CONSTRUCTION AND USE OF REAGENTS FOR CONJUGATION TO BIOLIGANDS FOR IMAGING AND RADIOPHARMACEUTICAL APPLICATIONS

RELATED APPLICATION DATA

The present application claims priority pursuant to Article 8 of the Patent Cooperation Treaty to United States Provisional Patent Application Serial Number 63/561,399 filed March 5, 2024 and United States Provisional Patent Application Serial Number 63/667,212 filed July 3, 2024, each of which is incorporated herein by reference.

FIELD OF INVENTION

The disclosure relates to aromatic electrophilic prosthetic groups for the preparation of theranostic agents. The diagnostic agent of the theranostic pair is radiolabeled with PET or SPECT radioisotopes and the therapeutic agent of the theranostic pair is labeled with alpha- or beta-emitting radioisotopes and are used in the preparation of radiolabeled bioactive ligands for the treatment and/or imaging of cancer.

GOVERNMENTAL SUPPORT

This invention was made with government support under Grant No. EB029451 awarded by National Institutes of Health. The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

Positron emission tomography (PET) is a noninvasive molecular imaging technique which provides real-time biodistribution information. Among various available positron-emitting radionuclides, fluorine-18 has received significant attention in PET imaging research due to its appealing chemical and physical properties, including its small size, strong covalent bonds with carbon, nearly 100% positron efficiency, high molar activity, short half-life to reduce post-procedural radiation exposure and low positron energy resulting in high imaging resolution. However, the development of novel ^{18}F-labeled PET agents has been impeded by the harsh conditions that are typically required for the formation of the C–[18]F bond, necessitating protection of labile functional groups.

To avoid the harsh conditions that are oftentimes adopted in direct radiofluorination reactions, conjugation of bioactive ligands with ^{18}F-labeled prosthetic groups have become an

important strategy to construct novel PET agents under mild conditions when the ligands are structurally sensitive. Prosthetic groups with [18F]fluoroarene motifs are especially appealing due to their stability in physiological environments. However, their preparation can be intricate, often requiring multi-step radiosynthesis with functional group conversions to prevent the decomposition of unprotected reactive prosthetic groups during the harsh radiofluorination.

Chelated aluminum-[18F]fluoride,[1,2] silicon fluoride acceptors (SiFA)[3] and [18F]trifluoroborates[4,5] have been developed as alternatives to direct radiofluorination targets, though the conventional [18F]-fluoroalkyl and ^{18}F-fluoroaryl motifs are still the predominant targets in PET radiochemistry because of their small size and high stability. Thus, it is clear that there is a great unmet need to develop radiolabeling methods for the preparation of ^{18}F-labeled prosthetic groups which are mild, high yielding and can be obtained in a single step.

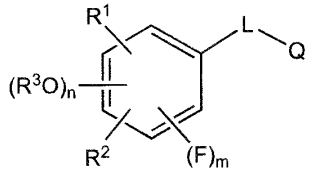
Targeted radiotherapy is an emerging modality for the treatment of otherwise intractable cancers. This modality relies on the incorporation of destructive alpha- or beta-emitting isotopes into small molecules, ligands or biomolecules to target cancer cells selectively for elimination. The proximity of the destructive radioisotope to the cancerous cells results in cell death after decay of the therapeutic radioisotope. A strategy to bring these destructive isotopes in close proximity to cancer cells is to link them to a targeting ligand such as a peptide or biologic, such as an antibody, to produce a cancer-killing warhead with exquisite selectivity for cancerous cells over normal cells. Due to the often-sensitive nature of the targeting ligands, the chemistry to attach the radionuclide payload can present significant stability challenges. Prosthetic groups offer a simple and mild means for the incorporation of alpha- and beta-emitting radioisotopes such as [211]At and ^{131}I, respectively, to furnish [211]At/^{131}I-containing synthons which can be easily conjugated to the targeting ligand of choice.

SUMMARY OF THE INVENTION

Described herein are methods to generate well-matched prosthetic theranostic pairs via the synthesis of electrophilic synthons. For the diagnostic prosthetic groups, a variety of highly reactive ^{18}F-labeled electrophiles is demonstrated via a one-step organophotoredox-mediated radiofluorination. The matched pair therapeutic prosthetic electrophiles often bear [123/131]I or [211]At. Both prosthetic theranostic electrophiles are conjugated under mild conditions to furnish

the active theranostic targeting agents. The method benefits from high step-economy, reaction efficiency, functional group tolerance and accessible precursors. The obtained prosthetic groups can be applied to PET/SPECT and/or alpha- or beta-therapeutic agent constructions for imaging or therapeutic applications.

Specifically, the current disclosure is directed towards developing innovative imaging and therapeutic agents for the management of cancers by employing the radioligands disclosed herein. Specifically, the disclosure is directed to 1) highly innovative photoredox methods (*used to generate radiofluorinated aromatic electrophilic prosthetic groups*), which not only allows for easy conversion of peptide-based drug molecules and/or bioactive ligands to PET/SPECT agents, but can also be used to produce established peptide-based agents on a large scale that were previously complicated to synthesize. The recent development of S_NAr radiofluorination allows precise control of the labeling position. Unlike traditional labeling reactions, the disclosed photoredox system features mild labeling conditions, and is a metal-free catalyst system. This method provides easy access to unique prosthetic groups, which can be coupled to peptide-based drug molecules and other bioactive ligands for PET imaging; 2) developing theranostic agents. The disclosed methods allow for the generation of halogenated reagents for labeling of bioactive ligands that can be used for cancer prognosis (based on ^{18}F) and radionuclide-based therapy (based primarily on ^{131}I and [211]At), all of which can impact the care of cancer patients. As such, one aspect, the prosthetic groups disclosed herein comprise a compound of Formula (I):



Formula (I)

wherein R^1 is H, I, Br, Cl, F or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

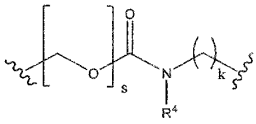
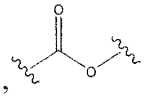
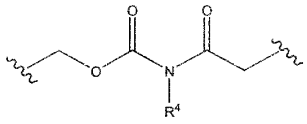
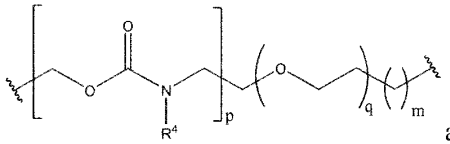
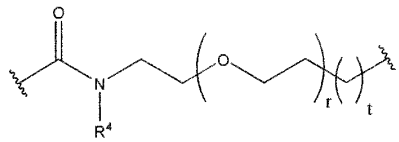
R^2 is H, F, I, Br, Cl, F or radioisotope ^{18}F;

R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

m is 0, 1, 2 or 3;

n is 0, 1 or 2;

L is selected from the group consisting of a bond, -(C_1-C_6) alkyl,





and

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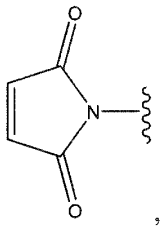
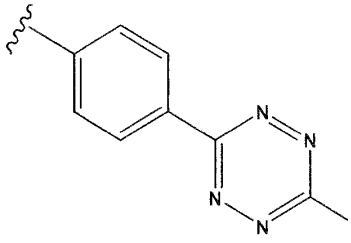
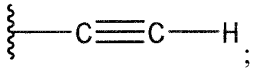
wherein k, s, m, p, q, r and t, in each instance, are integers independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;

Q is selected from the group consisting of halogen, sulfonate, phosphonate, succinimide, -NCO, -NC, -N_3, -NR^4R^5, -PG, OR^5, , norbornene, trans-cyclooctene, 
and ;

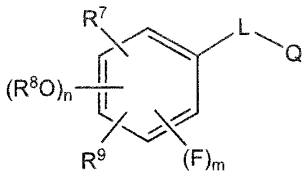
R^4 and R^5 are independently selected from -H, -PG, and –(C_1-C_6) alkyl, wherein -PG is a protecting group;

R^6 is -H, (C_1-C_4) alkyl, aryl, or heteroaryl; and

any stereoisomer and/or salt thereof.

Another aspect disclosed herein is directed toward methods for the preparation of compounds of Formula (I), wherein R^1 is a radioisotope R* selected from the group consisting of ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, [211]At, [76]Br, [77]Br and [82]Br, the method comprising

(a) obtaining a starting material of Formula (I-A):



Formula (I-A)

wherein R^7 is -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -B(OH)$_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)3, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

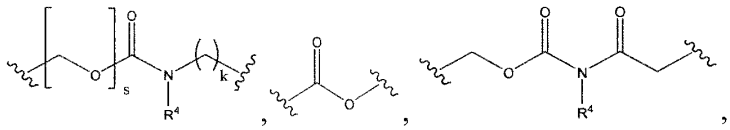
R^9 is H, F, I, Br, Cl, F or radioisotope ^{18}F;

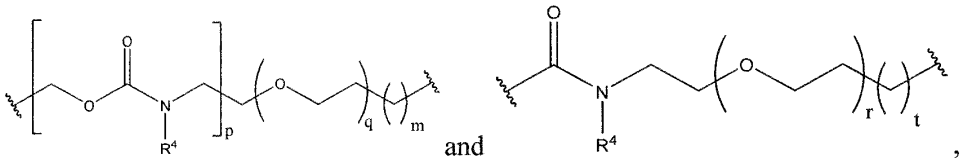
R^8 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

m is 0, 1, 2 or 3;

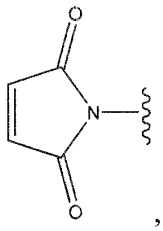
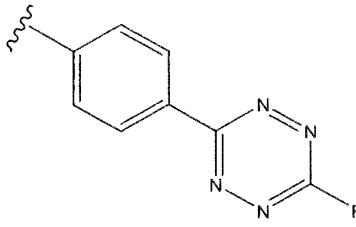
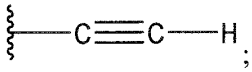
n is 0, 1 or 2;

L is selected from the group consisting of a bond, -(C_1-C_6) alkyl,





wherein k, s, m, p, q, r and t, in each instance, are integers independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;

Q is selected from the group consisting of halogen, sulfonate, phosphonate, succinimide, -NCO, -NC, $-N_3$, $-NR^4R^5$, -PG, OR^5, , norbornene, trans-cyclooctene,  and ;

R^4 and R^5 are independently selected from H, -PG, and $-(C_1\text{-}C_6)$ alkyl, wherein -PG is a protecting group;

R^6 is H, $(C_1\text{-}C_4)$ alkyl, aryl, or heteroaryl; and

any stereoisomer and/or salt thereof; and

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render a compound of Formula (I), wherein R^1 is a radioisotope R* selected from the group consisting of ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, [211]At, [76]Br, [77]Br and [82]Br.

Another aspect disclosed herein is a method of imaging a subject for diagnosing a disease or assessing efficacy of a treatment, the method comprising:

(a) administering to the subject in need thereof an effective amount of a labeled bioactive ligand, wherein the bioactive ligand contains a radioisotope; and

(b) acquiring at least one image of at least one portion of the subject.

Another aspect disclosed herein is a method of treating a subject in need thereof, the method comprising administering to the patient in need thereof a labeled bioactive ligand as disclosed herein.

Another aspect of the disclosure is directed to a pharmaceutical composition comprising a labeled bioactive ligand as disclosed herein or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carrier(s).

Another aspect disclosed herein is a method for treating cancer and/or a hyperproliferative disorder, the method comprising administering to a subject in need thereof a therapeutically effective amount of a labeled bioactive ligand, prodrug, or a pharmaceutical composition as disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows that the functional group tolerant organophotoredox-catalyzed radiofluorination enables one-step radiosynthesis of prosthetic groups with [18F]fluoroaryl motif.

FIG. 2 shows reaction schemes of PET agent constructions utilizing [18F]SFB analog 2c, [18F]FBB analog 2d and isocyanate synthon 2h. [a]PSMA, DIPEA, MeCN, DMF, 60 °C. [b]FAPI, DIPEA, MeCN, 60 °C. [c]NT20.3, MeCN, water, 60 °C. [d]PSMA, MeCN, water, DMF, Na_2CO_3, 70 °C. [e]PSMA, MeCN, DIPEA, DMF, Na_2CO_3, 70 °C. [f]PSMA, MeCN, water, Na_2CO_3, 70 °C. [g]Estimated RCY of 3f was calculated based on the isolated RCY of 3e and the radio-HPLC peak integration ratio between 3e and 3f.

FIG. 3 shows the organ uptake of PET tracer **3a in** PC3-PSMA tumor bearing mice.

FIG. 4 shows PET/CT imaging of PC3-PSMA tumor bearing mice with PET tracer **3a.**

FIG. 5 shows reaction schemes of the three different disclosed radiofluorination methods A–C employed for the preparation of ^{18}F radiolabeled compounds disclosed herein.

FIG. 6 shows a graphical representation of radio-HPLC purification by HPLC condition **1** of 2,5-dioxopyrrolidin-1-yl 3-fluoro-5-(fluoro-^{18}F)-2-iodo-6-methoxybenzoate.

FIG. 7 shows a graphical representation of quality control analysis of 2,5-dioxopyrrolidin-1-yl 3-fluoro-5-(fluoro-^{18}F)-2-iodo-6-methoxybenzoate by HPLC condition **2**.

FIG. 8 shows a graphical representation of ^{19}F-standard (2,5-dioxopyrrolidin-1-yl 3,5-difluoro-2-iodo-6-methoxybenzoate) analysis by HPLC condition **2**.

FIG. 9 shows a graphical representation of radio-HPLC purification by HPLC condition **2** of (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3-fluoro-5-(fluoro-^{18}F)-2-iodo-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid.

FIG. 10 shows a graphical representation of quality control analysis of (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3-fluoro-5-(fluoro-^{18}F)-2-iodo-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid by HPLC condition **2**.

FIG. 11 shows an imaging analysis using F-18 imaging for biodistribution for (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3-fluoro-5-(fluoro-^{18}F)-2-iodo-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid. The dose was 110 uCi per mouse, with a PC3-PIP tumor model.

FIG. 12 shows a graphical analysis of (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3,5-difluoro-2-iodo-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid by HPLC condition **2**.

FIG. 13 shows a graphical representation of radio-HPLC purification by HPLC condition **3** of 3,5-difluoro-2-(iodo-^{131}I)-6-methoxybenzoic acid.

FIG. 14 shows a graphical representation of quality control analysis of 3,5-difluoro-2-(iodo-^{131}I)-6-methoxybenzoic acid by HPLC condition **4**.

FIG. 15 shows a graphical representation of an ^{127}I standard (3,5-difluoro-2-iodo-6-methoxybenzoic acid) analysis by HPLC condition **4**.

FIG. 16 shows a graphical representation of radio-HPLC purification by HPLC condition **4** of 2,5-dioxopyrrolidin-1-yl 3,5-difluoro-2-(iodo-^{131}I)-6-methoxybenzoate.

FIG. 17 shows a graphical representation of an ^{127}I-standard (2,5-dioxopyrrolidin-1-yl 3,5-difluoro-2-iodo-6-methoxybenzoate) analysis by HPLC condition **4**.

FIG. 18 shows a graphical representation of radio-HPLC purification by HPLC condition **4** (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3,5-difluoro-2-(iodo-^{131}I)-6-

methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid.

FIG. 19 shows a graphical representation of quality control analysis of (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3,5-difluoro-2-(iodo-^{131}I)-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid by HPLC condition **4**.

FIG. 20 shows a graphical representation of an ^{127}I-standard ((((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3,5-difluoro-2-iodo-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid) analysis by HPLC condition **4.**

DETAILED DESCRIPTION

The presently disclosed subject matter will now be described more fully hereinafter. However, many modifications and other embodiments of the presently disclosed subject matter set forth herein will come to mind to one skilled in the art to which the presently disclosed subject matter pertains to having the benefit of the teachings presented in the foregoing descriptions. Therefore, it is to be understood that the presently disclosed subject matter is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims. In other words, the subject matter described herein covers all alternatives, modifications, and equivalents. In the event that one or more of the incorporated literature, patents, and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in this field. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

Furthermore, any Formulae described below, including their substituents, are meant to be read from "left to right" as would be recognized by any skilled person in the art. For example, for a Formula A-B-C, wherein C can be a substituent -D-E-, the Formula encompasses species A-B-D-E not A-B-E-D.

As already mentioned above, the development of novel ^{18}F-labeled PET agents has been impeded by the harsh conditions that are typically required for the formation of the C–[18]F bond, necessitating protection of labile functional groups. To avoid these harsh C–[18]F bond formation conditions, small molecule PET agents are usually radiofluorinated in a protected form and deprotected thereafter. In particular, conjugation with ^{18}F-labeled prosthetic groups is one of the most important strategies in constructing PET agents with structurally complicated and labile ligands.

Prosthetic groups are small organic molecules that contain both ^{18}F and a highly reactive functional group that can be coupled to bioactive ligands efficiently. The ideal prosthetic group should present both high reactivity on its coupling site, and high stability on other parts of the molecule, especially the C–[18]F bond. Prosthetic groups with [18F]fluoroaryl[6,7] and [18F]fluoroalkyl motifs[8] are common substructures in novel PET agents, and can greatly affect the biodistribution properties of the bioactive ligands. The utility of ^{18}F-labeled alkyl fluoride substructures has been demonstrated in many FDA-approved PET agents,[9] as well as countless probes under investigation in biomedical studies. However, the stability of alkyl fluorides can be compromised in physiological environments by both substitution reactions with biological nucleophiles, as well as many enzymatic metabolic pathways.[10-14] These facile *in vivo* defluorination processes are oftentimes responsible for high bone uptake in the subsequent PET imaging studies. Therefore, radiofluorinated arenes with higher *in vivo* stabilities are appealing substructures in the design of new PET agents.

To incorporate such motifs, both electrophilic fluorination and nucleophilic aromatic substitution (S_NAr) radiofluorination methods have been developed, offering a variety of choices for radiochemists.[15,16] Electrophilic radiofluorinations can utilize organotin,[17,18] organosilicon,[19-21] organomercury,[22-25] organoboron[26] and organogermanium precursors[27]. Balz-Schiemann and Wallach reactions with diazonium precursors/intermediates,[28-31] and direct S_NAr with nitro,[32] ammonium[33], halogen[34], sulfonium[35-38] and iodonium[39] leaving groups have been applied for decades. Transition metal-catalyzed reactions,[40-49] oxidative fluorinations,[50, 51] C—H functionalization,[52-54] and deoxyfluorination of phenols[55, 56] have also been reported. These established methods supported the radiosynthesis of ^{18}F-labeled aryl fluoride motifs and the related PET agents. However, limitations of these methods are widely acknowledged either in the

efficiency, feasibility, residue metal toxicity concerns, or functional group tolerance. As a result, multistep ^{18}F-radiosynthesis is usually employed, where the functional group constructions are carried out after the radiofluorination of arenes. The prolonged total synthesis time reduces the efficiency due to rapid decay loss of fluorine-18 and hinders the implementation of radiofluorinated arene motifs in new PET agent development. New radiofluorination methods with higher efficiency, step-economy, and functional group tolerance are still in high demand.

As disclosed herein, organophotoredox-catalyzed cation radical accelerated S_NAr reactions have demonstrated broad applications in the functionalization of arenes.[57-65] Featuring mild conditions and highly reactive intermediates, this method allows for the efficient conversion of arenes while offering high functional group tolerance. This method can be applied to radiochemistry, affording direct C—H radiofluorination,[66,67] (pseudo) halide interconversion radiofluorination[68] and deoxyfluorination[69] in addition to a series of radiocyanation reactions.[70, 71] Several PET imaging agents including [18F]fenoprofen[66] and ^{18}F-DOPA[68] have been prepared using this method. However, the efficient synthesis of ^{18}F-labeled prosthetic groups has not yet benefited from these methods. Despite the robust reactivity in conjugations, many coupling functionalities in prosthetic groups are electron deficient, making them inert under the photoredox conditions disclosed herein due to their high oxidation potential. Taking advantage of this, the organophotoredox-mediated method disclosed herein can be used in a one-step radiosynthesis of prosthetic groups with robust functionalities.

Disclosed herein is the utilization of organophotoredox-catalyzed deoxyradiofluorination in the efficient and step-economic preparation of prosthetic groups with an [18F]fluoroaryl motif, including a one-step metal-free preparation of [18F]fluorobenzyl bromide analog, [18F]*N*-succinimidylfluorobenzoate analog, and the preparation of an ^{18}F-labeled aryl fluoride isocyanate synthon and a radiofluorinated isocyanide synthon. In addition, examples of PET agent constructions with some of these synthons and provided guidelines on the coupling procedures are disclosed herein. The improved efficiency in the preparation of these synthons will promote the development of new PET agents, reduce cost and facilitate the use of PET imaging for a range of applications.

Targeted radiotherapy (TRT) is a promising modality for the treatment of various cancers via the incorporation of either alpha- or beta-emitting radioisotopes on targeting moieties such as

peptides and small biomolecules. Halogen-based alpha- or beta-emitting radionuclides such as ^{131}I or [211]At have shown preliminary promise as TRT agents given their properties (e.g. ideal half-life, ease of production, readily available precursors, etc.) and their ready incorporation into organic molecules. When paired with a structurally related diagnostic PET agent, a true theranostic pair can be generated to both diagnose and treat otherwise intractable forms of cancer. Despite the promise of ^{131}I and [211]At, few truly structurally matched theranostic agents have been prepared and evaluated in the context of cancer treatments. Herein, we describe the development of new TRT agents based on ^{131}I and [211]At with companion ^{18}F diagnostic agents to form true theranostic pairs. Specifically, this invention describes the synthesis of TRT agents nearly identically matched with a companion PET diagnostic.

I. Definitions

As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an alkyl group" or "a phenyl" includes mixtures of two or more such alkyl groups or phenyls.

Ranges can be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that each unit between two particular units is also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed. Further, unless specified by the term "integer," the number specified includes fractions or numbers with decimals. For example, the range of "from about 1 to about 5" includes numbers such as 1, 1.1, 1.5, 2.0, 2.2, and so on. As used herein, the term "integer" refers to a number that is a whole number, and not a fraction.

References in the specification and concluding claims to parts by weight of a particular element or component in a composition denote the weight relationship between the element or component and any other elements or components in the composition or article for which a part by weight is expressed. Thus, in a compound containing 2 parts by weight of component X and 5 parts by weight component Y, X and Y are present at a weight ratio of 2:5 and are present in such ratio regardless of whether additional components are contained in the compositions.

Throughout this specification and the claims, the words "comprise," "comprises," and "comprising" are used in a non-exclusive sense, except where the context requires otherwise. It is understood that embodiments described herein include "consisting of" and/or "consisting essentially of" embodiments.

As used herein, the term "alkyl group" refers to a saturated hydrocarbon radical containing 1 to 8, 1 to 6, 1 to 4, or 5 to 8 carbons. In some embodiments, the saturated radical contains more than 8 carbons. An alkyl group is structurally similar to a noncyclic alkane compound modified by the removal of one hydrogen from the noncyclic alkane and the substitution therefore of a non-hydrogen group or radical. Alkyl group radicals can be branched or unbranched. Lower alkyl group radicals have 1 to 4 carbon atoms. Higher alkyl group radicals have 5 to 8 carbon atoms. Examples of alkyl, lower alkyl, and higher alkyl group radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, amyl, t-amyl, n-pentyl, n-hexyl, i-octyl and like radicals.

As used therein, the term "PG" stands for protecting group, which is a functionality that is designed to protect amines, hydroxyl, phenoxyl and/or acids from certain reaction conditions. A skilled artisan would generally be familiar with this methodology and would consider "Greene's Protective Groups in Organic Synthesis" by Peter G. M. Wuts, Theodora W. Greene, First published:10 April 2006, John Wiley & Sons, Inc.

The term "aryl" refers to a hydrocarbon monocyclic, bicyclic or tricyclic aromatic ring system. Aryl groups may be optionally substituted with one or more substituents. In one embodiment, 0, 1, 2, 3, 4, 5 or 6 atoms of each ring of an aryl group may be substituted by a substituent. Examples of aryl groups include phenyl, naphthyl, anthracenyl, fluorenyl, indenyl,

azulenyl, and the like. Examples of substituents include, but are not limited to halogens (e.g., -Cl), acids, nitriles, esters, amides, NO_2, etc.

The term "cycloalkyl" refers to a hydrocarbon with 3-8 members or 3-7 members or 3-6 members or 3-5 members or 3-4 members and can be monocyclic or bicyclic. The ring may be saturated or may have some degree of unsaturation. In some cases, the degree of saturation encompasses aromatic compounds. Cycloalkyl groups may be optionally substituted with one or more substituents. In one embodiment, 0, 1, 2, 3, or 4 atoms of each ring of a cycloalkyl group may be substituted by a substituent. Representative examples of cycloalkyl group include cyclopropyl, cyclopentyl, cyclohexyl, cyclobutyl, cycloheptyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, phenyl, and the like.

As used herein, the terms "halo," "halogen," and "halide" refer to any suitable halogen, including -F, -Cl, -Br, -I and -At.

As used herein, the term "ester", used alone or as part of another group, refers to a -C(O)OR radical, where R is any suitable substituent such as alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

As used herein, the term "amide", used alone or as part of another group, refers to a -$C(O)NR^aR^b$ radical, where R^a and R^b are any suitable substituent such as alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

As used herein, the terms "increase," "increases," "increased," "increasing", "improve," "enhance," and similar terms indicate an elevation in the specified parameter of at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 150%, 200%, 300%, 400%, 500%, or more.

As used herein, the terms "reduce," "reduces," "reduced," "reduction," "inhibit," and similar terms refer to a decrease in the specified parameter of at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 100%.

As used herein, the "contacting" refers to reagents in close proximity so that a reaction may occur.

As used herein, the term "stereoisomer" refers to compounds which have identical chemical constitution, but differ with regards to the arrangement of the atoms or groups in space. These "stereoisomers" have a "stereogenic center" which may be a chiral center.

As used herein, the term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

As used herein, the term "diastereomers" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g., melting points, boiling points, spectral properties, and reactivity. Mixtures of diastereomers may separate under high-resolution analytical procedures such as electrophoresis and chromatography.

As used herein, the term "enantiomers" refers *to* two stereoisomers of a compound which are non-superimposable mirror images of one another. Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wiley, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. The compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including, but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Mixtures of stereoisomers may separate under high-resolution analytical procedures such as electrophoresis, chiral salt formation and chromatography.

As used herein, the term "theranostic agent" refers to compounds that are able to detect as well as treat a disease or condition (therapeutic and diagnostic). For example, the compounds disclosed herein can contain two different halogens, such as a fluorine atom, an iodine atom and an astatine atom. A theranostic agent may be one compound labeled with ^{18}F used for imaging and another theranostic agent may be labeled with ^{131}I or [211]At for treatment. Both theranostic agents maintain the same atom connectivity regardless of the radioisotope and are referred to as a "theranostic pair".

As used herein, the term "subject" broadly refers to any animal, including but not limited to, human and non-human animals (e.g., mice, rats, dogs, pigs, cats, cows, horses, sheep, poultry, fish, crustaceans, etc.). As used herein, the term "patient" typically refers to a subject that is being treated for a disease or condition.

As used herein, the term "effective amount" refers to the amount of a composition sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route.

As used herein, the terms "administration" and "administering" refer to the act of giving a drug, prodrug, or other agent, or therapeutic treatment to a subject or in vivo, in vitro, or ex vivo cells, tissues, and organs. Exemplary routes of administration to the human body can be through space under the arachnoid membrane of the brain or spinal cord (intrathecal), the eyes (ophthalmic), mouth (oral), skin (topical or transdermal), nose (nasal), lungs (inhalant), oral mucosa (buccal), ear, rectal, vaginal, by injection (e.g., intravenously, subcutaneously, intratumorally, intraperitoneally, etc.) and the like.

As used herein, the terms "co-administration" and "co-administering" refer to the administration of at least two agent(s) (e.g., cell cycle checkpoint inhibitor and one or more additional therapeutics) or therapies to a subject. In some embodiments, the co-administration of two or more agents or therapies is concurrent. In other embodiments, a first agent/therapy is administered prior to a second agent/therapy. Those of skill in the art understand that the formulations and/or routes of administration of the various agents or therapies used may vary. The appropriate dosage for co-administration can be readily determined by one skilled in the art. In some embodiments, when agents or therapies are co-administered, the respective agents or therapies are administered at lower dosages than appropriate for their administration alone. Thus, co-administration is especially desirable in embodiments where the co-administration of the agents or therapies lowers the requisite dosage of a potentially harmful (e.g., toxic) agent(s), and/or when co-administration of two or more agents results in sensitization of a subject to beneficial effects of one of the agents via co-administration of the other agent.

As used herein, the term "pharmaceutical composition or formulation" refers to the combination of an active agent with a carrier, inert or active, making the composition or formulation especially suitable for diagnostic or therapeutic use in vitro, in vivo or ex vivo.

The terms "pharmaceutically acceptable" or "pharmacologically acceptable," as used herein, refer to compositions that do not substantially produce adverse reactions, e.g., toxic, allergic, or immunological reactions, when administered to a subject.

"Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers that are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Non-limiting examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, dextrin or cyclodextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium, potassium, calcium, and magnesium; and/or nonionic surfactants such as TWEEN™, polyethylene glycol (PEG), and PLURONICS™. In certain embodiments, the pharmaceutically acceptable carrier is a non-naturally occurring pharmaceutically acceptable carrier.

As used herein, the term "pharmaceutically acceptable salt" refers to any pharmaceutically acceptable salt (e.g., acid or base) of a compound of the present invention which, upon administration to a subject, is capable of providing a compound of this invention or an active metabolite or residue thereof. As is known to those of skill in the art, "salts" of the compounds of the present invention may be derived from inorganic or organic acids and bases. Examples of acids include, but are not limited to, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic acid, and the like. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition

salts.

As used herein, the term "inhibit", "inhibition" or "inhibiting" refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term "treat", "treating" or "treatment" of any disease or disorder refers to alleviating or ameliorating the disease or disorder (i.e., slowing or arresting the development of the disease or at least one of the clinical symptoms thereof); or alleviating or ameliorating at least one physical parameter of biomarker associated with the disease or disorder, including those which may not be discernible to the patient.

As used herein, the term "prevent", "preventing" or "prevention" of any disease or disorder refers to the prophylactic treatment of the disease or disorder; or delaying the onset or progression of the disease or disorder.

As used herein, a subject is "in need of a treatment" if such a subject would benefit biologically, medically or in quality of life from such treatment.

As used herein, the term "a therapeutically effective amount" of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, reduction in tumor volume, or ameliorate symptoms, alleviate condition, slow or delay disease progression or prevent a disease, etc.

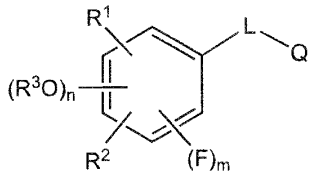
As used herein, the term "anticancer agent" or antineoplastic agent, refers to a therapeutic agent that is useful for treating or controlling the growth of cancerous cells.

II. Compounds

A. Radiolabeled Prosthetic Groups

Provided herein are prosthetic groups that are small organic molecules that contain both a radioactive atom and a reactive functional group that can be coupled to bioactive ligands. Such reactive functional groups generally comprise functional groups which allow coupling to bioactive ligands under mild conditions. A skilled artisan would generally be familiar with the functional groups that could be employed for such coupling conditions.

In one aspect, the prosthetic groups disclosed herein comprise a compound of Formula (I):



Formula (I)

wherein R^1 is H, I, Br, Cl, F or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

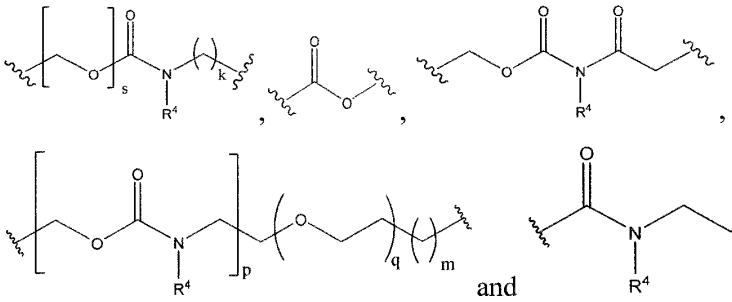
R^2 is H, F, I, Br, Cl, F or radioisotope ^{18}F;

R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

m is 0, 1, 2 or 3;

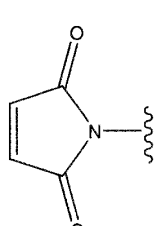
n is 0, 1 or 2;

L is selected from the group consisting of a bond, -(C_1-C_6) alkyl,



wherein k, s, m, p, q, r and t, in each instance, are integers independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;

Q is selected from the group consisting of halogen, sulfonate, phosphonate, succinimide, -NCO, -NC, -N_3, -NR^4R^5, -PG, OR^5,



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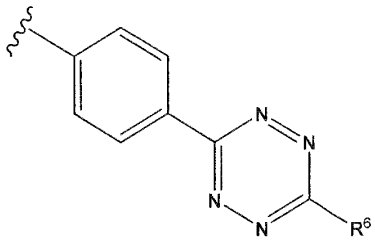
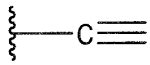


and

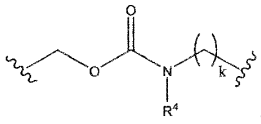
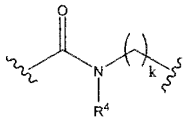


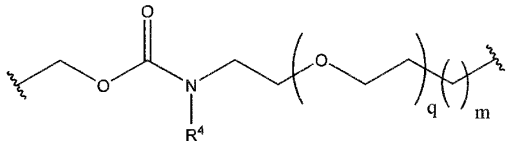
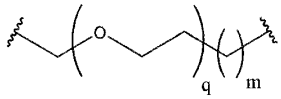
;

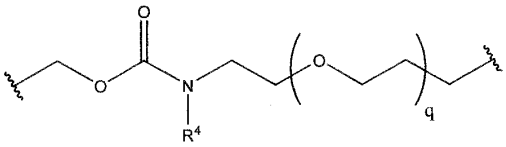
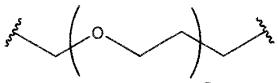
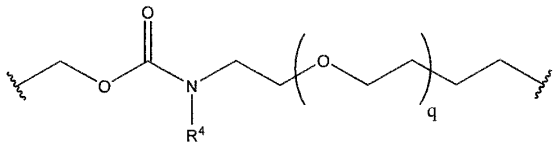
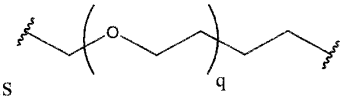
R^4 and R^5 are independently selected from -H, -PG, and –(C_1-C_6) alkyl, wherein -PG is a protecting group;

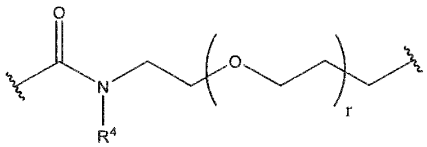
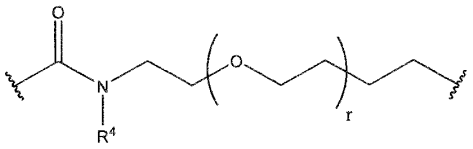
R^6 is -H, (C_1-C_4) alkyl, aryl, or heteroaryl; and

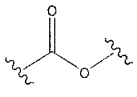
any stereoisomer and/or salt thereof.

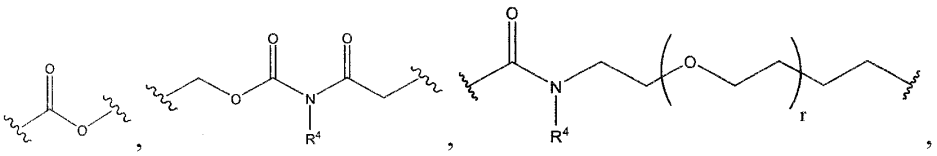
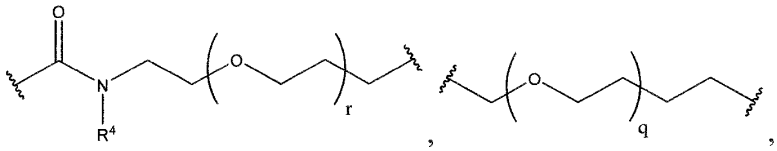
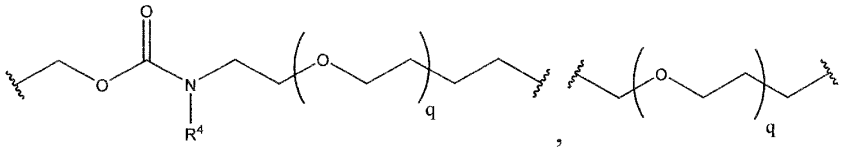
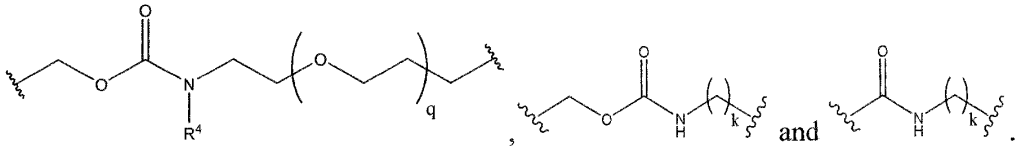
In some embodiments, s is 0 or 1. In some embodiments, s is 1. In some embodiments, L is  . In some embodiments, L is  . In such embodiments, k is an integer from 2-6. In such embodiments, R^4 is -H, -CH_3, or -PG.

In some embodiments, p is 0 or 1. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, L is  . In some embodiments, L is  . In such embodiments, m is 1 or 2.

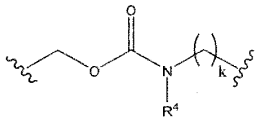
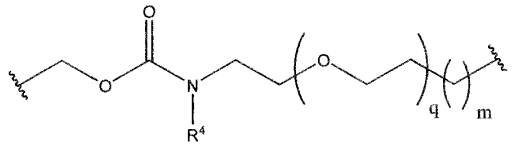
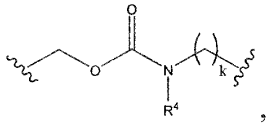
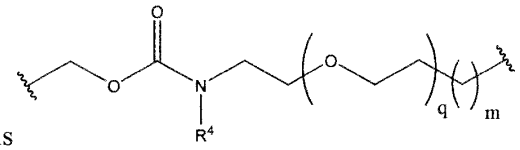
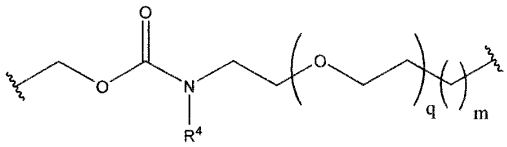
In some embodiments, p is 1 and m is 1. In such embodiments, L is  . In some embodiments, p is 0 and m is 1. In such embodiments, L is  . In some embodiments, p is 1 and m is 2. In some embodiments, L is  . In some embodiments, p is 0 and m is 2. In some embodiments, L is  . In such embodiments, R^4 is -H, -CH_3, or PG and/or q is an integer from 1-6.

In some embodiments, t is 1 or 2. In some embodiments, t is 1. In some embodiments, t is 2. In some embodiments, L is . In some embodiments, L is . In such embodiments, R^4 is -H, $-CH_3$, or PG and/or r is an integer from 1-6.

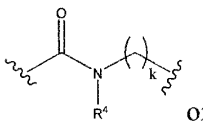
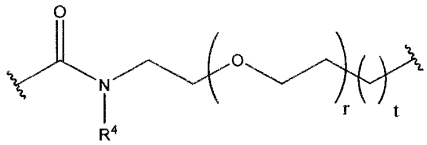
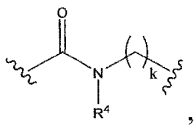
In some embodiments, L is . In some embodiments, L is a bond. In some embodiments, L is a $-(C_1-C_6)$ alkyl selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-C(CH_3)_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2C(CH_3)_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2C(CH_3)_2-$. In some embodiments, L is $-CH_2-$.

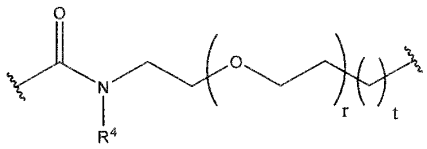
In some embodiments, L is selected from the group consisting of a bond, $-CH_2-$, , , , , ,  and .

In some embodiments, r and q are selected from an integer from 1-6. In some embodiments, k is an integer from 2-6. In some embodiments, R^4 is -H, $-CH_3$, or -PG.

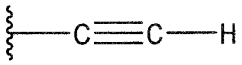
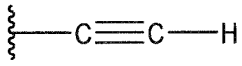
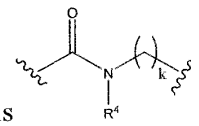
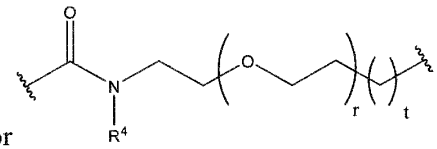
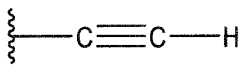
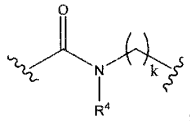
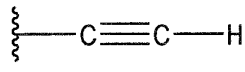
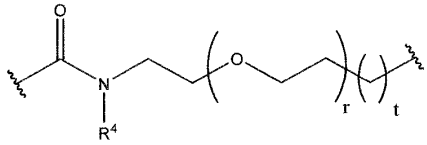
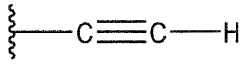
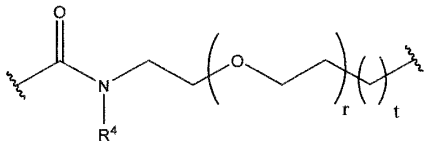
In some embodiments, Q is NCO. In some embodiments Q is NCO and L is  or . In some embodiments, Q is NCO and L is , wherein k is an integer from 2 to 6. In some embodiments, Q is NCO and L is , wherein q is an integer from 1 to 6 and/or m is 1. In some embodiments, Q is NCO and L is , wherein q is an integer from 1 to 6 and/or m is 2. In such embodiments, R^4 is -H, $-CH_3$, or PG.

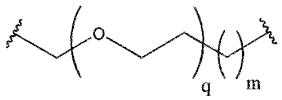
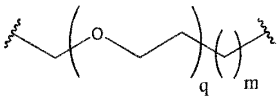
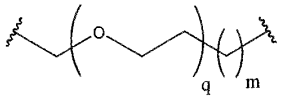
In some embodiments, Q is -NC. In some embodiments, Q in NC and L is $-(C_1-C_6)$ alkyl. In some embodiments, Q is -NC and L is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-C(CH_3)_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2C(CH_3)_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2C(CH_3)_2-$. In some embodiments, Q is -NC and L is $-CH_2-$.

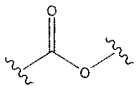
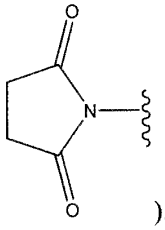
In some embodiments, Q is N_3. In some embodiments, Q is N_3 and L is  or . In some embodiments, Q is N_3 and L is ,

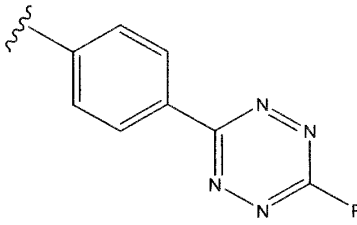
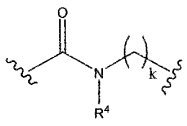
wherein k is an integer from 2-6. In some embodiments, Q is N_3 and L is , wherein r is an integer from 1-6 and/or t is 2. In such embodiments, R^4 is -H, $-CH_3$ or PG.

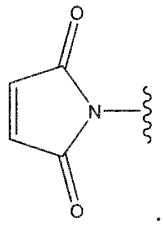
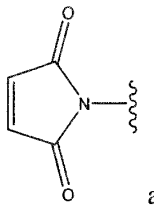
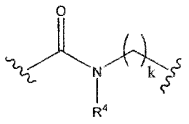
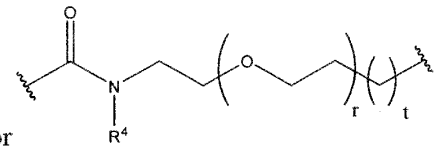
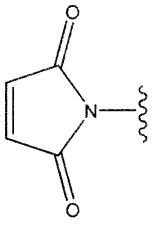
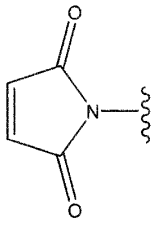
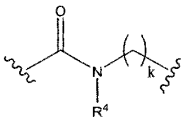
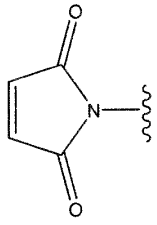
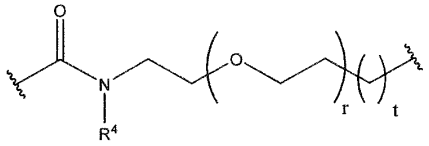
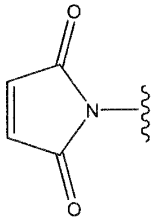
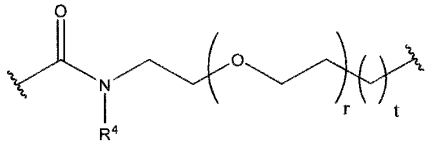
In some embodiments, Q is $-NR^4R^5$. In some embodiments, Q is $-NR^4R^5$ and L is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-C(CH_3)_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2C(CH_3)_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2C(CH_3)_2-$. In some embodiments, Q is $-NR^4R^5$ and L is $-CH_2-$.

In some embodiments, Q is . In some embodiments, Q is  and L is  or . In some embodiments, Q is  and L is , wherein k is an integer from 1-6. In some embodiments, Q is  and L is , wherein r is an integer from 1-6 and/or t is 1. In some embodiments, Q is  and L is , wherein r is an integer from 1-6 and/or t is 2. In such embodiments, R^4 is -H, $-CH_3$ or PG.

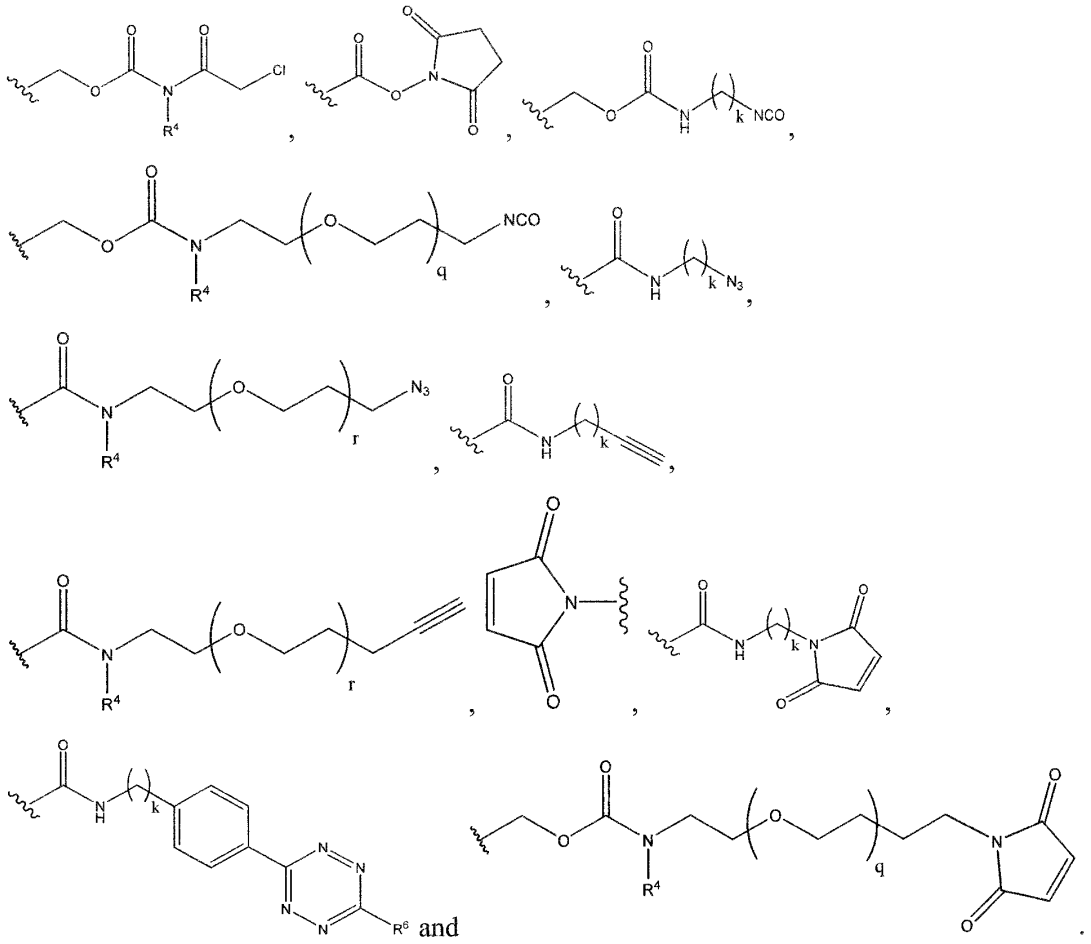
In some embodiments, Q is -OR^5, wherein R^5 is -H, -PG or –(C_1-C_4) alkyl. In some embodiments, Q is -OR^5 and L is –(C_1-C_6) alkyl or , wherein R^5 is -H, -PG or –(C_1-C_4) alkyl. In some embodiments, Q is -OR^5 and L is –(C_1-C_6) alkyl, wherein R^5 is -H, -PG or –(C_1-C_4) alkyl. In some embodiments, Q is -OR^5, wherein R^5 is -H, -PG or –(C_1-C_4) alkyl; and L is selected from the group consisting of -CH_2-, -CH_2CH_2-, -$C(CH_3)_2$-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, -$CH_2C(CH_3)_2$-, -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2C(CH_3)_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2$- and -$CH_2CH_2CH_2C(CH_3)_2$-. In some embodiments, Q is -OR^5, wherein R^5 is -H, -PG or –(C_1-C_4) alkyl; and L is -CH_2-. In some embodiments, Q is -OR^5 and L is , wherein q is an integer from 1-6; m is 1; and R^5 is -H, -PG or –(C_1-C_4) alkyl. In some embodiments, Q is -OR^5 and L is , wherein q is an integer from 1-6; m is 2; and R^5 is -H, -PG or –(C_1-C_4) alkyl.

In some embodiments, Q is succinimide. In some embodiments, L is  and Q is succinimide (i.e., ).

In some embodiments, Q is  and L is .

In some embodiments, Q is . In some embodiments, Q is  and L is a bond,  or . In some embodiments, Q is  and L is a bond. In some embodiments, Q is  and L is , wherein k is an integer from 1 to 6. In some embodiments, Q is  and L is , wherein r is an integer from 1-6 and/or t is 1. In some embodiments, Q is  and L is , wherein r is an integer from 1-6 and/or t is 2. In such embodiments, R^4 is -H, $-CH_3$ or PG.

In some embodiments, Q-L is selected from the group consisting of -CH_2Br, -CH_2NC,



In some embodiments, Q-L is as described above and R^4 is -H, -CH_3 or PG and/or k, q and r are integers selected from the group consisting of 1-6.

In some embodiments, n is 2. In some embodiments, n is 1. In some embodiments, n is 0.

In some embodiments, R^3 is -(C_1-C_6) alkyl. In some embodiments, R^3 is selected from the group consisting of -CH_3, -CH_2CH_3, -$CH(CH_3)_2$, -$CH_2CH_2CH_3$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$C(CH_3)_3$, -$CH_2CH_2CH_2CH_2CH_3$, -$CH_2C(CH_3)_3$, -$CH_2CH_2CH(CH_3)_2$, -$CH_2CH_2CH_2CH_2CH_2CH_3$, -$CH_2CH_2C(CH_3)_3$ and -$CH_2CH_2CH_2CH(CH_3)_2$. In some embodiments, R^3 is selected from the group consisting of CH_3, -CH_2CH_3, -$CH(CH_3)_2$, and -$CH_2CH_2CH_3$. In some embodiments, R^3 is -CH_3.

In some embodiments, R^3 is -(C_3-C_6) cycloalkyl. In some embodiments R^3 is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

In some embodiments, R^3 is aryl (e.g., phenyl optionally substituted with the groups consisting, but not limited to, H, halogen, acids, nitriles, esters, amides, NO_2, etc).

As the aryl ring of Formula (I) has multiple substitution sites, n can be 0, 1, 2 or 3, in some embodiments. For example, 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, n is 1 and R^3 is -(C_1-C_6) alkyl or aryl (e.g., phenyl and the like). In some embodiments, n is 1 and R^3 is -CH_3. In some embodiments, n is 1 and R^3 is aryl. In some embodiments, n is 2 and R^3, in each instance, is -(C_1-C_6) alkyl or aryl (e.g., phenyl and the like). In some embodiments, n is 2 and R^3 is -CH_3. In some embodiments, n is 2 and R^3 is aryl. In some embodiments, n is 3 and R^3, in each instance, is -(C_1-C_6) alkyl or aryl (e.g., phenyl and the like). In some embodiments, n is 3 and R^3, in each instance, is -CH_3 or aryl.

In some embodiments, m is 0, 1, 2 or 3. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 0 and n is 0, 1, 2 or 3. In some embodiments, m is 1 and n is 0, 1, 2 or 3. In some embodiments, m is 2 and n is 0, 1, 2, or 3. In some embodiments, m is 2 and n is 0, 1, 2, or 3. In some embodiments, m is 3 and n is 0, 1, 2, or 3.

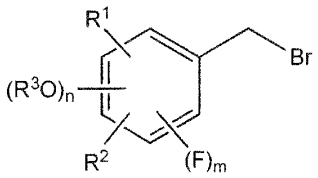
In some embodiments, R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At. In some embodiments, R^1 is I or Br. In some embodiments, R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At. In some embodiments, R^1 is H.

In some embodiments, R^2 is F or radioisotope [18]F. In some embodiments, R^2 is H. In some embodiments, R^2 is F. In some embodiments, R^2 is radioisotope [18]F. In some embodiments, R^2 is H and R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At. In some embodiments, R^2 is F and R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At. In some embodiments, R^2 is radioisotope ^{18}F and

R^1 is I or Br. In some embodiments, R^2 is radioisotope ^{18}F and R^1 is H. In some embodiments, R^2 is radioisotope ^{18}F and R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At.

In some embodiments, n is 1, m is 0; R^1 is H; R^2 is radioisotope ^{18}F; and R^3 is $-CH_3$. In such embodiments, $-OR^3$ and R^2 are ortho to each other. In such embodiments, L and R^2 are para to each other. In such embodiments, L and Q are as described above.

In some embodiments, R^1 is H, I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At; R^2 is H, F or radioisotope ^{18}F; L is $-(C_1\text{-}C_6)$ alkyl (e.g., $-CH_2-$); and Q is a halogen (e.g., Br), $-OR^5$, or -NC. In some embodiments, the compound of Formula (I) is a compound of Formula (II):



Formula (II)

wherein R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

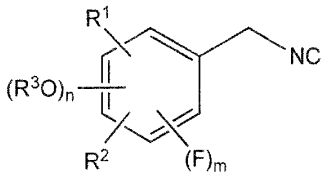
R^2 is F or radioisotope ^{18}F;

R^3 is H, -PG, -aryl, $-(C_1\text{-}C_6)$ alkyl or $-(C_3\text{-}C_6)$ cycloalkyl;

m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof.

In some embodiments, the compound of Formula (I) is a compound of Formula (VII):



Formula (VII)

wherein R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At;

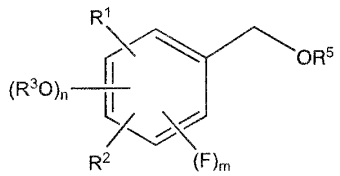
R^2 is F or radioisotope ^{18}F;

R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

m is 0, 1, 2 or 3; and

n is 0, 1 or 2;

In some embodiments, the compound of Formula (I) is a compound of Formula (XVI):



Formula (XVI)

wherein R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

R^2 is F or radioisotope ^{18}F;

R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

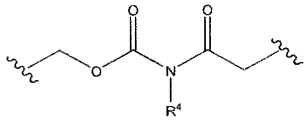
R^5 is H, -PG or -(C_1-C_4) alkyl;

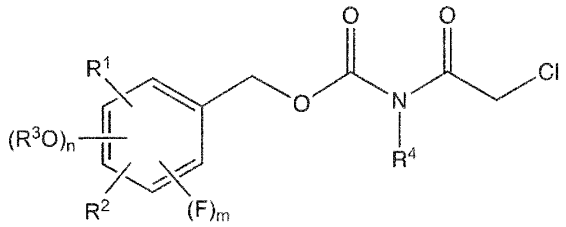
PG, in each instance, is a protecting group;

m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof.

In some embodiments, R^1 is H, I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

R^2 is H, F or radioisotope ^{18}F; L is  ; and Q is a halogen (e.g., Cl). In some embodiments, the compound of Formula (I) is a compound of Formula (III):



Formula (III)

wherein R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

R^2 is F or radioisotope ^{18}F;

R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

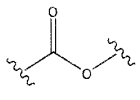
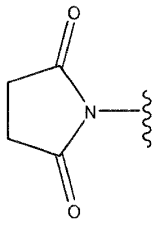
R^4 is H, -PG or -(C_1-C_4) alkyl;

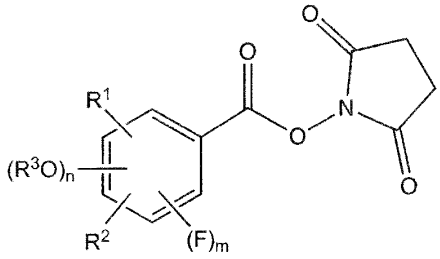
PG, in each instance, is a protecting group;

m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof.

In some embodiments, R^1 is H, I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

R^2 is H, F or radioisotope ^{18}F; L is  and Q is succinimide (i.e., ). In some embodiments, the compound of Formula (I) is a compound of Formula (IV):



Formula (IV)

wherein R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

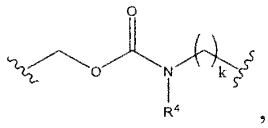
R^2 is F or radioisotope ^{18}F;

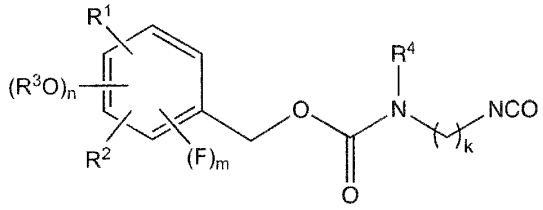
R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof.

In some embodiments, R^1 is H, I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

R^2 is H, F or radioisotope ^{18}F; L is , wherein k is an integer from 2 to 6; and Q is NCO. In some embodiments, the compound of Formula (I) is a compound of Formula (V):



Formula (V)

wherein R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

R^2 is F or radioisotope ^{18}F;

R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is H, -PG or -(C_1-C_4) alkyl;

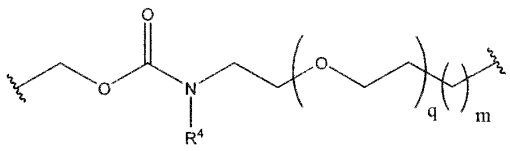
PG, in each instance, is a protecting group;

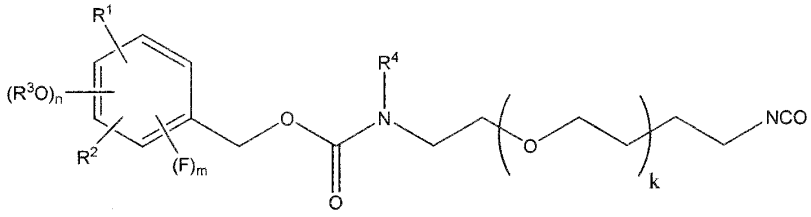
k is 2-6;

m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof.

In some embodiments, R^1 is H, I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

R^2 is H, F or radioisotope ^{18}F; L is  and Q is NCO. In some embodiments, the compound of Formula (I) is a compound of Formula (VI):



Formula (VI)

wherein R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

R^2 is F or radioisotope ^{18}F;

R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is H, -PG or -(C_1-C_4) alkyl;

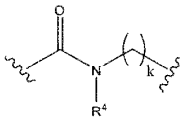
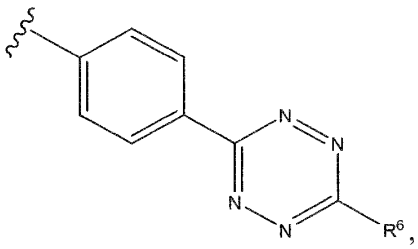
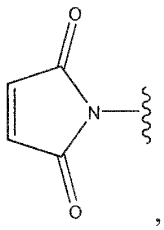
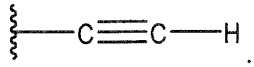
PG, in each instance, is a protecting group;

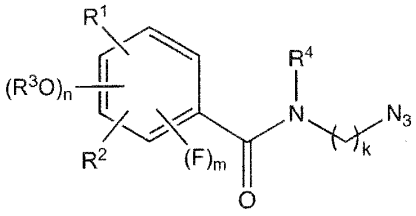
k is 1-6;

m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof.

In some embodiments, R^1 is H, I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

R^2 is H, F or radioisotope ^{18}F; L is  and/or Q is N_3,  ,  , or  . In some embodiments, the compound of Formula (I) is a compound of Formula (VIII):



Formula (VIII)

wherein R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At;

R^2 is F or radioisotope ^{18}F;

R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is H, -PG or -(C_1-C_4) alkyl;

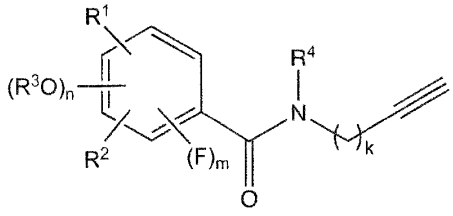
PG, in each instance, is a protecting group;

k is 2-6;

m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof.

In some embodiments, the compound of Formula (I) is a compound of Formula (X):



Formula (X)

wherein R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At;

R^2 is F or radioisotope ^{18}F;

R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is H, -PG or -(C_1-C_4) alkyl;

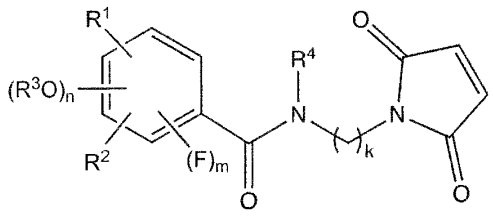
PG, in each instance, is a protecting group;

k is 1-6;

m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof.

In some embodiments, the compound of Formula (I) is a compound of Formula (XIII):



Formula (XII)

wherein R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At;

R^2 is F or radioisotope ^{18}F;

R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is H, -PG or -(C_1-C_4) alkyl;

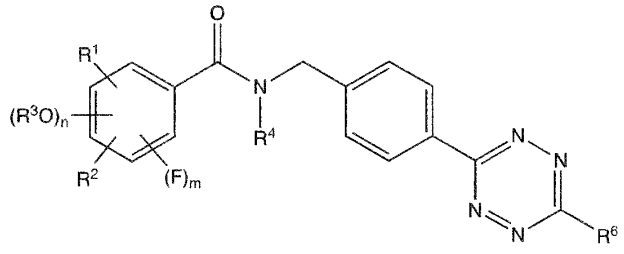
PG, in each instance, is a protecting group;

k is 2-6;

m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof.

In some embodiments, the compound of Formula (I) is a compound of Formula (XVIII):



Formula (XV)

wherein R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At;

R^2 is F or radioisotope ^{18}F;

R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is selected from H, -PG and -(C_1-C_4) alkyl;

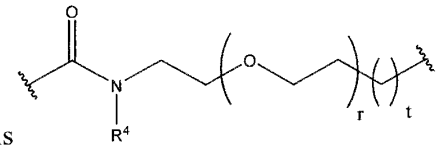
PG, in each instance, is a protecting group;

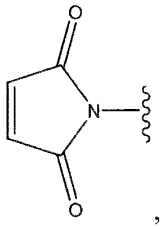
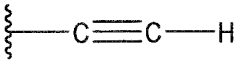
R^6 is H, -(C_1-C_4) alkyl, aryl or heteroaryl;

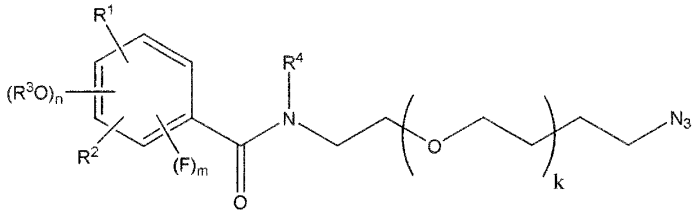
m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof.

In some embodiments, R^1 is H, I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

R^2 is H, F or radioisotope ^{18}F; L is  and/or Q is

 N_3, . In some embodiments, the compound of Formula (I) is a compound of Formula (IX):



Formula (IX)

wherein R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At;

R^2 is F or radioisotope ^{18}F;

R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is H, -PG or -(C_1-C_4) alkyl;

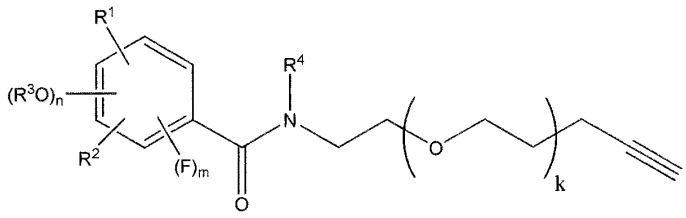
PG, in each instance, is a protecting group;

k is 1-6;

m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof.

In some embodiments, the compound of Formula (I) is a compound of Formula (XI):



Formula (XI)

wherein R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At;

R^2 is F or radioisotope ^{18}F;

R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is H, -PG or -(C_1-C_4) alkyl;

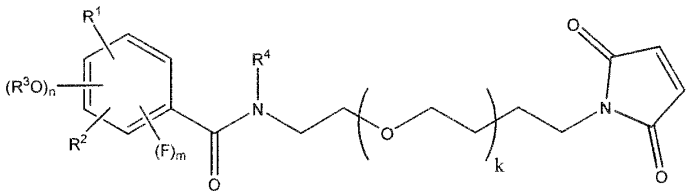
PG, in each instance, is a protecting group;

k is 1-6;

m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof.

In some embodiments, the compound of Formula (I) is a compound of Formula (XIV):



Formula (XIV)

wherein R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At;

R^2 is F or radioisotope ^{18}F;

R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is H, -PG or -(C_1-C_4) alkyl;

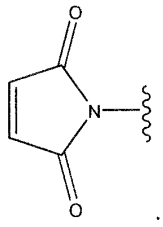
PG, in each instance, is a protecting group;

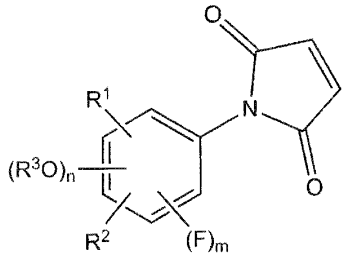
k is 1-6;

m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof.

In some embodiments, R^1 is H, I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

R^2 is H, F or radioisotope ^{18}F; L is a bond and/or Q is . In some embodiments, the compound of Formula (I) is a compound of Formula (XII):



Formula (XIII)

wherein R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At;

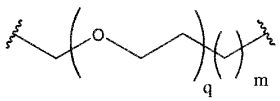
R^2 is F or radioisotope ^{18}F;

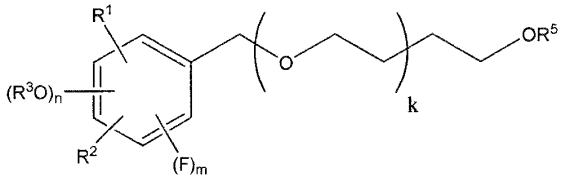
R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof.

In some embodiments, R^1 is H, I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

R^2 is H, F or radioisotope ^{18}F; L is  and/or Q is -OR^5. In some embodiments, the compound of Formula (I) is a compound of Formula (XVII):



Formula (XVII)

wherein R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

R^2 is F or radioisotope ^{18}F;

R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

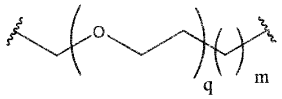
R^5 is H, -PG or -(C_1-C_4) alkyl;

PG, in each instance, is a protecting group;

m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof.

In some embodiments, R^1 is H, I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

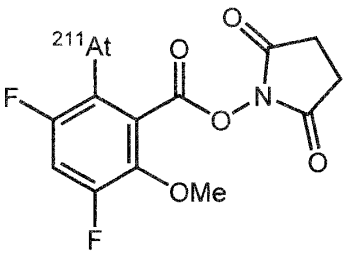
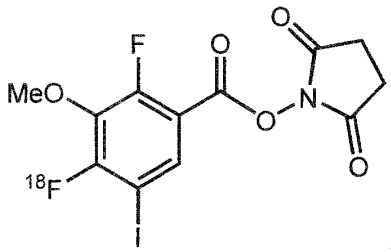
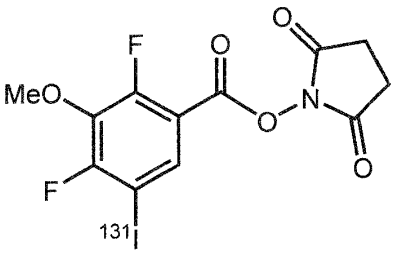
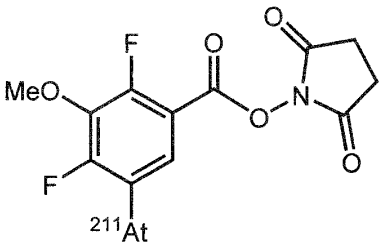
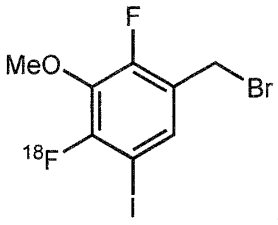
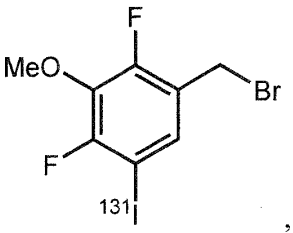
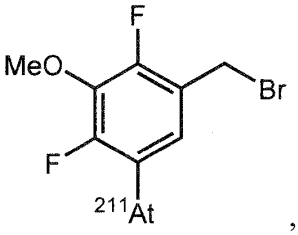
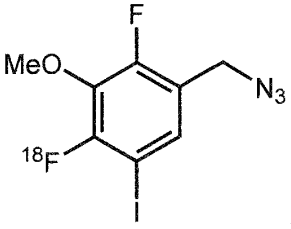
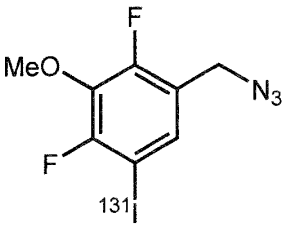
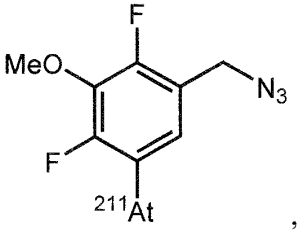
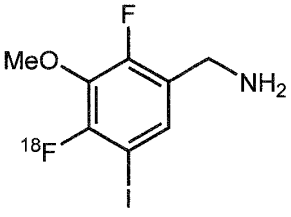
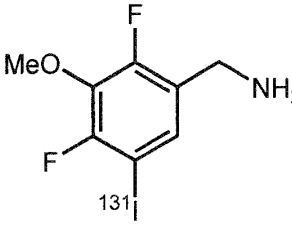
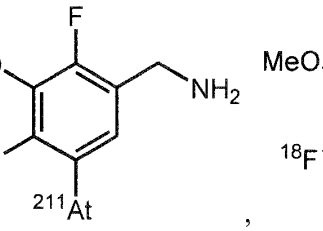
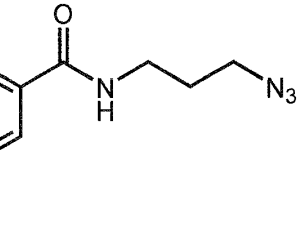
R^2 is H, F or radioisotope ^{18}F; L is  and/or Q is $-OR^5$.

In some embodiments, PG is a protecting group for amines, hydroxyl and/or acid functionality. In some embodiments, PG is a protecting group for hydroxyl moieties (e.g., -OH). In some embodiments, for example, propargyl protecting groups are employed for alcohols herein. In some embodiments, PG is a protecting group for amine moieties (e.g., primary amines or secondary amines). In some embodiments, PG is a protecting group for carboxylic acids (e.g. -COOH). In some embodiments, PG is a protecting group for carboxamides (e.g., $-CONH_2$ or-CONHR).

In some embodiments, PG is an amine protecting group such as, but not limited to, -BOC, -benzyl, -Cbz, FMoc, Teoc, Troc, SEM, MOM, TPDPS, TIPS, benzhydryl, Trityl, propargyl, and the like.

In some embodiments, the compounds of Formulae (I)-(XVII) contain a single halogen atom (e.g., Br, Cl, F, I, and/or At). In such embodiments, the single halogen atom is radioactive, i.e., it is a radioisotope as disclosed herein. In some embodiments, the single halogen atom is -F or [18]F. In some embodiments, the compounds of Formula (I) contain at least two halogen atoms. In such embodiments, at least one of the two halogen atoms is radioactive, i.e., it is a radioisotope as disclosed herein.

Non-limiting exemplary compounds of one or more for Formulae (I)-(XVII) are as follows:

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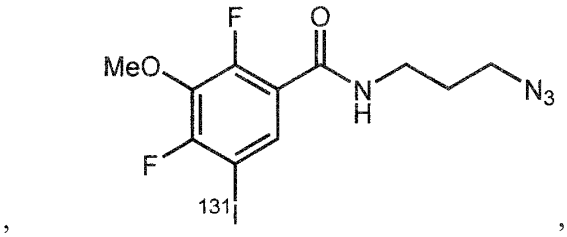
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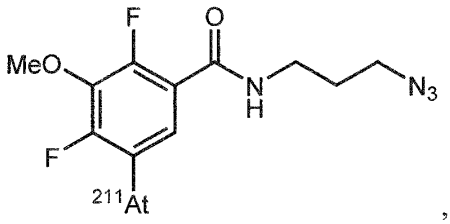
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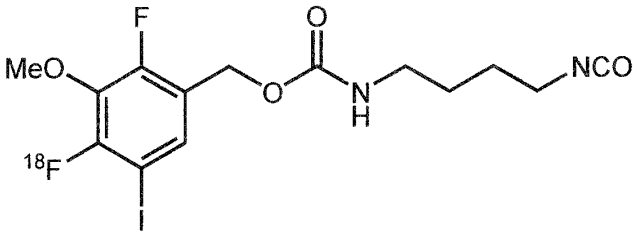
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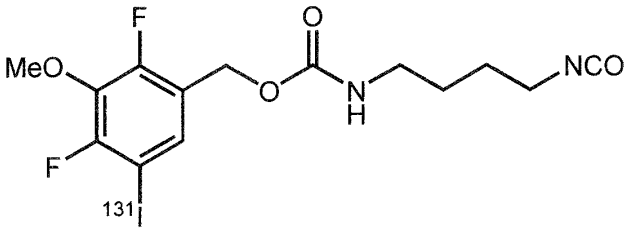
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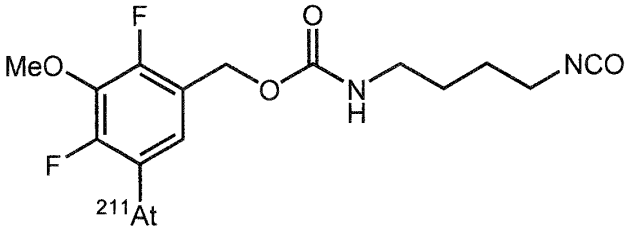
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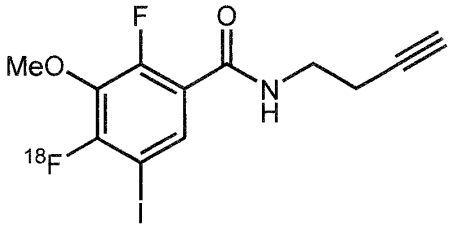
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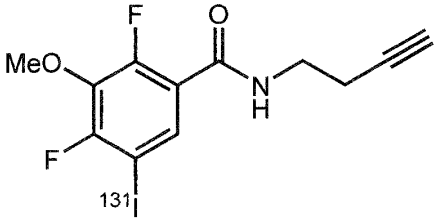
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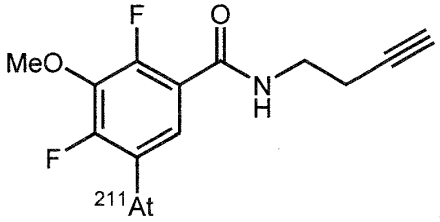
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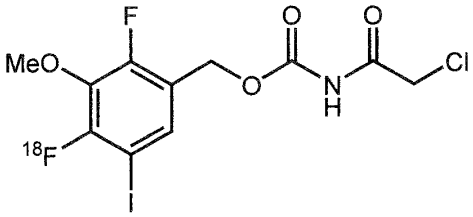
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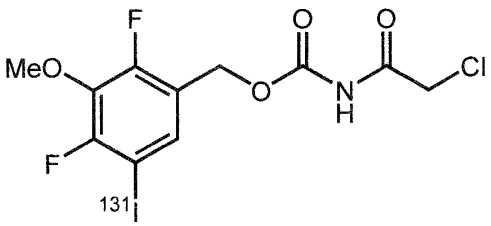
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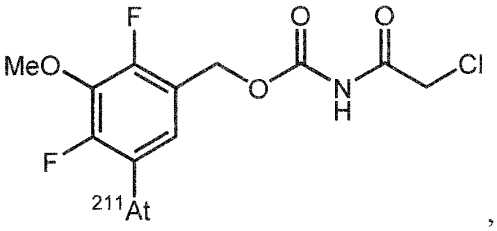
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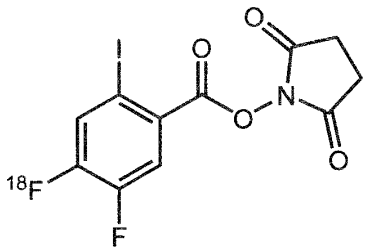
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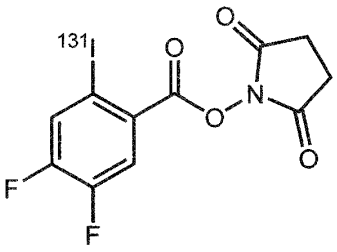
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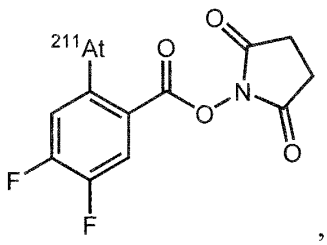
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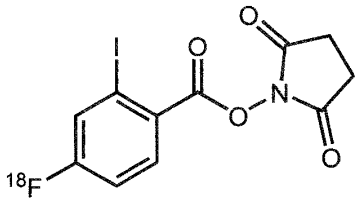
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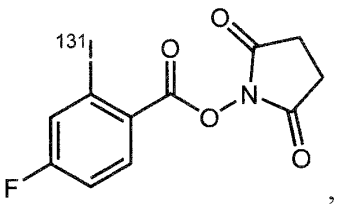
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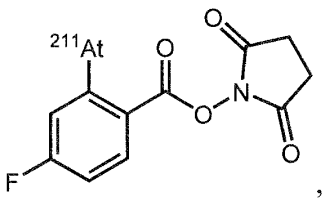
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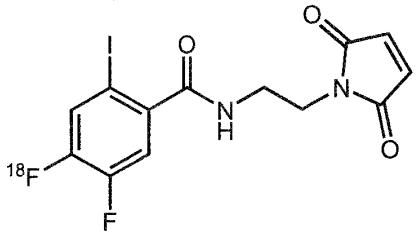
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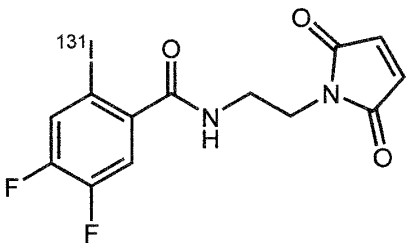
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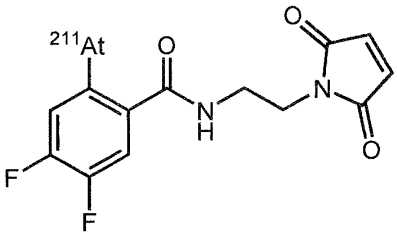
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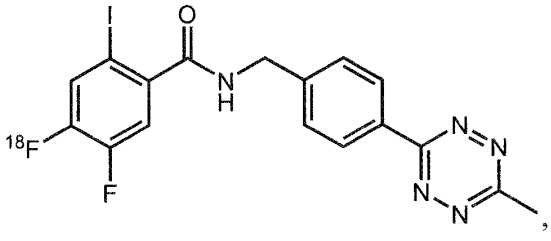
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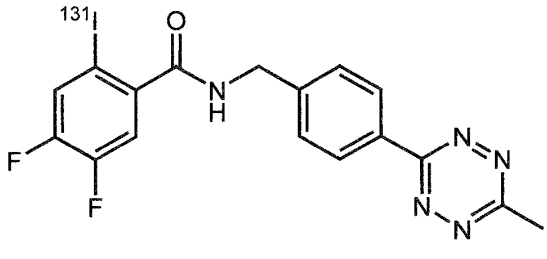
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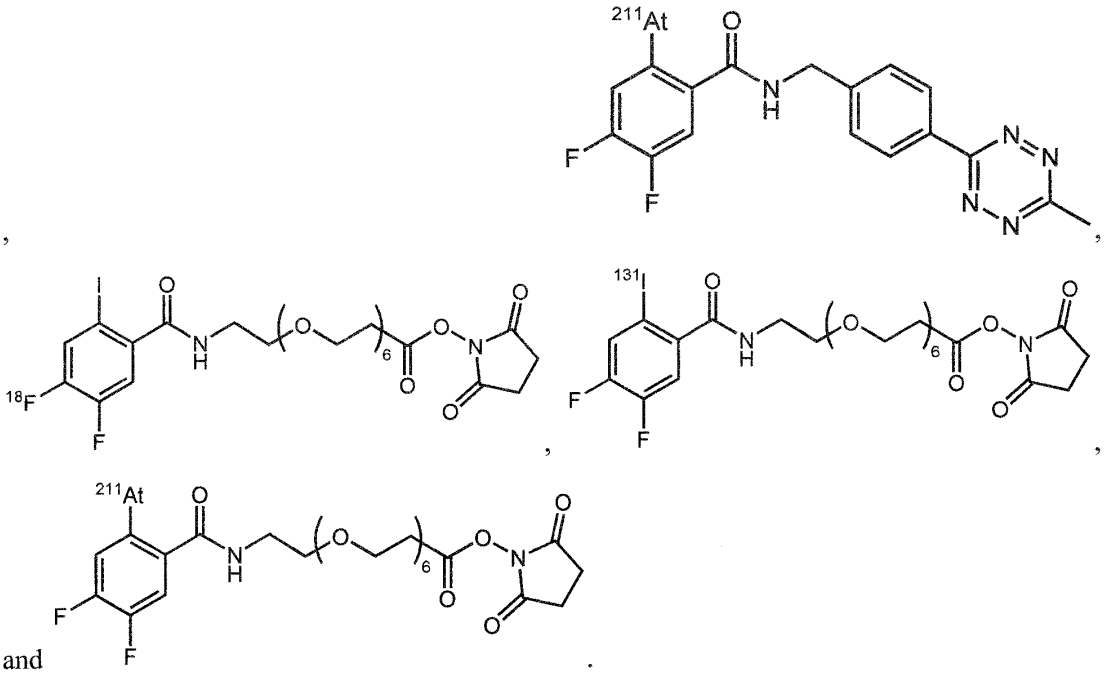


In some embodiments, the compounds described herein may in some cases exist as diastereomers, enantiomers, or other stereoisomeric forms. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Separation of stereoisomers may be performed by chromatography and/or recrystallization or by the forming diastereomers, including diastereomeric salts, and separation thereof (Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981). Stereoisomers may also be obtained by stereoselective synthesis using synthetic methods known in the art. In some embodiments, the compounds disclosed herein are enantiomers having an enantiomeric excess (% ee) of at least about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, or about 99.5%. In some embodiments, the compounds disclosed herein are diastereomers having a diastereomeric excess (% de) of at least about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, or about 99.5%. In some embodiments, the compounds disclosed herein are present as enantiomeric or diastereomeric mixtures. In some embodiments, the compounds disclosed herein are derivatives of phenylalanine, an amino acid. In such embodiments, the compounds disclosed herein are the L-isomer of phenylalanine and/or its derivative thereof. In some embodiments, the compound

disclosed herein is the L-isomer of any given amino acid, natural or unnatural (not present in nature). In some embodiments, the compounds disclosed herein are the D-isomer of phenylalanine and/or its derivative thereof. In some embodiments, the compound disclosed herein is the D-isomer of any given amino acid, natural or unnatural (not present in nature).

The methods and compositions described herein include the use of amorphous forms as well as crystalline forms (also known as polymorphs). The compounds described herein may be in the form of pharmaceutically acceptable salts. Active metabolites of these compounds having the same type of activity are included in the scope of the present disclosure.

In some embodiments, the compounds described herein may be formed as, and/or used as, salts and/or pharmaceutically acceptable salts. Exemplary pharmaceutical acceptable salts, include, but are not limited to: (1) acid addition salts, formed by reacting the free base form of the compound with a pharmaceutically acceptable: inorganic acid, such as, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, metaphosphoric acid, and the like; or with an organic acid, such as, for example, acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, trifluoroacetic acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4′-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, butyric acid, phenylacetic acid, phenylbutyric acid, valproic acid, and the like; (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, e.g., an alkali metal ion (e.g. lithium, sodium, potassium), an alkaline earth ion (e.g. magnesium, or calcium), or an aluminum ion. In some cases, compounds described herein may coordinate with an organic base, such as, but not limited to, ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, dicyclohexylamine, tris(hydroxymethyl)methylamine and the like. Acceptable inorganic bases used to form salts with compounds that include an acidic proton, include, but are

not limited to, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like.

In some embodiments, the compounds and salts described herein include isotopically-labeled compounds. In general, isotopically-labeled compounds are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most common in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine, for example, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, [17]O, ^{18}F, [37]Cl, [36]Cl, respectively. However, additional isotopes for iodine, bromine, and astatine are also included herein. Certain isotopically-labeled compounds described herein, for example those into which radioactive isotopes are also incorporated as they are useful in drug and/or substrate tissue distribution assays. Further, substitution with isotopes such as deuterium, i.e., 2H, can afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased in vivo half-life or reduced dosage requirements.

B. Bioactive ligands

The prosthetic groups disclosed herein can be coupled to bioactive ligands, which will be described in more detail below. The bioactive ligands disclosed herein can be found in nature (e.g., in an organism and/or plant) or can be prepared synthetically. Certain disclosed bioactive ligands are able to modulate a biological process in an organism (e.g., a mammal). Exemplary bioactive ligands include, but are not limited to, proteins (natural and designed) and protein complexes (e.g., viral capsid and/or virus-like proteins (VLP), oligonucleotides, polynucleotides, cyclic and linear oligopeptides, cyclic and linear oligonucleotides (with both natural and unnatural bases, and/or natural or unnatural termini), peptoids, messenger molecules, aptamers, and/or antibodies).

In some embodiments, the bioactive ligand is a drug molecule, e.g., a peptide-based drug molecule. In some embodiments, the bioactive ligand is an oligopeptide (also referred to as "peptide"). In some embodiments, the peptide is natural (i.e., found in nature). In some embodiments, the peptide is unnatural (prepared synthetically). In some embodiments, the peptide is a linear peptide. In some embodiments, the peptide is a cyclic peptide or a peptoid. In some

embodiments, the peptide is an approved pharmaceutical drug and/or a clinical drug candidate and/or an investigative research compound.

In some embodiments, the bioactive ligand contributes to and/or interferes with the pathogenesis of cancer and/or a proliferative disorder. In some embodiments, the bioactive ligand (e.g., peptide) can be employed to specifically target cancer cells. In some embodiments, the bioactive ligand can be labeled with the radioisotope-containing prosthetic groups disclosed herein. In some embodiments, the labeled bioactive ligand can be used as a diagnostic or radiotherapeutic agent. In some embodiments the labeled bioactive ligand can be used as a diagnostic agent. In some embodiments the bioactive ligand can be used as a therapeutic agent. In some embodiments the labeled bioactive ligand can be used to target and reduce/kill cancer cells or to kill/reduce non-cancerous or pre-cancerous hyperproliferative/hyperproliferating cells.

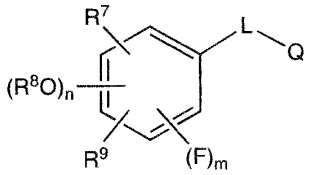
III. Methods of Preparation

The present disclosure provides methods for preparing an aromatic electrophilic prosthetic group such as compounds of Formula (I), wherein the aromatic electrophilic prosthetic group can be radioactive or non-radioactive. For example, the present disclosure provides three different methods for preparing compounds of Formula (I) containing a radioactive ^{18}F moiety, which is one of the most important radioisotopes in the radiopharmaceutical industry, as it possesses a diagnostically useful half-life ($t_{1/2}$ = 110 min) and decays with high efficiency by positron emission efficiency (97%). Photoredox radiochemistry and late-stage radiolabeling can be utilized to incorporate ^{18}F and/or ^{131}I and/or [211]At into aromatic compounds such as compounds of Formula (I). Disclosed herein are three different photoredox radiolabeling methods for the introduction of an ^{18}F moiety using mild reaction conditions providing rapid introduction of an ^{18}F moiety into compounds of Formula (I) (**FIG. 5**). *Method A. Direct C-H bond conversion:* Unlike most of the existing methods, the developed arene C–H radiolabeling disclosed herein converts aromatic electrophile prosthetic groups of Formula (I) without harsh conditions (e.g. *O_2 free, moisture free, high temperature, strong acid or base etc.*) or the need for complicated synthesis to achieve the desired product. *Method B. Direct C-O bond conversion:* Transition metal catalysis and concerted S_NAr methods have been utilized for the direct fluorination of activated C–O bonds, but there is a dearth of methods for site-selective deoxyfluorinations with relatively unactivated nucleofuges. Disclosed herein is a highly efficient

method – nucleophilic aromatic substitution (S_NAr) – which is able to install an ^{18}F moiety to the target molecules in a site-specific manner using alkoxyarenes as substrates where alcohols are the leaving groups. *Method C. Direct C-X (X = F, Cl, Br, I, NO_2) bond conversion.* As a major substrate class for arene functionalization, aryl (pseudo)halides are commonly used intermediates *en* route to synthesizing organometallic or prefunctionalized arene precursors for radiofluorination. Methods that could directly radiofluorinate electron-rich aryl halides are highly desired due to their simplicity. These methods can also be used for the preparation of compounds of Formula (I) containing ^{19}F moieties, i.e., non-radioactive fluorine moieties.

Aromatic electrophilic prosthetic groups of compounds of Formula (I) containing radioactive iodine moieties (i.e., ^{123}I, [124]I, ^{125}I and ^{131}I), radioactive astatine moieties (i.e., [210]At and [211]At), or radioactive bromine moieties (i.e., [76]Br, [77]Br and [82]Br), are ideally prepared from [127]I, boron-, silicon-, tin- or germanium-containing starting materials. Specifically, the method for preparing a compound of Formula (I), wherein R* is a radioisotope R* selected from the group consisting of ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, [211]At, [76]Br, [77]Br and [82]Br, can be prepared by, but is not limited to, the following steps:

(a) obtaining a starting material of Formula (I-A):



Formula (I-A)

wherein R^7 is -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -B(OH)$_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)$_3$, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

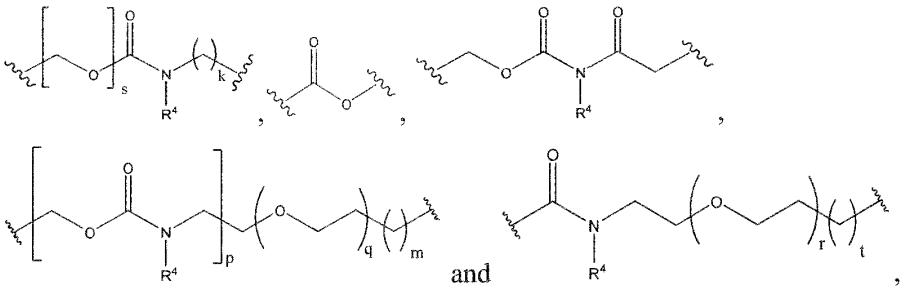
R^9 is H, F, I, Br, Cl, F or radioisotope ^{18}F;

R^8 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

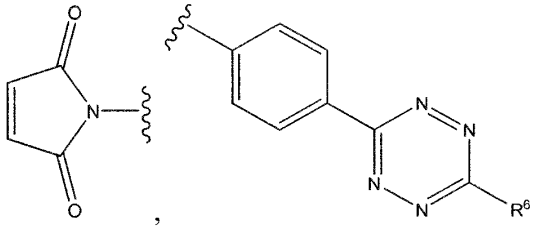
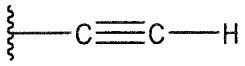
m is 0, 1, 2 or 3;

n is 0, 1 or 2;

L is selected from the group consisting of a bond, -(C_1-C_6) alkyl,



wherein k, s, m, p, q, r and t, in each instance, are integers independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;

Q is selected from the group consisting of halogen, sulfonate, phosphonate, succinimide, -NCO, -NC, $-N_3$, $-NR^4R^5$, -PG, OR^5,  and ;

R^4 and R^5 are independently selected from -H, -PG, and $-(C_1-C_6)$ alkyl, wherein -PG is a protecting group;

R^6 is -H, (C_1-C_4) alkyl, aryl, or heteroaryl; and

any stereoisomer and/or salt thereof; and

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render the compound of Formula (I), wherein R* is a radioisotope selected from the group consisting of ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, [211]At, [76]Br, [77]Br and [82]Br.

In some embodiments, PG is a protecting group for hydroxyl moieties (e.g., -OH). In some embodiments, PG is a protecting group for amine moieties (e.g., primary amines or secondary amines). In some embodiments, PG is a protecting group for carboxylic acids (e.g. -COOH). In some embodiments, PG is a protecting group for carboxamides (e.g., $-CONH_2$ or-CONHR).

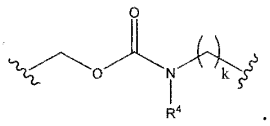
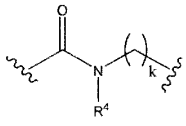
In some embodiments, PG is an amine protecting group such as, but not limited to, -BOC, -benzyl, -Cbz, FMoc, Teoc, Troc, SEM, MOM, TPDPS, TIPS, benzhydryl, Trityl and the like.

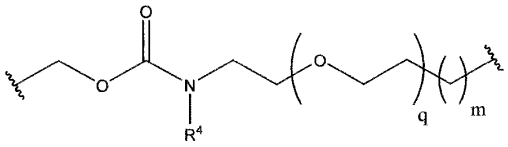
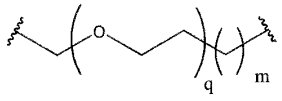
In some embodiments, R^7 in Formula (I-A) is boronic acid pinacol ester. In some embodiments R^7 is -$B(OH)_2$, -BF_3K, N-methyliminodiacetic acid boronate, -$Sn(C_1$-C_4 alkyl$)_3$, -$Ge[(C_1$-$C_6)$ alkyl$]_3$ and -$Si[(C_1$-$C_6)$ alkyl$]_3$

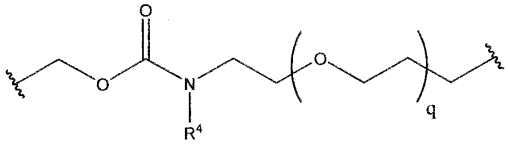
In some embodiments, n is 2. In some embodiments, n is 1. In some embodiments, n is 0.

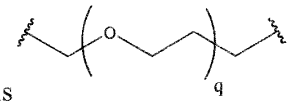
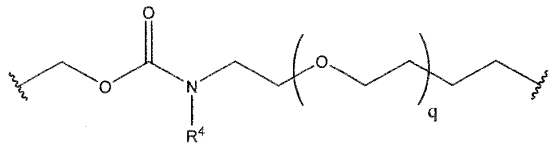
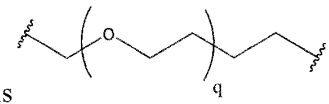
In some embodiments, R^8 is -$(C_1$-$C_6)$ alkyl. In some embodiments, R^8 is selected from the group consisting of -CH_3, -CH_2CH_3, -$CH(CH_3)_2$, -$CH_2CH_2CH_3$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$C(CH_3)_3$, -$CH_2CH_2CH_2CH_2CH_3$, -$CH_2C(CH_3)_3$, -$CH_2CH_2CH(CH_3)_2$, -$CH_2CH_2CH_2CH_2CH_2CH_3$, -$CH_2CH_2C(CH_3)_3$ and -$CH_2CH_2CH_2CH(CH_3)_2$. In some embodiments, R^8 is selected from the group consisting of CH_3, -CH_2CH_3, -$CH(CH_3)_2$, and -$CH_2CH_2CH_3$. In some embodiments, R^8 is -CH_3.

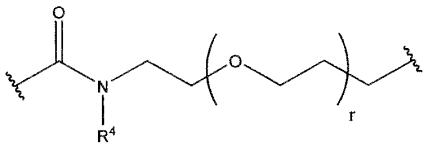
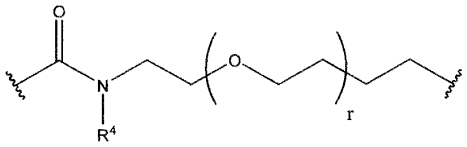
In some embodiments, R^8 is -$(C_3$-$C_6)$ cycloalkyl. In some embodiments R^8 is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl. In some embodiments, R^8 is aryl (e.g., phenyl and the like).

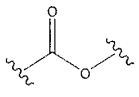
In some embodiments, s is 0 or 1. In some embodiments, s is 1. In some embodiments, L is  . In some embodiments, L is  . In such embodiments, k is an integer from 2-6. In such embodiments, R^4 is -H, -CH_3, or -PG.

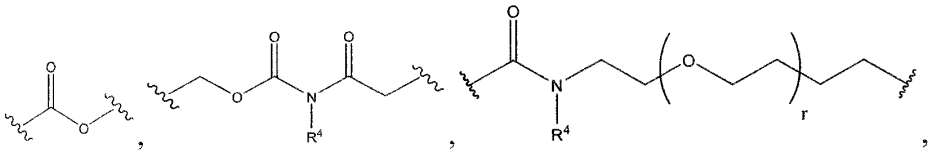
In some embodiments, p is 0 or 1. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, L is  . In some embodiments, L is  . In such embodiments, m is 1 or 2.

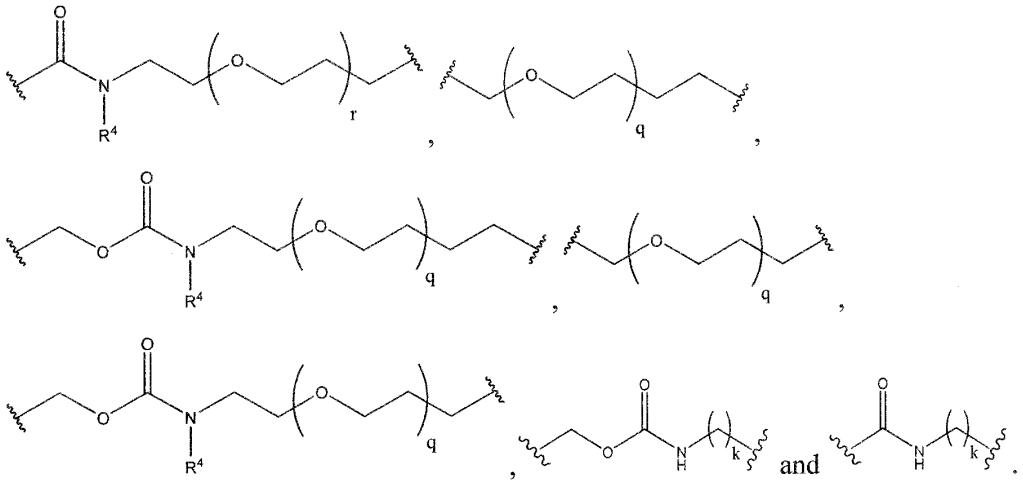
In some embodiments, p is 1 and m is 1. In such embodiments, L is  . In some embodiments, p is 0 and m is 1. In such

embodiments, L is . In some embodiments, p is 1 and m is 2. In some embodiments, L is . In some embodiments, p is 0 and m is 2. In some embodiments, L is . In such embodiments, R^4 is -H, $-CH_3$, or PG and/or q is an integer from 1-6.

In some embodiments, t is 1 or 2. In some embodiments, t is 1. In some embodiments, t is 2. In some embodiments, L is . In some embodiments, L is . In such embodiments, R^4 is -H, $-CH_3$, or PG and/or r is an integer from 1-6.

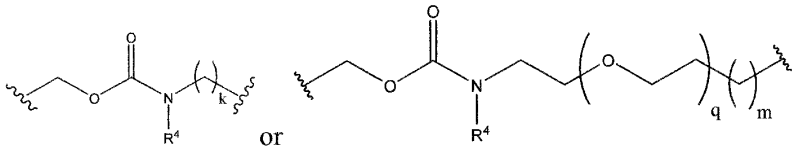
In some embodiments, L is . In some embodiments, L is a bond. In some embodiments, L is a $-(C_1-C_6)$ alkyl selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-C(CH_3)_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2C(CH_3)_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2C(CH_3)_2-$. In some embodiments, L is $-CH_2-$.

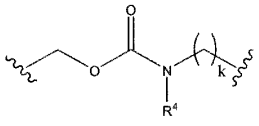
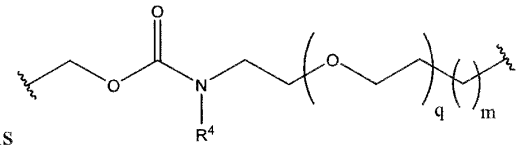
In some embodiments, L is selected from the group consisting of a bond, $-CH_2-$, ,

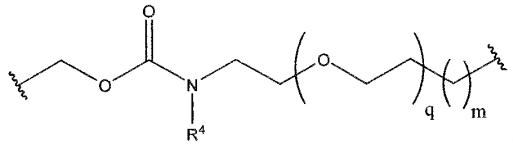


In some embodiments, r and q are selected from an integer from 1-6. In some embodiments, k is an integer from 2-6. In some embodiments, R^4 is -H, $-CH_3$, or -PG, wherein PG is a nitrogen protecting group (e.g., FMOC and/or BOC).

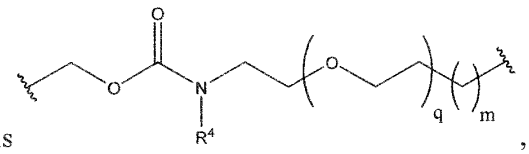
In some embodiments, Q is NCO. In some embodiments Q is NCO and L is



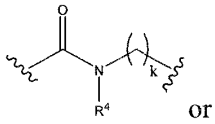
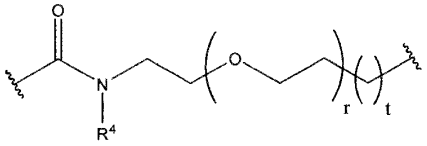
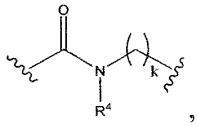
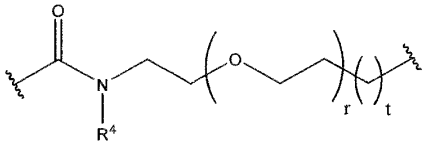
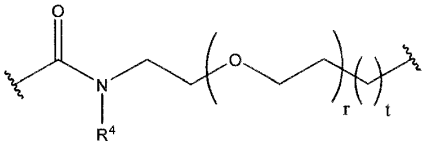
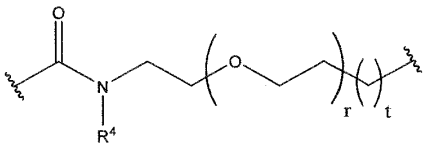
. In some embodiments, Q is NCO and L is , wherein k is an integer from 2 to 6. In some embodiments, Q is NCO and L is , wherein q is an integer from 1 to 6 and/or m is 2. In some embodiments, Q is NCO and L is

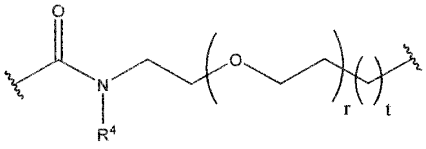


, wherein q is an integer from 1 to 6 and m is 2. In

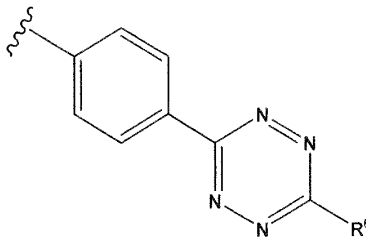
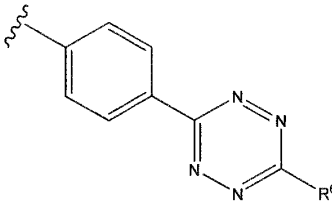
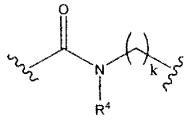
some embodiments, Q is NCO and L is , wherein m is 2. In such embodiments, R^4 is -H, $-CH_3$, or PG, wherein PG is a protecting group (e.g., BOC and/or FMOC).

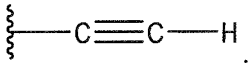
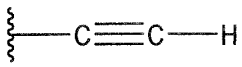
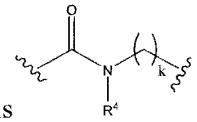
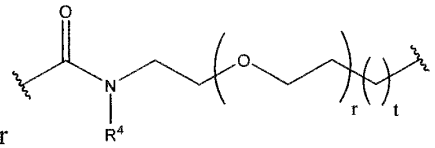
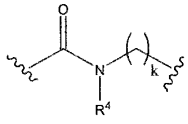
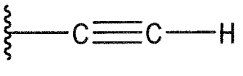
In some embodiments, Q is -NC. In some embodiments, Q in NC and L is $-(C_1\text{-}C_6)$ alkyl. In some embodiments, Q is -NC and L is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-C(CH_3)_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2C(CH_3)_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2C(CH_3)_2-$. In some embodiments, Q is -NC and L is $-CH_2-$.

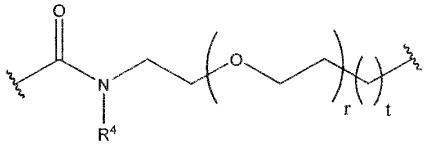
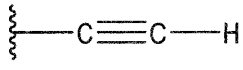
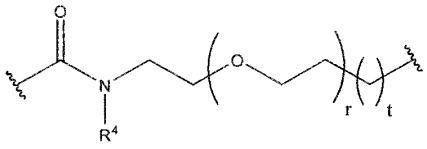
In some embodiments, Q is N_3. In some embodiments, Q is N_3 and L is  or . In some embodiments, Q is N_3 and L is , wherein k is an integer from 2-6. In some embodiments, Q is N_3 and L is , wherein r is an integer from 1-6 and/or t is 2. In some embodiments, Q is N_3 and L is , wherein r is an integer from 1-6 and/or t is 1. In some embodiments, Q is N_3 and L is ,

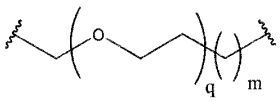
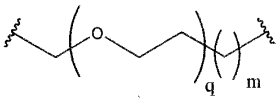
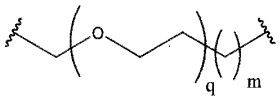
wherein r is an integer from 1-6 and t is 1. In some embodiments, Q is N_3 and L is , wherein t is 1. In such embodiments, R^4 is -H, $-CH_3$ or PG.

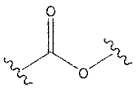
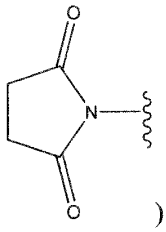
In some embodiments, Q is $-NR^4R^5$. In some embodiments, Q is $-NR^4R^5$ and L is $-(C_1-C_6)$ alkyl. In some embodiments, Q is $-NR^4R^5$ and L is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-C(CH_3)_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2C(CH_3)_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2C(CH_3)_2-$. In some embodiments, Q is $-NR^4R^5$ and L is $-CH_2-$.

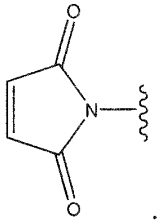
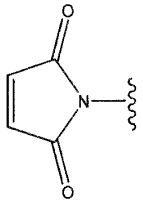
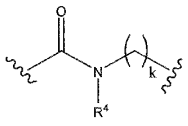
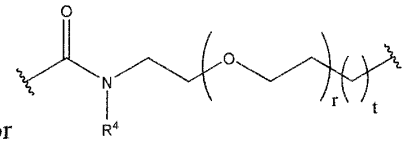
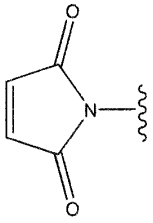
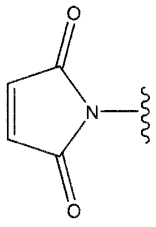
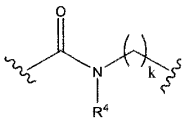
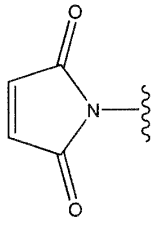
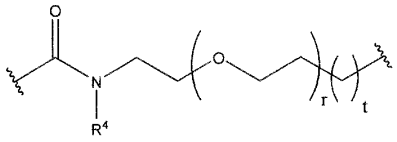
In some embodiments, Q is . In some embodiments, Q is  and L is . In such embodiments, R^4 is selected from -H, $-CH_3$, or -PG; R^6 is -H, (C_1-C_4) alkyl, aryl, or heteroaryl; and/or k is an integer from 1-6.

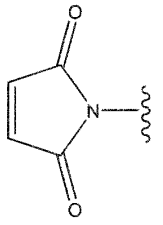
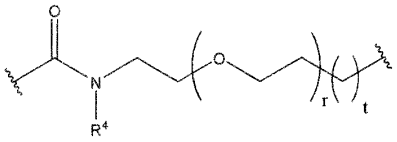
In some embodiments, Q is . In some embodiments, Q is  and L is  or . In some embodiments, Q is  and L is , wherein k is an integer from 1-6. In some embodiments, Q is  and L is


, wherein r is an integer from 1-6 and/or t is 1. In some embodiments, Q is  and L is , wherein r is an integer from 1-6 and/or t is 2. In such embodiments, R^4 is -H, $-CH_3$ or PG, wherein PG is a protecting group (e.g., BOC, FMOC).

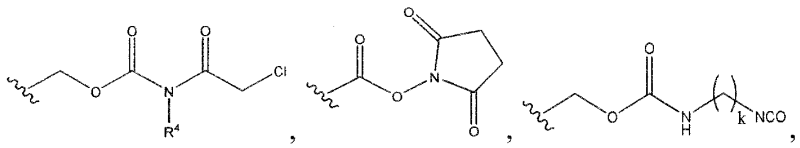
In some embodiments, Q is $-OR^5$, wherein R^5 is -H, -PG or $-(C_1-C_4)$ alkyl. In some embodiments, Q is $-OR^5$ and L is $-(C_1-C_6)$ alkyl or , wherein R^5 is -H, -PG or $-(C_1-C_4)$ alkyl. In some embodiments, Q is $-OR^5$ and L is $-(C_1-C_6)$ alkyl, wherein R^5 is -H, -PG or $-(C_1-C_4)$ alkyl. In some embodiments, Q is $-OR^5$, wherein R^5 is -H, -PG or $-(C_1-C_4)$ alkyl; and L is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-C(CH_3)_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2C(CH_3)_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2C(CH_3)_2-$. In some embodiments, Q is $-OR^5$, wherein R^5 is -H, -PG or $-(C_1-C_4)$ alkyl; and L is $-CH_2-$. In some embodiments, Q is $-OR^5$ and L is , wherein q is an integer from 1-6; m is 1; and R^5 is -H, -PG or $-(C_1-C_4)$ alkyl. In some embodiments, Q is $-OR^5$ and L is , wherein q is an integer from 1-6; m is 2; and R^5 is -H, -PG or $-(C_1-C_4)$ alkyl.

In some embodiments, Q is succinimide. In some embodiments, L is  and Q is succinimide (i.e., ).

In some embodiments, Q is . In some embodiments, Q is  and L is a bond,  or . In some embodiments, Q is  and L is a bond. In some embodiments, Q is  and L is , wherein k is an integer from 1 to 6. In some embodiments, Q is  and L is , wherein r is an integer from 1-6 and/or t is 1. In some

embodiments, Q is  and L is , wherein r is an integer from 1-6 and/or t is 2. In such embodiments, R^4 is -H, $-CH_3$ or PG.

In some embodiments, Q-L is selected from the group consisting of $-CH_2Br$, $-CH_2NC$,

,
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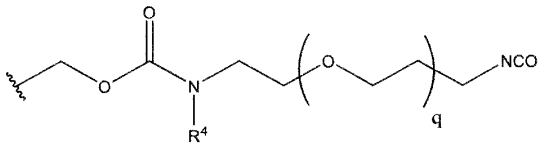
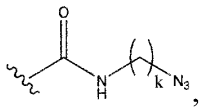
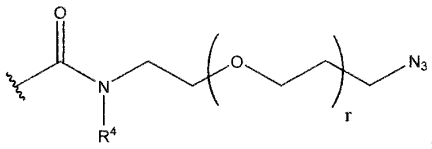
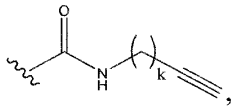
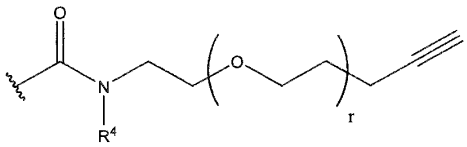
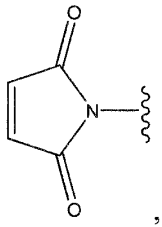
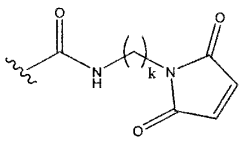
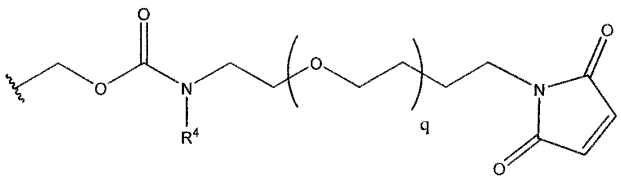
,
,
,
,
,
,
, and
. In some embodiments, Q-L is as described above and R^4 is -H, $-CH_3$ or PG and/or k, q and r are integers selected from the group consisting of 1-6.

In some embodiments, n is 2. In some embodiments, n is 1. In some embodiments, n is 0.

In some embodiments, R^8 is -(C_1-C_6) alkyl. In some embodiments, R^8 is selected from the group consisting of -CH_3, -CH_2CH_3, -$CH(CH_3)_2$, -$CH_2CH_2CH_3$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$C(CH_3)_3$, -$CH_2CH_2CH_2CH_2CH_3$, -$CH_2C(CH_3)_3$, -$CH_2CH_2CH(CH_3)_2$, -$CH_2CH_2CH_2CH_2CH_2CH_3$, -$CH_2CH_2C(CH_3)_3$ and -$CH_2CH_2CH_2CH(CH_3)_2$. In some embodiments, R^8 is selected from the group consisting of CH_3, -CH_2CH_3, -$CH(CH_3)_2$, and -$CH_2CH_2CH_3$. In some embodiments, R^8 is -CH_3.

In some embodiments, R^8 is -(C_3-C_6) cycloalkyl. In some embodiments R^8 is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

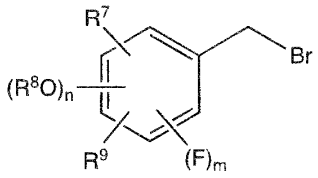
In some embodiments, R^8 is aryl (e.g., phenyl and the like).

As provided hereinabove, in some embodiments, n of compounds described herein can be 0, 1, 2 or 3. 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, n is 1 and R^8 is -(C_1-C_6) alkyl or aryl (e.g., phenyl and the like). In some embodiments, n is 1 and R^8 is -CH_3. In some embodiments, n is 1 and R^8 is phenyl. In some embodiments, n is 2 and R^8, in each instance, is -(C_1-C_6) alkyl or aryl (e.g., phenyl and the like). In some embodiments, n is 2 and R^8 is -CH_3. In some embodiments, n is 2 and R^8 is phenyl. In some embodiments, n is 3 and R^8, in each instance, is -(C_1-C_6) alkyl or aryl (e.g., phenyl and the like). In some embodiments, n is 3 and R^8, in each instance, is -CH_3 or phenyl and the like.

In some embodiments, m is 0, 1, 2 or 3. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 0 and n is 0, 1, 2 or 3. In some embodiments, m is 1 and n is 0, 1, 2 or 3. In some embodiments, m is 2 and n is 0, 1, 2, or 3. In some embodiments, m is 2 and n is 0, 1, 2, or 3. In some embodiments, m is 3 and n is 0, 1, 2, or 3.

In some embodiments, the method for preparing a compound of Formula (II), wherein R* is a radioisotope R* selected from the group consisting of ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, [211]At, [76]Br, [77]Br and [82]Br, can be prepared by, but is not limited to, the following steps:

(a) obtaining a starting material of Formula (II-A):



Formula (II-A)

wherein R^9 is H, F or radioisotope ^{18}F;

R^8 is -H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^7 is selected from the group consisting of -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -$B(OH)_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)$_3$, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

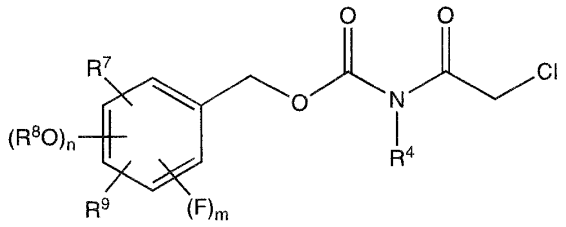
m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof; and

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render a compound of Formula (II), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At.

In some embodiments, the method for the preparation of compounds of Formula (III), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At, comprises the following steps:

(a) obtaining a starting material of Formula (III-A):



Formula (III-A)

wherein R^9 is H, F or radioisotope ^{18}F;

R^8 is H, -PG, aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is H, -PG or -(C_1-C_4) alkyl;

PG, in each instance, is a protecting group;

R^7 is selected from the group consisting of -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -B(OH)$_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)$_3$, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

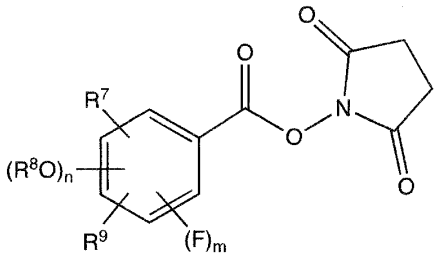
m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof; and

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render a compound of Formula (III), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At.

In some embodiments, the method for the preparation of compounds of Formula (IV), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At, the method comprising

(a) obtaining a starting material of Formula (IV-A):



Formula (IV-A)

wherein R^9 is H, F or radioisotope ^{18}F;

R^8 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^7 is selected from the group consisting of -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -B(OH)$_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)$_3$, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

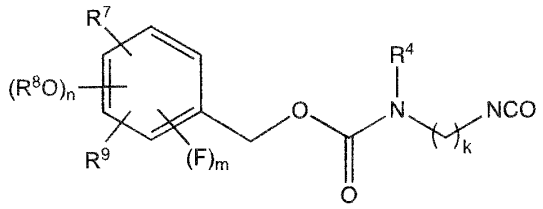
m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof; and

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render a compound of Formula (IV), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At.

In some embodiments, the methods for the preparation of compounds of Formula (V), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At, comprises the following steps:

(a) obtaining a starting material of Formula (V-A):



Formula (V-A)

wherein R^9 is H, F or radioisotope ^{18}F;

R^8 is H, -PG, aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is H, -PG or -(C_1-C_4) alkyl;

PG, in each instance, is a protecting group;

R^7 is selected from the group consisting of -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -B(OH)$_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)$_3$, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

k is 2-6;

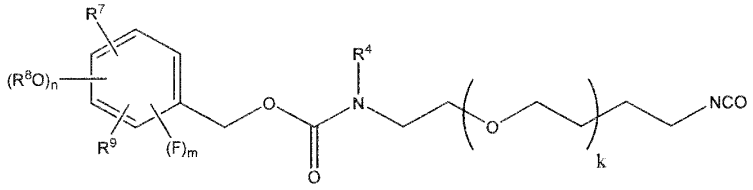
m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof; and

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render a compound of Formula (IV), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At.

In some embodiments, the methods for the preparation of compounds of Formula (VI), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At, comprising the following steps:

(a) obtaining a starting material of Formula (VI-A):



Formula (VI-A)

wherein R^9 is H, F or radioisotope ^{18}F;

R^8 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is H, -PG or -(C_1-C_4) alkyl;

PG, in each instance, is a protecting group;

R^7 is selected from the group consisting of -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -B(OH)$_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)$_3$, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

k is 1-6;

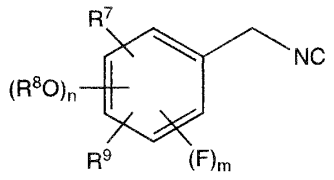
m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof; and

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render a compound of Formula (VI), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At.

In some embodiments, the methods for the preparation of compounds of Formula (VII), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At, comprises the following steps:

(a) obtaining a starting material of Formula (VII-A):



Formula (VII-A)

wherein R^9 is H, F or radioisotope ^{18}F;

R^8 is H, -PG, aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^7 is selected from the group consisting of -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -B(OH)$_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)$_3$, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

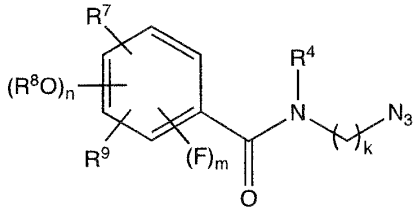
m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof; and

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render a compound of Formula (VII), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At.

In some embodiments, the method for the preparation of compounds of Formula (VIII), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At, the method comprising

(a) obtaining a starting material of Formula (VIII-A):



Formula (VIII-A)

wherein R^9 is H, F or radioisotope ^{18}F;

R^8 is H, -PG, aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is H, -PG or -(C_1-C_4) alkyl;

PG, in each instance, is a protecting group;

R^7 is selected from the group consisting of -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -B(OH)$_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)$_3$, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

k is 2-6;

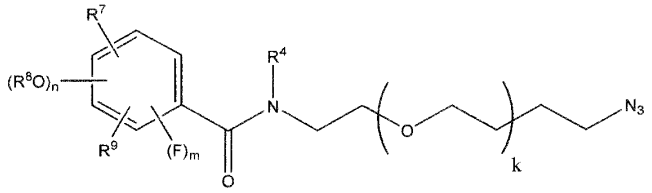
m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof; and

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render a compound of Formula (VIII), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At.

In some embodiments, the methods for the preparation of compounds of Formula (IX), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At, the method comprising

(a) obtaining a starting material of Formula (IX-A):



Formula (IX-A)

wherein R^9 is H, F or radioisotope ^{18}F;

R^8 is H, -PG, aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is H, -PG or -(C_1-C_4) alkyl;

PG, in each instance, is a protecting group;

R^7 is selected from the group consisting of -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -$B(OH)_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)$_3$, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

k is 1-6;

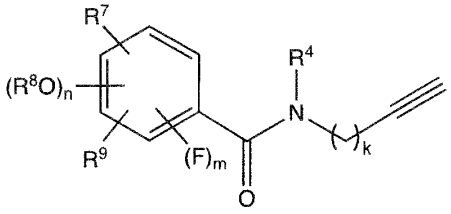
m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof;

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render a compound of Formula (IX), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At.

In some embodiments, the methods for the preparation of compounds of Formula (X), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At, the method comprising

(a) obtaining a starting material of Formula (X-A):



Formula (X-A)

wherein R^9 is H, F or radioisotope ^{18}F;

R^8 is H, -PG, aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is H, -PG or -(C_1-C_4) alkyl;

PG, in each instance, is a protecting group;

R^7 is selected from the group consisting of -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -B(OH)$_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)$_3$, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

k is 1-6;

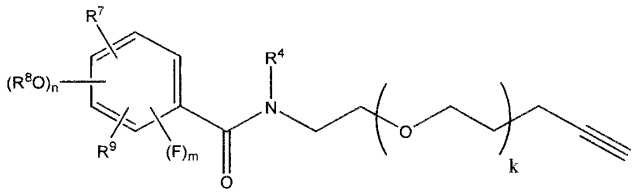
m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof; and

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render a compound of Formula (X), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At.

In some embodiments, the methods for the preparation of compounds of Formula (XI), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At, the method comprising

(a) obtaining a starting material of Formula (XI-A):



Formula (XI-A)

wherein R^9 is H, F or radioisotope ^{18}F;

R^8 is H, -PG, aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is H, -PG or -(C_1-C_4) alkyl;

PG, in each instance, is a protecting group;

R^7 is selected from the group consisting of -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -B(OH)$_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)$_3$, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

k is 1-6;

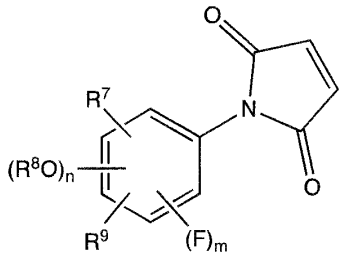
m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof; and

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render a compound of Formula (XI), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At.

In some embodiments, the methods for the preparation of compounds of Formula (XII), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At, the method comprising:

(a) obtaining a starting material of Formula (XII-A):



Formula (XII-A)

wherein R^9 is H, F or radioisotope ^{18}F;

R^8 is H, -PG, aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^7 is selected from the group consisting of -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -B(OH)$_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)$_3$, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

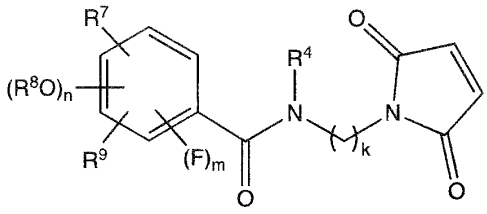
m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof; and

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render a compound of Formula (XII), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At.

In some embodiments, the method for the preparation of compounds of Formula (XIII), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At, the method comprising

(a) obtaining a starting material of Formula (XIII-A):



Formula (XIII-A)

wherein R^9 is H, F or radioisotope ^{18}F;

R^8 is H, -PG, aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is H, -PG, or -(C_1-C_4) alkyl;

PG, in each instance, is a protecting group;

R^7 is selected from the group consisting of -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -$B(OH)_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)$_3$, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

k is 2-6;

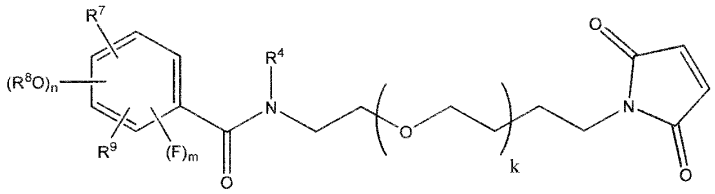
m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof; and

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render a compound of Formula (XIII), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At.

In some embodiments, the method for the preparation of compounds of Formula (XIV), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At, the method comprising

(a) obtaining a starting material of Formula (XIV-A):



Formula (XIV-A)

wherein R^9 is H, F or radioisotope ^{18}F;

R^8 is H, -PG, aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is H, -PG or -(C_1-C_4) alkyl;

PG, in each instance, is a protecting group;

R^7 is selected from the group consisting of -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -B(OH)$_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)$_3$, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

k is 1-6;

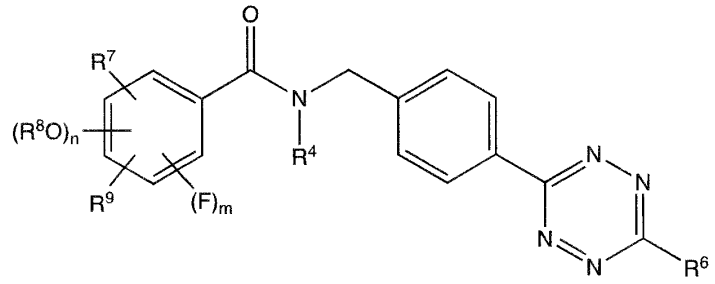
m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof; and

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render a compound of Formula (XIV), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At.

In some embodiments, the method for the preparation of compounds of Formula (XV), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At, the method comprising:

(a) obtaining a starting material of Formula (XV-A):



Formula (XV-A)

wherein R^9 is H, F or radioisotope ^{18}F;

R^8 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^4 is selected from H, -PG or -(C_1-C_4) alkyl;

PG, in each instance, is a protecting group;

R^7 is selected from the group consisting of -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -$B(OH)_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)$_3$, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

R^6 is H, -(C_1-C_4) alkyl, aryl or heteroaryl

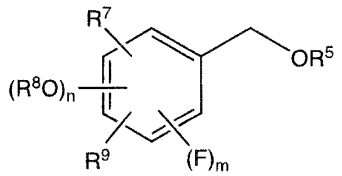
m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render a compound of Formula (XV), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At.

In some embodiments, the method for the preparation of compounds of Formula (XVI), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At, the method comprising

(a) obtaining a starting material of Formula (XVI-A):



Formula (XVI-A)

wherein R^9 is H, F or radioisotope ^{18}F;

R^8 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^5 is H, -PG or -(C_1-C_4) alkyl;

PG, in each instance, is a protecting group;

R^7 is selected from the group consisting of -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -B(OH)$_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)$_3$, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

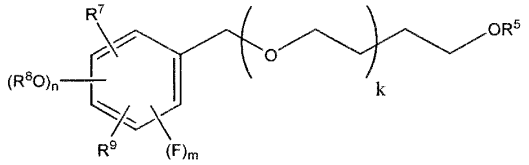
m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof; and

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render a compound of Formula (XVI), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At.

In some embodiments, the method for the preparation of compounds of Formula (XVII), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At, the method comprising

(a) obtaining a starting material of Formula (XVII-A):



Formula (XVII-A)

wherein R^9 is H, F or radioisotope ^{18}F;

R^8 is H, -aryl, -PG, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

R^5 is H, -PG or -(C_1-C_4) alkyl;

PG, in each instance, is a protecting group;

R^7 is selected from the group consisting of -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -B(OH)$_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)$_3$, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

k is 1-6;

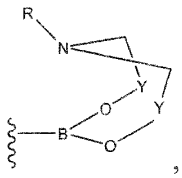
m is 0, 1, 2 or 3;

n is 0, 1 or 2; and any stereoisomer and/or salt thereof; and

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render a compound of Formula (XVII), wherein R^1 is a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, and [211]At.

In some embodiments, the oxidant is an N-halosuccinimide (e.g., N-bromosuccinimide, N-iodosuccinimide, N-chlorosuccinimide, and/or N-astatosuccinimide), H_2O_2, DDQ, CuO_2 or the like, although the oxidant should not be limited thereto.

In some embodiments, the N-methyliminodiacetic acid boronate is



, wherein R is (C_1-C_6) alkyl; and Y is -C(=O)-.

In some embodiments, the method further comprises a base activator, e.g., KOAc or KOtBu. In some embodiments, the base activator is an organic or inorganic fluoride (F^-) source. Exemplary inorganic fluoride sources include, but are not limited to, KHF_2, MgF_2, CsF, KF, CaF_2, and NaF.

In some embodiments, the method disclosed herein is carried out around room temperature (i.e., 22-27 °C). In some embodiments, the method disclosed herein is carried out at elevated temperature (i.e. 40-150 °C).

A skilled artisan would be able to adjust amounts of each reagent, temperature and reaction time accordingly depending on what radioisotope is being used. Moreover, Q groups not specifically provided in examples herein can be installed by methods analogous to those provided herein.

These radiolabeled aromatic electrophilic prosthetic groups can now be coupled with bioactive ligands under mild conditions to render imaging agents (i.e., SPECT and/or PET imaging agents) as well as radiolabeled-based therapy agents.

Thus, another aspect of the current disclosure is to employ the compounds of Formula (I) containing at least one radioisotope in methods of making radiolabeled bioactive ligands. In some embodiments, such methods comprise:

(a) obtaining bioactive ligands as disclosed herein; and

(b) contacting the bioactive ligands with a compound of Formula (I) containing at least one radioisotope to form radiolabeled bioactive ligands.

In some embodiments, the contacting step comprises a base (e.g., DIPEA, Na_2CO_3). In some embodiments, the contacting step is carried out above room temperature (e.g., at a temperature ranging from about 30 °C to about 75 °C). In some embodiments, the contacting step is carried out in an aprotic non-polar solvent (e.g., acetonitrile (ACN), dimethyl formamide (DMF)).

These are just exemplary conditions for the contacting step and should not be limited thereto. A skilled artisan would be aware that the condition for the contacting step varies, in part, on the functionality of Q. For example, the above described conditions for the contacting step may be suitable for aromatic electrophile prosthetic groups comprising compounds of Formula (II-A), (IV-A) and/or (XVI-A).

IV. Synthesis Of Specific Radiolabeled Prosthetic Groups And Their Use In Radiolabeling Bioactive Ligands

Discussed in more detail below in the Examples is the preparation and use of various prosthetic groups disclosed herein and their ability to couple with exemplary bioactive ligands to generate bioactive ligands tagged with a SPECT and/or PET radioisotope. As already mentioned above, these prosthetic groups are electrophilic and can be used in various types of chemistry to couple with functional groups of bioactive ligands thereby forming a covalent bond.

V. Pharmaceutical Formulation

In certain embodiments, compounds, prodrugs or salts of the labeled bioactive ligands disclosed herein, are combined with one or more additional agents to form pharmaceutical formulations. In some embodiments, compounds, prodrugs or salts of the labeled bioactive ligands disclosed herein are non-radioactive (meaning they contain no radioisotope) and are formulated as formulations for treating a disease or condition in a subject in need thereof. In some embodiments, compounds, prodrugs or salts of the labeled bioactive ligands disclosed herein are radioactive (meaning they contain a radioisotope) and are formulated as radionuclide-based formulations for treating a disease or condition in a subject in need thereof. In some embodiments, compounds, prodrugs or salts of the labeled bioactive ligands disclosed herein are formulated as imaging agents to evaluate the potential efficacy of a treatment in a subject in need thereof or to diagnose a disease or condition in a subject. A skilled artisan would be aware that the pharmaceutical formulation of

compounds, prodrugs or salts of the labeled bioactive ligands differ depending on their composition (radioactive or nonradioactive) and use (radiolabeled-based therapy agent or imaging agent).

In some embodiments, the labeled bioactive ligands are already in the form of a prodrug. Pharmaceutical formulations may be formulated in a conventional manner using one or more physiologically acceptable carriers including excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Additional details about suitable excipients for pharmaceutical compositions described herein may be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa. 1975; Liberman, H. A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference for such disclosure. A skilled artisan would generally be aware of the suitable excipients for pharmaceutical formulations and compositions required for any particular mode of administration.

A pharmaceutical formulation, as used herein, refers to a mixture of a compound or salt or prodrug of the labeled bioactive ligands disclosed herein with any suitable substituents and functional groups disclosed herein, with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical formulation facilitates administration of the compound to an organism. In practicing the methods of treatment or use provided herein, therapeutically effective amounts of compounds described herein are administered in a pharmaceutical formulation to a mammal having a disease, disorder, or condition to be treated. In some embodiments, the mammal is a human. A therapeutically effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds or salts of the labeled bioactive ligands with any suitable substituents and functional groups disclosed herein, can be used singly or in combination with one or more therapeutic agents as components of mixtures (as in combination therapy).

The pharmaceutical formulations described herein can be administered to a subject by multiple administration routes, including but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular, intratumoral), intranasal, buccal, topical, rectal, or transdermal administration routes. Moreover, the pharmaceutical formulation described herein, which include a labeled bioactive ligands as disclosed herein with any suitable substituents and functional groups disclosed herein, can be formulated into any suitable dosage form, including but not limited to, aqueous oral dispersions, liquids (e.g., injectables), gels, syrups, elixirs, slurries, suspensions, aerosols, fast melt formulations, effervescent formulations, lyophilized formulations, tablets, powders, pills, dragees, and capsules. In some embodiments, the pharmaceutical formulations described herein are administered to a subject by parenteral administration (e.g., intravenous, subcutaneous, intramuscular, intratumoral). In some embodiments, the pharmaceutical formulations described herein are administered to a subject intravenously. In general, a skilled artisan would be aware of the different modes of administration and as to their suitable formulations (and excipients present therein).

One may administer the compounds and/or formulations in a local rather than systemic manner, for example, via injection of the compound directly into an organ or tissue, often in a depot preparation or sustained release formulation. Such long-acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with an organ-specific antibody. The liposomes will be targeted to and taken up selectively by the organ. In addition, the drug may be provided in the form of a rapid release formulation, in the form of an extended-release formulation, or in the form of an intermediate release formulation.

The pharmaceutical formulation will include at least one labeled bioactive ligands as disclosed herein, as an active ingredient in free-acid or free-base form, or in a pharmaceutically acceptable salt form.

In some embodiments, formulations provided herein may also include one or more preservatives to inhibit microbial activity. Suitable preservatives include, but are not limited to, quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

For intravenous injections, compounds described herein may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally recognized in the field. For other parenteral injections, appropriate formulations may include aqueous or nonaqueous solutions, preferably with physiologically compatible buffers or excipients. Such excipients are generally recognized in the field.

Parenteral injections may involve bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The pharmaceutical formulations described herein may be in a form suitable for parenteral injection as sterile suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or various dextrans. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

In certain embodiments, delivery systems for pharmaceutical compounds may be employed, such as, for example, liposomes and emulsions. In certain embodiments, compositions provided herein also include an mucoadhesive polymer, selected from among, for example, carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and various dextrans.

In some embodiments, the employed delivery system are lipid nanoparticles for delivering bioactive ligands such as labeled peptides and/or proteins with at least one radioisotope as

disclosed herein. In some embodiments, the delivery systems are protein conjugated polymers which comprise tunable rates of release of conjugated proteins/peptides from the polymer.

In some embodiments, the labeled bioactive ligands disclosed herein are combined with other therapeutic agents, such as other anti-cancer agents, anti-allergic agents, anti-nausea agents (or anti-emetics), pain relievers, cytoprotective agents, and combinations thereof.

In another embodiment, the labeled bioactive ligands disclosed herein are combined with another therapeutic agent capable of inhibiting BRAF, MEK, KRAS, SOS1, CDK4/6, SHP-2, HDAC, EGFR, MET, mTOR, PI3K or AKT, or anti-PD1 drugs such as Nivolumab, Pembrolizumab, Cemiplimab, or anti-PDL1 drugs such as Atezolizumab, Durvalumab, Avelumab, or anti-CTL4 drugs such as Ipilimumab or Tremelinumab, or other checkpoint inhibitors including bi-specific antibodies, or PARP inhibitors such as Olaparib, Niraparib, Velaparib, Rucaparib, Talazoparib, Pamiparib, Fluzoparib, or cell therapies such as T-cell receptor therapies, tumor-infiltrating lymphocytes, CAR-T, or immunotherapies such as APC-directed and macrophage-directed antibodies, or vaccines such as mRNA neoantigen vaccines, GM-CSF producing vaccines, peptide vaccines, or a combination thereof.

Generally, an agent, such as a labeled bioactive ligand as disclosed herein, is administered in an amount effective for treating the disease or disorder (i.e., a therapeutically effective amount). Thus, a therapeutically effective amount can be an amount that is capable of at least partially treating, preventing or reversing a disease or disorder. The dose required to obtain an effective amount may vary depending on the agent, formulation, disease or disorder, and individual to whom the agent is administered.

Determination of effective amounts may also involve in vitro assays in which varying doses of the compound disclosed herein is administered to cells in culture and the concentration of the compound effective for ameliorating some or all symptoms is determined in order to calculate the concentration required *in vivo*. Effective amounts may also be based on in *vivo* animal studies.

A compound as disclosed herein can be administered prior to, concurrently with and subsequent to the appearance of symptoms of a disease or disorder. In some embodiments, the compound disclosed herein is administered to a subject with a family history of the disease or

disorder, or who has a phenotype that may indicate a predisposition to a disease or disorder, or who has a genotype which predisposes the subject to the disease or disorder.

The dosing and administration regimes of radionuclide-based formulations containing labeled bioactive ligands to be administered is based on various factors such as the type of radionuclide present in the labeled bioactive ligands, the disease or disorder to be treated, and the subject (age, weight, sex, etc.). Dosing for a therapeutic is typically higher than when used as an imaging agent and can be once a day or multiple times per day for one or more consecutive days. The amount of radioactivity administered during such a treatment course may vary from dose to dose of the radioactive labeled bioactive ligands. The amount of radioactivity of a radioactive labeled bioactive ligand and its frequency and duration of administration is determined by a skilled person in the art, e.g., a physician knowledgeable in Nuclear Medicine, as would be apparent to a skilled artisan. Specifically, a skilled artisan would be aware that for beta-particle therapy (e.g., ^{131}I) the radiolabeled-based therapeutic is administered over a 100-300 mCi range, whereas for alpha-particle therapy (e.g., [211]At) the radiolabeled-based therapeutic would generally be administered over a 1-10 mCi range. It would be understood by a skilled artisan that the radiolabeled-based therapeutics disclosed herein would be administered at doses encompassed by, but not limited to, the above-mentioned ranges depending on the type of therapy (alpha-particle vs. beta-particle).

VI. Methods of Treatment

The disclosure provides labeled bioactive ligands and methods for treating a subject suffering from a disease, comprising administration of a labeled bioactive ligands, prodrug or salt described herein, for example, a prodrug or salt of a labeled bioactive ligands as disclosed herein, to the subject. In some embodiments, the disease is selected from a disease associated with expression of cellular targets involved in aberrant expression, overexpression and/or activity of cellular targets involved in cancer and/or other hyperproliferative disorders. In some embodiments, the cancer and/or hyperproliferative disorder is treatable by the modulation of cellular targets. In some embodiments, the method comprises treating cancer and/or a hyperproliferative disorder that is treatable by modulation of cellular targets involved in cancer and/or hyperproliferative disorders by administering to a subject in need thereof a therapeutically effective amount of a labeled bioactive ligands, prodrug, or a salt thereof or a pharmaceutical composition as disclosed herein.

In some embodiments, the disclosure provides a method for treating cancer in a subject, comprising administration of a labeled bioactive ligands, prodrug or salt described herein, to the subject. In some embodiments, the cancer is mediated by an expression, aberrant expression, overexpression (etc.), of one or more cellular targets involved in cancer and/or hyperproliferative disorders. For example, in some embodiments, the cellular targets involved in cancer are over-expressed in diseased cells (e.g., cancer cells) compared to healthy cells (i.e., cells free of disease).

In certain embodiments, the disclosure provides method of treating cancer and/or a hyperproliferative disorder in a subject, wherein the method comprises determining if the subject has cancer, and administering to the subject a therapeutically effective dose of a labeled bioactive ligands, prodrug or salt described herein.

The disclosure provides methods for treating cancer and/or a hyperproliferative disorder by administering a prodrug, or salt of a labeled bioactive ligands as disclosed herein, to a subject suffering from cancer, wherein the labeled bioactive ligands binds to or is transported by a cellular target involved in the pathogenesis of cancer and/or a hyperproliferative disease. In some embodiments, the compound binds to or is transported by the cellular target involved in the pathogenesis of cancer and/or a hyperproliferative disorder.

In some embodiments, the method relates to the treatment of cancer such as acute myeloid leukemia, cancer in adolescents, childhood adrenocortical carcinoma, AIDS-related cancers, e.g., lymphoma and Kaposi's Sarcoma, anal cancer, appendix cancer, astrocytomas, atypical teratoid, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumors, burkitt lymphoma, carcinoid tumor, atypical teratoid, embryonal tumors, germ cell tumor, primary lymphoma, cervical cancer, childhood cancers, chordoma, cardiac tumors, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myleoproliferative disorders, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, extrahepatic ductal carcinoma in situ (DCIS), embryonal tumors, CNS cancer, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, eye cancer, fibrous histiocytoma of bone, gall bladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic tumor, hairy cell leukemia, head and neck cancer, heart cancer, liver cancer, hodgkin lymphoma,

hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, kidney cancer, laryngeal cancer, lip and oral cavity cancer, liver cancer, lobular carcinoma in situ (LCIS), lung cancer, lymphoma, metastatic squamous neck cancer with occult primary, midline tract carcinoma, mouth cancer multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, multiple myeloma, merkel cell carcinoma, malignant mesothelioma, malignant fibrous histiocytoma of bone and osteosarcoma, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-hodgkin lymphoma, non-small cell lung cancer (NSCLC), oral cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer, stomach (gastric) cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, T-Cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, trophoblastic tumor, unusual cancers of childhood, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, or Viral-Induced cancer. In some embodiments, the method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin, e.g., psoriasis, restenosis, or prostate, e.g., benign prostatic hypertrophy (BPH). In some cases, the method relates to the treatment of leukemia, hematologic malignancy, solid tumor cancer, prostate cancer, e.g., castration-resistant prostate cancer, breast cancer, Ewing's sarcoma, bone sarcoma, primary bone sarcoma, T-cell prolymphocyte leukemia, glioma, glioblastoma, liver cancer, e.g., hepatocellular carcinoma, or diabetes. In some embodiments, the cancer is pancreatic cancer or brain cancer. In some embodiments, brain cancer is selected from the group consisting of Meningioma, Astrocytomas, Gliomas, Glioblastoma multiforme, Medulloblastoma, Ependymoma, Oligodendroglioma, Craniopharyngioma, Pituitary adenoma, Brainstem glioma, Schwannoma, Vestibular schwannoma, Anaplastic astrocytoma, Primary central nervous system lymphoma, Germ cell tumor, Primitive neuroectodermal tumor, Pilocytic astrocytoma, Mixed glioma, Chordoma, Optic nerve glioma and diffuse Astrocytomas.

Subjects that can be treated with labeled bioactive ligands as disclosed herein, or pharmaceutically acceptable salt, ester, prodrug, or stereoisomer of the labeled bioactive ligands, according to the methods of this disclosure include, for example, subjects that have been diagnosed as having acute myeloid leukemia, cancer in adolescents, adrenocortical carcinoma childhood, AIDS-related cancers, e.g., lymphoma and Kaposi's Sarcoma, anal cancer, appendix cancer, astrocytomas, atypical teratoid, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumors, burkitt lymphoma, carcinoid tumor, atypical teratoid, embryonal tumors, germ cell tumor, primary lymphoma, cervical cancer, childhood cancers, chordoma, cardiac tumors, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myleoproliferative disorders, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, extrahepatic ductal carcinoma in situ (DCIS), embryonal tumors, CNS cancer, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, eye cancer, fibrous histiocytoma of bone, gall bladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic tumor, hairy cell leukemia, head and neck cancer, heart cancer, liver cancer, hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, kidney cancer, laryngeal cancer, lip and oral cavity cancer, liver cancer, lobular carcinoma in situ (LCIS), lung cancer, lymphoma, metastatic squamous neck cancer with occult primary, midline tract carcinoma, mouth cancer multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, multiple myeloma, merkel cell carcinoma, malignant mesothelioma, malignant fibrous histiocytoma of bone and osteosarcoma, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-hodgkin lymphoma, non-small cell lung cancer (NSCLC), oral cancer, lip and oral cavity cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer, stomach (gastric) cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, T-Cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma,

thyroid cancer, transitional cell cancer of the renal pelvis and ureter, trophoblastic tumor, unusual cancers of childhood, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Viral-Induced cancer, leukemia, hematologic malignancy, solid tumor cancer, prostate cancer, castration-resistant prostate cancer, breast cancer, Ewing's sarcoma, bone sarcoma, primary bone sarcoma, T-cell prolymphocyte leukemia, glioma, glioblastoma, hepatocellular carcinoma, liver cancer, or diabetes. In some embodiments subjects that are treated with the compounds of the disclosure include subjects that have been diagnosed as having a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin, e.g., psoriasis, restenosis, or prostate, e.g., benign prostatic hypertrophy (BPH).

In some embodiments, subjects that can be treated with labeled bioactive ligands as disclosed herein, or pharmaceutically acceptable salt, ester, prodrug, or stereoisomer of such labeled bioactive ligands, according to the methods of this disclosure include, for example, subjects that have been diagnosed as having pancreatic cancer or brain cancer. In some embodiments, brain cancer is selected from the group consisting of Meningioma, Astrocytomas, Gliomas, Glioblastoma multiforme, Medulloblastoma, Ependymoma, Oligodendroglioma, Craniopharyngioma, Pituitary adenoma, Brainstem glioma, Schwannoma, Vestibular schwannoma, Anaplastic astrocytoma, Primary central nervous system lymphoma, Germ cell tumor, Primitive neuroectodermal tumor, Pilocytic astrocytoma, Mixed glioma, Chordoma, Optic nerve glioma and diffuse Astrocytomas.

In some embodiments, the disclosure provides methods of utilizing a cellular target involved in cellular processes in a cell by contacting the cell with an amount of a labeled bioactive ligands as disclosed herein sufficient to modulate its activity. In some embodiments, the disclosure provides methods of modulating activity of the cellular target of cancer and/or a hyperproliferative disorder in a tissue by contacting the tissue with an amount of a prodrug or salt of a labeled bioactive ligands as disclosed herein, sufficient to modulate or utilize the activity of the cellular target in the tissue.

The compositions containing the labeled bioactive ligands or salts thereof described herein can be administered for prophylactic and/or therapeutic treatments. In therapeutic applications, the compositions are administered to a patient already suffering from a disease, in an amount sufficient to cure or at least partially arrest the symptoms of the disease. Amounts effective for this use will

depend on the severity and course of the disease, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating clinician. In some embodiments, the disease is cancer and/or a hyperproliferative disorder.

The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease and its severity, the identity (e.g., weight) of the subject or host in need of treatment, but can nevertheless be determined in a manner recognized in the field according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

Method of Use

The disclosed labeled bioactive ligands containing a radioisotope (also referred to as radioactive compounds) have use as both radiopharmaceutical agents and also imaging agents in imaging modalities such as PET and SPECT technologies. Typically, imaging modalities are employed to screen for and/or diagnose various disease states and/or follow treatment of various disease states in subjects. In some embodiments, the disease is a hyperproliferative disease. In some embodiments, the disease is cancer.

Thus, one aspect of the current disclosure is that the labeled bioactive ligands disclosed herein can be used as a treatment agent and as an imaging agent. The disclosure refers to such compounds as theranostic agents or as a "theranostic pair" of compounds (e.g., an initial diagnostic agent and a second therapeutic agent). The theranostic agents disclosed herein comprise at least one halogen atom.

In some embodiments, the first theranostic agent and the second theranostic agent are the same, comprising the same radionuclide. Such a theranostic pair would have the same agent being the radiolabeled-based therapy agent (e.g., ^{131}I and [211]At) and the imaging agent (e.g. [18]F, ^{131}I and [211]At).

In some embodiments, the first theranostic agent and the second theranostic agent are not the same. In some embodiments, the first theranostic agent is a therapeutic agent and is a bioactive ligand containing no radioisotopes. In such embodiments, the second theranostic agent is a bioactive ligand comprising a radionuclide generally known to be used in SPECT and PET

imaging modalities (e.g., ^{18}F, [124]I, [75]Br, [76]Br, and [77]Br, ^{123}I, ^{125}I, ^{131}I, [210]At or [211]At).

In an alternate embodiment, the first theranostic agent is a radiolabeled-based therapy agent and are labeled bioactive ligands containing a radioisotope generally known to be used as radiolabeled-based therapy agents (e.g., ^{131}I and/or [211]At). In such embodiments, the second theranostic agent is a labeled bioactive ligand comprising a radionuclide generally known to be used in SPECT and PET imaging modalities (e.g., ^{18}F, [124]I, [75]Br, [76]Br,[77]Br, ^{123}I, ^{125}I, ^{131}I, [210]At or [211]At).

In some embodiments, the atom connectivity (regardless of radioactivity) is the same in both theranostic agents. In other words, often a non-radioactive halogen can be replaced in one theranostic agent with the same or similar halogen but now being a radioisotope, and vice versa. Note that iodine or bromine can be exchanged with radioisotopes of astatine.

Thus, one aspect of the current disclosure is to employ a radioactive compound as disclosed (i.e., labeled bioactive ligands comprising a radioisotope) herein in methods of imaging a subject for diagnosing a disease or monitoring efficacy of treatment of a disease by a) administering to a subject in need thereof radioactive bioactive ligands as disclosed herein in an effective amount; and b) acquiring at least one image of at least a portion of the subject.

The radioactive compound disclosed herein is a labeled bioactive ligand containing a radioisotope suitable for use in imaging modalities such as PET and SPECT technologies. For example, a suitable radioisotope for use in PET imaging is selected from the group consisting of ^{18}F, [124]I, [75]Br, [76]Br, [77]Br and [210]At. A suitable radioisotope for use in SPECT imaging is ^{123}I, ^{125}I, ^{131}I, or [211]At. Thus, the compounds employed in the methods disclosed herein are labeled bioactive ligands containing a radioisotope R* selected from the group consisting of ^{123}I, [124]I, ^{125}I, ^{131}I, [76]Br, [77]Br, [82]Br, ^{18}F, [210]At and [211]At.

In some embodiments, the radioactive compound disclosed herein is part of a theranostic pair as described above. In some embodiments, the radioactive compound disclosed herein is used by itself and is not part of a theranostic pair as described herein.

As already mentioned above, in some embodiments, the radioactive compound disclosed herein is formulated into a pharmaceutical composition/formulation comprising at least one

pharmaceutically acceptable excipient and/or carrier. As will be apparent to those skilled in the art, that one or more pharmaceutically acceptable excipients or carriers will vary depending on the mode of administration of the radioactive compound to a subject in need thereof. In some embodiments, the pharmaceutical composition is in the form of a saline-based solution, a suspension, an emulsion, liposome-based preparation, microsphere-based preparation or any other pharmaceutical formulations in liquid form suitable for injection.

The effective amount of the radioactive compound can vary and depends on the mode of administration; the patient's age, weight, and health; as well as the area to be imaged. A skilled artisan would know how to best determine effective amounts of the disclosed radioactive compound.

In some embodiments, the imaging method disclosed herein are employed for diagnosing a disease or assessing efficacy of treatment of a disease or condition in a patient in need thereof. In some embodiments, the disease or condition is cancer. Various cancer types have already been mentioned above. In some embodiments, the cancer type is pancreatic cancer, breast cancer, glioma, certain ovarian cancers, and others. In some embodiments, the disease or condition is a hyperproliferative disorder of the type as already mentioned above. In some embodiments, the imaging method is employed for diagnosing cancer.

In other embodiments, the imaging method disclosed herein is employed for assessing the efficacy of a treatment to treat a disease or conditions in a person in need thereof. In some embodiments, the disease or condition is cancer. In some embodiments, the treatment comprises administration to the subject in need thereof a therapeutically effective amount of at least one therapeutic agent, i.e., an anti-cancer agent. A skilled artisan would generally be familiar with current anti-cancer treatments, which include, but are not limited to, administration of one or more anti-cancer drugs, radiation, surgery, radiolabeled-based therapy, and/or any combination thereof. In some embodiments, the anti-cancer treatment comprises administration of a compound of Formula (I) as already described above. In some embodiments, the labeled bioactive ligands are not radioactive. In some embodiments, the anti-cancer treatment comprises administration of labeled bioactive ligands as disclosed herein. In some embodiments, the labeled bioactive ligands are radioactive (and thus contain a radionuclide).

In some embodiments, the anti-cancer treatment comprises administration of a commercially available anti-cancer agent. Exemplary anti-cancer agents include, but are not limited to, Altretamine, Bendamustine, Busulfan, Carmustine, Chlorambucil, Cyclophosphamide, Dacarbazine, Ifosfamide, Lomustine, Lurbinectedin, Mechlorethamine, Melphalan, Procarbazine, Streptozocin, Temozolomide, Thiotepa, Trabectedin, Carboplatin, Cisplatin, Oxaliplatin, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitomycin, Mitoxantrone, Plicamycin, Valrubicin, Methotrexate, Pemetrexed, Pralatrexate, Trimetrexate, Azathioprine, Cladribine, Fludarabine, Mercaptopurine, Thioguanine, Azacitidine, Capecitabine, Cytarabine, Decitabine, Floxuridine, Fluorouracil, Gemcitabine, Trifluridine/Tipracil, Aldesleukin (IL-2), Denileukin Diftitox, Interferon Gamma, Belinostat, Panobinostat, Romidepsin, Vorinostat, Antiandrogens: Abiraterone, Apalutamide, Bicalutamide, Cyproterone, Enzalutamide, Flutamide, Nilutamide, Antiestrogens (including Aromatase Inhibitors): Anastrozole, Exemestane, Fulvestrant, Letrozole, Raloxifene, Tamoxifen, Toremifene, Gonadotropin Releasing Hormone Analogues: Degarelix, Goserelin, Histrelin, Leuprolide, Relugolix, Triptorelin, Lanreotide, Octreotide, Pasireotide, Alemtuzumab, Atezolizumab, Avelumab, Bevacizumab, Blinatumomab, Brentuximab, Cemiplimab, Cetuximab, Daratumumab, Dinutuximab, Dostarlimab, Durvalumab, Elotuzumab, Gemtuzumab, Inotuzumab Ozogamicin, Ipilimumab, Mogamulizumab, Moxetumomab Pasudotox, Necitumumab, Nivolumab, Ofatumumab, Olaratumab, Panitumumab, Pembrolizumab, Pertuzumab, Ramucirumab, Rituximab, Teclistamab, Tositumomab, Trastuzumab, Tremelimumab, Abemaciclib, Acalabrutinib, Afatinib, Alectinib, Alpelisib, Axitinib, Binimetinib, Bortezomib, Bosutinib, Brigatinib, Cabozantinib, Carfilzomib, Ceritinib, Cobimetinib, Copanlisib, Crizotinib, Dabrafenib, Dacomitinib, Dasatinib, Duvelisib, Enasidenib, Encorafenib, Entrectinib, Erdafitinib, Erlotinib, Fedratinib, Futibatinib, Gefitinib, Gilteritinib, Glasdegib, Ibrutinib, Idelalisib, Imatinib, Infigratinib, Ivosidenib, Ixazomib, Lapatinib, Larotrectinib, Lenvatinib, Lorlatinib, Midostaurin, Neratinib, Nilotinib, Niraparib, Olaparib, Osimertinib, Palbociclib, Pazopanib, Pemigatinib, Pexidartinib, Ponatinib, Regorafenib, Ribociclib, Rucaparib, Ruxolitinib, Selumetinib, Sonidegib, Sorafenib, Sunitinib, Talazoparib, Trametinib, Vandetanib, Vemurafenib, Vismodegib, Zanubrutinib, Cabazitaxel, Docetaxel, Paclitaxel, Etoposide, Irinotecan, Teniposide, Topotecan, Vinblastine, Vincristine, Vinorelbine, Asparaginase (Pegaspargase), Belzutifan, Bexarotene, Cedazuridine, Eribulin, Everolimus, Hydroxyurea, Ixabepilone, Lenalidomide, Mitotane,

Omacetaxine, Pomalidomide, Selinexor, Tagraxofusp, Tazemetostat, Tebentafusp, Telotristat, Temsirolimus, Thalidomide, and Venetoclax.

In some embodiments, the treatment comprises a commercially available radiolabeled-based therapeutic agent. Exemplary commercially available radiolabel-based therapeutic agent include, but are not limited to, radium-223 dichloride (Xofigo®), sodium iodide I-131 (Hicon®), lobenguane iodine-131 (Azedra®), lutetium-177 (Lutathera® and Pluvicto®) and yttrium-90 (Zevalin®).

In some embodiments, the therapeutic agent is administered prior to administration of the imaging agent disclosed herein.

Using the imaging methods disclosed herein can aid in identifying the presence or absence of tumors and/or changes in size of identified tumors.

EXAMPLES

General methods and materials

Commercially available chemicals and reagents were purchased from Fisher Scientific, Millipore Sigma, Acros, Alfa Aesar, TCI, Matrix Scientific, Combi-Blocks, Oakwood Chemical, Bide Pharm, or an appropriate vendor and were used as received unless otherwise noted.

Diethyl ether, dichloromethane, tetrahydrofuran, toluene, acetonitrile, dimethylsulfoxide and dimethylformamide were dried by passing through activated alumina under nitrogen prior to use or as anhydrous solvents provided by the vendor.

Column chromatography purifications were performed using technical grade silica gel (60Å, 230-400 mesh, 40-63 μm particle size) from Millipore Sigma, or using SiliaFlash P60 silica gel (40-63 μm) from Silicycle. Prepacked silica columns or C18-functionalized silica columns (20-35 μm) were typically obtained from Teledyne ISCO.

All catalyst and substrate syntheses were run under a nitrogen atmosphere unless otherwise noted.

Nuclear magnetic resonance (NMR) spectra were obtained using Varian or Bruker 400 MR spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz, ^{19}F NMR at 376 MHz). Some NMR spectra were obtained using Bruker Neo Console 500 MHz NMR spectrometer with a cryoprobe

(^{1}H NMR at 500 MHz, ^{13}C NMR at 125 MHz, ^{19}F NMR at 470 MHz). All spectra were reported as parts per million. ^{1}H NMR and ^{13}C NMR spectra were referenced to the residual protium solvent peaks of chloroform-d (^{1}H NMR: 7.26 ppm, ^{13}C NMR: 77.16 ppm), D_2O (^{1}H NMR: 4.80 ppm) or dimethyl sulfoxide-d_6 (^{1}H NMR: 2.50 ppm, ^{13}C NMR: 39.52 ppm).

High resolution mass spectra (HRMS) data were obtained via direct infusion using a ThermoScientific Q Exactive™ HF-X mass spectrometer with positive mode electrospray ionization, positive mode atmospheric-pressure chemical ionization, and/or atmospheric-pressure photoionization. Some HRMS data were obtained via direct infusion using a Thermo LTQ FT mass spectrometer with positive mode electrospray ionization. Most LCMS data was obtained on a Shimadzu LCMS-2020 using electrospray ionization. Most GCMS data was obtained on an Agilent 8890 GC System 5977B MSD using electron ionization.

General radiochemistry methods and materials

[^{18}F]Fluoride was produced via the ^{18}O (p, n) ^{18}F reaction by proton irradiation (40 μA, 45 min) of an [^{18}O]H_2O containing target in a GE PETTrace cyclotron. The aqueous solution of [^{18}F]Fluoride was delivered into a hot cell, and passed through a QMA cartridge (water preconditioning). The [^{18}F]Fluoride was then eluted from the cartridge with a solution mixture containing tetrabutylammonium bicarbonate aqueous solution (20%, w/w, 70 μL), water (53 μL), and acetonitrile (477 μL). After azeotropic drying with acetonitrile (1 mL X3) under stream of Argon at 95 °C, the residue was dissolved in acetonitrile (1 mL) to afford the TBA[^{18}F]/MeCN solution for radiolabeling reactions.

The activities of fluorine-18 samples were measured by CRC-25 PET detector from Capintec, or by Atomlab 400 dose calibrator from Biodex.

After each reaction, an aliquot of reaction mixture was taken for the HPLC analysis/purification. The activity injected for HPLC was measured (α) and the time of injection was recorded. The fraction corresponding to the radiolabeled product was collected, the activity of the collected fraction was measured (β) and the time was recorded. The decay corrected β was calculated from the recorded isolation time. The decay corrected RCY was calculated by dividing decay corrected β by α.

Quality controls (QC) were done for most samples in order to confirm the purity of each isolated product: an aliquot of the fraction collected from radio-HPLC (containing the ^{18}F-labeled product) was injected for a separate HPLC analysis with both radio detector and UV detector.

Co-injections were done for most samples in order to confirm the identity of each isolated product: an aliquot of the fraction collected from radio-HPLC (containing the ^{18}F-labeled product) was mixed with ^{19}F-containing standard, then injected for a separate HPLC analysis with both radio detector and UV detector. For the samples without co-injections, the identities of the radiolabeled compounds were confirmed by comparison to authentic fluorine-19 standards.

General HPLC conditions

Reversed-phase high performance liquid chromatography (HPLC) was typically performed on an Agilent chromatography system (Model 1260 Infinity), or on a SHIMADZU chromatography system (Model CBM-20A).

HPLC column 1: Gemini® C18 10μ 110Å 250X4.6mm column

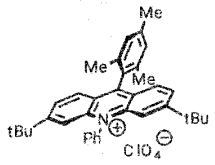
HPLC column 2: Luna® 5μ C18(2) 100Å 250X4.6mm column

HPLC gradient elution method A: using solvent A (0.1% TFA water) and solvent B (0.1% TFA acetonitrile). Flow rate: 1 mL/min. Grad/isocrat: 0 to 2 min: isocratic elution at 40% solvent B; 2 to 12 min: 40% to 95% solvent B; after 12 min: isocratic elution at 95% solvent B.

HPLC gradient elution method B: using solvent A (0.1% TFA water) and solvent B (0.1% TFA acetonitrile). Flow rate: 1 mL/min. Grad/isocrat: 0 to 2 min: isocratic elution at 5% solvent B; 2 to 22 min: 5% to 95% solvent B; after 22 min: isocratic elution at 95% solvent B.

HPLC gradient elution method C: using solvent A (0.1% TFA water) and solvent B (0.1% TFA acetonitrile). Flow rate: 1 mL/min. Grad/isocrat: 0 to 2 min: isocratic elution at 20% solvent B; 2 to 22 min: 20% to 60% solvent B; after 22 min: isocratic elution at 60% solvent B.

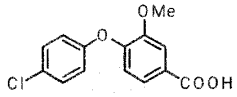
Preparation of precursors and cold references



S1

Example 1: **Synthesis of 9-mesityl-3,6-di-*tert*-butyl-10-phenylacridinium perchlorate (S1)**

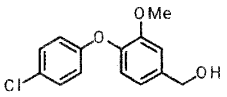
The acridinium photocatalyst **S1** was prepared according to a published procedure; spectral data are in agreement with literature values.[66]



S2

Example 2: **Synthesis of 4-(4-chlorophenoxy)-3-methoxybenzoic acid (S2)**

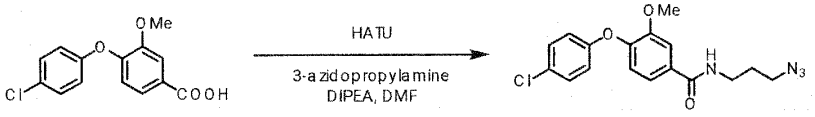
Carboxylic acid **S2** was prepared according to a published procedure; spectral data are in agreement with literature values.[69]



S3

Example 3: **Synthesis of (4-(4-chlorophenoxy)-3-methoxyphenyl)methanol (S3)**

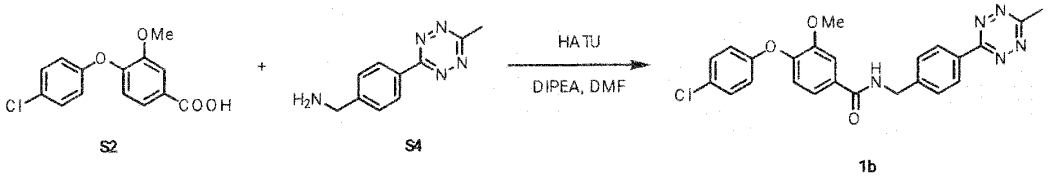
Alcohol **S3** was prepared according to a published procedure; spectral data are in agreement with literature values. [69]



S2 **1a**

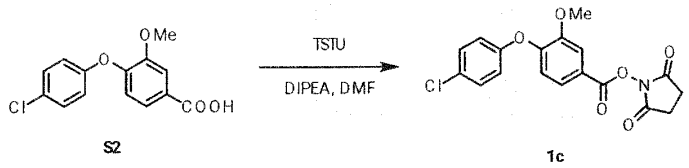
Example 4: **Synthesis of N-(3-azidopropyl)-4-(4-chlorophenoxy)-3-methoxybenzamide (1a)**

To a solution of **S2** (14 mg, 0.050 mmol) in DMF (0.2 mL) was added HATU (38 mg, 0.10 mmol) and DIPEA (43.5 μL, 0.25 mmol). After 1 hour, 3-azidopropylamine (4.9 μL, 0.050 mmol) was added. After 3 days, flash chromatography (33% EtOAc in hexane) afforded **1a** (6.8 mg, 38% yield) as an off-white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 1.7 Hz, 1H), 7.27 (d, J = 9.2 Hz, 2H), 7.20 (dd, J = 8.2, 1.9 Hz, 1H), 6.95-6.86 (m, 3H), 6.36 (br s, 1 H), 3.89 (s, 3H), 3.56 (dt, apparent q, J = 6.4 Hz, 2H), 3.46 (t, J = 6.4 Hz, 2H), 1.92 (tt, apparent quintet, J = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 155.8, 151.3, 148.1, 131.2, 129.8, 128.5, 119.7, 119.3, 119.0, 112.4, 56.3, 49.8, 38.1, 28.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{18}ClN_4O_3$ 361.1067; found 361.1062.



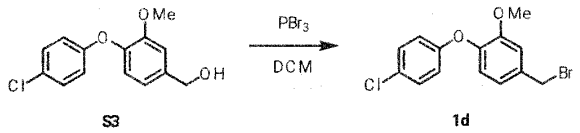
Example 5: Synthesis of 4-(4-chlorophenoxy)-3-methoxy-N-(4-(6-methyl-1,2,4,5-tetrazin-3-yl)benzyl)benzamide (1b)

To a solution of **S2** (14 mg, 0.050 mmol) in DMF (0.2 mL) was added HATU (38 mg, 0.10 mmol) and DIPEA (43.5 µL, 0.25 mmol). After 1 hour, amine **S4** (10 mg, 0.050 mmol) was added. After 2 days, gradient flash chromatography (9% EtOAc in hexane to 33% EtOAc in hexane) afforded **1b** (12.2 mg, 53% yield) as a purple powder: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 1.4 Hz, 1H), 7.54 (d, J = 8.2 Hz, 2H), 7.31-7.23 (m, 3H), 6.93-6.85 (m, 3H), 6.72 (t, J = 5.8 Hz, 1H), 4.75 (d, J = 5.7 Hz, 2H), 3.88 (s, 3H), 3.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 166.8, 163.8, 155.5, 151.2, 148.2, 143.1, 131.1, 130.6, 129.7, 128.5, 128.4, 128.3, 119.5, 119.2, 119.0, 112.4, 56.1, 43.8, 21.2; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{21}ClN_5O_3$ 462.1333; found 462.1327.



Example 6: Synthesis of 2,5-dioxopyrrolidin-1-yl 4-(4-chlorophenoxy)-3-methoxybenzoate (1c)

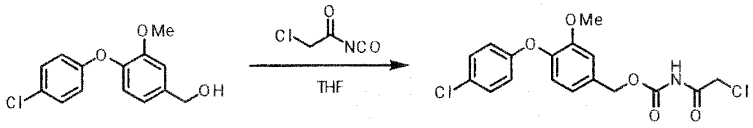
To a solution of carboxylic acid **S2** (249 mg, 0.89 mmol) in DMF (3.0 mL) was added *N,N,N',N'*-tetramethyl-*O*-(*N*-succinimidyl)uronium tetrafluoroborate (TSTU, 536 mg, 1.78 mmol) and DIPEA (472 µL, 2.70 mmol). After 20 hours, flash chromatography (33% EtOAc in hexane) furnished the succinimidyl ester **1c** (250 mg, 74% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.68 (m, 2H), 7.33 (d, J = 8.9 Hz, 2H), 6.96 (d, J = 8.9 Hz, 2H), 6.91 (d, J = 8.4 Hz, 1H), 3.93 (s, 3H), 2.91 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 161.2, 154.5, 151.7, 150.6, 130.0, 129.4, 124.6, 120.5, 120.3, 118.4, 114.1, 56.2, 25.7; HRMS (APCI) m/z $[M]^+$ calcd for $C_{18}H_{14}ClO_6N$ 375.0510; found 375.0507.



S3 1d

Example 7: **Synthesis of 4-(bromomethyl)-1-(4-chlorophenoxy)-2-methoxybenzene (1d).**

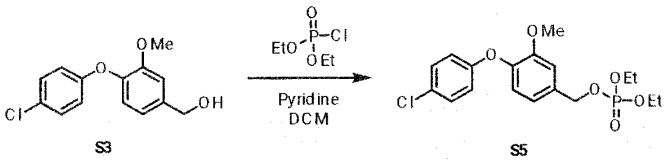
To a solution of alcohol **S3** (380 mg, 1.44 mmol) in DCM (14.4 mL) was added phosphorus tribromide solution (2.16 mL, 1 M solution in DCM, 2.16 mmol). After 6 hours, water (1 mL) was added. The mixture was extracted with EtOAc. Concentration and flash chromatography (9% EtOAc in hexane) furnished brominated **1d** (363 mg, 77% yield) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.22 (m, 2H), 7.03 (d, J = 1.7 Hz, 1H), 6.97-6.85 (m, 4H), 4.50 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 151.4, 145.1, 134.8, 129.7, 127.9, 121.9, 120.9, 118.8, 113.7, 56.2, 33.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{13}BrClO_2$ 326.9787; found 326.9779.



S3 1e

Example 8: **Synthesis of 4-(4-chlorophenoxy)-3-methoxybenzyl (2-chloroacetyl)carbamate (1e).**

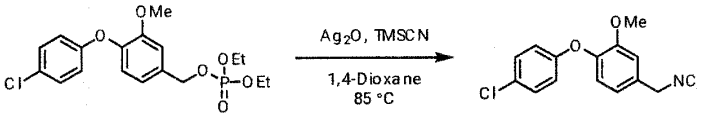
To a solution of alcohol **S3** (300 mg, 1.13 mmol) in THF (11.3 mL) was added chloroacetyl isocyanate (96 μL, 1.13 mmol). After 4 hours, mixture was concentrated. Gradient flash chromatography (9% EtOAc in hexane to 33% EtOAc in hexane) afforded **1e** (202 mg, 46% yield) as a pale yellow solid: ^{1}H NMR (400 MHz, DMSO-d6) δ 11.06 (s, 1H), 7.35 (d, J = 8.9 Hz, 2H), 7.25 (s, 1H), 7.12-7.01 (m, 2H), 6.83 (d, J = 8.9 Hz, 2H), 5.16 (s, 2H), 4.50 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d6) δ 166.7, 156.7, 151.4, 151.2, 143.0, 133.4, 129.5, 125.9, 121.8, 121.0, 117.6, 113.5, 66.4, 55.8, 44.2; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{15}Cl_2NO_5Na$ 406.0225; found 406.0226.



S3 S5

Example 11: **Synthesis of 4-(4-chlorophenoxy)-3-methoxybenzyl diethyl phosphate (S5)**

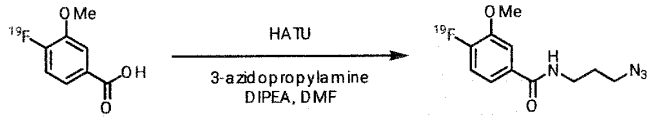
To a solution of alcohol **S3** (771 mg, 2.91 mmol) in DCM (5.8 mL) was added diethyl chlorophosphate (0.84 mL, 5.8 mmol) and pyridine (0.59 mL, 7.3 mmol). After 3.5 hours, water (10 mL) was added. The mixture was extracted with DCM. Concentration and flash chromatography (50% EtOAc in hexane) afforded **S5** (978 mg, 84% yield) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.9 Hz, 2H), 7.06 (s, 1H), 6.94 (s, 2H), 6.86 (d, J = 8.9 Hz, 2H), 5.04 (d, J = 8.2 Hz, 2H), 4.12 (dt, J = 14.4, 7.3 Hz, 4H), 3.84 (s, 3H), 1.33 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 151.5, 145.0, 133.4 (d, J = 7.0 Hz), 129.6, 127.8, 121.0, 120.8, 118.6, 112.7, 68.9 (d, J = 5.5 Hz), 64.0 (d, J = 5.9 Hz), 56.2, 16.3 (d, J = 6.7 Hz); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{18}H_{22}ClO_6PNa$ 423.0740, found 423.0727.



S5 1i

Example 12: **Synthesis of 1-(4-chlorophenoxy)-4-(isocyanomethyl)-2-methoxybenzene (1i)**

To a solution of **S5** (200 mg, 0.50 mmol) in 1,4-dioxane (1 mL) was added silver oxide (11.6 mg, 0.05 mmol) and TMSCN (125 µL, 1.0 mmol). The mixture was heated at 85 °C for 30 min. Flash chromatography (25% EtOAc in hexane) afforded **1i** (54.3 mg, 40% yield) as a pale-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.9 Hz, 2H), 7.00-6.95 (m, 2H), 6.91-6.83 (m, 3H), 4.63 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1 (t, J = 5.3 Hz), 156.4, 151.9, 145.0, 129.7, 129.4, 127.9, 121.4, 119.5, 118.6, 111.4, 56.2, 45.4 (t, J = 7.1 Hz); HRMS (APCI/APPI) m/z $[M]^+$ calcd for $C_{15}H_{12}ClNO_2$ 273.0557, found 273.0549.

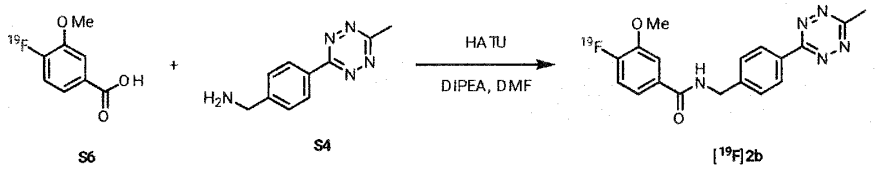


S6 [^{19}F]2a

Example 13: **Synthesis of N-(3-azidopropyl)-4-fluoro-3-methoxybenzamide ([^{19}F]2a)**

To a solution of carboxylic acid **S6** (8.5 mg, 0.050 mmol) in DMF (0.2 mL) was added HATU (38 mg, 0.10 mmol) and DIPEA (43.5 µL, 0.25 mmol). After 1 hour, 3-azidopropylamine (4.9 µL, 0.050 mmol) was added. After 3 days, flash chromatography (33% EtOAc in hexane) afforded [^{19}F]**2a** (6.6 mg, 52% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.1, 1.7 Hz, 1H), 7.24-7.17 (m, 1H), 7.08 (dd, J = 10.6, 8.4 Hz, 1H), 6.50 (br s, 1H), 3.92 (s,

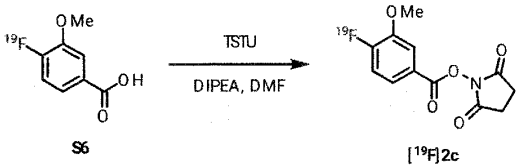
3H), 3.54 (dd, J = 12.3, 6.3 Hz, 2H), 3.44 (t, J = 6.5 Hz, 2H), 1.90 (tt, apparent quintet, J = 6.5 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -130.0-(-)130.1 (m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 154.4 (d, J = 254.5 Hz), 147.9 (d, J = 11.0 Hz), 130.9 (d, J = 3.6 Hz), 118.8 (d, J = 7.6 Hz), 115.8 (d, J = 19.3 Hz), 113.0 (d, J = 2.8 Hz), 56.3, 49.6, 38.0, 28.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{11}H_{14}FN_4O_2$ 253.1101; found 253.1095.



S6 S4 [^{19}F]2b

Example 14: **Synthesis of 4-fluoro-3-methoxy-N-(4-(6-methyl-1,2,4,5-tetrazin-3-yl)benzyl)benzamide ([^{19}F]2b)**

To a solution of carboxylic acid **S6** (8.5 mg, 0.050 mmol) in DMF (0.2 mL) was added HATU (38 mg, 0.10 mmol) and DIPEA (43.5 μL, 0.25 mmol). After 1 hour, amine **S4** (10 mg, 0.05 mmol) was added. After 18 hours, flash chromatography (33% EtOAc in hexane) afforded [^{19}F]**2b** (13.5 mg, 77% yield) as a purple solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 8.2 Hz, 2H), 7.60-7.53 (m, 3H), 7.26 (s, 1H), 7.10 (dd, J = 10.5, 8.5 Hz, 1H), 6.60 (br s, 1H), 4.75 (d, J = 5.7 Hz, 2H), 3.94 (s, 3H), 3.09 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -129.5-(-)129.7 (m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 166.7, 164.0, 154.7 (d, J = 252.3 Hz), 148.2 (d, J = 10.8 Hz), 143.1, 131.3, 130.8 (d, J = 3.7 Hz), 128.6, 128.5, 119.0 (d, J = 7.6 Hz), 116.0 (d, J = 19.2 Hz), 113.3 (d, J = 2.9 Hz), 56.5, 44.0, 21.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{17}FN_5O_2$ 354.1366; found 354.1360.

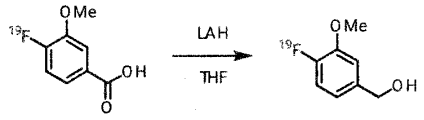


S6 [^{19}F]2c

Example 15: **Synthesis of 2,5-dioxopyrrolidin-1-yl 4-fluoro-3-methoxybenzoate ([^{19}F]2c)**

To a solution of carboxylic acid **S6** (50 mg, 0.29 mmol) in DMF (970 μL) was added *N,N,N',N'*-tetramethyl-*O*-(*N*-succinimidyl)uronium tetrafluoroborate (174 mg, 0.58 mmol) and DIPEA (152 μL, 0.87 mmol). After 19 hours, flash chromatography (33% EtOAc in hexane) furnished succinimidyl ester [^{19}F]**2c** (71 mg, 91% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.74 (m, 1H), 7.70 (dd, J = 8.1, 1.8 Hz, 1H), 7.20 (dd, J = 10.5, 8.5 Hz, 1H), 3.95

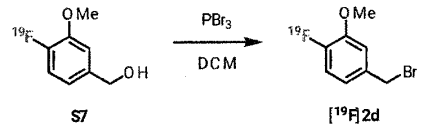
(s, 3H), 2.91 (s, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -123.1-(-)123.2 (m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 161.1, 156.8 (d, J = 257.4 Hz), 148.2, (d, J = 11.2 Hz), 124.6 (d, J = 8.4 Hz), 121.5 (d, J = 3.6 Hz), 116.7 (d, J = 19.5 Hz), 115.2 (d, J = 3.7 Hz), 56.5, 25.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{11}FNO_5$ 268.0621; found 268.0616.



S6 S7

Example 16: **Synthesis of (4-fluoro-3-methoxyphenyl)methanol (S7).**

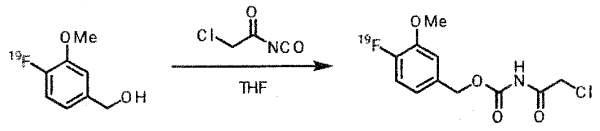
To a solution of carboxylic acid **S6** (500 mg, 2.94 mmol) in THF (2.9 mL) was added lithium aluminum hydride powder (223 mg, 5.88 mmol). After 20 minutes, water (10 mL) was added slowly. The mixture was extracted with EtOAc. The organic layer was concentrated. Gradient flash chromatography (9% EtOAc in hexane to 33% EtOAc in hexane) afforded **S7** (463 mg, quantitative yield) as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08-6.98 (m, 2H), 6.89-6.82 (m, 1H), 4.64 (s, 2H), 3.90 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -136.9-(-)137.0 (m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0 (d, J = 245.3 Hz), 147.9 (d, J = 10.7 Hz), 137.3 (d, J = 3.8 Hz), 119.3 (d, J = 7.0 Hz), 116.0 (d, J = 18.5 Hz), 112.3 (d, J = 2.0 Hz), 65.0, 56.3; HRMS (APCI/APPI) m/z $[M]^+$ calcd for $C_8H_9FO_2$ 156.0587; found 156.0580.



S7 [^{19}F]2d

Example 17: **Synthesis of 4-(bromomethyl)-1-fluoro-2-methoxybenzene ([^{19}F]2d).**

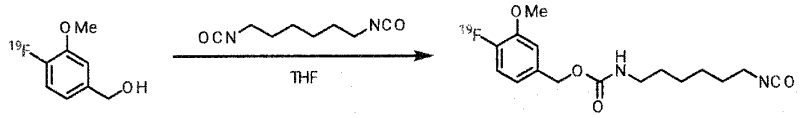
To a solution of alcohol **S7** (20 mg, 0.13 mmol) in DCM (1.3 mL) was added phosphorus tribromide solution (0.20 mL, 1 M solution in DCM, 0.20 mmol). After 1 hour, water (1 mL) was added. The mixture was extracted with EtOAc. The organic layer was concentrated. Flash chromatography (33% EtOAc in hexane) afforded brominated [^{19}F]**2d** (13.7 mg, 49% yield) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06-6.97 (m, 2H), 6.94-6.89 (m, 1H), 4.46 (s, 2H), 3.90(s, 3H); ^{19}F NMR (375 MHz, $CDCl_3$) δ -137.8-(-)134.8 (m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5 (d, J = 257.8 Hz), 147.9 (d, J = 10.9 Hz), 134.2 (d, J = 3.9 Hz), 121.6 (d, J = 7.3 Hz), 116.28 (d, J = 18.6 Hz), 114.3 (d, J = 2.2 Hz), 56.4, 33.3; HRMS (APCI/APPI) m/z $[M]^+$ calcd for C_8H_8BrFO 217.9743; found 217.9736.



S7 [19F]2e

Example 18: **Synthesis of 4-fluoro-3-methoxybenzyl (2-chloroacetyl)carbamate ([^{19}F]2e).**

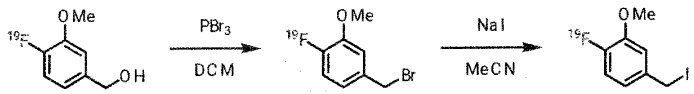
To a solution of alcohol **S7** (20 mg, 0.13 mmol) in THF (1.3 mL) was added chloroacetyl isocyanate (17 μL, 0.20 mmol). After 19 hours, the mixture was concentrated. Flash chromatography (33% EtOAc in hexane) afforded [^{19}F]**2e** (23.2 mg, 66% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.07 (dd, J = 11.0, 8.2 Hz, 1H), 6.99 (dd, J = 8.0, 1.7 Hz, 1H), 6.94-6.88 (m, 1H), 5.15 (s, 2H), 4.46 (s, 2H), 3.90 (s, 3H); ^{19}F NMR (375 MHz, $CDCl_3$) δ -134.3-(-)134.2 (m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 152.8 (d, J = 248.2 Hz), 151.0, 148.0 (d, J = 10.7 Hz), 130.9 (d, J = 3.9 Hz), 121.5 (d, J = 7.2 Hz), 116.4 (d, J = 18.7 Hz), 114.1 (d, J = 2.3 Hz), 68.2, 56.4, 43.6; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{11}H_{11}ClFNO_4Na$ 298.0258; found 298.0253.



S7 [19F]2h

Example 19: **Synthesis of 4-fluoro-3-methoxybenzyl (6-isocyanatohexyl)carbamate ([^{19}F]2h)**

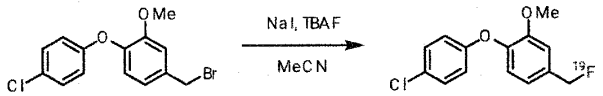
To a solution of alcohol **S7** (20 mg, 0.13 mmol) in THF (152 μL) was added hexamethylene diisocyanate (122 μL, 0.76 mmol). After 7 days, the mixture was concentrated. Gradient flash chromatography (9% EtOAc in hexane to 33% EtOAc in hexane) furnished isocyanate [^{19}F]**2h** (12 mg, 29% yield) as pale-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (dd, J = 11.1, 8.3 Hz, 1H), 6.97 (dd, J = 8.1, 1.4 Hz, 1H), 6.92-6.85 (m, 1H), 5.03 (s, 2H), 4.73 (br s, 1H), 3.89 (s, 3H), 3.29 (t, J = 6.6 Hz, 2H), 3.20 (dt, apparent q, J = 6.5 Hz, 2H), 1.66-1.46 (m, 4H), 1.45-1.29 (m, 4H); ^{19}F NMR (375 MHz, $CDCl_3$) δ -135.8-(-)135.9 (m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 152.4 (d, J = 247.9 Hz), 147.8 (d, J = 11.0 Hz), 133.1 (d, J = 3.9 Hz), 120.9 (d, J = 6.9 Hz), 116.1 (d, J = 18.4 Hz), 113.7 (d, J = 1.9 Hz), 99.9, 66.4, 56.4, 43.0, 41.1, 31.2, 30.0, 26.3, 26.2; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{22}FN_2O_4$ 325.1563; found 325.1555.



S7 [^{19}F]2d [^{19}F]2f

Example 20: **Synthesis of 1-fluoro-4-(iodomethyl)-2-methoxybenzene ([^{19}F]2f)**

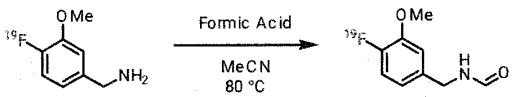
Bromide [^{19}F]**2d** was prepared from alcohol **S7** (30 mg, 0.19 mmol) via the aforementioned procedure. To a solution of the obtained [^{19}F]**2d** in MeCN (3.8 mL) was added sodium iodide (85 mg, 0.57 mmol). After 48 hours, concentration and flash chromatography (20% EtOAc in hexane) afforded [^{19}F]**2f** (21.9 mg, 43% yield over 2 steps) as a pale-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02-6.94 (m, 2H), 6.94-6.88 (m, 1H), 4.42 (s, 2H), 3.89 (s, 3H); ^{19}F NMR (375 MHz, $CDCl_3$) δ -135.2-(-)135.4 (m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0 (d, J = 246.9 Hz), 147.8 (d, J = 11.0 Hz), 135.7 (d, J = 3.8 Hz), 121.2 (d, J = 7.0 Hz), 116.3 (d, J = 18.8 Hz), 114.1 (d, J = 2.2 Hz), 56.4, 5.2; HRMS (APCI/APPI) m/z [M+H]$^+$ calcd for C_8H_9FIO 266.9682; found 266.9674.



1d [^{19}F]2g

Example 21: **Synthesis of 1-(4-chlorophenoxy)-4-(fluoromethyl)-2-methoxybenzene ([^{19}F]2g)**

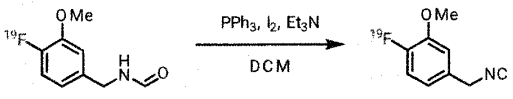
To a solution of bromide **1d** (43 mg, 0.13 mmol) in MeCN (2.6 mL) was added sodium iodide (58 mg, 0.39 mmol) and TBAF (1.1 mL, 1 M solution in THF, 1.1 mmol). After 23 hours, concentration and flash chromatography (9% EtOAc in hexane) afforded [^{19}F]**2g** (34.7 mg, 99% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 9.1 Hz, 2H), 7.04 (s, 1H), 6.99-6.90 (m, 2H), 6.87 (d, J = 8.9 Hz, 2H), 5.36 (d, J = 47.9 Hz, 2H), 3.85 (s, 3H); ^{19}F NMR (375 MHz, $CDCl_3$) δ -204.7 (t, J = 48.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 151.6, 145.2 (d, J = 3.4 Hz), 133.4 (d, J = 17.2 Hz), 129.7, 127.8, 121.0 (d, J = 1.3 Hz), 120.6 (d, J = 6.0 Hz), 118.6, 112.3 (d, J = 5.6 Hz), 84.5 (d, J = 166.8 Hz), 56.1; HRMS (APCI/APPI) m/z [M]$^+$ calcd for $C_{14}H_{12}ClFO_2$ 266.0510; found 266.0502.



S8 S9

Example 22: **Synthesis of N-(4-fluoro-3-methoxybenzyl)formamide (S9)**

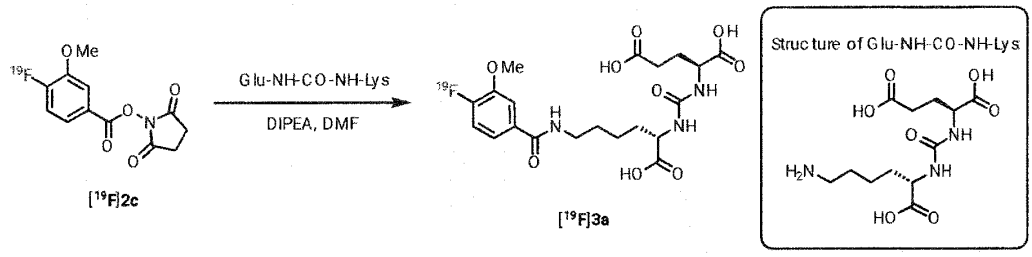
To a solution of amine **S8** (300 mg, 1.93 mmol, liquid measured by weight) in MeCN (7.7 mL) was added formic acid (0.36 mL, 9.6 mmol). The mixture was heated at 80 °C. After 7 hours, mixture was cooled to room temperature, and saturated sodium bicarbonate aqueous solution (20 mL) was added. The mixture was extracted with EtOAc. Concentration and gradient flash chromatography (17% EtOAc in hexane to 50% EtOAc in hexane to 83% EtOAc in hexane) afforded **S9** (194 mg, 55% yield) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.02 (dd, J = 11.1, 8.2 Hz, 1H), 6.91 (dd, J = 8.0, 1.9 Hz, 1H), 6.83-6.75 (m, 1H), 5.84 (s, 1H), 4.44 (d, J = 6.0 Hz), 3.88 (s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -136.4-(-)136.7 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 152.1 (d, J = 245.7 Hz), 148.0 (d, J = 11.0 Hz), 134.1 (d, J = 4.1 Hz), 120.2 (d, J = 6.4 Hz), 116.2 (d, J = 18.4 Hz), 113.2 (d, J = 1.8 Hz), 56.4, 42.0; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_9H_{10}FNO_2Na$ 206.0593, found 206.0586.



S9 [^{19}F]2i

Example 23: **Synthesis of 1-fluoro-4-(isocyanomethyl)-2-methoxybenzene ([^{19}F]2i)**

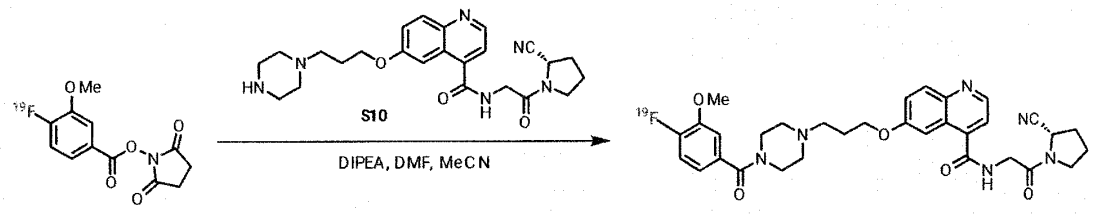
To a solution of **S9** (30 mg, 0.16 mmol) in DCM (0.48 mL) was added triphenylphosphine (63 mg, 0.24 mmol), iodine (61 mg, 0.24 mmol), and triethylamine (67 μL, 0.48 mmol). After 1 hour, saturated sodium thiosulfate aqueous solution (5 mL) was added. The mixture was extracted with DCM. Concentration and gradient flash chromatography (9% EtOAc in hexane to 17% EtOAc in hexane) afforded the isocyanide [^{19}**F**]**2i** (10 mg, 37% yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (dd, J = 10.9, 8.3 Hz, 1H), 6.96 (dd, J = 7.8, 2.1 Hz, 1H), 6.88-6.83 (m, 1H), 4.60 (s, 2H), 3.92 (s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -135.2-(-)135.3 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1 (t, J = 5.0 Hz), 152.4 (d, J = 247.5 Hz), 148.2 (d, J = 11.1 Hz), 128.7 (d, J = 3.8 Hz), 119.2 (d, J = 7.1 Hz), 116.5 (d, J = 18.4 Hz), 112.0, 56.5, 45.3 (d, J = 7.3 Hz); HRMS (APCI/APPI) m/z $[M]^+$ calcd for C_9H_8FNO 165.0590, found 165.0584.



[^{19}F]2c [^{19}F]3a

Example 24: **Synthesis of (((S)-1-carboxy-5-(4-fluoro-3-methoxybenzamido)pentyl)carbamoyl)-L-glutamic acid ([^{19}F]3a).**

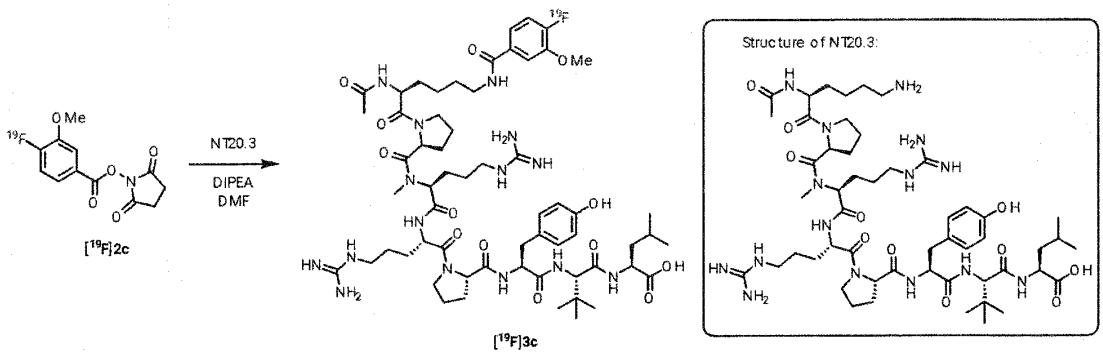
To a solution of [^{19}F]**2c** (0.2 mg, 0.75 μmol) in DMF (40 μL) was added Glu-NH-CO-NH-Lys (0.1 mg, 0.31 μmol, in 10 μL DMF). More DMF (150 μL) and DIPEA (10 μL) were then added. After 24 hours, the mixture was purified by HPLC (HPLC column 2, HPLC gradient elution method B), affording [^{19}F]**3a** in 32% yield (estimated by the crude HPLC trace with 212 nm detector, based on peak integration of [^{19}F]**3a** and all other peaks) HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{20}H_{26}FN_3O_9Na$ 494.1551; found 494.1540.



[^{19}F]2c [^{19}F]3b

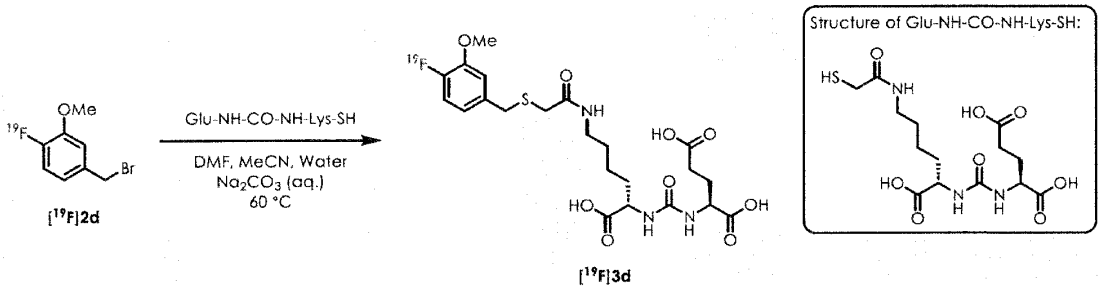
Example 25: **Synthesis of (S)-N-(2-(2-cyanopyrrolidin-1-yl)-2-oxoethyl)-6-(3-(4-(4-fluoro-3-methoxybenzoyl)piperazin-1-yl)propoxy)quinoline-4-carboxamide ([^{19}F]3b)**

To a solution of [^{19}F]**2c** (0.2 mg, 0.75 μmol) in DMF (40 μL) was added FAPI **S10** (0.1 mg, 0.22 μmol, in 3.6 μL MeCN). DIPEA (10 μL) was then added. After 6 hours, the mixture was purified by HPLC (HPLC column 2, HPLC gradient elution method B), affording [^{19}F]**3b** in 38% yield (estimated by the crude HPLC trace with 254 nm detector, based on peak integration of [^{19}F]**3b** and all other peaks) HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{32}H_{36}FN_6O_5$ 603.2731; found 603.2717.



Example 26: **Synthesis of ((S)-2-((S)-2-((S)-1-(N2-N2-acetyl-N6-(4-fluoro-3-methoxybenzoyl)-L-lysyl-L-prolyl-N2-methyl-L-arginyl-L-arginyl)pyrrolidine-2-carboxamido)-3-(4-hydroxyphenyl)propanamido)-3,3-dimethylbutanoyl)-L-leucine ([^{19}F]3c).**

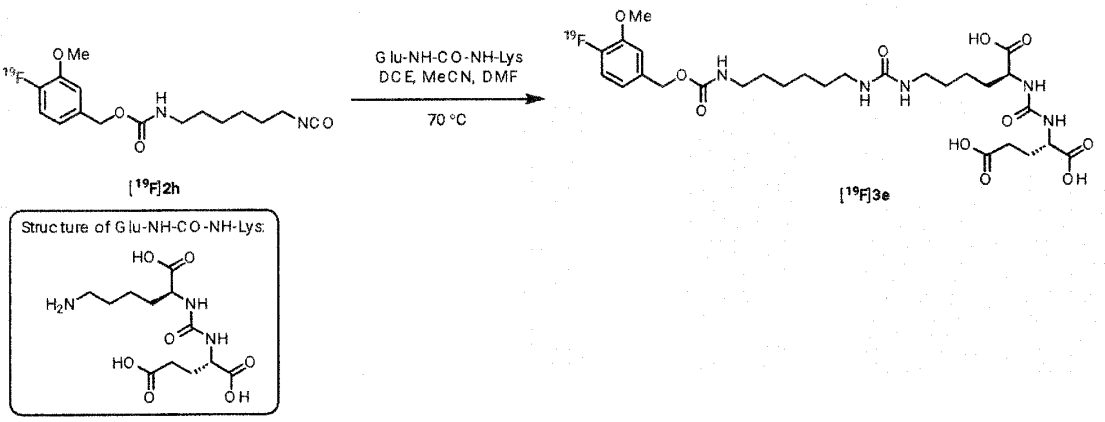
To a solution of [^{19}F]**2c** (0.2 mg, 0.75 μmol) in DMF (40 μL) was added NT20.3 (0.1 mg, 0.080 μmol, in 10 μL DMF). More DMF (150 μL) and DIPEA (10 μL) were then added. After 24 hours, the mixture was purified by HPLC (HPLC column 2, HPLC gradient elution method B), affording [^{19}F]**3c** in 70% yield (estimated by the crude HPLC trace with 254 nm detector, based on peak integration of [^{19}F]**3c** and all other peaks). HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{60}H_{92}FN_{15}O_{13}Na$ 1272.6881; found 1272.6939.



Example 27: **Synthesis of (10S,14S)-1-(4-fluoro-3-methoxyphenyl)-4,12-dioxo-2-thia-5,11,13-triazahexadecane-10,14,16-tricarboxylic acid ([^{19}F]3d)**

To a stock solution of [^{19}F]**2d** (0.11 mg, 0.50 μmol, 4.4 μL 0.11 M stock solution) in a microcentrifuge tube was added Glu-NH-CO-NH-Lys-SH stock solution (0.10 mg, 0.25 μmol, 3.3 μL 0.078 M stock solution). MeCN (50 μL), water (50 μL), and sodium carbonate aqueous buffer solution (50 μL, 0.5 M) were then added. The mixture was heated at 60 °C. After 1 hour,

HPLC purification (HPLC column 2, HPLC gradient elution method B) afforded [^{19}F]**3d** in 38% yield (estimated by the crude HPLC trace with 212 nm detector, based on peak integration of [^{19}F]**3d** and all other major peaks after solvent front). HRMS (ESI) m/z [M + H]$^+$ calcd for 532.1766, found 532.1760.



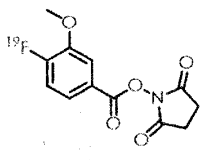
Example 28: **Synthesis of (18S,22S)-1-(4-fluoro-3-methoxyphenyl)-3,12,20-trioxo-2-oxa-4,11,13,19,21-pentaazatetracosane-18,22,24-tricarboxylic acid ([^{19}F]3e)**

The solution of [^{19}F]**2h** (1 mg, 3 μmol) in DCE (20 μL) and the solution of Glu-NH-CO-NH-Lys (1 mg, 3 μmol) in MeCN (200 μL) and DMF (200 μL) were mixed in a microcentrifuge tube. The mixture was heated at 70 °C. After 1 hour, HPLC purification (HPLC column 2, HPLC gradient elution method B) afforded [^{19}F]**3e** in 22% yield (estimated by the crude HPLC trace with 254 nm detector, based on peak integration of [^{19}F]**3e** and all other major peaks). HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{28}H_{42}FN_5O_{11}Na$ 666.2763, found 666.2755.

Example 29: **Molar activity measurement**

Molar activity was calculated using the standard curve of [^{19}F]**2c**, which was created from HPLC traces (with 254 nm detector) of a series of [^{19}F]**2c** standard solutions. The HPLC purified [^{18}F]**2c** was then analyzed by HPLC again for quality control, the UV area (254 nm detector) overlapping with the desired radio peak was recorded.

Table S1. Standard [^{19}F]**2c** solution and UV area from HPLC



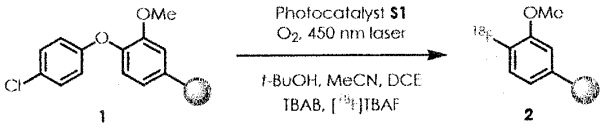
[^{19}F]2c

Injected [^{19}F]**2c** (μg)	UV Area (mAU·s)
1	822.6

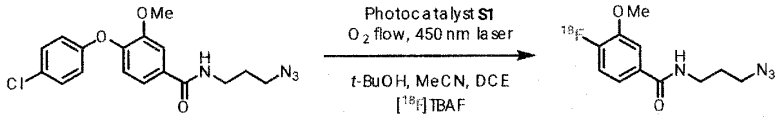
0.4	344.1
0.2	176.8
0.1	94.5
0.05	51.4
0.01	16.1

The UV area of [^{18}F]**2c** was recorded to be 16.6 mAU·s. The mole number was calculated to be 1.93 X 10^{-5} μmol. Decay corrected (EOB) activity was 46.8 μCi. The molar activity was calculated to be 2.42 Ci/μmol.

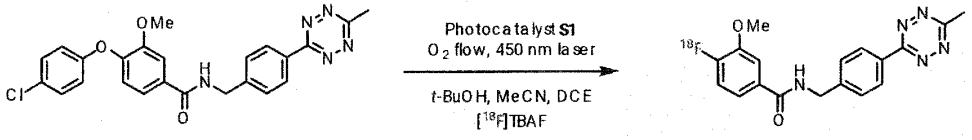
Example 30: **Radiochemistry**



General photoredox method - A solution of precursor **1** (0.05 mmol) in a solvent mixture (*t*-butyl alcohol:DCM:MeCN = 4:3:1, 800 μL or 400 μL) was prepared in a 5 mL V vial in the open air. The photocatalyst **S1** (1.5 mg, 0.0025 mmol) and tetrabutylammonium bicarbonate solution (60 mg/mL solution in MeCN, 25 μL, 15 μL or 0 μL) were then added. [^{18}F]TBAF/MeCN solution (typically 10 – 20 mCi) was added last. A balloon (filled with pure oxygen or air) was attached to a needle, which was inserted into the reaction mixture and provided steady oxygen (or air) flow in a bubbling manner. The V vial containing the mixture was then irradiated top-down with a laser (MDL-D-450, 450 nm, 3.5 W, 30 min or 20 min irradiation). An aliquot of the resulting mixture was analyzed and purified by HPLC, furnishing the corresponding ^{18}F-labeled synthons.

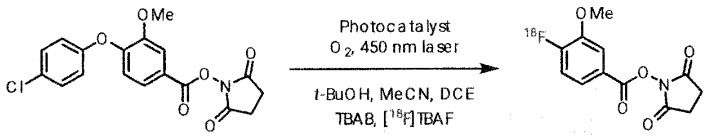


Radiosynthesis: **[^{18}F]2a** was prepared via general photoredox procedure (800 µL solvent mixture, 15 µL TBAB/MeCN, oxygen flow and 30 min laser irradiation). RCY #1: 30.6%; RCY #2: 62.7%; RCY #3: 53.2%; Average RCY: 48.8±22.7% (n=3).



1b **[^{18}F]2b**

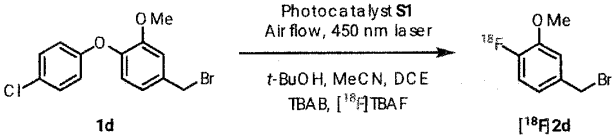
Radiosynthesis: **[^{18}F]2b** was prepared via general photoredox procedure (800 µL solvent mixture, 15 µL TBAB/MeCN, oxygen flow and 30 min laser irradiation) in 8.7% RCY (n=1)



1c **[^{18}F]2c**

Radiosynthesis: **[^{18}F]2c** was initially prepared via general photoredox procedure (800 µL solvent mixture, 15 µL TBAB/MeCN, oxygen flow and 30 min laser irradiation) in 16.3±1.7% (n=3). Due to the stability concern of **[^{18}F]2c** under basic conditions, TBAB/MeCN additive was later removed from the reaction condition. This synthon was then synthesized via general photoredox procedure (800 µL solvent mixture, no TBAB/MeCN, air flow and 20 min laser irradiation) in 29.6±9.6% (n=3) RCY. Initial photoredox procedure (800 µL solvent mixture, 15 µL TBAB/MeCN, oxygen flow and 30 min laser irradiation): Run #1: 18.3%, Run #2: 15.6%, Run #3: 15.1%, Average RCY: 16.3±1.7% (n=3).

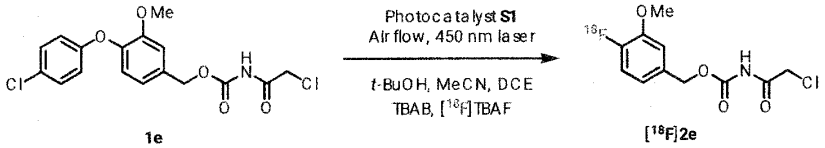
Modified photoredox procedure (800 µL solvent mixture, no TBAB/MeCN, air flow and 20 min laser irradiation): Run #1: 28.2%, Run #2: 39.9%, Run #3: 20.8%, Average RCY: 29.6±9.6% (n=3).



1d **[^{18}F]2d**

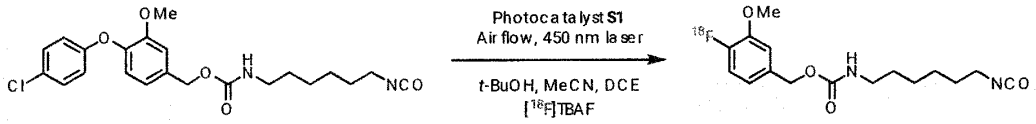
Radiosynthesis: **[^{18}F]2d** was prepared from bromide precursor **1d** via general photoredox procedure (400 µL solvent mixture, 25 µL TBAB/MeCN, air flow and 20 min laser irradiation) in 51.3±9.7% (n=3) RCY.

The radio product [^{18}F]**2d** is mildly volatile. The heat from the laser slowly evaporated the solvent mixture, and [^{18}F]**2d** could also evaporate if solvent volume was reduced to less than 200 μL. The solvent mixture was refilled every 4 min during the laser irradiation to maintain the 400 μL reaction mixture volume. No radioactivity loss was observed when solvent refill was performed. Run #1: 62.4%, Run #2: 47.1%, Run #3: 44.5%, Average RCY: 51.3±9.7% (n=3).



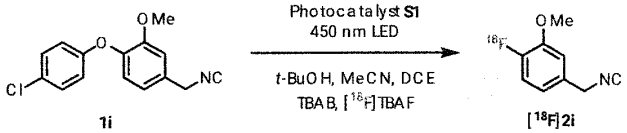
1e [^{18}F]**2e**

Radiosynthesis: [^{18}F]**2e** was prepared from chloride precursor **1e** via general photoredox procedure (400 μL solvent mixture, 25 μL TBAB/MeCN, air flow and 20 min laser irradiation) in 23.2% RCY. RCY #1: 23.2%, RCY #2: 22.3%, RCY #3: 16.8%, Average RCY: 20.8±3.5% (n=3).



1h [^{18}F]**2h**

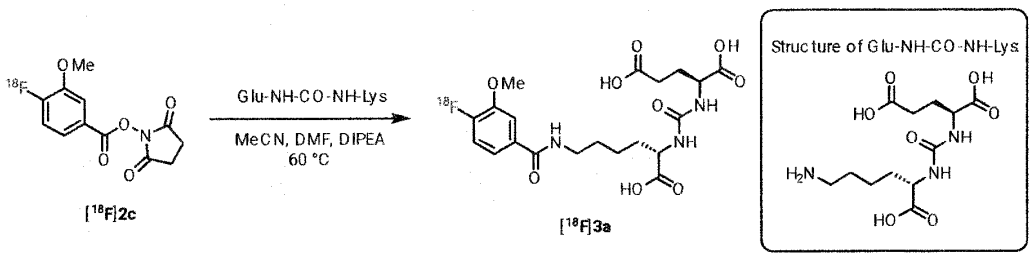
Radiosynthesis: [^{18}F]**2h** was prepared from isocyanate precursor **1h** via general photoredox procedure (400 μL solvent mixture, no TBAB/MeCN, air flow and 20 min laser irradiation) in 28.5±3.6% (n=3) RCY. Run #1: 32.5%, Run #2: 27.6%, Run #3: 25.4%, Average RCY: 28.5±3.6% (n=3).



1i [^{18}F]**2i**

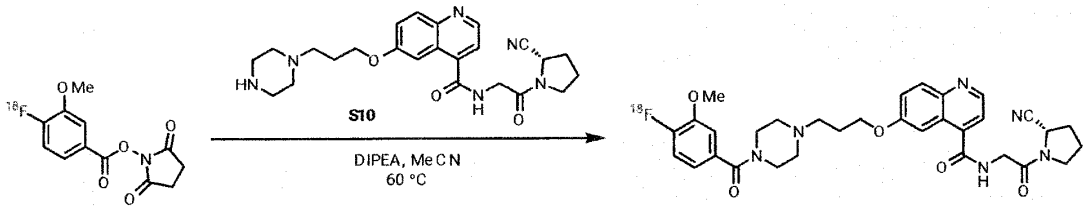
Radiosynthesis: [^{18}F]**2i** was prepared via a modified procedure where isocyanide **1i** (4.5 mg, 0.016 mmol) was dissolved in solvent mixture (*t*-butyl alcohol:DCM:MeCN = 4:3:1, 133 μL) in a quartz tube opened to air. Photocatalyst **S1** (0.5 mg, 8.5 μmol), tetrabutylammonium bicarbonate solution (60 mg/mL solution in MeCN, 8.3 μL), and [^{18}F]TBAF/MeCN solution (1.7 mCi to 8.1 mCi) were added. The quartz tube was then sealed with a plastic screw cap, and irradiated with a 450 nm LED for 20 min. An aliquot of the resulting mixture was analyzed and

purified by HPLC, affording the [^{18}F]**2i** in 4.7±0.4% RCY (n=3). Run #1: 4.7%, Run #2: 5.0%, Run #3: 4.3%, Average RCY: 4.7±0.4% (n=3).



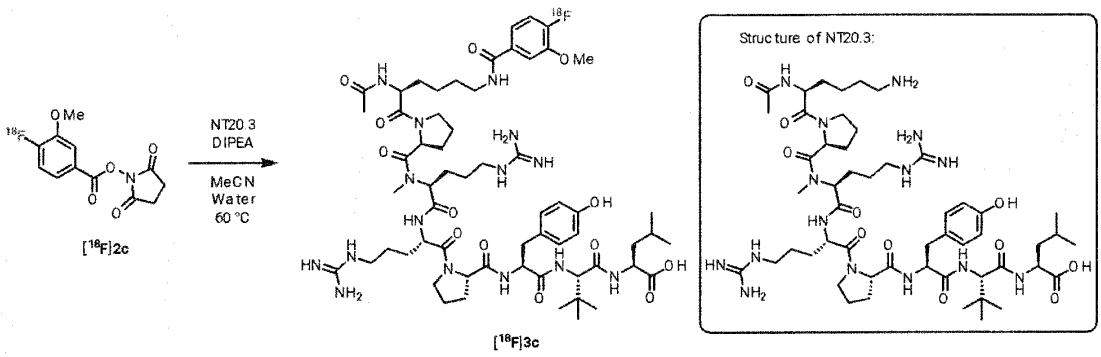
[^{18}F]**2c** [^{18}F]**3a**

Radiosynthesis: [^{18}F]**3a**: The HPLC purified [^{18}F]**2c** was concentrated to remove MeCN, water and TFA. Anhydrous MeCN was then added to redissolve [^{18}F]**2c**. To a solution of [^{18}F]**2c** (100 μCi to 400 μCi each experiment) in MeCN (200 μL) was added the Glu-NH-CO-NH-Lys (0.1 mg, in 10 μL DMF) and DIPEA (6 μL). The mixture was heated at 60 °C 30 minutes. An aliquot of the mixture was then purified by HPLC. Run #1: 24.6% RCY, Run #2: 28.9% RCY, Run #3: 48.6% RCY, Average RCY: 34.0±12.8% (n=3).

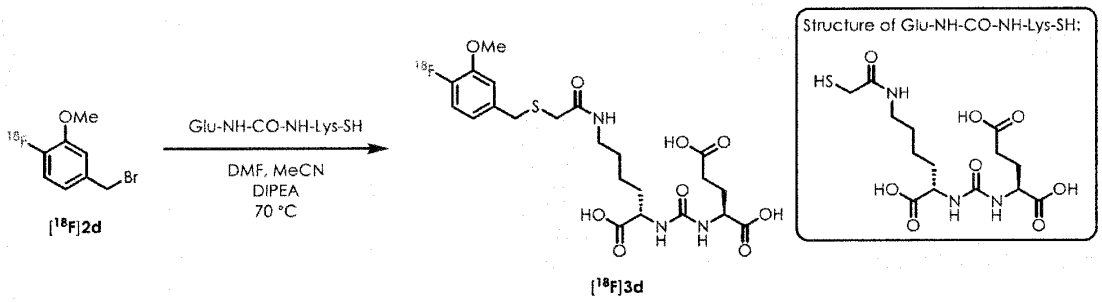


[^{18}F]**2c** [^{18}F]**3b**

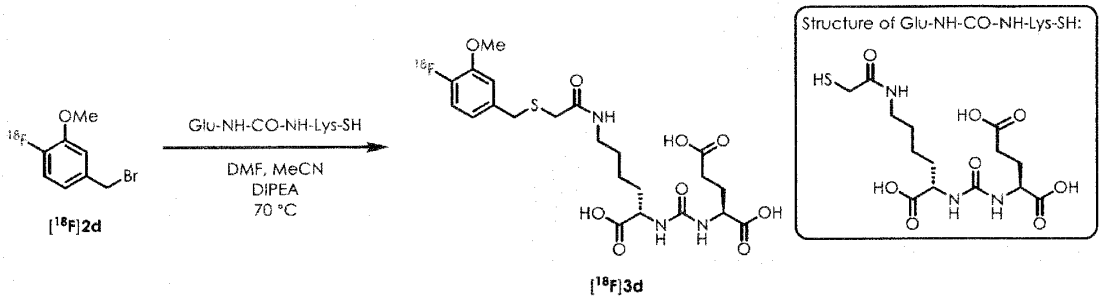
[^{18}F]**3b**: The HPLC purified [^{18}F]**2c** was concentrated to remove MeCN, water and TFA. Anhydrous MeCN was then added to redissolve [^{18}F]**2c**. To a solution of [^{18}F]**2c** (100 μCi to 400 μCi each experiment) in MeCN (100 μL) was added the FAPI (0.41 mg, in 30 μL MeCN) and DIPEA (3 μL). The mixture was heated at 60 °C for 30 minutes. An aliquot of the mixture was then purified by HPLC. Run #1: 39.4%, Run #2: 38.2%, Run #3: 22.8%, Average RCY: 33.5±9.2% (n=3).



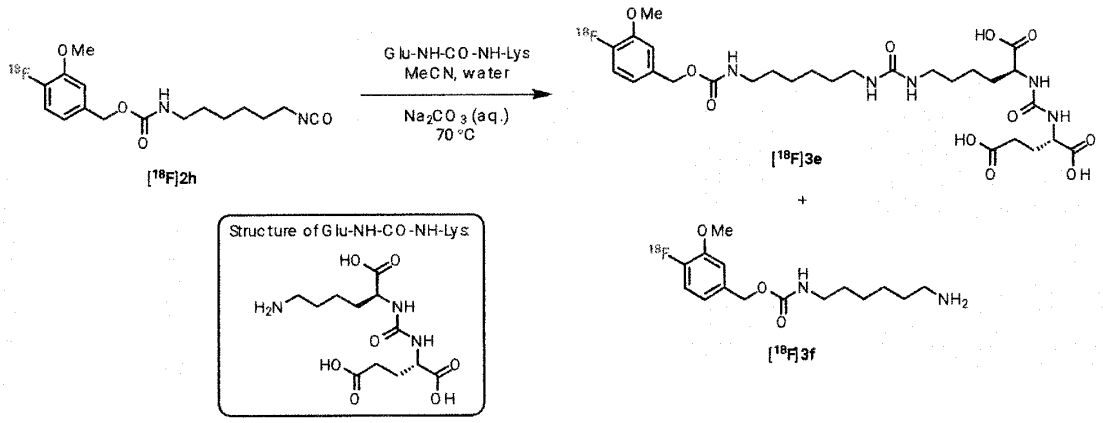
Radiosynthesis: [^{18}F]**3c**: The HPLC purified [^{18}F]**2c** was concentrated to remove MeCN, water and TFA. Anhydrous MeCN was then added to redissolve [^{18}F]**2c**. To a solution of [^{18}F]**2c** (197 μCi) in MeCN (100 μL) was added the NT20.3 peptide (0.4 mg, in 40 μL 1:1 MeCN:water) and DIPEA (3 μL). The mixture was heated at 60 °C for 30 minutes. An aliquot of the mixture was then purified by HPLC. Run #1: 77.0% RCY (n=1).



Radiosynthesis: [^{18}F]**3d** preparation via water-free condition: HPLC isolated [^{18}F]**2d** (in MeCN/water mixture) was loaded into a C18 cartridge. A large amount of air was passed through the C18 cartridge to remove residue water. [^{18}F]**2d** was then eluted from the C18 cartridge with anhydrous MeCN. A fraction of this [^{18}F]**2d** MeCN solution (100 μL) was mixed with Glu-NH-CO-NH-Lys-SH stock solution (0.1 mg, 0.25 μmol, 3.3 μL 0.078 M stock solution in DMF) in a microcentrifuge tube. DIPEA (2 μL) was added last, and the mixture was heated at 70 °C. After 30 min, HPLC purification afforded [^{18}F]**3d** in 75.4% RCY.



Radiosynthesis: [^{18}F]**3d** preparation via aqueous condition: HPLC isolated [^{18}F]**2d** (100 µL, in MeCN/water mixture) was mixed with Glu-NH-CO-NH-Lys-SH stock solution (0.1 mg, 0.25 µmol, 3.3 µL 0.078 M stock solution in DMF) in a microcentrifuge tube. Sodium carbonate buffer solution (50 µL, 0.5 M in water) was then added. The mixture was heated at 70 °C. After 30 min, HPLC purification afforded [^{18}F]**3d** in 72.8% RCY. Run #1: 74.1%, Run #2: 71.4%, Average RCY: 72.8±1.9% (n=2).



Radiosynthesis: [^{18}F]**3e**: To a solution of Glu-NH-CO-NH-Lys (0.5 mg, 1.6 µmol) in MeCN (10 µL) and water (10 µL) was added sodium carbonate aqueous buffer solution (0.5 M in water, 100 µL). The HPLC purified [^{18}F]**2h** (100 µL, 84 µCi to 192 µCi activity) was then added. The mixture was heated at 70 °C. After 30 min, the mixture was purified by HPLC. The RCY of [^{18}F]**3e** was calculated based on the amount of radioactive material isolated, the RCY of [^{18}F]**3f** was estimated based on the HPLC radio trace peak integration ratio and the isolated RCY of [^{18}F]**3e**.

[^{18}F]**3e** RCY #1: 28.4% estimated [^{18}F]**3f** RCY #1: 43.4%

[^{18}F]**3e** RCY #2: 31.3% estimated [^{18}F]**3f** RCY #2: 47.0%

[^{18}F]**3e** RCY #3: 22.3% estimated [^{18}F]**3f** RCY #3: 47.5%

Average RCY of [^{18}F]**3e**: 27.3±4.6% (n=3)

Average estimated RCY of [^{18}F]**3f**: 46.0±2.2% (n=3)

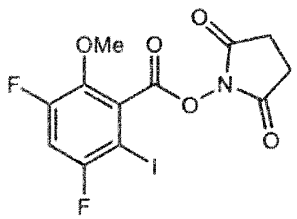
Example 31: Small animal PET imaging study

The human prostate cancer cell line with high PSMA expression, PC3-PSMA, was obtained from the Tissue Culture Facility, UNC Lineberger Comprehensive Cancer Center. PC3-PSMA cells were cultured in DMEM medium supplemented with 10% FBS and 100 U/ml of penicillin and 100 μg/ml streptomycin in a humidified atmosphere of 5% CO_2 at 37°C. Nude mice were obtained from the Animal Study Facility of UNC Chapel Hill. When the mice were 4-6 weeks old, about 2X106 PC3-PSMA cells per 0.1mL were injected subcutaneously in the right shoulder of nude mice for tumor xenograft. When tumors reached 200 mm^3 in size, mice were used for imaging studies. All animal procedures were approved by the University of North Carolina Institutional Animal Care and Use Committee.

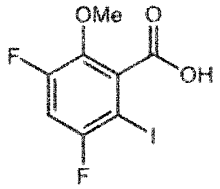
Static PET and CT images were acquired at 0.5h, 1.5h, and 3h post-injection for 3a under isoflurane anesthesia for 15 min. About 1 MBq of 3a were injected to the PC3-PSMA xenograft mouse (n=4) intravenously. The mice were awakened between imaging times. List-mode data were collected and reconstructed with the algorithm described before.[72] The regions of interest (ROIs) were drawn using AMIDE software on coronal PET/CT images. Organ and tumor uptake are expressed as mean ± standard deviation (SD) percentage injected dose per gram (%ID/g) after correcting for radioactivity decay (*see* FIGS. 3 and 4).

Example 32: Synthesis of 2,5-dioxopyrrolidin-1-yl 3,5-difluoro-2-iodo-6-methoxybenzoate

Scheme 1. Representation of 2,5-dioxopyrrolidin-1-yl 3,5-difluoro-2-iodo-6-methoxybenzoate.



Scheme 2. Representation of 3,5-difluoro-2-iodo-6-methoxybenzoic acid.

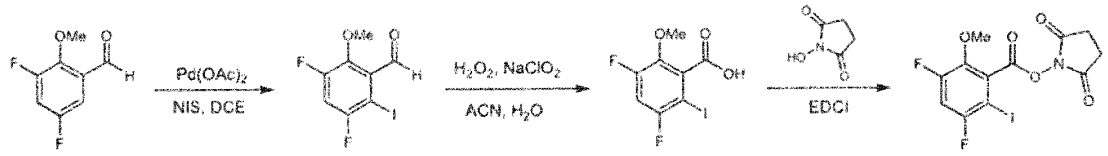


The preparation of 2,5-dioxopyrrolidin-1-yl 3,5-difluoro-2-iodo-6-methoxybenzoate (Scheme 1) is shown schematically in Scheme 3. To a stirred mixture of 3,5-difluoro-2-methoxybenzaldehyde (3.00 g, 17.4 mmol) and 4-chloro-2-(trifluoromethyl)aniline (1.70 g, 8.70 mmol) in TFA (25 mL) and DCE (75 mL) under a N_2 was added $Pd(OAc)_2$ (980 mg, 4.35 mmol) and NIS (15.7 g, 69.7 mmol), whereupon it was heated at 60 °C. After 16 h, the mixture was poured into ice-water (100 mL) and extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by reverse flash chromatography (C18 silica gel, ACN-water, 0-80% with 0.1% FA), affording 3,5-difluoro-2-iodo-6-methoxybenzaldehyde (700 g, 13%) as a brown solid. LCMS (ES, m/z): 298.90 $[M+H]^+$.

To a stirred mixture of 3,5-difluoro-2-iodo-6-methoxybenzaldehyde (700 mg, 2.35 mmol) in ACN (8 mL) was added $NaH_2PO_4 \cdot H_2O$ (311 mg, 2.59 mmol) in H_2O (2 mL), $NaClO_2$ (234 mg, 2.59 mmol) and H_2O_2 (25% aq, 2.59 mmol), dropwise. After 4 h, the mixture was partially concentrated and purified by reverse flash chromatography (C18 silica gel, ACN-water, 0-60% with 0.1% FA), affording 3,5-difluoro-2-iodo-6-methoxybenzoic acid (Scheme 2) (500 mg, 67%) as a white solid.

To a stirred mixture of 3,5-difluoro-2-iodo-6-methoxybenzoic acid (300 mg, 0.96 mmol) in DMF (3 mL) was added EDCI (230 mg, 1.20 mmol) and N-hydroxysuccinimide (144 mg, 1.25 mmol). After 2 h, the mixture was poured into ice-water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by reverse flash chromatography (C18 silica gel, ACN-water, 0-60% with 0.1% FA) to afford the title compound (210 mg, 53%) as a white solid.

Scheme 3. Representative schematic route to achieve 2,5-dioxopyrrolidin-1-yl 3,5-difluoro-2-iodo-6-methoxybenzoate.

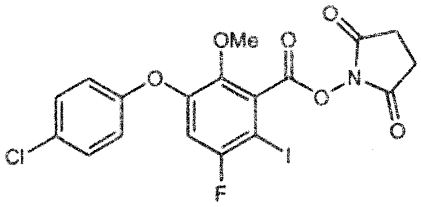


For 3,5-difluoro-2-iodo-6-methoxybenzoic acid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.90 (s, 1H), 7.57 (dd, J = 11.4, 8.1 Hz, 1H), 3.82 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -94.67 (d, J = 6.4 Hz), -125.45. GCMS (EI, m/z): 313.90 [M].

For 2,5-dioxopyrrolidin-1-yl 3,5-difluoro-2-iodo-6-methoxybenzoate, ^{1}H NMR (400 MHz, DMSO) δ 7.82 (dd, J = 11.5, 8.0 Hz, 1H), 3.92 (s, 3H), 2.89 (br s, 4H). ^{19}F NMR (376 MHz, DMSO) δ -93.27 (d, J = 6.8 Hz), -124.32 (d, J = 6.9 Hz). LCMS (ES, m/z): 433.85 $[M+Na]^+$. 99.8% purity (254 nm).

Example 33: Synthesis of 2,5-dioxopyrrolidin-1-yl 3-(4-chlorophenoxy)-5-fluoro-6-iodo-2-methoxybenzoate

Scheme 4. Representation of 2,5-dioxopyrrolidin-1-yl 3-(4-chlorophenoxy)-5-fluoro-6-iodo-2-methoxybenzoate.



The preparation of 2,5-dioxopyrrolidin-1-yl 3-(4-chlorophenoxy)-5-fluoro-6-iodo-2-methoxybenzoate (Scheme 4) is shown schematically in Scheme 5. To a solution of methyl 5-fluoro-2-hydroxybenzoate (20.0 g, 118 mmol) in DMF (200 mL) was added NIS (31.7 g, 141 mmol). After 4 days, the mixture was poured into water (500 mL) and extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by reverse flash chromatography (C18 silica gel, ACN-water, 0-50% with 0.1% FA) to afford methyl 5-fluoro-2-hydroxy-3-iodobenzoate (21 g, 60%) as a white solid. LCMS (ES, m/z): 295.10 $[M-H]^-$.

To a solution of methyl 5-fluoro-2-hydroxy-3-iodobenzoate (21.0 g, 70.9 mmol) and K_2CO_3 (19.6 g, 142 mmol) in DMF (200 mL) was added methyl iodide (16.1 g, 113 mmol). After 2 h, the mixture was poured into water (500 mL) and extracted with EtOAc (3 x 300 mL). The

combined organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (EA-petroleum ether, 20%), affording methyl 5-fluoro-3-iodo-2-methoxybenzoate (17 g, 77%) as a yellow oil. GCMS (EI, m/z): 310.10[M].

A mixture of methyl 5-fluoro-3-iodo-2-methoxybenzoate (10.0 g, 32.3 mmol), chlorophenol (8.3 g, 64.5 mmol), *t*-BuBrettPhos Pd G3 (2.76 g, 3.2 mmol), *t*-BuBrettPhos (1.56 g, 3.2 mmol) and Cs_2CO_3 (21 g, 64.5 mmol) in toluene (100 mL) under an N_2 atmosphere was heated at 100 °C. After 16 h, the mixture was cooled to rt and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (EA-petroleum ether, 20%), affording methyl 3-(4-chlorophenoxy)-5-fluoro-2-methoxybenzoate (6.0 g, 59%) as a yellow oil. GCMS (EI, m/z): 310.10, 312.10[M].

To a solution of methyl 3-(4-chlorophenoxy)-5-fluoro-2-methoxybenzoate (6.00 g, 19.3 mmol) in THF (45 mL) was added LiOH (920 mg, 38.6 mmol) in H_2O (15 mL). After 2 h, the mixture was cooled to 0 °C and acidified to pH~3 with HCl (2 M) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 3-(4-chlorophenoxy)-5-fluoro-2-methoxybenzoic acid (3.6 g, 62%) as a white solid. LCMS (ES, m/z): 295.10, 297.10 $[M-H]^-$.

To a solution of 3-(4-chlorophenoxy)-5-fluoro-2-methoxybenzoic acid (3.60 g, 12.1 mmol) in THF (30 mL) at 0 °C was added borane-tetrahydrofuran complex (1 M in THF, 60 mL, 60 mmol) dropwise. After 16 h, the mixture was slowly added into MeOH (100 mL) and heated at 70 °C for 2 h. Upon cooling to rt, the mixture was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (EA-petroleum ether, 35%), affording [3-(4-chlorophenoxy)-5-fluoro-2-methoxyphenyl]methanol (2.6 g, 76%) as a yellow oil. LCMS (ES, m/z): 265.10, 267.10 $[M-OH]^+$.

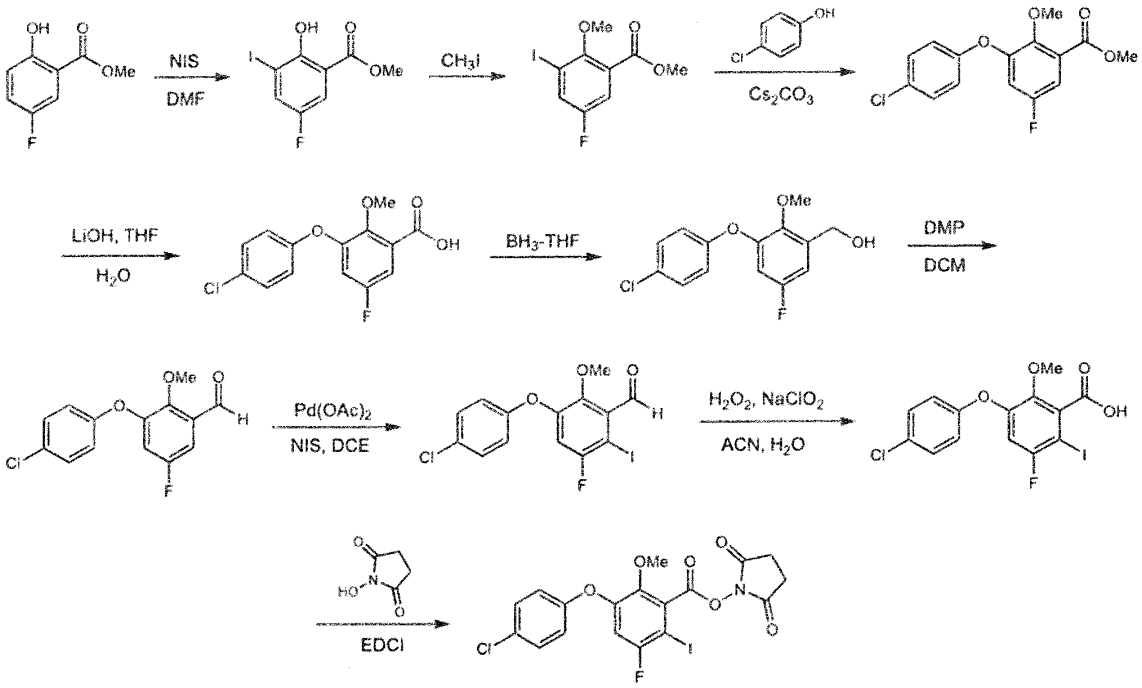
To a solution of [3-(4-chlorophenoxy)-5-fluoro-2-methoxyphenyl]methanol (2.60 g, 9.20 mmol) in DCM (30 mL) at 0 °C was added Dess-Martin periodinane (7.80 g, 18.4 mmol). After 3 h, the mixture was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (EA-petroleum ether, 25%), affording 3-(4-chlorophenoxy)-5-fluoro-2-methoxybenzaldehyde (1.70 g, 65%) as a yellow solid. LCMS (ES, m/z): 281.10, 283.10 $[M+H]^+$.

To a mixture of 3-(4-chlorophenoxy)-5-fluoro-2-methoxybenzaldehyde (1.70 g, 6.10 mmol) and 4-chloro-2-(trifluoromethyl)aniline (590 mg, 3.0 mmol) in DCE (15 mL) and TFA (3 mL) under an N_2 atmosphere was added $Pd(OAc)_2$ (340 mg, 1.51 mmol) and NIS (1.64 g, 7.30 mmol). After heating at 60 °C for 16 h, the mixture was cooled to rt and concentrated under reduced pressure. The crude residue was purified by reverse flash chromatography (C18 silica gel, ACN-water, 30-100% with 0.1% FA) to afford 3-(4-chlorophenoxy)-5-fluoro-6-iodo-2-methoxybenzaldehyde (800 mg, 32%) as a white solid. GCMS (EI, m/z): 405.90, 407.90[M].

To a mixture of 3-(4-chlorophenoxy)-5-fluoro-6-iodo-2-methoxybenzaldehyde (800 mg, 2.00 mmol) in MeCN (10 mL) and H_2O (2 mL) was added $NaClO_2$ (391 mg, 4.30 mmol), NaH_2PO_4 (519 mg, 4.30 mmol) and H_2O_2 (25% aq, 4.30 mmol). After 2 h, the mixture was concentrated under reduced pressure and purified by reverse flash chromatography (C18 silica gel, ACN-water, 30-100% with 0.1% FA) to afford 3-(4-chlorophenoxy)-5-fluoro-6-iodo-2-methoxybenzoic acid (760 mg, 90%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.82 (br s, 1H), 7.49-7.40 (m, 2H), 7.13 (d, J = 8.6 Hz, 1H), 7.11-7.06 (m, 2H), 3.73 (s, 3H).

To a mixture of 3-(4-chlorophenoxy)-5-fluoro-6-iodo-2-methoxybenzoic acid (800 mg, 1.90 mmol) in DMF (5 mL) was added N-hydroxysuccinimide (326 mg, 2.80 mmol) and EDCI (440 mg, 2.80 mmol). After 2 h, the mixture was purified by reverse flash chromatography (C18 silica gel, ACN-water, 30-100% with 0.1% FA) to afford the title compound (460.3 mg, 46%) as a white solid.

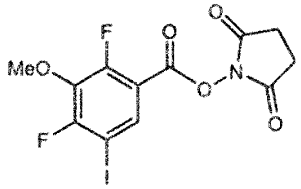
Scheme 5. Representative schematic route to achieve 2,5-dioxopyrrolidin-1-yl 3-(4-chlorophenoxy)-5-fluoro-6-iodo-2-methoxybenzoate.



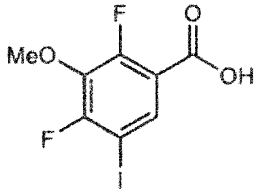
For 2,5-dioxopyrrolidin-1-yl 3-(4-chlorophenoxy)-5-fluoro-6-iodo-2-methoxybenzoate, ^{1}H NMR (400 MHz, DMSO) δ 7.51-7.44 (m, 2H), 7.34 (d, J = 8.6 Hz, 1H), 7.20-7.13 (m, 2H), 3.85 (s, 3H), 2.89 (br s, 4H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -93.68. LCMS (ES, m/z): 541.80 [M+Na]$^+$. 99.0% purity (254 nm).

Example 34: 2,5-dioxopyrrolidin-1-yl 2,4-difluoro-5-iodo-3-methoxybenzoate

Scheme 6. Representation of 2,5-dioxopyrrolidin-1-yl 2,4-difluoro-5-iodo-3-methoxybenzoate.



Scheme 7. Representation of 2,4-difluoro-5-iodo-3-methoxybenzoic acid.



The preparation of 2,5-dioxopyrrolidin-1-yl 2,4-difluoro-5-iodo-3-methoxybenzoate (Scheme 6) is shown schematically in Scheme 8. To a stirred mixture of 2-amino-4-fluoro-3-methoxybenzoic acid (20.0 g, 108 mmol) in DMF (160 mL) at 0 °C was added NIS (36.5 g, 162 mmol). After 16 h at rt, the mixture was diluted with water (150 mL), the solids were collected by filtration, washed with water (2 x 20 mL) and dried under vacuum to afford 2-amino-4-fluoro-5-iodo-3-methoxybenzoic acid (30.0 g) as a red solid. LCMS (ES, m/z): 311.95 $[M+H]^+$.

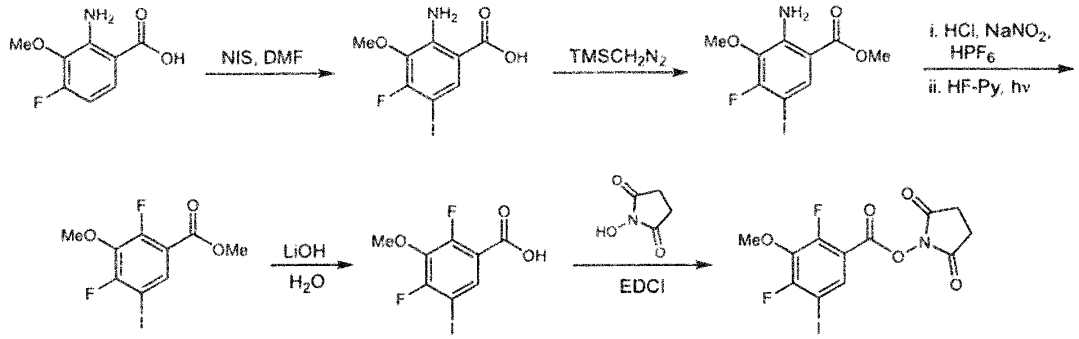
To a mixture of 2-amino-4-fluoro-5-iodo-3-methoxybenzoic acid (30.0 g) in THF/MeOH (1:1, 600 mL) at 0 °C was slowly added (diazomethyl)trimethylsilane (2.0 M in THF, 216 mL, 432 mmol). After 16 h at rt, the mixture was concentrated under reduced pressure and the crude residue was purified by silica gel chromatography (EA-Petroleum ether, 20%), affording methyl 2-amino-4-fluoro-5-iodo-3-methoxybenzoate (26 g, 74%, two-steps) as a white solid. LCMS (ES, m/z): 325.95 $[M+H]^+$.

To a stirred mixture of methyl 2-amino-4-fluoro-5-iodo-3-methoxybenzoate (15.0 g, 46.2 mmol) in HCl (6 M, 120 mL) at 0 °C was added a solution of $NaNO_2$ (4.78 g, 69.3 mmol) in H_2O (20 mL), dropwise. After 1 h at 0 °C, hexafluorophosphoric acid (60% aq, 22.5 g, 92.4 mmol) was added, dropwise. The resulting mixture was held at 0 °C for 0.5 h then filtered. The filter cake was washed with cold water (10 mL) and dried under an IR lamp to afford a diazonium salt (22.5 g). A solution of the salt in HF-pyridine (70%, 920 mL) was circulated through a medium pressure mercury lamp flow reactor (1.3 mL/min) for 1 h at rt, whereupon the mixture was poured into ice-water (2 L) and extracted with EA (3 x 1.5 L). The combined organic layers were washed with brine (1 L), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (EA-Petroleum ether, 15%), to afford methyl 2,4-difluoro-5-iodo-3-methoxybenzoate (9.60 g, 63%) as a white solid. GCMS (EI, m/z): 328.00 [M].

To a stirred mixture of methyl 2,4-difluoro-5-iodo-3-methoxybenzoate (9.60 g, 29.3 mmol) in THF (90 mL) was added a solution of $LiOH \cdot H_2O$ (12.6 g, 293 mmol) in H_2O (90 mL). After 16 h, the mixture was diluted with water (100 mL), cooled to 0 °C, acidified with HCl (2 M) to pH~6 and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 2,4-difluoro-5-iodo-3-methoxybenzoic acid (Scheme 7) (9.40 g) as a white solid.

A mixture of 2,4-difluoro-5-iodo-3-methoxybenzoic acid (600 mg, 1.91 mmol), N-hydroxysuccinimide (264 mg, 2.29 mmol) and EDCI (356 mg, 2.29 mmol) in DMF (5 mL) was stirred for 1 h, whereupon it was directly purified by reverse flash chromatography (C18 silica gel, ACN-water, 10-50% with 0.1% FA) to afford the title compound (210 mg, 26.7%yield) as a white solid.

Scheme 8. Representative schematic route to achieve 2,5-dioxopyrrolidin-1-yl 2,4-difluoro-5-iodo-3-methoxybenzoate.

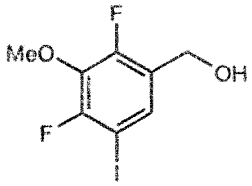


For intermediate 2,4-difluoro-5-iodo-3-methoxybenzoic acid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.62 (br s, 1H), 7.96 (t, J = 7.23 Hz, 1H), 3.95 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -101.52 (d, J = 15.1 Hz), -124.84 (d, J = 15.2 Hz). LCMS (ES, m/z): 312.80 $[M-H]^-$.

For 2,5-dioxopyrrolidin-1-yl 2,4-difluoro-5-iodo-3-methoxybenzoate, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (t, J = 6.8 Hz, 1H), 4.00 (s, 3H), 2.89 (s, 4H). ^{19}F NMR (376 MHz, DMSO) δ -96.14 (d, J = 18.1 Hz), -121.37 (d, J = 18.4 Hz). LCMS (ES, m/z): 411.85$[M+H]^+$, 452.90 $[M+CH_3CN+H]^+$; 98.4% purity (254 nm).

Example 35: (2,4-difluoro-5-iodo-3-methoxyphenyl)methanol

Scheme 9. Representation of (2,4-difluoro-5-iodo-3-methoxyphenyl)methanol.

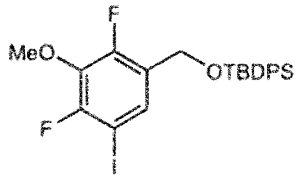


The title compound, (2,4-difluoro-5-iodo-3-methoxyphenyl)methanol (Scheme 9) (600 mg, 63%), was prepared from the intermediate, 2,4-difluoro-5-iodo-3-methoxybenzoic acid, in an analogous manner to methods described herein in Example 34.

For (2,4-difluoro-5-iodo-3-methoxyphenyl)methanol, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 (t, J = 7.2 Hz, 1H), 5.38 (t, J = 5.8 Hz, 1H), 4.48 (d, J = 5.8 Hz, 2H), 3.91 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -110.38 (d, J = 8.7 Hz), -134.00 (d, J = 9.6 Hz). GCMS (EI, m/z): 299.9 [M]; 96.5% purity (220 nm).

Example 36: ***tert*-butyl((2,4-difluoro-5-iodo-3-methoxybenzyl)oxy)diphenylsilane**

Scheme 10. Representation of *tert*-butyl((2,4-difluoro-5-iodo-3-methoxybenzyl)oxy)diphenylsilane.



The preparation of *tert*-butyl((2,4-difluoro-5-iodo-3-methoxybenzyl)oxy)diphenylsilane (Scheme 10) is shown schematically in Scheme 11. To a solution of (2,4-difluoro-5-iodo-3-methoxyphenyl)methanol (100 mg, 0.33 mmol) and imidazole (45 mg, 0.67 mmol) in DMF (1 mL) at 0 °C was added tert-butyl(chloro)diphenylsilane (137 mg, 0.50 mmol). After 2 h at rt, the mixture was directly purified by reverse flash chromatography (C18 silica gel, ACN-water, 10-80% with 0.1% FA) to afford the title compound (60 mg, 33%) as a white solid.

Scheme 11. Representative schematic route to achieve *tert*-butyl((2,4-difluoro-5-iodo-3-methoxybenzyl)oxy)diphenylsilane.

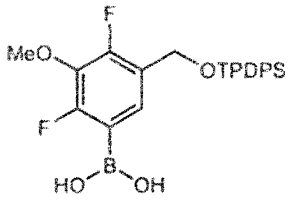


For *tert*-butyl((2,4-difluoro-5-iodo-3-methoxybenzyl)oxy)diphenylsilane, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65-7.58 (m, 4H), 7.53 (t, J = 7.1 Hz, 1), 7.51-7.41 (m, 6H), 4.73 (s, 2H), 3.89

(s, 3H), 1.02 (s, 9H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -109.38 (d, J = 9.7 Hz), -133.25 (d, J = 10.0 Hz). GCMS (EI, m/z): 481.0 [M-tBu]. 99.2% purity (254 nm).

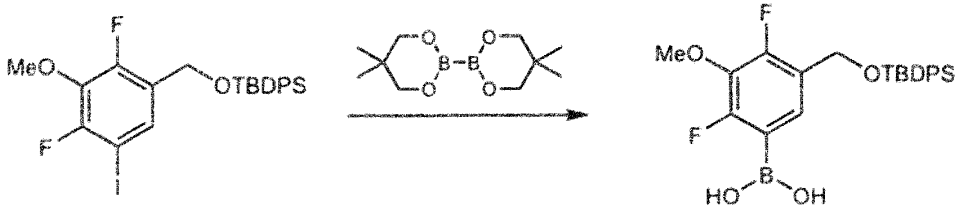
Example 37: (5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,4-difluoro-3-methoxyphenyl)boronic acid

Scheme 12. Representation of (5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,4-difluoro-3-methoxyphenyl)boronic acid.



The preparation of (5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,4-difluoro-3-methoxyphenyl)boronic acid (Scheme 12) is shown schematically in Scheme 13. A mixture of *tert*-butyl((2,4-difluoro-5-iodo-3-methoxybenzyl)oxy)diphenylsilane (200 mg, 0.37 mmol), 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,5-dimethyl-1,3,2-dioxaborinane (126 mg, 0.56 mmol), potassium 2,2-dimethylpropanoate (104 mg, 0.74 mmol) and XPhos Pd(crotyl)Cl (25 mg, 0.04 mmol) in THF/IPA (1.5 mL, 4:1) under a N_2 atmosphere was heated at 50 °C. After 16 h, the mixture was cooled to rt and directly purified by reverse flash chromatography (C18 silica gel, ACN-water, 5-80% with 0.1% FA), affording the title compound (60 mg, 35%) as a white solid.

Scheme 13. Representative schematic route to achieve (5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,4-difluoro-3-methoxyphenyl)boronic acid.

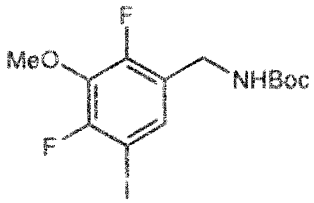


For (5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,4-difluoro-3-methoxyphenyl)boronic acid, ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 1H NMR (400 MHz, DMSO) δ 7.58-7.52 (m, 4H), 7.46-7.29 (m, 7H), 4.66 (s, 2H), 3.78 (s, 3H), 0.94 (s, 9H). ^{19}F NMR (376 MHz, DMSO-d_6/D_2O)

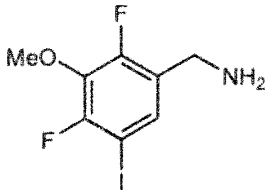
δ -121.27 (d, J = 11.1 Hz), -131.90 (d, J = 11.1 Hz). LCMS (EI, m/z): 355.1 [M-$B(OH)_2$-tBu]; 99.9% purity (254 nm).

Example 38: Synthesis of *tert*-butyl (2,4-difluoro-5-iodo-3-methoxybenzyl)carbamate

Scheme 14. Representation of *tert*-butyl (2,4-difluoro-5-iodo-3-methoxybenzyl)carbamate.



Scheme 15. Representation of 1-(2,4-difluoro-5-iodo-3-methoxyphenyl)methanamine.



The preparation of *tert*-butyl (2,4-difluoro-5-iodo-3-methoxybenzyl)carbamate (Scheme 14) is shown schematically in Scheme 16. To a mixture of 2,4-difluoro-5-iodo-3-methoxybenzoic acid (1.00 g, 3.18 mmol), HATU (1.45 g, 3.82 mmol) and NH_4Cl (204 mg, 3.82 mmol) in DMF (10 mL) was added DIEA (1.23 g, 9.55 mmol). After 1 h, the mixture was purified by reverse flash chromatography (C18 silica gel, ACN-water, 10-60% with 0.1% FA) to afford 2,4-difluoro-5-iodo-3-methoxybenzamide (500 mg, 50%) as a brown solid. LCMS (ES, m/z): 314.20 $[M+H]^+$.

To a solution of 2,4-difluoro-5-iodo-3-methoxybenzamide (1.00 g, 3.19 mmol) in THF (3 mL) at 0 °C was added borane-tetrahydrofuran complex (1 M in THF, 9.6 mL, 9.58 mmol), whereupon it was heated at 60 °C. After 16 h, the mixture was slowly added to MeOH (10 mL) and the resulting mixture was heated at 70 °C for 1 h. Upon cooling to rt, the mixture was concentrated under reduced pressure and purified by reverse flash chromatography (C18 silica gel, ACN-water, 10-50% with 0.1% FA). The resulting material was further purified by prep-SFC [Column: DAICEL DCpak PMPC 5 μm 30 x 150 mm; Mobile Phase A: CO_2, Mobile phase B: MeOH (with 0.3%-7M-NH_3-MeOH) Flow rate: 80 mL/min; Column Temperature: 35 °C; Back Pressure: 100 bar; Wavelength: 220 nm], affording 1-(2,4-difluoro-5-iodo-3-methoxyphenyl)methanamine (150 mg, 16%) (Scheme 15) as a white solid.

A mixture of 1-(2,4-difluoro-5-iodo-3-methoxyphenyl)methanamine (300 mg, 1.00 mmol) and TEA (304 mg, 3.01 mmol) in DCM (4 mL) was added $(Boc)_2O$ (328 mg, 1.50 mmol). After 1 h, the mixture was concentrated under reduced pressure and purified by silica gel chromatography (EA-Petroleum ether, 15%) followed by reverse flash chromatography (C18 silica gel, ACN-water, 10-90% with 0.1% FA) to afford the title compound (200 mg, 50%) as a white solid.

Scheme 16. Representative schematic route to achieve *tert*-butyl (2,4-difluoro-5-iodo-3-methoxybenzyl)carbamate.

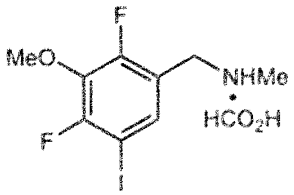


For 1-(2,4-difluoro-5-iodo-3-methoxyphenyl)methanamine, ^1H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.60 (t, J = 7.2 Hz, 1H), 3.88 (s, 3H), 3.65 (d, J = 5.2 Hz, 2H). ^{19}F NMR (376 MHz, DMSO-d_6/D_2O) δ -111.17 (d, J = 9.3 Hz), -133.88 (d, J = 8.6 Hz). LCMS (ES, m/z) 300.00 $[M+H]^+$.

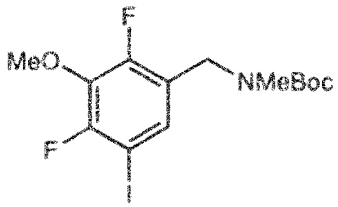
For *tert*-butyl (2,4-difluoro-5-iodo-3-methoxybenzyl)carbamate, ^1H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.48-7.32 (m, 2H), 4.14-3.99 (m, 2H), 3.88 (s, 3H), 1.40-1.24 (m, 9H). ^{19}F NMR (376 MHz, DMSO-d_6/D_2O) δ -110.10 (d, J = 9.2 Hz), -132.77 (d, J = 9.2 Hz). LCMS (ES, m/z): 343.85 $[M-tBu+2H]^+$; 98.4% purity (254 nm).

Example 39: Synthesis of 1-(2,4-difluoro-5-iodo-3-methoxyphenyl)-N-methylmethanamine hydroformate and *tert*-butyl (2,4-difluoro-5-iodo-3-methoxybenzyl)(methyl)carbamate

Scheme 17. Representation of 1-(2,4-difluoro-5-iodo-3-methoxyphenyl)-N-methylmethanamine hydroformate.



Scheme 18. Representation of *tert*-butyl (2,4-difluoro-5-iodo-3-methoxybenzyl)(methyl)carbamate.



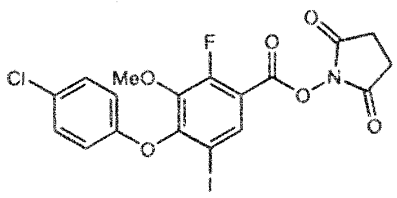
The preparation of 1-(2,4-difluoro-5-iodo-3-methoxyphenyl)-N-methylmethanamine hydroformate (Scheme 17) and *tert*-butyl (2,4-difluoro-5-iodo-3-methoxybenzyl)(methyl)carbamate (Scheme 18) were from the intermediate, 2,4-difluoro-5-iodo-3-methoxybenzoic acid in an analogous manner to methods described in Example 38.

For 1-(2,4-difluoro-5-iodo-3-methoxyphenyl)-N-methylmethanamine hydroformate, ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 8.30 (br s, 1H), 7.66 (t, J = 7.0 Hz, 1H), 3.92 (s, 2H), 3.91 (s, 3H), 2.44 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6/D_2O) δ -107.46 (d, J = 10.5 Hz), -130.19 (d, J = 10.7 Hz). LCMS (ES, m/z) 313.85 $[M\text{-}FA+H]^+$; 98.9% purity (220 nm).

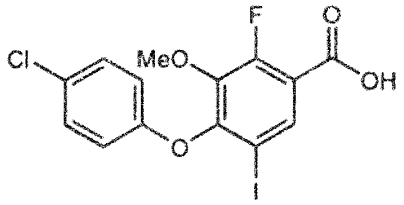
For *tert*-butyl (2,4-difluoro-5-iodo-3-methoxybenzyl)(methyl)carbamate, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38 (br s, 1H), 4.37 (s, 2H), 3.93 (s, 3H), 2.79 (s, 3H), 1.47-1.34 (m, 9H). 19F NMR (376 MHz, DMSO-d_6) δ -109.49, (minor rotamer), -109.49 (major rotamer), -132.17 (major rotamer), -132.55 (minor rotamer). LCMS (ES, m/z): 357.90 $[M\text{-}tBu+2H]^+$; 98.2% purity (220 nm).

<u>Example 40:</u> Synthesis of 2,5-dioxopyrrolidin-1-yl 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzoate

Scheme 19. Representation of 2,5-dioxopyrrolidin-1-yl 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzoate.



Scheme 20. Representation of 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzoic acid.

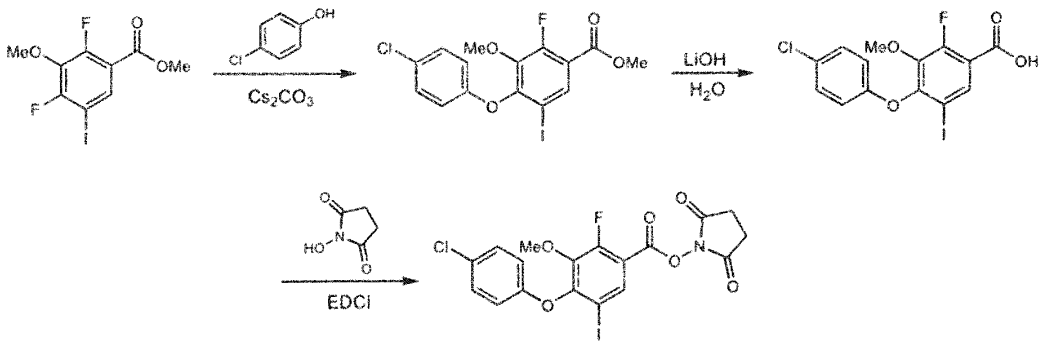


The preparation of 2,5-dioxopyrrolidin-1-yl 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzoate (Scheme 19) is shown schematically in Scheme 21. A mixture of methyl 2,4-difluoro-5-iodo-3-methoxybenzoate (5.00 g, 15.2 mmol), Cs_2CO_3 (10.0 g, 30.5 mmol) and 4-chlorophenol (1.97 g, 15.2 mmol) in DMF (100 mL) was heated at 60 °C for 16 h. Upon cooling to rt, the mixture poured into ice-water (150 mL) and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (EA-Petroleum ether, 15%), to afford methyl 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzoate (5.00 g, 75%) as a white solid. GCMS (EI, m/z): 436.00 [M].

To a mixture of methyl 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzoate (5.00 g, 11.5 mmol) in THF (40 mL) was added a solution of $LiOH•H_2O$ (4.82 g, 115 mmol) in H_2O (40 mL). After 16 h, the mixture was diluted with water (80 mL), cooled to 0 °C, acidified to pH~6 with HCl (2 M) and extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzoic acid (4.8 g, 99%) (Scheme 20) as a light yellow solid.

To a mixture of 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzoic acid (1.00 g, 2.37 mmol) in DMF (10 mL) was added EDCI (567 mg, 2.96 mmol), DMAP (58 mg, 0.47 mmol) and 1-hydroxypyrrolidine-2,5-dione (408 mg, 3.55 mmol). After 4 h, the mixture was poured into ice-water (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by reverse flash chromatography (C18 silica gel, ACN-water, 0-80% with 0.1% FA) to afford the title compound (541 mg, 43%, 2-steps) as a white solid.

Scheme 21. Representative schematic route to achieve 2,5-dioxopyrrolidin-1-yl 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzoate.

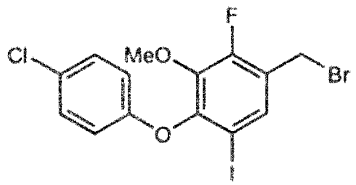


For 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzoic acid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.61 (br s, 1H), 8.08 (d, J = 7.4 Hz, 1H), 7.43-7.37 (m, 2H), 6.96-6.91 (m, 2H), 3.73 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -125.44. LCMS (ES, m/z): 420.80 $[M-H]^-$.

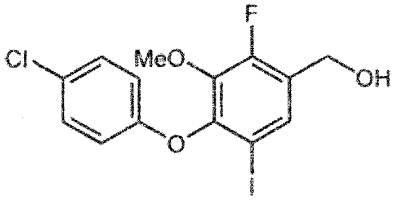
For 2,5-dioxopyrrolidin-1-yl 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzoate, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, J = 7.0 Hz, 1H), 7.43-7.36 (m, 2H), 7.04-6.98 (m, 2H), 3.77 (s, 3H), 2.91 (s, 4H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -121.99.

Example 41: Synthesis of 1-(bromomethyl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzene

Scheme 22. Representation of 1-(bromomethyl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzene.



Scheme 23. Representation of (4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxyphenyl)methanol.

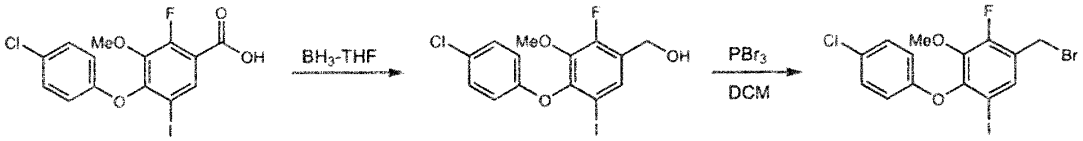


The preparation of 1-(bromomethyl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzene (Scheme 22) is shown schematically in Scheme 24. To a mixture of 4-(4-

chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzoic acid (2.00 g, 4.74 mmol, 1.00 equiv) in THF (16 mL) at 0 °C was added borane-tetrahydrofuran complex (1 M in THF, 48.0 mL, 47.4 mmol) dropwise. The mixture was warmed to 30 °C and stirred for 16 h, whereupon it was slowly poured into MeOH (50 mL) and heated at 70 °C for 1 h. After cooling to rt it was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (EA-Petroleum ether, 20%), to afford (4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxyphenyl)methanol (1.10 g, 56%) as a white solid (Scheme 23).

To a stirred mixture of [4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxyphenyl]methanol (200 mg, 0.49 mmol) in DCM (2 mL) at 0 °C was added PBr_3 (265 mg, 0.98 mmol) dropwise. After 4 h at 30 °C, the mixture was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (EA-Petroleum ether, 20%), to afford the title compound (116 mg, 50%) as a white solid.

Scheme 24. Representative schematic route to achieve 1-(bromomethyl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzene.

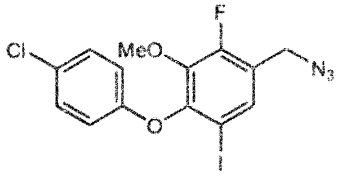


For (4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxyphenyl)methanol, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (d, J = 7.4 Hz, 1H), 7.41-7.35 (m, 2H), 6.89-6.82 (m, 2H), 5.43 (t, J = 5.8 Hz, 1H), 4.54 (d, J = 5.8 Hz, 2H), 3.72 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -134.25. GCMS (EI, m/z): 407.90 [M].

For 1-(bromomethyl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzene, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, J = 7.6 Hz, 1H), 7.41-7.37 (m, 2H), 6.90-6.83 (m, 2H), 4.70 (s, 2H), 3.74 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -130.57. GCMS (EI, m/z): 469.80, 471.8 [M]; 95.7% purity (245 nm).

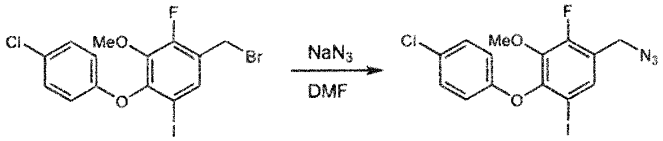
Example 42: Synthesis of 1-(azidomethyl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzene

Scheme 25. Representation of 1-(azidomethyl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzene.



The preparation of 1-(azidomethyl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzene (Scheme 25) is shown schematically in Scheme 26. To a solution of 1-(bromomethyl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzene (100 mg, 0.22 mmol) in DMF (1 mL) was added NaN_3 (69 mg, 1.06 mmol), whereupon it was heated at 60 °C. After 4 h, the mixture was cooled to rt and purified by reverse flash chromatography (C18 silica gel, ACN-water, 0-80% with 10 mM NH_4HCO_3), affording the title compound (55.8 mg, 60%) as a colorless oil.

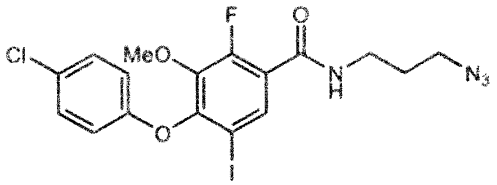
Scheme 26. Representative schematic route to achieve 1-(azidomethyl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzene.



For 1-(azidomethyl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzene, ^1H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 7.4 Hz, 1H), 7.42-7.35 (m, 2H), 6.90-6.84 (m, 2H), 4.55 (s, 2H), 3.74 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -131.93. LCMS (ES, m/z): 405.90 [M-N_2+H]$^+$; 99.9% purity (245 nm).

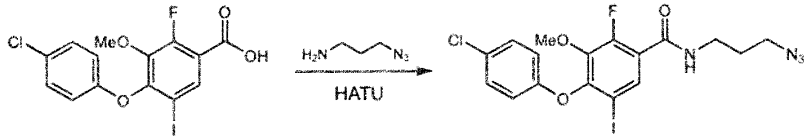
Example 43: Synthesis of *N*-(3-azidopropyl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzamide

Scheme 27. Representation of *N*-(3-azidopropyl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzamide.



The preparation of *N*-(3-azidopropyl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzamide (Scheme 27) is shown schematically in Scheme 28. To a mixture of 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzoic acid (300 mg, 0.71 mmol) in DMF (3 mL) was added DIEA (458 mg, 3.55 mmol), HATU (405 mg, 1.07 mmol) and 3-azidopropan-1-amine (142 mg, 1.42 mmol). After 16 h at 30 °C, the mixture was purified by reverse flash chromatography (C18 silica gel, ACN-water, 0-60% with 0.1% FA), affording the title compound (119 mg, 33%) as a white solid.

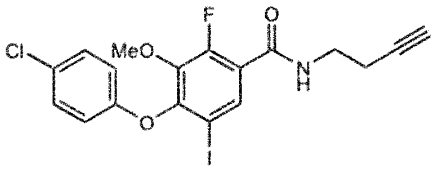
Scheme 28. Representative schematic route to achieve *N*-(3-azidopropyl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzamide.



For *N*-(3-azidopropyl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzamide, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (br t, J = 5.2 Hz, 1H), 7.83 (d, J = 7.1 Hz, 1H), 7.43-7.36 (m, 2H), 6.91-6.85 (m, 2H), 3.74 (s, 3H), 3.43 (t, J = 6.8 Hz, 2H), 3.37-3.27 (m, 2H), 1.77 (p, J = 6.7 Hz, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -129.40. LCMS (ES, m/z): 504.90 $[M+H]^+$.

Example 44: Synthesis of *N*-(but-3-yn-1-yl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzamide

Scheme 29. Representation of *N*-(but-3-yn-1-yl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzamide.



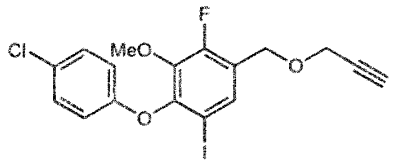
The preparation of *N*-(but-3-yn-1-yl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzamide (Scheme 29) (131 mg, 43%) was from 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzoic acid in an analogous manner to methods described in Example 43.

For *N*-(but-3-yn-1-yl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzamide, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63-8.56 (m, 1H), 7.82 (d, J = 7.1 Hz, 1H), 7.43-7.36 (m, 2H),

6.92-6.85 (m, 2H), 3.74 (s, 3H), 3.41-3.34 (m, 2H), 2.88 (t, J = 2.6 Hz, 1H), 2.43 (td, J = 7.1, 2.6 Hz, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -129.05. LCMS (ES, m/z): 473.90 $[M+H]^+$; 95.0% purity (254 nm).

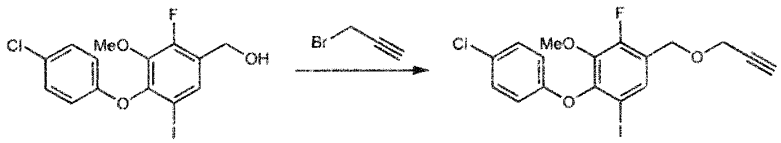
Example 45: Synthesis of 2-(4-chlorophenoxy)-4-fluoro-1-iodo-3-methoxy-5-((prop-2-yn-1-yloxy)methyl)benzene

Scheme 30. Representation of 2-(4-chlorophenoxy)-4-fluoro-1-iodo-3-methoxy-5-((prop-2-yn-1-yloxy)methyl)benzene.



The preparation of 2-(4-chlorophenoxy)-4-fluoro-1-iodo-3-methoxy-5-((prop-2-yn-1-yloxy)methyl)benzene (Scheme 30) is shown schematically in Scheme 31. To a mixture of (4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxyphenyl)methanol (250 mg, 0.61 mmol) in DMF (3 mL) at 0 °C was added NaH (60% in mineral oil, 37 mg, 0.92 mmol). After 30 min at 0 °C, 3-bromoprop-1-yne (146 mg, 1.22 mmol, 2.00 equiv) was added and the mixture was allowed to warm to rt. After 2 h, the mixture was slowly poured into ice-water (30 mL) and extracted with EA (2 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by reverse flash chromatography (C18 silica gel, ACN-water, 0-90% with 10 mM NH_4HCO_3) to afford the title compound (110 mg, 40%) as a light yellow solid.

Scheme 31. Representative schematic route to achieve 2-(4-chlorophenoxy)-4-fluoro-1-iodo-3-methoxy-5-((prop-2-yn-1-yloxy)methyl)benzene.

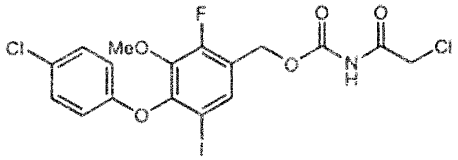


For 2-(4-chlorophenoxy)-4-fluoro-1-iodo-3-methoxy-5-((prop-2-yn-1-yloxy)methyl)benzene, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (d, J = 7.3 Hz, 1H), 7.41-7.35 (m, 2H), 6.90-6.84 (m, 2H), 4.57 (s, 2H), 4.25 (d, J = 2.4 Hz, 2H), 3.73 (s, 3H), 3.53 (t, J = 2.4 Hz,

1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -132.83. GCMS (EI, m/z): 445.98 [M]; 99.9% purity (254 nm).

Example 46: Synthesis of 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl (2-chloroacetyl)carbamate

Scheme 32. Representation of 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl (2-chloroacetyl)carbamate.

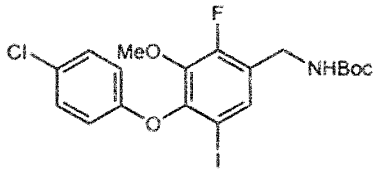


The preparation of 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl (2-chloroacetyl)carbamate (Scheme 32) proceeds as follows: to a solution of (4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxyphenyl)methanol (300 mg, 0.74 mmol) in MeCN (3 mL) at 0 °C was added DBU (22.4 mg, 0.15 mmol) and 2-chloroethanecarbonyl isocyanate (97 mg, 0.81 mmol). After 16 h at rt, the mixture was directly purified by reverse flash chromatography (C18 silica gel, ACN-water, 0-80% with 10 mM NH_4HCO_3), affording the title compound (77.5 mg, 20%) as a white solid.

For 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl (2-chloroacetyl)carbamate, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (br s, 1H), 7.83 (d, J = 7.4 Hz, 1H), 7.45-7.36 (m, 2H), 6.92-6.82 (m, 2H), 5.20 (s, 2H), 4.49 (s, 2H), 3.73 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -131.99. LCMS (ES, m/z): 525.75, 527.75 $[M-H]^-$; 95.1% purity (254 nm).

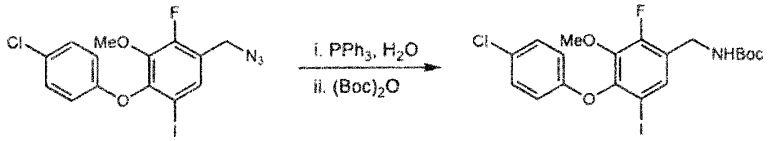
Example 47: Synthesis of *tert*-butyl (4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl)carbamate

Scheme 33. Representation of *tert*-butyl (4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl)carbamate.



The preparation of *tert*-butyl (4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl)carbamate (Scheme 33) is shown schematically in Scheme 34. To a mixture of 1-(azidomethyl)-4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzene (350 mg, 0.81 mmol) in THF/H_2O (10:1, 3.3 mL) was added PPh_3 (424 mg, 1.62 mmol). After 16 h, the mixture was cooled to 0 °C and TEA (246 mg, 2.43 mmol) followed by $(Boc)_2O$ (265 mg, 1.22 mmol) were added, whereupon it was allowed to warm to rt. After 4 h, the mixture was directly purified by reverse flash chromatography (C18 silica gel, ACN-water, 0-80% with 10 mM NH_4HCO_3), affording the title compound (160 mg, 39%) as a white solid.

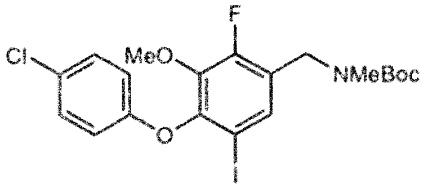
Scheme 34. Representative schematic route to achieve *tert*-butyl (4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl)carbamate.



For *tert*-butyl (4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl)carbamate, ^1H NMR (400 MHz, DMSO-d_6) δ 7.64-7.50 (m, 1H), 7.48-7.41 (m, 1H), 7.41-7.34 (m, 2H), 6.88-6.81 (m, 2H), 4.23-4.07 (m, 2H), 3.72 (s, 3H), 1.47-1.30 (m, 9H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -133.33. LCMS (ES, m/z): 451.85 $[M\text{-}tBu+2H]^+$; 98.6% purity (254 nm).

Example 48: Synthesis of *tert*-butyl (4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl)(methyl)carbamate

Scheme 35. Representation of *tert*-butyl (4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl)(methyl)carbamate.



The preparation of *tert*-butyl (4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl)(methyl)carbamate (Scheme 35) is shown schematically in Scheme 36. To a stirred mixture of NaH (60% in mineral oil, 16 mg, 0.40 mmol) in DMF (0.3 mL) at 0 °C under a

N_2 atmosphere was added a solution of *tert*-butyl (4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl)carbamate (100 mg, 0.20 mmol) in DMF (0.5 mL) dropwise. After 30 min at 0 °C, a solution of MeI (56 mg, 0.40 mmol) in DMF (0.2 mL) was added dropwise, whereupon it was allowed to warm to rt. After 4 h, ice-water (0.3 mL) was added and the resulting mixture was directly purified by reverse flash chromatography (C18 silica gel, ACN-water, 0-80% with 10 mM NH_4HCO_3), affording the title compound (68.4 mg, 66%) as a white solid.

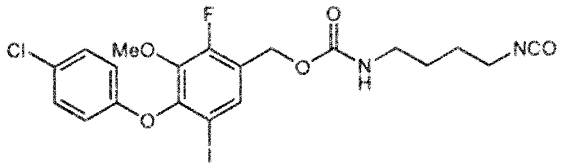
Scheme 36. Representative schematic route to achieve *tert*-butyl (4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl)(methyl)carbamate.



For *tert*-butyl (4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl)(methyl)carbamate, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56-7.41 (m, 1H), 7.40-7.32 (m, 2H), 6.96-6.79 (m, 2H), 4.40 (s, 2H), 3.72-3.67 (m, 3H), 2.86-2.78 (m, 3H), 1.47-1.31 (m, 9H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -132.40 (major rotamer), -132.75 (minor rotamer), -136.62 (major rotamer), -136.96 (minor rotamer). 465.95 $[M\text{-}tBu+2H]^+$; 97.4% purity (254 nm).

Example 49: Synthesis of 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl (4-isocyanatobutyl)carbamate

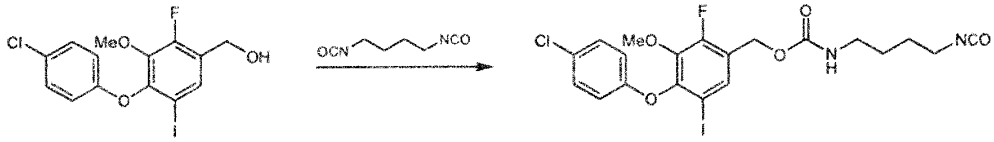
Scheme 37. Representation of 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl (4-isocyanatobutyl)carbamate.



The preparation of 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl (4-isocyanatobutyl)carbamate (Scheme 37) is shown schematically in Scheme 38. To a solution of 1,4-diisocyanatobutane (82 mg, 0.59 mmol) in THF (3 mL) was added (4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxyphenyl)methanol (120 mg, 0.29 mmol) and TEA (29.6 mg, 0.29 mmol). After 16 h, the mixture directly purified by reverse flash chromatography (C18 silica gel, ACN-

water, 0-80% with 0.1% FA). The resultant product was further purified by Prep-HPLC [Column: XBridge Prep Shield RP18 OBD C18 5 μm, 30 x 150 mm; Mobile Phase: ACN-water, 52-83%; Flow rate: 60 mL/min; Wavelength: 254/220 nm], affording the title compound (20 mg, 12%) as a white solid.

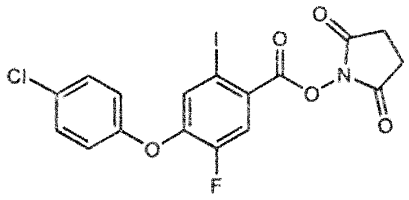
Scheme 38. Representative schematic route to achieve 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl (4-isocyanatobutyl)carbamate.



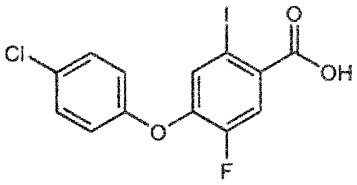
For 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzyl (4-isocyanatobutyl)carbamate, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.1 Hz, 1H), 7.29-7.24 (m, 2H), 6.84-6.77 (m, 2H), 5.23-5.10 (s, 2H), 4.83 (br s, 1H), 3.80 (s, 3H), 3.39 (t, J = 6.0 Hz, 2H), 3.32-3.22 (m, 2H), 1.75-1.55 (m, 4H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -132.11. 570.90 $[M+Na]^+$.

Example 50: Synthesis of 2,5-dioxopyrrolidin-1-yl 4-(4-chlorophenoxy)-5-fluoro-2-iodobenzoate

Scheme 39. Representation of 2,5-dioxopyrrolidin-1-yl 4-(4-chlorophenoxy)-5-fluoro-2-iodobenzoate.



Scheme 40. Representation of 4-(4-chlorophenoxy)-5-fluoro-2-iodobenzoic acid.



The preparation of 2,5-dioxopyrrolidin-1-yl 4-(4-chlorophenoxy)-5-fluoro-2-iodobenzoate (Scheme 39) is shown schematically in Scheme 41. To a solution of of 4,5-difluoro-2-iodobenzoic

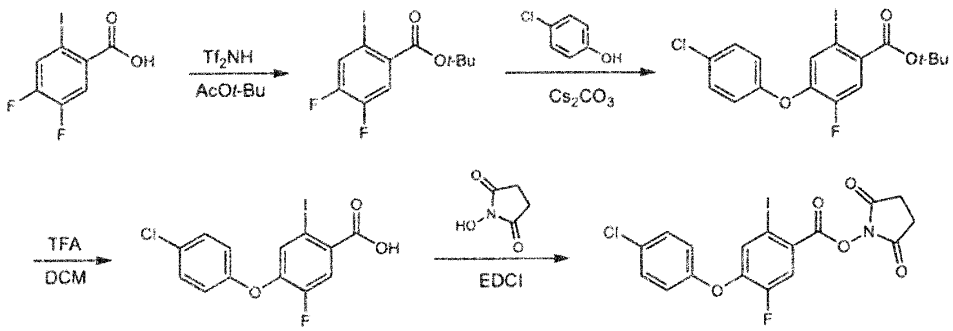
acid (10.0 g, 35.2 mmol) in *tert*-butyl acetate (100 mL) at 0 °C was added a solution of trifluoromethanesulfonimide (198 mg, 0.70 mmol) in DCM (9 mL), dropwise. After 1 h at rt, the pH was adjusted to ~9 with $NaHCO_3$ (satd, aq) and extracted with EA (2 x 400 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (EA-petroleum ether, 20%) to afford *tert*-butyl 4,5-difluoro-2-iodobenzoate (8 g, 67%) as a colorless oil. GCMS (EI, m/z): 340.00 [M].

A mixture of *tert*-butyl 4,5-difluoro-2-iodobenzoate (4.00 g, 11.8 mmol), 4-chlorophenol (1.51 g, 11.8 mmol) and Cs_2CO_3 (11.5 g, 35.3 mmol) in DMF (30 mL) was heated at 80 °C for 16 h, whereupon it was cooled to rt, diluted with water (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 200 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by reverse flash chromatography (C18 silica gel, ACN-water, 0-85% with 0.1% FA) to afford 4-(4-chlorophenoxy)-5-fluoro-2-iodobenzoate (3.50 g, 66%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.73 (dd, J = 11.3, 1.0 Hz, 1H), 7.61 (dd, J = 7.9, 1.1 Hz, 1H), 7.51-7.45 (m, 2H), 7.18-7.12 (m, 2H), 1.57 (s, 9H). GCMS (EI, m/z) 447.9 [M].

To a solution of tert-butyl 4-(4-chlorophenoxy)-5-fluoro-2-iodobenzoate (700 mg, 1.56 mmol) in DCM (3 mL) was added TFA (1 mL). After 1 h, the mixture concentrated under reduced pressure and the crude residue was purified by silica gel chromatography (MeOH-DCM, 10%) to afford 4-(4-chlorophenoxy)-5-fluoro-2-iodobenzoic acid (500 mg, 81%) as a yellow solid (Scheme 40).

A mixture of 4-(4-chlorophenoxy)-5-fluoro-2-iodobenzoic acid (150 mg, 0.38 mmol), N-hydroxysuccinimide (66 mg, 0.57 mmol) and EDCI (109 mg, 0.57 mmol, 1.50 equiv) in DMF (2 mL) was stirred for 4 h, whereupon it was directly purified by reverse flash chromatography (C18 silica gel, ACN-water, 10-80% with 0.1% FA), affording the title compound (60.0 mg, 32%) as a white solid.

Scheme 41. Representative schematic route to achieve 2,5-dioxopyrrolidin-1-yl 4-(4-chlorophenoxy)-5-fluoro-2-iodobenzoate.

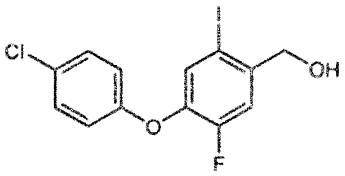


For 4-(4-chlorophenoxy)-5-fluoro-2-iodobenzoic acid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.51 (br s, 1H), 7.80 (d, J = 11.4 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.51-7.45 (m, 2H), 7.19-7.12 (m, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -131.52. LCMS (ES, m/z): 390.20 [M-H]$^-$.

For 2,5-dioxopyrrolidin-1-yl 4-(4-chlorophenoxy)-5-fluoro-2-iodobenzoate, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, J = 11.2 Hz, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.56-7.50 (m, 2H), 7.30-7.24 (m, 2H), 2.91 (s, 4H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -130.49. LCMS (ES, m/z): 392.80 [M-succinimide+2H]$^+$; 99.6% purity (254 nm).

Example 51: Synthesis of (4-(4-chlorophenoxy)-5-fluoro-2-iodophenyl)methanol

Scheme 42. Representation of (4-(4-chlorophenoxy)-5-fluoro-2-iodophenyl)methanol.

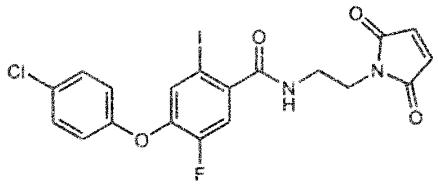


The title compound (4-(4-chlorophenoxy)-5-fluoro-2-iodophenyl)methanol (Scheme 42) (71 mg) was prepared from 4-(4-chlorophenoxy)-5-fluoro-2-iodobenzoic acid in an analogous manner to methods described in Example 41.

For (4-(4-chlorophenoxy)-5-fluoro-2-iodophenyl)methanol, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, J = 8.0 Hz, 1H), 7.46-7.38 (m, 3H), 7.06-6.99 (m, 2H), 5.65 (t, J = 5.5 Hz, 1H), 4.38 (d, J = 5.4 Hz, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -131.14. LCMS (EI, m/z): 377.90 [M]; 99.9% purity (254 nm).

Example 52: Synthesis of 4-(4-chlorophenoxy)-*N*-(2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl)-5-fluoro-2-iodobenzamide

Scheme 43. Representation of 4-(4-chlorophenoxy)-*N*-(2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl)-5-fluoro-2-iodobenzamide.

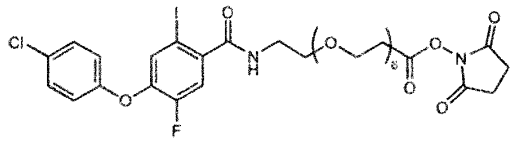


The title compound 4-(4-chlorophenoxy)-*N*-(2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl)-5-fluoro-2-iodobenzamide (Scheme 43) (21 mg) was prepared from 4-(4-chlorophenoxy)-5-fluoro-2-iodobenzoic acid in an analogous manner to methods described in Example 43.

For 4-(4-chlorophenoxy)-*N*-(2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl)-5-fluoro-2-iodobenzamide, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (t, J = 6.1 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.50-7.44 (m, 2H), 7.30 (d, J = 11.0 Hz, 1H), 7.11-7.03 (m, 4H), 3.61-3.55 (m, 2H), 3.42-3.34 (m, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -131.71. LCMS (ES, m/z): 514.90 $[M+H]^+$; 95.6% purity (254 nm).

Example 53: Synthesis of 2,5-dioxopyrrolidin-1-yl 1-(4-(4-chlorophenoxy)-5-fluoro-2-iodophenyl)-1-oxo-5,8,11,14,17,20-hexaoxa-2-azatricosan-23-oate

Scheme 44. Representation of 2,5-dioxopyrrolidin-1-yl 1-(4-(4-chlorophenoxy)-5-fluoro-2-iodophenyl)-1-oxo-5,8,11,14,17,20-hexaoxa-2-azatricosan-23-oate.



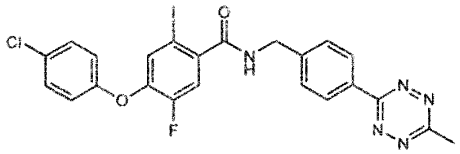
The title compound of 2,5-dioxopyrrolidin-1-yl 1-(4-(4-chlorophenoxy)-5-fluoro-2-iodophenyl)-1-oxo-5,8,11,14,17,20-hexaoxa-2-azatricosan-23-oate (Scheme 44) (70 mg) was prepared from 4-(4-chlorophenoxy)-5-fluoro-2-iodobenzoic acid and *tert*-butyl 1-amino-3,6,9,12,15,18-hexaoxahenicosan-21-oate in an analogous manner to methods described herein..

For 2,5-dioxopyrrolidin-1-yl 1-(4-(4-chlorophenoxy)-5-fluoro-2-iodophenyl)-1-oxo-5,8,11,14,17,20-hexaoxa-2-azatricosan-23-oate, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52-8.45 (m, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 8.6 Hz, 1H), 7.07 (d, J = 8.6

Hz, 2H), 3.72 (br t, J = 5.9 Hz, 2H), 3.61- 3.47 (m, 20H), 3.42-3.33 (m, 2H), 2.92 (br t, J = 5.8 Hz, 2H), 2.81 (s, 4H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -131.74. LCMS (ES, m/z): 825.05 $[M+H]^+$; 95.1% purity (254 nm).

Example 54: Synthesis of 4-(4-chlorophenoxy)-5-fluoro-2-iodo-*N*-(4-(6-methyl-1,2,4,5-tetrazin-3-yl)benzyl)benzamide

Scheme 45. Representation of 4-(4-chlorophenoxy)-5-fluoro-2-iodo-*N*-(4-(6-methyl-1,2,4,5-tetrazin-3-yl)benzyl)benzamide.

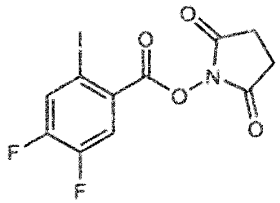


The title compound of 4-(4-chlorophenoxy)-5-fluoro-2-iodo-*N*-(4-(6-methyl-1,2,4,5-tetrazin-3-yl)benzyl)benzamide (Scheme 45) (25 mg) was prepared from 4-(4-chlorophenoxy)-2-fluoro-5-iodo-3-methoxybenzoic acid in an analogous manner to methods described in Example 43.

For 4-(4-chlorophenoxy)-5-fluoro-2-iodo-*N*-(4-(6-methyl-1,2,4,5-tetrazin-3-yl)benzyl)benzamide, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (t, J = 5.9 Hz, 1H), 8.46 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 10.9 Hz, 1H), 7.52-7.46 (m, 2H), 7.13-7.06 (m, 2H), 4.58 (d, J = 5.9 Hz, 2H), 3.00 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -131.62. LCMS (ES, m/z): 576.00$[M+H]^+$; 96.5% purity (254 nm).

Example 55: Synthesis of 2,5-dioxopyrrolidin-1-yl 4,5-difluoro-2-iodobenzoate

Scheme 46. Representation of 2,5-dioxopyrrolidin-1-yl 4,5-difluoro-2-iodobenzoate.

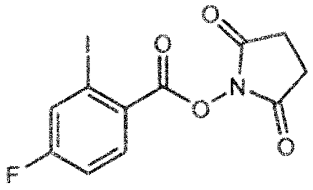


The title compound of 2,5-dioxopyrrolidin-1-yl 4,5-difluoro-2-iodobenzoate (Scheme 46) (60 mg) was prepared from 4,5-difluoro-2-iodobenzoic acid in an analogous manner to methods described herein.

For 2,5-dioxopyrrolidin-1-yl 4,5-difluoro-2-iodobenzoate, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (dd, J = 10.0, 7.8 Hz, 1H), 8.07 (dd, J = 10.7, 8.0 Hz, 1H), 2.91 (s, 4H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -127.66 (d, J = 22.1 Hz), -136.06 (d, J = 22.2 Hz). 99.9% purity (254 nm).

Example 56: Synthesis of 2,5-dioxopyrrolidin-1-yl 4-fluoro-2-iodobenzoate

Scheme 47. Representation of 2,5-dioxopyrrolidin-1-yl 4-fluoro-2-iodobenzoate.

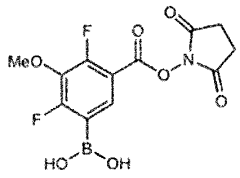


The title compound of 2,5-dioxopyrrolidin-1-yl 4-fluoro-2-iodobenzoate (Scheme 47) (103 mg) was prepared from 4-fluoro-2-iodobenzoic acid in an analogous manner to methods described herein.

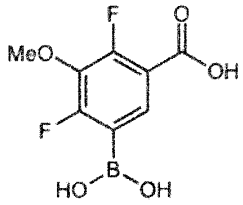
For 2,5-dioxopyrrolidin-1-yl 4-fluoro-2-iodobenzoate, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18-8.04 (m, 2H), 7.59-7.49 (m, Hz, 1H), 2.91 (s, 4H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -103.11. LCMS (ES, m/z): 385.94 $[M+Na]^+$; 96.4% purity (254 nm).

Example 57: Synthesis of (5-(((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)-2,4-difluoro-3-methoxyphenyl)boronic acid

Scheme 48. Representation of (5-(((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)-2,4-difluoro-3-methoxyphenyl)boronic acid.



Scheme 49. Representation of 5-(dihydroxyboranyl)-2,4-difluoro-3-methoxybenzoic acid.



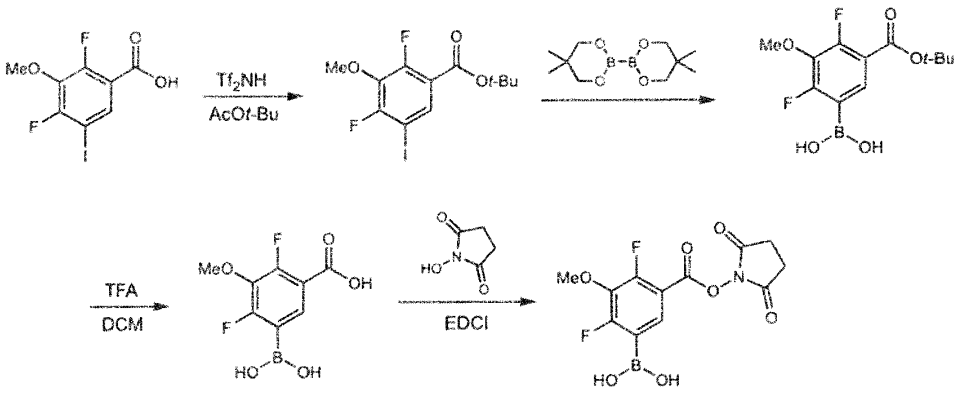
The preparation of (5-(((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)-2,4-difluoro-3-methoxyphenyl)boronic acid (Scheme 48) is shown schematically in Scheme 50. To a solution of 2,4-difluoro-5-iodo-3-methoxybenzoic acid (2.00 g, 6.37 mmol) in *tert*-butyl acetate (20 mL) at 0 °C was added 1,1,1-trifluoro-N-(trifluoromethane)sulfonylmethanesulfonamide (36 mg, 0.13 mmol) in DCM (1 mL). After 1 h at rt, the pH was adjusted to ~9 with $NaHCO_3$ (satd, aq) and extracted with EA (2 x 300 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (EA-petroleum ether, 15%) to afford tert-butyl 2,4-difluoro-5-iodo-3-methoxybenzoate (1.5 g, 63%) as a colorless oil. GCMS (EI, m/z) 370.0[M].

A mixture of *tert*-butyl 2,4-difluoro-5-iodo-3-methoxybenzoate (1.00 g, 2.70 mmol), 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,5-dimethyl-1,3,2-dioxaborinane (915 mg, 4.05 mmol), potassium 2,2-dimethylpropanoate (455 mg, 3.24 mmol) and XPhos Pd(crotyl)Cl (182 mg, 0.27 mmol) THF/IPA (10 mL, 4:1) under a N_2 atmosphere was heated at 50 °C. After 16 h, the mixture was cooled to rt, concentrated under reduced pressure and purified by reverse flash chromatography (C18 silica gel, ACN-water, 10-80% with 0.1% FA) to afford 5-(*tert*-butoxycarbonyl)-2,4-difluoro-3-methoxyphenylboronic acid (500 mg, 64%) as a white solid.

To a solution of 5-(*tert*-butoxycarbonyl)-2,4-difluoro-3-methoxyphenylboronic acid (500 mg, 1.74 mmol) in DCM (3 mL) was added TFA (1 mL). After 1h, the mixture was concentrated under reduced pressure and purified by reversed flash chromatography (C18 silica gel, ACN-water, 0-80% with 0.1% FA) to afford 5-(dihydroxyboranyl)-2,4-difluoro-3-methoxybenzoic acid (Scheme 49) (300 mg, 74%) as a white solid.

A mixture of 5-(dihydroxyboranyl)-2,4-difluoro-3-methoxybenzoic acid (300 mg, 1.29 mmol), N-hydroxysuccinimide (223 mg, 1.94 mmol) in DMF (3 mL) was added EDCI (370 mg, 1.94 mmol). After 2 h, the mixture was directly purified by reversed flash chromatography (C18 silica gel, ACN-water, 0-80% with 0.1% FA) to afford the title compound (100 mg, 24%) as a white solid.

Scheme 50. Representative schematic route to achieve (5-(((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)-2,4-difluoro-3-methoxyphenyl)boronic acid.



For 5-(*tert*-butoxycarbonyl)-2,4-difluoro-3-methoxyphenylboronic acid, ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.72 (dd, J = 8.2, 6.5 Hz, 1H), 3.88 (s, 3H), 1.52 (s, 9H). ^{19}F NMR (376 MHz, DMSO-d_6/D_2O) δ -112.37 (d, J = 16.2 Hz), -124.19 (d, J = 16.5 Hz). 96.6% purity (254 nm).

For 5-(dihydroxyboranyl)-2,4-difluoro-3-methoxybenzoic acid, ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.76 (dd, J = 8.1, 6.6 Hz, 1H), 3.85 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6/D_2O) δ -112.34 (d, J = 16.7 Hz), -123.35 (d, J = 16.8 Hz). LCMS (ES, m/z): 230.95[M-H]$^-$; 96.6% purity (254 nm).

For (5-(((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)-2,4-difluoro-3-methoxyphenyl)boronic acid, ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.95 (dd, J = 7.6, 6.2 Hz, 1H), 3.95 (s, 3H), 2.88 (s, 4H). ^{19}F NMR (376 MHz, DMSO-d_6/D_2O) δ -106.89 (d, J = 19.4 Hz), -120.52 (d, J = 19.6 Hz). 99.9% purity (254 nm).

Example 58: Radiochemical procedures

General methods and materials for photoredox [^{18}F]Fluorination

Photocatalyst (Mes-Acr-Ph$^+$$ClO_4^-$), anhydrous MeCN, anhydrous DMSO, anhydrous [^{18}F]TBAF, and 20% TBAB MeCN solution, *tert*-butanol, dichloroethane were obtained according to previous studies (Tay et al. *Nat. Catal.* 2020, *3*, 9, 734.). Radio-HPLC was carried out with a Thermo Fisher Scientific Vanquish HPLC system equipped with a UV detector followed by a γ-detector.

HPLC condition 1 for isolation and analysis of [^{18}F]F-products: Column: Phenomenex, Kinetex® EVO C18, 5 μm, 100 Å, 250 x 4.6 mm; Solvent A: 0.1%TFA water; Solvent B: 0.1%TFA MeCN; Eluent: 0 to 2 min: 20% to 70% solvent B, 2 to 22 min: 70% to 95% solvent B,

22 to 30 min: 95% to 95% solvent B, 30 to 30.1 min: 95% to 20% solvent B, 30.1 to 35 min: isocratic elution at 20% solvent B. Flow rate: 1 mL/min, column temperature: 19 to 21 °C.

HPLC condition 2 for isolation and analysis of [^{18}F]F-products: Column: Phenomenex, Kinetex® EVO C18, 5 μm, 100 Å, 250 x 4.6 mm; Solvent A: 0.1%TFA water; Solvent B: 0.1%TFA MeCN; Eluent: 0 to 2 min: 5% to 5% solvent B, 2 to 22 min: 5% to 95% solvent B, 22 to 30 min: 95% to 95% solvent B, 30 to 30.1 min: 95% to 5% solvent B, 30.1 to 35 min: isocratic elution at 5% solvent B. Flow rate: 1 mL/min, column temperature: 19 to 21 °C.

Procedure A for organic photoredox deoxyradiofluorination:

[^{18}F]Fluoride was produced via the ^{18}O(p,n)^{18}F reaction in a GE PETTrace cyclotron. The aqueous ($H_2{}^{18}O$) solution of [^{18}F]fluoride was directly trapped on a pre-activated QMA cartridge before elution into the reactor vessel (5mL V-vial) with an aqueous solution of tetrabutylammonium bicarbonate (TBAB). This solution was azeotropically dried under nitrogen and then redissolved with anhydrous MeCN.

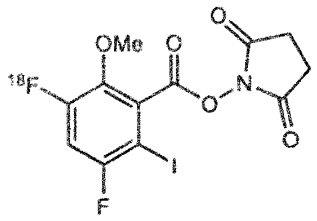
The photocatalyst (1.5 mg), substrate (0.03 mmol), anhydrous $TBAHCO_3$ solution (0.2 M in MeCN, 25 μL, 5 μmol) and [^{18}F]TBAF solution in MeCN (typically 0.37 to 3.7 GBq and ≤40 μL) were added to a 5 mL V-vial, whereupon anhydrous *t*-BuOH (400 μL) and DCM (350 μL) were added followed by a requisite amount of anhydrous MeCN (~35 μL, 100 μL in total) to form a homogeneous solution. The amount of [^{18}F]TBAF activity in solution was measured by a dose calibrator. The solution (~850 μL) was cooled to 0 °C and equipped with an oxygen (O_2) balloon sparge followed by illumination from above with a 450 nm laser (450 nm, 3.5 W after fiber coupling). After 30 min, the mixture was diluted with MeCN (0.5 mL) and passed through an aluminum cartridge (preconditioned with 10 mL DI water) to remove the unconverted [^{18}F]fluoride. Then the reaction vial was rinsed with additional MeCN (0.4 mL) which was also passed through the cartridge. The radioactivity of the total eluted volume was measured by a dose calibrator to determine the radio-chemical yield. An aliquot of the elution (usually 200 μL) was transferred to an Eppendorf tube, followed by addition of AcOH (5% aq, 600 μL). The resulting solution was thoroughly mixed before being subjected to radio-HPLC analysis/purification (HPLC condition **1**). The eluent containing product was concentrated under reduced pressure to afford the [^{18}F]F-labeled substrate.

Procedure B for the conjugation between the ^{18}F-radiotag and Vipivotide tetraxetan (PSMA-617): To a solution of [^{18}F]F-labeled substrate (15.0-30.0 MBq each experiment) in anhydrous DMSO (40 μL) was added a solution of Vipivotide tetraxetan (0.6 mg) in DMSO (10 μL) followed by DIPEA (6 μL), whereupon the mixture was heated at 70 °C. After 30 min, the resulting solution was subjected to radio-HPLC analysis/purification (HPLC condition **2**) to afford the [^{18}F]F-labeled PET tracer [7.0-15.0 MBq, 98.0% radiochemical purity (RCP)]. The radiochemical yields (RCYs) of all [^{18}F]F-labeled molecules were calculated based on the HPLC-isolated products. The [^{18}F]F-radiolabeled products were confirmed by comparing with the ^{19}F-standard under the same HPLC conditions. Quality control was run separately to ensure the purity of the isolated radiolabeled products.

In vivo formulation: According to the original volume of the vial containing the final product HPLC solution (containing 0.1% TFA), a certain volume of NaOH (1 N) was added into to ensure the pH~7. The solution was then concentrated under reduced pressure until less than 100 μL of volume remained. To the vile was added ethanol and phosphate-buffered saline (PBS, 1×) in a volume ratio of 1/10 to form an injectable solution for the imaging study (150 μL/mouse).

Example 59: Synthesis of 2,5-dioxopyrrolidin-1-yl 3-fluoro-5-(fluoro-18F)-2-iodo-6-methoxybenzoate

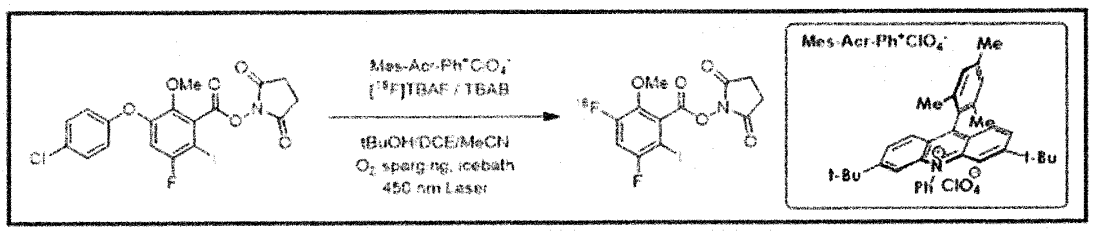
Scheme 51. Representation of 2,5-dioxopyrrolidin-1-yl 3-fluoro-5-(fluoro-18F)-2-iodo-6-methoxybenzoate.



The title compund of 2,5-dioxopyrrolidin-1-yl 3-fluoro-5-(fluoro-18F)-2-iodo-6-methoxybenzoate (Scheme 51) was prepared as shown schematically in Scheme 52. Briefly, 2,5-dioxopyrrolidin-1-yl 3-(4-chlorophenoxy)-5-fluoro-6-iodo-2-methoxybenzoate (15.6 mg, 0.03 mmol) was radiolabeled according to procedure A of Example 58 to afford the title compound (RCY = 36.0 ± 2.7%, n = 3, non-decay corrected). Radio-HPLC purification by HPLC condition 1 is shown in FIG. 6.

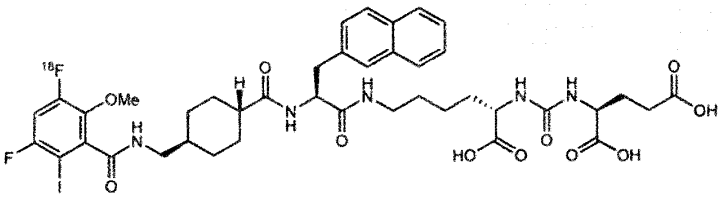
Quality Control analysis of Example 59 by HPLC condition 2 is shown in FIG. 7. ^{19}F-standard (Example 32) analysis by HPLC condition 2 is shown in FIG. 8.

Scheme 52. Representative schematic route to achieve 2,5-dioxopyrrolidin-1-yl 3-fluoro-5-(fluoro-18F)-2-iodo-6-methoxybenzoate.



Example 60: Synthesis of (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3-fluoro-5-(fluoro-^{18}*F*)-2-iodo-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid

Scheme 53. Representation of (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3-fluoro-5-(fluoro-^{18}*F*)-2-iodo-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid.

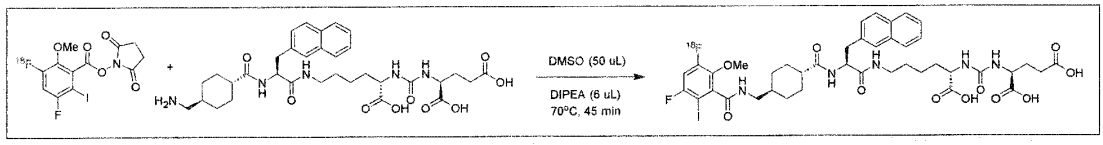


The preparation of (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3-fluoro-5-(fluoro-^{18}*F*)-2-iodo-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid (Scheme 53) is shown schematically in Scheme 54. The title compound (RCY = 67.0%, n = 3, non-decay corrected) was prepared according to procedure B of Example 58. Radio-HPLC purification by HPLC condition 2 is shown in FIG. 9. Quality Control analysis of Example 60 by HPLC condition 2 is shown in FIG. 10.

F-18 imaging, biodistribution for Example 60 is shown in FIG. 11. According to the original volume of the vial containing the final product HPLC solution (containing 0.1% TFA), a

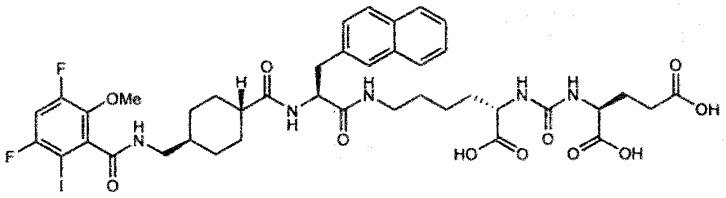
certain volume of NaOH (1 N) was added into to ensure the pH~7. The solution was then concentrated under reduced pressure until less than 100 μL of volume remained. To the vial was added ethanol and phosphate-buffered saline (PBS, 1×) in a volume ratio of 1/10 to form an injectable solution for the imaging study (150 μL/mouse).

Scheme 54. Representative schematic route to achieve (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3-fluoro-5-(fluoro-^{18}F)-2-iodo-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid.



Example 61: Synthesis of (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3,5-difluoro-2-iodo-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid

Scheme 55. Representation of (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3,5-difluoro-2-iodo-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid.



The title compound of (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3,5-difluoro-2-iodo-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid (Scheme 55) (^{19}F-standard) was prepared in an analogous manner to that described in Example 60. LCMS (ES, m/z): 952.25 $[M+H]^+$. Analysis by HPLC condition 2 is shown in FIG. 12.

For (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3,5-difluoro-2-iodo-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-

yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.52 (br s, 2H), 8.46 (t, *J* = 5.8 Hz, 1H), 8.01-7.90 (m, 2H), 7.88-7.83 (m, 1H), 7.82-7.77 (m, 2H), 7.69 (s, 1H), 7.51 (dd, J = 11.3, 8.0 Hz, 1H), 7.48-7.37 (m, 3H), 6.36-6.25 (m, 2H), 4.60-4.50 (m, 1H), 4.15-4.06 (m, 1H), 4.06-3.98 (m, 1H), 3.76 (s, 3H), 3.17-2.88 (m, 6H), 2.30-2.21 (m, 2H), 2.16-2.04 (m, 1H), 1.95-1.55 (m, 6H), 1.55-1.18 (m, 8H), 1.14-1.01 (m, 1H), 1.00-0.82 (m, 2H).

Example 62: General Methods and Materials for I-131 Radiolabeling

2,5-dihydroxybenzoic acid (> 99.0%), Tin(II) sulfate ($SnSO_4$, > 99.0%), Copper(II) sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$, > 99.0%), citric acid (> 99.0%), glacial acetic acid were used as it was purchased from the vendors. The Milli-Q water was used after degassed under vacuum and ultrasonication. [^{131}I]NaI solution (30 mCi) was purchased from Cardinal Health.

HPLC condition **3** for isolation and analysis of [131I]I-labeled products: Column: Phenomenex, Kinetex® EVO C18, 5μm 100 Å, 250 x 4.6 mm. Solvent A: 0.1%TFA water; Solvent B: 0.1%TFA MeCN; Eluent: 0 to 11 min: 5% solvent B, 11 to 28 min: 5% to 95% solvent B, 28 to 30 min: 95% solvent B, 30 to 30.1 min: 95% to 5% solvent B, 30.1 to 35 min: isocratic elution at 5% solvent B. Flow rate: 1 mL/min, column temperature: 19 to 21 °C.

HPLC condition **4** for isolation and analysis of [131I]I-labeled products: Column: Phenomenex, Kinetex® EVO C18, 5μm, 100 Å, 250 x 4.6 mm. Solvent A: 0.1%TFA water; Solvent B: 0.1%TFA acetonitrile; Eluent: 0 to 2 min: 5% solvent B, 2 to 22 min: 5% to 95% solvent B, 22 to 30 min: 95% to 95% solvent B, 30 to 30.1 min: 95% to 5% solvent B, 30.1 to 35 min: isocratic elution at 5% solvent B. Flow rate: 1 mL/min, column temperature: 19 to 21 °C.

Procedure **C** for the copper-mediated ^{127}I/^{131}I exchange reaction: A stock acidic reducing solution was prepared by dissolving 2,5-dihydroxybenzoic acid (25 mg), citric acid (35 mg), glacial acetic acid (35 μL) and $SnSO_4$ (1 mg) in Milli-Q water (2.5 mL, degassed by vacuum-sonication). A stock solution of $CuSO_4$ was prepared by dissolving $CuSO_4 \cdot 5H_2O$ (32.5 mg) in Milli-Q water (10 mL, degassed by vacuum-sonication). A 5 mL borosilicate glass vial was charged with 3,5-difluoro-2-iodo-6-methoxybenzoic acid (0.6 mg), the stock acidic reducing solution (455 μL) and the $CuSO_4$ (30 μL) stock solution. The mixture was gently purged with N_2 for 5 mins followed by addition of NaOH (0.1 M, 40 μL) and [^{131}I]NaI solution (used as received, 1.45 mCi). The vessel was sealed with a PTFE-lined screw cap and heated at 140 °C. After for 30, the mixture was cooled to rt and diluted with acetic acid (5% aq, ~300 μL final volume) then

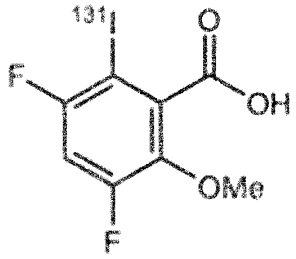
subjected to radio-HPLC analysis/purification (HPLC condition **3**). The eluent containing product was concentrated under reduced pressure to afford the [^{131}I]I-labeled substrate.

Procedure **D** for preparation of [^{131}I]I-NHS ester: To an Eppendorf tube (1.5 mL) was added N,N,N'N'-Tetramethyl-O-(N-succinimidyl)uronium tetrafluoroborate (2 mg) and DIPEA (4 μL) followed by a solution of [^{131}I]I-labeled substrate in anhydrous DMSO (100 μL of a 200 μL solution) and heated at 50 °C. After 18 h, the mixture was cooled to rt and diluted with Milli-Q water (~600 μL final volume) then subjected to radio-HPLC analysis/purification (HPLC condition **4**). The eluent containing product was concentrated under reduced pressure to afford the [^{131}I]I-NHS ester.

Procedure **E** for the conjugation between [^{131}I]I-NHS ester and Vipivotide tetraxetan (PSMA-617): To a solution of [^{131}I]I-NHS ester (50 μCi each experiment) in anhydrous DMSO (40 μL) was added a solution of Vipivotide tetraxetan (0.6 mg) in DMSO (10 μL) followed by DIPEA (6 μL), whereupon the mixture was heated at 70 °C. After 45 min, the resulting solution was directly subjected to radio-HPLC analysis/purification (HPLC condition **4**). to afford the [^{131}I]I-labeled product [30 μCi, 98.0% radiochemical purity (RCP)]. The radiochemical yields (RCYs) of all [^{131}I]I-labeled molecules were calculated based on the HPLC-isolated products. The [^{131}I]I-radiolabeled products were confirmed by comparing with the ^{127}I-standard under the same HPLC conditions. Quality control was run separately to ensure the purity of the isolated radiolabeled products.

Example 63: Synthesis of 3,5-difluoro-2-(iodo-^{131}*I*)-6-methoxybenzoic acid

Scheme 56. Representation of 3,5-difluoro-2-(iodo-^{131}*I*)-6-methoxybenzoic acid

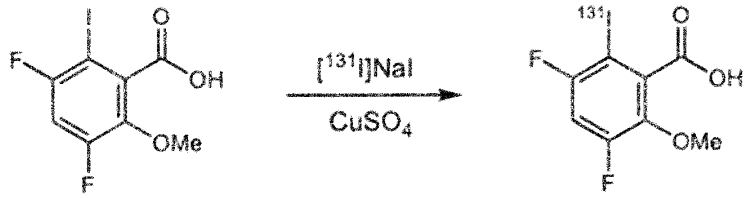


The preparation of 3,5-difluoro-2-(iodo-^{131}*I*)-6-methoxybenzoic acid (Scheme 56) is shown schematically in Scheme 57. 3,5-difluoro-2-iodo-6-methoxybenzoic acid (0.6 mg, 1.9 mmol) was radiolabeled with [^{131}I]NaI (1.3 mCi) according to procedure **C** of Example 62 to afford

the title compound (isolated RCY = 89.6%). Radio-HPLC purification by HPLC condition **3** is shown in FIG. 13.

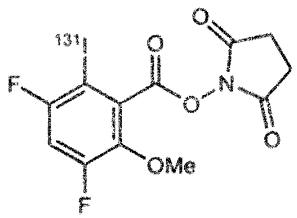
Quality control analysis of Example 63 by HPLC condition **4** is shown in FIG. 14. ^{127}I standard (Example 32) analysis by HPLC condition **4** is shown in FIG. 15.

Scheme 57. Representative schematic route to achieve 3,5-difluoro-2-(iodo-^{131}I)-6-methoxybenzoic acid.



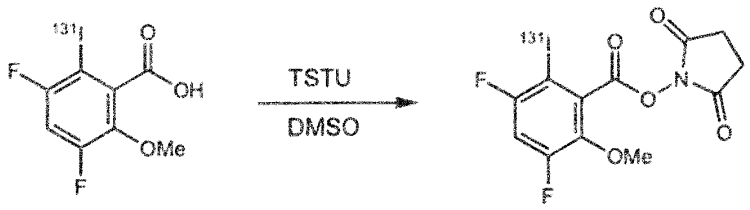
Example 64: Synthesis of 2,5-dioxopyrrolidin-1-yl 3,5-difluoro-2-(iodo-^{131}I)-6-methoxybenzoate

Scheme 58. Representation of 2,5-dioxopyrrolidin-1-yl 3,5-difluoro-2-(iodo-^{131}I)-6-methoxybenzoate



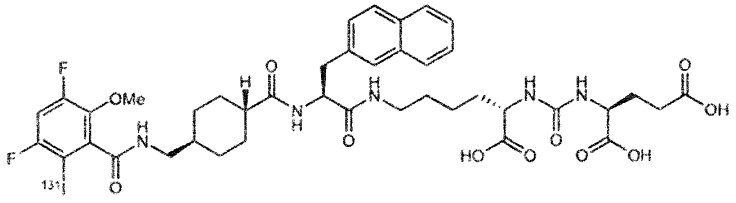
The preparation of 2,5-dioxopyrrolidin-1-yl 3,5-difluoro-2-(iodo-^{131}I)-6-methoxybenzoate (Scheme 58) is shown schematically in Scheme 59. The title compound (isolated RCY = 17.9%) was prepared from 3,5-difluoro-2-(iodo-^{131}I)-6-methoxybenzoic acid according to procedure **D** of Example 62. Radio-HPLC purification by HPLC condition **4** is shown in FIG. 16. ^{127}I-standard (Example 32) analysis by HPLC condition **4** is shown in FIG. 17.

Scheme 59. Representative schematic route to achieve 2,5-dioxopyrrolidin-1-yl 3,5-difluoro-2-(iodo-^{131}I)-6-methoxybenzoate.



Example 65: Synthesis of (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3,5-difluoro-2-(iodo-^{131}I)-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid

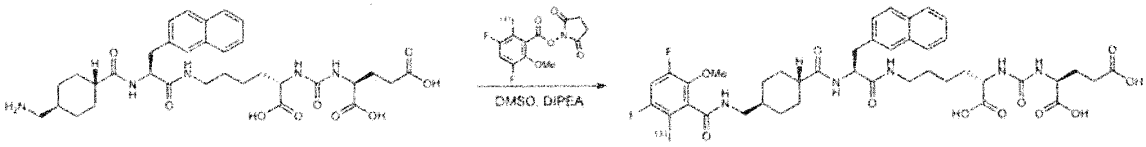
Scheme 60. Representation of (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3,5-difluoro-2-(iodo-^{131}I)-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid



The preparation of (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3,5-difluoro-2-(iodo-^{131}I)-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid (Scheme 60) is shown schematically in Scheme 61. The title compound (RCY = 64.1%, non-decay corrected) was prepared according to procedure **E** of Example 62. Radio-HPLC purification by HPLC condition **4** is shown in FIG. 18.

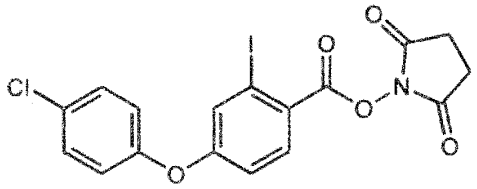
Quality control analysis of Example 65 by HPLC condition **4** is shown in FIG. 19. ^{127}I-standard (Example 61) analysis by HPLC condition **4** is shown in FIG. 20.

Scheme 61. Representative schematic route to achieve (((*S*)-1-carboxy-5-((*S*)-2-((1*r*,4*S*)-4-((3,5-difluoro-2-(iodo-^{131}I)-6-methoxybenzamido)methyl)cyclohexane-1-carboxamido)-3-(naphthalen-2-yl)propanamido)pentyl)carbamoyl)-*L*-glutamic acid.



Example 66: Synthesis of 2,5-dioxopyrrolidin-1-yl 4-(4-chlorophenoxy)-2-iodobenzoate

Scheme 62. Representation of 2,5-dioxopyrrolidin-1-yl 4-(4-chlorophenoxy)-2-iodobenzoate

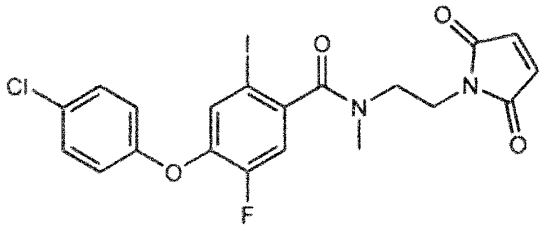


The title compound, 2,5-dioxopyrrolidin-1-yl 4-(4-chlorophenoxy)-2-iodobenzoate (Scheme 62) (166.5 mg) was prepared from 4-fluoro-2-iodobenzoic acid in an analogous manner to methods described in Example 50.

For 2,5-dioxopyrrolidin-1-yl 4-(4-chlorophenoxy)-2-iodobenzoate, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 2.5 Hz, 1H), 7.58-7.52 (m, 2H), 7.29-7.23 (m, 2H), 7.18 (dd, J = 8.8, 2.5 Hz, 1H), 2.89 (s, 4H). LCMS (ES, m/z): 493.90 $[M+Na]^+$; 99.9% purity (254 nm).

Example 67: Synthesis of 4-(4-chlorophenoxy)-*N*-(2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl)-5-fluoro-2-iodo-*N*-methylbenzamide

Scheme 63. Representation of 4-(4-chlorophenoxy)-*N*-(2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl)-5-fluoro-2-iodo-*N*-methylbenzamide

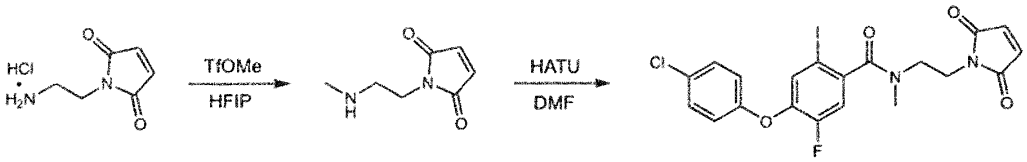


The preparation of 4-(4-chlorophenoxy)-*N*-(2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl)-5-fluoro-2-iodo-*N*-methylbenzamide (Scheme 63) is shown schematically in Scheme 64. To a mixture of 1-(2-aminoethyl)-1H-pyrrole-2,5-dione hydrochloride (500 mg, 2.84 mmol) in HFIP (10 mL) was added $NaHCO_3$ (239 mg, 2.84 mmol) and methyl trifluoromethanesulfonate (700 mg, 4.26 mmol). After 2 h, the mixture was concentrated under reduced pressure and the resulting solids were suspended in DCM/MeOH (10:1, 10 mL), filtered and washed with

DCM/MeOH (10:1, 2 x 5 mL). The filtrate was concentrated under reduced pressure to afford 1-(2-(methylamino)ethyl)-1H-pyrrole-2,5-dione (600 mg, crude) as a slightly pink solid. LCMS (ES, m/z): 155.10 $[M+H]^+$.

The title compound was prepared from 1-(2-(methylamino)ethyl)-1H-pyrrole-2,5-dione and 4-(4-chlorophenoxy)-5-fluoro-2-iodobenzoic acid in an analogous manner to methods described in Example 43. LCMS (ES, m/z): 529.00 $[M+H]^+$; 550.95 $[M+Na]^+$.

Scheme 64. Representative schematic route to achieve 4-(4-chlorophenoxy)-*N*-(2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl)-5-fluoro-2-iodo-*N*-methylbenzamide.



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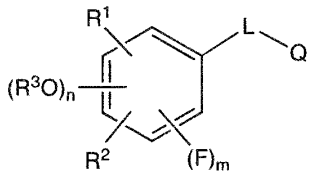
5

CLAIMS

1. A compound of Formula (I):



Formula (I)

wherein R^1 is H, I, Br, Cl, F or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At;

R^2 is H, F, I, Br, Cl, F or radioisotope ^{18}F;

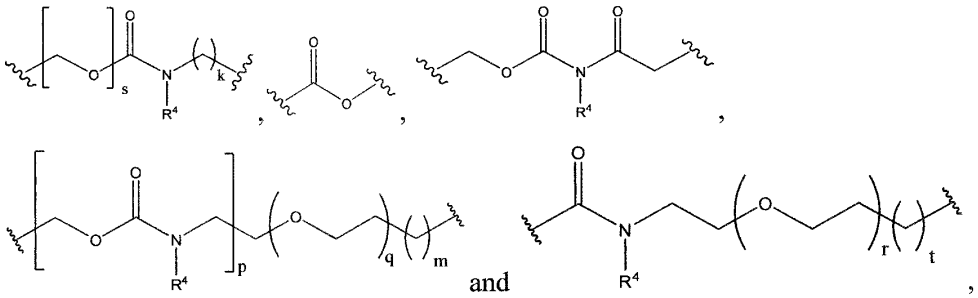
provided that at least one of R^1 or R^2 is a radioisotope as defined above;

R^3 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

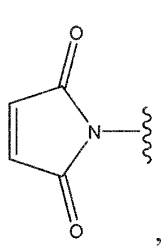
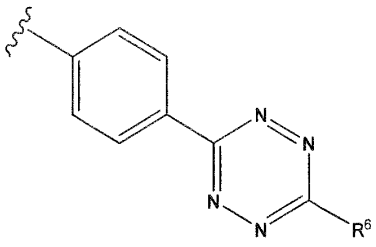
m is 0, 1, 2 or 3;

n is 0, 1 or 2;

L is selected from the group consisting of a bond, -(C_1-C_6) alkyl,



wherein k, s, m, p, q, r and t, in each instance, are integers independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;

Q is selected from the group consisting of halogen, sulfonate, phosphonate, succinimide, -NCO, -NC, -N_3, -NR^4R^5, -PG, OR^5,  ,  and —C≡C—H;

R^4 and R^5 are independently selected from -H, -PG, and –(C_1-C_6) alkyl, wherein -PG is a protecting group;

R^6 is -H, (C_1-C_4) alkyl, aryl, or heteroaryl; and

any stereoisomer and/or salt thereof.

2. The compound of claim 1, wherein R^1 is I, Br or a radioisotope R* selected from the group consisting of [76]Br, [77]Br, [82]Br, ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At and [211]At.

3. The compound of claim 1 or 2, wherein R^2 is F or radioisotope [18]F.

4. The compound of any one of the preceding claims, wherein m is 0, 1, 2, or 3.

5. The compound of any one of the preceding claims, wherein n is 0, 1, or 2.

6. The compound of any one of claims 1 to 5, wherein m is 1, n is 1, R^1 is I or Br, and R^2 is the radioisotope [18]F.

7. The compound of any one of claims 1 to 5, wherein m is 1, n is 1, R^1 is I, and R^2 is the radioisotope [18]F.

8. The compound of any one of claims 1 to 5, wherein n is 1, R^2 is F, and R^1 is the radioisotope R* selected from the group consisting of [124]I, ^{131}I, [210]At, [211]At, [76]Br, [77]Br, and [82]Br.

9. The compound of any one of claims 1 to 5, wherein n is 1, R^2 is F, and R^1 is the radioisotope R* [131]I.

10. The compound of any one of claims 1 to 5, wherein m is 1, n is 0, R^1 is I, and R^2 is the radioisotope [18]F.

11. The compound of any one of claims 1 to 5, wherein m is 1, n is 0, R^1 is I, and R^2 is the radioisotope [18]F.

12. The compound of any one of claims 1 to 5, wherein m is 1, n is 0, R^2 is F, and R^1 is the radioisotope R* selected from the group consisting of [124]I, ^{131}I, [210]At, [211]At, [76]Br, [77]Br, and [82]Br.

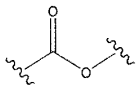
13. The compound of any one of claims 1 to 5, wherein m is 1, n is 0, R^2 is F, and R^1 is the radioisotope R* [131]I.

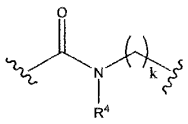
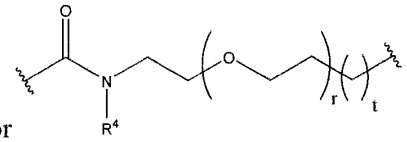
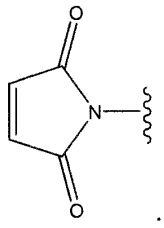
14. The compound of any one of claims 1 to 5, wherein m is 0, n is 0, R^1 is I or Br, and R^2 is F..

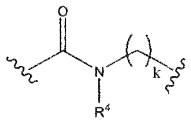
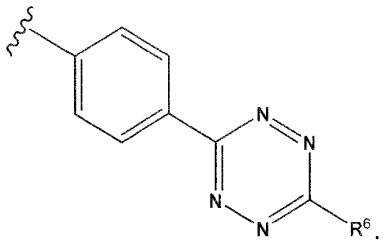
15. The compound of any one of claims 1 to 5, wherein m is 0, n is 0, R^1 is I, and R^2 is F.

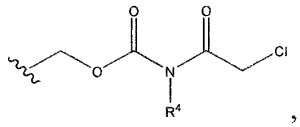
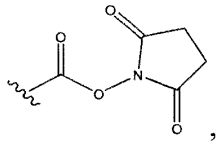
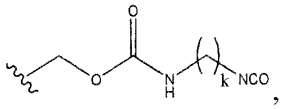
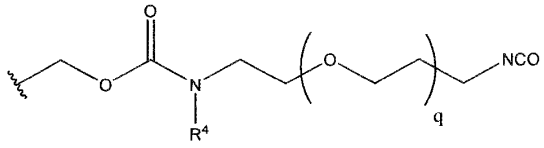
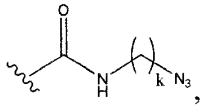
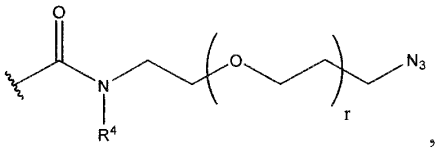
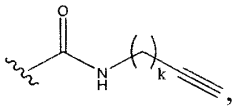
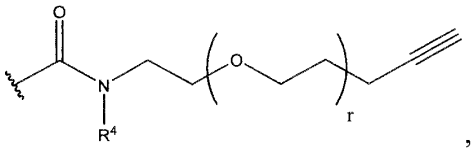
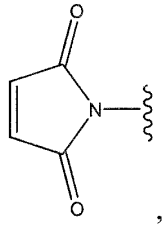
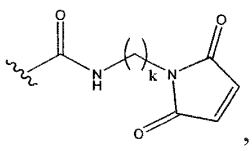
16. The compound of any one of claims 1 to 5, wherein m is 0, n is 0, R^2 is F, and R^1 is the radioisotope R* selected from the group consisting of [124]I, ^{131}I, [210]At, [211]At, [76]Br, [77]Br, and [82]Br.

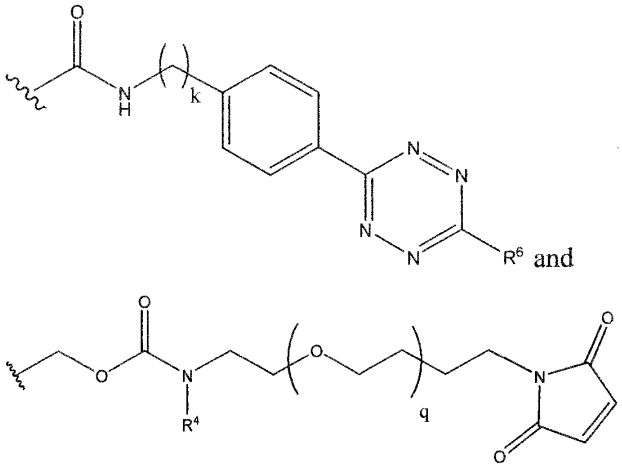
17. The compound of any one of claims 1 to 5, wherein m is 0, n is 0, R^2 is F, and R^1 is the radioisotope R* [131]I.

18. The compound of any one of the preceding claims, wherein L is  and Q is succinimide.

19. The compound of any one of the preceding claims, wherein L is a bond,  or  ; t is 1 or 2; and Q is  .

20. The compound of any one of the preceding claims, wherein L is  and Q is .

21. The compound of any one of the preceding claims, wherein L-Q is selected from the group consisting of $-CH_2Br$, $-CH_2NC$, , , , , , , , , , .



and

22. The compound of any one of the preceding claims, wherein the compound is a PET imaging agent, a SPECT imaging agent, or a radiolabeled-based therapeutic agent.

23. A pharmaceutical formulation comprising a compound of any one of the preceding claims and at least one pharmaceutically acceptable carrier.

24. A method of imaging a subject for diagnosing a disease or monitoring efficacy of a treatment, the method comprising:

administering to the subject in need thereof an effective amount of a labeled bioactive ligand; and

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

25. The method of claim 24, wherein the disease is cancer.

26. The method of claim 25, wherein the cancer is selected from the group consisting of pancreatic cancer and brain cancer (e.g., glioblastoma).

27. The method of any one of claims 24-26, wherein the subject is imaged using PET or SPECT imaging technologies.

28. The method of any one of claims 24-27, wherein the subject is a mammal.

29. The method of claims 24-28, wherein the treatment comprises administration to the subject in need thereof a therapeutically effective amount of a therapeutic agent, wherein the therapeutic agent is an anti-cancer agent.

30. The method of claim 29, wherein the anti-cancer agent is a radiolabeled-based therapeutic agent selected from

(a) a labeled bioactive ligand comprising a radioisotope selected from the group consisting of ^{131}I and [211] At; and

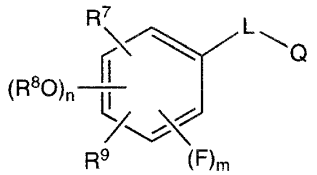
(b) a commercially available radiolabeled-based therapeutic agent.

31. The method of claim 29, wherein the anti-cancer agent is a commercially available drug.

32. The method of any one of claims 28-31, wherein the therapeutic agent is administered prior to administration of the bioactive ligand.

33. A method of making a compound of Formula (I) according to claim 1, the method comprising:

(a) obtaining a starting material of Formula (I-A):



Formula (I-A)

wherein R^7 is -B[O(C_1-C_6) alkyl]$_2$, -B[-O((C_1-C_6) alkyl)O-], -B(OH)$_2$, -BF_3K, N-methyliminodiacetic acid boronate, -Sn(C_1-C_4 alkyl)3, -Ge[(C_1-C_6) alkyl]$_3$ and -Si[(C_1-C_6) alkyl]$_3$;

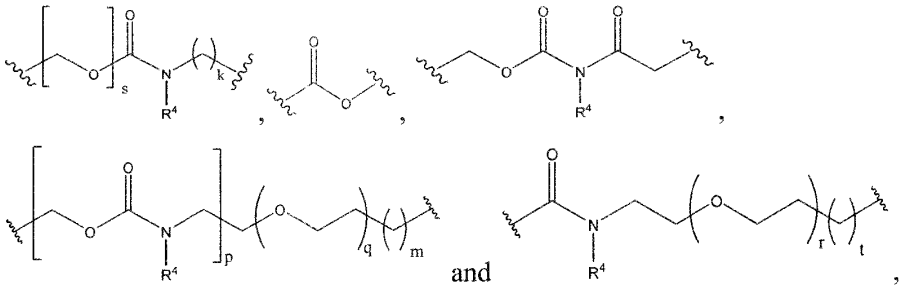
R^9 is H, I, Br, Cl, F or radioisotope ^{18}F;

R^8 is H, -PG, -aryl, -(C_1-C_6) alkyl or -(C_3-C_6) cycloalkyl;

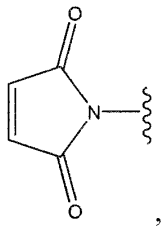
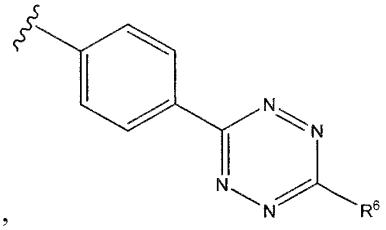
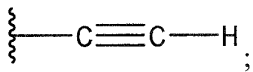
m is 0, 1, 2 or 3;

n is 0, 1 or 2;

L is selected from the group consisting of a bond, -(C_1-C_6) alkyl,



wherein k, s, m, p, q, r and t, in each instance, are integers independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;

Q is selected from the group consisting of halogen, sulfonate, phosphonate, succinimide, -NCO, -NC, $-N_3$, $-NR^4R^5$, -PG, OR^5, ,  and ;

R^4 and R^5 are independently selected from -H, -PG, and $-(C_1\text{-}C_6)$ alkyl, wherein -PG is a protecting group;

R^6 is -H, $(C_1\text{-}C_4)$ alkyl, aryl, or heteroaryl; and

any stereoisomer and/or salt thereof; and

(b) contacting the starting material with a radioisotope source in the presence of a suitable oxidant to render the compound of Formula (I), wherein R* is a radioisotope selected from the group consisting of ^{123}I, [124]I, ^{125}I, ^{131}I, [210]At, [211]At, [76]Br, [77]Br and [82]Br.

34. The method of claim 33, wherein R^2 is I, Br, Cl, F or radioisotope [18]F.

35. The method of claim 33 or 34, wherein the method further comprises a base activator.

36. The method of claim 35, wherein the base activator is selected from organic or inorganic fluoride sources.

37. The method of claim 46, wherein the base activator is selected from the group consisting of KOAc, KOtBu, KHF_2 and F^-.

38. The method of any one of claims 33-37, wherein the halo N-succinimide is N-chlorosuccinimide.