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(54) Title: SACCHARIDE ANALOGS AND AGENTS FOR THE DIAGNOSIS AND THERAPY OF BACTERIAL INFECTIONS

(57) Abstract: This disclosure relates saccharide analogs such as thiomaltose-based analogs for targeting bacteria and related uses. In certain embodiments, the disclosure relates to methods of transferring a molecule of interest into bacteria comprising mixing bacteria with a non-naturally occurring conjugate, wherein the conjugate comprises a thiomaltose-based analog and a molecule of interest under conditions such that the conjugate is transported across the bacterial cell wall. In certain embodiments, the molecule of interest can be a tracer or an antibiotic.

SACCHARIDE ANALOGS AND AGENTS FOR THE DIAGNOSIS AND THERAPY OF BACTERIAL INFECTIONS

CROSS REFRENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Applications 62/052,545, filed on September 19, 2014, and 62/068,984, filed on October 27, 2014, the contents of which are hereby incorporated in their entirety.

BACKGROUND

The diagnosis and therapy of bacterial infections remains a central challenge in medicine. Infections are currently diagnosed by using blood cultures or tissue biopsy; however, these methods can only detect late stage infections that are challenging to treat, and also cannot detect bacterial drug resistance. A major limitation preventing the effective treatment of bacterial infection is an inability to image infections in vivo with accuracy and sensitivity. Consequently, bacterial infections can be diagnosed only after they have become systematic or have caused significant anatomical tissue damage, a stage at which they are challenging to treat owing to the high bacterial burden. Although contrast agents have been developed to image bacteria, their clinical impact has been minimal because they are unable to detect small numbers of bacteria in vivo and cannot distinguish infections from other pathologies such as cancer and inflammation. There is a need for the development of contrast agents that can image small numbers of bacteria accurately in vivo.

Bacteria can utilize glycogen, starch, and amylose as carbon sources. Prior to transport through the cell membrane, these polysaccharides are hydrolyzed by the extracellular α-amylase into smaller maltodextrins, maltose and isomaltose. The maltose ABC importer (type I) of Escherichia coli enables the bacteria to feed on maltose and maltodextrins (Bordignon et al., Mol Microbiol., 2010, 77(6):1354-1366). Although, maltohexaose contrast agents have been developed to image bacteria, they are hydrolyzed by the serum amylase. There is a great need for the development of more stable targeting agents that can diagnose and treat the bacterial infections.

Murthy et al. report oligosaccharides conjugates for targeting bacteria. See WO/2012/097223.

Hindsgaul reports the preparation of thio galactosides as toxin inhibitor bactericides, virucides, and fungicides. US Patent 5,932,554

Zeng et al. report a process for selective removal of saccharide thioacetyl protective group. CN Patent 103554195.

Gottschaldt et al. report the synthesis of sugar-substituted polypyridine metal complexes and their use as diagnostic, visualization, or therapeutic agents in the treatment of disease. DE Patent 102007032799.

References cited herein are not an admission of prior art.

SUMMARY

This disclosure relates saccharide analogs such as thiomaltose-based analogs for targeting bacteria and related uses. In certain embodiments, the disclosure relates to methods of transferring a molecule of interest into bacteria comprising mixing bacteria with a non-naturally occurring conjugate, wherein the conjugate comprises a thiomaltose-based analog and a molecule of interest under conditions such that the conjugate is transported across the bacterial cell wall. In certain embodiments, the molecule of interest can be a tracer or an antibiotic.

In certain embodiments, the disclosure relates to a composition comprising a tracer molecule conjugated to thiol bridging saccharides. In certain embodiments the tracer molecule is a positron-emitting radionuclide. In certain embodiments, the positron-emitting radionuclide is selected from carbon-11, nitrogen-13, oxygen-15, fluorine-18, rubidium-82, and strontium-82. In certain embodiments the tracer is a fluorescent molecule. In certain embodiments, the fluorescent molecule is a fluorescent dye. In certain embodiments, the thiol bridging saccharide is thiomaltose-perylene.

With regard to any of the conjugates disclosed herein, the saccharides can be a polysaccharide of greater than 2, 3, 4, 5, or 6 sugar oligomers bridged by one or more thiol linkages which are typically isolated or substantially purified. In some embodiments, the polysaccharide comprises glucose oligomers, e.g., maltohexaose, a polysaccharide with 6 glucose oligomers. Typically, the glucose oligomers are linked by a thiol bridging alpha 1→4, i.e., 1 to 4, covalent bond. In certain embodiments, the disclosure contemplates thiomaltose-based analog of glucose oligomers and/or 2-deoxyglucose oligomers wherein one or more of the glucose monomers are substituted with a positron-emitting radionuclide ^{18}F.

In certain embodiments, any of the compounds or saccharide analogs disclosed herein or derivatives can be optionally substituted with one or more, the same or different, substituents.

In certain embodiments, the disclosure relates to an antibiotic conjugated to a saccharide analog disclosed herein. In certain embodiments, the antibiotic is selected from

the group comprising sulfonamides, carbapenems, penicillins, diaminopyrimidines, quinolones, beta-lactam antibiotics, cephalosporins, tetracyclines, notribenzenes, aminoglycosides, macrolide antibiotics, polypeptide antibiotics, nitrofurans, nitroimidazoles, nicotinin acids, polyene antibiotics, imidazoles, glycopeptides, cyclic lipopeptides, glycylcyclines, and oxazolidinones. In certain embodiments, the antibiotic is selected from dapsone, paraaminosalicyclic, sulfanilamide, sulfamethizole, sulfamethoxazole, sulfapyridine, trimethoprim, pyrimethamine, nalidixic acid, norfloxacin, ciproflaxin, cinoxacin, enoxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, lomefloxacin, moxifloxacin, ofloxacin, pefloxacin, sparfloxacin, trovafloxacin, amoxicillin, ampicillin, azlocillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, hetacillin, oxacillin, mezlocillin, penicillin G, penicillin V, piperacillin, cefacetrile, cefadroxil, cefalexin, cefaloglycin, cefalonium, cefaloridin, cefalotin, cefapirin, cefatrizine, cefazaflur, cefazedone, cefazolin, cefradine, cefroxadine, ceftezole, cefaclor, cefonicid, ceforanide, cefprozil, cefuroxime, cefuzonam, cefmetazole, cefoteta, cefoxitin, cefcapene, cefdaloxime, cefdinir, cefditoren, cefetamet, cefixime, cefmenoxime, cefodizime, cefoperazone, cefotaxime, cefotiam, cefpimizole, cefpiramide, cefpodoxime, cefteram, ceftibuten, ceftiofur, ceftiolen, ceftizoxime, ceftriaxone, cefoperazone, ceftazidime, cefepime, moxolactam, imipenem, ertapenem, meropenem, aztreonam, oxytetracycline, chlortetracycline, clomocycline, demeclocycline, tetracycline, doxycycline, lymecycline, meclocycline, methacycline, minocycline, rolitetracycline, chloramphenicol, amikacin, gentamicin, framycetin, kanamycin, neomicin, neomycin, netilmicin, streptomycin, tobramycin, azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, telithromycin, polymyxin-B, colistin, bacitracin, tyrothricin, notrifurantoin, furazolidone, metronidazole, tinidazole, isoniazid, pyrazinamide, ethionamide, nystatin, amphotericin-B, hamycin, miconazole, clotrimazole, ketoconazole, fluconazole, rifampacin, lincomycin, clindamycin, spectinomycin, chloramphenicol, clindamycin, colistin, fosfomycin, loracarbef, nitrofurantoin, procain, spectinomycin, tinidazole, ramoplanin, teicoplanin, and vancomycin.

In certain embodiments, the disclosure relates to a method of transferring a molecule of interest into bacteria comprising mixing bacteria with a non-naturally occurring conjugate under conditions such that the conjugate is transported across the bacterial cell wall wherein the conjugate comprises a saccharide analog and a molecule of interest.

In certain embodiments, the disclosure relates to an imaging method comprising a) administering a tracer molecule conjugated to a saccharide analog to a subject; and b)

scanning the subject for a physical property of the tracer molecule. In certain embodiments the imaging method further comprises the step of detecting the physical property of the tracer molecule and creating an image highlighting the location of the tracer molecule in the subject.

In certain embodiments, the disclosure relates to a method of treating or preventing a bacterial infection comprising administering an effective amount of an isolated conjugate to a subject in need thereof wherein the isolated conjugate comprises an antibiotic and a saccharide analog. In certain embodiments the isolated conjugate is administered in combination with another antibiotic.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates saccharide analogs, e.g., thiomaltose-based analogs designed to image bacterial infections. Left side: illustrates bacteria internalized PET contrast agent (1) with an ^{18}F derivatized maltodextrin probe (MDP) (1) through the maltodextrin transporter (2). ^{18}F-thiomaltose is designed to image bacteria in vivo by targeting the maltodextrin transport pathway. ^{18}F-thiomaltose is internalized by bacteria. Maltodextrin transporters are not present in mammalian cells and ^{18}F-thiomaltose-based analogs therefore have high specificity for bacteria over mammalian cells. Right side: illustrates imaging bacterial infections in implanted device due to robust accumulation of ^{18}F- MDPs. Systemic injection (4) of ^{18}F-MDPs can be used to image bacterial implant infections and generate an imaging agent that can diagnose early stage bacterial implant infections at the site of implant (3).

Figure 2 Synthesis of thiomaltose-perylene: a) $NaOCH_3$, MeOH, 55%. b) Tf_2O, DCM-Pyridine, 63%. c) TEA, DMF, 38%. d) $NaOCH_3$, MeOH, 83%. e) Pyridine, Ac_2O, 78%. f) NH_2NH_2.HOAc, DMF, 81%. g) Trichloroacetonitrile, DBU, DCM, 97%. h) Azidopropanol, TMSOTf, DCM, 63%. i) 1. alkyne-perylene, CuI, DIPEA, DMF; 2. LiOH, MeOH, H2O, 65% in two steps

Figure 3 Synthesis of ^{18}F-thiomaltose: a) 2, CuI, DIPEA, DMF. b) 1. $K^{18}F$, CH_3CN, 110°C; 2. NaOH, H_2O.

Figure 4 schematically illustrates the retrosynthesis of thiomaltose.

Figure 5 schematically illustrates the synthesis of the glucose building block.

Figure 6 schematically illustrates the synthesis of the galactose building block.

Figure 7 schematically illustrates the synthesis of the galactose building block.

Figure 8 schematically illustrates the synthesis of the galactose building block.

Figure 9 schematically illustrates glycosylation.

Figure 10 schematically illustrates the synthesis of perylene-thiomaltose.

Figure 11 shows uptake of thiomaltose-perylene in Mtb cells. Thiomaltose-perylene (50 μM), and uptake was measured using a plate reader (fluorescence intensity at 410/480).

Figure 12 shows a table of uptake of thiomaltose-perylene in Salmonella and pseudomonas cells.

Figure 13 shows uptake studies in bacterial and mammalian cells. Bacteria (E coli) and macrophages were incubated with thiomaltose-perylene (20 μM) for 2 hours. Cells were washed 3 times with PBS. Cells were lysed using they lysis buffer. The fluorescence intensity from bacteria and mammalian cells was measured by plate reader at 410/480 and the background of lysis buffer was subtracted. The protein content was analyzed by BCA assay. The uptake of thiomaltose-perylene in bacteria was 98 fold higher than in macrophages.

Figure 14 shows data indicating that thiomaltose is resistant to maltase hydrolysis. Maltose is hydrolyzed completely in 3 hours, whereas thiomaltose is less than 1% hydrolyzed.

Figure 15 illustrates certain embodiments of the disclosure.

Figure 16 illustrates certain embodiments of the disclosure.

Figure 17 illustrates certain embodiments of the disclosure.

Figure 18 illustrates certain embodiments of the disclosure.

Figure 19 shows data indicating that the thiomaltose-radezolid inhibits bacterial growth. E. Coli were grown in a 96 well plate, starting at an O.D. of 0.05. Thiomaltose – radezolid was added to the bacteria, and the bacteria were shaken at 37C between 1-24 hours. The O.D. of the bacteria was then measured and normalized to untreated bacteria IC_{50} at 24 hours is approximately 0.5 micromolar.

Figure 20 illustrates certain embodiments of the disclosure.

Figure 21 illustrates certain embodiments of the disclosure.

Figure 22 illustrates certain embodiments of the disclosure.

Figure 23 shows data indicating TM-R can effectively kill P. aeruginosa. TM-R and free radezolid were incubated with P. aeruginosa for 24 hours. OD600 were used to determine the bacteria growth.

Figure 24 illustrates certain embodiments of the disclosure.

Figure 25 illustrates certain embodiments of the disclosure.

DETAILED DESCRIPTION

Before the present disclosure is described in greater detail, it is to be understood that this disclosure is not limited to particular embodiments described, and as such can, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present disclosure will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure, the preferred methods and materials are now described.

All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference and are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present disclosure is not entitled to antedate such publication by virtue of prior disclosure. Further, the dates of publication provided could be different from the actual publication dates that can need to be independently confirmed.

As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which can be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present disclosure. Any recited method can be carried out in the order of events recited or in any other order that is logically possible.

Embodiments of the present disclosure will employ, unless otherwise indicated, techniques of medicine, organic chemistry, biochemistry, molecular biology, pharmacology, and the like, which are within the skill of the art. Such techniques are explained fully in the literature.

Targeting Bacteria

A central problem in imaging bacterial infections is to develop targeting strategies that can deliver large quantities of imaging probes to bacteria. This has been challenging

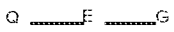
because typical imaging probes target the bacterial cell wall and cannot access the bacterial intracellular volume. Although numerous contrast agents have been developed to image bacteria, their clinical impact has been minimal because they are unable to detect small numbers of bacteria in vivo, and cannot distinguish infections from other pathologies such as cancer and inflammation. Within certain embodiments, the disclosure relates to a thiomaltose-based imaging probe which can detect bacteria in vivo with a sensitivity two orders of magnitude higher than previously reported, and can detect bacteria using a bacteria-specific mechanism that is independent of host response and secondary pathologies.

In certain embodiments, the thiomaltose-based imaging probe is composed of a fluorescent dye conjugated to a thiomaltose-based analog and is rapidly internalized through the bacteria-specific maltodextrin transport pathway, endowing the thiomaltose-based imaging probes with a unique combination of high sensitivity and specificity for bacteria. Certain thiomaltose-based imaging probes selectively accumulate within bacteria at millimolar concentrations, and are a thousand-fold more specific for bacteria than mammalian cells. Furthermore, thiomaltose-based imaging probes can image as few as 10^5 colony-forming units in vivo and can discriminate between active bacteria and inflammation induced by either lipopolysaccharides or metabolically inactive bacteria.

Contrast agents that are robustly internalized through the bacteria-specific maltodextrin transporter and can image bacterial infections in vivo with improved sensitivity and specificity (see figures 11-14). Thiomaltose-based imaging probes can deliver millimolar concentrations of imaging probes into bacteria, making it possible to image low numbers of bacteria. Thiomaltose-based imaging probes also have high specificity for bacteria because mammalian cells do not express the maltodextrin transporter and cannot internalize contrast agents conjugated to thiomaltose-based analogs (figure 13). Thiomaltose-based imaging probes are typically composed of α (1→4)-thiol linked glucose oligomers. Because thiomaltose-based imaging probes are typically hydrophilic and membrane impermeable, they are efficiently cleared from uninfected tissues in vivo, leading to a low background. Furthermore, the lumen of intestinal tissues or the outer layers of the skin are not permeable to glucose oligomers. Thiomaltose-based imaging probes delivered systemically should therefore not be internalized by the resident bacterial microflora present in healthy subjects.

Conjugates, Derivatives, and Related Compounds

In certain embodiments, the disclosure relates to compounds of formula I,



Formula I

or salts thereof wherein,

Q is a polysaccharide comprising a 1 to 4-thiol or oxygen linkage such as thiomaltose;

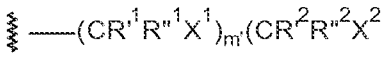
E is a linking group; and

G is a tracer, a drug, an antibiotic, an azide group, or other molecule of interest.

In certain embodiments, Q is a thiomaltose-based analog comprising glucose, a glucose derivative, and/or a substituted glucose oligomer.

In certain embodiments, E contains a triazole positioned between linking groups such as the following groups alone or in combination, methylene, ethylene, ether, amine, amide, ester, carbonyl, thiol, dithiol, thiolester, aromatic, heteroaromatic, or saturated or unsaturated hydrocarbon groups.

In certain embodiments, E can be represented by a formula:



wherein the symbol  represents the point of attachement to Q and G;

m' is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ,11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

R'^1, R''^1, R'^2 and R''^2 are at each occurrence individually and independently hydrogen, halogen, alkyl, alkoxy, or hydroxyl;

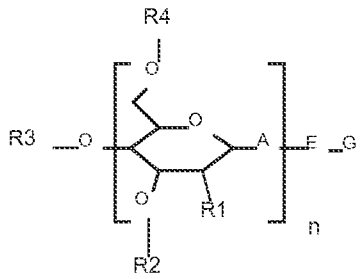
X^1, X^2 and Y is each occurrence individually and independently -O-, -S-, -S-S-, -NH-, -(C=O)-,-NH(C=O)-, (C=O)NH- -O(C=O)-, -(C=O)O-, -S(C=O)-, -(C=O)S-, -SO-, -SO_2, - $NHSO_2$-, -SO_2NH-,-$(CH2CH2O)_q$-,-$(CH_2)_r$-, a disubstituted carbocyclyl, a di-substituted aryl, a disubstituted heterocyclyl, or absent;

q can be 1 to 1000;

r can be 1 to 22.

In certain embodiments, E can be connected to Q via the the anomeric carbon at the reducing end of the polysaccharide

In certain embodiments, the disclosure relates to compounds of formula I with Formula IA



Formula IA

or salts thereof wherein,

A is independently O or S at each occurrence;

n is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15;

E is a linking group, for instance as defined above;

G is a molecule of interest such as a radionuclide, fluorescent moiety, an antibiotic, or an azide group;

R1, R2, R3, and R4, are each individually and independently a protecting group, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)2amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R1, R2, R3, and R4 are optionally substituted with one or more, the same or different, R5;

R5 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R5 is optionally substituted with one or more, the same or different, R6; and

R6 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-Nethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl,

N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, A must be S at least once or all of A are S.

In certain embodiments, n is 5 or 6 or more, or n is 3 or 4 or more.

In certain embodiments, R2, R3, and R4 are hydrogen or alkanoyl optionally substituted with R5.

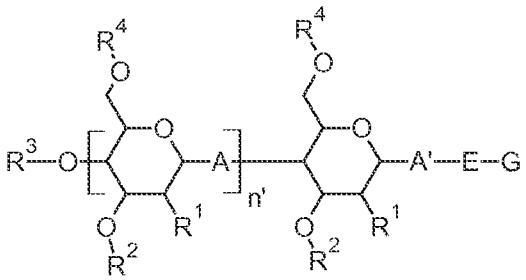
In certain embodiments, R1 is hydrogen, halogen, or hydroxy substituted with a protecting group.

In certain embodiments, R1 is ^{18}F.

In certain embodiments, E is triazole positioned between linking groups such as the following groups alone or in combination, ether, amine, amide, ester, carbonyl, thiol, dithiol, thiolester, aromatic, heteroaromatic, or hydrocarbon groups.

In certain embodiments, G is ^{18}F.

Certain embodiments include compounds of Formula IA-1:



(IA-1),

Wherein A is either S or O, and A' is O, provided that at least one A is S.

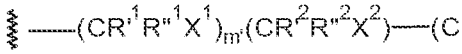
In certain embodiments, n' 1 or 2, n' is 5 or 6 or more, or n' is 3 or 4 or more.

In certain embodiments, R^2, R^3, and R^4 are hydrogen or alkanoyl optionally substituted with R5.

In certain embodiments, R^1 is hydrogen, halogen, or hydroxyl, optionally substituted with a protecting group.

In certain embodiments, R^1 is ^{18}F.

E is a linker, and in certain embodiments, E can be represented by a formula:



wherein the symbol represents the point of attachement to A' and G;

m' is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ,11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

R'1, R"1, R'2 and R"2 are at each occurrence individually and independently hydrogen, halogen, alkyl, alkoxy, or hydroxyl;

X1, X2 and Y is each occurrence individually and independently -O-, -S-, -S-S-, -NH-, -(C=O)-,-NH(C=O)-, (C=O)NH- -O(C=O)-, -(C=O)O-, -S(C=O)-, -(C=O)S-, -SO-, -SO_2, - $NHSO_2$-, -SO_2NH-,-$(CH2CH2O)_q$-,-$(CH_2)_r$-, a disubstituted carbocyclyl, a di-substituted aryl, a disubstituted heterocyclyl, or absent;

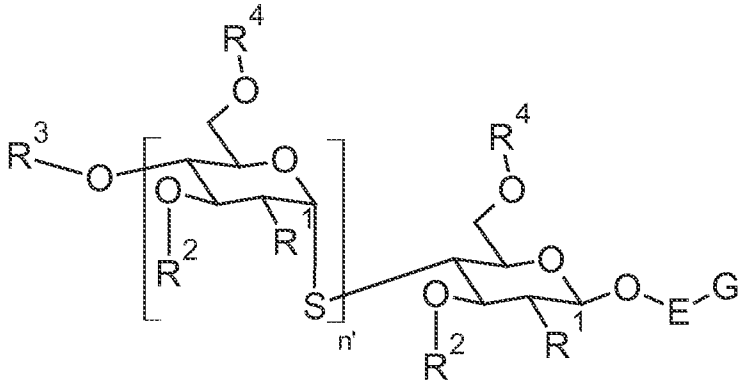
q can be 1 to 1000;

r can be 1 to 22.

In certain embodiments, E is triazole positioned between linking groups such as the following groups alone or in combination, ether, amine, amide, ester, carbonyl, thiol, dithiol, thiolester, aromatic, heteroaromatic, or hydrocarbon groups.

In certain embodiments, G is ^{18}F.

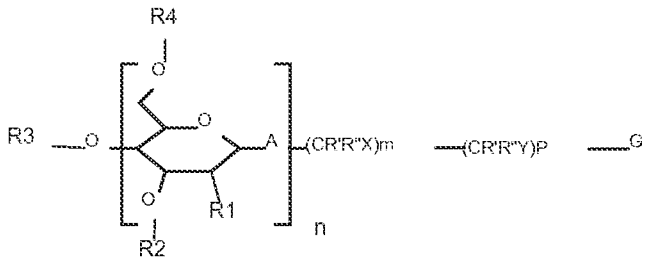
Certain embodiments include thioglycoside compounds of Formula IA-2:



(IA-2),

Wherein R^1-R^4, n', E and G are as defined above. In certain embodiments, R^2, R^3 and R^4 are each hydrogen, and R^1 is either hydroxyl, hydrogen or halogen, preferably ^{18}F.

In certain embodiments, the disclosure relates to compounds of formula I with formula IB



Formula IB

or salts thereof wherein,

A is O or S at each occurrence provided A must be S at least once or all of A are S;

n is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15;

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ,11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

R' and R" are at each occurrence individually and independently hydrogen, halogen, alkyl, alkoxy, or hydroxyl;

X and Y are at each occurrence individually and independently -O-, -S-, -S-S-, -NH-, -(C=O)-,-NH(C=O)-, (C=O)NH- -O(C=O)-, -(C=O)O-, -S(C=O)-, -(C=O)S-, -SO-, $-SO_2$, $-NHSO_2$-, $-SO_2NH$-,$-(CH2CH2O)_q$-,$-(CH_2)_r$-, a disubstituted carbocyclyl, a di-substituted aryl, a disubstituted heterocyclyl, or absent;

q can be 1 to 1000;

r can be 1 to 22;

G is a radionuclide, fluorescent molecule, an antibiotic, or an azide group;

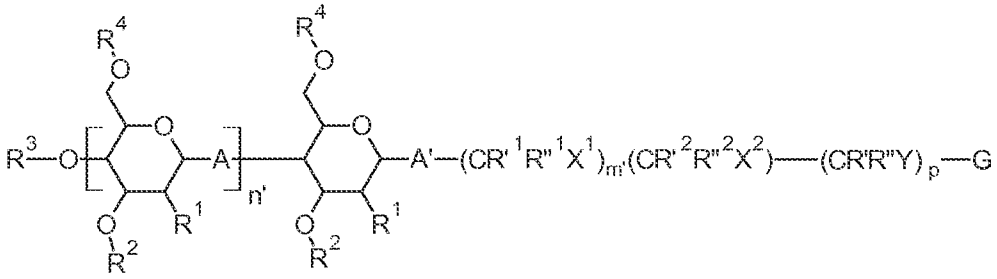
R1, R2, R3, and R4, are each individually and independently hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R1, R2, R3, and R4 are optionally substituted with one or more, the same or different, R5;

R5 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R5 is optionally substituted with one or more, the same or different, R6; and

R6 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, thylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-Nethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl,
methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, X or Y is a di-substituted 1,2,3-triazole.

In certain embodiments, the compound of Formula IB can be represented by the compound of Formula IB-1:



(IB-1)

or salts thereof wherein,

A is O or S at each occurrence provided A must be S at least once or all of A are S;

A' is O;

n' is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14;

m' is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ,11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

R'^{1}, R"^{1}, R'^{2} and R"^{2} are at each occurrence individually and independently hydrogen, halogen, alkyl, alkoxy, or hydroxyl;

X^1 is in each occurence absent;

X^2 and Y are at each occurrence individually and independently -O-, -S-, -S-S-, -NH-, -(C=O)-,-NH(C=O)-, (C=O)NH- -O(C=O)-, -(C=O)O-, -S(C=O)-, -(C=O)S-, -SO-, -SO_2, - $NHSO_2$-, -SO_2NH-,-$(CH2CH2O)_q$-,-$(CH_2)_r$-, a disubstituted carbocyclyl, a di-substituted aryl, a disubstituted heterocyclyl, or absent;

q can be 1 to 1000;

r can be 1 to 22;

G is a radionuclide, fluorescent molecule, an antibiotic, or an azide group;

R1, R2, R3, and R4, are each individually and independently hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R1, R2, R3, and R4 are optionally substituted with one or more, the same or different, R5;

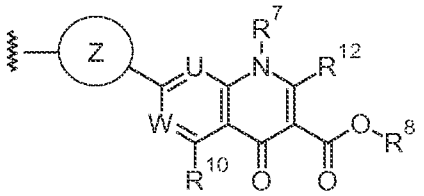
R5 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R5 is optionally substituted with one or more, the same or different, R6; and

R6 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, thylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino,

acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-Nethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl,
methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, X^2 is a di-substituted 1,2,3-triazole, in other embodiments, Y is absent, and in certain preferred embodiments, X^2 is a di-substituted 1,2,3-triazole and Y is absent.

In some embodiments, G can be the following:



wherein the symbol ≋ represents the point of attachement to E;

U is N or CR^{11};

W is N or CR^9;

Z is a carbocyclic or heterocyclic ring;

R^7 is alkyl, carbocyclyl, or aryl, wheren R^7 is optionally substituted with one or more R^{13}; or R^7 and R^{11} form a heterocarbocyclic ring optionally substituted with R^{13};

R^8 is hydrogen, alkyl or alkanoyl;

R^9 is a hydrogen or halogen;

R^{10} is hydrogen, alkoxy, amino, or alkyl;

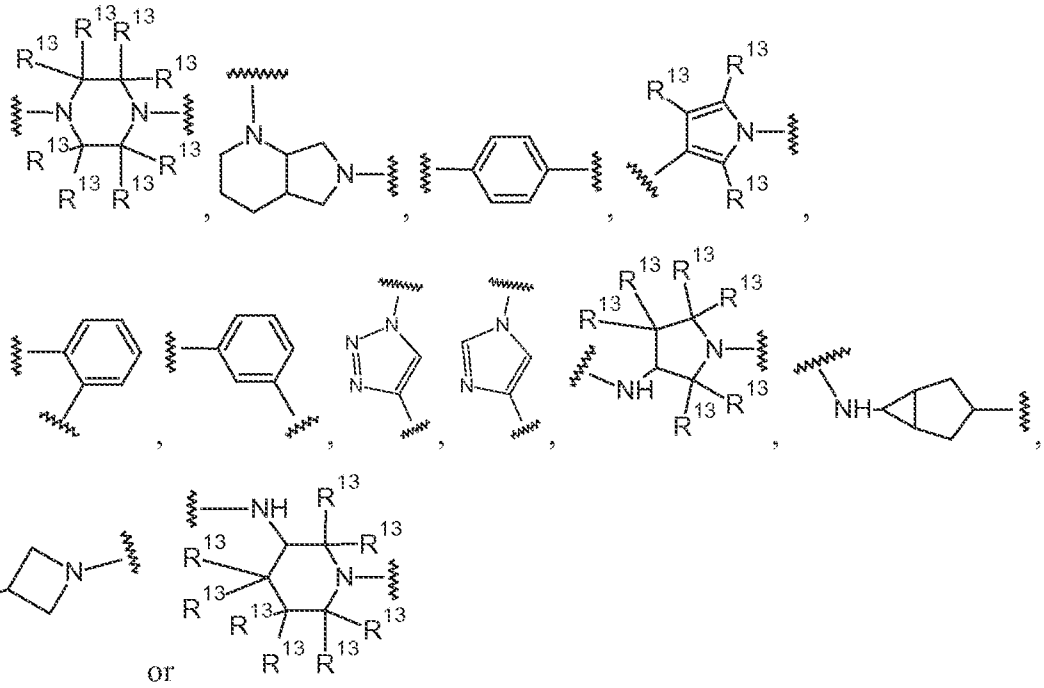
R^{11} is hydrogen, alkoxy, or halogen; and

R^{12} is hydrogen;

R^{13} is in each occurrence independently selected from halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl,

or heterocyclyl. In certain preferred embodiments, R7 is cyclopropyl or phenyl, optionally substituted by one or more fluorine atoms.

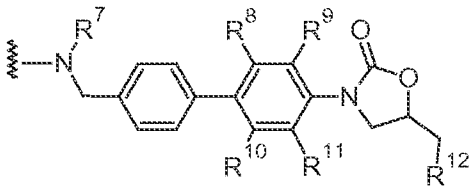
In certain embodiments, Z can have the formula:



or

wherein the symbol ⁞ represents the point of attachement to E or or the quinolone fragment and R^{13} is as defined above. In preferred embodiments, R^{13} is in each case independently selected from hydrogen, methyl, or ethyl.

In some embodiments, G can be the following:



wherein the symbol ⁞ represents the point of attachement to E;

R^7 is hydrogen, alkyl, carbocyclyl, or aryl, wheren R^7 is optionally substituted with one or more, the same or different R^{13};

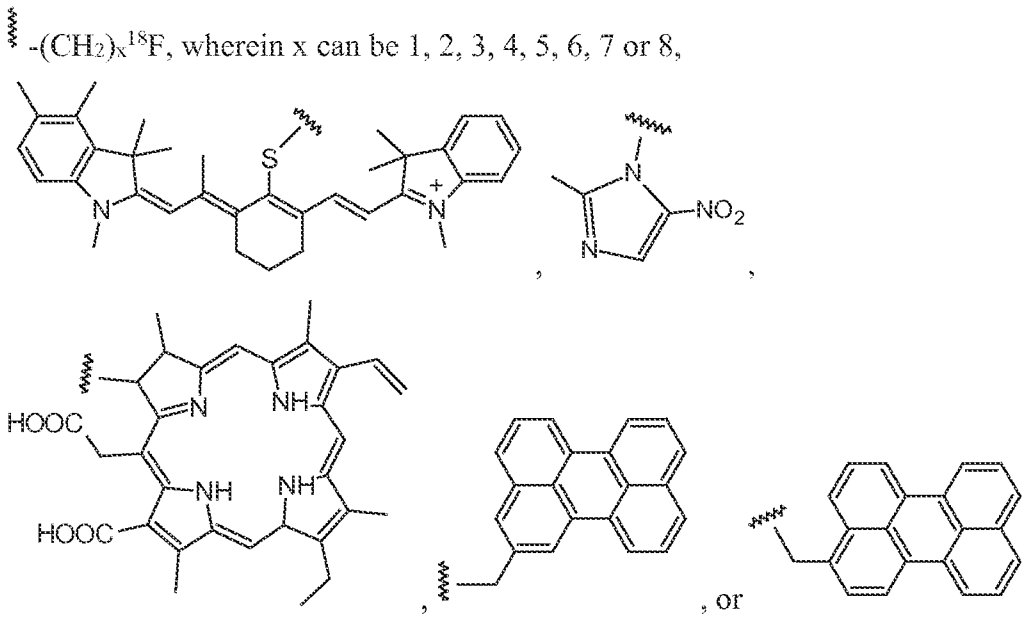
R^8, R^9, R^{10}, and R^{11} are each individually and independently hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R^8, R^9, R^{10}, and R^{11} are optionally substituted with one or more, the same or different, R^{13};

R^{12} is acetylamino, hydrogen, alkyl, halogen, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl optionally substituted with one or more, the same or different, R^{13};

R^{13} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

It certain preferred embodiments, R^{12} is acetylamino.

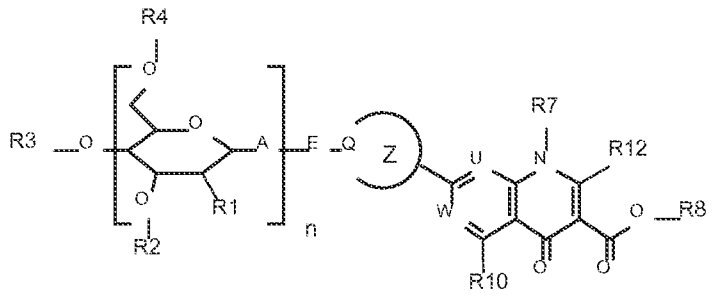
In certain embodiments, G can be:



wherein the symbol ~ represents the point of attachment to E.

For embodiments in which G is $-(CH_2)_x{}^{18}F$, it is preferred that p is 0.

In certain embodiments, the disclosure relates to compounds of formula I with formula IC,



Formula IC

or salts thereof wherein,

n is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15;

A is O or S at each occurrence provided A must be S at least once or all of A are S;

E is a linking group;

Q is N in the ring of Z, or N is an amino or alkylamino group attached to the Z ring; or Q is O of an oxygen attached to the Z ring, wherein the Z ring can be optionally substituted with one or more, the same or different, R13;

U is N or CR11;

W is N or CR9;

Z is a carbocyclic or heterocyclic ring;

R1, R2, R3, and R4, are each individually and independently hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R1, R2, R3, and R4 are optionally substituted with one or more, the same or different, R5;

R5 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R5 is optionally substituted with one or more, the same or different, R6;

R6 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-Nethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

R7 is alkyl, carbocyclyl, or aryl, wheren R7 is optionally substituted with one or

more, the same or different R13; or R7 and R11 form a heterocarbocyclic ring optionally substituted

with R13;

R8 is hydrogen, alkyl or alkanoyl;

R9 is a hydrogen or halogen;

R10 is hydrogen, alkoxy, amino, or alkyl;

R11 is hydrogen, alkoxy, or halogen; and

R12 is hydrogen;

R13 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, E is $-(CR'R''X)_m-(CR'R''Y)_p-$ wherein

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ,11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

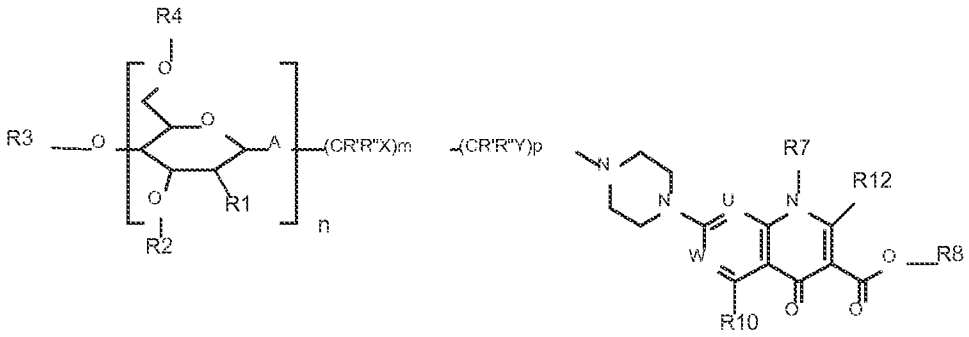
R' and R" are at each occurrence individually and independently hydrogen, alkyl, halogen, or hydroxyl;

X and Y are at each occurrence individually and independently -O-, -S-, -S-S-, -NH-, -(C=O)-, -NH(C=O)-, (C=O)NH- -O(C=O)-, -(C=O)O-, -S(C=O)-, -(C=O)S-, -SO-, $-SO_2$, $-NHSO_2-$, $-SO_2NH-$, $-(CH_2CH_2O)_q-$, $-(CH_2)_r-$, a disubstituted carbocyclyl, a di-substituted aryl, a disubstituted heterocyclyl, or absent;

q can be 1 to 1000; and

r can be 1 to 22.

In certain embodiments, the disclosure relates to compounds of formula I with formula ID,



Formula ID

or salts thereof wherein,

U is N or CR11;

W is N or CR9;

A is O or S at each occurrence provided A must be S at least once or all of A are S;

n is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15;

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ,11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

R' and R" are at each occurrence individually and independently hydrogen, alkyl, halogen, or hydroxyl;

X and Y are at each occurrence individually and independently -O-, -S-, -S-S-, -NH-, -(C=O)-, -NH(C=O)-, (C=O)NH- -O(C=O)-, -(C=O)O-, -S(C=O)-, -(C=O)S-, -SO-, $-SO_2$, $-NHSO_2$-, $-SO_2NH$-, $-(CH_2CH_2O)_q$-, $-(CH_2)_r$-, a disubstituted carbocyclyl, a di-substituted aryl, a disubstituted heterocyclyl, or absent;

q can be 1 to 1000;

r can be 1 to 22;

R1, R2, R3, and R4, are each individually and independently hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R1, R2, R3, and R4 are optionally substituted with one or more, the same or different, R5;

R5 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R5 is optionally substituted with one or more, the same or different, R6;

R6 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

R7 is alkyl, carbocyclyl, or aryl, wheren R7 is optionally substituted with one or more, the same or different R13; or R7 and R11 form a heterocarbocyclic ring optionally substituted with R13;

R8 is hydrogen, alkyl or alkanoyl;

R9 is a hydrogen or halogen;

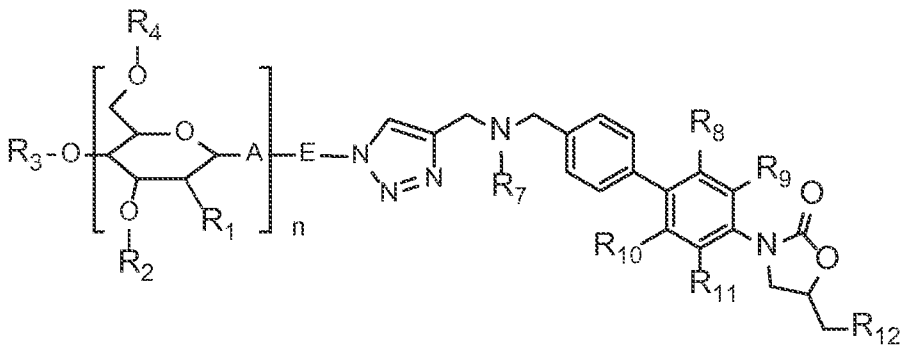
R10 is hydrogen, alkoxy, amino, or alkyl;

R11 is hydrogen, alkoxy, or halogen; and

R12 is hydrogen;

R13 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-Nethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, the disclosure relates to compounds of formula I with formula IF,



Formula IF

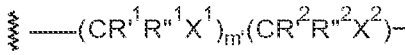
or salts thereof wherein,

n is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15;

A is O or S at each occurrence provided A must be S at least once or all of A are S;

E is a linking group; for example, of formula

In certain embodiments, E can be represented by a formula:



wherein the symbol  represents the point of attachement to A and the triazole

m' is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ,11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

R'1, R"1, R'2 and R"2 are at each occurrence individually and independently hydrogen, halogen, alkyl, alkoxy, or hydroxyl;

X^1 is each occurrence individually and independently -O-, -S-, -S-S-, -NH-, -(C=O)-,-NH(C=O)-, (C=O)NH- -O(C=O)-, -(C=O)O-, -S(C=O)-, -(C=O)S-, -SO-, -SO_2, - $NHSO_2$-, -SO_2NH-,-(CH2CH2O)$_q$-,-(CH_2)$_r$-, a disubstituted carbocyclyl, a di-substituted aryl, a disubstituted heterocyclyl, or absent;

X^2 and Y are at each occurrence individually and independently -O-, -S-, -S-S-, -NH-, -(C=O)-,-NH(C=O)-, (C=O)NH- -O(C=O)-, -(C=O)O-, -S(C=O)-, -(C=O)S-, -SO-, -SO_2, - $NHSO_2$-, -SO_2NH-,-(CH2CH2O)$_q$-,-(CH_2)$_r$-, a disubstituted carbocyclyl, a di-substituted aryl, a disubstituted heterocyclyl, or absent;

q can be 1 to 1000;

r can be 1 to 22;

R1, R2, R3, and R4, are each individually and independently hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R1, R2, R3, and R4 are optionally substituted with one or more, the same or different, R5;

R5 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R5 is optionally substituted with one or more, the same or different, R6;

R6 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino,

acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-Nethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

R7 is hydrogen, alkyl, carbocyclyl, or aryl, wheren R7 is optionally substituted with one or more, the same or different R13;

R8, R9, R10, and R11 are each individually and independently hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R8, R9, R10, and R11 are optionally substituted with one or more, the same or different, R13;

R12 is acetylamino, hydrogen, alkyl, halogen, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl optionally substituted with one or more, the same or different, R13;

R13 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, E is $-(CR'R''X)_m-(CR'R''Y)_p-$ wherein

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ,11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

In certain embodiments, E is $-(CH_2)_m-$ wherein m is is 1, 2, or 3.

R' and R" are at each occurrence individually and independently hydrogen, alkyl, halogen, or hydroxyl;

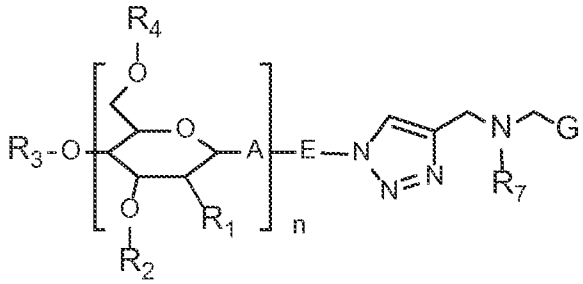
X and Y are at each occurrence individually and independently -O-, -S-, -S-S-, -NH-, -(C=O)-, -NH(C=O)-, (C=O)NH- -O(C=O)-, -(C=O)O-, -S(C=O)-, -(C=O)S-, -SO-, $-SO_2$,

- $NHSO_2$-, -SO_2NH-, -$(CH_2CH_2O)_q$-, -$(CH_2)_r$-, a disubstituted carbocyclyl, a di-substituted aryl, a disubstituted heterocyclyl, or absent;

q can be 1 to 1000; and

r can be 1 to 22.

In certain embodiments, the disclosure relates to compounds of formula I with formula IG,



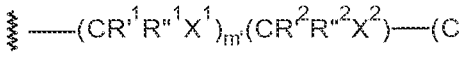
Formula IG

or salts thereof wherein,

n is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15;

A is O or S at each occurrence provided A must be S at least once or all of A are S;

E is a linking group; for example a formula:



wherein the symbol represents the point of attachement to A and triazole;

m' is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ,11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

R'[1], R"[1], R'[2] and R"[2] are at each occurrence individually and independently hydrogen, halogen, alkyl, alkoxy, or hydroxyl;

X^1 is each occurrence individually and independently -O-, -S-, -S-S-, -NH-, -(C=O)-, -NH(C=O)-, (C=O)NH- -O(C=O)-, -(C=O)O-, -S(C=O)-, -(C=O)S-, -SO-, -SO_2, - $NHSO_2$-, -SO_2NH-,-$(CH2CH2O)_q$-,-$(CH_2)_r$-, a disubstituted carbocyclyl, a di-substituted aryl, a disubstituted heterocyclyl, or absent;

X^2 and Y are at each occurrence individually and independently -O-, -S-, -S-S-, -NH-, -(C=O)-,-NH(C=O)-, (C=O)NH- -O(C=O)-, -(C=O)O-, -S(C=O)-, -(C=O)S-, -SO-, -SO_2, - $NHSO_2$-, -SO_2NH-,-$(CH2CH2O)_q$-,-$(CH_2)_r$-, a disubstituted carbocyclyl, a di-substituted aryl, a disubstituted heterocyclyl, or absent;

q can be 1 to 1000;

r can be 1 to 22;

G is an tracer, a drug, an antibiotic, an azide group, or other molecule of interest;

R1, R2, R3, and R4, are each individually and independently -(C=O)OCH_2(C=O)alkyl, -O(C=O)OCH_2(C=O)alkyl, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R1, R2, R3, and R4 are optionally substituted with one or more, the same or different, R5;

R5 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R5 is optionally substituted with one or more, the same or different, R6;

R6 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-Nethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

R7 is -(C=O)OCH_2O(C=O)alkyl, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R7 is optionally substituted with one or more, the same or different, R13;

R13 is hydrogen, alkyl, halogen, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl optionally substituted with one or more, the same or different, R14;

R14 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl,

N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, E is -(CR'R"X)$_m$-(CR'R"Y)$_p$- wherein

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ,11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

In certain embodiments, E is -$(CH_2)_m$- wherein m is is 1, 2, or 3.

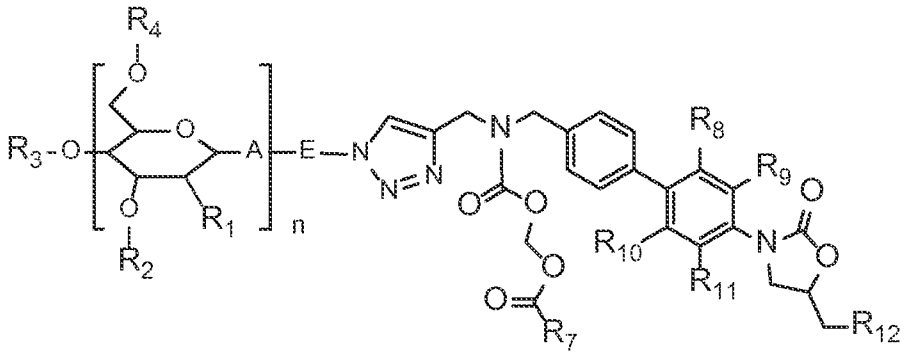
R' and R" are at each occurrence individually and independently hydrogen, alkyl, halogen, or hydroxyl;

X and Y are at each occurrence individually and independently -O-, -S-, -S-S-, -NH-, -(C=O)-, -NH(C=O)-, (C=O)NH- -O(C=O)-, -(C=O)O-, -S(C=O)-, -(C=O)S-, -SO-, -SO_2, - $NHSO_2$-, -SO_2NH-, -$(CH_2CH_2O)_q$-, -$(CH_2)_r$-, a disubstituted carbocyclyl, a di-substituted aryl, a disubstituted heterocyclyl, or absent;

q can be 1 to 1000; and

r can be 1 to 22.

In certain embodiments, the disclosure relates to compounds of formula I with formula IH,



Formula IH

or salts thereof wherein,

n is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15;

A is O or S at each occurrence provided A must be S at least once or all of A are S;

E is a linking group;

R1, R2, R3, and R4, are each individually and independently independently -(C=O)OCH_2(C=O)alkyl , -O(C=O)OCH_2(C=O)alkyl, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or

heterocyclyl, wherein each R1, R2, R3, and R4 are optionally substituted with one or more, the same or different, R5;

R5 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R5 is optionally substituted with one or more, the same or different, R6;

R6 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-Nethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

R7 is hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R7 is optionally substituted with one or more, the same or different, R13;

R8, R9, R10, and R11 are each individually and independently hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R8, R9, R10, and R11 are optionally substituted with one or more, the same or different, R13;

R12 is acetylamino, hydrogen, alkyl, halogen, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl optionally substituted with one or more, the same or different, R13;

R13 is hydrogen, alkyl, halogen, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl optionally substituted with one or more, the same or different, R14;

R14 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino,

acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, E is $-(CR'R''X)_m-(CR'R''Y)_p-$ wherein

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ,11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

In certain embodiments, E is $-(CH_2)_m-$ wherein m is is 1, 2, or 3.

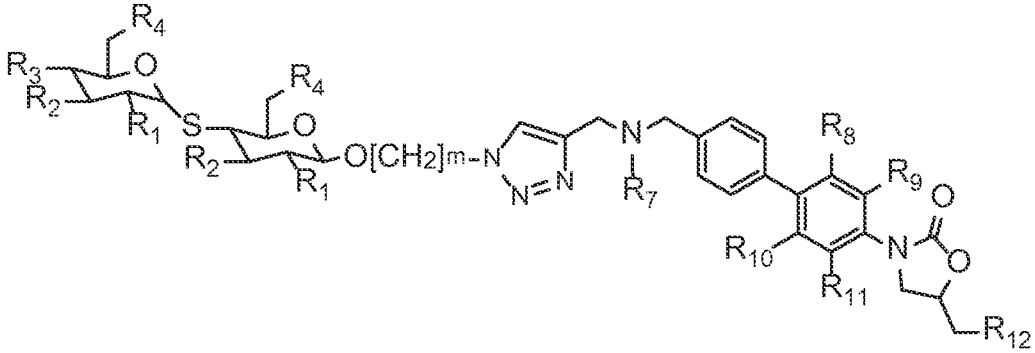
R' and R" are at each occurrence individually and independently hydrogen, alkyl, halogen, or hydroxyl;

X and Y are at each occurrence individually and independently -O-, -S-, -S-S-, -NH- , -(C=O)-, -NH(C=O)-, (C=O)NH- -O(C=O)-, -(C=O)O-, -S(C=O)-, -(C=O)S-, -SO-, $-SO_2$, - $NHSO_2$-, $-SO_2NH-$, $-(CH_2CH_2O)_q-$, $-(CH_2)_r-$, a disubstituted carbocyclyl, a di-substituted aryl, a disubstituted heterocyclyl, or absent;

q can be 1 to 1000; and

r can be 1 to 22.

In certain embodiments, the disclosure relates to compounds of formula I with formula IK,



Formula IK

or salts thereof wherein,

m is 2, 3, or 4;

R1, R2, R3, and R4, are each individually and independently $-O(C=O)OCH_2O(C=O)$alkyl, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl,

wherein each R1, R2, R3, and R4 are optionally substituted with one or more, the same or different, R5;

R5 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R5 is optionally substituted with one or more, the same or different, R6;

R6 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-Nethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

R7 is $-(C=O)OCH_2O(C=O)$alkyl, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R7 is optionally substituted with one or more, the same or different, R13;

R8, R9, R10, and R11 are each individually and independently hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R8, R9, R10, and R11 are optionally substituted with one or more, the same or different, R13;

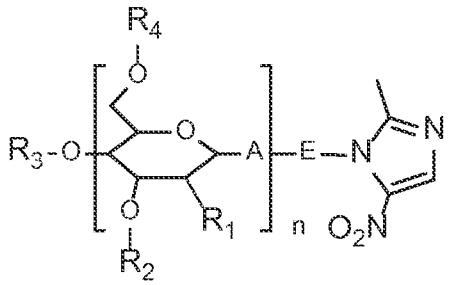
R12 is acetylamino, hydrogen, alkyl, halogen, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl optionally substituted with one or more, the same or different, R13;

R13 is hydrogen, alkyl, halogen, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl optionally substituted with one or more, the same or different, R14;

R14 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino,

acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, the disclosure relates to compounds of formula I with formula IL,



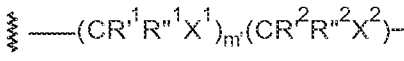
Formula IL

or salts thereof wherein,

n is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15;

A is O or S at each occurrence provided A must be S at least once or all of A are S;

E is a linking group; for example a formula:



wherein the symbol represents the point of attachement to A and imidazole;

m' is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ,11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

R'^{1}, R"^{1}, R'^{2} and R"^{2} are at each occurrence individually and independently hydrogen, halogen, alkyl, alkoxy, or hydroxyl;

X^1 is each occurrence individually and independently -O-, -S-, -S-S-, -NH-, -(C=O)-, -NH(C=O)-, (C=O)NH-, -O(C=O)-, -(C=O)O-, -S(C=O)-, -(C=O)S-, -SO-, -SO_2, -$NHSO_2$-, -SO_2NH-, -$(CH2CH2O)_q$-,-$(CH_2)_r$-, a disubstituted carbocyclyl, a di-substituted aryl, a disubstituted heterocyclyl, or absent;

X^2 and Y are at each occurrence individually and independently -O-, -S-, -S-S-, -NH-, -(C=O)-,-NH(C=O)-, (C=O)NH-, -O(C=O)-, -(C=O)O-, -S(C=O)-, -(C=O)S-, -SO-, -SO_2, - $NHSO_2$-, -SO_2NH-, -$(CH2CH2O)_q$-, -$(CH_2)_r$-, a disubstituted carbocyclyl, a di-substituted aryl, a disubstituted heterocyclyl, or absent;

q can be 1 to 1000;

r can be 1 to 22;;

R1, R2, R3, and R4, are each individually and independently -(C=O)OCH_2O(C=O)alkyl, -O(C=O)OCH_2O(C=O)alkyl, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R1, R2, R3, and R4 are optionally substituted with one or more, the same or different, R5;

R5 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R5 is optionally substituted with one or more, the same or different, R6; and

R6 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-Nethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, E is $-(CR'R''X)_m-(CR'R''Y)_p-$ wherein

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ,11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

In certain embodiments, E is $-(CH_2)_m-$ wherein m is is 1, 2, or 3.

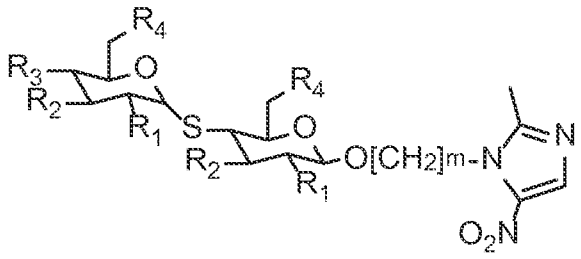
R' and R'' are at each occurrence individually and independently hydrogen, alkyl, halogen, or hydroxyl;

X and Y are at each occurrence individually and independently -O-, -S-, -S-S-, -NH-, -(C=O)-, -NH(C=O)-, (C=O)NH-, -O(C=O)-, -(C=O)O-, -S(C=O)-, -(C=O)S-, -SO-, $-SO_2$-, - $NHSO_2$-, $-SO_2NH$-, $-(CH_2CH_2O)_q-$, $-(CH_2)_r-$, a disubstituted carbocyclyl, a di-substituted aryl, a disubstituted heterocyclyl, or absent;

q can be 1 to 1000; and

r can be 1 to 22.

In certain embodiments, the disclosure relates to compounds of formula I with formula IK,



Formula IK

or salts thereof wherein,

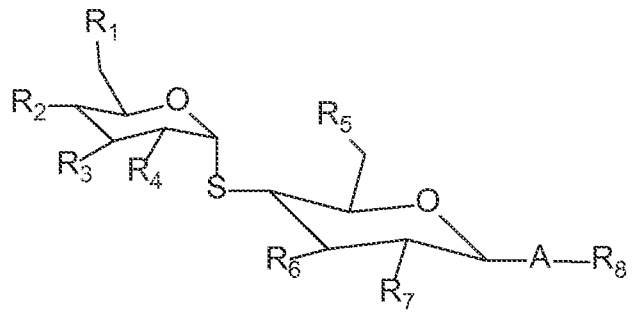
m is 2, 3, or 4;

R1, R2, R3, and R4, are each individually and independently –O(C=O)OCH$_2$O(C=O)alkyl, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R1, R2, R3, and R4 are optionally substituted with one or more, the same or different, R5;

R5 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R5 is optionally substituted with one or more, the same or different, R6; and

R6 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-Nethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, the disclosure relates to a composition comprising a compound of formula II:



Formula II

or derivatives thereof wherein,

A is O, NH, S or a direct bond to R8;

R1, R2, R3, R4, R5, R6, and R7 are, the same or different, hydrogen, hydroxy, mercapto, halogen, amino, alkyl, alkoxy, tracer, ^{18}F optionally substituted with a protecting group or optionally substituted with one or more, the same or different, R9;

R8 is E-G, wherein E is a linking group; G is an tracer, a drug, an antibiotic, an azide group, or other molecule of interest; or

R8 is a protecting group, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)2amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R8 is optionally substituted with one or more, the same or different, R9;

R9 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)2amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R9 is optionally substituted with one or more, the same or different, R10;

R10 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)2amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R10 is optionally substituted with one or more, the same or different, R11;

R11 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)2amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R11 is optionally substituted with one or more, the same or different, R12;

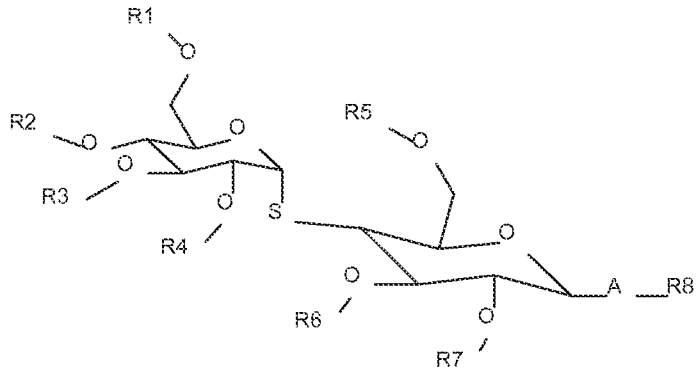
R12 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)2amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R12 is optionally substituted with one or more, the same or different, R13; and

R13 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl,
N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-Nethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl,

methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, R1, R2, R3, R4, R5, R6, and R7 are, the same or different -O(C=O)OCH$_2$O(C=O)alkyl, hydrogen, hydroxy, mercapto, halogen, amino, alkyl, alkoxy, tracer, ^{18}F optionally substituted with a protecting group or optionally substituted with one or more, the same or different, R9.

In certain embodiments, the disclosure relates to compounds of formula II with formula IIA,



Formula IIA

or derivatives thereof wherein,

A is O, NH, S or a direct bond to R8;

R1, R2, R3, R4, R5, R6, and R7 are, the same or different, hydrogen or a protecting group;

R8 is E-G, wherein E is a linking group; G is an tracer, a drug, an antibiotic, an azide group, or other molecule of interest; or

R8 is a protecting group, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R8 is optionally substituted with one or more, the same or different, R9;

R9 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R9 is optionally substituted with one or more, the same or different, R10;

R10 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl,

alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R10 is optionally substituted with one or more, the same or different, R11;

R11 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R11 is optionally substituted with one or more, the same or different, R12;

R12 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R12 is optionally substituted with one or more, the same or different, R13; and

R13 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-Nethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

R1, R2, R3, R4, R5, R6, and R7 are, the same or different, hydrogen or -$(C{=}O)OCH_2(C{=}O)$alkyl.

Pharmaceutical Formulations

Within certain embodiments, the disclosure contemplates compounds and conjugates disclosed herein in pharmaceutical composition, optionally as a pharmaceutically acceptable salt, in combination with a pharmaceutically acceptable excipient. Pharmaceutical compositions of the compounds of this application, or derivatives thereof, can be formulated as solutions or lyophilized powders for parenteral administration. Powders can be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation is generally a buffered, isotonic aqueous solution. Examples of suitable diluents are normal isotonic saline solution, 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulations are especially suitable for parenteral administration but can also be used for oral administration. Excipients, such as polyvinylpyrrolidinone, gelatin, hydroxycellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate, can also be added.

Alternatively, these compounds can be encapsulated, tableted, or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers can be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin, saline, alcohols or water. Solid carriers include starch, lactose, calcium sulfate, dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier can also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulation, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation can be in the form of a syrup, elixir, emulsion, or an aqueous or non-aqueous suspension. Such a liquid formulation can be administered directly p.o. or filled into a soft gelatin capsule.

The pharmaceutical compositions of the application can be in the form of a sterile injectable preparation. Formulations suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which can contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which can include suspending agents and thickening agents.

In some cases, protective groups can be introduced and finally removed. Certain "protective groups" such as an N-acetyl group, can be incorporated and remain as part of the desired compound. Suitable protective groups for amino, hydroxy and carboxy groups are described in Greene et al., Protective Groups in Organic Synthesis, Second Edition, John Wiley and Sons, New York, 1991. Standard organic chemical reactions can be achieved by using a number of different reagents, for examples, as described in Larock: Comprehensive Organic Transformations, VCH Publishers, New York, 1989.

Radio-labeling a small molecule, such as a compound of the present application, usually involves displacement of a suitably activated precursor with a radioactive moiety in a compatible reaction media. In the case of ^{18}F-labeling, the [^{18}F]fluoride attachment to the precursor occurs via nucleophilic substitution of a leaving group, such as mesylate, tosylate, bromide, iodide or diazonium salt, or nitro group. Depending on the compound, the preparation of a radio-labeled compound generally consists of at least two steps. The first step involves the preparation of radiolabeling precursor, in which various functional groups have been appropriately protected and a proper leaving group has been incorporated. The

second sequence then involves the radio-labeling, and removal of the protecting group as known in the art

Terms

As used herein, "alkyl" means a noncyclic straight chain or branched, unsaturated or saturated hydrocarbon such as those containing from 1 to 10 carbon atoms, while the term "lower alkyl" or "C1- 4 alkyl" has the same meaning as alkyl but contains from 1 to 4 carbon atoms. The term "higher alkyl" has the same meaning as alkyl but contains from 7 to 20 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n hexyl, n-septyl, n-octyl, n-nonyl, and the like; while saturated branched alkyls include isopropyl, sec-butyl, isobutyl, tert-butyl, isopentyl, and the like. Unsaturated alkyls contain at least one double or triple bond between adjacent carbon atoms (referred to as an "alkenyl" or "alkynyl", respectively). Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2- butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3 -methyl- 1-butenyl, 2-methyl-2-butenyl, 2,3- dimethyl-2-butenyl, and the like; while representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3- methyl-1-butynyl, and the like.

Non-aromatic mono or polycyclic alkyls are referred to herein as "carbocycles" or "carbocyclyl" groups. Representative saturated carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like; while unsaturated carbocycles include cyclopentenyl and cyclohexenyl, and the like.

"Heterocarbocycles" or heterocarbocyclyl" groups are carbocycles which contain from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur which can be saturated or unsaturated (but not aromatic), monocyclic or polycyclic, and wherein the nitrogen and sulfur heteroatoms can be optionally oxidized, and the nitrogen heteroatom can be optionally quaternized. Heterocarbocycles include morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Aryl" means an aromatic carbocyclic monocyclic or polycyclic ring such as phenyl or naphthyl. Polycyclic ring systems can, but are not required to, contain one or more non-aromatic rings, as long as one of the rings is aromatic.

As used herein, "heteroaryl" refers an aromatic heterocarbocycle having 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono- and polycyclic ring systems. Polycyclic ring systems can, but are not required to, contain one or more non-aromatic rings, as long as one of the rings is aromatic. Representative heteroaryls are furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinolinyl, isoquinolinyl, oxazolyl, isooxazolyl, benzoxazolyl, pyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl. It is contemplated that the use of the term "heteroaryl" includes N-alkylated derivatives such as a 1-methylimidazol-5-yl substituent.

As used herein, "heterocycle" or "heterocyclyl" refers to mono- and polycyclic ring systems having 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom. The mono- and polycyclic ring systems can be aromatic, non-aromatic or mixtures of aromatic and non-aromatic rings. Heterocycle includes heterocarbocycles, heteroaryls, and the like.

"Alkylthio" refers to an alkyl group as defined above attached through a sulfur bridge. An example of an alkylthio is methylthio, (i.e., -S-CH_3).

"Alkoxy" refers to an alkyl group as defined above attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n- pentoxy, and s-pentoxy. Preferred alkoxy groups are methoxy, ethoxy, n-propoxy, i- propoxy, n-butoxy, s-butoxy, t-butoxy.

"Alkylamino" refers an alkyl group as defined above attached through an amino bridge. An example of an alkylamino is methylamino, (i.e., -NH-CH_3).

"Alkanoyl" refers to an alkyl as defined above attached through a carbonyl bride (i.e., -(C=O)alkyl).

"Alkylsulfonyl" refers to an alkyl as defined above attached through a sulfonyl bridge (i.e., -S(=O)2alkyl) such as mesyl and the like, and "Arylsulfonyl" refers to an aryl attached through a sulfonyl bridge (i.e., - S(=O)$_2$aryl).

"Alkylsulfinyl" refers to an alkyl as defined above attached through a sulfinyl bridge (i.e. -S(=O)alkyl).

The term "substituted" refers to a molecule wherein at least one hydrogen atom is replaced with a substituent. When substituted, one or more of the groups are "substituents." The molecule can be multiply substituted. In the case of an oxo substituent ("=O"), two hydrogen atoms are replaced. Example substituents within this context can include halogen,

hydroxy, alkyl, alkoxy, nitro, cyano, oxo, carbocyclyl, carbocycloalkyl, heterocarbocyclyl, heterocarbocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, -NRaRb, -NRaC(=O)Rb, -NRaC(=O)NRaNRb, -NRaC(=O)ORb, - NRaSO2Rb, -C(=O)Ra, -C(=O)ORa, -C(=O)NRaRb, -OC(=O)NRaRb, -ORa, -SRa, -SORa, - $S(=O)_2Ra$, $-OS(=O)_2Ra$ and - $S(=O)_2ORa$. Ra and Rb in this context can be the same or different and independently hydrogen, halogen hydroxyl, alkyl, alkoxy, alkyl, amino, alkylamino, dialkylamino, carbocyclyl, carbocycloalkyl, heterocarbocyclyl, heterocarbocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl.

The term "optionally substituted," as used herein, means that substitution is optional and therefore it is possible for the designated atom to be unsubstituted.

As used herein, the terms "prevent" and "preventing" include the prevention of the recurrence, spread or onset. It is not intended that the present disclosure be limited to complete prevention. In some embodiments, the onset is delayed, or the severity of the disease is reduced.

As used herein, the terms "treat" and "treating" are not limited to the case where the subject (e.g., patient) is cured and the disease is eradicated. Rather, embodiments, of the present disclosure also contemplate treatment that merely reduces symptoms, and/or delays disease progression.

As used herein, the term "combination with" when used to describe administration with an additional treatment means that the agent can be administered prior to, together with, or after the additional treatment, or a combination thereof.

As used herein, "salts" refer to derivatives of the disclosed compounds where the parent compound is modified making acid or base salts thereof. Examples of salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkylamines, or dialkylamines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. In preferred embodiment the salts are conventional nontoxic pharmaceutically acceptable salts including the quaternary ammonium salts of the parent compound formed, and non-toxic inorganic or organic acids. Preferred salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2- acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

"Subject" refers any animal, preferably a human patient, livestock, rodent, monkey or domestic pet.

As used herein, the term "derivative" refers to a structurally similar compound that retains sufficient functional attributes of the identified analog. The derivative can be structurally similar because it is lacking one or more atoms, substituted, a salt, in different hydration/oxidation states, or because one or more atoms within the molecule are switched, such as, but not limited to, replacing an oxygen atom with a sulfur or nitrogen and hydrogen or replacing an amino group with a hydroxyl group or vice versa. The derivative can be a prodrug. Derivatives can be prepare by any variety of synthetic methods or appropriate adaptations presented in synthetic or organic chemistry text books, such as those provide in March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Wiley, 6th Edition (2007) Michael B. Smith or Domino Reactions in Organic Synthesis, Wiley (2006) Lutz F. Tietze hereby incorporated by reference.

As used herein, the term "saccharide" refers to sugars or sugar derivatives, polyhydroxylated aldehydes and ketones, e.g., with an empirical formula that approximates Cm(H2O)n, i.e., wherein m and n are the same or about the same. Contemplated saccharides include, e.g., maltose, isomaltose, and lactose with an empirical formula of C12H22O11. The term is intended to encompass sugar monomers, oligomers, and polymers. The terms oligosaccharide and polysaccharide are used interchangeably, and these saccharides typically contain between two and ten monosaccharide units, or greater than ten monosaccharide units. In certain embodiments of the disclosure, the saccharide is a dextrin, maltodextrin, or cyclodextrin. Dextrins are mixtures of polymers of D-glucose units linked by α-(1→4) or α-(1→6) glycosidic bonds. Maltodextrin consists of D-glucose units connected in chains of variable length. The glucose units are primarily linked with α(1→4) glycosidic bonds. Maltodextrin is typically composed of a mixture of chains that vary from three to nineteen glucose units long. Maltose is a disaccharide formed from two units of glucose joined with an α(1→4)bond. Isomaltose has two glucose molecules linked through an α(1→6) bond. In certain embodiments, the disclosure contemplates cyclic and non-cyclic polysaccharides. Typical cyclodextrins contain a number of glucose monomers ranging from six to eight units in a ring, such as alpha cyclodextrin; a six membered sugar ring molecule; beta cyclodextrin, a seven sugar ring molecule; and gamma cyclodextrin, an eight sugar ring molecule.

The term "thiomaltose" and "thiomaltose" analogs refers to maltose, saccharides, or polysaccharides, wherein one or more to the sugar units are connect by a bridging thiol. In

certain embodiments, the sugar units are glucose bridged by thiol through a 1→4 and or 1→6 bond.

As used herein, the term "conjugate" or "conjugated," and the like refer to molecular entities being linked together through covalent bonds. Conjugation can be accomplished by directly coupling the two molecular entities, e.g., creating an ester or amide from a hydroxyl group, amino group, and a carboxylic acid. Conjugation can be accomplished by indirectly coupling the two molecular entities, e.g., instituting a linking group such as a polyethylene glycol. Conjugation can be accomplished by modifying the molecular entities with chemical groups that react with one another, e.g., alkyne-functionalized entity with an azide-functionalized entity or the reduction of thiol groups on individual entities to form a disulfide bond.

"Positron emission tomography (PET) refers to an imaging technique that produces a three-dimensional image by detecting pairs of gamma rays emitted indirectly by a positron-emitting radionuclide tracer. Three-dimensional images of tracer concentration within the area are then constructed by computer analysis. A radioactive tracer is administered to a subject e.g., into blood circulation. Typically there is a waiting period while tracer becomes concentrated in areas of interest; then the subject is placed in the imaging scanner. As the radioisotope undergoes positron emission decay, it emits a positron, an antiparticle of the electron with opposite charge, until it decelerates to a point where it can interact with an electron, producing a pair of (gamma) photons moving in approximately opposite directions. These are detected in the scanning device. The technique typically utilizes simultaneous or coincident detection of the pair of photons moving in approximately opposite direction (the scanner typically has a built-in slight direction-error tolerance). Photons that do not arrive in pairs (i.e. within a timing-window) are typically ignored. One typically localizes the source of the photons along a straight line of coincidence (also called the line of response, or LOR). This data is used to generate an image.

The term "radionuclide" or "radioactive isotope" refers to isotopes exhibiting radioactive decay (i.e., emitting positrons) and radiolabeling agents comprising a radioactive isotope (e.g., [11C]methane, [^{11}C]carbon monoxide, [^{11}C]carbon dioxide, [^{11}C]phosgene, [^{11}C]urea, [^{11}C]cyanogen bromide, as well as various acid chlorides, carboxylic acids, alcohols, aldehydes and ketones containing carbon-11). Such isotopes are also referred to in the art as radioisotopes or radionuclides. Radioactive isotopes are named herein using various commonly used combinations of the name or symbol of the element

and its mass number (e.g., ^{18}F, F-18, or fluorine-18). Exemplary radioactive isotopes include I-124, F-18 fluoride, C-11, N-13, and O-15, which have half-lives of 4.2 days, 110 minutes, 20 minutes, 10 minutes and 2 minutes, respectively. The radioactive isotope is preferably dissolved in an organic solvent, such as a polar aprotic solvent. Preferably, the radioactive isotopes used in the present method include F-18, C-11, I-123, I-124, I-127, I-131, Br-76, Cu-64, Tc-99m, Y-90, Ga-67, Cr-51, Ir-192, Mo-99, Sm-153 and Tl-201. Other radioactive isotopes that can be employed include: As-72, As-74, Br-75, Co-55, Cu-61, Cu-67, Ga-68, Ge-68, I-125, I-132, In-111, Mn-52, Pb-203 and Ru-97.

Other methods of preparing radiolabeled ligands are well known in the art. Example of such methods are disclosed in, for example: 1) Jewett, D. M. (1992) A Simple Synthesis of [^{11}C]Methyl Triflate Appl. Radiat. Isot. 43, 1383-1385; 2) Crouzel, C. Langstrom, B., Pike, V. W., and Coenen, H. H. (1987) Recommendations for a practical production of [^{11}C]methyl iodide Appl. Radiat. Isot. Int. J. Appl. Instrum. Part A 38, 601-603; Dannals, R. F., Ravert, H. T.; 3) Wilson, A. A. (1990) Radiochemistry of Tracers for Neurotransmitter Receptor Studies. In: Quantitative Imaging: Neuroreceptors, Neurotransmitters, and Enzymes. (Edited by Frost), J. J. Wagner Jr., H. N. pp. 19-35, Raven Press, New York; 4) Jewett, D. M., Manger, T. J., and Watkins, G. L. (1991) Captive Solvent Methods for Fast Simple Carbon-11 Radioalkylations. In: New Trends in Radiopharmaceutical Synthesis, Quality Assurance and Regulatory Control (Edited by Emran, A. M.) pp. 387-391. Plenum Press, New York; 5) Marazano, C., Maziere, M., Berger, G., and Comar, D. (1977) Synthesis of methyl iodide-.sup.11C and formaldehyde-11C. Appl. Radiat. Isot. 28, 49-52; 6) Watkins, G., Jewett, D., Mulholland, G., Kitbourn, M., and Toorongian, S. (1988) A Captive Solvent Method for Rapid N-[^{11}C]Methylation of Secondary Amides Application to the Benzodiazepine, 4'-Chlorodiazepam (RO5-4864) Appl. Radiat. Isot. 39, 441-444; and 7) Wilson, A. A., DaSilva, J. N., and Houle, S. (1996) In vivo evaluation of [^{11}C] and [^{15}F]-labeled cocaine analogs as potential dopamine transporter ligands for positron emission tomography Nucl. Med. Biol. 23, 141-146. The subject matter of all references cited herein are incorporated herein by reference in their entirety.

As used herein, a "linker" refers to any molecular configuration that joins molecular moieties. It includes molecules with covalent and non-covalent interactions. A prefer linker is a polymer, i.e., molecule with repeated linking moieties. The linked moieties can be identical in structure or vary, e.g., copolymers. Linking polymers include, but are not limited to, biological polymers, polyethylene glycols, hydrocarbon chains, alkylacrylates, alkylacrylamides, amides, esters, polypeptides, and derivatives thereof.

A "protecting group" refers to those moieties that are introduced into a molecule by chemical modification of a functional group in order to obtain chemoselectivity in a subsequent chemical reaction or to facilitate purification. Protecting groups can be categorized by the reaction conditions and/or reagents that are used to remove them such as acid labile protecting groups, base labile protecting groups and hydrogenation removable protecting groups. For example, acid labile protecting groups, such as tBu or Boc, typically decompose when exposed to strong acidic conditions providing a hydrogen substituent in place of tBu or Boc protecting group. Acetyl esters and thioesters of alcohols and thiols are examples of base labile protecting groups. Additional examples of protecting groups include, but are not limited to, 4-methoxy-2,3,6-trimethylphenyl)sulfonyl (Mtr), 2,2,5,7,8-pentamethyl-chroman-6-sulphonyl (Pmc), tosyl (Tos), mesitylenesulfonyl (Mts), 4,4'-dimethoxybenzhydryl (Mbh), 2,4,6-trimethoxybenzyl (Tmob), tripheylmethyl (Trt), 9-fluorenylmethyloxycarbonyl (fmoc), tert-butyl (tBu), benzyl (Bzl), t-butoxymethyl ether (Bum), (2,4-dinitrophenol) Dnp, benzyloxymethyl (Bom), benzyloxycarbonyl (Z), 2-chloro-benzyloxycarbonyl (ClZ), t-butyloxycarbonyl (Boc), formyl (CHO) or 2-bromobenzyloxycarbonyl (BrZ) and heterocycles such as succinimide, maleimide, and phathalimide. Protecting groups can be in the form of derivatives, e.g., having one or more substituents.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the assay, screening, and therapeutic methods of the disclosure, and are not intended to limit the scope of what the claimed embodiments.

Synthesis of thiomaltose-perylene

In order to test the specificity of thiomaltose for bacteria, a thiomaltose derivative labeled with the fluorescent dye was synthesized, perylene (15), using an azido-thiomaltose (14) as the synthetic intermediate. The procedure used for the synthesis of thiomaltose-perylene (15) is shown in Figure 2. Azido-thiomaltose (14) was first synthesized by lewis acid promoted glycosylation between the thiomaltose imidate donor (13) and azidopropanol. Thiomaltose-perylene was then synthesized by conjugating the perylene dye onto azidothiomaltose (14) via the click reaction, followed by deprotection of the acetyl

protecting groups using lithium hydroxide. Synthetic details for the synthesis of thiomaltose (10), azidothiomaltose (14) and thiomaltose-perylene (15) are provided.

Synthesis of thiomaltose (10)

To a stirred solution of α-D-glucopyranose, 4-S-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-thio-1,2,3,6-tetrabenzoate **9** (1.0 g, 10 mmol) in anhydrous CH_3OH (15 mL) was added $NaOCH_3$ (100 mg, 20 mmol) under an atmosphere of N_2 at room temperature, and the reaction was stirred at room temperature for 12 hours. The reaction mixture was neutralized by adding acidic DOWEX resins, filtered, and concentrated *in vacuo*. The resulting residue was re-dissolved in DMF (10 mL), and precipitated by adding ether (100 mL). The precipitated powder was collected and dried *in vacuo* to afford the product **10** (300 mg, 83%) (α and β mixture). ^{1}H NMR (D2O, 400 MHz): δ (ppm) 5.01 (d, 3*J* (H,H) = 10.2 Hz, 0.6H), 4.82 (d, 3*J* (H,H) = 4.8 Hz, 1H), 4.33 (d, 3*J* (H,H) = 3.6 Hz, 0.4H), 3.71-3.74 (m, 2H), 3.67-3.63 (m, 3H), 3.5-3.49 (m, 2H), 3.43 (dd, 3*J* (H,H) = 10.2 Hz, 1H), 3.26-3.21 (m, 3H), 3.0-2.98 (m, 1H), 2.83-2.85 (m, 1H). 13C NMR (D2O, 100 MHz): δ (ppm) 95.8, 91.5, 85.2, 85.1, 85.1, 81.2, 80.0, 79.6, 78.5, 77.9, 77.8, 77.0, 76.8, 75.8, 74.3, 74.1, 73.7, 73.1, 70.8, 62.8, 62.7, 62.2, 61.5, 48.1, 47.5. MS (MALDI) m/z Found: 381.79, calculated: $C_{12}H_{22}O_{10}SNa$ [M+Na+] 381.08.

Synthesis of azidothiomaltose (14)

To a stirred solution of thiomaltose imidate **13** (0.16 g, 0.2 mmol) and 3-azidopropanol (0.1 g, 1.0 mmol) in dry DCM (5 mL) was added 4Å M.S. The mixture was stirred under nitrogen at 0 °C for 1 hour. TMSOTf (45 μL, 0.20 mmol) was then added and the mixture was stirred at 0 °C for 2 hour. The reaction was quenched with Et_3N and concentrated *in vacuo*. The residue was dissolved in EtOAc (20 mL) and washed with water (5 mL x 2) and brine (10 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 1:1) to afford **14** (92.6 mg, 63%). ^{1}H NMR (400 MHz, CDCl3): *δ (ppm)* 5.89 (d, 1 H, *J* = 5.8 Hz, 1-H (α thiol linkage)), 5.28-5.21 (m, 2H), 5.06 (1H, m), 4.95 (1H, m), 4.78 (1H, m), 4.65 (1H, m), 4.46 (1H, d, *J* = 8.6 Hz, 1-H (β)), 4.33 (1H, m), 4.25-4.20 (2H, m), 4.11 (1H, m), 3.89 (1H, m), 3.58-3.63 (2H, m), 3.35 (2H, t, *J* = 6.0 Hz, CH2), 2.97 (2H, t, *J* = 6.0 Hz, CH2), 2.12-1.99 (s, 21 H, CH3), 1.83 (2H, m, CH2). 13CNMR (100 MHz, CDCl3): *δ (ppm)* 170.5, 170.4, 170.2, 169.9, 169.8, 169.5, 169.4, 100.3, 82.4, 76.7, 75.7, 72.7, 72.5, 70.3, 70.1, 69.7, 68.6, 67.9, 66.3, 63.6, 61.5, 47.9, 43.7,

28.9, 20.8, 20.7, 20.6, 20.6, 20.5, 20.4. HRMS (MALDI) m/z Found: 758.2089, calculated: 758.2054 for $C_{29}H_{41}N_3O_{17}SNa$ [*M*+Na]+.

Synthesis of thiomaltose-perylene (15)

To a stirred solution of **14** (15.0 mg, 0.02 mmol) and alkyne functionalized perylene dye (13.0 mg, 0.04 mmol) in DMF (5 mL) was added CuI (0.2 mg, 1.0 μmol) and DIPEA (1.2 mg, 0.01 mmol). The mixture was stirred at room temperature for 12 hours under nitrogen and the solvent was removed *in vacuo*. The residue was dissolved in DCM (10 mL) and washed with water (5 mL x 2) and brine (5 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness *in vacuo*. The residue was dissolved in CH_3OH (5 mL), and aqueous LiOH (1.0 M, 2 mL) was added into the reaction mixture under nitrogen. The reaction mixture was stirred at room temperature for 24 hours. The mixture was then neutralized with Dowex 50W resin, filtered and concentrated *in vacuo*. The residue was purified by HPLC to afford **15** (10.0 mg, 65% in two steps). ^{1}H-NMR (400 MHz, DMSO-d6): *δ (ppm)* 7.85-7.76 (m, 3H, Aromatic), 7.72 (d, 1H, *J* = 8.0 Hz, ArH), 7.51 (d, 1H, *J* = 8.0 Hz, ArH), 7.39 (s, 1H, triazole), 7.21 (d, 2H, *J* = 8.0 Hz, ArH), 7.13-7.03 (m, 4 H, ArH), 5.96 (d, 1 H, *J* = 6.0 Hz, 1-H' (α thiol linkage), 4.96-4.91 (2H, m), 4.71 (m, 2H, ArC*H2*O), 4.55 (s, 2H, C*H2*-C=C), 4.45 (*d*, 1H, *J* = 8.4 Hz, 1-H (β)), 3.78-3.71 (5H, m), 3.69-3.67 (2H, m), 3.43-3.31 (5H, m), 3.22-3.20 (m, 3H), 2.91-2.89 (m, 1H), 1.91 (2H, m). 13C NMR (100 MHz, DMSO-d6): *δ (ppm)* 143.3, 134.8, 133.1, 132.8, 131.9, 131.7, 131.0, 128.9 128.5, 127.9, 127.9, 126.7, 126.5, 126.1, 123.7, 123.6, 120.1, 120.0, 120.0, 119.5, 103.6(1-C (β)), 97.8 (1-C (α thiol linkage)), 81.5, 79.1, 77.3, 76.9, 75.7, 73.8, 73.1, 72.8, 70.6, 68.1, 64.3, 62.0, 48.7, 47.9, 28.5. HRMS (MALDI) m/z Found: 784.2543, calculated: 784.2516 for $C_{39}H_{43}N_3O_{11}SNa$ [*M*+Na]+.

Thiomaltose has high specificity for bacteria over mammalian cells

Thiomaltose-perylene has high specificity for bacteria over mammalian cells. The uptake of thiomaltose-perylene was investigated in *E .coli* and in Raw 264.7 murine macrophages. A 500 μL suspension of *E .coli* (O.D=0.6) was incubated with 20 μM thiomaltose-perylene for 2 hours. The bacterial cells were washed in PBS and lysed. The fluorescence intensity of the sample was measured and normalized to the protein content. Similarly, 10^5 macrophage cells were incubated with 20 μM thiomaltose-perylene for 2 hours and the cells were lysed. The specificity of thiomaltose-perylene for bacteria was determined by comparing the fluorescence intensity in bacteria versus macrophages,

normalized to intracellular protein content. Figures 13 indicates that thiomaltose-perylene has high specificity for bacteria, as the uptake of thiomaltose-perylene was 98 fold higher in bacteria when compared to mammalian cells.

Thiomaltose is stable to maltase

Thiomaltose is stable to maltase hydrolysis. The stability of thiomaltose and maltose was investigated in the presence of maltase. Thiomaltose and maltose were incubated with 10 units of maltase, which is an enzyme that breaks maltose into two glucose molecules. The hydrolysis kinetics of thiomaltose and maltose was determined by quantifying the glucose released from thiomaltose or maltose hydrolysis. Figure 14 demonstrates that thiomaltose is orders of magnitude more stable to maltase hydrolysis than maltose. For example, the half-life of maltose is approximately 30 minutes, under these conditions, whereas thiomaltose had negligible hydrolysis after 3 hours.

Synthesis of ^{18}F-thiomaltose

One can synthesize ^{18}F-thiomaltose (**17**), following the general procedure shown in Figure 3. Briefly, one converts azido-thiomaltose (**14**) into a brosylate precursor (**16**) via a click reaction with pent-4-yn-1-yl 4-bromobenzenesulfonate (**2**). One obtains ^{18}F-thiomaltose (**17**) by reacting the precursor (**16**) with K^{18}F, followed by deprotection of the acetyl protecting groups with aqueous NaOH. One can purify intermediates by flash column chromatography on silica gel and characterized by NMR and HRMS, and one can purify ^{18}F-thiomaltose by HPLC.

Synthesis of thiomaltose-metronidazole TMM (14)

One can conjugate metroinadazole to thiomaltose and generate TMM (See Fig. 20). To a stirred solution of thiomaltose imidate 9 (100 mg, 0.13 mmol) and metronidazole 12 (43 mg, 0.26 mmol) in dry DCM (5 mL) was added 4Å M.S. The mixture was stirred under nitrogen at 0 °C for 1 hour. TMSOTf (10 μL, 0.044 mmol) was then added and the mixture was stirred at 0 °C for 2 hour. The reaction was quenched with Et3N and concentrated in vacuo. The residue was dissolved in EtOAc (20 mL) and washed with water (5 mL x 2) and brine (10 mL). The organic phase was dried over Na2SO4, filtered and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 1:1) to afford 13 (53 mg, 52%). 1H NMR (400 MHz, CDCl3): δ (ppm) 7.95 (s, 1H), 5.87 (d, 1H), 5.28-5.16 (m, 2H), 5.07 (t, 1H) 4.98-4.94 (m, 1H), 4.74 (t, 1H),

4.64-4.56 (m, 2H), 4.39-4.32 (m, 3H), 4.24-4.08 (m, 6H), 3.86 (t, 1H), 3.59 (t, 1H), 2.95 (t, 1H), 2.46 (s, 3H), 2.14-1.95 (m, 21H). ESI-MS m/z Found: 837.2286, calculated: 806.2284 for C32H44N3O19S [M+H]+.

TMM 14 was synthesized by deprotection of 13 with NaOH. To a stirred solution of 13 (40 mg, 0.005 mmol) in MeOH (2 mL) and water (0.5 mL) was added NaOH (40 mg, 1.0 mmol). The mixture was stirred overnight and purified by HPLC to afford TMM (9.1 mg, 27.6%). 1H NMR (400 MHz, D2O): δ (ppm) 8.39 (s, 1H), 5.50 (d, 1H), 4.24-4.15 (m, 3H), 4.04-3.95 (m, 2H) 3.86-3.83 (m, 4H), 3.74-3.94 (m, 15H), 3.26 (t, 2H), 3.05 (t, 2H), 2.67 (s, 5H), 2.56 (t, 2H). MALDI-MS m/z Found: 514.6, calculated: 512.1544 for C18H30N3O12S [M+H]+.

TMM is effective at killing Giardia

Methods for evaluating EC50 measurements in Giardia were established. Giardia cells were cultured in 96 well microtiter plates in anaerobic BD Bio-Bags (Becton Dickinson). Growth was assayed with a MoxiZ coulter counter (Orflo Technologies). The TMM and metroinadazole stock solutions contained DMSO to improve solubility. Giardia growth in 96 well plates with various volumes of TYDK media 10 and DMSO concentrations were evaluated over several days at 37°C. Cells grew more consistently in higher volumes of media and noted reduced growth in DMSO concentrations above 0.25%. Culture volumes of 180uL (10,000 cells/mL starting concentration) and the DMSO concentrations at or below 0.1% were used. Growth was evaluated after 48 hours. The 48 hour time point allows several cell cycles of log phase growth, but stops before maximum densities of 1×10^6 cells/mL are reached TMM has an EC50 of 1.53 μM while metronidazole has an EC50 of 1.7 μM indicating that TMM is at least as good as metronidazole but appears more potent, thus demonstrating that thiomaltose conjugation does not interfere with the efficacy of metronidazole.

Synthesis of thiomaltose-radezolid (TMR) (14)

The synthesis of a conjugate of thiomaltose and radezolid (TMR) is illustrated in Fig. 22. The synthesis of TMR is described below. To a stirred solution of 12 (8.0 mg, 0.02 mmol) and 13 (8.8 mg, 0.02 mmol) in DMF (2 mL) was added DIPEA (50 μL) and CuI (0.1 mg, 0.53 μmol), after stirring for 24 h, the solvent was removed in vacuo. The crude product was purified by HPLC to afford thiomaltose-radezolid (TMR, 14) (12.0 mg, 71%). 1H NMR (400 MHz, D2O): δ (ppm) 8.06 (s, 1H), 7.56-7.33 (m, 6H), 7.21 (d, 1H),

5.60 (d, 1H), 4.51 (t, 2H), 4.40 (s, 1H) 4.33-4.20 (m, 4H), 4.11 (t, 1H), 3.92 (d, 2H), 3.85-3.70 (m, 7H), 3.60-3.33 (m, 8H), 3.22-3.11 (m, 2H), 2.84 (s, 2H), 2.70 (t, 1H), 2.18-2.07 (m, 2H), 1.98 (s, 3H), 1.34-1.27 (m, 2H). ESI-MS m/z Found: 837.3122, calculated: 837.3135 for C37H50FN6O13S [M+H]+.

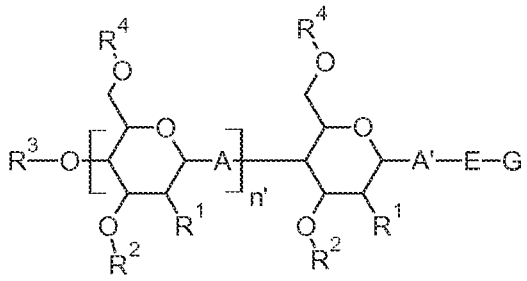
TMR is more effective at killing P. aeruginosa than free radezolid

The efficacy of radezolid can be increased by conjugating it to thiomaltose. P. aeruginosa ($5x10^8$CFUs) were incubated with various concentrations of either radezolid or TMR and the MIC was determined via absorption measurements. The P. aeruginosa strain used in this experiment was a clinical isolate, resistant to multiple antibiotics, obtained from a blood stream infection. Figure 23 shows data indicating that TMR is 1-2 orders of magnitude more effective at killing pseudomonas than free radezolid. For example, a 0.5 μM concentration of TMR causes a 95% reduction in P. aeruginosa growth, whereas free radezolid had no efficacy up to a 10 μM concentration. Thus TMR is able to improve the efficacy of radezolid, presumably by enhancing its transport into GNB.

CLAIMS

What is claimed is:

1. A compound having the formula:



or a salt thereof,

wherein,

R^1, R^2, R^3, and R^4, are each individually and independently hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R^1, R^2, R^3, and R^4 are optionally substituted with one or more, the same or different, R^5;

R^5 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^5 is optionally substituted with one or more, the same or different, R^6;

R^6 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, thylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

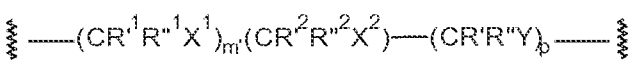
A is O or S at each occurrence provided A must be S at least once or all of A are S;

A' is O or S;

E is a linking group; and

G is a radionuclide, fluorescent molecule, an antibiotic, or an azide group.

2. The compound according to claim 1, wherein E is:



wherein the symbol  represents the point of attachement to A' and G;

n' is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14;

m' is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ,11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

R'^1, R''^1, R'^2 and R''^2 are at each occurrence individually and independently hydrogen, halogen, alkyl, alkoxy, or hydroxyl;

X^1, X^2 and Y are at each occurrence individually and independently -O-, -S-, -S-S-, -NH-, -(C=O)-,-NH(C=O)-, (C=O)NH- -O(C=O)-, -(C=O)O-, -S(C=O)-, -(C=O)S-, -SO-, -SO_2, - $NHSO_2$-, -SO_2NH-,-$(CH2CH2O)_q$-,-$(CH_2)_r$-, a disubstituted carbocyclyl, a di-substituted aryl, a disubstituted heterocyclyl, or absent;

q can be 1 to 1000; and

r can be 1 to 22;2.

3. The compound according to claim 1 or claim 2, wherein A' is O.

4. The compound according to any of claims 2-3, wherein X^1 is in each case absent.

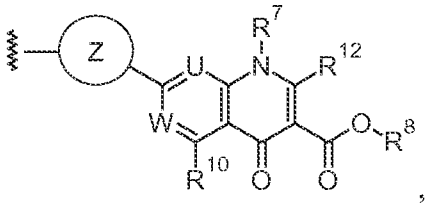
5. The compound according to any of claims 2-3, wherein X^2 is a hetrocyclic ring.

6. The compound according to any of claims 2-5, wherein X^2 is a triazole ring.

7. The compound according to any of claims 1-6, wherein R^2, R^3, and R^4 are in each case hydrogen.

8. The compound according to any of claims 1-7, wherein R^1 is independently selected from H, OH, or F.

9. The compound according to any of claims 1-8, wherein G is selected from -$(CH_2)_x{}^{18}$F, wherein x can be 1, 2, 3, 4, 5, 6, 7 or 8,



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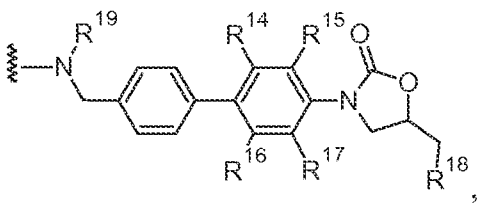

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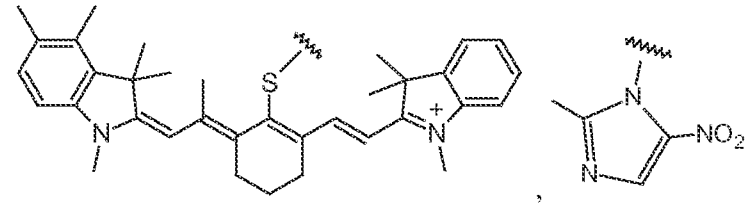
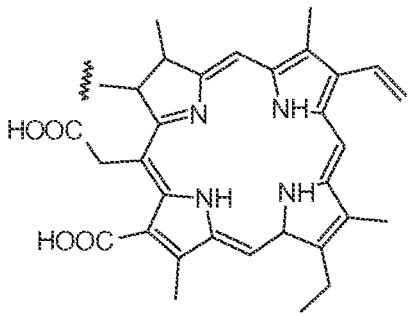
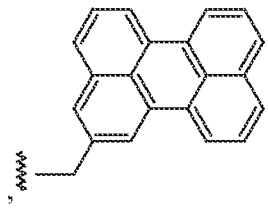
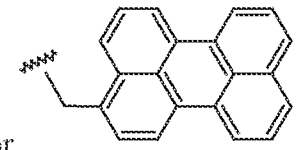



, or

,

wherein the symbol ⁂ represents the point of attachement to E;

U is N or CR^{11};

W is N or CR^{9};

Z is a carbocyclic or heterocyclic ring;

R^{7} is alkyl, carbocyclyl, or aryl, wheren R^{7} is optionally substituted with one or more, the same or different R^{13}; or R^{7} and R^{11} form a heterocarbocyclic ring optionally substituted with R^{13};

R^{8} is hydrogen, alkyl or alkanoyl;

R^{9} is a hydrogen or halogen;

R^{10} is hydrogen, alkoxy, amino, or alkyl;

R^{11} is hydrogen, alkoxy, or halogen;

R^{12} is hydrogen;

R^{13} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl;

R^{19} is hydrogen, alkyl, carbocyclyl, or aryl, wheren R^{7} is optionally substituted with one or more, the same or different R^{13};

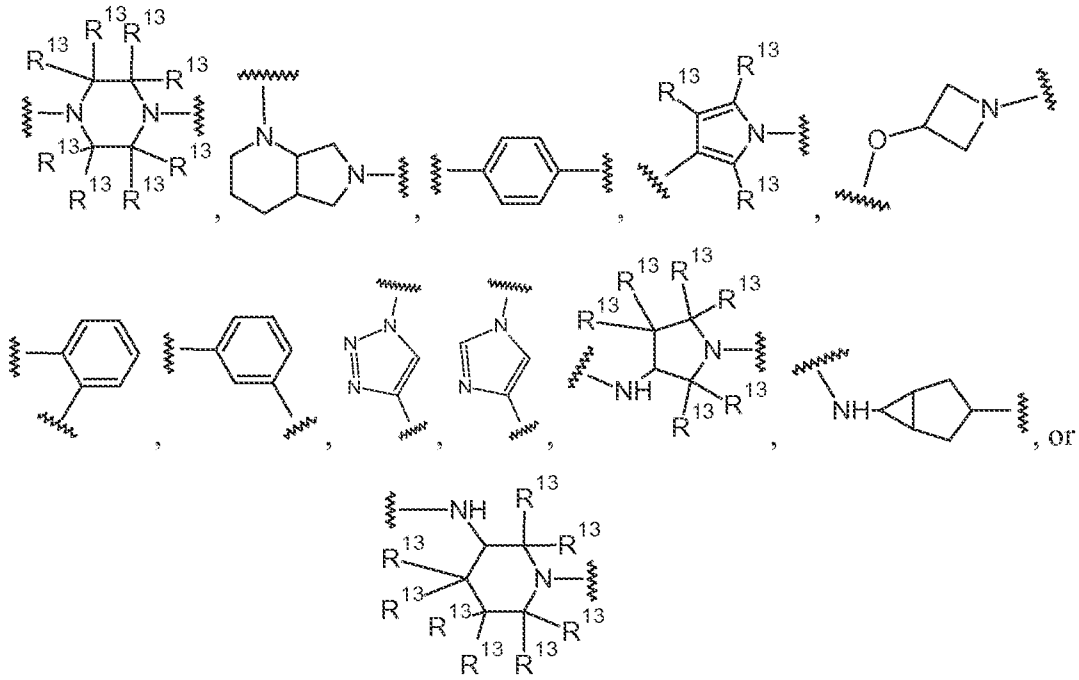
R^{14}, R^{15}, R^{16}, and R^{17} are each individually and independently hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl,

alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein each R^{14}, R^{15}, R^{16}, and R^{17} are optionally substituted with one or more, the same or different, R^{20};

R^{18} is acetylamino, hydrogen, alkyl, halogen, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl optionally substituted with one or more, the same or different, R^{13}; and

R^{20} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

10. The compound according to claim 9, wherein Z is:



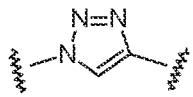
wherein the symbol * represents the point of attachement to E or or the quinolone fragment and R^{13} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-

diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

11. The compound according to claim 10, wherein R^{13} is independently selected from hydrogen, methyl, or ethyl.

12. The compound according to any of claims 2-11, wherein X^1 is in each case absent, R', R", R'^1, $R"^1$, R'^2, $R"^2$ are in each case hydrogen and X^2 is heterocycle.

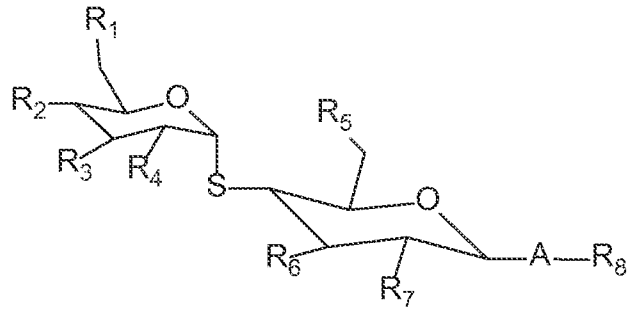
13. The compound according to any of claims 1-12, wherein X^2 is:



14. The compound according to any of claims 2-12, wherein Y is absent.

15. The compound according to any of claims 2-14, wherein n' is 1, 2, 3, or 4.

16. A composition comprising a thiomaltose-based analog of the following formula:



wherein,

A is O, NH, S or a direct bond to R8;

R1, R2, R3, R4, R5, R6, and R7 are, the same or different, hydrogen, hydroxy, halogen, alkyl, alkoxy, tracer, or ^{18}F;

R8 is E-G, wherein E is a linking group; and

G is a tracer, a drug, an antibiotic, an azide group, or other molecule of interest.

17. The composition of claim 16 wherein, E is triazole positioned between linking groups such as the following groups alone or in combination, ether, amine, amide, ester, carbonyl, thiol, dithiol, thiolester, aromatic, heteroaromatic, or hydrocarbon groups.

18. A composition comprising a tracer molecule conjugated to a thiomaltose-based analog.

19. The composition of claim 18, wherein the tracer molecule is a positron-emitting radionuclide.

20. The composition of claim 19, wherein the positron-emitting radionuclide is selected from carbon-11, nitrogen-13, oxygen-15, fluorine-18, rubidium-82, and strontium-82.

21. The composition of claim 20, wherein the tracer molecule is fluorescent molecule.

22. The composition of claim 21, wherein the fluorescent molecule is a fluorescent dye.

23. The composition of any of claims 16-22, wherein the thiomaltose-based analog is greater than 2, 3, 4, 5 or 6 sugar oligomers.

24. The composition of claim 23, wherein the thiomaltose-based analog comprises glucose oligomers.

25. The composition of claim 24, wherein the glucose oligomers are linked by an $\alpha(1\rightarrow4)$ glycosidic bond comprising thiol group.

26. A composition comprising an antibiotic conjugated to a thiomaltose-based analog.

27. The composition of claim 26, wherein the thiomaltose-based analog is greater than 2, 3, 4, 5 or 6 sugar oligomers.

28. The composition of claim 27, wherein the thiomaltose-based analog comprises glucose oligomers.

29. A method of transferring a molecule of interest into bacteria comprising mixing bacteria with a non-naturally occurring conjugate under conditions such that the conjugate is transported across the bacterial cell wall wherein the conjugate comprises a thiomaltose-based analog and a molecule of interest.

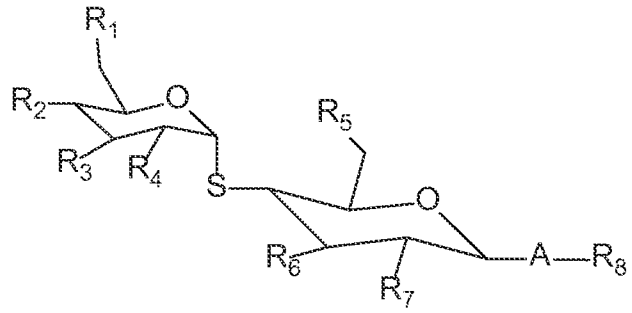
30. The method of claim 29, wherein the conjugate is the compound of any of claims 1-15.

31. An imaging method comprising a) administering a tracer molecule conjugated to a thiomaltose-based analog as in any of claims 16-28 to a subject; and b) scanning the subject for a physical property of the tracer molecule.

32. The imaging method of claim 31, further comprising the step of detecting the physical property of the tracer molecule and creating an image highlighting the location of the tracer molecule in the subject.

33. A method of treating or preventing a bacterial infection comprising administering an effective amount of an isolated conjugate to a subject in need thereof wherein the isolated conjugate comprises an antibiotic and an thiomaltose-based analog as in any of claims 16-28.

34. A compound having the following formula:



or derivative thereof wherein,

A is O, NH, S or a direct bond to R8;

R1, R2, R3, R4, R5, R6, and R7 are, the same or different, hydrogen, hydroxy, halogen, alkyl, alkoxy, tracer, or ^{18}F;

R8 is E-G, wherein E is a linking group; G is an tracer, a drug, an antibiotic, an azide group, or other molecule of interest; or

R8 is a protecting group, hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)2amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R8 is optionally substituted with one or more, the same or different, R9;

R9 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)2amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R9 is optionally substituted with one or more, the same or different, R10;

R10 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)2amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R10 is optionally substituted with one or more, the same or different, R11;

R11 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)2amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R11 is optionally substituted with one or more, the same or different, R12;

R12 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, alkanoyl, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)2amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R12 is optionally substituted with one or more, the same or different, R13; and

R13 is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, Nmethylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-Nethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

35. The composition of Claim 34 wherein, E is triazole positioned between linking groups such as the following groups alone or in combination, ether, amine, amide, ester, carbonyl, thiol, dithiol, thiolester, aromatic, heteroaromatic, or hydrocarbon groups.

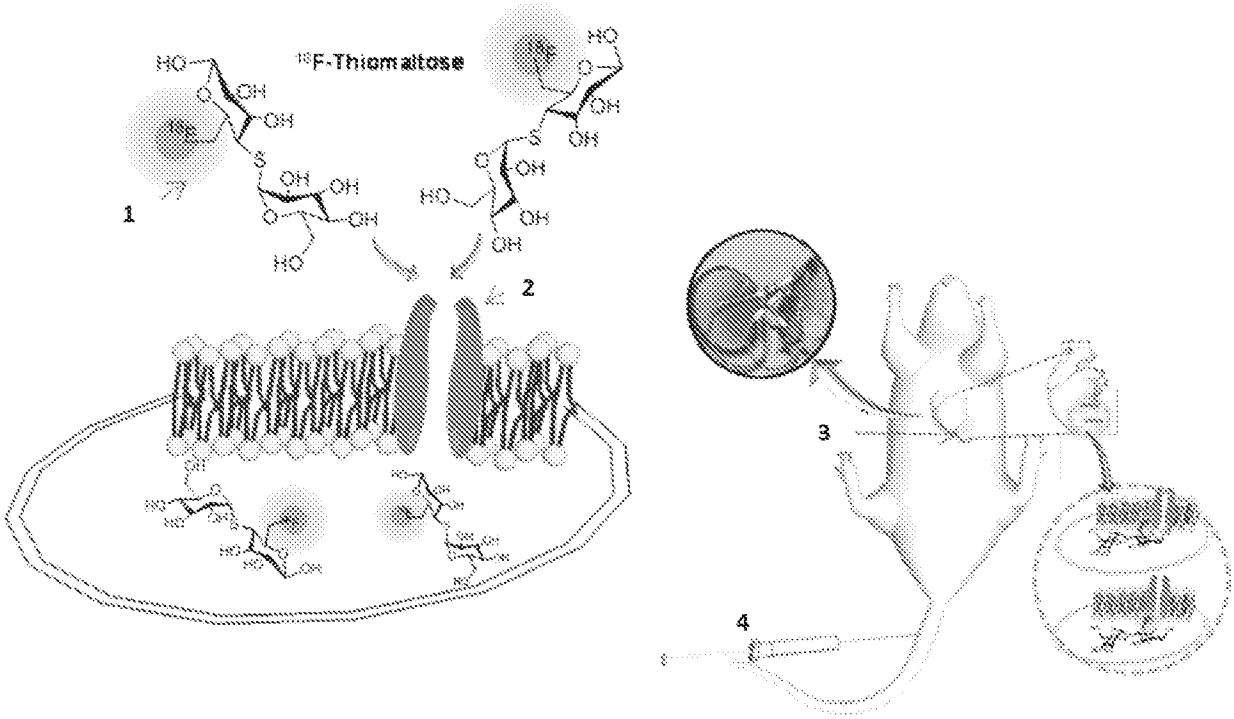


FIG. 1

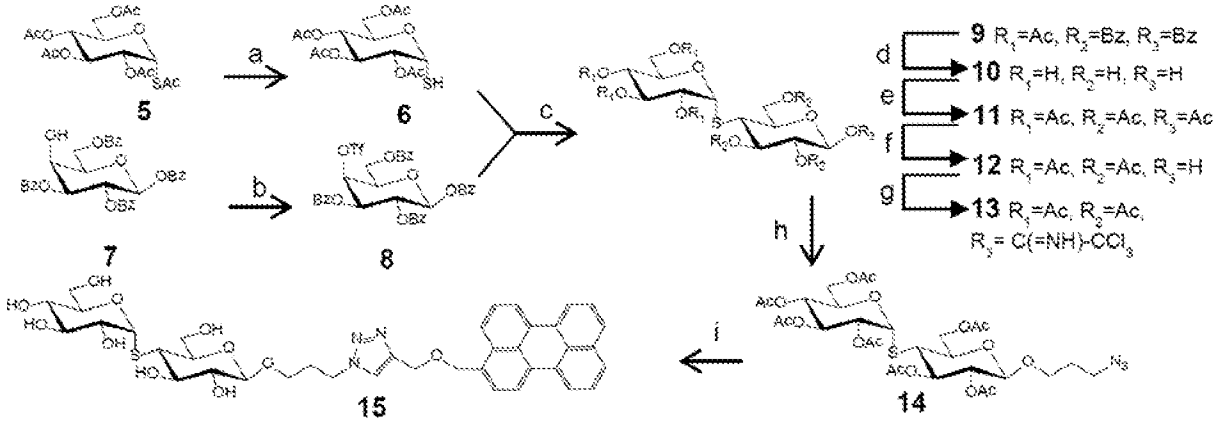

a
b
c
d
e
f
g
h
i
9 R1=Ac, R2=Bz, R3=Bz
10 R1=H, R2=H, R3=H
11 R1=Ac, R2=Ac, R3=Ac
12 R1=Ac, R2=Ac, R3=H
13 R1=Ac, R2=Ac, R3= C(=NH)-OCl3
5
6
7
8
14
15

FIG. 2

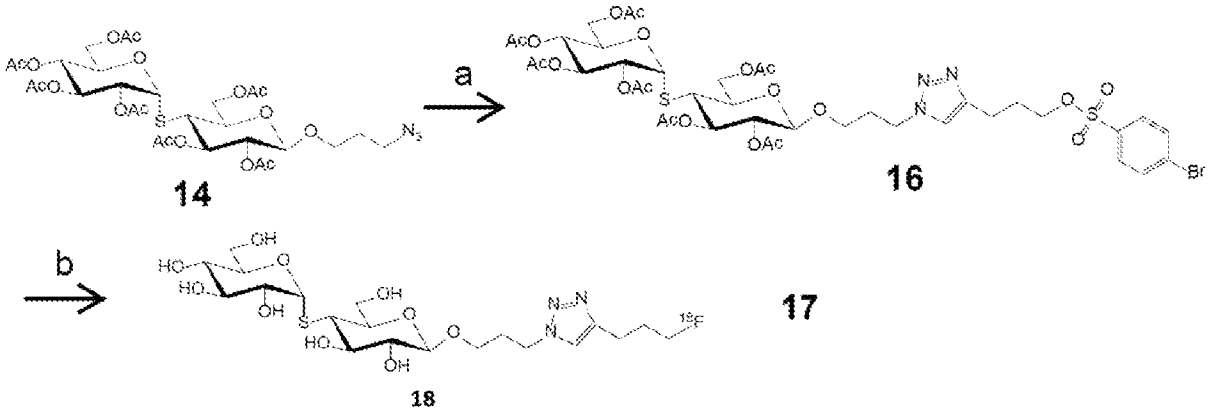

a
b
14
16
17
18

FIG. 3

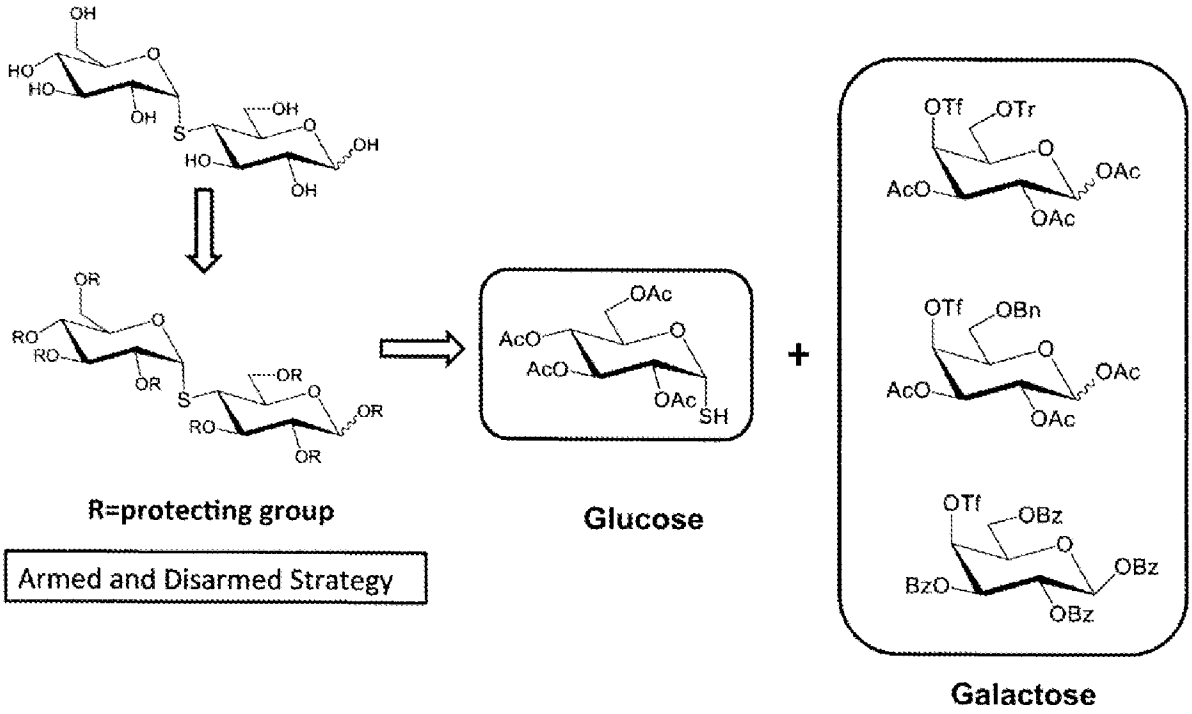

R=protecting group
Armed and Disarmed Strategy
Glucose
Galactose

FIG. 4

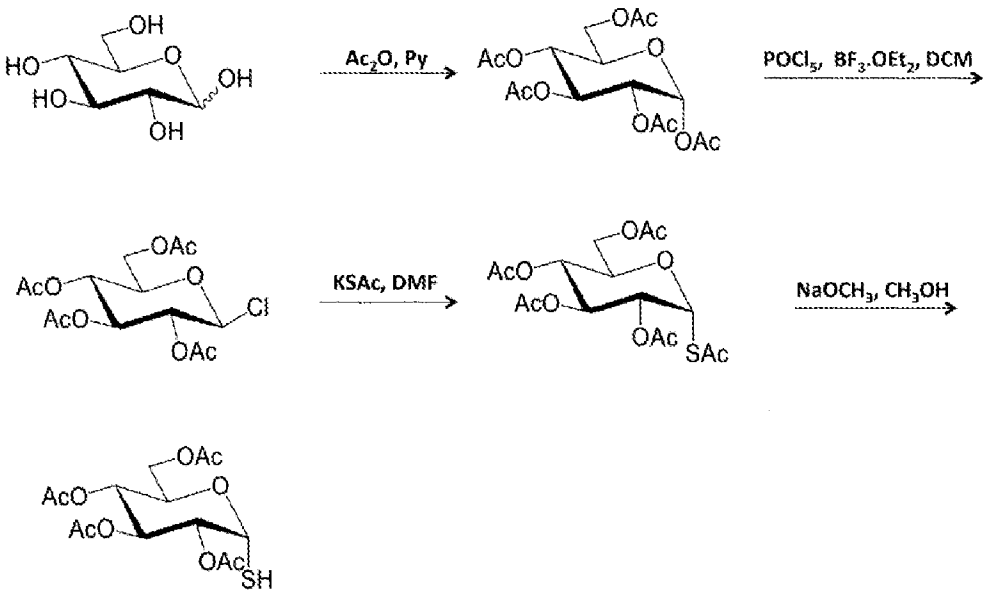

Ac2O, Py
POCl3, BF3.OEt2, DCM
KSAc, DMF
NaOCH3, CH3OH

FIG. 5

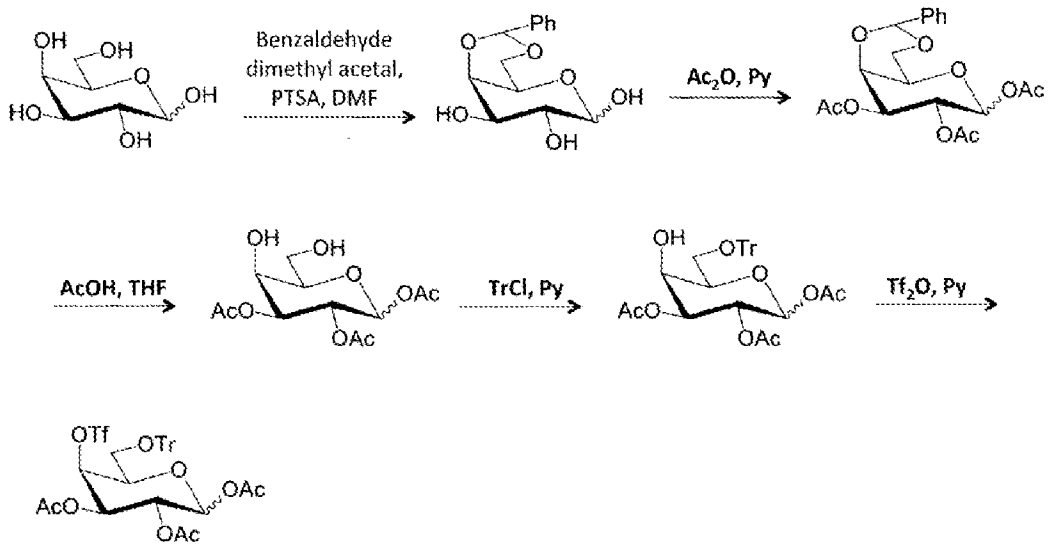

Benzaldehyde
dimethyl acetal,
PTSA, DMF
Ac2O, Py
AcOH, THF
TrCl, Py
Tf2O, Py

FIG. 6

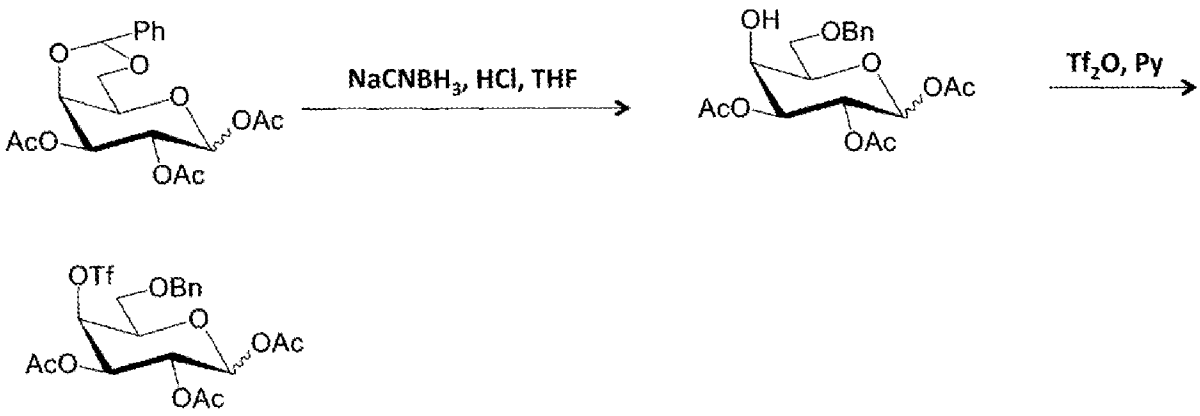

NaCNBH3, HCl, THF
Tf2O, Py

FIG. 7

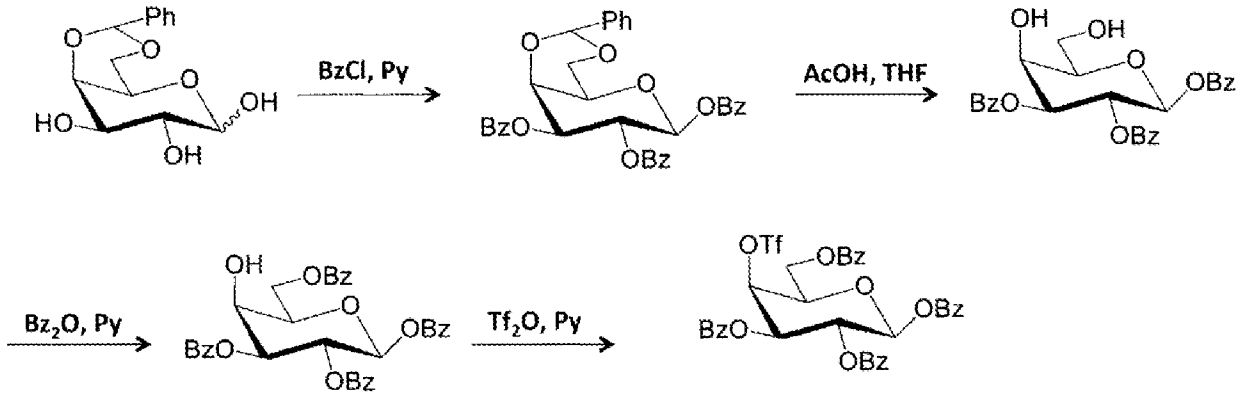

Ph
O
O
O
HO
OH
OH
BzCl, Py
Ph
O
O
O
BzO
OBz
OBz
AcOH, THF
OH
OH
O
OBz
BzO
OBz
Bz2O, Py
OH
OBz
O
OBz
BzO
OBz
Tf2O, Py
OTf
OBz
O
OBz
BzO
OBz

FIG. 8

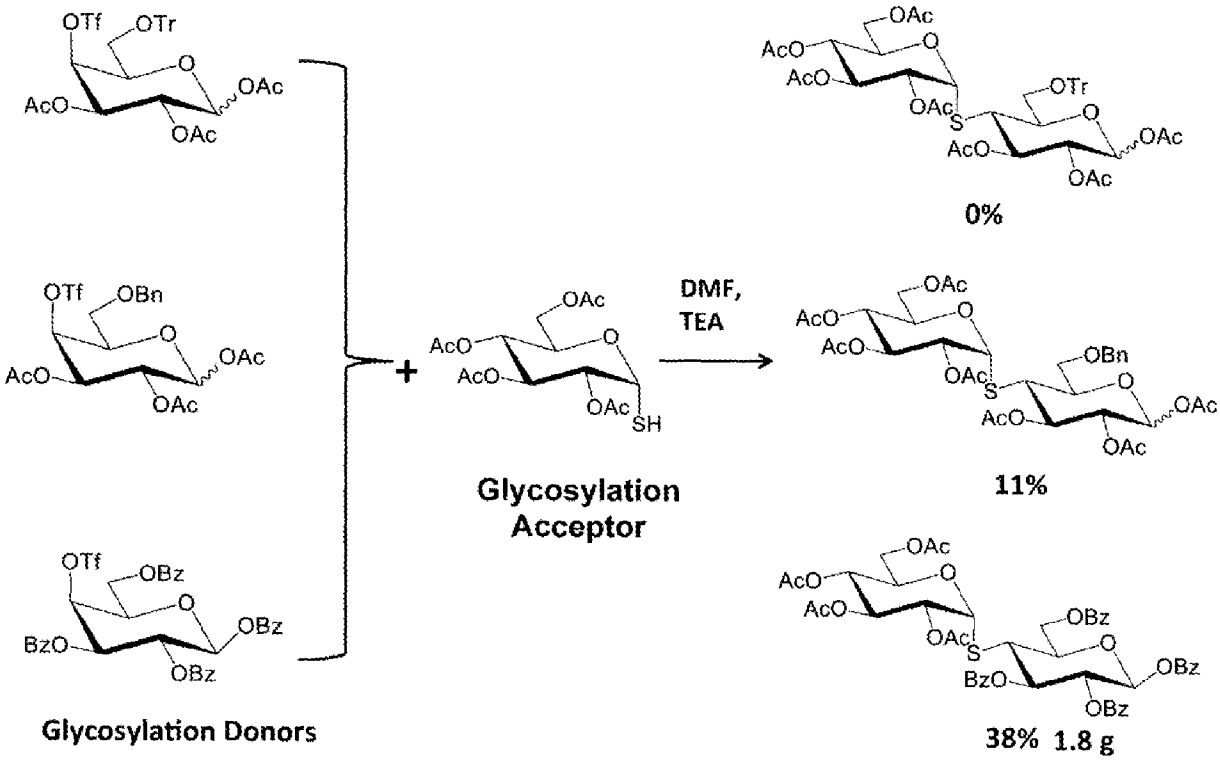

OTf
OTr
O
OAc
AcO
OAc
OTf
OBn
O
OAc
AcO
OAc
OTf
OBz
O
OBz
BzO
OBz
Glycosylation Donors
+
OAc
O
AcO
AcO
OAc
SH
Glycosylation Acceptor
DMF, TEA
OAc
AcO
AcO
OAc
S
OTr
O
OAc
AcO
OAc
0%
OAc
AcO
AcO
OAc
S
OBn
O
OAc
AcO
OAc
11%
OAc
AcO
AcO
OAc
S
OBz
O
OBz
BzO
OBz
38% 1.8 g

FIG. 9

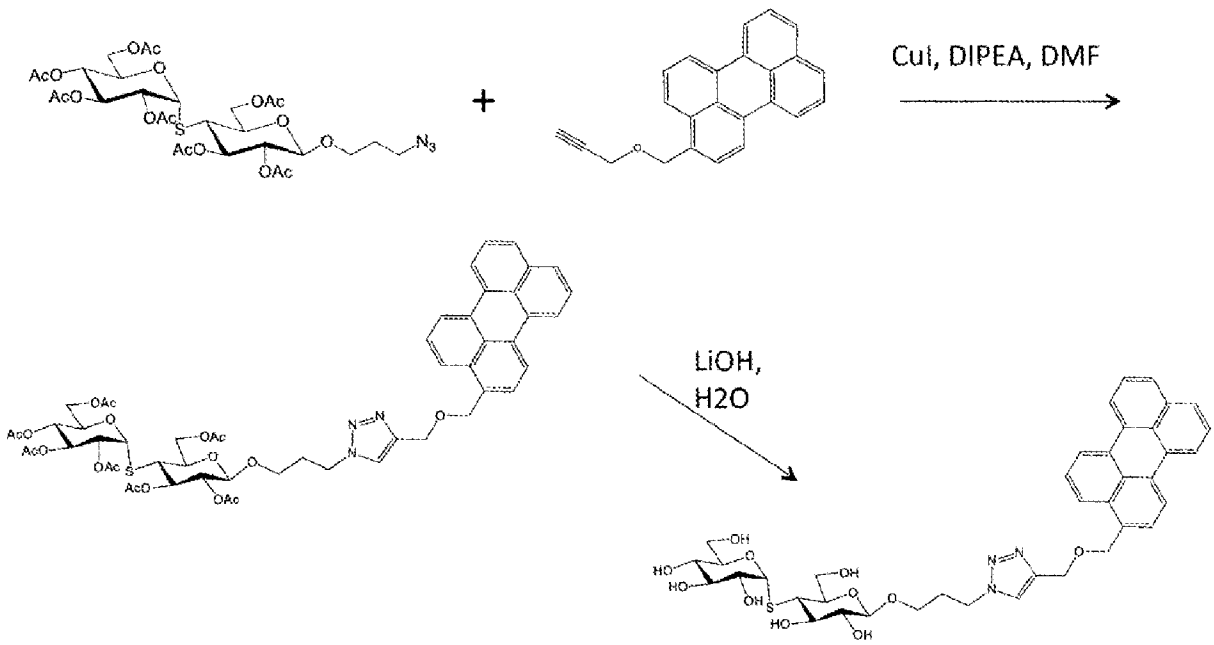

CuI, DIPEA, DMF
LiOH,
H2O

FIG. 10

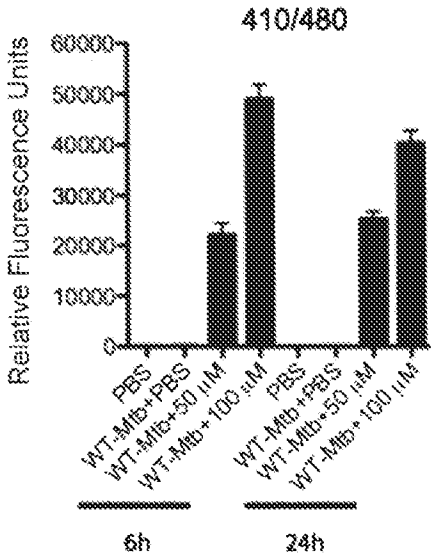

410/480
Relative Fluorescence Units
60000
50000
40000
30000
20000
10000
0
PBS
WT-Mb+PBS
WT-Mb+50 uM
WT-Mb+100 uM
PBS
WT-Mb+PBS
WT-Mb+50 uM
WT-Mb+100 uM
6h
24h

FIG. 11

Samples		Protein Conc. (mg/ml)	Perylene Conc. (μM)	Peylene Conc. (μM/mg protein)
Salmonella Typhimurium (Harvest A_{550} = 0.582)	0	0.46	0.10	0.22
	0	0.41	0.10	0.25
	NaAzide +Perylene	0.45	1.15	2.55
	NaAzide +Perylene	0.45	1.10	2.43
	Perylene	0.47	1.22	2.62
	Perylene	0.42	1.24	2.94
Pseudomonas aeruginosa (Harvest A_{550} = 0.492)	0	0.29	0.11	0.37
	0	0.37	0.11	0.29
	Perylene	0.39	0.62	1.60
	Perylene	0.28	0.83	2.99

FIG. 12

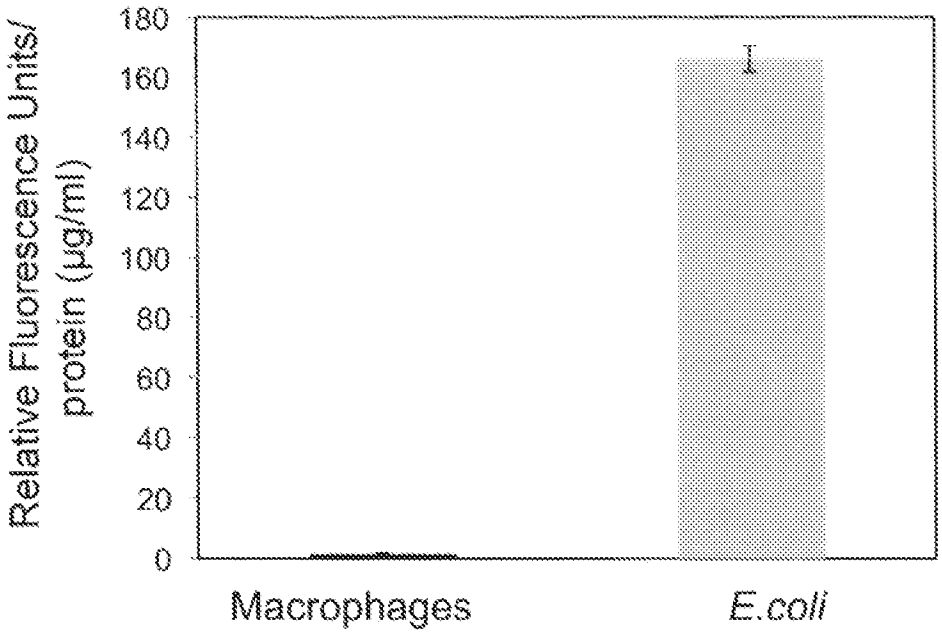


FIG. 13

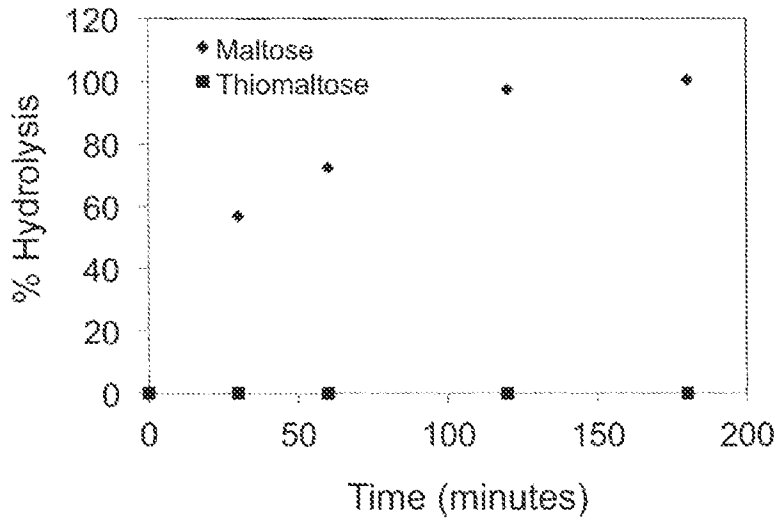

120
100
80
60
40
20
0
% Hydrolysis
Maltose
Thiomaltose
0
50
100
150
200
Time (minutes)

FIG. 14

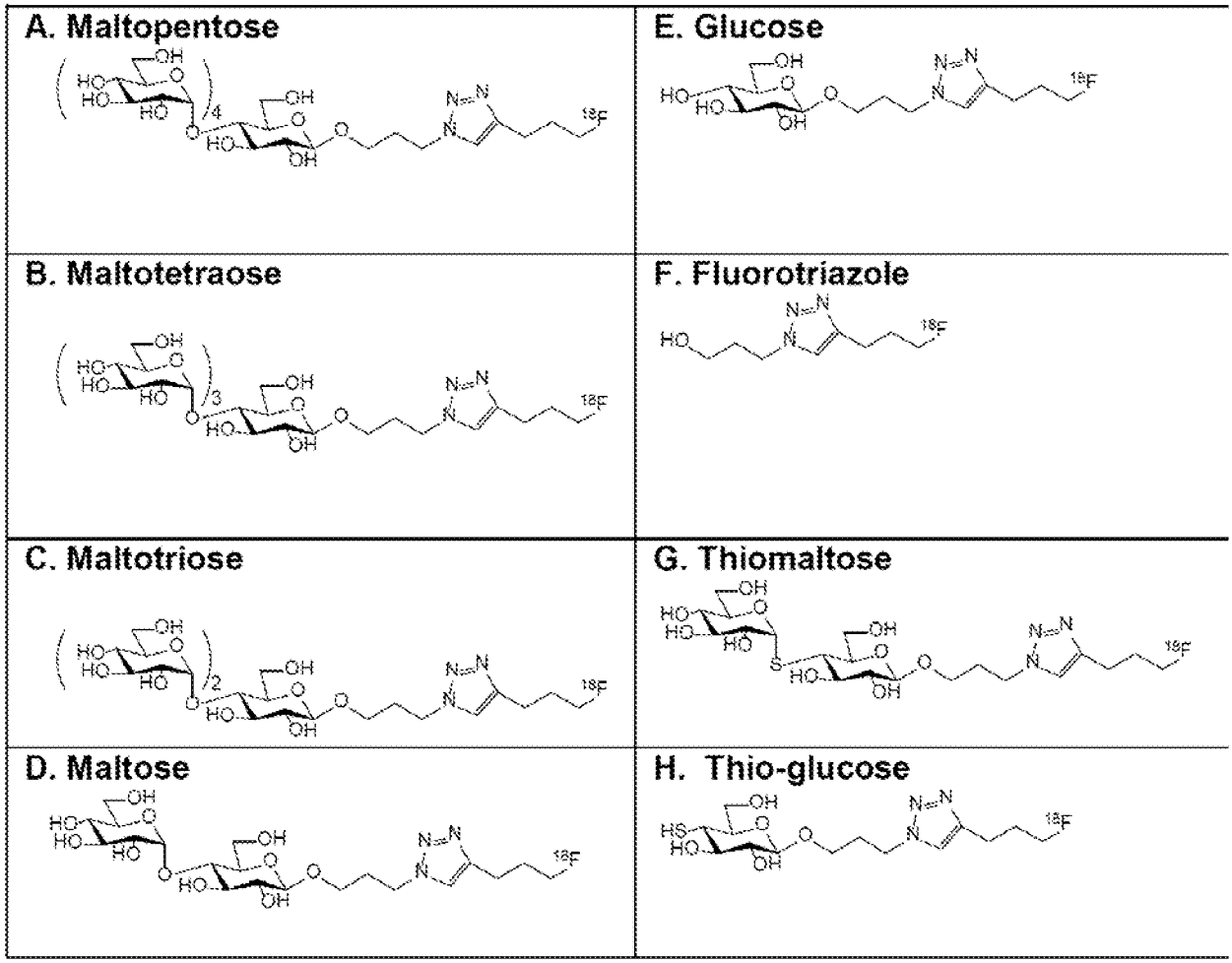

A. Maltopentose
E. Glucose
B. Maltotetraose
F. Fluorotriazole
C. Maltotriose
G. Thiomaltose
D. Maltose
H. Thio-glucose

FIG. 15

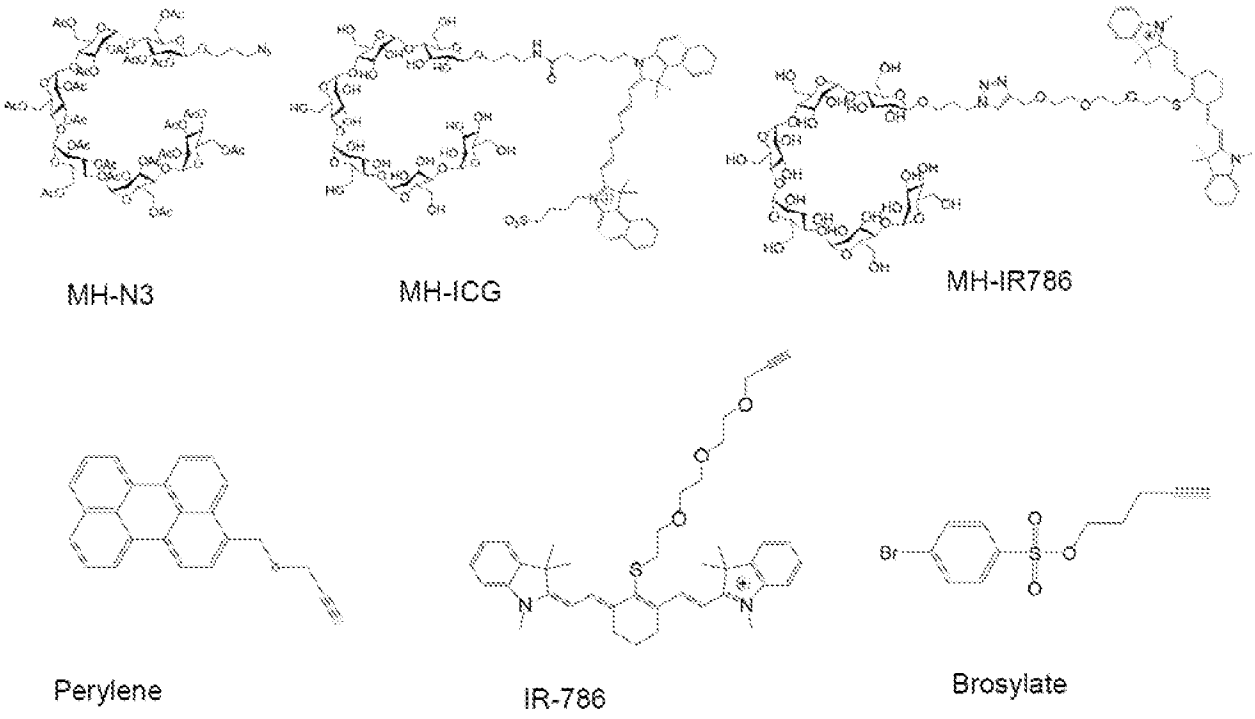
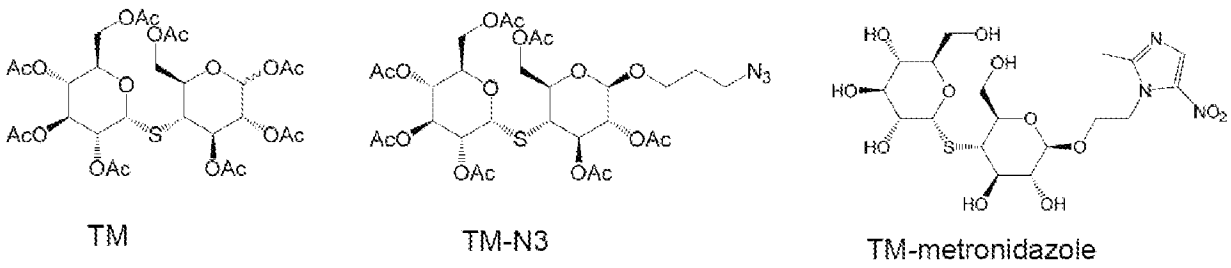

MH-N3
MH-ICG
MH-IR786
Perylene
IR-786
Brosylate

FIG. 16


TM
TM-N3
TM-metronidazole

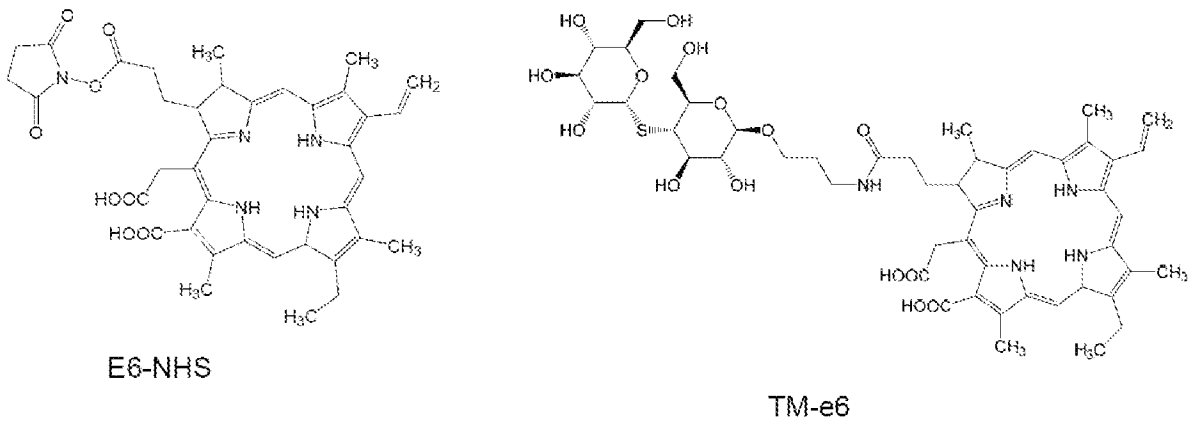

E6-NHS
TM-e6

FIG. 17

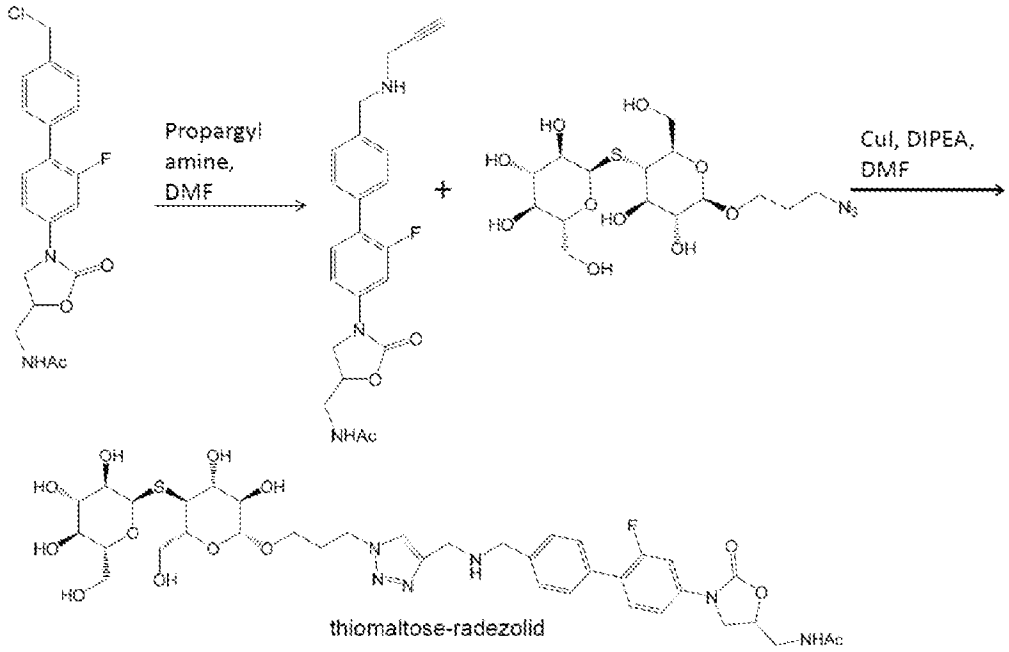

Propargyl amine, DMF
CuI, DIPEA, DMF
thiomaltose-radezolid

FIG. 18

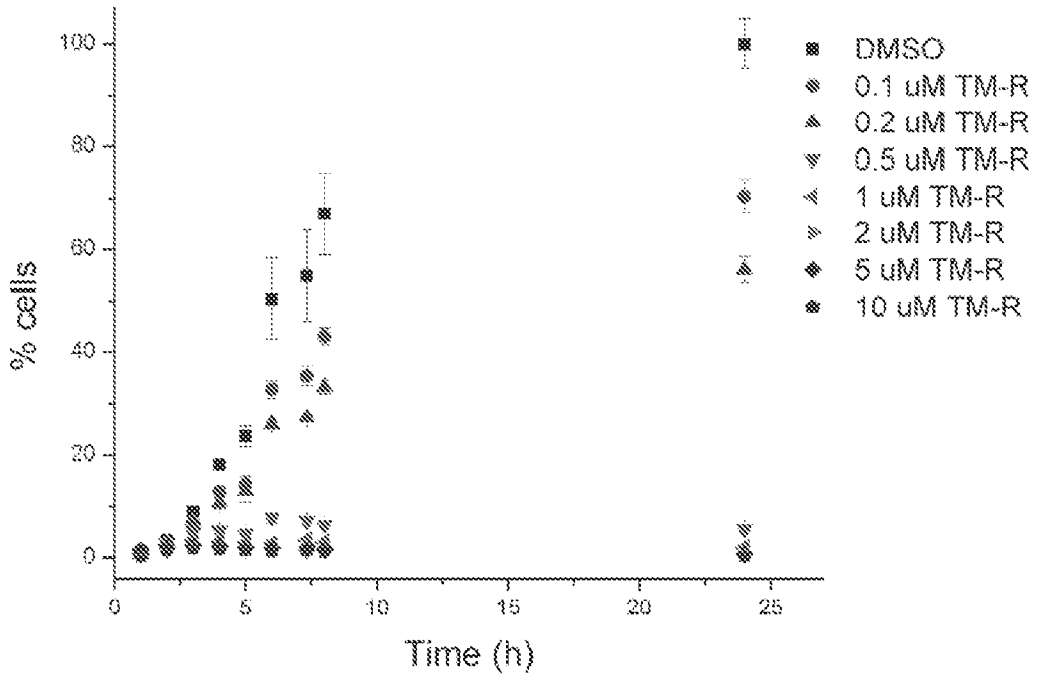

% cells
Time (h)
DMSO
0.1 uM TM-R
0.2 uM TM-R
0.5 uM TM-R
1 uM TM-R
2 uM TM-R
5 uM TM-R
10 uM TM-R

FIG. 19

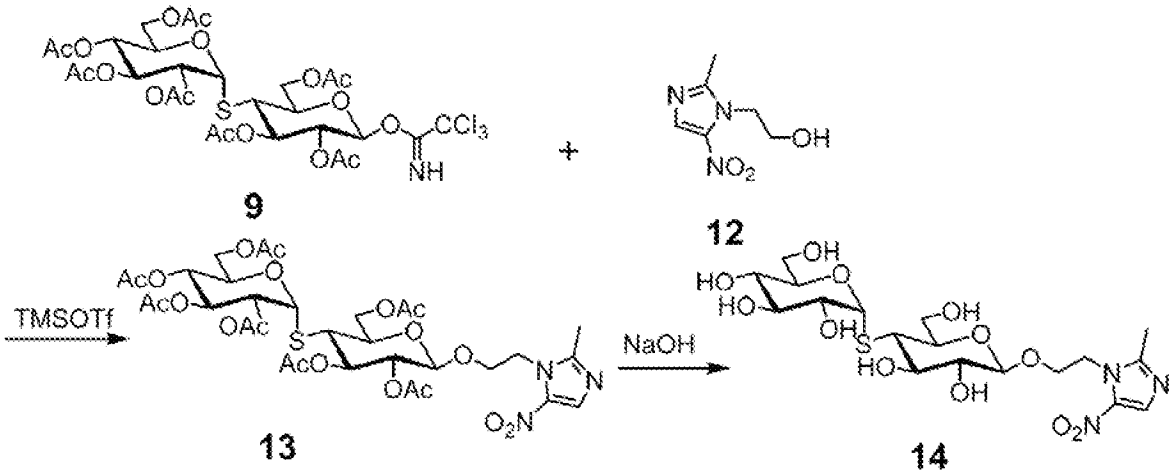


FIG. 20

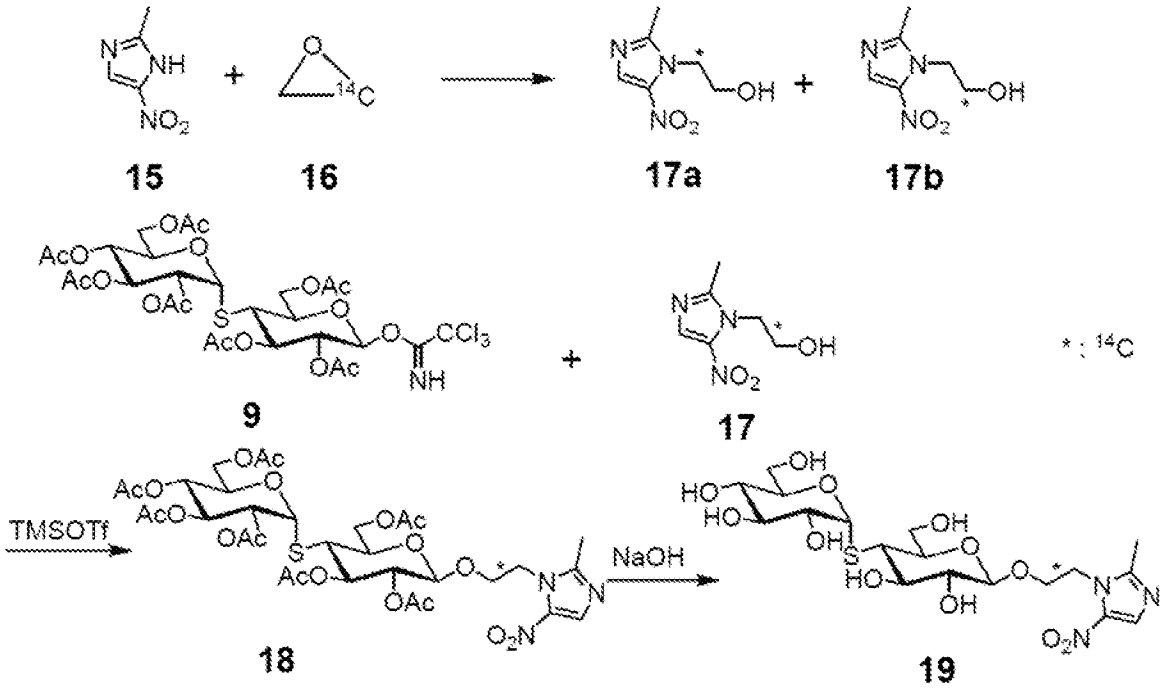


FIG. 21

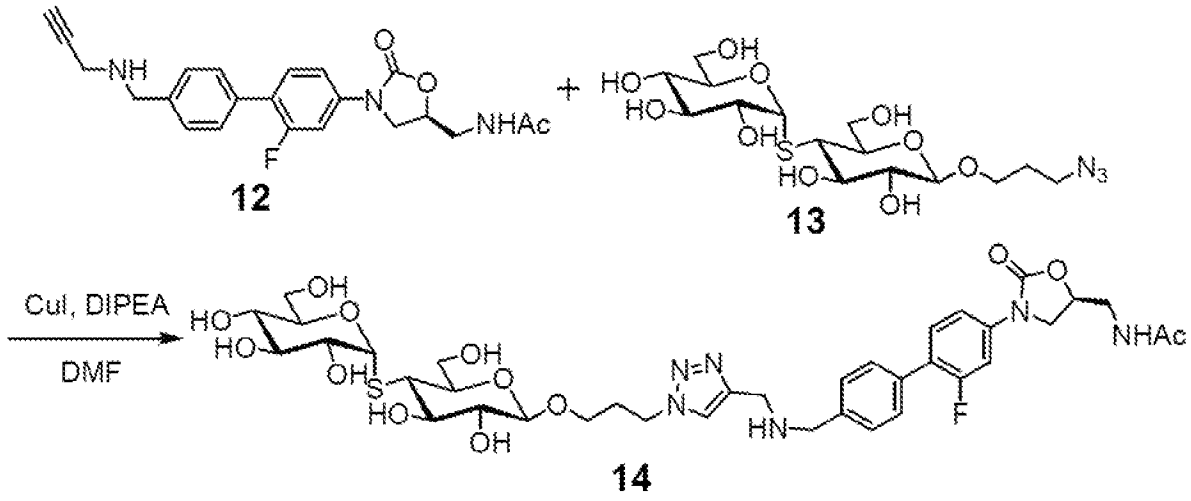

NH
NHAc
F
12
HO
OH
S
N3
13
CuI, DIPEA
DMF
N=N
HN
14

FIG. 22

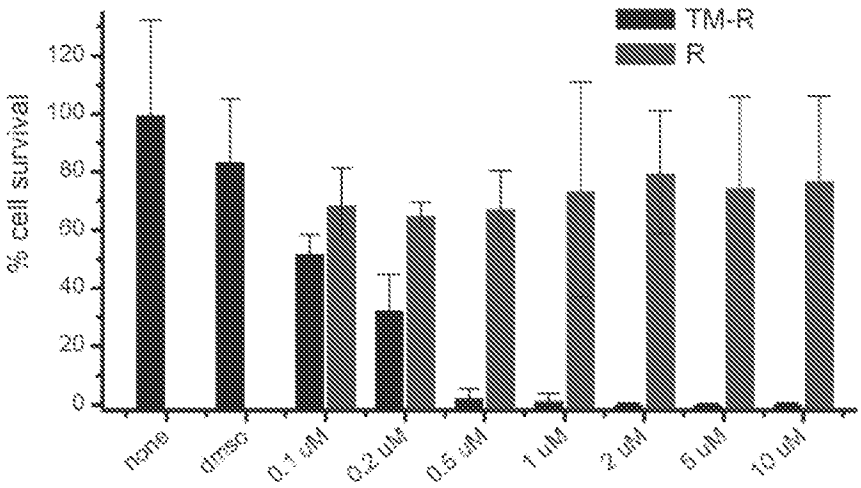

TM-R
R
% cell survival
120
100
80
60
40
20
0
none
dmso
0.1 uM
0.2 uM
0.5 uM
1 uM
2 uM
5 uM
10 uM

FIG. 23

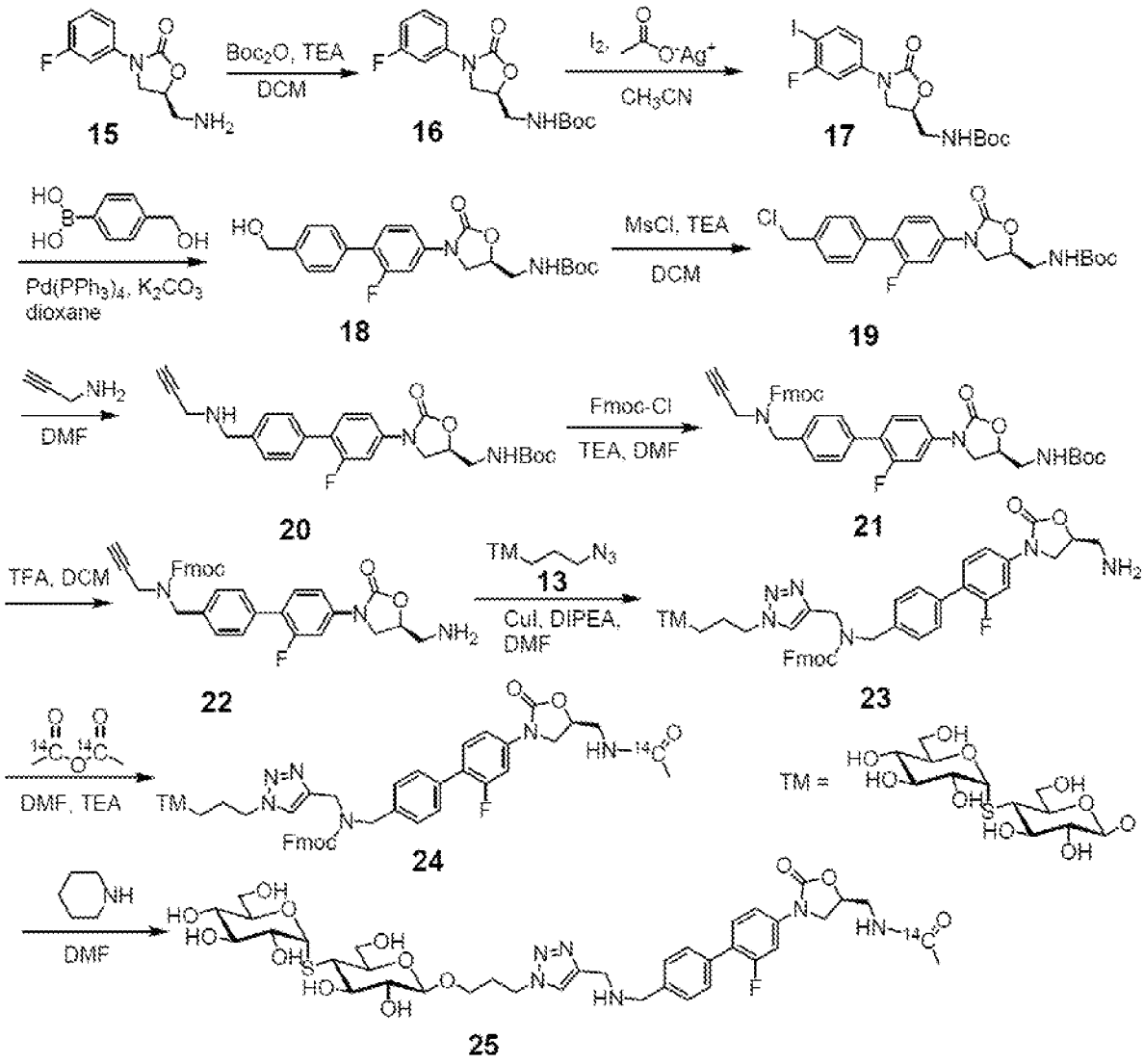

Boc2O, TEA
DCM
I2,
CH3CN
15
16
17
Pd(PPh3)4, K2CO3
dioxane
MsCl, TEA
DCM
18
19
DMF
Fmoc-Cl
TEA, DMF
20
21
TFA, DCM
13
CuI, DIPEA,
DMF
22
23
DMF, TEA
TM =
24
DMF
25

FIG. 24

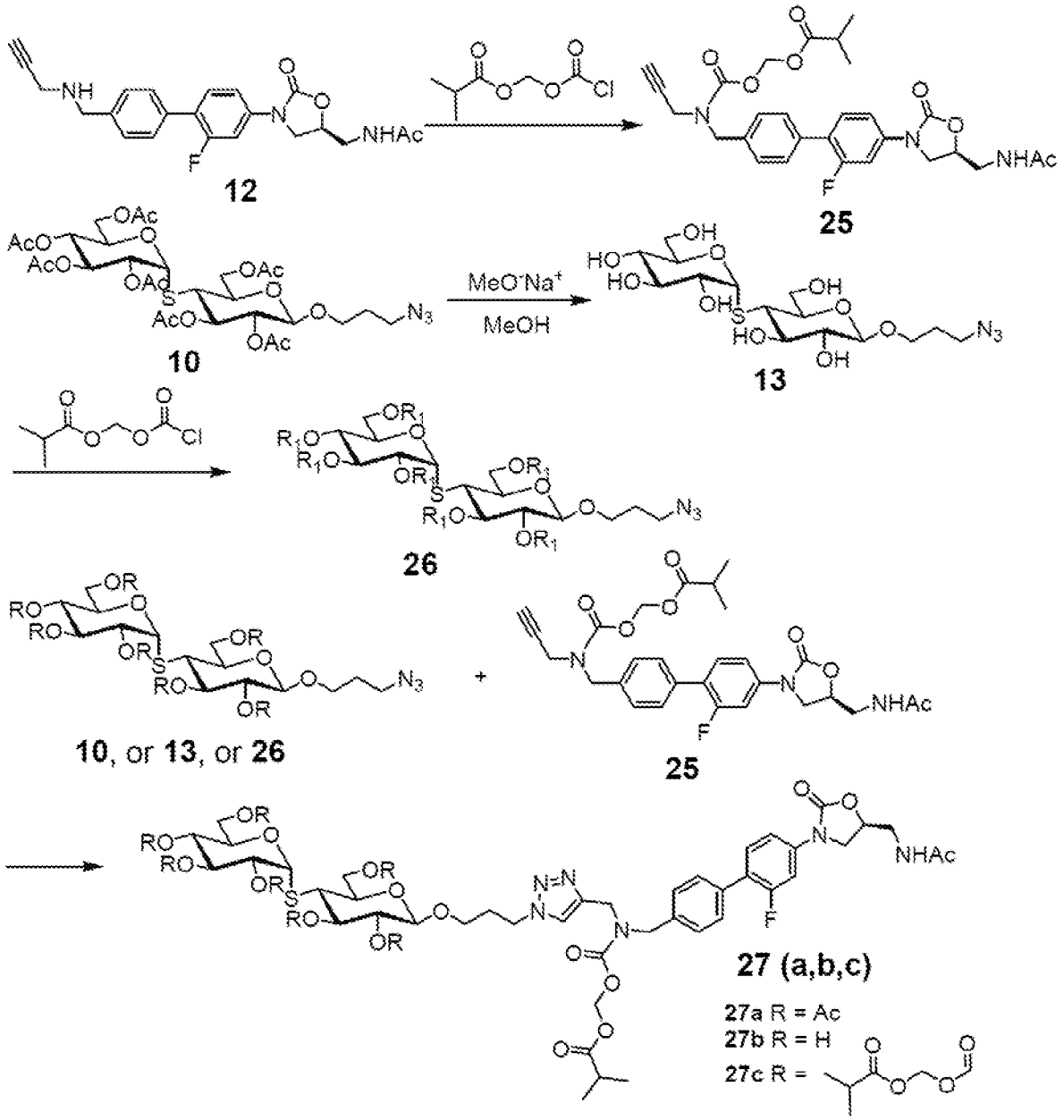

12
25
10
MeO⁻Na⁺
MeOH
13
26
10, or 13, or 26
25
27 (a,b,c)
27a R = Ac
27b R = H
27c R =

FIG. 25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/51262

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 51/00 (2015.01)
CPC - A61K 51/0491; A61K 2123/00; A61K 51/0497
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 51/00 (2015.01)
CPC - A61K 51/0491; A61K 2123/00; A61K 51/0497

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/1.73, 536/123.13, 536/123.1

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Patbase, Google Patents, Google Web
Search terms used - thio maltose thiomaltose radionuclide fluoresecent antibiotic saccharide conjugate thiocellubiose
Pubchem - substructure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0002588 B1 (Eli Lilly and Company) 06 April 1983 (06.04.1983); pg. 4, line 10-11, 14-15; example 54	26-28
Y	US 2014/0219917 A1 (Murthy et al.) 07 August 2014 (07.08.2014); para [0007], [0152], [0176], [0180]; page 3, figure 2, compound MDP-1; pg 10, figure 11, compound 4; pg 16, figure 16, compound MDC-1	1-3, 16-25, 29, 34-35
Y	Bornaghi et al. "Transfer reactions catalyzed by cyclodextrin glucosyltransferase using 4-thiomaltosyl and C-maltosyl fluorides as artificial donors" Carbohydrate Research. Volume 305. August 1997. Pages 561-568; pg. 562, scheme 1, compound 1	1-3, 16-25, 29, 34-35
A	US 2006/0035342 A1 (Withers et al.) 16 February 2006 (16.02.2006); para [0003]; figure 6	1-3, 16-29, 34-35

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 2015	28 DEC 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/51262

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-15, 30-33
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.