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(54) **QUATERNARY AMMONIUM SALTS AS INHIBITORS OF TRIMETHYLAMINE PRODUCTION**

(71) Applicant: **Senda Biosciences, Inc.**, Cambridge, MA (US)

(72) Inventors: **Kathleen NUDEL**, Jamaica Plain, MA (US); **Jenny LIU**, Cambridge, MA (US); **Timothy BRIGGS**, Waltham, MA (US); **Dinara Shashanka GUNASEKERA**, Cambridge, MA (US); **Ana MARTINEZ-DEL CAMPO**, Somerville, MA (US); **Elijah BOGART**, Cambridge, MA (US); **Steven TAYLOR**, Winchester, MA (US); **John PROUDFOOT**, Newtown, CT (US); **Cheri ROSS**, Winthrop, MA (US); **Yohannes TEFFERA**, Topsfield, MA (US); **Koji YASUDA**, Boston, MA (US); **Devin Forest Reed DOUD**, Arlington, MA (US); **Gabriel BILLINGS**, Somerville, MA (US); **Spencer Cory PECK**, Watertown, MA (US); **Danny LAFRANCE**, Natick, MA (US); **Kehinde AJAYI**, Medford, MA (US)

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(57) **ABSTRACT**

Provided are compounds that can inhibit pathogenic, bacterial metabolite production and conjugates of the same. Also provided are pharmaceutical compositions comprising the same and methods of using the same.

QUATERNARY AMMONIUM SALTS AS INHIBITORS OF TRIMETHYLAMINE PRODUCTION

[0001] This application claims priority to U.S. provisional application No. 62/776,459, filed Dec. 6, 2018, the disclosure of which is incorporated herein by reference in its entirety.

[0002] Disclosed herein are novel compounds, pharmaceutical compositions comprising the same, and methods of using the same.

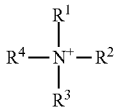
[0003] Mammalian microbiota can engage in a bidirectional communication with the mammalian host system. In some instances, mammalian microbiota may be responsible for producing enzymes that can mediate formation of pathologic metabolites. These metabolites, in sufficient quantities, can compromise the host's health and often lead to debilitating diseases.

[0004] For example, choline-trimethylamine lyase (CutC) from *Clostridium sporogenes* and from *Proteus mirabilis* can mediate production of trimethylamine (TMA) from choline. Trimethylamine can be also oxidized in vivo (e.g., by Flavin monooxygenase 3 (FMO3)) to produce a trimethylamine N-oxide (TMAO). Trimethylaminuria can be characterized by elevated TMA and/or TMAO levels in a subject, a decreased rate of conversion of TMA to TMAO in a subject, or a high ratio of TMA to TMAO in a subject. Trimethylaminuria often leads to, e.g., cardiovascular disease, reduced or impaired kidney function, kidney disease, chronic kidney disease, end-stage renal disease, or diabetes mellitus.

[0005] There is a need for therapeutic strategies that address disease etiology. In particular, there is a need for therapeutic strategies that target enzymatic production of the pathogenic, bacterial metabolites.

[0006] The present disclosure provides novel compounds which may act as inhibitors of enzymatic production of pathogenic, bacterial metabolites, pharmaceutical compositions comprising at least one of such compounds, and methods of using the same, such as, for example, in methods for modulating an autoimmunity marker in a subject, and in methods of treating an autoimmunity disorder in a subject. In some embodiments, the disclosure provides compounds for the inhibition of choline-trimethylamine lyase (CutC). In some embodiments, the disclosure provides compounds for the inhibition of carnitine monooxygenase (CntA). In some embodiments, the disclosure provides compounds for the inhibition of betaine reductase. In some embodiments, compounds of the present disclosure consist of a cation and a pharmaceutically acceptable counterion. In some embodiments, the cation includes at least one glycoside or acylated sugar, and thus the cation is a conjugate which can be advantageous for targeted delivery to a tissue (e.g., a small intestine) having the highest abundance of CutC from *Clostridium sporogenes* and/or *Proteus mirabilis*. CutC may be found and targeted in a host of other bacterial species, including, but not limited to, *Proteus hauseri, Klebsiella oxytoca, Escherichia coli, Escherichia fergusonii, Paenibacillus thiaminolyticus, Paenibacillus alvei, Paenibacillus uliginis, Streptococcus dysgalactiae, Streptococcus intermedius, Streptococcus suis, Streptococcus castoreus, Streptococcus merionis, Streptococcus ovis, Collinsella tanakaei, Anaerococcus hydrogenalis, Anaerococcus tetradius, Anaerococcus obesiensis, Anaerococcus vaginalis, Eubacterium* sp., *Lachnospiraceae bacterium, Hungatella hathewayi, Clostridium phytofermentans, Clostridium saccharolyticum, Clostridium indolis, Clostridium methoxybenzovorans, Clostridium citroniae, Clostridium asparagiforme, Clostridium chauvoei, Clostridium sartagoforme, Clostridium tetani, Clostridium botulinum, Desulfovibrio desulfuricans*, and *Desulfovibrio alaskensis*. Among these species, strains exhibiting a high abundance of CutC include, but are not limited to, *Proteus hauseri* ZMd44, *Proteus mirabilis* ATCC29906, *Klebsiella oxytoca*-, *Escherichia coli* MS 69-1, *Escherichia fergusonii* ECD227, *Paenibacillus thiaminolyticus, Paenibacillus alvei* TS-15, *Paenibacillus uliginis* N3/975, *Streptococcus dysgalactiae* subsp. *equisimilis* ATCC 12394, *Streptococcus intermedius* ATCC 27335, *Streptococcus suis* YS10-2, *Streptococcus* castoreus DSM 17536, *Streptococcus merionis, Streptococcus ovis, Collinsella tanakaei* YIT 12063, *Anaerococcus hydrogenalis* DSM 7454, *Anaerococcus tetradius* ATCC 35098, *Anaerococcus obesiensis, Anaerococcus vaginalis* ATCC 51170, *Eubacterium* sp. 68-3-10, *Eubacterium* sp. AB3007, *Lachnospiraceae bacterium, Hungatella hathewayi, Clostridium phytofermentans* ISDg, *Clostridium saccharolyticum* WM1, *Clostridium indolis* DSM 755, *Clostridium methoxybenzovorans* SR3, *Clostridium citroniae* WAL-17108, *Clostridium asparagiforme, Clostridium chauvoei* JF4335, *Clostridium sartagoforme* MU1, *Clostridium tetani* 12124569, *Clostridium botulinum* F 230613, *Clostridium sporogenes* ATCC15579, *Desulfovibrio desulfuricans* subsp. *desulfuricans* ATCC 27774, and *Desulfovibrio alaskensis* G20.

[0007] In some embodiments, disclosed are compounds consisting of a cation and a pharmaceutically acceptable counterion, wherein the cation is a structure of formula (I):


(I)

wherein

[0008] R^1 is

[0009] C_{2-6} alkyl substituted with —O-(acylated sugar) or isosorbide, wherein said C_{2-6} alkyl is further optionally substituted with oxo and/or methene;

[0010] C_4 cycloalkyl optionally substituted with hydroxyl, ethynyl, or —O-(acylated sugar); or

[0011] C_3 cycloalkyl substituted with C_{1-6} alkyl, hydroxyl, ethynyl, or —O-(acylated sugar)

[0012] C_{3-4} cycloalkyl C_{1-2} alkyl;

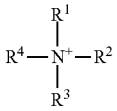
[0013] R^2 is C_{2-6} alkyl optionally substituted with one or two hydroxyl, oxo, and —O-(acylated sugar);

[0014] or R^1 and R^2, together with the nitrogen atom to which both are attached, combine to form a 4- or 5-membered heterocyclic ring optionally substituted with ethynyl or $—(CH_2)_n—OR^s$ or an acylated sugar, wherein n is 0 or 1, R^s is hydrogen or an acylated sugar;

[0015] R^3 is C_{1-6} alkyl optionally substituted with a halogen or hydroxyl; and

[0016] R^4 is C_{1-6} alkyl or propargyl.

[0017] In some embodiments, provided herein are compounds consisting of a cation and a pharmaceutically acceptable counterion, wherein the cation is a structure of formula (II):



(II)

wherein

[0018] R^1 is

[0019] C_{1-6} alkyl optionally substituted with one or more oxo, hydroxyl, halogen, cyano, —COOMe, amino, methene, ethenyl, ethynyl, hydroxyphenyl, C_{3-4} cycloalkyl, —OCH_2CH_2OH, —$HNC(O)OCMe_3$, —SMe, —OMe, —$HNS(O)_2Me$, —SO_3H, $B(OH)_2$, PO_3H_2, PO_2H_2, —$P(O)(OCH_2CH_3)_2$, —$P(O)(OH)(OCH_2CH_3)$, heteroaryl ring;

[0020] phenyl;

[0021] benzyl;

[0022] C_{3-4} heterocyclyl optionally substituted with C_1 alkyl

[0023] C_4 heterocycloalkyl C_1 alkyl; or

[0024] C_4 cycloalkyl;

[0025] R^2 is

[0026] C_{1-6} alkyl optionally substituted with one or two hydroxyl, oxo, methene, cyano, ethynyl, —HNC(O)H, or —C≡C—CH_2OH; or

[0027] —$HN(CH_2)_3C(O)OH$;

[0028] or R^1 and R^2, together with the nitrogen atom to which both are attached and optionally one or more additional heteroatoms, combine to form a 4-8 membered mono- or bi-cyclic heterocycle optionally substituted with ethynyl, trifluoromethyl, —CH_2Ph, —OH, or —$(CH_2)OH$;

[0029] R^3 is methyl or propargyl; and

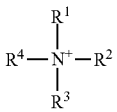
[0030] R^4 is methyl or propargyl,

[0031] with the proviso that

[0032] (1) when two of R^1, R^2, R^3, and R^4 are methyl and one of the other two of R^1, R^2, R^3, and R^4 is propargyl, then the other of R^1, R^2, R^3, and R^4 is not methyl, a monohalomethyl, —CH_2CH_2OH, —COOH, —$(CH_2)_4C(O)OH$, or —$CH_2C(CH_2)CN$; and

[0033] (2) when two of R^1, R^2, R^3, and R^4 are methyl and one of the other two of R^1, R^2, R^3, and R^4 is —CH_2CH_2OH or —$CH_2C(O)OH$, then the other of R^1, R^2, R^3, and R^4 is not a monohalomethyl.

[0034] In some embodiments, provided herein are compounds consisting of a cation and a pharmaceutically acceptable counterion, wherein the cation is a structure of formula (III):



(III)

wherein

[0035] R^1 is

[0036] C_{1-6} alkyl optionally substituted with one or more oxo, hydroxyl, halogen, cyano, —COOMe, —COOH, methene, ethenyl, ethynyl, C_{3-4} cycloalkyl, —OCH_2CH_2OH, —SMe, —OMe, —$HNS(O)_2Me$, —$P(O)(OCH_2CH_3)_2$, —$P(O)(OH)(OCH_2CH_3)$, or 5-membered heteroaryl ring;

[0037] R^2 is

[0038] C_{1-6} alkyl optionally substituted with one or two hydroxyl, oxo, methene, cyano, ethynyl, —HNC(O)H, or —C≡C—CH_2OH; or

[0039] —$HN(CH_2)_3C(O)OH$;

[0040] or R^1 and R^2, together with the nitrogen atom to which both are attached and optionally one or more additional heteroatoms, combine to form a 4-8 membered mono- or bi-cyclic heterocycle optionally substituted with ethynyl, —OH, or —$(CH_2)OH$;

[0041] R^3 is C_{1-6} alkyl optionally substituted with a halogen, hydroxyl, or ethynyl; and

[0042] R^4 is C_{1-6} alkyl or propargyl,

with the proviso that

[0043] (1) when two of R^1, R^2, R^3, and R^4 are methyl and one of the other two of R^1, R^2, R^3, and R^4 is propargyl, then the other of R^1, R^2, R^3, and R^4 is not methyl, a monohalomethyl, —CH_2CH_2OH, —COOH, —$(CH_2)_4C(O)OH$, or —$CH_2C(CH_2)CN$; and

[0044] (2) when two of R^1, R^2, R^3, and R^4 are methyl and one of the other two of R^1, R^2, R^3, and R^4 is —CH_2CH_2OH or —$CH_2C(O)OH$, then the other of R^1, R^2, R^3, and R^4 is not a monohalomethyl.

[0045] In some embodiments, the disclosure provides a pharmaceutical composition comprising a pharmaceutically acceptable excipient and at least one of the compounds described above.

[0046] In some embodiments, provided herein is a method of modulating a trimethylaminuria marker in a subject in need thereof, the method comprising administering to the subject in need thereof a therapeutically effective amount of at least one of the compounds or pharmaceutical compositions disclosed herein. In some embodiments, the trimethylaminuria marker is the trimethylamine and/or trimethylamine oxide level in the subject's blood, plasma, serum, or urine.

[0047] In some embodiments, provided herein is a method of treating or preventing a disease associated with elevated levels of trimethylamine (TMA) or trimethylamine N-oxide (TMAO), a decreased rate of conversion of TMA to TMAO, or a high ratio of TMA to TMAO in a subject in need thereof, the method comprising administering a therapeutically effective amount of at least one of the compounds or pharmaceutical compositions disclosed herein to the subject. In some embodiments, the method further comprises detecting the presence of one or more genetic variants of the FMO3 gene of the subject in need before the administering step. In some embodiments, the disease associated with elevated levels of TMA or TMAO, a decreased rate of conversion of TMA to TMAO, or a high ratio of TMA to TMAO is a cardiovascular disease, reduced or impaired kidney function, kidney disease, chronic kidney disease, end-stage renal disease, or diabetes mellitus. In some embodiments, the cardiovascular disease is angina, arrhythmia, atherosclerosis, cardiomyopathy, congestive heart failure, coronary artery disease, carotid artery disease, endocarditis, coronary thrombosis, myocardial infarction, high blood pressure/hypertension, hypercholesterolemia, hyperlipidemia, mitral valve prolapse, peripheral artery disease, or stroke.

[0048] In some embodiments, provided herein is a method of inhibiting a CutC choline lyase-mediated conversion of

choline to trimethylamine, the method comprising contacting at least one of the compounds or pharmaceutical compositions disclosed herein with the CutC choline lyase.

[0049] In some embodiments, provided herein is a method of inhibiting a CntA carnitine monooxygenase-mediated conversion of carnitine to trimethylamine, the method comprising contacting at least one of the compounds or pharmaceutical compositions disclosed herein with the CntA carnitine monooxygenase.

[0050] In some embodiments, provided herein is a method of inhibiting a betaine reductase-mediated conversion of betaine or gamma-butyrobetaine to trimethylamine, the method comprising contacting at least one of the compounds or pharmaceutical compositions disclosed herein with the betaine reductase.

[0051] In some embodiments, provided herein is a method of treating a subject in need of treatment for trimethylaminuria comprising contacting bacteria in vivo with a therapeutically effective amount of at least one of the compounds or pharmaceutical compositions disclosed herein to the subject. In some embodiments, the bacteria are localized in the colon of the subject.

[0052] In some embodiments, the present disclosure provides a method of modulating a trimethylamine marker in a subject in need thereof, the method consisting of administering to the subject in need thereof a therapeutically effective amount of at least one compound of the present disclosure or a pharmaceutical composition of the present disclosure.

[0053] In some embodiments, the trimethylaminuria marker is the trimethylamine and/or trimethylamine oxide levels in the subject's blood, plasma, serum, or urine.

[0054] In some embodiments, the present disclosure provides a method of treating or preventing a disease associated with trimethylaminuria in a subject in need thereof, the method comprising administering a therapeutically effective amount of at least one pharmaceutically acceptable salt of at least one compound of the present disclosure or a pharmaceutical composition of the present disclosure to the subject.

[0055] In some embodiments, provided herein is a method of identifying a subject suffering from trimethylaminuria, or predicting a predisposition for developing trimethylaminura in a subject, comprising: (i) analyzing a sample from the patient to detect the presence of at least one FMO3 genetic variant in the patient, and (ii) identifying identifying a subject suffering from trimethylaminuria or predicting a predisposition for developing trimethylaminura in a subject. In some embodiments, the method further comprises (iii) administering a therapeutically effective amount of at least one of the compounds or pharmaceutical compositions disclosed herein to the subject.

[0056] In some embodiments, the FMO3 genetic variant is identified based on public databases reporting pathogenic variants associated with TMAU. In some embodiments, the FMO3 genetic variant is identified based on predicted loss of function of the FMO3 gene product, such as variants introducing frameshifts or premature stop codons into the coding sequence of FMO3. In some embodiments, the variant is identified based on predicted structural modification to the exonic sequence of FMO3. In some embodiments, the FMO3 genetic variant is chosen from g.-2092 to 10145del, g.94G>A+A29A2:A30, g.110T>C, g.11145A>G, g.11148G>T, g.11166G>A, g.11177A>G, g.11185delA, g.11192G>T, g.11239T>C, g.15036A>G, g.15123T>A, g.15137G>T, g.15153C>T, g.15526_15527delTG, g.15531T>A, g.15533T>C, g.15539C>A, g.18177G>A, g.18225G>C, g.21429G>T, g.21460G>T, g.21680G>T, g.21684G>A, g.21702delG, g.23580delG, g.24486G>A, g.24592C>T, g.24608G>A, g.24658C>T, and g.24682C>T.

[0057] As used herein, the term "acyl," as used herein, represents a chemical substituent of formula —C(O)—R, where R is alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclyl alkyl, heteroaryl, or heteroaryl alkyl. An optionally substituted acyl is an acyl that is optionally substituted as described herein for each group R. Non-limiting examples of acyl include fatty acid acyls (e.g., short chain fatty acid acyls (e.g., acetyl, propionyl, or butyryl)).

[0058] The term "acylated sugar," as used herein, refers to a carbohydrate, sugar acid, or sugar alcohol having one or more hydroxyls substituted with an acyl (e.g., a fatty acid acyl). In some embodiments, the carbohydrate is a monosaccharide. In some embodiments, the carbohydrate is a disaccharide. In some embodiments, the fatty acid acyl is a short chain fatty acid acyl (e.g., propionyl or butyryl). An acylated sugar can be a compound or a monovalent group. When an acylated sugar is a monovalent group, the group includes one and only one valency for attaching to another molecular fragment. When an acylated sugar is covalently bonded to a carbon atom of another molecular fragment, the valency is on an oxygen atom of the acylated sugar. When an acylated sugar is covalently bonded to an oxygen atom of another molecular fragment, the valency is on the anomeric carbon atom of the acylated sugar. Non-limiting examples of a monosaccharide include arabinose, xylose, fructose, galactose, glucose, glucosinolate, ribose, tagatose, fucose, and rhamnose. Non-limiting examples of a disaccharide include lactose, sucrose, melibiose, gentiobiose, kojibiose, cellobiose, maltose, trehalose and chitobiose. Non-limiting examples of a sugar acid include xylonic acid, gluconic acid, glucuronic acid, galacturonic acid, tartaric acid, saccharic acid, or mucic acid. Non-limiting examples of sugar alcohols are glycerol, erythritol, theritol, arabitol, xylitol, tibitol, mannitol, sorbitol, galactitol, fucitol, iditol, or inositol.

[0059] The term "acyloxy," as used herein, represents a chemical substituent of formula —OR, where R is acyl. An optionally substituted acyloxy is an acyloxy that is optionally substituted as described herein for acyl.

[0060] The term "alcohol oxygen atom," as used herein, refers to a divalent oxygen atom, where at least one valency of the oxygen atom is bonded to an sp^3-hybridized carbon atom.

[0061] The term "alkanoyl," as used herein, represents a chemical substituent of formula —C(O)—R, where R is alkyl. An optionally substituted alkanoyl is an alkanoyl that is optionally substituted as described herein for alkyl.

[0062] The term "alkoxy," as used herein, represents a chemical substituent of formula —OR, where R is a C_{1-6} alkyl group, unless otherwise specified. An optionally substituted alkoxy is an alkoxy group that is optionally substituted as defined herein for alkyl.

[0063] The term "alkenyl," as used herein, represents acyclic monovalent straight or branched chain hydrocarbon groups containing one, two, or three carbon-carbon double bonds. Alkenyl, when unsubstituted, has from 2 to 12 carbon atoms (e.g., 1 to 8 carbons), unless specified otherwise. Non-limiting examples of the alkenyl groups include ethenyl, prop-1-enyl, prop-2-enyl, 1-methylethenyl, but-1-enyl, but-2-enyl, but-3-enyl, 1-methylprop-1-enyl, 2-methylprop-

1-enyl, and 1-methylprop-2-enyl. Alkenyl groups may be optionally substituted as defined herein for alkyl.

[0064] The term "alkyl," as used herein, refers to an acyclic, straight or branched, saturated hydrocarbon group, which, when unsubstituted, has from 1 to 12 carbons (e.g., 1 to 6 carbons), unless otherwise specified. Alkyl groups are exemplified by methyl; ethyl; n- and iso-propyl; n-, sec-, iso- and tert-butyl; neopentyl, and the like, and may be optionally substituted, valency permitting, with one, two, three, or, in the case of alkyl groups of two carbons or more, four or more substituents independently selected from the group consisting of: alkoxy; acyloxy; alkylsulfinyl; alkylsulfonyl; amino; aryl; aryloxy; azido; cycloalkyl; cycloalkoxy; halo; heterocyclyl; heteroaryl; heterocyclylalkyl; heteroarylalkyl; heterocyclyloxy; heteroaryloxy; hydroxy; nitro; thioalkyl; thioalkenyl; thioaryl; thiol; cyano; oxo (=O); thio (=S); and imino (=NR'), where R' is H, alkyl, aryl, or heterocyclyl. Each of the substituents may itself be unsubstituted or, valency permitting, substituted with unsubstituted substituent(s) defined herein for each respective group.

[0065] The term "alkylene," as used herein, refers to a divalent, straight or branched, saturated hydrocarbon, in which two valencies replace two hydrogen atoms. Alkyl, when unsubstituted, has from 2 to 12 carbon atoms (e.g., 2 to 6 carbons), unless specified otherwise. Non-limiting examples of the alkylene group include methylene, ethane-1,2-diyl, ethane-1,1-diyl, propane-1,3-diyl, propane-1,2-diyl, propane-1,1-diyl, propane-2,2-diyl, butane-1,4-diyl, butane-1,3-diyl, butane-1,2-diyl, butane-1,1-diyl, and butane-2,2-diyl, butane-2,3-diyl. An optionally substituted alkylene is an alkylene that is optionally substituted as described herein for alkyl.

[0066] The term "alkylsulfinyl," as used herein, represents a group of formula —S(O)-(alkyl). An optionally substituted alkylsulfinyl is an alkylsulfinyl that is optionally substituted as described herein for alkyl.

[0067] The term "alkylsulfonyl," as used herein, represents a group of formula —$S(O)_2$-(alkyl). An optionally substituted alkylsulfonyl is an alkylsulfonyl that is optionally substituted as described herein for alkyl.

[0068] The term "alkynyl," as used herein, represents an acyclic, monovalent, straight or branched chain hydrocarbon groups containing one, two, or three carbon-carbon triple bonds. Alkynyl, when unsubstituted, has from 2 to 12 carbon atoms (e.g., 2 to 6 carbons), unless specified otherwise. Non-limiting examples of the alkynyl groups include ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, and 1-methylprop-2-ynyl. An optionally substituted alkynyl is an alkynyl that is optionally substituted as defined herein for alkyl.

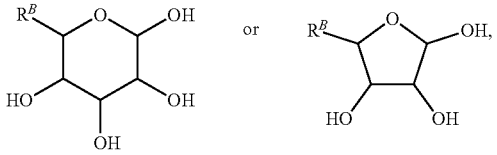
[0069] The term "aryl," as used herein, represents a mono-, bicyclic, or multicyclic carbocyclic ring system having one or two aromatic rings. Aryl group may include from 6 to 10 carbon atoms. All atoms within an unsubstituted carbocyclic aryl group are carbon atoms. Non-limiting examples of carbocyclic aryl groups include phenyl, naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, fluorenyl, indanyl, indenyl, etc. The aryl group may be unsubstituted or substituted with one, two, three, four, or five substituents independently selected from the group consisting of: alkyl; alkenyl; alkoxy; acyloxy; amino; aryl; aryloxy; azido; cycloalkyl; cycloalkoxy; halo; heterocyclyl; heteroaryl; heterocyclylalkyl; heteroarylalkyl; heterocyclyloxy; heteroaryloxy; hydroxy; nitro; thioalkyl; thioalkenyl; thioaryl; thiol; and cyano. Each of the substituents may itself be unsubstituted or substituted with unsubstituted substituent(s) defined herein for each respective group.

[0070] The term "aryl alkyl," as used herein, represents an alkyl group substituted with an aryl group. An optionally substituted aryl alkyl is an aryl alkyl, in which aryl and alkyl portions may be optionally substituted as the individual groups as described herein.

[0071] The term "aryloxy," as used herein, represents a group —OR, where R is aryl. Aryloxy may be an optionally substituted aryloxy. An optionally substituted aryloxy is aryloxy that is optionally substituted as described herein for aryl.

[0072] The term "carbamate linker," as used herein, refers to a group R^1—(CO)—R^2, where R^1 is a bond to an alcohol or phenolic oxygen atom, and R^2 is a bond to a nitrogen atom.

[0073] The term "carbohydrate," as used herein, refers to a monosaccharide, disaccharide, or an oligosaccharide or an analog of the following structure:



where R^B is H, optionally substituted C_{1-6} alkyl, or —CH_2—OH.

[0074] The term "carbohydrate" may refer to a compound or to a monovalent or multivalent chemical substituent. When the term "carbohydrate" refers to a chemical substituent, the valence(s) reside on the anomeric carbon atom and/or alcohol oxygen atoms. An optionally substituted carbohydrate is a carbohydrate, in which at least one hydroxyl is substituted with an acyl (e.g., a fatty acid acyl).

[0075] The term "carbonate linker," as used herein, refers to a group R^1—C(O)—R^2 where R^1 is a bond to a first alcohol or phenolic oxygen atom, and R^2 is a bond to a second alcohol or phenolic oxygen atom.

[0076] The term "carbonyl," as used herein, refers to a divalent group —C(O)—.

[0077] The term "carboxylate," as used herein, represents group —COOH or a salt thereof.

[0078] The term "cycloalkoxy," as used herein, represents a group —OR, where R is cycloalkyl. An optionally substituted cycloalkoxy is cycloalkoxy that is optionally substituted as described herein for cycloalkyl.

[0079] The term "ester bond," as used herein, refers to a covalent bond between an alcohol or phenolic oxygen atom and a carbonyl group that is further bonded to a carbon atom.

[0080] The term "fatty acid," as used herein, refers to a short-chain fatty acid, a medium chain fatty acid, a long chain fatty acid, a very long chain fatty acid, or an unsaturated analogue thereof, or a phenyl-substituted analogue thereof. Short chain fatty acids contain from 1 to 6 carbon atoms, medium chain fatty acids contain from 7 to 13 carbon atoms, and long-chain fatty acids contain from 14 to 22 carbon atoms. A fatty acid may be saturated or unsaturated. An unsaturated fatty acid includes 1, 2, 3, 4, 5, or 6 carbon-carbon double bonds. In some embodiments, the carbon-carbon double bonds in unsaturated fatty acids have

Z stereochemistry. In some embodiments, the carbon-carbon double bonds in unsaturated fatty acids have E stereochemistry.

[0081] The term "fatty acid acyl," as used herein, refers to a fatty acid, in which the hydroxyl group is replaced with a valency. In some embodiments, a fatty acid acyl is a short chain fatty acid acyl.

[0082] The term "fatty acid acyloxy," as used herein, refers to group —OR, where R is a fatty acid acyl.

[0083] The term "glycoside," as used herein, refers to a monovalent group that is a monosaccharide, disaccharide, or sugar acid having a valency on an anomeric carbon. Non-limiting examples of monosaccharides include arabinose, xylose, fructose, galactose, glucose, ribose, tagatose, fucose, and rhamnose. Non-limiting examples of disaccharides include lactose, sucrose, melibiose, gentiobiose, kojibiose, cellobiose, maltose, trehalose and chitobiose. Non-limiting examples of sugar acids include xylonic acid, gluconic acid, glucuronic acid, galacturonic acid, tartaric acid, saccharic acid, or mucic acid.

[0084] The term "glycosidic bond," as used herein, refers to a covalent bond between an oxygen atom and an anomeric carbon atom in a monosaccharide, disaccharide, or sugar acid having an anomeric carbon atom.

[0085] The term "halogen," as used herein, represents a halogen selected from bromine, chlorine, iodine, and fluorine.

[0086] The term "heteroaryl," as used herein, represents a monocyclic 5-, 6-, 7-, or 8-membered ring system, or a fused or bridging bicyclic, tricyclic, or tetracyclic ring system; the ring system contains one, two, three, or four heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur; and at least one of the rings is an aromatic ring. Non-limiting examples of heteroaryl groups include benzimidazolyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, furyl, imidazolyl, indolyl, isoindazolyl, isoquinolinyl, isothiazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, purinyl, pyrrolyl, pyridinyl, pyrazinyl, pyrimidinyl, qunazolinyl, quinolinyl, thiadiazolyl (e.g., 1,3,4-thiadiazole), thiazolyl, thienyl, triazolyl, tetrazolyl, dihydroindolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, etc. The term bicyclic, tricyclic, and tetracyclic heteroaryls include at least one ring having at least one heteroatom as described above and at least one aromatic ring. For example, a ring having at least one heteroatom may be fused to one, two, or three carbocyclic rings, e.g., an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring, or another monocyclic heterocyclic ring. Examples of fused heteroaryls include 1,2,3,5,8,8a-hexahydroindolizine; 2,3-dihydrobenzofuran; 2,3-dihydroindole; and 2,3-dihydrobenzothiophene. Heteroaryl may be optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of: alkyl; alkenyl; alkoxy; acyloxy; aryloxy; alkylsulfinyl; alkylsulfonyl; amino; arylalkoxy; cycloalkyl; cycloalkoxy; halogen; heterocyclyl; heterocyclyl alkyl; heteroaryl; heteroaryl alkyl; heterocyclyloxy; heteroaryloxy; hydroxyl; nitro; thioalkyl; thioalkenyl; thioaryl; thiol; cyano; =O; —NR_2, where each R is independently hydrogen, alkyl, acyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, or heteroaryl; —$COOR^A$, where R^A is hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, or heteroaryl; and —$CON(R^B)_2$, where each R^B is independently hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, or heteroaryl. Each of the substituents may itself be unsubstituted or substituted with unsubstituted substituent(s) defined herein for each respective group.

[0087] The term "heteroaryloxy," as used herein, refers to a structure —OR, in which R is heteroaryl. Heteroaryloxy can be optionally substituted as defined for heteroaryl.

[0088] The term "heterocyclyl," as used herein, represents a monocyclic, bicyclic, tricyclic, or tetracyclic non-aromatic ring system having fused or bridging 4-, 5-, 6-, 7-, or 8-membered rings, unless otherwise specified, the ring system containing one, two, three, or four heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. Non-aromatic 5-membered heterocyclyl has zero or one double bonds, non-aromatic 6- and 7-membered heterocyclyl groups have zero to two double bonds, and non-aromatic 8-membered heterocyclyl groups have zero to two double bonds and/or zero or one carbon-carbon triple bond. Heterocyclyl groups have a carbon count of 1 to 16 carbon atoms unless otherwise specified. Certain heterocyclyl groups may have a carbon count up to 9 carbon atoms. Non-aromatic heterocyclyl groups include pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, homopiperidinyl, piperazinyl, pyridazinyl, oxazolidinyl, isoxazolidiniyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, thiazolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, pyranyl, dihydropyranyl, dithiazolyl, etc. The term "heterocyclyl" also represents a heterocyclic compound having a bridged multicyclic structure in which one or more carbons and/or heteroatoms bridges two non-adjacent members of a monocyclic ring, e.g., quinuclidine, tropanes, or diaza-bicyclo[2.2.2]octane. The term "heterocyclyl" includes bicyclic, tricyclic, and tetracyclic groups in which any of the above heterocyclic rings is fused to one, two, or three carbocyclic rings, e.g., a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring, or another heterocyclic ring. Examples of fused heterocyclyls include 1,2,3,5,8,8a-hexahydroindolizine; 2,3-dihydrobenzofuran; 2,3-dihydroindole; and 2,3-dihydrobenzothiophene. The heterocyclyl group may be unsubstituted or substituted with one, two, three, four or five substituents independently selected from the group consisting of: alkyl; alkenyl; alkoxy; acyloxy; alkylsulfinyl; alkylsulfonyl; aryloxy; amino; arylalkoxy; cycloalkyl; cycloalkoxy; halogen; heterocyclyl; heterocyclyl alkyl; heteroaryl; heteroaryl alkyl; heterocyclyloxy; heteroaryloxy; hydroxyl; nitro; thioalkyl; thioalkenyl; thioaryl; thiol; cyano; =O; =S; —NR_2, where each R is independently hydrogen, alkyl, acyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, or heteroaryl; —$COOR^A$, where R^A is hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, or heteroaryl; and —$CON(R^B)_2$, where each R^B is independently hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, or heteroaryl.

[0089] The term "heterocyclyl alkyl," as used herein, represents an alkyl group substituted with a heterocyclyl group. The heterocyclyl and alkyl portions of an optionally substituted heterocyclyl alkyl are optionally substituted as the described for heterocyclyl and alkyl, respectively.

[0090] The term "heterocyclyloxy," as used herein, refers to a structure —OR, in which R is heterocyclyl. Heterocyclyloxy can be optionally substituted as described for heterocyclyl.

[0091] The terms "hydroxyl" and "hydroxy," as used interchangeably herein, represent —OH. A hydroxyl substi-

tuted with an acyl is an acyloxy. A protected hydroxyl is a hydroxyl, in which the hydrogen atom is replaced with an O-protecting group.

[0092] The term "hydroxyalkyl," as used herein, refers to a C_{1-6} alkyl group that is substituted with one or more hydroxyls, provided that each carbon atom in the hydroxyalkyl is attached either to no more than one hydroxyl. Non-limiting examples of hydroxyalkyls include hydroxymethyl, 2-hydroxyethyl, and 1-hydroxyethyl.

[0093] The term "methene," as used herein, represents a double bonded carbon atom (e.g., the structure of methene may be shown as $=CH_2$).

[0094] The term "modulating," as used herein, refers to an observable change in the level of a marker in a subject, as measured using techniques and methods known in the art for the measurement of the marker. Modulating the marker level in a subject may result in a change of at least 1% relative to prior to administration (e.g., at least 5%, 10%, 15%, 20%, 25%, 30%, 35%0, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or at least 98% or more relative to prior to administration; e.g., up to 100% relative to prior to administration). In some embodiments, modulating is increasing the level of a marker in a subject. Increasing the marker level in a subject may result in an increase of at least 1% relative to prior to administration (e.g., at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or at least 98% or more relative to prior to administration; e.g., up to 100% relative to prior to administration). In other embodiments, modulating is decreasing the level of a marker in a subject. Decreasing the marker level in a subject may result in a decrease of at least 1% relative to prior to administration (e.g., at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or at least 98% or more relative to prior to administration; e.g., up to 100% relative to prior to administration). In embodiments in which a parameter is increased or decreased (or reduced) in a subject following a step of administering a composition described herein, the increase or decrease may take place and/or be detectable within a range of time following the administration (e.g., within six hours, 24 hours, 3 days, a week or longer), and may take place and/or be detectable after one or more administrations (e.g., after 2, 3, 4, 5, 6, 7, 8, 9, 10 or more administrations, e.g., as part of a dosing regimen for the subject).

[0095] The term "oxo," as used herein, represents a divalent oxygen atom (e.g., the structure of oxo may be shown as $=O$).

[0096] The term "pharmaceutically acceptable salt," as used herein, represents those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response and the like and are commensurate with a reasonable benefit/risk ratio. Principles for preparing pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in Berge et al., *J. Pharmaceutical Sciences* 66:1-19, 1977 and in *Pharmaceutical Salts: Properties, Selection, and Use*, (Eds. P. H. Stahl and C. G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final isolation and purification of the compounds described herein, by reacting the free base group with a suitable electrophile, by use of an alkylating agent or via exchange resin, or by exchanging in solution. Representative counterions useful for pharmaceutically acceptable salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, bromide, chloride, iodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like.

[0097] The term "phenolic oxygen atom," as used herein, refers to a divalent oxygen atom within the structure of a compound, where at least one valency of the phenolic oxygen atom is bonded to an sp^2-hybridized carbon atom within an aromatic ring.

[0098] The term "physiological conditions," as used herein, refers to the conditions prevalent in vivo. For example, incubation in simulated gastric fluid (SGF) or simulated intestinal fluid (SIF) at physiologically relevant temperatures (e.g., about 36-37° C.) may be used to simulate physiological conditions representative of a stomach or upper intestine, respectively. Colon conditions may be simulated using a slurry of a healthy human fecal matter under anaerobic conditions.

[0099] The term "prevent," as used herein in reference to the medical effect of a compound of the disclosure on a subject, refers to minimizing or partially or completely inhibiting the development of the associated disease, disorder, or condition. Non-limiting examples of the disease, disorder, or condition are those described herein.

[0100] The term "protecting group," as used herein, represents a group intended to protect a hydroxy, an amino, or a carbonyl from participating in one or more undesirable reactions during chemical synthesis. The term "O-protecting group," as used herein, represents a group intended to protect a hydroxy or carbonyl group from participating in one or more undesirable reactions during chemical synthesis. The term "N-protecting group," as used herein, represents a group intended to protect a nitrogen containing (e.g., an amino or hydrazine) group from participating in one or more undesirable reactions during chemical synthesis. Commonly used O- and N-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis," 3rd Edition (John Wiley & Sons, New York, 1999), which is incorporated herein by reference. Exemplary O- and N-protecting groups include alkanoyl, aryloyl, or carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, t-butyldimethylsilyl, tri-iso-propylsilyloxymethyl, 4,4'-dimethoxytrityl, isobutyryl, phenoxyacetyl, 4-isopropylpehenoxyacetyl, dimethylformamidino, and 4-nitrobenzoyl.

[0101] Exemplary O-protecting groups for protecting carbonyl containing groups include, but are not limited to: acetals, acylals, 1,3-dithianes, 1,3-dioxanes, 1,3-dioxolanes, and 1,3-dithiolanes.

[0102] Other O-protecting groups include, but are not limited to: substituted alkyl, aryl, and aryl-alkyl ethers (e.g., trityl; methylthiomethyl; methoxymethyl; benzyloxymethyl;

siloxymethyl; 2,2,2,-trichloroethoxymethyl; tetrahydropyranyl; tetrahydrofuranyl; ethoxyethyl; 1-[2-(trimethylsilyl) ethoxy]ethyl; 2-trimethylsilylethyl; t-butyl ether; p-chlorophenyl, p-methoxyphenyl, p-nitrophenyl, benzyl, p-methoxybenzyl, and nitrobenzyl); silyl ethers (e.g., trimethylsilyl; triethylsilyl; triisopropylsilyl; dimethylisopropylsilyl; t-butyldimethylsilyl; t-butyldiphenylsilyl; tribenzylsilyl; triphenylsilyl; and diphenymethylsilyl); carbonates (e.g., methyl, methoxymethyl, 9-fluorenylmethyl; ethyl; 2,2,2-trichloroethyl; 2-(trimethylsilyl)ethyl; vinyl, allyl, nitrophenyl; benzyl; methoxybenzyl; 3,4-dimethoxybenzyl; and nitrobenzyl).

[0103] Other N-protecting groups include, but are not limited to, chiral auxiliaries such as protected or unprotected D, L or D, L-amino acids such as alanine, leucine, phenylalanine, and the like; sulfonyl-containing groups such as benzenesulfonyl, p-toluenesulfonyl, and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyl oxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl, and the like, arylalkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl, and the like and silyl groups such as trimethylsilyl, and the like. Useful N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, alanyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

[0104] The term "subject," as used herein, represents a human or non-human animal (e.g., a mammal) that is suffering from, or is at risk of, disease, disorder, or condition, as determined by a qualified professional (e.g., a doctor or a nurse practitioner) with or without known in the art laboratory test(s) of sample(s) from the subject. Non-limiting examples of diseases, disorders, and conditions include those described herein.

[0105] The term "sugar acid," as used herein, refers to a monosaccharide, in the linear form of which one or both terminal positions are oxidized to a carboxylic acid. There are at least four classes of sugar acids: aldonic acid, ulosonic acid, uronic acid, and aldaric acid. Any of the four sugar acid classes may be used in conjugates disclosed herein. Non-limiting examples of sugar acids include xylonic acid, gluconic acid, glucuronic acid, galacturonic acid, tartaric acid, saccharic acid, or mucic acid.

[0106] The term "sugar acid acyl," as used herein, refers to a monovalent group that is a sugar acid having a carboxylate, in which —OH is replaced with a valency.

[0107] The term "thioalkenyl," as used herein, represents a group —SR, where R is alkenyl. An optionally substituted thioalkenyl is thioalkenyl that is optionally substituted as described herein for alkenyl.

[0108] The term "thioalkyl," as used herein, represents a group —SR, where R is alkyl. An optionally substituted thioalkyl is thioalkyl that is optionally substituted as described herein for alkyl.

[0109] The term "thioaryl," as used herein, represents a group —SR, where R is aryl. An optionally substituted thioaryl is thioaryl that is optionally substituted as described herein for aryl.

[0110] "Treatment" and "treating," as used herein, refer to the medical management of a subject with the intent to improve, ameliorate, stabilize, or cure a disease, disorder, or condition. This term includes active treatment (treatment directed to improve the disease, disorder, or condition); causal treatment (treatment directed to the cause of the associated disease, disorder, or condition); palliative treatment (treatment designed for the relief of symptoms of the disease, disorder, or condition); and supportive treatment (treatment employed to supplement another therapy).

[0111] The compounds described herein, unless otherwise noted, encompass isotopically enriched compounds (e.g., deuterated compounds), tautomers, and all stereoisomers and conformers (e.g. enantiomers, diastereomers, E/Z isomers, atropisomers, etc.), as well as racemates thereof and mixtures of different proportions of enantiomers or diastereomers, or mixtures of any of the foregoing forms as well as salts (e.g., pharmaceutically acceptable salts).

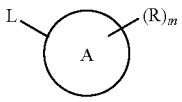
[0112] Other features and advantages of the disclosure will be apparent from the disclosure.

[0113] As mentioned above, provided herein are compounds, pharmaceutical compositions, and methods of their use. The compounds of the disclosure may target the production of pathogenic metabolites by certain bacteria in a subject, thereby reducing the pathogenic metabolite levels in the subject.

[0114] The compounds of the disclosure may be a conjugate of the disclosure, e.g., those compounds including a glycoside or an acylated sugar. Upon administration of the conjugate of the disclosure, the conjugate may be cleaved in vivo to remove the glycoside or an acylated sugar from the compound and to release the corresponding unconjugated compound of the disclosure. Conjugates of the disclosure may be advantageous in therapeutic applications benefitting from a particular tissue-targeted delivery of an unconjugated compound of the disclosure.

[0115] Compounds of the disclosure that include at least one glycoside or at least one acylated sugar are conjugates. Compounds having a fatty acid acyl (e.g., a short chain fatty acid acyl) attached through an ester bond are also conjugates.

[0116] Acylated sugars that may be used in the conjugates disclosed herein include an acyl (e.g., a fatty acid acyl) and a core selected from the group consisting of a carbohydrate (e.g., a monosaccharide or disaccharide), sugar acid, and sugar alcohol. For example, an acylated sugar may be a monovalent group of the following formula:



where

[0117] L is a bond to a pharmaceutically active agent, a compound of formula (I), a compound of formula (II), a compound of formula (III), a carbonate linker, or a carbamate linker;

[0118] group A is a core selected from the group consisting of carbohydrate (e.g., a monosaccharide or dissaccharide), sugar acid, and sugar alcohol;

[0119] each R is independently an acyl bonded to an oxygen atom in group A; and

[0120] m is an integer from 0 to the total number of available hydroxyl groups in group A (e.g., 1, 2, 3, 4, or 5).

[0121] In some embodiments, L may be attached to a carbon atom in group A (e.g., an anomeric carbon atom or a carbonyl carbon atom). In some embodiments, L may be attached to an oxygen atom in group A (e.g., an alcoholic oxygen atom, a phenolic oxygen atom, or a carboxylate oxygen atom).

[0122] In some embodiments, at least one R is a fatty acid acyl.

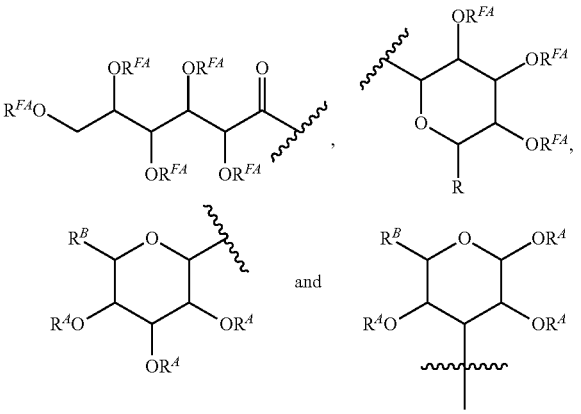
[0123] In some embodiments, the fatty acid(s) are short chain fatty acid acyls. In some embodiments, the short chain fatty acid acyl is a C_{3-6} short chain fatty acid acyl (e.g., propionyl or butyryl).

[0124] In some embodiments, the acylated sugar is per-acylated, i.e., all of the available hydroxyls in the acylated sugar are substituted with an acyl.

[0125] A monosaccharide may be, e.g., arabinose, xylose, fructose, galactose, glucose, ribose, tagatose, fucose, or rhamnose. In some embodiments, the monosaccharide is L-arabinose, D-xylose, fructose, galactose, D-glucose, D-ribose, D-tagatose, L-fucose, or L-rhamnose (e.g., the monosaccharide is D-xylose). A disaccharide may be, e.g., lactose, sucrose, melibiose, gentiobiose, kojibiose, cellobiose, maltose, trehalose and chitobiose. A sugar acid may be, e.g., aldonic acid, ulosonic acid, uronic acid, or aldaric acid. A sugar acid may be, e.g., xylonic acid, gluconic acid, glucuronic acid, galacturonic acid, tartaric acid, saccharic acid, or mucic acid. A sugar alcohol may be, e.g., glycerol, erythritol, threitol, arabitol, xylitol, tibitol, mannitol, sorbitol, galactitol, fucitol, iditol, or inositol.

[0126] An acylated sugar may be covalently linked to a pharmaceutically active agent through a carbon-oxygen bond that is cleavable in vivo, a carbonate linker, or a carbamate linker. The carbon-oxygen bond may be, e.g., a glycosidic bond or ester bond. Acylated sugars having a monosaccharide, disaccharide, or a sugar acid as a core may be covalently linked to a pharmaceutically active agent through a carbon-oxygen bond that is cleavable in vivo (e.g., a glycosidic bond or ester bond), a carbonate linker, or a carbamate linker. In the sugar acid core, one or both carboxylates may be present as O-protected versions (e.g., as alkyl esters (e.g., methyl or ethyl esters)). Acylated sugars having a sugar alcohol as a core may be covalently linked to a pharmaceutically active agent through a carbon-oxygen bond that is cleavable in vivo (e.g., an ester bond), a carbonate linker, or a carbamate linker.

[0127] Non-limiting examples of acylated sugars are:



[0128] where

[0129] R is H, —CH_3, or —CH_2OR^{FA};

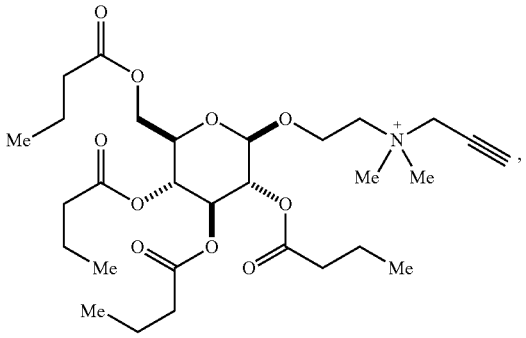
[0130] each R^{FA} is independently H or a fatty acid acyl (e.g., a short chain fatty acid acyl);

[0131] each R^A is independently H or fatty acid acyl; and

[0132] R^B is H, —CH_3, —CH_2—OR^A, —OCH_3, —$COOCH_3$, or —COOH.

[0133] In some embodiments, the disclosure provides a compound of a cation and a pharmaceutically acceptable counterion, where the cation is chosen from the following cations:

1



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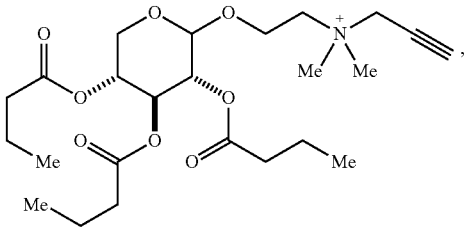

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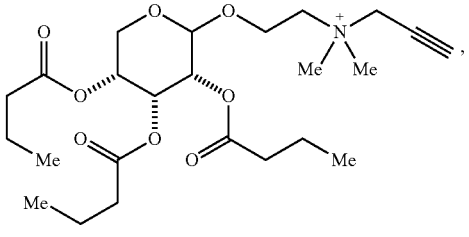

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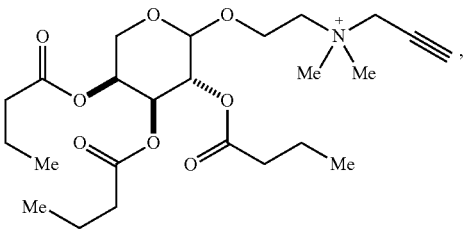

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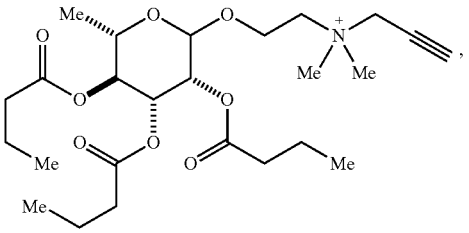

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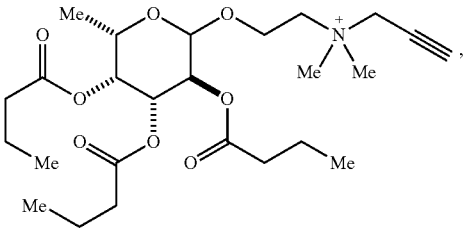

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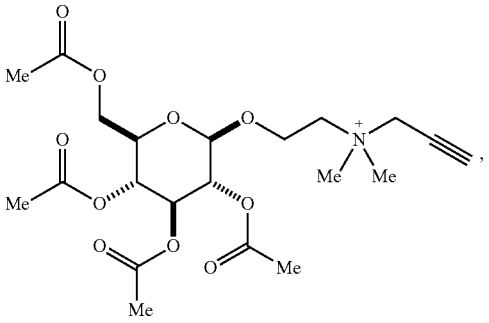

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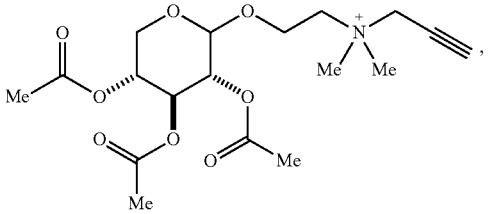

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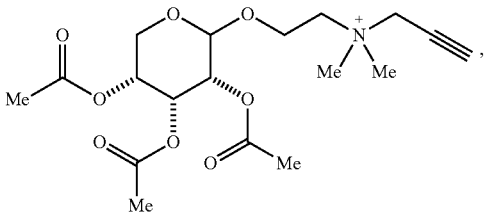

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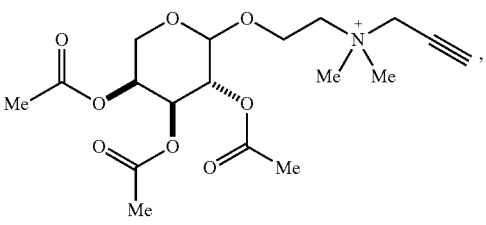

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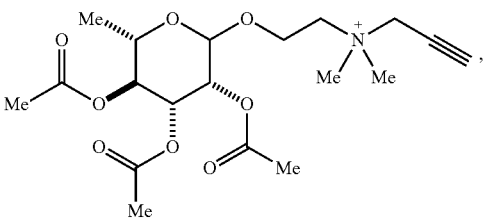

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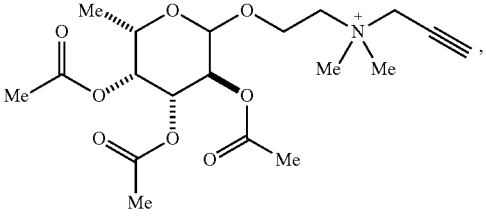

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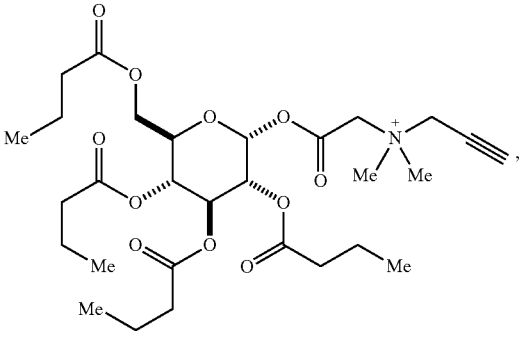

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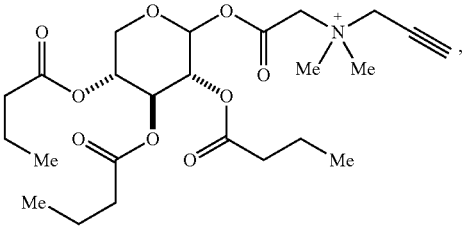

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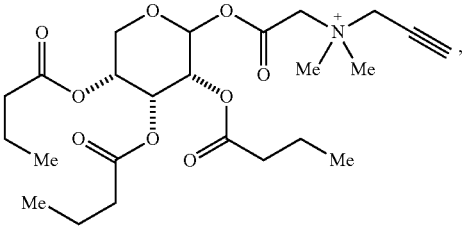

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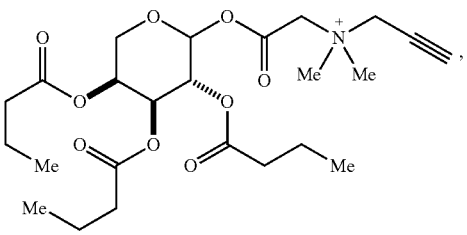

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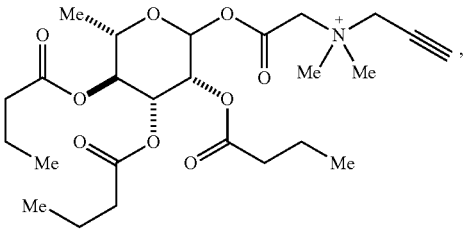

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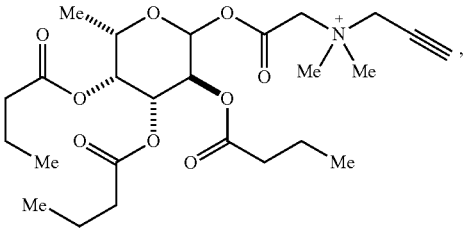

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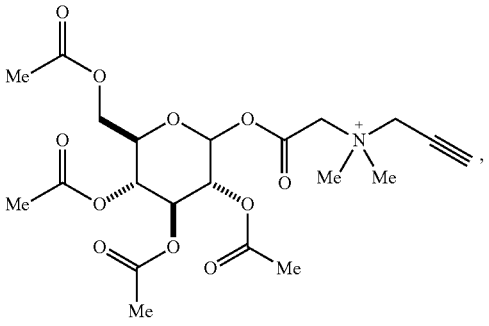

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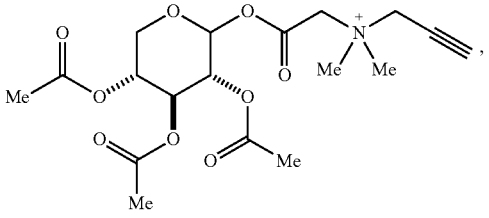

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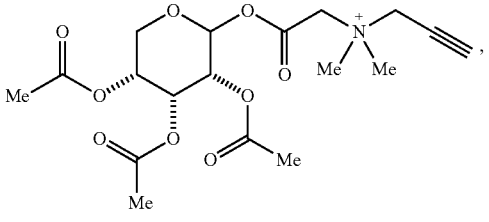

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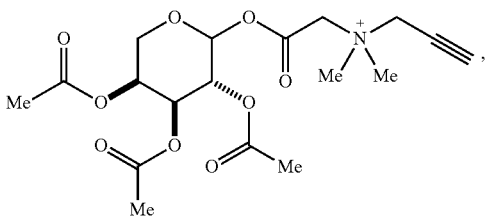

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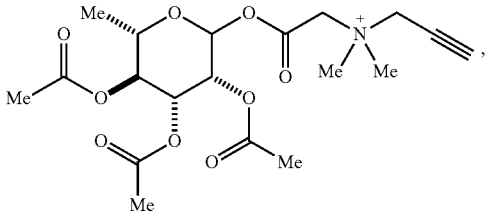

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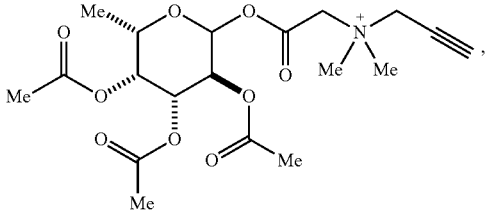

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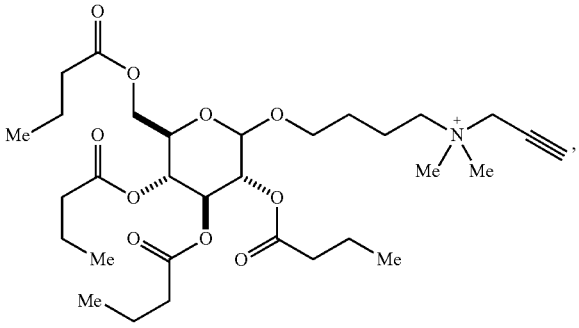

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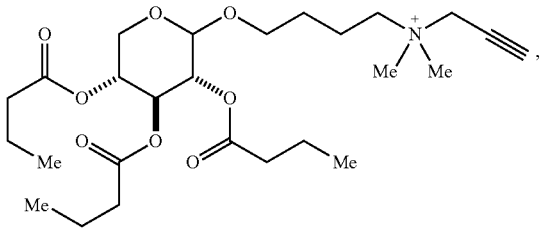

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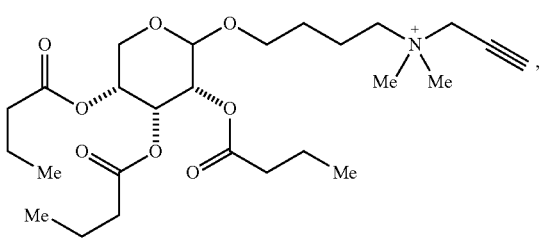

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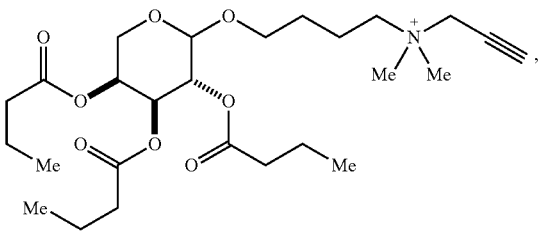

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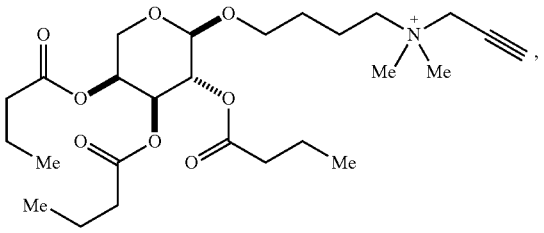

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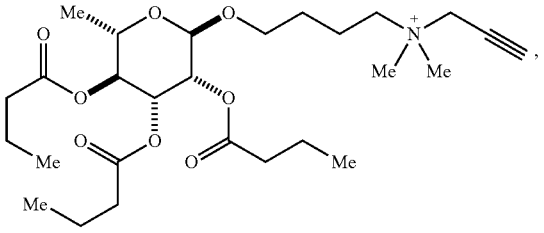

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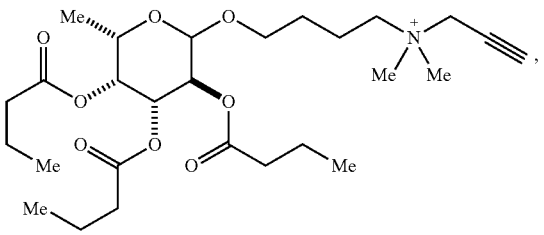

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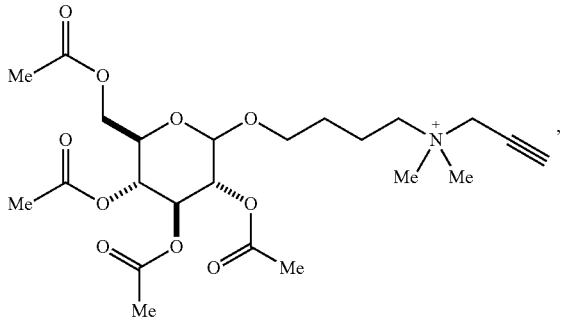

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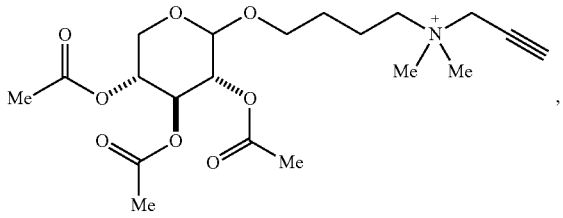

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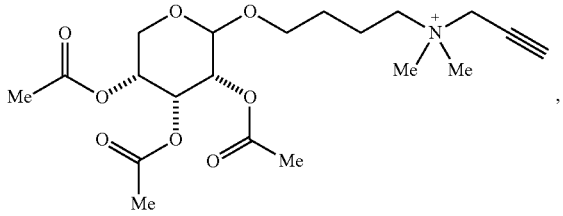

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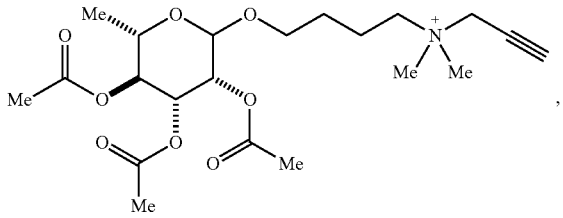

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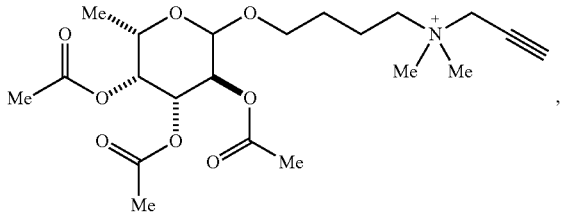

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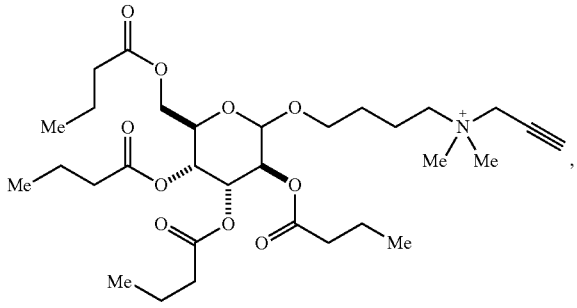

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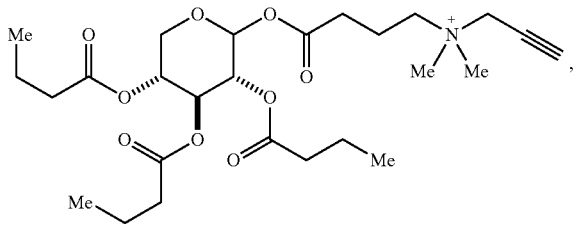

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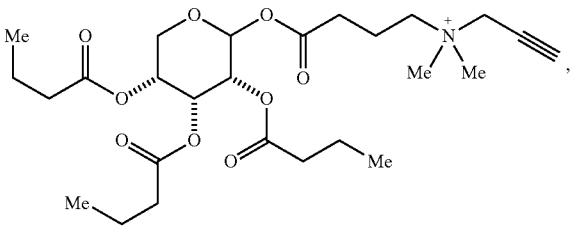

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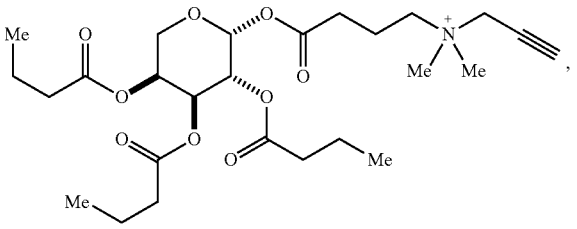

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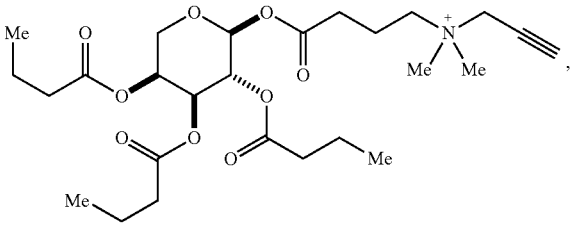

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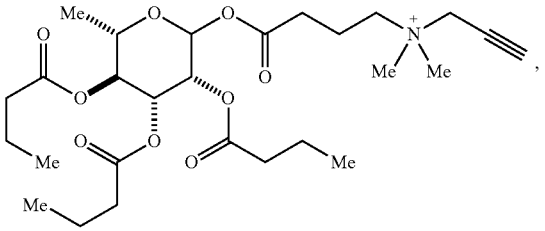

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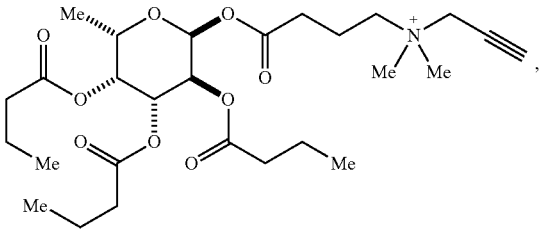

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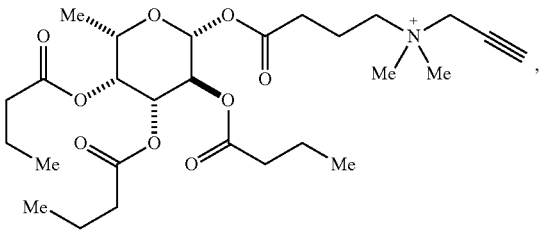

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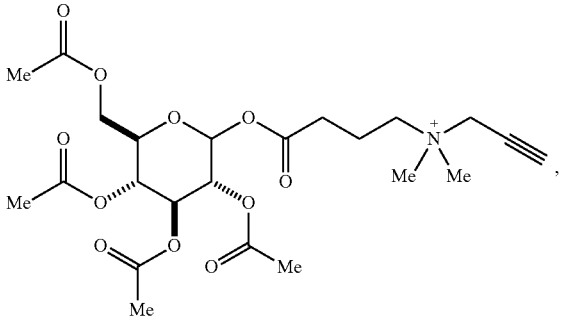

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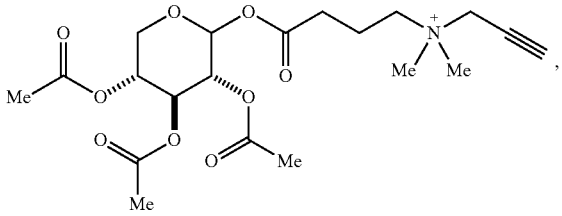

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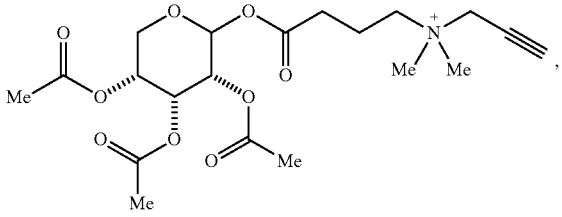

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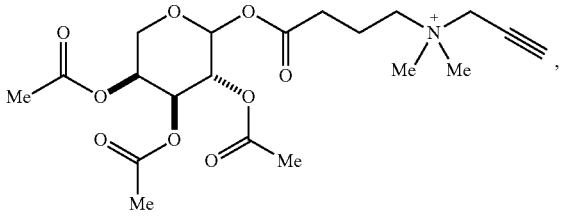

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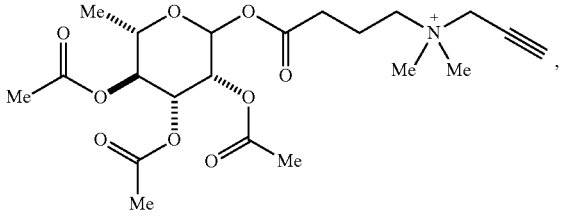

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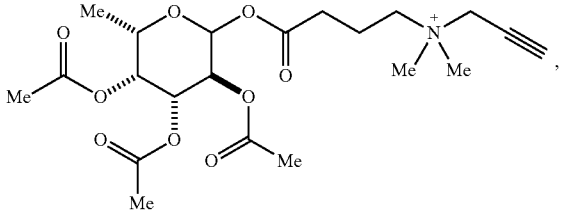

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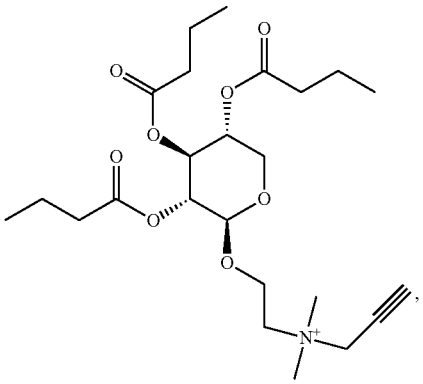

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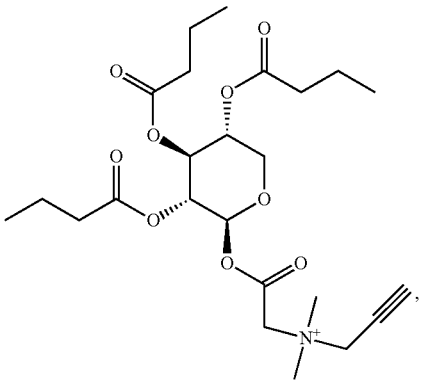

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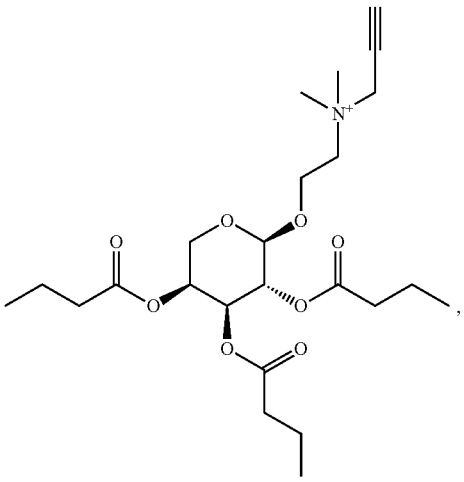

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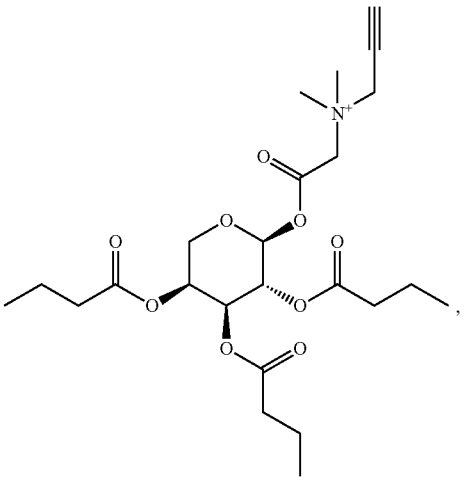

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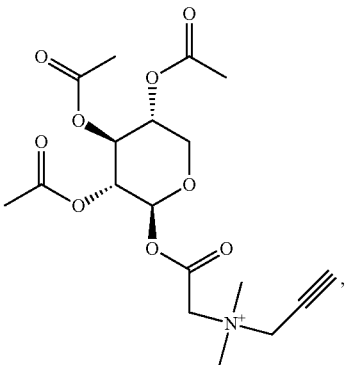

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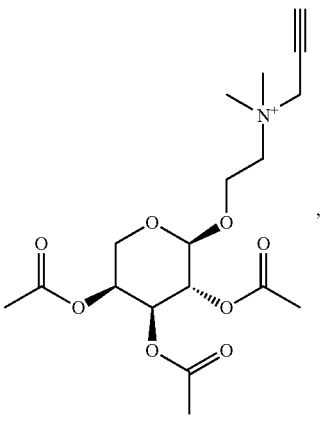

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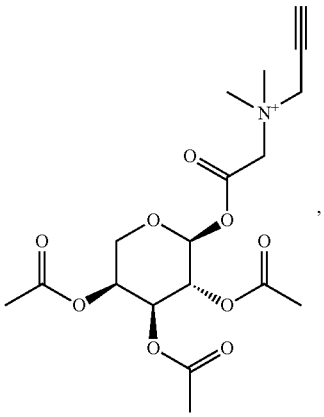

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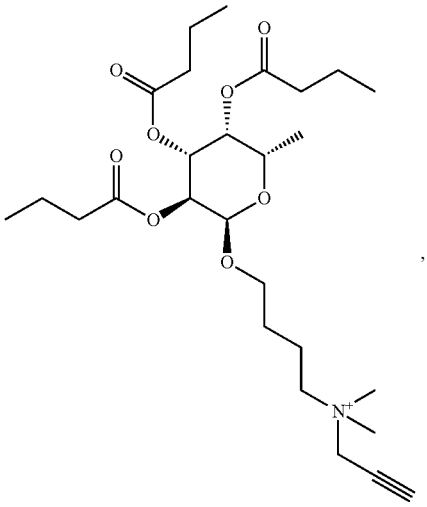

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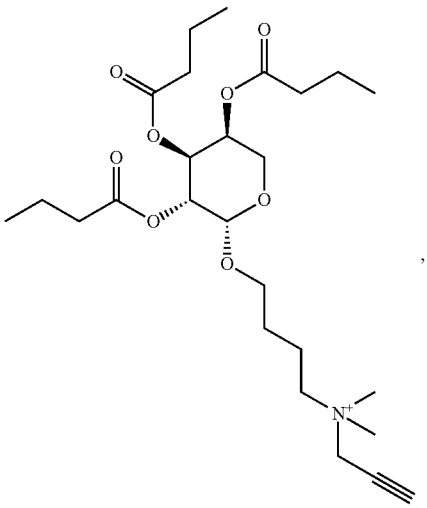

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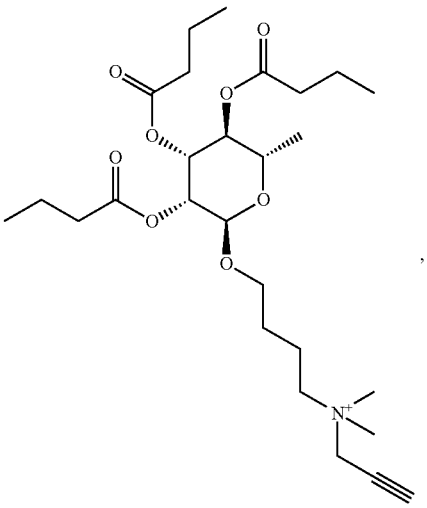

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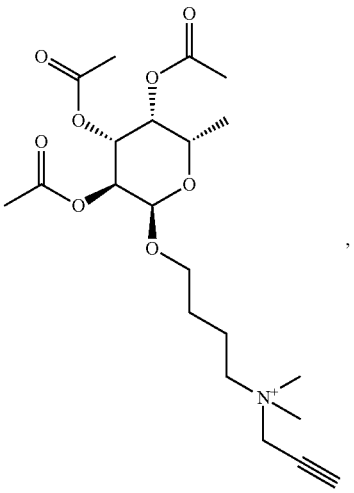

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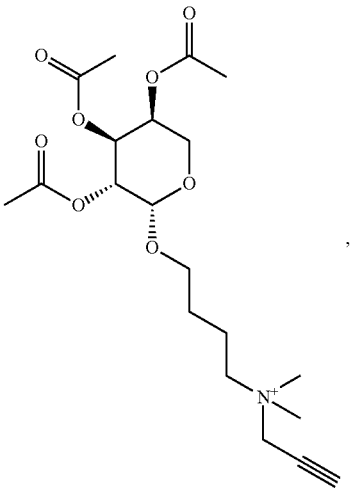

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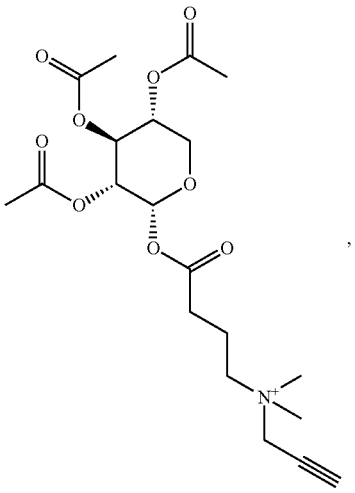

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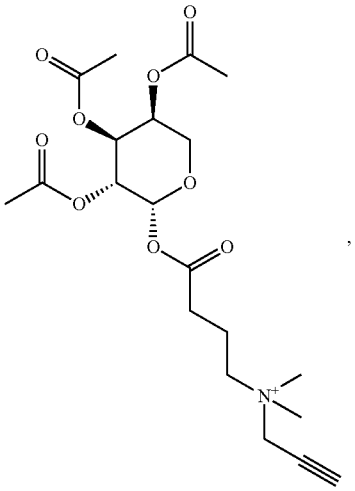

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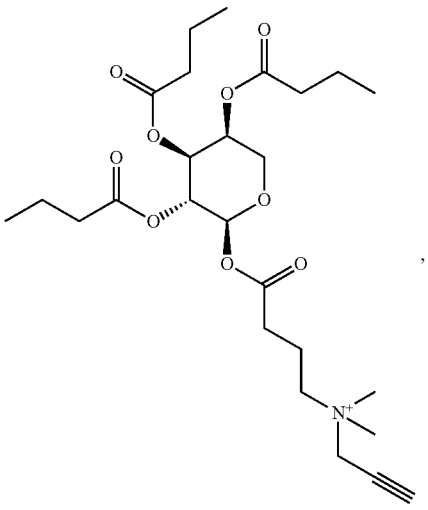

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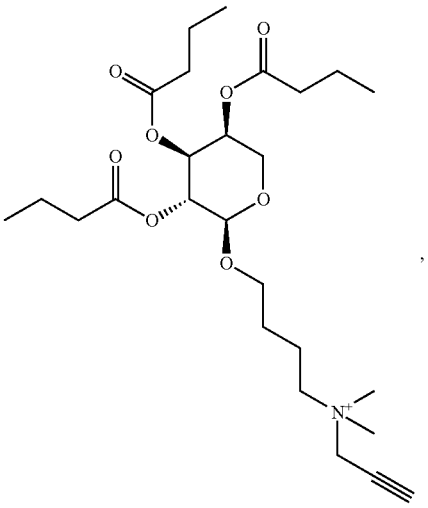

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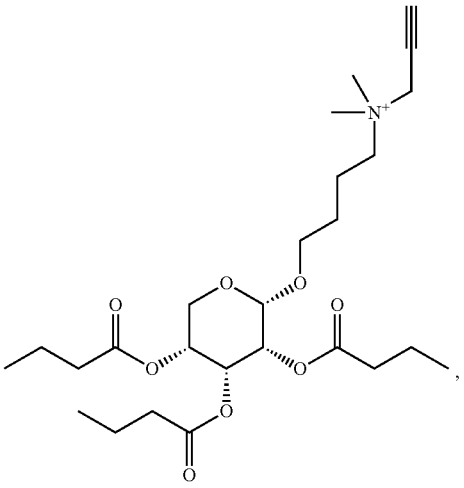

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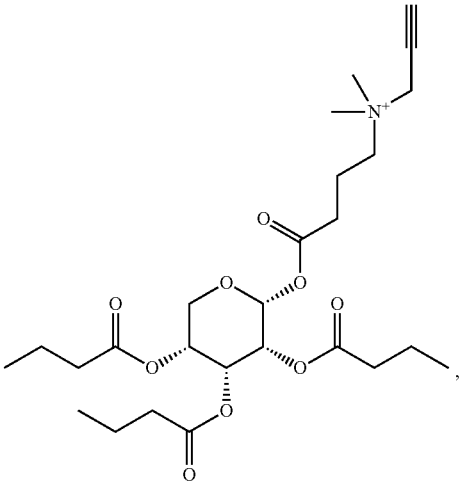

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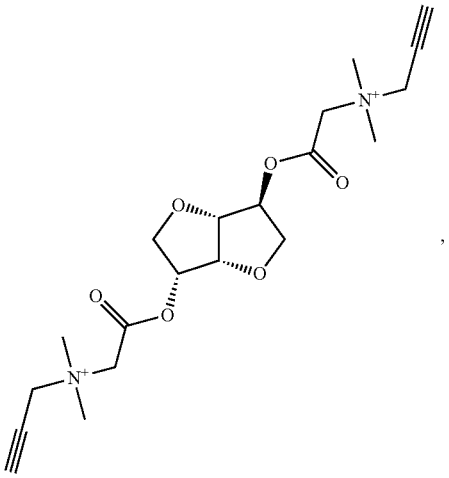

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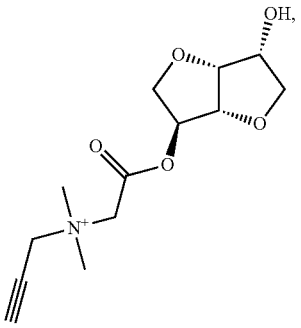

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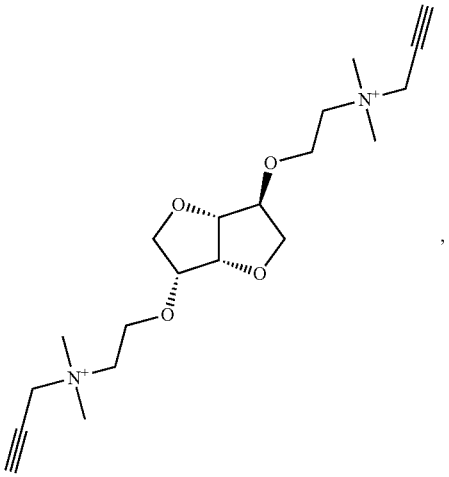

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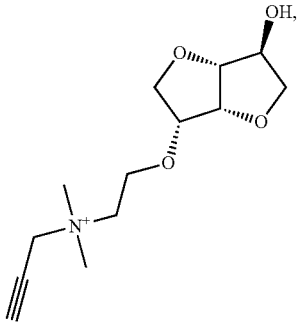

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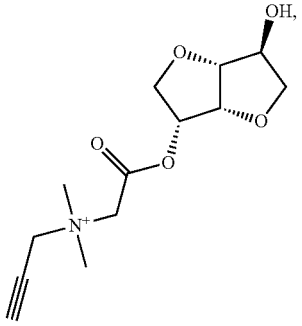

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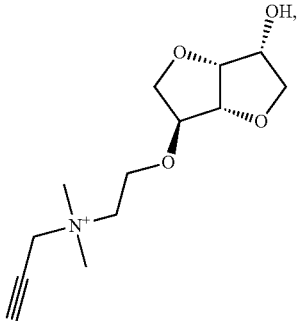

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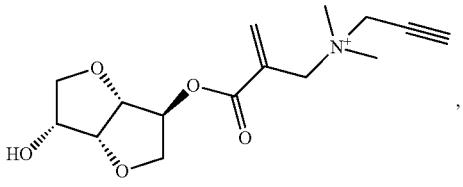

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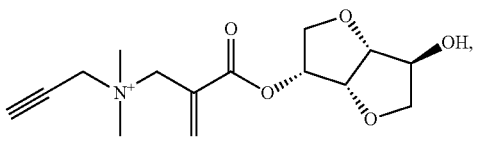

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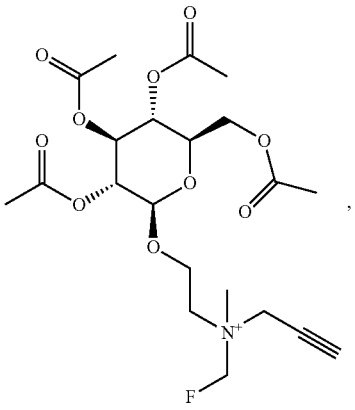

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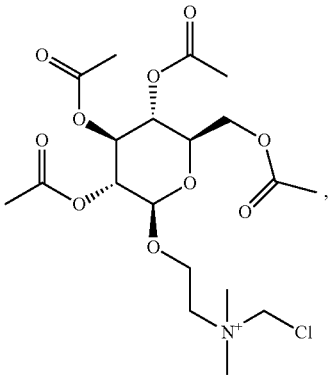

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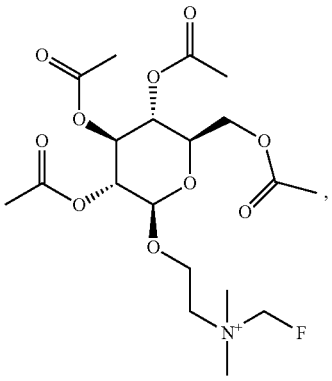

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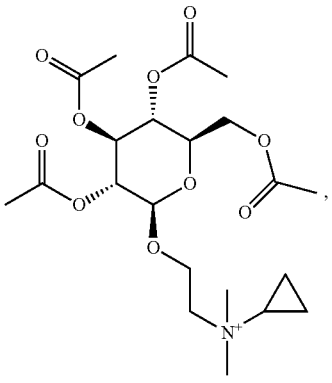

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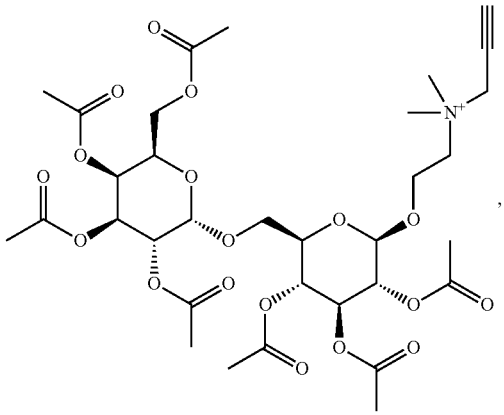

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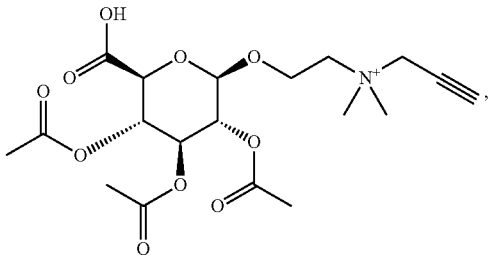

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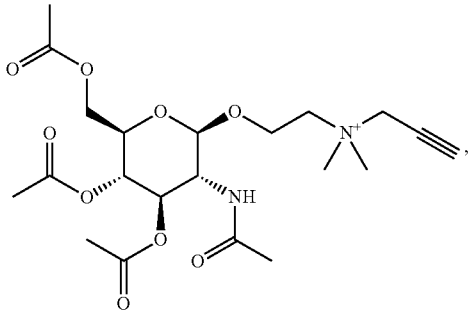

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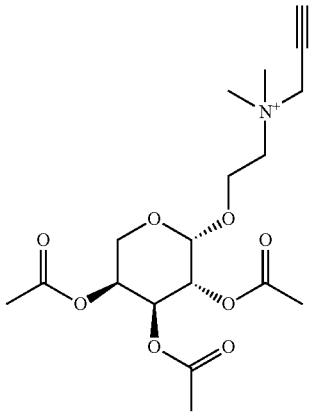

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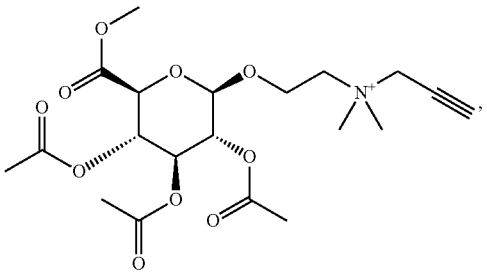

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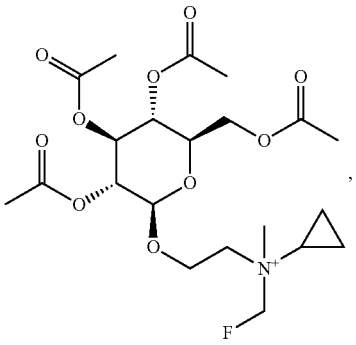

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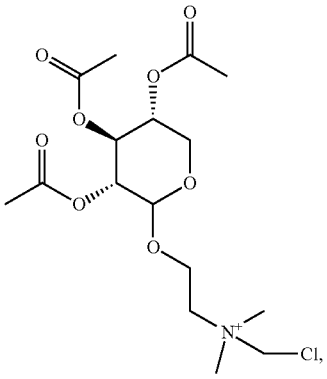

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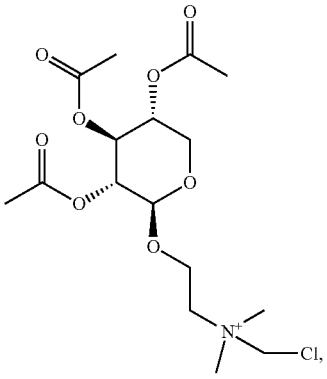

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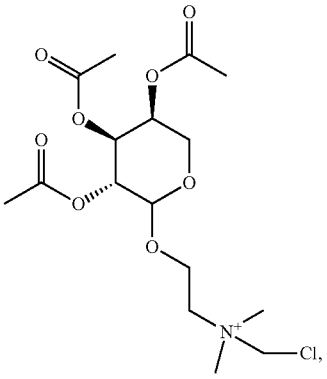

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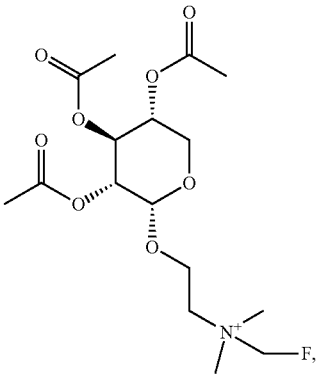

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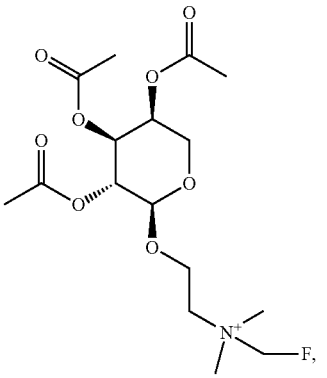

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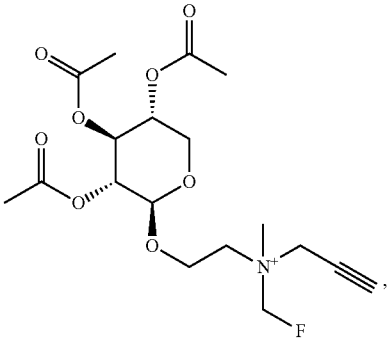

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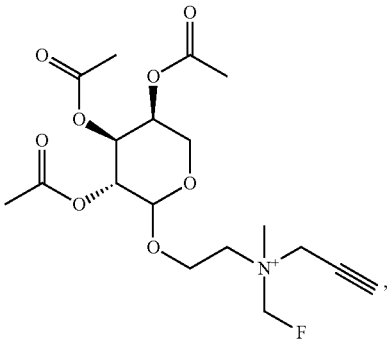

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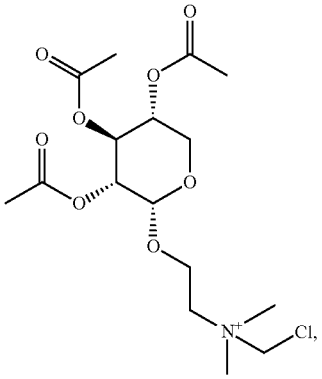

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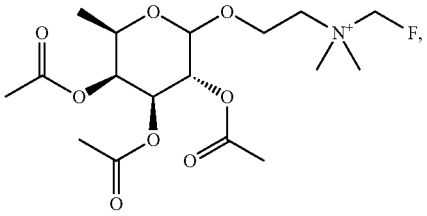

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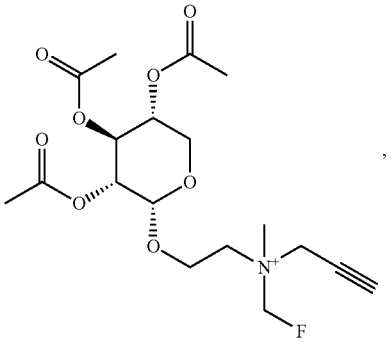

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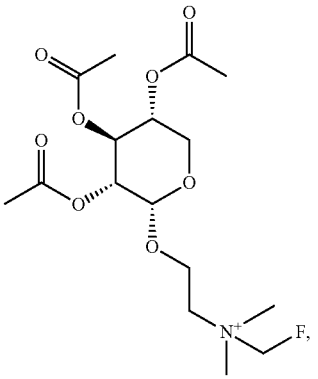

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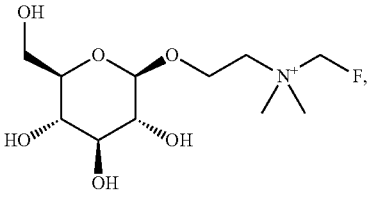

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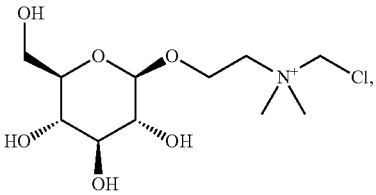

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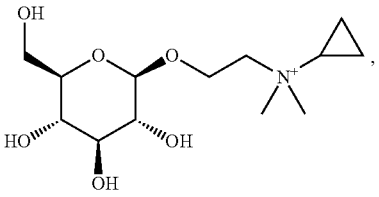

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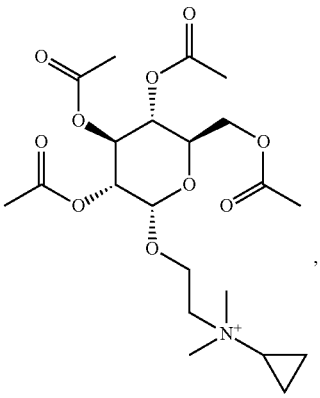

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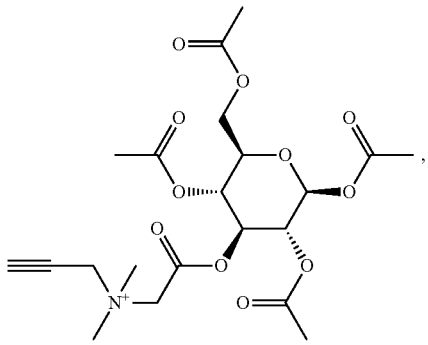

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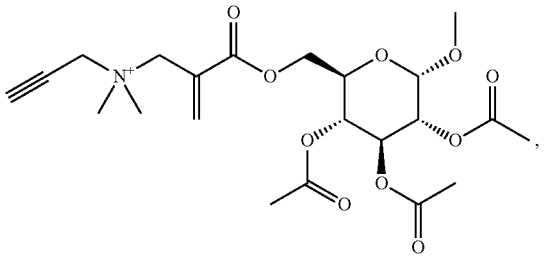

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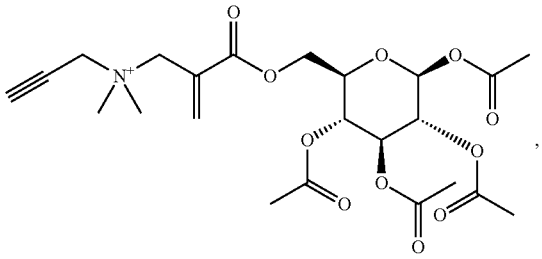

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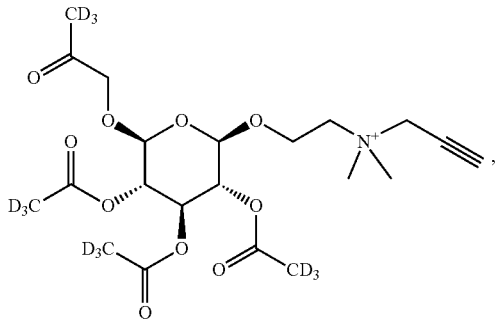

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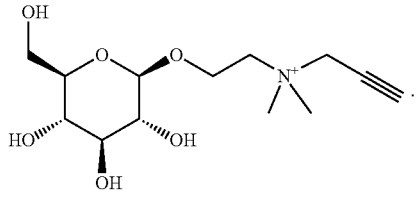
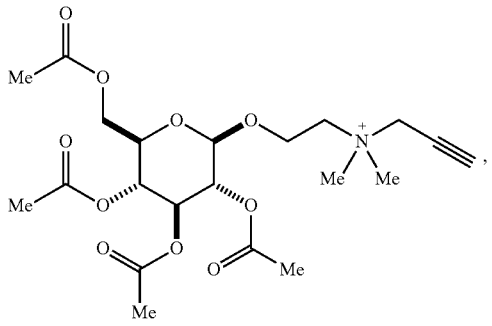


[0134] In some embodiments, the disclosure provides a compound of a cation and a pharmaceutically acceptable counterion, where the cation is chosen from the following cations:

7



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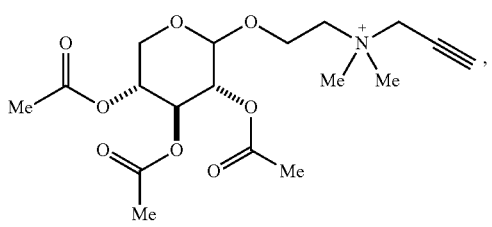

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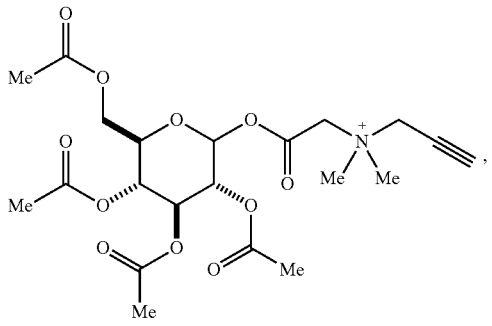

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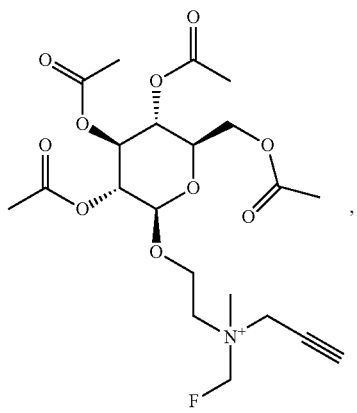

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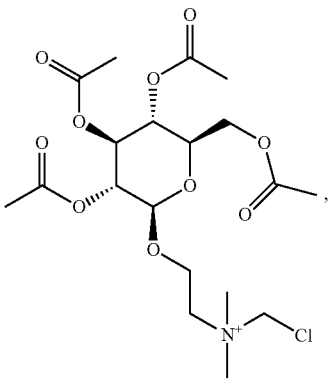

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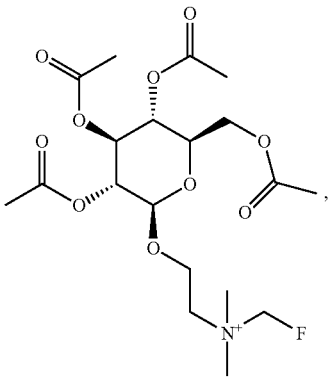

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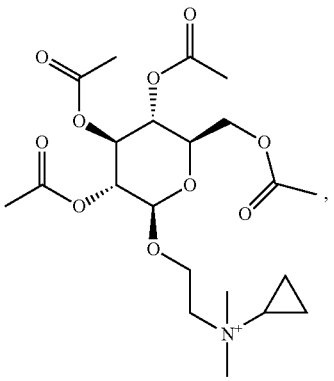

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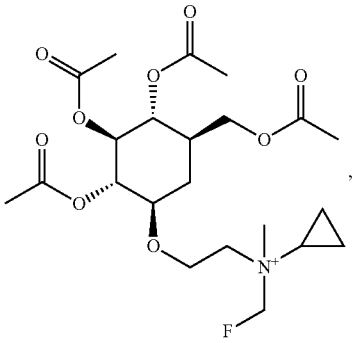

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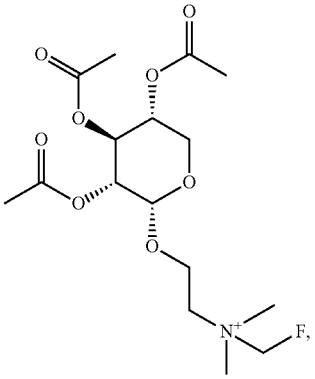

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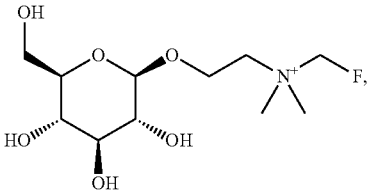

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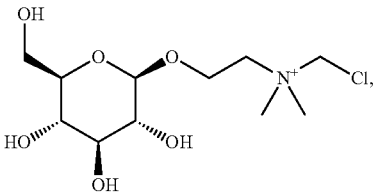

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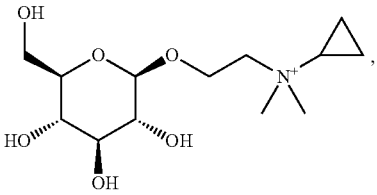

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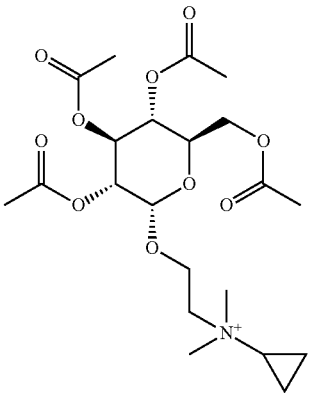

[0135] In some embodiments, provided here are compounds consisting of a cation and a pharmaceutically acceptable counterion, wherein the cation is chosen from the following cations:

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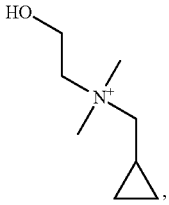
107



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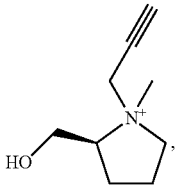

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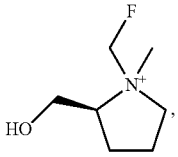

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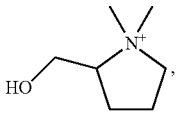

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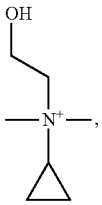

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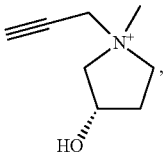

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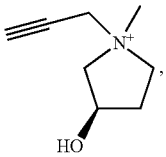

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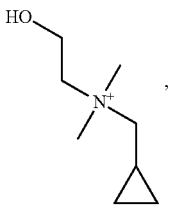

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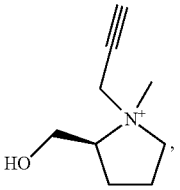

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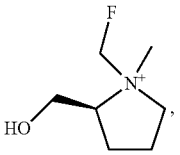

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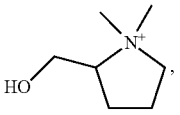

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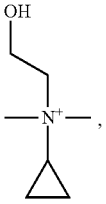

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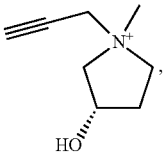

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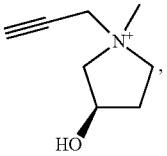

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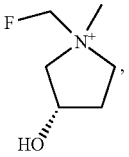

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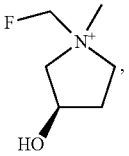

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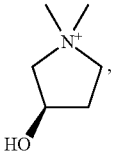

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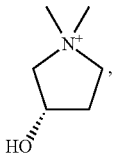

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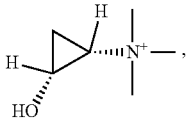

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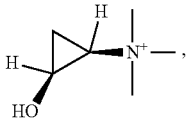

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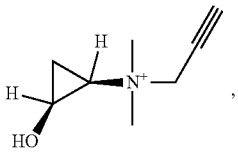

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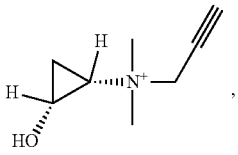

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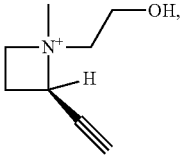

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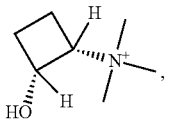

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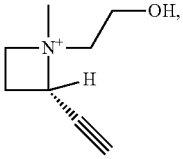

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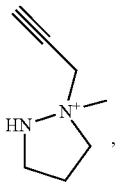

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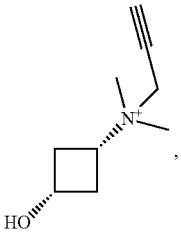

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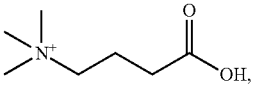

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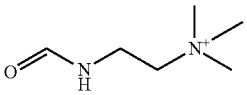

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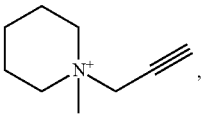

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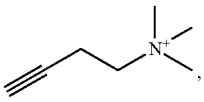

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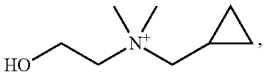

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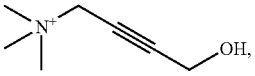

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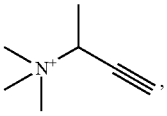

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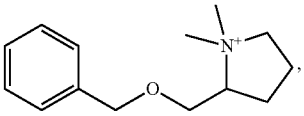

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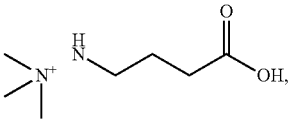

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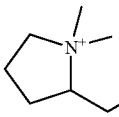

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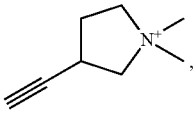

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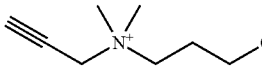

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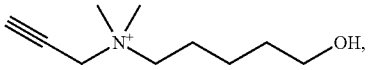

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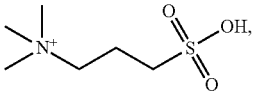

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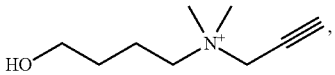

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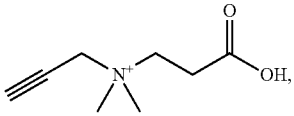

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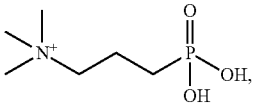

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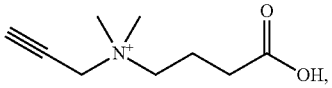

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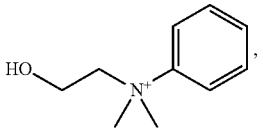

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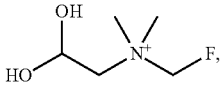

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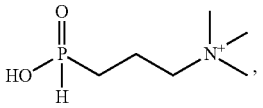

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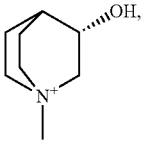

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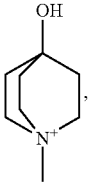

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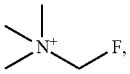

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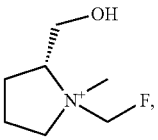

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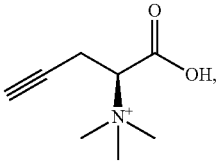

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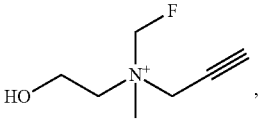

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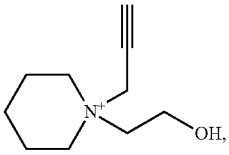

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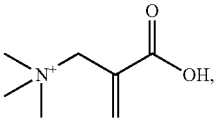

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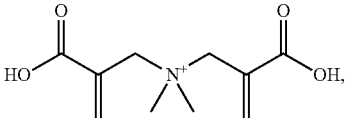

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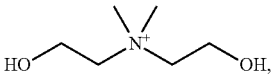

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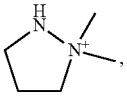

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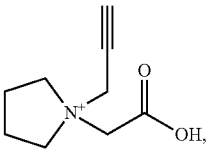

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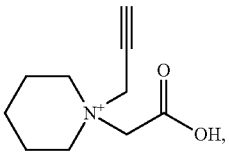

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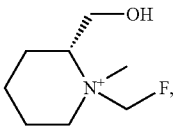

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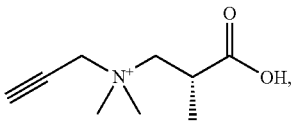

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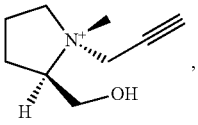

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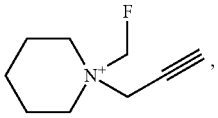

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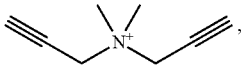

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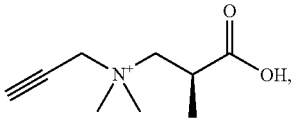

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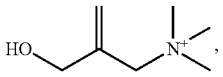

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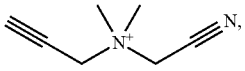

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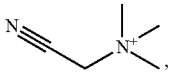

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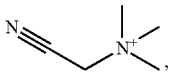

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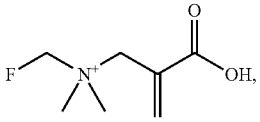

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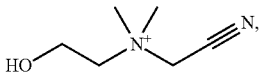

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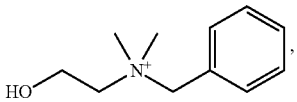

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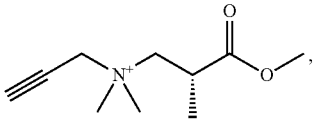

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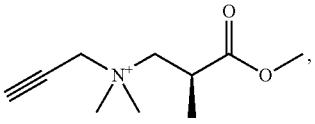

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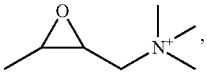

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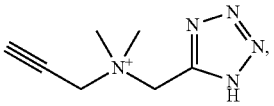

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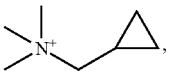

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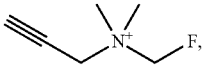

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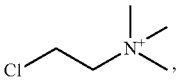

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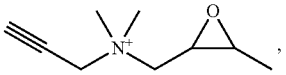

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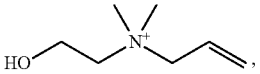

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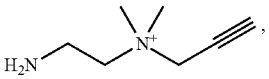

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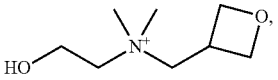

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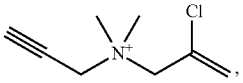

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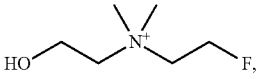

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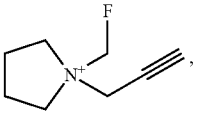

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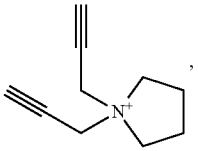

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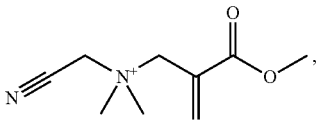

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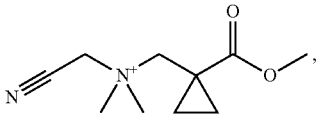

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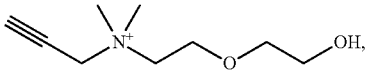

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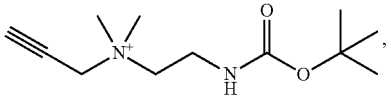

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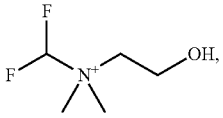

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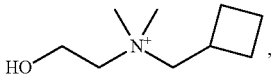

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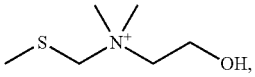

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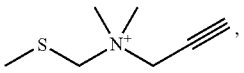

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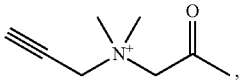

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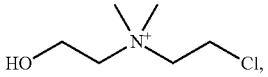

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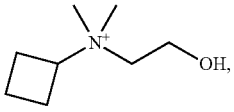

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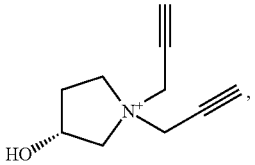

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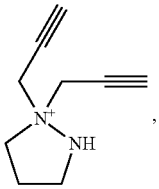

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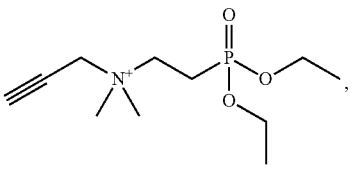

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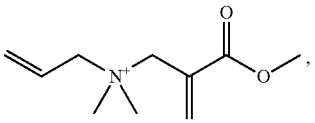

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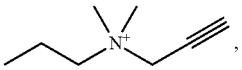

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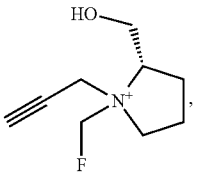

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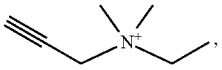

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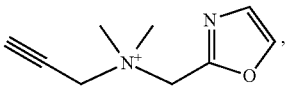

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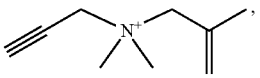

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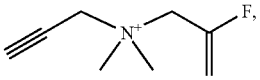

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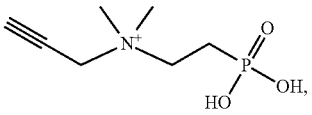

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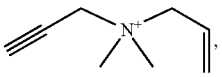

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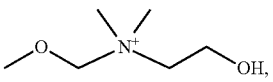

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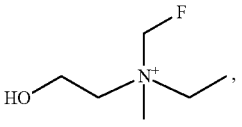

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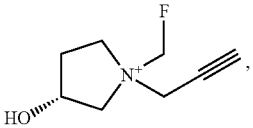

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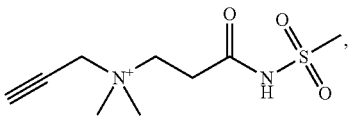

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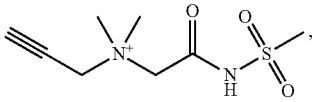

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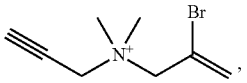

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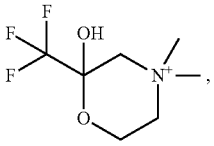

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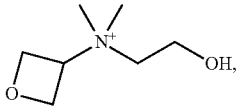

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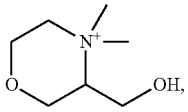

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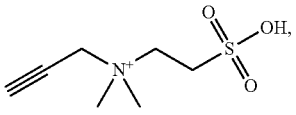

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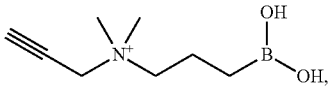

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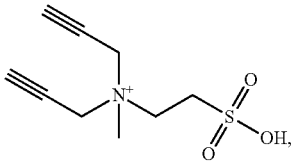

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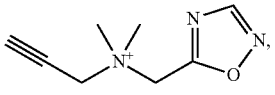

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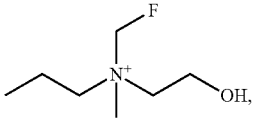

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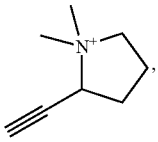

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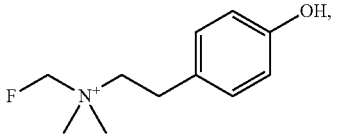

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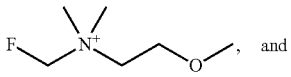

and

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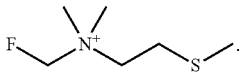
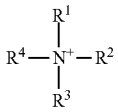


[0136] The disclosure provides a compound consisting of a cation and a pharmaceutically acceptable counterion, where the cation is a structure of formula (I):

(I)



wherein

[0137] R^1 is

[0138] C_{2-6} alkyl substituted with —O-(acylated sugar) or isosorbide, wherein said C_{2-6} alkyl is further optionally substituted with oxo and/or methene;

[0139] C_4 cycloalkyl optionally substituted with hydroxyl, ethynyl, or —O-(acylated sugar); or

[0140] C_3 cycloalkyl substituted with C_{1-6} alkyl, hydroxyl, ethynyl, or —O-(acylated sugar)

[0141] C_{3-4} cycloalkyl C_{1-2} alkyl;

[0142] R^2 is C_{2-6} alkyl optionally substituted with one or two hydroxyl, oxo, and —O-(acylated sugar);

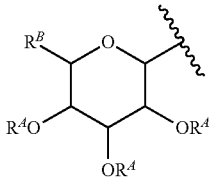
[0143] or R^1 and R^2, together with the nitrogen atom to which both are attached, combine to form a 4- or 5-membered heterocyclic ring optionally substituted with ethynyl or $—(CH_2)_n—OR^s$ or an acylated sugar, wherein n is 0 or 1, R^s is hydrogen or an acylated sugar;

[0144] R^3 is C_{1-6} alkyl optionally substituted with a halogen or hydroxyl; and

[0145] R^4 is C_{1-6} alkyl or propargyl.

[0146] In some embodiments, the cation comprises at least one acylated sugar. In some embodiments, the acylated sugar is chosen from groups of formula (A), groups of formula (B), and groups of formula (C):

(A)



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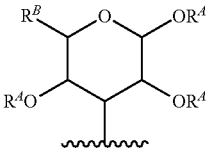
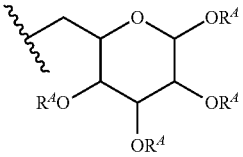
and



(B)

and



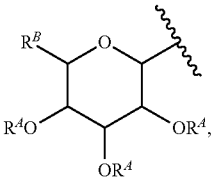
(C)

wherein

[0147] each R^A is independently H or fatty acid acyl; and

[0148] R^B is H, —C_{1-6}alkyl, —C_{1-6}alkylene-OR^A, —OC_{1-6}alkyl, —$COOC_{1-6}$alkyl, or —COOH.

[0149] In some embodiments, acylated sugar is a group of formula (A).



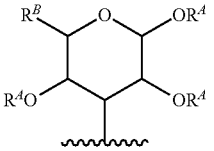
(A)

where

[0150] each R^A is independently H or fatty acid acyl; and

[0151] R^B is H, —CH_3, —CH_2—OR^A, —OCH_3, —$COOCH_3$, or —COOH.

[0152] In some embodiments, acylated sugar is a group of formula (B):



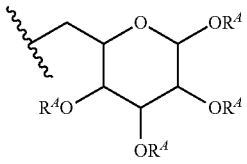
(B)

where

[0153] each R^A is independently H or fatty acid acyl; and

[0154] R^B is H, —CH_3, —CH_2—OR^A, —OCH_3, —$COOCH_3$, or —COOH.

[0155] In some embodiments, acylated sugar is a group of formula (C):



(C)

where

[0156] each R^A is independently H or fatty acid acyl; and

[0157] R^B is H, —CH_3, —CH_2—OR^A, —OCH_3, —$COOCH_3$, or —COOH.

[0158] In some embodiments, in groups of formula (A), (B), and (C), each R^A is independently chosen from fatty acid acyls. In some embodiments, each R^A is independently chosen from short chain fatty acid acyls.

[0159] In some embodiments, the acylated sugar is chosen from groups of formula (A).

[0160] In some embodiments, at least one R^A is H. In some embodiments, at least one R^A is —$COCH_3$. In some embodiments, at least one R^A is —$COCH_2CH_3$. In some embodiments, at least one R^A is —$COCH_2CH_2CH_3$.

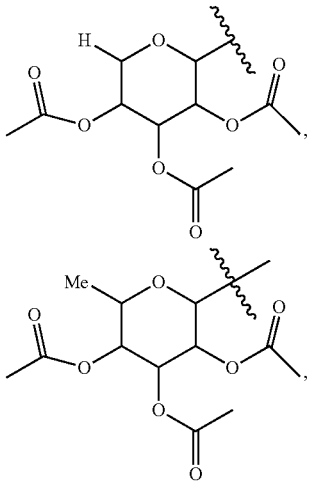
[0161] In some embodiments, at least three R^A are H. In some embodiments, at least three R^A are —$COCH_3$. In some embodiments, at least three R^A are —$COCH_2CH_3$. In some embodiments at least three R^A are —$COCH_2CH_2CH_3$.

[0162] In some embodiments, R^B is H. In some embodiments, R^B is —CH_3. In some embodiments, R^B is —CH_2OH. In some embodiments, R^B is —CH_2—$OCOCH_3$. In some embodiments, R^B is —CH_2—$OCOCH_2CH_3$. In some embodiments, R^B is —COOH. In some embodiments, R^B is —$COOCH_3$.

[0163] In some embodiments, R^B is H, —CH_3, —CH_2—OR^A, —OCH_3, —$COOCH_3$, or —COOH. In some embodiments, R^B is H, —C_{1-6}alkyl, or —C_{1-6}alkylene-OR^A wherein R^A is H or fatty acid acyl.

[0164] In some embodiments, R^B is H, —CH_3, or —CH_2—OR^A, wherein R^A is H or fatty acid acyl. In some embodiments, R^B is —OC_{1-6}alkyl, —$COOC_{1-6}$alkyl, or —COOH. In some embodiments, R^B is —OCH_3, —$COOCH_3$, or —COOH.

[0165] In some embodiments, the acylated sugar is a group of the following formula:



or

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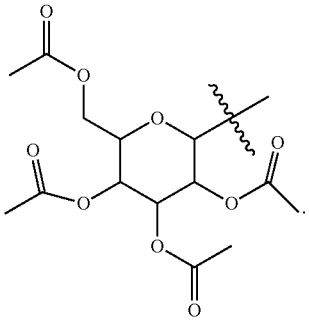
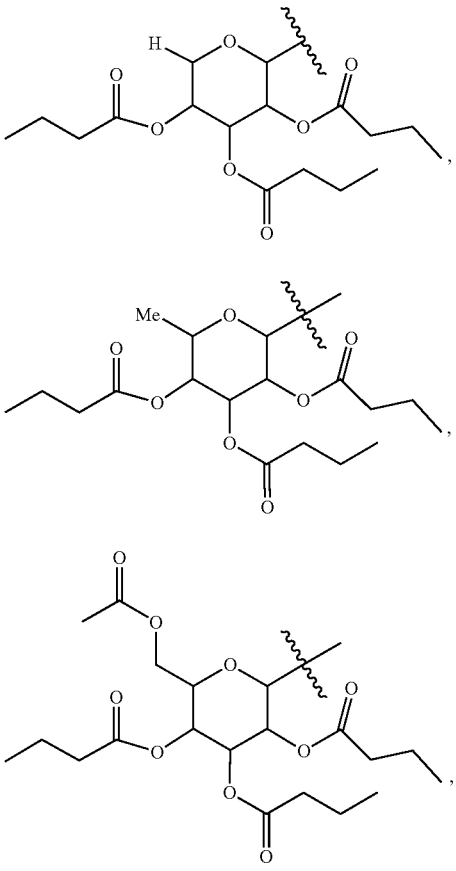


[0166] In some embodiments, the acylated sugar is a group of the following formula:



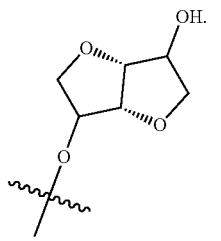
[0167] In some embodiments, R^1 is C_{2-6} alkyl substituted with —O-(acylated sugar), wherein said C_{2-6} alkyl is further optionally substituted with oxo. In some embodiments, R^1 is C_{2-6} alkyl substituted with oxo and —O-(acylated sugar). In some embodiments, R^1 is C_{3-4} cycloalkyl substituted with hydroxyl, ethynyl, or —O-(acylated sugar). In some embodiments, R^1 is C_{3-4} cycloalkyl C_{1-2} alkyl. In some embodiments, R^2 is methyl. In some embodiments, R^2 is C_{2-6} alkyl, wherein the C_{2-6} alkyl is substituted with one or two substituents independently selected from the group consisting of hydroxyl, oxo, and —O-(acylated sugar). In some embodiments, R^1 and R^2, together with the nitrogen atom to which both are attached, combine to form a 4- or 5-membered heterocyclic ring optionally substituted with ethynyl or $—(CH_2)_n—OR^A$, wherein n is 0 or 1, and R^A is hydrogen or an acylated sugar. In some embodiments, R^S is hydrogen. In another embodiment, R^3 is C_{1-6} alkyl substituted with a halogen or hydroxyl. In some embodiments, R^4 is propargyl. In some embodiments, R^4 is C_{1-6} alkyl.

[0168] In some embodiments, R^1 is C_{2-6} alkyl substituted with —O-(acylated sugar) and is optionally further substituted with oxo; R^2 is methyl; R^3 is C_{1-6} alkyl; and R^4 is propargyl. In some embodiments, R^1 is C_{2-6} alkyl substituted with isosorbide and is optionally further substituted with oxo and/or methene; R^2 is methyl; R^3 is C_{1-6} alkyl; and R^4 is propargyl. In some embodiments, R^1 is C_{2-6} alkyl substituted with —O-(acylated sugar) and is optionally further substituted with oxo. In some embodiments, R^1 is C_{2-6} alkyl substituted with —O-(acylated sugar) and further substituted with oxo.

[0169] In some embodiments, R^1 is chosen from C_2 alkyl substituted with —O-(acylated sugar) and optionally further substituted with oxo and C_4 alkyl substituted with —O-(acylated sugar) and optionally further substituted with oxo.

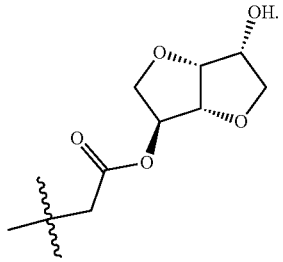
[0170] In some embodiments, R^1 is chosen from C_2 alkyl substituted with —O-(acylated sugar) and optionally further substituted with oxo. In some embodiments, R^1 is chosen from C_2 alkyl substituted with —O-(acylated sugar) and further substituted with oxo. In some embodiments, R^1 is chosen from C_4 alkyl substituted with —O-(acylated sugar) and optionally further substituted with oxo. In some embodiments, R^1 is chosen from C_4 alkyl substituted with —O-(acylated sugar) and further substituted with oxo.

[0171] In some embodiments, R^1 is C_{2-6} alkyl substituted with isosorbide and is optionally further substituted with oxo and/or methene. In some embodiments, isosorbide is chosen from groups of formula (C):

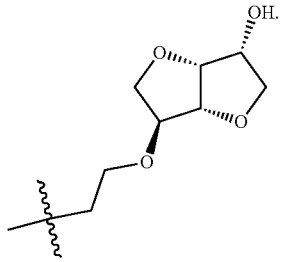


(C)

[0172] In some embodiments, R^1 is C_2 alkyl substituted with isosorbide. In some embodiments, R^1 is C_{2-6} alkyl substituted with isosorbide and further substituted with oxo and/or methene. In some embodiments, R^1 is C_{2-6} alkyl substituted with isosorbide and further substituted with oxo. In some embodiments, R^1 is C_2 alkyl substituted with isosorbide and further substituted with oxo. In some embodiments, R^1 is C_{2-6} alkyl substituted with isosorbide and further substituted with methene. In some embodiments, R^1 is C_{2-6} alkyl substituted with isosorbide and further substituted with oxo and methene. In some embodiments, R^1 is



In some embodiments, R^1 is



[0173] In some embodiments, R^1 is C_{3-4} cycloalkyl C_{1-2} alkyl. In some embodiments, R^1 is C_{3-4} cycloalkyl C_1 alkyl. In some embodiments, R^1 is cyclopropylmethyl. In some embodiments, R^1 is cyclobutylmethyl.

[0174] In some embodiments, R^2 is C_{2-6} alkyl optionally substituted with one or two hydroxyl, oxo, and —O-(acylated sugar). In some embodiments, R^2 is methyl.

[0175] In some embodiments, R^1 and R^2, together with the nitrogen atom to which both are attached, combine to form a 4- or 5-membered heterocyclic ring optionally substituted with ethynyl or $—(CH_2)_n—OR^s$ or an acylated sugar, wherein n is 0 or 1, R^s is hydrogen or an acylated sugar.

[0176] In some embodiments, R^3 is C_{1-6} alkyl optionally substituted with a halogen or hydroxyl. In some embodiments, R^3 is C_{1-6} alkyl. In some embodiments, R^3 is C_{1-6} alkyl optionally substituted with a halogen or hydroxyl. In some embodiments, R^3 is C_{1-6} alkyl optionally substituted with a halogen and/or hydroxyl. In some embodiments, R^3 is C_{1-6} alkyl optionally substituted with a halogen or hydroxyl. In some embodiments, R^3 is C_{1-6} alkyl substituted with a halogen. In some embodiments, R^3 is C_{1-6} alkyl substituted with a hydroxyl.

[0177] In some embodiments, R^3 is C_1 alkyl optionally substituted with a halogen. In some embodiments, R^3 is C_1 alkyl substituted with a halogen.

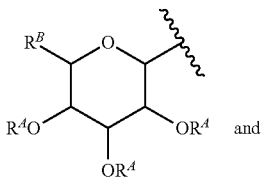
[0178] In some embodiments, R^4 is C_{1-6} alkyl or propargyl. In some embodiments, R^4 is C_1 alkyl or propargyl. In some embodiments, R^4 is propargyl.

[0179] In some embodiments, R^1 is C_{2-6} alkyl substituted with —O-(acylated sugar) and is optionally further substituted with oxo; R^2 is methyl; R^3 is C_{1-6} alkyl; and R^4 is propargyl.

[0180] In some embodiments, R^1 is C_{2-6} alkyl substituted with isosorbide and is optionally further substituted with oxo and/or methene; R^2 is methyl; R^3 is C_{1-6} alkyl; and R^4 is propargyl.

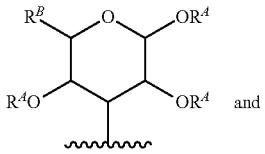
[0181] In some embodiments, R^1 is chosen from C_2 alkyl substituted with —O-(acylated sugar) and optionally further substituted with oxo and C_4 alkyl substituted with —O-(acylated sugar) and optionally further substituted with oxo; wherein the acylated sugar is chosen from groups of formula (A), groups of formula (B), and groups of formula (C):

(A)



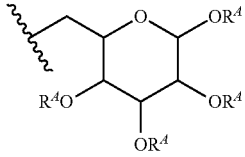
and

(B)



and

(C)



[0182] wherein

[0183] each R^A is independently H or fatty acid acyl; and

[0184] R^B is H, $—CH_3$, $—CH_2—OR^A$, $—OCH_3$, $—COOCH_3$, or —COOH.

[0185] R^2 is methyl;

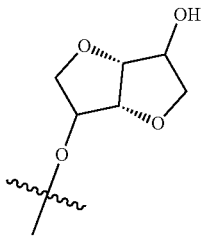
[0186] R^3 is methyl; and

[0187] R^4 is propargyl.

[0188] In some embodiments, R^1 is chosen from C_2 alkyl substituted with isosorbide and optionally further substituted with oxo and C_3 alkyl substituted with isosorbide and optionally further substituted with oxo and methene;

[0189] wherein isosorbide is chosen from groups of formula (C):

(C)



[0190] R^2 is methyl;

[0191] R^3 is methyl; and

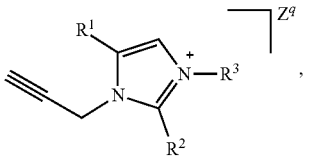
[0192] R^4 is propargyl.

[0193] In some embodiments, R^1 is C_{3-4} cycloalkyl C_{1-2} alkyl; R^2 is C_{2-6} alkyl optionally substituted with one or two hydroxyl, oxo, and —O-(acylated sugar); or R^1 and R^2, together with the nitrogen atom to which both are attached, combine to form a 4- or 5-membered heterocyclic ring optionally substituted with ethynyl or $—(CH_2)_n—OR^s$ or an

acylated sugar, wherein n is 0 or 1, R^s is hydrogen or an acylated sugar; R^3 is C_{1-6} alkyl optionally substituted with a halogen or hydroxyl; and R^4 is C_{1-6} alkyl or propargyl. In some embodiments, R^1 is C_{3-4} cycloalkyl C_1 alkyl. In some embodiments, R^2 is C_2 alkyl optionally substituted with one or two hydroxyl groups. In some embodiments, R^1 and R^2 together with the nitrogen atom to which both are attached, combine to form a 5-membered heterocyclic ring optionally substituted with ethynyl, —OH, or —CH_2OH. In some embodiments, R^3 is C_1 alkyl optionally substituted with a halogen. In some embodiments, R^4 is C_1 alkyl or propargyl.

[0194] In some embodiments, provided herein are a method of treating a subject in need thereof, the method comprising administering to the subject in need thereof a therapeutically effective amount of a compound of the invention, a pharmaceutical composition of the invention, or the compound of formula (I-a) or (I-b), where the compound of formula (I-a) is:

(I-a)



where

[0195] R^1 is H or C_{1-3} alkyl optionally substituted with hydroxyl;

[0196] R^2 is H or C_{1-3} alkyl optionally substituted with hydroxyl;

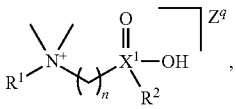
[0197] R^3 is absent or alkyl;

[0198] Z^q is absent or a pharmaceutically acceptable counterion present in the stoichiometric ratio appropriate for the compound of formula (I-a) to have no net charge,

[0199] when R^3 is absent, Z^q is absent; and

[0200] where the compound of formula (I-b) is:

(I-b)



where

[0201] n is 2, 3, or 4;

[0202] X^1 is C, S, or P;

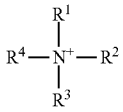
[0203] R^1 is propargyl or C_{1-6} alkyl;

[0204] R^2 is absent, hydroxyl, or oxo;

[0205] Z^q is a pharmaceutically acceptable counterion present in the stoichiometric ratio appropriate for the compound of formula (I-b) to have no net charge.

[0206] In some embodiments, provided herein are compounds consisting of a cation and a pharmaceutically acceptable counterion, wherein the cation is a structure of formula (II):

(II)



wherein

[0207] R^1 is

[0208] C_{1-6} alkyl optionally substituted with one or more oxo, hydroxyl, halogen, cyano, —COOMe, amino, methene, ethenyl, ethynyl, hydroxyphenyl, C_{3-4} cycloalkyl, —OCH_2CH_2OH, —$HNC(O)OCMe_3$, —SMe, —OMe, —$HNS(O)_2Me$, —SO_3H, $B(OH)_2$, PO_3H_2, PO_2H_2, —$P(O)(OCH_2CH_3)_2$, —P(O)(OH)(OCH_2CH_3), heteroaryl ring;

[0209] phenyl;

[0210] benzyl;

[0211] C_{3-4} heterocyclyl optionally substituted with C_1 alkyl

[0212] C_4 heterocyclylalkyl C_1 alkyl; or

[0213] C_4 cycloalkyl;

[0214] R^2 is

[0215] C_{1-6} alkyl optionally substituted with one or two hydroxyl, oxo, methene, cyano, ethynyl, —HNC(O)H, or —C≡C—CH_2OH; or

[0216] —$HN(CH_2)_3C(O)OH$;

[0217] or R^1 and R^2, together with the nitrogen atom to which both are attached and optionally one or more additional heteroatoms, combine to form a 4-8 membered mono- or bi-cyclic heterocycle optionally substituted with ethynyl, trifluoromethyl, —CH_2Ph, —OH, or —(CH_2)OH;

[0218] R^3 is methyl or propargyl; and

[0219] R^4 is methyl or propargyl,

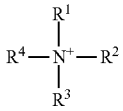
[0220] with the proviso that

[0221] (1) when two of R^1, R^2, R^3, and R^4 are methyl and one of the other two of R^1, R^2, R^3, and R^4 is propargyl, then the other of R^1, R^2, R^3, and R^4 is not methyl, a monohalomethyl, —CH_2CH_2OH, —COOH, —$(CH_2)_4C(O)OH$, or —$CH_2C(CH_2)CN$; and

[0222] (2) when two of R^1, R^2, R^3, and R^4 are methyl and one of the other two of R^1, R^2, R^3, and R^4 is —CH_2CH_2OH or —$CH_2C(O)OH$, then the other of R^1, R^2, R^3, and R^4 is not a monohalomethyl.

[0223] In some embodiments, provided herein are compounds consisting of a cation and a pharmaceutically acceptable counterion, wherein the cation is a structure of formula (III):

(III)



wherein

[0224] R^1 is

[0225] C_{1-6} alkyl optionally substituted with one or more oxo, hydroxyl, halogen, cyano, —COOMe, —COOH, methene, ethenyl, ethynyl, C_{3-4}cycloalkyl, —OCH_2CH_2OH, —SMe, —OMe, —$HNS(O)_2Me$,

—P(O) $(OCH_2CH_3)_2$, —P(O)(OH)(OCH_2CH_3), or 5-membered heteroaryl ring;

[0226] R^2 is

[0227] C_{1-6} alkyl optionally substituted with one or two hydroxyl, oxo, methene, cyano, ethynyl, —HNC(O)H, or —C≡C—CH_2OH; or

[0228] —$HN(CH_2)_3C(O)OH$;

[0229] or R^1 and R^2, together with the nitrogen atom to which both are attached and optionally one or more additional heteroatoms, combine to form a 4-8 membered mono- or bi-cyclic heterocycle optionally substituted with ethynyl, —OH, or —$(CH_2)OH$;

[0230] R^3 is C_{1-6} alkyl optionally substituted with a halogen, hydroxyl, or ethynyl; and

[0231] R^4 is C_{1-6} alkyl or propargyl,

with the proviso that

[0232] (1) when two of R^1, R^2, R^3, and R^4 are methyl and one of the other two of R^1, R^2, R^3, and R^4 is propargyl, then the other of R^1, R^2, R^3, and R^4 is not methyl, a monohalomethyl, —CH_2CH_2OH, —COOH, —$(CH_2)_4C(O)OH$, or —$CH_2C(CH_2)CN$; and

[0233] (2) when two of R^1, R^2, R^3, and R^4 are methyl and one of the other two of R^1, R^2, R^3, and R^4 is —CH_2CH_2OH or —$CH_2C(O)OH$, then the other of R^1, R^2, R^3, and R^4 is not a monohalomethyl.

[0234] In some embodiments, in cations of formula (II) or (III), R^2, R^3, and R^4 are methyl.

[0235] Production of trimethylamine by CutC may be inhibited using the compounds described above. Accordingly, a method of inhibiting a CutC choline lyase-mediated conversion of choline to trimethylamine includes contacting the compound described above with the CutC choline lyase.

[0236] Inhibition of CutC may lead to the modulation of trimethylaminuria markers. Accordingly, a method of modulating a trimethylamine marker in a subject in need thereof includes administering to the subject in need thereof a therapeutically effective amount of the compound described above (e.g., as a pharmaceutical composition). The trimethylaminuria marker can be, e.g., trimethylamine and/or trimethylamine oxide levels in the subject's blood, plasma, serum, or urine. The amount of the trimethylaminuria marker can be reduced in accordance with the methods of the disclosure.

[0237] Trimethylaminuria and the associated cardiovascular disorders can be treated using the compounds described above. Accordingly, a method of treating a subject in need thereof includes administering to the subject in need thereof a therapeutically effective amount of the compound described above. For example, a method of treating or preventing a disease associated with trimethylaminuria in a subject in need thereof includes administering a therapeutically effective amount of the compound described above (e.g., as a pharmaceutical composition). The disease associated with trimethylaminuria may be, e.g., a cardiovascular disease, reduced or impaired kidney function, kidney disease, chronic kidney disease, end-stage renal disease, or diabetes mellitus. The cardiovascular disease may be, e.g., angina, arrhythmia, atherosclerosis, cardiomyopathy, congestive heart failure, coronary artery disease, carotid artery disease, endocarditis, coronary thrombosis, myocardial infarction, high blood pressure/hypertension, hypercholesterolemia, hyperlipidemia, mitral valve prolapse, peripheral artery disease, or stroke.

[0238] In some embodiments, provided herein is a method of modulating a trimethylaminuria marker in a subject in need thereof, the method comprising administering to the subject in need thereof a therapeutically effective amount of at least one of the compounds or pharmaceutical compositions disclosed herein. In some embodiments, the trimethylaminuria marker is the trimethylamine and/or trimethylamine oxide level in the subject's blood, plasma, serum, or urine.

[0239] In some embodiments, provided herein is a method of treating or preventing a disease associated with elevated levels of trimethylamine (TMA) or trimethylamine N-oxide (TMAO), a decreased rate of conversion of TMA to TMAO, or a high ratio of TMA to TMAO in a subject in need thereof, the method comprising administering a therapeutically effective amount of at least one of the compounds or pharmaceutical compositions disclosed herein to the subject. In some embodiments, the method further comprises detecting the presence of one or more genetic variants of the FMO3 gene of the subject in need before the administering step. In some embodiments, the disease associated with elevated levels of TMA or TMAO, a decreased rate of conversion of TMA to TMAO, or a high ratio of TMA to TMAO is a cardiovascular disease, reduced or impaired kidney function, kidney disease, chronic kidney disease, end-stage renal disease, or diabetes mellitus. In some embodiments, the cardiovascular disease is angina, arrhythmia, atherosclerosis, cardiomyopathy, congestive heart failure, coronary artery disease, carotid artery disease, endocarditis, coronary thrombosis, myocardial infarction, high blood pressure/hypertension, hypercholesterolemia, hyperlipidemia, mitral valve prolapse, peripheral artery disease, or stroke.

[0240] In some embodiments, provided herein is a method of inhibiting a CutC choline lyase-mediated conversion of choline to trimethylamine, the method comprising contacting at least one of the compounds or pharmaceutical compositions disclosed herein with the CutC choline lyase.

[0241] In some embodiments, provided herein is a method of inhibiting a CntA carnitine monooxygenase-mediated conversion of carnitine to trimethylamine, the method comprising contacting at least one of the compounds or pharmaceutical compositions disclosed herein with the CntA carnitine monooxygenase.

[0242] In some embodiments, provided herein is a method of inhibiting a betaine reductase-mediated conversion of betaine or gamma-butyrobetaine to trimethylamine, the method comprising contacting at least one of the compounds or pharmaceutical compositions disclosed herein with the betaine reductase.

[0243] In some embodiments, provided herein is a method of treating a subject in need of treatment for trimethylaminuria comprising contacting bacteria in vivo with a therapeutically effective amount of at least one of the compounds or pharmaceutical compositions disclosed herein to the subject. In some embodiments, the bacteria are localized in the colon of the subject.

[0244] In some embodiments, the present disclosure provides a method of modulating a trimethylamine marker in a subject in need thereof, the method consisting of administering to the subject in need thereof a therapeutically effective amount of at least one compound of the present disclosure or a pharmaceutical composition of the present disclosure.

[0245] In some embodiments, the trimethylaminuria marker is the trimethylamine and/or trimethylamine oxide levels in the subject's blood, plasma, serum, or urine.

[0246] In some embodiments, the present disclosure provides a method of treating or preventing a disease associated with trimethylaminuria in a subject in need thereof, the method comprising administering a therapeutically effective amount of at least one pharmaceutically acceptable salt of at least one compound of the present disclosure or a pharmaceutical composition of the present disclosure to the subject.

[0247] The compounds disclosed herein may be formulated into pharmaceutical compositions for administration to human subjects in a biologically compatible form suitable for administration in vivo. Pharmaceutical compositions typically include a compound as described herein and a physiologically acceptable excipient (e.g., a pharmaceutically acceptable excipient).

[0248] The compound described herein can also be used in the form of the free acid/base, in the form of salts, zwitterions, or as solvates. All forms are within the scope of the disclosure. The compounds, salts, zwitterions, solvates, or pharmaceutical compositions thereof, may be administered to a subject in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds described herein may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump, or transdermal administration, and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal, and topical modes of administration. Parenteral administration may be by continuous infusion over a selected period of time.

[0249] For human use, a compound disclosed herein can be administered alone or in admixture with a pharmaceutical carrier selected regarding the intended route of administration and standard pharmaceutical practice. Pharmaceutical compositions for use in accordance with the present disclosure thus can be formulated in a conventional manner using one or more physiologically acceptable carriers having excipients and auxiliaries that facilitate processing of compounds disclosed herein into preparations which can be used pharmaceutically.

[0250] This disclosure also includes pharmaceutical compositions which can contain one or more physiologically acceptable carriers. In making the pharmaceutical compositions of the disclosure, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semisolid, or liquid material (e.g., normal saline), which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, and soft and hard gelatin capsules. As is known in the art, the type of diluent can vary depending upon the intended route of administration. The resulting compositions can include additional agents, e.g., preservatives.

[0251] The excipient or carrier is selected on the basis of the mode and route of administration. Suitable pharmaceutical carriers, as well as pharmaceutical necessities for use in pharmaceutical formulations, are described in Remington: The Science and Practice of Pharmacy, 21st Ed., Gennaro, Ed., Lippencott Williams & Wilkins (2005), a well-known reference text in this field, and in the USP/NF (United States Pharmacopeia and the National Formulary). Examples of suitable excipients are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include lubricating agents, e.g., talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents, e.g., methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. Other exemplary excipients are described in Handbook of Pharmaceutical Excipients, 6th Edition, Rowe et al., Eds., Pharmaceutical Press (2009).

[0252] These pharmaceutical compositions can be manufactured in a conventional manner, e.g., by conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Methods well known in the art for making formulations are found, for example, in Remington: The Science and Practice of Pharmacy, 21st Ed., Gennaro, Ed., Lippencott Williams & Wilkins (2005), and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York. Proper formulation is dependent upon the route of administration chosen. The formulation and preparation of such compositions is well-known to those skilled in the art of pharmaceutical formulation. In preparing a formulation, the compounds can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, e.g., about 40 mesh.

[0253] The dosage of the compound used in the methods described herein, or pharmaceutically acceptable salts or prodrugs thereof, or pharmaceutical compositions thereof, can vary depending on many factors, e.g., the pharmacodynamic properties of the compound; the mode of administration; the age, health, and weight of the recipient; the nature and extent of the symptoms; the frequency of the treatment, and the type of concurrent treatment, if any; and the clearance rate of the compound in the subject to be treated. One of skill in the art can determine the appropriate dosage based on the above factors. The compounds used in the methods described herein may be administered initially in a suitable dosage that may be adjusted as required, depending on the clinical response. In general, a suitable daily dose of a compound disclosed herein will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above.

[0254] A compound disclosed herein may be administered to the subject in a single dose or in multiple doses. When multiple doses are administered, the doses may be separated from one another by, for example, 1-24 hours, 1-7 days, or 1-4 weeks. The compound may be administered according to a schedule, or the compound may be administered without a predetermined schedule. It is to be understood that, for any particular subject, specific dosage regimes should be adjusted over time according to the individual need and the

professional judgment of the person administering or supervising the administration of the compositions.

[0255] The compounds may be provided in a dosage form. In some embodiments, the unit dosage form may be an oral unit dosage form (e.g., a tablet, capsule, suspension, liquid solution, powder, crystals, lozenge, sachet, cachet, elixir, syrup, and the like) or a food product serving (e.g., the active agents may be included as food additives or dietary ingredients). In certain embodiments, the dosage form is designed for administration of at least one compound disclosed herein, where the total amount of an administered compound is from 0.1 g to 10 g (e.g., 0.5 g to 9 g, 0.5 g to 8 g, 0.5 g to 7 g, 0.5 g to 6 g, 0.5 g to 5 g, 0.5 g to 1 g, 0.5 g to 1.5 g, 0.5 g to 2 g, 0.5 g to 2.5 g, 1 g to 1.5 g, 1 g to 2 g, 1 g to 2.5 g, 1.5 g to 2 g, 1.5 g to 2.5 g, or 2 g to 2.5 g). In other embodiments, the compound is consumed at a rate of 0.1 g to 10 g per day (e.g., 0.5 g to 9 g, 0.5 g to 8 g, 0.5 g to 7 g, 0.5 g to 6 g, 0.5 g to 5 g, 0.5 g to 1 g per day, 0.5 g to 1.5 g per day, 0.5 g to 2 g per day, 0.5 g to 2.5 g per day, 1 g to 1.5 g per day, 1 g to 2 g per day, 1 g to 2.5 g per day, 1.5 g to 2 g per day, 1.5 g to 2.5 g per day, or 2 g to 2.5 g per day) or more. The attending physician ultimately will decide the appropriate amount and dosage regimen, an effective amount of the compound disclosed herein may be, for example, a total daily dosage of, e.g., between 0.5 g and 5 g (e.g., 0.5 to 2.5 g) of any of the compound described herein. Alternatively, the dosage amount can be calculated using the body weight of the subject. When daily dosages exceed 5 g/day, the dosage of the compound may be divided across two or three daily administration events.

[0256] In the methods of the disclosure, the time period during which multiple doses of a compound disclosed herein are administered to a subject can vary. For example, in some embodiments doses of the compounds are administered to a subject over a time period that is 1-7 days; 1-12 weeks; or 1-3 months. In other embodiments, the compounds are administered to the subject over a time period that is, for example, 4-11 months or 1-30 years. In yet other embodiments, the compounds disclosed herein are administered to a subject at the onset of symptoms. In any of these embodiments, the amount of the compound that is administered may vary during the time period of administration. When a compound is administered daily, administration may occur, for example, 1, 2, 3, or 4 times per day.

[0257] A compound described herein may be administered to a subject with a pharmaceutically acceptable diluent, carrier, or excipient, in unit dosage form. Conventional pharmaceutical practice may be employed to provide suitable formulations or compositions to administer the compound to subjects suffering from a disorder. Administration may begin before the subject is symptomatic.

[0258] Exemplary routes of administration of the compounds disclosed herein or pharmaceutical compositions thereof, used in the present disclosure include oral, sublingual, buccal, transdermal, intradermal, intramuscular, parenteral, intravenous, intra-arterial, intracranial, subcutaneous, intraorbital, intraventricular, intraspinal, intraperitoneal, intranasal, inhalation, and topical administration. The compounds desirably are administered with a physiologically acceptable carrier (e.g., a pharmaceutically acceptable carrier). Pharmaceutical formulations of the compounds described herein formulated for treatment of the disorders described herein are also part of the present disclosure. In some embodiments, the compounds disclosed herein are administered to a subject orally. In some embodiments, the compounds disclosed herein are administered to a subject topically.

[0259] The pharmaceutical compositions contemplated by the disclosure include those formulated for oral administration ("oral dosage forms"). Oral dosage forms can be, for example, in the form of tablets, capsules, a liquid solution or suspension, a powder, or liquid or solid crystals, which contain the active ingredient(s) in a mixture with physiologically acceptable excipients (e.g., pharmaceutically acceptable excipients). These excipients may be, for example, inert diluents or fillers (e.g., sucrose, sorbitol, sugar, mannitol, microcrystalline cellulose, starches including potato starch, calcium carbonate, sodium chloride, lactose, calcium phosphate, calcium sulfate, or sodium phosphate); granulating and disintegrating agents (e.g., cellulose derivatives including microcrystalline cellulose, starches including potato starch, croscarmellose sodium, alginates, or alginic acid); binding agents (e.g., sucrose, glucose, sorbitol, acacia, alginic acid, sodium alginate, gelatin, starch, pregelatinized starch, microcrystalline cellulose, magnesium aluminum silicate, carboxymethylcellulose sodium, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, polyvinylpyrrolidone, or polyethylene glycol); and lubricating agents, glidants, and antiadhesives (e.g., magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, or talc). Other physiologically acceptable excipients (e.g., pharmaceutically acceptable excipients) can be colorants, flavoring agents, plasticizers, humectants, buffering agents, and the like.

[0260] Formulations for oral administration may also be presented as chewable tablets, as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent (e.g., potato starch, lactose, microcrystalline cellulose, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules where the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil. Powders, granulates, and pellets may be prepared using the ingredients mentioned above under tablets and capsules in a conventional manner using, e.g., a mixer, a fluid bed apparatus or a spray drying equipment.

[0261] Controlled release compositions for oral use may be constructed to release the active drug by controlling the dissolution and/or the diffusion of the active drug substance. Any of a number of strategies can be pursued in order to obtain controlled release and the targeted plasma concentration versus time profile. In one example, controlled release is obtained by appropriate selection of various formulation parameters and ingredients, including, e.g., various types of controlled release compositions and coatings. Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, microspheres, nanoparticles, patches, and liposomes. In certain embodiments, compositions include biodegradable, pH, and/or temperature-sensitive polymer coatings.

[0262] Dissolution or diffusion-controlled release can be achieved by appropriate coating of a tablet, capsule, pellet, or granulate formulation of compounds, or by incorporating the compound into an appropriate matrix. A controlled release coating may include one or more of the coating substances mentioned above and/or, e.g., shellac, beeswax, glycowax, castor wax, carnauba wax, stearyl alcohol, glyceryl monostearate, glyceryl distearate, glycerol palmitoste-

arate, ethylcellulose, acrylic resins, dl-polylactic acid, cellulose acetate butyrate, polyvinyl chloride, polyvinyl acetate, vinyl pyrrolidone, polyethylene, polymethacrylate, methylmethacrylate, 2-hydroxymethacrylate, methacrylate hydrogels, 1,3 butylene glycol, ethylene glycol methacrylate, and/or polyethylene glycols. In a controlled release matrix formulation, the matrix material may also include, e.g., hydrated methylcellulose, carnauba wax and stearyl alcohol, carbopol 934, silicone, glyceryl tristearate, methyl acrylate-methyl methacrylate, polyvinyl chloride, polyethylene, and/or halogenated fluorocarbon.

[0263] The liquid forms in which the compounds and compositions of the present disclosure can be incorporated for administration orally include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils, e.g., cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

[0264] Dosages for buccal or sublingual administration typically are 0.1 to 500 mg per single dose as required. In practice, the physician determines the actual dosing regimen which is most suitable for an individual subject, and the dosage varies with the age, weight, and response of the particular subject. The above dosages are exemplary of the average case, but individual instances exist where higher or lower dosages are merited, and such are within the scope of this disclosure.

[0265] For buccal administration, the compositions may take the form of tablets, lozenges, etc. formulated in a conventional manner. Liquid drug formulations suitable for use with nebulizers and liquid spray devices and electrohydrodynamic (EHD) aerosol devices will typically include a compound disclosed herein with a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutically acceptable carrier is a liquid, e.g., alcohol, water, polyethylene glycol, or a perfluorocarbon. Optionally, another material may be added to alter the aerosol properties of the solution or suspension of compounds disclosed herein. Desirably, this material is liquid, e.g., an alcohol, glycol, polyglycol, or a fatty acid. Other methods of formulating liquid drug solutions or suspension suitable for use in aerosol devices are known to those of skill in the art (see, e.g., U.S. Pat. Nos. 5,112,598 and 5,556,611, each of which is herein incorporated by reference).

[0266] The compounds may also be formulated for nasal administration. Compositions for nasal administration also may conveniently be formulated as aerosols, drops, gels, and powders. The formulations may be provided in a single or multidose form. In the case of a dropper or pipette, dosing may be achieved by the subject administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved, for example, by means of a metering atomizing spray pump.

[0267] The compounds may further be formulated for aerosol administration, particularly to the respiratory tract by inhalation and including intranasal administration. The compounds for nasal or inhalation administration will generally have a small particle size for example on the order of five (5) microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant, e.g., a chlorofluorocarbon (CFC), for example, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, or carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant, e.g., lecithin. The dose of drug may be controlled by a metered valve. Alternatively, the active ingredients may be provided in a form of a dry powder, e.g., a powder mix of the compound in a suitable powder base, e.g., lactose, starch, and starch derivatives, e.g., hydroxypropylmethyl cellulose, and polyvinylpyrrolidine (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of e.g., gelatin or blister packs from which the powder may be administered by means of an inhaler.

[0268] Aerosol formulations typically include a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device, e.g., a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant, which can be a compressed gas, e.g., compressed air or an organic propellant, e.g., fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer.

[0269] The compounds described herein for use in the methods of the disclosure can be administered in a pharmaceutically acceptable parenteral (e.g., intravenous or intramuscular) formulation as described herein. The pharmaceutical formulation may also be administered parenterally (intravenous, intramuscular, subcutaneous or the like) in dosage forms or formulations containing conventional, non-toxic pharmaceutically acceptable carriers and adjuvants. In particular, formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. For example, to prepare such a composition, the compounds disclosed herein may be dissolved or suspended in a parenterally acceptable liquid vehicle. Among acceptable vehicles and solvents that may be employed are water, water adjusted to a suitable pH by addition of an appropriate amount of hydrochloric acid, sodium hydroxide or a suitable buffer, 1,3-butanediol, Ringer's solution and isotonic sodium chloride solution. The aqueous formulation may also contain one or more preservatives, for example, methyl, ethyl or n-propyl p-hydroxybenzoate. Additional information regarding parenteral formulations can be found, for example, in the United States Pharmacopeia-National Formulary (USP-NF), herein incorporated by reference.

[0270] The parenteral formulation can be any of the five general types of preparations identified by the USP-NF as suitable for parenteral administration:

[0271] (1) "Drug Injection:" a liquid preparation that is a drug substance (e.g., a compound disclosed herein or a solution thereof);

[0272] (2) "Drug for Injection:" the drug substance (e.g., a compound disclosed herein) as a dry solid that will be combined with the appropriate sterile vehicle for parenteral administration as a drug injection;

[0273] (3) "Drug Injectable Emulsion:" a liquid preparation of the drug substance (e.g., a compound disclosed herein) that is dissolved or dispersed in a suitable emulsion medium;

[0274] (4) "Drug Injectable Suspension:" a liquid preparation of the drug substance (e.g., a compound disclosed herein) suspended in a suitable liquid medium; and

[0275] (5) "Drug for Injectable Suspension:" the drug substance (e.g., a compound disclosed herein) as a dry solid that will be combined with the appropriate sterile vehicle for parenteral administration as a drug injectable suspension.

[0276] Exemplary formulations for parenteral administration include solutions of the compounds prepared in water suitably mixed with a surfactant, e.g., hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington: The Science and Practice of Pharmacy, 21st Ed., Gennaro, Ed., Lippencott Williams & Wilkins (2005) and in The United States Pharmacopeia: The National Formulary (USP 36 NF31), published in 2013.

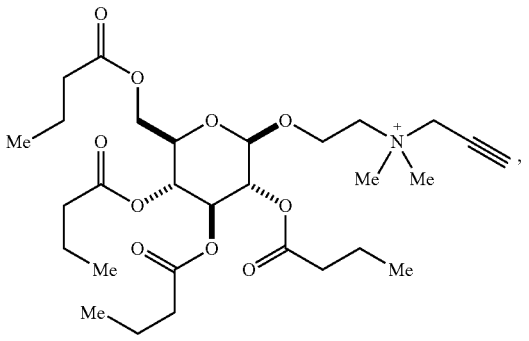
[0277] Formulations for parenteral administration may, for example, contain excipients, sterile water, or saline, polyalkylene glycols, e.g., polyethylene glycol, oils of vegetable origin, or hydrogenated napthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds or biologically active agents within the compounds. Other potentially useful parenteral delivery systems for compounds include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel.

[0278] The parenteral formulation can be formulated for prompt release or for sustained/extended release of the compound. Exemplary formulations for parenteral release of the compound include: aqueous solutions, powders for reconstitution, cosolvent solutions, oil/water emulsions, suspensions, oil-based solutions, liposomes, microspheres, and polymeric gels.

[0279] Non-limiting embodiments of the present disclosure include the following:

1. A compound consisting of a cation and a pharmaceutically acceptable counterion, wherein the cation is chosen from:

1



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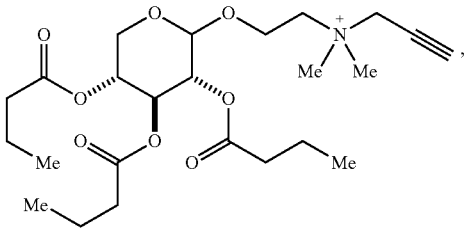

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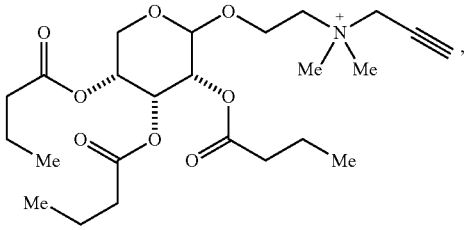

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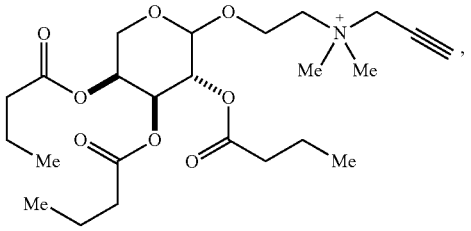

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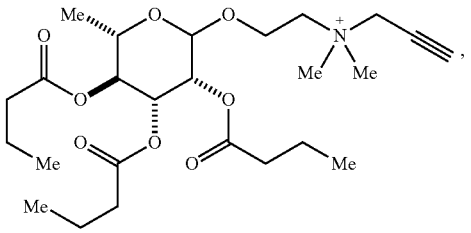

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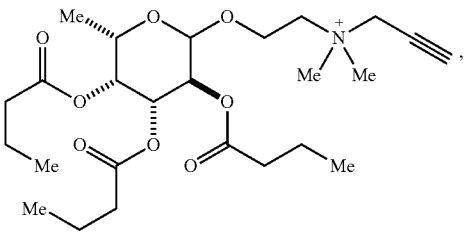

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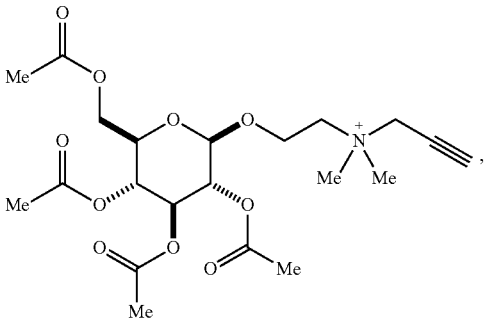

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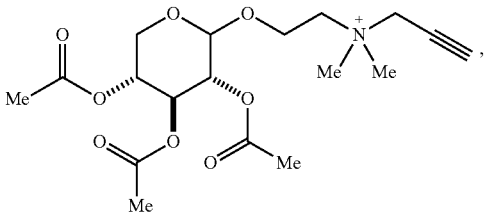

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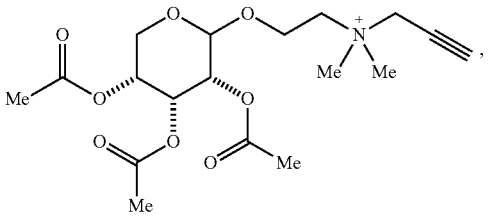

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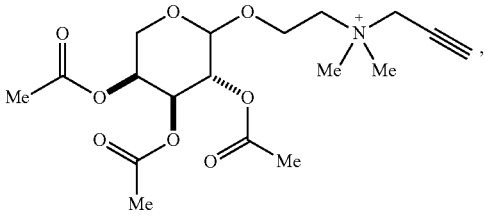

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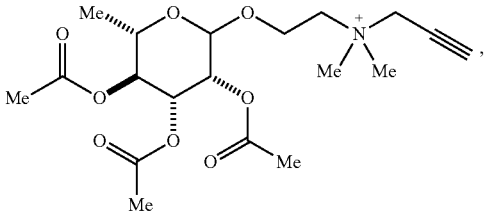

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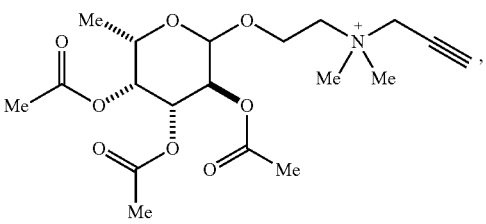

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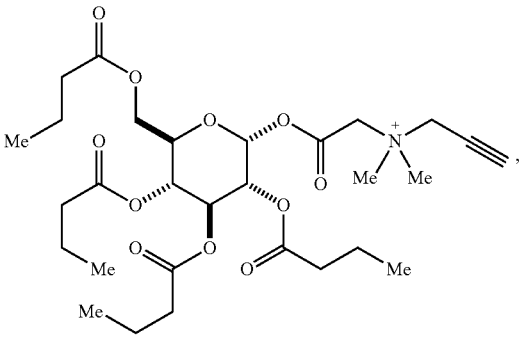

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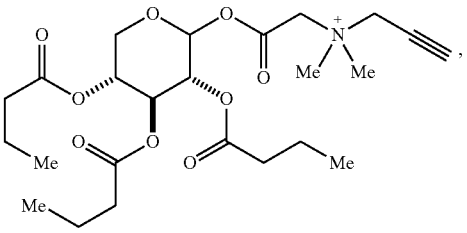

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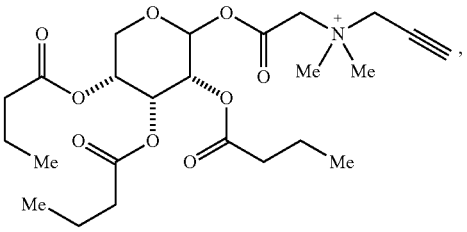

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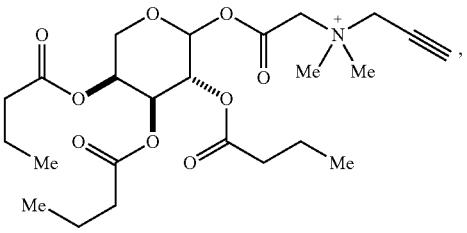

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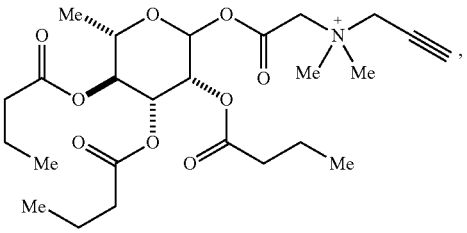

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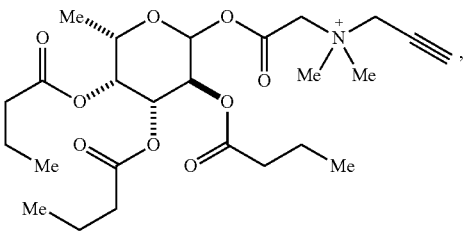

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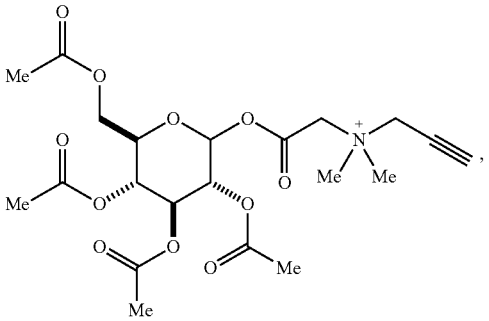

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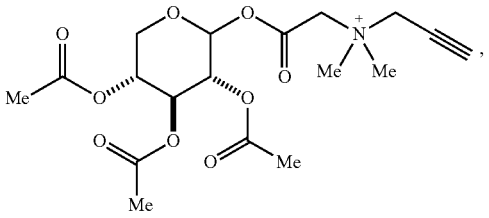

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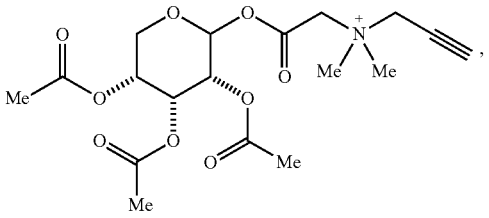

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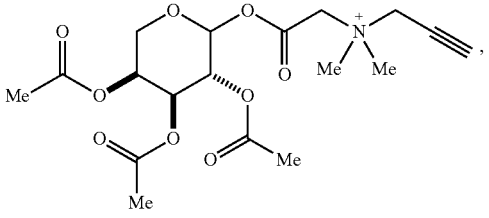

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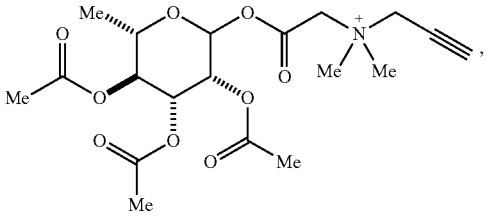

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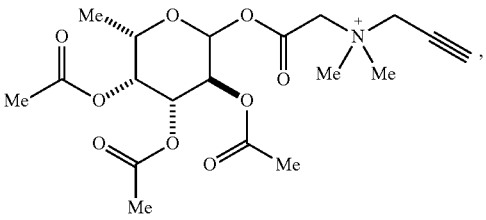

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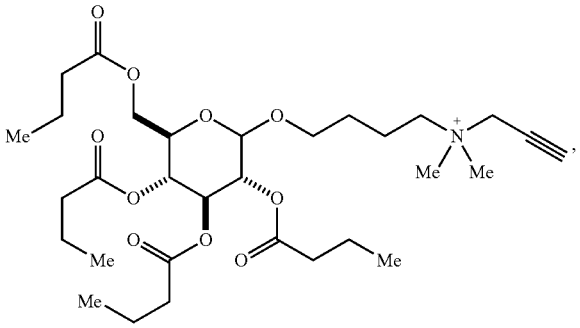

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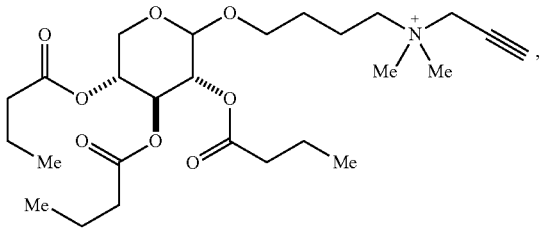

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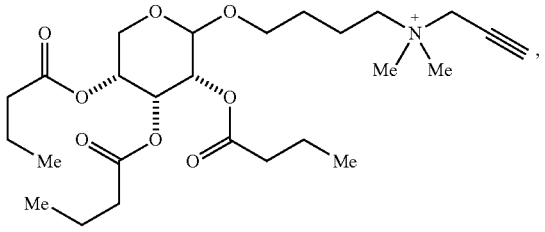

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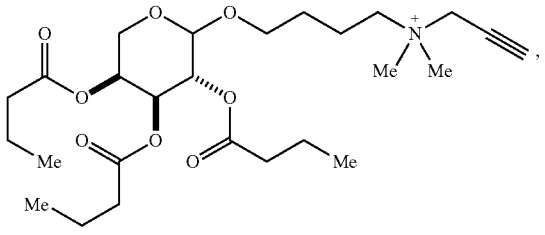

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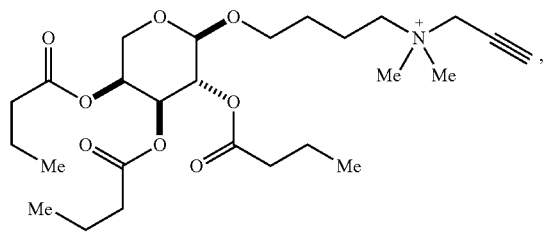

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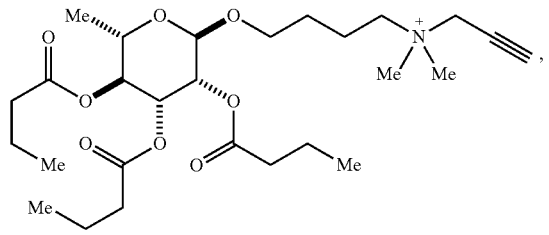

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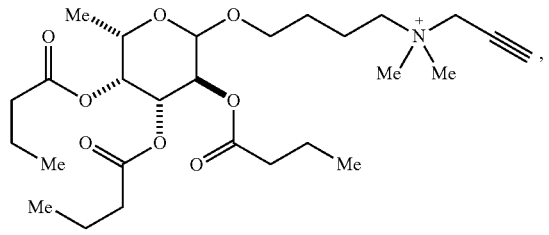

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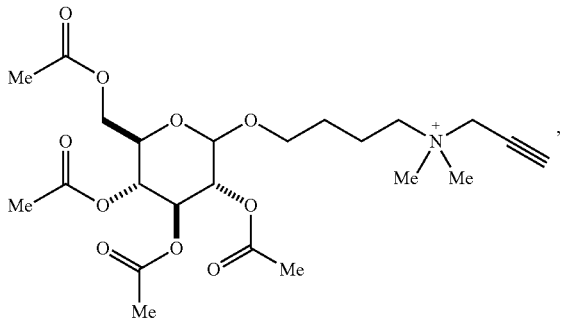

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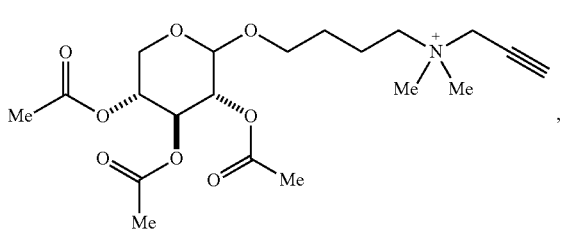

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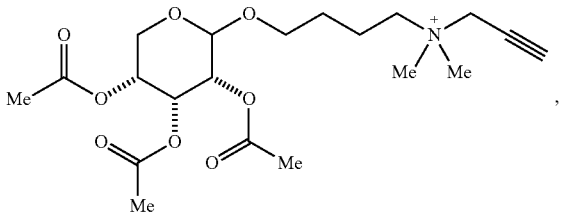

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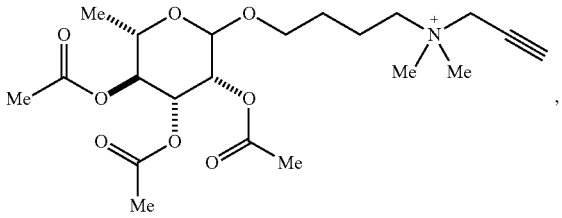

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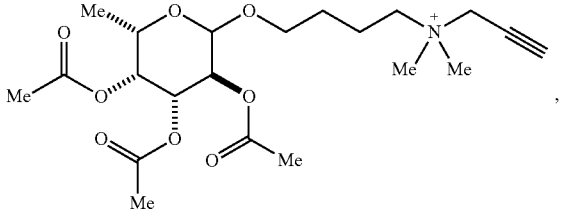

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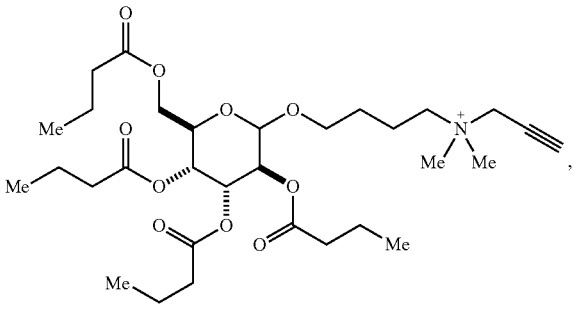

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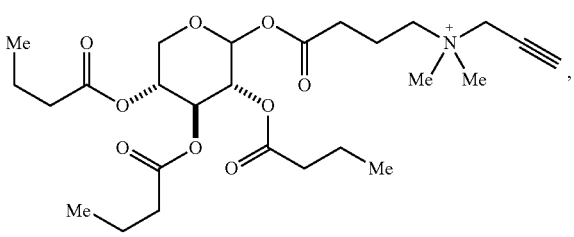

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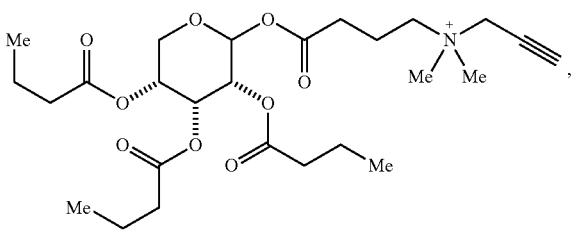

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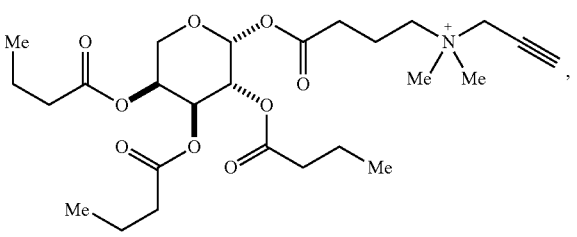

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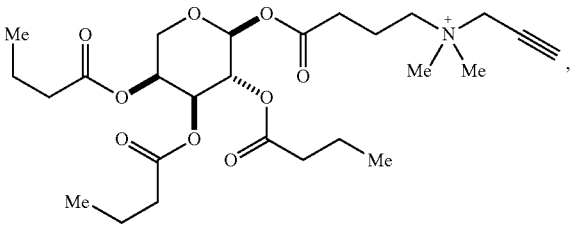

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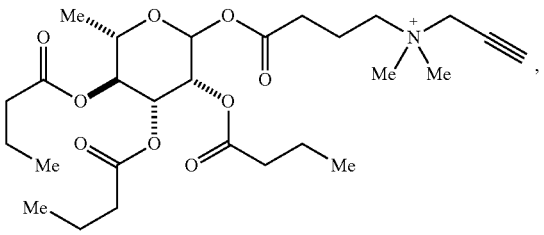

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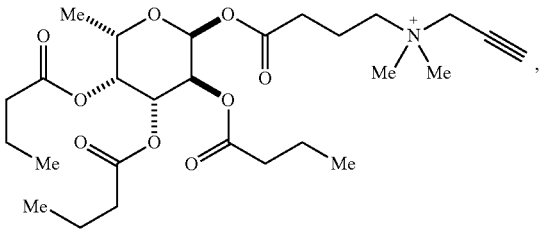

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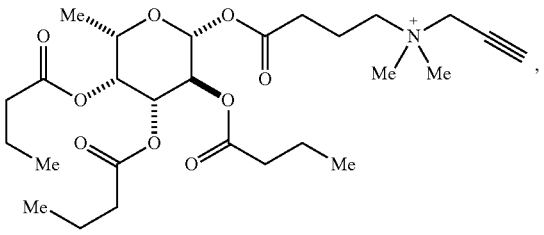

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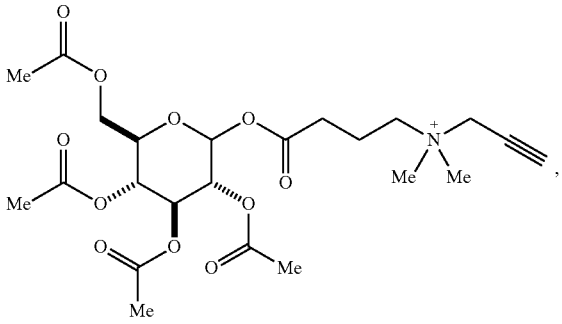

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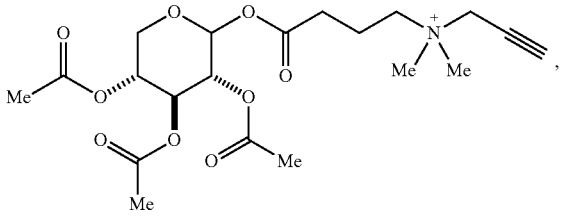

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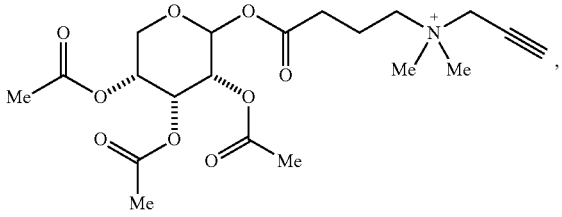

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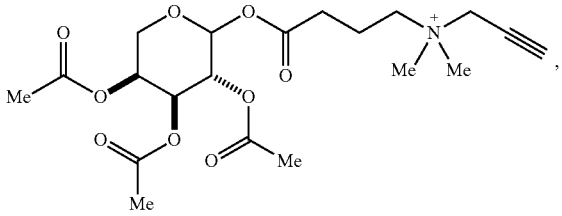

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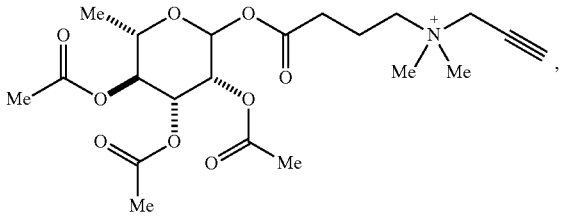

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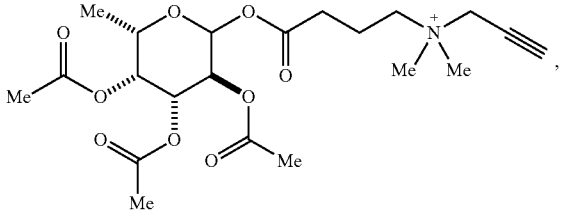

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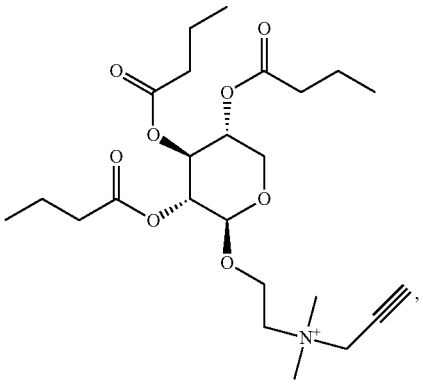

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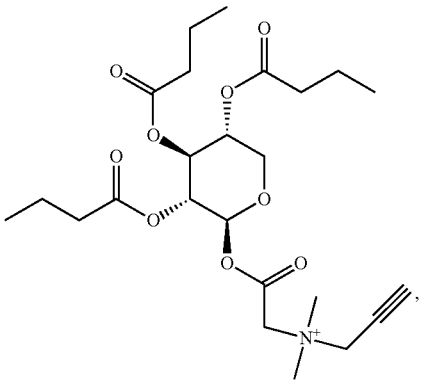

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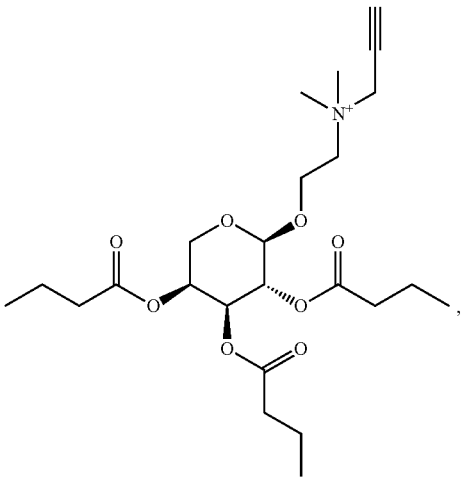

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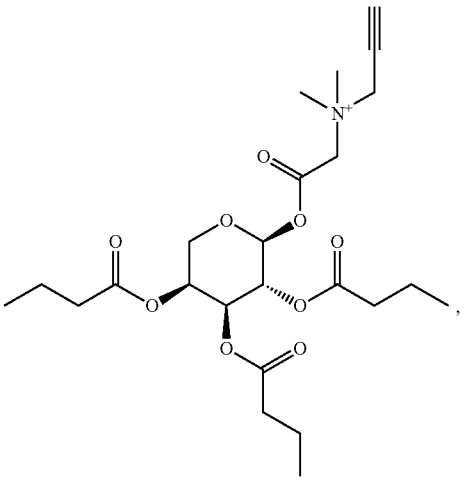

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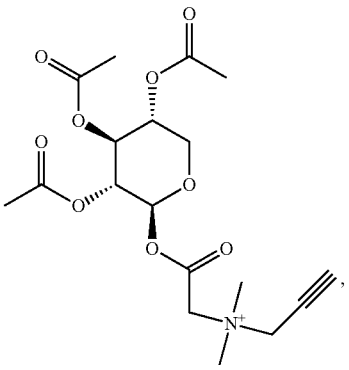

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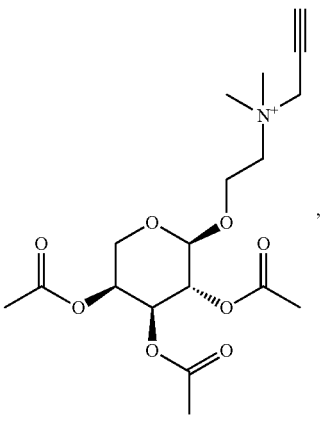

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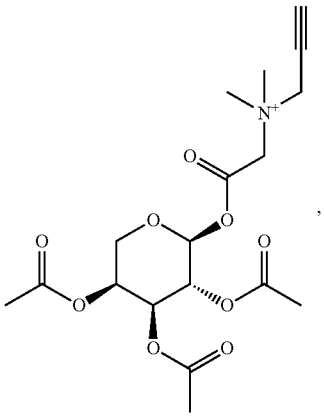

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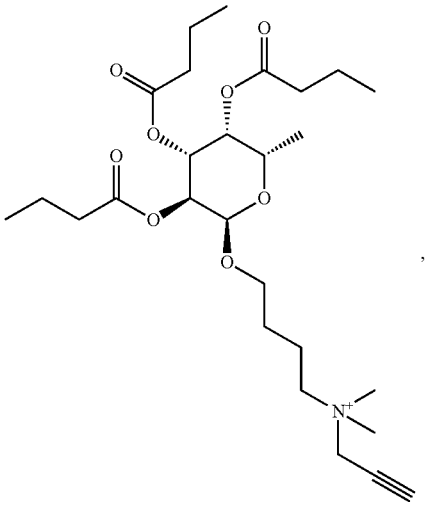

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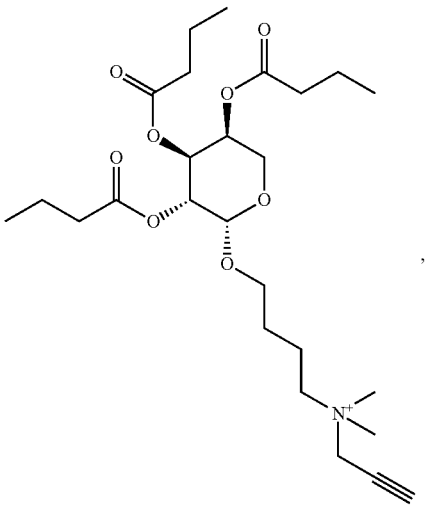

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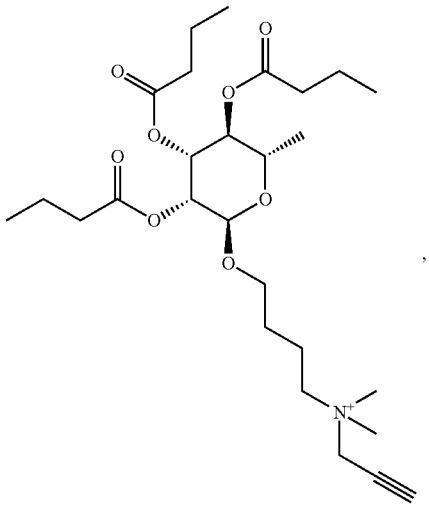

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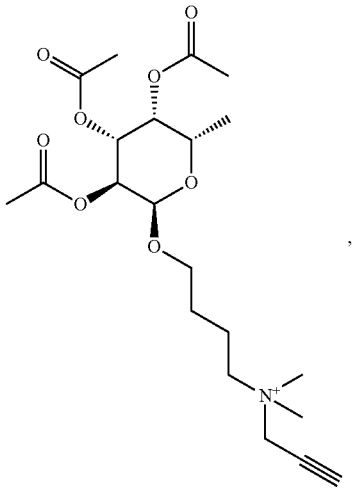

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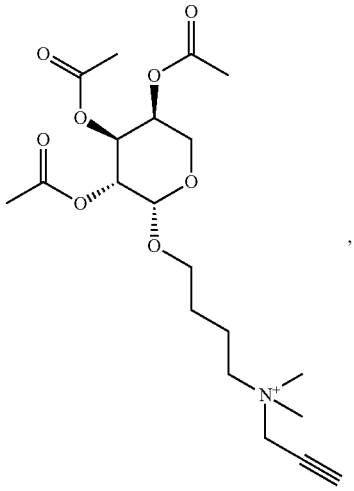

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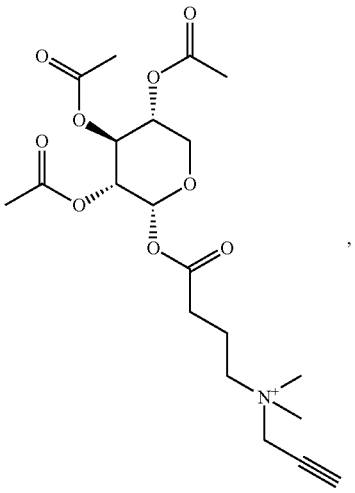

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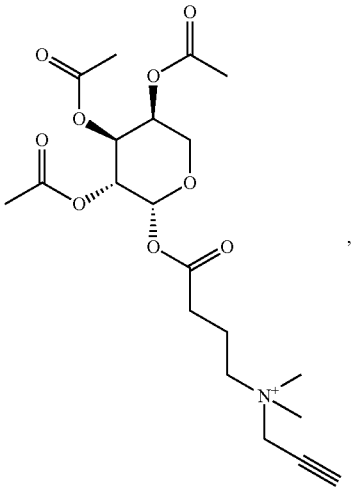

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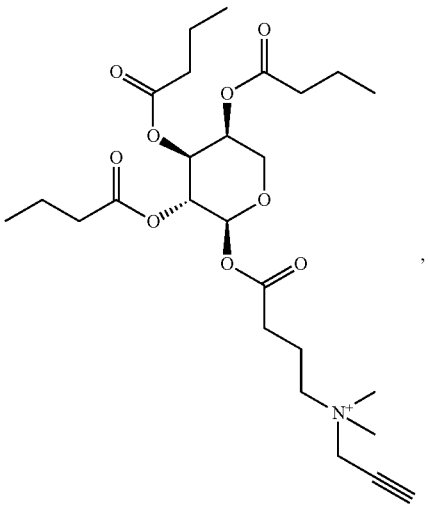

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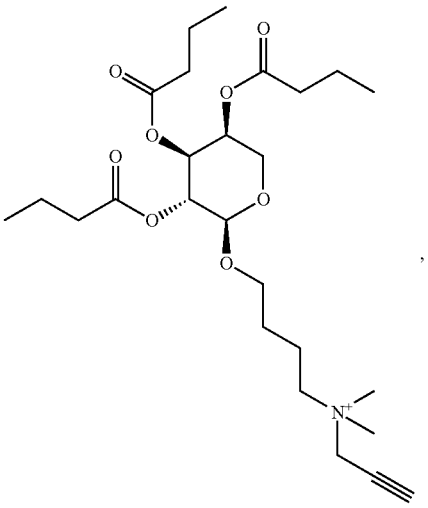

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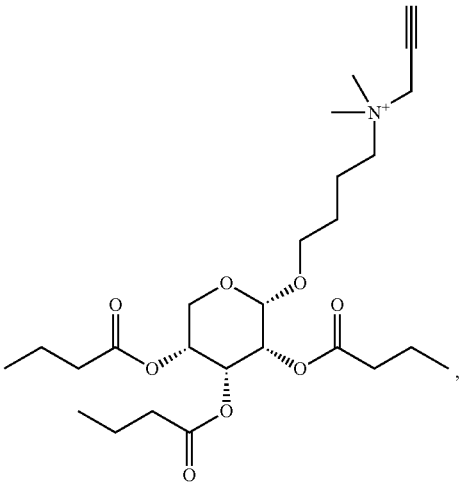

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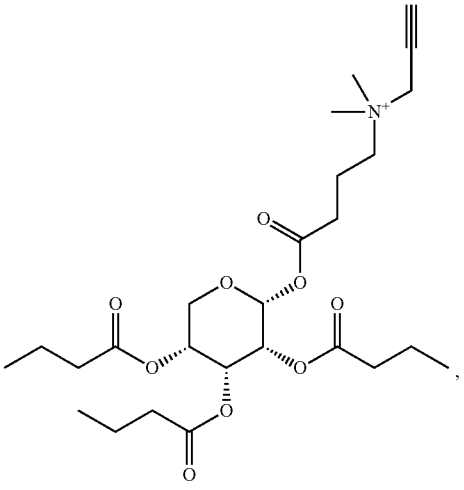

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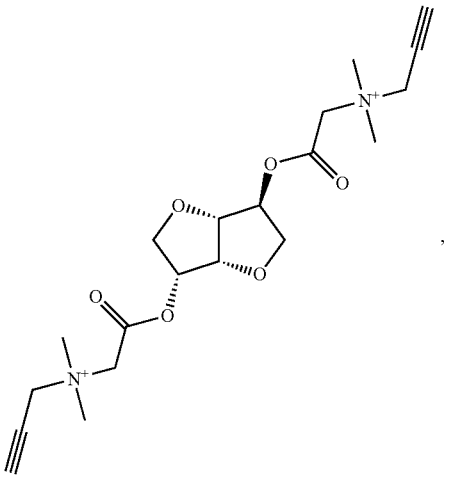

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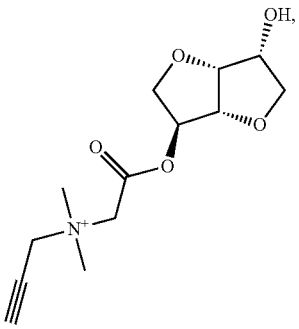

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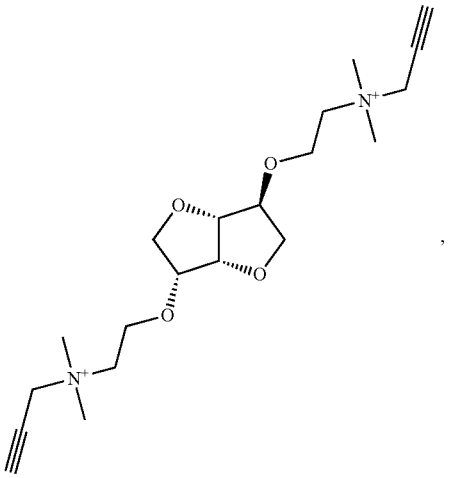

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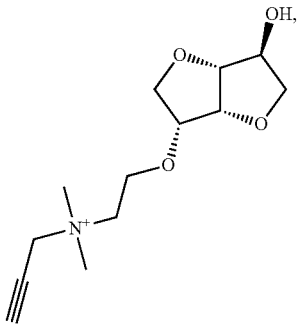

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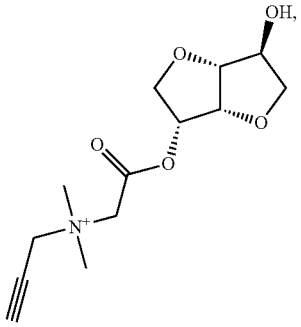

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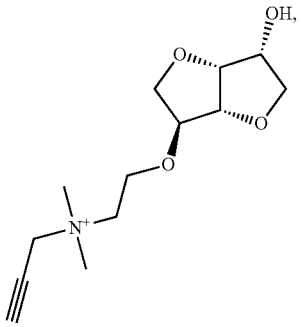

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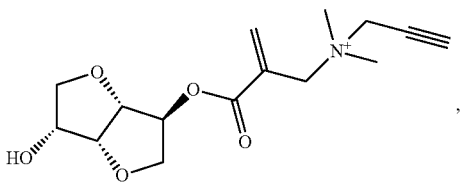

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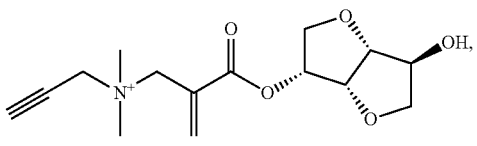

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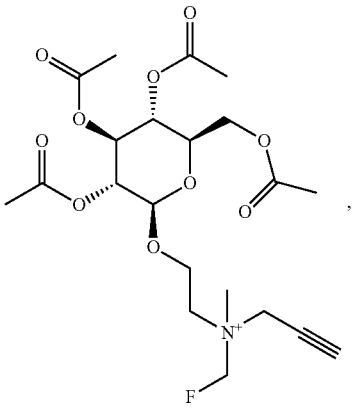

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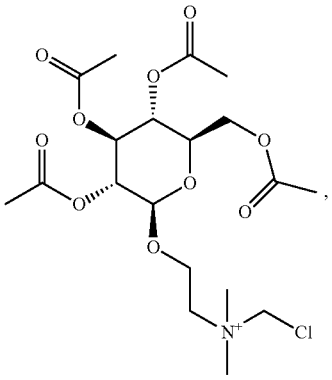

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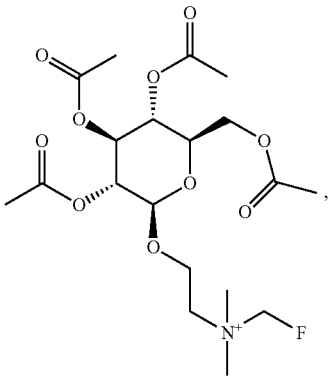

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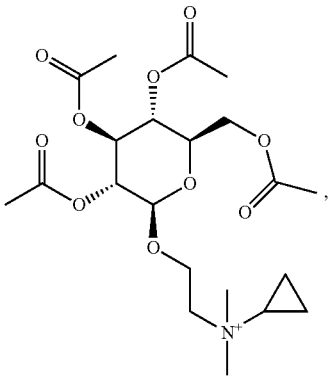

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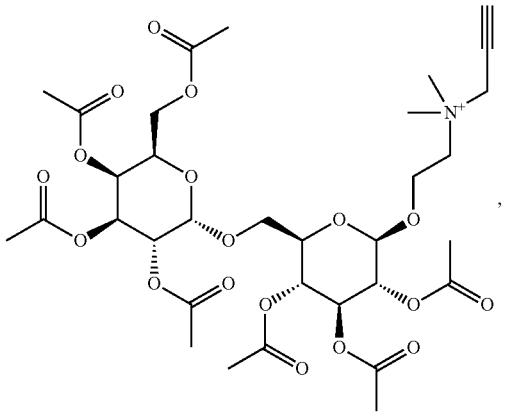

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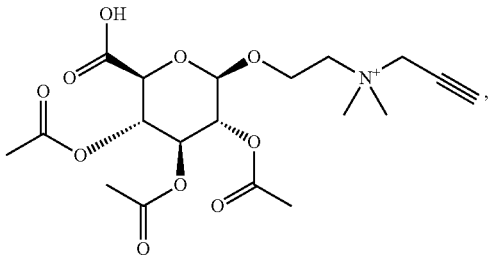

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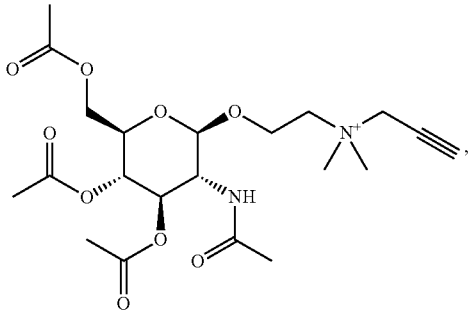

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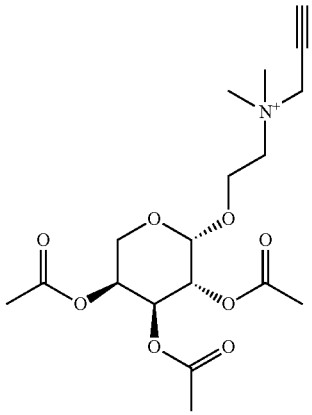

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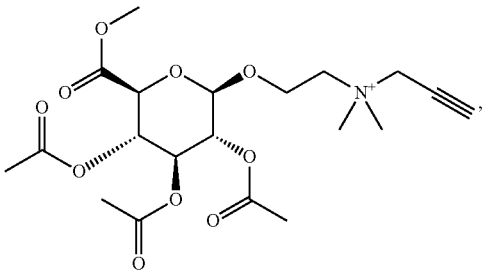

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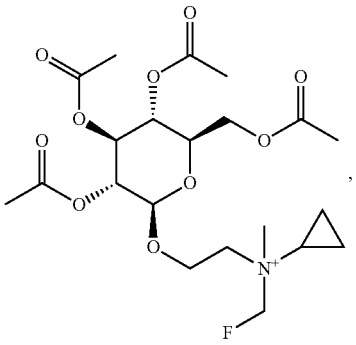

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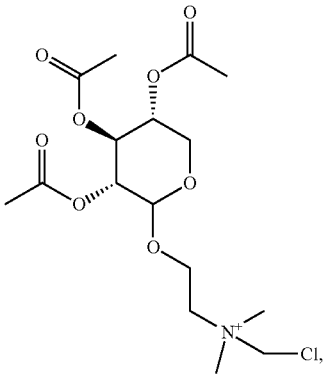

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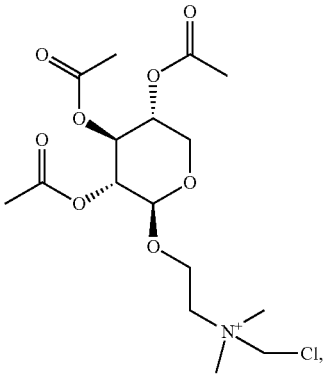

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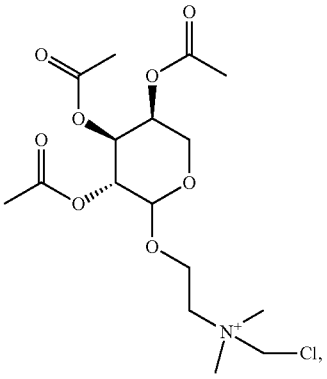

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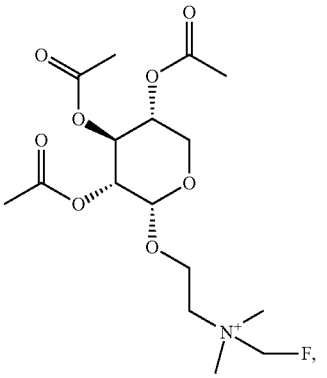

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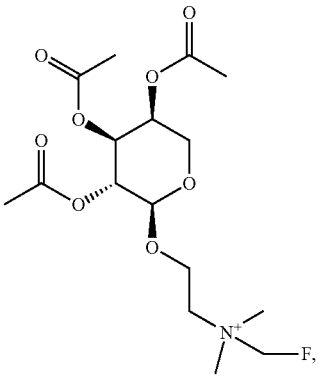

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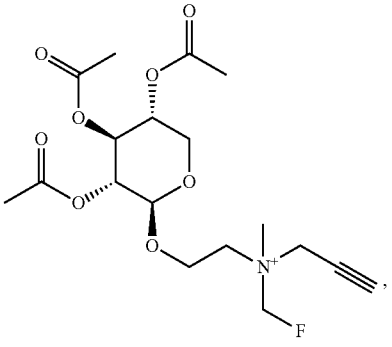

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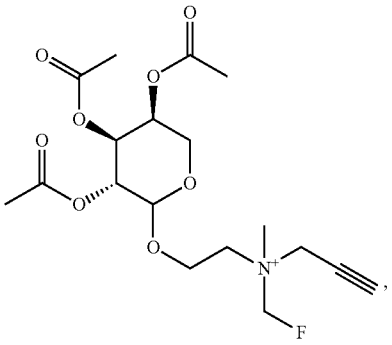

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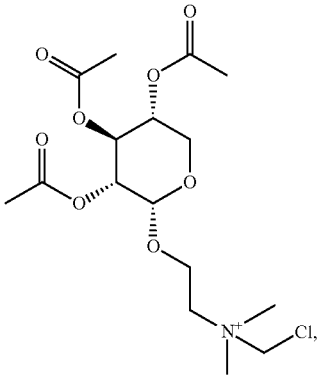

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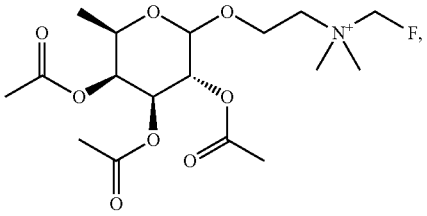

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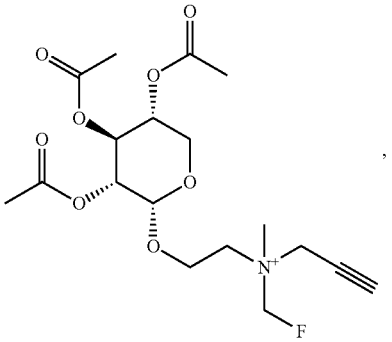

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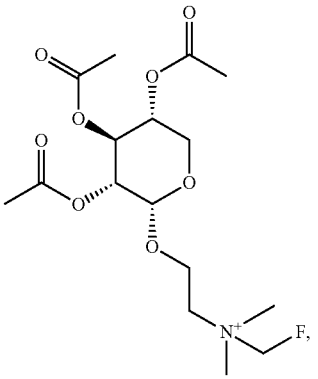

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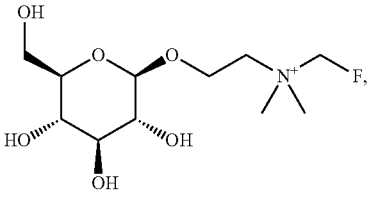

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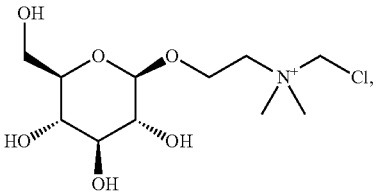

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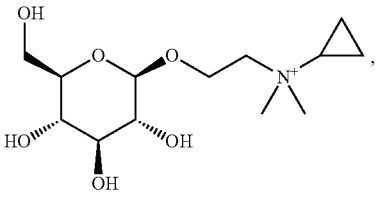

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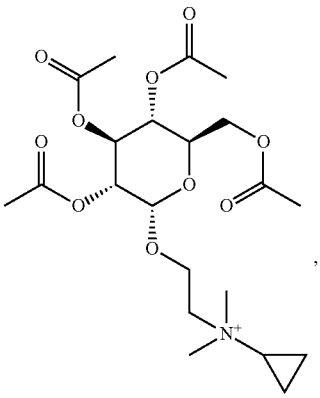

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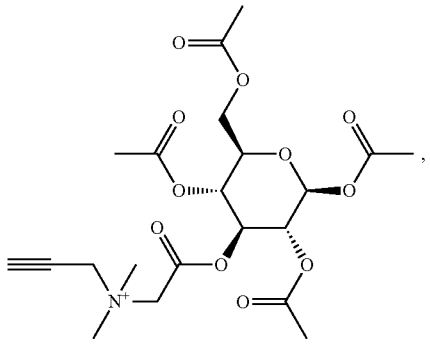

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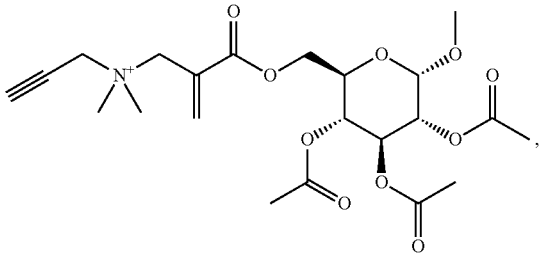

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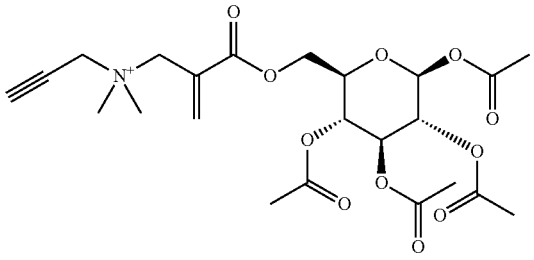

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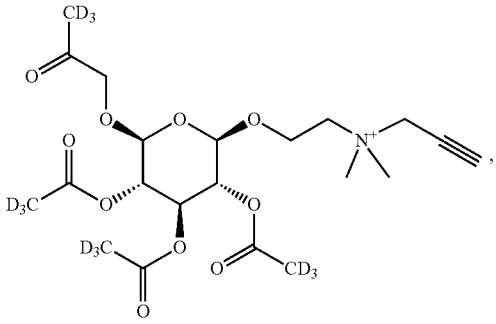

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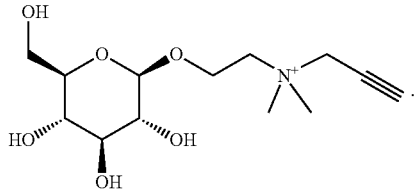
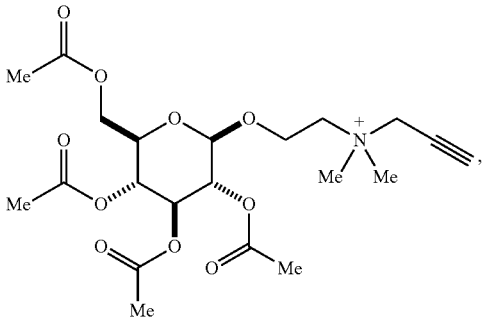


2. The compound according to embodiment 1, wherein the cation is chosen from:

7



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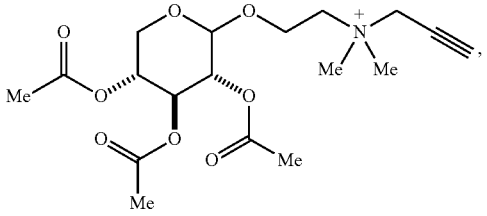

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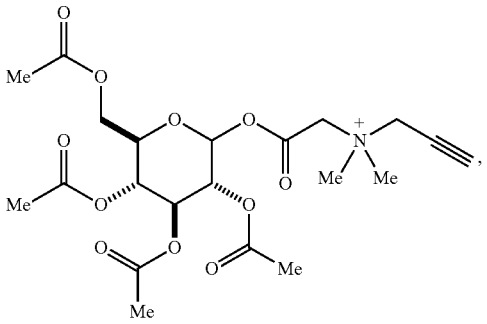

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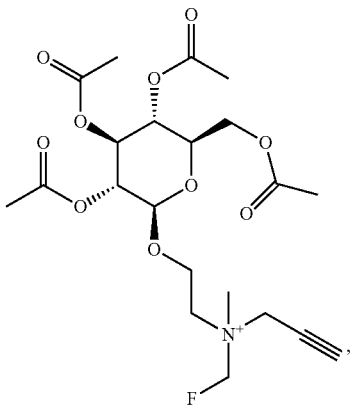

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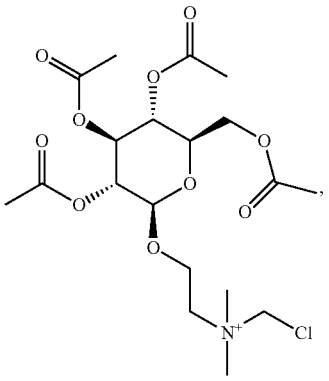

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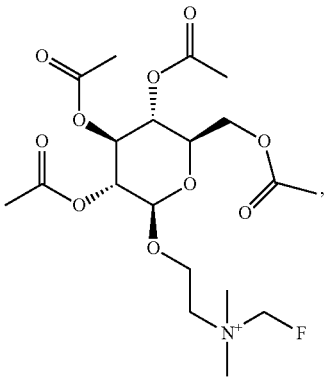

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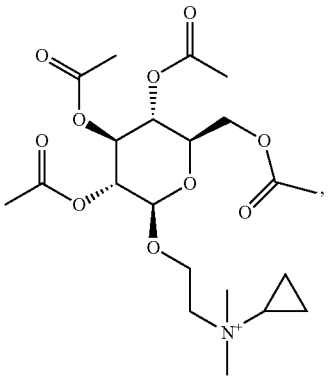

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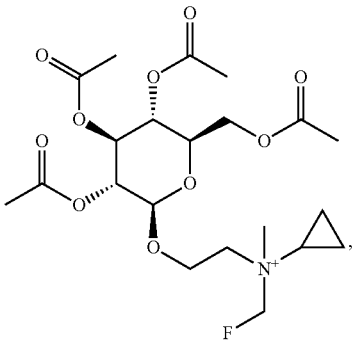

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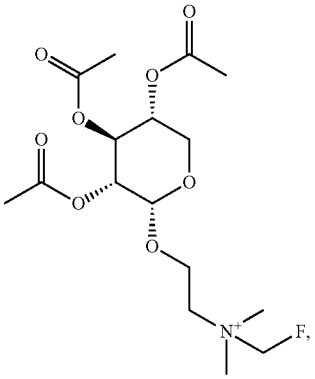

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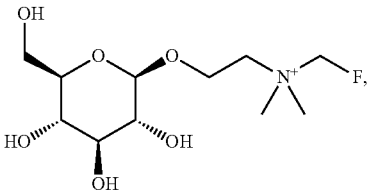

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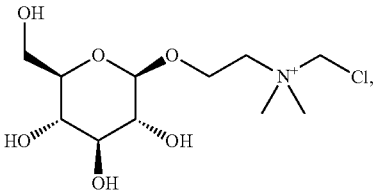

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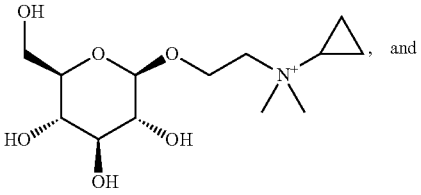

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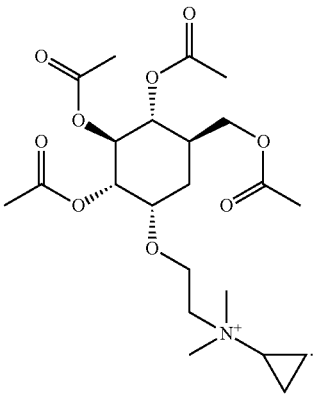
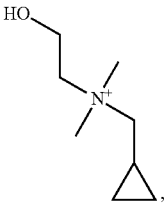


3. A compound consisting of a cation and a pharmaceutically acceptable counterion, wherein the cation is chosen from:

107



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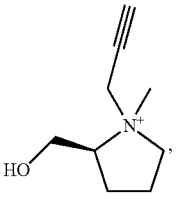

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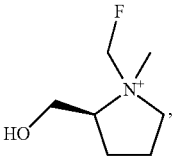

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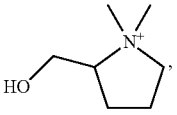

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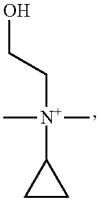

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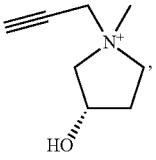

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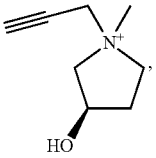

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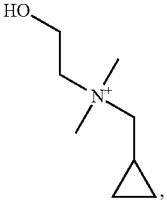

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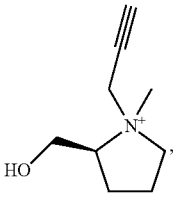

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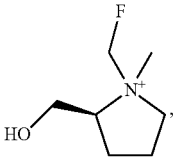

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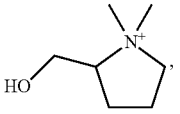

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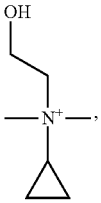

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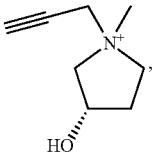

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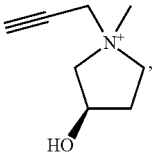

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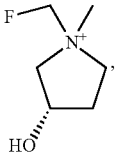

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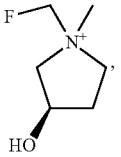

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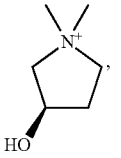

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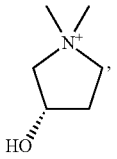

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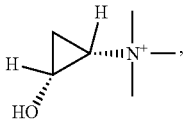

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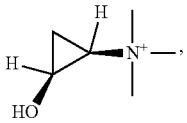

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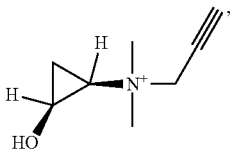

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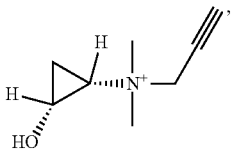

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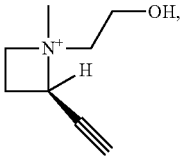

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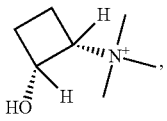

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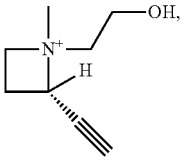

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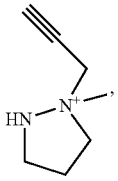

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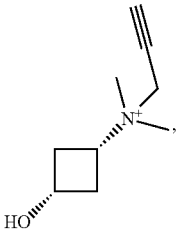

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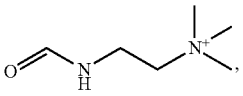

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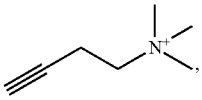

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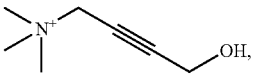

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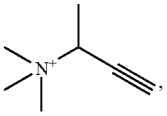

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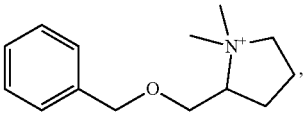

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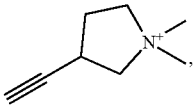

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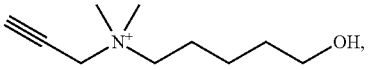

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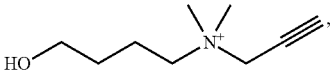

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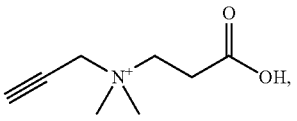

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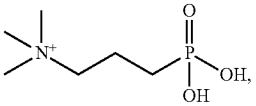

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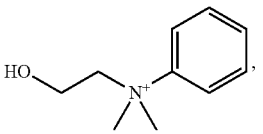

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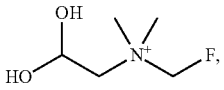

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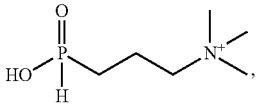

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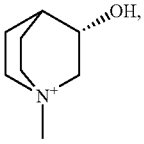

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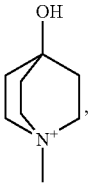

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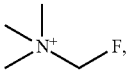

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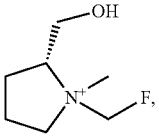

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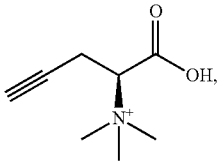

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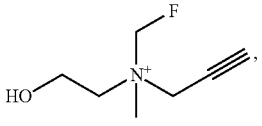

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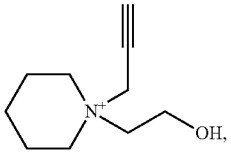

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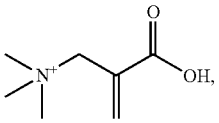

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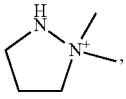

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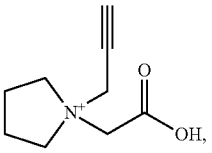

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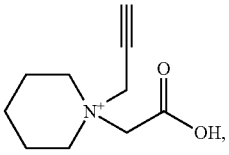

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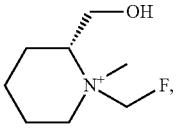

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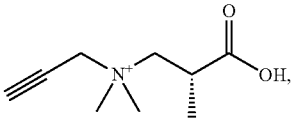

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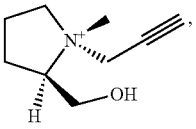

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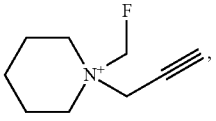

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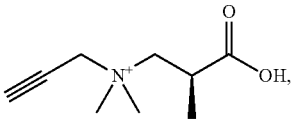

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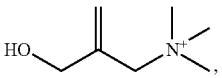

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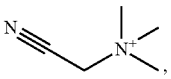

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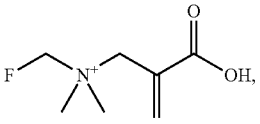

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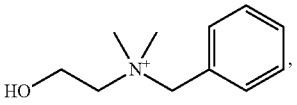

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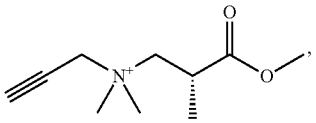

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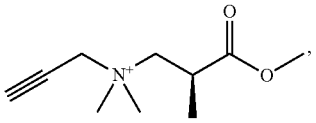

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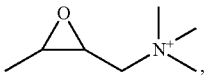

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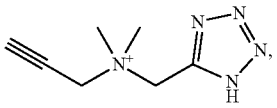

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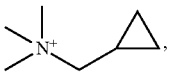

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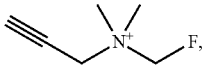

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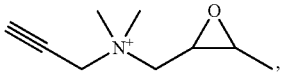

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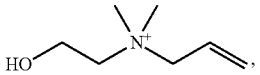

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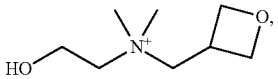

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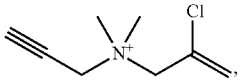

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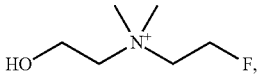

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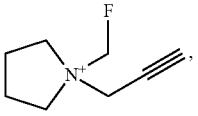

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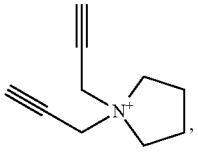

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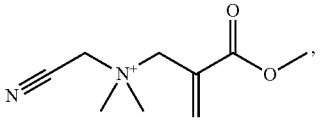

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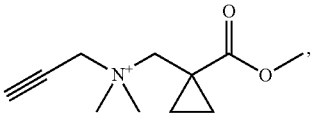

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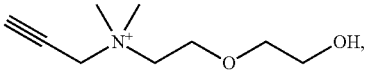

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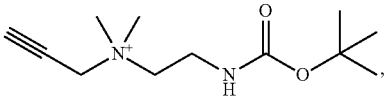

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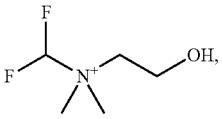

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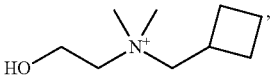

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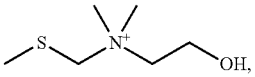

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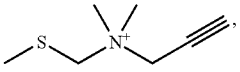

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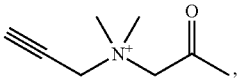

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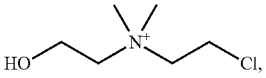

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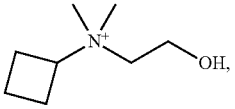

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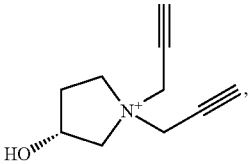

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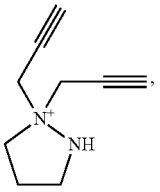

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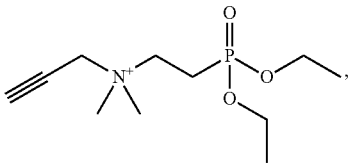

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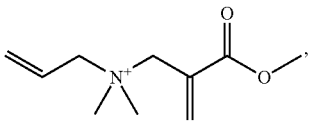

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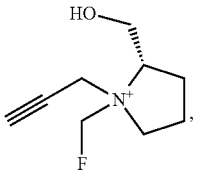

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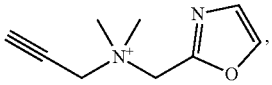

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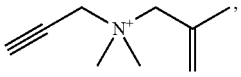

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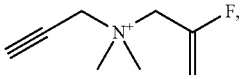

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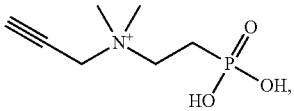

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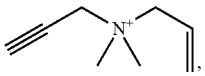

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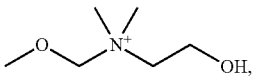

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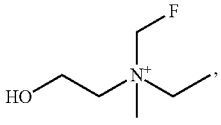

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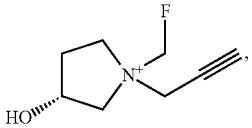

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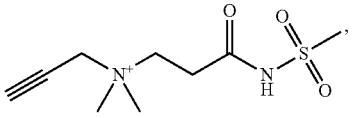

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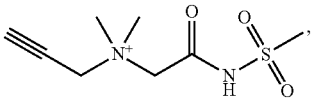

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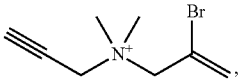

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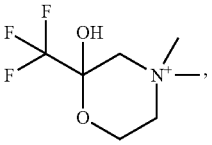

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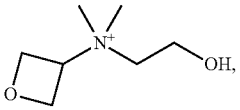

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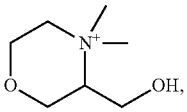

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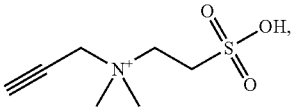

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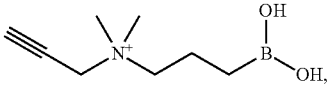

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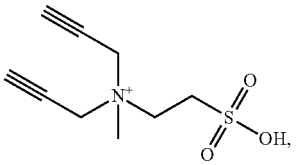

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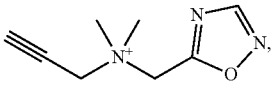

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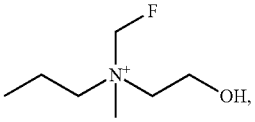

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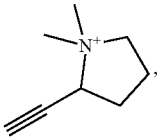

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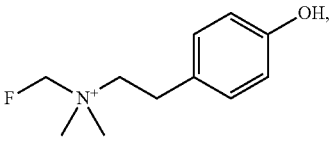

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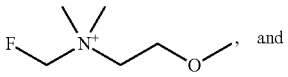

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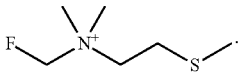
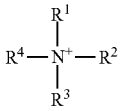


4. A compound consisting of a cation and a pharmaceutically acceptable counterion, wherein the cation is a structure of formula (I):

(I)



wherein

[0280] R^1 is

[0281] C_{2-6} alkyl substituted with —O-(acylated sugar) or isosorbide, wherein said C_{2-6} alkyl is further optionally substituted with oxo and/or methene;

[0282] C_4 cycloalkyl optionally substituted with hydroxyl, ethynyl, or —O-(acylated sugar); or

[0283] C_3 cycloalkyl substituted with C_{1-6} alkyl, hydroxyl, ethynyl, or —O-(acylated sugar)

[0284] C_{3-4} cycloalkyl C_{1-2} alkyl;

[0285] R^2 is C_{2-6} alkyl optionally substituted with one or two hydroxyl, oxo, and —O-(acylated sugar);

[0286] or R^1 and R^2, together with the nitrogen atom to which both are attached, combine to form a 4- or 5-membered heterocyclic ring optionally substituted with ethynyl or $—(CH_2)_n—OR^s$ or an acylated sugar, wherein n is 0 or 1, R^s is hydrogen or an acylated sugar;

[0287] R^3 is C_{1-6} alkyl optionally substituted with a halogen or hydroxyl; and

[0288] R^4 is C_{1-6} alkyl or propargyl.

5. The compound of embodiment 4, wherein R^1 is C_{2-6} alkyl substituted with —O-(acylated sugar) and is optionally further substituted with oxo.

6. The compound of embodiment 4 or 5, wherein R^2 is methyl.

7. The compound of any one of embodiments 4, 5, and 6, wherein R^3 is C_{1-6} alkyl.

8. The compound of any one of embodiments 4-7, wherein R^4 is propargyl.

9. The compound of embodiment 4, wherein

[0289] R^1 is C_{2-6} alkyl substituted with —O-(acylated sugar) and is optionally further substituted with oxo;

[0290] R^2 is methyl;

[0291] R^3 is C_{1-6} alkyl; and

[0292] R^4 is propargyl.

10. The compound of embodiment 4, wherein

[0293] R^1 is C_{2-6} alkyl substituted with isosorbide and is optionally further substituted with oxo and/or methene;

[0294] R^2 is methyl;

[0295] R^3 is C_{1-6} alkyl; and

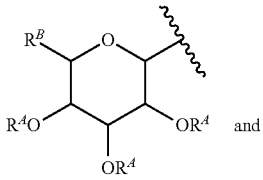
[0296] R^4 is propargyl.

11. The compound of embodiment 4, wherein

[0297] R^1 is chosen from C_2 alkyl substituted with —O-(acylated sugar) and optionally further substituted with oxo and C_4 alkyl substituted with —O-(acylated sugar) and optionally further substituted with oxo;

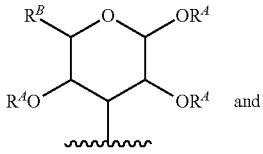
[0298] wherein the acylated sugar is chosen from groups of formula (A), groups of formula (B), and groups of formula (C):

(A)



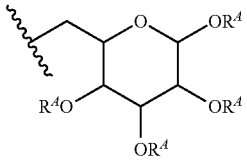
and

(B)



and

(C)



[0299] wherein

[0300] each R^A is independently H or fatty acid acyl, provided at least one R^A is a fatty acid acyl; and

[0301] R^B is H, $—CH_3$, $—CH_2—OR^A$, $—OCH_3$, $—COOCH_3$, or —COOH;

[0302] R^2 is methyl;

[0303] R^3 is methyl; and

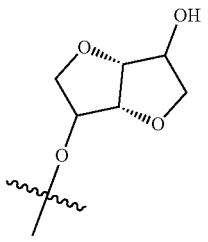
[0304] R^4 is propargyl.

12. The compound of embodiment 4, wherein

[0305] R^1 is chosen from C_2 alkyl substituted with isosorbide and optionally further substituted with oxo and C_3 alkyl substituted with isosorbide and optionally further substituted with oxo and methene;

[0306] wherein isosorbide is chosen from groups of formula (C):

(C)



[0307] R^2 is methyl;

[0308] R^3 is methyl; and

[0309] R^4 is propargyl.

13. The compound of embodiment 4, wherein

[0310] R^1 is C_{3-4} cycloalkyl C_{1-2} alkyl;

[0311] R^2 is C_{2-6} alkyl optionally substituted with one or two hydroxyl, oxo, and —O-(acylated sugar);

[0312] or R^1 and R^2, together with the nitrogen atom to which both are attached, combine to form a 4- or 5-membered heterocyclic ring optionally substituted with ethynyl or $—(CH_2)_n—OR^s$ or an acylated sugar, wherein n is 0 or 1, R^s is hydrogen or an acylated sugar;

[0313] R^3 is C_{1-6} alkyl optionally substituted with a halogen or hydroxyl; and

[0314] R^4 is C_{1-6} alkyl or propargyl.

14. The compound of embodiment 13, wherein R^1 is C_{3-4} cycloalkyl C_1 alkyl.

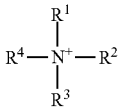
15. The compound of embodiment 13 or 14, wherein R^2 is C_2 alkyl optionally substituted with one or two hydroxyl groups.

16. The compound of embodiment 13, wherein R^1 and R^2, together with the nitrogen atom to which both are attached, combine to form a 5-membered heterocyclic ring optionally substituted with ethynyl, —OH, or $—CH_2OH$.

17. The compound of any one of embodiments 13-16, wherein R^3 is C_1 alkyl optionally substituted with a halogen.

18. The compound of any one of embodiments 13-17, wherein R^4 is C_1 alkyl or propargyl.

19. A compound consisting of a cation and a pharmaceutically acceptable counterion, wherein the cation is a structure of formula (II):



(II)

wherein

[0315] R^1 is

[0316] C_{1-6} alkyl optionally substituted with one or more oxo, hydroxyl, halogen, cyano, —COOMe, amino, methene, ethenyl, ethynyl, hydroxyphenyl, C_{3-4} cycloalkyl, $—OCH_2CH_2OH$, $—HNC(O)OCMe_3$, —SMe, —OMe, $—HNS(O)_2Me$, $—SO_3H$, $B(OH)_2$, PO_3H_2, PO_2H_2, $—P(O)(OCH_2CH_3)_2$, $—P(O)(OH)(OCH_2CH_3)$, heteroaryl ring;

[0317] phenyl;

[0318] benzyl;

[0319] C_{3-4} heterocyclyl optionally substituted with C_1 alkyl

[0320] C_4 heterocycloalkyl C_1 alkyl; or

[0321] C_4 cycloalkyl;

[0322] R^2 is

[0323] C_{1-6} alkyl optionally substituted with one or two hydroxyl, oxo, methene, cyano, ethynyl, —HNC(O)H, or $—C≡C—CH_2OH$; or

[0324] $—HN(CH_2)_3C(O)OH$;

[0325] or R^1 and R^2, together with the nitrogen atom to which both are attached and optionally one or more additional heteroatoms, combine to form a 4-8 membered mono- or bi-cyclic heterocycle optionally substituted with ethynyl, trifluoromethyl, $—CH_2Ph$, —OH, or $—(CH_2)OH$;

[0326] R^3 is methyl or propargyl; and

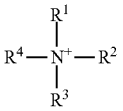
[0327] R^4 is methyl or propargyl,

[0328] with the proviso that

[0329] (1) when two of R^1, R^2, R^3, and R^4 are methyl and one of the other two of R^1, R^2, R^3, and R^4 is propargyl, then the other of R^1, R^2, R^3, and R^4 is not methyl, a monohalomethyl, $—CH_2CH_2OH$, —COOH, $—(CH_2)_4C(O)OH$, or $—CH_2C(CH_2)CN$; and

[0330] (2) when two of R^1, R^2, R^3, and R^4 are methyl and one of the other two of R^1, R^2, R^3, and R^4 is $—CH_2CH_2OH$ or $—CH_2C(O)OH$, then the other of R^1, R^2, R^3, and R^4 is not a monohalomethyl.

20. A compound consisting of a cation and a pharmaceutically acceptable counterion, wherein the cation is a structure of formula (III):



(III)

wherein

[0331] R^1 is

[0332] C_{1-6} alkyl optionally substituted with one or more oxo, hydroxyl, halogen, cyano, —COOMe, —COOH, methene, ethenyl, ethynyl, C_{3-4} cycloalkyl, $—OCH_2CH_2OH$, —SMe, —OMe, $—HNS(O)_2Me$, $—P(O)(OCH_2CH_3)_2$, $—P(O)(OH)(OCH_2CH_3)$, or 5-membered heteroaryl ring;

[0333] R^2 is

[0334] C_{1-6} alkyl optionally substituted with one or two hydroxyl, oxo, methene, cyano, ethynyl, —HNC(O)H, or $—C≡C—CH_2OH$; or

[0335] $—HN(CH_2)_3C(O)OH$;

[0336] or R^1 and R^2, together with the nitrogen atom to which both are attached and optionally one or more additional heteroatoms, combine to form a 4-8 membered mono- or bi-cyclic heterocycle optionally substituted with ethynyl, —OH, or $—(CH_2)OH$;

[0337] R^3 is C_{1-6} alkyl optionally substituted with a halogen, hydroxyl, or ethynyl; and

[0338] R^4 is C_{1-6} alkyl or propargyl;

[0339] with the proviso that

[0340] (1) when two of R^1, R^2, R^3, and R^4 are methyl and one of the other two of R^1, R^2, R^3, and R^4 is propargyl, then the other of R^1, R^2, R^3, and R^4 is not methyl, a monohalomethyl, $—CH_2CH_2OH$, —COOH, $—(CH_2)_4C(O)OH$, or $—CH_2C(CH_2)CN$; and

[0341] (2) when two of R^1, R^2, R^3, and R^4 are methyl and one of the other two of R^1, R^2, R^3, and R^4 is $—CH_2CH_2OH$ or $—CH_2C(O)OH$, then the other of R^1, R^2, R^3, and R^4 is not a monohalomethyl.

21. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and the compound of any one of embodiments 1 to 20.

22. A method of modulating a trimethylaminuria marker in a subject in need thereof, the method comprising administering to the subject in need thereof a therapeutically effective amount of the compound of any one of embodiments 1 to 20 or the pharmaceutical composition of embodiment 21.

23. The method of embodiment 22, wherein the trimethylaminuria marker is the trimethylamine and/or trimethylamine oxide levels in the subject's blood, plasma, serum, or urine.

24. A method of treating or preventing a disease associated with elevated levels of trimethylamine (TMA) or trimethylamine N-oxide (TMAO), a decreased rate of conversion of

TMA to TMAO, or a high ratio of TMA to TMAO in a subject in need thereof, the method comprising administering a therapeutically effective amount of the compound of any one of embodiments 1 to 20 or the pharmaceutical composition of embodiment 21 to the subject.

25. The method of embodiment 24, further comprising detecting the presence of one or more genetic variants of the FMO3 gene of the subject in need before the administering step.

26. The method of embodiment 24, wherein the disease associated with elevated levels of trimethylamine (TMA) or trimethylamine N-oxide (TMAO), a decreased rate of conversion of TMA to TMAO, or a high ratio of TMA to TMAO is a cardiovascular disease, reduced or impaired kidney function, kidney disease, chronic kidney disease, end-stage renal disease, or diabetes mellitus.

27. A method of inhibiting a CutC choline lyase-mediated conversion of choline to trimethylamine, the method comprising contacting the compound of any one of embodiments 1 to 20 with the CutC choline lyase.

28. A method of inhibiting a CntA carnitine monooxygenase-mediated conversion of carnitine to trimethylamine, the method comprising contacting the compound of any one of embodiments 1 to 20 with the CntA carnitine monooxygenase.

29. A method of treating a subject in need of treatment for trimethylaminuria comprising contacting bacteria in vivo with a therapeutically effective amount of the compound of any one of embodiments 1 to 20 or the pharmaceutical composition of embodiment 21 to the subject.

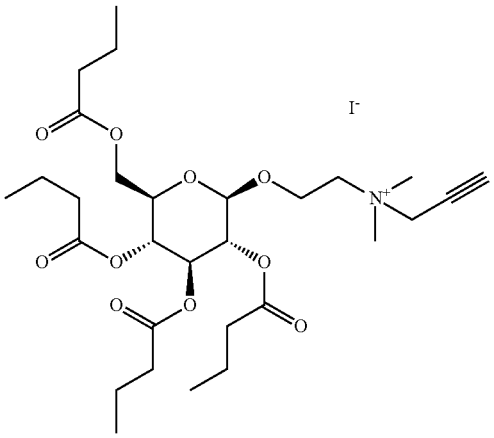
30. The method of embodiment 29, wherein the bacteria are localized in the colon of the subject.

[0342] The following examples are meant to illustrate the disclosure. They are not meant to limit the disclosure in any way.

EXAMPLES

Example 1: Preparation of Exemplary Compounds

[0343] In the following examples, the title compounds may exist as a trifluoroacetate salt after prep-HPLC but one of ordinary skill in the art would understand that the salt may be changed by conventional methods of salt formation.



Compound 1: N,N-dimethyl-N-(2-(((2R,3R,4S,5R,6R)-3,4,5-tris(butyryloxy)-6-((butyryloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium iodide

[0344] Step 1:

[0345] A mixture of (3R,4S,5S,6R)-6-(hydroxymethyl) tetrahydropyran-2,3,4,5-tetrol (20 g, 111.01 mmol, 1 eq) and butanoyl butanoate (96.59 g, 610.58 mmol, 99.89 mL, 5.5 eq) in Pyridine (200 mL) was degassed and purged with N2 for 3 times, and then the mixture was stirred at 20° C. for 12 h. TLC indicated the starting material was consumed completely and one new spot formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1 to 20:1). [(2R,3R,4S,5R)-3,4,5,6-tetra(butanoyloxy)tetrahydropyran-2-yl] methyl butanoate (100 g, crude) was obtained as colorless oil.

[0346] Step 2:

[0347] To a mixture of [(2R,3R,4S,5R)-3,4,5,6-tetra(butanoyloxy)tetrahydropyran-2-yl]methyl butanoate (10 g, 18.85 mmol, 1 eq) in THF (100 mL) was added $MeNH_2$ aq. solution (2.4 g, 30.91 mmol, 40% purity, 1.64 eq) in one portion at 20° C. under N2. The mixture was stirred at 20° C. for 12 h. TLC indicated [(2R,3R,4S,5R)-3,4,5,6-tetra (butanoyloxy)tetrahydropyran-2-yl]methyl butanoate was consumed completely and one new spot formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 20:1). Compound [(2R,3R,4S,5R)-3,4,5-tri (butanoyloxy)-6-hydroxy-tetrahydropyran-2-yl]methyl butanoate (5 g, 10.86 mmol, 57.6% yield) was obtained as colorless oil.

[0348] Step 3:

[0349] To a mixture of [(2R,3R,4S,5R)-3,4,5-tri(butanoyloxy)-6-hydroxy-tetrahydropyran-2-yl]methyl butanoate (2 g, 4.34 mmol, 1 eq) and DBU (330.58 mg, 2.17 mmol, 327.31 uL, 0.5 eq) in DCM (20 mL) was added 2,2,2-trichloroacetonitrile (6.27 g, 43.43 mmol, 4.35 mL, 10 eq) in one portion at 20° C. The mixture was stirred at 20° C. for 12 h. TLC showed [(2R,3R,4S,5R)-3,4,5-tri(butanoyloxy)-6-hydroxy-tetrahydropyran-2-yl]methyl butanoate was consumed completely and one new spot formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=30/1 to 20:1). Compound [(2R,3R,4S,5R)-3,4,5-tri(butanoyloxy)-6-(2,2,2-trichloroethanimidoyl)oxy-tetrahydropyran-2-yl]methyl butanoate (1.8 g, 2.98 mmol, 68.5% yield) was obtained as colorless oil.

[0350] Step 4:

[0351] To a solution of [(2R,3R,4S,5R)-3,4,5-tri(butanoyloxy)-6-(2,2,2-trichloroethanimidoyl) oxy-tetrahydropyran-2-yl]methyl butanoate (1 g, 1.65 mmol, 1 eq) and 2-bromoethanol (247.90 mg, 1.98 mmol, 140.85 uL, 1.2 eq) in DCM (10 mL) was added $BF_3.Et_2O$ (1.17 g, 8.27 mmol, 1.02 mL, 5 eq). The mixture was stirred at 0° C. for 3 h and then warmed to 20° C. stirred for 12 h. TLC indicated [(2R,3R,4S,5R)-3,4,5-tri(butanoyloxy)-6-(2,2,2-trichloroethanimidoyl)oxy-tetrahydropyran-2-yl]methyl butanoate was consumed completely. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2,

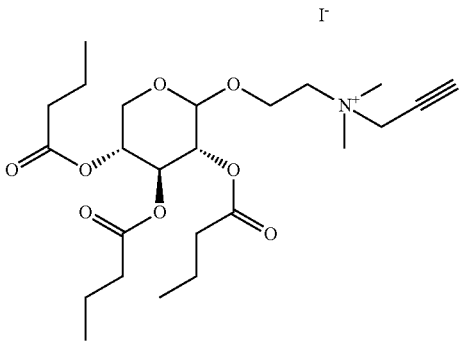
Petroleum ether/Ethyl acetate=30/1 to 20:1). Compound [(2R,3R,4S,5R)-6-(2-bromoethoxy)-3,4,5-tri(butanoyloxy) tetrahydropyran-2-yl]methyl butanoate (0.8 g, 1.41 mmol, 85.3% yield) was obtained as colorless oil.

[0352] Step 5:

[0353] A mixture of [(2R,3R,4S,5R)-6-(2-bromoethoxy)-3,4,5-tri(butanoyloxy)tetrahydropyran-2-yl] methyl butanoate (0.1 g, 176.22 umol, 1 eq), N-methylprop-2-yn-1-amine (36.53 mg, 528.67 umol, 44.02 uL, 3 eq) in THF (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20° C. for 2 hr under N_2 atmosphere, then warmed to 70° C. and stirred for 12 h. TLC indicated [(2R,3R,4S,5R)-6-(2-bromoethoxy)-3,4,5-tri(butanoyloxy) tetrahydropyran-2-yl]methyl butanoate was consumed completely and one new spot formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate=2:1). Compound [(2R,3R,4S,5R)-3,4,5-tri(butanoyloxy)-6-[2-[methyl(prop-2-ynyl)amino] ethoxy]tetrahydropyran-2-yl]methyl butanoate (0.03 g, 54 umol, 30.6% yield) was obtained as colorless oil.

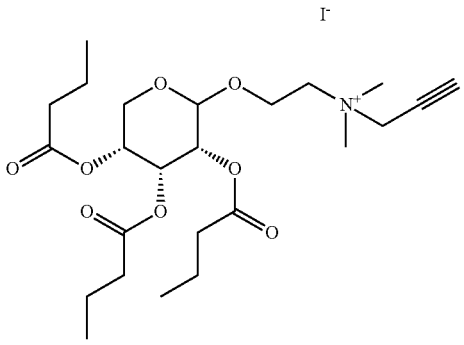
[0354] Step 6:

[0355] A mixture of [(2R,3R,4S,5R)-3,4,5-tri(butanoyloxy)-6-[2-[methyl(prop-2-ynyl)amino]ethoxy] tetrahydropyran-2-yl]methyl butanoate (0.06 g, 107.98 umol, 1 eq), MeI (30.65 mg, 215.96 umol, 13.44 uL, 2 eq) in THF (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20° C. for 2 hr under N_2 atmosphere. LC-MS showed [(2R,3R,4S,5R)-3,4,5-tri(butanoyloxy)-6-[2-[methyl(prop-2-ynyl)amino]ethoxy]tetrahydropyran-2-yl]methyl butanoate was consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. The title compound (0.007 g, 12.1 umol, 11% yield) was obtained as colorless oil. LCMS (M^+): 570.3 ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.33 (t, J=9.5 Hz, 1H), 5.04-4.81 (m, 3H), 4.37 (d, J=2.5 Hz, 2H), 4.22-4.00 (m, 6H), 3.62 (t, J=4.9 Hz, 2H), 3.09 (s, 6H), 2.33-2.11 (m, 8H), 1.61-1.38 (m, 8H), 0.93-0.78 (m, 12H



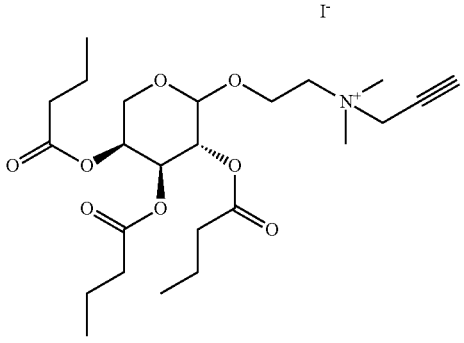
Compound 2 and Compound 51: N,N-dimethyl-N-(2-(((3R,4S,5R)-3,4,5-tris(butyryloxy)tetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium Iodide

[0356] This compound may be synthesized according to the experimental procedure described for Compound 1.



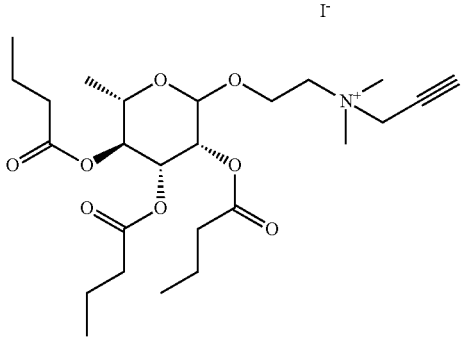
Compound 3: N,N-dimethyl-N-(2-(((3R,4R,5R)-3,4,5-tris(butyryloxy)tetrahydro-2H-pyran-2-yl)oxy) ethyl)prop-2-yn-1-aminium Iodide

[0357] This compound may be synthesized according to the experimental procedure described for Compound 1.



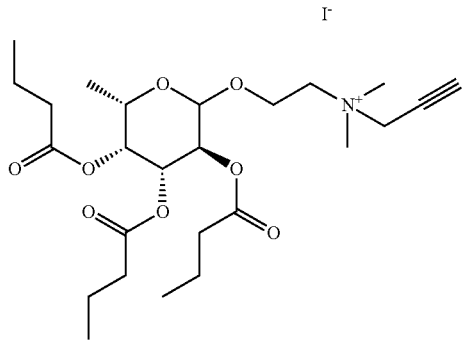
Compound 4 and Compound 53 and Compound 84: N,N-dimethyl-N-(2-(((3R,4S,5S)-3,4,5-tris(butyryloxy)tetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium iodide

[0358] This compound may be synthesized according to the experimental procedure described for Compound 1.



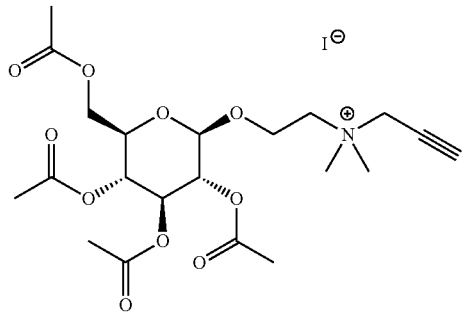
Compound 5: N,N-dimethyl-N-(2-(((3R,4R,5S,6S)-3,4,5-tris(butyryloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium Iodide

[0359] This compound may be synthesized according to the experimental procedure described for Compound 1.



Compound 6: N,N-dimethyl-N-(2-(((3S,4R,5R,6S)-3,4,5-tris(butyryloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium Iodide

[0360] This compound may be synthesized according to the experimental procedure described for Compound 1.



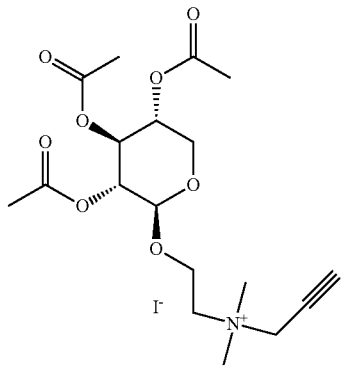
Compound 7: N,N-dimethyl-N-(2-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium Iodide

[0361] Step 1:

[0362] Compound β-D-Glucose pentaacetate (20 g, 51.2 mmol, 1 eq) was dissolved in DCM (100 mL) and cooled to 0° C. under N_2, followed by addition of 2-bromoethanol (5.5 mL, 77.6 mmol, 1.5 eq) and boron trifluoride diethyl etherate (32 mL, 259 mmol, 5 eq). The ice bath was removed and the reaction was stirred at room temperature overnight. Silica was added to the reaction mixture and solution was concentrated to dryness to dry-load onto silica before purification by column chromatography (gradient: 0-100% EtOAc in hexanes, product eluted around 40-50% EtOAc in hexanes). Fractions containing product were concentrated and recrystallized by dissolution in ethyl acetate, followed by slow addition of hexanes until crystals started to form, at which point it was placed in the fridge for further crystallization. The white crystals were filtered and washed with hexanes to yield 1-(2-bromoethoxy)-2,3,4,6-tetra-O-acetyl-beta-D-glucopyranose (8.9 g, 19.5 mmol, 38%).

[0363] Step 2:

[0364] Compound 1-(2-bromoethoxy)-2,3,4,6-tetra-O-acetyl-beta-D-glucopyranose (1.7 g, 3.7 mmol, 1 eq) was stirred with sodium iodide (0.614 g, 4.1 mmol, 1.1 eq) for a few minutes, followed by addition of 3-dimethylamino-1-propyne (1.2 mL, 11.1 mmol, 3 eq). The reaction mixture was stirred overnight at 40° C. filtered, then cooled to 4° C. in the fridge for recrystallization. The crystals were washed with cold acetone to yield the title compound as a white crystalline solid (300 mg, 0.51 mmol, 14%, iodide salt-confirmed by ion chromatography). The remaining filtrate was concentrated and washed with cold acetone and ethyl acetate to yield the title compound as an amorphous powder (1.2 g, 2.05 mmol, 55%, iodide salt-confirmed by ion chromatography). LCMS (M+): 458.1 ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.26 (t, J=9.5 Hz, 1H), 4.98-4.77 (m, 3H), 4.36 (d, J=2.5 Hz, 2H), 4.24-3.97 (m, 6H), 3.67-3.54 (m, 2H), 3.08 (s, 6H), 2.05-1.89 (m, 12H).



Compound 8: N,N-dimethyl-N-(2-(((3R,4S,5R)-3,4,5-triacetoxytetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium iodideiodideiodideiodideiodide

[0365] Step 1:

[0366] To a solution of (3R,4S,5R)-tetrahydropyran-2,3,4,5-tetrol (20 g, 133.22 mmol, 1 eq) in Pyridine (200 mL) was added acetyl acetate (108.80 g, 1.07 mol, 99.82 mL, 8 eq) at 15° C. The mixture was stirred at 15° C. for 12 hr. TLC indicated new spots formed. The reaction mixture was concentrated under reduced pressure to give yellow oil. The oil was diluted with ethyl acetate 100 mL and washed with H_2O (100 mL*3). The combined organic layers were washed with brine 100 mL, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give yellow oil. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:0). Compound [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (42 g, crude) was obtained as a yellow oil.

[0367] Step 2:

[0368] To a solution of [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (21 g, 65.98 mmol, 1 eq) in THF (120 mL) was added aq. $MeNH_2$ (7.51 g, 72.58 mmol, 30% purity, 1.1 eq) at 15° C. The mixture was stirred at 15° C. for 12 hr. TLC indicated new spots formed. The reaction mix-

ture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:1 to 0:1). Compound [(3R,4S,5R)-4,5-diacetoxy-6-hydroxy-tetrahydropyran-3-yl] acetate (9 g, 32.58 mmol, 49.38% yield) was obtained as a yellow solid.

[0369] Step 3:

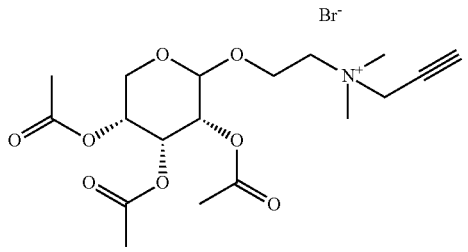
[0370] To a solution of [(3R,4S,5R)-4,5-diacetoxy-6-hydroxy-tetrahydropyran-3-yl]acetate (5 g, 18.10 mmol, 1 eq) in DCM (20 mL) was added DBU (1.38 g, 9.05 mmol, 1.36 mL, 0.5 eq) and 2,2,2-trichloroacetonitrile (26.13 g, 181.00 mmol, 18.15 mL, 10 eq) at 15° C. The mixture was stirred at 15° C. for 1 hr. TLC indicated a new spot formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:1). Compound [(3R,4S,5R)-4,5-diacetoxy-6-(2,2,2-trichloroethanimidoyl)oxy-tetrahydropyran-3-yl] acetate (6 g, 14.26 mmol, 78.81% yield) was obtained as a yellow oil.

[0371] Step 4:

[0372] To a solution of [(3R,4S,5R)-4,5-diacetoxy-6-(2,2,2-trichloroethanimidoyl)oxy-tetrahydropyran-3-yl] acetate (3 g, 7.13 mmol, 1 eq) and 2-bromoethanol (891.27 mg, 7.13 mmol, 506.41 uL, 1 eq) in DCM (30 mL) was added $BF_3.Et_2O$ (5.06 g, 35.66 mmol, 4.40 mL, 5 eq) at 0° C. The mixture was stirred at 0° C. for 2 hr. TLC indicated new spots formed. The reaction mixture was quenched by addition H_2O (30 mL) at 0° C., and extracted with ethyl acetate (50 mL*3). The combined organic layers were washed with brine 30 mL, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10:1 to 1:1). Compound [(3R,4S,5R)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (1.3 g, 3.39 mmol, 47.57% yield) was obtained as a white solid.

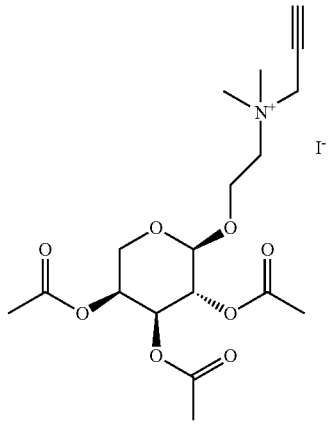
[0373] Step 5:

[0374] To a solution of [(3R,4S,5R)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (1.3 g, 3.39 mmol, 1 eq) in acetone (20 mL) was added N,N-dimethylprop-2-yn-1-amine (564.06 mg, 6.79 mmol, 719.46 uL, 2 eq) and NaI (1.02 g, 6.79 mmol, 2 eq) at 15° C. The mixture was stirred at 80° C. for 4 hr. LCMS showed the desired compound was detected. TLC indicated 50% of [(3R,4S,5R)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (1.3 g, 3.39 mmol, 1 eq) remained. The mixture was stirred at 80° C. for 8 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:1 to Ethyl acetate:Methanol=1:1) The title compound (530 mg, 1.03 mmol, 30.30% yield) was obtained as a white solid. LCMS: ($M+H^+$): 386.1 ^1H NMR (400 MHz, Deuterium Oxide) δ 5.10 (t, J=7.6 Hz, 1H), 4.93-4.79 (m, 2H), 4.71 (d, J=6.1 Hz, 1H), 4.20-4.14 (m, 3H), 4.06 (dd, J=12.3, 4.7 Hz, 1H), 3.98-3.90 (m, 1H), 3.70-3.59 (m, 2H), 3.50 (dd, J=12.3, 7.9 Hz, 1H), 3.19-3.13 (m, 1H), 3.11 (s, 6H), 2.02-1.92 (m, 9H).



Compound 9: N,N-dimethyl-N-(2-(((3R,4R,5R)-3,4,5-triacetoxytetrahydro-2H-pyran-2-yl)oxy)ethyl) prop-2-yn-1-aminium bromide

[0375] This compound may be synthesized according to the experimental procedure described for Compound 7.



Compound 10 and Compound 56: N,N-dimethyl-N-(2-(((3R,4S,5S)-3,4,5-triacetoxytetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium Iodide

[0376] Step 1:

[0377] To a mixture of (2R,3S,4S)-2,3,4,5-tetrahydroxypentanal (10 g, 66.61 mmol, 1 eq) in pyridine (100 mL) was added Ac_2O (40.80 g, 399.65 mmol, 37.43 mL, 6 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 12 hours. TLC indicated one new spot formed. The reaction mixture was concentrated under reduced pressure to remove pyridine. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=30/1 to 0/1). Compound [(3S,4S,5R,6S)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (20 g, crude) was obtained as yellow oil.

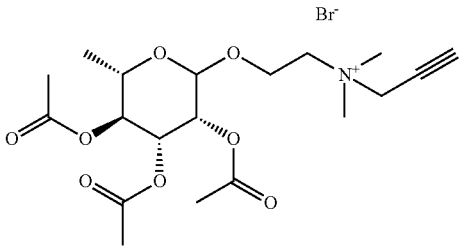
[0378] Step 2:

[0379] To a mixture of [(3S,4S,5R,6S)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (10 g, 31.42 mmol, 1 eq) in DCM (100 mL) was added 2-bromoethanol (5.89 g, 47.13 mmol, 3.35 mL, 1.5 eq) and $BF_3.Et_2O$ (22.30 g, 157.10 mmol, 19.39 mL, 5 eq) in one portion at 0° C. under N_2. The

mixture was heated to 25° C. and stirred for 12 hours. TLC indicated [(3S,4S,5R,6S)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate was consumed and one new spot formed. The reaction mixture was quenched by addition of H_2O (50 mL), and then diluted with H_2O (100 mL) and extracted with DCM (100 mL*2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1). Then the residue was purified by prep-HPLC [water (0.10% TFA)-ACN]. ^{1}HNMR indicated the compound [(3S,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (1.2 g, 3.13 mmol, 9.97% yield) was obtained as yellow oil and compound[(3S,4S,5R,6R)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (2.3 g, 6.00 mmol, 19.10% yield) was obtained as yellow oil.

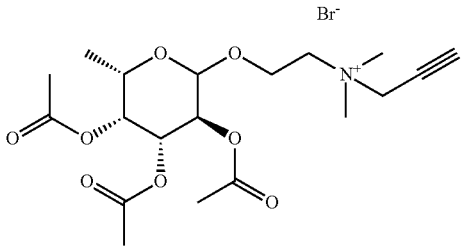
[0380] Step 3:

[0381] To a mixture of [(3S,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (1 g, 2.61 mmol, 1 eq) in acetone (10 mL) was added NaI (430.29 mg, 2.87 mmol, 1.1 eq) in one portion at 25° C. under N_2. Then N,N-dimethylprop-2-yn-1-amine (1.08 g, 13.05 mmol, 1.38 mL, 5 eq) was added. The mixture was heated to 90° C. and stirred for 2 hours. TLC indicated [(3S,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate was consumed and one new spot formed. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 Ethyl acetate:Methanol=3/1).dimethyl-prop-2-ynyl-[2-[(2R,3R,4S,5S)-3,4,5-triacetoxytetrahydropyran-2-yl]oxyethyl]ammonium (318 mg, 617.64 umol, 23.67% yield, 99.7% purity, I) was obtained as white solid. LCMS: (M+): 386.2 1H NMR (400 MHz, Chloroform-d) δ 5.26-5.20 (m, 1H), 5.08 (dd, J=10.0, 7.4 Hz, 1H), 4.99 (dd, J=10.0, 3.5 Hz, 1H), 4.75 (t, J=3.0 Hz, 2H), 4.48 (d, J=7.4 Hz, 1H), 4.37-4.26 (m, 1H), 4.17-4.06 (m, 2H), 4.09-4.00 (m, 1H), 3.95 (dd, J=13.3, 2.5 Hz, 1H), 3.66 (dd, J=13.4, 1.5 Hz, 1H), 3.46 (s, 6H), 2.82 (t, J=2.5 Hz, 1H), 2.10 (s, 3H), 2.04 (s, 3H), 1.95 (s, 3H))))).



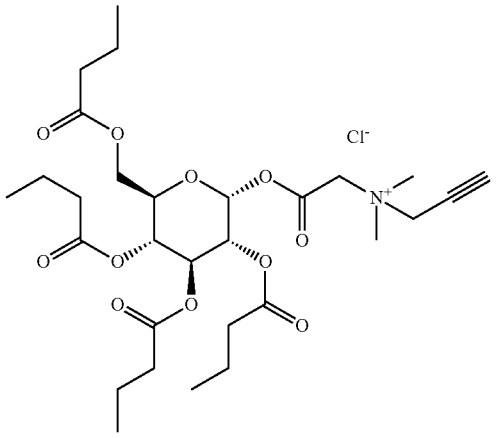
Compound 11: N,N-dimethyl-N-(2-(((3R,4R,5S,6S)-3,4,5-triacetoxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium bromide

[0382] This compound may be synthesized according to the experimental procedure described for Compound 7.



Compound 12: N,N-dimethyl-N-(2-(((3S,4R,5R,6S)-3,4,5-triacetoxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium bromide

[0383] This compound may be synthesized according to the experimental procedure described for Compound 7.



Compound 13: N,N-dimethyl-N-(2-oxo-2-(((3R,4S,5R,6R)-3,4,5-tris(butyryloxy)-6-((butyryloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium chloride

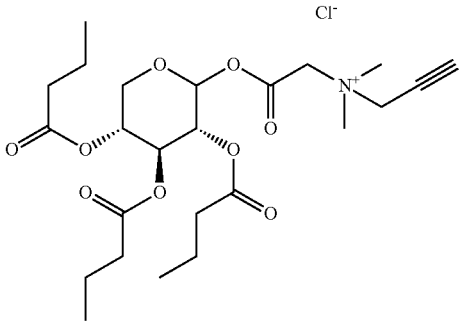
[0384] Step 1:

[0385] To a mixture of [(2R,3R,4S,5R)-3,4,5-tri(butanoyloxy)-6-hydroxy-tetrahydropyran-2-yl]methyl butanoate (1 g, 2.17 mmol, 1 eq) and 2-chloroacetyl chloride (735.76 mg, 6.51 mmol, 518.14 uL, 3 eq) in DCM (10 mL) was added pyridine (858.82 mg, 10.86 mmol, 876.35 uL, 5 eq) in one portion at 20° C. The mixture was stirred at 20° C. for 12 h. TLC showed [(2R,3R,4S,5R)-3,4,5-tri(butanoyloxy)-6-hydroxy-tetrahydropyran-2-yl]methyl butanoate was consumed completely and one new spot formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 20:1). Compound [(2R,3R,4S,5R)-3,4,5-tri(butanoyloxy)-6-(2-chloroacetyl)oxy-tetrahydropyran-2-yl]methyl butanoate (0.8 g, crude) was obtained as colorless oil.

[0386] Step 2:

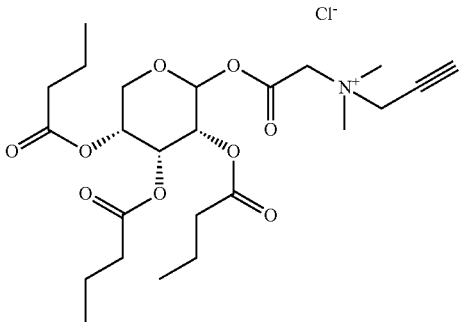
[0387] A mixture of [(2R,3R,4S,5R)-3,4,5-tri(butanoyloxy)-6-(2-chloroacetyl)oxy-tetrahydropyran-2-yl] methyl butanoate (0.2 g, 372.44 umol, 1 eq) and N,N-dimethylprop-2-yn-1-amine (92.89 mg, 1.12 mmol, 118.48 uL, 3 eq) in

acetone (3 mL) was stirred at 90° C. for 0.5 h. LCMS showed [(2R,3R,4S,5R)-3,4,5-tri(butanoyloxy)-6-(2-chloroacetyl)oxy-tetrahydropyran-2-yl]methyl butanoate was consumed completely. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. The title compound (0.049 g, 67 umol, 18% yield) was obtained as colorless oil. LCMS (M^+): 584.3 ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.30 (d, J=3.4 Hz, 1H), 5.46-5.35 (m, 1H), 5.25-5.11 (m, 2H), 4.80-4.63 (m, 2H), 4.61-4.46 (m, 2H), 4.30-3.98 (m, 4H), 3.30-3.16 (m, 6H), 2.37-2.10 (m, 8H), 1.63-1.41 (m, 8H), 0.95-0.75 (m, 12H).



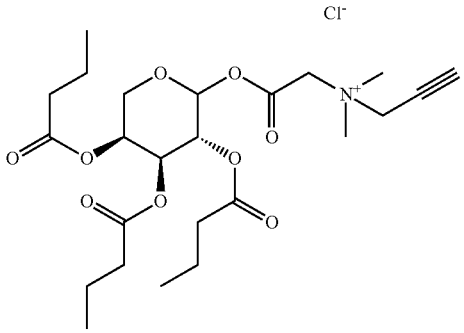
Compound 14 and Compound 52: N,N-dimethyl-N-(2-oxo-2-(((3R,4S,5R)-3,4,5-tris(butyryloxy)tetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium chloride

[0388] This compound may be synthesized according to the experimental procedure described for Compound 13.



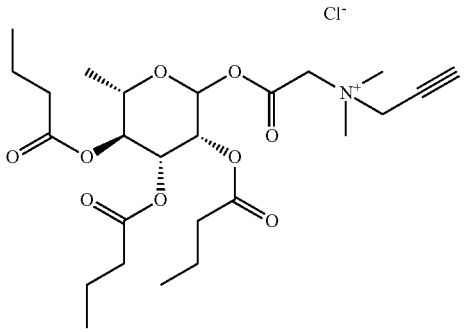
Compound 15: N,N-dimethyl-N-(2-oxo-2-(((3R,4R,5R)-3,4,5-tris(butyryloxy)tetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium chloride

[0389] This compound may be synthesized according to the experimental procedure described for Compound 13.



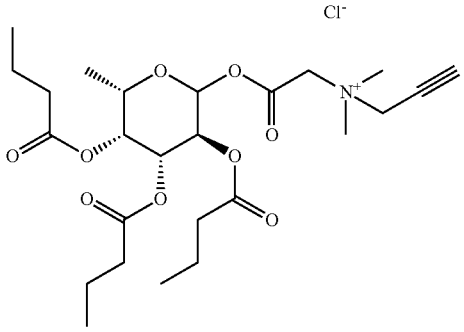
Compound 16 and Compound 54: N,N-dimethyl-N-(2-oxo-2-(((3R,4S,5S)-3,4,5-tris(butyryloxy)tetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium chloride

[0390] This compound may be synthesized according to the experimental procedure described for Compound 13.



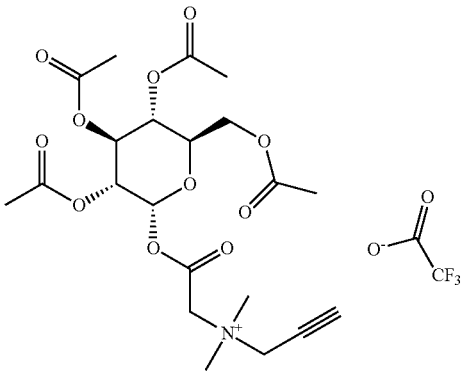
Compound 17 and Compound 60: N,N-dimethyl-N-(2-oxo-2-(((3R,4R,5S,6S)-3,4,5-tris(butyryloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium chloride

[0391] This compound may be synthesized according to the experimental procedure described for Compound 13.



Compound 18: N,N-dimethyl-N-(2-oxo-2-(((3S,4R,5R,6S)-3,4,5-tris(butyryloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium chloride

[0392] This compound may be synthesized according to the experimental procedure described for Compound 13.



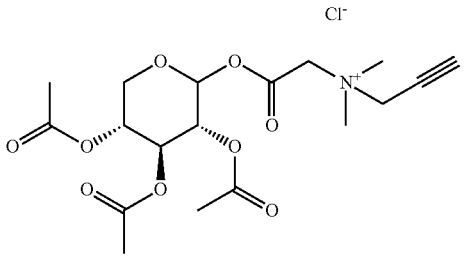
Compound 19: N,N-dimethyl-N-(2-oxo-2-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium trifluoroacetate

[0393] Step 1

[0394] Compound 2,3,4,6-tetra-O-acetyl-D-glucopyranose (Carbosynth, 2 g, 5.7 mmol, 1 eq) was dissolved in DCM (10 mL), followed by addition of 2-chloroacetyl chloride (1.4 mL, 17.6 mmol, 3 eq), DMAP (0.6 g, 4.9 mmol, 0.9 eq), and DIPEA (3 mL, 17.2 mmol, 3 eq). The reaction mixture was stirred at room temperature overnight, followed by filtration and multiple purifications by column chromatography (0-100% EtOAc in hexanes) to yield 1-(2-chloroacetoxy)-2,3,4,6-tetra-O-acetyl-D-glucopyranose (0.8 g, 1.9 mmol, mixture of anomers, 33% yield).

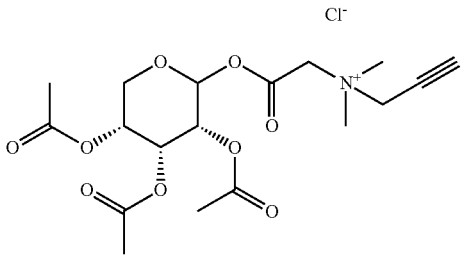
[0395] Step 2

[0396] Compound 1-(2-chloroacetoxy)-2,3,4,6-tetra-O-acetyl-D-glucopyranose (0.6 g, 1.4 mmol, 1 eq) was dissolved in acetone, followed by addition of sodium iodide (0.6 g, 4.0 mmol, 3 eq). The reaction was stirred for a few minutes, and dimethylamino-1-propyne (0.5 mL, 4.6 mmol, 3.3 eq) was added. The reaction was stirred at room temperature overnight, then filtered. The filtrate was concentrated, diluted with DMSO and water, then purified by reverse phase C_{18} column chromatography (0.1% TFA in 95% water/5% MeCN to 100% MeCN). Fractions containing product were lyophilized to yield an off-white powder (230 mg, 0.39 mmol, 28% yield, TFA salt). LCMS (M+): 472.4 ^{1}H NMR (400 MHz, DMSO-d6) δ 6.27 (d, J=3.6 Hz, 1H), 5.35 (t, J=9.9 Hz, 1H), 5.17-5.08 (m, 2H), 4.76-4.62 (m, 2H), 4.53 (d, J=2.5 Hz, 2H), 4.30-3.97 (m, 4H), 3.26 (s, 6H), 2.08-1.91 (m, 12H).



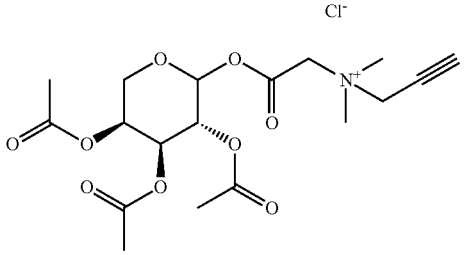
Compound 20 and Compound 55: N,N-dimethyl-N-(2-oxo-2-(((3R,4S,5R)-3,4,5-triacetoxytetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium chloride

[0397] This compound may be synthesized according to the experimental procedure described for Compound 19.



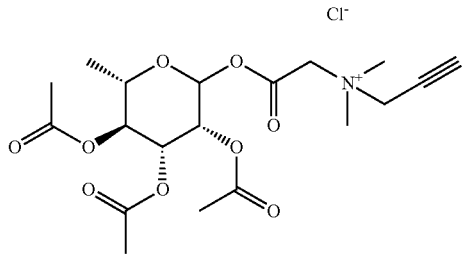
Compound 21: N,N-dimethyl-N-(2-oxo-2-(((3R,4R,5R)-3,4,5-triacetoxytetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium chloride

[0398] This compound may be synthesized according to the experimental procedure described for Compound 19.



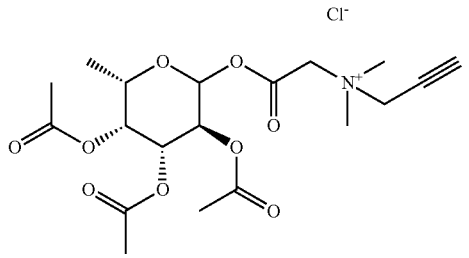
Compound 22 and Compound 57: N,N-dimethyl-N-(2-oxo-2-(((3R,4S,5S)-3,4,5-triacetoxytetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium chloride

[0399] This compound may be synthesized according to the experimental procedure described for Compound 19.



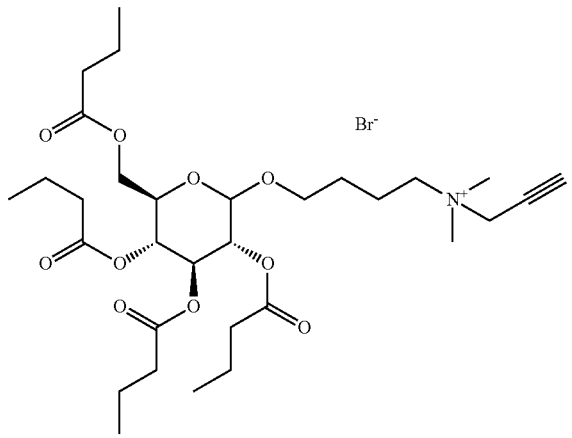
Compound 23: N,N-dimethyl-N-(2-oxo-2-(((3R,4R,5S,6S)-3,4,5-triacetoxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium chloride

[0400] This compound may be synthesized according to the experimental procedure described for Compound 19.



Compound 24: N,N-dimethyl-N-(2-oxo-2-(((3S,4R,5R,6S)-3,4,5-triacetoxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium chloride

[0401] This compound may be synthesized according to the experimental procedure described for Compound 19.



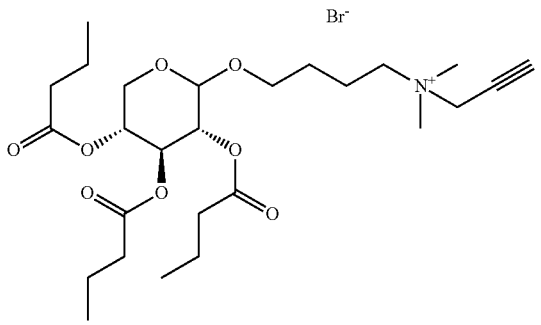
Compound 25: N,N-dimethyl-N-(prop-2-yn-1-yl)-4-(((3R,4S,5R,6R)-3,4,5-tris(butyryloxy)-6-((butyryloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0402] Step 1:

[0403] To a solution of [(2R,3R,4S,5R)-3,4,5-tri(butanoyloxy)-6-(2,2,2-trichloroethanimidoyl)oxy-tetrahydropyran-2-yl]methyl butanoate (1.5 g, 2.48 mmol, 1 eq) and 4-bromobutan-1-ol (455.33 mg, 2.98 mmol, 1.2 eq) in DCM (15 mL) was added $BF_3.Et_2O$ (1.76 g, 12.40 mmol, 1.53 mL, 5 eq). The mixture was stirred at 0° C. for 3 h and then warmed to 20° C. and stirred for 12 h. LC-MS showed[(2R,3R,4S,5R)-3,4,5-tri(butanoyloxy)-6-(2,2,2-trichloroethanimidoyl) oxy-tetrahydropyran-2-yl]methyl butanoate was consumed completely. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 3:1). Desired compound [(2R,3R,4S,5R)-6-(4-bromobutoxy)-3,4,5-tri(butanoyloxy)tetrahydropyran-2-yl]methyl butanoate (1 g, crude) was obtained as colorless oil.

[0404] Step 2:

[0405] To a mixture of [(2R,3R,4S,5R)-6-(4-bromobutoxy)-3,4,5-tri(butanoyloxy)tetrahydropyran-2-yl]methyl butanoate (0.2 g, 335.84 umol, 1 eq) and N,N-dimethylprop-2-yn-1-amine (83.76 mg, 1.01 mmol, 106.83 uL, 3 eq) in Acetone (3 mL) stirred at 90° C. for 2 h under N_2. LCMS showed [(2R,3R,4S,5R)-6-(4-bromobutoxy)-3,4,5-tri(butanoyloxy)tetrahydropyran-2-yl]methyl butanoate was consumed completely. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.10% TFA)-ACN]. The title compound (0.019 g, 28 μmol, 8.3% yield, mixture of anomers, Br) was obtained as colorless oil. LCMS (M^-): 598.4 ^1H NMR (400 MHz, DMSO-d_6) δ 5.41-5.27 (m, 1H), 5.11-4.77 (m, 3H), 4.35 (dd, J=10.3, 2.6 Hz, 2H), 4.23-3.97 (m, 4H), 3.79-3.65 (m, 1H), 3.59-3.44 (m, 1H), 3.11-3.04 (m, 6H), 2.34-2.11 (m, 8H), 1.80-1.39 (m, 12H), 0.96-0.78 (m, 12H).



Compound 26: N,N-dimethyl-N-(prop-2-yn-1-yl)-4-(((3R,4S,5R)-3,4,5-tris(butyryloxy)tetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0406] Step 1

[0407] To a solution of (3R,4S,5R)-tetrahydropyran-2,3,4,5-tetrol (10 g, 66.61 mmol, 1 eq) in Pyridine (100 mL) was added butanoyl butanoate (63.22 g, 399.66 mmol, 65.38 mL, 6 eq). The mixture was stirred at 25° C. for 10 h. TLC

showed the starting reactant was consumed. The mixture was concentrated. The crude product [(3R,4S,5R)-4,5,6-tri (butanoyloxy)tetrahydropyran-3-yl] butanoate (64.89 g, crude) was obtained as yellow oil.

[0408] Step 2

[0409] To a solution of [(3R,4S,5R)-4,5,6-tri(butanoyloxy)tetrahydropyran-3-yl]butanoate (10 g, 23.23 mmol, 1 eq) in THF (100 mL) was added $MeNH_2$ aq. solution (4.33 g, 41.81 mmol, 30% purity, 1.8 eq) in H_2O. The mixture was stirred at 25° C. for 10 h. TLC showed the starting reactant was consumed. The mixture reaction was concentrated. The residue was purified by flash silica gel chromatography (PE:EA=5:1). [(3R,4S,5R)-4,5-di(butanoyloxy)-6-hydroxy-tetrahydropyran-3-yl] butanoate (2.65 g, 6.61 mmol, 28.4% yield, 90% purity) was obtained as yellow oil.

[0410] Step 3

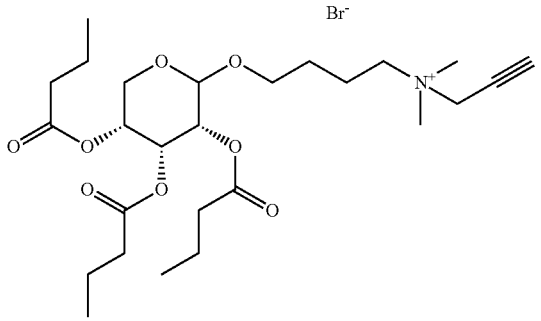
[0411] To a solution of [(3R,4S,5R)-4,5-di(butanoyloxy)-6-hydroxy-tetrahydropyran-3-yl] butanoate (500 mg, 1.39 mmol, 1 eq) in DCM (10 mL) was added 2,2,2-trichloroacetonitrile (2.00 g, 13.87 mmol, 1.39 mL, 10 eq) and DBU (105.61 mg, 693.68 umol, 104.56 uL, 0.5 eq). The mixture was stirred at 25° C. for 10 h. TLC showed the starting reactant was consumed. The mixture was concentrated. The residue was purified by flash silica gel chromatography (PE:EA=5:1). Compound [(3R,4S,5R)-4,5-di(butanoyloxy)-6-(2,2,2-trichloroethanimidoyl)oxy-tetrahydropyran-3-yl] butanoate (0.5 g, 792.42 umol, 57.1% yield, 80% purity) was obtained as a white solid.

[0412] Step 4

[0413] To a solution of [(3R,4S,5R)-4,5-di(butanoyloxy)-6-(2,2,2-trichloroethanimidoyl)oxy-tetrahy-dropyran-3-yl] butanoate (400 mg, 792.42 umol, 1 eq) and 4-bromobutan-1-ol (181.88 mg, 1.19 mmol, 1.5 eq) in DCM (40 mL) was added $BF_3.Et_2O$ (562.34 mg, 3.96 mmol, 489 uL, 5 eq) under dark at 0° C. and stirred for 3 h. Then the mixture was stirred at 25° C. for 12 h. TLC showed the starting reactant was consumed. The mixture was concentrated. The residue was purified by silica gel chromatography (PE:EA=5:1). [(3R,4S,5R)-6-(4-bromobutoxy)-4,5-di(butanoyloxy) tetrahydropyran-3-yl] butanoate (160 mg, crude) was obtained as yellow oil.

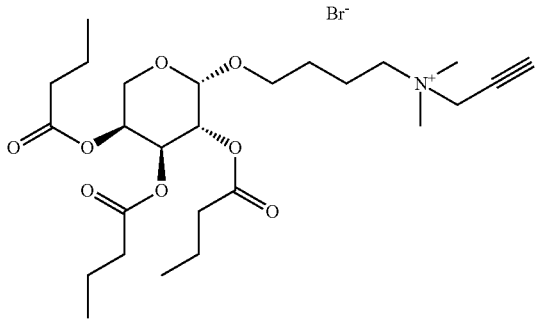
[0414] Step 5

[0415] A solution of [(3R,4S,5R)-6-(4-bromobutoxy)-4,5-di(butanoyloxy)tetrahydropyran-3-yl] butanoate (643 mg, 1.30 mmol, 1 eq) and N,N-dimethylprop-2-yn-1-amine (323.70 mg, 3.89 mmol, 412.88 uL, 3 eq) in acetone (10 mL) was stirred at 90° C. for 3 h. LCMS showed the product formed. The mixture was concentrated. The residue was purified by prep-HPLC (column: Xbridge 150*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 25%-55%, 10 min). The title compound (10 mg, 16.9 umol, 1.3% yield, mixture of anomers, Br) was obtained as yellow oil. LCMS (M^+): 498.3 ^1H NMR (400 MHz, Chloroform-d) δ 5.45-5.12 (m, 1H), 4.95-4.74 (m, 3H), 4.46-4.32 (m, 2H), 3.80-3.67 (m, 2H), 3.58-3.35 (m, 4H), 3.31-3.18 (m, 6H), 2.91-2.79 (m, 1H), 2.32-2.10 (m, 6H), 1.87-1.45 (m, 10H), 0.93-0.79 (m, 9H).



Compound 27 and Compound 67: N,N-dimethyl-N-(prop-2-yn-1-yl)-4-(((3R,4R,5R)-3,4,5-tris(butyryloxy)tetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0416] This compound may be synthesized according to the experimental procedure described for Compound 26.



Compound 28 and Compound 59: N,N-dimethyl-N-(prop-2-yn-1-yl)-4-(((2S,3R,4S,5S)-3,4,5-tris(butyryloxy)tetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0417] Step 1:

[0418] To a solution of (3R,4S,5S)-tetrahydropyran-2,3,4,5-tetrol (5 g, 33.30 mmol, 1 eq) in pyridine (50 mL) was added butanoyl butanoate (31.61 g, 199.83 mmol, 32.69 mL, 6 eq). The mixture was stirred at 25° C. for 12 h. TLC showed the starting reactant was consumed. The mixture was concentrated. [(3S,4S,5R)-4,5,6-tri(butanoyloxy)tetrahydropyran-3-yl] butanoate (15 g, crude) was obtained as yellow oil.

[0419] Step 2

[0420] To a solution of [(3S,4S,5R)-4,5,6-tri(butanoyloxy) tetrahydropyran-3-yl]butanoate (15 g, 34.84 mmol, 1 eq) in THF (50 mL) was added $MeNH_2$ aq. solution (5.41 g, 52.27 mmol, 30% purity, 1.5 eq) and stirred at 25° C. for 12 h. TLC showed the starting reactant was consumed. The mixture reaction was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 5:1). [(3S,4S,5R)-4,5-di(butanoyloxy)-6-hydroxy-tetrahydropyran-3-yl] butanoate (4 g, 8.88 mmol, 25.5% yield, 80% purity) was obtained as yellow oil.

[0421] Step 3

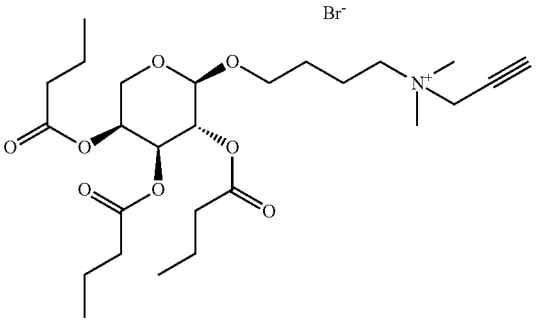
[0422] To a solution of [(3S,4S,5R)-4,5-di(butanoyloxy)-6-hydroxy-tetrahydropyran-3-yl] butanoate (2 g, 5.55 mmol, 1 eq) and 2,2,2-trichloroacetonitrile (8.01 g, 55.49 mmol, 5.56 mL, 10 eq) in DCM (20 mL) was added DBU (422.42 mg, 2.77 mmol, 418.24 uL, 0.5 eq) at 25° C. and stirred for 12 h. TLC showed the starting reactant was consumed. The mixture was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 3:1). [(3S,4S,5R)-4,5-di(butanoyloxy)-6-(2,2,2-trichloroethanimidoyl)oxy-tetrahydropyran-3-yl] butanoate (1.5 g, 2.67 mmol, 48.2% yield, 90% purity) was obtained as yellow oil.

[0423] Step 4

[0424] [(3S,4S,5R)-4,5-di(butanoyloxy)-6-(2,2,2-trichloroethanimidoyl)oxy-tetrahydropyran-3-yl]butanoate (1.5 g, 2.97 mmol, 1 eq) and 4-bromobutan-1-ol (682.05 mg, 4.46 mmol, 1.5 eq) was dissolved with DCM (20 mL) and stirred at 0° C. for 3 h in dark. $BF_3.Et_2O$ (2.11 g, 14.86 mmol, 1.83 mL, 5 eq) was added into the mixture at 0° C. and stirred for 12 h at 25° C. TLC showed the starting reactant was consumed. The mixture was concentrated. The residue was purified by flash silica gel chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1). Compound [(3S,4S,5R)-6-(4-bromobutoxy)-4,5-di(butanoyloxy)tetrahydropyran-3-yl] butanoate (1.6 g, crude) was obtained as brown oil.

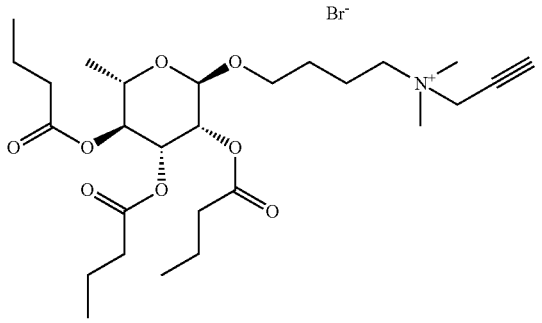
[0425] Step 5

[0426] To a solution of [(3S,4S,5R)-6-(4-bromobutoxy)-4,5-di(butanoyloxy)tetrahydropyran-3-yl] butanoate (1.6 g, 3.23 mmol, 1 eq) in acetone (10 mL) was added N,N-dimethylprop-2-yn-1-amine (805.47 mg, 9.69 mmol, 1.03 mL, 3 eq) and stirred at 90° C. for 2 h. LCMS showed the product formed. The mixture was concentrated. The residue was purified by prep-HPLC (column: Luna C18 100*30 5u; mobile phase: [water (0.1% TFA)-ACN]; B %: 25%-50%, 12 min). The title compound (42 mg, 69 μmol, 2.1% yield, Br) as a yellow oil was obtained. The anomer (Compound 29) was also isolated. LCMS (M^+): 498.3 ^1H NMR (400 MHz, DMSO-d_6) δ 5.30-5.24 (m, 1H), 5.22 (dd, J=9.9, 3.6 Hz, 1H), 5.06-4.97 (m, 2H), 4.33 (d, J=2.6 Hz, 2H), 4.04 (t, J=2.4 Hz, 1H), 3.92 (dd, J=13.4, 1.6 Hz, 1H), 3.66-3.57 (m, 2H), 3.50-3.28 (m, 3H), 3.05 (s, 6H), 2.37-2.29 (m, 2H), 2.25 (td, J=7.2, 2.3 Hz, 2H), 2.14 (td, J=7.2, 1.8 Hz, 2H), 1.78-1.66 (m, 2H), 1.62-1.39 (m, 8H), 0.94-0.77 (m, 9H).



Compound 29 and Compound 66: N,N-dimethyl-N-(prop-2-yn-1-yl)-4-(((2R,3R,4S,5S)-3,4,5-tris(butyryloxy)tetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0427] This compound was synthesized according to the experimental procedure described for Compound 28. The title compound (21 mg, 34.5 μmol, 1.1% yield, Br) was isolated as a yellow oil. LCMS (M^+): 498.2 ^1H NMR (400 MHz, DMSO-d_6) δ 5.20-5.14 (m, 1H), 5.11 (dd, J=10.1, 3.6 Hz, 1H), 4.95 (dd, J=10.1, 7.7 Hz, 1H), 4.57 (d, J=7.7 Hz, 1H), 4.30 (d, J=2.6 Hz, 2H), 4.06-4.00 (m, 1H), 3.85-3.76 (m, 2H), 3.76-3.66 (m, 1H), 3.56-3.42 (m, 1H), 3.03 (s, 6H), 2.31 (t, J=7.2 Hz, 2H), 2.24 (td, J=7.2, 3.5 Hz, 2H), 2.17-2.09 (m, 2H), 1.73-1.62 (m, 2H), 1.60-1.38 (m, 8H), 0.95-0.76 (m, 9H).



Compound 30: N,N-dimethyl-N-(prop-2-yn-1-yl)-4-(((2R,3R,4R,5S,6S)-3,4,5-tris(butyryloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0428] Step 1:

[0429] To a solution of (3R,4R,5R,6S)-6-methyltetrahydro-2H-pyran-2,3,4,5-tetraol (10 g, 60.92 mmol, 1 eq) in Pyridine (100 mL) was added butanoyl butanoate (57.82 g, 365.51 mmol, 59.79 mL, 6 eq) at 25° C. The mixture was stirred at 25° C. for 12 h. TLC indicated new spots formed. The reaction mixture was concentrated under reduced pressure to give a residue. The reaction mixture was washed with saturated sodium bicarbonate solution 300 mL (100 mL*3) and extracted with ethyl acetate 100 mL. The organic layer were washed with brine 50 mL, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (3R,4R,5S,6S)-6-methyltetrahydro-2H-pyran-2,3,4,5-tetrayl tetrabutyrate (34 g, crude) as yellow oil.

[0430] Step 2:

[0431] To a solution of (3R,4R,5S,6S)-6-methyltetrahydro-2H-pyran-2,3,4,5-tetrayl tetrabutyrate (34 g, 76.49 mmol, 1 eq) in THF (20 mL) was added $MeNH_2$ aq. solution (10.69 g, 137.68 mmol, 40% purity, 1.8 eq) at 25° C. The mixture was stirred at 25° C. for 12 hr. TLC indicated new spots formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 1:1) to give (3R,4R,5S,6S)-2-hydroxy-6-methyltetrahydro-2H-pyran-3,4,5-triyl tributyrate (18 g, 48.1 mmol, 62.9% yield) as yellow oil.

[0432] Step 3:

[0433] To a solution of (3R,4R,5S,6S)-2-hydroxy-6-methyltetrahydro-2H-pyran-3,4,5-triyl tributyrate (5 g, 13.35 mmol, 1 eq) in DCM (50 mL) was added DBU (1.02 g, 6.68 mmol, 1.01 mL, 0.5 eq) and 2,2,2-trichloroacetonitrile (19.28 g, 133.54 mmol, 13.39 mL, 10 eq) at 25° C. The mixture was stirred at 25° C. for 2 h. TLC indicated new spots

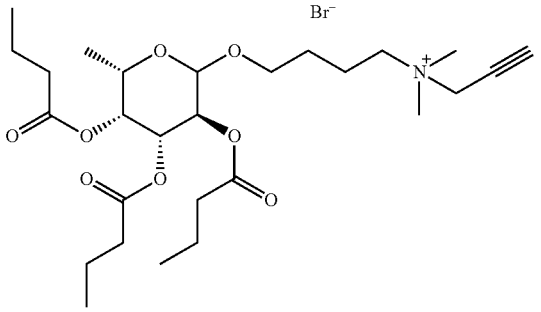
formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 1:1) to give (2S,3S,4R,5R)-2-methyl-6-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2H-pyran-3,4,5-triyl tributyrate (4 g, 7.7 mmol, 57.7% yield) as yellow oil.

[0434] Step 4:

[0435] To a solution of 4-bromobutan-1-ol (766.84 mg, 5.01 mmol, 1 eq) and (2S,3S,4R,5R)-2-methyl-6-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2H-pyran-3,4,5-triyl tributyrate (2.6 g, 5.01 mmol, 1 eq) in DCM (30 mL) was added $BF_3.Et_2O$ (3.56 g, 25.06 mmol, 3.09 mL, 5 eq) at 0° C. The mixture was stirred at 0° C. for 3 hr. The mixture was stirred at 25° C. for 12 hr. TLC indicated new spots formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20:1) to give (3R,4R,5S,6S)-2-(4-bromobutoxy)-6-methyltetrahydro-2H-pyran-3,4,5-triyl tributyrate (600 mg, 1.2 mmol, 23.5% yield) as yellow oil.

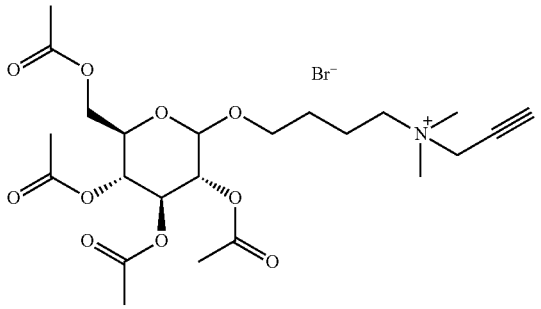
[0436] Step 5:

[0437] To a solution of (3R,4R,5S,6S)-2-(4-bromobutoxy)-6-methyltetrahydro-2H-pyran-3,4,5-triyl tributyrate (600 mg, 1.18 mmol, 1 eq) in Acetone (5 mL) was added N,N-dimethylprop-2-yn-1-amine (293.73 mg, 3.53 mmol, 374.66 uL, 3 eq) at 25° C. The mixture was stirred at 90° C. for 2 h. LCMS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Luna C18 100*30 5u; mobile phase: [water (0.1% TFA)-ACN]; B %: 25%-55%, 12 min) to give the title compound (150 mg, 253 μmol, 21.5% yield) as a yellow oil. LCMS (M^+): 512.3 ^1H NMR (400 MHz, DMSO-d_6) δ 5.16-5.06 (m, 2H), 4.91 (t, J=9.9 Hz, 1H), 4.78 (d, J=1.6 Hz, 1H), 4.34 (d, J=2.5 Hz, 2H), 4.00 (t, J=2.5 Hz, 1H), 3.87-3.76 (m, 1H), 3.65 (dt, J=9.9, 6.1 Hz, 1H), 3.50-3.40 (m, 1H), 3.40-3.31 (m, 2H), 3.06 (s, 6H), 2.38-2.08 (m, 6H), 1.81-1.68 (m, 2H), 1.62-1.39 (m, 8H), 1.10 (d, J=6.2 Hz, 3H), 0.90 (t, J=7.4 Hz, 3H), 0.87-0.75 (m, 6H).



Compound 31 and Compound 58: N,N-dimethyl-N-(prop-2-yn-1-yl)-4-(((3S,4R,5R,6S)-3,4,5-tris(butyryloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0438] This compound may be synthesized according to the experimental procedure described for Compound 30.



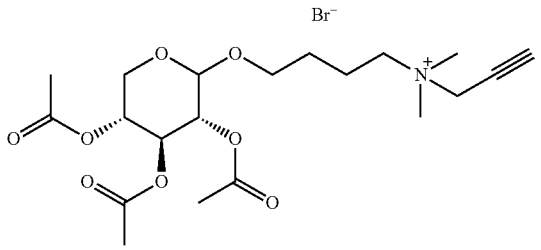
Compound 32: N,N-dimethyl-N-(prop-2-yn-1-yl)-4-(((3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0439] Step 1:

[0440] To a mixture of [(2R,3R,4S,5R)-3,4,5-triacetoxy-6-(2,2,2-trichloroethanimidoyl)oxy-tetrahydropyran-2-yl]methyl acetate (1 g, 2.03 mmol, 1 eq) and 4-bromobutan-1-ol (372.69 mg, 2.44 mmol, 1.2 eq) in DCM (10 mL) was added $BF_3.Et_2O$ (1.44 g, 10.15 mmol, 1.25 mL, 5 eq) in one portion at 0° C. under N_2. The mixture was stirred at 0° C. for 3 h and then heated to 20° C. and stirred for 12 h. TLC indicated the starting material was consumed completely. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 2:1). [(2R,3R,4S,5R)-3,4,5-triacetoxy-6-(4-bromobutoxy)tetrahydropyran-2-yl]methyl acetate (1 g, crude) was obtained as colorless oil.

[0441] Step 2:

[0442] To a mixture of [(2R,3R,4S,5R)-3,4,5-triacetoxy-6-(4-bromobutoxy)tetrahydropyran-2-yl]methyl acetate (0.2 g, 413.82 umol, 1 eq) and N,N-dimethylprop-2-yn-1-amine (103.20 mg, 1.24 mmol, 131.64 uL, 3 eq) in acetone (3 mL) was stirred at 90° C. for 2 h. LC-MS showed [(2R,3R,4S,5R)-3,4,5-triacetoxy-6-(4-bromobutoxy)tetrahydropyran-2-yl]methyl acetate was consumed completely. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. The title compound (0.006 g, 10.5 μmol, 2.5% yield, mixture of anomers) was obtained as colorless oil. LCMS (M^+): 486.2 ^1H NMR (400 MHz, DMSO-d_6) δ 5.44-5.19 (m, 1H), 5.15-4.65 (m, 3H), 4.39-4.32 (m, 2H), 4.22-3.94 (m, 4H), 3.75-3.65 (m, 1H), 3.59-3.35 (m, 3H), 3.13-3.04 (m, 6H), 2.15-1.89 (m, 12H), 1.79-1.74 (m, 2H), 1.66-1.58 (m, 2H).



Compound 33: N,N-dimethyl-N-(prop-2-yn-1-yl)-4-(((3R,4S,5R)-3,4,5-triacetoxytetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0443] Step 1

[0444] To a solution of (3R,4S,5R)-tetrahydropyran-2,3,4,5-tetrol (10 g, 66.61 mmol, 1 eq) in Pyridine (100 mL) was added acetyl acetate (40.80 g, 399.65 mmol, 37.43 mL, 6 eq). The mixture was stirred at 25° C. for 10 h. TLC showed the starting reactant was consumed. The mixture was concentrated. Compound [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (10.6 g, crude) was obtained as a white solid.

[0445] Step 2

[0446] To a solution of [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (5 g, 15.71 mmol, 1 eq) in THF (50 mL) was added $MeNH_2$ aq. solution (2.93 g, 28.28 mmol, 30% purity, 1.8 eq). The mixture was stirred at 25° C. for 10 h. TLC showed the starting reactant was consumed. The mixture reaction was concentrated. The residue was purified by flash silica gel chromatography (PE:EA=2:1). [(3R,4S,5R)-4,5-diacetoxy-6-hydroxy-tetrahydropyran-3-yl] acetate (1.53 g, 4.98 mmol, 31.7% yield, 90% purity) was obtained as a yellow solid.

[0447] Step 3

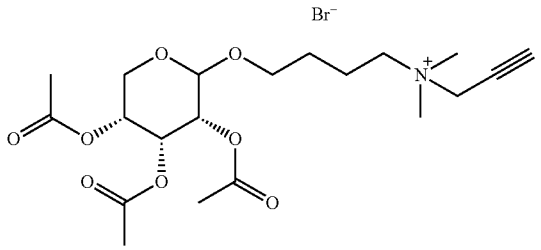
[0448] To a solution of [(3R,4S,5R)-4,5-diacetoxy-6-hydroxy-tetrahydropyran-3-yl]acetate (1 g, 3.62 mmol, 1 eq) in DCM (20 mL) was added 2,2,2-trichloroacetonitrile (5.23 g, 36.20 mmol, 3.63 mL, 10 eq) and DBU (275.55 mg, 1.81 mmol, 272.82 uL, 0.5 eq). The mixture was stirred at 25° C. for 10 h. TLC showed the starting reactant was consumed. The mixture was concentrated. The residue was purified by flash silica gel chromatography (PE:EA=5:1). Compound [(3R,4S,5R)-4,5-diacetoxy-6-(2,2,2-trichloroethanimidoyl) oxy-tetrahydropyran-3-yl] acetate (1.09 g, 2.07 mmol, 57.3% yield, 80% purity) was obtained as a white solid.

[0449] Step 4

[0450] To a solution of [(3R,4S,5R)-4,5-diacetoxy-6-(2,2,2-trichloroethanimidoyl)oxy-tetrahydropyran-3-yl] acetate (1.09 g, 2.59 mmol, 1 eq) and 4-bromobutan-1-ol (594.79 mg, 3.89 mmol, 1.5 eq) in DCM (10 mL) was added $BF_3.Et_2O$ (1.84 g, 12.96 mmol, 1.60 mL, 5 eq) in dark and stirred at 0° C. for 3 h. Then the mixture was stirred at 25° C. for 12 h. TLC showed the starting reactant was consumed. The mixture was concentrated and purified by flash silica gel chromatography (PE:EA=5:1). [(3R,4S,5R)-4,5-diacetoxy-6-(4-bromobutoxy)tetrahydropyran-3-yl] acetate (429 mg, 835 umol, 32.2% yield, 80% purity) was obtained as yellow oil.

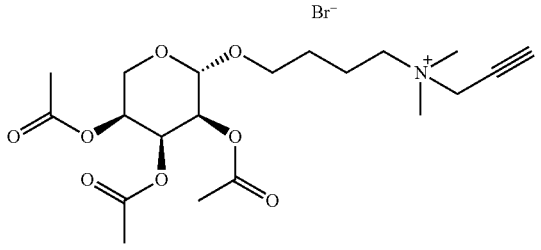
[0451] Step 5

[0452] The solution of [(3R,4S,5R)-4,5-diacetoxy-6-(4-bromobutoxy)tetrahydropyran-3-yl] acetate (429 mg, 1.04 mmol, 1 eq) and N,N-dimethylprop-2-yn-1-amine (260.16 mg, 3.13 mmol, 331.84 uL, 3 eq) in acetone (10 mL) was stirred at 90° C. for 3 h. LCMS showed the product formed. The mixture was concentrated. The residue was purified by prep-HPLC (column: Xbridge 150*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 25%-55%, 10 min). The title compound (10 mg, 23.2 μmol, 2.2% yield, mixture) was obtained as a yellow oil. LCMS (M^+) 414.2 ^1H NMR (400 MHz, Chloroform-d) δ 5.5-5.1 (m, 1H), 5.0-4.8 (m, 3H), 4.6-4.4 (m, 2H), 3.9-3.7 (m, 2H), 3.7-3.4 (m, 4H), 3.4-3.2 (m, 6H), 3.0-2.6 (m, 1H), 2.4-2.0 (m, 9H), 2.0-1.6 (m, 4H).



Compound 34: N,N-dimethyl-N-(prop-2-yn-1-yl)-4-(((3R,4R,5R)-3,4,5-triacetoxytetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0453] This compound may be synthesized according to the experimental procedure described for Compound 33.



Compound 35 and compound 62: N,N-dimethyl-N-(prop-2-yn-1-yl)-4-(((2S,3R,4S,5S)-3,4,5-triacetoxytetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0454] Step 1

[0455] To a solution of (3R,4S,5S)-tetrahydropyran-2,3,4,5-tetrol (3 g, 19.98 mmol, 1 eq) in Pyridine (50 mL) was added acetyl acetate (12.24 g, 119.90 mmol, 11.23 mL, 6 eq) and then the mixture was stirred at 25° C. for 12 h. TLC showed the starting reactant was consumed. To the mixture was added H_2O (250 mL) at 0° C., extracted with EtOAc (300 mL) and the organic layer was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 4:1). [(3S,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (5 g, crude) was obtained as yellow solid.

[0456] Step 2

[0457] To a solution of [(3S,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (5 g, 15.71 mmol, 1 eq) in THF (50 mL) was added $MeNH_2$ aq. solution (2.44 g, 23.56 mmol, 30% purity, 1.5 eq) and stirred at 25° C. for 12 h. TLC showed the starting reactant was consumed. The mixture reaction was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 5:1). [(3S,4S,5R)-4,5-diacetoxy-6-hydroxy-tetrahydropyran-3-yl] acetate (2 g, 6.5 mmol, 41.5% yield, 90% purity) was obtained as yellow solid.

[0458] Step 3

[0459] To a solution of [(3S,4S,5R)-4,5-diacetoxy-6-hydroxy-tetrahydropyran-3-yl]acetate (2 g, 7.24 mmol, 1 eq) and 2,2,2-trichloroacetonitrile (10.45 g, 72.40 mmol, 7.26 mL, 10 eq) in DCM (10 mL) was added DBU (551.11 mg,

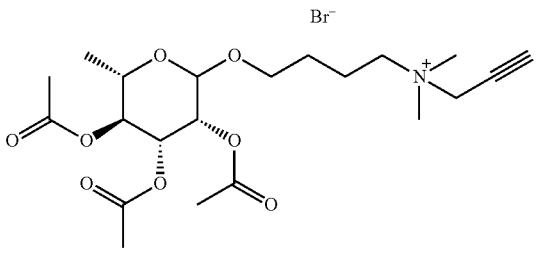
3.62 mmol, 545.65 uL, 0.5 eq) at 25° C. and stirred for 12 h. TLC showed the starting reactant was consumed. The mixture was combined work-up with another batch in Et16408-556. The combined mixture was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 3:1). [(3S,4S,5R)-4,5-diacetoxy-6-(2,2,2-trichloroethanimidoyl)oxy-tetrahydropyran-3-yl] acetate (1.5 g in total) was obtained as white solid.

[0460] Step 4

[0461] [(3S,4S,5R)-4,5-diacetoxy-6-(2,2,2-trichloroethanimidoyl)oxy-tetrahydropyran-3-yl] acetate (500 mg, 1.19 mmol, 1 eq) and 4-bromobutan-1-ol (236.46 mg, 1.55 mmol, 1.3 eq) was dissolved with DCM (5 mL) and stirred at 0° C. for 3 h in dark. $BF_3.Et_2O$ (843.55 mg, 5.94 mmol, 733.52 uL, 5 eq) was added into the mixture at 0° C. and stirred for 12 h at 25° C. TLC showed the starting reactant was consumed. The mixture was concentrated. The residue was purified by flash silica gel chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1). [(3S,4S,5R)-4,5-diacetoxy-6-(4-bromobutoxy)tetrahydropyran-3-yl] acetate (500 mg, crude) was obtained as brown oil.

[0462] Step 5

[0463] To a solution of [(3S,4S,5R)-4,5-diacetoxy-6-(4-bromobutoxy)tetrahydropyran-3-yl] acetate (500 mg, 1.22 mmol, 1 eq) in acetone (5 mL) was added N,N-dimethylprop-2-yn-1-amine (303.22 mg, 3.65 mmol, 386.76 uL, 3 eq) and stirred at 90° C. for 2 h. LCMS showed the product formed. The reaction mixture was concentrated. The residue was purified by prep-HPLC (column: Luna C18 100*30 5u; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-30%, 12 min). The title compound (120 mg, 290 umol, 23.8% yield) was obtained as colorless oil. LCMS (M^+): 414.2 ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.30-5.25 (m, 1H), 5.22 (dd, J=9.9, 3.6 Hz, 1H), 5.06-4.97 (m, 2H), 4.36 (d, J=2.6 Hz, 2H), 4.07 (t, J=2.5 Hz, 1H), 3.93 (dd, J=13.4, 1.5 Hz, 1H), 3.71-3.61 (m, 2H), 3.51-3.34 (m, 3H), 3.08 (s, 6H), 2.13-2.01 (m, 6H), 1.96 (s, 3H), 1.82-1.72 (m, 2H), 1.61 (q, J=6.7 Hz, 2H).



Compound 36: N,N-dimethyl-N-(prop-2-yn-1-yl)-4-(((3R,4R,5S,6S)-3,4,5-triacetoxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0464] Step 1

[0465] To a solution of (3R,4R,5R,6S)-6-methyltetrahydropyran-2,3,4,5-tetrol (10 g, 60.92 mmol, 1 eq) in Pyridine (100 mL) was added acetyl acetate (37.31 g, 365.51 mmol, 34.23 mL, 6 eq) at 25° C. The mixture was stirred at 25° C. for 12 hr. TLC indicated new spots formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10:1 to 1:1) to give [(2S,3S,4R,5R)-4,5,6-triacetoxy-2-methyl-tetrahydropyran-3-yl] acetate (16 g, 48 mmol, 79% yield) as a colorless oil.

[0466] Step 2

[0467] To a solution of [(2S,3S,4R,5R)-4,5,6-triacetoxy-2-methyl-tetrahydropyran-3-yl] acetate (16 g, 48.15 mmol, 1 eq) in THF (160 mL) was added $MeNH_2$ aq. (6.73 g, 86.67 mmol, 40% purity, 1.8 eq) at 25° C. The mixture was stirred at 25° C. for 12 hr. TLC indicated new spots formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 0:1) to give [(2S,3S,4R,5R)-4,5-diacetoxy-6-hydroxy-2-methyl-tetrahydropyran-3-yl] acetate (8 g, 28 mmol, 57% yield) as a white solid.

[0468] Step 3

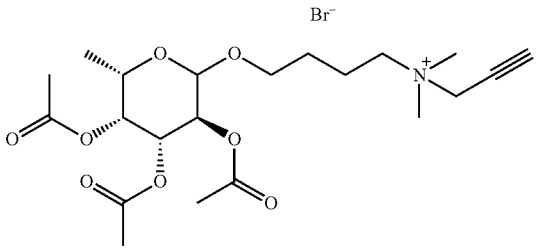
[0469] To a solution of [(2S,3S,4R,5R)-4,5-diacetoxy-6-hydroxy-2-methyl-tetrahydropyran-3-yl] acetate (3 g, 10.34 mmol, 1 eq) in DCM (30 mL) was added DBU (786.71 mg, 5.17 mmol, 778.92 uL, 0.5 eq) and 2,2,2-trichloroacetonitrile (14.92 g, 103.35 mmol, 10.36 mL, 10 eq) at 25° C. The mixture was stirred at 25° C. for 2 hr. TLC indicated new spots formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10:1 to 9:1) to give [(2S,3S,4R,5R)-4,5-diacetoxy-2-methyl-6-(2,2,2-trichloroethanimidoyl)oxy-tetrahydropyran-3-yl] acetate (3 g, 6.9 mmol, 66.8% yield) as a yellow oil.

[0470] Step 4

[0471] To a solution of [(2S,3S,4R,5R)-4,5-diacetoxy-2-methyl-6-(2,2,2-trichloroethanimidoyl)oxy-tetrahydropyran-3-yl] acetate (1.5 g, 3.45 mmol, 1 eq) and 4-bromobutan-1-ol (686.49 mg, 4.49 mmol, 1.3 eq) in DCM (15 mL) was added $BF_3.Et_2O$ (2.45 g, 17.26 mmol, 2.13 mL, 5 eq) at 0° C. The mixture was stirred at 0° C. for 3 hr. The mixture was stirred at 25° C. for 12 hr. TLC indicated new spots formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10:1 to 1:1) to give [(2S,3S,4R,5R)-4,5-diacetoxy-6-(4-bromobutoxy)-2-methyl-tetrahydropyran-3-yl]acetate (300 mg, 705 umol, 20% yield) as a yellow oil.

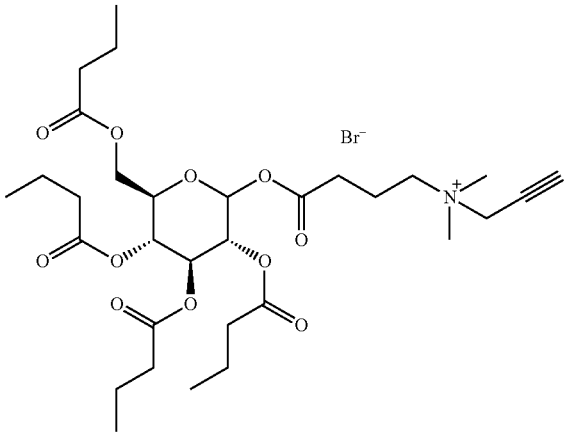
[0472] Step 5

[0473] To a solution of [(2S,3S,4R,5R)-4,5-diacetoxy-6-(4-bromobutoxy)-2-methyl-tetrahydropyran-3-yl] acetate (250 mg, 587.9 umol, 1 eq) in acetone (5 mL) was added N,N-dimethylprop-2-yn-1-amine (146.61 mg, 1.76 mmol, 187.00 uL, 3 eq) at 25° C. The mixture was stirred at 90° C. for 4 hr. LCMS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Luna C18 100*30 5u; mobile phase: [water (water (0.1% TFA)-ACN]; B %: 10%-35%, 12 min) to give the title compound (47 mg, 90.6 umol, 15.4% yield, mixture of anomers) as a yellow solid. LCMS (M^+): 428.2 ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.12-5.03 (m, 2H), 4.87 (t, J=9.8 Hz, 1H), 4.79 (d, J=1.6 Hz, 1H), 4.34 (d, J=2.6 Hz, 2H), 4.01 (t, J=2.5 Hz, 1H), 3.86-3.75 (m, 1H), 3.70-3.60 (m, 1H), 3.50-3.36 (m, 1H), 3.39-3.31 (m, 2H), 3.06 (s, 6H), 2.09 (s, 3H), 2.02 (s, 3H), 1.92 (s, 3H), 1.79-1.68 (m, 2H), 1.64-1.46 (m, 2H), 1.11 (d, J=6.2 Hz, 3H).



Compound 37 and Compound 37: N,N-dimethyl-N-(prop-2-yn-1-yl)-4-(((3S,4R,5R,6S)-3,4,5-triacetoxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0474] This compound may be synthesized according to the experimental procedure described for Compound 36.



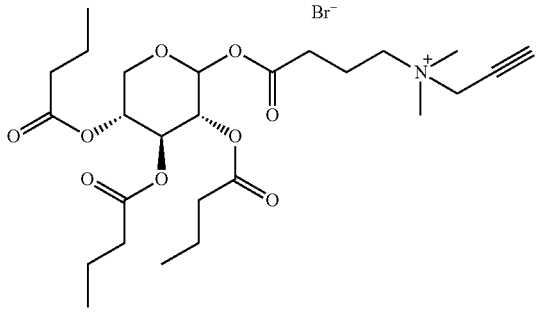
Compound 38: N,N-dimethyl-4-oxo-N-(prop-2-yn-1-yl)-4-(((3R,4S,5R,6R)-3,4,5-tris(butyryloxy)-6-((butyryloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy) butan-1-aminium bromide

[0475] Step 1:

[0476] To a mixture of [(2R,3R,4S,5R)-3,4,5-tri(butanoyloxy)-6-hydroxy-tetrahydropyran-2-yl]methyl butanoate (1 g, 2.17 mmol, 1 eq) in DCM (10 mL) was added 4-bromobutanoyl chloride (1.21 g, 6.51 mmol, 755.05 uL, 3 eq) and Pyridine (858.82 mg, 10.86 mmol, 876.35 uL, 5 eq) in one portion at 20° C. under N_2. The mixture was stirred at 20° C. for 12 h. TLC showed indicated[(2R,3R,4S,5R)-3,4,5-tri(butanoyloxy)-6-hydroxy-tetrahydropyran-2-yl]methyl butanoate was consumed completely. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 5:1). Compound [(3R,4S,5R,6R)-3,4,5-tri(butanoyloxy)-6-(butanoyloxymethyl)tetrahydropyran-2-yl]4-bromobutanoate (1.5 g, crude) was obtained as colorless oil.

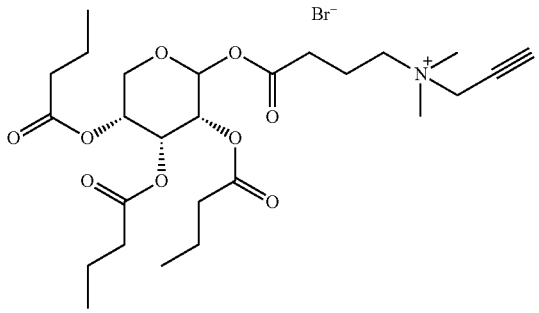
[0477] Step 2:

[0478] To a mixture of [(3R,4S,5R,6R)-3,4,5-tri(butanoyloxy)-6-(butanoyloxymethyl)tetrahydropyran-2-yl] 4-bromobutanoate (0.2 g, 328.14 umol, 1 eq) and N,N-dimethylprop-2-yn-1-amine (81.84 mg, 984.41 umol, 104.38 uL, 3 eq) in Acetone (3 mL) was stirred at 90° C. for 2 h. LCMS showed [(3R,4S,5R,6R)-3,4,5-tri(butanoyloxy)-6-(butanoyloxymethyl)tetrahydropyran-2-yl]4-bromobutanoate (0.2 g, 328.14 umol, 1 eq) was consumed completely. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. The title compound (0.028 g, 40.4 μmol, 12.3% yield, mixture of anomers, Br) was obtained as a colorless oil. LCMS (M^+): 612.3 ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.28-5.95 (m, 1H), 5.56-5.34 (m, 1H), 5.20-4.94 (m, 2H), 4.44-4.35 (m, 2H), 4.30-4.12 (m, 2H), 4.10-3.98 (m, 2H), 3.45-3.30 (m, 2H), 3.14-3.06 (m, 6H), 2.78-2.40 (m, 2H), 2.34-2.13 (m, 8H), 2.06-1.88 (m, 2H), 1.61-1.40 (m, 8H), 0.93-0.79 (m, 12H).



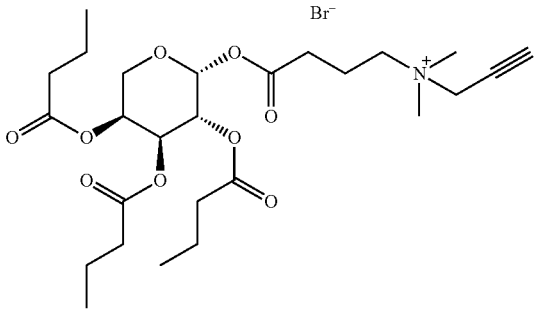
Compound 39: N,N-dimethyl-4-oxo-N-(prop-2-yn-1-yl)-4-(((3R,4S,5R)-3,4,5-tris(butyryloxy)tetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0479] This compound may be synthesized according to the experimental procedure described for Compound 38.



Compound 40 and Compound 68: N,N-dimethyl-4-oxo-N-(prop-2-yn-1-yl)-4-(((3R,4R,5R)-3,4,5-tris(butyryloxy)tetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0480] This compound may be synthesized according to the experimental procedure described for Compound 38.



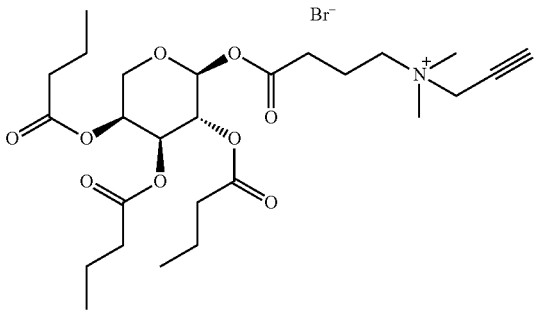
Compound 41A: N,N-dimethyl-4-oxo-N-(prop-2-yn-1-yl)-4-(((2R,3R,4S,5S)-3,4,5-tris(butyryloxy) tetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0481] Step 1

[0482] [(3S,4S,5R)-4,5-di(butanoyloxy)-6-hydroxy-tetrahydropyran-3-yl] butanoate (500 mg, 1.39 mmol, 1 eq) and 4-bromobutanoyl chloride (771.84 mg, 4.16 mmol, 482.40 uL, 3 eq) was dissolved with DCM (5 mL). Then Pyridine (548.70 mg, 6.94 mmol, 559.90 uL, 5 eq) was added into the mixture and stirred for 12 h at 25° C. TLC showed the starting reactant was consumed. The reaction mixture was concentrated. [(3R,4S,5S)-3,4,5-tri(butanoyloxy)tetrahydropyran-2-yl] 4-bromobutanoate (0.5 g, crude) was obtained as colorless oil.

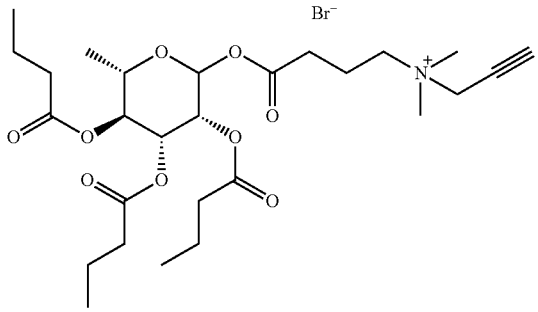
[0483] Step 2

[0484] To a solution of [(3R,4S,5S)-3,4,5-tri(butanoyloxy) tetrahydropyran-2-yl] 4-bromobutanoate (500 mg, 981.58 umol, 1 eq) in Acetone (5 mL) was added N,N-dimethylprop-2-yn-1-amine (244.80 mg, 2.94 mmol, 312.24 uL, 3 eq) and stirred at 90° C. for 2 h. LCMS showed the product formed. The mixture was concentrated. The residue was purified by prep-HPLC (column: Luna C18 100*30 Su; mobile phase: [water (0.1% TFA)-ACN]; B %: 25%-50%, 12 min). The title compound (67 mg, 107 umol, 11% yield, Br) as a yellow oil was obtained. The anomer (Compound 42) was also isolated. LCMS (M^+): 512.3 ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.23 (d, J=3.6 Hz, 1H), 5.41-5.35 (m, 1H), 5.32 (dd, J=10.7, 3.4 Hz, 1H), 5.18 (dd, J=10.7, 3.6 Hz, 1H), 4.39 (d, J=2.6 Hz, 2H), 4.17-4.06 (m, 2H), 3.80 (dd, J=13.4, 2.0 Hz, 1H), 3.41-3.34 (m, 2H), 3.10 (s, 6H), 2.70-2.58 (m, 2H), 2.43-2.34 (m, 2H), 2.34-2.14 (m, 4H), 2.05-1.90 (m, 2H), 1.66-1.44 (m, 6H), 0.97-0.81 (m, 9H).



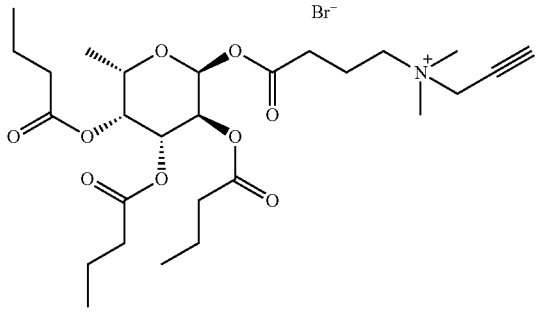
Compound 41B and Compound 65: N,N-dimethyl-4-oxo-N-(prop-2-yn-1-yl)-4-(((2S,3R,4S,5S)-3,4,5-tris(butyryloxy)tetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0485] This compound was synthesized according to the experimental procedure described for Compound 41. The title compound (30 mg, 48.1 μmol, 4.9% yield, Br) was obtained as a yellow oil. LCMS (M^+): 512.3 ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.81 (d, J=7.8 Hz, 1H), 5.40-5.28 (m, 1H), 5.27-5.08 (m, 2H), 4.43-4.35 (m, 2H), 4.15-3.84 (m, 4H), 3.40-3.31 (m, 2H), 3.09 (s, 6H), 2.49-2.14 (m, 8H), 1.97-1.90 (m, 2H), 1.66-1.42 (m, 6H), 0.93 (t, J=7.4 Hz, 3H), 0.92-0.80 (m, 6H).



Compound 42: N,N-dimethyl-4-oxo-N-(prop-2-yn-1-yl)-4-(((3R,4R,5S,6S)-3,4,5-tris(butyryloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0486] This compound may be synthesized according to the experimental procedure described for Compound 38.



Compound 43: N,N-dimethyl-4-oxo-N-(prop-2-yn-1-yl)-4-(((2S,3S,4R,5R,6S)-3,4,5-tris(butyryloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0487] Step 1:

[0488] (3S,4R,5S,6S)-6-methyltetrahydro-2H-pyran-2,3,4,5-tetraol (5 g, 30.46 mmol, 1 eq) was dissolved in Pyridine

(50 mL) and butanoyl butanoate (28.91 g, 182.75 mmol, 29.90 mL, 6 eq) was added. The mixture was stirred at 25° C. for 12 h. TLC indicated the starting material was consumed completely. The reaction mixture was concentrated under reduced pressure to give a residue. (3S,4R,5R,6S)-6-methyltetrahydro-2H-pyran-2,3,4,5-tetrayl tetrabutyrate (12.8 g, crude) was obtained as yellow oil.

[0489] Step 2:

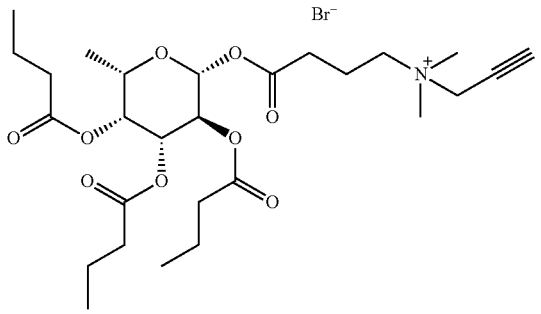
[0490] To a solution of (3S,4R,5R,6S)-6-methyltetrahydro-2H-pyran-2,3,4,5-tetrayl tetrabutyrate (12.5 g, 28.12 mmol, 1 eq) in THF (100 mL) was added $MeNH_2$ aq. solution (5.24 g, 50.62 mmol, 30% purity, 1.8 eq). The mixture was stirred at 25° C. for 12 h. TLC indicated the starting material was consumed completely. The reaction mixture was concentrated under reduced pressure to give a residue as colorless oil. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 3:1). (3S,4R,5R,6S)-2-hydroxy-6-methyltetrahydro-2H-pyran-3,4,5-triyl tributyrate (4.0 g, crude) was obtained as a colorless oil.

[0491] Step 3:

[0492] To a solution of (3S,4R,5R,6S)-2-hydroxy-6-methyltetrahydro-2H-pyran-3,4,5-triyl tributyrate (1 g, 2.67 mmol, 1 eq) in DCM (10 mL) was added 4-bromobutanoyl chloride (1.49 g, 8.01 mmol, 928.66 uL, 3 eq) and Pyridine (1.06 g, 13.35 mmol, 1.08 mL, 5 eq). The mixture was stirred at 25° C. for 12 h. TLC indicated the reaction was completed. The reaction mixture was concentrated under reduced pressure to give a residue as yellow oil. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=15:1 to 5:1). (3S,4R,5R,6S)-2-((4-bromobutanoyl)oxy)-6-methyltetrahydro-2H-pyran-3,4,5-triyl tributyrate (600 mg, crude) was obtained as a yellow oil.

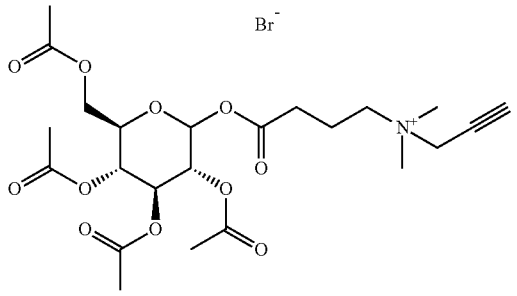
[0493] Step 4:

[0494] To a solution of (3S,4R,5R,6S)-2-((4-bromobutanoyl)oxy)-6-methyltetrahydro-2H-pyran-3,4,5-triyl tributyrate (0.3 g, 573.16 umol, 1 eq) in acetone (10 mL) was added N,N-dimethylprop-2-yn-1-amine (142.94 mg, 1.72 mmol, 182.33 uL, 3 eq). The mixture was stirred at 90° C. for 2 h. LCMS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue as brown liquid. The residue was purified by prep-HPLC (column: Xbridge 150*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]) to give the crude product (0.12 g, 227.86 umol, 39.75% yield) as a brown liquid. Then the crude product was purified twice by prep-HPLC (column: Luna C18 100*30 5u; mobile phase: [water (0.1% TFA)-ACN]) to afford the title compound (9.5 mg, 16 μmol, 2.7% yield) and the anomer (Compound 45) as yellow oils. LCMS (M^+): 526.3 ^1H NMR (400 MHz, Chloroform-d) δ 5.60 (d, J=8.3 Hz, 1H), 5.28-5.18 (m, 2H), 5.05 (dd, J=10.4, 3.5 Hz, 1H), 4.43 (s, 2H), 3.90 (q, J=6.4 Hz, 1H), 3.57-3.53 (m, 2H), 3.25 (s, 6H), 2.81 (s, 1H), 2.52-2.46 (m, 2H), 2.36 (td, J=7.3, 2.2 Hz, 2H), 2.23-2.09 (m, 4H), 2.02 (s, 2H), 1.71-1.59 (m, 2H), 1.57-1.44 (m, 4H), 1.15 (d, J=6.4 Hz, 3H), 0.93 (t, J=7.4 Hz, 3H), 0.84 (t, J=7.4 Hz, 6H).



Compound 44: N,N-dimethyl-4-oxo-N-(prop-2-yn-1-yl)-4-(((2R,3S,4R,5R,6S)-3,4,5-tris(butyryloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0495] This compound was synthesized according to the experimental procedure described for Compound 44. The title compound (19 mg, 31 μmol, 5.5% yield) was isolated as a yellow oil. LCMS (M^+): 526.3 ^1H NMR (400 MHz, Chloroform-d) δ 6.38 (s, 1H), 5.41-5.35 (m, 3H), 4.54-4.50 (m, 2H), 4.33-4.26 (m, 1H), 3.75-3.71 (m, 2H), 3.35 (s, 6H), 2.89 (s, 1H), 2.67-2.62 (m, 2H), 2.44 (t, J=7.3 Hz, 2H), 2.21 (dd, J=24.3, 16.5 Hz, 6H), 1.80-1.66 (m, 2H), 1.68-1.57 (m, 4H), 1.18 (d, J=6.1 Hz, 3H), 1.02 (t, J=7.4 Hz, 3H), 0.93 (t, J=7.3 Hz, 6H).



Compound 45: N,N-dimethyl-4-oxo-N-(prop-2-yn-1-yl)-4-(((3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

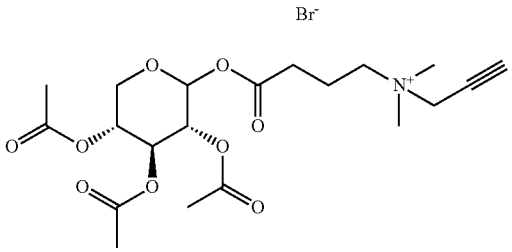
[0496] Step 1:

[0497] To a mixture of [(2R,3R,4S,5R)-3,4,5-triacetoxy-6-hydroxy-tetrahydropyran-2-yl]methyl acetate (2 g, 5.74 mmol, 1 eq) and Pyridine (2.27 g, 28.71 mmol, 2.32 mL, 5 eq) in DCM (10 mL) was added 4-bromobutanoyl chloride (3.19 g, 17.23 mmol, 2.00 mL, 3 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 12 hours. TLC indicated SM 1 was consumed completely and one new spot formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum

ether/Ethyl acetate=5/1 to 2:1). Desired compound [(3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydropyran-2-yl] 4-bromobutanoate (1.5 g, crude) was obtained as colorless oil.

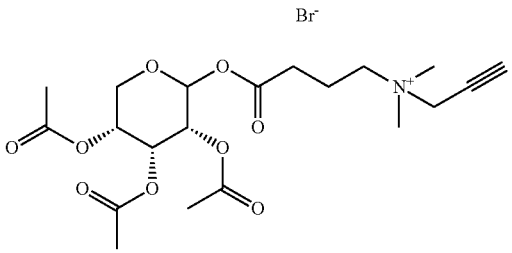
[0498] Step 2:

[0499] To a mixture of [(3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydropyran-2-yl] 4-bromobutanoate (0.2 g, 402.18 umol, 1 eq) and N,N-dimethylprop-2-yn-1-amine (100.30 mg, 1.21 mmol, 127.94 uL, 3 eq) in Acetone (3 mL) was stirred at 90° C. for 2 hours. LC-MS showed the reaction was completed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. The title compound (0.039 g, 67.2 umol, 16.7% yield, mixture of anomers, Br) was obtained as colorless oil. LCMS (M^+): 500.2 ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.30-5.92 (m, 1H), 5.52-5.21 (m, 1H), 5.17-4.90 (m, 2H), 4.43-4.36 (m, 2H), 4.28-4.10 (m, 2H), 4.09-3.97 (m, 2H), 3.45-3.32 (m, 2H), 3.14-3.07 (m, 6H), 2.75-2.43 (m, 2H), 2.08-1.89 (m, 14H).



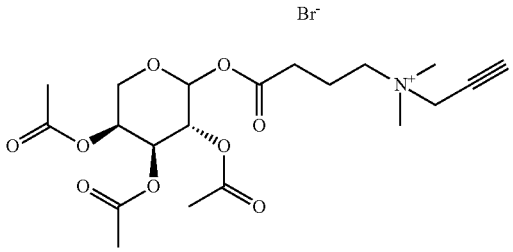
Compound 46 and Compound 53: N,N-dimethyl-4-oxo-N-(prop-2-yn-1-yl)-4-(((3R,4S,5R)-3,4,5-triacetoxytetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0500] This compound may be synthesized according to the experimental procedure described for Compound 45.



Compound 47: N,N-dimethyl-4-oxo-N-(prop-2-yn-1-yl)-4-(((3R,4R,5R)-3,4,5-triacetoxytetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0501] This compound may be synthesized according to the experimental procedure described for Compound 45.



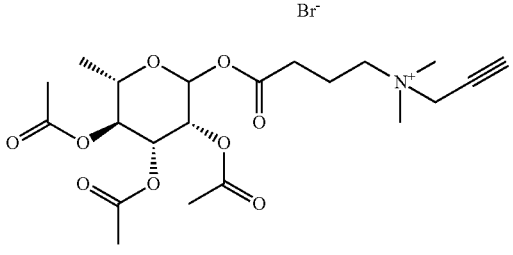
Compound 48 and Compound 64: N,N-dimethyl-4-oxo-N-(prop-2-yn-1-yl)-4-(((3R,4S,5S)-3,4,5-triacetoxytetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0502] Step 1

[0503] [(3S,4S,5R)-4,5-diacetoxy-6-hydroxy-tetrahydropyran-3-yl] acetate (200 mg, 724.01 umol, 1 eq) and 4-bromobutanoyl chloride (402.80 mg, 2.17 mmol, 251.75 uL, 3 eq) was dissolved with DCM (2 mL). Then Pyridine (286.35 mg, 3.62 mmol, 292.19 uL, 5 eq) was added into the mixture and stirred for 12 h at 25° C. TLC showed the starting reactant was consumed. The reaction mixture was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1). [(3R,4S,5S)-3,4,5-triacetoxytetrahydropyran-2-yl] 4-bromobutanoate (200 mg, 400 umol, 55% yield, 85% purity) was obtained as a yellow oil.

[0504] Step 2

[0505] To a solution of [(3R,4S,5S)-3,4,5-triacetoxytetrahydropyran-2-yl] 4-bromobutanoate (200 mg, 470.34 umol, 1 eq) in acetone (5 mL) was added N,N-dimethylprop-2-yn-1-amine (117.30 mg, 1.41 mmol, 149.62 uL, 3 eq) and stirred at 90° C. for 2 h. LCMS showed the product formed and the starting reactant was consumed. The mixture reaction was concentrated. The residue was purified by prep-HPLC (column: Luna C18 100*30 5u; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-30%, 12 min). The title compound (30 mg, 63.0 μmol, 13.4% yield, mixture of anomers) was obtained as a colorless oil. LCMS (M^+): 428.1 ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.26-5.75 (m, 1H), 5.37-5.23 (m, 2H), 5.22-5.04 (m, 1H), 4.42-4.35 (m, 2H), 4.16-3.77 (m, 3H), 3.43-3.30 (m, 2H), 3.12-3.06 (m, 6H), 2.66-2.57 (m, 2H), 2.19-1.94 (m, 11H).



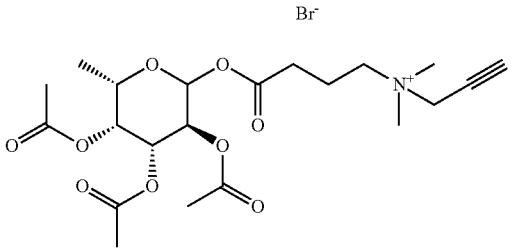
Compound 49: N,N-dimethyl-4-oxo-N-(prop-2-yn-1-yl)-4-(((3R,4R,5S,6S)-3,4,5-triacetoxy-6-methyl-tetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0506] Step 1

[0507] To a solution of [(2S,3S,4R,5R)-4,5-diacetoxy-6-hydroxy-2-methyl-tetrahydropyran-3-yl] acetate (1 g, 3.45 mmol, 1 eq) in DCM (10 mL) was added pyridine (1.36 g, 17.23 mmol, 1.39 mL, 5 eq) and 4-bromobutanoyl chloride (1.92 g, 10.34 mmol, 1.20 mL, 3 eq) at 25° C. The mixture was stirred at 25° C. for 12 hr. TLC indicated new spots formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=15:1 to 5:1) to give [(3R,4R,5S,6S)-3,4,5-triacetoxy-6-methyl-tetrahydropyran-2-yl] 4-bromobutanoate (1.2 g, 2.73 mmol, 79.3% yield) as a yellow oil.

[0508] Step 2

[0509] To a solution of [(3R,4R,5S,6S)-3,4,5-triacetoxy-6-methyl-tetrahydropyran-2-yl] 4-bromobutanoate (200 mg, 455.32 umol, 1 eq) in acetone (5 mL) was added N,N-dimethylprop-2-yn-1-amine (113.55 mg, 1.37 mmol, 144.84 uL, 3 eq) at 25° C. The mixture was stirred at 90° C. for 4 hr. LCMS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Luna C18 100*30 5u; mobile phase: [water (0.1% TFA)-ACN]; B %: 5%-35%, 12 min) to afford the title compound (71 mg, 132 μmol, 30.0% yield, mixture of anomers) as a yellow solid. LCMS (M^+): 442.2 ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.97-5.74 (m, 1H), 5.18-4.71 (m, 3H), 4.39-4.32 (m, 2H), 4.07-3.88 (m, 2H), 3.40-3.29 (m, 2H), 3.10-3.03 (m, 6H), 2.67-2.50 (m, 2H), 2.19-1.86 (m, 11H), 1.13-0.98 (m, 3H).



Compound 50: N,N-dimethyl-4-oxo-N-(prop-2-yn-1-yl)-4-(((3S,4R,5R,6S)-3,4,5-triacetoxy-6-methyl-tetrahydro-2H-pyran-2-yl)oxy)butan-1-aminium bromide

[0510] Step 1

[0511] (3S,4R,5S,6S)-6-methyltetrahydropyran-2,3,4,5-tetrol (5 g, 30.46 mmol, 1 eq) was dissolved with Pyridine (50 mL) and acetyl acetate (18.66 g, 182.76 mmol, 17.12 mL, 6 eq) was added to the mixture. The mixture was stirred at 25° C. for 12 h. TLC showed the reaction was completed. The mixture was concentrated. [(2S,3R,4R,5S)-4,5,6-triacetoxy-2-methyl-tetrahydropyran-3-yl] acetate (10 g, crude) was obtained as yellow oil.

[0512] Step 2

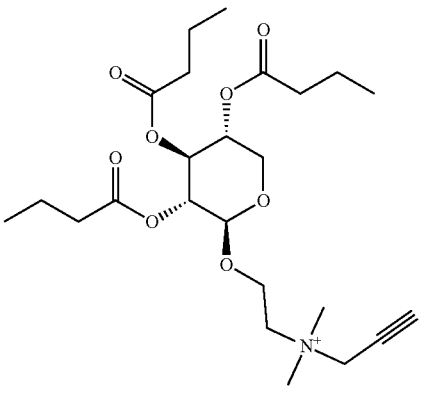
[0513] To a solution of [(2S,3R,4R,5S)-4,5,6-triacetoxy-2-methyl-tetrahydropyran-3-yl] acetate (10 g, 30.09 mmol, 1 eq) in THF (50 mL) was added $MeNH_2$ aq. solution (5.61 g, 54.17 mmol, 30% purity, 1.8 eq) and stirred at 25° C. for 12 h. TLC showed the starting reactant consumed. The mixture reaction was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 5:1). [(2S,3R,4R,5S)-4,5-diacetoxy-6-hydroxy-2-methyl-tetrahydropyran-3-yl] acetate (6 g, 18.60 mmol, 61.8% yield, 90% purity) was obtained as yellow oil.

[0514] Step 3

[0515] To a solution of [(2S,3R,4R,5S)-4,5-diacetoxy-6-hydroxy-2-methyl-tetrahydropyran-3-yl] acetate (1 g, 3.45 mmol, 1 eq) and 4-bromobutanoyl chloride (1.66 g, 8.96 mmol, 1.04 mL, 2.6 eq) in DCM (20 mL) was added Pyridine (1.36 g, 17.23 mmol, 1.39 mL, 5 eq). The mixture was stirred at 25° C. for 12 h. TLC showed the starting reactant consumed. The mixture was concentrated. The residue was purified by flash silica gel chromatography (PE:EA=5:1). [(3S,4R,5R,6S)-3,4,5-triacetoxy-6-methyl-tetrahydropyran-2-yl] 4-bromobutanoate (1.93 g, crude) was obtained as yellow oil.

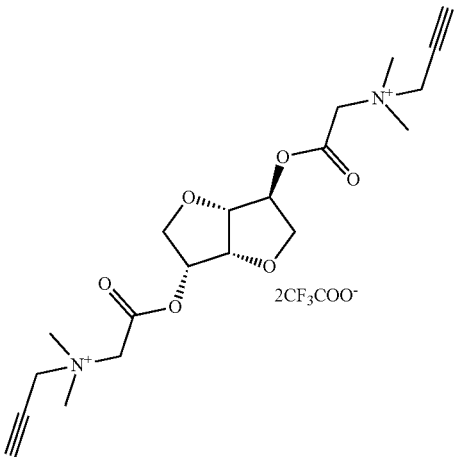
[0516] Step 4

[0517] To a solution of [(3S,4R,5R,6S)-3,4,5-triacetoxy-6-methyl-tetrahydropyran-2-yl] 4-bromobutanoate (1.83 g, 4.17 mmol, 1 eq) in acetone (20 mL) was added N,N-dimethylprop-2-yn-1-amine (1.04 g, 12.50 mmol, 1.33 mL, 3 eq). The mixture was stirred at 90° C. for 12 h. LCMS showed the starting reactant was consumed. The mixture was concentrated. The residue was purified by prep-HPLC (column: Xbridge 150*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-60%, 10 min). The title compound (100.9 mg, 183.5 μmol, 4.4% yield, mixture of anomers, Br) was obtained as a colorless oil. LCMS (M^+): 442.2 ^{1}H NMR (400 MHz, Chloroform-d) δ 6.4-6.3 (m, 1H), 5.4-5.3 (m, 3H), 4.6-4.4 (m, 2H), 4.3-4.2 (m, 1H), 3.8-3.6 (m, 2H), 3.34 (s, 6H), 2.9 (s, 1H), 2.7-2.5 (m, 2H), 2.2-2.0 (m, 11H), 1.16 (d, 3H).



Compound 51: dimethyl(prop-2-yn-1-yl)(2-{[(2R,3R,4S,5R)-3,4,5-tris(butanoyloxy)oxan-2-yl]oxy}ethyl)azanium

[0518] This compound may be synthesized according to the experimental procedure described for Compound 1.



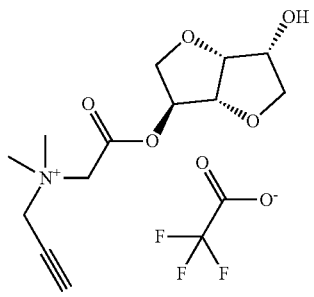
Compound 69: N,N'-((((3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(oxy))bis(2-oxoethane-2,1-diyl))bis(N,N-dimethylprop-2-yn-1-aminium) bistrifluoroacetate

[0519] Step 1:

[0520] To a solution of (3R,3aR,6S,6aR)-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3,6-diol (500 mg, 3.42 mmol, 1 eq) in CHCl3 (5 mL) was added pyridine (1.62 g, 20.53 mmol, 1.66 mL, 6 eq) and (2-chloroacetyl) 2-chloroacetate (2.34 g, 13.69 mmol, 4 eq) at 0° C. The mixture was stirred at 15° C. for 12 h. TLC indicated new spots formed. The reaction mixture was quenched by addition aq. HCl (1M, 10 mL) and extracted with ethyl acetate (20 mL*3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 5:1). Compound [(3R,3aR,6S,6aR)-6-(2-chloroacetyl)oxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3-yl] 2-chloroacetate (750 mg, 2.51 mmol, 73.29% yield) was obtained as a yellow oil.

[0521] Step 2:

[0522] To a solution of [(3R,3aR,6S,6aR)-6-(2-chloroacetyl)oxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b] furan-3-yl] 2-chloroacetate (550 mg, 1.84 mmol, 1 eq) in ACN (3 mL) was added N,N-dimethylprop-2-yn-1-amine (336.30 mg, 4.05 mmol, 428.95 uL, 2.2 eq) at 15° C. The mixture was stirred at 80° C. for 4 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Xbridge 150*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %:1%-20%, 10 min). The title compound (190 mg, 305.22 umol, 16.60% yield, $2CF_3COO$—)—) was obtained as a colorless oil. LCMS: (M+/2): 197.1 ^{1}H NMR (400 MHz, Methanol-d4) δ 5.39-5.33 (m, 2H), 4.93 (t, J=5.4 Hz, 1H), 4.62-4.45 (m, 8H), 4.16-3.88 (m, 4H), 3.64 (t, J=2.5 Hz, 2H), 3.38 (d, J=2.8 Hz, 12H).



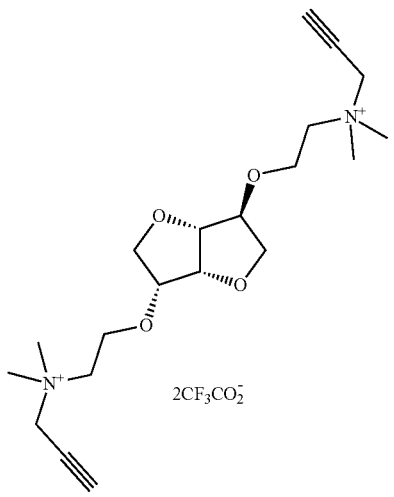
Compound 70: N-(2-(((3S,3aR,6R,6aR)-6-hydroxy-hexahydrofuro[3,2-b]furan-3-yl)oxy)-2-oxoethyl)-N,N-dimethylprop-2-yn-1-aminium trifluoroacetate

[0523] Step 1:

[0524] To a solution of (3R,3aR,6S,6aR)-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3,6-diol (300 mg, 2.05 mmol, 1 eq) in ACN (8 mL) was added K_2CO_3 (283.71 mg, 2.05 mmol, 1 eq) and 2-chloroacetyl chloride (231.85 mg, 2.05 mmol, 163.27 uL, 1 eq) at 0° C. Then the mixture was stirred at 15° C. for 2 h under N_2. TLC indicated one major new spot was detected. Compound [(3S,3aR,6R,6aR)-3-hydroxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-6-yl] 2-chloroacetate was obtained as liquid (~2.05 mmol, 8 mL in ACN). The crude product was used into the next step without further purification.

[0525] Step 2:

[0526] To a solution of [(3S,3aR,6R,6aR)-3-hydroxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-6-yl] 2-chloroacetate (2.05 mmol, 8 mL in ACN, 1 eq) was added N,N-dimethylprop-2-yn-1-amine (170.65 mg, 2.05 mmol, 217.67 uL, 1 eq). The mixture was stirred at 70° C. for 10 h under N_2. LCMS showed expected mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Xbridge 150*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-10%, 10 min) to give N-(2-(((3S,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl)oxy)-2-oxoethyl)-N,N-dimethylprop-2-yn-1-aminium trifluoroacetate (34 mg, 107.86 umol, 5.25% yield, CF_3COO—) as colorless oil. LCMS: (M+) 270.1 ^{1}H NMR (400 MHz, Methanol-d4) δ 5.33 (t, J=2.3 Hz, 1H), 4.59 (t, J=2.7 Hz, 4H), 4.53 (s, 2H), 4.41-4.22 (m, 1H), 4.08 (d, J=2.3 Hz, 2H), 3.89 (dd, J=8.9, 6.3 Hz, 1H), 3.68-3.62 (m, 1H), 3.55 (dd, J=8.9, 7.0 Hz, 1H), 3.41 (s, 6H).



Compound 71: N,N'-((((3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(oxy))bis(ethane-2,1-diyl))bis(N,N-dimethylprop-2-yn-1-aminium) bistrifluoroacetate

[0527] Step 1:

[0528] To a solution of (3R,3aR,6S,6aR)-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3,6-diol (4 g, 27.37 mmol, 1 eq) in DMF (40 mL) was added NaH (3.28 g, 82.11 mmol, 60% purity, 3 eq) at 0° C. for 0.5 h. Then to the mixture was added 2-bromoethoxy-tert-butyl-dimethyl-silane (19.64 g, 82.11 mmol, 3 eq). The mixture was stirred at 15° C. for 11.5 h. TLC showed the starting reactant was consumed and three new spots formed. The reaction mixture was quenched by addition of H_2O (30 mL) at 0° C., and extracted with EtOAc (30 mL*3). Then the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50:1 to 20:1). Compound 2-[[(3R,3aR,6S,6aR)-3-[2-[tert-butyl(dimethyl)silyl]oxyethoxy]-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-6-yl]oxy]ethoxy-tert-butyl-dimethyl-silane (3.35 g, 7.24 mmol, 26.45% yield) was obtained as yellow oil.

[0529] Step 2:

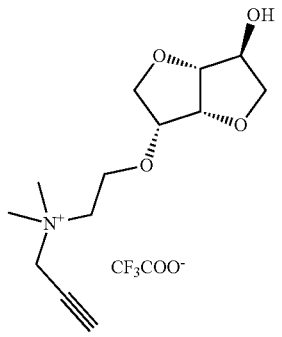
[0530] To a solution of 2-[[(3R,3aR,6S,6aR)-3-[2-[tert-butyl(dimethyl)silyl]oxyethoxy]-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-6-yl]oxy]ethoxy-tert-butyl-dimethyl-silane (2.3 g, 4.97 mmol, 1 eq) in THF (20 mL) was added pyridine.hydrofluoride (2.81 g, 19.88 mmol, 2.56 mL, 70%, 4 eq). The mixture was stirred at 15° C. for 12 h. TLC showed the starting reactant was consumed and one new spot formed. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum Ether:Ethyl Aacetate=0:1 to EA:EtOH=20:1). Compound 2-[[(3R,3aR,6S,6aR)-6-(2-hydroxyethoxy)-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3-yl]oxy]ethanol (800 mg, 3.42 mmol, 68.72% yield) was obtained as yellow oil.

[0531] Step 3:

[0532] To a solution of 2-[[(3R,3aR,6S,6aR)-6-(2-hydroxyethoxy)-2,3,3a,5,6,6a-hexahydrofuro[3,2-b] furan-3-yl]oxy]ethanol (1 g, 4.27 mmol, 1 eq) in THF (10 mL) was added imidazole (1.16 g, 17.08 mmol, 4 eq) and PPh3 (4.48 g, 17.08 mmol, 4 eq). Then to the mixture was added iodine (4.33 g, 17.08 mmol, 3.44 mL, 4 eq). The mixture was stirred at 15° C. for 2 h. LCMS showed the starting reactant was consumed. The reaction mixture was quenched by addition 15% aq. Na_2S2O_4 (10 mL) at 0° C., and extracted with EtOAc (10 mL*3). Then the organic layer was dried over Na_2SO_4 and concentrated reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 20:1). Compound (3R,3aR,6S,6aR)-3,6-bis(2-iodoethoxy)-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan (1.2 g, 2.64 mmol, 61.91% yield) was obtained as yellow oil.

[0533] Step 4:

[0534] To a solution of N,N-dimethylprop-2-yn-1-amine (1.10 g, 13.21 mmol, 1.40 mL, 6 eq) in acetone (10 mL) was added (3R,3aR,6S,6aR)-3,6-bis(2-iodoethoxy)-2,3,3a,5,6,6a-hexahydrofuro[3,2-b] furan (1 g, 2.20 mmol, 1 eq). The mixture was stirred at 90° C. for 4 h. LCMS showed the starting reactant was consumed. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Xbridge 150*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-60%, 10 min). N,N'-((((3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(oxy))bis(ethane-2,1-diyl))bis(N,N-dimethylprop-2-yn-1-aminium) bistrifluoroacetate (470 mg, 793.22 umol, 36.02% yield, 100% purity, 2CF3CO2-) was obtained as colorless oil. LCMS: (M^{2+}/2): 183.2 ^1H NMR (400 MHz, DMSO-d_6) δ 4.63 (t, J=4.6 Hz, 1H), 4.51 (d, J=4.5 Hz, 1H), 4.39 (dd, J=11.9, 2.5 Hz, 4H), 4.13-4.01 (m, 4H), 4.01-3.83 (m, 5H), 3.81 (dd, J=8.9, 6.5 Hz, 1H), 3.72 (dd, J=10.3, 3.6 Hz, 1H), 3.68-3.51 (m, 4H), 3.45 (dd, J=8.9, 7.1 Hz, 1H), 3.14-3.07 (m, 12H).



Compound 72: 343: N-(2-(((3R,3aR,6S,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl)oxy)ethyl)-N,N-dimethylprop-2-yn-1-aminium trifluoroacetate

[0535] Step 1:

[0536] To a solution of (3R,3aR,6S,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3-ol (1.9 g, 8.04 mmol, 1 eq) in DMF (30 mL) was added NaH (482.47 mg, 12.06 mmol, 60% purity, 1.5 eq) at 0° C. and stirred for 0.5 h. Then 2-bromoethoxy-tert-butyl-dimethyl-silane (2.89 g, 12.06 mmol, 1.5 eq) was added to the mixture and stirred at 15° C. for 9.5 h. TLC indicated three new spots formed. The reaction mixture was quenched by addition of H_2O (40 mL) at 0° C., and then diluted with EtOAc (40 mL) and extracted with EtOAc (40 mL*3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated

under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0:1) to give 2-[[(3R,3aR,6S,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b] furan-3-yl] oxy]ethoxy-tert-butyl-dimethyl-silane (1.9 g, 4.82 mmol, 59.88% yield) as yellow oil.

[0537] Step 2:

[0538] To a solution of 2-[[(3R,3aR,6S,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b] furan-3-yl]oxy] ethoxy-tert-butyl-dimethyl-silane (1.9 g, 4.82 mmol, 1 eq) in THF (20 mL) was added pyridine; hydrofluoride (2.05 g, 14.45 mmol, 1.86 mL, 70% purity, 3 eq). The mixture was stirred at 15° C. for 10 hr under N_2. TLC indicated one new spot formed. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 0/1) to give 2-[[(3R,3aR,6S,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3-yl]oxy]ethanol (1.1 g, 3.92 mmol, 81.49% yield) as yellow oil.

[0539] Step 3:

[0540] To a solution of 2-[[(3R,3aR,6S,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b] furan-3-yl]oxy] ethanol (1.1 g, 3.92 mmol, 1 eq) in THF (50 mL) was added PPh3 (2.32 g, 8.83 mmol, 2.25 eq) and imidazole (801.44 mg, 11.77 mmol, 3 eq). Then 12 (2.49 g, 9.81 mmol, 1.98 mL, 2.5 eq) was added to the mixture and stirred at 15° C. for 2 hr. TLC indicated one new spot was detected. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1) to give (3R,3aR,6S,6aR)-6-benzyloxy-3-(2-iodoethoxy)-2,3,3a,5,6,6a-hexahydrofuro [3,2-b]furan (1.5 g, 3.84 mmol, 97.96% yield) as yellow oil.

[0541] Step 4:

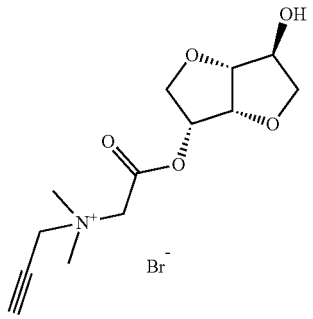
[0542] A mixture of (3R,3aR,6S,6aR)-6-benzyloxy-3-(2-iodoethoxy)-2,3,3a,5,6,6a-hexahydrofuro [3,2-b]furan (1 g, 2.56 mmol, 1 eq) in THF (10 mL) was dropped to dimethylamine (2 M, 10.00 mL, 7.80 eq, THF) and degassed and purged with N_2 3 times, and then the mixture was stirred at 15° C. for 10 hr under N_2 atmosphere. TLC indicated one new spot was detected. LCMS showed desired compound was detected. The reaction mixture was quenched by addition of H_2O (10 mL) at 15° C., and then diluted with EtOAc (10 mL) and extracted with EtOAc (10 mL*3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give 2-[[(3R,3aR,6S,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3-yl]oxy]-N,N-dimethyl-ethanamine (0.8 g, crude) as yellow oil. LCMS: (M+H+) 308.1

[0543] Step 5:

[0544] To a solution of 2-[[(3R,3aR,6S,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3-yl]oxy]-N, N-dimethyl-ethanamine (0.9 g, 2.93 mmol, 1 eq) in EtOH (100 mL) was added Pd(OH)2/C (0.9 g, 20% purity). The mixture was stirred at 80° C. for 12 hr under H2 (50 Psi). TLC indicated one major new spot was detected. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 0/1) to give (3S,3aR,6R,6aR)-6-[2-(dimethylamino)ethoxy]-2,3,3a,5,6,6a-hexahydrofuro [3,2-b]furan-3-ol (0.5 g, 2.30 mmol, 78.60% yield) as yellow oil.

[0545] Step 6:

[0546] To a solution of (3S,3aR,6R,6aR)-6-[2-(dimethylamino)ethoxy]-2,3,3a,5,6,6a-hexahydrofuro [3,2-b]furan-3-ol (500 mg, 2.30 mmol, 1 eq) in ACN (10 mL) was added 3-bromoprop-1-yne (301.15 mg, 2.53 mmol, 218.22 uL, 1.1 eq). The mixture was stirred at 15° C. for 5 hr under N_2. LCMS showed desired compound was detected. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 100*19 mm*5 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-10%, 10 min) to N-(2-(((3R,3aR,6S,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl)oxy)ethyl)-N,N-dimethylprop-2-yn-1-aminium trifluoroacetate (290 mg, 785.20 umol, 34.12% yield, CF_3COO—) as colorless oil. LCMS: (M+) 256.1 1H NMR (400 MHz, Methanol-d4) δ 4.80 (t, J=4.4 Hz, 1H), 4.48 (d, J=2.6 Hz, 2H), 4.44 (dd, J=4.2, 1.2 Hz, 1H), 4.27-4.21 (m, 1H), 4.23-4.13 (m, 2H), 3.99-3.93 (m, 2H), 3.96-3.86 (m, 2H), 3.79 (ddd, J=14.2, 8.8, 2.4 Hz, 1H), 3.67 (ddd, J=14.2, 5.0, 2.2 Hz, 1H), 3.62-3.53 (m, 2H), 3.30 (d, J=1.8 Hz 6H).



Compound 73: N-(2-(((3R,3aR,6S,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl)oxy)-2-oxoethyl)-N, N-dimethylprop-2-yn-1-aminium bromide

[0547] Step 1:

[0548] To a solution of (3R,3aR,6S,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3-ol (500 mg, 2.12 mmol, 1 eq) in DCM (5 mL) was added TEA (428.29 mg, 4.23 mmol, 589.13 uL, 2 eq). Then 2-chloroacetyl chloride (262.92 mg, 2.33 mmol, 185.16 uL, 1.1 eq) was dropped to the mixture at 0° C. and stirred at 15° C. for 10 hr. TLC indicated (3R,3aR,6S,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3-ol was consumed completely and one new spot formed. The reaction mixture was quenched by addition of H_2O (5 mL) at 15° C., and then diluted with EtOAc (5 mL) and extracted with EtOAc (5 mL*3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=0/1 to 1/1) to give [(3S,3aR,6R,6aR)-3-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-6-yl] 2-chloroacetate (230 mg, 735.42 umol, 34.75% yield) as yellow oil.

[0549] Step 2:

[0550] A mixture of [(3S,3aR,6R,6aR)-3-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-6-yl] 2-chloroacetate (230 mg, 735.42 umol, 1 eq) in THF (5 mL) was dropped to dimethylamine (2 mL, 2M, in THF) and degassed and

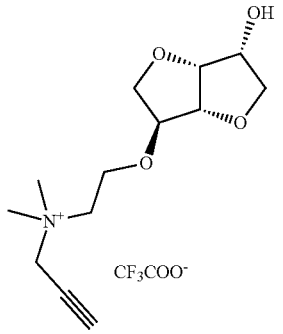
purged with N_2 3 times. And then the mixture was stirred at 15° C. for 10 hr under N_2 atmosphere. TLC indicated [(3S,3aR,6R,6aR)-3-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-6-yl] 2-chloroacetate was consumed completely and one new spot formed. LCMS showed desired mass was detected. The reaction mixture was quenched by addition of H_2O (5 mL) at 15° C., and then diluted with EtOAc (5 mL) and extracted with EtOAc (5 mL*3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH=10:1) to give [(3S,3aR,6R,6aR)-3-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-6-yl] 2-(dimethylamino)acetate (180 mg, 503.03 umol, 68.40% yield, HCl) as yellow oil. LCMS: (M+H+) 322.1

[0551] Step 3:

[0552] A mixture of [(3S,3aR,6R,6aR)-3-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-6-yl] 2-(dimethylamino)acetate (180 mg, 503.03 umol, 1 eq, HCl) and $Pd(OH)_2/C$ (0.18 g, 20% purity) in EtOH (20 mL) was degassed and purged with H_2 3 times. And then the mixture was stirred at 60° C. for 10 hr under H_2 (15 Psi) atmosphere. LCMS showed desired compound was detected. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH=10:1, 5% NH_3H_2O) to give compound [(3S,3aR,6R,6aR)-3-hydroxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-6-yl] 2-(dimethylamino)acetate (100 mg, 432.44 umol, 85.97% yield) as colorless oil. LCMS: (M+H+) 232.1

[0553] Step 4:

[0554] To a solution of [(3S,3aR,6R,6aR)-3-hydroxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-6-yl] 2-(dimethylamino)acetate (100 mg, 432.44 umol, 1 eq) in ACN (5 mL) was added 3-bromoprop-1-yne (56.59 mg, 475.69 umol, 41.01 uL, 1.1 eq). The mixture was stirred at 15° C. for 10 hr. LCMS showed desired mass was detected. The reaction mixture was filtered and the filter cake was concentrated under reduced pressure to give N-(2-(((3R,3aR,6S,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl)oxy)-2-oxoethyl)-N,N-dimethylprop-2-yn-1-aminium bromide (60 mg, 131.92 umol, 30.51% yield, 77% purity, Br—) as a white solid. LCMS: (M+) 270.1 ^1H NMR (400 MHz, DMSO-d_6) δ 5.26-5.16 (m, 2H), 4.75 (t, J=5.3 Hz, 1H), 4.57-4.40 (m, 4H), 4.21 (d, J=4.8 Hz, 1H), 4.17-4.11 (m, 1H), 4.08 (t, J=3.5 Hz, 1H), 3.77 (d, J=4.2 Hz, 2H), 3.71 (d, J=9.4 Hz, 1H), 3.64 (dd, J=9.4, 3.2 Hz, 1H), 3.24 (s, 6H).



Compound 74: N-(2-(((3S,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl)oxy)ethyl)-N,N-dimethylprop-2-yn-1-aminium trifluoroacetate

[0555] Step 1:

[0556] To a solution of (3S,3aR,6R,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3-ol (7 g, 29.63 mmol, 1 eq) in DMF (70 mL) was added NaH (1.78 g, 44.44 mmol, 60% purity, 1.5 eq) at 0° C. and stirred for 0.5 h. Then 2-bromoethoxy-tert-butyl-dimethyl-silane (10.63 g, 44.44 mmol, 1.5 eq) was added to the mixture and stirred at 15° C. for 11.5 h. TLC indicated (3S,3aR,6R,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3-ol was consumed completely and two new spots formed. The reaction mixture was quenched by addition of H_2O (80 mL) at 0° C., diluted with EtOAc (80 mL) and extracted with EtOAc (100 mL*4). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=0/1 to 2/1) to give 2-[[(3S,3aR,6R,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3-yl]oxy] ethoxy-tert-butyl-dimethyl-silane (4.2 g, 10.64 mmol, 35.93% yield) as yellow oil.

[0557] Step 2:

[0558] To a solution of 2-[[(3S,3aR,6R,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b] furan-3-yl]oxy] ethoxy-tert-butyl-dimethyl-silane (4.2 g, 10.64 mmol, 1 eq) in THF (40 mL) was added HF.Py (4.52 g, 31.93 mmol, 4.11 mL, 70%, 3 eq). The mixture was stirred at 15° C. for 12 hr under N_2. LCMS showed desired mass was detected. TLC indicated 2-[[(3S,3aR,6R,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3-yl]oxy]ethoxy-tert-butyl-dimethyl-silane was consumed completely and one new spot formed. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Ethyl acetate/Methanol=1/0 to 0/1) to give 2-[[(3S,3aR,6R,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b] furan-3-yl]oxy]ethanol (1.67 g, 5.96 mmol, 55.97% yield) as yellow oil. LCMS: (M+H+) 281.1

[0559] Step 3:

[0560] To a solution of 2-[[(3S,3aR,6R,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3-yl] oxy] ethanol (1.67 g, 5.96 mmol, 1 eq) in THF (17 mL) was added PPh3 (3.52 g, 13.40 mmol, 2.25 eq) and imidazole (1.22 g, 17.87 mmol, 3 eq). Then 12 (3.78 g, 14.89 mmol, 3.00 mL, 2.5 eq) was added to the mixture and stirred at 15° C. for 12 hr. TLC indicated two new spots formed. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 2/1) to give (3S,3aR,6R,6aR)-6-benzyloxy-3-(2-iodoethoxy)-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan (2 g, 5.13 mmol, 86.03% yield) as yellow oil.

[0561] Step 4:

[0562] A mixture of (3S,3aR,6R,6aR)-6-benzyloxy-3-(2-iodoethoxy)-2,3,3a,5,6,6a-hexahydrofuro [3,2-b]furan (2 g, 5.13 mmol, 1 eq) in THF (20 mL) was dropped to dimethylamine (20 mL, 2 M, in THF) and degassed and purged with N_2 3 times, and then the mixture was stirred at 15° C. for 10 hr under N_2 atmosphere. TLC indicated one new spot formed. LCMS showed desired compound was detected. The reaction mixture was quenched by addition of H_2O (30 mL) at 15° C., and then diluted with EtOAc (30 mL) and

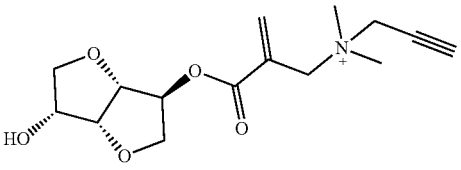
extracted with EtOAc (30 mL*4). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Ethyl acetate/Methanol=1/0 to 0/1) to give 2-[[(3S,3aR,6R,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3-yl]oxy]-N,N-dimethyl-ethanamine (1.9 g, 4.36 mmol, 85.16% yield, HI) as yellow oil. LCMS: (M+H+) 308.1

[0563] Step 5:

[0564] To a solution of 2-[[(3S,3aR,6R,6aR)-6-benzyloxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-b] furan-3-yl]oxy]-N,N-dimethyl-ethanamine (1.9 g, 4.36 mmol, 1 eq, HI) in EtOH (40 mL) was added $Pd(OH)_2/C$ (1.4 g, 20% purity). The mixture was stirred at 80° C. for 10 hr under H_2 (15 Psi). TLC indicated one new spot formed. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give (3R,3aR,6S,6aR)-6-[2-(dimethylamino) ethoxy]-2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan-3-ol as yellow oil without further purification.

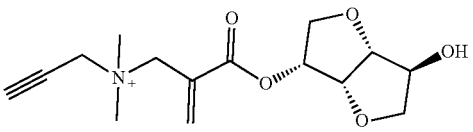
[0565] Step 6:

[0566] To a solution of (3R,3aR,6S,6aR)-6-[2-(dimethylamino)ethoxy]-2,3,3a,5,6,6a-hexahydrofuro [3,2-b]furan-3-ol (0.88 g, 4.05 mmol, 1 eq) in ACN (10 mL) was added 3-bromoprop-1-yne (530.02 mg, 4.46 mmol, 384.07 uL, 1.1 eq). The mixture was stirred at 15° C. for 10 hr. LCMS showed desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-10%, 10 min) to give N-(2-(((3S,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl)oxy)ethyl)-N,N-dimethylprop-2-yn-1-aminium trifluoroacetate (671 mg, 1.82 mmol, 44.85% yield, 100.0% purity, CF3CO2-) as yellow oil. LCMS: (M+) 256.1 1H NMR (400 MHz, Methanol-d4) δ 4.56-4.46 (m, 2H), 4.38 (d, J=2.6 Hz, 2H), 4.31-4.22 (m, 1H), 4.15-3.96 (m, 4H), 3.93-3.80 (m, 2H), 3.75-3.65 (m, 2H), 3.56 (t, J=2.5 Hz, 1H), 3.48 (dd, J=8.8, 7.2 Hz, 1H), 3.23 (s, 6H).



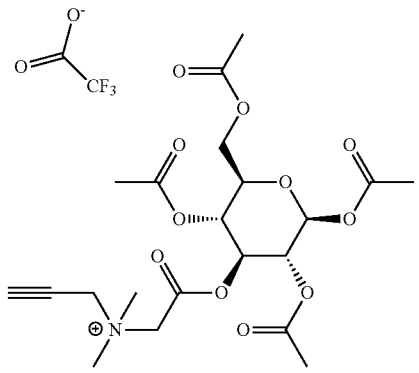
Compound 75: (3-{[(3S,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-oxopropyl)dimethyl(prop-2-yn-1-yl)azanium

[0567] This compound may be synthesized according to the experimental procedure described for Compound 344.



Compound 76: (3-{[(3R,3aR,6S,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl]oxy}-2-methylidene-3-oxopropyl)dimethyl(prop-2-yn-1-yl)azanium

[0568] This compound may be synthesized according to the experimental procedure described for Compound 344.



Compound 102: N,N-dimethyl-N-(2-oxo-2-(((2S,3R,4S,5R,6R)-2,3,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-4-yl)oxy)ethyl)prop-2-yn-1-aminium trifluoroacetate

[0569] Step 1:

[0570] Tetrahydrofuran (5 mL) was added to 60% NaH (0.2 g, 5.0 mmol, 1.3 eq) in mineral oil under nitrogen, followed by addition of TBAI (71 mg, 0.22 mmol, 0.05 eq), then cooled to 0° C. Compound 1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose (Sigma Aldrich, CAS: 582-52-5, 1 g, 3.8 mmol, 1 eq) in THF (3 mL) was added dropwise, followed by dropwise addition of benzyl bromide (0.55 mL, 4.6 mmol, 1.2 eq). The ice bath was removed and the reaction was warmed to 55° C., and stirred overnight. The reaction was quenched with methanol (1 mL), then filtered and loaded onto silica. Purification by column chromatography (100% hexane to 100% ethyl acetate) yielded 3-benzyl-1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose as a viscous oil (877 mg, 2.5 mmol 65% yield).

[0571] Step 2:

[0572] Compound 3-benzyl-1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose (877 mg, 2.5 mmol, 1 eq) was dissolved in TFA (1 mL) followed by addition of water (1 mL), then stirred overnight. The reaction solution was concentrated by rotary evaporation, and the solids were precipitated out in ethyl acetate and washed with diethyl ether. Solids were dried in vacuo to 3-benzyl-beta-D-glucopyranose as a white solid (400 mg, 1.48 mmol, 59% yield).

[0573] Step 3:

[0574] Compound 3-benzyl-beta-D-glucopyranose (400 mg, 1.48 mmol, 1 eq) was stirred in acetic anhydride (1.6 mL, 16.9 mmol, 11.4 eq) and pyridine (1.6 mL, 19.9 mmol, 13.4 eq) overnight at room temperature. The reaction was concentrated by rotary evaporation and purified by column chromatography (100% hexanes to 100% ethyl acetate) to

yield 3-benzyl-1,2,4,6-tetra-O-acetyl-beta-D-glucopyranose as a waxy solid (436 mg, 0.99 mmol, 67% yield).

[0575] Step 4:

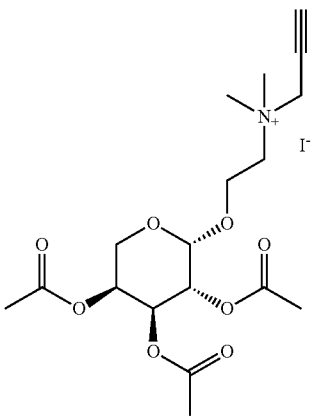
[0576] Compound 3-benzyl-1,2,4,6-tetra-O-acetyl-beta-D-glucopyranose (500 mg, 1.14 mmol, 1 eq) was dissolved in methanol (approximately 10 mL), and flowed through an H-cube hydrogenation flow system with a 10% Pd/C catalyst cartridge at 0.4 mL/min and hydrogen pressure at 30 bar. Reaction was continuously fed through the H-cube until completed as monitored by LCMS. If necessary, the cartridge was replaced. The solution was concentrated by rotary evaporation and dried in vacuo to yield 1,2,4,6-tetra-O-acetyl-beta-D-glucopyranose (170 mg, 0.49 mmol, 43% yield).

[0577] Step 5:

[0578] Compound 3-benzyl-1,2,4,6-tetra-O-acetyl-beta-D-glucopyranose (170 mg, 0.49 mmol, 1 eq) was dissolved in DCM (2 mL), followed by addition of chloroacetyl chloride (0.11 mL, 1.38 mmol, 2.8 eq) and pyridine (0.12 mL, 1.49 mmol, 3 eq). The reaction was stirred overnight, filtered, concentrated, and purified by column chromatography (100% hexanes to 100% ethyl acetate) to yield 3-(2-chloroacetoxy)-1,2,4,6-tetra-O-acetyl-beta-D-glucopyranose as a yellow viscous oil (0.19 g, 0.45 mmol, 91% yield).

[0579] Step 6:

[0580] Compound 3-(2-chloroacetoxy)-1,2,4,6-tetra-O-acetyl-beta-D-glucopyranose (0.19 g, 0.45 mmol, 1 eq) was dissolved in acetone (4 mL), followed by addition of sodium iodide (0.1 g, 0.68 mmol, 1.5 eq). The reaction was stirred for a few minutes, and 3-dimethylamino-1-propyne (0.144 mL, 1.3 mmol, 3 eq) was added. The reaction was stirred at room temperature overnight, then filtered. The filtrate was concentrated, diluted with DMSO and water, and injected onto reverse phase C18 column chromatography (0.1% TFA in 95% water/5% MeCN to 100% MeCN). Fractions containing product were lyophilized to yield an off-white powder (113 mg, 0.19 mmol, 43% yield). LCMS (M+): 472.1 ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.00 (d, J=8.2 Hz, 1H), 5.64 (t, J=9.5 Hz, 1H), 5.11-4.98 (m, 2H), 4.58-4.44 (m, 4H), 4.29-4.10 (m, 3H), 4.00 (dd, J=12.5, 2.3 Hz, 1H), 3.21 (s, 6H), 2.12-1.93 (m, 12H).



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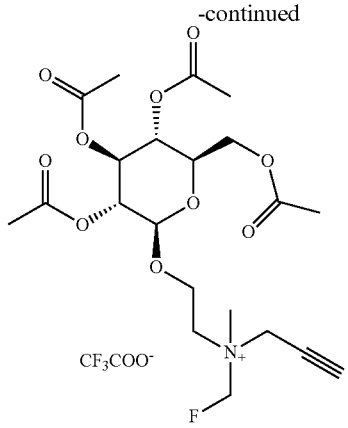


Compound 77: (fluoromethyl)(methyl)(prop-2-yn-1-yl)(2-{[(2R,3R,4S,5R,6R)-3,4,5-tris(acetyloxy)-6-[(acetyloxy)methyl]oxan-2-yl]oxy}ethyl)azanium

[0581] Step 1:

[0582] To a mixture of [(2R,3R,4S,5R,6S)-3,4,5,6-tetraacetoxytetrahydropyran-2-yl]methyl acetate (20 g, 51.24 mmol, 1 eq) in DCM (300 mL) was added 2-bromoethanol (9.60 g, 76.86 mmol, 5.46 mL, 1.5 eq) and $BF_3.Et_2O$ (36.36 g, 256.19 mmol, 31.62 mL, 5 eq) in one portion at 0° C. under N_2. The mixture stirred at 25° C. for 12 hours. TLC indicated the starting material was consumed and one new spot formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1). Compound [(2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(2-bromoethoxy)tetrahydropyran-2-yl]methyl acetate (10 g, 21.97 mmol, 42.87% yield) was obtained as white solid.

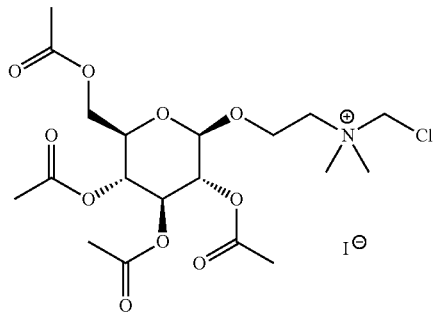
[0583] Step 2:

[0584] To a mixture of [(2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(2-bromoethoxy)tetrahydropyran-2-yl]methyl acetate (2 g, 4.39 mmol, 1 eq) and N-methylprop-2-yn-1-amine (1.67 g, 24.16 mmol, 2.01 mL, 5.5 eq) in THF (5 mL) was added Na_2CO_3 (931.26 mg, 8.79 mmol, 2 eq) and NaI (658.51 mg, 4.39 mmol, 1 eq) in one portion at 25° C. under at 25° C. under N_2. Then mixture was heated to 70° C. and stirred for 12 hours. TLC indicated the stating material was consumed and one new spot formed. LCMS showed the expected mass was detected. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1). Compound[(2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-[2-[methyl(prop-2-ynyl)amino]ethoxy]tetrahydropyran-2-yl]methyl acetate (1.6 g, crude) was obtained as a yellow oil. LCMS: (M+H+): 444.3@ 0.125 min

[0585] Step 3:

[0586] To a mixture of [(2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-[2-[methyl(prop-2-ynyl)amino]ethoxy]tetrahydropyran-2-yl]methyl acetate (1 g, 2.26 mmol, 1 eq) in acetone (10 mL) was added fluoro(iodo)methane (1.80 g, 11.28 mmol, 5 eq) in one portion at 25° C. under N_2. The mixture was heated to 90° C. and stirred for 2 hours. TLC indicated the starting material was consumed and one new spot formed. LCMS showed one main peak with expected mass

was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to Ethyl acetate/Methanol=3/1). Then the residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. The title compound (266 mg, 441.46 umol, 19.58% yield, 98% purity, TFA) was obtained as colorless oil. LCMS: (M+): 476.2 ^{1}H NMR (400 MHz, Chloroform-d) δ 5.72 (d, J=48.1 Hz, 2H), 5.24 (t, J=9.5 Hz, 1H), 5.08 (t, J=9.4 Hz, 1H), 4.99 (t, J=8.8 Hz, 1H), 4.65-4.58 (m, 3H), 4.40 (s, 1H), 4.32-4.18 (m, 5H), 3.82-3.73 (m, 1H), 3.42 (s, 3H), 2.91 (s, 1H), 2.07 (dd, J=21.9, 12.1 Hz, 12H).



Compound 78: N-(chloromethyl)-N,N-dimethyl-2-(((2S,3S,4R,5S,6S)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)ethan-1-aminium Iodide

[0587] Step 1:

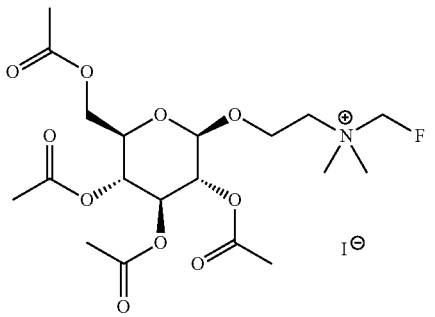
[0588] To a solution of (2S,3R,4S,5R,6R)-6-(acetoxymethyl)tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate (60.0 g, 1 Eq, 154 mmol) in anhydrous DCM (300 mL) at 0° C. under nitrogen, 2-bromoethan-1-ol (28.8 g, 16.3 mL, 1.5 Eq, 231 mmol) was added followed by BF_3OEt_2 (109 g, 97.4 mL, 5 Eq, 769 mmol). The reaction was stirred at room temperature for 18 hrs. Reaction was quenched slowly with 300 mL of H_2O in an ice bath and 50 mL of saturated sodium bicarbonate was added. The layers were separated. The water layer was washed 2× with 200 mL DCM. Organic layers were combined, concentrated and residue was purified by normal phase flash chromatography (0-40% ethyl acetate in hexanes). Filtrate was concentrated and recrystallized by dissolving in minimal ethyl acetate and adding hexanes until crystals began forming, then solution was cooled to 4° C. overnight. Crystals were collected and washed with cold 1:2 ethyl acetate/hexanes followed by cold hexanes. (2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(2-bromoethoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (39.41 g, 56.3%) was obtained as a white crystalline solid.

[0589] Step 2:

[0590] To a stirred solution of (2S,3S,4R,5S,6S)-2-(acetoxymethyl)-6-(2-bromoethoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3.60 g, 1 Eq, 7.90 mmol) in 16 mL anhydrous THF, 2 M dimethylamine in THF (16.0 mL, 4.0 Eq, 32.0 mmol) was added followed by sodium iodide (1.2 g, 1 Eq, 7.9 mmol). Reaction was stirred under nitrogen at room temperature for 18 hours, filtered, and concentrated. Residue was purified by normal phase flash chromatography (0-10% methanol in DCM) to give (2S,3S,4R,5S,6S)-2-(acetoxymethyl)-6-(2-(dimethylamino)ethoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate, Iodide (1.6 g, 37%) as a yellow oil that crystallized upon standing.

[0591] Step 3:

[0592] To a stirred solution of (2S,3S,4R,5S,6S)-2-(acetoxymethyl)-6-(2-(dimethylamino)ethoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate, iodide (1.15 g, 1 Eq, 2.10 mmol) in 10 mL anhydrous DCM at room temperature, chloroiodomethane (766 μL, 5 Eq, 10.5 mmol) was added followed by DIEA (0.40 mL, 1.1 Eq, 2.32 mmol). Vial was sealed and flushed with nitrogen. Reaction was heated to 40° C. and stirred for 2.5 hours. Reaction was allowed to come to room temperature, concentrated by rotary evaporation, and purified by normal phase HPLC (0-10% methanol in DCM) to give N-(chloromethyl)-N,N-dimethyl-2-(((2S,3S,4R,5S,6S)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)ethan-1-aminium, Iodide (250 mg, 19.9%) as a slightly yellow solid. LCMS (M^+): 468.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.33 (s, 2H), 5.28 (t, 1H), 4.99-4.81 (m, 3H), 4.19 (dd, 1H), 4.16-4.01 (m, 4H), 3.72-3.67 (m, 2H), 3.15 (s, 6H), 2.03 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.94 (s, 3H).



Compound 79: N-(fluoromethyl)-N,N-dimethyl-2-(((2S,3S,4R,5S,6S)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)ethan-1-aminium Iodide

[0593] Step 1:

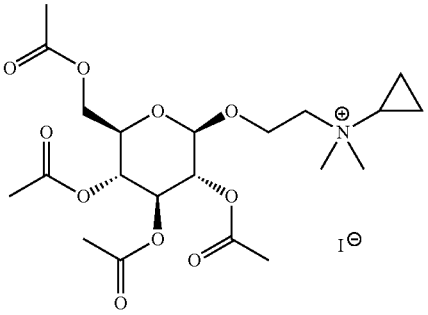
[0594] To a solution of (2S,3R,4S,5R,6R)-6-(acetoxymethyl)tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate (60.0 g, 1 Eq, 154 mmol) in anhydrous DCM (300 mL) at 0° C. under nitrogen, 2-bromoethan-1-ol (28.8 g, 16.3 mL, 1.5 Eq, 231 mmol) was added followed by BF_3OEt_2 (109 g, 97.4 mL, 5 Eq, 769 mmol). The reaction was stirred at room temperature for 18 hrs. Reaction was quenched slowly with 300 mL of H_2O in an ice bath and 50 mL of saturated sodium bicarbonate was added. The layers were separated. The water layer was washed 2× with 200 mL DCM. Organic layers were combined, concentrated and residue was purified by normal phase flash chromatography (0-40% ethyl acetate in hexanes). Filtrate was concentrated and recrystallized by dissolving in minimal ethyl acetate and adding hexanes until crystals began forming, then solution was cooled to 4° C. overnight. Crystals were collected and washed with cold 1:2 ethyl acetate/hexanes followed by cold hexanes. Yielded (2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(2-bromoethoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (39.41 g, 56.3%) as a white crystalline solid.

[0595] Step 2:

[0596] To a stirred solution of (2S,3S,4R,5S,6S)-2-(acetoxymethyl)-6-(2-bromoethoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (2.00 g, 1 Eq, 4.39 mmol) in 8.8 mL anhydrous THF, dimethylamine (792 mg, 8.8 mL, 4.0 Eq, 17.6 mmol) was added followed by sodium iodide (658 mg, 1 Eq, 4.39 mmol). Reaction was stirred under nitrogen at room temperature for 18 hours, filtered, and concentrated. Residue was purified by normal phase flash chromatography (0-10% methanol in DCM) to give (2S,3S,4R,5S,6S)-2-(acetoxymethyl)-6-(2-(dimethylamino)ethoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate, Iodide (1.0 g, 42%) as a yellow oil that crystallized upon standing.

[0597] Step 3:

[0598] To a stirred solution of (2S,3S,4R,5S,6S)-2-(acetoxymethyl)-6-(2-(dimethylamino)ethoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate, Iodide (517 mg, 1 Eq, 946 μmol) in 15 mL anhydrous dichloromethane at room temperature, fluoroiodomethane (757 mg, 320 μL, 5 Eq, 4.73 mmol) was added followed by DIEA (135 mg, 0.18 mL, 1.1 Eq, 1.04 mmol). Reaction vessel was flushed with nitrogen, then reaction was stirred for 2 hours at 40° C. Reaction was then allowed to come to room temperature, concentrated, and purified by normal phase flash HPLC 0-10% MeOH in DCM to give N-(fluoromethyl)-N,N-dimethyl-2-(((2S,3S,4R,5S,6S)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)ethan-1-aminium, Iodide (231 mg, 42.1%) as a light yellow solid. LC-MS (M^+): 452.3. ^{1}H NMR (400 MHz, Chloroform-d) δ 5.75 (s, 1H), 5.63 (s, 1H), 5.22 (t, 1H), 5.06 (t, 1H), 4.95 (dd, 1H), 4.75-4.68 (m, 1H), 4.49-4.37 (m, 1H), 4.33-4.14 (m, 5H), 3.85 (ddd, 1H), 3.51 (t, 6H), 2.12 (s, 3H), 2.09 (d, 3H), 2.04 (d, 3H), 2.00 (s, 3H).



Compound 80: N,N-dimethyl-N-(2-{[(3R,4S,5R,6R)-3,4,5-tris(acetyloxy)-6-[(acetyloxy)methyl]oxan-2-yl]oxy}ethyl)cyclopropanaminium Iodide

[0599] Step 1:

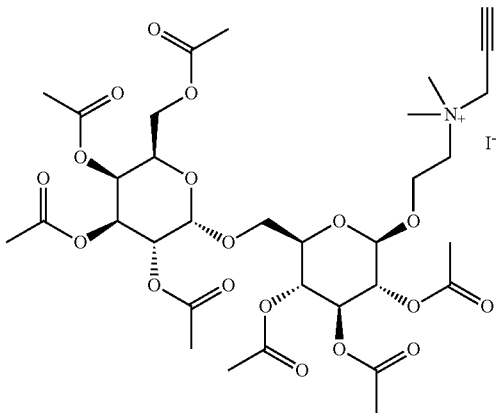
[0600] To a mixture of [(2R,3R,4S,5R,6S)-3,4,5,6-tetraacetoxytetrahydropyran-2-yl]methyl acetate (20 g, 51.24 mmol, 1 eq) in DCM (300 mL) was added 2-bromoethanol (9.60 g, 76.86 mmol, 5.46 mL, 1.5 eq) and $BF_3.Et_2O$ (36.36 g, 256.19 mmol, 31.62 mL, 5 eq) in one portion at 0° C. under N_2. The mixture stirred at 25° C. for 12 hours. TLC indicated the starting material was consumed and one new spot formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1). Compound [(2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(2-bromoethoxy)tetrahydropyran-2-yl]methyl acetate (10 g, 21.97 mmol, 42.87% yield) was obtained as white solid.

[0601] Step 2:

[0602] To a mixture of [(2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(2-bromoethoxy)tetrahydropyran-2-yl]methyl acetate (2 g, 4.39 mmol, 1 eq) in THF (20 mL) was added NaI (658.51 mg, 4.39 mmol, 1 eq) and Na_2CO_3 (931.26 mg, 8.79 mmol, 2 eq) in one portion at 25° C. under N_2. Then N-methylcyclopropanamine (2.60 g, 24.16 mmol, 5.5 eq, HCl) was added. The mixture was heated to 70° C. and stirred for 12 hours. TLC indicated [(2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(2-bromoethoxy)tetrahydropyran-2-yl]methyl acetate was consumed and one new spot formed. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1). Compound[(2R,3R,4S,5R)-3,4,5-triacetoxy-6-[2-[cyclopropyl(methyl)amino]ethoxy]tetrahydropyran-2-yl]methyl acetate (1.4 g, 3.14 mmol, 71.54% yield) was obtained as yellow oil. LCMS: (M+H+): 446.3

[0603] Step 3:

[0604] To a mixture of [(2R,3R,4S,5R)-3,4,5-triacetoxy-6-[2-[cyclopropyl(methyl)amino]ethoxy]tetrahydropyran-2-yl]methyl acetate (1.4 g, 3.14 mmol, 1 eq) in Acetone (15 mL) was added MeI (2.23 g, 15.71 mmol, 978.26 uL, 5 eq) in one portion at 25° C. under N_2. Then mixture was heated to 90° C. and stirred for 2 hours. TLC indicated the starting material was consumed and one new spot formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to Ethyl acetate:Methanol=3/1). Compound N,N-dimethyl-N-(2-{[(3R,4S,5R,6R)-3,4,5-tris(acetyloxy)-6-[(acetyloxy)methyl]oxan-2-yl]oxy}ethyl)cyclopropanaminium iodide (1 g, 1.70 mmol, 54.17% yield, 100% purity, I) was obtained as yellow solid. LCMS: (M+): 460.2 ^{1}H NMR (400 MHz, Chloroform-d) δ 5.21 (t, J=9.6 Hz, 1H), 5.04 (t, J=9.7 Hz, 1H), 4.94 (dd, J=9.7, 8.0 Hz, 1H), 4.67 (d, J=8.0 Hz, 1H), 4.51-4.42 (m, 1H), 4.36-4.06 (m, 6H), 3.83 (dt, J=10.2, 3.5 Hz, 1H), 3.70-3.60 (m, 1H), 3.20 (d, J=9.6 Hz, 6H), 2.16-1.97 (m, 12H), 1.29-1.21 (m, 2H), 1.09-0.96 (m, 2H).



Compound 81: dimethyl(prop-2-yn-1-yl)(2-{[(2R,3R,4S,5R,6R)-3,4,5-tris(acetyloxy)-6-({[(2S,3R,4S,5S,6R)-3,4,5-tris(acetyloxy)-6-[(acetyloxy)methyl]oxan-2-yl]oxy}methyl)oxan-2-yl]oxy}ethyl)azanium Iodide

[0605] Step 1:

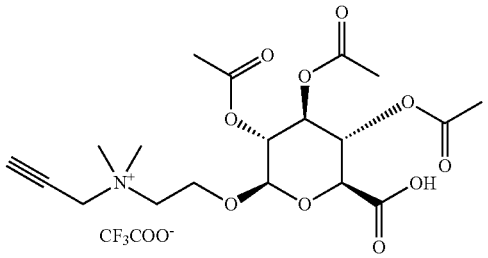
[0606] Preparation of solution 1: Ac_2O (64.31 g, 629.94 mmol, 59 mL, 21.56 eq) and NaOAc (4.21 g, 51.32 mmol, 1.76 eq) was stirred at reflux under N_2. (3R,4S,5S,6R)-6-[[(2S,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxymethyl]tetrahydropyran-2,3,4,5-tetrol (10 g, 29.21 mmol, 1 eq) in toluene (150 mL) was stirred at 100° C. Then the mixture was added to solution 1 and stirred at 100° C. for 1 hour. TLC indicated one new spot formed. The reaction mixture was poured into ice water (400 mL), extracted with ethyl acetate (200 mL*3). The combined organic layers were washed with $NaHCO_3$ (200 mL*2), dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1). Compound [(2R,3S,4S,5R,6S)-3,4,5-triacetoxy-6-[[(2R,3R,4S,5R,6S)-3,4,5,6-tetraacetoxytetrahydropyran-2-yl]methoxy]tetrahydropyran-2-yl]methyl acetate (5.8 g, 8.55 mmol, 29.26% yield) was obtained as white solid.

[0607] Step 2:

[0608] To a mixture of [(2R,3S,4S,5R,6S)-3,4,5-triacetoxy-6-[[(2R,3R,4S,5R,6S)-3,4,5,6-tetraacetoxytetrahydropyran-2-yl]methoxy]tetrahydropyran-2-yl]methyl acetate (5.8 g, 8.55 mmol, 1 eq) in DCM (50 mL) was added 2-bromoethanol (1.60 g, 12.82 mmol, 910.31 uL, 1.5 eq) and $BF_3.Et_2O$ (6.07 g, 42.74 mmol, 5.27 mL, 5 eq) in one portion at 0° C. under N_2. Then the mixture was heated to 25° C. and stirred for 12 hours. TLC indicated [(2R,3S,4S,5R,6S)-3,4,5-triacetoxy-6-[[(2R,3R,4S,5R,6S)-3,4,5,6-tetraacetoxytetrahydropyran-2-yl]methoxy]tetrahydropyran-2-yl]methyl acetate was consumed and one new spot formed. The reaction mixture was quenched by addition of H_2O (50 mL), diluted with H_2O (50 mL) and extracted with ethyl acetate (50 mL*3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1). [(2R,3S,4S,5R,6S)-3,4,5-triacetoxy-6-[[(2R,3R,4S,5R)-3,4,5-triacetoxy-6-(2-bromoethoxy)tetrahydropyran-2-yl]methoxy]tetrahydropyran-2-yl]methyl acetate (2 g, crude) was obtained as yellow oil.

[0609] Step 3:

[0610] To a mixture of [(2R,3S,4S,5R,6S)-3,4,5-triacetoxy-6-[[(2R,3R,4S,5R)-3,4,5-triacetoxy-6-(2-bromoethoxy)tetrahydropyran-2-yl]methoxy]tetrahydropyran-2-yl]methyl acetate (2.00 g, 2.69 mmol, 1 eq) in Acetone (20 mL) was added NaI (443.53 mg, 2.96 mmol, 1.1 eq) and N,N-dimethylprop-2-yn-1-amine (1.12 g, 13.45 mmol, 1.43 mL, 5 eq) in one portion at 25° C. under N_2. Then the mixture was heated to 80° C. and stirred for 10 hours. TLC indicated [(2R,3S,4S,5R,6S)-3,4,5-triacetoxy-6-[[(2R,3R,4S,5R)-3,4,5-triacetoxy-6-(2-bromoethoxy)tetrahydropyran-2-yl]methoxy]tetrahydropyran-2-yl]methyl acetate was consumed and one new spot formed. LCMS showed desired m/z was detected. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. The title compound (136 mg, 155.67 umol, 5.6% yield, 100% purity, I—) was obtained as white solid. LCMS: (M+): 746.3 ^1H NMR (400 MHz, Methanol-d4) δ 5.49-5.43 (m, 1H), 5.37-5.27 (m, 3H), 5.24-5.02 (m, 3H), 4.95 (dd, J=9.7, 8.0 Hz, 1H), 4.79 (d, J=8.0 Hz, 1H), 4.51-4.39 (m, 2H), 4.38-4.26 (m, 2H), 4.24-4.16 (m, 1H), 4.14-4.05 (m, 2H), 3.95-3.87 (m, 1H), 3.84-3.72 (m, 3H), 3.65-3.58 (m, 1H), 3.28 (s, 6H), 2.20-1.95 (m, 21H).



Compound 82: dimethyl(prop-2-yn-1-yl)(2-{[(2R,3R,4S,5S,6S)-3,4,5-tris(acetyloxy)-6-carboxyoxan-2-yl]oxy}ethyl)azanium trifluoroacetate

[0611] Step 1:

[0612] To a solution of (2S,3S,4S,5R)-3,4,5,6-tetrahydroxytetrahydropyran-2-carboxylic acid (10 g, 51.51 mmol, 1 eq) in DMF (100 mL) was added DBU (8.63 g, 56.66 mmol, 8.54 mL, 1.1 eq), stirred for 15 min at 25° C., and then 3-bromoprop-1-ene (7.48 g, 61.81 mmol, 1.2 eq) was added to the mixture at 0° C. The mixture was stirred for 10 h at 25° C. under N_2. TLC showed the starting reactant was consumed and one new spot formed. The mixture was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=30/1 to 0/1). Allyl (2S,3S,4S,5R)-3,4,5,6-tetrahydroxytetrahydropyran-2-carboxylate (10 g, 38.43 mmol, 74.60% yield, 90% purity) was obtained as a white solid.

[0613] Step 2:

[0614] To a solution of allyl (2S,3S,4S,5R)-3,4,5,6-tetrahydroxytetrahydropyran-2-carboxylate (10 g, 42.70 mmol, 1 eq) in Pyridine (100 mL) was added Ac_2O (43.59 g, 426.98 mmol, 39.99 mL, 10 eq). The mixture was stirred at 25° C. for 12 h. TLC showed the starting reactant was consumed completely and one new spot formed. The reaction was clean according to TLC. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 2/1). Allyl (2S,3S,4S,5R)-3,4,5,6-tetraacetoxytetrahydropyran-2-carboxylate (13 g, 29.08 mmol, 68.10% yield, 90% purity) was obtained as a yellow solid.

[0615] Step 3:

[0616] To a mixture of allyl (2S,3S,4S,5R)-3,4,5,6-tetraacetoxytetrahydropyran-2-carboxylate (5 g, 12.43 mmol, 1 eq), 2-bromoethanol (4.66 g, 37.28 mmol, 2.65 mL, 3 eq) in DCM (50 mL) at 0° C. was added $BF_3.Et_2O$ (17.64 g, 124.27 mmol, 15.34 mL, 10 eq), purged with N_2 3 times, and then the mixture was stirred at 25° C. for 12 h under N_2 atmosphere. To the mixture was added H_2O (30 mL), the mixture was extracted with EtOAc (10 mL*3), the organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated. The residue was purified by prep-HPLC [water (0.10% TFA)-ACN]. Allyl (2S,3S,4S,5R)-3,4,5-triac-

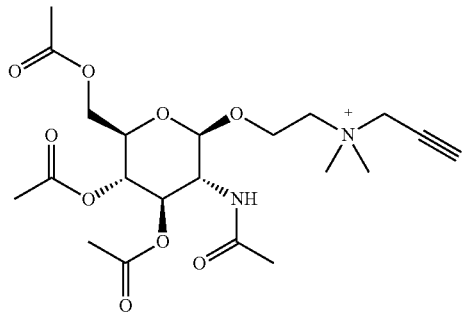
etoxy-6-(2-bromoethoxy)tetrahydropyran-2-carboxylate (660 mg, 1.27 mmol, 10.23% yield, 90% purity) was obtained as yellow oil.

[0617] Step 4:

[0618] To a solution of allyl (2S,3S,4S,5R)-3,4,5-triacetoxy-6-(2-bromoethoxy)tetrahydropyran-2-carboxylate (280 mg, 599.24 umol, 1 eq) in ACN (10 mL) was added pyridine (56.00 mg, 787.39 umol, 65.73 uL, 1.31 eq) and $Pd(PPh3)_4$ (84.00 mg, 72.69 umol, 1.21 eq) at 0° C. The mixture was stirred at 0° C. for 1 h. TLC showed the starting reactant was consumed. The reaction mixture was concentrated. The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. Compound (2S,3S,4S,5R)-3,4,5-triacetoxy-6-(2-bromoethoxy)tetrahydropyran-2-carboxylic acid (156 mg, 346.91 umol, 28.95% yield, 95% purity) was obtained as a yellow solid. LCMS: (M+H+): 427.0.

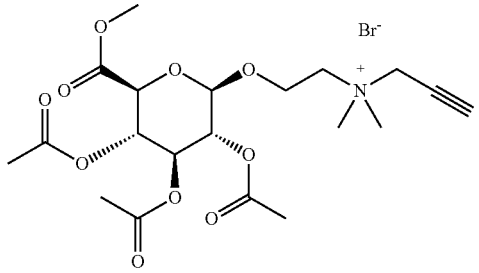
[0619] Step 5:

[0620] To a solution of (2S,3S,4S,5R)-3,4,5-triacetoxy-6-(2-bromoethoxy)tetrahydropyran-2-carboxylic acid (67 mg, 156.84 umol, 1 eq) in acetone (5 mL) was added N,N-dimethylprop-2-yn-1-amine (65.19 mg, 784.18 umol, 83.15 uL, 5 eq). The mixture was stirred at 80° C. for 12 h. LCMS showed the reactant was consumed completely. The reaction mixture was concentrated. The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. The title compound (6 mg, 12.84 umol, 8.19% yield, 90% purity) was obtained as a yellow solid. LCMS: (M): 430.2 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 5.35 (t, J=9.6 Hz, 1H), 5.13-4.97 (m, 3H), 4.31-4.15 (m, 3H), 4.12-4.04 (m, 1H), 3.98-3.88 (m, 1H), 3.84-3.74 (m, 1H), 3.58 (dd, J=14.5, 4.2 Hz, 1H), 3.20-3.11 (m, 7H), 1.98-1.87 (m, 9H).



Compound 83: (2-{[(2R,3R,4R,5S,6R)-4,5-bis(acetyloxy)-6-[(acetyloxy)methyl]-3-acetamidooxan-2-yl]oxy}ethyl)dimethyl(prop-2-yn-1-yl)azanium

[0621] This compound may be synthesized according to the experimental procedure described for Compound 7.



Compound 85: dimethyl(prop-2-yn-1-yl)(2-{[(2R,3R,4S,5S,6S)-3,4,5-tris(acetyloxy)-6-(methoxycarbonyl)oxan-2-yl]oxy}ethyl)azanium bromide

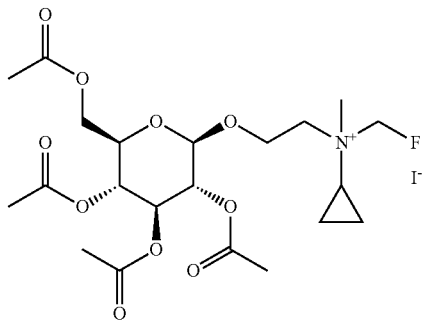
[0622] Step 1:

[0623] To a solution of methyl (2S,3S,4S,5R,6S)-3,4,5,6-tetraacetoxytetrahydropyran-2-carboxylate (5 g, 13.29 mmol, 1 eq) and 2-bromoethanol (2.49 g, 19.93 mmol, 1.42 mL, 1.5 eq) in DCM (50 mL) was added dropwise $BF_3.Et_2O$ (9.43 g, 66.43 mmol, 8.20 mL, 5 eq) at 0° C., stirred at 0° C. for 1 h, then stirred at 25° C. for 11 h. TLC showed the starting reactant was consumed. The mixture was poured into H_2O (50 mL) at 0° C., and extracted with DCM (20 mL*3). The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=30/1 to 3/1). Methyl (2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(2-bromoethoxy)tetrahydropyran-2-carboxylate (3 g, 5.44 mmol, 40.94% yield, 80% purity) was obtained as colorless oil.

[0624] Step 2:

[0625] To a solution of methyl (2S,3S,4S,5R,6R)-3,4,5-triacetoxy-6-(2-bromoethoxy)tetrahydropyran-2-carboxylate (260 mg, 589.27 umol, 1 eq) in acetone (10 mL) was added N,N-dimethylprop-2-yn-1-amine (244.94 mg, 2.95 mmol, 312.42 uL, 5 eq), stirred at 90° C. for 2 h. LCMS showed the starting reactant was consumed. The mixture was concentrated. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100*30 mm*5 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-28%, 12 min). The title compound (50 mg, 82.01 umol, 13.92% yield, 86% purity, Br—) was obtained as white solid.

[0626] LCMS: (M+): 444.1 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 5.5 (m, 1H), 5.2-5.1 (m, 4H), 4.5 (m, 1H), 4.4-4.3 (m, 2H), 4.2 (m, 1H), 4.1 (m, 1H), 3.9 (m, 1H), 3.7 (m, 3H), 3.3-3.2 (m, 7H), 2.1-2.0 (m, 9H).



Compound 86: N-(fluoromethyl)-N-methyl-N-(2-{[(2R,3R,4S,5R,6R)-3,4,5-tris(acetyloxy)-6-[(acetyloxy)methyl]oxan-2-yl]oxy}ethyl)cyclopropanaminium Iodide

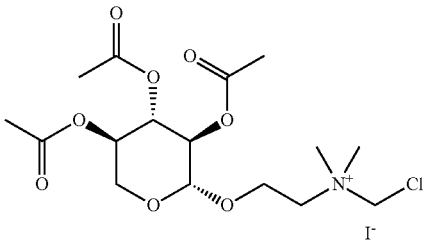
[0627] Step 1:

[0628] To a mixture of [(2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(2-bromoethoxy)tetrahydropyran-2-yl]methyl acetate (2 g, 4.39 mmol, 1 eq) in THF (20 mL) was added NaI (658.51 mg, 4.39 mmol, 1 eq), Na_2CO_3 (931.26 mg, 8.79 mmol, 2 eq) and N-methylcyclopropanamine (2.60 g, 24.16 mmol, 5.5 eq, HCl) in one portion at 25° C. under N_2. The mixture was heated to 70° C. and stirred for 12 hours.

TLC indicated [(2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(2-bromoethoxy)tetrahydropyran-2-yl]methyl acetate was consumed and one new spot formed. LCMS showed one main peak with expected mass was detected. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 0/1). 1.2 g crude product was obtained. 200 mg of the crude product was further purified by prep-HPLC [water (0.10% TFA)-ACN] to get 82 mg of product (99% purity, TFA) as white solid. The crude compound [(2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-[2-[cyclopropyl(methyl)amino]ethoxy]tetrahydropyran-2-yl]methyl acetate (1 g, 40.28% yield, crude) as white solid was used in the next step directly. LCMS: (M+H)+: 446.2

[0629] Step 2:

[0630] To a mixture of [(2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-[2-[cyclopropyl(methyl)amino]ethoxy]tetrahydropyran-2-yl]methyl acetate (1.78 g, 2.20 mmol, 1 eq) in acetone (20 mL) was added fluoro(iodo)methane (1.76 g, 11.00 mmol, 5 eq) in one portion at 25° C. under N_2. The mixture was heated to 90° C. and stirred for 2 hours. TLC indicated [(2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-[2-[cyclopropyl(methyl)amino]ethoxy]tetrahydropyran-2-yl]methyl acetate was consumed and one new spot formed. LCMS showed one main peak with expected mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Ethyl acetate:Methanol=1/0 to 3/1). The title compound (1.11 g, 58% yield 99% purity, I—) was obtained as yellow solid. LCMS: (M+): 478.2 ^{1}H NMR (400 MHz, Methanol-d4) δ 5.58 (s, 1H), 5.46 (s, 1H), 5.32 (t, J=9.5 Hz, 1H), 5.08 (t, J=9.8 Hz, 1H), 4.98 (dd, J=9.7, 8.0 Hz, 1H), 4.86-4.81 (m, 1H), 4.50-4.35 (m, 1H), 4.30 (d, J=3.5 Hz, 2H), 4.27-4.10 (m, 1H), 4.02-3.93 (m, 1H), 3.92-3.82 (m, 2H), 2.97 (dd, J=6.0, 2.2 Hz, 3H), 2.14-2.02 (m, 9H), 2.00 (s, 3H), 1.47-1.30 (m, 2H), 1.12-0.95 (m, 2H).



Compound 88: (chloromethyl)dimethyl(2-{[(2R,3R,4S,5R)-3,4,5-tris(acetyloxy)oxan-2-yl]oxy}ethyl)azanium Iodide

[0631] Step 1:

[0632] To a mixture of (2R,3R,4S,5R)-tetrahydropyran-2,3,4,5-tetrol (50 g, 333.04 mmol, 1 eq) in pyridine (300 mL) was added acetyl acetate (204.00 g, 2.00 mol, 187.16 mL, 6 eq) in one portion at 0° C. under N_2. The mixture was heated to 25° C. and stirred for 12 hours. TLC indicated one new spot formed. The reaction was clean according to TLC. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 0/1). Compound [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl]acetate (80 g, 251.35 mmol, 75.47% yield) was obtained as yellow oil.

[0633] Step 2:

[0634] To a mixture of [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (20 g, 62.84 mmol, 1 eq) in DCM (200 mL) was added 2-bromoethanol (11.78 g, 94.26 mmol, 6.69 mL, 1.5 eq) and $BF_3.Et_2O$ (9.10 g, 62.84 mmol, 7.91 mL, 98% purity, 1 eq) in one portion at 0° C. under N_2. The mixture was heated to 25° C. and stirred for 12 hours. TLC indicated [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate was consumed and one new spot formed. The reaction mixture was quenched by addition of H_2O (100 mL), and then diluted with H_2O (200 mL) and extracted with ethyl acetate (200 mL*3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The crude product was purified by re-crystallization from ethyl acetate:Petroleum ether (40 ml:30 mL) at 0° C. for 12h. The mixture was filtered and the filter cake was concentrated under reduced pressure to give a residue. The filtrate was purified by prep-HPLC [water (0.1% TFA)-ACN].[(3R,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (3.4 g, 8.87 mmol, 14.12% yield) was obtained as a white solid. Compound [(3R,4S,5R,6R)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (3.5 g, 9.13 mmol, 14.54% yield) was obtained as yellow oil.

[0635] Step 3:

[0636] To a mixture of [(3R,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (3.4 g, 8.87 mmol, 1 eq) in THF (30 mL) was added NaI (1.33 g, 8.87 mmol, 1 eq) and Na_2CO_3 (1.88 g, 17.75 mmol, 2 eq) in one portion at 25° C. under N_2. N-methylmethanamine (2 M, 24.40 mL, 5.5 eq) was added. The mixture was heated to 70° C. and stirred for 12 hours. TLC indicated [(3R,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate was consumed incompletely and one new spot formed. LCMS showed [(3R,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate was consumed and one main peak with expected mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Ethyl acetate:Methanol=1/0 to 1/1). The 200 mg crude product was purified by prep-HPLC [water (0.1% TFA)-ACN]. Compound [(3R,4S,5R,6R)-4,5-diacetoxy-6-[2-(dimethylamino)ethoxy]tetrahydropyran-3-yl] acetate (3.1 g, crude) was obtained as yellow oil. Compound [(3R,4S,5R,6R)-4,5-diacetoxy-6-[2-(dimethylamino)ethoxy]tetrahydropyran-3-yl] acetate (14.7 mg, 98% purity) was obtained as white solid. LCMS: $(M+H)^+$: 348.1

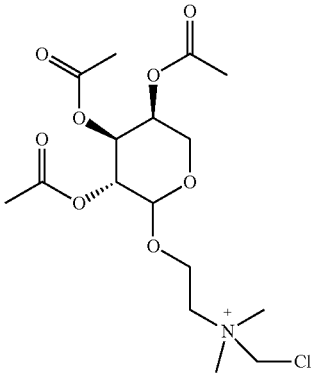
[0637] Step 4:

[0638] To a mixture of [(3R,4S,5R,6R)-4,5-diacetoxy-6-[2-(dimethylamino)ethoxy]tetrahydropyran-3-yl] acetate (3 g, 8.64 mmol, 1 eq) in acetone (30 mL) was added chloro(iodo)methane (7.62 g, 43.18 mmol, 3.13 mL, 5 eq) in one portion at 25° C. under N_2. The mixture was heated to 90° C. and stirred for 2 hours. LCMS showed [(3R,4S,5R,6R)-4,5-diacetoxy-6-[2-(dimethylamino)ethoxy]tetrahydropyran-3-yl]acetate was consumed and one main peak with expected mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. Compound chloromethyl-dimethyl-[2-

[(2R,3R,4S,5R)-3,4,5-triacetoxytetrahydropyran-2-yl]oxy-ethyl]ammonium (315 mg, 589.41 umol, 6.82% yield, 98% purity, I—) was obtained as yellow oil. LCMS: $(M+)^+$: 396.1

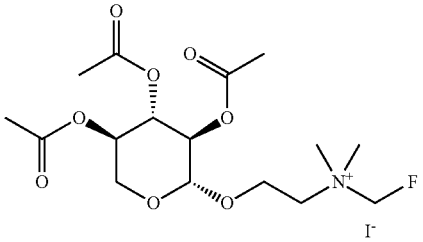
[0639] Step 5:

[0640] To a mixture of [(3R,4S,5R,6R)-4,5-diacetoxy-6-[2-(dimethylamino)ethoxy]tetrahydropyran-3-yl] acetate (2.8 g, 8.06 mmol, 1 eq) in DCM (20 mL) was added chloro(iodo)methane (7.11 g, 40.30 mmol, 2.93 mL, 5 eq) and DIPEA (1.06 g, 8.06 mmol, 1.43 mL, 98% purity, 1 eq) in one portion at 25° C. under N_2. The mixture was stirred at 40° C. for 12 hours in a 50 mL sealed tube. TLC indicated [(3R,4S,5R,6R)-4,5-diacetoxy-6-[2-(dimethylamino) ethoxy]tetrahydropyran-3-yl] acetate was consumed incompletely and one new spot formed. LCMS showed one main peak with expected mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Ethyl acetate:Methanol=1/0 to 2/1). The residue was then purified by prep-HPLC [water (0.1% TFA)-ACN]. Compound chloromethyl-dimethyl-[2-[(2R,3R,4S,5R)-3,4,5-triacetoxytetrahydropyran-2-yl]oxyethyl]ammonium (617 mg, 1.18 mmol, 14.6% yield, 100% purity, I—) was obtained as yellow solid. LCMS: $(M+)^+$: 396.1 ^1H NMR (400 MHz, Methanol-d4) δ 5.31 (s, 2H), 5.32-5.22 (m, 1H), 5.06-4.91 (m, 2H), 4.73 (d, J=7.4 Hz, 1H), 4.35-4.26 (m, 1H), 4.19-4.02 (m, 2H), 3.87-3.73 (m, 2H), 3.52 (dd, J=11.7, 9.6 Hz, 1H), 3.29 (s, 6H), 2.15-1.99 (m, 9H).



Compound 89: (chloromethyl)dimethyl(2-{[(3R,4S,5S)-3,4,5-tris(acetyloxy)oxan-2-yl]oxy}ethyl)azanium

[0641] This compound may be synthesized according to the experimental procedure described for Compound 325.



Compound 90: (fluoromethyl)dimethyl(2-{[(2R,3R,4S,5R)-3,4,5-tris(acetyloxy)oxan-2-yl]oxy}ethyl) azanium Iodide

[0642] Step 1:

[0643] To a solution of (2R,3R,4S,5R)-tetrahydropyran-2,3,4,5-tetrol (50 g, 333.04 mmol, 1 eq) in pyridine (500 mL) was added Ac_2O (204.00 g, 2.00 mol, 187.16 mL, 6 eq). The mixture was stirred at 25° C. for 12 hr. TLC indicated (2R,3R,4S,5R)-tetrahydropyran-2,3,4,5-tetrol was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=80/1 to 0/1). Compound [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (100 g, 314.19 mmol, 94.34% yield) was obtained as a yellow oil.

[0644] Step 2:

[0645] To a solution of [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (20 g, 62.84 mmol, 1 eq) in DCM (150 mL) was added dropwise 2-bromoethanol (11.78 g, 94.26 mmol, 6.69 mL, 1.5 eq) and $BF_3.Et_2O$ (45.50 g, 314.19 mmol, 39.57 mL, 98% purity, 5 eq) at 0° C. The mixture was warmed to 25° C. and was stirred at 25° C. for 12 hr. TLC indicated [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate was consumed completely and new spots formed. 5 batches were combined for work-up. The reaction mixture was quenched by addition of H_2O (500 mL) at 25° C. and extracted with EtOAc (900 mL, 300 mL*3). The combined organic layers were concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1). The crude product was purified by re-crystallization from ethyl acetate:Petroleum ether (40 ml:30 mL) at 0° C. for 12h. Compound [(3R,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (3 g, 7.83 mmol, 2.49% yield) was obtained as a white solid. The filtrate was purified by prep-HPLC [water (0.1% TFA)-ACN]. Compound [(3R,4S,5R,6R)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (7 g, 18.27 mmol, 5.81% yield) was obtained as a colorless oil.

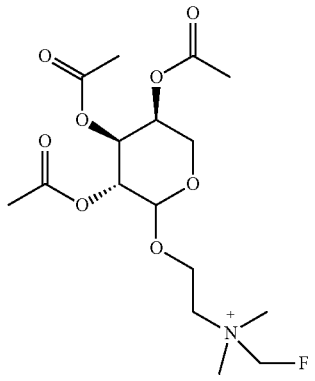
[0646] Step 3:

[0647] To a solution of [(3R,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (1 g, 2.61 mmol, 1 eq) in THF (10 mL) was added $Me_2NH.THF$ (2 M, 7.18 mL, 5.50 eq) and DIEA (674.57 mg, 5.22 mmol, 909.12 uL, 2 eq). The mixture was stirred at 70° C. for 12 hr. LCMS showed [(3R,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy) tetrahydropyran-3-yl] acetate was consumed completely and the expected mass was detected. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Ethyl acetate/Methanol=100/1 to 0/1). Compound [(3R,4S,5R,6R)-4,5-diacetoxy-6-[2-(dimethylamino)ethoxy]tetrahydropyran-3-yl] acetate (500 mg, 1.44 mmol, 55.16% yield) was obtained as a yellow solid.

[0648] Step 4:

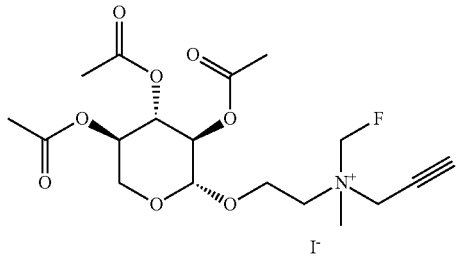
[0649] To a solution of [(3R,4S,5R,6R)-4,5-diacetoxy-6-[2-(dimethylamino)ethoxy]tetrahydropyran-3-yl] acetate (500 mg, 1.44 mmol, 1 eq) in DCM (5 mL) was added fluoro(iodo)methane (1.15 g, 7.20 mmol, 5 eq) and DIEA (186.04 mg, 1.44 mmol, 250.72 uL, 1 eq). The mixture was stirred at 40° C. for 3 hr. LCMS showed the reaction was completed and one main peak with expected mass was detected. The mixture was filtered and the filter cake was concentrated under reduced pressure to give a residue. The

crude product was washed with ethyl acetate (10 mL). The mixture was filtered and the filter cake was concentrated under reduced pressure to give a residue. The title compound (397 mg, 782.59 umol, 54.37% yield, 100% purity, I—) was obtained as a white solid. LCMS: (M+): 380.1 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 5.35 (s, 1H), 5.24 (s, 1H), 5.14 (t, J=7.6 Hz, 1H), 4.96-4.83 (m, 2H), 4.75 (d, J=6.1 Hz, 1H), 4.21 (d, J=13.8 Hz, 1H), 4.10 (dd, J=12.3, 4.7 Hz, 1H), 3.99 (d, J=13.6 Hz, 1H), 3.70-3.63 (m, 2H), 3.54 (dd, J=12.3, 7.9 Hz, 1H), 3.13 (d, J=2.0 Hz, 6H), 2.06-1.97 (m, 9H).



Compound 91 and Compound 97: (fluoromethyl) dimethyl(2-{[(3R,4S,5S)-3,4,5-tris(acetyloxy)oxan-2-yl]oxy}ethyl)azanium

[0650] This compound may be synthesized according to the experimental procedure described for Compound 311.



Compound 92: (fluoromethyl)(methyl)(prop-2-yn-1-yl)(2-{[(2R,3R,4S,5R)-3,4,5-tris(acetyloxy)oxan-2-yl]oxy}ethyl)azanium Iodide

[0651] Step 1:

[0652] To a mixture of (2R,3R,4S,5R)-tetrahydropyran-2,3,4,5-tetrol (50 g, 333.05 mmol, 1 eq) in pyridine (300 mL) was added acetyl acetate (204.00 g, 2.00 mol, 187.16 mL, 6 eq) in one portion at 0° C. under N_2. The mixture was heated to 25° C. and stirred for 12 hours. TLC indicated one new spot formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 0/1). Compound [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (100 g, 314.19 mmol, 94.34% yield) was obtained as yellow oil.

[0653] Step 2:

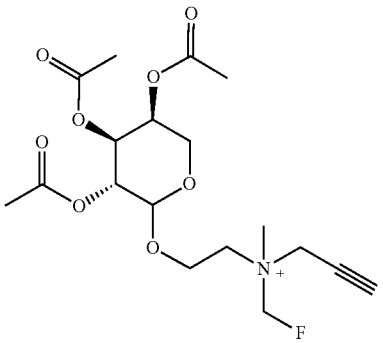
[0654] To a solution of [of [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (20 g, 62.84 mmol, 1 eq) in DCM (150 mL) was added dropwise 2-bromoethanol (11.78 g, 94.26 mmol, 6.69 mL, 1.5 eq) and $BF_3.Et_2O$ (45.50 g, 314.19 mmol, 39.57 mL, 98% purity, 5 eq) at 0° C. The mixture was warmed to 25° C. and stirred at 25° C. for 12 hr. TLC indicated [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate was consumed completely and two new spots formed. The reaction mixture was quenched by addition of H_2O (500 mL) and extracted with EtOAc (900 mL, 300 mL*3). The combined organic layers were concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1). Two batches were obtained successively. The batch 1 was further purified by recrystallization from ethyl acetate:Petroleum etherat 0° C. for 12h. Compound [(3R,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (3 g, 2.5% yield) was obtained as a white solid. The batch 2 was further purified by prep-HPLC [water (0.1% TFA)-ACN]. Compound [(3R,4S,5R,6R)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (7 g, 5.8% yield) was obtained as a colorless oil.

[0655] Step 3:

[0656] To a solution of [(3R,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (1.8 g, 4.70 mmol, 1 eq) in THF (20 mL) was added N-methylprop-2-yn-1-amine (1.79 g, 25.84 mmol, 2.15 mL, 5.5 eq) and DIPEA (1.21 g, 9.39 mmol, 1.64 mL, 2 eq). The mixture was stirred at 70° C. for 12 hr. LCMS showed [(3R,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate was consumed completely and one main peak with expected mass was detected. The reaction mixture was concentrated under reduced pressure. The crude product (300 mg) was purified by prep-HPLC [water (0.1% TFA)-ACN]. Compound [(3R,4S,5R,6R)-4,5-diacetoxy-6-[2-[methyl(prop-2-ynyl)amino]ethoxy]tetrahydropyran-3-yl] acetate (97 mg, 100% purity, TFA) was obtained as white solid. The other crude product[(3R,4S,5R,6R)-4,5-diacetoxy-6-[2-[methyl(prop-2-ynyl)amino]ethoxy]tetrahydropyran-3-yl] acetate (1.4 g) was used into the next step without further purification. LCMS: $(M+H)^+$: 372.1

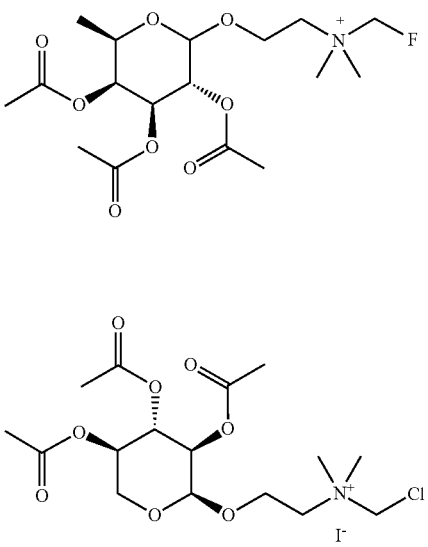
[0657] Step 4:

[0658] To a solution of [(3R,4S,5R,6R)-4,5-diacetoxy-6-[2-[methyl(prop-2-ynyl)amino]ethoxy]tetrahydropyran-3-yl] acetate (800 mg, 2.15 mmol, 1 eq) in DCM (8 mL) was added fluoro(iodo)methane (1.72 g, 10.77 mmol, 5 eq) and DIPEA (278.40 mg, 2.15 mmol, 375.21 uL, 1 eq). The mixture was stirred at 40° C. for 3 hr. LCMS showed [(3R,4S,5R,6R)-4,5-diacetoxy-6-[2-[methyl(prop-2-ynyl)amino]ethoxy]tetrahydropyran-3-yl] acetate was consumed completely and expected mass was detected. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC [water (0.10% TFA)-ACN]. The title compound (234 mg, 20.5% yield, 100% purity, I—) was obtained as yellow oil. LCMS:(M+): 404.1 δ 1H NMR (400 MHz, Methanol-d4) δ 5.65 (s, 1H), 5.54 (s, 1H), 5.26 (t, J=9.1 Hz, 1H), 5.03-4.91 (m, 2H), 4.73 (d, J=7.3, 0.7 Hz, 1H), 4.57-4.51 (m, 2H), 4.38-4.27 (m, 1H), 4.19-4.05 (m, 2H), 3.93-3.79 (m, 2H), 3.66 (t, J=2.6 Hz, 1H), 3.52 (dd, J=11.8, 9.6 Hz, 1H), 3.30 (d, J=2.1 Hz, 3H), 2.12-2.01 (m, 9H).



Compound 93: (fluoromethyl)(methyl)(prop-2-yn-1-yl)(2-{[(3R,4S,5S)-3,4,5-tris(acetyloxy)oxan-2-yl]oxy}ethyl)azanium

[0659] This compound may be synthesized according to the experimental procedure described for Compound 309.



Compound 94: (chloromethyl)dimethyl(2-{[(2S,3R,4S,5R)-3,4,5-tris(acetyloxy)oxan-2-yl]oxy}ethyl)azanium Iodide

[0660] Step 1:

[0661] To a mixture of (2R,3R,4S,5R)-tetrahydropyran-2,3,4,5-tetrol (50 g, 333.04 mmol, 1 eq) in pyridine (300 mL) was added acetyl acetate (204.00 g, 2.00 mol, 187.16 mL, 6 eq) in one portion at 0° C. under N_2. The mixture was heated to 25° C. and stirred for 12 hours. TLC indicated one new spot. The reaction was clean according to TLC. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 0/1). Compound [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (80 g, 251.35 mmol, 75.47% yield) was obtained as yellow oil.

[0662] Step 2:

[0663] To a mixture of [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (20 g, 62.84 mmol, 1 eq) in DCM (200 mL) was added 2-bromoethanol (11.78 g, 94.26 mmol, 6.69 mL, 1.5 eq) and $BF_3.Et_2O$ (9.10 g, 62.84 mmol, 7.91 mL, 98% purity, 1 eq) in one portion at 0° C. under N_2. The mixture was heated to 25° C. and stirred for 12 hours. TLC indicated [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate was consumed and one new spot formed. The reaction mixture was quenched by addition of H_2O (100 mL), and then diluted with H_2O (200 mL) and extracted with ethyl acetate (200 mL*3). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to give a residue. The crude product was purified by re-crystallization from ethyl acetate: Petroleum ether (40 ml:30 mL) at 0° C. for 12h. The mixture was filtered and the filter cake was concentrated under reduced pressure to give a residue. The filtrate was purified by prep-HPLC [water (0.1% TFA)-ACN]. [(3R,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (3.4 g, 8.87 mmol, 14.12% yield) was obtained as a white solid. Compound [(3R,4S,5R,6R)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (3.5 g, 9.13 mmol, 14.54% yield) was obtained as yellow oil.

[0664] Step 3:

[0665] To a mixture of [(3R,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (3.4 g, 8.87 mmol, 1 eq) in THF (30 mL) was added NaI (1.33 g, 8.87 mmol, 1 eq) and Na_2CO_3 (1.88 g, 17.75 mmol, 2 eq) in one portion at 25° C. under N_2. Then N-methylmethanamine (2 M, 24.40 mL, 5.5 eq) was added. The mixture was heated to 70° C. and stirred for 12 hours. TLC indicated [(3R,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate was consumed incompletely and one new spot formed. LCMS showed [(3R,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate was consumed and one main peak with desired m/z was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Ethyl acetate:Methanol=1/0 to 1/1). The 200 mg crude product was purified by prep-HPLC [water (0.1% TFA)-ACN]. Compound [(3R,4S,5R,6R)-4,5-diacetoxy-6-[2-(dimethylamino)ethoxy]tetrahydropyran-3-yl] acetate (3.1 g, crude) was obtained as yellow oil. Compound [(3R,4S,5R,6R)-4,5-diacetoxy-6-[2-(dimethylamino)ethoxy]tetrahydropyran-3-yl] acetate (14.7 mg, 98% purity) was obtained as white solid. LCMS: $(M+H)^+$: 348.1

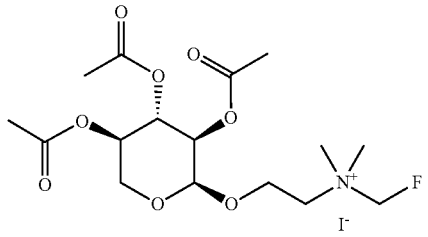
[0666] Step 4:

[0667] To a mixture of [(3R,4S,5R,6R)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (3.5 g, 9.13 mmol, 1 eq) in THF (30 mL) was added NaI (1.37 g, 9.13 mmol, 1 eq), Na_2CO_3 (1.94 g, 18.27 mmol, 2 eq) and N-methylmethanamine (2 M, 25.12 mL, 5.5 eq) in one portion at 25° C. under N_2. The mixture was heated to 70° C. and stirred for 12 hours. LCMS showed [(3R,4S,5R,6R)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate was consumed and one main peak with desired m/z was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The 500 mg crude product was purified by prep-HPLC [water (0.10% TFA)-ACN]. Compound [(3R,4S,5R,6S)-4,5-diacetoxy-6-[2-(dimethylamino)ethoxy]tetrahydropyran-3-yl] acetate (34 mg, 73.69 umol, 5.12% yield, 100% purity, TFA) was obtained as colorless oil. Compound [(3R,4S,5R,6S)-4,5-

diacetoxy-6-[2-(dimethylamino)ethoxy]tetrahydropyran-3-yl] acetate (4.2 g, crude) was obtained as yellow oil and the crude product was used into the next step without further purification. LCMS: $(M+H)^+$: 348.1

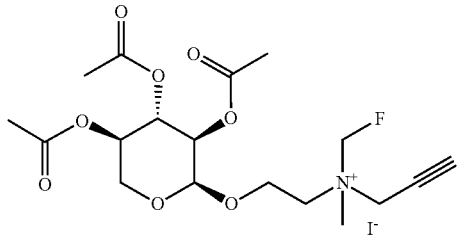
[0668] Step 5:

[0669] To a mixture of [(3R,4S,5R,6S)-4,5-diacetoxy-6-[2-(dimethylamino)ethoxy]tetrahydropyran-3-yl] acetate (4.2 g, 12.09 mmol, 1 eq) in acetone (40 mL) was added chloro(iodo)methane (10.66 g, 60.46 mmol, 4.39 mL, 5 eq) in one portion at 25° C. under N_2. The mixture was heated to 90° C. and stirred for 2 hours. TLC indicated [(3R,4S,5R,6S)-4,5-diacetoxy-6-[2-(dimethylamino)ethoxy]tetrahydropyran-3-yl] acetate was consumed and one new spot formed. LCMS showed one main peak with desired m/z. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Ethyl acetate: Methanol=1/0 to 2/1). Then the residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. The title compound (26 mg, 49.64 umol, 9.85% yield, I—) was obtained as yellow oil. LCMS: $(M^+)^+$: 396.0 ^{1}H NMR (400 MHz, Methanol-d4) δ 5.45-5.25 (m, 4H), 5.18 (s, 1H), 4.42-4.31 (m, 2H), 4.30-4.15 (m, 2H), 4.07-3.97 (m, 1H), 3.82 (t, J=4.7 Hz, 2H), 3.32 (s, 6H), 2.16-2.04 (m, 9H).



Compound 95: (fluoromethyl)dimethyl(2-{[(3R,4S,5S,6R)-3,4,5-tris(acetyloxy)-6-methyloxan-2-yl]oxy}ethyl)azanium

[0670] This compound may be synthesized according to the experimental procedure described for Compound 311.



Compound 96: (fluoromethyl)(methyl)(prop-2-yn-1-yl)(2-{[(2S,3R,4S,5R)-3,4,5-tris(acetyloxy)oxan-2-yl]oxy}ethyl)azanium Iodide

[0671] Step 1:

[0672] To a mixture of (2R,3R,4S,5R)-tetrahydropyran-2,3,4,5-tetrol (50 g, 333.05 mmol, 1 eq) in pyridine (300 mL) was added acetyl acetate (204.00 g, 2.00 mol, 187.16 mL, 6 eq) in one portion at 0° C. under N_2. The mixture was heated to 25° C. and stirred for 12 hours. TLC indicated one new spot formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 0/1). Compound [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (100 g, 314.19 mmol, 94.34% yield) was obtained as yellow oil.

[0673] Step 2:

[0674] To a solution of [of [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (20 g, 62.84 mmol, 1 eq) in DCM (150 mL) was added dropwise 2-bromoethanol (11.78 g, 94.26 mmol, 6.69 mL, 1.5 eq) and $BF_3.Et_2O$ (45.50 g, 314.19 mmol, 39.57 mL, 98% purity, 5 eq) at 0° C. The mixture was warmed to 25° C. and stirred at 25° C. for 12 hr. TLC indicated [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate was consumed completely and two new spots formed. The reaction mixture was quenched by addition of H_2O (500 mL) and extracted with EtOAc (900 mL, 300 mL*3). The combined organic layers were concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1). Two batches were obtained successively. The batch 1 was further purified by re-crystallization from ethyl acetate:Petroleum ether at 0° C. for 12h. Compound [(3R,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (3 g, 2.5% yield) was obtained as a white solid. The batch 2 was further purified by prep-HPLC [water (0.10% TFA)-ACN]. The title compound (7 g, 5.8% yield) was obtained as colorless oil.

[0675] Step 3:

[0676] To a solution of [(3R,4S,5R,6R)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (1.50 g, 3.91 mmol, 1 eq) in THF (15 mL) was added N-methylprop-2-yn-1-amine (1.49 g, 21.53 mmol, 1.79 mL, 5.5 eq) and DIPEA (1.01 g, 7.83 mmol, 1.36 mL, 2 eq). The mixture was stirred at 70° C. for 12 hr. LCMS showed [(3R,4S,5R,6R)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate was consumed completely and one main peak with expected mass was detected. The reaction mixture was concentrated under reduced pressure. The crude product (300 mg) was purified by prep-HPLC [water (0.1% TFA)-ACN]. Compound[(3R,4S,5R,6S)-4,5-diacetoxy-6-[2-[methyl(prop-2-ynyl)amino]ethoxy]tetrahydropyran-3-yl] acetate (110 mg, 100% purity, TFA) was obtained as yellow oil. The other crude product [(3R,4S,5R,6S)-4,5-diacetoxy-6-[2-[methyl(prop-2-ynyl)amino]ethoxy]tetrahydropyran-3-yl] acetate (600 mg, crude) was used in the next step without further purification. LCMS: $(M+H)^+$: 372.1

[0677] Step 4:

[0678] To a solution of [(3R,4S,5R,6S)-4,5-diacetoxy-6-[2-[methyl(prop-2-ynyl)amino]ethoxy]tetrahydropyran-3-yl] acetate (300 mg, 807.80 umol, 1 eq) in DCM (3 mL) was added fluoro(iodo)methane (645.95 mg, 4.04 mmol, 5 eq) and DIPEA (104.40 mg, 807.80 umol, 140.70 uL, 1 eq). The mixture was stirred at 40° C. for 3 hr. LCMS showed [(3R,4S,5R,6S)-4,5-diacetoxy-6-[2-[methyl(prop-2-ynyl)amino]ethoxy]tetrahydropyran-3-yl] acetate was consumed completely and the expected mass was detected. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC [water (0.10% TFA)-ACN]. Compound fluoromethyl-methyl-prop-2-ynyl-[2-[(2R,3R,4S,5R)-3,4,5-triacetoxytetrahydropyran-2-yl]oxy-ethyl]ammonium (95 mg, 29.1% yield, 100% purity, I—) was obtained as yellow oil. LCMS: (M+): 404.1 ^{1}H NMR

(400 MHz, Methanol-d4) δ 5.72 (d, J=2.1 Hz, 1H), 5.61 (d, J=2.1 Hz, 1H), 5.41 (td, J=9.8, 2.5 Hz, 1H), 5.11-5.05 (m, 1H), 5.05-4.94 (m, 2H), 4.61 (dd, J=2.8, 1.4 Hz, 2H), 4.19 (d, J=12.4 Hz, 1H), 4.07-3.91 (m, 2H), 3.91-3.83 (m, 2H), 3.77-3.61 (m, 2H), 3.34 (d, J=2.1 Hz, 3H), 2.14-1.97 (m, 9H).

Compound 97: (fluoromethyl)dimethyl(2-{[(2S,3R, 4S,5R)-3,4,5-tris(acetyloxy)oxan-2-yl]oxy}ethyl) azanium Iodide

[0679] Step 1:

[0680] To a solution of (2R,3R,4S,5R)-tetrahydropyran-2, 3,4,5-tetrol (50 g, 333.04 mmol, 1 eq) in pyridine (500 mL) was added Ac_2O (204.00 g, 2.00 mol, 187.16 mL, 6 eq). The mixture was stirred at 25° C. for 12 hr. TLC indicated (2R,3R,4S,5R)-tetrahydropyran-2,3,4,5-tetrol was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=80/1 to 0/1). Compound [(3R,4S, 5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (100 g, 314.19 mmol, 94.34% yield) was obtained as a yellow oil.

[0681] Step 2:

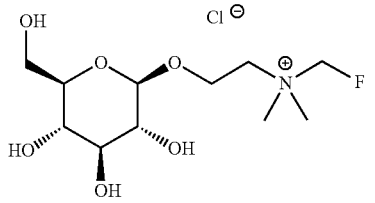
[0682] To a solution of [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate (20 g, 62.84 mmol, 1 eq) in DCM (150 mL) was added dropwise 2-bromoethanol (11.78 g, 94.26 mmol, 6.69 mL, 1.5 eq) and $BF_3.Et_2O$ (45.50 g, 314.19 mmol, 39.57 mL, 98% purity, 5 eq) at 0° C. The mixture was warmed to 25° C. and was stirred at 25° C. for 12 hr. TLC indicated [(3R,4S,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate was consumed completely and new spots formed. 5 batches were combined for work-up. The reaction mixture was quenched by addition of H_2O (500 mL) at 25° C. and extracted with EtOAc (900 mL, 300 mL*3). The combined organic layers were concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/ Ethyl acetate=20/1 to 0/1). The crude product was purified by re-crystallization from ethyl acetate:Petroleum ether (40 ml:30 mL) at 0° C. for 12h. Compound [(3R,4S,5R,6S)-4, 5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (3 g, 7.83 mmol, 2.49% yield) was obtained as a white solid. The filtrate was purified by prep-HPLC [water (0.1% TFA)-ACN]. Compound [(3R,4S,5R,6R)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (7 g, 18.27 mmol, 5.81% yield) was obtained as a colorless oil.

[0683] Step 3:

[0684] To a mixture of [(3R,4S,5R,6R)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (0.5 g, 1.30 mmol, 1 eq) in THF (5 mL) was added $MeNH_2$ (810.49 mg, 5.22 mmol, 20% purity, 4 eq) and NaI (195.59 mg, 1.30 mmol, 1 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 12 hours. LCMS showed the expected mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Ethyl acetate/MeOH=0/1 to 10/1). The crude product [(3R, 4S,5R,6S)-4,5-diacetoxy-6-[2-(dimethylamino)ethoxy]tetrahydropyran-3-yl] acetate (0.38 g, 1.09 mmol, 83.84% yield) was obtained as yellow oil, and used into the next step without further purification.

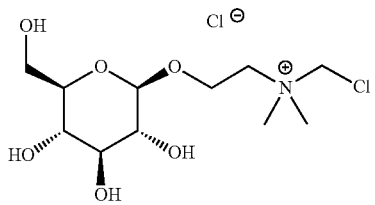
[0685] Step 4:

[0686] To a mixture of [(3R,4S,5R,6S)-4,5-diacetoxy-6-[2-(dimethylamino)ethoxy]tetrahydropyran-3-yl] acetate (370 mg, 1.07 mmol, 1 eq) in DCM (5 mL) was added fluoro(iodo)methane (851.76 mg, 5.33 mmol, 5 eq). The mixture was stirred at 40° C. for 3 hours. LCMS showed desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.10% TFA)-ACN]. The title compound (14 mg, 36.07 umol, 3.39% yield, 98% purity) was obtained as colorless oil. (M+): 380.1 ^1H NMR (400 MHz, Methanol-d4) δ 5.58 (s, 1H), 5.47 (s, 1H), 5.42 (t, J=9.7 Hz, 1H), 5.11 (d, J=3.7 Hz, 1H), 5.07-4.96 (m, 2H), 4.20 (d, J=13.2 Hz, 1H), 4.02 (t, J=11.0 Hz, 1H), 3.94-3.82 (m, 2H), 3.82-3.74 (m, 1H), 3.68 (t, J=10.8 Hz, 1H), 3.31 (d, J=2.1 Hz, 6H), 3.04-2.94 (m, 1H), 2.09-2.01 (m, 9H).



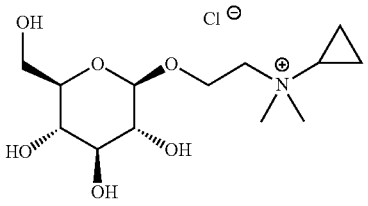
Compound 98: (fluoromethyl)dimethyl(2-{[(2R,3R, 4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy}ethyl)azanium Chloride

[0687] N-(fluoromethyl)-N,N-dimethyl-2-(((3R,4S,5R, 6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)ethan-1-aminium iodide (1.00 g, 1 Eq, 1.73 mmol) is dissolved in methanol (3 mL), followed by addition of 0.5M NaOMe in methanol (9.32 mg, 0.35 mL, 0.1 Eq, 173 μmol). The reaction was stirred at room temperature for a few hours, then concentrated by rotary evaporation. The sample was redissolved in MeOH, then purified by column chromatography (C18AQ flash column, elutes at 100% Water with 0.1% TFA). The pure fractions were lyophilized and collected. The product was redissolved in water and stirred with Amberlyst IRA-400 Cl-resin (300 mg resin/100 mg of TFA salt), then lyophilized to yield the title compound (0.400 g, 72.5%)). LCMS M+: 284.2. ^1H NMR (400 MHz, Deuterium Oxide) δ 5.39 (s, 1H), 5.28 (s, 1H), 4.41 (dd, J=8.0, 0.9 Hz, 1H), 4.35-4.25 (m, 1H), 4.09-3.99 (m, 1H), 3.87-3.79 (m, 1H), 3.74-3.59 (m, 3H), 3.45-3.33 (m, 2H), 3.33-3.27 (m, 1H), 3.31-3.19 (m, 1H), 3.16 (d, J=2.1 Hz, 6H).



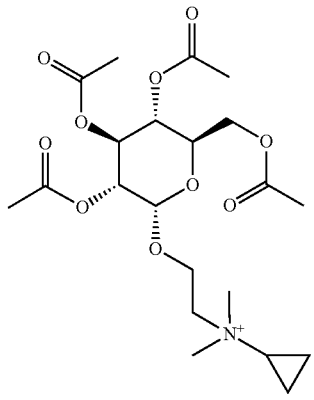
Compound 99: (chloromethyl)dimethyl(2-{[(2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy}ethyl)azanium Chloride

[0688] N,N-dimethyl-N-(2-(((3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)ethyl)cyclopropanaminium iodide (1.00 g, 1 Eq, 1.70 mmol, as synthesized in Compound 310) is dissolved in methanol (3 mL), followed by addition of 0.5M NaOMe in methanol (18.4 mg, 0.68 mL, 0.2 Eq, 340 μmol). The reaction was stirred at room temperature for a few hours, then concentrated by rotary evaporation. The sample was redissolved in MeOH, then purified by column chromatography (C18AQ flash column, elutes at 100% Water with 0.1% TFA). The pure fractions were lyophilized and collected. The product was redissolved in water and stirred with Amberlyst IRA-400 Cl-resin (300 mg resin/100 mg of TFA salt), then lyophilized to yield the title compound (0.200 g, 35.8%). LCMS M+: 300.2. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 5.15 (s, 2H), 4.41 (d, J=7.9 Hz, 1H), 4.35-4.25 (m, 1H), 4.09-3.99 (m, 1H), 3.83 (dd, J=12.3, 2.2 Hz, 1H), 3.79-3.69 (m, 2H), 3.63 (dd, J=12.3, 5.8 Hz, 1H), 3.44-3.33 (m, 2H), 3.33-3.17 (m, 2H), 3.20 (s, 6H).



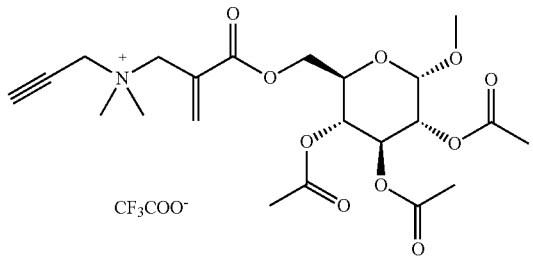
Compound 100: N,N-dimethyl-N-(2-{[(2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy}ethyl)cyclopropanaminium Chloride

[0689] N,N-dimethyl-N-(2-(((3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)ethyl)cyclopropanaminium iodide (1.00 g, 1 Eq, 1.70 mmol, as synthesized in Compound 312) is dissolved in methanol (3 mL), followed by addition of 0.5M NaOMe in methanol (18.4 mg, 0.68 mL, 0.2 Eq, 340 μmol). The reaction was stirred at room temperature for a few hours, then concentrated by rotary evaporation. The sample was redissolved in MeOH, then purified by column chromatography (C18AQ flash column, elutes at 100% Water with 0.1% TFA). The pure fractions were lyophilized and collected. The product was redissolved in water and stirred with Amberlyst IRA-400 Cl-resin (300 mg resin/100 mg of TFA salt), then lyophilized to yield the title compound (0.200 g, 35.8%). LCMS M+: 292.3. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 4.40 (dd, J=8.0, 1.0 Hz, 1H), 4.37-4.28 (m, 1H), 4.12-4.02 (m, 1H), 3.82 (dd, J=12.4, 2.1 Hz, 1H), 3.69-3.57 (m, 3H), 3.44-3.33 (m, 2H), 3.33-3.24 (m, 1H), 3.24-3.16 (m, 1H), 3.16-3.08 (m, 1H), 2.93 (d, J=2.0 Hz, 6H), 1.18-1.09 (m, 2H), 0.91-0.80 (m, 2H).



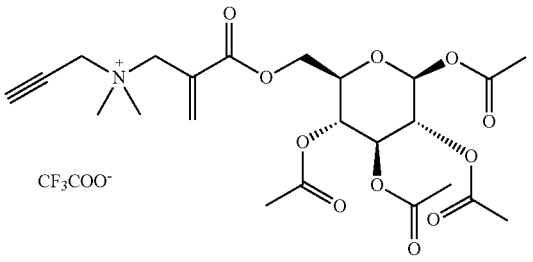
Compound 101: N,N-dimethyl-N-(2-{[(2S,3R,4S,5R,6R)-3,4,5-tris(acetyloxy)-6-[(acetyloxy)methyl]oxan-2-yl]oxy}ethyl)cyclopropanaminium

[0690] This compound may be synthesized according to the experimental procedure described for Compound 312.



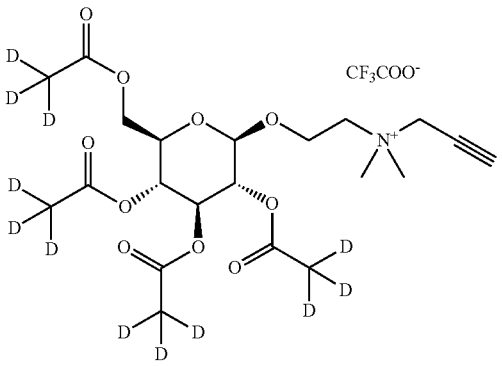
Compound 103: N,N-dimethyl-N-(prop-2-yn-1-yl)-2-((((2R,3R,4S,5R)-3,4,5-triacetoxy-6-methoxytetrahydro-2H-pyran-2-yl)methoxy)carbonyl)prop-2-en-1-aminium 2,2,2-trifluoroacetate

[0691] Compound 2-carboxy-N,N-dimethyl-N-(prop-2-yn-1-yl)prop-2-en-1-aminium (315 mg, 2 Eq, 1.87 mmol) and EDC (359 mg, 2 Eq, 1.87 mmol) were stirred in DMF (3 mL). Next (2R,3R,4S,5R)-2-(hydroxymethyl)-6-methoxytetrahydro-2H-pyran-3,4,5-triyl triacetate (300 mg, 1 Eq, 937 μmol) was added to the solution and the reaction was stirred at room temperature overnight. The reaction mixture was injected directly onto reverse phase C18 column chromatography (5% ACN in water with 0.1% TFA to 100% ACN), and product containing fractions were lyophilized to yield N,N-dimethyl-N-(prop-2-yn-1-yl)-2-((((2R,3R,4S,5R)-3,4,5-triacetoxy-6-methoxytetrahydro-2H-pyran-2-yl)methoxy)carbonyl)prop-2-en-1-aminium 2,2,2-trifluoroacetate (18 mg, 3.3%). LCMS M+: 470.1. ^{1}H NMR (400 MHz, DMSO-d6) δ 6.90 (s, 1H), 6.52 (s, 1H), 5.31 (t, J=9.7 Hz, 1H), 5.07 (t, J=9.9 Hz, 1H), 4.96-4.83 (m, 2H), 4.37 (d, J=2.5 Hz, 2H), 4.33-4.21 (m, 4H), 4.11-4.05 (m, 1H), 4.00 (dt, J=10.3, 3.3 Hz, 1H), 3.34 (s, 3H), 3.03 (s, 6H), 2.02-1.93 (m, 9H).



Compound 104: N,N-dimethyl-N-(prop-2-yn-1-yl)-2-((((2R,3R,4S,5R)-3,4,5,6-tetraacetoxytetrahydro-2H-pyran-2-yl)methoxy)carbonyl)prop-2-en-1-aminium2,2,2-trifluoroacetate

[0692] 2-carboxy-N,N-dimethyl-N-(prop-2-yn-1-yl)prop-2-en-1-aminium (193 mg, 2 Eq, 1.15 mmol) and EDC (220 mg, 2 Eq, 1.15 mmol) were stirred in DMF (3 mL). Next (3R,4S,5R,6R)-6-(hydroxymethyl)tetrahydro-2H-pyran-2, 3,4,5-tetrayltetraacetate (200 mg, 1 Eq, 574 mol) was added to the solution and the reaction was stirred at room temperature overnight. The reaction mixture was injected directly onto reverse phase C18 column chromatography (5% ACN in water with 0.1% TFA to 100% ACN; two column purifications were performed), and product containing fractions were lyophilized to yield N,N-dimethyl-N-(prop-2-yn-1-yl)-2-((((2R,3R,4S,5R)-3,4,5,6-tetraacetoxytetrahydro-2H-pyran-2-yl)methoxy)carbonyl)prop-2-en-1-aminium2,2,2-trifluoroacetate (33 mg, 9.4%). LCMS M+: 498.1. ^{1}HNMR (400 MHz, DMSO-d6) δ 6.88 (s, 1H), 6.51 (s, 1H), 5.94 (d, J=8.3 Hz, 1H), 5.45 (t, J=9.6 Hz, 1H), 5.08 (t, J=9.4 Hz, 1H), 5.00 (dd, J=9.7, 8.3 Hz, 1H), 4.36 (d, J=2.5 Hz, 2H), 4.32-4.16 (m, 5H), 4.08 (t, J=2.4 Hz, 1H), 3.02 (s, 6H), 2.11-1.90 (m, 12H).



Compound 105: N,N-dimethyl-N-(2-(((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium 2,2,2-trifluoroacetate

[0693] Step 1:

[0694] To a solution of compound 1 (200 g, 512 mmol, 1.00 eq) in DCM (1000 mL) was added 4A molecular sieves (100 g). 2-iodoethanol (88.1 g, 512 mmol, 40.0 mL, 1.00 eq) was added to the suspension drop-wise at 0° C. and the resulting suspension was stirred at 0° C. for 30 mins. $BF_3.Et_2O$ (218 g, 1.54 mol, 190 mL, 3.00 eq) was added to the suspension drop-wise at 0° C. under N_2. After addition, the suspension was stirred at 20° C. for 18 hrs. TLC (Petroleum ether:Ethyl acetate=2:1, R_f of material=0.4) showed the reaction was completed. K_2CO_3 (280 g) was added to the suspension in one portion, and the suspension was stirred for 30 mins. The suspension was filtered. The filtrate was washed by water (1500 mL×2) followed by brine (1000 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to give a crude product. The crude product was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=100/1 to 5/1) to give a solid. The solid was re-crystallized from MTBE/Petroleum ether (3:1, 300 mL) to give compound 2 (195 g, 388 mmol, 37.9% yield) as a white solid.

[0695] Step 2:

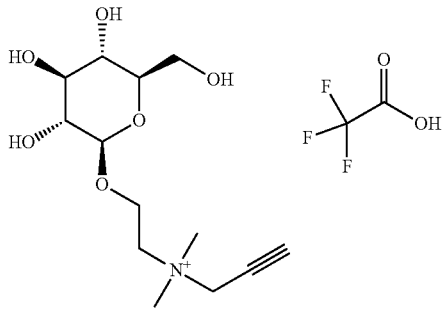
[0696] To a solution of compound 2 (80 g, 159 mmol, 1.00 eq) in acetone (500 mL) was added compound 2A (19.9 g, 239 mmol, 25.3 mL, 1.50 eq). After addition, the solution was stirred at 40° C. for 16 hrs. TLC (Petroleum ether:Ethyl acetate=2:1, Rf of material=0.5) showed the reaction was completed. The solution was cooled to 0° C. and solid precipitated out. The solid was filtered, collected and concentrated under vacuum to give 3 (100 g, 171 mmol, 53.6% yield) as a white solid.

[0697] Step 3:

[0698] N,N-dimethyl-N-(2-(((3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy) ethyl)prop-2-yn-1-aminium iodide (3.00 g, 1 Eq, 5.12 mmol) is dissolved in methanol (3 mL), followed by addition of 0.5M NaOMe in methanol (sodium methoxide (277 mg, 10 mL, 1 Eq, 5.12 mmol)). The reaction was stirred at room temperature for a few hours, then concentrated by rotary evaporation. The sample was dissolved in water, then purified by column chromatography (C18AQ flash column, elutes at 100% Water with 0.1% TFA). The pure fractions were lyophilized to yield product N,N-dimethyl-N-(2-(((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium 2,2,2-trifluoroacetate (590 mg, 28.5%)).

[0699] Step 4:

[0700] Compound N,N-dimethyl-N-(2-(((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium (0.300 g, 1 Eq, 1.03 mmol) was stirred in acetic-2,2,2-d3 anhydride (1.12 g, 977 μL, 10 Eq, 10.3 mmol) and pyridine (817 mg, 836 μL, 10 Eq, 10.3 mmol). The reaction was diluted in dichloromethane then purified by column chromatography (100% DCM to 10% MeOH in DCM; product elutes around 8% MeOH in DCM). Fractions containing product were dried in vacuo to yield N,N-dimethyl-N-(2-(((2R,3R,4S,5R,6R)-3,4,5-tris(acetoxy-d3)-6-((acetoxy-d3)methyl)tetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium 2,2,2-trifluoroacetate (75 mg, 12%). LCMS M+: 470.4. ^{1}H NMR (400 MHz, DMSO-d6) δ 5.26 (t, J=9.5 Hz, 1H), 4.99-4.74 (m, 3H), 4.36 (d, J=2.5 Hz, 2H), 4.24-3.94 (m, 6H), 3.61 (t, J=5.0 Hz, 2H), 3.08 (s, 6H).



Compound 106: N,N-dimethyl-N-(2-(((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium 2,2,2-trifluoroacetate

[0701] Step 1:

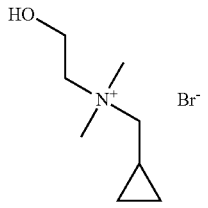
[0702] To a solution of compound 1 (200 g, 512 mmol, 1.00 eq) in DCM (1000 mL) was added 4A molecular sieves (100 g). 2-iodoethanol (88.1 g, 512 mmol, 40.0 mL, 1.00 eq) was added to the suspension drop-wise at 0° C. and the resulting suspension was stirred at 0° C. for 30 mins. $BF_3.Et_2O$ (218 g, 1.54 mol, 190 mL, 3.00 eq) was added to the suspension drop-wise at 0° C. under N_2. After addition, the suspension was stirred at 20° C. for 18 hrs. TLC (Petroleum ether:Ethyl acetate=2:1, Rf of material=0.4) showed the reaction was completed. K_2CO_3 (280 g) was added to the suspension in one portion, and the suspension was stirred for 30 mins. The suspension was filtered. The filtrate was washed by water (1500 mL×2) followed by brine (1000 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to give a crude product. The crude product was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=100/1 to 5/1) to give a solid. The solid was re-crystallized from MTBE/Petroleum ether (3:1, 300 mL) to give compound 2 (195 g, 388 mmol, 37.9% yield) as a white solid.

[0703] Step 2:

[0704] To a solution of compound 2 (80 g, 159 mmol, 1.00 eq) in acetone (500 mL) was added compound 2A (19.9 g, 239 mmol, 25.3 mL, 1.50 eq). After addition, the solution was stirred at 40° C. for 16 hrs. TLC (Petroleum ether:Ethyl acetate=2:1, Rf of material=0.5) showed the reaction was completed. The solution was cooled to 0° C. and lots of solid precipitated out. The solid was filtered, collected and concentrated under vacuum to give 3 (100 g, 171 mmol, 53.6% yield) as a white solid.

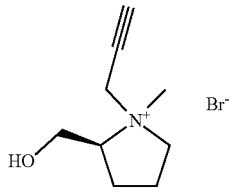
[0705] Step 3:

[0706] N,N-dimethyl-N-(2-(((3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy) ethyl)prop-2-yn-1-aminium iodide (3.00 g, 1 Eq, 5.12 mmol) is dissolved in methanol (3 mL), followed by addition of 0.5M NaOMe in methanol (sodium methoxide (277 mg, 10 mL, 1 Eq, 5.12 mmol)). The reaction was stirred at room temperature for a few hours, then concentrated by rotary evaporation. The sample was dissolved in water, then purified by column chromatography (C18AQ flash column, elutes at 100% Water with 0.1% TFA). The pure fractions were lyophilized to yield product N,N-dimethyl-N-(2-(((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium 2,2,2-trifluoroacetate (590 mg, 28.5%)). LCMS M+: 290.2. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 4.43 (d, J=7.9 Hz, 1H), 4.36-4.23 (m, 3H), 4.11-4.00 (m, 1H), 3.84 (dd, J=12.4, 2.2 Hz, 1H), 3.73-3.61 (m, 3H), 3.46-3.35 (m, 2H), 3.34-3.18 (m, 3H), 3.18 (s, 6H).



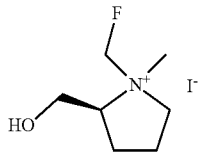
Compound 107 and Compound 131: N-(cyclopropylmethyl)-2-hydroxy-N,N-dimethylethan-1-aminium Bromide

[0707] To a solution of 2-(dimethylamino) ethanol (1 g, 11.22 mmol, 1.13 mL, 1 eq) in THF (10 mL) was added (bromomethyl) cyclopropane (1.67 g, 12.34 mmol, 1.18 mL, 1.1 eq) at 20° C. The mixture was stirred at 20° C. for 12 h. The reaction mixture was filtered to give a residue. The residue was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL). The water layer was freeze-drying to give N-(cyclopropylmethyl)-2-hydroxy-N, N-dimethyl-ethanaminium bromide (170 mg, 758.46 umol, 6.76% yield) as a white solid. MS: M^+=144.1 ^{1}H NMR (400 MHz, D2O) δ 4.0 (m, 2H), 3.5 (m, 2H), 3.2 (d, 2H), 3.1 (s, 6H), 1.2 (m, 1H), 0.8 (m, 2H), 0.4 (m, 2H) ppm.



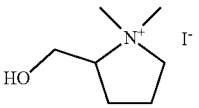
Compound 108: (2S)-2-(hydroxymethyl)-1-methyl-1-(prop-2-yn-1-yl)pyrrolidin-1-ium bromide

[0708] To a solution of [(2S)-1-methylpyrrolidin-2-yl] methanol (200 mg, 1.74 mmol, 206.19 uL, 1 eq) in DCM (5 mL) was added 3-bromoprop-1-yne (247.89 mg, 2.08 mmol, 179.63 uL, 1.2 eq). The mixture was stirred at 25° C. for 5 h. Some solid precipitate out. The mixture was filtered and the filter cake was washed with DCM (5 mL*2) and concentrated to dryness. Compound (2S)-2-(hydroxymethyl)-1-methyl-1-(prop-2-yn-1-yl) pyrrolidin-1-ium bromide (346 mg, crude) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 5.5 (m, 1H), 4.3 (m, 2H), 3.8 (m, 5H), 3.3 (s 6H), 2.0 (m, 4H) ppm.



Compound 109: (2S)-1-(fluoromethyl)-2-(hydroxymethyl)-1-methylpyrrolidin-1-ium iodide

[0709] To a solution of (3S)-1-methylpyrrolidin-3-ol (200 mg, 1.98 mmol, 201.41 uL, 1 eq) in DCM (5 mL) was added fluoro (iodo) methane (379.48 mg, 2.37 mmol, 1.2 eq). The mixture was stirred at 25° C. for 5 h. MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was dissolved in H_2O (1 mL), washed with EtOAc (2 mL*2) and lyophilized the aqueous phase to give a residue. Compound (2S)-1-(fluoromethyl)-2-(hydroxymethyl)-1-methylpyrrolidin-1-ium iodide (111 mg, crude) was obtained as a white solid. ^1H NMR (400 MHz, DMSO) δ 5.6 (m, 3H), 3.8 (m, 4H), 3.5 (m, 1H), 3.1 (s, 3H), 2.0 (m, 4H) ppm

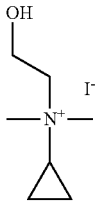


Compound 110: 2-(hydroxymethyl)-1,1-dimethylpyrrolidin-1-ium Iodide

[0710] To a solution of (1-methylpyrrolidin-2-yl) methanol (300 mg, 2.60 mmol, 1 eq) and DMAP (159.11 mg, 1.30 mmol, 0.5 eq) in THF (5 mL) was added $(Boc)_2O$ (1.42 g, 6.51 mmol, 1.50 mL, 2.5 eq) at 25° C. The mixture was stirred at 25° C. for 12 h. LCMS showed the desired compound was detected. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=3:1 to 1:1) to give tert-butyl ((1-methylpyrrolidin-2-yl) methyl) carbonate (190 mg, 882.54 umol, 33.88% yield) as a yellow oil.

[0711] To a solution of tert-butyl ((1-methylpyrrolidin-2-yl) methyl) carbonate (190 mg, 882.54 umol, 1 eq) in THF (5 mL) was added MeI (250.53 mg, 1.77 mmol, 109.88 uL, 2 eq) at 25° C. The mixture was stirred at 25° C. for 5 h. LCMS showed the desired compound was detected. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL). The water layer was freeze-drying to give 2-(((tert-butoxycarbonyl)oxy)methyl)-1,1-dimethylpyrrolidin-1-ium iodide (200 mg, 559.87 umol, 63.44% yield) as a yellow solid.

[0712] To a solution of 2-(((tert-butoxycarbonyl)oxy) methyl)-1,1-dimethylpyrrolidin-1-ium iodide (180 mg, 503.88 umol, 1 eq) in HCl/dioxane (0.5 mL, 4M) and dioxane (1 mL) was stirred at 25° C. for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL). The water layer was freeze-drying to give 2-(hydroxymethyl)-1,1-dimethylpyrrolidin-1-ium iodide (70 mg, 272.26 umol, 54.03% yield) as a yellow solid. MS: M^+=130.1 ^1H NMR (400 MHz, DMSO) δ 3.9 (m, 2H), 3.7 (m, 1H), 3.5 (m, 2H), 3.2 (s, 3H), 3.0 (s, 3H), 2.3 m, 1H0, 2.1 (m, 2H), 1.8 (m, 1H) ppm.

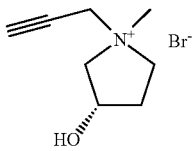


Compound 111: N-(2-hydroxyethyl)-N,N-dimethylcyclopropanaminium Iodide

[0713] To a solution of N-methylcyclopropanamine (150 mg, 2.11 mmol, 1.68 eq) and (2-bromoethoxy)(tert-butyl) dimethylsilane (300 mg, 1.25 mmol, 1 eq) in ACN (5 mL) was added K_2CO_3 (173.32 mg, 1.25 mmol, 1 eq) at 25° C. The mixture was stirred at 50° C. for 12 h. TLC indicated new spot formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5:1 to 1:1) to give N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-N-methylcyclopropanamine (120 mg, 523.03 umol, 41.71% yield) as colorless oil.

[0714] To a solution of N-(2-((tert-butyldimethylsilyl) oxy) ethyl)-N-methylcyclopropanamine (70 mg, 305.10 umol, 1 eq) in THF (2 mL) was added MeI (86.61 mg, 610.20 umol, 37.99 uL, 2 eq) at 25° C. The mixture was stirred at 25° C. for 12 h. The solid was filtered and the filter cake was concentrated to give N-(2-((tert-butyldimethylsilyl) oxy) ethyl)-N, N-dimethylcyclopropanaminium iodide (50 mg, 134.64 umol, 44.13% yield) as a white solid.

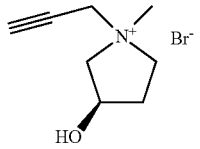
[0715] To a solution of N-(2-((tert-butyldimethylsilyl) oxy) ethyl)-N, N-dimethylcyclopropanaminium iodide (20 mg, 53.85 umol, 1 eq) in H_2O (2 mL) was added KF (31.29 mg, 538.54 umol, 12.62 uL, 10 eq) at 25° C. The mixture was stirred at 25° C. for 12 h. The precipitation was separated out by filtration. And the filtrate was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL). The water layer was concentrated under reduced pressure to give a residue. The residue was washed by acetonitrile (2 mL). The acetonitrile layer was filtered and the filtrate was concentrated under reduced pressure to give N-(2-hydroxyethyl)-N, N-dimethylcyclopropanaminium iodide (10 mg, 38.89 umol, 72.22% yield) as a white solid. ^1H NMR (400 MHz, D2O) δ 4.1 (m, 2H), 3.6 (m, 2H), 3.2 (m, 1H), 3.0 (s, 6H), 1.2 (m, 2H), 0.9 (m, 2H) ppm.



Compound 112: (3S)-3-hydroxy-1-methyl-1-(prop-2-yn-1-yl)pyrrolidin-1-ium bromide

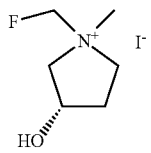
[0716] To a solution of (3S)-1-methylpyrrolidin-3-ol (200 mg, 1.98 mmol, 201.41 uL, 1 eq) in DCM (5 mL) was added 3-bromoprop-1-yne (282.27 mg, 2.37 mmol, 204.54 uL, 1.2

eq). The mixture was stirred at 25° C. for 5 h. MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was dissolved in H_2O (1 mL), washed with EtOAc (2 mL*2) and lyophilized the aqueous phase to give a residue. Compound (3S)-3-hydroxy-1-methyl-1-(prop-2-yn-1-yl) pyrrolidin-1-ium bromide (311 mg, crude) was obtained as yellow oil. ^{1}H NMR (400 MHz, DMSO) δ 5.6 (m, 1H), 4.4 (m, 3H), 4.0 (m, 1H), 3.6 (m, 4H), 3.1 (m, 3H), 2.4 (m, 1H), 1.9 (m 1H) ppm.



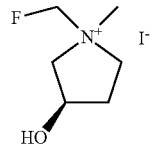
Compound 113: (3R)-3-hydroxy-1-methyl-1-(prop-2-yn-1-yl)pyrrolidin-1-ium bromide

[0717] To a solution of (3R)-1-methylpyrrolidin-3-ol (200 mg, 1.98 mmol, 217.16 uL, 1 eq) in DCM (5 mL) was added 3-bromoprop-1-yne (282.27 mg, 2.37 mmol, 204.54 uL, 1.2 eq). The mixture was stirred at 25° C. for 5 h. MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was dissolved in H_2O (1 mL), washed with EtOAc (2 mL*2) and lyophilized the aqueous phase to give a residue. Compound (3R)-3-hydroxy-1-methyl-1-(prop-2-yn-1-yl) pyrrolidin-1-ium bromide (368 mg, crude) was obtained as yellow oil. ^{1}H NMR (400 MHz, DMSO) δ 5.6 (m, 1H), 4.4 (m, 3H), 4.0 (m, 1H), 3.6 (m, 4H), 3.1 (m, 3H), 2.4 (m, 1H), 1.9 (m 1H) ppm.



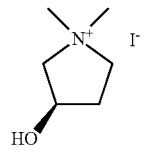
Compound 114: (3S)-1-(fluoromethyl)-3-hydroxy-1-methylpyrrolidin-1-ium Iodide

[0718] To a solution of (3S)-1-methylpyrrolidin-3-ol (200 mg, 1.98 mmol, 201.41 uL, 1 eq) in DCM (5 mL) was added fluoro (iodo) methane (379.48 mg, 2.37 mmol, 1.2 eq). The mixture was stirred at 25° C. for 5 h. MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was dissolved in H_2O (1 mL), washed with EtOAc (2 mL*2) and lyophilized the aqueous phase to give a residue. Compound (3S)-1-(fluoromethyl)-3-hydroxy-1-methylpyrrolidin-1-ium iodide (111 mg, crude) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 5.7 (m, 1H), 5.4 (m, 2H), 4.5 (m, 1H), 3.6 (m, 4H), 3.2 (s, 3H), 2.4 (m, 1H), 1.9 (m, 1H) ppm.



Compound 115: (3R)-1-(fluoromethyl)-3-hydroxy-1-methylpyrrolidin-1-ium Iodide

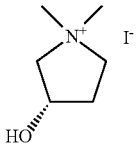
[0719] To a solution of (3R)-1-methylpyrrolidin-3-ol (0.2 g, 1.98 mmol, 217.16 uL, 1 eq) in DCM (5 mL) was added fluoro (iodo) methane (379.48 mg, 2.37 mmol, 1.2 eq). The mixture was stirred at 25° C. for 5 h. MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was dissolved in H_2O (1 mL), washed with EtOAc (2 mL*2) and lyophilized the aqueous phase to give a residue. Compound (3R)-1-(fluoromethyl)-3-hydroxy-1-methylpyrrolidin-1-ium iodide (358 mg, crude) was obtained as yellow oil. ^{1}H NMR (400 MHz, DMSO) δ 5.7 (m, 1H), 5.4 (m, 2H), 4.5 (m, 1H), 3.6 (m, 4H), 3.2 (s, 3H), 2.4 (m, 1H), 1.9 (m, 1H) ppm.



Compound 116: (R)-3-hydroxy-1,1-dimethylpyrrolidin-1-ium Iodide

[0720] To a solution of (3R)-pyrrolidin-3-ol (4 g, 32.37 mmol, 3.81 mL, 1 eq, HCl) in THF (50 mL) was added NaOH (1.29 g, 32.37 mmol, 1 eq) at 25° C. After addition, the mixture was stirred at this temperature for 20 min. Then paraformaldehyde (1.17 g, 38.84 mmol, 1.2 eq) and HCOOH (4.82 g, 100.34 mmol, 3.1 eq) were added 25° C. The resulting mixture was stirred at 60° C. for 5 h 40 min. TLC indicated the reaction was completed. The reaction mixture was cooled to 0° C., quenched by addition 10N NaOH to pH about 10, and extracted with EtOAc (30 mL*3). The combined organic layers were washed with H_2O (100 mL*1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product (3R)-1-methylpyrrolidin-3-ol (0.7 g, crude) as yellow oil was used into the next step without further purification.

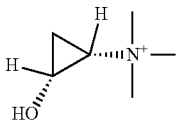
[0721] To a solution of (3R)-1-methylpyrrolidin-3-ol (0.2 g, 1.98 mmol, 217.16 uL, 1 eq) in DCM (10 mL) was added MeI (561.32 mg, 3.95 mmol, 246.19 uL, 2 eq). The mixture was stirred at 25° C. for 12 h. Some solid precipitate out and the solid was filtered. The filter cake was washed with DCM (5 mL*2) and concentrated to dryness. Compound (R)-3-hydroxy-1,1-dimethylpyrrolidin-1-ium iodide (333 mg, crude) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 5.5 (s, 1H), 4.5 (m, 1H), 3.6 (4H), 3.2 (s, 3H), 3.1 (s, 3H), 2.4 (m, 1H), 1.9 (m, 1H) ppm.



Compound 117:
(S)-3-hydroxy-1,1-dimethylpyrrolidin-1-ium Iodide

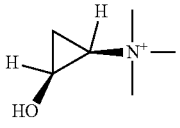
[0722] To a solution of (3S)-pyrrolidin-3-ol (4 g, HCl salt, 32.37 mmol, 3.70 mL, 1 eq) in THF (50 mL) was added NaOH (1.29 g, 32.37 mmol, 1 eq) at 25° C. After addition, the mixture was stirred at this temperature for 20 min. Then Paraformaldehyde (1.13 g, 38.84 mmol, 1.2 eq) and HCOOH (4.82 g, 100.34 mmol, 3.1 eq) were added at 25° C. The resulting mixture was stirred at 60° C. for 5 h 40 min. TLC indicated the reaction was completed. The reaction mixture was cooled to 0° C. and quenched by addition 10N NaOH to pH about 10, and extracted with EtOAc (30 mL*3). The combined organic layers were washed with H_2O (100 mL*1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product (3S)-1-methylpyrrolidin-3-ol (0.7 g, crude) as yellow oil was used into the next step without further purification.

[0723] To a solution of (3S)-1-methylpyrrolidin-3-ol (0.2 g, 1.98 mmol, 201.41 uL, 1 eq) in DCM (10 mL) was added MeI (561.32 mg, 3.95 mmol, 246.19 uL, 2 eq). The mixture was stirred at 25° C. for 12 h. Some solid precipitate out and the solid was filtered. The filter cake was washed with DCM (5 mL*2) and concentrated to dryness. Compound (S)-3-hydroxy-1,1-dimethylpyrrolidin-1-ium iodide (272 mg, crude) was obtained as a white solid. ^1H NMR (400 MHz, DMSO) δ 5.5 (s, 1H), 4.5 (m, 1H), 3.6 (m, 4H), 3.2 (s, 3H), 3.1 (s, 3H), 2.4 (m, 1H), 1.0 (m, 1H) ppm.



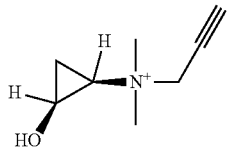
Compound 118: (1R,2S)-2-hydroxy-N,N,N-trimethylcyclopropan-1-aminium Iodide

[0724] (1R, 2S), 2-dimethylamino cyclopropanol is dissolved in THF followed by the dropwise addition of methyl iodide. The resulting precipitate is collected and dried and recrystallized to afford the title compound.



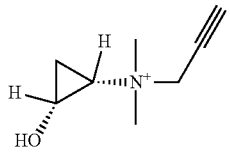
Compound 119: (1S,2R)-2-hydroxy-N,N,N-trimethylcyclopropan-1-aminium Iodide

[0725] (1S, 2R), 2-dimethylamino cyclopropanol is dissolved in THF followed by the dropwise addition of methyl iodide. The resulting precipitate is collected and dried and recrystallized to afford the title compound.



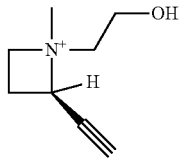
Compound 120: (1S,2R)-2-hydroxy-N,N-dimethyl-N-(prop-2-yn-1-yl)cyclopropan-1-aminium Iodide

[0726] (1S, 2R), 2-dimethylamino cyclopropanol is dissolved in THF followed by the dropwise addition of propargyl iodide. The resulting precipitate is collected and dried and recrystallized to afford the title compound.



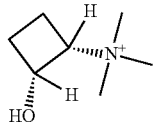
Compound 121: (1R,2S)-2-hydroxy-N,N-dimethyl-N-(prop-2-yn-1-yl)cyclopropan-1-aminium Iodide

[0727] (1R, 2S), 2-dimethylamino cyclopropanol is dissolved in THF followed by the dropwise addition of propargyl iodide. The resulting precipitate is collected and dried and recrystallized to afford the title compound.



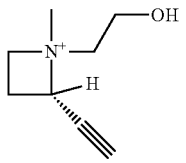
Compound 122: (2R)-2-ethynyl-1-(2-hydroxyethyl)-1-methylazetidin-1-ium Iodide

[0728] (2R) 2-ethynyl azetidine is dissolved in THF water and 2-hydroxyacetaldehyde is added to the mixture. The resulting mixture is stirred at room temperature and then sodium cyanoborohydide is added portion wise to the mixture. The mixture is stirred for 1 hour then quenched by the addition of water ethyl acetate. The resulting material is taken up in ether, and treated with dropwise addition of methyl iodide. The resulting precipitate is collected and dried and recrystallized to afford the title compound.



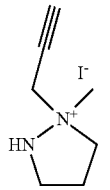
Compound 123: (1S,2R)-2-hydroxy-N,N,N-trimethylcyclobutan-1-aminium Iodide

[0729] (1S,2R)-2-hydroxy dimethylamino cyclobutanol is dissolved in THF and then treated with the dropwise addition of methyl iodide. The resulting precipitate is collected and dried and recrystallized to afford the title compound.



Compound 124: (2S)-2-ethynyl-1-(2-hydroxyethyl)-1-methylazetidin-1-ium Iodide

[0730] (2S) 2-ethynyl azetidine is dissolved in THF water and 2-hydroxyacetaldehyde is added to the mixture. The resulting mixture is stirred at room temperature and then sodium cyanoborahydide is added portion wise to the mixture. The mixture is stirred for 1 hour then quenched by the addition of water ethyl acetate. The resulting material is taken up in ether, and treated with dropwise addition of methyl iodide. The resulting precipitate is collected and dried and recrystallized to afford the title compound.



Compound 125: 1-methyl-1-(prop-2-yn-1-yl)pyrazolidin-1-ium Iodide

[0731] Step 1:

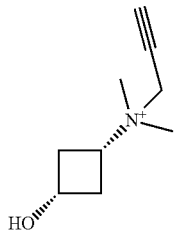
[0732] To a solution of tert-butyl pyrazolidine-1-carboxylate (200 mg, 1.16 mmol, 1 eq) in THF (10 mL) was added K2CO3 (176.54 mg, 1.28 mmol, 1.1 eq) at 15° C. and stirred at 15° C. for 10 min. Then 3-bromoprop-1-yne (207.22 mg, 1.74 mmol, 150.16 uL, 1.5 eq) was added to the mixture and the mixture was stirred at 15° C. for 12 h. TLC indicated reactant was consumed completely. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, PE:EtOAc=1:1). Compound tert-butyl 2-prop-2-ynylpyrazolidine-1-carboxylate (170 mg, 808.48 umol, 69.62% yield) was obtained as a white solid.

[0733] Step 2:

[0734] To a solution of tert-butyl 2-prop-2-ynylpyrazolidine-1-carboxylate (170 mg, 808.48 umol, 1 eq) in THF (5 mL) was added MeI (688.52 mg, 4.85 mmol, 301.98 uL, 6 eq). The mixture was stirred at 15° C. for 12 h. MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product tert-butyl 2-methyl-2-prop-2-ynyl-pyrazolidin-2-ium-1-carboxylate (200 mg, crude, I—) as a yellow solid was used into the next step without further purification. LCMS: (M+): 225.2

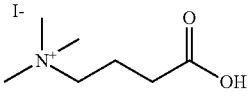
[0735] Step 3:

[0736] To a solution of tert-butyl 2-methyl-2-prop-2-ynyl-pyrazolidin-2-ium-1-carboxylate (200 mg, 887.68 umol, 1 eq) in HCl/dioxane (4 M, 5 mL, 22.53 eq). The mixture was stirred at 15° C. for 4 h. MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC ([water (0.1% TFA)-ACN]). Compound 1-methyl-1-(prop-2-yn-1-yl)pyrazolidin-1-ium iodide (26 mg, 103.14 umol, 11.6% yield) was obtained as a colorless oil. LCMS: (M+): 125.1 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 4.42-4.28 (m, 2H), 3.91-3.80 (m, 1H), 3.75-3.64 (m, 1H), 3.44-3.23 (m, 5H), 3.16-3.11 (m, 1H), 2.37 (p, J=7.4 Hz, 2H).



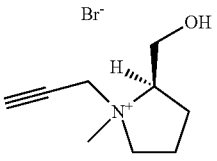
Compound 126: (1S,3S)-3-hydroxy-N,N-dimethyl-N-(prop-2-yn-1-yl-)cyclobutan-1-aminium Iodide

[0737] Cis-3-dimethylamine cyclobutanol is taken up in THF and treated with drop wise addition of propargyl iodide. The resulting precipitate is collected and dried and recrystallized to afford the title compound.



Compound 127: 3-carboxy-N,N,N-trimethylpropan-1-aminium Iodide

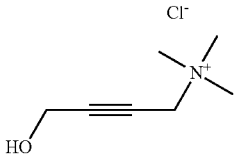
[0738] 4-(dimethylamino)butanoic acid is taken up in THF and treated with drop wise addition of methyl iodide. The resulting precipitate is collected and dried and recrystallized to afford the title compound.



Compound 129: (1R,2R)-2-(hydroxymethyl)-1-methyl-1-(prop-2-yn-1-yl)pyrrolidin-1-ium Bromide

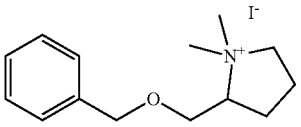
[0739] To a solution of [(2R)-1-methylpyrrolidin-2-yl] methanol (200 mg, 1.74 mmol, 1 eq) in THF (10 mL) was

added 3-bromoprop-1-yne (826.30 mg, 6.95 mmol, 598.77 uL, 4 eq). The mixture was stirred at 15° C. for 24 hr. MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC ([water (0.10% TFA)-ACN]). The title compound (60 mg, 389.03 umol, 22.40% yield, Br) was obtained as a colorless oil. LCMS:(M+) 154.1 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 4.46-4.23 (m, 1H), 4.15 (d, J=2.5 Hz, 1H), 4.04-3.69 (m, 4H), 3.63-3.39 (m, 1H), 3.24 (s, 1H), 3.14-3.01 (m, 3H), 2.33-2.02 (m, 3H), 1.99-1.77 (m, 1H).



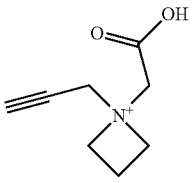
Compound 132:
4-hydroxy-N,N,N-trimethylbut-2-yn-1-aminium Chloride

[0740] To a solution of 4-chlorobut-2-yn-1-ol (88.17 mg, 843.45 umol, 1 eq) in THE (5 mL) was added N, N-dimethylmethanamine (3 M, 562.30 uL, 2 eq, in THF). The mixture was stirred at 25° C. for 12 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL). The water layer was freeze-drying to give 4-hydroxy-N, N, N-trimethylbut-2-yn-1-aminium chloride (55 mg, 336.09 umol, 39.85% yield) as colorless oil. MS: M^+=128.1 ^{1}H NMR (400 MHz, DMSO) δ 4.3 (m, 4H), 3.1 (s, 9H) ppm.



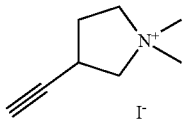
Compound 134: 2-[(benzyloxy)methyl]-1,1-dimethylpyrrolidin-1-ium Iodide

[0741] The title compound may be synthesized by reacting Compound 57 with benzyl bromide, followed by purification by recrystallization.



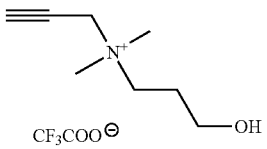
Compound 135: 1-(carboxymethyl)-1-(prop-2-yn-1-yl)azetidin-1-ium

[0742] This compound may be synthesized according to the experimental procedure described for Compound 133.



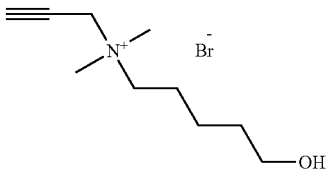
Compound 137:
3-ethynyl-1,1-dimethylpyrrolidin-1-ium Iodide

[0743] This compound may be synthesized according to the experimental procedure described for Compound 262.



Compound 138: N-(3-hydroxypropyl)-N,N-dimethylprop-2-yn-1-aminium Trifluoroacetate

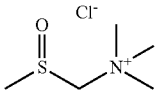
[0744] The mixture of N,N-dimethylprop-2-yn-1-amine (500 mg, 6.01 mmol, 637.76 uL, 1 eq) and 3-bromopropan-1-ol (1.00 g, 7.22 mmol, 651.40 uL, 1.2 eq) in EtOH (5 mL) was stirred at 80° C. under N_2 2 hours. LCMS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. Then the residue was purified by prep-HPLC (column: Xbridge 150*30 mm*10 um; mobile phase: [water (0.10% TFA)-ACN]; B %: 1%-10%, 10 min) to give N-(3-hydroxypropyl)-N,N-dimethylprop-2-yn-1-aminium trifluoroacetate (107 mg, 409.35 umol, 6.81% yield, TFA) as a colorless oil. LCMS: (M+) 142.2 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 4.08 (d, J=2.6 Hz, 2H), 3.53 (t, J=5.9 Hz, 2H), 3.40-3.32 (m, 2H), 3.07 (t, J=2.5 Hz, 1H), 3.01 (s, 6H), 1.91-1.79 (m, 2H).



Compound 139: 5-hydroxy-N,N-dimethyl-N-(prop-2-yn-1-yl)pentan-1-aminium Bromide

[0745] A mixture of N,N-dimethylprop-2-yn-1-amine (500 mg, 6.01 mmol, 637.76 uL, 1 eq) and 5-bromopentan-1-ol (1.05 g, 6.31 mmol, 1.05 eq) in EtOH (5 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 80° C. for 10 hr under N_2 atmosphere. LCMS showed desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O 20 mL and washed with EtOAc (20 mL*3). Then the water layers were lyophilized to afford 5-hydroxy-N,N-dimethyl-N-(prop-2-yn-1-yl)pentan-1-aminium bromide (625 mg, 1.98 mmol, 32.90% yield)

as a yellow oil. LCMS: (M+) 170.1 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 4.17 (s, 2H), 3.55 (t, J=6.5 Hz, 2H), 3.42-3.33 (m, 2H), 3.19-3.14 (m, 1H), 3.10 (s, 6H), 1.81-1.69 (m, 2H), 1.61-1.49 (m, 2H), 1.42-1.30 (m, 2H).



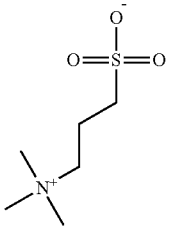
Compound 140:
(methanesulfinylmethyl)trimethylazanium Chloride

[0746] Step 1:

[0747] To a solution of chloro(methylsulfanyl)methane (200 mg, 2.07 mmol, 173.91 uL, 1 eq) in THF (5 mL) was added N,N-dimethylmethanamine (1 M, 4.14 mL, 2 eq, in THF) at 15° C. The mixture was stirred at 70° C. for 12 hr. The precipitation was found. The reaction mixture was filtered to give a residue. Compound methylsulfanyl-[N,N,N-(trimethyl)-azanyl]methane (100 mg, crude) was obtained as a white solid.

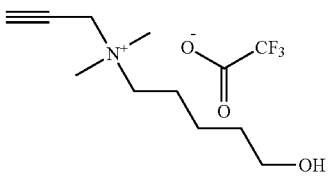
[0748] Step 2:

[0749] A mixture of methylsulfanyl-[N,N,N (trimethyl)-azanyl]methane (50 mg, 321.15 umol, 1 eq) in H_2O_2 (2 mL, 30%) and H_2O (2 mL) was stirred at 80° C. for 12 hr. LCMS showed the desired compound was detected. The reaction mixture was quenched by saturated sodium sulfite (30 mL), and the aqueous phase was freeze-dried. The residue was diluted with methanol (50 mL) and filtered. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-20%, 10 min). The residue was purified by prep-HPLC (column: YMC-Actus Triart Diol-Hilic 100*30 mm Sum; mobile phase: [water (0.1% TFA)-ACN]; B %: 99%-85%, 12 min). The title compound (5 mg, 28.46 umol, Cl-salt, 24.43% yield, 97.73% purity) was obtained as a colorless oil. LCMS: (M+): 136.1 1H NMR (400 MHz, Deuterium Oxide) δ 4.62-4.53 (m, 2H), 3.25 (s, 9H), 2.75 (s, 3H).



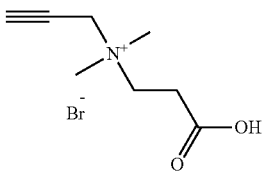
Compound 140A:
3-(trimethylammonio)propane-1-sulfonate

[0750] To a solution of oxathiolane 2, 2-dioxide (200 mg, 1.64 mmol, 143.88 uL, 1 eq) in acetone (5 mL) was added N,N-dimethylmethanamine (322.63 mg, 1.64 mmol, 377.34 uL, 1 eq) at 25° C. The mixture was stirred at 25° C. for 12 h. The precipitate was separated from the reaction mixture by filtration and the solid was concentrated under reduced pressure to dryness. Compound 3-(trimethylammonio) propane-1-sulfonate (157 mg, 0.87 mmol, 53% yield) was obtained as a white solid. LCMS (M+H$^+$): 182.0 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 3.47-3.43 (m, 2H), 3.11 (s, 9H), 2.95 (t, 2H), 2.24-2.18 (m, 2H).2.95 (t, 2H), 2.24-2.18 (m, 2H).



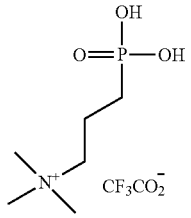
Compound 141: 4-hydroxy-N,N-dimethyl-N-(prop-2-yn-1-yl)butan-1-aminium Trifluoroacetate

[0751] A mixture of N,N-dimethylprop-2-yn-1-amine (500 mg, 6.01 mmol, 637.76 uL, 1 eq) and 4-bromobutan-1-ol (966.35 mg, 6.32 mmol, 1.05 eq) in EtOH (5 mL) was degassed and purged with N_2 3 times. Then the mixture was stirred at 80° C. for 10 hr under N_2 atmosphere. LCMS showed expected mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Xbridge 150*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-5%, 10 min) to give 4-hydroxy-N,N-dimethyl-N-(prop-2-yn-1-yl)butan-1-aminium trifluoroacetate (150 mg, 529.64 umol, 8.81% yield) as colorless oil. LCMS: (M+) 156.3 1H NMR (400 MHz, Deuterium Oxide) δ 4.1 (d, 2H), 3.6-3.5 (m, 2H), 3.4-3.3 (m, 2H), 3.1-3.0 (m, 1H), 3.0 (s, 6H), 1.8-1.7 (m, 2H), 1.5-1.4 (m, 2H).



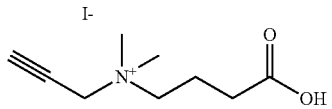
Compound 142:
N-(2-carboxyethyl)-N,N-dimethylprop-2-yn-1-aminium Bromide

[0752] A mixture of N,N-dimethylprop-2-yn-1-amine (500 mg, 6.01 mmol, 637.76 uL, 1 eq) 3-bromopropanoic acid (966.08 mg, 6.32 mmol, 652.76 uL, 1.05 eq) in EtOH (5 mL) was degassed and purged with N_2 3 times. And then the mixture was stirred at 80° C. for 10 hr under N_2 atmosphere. LCMS showed desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Xbridge 150*30 mm*10 um; mobile phase: [water (0.04% NH_3H_2O)-ACN]; B %: 1%-10%, 10 min) to give N-(2-carboxyethyl)-N,N-dimethylprop-2-yn-1-aminium bromide (95 mg, 345.71 umol, 5.75% yield) as colorless oil. LCMS: (M+) 156.1 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 4.2 (d, 2H), 3.8-3.6 (m, 2H), 3.2-3.1 (m, 1H), 3.1 (s, 6H), 2.7-2.6 (m, 2H).



Compound 143: N,N,N-trimethyl-3-phosphonopropan-1-aminium Trifluoroacetatetrifluoroacetatetrifluoroacetatetrifluoroacetatetrifluoroacetate

[0753] To a solution of 1-bromo-3-diethoxyphosphoryl-propane (500 mg, 1.93 mmol, 370.37 uL, 1 eq) in ACN (5 mL) was added 1-bromo-3-diethoxyphosphoryl-propane (500 mg, 1.93 mmol, 370.37 uL, 1 eq.). The mixture was stirred at 15° C. for 48 h. Then the reaction mixture was concentrated under reduced pressure to give a residue. Then HCl aq. (5 mL, 12 M) was added to the residue at 15° C. and the mixture was stirred at 80° C. for 12 h. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC ([water (0.10% TFA)-ACN]). The title compound (225 mg, 1.22 mmol, 63.36% yield) was obtained as a white solid. LCMS: (M+): 182.2 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 3.36-3.26 (m, 2H), 3.06-3.00 (m, 9H), 2.02-1.92 (m, 2H), 1.78-1.65 (m, 2H).



Compound 144: N-(3-carboxypropyl)-N,N-dimethylprop-2-yn-1-aminium Iodide

[0754] 4-(dimethylamino)butanoic acid is taken up in THF and treated with drop wise addition of propargyl iodide. The resulting precipitate is collected and dried and recrystallized to afford the title compound.

Compound 147: 3-(hydroxyhydrophosphoryl)-N,N,N-trimethylpropan-1-aminium Chloridechloridechloridechloridechloride

[0755] Step 1:

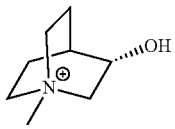
[0756] To a solution of 1-[ethoxy(ethoxyphosphonoyl) methoxy]ethane (1 g, 5.10 mmol, 1 eq) in THF (40 mL) was added slowly NaH (224.26 mg, 5.61 mmol, 60% purity, 1.1 eq) at 0° C. under N_2. Then the mixture was stirred at 15° C. for 1 h under N_2 atmosphere. Then the mixture was dropwise added to the solution of 1,3-dibromopropane (2.79 g, 13.81 mmol, 1.41 mL, 2.71 eq) in THF (20 mL) at 15° C. Then the mixture was stirred at 15° C. for 9 h under N_2 atmosphere. TLC indicated 1-[ethoxy(ethoxyphosphonoyl) methoxy]ethane was consumed completely and one new spot formed. The reaction mixture was quenched by addition of H_2O (100 mL) at 0° C. and extracted with EtOAc (20 mL*3). The combined organic layers were washed with brine (30 mL). The combined organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/1). Compound 1-bromo-3-[diethoxymethyl (ethoxy)phosphoryl] propane (400 mg, 1.26 mmol, 24.74% yield) was obtained as yellow oil.

[0757] Step 2:

[0758] A mixture of 1-bromo-3-[diethoxymethyl(ethoxy) phosphoryl]propane (400 mg, 1.26 mmol, 1 eq), trimethylamine (1.49 g, 7.57 mmol, 30% purity, 6 eq., in EtOH) in ACN (5 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 15° C. for 96 hr under N_2 atmosphere. TLC indicated 20% of 1-bromo-3-[diethoxymethyl(ethoxy)phos-phoryl]propane (400 mg, 1.26 mmol, 1 eq) remained and one major new spot with larger polarity was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition; column: Luna C18 100*30 5u; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-25%, 12 min). Compound 3-[diethoxymethyl(ethoxy)phosphoryl] propyl-trimethyl-ammonium (150 mg, 366.41 umol, 29.05% yield, CF3CO2-) was obtained as colorless oil.

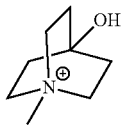
[0759] Step 3:

[0760] A mixture of 3-[diethoxymethyl(ethoxy)phosphoryl]propyl-trimethyl-ammonium (150 mg, 366.41 umol, 1 eq, CF_3COO—), in conc. HCl (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 110° C. for 10 hr under N_2 atmosphere. LC-MS showed 100% desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a colorless oil. Compound 3-(hydroxyhydrophosphoryl)-N,N,N-trimethylpropan-1-aminium chloride (120 mg, quantitative yield, Cl—) was obtained as colorless oil. LCMS: (M+): 166.1 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 6.95 (dt, J=546.5, 1.8 Hz, 1H), 3.31-3.22 (m, 2H), 2.99 (s, 9H), 1.98-1.83 (m, 2H), 1.71-1.58 (m, 2H).)



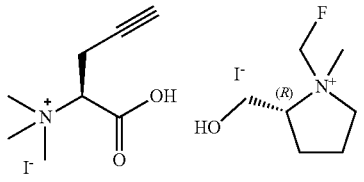
Compound 148: (1s,4s)-3-hydroxy-1-methylquinuclidin-1-ium

[0761] (S)-(+)-3-quinuclidinol (1 equiv) is stirred with methyl iodide (1.1 equiv) to yield the title compound.



Compound 149: 4-hydroxy-1-methylquinuclidin-1-ium

[0762] 1-azabicyclo[2.2.2]octan-4-ol (1 equiv) is stirred with methyl iodide (1.1 equiv) to yield the title compound.

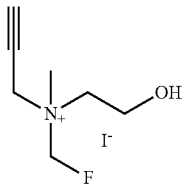


Compound 151: (2R)-1-(fluoromethyl)-2-(hydroxymethyl)-1-methylpyrrolidin-1-ium Iodide

[0763] A mixture of [(2R)-1-methylpyrrolidin-2-yl]methanol (251 mg, 2.18 mmol, 1 eq), fluoro(iodo)methane (348.54 mg, 2.18 mmol, 1 eq) in THF (5 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 15° C. for 2 hr under N_2 atmosphere. TLC indicated [(2R)-1-methylpyrrolidin-2-yl]methanol was consumed completely and one new spot formed. The reaction mixture was filtered and the filter cake was concentrated under reduced pressure to give a residue. Then the crude product was purified by p-HPLC (column: Phenomenex Luna C18 100*30 mm*5 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-3%, 4 min) to get the desired product (2R)-1-(fluoromethyl)-2-(hydroxymethyl)-1-methylpyrrolidin-1-ium iodide (150 mg, 545.25 umol, 25.02% yield) as a yellow solid. LCMS (M+): 148.1 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 5.47-5.31 (m, 1H), 5.34-5.22 (m, 1H), 3.93-3.60 (m, 4H), 3.54-3.36 (m, 1H), 3.15-2.94 (m, 3H), 2.21-1.71 (m, 4H).

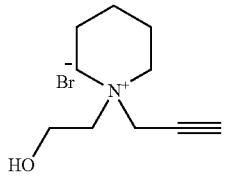
Compound 152: (S)-1-carboxy-N,N,N-trimethylbut-3-yn-1-aminium Iodide

[0764] To a solution of (2S)-2-aminopent-4-ynoic acid (1 g, 8.84 mmol, 1 eq) in MeOH (10 mL) was added NaOH (800.06 mg, 20.00 mmol, 2.26 eq) in EtOH (2 mL) and MeI (3.76 g, 26.52 mmol, 1.65 mL, 3 eq) at 15° C. The mixture was stirred at 15° C. for 12 hr. LCMS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100*30 mm*5 um; mobile phase: [water (0.2% FA)-ACN]; B %: 1%-1%, 4 min). The mixture was freeze-dried. The residue was re-purified by prep-HPLC (column: Phenomenex Luna C18 100*30 mm*5 um; mobile phase: [water (0.2% FA)-ACN]; B %: 1%-1%, 4 min). The title compound (48 mg, 158.73 umol, I-salt, 1.80% yield) was obtained as a white solid. LCMS: (M+): 156.1 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 3.82 (ddd, J=8.9, 5.1, 0.9 Hz, 1H), 3.16 (s, 9H), 2.96-2.77 (m, 2H), 2.49-2.40 (m, 1H).



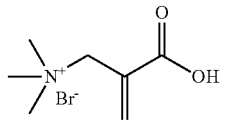
Compound 153: N-(fluoromethyl)-N-(2-hydroxyethyl)-N-methylprop-2-yn-1-aminium Iodide

[0765] To a solution of 2-[methyl(prop-2-ynyl)amino]ethanol (400 mg, 3.53 mmol, 1 eq) in THF (5 mL) was added fluoro(iodo)methane (565.33 mg, 3.53 mmol, 1 eq) at 15° C. The mixture was stirred at 15° C. for 12 hr. TLC indicated 2-[methyl(prop-2-ynyl)amino]ethanol (400 mg, 3.53 mmol, 1 eq) was consumed completely. The reaction mixture was diluted with H2O (10 mL) and extracted with ethyl acetate 40 mL. The aqueous phase is freeze-dried. Compound N-(fluoromethyl)-N-(2-hydroxyethyl)-N-methylprop-2-yn-1-aminium iodide (247 mg, 882.41 umol, 24.96% yield) was obtained as a white solid. LCMS (M+): 146.1 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 5.56-5.37 (m, 2H), 4.35 (s, 2H), 3.95 (s, 2H), 3.63-3.56 (m, 2H), 3.19-3.14 (m, 4H).



Compound 154: 1-(2-hydroxyethyl)-1-(prop-2-yn-1-yl)piperidin-1-ium Bromide

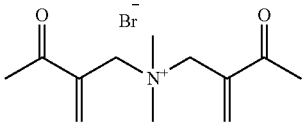
[0766] To a solution of 2-(1-piperidyl)ethanol (300 mg, 2.32 mmol, 308.32 uL, 1 eq) in THF (5 mL) was added 3-bromoprop-1-yne (303.85 mg, 2.55 mmol, 220.18 uL, 1.1 eq). The mixture was stirred at 15° C. for 12 hr. The precipitation was found. The reaction mixture was filtered to give a residue. The residue was washed with ethyl acetate 20 mL. Compound 1-(2-hydroxyethyl)-1-(prop-2-yn-1-yl)piperidin-1-ium bromide (554 mg, 2.18 mmol, 94% yield) was obtained as a white solid. LCMS: (M+): 168.1 ^{1}H NMR (400 MHz, DMSO-d6) δ 5.36 (t, J=4.9 Hz, 1H), 4.53 (d, J=2.5 Hz, 2H), 4.04 (t, J=2.5 Hz, 1H), 3.86 (q, J=5.1 Hz, 2H), 3.59-3.49 (m, 4H), 3.49-3.38 (m, 2H), 1.83 (p, J=5.9 Hz, 4H), 1.65-1.45 (m, 2H).



Compound 155: 2-carboxy-N,N,N-trimethylprop-2-en-1-aminium Bromide

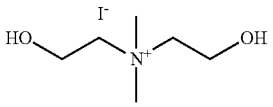
[0767] To a solution of 2-(bromomethyl)prop-2-enoic acid (200 mg, 1.21 mmol, 1 eq) in THF (3 mL) was added N,N-dimethylmethanamine (1 M, 1.21 mL, 1 eq., in THF) at 15° C. The mixture was stirred at 15° C. for 12 hr. The precipitation was found. The reaction mixture was filtered to give a residue. The residue was washed by ethyl acetate 10 mL. Compound 2-carboxy-N,N,N-trimethylprop-2-en-1-aminium bromide (131 mg, 561.19 umol, 46.29% yield) was

obtained as a white solid. LCMS: (M+): 144.1 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 6.77 (s, 1H), 6.23 (s, 1H), 4.09 (s, 2H), 2.96 (s, 9H).



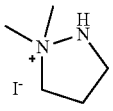
Compound 156: 2-carboxy-N-(2-carboxyallyl)-N,N-dimethylprop-2-en-1-aminium Bromide

[0768] To a solution of 2-(bromomethyl)prop-2-enoic acid (600 mg, 3.64 mmol, 3 eq) in acetone (5 mL) was added N-methylmethanamine (2 M, 606.12 uL, 1 eq., in THF) at 15° C. The mixture was stirred at 15° C. for 12 hr, and a precipitate formed. The reaction mixture was filtered to give a residue. The residue was washed by acetone 10 mL. Compound 2-carboxy-N-(2-carboxyallyl)-N,N-dimethyl-prop-2-en-1-aminium bromide (100 mg, 310.22 umol, 25.59% yield) was obtained as a white solid. LCMS: (M+): 214.1 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 6.9 (s, 2H), 6.4 (s, 2H), 4.2 (s, 4H), 2.9 (s, 6H).



Compound 157: 2-hydroxy-N-(2-hydroxyethyl)-N, N-dimethylethan-1-aminium Iodide

[0769] To a solution of 2-(dimethylamino)ethanol (100 mg, 1.12 mmol, 112.61 uL, 1 eq) in THF (5 mL) was added 2-iodoethanol (578.77 mg, 3.37 mmol, 263.08 uL, 3 eq) at 15° C. The mixture was stirred at 50° C. for 12 hr. The precipitation was found. The reaction mixture was filtered to give a residue. The residue was washed by ethyl acetate 10 mL. Compound 2-hydroxy-N-(2-hydroxyethyl)-N,N-dimethylethan-1-aminium iodide (230 mg, 872.08 umol, 77.73% yield) was obtained as a white solid. LCMS: (M+): 134.2 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 3.95-3.87 (m, 4H), 3.48-3.40 (m, 4H), 3.07 (s, 6H).



Compound 158: 1,1-dimethylpyrazolidin-1-ium Iodide

[0770] Step 1

[0771] To a solution of NaH (600.78 mg, 15.02 mmol, 60% purity, 2 eq.) in DMF (20 mL) at 0° C. was added tert-butyl N-(benzyloxycarbonylamino)carbamate (2 g, 7.51 mmol, 1 eq) at 0° C. and stirred at 0° C. for 20 min. Then 1,3-dibromopropane (1.52 g, 7.51 mmol, 765.80 uL, 1 eq) was added to the mixture at 0° C. The mixture was stirred at 15° C. for 12 h. TLC indicated reactant was consumed completely. The reaction mixture was quenched by addition of H_2O 100 mL at 0° C., and then diluted with H_2O 100 mL and extracted with EtOAc (200 mL*2). The combined organic layers were washed with saturate brine 300 mL (150 mL*2), dried over, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 4/1). Compound 02-benzyl 01-tert-butyl pyrazolidine-1,2-dicarboxylate (1.5 g, 4.90 mmol, 65.19% yield) was obtained as a colorless oil.

[0772] Step 2

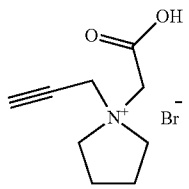
[0773] To a solution of 02-benzyl 01-tert-butyl pyrazolidine-1,2-dicarboxylate (800 mg, 2.61 mmol, 1 eq) in THF (15 mL) was added Pd/C (0.5 g, 2.61 mmol, 10% purity). The suspension was degassed and purged with H_2 3 times. The mixture was stirred under H_2 (15 Psi.) at 15° C. for 3 h. TLC indicated reactant was consumed completely. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. Compound tert-butyl pyrazolidine-1-carboxylate (400 mg, 2.32 mmol, 88.94% yield) was obtained as a colorless oil and used into the next step without further purification.

[0774] Step 3

[0775] To a solution of tert-butyl pyrazolidine-1-carboxylate (200 mg, 1.16 mmol, 1 eq) in THF (10 mL) was added MeI (494.49 mg, 3.48 mmol, 216.88 uL, 3 eq). The mixture was stirred at 15° C. for 12 h. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. Compound tert-butyl 2,2-dimethylpyrazolidin-2-ium-1-carboxylate (150 mg, crude, I—) was obtained as a yellow solid was used into the next step without further purification. LCMS: (M+): 201.2.

[0776] Step 4

[0777] A solution of tert-butyl 2,2-dimethylpyrazolidin-2-ium-1-carboxylate (150 mg, 745.21 umol, 1 eq) in HCl/dioxane (4 M, 10 mL, 53.68 eq) was stirred at 15° C. for 1 h. MS showed the desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC ([water (0.1% TFA)-ACN]). Compound 1,1-dimethylpyrazolidin-1-ium iodide (10 mg, 43.85 umol, 5.88% yield, I—) was obtained as a colorless oil. MS: (M+): 101.1. ^{1}H NMR (400 MHz, Chloroform-d) δ 3.77 (t, J=7.7 Hz, 2H), 3.42 (t, J=7.5 Hz, 2H), 3.36 (s, 6H), 2.43 (p, J=7.6 Hz, 2H).



Compound 159: 1-(carboxymethyl)-1-(prop-2-yn-1-yl)pyrrolidin-1-ium Bromide

[0778] Step 1:

[0779] A mixture of pyrrolidine (5 g, 70.30 mmol, 5.87 mL, 1 eq), benzyl 2-bromoacetate (14.49 g, 63.27 mmol,

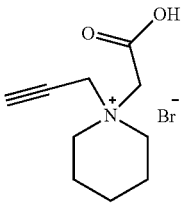
9.93 mL, 0.9 eq), Na_2CO_3 (7.45 g, 70.30 mmol, 1 eq) in THF (100 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 15° C. for 10 hr under N_2 atmosphere. TLC indicated reactant was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 1:1). Compound benzyl 2-pyrrolidin-1-ylacetate (8 g, 36.48 mmol, 51.89% yield) was obtained as yellow oil.

[0780] Step 2:

[0781] A mixture of benzyl 2-pyrrolidin-1-ylacetate (5 g, 22.80 mmol, 1 eq), Pd/C (2 g, 22.80 mmol, 10% purity) in EtOH (100 mL) was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 15° C. for 10 hr under H_2 atmosphere at 15 psi. TLC indicated benzyl 2-pyrrolidin-1-ylacetate was consumed completely and one new spot formed. The reaction mixture was filtered and the filtrate was concentrated to give the crude product. Compound 2-pyrrolidin-1-ylacetic acid (2 g, 15.49 mmol, 67.91% yield) was obtained as a white solid. The crude was used directly in next step.

[0782] Step 3:

[0783] A mixture of 2-pyrrolidin-1-ylacetic acid (300 mg, 2.32 mmol, 1 eq), 3-bromoprop-1-yne (303.95 mg, 2.56 mmol, 220.25 uL, 1.1 eq) in DMF (5 mL) was stirred at 15° C. for 10 hrs under N_2. LCMS indicated desired mass was detected. The reaction mixture was concentrated under reduced pressure to give the crude product. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.10% TFA)-ACN]; B %: 1%). Compound 1-(carboxymethyl)-1-(prop-2-yn-1-yl)pyrrolidin-1-ium bromide (48 mg, 193.03 umol, 8.31% yield) was obtained as a white solid. LCMS: (M+): 168.1 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 4.40 (d, J=2.6 Hz, 2H), 4.11 (s, 2H), 3.77-3.69 (m, 2H), 3.61-3.54 (m, 2H), 3.03 (d, J=2.6 Hz, 1H), 2.12-2.06 (m, 4H).



Compound 160: 1-(carboxymethyl)-1-(prop-2-yn-1-yl)piperidin-1-ium bromide

[0784] Step 1:

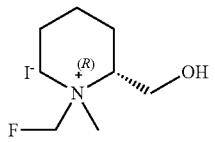
[0785] A mixture of piperidine (5 g, 58.72 mmol, 5.80 mL, 1 eq), benzyl 2-bromoacetate (13.45 g, 58.72 mmol, 9.21 mL, 1 eq), Na2CO3 (6.22 g, 58.72 mmol, 1 eq), in THF (100 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 15° C. for 10 hr under N_2 atmosphere. LC-MS showed 15.64% of desired compound was detected. The reaction mixture was filtered. Then the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/1). Compound benzyl 2-(1-piperidyl)acetate (10 g, 42.86 mmol, 72.99% yield) was obtained as a yellow oil. LCMS: ($M+H^+$): 234.2

[0786] Step 2:

[0787] A mixture of benzyl 2-(1-piperidyl)acetate (10 g, 42.86 mmol, 1 eq), Pd/C (2 g, 10% purity), in EtOH (100 mL) was degassed and purged with H2 for 3 times, and then the mixture was stirred at 15° C. for 10 hr under H2 atmosphere at 15 psi. TLC indicated benzyl 2-(1-piperidyl) acetate (10 g, 42.86 mmol, 1 eq) was consumed completely and one new spot formed. LC-MS showed desired compound was detected. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. Compound 2-(1-piperidyl)acetic acid (2.5 g, 17.46 mmol, 40.74% yield) was obtained as a white solid. The crude was used directly for next step. LCMS: ($M+H^+$): 144.1

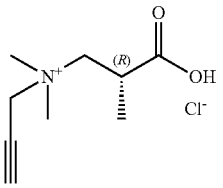
[0788] Step 3:

[0789] A mixture of 2-(1-piperidyl)acetic acid (300 mg, 2.10 mmol, 1 eq), 3-bromoprop-1-yne (288.60 mg, 2.30 mmol, 209.13 uL, 1.1 eq), in DMF (20 mL) was stirred at 15° C. for 10 hr under N_2 atmosphere. LC-MS showed desired mass was detected. The reaction mixture was concentrated under reduced pressure to give the crude product. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %:1%-10%, 10 min). Compound 2-(1-prop-2-ynylpiperidin-1-ium-1-yl)acetic acid (18 mg, 68.52 umol, 3.27% yield, 99.79% purity, Br—)—) was obtained as white solid. Compound 1-(carboxymethyl)-1-(prop-2-yn-1-yl)piperidin-1-ium bromide (19 mg, 64.35 umol, 3.07% yield) was obtained as white solid. LCMS: (M+): 182 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 4.49 (s, 2H), 4.04-4.00 (m, 2H), 3.63-3.55 (m, 2H), 3.51-3.43 (m, 2H), 3.06 (s, 1H), 1.81-1.74 (m, 4H), 1.60-1.50 (m, 2H).



Compound 161: (2R)-1-(fluoromethyl)-2-(hydroxymethyl)-1-methylpiperidin-1-ium Iodide

[0790] To a solution of [(2R)-1-methyl-2-piperidyl]methanol (80 mg, 619.20 umol, 1 eq) in THF (5 mL) was added fluoro(iodo)methane (148.54 mg, 928.79 umol, 1.5 eq). The mixture was stirred at 15° C. for 12 hr. LCMS showed the desired compound was detected. The precipitation was found. The reaction mixture was filtered to give a residue. The residue was washed by acetone 20 mL. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-10%, 10 min). Compound (2R)-1-(fluoromethyl)-2-(hydroxymethyl)-1-methylpiperidin-1-ium iodide (40 mg, 138.14 umol, 22.31% yield) was obtained as a yellow oil. LCMS: (M+): 162.2 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 5.56 (d, J=6.1 Hz, 0.5H), 5.51-5.38 (m, 1H), 5.30 (d, J=6.0 Hz, 0.5H), 3.84-3.70 (m, 2H), 3.70-3.58 (m, 1H), 3.49-3.38 (m, 2H), 3.19-2.96 (m, 3H), 1.81-1.73 (m, 5H), 1.57-1.35 (m, 1H).



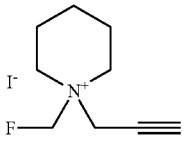
Compound 162: (R)—N-(2-carboxypropyl)-N,N-dimethylprop-2-yn-1-aminium Chloride

[0791] Step 1:

[0792] To a solution of methyl (2S)-3-bromo-2-methyl-propanoate (300 mg, 1.66 mmol, 1.3 eq) in ACN (5 mL) was added N,N-dimethylprop-2-yn-1-amine (105.97 mg, 1.27 mmol, 135.17 uL, 1 eq) at 15° C. The mixture was stirred at 80° C. for 12 hr. LCMS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-10%, 10 min). Compound [(2R)-3-methoxy-2-methyl-3-oxo-propyl]-dimethyl-prop-2-ynyl-ammonium (15 mg, 48.50 umol, 3.80% yield, CF_3COO—) was obtained as a colorless oil.

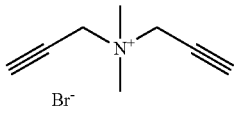
[0793] Step 2:

[0794] To a solution of [(2R)-3-methoxy-2-methyl-3-oxo-propyl]-dimethyl-prop-2-ynyl-ammonium (10 mg, 33.64 umol, 1 eq, CF_3COO—) in dioxane (2 mL) and aq. HCl (8 mL, 6 M) was stirred at 50° C. for 4 hr. LCMS showed the desired compound was detected and 50% of [(2R)-3-methoxy-2-methyl-3-oxo-propyl]-dimethyl-prop-2-ynyl-ammonium (10 mg, 33.64 umol, 1 eq, CF_3COO—) remained. The mixture was stirred at 50° C. for 12 hr. LCMS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.10% TFA)-ACN]; B %: 1%-10%, 10 min). Compound (2R)-3-(N,N-dimethyl-prop-2-ynyl-azanyl)-2-methyl-propanoic acid (Cl-salt) was obtained as a yellow oil. LCMS: (M+): 170.2 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 4.20 (d, J=2.6 Hz, 2H), 3.91 (dd, J=13.8, 8.9 Hz, 1H), 3.36 (dd, J=13.9, 2.2 Hz, 1H), 3.20 (t, J=2.6 Hz, 1H), 3.10 (s, 6H), 3.03 (ddd, J=9.3, 7.2, 2.1 Hz, 1H), 1.25 (d, J=7.3 Hz, 3H).



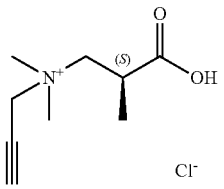
Compound 164: 1-(fluoromethyl)-1-(prop-2-yn-1-yl)piperidin-1-ium Iodide

[0795] To a solution of 1-prop-2-ynylpiperidine (100 mg, 811.72 umol, 1 eq) in THE (5 mL) was added fluoro(iodo) methane (389.45 mg, 2.44 mmol, 3 eq) at 15° C. The mixture was stirred at 15° C. for 12 hr. The precipitation was found. The reaction mixture was diluted with H2O6060 mL and extracted with ethyl acetate 60 mL. The aqueous phase is freeze-dried to give the residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-10%, 10 min). Compound 1-(fluoromethyl)-1-(prop-2-yn-1-yl)piperidin-1-ium iodide (60 mg, 211.92 umol, 41.10% yield) was obtained as a colorless oil. LCMS (M+): 156.2 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 5.51 (d, J=44.9 Hz, 2H), 4.39 (d, J=1.8 Hz, 2H), 3.61-3.33 (m, 5H), 1.89 (p, J=6.3 Hz, 4H), 1.77-1.58 (m, 2H).



Compound 165: N,N-dimethyl-N-(prop-2-yn-1-yl) prop-2-yn-1-aminium Bromide

[0796] To a solution of N,N-dimethylprop-2-yn-1-amine (100 mg, 1.20 mmol, 127.55 uL, 1 eq) in THF (5 mL) was added 3-bromoprop-1-yne (143.10 mg, 1.20 mmol, 103.69 uL, 1 eq) at 15° C. The mixture was stirred at 15° C. for 12 hr. The precipitation was found. The reaction mixture was filtered to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-3%, 10 min). Compound N,N-dimethyl-N-(prop-2-yn-1-yl)prop-2-yn-1-aminium bromide (88 mg, 435.45 umol, 56.77% yield) was obtained as a white solid. LCMS: (M+): 122.1 ^{1}H NMR (400 MHz, DMSO-d6) δ 4.4 (s, 4H), 4.1 (s, 2H), 3.1 (s, 6H).



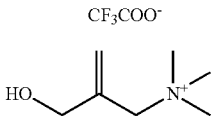
Compound 166: (S)—N-(2-carboxypropyl)-N,N-dimethylprop-2-yn-1-aminium Chloride

[0797] Step 1:

[0798] To a solution of methyl (2R)-3-bromo-2-methyl-propanoate (500 mg, 2.76 mmol, 1 eq) in ACN (10 mL) was added N,N-dimethylprop-2-yn-1-amine (160.73 mg, 1.93 mmol, 205.01 uL, 0.7 eq) at 15° C. The mixture was stirred at 80° C. for 12 hr. TLC indicated most of N,N-dimethyl-prop-2-yn-1-amine remained. The mixture was stirred at 80° C. for 24 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-20%, 10 min). Compound methyl (2S)-3-(N,N-dimethyl-prop-2-ynyl-azanyl)-2-methyl-propanoate (10 mg, 37.86 umol, Br-salt, 3.33% yield) was obtained as a colorless oil.

[0799] Step 2:

[0800] A solution of methyl (2S)-3-(N,N-dimethyl-prop-2-ynyl-azanyl)-2-methyl-propanoate (10 mg, 37.86 umol, 1 eq) in dioxane (2 mL) and HCl (8 mL) (6 M, H2O) was stirred at 50° C. for 16 hr. LCMS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters XbridgeBEH C18 100*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-10%, 10 min). The residue was further purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-10%, 10 min) to give the title compound (6 mg, 29.17 umol, Cl-salt, 60.00% yield) as a yellow oil. LCMS: (M+): 170.2 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 4.15 (d, J=2.6 Hz, 2H), 3.85 (dd, J=13.8, 8.9 Hz, 1H), 3.30 (dd, J=13.8, 2.2 Hz, 1H), 3.14 (t, J=2.5 Hz, 1H), 3.04 (s, 6H), 3.01-2.90 (m, 1H), 1.18 (d, J=7.2 Hz, 3H).



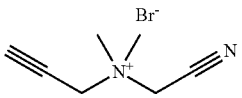
Compound 167: (3-hydroxy-2-methylidenepropyl)trimethylazanium trifluoroacetate

[0801] Step 1:

[0802] To a solution of 2-methylenepropane-1,3-diol (1 g, 11.35 mmol, 925.93 uL, 1 eq) in DCM (10 mL) was added SOCl2 (2.03 g, 17.03 mmol, 1.24 mL, 1.5 eq) at −78° C. and the mixture was stirred at 15° C. for 1.5 h. TLC indicated Reactant was consumed completely. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product 5-methylene-1,3,2-dioxathiane 2-oxide (1.5 g, crude) as a brown liquid was used into the next step without further purification.

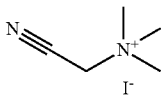
[0803] Step 2:

[0804] To a solution of 5-methylene-1,3,2-dioxathiane 2-oxide (600 mg, 4.47 mmol, 1 eq) in THF (10 mL) was added N,N-dimethylmethanamine (1 M, 4.92 mL, 1.1 eq. in THF) at 15° C. and the mixture was stirred at 70° C. for 12 h. MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC ([water (0.10% TFA)-ACN]) to give the title compound (21 mg, 85.82 umol, 1.92% yield, 99.4% purity, CF3CO2-) was obtained as a colorless oil. MS: (M+) 130.1 ^{1}H NMR (400 MHz, Methanol-d4) δ 5.84 (s, 1H), 5.62 (s, 1H), 4.23 (s, 2H), 4.04 (s, 2H), 3.17 (s, 9H).



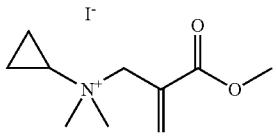
Compound 168: (cyanomethyl)dimethyl(prop-2-yn-1-yl)azanium Bromide

[0805] A mixture of N,N-dimethylprop-2-yn-1-amine (500 mg, 6.01 mmol, 637.76 uL, 1 eq), 2-bromoacetonitrile (721.43 mg, 6.01 mmol, 400.80 uL, 1 eq) in THF (5 mL) degassed and purged with N_2 3 times, and then the mixture was stirred at 15° C. for 10 hr under N_2 atmosphere. LC-MS showed 80.4% desired compound was detected. The reaction mixture was filtered and the filter cake was concentrated under reduced pressure to give a residue. Then the residue was washed with THF (4 mL) to give the title compound (1.0 g, 4.15 mmol, 69.07% yield, 84.37% purity, Br—) as a white solid. LCMS: (M+) 123.1 1H NMR (400 MHz, DMSO-d_6) δ 4.98 (s, 2H), 4.61 (d, J=2.6 Hz, 2H), 4.23 (t, J=2.5 Hz, 1H), 3.28 (s, 6H).



Compound 169: (cyanomethyl)trimethylazanium Iodide

[0806] A mixture of N,N-dimethylmethanamine (1 M, 8.46 mL, 1 eq), 2-bromoacetonitrile (1.01 g, 8.46 mmol, 563.68 uL, 1 eq) in THF (5 mL) was degassed and purged with N2 for 3 times, and then the mixture was stirred at 15° C. for 10 hr under N2 atmosphere. TLC indicated N,N-dimethylmethanamine was consumed completely and one new spot larger polarity was formed. The reaction mixture was filtered and the filter cake was concentrated under reduced pressure to give a residue. Then the residue was washed with THF (4 mL) to give a residue as compound cyanomethyl(trimethyl)azanium (1.38 g, 7.71 mmol, 91.11% yield, 100% purity, I—) was obtained as a white solid. LCMS: (M+) 99.1 1H NMR (400 MHz, DMSO-d6) δ 4.98 (s, 2H), 3.26 (s, 9H).



Compound 170: N-(3-methoxy-2-methylidene-3-oxopropyl)-N,N-dimethylcyclopropanaminium Iodide

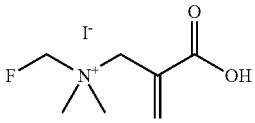
[0807] Step 1:

[0808] To a solution of N-methylcyclopropanamine (300 mg, 4.22 mmol, 1 eq) in THF (10 mL) was added methyl 2-(bromomethyl)prop-2-enoate (755.43 mg, 4.22 mmol, 1 eq) and K2CO3 (874.84 mg, 6.33 mmol, 1.5 eq) at 25° C. The mixture was stirred at 70° C. for 12 hr. LCMS showed the desired compound was detected. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10:1 to 1:1). Compound methyl 2-[[cyclopropyl(methyl)amino]methyl]prop-2-enoate (400 mg, 2.36 mmol, 56.01% yield) was obtained as a colorless liquid.

[0809] Step 2:

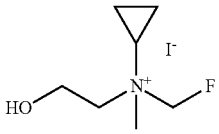
[0810] To a solution of methyl 2-[[cyclopropyl(methyl)amino]methyl]prop-2-enoate (100 mg, 590.95 umol, 1 eq) in

THF (10 mL) was added MeI (503.27 mg, 3.55 mmol, 220.73 uL, 6 eq) at 25° C. The mixture was stirred at 25° C. for 12 hr. The precipitation was found. The reaction mixture was filtered to give a residue. The title compound (106 mg, 340.66 umol, I-salt, 57.65% yield, 100% purity) was obtained as a white solid. LCMS: (M+): 184.1 1H NMR (400 MHz, Deuterium Oxide) δ 6.79 (s, 1H), 6.28 (s, 1H), 4.24 (s, 2H), 3.71 (s, 3H), 3.05-2.98 (m, 1H), 2.81 (s, 6H), 1.07-0.99 (m, 2H), 0.78-0.68 (m, 2H).



Compound 171: (2-carboxy-2-methylideneethyl) (fluoromethyl)dimethylazanium Iodide

[0811] To a solution of 2-[(dimethylamino)methyl]prop-2-enoic acid (30 mg, 232.28 umol, 1 eq) in ACN (5 mL) was added fluoro added fluoro(iodo)methane (185.74 mg, 1.16 mmol, 5 eq) at 15° C. The mixture was stirred at 15° C. for 24 hr. LCMS showed the LCMS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-10%, 10 min). The title compound (3 mg, 8.05 umol, I-salt, 3.47% yield, 77.59% purity) was obtained as a colorless oil. LCMS: (M+): 162.1 1H NMR (400 MHz, Deuterium Oxide) δ 6.76 (s, 1H), 6.31 (s, 1H), 5.78 (s, 1H), 5.65 (s, 1H), 3.92 (s, 2H), 2.75 (s, 6H).



Compound 172: N-(fluoromethyl)-N-(2-hydroxyethyl)-N-methylcyclopropanaminium Iodide

[0812] Step 1:

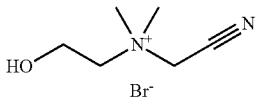
[0813] To a solution of N-methylcyclopropanamine (1 g, 14.06 mmol, 1.68 eq) and 2-bromoethoxy-tert-butyl-dimethyl-silane (2.00 g, 8.37 mmol, 1 eq) in acetonitrile (20 mL) was added K2CO3 (1.16 g, 8.37 mmol, 1 eq) at 25° C. The mixture was stirred at 50° C. for 12 hr. TLC indicated new spots formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10:1 to 1:1). Compound N-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-N-methyl-cyclopropanamine (3.2 g, 13.95 mmol, 83.32% yield) was obtained as a colorless oil.

[0814] Step 2:

[0815] To a solution of N-[2-[tert-butyl(dimethyl)silyl] oxyethyl]-N-methyl-cyclopropanamine (200 mg, 871.71 umol, 1 eq) in THF (10 mL) was added fluoro(iodo)methane (418.24 mg, 2.62 mmol, 3 eq) at 25° C. The mixture was stirred at 25° C. for 12 hr. LCMS showed 50% of N-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-N-methyl-cyclopropanamine remained. Fluoro(iodo)methane (418.24 mg, 2.62 mmol, 3 eq) was added. The mixture was stirred at 25° C. for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. Compound tert-butyl-[2-[N-cyclopropyl-(fluoromethyl)-methyl-azanyl]ethoxy]-dimethyl-silane (200 mg, 513.66 umol, 58.93% yield) was obtained as a white solid.

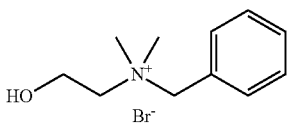
[0816] Step 3:

[0817] To a solution of tert-butyl-[2-[N-cyclopropyl-(fluoromethyl)-methyl-azanyl]ethoxy]-dimethyl-silane (200 mg, 513.66 umol, 1 eq) in H_2O (10 mL) was added KF (298.42 mg, 5.14 mmol, 120.33 uL, 10 eq) at 25° C. The mixture was stirred at 25° C. for 12 hr. LCMS showed the desired compound was detected. The reaction mixture was extracted with ethyl acetate (50 mL). The aqueous phase is freeze-dried. The residue was washed with washed by acetonitrile (100 mL). The acetonitrile layer was filtered and the filtrate was concentrated under reduced pressure to give a residue. The solid was diluted with H_2O (3 mL) and extracted with ethyl acetate (5 mL*4). The aqueous phase was freeze-dried. The title compound (36 mg, 130.86 umol, I-salt, 85.71% yield) was obtained as a white solid. LCMS: (M+): 148.1 1H NMR (400 MHz, Deuterium Oxide) δ 5.39 (q, J=5.8 Hz, 1H), 5.28 (q, J=5.8 Hz, 1H), 4.02-3.97 (m, 2H), 3.58-3.51 (m, 2H), 3.16-3.12 (m, 1H), 2.78 (d, J=2.2 Hz, 3H), 1.18-1.14 (m, 2H), 0.96-0.79 (m, 2H).



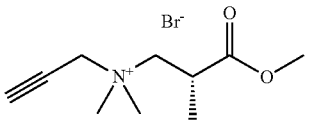
Compound 172A: (cyanomethyl)(2-hydroxyethyl)dimethylazanium Bromide

[0818] A mixture of 2-(dimethylamino)ethanol (500 mg, 5.61 mmol, 563.06 uL, 1 eq) in THF (5 mL) was added slowly 2-bromoacetonitrile (672.84 mg, 5.61 mmol, 373.80 uL, 1 eq) at 15° C., and then the mixture was stirred at 15° C. for 10 hr under N2 atmosphere. TLC indicated 2-(dimethylamino) ethanol was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was filtered and the filter cake was concentrated under reduced pressure to give a residue. The crude product was washed with THE (4 mL). The title compound (200 mg, 956.55 umol, 17.05% yield, 100% purity, Br—) was obtained as a white solid. LCMS: (M+) 129.1 1H NMR (400 MHz, DMSO-d6) δ 5.45 (t, J=4.8 Hz, 1H), 4.91 (s, 2H), 3.91-3.82 (m, 2H), 3.63-3.53 (m, 2H), 3.26 (s, 6H).



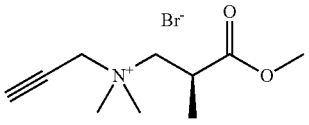
Compound 173: benzyl(2-hydroxyethyl)dimethylazanium

[0819] A mixture of 2-(dimethylamino)ethanol (500 mg, 5.61 mmol, 563.06 uL, 1 eq) and bromomethylbenzene (959.40 mg, 5.61 mmol, 666.25 uL, 1 eq) in THF (5 mL) was degassed and purged with N_2 for 3 times. And then the mixture was stirred at 15° C. for 10 hr under N_2 atmosphere. TLC indicated 2-(dimethylamino)ethanol was consumed completely and one new spot larger polarity formed. The reaction mixture was filtered and the filter cake was concentrated under reduced pressure to give a residue. The crude product was triturated with THF (30 mL) at 15° C. for 30 min. Then the reaction mixture was filtered and the filter cake was concentrated under reduced pressure to give a residue. The title compound (200 mg, 699.54 umol, 12.47% yield, 91% purity, Br—) was obtained as a white solid. LCMS: (M+) 180.1 1H NMR (400 MHz, Methanol-d4) δ 7.64-7.48 (m, 5H), 4.63 (s, 2H), 4.11-4.03 (m, 2H), 3.52-3.45 (m, 2H), 3.12 (s, 6H).



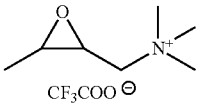
Compound 174: [(2R)-3-methoxy-2-methyl-3-oxo-propyl]dimethyl(prop-2-yn-1-yl)azanium

[0820] To a solution of methyl (2S)-3-bromo-2-methyl-propanoate (300 mg, 1.66 mmol, 2 eq) in ACN (10 mL) was added N,N-dimethylprop-2-yn-1-amine (68.88 mg, 828.60 umol, 87.86 uL, 1 eq) at 15° C. The mixture was stirred at 80° C. for 12 hr. LCMS showed most of N,N-dimethylprop-2-yn-1-amine remained. Then the mixture Then the mixture was stirred at 80° C. for 24 hr. LCMS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-20%, 10 min). The title compound (7 mg, 26.50 umol, Br-salt, 3.20% yield, 100% purity) was obtained as a yellow oil. LCMS: (M+): 184.1 1H NMR (400 MHz, Deuterium Oxide) δ 4.18 (d, J=2.5 Hz, 2H), 3.94 (dd, J=13.9, 8.7 Hz, 1H), 3.69 (s, 3H), 3.37 (dd, J=13.9, 2.2 Hz, 1H), 3.26-3.14 (m, 1H), 3.17-3.08 (m, 1H), 3.07 (s, 6H), 1.23 (d, J=7.2 Hz, 3H).



Compound 175: [(2S)-3-methoxy-2-methyl-3-oxo-propyl]dimethyl(prop-2-yn-1-yl)azanium

[0821] To a solution of methyl (2R)-3-bromo-2-methyl-propanoate (300 mg, 1.66 mmol, 1 eq) in ACN (10 mL) was added N,N-dimethylprop-2-yn-1-amine (68.88 mg, 828.60 umol, 87.86 uL, 0.5 eq) at 15° C. The mixture was stirred at 80° C. for 24 hr. LCMS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-20%, 10 min). The title compound (5 mg, 18.93 umol, Br-salt, 1.14% yield, 100% purity) was obtained as a yellow oil. LCMS: (M+): 184.1 1H NMR (400 MHz, Deuterium Oxide) δ 4.17 (d, J=2.5 Hz, 2H), 3.93 (ddd, J=13.9, 8.7, 1.3 Hz, 1H), 3.67 (d, J=1.3 Hz, 3H), 3.35 (dd, J=13.9, 2.1 Hz, 1H), 3.18 (t, J=2.5 Hz, 1H), 3.12 (dd, J=8.9, 7.0 Hz, 1H), 3.05 (s, 6H), 1.22 (dd, J=7.2, 1.3 Hz, 3H).



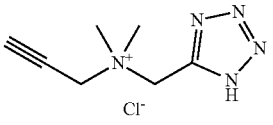
Compound 176: trimethyl[(3-methyloxiran-2-yl)methyl]azanium

[0822] Step 1:

[0823] To a solution of mCPBA (14.29 g, 66.26 mmol, 1.2 eq) (80% purity) in CHCl3 (100 mL) was added (E)-1-chlorobut-2-ene (5 g, 55.22 mmol, 1 eq) at 0° C. The mixture was stirred at 25° C. for 12 h. TLC indicated the reactant was consumed completely. The reaction mixture was quenched by addition Na_2SO_3 aqueous solution (500 ml), and then the mixture was partitioned and the organic phase was separated, dried over Na_2SO_4, then filtered and the crude solution as 0.55 mol/L of 2-(chloromethyl)-3-methyl-oxirane (crude) in CHCl3 (100 ml) was used in the next step without further purification.

[0824] Step 2:

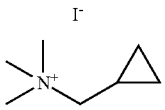
[0825] A solution of N,N-dimethylmethanamine (1 M, 57.86 mL, 1.23 eq) (THF) and 0.55 mol/L of 2-(chloromethyl)-3-methyl-oxirane (55 mmol, 100 mL, 1 eq) in $CHCl_3$ (100 ml) was stirred at 25° C. for 12 h. MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC ([water (0.10% TFA)-ACN]). The title compound (5 mg, 19.12 umol, 93.00% yield, 93% purity, TFA-) was obtained as colorless oil. LCMS: (M+): 130.2. 1H NMR (400 MHz, Methanol-d4) δ 3.89 (dd, J=13.6, 1.8 Hz, 1H), 3.29-3.21 (m, 10H), 3.15 (dd, J=13.6, 9.1 Hz, 1H), 3.00 (qd, J=5.2, 1.9 Hz, 1H), 1.38 (d, J=5.2 Hz, 3H).



Compound 177: dimethyl(prop-2-yn-1-yl)[(1H-1,2,3,4-tetrazol-5-yl)methyl]azanium

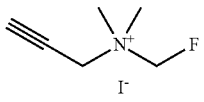
[0826] A mixture of 5-(chloromethyl)-1H-tetrazole (500 mg, 4.22 mmol, 1 eq) and N,N-dimethylprop-2-yn-1-amine (350.69 mg, 4.22 mmol, 447.31 uL, 1 eq) in THF (5 mL) was degassed and purged with N_2 3 times, and then the mixture

was stirred at 15° C. for 10 hr under N2 atmosphere. LCMS showed desired compound was detected. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.04% NH3H2O)-ACN]; B %: 1%-3%, 10 min). The residue was further purified by SFC (column: DAICEL CHIRALPAK AD (250 mm*30 mm, 10 um); mobile phase: [0.1% NH3H2O EtOH]; B %: 20%-20%, 20 min). The title compound (6 mg, 29.75 umol, 60.00% yield, 100% purity) was obtained as a white solid. LCMS: (M+): 166.1 1H NMR (400 MHz, DMSO-d6) δ 4.68 (s, 2H), 4.36 (d, J=2.5 Hz, 2H), 4.04 (t, J=2.4 Hz, 1H), 3.00 (s, 6H).



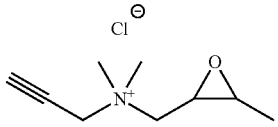
Compound 178:
(cyclopropylmethyl)trimethylazanium Iodide

[0827] To a solution of cyclopropylmethanamine (1 g, 9.30 mmol, 1 eq, HCl) in DCM (10 mL) was added dropwise MeI (26.39 g, 185.91 mmol, 11.57 mL, 20 eq) at 0° C. After addition, the mixture was stirred at 25° C. for 12h. TLC indicated reactant 1 was consumed completely. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in MeOH (7 mL), then to the solution was added MTBE (70 mL) and precipitation formed, was filtered and the filter cake was dissolved in MeOH (7 mL), then MTBE (70 mL) was added and precipitation formed, was filtered and the filter cake was concentrated under reduce pressure to give the target. The title compound (676 mg, 2.78 mmol, 29.86% yield, 99% purity, I—) was obtained as a white solid. LCMS: (M+): 114.2 1H NMR (400 MHz, Deuterium Oxide) δ 3.00 (d, J=7.3 Hz, 2H), 2.91 (s, 9H), 1.01-0.86 (m, 1H), 0.62-0.51 (m, 2H), 0.24-0.15 (m, 2H).



Compound 179:
(fluoromethyl)dimethyl(prop-2-yn-1-yl)azanium Iodide

[0828] To a mixture of N,N-dimethylprop-2-yn-1-amine (0.20 g, 2.39 mmol, 1 eq) in THF (5 mL) was added fluoro(iodo)methane (1.15 g, 7.18 mmol, 3 eq). The mixture was stirred at 25° C. for 10 h. The reaction mixture was filtered and the filter cake was dried under reduced pressure to give a crude product. The crude product was washed with EtOAc (10 mL) and then dried. The title compound (0.35 g, 1.44 mmol, 60.19% yield, 100% purity, I—) was obtained as a white solid. LCMS: (M+): 116.2 1H NMR (400 MHz, Chloroform-d) δ 6.29 (d, J=1.7 Hz, 1H), 5.79 (d, J=1.5 Hz, 1H), 3.79 (s, 3H), 3.39 (d, J=2.4 Hz, 2H), 2.35 (s, 3H), 2.25 (t, J=2.3 Hz, 1H).



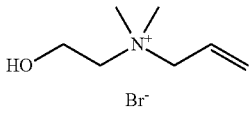
Compound 181: dimethyl[(3-methyloxiran-2-yl) methyl](prop-2-yn-1-yl)azanium

[0829] Step 1:

[0830] To a solution of m-CPBA (8.58 g, 39.76 mmol, 80% purity, 1.2 eq) in CHCl3 (100 mL) was added (E)-1-chlorobut-2-ene (3 g, 33.13 mmol, 1 eq) at 0° C. The mixture was stirred at 25° C. for 12 hr. TLC indicated (E)-1-chlorobut-2-ene was consumed completely. The reaction mixture was filtered to give organic layers. The combined organic layers were quenched by saturated sodium sulfite solution (200 mL), and then extracted to give organic layers. Compound 0.33 mol/L of 2-(chloromethyl)-3-methyl-oxirane (crude) in $CHCl_3$ (100 mL) was obtained as a colorless liquid and used into the next step without further purification.

[0831] Step 2:

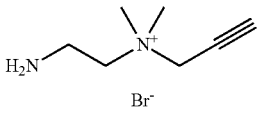
[0832] To a solution of 2-(chloromethyl)-3-methyl-oxirane (0.33 M, 100 mL, 1 eq) ($CHCl_3$) was added N,N-dimethylprop-2-yn-1-amine (2.74 g, 33.00 mmol, 3.50 mL, 1 eq) at 25° C. The mixture was stirred at 25° C. for 12 hr. LCMS indicated desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a liquid. The liquid was purified liquid was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-10%, 10 min). Compound 2-[(N,N-dimethyl-prop-2-ynyl-azanyl)methyl]-3-methyl-oxirane (20 mg, 105.44 umol, 0.32% yield) was obtained as a colorless oil. The oil was further purified by prep-HPLC (column: Waters XbridgeBEH $C_{18\ 100*30}$ mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-5%, 10 min). The title compound (7 mg, 36.90 umol, Cl-salt, 35.00% yield, 100% purity) was obtained as a colorless oil. LCMS: (M+): 154.2 ^{1}H NMR (400 MHz, Methanol-d4) δ 4.49-4.35 (m, 2H), 3.99 (d, J=12.3 Hz, 1H), 3.33-3.18 (m, 9H), 3.07-2.97 (m, 1H), 1.36 (d, J=5.2 Hz, 3H).



Compound 182:
(2-hydroxyethyl)dimethyl(prop-2-en-1-yl)azanium Bromide

[0833] To a solution of 2-(dimethylamino)ethanol (200 mg, 2.24 mmol, 225.23 uL, 1 eq) in THF (10 mL) was added 3-bromoprop-1-ene (271.44 mg, 2.24 mmol, 1 eq) at 0° C. The mixture was stirred at 25° C. for 12 hr. The precipitation was found. LCMS showed desired compound was detected. The reaction mixture was diluted with H_2O (60 mL) and extracted with ethyl acetate (60 mL). The aqueous phase is freeze-dried. The residue was washed with ethyl acetate (50

mL) at 0° C. Compound (2-hydroxyethyl)dimethyl(prop-2-en-1-yl)azanium (160 mg, 761.50 umol, 33.94% yield, 100% purity) was obtained as a white solid. LCMS: (M+): 130. 1H NMR (400 MHz, Deuterium Oxide) δ 6.00-5.82 (m, 1H), 5.64-5.51 (m, 2H), 3.96-3.83 (m, 4H), 3.37-3.30 (m, 2H), 2.98 (s, 6H).



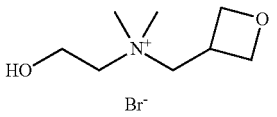
Compound 183: (2-aminoethyl)dimethyl(prop-2-yn-1-yl)azanium

[0834] Step 1:

[0835] To a solution of tert-butyl N-(2-bromoethyl)carbamate (200 mg, 892.48 umol, 1 eq) in THF (10 mL) was added N,N-dimethylprop-2-yn-1-amine (74.19 mg, 892.48 umol, 94.63 uL, 1 eq) at 25° C. The mixture was stirred at 25° C. for 5 hr. LCMS showed LCMS showed most of tert-butyl N-(2-bromoethyl)carbamate was remained. The mixture was stirred at 70° C. for 12 hr. LCMS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O 60 mL and extracted with ethyl acetate 60 mL. The aqueous phase is freeze-dried. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-60%, 9 min). Compound tert-butyl N-[2-(N,N,N-dimethyl-prop-2-ynyl-azanyl)ethyl]carbamate (120 mg, 390.59 umol, Br-salt, 80.00% yield, 100% purity) was obtained as a colorless soil. LCMS: (M+): 227.2

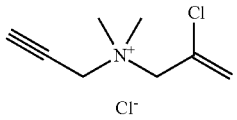
[0836] Step 2:

[0837] To a solution of tert-butyl N-[2-(N,N-dimethyl-prop-2-ynyl-azanyl)ethyl]carbamate (50 mg, 162.75 umol, 1 eq) in DCM (3 mL) and TFA (0.3 mL) was stirred at 25° C. for 12 hr. LCMS showed tert-butyl N-[2-(N,N-dimethyl-prop-2-ynyl-azanyl)ethyl]carbamate was consumed completely and the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The title compound (30 mg, 144.85 umol, Br-salt, 89.00% yield, 100% purity) was obtained as a colorless oil. LCMS: (M+): 127.1 1H NMR (400 MHz, Deuterium Oxide) δ 4.24 (d, J=2.5 Hz, 2H), 3.73-3.64 (m, 2H), 3.47-3.38 (m, 2H), 3.23 (t, J=2.4 Hz, 1H), 3.15 (s, 6H).



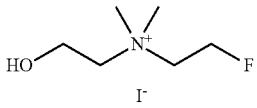
Compound 184: (2-hydroxyethyl)dimethyl[(oxetan-3-yl)methyl]azanium Bromide

[0838] To a solution of 2-(dimethylamino)ethanol (100 mg, 1.12 mmol, 112.61 uL, 1 eq) in ACN (5 mL) was added 3-(bromomethyl)oxetane (169.41 mg, 1.12 mmol, 1 eq) at 25° C. The mixture was stirred at 70° C. for 12 hr. The reaction mixture was diluted with H_2O 60 mL and extracted with ethyl acetate 60 mL. The aqueous phase is freeze-dried. Compound 2-[N,N-dimethyl-(oxetan-3-ylmethyl)-azanyl] ethanol (70 mg, 290.26 umol, 25.87% yield, Br-salt, 99.576% purity) was obtained as a white solid. LCMS: (M+): 160.1 1H NMR (400 MHz, Deuterium Oxide) δ 4.81-4.73 (m, 2H), 4.55-4.47 (m, 2H), 3.94-3.86 (m, 2H), 3.76-3.61 (m, 3H), 3.37-3.30 (m, 2H), 2.95 (s, 6H).



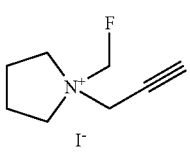
Compound 185: (2-chloroprop-2-en-1-yl)dimethyl (prop-2-yn-1-yl)azanium Chloride

[0839] To a mixture of N of N,N-dimethylprop-2-yn-1-amine (200 mg, 2.41 mmol, 255.10 uL, 1 eq) in THF (3 mL) was added 2,3-dichloroprop-1-ene (533.95 mg, 4.81 mmol, 441.28 uL, 2 eq) in one portion at 25° C. under N_2. Then the mixture was heated to 66° C. and stirred for 12 hours. LCMS showed one main peak with desired m/z was detected. The reaction mixture was diluted with H_2O (55 mL) and extracted with ethyl acetate (9 mL, 3 mL*3). The combined aqueous layer was lyophilized. Compound 2-chloroallyl-dimethyl-prop-2-ynyl-ammonium (266 mg, 1.36 mmol, 56.67% yield, 100% purity, Cl—) was obtained as yellow solid. LCMS: (M+): 158.1 1H NMR (400 MHz, Deuterium Oxide) δ 5.89 (dd, J=20.2, 2.3 Hz, 2H), 4.27-4.20 (m, 4H), 3.19 (t, J=2.6 Hz, 1H), 3.15 (s, 6H).



Compound 186: (2-fluoroethyl)(2-hydroxyethyl)dimethylazanium

[0840] To a solution of 2-(dimethylamino)ethanol (100 mg, 1.12 mmol, 112.61 uL, 1 eq) in THF (5 mL) was added 1-fluoro-2-iodo-ethane (195.16 mg, 1.12 mmol, 1 eq) at 25° C. The mixture was stirred at 25° C. for 5 hr. The mixture was stirred at 70° C. for 12 hr. The precipitate was washed with tetrahydrofuran (10 mL). The mixture was diluted with H_2O 60 mL and extracted with ethyl acetate 100 mL. The aqueous phase is freeze-dried. The title compound (83 mg, 315.48 umol, I-salt, 28.12% yield, 100% purity) was obtained as a white solid. LCMS: (M+): 136.1 1H NMR (400 MHz, Deuterium Oxide) δ 4.93-4.86 (m, 1H), 4.82-4.74 (m, 1H), 3.97-3.89 (m, 2H), 3.79-3.73 (m, 1H), 3.72-3.66 (m, 1H), 3.51-3.44 (m, 2H), 3.11 (s, 6H).



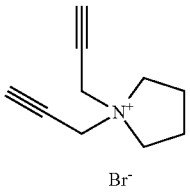
Compound 187: 1-(fluoromethyl)-1-(prop-2-yn-1-yl)pyrrolidin-1-ium

[0841] Step 1:

[0842] To a mixture of pyrrolidine (1 g, 14.06 mmol, 1.17 mL, 1 eq) and 3-bromoprop-1-yne (1.84 g, 15.47 mmol, 1.33 mL, 1.1 eq) in EtOH (10 mL) was added $NaHCO_3$ (2.95 g, 35.15 mmol, 1.37 mL, 2.5 eq). The mixture was stirred at 25° C. for 5 h. LC-MS showed the desired product was detected. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100*30 mm*5 um; mobile phase: [water (0.04% HCl)-ACN]; B %: 1%-1%, 12 min). The solution of 1-prop-2-ynylpyrrolidine (after prep-HPLC) was adjusted to pH=8 by $NaHCO_3$. The mixture was extracted with ethyl acetate (40 mL*2). The combined organic phase dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. 1-prop-2-ynylpyrrolidine (in EtOAc (80 mL) was obtained. LCMS: (M+): 110.2

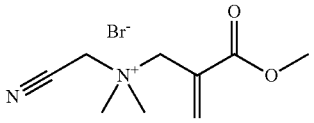
[0843] Step 2:

[0844] To the solution of 1-prop-2-ynylpyrrolidine (60 mL, 1 eq) in EtOAc (60 mL) was added fluoro(iodo)methane (0.8 g, 5.00 mmol, 1 eq) at 25° C. The mixture was stirred at 25° C. for 5 hr. TLC (Dichloromethane:Methanol=10:1, Rf=0.04) indicated reactant was consumed completely. The mixture was concentrated in reduced pressure. To the mixture was added H_2O (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL*2). The aqueous phase was lyophilized to give a yellow solid. 1-(fluoromethyl)-1-prop-2-ynyl-pyrrolidin-1-ium (70 mg, 254.78 umol, 97.942% purity, I—) was obtained as yellow solid. LCMS: (M+): 142.1 ^{1}H NMR (400 MHz, Methanol-d4) δ 5.55 (d, J=45.1 Hz, 2H), 4.50 (d, J=1.6 Hz, 2H), 3.82-3.71 (m, 4H), 3.55 (s, 1H), 2.30-2.23 (m, 4H).



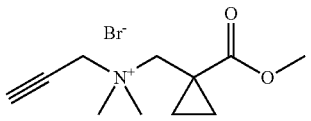
Compound 188: 1,1-bis(prop-2-yn-1-yl)pyrrolidin-1-ium Bromidebromide

[0845] To pyrrolidine (1 g, 14.06 mmol, 1.17 mL, 1 eq) was added 3-bromoprop-1-yne (836.32 mg, 7.03 mmol, 606.03 uL, 0.5 eq) at −10° C. under N_2. The mixture was stirred at 25° C. for 12 h. LCMS showed the desired compound was detected. The mixture was purified directly without work-up. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100*30 mm*5 um; mobilephase: [water (0.04% HCl)-ACN]; B %: 1%-1%, 12 min). The title compound (150 mg, 98.62% purity) was obtained as yellow solid. LCMS: (M+): 148.2. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 4.70-4.60 (m, 4H), 3.72 (t, 4H), 3.20-3.10 (m, 2H), 2.25-2.15 (m, 4H).



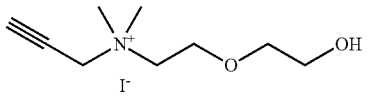
Compound 189: N-(cyanomethyl)-2-(methoxycarbonyl)-N,N-dimethylprop-2-en-1-aminium Bromide

[0846] Methyl 2-(bromomethyl)acrylate (0.200 g, 1 Eq, 1.12 mmol) was dissolved in DCM (3 mL), followed by addition of 2-(dimethylamino)acetonitrile (94.0 mg, 109 μL, 1 Eq, 1.12 mmol). The reaction was stirred at 40° C. overnight. The solution was concentrated by rotary evaporation until product started to precipitate out. More DCM was added and material was triturated in DCM. The solids were further washed in DCM and dried in vacuo to yield product N-(cyanomethyl)-2-(methoxycarbonyl)-N,N-dimethylprop-2-en-1-aminiumbromide (0.24 g, 82%) as a white solid. LCMS M+: 183.3 ^{1}H NMR (400 MHz, DMSO-d6) δ 6.86 (s, 1H), 6.55 (s, 1H), 4.90 (s 2H), 4.41 (s, 2H), 3.76 (s, 3H), 3.20 (s, 6H).



Compound 190: N-((1-(methoxycarbonyl)cyclopropyl)methyl)-N,N-dimethylprop-2-yn-1-aminium Bromide

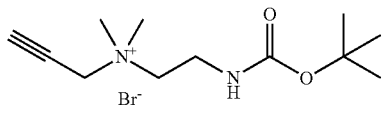
[0847] Compound methyl 1-(bromomethyl)cyclopropane-1-carboxylate (0.100 g, 1 Eq, 518 μmol) was dissolved in DCM (3 mL), followed by addition of N,N-dimethylprop-2-yn-1-amine (45.2 mg, 58.6 μL, 1.05 Eq, 544 μmol). The reaction was stirred at 40° C. overnight, after which an immiscible viscous oil appeared. The oil was washed with DCM multiple times and dried in vacuo to yield product N-((1-(methoxycarbonyl)cyclopropyl)methyl)-N,N-dimethylprop-2-yn-1-aminium bromide (0.025 g, 17%) as a viscous glassy oil. LCMS M+: 196.3 ^{1}H NMR (400 MHz, DMSO-d6) δ 4.38 (d, J=2.5 Hz, 2H), 4.06 (t, J=2.5 Hz, 1H), 3.77 (s, 2H), 3.63 (s, 3H), 3.09 (s, 6H), 1.44 (q, J=4.5 Hz, 2H), 1.27 (q, J=4.4 Hz, 2H).



Compound 191: [2-(2-hydroxyethoxy)ethyl]dimethyl(prop-2-yn-1-yl)azanium

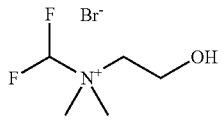
[0848] To a solution of 2-(2-chloroethoxy)ethanol (299.68 mg, 2.41 mmol, 253.97 uL, 1 eq) in THF (10 mL) was added NaI (1.08 g, 7.22 mmol, 3 eq) at 25° C. The mixture was stirred at 70° C. for 0.5 hr. N,N-dimethylprop-2-yn-1-amine (200 mg, 2.41 mmol, 255.10 uL, 1 eq) was added and stirred

at 70° C. for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.10% TFA)-ACN]; B %: 1%-5%, 9 min). The title compound (79 mg, 262.62 umol, I-salt, 10.92% yield, 99.447% purity) was obtained as yellow oil. LCMS: (M+): 172.1 1H NMR (400 MHz, Deuterium Oxide) δ 4.17 (d, J=2.6 Hz, 2H), 3.86-3.79 (m, 2H), 3.61-3.51 (m, 4H), 3.54-3.45 (m, 2H), 3.11-3.06 (m, 7H).



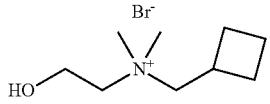
Compound 192: tert-butyl N-{2-[dimethyl(prop-2-yn-1-yl)azaniumyl]ethyl}carbamate Bromide

[0849] To a solution of tert-butyl N-(2-bromoethyl)carbamate (200 mg, 892.48 umol, 1 eq) in THF (10 mL) was added N,N-dimethylprop-2-yn-1-amine (74.19 mg, 892.48 umol, 94.63 uL, 1 eq) at 25° C. The mixture was stirred at 25° C. for 5 hr. LCMS showed most of the tert-butyl N-(2-bromoethyl)carbamate remained. The mixture was stirred at 70° C. for 12 hr. LCMS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O 60 mL and extracted with ethyl acetate 60 mL. The aqueous phase is freeze-dried. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-60%, 9 min). The title compound (120 mg, 390.59 umol, Br-salt, 80.00% yield, 100% purity) was obtained as a colorless oil. LCMS: (M+): 227.2 1H NMR (400 MHz, Deuterium Oxide) δ 4.22 (d, J=2.5 Hz, 2H), 3.51 (s, 4H), 3.23 (s, 1H), 3.16 (s, 6H), 1.37 (s, 9H).



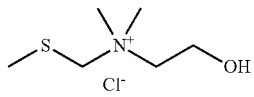
Compound 193: (difluoromethyl)(2-hydroxyethyl)dimethylazanium

[0850] To a solution of 2-(dimethylamino)ethanol (500 mg, 5.61 mmol, 563.06 uL, 1 eq) in DCM (10 mL) was added MeOH (197.71 mg, 6.17 mmol, 249.70 uL, 1.1 eq) and 1-[[bromo(difluoro)methyl]-ethoxy-phosphoryl]oxy-ethane (4.49 g, 16.83 mmol, 3 eq) at 25° C. The mixture was stirred at 25° C. for 12 hr. The precipitation was formed. The reaction mixture was filtered to give a residue. To the residue was added solvent (ethyl acetate:petroleum ether=1:1, 1 mL). The mixture was diluted with H_2O (1 mL). The aqueous phase was freeze-dried. Compound 2-[N-(difluoromethyl)-dimethyl-azanyl]ethanol (39 mg, 177.23 umol, Br-salt, 4.2% yield, 100% purity) was obtained n as a white solid. LCMS: (M+): 140.1 1H NMR (400 MHz, Deuterium Oxide) δ 7.02 (t, J=58.7 Hz, 1H), 3.96 (t, J=4.8 Hz, 2H), 3.64-3.57 (m, 2H), 3.18 (t, J=1.5 Hz, 6H).



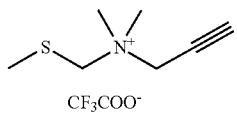
Compound 194: (cyclobutylmethyl)(2-hydroxyethyl)dimethylazanium Bromide

[0851] To a mixture of 2-(dimethylamino)ethanol (200 mg, 2.24 mmol, 225.23 uL, 1 eq) in THF (3 mL) was added bromomethylcyclobutane added bromomethylcyclobutane (668.77 mg, 4.49 mmol, 502.83 uL, 2 eq) in one portion at 25° C. under N_2. Then the mixture was heated to 66° C. and stirred for 12 hours. LCMS showed one main peak with desired m/z was detected. The reaction mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (9 mL, 3 mL*3). The aqueous layer was lyophilized. The residue was purified by prep-HPLC [water (0.10% TFA)-ACN]. The title compound (76 mg, 319.11 umol, 14.22% yield, 100% purity, Br—) was obtained as colorless oil. LCMS: (M+): 158.2 1H NMR (400 MHz, Deuterium Oxide) δ 3.90-3.83 (m, 2H), 3.33-3.24 (m, 4H), 2.92 (s, 6H), 2.74 (p, J=7.9 Hz, 1H), 2.06-1.95 (m, 2H), 1.93-1.61 (m, 4H).



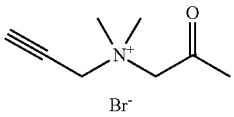
Compound 195: (2-hydroxyethyl)dimethyl[(methylsulfanyl)methyl]azanium

[0852] To a mixture of 2-(dimethylamino)ethanol (200 mg, 2.24 mmol, 225.23 uL, 1 eq) in THF (3 mL) was added chloro added chloro(methylsulfanyl)methane (433.40 mg, 4.49 mmol, 376.87 uL, 2 eq) in one portion at 25° C. under N_2. Then the mixture was heated to 66° C. and stirred for 12 hours. LCMS showed one main peak with desired m/z was detected. The reaction mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (9 acetate 9 mL, 3 mL*3). The aqueous layer was lyophilized was lyophilized. The residue was purified by prep-HPLC [water (0.10% TFA)-ACN]. Compound 2-hydroxyethyl-dimethyl-(methylsulfanylmethyl)azanium (72 mg, 387.69 umol, 17.28% yield, 100% purity, Cl—)—) was obtained as colorless oil. LCMS: (M+): 150.1 1H NMR (400 MHz, Deuterium Oxide) δ 4.47 (s, 2H), 3.91-3.83 (m, 2H), 3.43-3.36 (m, 2H), 2.99 (s, 6H) 2.23 (s, 3H).



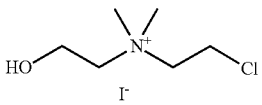
Compound 196: dimethyl[(methylsulfanyl)methyl](prop-2-yn-1-yl)azanium

[0853] To a mixture of N,N-dimethylprop-2-yn-1-amine (200 mg, 2.41 mmol, 255.10 uL, 1 eq) in THF (3 mL) was added chloro(methylsulfanyl)methane (464.71 mg, 4.81 mmol, 404.09 uL, 2 eq) in one portion at 25° C. under N_2. Then the mixture was heated to 66° C. and stirred for 12 hours. LCMS showed one main peak with desired m/z was detected. The reaction mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (9 mL, 3 mL*3). The aqueous layer was lyophilized. The residue was purified by prep-HPLC [water (0.10% TFA)-ACN]. Compound dimethyl[(methylsulfanyl)methyl](prop-2-yn-1-yl)azanium (93 mg, 507.15 umol, 21.08% yield, 98% purity, TFA) was obtained as colorless oil. LCMS: (M+): 144.1 1H NMR (400 MHz, Deuterium Oxide) δ 4.59 (s, 2H), 4.23 (d, J=2.6 Hz, 2H), 3.17 (t, J=2.6 Hz, 1H), 3.10 (s, 6H), 2.34 (s, 3H).



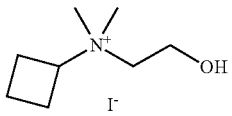
Compound 197: dimethyl(2-oxopropyl)(prop-2-yn-1-yl)azanium Bromide

[0854] To a mixture of N,N-dimethylprop-2-yn-1-amine (200 mg, 2.41 mmol, 255.10 uL, 1 eq) in THF (3 mL) was added 1-bromopropan-2-one (659.07 mg, 4.81 mmol, 2 eq) in one portion at 25° C. under N_2. Then the mixture the mixture was heated to 66° C. and stirred for 12 hours. LCMS showed one main peak with desired m/z was detected. The reaction mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate9 mL (3 mL*3). The aqueous layer was lyophilized. The residue was purified by prep-HPLC [water (0.10% TFA)-ACN]. The title compound (155 mg, 704.21 umol, 29.27% yield, 100% purity, Br—)—) was obtained as white solid. LCMS: (M+): 140.1 1H NMR (400 MHz, Deuterium Oxide) δ 4.55 (s, 2H), 4.38 (d, J=2.6 Hz, 2H), 3.24 (s, 6H), 3.20 (t, J=2.6 Hz, 1H), 2.18 (s, 3H).



Compound 198: (2-chloroethyl)(2-hydroxyethyl)dimethylazanium Iodide

[0855] To a solution of 2-(dimethylamino)ethanol (200 mg, 2.24 mmol, 225.23 uL, 1 eq) in THF (10 mL) was added 1-chloro-2-iodo-ethane (427.24 mg, 2.24 mmol, 1 eq) at 25° C. The mixture was stirred at 25° C. for 12 hr. LCMS showed most of 2-(dimethylamino)ethanol was remained and a little of desired compound was detected. The mixture was stirred at 70° C. for 6 hr. The precipitation was found. The reaction mixture was diluted with H_2O (60 mL) and extracted with ethyl acetate (100 mL). The aqueous phase is freeze-dried. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100*30 mm*5 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-1%, 12 min). The title compound (39 mg, 135.99 umol, I-salt, 9.50% yield, 97.478% purity) was obtained as a colorless oil. LCMS: (M+): 152.1 1H NMR (400 MHz, Deuterium Oxide) δ 3.95-3.82 (m, 4H), 3.68 (t, J=6.7 Hz, 2H), 3.47-3.40 (m, 2H), 3.08 (s, 6H).



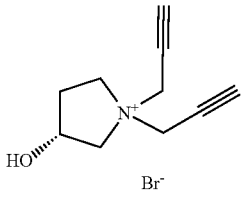
Compound 199: N-(2-hydroxyethyl)-N,N-dimethylcyclobutanaminium

[0856] Step 1:

[0857] To a mixture of 2 of 2-(methylamino)ethanol (500 mg, 6.66 mmol, 534.76 uL, 1 eq) in DCE (5 mL) was added HOAc (799.53 mg, 13.31 mmol, 761.46 uL, 2 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 0.5 h, then cyclobutanone (933.17 mg, 13.31 mmol, 994.85 uL, 2 eq) and $NaBH(OAc)_3$ (2.82 g, 13.31 mmol, 2 eq) was added. Then the mixture was stirred at 25° C. for 11.5 hours. LCMS showed one main peak with expected mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Compound 2-[cyclobutyl(methyl)amino]ethanol (1 g, crude) was obtained as yellow oil. LCMS: (M+): 130.1

[0858] Step 2:

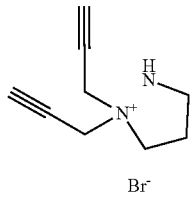
[0859] To a mixture of 2-[cyclobutyl(methyl)amino]ethanol (430 mg, 3.33 mmol, 1 eq) in THF (3 mL) was added MeI (2.36 g, 16.64 mmol, 1.04 mL, 5 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 12 hours. LCMS showed one main peak with desired m/z was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.10% TFA)-ACN] and by prep-HPLC [water (0.2% FA)-ACN]. Compound cyclobutyl-(2-hydroxyethyl)-dimethyl-ammonium (38 mg, 140.15 umol, 4.21% yield, I—)—) was obtained as colorless oil. LCMS: (M+): 144.1 1H NMR (400 MHz, Deuterium Oxide) δ 3.99 (p, J=8.9 Hz, 1H), 3.90-3.86 (m, 2H), 3.25-3.18 (m, 2H), 2.88 (s, 6H), 2.24 (p, J=10.3 Hz, 2H), 2.13-2.02 (m, 2H), 1.76-1.51 (m, 2H).



Compound 200: (3R)-3-hydroxy-1,1-bis(prop-2-yn-1-yl)pyrrolidin-1-ium

[0860] To a mixture of (3R)-pyrrolidin-3-ol (0.5 g, 5.74 mmol, 476.19 uL, 1 eq) in THF (10 mL) and EtOH (10 mL)

was added 3 added 3-bromoprop-1-yne (1.37 g, 11.48 mmol, 989.61 uL, 2 eq) in one portion at −5° C. under N_2. The mixture was stirred at 25° C. for 5h. LCMS (product: RT=0.142 min) showed the starting material was consumed completely. The mixture was concentrated in reduced pressure at 45° C. The residue was poured into water (20 mL). The aqueous phase was extracted with ethyl acetate (10 mL*3). The aqueous phase was lyophilized to give yellow oil. The crude product was purified by prep-HPLC (column: PhenomenexLuna C18 100*30 mm*5 um; mobile phase: [water (0.1% TFA)-ACN]; B %: 1%-1%, 12 min). The product was added to ACN (10 mL). The mixture was stirred at 25° C. for 30 min. The mixture was filtered. The organic phase was concentrated in vacuum. The title compound (60 mg, 4.4% yield, Br—)—) was obtained as yellow oil. LCMS: (M+): 164.1 ^{1}H NMR (400 MHz, Methanol-d4) δ 4.67 (s, 1H), 4.61 (d, J=2.5 Hz, 2H), 4.55-4.42 (m, 2H), 4.03-3.91 (m, 1H), 3.91-3.81 (m, 1H), 3.83-3.72 (m, 2H), 3.54-3.47 (m, 2H), 2.59-2.45 (m, 1H), 2.25-2.17 (m, 1H).



Compound 201:
1,1-bis(prop-2-yn-1-yl)pyrazolidin-1-ium Bromide

[0861] Step 1:

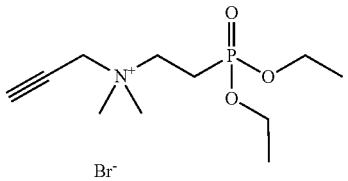
[0862] To a solution of tert-butyl pyrazolidine-1-carboxylate (2 g, 11.61 mmol, 1 eq) in THF (20 mL) was added K_2CO_3 (1.77 g, 12.77 mmol, 1.1 eq) and 3-bromoprop-1-yne (1.66 g, 13.94 mmol, 1.20 mL, 1.2 eq). The mixture was stirred at 25° C. for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10:1 to 1:1). Compound tert-butyl 2-prop-2-ynylpyrazolidine-1-carboxylate (1.8 g, 8.56 mmol, 73.71% yield) was obtained as a yellow solid. LCMS: (M-56): 155.1

[0863] Step 2:

[0864] To a solution of tert-butyl 2-prop-2-ynylpyrazolidine-1-carboxylate (50 mg, 237.79 umol, 1 eq) in THF (5 mL) was added 3-bromoprop-1-yne (113.15 mg, 951.15 umol, 81.99 uL, 4 eq) at 25° C. The mixture was stirred at 25° C. for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was washed with tetrahydrofuran (20 mL). Compound tert-butyl-2,2-bis (prop-2-ynyl)-1,2-diazolidine-1-carboxylate (50 mg, 151.87 umol, Br-salt, 63.87% yield) was obtained as a white solid. LCMS: (M+): 249.2

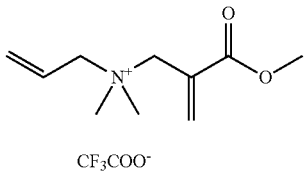
[0865] Step 3:

[0866] A solution of tert-butyl 2,2-bis(prop-2-ynyl)-1,2-diazolidine-1-carboxylate (50 mg, 151.87 umol, 1 eq) in TFA (0.5 mL) and DCM (5 mL) was stirred at 25° C. for 12 hr. LCMS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. Compound 1,1-bis(prop-2-ynyl)-1,2-diazolidine (22 mg, 96.02 umol, Br-salt, 63.23% yield, 100% purity) was obtained as a yellow oil. LCMS: (M+H+): 149.1 1H NMR (400 MHz, Deuterium Oxide) δ 4.50-4.36 (m, 4H), 3.84 (t, J=7.6 Hz, 2H), 3.31 (t, J=7.0 Hz, 2H), 3.10 (t, J=2.5 Hz, 2H), 2.36-2.24 (m, 2H).



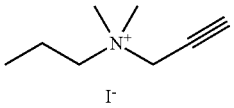
Compound 202: diethyl {2-[dimethyl(prop-2-yn-1-yl)azaniumyl]ethyl}phosphonate Bromide

[0867] A mixture of N,N-dimethylprop-2-yn-1-amine (0.5 g, 6.01 mmol, 637.76 uL, 1 eq) and 1-bromo-2-diethoxyphosphoryl-ethane (1.77 g, 7.22 mmol, 1.2 eq) in THF (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 25 at 25° C. for 10 hr under N_2 atmosphere. LC-MS showed N,N-dimethylprop-2-yn-1-amine was remained. Desired compound was detected by LCMS. Then crude product was added water added water (20 mL), and the aqueous phase is freeze-dried. The title compound (100 mg, 398.75 umol, 6.63% yield, 99% purity) was obtained as a white oil. LCMS (M+): 248.1. ^{1}H NMR (400 MHz, Methanol-d4) δ 4.40 (d, J=2.5 Hz, 2H), 4.24-4.11 (m, 4H), 3.75-3.64 (m, 2H), 3.62-3.56 (m, 1H), 3.21 (s, 6H), 2.53-2.39 (m, 2H), 1.36 (t, J=7.1 Hz, 6H).



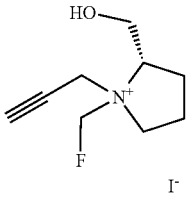
Compound 203: N-allyl-2-(methoxycarbonyl)-N,N-dimethylprop-2-en-1-aminium 2,2,2-trifluoroacetate

[0868] Methyl 2-(bromomethyl)acrylate (0.200 g, 1 Eq, 1.12 mmol) was dissolved in DCM (3 mL), followed by addition of N,N-dimethylprop-2-en-1-amine (95.1 mg, 132 μL, 1 Eq, 1.12 mmol). The reaction was stirred at 40° C. overnight, then concentrated by rotary evaporation. The reaction mixture was purified by reverse phase column chromatography on an C18AQ column (100% water with 0.1% TFA). Fractions containing product were lyophilized to yield N-allyl-2-(methoxycarbonyl)-N,N-dimethylprop-2-en-1-aminium 2,2,2-trifluoroacetate (150 mg, 45.2%) as a gel-like solid. LCMS M+: 184.3. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 6.90 (s, 1H), 6.34 (s, 1H), 6.09-5.91 (m, 1H), 5.74-5.55 (m, 2H), 4.16 (s, 2H), 3.86 (d, J=7.4 Hz, 2H), 3.76 (s, 3H), 2.91 (s, 6H).



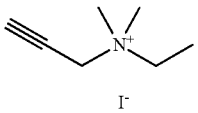
Compound 204:
dimethyl(prop-2-yn-1-yl)propylazanium Iodide

[0869] N,N-dimethylprop-2-yn-1-amine (500 mg, 6.01 mmol, 637.76 uL, 1 eq) and 1-iodopropane (2.04 g, 12.03 mmol, 1.18 mL, 2 eq) in THF (2 mL) was stirred at 25° C. for 10 h. LCMS showed the starting reactant consumed completely. The mixture was filtered and filter cake was washed by EtOAc (10 mL*3). The filter cake was concentrated. The title compound (250 mg, 4% yield, I—) was obtained as a white solid. LCMS: (M+): 126.2 1H NMR (400 MHz, Deuterium Oxide) δ 4.10 (s, 2H), 3.30-3.21 (m, 2H), 3.03 (s, 6H), 1.75-1.60 (m, 2H), 0.85 (t, J=7.3 Hz, 3H).



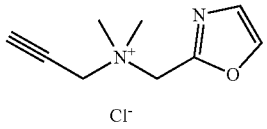
Compound 205: (2S)-1-(fluoromethyl)-2-(hydroxymethyl)-1-(prop-2-yn-1-yl)pyrrolidin-1-ium Iodide

[0870] To a mixture of [of [(2S)-1-prop-2-ynylpyrrolidin-2-yl]methanol (100 mg, 718.42 umol, 1 eq) in THF (3 mL) was added fluoro added fluoro(iodo)methane (574.48 mg, 3.59 mmol, 5 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 12 at 25° C. for 12 hours. LCMS showed one main peak with desired m/z was detected. The reaction mixture was diluted with H_2O (3 mL). The aqueous layer was washed with ethyl acetate (3 mL*4). Then the aqueous layer was lyophilized. Compound [(2S)-1-(fluoromethyl)-1-prop-2-ynyl-pyrrolidin-1-ium-2-yl] methanol (115 mg, 384.46 umol, 53.51% yield, I—) was obtained as white solid. LCMS: (M+): 172.1 1H NMR (400 MHz, Deuterium Oxide) δ 5.65-5.39 (m, 2H), 4.49-4.40 (m, 1H), 4.40-4.30 (m, 1H), 4.20-3.99 (m, 1H), 3.99-3.91 (m, 1H), 3.90-3.64 (m, 3H), 3.12 (t, J=2.6 Hz, 1H), 2.28-2.18 (m, 1H), 2.18-2.03 (m, 2H), 2.06-1.87 (m, 1H).



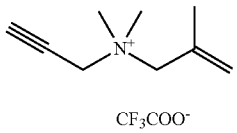
Compound 206:
ethyldimethyl(prop-2-yn-1-yl)azanium Iodide

[0871] A mixture of N,N-dimethylprop-2-yn-1-amine (500 mg, 6.01 mmol, 637.76 uL, 1 eq) and iodoethane (1.88 g, 12.03 mmol, 962.11 uL, 2 eq) in THF (2 mL) was stirred at 25° C. for 10 h. TLC showed Reactant was consumed completely. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was diluted with water (30 mL) and extracted with EtOAc (10 mL*3). The water layer was concentrated by lyophilization. The title compound (200 mg, 794.66 umol, 13.21% yield, 95% purity, I—) was obtained as a yellow solid. LCMS: (M+): 112.1 1H NMR (400 MHz, Deuterium Oxide) δ 4.09 (s, 2H), 3.39 (q, J=7.3 Hz, 2H), 3.03-2.99 (m, 6H), 1.25 (t, J=7.4 Hz, 3H).



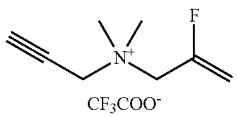
Compound 207: dimethyl[(1,3-oxazol-2-yl)methyl](prop-2-yn-1-yl)azanium Chloride

[0872] A mixture of N,N-dimethylprop-2-yn-1-amine (100 mg, 1.20 mmol, 127.55 uL, 1 eq) and 2-(chloromethyl) oxazole (141.38 mg, 1.20 mmol, 1 eq) in THF (2 mL) was stirred at 25° C. for 10 h. LCMS showed the starting reactant was consumed completely. The reaction mixture was concentrated. The residue was dissolved with H_2O (10 mL) and extracted with EtOAc (10 mL*3), Water phase was freeze-dried. The title compound (95 mg, crude, Cl—) was obtained as yellow solid. LCMS: (M+): 165.1 1H NMR (400 MHz, Deuterium Oxide) δ 7.95 (d, J=0.9 Hz, 1H), 7.25 (d, J=0.9 Hz, 1H), 4.74 (s, 2H), 4.22 (d, J=2.5 Hz, 2H), 3.28-3.17 (m, 1H), 3.15 (s, 6H).



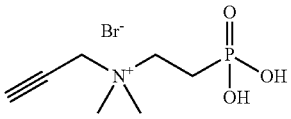
Compound 208: N,N,2-trimethyl-N-(prop-2-yn-1-yl) prop-2-en-1-aminium 2,2,2-trifluoroacetate

[0873] N,N-dimethylprop-2-yn-1-amine (116 mg, 0.150 mL, 1 Eq, 1.39 mmol) and 3-bromo-2-methylprop-1-ene (188 mg, 1 Eq, 1.39 mmol) were added to a vial with DCM (2 mL), and the reaction was stirred at 40 C overnight. The mixture was concentrated and re-dissolved in water before purification by reverse phase column chromatography on a C18AQ column (100% water with 0.1% TFA). Fractions containing product were lyophilized to yield N,N,2-trimethyl-N-(prop-2-yn-1-yl)prop-2-en-1-aminium 2,2,2-trifluoroacetate (0.0290 g, 8.29%) as a clear viscous oil. LCMS M+: 138.2 1H NMR (400 MHz, Deuterium Oxide) δ 5.52 (s, 1H), 5.35 (s, 1H), 4.14 (d, J=2.6 Hz, 2H), 3.91 (s, 2H), 3.20 (t, J=2.6 Hz, 1H), 3.09 (s, 6H), 1.90 (s, 3H).



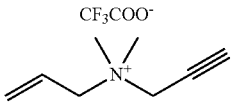
Compound 209: 2-fluoro-N,N-dimethyl-N-(prop-2-yn-1-yl)prop-2-en-1-aminium 2,2,2-trifluoroacetate

[0874] N,N-dimethylprop-2-yn-1-amine (116 mg, 0.150 mL, 1 Eq, 1.39 mmol) and 3-bromo-2-fluoroprop-1-ene (194 mg, 1 Eq, 1.39 mmol) were added to a vial with DCM (2 mL), and the reaction was stirred at 40° C. overnight. The mixture was concentrated and re-dissolved in water before purification by reverse phase column chromatography on an C18AQ column (100% water with 0.1% TFA). Fractions containing product were lyophilized to yield 2-fluoro-N,N-dimethyl-N-(prop-2-yn-1-yl)prop-2-en-1-aminium 2,2,2-trifluoroacetate (262 mg, 73.7%) as a clear viscous oil. LCMS M+: 142.2. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 5.31 (dd, J=15.8, 4.0 Hz, 1H), 5.12 (dd, J=47.9, 3.9 Hz, 1H), 4.31-4.17 m 4H 3.24 (t, J=2.6 Hz, 1H), 3.17 (s, 6H).



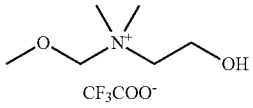
Compound 210: {2-[dimethyl(prop-2-yn-1-yl)azaniumyl]ethyl}phosphonic Acid

[0875] A mixture/n of 3-[N-(2-diethoxyphosphorylethyl)-dimethyl-azanyl]prop-1-yne (300 mg, 914.13 umn/ol, 1 eq) in aq. HCl (20 mL, 12 N) was stirred at 100° C. for 15 hr. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100*30 mm*5 um; mobile phase: [water (0.10% TFA)-ACN]; B %: 1%-1%, 12 min). Compound 2-(N,N-dimethyl-prop-2-ynyl-azanyl)ethylphosphonic acid (44 mg, 161.72 umol, Br-salt, 17.69% yield, 100% purity) was obtained as a white solid. LCMS: (M+): 192.1. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 4.12 (d, J=2.6 Hz, 2H), 3.54-3.44 (m, 2H), 3.12 (t, J=2.5 Hz, 1H), 3.04 (s, 6H), 2.05-1.91 (m, 2H).



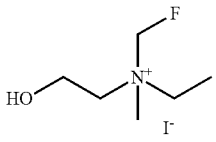
Compound 211: N,N-dimethyl-N-(prop-2-yn-1-yl) prop-2-en-1-aminium 2,2,2-trifluoroacetate

[0876] Compound 3-bromoprop-1-yne (200 mg, 0.150 mL, 1 Eq, 1.68 mmol) and N,N-dimethylprop-2-en-1-amine (143 mg, 199 μL, 1 Eq, 1.68 mmol) were added to a vial with DCM (2 mL), and the reaction was stirred at 40 C overnight. The mixture was concentrated and re-dissolved in water before purification by reverse phase column chromatography on a C18AQ column (100% water with 0.1% TFA). Fractions containing product were lyophilized to yield N,N-dimethyl-N-(prop-2-yn-1-yl)prop-2-en-1-aminium 2,2,2-trifluoroacetate (260 mg, 65.1%) as a clear viscous oil. LCMS M+: 124.2. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 6.03-5.88 (m, 1H), 5.75-5.61 (m, 2H), 4.12 (d, J=2.4 Hz, 2H), 3.95 (d, J=7.4 Hz, 2H), 3.21-3.14 (m, 1H), 3.07 (s, 6H).



Compound 212: (2-hydroxyethyl)(methoxymethyl)dimethylazanium trifluoroacetate

[0877] To a solution of 2-(dimethylamino)ethanol (500 mg, 5.61 mmol, 563.06 uL, 1 eq) in DCM (5 mL) was added MOMCl (677.45 mg, 8.41 mmol, 639.10 uL, 1.5 eq) at 0° C. The mixture was stirred at 25° C. for 5 h. LCMS showed Reactant was consumed completely. The mixture was quenched with water (10 mL) then extracted with EtOAc (10 mL*3). The aqueous phase was concentrated by lyophilization. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100*30 mm*5 um; mobile phase: [water (0.10% TFA)-ACN]. The title compound (135 mg, 905.39 umol, 16.14% yield, 90% purity, TFA salt) was obtained as yellow oil. LCMS: (M): 134.1 1H NMR (400 MHz, Deuterium Oxide) δ 4.50 (s, 2H), 3.91-3.82 (m, 2H), 3.52 (s, 3H), 3.35-3.28 (m, 2H), 2.94 (s, 6H).



Compound 213: ethyl(fluoromethyl)(2-hydroxyethyl)(methyl)azanium Iodide

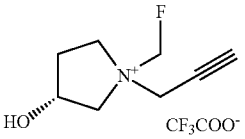
[0878] Step 1:

[0879] To a solution of 2-bromoethanol (1 g, 8.00 mmol, 568.18 uL, 1 eq) in THF (10 mL) was added K_2CO_3 (1.22 g, 8.80 mmol, 1.1 eq) and N-methylethanamine (520.31 mg, 8.80 mmol, 756.27 uL, 1.1 eq). The mixture was stirred at 25° C. for 12 hr. LCMS showed the desired compound was detected. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=0:1 to Ethyl acetate:Methanol=1:1). Compound 2-[ethyl(methyl)amino]ethanol (120 mg, 1.14 mmol, 14.25% yield, 98% purity) was obtained as a yellow oil. LCMS: (M+H+): 104.1

[0880] Step 2:

[0881] To a solution of 2-[ethyl(methyl)amino]ethanol (100 mg, 969.35 umol, 1 eq) in THF (5 mL) was added fluoro(iodo)methane (775.13 mg, 4.85 mmol, 5 eq). The mixture was stirred at 25° C. for 12 hr. LCMS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O (50 mL) and extracted with ethyl acetate (50 mL*3). The aqueous phase is freeze-dried. Compound 2-[N-ethyl-N-(fluoromethyl)-methyl-azanyl] ethanol (60 mg, 221.85 umol, 23.53% yield, I-salt, 97.28% purity) was obtained as a yellow solid. LCMS: (M+): 136.1

1H NMR (400 MHz, Deuterium Oxide) δ 5.46 (s, 1H), 5.35 (s, 1H), 4.01-3.95 (m, 2H), 3.61-3.46 (m, 4H), 3.10 (d, J=2.2 Hz, 3H), 1.37-1.22 (m, 3H).



Compound 214: (3R)-1-(fluoromethyl)-3-hydroxy-1-(prop-2-yn-1-yl)pyrrolidin-1-ium

[0882] Fluoro(iodo)methane (1.28 g, 7.99 mmol, 5 eq) and (3R)-1-prop-2-ynylpyrrolidin-3-ol (200 mg, 1.60 mmol, 1 eq) in DCM (2 mL) was stirred at 25° C. for 12 h. LCMS showed the starting reactant was consumed completely. The reaction mixture was concentrated. The residue was dissolved by water (30 mL) and extracted with ethyl acetate (10 mL*3). Water phase was concentrated by lyophilization. The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. Compound (3R)-1-(fluoromethyl)-1-prop-2-ynyl-pyrrolidin-1-ium-3-ol (80 mg, 252.55 umol, 15.81% yield, 90% purity, CF3CO2-) was obtained as yellow oil. LCMS: (M+): 158. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 5.56-5.48 (m, 1H), 5.46-5.37 (m, 1H), 4.30 (d, J=1.2 Hz, 2H), 3.87-3.74 (m, 3H), 3.78-3.61 (m, 3H), 2.45-2.26 (m, 1H), 2.15-2.10 (m, 1H).

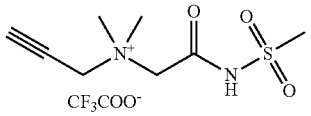
Compound 215: [2-(methanesulfonylcarbamoyl) ethyl]dimethyl(prop-2-yn-1-yl)azanium

[0883] Step 1:

[0884] To a solution of 3-bromopropanoyl chloride (5 g, 29.17 mmol, 2.94 mL, 1 eq) in toluene (50 mL) was added methanesulfonamide (1.14 g, 11.98 mmol, 4.11e-1 eq). The mixture was stirred at 110° C. for 5 hr. LCMS showed 3-bromopropanoyl chloride was consumed completely and desired m/z was detected. The reaction mixture was cooled to 0-5° C. with ice, and the resulting solid was filtered. The filter cake was washed with cold toluene. Compound 3-bromo-N-methylsulfonyl-propanamide (2.8 g, crude) was obtained as white solid and used into the next step without further purification. LCMS: (M+H)+: 230.1

[0885] Step 2:

[0886] To a solution of 3-bromo-N-methylsulfonyl-propanamide (500 mg, 2.17 mmol, 1.2 eq) in ACN (5 mL) was added N,N-dimethylprop-2-yn-1-amine (150.55 mg, 1.81 mmol, 192.03 uL, 1 eq). The mixture was stirred at 25 at 25° C. for 5 hr. LCMS showed N,N-dimethylprop-2-yn-1-amine was consumed completely and desired m/z was detected. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. The title compound (93 mg, 575.82 umol, 31.80% yield, TFA) was obtained as a white solid. Mass: (M+): 233.2 1H NMR (400 MHz, Methanol-d4) δ 4.37 (d, J=2.6 Hz, 2H), 3.80 (t, J=7.3 Hz, 2H), 3.61 (t, J=2.6 Hz, 1H), 3.25 (s, 3H), 3.19 (s, 6H), 2.99-2.90 (m, 2H).



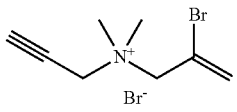
Compound 216: [(methanesulfonylcarbamoyl) methyl]dimethyl(prop-2-yn-1-yl)azanium

[0887] Step 1:

[0888] To a solution of methanesulfonamide (2 g, 21.03 mmol, 1 eq) in EtOAc (30 mL) was added 2-bromoacetyl bromide (4.24 g, 21.01 mmol, 1.83 mL, 1 eq). The mixture was stirred at 65° C. for 5 hr. LCMS showed methanesulfonamide was consumed completely and desired m/z was detected. The reaction was cooled, and a large amount of white solid precipitated. The mixture was filtered and the filter cake was concentrated under reduced pressure to give a residue. Compound 2-bromo-N-methylsulfonyl-acetamide (1.7 g, crude) was obtained as white solid and used in the next step without further purification. LCMS: (M+H)+: 216.0

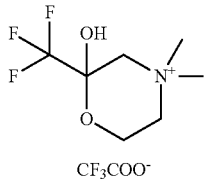
[0889] Step 2:

[0890] To a solution of N,N-dimethylprop-2-yn-1-amine (160.32 mg, 1.93 mmol, 204.49 uL, 1 eq) in THF (4 mL) was added 2-bromo-N-methylsulfonyl-acetamide (500 mg, 2.31 mmol, 1.2 eq). The mixture was stirred at 25° C. for 5 hr. LCMS showed N,N-dimethylprop-2-yn-1-amine was consumed completely and one main peak with desired m/z was detected. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC [water (0.1% TFA)-ACN].[2-(methanesulfonamido)-2-oxo-ethyl]-dimethyl-prop-2-ynyl-ammonium (68 mg, 227.28 umol, 11.79% yield, 100% purity, TFA salt) was obtained as white solid. LCMS: (M+): 219.1 1H NMR (400 MHz, Methanol-d4) δ 4.61 (d, J=2.6 Hz, 2H), 4.31 (s, 2H), 3.64 (t, J=2.6 Hz, 1H), 3.41 (s, 6H), 3.26 (s, 3H).



Compound 217: (2-bromoprop-2-en-1-yl)dimethyl (prop-2-yn-1-yl)azanium

[0891] To a solution of N,N-dimethylprop-2-yn-1-amine (200 mg, 2.41 mmol, 255.10 uL, 1 eq) in THF (4 mL) was added 2 added 2,3-dibromoprop-1-ene (528.94 mg, 2.65 mmol, 258.02 uL, 1.1 eq). The mixture was stirred at 25 at 25° C. for 5 hr. LCMS showed N,N-dimethylprop-2-yn-1-amine was consumed completely and one main peak with desired m/z was detected. The mixture was filtered and the filter cake was concentrated under reduced pressure to give a residue. The title compound (90 mg, 318.02 umol, 13.22% yield, 100% purity, Br—) was obtained as a yellow solid. LCMS: (M+): 202.0 1H NMR (400 MHz, Deuterium Oxide) δ 6.38 (d, J=2.5 Hz, 1H), 6.28 (d, J=2.6 Hz, 1H), 4.40 (s, 2H), 4.31 (d, J=2.1 Hz, 2H), 3.27 (t, J=2.5 Hz, 1H), 3.23 (s, 6H).



Compound 218: 2-hydroxy-4,4-dimethyl-2-(trifluoromethyl)morpholin-4-ium trifluoroacetate

[0892] Step 1:

[0893] To a mixture of 2-(dimethylamino)ethanol (1 g, 11.22 mmol, 1.13 mL, 1 eq) in THF (10 mL) was added DMAP (137.06 mg, 1.12 mmol, 0.1 eq) and Boc2O (2.69 g, 12.34 mmol, 2.84 mL, 1.1 eq) in one portion at 25 at 25° C. under N_2. The mixture was heated to 50° C. and stirred for 12 hours. TLC indicated 2-(dimethylamino) ethanol was consumed and one new spot formed. LCMS showed one main peak with desired m/z was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 0/1). Desired compound tert-butyl 2-(dimethylamino)ethyl carbonate (850 mg, 4.49 mmol, 40.03% yield) was obtained as colorless oil.

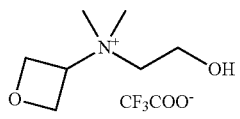
[0894] Step 2:

[0895] To a mixture of tert-butyl 2-(dimethylamino)ethyl carbonate (850 mg, 4.49 mmol, 1 eq) in THF (8 mL) was added 3 added 3-bromo-1,1,1-trifluoro-propan-2-one (1.72 g, 8.98 mmol, 932.19 uL, 2 eq) in one portion at 0° C. under N_2. The mixture was stirred at 25° C. for 10 hours. LCMS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was diluted with H_2O (3 mL). The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. Compound 2-tert-butoxycarbonyloxyethyl-dimethyl-(3,3,3-trifluoro-2-oxo-propyl)ammonium (50 mg, 166.50 umol, 3.71% yield) was obtained as a white solid.

[0896] Step 3:

[0897] 2-tert-butoxycarbonyloxyethyl-dimethyl-(3,3,3-trifluoro-2-oxo-propyl)ammonium (0.05 g, 166.50 umol, 1 eq) in DCM (3 mL) and TFA (1 mL) was stirred at 25° C. for 3 hours. LCMS showed LCMS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC[water (0.1% TFA)-ACN]. The title compound (0.029 g, 92.30 umol, 55.43% yield, TFA) was obtained as white solid.

[0898] MS: (M+): 200.1 1H NMR (400 MHz, Deuterium Oxide) δ 4.48-4.36 (m, 1H), 4.10 (d, J=14.1 Hz, 1H), 3.69 (d, J=13.4 Hz, 1H), 3.65-3.51 (m, 3H), 3.41 (s, 3H), 3.23 (s, 3H).



Compound 219: N-(2-hydroxyethyl)-N,N-dimethyloxetan-3-aminium trifluoroacetate

[0899] Step 1:

[0900] To a mixture of 2-(methylamino)ethanol (1 g, 13.31 mmol, 1.07 mL, 1 eq) in DCM in DCM (5 mL) was added TBDPSCl (4.03 g, 14.65 mmol, 3.76 mL, 1.1 eq), TEA (1.48 g, 14.65 mmol, 2.04 mL, 1.1 eq) and DMAP (813.26 mg, 6.66 mmol, 0.5 eq) in one portion at 25° C. under N_2, then heated to 40° C. and stirred for 12 hours. LCMS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=30/1 to 1/1). ^{1}HNMR indicated the desired compound 2-[tert-butyl(diphenyl)silyl]oxy-N-methyl-ethanamine (1.2 g, crude) was obtained as colorless oil.

[0901] Step 2:

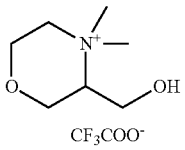
[0902] To a mixture of 2-[tert-butyl(diphenyl)silyl]oxy-N-methyl-ethanamine (1 g, 3.19 mmol, 1 eq) in DCE (10 mL) was added AcOH added AcOH (1.92 g, 31.90 mmol, 1.82 mL, 10 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 0.5h, then oxetan-3-one (459.72 mg, 6.38 mmol, 2 eq) and $NaBH(OAc)_3$ (1.35 g, 6.38 mmol, 2 eq) were added, and the mixture stirred for 11.5 hours. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1). The crude product N-[2-[tert-butyl(diphenyl)silyl]oxyethyl]-N-methyl-oxetan-3-amine (0.72 g, crude) as white solid.

[0903] Step 3:

[0904] To a mixture of N-[2-[tert-butyl(diphenyl)silyl]oxyethyl]-N-methyl-oxetan-3-amine (0.72 g, 1.95 mmol, 1 eq) in THF (5 mL) was added MeI (1.66 g, 11.69 mmol, 727.70 uL, 6 eq) in one portion at 25° C. under N_2. The mixture was stirred at 70° C. for 12 hours. LCMS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 1/1). The crude product 2-[tert-butyl(diphenyl)silyl]oxyethyl-dimethyl-(oxetan-3-yl)ammonium iodide (0.67 g, crude, I) was obtained as yellow solid.

[0905] Step 4:

[0906] To a mixture of 2-[tert-butyl(diphenyl)silyl]oxyethyl-dimethyl-(oxetan-3-yl)ammonium (300 mg, 586.50 umol, 1 eq, I) in THF (3 mL) was added pyridine hydrofluoride (174.38 mg, 1.76 mmol, 158.52 uL, 3 eq) in one portion at 5° C. under N_2. The mixture was stirred at 25° C. for 12 hours. LCMS showed desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.10% TFA)-ACN]. The title compound (38 mg, 146.02 umol, 24.90% yield, TFA) as obtained as white gum. LCMS: (M+): 146.1 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 4.93-4.85 (m, 2H), 4.89-4.70 (m, 3H), 3.86 (dq, J=5.2, 2.6 Hz, 2H), 3.42-3.35 (m, 2H), 3.12 (s, 6H).



Compound 220:
3-(hydroxymethyl)-4,4-dimethylmorpholin-4-ium

[0907] Step 1:

[0908] To a mixture of 2-(methylamino)ethanol (1 g, 13.31 mmol, 1.07 mL, 1 eq) in DCM (5 mL) was added TBDPSCI added TBDPSCl (4.03 g, 14.65 mmol, 3.76 mL, 1.1 eq), TEA (1.48 g, 14.65 mmol, 2.04 mL, 1.1 eq) and DMAP (813.26 mg, 6.66 mmol, 0.5 eq) in one portion at 25° C. under N2, then heated to 40° C. and stirred for 12 hours. LCMS showed LCMS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=30/1 to 1/1). 1HNMR indicated the desired compound 2-[tert-butyl(diphenyl)silyl]oxy-N-methyl-ethanamine (1.2 g, crude) was obtained as colorless oil.

[0909] Step 2:

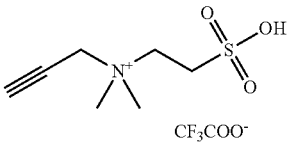
[0910] To a mixture of 2-[tert-butyl(diphenyl)silyl]oxy-N-methyl-ethanamine (1 g, 3.19 mmol, 1 eq) in DCE (10 mL) was added AcOH added AcOH (1.92 g, 31.90 mmol, 1.82 mL, 10 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 0.5h, then oxetan-3-one (459.72 mg, 6.38 mmol, 2 eq) and $NaBH(OAc)_3$ (1.35 g, 6.38 mmol, 2 eq) were added, and the mixture stirred for 11.5 hours. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1). The crude product N-[2-[tert-butyl(diphenyl)silyl]oxy-ethyl]-N-methyl-oxetan-3-amine (0.72 g, crude) as white solid.

[0911] Step 3:

[0912] To a mixture of N-[2-[tert-butyl(diphenyl)silyl] oxyethyl]-N-methyl-oxetan-3-amine (0.72 g, 1.95 mmol, 1 eq) in THF (5 mL) was added MeI added MeI (1.66 g, 11.69 mmol, 727.70 uL, 6 eq) in one portion at 25° C. under N_2. The mixture was stirred at 70° C. for 12 hours. LCMS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 1/1). The crude product 2-[tert-butyl(diphenyl)silyl]oxyethyl-dimethyl-(oxetan-3-yl)ammonium (0.67 g, crude, I) was obtained as yellow solid.

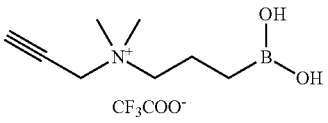
[0913] Step 4:

[0914] 2-[tert-butyl(diphenyl)silyl]oxyethyl-dimethyl-(oxetan-3-yl)ammonium (0.2 g, 520.01 umol, 1 eq) and KF (151.06 mg, 2.60 mmol, 60.91 uL, 5 eq) in THF (5 mL) was stirred at 25 at 25° C. for 12 hours. LC-MS showed desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. The title compound (54 mg, 207.51 umol, 39.90% yield, TFA) was obtained as colorless oil. MS: (M+): 146.1 1H NMR (400 MHz, Deuterium Oxide) δ 3.99-3.77 (m, 6H), 3.57-3.43 (m, 2H), 3.42-3.33 (m, 1H), 3.19 (s, 3H), 3.08 (s, 3H).



Compound 221:
dimethyl(prop-2-yn-1-yl)(2-sulfoethyl)azanium Trifluoroacetate

[0915] To a solution of 2-(methylamino)ethanesulfonic acid (100 mg, 718.53 umol, 1 eq) in H_2O (3 mL) and EtOH (3 mL) was added $NaCO_3$ (178.91 mg, 2.16 mmol, 3 eq) and 3-bromoprop-1-yne (85.48 mg, 718.53 umol, 61.94 uL, 1 eq). The mixture was stirred at 25° C. for 12 hr. The mixture was added MeI (305.96 mg, 2.16 mmol, 134.19 uL, 3 eq) at 25° C. The mixture was stirred at 25° C. for 12 hr. LCMS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. Compound 2-[dimethyl(prop-2-ynyl) ammonio]ethanesulfonate (72 mg, 376.48 umol, 52.4% yield) was obtained as white solid. LCMS: (M+H)+: 192.1. ^1H NMR (400 MHz, Deuterium Oxide) δ 4.27-4.22 (m, 2H), 3.81-3.72 (m, 2H), 3.43-3.34 (m, 2H), 3.27-3.21 (m, 1H), 3.17 (s, 6H).



Compound 222: {3-[dimethyl(prop-2-yn-1-yl)azani-umyl]propyl}boronic Acid

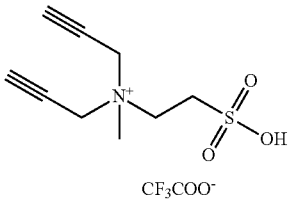
[0916] Step 1:

[0917] To 3-bromoprop-1-ene (500 mg, 4.13 mmol, 1 eq) was added 1,3,2-benzodioxaborole (495.61 mg, 4.13 mmol, 517.34 uL, 1 eq). The mixture was stirred at 100° C. for 4 hr. LCMS showed 3-bromoprop-1-ene was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure. Compound 2-(3-bromopropyl)-1,3,2-benzodioxaborole (~1 g, crude) as a yellow oil was obtained and the crude product was used in the next step without further purification.

[0918] Step 2:

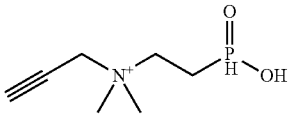
[0919] To a solution of 2-(3-bromopropyl)-1,3,2-benzodi-oxaborole (1 g, 4.15 mmol, 1 eq) in THF (3 mL) was added N added N,N-dimethylprop-2-yn-1-amine (345.10 mg, 4.15 mmol, 440.18 uL, 1 eq). The mixture was stirred at 25° C. for 12 hr. LCMS showed 2-(3-bromopropyl)-1,3,2-benzodi-oxaborole was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC [water (0.10% TFA)-ACN]. The title compound (40 mg, 139.41 umol, 3.36% yield, 99% purity, TFA) was obtained as white solid. LCMS: (M+): 170.0 1H NMR (400 MHz,

Deuterium Oxide) δ 4.14 (d, J=2.6 Hz, 2H), 3.35-3.27 (m, 2H), 3.16 (t, J=2.5 Hz, 1H), 3.08 (s, 6H), 1.84-1.71 (m, 2H), 0.74 (t, J=8.0 Hz, 2H).



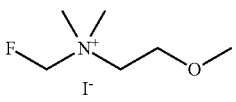
Compound 223: methylbis(prop-2-yn-1-yl)(2-sulfoethyl)azanium

[0920] To a solution of 2-(methylamino)ethanesulfonic acid (100 mg, 718.53 umol, 1 eq) in DMF (5 mL) was added NaH (57.48 mg, 1.44 mmol, 60% purity, 2 eq) at 0° C. The mixture was stirred at 0° C. for 0.5 hr. Then 3-bromoprop-1-yne (94.02 mg, 790.38 umol, 68.13 uL, 1.1 eq) in DMF (1 mL) was added slowly via syringe at 0° C. The mixture was stirred at 25° C. for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was quenched by addition of H_2O (1 mL) at 0° C. and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. The title compound (13 mg, 43.89 umol, 6.11% yield, 100% purity) was obtained as a white solid. LCMS: (M+): 216.0 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 4.38 (d, J=2.5 Hz, 4H), 3.92-3.84 (m, 2H), 3.45-3.37 (m, 2H), 3.29 (t, J=2.5 Hz, 2H), 3.24 (s, 3H).



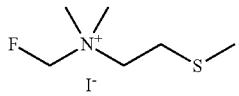
Compound 227: {2-[dimethyl(prop-2-yn-1-yl)azaniumyl]ethyl}phosphinic Acid

[0921] This compound may be synthesized according to the experimental procedure described for Compound 226.



Compound 228: (fluoromethyl)(2-methoxyethyl)dimethylazanium Iodide

[0922] 2-methoxy-N,N-dimethyl-ethanamine (50 mg, 484.67 umol, 1 eq) and fluoro(iodo)methane (232.54 mg, 1.45 mmol, 3 eq) in THF (3 mL) was stirred at 25 was stirred at 25° C. for 12 hours. The reaction mixture was filtered and the filter cake was concentrated under reduced pressure to give a residue. The title compound (71 mg, 269.87 umol, 55.68% yield, I) was obtained as white solid. MS: (M+): 136.2 1H NMR (400 MHz, Deuterium Oxide) δ 5.40 (s, 1H), 5.29 (s, 1H), 3.90-3.81 (m, 2H), 3.67-3.60 (m, 2H), 3.35 (s, 3H), 3.17 (s, 6H).



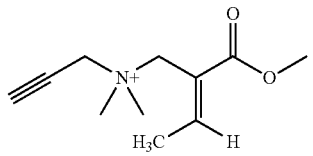
Compound 229: (fluoromethyl)dimethyl[2-(methylsulfanyl)ethyl]azanium

[0923] Step 1:

[0924] To a mixture of 1-chloro-2-methylsulfanyl-ethane (500 mg, 4.52 mmol, 446.43 uL, 1 eq) in THF (5 mL) was added NaI (1.36 g, 9.04 mmol, 2 eq) and N-methylmethanamine (2 M, 6.78 mL, 3 eq) in one portion at 25° C. under N_2. The mixture was heated to 50° C. and stirred for 12 hours. LCMS showed one main peak with desired mass was detected. The crude product N,N-dimethyl-2-methylsulfanyl-ethanamine (500 mg, crude) was obtained as colorless oil and used into the next step without further purification. LCMS: (M+H+): 120.1

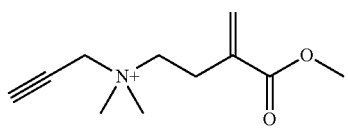
[0925] Step 2:

[0926] To a mixture of N,N-dimethyl-2-methylsulfanyl-ethanamine (200 mg, 1.68 mmol, 1 eq) in THF (5 mL) was added NaI added NaI (502.88 mg, 3.35 mmol, 2 eq) and fluoro(iodo)methane (804.82 mg, 5.03 mmol, 3 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 12 hours. LCMS showed N,N-dimethyl-2-methylsulfanyl-ethanamine was consumed incompletely and one new peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.10% TFA)-ACN]. The title compound (62 mg, 222.10 umol, 13.24% yield, I—)—) was obtained as yellow oil. LCMS: (M+): 152.1 1H NMR (400 MHz, Deuterium Oxide) δ 5.27 (s, 1H), 5.16 (s, 1H), 3.54-3.45 (m, 2H), 3.02 (d, J=2.0 Hz, 6H), 2.83-2.70 (m, 2H), 1.99 (d, J=1.0 Hz, 3H).



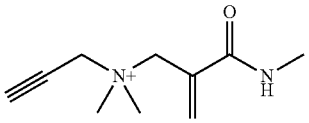
Compound 230: [(2E)-2-ethylidene-3-methoxy-3-oxopropyl]dimethyl(prop-2-yn-1-yl)azanium

[0927] This compound may be synthesized according to the experimental procedure described for Compound 52.



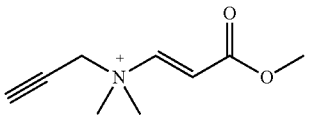
Compound 231: (4-methoxy-3-methylidene-4-oxobutyl)dimethyl(prop-2-yn-1-yl)azanium

[0928] This compound may be synthesized according to the experimental procedure described for Compound 52.



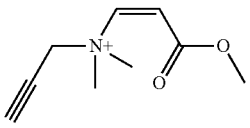
Compound 236: dimethyl[2-(methylcarbamoyl)-2-methylideneethyl](prop-2-yn-1-yl)azanium

[0929] This compound may be synthesized by reacting Compound 88 with methylamine, followed by concentration in vacuo and purification by recrystallization.



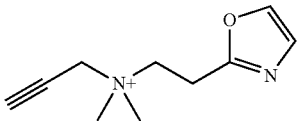
Compound 237: [(1E)-3-methoxy-3-oxoprop-1-en-1-yl]dimethyl(prop-2-yn-1-yl)azanium

[0930] This compound may be synthesized according to the experimental procedure described for Compound 52.



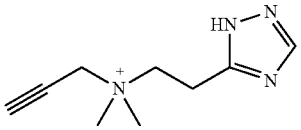
Compound 238: [(1Z)-3-methoxy-3-oxoprop-1-en-1-yl]dimethyl(prop-2-yn-1-yl)azanium

[0931] This compound may be synthesized according to the experimental procedure described for Compound 52.



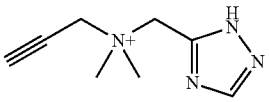
Compound 240: dimethyl[2-(1,3-oxazol-2-yl)ethyl](prop-2-yn-1-yl)azanium

[0932] This compound may be synthesized according to the experimental procedure described for Compound 239.



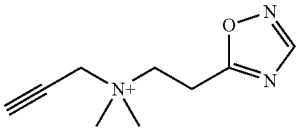
Compound 241: dimethyl(prop-2-yn-1-yl)[2-(1H-1,2,4-triazol-5-yl)ethyl]azanium

[0933] This compound may be synthesized according to the experimental procedure described for Compound 239.



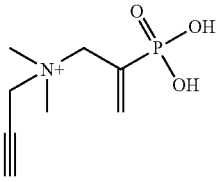
Compound 242: dimethyl(prop-2-yn-1-yl)[(1H-1,2,4-triazol-5-yl)methyl]azanium

[0934] This compound may be synthesized according to the experimental procedure described for Compound 239.



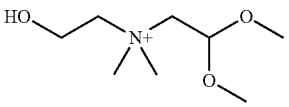
Compound 243: dimethyl[2-(1,2,4-oxadiazol-5-yl)ethyl](prop-2-yn-1-yl)azanium

[0935] This compound may be synthesized according to the experimental procedure described for Compound 239.



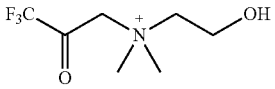
Compound 246: {3-[dimethyl(prop-2-yn-1-yl)azaniumyl]prop-1-en-2-yl}phosphonic Acid

[0936] This compound may be synthesized according to the experimental procedure described for Compound 245, followed by hydrolysis of the phosphate esters with NaOH in water and purification by recrystallization.



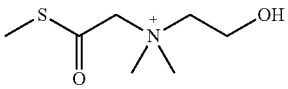
Compound 248: (2,2-dimethoxyethyl)(2-hydroxyethyl)dimethylazanium

[0937] This compound may be synthesized according to the experimental procedure described for Compound 247.



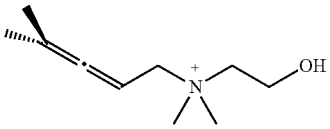
Compound 249: (2-hydroxyethyl)dimethyl(3,3,3-trifluoro-2-oxopropyl)azanium

[0938] This compound may be synthesized according to the experimental procedure described for Compound 247.



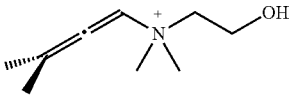
Compound 250: (2-hydroxyethyl)dimethyl[2-(methylsulfanyl)-2-oxoethyl]azanium

[0939] This compound may be synthesized according to the experimental procedure described for Compound 247.



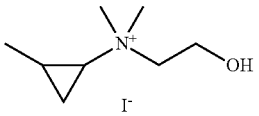
Compound 253: (2-hydroxyethyl)dimethyl(4-methylpenta-2,3-dien-1-yl)azanium

[0940] This compound may be synthesized according to the experimental procedure described for Compound 60.



Compound 254: (2-hydroxyethyl)dimethyl(3-methylbuta-1,2-dien-1-yl)azanium

[0941] This compound may be synthesized according to the experimental procedure described for Compound 60.



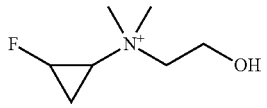
Compound 255: N-(2-hydroxyethyl)-N,N,2-trimethylcyclopropan-1-aminium

[0942] Step 1:

[0943] To a mixture of 2-methylcyclopropanamine (0.2 g, 1.86 mmol, 1 eq, HCl) in HCO2H (3 mL) was added HCHO (1.51 g, 18.59 mmol, 1.38 mL, 37% purity, 10 eq) in one portion at 25° C. under N_2. The mixture was stirred at 90° C. for 12 hours. LCMS showed desired m/z was detected. The reaction mixture was concentrated under reduced pressure to remove HCHO and HCO2H. The residue was diluted with H_2O (3 mL). The residue was purified by prep-HPLC [water (0.10% TFA)-ACN]. Compound N,2-trimethylcyclopropanamine (0.176 g, 825.53 umol, 44.41% yield, TFA) was obtained as colorless oil.

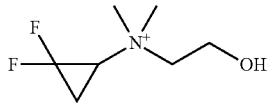
[0944] Step 2:

[0945] To a mixture of N,N,2-trimethylcyclopropanamine (0.1 g, 1.01 mmol, 1 eq) and 2-bromoethanol (252.01 mg, 2.02 mmol, 143.19 uL, 2 eq) in THF (3 mL) was added Na_2CO_3 (213.74 mg, 2.02 mmol, 2 eq) and NaI (151.14 mg, 1.01 mmol, 1 eq) in one portion at 25° C. under N_2. The mixture was stirred at 70° C. for 12 hours. LCMS showed desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]). The title compound (72 mg, 265.55 umol, 26.34% yield, I) was obtained as colorless oil. MS: (M+): 144.2. ^1H NMR (400 MHz, Deuterium Oxide) δ 4.07-3.99 (m, 2H), 3.58-3.45 (m, 2H), 2.95 (d, J=6.4 Hz, 6H), 2.88-2.81 (m, 1H), 1.59-1.51 (m, 1H), 1.34-1.24 (m, 1H), 1.05 (d, J=6.1 Hz, 3H), 0.72 (q, J=7.3 Hz, 1H).



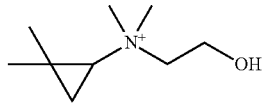
Compound 256: 2-fluoro-N-(2-hydroxyethyl)-N,N-dimethylcyclopropan-1-aminium

[0946] This compound may be synthesized according to the experimental procedure described for Compound 255.



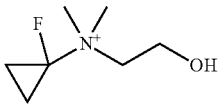
Compound 257: 2,2-difluoro-N-(2-hydroxyethyl)-N,N-dimethylcyclopropan-1-aminium

[0947] This compound may be synthesized according to the experimental procedure described for Compound 255.



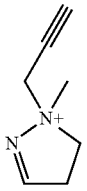
Compound 258: N-(2-hydroxyethyl)-N,N,2,2-tetramethylcyclopropan-1-aminium

[0948] This compound may be synthesized according to the experimental procedure described for Compound 255.



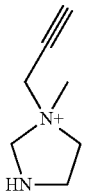
Compound 259: 1-fluoro-N-(2-hydroxyethyl)-N,N-dimethylcyclopropan-1-aminium

[0949] This compound may be synthesized according to the experimental procedure described for Compound 255.



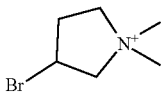
Compound 260: 1-methyl-1-(prop-2-yn-1-yl)-4,5-dihydro-1H-pyrazol-1-ium

[0950] This compound may be synthesized according to the experimental procedure described for Compound 208.



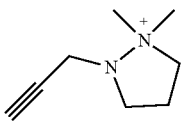
Compound 261: 1-methyl-1-(prop-2-yn-1-yl)imidazolidin-1-ium

[0951] This compound may be synthesized according to the experimental procedure described for Compound 208 using boc-protected imidazolidine, followed by deprotection to yield the title compound.



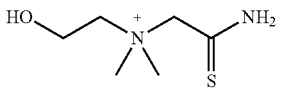
Compound 264: 3-bromo-1,1-dimethylpyrrolidin-1-ium Bromide

[0952] This compound may be synthesized according to the experimental procedure described for Compound 262.



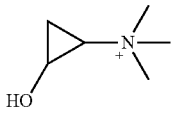
Compound 265: 1,1-dimethyl-2-(prop-2-yn-1-yl) pyrazolidin-1-ium

[0953] The title compound may be synthesized by reaction Compound 127 with propargyl bromide, followed by purification by recrystallization.



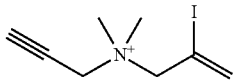
Compound 266: (carbamothioylmethyl)(2-hydroxyethyl)dimethylazanium

[0954] This compound may be synthesized according to the experimental procedure described for Compound 247.



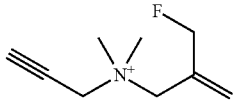
Compound 267: 2-hydroxy-N,N,N-trimethylcyclopropan-1-aminium

[0955] This compound may be synthesized according to the experimental procedure described for Compound 184.



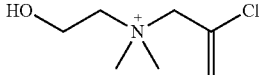
Compound 271: (2-iodoprop-2-en-1-yl)dimethyl (prop-2-yn-1-yl)azanium

[0956] This compound may be synthesized according to the experimental procedure described for Compound 270.



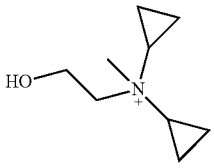
Compound 272: [2-(fluoromethyl)prop-2-en-1-yl] dimethyl(prop-2-yn-1-yl)azanium

[0957] This compound may be synthesized according to the experimental procedure described for Compound 270.



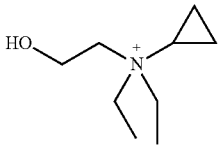
Compound 273: (2-chloroprop-2-en-1-yl)(2-hydroxyethyl)dimethylazanium

[0958] This compound may be synthesized according to the experimental procedure described for Compound 270.



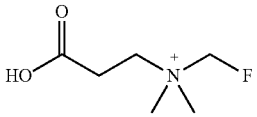
Compound 274: N-cyclopropyl-N-(2-hydroxyethyl)-N-methylcyclopropanaminium

[0959] This compound may be synthesized according to the experimental procedure described for Compound 58.



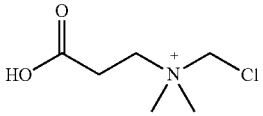
Compound 275: N,N-diethyl-N-(2-hydroxyethyl)cyclopropanaminium

[0960] This compound may be synthesized according to the experimental procedure described for Compound 58.



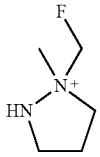
Compound 276: (2-carboxyethyl)(fluoromethyl)dimethylazanium

[0961] This compound may be synthesized according to the experimental procedure described for Compound 111.



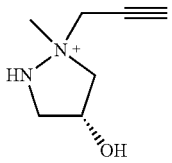
Compound 277: (2-carboxyethyl)(chloromethyl)dimethylazanium

[0962] This compound may be synthesized according to the experimental procedure described for Compound 111.



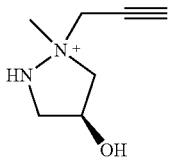
Compound 278: 1-(fluoromethyl)-1-methylpyrazolidin-1-ium

[0963] This compound may be synthesized according to the experimental procedure described for Compound 74.



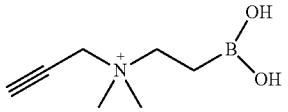
Compound 279: (4R)-4-hydroxy-1-methyl-1-(prop-2-yn-1-yl)pyrazolidin-1-ium

[0964] This compound may be synthesized according to the experimental procedure described for Compound 74, followed by SFC purification of stereoisomers.



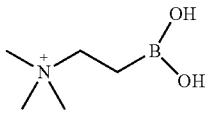
Compound 280: (4S)-4-hydroxy-1-methyl-1-(prop-2-yn-1-yl)pyrazolidin-1-ium

[0965] This compound may be synthesized according to the experimental procedure described for Compound 74, followed by SFC purification of stereoisomers.



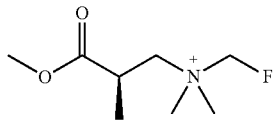
Compound 284: {2-[dimethyl(prop-2-yn-1-yl)azaniumyl]ethyl}boronic Acid

[0966] This compound may be synthesized according to the experimental procedure described for Compound 283.



Compound 285: [2-(trimethylazaniumyl)ethyl]boronic Acid

[0967] This compound may be synthesized according to the experimental procedure described for



Compound 289: (fluoromethyl)[(2R)-3-methoxy-2-methyl-3-oxopropyl]dimethylazanium

[0968] Step 1:

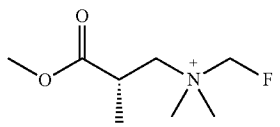
[0969] To a solution of (2R)-3-amino-2-methyl-propanoic acid (300 mg, 2.91 mmol, 1 eq) in HCOOH (5 mL) was added formaldehyde (2.36 g, 29.09 mmol, 2.17 mL, 37% purity, 10 eq). The mixture was stirred at 90° C. for 12 hr. LCMS showed the starting reactant was consumed and the product had the desired mass. The mixture was concentrated. The residue was purified by prep-HPLC [water (0.04% HCl)-ACN]. Compound (2R)-3-(dimethylamino)-2-methyl-propanoic acid (300 mg, 2.29 mmol, 78.61% yield) was obtained as a white solid.

[0970] Step 2:

[0971] To a solution of (2R)-3-(dimethylamino)-2-methyl-propanoic acid (250.00 mg, 1.91 mmol, 1 eq) in MeOH (5 mL) was added SOCl2 (453.49 mg, 3.81 mmol, 276.52 uL, 2 eq) at 0° C. The mixture was stirred at 15° C. for 12 hr. LCMS showed the starting reactant was consumed and have the desired mass. The mixture was concentrated. Compound methyl (2R)-3-(dimethylamino)-2-methyl-propanoate (313 mg, crude) was obtained as a white solid and used in the next step without further purification.

[0972] Step 3:

[0973] To a solution of methyl (2R)-3-(dimethylamino)-2-methyl-propanoate (100 mg, 688.71 umol, 1 eq) in THF (5 mL) was added Na_2CO_3 (73.00 mg, 688.71 umol, 1 eq) and fluoro(iodo)methane (330.43 mg, 2.07 mmol, 3 eq). The mixture was stirred at 15° C. for 10 h and stirred at 50° C. for 2 h. LCMS showed the starting reactant was consumed and the product had the desired mass. The mixture was filtered and the filtrate was concentrated. The residue was purified by prep-HPLC [water (0.04% HCl)-ACN]. Compound fluoromethyl-[(2R)-3-methoxy-2-methyl-3-oxo-propyl]-dimethyl-ammonium (19 mg, 62.27 umol, 9.04% yield, I—)—) was obtained as a white solid. MS: (M+): 178.1 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 5.30 (q, J=6.0 Hz, 1H), 5.18 (q, J=6.0 Hz, 1H), 3.92 (dd, J=14.0, 8.9 Hz, 1H), 3.65 (s, 3H), 3.37-3.29 (m, 1H), 3.17-3.10 (m, 1H), 3.04 (dd, J=7.2, 2.1 Hz, 6H), 1.19 (d, J=7.2 Hz, 3H).



Compound 290: (fluoromethyl)[(2S)-3-methoxy-2-methyl-3-oxopropyl]dimethylazanium

[0974] Step 1:

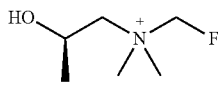
[0975] To a mixture of (2S)-3-amino-2-methyl-propanoic acid (0.3 g, 2.91 mmol, 1 eq) in HCOOH (5 mL) was added aq. HCHO (2.36 g, 29.09 mmol, 2.17 mL, 37% purity, 10 eq) in one portion at 25° C. under N_2. The mixture was stirred at 90° C. for 12 hours. LCMS showed the desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]; B %:1%-5%, 12 min). Compound (2S)-3-(dimethylamino)-2-methyl-propanoic acid (0.2 g, 815.68 umol, 28.04% yield, TFA) was obtained as colorless oil.

[0976] Step 2:

[0977] To a mixture of (2S)-3-(dimethylamino)-2-methyl-propanoic acid (0.2 g, 1.13 mmol, 1 eq) in MeOH (5 mL) was added $SOCl_2$ (268.56 mg, 2.26 mmol, 163.76 uL, 2 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 12 hours. LCMS showed desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. No further purification was performed. Compound methyl (2S)-3-(dimethylamino)-2-methyl-propanoate (150 mg, 1.03 mmol, 91.53% yield) was obtained as a white solid.

[0978] Step 3:

[0979] To a mixture of methyl (2S)-3-(dimethylamino)-2-methyl-propanoate (50 mg, 276.78 umol, 1 eq, C_1) and fluoro(iodo)methane (132.79 mg, 830.33 umol, 3 eq) in THF (5 mL) was added Na2CO3 added Na2CO3 (88.01 mg, 830.33 umol, 3 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 12 hours. LCMS showed desired mass was detected. The reaction mixture was filtered and concentrated under remove THF, then the residue was diluted with H_2O (3 ml), washed by EtOAc 9 ml (3 ml*3). The water phase was lyophilized. The title compound (32 mg, 179.55 umol, 64.87% yield) was obtained as white solid. MS: (M+): 178.1 1H NMR (400 MHz, Deuterium Oxide) δ 5.28 (q, J=6.0 Hz, 1H), 5.17 (q, J=6.0 Hz, 1H), 3.91 (dd, J=14.0, 9.0 Hz, 1H), 3.64 (s, 3H), 3.36-3.28 (m, 1H), 3.16-3.08 (m, 1H), 3.03 (dd, J=7.4, 2.1 Hz, 6H), 1.18 (d, J=7.3 Hz, 3H).



Compound 291: (fluoromethyl)[(2R)-2-hydroxypropyl]dimethylazanium

[0980] Step 1:

[0981] To a solution of methyl (2R)-2-hydroxypropanoate (10 g, 96.06 mmol, 9.17 mL, 1 eq) and imidazole (13.08 g, 192.12 mmol, 2.0 eq) in DCM (100 mL) was added tert added tert-butyl-chloro-dimethyl-silane (28.96 g, 192.12 mmol, 23.54 mL, 2 eq) at 0° C. The mixture was stirred at 25° C. for 12 hr. TLC indicated methyl (2R)-2-hydroxypropanoate was consumed completely and many new spots formed. The reaction mixture was diluted with H_2O (150 mL) and extracted with ethyl acetate 450 mL (150 mL*3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced

pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:0). Compound methyl (2R)-2-[tert butyl(dimethyl)silyl]oxypropanoate (15 g, 68.69 mmol, 71.51% yield) was obtained as a colorless oil.

[0982] Step 2:

[0983] To a solution of methyl (2R)-2-[tert-butyl(dimethyl)silyl]oxypropanoate (5 g, 22.90 mmol, 1 eq) in THF (100 mL) was added DIBAL added DIBAL-H (1 M, 45.79 mL, 2 eq, in Tol.) at 0° C. The mixture was stirred at 25 at 25° C. for 12 hr. TLC indicated new spots formed. The reaction mixture was quenched by addition of H_2O (100 mL) at 0° C., and then diluted with ethyl acetate 50 mL. The mixture was filtered. The filtrate was extracted with ethyl acetate 300 mL (100 mL*3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:0 to 10:1). Compound (2R)-2-[tert-butyl(dimethyl)silyl]oxypropan-1-ol (6 g, 36.77 mmol, 80.30% yield) was obtained as a colorless oil without further purification.

[0984] Step 3:

[0985] To a solution of (2R)-2-[tert-butyl(dimethyl)silyl]oxypropan-1-ol (6 g, 31.52 mmol, 1 eq) in DCM (60 mL) was added imidazole (10.73 g, 157.60 mmol, 5 eq), PPh3 (20.67 g, 78.80 mmol, 2.5 eq) and 12 (24.00 g, 94.56 mmol, 19.05 mL, 3 eq) at 25° C. The mixture was stirred at 25° C. for 12 hr. TLC indicated (2R)-2-[tert-butyl(dimethyl)silyl]oxypropan-1-ol was consumed completely. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:0). Compound tert-butyl-[(1R)-2-iodo-1-methyl-ethoxy]-dimethyl-silane (6 g, 19.98 mmol, 63.40% yield) was obtained as a colorless oil.

[0986] Step 4:

[0987] To a solution of tert-butyl-[(1R)-2-iodo-1-methyl-ethoxy]-dimethyl-silane (4 g, 13.32 mmol, 1 eq) in THF (50 mL) was added N-methylmethanamine (2 M, 33.31 mL, 5 eq)(in THF) at 25° C. The mixture was stirred at 25° C. for 12 hr. LCMS showed the desired compound was detected. TLC indicated most of tert-butyl-[(1R)-2-iodo-1-methyl-ethoxy]-dimethyl-silane remained. The mixture was stirred at 70° C. for 12 hr. The reaction mixture was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1:0 to 0:1). Compound (2R)-2-[tert-butyl(dimethyl)silyl]oxy-N,N-dimethyl-propan-1-amine (3 g, 8.69 mmol, 65.21% yield, HI) was obtained as yellow oil.

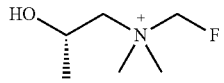
[0988] Step 5:

[0989] To a solution of (2R)-2-[tert-butyl(dimethyl)silyl]oxy-N,N-dimethyl-propan-1-amine (3 g, 8.69 mmol, 1 eq, HI) in THF (30 mL) was added fluoro(iodo)methane (6.95 g, 43.44 mmol, 5 eq) at 25° C. The mixture was stirred at 25° C. for 12 hr. TLC indicated (2R)-2-[tert-butyl(dimethyl)silyl]oxy-N,N-dimethyl-propan-1-amine was remained. The mixture was added another batch of fluoro(iodo)methane (4.17 g, 26.06 mmol, 3 eq) at 25° C. The mixture was stirred at 50° C. for 3 hr. TLC indicated (2R)-2-[tert-butyl(dimethyl)silyl]oxy-N,N-dimethyl-propan-1-amine was consumed completely. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O 100 mL and extracted with ethyl acetate 150 mL (50 mL*3). The aqueous phase was freeze-dried.

[0990] Compound tert-butyl-[(1R)-2-[N-(fluoromethyl)-dimethyl-azanyl]-1-methyl-ethoxy]-dimethyl-silane (900 mg, 2.39 mmol, 27.45% yield) was obtained as a white solid without further purification.

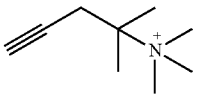
[0991] Step 6:

[0992] To a solution of tert-butyl-[(1R)-2-[N-(fluoromethyl)-dimethyl-azanyl]-1-methyl-ethoxy]-dimethyl-silane (500 mg, 1.33 mmol, 1 eq) in H_2O (20 mL) was added KF (1.54 g, 26.50 mmol, 620.80 uL, 20 eq) at 25° C. The mixture was stirred at 50° C. for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O 5 mL and extracted with ethyl acetate 15 mL (5 mL*3). The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. Compound fluoromethyl-[(2R)-2-hydroxypropyl]-dimethyl-ammonium (98 mg, 372.49 umol, 28.11% yield, I—) was obtained as yellow oil. MS: (M+): 136.1 ^{1}H NMR (400 MHz, Deuterium Oxide) δ 5.48-5.37 (m, 1H), 5.37-5.26 (m, 1H), 4.37 (q, J=6.4 Hz, 1H), 3.42-3.36 (m, 2H), 3.20-3.14 (m, 6H), 1.18 (d, J=6.4 Hz, 3H).



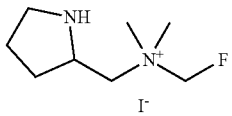
Compound 292: (fluoromethyl)[(2S)-2-hydroxypropyl]dimethylazanium

[0993] This compound may be synthesized according to the experimental procedure described for Compound 169.



Compound 294: trimethyl(2-methylpent-4-yn-2-yl)azanium

[0994] This compound may be synthesized according to the experimental procedure described for Compound 174.



Compound 295: (fluoromethyl)dimethyl[(pyrrolidin-2-yl)methyl]azanium Iodide

[0995] Step 1:

[0996] To a mixture of pyrrolidin-2-ylmethanol (5 g, 49.43 mmol, 1 eq) and ethyl 2,2,2-trifluoroacetate (10.53 g, 74.15 mmol, 10.23 mL, 1.5 eq) in MeOH (50 mL) was added TEA added TEA (5.50 g, 54.38 mmol, 7.57 mL, 1.1 eq) in one portion at 25° C. under N_2. The mixture as heated to 70° C. and stirred for 12 hours. TLC indicated pyrrolidin-2-ylmethanol was consumed and one new spot formed. The

reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 0/1). Compound 2,2,2-trifluoro-1-[2-(hydroxymethyl)pyrrolidin-1-yl]ethanone (5 g, 25.36 mmol, 51.30% yield) was obtained as yellow oil. LCMS: (M+H+): 198.0.

[0997] Step 2:

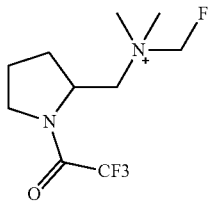
[0998] To a mixture of PPh3 (6.39 g, 24.35 mmol, 2.4 eq) in DCM (15 mL) was added imidazole (3.45 g, 50.72 mmol, 5 eq) and 12 (6.44 g, 25.36 mmol, 2.5 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 6 min, then 2,2,2-trifluoro-1-[2-(hydroxymethyl)pyrrolidin-1-yl] ethanone (2 g, 10.14 mmol, 1 eq) was added. The mixture was stirred at 25° C. for 11.9 hours. TLC indicated 2,2,2-trifluoro-1-[2-(hydroxymethyl)pyrrolidin-1-yl]ethanone was consumed and many new spots formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=100/1 to 5/1). Compound 2,2,2-trifluoro-1-[2-(iodomethyl)pyrrolidin-1-yl]ethanone (2.7 g, crude) was obtained as colorless oil.

[0999] Step 3:

[1000] To a mixture of 2,2,2-trifluoro-1-[2-(iodomethyl) pyrrolidin-1-yl]ethanone (1 g, 3.26 mmol, 1 eq) in THF (5 mL) was added Na_2CO_3 (690.37 mg, 6.51 mmol, 2 eq) and N-methylmethanamine (2 M, 4.89 mL, 3 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 12 hours. TLC indicated 2,2,2-trifluoro-1-[2-(iodomethyl)pyrrolidin-1-yl]ethanone was consumed and one new spot formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=80/1 to 0/1). Compound 1-[2-[(dimethylamino) methyl]pyrrolidin-1-yl]-2,2,2-trifluoro-ethanone (150 mg, crude) was obtained as yellow oil. LCMS: (M+H+): 225.1

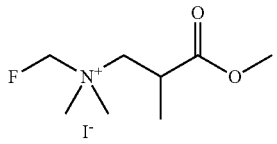
[1001] Step 4:

[1002] To a mixture of 1-[2-[(dimethylamino)methyl]pyrrolidin-1-yl]-2,2,2-trifluoro-ethanone (100 mg, 445.98 umol, 1 eq) in THF (3 mL) was added NaI (133.70 mg, 891.97 umol, 2 eq), Na_2CO_3 (94.54 mg, 891.97 umol, 2 eq) and fluoro(iodo)methane (213.98 mg, 1.34 mmol, 3 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 12 hours. LCMS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. The title compound (88 mg, 305.40 umol, 68.48% yield, I) was obtained as colorless oil. LCMS: (M+H+): 161.2 1H NMR (400 MHz, Deuterium Oxide) δ 5.42 (s, 1H), 5.31 (s, 1H), 4.12-4.03 (m, 1H), 3.96-3.81 (m, 2H), 3.31 (dd, J=8.5, 6.4 Hz, 2H), 3.17 (s, 6H), 2.40-2.30 (m, 1H), 2.05-2.00 (m, 1H), 1.98-1.84 (m, 1H), 1.84-1.69 (m, 1H).



Compound 296: (fluoromethyl)dimethyl{[1-(2,2,2-trifluoroacetyl)pyrrolidin-2-yl]methyl}azanium

[1003] This compound may be synthesized by reacting Compound 295 with trifluoracetic anhydride, followed by purification by recrystallization.



Compound 297: (fluoromethyl)(3-methoxy-2-methyl-3-oxopropyl)dimethylazanium Iodide

[1004] Step 1:

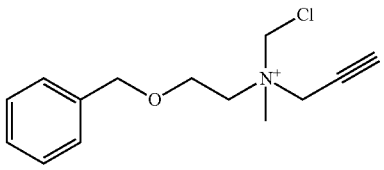
[1005] To a mixture of 3-amino-2-methyl-propanoic acid (300 mg, 2.91 mmol, 1 eq) in HCOOH (5 mL) was added HCHO (2.36 g, 29.09 mmol, 2.17 mL, 37% purity, 10 eq) in one portion at 25° C. under N_2. The mixture was stirred at 90° C. for 12 hours. LCMS showed desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [water (0.10% TFA)-ACN]. Compound 3-(dimethylamino)-2-methyl-propanoic acid (100 mg, 762.36 umol, 26.20% yield) was obtained as colorless oil.

[1006] Step 2:

[1007] To a mixture of 3-(dimethylamino)-2-methyl-propanoic acid (50 mg, 381.18 umol, 1 eq) in MeOH (3 mL) was added $SOCl_2$ (90.70 mg, 762.35 umol, 55.30 uL, 2 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 12 hours. LCMS showed desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. No further purification was performed. The crude product methyl 3-(dimethylamino)-2-methyl-propanoate (50 mg, crude) was obtained as colorless oil, and used in the next step without further purification.

[1008] Step 3:

[1009] To a mixture of methyl 3-(dimethylamino)-2-methyl-propanoate (50 mg, 344.35 umol, 1 eq) in THF (3 mL) was added Na_2CO_3 (73.00 mg, 688.71 umol, 2 eq) in one portion at 25° C. under N_2, then fluoro(iodo)methane (165.22 mg, 1.03 mmol, 3 eq) was added. The mixture was stirred at 25° C. for 12 hours. LCMS showed desired compound was detected. The reaction mixture was filtered and concentrated under reduced pressure to remove THF, then 5 ml H_2O was added, extracted with EtOAc (15 ml, 5 ml*3). The water phase was lyophilized. The title compound (39.4 mg, 221.07 umol, 64.20% yield) was obtained as white solid. LCMS: (M+H+): 178.1 ^1H NMR (400 MHz, Deuterium Oxide) δ 5.4 (m, 1H), 5.3 (m, 1H), 4.1-4.0 (m, 1H), 3.8 (s, 3H), 3.4 (m, 1H), 3.2 (m, 1H), 3.2-3.1 (m, 6H), 1.3 (m, 3H).



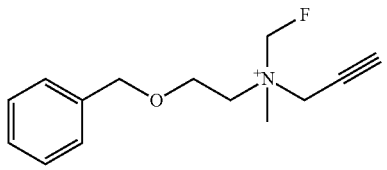
Compound 298: [2-(benzyloxy)ethyl](chloromethyl) methyl(prop-2-yn-1-yl)azanium

[1010] Step 1:

[1011] To a mixture of 2-benzyloxyacetaldehyde (500 mg, 3.33 mmol, 467.29 uL, 1 eq) and N-methylprop-2-yn-1-amine (230.08 mg, 3.33 mmol, 277.21 uL, 1 eq) in THF (3 mL) was added AcOH (10.00 mg, 166.47 umol, 9.52 uL, 0.05 eq) in one portion at 0° C. under N_2. The mixture was stirred at 0° C. for 30 min, then $NaBH(OAc)_3$ (1.41 g, 6.66 mmol, 2 eq) was added heated to 25° C. and stirred for 11.5 hours. LC-MS showed desired mass was detected. The reaction mixture was diluted with H_2O (3 mL) and extracted with EtOAc 15 mL (5 mL*3), filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 1/1). compound N-(2-benzyloxyethyl)-N-methyl-prop-2-yn-1-amine (600 mg, 2.95 mmol, 88.65% yield) was obtained as yellow oil.

[1012] Step 2:

[1013] To a mixture of N-(2-benzyloxyethyl)-N-methyl-prop-2-yn-1-amine (20 mg, 98.39 umol, 1 eq) in acetone (0.5 mL) was added chloro(iodo)methane (86.77 mg, 491.93 umol, 35.71 uL, 5 eq). The mixture was stirred at 25° C. for 12 hours. LCMS showed desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (0.04% HCl)-ACN]; B %: 5%-35%, 12 min). The title compound (18 mg, 47.41 umol, 48.19% yield, I—) was obtained as colorless oil. LCMS: (M+): 252.1 ^1H NMR (400 MHz, Deuterium Oxide) δ 7.45-7.36 (m, 5H), 5.30 (s, 2H), 4.60 (s, 2H), 4.44 (d, J=2.5 Hz, 2H), 4.03-3.97 (m, 2H), 3.87-3.80 (m, 2H), 3.27 (s, 4H).



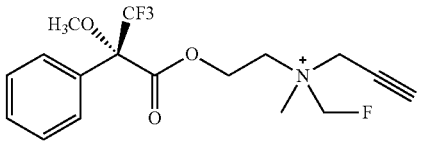
Compound 299: [2-(benzyloxy)ethyl](fluoromethyl) methyl(prop-2-yn-1-yl)azanium

[1014] Step 1:

[1015] To a mixture of 2-benzyloxyacetaldehyde (500 mg, 3.33 mmol, 467.29 uL, 1 eq) and N-methylprop-2-yn-1-amine (230.08 mg, 3.33 mmol, 277.21 uL, 1 eq) in THF (3 mL) was added AcOH (10.00 mg, 166.47 umol, 9.52 uL, 0.05 eq) in one portion at 0° C. under N_2. The mixture was stirred at 0° C. for 30 min, then $NaBH(OAc)_3$ (1.41 g, 6.66 mmol, 2 eq) was added heated to 25° C. and stirred for 11.5 hours. LC-MS showed desired mass was detected. The reaction mixture was diluted with H_2O (3 mL) and extracted with EtOAc 15 mL (5 mL*3), filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 1/1). compound N-(2-benzyloxyethyl)-N-methyl-prop-2-yn-1-amine (600 mg, 2.95 mmol, 88.65% yield) was obtained as yellow oil.

[1016] Step 2:

[1017] To a solution of N-(2-benzyloxyethyl)-N-methyl-prop-2-yn-1-amine (100 mg, 491.93 umol, 1 eq) in THF (5 mL) was added fluoro(iodo)methane (236.02 mg, 1.48 mmol, 3 eq) at 25° C. The mixture was stirred at 25° C. for 12 hr. LCMS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O 5 mL and extracted with ethyl acetate 15 mL (5 mL*3). The residue was purified by prep-HPLC [water (0.04% HCl)-ACN]. Desired compound 2-benzyloxyethyl-(fluoromethyl)-methyl-prop-2-ynyl-ammonium (58 mg, 159.69 umol, 32.46% yield, I—) was obtained as colorless oil. LCMS: (M+): 236.1 1H NMR (400 MHz, Methanol-d4) δ 7.41-7.27 (m, 5H), 5.70-5.62 (m, 1H), 5.59-5.51 (m, 1H), 4.60 (s, 2H), 4.57-4.51 (m, 2H), 3.99-3.94 (m, 2H), 3.86-3.79 (m, 2H), 3.62 (t, J=2.6 Hz, 1H), 3.28 (d, J=2.1 Hz, 3H).



Compound 300: (fluoromethyl)(methyl)(prop-2-yn-1-yl)(2-{[(2S)-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoyl]oxy}ethyl)azanium

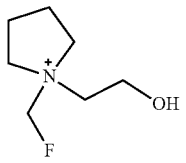
[1018] Step 1:

[1019] A mixture of (2S)-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoic acid (0.6 g, 2.56 mmol, 461.54 uL, 1 eq), 2-[methyl(prop-2-ynyl)amino]ethanol (318.65 mg, 2.82 mmol, 1.1 eq), DCC (581.02 mg, 2.82 mmol, 569.62 uL, 1.1 eq), DMAP (156.38 mg, 1.28 mmol, 0.5 eq) in DCM (15 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 0° C. for 0.5 hr. LCMS showed desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=90/1 to 30/1). Compound 2-[methyl(prop-2-ynyl)amino]ethyl (2S)-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoate (100 mg, 303.66 umol, 11.86% yield) was obtained as colorless oil.

[1020] Step 2:

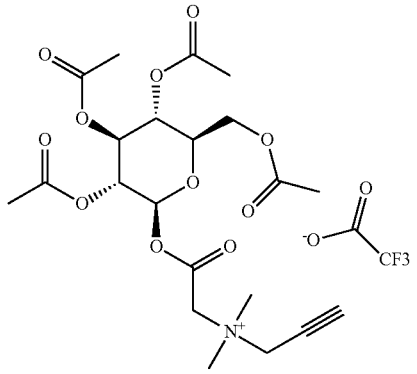
[1021] 2-[methyl(prop-2-ynyl)amino]ethyl (2S)-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoate (200 mg, 607.32 umol, 1 eq) in fluoro(iodo)methane (1.94 g, 12.15 mmol, 20 eq) was stirred at 25° C. for 12 hours. LC-MS showed desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC

[water (0.04% HCl)-ACN]. The title compound (47 mg, 96.07 umol, 15.82% yield, I—) was obtained as white solid. MS (M+): 362.0 1H NMR (400 MHz, Deuterium Oxide) δ 7.58-7.47 (m, 5H), 5.46-5.36 (m, 1H), 5.34-5.25 (m, 1H), 4.84 (s, 2H), 4.31-4.17 (m, 2H), 3.95 (s, 2H), 3.47 (s, 3H), 3.27-3.22 (m, 1H), 3.08 (s, 3H).



Compound 301: 1-(fluoromethyl)-1-(2-hydroxy-ethyl)pyrrolidin-1-ium

[1022] To a mixture of 2-pyrrolidin-1-ylethanol (100 mg, 868.26 umol, 101.52 uL, 1 eq) in THF (3 mL) was added fluoro added fluoro(iodo)methane (416.58 mg, 2.60 mmol, 3 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 12 hours. LCMS showed desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove THF, and diluted with H_2O 3 mL and extracted with EtOAc (15 mL, 5 mL*3). The water phase was lyophilized. The title compound (90 mg, 327.15 umol, 37.68% yield, I—) was obtained as yellow solid. MS (M+): 148.0 1H NMR (400 MHz, Deuterium Oxide) δ 5.47 (s, 1H), 5.35 (s, 1H), 4.03-3.96 (m, 2H), 3.78-3.68 (m, 2H), 3.70-3.59 (m, 4H), 2.24-2.05 (m, 4H).



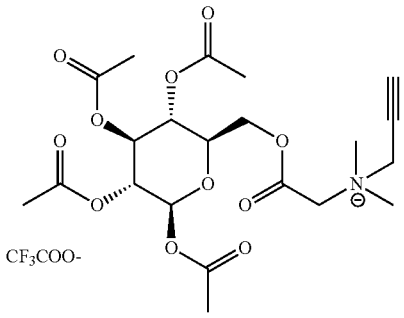
Compound 303: N,N-dimethyl-N-(2-oxo-2-(((2S, 3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl) tetrahydro-2H-pyran-2-yl)oxy)ethyl)prop-2-yn-1-aminium Trifluoroacetate

[1023] Step 1

[1024] Compound 2,3,4,6-tetra-O-acetyl-D-glucopyranose (Carbosynth, 2 g, 5.7 mmol, 1 eq) was dissolved in DCM (10 mL), and cooled to 0° C. under N_2. Then 2-chloroacetyl chloride (1.4 mL, 17.6 mmol, 3 eq) and pyridine (1.4 mL, 17.4 mmol, 3 eq) in DCM (10 mL) were added over ice, the reaction was stirred overnight. The reaction mixture was filtered and purified by column chromatography (0-100% EtOAc in hexanes) to yield 1-(2-chloroacetoxy)-2,3,4,6-tetra-O-acetyl-D-glucopyranose (1.18 g, 2.8 mmol, 48% yield).

[1025] Step 2

[1026] Compound 1-(2-chloroacetoxy)-2,3,4,6-tetra-O-acetyl-D-glucopyranose (1.18 g, 2.8 mmol, 1 eq) was dissolved in acetone, followed by addition of sodium iodide (0.625 g, 4.2 mmol, 1.5 eq). The reaction was stirred for a few minutes, followed by addition of dimethylamino-1-propyne (0.76 mL, 7.1 mmol, 2.5 eq). The reaction was stirred at room temperature overnight, then filtered. The filtrate was concentrated, diluted with DMSO and water, then purified by reverse phase C18 column chromatography (0.1% TFA in 95% water/5% MeCN to 100% MeCN). Fractions containing product were lyophilized to yield an off-white powder (420 mg, 0.72 mmol, 26% yield). LCMS (M+): 472.4 ^{1}H NMR (400 MHz, DMSO-d6) δ 6.13 (d, J=8.2 Hz, 1H), 5.48 (t, J=9.6 Hz, 1H), 5.08-4.94 (m, 2H), 4.75-4.46 (m, 4H), 4.35-3.95 (m, 4H), 3.28-3.15 (m, 6H), 2.07-1.86 (m, 12H).



Compound 304: N,N-dimethyl-N-(2-oxo-2-(((2R, 3R,4S,5R)-3,4,5,6-tetraacetoxytetrahydro-2H-pyran-2-yl)methoxy)ethyl)prop-2-yn-1-aminium Trifluoro-acetate

[1027] Step 1:

[1028] Compound 1,2,3,4-tetra-O-acetyl-beta-D-glucopyranose (Alfa Aesar, CAS: 13100-46-4, 0.5 g, 1.44 mmol, 1 eq) was dissolved in DCM (5 mL) and cooled to 0° C. Chloroacetyl chloride (0.3425 mL, 4.3 mmol, 3 eq) was added, followed by dropwise addition of pyridine (0.35 mL, 4.3 mmol, 3 eq). The reaction was directly loaded onto silica, and purified by column chromatography (100% hexanes to 100% ethyl acetate) to yield 6-(2-chloroacetoxy)-1,2,3,4-tetra-O-acetyl-beta-D-glucopyranose as an off-white to yellow solid (0.5 g, 1.18 mmol, 82% yield).

[1029] Step 2:

[1030] Compound 6-(2-chloroacetoxy)-1,2,3,4-tetra-O-acetyl-beta-D-glucopyranose (0.5 g, 1.18 mmol, 1 eq) was dissolved in acetone, followed by addition of sodium iodide (0.35 g, 2.3 mmol, 2 eq). The reaction was stirred for a few minutes, followed by addition of 3-dimethylamino-1-propyne (0.25 mL, 2.3 mmol, 2 eq) was added. The reaction was stirred at room temperature overnight, then filtered. The filtrate was concentrated, diluted with DMSO and water and purified by reverse phase C18 column chromatography (0.1% TFA in water 95%/MeCN 5% to 100% MeCN). Fractions containing product was lyophilized to yield an off-white powder (476 mg, 0.81 mmol, 69% yield). LCMS (M+): 472.1 1H NMR (400 MHz, DMSO-d6) δ 5.98 (d, J=8.3 Hz, 1H), 5.47 (t, J=9.6 Hz, 1H), 5.10-4.84 (m, 2H),

4.50 (t, J=2.2 Hz, 4H), 4.41-4.17 (m, 3H), 4.16-4.07 (m, 1H), 3.23 (d, J=145.8 Hz, 6H), 2.15-1.88 (m, 12H).

Compound 306: dimethyl(prop-2-yn-1-yl)(2-{[(2S, 3R,4S,5S)-3,4,5-tris(acetyloxy)oxan-2-yl]oxy}ethyl) azanium Iodide

[1031] Step 1:

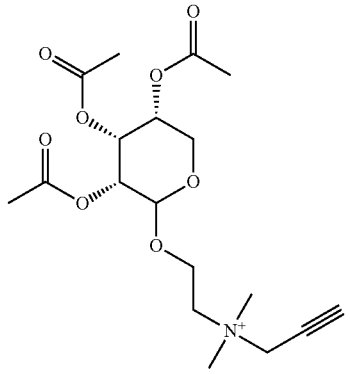
[1032] To a mixture of (2R,3S,4S)-2,3,4,5-tetrahydroxy-pentanal (10 g, 66.61 mmol, 1 eq) in pyridine (100 mL) was added Ac_2O (40.80 g, 399.65 mmol, 37.43 mL, 6 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 12 hours. TLC indicated one new spot formed. The reaction mixture was concentrated under reduced pressure to remove pyridine. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=30/1 to 0/1). Compound [(3S,4S,5R,6S)-4,5,6-triacetoxytetrahydro-pyran-3-yl] acetate (20 g, crude) was obtained as yellow oil.

[1033] Step 2:

[1034] To a mixture of [(3S,4S,5R,6S)-4,5,6-triacetoxytet-rahydropyran-3-yl] acetate (10 g, 31.42 mmol, 1 eq) in DCM (100 mL) was added 2-bromoethanol (5.89 g, 47.13 mmol, 3.35 mL, 1.5 eq) and $BF_3.Et_2O$ (22.30 g, 157.10 mmol, 19.39 mL, 5 eq) in one portion at 0° C. under N_2. The mixture was heated to 25° C. and stirred for 12 hours. TLC indicated [(3S,4S,5R,6S)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate was consumed and one new spot formed. The reaction mixture was quenched by addition of H_2O (50 mL), and then diluted with H_2O (100 mL) and extracted with DCM (100 mL*2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1). Then the residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. ^{1}HNMR indicated compound [(3S,4S,5R,6S)-4,5-diacetoxy-6-(2-bromoeth-oxy)tetrahydropyran-3-yl] acetate (1.2 g, 3.13 mmol, 9.97% yield) was obtained as yellow oil and compound[(3S,4S,5R, 6R)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (2.3 g, 6.00 mmol, 19.10% yield) was obtained as yellow oil.

[1035] Step 3:

[1036] To a mixture of [(3S,4S,5R,6R)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (1.00 g, 2.61 mmol, 1 eq) in acetone (10 mL) was added NaI (430.29 mg, 2.87 mmol, 1.1 eq) in one portion at 25° C. under N_2. Then N,N-dimethylprop-2-yn-1-amine (1.08 g, 13.05 mmol, 1.38 mL, 5 eq) was added. The mixture was heated to 90° C. and stirred for 2 hours. TLC indicated [(3S,4S,5R,6R)-4,5-diac-etoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate was consumed and one new spot formed. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to Ethyl acetate:Methanol=3/1). The title compound (109 mg, 210.22 umol, 8.06% yield, 99% purity, I) was obtained as white solid. LCMS: (M+): 386.1 1H NMR (400 MHz, Methanol-d4) δ 5.21 (s, 1H), 5.12-5.06 (m, 2H), 4.48 (d, J=2.5 Hz, 2H), 4.43 (dd, J=11.6, 3.9 Hz, 1H), 4.38 (q, J=4.4 Hz, 1H), 4.29-4.16 (m, 2H), 4.06-3.96 (m, 1H), 3.86-3.74 (m, 2H), 3.61 (t, J=2.5 Hz, 1H), 3.31 (s, 6H), 2.20-1.95 (m, 9H).



Compound 308: dimethyl(prop-2-yn-1-yl)(2-{[(3R, 4R,5R)-3,4,5-tris(acetyloxy)oxan-2-yl]oxy}ethyl) azanium

[1037] Step 1:

[1038] To a mixture of (2R,3R,4R)-2,3,4,5-tetrahydroxy-pentanal (10 g, 66.61 mmol, 1 eq) in pyridine (100 mL) was added Ac_2O (40.80 g, 399.65 mmol, 37.43 mL, 6 eq) in one portion at 25° C. under N_2. The mixture was stirred at 25° C. for 12 hours. TLC indicated one new spot formed. The reaction mixture was concentrated under reduced pressure to remove the pyridine. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=30/1 to 0/1). Compound [(3R,4R,5R)-4,5,6-triacetoxytetrahydro-pyran-3-yl] acetate (20 g, crude) was obtained as white solid.

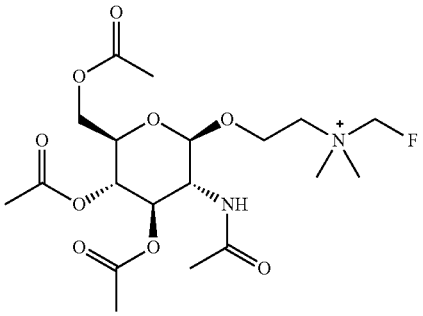
[1039] Step 2:

[1040] To a mixture of [(3R,4R,5R)-4,5,6-triacetoxytetra-hydropyran-3-yl] acetate (10 g, 31.42 mmol, 1 eq) in DCM (50 mL) was added 2-bromoethanol (5.89 g, 47.13 mmol, 3.35 mL, 1.5 eq) in one portion at 0° C. under N_2. $BF_3.Et_2O$ was added (22.30 g, 157.10 mmol, 19.39 mL, 5 eq) and stirred at 0° C. for 6 minutes, then heated to 25° C. and stirred for 11.9 hours. TLC indicated [(3R,4R,5R)-4,5,6-triacetoxytetrahydropyran-3-yl] acetate was consumed and one new spot formed. The reaction mixture was quenched by addition H_2O (20 mL), then diluted with H_2O (50 mL) and extracted with DCM (100 mL, 50 mL*2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1). Then the residue was purified by prep-HPLC [water (0.1% TFA)-ACN]. Compound [(3R,4R,5R)-4,5-diacetoxy-6-(2-bromo-ethoxy)tetrahydropyran-3-yl] acetate (2.6 g, 6.79 mmol, 21.60% yield) was obtained as a yellow oil.

[1041] Step 3:

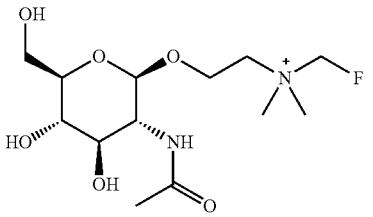
[1042] To a mixture of [(3R,4R,5R)-4,5-diacetoxy-6-(2-bromoethoxy)tetrahydropyran-3-yl] acetate (1.5 g, 3.91 mmol, 1 eq) in acetone (15 mL) was added N,N-dimethyl-prop-2-yn-1-amine (1.63 g, 19.57 mmol, 2.08 mL, 5 eq) in one portion at 25° C. under N_2. Then the mixture was heated to 90° C. and stirred for 2 hours. LCMS showed one main peak with expected mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. Then the residue was purified by prep-HPLC [water (0.10% TFA)-ACN]. The title compound (619 mg, 1.33 mmol,

33.91% yield, 100% purity, Br—) was obtained as colorless oil. LCMS: (M+): 386.2 ^{1}H NMR (400 MHz, Methanol-d4) δ 5.49 (t, J=3.3 Hz, 1H), 5.11 (dt, J=6.8, 3.5 Hz, 1H), 5.01 (dd, J=5.2, 3.3 Hz, 1H), 4.96 (d, J=5.1 Hz, 1H), 4.42 (d, J=2.6 Hz, 2H), 4.26 (dt, J=13.5, 4.4 Hz, 1H), 4.13-3.99 (m, 2H), 3.86 (dd, J=12.1, 6.6 Hz, 1H), 3.78 (t, J=4.7 Hz, 2H), 3.59 (t, J=2.5 Hz, 1H), 3.27 (s, 6H), 2.16-1.99 (m, 9H).



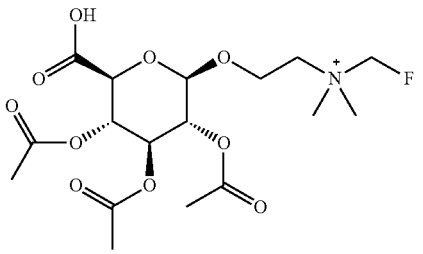
Compound 336: (2-{[(2R,3R,4R,5S,6R)-4,5-bis (acetyloxy)-6-[(acetyloxy)methyl]-3-acetamidooxan-2-yl]oxy}ethyl)(fluoromethyl)dimethylazanium

[1043] This compound may be synthesized according to the experimental procedure described for Compound 311.



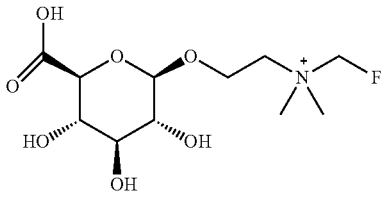
Compound 337: (2-{[(2R,3R,4R,5S,6R)-3-acetamido-4,5-dihydroxy-6-(hydroxymethyl)oxan-2-yl] oxy}ethyl)(fluoromethyl)dimethylazanium

[1044] This compound may be synthesized according to the experimental procedure described for Compound 317.



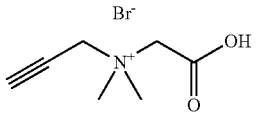
Compound 338: (fluoromethyl)dimethyl(2-{[(2R, 3R,4S,5S,6S)-3,4,5-tris(acetyloxy)-6-carboxyoxan-2-yl]oxy}ethyl)azanium

[1045] This compound may be synthesized according to the experimental procedure described for Compound 321.



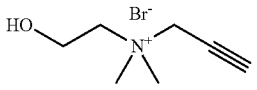
Compound 339: (2-{[(2R,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxyoxan-2-yl]oxy}ethyl)(fluoromethyl) dimethylazanium

[1046] This compound may be synthesized according to the experimental procedure described for Compound 321, followed by deacetylation following procedure for Compound 317.



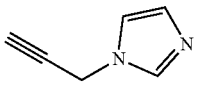
Compound 159: N-(carboxymethyl)-N,N-dimethylprop-2-yn-1-aminium Bromide

[1047] To the mixture of N,N-dimethylprop-2-yn-1-amine (1 g, 12.03 mmol, 1.28 mL, 1 eq) in Acetone (20 mL) was added dropwise 2-bromoacetic acid (1.82 g, 13.11 mmol, 943.97 uL, 1.09 eq), and then the mixture was stirred at 15° C. for 20 min. TLC indicated N,N-dimethylprop-2-yn-1-amine was consumed completely and one new spot formed. The reaction mixture was filtered and filter cake was concentrated under reduced pressure to give a residue. Compound carboxymethyl-dimethyl-prop-2-ynyl-ammonium (700 mg, 3.15 mmol, 26.20% yield, Br—) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 4.5 (s, 2H), 4.0 (m, 3H), 3.2 (s, 6H) ppm.



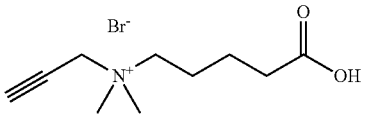
[1048] Compound J60: N-(2-hydroxyethyl)-N,N-dimethylprop-2-yn-1-aminium Iodide

[1049] To a solution of N,N-dimethylprop-2-yn-1-amine (1 g, 12.03 mmol, 1.28 mL, 1 eq) in THF (3 mL) was added dropwise 2-iodoethanol (2.17 g, 12.63 mmol, 987.35 uL, 1.05 eq) at 0° C. The mixture was warmed to 15° C. for 5 hr. TLC indicated N,N-dimethylprop-2-yn-1-amine was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was filtered and filter cake was concentrated under reduced pressure to give a residue. Compound N-(2-hydroxyethyl)-N,N-dimethyl-prop-2-ynyl-ammonium iodide (2 g, 7.84 mmol, 65.17% yield, I—) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 5.3 (m, 1H), 4.4 (s, 2H), 4.0 (s, 1H), 3.8 (m, 2H), 3.4 (m, 2H), 3.1 (s, 6H) ppm.



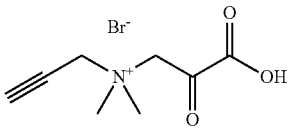
Compound Z76: 1-(prop-2-yn-1-yl)-1H-imidazole

[1050] Imidazole is reacted with propargyl bromide in THF and diisopropyl ethyl amine. The resulting compound is purified to afford the title compound.



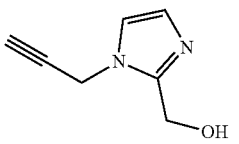
Compound A51: 4-carboxy-N,N-dimethyl-N-(prop-2-yn-1-yl)butan-1-aminium Bromide

[1051] To a solution of N, N-dimethylprop-2-yn-1-amine (300 mg, 3.61 mmol, 382.65 uL, 1.08 eq) in acetone (5 mL) was added 5-bromopentanoic acid (604.89 mg, 3.34 mmol, 1 eq) at 15° C. The mixture was stirred at 60° C. for 16 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL*2). The combined water layer was freeze-dried to get 4-carboxy-N, N-dimethyl-N-(prop-2-yn-1-yl) butan-1-aminium bromide (89 mg, 336.92 umol, 10.08% yield) as a yellow solid. ^{1}H NMR (400 MHz, D2O) δ 4.22 brS, 2H), 3.4 (m, 2H), 3.1 s (1H), 3.05 (brs, 6H), 2.4 (t, 2H), 1.8 (m, 2H), 1.6 m, 2H).



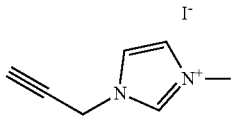
[1052] Compound B52: 2-carboxy-N,N-dimethyl-N-(prop-2-yn-1-yl)prop-2-en-1-aminium Bromide

[1053] To a solution of N,N-dimethylprop-2-yn-1-amine (200 mg, 2.41 mmol, 255.10 uL, 1 eq) in ACN (10 mL) was added dropwise 2-(bromomethyl)prop-2-enoic acid (417.49 mg, 2.53 mmol, 1.05 eq) at 15° C. After addition the mixture was stirred at 15° C. for 12 h. The white precipitate was formed and TLC showed the starting reactant was consumed. The mixture reaction was filtered to obtain white solid. Compound 2-carboxy-N,N-dimethyl-N-(prop-2-yn-1-yl)prop-2-en-1-aminium bromide (103 mg, 551.09 umol, 22.87% yield) was obtained as a white solid. LCMS: (M+): 168.1 1H NMR (400 MHz, Deuterium Oxide) δ 6.79 (s, 1H), 6.30 (s, 1H), 4.19 (s, 2H), 4.10 (d, J=2.6 Hz, 2H), 3.14 (t, J=2.6 Hz, 1H), 2.99 (s, 6H).



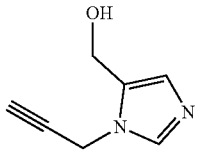
Compound AA 77: (1-(prop-2-yn-1-yl)-1H-imidazol-2-yl)methanol

[1054] 1-(prop-2-yn-1-yl)-1H-imidazole is dissolved in THF and cooled to −78° C. n-Butyl lithium is added followed by paraformaldehyde. The resulting mixture is stirred at −78 then quenched with water followed by ethyl acetate. The material was purified to afford the title compound.



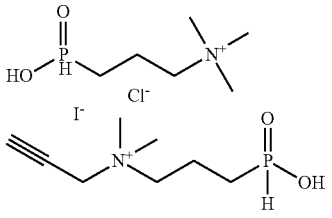
Compound AB78: 3-methyl-1-(prop-2-yn-1-yl)-1H-imidazol-3-ium Iodide

[1055] Imidazole is reacted with propargyl bromide in THF and diisopropyl ethyl amine. The resulting compound is purified to afford 1-(prop-2-yn-1-yl)-1H-imidazole. This material is taken up in diethyl ether and treated with dropwise addition of methyl iodide. The resulting precipitate is collected and dried and recrystallized to afford the title compound.



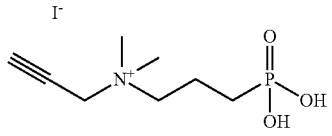
Compound AC79: (1-(prop-2-yn-1-yl)-1H-imidazol-5-yl)methanol

[1056] (1H-imidazol-4-yl)methanol is treated with propargyl bromide and diisopropyl ethyl amine in THF overnight. The resulting material is purified to afford the title compound.



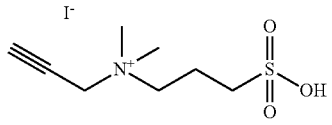
Compound AE81: N-(3-(hydroxyhydrophosphoryl) propyl)-N,N-dimethylprop-2-yn-1-aminium

[1057] (3-(dimethylamino)propyl)phosphinic acid is taken up in THF and treated with drop wise addition of propargyl iodide. The resulting precipitate is collected and dried and recrystallized to afford the title compound.



Compound AG83: N,N-dimethyl-N-(3-phosphono-propyl)prop-2-yn-1-aminium Iodide

[1058] (3-(dimethylamino)propyl)phosphonic acid is taken up in THF and treated with drop wise addition of propargyl iodide. The resulting precipitate is collected and dried and recrystallized to afford the title compound.



Compound AI85: N,N-dimethyl-N-(3-sulfopropyl)prop-2-yn-1-aminium Iodide

[1059] 3-(dimethylamino)propane-1-sulfonic acid is taken up in THF and treated with drop wise addition of propargyl iodide. The resulting precipitate is collected and dried and recrystallized to afford the title compound.

Example 2: Cell-Based Assay for TMA Production from a Native Producer

[1060] Trimethylamine lyase (CutC) from *Clostridium sporogenes* ATCC 15579 (protein EDU36695.1) and *Proteus mirabilis* strain HI4320 (protein WP_012368484.1) was identified as an enzyme that converts choline into trimethylamine. In each bacterium, CutC was modified into its activated form by a cognate activating enzyme, CutD (protein EDU36696.1 for *C. sporogenes*; protein WP_004249185.1 for *P. mirabilis*). We have also identified additional enzymes that convert carnitine into trimethylamine. Trimethylamine may subsequently be converted by human enzymes such as flavin monooxygenase 3 to trimethylamine N-oxide, which might be associated with negative health consequences in humans.

[1061] These examples of bacterial enzymes producing metabolites negatively associated with human health are not intended to be limiting.

[1062] A compound's ability to inhibit CutC from *Proteus mirabilis* and *C. sporogenes* from converting choline into trimethylamine was tested in cells as described. A BHI blood plate was inoculated with a frozen stock of *Proteus mirabilis* or *Clostridium sporogenes* under anaerobic conditions. A single colony was isolated from the plate and inoculated into 5 mL BHI supplemented with 1 mM choline under anaerobic conditions. The liquid cultures were grown overnight at 37° C.

[1063] To prepare each sample, 300 μL of the saturated culture was then inoculated into a 30 mL dilution blank under anaerobic conditions. 1 mM (trimethyl-d_9)-choline and a sufficient amount of a compound to obtain a final concentration of 10 μM were added to the inoculated dilution blank. Optionally, the IC_{50} of an inhibitor may instead be determined by adding an inhibitor across a range of concentrations, for example, 0, 0.001, 0.01, 0.1, 1, and 10 μM. The mixture was incubated at 37° C. for 5 h. Chilled 85% acetonitrile, 15% methanol and 0.2% formic acid was added to the reaction and the mixture was centrifuged. After centrifugation, the samples were analyzed by LCMS to determine the amount of d_9-TMA produced. Results are shown in Table 1.

TABLE 1

Compound No.	IC_{50} Whole cell C. sporogenes (uM)*	Average IC_{50} Whole cell *P. mirabilis* (uM)	Standard Deviation for IC_{50} in *P. mirabilis*	Number of assay runs for *P. mirabilis*
127	10.00	5.01	7.05	2
B52	0.01	0.03	0.04	3
Z76	10.00	4.04	5.26	3
128	10.00	10.00	N/A	1
159	0.76	3.51	5.63	3
159	10.00	0.28	0.37	2
129	10.00	10.00	0.00	2
J60	0.00	0.18	0.13	7
130	10.00	3.47	1.71	2
A51	0.93	1.10	1.39	2
107	10.00	10.00	0.00	2
132	10.00	10.00	N/A	1
133	0.44	0.66	N/A	1
134	10.00	10.00	N/A	1
110	10.00	10.00	N/A	1
111	—	0.14	0.12	2
137	10.00	10.00	N/A	1
117	10.00	10.00	N/A	1
116	10.00	10.00	N/A	1
109	0.42	0.62	0.58	6
108	2.46	2.19	N/A	1
113	1.25	0.70	N/A	1
114	1.63	2.08	N/A	1
115	9.85	2.07	N/A	1
116	10.00	10.00	N/A	1
138	5.35	1.05	0.28	3
112	0.28	0.55	0.30	2
140	10.00	10.00	N/A	1
141	10.00	5.25	4.20	3
111	0.22	0.27	N/A	1
143	10.00	10.00	0.00	2
144	0.70	0.58	N/A	1
145	1.38	10.00	0.00	2
146	1.50	10.00	N/A	1
147		10.00	0.00	2
148		10.00	N/A	1
149		10.00	N/A	1
Prodrug 7		3.16	N/A	1
Prodrug 19		1.730	N/A	1
Prodrug 8		10.00	N/A	1
Prodrug 69		10.00	N/A	1
Prodrug 73		10.00	N/A	1
Prodrug 70		10.00	N/A	1
Prodrug 71		10.00	N/A	1
Prodrug 72		10.00	N/A	1
Prodrug 73		10.00	N/A	1
Prodrug 74		10.00	N/A	1
Prodrug 106		10.00	N/A	1
Prodrug 78		10.00	N/A	1
Prodrug 78		10.00	N/A	1
Prodrug 77		10.00	N/A	1
Prodrug 79		10.00	N/A	1
Prodrug 79		10.00	N/A	1
Prodrug 80		10.00	N/A	1
Prodrug 86		10.00	N/A	1
Prodrug 98		0.00	N/A	1
Prodrug 99		0.00	N/A	1
151		0.89	1.16	2
152		10.00	N/A	1

TABLE 1-continued

Compound No.	IC_{50} Whole cell C. sporogenes (uM)*	Average IC_{50} Whole cell *P. mirabilis* (uM)	Standard Deviation for IC_{50} in *P. mirabilis*	Number of assay runs for *P. mirabilis*
153		0.02	0.01	2
159		10.00	N/A	1
160		10.00	N/A	1
161		10.00	N/A	1
162		0.29	0.23	2
125		0.19	0.02	2
164		10.00	N/A	1
165		2.13	N/A	1
J60		0.09	0.02	2
B52		0.04	N/A	1
166		1.26	N/A	1
167		10.00	N/A	1
168		0.87	N/A	1
169		10.00	N/A	1
171		10.00	N/A	1
172		10.00	N/A	1
173		10.00	N/A	1
174		0.17	N/A	1
175		0.17	N/A	1
154		10.00	N/A	1
155		2.58	N/A	1
156		10.00	N/A	1
157		10.00	N/A	1
176		10.00	N/A	1
177		7.57	N/A	1
178		10.00	N/A	1
179		0.11	N/A	1
180		>10	N/A	1
181		>10	N/A	1
182		3.150	N/A	1
183		>10	N/A	1
184		>10	N/A	1
185		0.235	N/A	1
186		>10	N/A	1
187		0.763	N/A	1
188		>10	N/A	1
189		>10	N/A	1
190		1.280	N/A	1
191		2.165	N/A	1
192		>10	N/A	1
193		1.375	N/A	1
194		>10	N/A	1
195		>10	N/A	1
196		7.780	N/A	1
197		4.970	N/A	1
198		>10	N/A	1
199		>10	N/A	1
200		2.740	N/A	1
201		>10	N/A	1
202		0.242	N/A	1
203		1.720	N/A	1
204		0.660	N/A	1
205		8.300	N/A	1
206		0.069	N/A	1
207		0.310	N/A	1
208		>10	N/A	1
209		6.800	N/A	1
210		>10	N/A	1
211		0.211	N/A	1
212		1.990	N/A	1
213		0.180	N/A	1
214		3.870	N/A	1
215		0.409	N/A	1
216		>10	N/A	1
217		0.771	N/A	1
218		>10	N/A	1
219		>10	N/A	1
220		>10	N/A	1
221		>10	N/A	1
222		>10	N/A	1
223		2.280	N/A	1

TABLE 1-continued

Compound No.	IC_{50} Whole cell C. sporogenes (uM)*	Average IC_{50} Whole cell *P. mirabilis* (uM)	Standard Deviation for IC_{50} in *P. mirabilis*	Number of assay runs for *P. mirabilis*
224		0.223	0.102	2
225		0.629	0.095	2
226		0.244	0.007	2
227		>10	N/A	1
228		>10	N/A	2
229		>100.000	N/A	1

IC_{50} values were given the value "10" when a best fit ICso line could not calculated or when the % TMA remaining at the highest concentration of inhibitor (10 μM) was higher than 15%

* C. sporogenes was run once

Example 3: Cell-Based Assay with Bacterial Enzymes

[1064] A vector may be designed to express an enzyme, such as those identified in Example 2, in its wild-type form or a catalytically inactive version. The vector may be transformed into a heterologous host, for example an *E. coli* expression strain. Alternatively, a strain natively encoding one of the enzymes identified in Example 2 may be procured.

[1065] The heterologous host (containing the wild-type enzyme, a catalytically inert version, or the empty vector) or the native strain may be grown to a desirable level.

[1066] The native substrate or an appropriately-chosen substrate analog may be added to the bacterial growth or uninoculated medium. Optionally, an inhibitor might be added to prevent conversion of substrate to product. The mixture may be incubated for a designated period of time.

[1067] After incubation, the mixture may be rendered compatible with LCMS analysis via addition of organic solvent or lyophilization followed by dissolution in organic solvent. The amount of residual starting material and of the product may be quantified by LCMS analysis.

[1068] For example, the following cell-based assay for TMA production from a heterologous host is a representative example of the above-described assays. *E. coli* strains capable of co-expressing full-length WT CutC and CutD, the catalytically inert G821A CutC and CutD, or empty pET28 can be produced by transforming the aforementioned plasmids into *E. coli* BL21(DE3) by heat shocking the cells. Transformants may be selected by growing on LB plates supplemented with kanamycin (50 μg/mL).

[1069] A single colony may be isolated from the plate and inoculated into 10 mL LB supplemented with kanamycin (50 μg/mL). The liquid cultures may be grown overnight at 37° C. with rocking on a nutator.

[1070] 500 μL of the saturated overnight culture may be inoculated into 30 mL LB-Kan50 under anaerobic conditions. The cultures may be grown at 37° C. until the optical density at 600 nm reached 0.6 A.U. Then, IPTG may be added to a final concentration of 0.5 mM.

[1071] To 1 mL of induced culture or a media blank may be added 1 mM (trimethyl-d_9)-choline. A compound to be tested for inhibition of CutC may also be added at this time at a fixed final concentration of, for example, 10 μM. Optionally, the IC_{50} of an inhibitor may instead be determined by adding an inhibitor across a range of concentrations, for example, 0, 0.001, 0.01, 0.1, 1, and 10 μM. The

mixture may be incubated at 37° C. for 8 h. Chilled 85% acetonitrile, 15% methanol and 0.2% formic acid may be added to the reaction. After centrifugation, the samples may be analyzed by LCMS, for example, to determine the amount of d_9-TMA that has been produced from the d_9-choline.

[1072] Another representative example of the above-described assays involves assaying active and inactive versions of the proteins listed above and in Example 2 for their ability to react with their native substrate or an appropriately chosen substrate analog in a cell-based assay. In each instance, this incubation may be carried out in the presence of an inhibitor. LCMS may be used to quantify the amount of product that is produced from the native substrate or the isotope-labeled substrate.

Example 4: Determination of Inhibitor Effect on Bacterial Growth

[1073] To verify that the inhibition of d_9-TMA (such as assayed by a method disclosed in Example 3 above) is due to inhibition of enzymatic activity and not cell death, the lag phase of the growth curve from either *P. mirabilis* or *C. sporogenes* was measured.

[1074] A single colony was isolated from the plate and inoculated into 5 mL BHI supplemented with 1 mM choline under anaerobic conditions. The liquid cultures were grown overnight at 37° C.

[1075] 300 μL of the saturated overnight culture was inoculated into 30 mL BHI under anaerobic conditions supplemented in the presence of 10 μM of compound to be tested. The growth of the bacteria was monitored with a spectrophotometer at an Optical Density of 600 nm for 24 hours. Results are shown in Table 2.

TABLE 2

Cmpd No.	Avg Lag Time (% compared to control) [*C. sporogenes*, Conc: 10 μM]	Number of *C.sporogenes* Replicates	SD of *C. sporogenes* Lag Time	Avg Lag Time (% compared to control) [*P. mirabilis*, Conc: 10 μM]	Number of *P.mirabilis* Replicates	SD of *P. mirabilis* Lag Time
B52	102.55	2	17.04	100.40	2	10.32
Z76	100.20	1	N/A	92.30	1	N/A
J60	98.30	2	2.26	101.93	3	7.29
H58	N/A	0	N/A	106.10	1	N/A
109	92.70	1	N/A	99.40	2	4.38
138	102.60	1	N/A	82.80	1	N/A
112	97.20	1	N/A	97.20	1	N/A
145	107.70	1	N/A	107.10	1	N/A
153	N/A	0	N/A	98.20	1	N/A
X74	N/A	0	N/A	98.40	1	N/A
78	93.8			109.4		
79	83.5			103.3		
80	95.9			95.3		
228	108.3			112.2		
317	83			111.1		
318	83.1			103		
229	96.9			112.4		

Example 5: Inhibition of Enzymatic Activity in Fecal Matter

[1076] Inhibition of enzymatic activity in fecal matter was determined by adding a substrate (d9-choline, 1 mM final concentration) and a compound in a range of concentrations in order to determine an IC_{50}. After incubation for a designated 16 hours at 37° C. in anaerobic conditions, samples were be prepared for LCMS analysis, and the amount of d9-TMA produced was determined using LCMS analysis as in the Examples above. Results are shown in Table 3.

TABLE 3

Compound	IC_{50}	Number of Runs
78	0.39	6
79	1.17	6
80	0.38	5
317	0.43	3

Example 6: Acute Mouse Model

[1077] The following acute mouse model may be used to determine inhibition of the CutC/D enzyme and thus the inhibition of the formation of trimethylamine (TMA) from choline.

[1078] On day 1, male C57BL/6 mice were given a chemically defined diet (Tekland Global Rodent Diet 2018) containing 1.0% choline (g/g) for the duration of the experiment. Concurrently on day 1, mice were orally gavaged with 200 μL of compounds of interest (formulated in water). Mice were orally gavaged with the compounds and vehicle control again on day 2 and day 3 at a fixed time. Twenty hours after the last gavage, mice were sacrificed, and plasma was collected and prepared for detection of trimethylamine-N-oxide (TMAO) via liquid chromatography with on-line tandem mass spectrometry (LC-MS/MS). Food consumption and mouse weight were measured each day.

[1079] Plasma samples were prepared for LCMS as follows: An aliquot of 20 μL plasma sample was protein precipitated with 200 μL internal standard solution (100 ng/mL Labetalol & 100 ng/mL Tolbutamide & 100 ng/mL Diclofenac in acetonitrile, the mixture was vortex-mixed and centrifuged at 4000 rpm for 15 min, 4° C. An aliquot of 100 μL supernatant was transferred to the sample plate for LCMS injection. 1 μL of sample was injected onto an LC column for TMAO LCMS analysis.

[1080] Concentrations of TMAO were determined with a calibration curve ranging 0.05-100 μM for d9-TMAO in control plasma. Results are shown in Tables 3a-3e.

TABLE 4a

Diet + Compound	Mean plasma TMAO (μM)	% change from vehicle control + choline diet
Normal Diet + Vehicle Control	4.56	−86.75
Choline Diet + Vehicle Control	34.39	0.00
Choline diet + Compound I59 (100 mg/kg)	10.85	−68.44
Choline diet + Compound 19 (333 mg/kg)	5.40	−84.29
Choline diet + Compound J60 (10 mg/kg)	31.06	−28.46
Choline diet + Compound J60 (33 mg/kg)	17.20	−60.39
Choline diet + Compound J60 (100 mg/kg)	5.52	−87.29
Choline diet + Compound 7 (358 mg/kg)	6.90	−79.95

TABLE 4b

Diet + Compound	Mean plasma TMAO (μM)	% change from vehicle control + choline diet
normal diet + vehicle	2.55	−89.74
choline diet + vehicle	24.9	0.00
choline diet + Compound J60 (10 mg/kg)	24.7	−0.69
choline diet + Compound B52 (10 mg/kg)	30.0	20.76
choline diet + Compound 141 (10 mg/kg)	2.92	−88.23
choline diet + Compound J60 (10 mg/kg)	27.4	10.16

TABLE 4c

Diet + Compound	Mean plasma TMAO (μM)	% change from vehicle control + choline diet
normal diet +vehicle	2.17	−89.66
choline diet + vehicle	21.0	0.00
choline diet + Compound J60 (100 mg/kg)	5.41	−74.22
choline diet + Compound 7 (35.8 mg/kg)	20.4	−2.97
choline diet + Compound 7 (107 mg/kg)	15.8	−24.83
choline diet + Compound 7 (358 mg/kg)	6.41	−69.46

TABLE 4d

Diet + Compound	Mean plasma TMAO (μM)	% change from vehicle control + choline diet
normal diet + vehicle	2.49	−87
choline diet + vehicle	18.8	0
choline diet + Compound J60 (100 mg/kg)	6.00	−68
choline diet + Compound 58 (10 mg/kg)	10.1	−46
choline diet + Compound 310 (33.8 mg/kg)	2.3	−88
choline diet + Compound 312 (35.4 mg/kg)	11.69	−38
choline diet + Compound 309 (32.6 mg/kg)	1.9	−90
choline diet + Compound 311 (37.0 mg/kg)	1.8	−90
choline diet + Compound 8 (100 mg/kg)	12.5	−33
choline diet + Compound 10 (100 mg/kg)	14.9	−21
choline diet + Compound 9 (100 mg/kg)	33.91	80

TABLE 4e

Diet + Compound	Mean plasma TMAO (μM)	% change from vehicle control + choline diet
normal diet + vehicle	1.90	−93
choline diet + vehicle	26.4	0
choline diet + Compound J60 (100 mg/kg)	3.81	−86
choline diet + Compound 185 (123.7 mg/kg)	22.2	−16

TABLE 4f

Diet + Compound	Mean plasma TMAO (μM)	% change from vehicle control + choline diet
normal diet + vehicle	3.91	−88
choline diet + vehicle	32.3	0
choline diet + Compound J60 (100 mg/kg)	6.20	−81
choline diet + Compound 98 (36.6 mg/kg)	10.1	−69
choline diet + Compound 98 (11.0 mg/kg)	34.3	6
choline diet + Compound 98 (3.70 mg/kg)	29.7	−8
choline diet + Compound 309 (37.2 mg/kg)	5.45	−83
choline diet + Compound 309 (11.0 mg/kg)	15.4	−52
choline diet + Compound 309 (3.70 mg/kg)	35.2	9
choline diet + Compound 311 (35.3 mg/kg)	11.23	−65
choline diet + Compound 311 (10.6 mg/kg)	17.4	−46
choline diet + Compound 311(3.5 mg/kg)	20.22	−37

TABLE 4g

Diet + Compound	Mean plasma TMAO (μM)	% change from vehicle control + choline diet
normal diet + vehicle	3.04	−89
choline diet + vehicle	27.8	0
choline diet + Compound J60 (100 mg/kg)	13.1	−53
choline diet + Compound 125 (97.7 mg/kg)	32.8	18
choline diet + Compound 125 (9.8 mg/kg)	26.2	−6
choline diet + Compound 86 (112 mg/kg)	4.72	−83
choline diet + Compound 86 (37.3 mg/kg)	18.6	−33
choline diet + Compound 109 (116 mg/kg)	2.71	−90
choline diet + Compound 151 (116 mg/kg)	29.4	6

TABLE 4h

Diet + Compound	Mean plasma TMAO (μM)	% change from vehicle control + choline diet
normal diet + vehicle	3.07	−93
choline diet + vehicle	44.4	0
choline diet + Compound J60 (100 mg/kg)	8.72	−80
choline diet + Compound 315 (226.5 mg/kg)	8.96	−80
choline diet + Compound 315 (67.9 mg/kg)	26.6	−40

[1081] The data in Tables 4a-4h show that compounds of the present disclosure can inhibit the production of trimethyl amine and thus can be useful in treating diseases in which CutC and the production of trimethylamine are implications (e.g. treating trimethylaminuria).

Example 7: Compound Efficacy in a Preclinical Chronic Kidney Disease Mouse Model

[1082] The following preclinical model has been used to determine the effect of TMA/TMAO on chronic kidney disease (CKD) (Tang et al 2015; Circulation Research, 116(3): 448-455.). C57BL/6 mice may be fed a chemically defined diet with or without 1.0% choline (g/g) for 16 weeks. Earlier time points of compound intervention may define the potential to prevent the progression of kidney disease. Later time points of intervention may determine the ability of the compounds to treat an established kidney disease phenotype. The weight and food consumption of each mouse will be monitored at regular intervals throughout the study.

[1083] All mice may be sacrificed after 16 weeks of defined diet and compound intervention. As described in the acute mouse model, plasma may be collected and prepared for detection of TMA and TMAO via LCMS. To assess the effect of compounds on renal function, protein in urine may be quantified and blood urea nitrogen (BUN) levels may be measured in the blood. To assess the effect of compounds on kidney injury, kidneys may be collected, and levels of fibrosis may be quantified via histological examination as well as expression of markers of kidney damage and inflammation. Additionally, aortas will be collected and examined for the presence of vascular injury via protein markers of vascular damage.

[1084] For histological examination, kidneys may be fixed and embedded. Fibrosis may be quantified via collagen deposition using the Mason trichome staining procedure (Tang et al 2015, supra, and Sun et al 2017*; Biochem. Biophys. Res. Commun.* 493(2): 964-970).

[1085] Expression of kidney damage markers, such as pSMAD3, kidney injury molecule (KIM)-1, TNFα, TL-1β, neutrophil gelatinase-associated lipocalin (NGAL), plasma cystatin C, urine albumin, and NOX-4, may be determined via Western blot analysis of homogenized kidneys. Expression of vascular damage markers, such as ICAM, VCAM, TNFα, and IL-1β, may be determined via the MesoScale Discovery instrument.

Example 8: Release of Active Agents from Conjugates

[1086] Sprague-Dawley rats (three rats per compound) were treated with a single intravenous (IV) 1 mg/kg dose or orally (PO) a single 10 mg/kg dose. Plasma concentrations of the conjugates were determined by LCMS at 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 and 24 hours post compound administration. For all conjugates, PO doses displayed substantially lower plasma exposure compared to IV administered rats and therefor all conjugates have a low bioavailability (% F) as shown in Table 5 below. In addition, the plasma exposure and bioavailability of the active agent of was lower when dosed as a conjugate instead of the active agent alone.

TABLE 5

Compound Dosed	Compound Measured	IV C_{max} (nmol/L)	PO C_{max} (nmol/L)	% F
78	78	8310	130	0.99
78	Active agent of 78	6	70	1.91
Active agent of 78	Active agent of 78	17200	970	4.20
79	79	13600	260	2.16
79	Active agent of 79	1	50	1.60
Active agent of 79	Active agent of 79	41700	2360	5.99
98	98	23600	306	0.72
Active agent of 98	Active agent of 98	134	142	3.78
80	80	7680	100	0.68
80	Active agent of 80	0	20	1.5
Active agent of 80	Active agent of 80	36900	1000	2.16
7	7	19700	16.2	1.1

Example 9. Targeted Delivery of Active Agents by Non-Systemic Conjugates

[1087] To confirm that the active agent component of the conjugate is released in the gastrointestinal tract, a pharmacokinetic study was conducted in male C57B3L/6 mice examining conjugate and active agent of concentrations in both the colon contents and plasma after oral dose of conjugate. Conjugate and active agent of were quantified by LCMS at 0 (pre-dose), 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose of compound. The results are shown in Table 6 below. The active agents of the conjugate was at least 100,000-fold more concentrated in the colon versus the plasma, suggesting non-systemic, gut restrictive delivery of the active agent by the conjugate.

TABLE 6

Compound Dosed	Compound Measured	Colon C_{max} (μmol/L)	Plasma C_{max} (μmol/L)
78	78	0.07	Not detected
78	Active agent of 78	7077	0.09
79	79	Not detected	0.005
79	Active agent of 79	4081	0.16
98	98	21.83	1.3
98	Active agent of 98	5522	0.40
80	80	0.13	Not detected
80	Active agent of 80	4759	Not detected

Example 10: In Vitro Stability Studies of Conjugates

Assay 1. Stability of Conjugates in Simulated Gastric Fluid (SGF)

[1088] This assay was used to assess the stability of a conjugate in a stomach.

[1089] Medium was prepared by dissolving 2 g of sodium chloride in 0.6 L in ultrapure water (MilliQ®, Millipore Sigma, Darmstadt, Germany). The pH was adjusted to 1.6

with 1N hydrochloric acid, and the volume was then adjusted to 1 L with purified water.

[1090] 60 mg FaSSIF powder (Biorelevant™, London, UK) were dissolved in 500 mL buffer (above). Pepsin was added (0.1 mg/mL) (Millipore Sigma, Darmstadt, Germany), and the solution was stirred. The resulting SGF media were used fresh for each experiment.

[1091] Test compounds were dissolved in DMSO stock to 1 mM. An aliquot of the DMSO stock solution was removed and diluted in the SGF Media in 15 mL falcon tubes to generate a total compound concentration of 1 μM. A 1 mL aliquot was immediately removed and diluted once with 1 volume of acetonitrile for T0 timepoint. The mixture was sealed and mixed at 37° C. in an incubator. Aliquots (1 mL) were removed at regular intervals and immediately quenched by the addition of 1 volume of acetonitrile. The resulting samples were analyzed by LCMS to determine degradation rates in SGF. The results for percent of compound remaining at 1 hour are shown in Table 7.

Assay 2. Stability of Conjugates in Simulated Intestinal Fluid (SIF).

[1092] This assay was used to assess the stability of a conjugate in a small intestine.

[1093] Phosphate buffer was prepared by dissolving 0.42 g of sodium hydroxide pellets and 3.95 g of monobasic sodium phosphate monohydrate and 6.19 g of sodium chloride in ultrapure water (MilliQ®, Millipore Sigma, Darmstadt, Germany). The pH was adjusted to 6.7 using aq. HCl and aq. NaOH, as necessary, and the solution was diluted with ultrapure water to produce 1 L of the pH 6.7 buffer.

[1094] 112 mg FaSSIF powder (Biorelevant™, London, UK) was dissolved in 50 mL of the pH 6.7 buffer. 2 to 3 mL of the resulting solution were then added to 500 mg pancreatin (Millipore Sigma, Darmstadt, Germany). The resulting mixture was agitated by finger tapping the vessel containing the mixture until milky suspension formed. At this time, the remainder of the 50 mL FaSSiF/pH 6.7 buffer solution was added. The resulting suspension was flipped upside down 10 times to produce SIF, which was used fresh.

[1095] Test compounds were dissolved in DMSO stock to 1 mM. An aliquot of the DMSO stock solution was removed and diluted in the SIF media in 15 mL falcon tubes to produce a mixture with a tested compound concentration of 1 μM. A 1 mL aliquot was immediately removed and diluted once with 1 volume of acetonitrile for T0 timepoint. The mixture was sealed and agitated at 37° C. in an incubator. Aliquots (1 mL) were removed at regular intervals and immediately quenched by the addition of 1 volume of acetonitrile. The resulting samples were analyzed by LCMS to determine degradation rates. The results for percent of compound remaining at 4 hours are shown in Table 7.

Assay 3. In Vitro Colonic Material Stability Assay.

[1096] This assay was used to assess the stability of a conjugate in a large intestine.

[1097] All experiments were performed in an anaerobic chamber containing 90% nitrogen, 5% hydrogen and 5% carbon dioxide. Colonic material was resuspended as a slurry (15% w/v final concentration) in pre-reduced, anaerobically sterilized dilution blanks (Anaerobe Systems AS-908). The colonic material was then inoculated into 96 well plates containing YCFAC media (Anaerobe Systems AS-680, 6.7 μL slurry into 1 mL total media). A compound was added to each individual well to reach a final analyte concentration of 1 μM, and the material was mixed by pipetting. Each sample was removed after set timepoints (0, 120, 240, 480, 1440, 2880 minutes after initiation of the assay), quenched with acetonitrile containing internal standard, and analyzed by LCMS. Results are shown in Table 7.

TABLE 7

Compound	Assay 1-FaSSGF Stability: % Remaining at 1 hr	Assay 2-FaSSIF Stability: % Remaining at 4 hr	Assay 3-Colonic Material Stability Assay % Remaining at 24 hr
1	84.79	30.79	80
7	85.06	121.01	56
7	100.35	93.47	51
19	101.36	11.06	2.5
19	85.52	1.52	0.18
303	60.49	0.03	0.16
304	114.28	13.44	0.94
70	98.36	28.06	47
305	92.73	0.25	0.04
72	102.71	—	110
73	107.49	62.73	44
74	107.3	121.56	99
8	105.93	113.28	17
315	109.96	120.35	68
310	97.99	115.11	55
309	97.94	94.72	16
311	104.43	97.27	33
80	145.32	99.34	25
86	—	—	56
317	96.24	82.34	

Example 11: Caco-2 Permeability Assay

[1098] Preparation of Caco-2 Cells: 50 μL and 25 mL of cell culture medium were added to each well of the Transwell insert and reservoir, respectively. The HTS transwell plates were incubated at 37° C., 5% CO_2 for 1 hour before cell seeding. Caco-2 cells were diluted to 6.86×105 cells/mL with culture medium and 50 μL of cell suspension were dispensed into the filter well of the 96-well HTS Transwell plate. Cells were cultivated for 14-18 days in a cell culture incubator at 37° C., 5% CO_2, 95% relative humidity. Cell culture medium was replaced every other day, beginning no later than 24 hours after initial plating.

[1099] Assessment of Cell Monolayer Integrity: Medium was removed from the reservoir and each Transwell insert and replaced with prewarmed fresh culture medium. Transepithelial electrical resistance (TEER) across the monolayer was measured using Millicell Epithelial Volt-Ohm measuring system (Millipore, USA). The Plate was returned to the incubator once the measurement was done. The TEER value was calculated according to the following equation:

TEER measurement (ohms)×Area of membrane (cm2)=TEER value (ohm·cm2)

TEER value should be greater than 230 ohm·cm2, which indicates the well-qualified Caco-2 monolayer.

[1100] Preparation of Solutions: 2 mM stock solutions in DMSO of control compounds were prepared and diluted with HBSS (10 mM HEPES, pH 7.4) to get 10 μM working solution. 0.2 mM stock solutions of test compounds in DMSO were prepared and diluted with HBSS (10 mM

HEPES, pH 7.4 with 0.5% BSA) to get 1 μM working solution. Metoprolol, erythromycin and cimetidine were used as control compounds.

[1101] Performing the Drug Transport Assay.

[1102] The Caco-2 plate was removed from the incubator. The monolayer was washed twice with pre-warmed HBSS (10 mM HEPES, pH 7.4). The plate was incubated at 37° C. for 30 minutes. To determine the rate of drug transport in the apical to basolateral direction, 125 μL of the working solution was added to the Transwell insert (apical compartment). A 50 μL sample was transferred immediately from the apical compartment to 200 μL of acetonitrile containing IS (100 nM alprazolam, 200 nM Caffeine and 100 nM tolbutamide) in a new 96-well plate as the initial donor sample (A-B) and it was vortexed at 1000 rpm for 10 minutes. The wells in the receiver plate (basolateral compartment) were filled with 235 μL of transport buffer. To determine the rate of drug transport in the basolateral to apical direction, 285 μL of the working solution were added to the receiver plate wells (basolateral compartment). A 50 μL sample was transferred immediately from the basolateral compartment to 200 μL of acetonitrile containing IS (100 nM alprazolam, 200 nM Caffeine and 100 nM tolbutamide) in a new 96-well plate as the initial donor sample (B-A) and it was vortexed at 1000 rpm for 10 minutes. The Transwell insert (apical compartment) was filled with 75 μL of transport buffer. The apical to basolateral direction and the basolateral to apical direction need to be done at the same time. The plates were incubated at 37° C. for 2 hours. At the end of the incubation, 50 μL samples from donor sides (apical compartment for Ap→Bl flux, and basolateral compartment for B1→Ap) and receiver sides (basolateral compartment for Ap→Bl flux, and apical compartment for B1→Ap) were transferred to wells of a new 96-well plate, followed by the addition of 4 volume of acetonitrile containing IS (100 nM alprazolam, 200 nM Caffeine and 100 nM tolbutamide). Samples were vortexed for 10 minutes, 50 μL samples were transferred to wells of a new 96-well plate, followed by the addition of 50 μL Hepes and 200 μL IS. All samples were vortexed for 10 minutes, and then centrifuged at 3,220 g for 40 minutes. An aliquot of 150 μL of the supernatant was mixed with an appropriate volume of ultra-pure water before LC-MS/MS analysis.

[1103] Data Analysis

[1104] All calculations were carried out using Microsoft Excel. Peak areas were determined from extracted ion chromatograms. Lucifer yellow leakage of monolayer can be calculated using the following equation:

$$LY\ \text{Leakage} = \left(\frac{I_{acceptor} \times 0.3}{I_{acceptor} \times 0.3 + I_{donor} \times 0.1}\right) \times 100\%$$

where $I_{acceptor}$ is the fluorescence intensity in the acceptor well (0.3 mL), and I_{donor} is the fluorescence intensity in the donor well (0.1 mL) and expressed as % leakage. Lucifer yellow percentage amount transported values should be less than 1.5%. However, if the lucifer yellow percentage amount transported value for a particular transwell is higher than 1.5 but the determined digoxin P_{app} in that transwell is qualitatively similar to that determined in the replicate transwells then, based upon the scientific judgement of the responsible scientist, the monolayer is considered acceptable.

[1105] Apparent permeability (P_{app}) can be calculated for drug transport assays using the following equation:

$$P_{app} = \frac{dQ/dt}{A \times D_o}$$

where:

[1106] P_{app} is apparent permeability (cm/s×10^{-6});

[1107] dQ/dt is the rate of drug transport (pmol/second);

[1108] A is the surface area of the membrane (cm^2); and

[1109] D_0 is the initial donor concentration (nM; pmol/cm^3).

[1110] Efflux ratio can be determined using the following equation:

$$\textit{Efflux}\ \text{Ratio} = \frac{P_{app(B-A)}}{P_{app(A-B)}}$$

where

[1111] $P_{app\ (B\text{-}A)}$ indicates the apparent permeability coefficient in basolateral to apical direction, and

[1112] $P_{app\ (A\text{-}B)}$ indicates the apparent permeability coefficient in apical to basolateral direction. The results are shown in Table 8 below.

TABLE 8

Compound No.	Papp A-B (*10^{-6} cm/s)	Papp B-A (*10^{-6} cm/s)
159	0.894	1.43
77	0.218	0.337
79	0.214	0.255
80	0.28	0.313
J60	11.07	6.23
107	26.8	31.1
7	0.1	0.15
111	0.8	0.8
109	0.6	0.5
315	0.3	0.3
125	0.466	0.482
310	0.206	0.23

OTHER EMBODIMENTS

[1113] Various modifications and variations of the described disclosure will be apparent to those skilled in the art without departing from the scope and spirit of the disclosure. Although the disclosure has been described in connection with specific embodiments, it should be understood that the disclosure as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the disclosure that are obvious to those skilled in the art are intended to be within the scope of the disclosure.

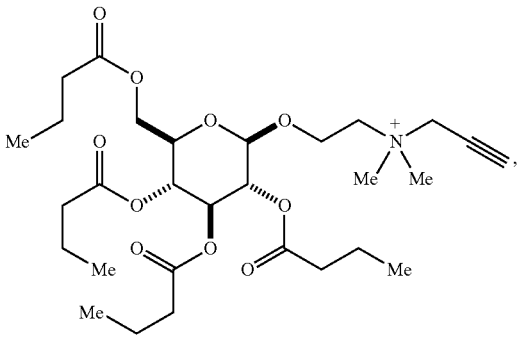
[1114] Other embodiments are in the claims.

What is claimed is:

1. A compound consisting of a cation and a pharmaceutically acceptable counterion, wherein the cation is chosen from:

-continued

1



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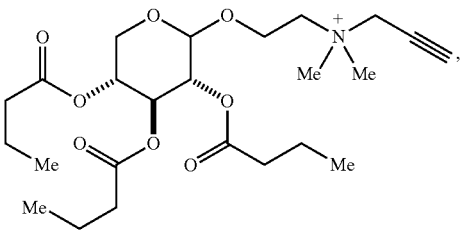

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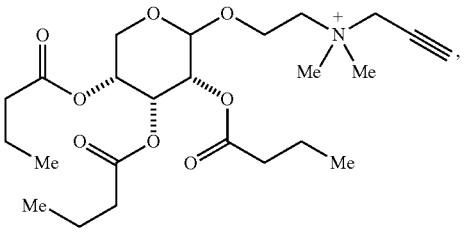

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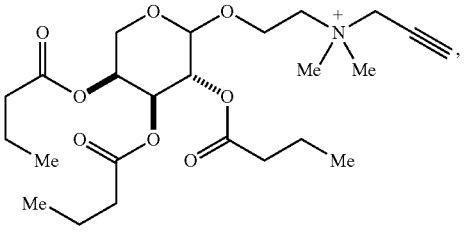

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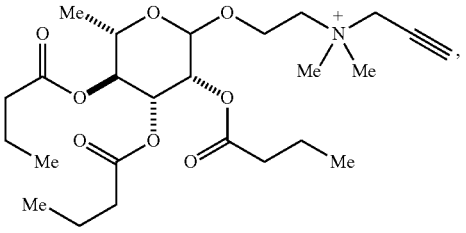

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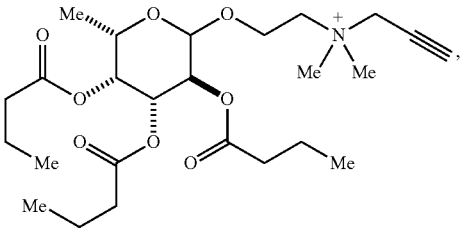

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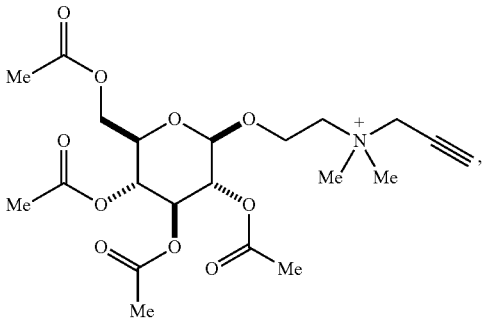

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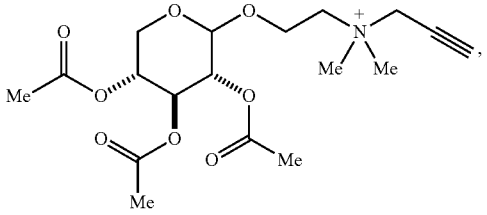

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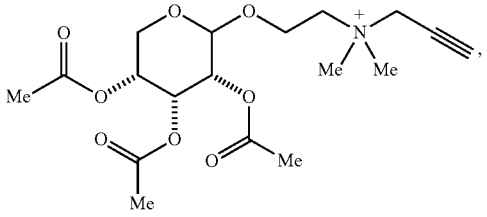

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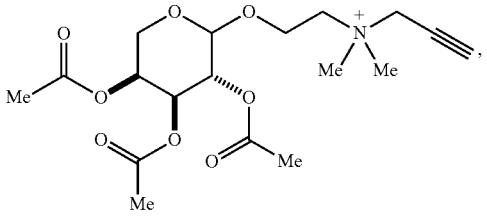

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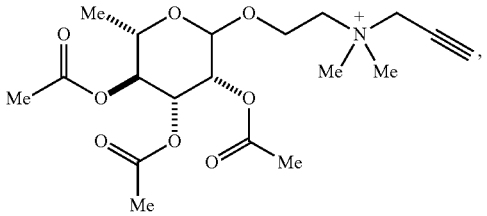

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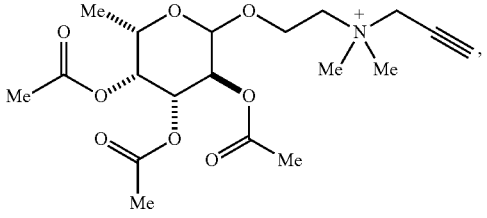

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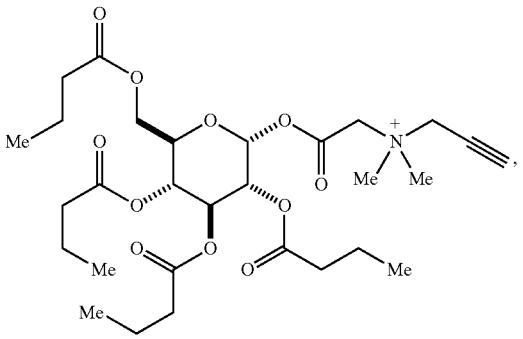

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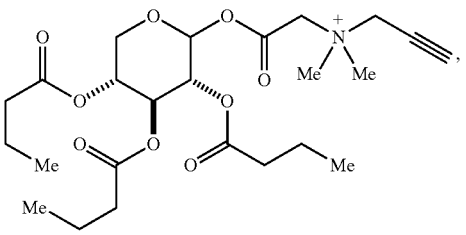

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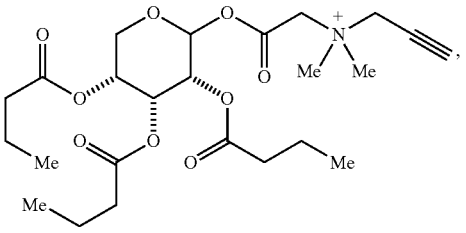

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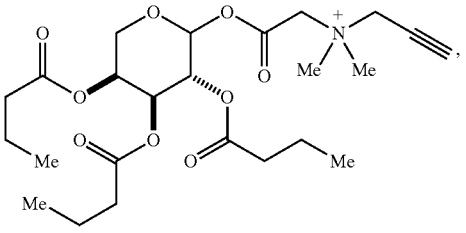

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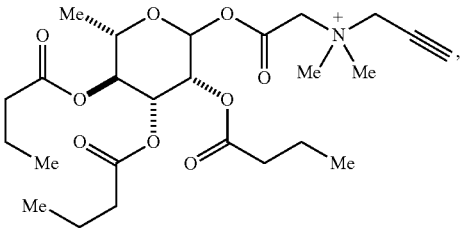

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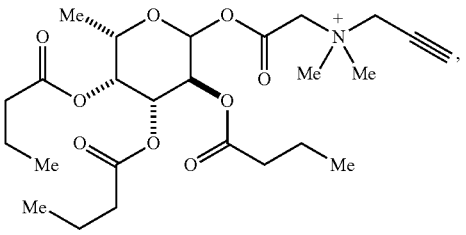

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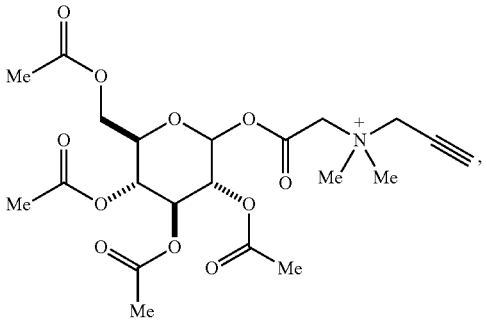

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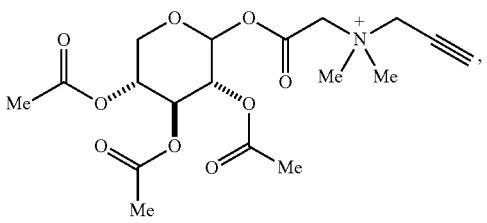

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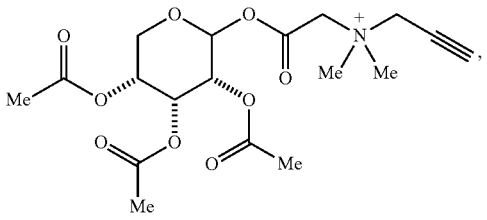

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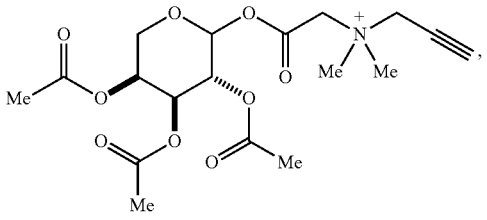

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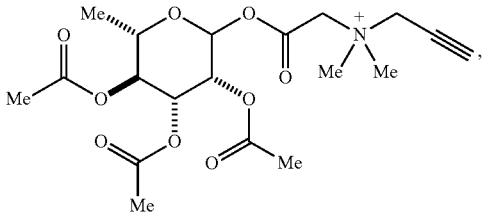

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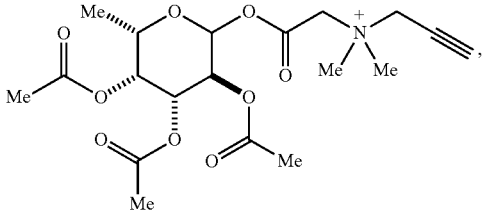

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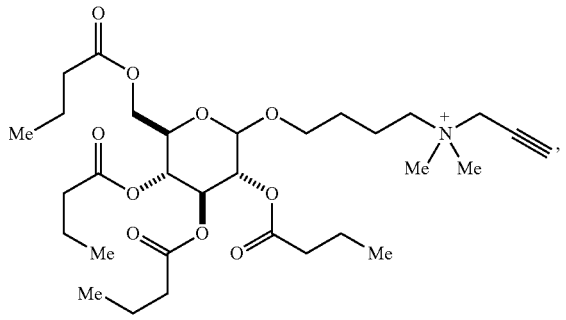

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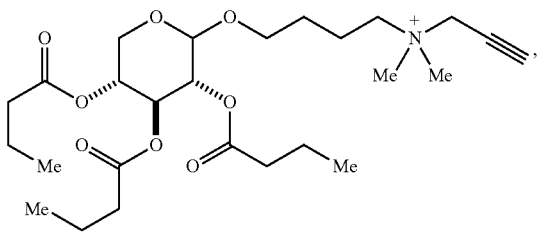

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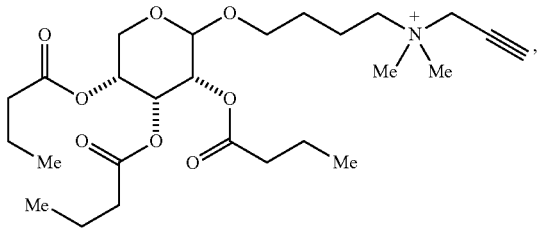

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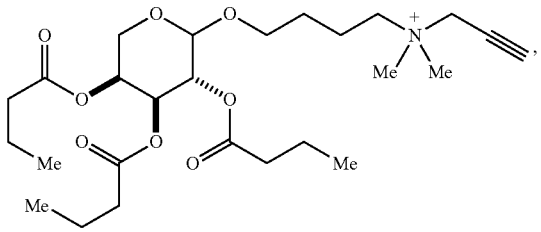

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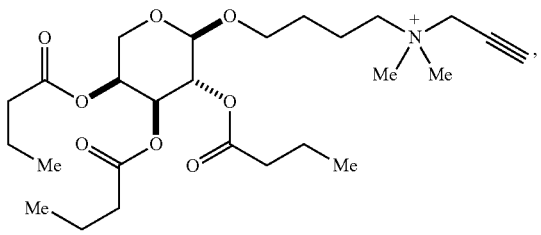

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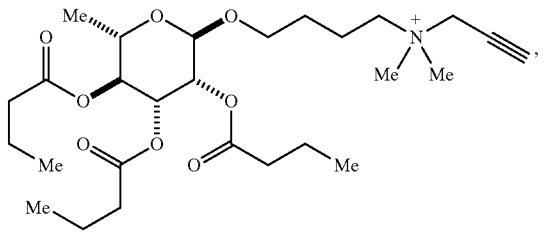

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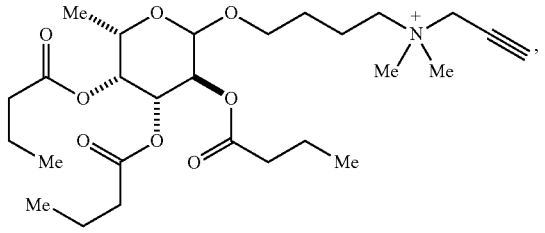

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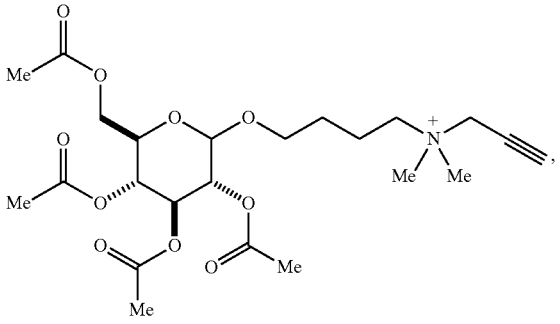

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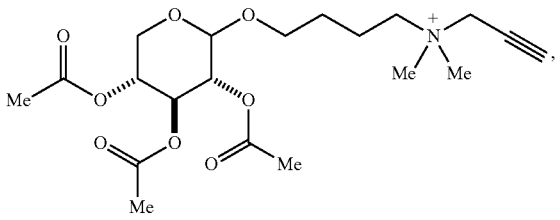

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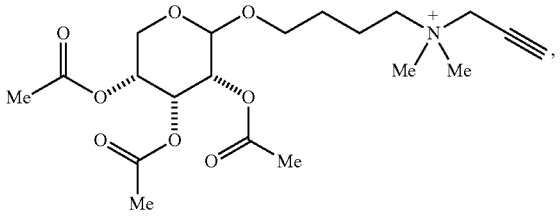

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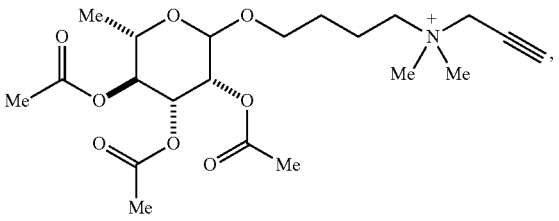

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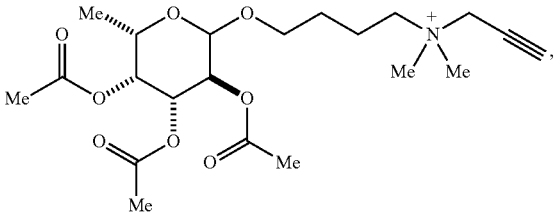

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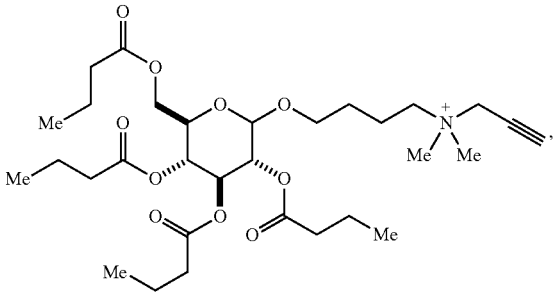

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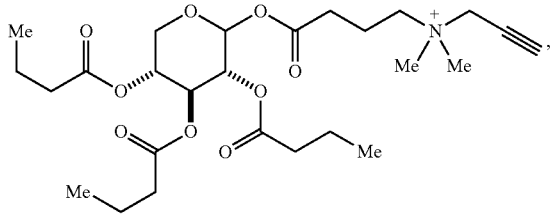

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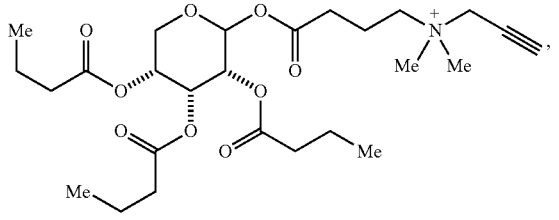

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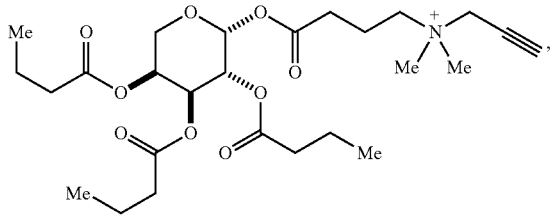

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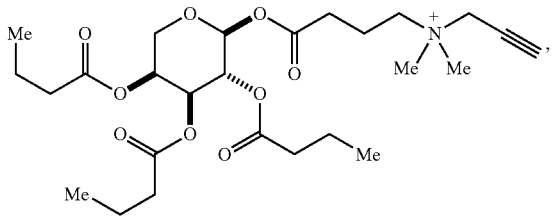

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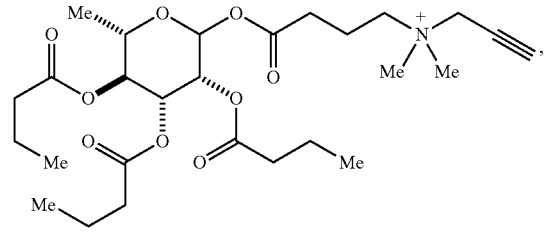

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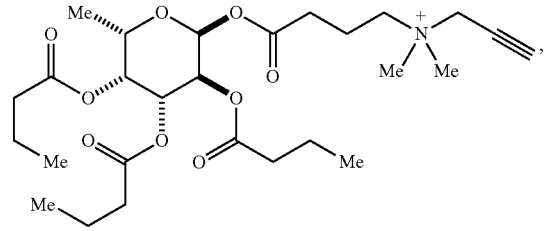

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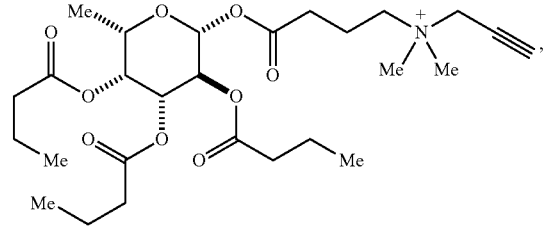

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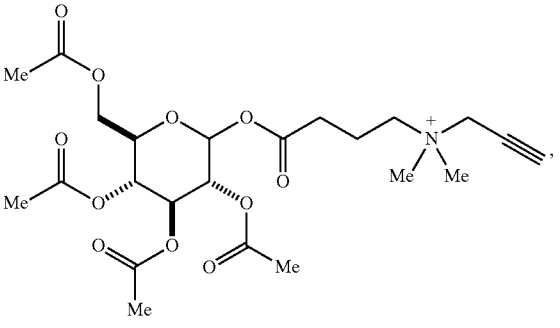

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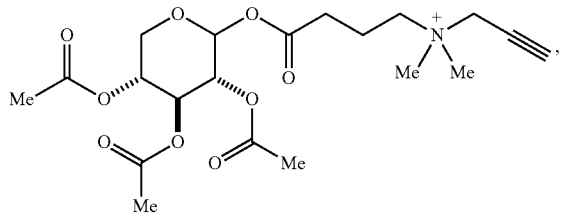

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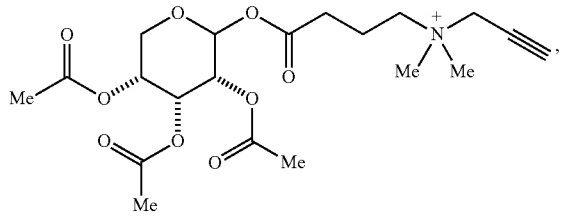

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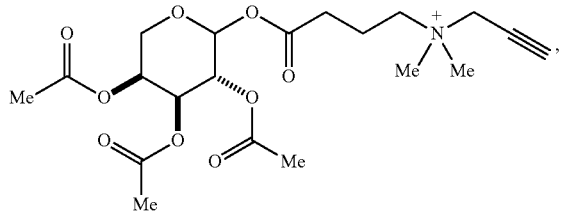

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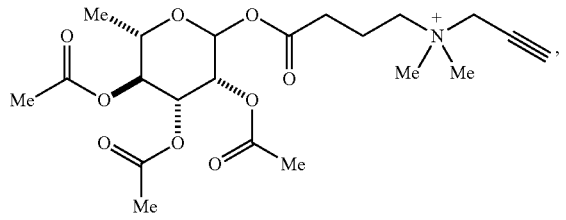

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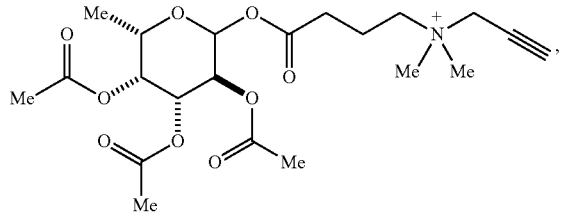

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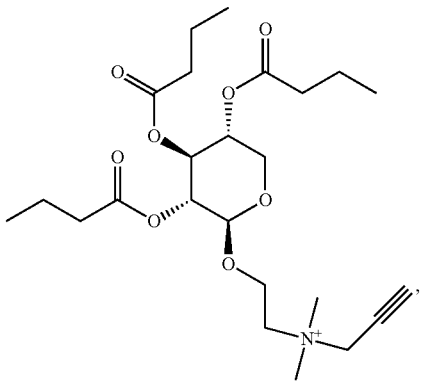

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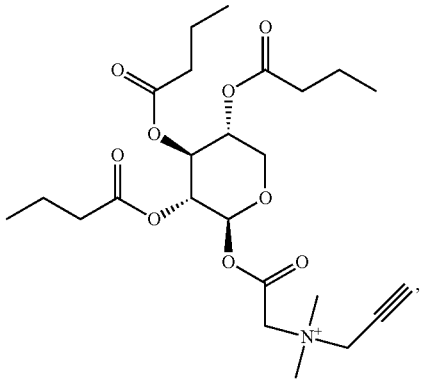

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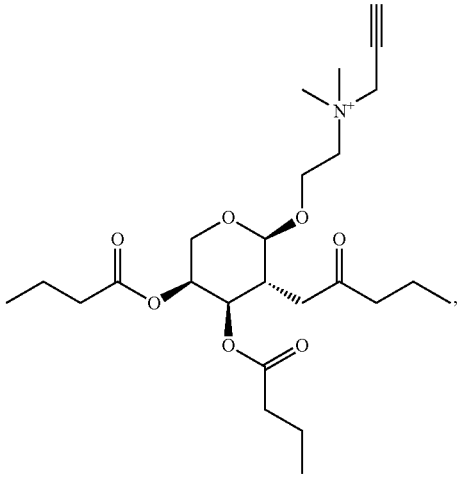

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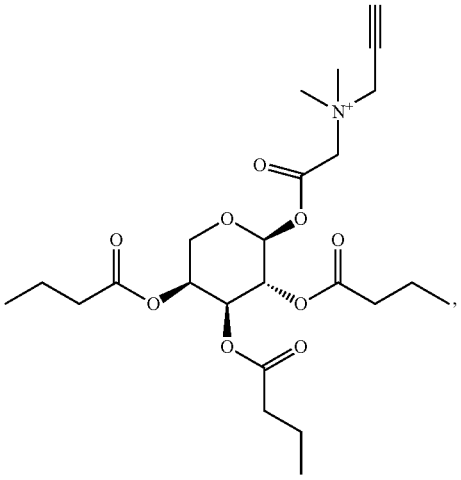

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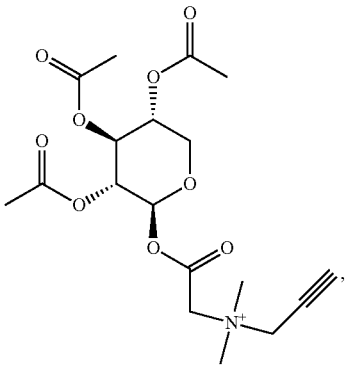

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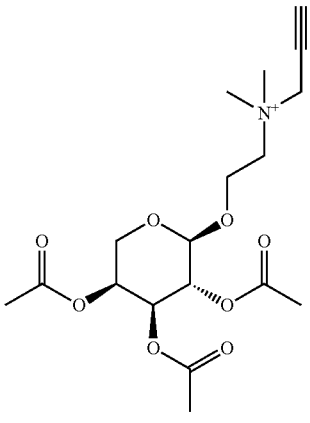

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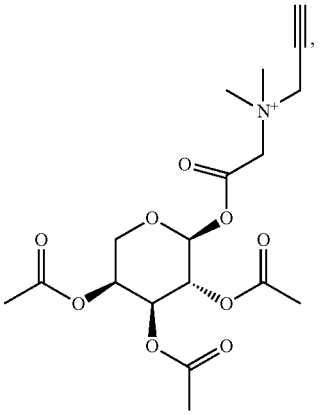

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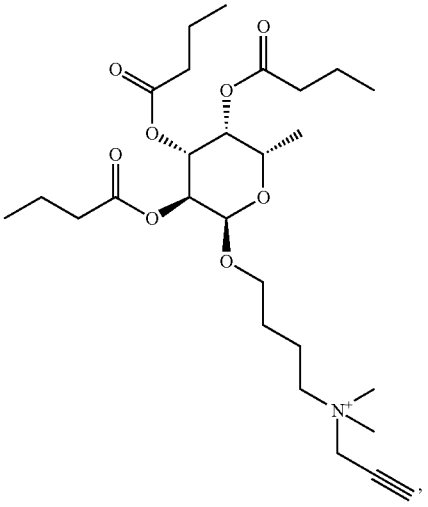

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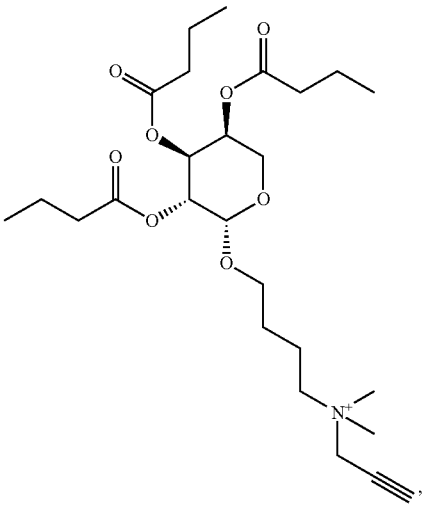

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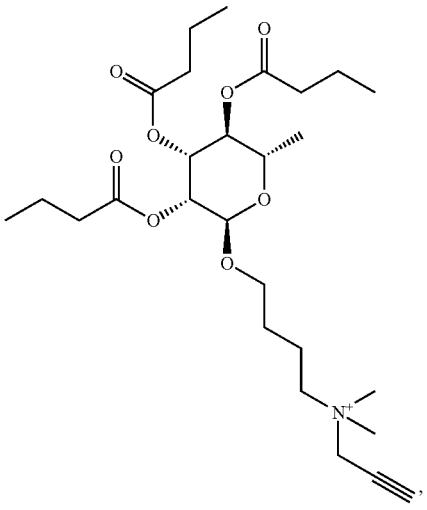

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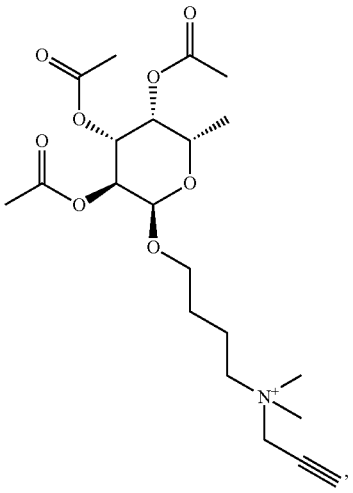

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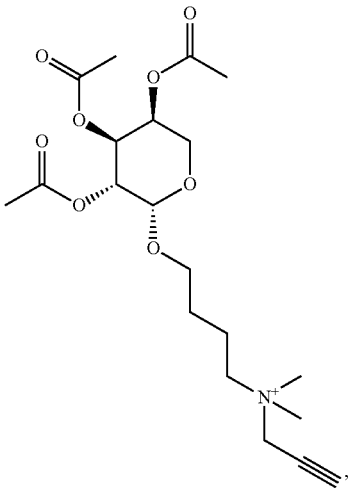

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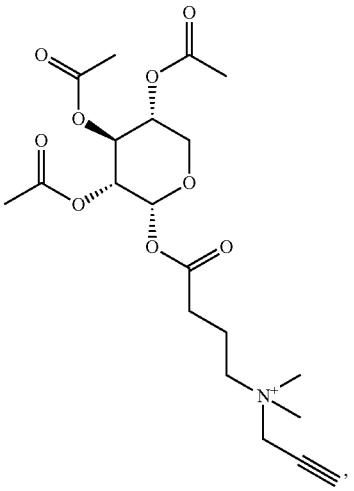

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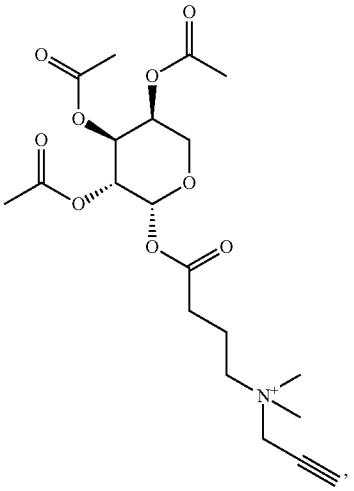

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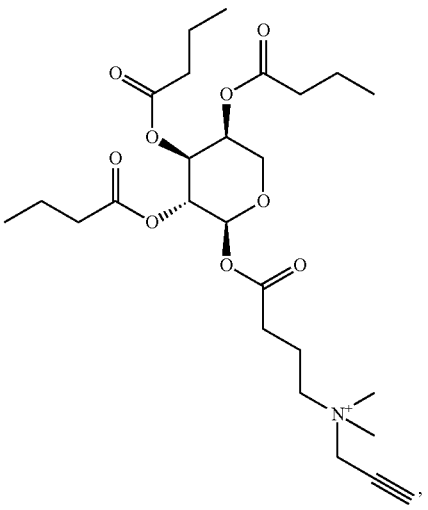

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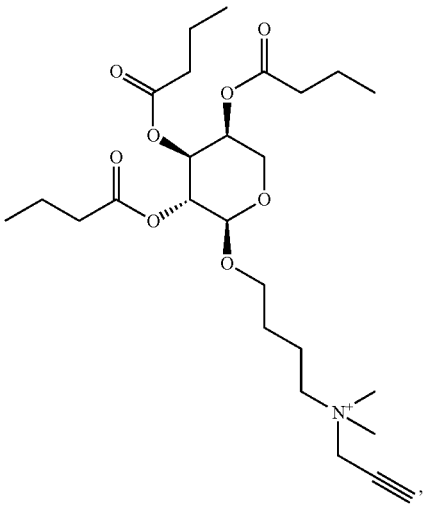

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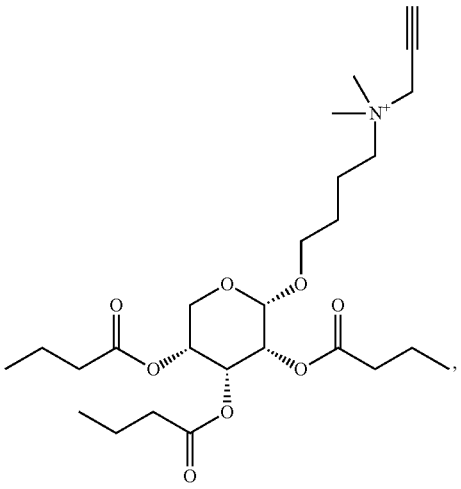

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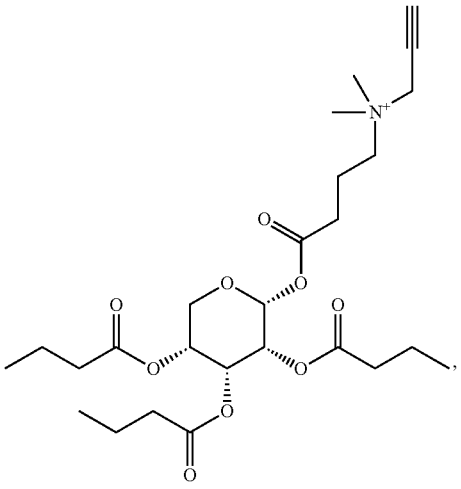

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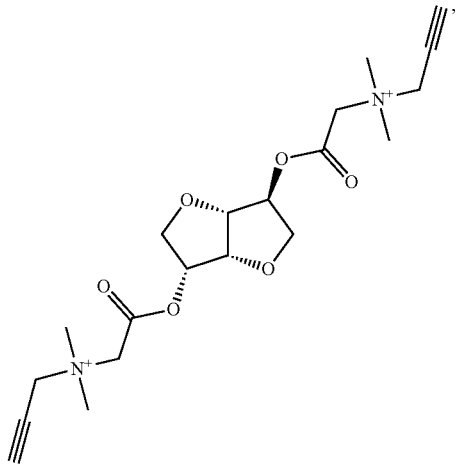

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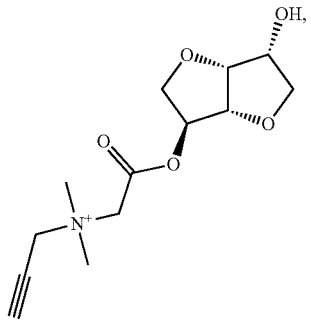

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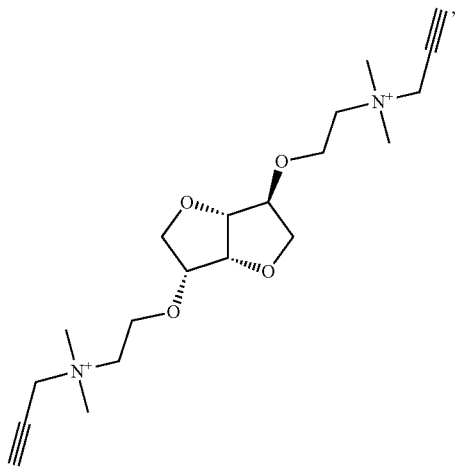

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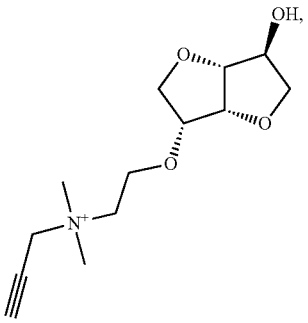

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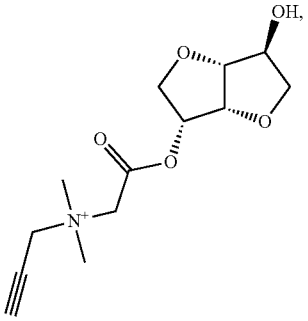

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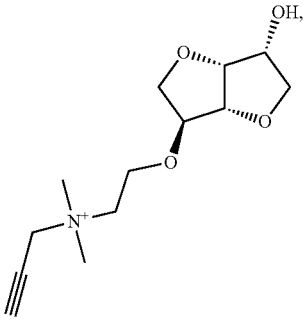

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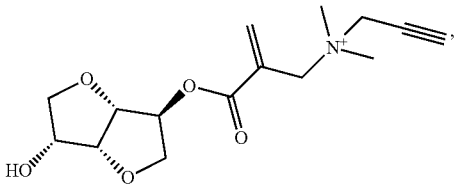

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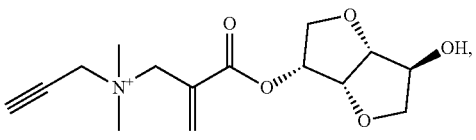

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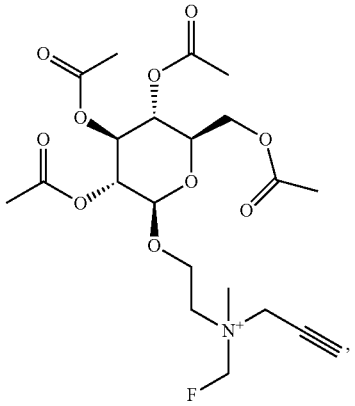

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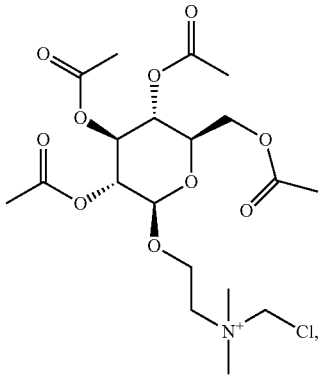

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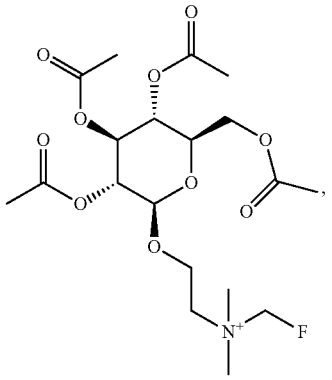

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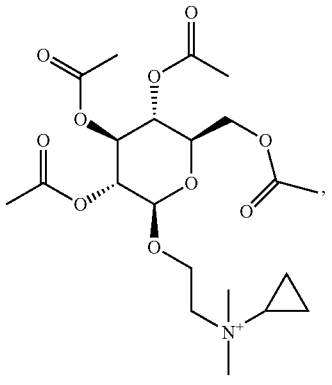

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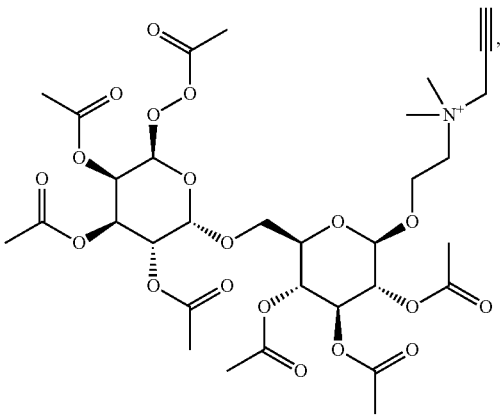

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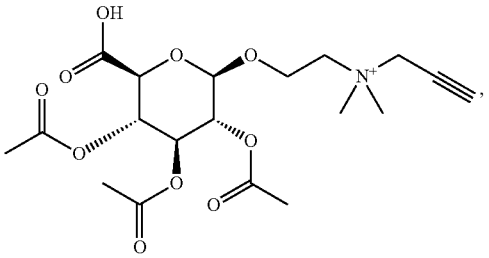

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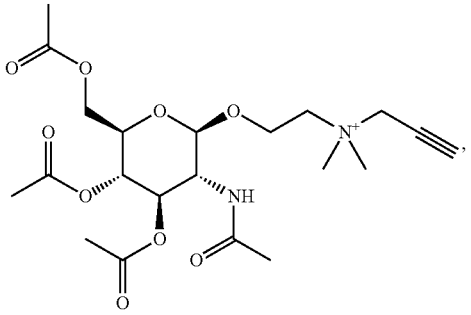

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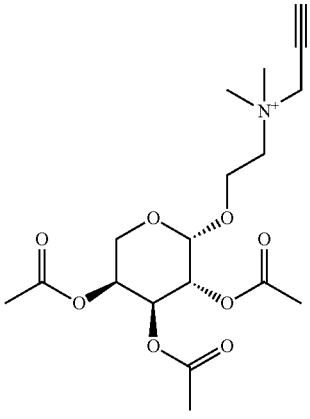

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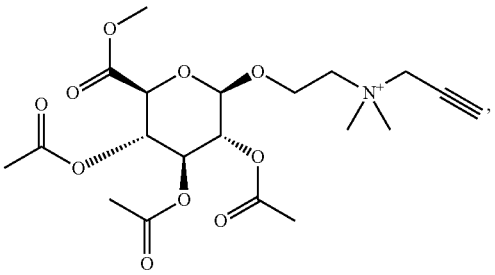

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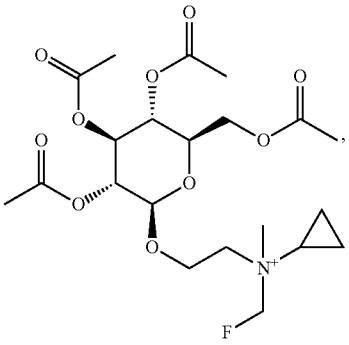

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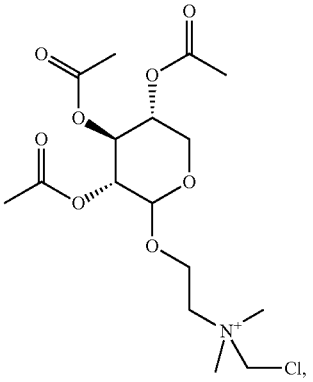

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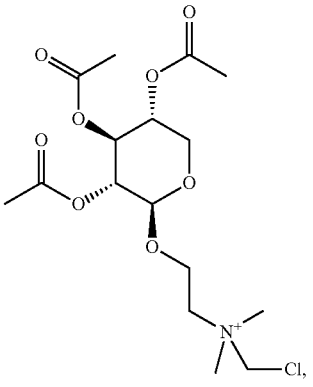

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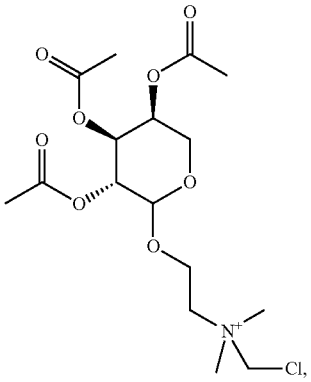

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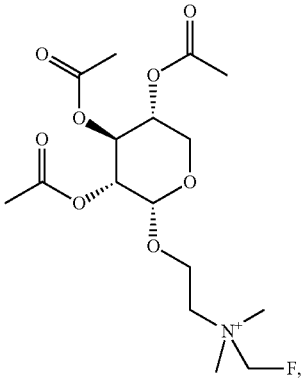

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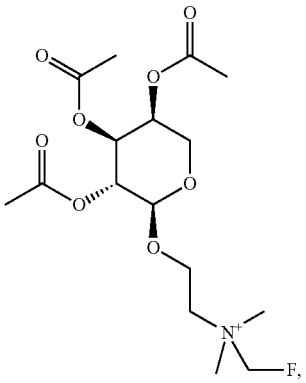

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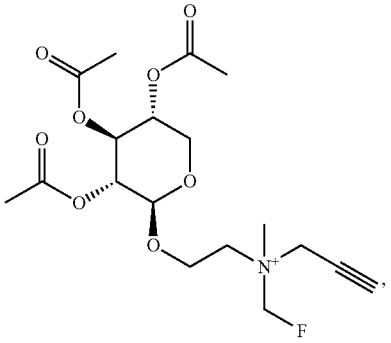

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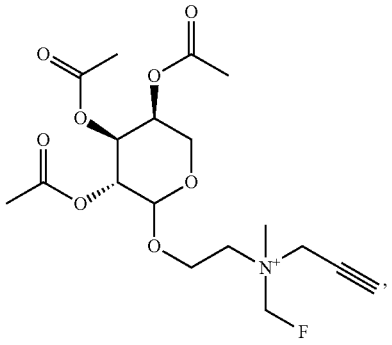

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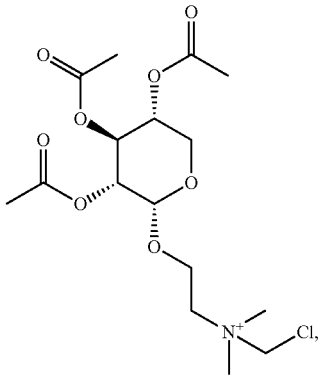

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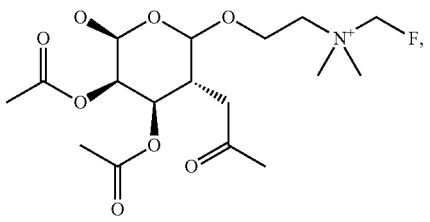

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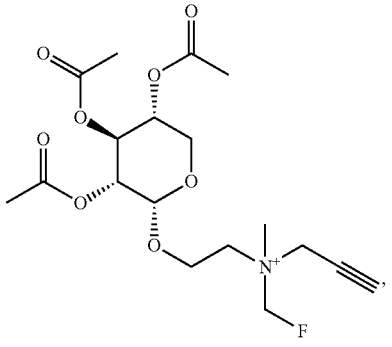

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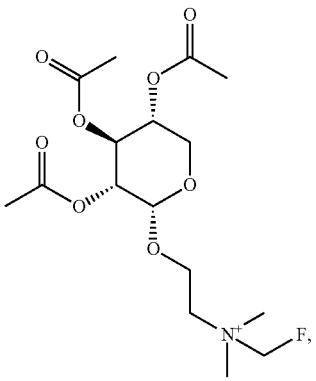

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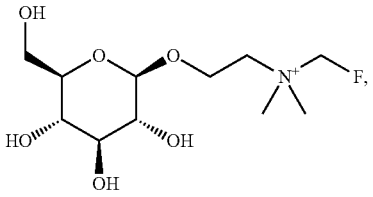

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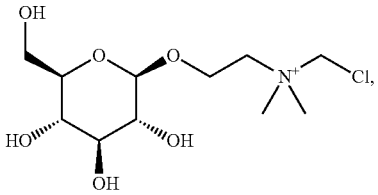

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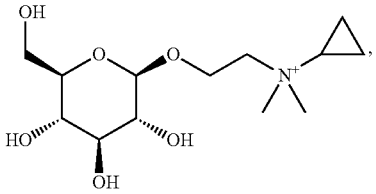

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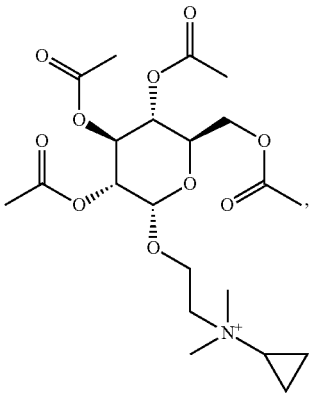

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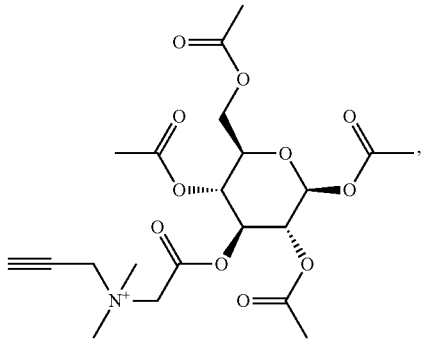

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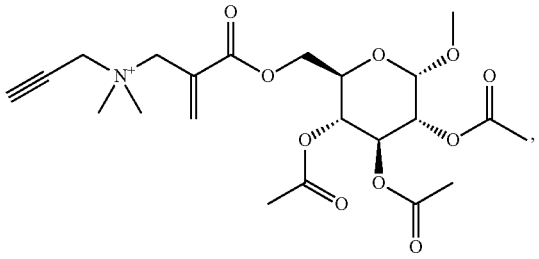

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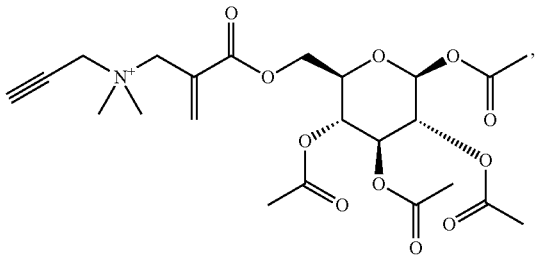

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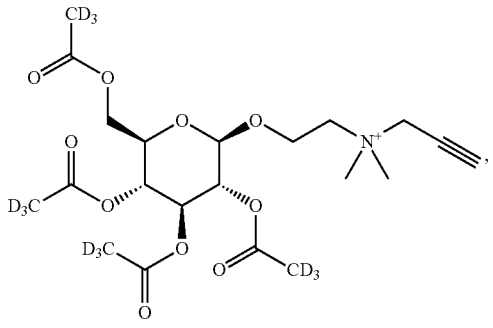

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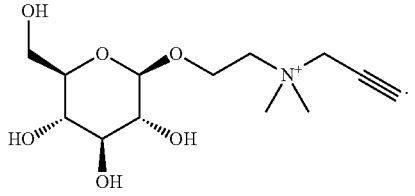
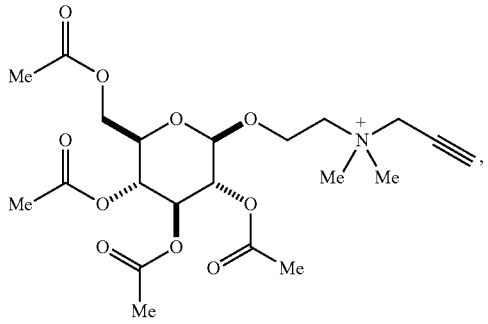


2. The compound according to claim **1**, wherein the cation is chosen from:

7



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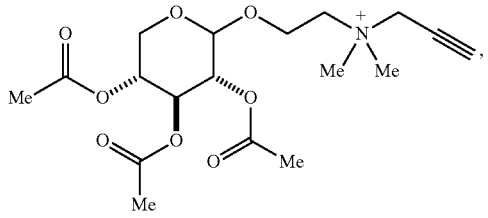

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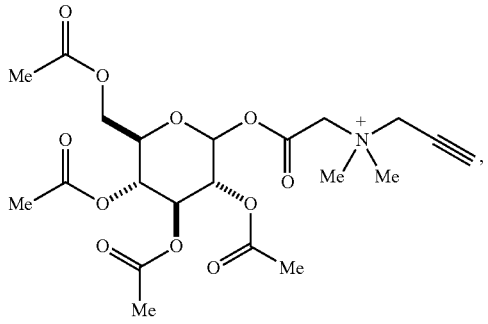

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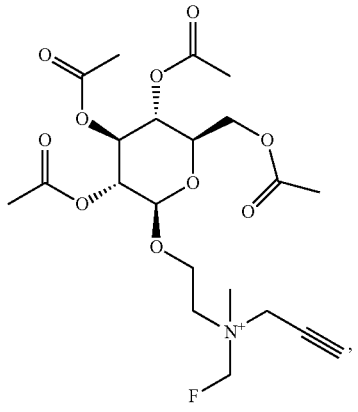

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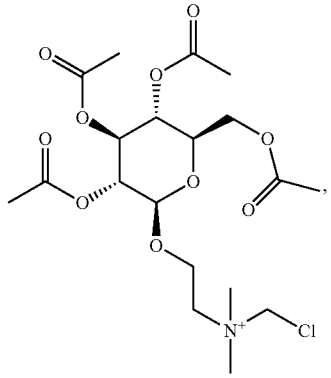

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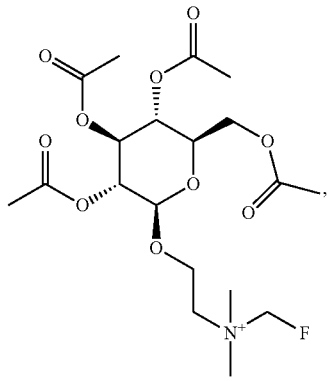

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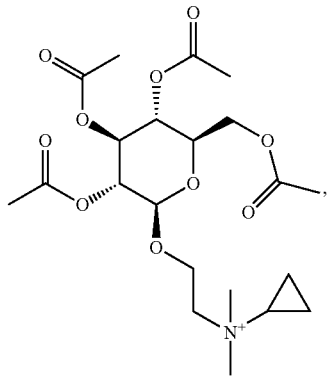

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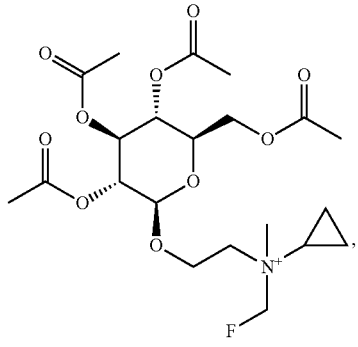

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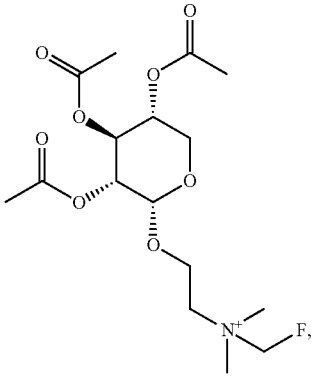

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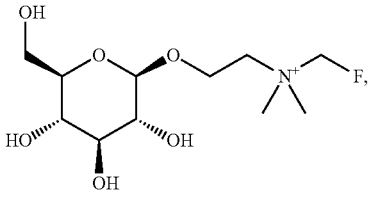

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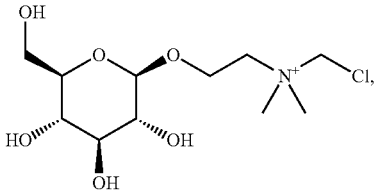

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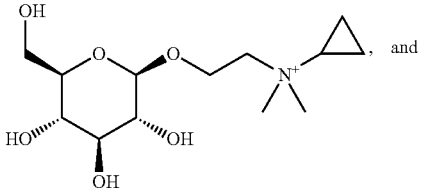

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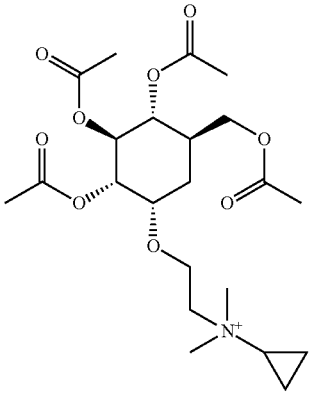
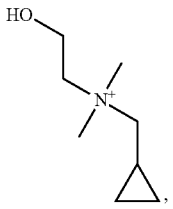


3. A compound consisting of a cation and a pharmaceutically acceptable counterion, wherein the cation is chosen from:

107



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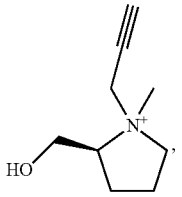

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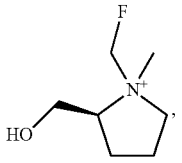

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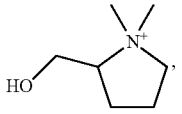

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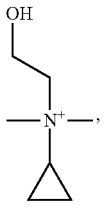

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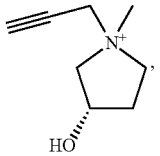

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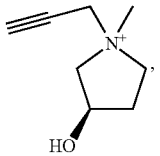

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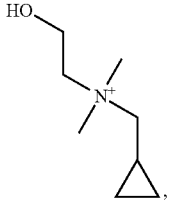

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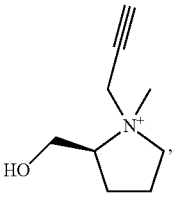

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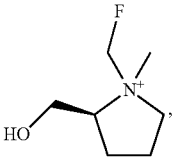

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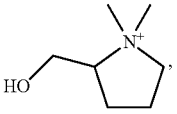

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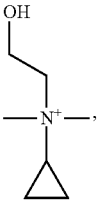

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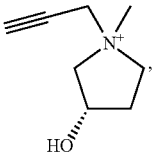

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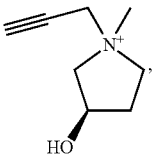

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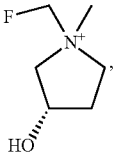

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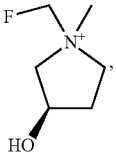

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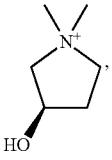

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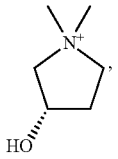

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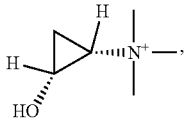

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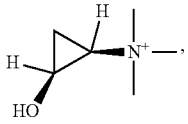

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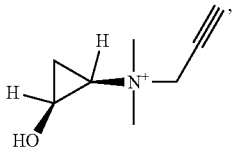

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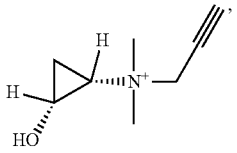

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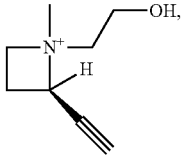

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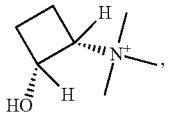

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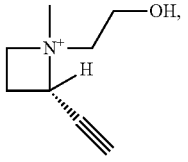

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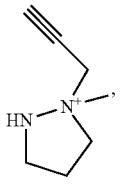

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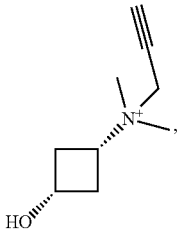

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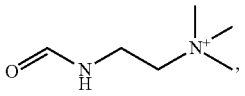

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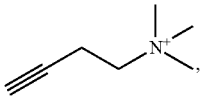

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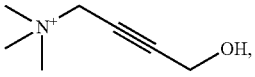

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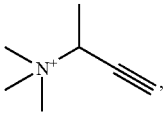

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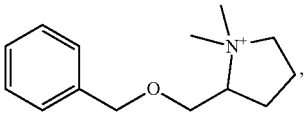

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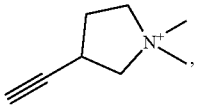

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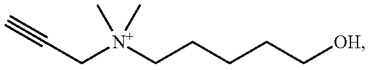

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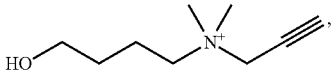

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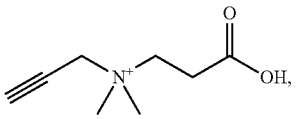

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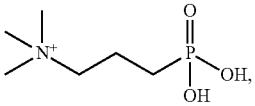

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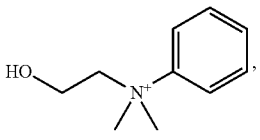

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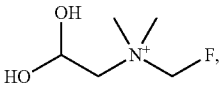

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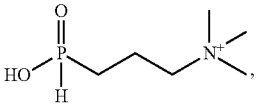

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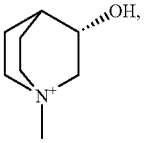

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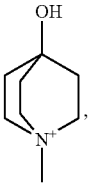

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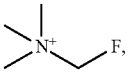

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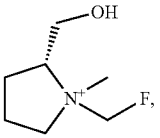

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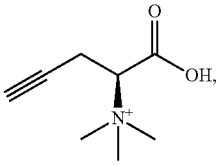

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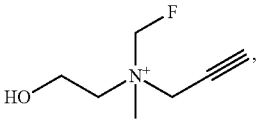

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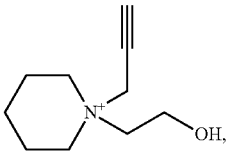

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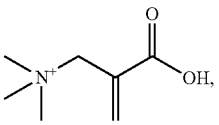

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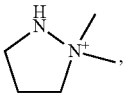

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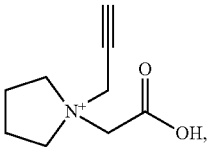

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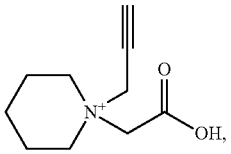

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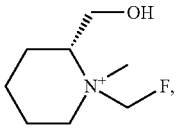

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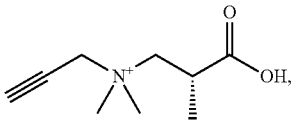

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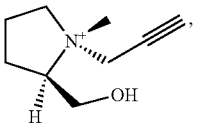

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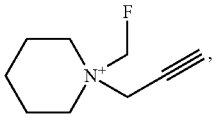

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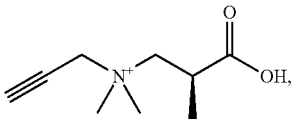

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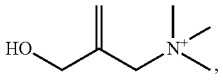

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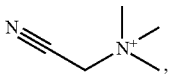

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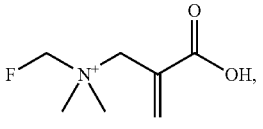

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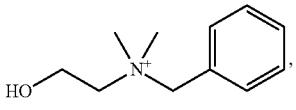

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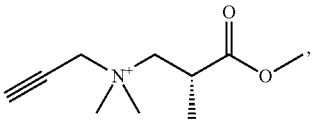

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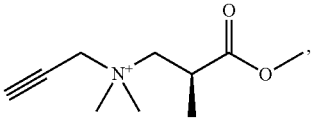

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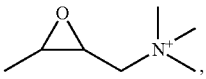

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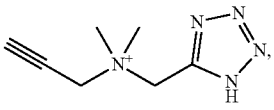

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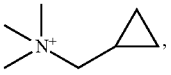

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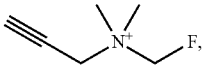

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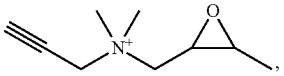

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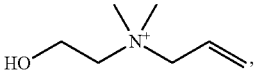

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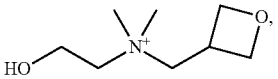

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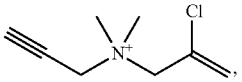

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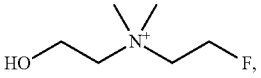

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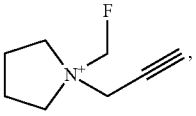

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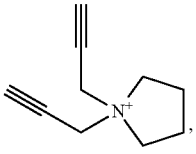

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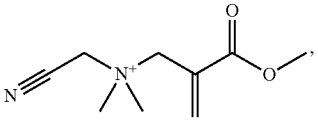

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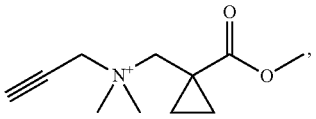

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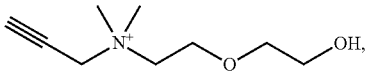

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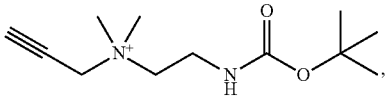

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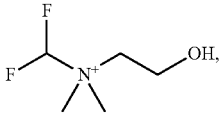

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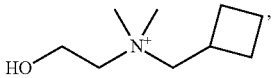

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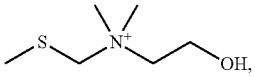

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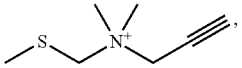

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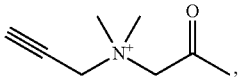

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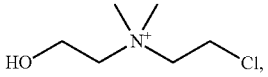

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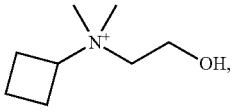

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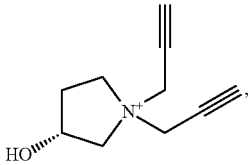

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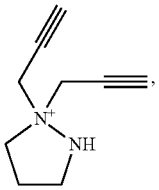

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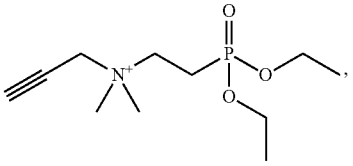

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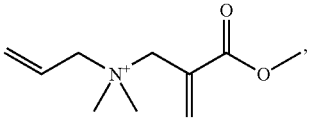

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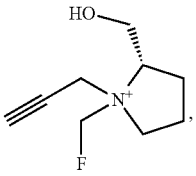

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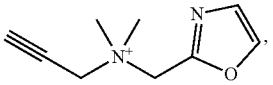

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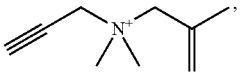

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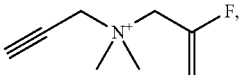

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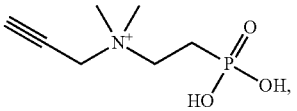

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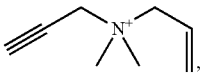

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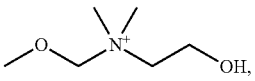

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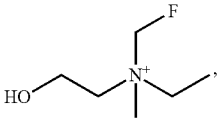

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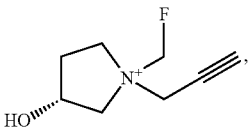

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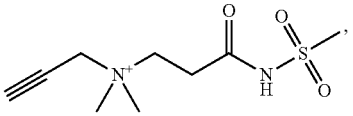

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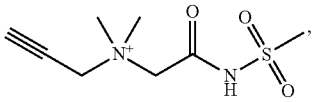

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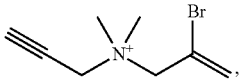

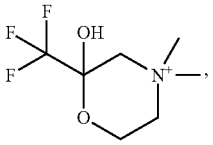

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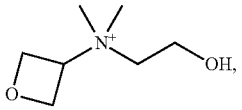

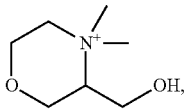

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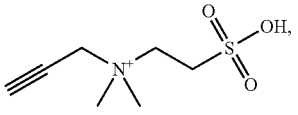

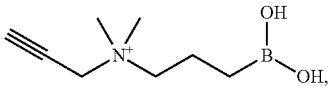

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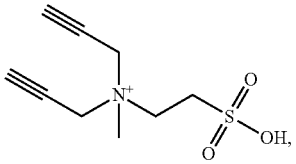

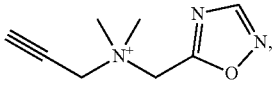

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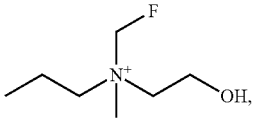

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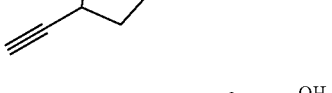

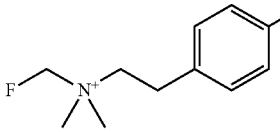

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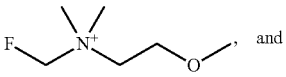

and

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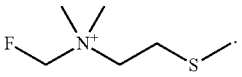
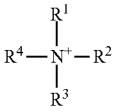


4. A compound consisting of a cation and a pharmaceutically acceptable counterion, wherein the cation is a structure of formula (I):

(I)



wherein

R^1 is

C_{2-6} alkyl substituted with —O-(acylated sugar) or isosorbide, wherein said C_{2-6} alkyl is further optionally substituted with oxo and/or methene;

C_4 cycloalkyl optionally substituted with hydroxyl, ethynyl, or —O-(acylated sugar); or

C_3 cycloalkyl substituted with C_{1-6} alkyl, hydroxyl, ethynyl, or —O-(acylated sugar)

C_{3-4} cycloalkyl C_{1-2} alkyl;

R^2 is C_{2-6} alkyl optionally substituted with one or two hydroxyl, oxo, and —O-(acylated sugar);

or R^1 and R^2, together with the nitrogen atom to which both are attached, combine to form a 4- or 5-membered heterocyclic ring optionally substituted with ethynyl or $—(CH_2)_n—OR^5$ or an acylated sugar, wherein n is 0 or 1, R^5 is hydrogen or an acylated sugar;

R^3 is C_{1-6} alkyl optionally substituted with a halogen or hydroxyl; and

R^4 is C_{1-6} alkyl or propargyl.

5. The compound of claim **4**, wherein R^1 is C_{2-6} alkyl substituted with —O-(acylated sugar) and is optionally further substituted with oxo.

6. The compound of claim **4** or **5**, wherein R^2 is methyl.

7. The compound of any one of claims **4**, **5**, and **6**, wherein R^3 is C_{1-6} alkyl.

8. The compound of any one of claims **4-7**, wherein R^4 is propargyl.

9. The compound of claim **4**, wherein

R^1 is C_{2-6} alkyl substituted with —O-(acylated sugar) and is optionally further substituted with oxo;

R^2 is methyl;

R^3 is C_{1-6} alkyl; and

R^4 is propargyl.

10. The compound of claim **4**, wherein

R^1 is C_{2-6} alkyl substituted with isosorbide and is optionally further substituted with oxo and/or methene;

R^2 is methyl;

R^3 is C_{1-6} alkyl; and

R^4 is propargyl.

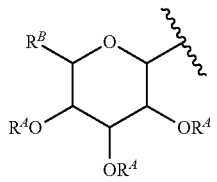
11. The compound of claim **4**, wherein

R^1 is chosen from C_2 alkyl substituted with —O-(acylated sugar) and optionally further substituted with oxo and

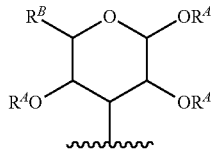
C_4 alkyl substituted with —O-(acylated sugar) and optionally further substituted with oxo;

wherein the acylated sugar is chosen from groups of formula (A), groups of formula (B), and groups of formula (C):

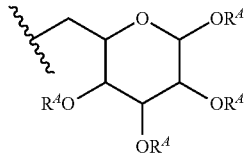
(A)



(B)



(C)



wherein

each R^A is independently H or fatty acid acyl; and

R^B is H, —CH_3, —CH_2—OR^A, —OCH_3, —$COOCH_3$, or —COOH;

R^2 is methyl;

R^3 is methyl; and

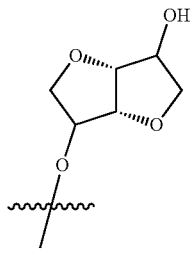
R^4 is propargyl.

12. The compound of claim **4**, wherein

R^1 is chosen from C_2 alkyl substituted with isosorbide and optionally further substituted with oxo and C_3 alkyl substituted with isosorbide and optionally further substituted with oxo and methene;

wherein isosorbide is chosen from groups of formula (C):

(C)



R^2 is methyl;

R^3 is methyl; and

R^4 is propargyl.

13. The compound of claim **4**, wherein

R^1 is C_{3-4} cycloalkyl C_{1-2} alkyl;

R^2 is C_{2-6} alkyl optionally substituted with one or two hydroxyl, oxo, and —O-(acylated sugar);

or R^1 and R^2, together with the nitrogen atom to which both are attached, combine to form a 4- or 5-membered heterocyclic ring optionally substituted with ethynyl or —$(CH_2)_n$—OR^s or an acylated sugar, wherein n is 0 or 1, R^s is hydrogen or an acylated sugar;

R^3 is C_{1-6} alkyl optionally substituted with a halogen or hydroxyl; and

R^4 is C_{1-6} alkyl or propargyl.

14. The compound of claim **13**, wherein R^1 is C_{3-4} cycloalkyl C_1 alkyl.

15. The compound of claim **13** or **14**, wherein R^2 is C_2 alkyl optionally substituted with one or two hydroxyl groups.

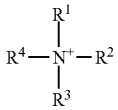
16. The compound of claim **13**, wherein R^1 and R^2, together with the nitrogen atom to which both are attached, combine to form a 5-membered heterocyclic ring optionally substituted with ethynyl, —OH, or —CH_2OH.

17. The compound of any one of claims **13-16**, wherein R^3 is C_1 alkyl optionally substituted with a halogen.

18. The compound of any one of claims **13-17**, wherein R^4 is C_1 alkyl or propargyl.

19. A compound consisting of a cation and a pharmaceutically acceptable counterion, wherein the cation is a structure of formula (II):

(II)



wherein

R^1 is

C_{1-6} alkyl optionally substituted with one or more oxo, hydroxyl, halogen, cyano, —COOMe, amino, methene, ethenyl, ethynyl, hydroxyphenyl, C_{3-4} cycloalkyl, —OCH_2CH_2OH, —$HNC(O)OCMe_3$, —SMe, —OMe, —$HNS(O)_2Me$, —SO_3H, $B(OH)_2$, PO_3H_2, PO_2H_2, —$P(O)(OCH_2CH_3)_2$, —P(O)(OH)(OCH_2CH_3), heteroaryl ring;

phenyl;

benzyl;

C_{3-4} heterocyclyl optionally substituted with C_1 alkyl

C_4 heterocyclylalkyl C_1 alkyl; or

C_4 cycloalkyl;

R^2 is

C_{1-6} alkyl optionally substituted with one or two hydroxyl, oxo, methene, cyano, ethynyl, —HNC(O)H, or —C≡C—CH_2OH; or

—$HN(CH_2)_3C(O)OH$;

or R^1 and R^2, together with the nitrogen atom to which both are attached and optionally one or more additional heteroatoms, combine to form a 4-8 membered mono- or bi-cyclic heterocycle optionally substituted with ethynyl, trifluoromethyl, —CH_2Ph, —OH, or —(CH_2)OH;

R^3 is methyl or propargyl; and

R^4 is methyl or propargyl,

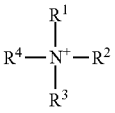
with the proviso that

(1) when two of R^1, R^2, R^3, and R^4 are methyl and one of the other two of R^1, R^2, R^3, and R^4 is propargyl, then the other of R^1, R^2, R^3, and R^4 is not methyl, a

monohalomethyl, —CH_2CH_2OH, —COOH, —$(CH_2)_4C(O)OH$, or —$CH_2C(CH_2)CN$; and

(2) when two of R^1, R^2, R^3, and R^4 are methyl and one of the other two of R^1, R^2, R^3, and R^4 is —CH_2CH_2OH or —$CH_2C(O)OH$, then the other of R^1, R^2, R^3, and R^4 is not a monohalomethyl.

20. A compound consisting of a cation and a pharmaceutically acceptable counterion, wherein the cation is a structure of formula (III):



(III)

wherein

R^1 is

C_{1-6} alkyl optionally substituted with one or more oxo, hydroxyl, halogen, cyano, —COOMe, —COOH, methene, ethenyl, ethynyl, C_{3-4} cycloalkyl, —OCH_2CH_2OH, —SMe, —OMe, —$HNS(O)_2Me$, —$P(O)(OCH_2CH_3)_2$, —$P(O)(OH)(OCH_2CH_3)$, or 5-membered heteroaryl ring;

R^2 is

C_{1-6} alkyl optionally substituted with one or two hydroxyl, oxo, methene, cyano, ethynyl, —HNC(O)H, or —C≡C—CH_2OH; or

—$HN(CH_2)_3C(O)OH$;

or R^1 and R^2, together with the nitrogen atom to which both are attached and optionally one or more additional heteroatoms, combine to form a 4-8 membered mono- or bi-cyclic heterocycle optionally substituted with ethynyl, —OH, or —$(CH_2)OH$;

R^3 is C_{1-6} alkyl optionally substituted with a halogen, hydroxyl, or ethynyl; and

R^4 is C_{1-6} alkyl or propargyl;

with the proviso that

(1) when two of R^1, R^2, R^3, and R^4 are methyl and one of the other two of R^1, R^2, R^3, and R^4 is propargyl, then the other of R^1, R^2, R^3, and R^4 is not methyl, a monohalomethyl, —CH_2CH_2OH, —COOH, —$(CH_2)_4C(O)OH$, or —$CH_2C(CH_2)CN$; and

(2) when two of R^1, R^2, R^3, and R^4 are methyl and one of the other two of R^1, R^2, R^3, and R^4 is —CH_2CH_2OH or —$CH_2C(O)OH$, then the other of R^1, R^2, R^3, and R^4 is not a monohalomethyl.

21. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and the compound of any one of claims **1** to **20**.

22. A method of modulating a trimethylaminuria marker in a subject in need thereof, the method comprising administering to the subject in need thereof a therapeutically effective amount of the compound of any one of claims **1** to **20** or the pharmaceutical composition of claim **21**.

23. The method of claim **22**, wherein the trimethylaminuria marker is the trimethylamine and/or trimethylamine oxide levels in the subject's blood, plasma, serum, or urine.

24. A method of treating or preventing a disease associated with elevated levels of trimethylamine (TMA), a decreased rate of conversion of TMA to trimethylamine oxide (TMAO), or a high ratio of TMA to TMAO in a subject in need thereof, the method comprising administering a therapeutically effective amount of the compound of any one of claims **1** to **20** or the pharmaceutical composition of claim **21** to the subject.

25. The method of claim **24**, further comprising detecting the presence of one or more genetic variants of the FMO3 gene of the subject in need before the administering step.

26. The method of claim **24**, wherein the disease associated with elevated levels of trimethylamine (TMA) or trimethylamine N-oxide (TMAO), a decreased rate of conversion of TMA to TMAO, or a high ratio of TMA to TMAO is a cardiovascular disease, reduced or impaired kidney function, kidney disease, chronic kidney disease, end-stage renal disease, or diabetes mellitus.

27. A method of inhibiting a CutC choline lyase-mediated conversion of choline to trimethylamine, the method comprising contacting the compound of any one of claims **1** to **20** with the CutC choline lyase.

28. A method of inhibiting a CntA carnitine monooxygenase-mediated conversion of carnitine to trimethylamine, the method comprising contacting the compound of any one of claims **1** to **20** with the CntA carnitine monooxygenase.

29. A method of treating a subject in need of treatment for trimethylaminuria comprising contacting bacteria in vivo with a therapeutically effective amount of the compound of any one of claims **1** to **20** or the pharmaceutical composition of claim **21** to the subject.

30. The method of claim **29**, wherein the bacteria are localized in the colon of the subject.

31. A method of identifying a subject suffering from trimethylaminuria, or predicting a predisposition for developing trimethylaminura in a subject, comprising:

(i) analyzing a sample from the patient to detect the presence of at least one FMO3 genetic variant in the patient, and

(ii) identifying a subject suffering from trimethylaminuria or predicting a predisposition for developing trimethylaminura in a subject.

32. The method of claim **31**, further comprising (iii) administering a therapeutically effective amount of the compound of any one of claims **1** to **20** or the pharmaceutical composition of claim **21**.

33. The method of claim **31** or **32**, wherein the FMO3 genetic variant is chosen from g.-2092 to 10145del, g.94G>A+A29A2:A30, g.110T>C, g.11145A>G, g.11148G>T, g.11166G>A, g.11177A>G, g.11185delA, g.11192G>T, g.11239T>C, g.15036A>G, g.15123T>A, g.15137G>T, g.15153C>T, g.15526_15527delTG, g.15531T>A, g.15533T>C, g.15539C>A, g.18177G>A, g.18225G>C, g.21429G>T, g.21460G>T, g.21680G>T, g.21684G>A, g.21702delG, g.23580delG, g.24486G>A, g.24592C>T, g.24608G>A, g.24658C>T, and g.24682C>T.

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