峰,用抗坏血酸稀释,随后在 5%乙醇的抗坏血酸溶液中调配。在常规制备期间,制备约 250mCi 氟化产物。

[2216] 表 3 :使用 Explora RN 化学模块的合成参数

[2217]

10	66A	15%	99%
36	66B	4%[a]	99%
34	66C	13%	99%
15	66D	29%	99%
2	66E	33%	99%
41	66F	35%	99%
46	66G	6%	99%
57A	66H	19%	99%
44	66I	5%	99%
48B	66J	9%	99%
61F	66K	20%	99%
62A	66L	14%[a]	99%
56C	66M	39%	99%

[2218] [a]采用 Kryptofix™与碳酸钾的组合。

[2219] B 部分 - 使用 GE TracerLab MX 化学模块制备造影剂

[2220] 图 17 描绘在经 GE TracerLab MX 化学模块制备造影剂期间所用较佳卡匣配置的示意图。

[2221] 将实例 65A 的产物从回旋加速器转移到合成模块，随后通过阴离子交换管柱过滤以移除未反应的 [^{18}O]H_2O；[^{18}F] 氟化物截留在阳离子树脂基体内。随后用碳酸氢四乙铵 (28.8μmol；0.500mL 57.5mM 水溶液）洗涤管柱，转移到反应容器中。用乙腈稀释所得溶液，随后浓缩成干燥。随后再添加乙腈且重复干燥处理若干次。用前驱体化合物 (23.0μmol；2.00mL 11.5mM 乙腈溶液）处理由此获得的无水氟化四乙铵和碳酸氢四乙铵的混合物，随后温热到 90℃且维持 10 分钟。随后用水稀释所得溶液且通过 HPLC 经 Waters Xterra MS C18 管柱使用水 / 乙腈溶离剂直接纯化。收集主要产物峰，用抗坏血酸稀释，随后通过 C18 Sep-Pak®滤筒过滤以移除乙腈；氟化物截留在 C18 树脂基体内且弃去滤液。相继用抗坏血酸、弃去的滤液、随后纯乙醇洗涤装载滤筒，且收集滤液。用抗坏血酸进一步稀释由此获得的造影剂的乙醇浓缩物，随后通过 0.22μm 灭菌过滤器自动传递到最终产物小瓶。

[2222] 2-(叔丁基)-4-氯-5-((4-((2-氟乙氧基）甲基）苯甲基）氧基）哒嗪-3(2H)-酮可使用本文所述的方法，以 52％放射化学产率由 4- 甲基苯磺酸 2-((4-(((1-(叔丁基)-5- 氯 -6- 侧氧基 -1,6- 二氢哒嗪 -4- 基）氧基）甲基）苯甲基）氧基）乙酯制备。使用本文所述的修正卡匣配置观测到药品滞留平均降低 1.5％。

[2223] C 部分 - 使用 ORA NEPTIS 化学模块制备造影剂

[2224] 图 17 描绘在经 ORA NEPTIS 化学模块制备造影剂期间所用较佳卡匣配置的示意图。

[2225] 将实例 65A 的产物从回旋加速器转移到合成模块，随后通过阴离子交换管柱过滤以移除未反应的 [^{18}O]H_2O；[^{18}F] 氟化物截留在阳离子树脂基体内。随后用碳酸氢四乙铵 (28.8μmol；0.500mL 57.5mM 水溶液）洗涤管柱，转移到反应容器中。用乙腈稀释所得溶液，随后浓缩成干燥。随后再添加乙腈且重复干燥处理若干次。用前驱体化合物 (23.0μmol；2.00mL 11.5mM 乙腈溶液）处理由此获得的无水氟化四乙铵和碳酸氢四乙铵

的混合物，随后温热到 90℃且维持 10 分钟。随后用水稀释所得溶液且通过 HPLC 经 Waters Xterra MS C18 管柱使用水 / 乙腈溶离剂直接纯化。收集主要产物峰，用抗坏血酸稀释，随后通过 C18 Sep-Pak® 滤筒过滤以移除乙腈；氟化物截留在 C18 树脂基体内且弃去滤液。相继用抗坏血酸、弃去的滤液、随后纯乙醇洗涤装载滤筒，且收集滤液。用抗坏血酸进一步稀释由此获得的造影剂的乙醇浓缩物，随后通过 0.22μm 灭菌过滤器自动传递至最终产物小瓶。

[2226] 2-(叔丁基)-4-氯-5-((4-((2-氟乙氧基)甲基)苯甲基)氧基)哒嗪-3(2H)-酮可使用本文所述的方法，以 48％放射化学产率自 4-甲基苯磺酸 2-((4-(((1-(叔丁基)-5-氯-6-侧氧基-1,6-二氢哒嗪-4-基)氧基)甲基)苯甲基)氧基)乙酯制备。

[2227] 实例 67

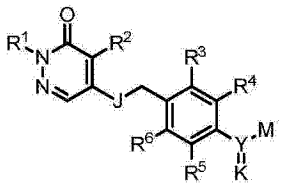
[2228] 大鼠中的组织分配和造影

[2229] A 部分 - 组织分配

[2230] 使通过尾部静脉接受静脉内注射造影剂（约 15μCi）的雄性史泊格多利大鼠 (Sprague Dawley rat)(250-350g) 麻醉 (50mg/kg 戊巴比妥钠 (sodium pentobarbital)，腹膜内或异氟烷气体吸入）。在注射后 15 或 60 分钟时，使动物安乐死且采集所需组织样品。随后称量所有样品且计算放射性 (Wallac Wizard 1480 或 Packard Cobra II Autogamma)；造影剂的区域组织吸收量由此表示为总注射剂量的百分比 / 克组织 (％ ID/g)。

[2231] 以下所描绘的通用结构突出显示分配实验期间所评估的特定结构特征。表 4-6 概述选择研究结果。

[2232]



[2233] 表 4：结构相关表

[2234]

67A	t-Bu	Cl	H	$CH_2O(CH_2)_2F$	H	H	O	N/A	N/A	H
67B	t-Bu	Cl	H	H	H	H	O	N/A	$(CH_2)_2O(CH_2)_2F$	O
67C	t-Bu	Cl	H	Cl	H	H	O	N/A	$(CH_2)_3F$	O
67D	t-Bu	Cl	H	H	H	H	O	N/A	$(CH_2)_2F$	O
67E	t-Bu	Cl	H	H	H	H	O	D，D	$O(CH_2)_2F$	C
67F	t-Bu	Cl	H	$O(CH_2)_2F$	H	H	O	N/A	N/A	H
67G	t-Bu	Cl	H	H	H	H	O	CH_3，H	$O(CH_2)_2F$	C
67H	i-Pr	Cl	H	H	H	H	O	H，H	$O(CH_2)_2F$	C
67I	t-Bu	CH_3	H	H	H	H	O	H，H	$O(CH_2)_2F$	C
67J	t-Bu	Cl	H	H	H	H	O	O	$O(CH_2)_2F$	C
67K	t-Bu	Cl	H	H	H	H	O	N/A	$C\equiv C(CH_2)_2F$	键
67L	t-Bu	Cl	H	H	H	H	O	N/A	2-氟嘧啶-5-基	键
67M	t-Bu	Cl	H	H	H	H	CH_2	H，H	$O(CH_2)_2F$	C
67N	t-Bu	Cl	H	H	H	H	O	t-Bu，t-Bu	F	Si
67O	t-Bu	Cl	H	H	H	H	O	N/A	2-氟吡啶-3-基	O

[2235] 表 5 :在 15 分钟时造影剂分配概述 (% ID/g±SEM)

[2236]

67A	0.03±0.01	0.08±0.03	0.65±0.36	0.07±0.01	0.05±0.01
67B	0.49±0.02	2.33±0.09	1.66±0.06	0.49±0.04	0.41±0.01
67C	0.26±0.05	2.67±0.17	4.21±0.29	0.50±0.08	0.37±0.05
67D	1.11	3.61	3.63	1.00	0.37
67E	0.17±0.02	0.66±0.09	4.80±0.27	0.39±0.05	0.36±0.08
67F	0.32±0.05	0.40±0.04	1.92±0.15	0.41±0.03	0.28±0.01
67G	0.50±0.18	0.33±0.10	2.19±0.36	0.46±0.12	0.32±0.11
67H	0.45±0.02	0.46±0.01	1.14±0.09	0.41±0.01	0.34±0.03
67I	0.11±0.02	0.33±0.02	2.34±0.57	0.19±0.03	0.18±0.01
67J	0.50±0.02	0.32±0.01	1.19±0.25	0.39±0.02	0.34±0.01
67K	0.07±0.03	0.99±0.06	2.68±0.35	0.37±0.15	0.31±0.09
67L	0.14±0.01	1.71±0.36	1.19±0.18	0.29±0.03	0.18±0.01
67M	0.53±0.13	0.96±0.10	2.54±0.20	0.97±0.13	0.35±0.05
67N	0.22±0.04	4.91±0.49	0.65±0.09	1.31±0.24	3.47±0.80
67O	0.07±0.03	0.99±0.06	2.68±0.35	0.37±0.15	0.31±0.09

[2237]

67A	0.15±0.05	0.38±0.08	0.14±0.05	0.06±0.02	0.09±0.04
67B	N/A	2.25±0.05	0.37±0.02	0.80±0.12	0.19±0.00
67C	N/A	3.04±0.21	0.42±0.01	0.33±0.01	0.24±0.04
67D	N/A	3.81	0.74	0.21	0.14
67E	0.82±0.07	2.61±0.18	0.97±0.11	0.50±0.04	0.77±0.09
67F	0.52±0.04	1.04±0.10	0.50±0.04	0.44±0.04	0.60±0.06
67G	0.41±0.03	0.88±0.05	0.59±0.03	0.40±0.05	0.35±0.04
67H	0.44±0.03	0.78±0.01	0.43±0.05	0.36±0.04	0.38±0.02
67I	0.43±0.10	1.13±0.11	0.49±0.10	0.28±0.04	0.28±0.13
67J	0.23±0.02	0.39±0.01	0.36±0.01	0.28±0.02	0.38±0.04
67K	0.55±0.10	1.35±0.14	0.36±0.04	0.27±0.02	0.28±0.02
67L	0.36±0.06	0.65±0.07	0.30±0.05	0.31±0.01	0.27±0.02
67M	N/A	0.79±0.07	0.55±0.31	0.52±0.19	0.24±0.04
67N	N/A	0.51±0.09	0.03±0.00	0.14±0.02	0.06±0.00
67O	0.55±0.10	1.35±0.14	0.36±0.04	0.27±0.02	0.28±0.02

[2238] 表 6 :在 60 分钟时造影剂分配概述 (% ID/g±SEM)

[2239]

67A	0.11±0.02	0.11±0.02	0.84±0.22	0.11±0.02	0.09±0.02
67B	0.26±0.04	1.34±0.22	1.58±0.13	0.27±0.03	0.20±0.04
67C	0.20±0.07	0.65±0.12	4.54±0.29	0.61±0.32	0.18±0.02
67D	1.00	1.49	4.66	0.96	0.23
67E	0.26±0.03	0.53±0.06	3.61±0.45	0.34±0.03	0.25±0.01
67F	0.48±0.01	0.39±0.04	0.87±0.02	0.44±0.03	0.31±0.01
67G	0.47±0.04	0.32±0.03	0.98±0.16	0.38±0.03	0.28±0.03
67H	0.55±0.02	0.40±0.02	0.55±0.03	0.42±0.01	0.35±0.02
67I	0.16±0.01	0.30±0.01	1.78±0.15	0.19±0.01	0.13±0.00
67J	0.58±0.04	0.35±0.02	0.50±0.03	0.42±0.02	0.37±0.02
67K	0.03±0.00	0.83±0.17	2.46±0.27	0.15±0.03	0.11±0.02
67L	0.10±0.02	2.06±0.27	0.62±0.12	0.21±0.02	0.11±0.02
67M	0.73±0.16	0.43±0.04	0.55±0.06	1.03±0.22	0.26±0.03
67O	0.03±0.00	0.83±0.17	2.46±0.27	0.15±0.03	0.11±0.02
67A	0.13±0.03	0.23±0.03	0.14±0.03	0.17±0.04	0.18±0.04
67B	N/A	1.17±0.20	0.30±0.02	0.78±0.22	0.15±0.04
67C	N/A	1.77±0.25	0.44±0.03	0.84±0.07	0.26±0.02
67D	N/A	1.71	0.69	0.26	0.18
67E	0.43±0.05	0.98±0.04	0.62±0.04	0.69±0.05	0.69±0.17
67F	0.48±0.01	0.60±0.03	0.38±0.01	0.57±0.04	0.43±0.07
67G	0.26±0.01	0.44±0.02	0.39±0.05	0.58±0.06	0.33±0.01
67H	0.32±0.02	0.49±0.03	0.43±0.02	0.71±0.06	0.31±0.02
67I	0.23±0.02	0.48±0.04	0.36±0.01	0.31±0.02	0.35±0.09
67J	0.23±0.03	0.42±0.02	0.43±0.02	0.40±0.03	0.31±0.02
67K	0.38±0.02	0.83±0.08	0.36±0.03	0.37±0.05	0.39±0.04
67L	0.33±0.08	0.40±0.08	0.22±0.03	0.78±0.15	0.20±0.06
67M	N/A	0.43±0.04	2.33±0.12	0.43±0.03	0.31±0.04
67O	0.38±0.02	0.83±0.08	0.36±0.03	0.37±0.05	0.39±0.04

[2240] B 部分 -PET 造影和资料重建构

[2241] 在如上所概述的经麻痹的史泊格多利大鼠中进行 PET 造影。随后使动物定位于微 PET 摄影机 (Focus220,CTI 分子造影公司 (CTI Molecular Imaging) 或飞利浦马赛克惠普公司 (Philips MOSAIC HP)) 中且通过尾部静脉导管注射造影剂 (约 1mCi)。在注射之后立即起始图像撷取且在 60 分钟时终止。在撷取之后,在 256×256 或 128×128 像素矩阵 (分别为 microPET Manager 和 ASIPro 或 PETview) 中重建构图像且修正衰减。由此使用 5 或 10 分钟间隔产生连续的断层摄影图像。

[2242] 图 1 显示 [^{18}F]67A 在大鼠中的代表性图像。

[2243] 图 2 显示 [^{18}F]67B 在大鼠中的代表性图像。

[2244] 图 3 显示 [^{18}F]67C 在大鼠中的代表性图像。

[2245] 图 4 显示 [^{18}F]67D 在大鼠中的代表性图像。

[2246] 图 5 显示 [^{18}F]67E 在大鼠中的代表性图像。

[2247] 图 6 显示 [^{18}F]67F 在大鼠中的代表性图像。

[2248] 图 7 显示 [^{18}F]67G 在大鼠中的代表性图像。

[2249] 图 8 显示 [^{18}F]67H 在大鼠中的代表性图像。

[2250] 图 9 显示 [^{18}F]67I 在大鼠中的代表性图像。

[2251] 图 10 显示 [^{18}F]67J 在大鼠中的代表性图像。

[2252] 图 11 显示 [^{18}F]67K 在大鼠中的代表性图像。

[2253] 图 12 显示 [^{18}F]67L 在大鼠中的代表性图像。

[2254] 图 13 显示 [^{18}F]67M 在大鼠中的代表性图像。

[2255] 图 14 显示 [^{18}F]67N 在大鼠中的代表性图像。

[2256] 图 15 显示 [^{18}F]67O 在大鼠中的代表性图像。

[2257] 实例 68

[2258] 造影剂的代谢概况

[2259] A 部分 - 肝细胞制备

[2260] 冷冻保存的肝细胞购自 Celsis 体外生物技术公司 (Celsis/In Vitro Technologies,Inc.)(马里兰州巴尔的摩市 (Baltimore,MD)) 且在使用之前储存在 -150℃下。使用人类 (混合性别 5- 供体库)、灵长类动物 (雄性,恒河猴 (rhesus monkey))、狗 (雄性,米格鲁犬 (beagle))、兔 (雄性,新西兰白兔) 以及大鼠 (雄性,史泊格多利大鼠) 的多种肝细胞。在研究当天,使冷冻保存小瓶中的肝细胞通风以释放任何液态 N_2,随后置放到 37℃水浴中持续 75-90 秒以解冻。将肝细胞转移到预先温热的 KHB 中且以 50×g 离心 5 分钟。弃去上清液且使肝细胞以 1×10^6 个细胞 / 毫升的浓度再悬浮于 KHB 中。通过锥虫蓝 (Trypan blue) 排除法证实细胞生存力。

[2261] B 部分 - 肝细胞培育

[2262] 使测试化合物在 37℃ /5% CO_2 下在肝细胞 (1×10^6 个细胞 / 毫升 ;0.5mL) 中培育,培育 0、15、30、60 或 180 分钟,随后直接转移到乙腈 (1.0mL) 中,涡流 30 秒且以 2500×g 离心 20 分钟。随后将上清液转移到新的离心管,在氮气流下在 37℃的加热块中蒸发乙腈且在水中复原之后,通过 HPLC 用无线电检测分析。

[2263] C 部分 -HPLC 分析

[2264] 维持在环境温度(25℃)和1.0mL/min流动速率下,经Agilent 1100HPLC(马萨诸塞州伯灵顿的安捷伦科技公司(Agilent Technologies,Burlington,MA))使用Phenomenex Luna C18管柱(5μ;4.6×150mm)分析提取物样品和标准物。移动相A含有0.1%甲酸的水溶液,且移动相B含有0.1%甲酸的乙腈溶液。使用从5%到90%B的线性梯度历时15分钟进行溶离。使用5%B的5分钟延后时间使管柱再平衡。使用在线γ或β流检测器(INUS,Tampa,FL)记录放射性产物。

[2265]

35	30
25	71
9	73
16	20
1	20
45	19
40	34
57B	31
43	63
48C	95
61G	6
62B	98

[2266] 所属领域的技术人员将显而易见,本揭示案并不限于上述说明性实例,且其可以其它特定形式实施而不背离其本质属性。因此,需要在所有方面中将实例视为说明性而非限制性的,参考随附申请专利范围而非上述实例,且因此,在申请专利范围的均等物的含义及范围内的所有变化均意欲包涵于其中。

[2267] 虽然本文中已描述和说明本发明的若干实施例,但所属领域的技术人员应易于设想多种其它方式和/或结构用于执行本文所述的功能和/或获得本文所述的结果和/或一或多个优点,且所述变化和/或修改的每一者均被认为属于本发明的范畴。更一般说来,所属领域的技术人员应易于了解本文所述的所有参数、尺寸、材料和配置意指例示性的且实际参数、尺寸、材料和/或配置应视特定应用或使用本发明教示的应用而定。仅仅使用常规实验,所属领域的技术人员将想到或能够确定本文所述的本发明的特定实施例的多个等效物。因此,应了解以上实施例仅通过实例来呈现且属于随附权利要求以及其等效物的范畴内,本发明可以不同于特定描述和要求的形式来实施。本发明涉及本文所述的每个个别特征、系统、制品、材料、试剂盒和/或方法。另外,如果所述特征、系统、物品、材料、试剂盒和/或方法相互间无不一致,则两种或两种以上这些特征、系统、物品、材料、试剂盒和/或方法的任何组合均包括于本发明的范畴内。

[2268] 除非明确指出与之相反,否则如本文所用的不定冠词"一(a/an)"在本说明书和权利要求中应理解为意指"至少一"。

[2269] 如本文所用的短语"和/或"在本说明书和权利要求中应理解为意指如此联合的要素的"任一者或两者",即要素在一些情况中联合存在且在其它情况下单独存在。除非明确指出与之相反,否则可任选地存在除由"和/或"项特定标识的要素以外的其它要素,无论与特定标识的要素相关或无关。因此,作为非限制性实例,当与如"包含"的开放式语言

联合使用时，提及“A 和 / 或 B”可在一个实施例中指有 A 无 B（任选地包括除 B 外的要素）；在另一实施例中指有 B 无 A（任选地包括除 A 外的要素）；在又一实施例中指 A 与 B（任选地包括其它要素）；等。

[2270] 如本文在本说明书和权利要求中所用，“或”应理解为具有与如上文所定义的“和 / 或”相同的含义。例如，当清单中分列条目时，“或”或“和 / 或”应解释为包括，即包括诸多要素或要素清单的至少一者，而且包括一者以上且任选地包括另外未列举的条目。除非术语明确指出与的相反，否则如“仅一者”或“就一者”当用于权利要求时，“由……组成”将指包括精确地一种要素或元素清单。一般说来，如本文所用的术语“或”当在排他性术语（如“任一”、“一者”、“仅一者”或“就一者”）之后时，应仅解释为指示排他性替代物（即“一者或另一者而非两者”）。“基本上由……组成”当用于权利要求中时，应具有其如专利法领域中所用的一般含义。

[2271] 如本文在本说明书和权利要求中所用，提及一或多个要素清单的短语“至少一”应理解为意指选自要素清单中任一或多个要素的至少一个要素，但并非必须包括要素清单内特定列举的每个要素中的至少一者且不排除要素清单中要素的任何组合。此定义也允许可任选地存在除短语“至少一”提及的要素清单内特定标识的要素以外的要素，无论与特定标识的要素相关或无关。因此，作为非限制性实例，“A 和 B 中至少一者”（或等效地“A 或 B 中至少一者”或等效地“A 和 / 或 B 中至少一者”）可在一个实施例中指至少一个、任选地包括一个以上 A 而无 B 存在（和任选地包括除 B 外的要素）；在另一实施例中指至少一个、任选地包括一个以上 B 而无 A 存在（和任选地包括除 A 外的要素）；在又一实施例中指至少一个、任选地包括一个以上 A 和至少一个、任选地包括一个以上 B（和任选地包括其它要素）；等。

[2272] 在申请专利范围以及上述说明书中，所有连接词 (transitional phrase)，如“包含”、“包括”、“带有”、“具有”、“含有”、“涉及”、“持有”等理解为开放式，即意指包括（但不限于）。如美国专利局专利审查程序手册章节 2111.03 中所提出，仅连接词“由……组成”和“基本上由……组成”应分别为密闭式或半封闭式连接词。

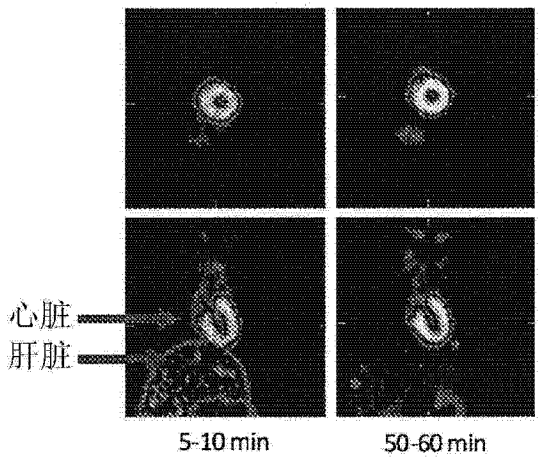

心脏
肝脏
5-10 min
50-60 min
注射后的时间(min)

图 1

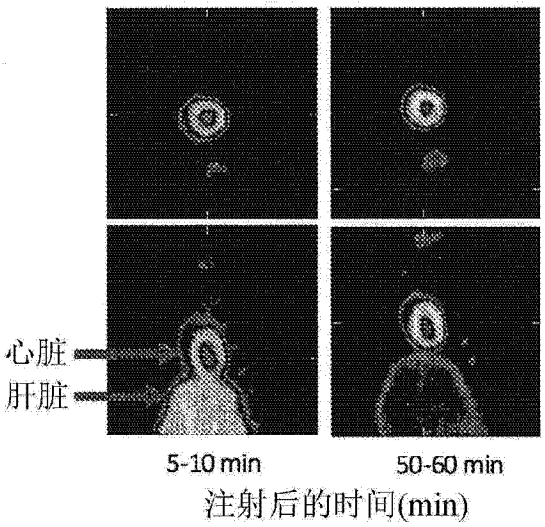

心脏
肝脏
5-10 min
50-60 min
注射后的时间(min)

图 2

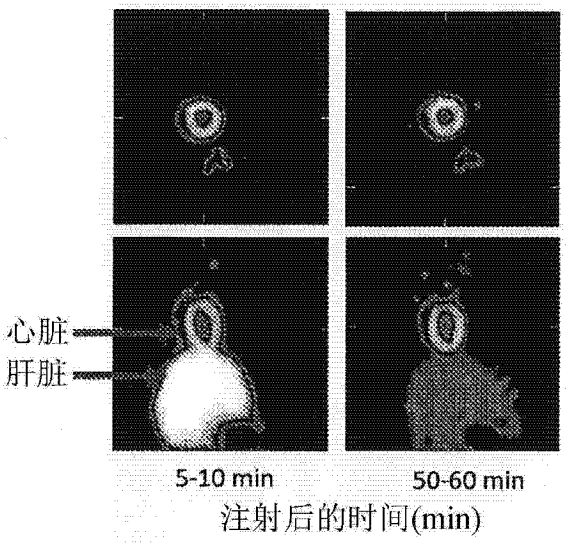

心脏
肝脏
5-10 min
50-60 min
注射后的时间(min)

图 3

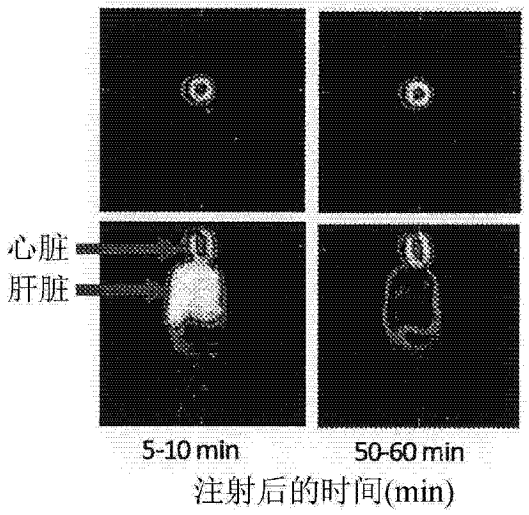

心脏
肝脏
5-10 min
50-60 min
注射后的时间(min)

图 4

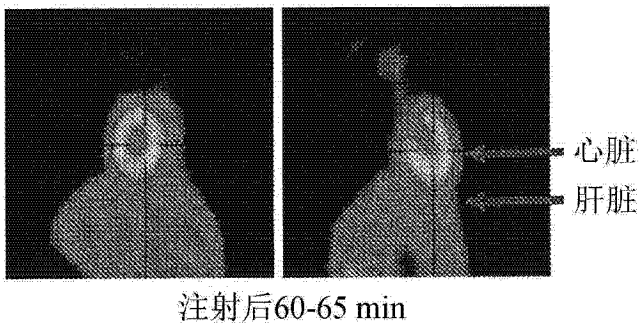

心脏
肝脏
注射后60-65 min

图 5

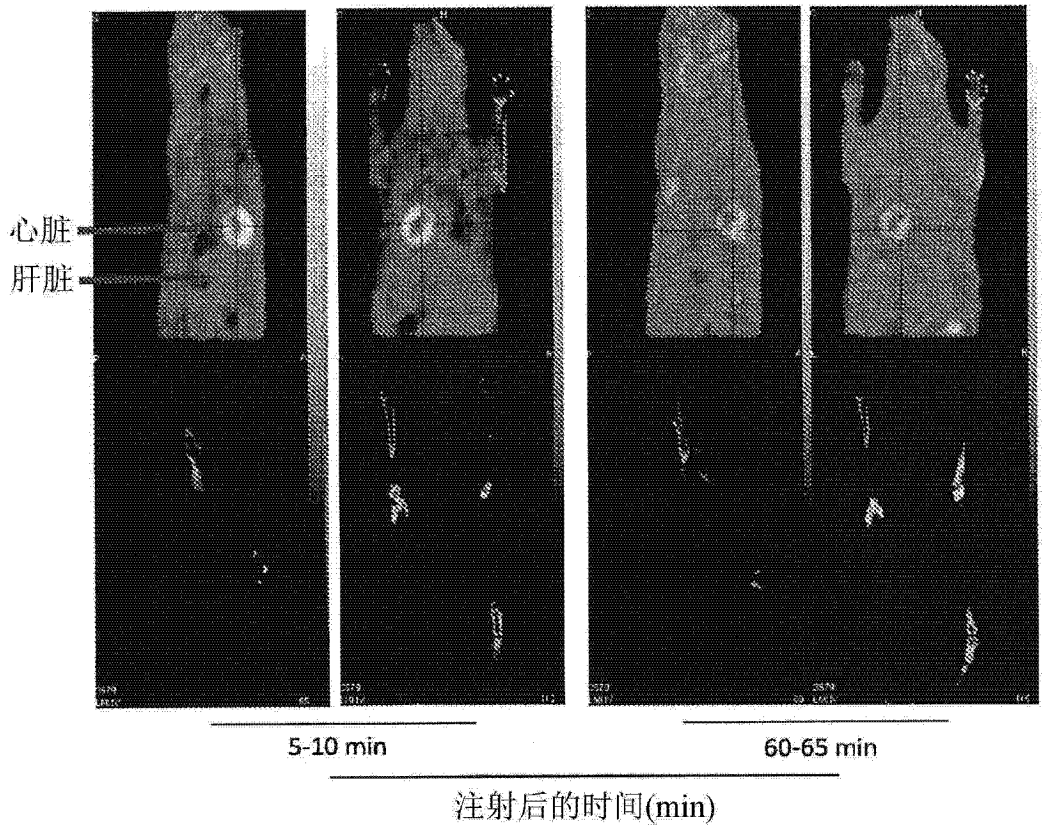

心脏
肝脏
5-10 min
60-65 min
注射后的时间(min)

图 6

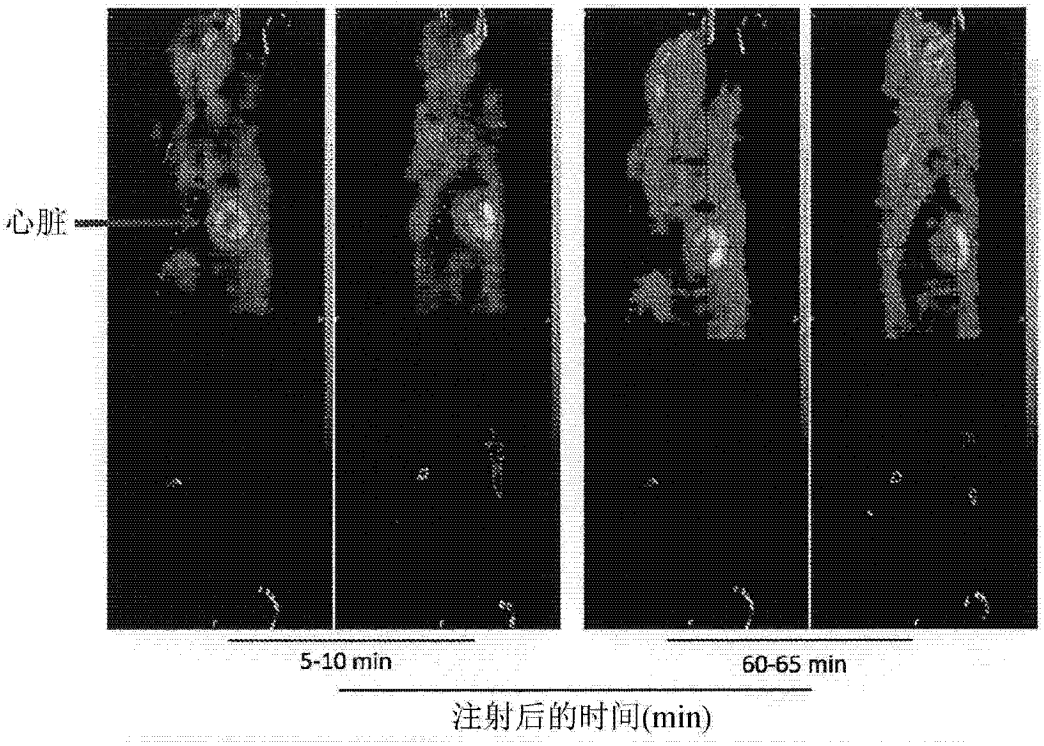

心脏
5-10 min
60-65 min
注射后的时间(min)

图 7

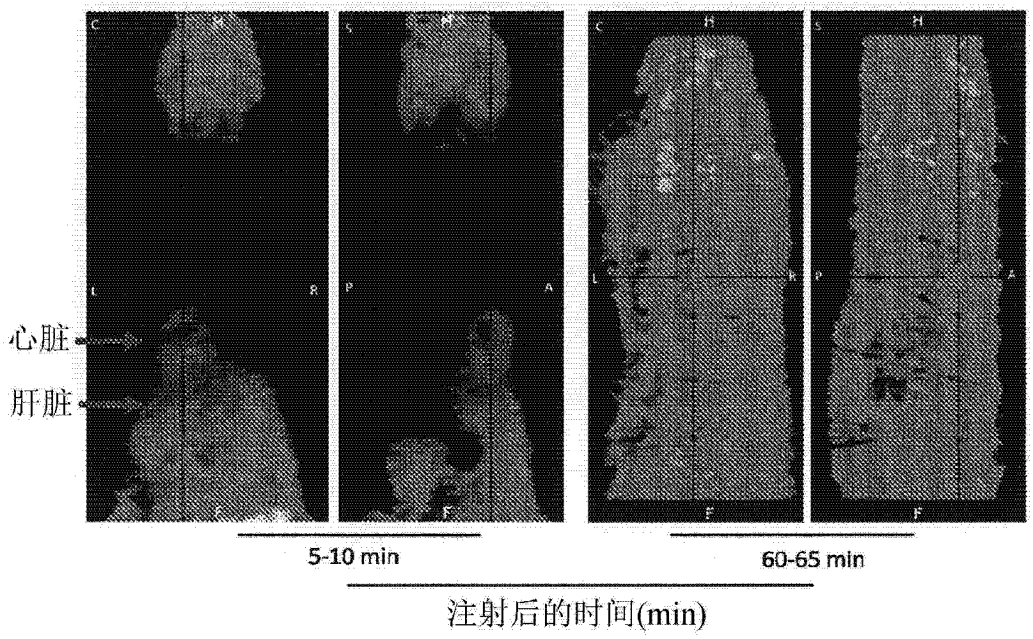

心脏
肝脏
5-10 min
60-65 min
注射后的时间(min)

图 8

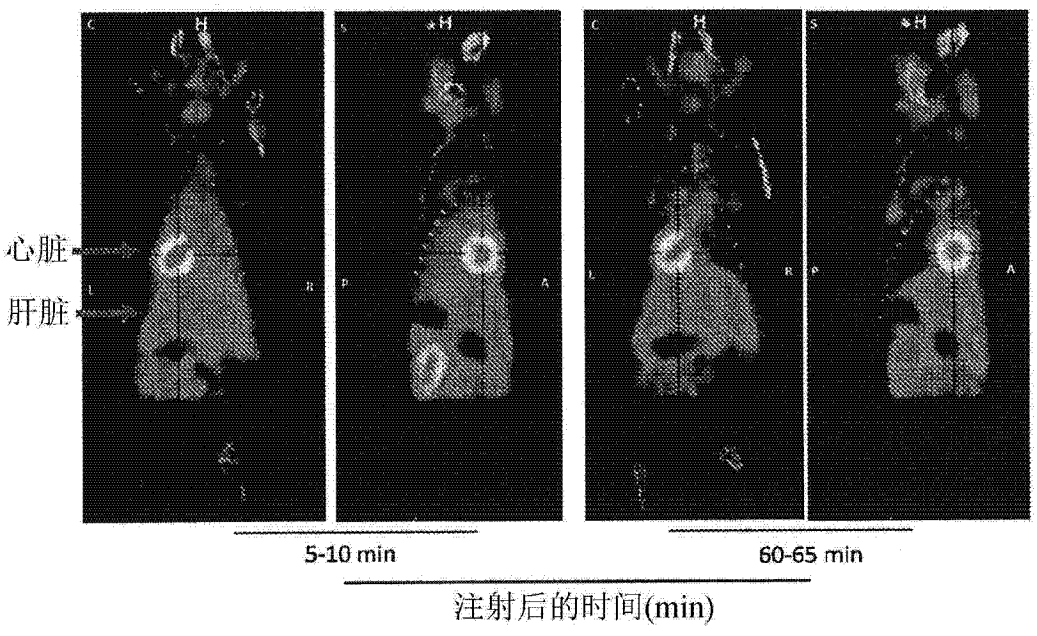

心脏
肝脏
5-10 min
60-65 min
注射后的时间(min)

图 9

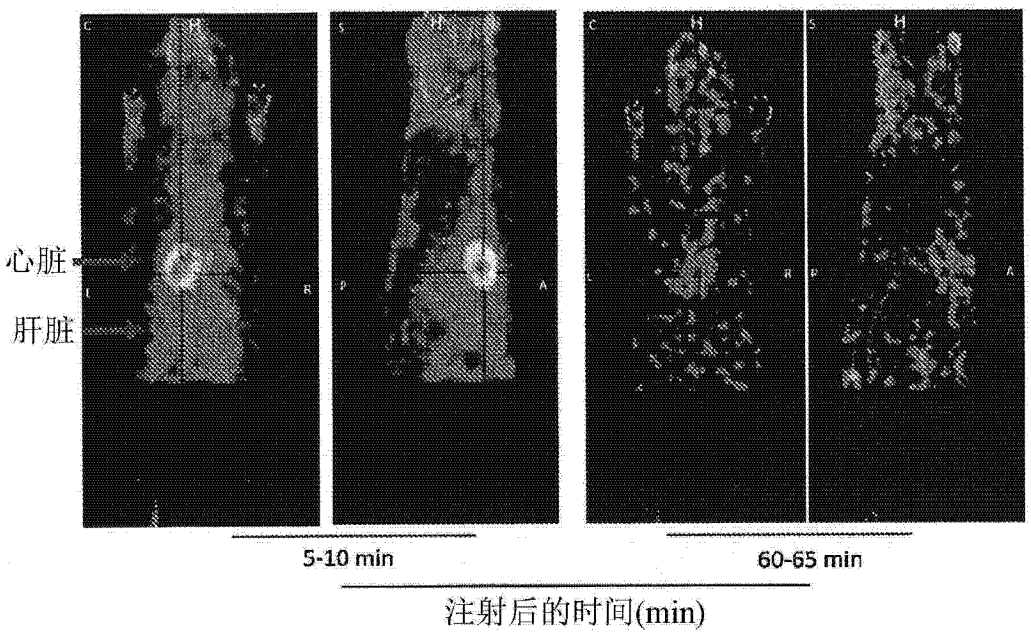

心脏
肝脏
5-10 min
60-65 min
注射后的时间(min)

图 10

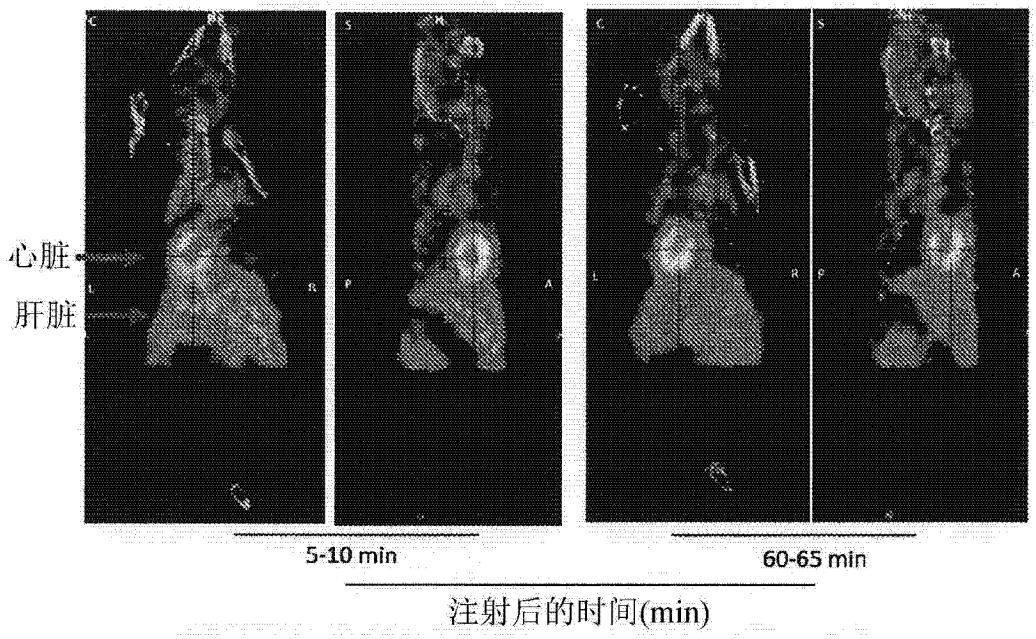

心脏
肝脏
5-10 min
60-65 min
注射后的时间(min)

图 11

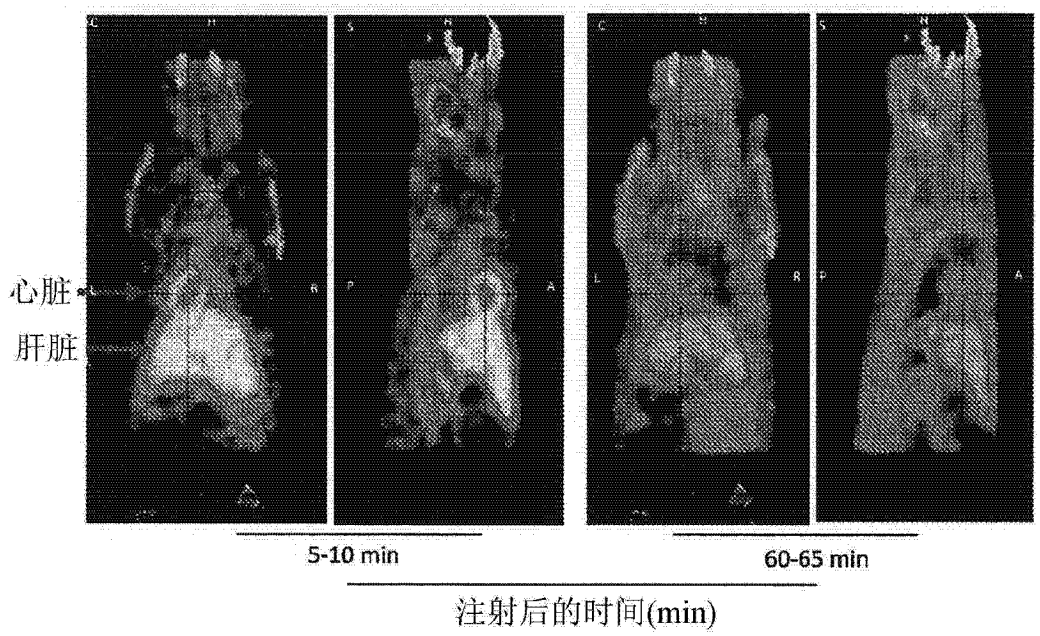

心脏
肝脏
5-10 min
60-65 min
注射后的时间(min)

图 12

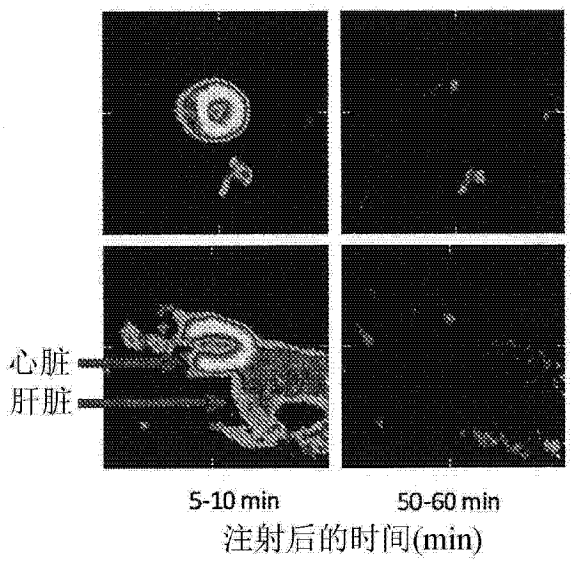

心脏
肝脏
5-10 min
50-60 min
注射后的时间(min)

图 13

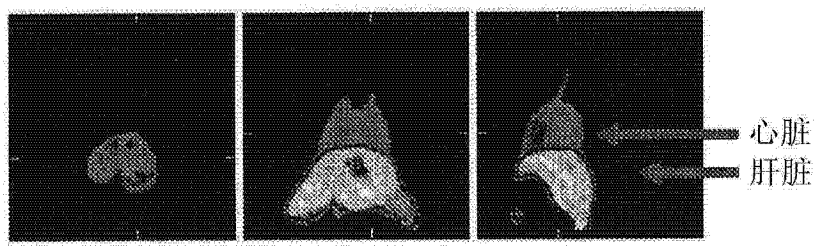


图 14

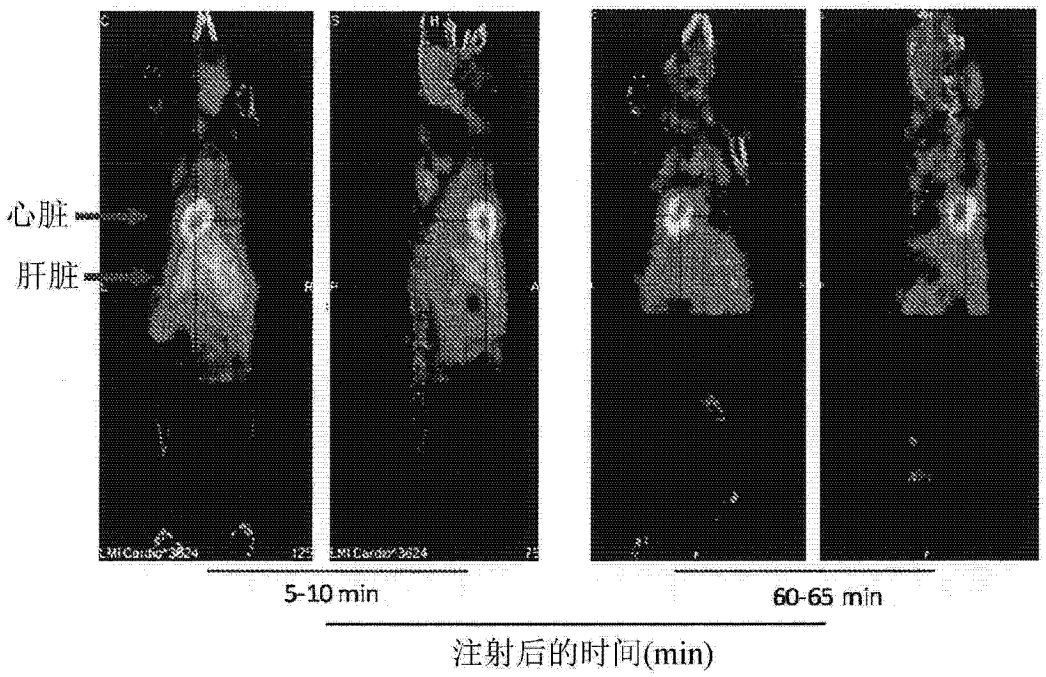


图 15

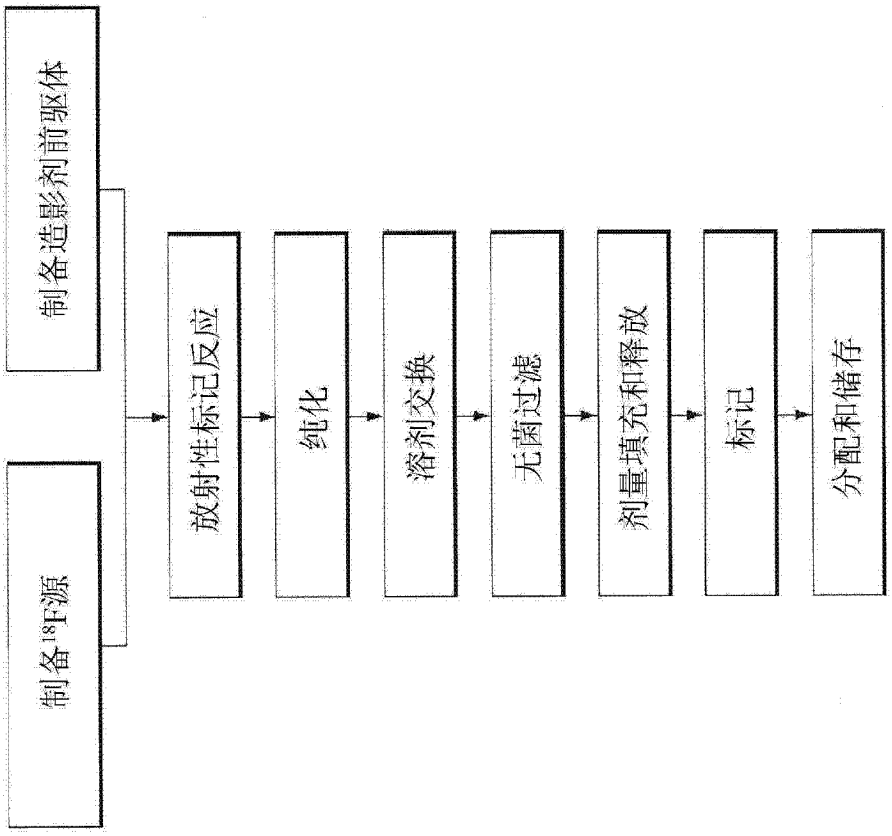
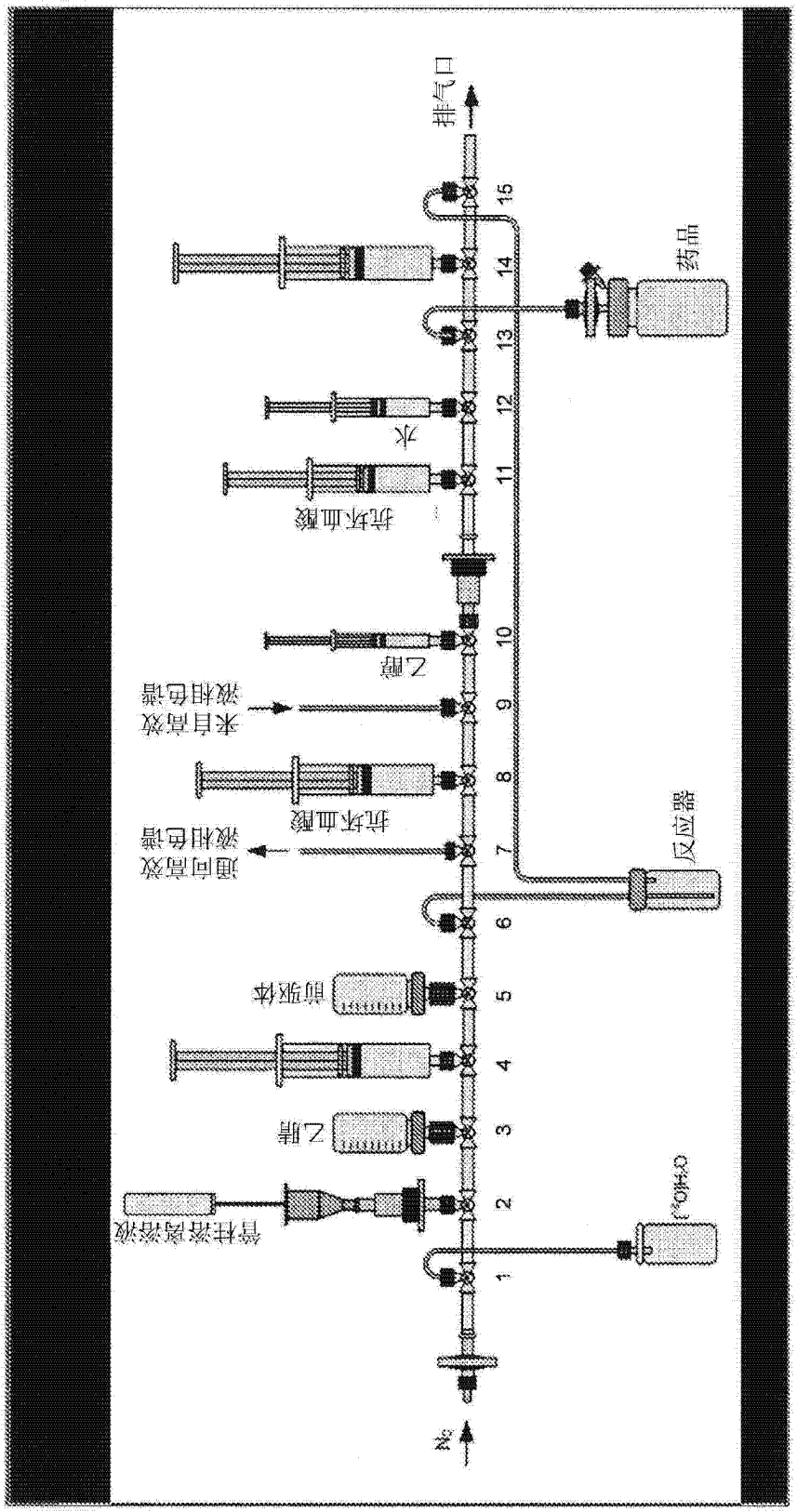


图 16


排气口
药品
水
抗坏血酸
乙醇
来自高效液相色谱
抗坏血酸
通向高效液相色谱
反应器
前驱体
乙腈
管柱溶离溶液
1
2
3
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7
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10
11
12
13
14
15

图 17