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(54) Title: COMPOUNDS AND METHODS FOR TREATING BACTERIAL INFECTIONS

(57) Abstract: The present invention encompasses compounds and methods for treating and preventing bacterial infections specifically urinary tract infections and those caused by bacteria containing type 1 pili and FimH. The present invention also encompasses compounds and methods for treating inflammatory bowel disease specifically Crohn's Disease.

COMPOUNDS AND METHODS FOR TREATING BACTERIAL INFECTIONS

GOVERNMENTAL RIGHTS

[0001] This invention was made with government support under RO1AI029549, P50DK064540 and RO1BK051406-12 awarded by the NIH. The government has certain rights in the invention.

CROSS REFERENCE TO RELATED APPLICATIONS

[0002] This application claims the priority of US provisional application number 61/828,954, filed May 30, 2013, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0003] The present invention encompasses compounds and methods for inhibiting the adhesin protein FimH and treating and preventing urinary tract infections and inflammatory bowel disease (e.g. Crohn's disease and ulcerative colitis).

BACKGROUND OF THE INVENTION

[0004] Urinary tract infection (UTI) caused by uropathogenic *Escherichia coli* (UPEC) is one of the most common infectious diseases in women. The morbidity and economic impact are enormous, with over $2.5 billion spent annually on treatment. Further, recurrent infections are a significant problem despite appropriate antibiotic therapy of the index case. The high rates of recurrence, and the large numbers of women that end up in urology clinics due to their chronic recurrent UTIs highlights the need for a better understanding of the pathogenic mechanisms involved in this disease and the development of new and better therapies.

[0005] Gram-negative bacteria are the causative agents of a wide variety of acute and chronic infectious diseases. Many of these infections are initiated by a critical interaction between host ligands (frequently polysaccharide moieties) and bacterial adhesins (frequently expressed at the distal tip of polymeric pilus fibers assembled by the chaperone/usher pathway). The mannose binding FimH adhesin of type 1 pili is critical for the colonization and invasion into the bladder epithelium. After invasion,

UPEC are able to rapidly multiply inside superficial umbrella cells of the bladder forming biofilm-like intracellular bacterial communities (IBCs). Upon maturation, bacteria disperse from the IBC, spread to neighboring cells, and form next generation IBCs. This is the mechanism by which UPEC rapidly amplify in numbers in the urinary tract and cause disease.

[0006] The X-ray crystal structure of FimH bound to mannose showed that mannose is bound in a negatively charged pocket on FimH. The mannose binding site is highly conserved as it is invariant in 300 *fimH* genes sequenced from clinical UPEC strains. Thus, FimH is the critical node of the entire UPEC pathogenic cascade.

[0007] Recurrence is a serious problem for many women. Women who present with an initial episode of acute UTI have a 25-44% chance of developing a second and a 3% chance of experiencing three episodes within six months of the initial UTI. Recurrence occurs despite appropriate antibiotic treatment and clearance of the initial infection from the urine. A large percentage of recurrent UTI are caused by the same strain of bacteria as the initial infection. One study followed 58 women and found that 68% of recurrences were caused by the same initial index strain of UPEC as determined by restriction fragment length polymorphism (RFLP) analysis. In a separate study, 50% of recurrent strains isolated from female college students appeared genotypically identical to the bacterial strain corresponding to the initial UTI. Another long-term prospective study demonstrated that the same strain of UPEC can cause a recurrent UTI up to 3 years later. The high frequency of same-strain recurrences supports the notion that a UPEC reservoir can exist in the affected individual. The inventors have shown that a quiescent intracellular reservoir (QIR) can form in the bladder tissue itself after acute infection and persist even after antibiotic therapy and urine cultures become sterile. Thus, reactivation of bacteria in QIRs may also be a contributing factor in recurrent UTIs.

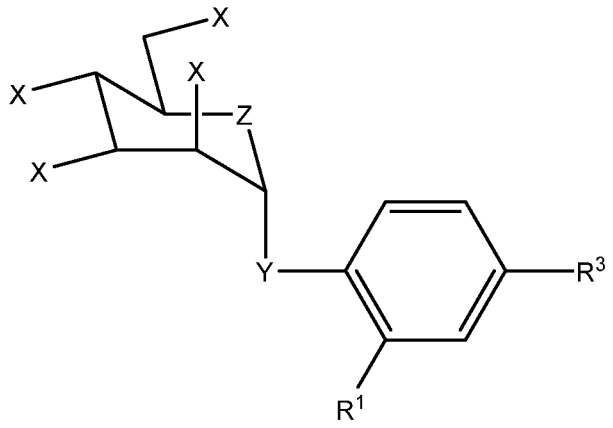
[0008] Inflammatory bowel disease (IBD) mainly consists of two disorders, ulcerative colitis and Crohn's disease (CD), with a combined prevalence of ~150–200 cases per 100,000 in Western countries. The abnormal inflammatory response observed in IBD requires interplay between host genetic factors and the intestinal microbiota. Adherent-invasive Escherichia coli (AIEC) have previously been shown to

induce gut inflammation in patients with Crohn's disease (CD). Mannosides have been shown to prevent AIEC attachment to the gut by blocking the FimH bacterial adhesin. Given the key role of AIEC in the chronic intestinal inflammation of CD patients, these results suggest a potential anti-adhesive treatment with the FimH inhibitors developed.

[0009] Therefore, there is a need for effective treatments that can cure urinary tract infections and prevent the formation of quiescent intracellular reservoir that are the source of so many recurrent infections. As well as effective treatments that can cure, prevent or reduce symptoms associated with Crohn's disease.

SUMMARY OF THE INVENTION

[0010] One aspect of the present invention encompasses a compound comprising formula (I):



(I)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(NR_5R_6)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

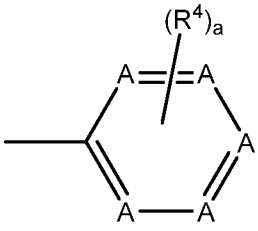
n is an integer from 1 to 10;

Z is O;

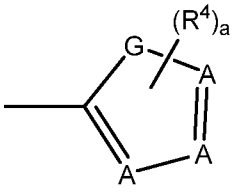
Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^3 is selected from the group consisting of formula (IA) and formula (IB):



(IA)



(IB)

A is independently selected from the group consisting of CR^5 and N;

G is independently selected from the group consisting of S, NR^5 and O;

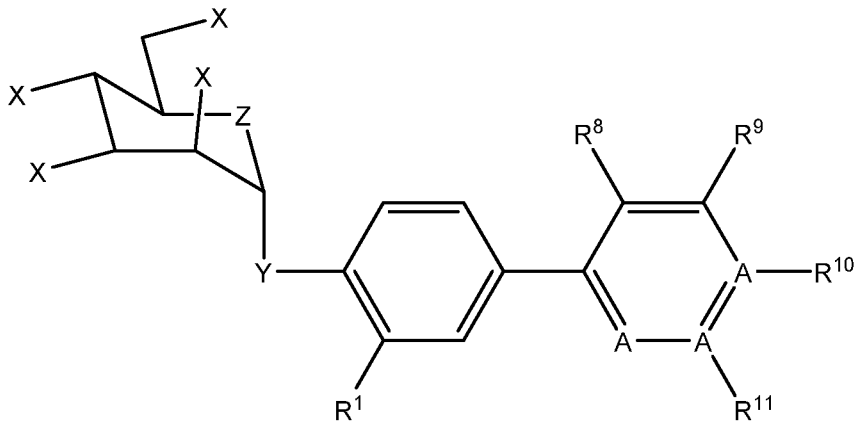
a is an integer from 1 to 4;

R^4 is selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$, or when a is greater than or equal to 2, R^4 may optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle.

[0011] Another aspect of the present invention encompasses a compound comprising Formula (II):



(II)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

A is independently selected from the group consisting of CR^5 and N;

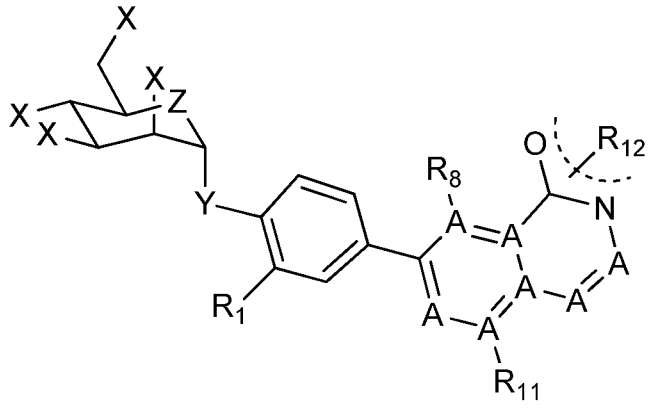
R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^8, R^9, R^{10} and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, $NHSO_2R^7$, and R^8 and R^9 together can optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring; and R^9 and R^{10} together can optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 is selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl and heterocycle.

[0012] Still another aspect of the present invention encompasses a compound comprising Formula (III):



(III)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

A is independently selected from the group consisting of CR^5 and N;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl,

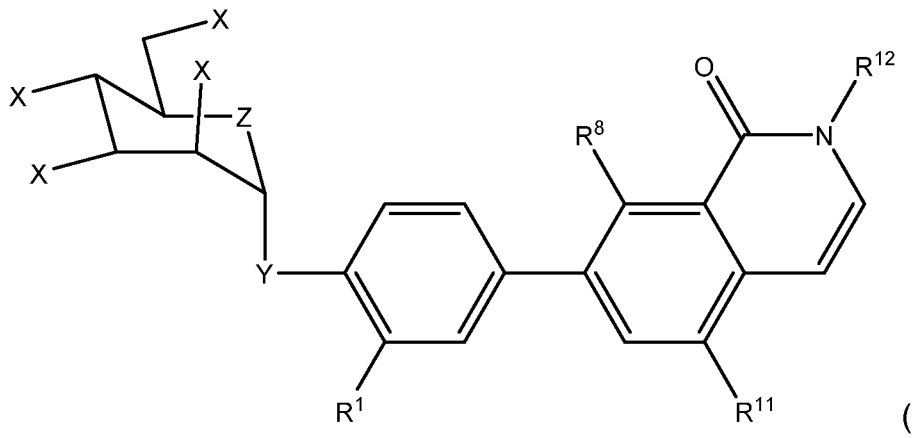
OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^{12} is substituted at the O or N and is selected from the group consisting of H, alkyl, CH_2R^{13}, CH_2COR^{13}, CH_2CONHR^{13}, $CH_2CONHR^{13}R^{14}$, $CH_2CONH(CH_2)_2R^{14}$, $(CH_2)_2NR^{13}$, $(CH_2)_nNR^{13}$, CH_2COOH, $CH_2CONH(CH_2)_2NH_2$, and $(CH_2)_2N(CH_3)_2$;

R^{13} is selected from the group consisting of –OH and an optionally substituted heterocycle, hydrocarbyl, and substituted hydrocarbyl;

R^{14} is selected from the group consisting of alkyl and NH_2.

[0013] Yet still another aspect of the present invention encompasses a compound comprising Formula (IV):



(IV)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

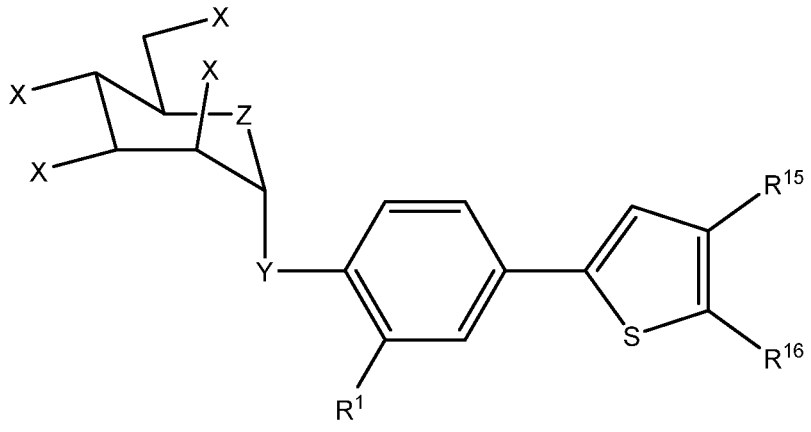
R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^{12} is selected from the group consisting of H, alkyl, CH_2R^{13}, CH_2COR^{13}, CH_2CONHR^{13}, $CH_2CONHR^{13}R^{14}$, $CH_2CONH(CH_2)_2R^{14}$, $(CH_2)_2NR^{13}$, $(CH_2)_nNR^{13}$, CH_2COOH, $CH_2CONH(CH_2)_2NH_2$, and $(CH_2)_2N(CH_3)_2$;

R^{13} is selected from the group consisting of –OH and an optionally substituted heterocycle, hydrocarbyl, and substituted hydrocarbyl;

R^{14} is selected from the group consisting of alkyl and NH_2.

[0014] Yet still another aspect of the present invention encompasses a compound comprising Formula (V):



(V)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

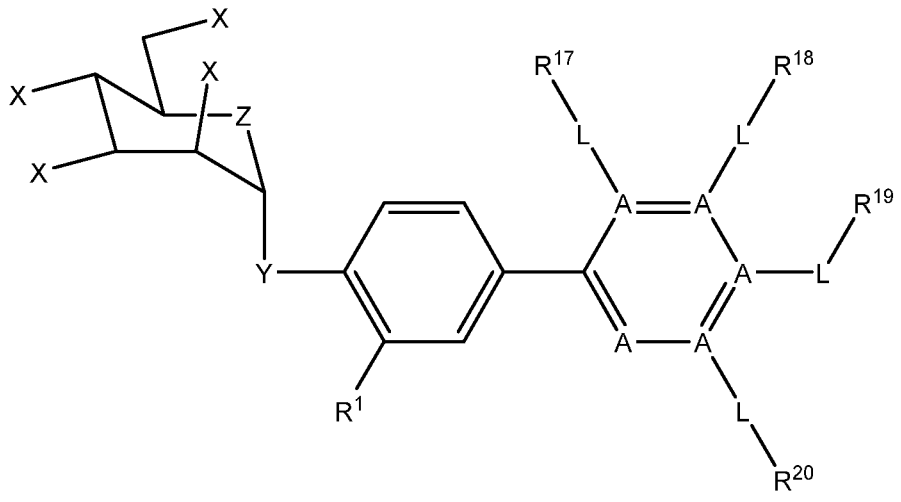
Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^{15} and R^{16} are independently selected from the group consisting of hydrogen, $NHCONH_2$, $COOCH_3$, and $CONHCH_3$, $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$ or R^{15} and R^{16} can optionally form a cycloalkyl, aryl or heterocyclo ring.

[0015] Yet still another aspect of the present invention encompasses a compound comprising Formula (VI):



(VI)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

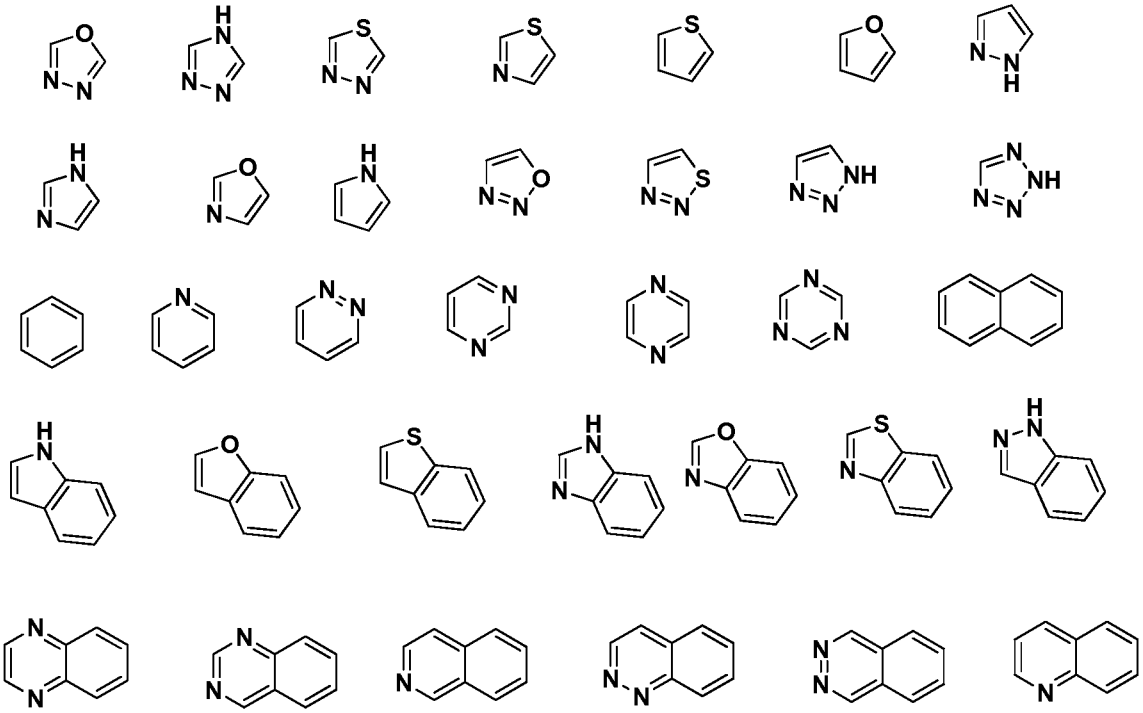
R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

A is independently selected from the group consisting of CR^5 and N;

L is independently selected from the group consisting of no atom, N, NH, O and S;

R^{17}, R^{18}, R^{19} and R^{20} are selected from the group consisting of H and an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring, 5-6

fused ring or 6-6 fused ring including but not limited to the following examples, wherein the example is attached via any available CH position:



[0016] The invention also encompasses a method of treating a urinary tract infection. The method comprises administering a compound of the invention to a subject in need thereof.

[0017] Further, the invention encompasses a method of preventing a urinary tract infection. The method comprises administering a compound of the invention to a subject in need thereof.

[0018] In another aspect, the invention encompasses a method of reducing the resistance of a bacterium to a bactericidal compound. The method comprises administering a compound of the invention a subject in need thereof.

[0019] In yet another aspect, the invention encompasses a method of treating inflammatory bowel disease. The method comprises administering a compound of the invention to a subject in need thereof.

[0020] In still yet another aspect, the invention encompasses a method of inhibiting FimH binding to mannose. The method comprises contacting a compound of

the invention with FimH, wherein the compound binds FimH and inhibits binding to mannose.

[0021] In still yet another aspect, the invention encompasses a method of treating a catheter-associated urinary tract infection. The method comprises administering a compound of the invention to a subject in need thereof.

BRIEF DESCRIPTION OF THE FIGURES

[0022] The application file contains at least one drawing executed in color. Copies of this patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0023] **Fig. 1** depicts the effect of mannoside compounds on preventing UTI in a mouse model of infection. The structures of compounds (**A**) ZFH-4269, (**B**) ZFH-5254 (Example 7) and (**C**) ZFH-5240 (Examle 18A) are depicted. (**D**) Shows that 50 mg/kg of 269, 254 and 240 reduced bacterial titers in the bladder relative to DMSO and PBS.

[0024] **Fig. 2** depicts the effects of mannoside compounds that are analogs of ZFH-5254 on preventing UTI in a mouse model of infection. The structures of compounds (**A**) ZFH-4269, (**B**) 1CJ68 (Example 16) and (**C**) 1CJ70 (Example 14) are depicted. (**D**) Shows that 25 mg/kg of compound ZFH269 most efficiently reduced bacterial titers in the bladder.

[0025] **Fig. 3** depicts the structures of the mannoside compounds evaluated for rat PK.

[0026] **Fig. 4** depicts a graph of the pharamacokinetics of the IV dose of the mannoside compounds in rats. FIM-5240 (Example 18A) showed the best PK.

[0027] **Fig. 5** depicts a graph of the pharamacokinetics of the oral (PO) dose of the mannoside compounds in rats.

[0028] **Fig. 6** depicts the pharmacokinetics of mannoside compounds in the mouse urine. The structures of compounds (**A**) ZFH-4269, (**B**) ZFH-5254 (Example 7), (**C**) ZFH-5240 (Example 18A) are depicted. (**D**) Shows the pharmacokinetics of 269, 254, Prodrug and 240.

[0029] **Fig. 7** depicts the efficacy of various mannoside prodrugs in the mouse model of acute UTI infection. (**A**) Shows that 25 mg/kg of ZFH269 and 25 mg/kg of ZFH-

4269 prodrug significantly reduced bacterial titers in the bladder in a mouse model of acute infection. (**B**) showed that all prodrug compounds reduced bacterial titers in the bladder in a mouse model of acute infection.

[0030] **Fig. 8** depicts the structure of the 3 prodrugs: (**A**) FIM-1231 (Example 20), (**B**) FIM-1233 (Example 21) and (**C**) FIM-6123 (Example 22).

[0031] **Fig. 9** depicts the plasma stability and metabolism of various mannoside compounds. The structures of compounds (**A**) 4ZFH269, (**B**) 5ZFH240 (Example 18A), (**C**) 5ZFH61 and (**D**) 1CJ87 (Example 4) are depicted. Compounds 5ZFH61 and 1CJ87 had more than twice the half life ($t_{1/2}$) relative to 4ZFH269 and 5ZFH240. (**E**) Demonstrates the metabolism of 4ZFH269 in the presence of plasma protease.

[0032] **Fig. 10** depicts illustrations of bacterial surface lectins and pili. (**A**) depicts the structure of gram positive and gram negative bacteria. (**B**) depicts carbohydrates expressed by the host and the bacterium that bind via a bacterial lectin. A carbohydrate drug can inhibit binding to the host carbohydrate. (**C**) depicts the structure of the glycosylation found on host cells.

[0033] **Fig. 11** depicts illustrations and images of FimH-mediated adhesion to the bladder. (**A**) Uropathogenic *E. coli* (UPEC) infect the bladder epithelium via the FimH adhesin on the Type 1 pilus depicted in (**B**). (**C**) FimH of UPEC specifically binds uroplakin on superficial umbrella cells.

[0034] **Fig. 12** depicts illustrations and graphs showing the FimH lectin domain and D-mannose binding. (**A**) Shows the FimH adhesin at the tip of the type 1 pilus. Mannose fits tightly in the FimH mannose binding pocket with numerous interactions with the surrounding amino acid residues. (**B**) shows that mutations to residues within the binding pocket abolish binding to mannose.

[0035] **Fig. 13** depicts the history of mannosides as UTI virulence inhibitors. 1987 to present the focus was on multivalent mannosides to increase avidity, low potency of monomeric mannosides was observed and there was a lack of target and structural information. Importantly, no oral bioavailability or in vivo studies were reported.

[0036] **Fig. 14** depicts a ribbon diagram of butyl mannose bound to FimH. The shape of the binding pocket and orientation of the mannose ring are similar to the D-mannose-FimH structure. There are new hydrophobic interactions between the butyl

group and Tyr48, Try137 and Ile52.

[0037] **Fig. 15** depicts the hemagglutination assay (HA) used to assess the compounds' ability to block FimH mediated binding. The HAI titer quantitatively measure the effect of inhibitors on blocking the FimH-mediated hemagglutination (HA) of guinea pig red blood cell infected with *E. coli*. HAI titer is defined as the effective concentration of compound which inhibits >90% hemagglutination of the red blood cells.

[0038] **Fig. 16** depicts the initial structure activity relationship (SAR) of phenyl mannosides. (**A**) shows the additional of substituents onto the phenyl ring and how this affects the HAI titer. (**B**) Based on HA titer, the ortho substituent is preferred. (**C**) A reverse trend is observed with amides.

[0039] **Fig. 17** depicts images showing the rational designed behind multi-ring mannosides. Multi-ring mannosides can target hydrophobic or π-π stacking interactions with Tyr48 and Try137.

[0040] **Fig. 18** depicts a graph showing compound 6 potentiates TMP-SMZ treatment. (**A**) depicts the structure of SMZ and (**B**) depicts the structure of TMP antibiotics. (**C**) depicts the structure of 2ZFH56 mannoside. (**D**) Total bacterial CFU were quantified 6 hours after infection. UTI89 colonization was reduced in mice treated with 6 (100 mg/kg), TMP-SMZ (54 and 270 μg/ml, respectively), and TMP-SMZ + 6. Horizontal lines indicate geometric mean. *P < 0.05; **P < 0.01; ***P < 0.0001, Mann-Whitney U test. (**E**) A growth curve was performed with and without ZFH-2056 in the presence of various concentrations of TMP-SMZ on PBC-1 which is a strain of UPEC that is clinically resistant to TMP-SMZ. Antibiotic with or without mannoside did not affect growth of PBC-1.

[0041] **Fig. 19** depicts A-ring ortho group compounds. A-ring ortho groups significantly enhance potency.

[0042] **Fig. 20** depicts the FimH structure in the presence of ortho-mannosides. The structure of mannoside compounds (**A**) FIM-4284 and (**B**) FIM-4269 are depicted. (**C**) The ortho methyl substitution binds in the small pocket to Asn138.

[0043] **Fig. 21** depicts compounds 7 to 10 show enhanced pharmacokinetics and potency at treating infection. (**A**) Optimized ortho-substituted biphenyl compounds 7 to 10. Cellular HAI titers (EC>90) are shown in parentheses. (**B**) Compounds7 to 10

show improved pharmacokinetics. Compounds 8and 10 at 50 mg/kg yielded concentrations in the urine 6 hours after treatment equivalent to compound 6 at 100 mg/kg. Numbers in the graph show the PAMPA predicted permeability of mannosides correlates with in vivo pharmacokinetics.

[0044] **Fig. 22** depicts the efficacy of biphenyl mannosides in chronic cystitis. (**A**) depicts the structure of mannoside 8. (**B**) depicts the structure of mannoside 10. (**C**) Chronically infected mice were treated with PBS or compound 6, 8, or 10 (orally, 50 mg/kg) or TMP-SMZ. Six hours after treatment, there was a significant drop in bacterial load in mannoside-treated mice relative to PBS-treated mice. The optimized compound 8 showed increased efficacy over 6. (**D**) Chronically infected mice were treated with PBS or compound 8 at one or three doses every 8 hours. Twenty-four hours after the initial treatment, both compound 8–treated groups showed a significant drop in bacterial counts over the PBS-treated animals. (**C** and **D**) Horizontal bars indicate geometric mean. *P < 0.05; **P < 0.01; ***P < 0.0001, Mann-Whitney U test.

[0045] **Fig. 23** depicts B ring heterocycles. The physical properties of B ring heterocycles are shown with HAI titer.

[0046] **Fig. 24** depicts the metabolism to D-mannose after PO dosing. (**A**) depicts the degradation products of FIM-2056. (**B**) The degradation product “R” was evaluated after oral dosing.

[0047] **Fig. 25** depicts various derviatives substituted at the glycoside bond. The substitution was evaluated to improve metabolic stability. (**A**) 2ZFH56, (**B**) 4ZFH123, (**C**) 4ZFH89, (**D**) 4ZFH131, (**E**) 4ZFH105, (**F**) 4ZFH44, (**G**) 4ZFH55, (**H**) 5ZFH049, (**I**) 5ZFH038, and (**J**) 5ZFH048.

[0048] **Fig. 26** depicts the mouse pharmacokinetics of lead compounds (**A**) FIM-4269, (**B**) FIM-5254 (Example 7), and (**C**) FIM-5240 (Example 18A). (**D**) depicts a graph of the concentration of mannoside in mouse urine out to 8h.

[0049] **Fig. 27** depicts the lead compounds in an acute UTI model. The structure of mannoside compounds (**A**) FIM-4269, (**B**) FIM-5254 (Example 7), and (**C**) FIM-5240 (Example 18A) are depicted. (**D**) ZFH269 and the prodrug of 269 significantly reduce bladder titers in an acute UTI model. (**E**) Kidney titers were not significantly different.

[0050] **Fig. 28** depicts the lead optimization pharmacokinetics scheme.

[0051] **Fig. 29** depicts the structure of mammalian glycoproteins. (**A**) depicts how glycoproteins are expressed on the mammalian cell surface. (**B**) depicts the structures of the various glycoproteins.

[0052] **Fig. 30** depicts the structure and assembly of type 1 pili.

[0053] **Fig. 31** depicts a schematic of the synthesis of S- and N-glycosides.

[0054] **Fig. 32** depicts a schematic of the synthesis of C-linked glycosides.

[0055] **Fig. 33** depicts a schematic of the synthesis of N-linked heterocycles.

[0056] **Fig. 34** depicts a schematic of the synthesis of a biaryl mannoside SAR library.

[0057] **Fig. 35** depicts a schematic of the synthesis of a biphenyl mannoside Suzuki library.

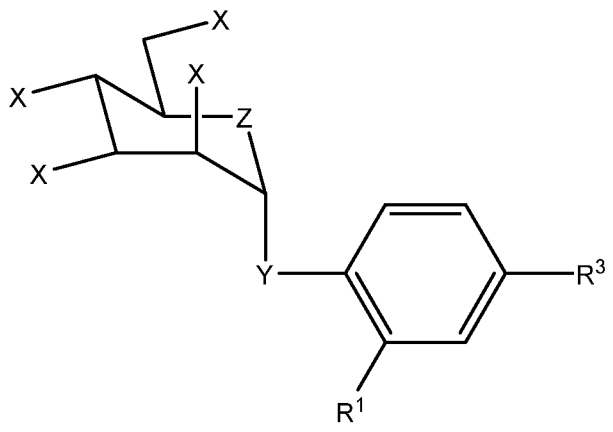
[0058] **Fig. 36** depicts a schematic and the physical properties of heterocycles. **(A, B)** shows two structures with ~2 μM in HA assay but had poor solubility. (**C**) shows the schematic of the synthesis of the heterocycles.

DETAILED DESCRIPTION OF THE INVENTION

[0059] Compounds that inhibit the function of type 1 pili of bacteria have been developed. The compounds may be useful for the treatment of urinary tract infections and Crohn's Disease. Significantly, the compounds may prevent bacterial colonization and invasion of the bladder tissue to prevent infection and the establishment of reservoirs that can serve as a source of recurrent infections. The invention also encompasses methods of use of a compound of the invention.

I. COMPOUNDS

[0060] One aspect of the invention is a compound of Formula (I):



(I)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(NR_5R_6)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

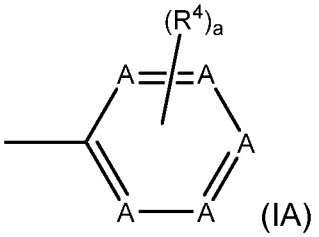
n is an integer from 1 to 10;

Z is O;

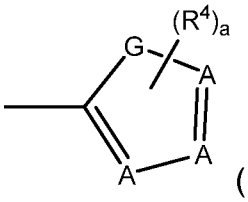
Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^3 is selected from the group consisting of formula (IA) and formula (IB):



(IA)



(IB)

A is independently selected from the group consisting of CR^5 and N;

G is independently selected from the group consisting of S, NR^5 and O;

a is an integer from 1 to 4;

R^4 is selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, $CONR_5$, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$, or when a is greater than or equal to 2, R^4 may optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle.

[0061] In one embodiment, a compound of the invention comprises Formula (I), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

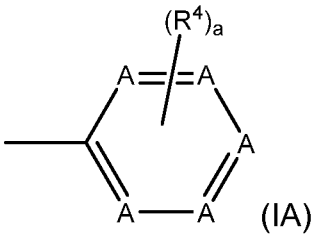
n is an integer from 1 to 4;

Z is O;

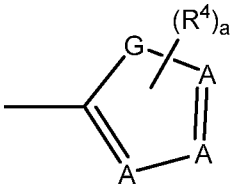
Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, OCH_3, CO_2CH_3, and $CONHCH_3$;

R^3 is selected from the group consisting of formula (IA) and formula (IB):



(IA)



(IB)

A is independently selected from the group consisting of CR^5 and N;

G is independently selected from the group consisting of S, NR^5 and O;

a is an integer from 1 to 3;

R^4 is selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, $CONR_5$, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$, or when a is greater than or equal to 2, R^4 may optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle.

[0062] In another embodiment, a compound of the invention comprises Formula (I), wherein:

X is selected from the group consisting of hydrogen and OR^2;

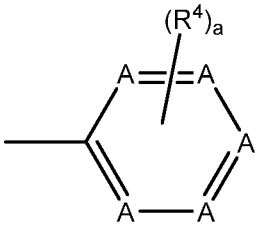
R^2 is independently selected from the group consisting of hydrogen, $-COCH_3$, $-PO(OH)_2$, $-COCH_2N(CH_3)_2$;

Z is O;

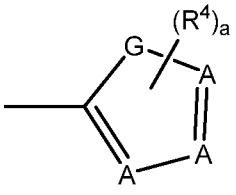
Y is selected from the group consisting of O, CH(OH) and CH_2;

R^1 is CH_3;

R^3 is selected from the group consisting of formula (IA) and formula (IB):



(IA)



(IB)

A is independently selected from the group consisting of CR^5 and N;

G is S;

a is an integer from 1 to 4;

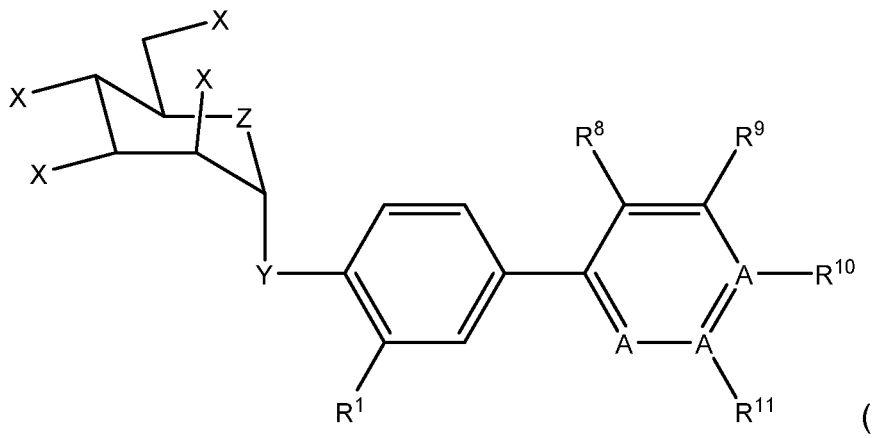
R^4 is selected from the group consisting of hydrogen, $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), $NHCONH_2$, and heterocycle, or when a is greater than or equal to 2, R^4 may optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl.

[0063] In an exemplary alternative of each of the foregoing embodiments, a compound comprising formula (I) is a compound comprising any of the Formulas in **Table 1**.

[0064] In a further exemplary alternative of each of the foregoing embodiments, a compound of the invention is Examples 1-23 and 25 from **Table 1**.

[0065] Another aspect of the invention is a compound of Formula (II):



(II)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

A is independently selected from the group consisting of CR^5 and N;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^8, R^9, R^{10} and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, $NHSO_2R^7$, and R^8 and R^9 together can optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring; and R^9 and R^{10} together can optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 is selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl and heterocycle.

[0066] In one embodiment, a compound of the invention comprises Formula (II), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

A is independently selected from the group consisting of CR^5 and N;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^8, R^9, R^{10} and R^{11} are independently selected from the group consisting of hydrogen, $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), and heterocycle, or R^8 and R^9 together may optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring, and R^9 and R^{10} together may optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl and heterocycle.

[0067] In another embodiment, a compound of the invention comprises Formula (II), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

A is independently selected from the group consisting of CR^5 and N;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, OCH_3, CO_2CH_3, and $CONHCH_3$;

R^8, R^9, R^{10} and R^{11} are independently selected from the group consisting of hydrogen, $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), and heterocycle, or R^8 and R^9 together may optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring, and R^9 and R^{10} together may optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl.

[0068] In another embodiment, a compound of the invention comprises Formula (II), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

A is independently selected from the group consisting of CR^5 and N;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, OCH_3, CO_2CH_3, and $CONHCH_3$;

R^8, R^{10} and R^{11} are hydrogen;

R^9 is selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, $NHSO_2R^7$, and R^8 and R^9 together can optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring; and R^9 and R^{10} together can optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle.

[0069] In another embodiment, a compound of the invention comprises Formula (II), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^8, R^9, R^{10} and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, aryl, cyclopropyl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, $NHSO_2R^7$, and R^8 and R^9 together can optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring;

and R^9 and R^{10} together can optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle.

[0070] In still another embodiment, a compound of the invention comprises Formula (II), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $-COCH_3$, $-PO(OH)_2$, and $-COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

A is independently selected from the group consisting of CR^5 and N;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^8, R^9, R^{10} and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, $NHSO_2R^7$, and R^8 and R^9 together can optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring; and R^9 and R^{10} together can optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl and heterocycle.

[0071] In still another embodiment, a compound of the invention comprises Formula (II), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $-COCH_3$, $-PO(OH)_2$, and $-COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

A is independently selected from the group consisting of CR^5 and N;

R^1 is CH_3;

R^8, R^9, R^{10} and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$, and R^8 and R^9 together can optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring; and R^9 and R^{10} together can optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl and heterocycle.

[0072] In still another embodiment, a compound of the invention comprises Formula (II), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $-COCH_3$, $-PO(OH)_2$, and $-COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

A is independently selected from the group consisting of CR^5 and N;

R^1 is CH_3;

R^8, R^9, R^{10} and R^{11} are independently selected from the group consisting of hydrogen, $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), and heterocycle, or R^8 and R^9 together may optionally form an optionally

substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring, and R^9 and R^{10} together may optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl.

[0073] In still yet another embodiment, a compound of the invention comprises Formula (II), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $-COCH_3$, $-PO(OH)_2$, and $-COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

A is independently selected from the group consisting of CR^5 and N;

R^1 is CH_3;

R^8, R^{10} and R^{11} are hydrogen;

R^9 is selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$, or R^8 and R^9 together can optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring; and R^9 and R^{10} together can optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl and heterocycle.

[0074] In still yet another embodiment, a compound of the invention comprises Formula (II), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, -$COCH_3$, -$PO(OH)_2$, and -$COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

A is independently selected from the group consisting of CR^5 and N;

R^1 is CH_3;

R^8, R^{10} and R^{11} are hydrogen;

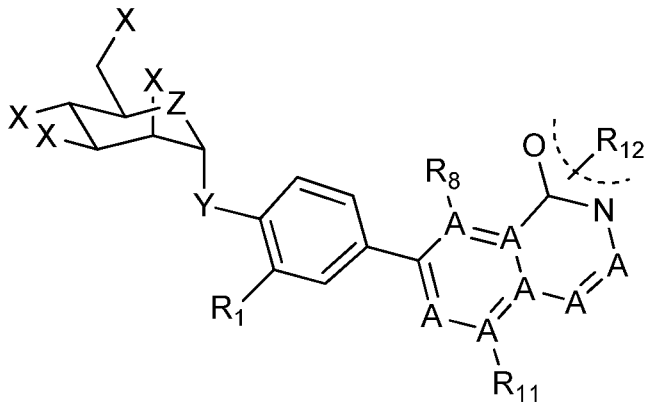
R^9 is selected from the group consisting of hydrogen, $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), and heterocycle;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl.

[0075] In an exemplary alternative of each of the foregoing embodiments, a compound comprising formula (II) is a compound comprising any of the Formulas in **Table 1**.

[0076] In a further exemplary alternative of each of the foregoing embodiments, a compound of the invention is Example 1-16, 18-23 and 25 from **Table 1**.

[0077] Another aspect of the invention is a compound of Formula (III):



(III)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), CH(OR^5), CHNR^5R^6, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

A is independently selected from the group consisting of CR^5 and N;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^{12} is substituted at the O or N and is selected from the group consisting of H, alkyl, CH_2R^{13}, CH_2COR^{13}, CH_2CONHR^{13}, $CH_2CONHR^{13}R^{14}$, $CH_2CONH(CH_2)_2R^{14}$, $(CH_2)_2NR^{13}$, $(CH_2)_nNR^{13}$, CH_2COOH, $CH_2CONH(CH_2)_2NH_2$, and $(CH_2)_2N(CH_3)_2$;

R^{13} is selected from the group consisting of –OH and an optionally substituted heterocycle, hydrocarbyl, and substituted hydrocarbyl;

R^{14} is selected from the group consisting of alkyl and NH_2.

[0078] In one embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), CH(OR^5), CHNR^5R^6, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

A is independently selected from the group consisting of CR^5 and N;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl and heterocycle;

R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^{12} is substituted at the O or N and is selected from the group consisting of H, alkyl, CH_2(heterocycle), $(CH_2)_2N(CH_3)_2$, CH_2COOH, CH_2CONH(heterocycle), $CH_2CONH(CH_2)_2NH_2$ and CH_2CO(heterocycle).

[0079] In another embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), CH(OR^5), CHNR^5R^6, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, OCH_3, CO_2CH_3, and $CONHCH_3$;

A is independently selected from the group consisting of CR^5 and N;

R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^{12} is substituted at the O or N and is selected from the group consisting of H, alkyl, CH_2(heterocycle), $(CH_2)_2N(CH_3)_2$, CH_2COOH, CH_2CONH(heterocycle), $CH_2CONH(CH_2)_2NH_2$ and CH_2CO(heterocycle);

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle.

[0080] In still another embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, OCH_3, CO_2CH_3, and $CONHCH_3$;

A is independently selected from the group consisting of CR^5 and N;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

R^8 and R^{11} are hydrogen;

R^{12} is substituted at the O or N and is selected from the group consisting of H, alkyl, CH_2R^{13}, CH_2COR^{13}, CH_2CONHR^{13}, $CH_2CONHR^{13}R^{14}$, $CH_2CONH(CH_2)_2R^{14}$, $(CH_2)_2NR^{13}$, $(CH_2)_nNR^{13}$, CH_2COOH, $CH_2CONH(CH_2)_2NH_2$, and $(CH_2)_2N(CH_3)_2$;

R^{13} is selected from the group consisting of –OH and an optionally substituted heterocycle, hydrocarbyl, and substituted hydrocarbyl;

R^{14} is selected from the group consisting of alkyl and NH_2.

[0081] In still another embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

A is independently selected from the group consisting of CR^5 and N;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^{12} is substituted at the O or N and is selected from the group consisting of H, CH_2R^{13}, CH_2COR^{13}, CH_2CONHR^{13}, $CH_2CONHR^{13}R^{14}$, $CH_2CONH(CH_2)_2R^{14}$,

$(CH_2)_2NR^{13}$, $(CH_2)_nNR^{13}$, CH_2COOH, $CH_2CONH(CH_2)_2NH_2$, and $(CH_2)_2N(CH_3)_2$;

R^{13} is selected from the group consisting of –OH and an optionally substituted heterocycle, hydrocarbyl and substituted hydrocarbyl;

R^{14} is selected from the group consisting of alkyl and NH_2.

[0082] In still yet another embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $-COCH_3$, $-PO(OH)_2$, and $-COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

A is independently selected from the group consisting of CR^5 and N;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^{12} is substituted at the O or N and is independently selected from the group consisting of H, alkyl, CH_2R^{13}, CH_2COR^{13}, CH_2CONHR^{13}, $CH_2CONHR^{13}R^{14}$, $CH_2CONH(CH_2)_2R^{14}$, $(CH_2)_2NR^{13}$, $(CH_2)_nNR^{13}$, CH_2COOH, $CH_2CONH(CH_2)_2NH_2$, and $(CH_2)_2N(CH_3)_2$;

R^{13} is selected from the group consisting of –OH and an optionally substituted heterocycle, hydrocarbyl and substituted hydrocarbyl;

R^{14} is selected from the group consisting of alkyl and NH_2.

[0083] In still yet another embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, -$COCH_3$, -$PO(OH)_2$, and -$COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

R^1 is CH_3;

A is independently selected from the group consisting of CR^5 and N;

R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

R^{12} is substituted at the O or N and is selected from the group consisting of H, alkyl, CH_2R^{13}, CH_2COR^{13}, CH_2CONHR^{13}, $CH_2CONHR^{13}R^{14}$, $CH_2CONH(CH_2)_2R^{14}$, $(CH_2)_2NR^{13}$, $(CH_2)_nNR^{13}$, CH_2COOH, $CH_2CONH(CH_2)_2NH_2$, and $(CH_2)_2N(CH_3)_2$;

R^{13} is selected from the group consisting of –OH and an optionally substituted heterocycle, hydrocarbyl and substituted hydrocarbyl;

R^{14} is selected from the group consisting of alkyl and NH_2.

[0084] In still yet another embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, -$COCH_3$, -$PO(OH)_2$, and -$COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

R^1 is CH_3;

A is independently selected from the group consisting of CR^5 and N;

R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

R^{12} is substituted at the O or N and is selected from the group consisting of H, CH_2(heterocycle), $(CH_2)_2N(CH_3)_2$, CH_2COOH, CH_2CONH(heterocycle), $CH_2CONH(CH_2)_2NH_2$ and CH_2CO(heterocycle).

[0085] In still yet another embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $-COCH_3$, $-PO(OH)_2$, and $-COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

R^1 is CH_3;

A is independently selected from the group consisting of CR^5 and N;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

R^8 and R^{11} are hydrogen;

R^{12} is substituted at the O or N and is selected from the group consisting of H, alkyl, CH_2R^{13}, CH_2COR^{13}, CH_2CONHR^{13}, $CH_2CONHR^{13}R^{14}$, $CH_2CONH(CH_2)_2R^{14}$, $(CH_2)_2NR^{13}$, $(CH_2)_nNR^{13}$, CH_2COOH, $CH_2CONH(CH_2)_2NH_2$, and $(CH_2)_2N(CH_3)_2$;

R^{13} is selected from the group consisting of –OH and an optionally substituted heterocycle, hydrocarbyl and substituted hydrocarbyl;

R^{14} is selected from the group consisting of alkyl and NH_2.

[0086] In still yet another embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $-COCH_3$, $-PO(OH)_2$, and $-COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

R^1 is CH_3;

A is independently selected from the group consisting of CR^5 and N;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

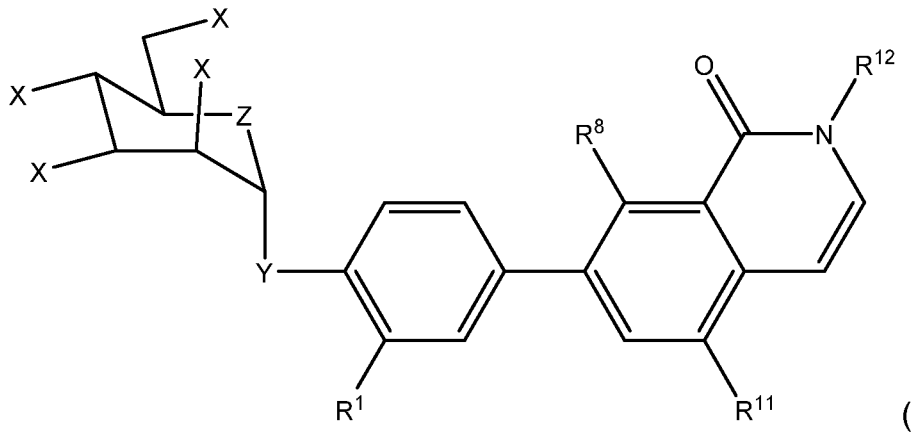
R^8 and R^{11} are hydrogen;

R^{12} is substituted at the O or N and is selected from the group consisting of H, CH_2(heterocycle), $(CH_2)_2N(CH_3)_2$, CH_2COOH, CH_2CONH(heterocycle), $CH_2CONH(CH_2)_2NH_2$ and CH_2CO(heterocycle).

[0087] In an exemplary alternative of each of the foregoing embodiments, a compound comprising formula (IV) is a compound comprising any of the Formulas in **Table 1**.

[0088] In a further exemplary alternative of each of the foregoing embodiments, a compound of the invention is Example 7-16 from **Table 1**.

[0089] Another aspect of the invention is a compound of Formula (IV):



(IV)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^{12} is selected from the group consisting of H, alkyl, CH_2R^{13}, CH_2COR^{13}, CH_2CONHR^{13}, $CH_2CONHR^{13}R^{14}$, $CH_2CONH(CH_2)_2R^{14}$, $(CH_2)_2NR^{13}$, $(CH_2)_nNR^{13}$, CH_2COOH, $CH_2CONH(CH_2)_2NH_2$, and $(CH_2)_2N(CH_3)_2$;

R^{13} is selected from the group consisting of –OH and an optionally substituted heterocycle, hydrocarbyl, and substituted hydrocarbyl;

R^{14} is selected from the group consisting of alkyl and NH_2.

[0090] In one embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl and heterocycle;

R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^{12} is selected from the group consisting of H, alkyl, CH_2(heterocycle), $(CH_2)_2N(CH_3)_2$, CH_2COOH, CH_2CONH(heterocycle), $CH_2CONH(CH_2)_2NH_2$ and CH_2CO(heterocycle).

[0091] In another embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, OCH_3, CO_2CH_3, and $CONHCH_3$;

R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^{12} is selected from the group consisting of H, alkyl, CH_2(heterocycle), $(CH_2)_2N(CH_3)_2$, CH_2COOH, CH_2CONH(heterocycle), $CH_2CONH(CH_2)_2NH_2$ and CH_2CO(heterocycle);

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle.

[0092] In still another embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, OCH_3, CO_2CH_3, and $CONHCH_3$;

R^8 and R^{11} are hydrogen;

R^{12} is selected from the group consisting of H, alkyl, CH_2R^{13}, CH_2COR^{13}, CH_2CONHR^{13}, $CH_2CONHR^{13}R^{14}$, $CH_2CONH(CH_2)_2R^{14}$, $(CH_2)_2NR^{13}$, $(CH_2)_nNR^{13}$, CH_2COOH, $CH_2CONH(CH_2)_2NH_2$, and $(CH_2)_2N(CH_3)_2$;

R^{13} is selected from the group consisting of –OH and an optionally substituted heterocycle, hydrocarbyl, and substituted hydrocarbyl;

R^{14} is selected from the group consisting of alkyl and NH_2.

[0093] In still another embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^{12} is selected from the group consisting of H, CH_2R^{13}, CH_2COR^{13}, CH_2CONHR^{13}, $CH_2CONHR^{13}R^{14}$, $CH_2CONH(CH_2)_2R^{14}$, $(CH_2)_2NR^{13}$, $(CH_2)_nNR^{13}$, CH_2COOH, $CH_2CONH(CH_2)_2NH_2$, and $(CH_2)_2N(CH_3)_2$;

R^{13} is selected from the group consisting of –OH and an optionally substituted heterocycle, hydrocarbyl and substituted hydrocarbyl;

R^{14} is selected from the group consisting of alkyl and NH_2.

[0094] In still yet another embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $-COCH_3$, $-PO(OH)_2$, and $-COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5,

halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^{12} are independently selected from the group consisting of H, alkyl, CH_2R^{13}, CH_2COR^{13}, CH_2CONHR^{13}, $CH_2CONHR^{13}R^{14}$, $CH_2CONH(CH_2)_2R^{14}$, $(CH_2)_2NR^{13}$, $(CH_2)_nNR^{13}$, CH_2COOH, $CH_2CONH(CH_2)_2NH_2$, and $(CH_2)_2N(CH_3)_2$;

R^{13} is selected from the group consisting of –OH and an optionally substituted heterocycle, hydrocarbyl and substituted hydrocarbyl;

R^{14} is selected from the group consisting of alkyl and NH_2.

[0095] In still yet another embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $-COCH_3$, $-PO(OH)_2$, and $-COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

R^1 is CH_3;

R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

R^{12} is selected from the group consisting of H, alkyl, CH_2R^{13}, CH_2COR^{13}, CH_2CONHR^{13}, $CH_2CONHR^{13}R^{14}$, $CH_2CONH(CH_2)_2R^{14}$, $(CH_2)_2NR^{13}$, $(CH_2)_nNR^{13}$, CH_2COOH, $CH_2CONH(CH_2)_2NH_2$, and $(CH_2)_2N(CH_3)_2$;

R^{13} is selected from the group consisting of –OH and an optionally substituted heterocycle, hydrocarbyl and substituted hydrocarbyl;

R^{14} is selected from the group consisting of alkyl and NH_2.

[0096] In still yet another embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $-COCH_3$, $-PO(OH)_2$, and $-COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

R^1 is CH_3;

R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

R^{12} is selected from the group consisting of H, CH_2(heterocycle), $(CH_2)_2N(CH_3)_2$, CH_2COOH, CH_2CONH(heterocycle), $CH_2CONH(CH_2)_2NH_2$ and CH_2CO(heterocycle).

[0097] In still yet another embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $-COCH_3$, $-PO(OH)_2$, and $-COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

R^1 is CH_3;

R^8 and R^{11} are hydrogen;

R^{12} is selected from the group consisting of H, alkyl, CH_2R^{13}, CH_2COR^{13}, CH_2CONHR^{13}, $CH_2CONHR^{13}R^{14}$, $CH_2CONH(CH_2)_2R^{14}$, $(CH_2)_2NR^{13}$, $(CH_2)_nNR^{13}$, CH_2COOH, $CH_2CONH(CH_2)_2NH_2$, and $(CH_2)_2N(CH_3)_2$;

R^{13} is selected from the group consisting of –OH and an optionally substituted heterocycle, hydrocarbyl and substituted hydrocarbyl;

R^{14} is selected from the group consisting of alkyl and NH_2.

[0098] In still yet another embodiment, a compound of the invention comprises Formula (IV), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $-COCH_3$, $-PO(OH)_2$, and $-COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

R^1 is CH_3;

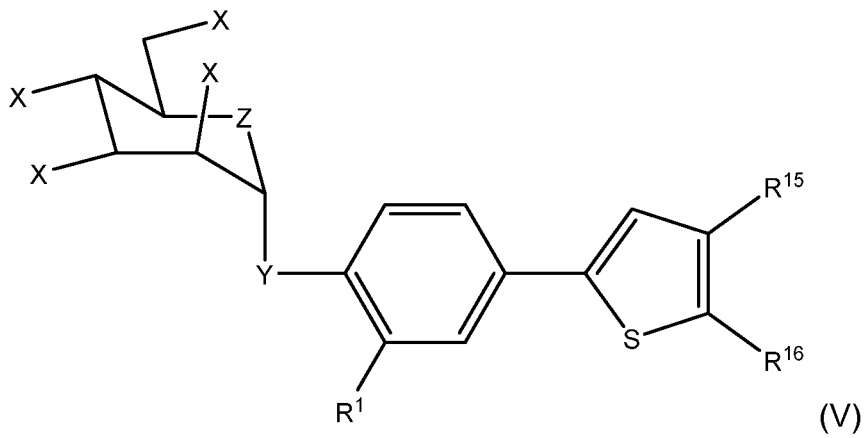
R^8 and R^{11} are hydrogen;

R^{12} is selected from the group consisting of H, CH_2(heterocycle), $(CH_2)_2N(CH_3)_2$, CH_2COOH, CH_2CONH(heterocycle), $CH_2CONH(CH_2)_2NH_2$ and CH_2CO(heterocycle).

[0099] In an exemplary alternative of each of the foregoing embodiments, a compound comprising formula (IV) is a compound comprising any of the Formulas in **Table 1**.

[0100] In a further exemplary alternative of each of the foregoing embodiments, a compound of the invention is Example 7-16 from **Table 1**.

[0101] Yet another aspect of the invention is a compound of Formula (V):



(V)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^{15} and R^{16} are independently selected from the group consisting of hydrogen, $NHCONH_2$, $COOCH_3$, and $CONHCH_3$, $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$ or R^{15} and R^{16} can optionally form a cycloalkyl, aryl or heterocyclo ring.

[0102] In one embodiment, a compound of the invention comprises Formula (V), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, OCH_3, CO_2CH_3, and $CONHCH_3$;

R^{15} and R^{16} are independently selected from the group consisting of hydrogen, $NHCONH_2$, $COOCH_3$, and $CONHCH_3$, $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$ or R^{15} and R^{16} can optionally form a cycloalkyl, aryl or heterocyclo ring.

[0103] In another embodiment, a compound of the invention comprises Formula (V), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), CH(OR^5), CHNR^5R^6, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

R^{15} and R^{16} are independently selected from the group consisting of hydrogen, $NHCONH_2$, $COOCH_3$, and $CONHCH_3$, and R^{15} and R^{16} can optionally form an optionally substituted cycloalkyl or heterocyclo 5 or 6 membered ring.

[0104] In yet another embodiment, a compound of the invention comprises Formula (V), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), CH(OR^5), CHNR^5R^6, CH_2, S, and NR^5;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, OCH_3, CO_2CH_3, and $CONHCH_3$;

R^{15} and R^{16} are independently selected from the group consisting of hydrogen, $NHCONH_2$, $COOCH_3$, and $CONHCH_3$, and R^{15} and R^{16} can optionally form an optionally substituted cycloalkyl or heterocyclo 5 or 6 membered ring.

[0105] In another embodiment, a compound of the invention comprises Formula (V), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^5 is selected from the group consisting of H, or an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

R^{15} and R^{16} are independently selected from the group consisting of hydrogen, $NHCONH_2$, $COOCH_3$, and $CONHCH_3$, $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$ or R^{15} and R^{16} can optionally form a cycloalkyl, aryl or heterocyclo ring.

[0106] In still another embodiment, a compound of the invention comprises Formula (V), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, OCH_3, CO_2CH_3, and $CONHCH_3$;

R^{15} and R^{16} are independently selected from the group consisting of hydrogen, $NHCONH_2$, $COOCH_3$, and $CONHCH_3$, and R^{15} and R^{16} can optionally form an optionally substituted cycloalkyl or heterocyclo 5 or 6 membered ring.

[0107] In still yet another embodiment, a compound of the invention comprises Formula (V), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $-COCH_3$, $-PO(OH)_2$, $-COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, OCH_3, CO_2CH_3, and $CONHCH_3$;

R^{15} and R^{16} are independently selected from the group consisting of hydrogen, $NHCONH_2$, $COOCH_3$, and $CONHCH_3$, $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$ or R^{15} and R^{16} can optionally form a cycloalkyl, aryl or heterocyclo ring;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle.

[0108] In still yet another embodiment, a compound of the invention comprises Formula (V), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $-COCH_3$, $-PO(OH)_2$, $-COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH(OH) and CH_2;

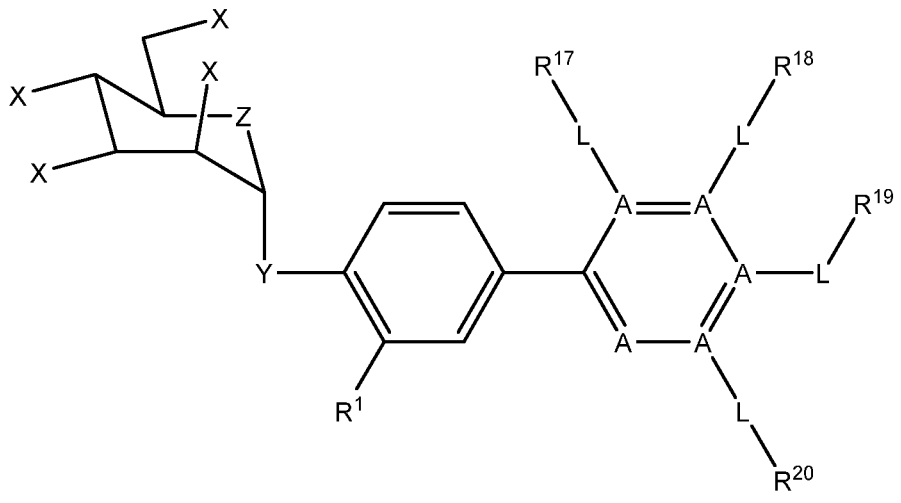
R^1 is CH_3;

R^{15} and R^{16} are independently selected from the group consisting of hydrogen, $NHCONH_2$, $COOCH_3$, and $CONHCH_3$, and R^{15} and R^{16} can optionally form an optionally substituted cycloalkyl or heterocyclo 5 or 6 membered ring.

[0109] In an exemplary alternative of each of the foregoing embodiments, a compound comprising formula (V) is a compound comprising any of the Formulas in **Table 1**.

[0110] In a further exemplary alternative of each of the foregoing embodiments, a compound of the invention is Example 17 from **Table 1**.

[0111] Yet still another aspect of the invention is a compound of Formula (VI):



(VI)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

Z is O;

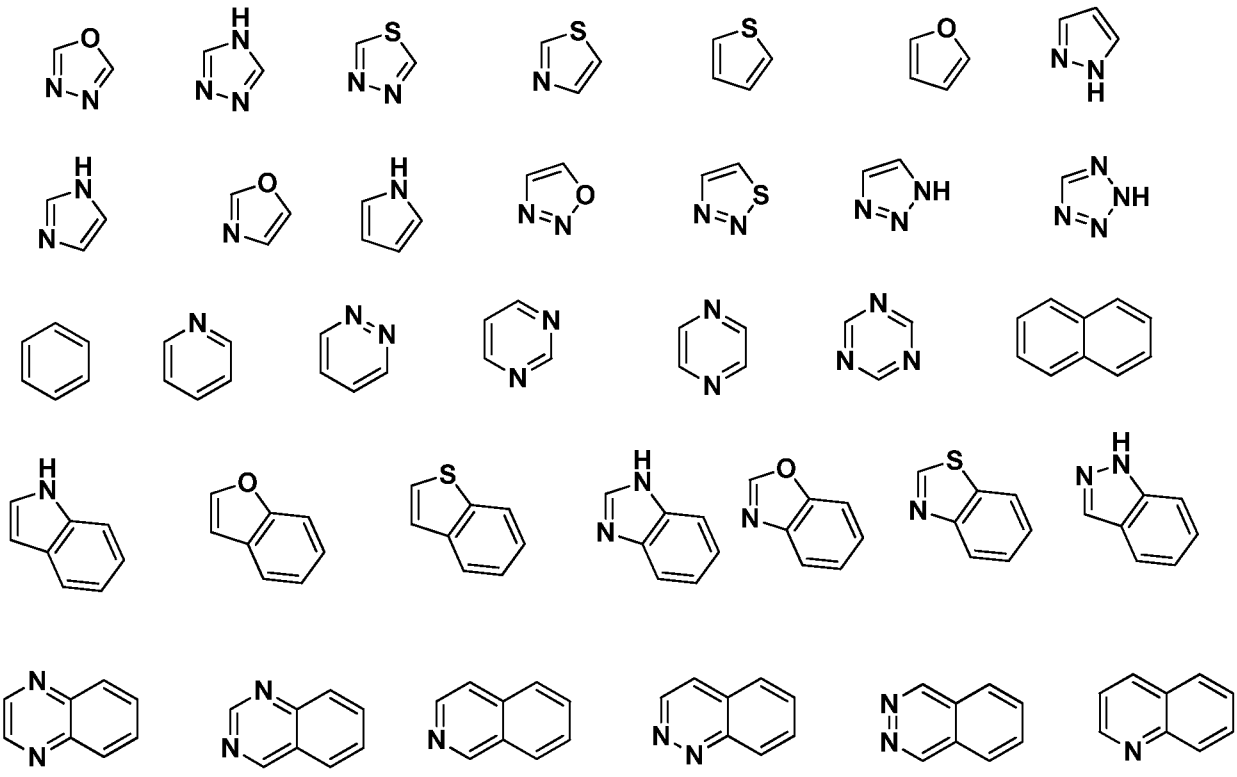
Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

A is independently selected from the group consisting of CR^5 and N;

L is independently selected from the group consisting of no atom, N, O and S;

R^{17}, R^{18}, R^{19} and R^{20} are selected from the group consisting of H and an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring including but not limited to the following examples, wherein the example is attached via any available CH position:



[0112] In one embodiment, a compound of the invention comprises Formula (VI), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

Z is O;

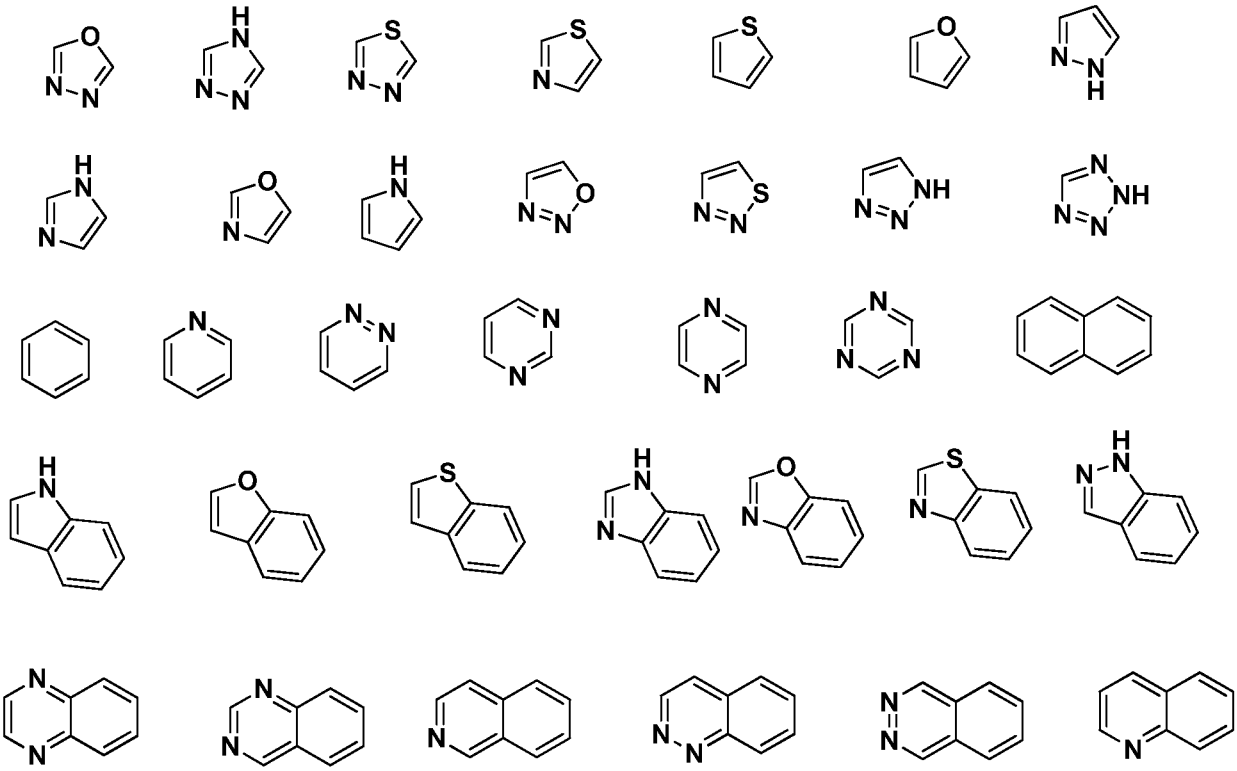
Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, OCH_3, CO_2CH_3, and $CONHCH_3$;

A is independently selected from the group consisting of CR^5 and N;

L is independently selected from the group consisting of no atom, N, O and S;

R^{17}, R^{18}, R^{19} and R^{20} are selected from the group consisting of H and an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring including but not limited to the following examples, wherein the example is attached via any CH position:



[0113] In another embodiment, a compound of the invention comprises Formula (VI), wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $-COCH_3$, $-PO(OH)_2$, and $-COCH_2N(CH_3)_2$;

Z is O;

Y is selected from the group consisting of O, CH_2O and CH_2;

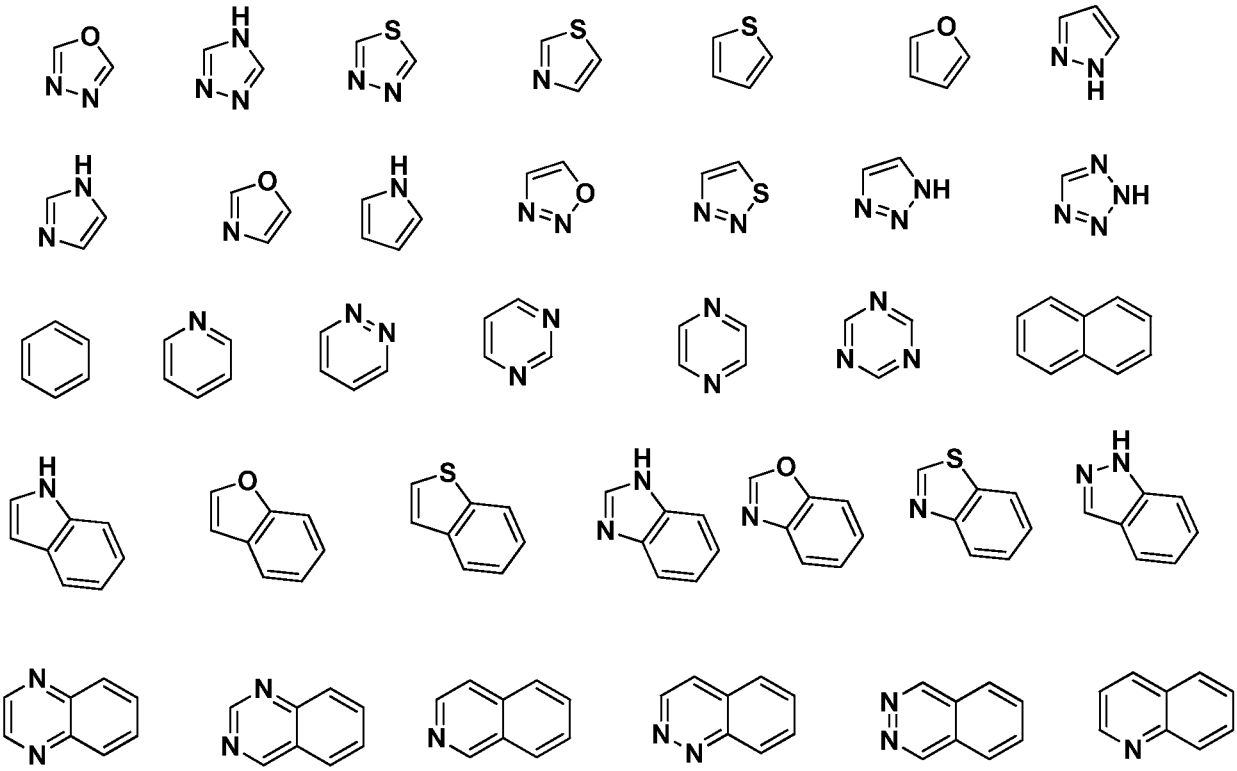
R^1 is CH_3;

A is independently selected from the group consisting of CR^5 and N;

L is independently selected from the group consisting of no atom, N, O and S;

R^{17} and R^{20} are H;

R^{18} and R^{19} are selected from the group consisting of H and an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring including but not limited to the following examples, wherein the example is attached via any CH position:



[0114] In an exemplary alternative of each of the foregoing embodiments, a compound comprising formula (VI) is a compound comprising any of the Formulas in **Table 1**.

[0115] In a further exemplary alternative of each of the foregoing embodiments, a compound of the invention is Examples 5-6 from **Table 1**.

[0116] In certain embodiments, the sugar residue of the above compounds may encompass a stereoisomer of mannose. In other embodiments, the sugar residue of the above compounds may encompass any stereoisomer of mannose other than glucose. In an exemplary embodiment, the sugar residue of the above compounds is alpha D mannose.

[0117] Exemplary methods of synthesizing a compound of the invention are detailed in the Examples.

[0118] A compound of the invention may also be an intermediate in the synthesis of a compound of formula (I) – (IV). For instance, in one embodiment, a compound of the invention may be an ester intermediate in the synthesis of a compound of formula (I) – (IV). In another embodiment, a compound of the invention may be a boronate ester of

a mannoside or a boronic acid ester of a mannoside. In still another embodiment, a compound of the invention may be a compound illustrated in Schemes I-XII in the Examples below.

[0119] A compound of the invention may also comprise an imaging agent, such as a fluorescent moiety. In an embodiment, the imaging agent is bound to the sugar portion of a compound of the invention, either directly, or via a linker.

[0120] Compounds of the invention may block the function of FimH of the type 1 pili of pathogenic bacteria and prevent bacterial adherence and invasion and thus prevent bacterial amplification in the IBC and subsequent spreading and repeated rounds of amplification via new generation IBCs.

[0121] FimH functional assays used to measure activity of the compounds are known to individuals skilled in the art. Non-limiting examples of functional assays include hemmagglutination titer using guinea pig red blood cells, affinity of binding to FimH, and the ability of the compounds to prevent biofilm formation.

[0122] In some embodiments, activity of the compound is measured using hemmagglutination titer of guinea pig red blood cells. Hemagglutination of guinea pig red blood cells by type1 piliated UPEC is dependent upon FimH mannose binding ability and serial dilutions allow a quantitative analysis. Hemagglutination titer may generally be defined as the amount of compound required for decreasing hemagglutination by 75%. In some embodiments, the hemmagglutination titer of the compound of the invention may be less than about 5, 4, 3, 2, or 1 μM. In a preferred alternative of the embodiments, the hemmagglutination titer of the compound of the invention may be less than about 1, 0.5, 0.4, 0.3, 0.2, or 0.1 μM. In another preferred alternative of the embodiments, the hemmagglutiantion titer of the compound of the invention may be less than about 0.1, 0.05, 0.04, 0.03, 0.02, 0.01 μM. In yet another preferred alternative of the embodiments, the hemmagglutination titer of the compound of the invention may less than about 0.01 μM.

[0123] In yet other embodiments, activity of the compound may be measured using the ability of the compound to prevent or disrupt biofilm formation. In general, titration curves measuring the ability of a compound inhibit biofilm formation may be performed to determine the IC_{50}. In some embodiments, the IC_{50} of the compound may

be less than about 700, 600, 500, 400, 300, 200 or 100μM. In other embodiments, the IC_{50} of the compound may be less than about 500, 400, 300, 200, 100, 50, 40, 30, 20 10, 9, 8, 7, 6, or 5μM. In preferred embodiments, the IC_{50} of the compound may be less than about 20μM. In other preferred embodiments, the IC_{50} of the compound may be less than about 9μM.

II. COMBINATIONS

[0124] Another aspect of the present invention encompasses a combination of a compound of the invention (described in **Section I** above) with one or more bactericidal compounds. In some embodiments, a compound of the invention may comprise a combination with 1, 2, 3, 4, or 5 bactericidal compounds. In one embodiment, the bactericidal compound is an antibiotic. Suitable antibiotics are known in the art, and may include Amikacin, Gentamicin, Kanamycin, Neomycin, Netilmicin, Tobramycin, Paromomycin, Geldanamycin, Herbimycin, Carbacephem, Loracarbef, Ertapenem, Doripenem, Imipenem/Cilastatin, Meropenem, Cefadroxil, Cefazolin, Cefalotin, Cefalexin, Cephalosporins, Cefaclor, Cefamandole, Cefoxitin, Cefprozil, Cefuroxime, Cefixime, Cefdinir, Cefditoren, Cefoperazone, Cefotaxime, Cefpodoxime, Ceftazidime, Ceftibuten, Ceftizoxime, Ceftriaxone, Cefepime, Ceftobiprole, Teicoplanin, Vancomycin, Telavancin, Clindamycin, Lincomycin, Azithromycin, Clarithromycin, Dirithromycin, Erythromycin, Roxithromycin, Troleandomycin, Telithromycin, Spectinomycin, Aztreonam, Furazolidone, Nitrofurantoin, Amoxicillin, Ampicillin, Azlocillin, Carbenicillin, Cloxacillin, Dicloxacillin, Flucloxacillin, Mezlocillin, Methicillin, Nafcillin, Oxacillin, Penicillin G, Penicillin V, Piperacillin, Temocillin, Ticarcillin, Bacitracin, Colistin, Polymyxin B, Ciprofloxacin, Enoxacin, Gatifloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Nalidixic acid, Norfloxacin, Ofloxacin, Trovafloxacin, Grepafloxacin, Sparfloxacin, Temafloxacin, Mafenide, Sulfonamidochrysoidine, Sulfacetamide, Sulfadiazine, Silver sulfadiazine, Sulfamethizole, Sulfamethoxazole (SMZ), Sulfanilimide, Sulfasalazine, Sulfisoxazole, Trimethoprim (TMP), Trimethoprim-Sulfamethoxazole (such as Bactrim, Septra), Demeclocycline, Doxycycline, Minocycline, Oxytetracycline, Tetracycline, Clofazimine, Dapsone, Capreomycin, Cycloserine, Ethambutol, Ethionamide, Isoniazid, Pyrazinamide, Rifampicin, Rifabutin,

Rifapentine, Streptomycin, Arsphenamine, Chloramphenicol, Fosfomycin, Fusidic acid, Linezolid, Metronidazole, Mupirocin, Platensimycin, Quinupristin/Dalfopristin, Rifaximin, Thiamphenicol, or Tinidazole. In an exemplary embodiment, the antibiotic is TMP, SMZ, or a combination thereof.

III. PHARMACEUTICAL COMPOSITIONS

[0125] Yet another aspect of the invention encompasses a pharmaceutical composition. A compound of the invention described in **Section I** above may exist in tautomeric, geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-geometric isomers, E- and Z-geometric isomers, R- and S-enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof and other mixtures thereof. Pharmaceutically acceptable salts of such tautomeric, geometric or stereoisomeric forms are also included within the invention. The terms "cis" and "trans", as used herein, denote a form of geometric isomerism in which two carbon atoms connected by a double bond will each have a hydrogen atom on the same side of the double bond ("cis") or on opposite sides of the double bond ("trans"). Some of the compounds described contain alkenyl groups, and are meant to include both cis and trans or "E" and "Z" geometric forms. Furthermore, some of the compounds described contain one or more stereocenters and are meant to include R, S, and mixtures of R and S forms for each stereocenter present.

[0126] In a further embodiment, the inhibitors of the present invention may be in the form of free bases or pharmaceutically acceptable acid addition salts thereof. The term "pharmaceutically-acceptable salts" are salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt may vary, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds for use in the present methods may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric,

citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, stearic, algenic, algenic, hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of use in the present methods include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N, N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine- (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with any of the compounds of the invention.

[0127] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are useful in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, and polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

[0128] Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compound is ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compound can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for

convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

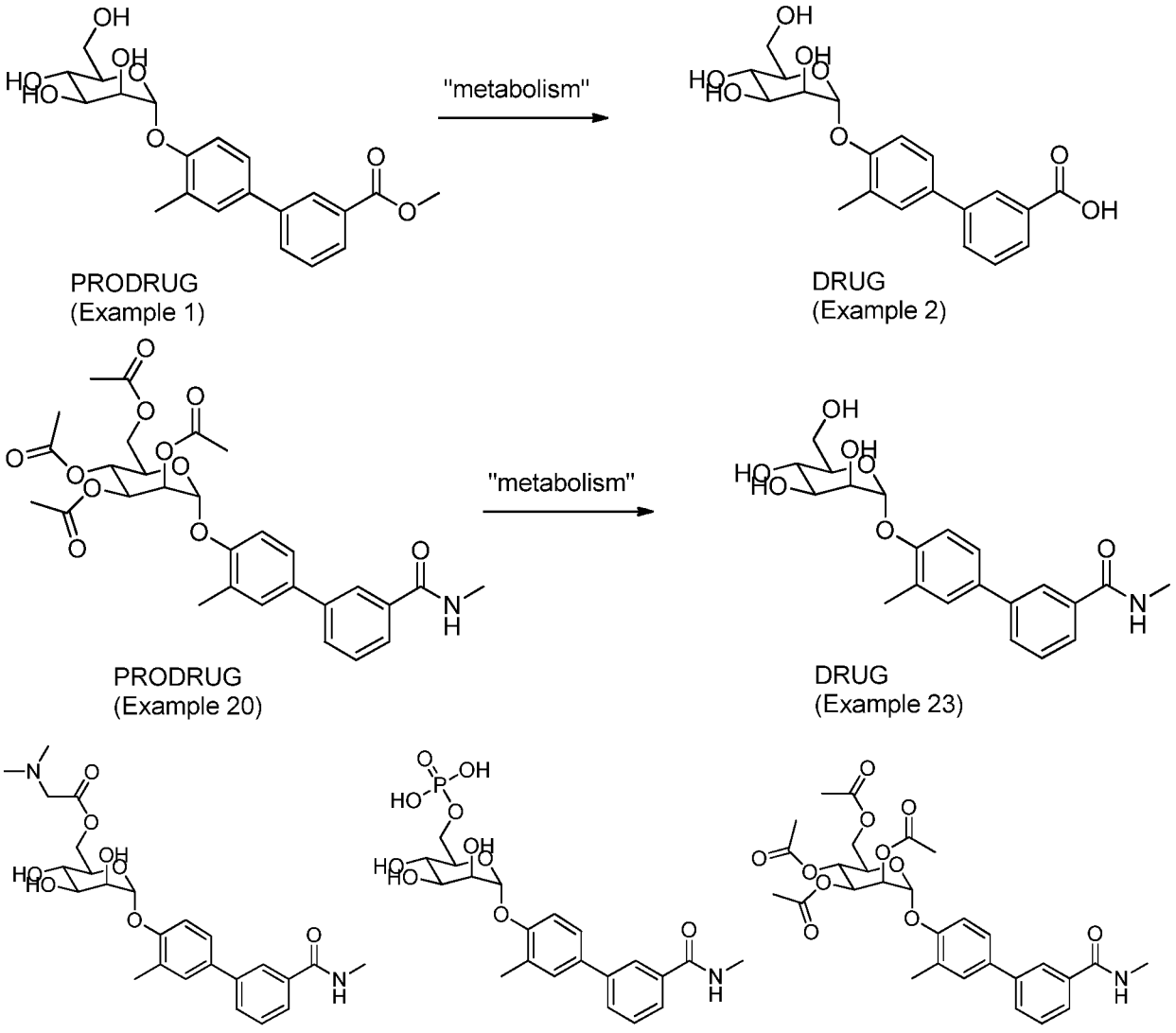
[0129] For therapeutic purposes, formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. For instance, a compound of the invention may be administered with a carrier. Non-limiting examples of such a carrier include protein carriers and lipid carriers.

[0130] Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

[0131] The amount of the compound of the invention that may be combined with the carrier materials to produce a single dosage of the composition will vary depending upon the subject and the particular mode of administration. Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711 and from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Tenth Edition (2001), Appendix II, pp. 475-493.

[0132] A compound of the invention may also be formulated as a prodrug. Such a prodrug formulation may increase the bioavailability of a compound of the invention. In one embodiment, the sugar portion of a compound of the invention may encompass a

prodrug. In another embodiment R_3 may comprise a prodrug. Non-limiting examples of a compound of the invention formulated as a prodrug include the compounds below:



Example 22 Example 21 Example 20

IV. METHODS OF THE INVENTION

[0133] Compounds of the invention may be used in methods of treating a bacterial infection and methods of reducing resistance to a bactericidal compound in a bacterium.

(a) methods of treating a bacterial infection

[0134] One embodiment of the invention encompasses a method for treating bacterial infections. Or, more specifically, the invention encompasses a method for treating a urinary tract infection. As used herein, "treating" refers to preventing infection in a subject not currently infected, and reducing or eliminating infection in a subject that is currently infected. As such, the invention also encompasses a method for preventing UTI. Generally, such a method comprises administering a pharmaceutical composition comprising a compound of the invention to a subject. As used herein, "subject" includes any mammal prone to urinary tract infections by E. coli. In one embodiment, a subject is prone to recurring UTIs. In some embodiments, a subject may not have clinical symptoms of a UTI. In such embodiments, the subject may have a latent infection. In other embodiments, a subject may have clinical symptoms of a UTI.

[0135] In some embodiments, a compound of the invention may be administered to a subject in combination with a bactericidal compound as described in **Section II** above. When administered in a combination, a compound of the invention may be administered before, simultaneously, or after administration of a bactericidal compound. When administered before or after a bactericidal compound, the time between administration of a compound of the invention and a bactericidal compound may be about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60 min. In another embodiment, the time between administration of a compound of the invention and a bactericidal compound may be about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, or 72 hours.

[0136] A compound or pharmaceutical composition of the invention may be administered by several different means that will deliver a therapeutically effective dose. Such compositions may be administered orally, parenterally, by inhalation spray, rectally, intradermally, intracisternally, intraperitoneally, transdermally, bucally, as an oral or nasal spray, topically (i.e. powders, ointments or drops), or via a urinary cathetar in dosage unit formulations containing conventional nontoxic pharmaceutically

acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, or intrasternal injection, or infusion techniques. In an exemplary embodiment, the pharmaceutical composition will be administered in an oral dosage form. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa. (1975), and Liberman, H. A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y. (1980).

[0137] The amount of a compound of the invention that constitutes an "effective amount" can and will vary. The amount will depend upon a variety of factors, including whether the administration is in single or multiple doses, and individual subject parameters including age, physical condition, size, and weight. Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711 and from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Tenth Edition (2001), Appendix II, pp. 475-493.

[0138] In order to selectively control the release of an inhibitor to a particular region of the gastrointestinal tract for release, the pharmaceutical compositions of the invention may be manufactured into one or several dosage forms for the controlled, sustained or timed release of one or more of the ingredients. In this context, typically one or more of the ingredients forming the pharmaceutical composition is microencapsulated or dry coated prior to being formulated into one of the above forms. By varying the amount and type of coating and its thickness, the timing and location of release of a given ingredient or several ingredients (in either the same dosage form, such as a multi-layered capsule, or different dosage forms) may be varied.

[0139] In an exemplary embodiment, the coating may be an enteric coating. The enteric coating generally will provide for controlled release of the ingredient, such that drug release can be accomplished at some generally predictable location in the lower intestinal tract below the point at which drug release would occur without the enteric coating. In certain embodiments, multiple enteric coatings may be utilized.

Multiple enteric coatings, in certain embodiments, may be selected to release the ingredient or combination of ingredients at various regions in the lower gastrointestinal tract and at various times.

[0140] As will be appreciated by a skilled artisan, the encapsulation or coating method can and will vary depending upon the ingredients used to form the pharmaceutical composition and coating, and the desired physical characteristics of the microcapsules themselves. Additionally, more than one encapsulation method may be employed so as to create a multi-layered microcapsule, or the same encapsulation method may be employed sequentially so as to create a multi-layered microcapsule. Suitable methods of microencapsulation may include spray drying, spinning disk encapsulation (also known as rotational suspension separation encapsulation), supercritical fluid encapsulation, air suspension microencapsulation, fluidized bed encapsulation, spray cooling/chilling (including matrix encapsulation), extrusion encapsulation, centrifugal extrusion, coacervation, alginate beads, liposome encapsulation, inclusion encapsulation, colloidosome encapsulation, sol-gel microencapsulation, and other methods of microencapsulation known in the art. Detailed information concerning materials, equipment and processes for preparing coated dosage forms may be found in Pharmaceutical Dosage Forms: Tablets, eds. Lieberman et al. (New York: Marcel Dekker, Inc., 1989), and in Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th Ed. (Media, Pa.: Williams & Wilkins, 1995).

[0141] A bacterium may be contacted with a compound of the invention in vivo, in vitro, in situ, or ex vivo. In some embodiments, a bacterium may be directly contacted with the compound of the invention. In other embodiments, an intracellular bacterium may be contacted with a compound of the invention. Suitable cells comprising one or more bacteria may be grown, sub-cultured, stored and manipulated using standard techniques known to individuals skilled in the art. Cell culture and microbiological techniques for growing, culturing, storing, and manipulating cells comprising one or more bacteria are commonly known in the art.

(b) methods of reducing bactericidal resistance

[0142] Another method of the invention comprises reducing the resistance of a bacterium to a bactericidal compound. Such a method comprises contacting a bacterium resistant to a bactericidal compound with a compound of the invention. For instance, a subject infected with a bacterium resistant to a bactericidal compound may be administered a compound of the invention, as described in **Section IV(a)** above. In an exemplary embodiment, a method comprises contacting a bacterium resistant to an antibiotic with a compound of the invention. In a further exemplary embodiment, a method comprises contacting a bacterium resistant to TMP or SMZ with a compound of the invention.

[0143] Methods of measuring resistance of a bacterium to an antibiotic are known in the art. For more details, see the examples.

(c) methods of treating catheter-associated urinary tract infections

[0144] In a further embodiment, a method of the invention encompasses a method for treating catheter-associated urinary tract infections. As used herein, "treating" refers to preventing infection in a subject not currently infected, and reducing or eliminating infection in a subject that is currently infected. Generally, such a method comprises administering a pharmaceutical composition comprising a compound of the invention to a subject. For this embodiment, "subject" refers to any mammal with an indwelling urinary catheter. In one embodiment, a subject with a urinary catheter is prone to recurring UTIs. In some embodiments, a subject with a urinary catheter may not have clinical symptoms of a UTI. In such embodiments, the subject may have a latent infection. In other embodiments, a subject with a urinary catheter may have clinical symptoms of a UTI.

[0145] In some embodiments, a compound of the invention may be administered to a subject in combination with a bactericidal compound as described in **Section II** and **Section IV(a)** above.

(d) methods of treating inflammatory bowel disease

[0146] In a further embodiment, a method of the invention encompasses a method for treating inflammatory bowel disease. Inflammatory bowel disease (IBD)

involves chronic inflammation of all or part of the digestive tract. IBD may include ulcerative colitits, Crohn's disease, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's disease and indeterminate colitis. As used herein, "treating" refers to reducing symptoms associated with inflammatory bowel disease. Alternatively, a method of the invention encompasses a method for reducing symptoms associated with inflammatory bowel disease. Symptoms may include ulcers, reduced appetite, rectal bleeding, rectal pain, a feeling of urgency or frequent, small bowel movements, bloody diarrhea, abdominal cramps and pain, inability to move the bowels in spite of the urge to do so (tenesmus), pain on the left side, unintended weight loss, fatigue, significant weight loss, profuse diarrhea, dehydration, shock, fever, fatigue, arthritis, eye inflammation, skin disorders, and inflammation of the liver or bile ducts.

[0147] Generally, such a method comprises administering a pharmaceutical composition comprising a compound of the invention to a subject. For this embodiment, "subject" refers to any mammal with inflammatory bowel disease.

V. COATINGS

[0148] An additional aspect of the present invention encompasses coatings comprising a compound of the invention. Such a coating may be used on a medical device to prevent bacterial adherence or infection of the host. Suitable means of coating medical devices are known in the art. In one embodiment, a catheter may be coated with a compound of the invention. In another embodiment, a urinary catheter may be coated with a compound of the invention.

VI. NUTRITIONAL SUPPLEMENT

[0149] An alternative aspect of the present invention encompasses a nutritional supplement that comprises a compound of the invention. Such a supplement may be used to treat a bacterial infection as described in section IV above.

DEFINITIONS

[0150] The term "acyl," as used herein alone or as part of another group, denotes the moiety formed by removal of the hydroxyl group from the group --COOH of an organic carboxylic acid, e.g., RC(O)--, wherein R is R', R1O--, R'R2 N--, or R1S--, R1

is hydrocarbyl, heterosubstituted hydrocarbyl, or heterocyclo and R2 is hydrogen, hydrocarbyl or substituted hydrocarbyl.

[0151] The term "acyloxy," as used herein alone or as part of another group, denotes an acyl group as described above bonded through an oxygen linkage (-- O--), e.g., RC(O)O-- wherein R is as defined in connection with the term "acyl."

[0152] Unless otherwise indicated, the alkyl groups described herein are preferably lower alkyl containing from one to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain or cyclic, also known as a cycloalkyl, and include methyl, ethyl, propyl, isopropyl, butyl, hexyl and the like.

[0153] Unless otherwise indicated, the alkenyl groups described herein are preferably lower alkenyl containing from two to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain or cyclic and include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, hexenyl, and the like.

[0154] Unless otherwise indicated, the alkynyl groups described herein are preferably lower alkynyl containing from two to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain and include ethynyl, propynyl, butynyl, isobutynyl, hexynyl, and the like.

[0155] The terms "aryl" or "ar" as used herein alone or as part of another group denote optionally substituted homocyclic aromatic groups, preferably monocyclic or bicyclic groups containing from 6 to 12 carbons in the ring portion, such as phenyl, biphenyl, naphthyl, substituted phenyl, substituted biphenyl or substituted naphthyl. Phenyl and substituted phenyl are the more preferred aryl.

[0156] As used herein, the term “functional group” includes a group of atoms within a molecule that is responsible for certain properties of the molecule and/or reactions in which it takes part. Non-limiting examples of functional groups include, alkyl, carboxyl, hydroxyl, amino, sulfonate, phosphate, phosphonate, thiol, alkyne, azide, halogen, and the like.

[0157] The terms "halogen" or "halo" as used herein alone or as part of another group refer to chlorine, bromine, fluorine, and iodine.

[0158] The terms "heterocyclo" or "heterocyclic" as used herein alone or as part of another group denote optionally substituted, fully saturated or unsaturated, monocyclic or bicyclic, aromatic or nonaromatic groups having at least one heteroatom in at least one ring, and preferably 5 or 6 atoms in each ring. The heterocyclo group preferably has 1 or 2 oxygen atoms, 1 or 2 sulfur atoms, and/or 1 to 4 nitrogen atoms in the ring, and may be bonded to the remainder of the molecule through a carbon or heteroatom. Exemplary heterocyclo include heteroaromatics such as furyl, thienyl, pyridyl, oxazolyl, pyrrolyl, indolyl, quinolinyl, or isoquinolinyl and the like. Exemplary substituents include one or more of the following groups: hydrocarbyl, substituted hydrocarbyl, keto, hydroxy, protected hydroxy, acyl, acyloxy, alkoxy, alkenoxy, alkynoxy, aryloxy, halogen, amido, amino, nitro, cyano, thiol, ketals, acetals, esters and ethers.

[0159] The term "heteroaromatic" as used herein alone or as part of another group denote optionally substituted aromatic groups having at least one heteroatom in at least one ring, and preferably 5 or 6 atoms in each ring. The heteroaromatic group preferably has 1 or 2 oxygen atoms, 1 or 2 sulfur atoms, and/or 1 to 4 nitrogen atoms in the ring, and may be bonded to the remainder of the molecule through a carbon or heteroatom. Exemplary heteroaromatics include furyl, thienyl, pyridyl, oxazolyl, pyrrolyl, indolyl, quinolinyl, or isoquinolinyl and the like. Exemplary substituents include one or more of the following groups: hydrocarbyl, substituted hydrocarbyl, keto, hydroxy, protected hydroxy, acyl, acyloxy, alkoxy, alkenoxy, alkynoxy, aryloxy, halogen, amido, amino, nitro, cyano, thiol, ketals, acetals, esters and ethers.

[0160] The terms "hydrocarbon" and "hydrocarbyl" as used herein describe organic compounds or radicals consisting exclusively of the elements carbon and hydrogen. These moieties include alkyl, alkenyl, alkynyl, and aryl moieties. These moieties also include alkyl, alkenyl, alkynyl, and aryl moieties substituted with other aliphatic or cyclic hydrocarbon groups, such as alkaryl, alkenaryl and alkynaryl. Unless otherwise indicated, these moieties preferably comprise 1 to 20 carbon atoms.

[0161] The "substituted hydrocarbyl" moieties described herein are hydrocarbyl moieties which are substituted with at least one atom other than carbon, including moieties in which a carbon chain atom is substituted (i.e. replaced) with a hetero atom

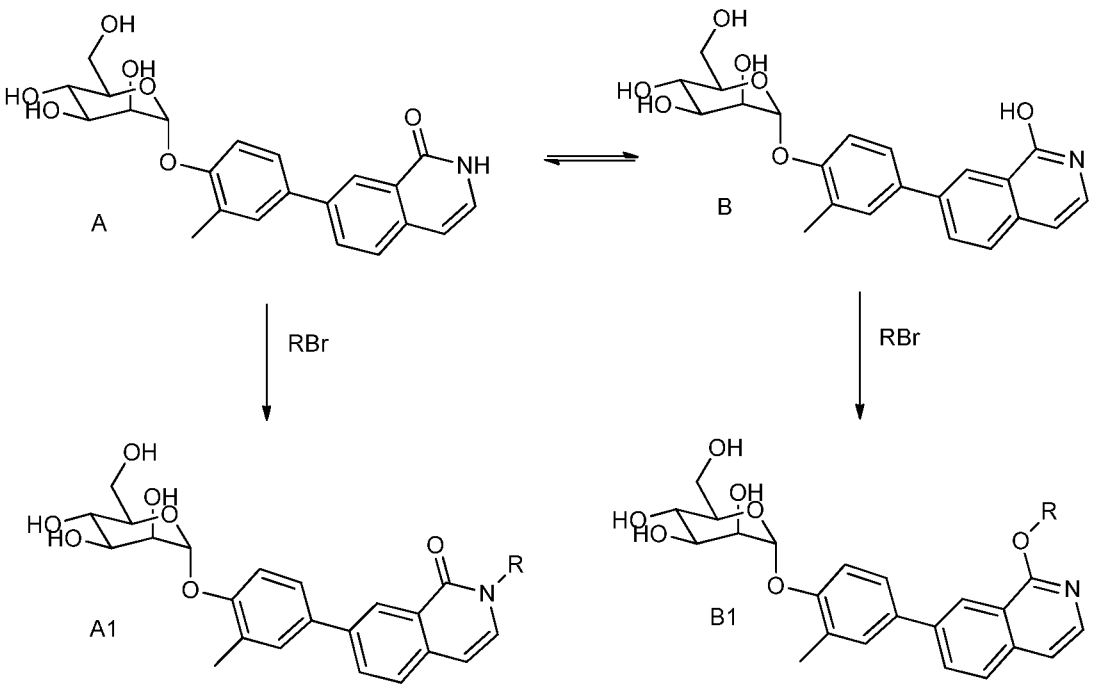
such as nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or a halogen atom. These moieties may include halogen, carbocycle, aryl, heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, keto, acyl, acyloxy, nitro, amino, amido, nitro, cyano, thiol, ketals, acetals, esters and ethers.

EXAMPLES

[0162] The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples that follow represent techniques discovered by the inventors to function well in the practice of the invention. Those of skill in the art should, however, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention, therefore all matter set forth or shown in the accompanying drawings is to be interpreted as illustrative and not in a limiting sense.

Introduction to Examples: ***General synthesis, purification, and analytical chemistry procedures.***

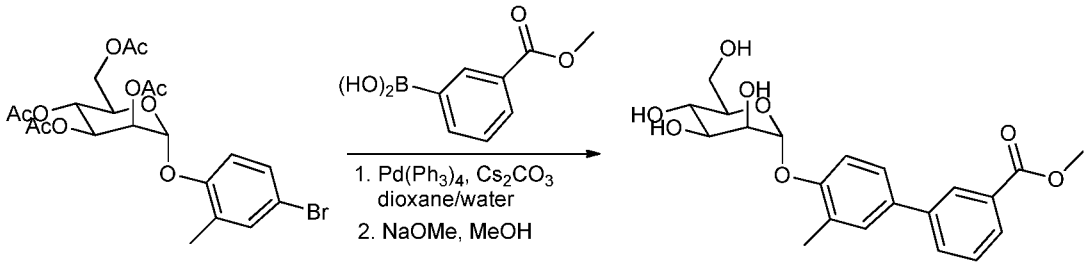
[0163] Certain compounds may exist as mixtures of isomers in equilibrium as described for isoquinolone isomer A in the scheme below which is in equilibrium with the hydroxyquinoline isomer B:



[0164] Therefore, it is understood that compounds containing isoquinolones may exist in the hydroxyisoquinoline form and the synthesis of analogs thereof may lead to the production of either one isomer A1 or B1 exclusively or a mixture. It is not always possible to confirm the identity of each individual isomer (e.g. A1 or B1).Thus, all possible isomers are claimed as the final product in examples which contain the isoquinolone ring.

[0165] Starting materials, reagents, and solvents were purchased from commercial vendors unless otherwise noted. In general anhydrous solvents are used for carrying out all reactions. ^{1}H NMR spectra were measured on a Varian 400 MHz NMR instrument equipped with an auto sampler. The chemical shifts were reported as δ ppm relative to TMS using residual solvent peak as the reference unless otherwise noted. The following abbreviations were used to express the peak multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. High-performance liquid chromatography (HPLC) was carried out on GILSON GX-281 using Waters C18 5μM, 4.6*50mm and Waters Prep C18 5μM, 19*150mm reverse phase columns, eluted with a gradient system of 5:95 to 95:5 acetonitrile:water with a buffer consisting of 0.05-0.1% TFA. Mass spectroscopy (MS) was performed on HPLC/MSD using a gradient system of 5:95 to 95:5 acetonitrile:water with a buffer consisting of 0.05-0.1% TFA on a C18 or

C8 reversed phased column and electrospray ionization (ESI) for detection. All reactions were monitored by thin layer chromatography (TLC) carried out on Merck silica gel plates (0.25 mm thick, 60F254), visualized by using UV (254 nm) or dyes such as $KMnO_4$, *p*-Anisaldehyde and CAM (Hannesian's Stain). Silica gel chromatography was carried out on a Teledyne ISCO CombiFlash purification system using pre-packed silica gel columns (12 g~330 g sizes). All compounds used for biological assays are greater than 95% purity based on NMR and HPLC by absorbance at 220 nm and 254 nm wavelengths.

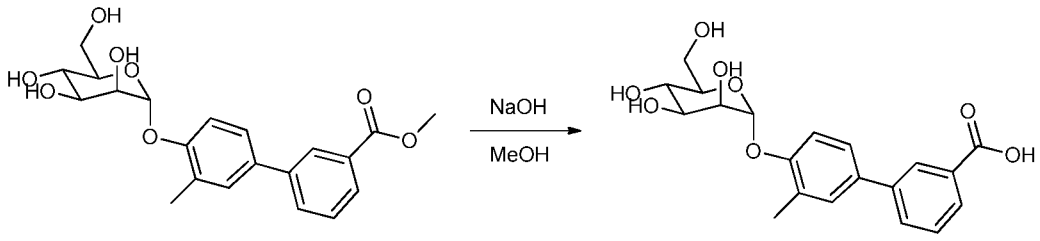


(**Scheme I**)

Example 1. <u>methyl 3-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]</u>benzoate (Han et. al., *J. Med. Chem.* 2012, 55, 3945−3959).

[0166] To a round-bottomed flask equipped with a reflux condenser and N_2 line was added [(2R,3R,4S,5R,6S)-4,5-diacetoxy-6-(acetoxymethyl)-2-(4-bromo-2-methyl-phenoxy)tetrahydropyran-3-yl] acetate (0.52 g, 1.0 mmol), (3-methoxycarbonylphenyl)boronic acid (0.22 g, 1.2 mmol), Cs_2CO_3 (0.98 g, 3 mmol) and $Pd(Ph_3)_4$ (0.12 g, 0.1 mmol) followed by 5:1 mixture of 1,4-dioxane/water (30 mL). The reaction flask was placed under high vacuum and then repressurized with N_2 repeated 3 times. The reaction was heated to 80 ºC under a N_2 atmosphere for 1 h. The solvent was removed *in vacuo* and the residue was dissolved in $CHCl_3$ and filtered. The filtrate was purified by silica gel chromatography (ISCO MPLC, MeOH/CH_2Cl_2, 0-10% gradient). Pure fractions as determined by TLC and LCMS were combined and then concentrated *in vacuo*. The residue was dissolved in MeOH (10 mL) and then charged with 0.002 M NaOMe/MeOH (5 mL). After the reaction was complete determined by LCMS, DOWEX 50WX4-100 ion exchange resin was added. After 15 minutes, the resin

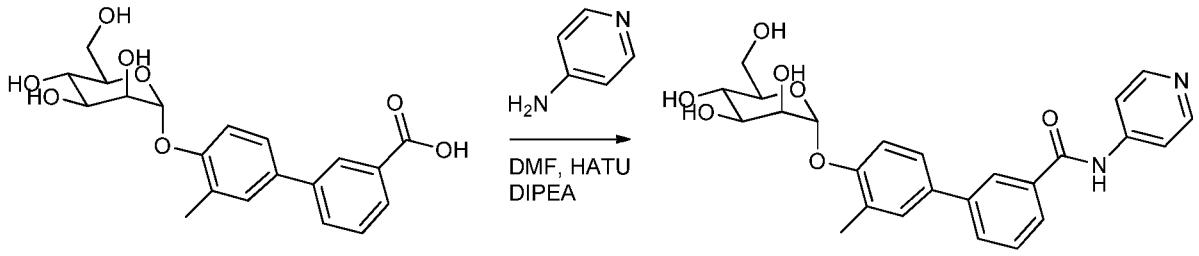
was filtered, washed with MeOH and then the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-25% MeOH/CH_2Cl_2) to yield the title compound (0.222 g, 55%) as a white solid. LCMS (ESI, M + Na^+ = 427.3),



(**Scheme II**)

Example 2. 3-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]benzoic acid.

[0167] To a solution of methyl 3-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]benzoate (0.222 g, 0.55 mmol) in MeOH (70 mL) was added 0.2 M NaOH (30 mL). The reaction was stirred overnight at RT. DOWEX 50WX4-100 ion exchange resin was added. After 15 minutes, the resin was filtered, washed with MeOH and then the filtrate was concentrated *in vacuo* to yield the title compound (0.2025 g, 94%) as a white solid. LCMS (ESI, M + Na^+ = 413.3); ^1H NMR δ ppm (d_3-MeOD; 2.31 (s, 3 H) 3.61 (ddd, J=9.78, 5.09, 2.74 Hz, 1 H) 3.69 - 3.84 (m, 3 H) 3.97 (dd, J=9.39, 3.52 Hz, 1 H) 4.08 (dd, J=3.33, 1.76 Hz, 1 H) 5.56 (d, J=1.96 Hz, 1 H) 7.31 (d, J=8.22 Hz, 1 H) 7.39 - 7.48 (m, 2 H) 7.51 (t, J=7.83 Hz, 1 H) 7.76 - 7.84 (m, 1 H) 7.95 (dt, J=7.83, 1.37 Hz, 1 H) 8.21 (t, J=1.76 Hz, 1 H)).



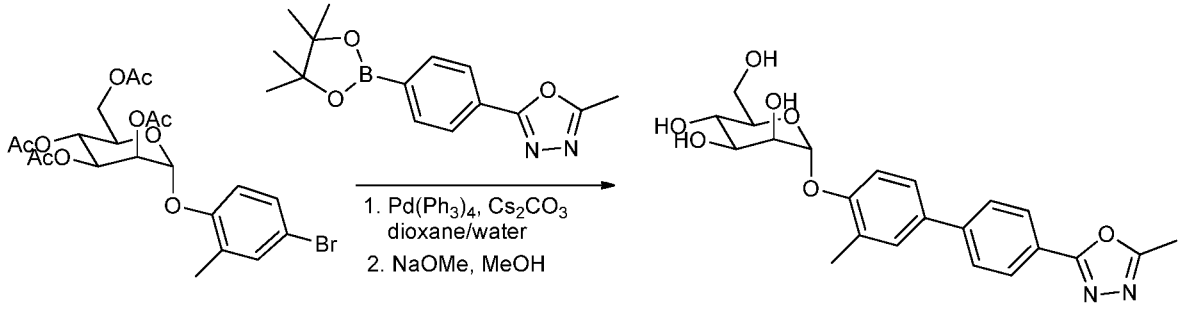
(**Scheme III**)

Example 3. 3-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-N-(4-pyridyl)benzamide.

[0168] To a stirred solution of 3-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]benzoic acid (0.039 g, 0.1 mmol) and HATU (0.046 g, 0.12 mmol) in DMF (5 mL) under a N2 atmosphere and cooled to 0 ºC was added 4-aminopyridine (0.011 g, 0.12 mmol), and DIPEA (0.054 mL, 0.3 mmol). The reaction was allowed to warm to RT and then stirred overnight. The solvent was removed in vacuo and the residue purified by reversed phase HPLC (5-85% acetonitrile/water/0.05% TFA). Pure fractions were combined and lyophilized to give the title compound as a white powder (0.047 g, 100%). LCMS (ESI, M + H^+ = 467.3); ^{1}H NMR δ ppm (d_3-MeOD; 2.34 (s, 3 H) 3.60 (ddd, J=9.78, 5.28, 2.54 Hz, 1 H) 3.68 - 3.85 (m, 3 H) 3.98 (dd, J=9.59, 3.33 Hz, 1 H) 4.09 (dd, J=3.33, 1.76 Hz, 1 H) 5.58 (d, J=1.57 Hz, 1 H) 7.34 (d, J=8.61 Hz, 1 H) 7.44 - 7.58 (m, 2 H) 7.63 (t, J=7.63 Hz, 1 H) 7.84 - 8.00 (m, 2 H) 8.19 - 8.27 (m, 1 H) 8.37 - 8.45 (m, 2 H) 8.62 - 8.72 (m, 2 H)).

Example 4. <u>3-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-N-(3-pyridyl)benzamide</u>.

[0169] Synthesized in a similar manner to **Example 3** using 3-aminopyridine to give (0.043 g, 94%). LCMS (ESI, M + H^+ = 467.3); ^{1}H NMR δ ppm (d_3-MeOD; 2.33 (s, 3 H) 3.61 (m, 1 H) 3.76 (m, 3 H) 3.97 (d, J=9.39 Hz, 1 H) 4.08 (m, 1 H) 5.57 (d, 1 H) 7.33 (d, J=6.26 Hz, 1 H) 7.43 - 7.56 (m, 2 H) 7.61 (m, 1 H) 7.85 (m, 1 H) 7.94 (m, 2 H) 8.22 (m, 1 H) 8.55 (m, 1 H) 8.66 (d, J=6.26 Hz, 1 H) 9.47 (m, 1 H)).



(**Scheme IV**)

Example 5. <u>(2S,3S,4S,5R,6R)-2-(hydroxymethyl)-6-[2-methyl-4-[4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]phenoxy]tetrahydropyran-3,4,5-triol</u>.

[0170] Synthesized in a similar manner to **Example 1** using 2-methyl-5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3,4-oxadiazole (purchased from

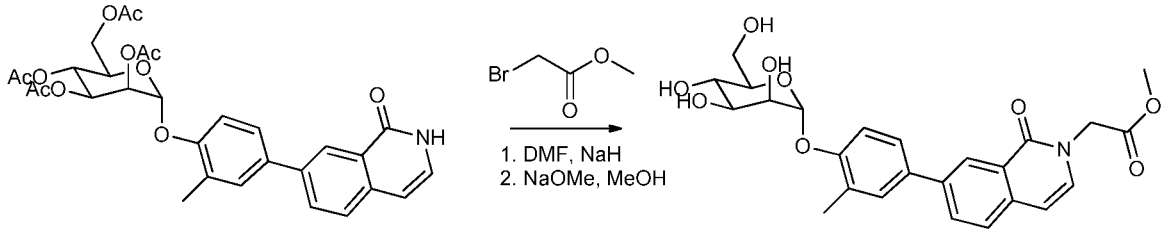
Boron Molecular). LCMS (ESI, M + H^+ = 429.3); ^{1}H NMR δ ppm (d_3-MeOD; 2.28 (s, 3 H) 2.63 (s, 3 H) 3.53 - 3.65 (m, 1 H) 3.70 - 3.88 (m, 3 H) 3.98 (dd, J=9.59, 3.33 Hz, 1 H) 4.09 (dd, J=3.13, 1.96 Hz, 1 H) 5.57 (d, J=1.17 Hz, 1 H) 7.24 (d, J=8.22 Hz, 1 H) 7.38 - 7.45 (m, 2 H) 7.48 (s, 1 H) 7.69 (m, J=8.61 Hz, 1.5 H) 8.02 (m, J=8.22 Hz, 1.5 H)).

Example 6. (2S,3S,4S,5R,6R)-2-(hydroxymethyl)-6-[2-methyl-4-[3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]phenoxy]tetrahydropyran-3,4,5-triol.

[0171] Synthesized in a similar manner to **Example 1** using [3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]boronic acid (purchased from Apollo Scientific). LCMS (ESI, M + H^+ = 429.3); ^{1}H NMR δ ppm (d_3-MeOD; 2.08 (s, 1.5 H) 2.32 (s, 1.5 H) 2.33 (s, 1.5 H) 2.65 (s, 1.5 H) 3.55 - 3.65 (m, 1 H) 3.69 - 3.83 (m, 3 H) 3.98 (dt, J=9.49, 2.69 Hz, 1 H) 4.06 - 4.12 (m, 1 H) 5.54 - 5.60 (m, 1 H) 7.27 - 7.38 (m, 1 H) 7.44- 7.65 (m, 3 H) 7.75 - 7.98 (m, 2 H) 8.07 - 8.25 (m, 1 H)).

Example 7. 7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-2H-isoquinolin-1-one.

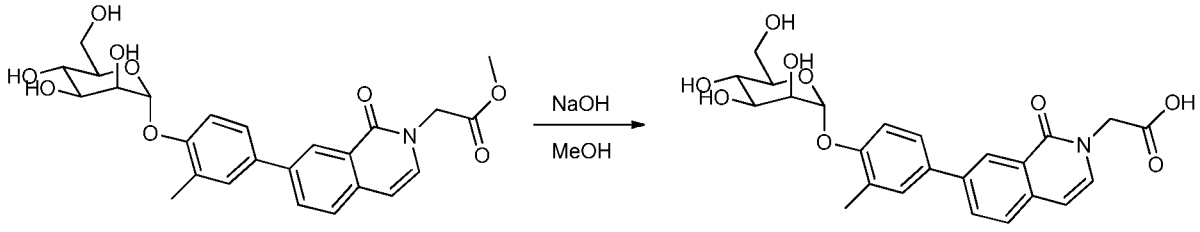
[0172] Synthesized in a similar manner to **Example 1** using [4,5-diacetoxy-6-(acetoxymethyl)-2-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]tetrahydropyran-3-yl] acetate (Han et. al., *J. Med. Chem.* 2012, 55, 3945−3959) and 7-bromo-2H-isoquinolin-1-one (purchased from AstaTech). LCMS (ESI, M + H^+ = 414.3); ^{1}H NMR δ ppm (d_3-MeOD; 2.32 (s, 3 H) 3.57 - 3.67 (m, 1 H) 3.70 - 3.85 (m, 3 H) 3.94 - 4.02 (m, 1 H) 4.05 - 4.13 (m, 1 H) 5.57 (d, J=1.57 Hz, 1 H) 6.70 (d, J=7.00 Hz, 1 H) 7.17 (d, J=7.04 Hz, 1 H) 7.33 (d, J=8.22 Hz, 1 H) 7.54 (s, 2 H) 7.70 (d, J=8.61 Hz, 1 H) 7.89 - 8.04 (m, 1 H) 8.49 (d, J=1.96 Hz, 1 H)).



(**Scheme V**)

Example 8. methyl 2-[7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6 (hydroxymethyl) tetrahydropyran-2-yl]oxy-phenyl]-1-oxo-2-isoquinolyl]acetate.

[0173] To a solution of [4,5-diacetoxy-6-(acetoxymethyl)-2-[2-methyl-4-(1-oxo-2H-isoquinolin-7-yl)phenoxy]tetrahydropyran-3-yl] acetate (0.116 g, 0.2 mmol) in DMF (5 mL) cooled to 0 ºC under a N_2 atmosphere was slowly added NaH (0.024 g, 0.6 mmol, 60% dispersion in mineral oil). After 10 min, methyl 2-bromoacetate (0.018 mL, 0.19 mmol) was added and the reaction was stirred for 1 h at 0 ºC under a N_2 atmosphere. The solvent was removed under high vacuum and the residue was dissolved in MeOH (5 mL) followed by the addition of 0.02 M NaOMe/MeOH (3 mL) and the reaction was stirred overnight at RT. DOWEX 50WX4-100 ion exchange resin was added. After 15 minutes, the resin was filtered, washed with MeOH and then the filtrate was concentrated *in vacuo*. The residue was purified by slica gel chromatography (0-20% MeOH/CH_2Cl_2) to give the title product (0.0558 g, 57%) as a white solid. LCMS (ESI, M + H^+ = 486.3); ^{1}H NMR δ ppm (d_3-MeOD; 2.32 (s, 3 H) 3.61 (ddd, J=9.68, 4.99, 2.54 Hz, 1 H) 3.68 - 3.85 (m, 3 H) 3.78 (s, 3H) 3.98 (dd, J=9.59, 3.33 Hz, 1 H) 4.04 - 4.14 (m, 1 H) 4.82 (s, 2 H) 5.53 - 5.62 (m, 1 H) 6.72 (d, J=7.04 Hz, 1 H) 7.32 (dd, J=7.83, 3.91 Hz, 2 H) 7.44 - 7.58 (m, 2 H) 7.70 (d, J=8.22 Hz, 1 H) 7.97 (dd, J=8.22, 1.96 Hz, 1 H) 8.43 - 8.49 (m, 1 H)).

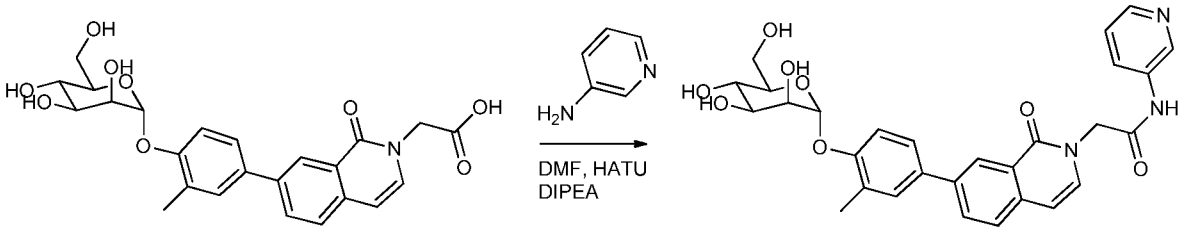


(**Scheme VI**)

Example 9. 2-[7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-1-oxo-2-isoquinolyl]acetic acid.

[0174] Following a similar procedure to **Example 2** using methyl 2-[7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6 (hydroxymethyl) tetrahydropyran-2-yl]oxy-phenyl]-1-oxo-2-isoquinolyl]acetate (0.050 g, 0.1 mmol) the title product was obtained as a white solid (0.045 g, 96%). LCMS (ESI, M + H^+ = 472.3); ^{1}H NMR δ ppm (d_3-MeOD; 2.32 (s, 3 H) 3.61 (ddd, J=9.59, 5.28, 2.35 Hz, 1 H) 3.67 - 3.86 (m, 3 H) 3.98

(dd, J=9.59, 3.33 Hz, 1 H) 4.08 (dd, J=3.33, 1.76 Hz, 1 H) 4.79 (s, 2 H) 5.50 - 5.62 (m, 1 H) 6.72 (d, J=7.43 Hz, 1 H) 7.32 (dd, J=8.02, 2.93 Hz, 2 H) 7.44 - 7.59 (m, 2 H) 7.70 (d, J=8.22 Hz, 1 H) 7.97 (dd, J=8.22, 1.96 Hz, 1 H) 8.44 - 8.55 (m, 1 H)).



(**Scheme VII**)

Example 10. 2-[7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-1-oxo-2-isoquinolyl]-N-(3-pyridyl)acetamide.

[0175] Following a similar procedure to **Example 3** using 2-[7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-1-oxo-2-isoquinolyl]acetic acid (0.024 g, 0.05 mmol) and 3-aminopyridine the title compound was obtained (22 mg, 81%) as a white solid. LCMS (ESI, M + H^+ = 548.4); ^{1}H NMR δ ppm (d_3-MeOD; 2.32 (s, 3 H) 3.55 - 3.66 (m, 1 H) 3.66 - 3.85 (m, 3 H) 3.97 (dd, J=9.59, 3.33 Hz, 1 H) 4.08 (dd, J=3.13, 1.96 Hz, 1 H) 4.96 (s, 2 H) 5.46 - 5.63 (m, 1 H) 6.77 (d, J=7.04 Hz, 1 H) 7.27 - 7.44 (m, 2 H) 7.46 - 7.58 (m, 2 H) 7.73 (d, J=8.22 Hz, 1 H) 7.88 (dd, J=8.61, 5.48 Hz, 1 H) 8.00 (dd, J=8.22, 1.96 Hz, 1 H) 8.42 (dd, J=8.61, 1.17 Hz, 1 H) 8.49 (s, 2 H) 9.18 - 9.29 (m, 1 H)).

Example 11. 2-[7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-1-oxo-2-isoquinolyl]-N-(4-pyridyl)acetamide.

[0176] Following a similar procedure to **Example 10** using 4-aminopyridine the title compound was obtained (13.3 mg, 52%). LCMS (ESI, M + H^+ = 548.4); ^{1}H NMR δ ppm (d_3-MeOD; 2.32 (s, 3 H) 3.60 (ddd, J=9.78, 5.09, 2.74 Hz, 1 H) 3.67 - 3.84 (m, 3 H) 3.97 (dd, J=9.59, 3.33 Hz, 1 H) 4.08 (dd, J=3.33, 1.76 Hz, 1 H) 5.00 (s, 2 H) 5.57 (d, J=1.57 Hz, 1 H) 6.78 (d, J=7.43 Hz, 1 H) 7.38 (d, J=7.43 Hz, 2 H) 7.33 (d, J=8.61 Hz, 1

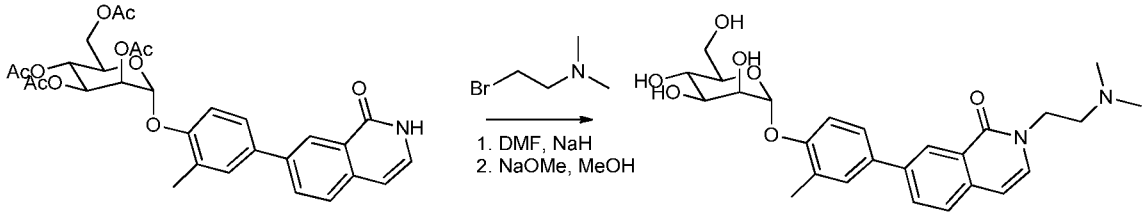
H) 7.49 - 7.58 (m, 2 H) 7.75 (d, J=8.22 Hz, 1 H) 8.01 (dd, J=8.41, 2.15 Hz, 1 H) 8.18 (m, J=7.04 Hz, 2 H) 8.49 (d, J=1.96 Hz, 1 H) 8.64 (m, J=7.43 Hz, 2 H)).

Example 12. 2-[2-(4-methylpiperazin-1-yl)-2-oxo-ethyl]-7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]isoquinolin-1-one.

[0177] Following a similar procedure to **Example 10** using 1-methylpiperazine the title compound was obtained (25.9 mg, 88%). LCMS (ESI, M + H^+ = 554.4); ^{1}H NMR δ ppm (d_3-MeOD; 2.33 (s, 3 H) 2.99 (s, 3 H) 3.26 (dt, J=3.23, 1.71 Hz, 1 H) 3.34 - 3.42 (m, 1 H) 3.49 (dd, J=3.52, 1.57 Hz, 1 H) 3.61 (ddd, J=9.78, 5.28, 2.54 Hz, 3 H) 3.70 - 3.86 (m, 4 H) 3.97 (dd, J=9.59, 3.33 Hz, 2 H) 4.08 (dd, J=3.52, 1.96 Hz, 2 H) 4.81 (s, 1 H) 5.57 (d, J=1.96 Hz, 1 H) 6.75 (d, J=7.43 Hz, 1 H) 7.20 - 7.40 (m, 3 H) 7.45 - 7.59 (m, 2 H) 7.72 (d, J=8.22 Hz, 1 H) 7.99 (dd, J=8.22, 1.96 Hz, 1 H) 8.49 (d, J=1.96 Hz, 1 H)).

Example 13. N-(2-aminoethyl)-2-[7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-1-oxo-2-isoquinolyl]acetamide.

[0178] Following a similar procedure to Example 10 using 1,2-diaminoethane the title compound was obtained (11.2 mg, 55%). LCMS (ESI, M + H^+ = 514.4); ^{1}H NMR δ ppm (d_3-MeOD; 2.33 (s, 3 H) 3.11 (t, J=5.67 Hz, 2 H) 3.54 (t, J=5.67 Hz, 2 H) 3.56 - 3.67 (m, 1 H) 3.68 - 3.84 (m, 3 H) 3.97 (dd, J=9.59, 3.33 Hz, 1 H) 4.08 (dd, J=3.33, 1.76 Hz, 1 H) 4.73 (s, 2 H) 5.48 - 5.64 (m, 1 H) 6.78 (d, J=7.43 Hz, 1 H) 7.34 (d, J=7.83 Hz, 2 H) 7.46 - 7.59 (m, 2 H) 7.74 (d, J=8.22 Hz, 1 H) 8.00 (dd, J=8.22, 1.96 Hz, 1 H) 8.50 (s, 1 H)).



(**Scheme VIII**)

Example 14. 2-(2-dimethylaminoethyl)-7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]isoquinolin-1-one.

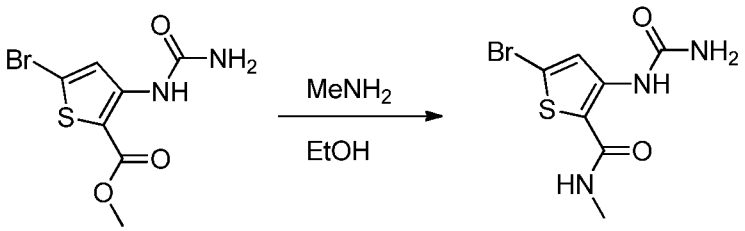
[0179] Following a similar procedure to **Example 8** using [4,5-diacetoxy-6-(acetoxymethyl)-2-[2-methyl-4-(1-oxo-2H-isoquinolin-7-yl)phenoxy]tetrahydropyran-3-yl] acetate (0.1 mmol) and 2-bromo-N,N-dimethyl-ethanamine (0.1 mmol), the title compound was obtained (0.0426 g, 88%). LCMS (ESI, M + H^+ = 485.4); ^{1}H NMR δ ppm (d_3-MeOD; 2.33 (s, 3 H) 3.05 (s, 6 H) 3.52 - 3.67 (m, 3 H) 3.68 - 3.84 (m, 3 H) 3.97 (dd, J=9.39, 3.52 Hz, 1 H) 4.08 (dd, J=3.33, 1.76 Hz, 1 H) 4.46 (t, J=5.87 Hz, 2 H) 5.47 - 5.64 (m, 1 H) 6.80 (d, J=7.43 Hz, 1 H) 7.38 (d, J=7.43 Hz, 1 H) 7.34 (d, J=8.61 Hz, 1 H) 7.47 - 7.59 (m, 2 H) 7.73 (d, J=8.61 Hz, 1 H) 8.01 (dd, J=8.41, 1.76 Hz, 1 H) 8.49 - 8.60 (m, 1 H)).

Example 15. 7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-2-(4-pyridylmethyl)isoquinolin-1-one.

[0180] Following a similar procedure to **Example 14** using 4-(bromomethyl)pyridine, the title compound was obtained (0.046 g, 92%). LCMS (ESI, M + H^+ = 505.4); ^{1}H NMR δ ppm (d_3-MeOD; 2.32 (s, 3 H) 3.53 - 3.66 (m, 1 H) 3.67 - 3.83 (m, 3 H) 3.96 (dd, J=9.59, 3.33 Hz, 1 H) 4.07 (dd, J=3.13, 1.96 Hz, 1 H) 5.52 (s, 2 H) 5.56 (s, 1 H) 6.84 (d, J=7.43 Hz, 1 H) 7.33 (d, J=8.61 Hz, 1 H) 7.44 - 7.57 (m, 3 H) 7.70 - 7.86 (m, 3 H) 8.02 (dd, J=8.22, 1.96 Hz, 1 H) 8.49 (s, 1 H) 8.73 (d, J=6.65 Hz, 2 H)).

Example 16. 7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-2-(3-pyridylmethyl)isoquinolin-1-one.

[0181] Following a similar procedure to **Example 14** using 3-(bromomethyl)pyridine, the title compound was obtained (0.046 g, 92%). LCMS (ESI, M + H^+ = 505.4); ^{1}H NMR δ ppm (d_3-MeOD; 2.32 (s, 3 H) 3.51 - 3.66 (m, 1 H) 3.66 - 3.85 (m, 3 H) 3.97 (dd, J=9.59, 3.33 Hz, 1 H) 4.08 (dd, J=3.13, 1.57 Hz, 1 H) 5.42 (s, 2 H) 5.56 (s, 1 H) 6.80 (d, J=7.43 Hz, 1 H) 7.33 (d, J=8.22 Hz, 1 H) 7.43 - 7.61 (m, 3 H) 7.72 (d, J=8.22 Hz, 1 H) 7.89 (dd, J=8.02, 5.67 Hz, 1 H) 7.99 (dd, J=8.41, 1.76 Hz, 1 H) 8.42 (d, J=8.22 Hz, 1 H) 8.46 - 8.54 (m, 1 H) 8.71 (d, J=5.48 Hz, 1 H) 8.86 (s, 1 H)).



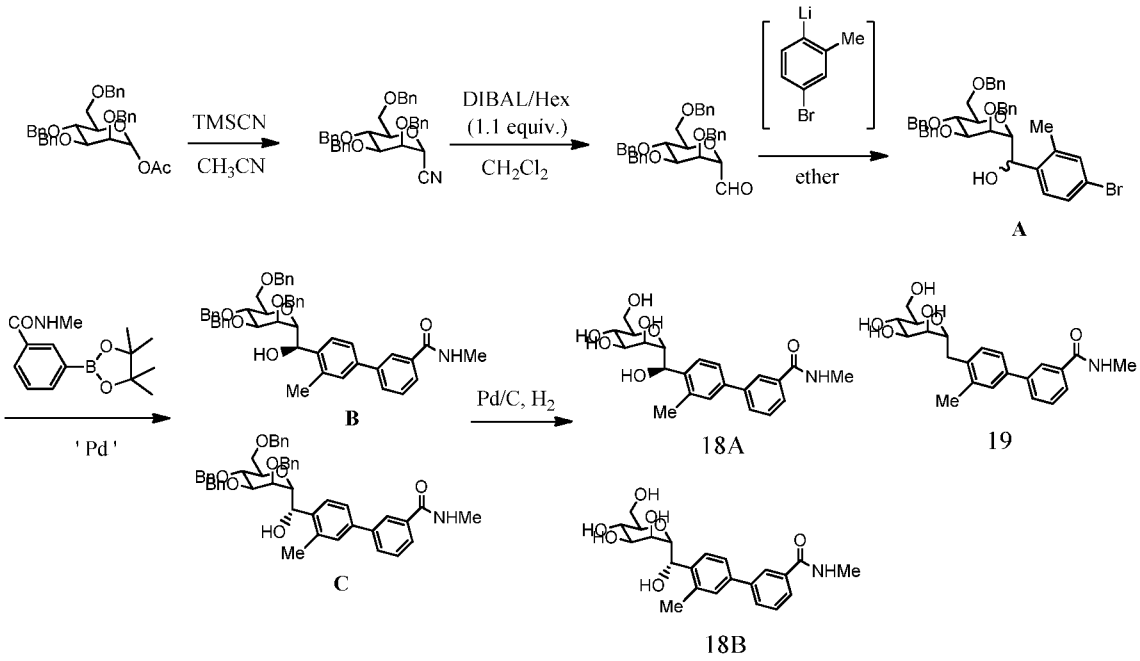
(**Scheme IX**)

Example 17-SM. 5-bromo-N-methyl-3-ureido-thiophene-2-carboxamide.

[0182] Methyl 5-bromo-3-ureido-thiophene-2-carboxylate (Han et. al., *J. Med. Chem.* 2012, 55, 3945−3959) (0.5 g) was stirred with 40 mL of 33% methylamine in EtOH overnight at RT. The solvent was removed in vacuo and the residue was triturated in CH_2Cl_2. The precipitate was filtered and dried to yield the title product as a white solid (0.26 g). LCMS (ESI, M + Na^+ = 300.1).

Example 17. N-methyl-5-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydropyran-2-yl]oxy-phenyl]-3-ureido-thiophene-2-carboxamide.

[0183] Synthesized in a similar manner to **Example 7** using 5-bromo-N-methyl-3-ureido-thiophene-2-carboxamide to give the title compound as a white powder (19 mg). LCMS (ESI, M + H^+ = 468.3); ^1H NMR δ ppm (d_3-MeOD; 2.27 (s, 3 H) 2.87 (s, 3 H) 3.52 - 3.61 (m, 1 H) 3.76 (d, J=1.17 Hz, 3 H) 3.91 - 3.99 (m, 1 H) 4.03 - 4.09 (m, 1 H) 5.56 (d, J=1.17 Hz, 1 H) 7.27 (m, 1 H) 7.47 (m, 2 H) 8.06 (s, 1 H)).



(**Scheme X**)

Introduction for Examples 18-19.

[0184] Under a N_2 atmosphere, to a solution of [(2R,3R,4S,5R,6S)-3,4,5-tribenzyloxy-6-(benzyloxymethyl)tetrahydropyran-2-yl] acetate (1.164 g, 2 mmol) in acetonitrile (20 mL) was added $BF_3.OEt_2$ (0.05 mL, 0.4 mmol) at 0 ºC. The mixture was stirred at RT until completion confirmed by TLC. The solvent was removed in vacuo and the resulting residue was partitioned between dichloromethane and water. The organic layer was collected, dried with Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography using a EtOAc/Hexane gradient to give (2R,3S,4R,5R,6S)-3,4,5-tribenzyloxy-6-(benzyloxymethyl)tetrahydropyran-2-carbonitrile (0.560 g) in 51% yield. MS (ESI): found [M + Na+], 572.2.

[0185] At -78 ºC, DIBAL/Hexanes (1.0 M, 0.52 mL) was added dropwise into the solution of (2R,3S,4R,5R,6S)-3,4,5-tribenzyloxy-6-(benzyloxymethyl)tetrahydropyran-2-carbonitrile (0.258 g, 0.47 mmol) in CH_2Cl_2 (5 mL). Then the mixture was warmed slowly to -40 ºC over 1 h. 0.5 N HCl aqueous was used to quench the reaction and EtOAc was used for extraction. The organic layer was collected, dried with Na_2SO_4 and concentrated to give (2S,3R,4S,5R,6S)-3,4,5-tribenzyloxy-6-(benzyloxymethyl)tetrahydropyran-2-carbaldehyde (0.235 g) as crude

product for the next step without further purification. Into another flask containing 5-bromo-2-iodotoluene (0.42 mL, 3.0 mmol) in ether (5 mL) was added BuLi/Hexanes (2.5 M, 1.0 mL) at -78 ºC. One hour later, (2S,3R,4S,5R,6S)-3,4,5-tribenzyloxy-6-(benzyloxymethyl)tetrahydropyran-2-carbaldehyde (0.235 g) was added. The mixture was warmed slowly to -20 ºC over 1 h 40 min. 0.5 N HCl aqueous was used to quench the reaction and EtOAc was use for extraction. The organic layer was collected, dried with Na_2SO_4 and concentrated. The resulting residue was purified by silica gel chromatography with a EtOAct/Hexane gradient as eluent to give (4-bromo-2-methyl-phenyl)-[(2R,3R,4S,5R,6S)-3,4,5-tribenzyloxy-6-(benzyloxymethyl) tetrahydropyran-2-yl]methanol (A), (0.130 g) in 38% yield. MS (ESI): found [M + Na+], 745.4.

[0186] Under nitrogen atmosphere, the mixture of A (0.130 g, 0.18 mmol), N-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (0.071g, 0.27 mmol), cesium carbonate (0.176 g, 0.54 mmol) and tetrakis(triphenylphosphine)palladium (0.021 g, 0.018 mmol) in dioxane/water (5 mL/1 mL) was heated at 80 ºC with stirring for 1 h. The solvent was removed and the resulting residue was purified by silica gel chromatography to give 3-[4-[(R)-hydroxy-[(2R,3R,4S,5R,6S)-3,4,5-tribenzyloxy-6-(benzyloxymethyl) tetrahydropyran-2-yl]methyl]-3-methyl-phenyl]-N-methyl-benzamide (B), (0.046 g) and 3-[4-[(S)-hydroxy-[(2R,3R,4S,5R,6S)-3,4,5-tribenzyloxy-6-(benzyloxymethyl)tetrahydropyran-2-yl]methyl]-3-methyl-phenyl]-N-methyl-benzamide (C), (0.055 g). MS (ESI): found [M + Na+], 800.6.

A mixture of intermediate B (0.046 g, 0.059 mmol) and Pd/C (10 wt%) (0.050 g, 0.024 mmol) in MeOH (5 mL) was stirred under H2 atmosphere overnight. Pd/C was filtered off and the filtrate was concentrated in vacuo. The resulting residue was purified by purified by HPLC (C18, 15*150 mm column; eluent: acetonitrile/water (0.05% TFA) to give Example 18A (0.020 g) in 81% yield. Example 19 was also isolated as a product (0.0030 g). Following the same procedure for Intermediate B, Intermediate C was converted to Example 18B and 19 in the same fashion.

Example 18A*. 3-[4-[(R)-hydroxy-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydropyran-2-yl]methyl]-3-methyl-phenyl]-N-methyl-benzamide.

[0187] LCMS (ESI, M + Na^+ = 440.3); ^1H NMR δ ppm (d_3-MeOD; 2.51 (s, 3 H) 2.95 (s, 3 H) 3.57 - 3.78 (m, 4 H) 4.00 - 4.07 (m, 1 H) 4.10 (dd, J=6.85, 2.54 Hz, 1 H) 4.25 (t, J=2.93 Hz, 1 H) 5.24 (d, J=6.65 Hz, 1 H) 7.45 - 7.57 (m, 3 H) 7.62 (d, J=8.22 Hz, 1 H) 7.71 - 7.83 (m, 2 H) 8.07 (t, J=1.56 Hz, 1 H)).

Example 18B*. 3-[4-[(S)-hydroxy-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]methyl]-3-methyl-phenyl]-N-methyl-benzamide.

[0188] LCMS (ESI, M + Na^+ = 440.3); ^1H NMR δ ppm (d_3-MeOD; 2.51 (s, 3 H) 2.95 (s, 3 H) 3.56 (dd, J=1.00 Hz, 1 H) 3.67 (m, 1 H) 3.70 - 3.82 (m, 3 H) 3.91 (m, 1 H) 4.10 (dd, J=9.00, 1.96 Hz, 1 H) 5.28 (d, J=8.61 Hz, 1 H) 7.34 - 7.63 (m, 4 H) 7.69 - 7.90 (m, 2 H) 8.07 (s, 1 H)).

[0189] *Note*: *the assignment of the R stereochemistry for 18A and S stereochemistry for 18B is only arbitrary and tentatively assigned by but not confirmed.*

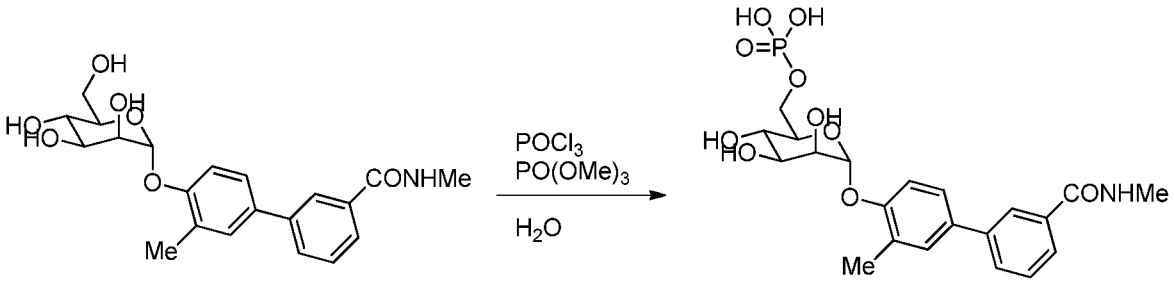
Example 19. N-methyl-3-[3-methyl-4-[[(2R,3R,4R,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]methyl]phenyl]benzamide.

[0190] LCMS (ESI, M + H^+ = 402.3); ^1H NMR δ ppm (d_3-MeOD; 2.44 (s, 3 H) 2.95 (s, 3 H) 3.04 (d, J=7.43 Hz, 2 H) 3.69 (m, 3 H) 3.83 (m, 2 H) 3.86 - 3.92 (m, 1 H) 4.04 - 4.21 (m, 1 H) 7.31 (d, J=7.83 Hz, 1 H) 7.42 - 7.47 (m, 1 H) 7.50 (m, 2 H) 7.75 (m, 2 H) 8.05 (s, 1 H)).

Example 20. [(2S,3R,4S,5R,6R)-3,4,5-triacetoxy-6-[2-methyl-4-[3-(methylcarbamoyl)phenyl]phenoxy]tetrahydropyran-2-yl]methyl acetate.

[0191] N-methyl-3-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]benzamide (Han et. al., *J. Med. Chem.* 2012, 55, 3945−3959), (0.072 g, 0.178 mmol) was dissolved in anhydrous pyridine (1 mL) and acetic anhydride (1 mL). The solvent was removed in vacuo and the residue purified by reversed phase HPLC (5-95% acetonitrile/water/0.05% TFA). Pure fractions were combined and lyophilized to give the title compound as a white powder (0.063 g). LCMS (ESI, M + Na^+ = 594.3); ^1H NMR δ ppm (d_6-DMSO; 1.94 (s, 3 H) 2.00 (s, 3 H) 2.05 (s, 3 H) 2.16 (s, 3 H) 2.32 (s, 3 H) 2.81 (d, J=4.30 Hz, 3 H) 3.93 - 4.11 (m, 2 H)

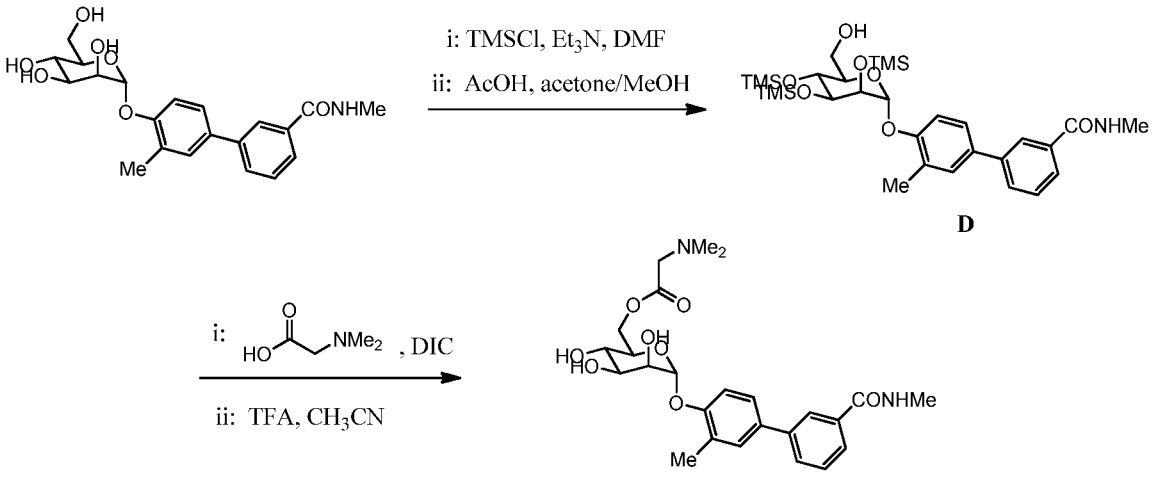
4.19 (dd, J=12.13, 5.09 Hz, 1 H) 5.22 (t, J=9.98 Hz, 1 H) 5.33 - 5.45 (m, 2 H) 5.80 (s, 1 H) 7.23 (d, J=8.61 Hz, 1 H) 7.46 - 7.65 (m, 3 H) 7.77 (d, J=7.83 Hz, 2 H) 8.07 (s, 1 H) 8.54 (d, J=4.30 Hz, 1 H)).



(**Scheme XI**)

Example 21. [(2S,3S,4S,5R,6R)-3,4,5-trihydroxy-6-[2-methyl-4-[3-(methylcarbamoyl)phenyl]phenoxy]tetrahydropyran-2-yl]methyl dihydrogen phosphate.

[0192] N-methyl-3-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]benzamide (Han et. al., *J. Med. Chem.* 2012, 55, 3945−3959), (0.20 g, 0.5 mmol) was dissolved in trimethyl phosphate (5 mL) and water (9 uL, 0.5 mmol). The reaction was cooled to 0 ºC and then phosphoryl trichloride (142 uL, 1.5 mmol) was slowly added and then stirred for 3 h at 0 ºC. The reaction was neutralized by adding crushed ice and then conc. ammonia. The solvent was removed in vacuo and the residue purified by reversed phase HPLC (5-95% acetonitrile/water/0.05% TFA). Pure fractions were combined and lyophilized to give the title compound as a white powder (0.070 g). LCMS (ESI, M + H^+ = 484.3); ^{1}H NMR δ ppm (d_6-DMSO; 2.26 (s, 3 H) 2.81 (d, J=4.70 Hz, 3 H) 3.42 - 3.68 (m, 3 H) 3.75 (dd, J=9.00, 3.13 Hz, 1 H) 3.86 - 3.97 (m, 2 H) 4.03 (dd, J=9.78, 5.87 Hz, 1 H) 5.45 (d, J=1.96 Hz, 1 H) 7.24 (d, J=8.61 Hz, 1 H) 7.43 - 7.60 (m, 3 H) 7.76 (dd, J=7.43, 1.57 Hz, 2 H) 8.06 (s, 1 H) 8.56 (d, J=4.30 Hz, 1 H)).



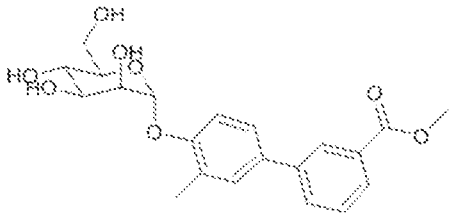
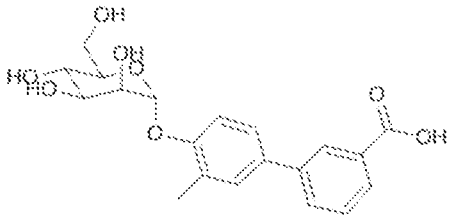
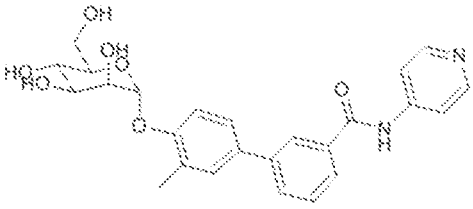
(**Scheme XII**)

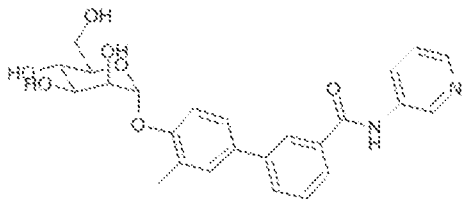
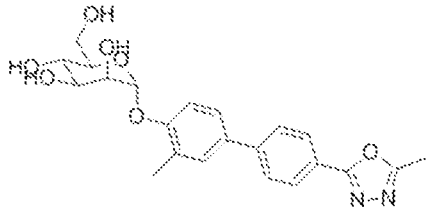
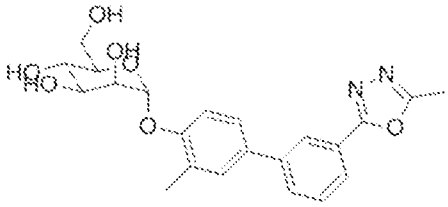
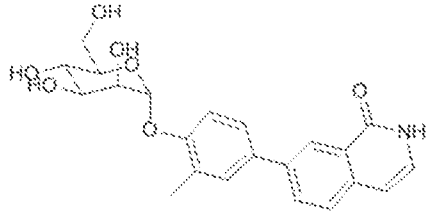
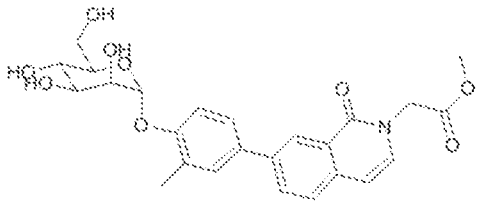
Example 22. [(2S,3S,4S,5R,6R)-3,4,5-trihydroxy-6-[2-methyl-4-[3-(methylcarbamoyl)phenyl]phenoxy]tetrahydropyran-2-yl]methyl 2-dimethylaminoacetate.

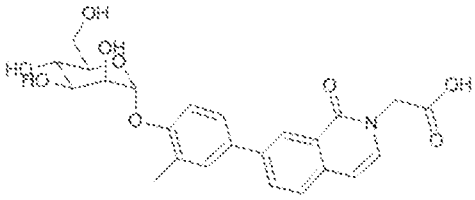
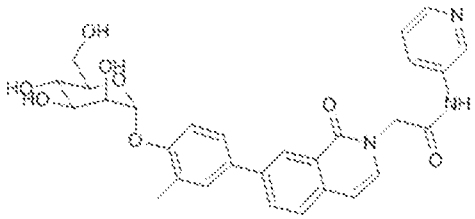
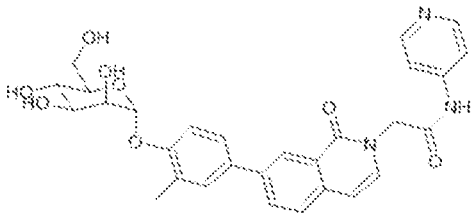
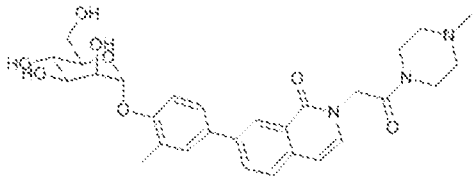
[0193] At 0 ºC TMSCl (0.35 mL, 2.75 mmol) was added slowly into the solution of N-methyl-3-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]benzamide (Han et. al., *J. Med. Chem.* 2012, 55, 3945−3959), (0.202 g, 0.5 mmol) and Et_3N (0.38 mL, 2.75 mmol) in DMF (2 mL). The mixture was stirred at RT for 3.5 h, then partitioned between EtOAc and water. The organic layer was collected, dried with Na_2SO_4 and concentrated. To the resulting residue, acetone (1 mL) and MeOH (1.5 mL) was added. Then the mixture was cooled at 0 ºC while AcOH (0.055 mL, 0.96 mmol) was added. The mixture was stirred at RT for 9 h, then $NaHCO_3$ (0.16 g, 1.9 mmol) was added. The solvents were removed. The resulting residue was purified by silica gel chromatography with a EtOAc/Hexanes gradient as eluent to give 3-[4-[(2R,3R,4S,5R,6S)-6-(hydroxymethyl)-3,4,5-tris(trimethylsilyloxy)tetrahydropyran-2-yl]oxy-3-methyl-phenyl]-N-methyl-benzamide (D), (0.190 g) in 61% yield. Into the mixture of *N,N'*-dimethylglycine hydrochloride (0.0154, 0.11 mmol), DMAP (0.0024 g, 0.02 mmol), $^{i}Pr_2NEt$ (0.035 mL, 0.2 mmol) and intermediate D (0.062 g, 0.1 mmol) in dichloromethane (2 mL) was added *N,N'*-diisopropylcarbodiimide (0.02 mL, 0.13 mmol). The mixture was stirred overnight at RT. The solvent was removed and the resulting residue was dissolved in acetonitrile (3 mL).

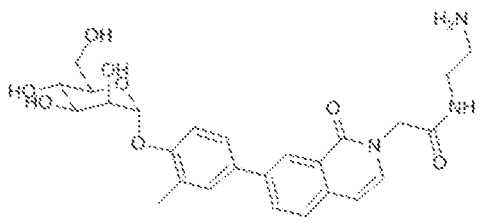
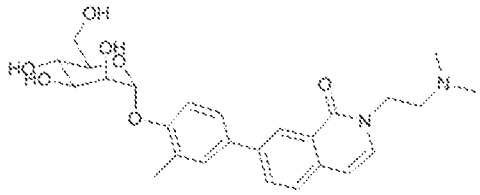
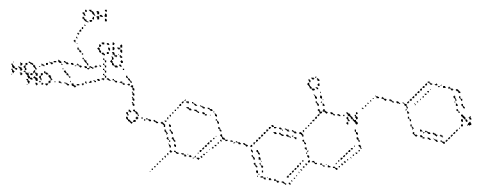
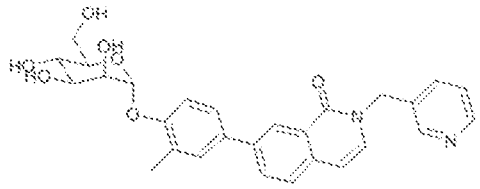
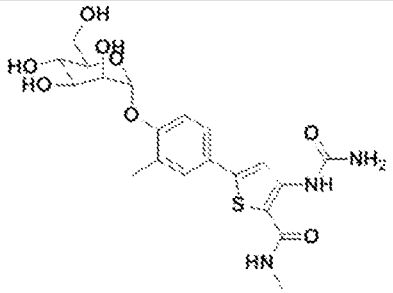
Then trifluoroacetic acid (0.08 mL) was added at 0 ºC. The mixture was stirred for 2 h at 0 ºC. The solvent was removed and the resulting residue was purified by HPLC (C18, 15*150 mm column; eluent: acetonitrile/water (0.05% TFA) to give the title compound (0.015 g) in 31% yield. LCMS (ESI, M + H^+ = 489.4); ^{1}H NMR δ ppm (d_3-MeOD; 2.32 (s, 3 H) 2.89 (s, 6 H) 2.95 (s, 3 H) 3.71 - 3.85 (m, 2 H) 3.94 - 4.00 (m, 1 H) 4.06 (d, J=5.48 Hz, 2 H) 4.11 (t, J=2.54 Hz, 1 H) 4.42 (m, 1 H) 4.61 (dd, J=11.74, 1.56 Hz, 1 H) 5.57 (d, J=1.57 Hz, 1 H) 7.23 (d, J=8.61 Hz, 1 H) 7.34 - 7.61 (m, 3 H) 7.66 - 7.88 (m, 2 H) 7.99 - 8.17 (m, 1 H)).

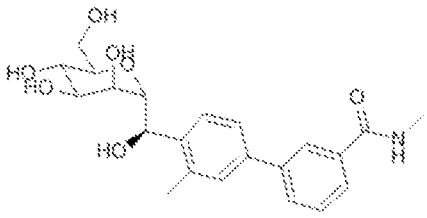
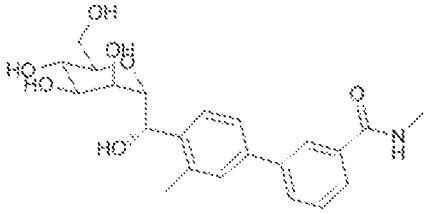
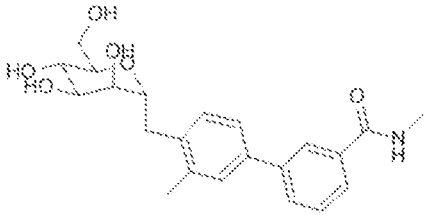
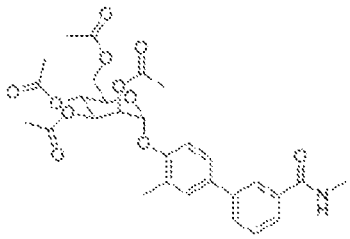
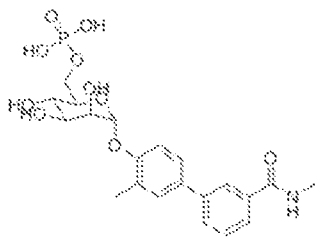
TABLE 1. Structural, analytical and biological data for Examples 1-22.

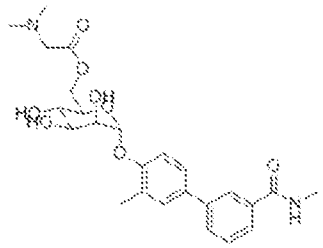
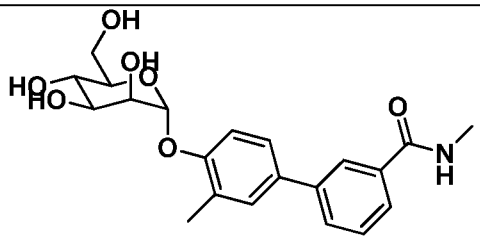
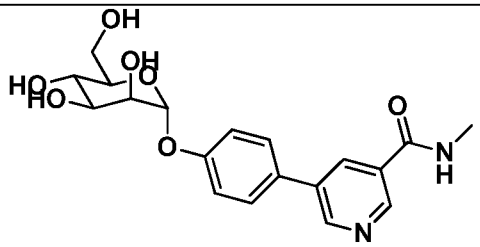
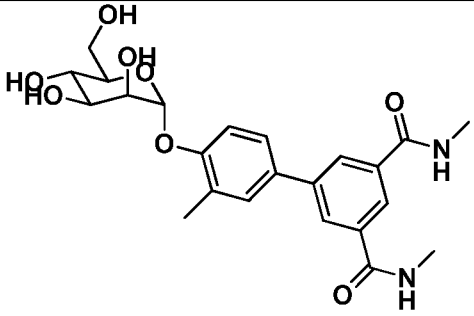
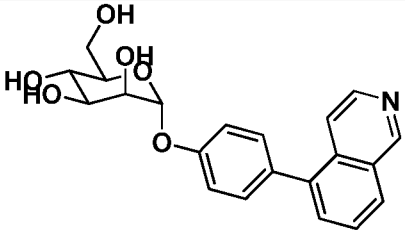
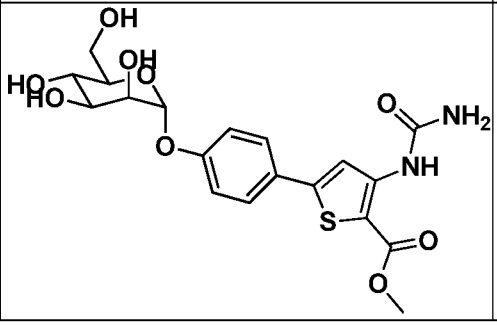
Ex.	Cmpnd Name	Structure	IUPAC Name	HAI Titer $EC_{>90}$ (μM)	Molecular Formula	MS (ESI, M + H^+)	^{1}H NMR δ ppm (d_3-MeOD unless otherwise noted)
1	1CJ84		methyl 3-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]benzoate	**0.12**	C21H24O8	427.3 (M+ Na^+)	8.20 (t, J = 1.51 Hz, 1H), 7.94 (td, J = 1.41, 7.90 Hz, 1H), 7.77-7.87 (m, 1H), 7.52 (t, J = 7.55 Hz, 1H), 7.39-7.48 (m, 2H), 7.27-7.38 (m, 1H), 5.56 (d, J = 1.65 Hz, 1H), 4.08 (dd, J = 1.92, 3.30 Hz, 1H), 3.94-4.01 (m, 1H), 3.90-3.94 (m, 3H), 3.68-3.83 (m, 3H), 3.55-3.65 (m, 1H), 2.31 (s, 3H).
2	1CJ85		3-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]benzoic acid		C20H22O8	413.3 (M+ Na^+)	2.31 (s, 3 H) 3.61 (ddd, J=9.78, 5.09, 2.74 Hz, 1 H) 3.69 - 3.84 (m, 3 H) 3.97 (dd, J=9.39, 3.52 Hz, 1 H) 4.08 (dd, J=3.33, 1.76 Hz, 1 H) 5.56 (d, J=1.96 Hz, 1 H) 7.31 (d, J=8.22 Hz, 1 H) 7.39 - 7.48 (m, 2 H) 7.51 (t, J=7.83 Hz, 1 H) 7.76 - 7.84 (m, 1 H) 7.95 (dt, J=7.83, 1.37 Hz, 1 H) 8.21 (t, J=1.76 Hz, 1 H)
3	1CJ86		3-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-N-(4-pyridyl)benzamide	**0.064**	C25H26N2O7	467.3	2.34 (s, 3 H) 3.60 (ddd, J=9.78, 5.28, 2.54 Hz, 1 H) 3.68 - 3.85 (m, 3 H) 3.98 (dd, J=9.59, 3.33 Hz, 1 H) 4.09 (dd, J=3.33, 1.76 Hz, 1 H) 5.58 (d, J=1.57 Hz, 1 H) 7.34 (d, J=8.61 Hz, 1 H) 7.44 - 7.58 (m, 2 H) 7.63 (t, J=7.63 Hz, 1 H) 7.84 - 8.00 (m, 2 H) 8.19 - 8.27 (m, 1 H) 8.37 - 8.45 (m, 2 H) 8.62 - 8.72 (m, 2 H)

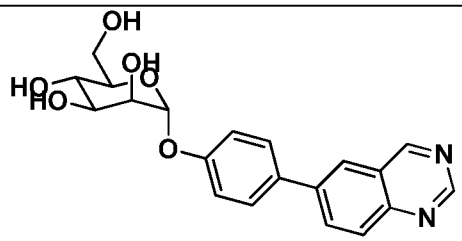
4	**1CJ87**		3-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-N-(3-pyridyl)benzamide	**0.032**	C25H26N2O7	467.3	2.33 (s, 3 H) 3.61 (m, 1 H) 3.76 (m, 3 H) 3.97 (d, J=9.39 Hz, 1 H) 4.08 (m, 1 H) 5.57 (d, 1 H) 7.33 (d, J=6.26 Hz, 1 H) 7.43 - 7.56 (m, 2 H) 7.61 (m, 1 H) 7.85 (m, 1 H) 7.94 (m, 2 H) 8.22 (m, 1 H) 8.55 (m, 1 H) 8.66 (d, J=6.26 Hz, 1 H) 9.47 (m, 1 H)
5	**1JWJ245**		(2S,3S,4S,5R,6R)-2-(hydroxymethyl)-6-[2-methyl-4-[4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]phenoxy]tetrahydropyran-3,4,5-triol	**0.062**	C22H24N2O7	429.3	2.28 (s, 3 H) 2.63 (s, 3 H) 3.53 - 3.65 (m, 1 H) 3.70 - 3.88 (m, 3 H) 3.98 (dd, J=9.59, 3.33 Hz, 1 H) 4.09 (dd, J=3.13, 1.96 Hz, 1 H) 5.57 (d, J=1.17 Hz, 1 H) 7.24 (d, J=8.22 Hz, 1 H) 7.38 - 7.45 (m, 2 H) 7.48 (s, 1 H) 7.69 (m, J=8.61 Hz, 1.5 H) 8.02 (m, J=8.22 Hz, 1.5 H)
6	**1JWJ244**		(2S,3S,4S,5R,6R)-2-(hydroxymethyl)-6-[2-methyl-4-[3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]phenoxy]tetrahydropyran-3,4,5-triol	**0.062**	C22H24N2O7	429.3	2.08 (s, 1.5 H) 2.32 (s, 1.5 H) 2.33 (s, 1.5 H) 2.65 (s, 1.5 H) 3.55 - 3.65 (m, 1 H) 3.69 - 3.83 (m, 3 H) 3.98 (dt, J=9.49, 2.69 Hz, 1 H) 4.06 - 4.12 (m, 1 H) 5.54 - 5.60 (m, 1 H) 7.27 - 7.38 (m, 1 H) 7.44- 7.65 (m, 3 H) 7.75 - 7.98 (m, 2 H) 8.07 - 8.25 (m, 1 H)
7	**5ZFH254**		7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-2H-isoquinolin-1-one	**0.030**	C22H23NO7	414.3	2.32 (s, 3 H) 3.57 - 3.67 (m, 1 H) 3.70 - 3.85 (m, 3 H) 3.94 - 4.02 (m, 1 H) 4.05 - 4.13 (m, 1 H) 5.57 (d, *J*=1.57 Hz, 1 H) 6.70 (d, *J*=7.00 Hz, 1 H) 7.17 (d, *J*=7.04 Hz, 1 H) 7.33 (d, *J*=8.22 Hz, 1 H) 7.54 (s, 2 H) 7.70 (d, *J*=8.61 Hz, 1 H) 7.89 - 8.04 (m, 1 H) 8.49 (d, *J*=1.96 Hz, 1 H)
8	**1CJ74**		methyl 2-[7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-1-oxo-2-isoquinolyl]acetate	**0.006**	C25H27NO9	486.3	2.32 (s, 3 H) 3.61 (ddd, J=9.68, 4.99, 2.54 Hz, 1 H) 3.68 - 3.85 (m, 3 H) 3.78 (s, 3H) 3.98 (dd, J=9.59, 3.33 Hz, 1 H) 4.04 - 4.14 (m, 1 H) 4.82 (s, 2 H) 5.53 - 5.62 (m, 1 H) 6.72 (d, J=7.04 Hz, 1 H) 7.32 (dd, J=7.83, 3.91 Hz, 2 H) 7.44 - 7.58 (m, 2 H) 7.70 (d, J=8.22 Hz, 1 H) 7.97 (dd, J=8.22, 1.96 Hz, 1 H) 8.43 - 8.49 (m, 1 H)

9	1CJ72B		2-[7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-1-oxo-2-isoquinolyl]acetic acid	**0.016**	C24H25NO9	472.3	2.32 (s, 3 H) 3.61 (ddd, J=9.59, 5.28, 2.35 Hz, 1 H) 3.67 - 3.86 (m, 3 H) 3.98 (dd, J=9.59, 3.33 Hz, 1 H) 4.08 (dd, J=3.33, 1.76 Hz, 1 H) 4.79 (s, 2 H) 5.50 - 5.62 (m, 1 H) 6.72 (d, J=7.43 Hz, 1 H) 7.32 (dd, J=8.02, 2.93 Hz, 2 H) 7.44 - 7.59 (m, 2 H) 7.70 (d, J=8.22 Hz, 1 H) 7.97 (dd, J=8.22, 1.96 Hz, 1 H) 8.44 - 8.55 (m, 1 H)
10	1CJ75		2-[7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-1-oxo-2-isoquinolyl]-N-(3-pyridyl)acetamide	**0.001**	C29H29N3O8	548.4	2.32 (s, 3 H) 3.55 - 3.66 (m, 1 H) 3.66 - 3.85 (m, 3 H) 3.97 (dd, J=9.59, 3.33 Hz, 1 H) 4.08 (dd, J=3.13, 1.96 Hz, 1 H) 4.96 (s, 2 H) 5.46 - 5.63 (m, 1 H) 6.77 (d, J=7.04 Hz, 1 H) 7.27 - 7.44 (m, 2 H) 7.46 - 7.58 (m, 2 H) 7.73 (d, J=8.22 Hz, 1 H) 7.88 (dd, J=8.61, 5.48 Hz, 1 H) 8.00 (dd, J=8.22, 1.96 Hz, 1 H) 8.42 (dd, J=8.61, 1.17 Hz, 1 H) 8.49 (s, 2 H) 9.18 - 9.29 (m, 1 H)
11	1CJ81		2-[7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-1-oxo-2-isoquinolyl]-N-(4-pyridyl)acetamide	**0.001**	C29H29N3O8	548.4	2.32 (s, 3 H) 3.60 (ddd, J=9.78, 5.09, 2.74 Hz, 1 H) 3.67 - 3.84 (m, 3 H) 3.97 (dd, J=9.59, 3.33 Hz, 1 H) 4.08 (dd, J=3.33, 1.76 Hz, 1 H) 5.00 (s, 2 H) 5.57 (d, J=1.57 Hz, 1 H) 6.78 (d, J=7.43 Hz, 1 H) 7.38 (d, J=7.43 Hz, 2 H) 7.33 (d, J=8.61 Hz, 1 H) 7.49 - 7.58 (m, 2 H) 7.75 (d, J=8.22 Hz, 1 H) 8.01 (dd, J=8.41, 2.15 Hz, 1 H) 8.18 (m, J=7.04 Hz, 2 H) 8.49 (d, J=1.96 Hz, 1 H) 8.64 (m, J=7.43 Hz, 2 H)
12	1CJ82		2-[2-(4-methylpiperazin-1-yl)-2-oxo-ethyl]-7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]isoquinolin-1-one	**0.008**	C29H35N3O8	554.4	2.33 (s, 3 H) 2.99 (s, 3 H) 3.26 (dt, J=3.23, 1.71 Hz, 1 H) 3.34 - 3.42 (m, 1 H) 3.49 (dd, J=3.52, 1.57 Hz, 1 H) 3.61 (ddd, J=9.78, 5.28, 2.54 Hz, 3 H) 3.70 - 3.86 (m, 4 H) 3.97 (dd, J=9.59, 3.33 Hz, 2 H) 4.08 (dd, J=3.52, 1.96 Hz, 2 H) 4.81 (s, 1 H) 5.57 (d, J=1.96 Hz, 1 H) 6.75 (d, J=7.43 Hz, 1 H) 7.20 - 7.40 (m, 3 H) 7.45 - 7.59 (m, 2 H) 7.72 (d, J=8.22 Hz, 1 H) 7.99 (dd, J=8.22, 1.96 Hz, 1 H) 8.49 (d, J=1.96 Hz, 1 H)

13	**1CJ76**		N-(2-aminoethyl)-2-[7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-1-oxo-2-isoquinolyl]acetamide	**0.016**	C26H31N3O8	514.4	2.33 (s, 3 H) 3.11 (t, J=5.67 Hz, 2 H) 3.54 (t, J=5.67 Hz, 2 H) 3.56 - 3.67 (m, 1 H) 3.68 - 3.84 (m, 3 H) 3.97 (dd, J=9.59, 3.33 Hz, 1 H) 4.08 (dd, J=3.33, 1.76 Hz, 1 H) 4.73 (s, 2 H) 5.48 - 5.64 (m, 1 H) 6.78 (d, J=7.43 Hz, 1 H) 7.34 (d, J=7.83 Hz, 2 H) 7.46 - 7.59 (m, 2 H) 7.74 (d, J=8.22 Hz, 1 H) 8.00 (dd, J=8.22, 1.96 Hz, 1 H) 8.50 (s, 1 H)
14	**1CJ70**		2-(2-dimethylaminoethyl)-7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]isoquinolin-1-one	**0.012**	C26H32N2O7	485.4	2.33 (s, 3 H) 3.05 (s, 6 H) 3.52 - 3.67 (m, 3 H) 3.68 - 3.84 (m, 3 H) 3.97 (dd, J=9.39, 3.52 Hz, 1 H) 4.08 (dd, J=3.33, 1.76 Hz, 1 H) 4.46 (t, J=5.87 Hz, 2 H) 5.47 - 5.64 (m, 1 H) 6.80 (d, J=7.43 Hz, 1 H) 7.38 (d, J=7.43 Hz, 1 H) 7.34 (d, J=8.61 Hz, 1 H) 7.47 - 7.59 (m, 2 H) 7.73 (d, J=8.61 Hz, 1 H) 8.01 (dd, J=8.41, 1.76 Hz, 1 H) 8.49 - 8.60 (m, 1 H)
15	**1CJ66**		7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-2-(4-pyridylmethyl)isoquinolin-1-one	**0.004**	C28H28N2O7	505.4	2.32 (s, 3 H) 3.53 - 3.66 (m, 1 H) 3.67 - 3.83 (m, 3 H) 3.96 (dd, J=9.59, 3.33 Hz, 1 H) 4.07 (dd, J=3.13, 1.96 Hz, 1 H) 5.52 (s, 2 H) 5.56 (s, 1 H) 6.84 (d, J=7.43 Hz, 1 H) 7.33 (d, J=8.61 Hz, 1 H) 7.44 - 7.57 (m, 3 H) 7.70 - 7.86 (m, 3 H) 8.02 (dd, J=8.22, 1.96 Hz, 1 H) 8.49 (s, 1 H) 8.73 (d, J=6.65 Hz, 2 H)
16	**1CJ68**		7-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-2-(3-pyridylmethyl)isoquinolin-1-one	**0.008**	C28H28N2O7	505.4	2.32 (s, 3 H) 3.51 - 3.66 (m, 1 H) 3.66 - 3.85 (m, 3 H) 3.97 (dd, J=9.59, 3.33 Hz, 1 H) 4.08 (dd, J=3.13, 1.57 Hz, 1 H) 5.42 (s, 2 H) 5.56 (s, 1 H) 6.80 (d, J=7.43 Hz, 1 H) 7.33 (d, J=8.22 Hz, 1 H) 7.43 - 7.61 (m, 3 H) 7.72 (d, J=8.22 Hz, 1 H) 7.89 (dd, J=8.02, 5.67 Hz, 1 H) 7.99 (dd, J=8.41, 1.76 Hz, 1 H) 8.42 (d, J=8.22 Hz, 1 H) 8.46 - 8.54 (m, 1 H) 8.71 (d, J=5.48 Hz, 1 H) 8.86 (s, 1 H)
17	**5ZFH302**		N-methyl-5-[3-methyl-4-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]oxy-phenyl]-3-ureido-thiophene-2-carboxamide	**0.024**	C20H25N3O8S	468.3	2.27 (s, 3 H) 2.87 (s, 3 H) 3.52 - 3.61 (m, 1 H) 3.76 (d, *J*=1.17 Hz, 3 H) 3.91 - 3.99 (m, 1 H) 4.03 - 4.09 (m, 1 H) 5.56 (d, *J*=1.17 Hz, 1 H) 7.27 (m, 1 H) 7.47 (m, 2 H) 8.06 (s, 1 H)

18A	**5ZFH240**		3-[4-[(R)-hydroxy-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]methyl]-3-methyl-phenyl]-N-methyl-benzamide	**0.031**	C21H26NO7	440.3 ($M+Na^+$)	2.51 (s, 3 H) 2.95 (s, 3 H) 3.57 - 3.78 (m, 4 H) 4.00 - 4.07 (m, 1 H) 4.10 (dd, *J*=6.85, 2.54 Hz, 1 H) 4.25 (t, *J*=2.93 Hz, 1 H) 5.24 (d, *J*=6.65 Hz, 1 H) 7.45 - 7.57 (m, 3 H) 7.62 (d, *J*=8.22 Hz, 1 H) 7.71 - 7.83 (m, 2 H) 8.07 (t, *J*=1.56 Hz, 1 H)
18B	**5ZFH244**		3-[4-[(S)-hydroxy-[(2R,3R,4S,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]methyl]-3-methyl-phenyl]-N-methyl-benzamide	**6.000**	C21H26NO7	440.3 ($M+Na^+$)	2.51 (s, 3 H) 2.95 (s, 3 H) 3.56 (dd, *J*=1.00 Hz, 1 H) 3.67 (m, 1 H) 3.70 - 3.82 (m, 3 H) 3.91 (m, 1 H) 4.10 (dd, *J*=9.00, 1.96 Hz, 1 H) 5.28 (d, *J*=8.61 Hz, 1 H) 7.34 - 7.63 (m, 4 H) 7.69 - 7.90 (m, 2 H) 8.07 (s, 1 H)
19	**5ZFH247**		N-methyl-3-[3-methyl-4-[[(2R,3R,4R,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]methyl]phenyl]benzamide	**2.000**	C22H27NO6	402.3	2.44 (s, 3 H) 2.95 (s, 3 H) 3.04 (d, *J*=7.43 Hz, 2 H) 3.69 (m, 3 H) 3.83 (m, 2 H) 3.86 - 3.92 (m, 1 H) 4.04 - 4.21 (m, 1 H) 7.31 (d, *J*=7.83 Hz, 1 H) 7.42 - 7.47 (m, 1 H) 7.50 (m, 2 H) 7.75 (m, 2 H) 8.05 (s, 1 H)
20	**1JWJ231**		[(2S,3R,4S,5R,6R)-3,4,5-triacetoxy-6-[2-methyl-4-[3-(methylcarbamoyl)phenyl]phenoxy]tetrahydropyran-2-yl]methyl acetate		C29H33NO11	594.3 ($M+Na^+$)	[d_6-DMSO] 1.94 (s, 3 H) 2.00 (s, 3 H) 2.05 (s, 3 H) 2.16 (s, 3 H) 2.32 (s, 3 H) 2.81 (d, J=4.30 Hz, 3 H) 3.93 - 4.11 (m, 2 H) 4.19 (dd, J=12.13, 5.09 Hz, 1 H) 5.22 (t, J=9.98 Hz, 1 H) 5.33 - 5.45 (m, 2 H) 5.80 (s, 1 H) 7.23 (d, J=8.61 Hz, 1 H) 7.46 - 7.65 (m, 3 H) 7.77 (d, J=7.83 Hz, 2 H) 8.07 (s, 1 H) 8.54 (d, J=4.30 Hz, 1 H)
21	**1JWJ232**		[(2S,3S,4S,5R,6R)-3,4,5-trihydroxy-6-[2-methyl-4-[3-(methylcarbamoyl)phenyl]phenoxy]tetrahydropyran-2-yl]methyl dihydrogen phosphate		C21H26NO10P	484.3	[d_6-DMSO] 2.26 (s, 3 H) 2.81 (d, *J*=4.70 Hz, 3 H) 3.42 - 3.68 (m, 3 H) 3.75 (dd, *J*=9.00, 3.13 Hz, 1 H) 3.86 - 3.97 (m, 2 H) 4.03 (dd, *J*=9.78, 5.87 Hz, 1 H) 5.45 (d, *J*=1.96 Hz, 1 H) 7.24 (d, *J*=8.61 Hz, 1 H) 7.43 - 7.60 (m, 3 H) 7.76 (dd, *J*=7.43, 1.57 Hz, 2 H) 8.06 (s, 1 H) 8.56 (d, *J*=4.30 Hz, 1 H)

22	6ZFH123		[(2S,3S,4S,5R,6R)-3,4,5-trihydroxy-6-[2-methyl-4-[3-(methylcarbamoyl)phenyl]phenoxy]tetrahydropyran-2-yl]methyl 2-dimethylaminoacetate		C25H32N2O8	489.4	2.32 (s, 3 H) 2.89 (s, 6 H) 2.95 (s, 3 H) 3.71 - 3.85 (m, 2 H) 3.94 - 4.00 (m, 1 H) 4.06 (d, *J*=5.48 Hz, 2 H) 4.11 (t, *J*=2.54 Hz, 1 H) 4.42 (m, 1 H) 4.61 (dd, *J*=11.74, 1.56 Hz, 1 H) 5.57 (d, *J*=1.57 Hz, 1 H) 7.23 (d, *J*=8.61 Hz, 1 H) 7.34 - 7.61 (m, 3 H) 7.66 - 7.88 (m, 2 H) 7.99 - 8.17 (m, 1 H)
23							
24							
25							
26							
27							

28							

Example 23. Biological and in vivo activity of compounds of Examples 1-22.

[0194] The inventors set out to develop and optimize orally active mannoside small-molecule antagonists of FimH bacterial adhesion for treatment and prevention of recurring urinary tract infection (UTI). The endpoint desired to determine orally active compounds was drug unchanged in the urine and/or bladder. First, the inventors rationally designed biaryl mannosides with potency and desirable properties. To do this, structure activity relationships (SAR) of substituents was determined. Ortho substitution on the biaryl ring was evaluated for FimH activity. Solubility, LogD and pKa was improved with heterocycles. It was further discovered that replacements to the glycosidic bond could improve metabolic stability and bioavailability. Alternate linkers of mannose to the biaryl ring were identified. N-, S- and C- mannosides were synthesized. Murine animal models of both acute and chronic UTI were used to further evaluate compound efficacy.

[0195] The inventors have developed compounds with a 2000-fold increase in cellular potency by X-ray structure-based design. Mannosides show good oral compound exposure for 6h at 100 mg/kg dose and prophylactically prevent IBC formation of UTI89 bacteria *in vivo*. Some metabolism/hydrolysis products (phenol) detected in the urine. Importantly, mannosides reverse antibiotic TMP-SMZ resistant strains of UTI *in vivo*. Ongoing optimization for decreased CI, increase $t_{1/2}$, V_{dss} (tissue exposure), and improved bioavailability by compound PK screeining in plasma and urine. Also, ongoing efficacy model development for demonstrating antibacterial effects post-infection as monotherapy and in combination with antibiotics. Further, the inventors are optimizing prodrugs and non-sugar mannoside mimetics.

[0196] The efficacy of *in vivo* mannoside treatment was evaluated after orally dosing animals with 50 mg/kg of mannosides ZFH-4269 (**Fig. 1A**), ZFH-5254 (**Fig. 1B**) and ZFH-5240 (**Fig. 1C**) or DMSO or PBS 30 min prior to infecting with UTI89. At 6

hours post-infection (hpi) the bladders were removed and total bacterial CFUs were quantitated. In all three of the mannoside-treated cohorts, there was a drop in bacterial counts demonstrating the efficacy of these mannosides in reducing overall colonization of the bladder (**Fig. 1D).** Next, analogs of 254 were evaluated in the same mouse model of urinary tract infection. Animals were orally dosed with 25 mg/kg of mannosides ZFH-4269 (**Fig. 2A**), 1CJ68 (**Fig. 2B**) and 1CJ70 (**Fig. 2C**) in 10% cyclodextrin or 10% cyclodextrin 30 min prior to infecting with UTI89. In the ZFH269-treated cohort, there was a drop in bacterial counts demonstrating the efficacy of this mannoside in reducing overall colonization of the bladder (**Fig. 2D).**

[0197] Mannoside compounds FIM-4269, FIM-5240, FIM-5254, FIM-1CJ82 and FIM-1CJ66 (**Fig. 3**) were evaluated for pharmacokinetics in the rat. Mannosides were dose IV at 3 mg/kg and PO at 10 mg/kg. Urine and plasma were collected at 15 min, 30 min, 1 hour, 2 hours, 4 hours and 8 hours. Following IV dosing, the mean plasma concentration of FIM-5240 was the highest relative to the other 4 mannosides and remained above the limit of detection to 2.5 hours (**Fig. 4**). Following PO dosing, again FIM-5240 exhibited the best pharmacokinetics relative to the other mannosides and feel below the limit of dection at 2 hours post-treatment (**Fig. 5**).

[0198] Based on these results, oral PK studies were performed in mice. Compounds ZFH-4269 (**Fig. 6A**), ZFH-5254 (**Fig. 6B**), ZFH5240 (**Fig. 6C**), and a Prodrug were dosed at 50 mg/kg and plasma and urine samples were taken at 1, 3, 6 and 8 hours after dosing. As demonstrated in **Fig. 6D**, all compounds were detectable in the urine out to 8 hours post-treatment. It was found that compounds 240 and the prodrug consistently maintained a high level of concentration in the urine, which is well above the predicted minimum effective concentration within a 6-hour period. Taken together, the high oral bioavailability and *in vivo* efficacy obsereved in animal studies support mannosides as promising therapeutic candidates for UTI treatment/prevention.

[0199] The efficacy of *in vivo* mannoside treatment was evaluated after orally dosing animals with 25 mg/kg of mannosides ZFH269, Prodrug FIM-4269, ZFH-5254, and ZFH-5240 in 10% cyclodextrin or 10% cyclodextrin 30 min prior to infecting with UTI89. At 6 hours post-infection (hpi) the bladders were removed and total bacterial CFUs were quantitated. In all of the mannoside-treated cohorts, there was a drop in

bacterial counts demonstrating the efficacy of these mannosides in reducing overall colonization of the bladder (**Fig. 7A).** Importantly, the prodrug of ZFH269 exhibited significantly better activity than ZFH269. Next, several different prodrugs were evaluated in the same mouse model of urinary tract infection. Animals were orally dosed with 25 mg/kg of mannosides ZFH-4269, prodrug FIM-1233 (**Fig. 8B**), prodrug FIM-6123 (**Fig. 8C**) and prodrug 269 in 10% cyclodextrin or 10% cyclodextrin 30 min prior to infecting with UTI89. In all of the mannoside-treated cohorts, there was a drop in bacterial counts demonstrating the efficacy of these mannosides in reducing overall colonization of the bladder (**Fig. 7B**).

Example 24. Uropathogenic *E. coli* (UPEC) pathogenesis in the urinary tract.

[0200] Clinically, it has been presumed that UPEC infection consists of a relatively simple extracellular colonization of the luminal surface after inoculation of fecal flora into the bladder via the urethra. In contrast, using a murine model of UPEC infection of the UT, the inventors have detailed an unexpectedly complex UPEC pathogenesis cycle that involves both intracellular and extracellular niches. Using genetic, biochemical and cell biological approaches together with a variety of imaging techniques including transmission, quick freeze-deep etch and scanning electron microscopy, as well as confocal and time lapse video microscopy, the inventors discovered that UPEC invade bladder facet cells via a FimH-dependent mechanism (see below). After invasion, cytoplasmic intracellular bacterial communities (IBCs) are formed. Rapid replication of the initial invading bacteria results in the formation of an early IBC of loosely-packed rod-shaped bacteria. The bacteria continue to replicate and progress to form a large densely packed mid-stage IBC of morphologically coccoid bacteria, with biofilm-like characteristics including positive periodic acid-Schiff (PAS) staining and differential gene expression throughout the community. After the IBC matures, bacteria detach from the biomass, often become filamentous, and spread to neighboring cells forming new generation IBCs. Thus, the IBC pathway facilitates massive expansion of the invading bacteria in a niche protected from host defenses. Translational studies have shown that the majority of UPEC isolates form IBCs when introduced into the murine bladder and that IBCs and filamentous bacteria occur in the urine of human UTI patients. Population dynamic

studies conducted by the inventors using *ex vivo* gentamicin protection assays demonstrated that ~10^4 UPEC of an initial 10^7 inoculum invaded the bladder tissue within 15 minutes after infection and that one percent of the invaded bacteria went on to form IBCs, resulting in an average of 100 IBCs per infected mouse bladder. If this is extrapolated to the human situation, innate defenses in the bladder most likely prevent the majority of bacterial inoculation events into the bladder from leading to disease. However, the ramifications of the IBC cascade are striking. Invasion of a single infecting bacterium can lead to rapid expansion of the infection via IBC formation, replicating within hours to 10^4 bacteria and even higher numbers followed by dispersal of the bacteria from the biomass and spreading to neighboring cells to reinitiate the IBC cascade. This process allows the bacteria to gain a critical foothold. Bacterial descendents of the acute IBC cascade have been shown using a murine model, to be able to form a quiescent intracellular reservoir (QIR) that can persist, protected from antibiotics and seemingly undetected by the host immune system even after the acute infection is resolved and bacteria are no longer detectable in the urine. Bacteria in the QIR can later seed a recurrent infection, manifested by IBC formation, bacteruria and inflammation.

Example 25. <u>FimH as a therapeutic target.</u>

[0201] There are several key implications from understanding UPEC pathogenesis. Mannosides and pilicides that block FimH function will prevent bacterial adherence and invasion and thus prevent bacterial amplification in the IBC and subsequent spreading and repeated rounds of amplification via new generation IBCs. These compounds will have potent therapeutic activity by preventing bacterial expansion which may also have the consequence of eliminating or significantly reducing the QIR thus reducing predisposition to recurrent infection.

Type 1 pili / FimH are critical for UPEC pathogenesis in the UT.

[0202] Type 1 pili are essential cystitis virulence determinants. Using scanning and high-resolution EM and the mouse cystitis model developed by the inventors, it was shown that adhesive type 1 piliated bacteria are able to bind and invade host superficial umbrella cells, while UPEC lacking type 1 pili are not. Colonization and invasion of the bladder epithelium is dependent on the FimH adhesion located at the distal end of the

pilus that binds mannose residues on bladder epithelial cells. High-resolution freeze-dry/deep-etch EM revealed that FimH interacts directly with receptors on the luminal surface of the bladder (**Fig. 11).** Standard gentamicin protection assays of infected tissue culture cells and *ex vivo* gentamicin treatment of infected bladders demonstrated that *fimH*$^{+}$ type 1 piliated clinical cystitis isolates, but not *fimH*$^{-}$ mutants, could invade bladder epithelial cells. Using immunohistochemistry and *Pfim-gfp* transcriptional fusions it was demonstrated that type 1 pili are expressed within IBCs. Using high-resolution EM, pilus-like fibers radiating from bacteria and interacting with matrix material within the intracellular IBC were also visualized**.** These results combined with work showing that type 1 pili are required for biofilm formation in *in vitro* systems led to the hypothesis that type 1 pili promote IBC formation and/or maintenance. Therefore, an anhydrotetracycline (AHT) inducible *fim* strain was constructed which can be "pre-piliate" UTI89 *in vitro* by growth in AHT before infecting mouse bladders, allowing the initial invasion event to normally. However, once inoculated into the mouse, AHT is no longer present, *fim* transcription ceases and piliation is diluted upon each bacterial division. Using this system, the earliest events of colonization and invasion were identical between the wild type and conditional strain. However, the inability of the conditional strain to produce type 1 pili intracellularly abolished its ability to form IBCs, as shown by confocal microscopy, and thus dramatically attenuated virulence as determined by CFUs at later time points. These results strongly suggest that type 1 pili are required for the survival and proliferation of UPEC within superficial facet cells. Additionally, this conditional mutant is significantly impaired in its ability to form QIRs, arguing that the bacteria in QIRs are descendents and thus dependent on the acute IBC cascade.

Structural studies of FimH and its ligand.

[0203] Adhesive type 1 pili are prototypic structures of a family of adhesive fibers produced by diverse Gram-negative bacteria via the chaperone/usher assembly pathway. Using biochemistry, mutational studies, nuclear magnetic resonance, and x- ray crystallography, the molecular basis of pili assembled by the chaperone/usher pathway in gram-negative bacteria, including type 1 pili of UPEC, were delineated (**Fig. 12**) The three

dimensional structure of FimH bound to its mannose receptor was solved in order to gain a molecular snapshot of a critical initial event in UTI pathogenesis.

[0204] FimH is a two domain protein, with a receptor binding domain linked to a typical pilin domain that joins the adhesin to the pilus fiber. The structure of the complex of the FimC chaperone bound to FimH (which was bound to D-mannopyranoside) was determined to 2.8Å resolution. The mannose binding site of FimH is a deep negatively charged pocket at the tip of its receptor-binding domain. The FimH pocket engages in extensive hydrogen bonding to mannose (**Fig. 14),** which are abundant in the oligosaccharide moieties of uroplakins that coat the lumenal surface of the bladder epithelium. A hydrophobic ridge surrounds the mannose binding pocket in a manner that may facilitate polar interactions within the FimH pocket. Mutational studies revealed that each residue is critical in mannose binding and pathogenesis, emphasizing why the pocket is invariant among UPEC isolates.

Devlopment of anti-adhesives.

[0205] The FimH-mannose interaction was further investigated in an effort to develop potential ligand-based antagonists of UTIs. The chitobiose unit on oligomannose was found to bridge various mannose derivatives to the asparagine in the Asn-X-Ser/Thr motif of FimH resulting in higher affinity binding. Crystallization of FimH in complex with oligomannose-3 revealed the mechanism of this higher affinity binding. The non-reducing Man4 anchors into the mannose-binding pocket while the GlcNAc folds over Thr51 allowing specific interactions with a hydrophobic tyrosine gate. Heptyl mannoside mimics the GlcNAc tail of oligomannose-3 and extends it further to increase interactions outside the binding pocket resulting in high affinity binding (Kd = 5 nM). Based on the high affinity of heptyl mannose for FimH, the ability of heptyl mannose to reduce bacterial infection in our mouse model of UTI was tested. First, biofilm formation as a surrogate for IBCs formed in the bladder was evaluated. Heptyl mannose at 1 mM inhibited UPEC biofilm formation *in vitro,* suggesting that the mannose binding properties of the FimH adhesin is required for biofilm formation. Thus, UPEC strain UTI89 was incubated with heptyl mannose prior to inoculation into the bladders of mice. This resulted in a significant attenuation of virulence at 6 hours post-infection at 5 mM heptyl mannose. The ability of these compounds to significantly attenuate virulence establishes mannosides as a

potential treatment for UTI. Therefore, more potent mannosides that mimic the natural receptor for FimH but with increased affinity and avidity in order to ultimately block bacterial colonization, invasion, IBC formation and disease were developed as described below.

Example 26. Mannosides inhibit the invasion of UPEC into the bladder tissue and potentiate the efficacy of TMP-SMZ.

[0206] The first-line treatment of choice for UTI has traditionally been a 3-day course of TMP-SMZ. Women suffering from chronic/recurrent UTIs are often given TMP-SMZ prophylactically to prevent recurrence. However, resistance to this TMP-SMZ regimen is rapidly expanding. It was hypothesized that by preventing bacterial invasion into the bladder tissue, a FimH inhibitor may result in anti-virulence synergism with TMP-SMZ and may curtail or circumvent the problem of TMP-SMZ resistance. This theory was evaluated in a preclinical animal model where mice given TMP-SMZ for 3 days were infected with either UTI89 or the TMP-SMZ^R strain, PBC-1. Mice were IP treated with 6 30 min prior to inoculation with bacteria and compared to a control group of untreated animals. After inoculation with UTI89 or PBC-1, bacterial CFUs were quantified at 6 hpi. As expected, treatment with TMP-SMZ alone resulted in a significant drop in bacterial load in the UTI89-infected mice but had no effect on PBC-1, since it is resistant to TMP-SMZ. Upon treatment with **6** alone there was a significant drop in bacterial load of both strains in the bladder. In the dual treatment group there was also a significant drop in bacterial CFUs compared to mannoside alone or TMP-SMZ alone for both strains which was most pronounced for PBC-1 (**Fig. 18**). It was determined that the presence of mannoside had no effect on growth or killing efficiency of either strain during growth in vitro in the presence or absence of TMP-SMZ. Therefore, the observation that in combination with **6**, the TMP-SMZ^R strain PBC-1 succumbed to antibiotic treatment suggested that the mannoside potentiates the efficacy of TMP-SMZ by a unique mechanism. Based on growth curves in TMP-SMZ, PBC-1 was calculated to have a Minimum Inhibition Concentration (MIC) of 256 and 1280 μg/ml for TMP and SMZ, respectively and UTI89 was calculated to have an MIC of 0.05 μg/ml TMP and 0.25 μg/ml SMZ. The presence of mannoside had no effect on growth or killing

efficiency of either strain. It is well established that TMP concentrates in the urine and this serendipitous feature is a major reason TMP-SMZ has been the preferred antibiotic for UTI over the last several decades. Using quantitative HPLC-MS, the concentration of TMP-SMZ was measured in the urine of mice after 3 days of treatment with 54 μg/ml and 270 μg/ml TMP and SMZ, respectively. TMP concentrations were determined to be 9.95 +/- 4.36 mg/ml and SMZ at 67.17 +/- 32.51 μg/ml. These results indicate that by preventing bacterial invasion, **6** compartmentalizes the microbes to the bladder lumen thus exposing them to TMP-SMZ concentrations above the MIC of PBC-1, resulting in augmentation of bacterial cell killing. Presumably TMP-SMZ concentrations reach tissue concentrations above the MIC needed for UTI89 killing but fail to reach tissue levels needed for killing PBC-1. These results clearly highlight the importance of the intracellular pathway in bacterial persistence. In addition to escaping the immune system in their intracellular niche, bacteria are also able to evade exposure to antibiotics as highlighted by the clinically TMP-SMZ resistant strain. In summary, mannosides could benefit those women on suppressive antibiotic therapy by inhibiting the invasion of UPEC into the bladder tissue and potentiating the efficacy of TMP-SMZ creating a cost-effective treatment, which is predicted to lower the rate of treatment failures.

Example 27. Mannoside treatment reduces IBC formation in CAUTI.

[0207] Having established that FimH is required for UPEC virulence in implanted bladders, we investigated this as a potential therapeutic target for CAUTI using small molecules inhibitors designed to interfere with FimH binding to mannosylated residues. This family of small molecules, called mannosides, has recently been shown to prevent acute and chronic UPEC infections and potentiated the effectiveness of antibiotics in combinatorial treatment.

[0208] To investigate the potential therapeutic effects of mannosides on CAUTI, we first assessed the inhibitory effects of methyl-α-D-mannopyranoside (methyl mannose), on UTI89 biofilm formation in urine under flow. Similar to the deletion of *fimH*, UTI89 biofilms grown in presence of 1% methyl mannose had significantly reduced biomass (p=0.0022) and biofilm-adherent cells (p=0.0012), compared to untreated controls. Since methyl mannose is a FimH antagonist, these data confirm the

critical role of type 1 pili to biofilm formation in urine as was previously described for biofilms formed in LB media.

[0209] The effects of mannoside treatment were then assessed *in vivo* by using IBC formation as well as implant and urinary tract colonization as benchmarks of disease progression. Mice were treated intraperitoneally (i.p.) with saline or 5mg/kg of mannoside 6, which is more potent than methyl mannose *in vitro* and *in vivo*, in PBS 30 min prior to urinary implantation. Catheter implantation was immediately followed by transurethral inoculation of UTI89. IBC formation and bacterial colonization were assayed by LacZ staining and CFU enumeration of implants, bladders, and kidneys at 6hpi and 24hpi, respectively. Mannoside treatment further reduced IBC formation (p=0.0051) and bladder colonization (p=0.0114) in implanted animals at 6hpi, suggesting that this treatment prevents intracellular infection. While eliminated from their intracellular niche, data further indicated that UPEC were able to persist in the extracellular milieu where they can colonize the surface of the implants to relatively similar levels as saline-treated animals (p=0.0547). No statistical difference was observed in kidney colonization in the presence or absence of mannosides. By 24hpi, a time point at which the mannosides have been eliminated from the bladder, similar bacterial loads were recovered from implants, bladders, and kidneys in implanted animals in the presence or absence of mannoside treatment.

Example 28. Mannoside treatment increases the efficiency of TMP-SMZ in preventing UPEC colonization.

[0210] In order to examine whether mannosides could prevent establishment of CAUTI when used in combination with antibiotics, animals were treated with 54 and 270μg/ml of TMP-SMZ, respectively, in their drinking water for three days and then treated with saline or mannoside (5mg/kg) i.p. 30 min prior to implantation and bacterial inoculation. At 6hpi, UPEC colonized the implants and bladders at significantly lower levels in animals that only received antibiotics compared to those who received water or were only administered mannoside. Interestingly, mannoside treatment in addition to TMP-SMZ further decreased UPEC colonization of implants, bladders, and kidneys compared to treatment with antibiotic alone (p<0.0005 in all cases). Furthermore,

treatment with mannosides alone did not reduce bacterial titers from a 24h old UPEC infection and in combination with TMP-SMZ showed no additive effects on established UPEC CAUTI 24hpi (data not shown). Together, these findings indicate that virulence-targeted therapies in combination with established antibiotic treatment can help prevent or delay the onset of CAUTI and that further research is warranted for enhancing mannosides potential as therapeutics against CAUTIs.

Methods for the Examples

[0211] *Biofilm Assay.* UTI89 was grown in LB broth in wells of PVC microtiter plates at 23°C in the presence of individual mannosides at varying concentrations. After 48 h of growth, wells were rinsed with water and stained with crystal violet for quantification as described. For biofilm disruption activity in PVC plates, UTI89 was grown in LB broth in wells of PVC microtiter plates at 23°C. After 24 h of growth, mannoside was added and biofilms were grown for an additional 16h. Wells were then rinsed, stained with crystal violet and quantified. For biofilm disruption activity on PVC coverslips, UTI89 was grown in LB broth in 50 mL conicals containing PBC coverslips at 23°C. After 24 h of growth, 0.3 μM ZFH-2056 was added and biofilm was grown for an additional 16 h. Coverslips were then rinsed, fixed with 2% paraformaldehyde (v/v), stained with SYTO9 (1:1000 in PBS; Molecular Probes) and observed with a Zeiss LSM410 confocal laser scanning microscope under a 63X objective.

[0212] *Animal infections.* Bacteria were grown under type 1 pili-inducing conditions (2x24 h at 37°C statically in LB). The bacteria were harvested and resuspended to an OD_{600} of 0.5 in PBS. Eight-week-old C3H/HeN (Harlan) female mice were anesthetized by inhalation of isoflurane and infected via transurethral catheterization with 50 pl of the bacterial suspension, resulting in 1-2 x 10^7 inoculum. At 6 hpi, mice were sacrificed by cervical dislocation under anesthesia and the bladders were immediately harvested and processed as described below. All animal studies using mice were approved by the Animal Studies Committee of Washington University (Animal Protocol Number 20100002).

[0213] *Pharamacokinetic analysis.* For intraperitoneal dosing, 50 µl of a 2 mg/ml (5 mg/kg) or 4 mg/ml (10 mg/kg) solution of ZFH-2056 in PBS was injected into the peritoneal cavity of the mouse. For oral dosing, 100 µl of a 20 mg/ml (100 mg/kg) solution of ZFH-2056 in 8% DMSO was inoculated with a gavage needle into the mouse stomach. Urine was collected at 30 min, 1, 2, 3, 4, 6, and 8 h post-treatment. An equal volume of 10 µM internal standard (ZFH-2050) was added to the urine. Mannosides were extracted from the urine by loading on C18 columns (100 mg, Waters), washing with 30% methanol, and eluting with 60% methanol. Vacuum-concentrated eluates were analyzed using liquid chromatography-mass spectrometry system30 with a lower heated capillary temperature of 190°C and a gradient as follows: Solvent B (80% acetonitrile in 0.1 % formic acid) was held constant at 5% for 5 minutes, increased to 44% B by 45 minutes, and then to a 95% B by 65 minutes. SRM mode quantification was performed with collision gas energy of 30% for the following MS/MS transitions (precursor m/z/product m/z): compound ZFH-2056, 447/285; compound ZFH-2050, 390/228. Absolute quantification was achieved by comparison to a calibration curve.

[0214] *Bladder tissue bacterial titer determination.* Mannoside ZFH-2056 was administered either IP (5 mg/kg) or orally (100 mg/kg) 30 min prior to inoculation with UTI89. To enumerate the bacteria present, mice were sacrificed at 6 hpi and bladders were aseptically removed and homogenized in 1 ml PBS, serially diluted and plated onto LB agar plates. CFU was enumerated after 16 h of growth at 37 ^{o}C.

[0215] *Gentamicin protection assay.* To enumerate bacteria present in the intracellular versus extracellular compartments, bladders were aseptically harvested at 6 hpi. The bladders were then bisected twice and washed three times in 500 µl of PBS each. The wash fractions were pooled, lightly spun at 500 rpm for 5 min to pellet exfoliated bladder cells, serially diluted, and plated onto LB agar to obtain the luminal fraction. The bladders were treated with 100 µg of gentamicin/ml for 90 min at 37 ^{o}C. After treatment, the bladders were washed twice with PBS to eliminate residual gentamicin, homogenized in 1 ml of PBS, serially diluted, and plated onto LB agar to enumberate the CFUs in the intracellular fraction.

[0216] *Antibiotic treatment.* Mice were given TMP-SMZ in the drinking water at a concentration of 54 µg/ml and 270 µg/ml, respectively. Water was changed daily for 3

days prior to inoculation with UTI89. Mice remained on TMP-SMZ during the infection. To determine TMP-SMZ concentration in the urine, urine was collected after 3 days of TMP-SMZ treatment and quantified by LC-MS following addition of sulfisoxazole as an internal standard.

[0217] *Growth curve.* An overnight culture of PBC-1 was diluted 1:1000 in LB in the absence or presence of TMP-SMZ and/or mannoside ZFH-2056. The highest concentration of TMP-SMZ used was 512 µg/ml and 2560 µg/ml, respectively. Two-fold dilutions of TMP-SMZ were performed. Mannoside ZFH-2056 was added at 100 µM. Growth curves were performed in a 96-well plate at 37°C with A600 readings taken every 30 min for 8 h.

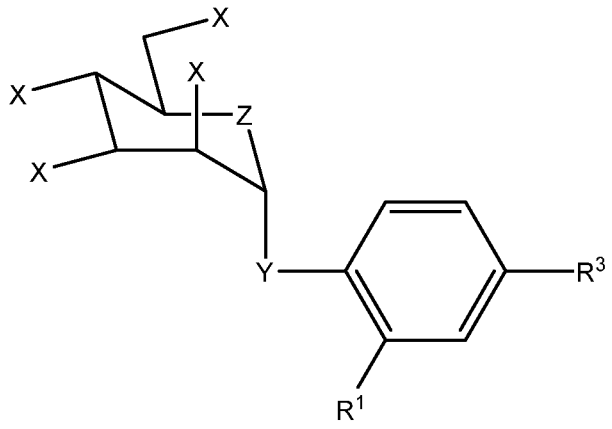
[0218] *Hemagglutination assay.* PBC-1 was grown statically in LB in the absence or presence of TMP-SMZ for 2x24 h at 37°C. The highest concentration of TMP-SMZ used was 256 µg/ml and 1280 µg/ml, respectively. Two-fold dilutions of TMP-SMZ were performed. Hemagglutination assays for mannose-sensitive agglutination of guinea pig red blood cells were performed as previously described.

[0219] *Statistical analysis.* Observed differences in bacterial titers and IBC numbers were analyzed for significance using the nonparametric Mann-Whitney U test (Prizm; GraphPad Software).

CLAIMS

What is claimed is:

1. A compound, the compound comprising Formula (I):



(I)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(NR_5R_6)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

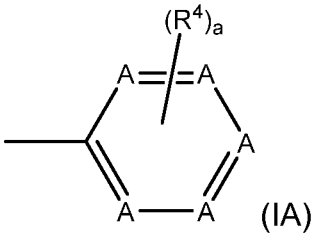
n is an integer from 1 to 10;

Z is O;

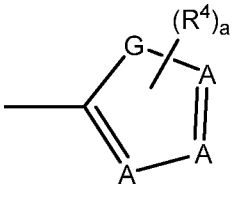
Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^3 is selected from the group consisting of formula (IA) and formula (IB):



(IA)



(IB)

A is independently selected from the group consisting of CR^5 and N;

G is independently selected from the group consisting of S, NR^5 and O;

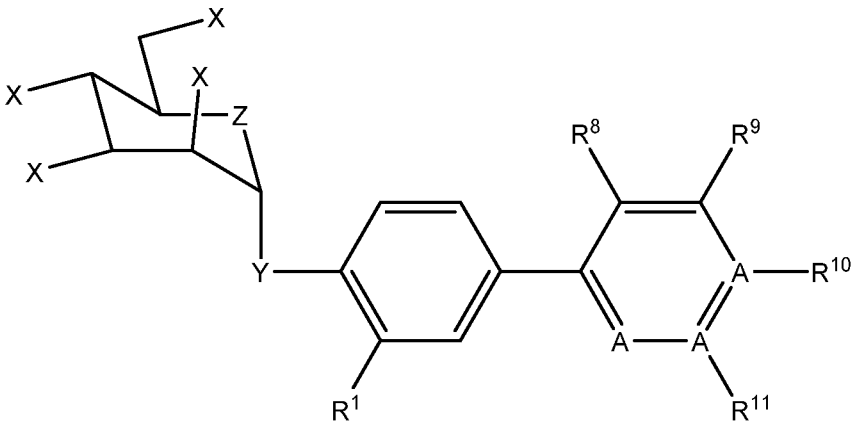
a is an integer from 1 to 4;

R^4 is selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, $CONR_5$, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$, or when a is greater than or equal to 2, R^4 may optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle.

2. A compound, the compound comprising Formula (II):



(II)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

A is independently selected from the group consisting of CR^5 and N;

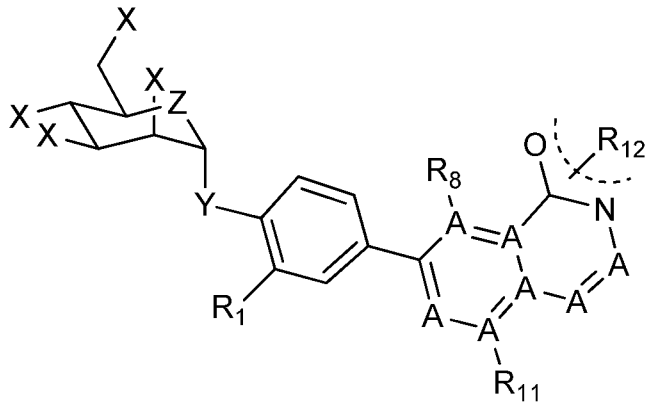
R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^8, R^9, R^{10} and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, $NHSO_2R^7$, and R^8 and R^9 together can optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring; and R^9 and R^{10} together can optionally form an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 is selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl and heterocycle.

3. A compound, the compound comprising Formula (III):



(III)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

A is independently selected from the group consisting of CR^5 and N;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

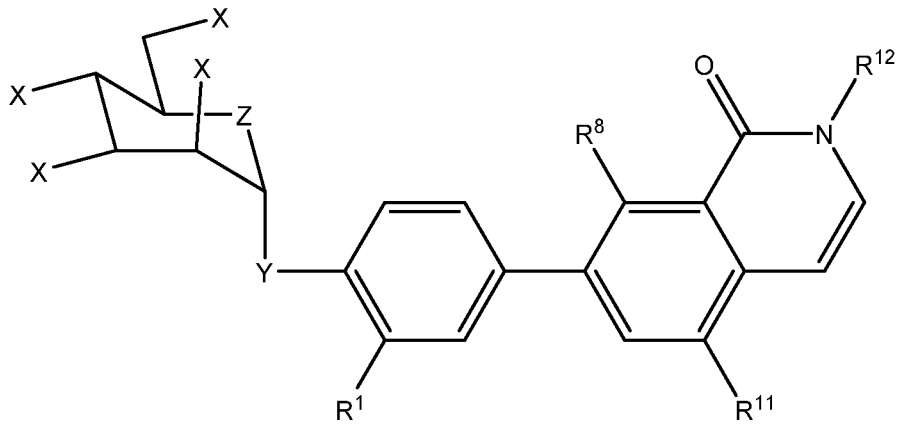
R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^{12} is substituted at the O or N and is selected from the group consisting of H, alkyl, CH_2R^{13}, CH_2COR^{13}, CH_2CONHR^{13}, $CH_2CONHR^{13}R^{14}$, $CH_2CONH(CH_2)_2R^{14}$, $(CH_2)_2NR^{13}$, $(CH_2)_nNR^{13}$, CH_2COOH, $CH_2CONH(CH_2)_2NH_2$, and $(CH_2)_2N(CH_3)_2$;

R^{13} is selected from the group consisting of –OH and an optionally substituted heterocycle, hydrocarbyl, and substituted hydrocarbyl;

R^{14} is selected from the group consisting of alkyl and NH_2.

4. A compound, the compound comprising Formula (IV):



(IV)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

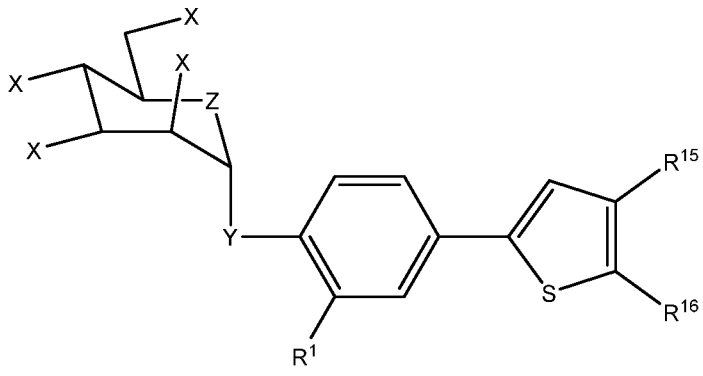
R^8 and R^{11} are independently selected from the group consisting of $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, H, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$;

R^{12} is selected from the group consisting of H, alkyl, CH_2R^{13}, CH_2COR^{13}, CH_2CONHR^{13}, $CH_2CONHR^{13}R^{14}$, $CH_2CONH(CH_2)_2R^{14}$, $(CH_2)_2NR^{13}$, $(CH_2)_nNR^{13}$, CH_2COOH, $CH_2CONH(CH_2)_2NH_2$, and $(CH_2)_2N(CH_3)_2$;

R^{13} is selected from the group consisting of –OH and an optionally substituted heterocycle, hydrocarbyl, and substituted hydrocarbyl;

R^{14} is selected from the group consisting of alkyl and NH_2.

5. A compound, the compound comprising Formula (V):



(V)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

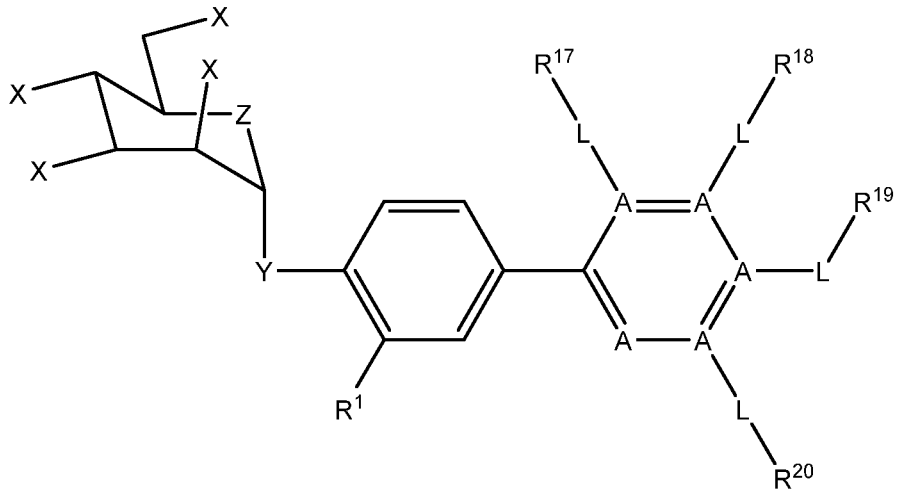
Z is O;

Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

R^{15} and R^{16} are independently selected from the group consisting of hydrogen, $NHCONH_2$, $COOCH_3$, and $CONHCH_3$, $CONHCH_3$, $COOCH_3$, COOH, CONH(heterocycle), heterocycle, alkyl, cyclopropyl, aryl, OR^5, NR^5R^6, NR^5COR^6, NR^5COOR^6, NR^5CONR^6, $NR^5SO_2R^6$, COR^5, SO_2R^5, halogen, CN, NO_2, $COOR^5$, $CONR^5R^6$, $NCOR^7$, $NCONR^7$, $NCOOR^7$, $SO_2NR^5R^6$, and $NHSO_2R^7$ or R^{15} and R^{16} can optionally form a cycloalkyl, aryl or heterocyclo ring.

6. A compound, the compound comprising Formula (VI):



(VI)

wherein:

X is selected from the group consisting of hydrogen and OR^2;

R^2 is independently selected from the group consisting of hydrogen, $PO(OH)_2$, acetyl, COR^5, $CO(OR^5)$, $CO(CH_2)_nNR^5R^6$, hydrocarbyl and substituted hydrocarbyl;

n is an integer from 1 to 10;

R^5 is selected from the group consisting of H and an optionally substituted alkyl, aryl, heterocycle, and cycloalkyl;

R^6 and R^7 are selected from the group consisting of an optionally substituted alkyl, cycolalkyl, aryl, and heterocycle;

Z is O;

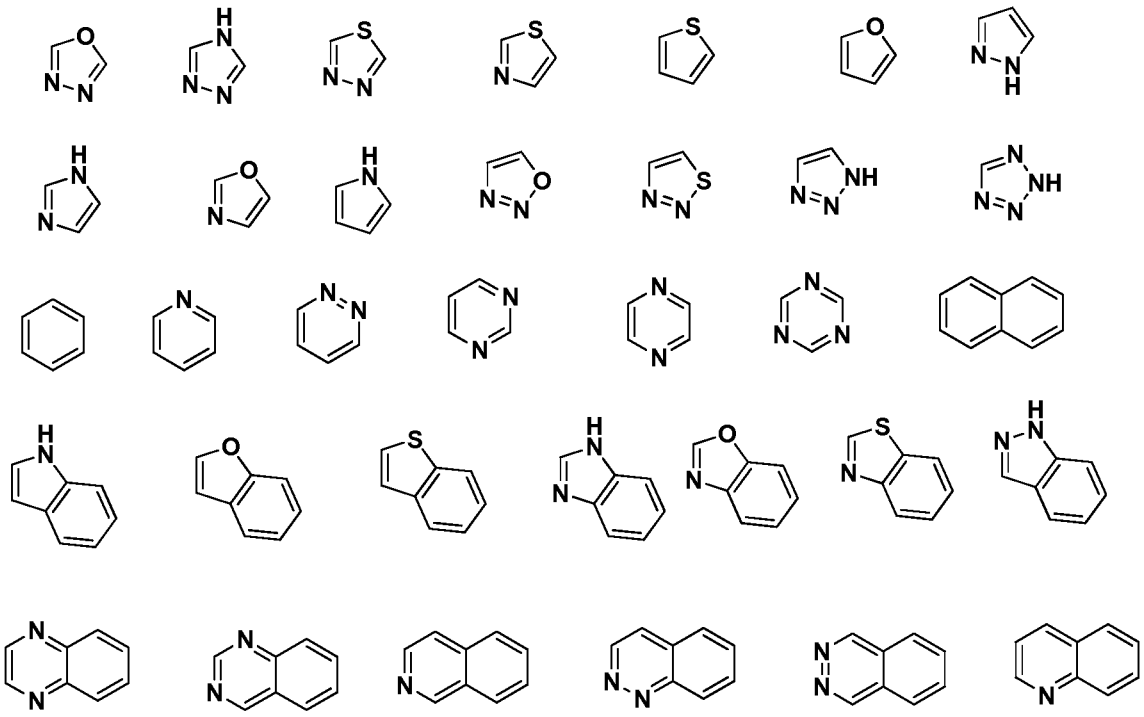
Y is selected from the group consisting of O, CH(OH), $CH(OR^5)$, $CHNR^5R^6$, CH_2, S, and NR^5;

R^1 is selected from the group consisting of CH_3, CF_3, halogen, Cl, F, Br, I, OH, NH_2, NR^5R^6, OCH_3, CO_2CH_3, $CONHCH_3$, alkyl, cyclopropyl, OR^5, CO_2R^5, $CONR^5R^6$, hydrocarbyl, and substituted hydrocarbyl;

A is independently selected from the group consisting of CR^5 and N;

L is independently selected from the group consisting of no atom, N, NH, O and S;

R^{17}, R^{18}, R^{19} and R^{20} are selected from the group consisting of H and an optionally substituted cycloalkyl, aryl or heterocyclo 5 or 6 membered ring, 5-6 fused ring or 6-6 fused ring including but not limited to the following examples, wherein the example is attached via any available CH position:



7. A method of treating a urinary tract infection, the method comprising administering a compound of any of the preceding claims to a subject in need thereof.

8. The method of claim 7, wherein the subject is further administered a bactericidal composition.

9. A method of preventing a urinary tract infection, the method comprising administering a compound of any of claims 1-6 to a subject in need thereof.

10. The method of claim 9, wherein the subject is further administered a bactericidal composition.

11. A method of reducing the resistance of a bacterium to a bactericidal compound, the method comprising administering a compound of any of claims 1-6 to a subject in need thereof.

12. A method of treating inflammatory bowel disease, the method comprising administering a compound of any of claims 1-6 to a subject in need thereof.

13. The method of claim 12, wherein the inflammatory bowel disease is Crohn's disease.

14. The method of claim 12, wherein treating comprises reducing symptoms associated with inflammatory bowel disease.

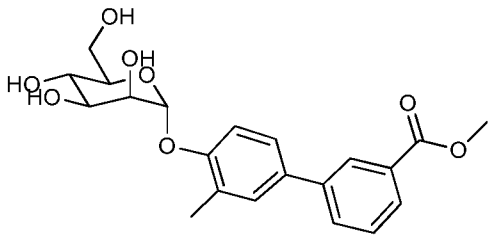
15. A method of inhibiting FimH binding to mannose, the method comprising contacting a compound of any of claims 1-6 with FimH, wherein the compound binds FimH and inhibits binding to mannose.

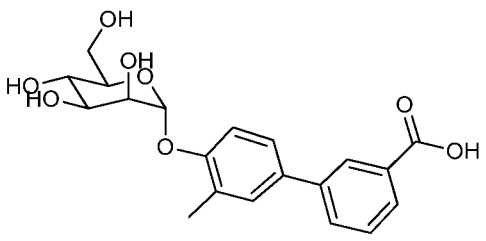
16. The method of claim 15, wherein the mannose is exposed on a bladder cell.

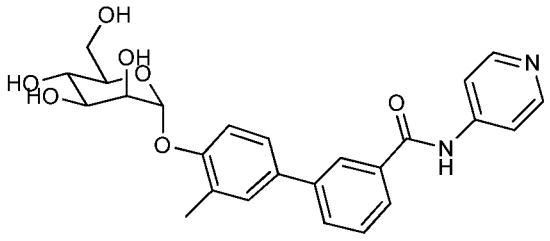
17. The method of claim 15, wherein the mannose is exposed on an intestinal cell.

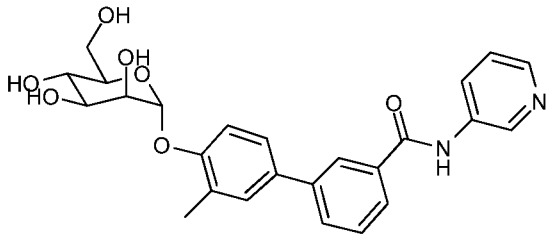
18. A method of treating a catheter-associated urinary tract infection, the method comprising administering a compound of any of the preceding claims to a subject in need thereof.

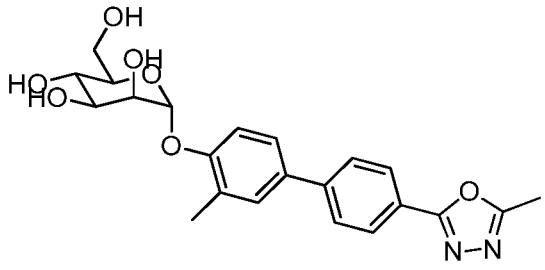
19. The compound of claim 1, wherein the compound is selected from the group consisting of:

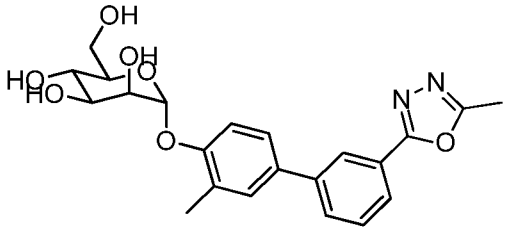
1. 

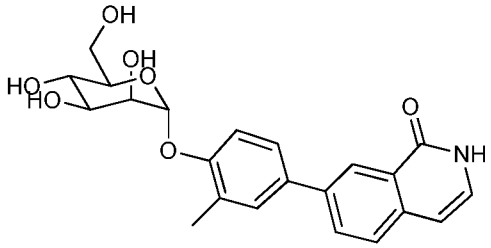
2. 

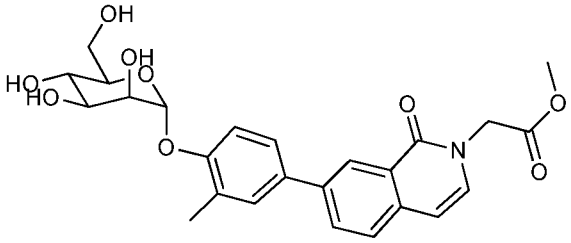
3. 

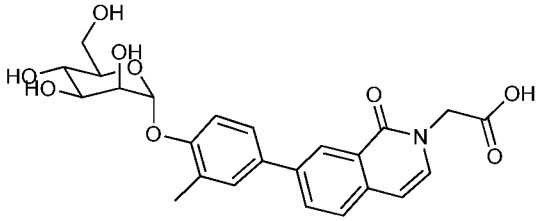
4. 

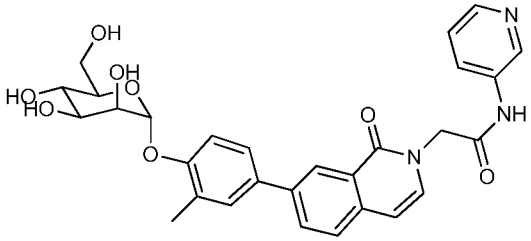
5. 

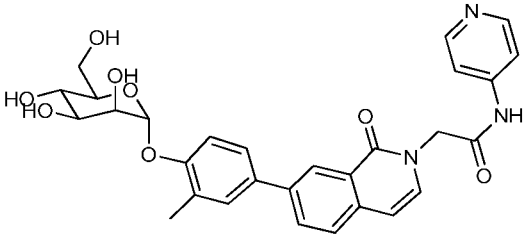
6. 

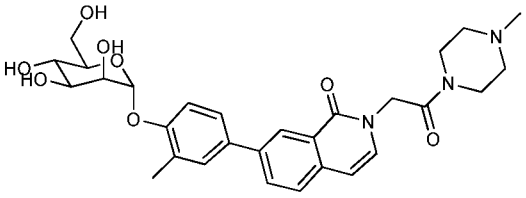
7. 

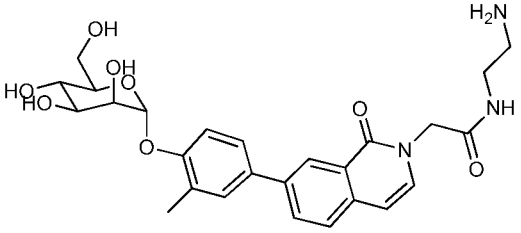
8. 

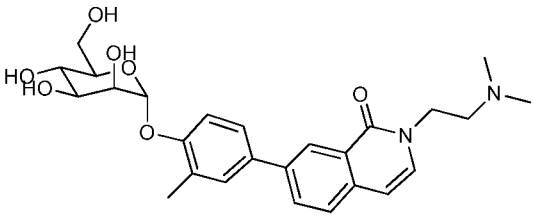
9. 

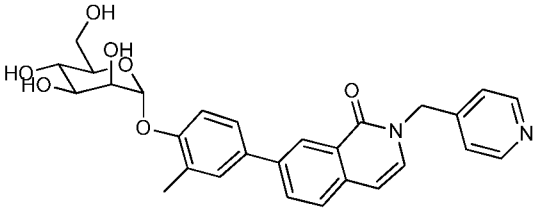
10. 

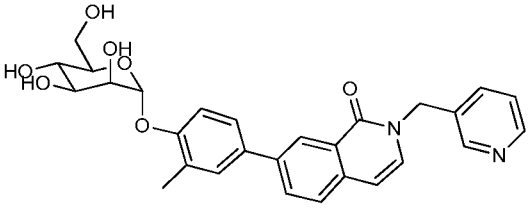
11. 

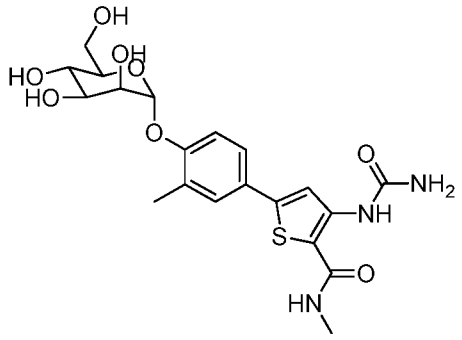
12. 

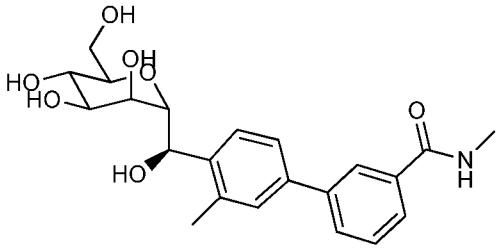
13. 

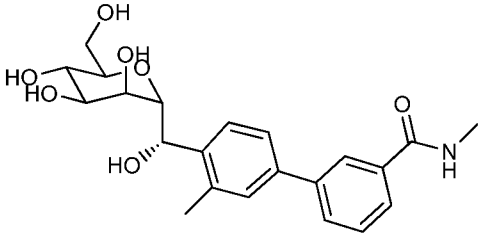
14. 

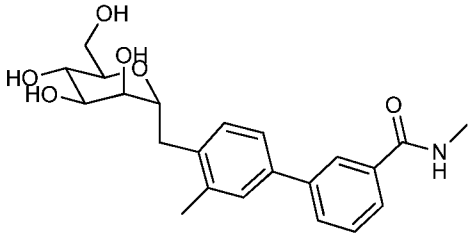
15. 

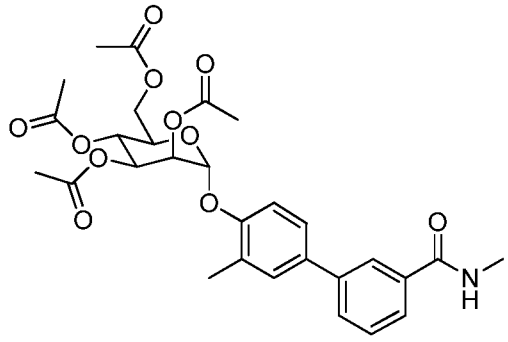
16. 

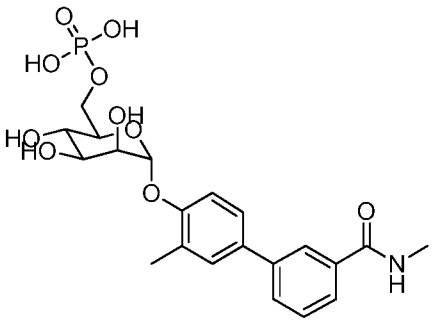
17. 

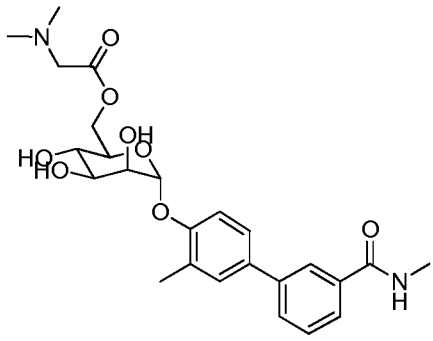
18A. 

18B. 

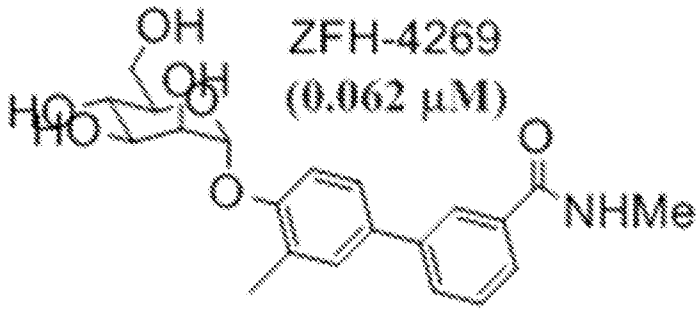
19. 

20. 

21. 

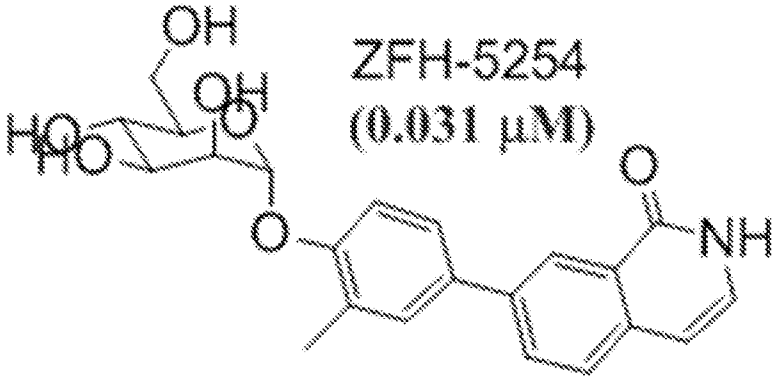
22. 

A



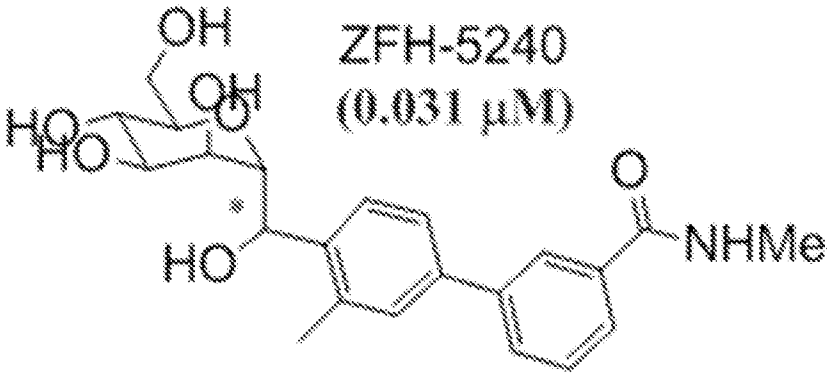
ZFH-4269
(0.062 μM)

B



ZFH-5254
(0.031 μM)

C



ZFH-5240
(0.031 μM)

FIG. 1

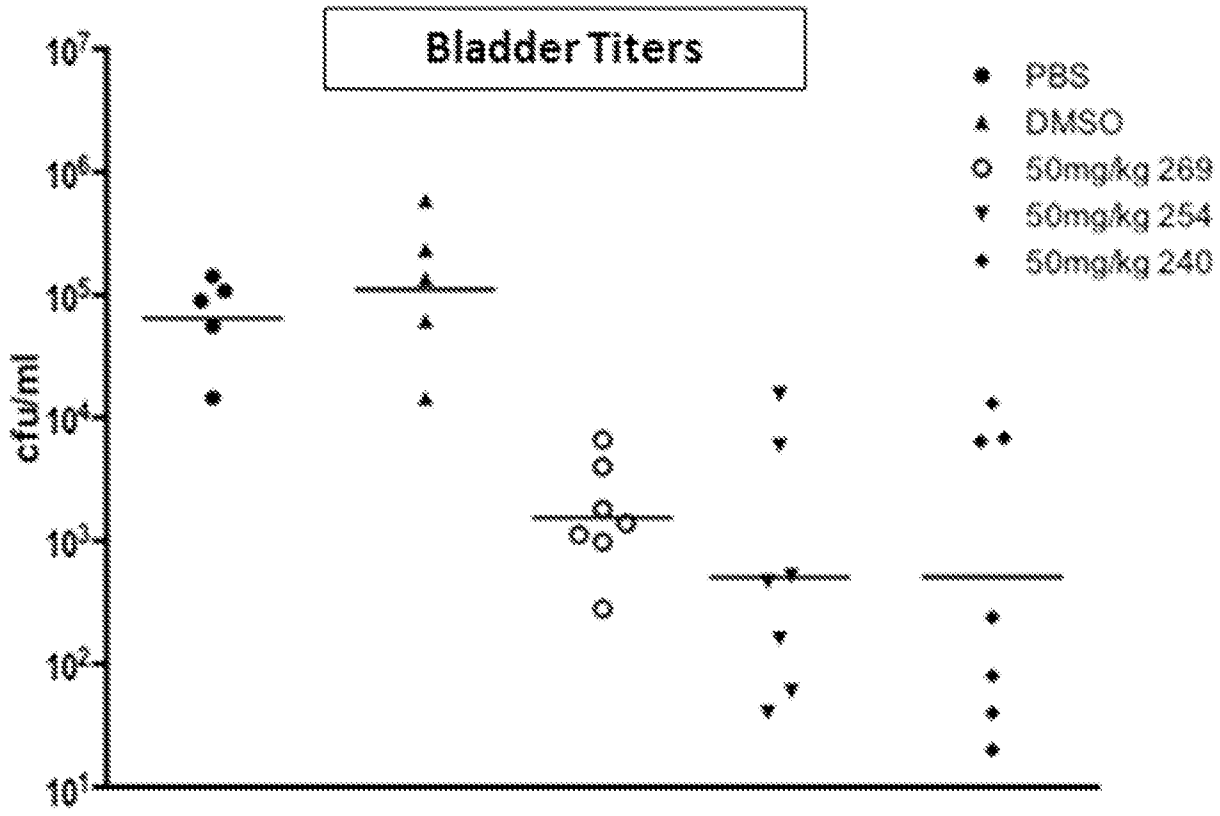

Bladder Titers
PBS
DMSO
50mg/kg 269
50mg/kg 254
50mg/kg 240
cfu/ml
10^7
10^6
10^5
10^4
10^3
10^2
10^1

FIG. 1D

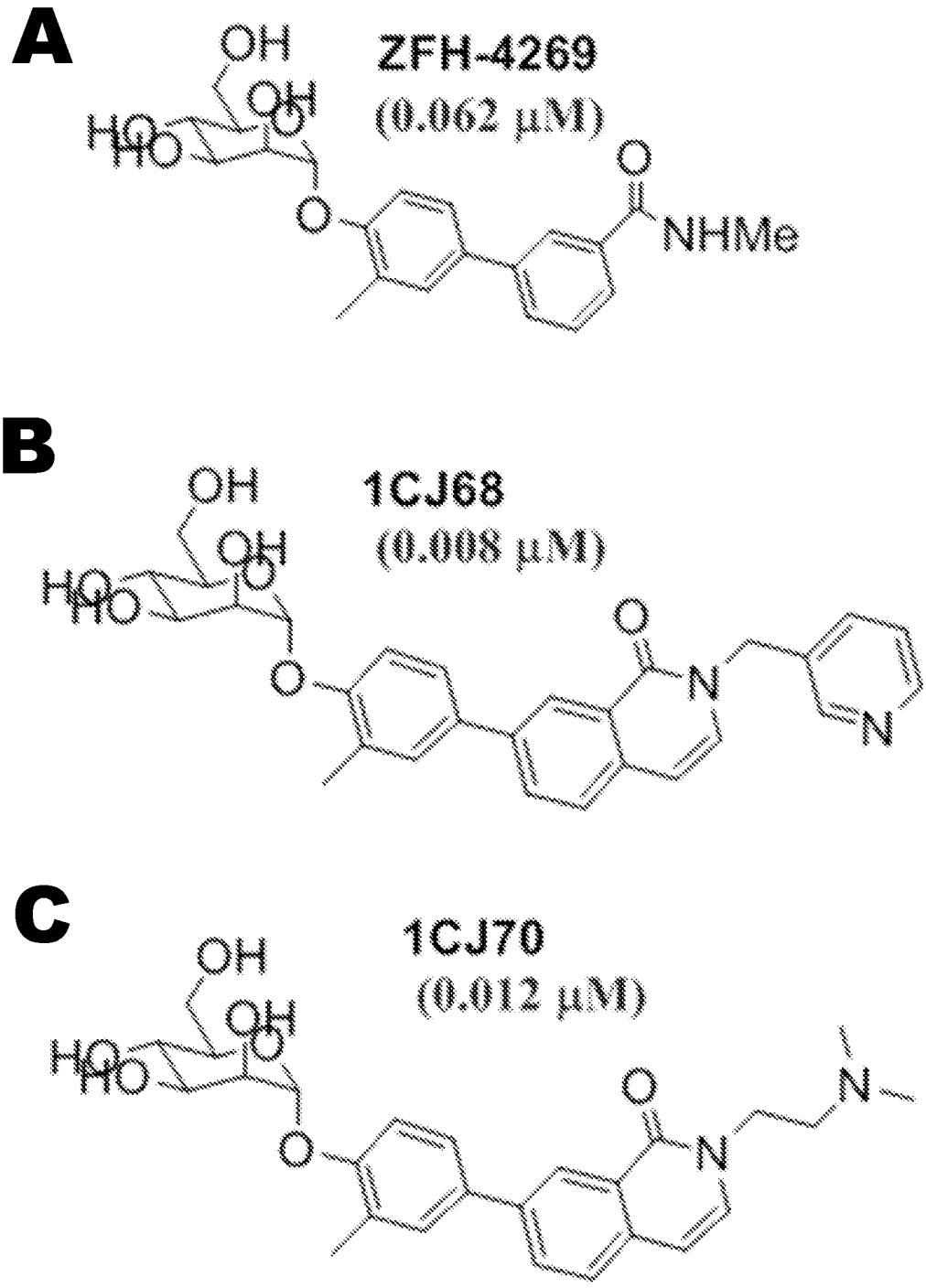

A
ZFH-4269
(0.062 μM)
OH
OH
HO
HO
O
O
O
NHMe
B
1CJ68
(0.008 μM)
OH
OH
HO
HO
O
O
O
N
N
C
1CJ70
(0.012 μM)
OH
OH
HO
HO
O
O
O
N
N

FIG. 2

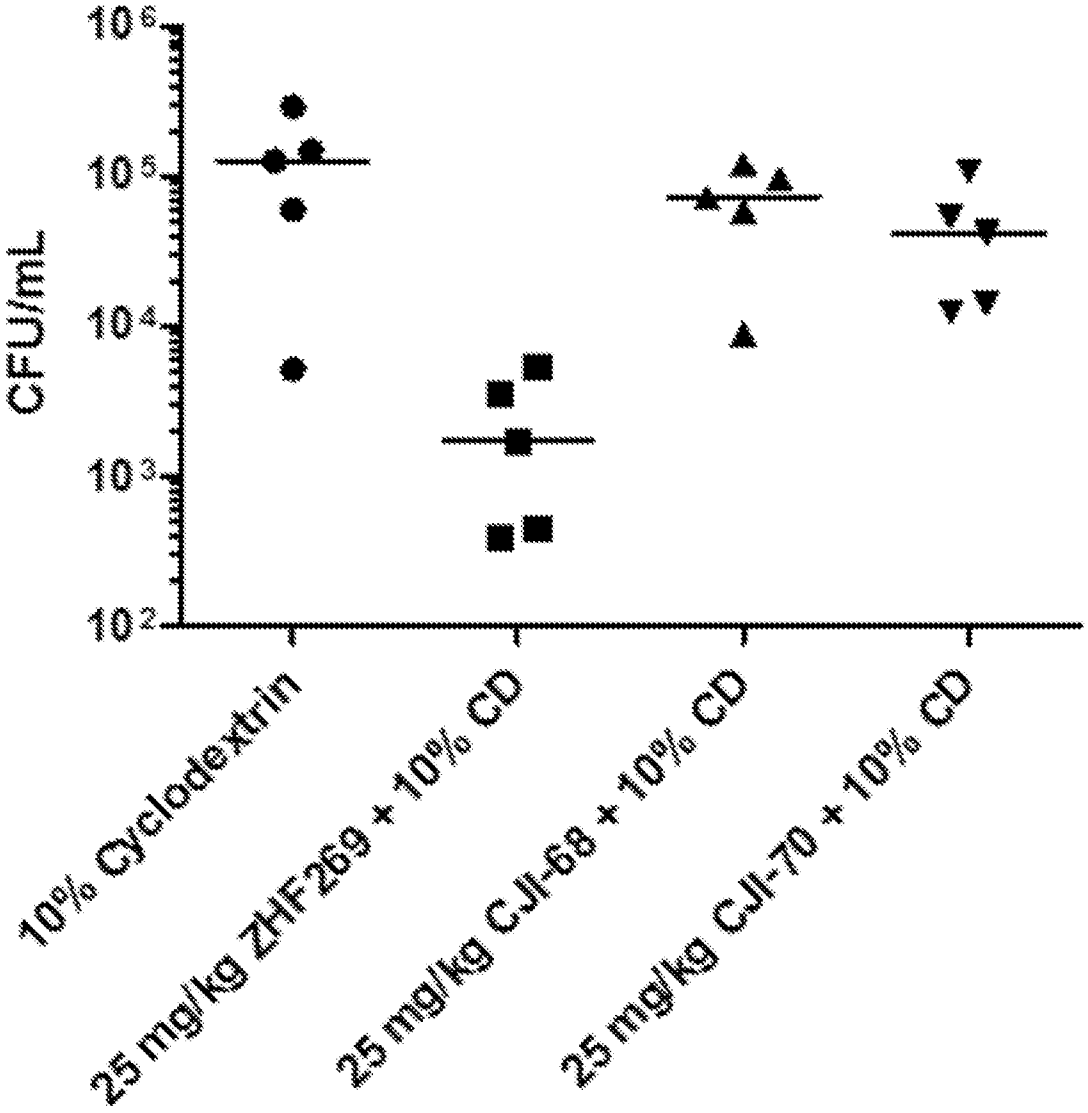

CFU/mL
10 6
10 5
10 4
10 3
10 2
10% Cyclodextrin
25 mg/kg ZHF269 + 10% CD
25 mg/kg CJI-68 + 10% CD
25 mg/kg CJI-70 + 10% CD

FIG. 2D

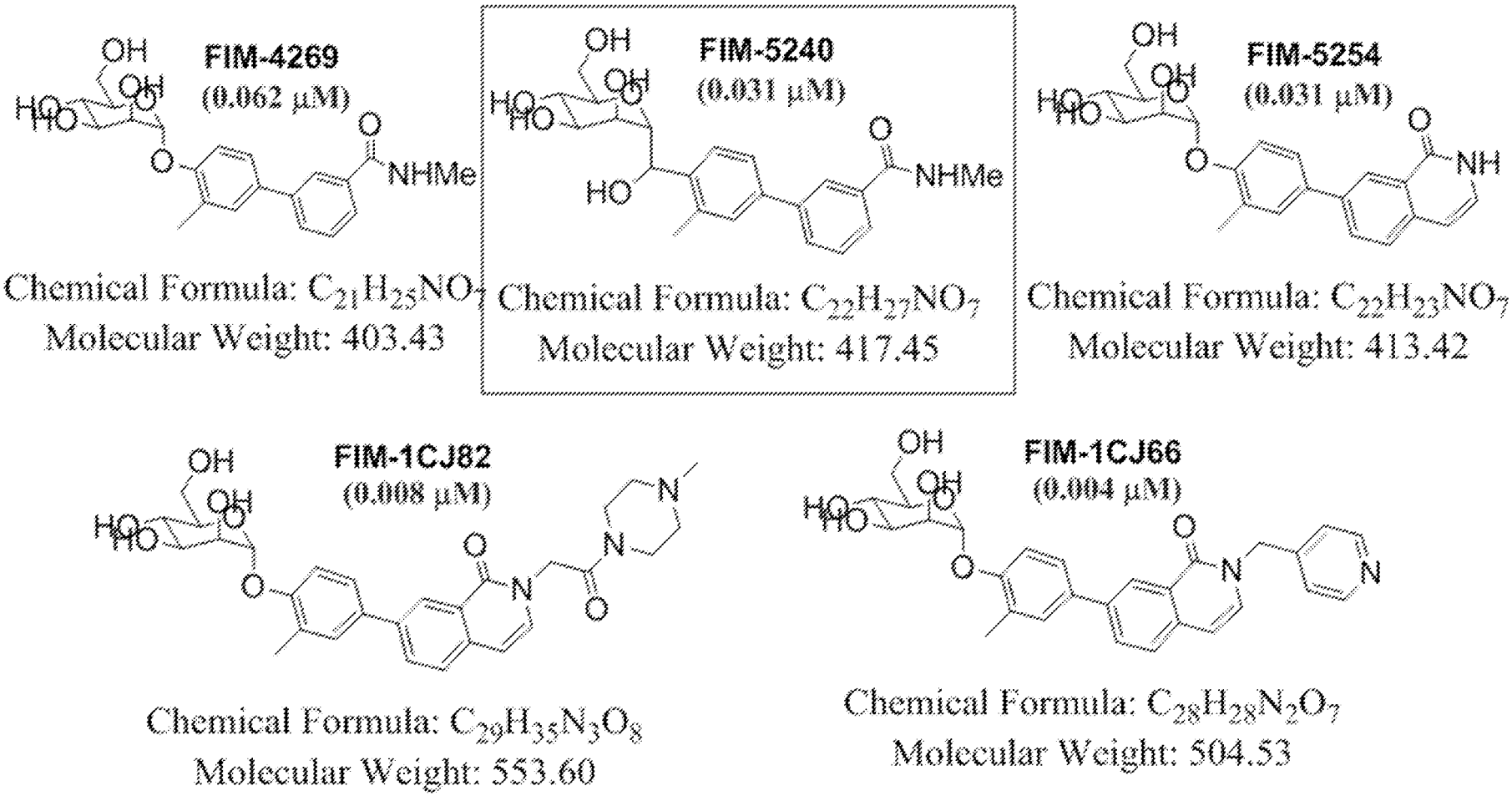

FIM-4269
(0.062 μM)
Chemical Formula: $C_{21}H_{25}NO_7$
Molecular Weight: 403.43
FIM-5240
(0.031 μM)
Chemical Formula: $C_{22}H_{27}NO_7$
Molecular Weight: 417.45
FIM-5254
(0.031 μM)
Chemical Formula: $C_{22}H_{23}NO_7$
Molecular Weight: 413.42
FIM-1CJ82
(0.008 μM)
Chemical Formula: $C_{29}H_{35}N_3O_8$
Molecular Weight: 553.60
FIM-1CJ66
(0.004 μM)
Chemical Formula: $C_{28}H_{28}N_2O_7$
Molecular Weight: 504.53

FIG. 3

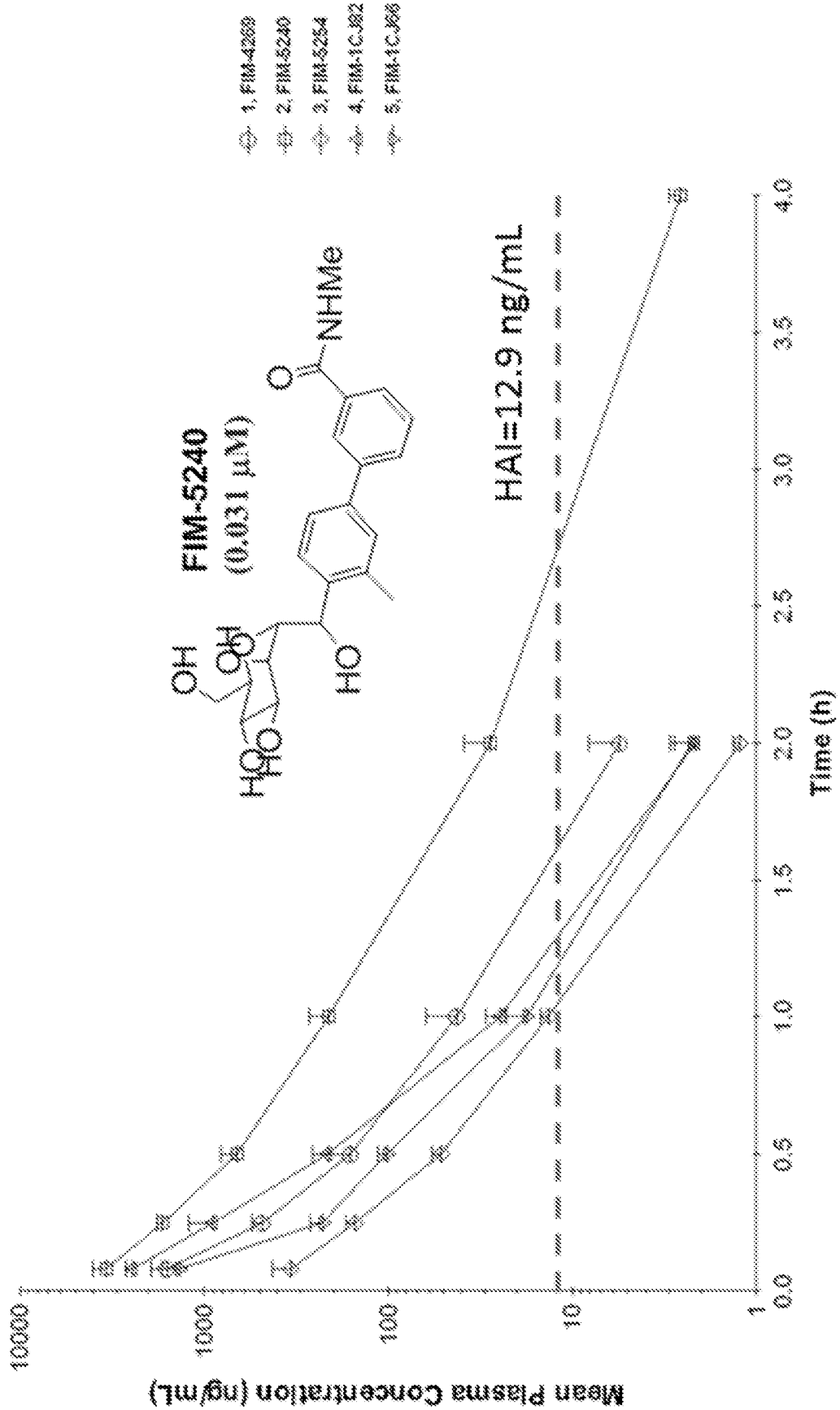

1, FIM-4269
2, FIM-5240
3, FIM-5254
4, FIM-1C-382
5, FIM-1C-366
FIM-5240
(0.031 μM)
HAI=12.9 ng/mL
Mean Plasma Concentration (ng/mL)
Time (h)
10000
1000
100
10
1
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0

FIG. 4

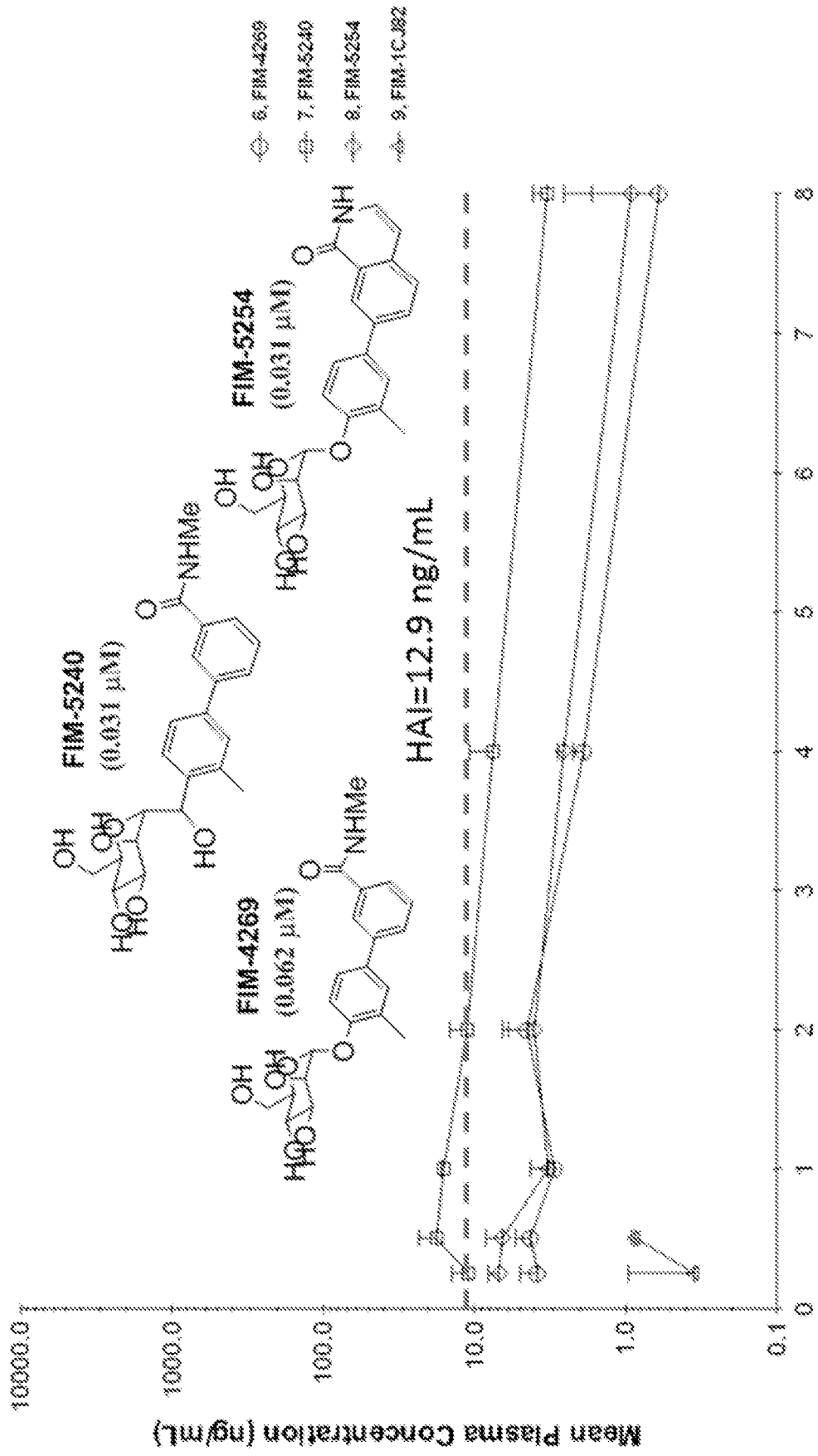
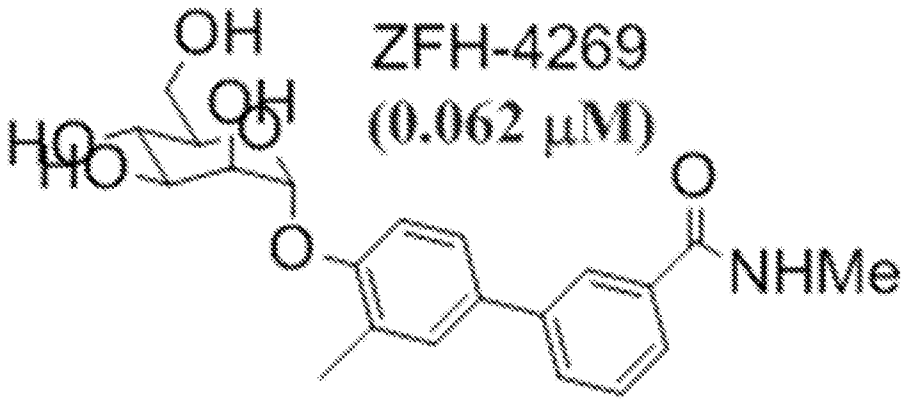
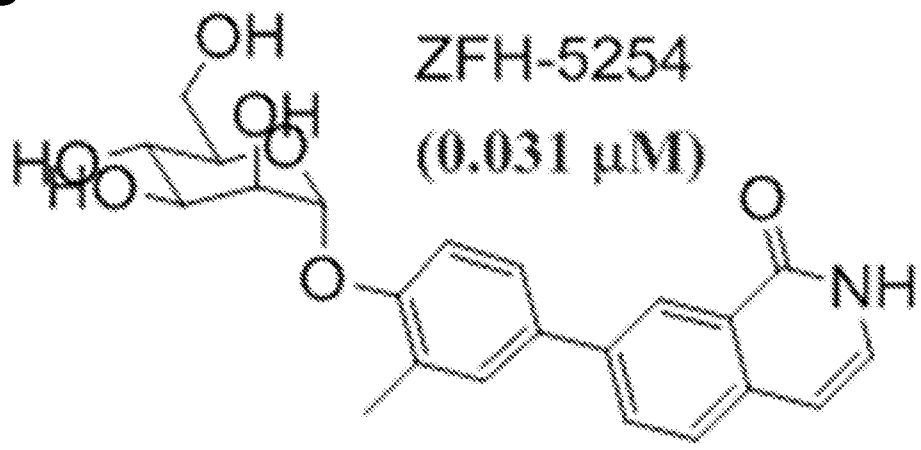

6, FIM-4269
7, FIM-5240
8, FIM-5254
9, FIM-1C-J82
FIM-5254
(0.031 μM)
FIM-5240
(0.031 μM)
FIM-4269
(0.062 μM)
HAI=12.9 ng/mL
Mean Plasma Concentration (ng/mL)
10000.0
1000.0
100.0
10.0
1.0
0.1
0
1
2
3
4
5
6
7
8
Time (h)

FIG. 5

A


OH
OH
HO
HO
O
O
O
NHMe
ZFH-4269
(0.062 μM)

B


OH
OH
HO
HO
O
O
O
NH
ZFH-5254
(0.031 μM)

C

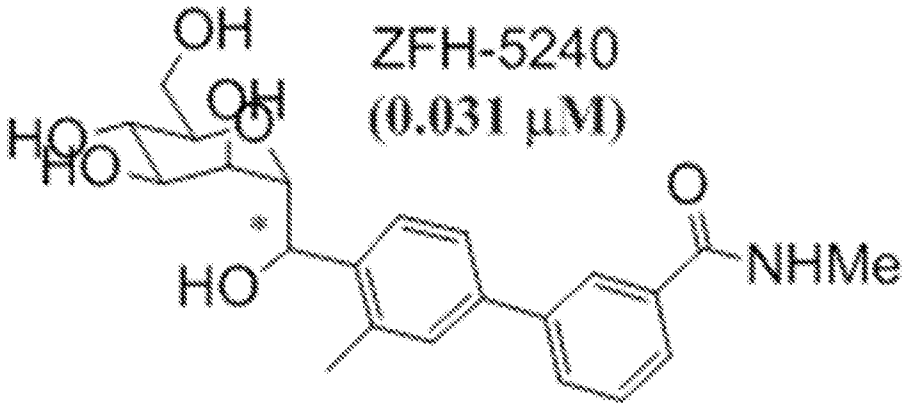

OH
OH
HO
HO
O
*
HO
O
NHMe
ZFH-5240
(0.031 μM)

FIG. 6

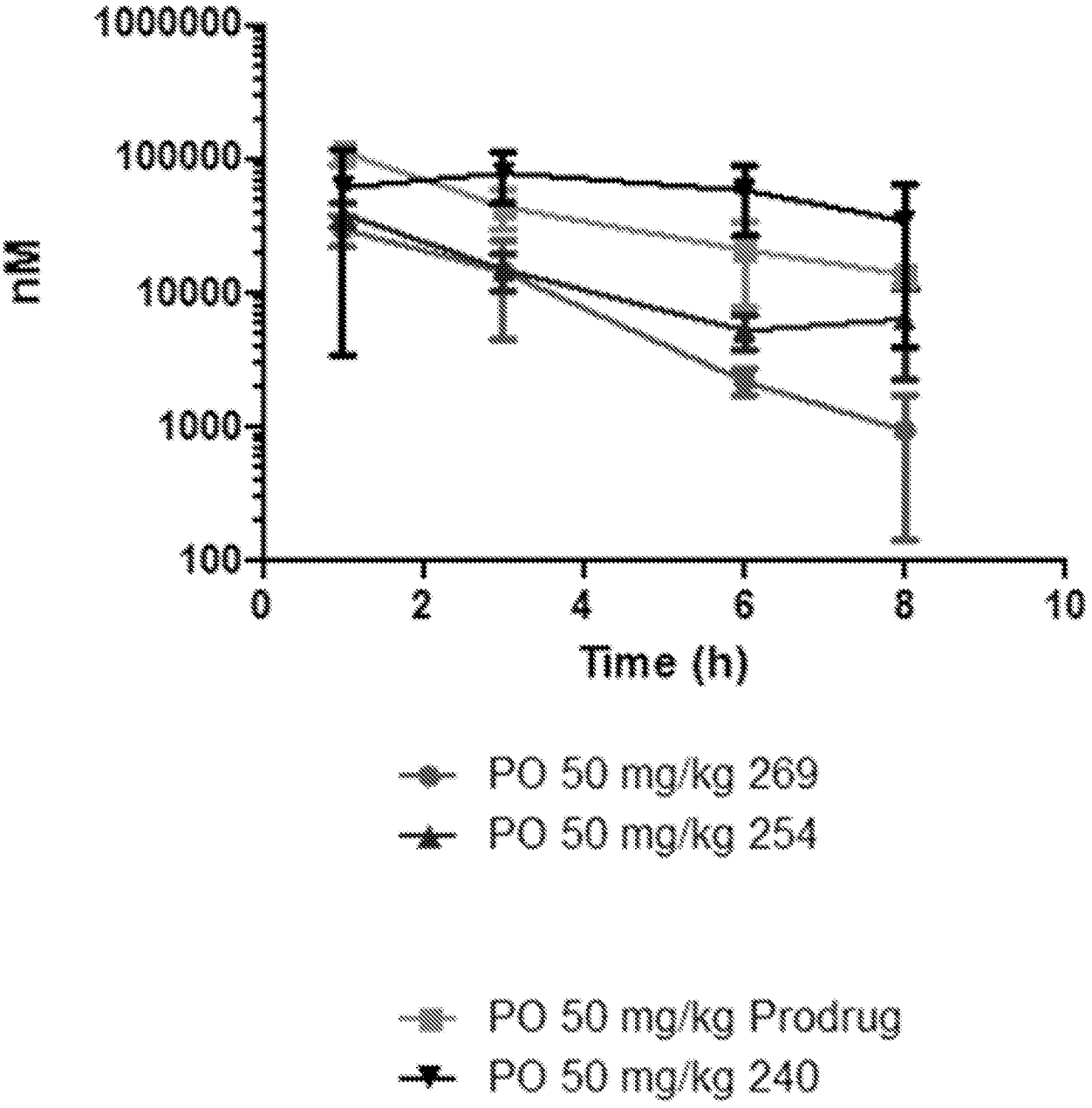

1000000
100000
10000
1000
100
nM
0
2
4
6
8
10
Time (h)
PO 50 mg/kg 269
PO 50 mg/kg 254
PO 50 mg/kg Prodrug
PO 50 mg/kg 240

FIG. 6D

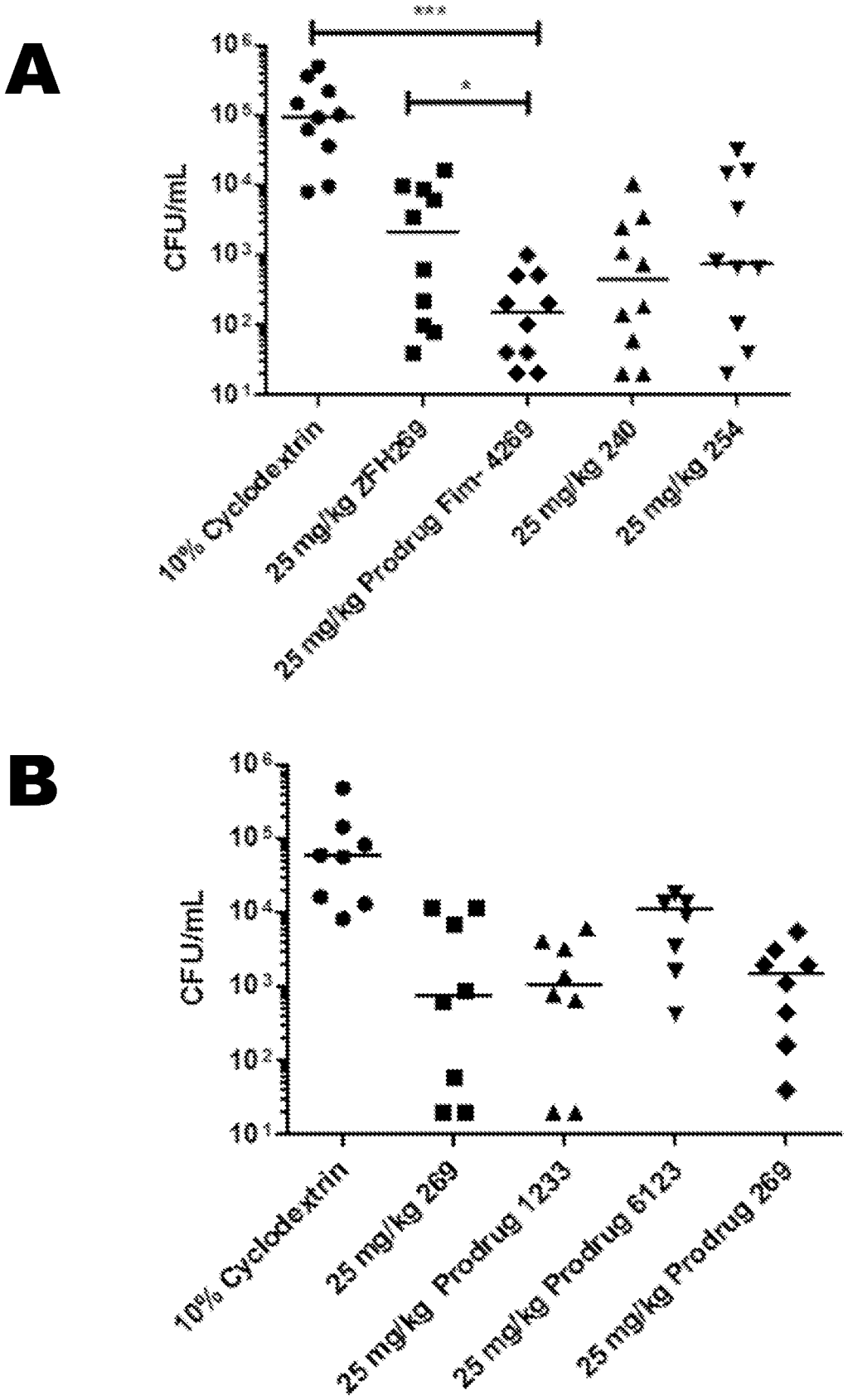
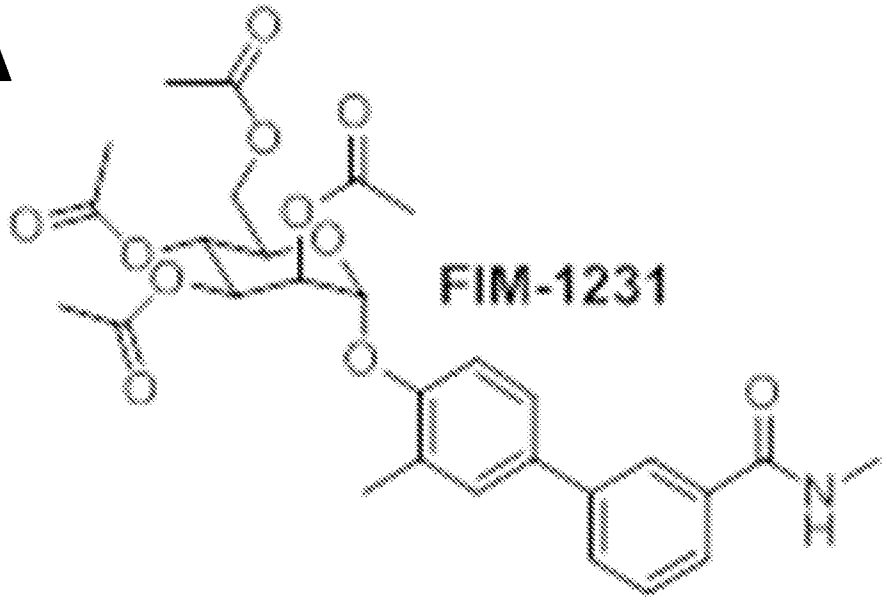

A
***
*
CFU/mL
10^6
10^5
10^4
10^3
10^2
10^1
10% Cyclodextrin
25 mg/kg ZFH269
25 mg/kg Prodrug Finr- 4269
25 mg/kg 240
25 mg/kg 254
B
CFU/mL
10^6
10^5
10^4
10^3
10^2
10^1
10% Cyclodextrin
25 mg/kg 269
25 mg/kg Prodrug 1233
25 mg/kg Prodrug 6123
25 mg/kg Prodrug 269

FIG. 7

A



B

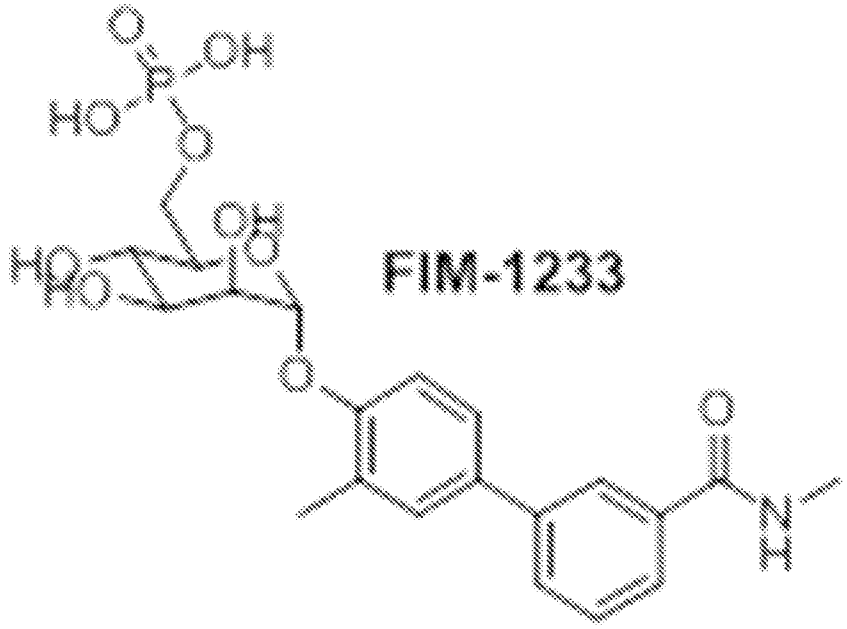


FIG. 8

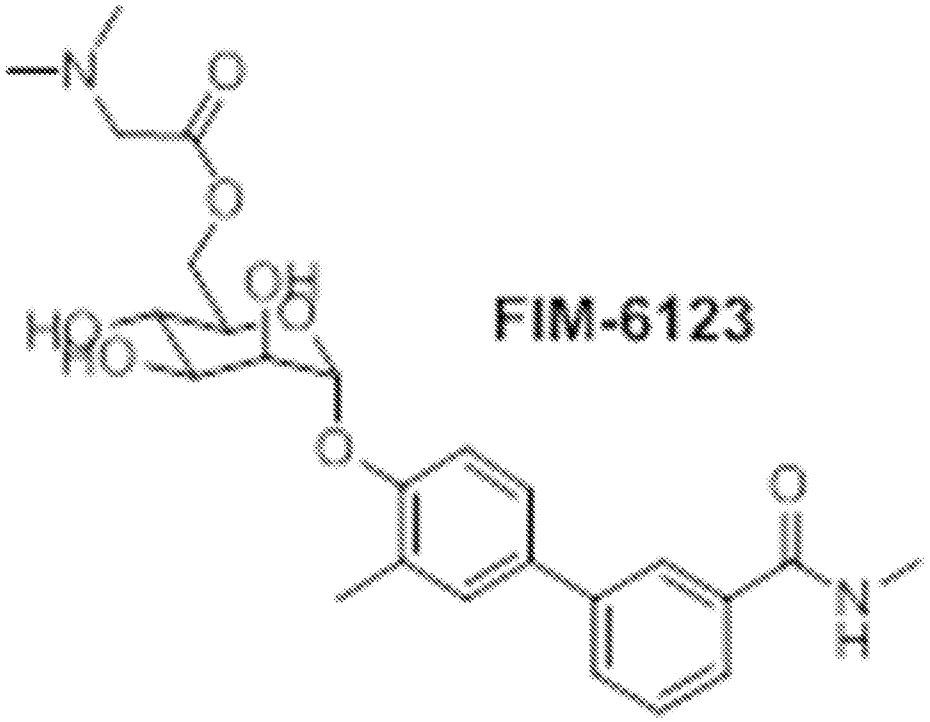


FIG. 8C

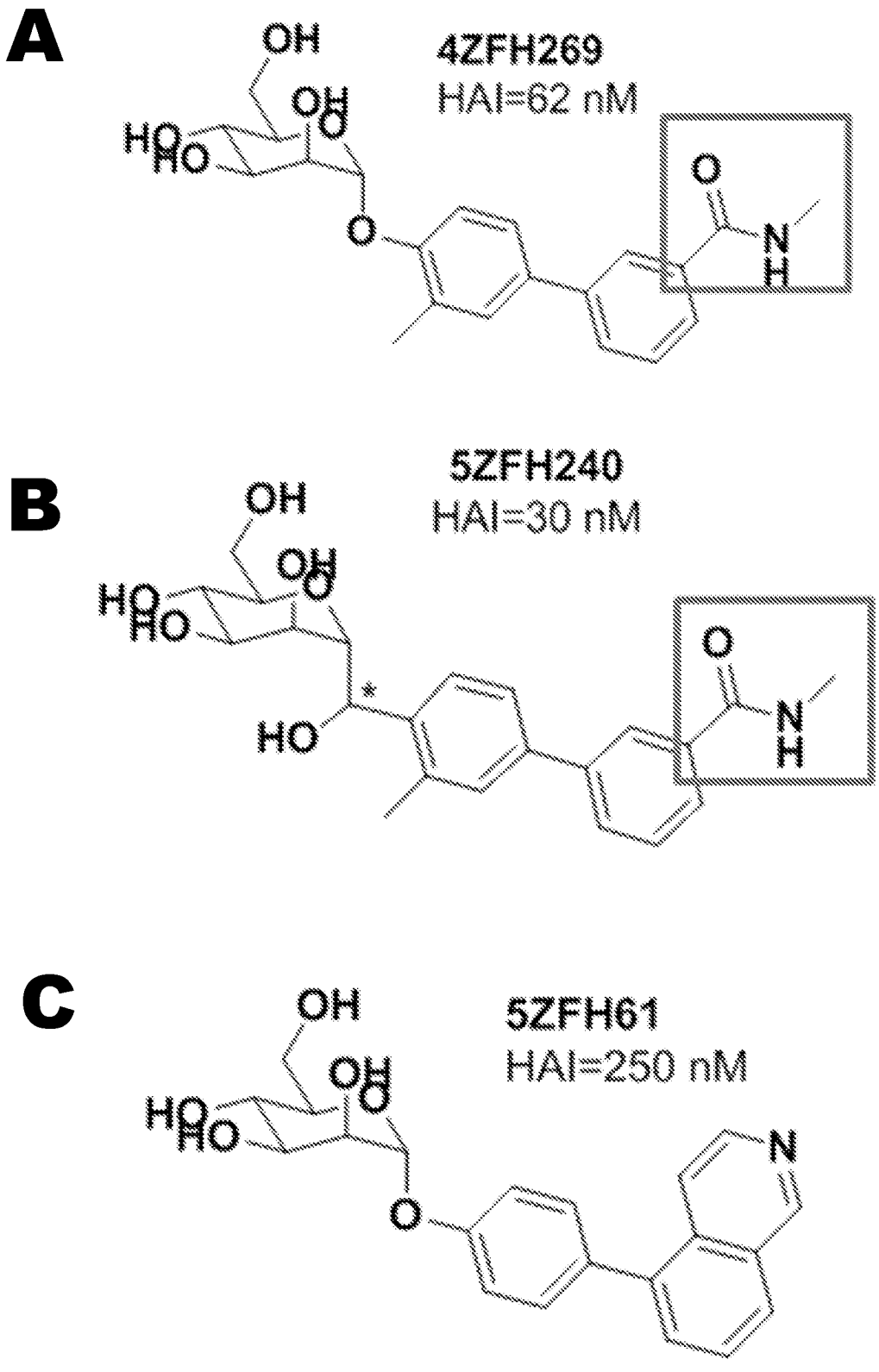
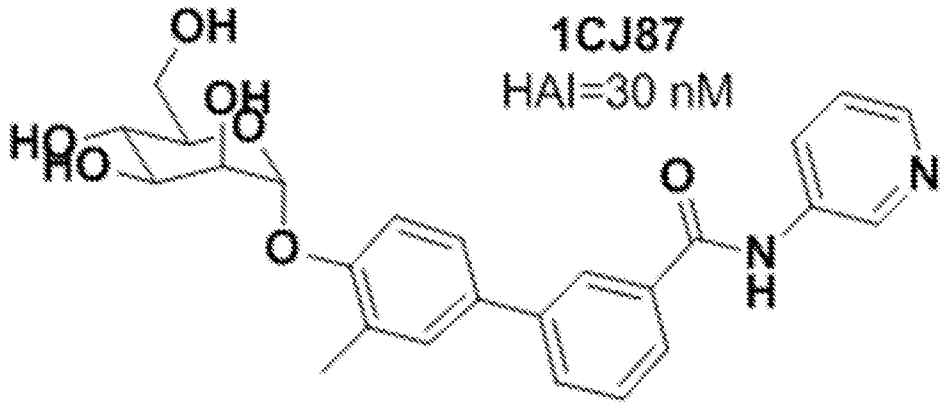


FIG. 9

D


1CJ87
HAI=30 nM
OH
OH
HO
HO
O
O
O
N
N
H

E

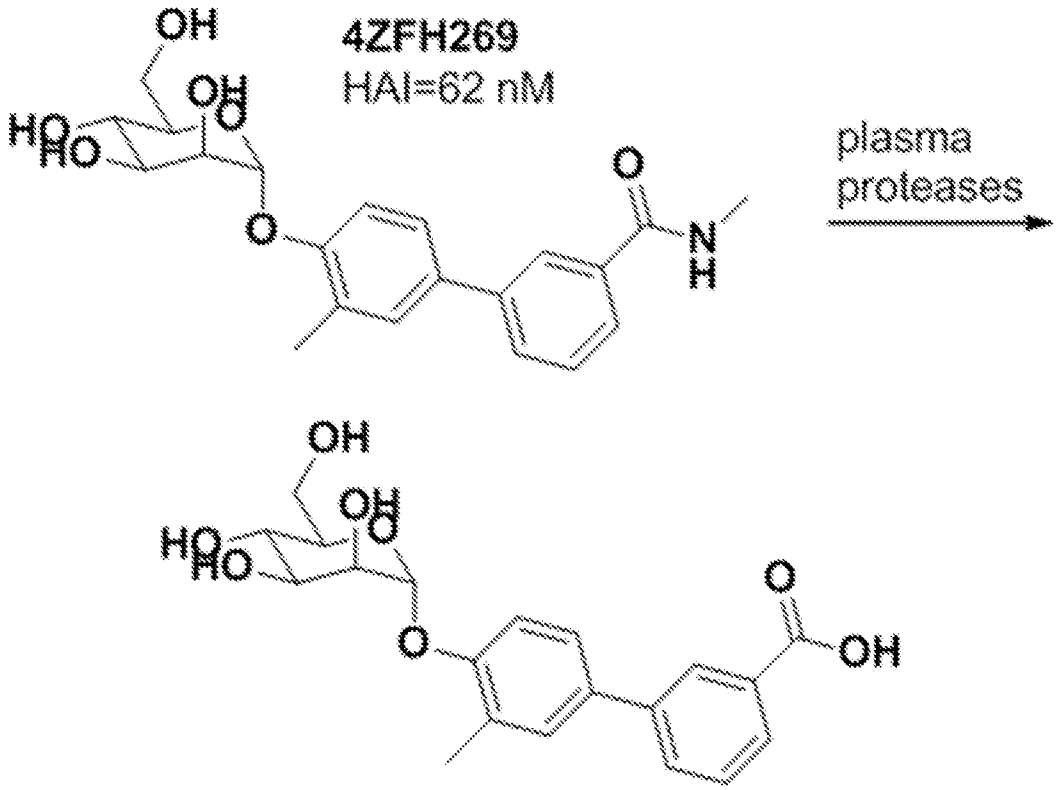

4ZFH269
HAI=62 nM
plasma
proteases
OH
OH
HO
HO
O
O
O
N
H
OH
OH
HO
HO
O
O
O
OH

FIG. 9

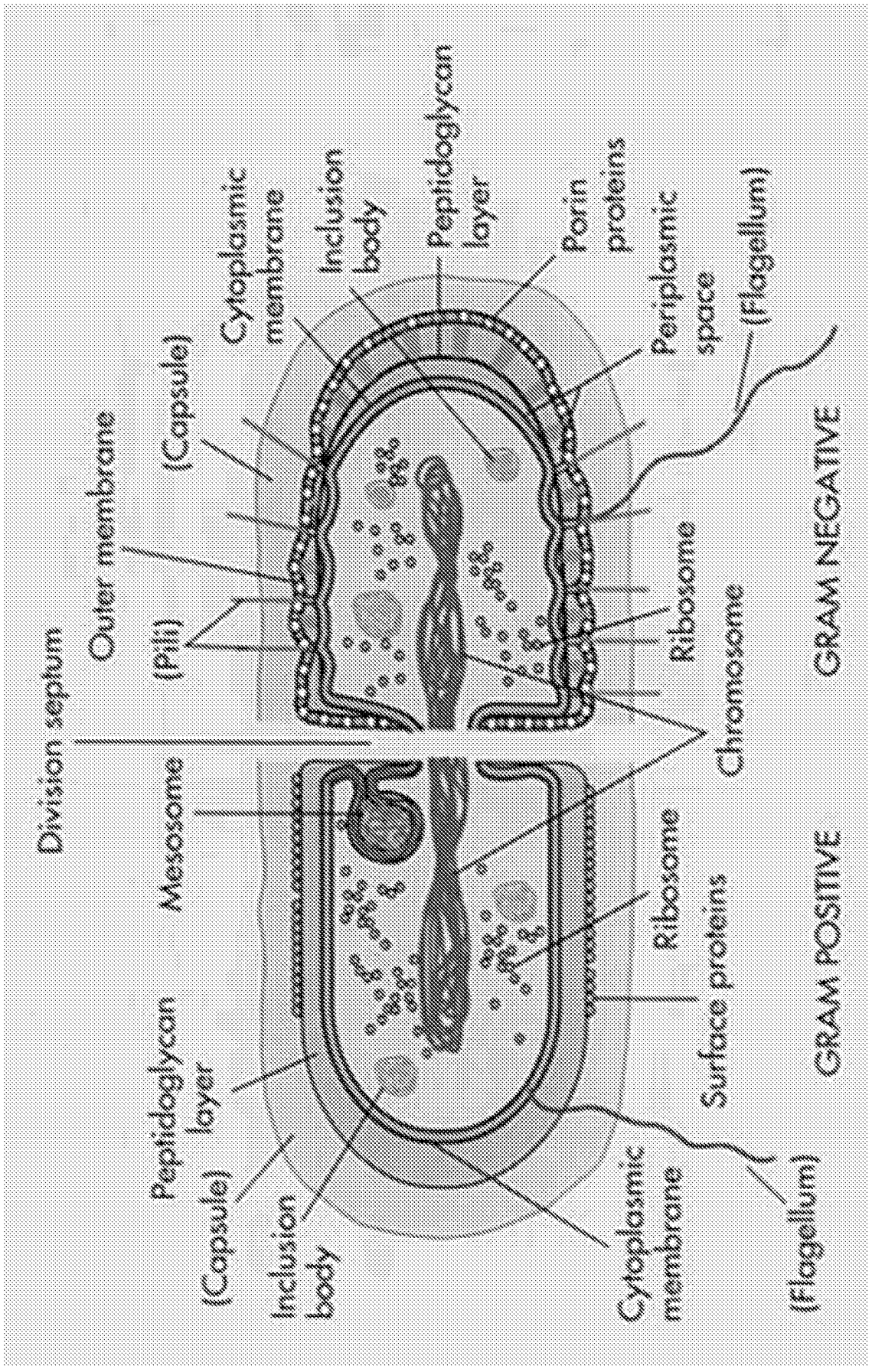

Division septum
Outer membrane
(Pili)
(Capsule)
Cytoplasmic membrane
Inclusion body
Peptidoglycan layer
Porin proteins
Periplasmic space
(Flagellum)
GRAM NEGATIVE
Mesosome
Peptidoglycan layer
(Capsule)
Inclusion body
Ribosome
Chromosome
Surface proteins
Cytoplasmic membrane
(Flagellum)
GRAM POSITIVE

FIG. 10A

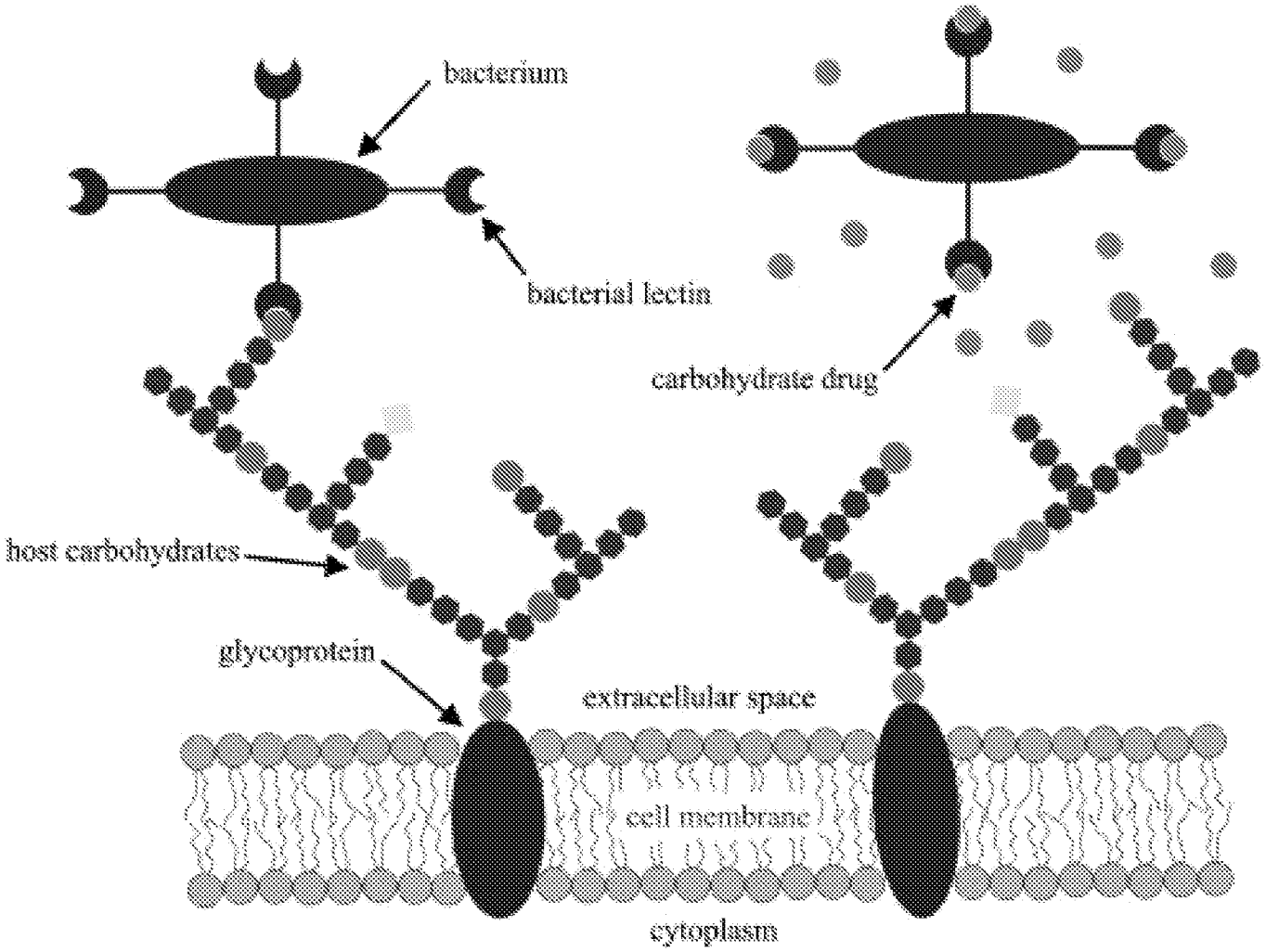

bacterium
bacterial lectin
carbohydrate drug
host carbohydrates
glycoprotein
extracellular space
cell membrane
cytoplasm

FIG. 10B

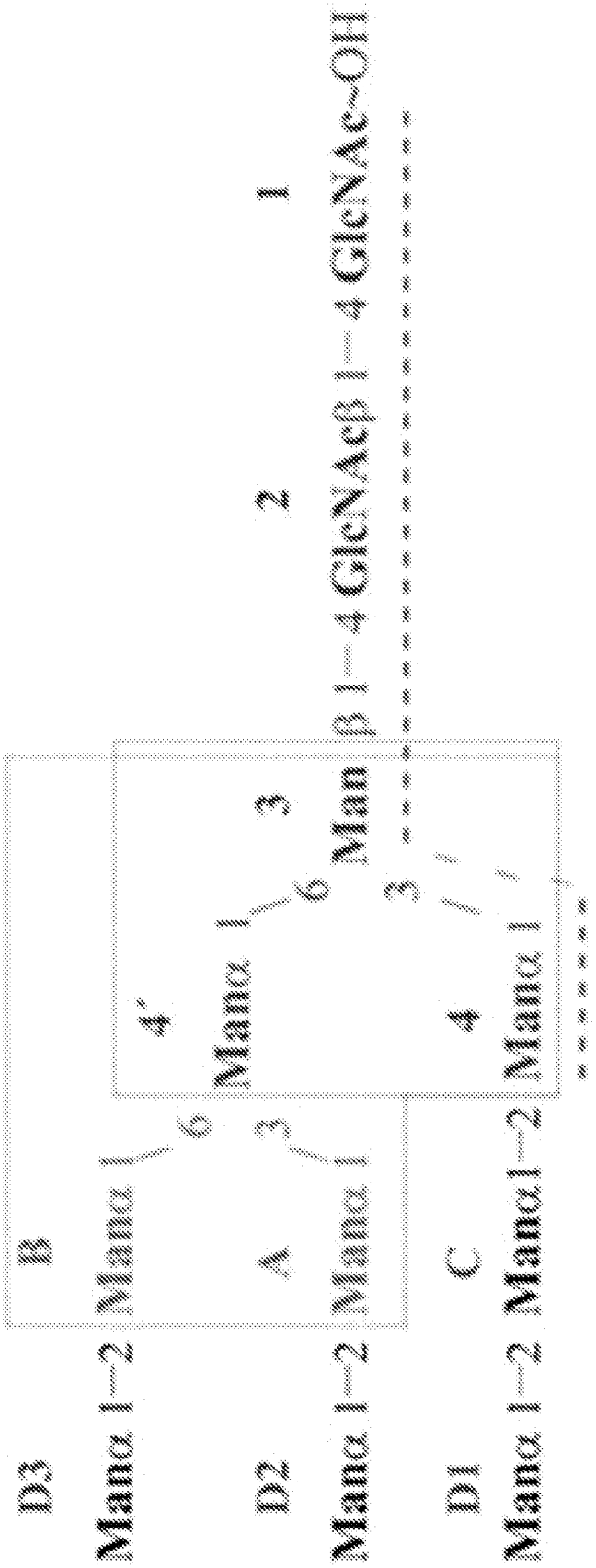
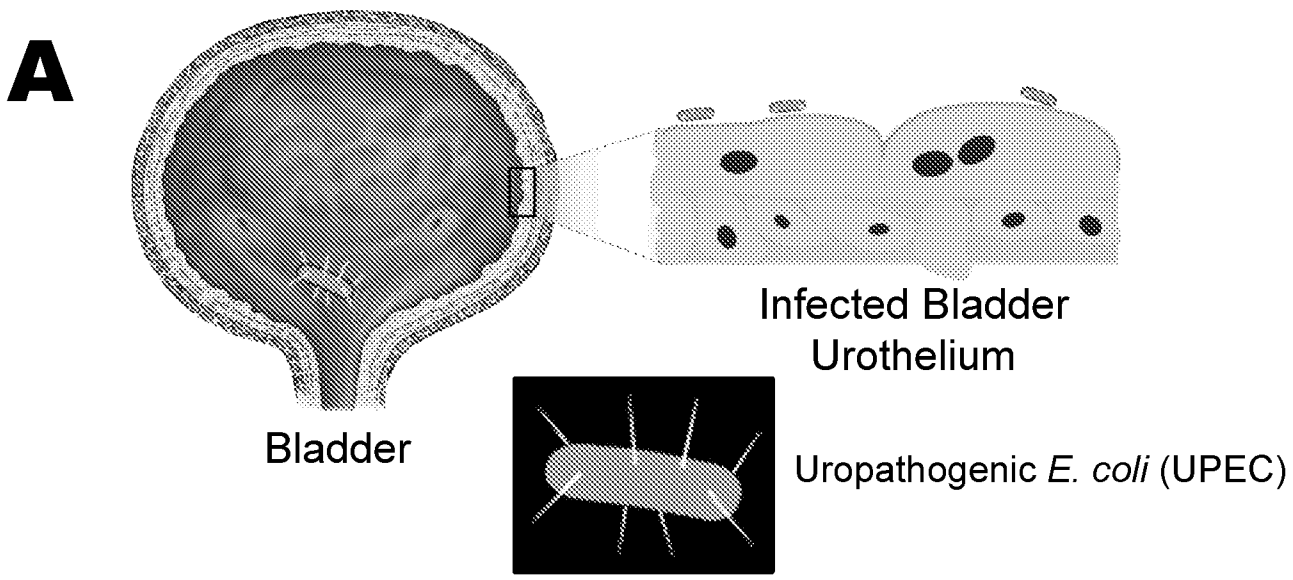

D3
Mana 1—2
B
Mana 1
6
D2
Mana 1—2
A
3
Mana 1
D1
Mana 1—2
C
Mana1—2
Mana 1
4'
6
Man
3
4
Mana 1
β 1—4 GlcNAcβ 1—4 GlcNAc-OH
1
2

FIG. 10C


A
Infected Bladder Urothelium
Bladder
Uropathogenic E. coli (UPEC)

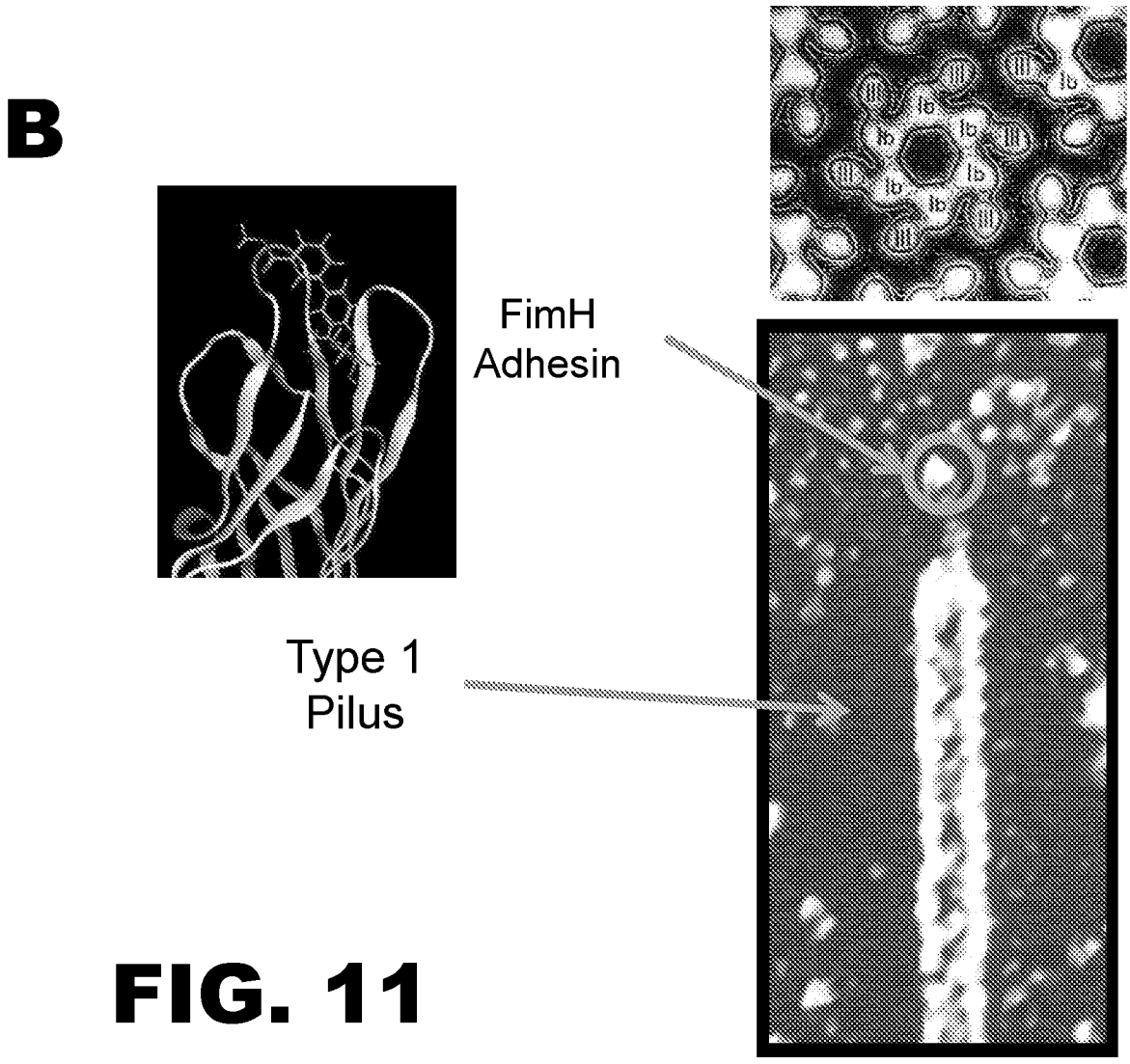

B
FimH Adhesin
Type 1 Pilus

FIG. 11

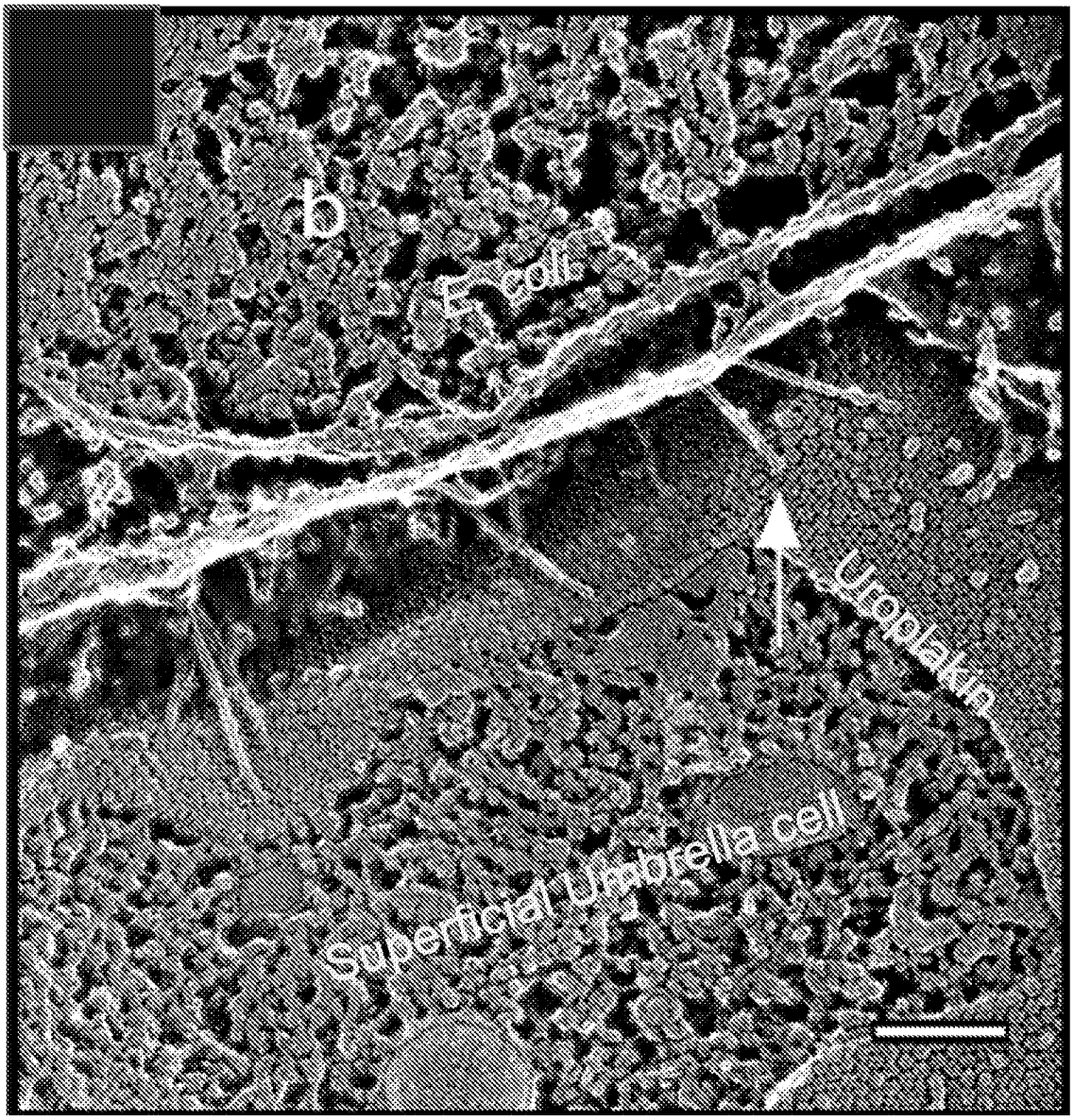
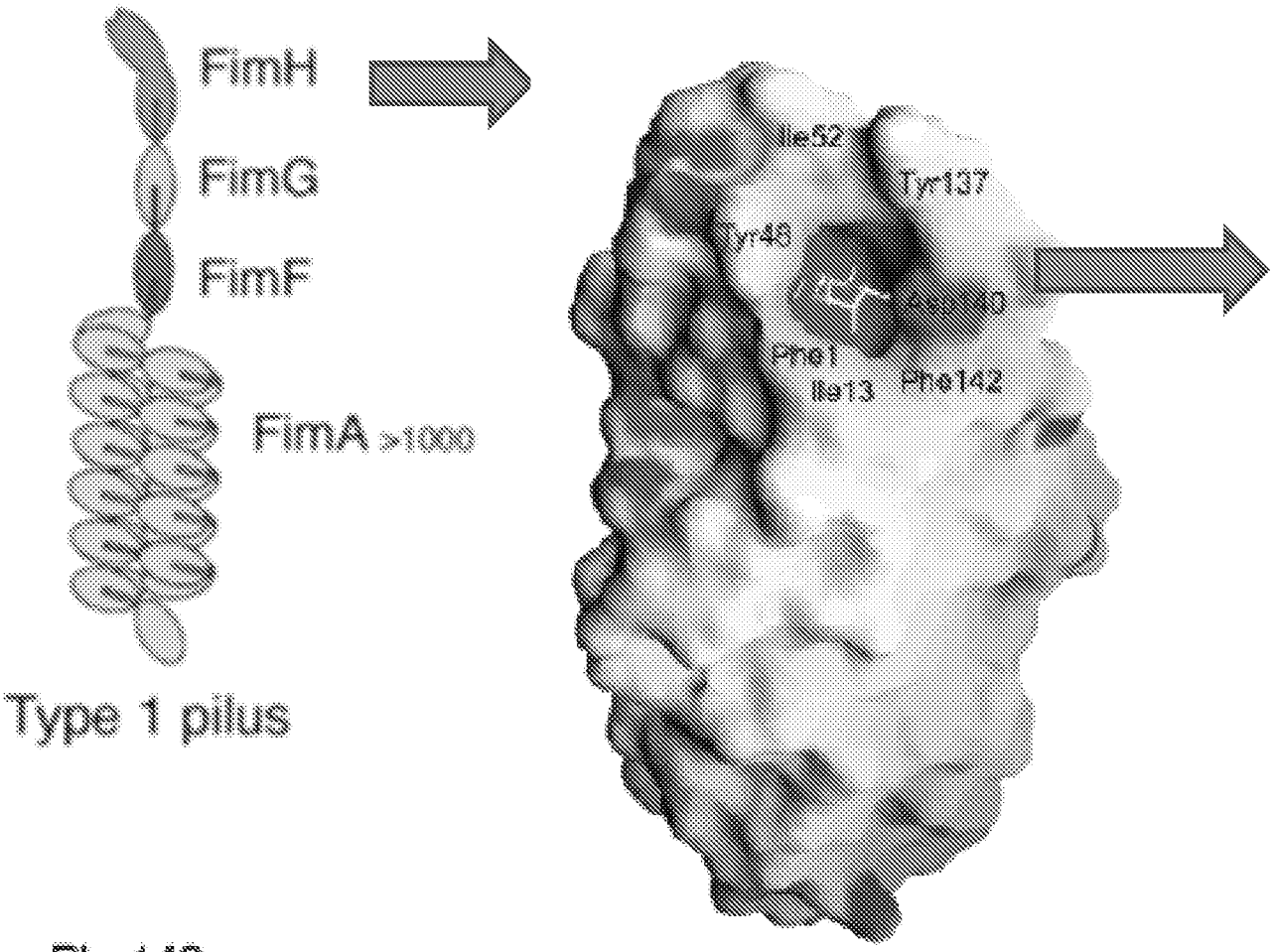


FIG. 11C


FimH
FimG
FimF
FimA >1000
Type 1 pilus
Ile52
Tyr137
Tyr48
Phe1
Ile13
Phe142

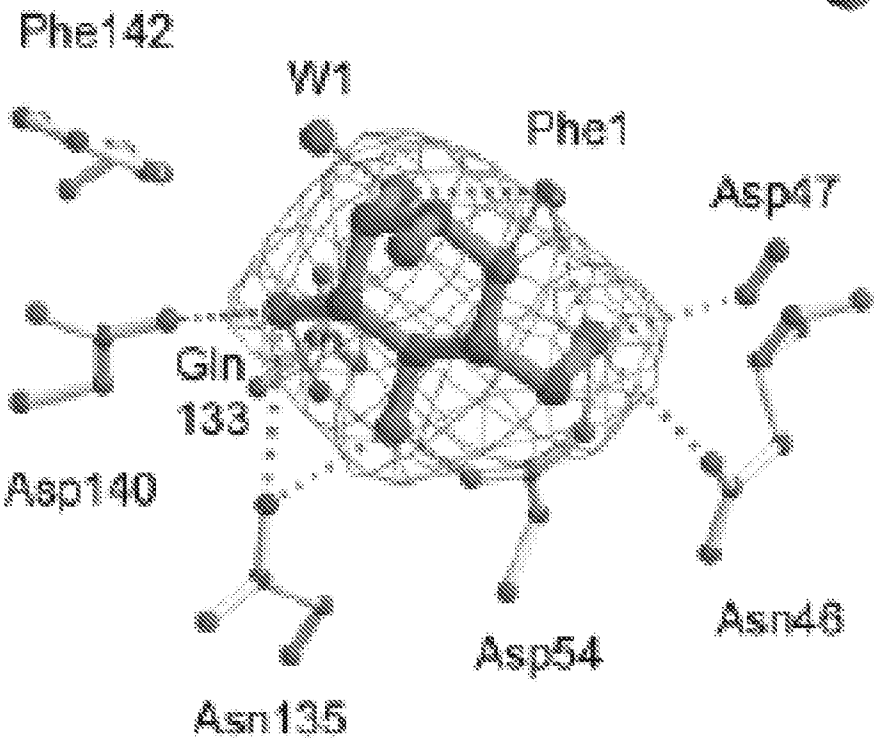

Phe142
W1
Phe1
Asp47
Gln
133
Asp140
Asp54
Asn46
Asn135

FIG. 12A

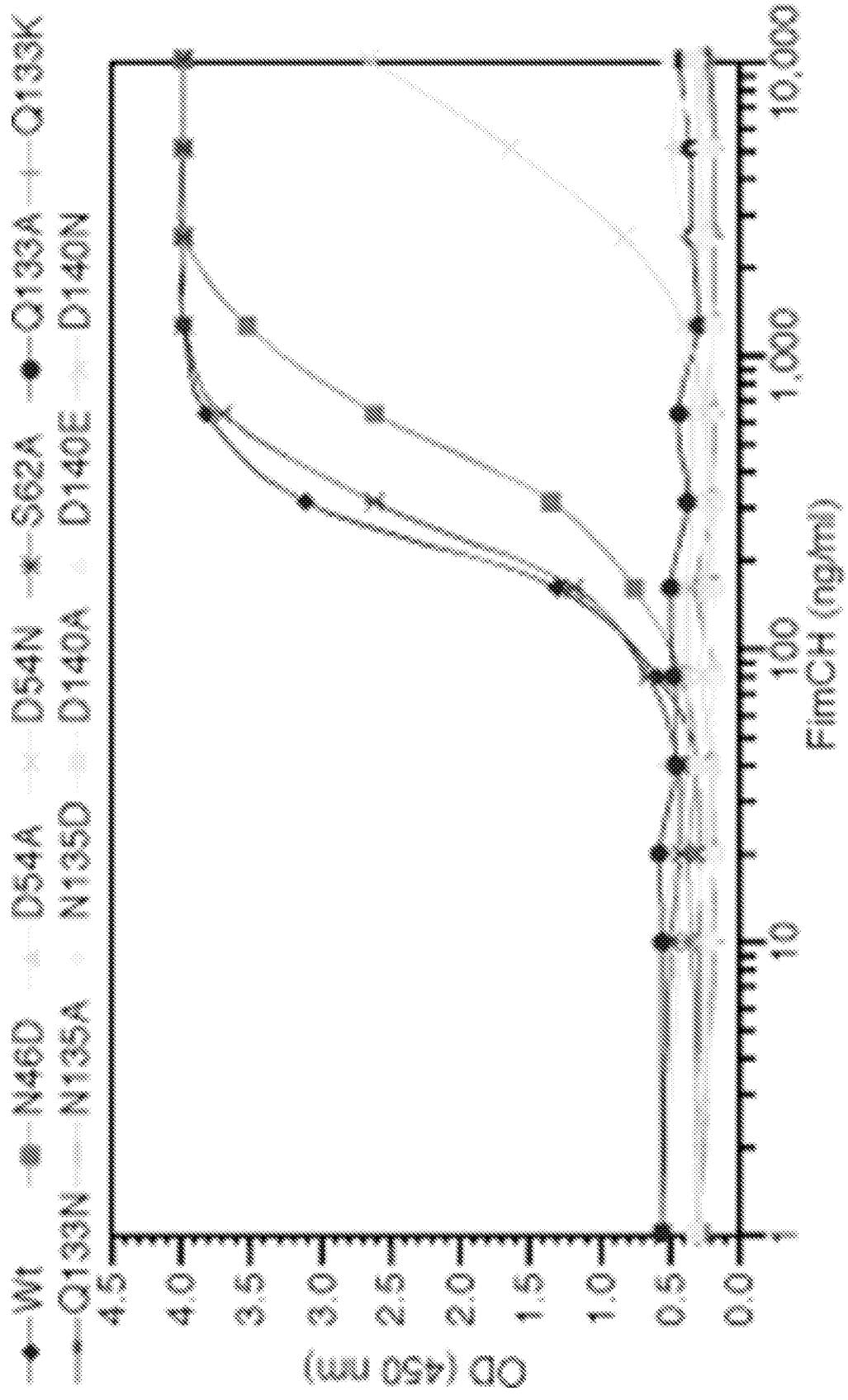
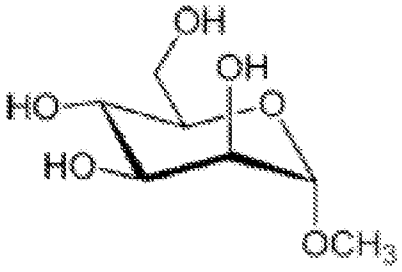
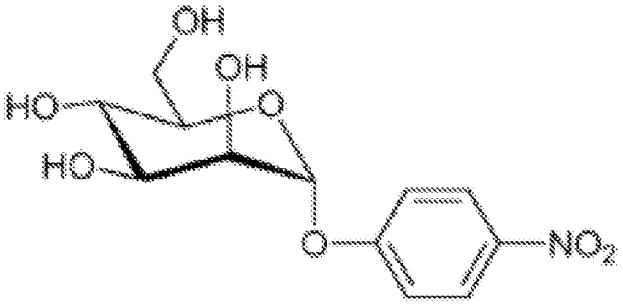

Wt
N46D
D54A
D54N
S62A
Q133A
Q133K
Q133N
N135A
N135D
D140A
D140E
D140N
OD (450 nm)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1
10
100
1,000
10,000
FimCH (ng/ml)

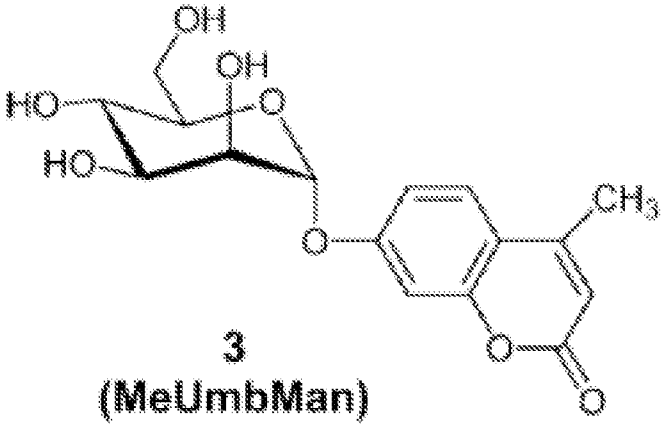
FIG. 12B



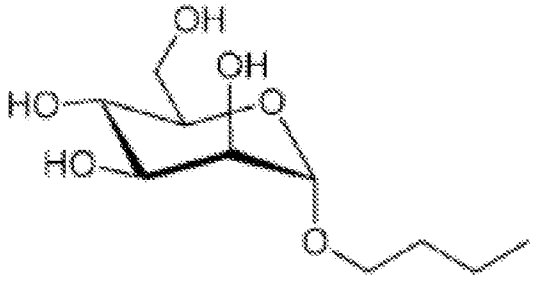
1
(MeMan)



2
(pNPMan)



3
(MeUmbMan)



4
(BuMan)

FIG. 13

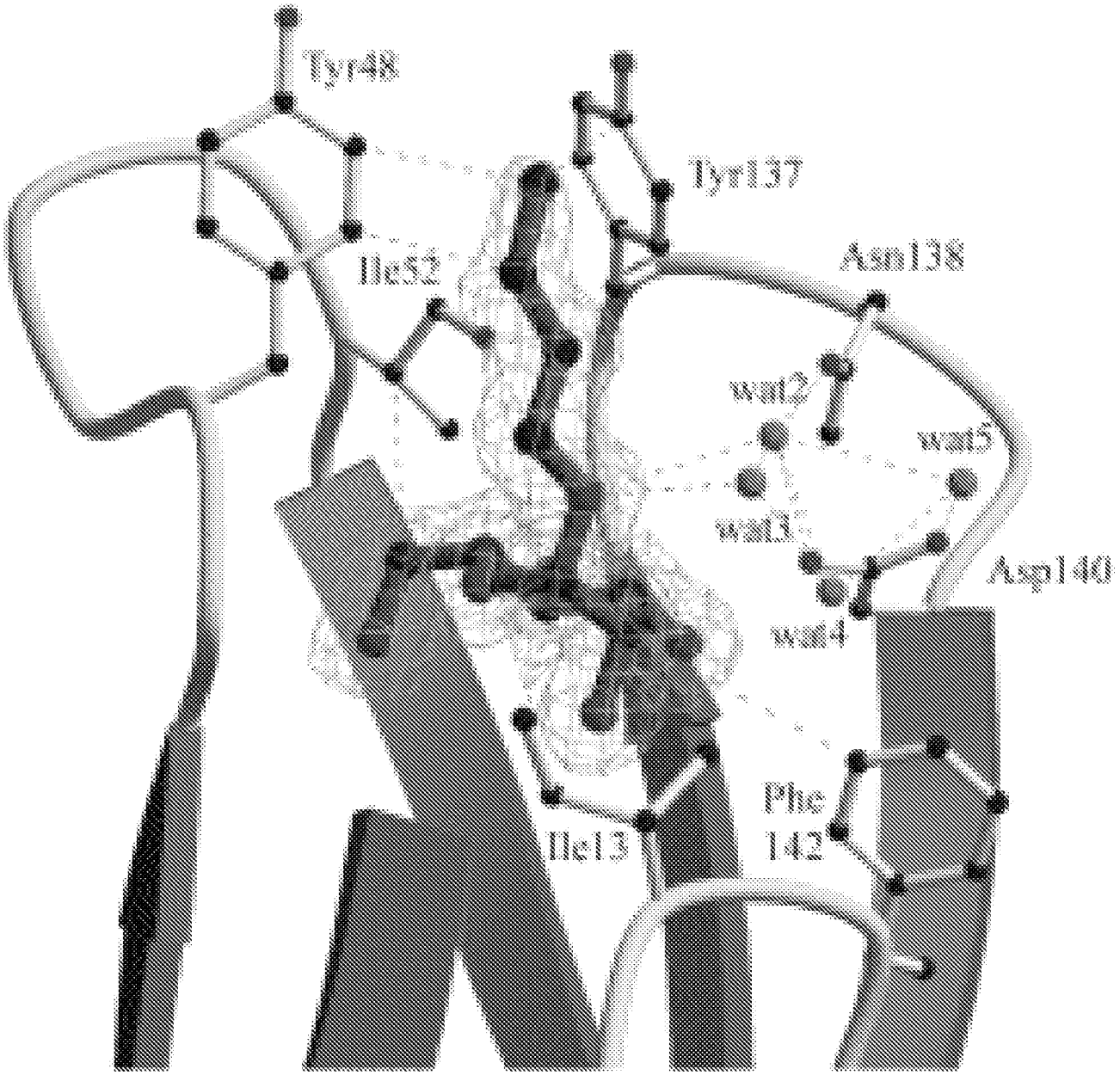

Tyr48
Tyr137
Ile52
Asn138
wat2
wat5
wat3
Asp140
wat4
Phe
142
Ile13

FIG. 14

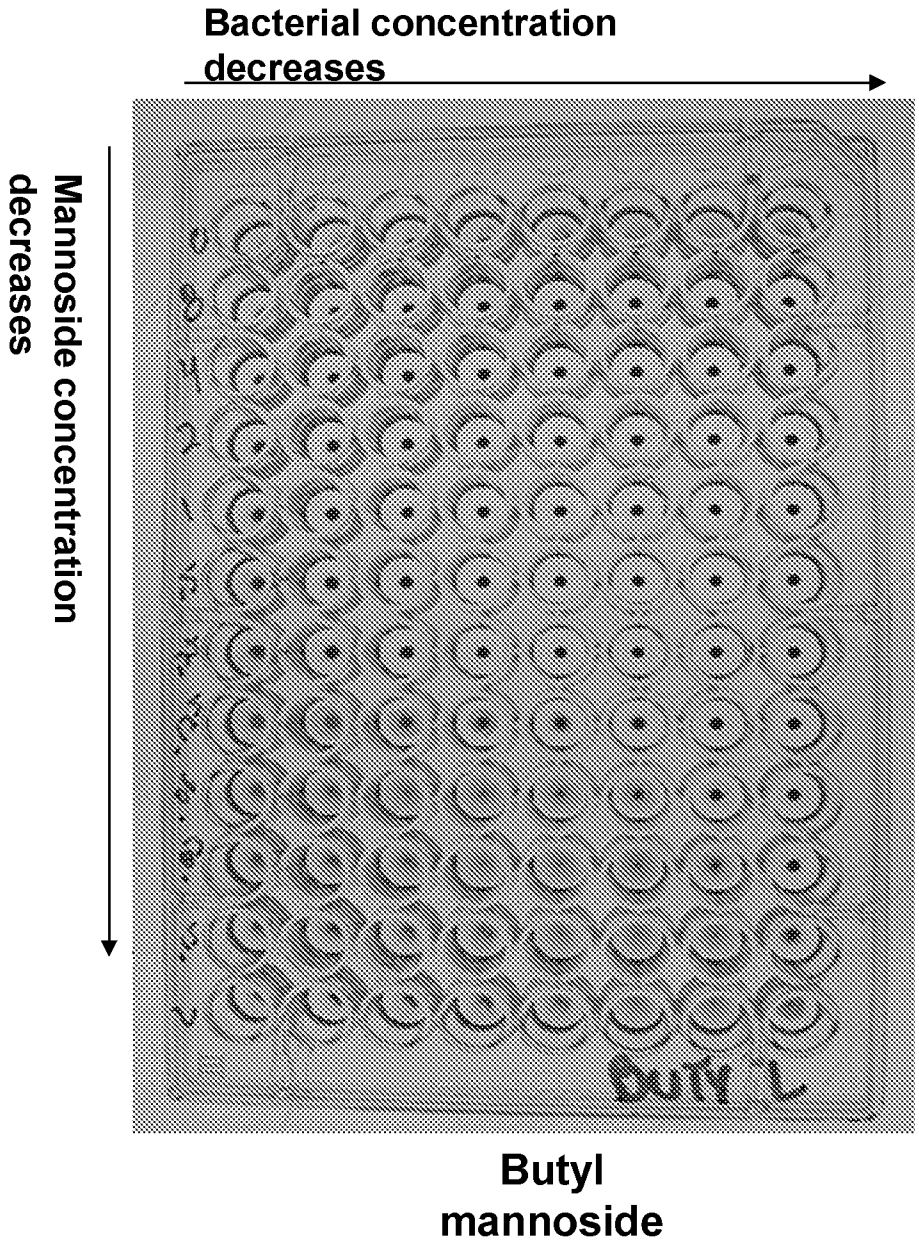

Bacterial concentration decreases
Mannoside concentration decreases
Butyl mannoside

FIG. 15

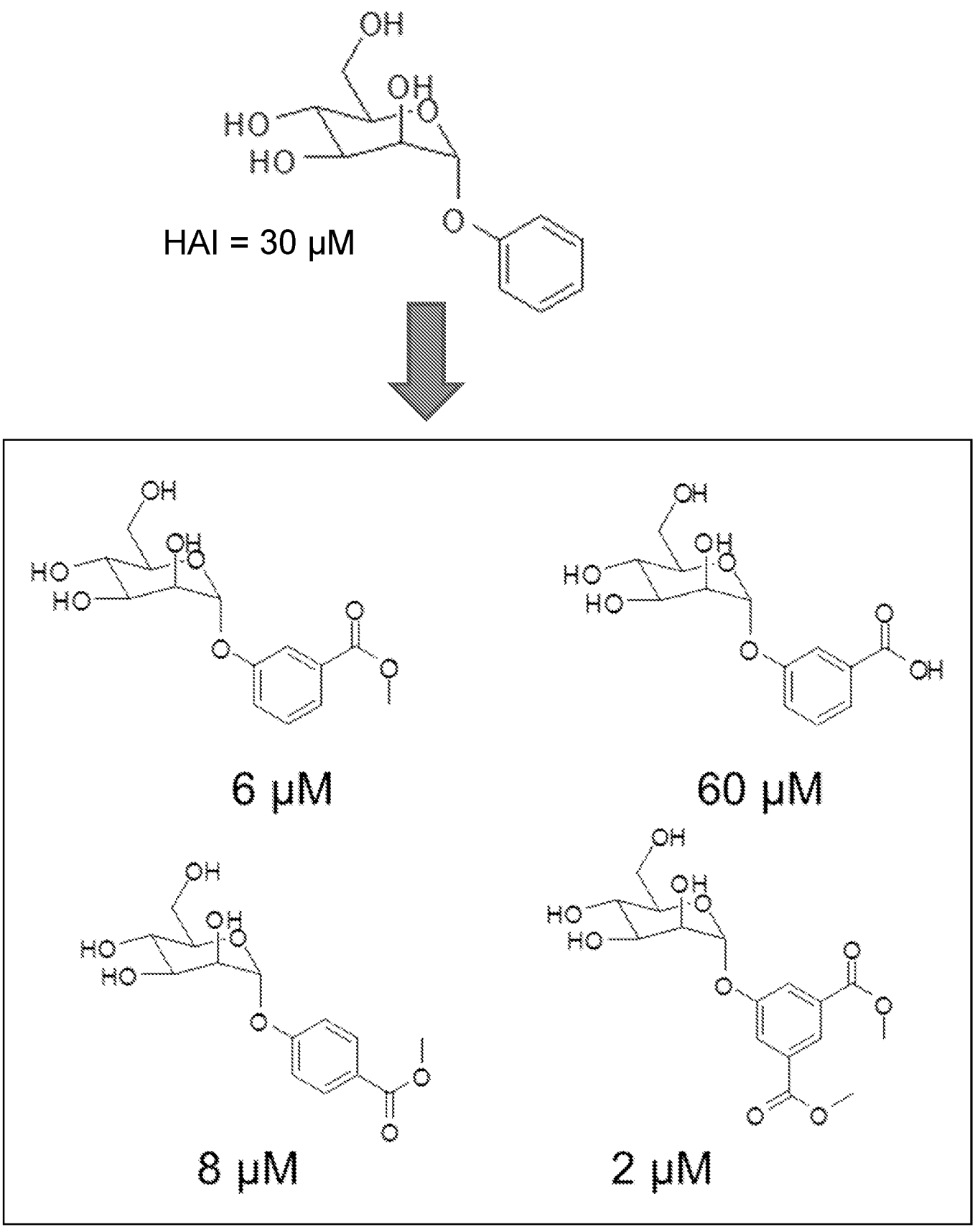
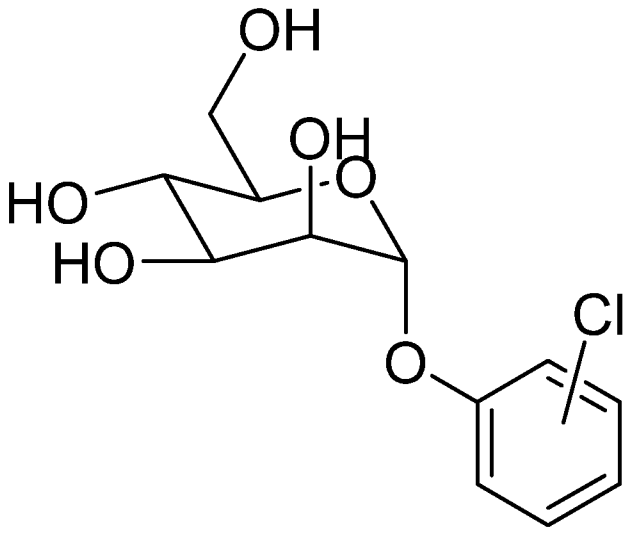


FIG. 16A

B



C

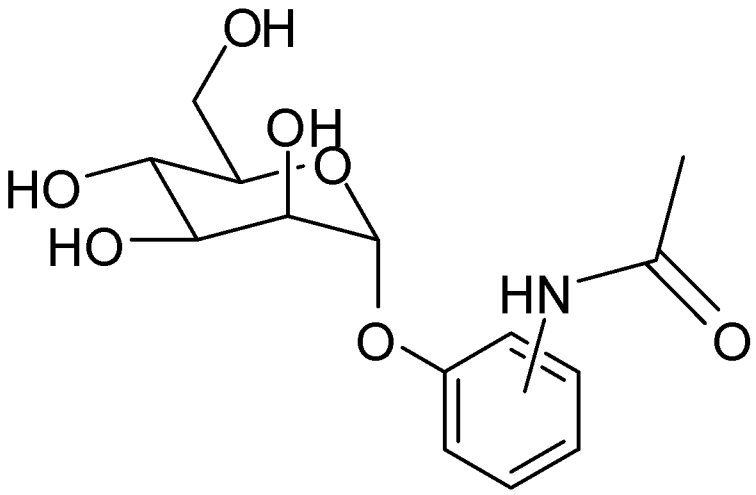


FIG. 16

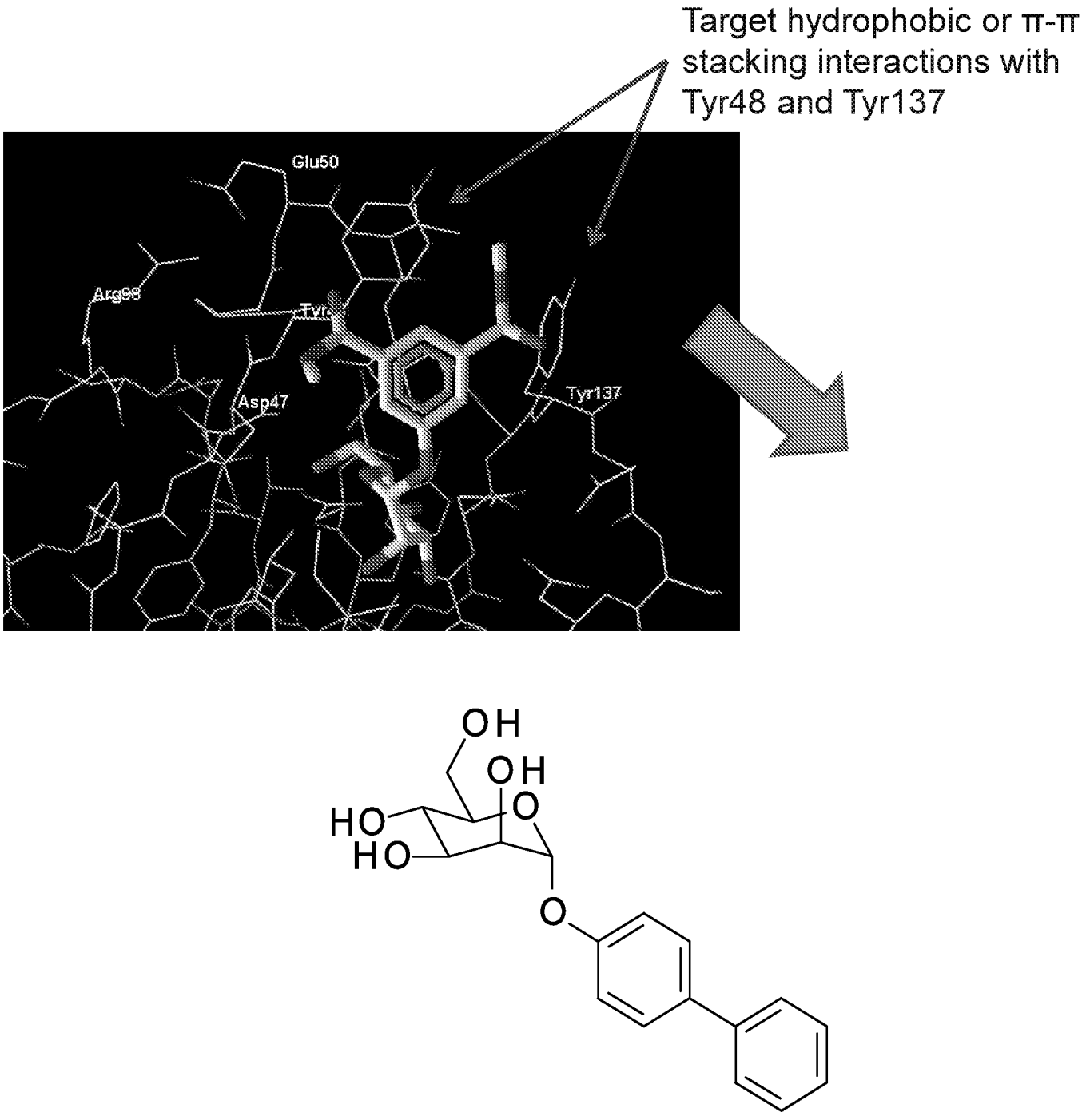

Target hydrophobic or π-π stacking interactions with Tyr48 and Tyr137
Glu50
Arg99
Asp47
Tyr137
OH
OH
HO
HO
O
O

FIG. 17

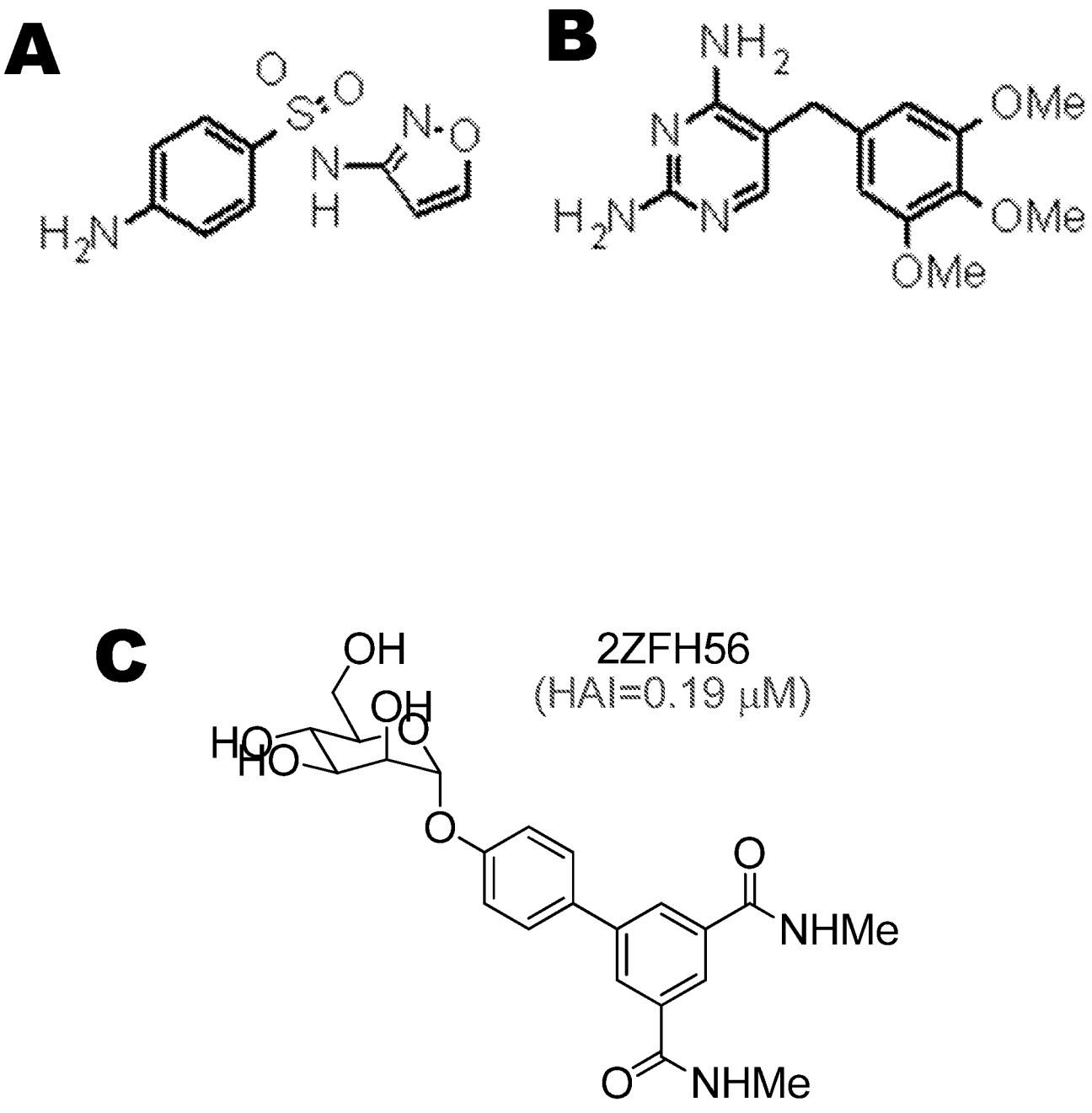


FIG. 18

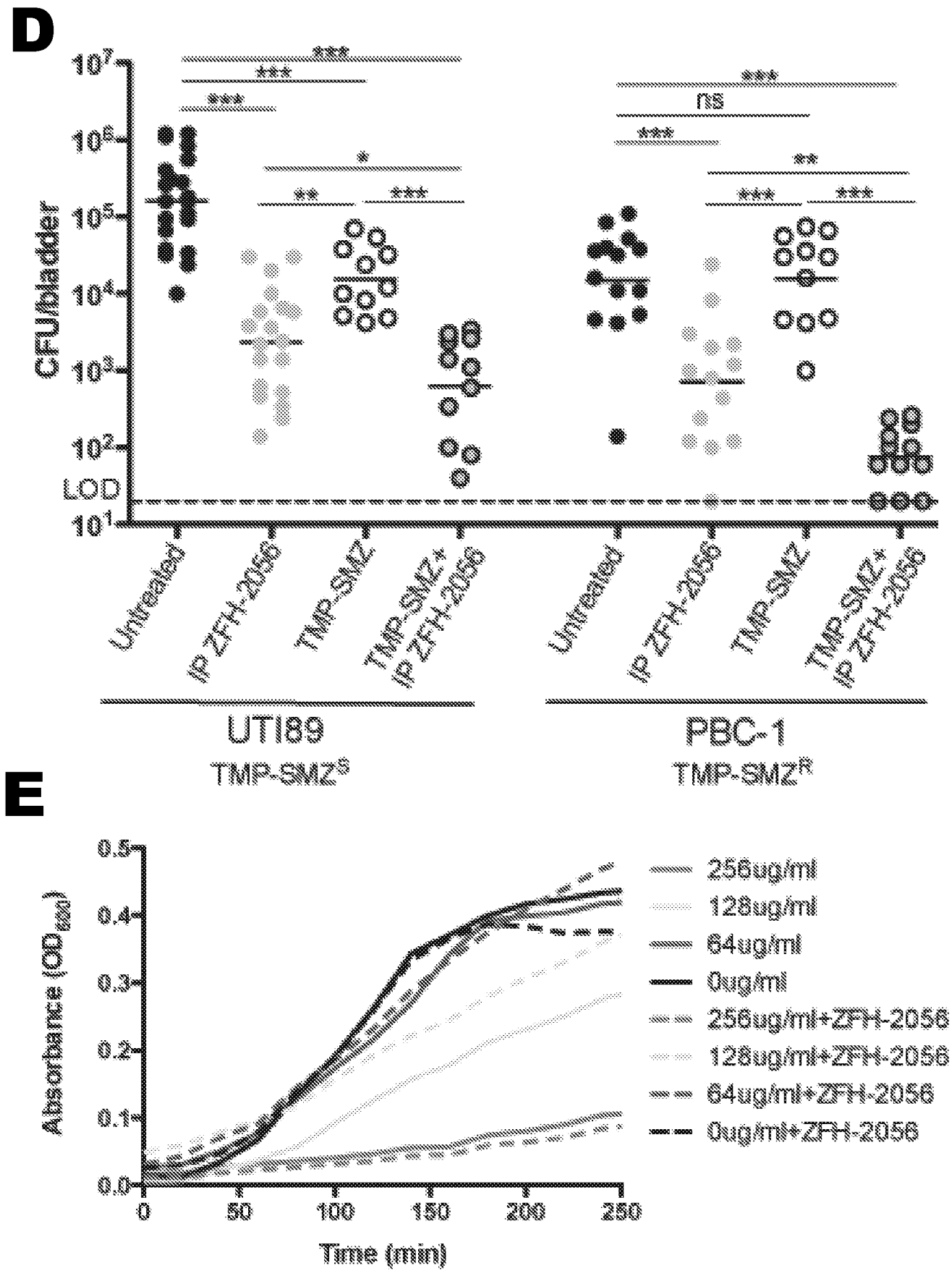

D
CFU/bladder
LOD
Untreated
IP ZFH-2056
TMP-SMZ
TMP-SMZ+ IP ZFH-2056
UTI89
TMP-SMZS
PBC-1
TMP-SMZR
ns
E
Absorbance (OD600)
Time (min)
256ug/ml
128ug/ml
64ug/ml
0ug/ml
256ug/ml+ZFH-2056
128ug/ml+ZFH-2056
64ug/ml+ZFH-2056
0ug/ml+ZFH-2056

FIG. 18

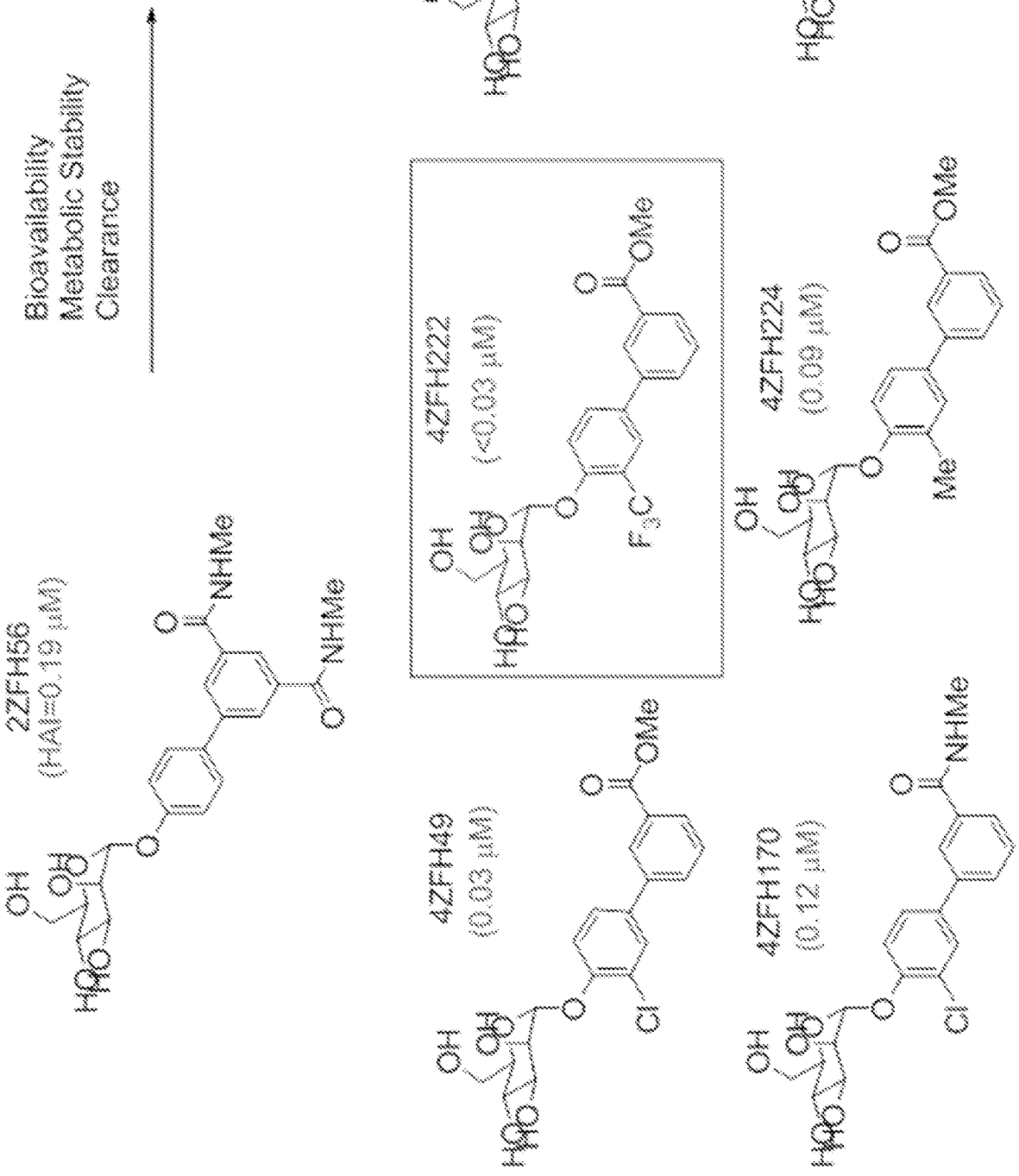
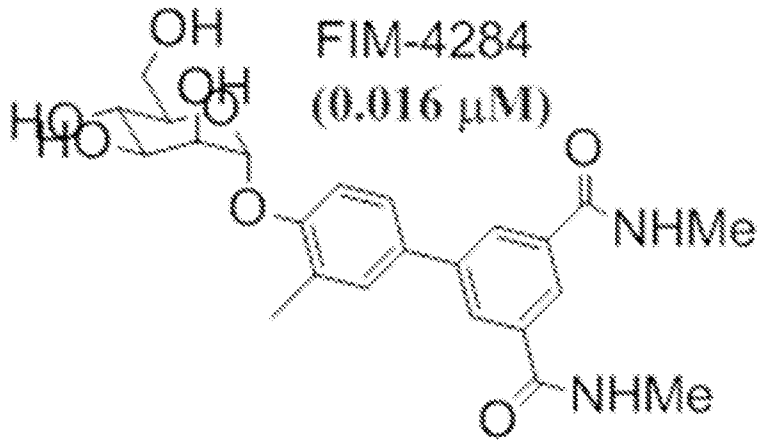

Bioavailability
Metabolic Stability
Clearance
2ZFH56
(HAI=0.19 μM)
4ZFH49
(0.03 μM)
4ZFH22
(<0.03 μM)
4ZFH24
(0.09 μM)
4ZFH170
(0.12 μM)
4ZFH228
(0.19 μM)
4ZFH220
(0.75 μM)

FIG. 19

A


OH
OH
HO
HO
O
O
FIM-4284
(0.016 μM)
O
NHMe
O
NHMe

B

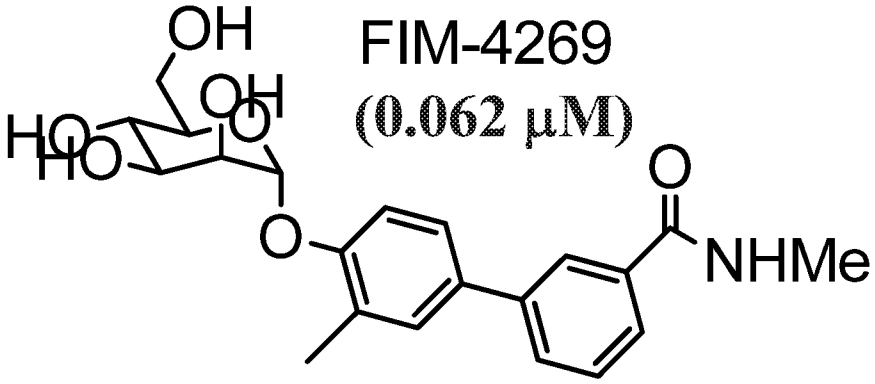

OH
OH
HO
HO
O
O
FIM-4269
(0.062 μM)
O
NHMe

FIG. 20

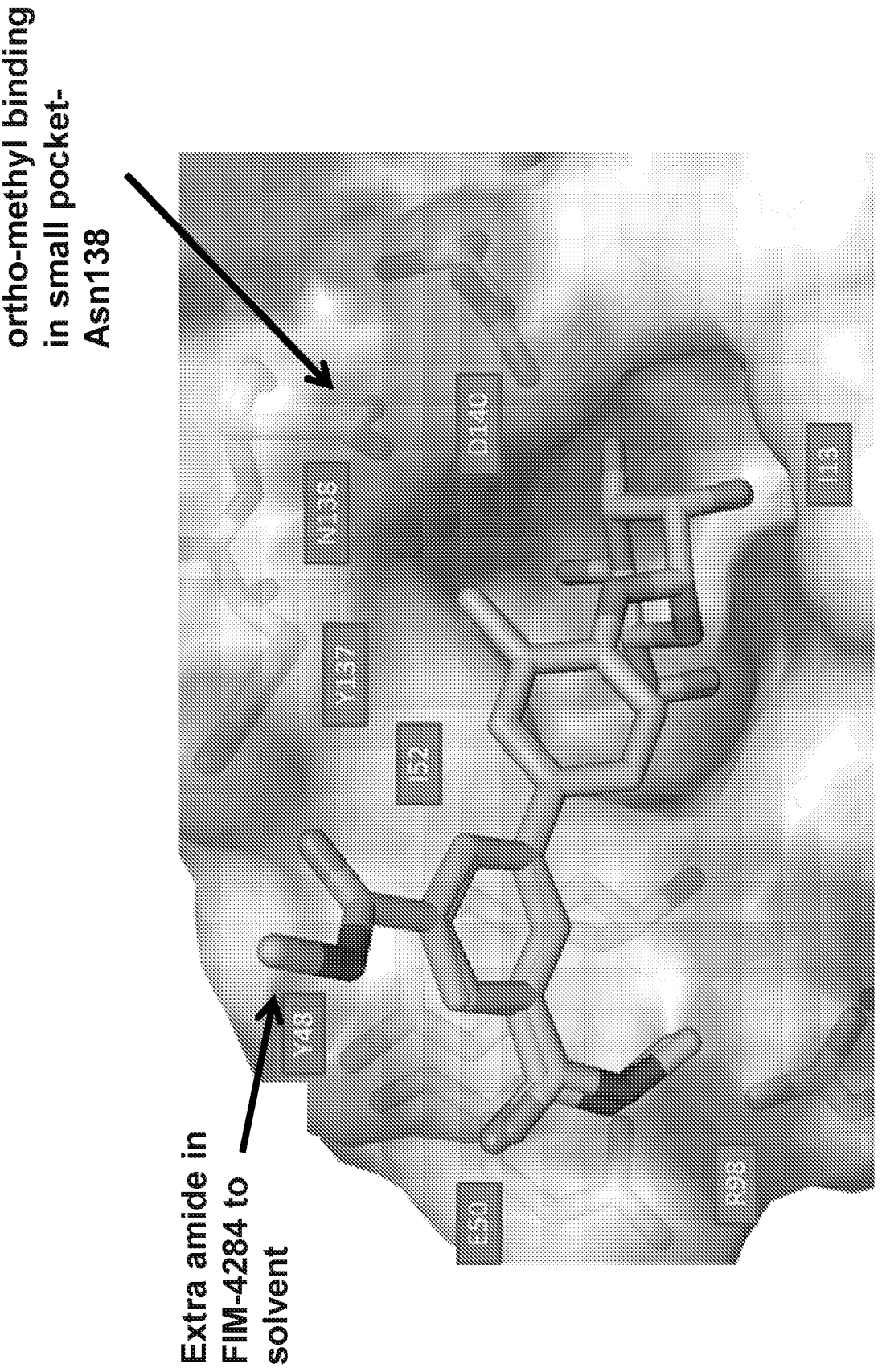

ortho-methyl binding in small pocket- Asn138
Extra amide in FIM-4284 to solvent
N138
D140
Y148
Y157
I52
E50
P53
I13

FIG. 20C

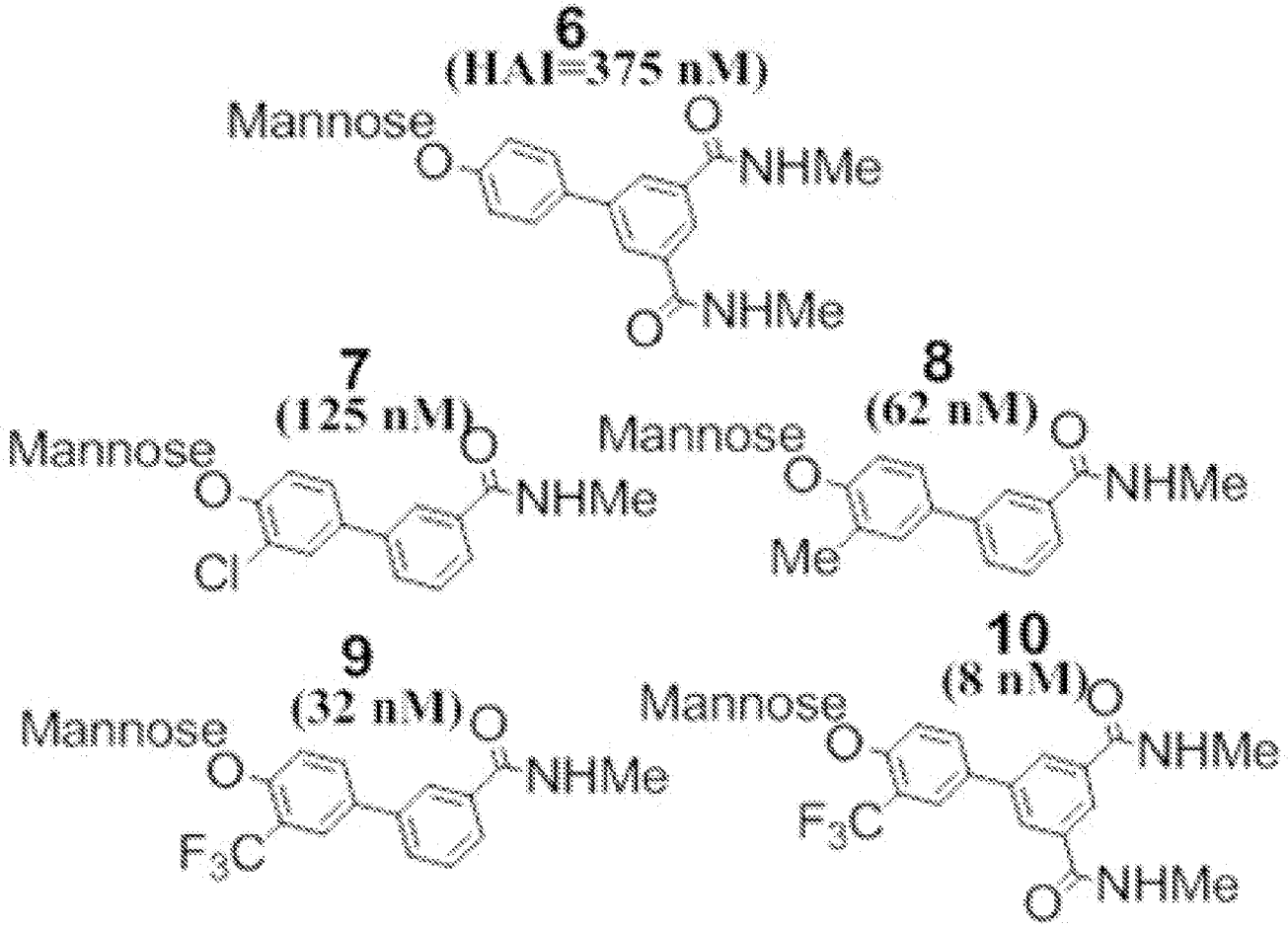

6
(HAI=375 nM)
Mannose
O
NHMe
NHMe
7
(125 nM)
Mannose
O
Cl
NHMe
8
(62 nM)
Mannose
O
Me
NHMe
9
(32 nM)
Mannose
O
F3C
NHMe
10
(8 nM)
Mannose
O
F3C
NHMe
NHMe

FIG. 21A

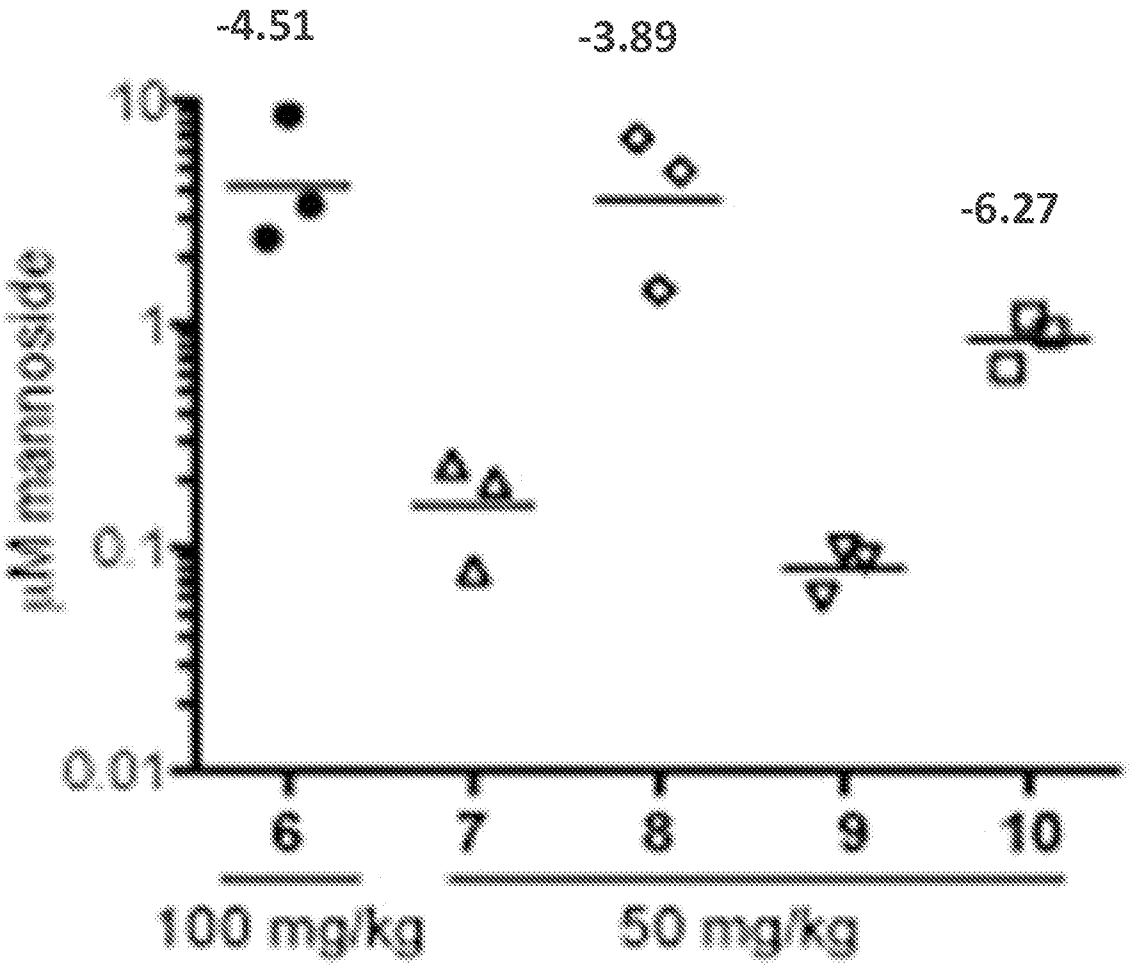


FIG. 21B

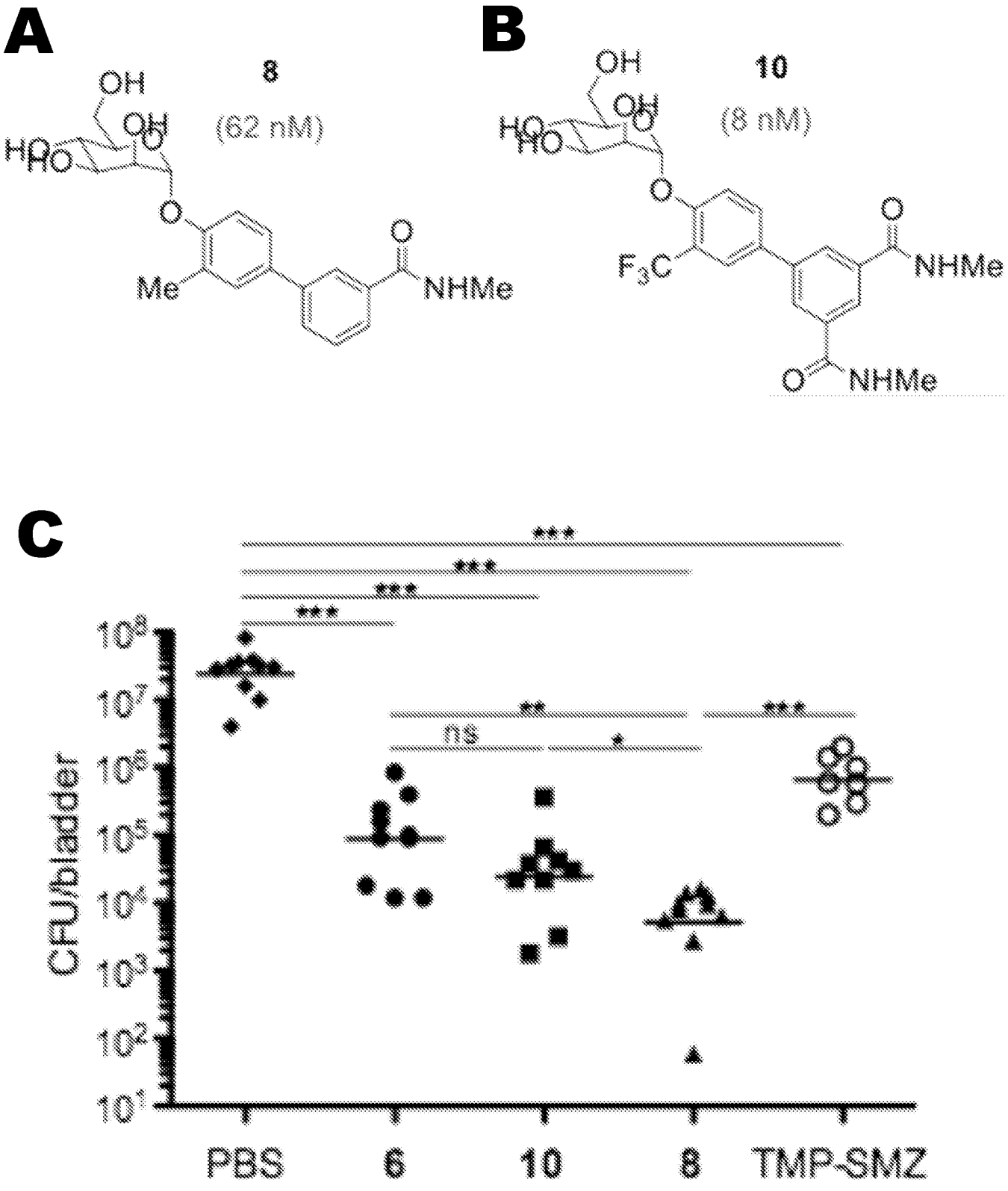

A
8
(62 nM)
OH
OH
HO
HO
O
Me
O
NHMe
B
10
(8 nM)
OH
OH
HO
HO
O
F3C
O
NHMe
O
NHMe
C
CFU/bladder
10^8
10^7
10^6
10^5
10^4
10^3
10^2
10^1
***
***
***
***
**
*
ns
***
PBS
6
10
8
TMP-SMZ

FIG. 22

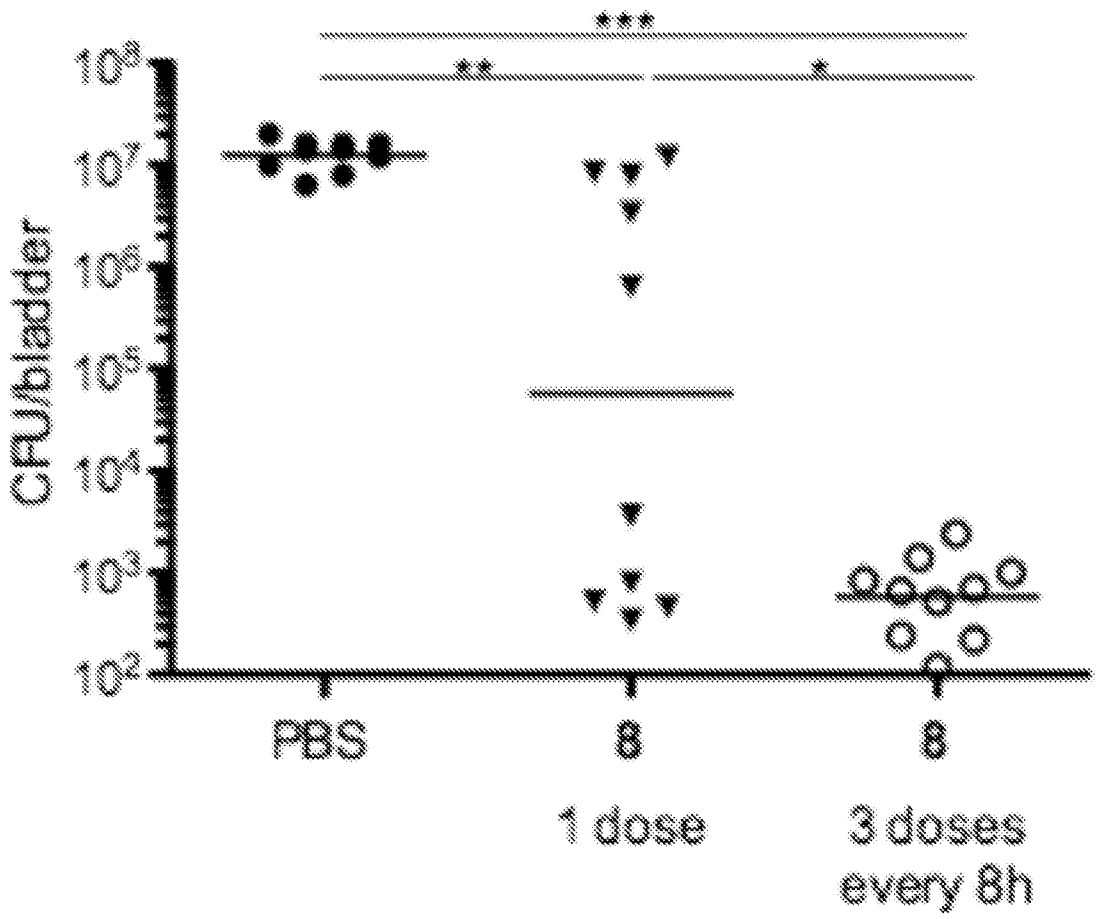

***
**
*
CFU/bladder
10^8
10^7
10^6
10^5
10^4
10^3
10^2
PBS
8
8
1 dose
3 doses
every 8h

FIG. 22D

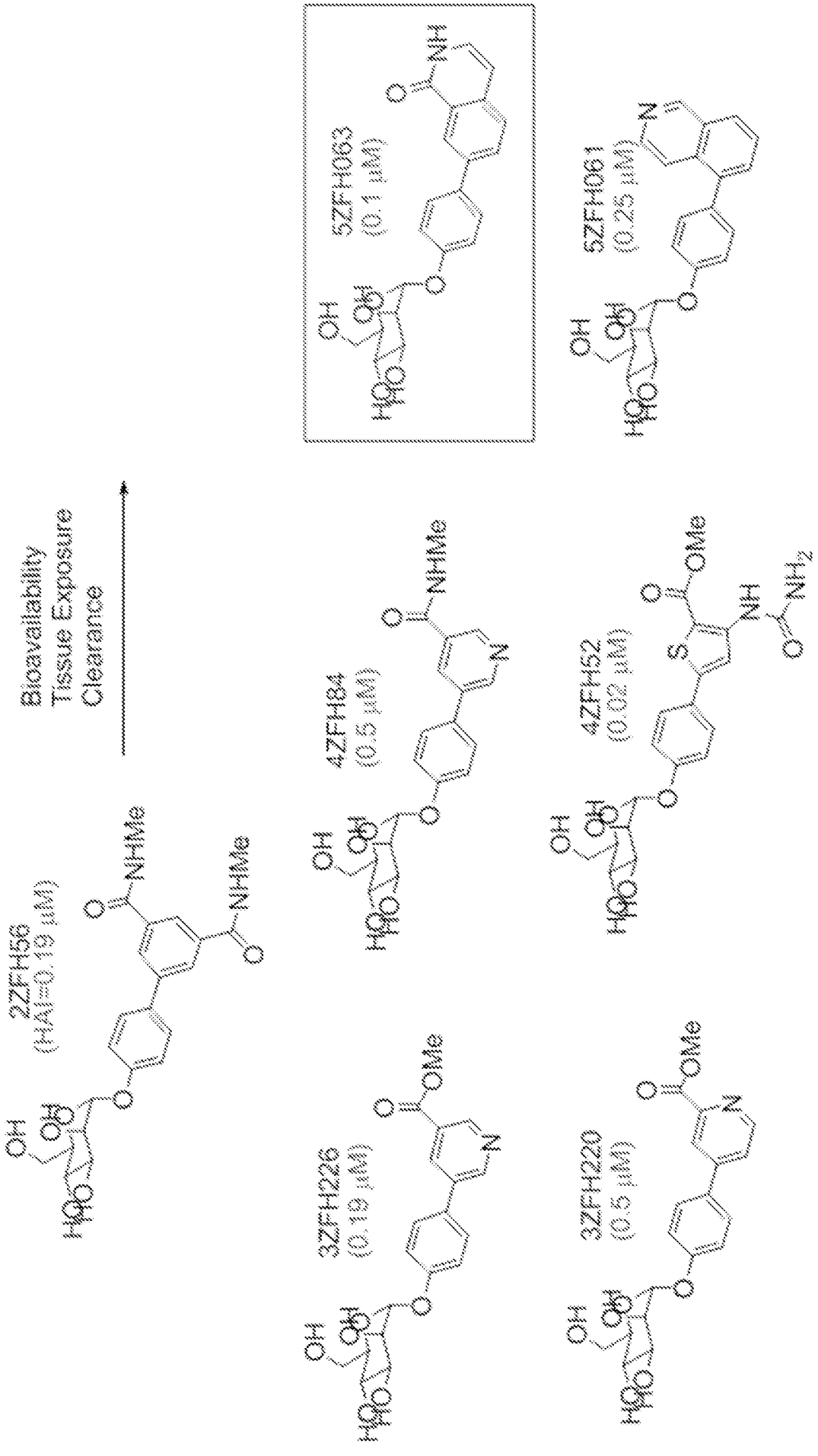

Bioavailability
Tissue Exposure
Clearance
2ZFH56
(HAI=0.19 μM)
4ZFH84
(0.5 μM)
4ZFH52
(0.02 μM)
3ZFH226
(0.19 μM)
3ZFH220
(0.5 μM)
5ZFH063
(0.1 μM)
5ZFH061
(0.25 μM)

FIG. 23

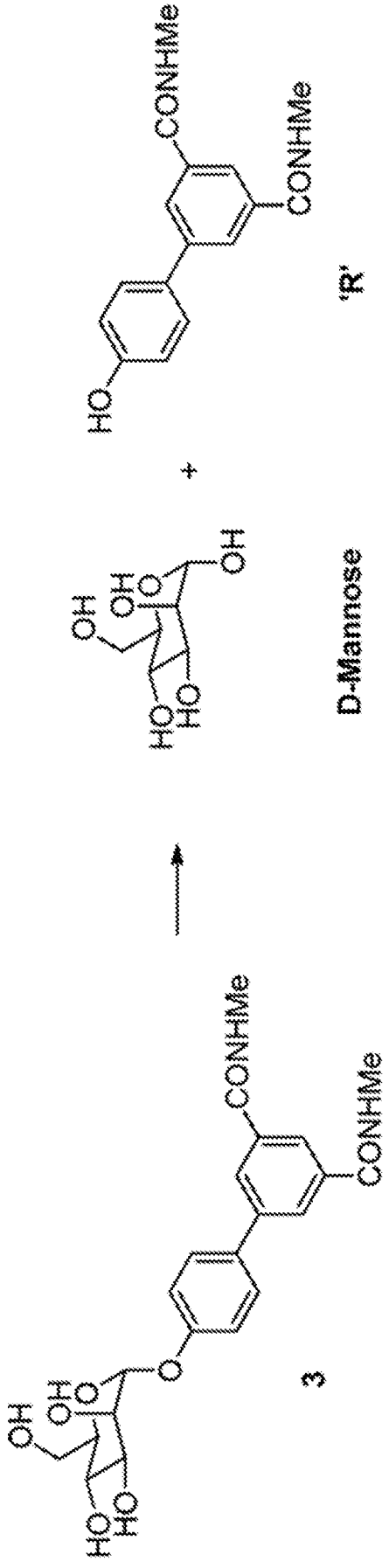

CONHMe
CONHMe
HO
'R'
+
OH
OH
O
OH
OH
HO
HO
D-Mannose
CONHMe
CONHMe
O
OH
OH
O
OH
OH
HO
HO
3

FIG. 24A

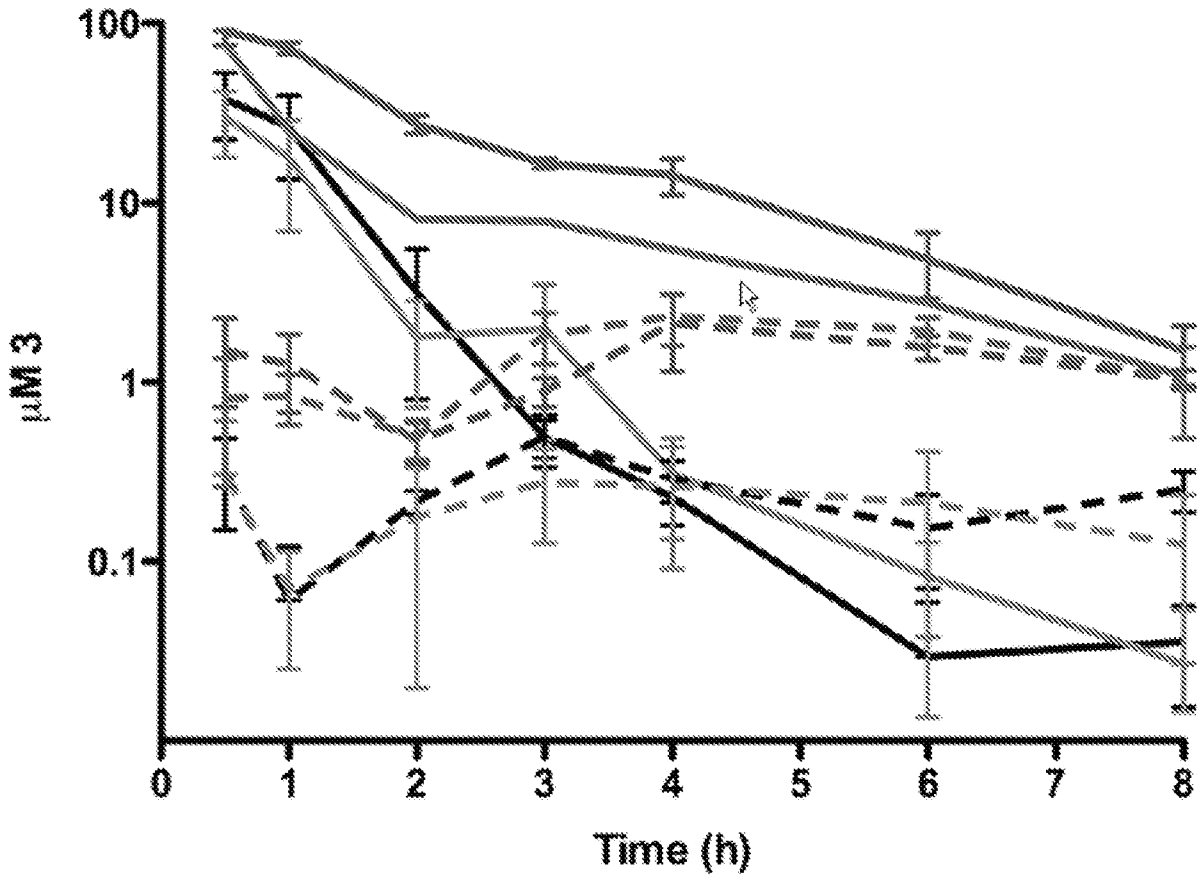

100
10
1
0.1
μM 3
0
1
2
3
4
5
6
7
8
Time (h)
PO 10mg/kg
PO 20mg/kg
PO 100mg/kg
PO 200mg/kg
PO 10mg/kg - R
PO 20mg/kg - R
PO 100mg/kg - R
PO 200mg/kg - R

FIG. 24B

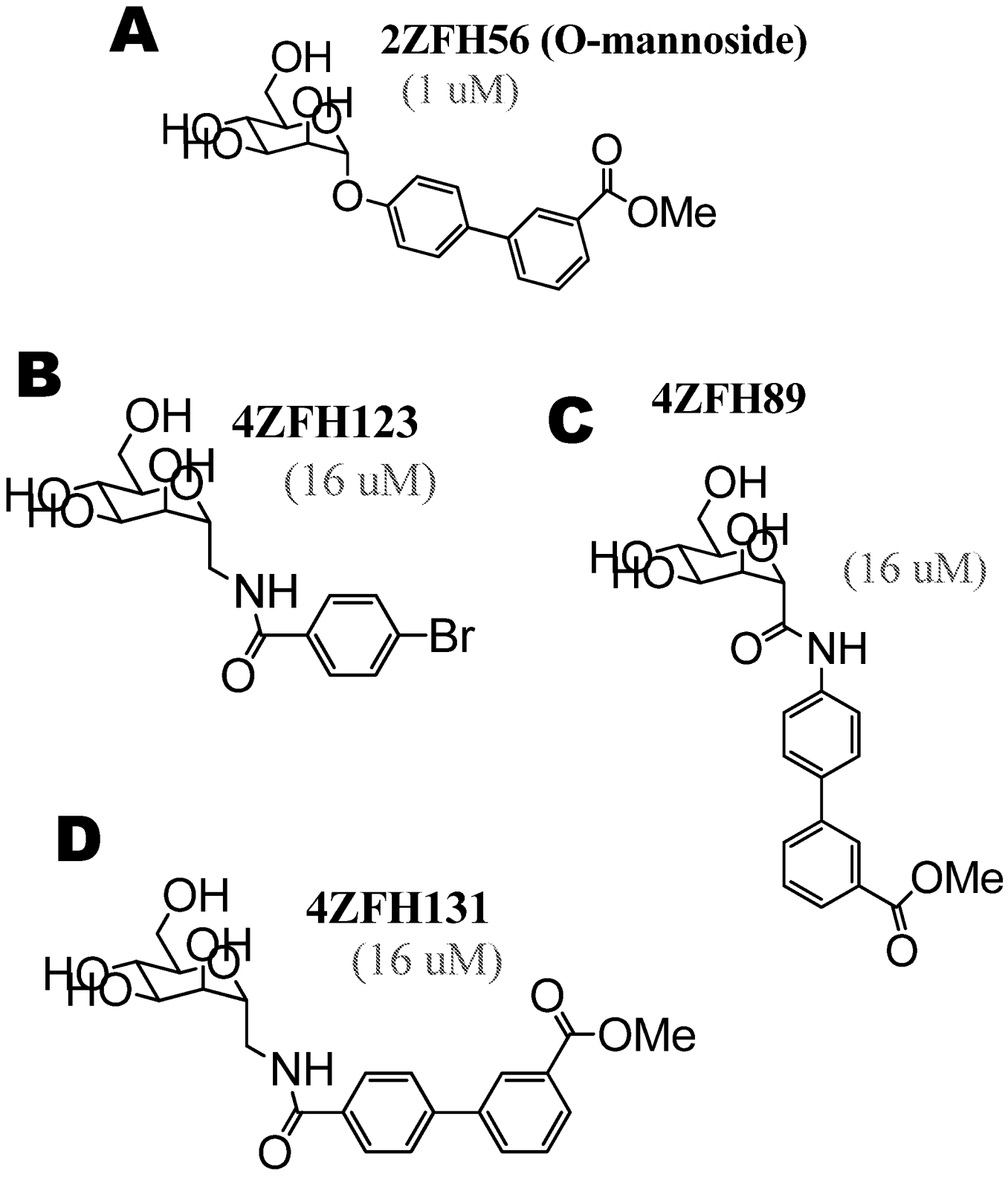
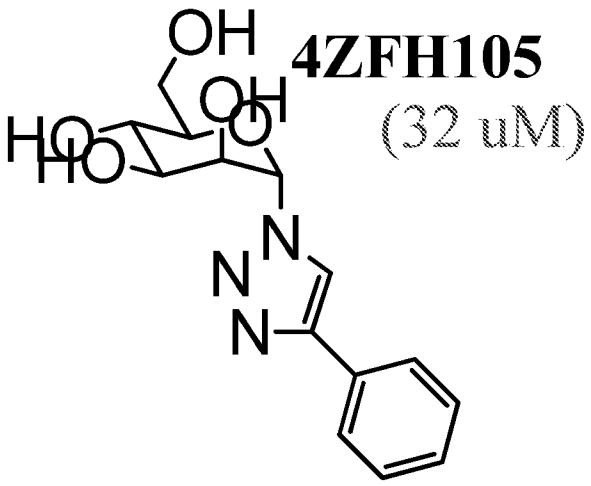

A
2ZFH56 (O-mannoside)
(1 uM)
OH
OH
HO
HO
O
O
O
OMe
B
4ZFH123
(16 uM)
OH
OH
HO
HO
O
NH
O
Br
C
4ZFH89
(16 uM)
OH
OH
HO
HO
O
O
NH
OMe
O
D
4ZFH131
(16 uM)
OH
OH
HO
HO
O
NH
O
O
OMe

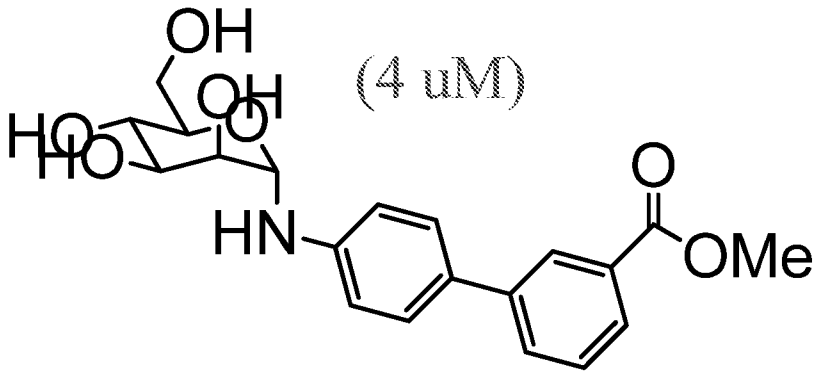
FIG. 25

E **4ZFH105**



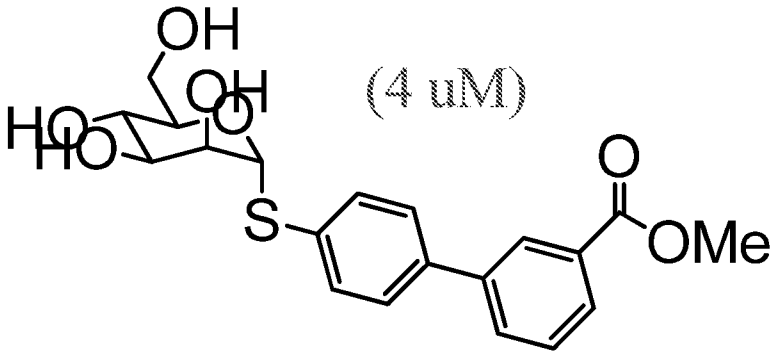
(32 uM)

F **4ZFH44 (N-mannoside)**



(4 uM)

G **4ZFH55 (S-mannoside)**

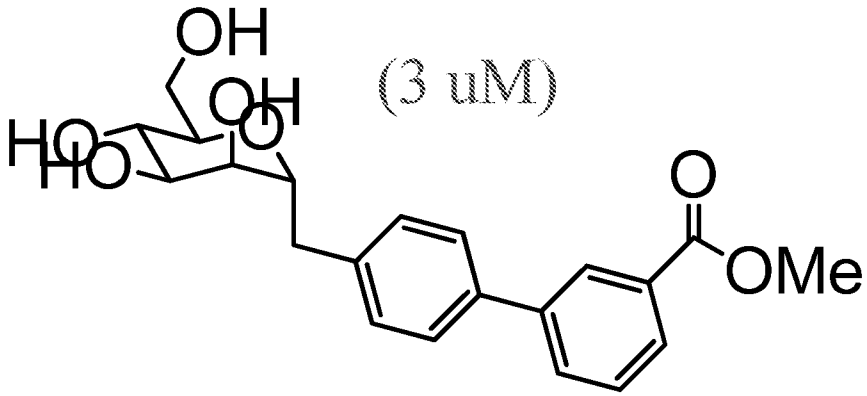


(4 uM)

FIG. 25

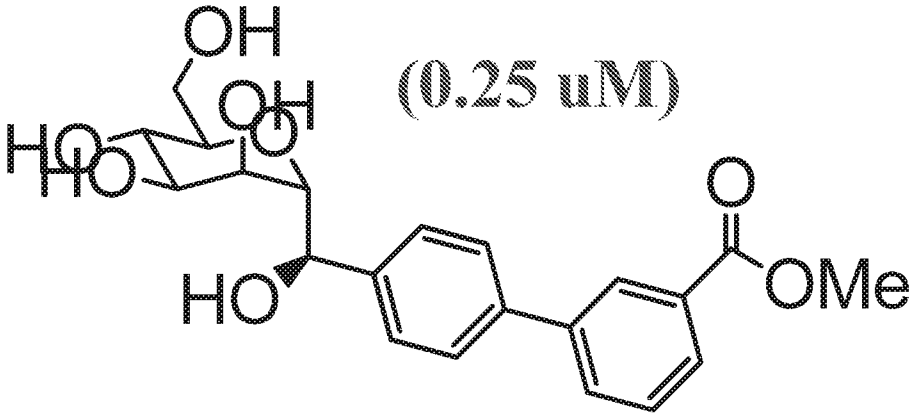
H

5ZFH049 (C-mannoside)



I

5ZFH038



J

5ZFH048

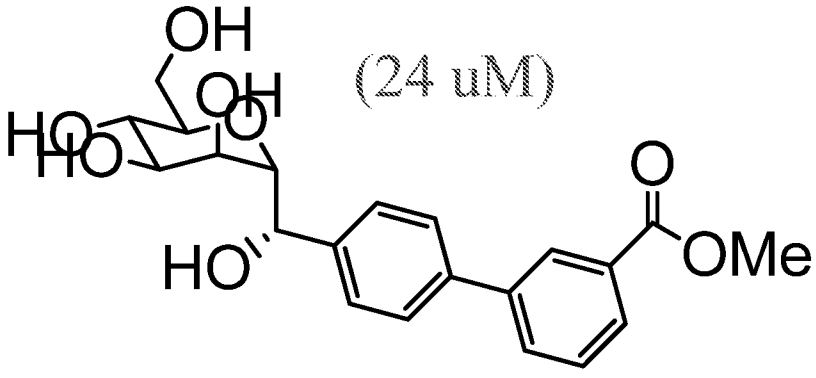


FIG. 25

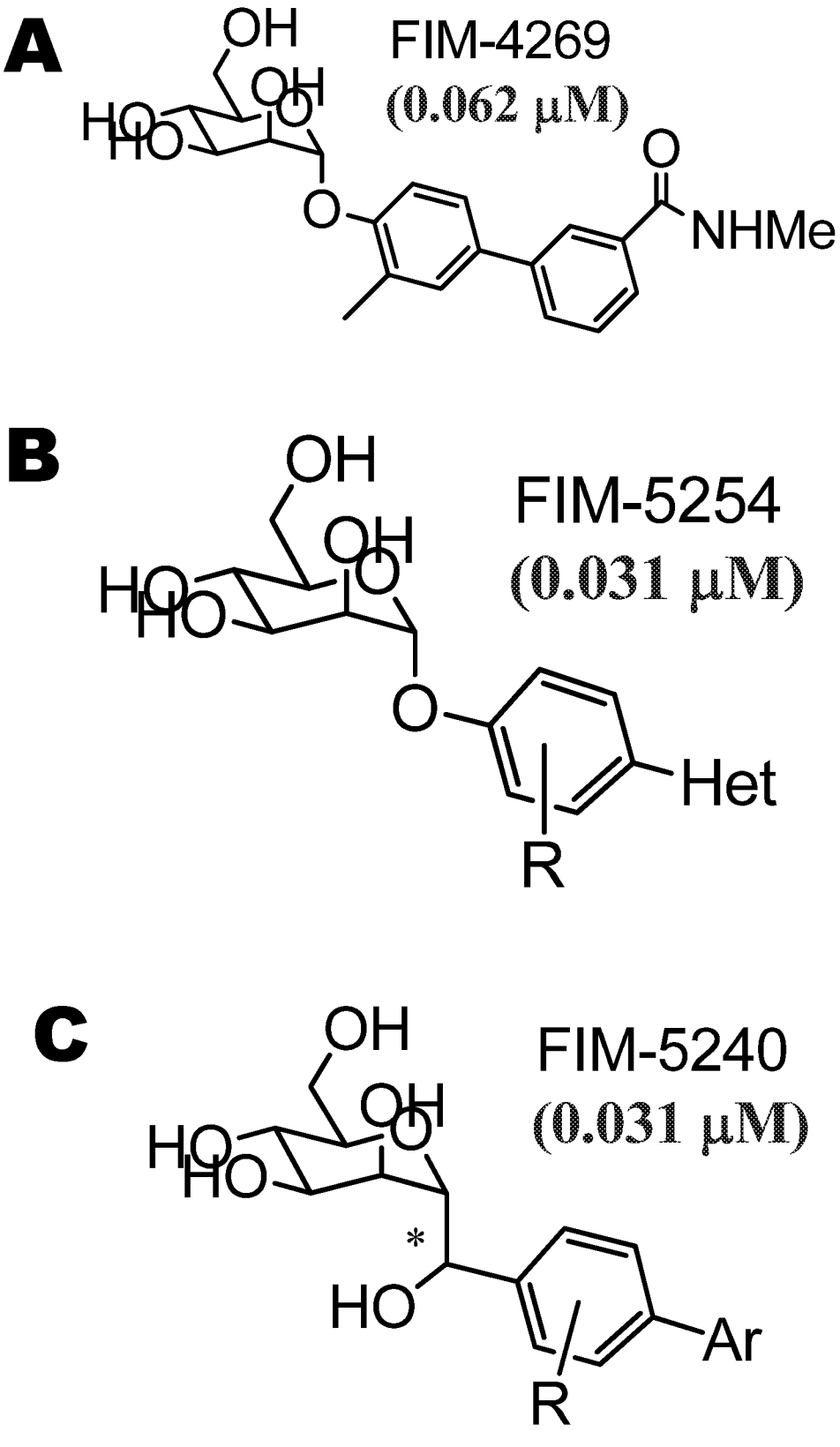

A
FIM-4269
(0.062 μM)
OH
OH
HO
HO
O
O
O
NHMe
B
FIM-5254
(0.031 μM)
OH
OH
HO
HO
O
O
Het
R
C
FIM-5240
(0.031 μM)
OH
OH
HO
HO
O
*
HO
Ar
R

FIG. 26

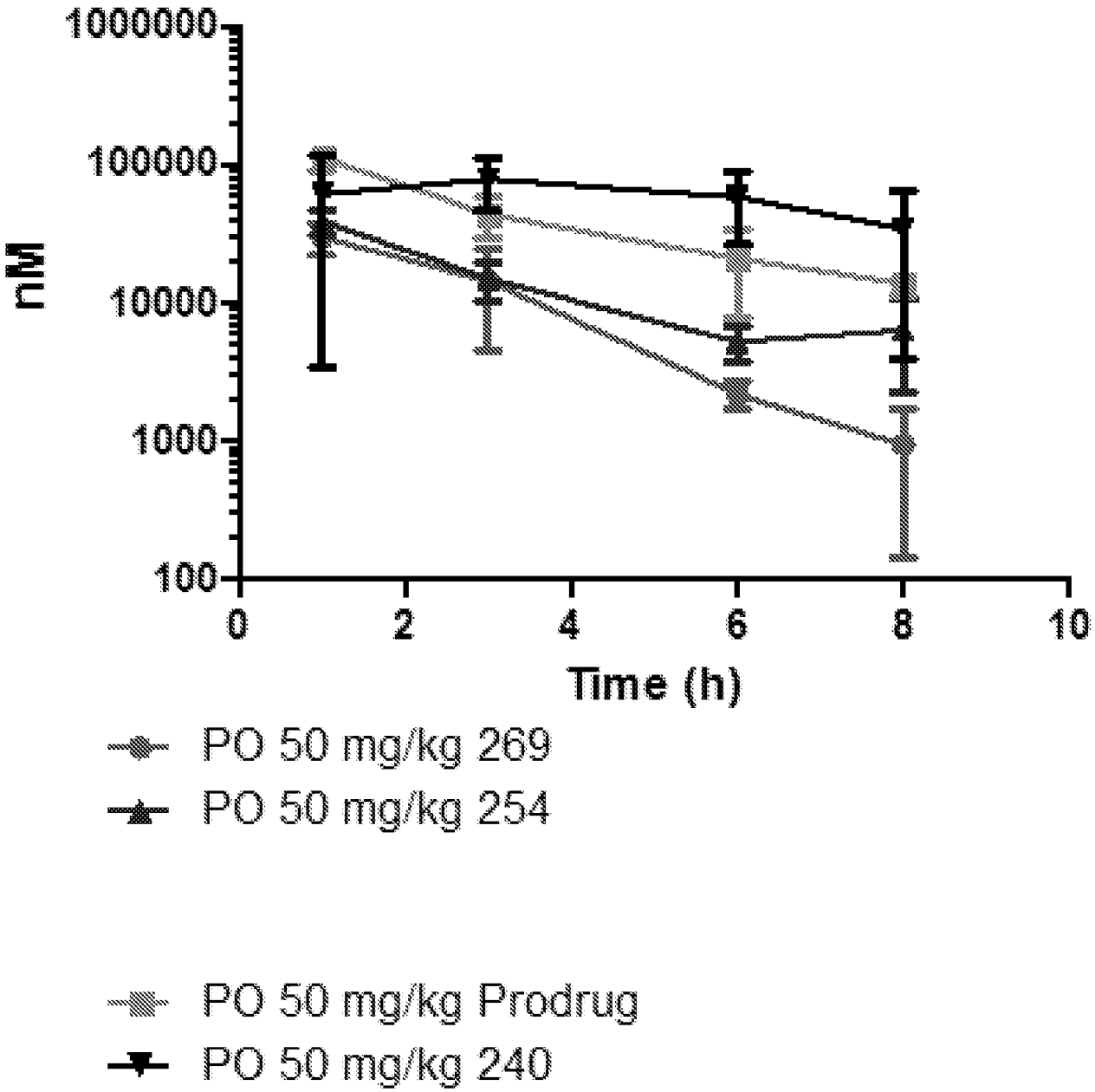
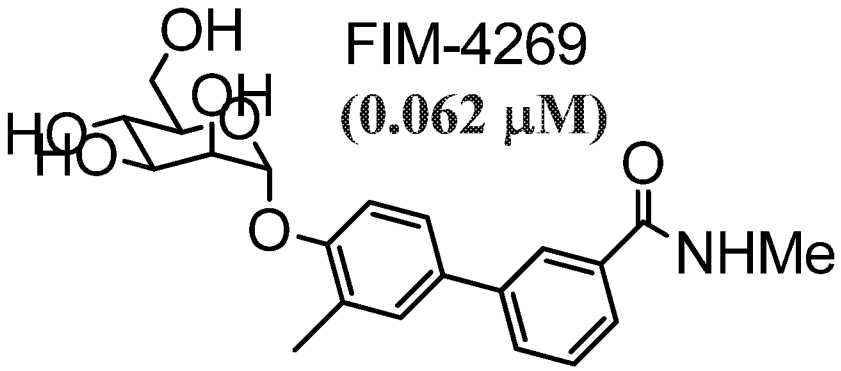

1000000
100000
10000
1000
100
nM
0
2
4
6
8
10
Time (h)
PO 50 mg/kg 269
PO 50 mg/kg 254
PO 50 mg/kg Prodrug
PO 50 mg/kg 240

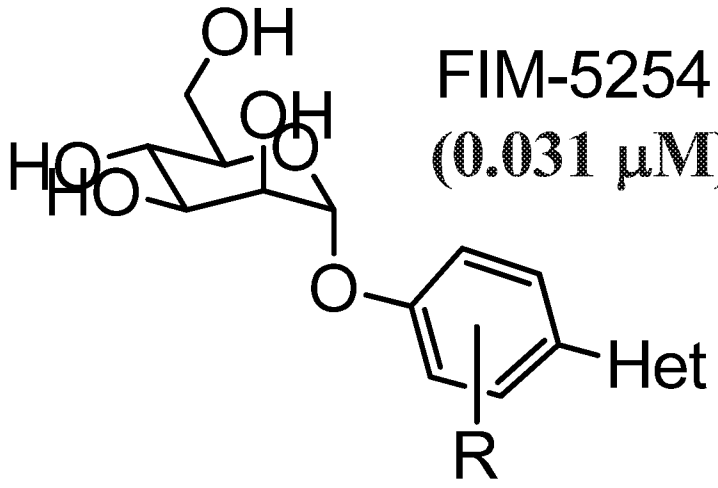
FIG. 26D

A



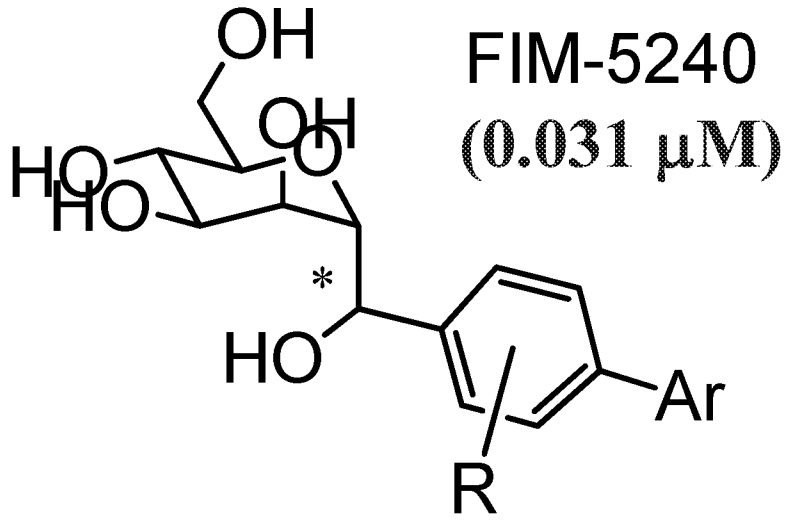
FIM-4269
(0.062 μM)

B



FIM-5254
(0.031 μM)

C



FIM-5240
(0.031 μM)

FIG. 27

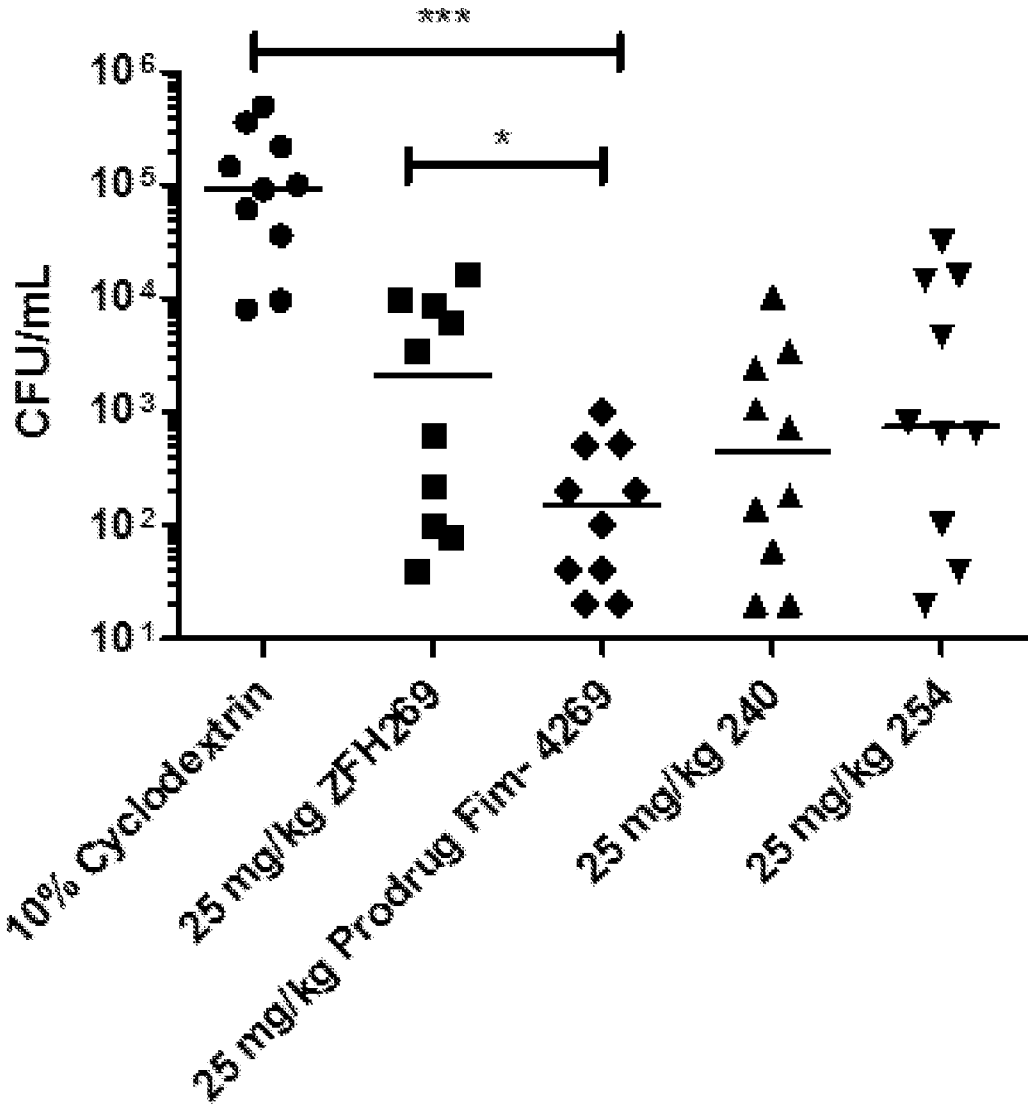

***
*
10^6
10^5
10^4
10^3
10^2
10^1
CFU/mL
10% Cyclodextrin
25 mg/kg ZFH269
25 mg/kg Prodrug Fim- 4269
25 mg/kg 240
25 mg/kg 254

FIG. 27D

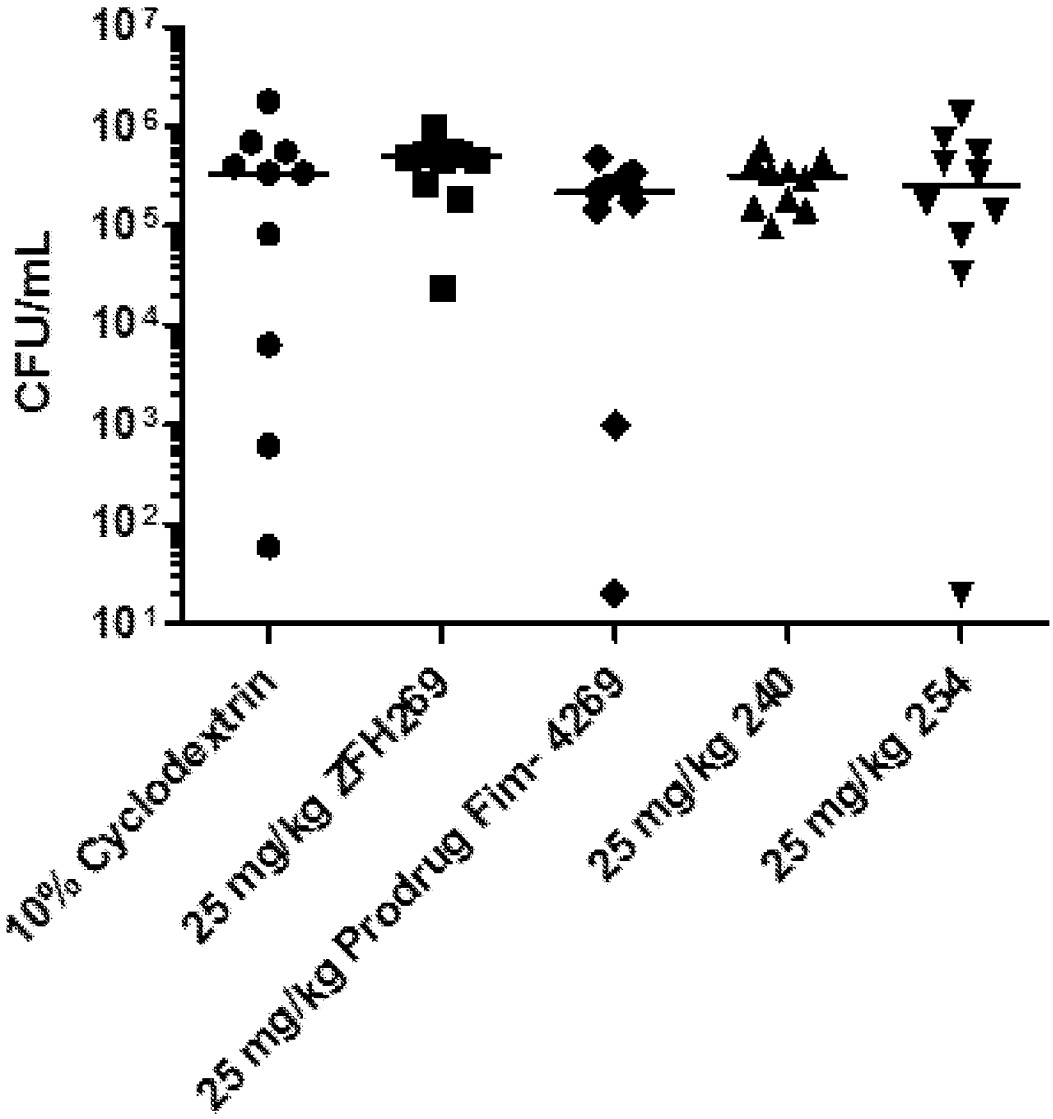

CFU/mL
10 7
10 6
10 5
10 4
10 3
10 2
10 1
10% Cyclodextrin
25 mg/kg ZFH269
25 mg/kg Prodrug Fim- 4269
25 mg/kg 240
25 mg/kg 254

FIG. 27E

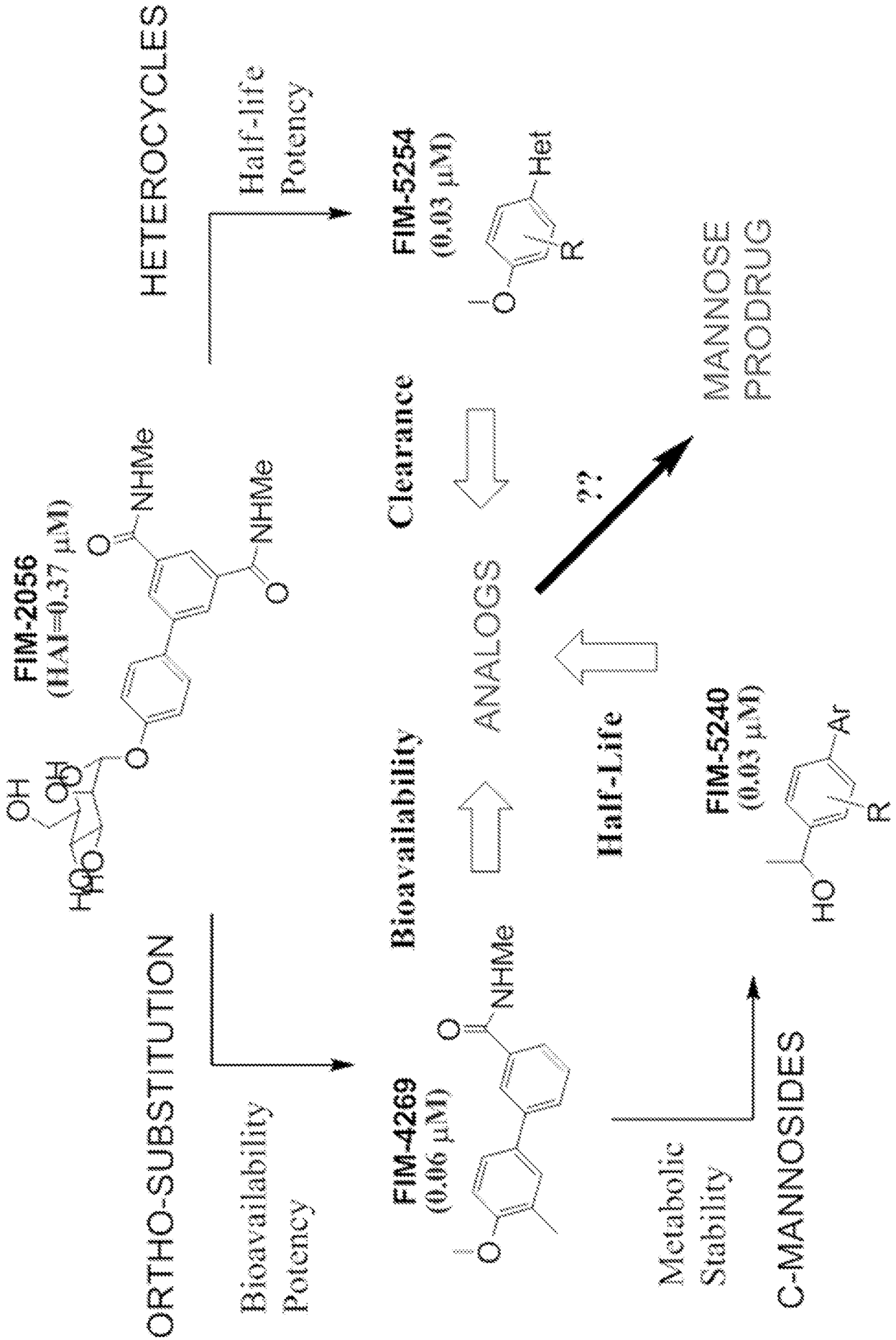

HETEROCYCLES
Half-life
Potency
FIM-5254
(0.03 μM)
Het
R
O
FIM-2056
(HAI=0.37 μM)
NHMe
NHMe
OH
OH
HO
HO
Clearance
ORTHO-SUBSTITUTION
Bioavailability
Potency
Bioavailability
ANALOGS
??
MANNOSE
PRODRUG
FIM-4269
(0.06 μM)
NHMe
Half-Life
FIM-5240
(0.03 μM)
Ar
R
HO
Metabolic
Stability
C-MANNOSIDES

FIG. 28

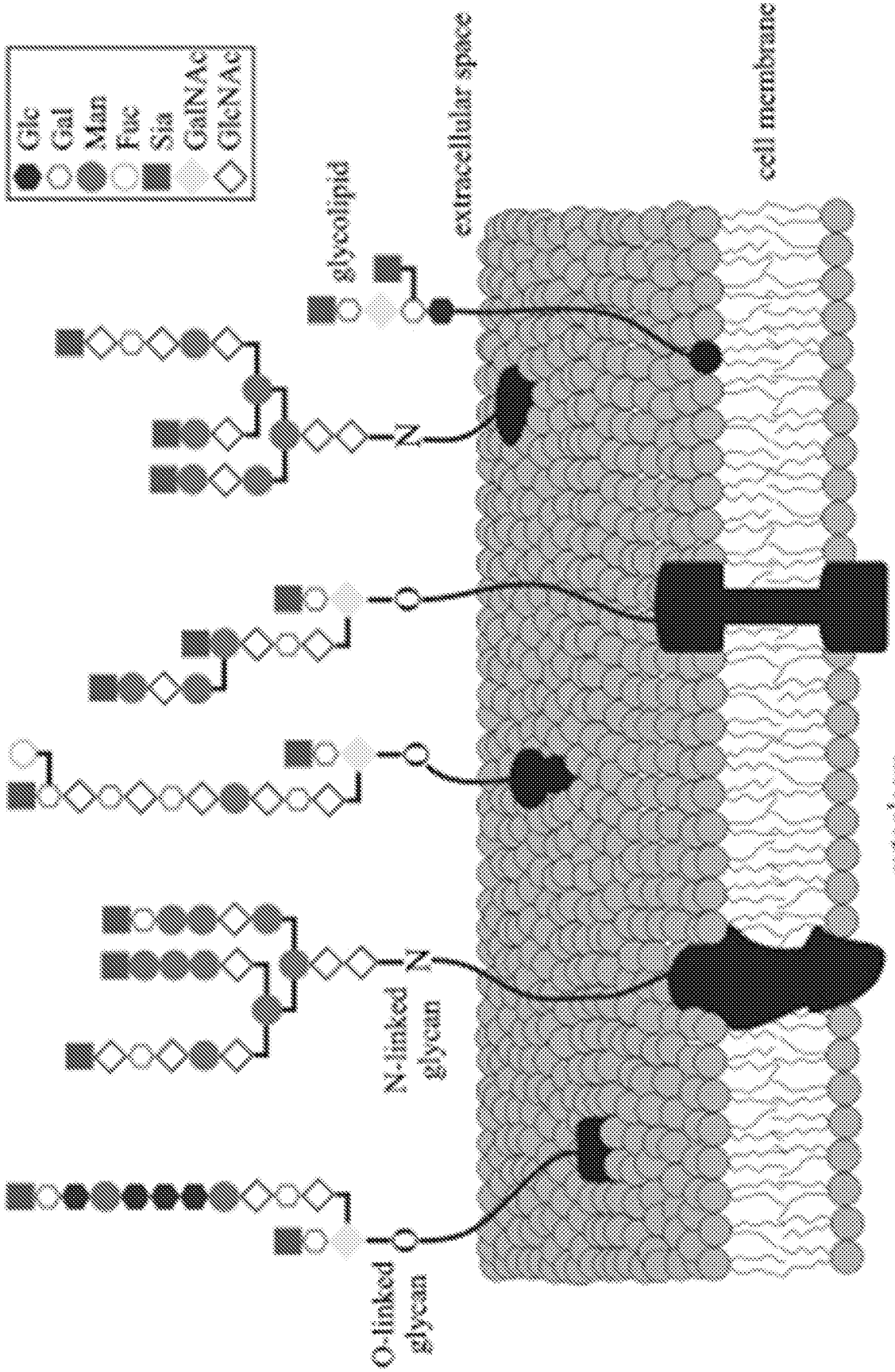
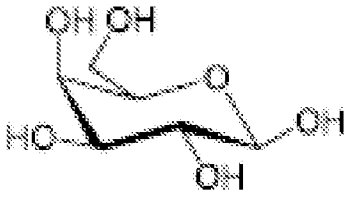
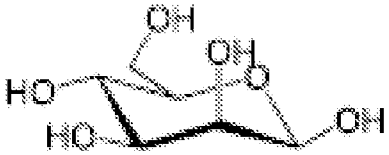

Glc
Gal
Man
Fuc
Sia
GalNAc
GlcNAc
glycolipid
extracellular space
cell membrane
N-linked glycan
O-linked glycan
cytoplasm

FIG. 29A

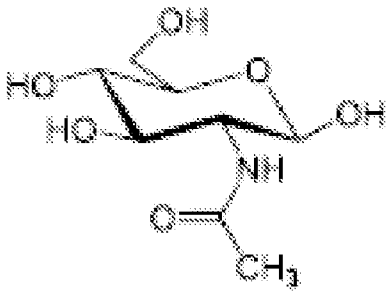
β-D-Glc



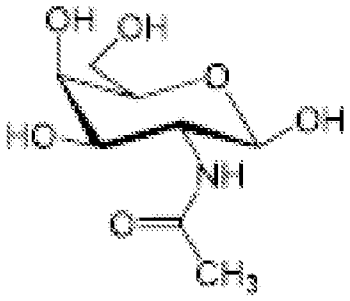
β-D-Gal



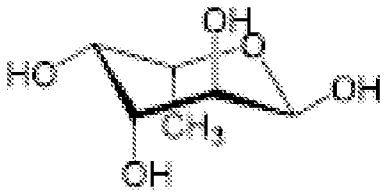
β-D-Man



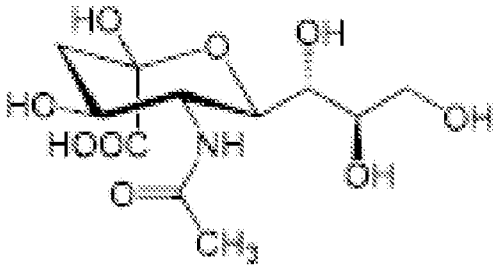
β-D-GlcNAc



β-D-GalNAc



α-L-Fuc



α-D-Neu5Ac

β-D-Xyl

FIG. 29B

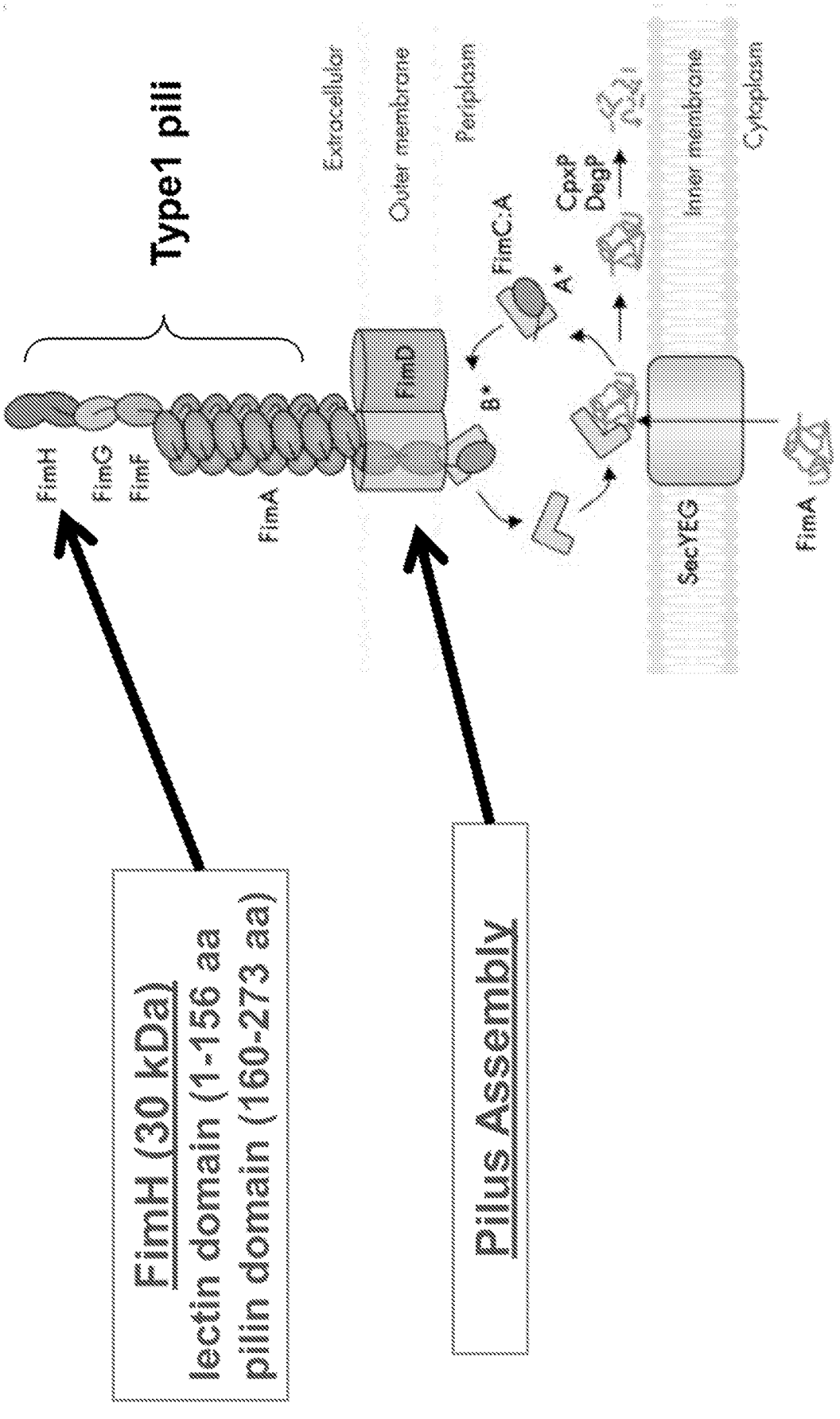

FimH (30 kDa)
lectin domain (1-156 aa
pilin domain (160-273 aa)
Pilus Assembly
Type1 pili
FimH
FimG
FimF
FimA
FimD
FimC:A
8*
A*
CpxP
DegP
Extracellular
Outer membrane
Periplasm
inner membrane
Cytoplasm
SecYEG
FimA

FIG. 30

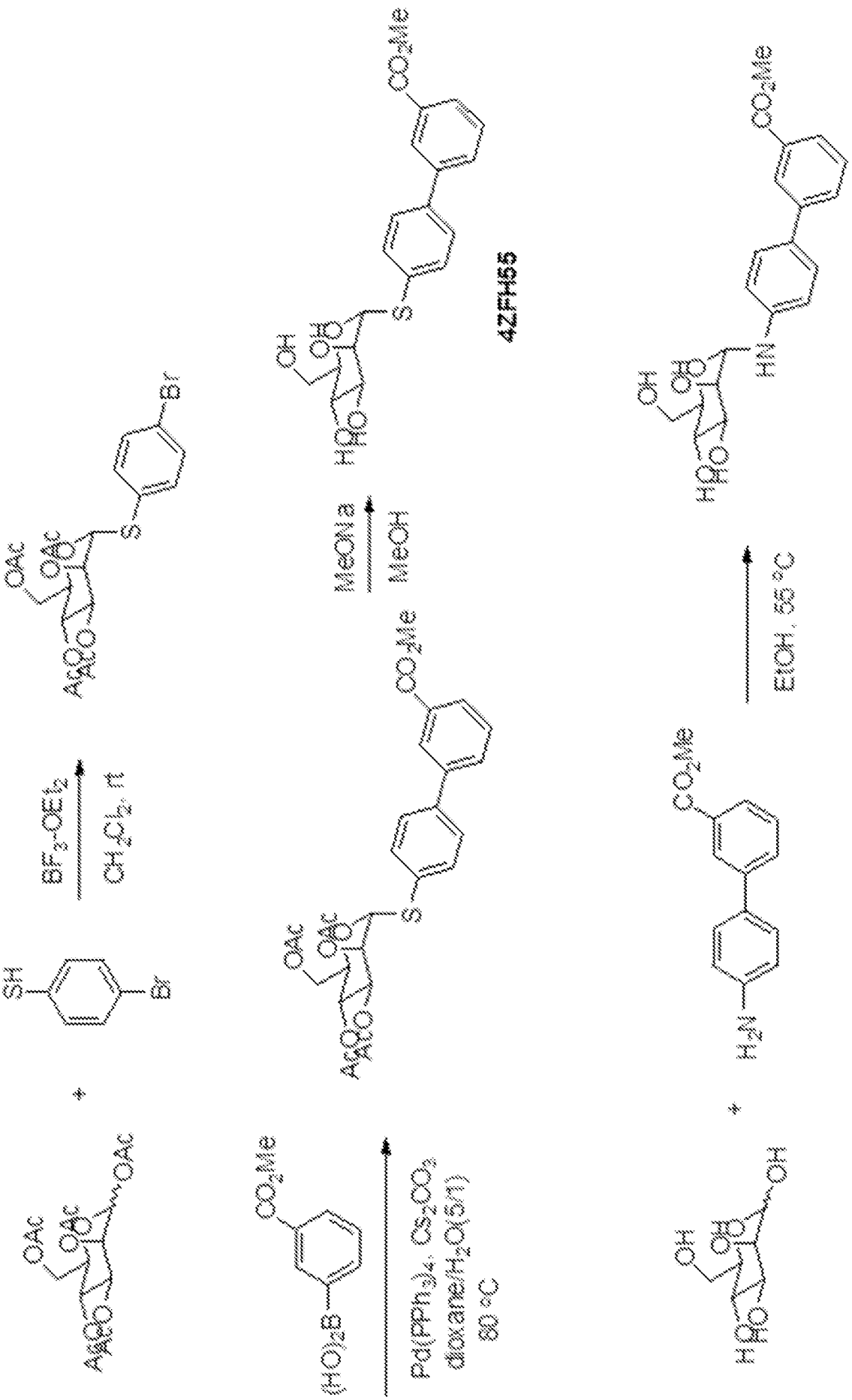

BF3-OEt2
CH2Cl2, rt
MeONa
MeOH
Pd(PPh3)4, Cs2CO3
dioxane/H2O(5/1)
80 °C
EtOH, 55 °C
4ZFH55
4ZFH44

FIG. 31

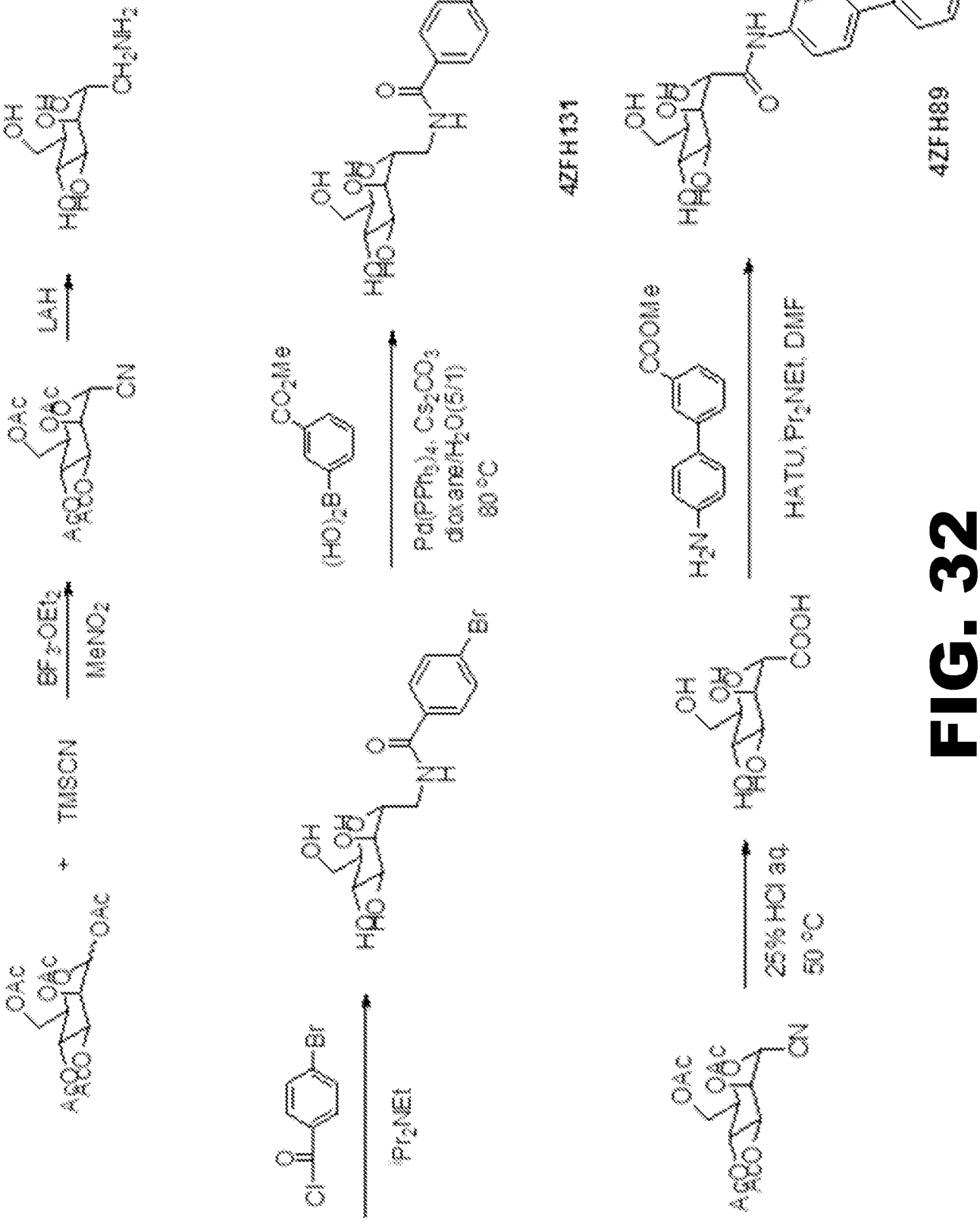
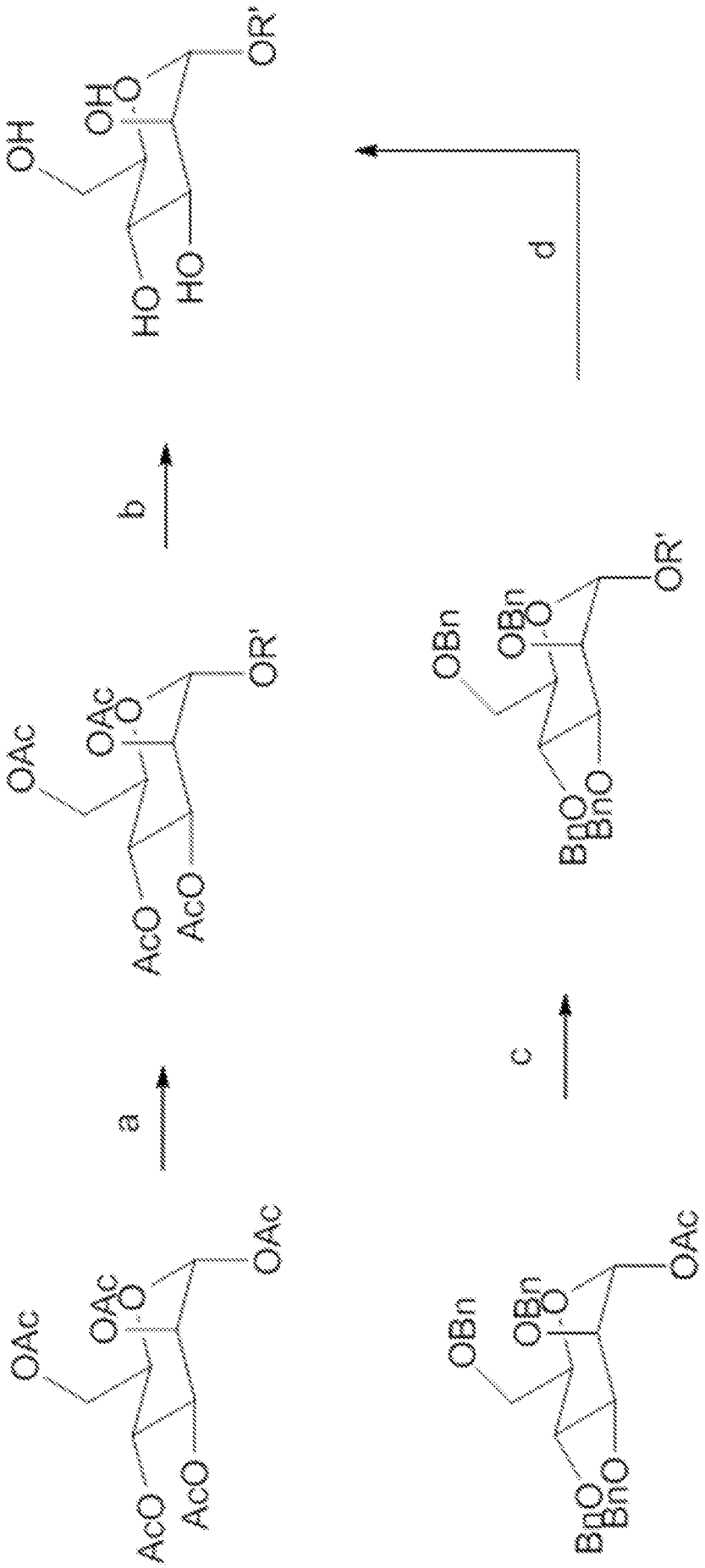


FIG. 32


TMSN3
SnCl4
CH2Cl2
CuSO4, Na ascorbate
EtOH
MeONa
MeOH
4ZFH105

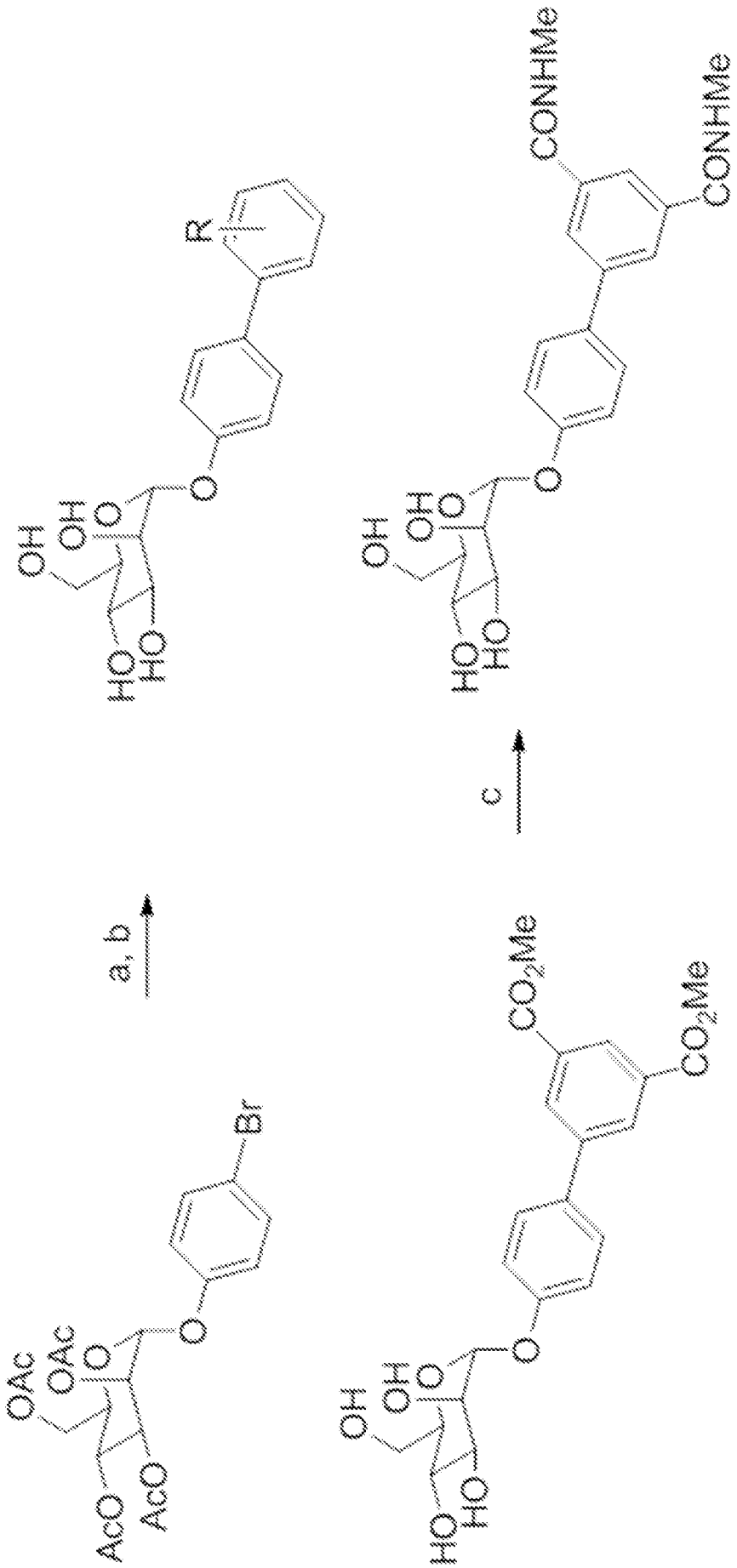
FIG. 33



Reagents and conditions:

(a) R'OH, BF_3-OEt_2, CH_2Cl_2, reflux;
(b) (i) NaOMe, MeOH; (ii) H^+ exchange resin;
(c) R'OH, BF_3-OEt_2, CH_2Cl_2, 0 ° C to 25 ° C;
(d) H_2, 10% Pd/C, EtOH, EtOAc.

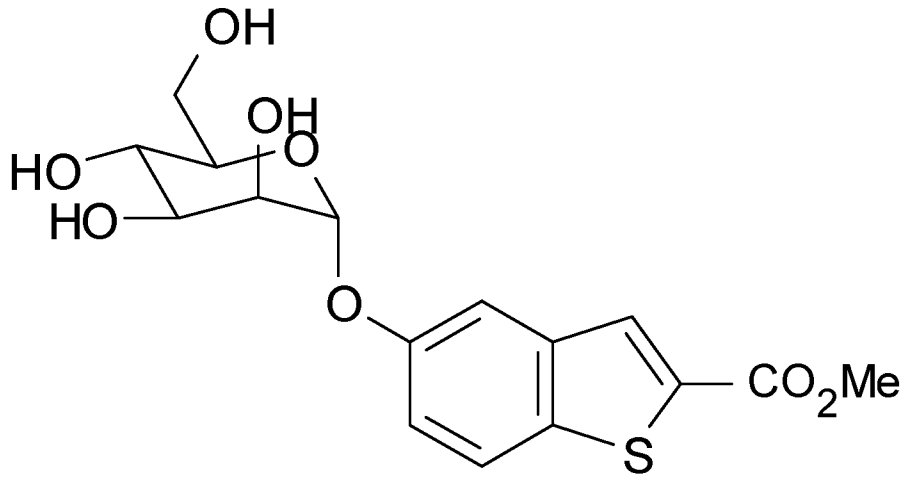
FIG. 34



Reagents and conditions: (a) RPh-B(OR)$_2$, Pd(Ph$_3$P)$_4$, dioxane/water (4:1), Cs_2CO_3, 80 ° C; (b) NaOMe, MeOH; (c) H_2NMe, EtOH

FIG. 35

A



B

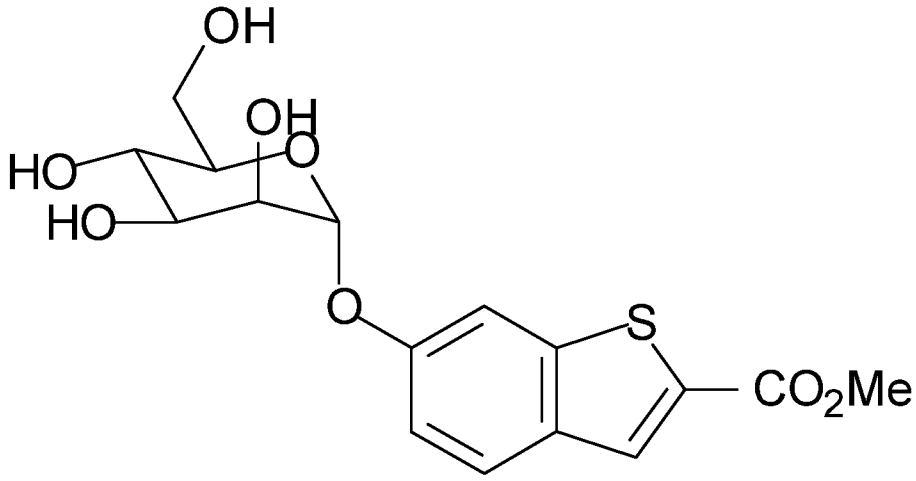
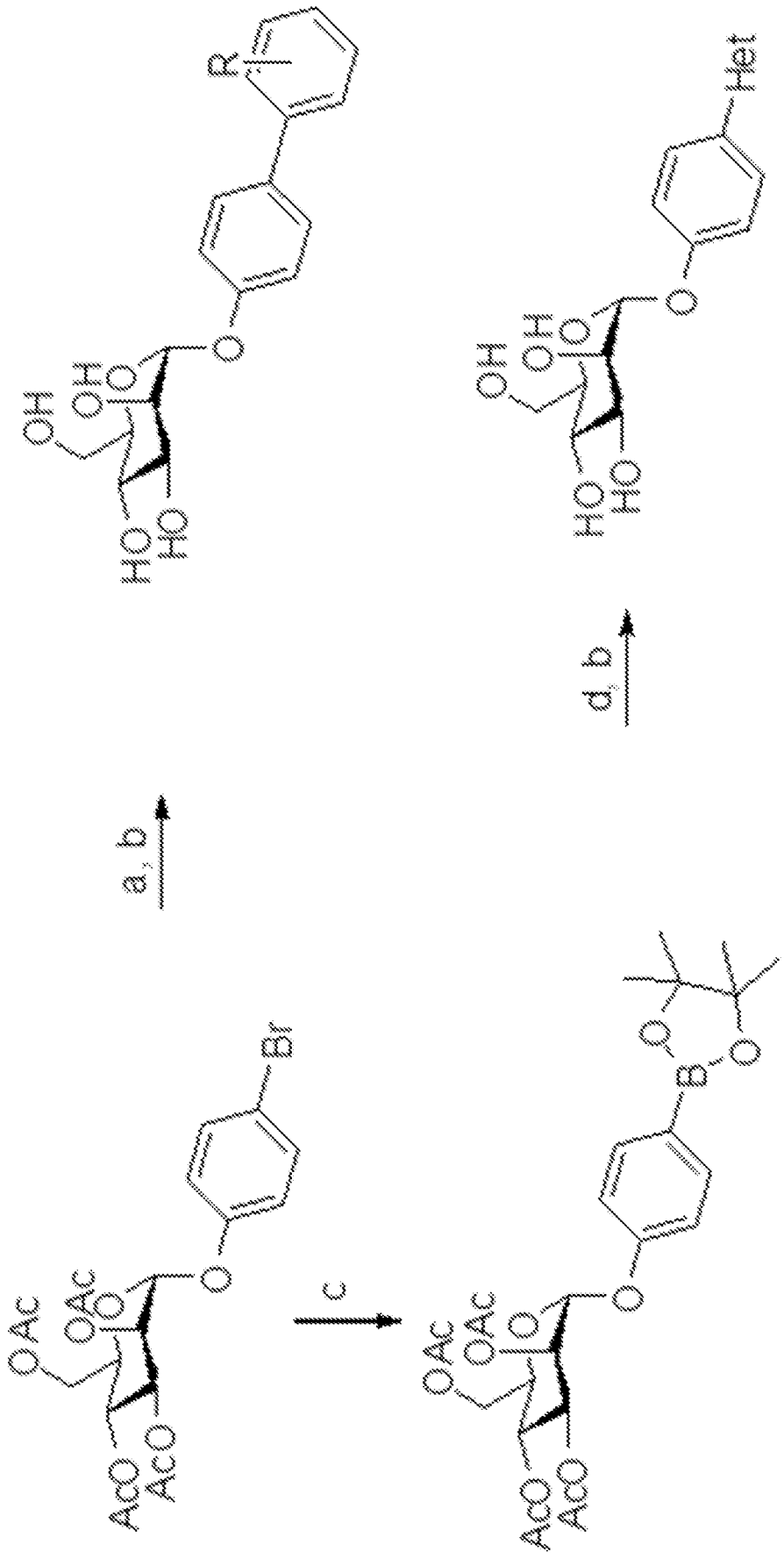


FIG. 36



(a) RPh-B(OR)$_2$, Pd(Ph$_3$P)$_4$, dioxane/water (4:1), Cs$_2$CO$_3$, 80 °C (b) NaOMe, MeOH;
(c) Pd(OAc)$_2$, pinacolborane; (d) Pd(0), Het-Br.

FIG. 36C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/040355

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/7034(2006.01)i, A61K 31/706(2006.01)i, A61K 31/7042(2006.01)i, A61K 31/704(2006.01)i, A61P 31/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 31/7034; A01N 43/04; A61K 31/70; A61K 31/7004; A61P 31/04; A61K 39/108; A61K 39/02; A61K 31/706; A61K 31/7042; A61P 31/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: bacterial infection, urinary tract infection, crohn's disease, FimH, mannoside

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012-109263 A1 (THE WASHINGTON UNIVERSITY) 16 August 2012 See abstract, claims 1-4, tables 7-8.	1-2,5-6,19
A		3-4
X	JIANG, X. et al., "Antiadhesion Therapy for Urinary Tract Infections-A Balanced PK/PD Profile Proved To Be Key for Success", Journal of Medical Chemistry, 23 April 2012, Vol. 55, Pages 4700-4713 See abstract, fig. 1.	1
A		2-6,19
X	CUSUMANO, C. K. et al., "Treatment and Prevention of Urinary Tract Infection with Orally Active FimH Inhibitors", Science Translational Medicine, 16 November 2011, Vol. 3, Issue 109, pages 109-115 See abstract, fig. 5.	1
A		2-6,19
A	US 2008-0171706 A1 (BERGLUND, J. et al.) 17 July 2008 See abstract, claim 10.	1-6,19
A	US 6153396 A (HULTGREN, S. et al.) 28 November 2000 See abstract.	1-6,19

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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

Date of the actual completion of the international search	Date of mailing of the international search report
22 September 2014 (22.09.2014)	**22 September 2014 (22.09.2014)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea
Facsimile No. +82-42-472-7140

Authorized officer
SIHN, Young Sihn
Telephone No. +82-42-481-8270

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/040355

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.: 7-18
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 7-18 pertain to a method for treatment of the human by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv), to search.

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.: 18
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 addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

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

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

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2014/040355

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012-109263 A1	16/08/2012	EP 2672820 A1	18/12/2013
		US 2012-309701 A1	06/12/2012
US 2008-0171706 A1	17/07/2008	EP 1755619 A2	28/02/2007
		WO 2005-089733 A2	29/09/2005
		WO 2005-089733 A3	01/12/2005
US 06153396 A	28/11/2000	AT 271060 T	15/07/2004
		AU 1995-11844 B2	15/04/1999
		AU 1995-84495 A	06/06/1995
		CA 2176808 A1	26/05/1995
		DE 69433901 D1	19/08/2004
		DE 69433901 T2	28/07/2005
		DK 730601 T3	06/06/2005
		EP 0730601 A1	17/12/2003
		EP 0730601 B1	14/07/2004
		ES 2225834 T3	16/03/2005
		JP 09-505309 A	27/05/1997
		US 06001823 A	14/12/1999
		US 2002-0034774 A1	21/03/2002
		US 2002-0045199 A1	18/04/2002
		US 2002-0146428 A1	10/10/2002
		US 2003-0198992 A1	23/10/2003
		US 2003-0224468 A1	04/12/2003
		US 6420127 B1	16/07/2002
		US 6548265 B2	15/04/2003
		US 6596504 B2	22/07/2003
		US 6872542 B1	29/03/2005
		US 6962791 B2	08/11/2005
		US 7025971 B2	11/04/2006
		WO 95-14028 A2	26/05/1995
		WO 95-14028 A3	15/06/1995

(19)中华人民共和国国家知识产权局

(12)发明专利申请

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(43)申请公布日 2016.06.15

(21)申请号 201480043010.1

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(30)优先权数据
61/828954 2013.05.30 US

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2016.01.29

(86)PCT国际申请的申请数据
PCT/US2014/040355 2014.05.30

(87)PCT国际申请的公布数据
WO2014/194270 EN 2014.12.04

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代理人 徐晶 林森

(51)Int.Cl.
A61K 31/7034(2006.01)
A61K 31/706(2006.01)
A61K 31/7042(2006.01)
A61K 31/704(2006.01)
A61P 31/00(2006.01)

权利要求书9页 说明书64页 附图58页

(54)发明名称

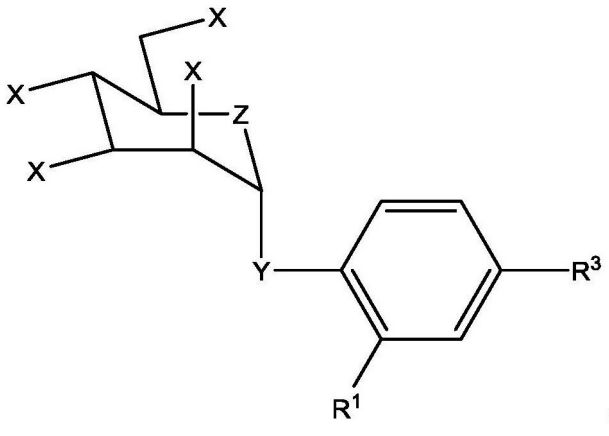
用于治疗细菌性感染的化合物和方法

(57)摘要

本发明涵盖用于治疗和预防细菌性感染(具体来说是尿路感染和由含有1型菌毛和FimH的细菌引起的那些感染)的化合物和方法。本发明也涵盖用于治疗炎症性肠病(具体来说是克罗恩氏病)的化合物和方法。

CN 105682665 A

1.一种化合物,所述化合物包括式(I):



(I)

其中:

X选自由以下组成的组:氢和OR^2;

R^2独立地选自由以下组成的组:氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(NR_5R_6)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基;

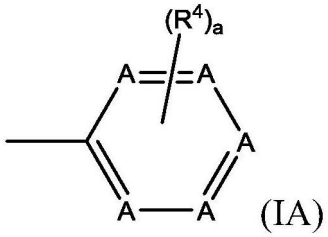
n是1至10的整数;

Z是O;

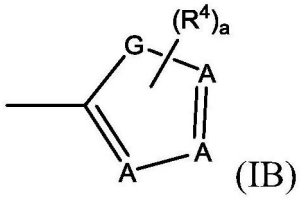
Y选自由以下组成的组:O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5;

R^1选自由以下组成的组:CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基;

R^3选自由以下组成的组:式(IA)和式(IB):



(IA)



(IB)

A独立地选自由以下组成的组:CR^5和N;

G独立地选自由以下组成的组:S、NR^5和O;

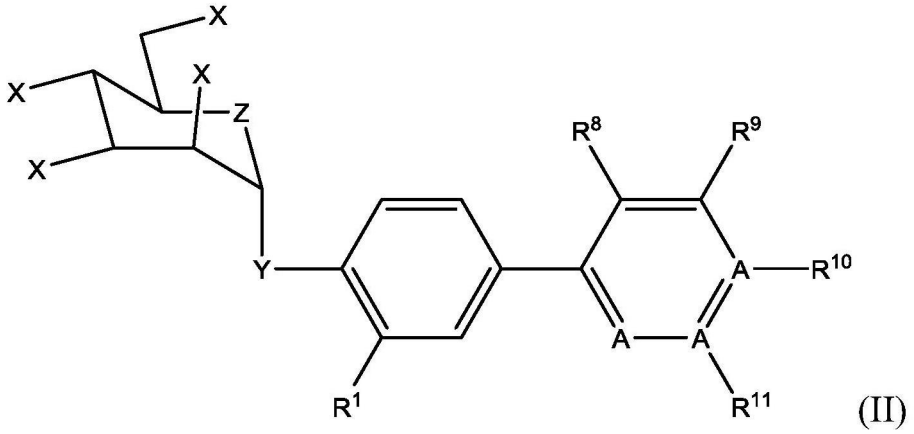
a是1至4的整数;

R^4选自由以下组成的组:$CONHCH_3$、$COOCH_3$、COOH、$CONR_5$、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$,或当a大于或等于2时,R^4可任选形成任选取代的环烷基、芳基或杂环5或6元环;

R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环。

2.一种化合物,所述化合物包括式(II):



(II)

其中:

X选自由以下组成的组:氢和OR^2;

R^2独立地选自由以下组成的组:氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基;

n是1至10的整数;

Z是O;

Y选自由以下组成的组:O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5;

A独立地选自由以下组成的组:CR^5和N;

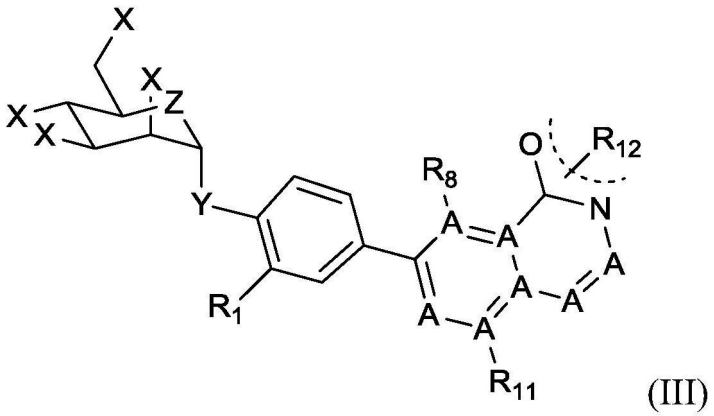
R^1选自由以下组成的组:CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基;

R^8、R^9、R^{10}和R^{11}独立地选自由以下组成的组:$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$、$NHSO_2R^7$,并且R^8和R^9一起可任选形成任选取代的环烷基、芳基或杂环5或6元环;并且R^9和R^{10}一起可任选形成任选取代的环烷基、芳基或杂环5或6元环;

R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环。

3.一种化合物,所述化合物包括式(III):



(III)

其中：

X选自由以下组成的组：氢和OR^2；

R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

n是1至10的整数；

Z是O；

Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

A独立地选自由以下组成的组：CR^5和N；

R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

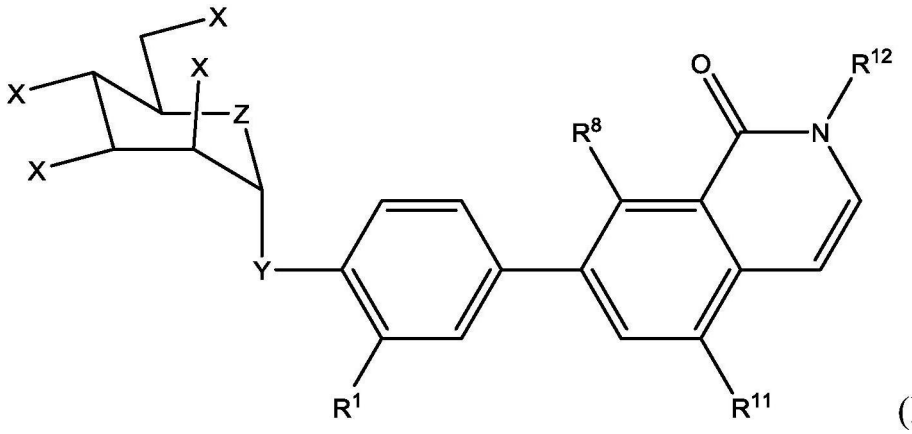
R^8和R^{11}独立地选自由以下组成的组：$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$；

R^{12}在O或N处被取代，并且选自由以下组成的组：H、烷基、CH_2R^{13}、CH_2COR^{13}、CH_2CONHR^{13}、$CH_2CONHR^{13}R^{14}$、$CH_2CONH(CH_2)_2R^{14}$、$(CH_2)_2NR^{13}$、$(CH_2)_nNR^{13}$、CH_2COOH、$CH_2CONH(CH_2)_2NH_2$和$(CH_2)_2N(CH_3)_2$；

R^{13}选自由以下组成的组：-OH以及任选取代的杂环、烷基和取代的烃基；

R^{14}选自由以下组成的组：烷基和NH_2。

4.一种化合物，所述化合物包括式(IV)：



(IV)

其中：

X选自由以下组成的组：氢和OR^2；

R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

n是1至10的整数；

Z是O；

Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、

烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

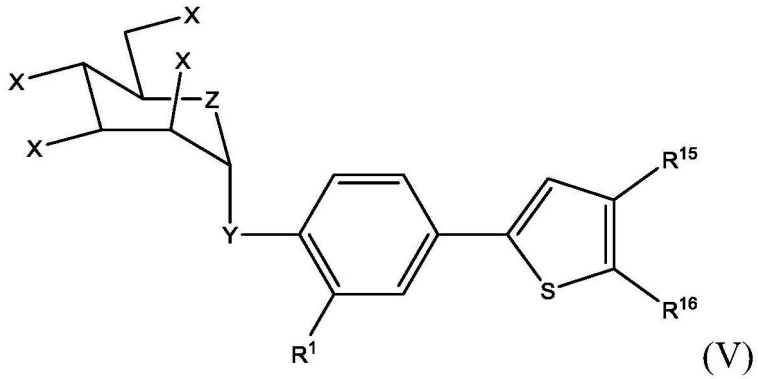
R^8和R^{11}独立地选自由以下组成的组：$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$；

R^{12}选自由以下组成的组：H、烷基、CH_2R^{13}、CH_2COR^{13}、CH_2CONHR^{13}、$CH_2CONHR^{13}R^{14}$、$CH_2CONH(CH_2)_2R^{14}$、$(CH_2)_2NR^{13}$、$(CH_2)_nNR^{13}$、CH_2COOH、$CH_2CONH(CH_2)_2NH_2$和$(CH_2)_2N(CH_3)_2$；

R^{13}选自由以下组成的组：-OH以及任选取代的杂环、烷基和取代的烷基；

R^{14}选自由以下组成的组：烷基和NH_2。

5.一种化合物，所述化合物包括式(V)：



(V)

其中：

X选自由以下组成的组：氢和OR^2；

R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

n是1至10的整数；

R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

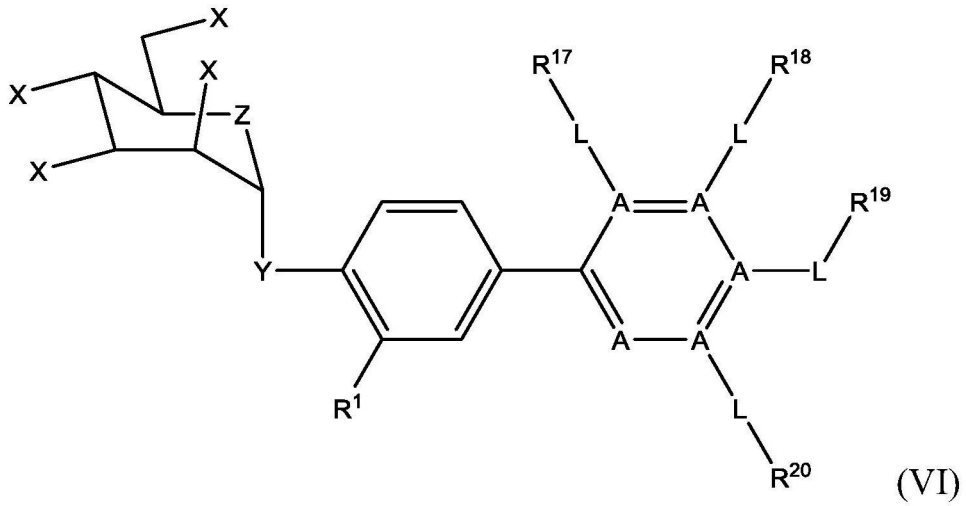
Z是O；

Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

R^{15}和R^{16}独立地选自由以下组成的组：氢、$NHCONH_2$、$COOCH_3$以及$CONHCH_3$、$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$，或R^{15}和R^{16}可任选形成环烷基、芳基或杂环。

6.一种化合物，所述化合物包括式(VI)：



(VI)

其中：

X选自由以下组成的组：氢和OR^2；

R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

n是1至10的整数；

R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

Z是O；

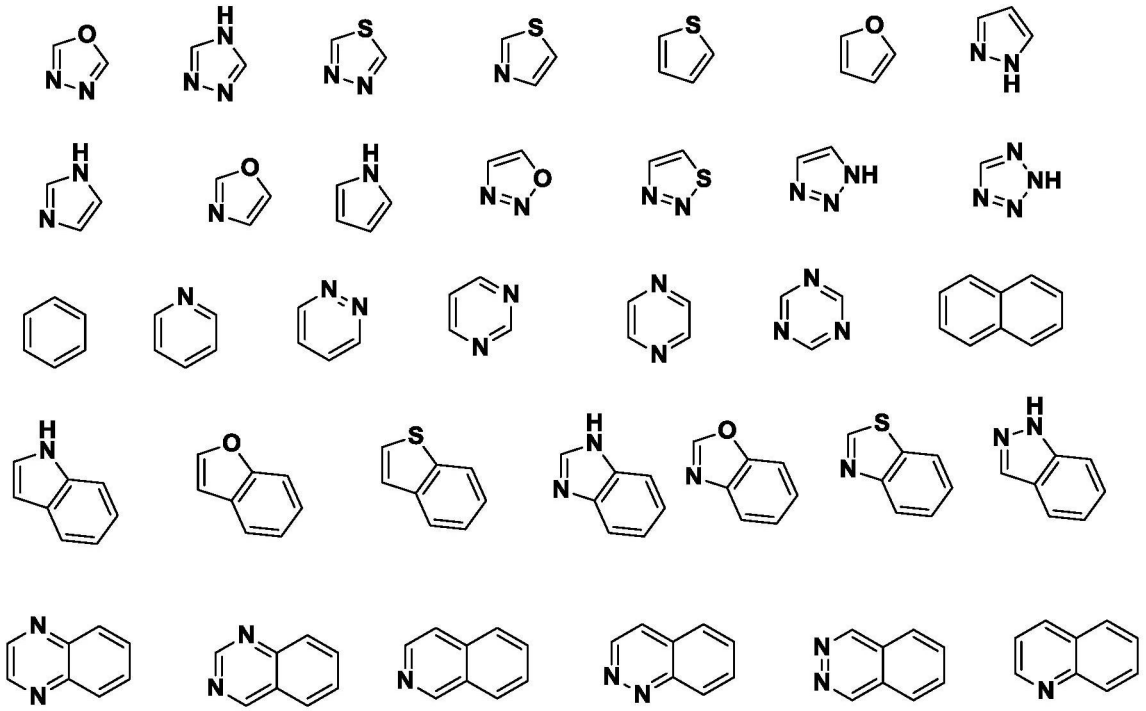
Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

A独立地选自由以下组成的组：CR^5和N；

L独立地选自由以下组成的组：无原子、N、NH、O和S；

R^{17}、R^{18}、R^{19}和R^{20}选自由以下组成的组：H以及任选取代的环烷基、芳基或杂环5或6元环、5-6稠环或6-6稠环，包括但不限于以下实例，其中所述实例通过任何可用的CH位置加以连接：



7.一种治疗尿路感染的方法，所述方法包括向有需要的受试者施用前述权利要求中任一项所述的化合物。

8.如权利要求7所述的方法，其中所述受试者被进一步施用杀菌组合物。

9.一种预防尿路感染的方法，所述方法包括向有需要的受试者施用权利要求1-6中任一项所述的化合物。

10.如权利要求9所述的方法，其中所述受试者被进一步施用杀菌组合物。

11.一种降低细菌对杀菌化合物的抗性的方法，所述方法包括向有需要的受试者施用权利要求1-6中任一项所述的化合物。

12.一种治疗炎症性肠病的方法，所述方法包括向有需要的受试者施用权利要求1-6中任一项所述的化合物。

13.如权利要求12所述的方法，其中所述炎症性肠病是克罗恩氏病。

14.如权利要求12所述的方法，其中治疗包括减轻与炎症性肠病相关的症状。

15.一种抑制FimH结合甘露糖的方法，所述方法包括使权利要求1-6中任一项所述的化合物与FimH接触，其中所述化合物结合FimH并抑制与甘露糖的结合。

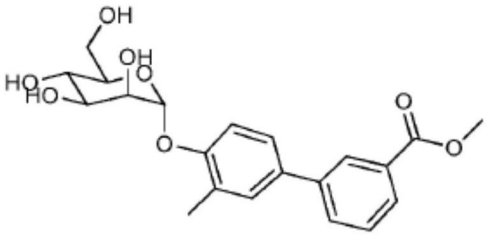
16.如权利要求15所述的方法，其中使所述甘露糖暴露在膀胱细胞上。

17.如权利要求15所述的方法，其中使所述甘露糖暴露在肠细胞上。

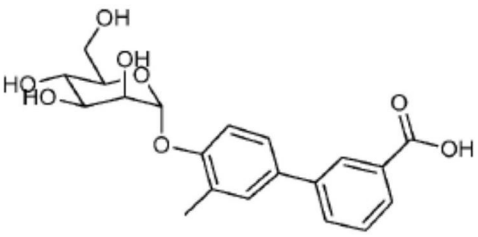
18.一种治疗导管相关的尿路感染的方法，所述方法包括向有需要的受试者施用前述权利要求中任一项所述的化合物。

19.如权利要求1所述的化合物，其中所述化合物选自由以下组成的组：

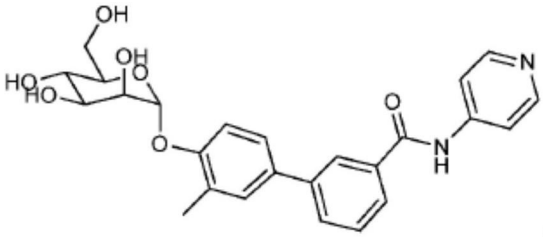
1.



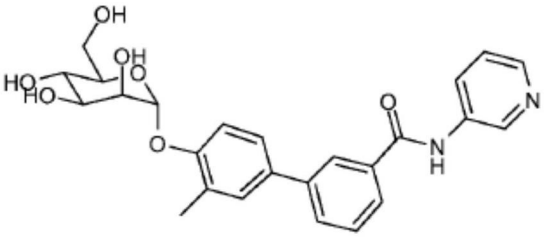
2.

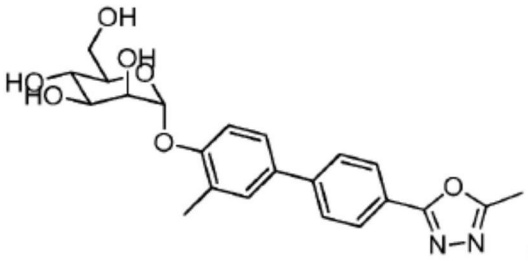


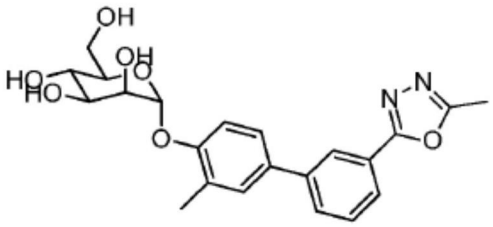
3.

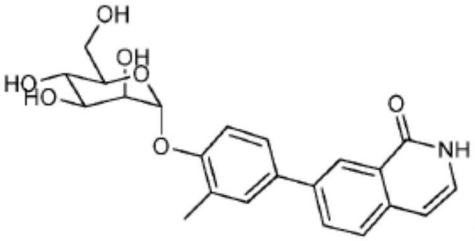


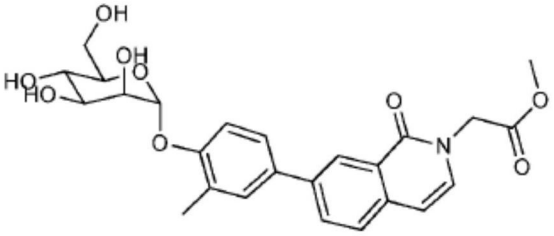
4.

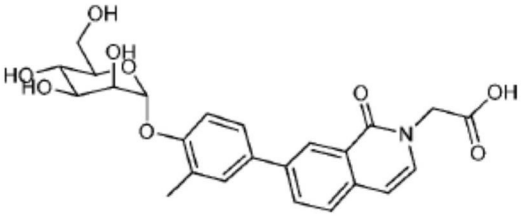


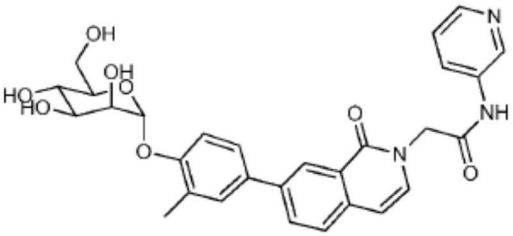
5. 

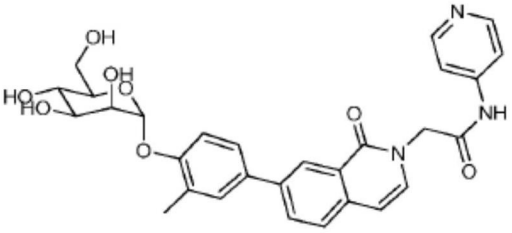
6. 

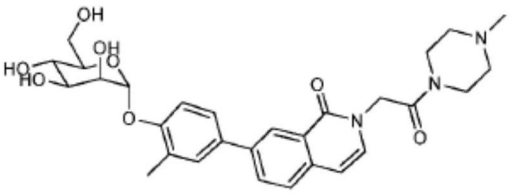
7. 

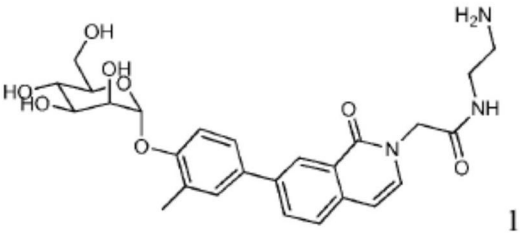
8. 

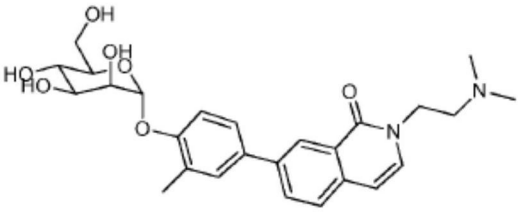
9. 

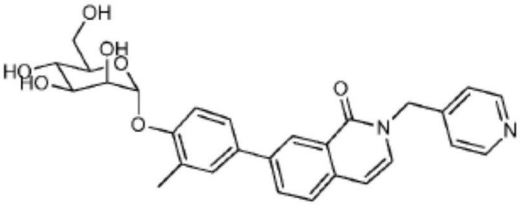
10. 

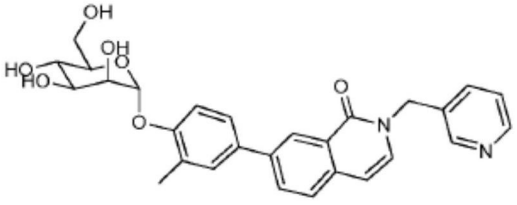
11. 

12. 

13. 

14. 

15. 

16. 

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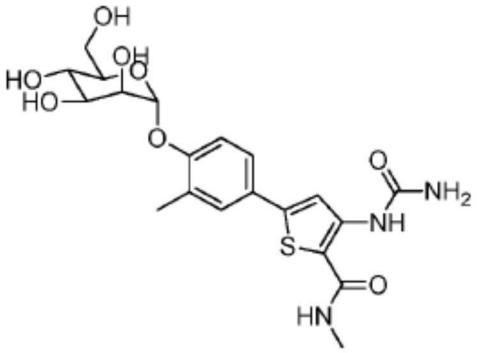

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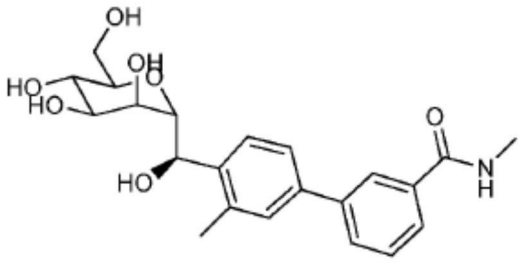

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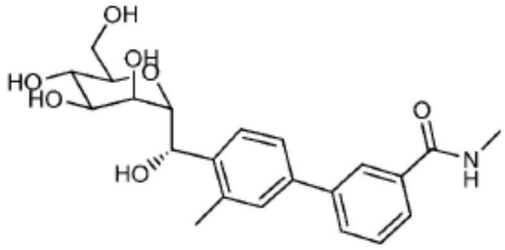

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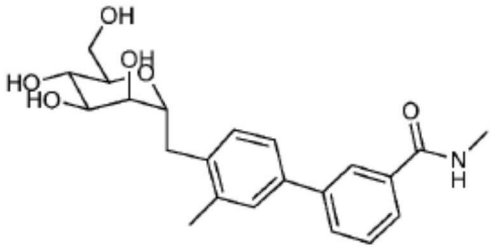

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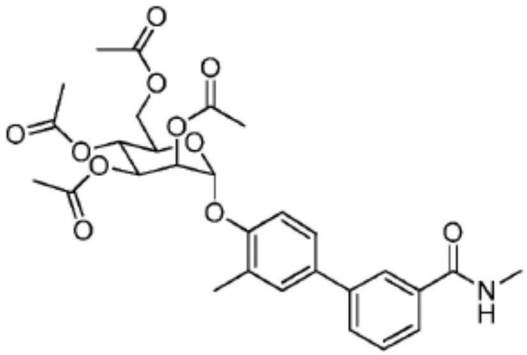

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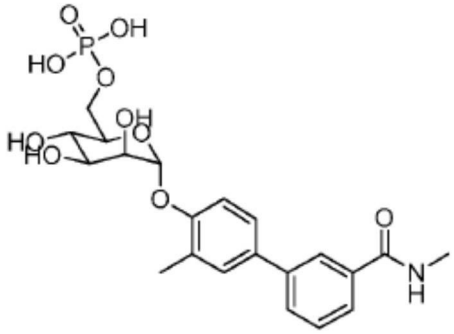

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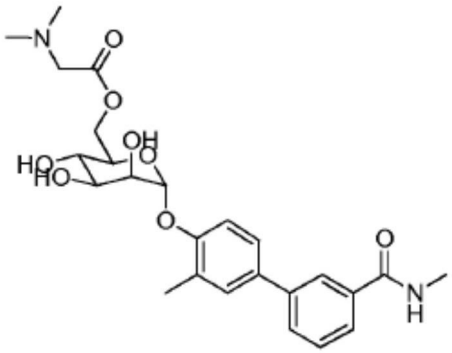


用于治疗细菌性感染的化合物和方法

[0001] 政府权利

[0002] 本发明在由NIH授予的RO1AI029549、P50DK064540和RO1BK051406-12下在政府资助下进行。政府享有本发明的某些权利。

[0003] 相关申请的交叉引用

[0004] 本申请要求2013年5月30日提交的美国临时申请号61/828,954的优先权,所述美国临时申请据此以引用的方式整体并入本文。

发明领域

[0005] 本发明涵盖用于抑制粘附素蛋白FimH以及治疗和预防尿路感染和炎症性肠病(例如克罗恩氏病和溃疡性结肠炎)的化合物和方法。

[0006] 发明背景

[0007] 由尿路病原性大肠杆菌(uropathogenic Escherichia coli,UPEC)引起的尿路感染(UTI)是妇女的一种最常见感染性疾病。发病率和经济影响是巨大的,其中每年在治疗方面花费超过25亿美元。此外,尽管对指示病例施加适当抗生素疗法,但复发性感染仍然是一个重大问题。高复发率以及由于她们的慢性复发性UTI而死于泌尿学临床中的妇女的巨大数目强调需要更充分了解这个疾病中涉及的发病机理以及开发新型和更佳疗法。

[0008] 革兰氏阴性细菌是广泛多种急性和慢性感染性疾病的病原体。这些感染中的许多由宿主配体(常常是多糖部分)与细菌粘附素(常常在通过侣伴/引导蛋白途径(chaperone/usher pathway)装配的聚合菌毛纤维的远端尖端处表达)之间的关键性相互作用引发。1型菌毛的甘露糖结合性FimH粘附素对定殖以及侵袭至膀胱上皮中至关重要。在侵袭之后,UPEC能够在膀胱的浅表伞状细胞内部快速繁殖,从而形成生物膜样细胞内细菌群落(IBC)。在成熟后,细菌从IBC分散,向相邻细胞散布,并且形成下一代IBC。这是UPEC在尿路中大量快速扩增并导致疾病所依的机理。

[0009] 结合于甘露糖的FimH的X射线晶体结构显示甘露糖被结合在FimH上的带负电荷口袋中。甘露糖结合位点是高度保守的,因为它在从临床UPEC菌株测序的300个fimH基因中是不变的。因此,FimH是整个UPEC病原性级联的关键节点。

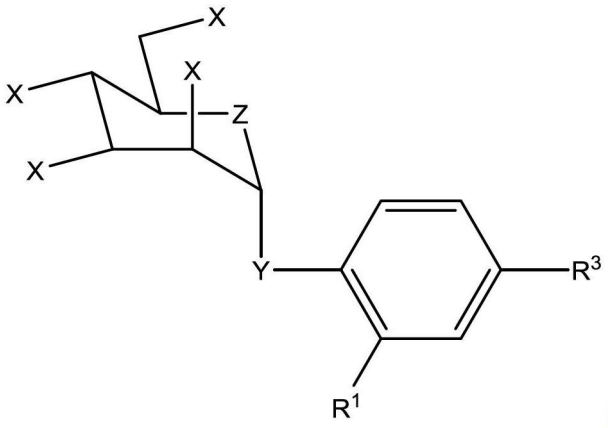
[0010] 对于许多妇女来说,复发是一个严重问题。呈现有急性UTI的初始发作的妇女在初始UTI的六个月内具有25-44%可能性显现第二次发作,以及具有3%可能性经历三次发作。尽管进行适当抗生素治疗以及从尿清除初始感染,但复发仍然发生。大百分比的复发性UTI与初始感染由相同细菌菌株引起。一项研究追踪58名妇女,并且发现68%的复发由UPEC的相同初始指示菌株引起,如通过限制性片段长度多态性(RFLP)分析所确定。在一单独研究中,从女性大学生分离的复发性菌株中的50%在基因型方面似乎与对应于初始UTI的细菌菌株相同。另一长期前瞻研究证明UPEC的相同菌株可在多达3年后导致复发性UTI。相同菌株高复发频率支持UPEC储库可存在于受影响个体中的见解。本发明者已显示在急性感染之后静息细胞内储库(QIR)可在膀胱组织自身中形成,并且甚至在抗生素疗法以及尿培养物变为无菌之后存留。因此,QIR中的细菌的再活化也可为复发性UTI中的影响因素。

[0011] 炎症性肠病(IBD)主要由两种病症,即溃疡性结肠炎和克罗恩氏病(CD)组成,其中在西方国家具有每100,000人中约150-200例病例的合并发病率。在IBD中观察到的异常炎症性应答要求宿主遗传因子与肠微生物丛之间的相互作用。先前已显示粘着侵袭性大肠杆菌(AIEC)诱发患有克罗恩氏病(CD)的患者的肠炎。已显示甘露糖苷通过阻断FimH细菌粘附素来阻止AIEC附着于肠。鉴于AIEC在CD患者的慢性肠炎中的关键作用,这些结果表明开发FimH抑制剂有可能进行抗粘附治疗。

[0012] 因此,对可治愈尿路感染,并且防止形成作为如此多的复发性感染的源头的静息细胞内储库的有效治疗存在需要。也需要可治愈、预防或减轻与克罗恩氏病相关的症状的有效治疗。

[0013] 发明概述

[0014] 本发明的一个方面涵盖一种包括式(I)的化合物:

[0015] 

(I)

[0016] 其中:

[0017] X选自由以下组成的组:氢和OR^2;

[0018] R^2独立地选自由以下组成的组:氢、PO(OH)2、乙酰基、COR^5、$CO(OR^5)$、$CO(NR_5R_6)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基;

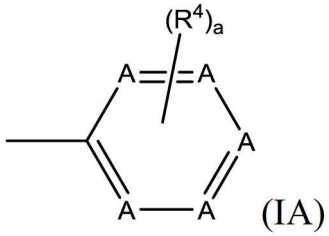
[0019] n是1至10的整数;

[0020] Z是O;

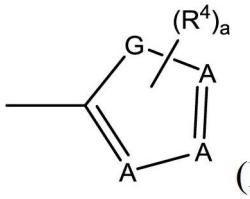
[0021] Y选自由以下组成的组:O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5;

[0022] R^1选自由以下组成的组:CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基;

[0023] R^3选自由以下组成的组:式(IA)和式(IB):

[0024] 

(IA)



(IB)

[0025] A独立地选自由以下组成的组:CR^5和N;

[0026] G独立地选自由以下组成的组:S、NR^5和O;

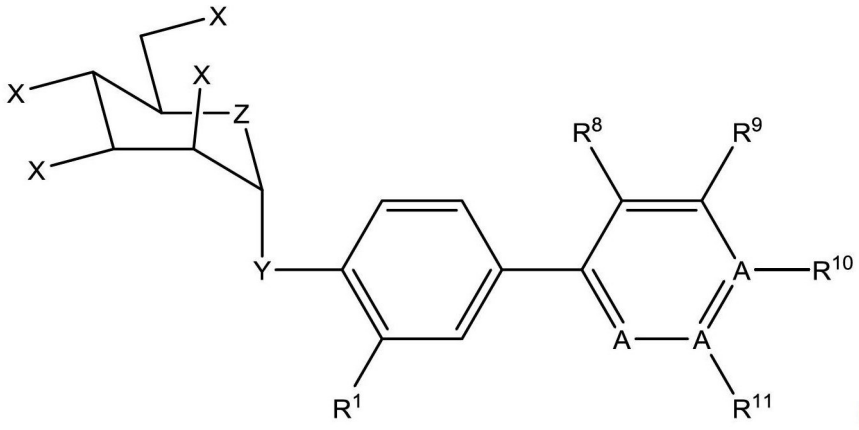
[0027] a是1至4的整数;

[0028] R^4选自由以下组成的组:$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$,或当a大于或等于2时,R^4可任选形成任选取代的环烷基、芳基或杂环5或6元环;

[0029] R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

[0030] R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环。

[0031] 本发明的另一方面涵盖一种包括式(II)的化合物:

[0032] 

(II)

[0033] 其中:

[0034] X选自由以下组成的组:氢和OR^2;

[0035] R^2独立地选自由以下组成的组:氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基;

[0036] n是1至10的整数;

[0037] Z是O;

[0038] Y选自由以下组成的组:O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5;

[0039] A独立地选自由以下组成的组:CR^5和N;

[0040] R^1选自由以下组成的组:CH_3、CF_3、卤素、Cl、F、B_r、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、

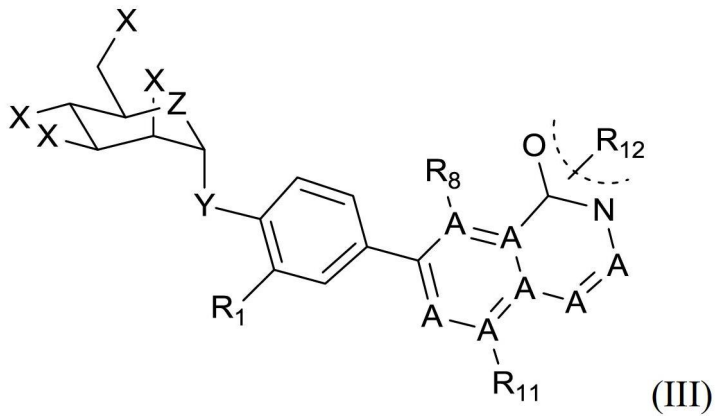
$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

[0041] R^8、R^9、R^{10}和R^{11}独立地选自由以下组成的组：$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$、$NHSO_2R^7$，并且R^8和R^9一起可任选形成任选取代的环烷基、芳基或杂环5或6元环；并且R^9和R^{10}一起可任选形成任选取代的环烷基、芳基或杂环5或6元环；

[0042] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0043] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环。

[0044] 本发明的另一方面涵盖一种包括式(III)的化合物：

[0045] 

(III)

[0046] 其中：

[0047] X选自由以下组成的组：氢和OR^2；

[0048] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0049] n是1至10的整数；

[0050] Z是O；

[0051] Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

[0052] R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

[0053] A独立地选自由以下组成的组：CR^5和N；

[0054] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0055] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

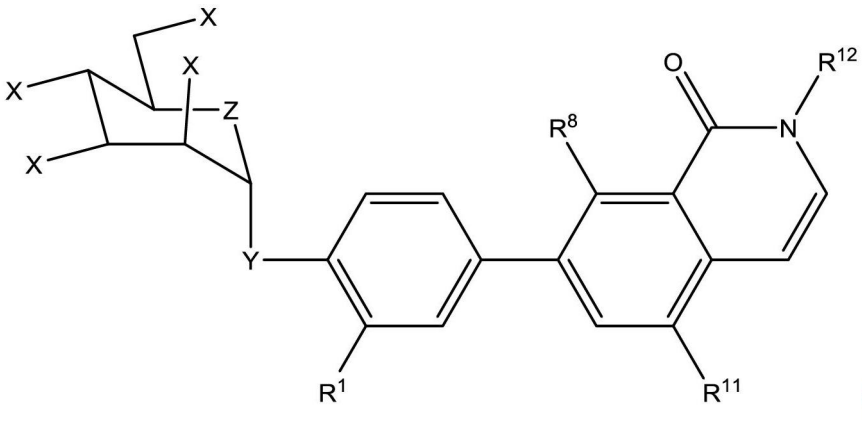
[0056] R^8和R^{11}独立地选自由以下组成的组：$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$；

[0057] R^{12}在O或N处被取代，并且选自由以下组成的组：H、烷基、CH_2R^{13}、CH_2COR^{13}、CH_2CONHR^{13}、$CH_2CONHR^{13}R^{14}$、$CH_2CONH(CH_2)_2R^{14}$、$(CH_2)_2NR^{13}$、$(CH_2)_nNR^{13}$、CH_2COOH、$CH_2CONH(CH_2)_2NH_2$和$(CH_2)_2N(CH_3)_2$；

[0058] R^{13}选自由以下组成的组：-OH以及任选取代的杂环、烃基和取代的烃基；

[0059] R^{14}选自由以下组成的组：烷基和NH_2。

[0060] 本发明的另一方面涵盖一种包括式(IV)的化合物：

[0061] 

(IV)

[0062] 其中：

[0063] X选自由以下组成的组：氢和OR^2；

[0064] R^2独立地选自由以下组成的组：氢、PO(OH)2、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0065] n是1至10的整数；

[0066] Z是O；

[0067] Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

[0068] R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

[0069] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0070] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

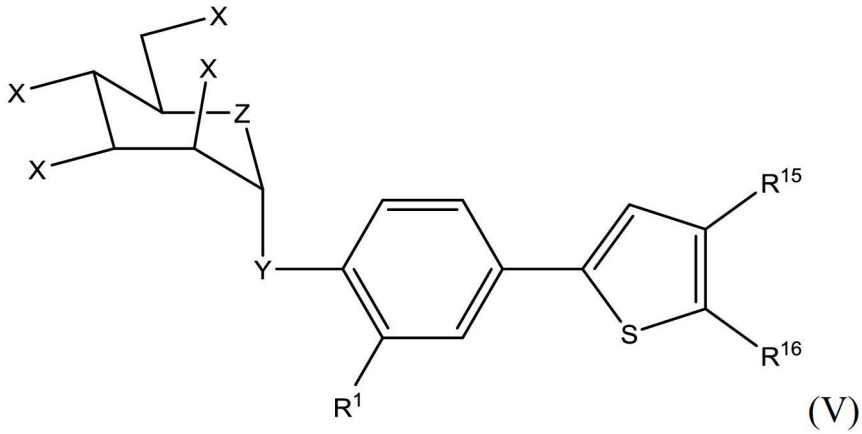
[0071] R^8和R^{11}独立地选自由以下组成的组：$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$；

[0072] R^{12}选自由以下组成的组：H、烷基、CH_2R^{13}、CH_2COR^{13}、CH_2CONHR^{13}、$CH_2CONHR^{13}R^{14}$、$CH_2CONH(CH_2)_2R^{14}$、$(CH_2)_2NR^{13}$、$(CH_2)_nNR^{13}$、CH_2COOH、$CH_2CONH(CH_2)_2NH_2$和$(CH_2)_2N(CH_3)_2$；

[0073] R^{13}选自由以下组成的组：-OH以及任选取代的杂环、烃基和取代的烃基；

[0074] R^{14}选自由以下组成的组：烷基和NH_2。

[0075] 本发明的另一方面涵盖一种包括式(V)的化合物：

[0076] 

(V)

[0077] 其中：

[0078] X选自由以下组成的组:氢和OR^2;

[0079] R^2独立地选自由以下组成的组:氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基;

[0080] n是1至10的整数;

[0081] R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

[0082] R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环;

[0083] Z是O;

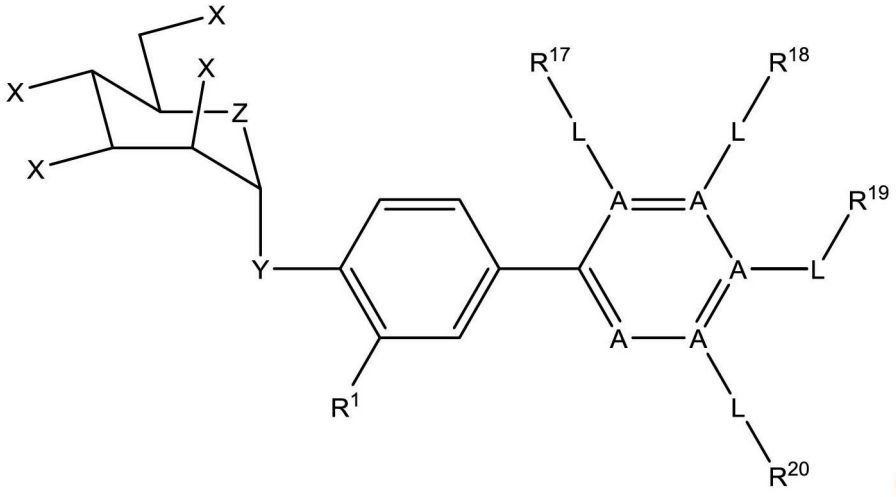
[0084] Y选自由以下组成的组:O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5;

[0085] R^1选自由以下组成的组:CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基;

[0086] R^{15}和R^{16}独立地选自由以下组成的组:氢、$NHCONH_2$、$COOCH_3$以及$CONHCH_3$、$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$,或R^{15}和R^{16}可任选形成环烷基、芳基或杂环。

[0087] 本发明的另一方面涵盖一种包括式(VI)的化合物:

[0088]



(VI)

[0089] 其中:

[0090] X选自由以下组成的组:氢和OR^2;

[0091] R^2独立地选自由以下组成的组:氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基;

[0092] n是1至10的整数;

[0093] R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

[0094] R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环;

[0095] Z是O;

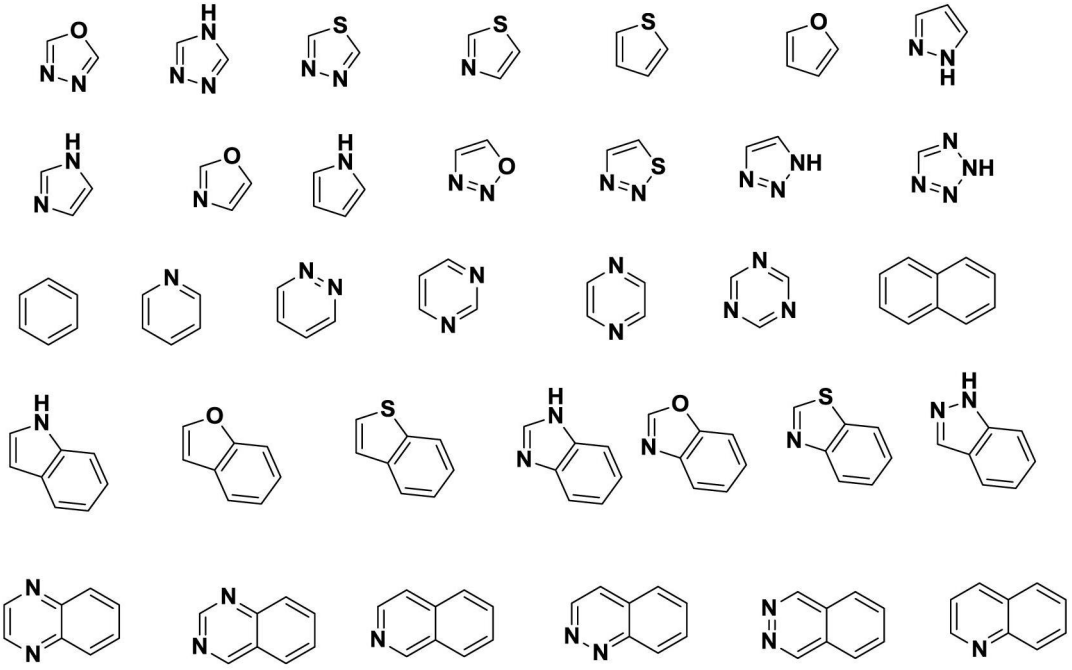
[0096] Y选自由以下组成的组:O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5;

[0097] R^1选自由以下组成的组:CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基;

[0098] A独立地选自由以下组成的组:CR^5和N;

[0099] L独立地选自由以下组成的组:无原子、N、NH、O和S;

[0100] R^{17}、R^{18}、R^{19}和R^{20}选自由以下组成的组:H以及任选取代的环烷基、芳基或杂环5或6元环、5-6稠环或6-6稠环,包括但不限于以下实例,其中该实例通过任何可用的CH位置加以连接:

[0101] 

[0102] 本发明也涵盖一种治疗尿路感染的方法。该方法包括向有需要的受试者施用本发明化合物。

[0103] 此外,本发明涵盖一种预防尿路感染的方法。该方法包括向有需要的受试者施用本发明化合物。

[0104] 在另一方面,本发明涵盖一种降低细菌对杀菌化合物的抗性的方法。该方法包括向有需要的受试者施用本发明化合物。

[0105] 在另一方面,本发明涵盖一种治疗炎症性肠病的方法。该方法包括向有需要的受试者施用本发明化合物。

[0106] 在另一方面,本发明涵盖一种抑制FimH结合甘露糖的方法。该方法包括使本发明化合物与FimH接触,其中该化合物结合FimH,并且抑制与甘露糖的结合。

[0107] 在另一方面,本发明涵盖一种治疗导管相关的尿路感染的方法。该方法包括向有需要的受试者施用本发明化合物。

[0108] 附图简述

[0109] 本申请文件含有至少一个以彩色制作的附图。具有彩色附图的本专利申请公布的复本将在请求并支付必要费用后由专利局提供。

[0110] 图1描绘甘露糖苷化合物对预防小鼠感染模型中的UTI的作用。描绘化合物(A)ZFH-4269、(B)ZFH-5254(实施例7)和(C)ZFH-5240(实施例18A)的结构。(D)显示50mg/kg的269、254和240相对于DMSO和PBS使膀胱中的细菌滴度降低。

[0111] 图2描绘作为ZFH-5254的类似物的甘露糖苷化合物对预防小鼠感染模型中的UTI的作用。描绘化合物(A)ZFH-4269、(B)1CJ68(实施例16)和(C)1CJ70(实施例14)的结构。(D)显示25mg/kg的化合物ZFH269最高效降低膀胱中的细菌滴度。

[0112] 图3描绘被评估大鼠PK的甘露糖苷化合物的结构。

[0113] 图4描绘静脉内给药的甘露糖苷化合物在大鼠中的药代动力学的图。FIM-5240(实施例18A)显示最佳PK。

[0114] 图5描绘口服(PO)给药的甘露糖苷化合物在大鼠中的药代动力学的图。

[0115] 图6描绘甘露糖苷化合物在小鼠尿中的药代动力学。描绘化合物(A)ZFH-4269、(B)ZFH-5254(实施例7)、(C)ZFH-5240(实施例18A)的结构。(D)显示269、254、前药和240的药代动力学。

[0116] 图7描绘各种甘露糖苷前药在小鼠急性UTI感染模型中的功效。(A)显示在小鼠急性感染模型中,25mg/kg的ZFH269和25mg/kg的ZFH-4269前药显著降低膀胱中的细菌滴度。(B)显示在小鼠急性感染模型中,所有前药化合物都降低膀胱中的细菌滴度。

[0117] 图8描绘3种前药:(A)FIM-1231(实施例20)、(B)FIM-1233(实施例21)和(C)FIM-6123(实施例22)的结构。

[0118] 图9描绘各种甘露糖苷化合物的血浆稳定性和代谢。描绘化合物(A)4ZFH269、(B)5ZFH240(实施例18A)、(C)5ZFH61和(D)1CJ87(实施例4)的结构。化合物5ZFH61和1CJ87相对于4ZFH269和5ZFH240具有超过两倍半衰期($t_{1/2}$)。(E)说明4ZFH269在血浆蛋白酶存在下的代谢。

[0119] 图10描绘细菌表面凝集素和菌毛的图解。(A)描绘革兰氏阳性和革兰氏阴性细菌的结构。(B)描绘由宿主表达的碳水化合物和细菌通过细菌凝集素进行结合。碳水化合物药物可抑制与宿主碳水化合物的结合。(C)描绘见于宿主细胞上的糖基化的结构。

[0120] 图11描绘FimH介导的对膀胱的粘附的图解和图像。(A)尿路病原性大肠杆菌(UPEC)通过描绘于(B)中的1型菌毛上的FimH粘附素感染膀胱上皮。(C)UPEC的FimH特异性结合浅表伞状细胞上的尿斑蛋白(uroplakin)。

[0121] 图12描绘显示FimH凝集素结构域和D-甘露糖结合的图解和图。(A)显示在1型菌毛的尖端处的FimH粘附素。甘露糖以与周围氨基酸残基的众多相互作用紧密配合于FimH甘露糖结合口袋中。(B)显示对结合口袋内的残基的突变使与甘露糖的结合消除。

[0122] 图13描绘甘露糖苷作为UTI毒性抑制剂的历史。1987年至今,焦点在用以增加亲合力的多价甘露糖苷上,观察到单体甘露糖苷的效价较低,并且缺乏靶标和结构信息。重要的是,未报道口服生物利用度或体内研究。

[0123] 图14描绘丁基甘露糖结合于FimH的带状图。结合口袋的形状以及甘露糖环的定向类似于D-甘露糖-FimH结构。在丁基与Tyr48、Try137和Ile52之间存在新型疏水性相互作用。

[0124] 图15描绘用于评估化合物阻断FimH介导的结合的能力的血凝测定(HA)。HAI滴度定量度量抑制剂对阻断被大肠杆菌感染的豚鼠红血细胞的FimH介导的血凝(HA)的作用。HAI滴度定义为化合物抑制红血细胞的＞90％血凝的有效浓度。

[0125] 图16描绘苯基甘露糖苷的初始结构活性关系(SAR)。(A)显示于苯基环上的额外取代基以及这如何影响HAI滴度。(B)基于HA滴度,邻位取代基是优选的。(C)在酰胺下观察到相反趋势。

[0126] 图17描绘在多环甘露糖苷背后的设计合理性的图像。多环甘露糖苷可靶向与Tyr48和Try137的疏水性或π-π堆积相互作用。

[0127] 图18描绘显示化合物6增强TMP-SMZ治疗的图。(A)描绘SMZ的结构，并且(B)描绘TMP抗生素的结构。(C)描绘2ZFH56甘露糖苷的结构。(D)在感染之后6小时定量总细菌CFU。在用6(100mg/kg)、TMP-SMZ(分别是54和270μg/ml)和TMP-SMZ+6处理的小鼠中，UTI89定殖降低。水平线指示几何平均值。*P＜0.05;**P＜0.01;***P＜0.0001，Mann-Whitney U检验。(E)在各种浓度的TMP-SMZ存在下，在具有以及不具有ZFH-2056下，作出PBC-1的生长曲线，所述PBC-1是在临床上对TMP-SMZ具有抗性的UPEC菌株。抗生素连同或不连同甘露糖苷并不影响PBC-1的生长。

[0128] 图19描绘A环邻位基团化合物。A环邻位基团显著增强效价。

[0129] 图20描绘在邻位甘露糖苷存在下的FimH结构。描绘甘露糖苷化合物(A)FIM-4284和(B)FIM-4269的结构。(C)邻位甲基取代在小口袋中结合Asn138。

[0130] 图21描绘化合物7至10在治疗感染方面显示增强的药代动力学和效价。(A)优化的邻位取代的联苯化合物7至10。细胞HAI滴度(EC＞90)显示于括号中。(B)化合物7至10显示改进的药代动力学。在处理之后6小时，在50mg/kg下的化合物8和10产生的尿中浓度等效于在100mg/kg下的化合物6。图中的数值显示甘露糖苷的PAMPA预测的可渗透性与体内药代动力学相关联。

[0131] 图22描绘联苯甘露糖苷在慢性膀胱炎中的功效。(A)描绘甘露糖苷8的结构。(B)描绘甘露糖苷10的结构。(C)慢性感染的小鼠用PBS或化合物6、8或10(口服，50mg/kg)或TMP-SMZ处理。在处理之后6小时，相对于PBS处理的小鼠，甘露糖苷处理的小鼠中的细菌载量存在显著下降。优化的化合物8显示超过6的功效增加。(D)慢性感染的小鼠用PBS或化合物8在一次剂量或每8小时1次的三次剂量下处理。在初始处理之后24小时，两个化合物8处理组均显示超过PBS处理的动物的细菌计数显著下降。(C和D)水平棒条指示几何平均值。*P＜0.05;**P＜0.01;***P＜0.0001，Mann-Whitney U检验。

[0132] 图23描绘B环杂环。连同HAI滴度一起显示B环杂环的物理性质。

[0133] 图24描绘在口服给药之后向D-甘露糖的代谢。(A)描绘FIM-2056的降解产物。(B)在口服给药之后评估降解产物“R”。

[0134] 图25描绘在糖苷键处取代的各种衍生物。评估取代以改进代谢稳定性。(A)2ZFH56、(B)4ZFH123、(C)4ZFH89、(D)4ZFH131、(E)4ZFH105、(F)4ZFH44、(G)4ZFH55、(H)5ZFH049、)(I)5ZFH038和(J)5ZFH048。

[0135] 图26描绘先导化合物(A)FIM-4269、(B)FIM-5254(实施例7)和(C)FIM-5240(实施例18A)的小鼠药代动力学。(D)描绘甘露糖苷在小鼠尿中直至8小时的浓度的图。

[0136] 图27描绘急性UTI模型中的先导化合物。描绘甘露糖苷化合物(A)FIM-4269、(B)FIM-5254(实施例7)和(C)FIM-5240(实施例18A)的结构。(D)ZFH269和269的前药在急性UTI模型中显著降低膀胱滴度。(E)肾滴度不显著不同。

[0137] 图28描绘先导物优化药代动力学流程。

[0138] 图29描绘哺乳动物糖蛋白的结构。(A)描绘糖蛋白如何在哺乳动物细胞表面上表达。(B)描绘各种糖蛋白的结构。

[0139] 图30描绘1型菌毛的结构和装配。

[0140] 图31描绘合成S-糖苷和N-糖苷的示意图。

[0141] 图32描绘合成C-连接的糖苷的示意图。

[0142] 图33描绘合成N-连接的杂环的示意图。

[0143] 图34描绘合成联芳甘露糖苷SAR文库的示意图。

[0144] 图35描绘合成联苯甘露糖苷Suzuki文库的示意图。

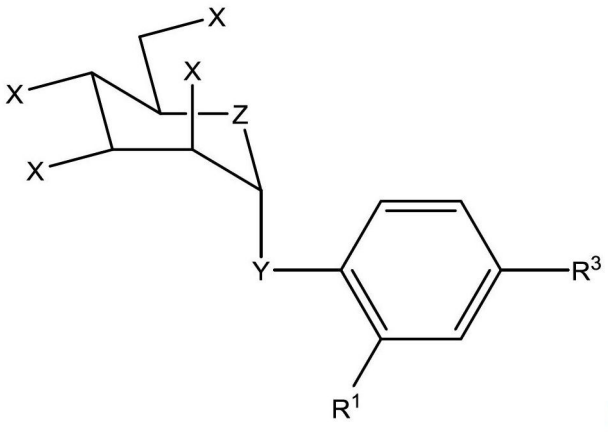
[0145] 图36描绘杂环的示意图和物理性质。(A、B)显示在HA测定中具有约2μM,但具有不良溶解度的两种结构。(C)显示合成杂环的示意图。

[0146] 发明详述

[0147] 已开发抑制细菌的1型菌毛的功能的化合物。所述化合物可适用于治疗尿路感染和克罗恩氏病。值得注意的是,所述化合物可防止细菌定殖和侵袭膀胱组织以防止感染以及建立可充当复发性感染的源头的储库。本发明也涵盖使用本发明化合物的方法。

[0148] I.化合物

[0149] 本发明的一个方面是一种式(I)化合物:

[0150] 

(I)

[0151] 其中:

[0152] X选自由以下组成的组:氢和OR^2;

[0153] R^2独立地选自由以下组成的组:氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(NR_5R_6)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基;

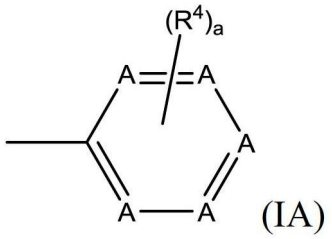
[0154] n是1至10的整数;

[0155] Z是O;

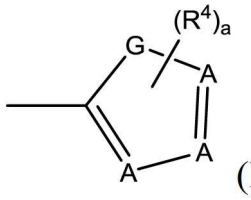
[0156] Y选自由以下组成的组:O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5;

[0157] R^1选自由以下组成的组:CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基;

[0158] R^3选自由以下组成的组:式(IA)和式)(IB):

[0159] 

(IA)

[0160] 

(IB)

[0161] A独立地选自由以下组成的组:CR^5和N;

[0162] G独立地选自由以下组成的组:S、NR^5和O;

[0163] a是1至4的整数;

[0164] R^4选自由以下组成的组:$CONHCH_3$、$COOCH_3$、COOH、$CONR_5$、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$,或当a大于或等于2时,R^4可任选形成任选取代的环烷基、芳基或杂环5或6元环;

[0165] R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

[0166] R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环。

[0167] 在一个实施方案中,本发明化合物包括式(I),其中:

[0168] X选自由以下组成的组:氢和OR^2;

[0169] R^2独立地选自由以下组成的组:氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基;

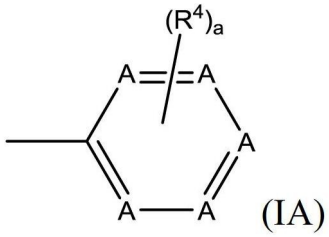
[0170] n是1至4的整数;

[0171] Z是O;

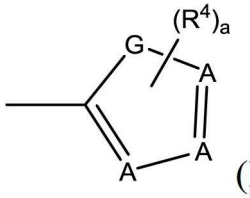
[0172] Y选自由以下组成的组:O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5;

[0173] R^1选自由以下组成的组:CH_3、CF_3、卤素、OCH_3、CO_2CH_3和$CONHCH_3$;

[0174] R^3选自由以下组成的组:式(IA)和式(IB):

[0175] 

(IA)



(IB)

[0176] A独立地选自由以下组成的组:CR^5和N;

[0177] G独立地选自由以下组成的组:S、NR^5和O;

[0178] a是1至3的整数;

[0179] R^4选自由以下组成的组:$CONHCH_3$、$COOCH_3$、COOH、$CONR_5$、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$,或当a大于或等于2时,R^4可任选形

成任选取代的环烷基、芳基或杂环5或6元环；

[0180] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0181] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环。

[0182] 在另一实施方案中，本发明化合物包括式(I)，其中：

[0183] X选自由以下组成的组：氢和OR^2；

[0184] R^2独立地选自由以下组成的组：氢、$-COCH_3$、$-PO(OH)_2$、$-COCH_2N(CH_3)_2$；

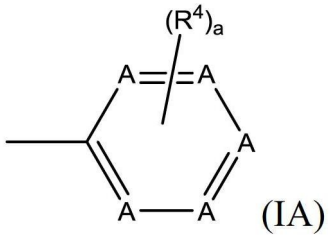
[0185] Z是O；

[0186] Y选自由以下组成的组：O、CH(OH)和CH_2；

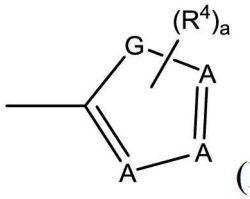
[0187] R^1是CH_3；

[0188] R^3选自由以下组成的组：式(IA)和式(IB)：

[0189]



(IA)



(IB)

[0190] A独立地选自由以下组成的组：CR^5和N；

[0191] G是S；

[0192] a是1至4的整数；

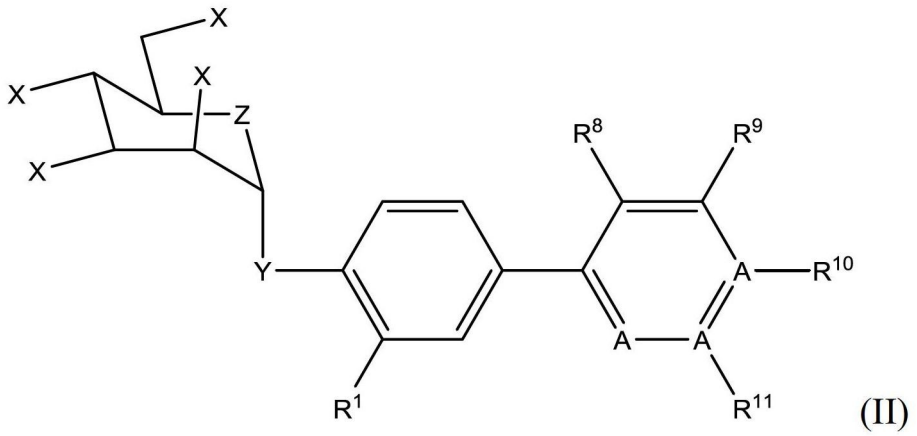
[0193] R^4选自由以下组成的组：氢、$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、$NHCONH_2$和杂环，或当a大于或等于2时，R4可任选形成任选取代的环烷基、芳基或杂环5或6元环；

[0194] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基。

[0195] 在各先前实施方案的一示例性替代方案中，包括式(I)的化合物是包括表1中的任何结构式的化合物。

[0196] 在各先前实施方案的另一示例性替代方案中，本发明化合物是来自表1的实施例1-23和25。

[0197] 本发明的另一方面是一种式(II)化合物：

[0198] 

(II)

[0199] 其中：

[0200] X选自由以下组成的组：氢和OR^2；

[0201] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0202] n是1至10的整数；

[0203] Z是O；

[0204] Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

[0205] A独立地选自由以下组成的组：CR^5和N；

[0206] R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

[0207] R^8、R^9、R^{10}和R^{11}独立地选自由以下组成的组：$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$、$NHSO_2R^7$，并且R^8和R^9一起可任选形成任选取代的环烷基、芳基或杂环5或6元环；并且R^9和R^{10}一起可任选形成任选取代的环烷基、芳基或杂环5或6元环；

[0208] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0209] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环。

[0210] 在一个实施方案中，本发明化合物包括式(II)，其中：

[0211] X选自由以下组成的组：氢和OR^2；

[0212] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0213] n是1至10的整数；

[0214] Z是O；

[0215] Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

[0216] A独立地选自由以下组成的组：CR^5和N；

[0217] R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

[0218] R^8、R^9、R^{10}和R^{11}独立地选自由以下组成的组：氢、$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)和杂环，或R^8和R^9一起可任选形成任选取代的环烷基、芳基或杂环5或6元环，并且R^9和R^{10}一

起可任选形成任选取代的环烷基、芳基或杂环5或6元环；

[0219] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0220] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环。

[0221] 在另一实施方案中，本发明化合物包括式(II)，其中：

[0222] X选自由以下组成的组：氢和OR^2；

[0223] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0224] n是1至10的整数；

[0225] Z是O；

[0226] Y选自由以下组成的组：O、$CH(OH)$、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

[0227] A独立地选自由以下组成的组：CR^5和N；

[0228] R^1选自由以下组成的组：CH_3、CF_3、卤素、OCH_3、CO_2CH_3和$CONHCH_3$；

[0229] R^8、R^9、R^{10}和R^{11}独立地选自由以下组成的组：氢、$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)和杂环，或R^8和R^9一起可任选形成任选取代的环烷基、芳基或杂环5或6元环，并且R^9和R^{10}一起可任选形成任选取代的环烷基、芳基或杂环5或6元环；

[0230] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基。

[0231] 在另一实施方案中，本发明化合物包括式(II)，其中：

[0232] X选自由以下组成的组：氢和OR^2；

[0233] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0234] n是1至10的整数；

[0235] Z是O；

[0236] Y选自由以下组成的组：O、$CH(OH)$、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

[0237] A独立地选自由以下组成的组：CR^5和N；

[0238] R^1选自由以下组成的组：CH_3、CF_3、卤素、OCH_3、CO_2CH_3和$CONHCH_3$；

[0239] R^8、R^{10}和R^{11}是氢；

[0240] R^9选自由以下组成的组：$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$、$NHSO_2R^7$，并且R^8和R^9一起可任选形成任选取代的环烷基、芳基或杂环5或6元环；并且R^9和R^{10}一起可任选形成任选取代的环烷基、芳基或杂环5或6元环；

[0241] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0242] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环。

[0243] 在另一实施方案中，本发明化合物包括式(II)，其中：

[0244] X选自由以下组成的组：氢和OR^2；

[0245] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0246] n是1至10的整数；

[0247] Z是O；

[0248] Y选自由以下组成的组:O、CH(OH)和CH_2;

[0249] R^1选自由以下组成的组:CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基;

[0250] R^8、R^9、R^{10}和R^{11}独立地选自由以下组成的组:$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、芳基、环丙基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$、$NHSO_2R^7$,并且R^8和R^9一起可任选形成任选取代的环烷基、芳基或杂环5或6元环;并且R^9和R^{10}一起可任选形成任选取代的环烷基、芳基或杂环5或6元环;

[0251] R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

[0252] R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环。

[0253] 在另一实施方案中,本发明化合物包括式(II),其中:

[0254] X选自由以下组成的组:氢和OR^2;

[0255] R^2独立地选自由以下组成的组:氢、$-COCH_3$、$-PO(OH)_2$和$-COCH_2N(CH_3)_2$;

[0256] Z是O;

[0257] Y选自由以下组成的组:O、CH(OH)和CH_2;

[0258] A独立地选自由以下组成的组:CR^5和N;

[0259] R^1选自由以下组成的组:CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基;

[0260] R^8、R^9、R^{10}和R^{11}独立地选自由以下组成的组:$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$、$NHSO_2R^7$,并且R^8和R^9一起可任选形成任选取代的环烷基、芳基或杂环5或6元环;并且R^9和R^{10}一起可任选形成任选取代的环烷基、芳基或杂环5或6元环;

[0261] R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

[0262] R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环。

[0263] 在另一实施方案中,本发明化合物包括式(II),其中:

[0264] X选自由以下组成的组:氢和OR^2;

[0265] R^2独立地选自由以下组成的组:氢、$-COCH_3$、$-PO(OH)_2$和$-COCH_2N(CH_3)_2$;

[0266] Z是O;

[0267] Y选自由以下组成的组:O、CH(OH)和CH_2;

[0268] A独立地选自由以下组成的组:CR^5和N;

[0269] R^1是CH_3;

[0270] R^8、R^9、R^{10}和R^{11}独立地选自由以下组成的组:$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$,并且R^8和R^9一起可任选形成任选取代的环烷基、芳基或杂环5或6元环;并且R^9和R^{10}一起可任选形成任选取代的环烷基、芳基或杂环5或6元环;

[0271] R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

[0272] R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环。

[0273] 在另一实施方案中，本发明化合物包括式(II)，其中：

[0274] X选自由以下组成的组：氢和OR^2；

[0275] R^2独立地选自由以下组成的组：氢、$-COCH_3$、$-PO(OH)_2$和$-COCH_2N(CH_3)_2$；

[0276] Z是O；

[0277] Y选自由以下组成的组：O、CH(OH)和CH_2；

[0278] A独立地选自由以下组成的组：CR^5和N；

[0279] R^1是CH_3；

[0280] R^8、R^9、R^{10}和R^{11}独立地选自由以下组成的组：氢、$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)和杂环，或R^8和R^9一起可任选形成任选取代的环烷基、芳基或杂环5或6元环，并且R^9和R^{10}一起可任选形成任选取代的环烷基、芳基或杂环5或6元环；

[0281] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基。

[0282] 在另一实施方案中，本发明化合物包括式(II)，其中：

[0283] X选自由以下组成的组：氢和OR^2；

[0284] R^2独立地选自由以下组成的组：氢、$-COCH_3$、$-PO(OH)_2$和$-COCH_2N(CH_3)_2$；

[0285] Z是O；

[0286] Y选自由以下组成的组：O、CH(OH)和CH_2；

[0287] A独立地选自由以下组成的组：CR^5和N；

[0288] R^1是CH_3；

[0289] R^8、R^{10}和R^{11}是氢；

[0290] R^9选自由以下组成的组：$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$，或R^8和R^9一起可任选形成任选取代的环烷基、芳基或杂环5或6元环；并且R^9和R^{10}一起可任选形成任选取代的环烷基、芳基或杂环5或6元环；

[0291] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0292] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环。

[0293] 在另一实施方案中，本发明化合物包括式(II)，其中：

[0294] X选自由以下组成的组：氢和OR^2；

[0295] R^2独立地选自由以下组成的组：氢、$-COCH_3$、$-PO(OH)_2$和$-COCH_2N(CH_3)_2$；

[0296] Z是O；

[0297] Y选自由以下组成的组：O、CH(OH)和CH_2；

[0298] A独立地选自由以下组成的组：CR^5和N；

[0299] R^1是CH_3；

[0300] R^8、R^{10}和R^{11}是氢；

[0301] R^9选自由以下组成的组：氢、$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)和杂环；

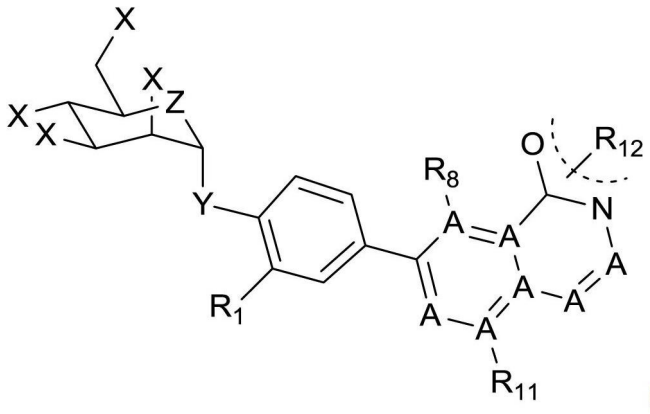
[0302] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基。

[0303] 在各先前实施方案的一示例性替代方案中，包括式)(II)的化合物是包括表1中的任何结构式的化合物。

[0304] 在各先前实施方案的另一示例性替代方案中，本发明化合物是来自表1的实施例

1-16、18-23和25。

[0305] 本发明的另一方面是一种式(III)化合物：

[0306] 

(III)

[0307] 其中：

[0308] X选自由以下组成的组：氢和OR^2；

[0309] R^2独立地选自由以下组成的组：氢、PO(OH)2、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0310] n是1至10的整数；

[0311] Z是O；

[0312] Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

[0313] R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

[0314] A独立地选自由以下组成的组：CR^5和N；

[0315] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0316] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

[0317] R^8和R^{11}独立地选自由以下组成的组：$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$；

[0318] R^{12}在O或N处被取代，并且选自由以下组成的组：H、烷基、CH_2R^{13}、CH_2COR^{13}、CH_2CONHR^{13}、$CH_2CONHR^{13}R^{14}$、$CH_2CONH(CH_2)_2R^{14}$、$(CH_2)_2NR^{13}$、$(CH_2)_nNR^{13}$、CH_2COOH、$CH_2CONH(CH_2)_2NH_2$和$(CH_2)_2N(CH_3)_2$；

[0319] R^{13}选自由以下组成的组：-OH以及任选取代的杂环、烃基和取代的烃基；

[0320] R^{14}选自由以下组成的组：烷基和NH_2。

[0321] 在一个实施方案中，本发明化合物包括式(IV)，其中：

[0322] X选自由以下组成的组：氢和OR^2；

[0323] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0324] n是1至10的整数；

[0325] Z是O；

[0326] Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

[0327] R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、

$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

[0328] A独立地选自由以下组成的组：CR^5和N；

[0329] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0330] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

[0331] R^8和R^{11}独立地选自由以下组成的组：$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$；

[0332] R^{12}在O或N处被取代，并且选自由以下组成的组：H、烷基、CH_2(杂环)、$(CH_2)_2N(CH_3)_2$、CH_2COOH、CH_2CONH(杂环)、$CH_2CONH(CH_2)_2NH_2$和CH_2CO(杂环)。

[0333] 在另一实施方案中，本发明化合物包括式(IV)，其中：

[0334] X选自由以下组成的组：氢和OR^2；

[0335] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0336] n是1至10的整数；

[0337] Z是O；

[0338] Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

[0339] R^1选自由以下组成的组：CH_3、CF_3、卤素、OCH_3、CO_2CH_3和$CONHCH_3$；

[0340] A独立地选自由以下组成的组：CR^5和N；

[0341] R^8和R^{11}独立地选自由以下组成的组：$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$；

[0342] R^{12}在O或N处被取代，并且选自由以下组成的组：H、烷基、CH_2(杂环)、$(CH_2)_2N(CH_3)_2$、CH_2COOH、CH_2CONH(杂环)、$CH_2CONH(CH_2)_2NH_2$和CH_2CO(杂环)；

[0343] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0344] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环。

[0345] 在另一实施方案中，本发明化合物包括式(IV)，其中：

[0346] X选自由以下组成的组：氢和OR^2；

[0347] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0348] n是1至10的整数；

[0349] Z是O；

[0350] Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

[0351] R^1选自由以下组成的组：CH_3、CF_3、卤素、OCH_3、CO_2CH_3和$CONHCH_3$；

[0352] A独立地选自由以下组成的组：CR^5和N；

[0353] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0354] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

[0355] R^8和R^{11}是氢；

[0356] R^{12}在O或N处被取代，并且选自由以下组成的组：H、烷基、CH_2R^{13}、CH_2COR^{13}、CH_2CONHR^{13}、$CH_2CONHR^{13}R^{14}$、$CH_2CONH(CH_2)_2R^{14}$、$(CH_2)_2NR^{13}$、$(CH_2)_nNR^{13}$、CH_2COOH、$CH_2CONH(CH_2)$

$_2NH_2$和$(CH_2)_2N(CH_3)_2$；

[0357] R^{13}选自由以下组成的组：-OH以及任选取代的杂环、烃基和取代的烃基；

[0358] R^{14}选自由以下组成的组：烷基和NH_2。

[0359] 在另一实施方案中，本发明化合物包括式(IV)，其中：

[0360] X选自由以下组成的组：氢和OR^2；

[0361] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0362] n是1至10的整数；

[0363] Z是O；

[0364] Y选自由以下组成的组：O、CH(OH)和CH_2；

[0365] R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

[0366] A独立地选自由以下组成的组：CR^5和N；

[0367] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0368] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

[0369] R^8和R^{11}独立地选自由以下组成的组：$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$；

[0370] R^{12}在O或N处被取代，并且选自由以下组成的组：H、CH_2R^{13}、CH_2COR^{13}、CH_2CONHR^{13}、$CH_2CONHR^{13}R^{14}$、$CH_2CONH(CH_2)_2R^{14}$、$(CH_2)_2NR^{13}$、$(CH_2)_nNR^{13}$、CH_2COOH、$CH_2CONH(CH_2)_2NH_2$和$(CH_2)_2N(CH_3)_2$；

[0371] R^{13}选自由以下组成的组：-OH以及任选取代的杂环、烃基和取代的烃基；

[0372] R^{14}选自由以下组成的组：烷基和NH_2。

[0373] 在另一实施方案中，本发明化合物包括式(IV)，其中：

[0374] X选自由以下组成的组：氢和OR^2；

[0375] R^2独立地选自由以下组成的组：氢、$-COCH_3$、$-PO(OH)_2$和$-COCH_2N(CH_3)_2$；

[0376] Z是O；

[0377] Y选自由以下组成的组：O、CH(OH)和CH_2；

[0378] R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

[0379] A独立地选自由以下组成的组：CR^5和N；

[0380] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0381] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

[0382] R^8和R^{11}独立地选自由以下组成的组：$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$；

[0383] R^{12}在O或N处被取代，并且独立地选自由以下组成的组：H、烷基、CH_2R^{13}、CH_2COR^{13}、CH_2CONHR^{13}、$CH_2CONHR^{13}R^{14}$、$CH_2CONH(CH_2)_2R^{14}$、$(CH_2)_2NR^{13}$、$(CH_2)_nNR^{13}$、CH_2COOH、$CH_2CONH(CH_2)_2NH_2$和$(CH_2)_2N(CH_3)_2$；

[0384] R^{13}选自由以下组成的组:-OH以及任选取代的杂环、烃基和取代的烃基;

[0385] R^{14}选自由以下组成的组:烷基和NH_2。

[0386] 在另一实施方案中,本发明化合物包括式(IV),其中:

[0387] X选自由以下组成的组:氢和OR^2;

[0388] R^2独立地选自由以下组成的组:氢、$-COCH_3$、$-PO(OH)_2$和$-COCH_2N(CH_3)_2$;

[0389] Z是O;

[0390] Y选自由以下组成的组:O、CH(OH)和CH_2;

[0391] R^1是CH_3;

[0392] A独立地选自由以下组成的组:CR^5和N;

[0393] R^8和R^{11}独立地选自由以下组成的组:$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$;

[0394] R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

[0395] R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环;

[0396] R^{12}在O或N处被取代,并且选自由以下组成的组:H、烷基、CH_2R^{13}、CH_2COR^{13}、CH_2CONHR^{13}、$CH_2CONHR^{13}R^{14}$、$CH_2CONH(CH_2)_2R^{14}$、$(CH_2)_2NR^{13}$、$(CH_2)_nNR^{13}$、CH_2COOH、$CH_2CONH(CH_2)_2NH_2$和$(CH_2)_2N(CH_3)_2$;

[0397] R^{13}选自由以下组成的组:-OH以及任选取代的杂环、烃基和取代的烃基;

[0398] R^{14}选自由以下组成的组:烷基和NH_2。

[0399] 在另一实施方案中,本发明化合物包括式(IV),其中:

[0400] X选自由以下组成的组:氢和OR^2;

[0401] R^2独立地选自由以下组成的组:氢、$-COCH_3$、$-PO(OH)_2$和$-COCH_2N(CH_3)_2$;

[0402] Z是O;

[0403] Y选自由以下组成的组:O、CH(OH)和CH_2;

[0404] R^1是CH_3;

[0405] A独立地选自由以下组成的组:CR^5和N;

[0406] R^8和R^{11}独立地选自由以下组成的组:$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$;

[0407] R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

[0408] R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环;

[0409] R^{12}在O或N处被取代,并且选自由以下组成的组:H、CH_2(杂环)、$(CH_2)_2N(CH_3)_2$、CH_2COOH、CH_2CONH(杂环)、$CH_2CONH(CH_2)_2NH_2$和CH_2CO(杂环)。

[0410] 在另一实施方案中,本发明化合物包括式(IV),其中:

[0411] X选自由以下组成的组:氢和OR^2;

[0412] R^2独立地选自由以下组成的组:氢、$-COCH_3$、$-PO(OH)_2$和$-COCH_2N(CH_3)_2$;

[0413] Z是O;

[0414] Y选自由以下组成的组:O、CH(OH)和CH_2;

[0415] R^1是CH_3;

[0416] A独立地选自由以下组成的组:CR^5和N;

[0417] R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

[0418] R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环;

[0419] R^8和R^{11}是氢;

[0420] R^{12}在O或N处被取代,并且选自由以下组成的组:H、烷基、CH_2R^{13}、CH_2COR^{13}、CH_2CONHR^{13}、$CH_2CONHR^{13}R^{14}$、$CH_2CONH(CH_2)_2R^{14}$、$(CH_2)_2NR^{13}$、$(CH_2)_nNR^{13}$、CH_2COOH、$CH_2CONH(CH_2)_2NH_2$和$(CH_2)_2N(CH_3)_2$;

[0421] R^{13}选自由以下组成的组:-OH以及任选取代的杂环、烃基和取代的烃基;

[0422] R^{14}选自由以下组成的组:烷基和NH_2。

[0423] 在另一实施方案中,本发明化合物包括式(IV),其中:

[0424] X选自由以下组成的组:氢和OR^2;

[0425] R^2独立地选自由以下组成的组:氢、$-COCH_3$、$-PO(OH)_2$和$-COCH_2N(CH_3)_2$;

[0426] Z是O;

[0427] Y选自由以下组成的组:O、CH(OH)和CH_2;

[0428] R^1是CH_3;

[0429] A独立地选自由以下组成的组:CR^5和N;

[0430] R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

[0431] R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环;

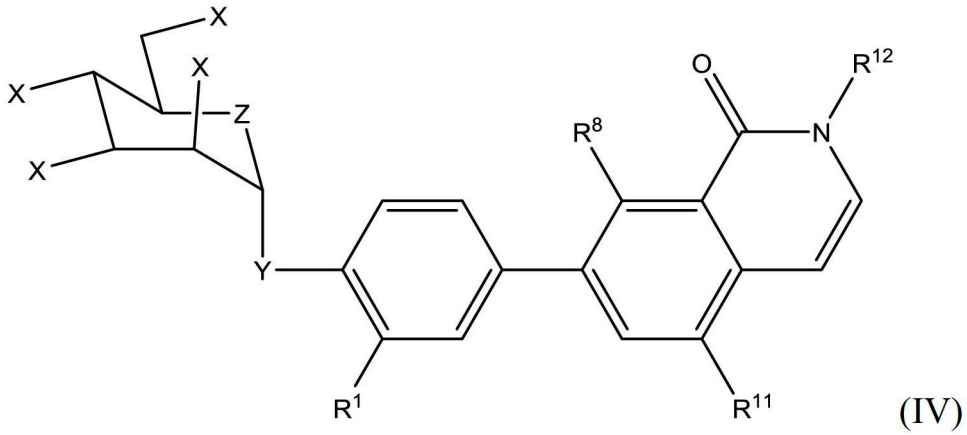
[0432] R^8和R^{11}是氢;

[0433] R^{12}在O或N处被取代,并且选自由以下组成的组:H、CH_2(杂环)、$(CH_2)_2N(CH_3)_2$、CH_2COOH、CH_2CONH(杂环)、$CH_2CONH(CH_2)_2NH_2$和CH_2CO(杂环)。

[0434] 在各先前实施方案的一示例性替代方案中,包括式(IV)的化合物是包括表1中的任何结构式的化合物。

[0435] 在各先前实施方案的另一示例性替代方案中,本发明化合物是来自表1的实施例7-16。

[0436] 本发明的另一方面是一种式(IV)化合物:

[0437] 

(IV)

[0438] 其中:

[0439] X选自由以下组成的组:氢和OR^2;

[0440] R^2独立地选自由以下组成的组:氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、

烃基和取代的烃基；

[0441] n是1至10的整数；

[0442] Z是O；

[0443] Y选自由以下组成的组：O、CH(OH)、CH(OR^5)、CHNR^5R^6、CH_2、S和NR^5；

[0444] R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

[0445] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0446] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

[0447] R^8和R^{11}独立地选自由以下组成的组：$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$；

[0448] R^{12}选自由以下组成的组：H、烷基、CH_2R^{13}、CH_2COR^{13}、CH_2CONHR^{13}、$CH_2CONHR^{13}R^{14}$、$CH_2CONH(CH_2)_2R^{14}$、$(CH_2)_2NR^{13}$、$(CH_2)_nNR^{13}$、CH_2COOH、$CH_2CONH(CH_2)_2NH_2$和$(CH_2)_2N(CH_3)_2$；

[0449] R^{13}选自由以下组成的组：-OH以及任选取代的杂环、烃基和取代的烃基；

[0450] R^{14}选自由以下组成的组：烷基和NH_2。

[0451] 在一个实施方案中，本发明化合物包括式(IV)，其中：

[0452] X选自由以下组成的组：氢和OR^2；

[0453] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0454] n是1至10的整数；

[0455] Z是O；

[0456] Y选自由以下组成的组：O、CH(OH)、CH(OR^5)、CHNR^5R^6、CH_2、S和NR^5；

[0457] R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

[0458] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0459] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

[0460] R^8和R^{11}独立地选自由以下组成的组：$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$；

[0461] R^{12}选自由以下组成的组：H、烷基、CH_2(杂环)、$(CH_2)_2N(CH_3)_2$、CH_2COOH、CH_2CONH(杂环)、$CH_2CONH(CH_2)_2NH_2$和CH_2CO(杂环)。

[0462] 在另一实施方案中，本发明化合物包括式(IV)，其中：

[0463] X选自由以下组成的组：氢和OR^2；

[0464] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0465] n是1至10的整数；

[0466] Z是O；

[0467] Y选自由以下组成的组：O、CH(OH)、CH(OR^5)、CHNR^5R^6、CH_2、S和NR^5；

[0468] R^1选自由以下组成的组：CH_3、CF_3、卤素、OCH_3、CO_2CH_3和$CONHCH_3$；

[0469] R^8和R^{11}独立地选自由以下组成的组:$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$;

[0470] R^{12}选自由以下组成的组:H、烷基、CH_2(杂环)、$(CH_2)_2N(CH_3)_2$、CH_2COOH、CH_2CONH(杂环)、$CH_2CONH(CH_2)_2NH_2$和CH_2CO(杂环);

[0471] R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

[0472] R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环。

[0473] 在另一实施方案中,本发明化合物包括式(IV),其中:

[0474] X选自由以下组成的组:氢和OR^2;

[0475] R^2独立地选自由以下组成的组:氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烷基和取代的烷基;

[0476] n是1至10的整数;

[0477] Z是O;

[0478] Y选自由以下组成的组:O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5;

[0479] R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

[0480] R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环;

[0481] R^1选自由以下组成的组:CH_3、CF_3、卤素、OCH_3、CO_2CH_3和$CONHCH_3$;

[0482] R^8和R^{11}是氢;

[0483] R^{12}选自由以下组成的组:H、烷基、CH_2R^{13}、CH_2COR^{13}、CH_2CONHR^{13}、$CH_2CONHR^{13}R^{14}$、$CH_2CONH(CH_2)_2R^{14}$、$(CH_2)_2NR^{13}$、$(CH_2)_nNR^{13}$、CH_2COOH、$CH_2CONH(CH_2)_2NH_2$和$(CH_2)_2N(CH_3)_2$;

[0484] R^{13}选自由以下组成的组:-OH以及任选取代的杂环、烷基和取代的烷基;

[0485] R^{14}选自由以下组成的组:烷基和NH_2。

[0486] 在另一实施方案中,本发明化合物包括式(IV),其中:

[0487] X选自由以下组成的组:氢和OR^2;

[0488] R^2独立地选自由以下组成的组:氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烷基和取代的烷基;

[0489] n是1至10的整数;

[0490] Z是O;

[0491] Y选自由以下组成的组:O、CH(OH)和CH_2;

[0492] R^1选自由以下组成的组:CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烷基和取代的烷基;

[0493] R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

[0494] R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环;

[0495] R^8和R^{11}独立地选自由以下组成的组:$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$;

[0496] R^{12}选自由以下组成的组:H、CH_2R^{13}、CH_2COR^{13}、CH_2CONHR^{13}、$CH_2CONHR^{13}R^{14}$、$CH_2CONH(CH_2)_2R^{14}$、$(CH_2)_2NR^{13}$、$(CH_2)_nNR^{13}$、CH_2COOH、$CH_2CONH(CH_2)_2NH_2$和$(CH_2)_2N(CH_3)_2$;

[0497] R^{13}选自由以下组成的组:-OH以及任选取代的杂环、烷基和取代的烷基;

[0498] R^{14}选自由以下组成的组:烷基和NH_2。

[0499] 在另一实施方案中,本发明化合物包括式(IV),其中:

[0500] X选自由以下组成的组:氢和OR^2;

[0501] R^2独立地选自由以下组成的组:氢、$-COCH_3$、$-PO(OH)_2$和$-COCH_2N(CH_3)_2$;

[0502] Z是O;

[0503] Y选自由以下组成的组:O、CH(OH)和CH_2;

[0504] R^1选自由以下组成的组:CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基;

[0505] R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

[0506] R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环;

[0507] R^8和R^{11}独立地选自由以下组成的组:$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$;

[0508] R^{12}独立地选自由以下组成的组:H、烷基、CH_2R^{13}、CH_2COR^{13}、CH_2CONHR^{13}、$CH_2CONHR^{13}R^{14}$、$CH_2CONH(CH_2)_2R^{14}$、$(CH_2)_2NR^{13}$、$(CH_2)_nNR^{13}$、CH_2COOH、$CH_2CONH(CH_2)_2NH_2$和$(CH_2)_2N(CH_3)_2$;

[0509] R^{13}选自由以下组成的组:-OH以及任选取代的杂环、烃基和取代的烃基;

[0510] R^{14}选自由以下组成的组:烷基和NH_2。

[0511] 在另一实施方案中,本发明化合物包括式(IV),其中:

[0512] X选自由以下组成的组:氢和OR^2;

[0513] R^2独立地选自由以下组成的组:氢、$-COCH_3$、$-PO(OH)_2$和$-COCH_2N(CH_3)_2$;

[0514] Z是O;

[0515] Y选自由以下组成的组:O、CH(OH)和CH_2;

[0516] R^1是CH_3;

[0517] R^8和R^{11}独立地选自由以下组成的组:$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$;

[0518] R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

[0519] R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环;

[0520] R^{12}选自由以下组成的组:H、烷基、CH_2R^{13}、CH_2COR^{13}、CH_2CONHR^{13}、$CH_2CONHR^{13}R^{14}$、$CH_2CONH(CH_2)_2R^{14}$、$(CH_2)_2NR^{13}$、$(CH_2)_nNR^{13}$、CH_2COOH、$CH_2CONH(CH_2)_2NH_2$和$(CH_2)_2N(CH_3)_2$;

[0521] R^{13}选自由以下组成的组:-OH以及任选取代的杂环、烃基和取代的烃基;

[0522] R^{14}选自由以下组成的组:烷基和NH_2。

[0523] 在另一实施方案中,本发明化合物包括式(IV),其中:

[0524] X选自由以下组成的组:氢和OR^2;

[0525] R^2独立地选自由以下组成的组:氢、$-COCH_3$、$-PO(OH)_2$和$-COCH_2N(CH_3)_2$;

[0526] Z是O;

[0527] Y选自由以下组成的组:O、CH(OH)和CH_2;

[0528] R^1是CH_3;

[0529] R^8和R^{11}独立地选自由以下组成的组:$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、H、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$;

[0530] R^5选自由以下组成的组:H以及任选取代的烷基、芳基、杂环和环烷基;

[0531] R^6和R^7选自由以下组成的组:任选取代的烷基、环烷基、芳基和杂环;

[0532] R^{12}选自由以下组成的组:H、CH_2(杂环)、$(CH_2)_2N(CH_3)_2$、CH_2COOH、CH_2CONH(杂环)、$CH_2CONH(CH_2)_2NH_2$和CH_2CO(杂环)。

[0533] 在另一实施方案中,本发明化合物包括式(IV),其中:

[0534] X选自由以下组成的组:氢和OR^2;

[0535] R^2独立地选自由以下组成的组:氢、$-COCH_3$、$-PO(OH)_2$和$-COCH_2N(CH_3)_2$;

[0536] Z是O;

[0537] Y选自由以下组成的组:O、CH(OH)和CH_2;

[0538] R^1是CH_3;

[0539] R^8和R^{11}是氢;

[0540] R^{12}选自由以下组成的组:H、烷基、CH_2R^{13}、CH_2COR^{13}、CH_2CONHR^{13}、$CH_2CONHR^{13}R^{14}$、$CH_2CONH(CH_2)_2R^{14}$、$(CH_2)_2NR^{13}$、$(CH_2)_nNR^{13}$、CH_2COOH、$CH_2CONH(CH_2)_2NH_2$和$(CH_2)_2N(CH_3)_2$;

[0541] R^{13}选自由以下组成的组:-OH以及任选取代的杂环、烃基和取代的烃基;

[0542] R^{14}选自由以下组成的组:烷基和NH_2。

[0543] 在另一实施方案中,本发明化合物包括式(IV),其中:

[0544] X选自由以下组成的组:氢和OR^2;

[0545] R^2独立地选自由以下组成的组:氢、$-COCH_3$、$-PO(OH)_2$和$-COCH_2N(CH_3)_2$;

[0546] Z是O;

[0547] Y选自由以下组成的组:O、CH(OH)和CH_2;

[0548] R^1是CH_3;

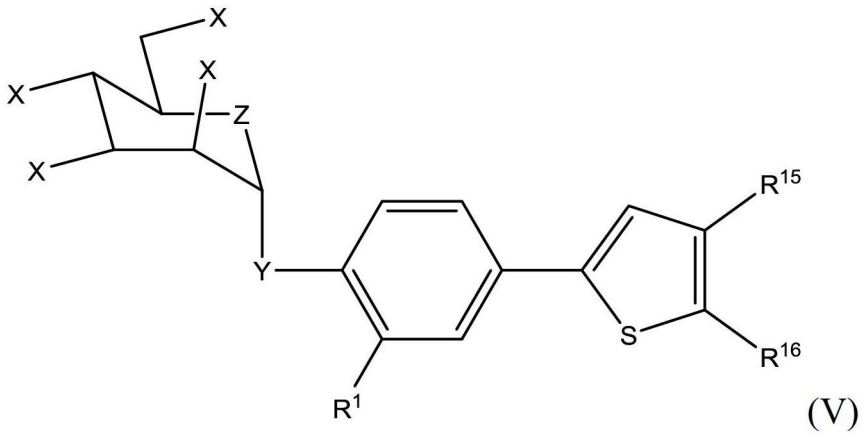
[0549] R^8和R^{11}是氢;

[0550] R^{12}选自由以下组成的组:H、CH_2(杂环)、$(CH_2)xN(CH_3)_2$、CH_2COOH、CH_2CONH(杂环)、$CH_2CONH(CH_2)_2NH_2$和CH_2CO(杂环)。

[0551] 在各先前实施方案的一示例性替代方案中,包括式(IV)的化合物是包括表1中的任何结构式的化合物。

[0552] 在各先前实施方案的另一示例性替代方案中,本发明化合物是来自表1的实施例7-16。

[0553] 本发明的另一方面是一种式(V)化合物:

[0554] 

(V)

[0555] 其中：

[0556] X选自由以下组成的组：氢和OR^2；

[0557] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0558] n是1至10的整数；

[0559] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0560] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

[0561] Z是O；

[0562] Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

[0563] R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

[0564] R^{15}和R^{16}独立地选自由以下组成的组：氢、$NHCONH_2$、$COOCH_3$以及$CONHCH_3$、$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$，或R^{15}和R^{16}可任选形成环烷基、芳基或杂环。

[0565] 在一个实施方案中，本发明化合物包括式(V)，其中：

[0566] X选自由以下组成的组：氢和OR^2；

[0567] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0568] n是1至10的整数；

[0569] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0570] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

[0571] Z是O；

[0572] Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

[0573] R^1选自由以下组成的组：CH_3、CF_3、卤素、OCH_3、CO_2CH_3和$CONHCH_3$；

[0574] R^{15}和R^{16}独立地选自由以下组成的组：氢、$NHCONH_2$、$COOCH_3$以及$CONHCH_3$、$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$，或R^{15}和R^{16}可任选形成环烷基、芳基或杂环。

[0575] 在另一实施方案中，本发明化合物包括式(V)，其中：

[0576] X选自由以下组成的组：氢和OR^2；

[0577] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0578] n是1至10的整数；

[0579] Z是O；

[0580] Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

[0581] R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

[0582] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0583] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

[0584] R^{15}和R^{16}独立地选自由以下组成的组：氢、$NHCONH_2$、$COOCH_3$和$CONHCH_3$，并且R^{15}和R^{16}可任选形成任选取代的环烷基或杂环5或6元环。

[0585] 在另一实施方案中，本发明化合物包括式(V)，其中：

[0586] X选自由以下组成的组：氢和OR^2；

[0587] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0588] n是1至10的整数；

[0589] Z是O；

[0590] Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

[0591] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0592] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

[0593] R^1选自由以下组成的组：CH_3、CF_3、卤素、OCH_3、CO_2CH_3和$CONHCH_3$；

[0594] R^{15}和R^{16}独立地选自由以下组成的组：氢、$NHCONH_2$、$COOCH_3$和$CONHCH_3$，并且R^{15}和R^{16}可任选形成任选取代的环烷基或杂环5或6元环。

[0595] 在另一实施方案中，本发明化合物包括式(V)，其中：

[0596] X选自由以下组成的组：氢和OR^2；

[0597] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0598] n是1至10的整数；

[0599] Z是O；

[0600] Y选自由以下组成的组：O、CH(OH)和CH_2；

[0601] R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

[0602] R^5选自由以下组成的组：H或任选取代的烷基、芳基、杂环和环烷基；

[0603] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

[0604] R^{15}和R^{16}独立地选自由以下组成的组：氢、$NHCONH_2$、$COOCH_3$以及$CONHCH_3$、$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$

和$NHSO_2R^7$，或R^{15}和R^{16}可任选形成环烷基、芳基或杂环。

[0605] 在另一实施方案中，本发明化合物包括式(V)，其中：

[0606] X选自由以下组成的组：氢和OR^2；

[0607] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0608] n是1至10的整数；

[0609] Z是O；

[0610] Y选自由以下组成的组：O、CH(OH)和CH_2；

[0611] R^1选自由以下组成的组：CH_3、CF_3、卤素、OCH_3、CO_2CH_3和$CONHCH_3$；

[0612] R^{15}和R^{16}独立地选自由以下组成的组：氢、$NHCONH_2$、$COOCH_3$和$CONHCH_3$，并且R^{15}和R^{16}可任选形成任选取代的环烷基或杂环5或6元环。

[0613] 在另一实施方案中，本发明化合物包括式(V)，其中：

[0614] X选自由以下组成的组：氢和OR^2；

[0615] R^2独立地选自由以下组成的组：氢、$-COCH_3$、$-PO(OH)_2$、$-COCH_2N(CH_3)_2$；

[0616] Z是O；

[0617] Y选自由以下组成的组：O、CH(OH)和CH_2；

[0618] R^1选自由以下组成的组：CH_3、CF_3、卤素、OCH_3、CO_2CH_3和$CONHCH_3$；

[0619] R^{15}和R^{16}独立地选自由以下组成的组：氢、$NHCONH_2$、$COOCH_3$以及$CONHCH_3$、$CONHCH_3$、$COOCH_3$、COOH、CONH(杂环)、杂环、烷基、环丙基、芳基、OR^5、NR^5R^6、NR^5COR^6、NR^5COOR^6、NR^5CONR^6、$NR^5SO_2R^6$、COR^5、SO_2R^5、卤素、CN、NO_2、$COOR^5$、$CONR^5R^6$、$NCOR^7$、$NCONR^7$、$NCOOR^7$、$SO_2NR^5R^6$和$NHSO_2R^7$，或R^{15}和R^{16}可任选形成环烷基、芳基或杂环；

[0620] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0621] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环。

[0622] 在另一实施方案中，本发明化合物包括式(V)，其中：

[0623] X选自由以下组成的组：氢和OR^2；

[0624] R^2独立地选自由以下组成的组：氢、$-COCH_3$、$-PO(OH)_2$、$-COCH_2N(CH_3)_2$；

[0625] Z是O；

[0626] Y选自由以下组成的组：O、CH(OH)和CH_2；

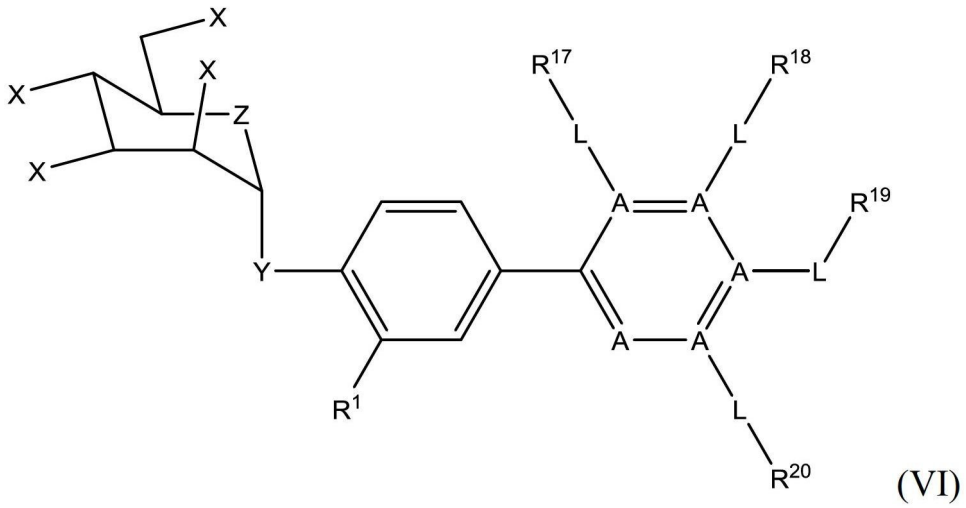
[0627] R^1是CH_3；

[0628] R^{15}和R^{16}独立地选自由以下组成的组：氢、$NHCONH_2$、$COOCH_3$和$CONHCH_3$，并且R^{15}和R^{16}可任选形成任选取代的环烷基或杂环5或6元环。

[0629] 在各先前实施方案的一示例性替代方案中，包括式(V)的化合物是包括表1中的任何结构式的化合物。

[0630] 在各先前实施方案的另一示例性替代方案中，本发明化合物是来自表1的实施例17。

[0631] 本发明的另一方面是一种式(VI)化合物：

[0632] 

(VI)

[0633] 其中：

[0634] X选自由以下组成的组：氢和OR^2；

[0635] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0636] n是1至10的整数；

[0637] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0638] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

[0639] Z是O；

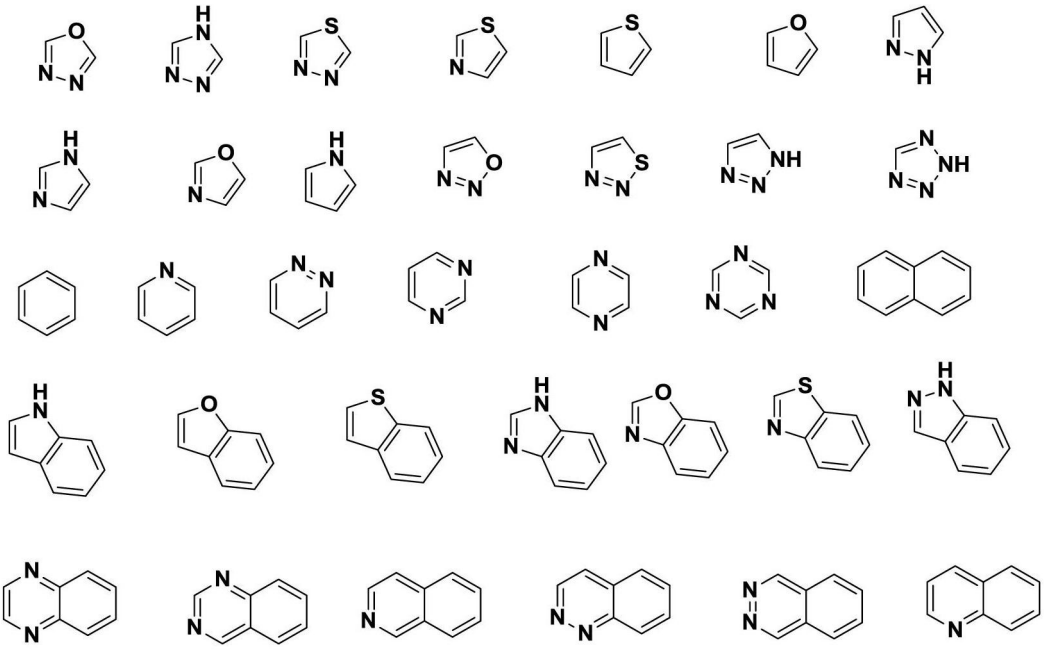
[0640] Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

[0641] R^1选自由以下组成的组：CH_3、CF_3、卤素、Cl、F、Br、I、OH、NH_2、NR^5R^6、OCH_3、CO_2CH_3、$CONHCH_3$、烷基、环丙基、OR^5、CO_2R^5、$CONR^5R^6$、烃基和取代的烃基；

[0642] A独立地选自由以下组成的组：CR^5和N；

[0643] L独立地选自由以下组成的组：无原子、N、O和S；

[0644] R^{17}、R^{18}、R^{19}和R^{20}选自由以下组成的组：H以及任选取代的环烷基、芳基或杂环5或6元环，包括但不限于以下实例，其中实例通过任何可用的CH位置加以连接：

[0645] 

[0646] 在一个实施方案中，本发明化合物包括式(VI)，其中：

[0647] X选自由以下组成的组：氢和OR^2；

[0648] R^2独立地选自由以下组成的组：氢、$PO(OH)_2$、乙酰基、COR^5、$CO(OR^5)$、$CO(CH_2)_nNR^5R^6$、烃基和取代的烃基；

[0649] n是1至10的整数；

[0650] R^5选自由以下组成的组：H以及任选取代的烷基、芳基、杂环和环烷基；

[0651] R^6和R^7选自由以下组成的组：任选取代的烷基、环烷基、芳基和杂环；

[0652] Z是O；

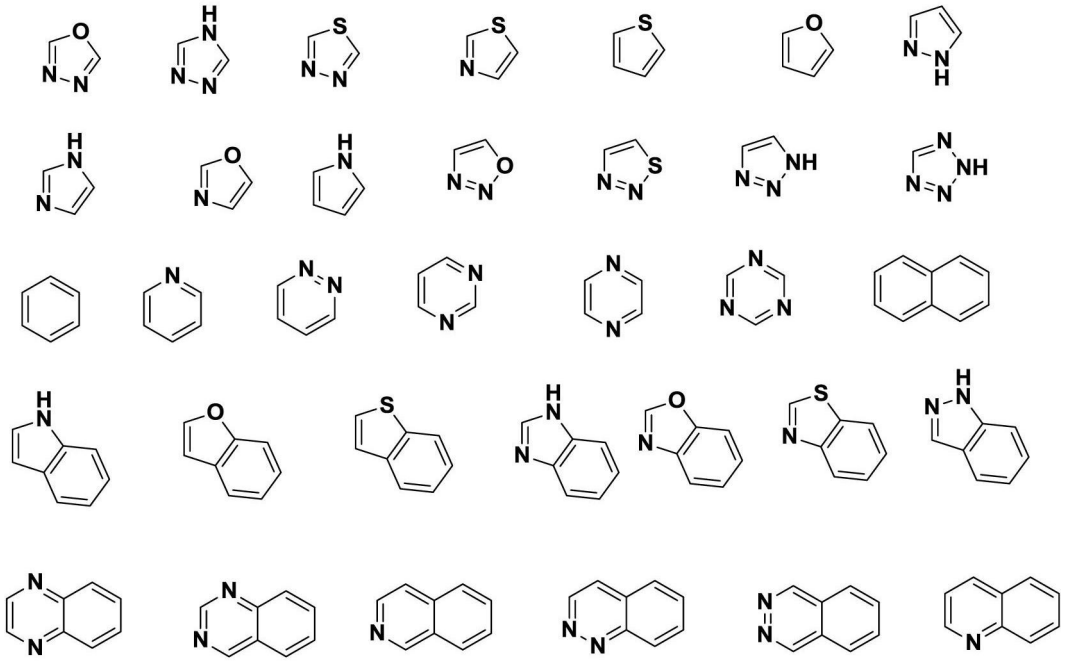
[0653] Y选自由以下组成的组：O、CH(OH)、$CH(OR^5)$、$CHNR^5R^6$、CH_2、S和NR^5；

[0654] R^1选自由以下组成的组：CH_3、CF_3、卤素、OCH_3、CO_2CH_3和$CONHCH_3$；

[0655] A独立地选自由以下组成的组：CR^5和N；

[0656] L独立地选自由以下组成的组：无原子、N、O和S；

[0657] R^{17}、R^{18}、R^{19}和R^{20}选自由以下组成的组：H以及任选取代的环烷基、芳基或杂环5或6元环，包括但不限于以下实例，其中实例通过任何CH位置加以连接：

[0658] 

[0659] 在另一实施方案中，本发明化合物包括式(VI)，其中：

[0660] X选自由以下组成的组：氢和OR^2；

[0661] R^2独立地选自由以下组成的组：氢、$-COCH_3$、$-PO(OH)_2$和$-COCH_2N(CH_3)_2$；

[0662] Z是O；

[0663] Y选自由以下组成的组：O、CH_2O和CH_2；

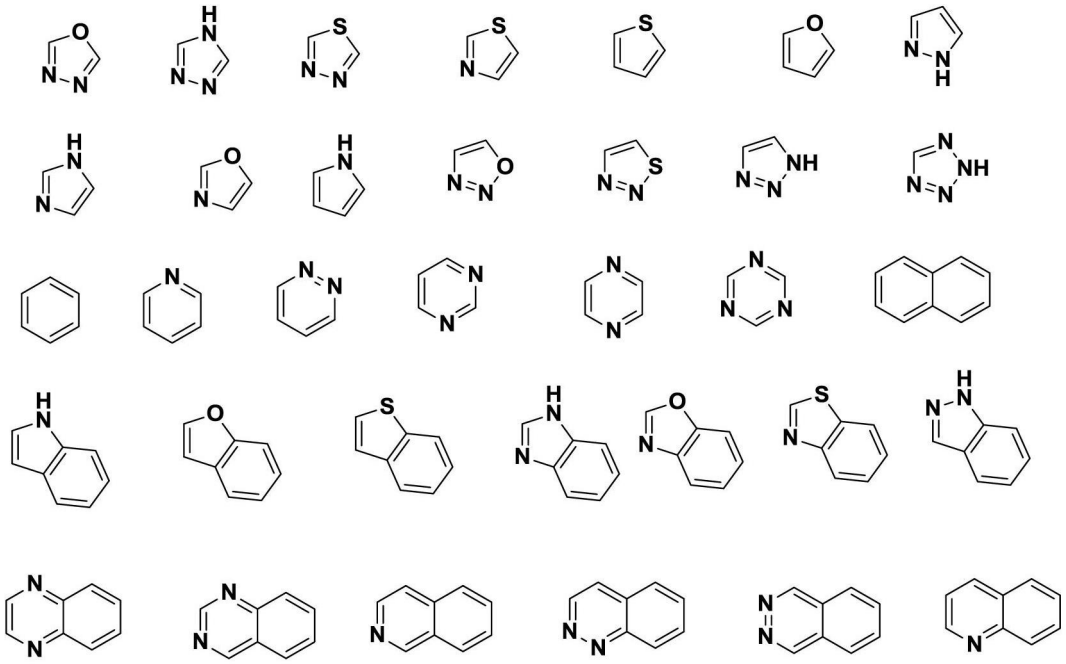
[0664] R^1是CH_3；

[0665] A独立地选自由以下组成的组：CR^5和N；

[0666] L独立地选自由以下组成的组：无原子、N、O和S；

[0667] R^{17}和R^{20}是H；

[0668] R^{18}和R^{19}选自由以下组成的组：H以及任选取代的环烷基、芳基或杂环5或6元环，包括但不限于以下实例，其中实例通过任何CH位置加以连接：

[0669] 

[0670] 在各先前实施方案的一示例性替代方案中，包括式(VI)的化合物是包括表1中的任何结构式的化合物。

[0671] 在各先前实施方案的另一示例性替代方案中，本发明化合物是来自表1的实施例5-6。

[0672] 在某些实施方案中，以上化合物的糖残基可涵盖甘露糖的立体异构体。在其它实施方案中，以上化合物的糖残基可涵盖甘露糖的除葡萄糖以外的任何立体异构体。在一示例性实施方案中，以上化合物的糖残基是αD甘露糖。

[0673] 合成本发明化合物的示例性方法详述于实施例中。

[0674] 本发明化合物也可为合成式(I)一(IV)化合物的中间体。举例来说，在一个实施方案中，本发明化合物可为合成式(I)一(IV)化合物的酯中间体。在另一实施方案中，本发明化合物可为甘露糖苷的硼酸酯(boronate ester)或甘露糖苷的硼酸酯(boronic acid ester)。在另一实施方案中，本发明化合物可为以下实施例中的流程I-XII中说明的化合物。

[0675] 本发明化合物也可包含成像剂，如荧光部分。在一实施方案中，成像剂直接或通过连接体结合于本发明化合物的糖部分。

[0676] 本发明化合物可阻断病原性细菌的1型菌毛的FimH的功能并防止细菌粘着和侵袭，并且因此防止IBC中的细菌扩增和后续散布以及通过新一代IBC进行重复多轮扩增。

[0677] 用于测量化合物的活性的FimH功能性测定为本领域中的熟练个体所知。功能性测定的非限制性实例包括使用豚鼠红血细胞的血凝滴度、结合FimH的亲和力、和化合物防止生物膜形成的能力。

[0678] 在一些实施方案中，使用豚鼠红血细胞的血凝滴度度量化合物的活性。由1型菌毛化UPEC达成的豚鼠红血细胞的血凝依赖于FimH甘露糖结合能力，并且连续稀释允许进行定量分析。血凝滴度可通常定义为使血凝降低75％所需的化合物的量。在一些实施方案中，本发明化合物的血凝滴度可小于约5、4、3、2或1μM。在实施方案的一优选替代方案中，本发明化合物的血凝滴度可小于约1、0.5、0.4、0.3、0.2或0.1μM。在实施方案的另一优选替代方案

中，本发明化合物的血凝滴度可小于约0.1、0.05、0.04、0.03、0.02、0.01μM。在实施方案的另一优选替代方案中，本发明化合物的血凝滴度可小于约0.01μM。

[0679] 在其它实施方案中，可使用化合物防止或破坏生物膜形成的能力度量化合物的活性。一般来说，可作出测量化合物抑制生物膜形成的能力的滴定曲线来确定IC_{50}。在一些实施方案中，化合物的IC_{50}可小于约700、600、500、400、300、200或100μM。在其它实施方案中，化合物的IC_{50}可小于约500、400、300、200、100、50、40、30、20、10、9、8、7、6或5μM。在优选实施方案中，化合物的IC_{50}可小于约20μM。在其它优选实施方案中，化合物的IC_{50}可小于约9μM。

[0680] II.组合

[0681] 本发明的另一方面涵盖本发明化合物(描述于以上章节I中)与一种或多种杀菌化合物的组合。在一些实施方案中，本发明化合物可包括与1、2、3、4或5种杀菌化合物组合。在一个实施方案中，杀菌化合物是抗生素。合适的抗生素在本领域中是已知的，并且可包括阿米卡星、庆大霉素、卡那霉素、新霉素、奈替米星、妥布霉素、巴龙霉素、格尔德霉素、除莠霉素、碳头孢烯、氯拉卡比、厄他培南、多利培南、亚胺培南/西司他丁、美罗培南、头孢羟氨苄、头孢唑啉、头孢噻吩、头孢氨苄、头孢菌素、头孢克洛、头孢羟唑、头孢西丁、头孢罗齐、头孢呋辛、头孢克肟、头孢地尼、头孢托仑、头孢哌酮、头孢噻肟、头孢泊肟、头孢他啶、头孢布坦、头孢唑肟、头孢曲松、头孢吡肟、头孢吡普、替考拉宁、万古霉素、替拉万星、克林霉素、林可霉素、阿奇霉素、克拉霉素、地红霉素、红霉素、罗红霉素、醋竹桃霉素、泰利霉素、壮观霉素、氨曲南、呋喃唑酮、呋喃妥因、阿莫西林、氨苄西林、阿洛西林、羧苄西林、氯唑西林、双氯西林、氟氯西林、美洛西林、甲氧西林、萘夫西林、苯唑西林、青霉素G、青霉素V、哌拉西林、替莫西林、替卡西林、杆菌肽、粘菌素、多粘菌素B、环丙沙星、依诺沙星、加替沙星、左氧氟沙星、洛美沙星、莫西沙星、萘啶酸、诺氟沙星、氧氟沙星、曲伐沙星、格帕沙星、司帕沙星、替马沙星、磺胺米隆、磺酰氨基柯衣定(Sulfonamidochrysoidine)、乙酰磺胺、磺胺嘧啶、磺胺嘧啶银、磺胺甲噻二唑、磺胺甲噁唑(SMZ)、磺胺(Sulfanilimide)、柳氮磺吡啶、磺胺异噁唑、三甲氧苄二氨嘧啶(TMP)、三甲氧苄二氨嘧啶磺胺甲噁唑(Trimethoprim-Sulfamethoxazole)(如巴可曲(Bactrim)、赛普拉(Septra))、地美环素、多西环素(Doxycycline)、米诺环素、氧四环素、四环素、氯苯吩嗪、氨苯砜、卷曲霉素、环丝氨酸、乙胺丁醇、乙硫异烟胺、异烟肼、吡嗪酰胺、利福平、利福布丁、利福喷丁、链霉素、肿凡纳明、氯霉素、磷霉素、梭链孢酸、利奈唑胺、甲硝哒唑、莫匹罗星、平板霉素、奎奴普丁/达福普汀、利福昔明、甲砜霉素或磺甲硝咪唑。在一示例性实施方案中，抗生素是TMP、SMZ或其组合。

[0682] III.药物组合物

[0683] 本发明的另一方面涵盖一种药物组合物。以上章节I中所述的本发明化合物可以互变异构、几何或立体异构形式存在。本发明涵盖所有此类化合物，包括顺式和反式几何异构体、E-几何异构体和Z-几何异构体、R-对映异构体和S-对映异构体、非对映异构体、d-异构体、l-异构体、其外消旋混合物及其其它混合物。此类互变异构、几何或立体异构形式的药学上可接受的盐也包括在本发明内。如本文所用的术语“顺式”和“反式”表示一种几何异构形式，其中通过双键连接的两个碳原子将各自在双键的同一侧上(“顺式”)或在双键的相对侧上(“反式”)具有氢原子。一些所述化合物含有烯基，并且意图包括顺式与反式或“E”与“Z”几何形式两者。此外，一些所述化合物含有一个或多个立体中心，并且意图包括存在的各立体中心的R、S形式以及R、S形式的混合物。

[0684] 在另一实施方案中，本发明的抑制剂可呈游离碱或其药学上可接受的酸加成盐形式。术语“药学上可接受的盐”是通常用于形成碱金属盐以及用于形成游离酸或游离碱的加成盐的盐。盐的性质可变化，条件是它是药学上可接受的。用于本发明方法中的化合物的合适的药学上可接受的酸加成盐可由无机酸或由有机酸制备。此类无机酸的实例是盐酸、氢溴酸、氢碘酸、硝酸、碳酸、硫酸和磷酸。适当有机酸可选自脂族、环脂族、芳族、芳脂族、杂环、羧酸和磺酸类别的有机酸，其实例是甲酸、乙酸、丙酸、琥珀酸、乙醇酸、葡萄糖酸、乳酸、苹果酸、酒石酸、柠檬酸、抗坏血酸、葡萄糖醛酸、顺丁烯二酸、反丁烯二酸、丙酮酸、天冬氨酸、谷氨酸、苯甲酸、邻氨基苯甲酸、甲磺酸(mesylic acid)、4-羟基苯甲酸、苯乙酸、杏仁酸、双羟萘酸(帕莫酸(pamoic acid))、甲烷磺酸、乙烷磺酸、苯磺酸、泛酸、硬脂酸、海藻酸、海藻酸、羟基丁酸、水杨酸、半乳糖二酸和半乳糖醛酸。用于本发明方法中的化合物的合适的药学上可接受的碱加成盐包括由铝、钙、锂、镁、钾、钠和锌制得的金属盐或由N,N′-二苯甲基乙二胺、氯普鲁卡因、胆碱、二乙醇胺、乙二胺、葡甲胺(N-甲基葡糖胺)和普鲁卡因制得的有机盐。所有这些盐都可通过常规手段，通过例如使适当酸或碱与任何本发明化合物反应来由相应化合物制备。

[0685] 例如无菌可注射水性或油性混悬液的可注射制剂可使用合适的分散剂或湿润剂以及混悬剂根据已知技术加以配制。无菌可注射制剂也可为于无毒胃肠外可接受的稀释剂或溶剂中的无菌可注射溶液或混悬液。在可被采用的可接受媒介物和溶剂之中的是水、林格氏溶液和等张氯化钠溶液。此外，无菌不挥发性油常规用作溶剂或混悬介质。出于这个目的，可采用任何温和不挥发性油，包括合成甘油单酯或甘油二酯。此外，如油酸的脂肪酸适用于制备可注射剂。可使用二甲基乙酰胺、表面活性剂(包括离子和非离子洗涤剂)和聚乙二醇。溶剂和湿润剂(如以上讨论的那些)的混合物也是适用的。

[0686] 供口服施用的固体剂型可包括胶囊、片剂、丸剂、粉末和颗粒剂。在此类固体剂型中，化合物通常与一种或多种合适的于所指示的施用途径的佐剂组合。如果口服施用，那么化合物可与乳糖、蔗糖、淀粉粉末、链烷酸的纤维素酯、纤维素烷基酯、滑石、硬脂酸、硬脂酸镁、氧化镁、磷酸和硫酸的钠盐和钙盐、明胶、阿拉伯胶、海藻酸钠、聚乙烯吡咯烷酮和/或聚乙烯醇掺合，接着制成片剂或囊封以达成方便施用。此类胶囊或片剂可含有如可以活性化合物于羟丙基甲基纤维素中的分散体形式提供的控释制剂。在胶囊、片剂和丸剂的情况下，剂型也可包含缓冲剂，如柠檬酸钠或碳酸镁或碳酸钙或碳酸氢镁或碳酸氢钙。可另外制备具有肠溶包衣的片剂和丸剂。

[0687] 出于治疗目的，供胃肠外施用的制剂可呈水性或非水性等张无菌注射溶液或混悬液形式。可由无菌粉末或颗粒剂制备具有一种或多种所提及的用于供口服施用的制剂中的载体或稀释剂的这些溶液和混悬液。可将化合物溶解于水、聚乙二醇、丙二醇、乙醇、玉米油、棉籽油、花生油、芝麻油、苯甲醇、氯化钠和/或各种缓冲剂中。其它佐剂和施用模式在药物领域中是充分以及广泛已知的。举例来说，本发明化合物可与载体一起施用。此类载体的非限制性实例包括蛋白质载体和脂质载体。

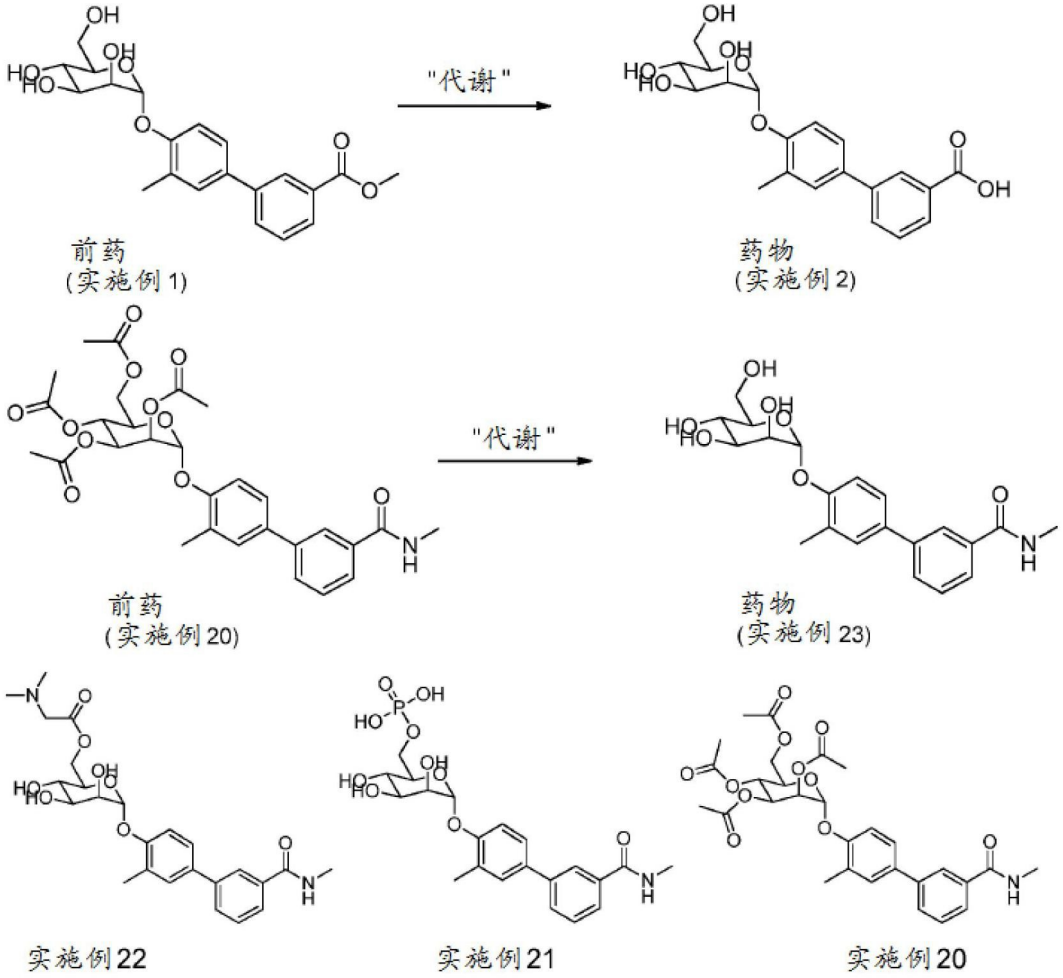
[0688] 供口服施用的液体剂型可包括含有通常用于本领域中的惰性稀释剂(如水)的药学上可接受的乳液、溶液、混悬液、糖浆和酏剂。此类组合物也可包含佐剂，如湿润剂、乳化剂和混悬剂、以及甜味剂、调味剂和芳香剂。

[0689] 可与载体物质组合以产生单一剂量的组合物的本发明化合物的量将视受试者和

特定施用模式而变化。本领域技术人员将了解也可用来自Goodman&Goldman′s The Pharmacological Basis of Therapeutics,第9版(1996),附录II,第1707-1711页以及来自Goodman&Goldman′s The Pharmacological Basis of Therapeutics,第10版(2001),附录II,第475-493页的指导确定剂量。

[0690] 本发明化合物也可被配制成前药。此类前药制剂可增加本发明化合物的生物利用度。在一个实施方案中,本发明化合物的糖部分可涵盖前药。在另一实施方案中,R_3可包含前药。配制成前药的本发明化合物的非限制性实例包括以下化合物:

[0691]



[0692] IV.本发明方法

[0693] 本发明化合物可用于治疗细菌性感染的方法和降低细菌中对杀菌化合物的抗性的方法中。

[0694] (a)治疗细菌性感染的方法

[0695] 本发明的一个实施方案涵盖一种用于治疗细菌性感染的方法。或者,更具体来说,本发明涵盖一种用于治疗尿路感染的方法。如本文所用,“治疗”是指预防当前未受感染的受试者的感染,以及减轻或消除当前受感染的受试者的感染。因此,本发明也涵盖一种用于预防UTI的方法。通常,此类方法包括向受试者施用包含本发明化合物的药物组合物。如本文所用,“受试者”包括易患由大肠杆菌达成的尿路感染的任何哺乳动物。在一个实施方案中,受试者易患复发性UTI。在一些实施方案中,受试者可不具有UTI的临床症状。在此类实施方案中,受试者可患有潜伏性感染。在其它实施方案中,受试者可具有UTI的临床症状。

[0696] 在一些实施方案中，本发明化合物可与如以上章节II中所述的杀菌化合物组合向受试者施用。当组合施用时，本发明化合物可在施用杀菌化合物之前、同时或之后施用。当在杀菌化合物之前或之后施用时，施用本发明化合物和杀菌化合物之间的时间可为约1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29、30、31、32、33、34、35、36、37、38、39、40、41、42、43、44、45、46、47、48、49、50、51、52、53、54、55、56、57、58、59或60分钟。在另一实施方案中，施用本发明化合物和杀菌化合物之间的时间可为约1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29、30、31、32、33、34、35、36、37、38、39、40、41、42、43、44、45、46、47、48、49、50、51、52、53、54、55、56、57、58、59、60、61、62、63、64、65、66、67、68、69、70、71或72小时。

[0697] 本发明的化合物或药物组合物可通过将递送治疗有效剂量的若干不同手段施用。此类组合物可以根据需要含有常规无毒药学上可接受的载体、佐剂和媒介物的剂量单位制剂形式口服、胃肠外、通过吸入喷雾、经直肠、皮内、脑池内、腹膜内、经皮、经颊、作为口服或鼻用喷雾剂、经局部(即粉末、软膏剂或滴剂)、或通过导尿管施用。局部施用也可涉及使用经皮施用，如经皮贴片或离子电渗装置。如本文所用的术语胃肠外包括皮下、静脉内、肌肉内或胸骨内注射或输注技术。在一示例性实施方案中，药物组合物将以口服剂型施用。药物的配制例如讨论于Hoover，John E.，Remington′s Pharmaceutical Sciences，Mack Publishing Co.，Easton，Pa.(1975)以及Liberman，H.A.和Lachman，L.编，Pharmaceutical Dosage Forms，Marcel Decker，New York，N.Y.(1980)中。

[0698] 本发明化合物的构成“有效量”的量可变化并且将变化。该量将取决于多种因素，包括施用以单剂量抑或多剂量进行以及个别受试者参数，包括年龄、身体状况、身材和重量。本领域技术人员将了解也可用来自Goodman&Goldman′s The Pharmacological Basis of Therapeutics，第9版(1996)，附录II，第1707-1711页以及来自Goodman&Goldman′s The Pharmacological Basis of Therapeutics，第10版(2001)，附录II，第475-493页的指导确定剂量。

[0699] 为选择性控制抑制剂向胃肠道的特定释放区域的释放，本发明的药物组合物可被制造成一种或若干用于控制、持续或定时释放一种或多种成分的剂型。在这个情形下，通常在配制成以上形式中的一种之前将一种或多种形成药物组合物的成分进行微囊封或干式包衣。通过改变包衣的量和类型以及它的厚度，给定成分或若干成分(在如多层胶囊的同一剂型或不同剂型中)的释放时机和位置可以变化。

[0700] 在一示例性实施方案中，包衣可为肠溶包衣。肠溶包衣通常将提供成分的控制释放，以使药物释放可在下肠道中低于将在无肠溶包衣下发生药物释放所处的地点的某一通常可预测位置处实现。在某些实施方案中，可利用多种肠溶包衣。在某些实施方案中，可选择多种肠溶包衣以在下胃肠道中的各种区域处以及在各种时间释放成分或成分的组合。

[0701] 如将由熟练技术人员所了解，囊封或包衣方法可以并且将视用于形成药物组合物和包衣的成分以及微胶囊自身的所需物理特征而变化。另外，可采用一种以上囊封方法以便产生多层微胶囊，或可依序采用相同囊封方法以便产生多层微胶囊。合适的微囊封方法可包括喷雾干燥、旋转盘囊封(也称为旋转混悬分离囊封)、超临界流体囊封、空气混悬微囊封、流化床囊封、喷雾冷却/冷冻(包括基质囊封)、挤出囊封、离心挤出、凝聚、海藻酸盐珠粒、脂质体囊封、包合囊封、胶体体(colloidosome)囊封、溶胶-凝胶微囊封和本领域中已知

的其它微囊封方法。关于用于制备包衣剂型的材料、设备和方法的详细信息可见于Pharmaceutical Dosage Forms:Tablets,Lieberman等编(New York:Marcel Dekker,Inc.,1989)中以及Ansel等,Pharmaceutical Dosage Forms and Drug Delivery Systems,第6版(Media,Pa.:Williams&Wilkins,1995)中。

[0702] 可在体内、在体外、原位或离体使细菌与本发明化合物接触。在一些实施方案中,可使细菌与本发明化合物直接接触。在其它实施方案中,可使细胞内细菌与本发明化合物接触。可使用为本领域中的熟练个体所知的标准技术来生长、亚培养、储存和操作包含一种或多种细菌的合适的细胞。用于生长、培养、储存和操作包含一种或多种细菌的细胞的细胞培养和微生物学技术通常在本领域中是已知的。

[0703] (b)降低杀菌抗性的方法

[0704] 本发明的另一方法包括降低细菌对杀菌化合物的抗性。此类方法包括使对杀菌化合物具有抗性的细菌与本发明化合物接触。举例来说,被对杀菌化合物具有抗性的细菌感染的受试者可如以上章节IV(a)中所述被施用本发明化合物。在一示例性实施方案中,方法包括使对抗生素具有抗性的细菌与本发明化合物接触。在另一示例性实施方案中,方法包括使对TMP或SMZ具有抗性的细菌与本发明化合物接触。

[0705] 测量细菌对抗生素的抗性的方法在本领域中是已知的。对于更多细节,参见实施例。

[0706] (c)治疗导管相关的尿路感染的方法

[0707] 在另一实施方案中,本发明方法涵盖一种用于治疗导管相关的尿路感染的方法。如本文所用,“治疗”是指预防当前未受感染的受试者的感染,以及减轻或消除当前受感染的受试者的感染。通常,此类方法包括向受试者施用包含本发明化合物的药物组合物。对于这个实施方案,“受试者”是指具有置留导尿管的任何哺乳动物。在一个实施方案中,具有导尿管的受试者易患复发性UTI。在一些实施方案中,具有导尿管的受试者可不具有UTI的临床症状。在此类实施方案中,受试者可患有潜伏性感染。在其它实施方案中,具有导尿管的受试者可具有UTI的临床症状。

[0708] 在一些实施方案中,本发明化合物可如以上章节II和章节IV(a)中所述与杀菌化合物组合向受试者施用。

[0709] (d)治疗炎症性肠病的方法

[0710] 在另一实施方案中,本发明方法涵盖一种用于治疗炎症性肠病的方法。炎症性肠病(IBD)涉及消化道的全部或部分的慢性炎症。IBD可包括溃疡性结肠炎、克罗恩氏病、胶原性结肠炎、淋巴细胞性结肠炎、缺血性结肠炎、转流性结肠炎、贝塞特氏病(Behcet’s disease)和未确定型结肠炎。如本文所用,“治疗”是指减轻与炎症性肠病相关的症状。或者,本发明方法涵盖一种用于减轻与炎症性肠病相关的症状的方法。症状可包括溃疡、食欲降低、直肠流血、直肠疼痛、感觉尿急或尿频、小肠运动、有血性腹泻、腹部痉挛和疼痛、尽管迫切要求使肠运动却不能这样做(里急后重)、左侧疼痛、非故意重量减轻、疲劳、显著重量减轻、腹泻过多、脱水、休克、发热、疲劳、关节炎、眼部炎症、皮肤病症以及肝或胆管炎症。

[0711] 通常,此类方法包括向受试者施用包含本发明化合物的药物组合物。对于这个实施方案,“受试者”是指患有炎症性肠病的任何哺乳动物。

[0712] V.涂布剂

[0713] 本发明的另一方面涵盖包含本发明化合物的涂布剂。此类涂布剂可在医学装置上用于防止细菌粘着或感染宿主。涂布医学装置的适合手段在本领域中是已知的。在一个实施方案中，导管可用本发明化合物涂布。在另一实施方案中，导尿管可用本发明化合物涂布。

[0714] VI.营养补充剂

[0715] 本发明的一替代性方面涵盖一种包含本发明化合物的营养补充剂。此类补充剂可用于如以上章节IV中所述治疗细菌性感染。

[0716] 定义

[0717] 如本文单独或作为另一基团的一部分所用的术语“酰基”表示通过从有机羧酸的基团--COOH移除羟基形成的部分，例如RC(O)--，其中R是R′、R1O--、R′R2N--或R1S--，R1是烃基、杂取代的烃基或杂环，并且R2是氢、烃基或取代的烃基。

[0718] 如本文单独或作为另一基团的一部分所用的术语“酰氧基”表示通过氧键联(--O--)键合的如上所述的酰基，例如RC(O)O--，其中R如关于术语“酰基”所定义。

[0719] 除非另外指示，否则本文所述的烷基优选是在主链中含有1至8个碳原子并且至多20个碳原子的低级烷基。它们可为直链或支链或环状的，也称为环烷基，并且包括甲基、乙基、丙基、异丙基、丁基、己基等。

[0720] 除非另外指示，否则本文所述的烯基优选是在主链中含有2至8个碳原子并且至多20个碳原子的低级烯基。它们可为直链或支链或环状的，并且包括乙烯基、丙烯基、异丙烯基、丁烯基、异丁烯基、己烯基等。

[0721] 除非另外指示，否则本文所述的炔基优选是在主链中含有2至8个碳原子并且至多20个碳原子的低级炔基。它们可为直链或支链，并且包括乙炔基、丙炔基、丁炔基、异丁炔基、己炔基等。

[0722] 如本文单独或作为另一基团的一部分所用的术语“芳基”或“芳”表示任选取代的同素环状芳族基团，优选是在环部分中含有6至12个碳的单环或双环基团，如苯基、联苯、萘基、取代的苯基、取代的联苯或取代的萘基。苯基和取代的苯基是更优选芳基。

[0723] 如本文所用，术语“官能团”包括分子内造成该分子的某些性质和/或该分子所参与的反应的一组原子。官能团的非限制性实例包括烷基、羧基、羟基、氨基、磺酸酯基、磷酸酯基、膦酸酯基、硫醇、炔、叠氮化物、卤素等。

[0724] 如本文单独或作为另一基团的一部分所用的术语“卤素”或“卤代基”是指氯、溴、氟和碘。

[0725] 如本文单独或作为另一基团的一部分所用的术语“杂环(heterocyclo)”或“杂环(heterocyclic)”表示在至少一个环中具有至少一个杂原子，并且优选在各环中具有5或6个原子，任选取代的完全饱和或不饱和、单环或双环、芳族或非芳族基团。杂环基团优选在环中具有1或2个氧原子、1或2个硫原子和/或1至4个氮原子，并且可通过碳或杂原子键合于分子的其余部分。示例性杂环包括杂芳族物，如呋喃基、噻吩基、吡啶基、噁唑基、吡咯基、吲哚基、喹啉基或异喹啉基等。示例性取代基包括以下基团中的一个或多个：烃基、取代的烃基、酮基、羟基、保护的羟基、酰基、酰氧基、烷氧基、烯氧基、炔氧基、芳基氧基、卤素、酰胺基、氨基、硝基、氰基、硫醇、缩酮、缩醛、酯和醚。

[0726] 如本文单独或作为另一基团的一部分所用的术语“杂芳族”表示在至少一个环中

具有至少一个杂原子，并且优选在各环中具有5或6个原子，任选取代的芳族基团。杂芳族基团优选在环中具有1或2个氧原子、1或2个硫原子和/或1至4个氮原子，并且可通过碳或杂原子键合于分子的其余部分。示例性杂芳族物包括呋喃基、噻吩基、吡啶基、噁唑基、吡咯基、吲哚基、喹啉基或异喹啉基等。示例性取代基包括以下基团中的一个或多个：烃基、取代的烃基、酮基、羟基、保护的羟基、酰基、酰氧基、烷氧基、烯氧基、炔氧基、芳基氧基、卤素、酰胺基、氨基、硝基、氰基、硫醇、缩酮、缩醛、酯和醚。

[0727] 如本文所用的术语“烃”和“烃基”描述仅由元素碳和氢组成的有机化合物或基团。这些部分包括烷基、烯基、炔基和芳基部分。这些部分也包括被其它脂族或环状烃基团取代的烷基、烯基、炔基和芳基部分，如烷芳基、烯芳基和炔芳基。除非另外指示，否则这些部分优选包含1至20个碳原子。

[0728] 本文所述的“取代的烃基”部分是被至少一个除碳以外的原子取代的烃基部分，包括其中碳链原子被如氮、氧、硅、磷、硼、硫或卤素原子的杂原子取代(即置换)的部分。这些部分可包括卤素、碳环、芳基、杂环、烷氧基、烯氧基、炔氧基、芳基氧基、羟基、保护的羟基、酮基、酰基、酰氧基、硝基、氨基、酰胺基、硝基、氰基、硫醇、缩酮、缩醛、酯和醚。

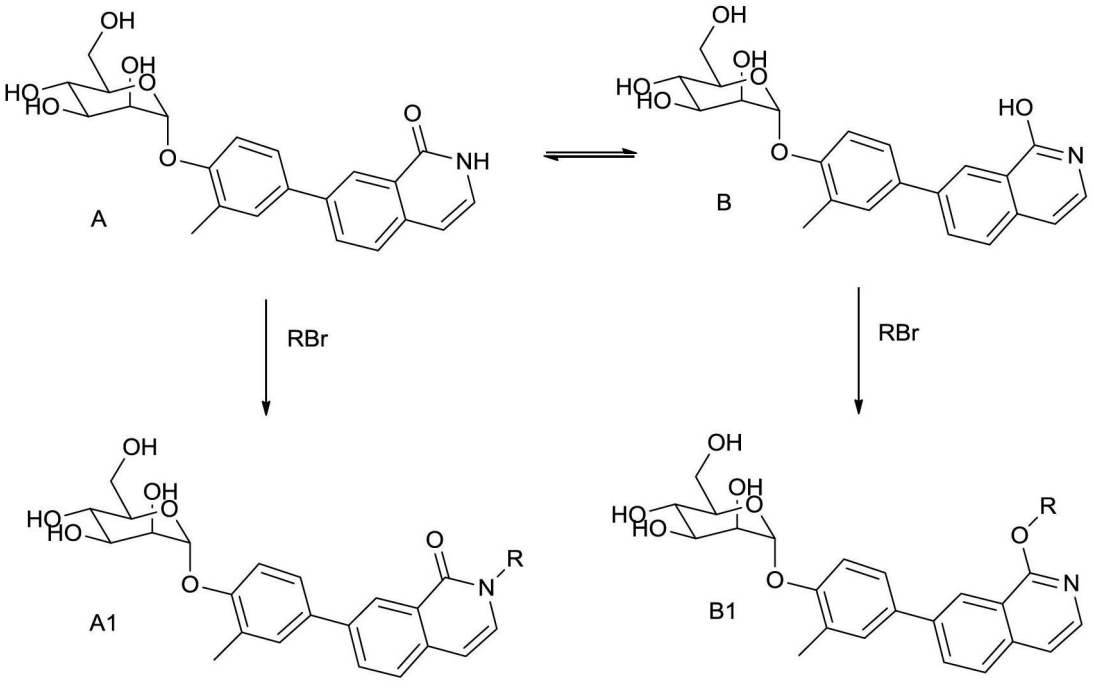
实施例

[0729] 包括以下实施例以说明本发明的优选实施方案。本领域技术人员应了解随后实施例中公开的技术表示由本发明者发现在实施本发明方面良好起作用的技术。然而，本领域技术人员应鉴于本公开而了解可在不脱离本发明的精神和范围下，在公开的特定实施方案中进行许多变化，并且仍然获得相似或类似结果，因此，附图中所述或所示的所有事项都应解释为说明性的而非具有限制意义。

[0730] 实施例的引言：一般性合成、纯化和分析化学程序。

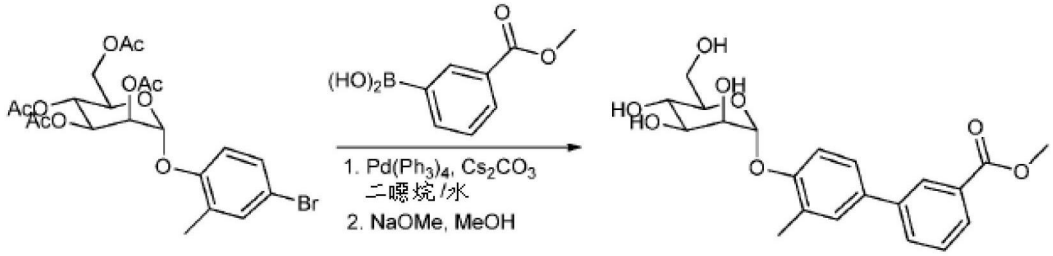
[0731] 如对于以下流程中的处于与羟基喹啉异构体B平衡的异喹啉酮异构体A所述，某些化合物可以处于平衡的异构体的混合物形式存在：

[0732]



[0733] 因此，应了解含有异喹啉酮的化合物可以羟基异喹啉形式存在，并且合成其类似物可导致产生单独一种异构体A1或B1或混合物。并非总是有可能确认各个别异构体(例如A1或B1)的身份。因此，所有可能异构体都被要求为含有异喹啉酮环的实施例中的最终产物。

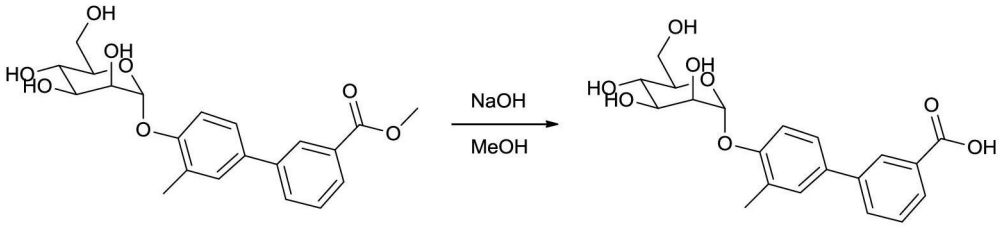
[0734] 除非另外指示，否则起始物质、试剂和溶剂购自商业供应商。一般来说，无水溶剂用于进行所有反应。在配备有自动取样器的Varian400MHz NMR仪器上测量^{1}H NMR光谱。除非另外指示，否则化学位移被报道为相对于TMS的δppm，使用残余溶剂峰作为参照。以下缩写用于表达峰多重性：s＝单峰；d＝双重峰；t＝三重峰；q＝四重峰；m＝多重峰；br＝宽峰。在GILSON GX-281上进行高效液相色谱法(HPLC)，使用Waters C18 5μM，4.6*50mm和Waters Prep C18 5μM，19*150mm反相柱，用5:95至95:5乙腈:水的梯度系统洗脱，水具有由0.05-0.1％TFA组成的缓冲剂。在HPLC/MSD上执行质谱分析法(MS)以达成检测，使用5:95至95:5乙腈:水的梯度系统，水具有由0.05-0.1％TFA组成的缓冲剂，采用C18或C8反相柱和电喷雾离子化(ESI)。所有反应都通过在Merck硅胶板(0.25mm厚，60F254)上进行的薄层色谱法(TLC)来监测，通过使用UV(254nm)或如$KMnO_4$、对甲氧基苯甲醛和CAM(哈呢森氏染色剂(Hannesian's Stain))的染料加以观察。使用预装填硅胶柱(12g～330g尺寸)，在Teledyne ISCO CombiFlash纯化系统上进行硅胶色谱法。基于NMR和根据在220nm和254nm波长下的吸光度的HPLC，用于生物测定的所有化合物的纯度都大于95％。

[0735] 

[0736] (流程I)

[0737] 实施例1. 3-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]苯甲酸甲酯(Han等，J.Med.Chem.2012,55,3945-3959)。

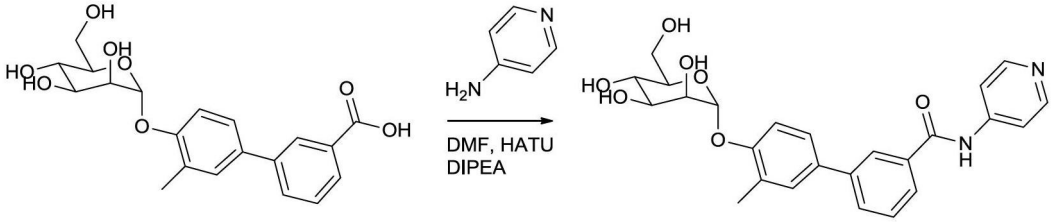
[0738] 向配备有回流冷凝器和N_2管线的圆底烧瓶中添加[(2R,3R,4S,5R,6S)-4,5-二乙酰氧基-6-(乙酰氧基甲基)-2-(4-溴-2-甲基-苯氧基)四氢吡喃-3-基]乙酸酯(0.52g，1.0mmol)、(3-甲氧基羰基苯基)硼酸(0.22g，1.2mmol)、Cs_2CO_3(0.98g，3mmol)和$Pd(Ph_3)_4$(0.12g，0.1mmol)，随后添加1,4-二噁烷/水的5:1混合物(30mL)。将反应烧瓶放置在高真空下，接着用N_2再加压，重复3次。在N_2氛围下加热反应至80℃，持续1小时。真空移除溶剂，并且将残余物溶解于$CHCl_3$中并过滤。通过硅胶色谱法(ISCO MPLC，MeOH/CH_2Cl_2，0-10％梯度)纯化滤液。合并如通过TLC和LCMS确定的纯级分，接着真空浓缩。将残余物溶解于MeOH(10mL)中，接着装以0.002M NaOMe/MeOH(5mL)。在通过LCMS确定反应完成之后，添加DOWEX 50WX4-100离子交换树脂。在15分钟之后，过滤树脂，用MeOH洗涤，接着真空浓缩滤液。通过硅胶色谱法(0-25％MeOH/CH_2Cl_2)纯化残余物以产生呈白色固体状的标题化合物(0.222g，55％)。LCMS(ESI，M+Na^+＝427.3)，

[0739] 

[0740] (流程II)

[0741] 实施例2. 3-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]苯甲酸。

[0742] 向3-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]苯甲酸甲酯(0.222g,0.55mmol)于MeOH(70mL)中的溶液中添加0.2M NaOH(30mL)。将反应在室温下搅拌过夜。添加DOWEX 50WX4-100离子交换树脂。在15分钟之后,过滤树脂,用MeOH洗涤,接着真空浓缩滤液以产生呈白色固体状的标题化合物(0.2025g,94%)。LCMS(ESI,M+Na^+=413.3);^{1}H NMRδppm(d3-MeOD;2.31(s,3H)3.61(ddd,J=9.78,5.09,2.74Hz,1H)3.69-3.84(m,3H)3.97(dd,J=9.39,3.52Hz,1H)4.08(dd,J=3.33,1.76Hz,1H)5.56(d,J=1.96Hz,1H)7.31(d,J=8.22Hz,1H)7.39-7.48(m,2H)7.51(t,J=7.83Hz,1H)7.76-7.84(m,1H)7.95(dt,J=7.83,1.37Hz,1H)8.21(t,J=1.76Hz,1H))。

[0743] 

[0744] (流程III)

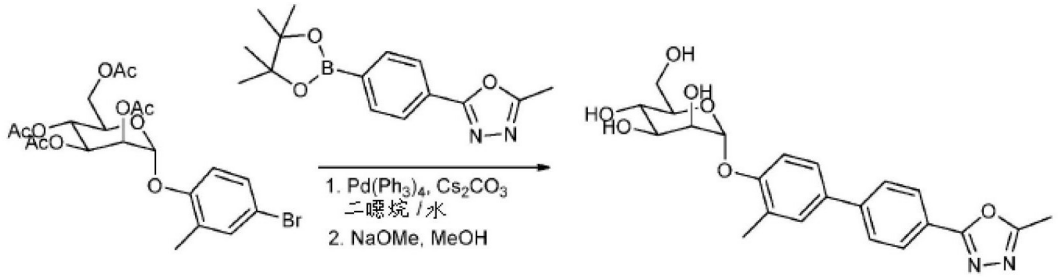
[0745] 实施例3. 3-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-N-(4-吡啶基)苯甲酰胺。

[0746] 在N2氛围以及冷却至0℃下向3-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]苯甲酸(0.039g,0.1mmol)和HATU(0.046g,0.12mmol)于DMF(5mL)中的搅拌溶液中添加4-氨基吡啶(0.011g,0.12mmol)和DIPEA(0.054mL,0.3mmol)。使反应升温至室温,接着搅拌过夜。真空移除溶剂,并且通过反相HPLC(5-85%乙腈/水/0.05%TFA)纯化残余物。合并纯级分,并且冻干以产生呈白色粉末状的标题化合物(0.047g,100%)。LCMS(ESI,M+H^+=467.3);^{1}H NMRδppm(d_3-MeOD;2.34(s,3H)3.60(ddd,J=9.78,5.28,2.54Hz,1H)3.68-3.85(m,3H)3.98(dd,J=9.59,3.33Hz,1H)4.09(dd,J=3.33,1.76Hz,1H)5.58(d,J=1.57Hz,1H)7.34(d,J=8.61Hz,1H)7.44-7.58(m,2H)7.63(t,J=7.63Hz,1H)7.84-8.00(m,2H)8.19-8.27(m,1H)8.37-8.45(m,2H)8.62-8.72(m,2H))。

[0747] 实施例4. 3-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-N-(3-吡啶基)苯甲酰胺。

[0748] 以与实施例3类似的方式,使用3-氨基吡啶进行合成以产生(0.043g,94%)。LCMS(ESI,M+H^+=467.3);^{1}H NMRδppm(d_3-MeOD;2.33(s,3H)3.61(m,1H)3.76(m,3H)3.97(d,J=9.39Hz,1H)4.08(m,1H)5.57(d,1H)7.33(d,J=6.26Hz,1H)7.43-7.56(m,2H)7.61(m,1H)

7.85(m,1H)7.94(m,2H)8.22(m,1H)8.55(m,1H)8.66(d,J＝6.26Hz,1H)9.47(m,1H))。

[0749] 

[0750] (流程IV)

[0751] 实施例5.(2S,3S,4S,5R,6R)-2-(羟甲基)-6-[2-甲基-4-[4-(5-甲基-1,3,4-噁二唑-2-基)苯基]苯氧基]四氢吡喃-3,4,5-三醇。

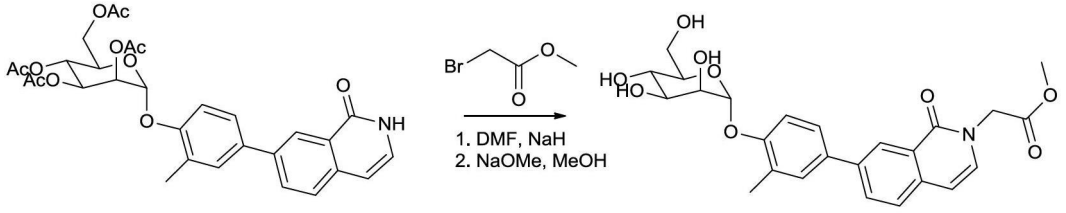
[0752] 以与实施例1类似的方式,使用2-甲基-5-[4-(4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷-2-基)苯基]-1,3,4-噁二唑(购自Boron Molecular)进行合成。LCMS(ESI,M+H$^+$＝429.3);^{1}H NMRδppm(d_3-MeOD;2.28(s,3H)2.63(s,3H)3.53-3.65(m,1H)3.70-3.88(m,3H)3.98(dd,J＝9.59,3.33Hz,1H)4.09(dd,J＝3.13,1.96Hz,1H)5.57(d,J＝1.17Hz,1H)7.24(d,J＝8.22Hz,1H)7.38-7.45(m,2H)7.48(s,1H)7.69(m,J＝8.61Hz,1.5H)8.02(m,J＝8.22Hz,1.5H))。

[0753] 实施例6.(2S,3S,4S,5R,6R)-2-(羟甲基)-6-[2-甲基-4-[3-(5-甲基-1,3,4-噁二唑-2-基)苯基]苯氧基]四氢吡喃-3,4,5-三醇。

[0754] 以与实施例1类似的方式,使用[3-(5-甲基-1,3,4-噁二唑-2-基)苯基]硼酸(购自Apollo Scientific)进行合成。LCMS(ESI,M+H$^+$＝429.3);^{1}H NMRδppm(d_3-MeOD;2.08(s,1.5H)2.32(s,1.5H)2.33(s,1.5H)2.65(s,1.5H)3.55-3.65(m,1H)3.69-3.83(m,3H)3.98(dt,J＝9.49,2.69Hz,1H)4.06-4.12(m,1H)5.54-5.60(m,1H)7.27-7.38(m,1H)7.44-7.65(m,3H)7.75-7.98(m,2H)8.07-8.25(m,1H))。

[0755] 实施例7.7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-2H-异喹啉-1-酮。

[0756] 以与实施例1类似的方式,使用[4,5-二乙酰氧基-6-(乙酰氧基甲基)-2-[2-甲基-4-(4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷-2-基)苯氧基]四氢吡喃-3-基]乙酸酯(Han等,J.Med.Chem.2012,55,3945-3959)和7-溴-2H-异喹啉-1-酮(购自AstaTech)进行合成。LCMS(ESI,M+H$^+$＝414.3);^{1}H NMRδppm(d_3-MeOD;2.32(s,3H)3.57-3.67(m,1H)3.70-3.85(m,3H)3.94-4.02(m,1H)4.05-4.13(m,1H)5.57(d,J＝1.57Hz,1H)6.70(d,J＝7.00Hz,1H)7.17(d,J＝7.04Hz,1H)7.33(d,J＝8.22Hz,1H)7.54(s,2H)7.70(d,J＝8.61Hz,1H)7.89-8.04(m,1H)8.49(d,J＝1.96Hz,1H))。

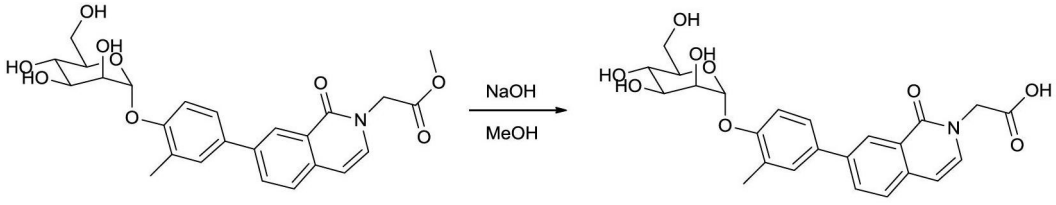
[0757] 

[0758] (流程V)

[0759] 实施例8.2-[7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6(羟甲基)四氢吡

喃-2-基]氧基-苯基]-1-氧代-2-异喹啉基]乙酸甲酯。

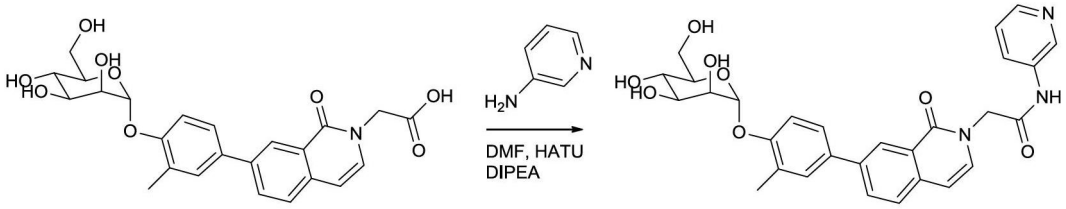
[0760] 在N2氛围下向冷却至0℃的[4,5-二乙酰氧基-6-(乙酰氧基甲基)-2-[2-甲基-4-(1-氧代-2H-异喹啉-7-基)苯氧基]四氢吡喃-3-基]乙酸酯(0.116g,0.2mmol)于DMF(5mL)中的溶液中缓慢添加NaH(0.024g,0.6mmol,于矿物油中的60％分散液)。在10分钟之后,添加2-溴乙酸甲酯(0.018mL,0.19mmol),并且在0℃下在N2氛围下搅拌反应1小时。在高真空下移除溶剂,并且将残余物溶解于MeOH(5mL)中,随后添加0.02M NaOMe/MeOH(3mL),并且将反应在室温下搅拌过夜。添加DOWEX 50WX4-100离子交换树脂。在15分钟之后,过滤树脂,用MeOH洗涤,接着真空浓缩滤液。通过硅胶色谱法(0-20％MeOH/CH_2Cl_2)纯化残余物以产生呈白色固体状的标题产物(0.0558g,57％)。LCMS(ESI,M+H$^+$=486.3);^{1}H NMRδppm(d_3-MeOD;2.32(s,3H)3.61(ddd,J=9.68,4.99,2.54Hz,1H)3.68-3.85(m,3H)3.78(s,3H)3.98(dd,J=9.59,3.33Hz,1H)4.04-4.14(m,1H)4.82(s,2H)5.53-5.62(m,1H)6.72(d,J=7.04Hz,1H)7.32(dd,J=7.83,3.91Hz,2H)7.44-7.58(m,2H)7.70(d,J=8.22Hz,1H)7.97(dd,J=8.22,1.96Hz,1H)8.43-8.49(m,1H))。

[0761] 

[0762] (流程VI)

[0763] 实施例9.2-[7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-1-氧代-2-异喹啉基]乙酸。

[0764] 遵循与实施例2类似的程序,使用2-[7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6(羟甲基)四氢吡喃-2-基]氧基-苯基]-1-氧代-2-异喹啉基]乙酸甲酯(0.050g,0.1mmol),获得呈白色固体状的标题产物(0.045g,96％)。LCMS(ESI,M+H$^+$=472.3);^{1}H NMRδppm(d_3-MeOD;2.32(s,3H)3.61(ddd,J=9.59,5.28,2.35Hz,1H)3.67-3.86(m,3H)3.98(dd,J=9.59,3.33Hz,1H)4.08(dd,J=3.33,1.76Hz,1H)4.79(s,2H)5.50-5.62(m,1H)6.72(d,J=7.43Hz,1H)7.32(dd,J=8.02,2.93Hz,2H)7.44-7.59(m,2H)7.70(d,J=8.22Hz,1H)7.97(dd,J=8.22,1.96Hz,1H)8.44-8.55(m,1H))。

[0765] 

[0766] (流程VII)

[0767] 实施例10.2-[7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-1-氧代-2-异喹啉基]-N-(3-吡啶基)乙酰胺。

[0768] 遵循与实施例3类似的程序,使用2-[7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-1-氧代-2-异喹啉基]乙酸(0.024g,0.05mmol)和3-氨基吡啶,获得呈白色固体状的标题化合物(22mg,81％)。LCMS(ESI,M+H$^+$=

548.4);^{1}H NMRδppm(d_3-MeOD;2.32(s,3H)3.55-3.66(m,1H)3.66-3.85(m,3H)3.97(dd,J＝9.59,3.33Hz,1H)4.08(dd,J＝3.13,1.96Hz,1H)4.96(s,2H)5.46-5.63(m,1H)6.77(d,J＝7.04Hz,1H)7.27-7.44(m,2H)7.46-7.58(m,2H)7.73(d,J＝8.22Hz,1H)7.88(dd,J＝8.61,5.48Hz,1H)8.00(dd,J＝8.22,1.96Hz,1H)8.42(dd,J＝8.61,1.17Hz,1H)8.49(s,2H)9.18-9.29(m,1H))。

[0769] 实施例11.2-[7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-1-氧代-2-异喹啉基]-N-(4-吡啶基)乙酰胺。

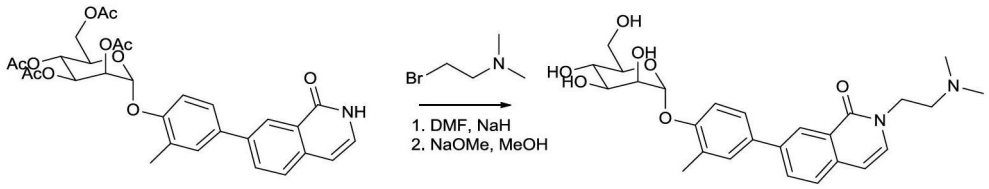
[0770] 遵循与实施例10类似的程序,使用4-氨基吡啶,获得标题化合物(13.3mg,52％)。LCMS(ESI,M+H$^+$＝548.4);^{1}H NMRδppm(d_3-MeOD;2.32(s,3H)3.60(ddd,J＝9.78,5.09,2.74Hz,1H)3.67-3.84(m,3H)3.97(dd,J＝9.59,3.33Hz,1H)4.08(dd,J＝3.33,1.76Hz,1H)5.00(s,2H)5.57(d,J＝1.57Hz,1H)6.78(d,J＝7.43Hz,1H)7.38(d,J＝7.43Hz,2H)7.33(d,J＝8.61Hz,1H)7.49-7.58(m,2H)7.75(d,J＝8.22Hz,1H)8.01(dd,J＝8.41,2.15Hz,1H)8.18(m,J＝7.04Hz,2H)8.49(d,J＝1.96Hz,1H)8.64(m,J＝7.43Hz,2H))。

[0771] 实施例12.2-[2-(4-甲基哌嗪-1-基)-2-氧代-乙基]7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]异喹啉-1-酮。

[0772] 遵循与实施例10类似的程序,使用1-甲基哌嗪,获得标题化合物(25-9mg,88％)。LCMS(ESI,M+H$^+$＝554.4);^{1}H NMRδppm(d_3-MeOD;2.33(s,3H)2.99(s,3H)3.26(dt,J＝3.23,1.71Hz,1H)3.34-3.42(m,1H)3.49(dd,J＝3.52,1.57Hz,1H)3.61(ddd,J＝9.78,5.28,2.54Hz,3H)3.70-3.86(m,4H)3.97(dd,J＝9.59,3.33Hz,2H)4.08(dd,J＝3.52,1.96Hz,2H)4.81(s,1H)5.57(d,J＝1.96Hz,1H)6.75(d,J＝7.43Hz,1H)7.20-7.40(m,3H)7.45-7.59(m,2H)7.72(d,J＝8.22Hz,1H)7.99(dd,J＝8.22,1.96Hz,1H)8.49(d,J＝1.96Hz,1H))。

[0773] 实施例13.N-(2-氨基乙基)-2-[7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-1-氧代-2-异喹啉基]乙酰胺。

[0774] 遵循与实施例10类似的程序,使用1,2-二氨基乙烷,获得标题化合物(11.2mg,55％)。LCMS(ESI,M+H$^+$＝514.4);^{1}H NMRδppm(d_3-MeOD;2.33(s,3H)3.11(t,J＝5.67Hz,2H)3.54(t,J＝5.67Hz,2H)3.56-3.67(m,1H)3.68-3.84(m,3H)3.97(dd,J＝9.59,3.33Hz,1H)4.08(dd,J＝3.33,1.76Hz,1H)4.73(s,2H)5.48-5.64(m,1H)6.78(d,J＝7.43Hz,1H)7.34(d,J＝7.83Hz,2H)7.46-7.59(m,2H)7.74(d,J＝8.22Hz,1H)8.00(dd,J＝8.22,1.96Hz,1H)8.50(s,1H))。

[0775] 

[0776] (流程VIII)

[0777] 实施例14.2-(2-二甲基氨基乙基)-7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]异喹啉-1-酮。

[0778] 遵循与实施例8类似的程序,使用[4,5-二乙酰氧基-6-(乙酰氧基甲基)-2-[2-甲基-4-(1-氧代-2H-异喹啉-7-基)苯氧基]四氢吡喃-3-基]乙酸酯(0.1mmol)和2-溴-N,N-二甲基-乙胺(0.1mmol),获得标题化合物(0.0426g,88％)。LCMS(ESI,M+H$^+$＝485.4);^{1}H NMRδ

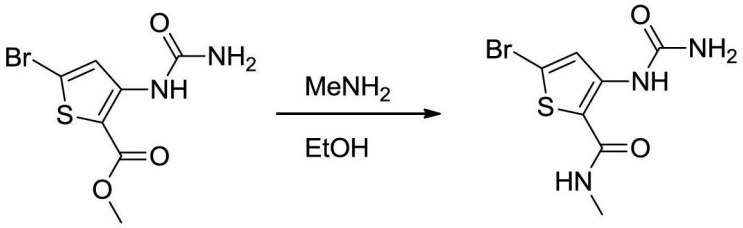
ppm(d_3-MeOD;2.33(s,3H)3.05(s,6H)3.52-3.67(m,3H)3.68-3.84(m,3H)3.97(dd,J＝9.39,3.52Hz,1H)4.08(dd,J＝3.33,1.76Hz,1H)4.46(t,J＝5.87Hz,2H)5.47-5.64(m,1H)6.80(d,J＝7.43Hz,1H)7.38(d,J＝7.43Hz,1H)7.34(d,J＝8.61Hz,1H)7.47-7.59(m,2H)7.73(d,J＝8.61Hz,1H)8.01(dd,J＝8.41,1.76Hz,1H)8.49-8.60(m,1H))。

[0779] 实施例15.7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-2-(4-吡啶基甲基)异喹啉-1-酮。

[0780] 遵循与实施例14类似的程序,使用4-(溴甲基)吡啶,获得标题化合物(0.046g,92%)。LCMS(ESI,M+H^+＝505.4);^{1}H NMRδppm(d_3-MeOD;2.32(s,3H)3.53-3.66(m,1H)3.67-3.83(m,3H)3.96(dd,J＝9.59,3.33Hz,1H)4.07(dd,J＝3.13,1.96Hz,1H)5.52(s,2H)5.56(s,1H)6.84(d,J＝7.43Hz,1H)7.33(d,J＝8.61Hz,1H)7.44-7.57(m,3H)7.70-7.86(m,3H)8.02(dd,J＝8.22,1.96Hz,1H)8.49(s,1H)8.73(d,J＝6.65Hz,2H))。

[0781] 实施例16.7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-2-(3-吡啶基甲基)异喹啉-1-酮。

[0782] 遵循与实施例14类似的程序,使用3-(溴甲基)吡啶,获得标题化合物(0.046g,92%)。LCMS(ESI,M+H^+＝505.4);^{1}H NMRδppm(d_3-MeOD;2.32(s,3H)3.51-3.66(m,1H)3.66-3.85(m,3H)3.97(dd,J＝9.59,3.33Hz,1H)4.08(dd,J＝3.13,1.57Hz,1H)5.42(s,2H)5.56(s,1H)6.80(d,J＝7.43Hz,1H)7.33(d,J＝8.22Hz,1H)7.43-7.61(m,3H)7.72(d,J＝8.22Hz,1H)7.89(dd,J＝8.02,5.67Hz,1H)7.99(dd,J＝8.41,1.76Hz,1H)8.42(d,J＝8.22Hz,1H)8.46-8.54(m,1H)8.71(d,J＝5.48Hz,1H)8.86(s,1H))。

[0783] 

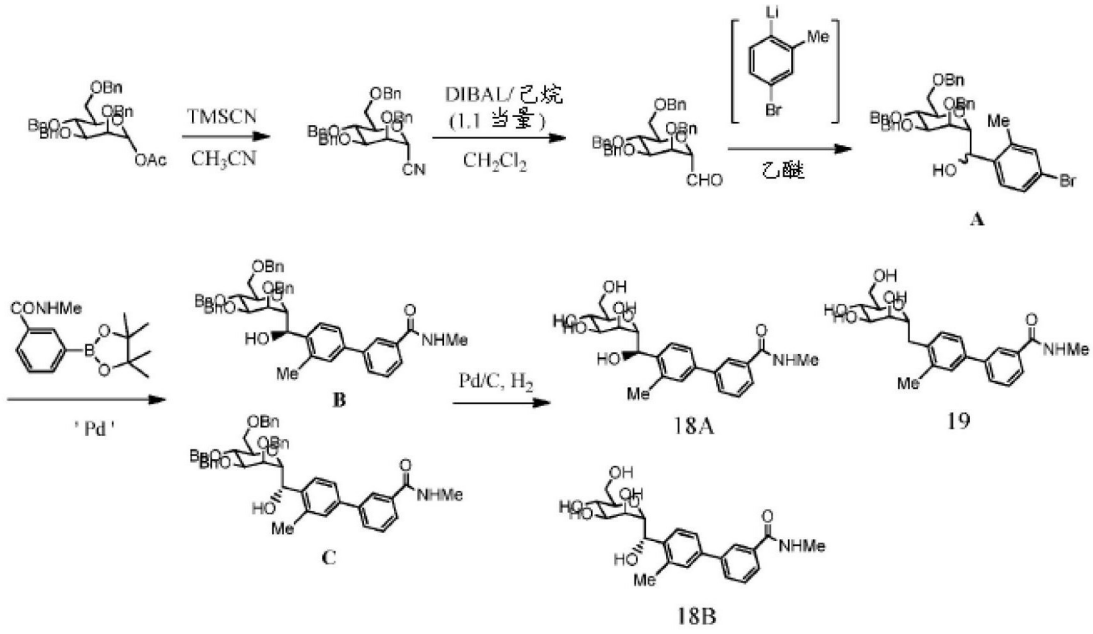
[0784] (流程IX)

[0785] 实施例17-SM.5-溴-N-甲基-3-脲基-噻吩-2-甲酰胺。

[0786] 在室温下将5-溴-3-脲基-噻吩-2-甲酸甲酯(Han等,J.Med.Chem.2012,55,3945-3959)(0.5g)与40mL含33%甲胺的EtOH一起搅拌过夜。真空移除溶剂,并且于CH_2Cl_2中湿磨残余物。过滤沉淀并干燥以产生呈白色固体状的标题产物(0.26g)。LCMS(ESI,M+Na^+＝300.1)。

[0787] 实施例17.N-甲基-5-[3-甲基-4-[2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-3-脲基-噻吩-2-甲酰胺。

[0788] 以与实施例7类似的方式,使用5-溴-N-甲基-3-脲基-噻吩-2-甲酰胺进行合成以产生呈白色粉末状的标题化合物(19mg)。LCMS(ESI,M+H^+＝468.3);^{1}H NMRδppm(d_3-MeOD;2.27(s,3H)2.87(s,3H)3.52-3.61(m,1H)3.76(d,J＝1.17Hz,3H)3.91-3.99(m,1H)4.03-4.09(m,1H)5.56(d,J＝1.17Hz,1H)7.27(m,1H)7.47(m,2H)8.06(s,1H))。



[0789]

[0790] (流程X)

[0791] 对实施例18-19的介绍。

[0792] 在0℃下,在N_2氛围下,向[(2R,3R,4S,5R,6S)-3,4,5-三苯甲基氧基-6-(苯甲基氧基甲基)四氢吡喃-2-基]乙酸酯(1.164g,2mmol)于乙腈(20mL)中的溶液中添加$BF_3.OEt_2$(0.05mL,0.4mmol)。在室温下搅拌混合物直至通过TLC确认完成。真空移除溶剂,并且将所得残余物分配于二氯甲烷与水之间。收集有机层,用Na_2SO_4干燥并浓缩。通过使用EtOAc/己烷梯度进行硅胶色谱法纯化残余物来以51%产率产生(2R,3S,4R,5R,6S)-3,4,5-三苯甲基氧基-6-(苯甲基氧基甲基)四氢吡喃-2-甲腈(0.560g)。MS(ESI):实测值:[M+Na+],572.2。

[0793] 在-78℃下,逐滴添加DIBAL/己烷(1.0M,0.52mL)至(2R,3S,4R,5R,6S)-3,4,5-三苯甲基氧基-6-(苯甲基氧基甲基)四氢吡喃-2-甲腈(0.258g,0.47mmol)于CH_2Cl_2(5mL)中的溶液中。接着历经1小时使混合物缓慢升温至-40℃。0.5N HCl水溶液用于淬灭反应,并且EtOAc用于萃取。收集有机层,用Na_2SO_4干燥并浓缩以产生呈不经进一步纯化即用于下一步骤的粗产物形式的(2S,3R,4S,5R,6S)-3,4,5-三苯甲基氧基-6-(苯甲基氧基甲基)四氢吡喃-2-甲醛(0.235g)。在-78℃下向含有含5-溴-2-碘甲苯(0.42mL,3.0mmol)的乙醚(5mL)的另一烧瓶中添加BuLi/己烷(2.5M,1.0mL)。1小时后,添加(2S,3R,4S,5R,6S)-3,4,5-三苯甲基氧基-6-(苯甲基氧基甲基)四氢吡喃-2-甲醛(0.235g)。历经1小时40分钟使混合物缓慢升温至-20℃。0.5N HCl水溶液用于淬灭反应,并且EtOAc用于萃取。收集有机层,用Na_2SO_4干燥并浓缩。通过硅胶色谱法,用EtOAct/己烷梯度作为洗脱剂纯化所得残余物来以38%产率产生(4-溴-2-甲基-苯基)-[(2R,3R,4S,5R,6S)-3,4,5-三苯甲基氧基-6-(苯甲基氧基甲基)四氢吡喃-2-基]甲醇(A)(0.130g)。MS(ESI):实测值:[M+Na+],745.4。

[0794] 在80℃下,在氮气氛围下,在搅拌下加热A(0.130g,0.18mmol)、N-甲基-3-(4,4,5,5-四甲基-[1,3,2]二氧杂环戊硼烷-2-基)-苯甲酰胺(0.071g,0.27mmol)、碳酸铯(0.176g,0.54mmol)和四(三苯基膦)钯(0.021g,0.018mmol)于二噁烷/水(5mL/1mL)中的混合物1小时。移除溶剂,并且通过硅胶色谱法纯化所得残余物以产生3-[4-[(R)-羟基-[(2R,3R,4S,5R,6S)-3,4,5-三苯甲基氧基-6-(苯甲基氧基甲基)四氢吡喃-2-基]甲基]-3-甲基-苯基]-

N-甲基-苯甲酰胺(B)(0.046g)和3-[4-[(S)-羟基-[(2R,3R,4S,5R,6S)-3,4,5-三苯甲基氧基-6-(苯甲基氧基甲基)四氢吡喃-2-基]甲基]-3-甲基-苯基]-N-甲基-苯甲酰胺(C)(0.055g)。MS(ESI):实测值:[M+Na+],800.6。

[0795] 在H2氛围下将中间体B(0.046g,0.059mmol)和Pd/C(10wt%)(0.050g,0.024mmol)于MeOH(5mL)中的混合物搅拌过夜。滤除Pd/C,并且真空浓缩滤液。通过HPLC(C18,15*150mm柱;洗脱剂:乙腈/水(0.05%TFA)纯化所得残余物来以81%产率产生实施例18A(0.020g)。实施例19也作为产物被分离(0.0030g)。遵循中间体B的相同程序,以相同方式使中间体C转化成实施例18B和19。

[0796] 实施例18A*.3-[4-[(R)-羟基-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]甲基]-3-甲基-苯基1-N-甲基-苯甲酰胺。

[0797] LCMS(ESI,M+Na$^+$=440.3);^{1}H NMRδppm(d_3-MeOD;2.51(s,3H)2.95(s,3H)3.57-3.78(m,4H)4.00-4.07(m,1H)4.10(dd,J=6.85,2.54Hz,1H)4.25(t,J=2.93Hz,1H)5.24(d,J=6.65Hz,1H)7.45-7.57(m,3H)7.62(d,J=8.22Hz,1H)7.71-7.83(m,2H)8.07(t,J=1.56Hz,1H))。

[0798] 实施例18B*.3-[4-[(S)-羟基-[(2R,3R,4S,5S,6S)-3,4,5-三羟基- 6-(羟甲基)四氢吡喃-2-基]甲基]-3-甲基-苯基]-N-甲基-苯甲酰胺。

[0799] LCMS(ESI,M+Na$^+$=440.3);^{1}H NMRδppm(d_3-MeOD;2.51(s,3H)2.95(s,3H)3.56(dd,J=1.00Hz,1H)3.67(m,1H)3.70-3.82(m,3H)3.91(m,1H)4.10(dd,J=9.00,1.96Hz,1H)5.28(d,J=8.61Hz,1H)7.34-7.63(m,4H)7.69-7.90(m,2H)8.07(s,1H))。

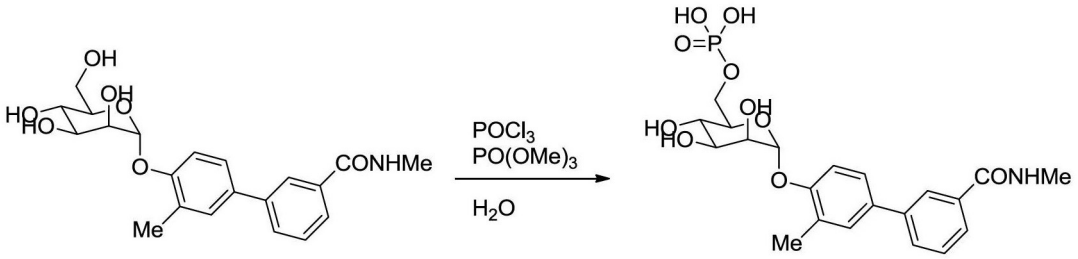
[0800] *注意:对18A的R立体化学以及18B的S立体化学的指定仅是任意的,并且是暂时指定而非确认。

[0801] 实施例19.N-甲基-3-[3-甲基-4-[[(2R,3R,4R,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]甲基]苯基]苯甲酰胺。

[0802] LCMS(ESI,M+H$^+$=402.3);^{1}H NMRδppm(d_3-MeOD;2.44(s,3H)2.95(s,3H)3.04(d,J=7.43Hz,2H)3.69(m,3H)3.83(m,2H)3.86-3.92(m,1H)4.04-4.21(m,1H)7.31(d,J=7.83Hz,1H)7.42-7.47(m,1H)7.50(m,2H)7.75(m,2H)8.05(s,1H))。

[0803] 实施例20.乙酸[(2S,3R,4S,5R,6R)-3,4,5-三乙酰氧基-6-[2-甲基-4-[3-(甲基氨基甲酰基)苯基]苯氧基]四氢吡喃-2-基]甲酯。

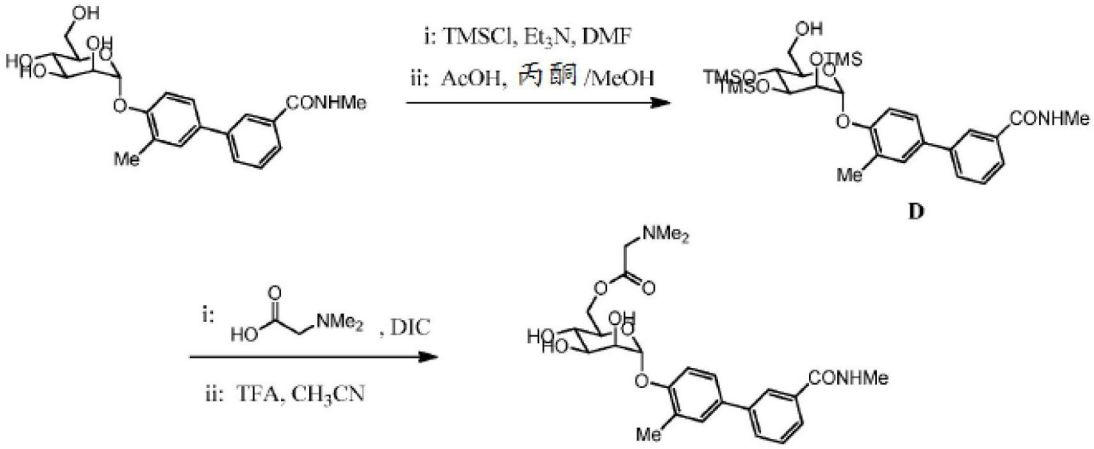
[0804] 将N-甲基-3-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]苯甲酰胺(Han等,J.Med.Chem.2012,55,3945-3959)(0.072g,0.178mmol)溶解于无水吡啶(1mL)和乙酸酐(1mL)中。真空移除溶剂,并且通过反相HPLC(5-95%乙腈/水/0.05%TFA)纯化残余物。合并纯级分,并且冻干以产生呈白色粉末状的标题化合物(0.063g)。LCMS(ESI,M+Na$^+$=594.3);^{1}H NMRδppm(d_6-DMSO;1.94(s,3H)2.00(s,3H)2.05(s,3H)2.16(s,3H)2.32(s,3H)2.81(d,J=4.30Hz,3H)3.93-4.11(m,2H)4.19(dd,J=12.13,5.09Hz,1H)5.22(t,J=9.98Hz,1H)5.33-5.45(m,2H)5.80(s,1H)7.23(d,J=8.61Hz,1H)7.46-7.65(m,3H)7.77(d,J=7.83Hz,2H)8.07(s,1H)8.54(d,J=4.30Hz,1H))。

[0805] 

[0806] (流程XI)

[0807] 实施例21.磷酸二氢[(2S,3S,4S,5R,6R)-3,4,5-三羟基-6-[2-甲基-4-[3-(甲基氨基甲酰基)苯基]苯氧基]四氢吡喃-2-基]甲酯。

[0808] 将N-甲基-3-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]苯甲酰胺(Han等,J.Med.Chem.2012,55,3945-3959)(0.20g,0.5mmol)溶解于磷酸三甲酯(5mL)和水(9μL,0.5mmol)中。冷却反应至0℃,接着缓慢添加磷酰三氯(142μL,1.5mmol),接着在0℃下搅拌3小时。通过依次添加碎冰和浓氨来中和反应。真空移除溶剂,并且通过反相HPLC(5-95%乙腈/水/0.05%TFA)纯化残余物。合并纯级分,并且冻干以产生呈白色粉末状的标题化合物(0.070g)。LCMS(ESI,M+H$^+$=484.3);^{1}H NMRδppm(d_6-DMSO;2.26(s,3H)2.81(d,J=4.70Hz,3H)3.42-3.68(m,3H)3.75(dd,J=9.00,3.13Hz,1H)3.86-3.97(m,2H)4.03(dd,J=9.78,5.87Hz,1H)5.45(d,J=1.96Hz,1H)7.24(d,J=8.61Hz,1H)7.43-7.60(m,3H)7.76(dd,J=7.43,1.57Hz,2H)8.06(s,1H)8.56(d,J=4.30Hz,1H))。

[0809] 

[0810] (流程XII)

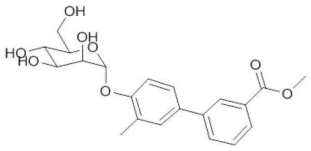
[0811] 实施例22. 2-二甲基氨基乙酸[(2S,3S,4S,5R,6R)-3,4,5-三羟基-6-[2-甲基-4-[3-(甲基氨基甲酰基)苯基]苯氧基]四氢吡喃-2-基]甲酯。

[0812] 在0℃下,缓慢添加TMSC1(0.35mL,2.75mmol)至N-甲基-3-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]苯甲酰胺(Han等,J.Med.Chem.2012,55,3945-3959)(0.202g,0.5mmol)和Et_3N(0.38mL,2.75mmol)于DMF(2mL)中的溶液中。在室温下搅拌混合物3.5小时,接着分配于EtOAc与水之间。收集有机层,用Na_2SO_4干燥并浓缩。向所得残余物中添加丙酮(1mL)和MeOH(1.5mL)。接着在0℃下冷却混合物,同时添加AcOH(0.055mL,0.96mmol)。在室温下搅拌混合物9小时,接着添加$NaHCO_3$(0.16g,1.9mmol)。移除溶剂。通过硅胶色谱法,用EtOAc/己烷梯度作为洗脱剂纯化所得残

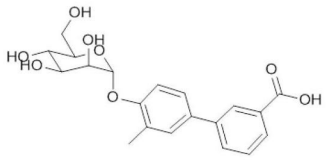
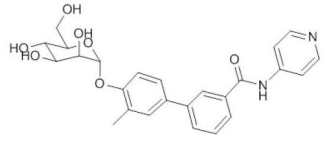
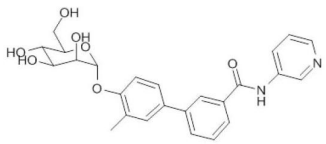
余物来以61％产率产生3-[4-[(2R,3R,4S,5R,6S)-6-(羟甲基)-3,4,5-三(三甲基甲硅烷基氧基)四氢吡喃-2-基]氧基-3-甲基-苯基]-N-甲基-苯甲酰胺(D)(0.190g)。向N,N'-二甲基甘氨酸盐酸盐(0.0154,0.11mmol)、DMAP(0.0024g,0.02mmol)、$^{i}Pr_2NEt$(0.035mL,0.2mmol)和中间体D(0.062g,0.1mmol)于二氯甲烷(2mL)中的混合物中添加N,N′-二异丙基碳二亚胺(0.02mL,0.13mmol)。将混合物在室温下搅拌过夜。移除溶剂,并且将所得残余物溶解于乙腈(3mL)中。接着在0℃下添加三氟乙酸(0.08mL)。在0℃下搅拌混合物2小时。移除溶剂,并且通过HPLC(C18,15*150mm柱;洗脱剂:乙腈/水(0.05％TFA))纯化所得残余物来以31％产率产生标题化合物(0.015g)。LCMS(ESI,M+H$^+$＝489.4);^{1}H NMRδppm(d_3-MeOD;2.32(s,3H)2.89(s,6H)2.95(s,3H)3.71-3.85(m,2H)3.94-4.00(m,1H)4.06(d,J＝5.48Hz,2H)4.11(t,J＝2.54Hz,1H)4.42(m,1H)4.61(dd,J＝11.74,1.56Hz,1H)5.57(d,J＝1.57Hz,1H)7.23(d,J＝8.61Hz,1H)7.34-7.61(m,3H)7.66-7.88(m,2H)7.99-8.17(m,1H))。

[0813]

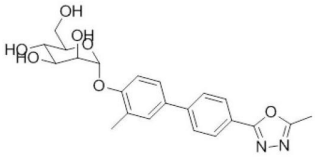
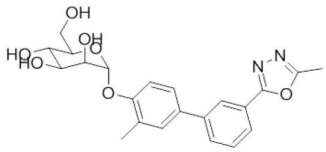
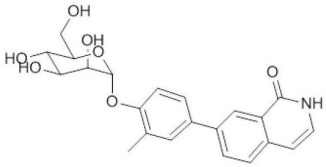
表 1. 实施例 1-22 的结构、分析和生物数据。

实施例	化合物名称	结构	IUPAC 名称	HAI 滴度 $EC_{>90}$(μM)	分子式	MS (ESI, M + H$^+$)	^{1}H NMR δ ppm(d_3-MeOD, 除非另外指示)
1	1CJ84		3-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]苯甲酸甲酯	0.12	C21 H24 O8	427.3 (M+ Na$^+$)	8.20 (t, J = 1.51 Hz, 1H), 7.94 (td, J = 1.41, 7.90 Hz, 1H), 7.77-7.87 (m, 1H), 7.52 (t, J = 7.55 Hz, 1H), 7.39-7.48 (m, 2H), 7.27-7.38 (m, 1H), 5.56 (d, J = 1.65 Hz, 1H), 4.08 (dd, J = 1.92, 3.30 Hz, 1H), 3.94-4.01 (m, 1H), 3.90-3.94 (m, 3H), 3.68-3.83 (m, 3H), 3.55-3.65 (m, 1H), 2.31 (s, 3H)。

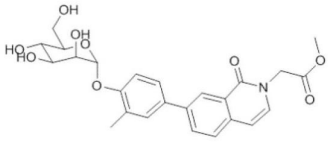
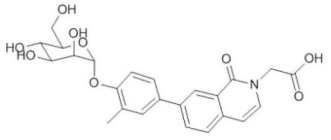
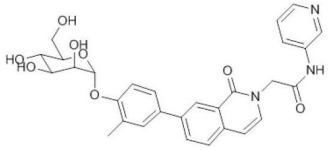
[0814]

2	**1CJ85**		3-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]苯甲酸		C20H22O8	413.3 (M+ Na^+)	2.31 (s, 3 H) 3.61 (ddd, J=9.78, 5.09, 2.74 Hz, 1 H) 3.69-3.84 (m, 3 H) 3.97 (dd, J=9.39, 3.52 Hz, 1 H) 4.08 (dd, J=3.33, 1.76 Hz, 1 H) 5.56 (d, J=1.96 Hz, 1 H) 7.31 (d, J=8.22 Hz, 1 H) 7.39-7.48 (m, 2 H) 7.51 (t, J=7.83 Hz, 1 H) 7.76-7.84 (m, 1 H) 7.95 (dt, J=7.83, 1.37 Hz, 1 H) 8.21 (t, J=1.76 Hz, 1 H)
3	**1CJ86**		3-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-N-(4-吡啶基)苯甲酰胺	**0.064**	C25H26N2O7	467.3	2.34 (s, 3 H) 3.60 (ddd, J=9.78, 5.28, 2.54 Hz, 1 H) 3.68-3.85 (m, 3 H) 3.98 (dd, J=9.59, 3.33 Hz, 1 H) 4.09 (dd, J=3.33, 1.76 Hz, 1 H) 5.58 (d, J=1.57 Hz, 1 H) 7.34 (d, J=8.61 Hz, 1 H) 7.44-7.58 (m, 2 H) 7.63 (t, J=7.63 Hz, 1 H) 7.84-8.00 (m, 2 H) 8.19-8.27 (m, 1 H) 8.37-8.45 (m, 2 H) 8.62-8.72 (m, 2 H)
4	**1CJ87**		3-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-N-(3-吡啶基)苯甲酰胺	**0.032**	C25H26N2O7	467.3	2.33 (s, 3 H) 3.61 (m, 1 H) 3.76 (m, 3 H) 3.97 (d, J=9.39 Hz, 1 H) 4.08 (m, 1 H) 5.57 (d, 1 H) 7.33 (d, J=6.26 Hz, 1 H) 7.43-7.56 (m, 2 H) 7.61 (m, 1 H) 7.85 (m, 1 H) 7.94 (m, 2 H) 8.22 (m, 1 H) 8.55 (m, 1 H) 8.66 (d, J=6.26 Hz, 1 H) 9.47 (m, 1 H)

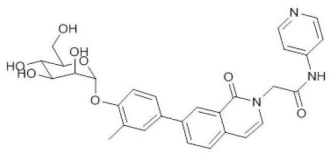
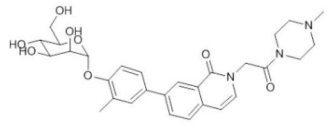
[0815]

5	**1JWJ245**		(2S,3S,4S,5R,6R)-2-(羟甲基)-6-[2-甲基-4-[4-(5-甲基-1,3,4-噁二唑-2-基)苯基]苯氧基]四氢吡喃-3,4,5-三醇	**0.062**	C22H24N2O7	429.3	2.28 (s, 3 H) 2.63 (s, 3 H) 3.53-3.65 (m, 1 H) 3.70-3.88 (m, 3 H) 3.98 (dd, J=9.59, 3.33 Hz, 1 H) 4.09 (dd, J=3.13, 1.96 Hz, 1 H) 5.57 (d, J=1.17 Hz, 1 H) 7.24 (d, J=8.22 Hz, 1 H) 7.38-7.45 (m, 2 H) 7.48 (s, 1 H) 7.69 (m, J=8.61 Hz, 1.5 H) 8.02 (m, J=8.22 Hz, 1.5 H)
6	**1JWJ244**		(2S,3S,4S,5R,6R)-2-(羟甲基)-6-[2-甲基-4-[3-(5-甲基-1,3,4-噁二唑-2-基)苯基]苯氧基]四氢吡喃-3,4,5-三醇	**0.062**	C22H24N2O7	429.3	2.08 (s, 1.5 H) 2.32 (s, 1.5 H) 2.33 (s, 1.5 H) 2.65 (s, 1.5 H) 3.55-3.65 (m, 1 H) 3.69-3.83 (m, 3 H) 3.98 (dt, J=9.49, 2.69 Hz, 1 H) 4.06-4.12 (m, 1 H) 5.54-5.60 (m, 1 H) 7.27-7.38 (m, 1 H) 7.44-7.65 (m, 3 H) 7.75-7.98 (m, 2 H) 8.07-8.25 (m, 1 H)
7	**5ZFH254**		7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-2H-异喹啉-1-酮	**0.030**	C22H23NO7	414.3	2.32 (s, 3 H) 3.57-3.67 (m, 1 H) 3.70-3.85 (m, 3 H) 3.94-4.02 (m, 1 H) 4.05-4.13 (m, 1 H) 5.57 (d, *J*=1.57 Hz, 1 H) 6.70 (d, *J*=7.00 Hz, 1 H) 7.17 (d, *J*=7.04 Hz, 1 H) 7.33 (d, *J*=8.22 Hz, 1 H) 7.54 (s, 2 H) 7.70 (d, *J*=8.61 Hz, 1 H) 7.89-8.04 (m, 1 H) 8.49 (d, *J*=1.96 Hz, 1 H)

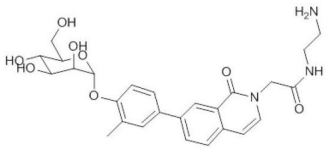
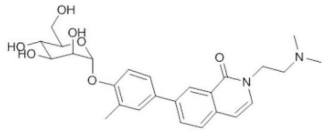
[0816]

8	**1CJ74**		2-[7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-1-氧代-2-异喹啉基]乙酸甲酯	**0.006**	C25H27NO9	486.3	2.32 (s, 3 H) 3.61 (ddd, J=9.68, 4.99, 2.54 Hz, 1 H) 3.68-3.85 (m, 3 H) 3.78 (s, 3H) 3.98 (dd, J=9.59, 3.33 Hz, 1 H) 4.04-4.14 (m, 1 H) 4.82 (s, 2 H) 5.53-5.62 (m, 1 H) 6.72 (d, J=7.04 Hz, 1 H) 7.32 (dd, J=7.83, 3.91 Hz, 2 H) 7.44-7.58 (m, 2 H) 7.70 (d, J=8.22 Hz, 1 H) 7.97 (dd, J=8.22, 1.96 Hz, 1 H) 8.43-8.49 (m, 1 H)
9	**1CJ72B**		2-[7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-1-氧代-2-异喹啉基]乙酸	**0.016**	C24H25NO9	472.3	2.32 (s, 3 H) 3.61 (ddd, J=9.59, 5.28, 2.35 Hz, 1 H) 3.67-3.86 (m, 3 H) 3.98 (dd, J=9.59, 3.33 Hz, 1 H) 4.08 (dd, J=3.33, 1.76 Hz, 1 H) 4.79 (s, 2 H) 5.50-5.62 (m, 1 H) 6.72 (d, J=7.43 Hz, 1 H) 7.32 (dd, J=8.02, 2.93 Hz, 2 H) 7.44-7.59 (m, 2 H) 7.70 (d, J=8.22 Hz, 1 H) 7.97 (dd, J=8.22, 1.96 Hz, 1 H) 8.44-8.55 (m, 1 H)
10	**1CJ75**		2-[7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-1-氧代-2-异喹啉基]-N-(3-吡啶基)乙酰胺	**0.001**	C29H29N3O8	548.4	2.32 (s, 3 H) 3.55-3.66 (m, 1 H) 3.66-3.85 (m, 3 H) 3.97 (dd, J=9.59, 3.33 Hz, 1 H) 4.08 (dd, J=3.13, 1.96 Hz, 1 H) 4.96 (s, 2 H) 5.46-5.63 (m, 1 H) 6.77 (d, J=7.04 Hz, 1 H) 7.27-7.44 (m, 2 H) 7.46-7.58 (m, 2 H) 7.73 (d, J=8.22 Hz, 1 H)

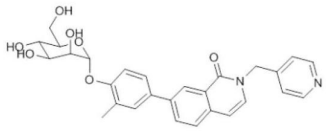
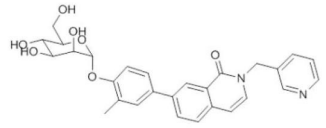
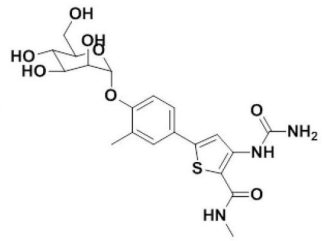
[0817]

							7.88 (dd, J=8.61, 5.48 Hz, 1 H) 8.00 (dd, J=8.22, 1.96 Hz, 1 H) 8.42 (dd, J=8.61, 1.17 Hz, 1 H) 8.49 (s, 2 H) 9.18-9.29 (m, 1 H)
11	**1CJ81**		2-[7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-1-氧代-2-异喹啉基]-N-(4-吡啶基)乙酰胺	**0.001**	C29H29N3O8	548.4	2.32 (s, 3 H) 3.60 (ddd, J=9.78, 5.09, 2.74 Hz, 1 H) 3.67-3.84 (m, 3 H) 3.97 (dd, J=9.59, 3.33 Hz, 1 H) 4.08 (dd, J=3.33, 1.76 Hz, 1 H) 5.00 (s, 2 H) 5.57 (d, J=1.57 Hz, 1 H) 6.78 (d, J=7.43 Hz, 1 H) 7.38 (d, J=7.43 Hz, 2 H) 7.33 (d, J=8.61 Hz, 1 H) 7.49-7.58 (m, 2 H) 7.75 (d, J=8.22 Hz, 1 H) 8.01 (dd, J=8.41, 2.15 Hz, 1 H) 8.18 (m, J=7.04 Hz, 2 H) 8.49 (d, J=1.96 Hz, 1 H) 8.64 (m, J=7.43 Hz, 2 H)
12	**1CJ82**		2-[2-(4-甲基哌嗪-1-基)-2-氧代-乙基]-7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]异喹啉-1-酮	**0.008**	C29H35N3O8	554.4	2.33 (s, 3 H) 2.99 (s, 3 H) 3.26 (dt, J=3.23, 1.71 Hz, 1 H) 3.34-3.42 (m, 1 H) 3.49 (dd, J=3.52, 1.57 Hz, 1 H) 3.61 (ddd, J=9.78, 5.28, 2.54 Hz, 3 H) 3.70-3.86 (m, 4 H) 3.97 (dd, J=9.59, 3.33 Hz, 2 H) 4.08 (dd, J=3.52, 1.96 Hz, 2 H) 4.81 (s, 1 H) 5.57 (d, J=1.96 Hz, 1 H) 6.75 (d, J=7.43 Hz, 1 H) 7.20-7.40 (m, 3 H) 7.45-7.59 (m, 2 H) 7.72 (d, J=8.22 Hz, 1 H) 7.99 (dd, J=8.22,

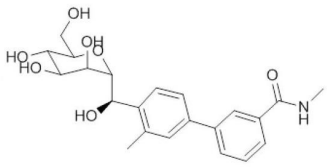
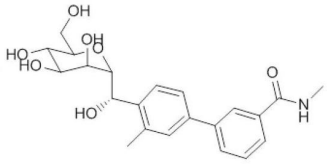
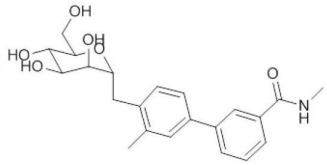
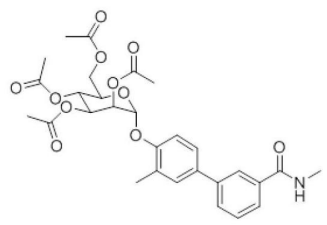
[0818]

							1.96 Hz, 1 H) 8.49 (d, J=1.96 Hz, 1 H)
13	**1CJ76**		N-(2-氨基乙基)-2-[7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-1-氧代-2-异喹啉基]乙酰胺	**0.016**	C26H31N3O8	514.4	2.33 (s, 3 H) 3.11 (t, J=5.67 Hz, 2 H) 3.54 (t, J=5.67 Hz, 2 H) 3.56-3.67 (m, 1 H) 3.68-3.84 (m, 3 H) 3.97 (dd, J=9.59, 3.33 Hz, 1 H) 4.08 (dd, J=3.33, 1.76 Hz, 1 H) 4.73 (s, 2 H) 5.48-5.64 (m, 1 H) 6.78 (d, J=7.43 Hz, 1 H) 7.34 (d, J=7.83 Hz, 2 H) 7.46-7.59 (m, 2 H) 7.74 (d, J=8.22 Hz, 1 H) 8.00 (dd, J=8.22, 1.96 Hz, 1 H) 8.50 (s, 1 H)
14	**1CJ70**		2-(2-二甲基氨基乙基)-7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]异喹啉-1-酮	**0.012**	C26H32N2O7	485.4	2.33 (s, 3 H) 3.05 (s, 6 H) 3.52-3.67 (m, 3 H) 3.68-3.84 (m, 3 H) 3.97 (dd, J=9.39, 3.52 Hz, 1 H) 4.08 (dd, J=3.33, 1.76 Hz, 1 H) 4.46 (t, J=5.87 Hz, 2 H) 5.47-5.64 (m, 1 H) 6.80 (d, J=7.43 Hz, 1 H) 7.38 (d, J=7.43 Hz, 1 H) 7.34 (d, J=8.61 Hz, 1 H) 7.47-7.59 (m, 2 H) 7.73 (d, J=8.61 Hz, 1 H) 8.01 (dd, J=8.41, 1.76 Hz, 1 H) 8.49-8.60 (m, 1 H)

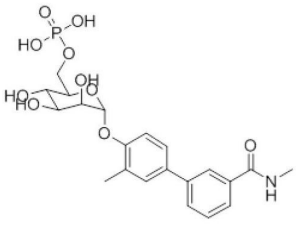
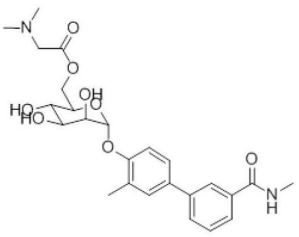
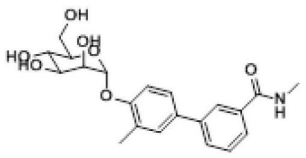
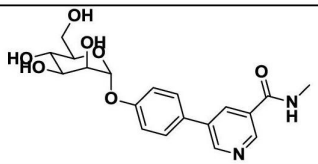
[0819]

15	**1CJ66**		7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-2-(4-吡啶基甲基)异喹啉-1-酮	**0.004**	C28H28N2O7	505.4	2.32 (s, 3 H) 3.53-3.66 (m, 1 H) 3.67-3.83 (m, 3 H) 3.96 (dd, J=9.59, 3.33 Hz, 1 H) 4.07 (dd, J=3.13, 1.96 Hz, 1 H) 5.52 (s, 2 H) 5.56 (s, 1 H) 6.84 (d, J=7.43 Hz, 1 H) 7.33 (d, J=8.61 Hz, 1 H) 7.44-7.57 (m, 3 H) 7.70-7.86 (m, 3 H) 8.02 (dd, J=8.22, 1.96 Hz, 1 H) 8.49 (s, 1 H) 8.73 (d, J=6.65 Hz, 2 H)
16	**1CJ68**		7-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-2-(3-吡啶基甲基)异喹啉-1-酮	**0.008**	C28H28N2O7	505.4	2.32 (s, 3 H) 3.51-3.66 (m, 1 H) 3.66-3.85 (m, 3 H) 3.97 (dd, J=9.59, 3.33 Hz, 1 H) 4.08 (dd, J=3.13, 1.57 Hz, 1 H) 5.42 (s, 2 H) 5.56 (s, 1 H) 6.80 (d, J=7.43 Hz, 1 H) 7.33 (d, J=8.22 Hz, 1 H) 7.43-7.61 (m, 3 H) 7.72 (d, J=8.22 Hz, 1 H) 7.89 (dd, J=8.02, 5.67 Hz, 1 H) 7.99 (dd, J=8.41, 1.76 Hz, 1 H) 8.42 (d, J=8.22 Hz, 1 H) 8.46-8.54 (m, 1 H) 8.71 (d, J=5.48 Hz, 1 H) 8.86 (s, 1 H)
17	**5ZFH302**		N-甲基-5-[3-甲基-4-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]氧基-苯基]-3-脲基-噻吩-2-甲酰胺	**0.024**	C20H25N3O8S	468.3	2.27 (s, 3 H) 2.87 (s, 3 H) 3.52-3.61 (m, 1 H) 3.76 (d, *J*=1.17 Hz, 3 H) 3.91-3.99 (m, 1 H) 4.03-4.09 (m, 1 H) 5.56 (d, *J*=1.17 Hz, 1 H) 7.27 (m, 1 H) 7.47 (m, 2 H) 8.06 (s, 1 H)

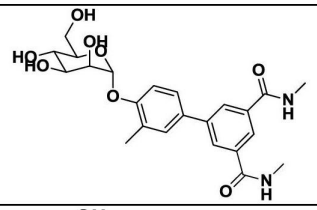
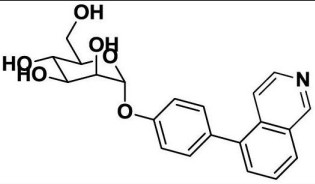
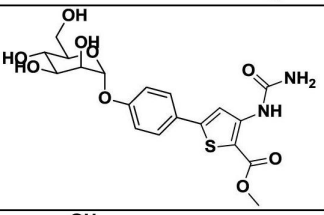
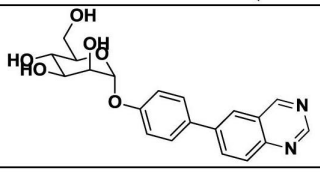
[0820]

18A	**5ZFH240**		3-[4-[(R)-羟基-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]甲基]-3-甲基-苯基]-N-甲基-苯甲酰胺	**0.031**	C21H26NO7	440.3 ($M+Na^+$)	2.51 (s, 3 H) 2.95 (s, 3 H) 3.57-3.78 (m, 4 H) 4.00-4.07 (m, 1 H) 4.10 (dd, *J*=6.85, 2.54 Hz, 1 H) 4.25 (t, *J*=2.93 Hz, 1 H) 5.24 (d, *J*=6.65 Hz, 1 H) 7.45-7.57 (m, 3 H) 7.62 (d, *J*=8.22 Hz, 1 H) 7.71-7.83 (m, 2 H) 8.07 (t, *J*=1.56 Hz, 1 H)
18B	**5ZFH244**		3-[4-[(S)-羟基-[(2R,3R,4S,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]甲基]-3-甲基-苯基]-N-甲基-苯甲酰胺	**6.000**	C21H26NO7	440.3 ($M+Na^+$)	2.51 (s, 3 H) 2.95 (s, 3 H) 3.56 (dd, *J*=1.00 Hz, 1 H) 3.67 (m, 1 H) 3.70-3.82 (m, 3 H) 3.91 (m, 1 H) 4.10 (dd, *J*=9.00, 1.96 Hz, 1 H) 5.28 (d, *J*=8.61 Hz, 1 H) 7.34-7.63 (m, 4 H) 7.69-7.90 (m, 2 H) 8.07 (s, 1 H)
19	**5ZFH247**		N-甲基-3-[3-甲基-4-[[(2R,3R,4R,5S,6S)-3,4,5-三羟基-6-(羟甲基)四氢吡喃-2-基]甲基]苯基]苯甲酰胺	**2.000**	C22H27NO6	402.3	2.44 (s, 3 H) 2.95 (s, 3 H) 3.04 (d, *J*=7.43 Hz, 2 H) 3.69 (m, 3 H) 3.83 (m, 2 H) 3.86-3.92 (m, 1 H) 4.04-4.21 (m, 1 H) 7.31 (d, *J*=7.83 Hz, 1 H) 7.42-7.47 (m, 1 H) 7.50 (m, 2 H) 7.75 (m, 2 H) 8.05 (s, 1 H)
20	**1JWJ231**		乙酸[(2S,3R,4S,5R,6R)-3,4,5-三乙酰氧基-6-[2-甲基-4-[3-(甲基氨基甲酰基)苯基]苯氧基]四氢吡喃-2-基]甲酯		C29H33NO11	594.3 ($M+Na^+$)	[d_6-DMSO] 1.94 (s, 3 H) 2.00 (s, 3 H) 2.05 (s, 3 H) 2.16 (s, 3 H) 2.32 (s, 3 H) 2.81 (d, J=4.30 Hz, 3 H) 3.93-4.11 (m, 2 H) 4.19 (dd, J=12.13, 5.09 Hz, 1 H) 5.22 (t, J=9.98 Hz, 1 H) 5.33-5.45 (m, 2 H) 5.80 (s, 1 H) 7.23 (d, J=8.61 Hz, 1 H)

[0821]

							7.46-7.65 (m, 3 H) 7.77 (d, J=7.83 Hz, 2 H) 8.07 (s, 1 H) 8.54 (d, J=4.30 Hz, 1 H)
21	**1JWJ232**		磷酸二氢[(2S,3S,4S,5R,6R)-3,4,5-三羟基-6-[2-甲基-4-[3-(甲基氨基甲酰基)苯基]苯氧基]四氢吡喃-2-基]甲酯		C21H26NO10P	484.3	[d_6-DMSO] 2.26 (s, 3 H) 2.81 (d, *J*=4.70 Hz, 3 H) 3.42-3.68 (m, 3 H) 3.75 (dd, *J*=9.00, 3.13 Hz, 1 H) 3.86-3.97 (m, 2 H) 4.03 (dd, *J*=9.78, 5.87 Hz, 1 H) 5.45 (d, *J*=1.96 Hz, 1 H) 7.24 (d, *J*=8.61 Hz, 1 H) 7.43-7.60 (m, 3 H) 7.76 (dd, *J*=7.43, 1.57 Hz, 2 H) 8.06 (s, 1 H) 8.56 (d, *J*=4.30 Hz, 1 H)
22	**6ZFH123**		2-二甲基氨基乙酸[(2S,3S,4S,5R,6R)-3,4,5-三羟基-6-[2-甲基-4-[3-(甲基氨基甲酰基)苯基]苯氧基]四氢吡喃-2-基]甲酯		C25H32N2O8	489.4	2.32 (s, 3 H) 2.89 (s, 6 H) 2.95 (s, 3 H) 3.71-3.85 (m, 2 H) 3.94-4.00 (m, 1 H) 4.06 (d, *J*=5.48 Hz, 2 H) 4.11 (t, *J*=2.54 Hz, 1 H) 4.42 (m, 1 H) 4.61 (dd, *J*=11.74, 1.56 Hz, 1 H) 5.57 (d, *J*=1.57 Hz, 1 H) 7.23 (d, *J*=8.61 Hz, 1 H) 7.34-7.61 (m, 3 H) 7.66-7.88 (m, 2 H) 7.99-8.17 (m, 1 H)
23							
24							

[0822]

25							
26							
27							
28							

[0823] 实施例23.实施例1-22的化合物的生物和体内活性。

[0824] 本发明者着手开发和优化FimH细菌粘附的口服活性甘露糖苷小分子拮抗剂以治疗和预防复发性尿路感染(UTI)。为确定口服活性化合物所需的终点是药物在尿和/或膀胱中不变。首先,本发明者合理设计具有效价和合乎需要的性质的联芳甘露糖苷。为此,确定取代基的结构活性关系(SAR)。评估在联芳环上邻位取代的FimH活性。在杂环的情况下,溶解度、LogD和pKa得以改进。进一步发现替换糖苷键可改进代谢稳定性和生物利用度。鉴定甘露糖与联芳环的替代性连接体。合成N-甘露糖苷、S-甘露糖苷和C-甘露糖苷。急性UTI与慢性UTI两者的鼠类动物模型用于进一步评估化合物功效。

[0825] 本发明者已通过基于X射线结构的设计开发细胞效价增加2000倍的化合物。在100mg/kg剂量下,甘露糖苷显示持续6小时的良好口服化合物暴露,并且在体内防治性防止UTI89细菌的IBC形成。在尿中检测到一些代谢/水解产物(酚)。重要的是,甘露糖苷在体内逆转UTI的抗生素TMP-SMZ抗性菌株。正在通过在血浆和尿中进行化合物PK筛选来针对降低CI、增加$t_{1/2}$、V_{dss}(组织暴露)以及改进生物利用度进行优化。此外,正在进行功效模型开发以证明作为单药疗法以及与抗生素组合的感染后抗菌作用。此外,本发明者正在优化前药和非糖甘露糖苷模拟物。

[0826] 在用UTI89感染之前30分钟用50mg/kg的甘露糖苷ZFH-4269(图1A)、ZFH-5254(图1B)和ZFH-5240(图1C)或DMSO或PBS对动物口服给药之后评估体内甘露糖苷治疗的功效。在感染后6小时(hpi),移除膀胱,并且定量总细菌CFU。在所有三个甘露糖苷治疗组中,都存在细菌计数下降,从而证明这些甘露糖苷在降低膀胱的总体定殖方面具有功效(图1D)。接着,在相同小鼠尿路感染模型中评估254的类似物。在用UTI89感染之前30分钟,用含25mg/kg的甘露糖苷ZFH-4269(图2A)、1CJ68(图2B)和1CJ70(图2C)的10%环糊精或10%环糊精对动物口服给药。在ZFH269治疗组中,存在细菌计数下降,从而证明这个甘露糖苷在降低膀胱的总体定殖方面具有功效(图2D)。

[0827] 评估甘露糖苷化合物FIM-4269、FIM-5240、FIM-5254、FIM-1CJ82和FIM-1CJ66(图3)在大鼠中的药代动力学。甘露糖苷在3mg/kg下静脉内给药,以及在10mg/kg下口服给药。在15分钟、30分钟、1小时、2小时、4小时和8小时收集尿和血浆。在静脉内给药之后,相对于其它4种甘露糖苷,FIM-5240的平均血浆浓度最高,并且保持在检测限以上直至2.5小时(图4)。在口服给药之后,相对于其它甘露糖苷,FIM-5240再次展现最佳药代动力学,并且在治疗后2小时下降至检测限以下(图5)。

[0828] 基于这些结果,在小鼠中进行口服PK研究。在50mg/kg下用化合物ZFH-4269(图6A)、ZFH-5254(图6B)、ZFH5240(图6C)和前药给药,并且在给药之后1、3、6和8小时获取血浆和尿样品。如图6D中所证明,所有化合物在尿中都可检测直至治疗后8小时。发现化合物240和前药在尿中始终维持高浓度水平,浓度在6小时时期内远高于预测的最小有效浓度。总之,在动物研究中观察到的高口服生物利用度和体内功效支持甘露糖苷作为用于UTI治疗/预防的有前途的治疗候选物。

[0829] 在用UTI89感染之前30分钟用含25mg/kg的甘露糖苷ZFH269、前药FIM-4269、ZFH-5254和ZFH-5240的10%环糊精或10%环糊精对动物口服给药之后评估体内甘露糖苷治疗的功效。在感染后6小时(hpi),移除膀胱,并且定量总细菌CFU。在所有甘露糖苷治疗组中,都存在细菌计数下降,从而证明这些甘露糖苷在降低膀胱的总体定殖方面具有功效(图7A)。重要的是,ZFH269的前药展现的活性显著好于ZFH269。接着,在相同小鼠尿路感染模型中评估若干不同前药。在用UTI89感染之前30分钟,用含25mg/kg的甘露糖苷ZFH-4269、前药FIM-1233(图8B)、前药FIM-6123(图8C)和前药269的10%环糊精或10%环糊精对动物口服给药。在所有甘露糖苷治疗组中,都存在细菌计数下降,从而证明这些甘露糖苷在降低膀胱的总体定殖方面具有功效(图7B)。

[0830] 实施例24.尿路病原性大肠杆菌(UPEC)在尿路中的发病机理。

[0831] 在临床上,已假定UPEC感染由在粪便菌群通过尿道接种至膀胱中之后相对简单的细胞外定殖于腔表面组成。相反,使用鼠类UT的UPEC感染模型,本发明者已详述涉及细胞内小生境(niche)与细胞外小生境两者的出乎意料复杂的UPEC发病机理循环。使用遗传、生物化学和细胞生物学方法以及多种成像技术(包括传输、快速冷冻-深度蚀刻和扫描电子显微术以及共焦和延时视频显微术),本发明者发现UPEC通过FimH依赖性机理侵袭膀胱盖细胞(bladder facet cell)(参见下文)。在侵袭之后,形成细胞质细胞内细菌群落(IBC)。初始侵袭性细菌的快速复制导致形成松散堆积的杆状细菌的早期IBC。细菌继续复制和进展以形成在形态上呈球状的细菌的大型密集堆积的中期IBC,具有生物膜样特征,包括过碘酸-希夫(periodic acid-Schiff,PAS)染色阳性和在整个群落中差异性基因表达。在IBC成熟之后,细菌从生物质拆离,常变为丝状,并且向相邻细胞散布,从而形成新一代IBC。因此,IBC途径有助于侵袭性细菌在被保护免遭宿主防御的小生境中大量扩增。转化研究已显示大多数UPEC分离株在引入鼠类膀胱中时形成IBC,并且IBC和丝状细菌存在于人UTI患者的尿中。由本发明者使用离体庆大霉素保护测定进行的群体动态研究证明初始10^7个接种物中有约10^4个UPEC在感染之后15分钟内侵袭膀胱组织,并且1%的侵袭细菌接着形成IBC,从而导致每个受感染小鼠膀胱有平均100个IBC。如果将此外推至人类情况,那么膀胱中的先天性防御很可能防止大多数向膀胱中的细菌接种事件导致疾病。然而,IBC级联的分枝是惊人的。单一感染性细菌的侵袭可通过形成IBC导致感染快速扩大,在数小时内复制成10^4个

细菌乃至更高数目，随后细菌从生物质分散并向相邻细胞散布以再引发IBC级联。这个过程允许细菌赢得关键据点。已使用鼠类模型显示急性IBC级联的细菌后代能够形成静息细胞内储库(QIR)，其可存留，被保护免遭抗生素以及似乎不被宿主免疫系统检测到，甚至在急性感染消散以及在尿中不再可检测出细菌之后。QIR中的细菌稍后可作为通过IBC形成、细菌尿和炎症表现的复发性感染的起因。

[0832] 实施例25.FimH作为治疗靶标。

[0833] 存在由了解UPEC发病机理而获得的若干关键暗示。阻断FimH功能的甘露糖苷和抑菌毛剂(pilicide)将防止细菌粘着和侵袭，并且因此防止IBC中的细菌扩增和后续散布以及通过新一代IBC进行重复多轮扩增。这些化合物将通过防止细菌扩增，此也可具有消除或显著降低QIR，由此降低对复发性感染的易患性的结果，而具有强力治疗活性。

[0834] 1型菌毛/FimH对UT中的UPEC发病机理至关重要。

[0835] 1型菌毛是主要膀胱炎毒性决定因素。使用扫描和高分辨率EM以及由本发明者开发的小鼠膀胱炎模型，显示粘附性1型菌毛化细菌能够结合和侵袭宿主浅表伞状细胞，而缺乏1型菌毛的UPEC并非如此。定殖和侵袭膀胱上皮依赖于位于菌毛的结合膀胱上皮细胞上的甘露糖残基的远端处的FimH粘附。高分辨率冷冻干燥/深度蚀刻EM揭示FimH直接与膀胱的腔表面上的受体相互作用(图11)。对受感染组织培养细胞的标准庆大霉素保护测定以及对受感染膀胱的离体庆大霉素治疗证明$fimH^{+}$1型菌毛化临床膀胱炎分离株而非$fimH^{-}$突变株可侵袭膀胱上皮细胞。使用免疫组织化学和Pfim-gfp转录融合，证明1型菌毛在IBC内表达。使用高分辨率EM，也观察到从细菌放射出以及与细胞内IBC内的基质物质相互作用的菌毛样纤维。这些结果与显示1型菌毛为在体外系统中形成生物膜所需的研究组合引出1型菌毛促进IBC形成和/或维持的假设。因此，构建无水四环素(AHT)诱导性fim菌株，其可通过在感染小鼠膀胱之前在AHT中生长而成为体外“预菌毛化”UTI89，从而使得初始侵袭事件符合通常情况。然而，一旦接种至小鼠中，AHT即不再存在，fim转录停止，并且菌毛化在各次细菌分裂后被稀释。使用这个系统，在野生型菌株与条件性菌株之间，最早定殖和侵袭事件是相同的。然而，条件性菌株不能在细胞内产生1型菌毛消除了它形成IBC的能力(如通过共焦显微术所示)，并且因此显著减弱毒性(如在稍后时间点通过CFU所确定)。这些结果强烈表明1型菌毛为UPEC在浅表盖细胞内存活和增殖所需。另外，这个条件性突变株在它形成QIR的能力方面显著受损，从而论证QIR中的细菌是后代，并且因此取决于急性IBC级联。

[0836] FimH和它的配体的结构研究。

[0837] 粘附性1型菌毛是由不同革兰氏阴性细菌通过侣伴/引导蛋白装配途径产生的粘附性纤维家族的原型结构。使用生物化学、突变研究、核磁共振和x射线结晶学，描绘了通过革兰氏阴性细菌中的侣伴/引导蛋白途径装配的菌毛，包括UPEC的1型菌毛的分子基础(图12)。解析FimH结合于它的甘露糖受体的三维结构以获得UTI发病机理中关键初始事件的分子瞬像。

[0838] FimH是一种两结构域蛋白质，其中受体结合结构域连接于典型菌毛蛋白结构域，菌毛蛋白结构域使粘附素接合于菌毛纤维。在2.8 Å分辨率下确定FimC侣伴蛋白结合于FimH(其被结合于D-吡喃甘露糖苷)的复合物的结构。FimH的甘露糖结合位点是在它的受体结合结构域的尖端处的纵深带负电荷口袋。FimH口袋以与甘露糖广泛氢键合进行啮合(图14)，甘露糖在包覆膀胱上皮的腔表面的尿斑蛋白的寡糖部分中是充足的。疏水性脊以可有

助于FimH口袋内的极性相互作用的方式围绕甘露糖结合口袋。突变研究揭示各残基在甘露糖结合和发病机理中是关键的，从而强调为何在UPEC分离株之中口袋是不变的。

[0839] 开发抗粘附剂。

[0840] 进一步探究FimH-甘露糖相互作用以试图开发UTI的潜在基于配体的拮抗剂。发现寡甘露糖上的壳二糖单元使各种甘露糖衍生物桥连于FimH的Asn-X-Ser/Thr基序中的天冬酰胺，从而导致较高亲和力结合。对与寡甘露糖-3复合的FimH的结晶揭示这个较高亲和力结合的机理。非还原性Man4锚定至甘露糖结合口袋中，同时GlcNAc在Thr51上折叠，从而允许与疏水性酪氨酸门特异性相互作用。庚基甘露糖苷模拟寡甘露糖-3的GlcNAc尾部，并且进一步使它延伸以增加在结合口袋外部的相互作用，从而导致高亲和力结合(Kd＝5nM)。基于庚基甘露糖对FimH的高亲和力，测试庚基甘露糖在我们的小鼠UTI模型中减轻细菌性感染的能力。首先，评估作为在膀胱中形成的IBC的替代的生物膜形成。在1mM下，庚基甘露糖体外抑制UPEC生物膜形成，表明FimH粘附素的甘露糖结合性质为形成生物膜所需。因此，在接种至小鼠的膀胱中之前使UPEC菌株UTI89与庚基甘露糖一起孵育。在5mM庚基甘露糖下，在感染后6小时，这导致毒性显著减弱。这些化合物显著减弱毒性的能力将甘露糖苷确定为UTI的一种潜在治疗。因此，如下所述开发模拟FimH的天然受体，但亲和力和亲合力增加以最终阻断细菌定殖、侵袭、IBC形成和疾病的更强力甘露糖苷。

[0841] 实施例26.甘露糖苷抑制UPEC侵袭至膀胱组织中并增强TMP-SMZ的功效。

[0842] 针对UTI的所选第一线治疗在传统上一直为3天疗程的TMP-SMZ。罹患慢性/复发性UTI的妇女常被防治性给予TMP-SMZ以预防复发。然而，对这个TMP-SMZ方案的抗性正快速扩大。据假设通过防止细菌侵袭至膀胱组织中，FimH抑制剂可产生与TMP-SMZ的抗毒性协同作用，并且可减少或规避TMP-SMZ抗性问题。在临床前动物模型中评估这个理论，其中被持续3天给予TMP-SMZ的小鼠用UTI89或TMP-SMZ^{R}菌株PBC-1感染。在用细菌接种之前30分钟，用6腹膜内处理小鼠，并且与对照组的未处理动物进行比较。在用UTI89或PBC-1接种之后，在6hpi时定量细菌CFU。如所预期，用单独TMP-SMZ处理导致受UTI89感染的小鼠中的细菌载量显著下降，但对PBC-1不具有作用，因为它对TMP-SMZ具有抗性。在用单独6处理后，膀胱中两种菌株的细菌载量均存在显著下降。在双重处理组中，相较于单独甘露糖苷或单独TMP-SMZ，两种菌株的细菌CFU也存在显著下降，此对于PBC-1最显著(图18)。确定的是在存在或不存在TMP-SMZ下，在体外生长期间，存在甘露糖苷对任一菌株的生长或杀灭效率不具有影响。因此，在与6组合下，TMP-SMZ^{R}菌株PBC-1死于抗生素处理的观察结果表明甘露糖苷通过独特机理增强TMP-SMZ的功效。基于在TMP-SMZ下的生长曲线，PBC-1被计算具有TMP和SMZ的分别是256和1280μg/ml的最小抑制浓度(MIC)，并且UTI89被计算具有0.05μg/ml TMP和0.25μg/ml SMZ的MIC。存在甘露糖苷对任一菌株的生长或杀灭效率不具有影响。明确确定的是TMP在尿中富集，并且这个偶然发现的特征是历经过去数十年，TMP-SMZ已成为针对UTI的优选抗生素的主要原因。在用分别54μg/ml和270μg/ml TMP和SMZ治疗3天之后，使用定量HPLC-MS，测量小鼠的尿中的TMP-SMZ的浓度。TMP浓度被测定为9.95+/-4.36mg/ml，并且SMZ处于67.17+/-32.51μg/ml下。这些结果指示通过防止细菌侵袭，6将微生物划分至膀胱管腔中，由此使它们暴露于高于PBC-1的MIC的TMP-SMZ浓度，从而导致增大细菌细胞杀灭。假定的是TMP-SMZ浓度达到高于为UTI89杀灭所需的MIC的组织浓度，但未能达到为杀灭PBC-1所需的组织水平。这些结果明确强调细胞内途径在细菌持久性中的重要性。除在它们的细胞

内小生境中逃脱免疫系统之外，细菌也能够逃避暴露于抗生素，如由临床TMP-SMZ抗性菌株所强调。总之，甘露糖苷可通过抑制UPEC侵袭至膀胱组织中以及增强TMP-SMZ的功效，从而产生有成本效益的治疗来使采用遏制性抗生素疗法的那些妇女受益，这被预测会降低治疗失败率。

[0843] 实施例27.甘露糖苷处理降低CAUTI中的IBC形成。

[0844] 已确定FimH为植入的膀胱中的UPEC毒性所需，我们使用被设计以干扰FimH结合甘露糖基化残基的小分子抑制剂探究这个FimH作为CAUTI的潜在治疗靶标。近来已显示这个称为甘露糖苷的小分子的家族会预防急性和慢性UPEC感染，并且增强组合治疗中的抗生素的有效性。

[0845] 为探究甘露糖苷对CAUTI的潜在治疗作用，我们首先评估甲基-α-D-吡喃甘露糖苷(甲基甘露糖)对处于流动的尿中UTI89生物膜形成的抑制作用。类似于fimH的缺失，相较于未处理的对照，在1％甲基甘露糖存在下生成的UTI89生物膜具有显著降低的生物质(p＝0.0022)和生物膜粘着细胞(p＝0.0012)。因为甲基甘露糖是FimH拮抗剂，所以这些数据确认1型菌毛对尿中生物膜形成的关键作用，如先前对于在LB培养基中形成的生物膜所述。

[0846] 接着通过使用IBC形成以及植入物和尿路定殖作为疾病进展的基准来体内评估甘露糖苷治疗作用。在泌尿性植入之前30分钟，用盐水或含5mg/kg甘露糖苷6(其在体外以及在体内比甲基甘露糖更强力)的PBS腹膜内(i.p.)处理小鼠。导管植入之后立刻经尿道接种UTI89。通过分别在6hpi和24hpi时对植入物、膀胱和肾的LacZ染色和CFU计数来测定IBC形成和细菌定殖。在6hpi时，甘露糖苷处理进一步降低植入动物中的IBC形成(p＝0.0051)和膀胱定殖(p＝0.0114)，表明这个处理会预防细胞内感染。尽管被从它们的细胞内小生境消除，但数据进一步指示UPEC能够存留于细胞外环境中，在环境中，它们可在与盐水处理的动物相对类似的水平上定殖于植入物的表面(p＝0.0547)。在存在或不存在甘露糖苷下，在肾定殖方面未观察到统计差异。截至24hpi，即甘露糖苷已从膀胱消除所处的时间点，在存在或不存在甘露糖苷处理下，从植入动物中的植入物、膀胱和肾回收类似细菌载量。

[0847] 实施例28.甘露糖苷处理增加TMP-SMZ在防止UPEC定殖方面的效率。

[0848] 为考查甘露糖苷在与抗生素组合使用时是否可防止产生CAUTI，持续3天用于它们的饮用水中的分别54和270μg/ml的TMP-SMZ处理动物，接着在植入和细菌接种之前30分钟用盐水或甘露糖苷(5mg/kg)腹膜内处理。在6hpi时，相较于接受水或仅被施用甘露糖苷的那些动物，在仅接受抗生素的动物中，UPEC在显著较低水平下定殖于植入物和膀胱。引起关注的是，相较于用单独抗生素处理，除TMP-SMZ之外也用甘露糖苷处理进一步降低UPEC对植入物、膀胱和肾的定殖(在所有情况下p＜0.0005)。此外，用单独甘露糖苷处理不降低由24时龄UPEC感染所致的细菌滴度，并且与TMP-SMZ组合显示对产生的24hpi UPEC CAUTI无累加作用(数据未显示)。总之，这些研究结果指示毒性靶向疗法与确定的抗生素治疗组合可有助于预防或延迟CAUTI的发作，并且有理由进行进一步研究以增强甘露糖苷作为针对CAUTI的治疗剂的潜力。

[0849] 用于实施例的方法

[0850] 生物膜测定。使UTI89在23℃下在不同浓度的个别甘露糖苷存在下于PVC微量滴定板的孔中在LB肉汤中生长。在生长48小时之后，各孔用水冲洗，并且用结晶紫染色以如所述进行定量。对于PVC板中的生物膜破坏活性，使UTI89在23℃下于PVC微量滴定板的孔中在LB

肉汤中生长。在生长24小时之后，添加甘露糖苷，并且使生物膜再增长16小时。接着冲洗各孔，用结晶紫染色并定量。对于PVC盖片上的生物膜破坏活性，使UTI89在23℃下于含有PBC盖片的50mL锥形容器中在LB肉汤中生长。在生长24小时之后，添加0.3μM ZFH-2056，并且使生物膜再增长16小时。接着冲洗盖片，用2％多聚甲醛(v/v)固定，用SYTO9(1:1000于PBS中；Molecular Probes)染色，并且用Zeiss LSM410共焦激光扫描显微镜在63X物镜下观察。

[0851] 动物感染。使细菌在1型菌毛诱导条件(2×24小时，在37℃下，静态，于LB中)下生长。收集细菌，并且于PBS中再混悬至OD_{600}是0.5。通过吸入异氟烷使8周龄C3H/HeN(Harlan)雌性小鼠麻醉，并且通过经尿道导管插入用50pl细菌混悬液感染，从而产生1-2×10^7个接种物。在6hpi时，通过在麻醉下进行颈部脱位来处死小鼠，并且立刻收集膀胱并如下所述进行处理。所有使用小鼠的动物研究都由华盛顿大学的动物研究委员会(Animal Studies Committee of Washington University)核准(动物方案编号20100002)。

[0852] 药代动力学分析。对于腹膜内给药，将50μl的ZFH-2056于PBS中的2mg/ml(5mg/kg)或4mg/ml(10mg/kg)溶液注射至小鼠的腹膜腔中。对于口服给药，用管饲针将100μl的ZFH-2056于8％DMSO中的20mg/ml(100mg/kg)溶液接种至小鼠胃中。在处理后30分钟、1、2、3、4、6和8小时收集尿。添加相等体积的10μM内标物(ZFH-2050)至尿中。通过装载于C18柱(100mg，Waters)上，用30％甲醇洗涤以及用60％甲醇洗脱来从尿提取甘露糖苷。使用液相色谱-质谱测定系统30分析真空浓缩的洗脱物，采用190℃的较低加热毛细管温度和如下梯度：溶剂B(含80％乙腈的0.1％甲酸)在5％下保持恒定5分钟，截至45分钟增加至44％B，接着截至65分钟增加至95％B。用30％的碰撞气体能量进行以下MS/MS跃迁(前体m/z/产物m/z)的SRM模式定量：化合物ZFH-2056，447/285；化合物ZFH-2050，390/228。通过与校正曲线比较来实现绝对定量。

[0853] 膀胱组织细菌滴度测定。在用UTI89接种之前30分钟腹膜内(5mg/kg)或口服(100mg/kg)施用甘露糖苷ZFH-2056。为计数存在的细菌，在6hpi时处死小鼠，并且无菌移除膀胱并于1ml PBS中均质化，连续稀释，并且涂铺于LB琼脂板上。在37℃下生长16小时之后计数CFU。

[0854] 庆大霉素保护测定。为相对于细胞外区室计数细胞内区室中存在的细菌，在6hpi时无菌收集膀胱。接着将膀胱对切两次，并且于各次500μl PBS中洗涤三次。汇合洗涤级分，在500rpm下轻微旋转5分钟以集结剥离的膀胱细胞，连续稀释，并且涂铺于LB琼脂上以获得腔级分。在37℃下用100μg庆大霉素/ml处理膀胱90分钟。在处理之后，用PBS洗涤膀胱两次以除去残余庆大霉素，于1ml PBS中均质化，连续稀释，并且涂铺于LB琼脂上以计数细胞内级分中的CFU。

[0855] 抗生素处理。在分别54μg/ml和270μg/ml的浓度下将于饮用水中的TMP-SMZ给予小鼠。在用UTI89接种之前，每日将水更换，持续3天。在感染期间小鼠保持采用TMP-SMZ。为测定TMP-SMZ在尿中的浓度，在TMP-SMZ处理3天之后收集尿，并且在添加磺胺异噁唑作为内标物之后通过LC-MS进行定量。

[0856] 生长曲线。在不存在或存在TMP-SMZ和/或甘露糖苷ZFH-2056下，于LB中1:1000稀释PBC-1的过夜培养物。TMP-SMZ的所用最高浓度分别是512μg/ml和2560μg/ml。对TMP-SMZ进行两倍稀释。在100μM下添加甘露糖苷ZFH-2056。在37℃下在96孔板中持续8小时每30分钟获取A600读数来作出生长曲线。

[0857] 血凝测定。使PBC-1在37℃下在不存在或存在TMP-SMZ下于LB中静态生长2×24小时。TMP-SMZ的所用最高浓度分别是256μg/ml和1280μg/ml。对TMP-SMZ进行两倍稀释。如先前所述进行针对豚鼠红血细胞的甘露糖敏感性凝集的血凝测定。

[0858] 统计分析。使用非参数Mann-Whitney U检验(Prizm;GraphPad Software)分析在细菌滴度和IBC数目方面观察到的差异的显著性。

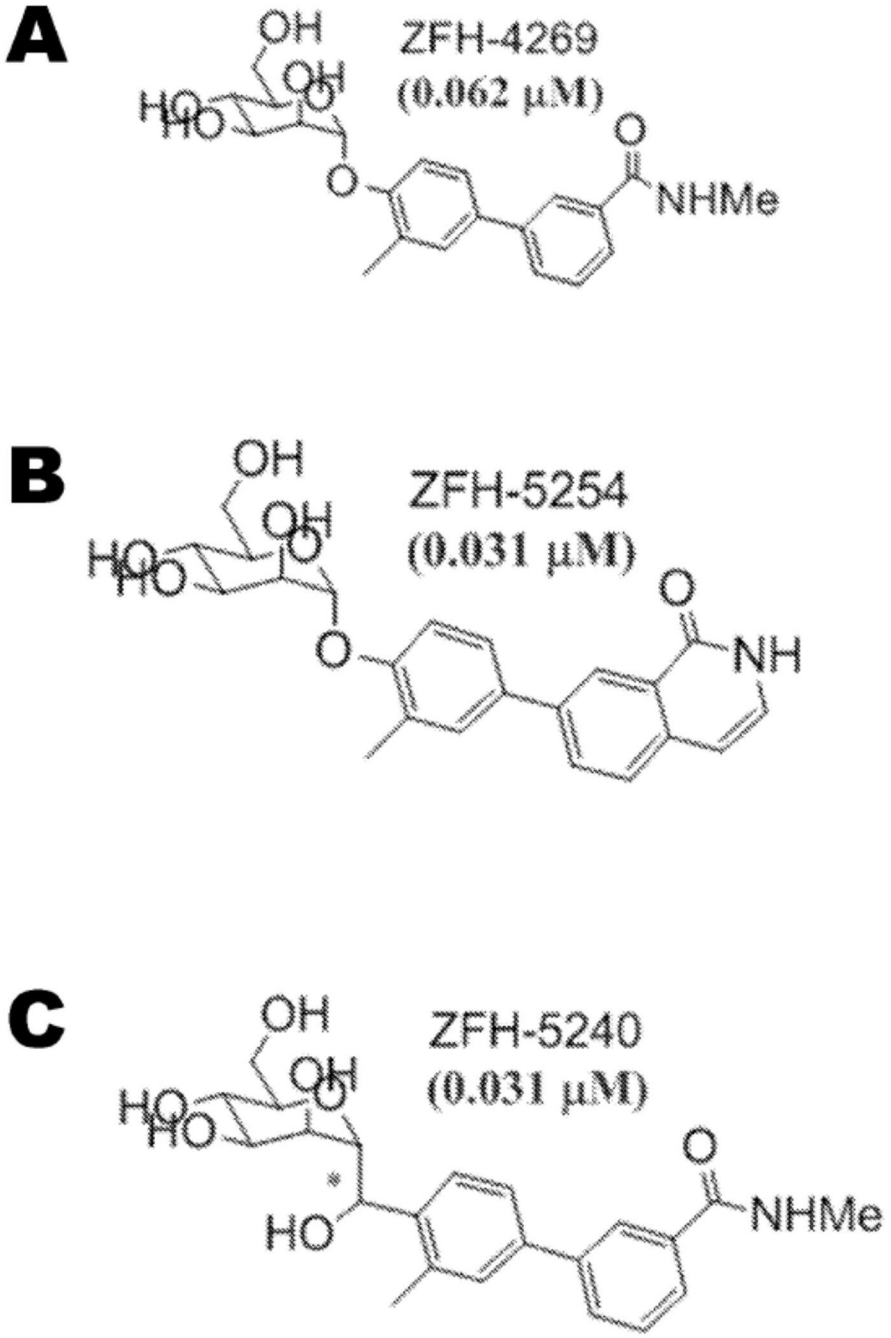

A
ZFH-4269
(0.062 μM)
OH
OH
HO
HO
O
O
NHMe
B
ZFH-5254
(0.031 μM)
OH
OH
HO
HO
O
O
NH
C
ZFH-5240
(0.031 μM)
OH
OH
HO
HO
O
HO
NHMe

图1

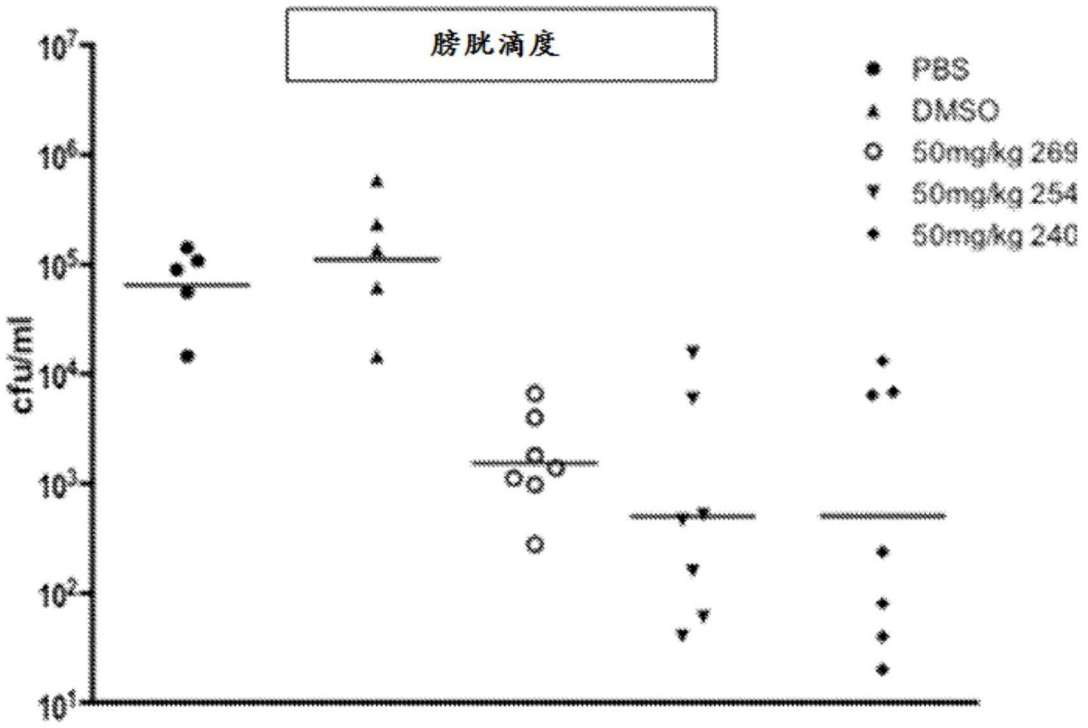

膀胱滴度
PBS
DMSO
50mg/kg 269
50mg/kg 254
50mg/kg 240
cfu/ml
10^7
10^6
10^5
10^4
10^3
10^2
10^1

图1D

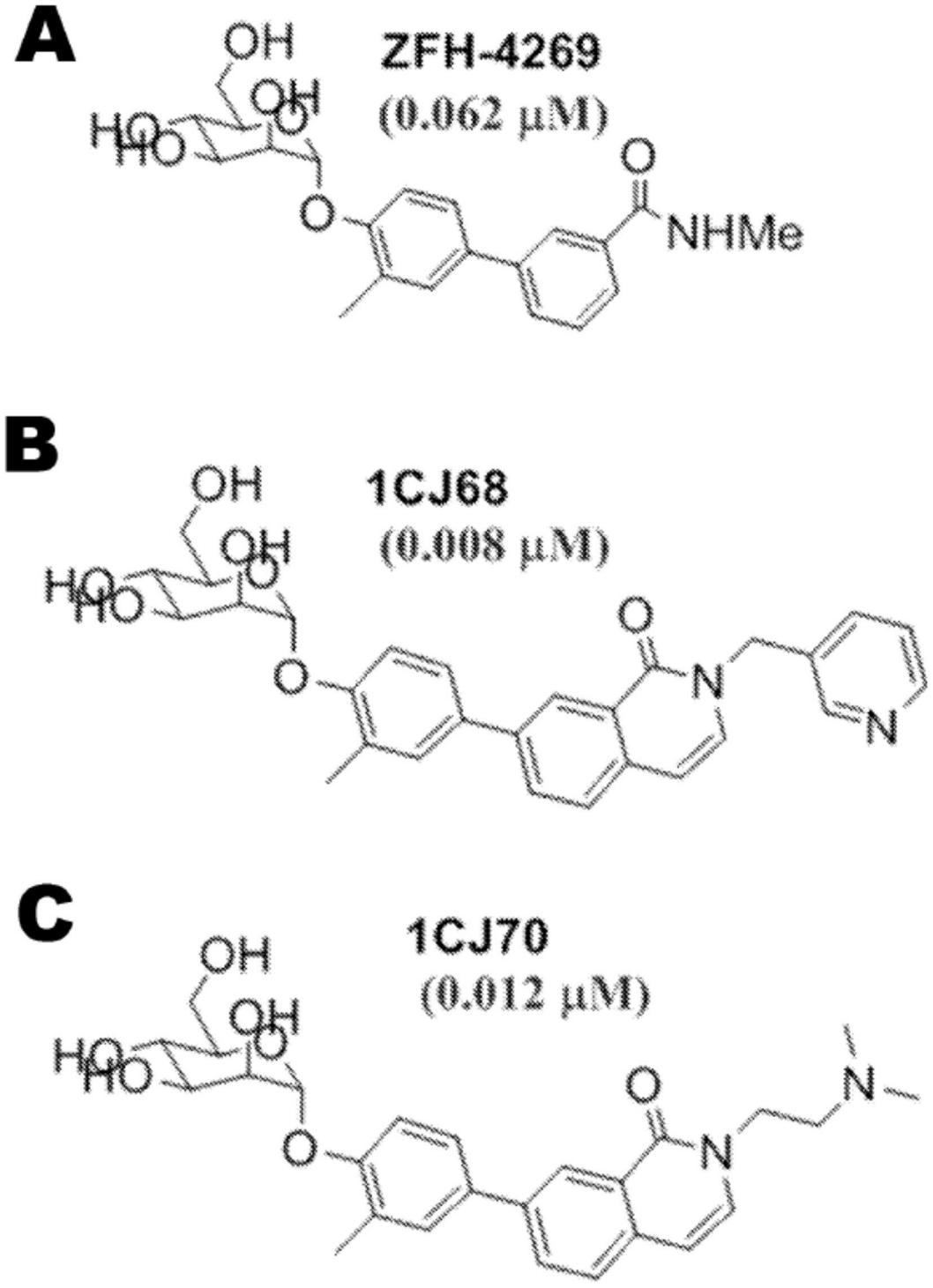

A
ZFH-4269
(0.062 μM)
OH
OH
HO
HO
O
O
NHMe
B
1CJ68
(0.008 μM)
OH
OH
HO
HO
O
O
N
N
C
1CJ70
(0.012 μM)
OH
OH
HO
HO
O
O
N
N

图2

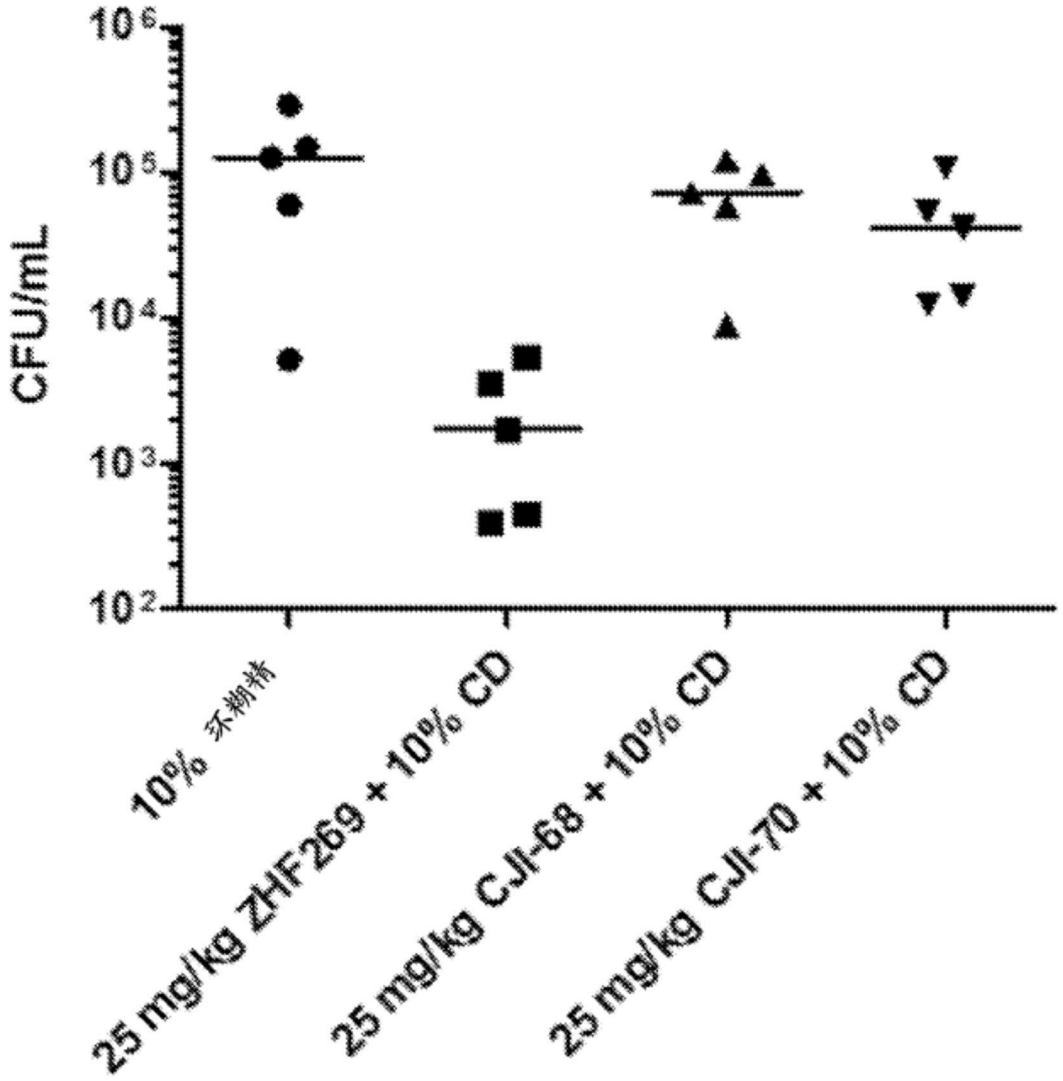

CFU/mL
10^6
10^5
10^4
10^3
10^2
10% 环糊精
25 mg/kg ZHF269 + 10% CD
25 mg/kg CJI-68 + 10% CD
25 mg/kg CJI-70 + 10% CD

图2D

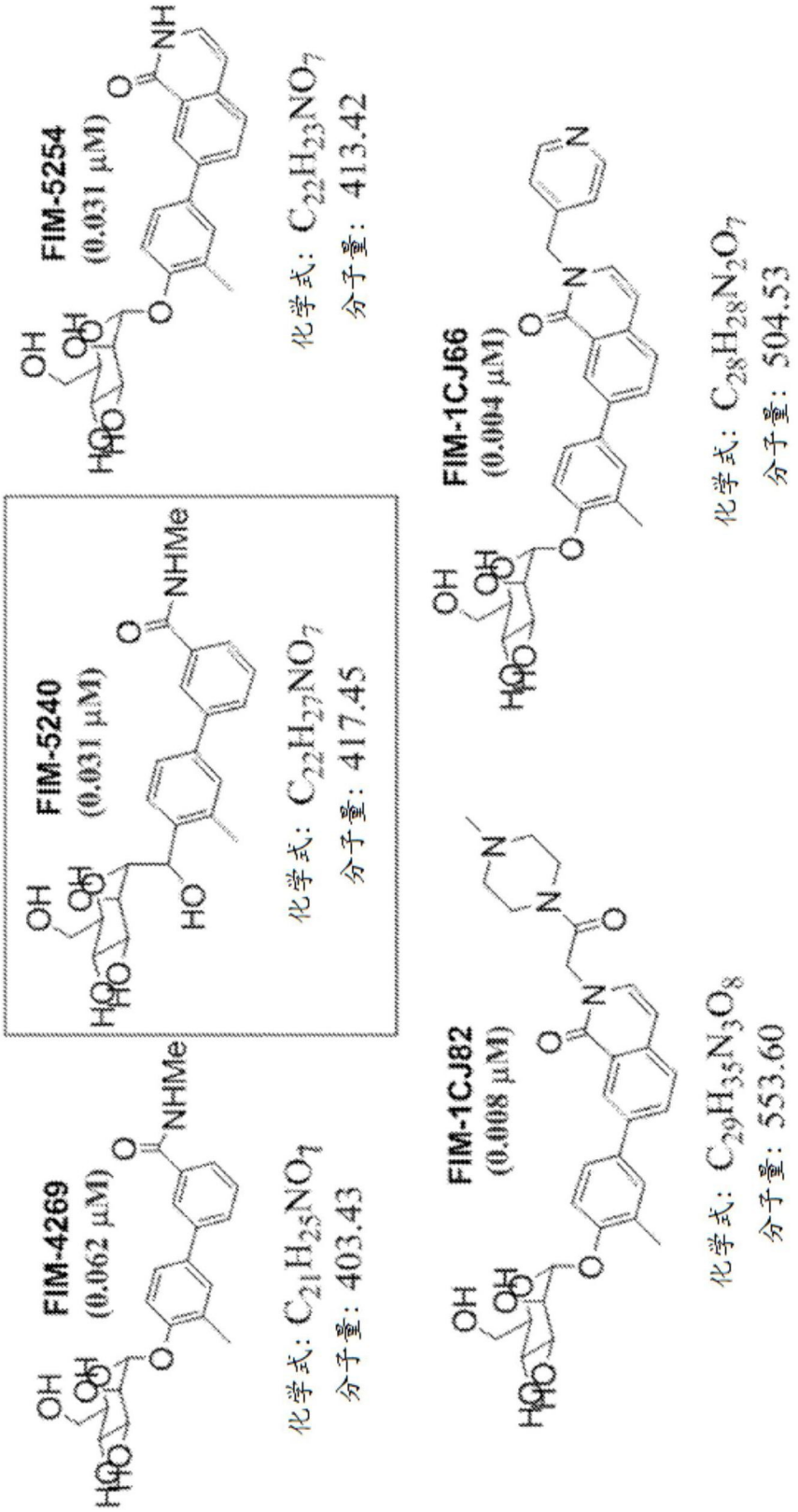

FIM-5254
(0.031 μM)
化学式：$C_{22}H_{23}NO_7$
分子量：413.42
FIM-5240
(0.031 μM)
化学式：$C_{22}H_{27}NO_7$
分子量：417.45
FIM-4269
(0.062 μM)
化学式：$C_{21}H_{25}NO_7$
分子量：403.43
FIM-1CJ66
(0.004 μM)
化学式：$C_{28}H_{28}N_2O_7$
分子量：504.53
FIM-1CJ82
(0.008 μM)
化学式：$C_{29}H_{35}N_3O_8$
分子量：553.60

图3

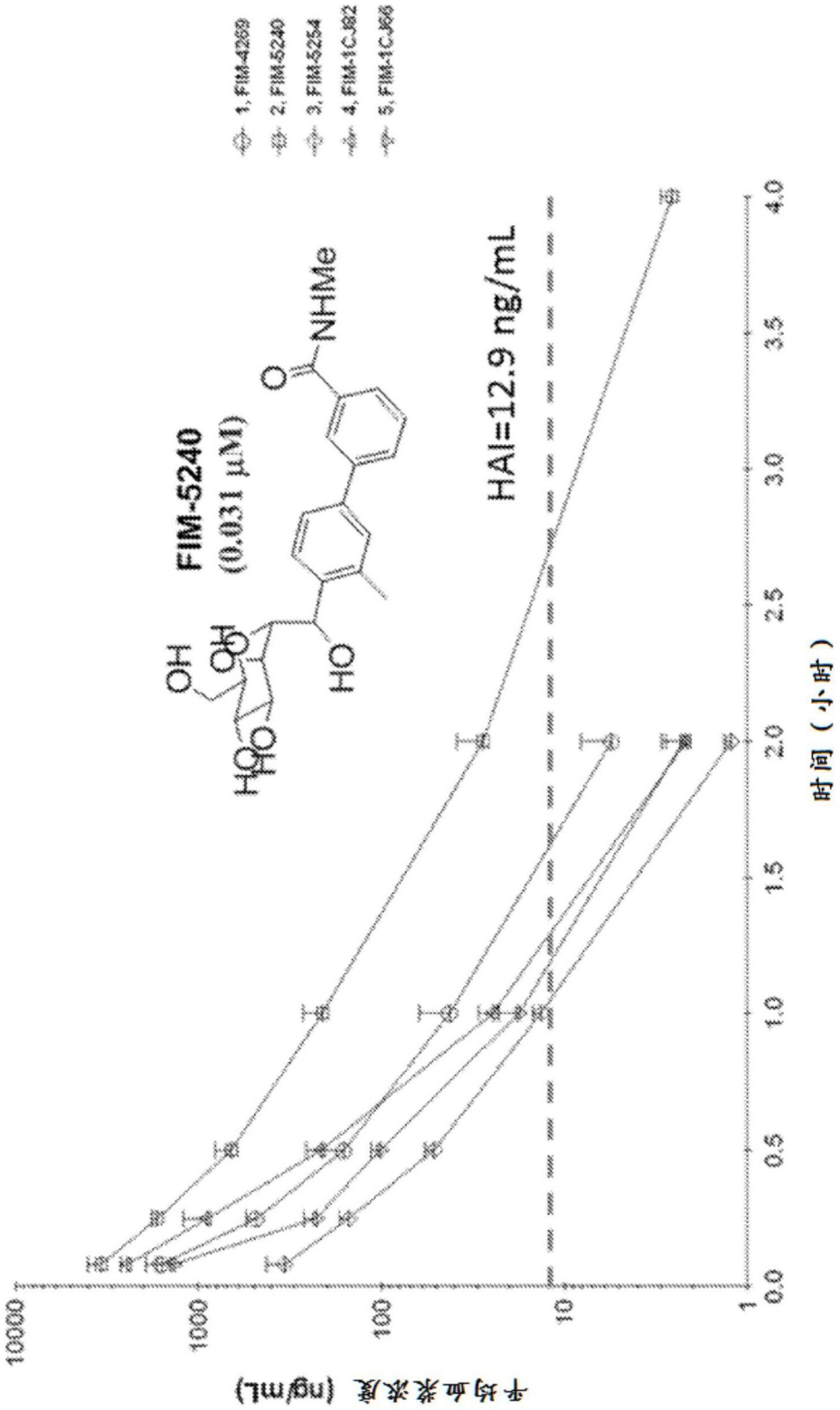

1, FIM-4269
2, FIM-5240
3, FIM-5254
4, FIM-1C-382
5, FIM-1C-366
FIM-5240
(0.031 μM)
NHMe
O
OH
OH
HO
HO
OH
HO
HAI=12.9 ng/mL
平均血浆浓度 (ng/mL)
10000
1000
100
10
1
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
时间（小时）

图4

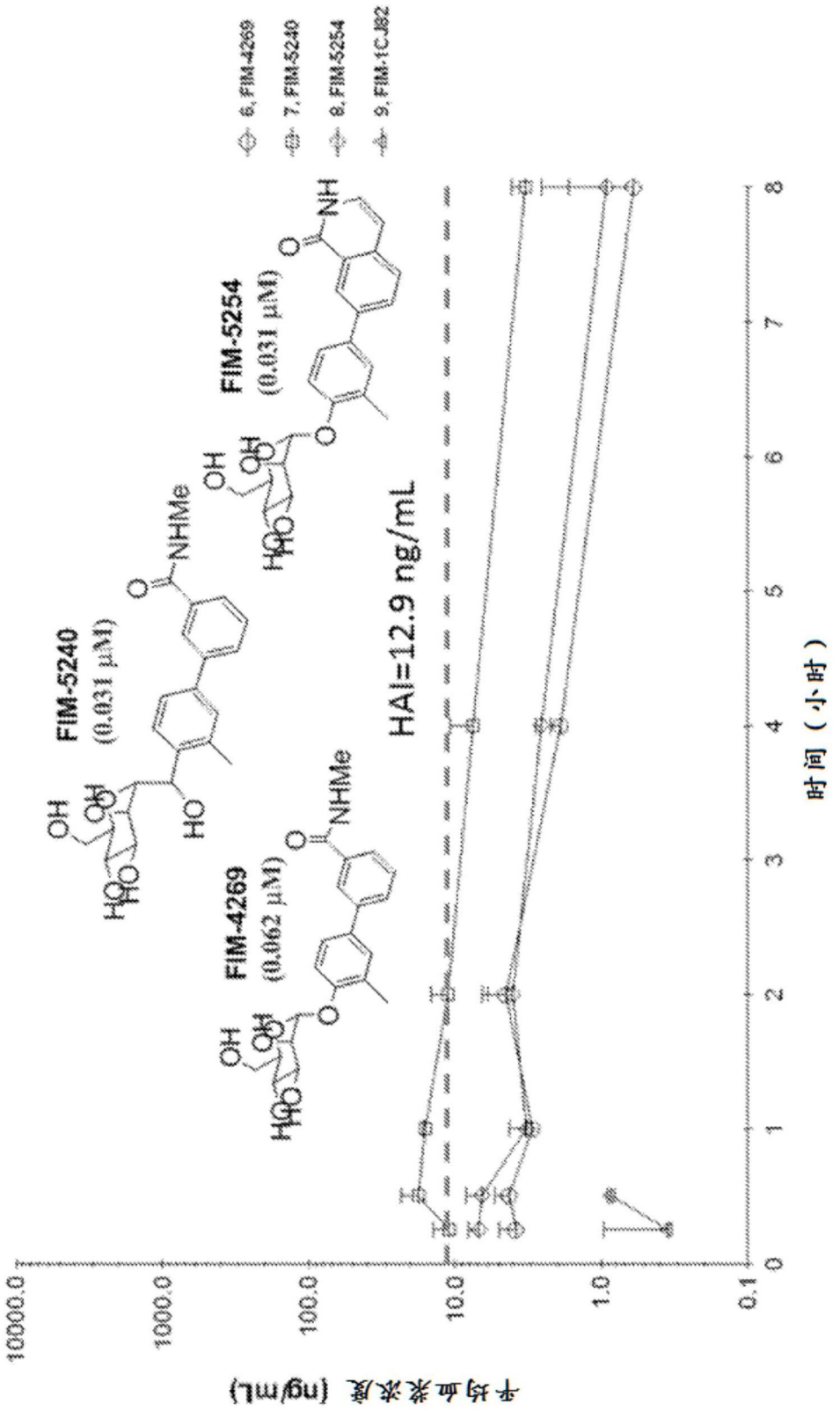

6, FIM-4269
7, FIM-5240
8, FIM-5254
9, FIM-1CJ82
FIM-5254
(0.031 μM)
FIM-5240
(0.031 μM)
FIM-4269
(0.062 μM)
HAI=12.9 ng/mL
平均血浆浓度 (ng/mL)
10000.0
1000.0
100.0
10.0
1.0
0.1
0
1
2
3
4
5
6
7
8
时间（小时）

图5

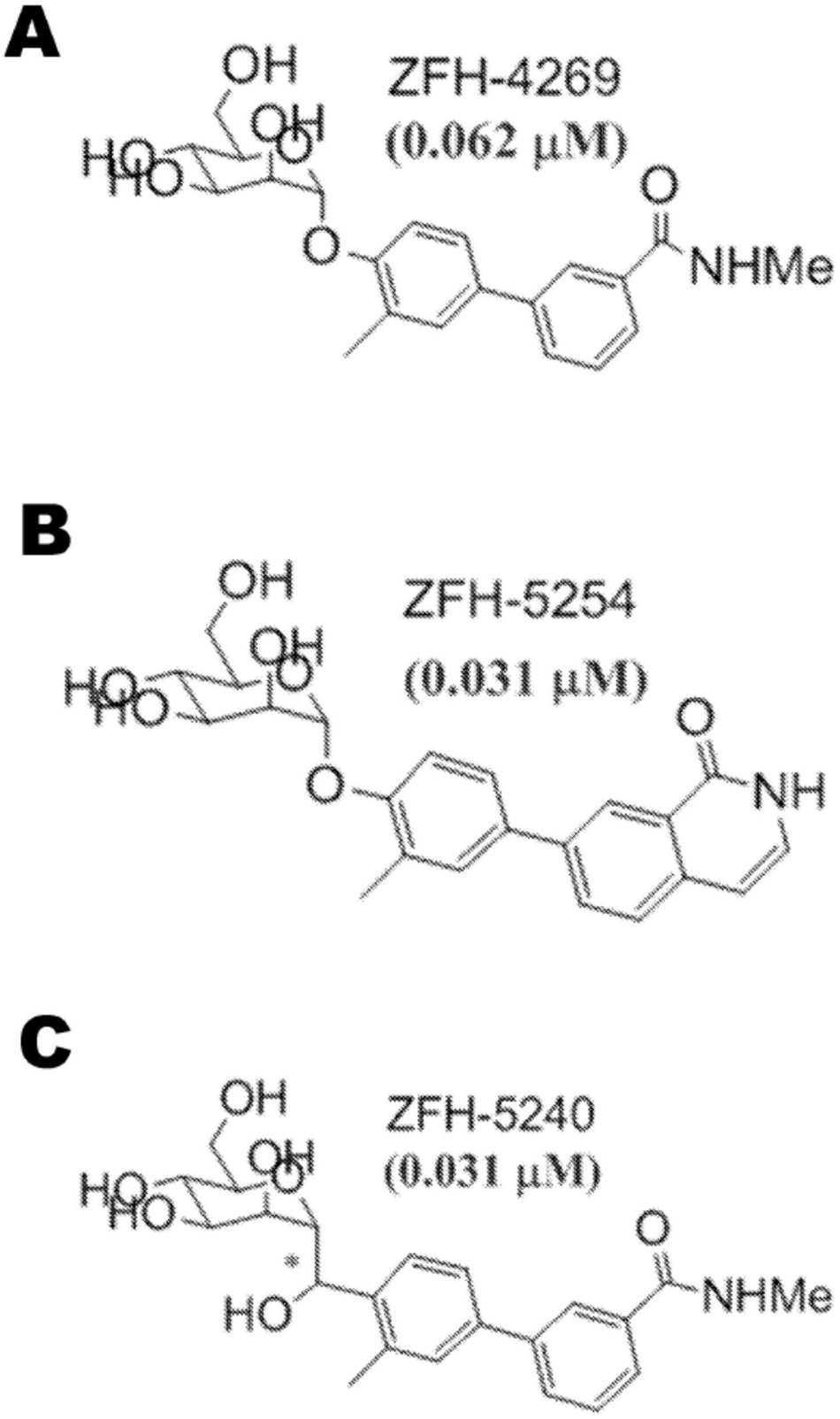

A
ZFH-4269
(0.062 μM)
OH
OH
HO
HO
O
O
NHMe
B
ZFH-5254
(0.031 μM)
OH
OH
HO
HO
O
O
NH
C
ZFH-5240
(0.031 μM)
OH
OH
HO
HO
*
HO
O
NHMe

图6

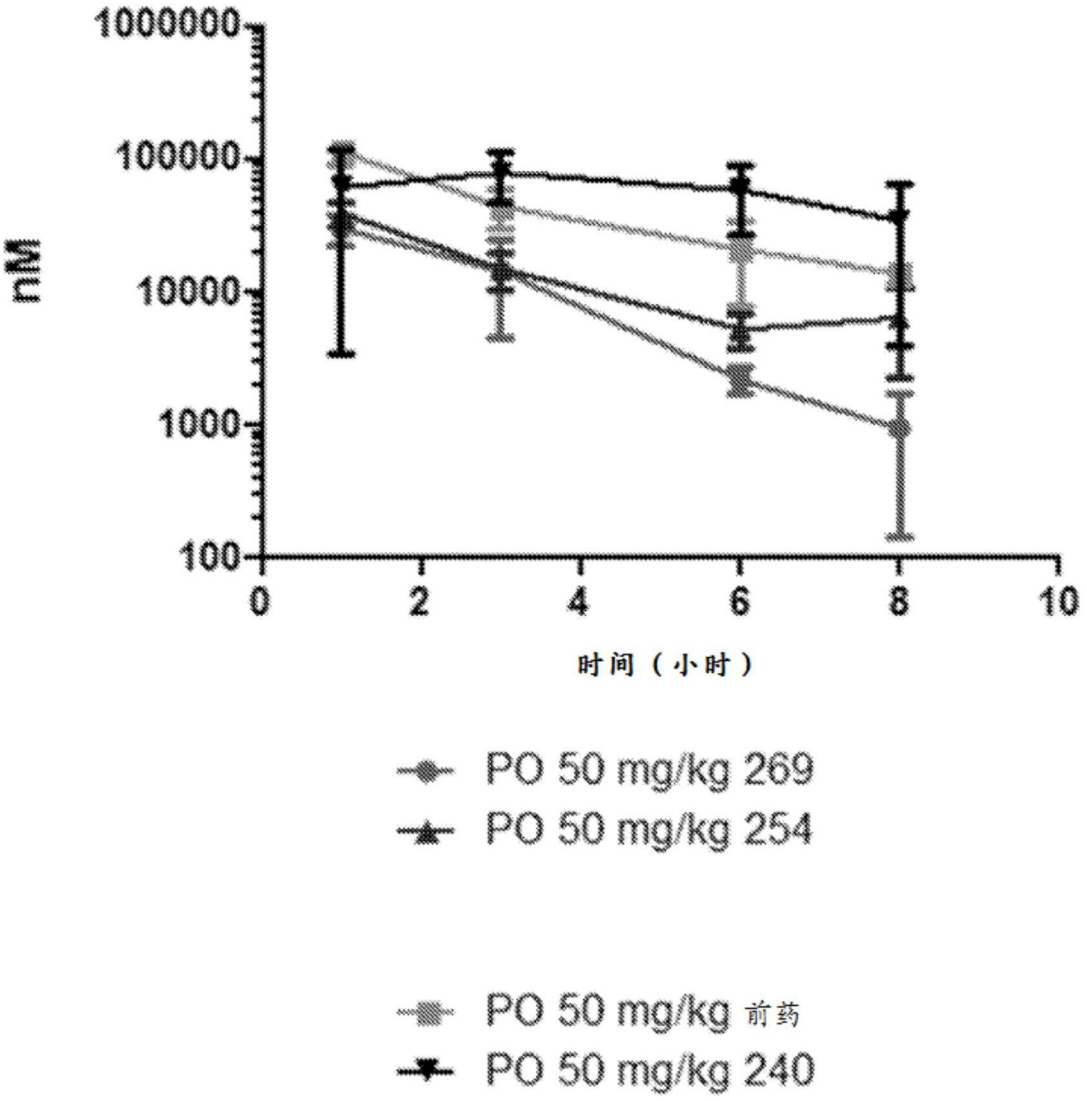

1000000
100000
10000
1000
100
nM
0
2
4
6
8
10
时间（小时）
PO 50 mg/kg 269
PO 50 mg/kg 254
PO 50 mg/kg 前药
PO 50 mg/kg 240

图6D

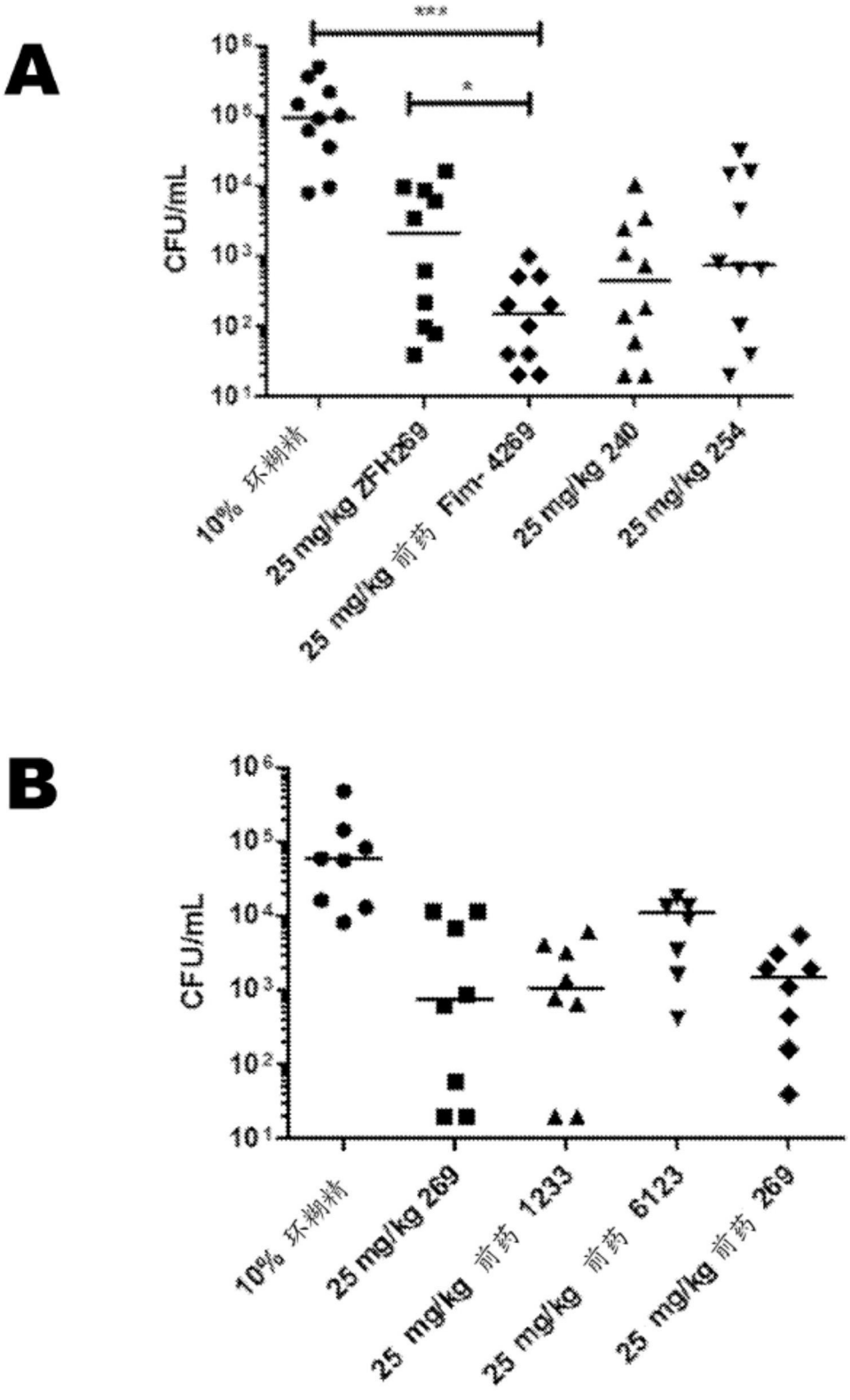

A
***
*
CFU/mL
10^6
10^5
10^4
10^3
10^2
10^1
10% 环糊精
25 mg/kg ZFH269
25 mg/kg 前药 Fim- 4269
25 mg/kg 240
25 mg/kg 254
B
CFU/mL
10^6
10^5
10^4
10^3
10^2
10^1
10% 环糊精
25 mg/kg 269
25 mg/kg 前药 1233
25 mg/kg 前药 6123
25 mg/kg 前药 269

图7

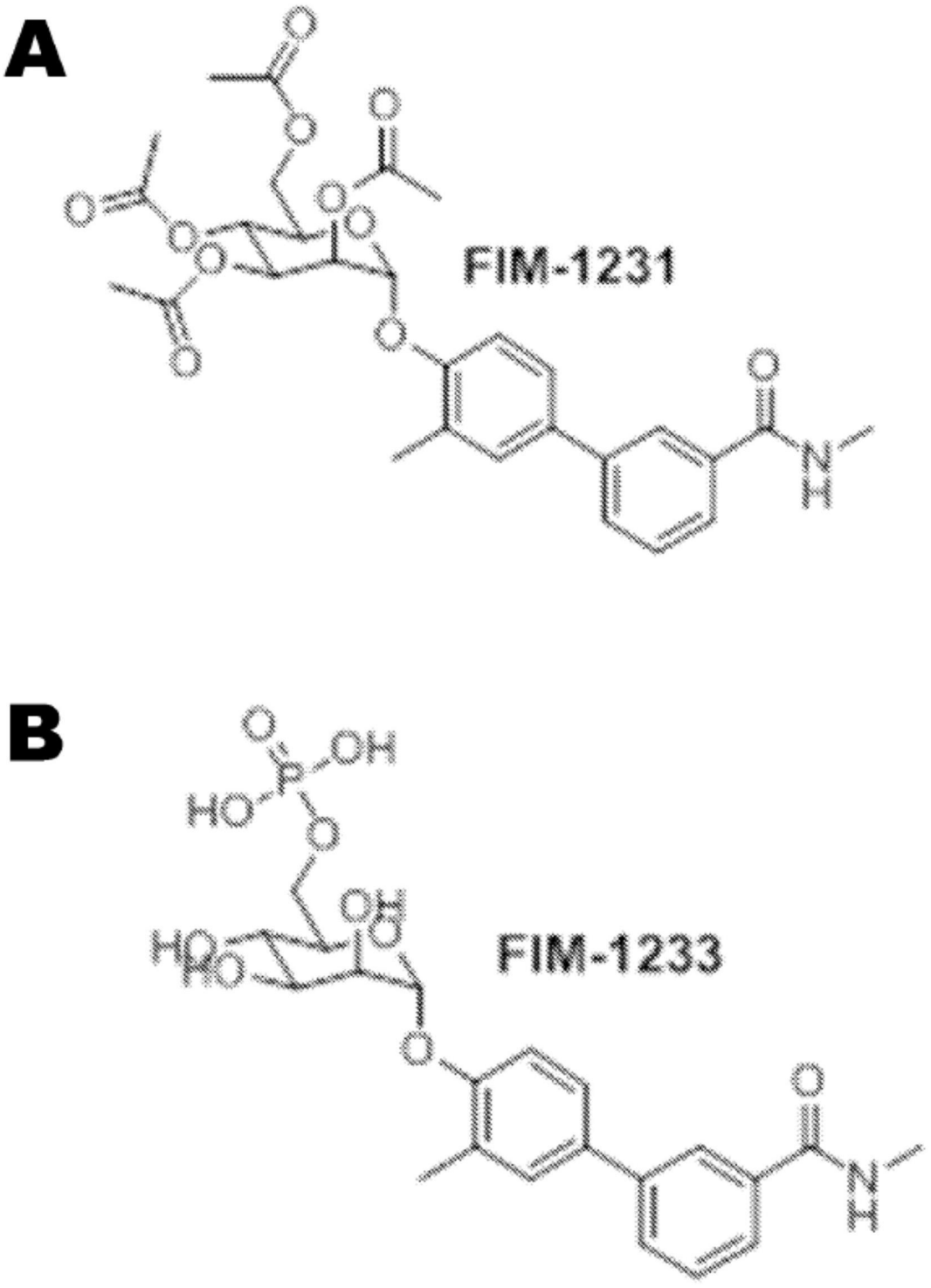


图8

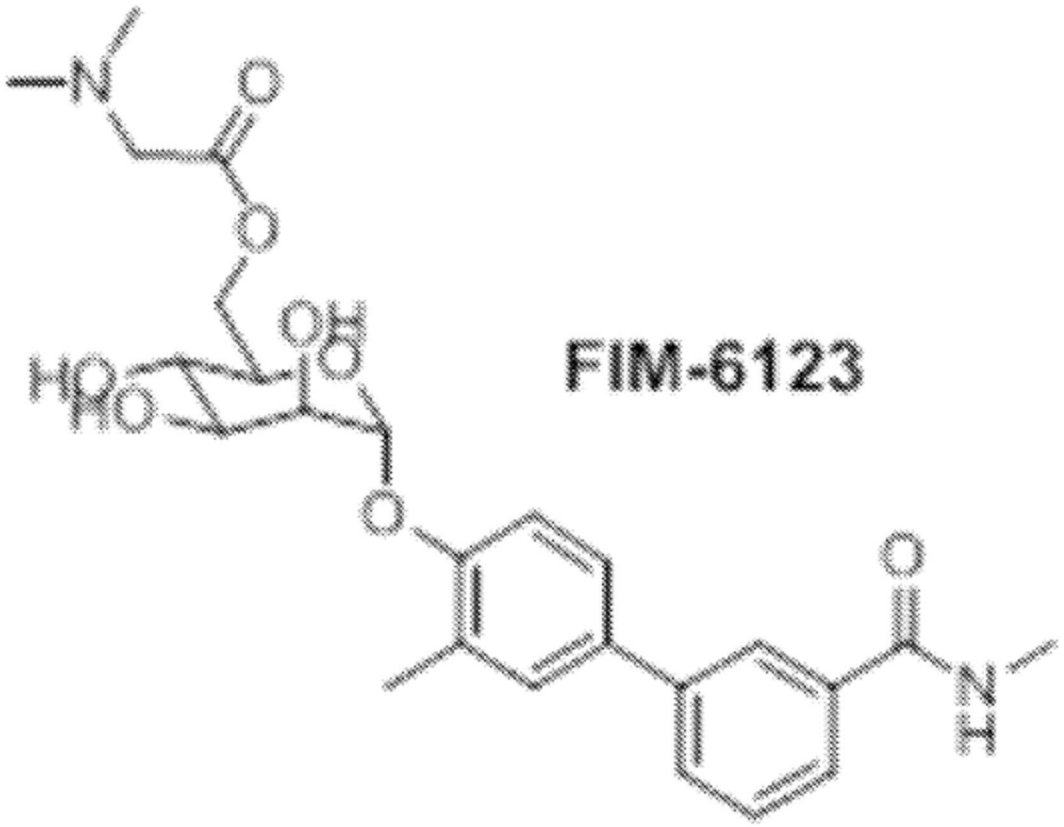
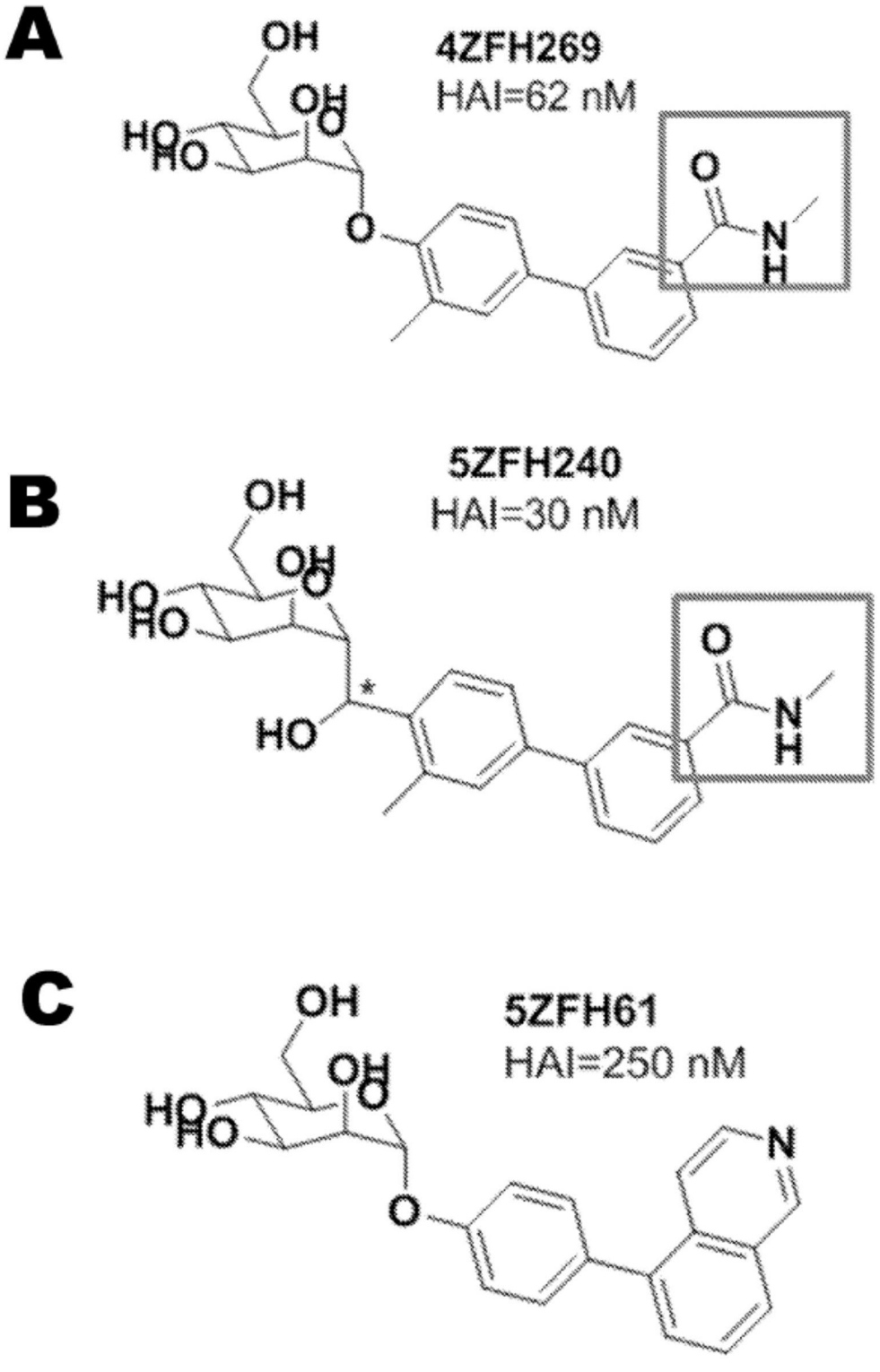


图8C


A
4ZFH269
HAI=62 nM
B
5ZFH240
HAI=30 nM
C
5ZFH61
HAI=250 nM

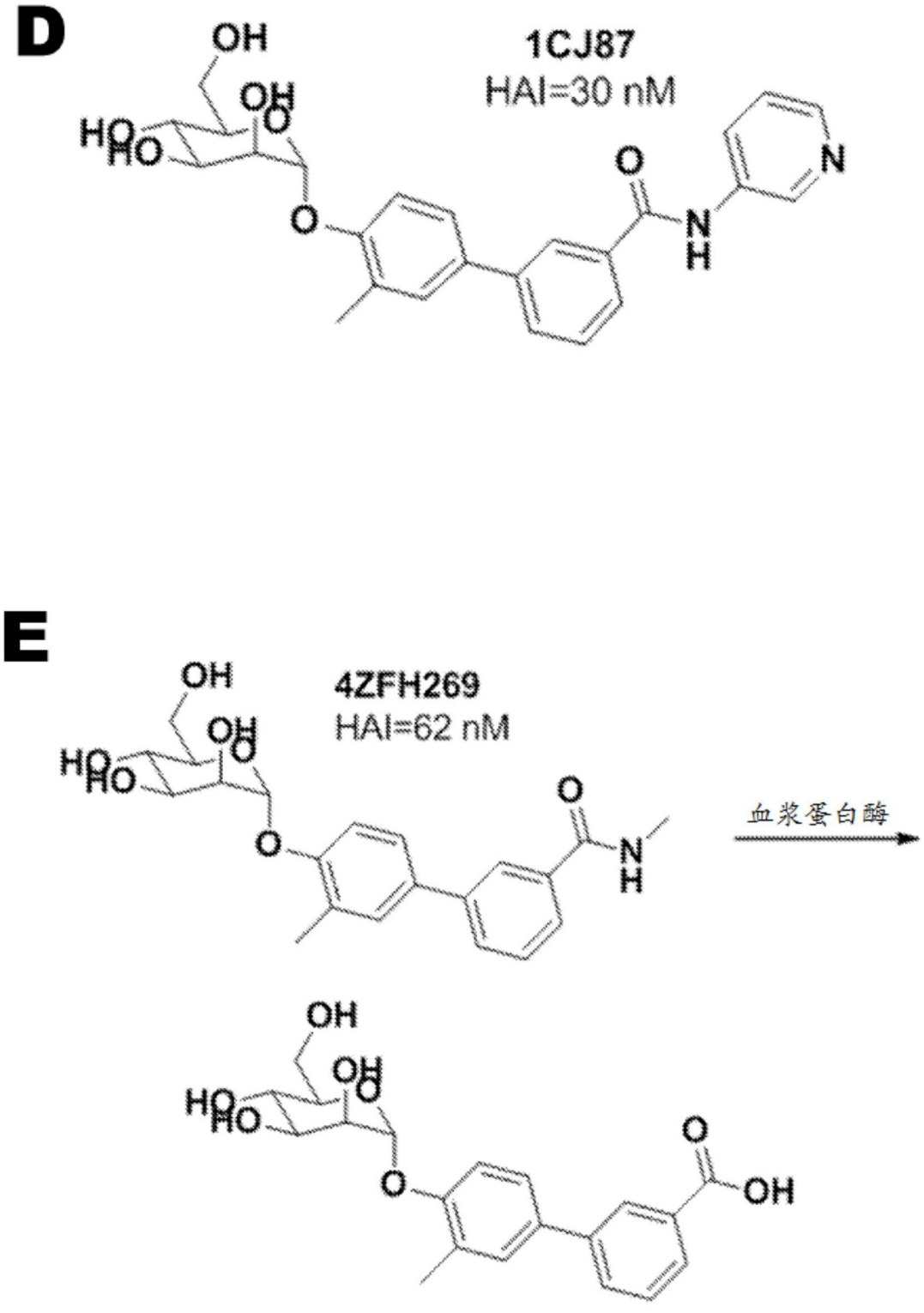


图9

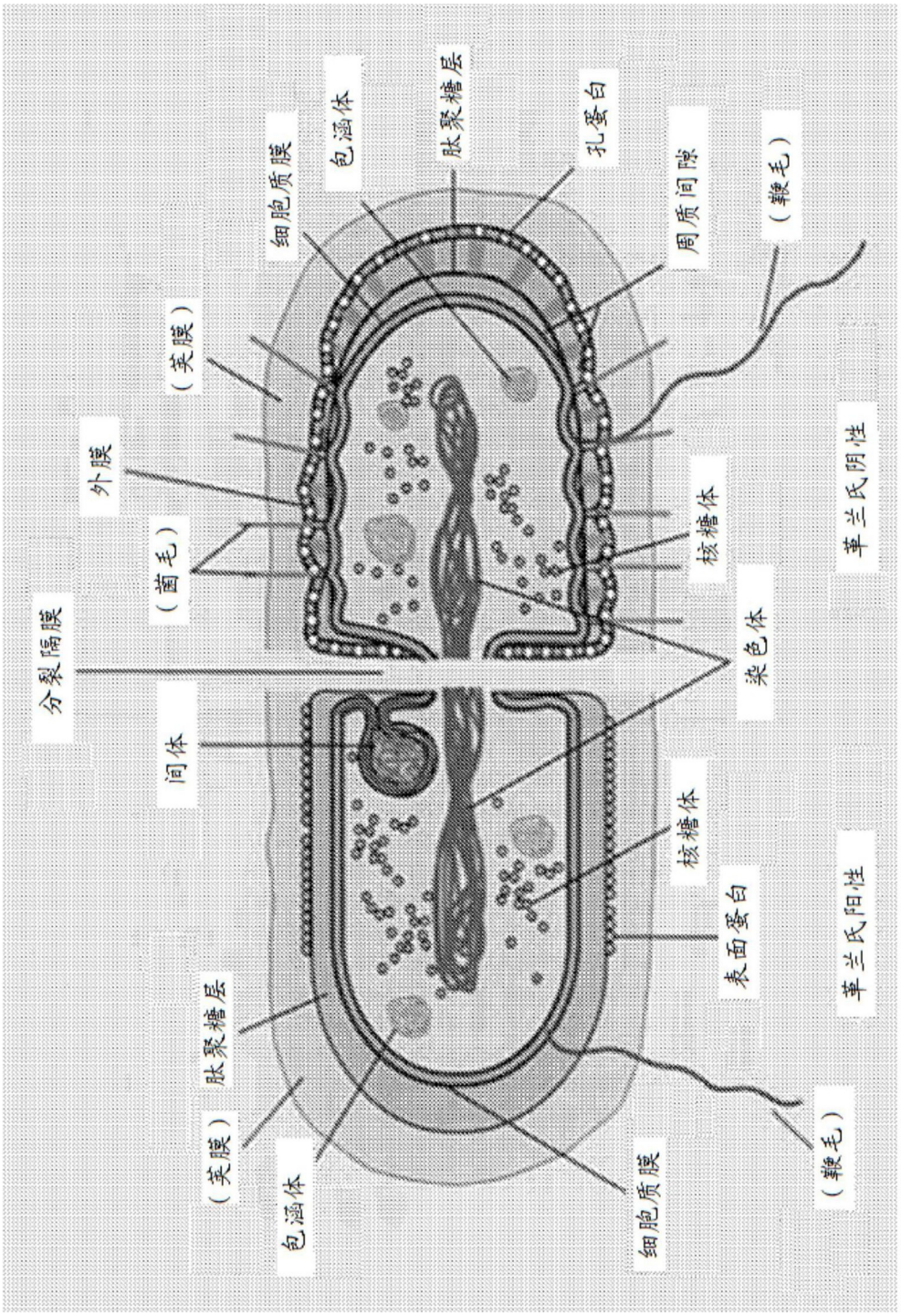

分裂隔膜
外膜
（菌毛）
（荚膜）
细胞质膜
包涵体
肽聚糖层
孔蛋白
周质间隙
（鞭毛）
革兰氏阴性
核糖体
染色体
间体
核糖体
表面蛋白
革兰氏阳性
肽聚糖层
（荚膜）
包涵体
细胞质膜
（鞭毛）

图10A

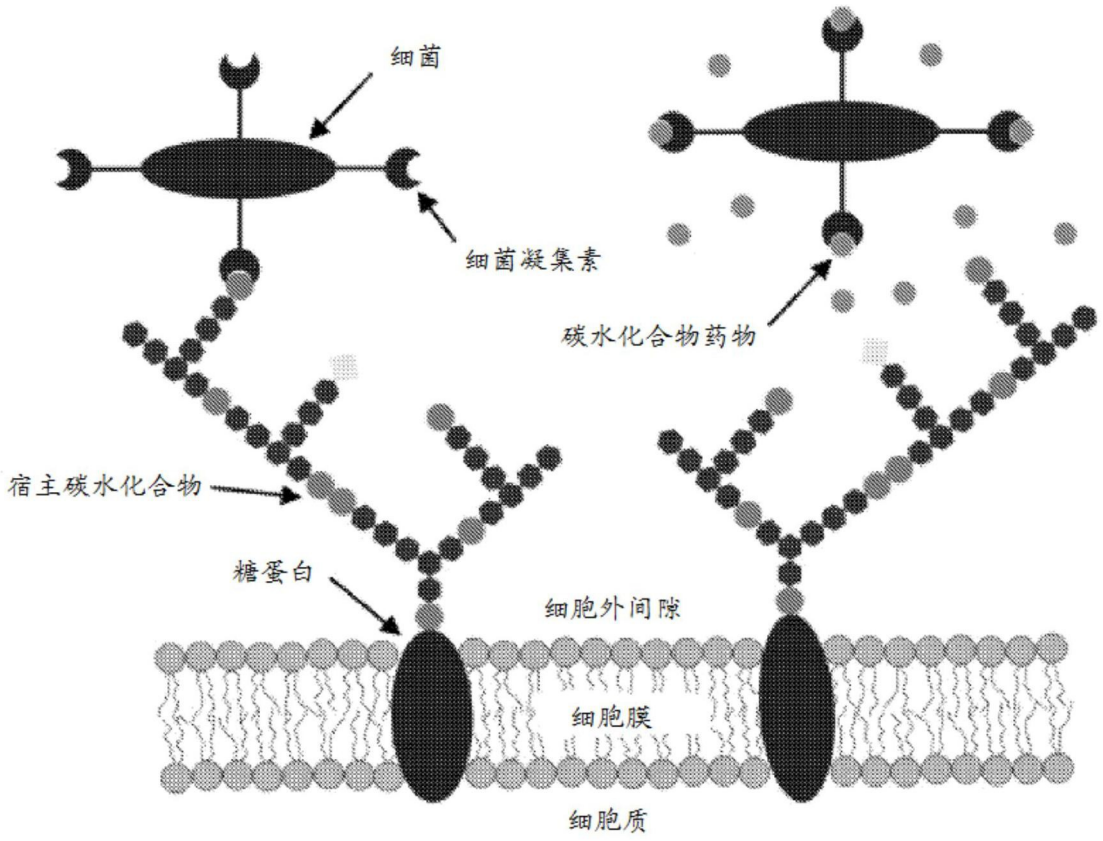


图10B

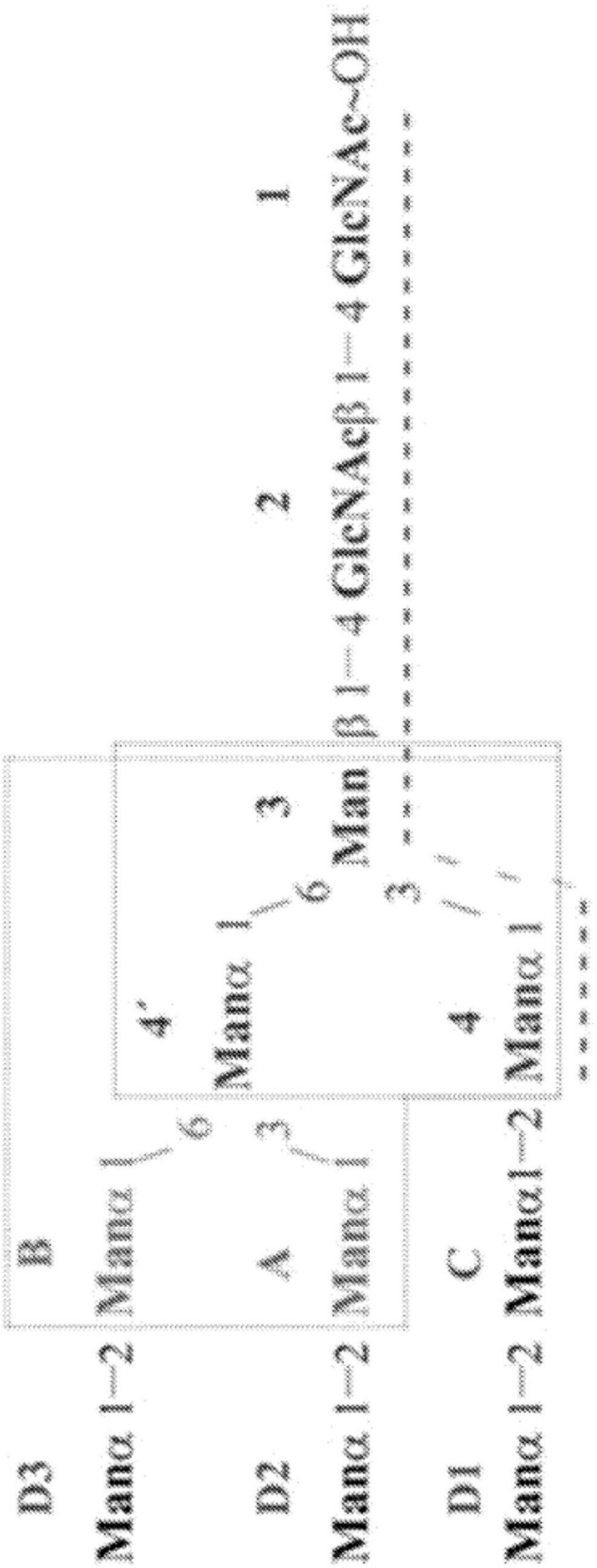

D3
Manα1—2
B
Manα1
6
D2
Manα1—2
A
Manα1
3
D1
Manα1—2
C
Manα1
4'
Manα1
6
3
Man
3
4
Manα1
2
β1—4GlcNAcβ1—4GlcNAc~OH
1

图10C

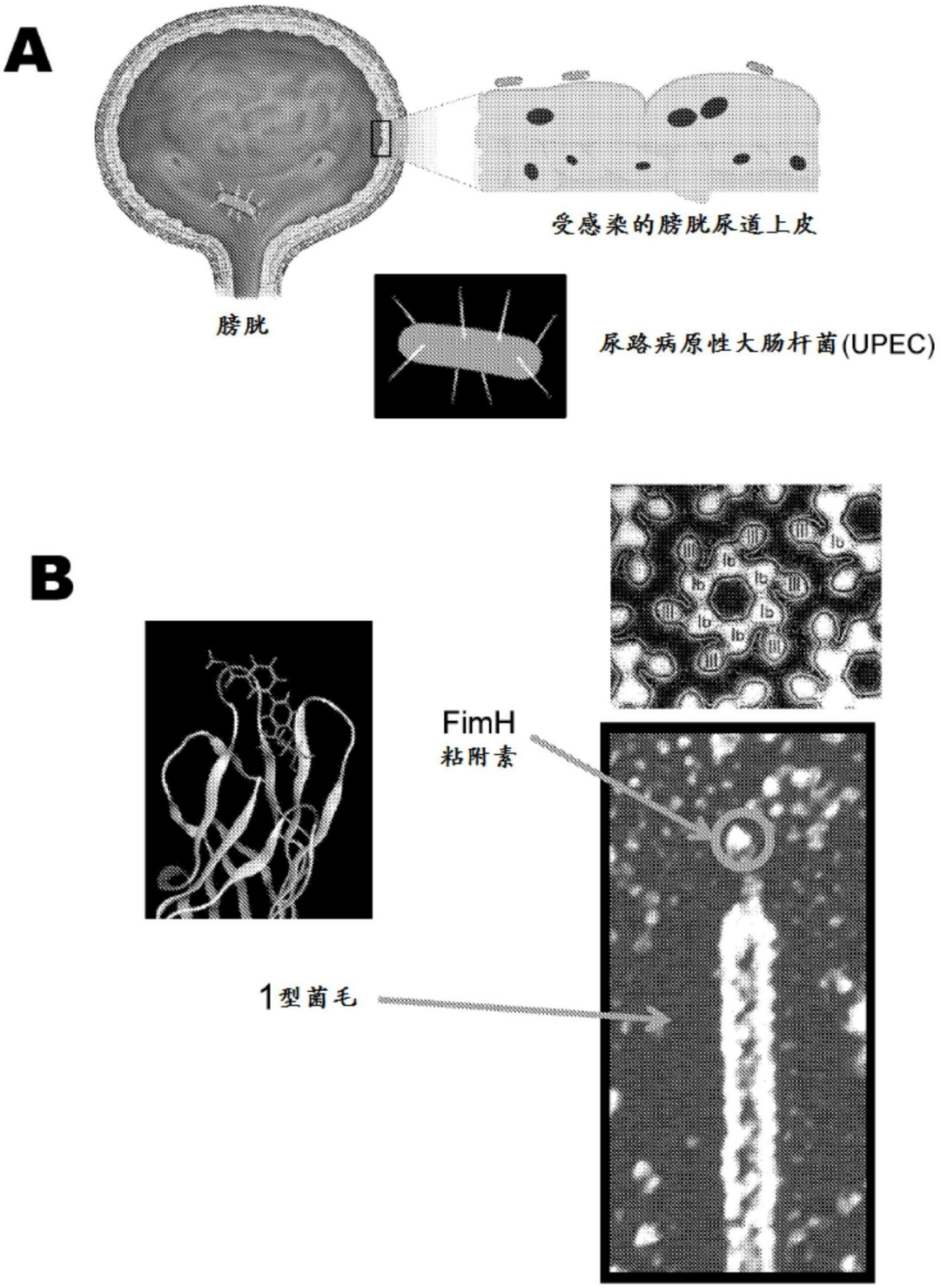


图11

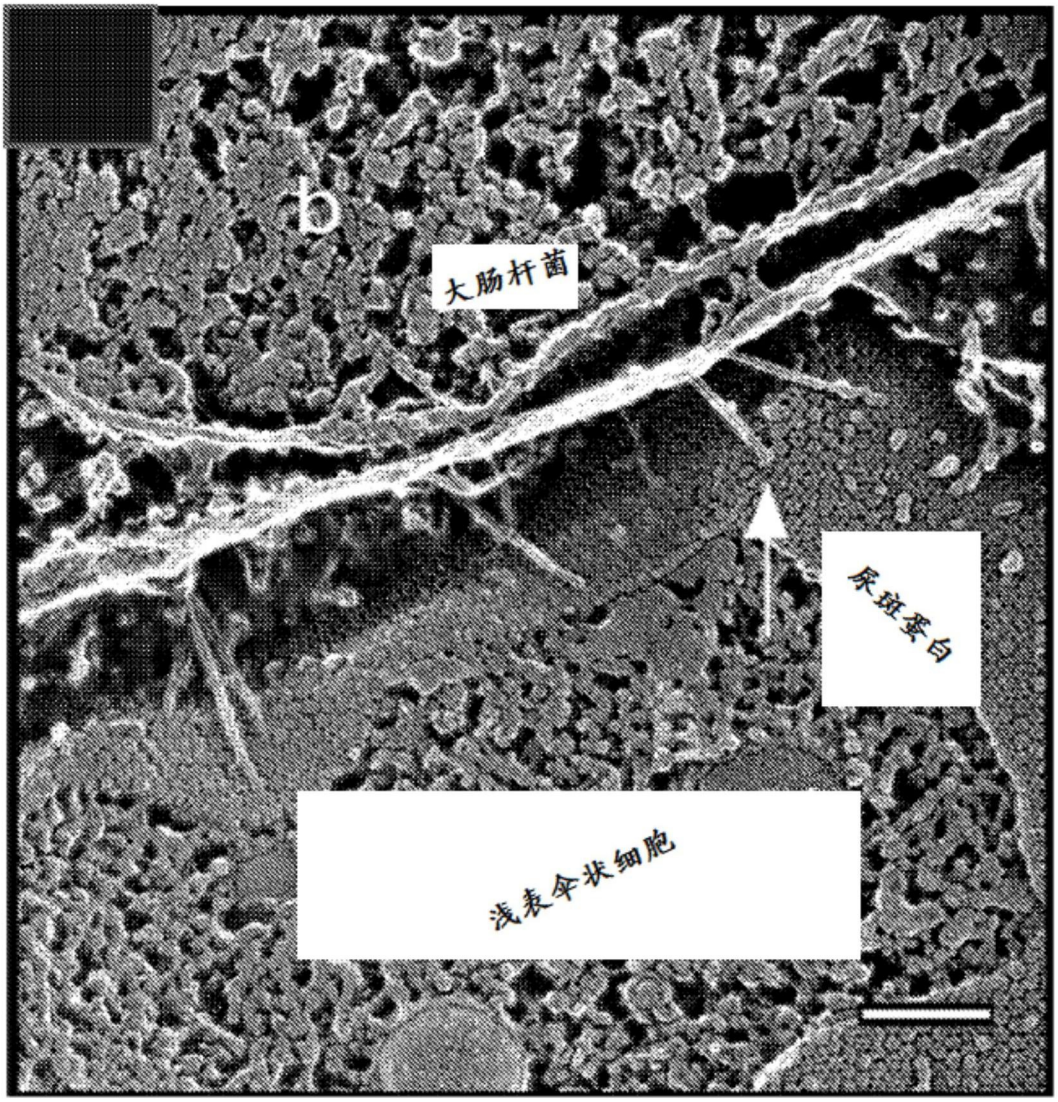


图11C

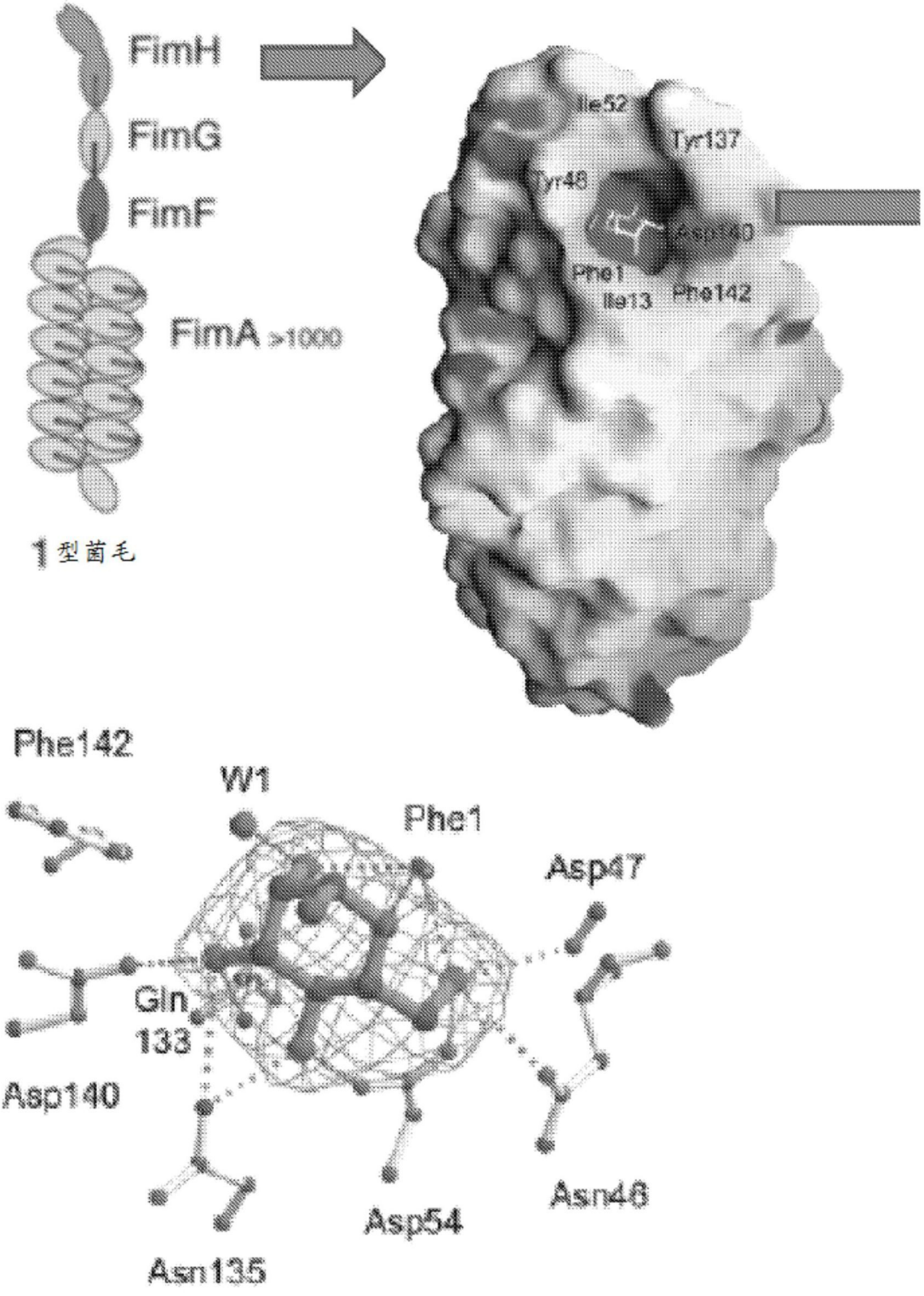

FimH
FimG
FimF
FimA >1000
1型菌毛
Ile52
Tyr137
Tyr48
Asp140
Phe1
Ile13
Phe142
Phe142
W1
Phe1
Asp47
Gln
133
Asp140
Asn46
Asp54
Asn135

图12A

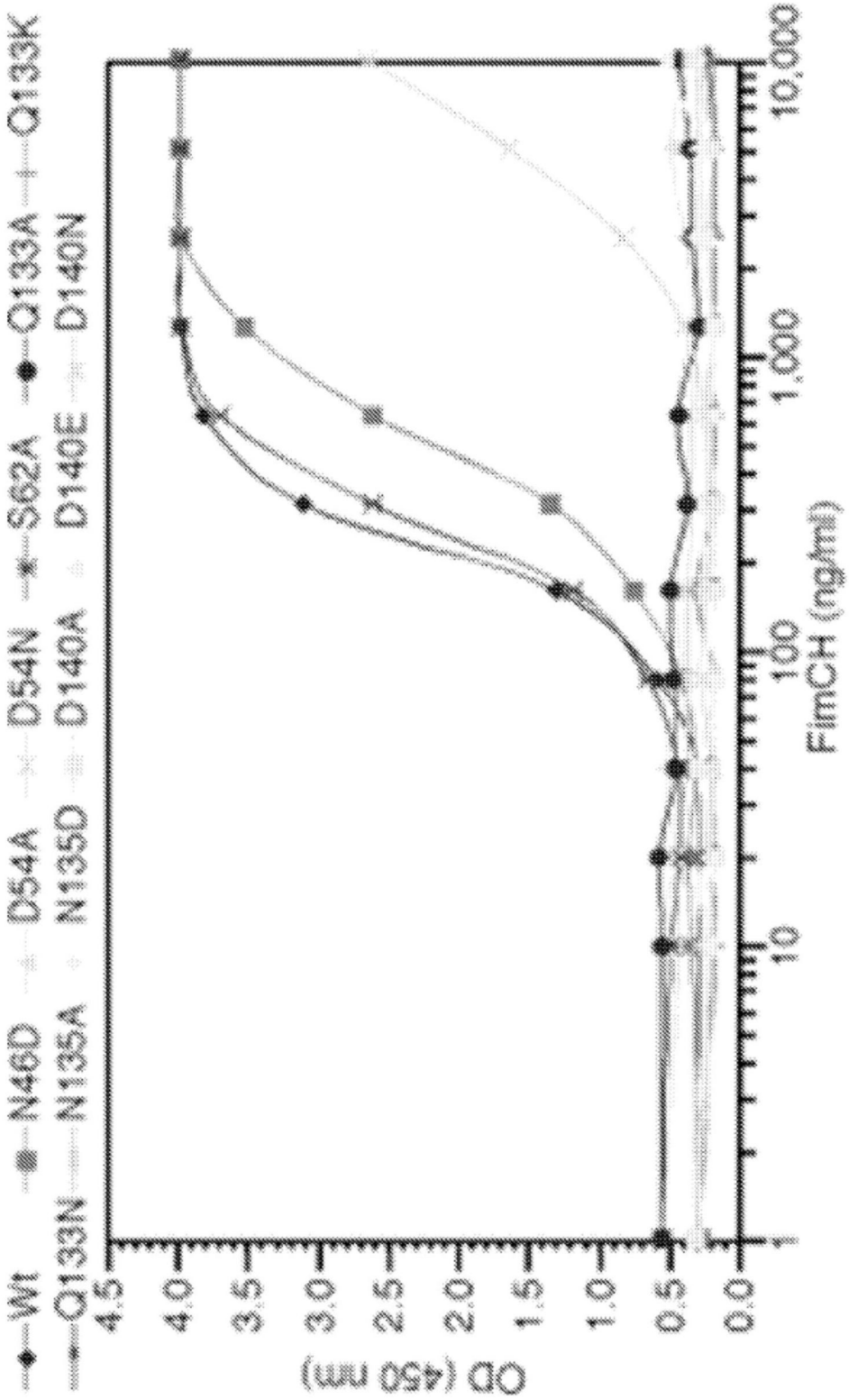

Wt
Q133N
N46D
N135A
D54A
N135D
D54N
D140A
S62A
D140E
Q133A
D140N
Q133K
OD (450 nm)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
FimCH (ng/ml)
10,000
1,000
100
10
1

图12B

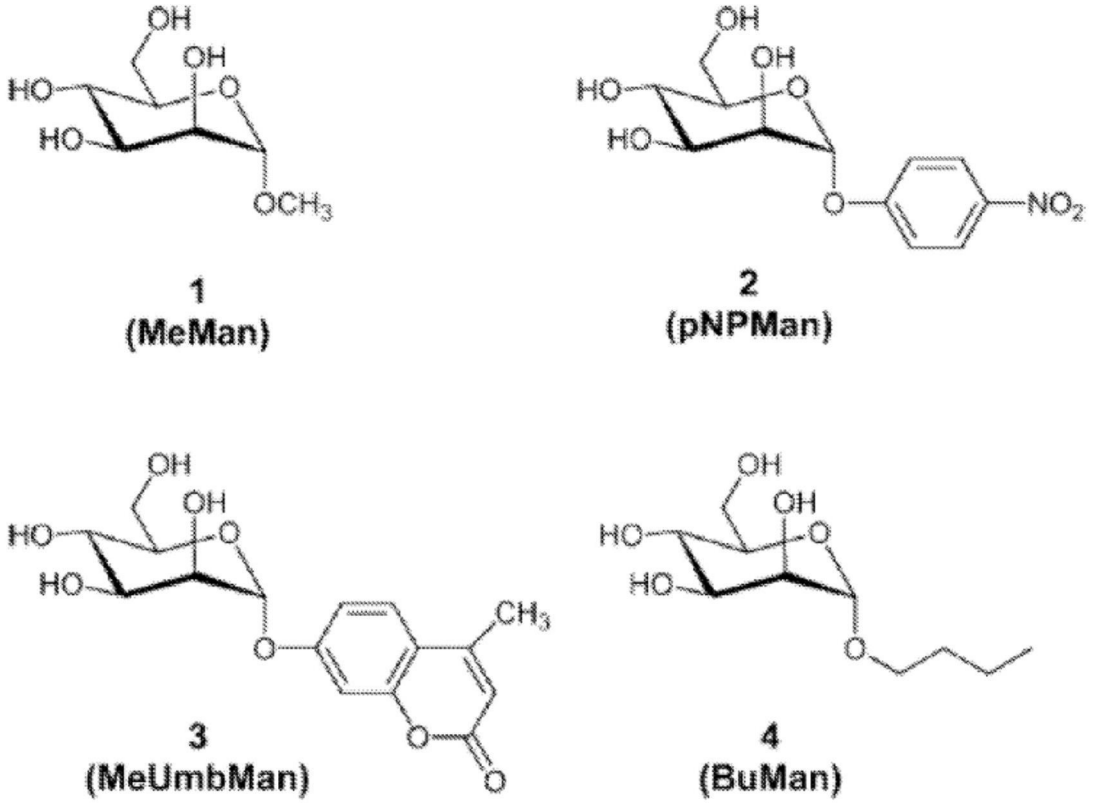

OH
OH
HO
HO
O
OCH3
1
(MeMan)
OH
OH
HO
HO
O
O
NO2
2
(pNPMan)
OH
OH
HO
HO
O
O
CH3
O
O
3
(MeUmbMan)
OH
OH
HO
HO
O
O
4
(BuMan)

图13

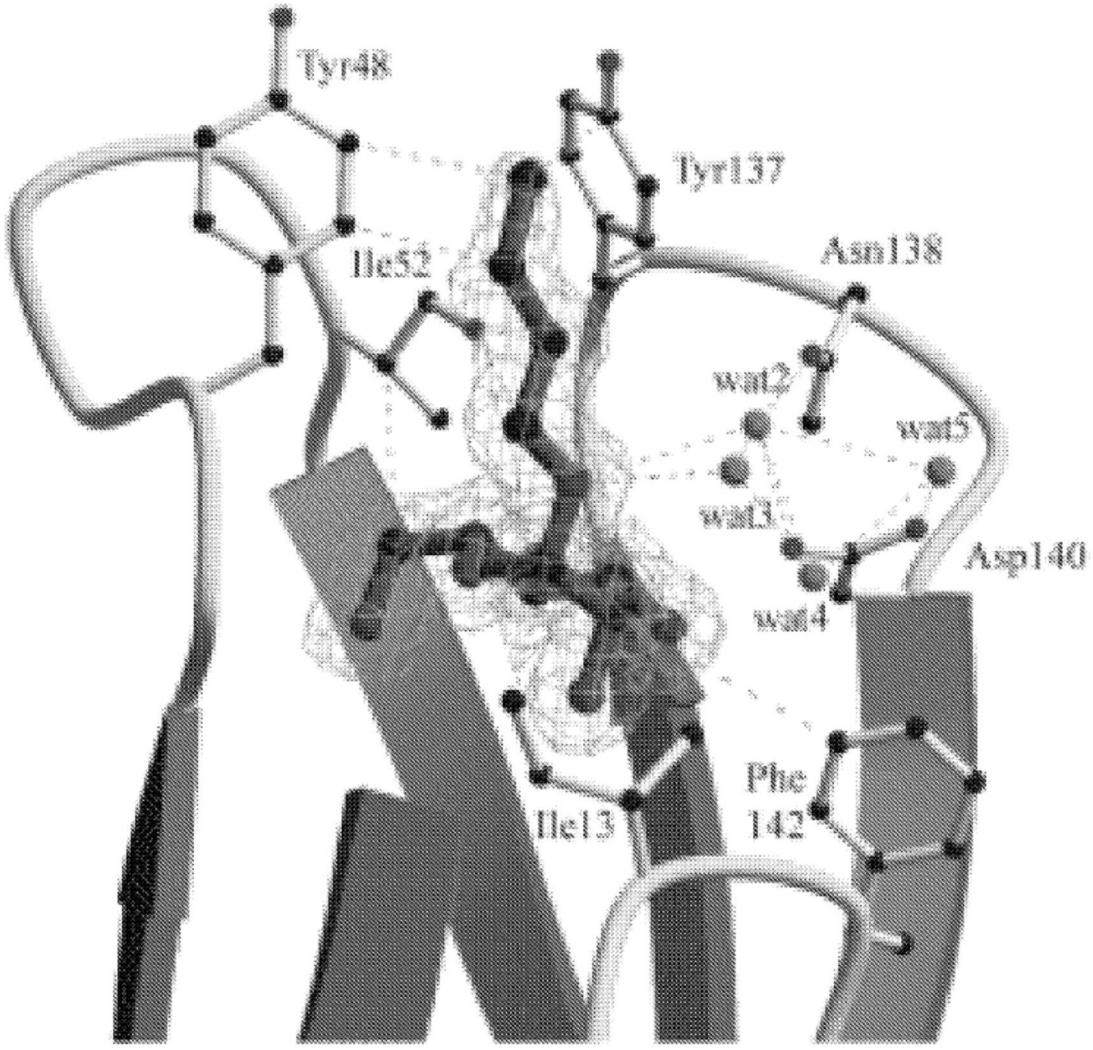

Tyr48
Tyr137
Ile52
Asn138
wat2
wat5
wat3
Asp140
wat4
Phe
142
Ile13

图14

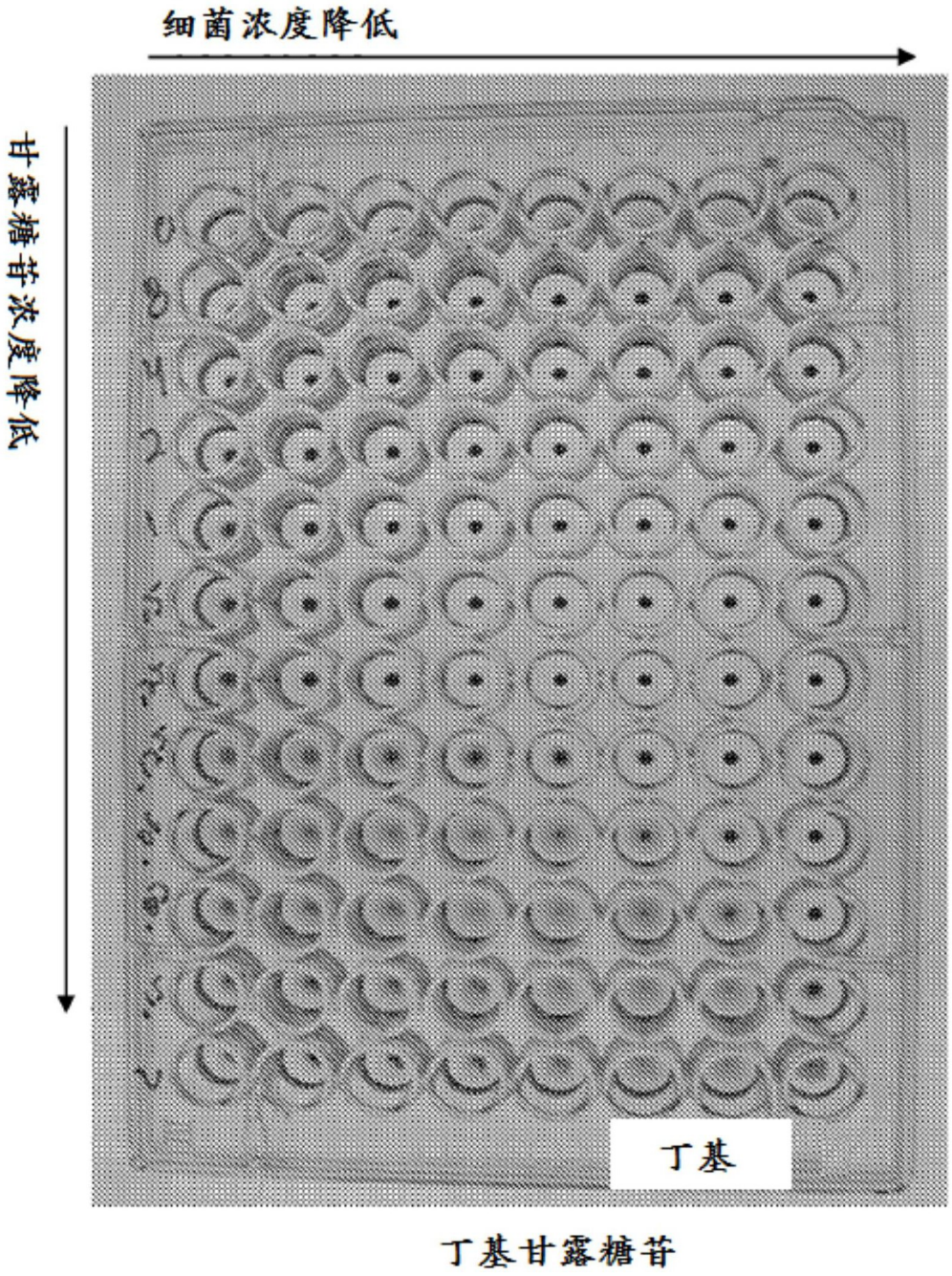


图15

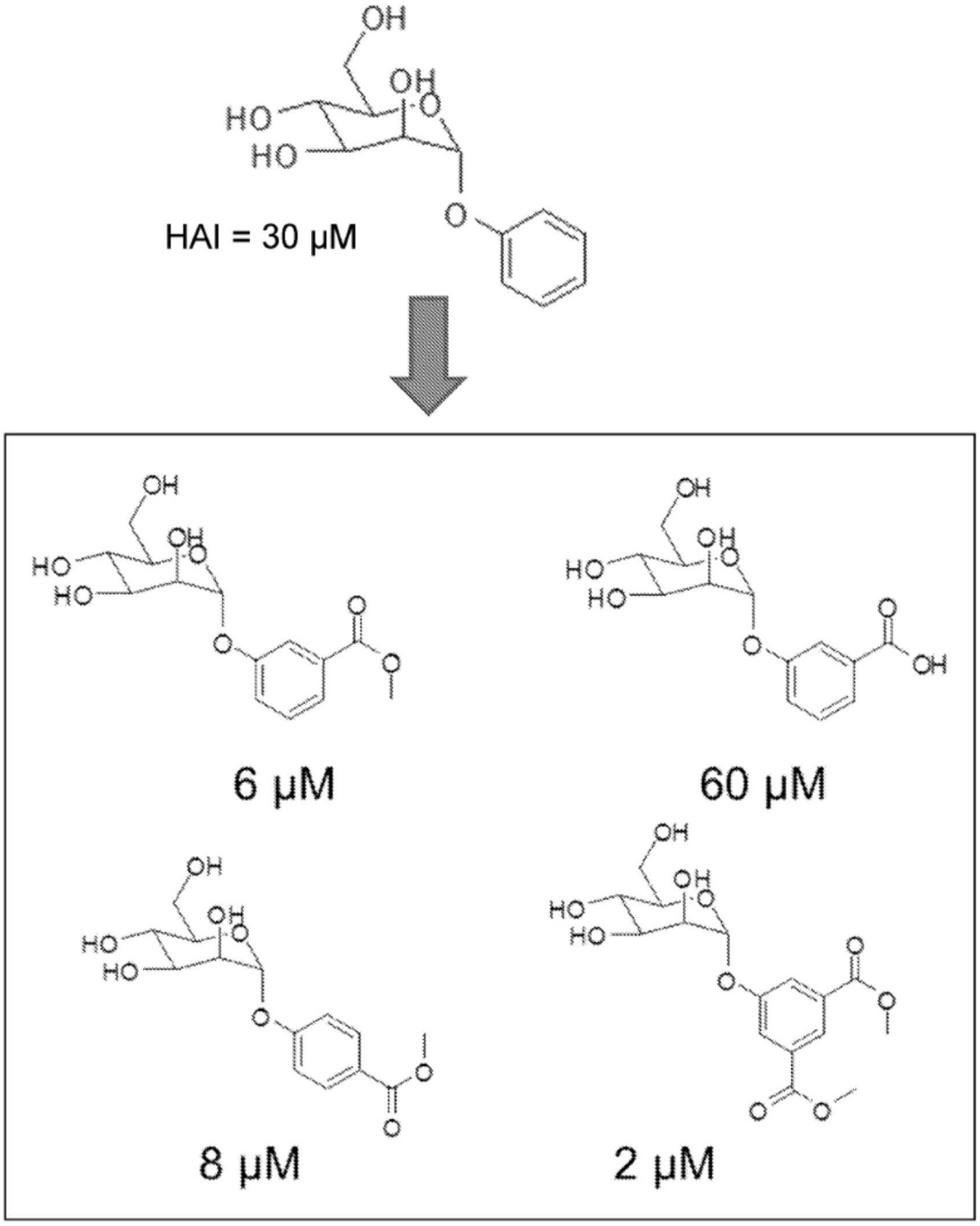


图16A

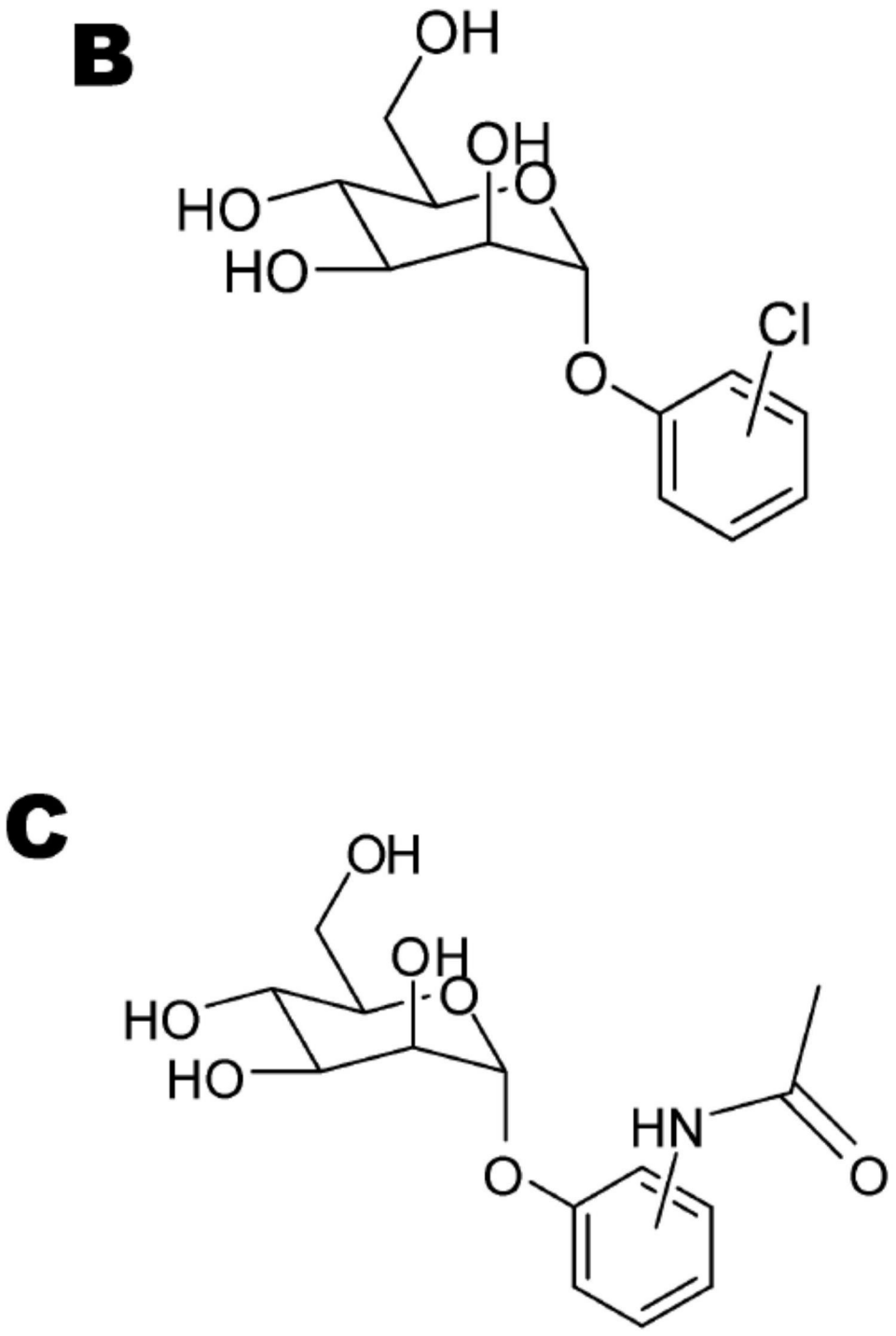


图16

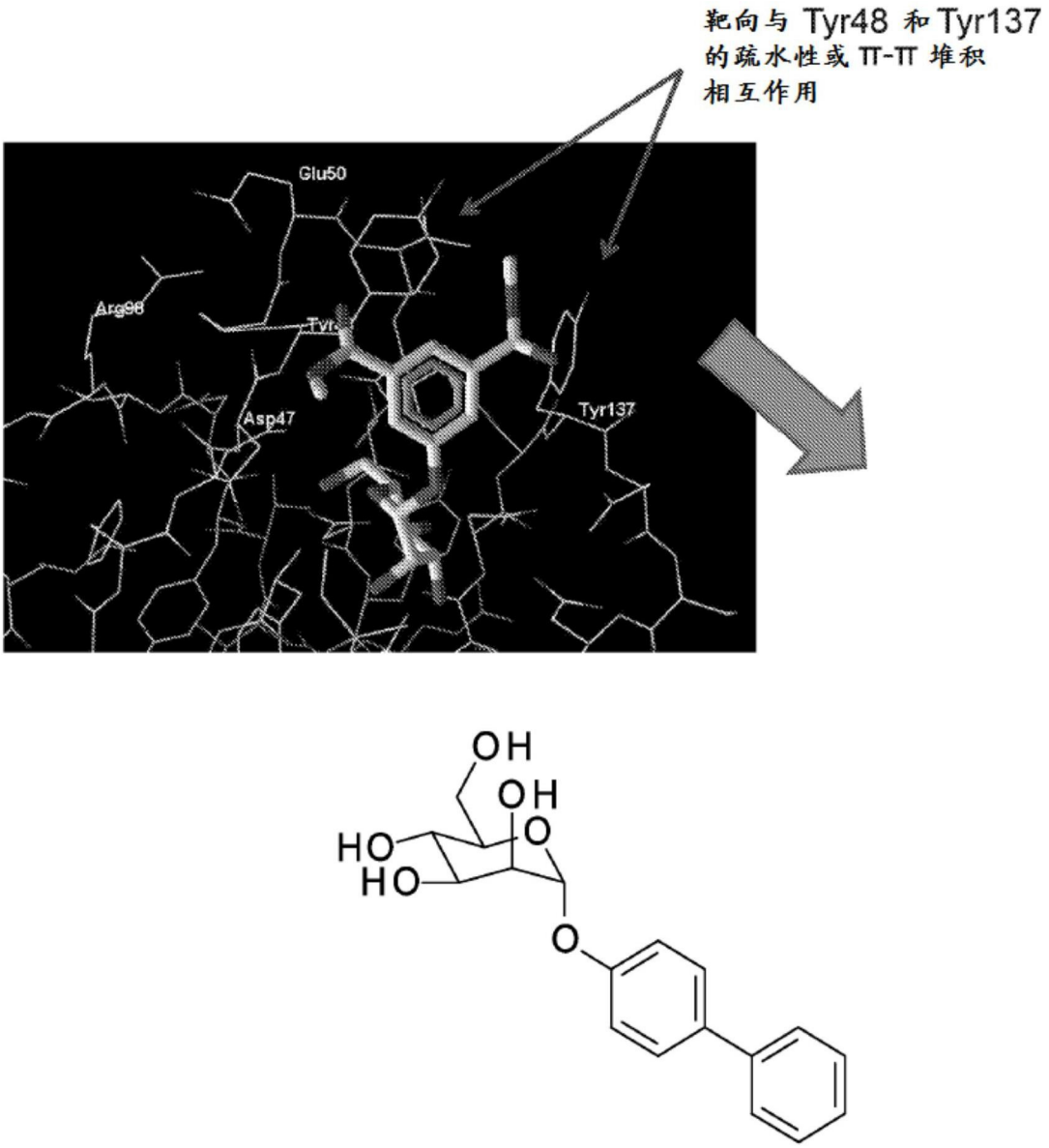
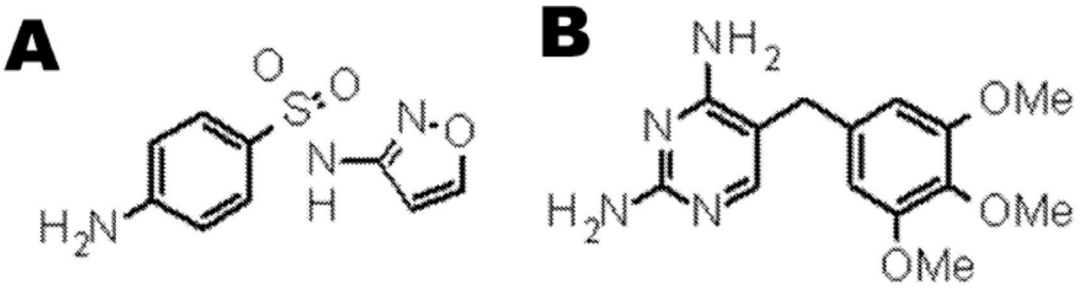
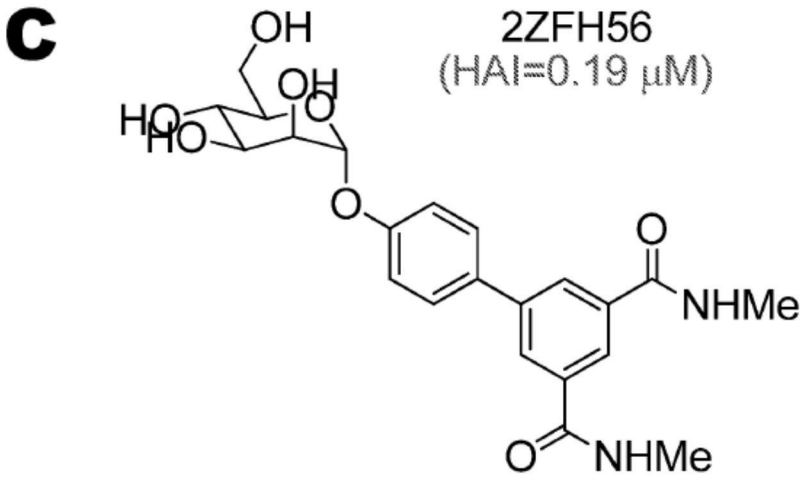

靶向与 Tyr48 和 Tyr137
的疏水性或 π-π 堆积
相互作用
Glu50
Arg98
Tyr
Asp47
Tyr137
OH
OH
O
HO
HO
O

图17


A
O
S
O
N
O
N
H
H2N
B
NH2
N
H2N
N
OMe
OMe
OMe


C
2ZFH56
(HAI=0.19 μM)
OH
OH
HO
HO
O
O
O
NHMe
O
NHMe

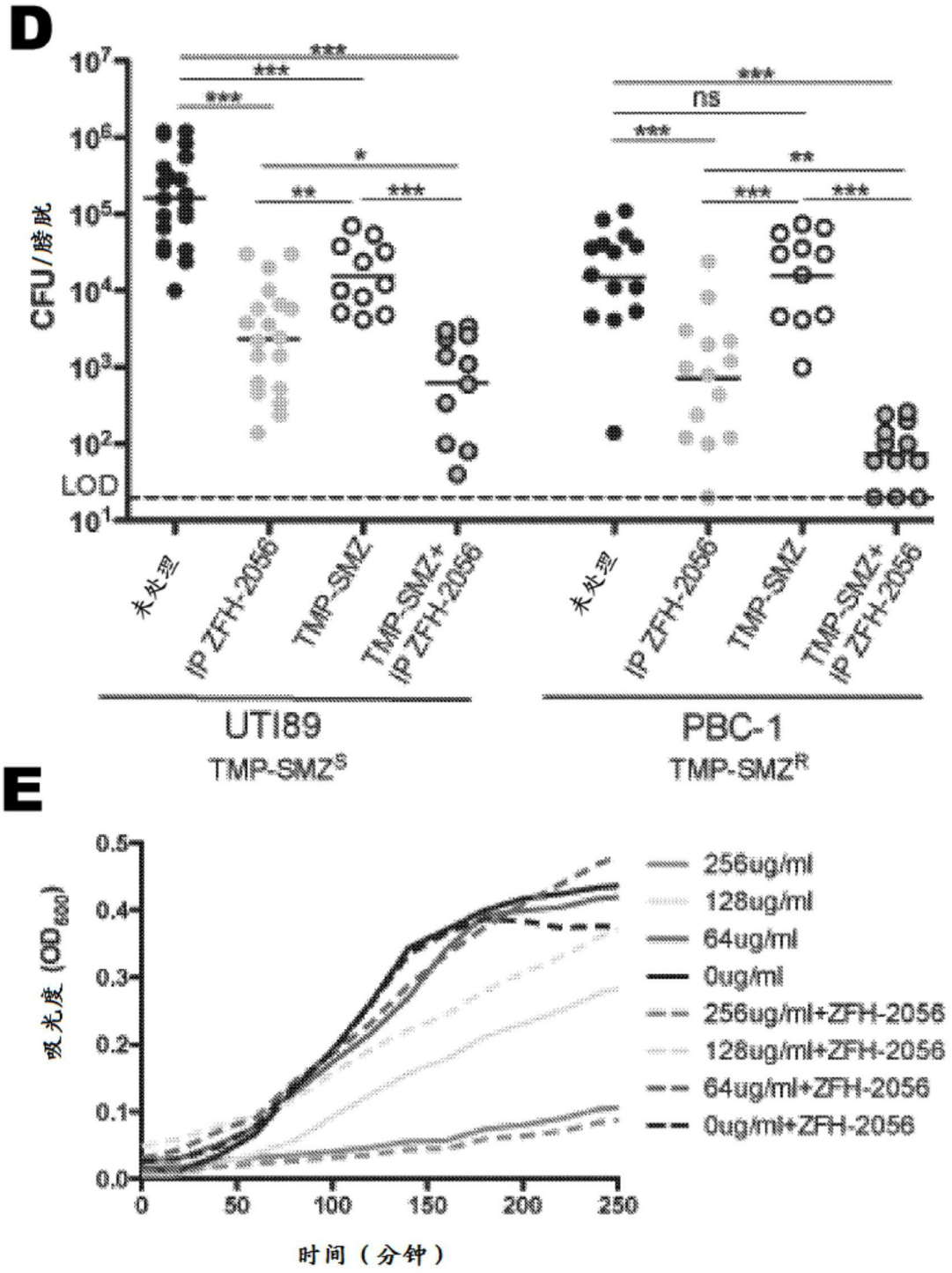

D
CFU/膀胱
LOD
未处理
IP ZFH-2056
TMP-SMZ
TMP-SMZ+ IP ZFH-2056
UTI89
TMP-SMZS
PBC-1
TMP-SMZR
E
吸光度 (OD600)
时间（分钟）
256ug/ml
128ug/ml
64ug/ml
0ug/ml
256ug/ml+ZFH-2056
128ug/ml+ZFH-2056
64ug/ml+ZFH-2056
0ug/ml+ZFH-2056

图18

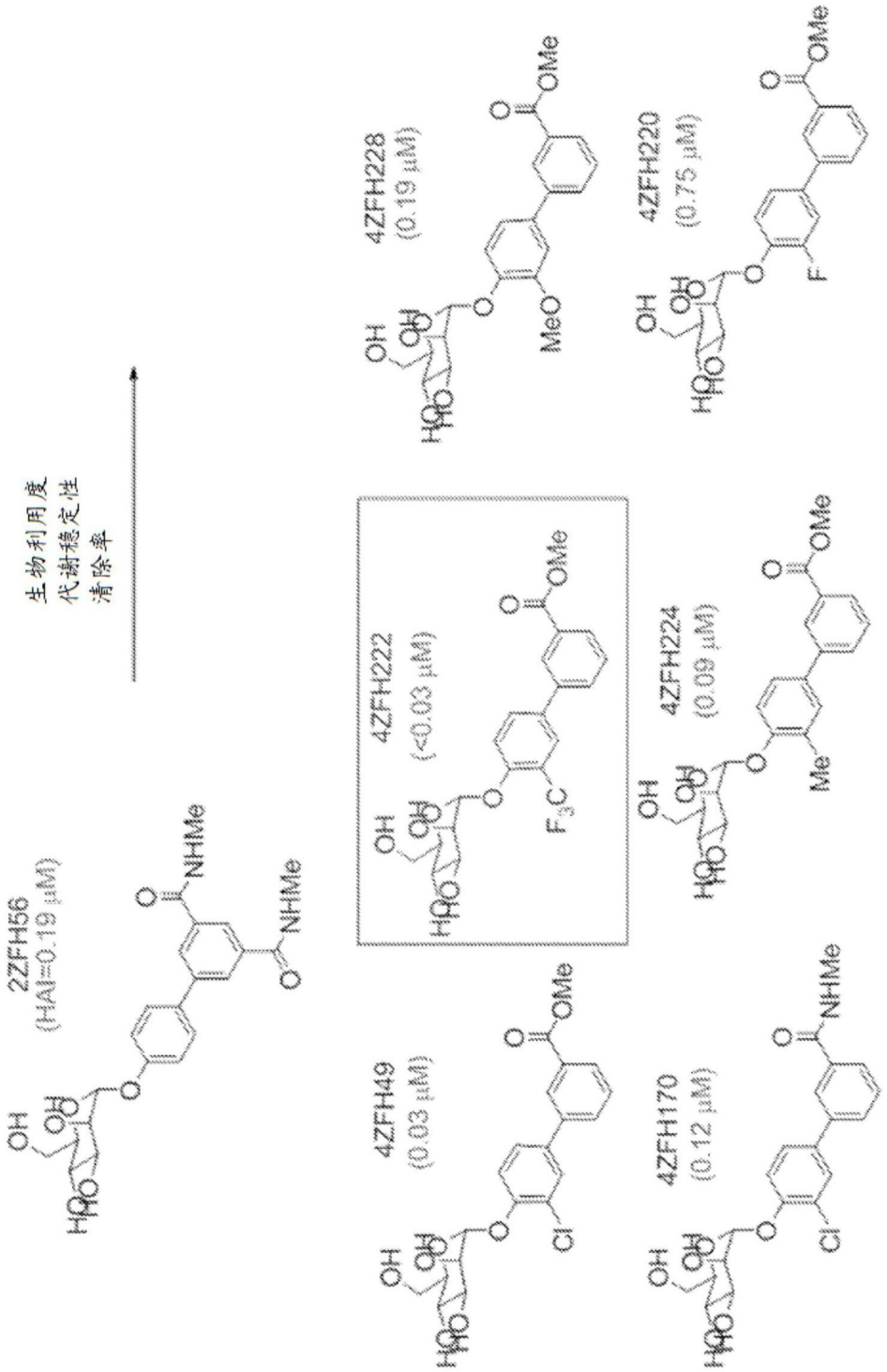

生物利用度
代谢稳定性
清除率
2ZFH56
(HAI=0.19 μM)
4ZFH49
(0.03 μM)
4ZFH222
(<0.03 μM)
4ZFH224
(0.09 μM)
4ZFH170
(0.12 μM)
4ZFH228
(0.19 μM)
4ZFH220
(0.75 μM)

图19

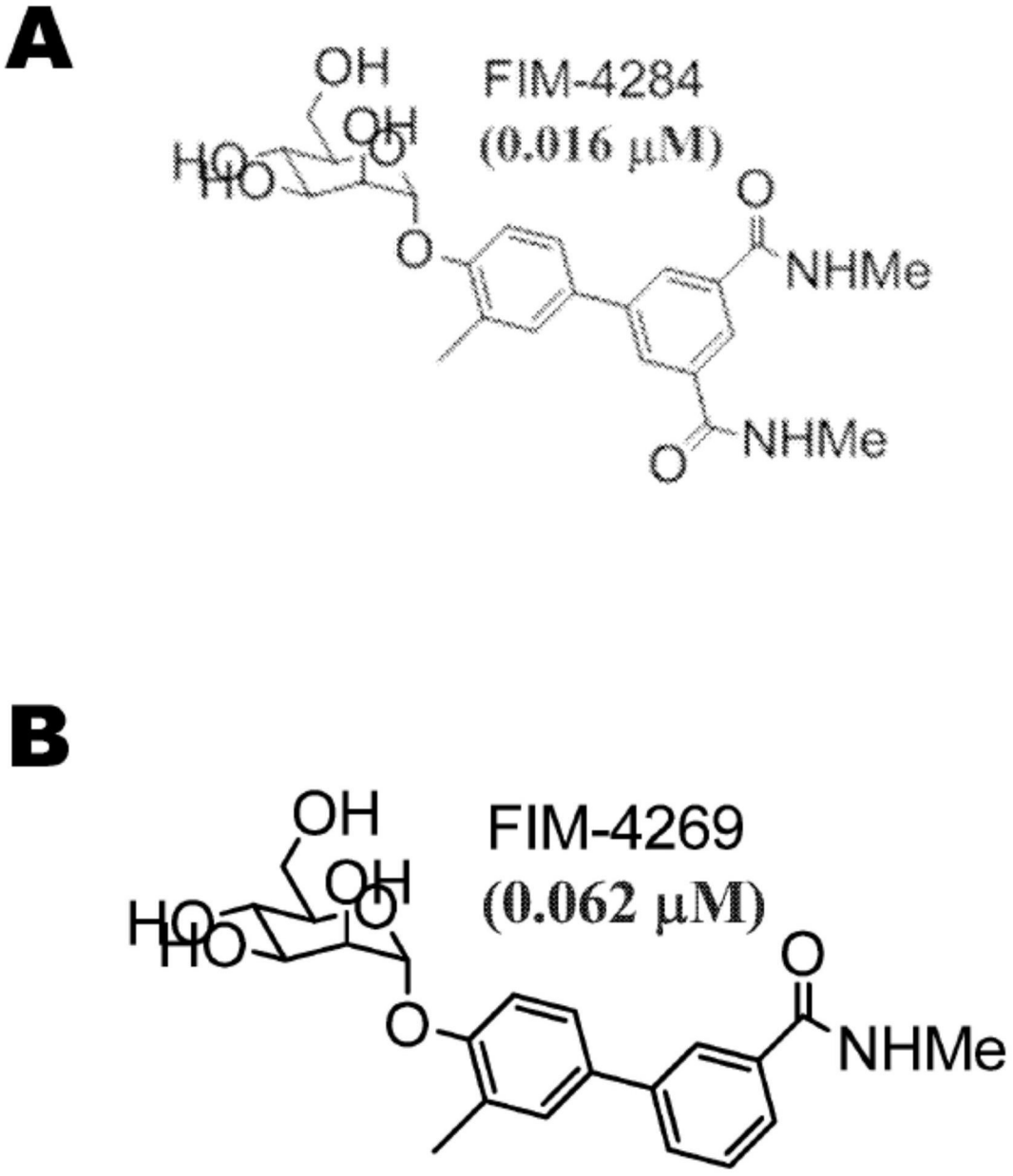

A
OH
OH
HO
HO
O
O
FIM-4284
(0.016 μM)
O
NHMe
O
NHMe
B
OH
OH
HO
HO
O
O
FIM-4269
(0.062 μM)
O
NHMe

图20

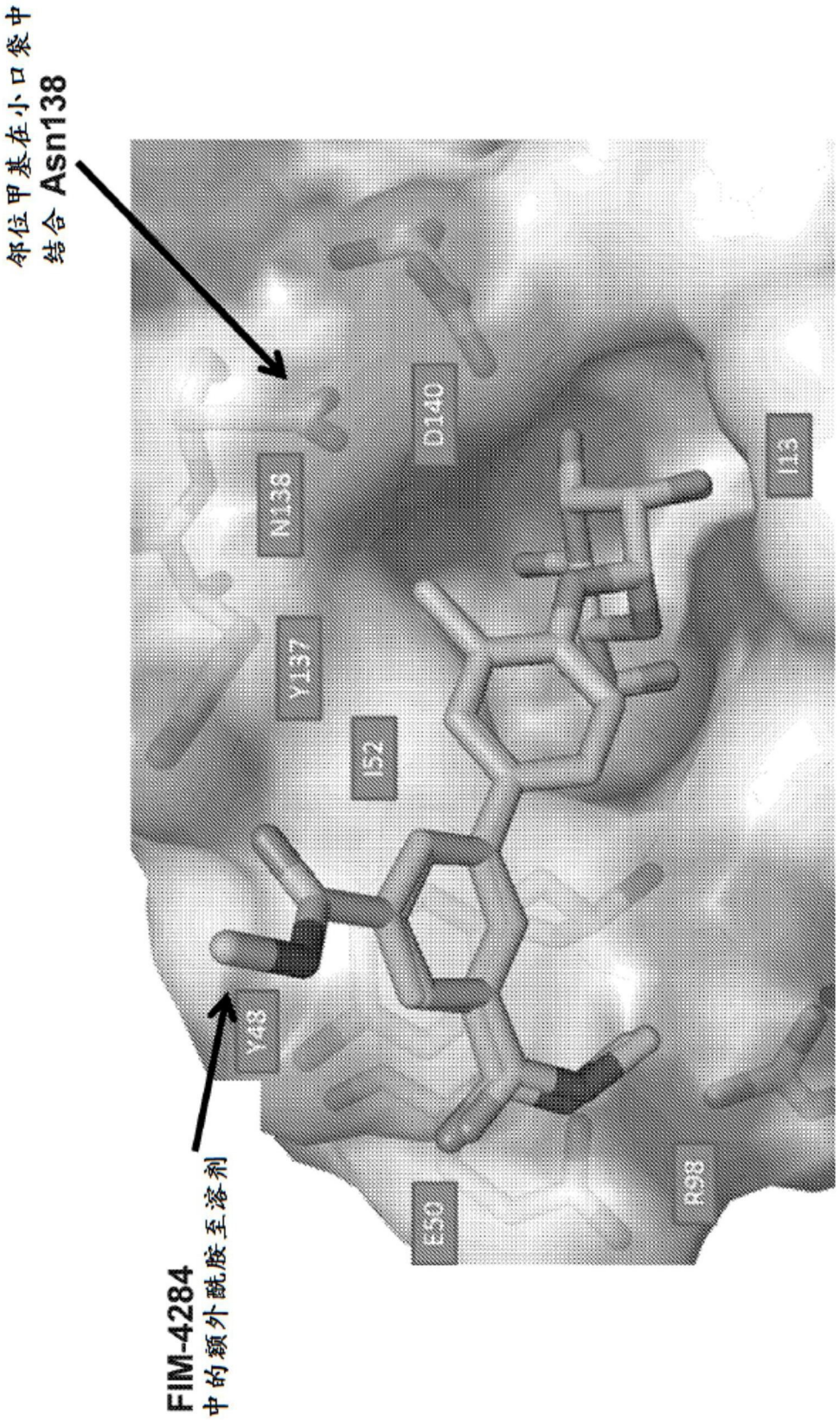

邻位甲基在小口袋中
结合 Asn138
FIM-4284
中的额外酰胺至溶剂
Y43
Y137
N138
D140
I52
I13
E50
R98

图20C

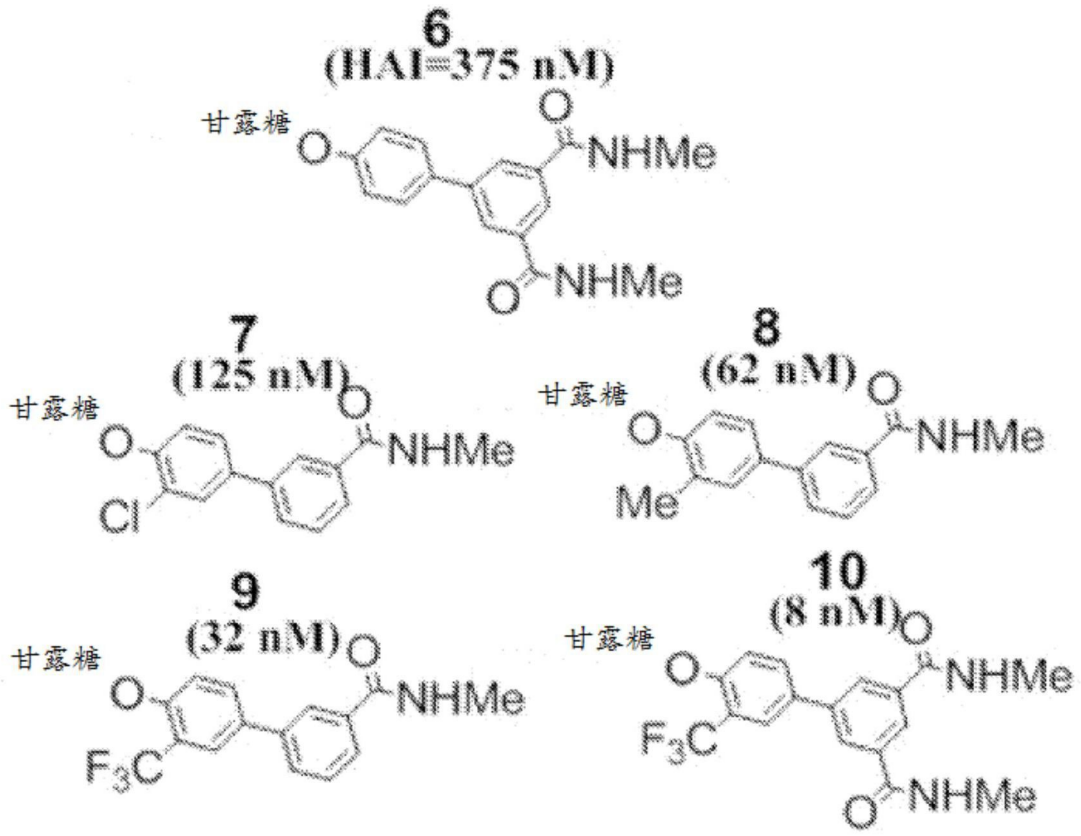

6
(HAI=375 nM)
甘露糖
O
NHMe
NHMe
7
(125 nM)
甘露糖
O
Cl
NHMe
8
(62 nM)
甘露糖
O
Me
NHMe
9
(32 nM)
甘露糖
O
F3C
NHMe
10
(8 nM)
甘露糖
O
F3C
NHMe
NHMe

图21A

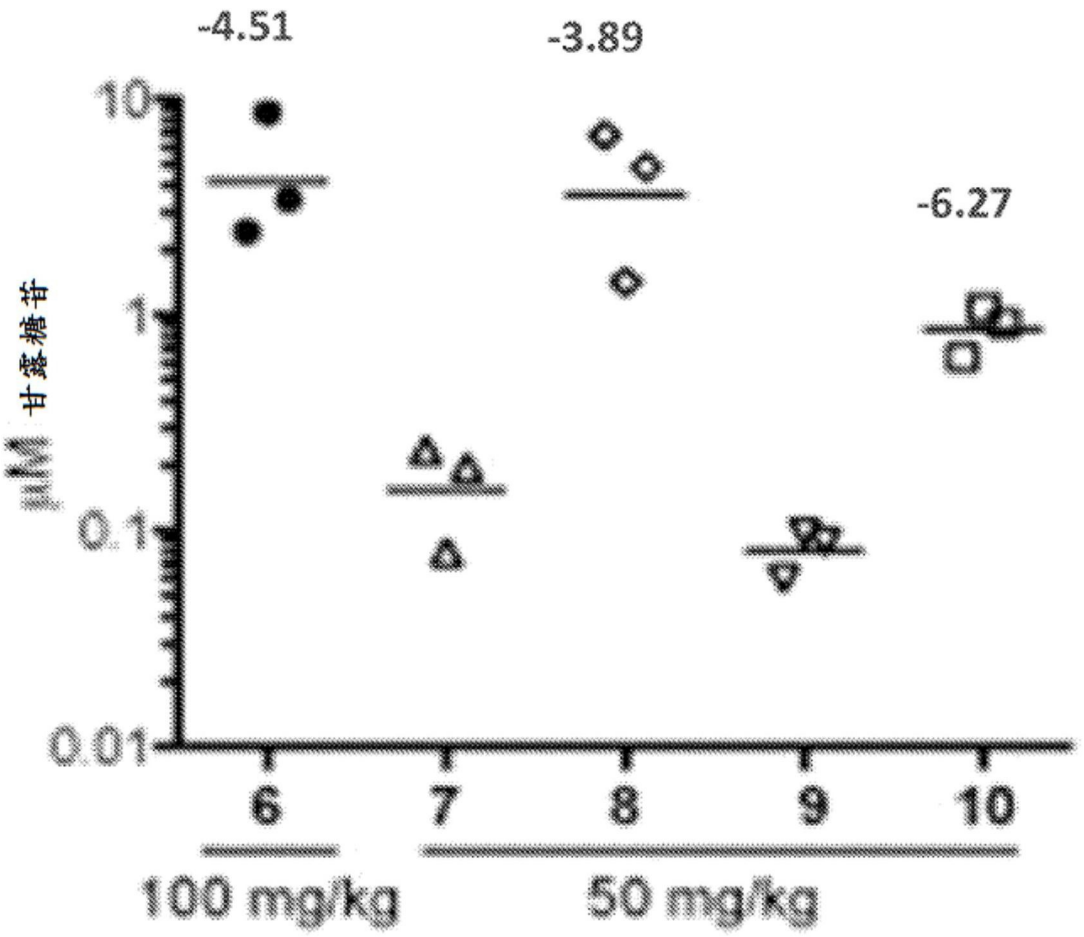


图21B

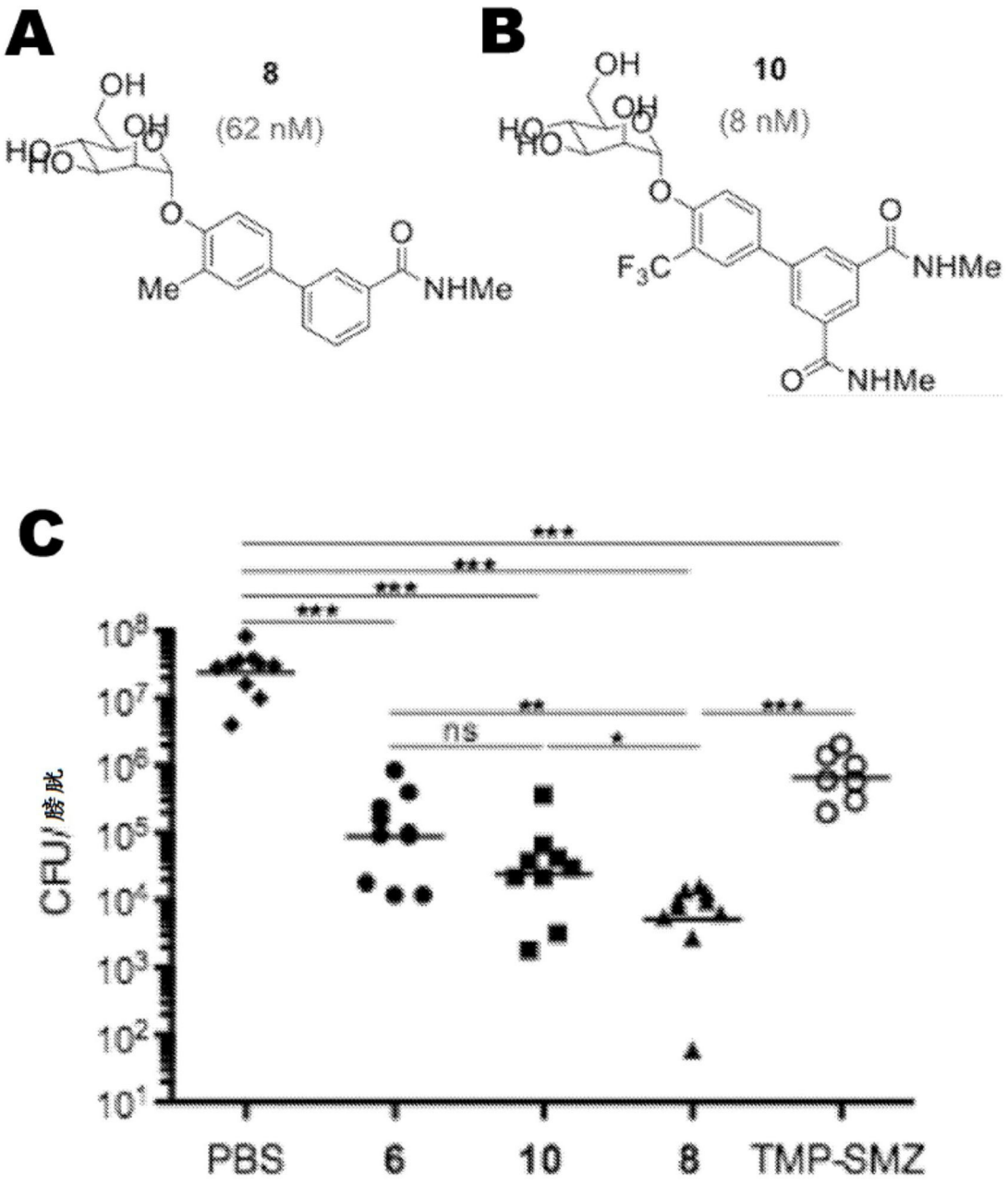

A
8
(62 nM)
OH
OH
HO
HO
O
Me
O
NHMe
B
10
(8 nM)
OH
OH
HO
HO
O
F3C
O
NHMe
O
NHMe
C
***
***
***
***
**
ns
*
***
CFU/ 感觉
10^8
10^7
10^6
10^5
10^4
10^3
10^2
10^1
PBS
6
10
8
TMP-SMZ

图22

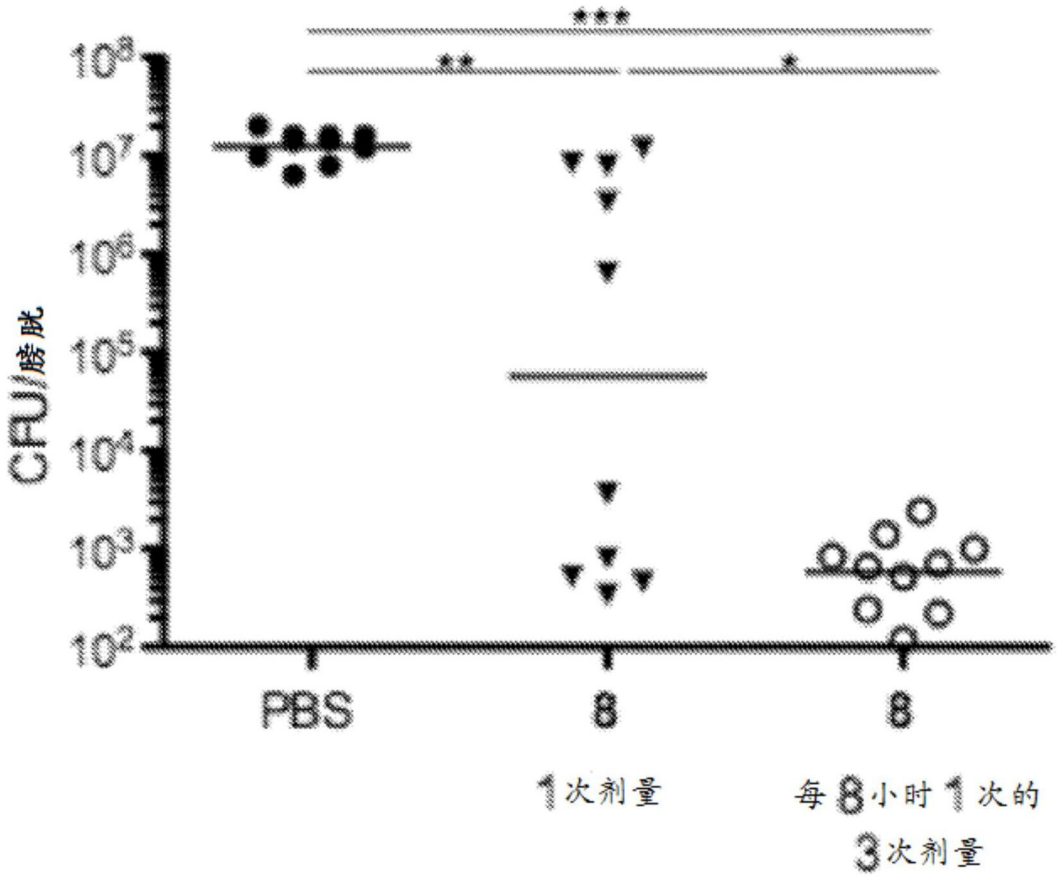


图22D

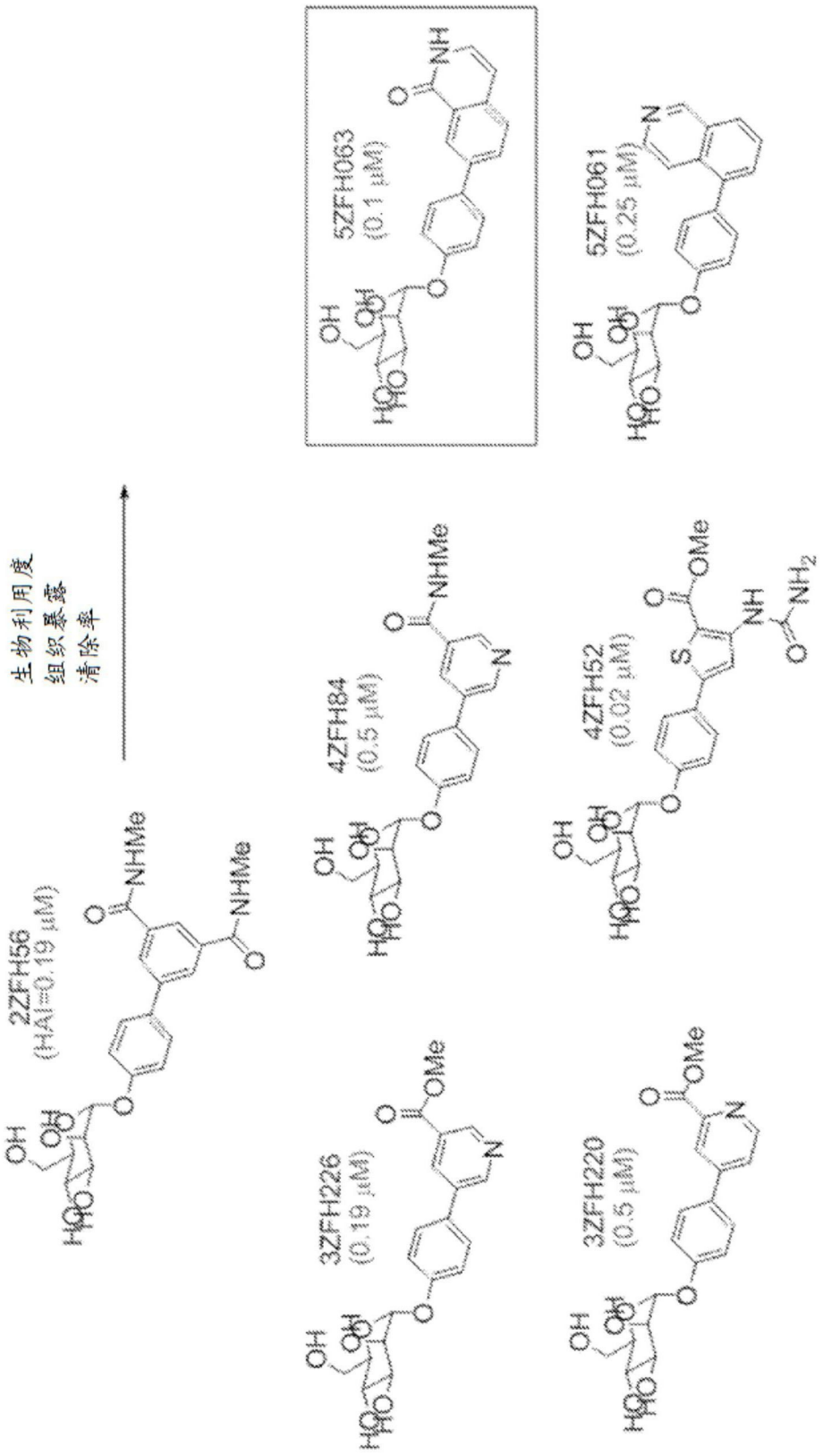

生物利用度
组织暴露
清除率
2ZFH56
(HAI=0.19 μM)
4ZFH84
(0.5 μM)
4ZFH52
(0.02 μM)
3ZFH226
(0.19 μM)
3ZFH220
(0.5 μM)
5ZFH063
(0.1 μM)
5ZFH061
(0.25 μM)

图23

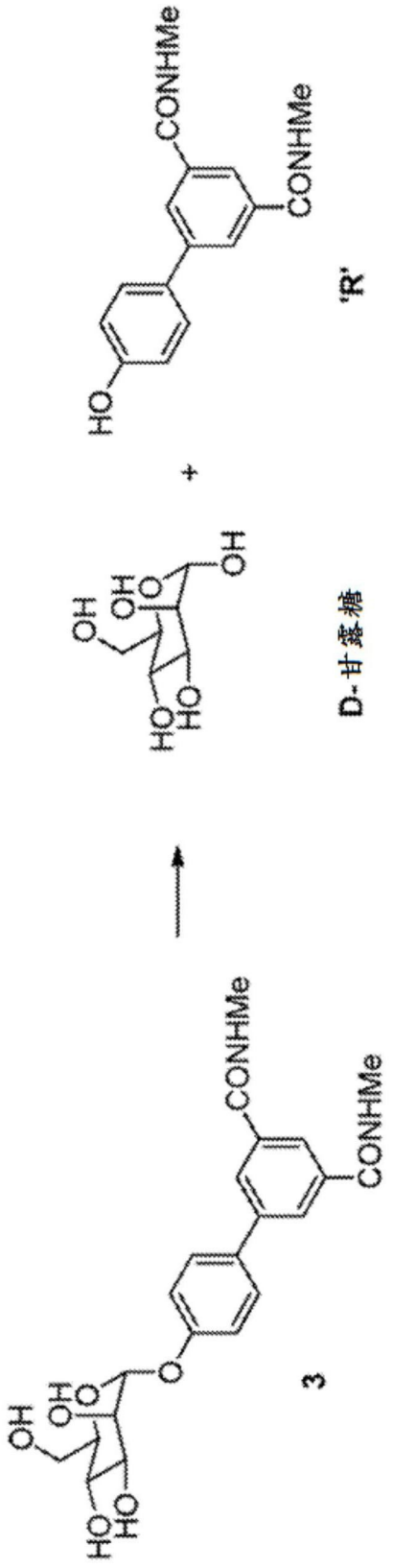

CONHMe
CONHMe
HO
'R'
+
OH
OH
O
OH
OH
HO
HO
D-甘露糖
CONHMe
CONHMe
O
OH
OH
OH
HO
HO
3

图24A

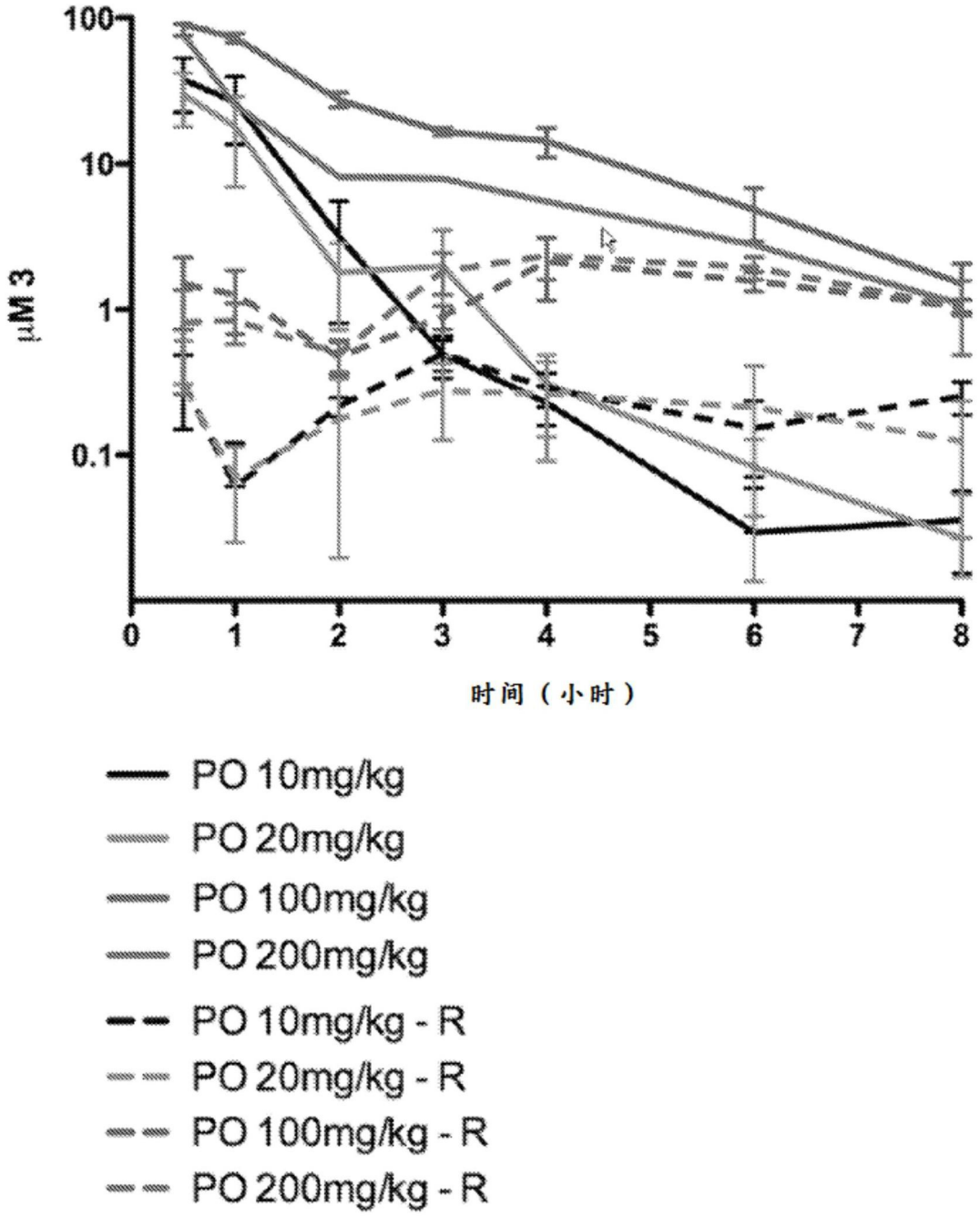
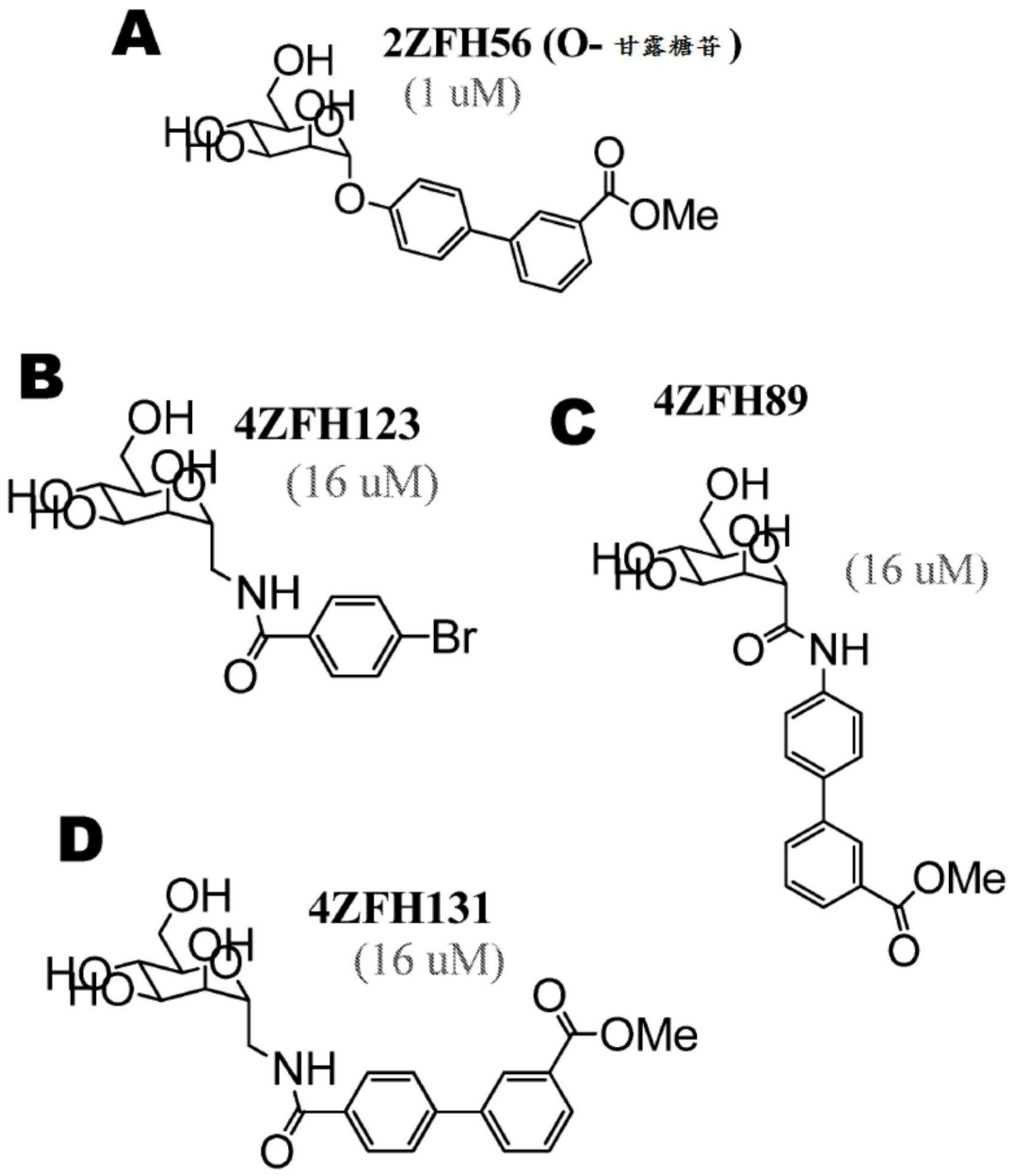
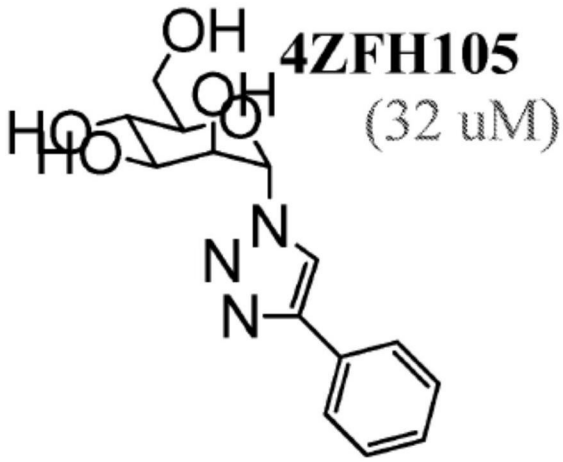

100
10
1
0.1
μM 3
0
1
2
3
4
5
6
7
8
时间（小时）
PO 10mg/kg
PO 20mg/kg
PO 100mg/kg
PO 200mg/kg
PO 10mg/kg - R
PO 20mg/kg - R
PO 100mg/kg - R
PO 200mg/kg - R

图24B

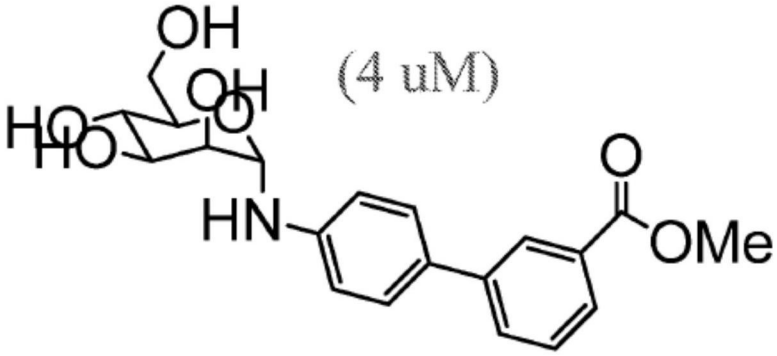

A
2ZFH56 (O- 甘露糖苷)
(1 uM)
OH
OH
HO
HO
O
O
OMe
B
4ZFH123
(16 uM)
OH
OH
HO
HO
NH
O
Br
C
4ZFH89
(16 uM)
OH
OH
HO
HO
O
NH
OMe
O
D
4ZFH131
(16 uM)
OH
OH
HO
HO
NH
O
O
OMe

E **4ZFH105**



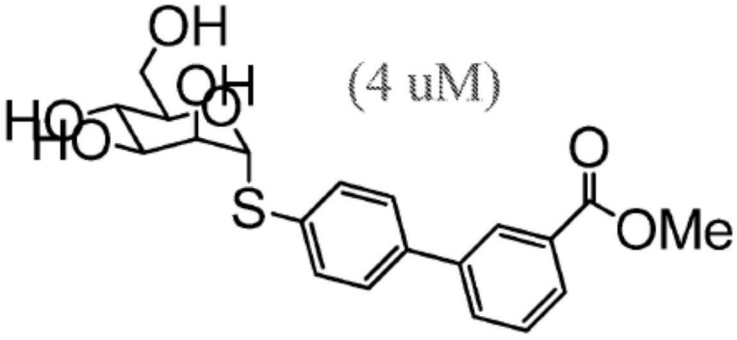
(32 uM)

F **4ZFH44 (N- 甘露糖苷)**



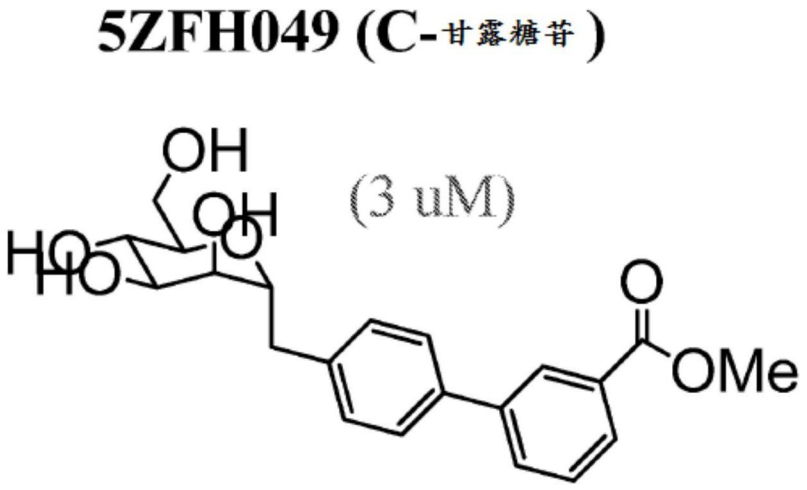
(4 uM)

G **4ZFH55 (S- 甘露糖苷)**

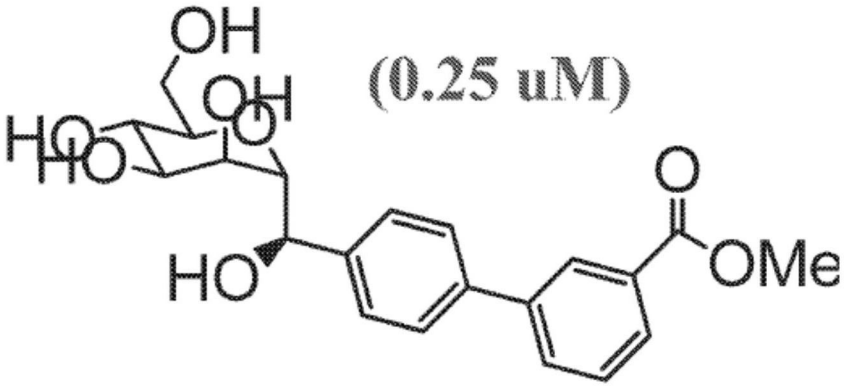


(4 uM)

H


5ZFH049 (C-甘露糖苷)
OH
OH
HO
HO
O
(3 uM)
O
OMe

I


5ZFH038
OH
OH
HO
HO
O
(0.25 uM)
HO
O
OMe

J

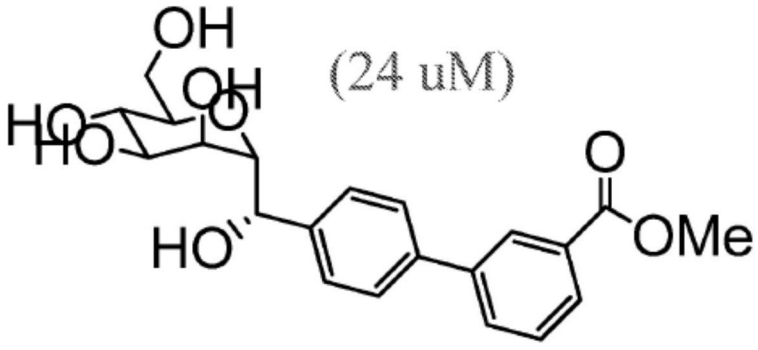

5ZFH048
OH
OH
HO
HO
O
(24 uM)
HO
O
OMe

图25

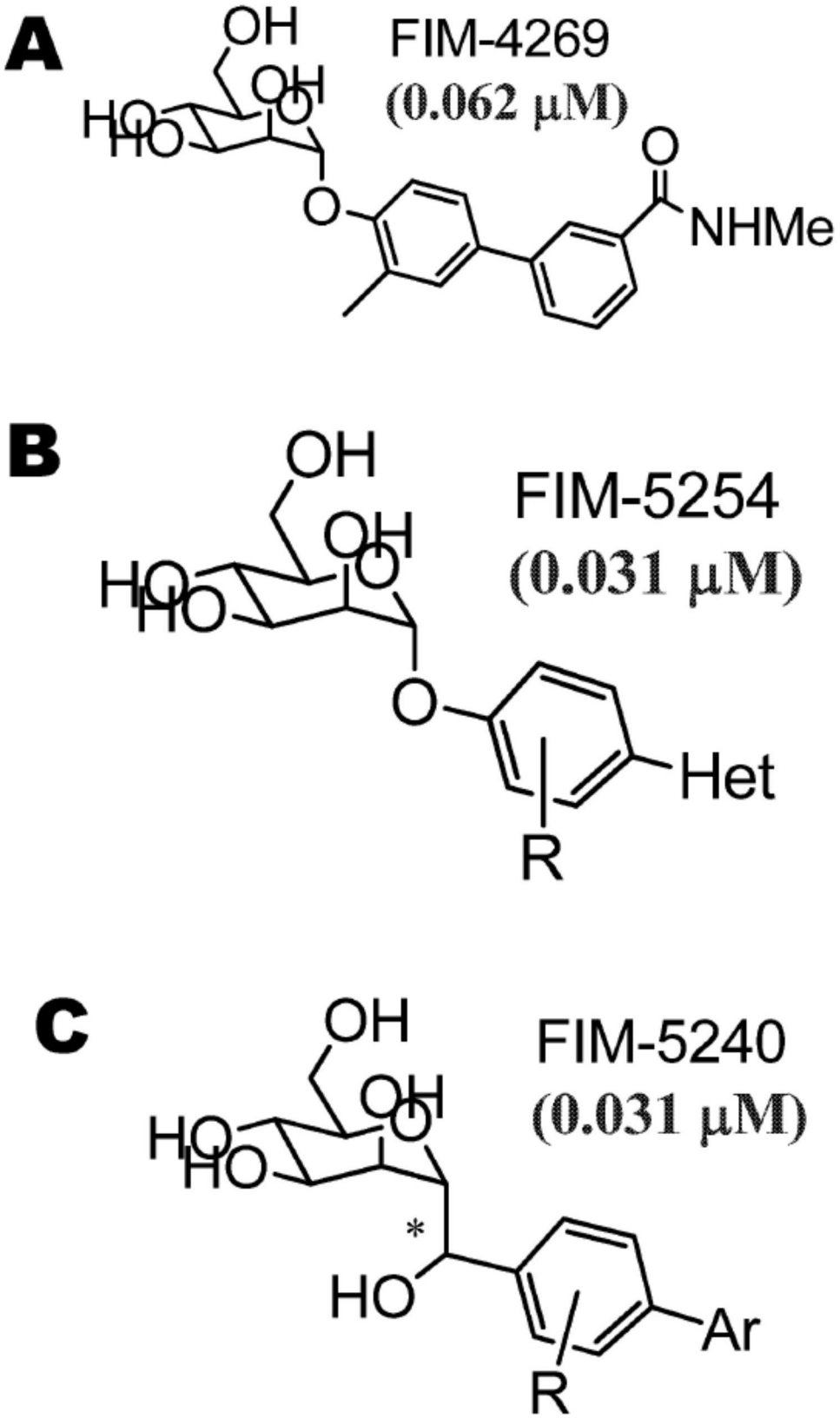

A
FIM-4269
(0.062 μM)
OH
OH
HO
HO
O
O
O
NHMe
B
FIM-5254
(0.031 μM)
OH
OH
HO
HO
O
O
Het
R
C
FIM-5240
(0.031 μM)
OH
OH
HO
HO
O
*
HO
Ar
R

图26

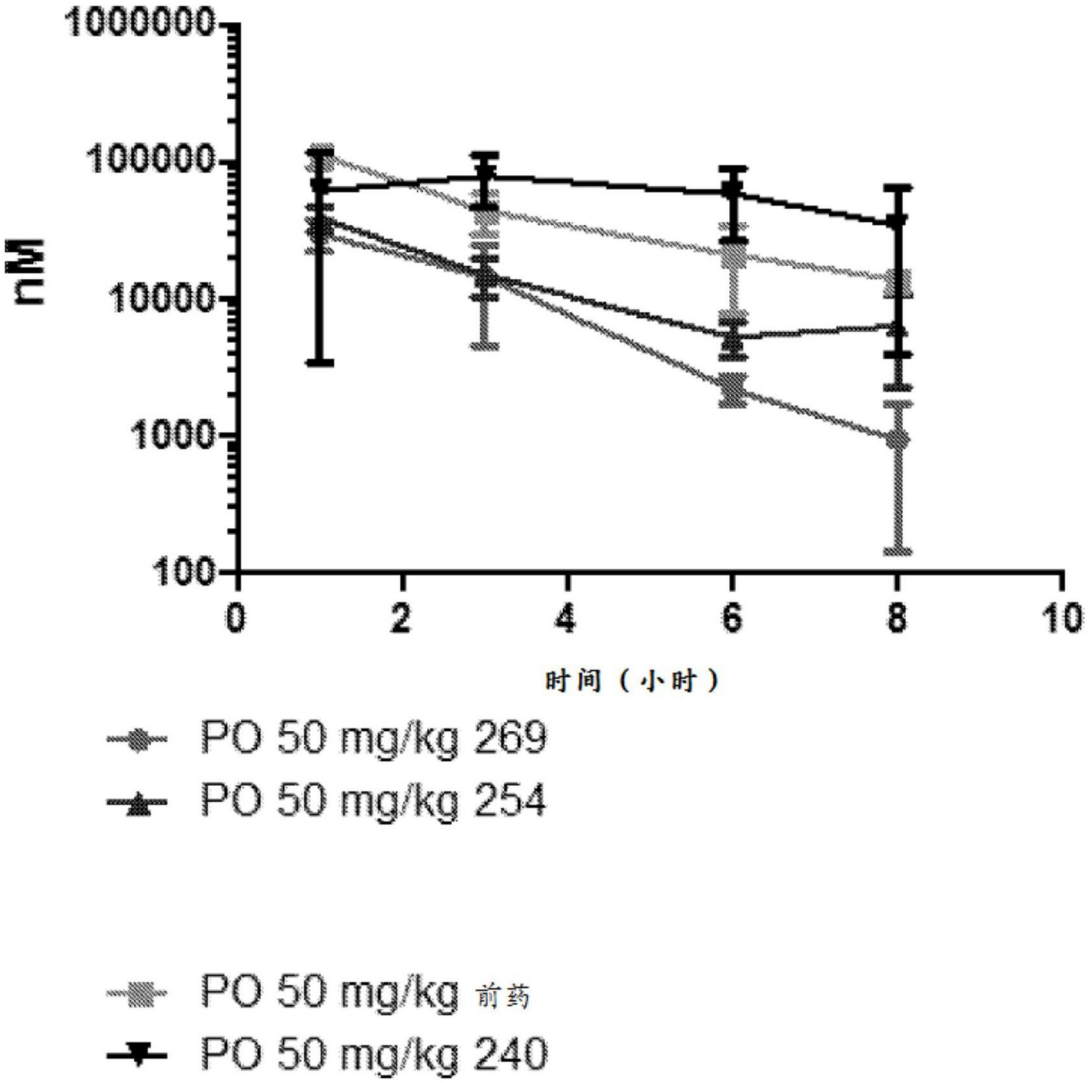

1000000
100000
10000
1000
100
nM
0
2
4
6
8
10
时间（小时）
PO 50 mg/kg 269
PO 50 mg/kg 254
PO 50 mg/kg 前药
PO 50 mg/kg 240

图26D

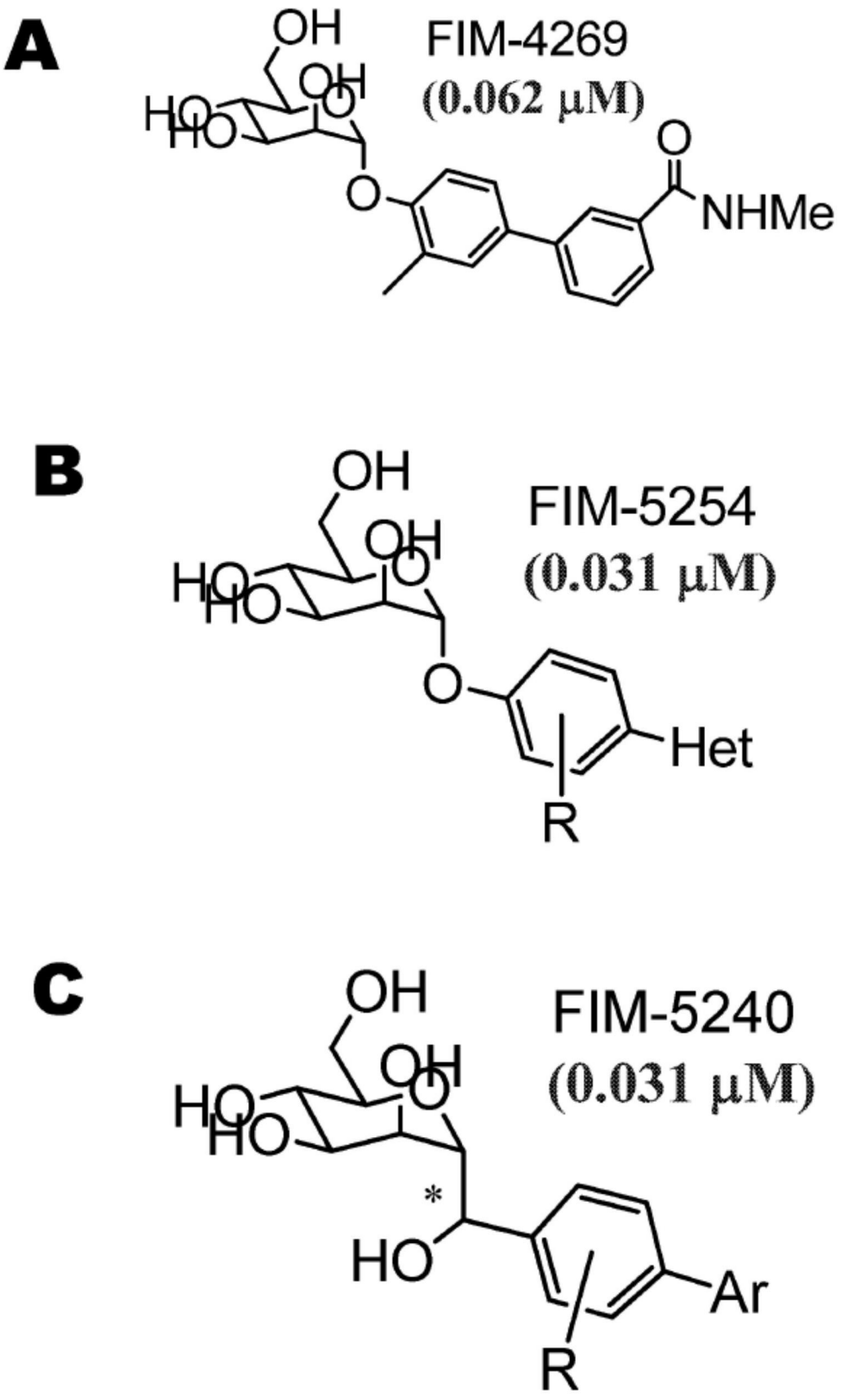

A
FIM-4269
(0.062 μM)
OH
OH
HO
HO
O
O
NHMe
B
FIM-5254
(0.031 μM)
OH
OH
HO
HO
O
O
Het
R
C
FIM-5240
(0.031 μM)
OH
OH
HO
HO
O
*
HO
Ar
R

图27

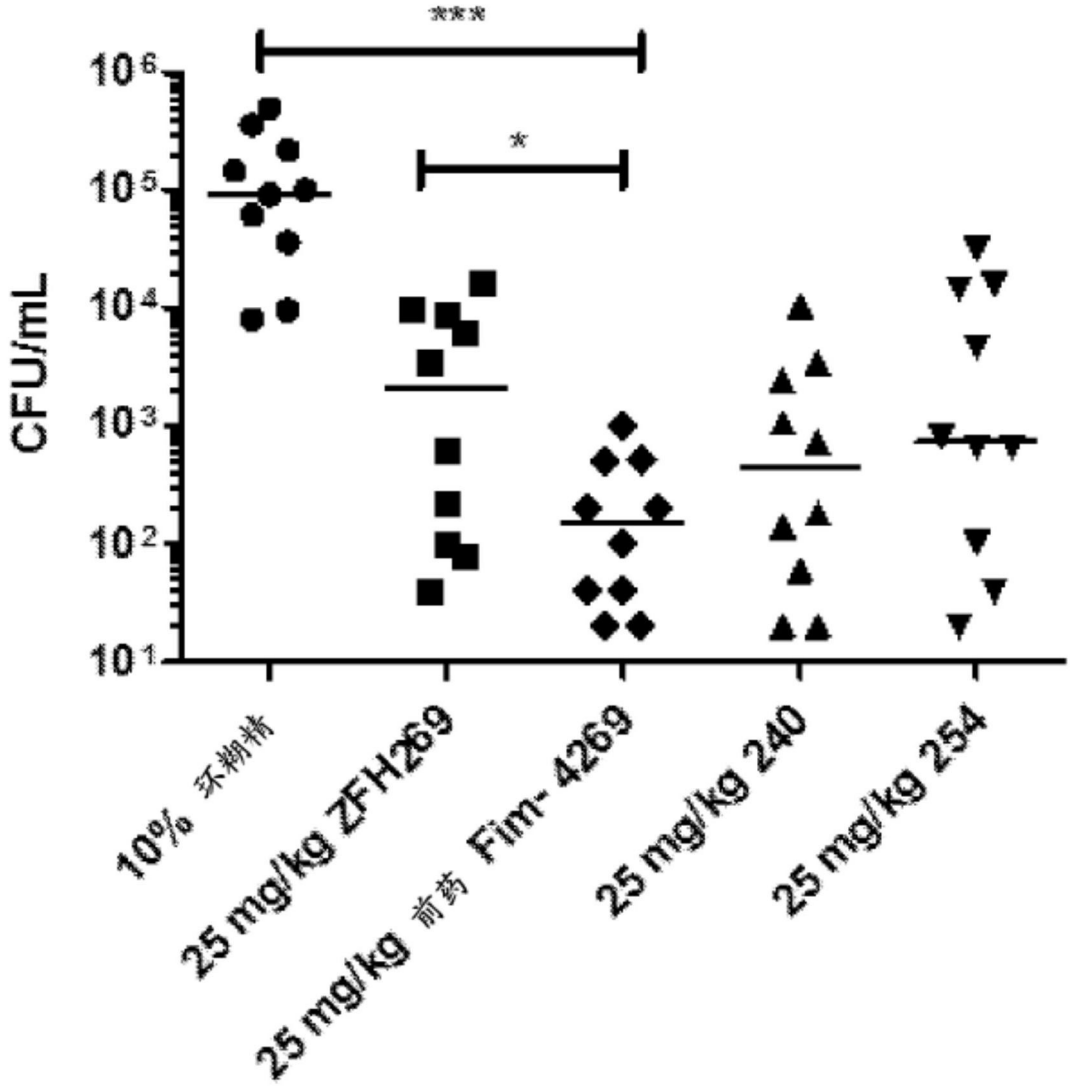

****
*
CFU/mL
10^6
10^5
10^4
10^3
10^2
10^1
10% 环糊精
25 mg/kg ZFH269
25 mg/kg 前药 Fim- 4269
25 mg/kg 240
25 mg/kg 254

图27D

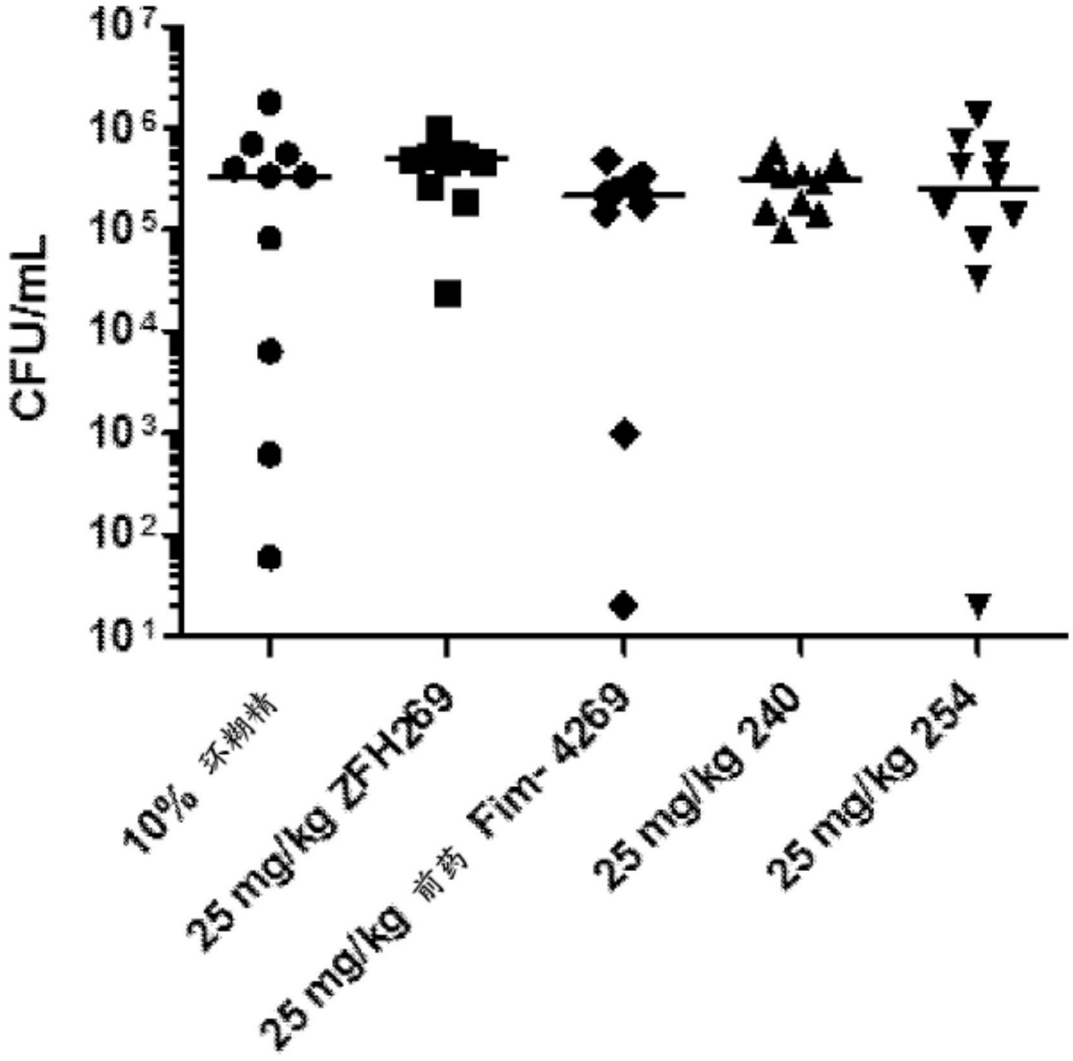

CFU/mL
10^7
10^6
10^5
10^4
10^3
10^2
10^1
10% 环糊精
25 mg/kg ZFH269
25 mg/kg 前药 Fim- 4269
25 mg/kg 240
25 mg/kg 254

图27E

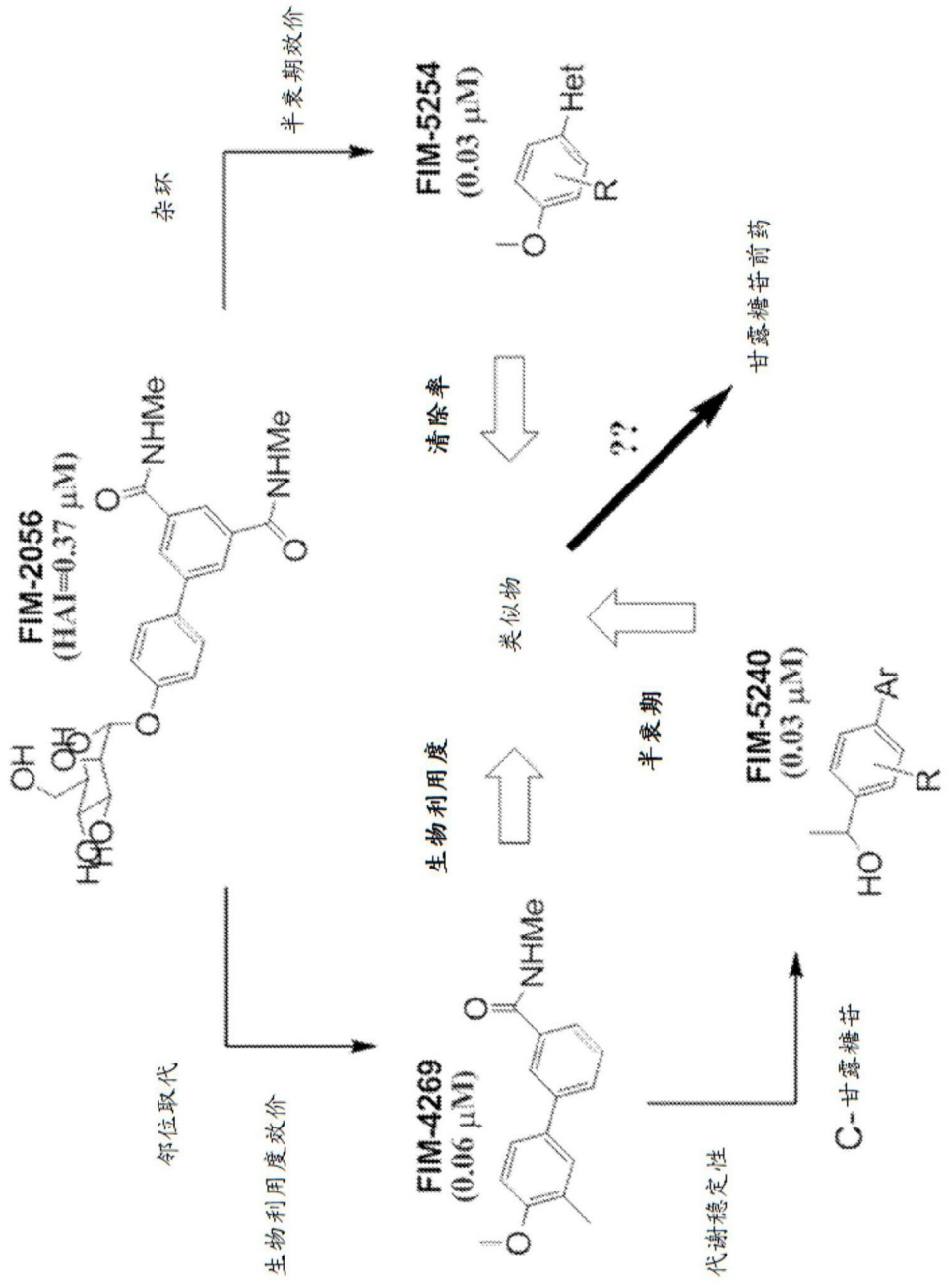

FIM-2056
(HAI=0.37 μM)
NHMe
NHMe
OH
OH
HO
O
杂环
半衰期效价
FIM-5254
(0.03 μM)
Het
R
O
清除率
??
甘露糖苷前药
类似物
生物利用度
半衰期
FIM-5240
(0.03 μM)
Ar
R
HO
邻位取代
生物利用度效价
FIM-4269
(0.06 μM)
NHMe
O
代谢稳定性
C-甘露糖苷

图28

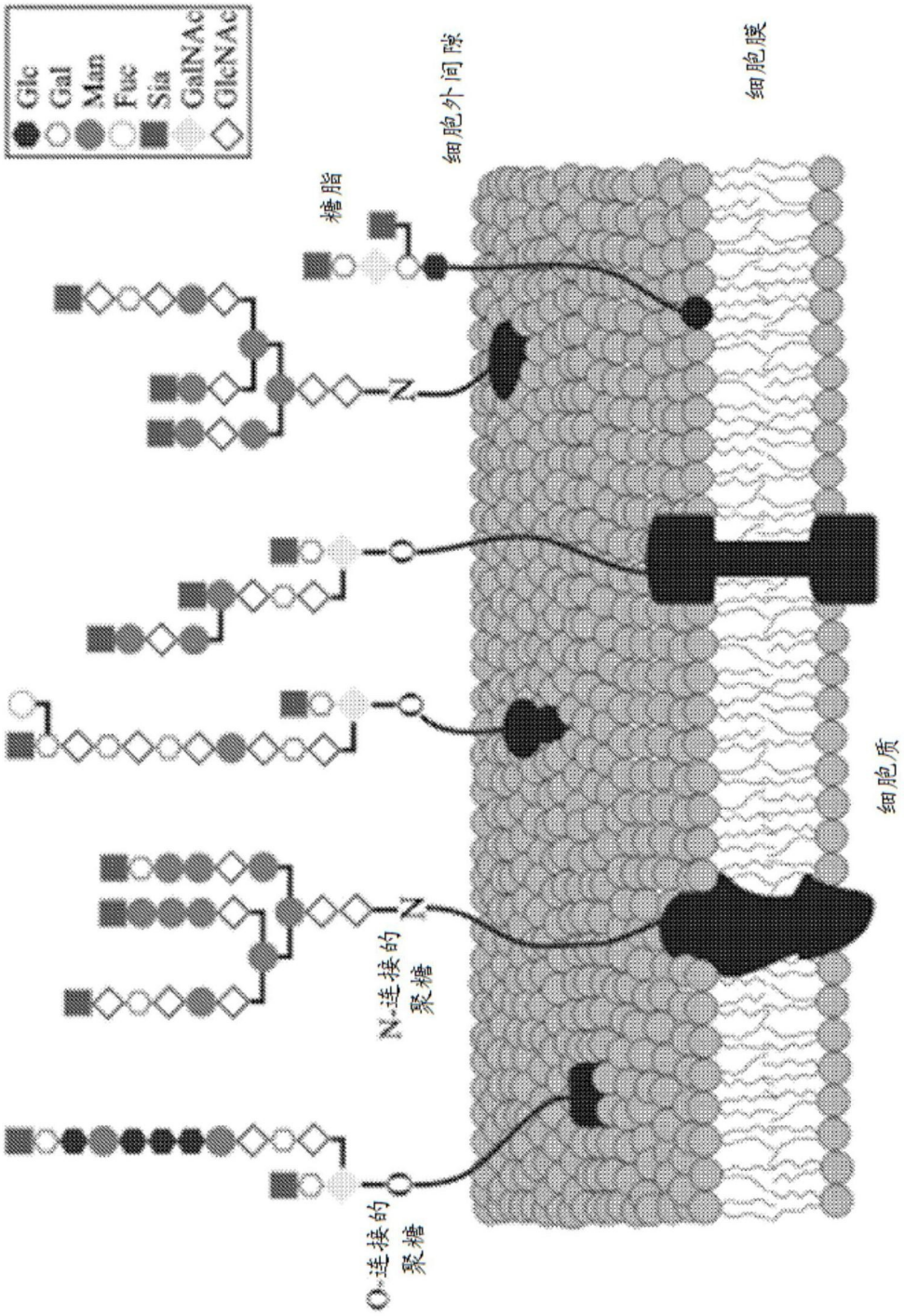

Glc
Gal
Man
Fuc
Sia
GalNAc
GlcNAc
糖脂
细胞外间隙
细胞膜
细胞质
N-连接的聚糖
O-连接的聚糖

图29A

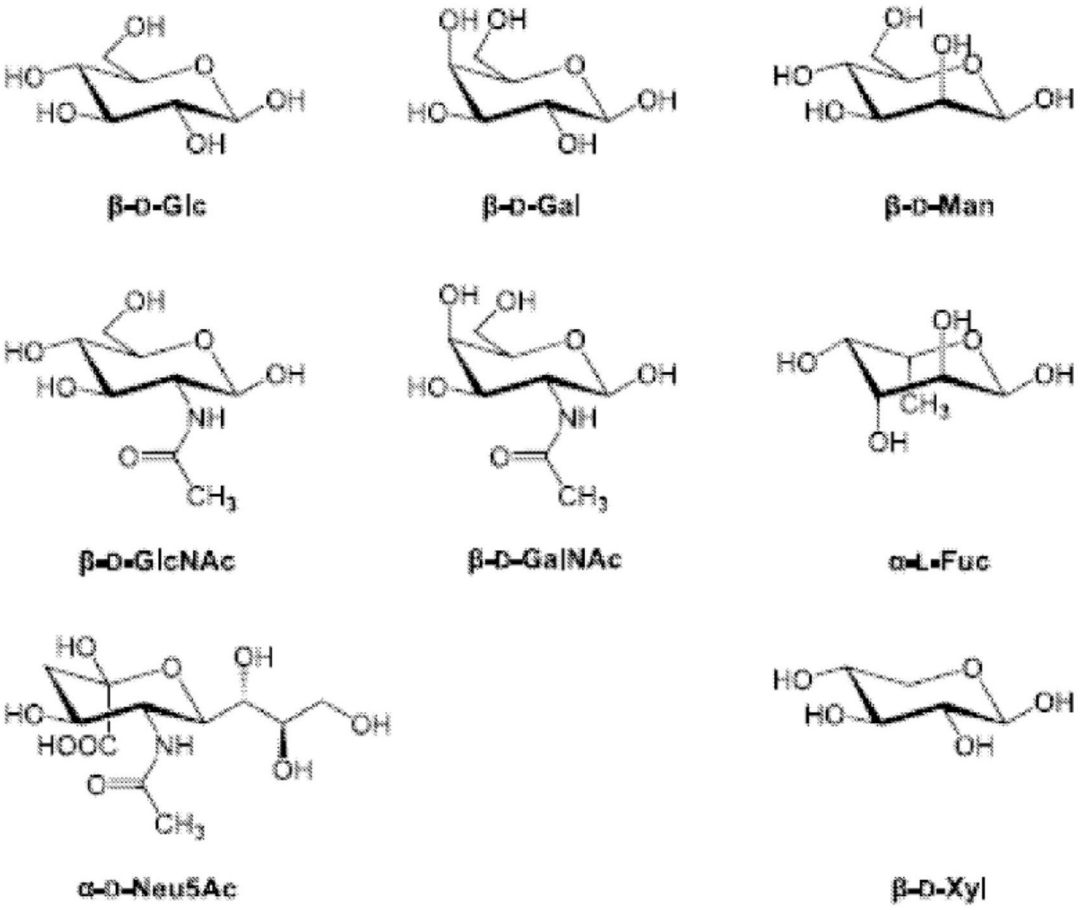


图29B

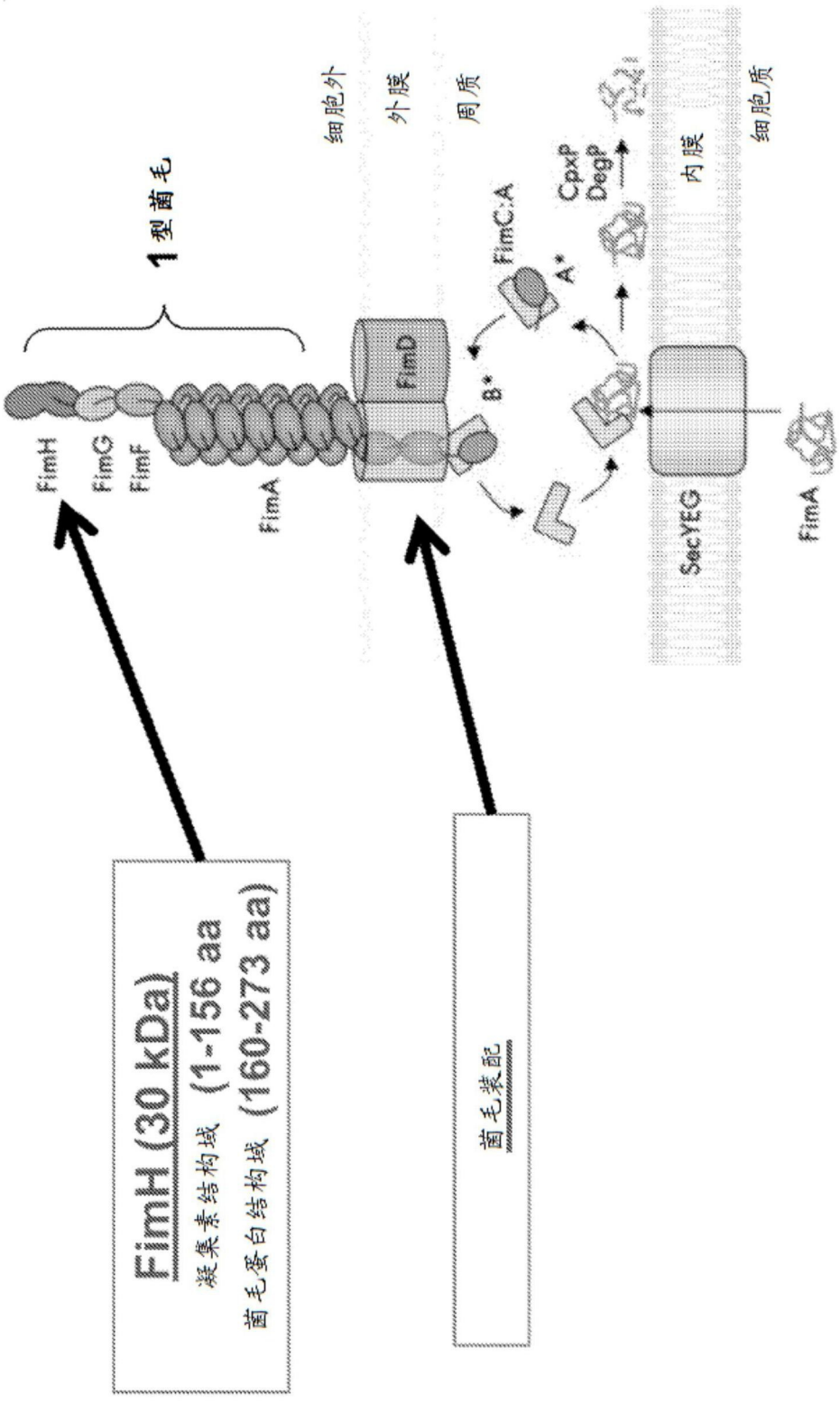

1型菌毛
细胞外
外膜
周质
内膜
细胞质
FimH
FimG
FimF
FimA
FimD
FimC:A
A*
B*
CpxP
DegP
SecYEG
FimA
FimH (30 kDa)
凝集素结构域 (1-156 aa
菌毛蛋白结构域 (160-273 aa)
菌毛装配

图30

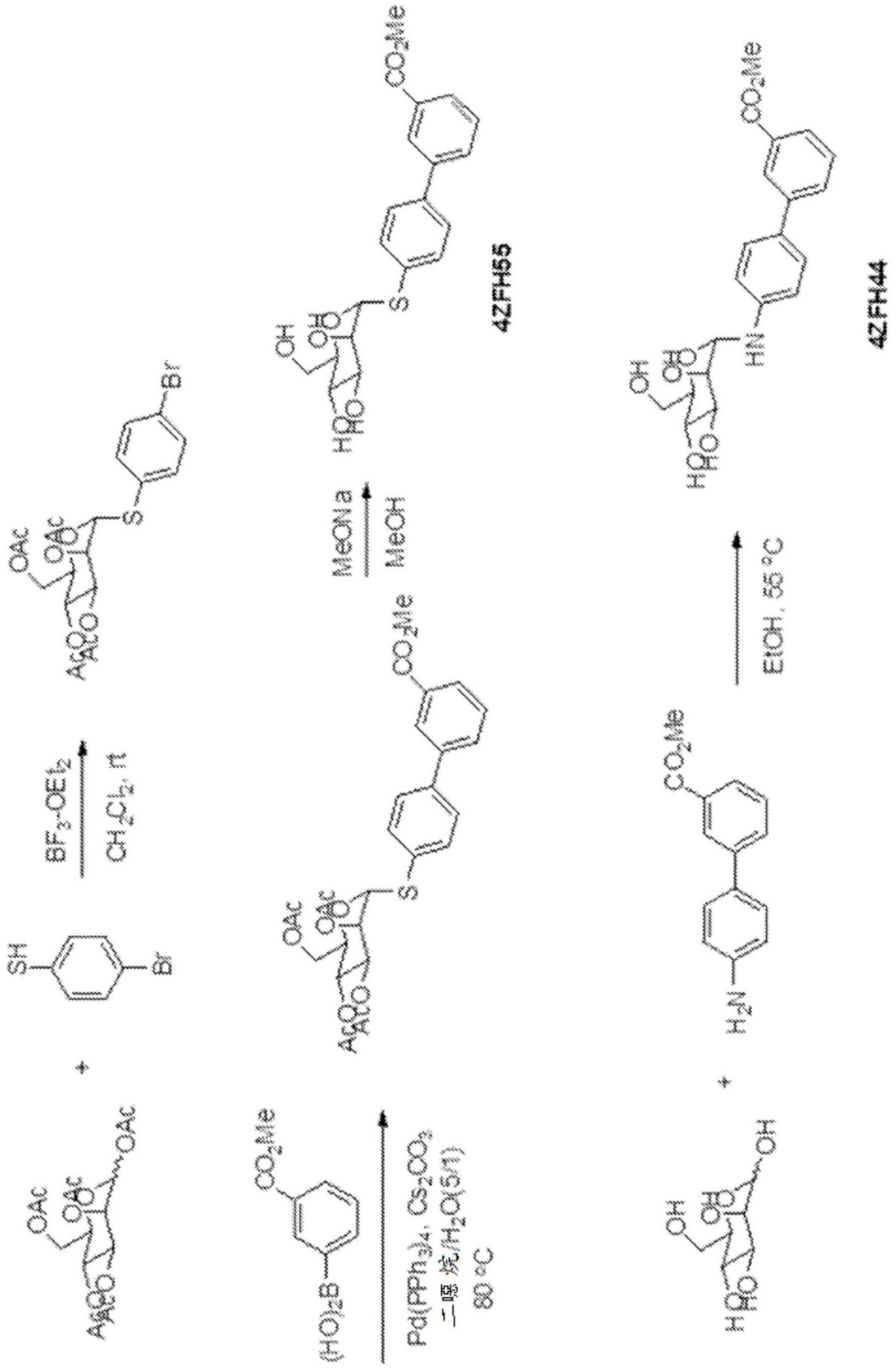

BF3-OEt2
CH2Cl2, rt
Pd(PPh3)4, Cs2CO3
二噁烷/H2O(5/1)
80 °C
MeONa
MeOH
EtOH, 55 °C
4ZFH55
4ZFH44

图31

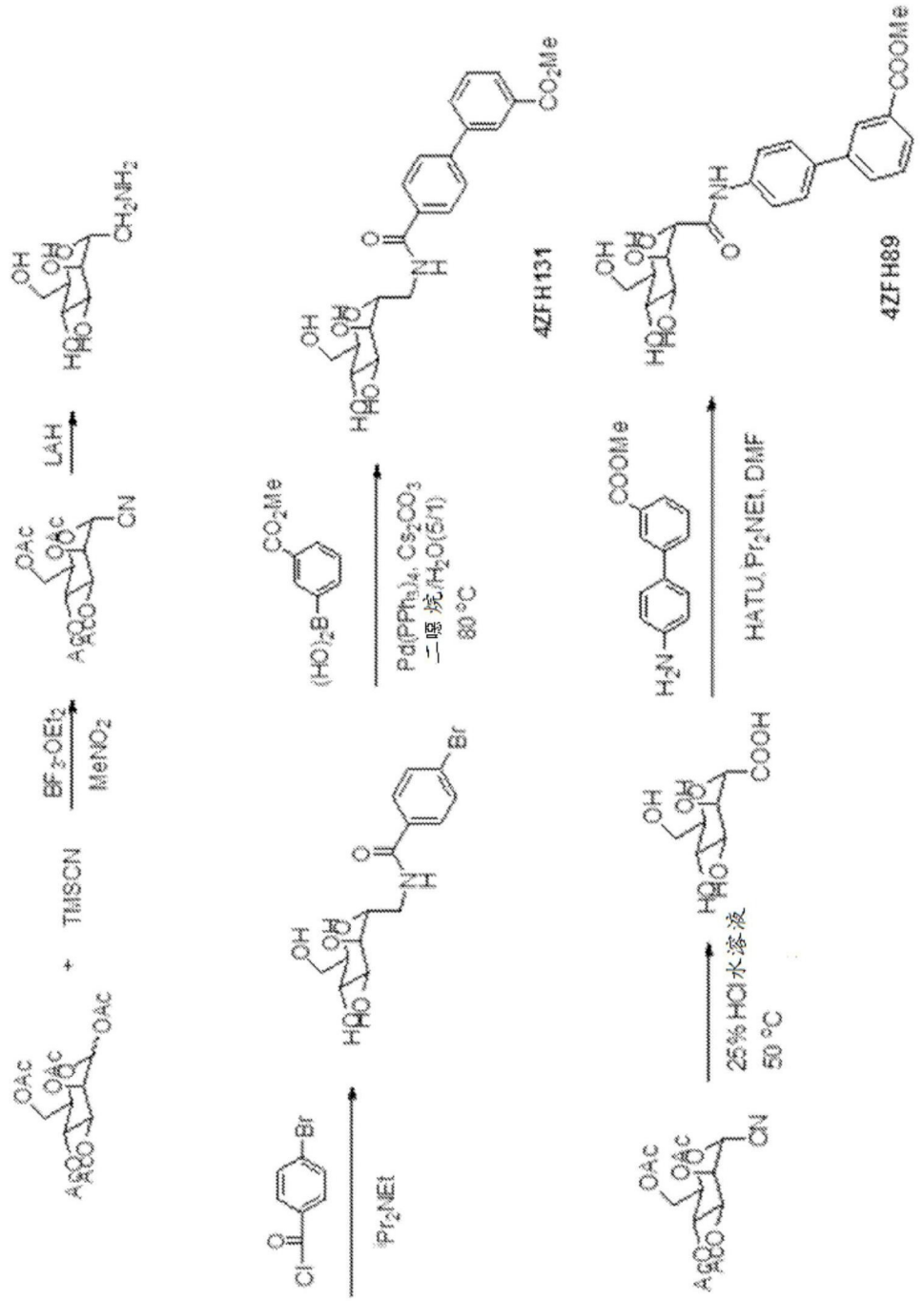

TMSCN
BF3-OEt2
MeNO2
LAH
Pr2NEt
Pd(PPh3)4, Cs2CO3
二噁烷/H2O(5/1)
80 °C
4ZFH131
HATU, Pr2NEt, DMF
25% HCl水溶液
50 °C
4ZFH89

图32

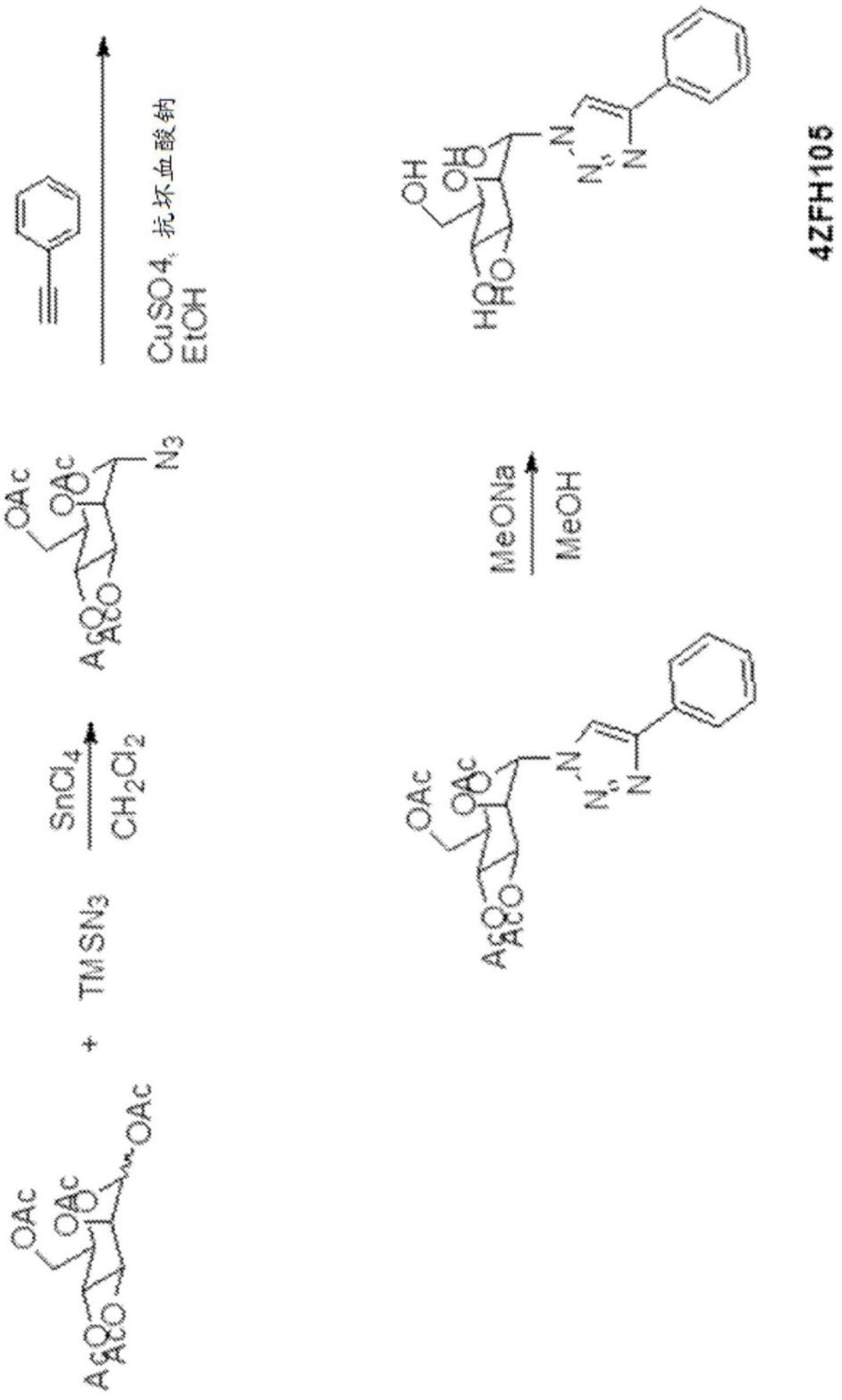


图33

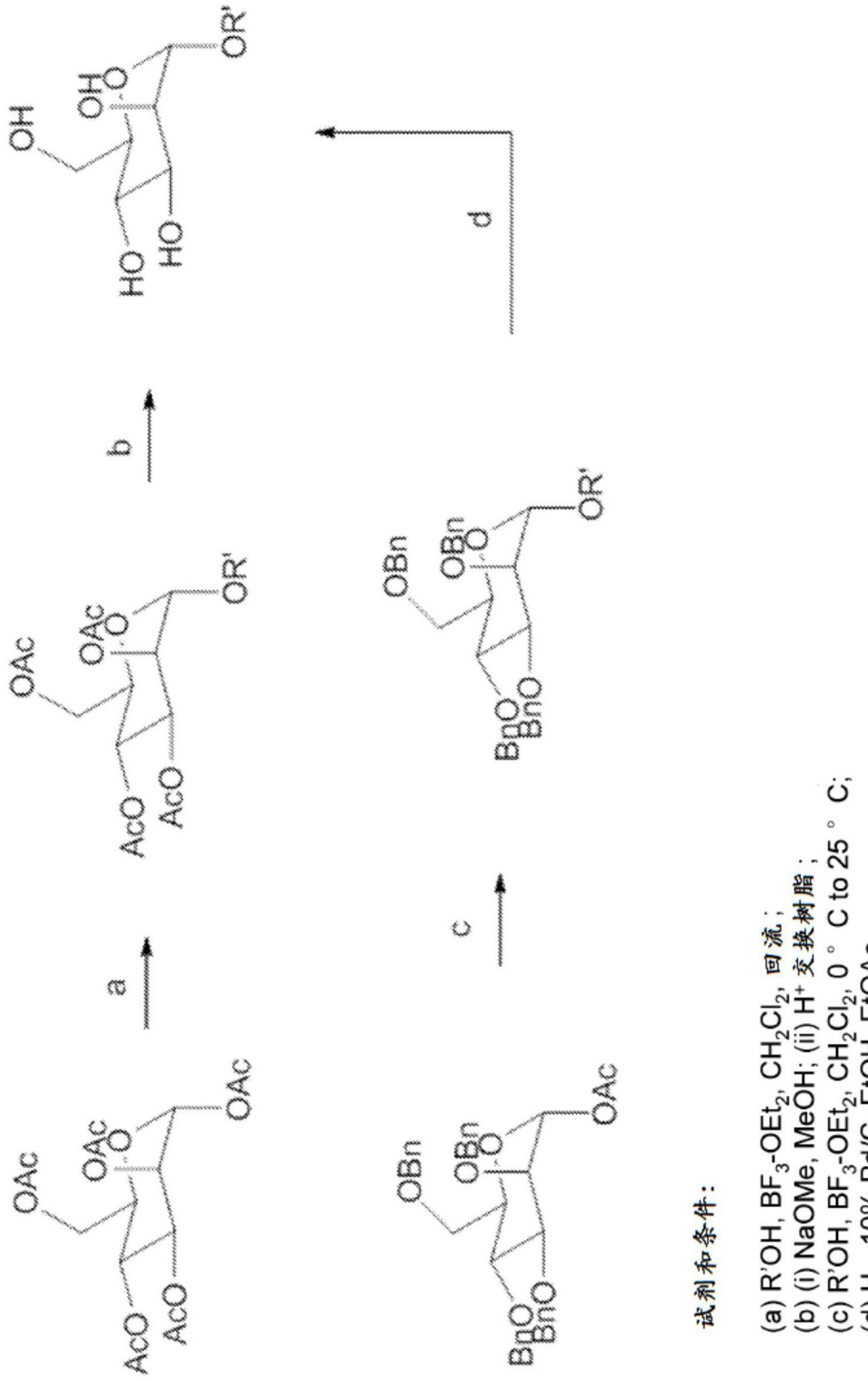

a
b
c
d
试剂和条件：
(a) R'OH, BF_3-OEt_2, CH_2Cl_2, 回流；
(b) (i) NaOMe, MeOH; (ii) H^+ 交换树脂；
(c) R'OH, BF_3-OEt_2, CH_2Cl_2, 0 ° C to 25 ° C;
(d) H_2, 10% Pd/C, EtOH, EtOAc。

图34

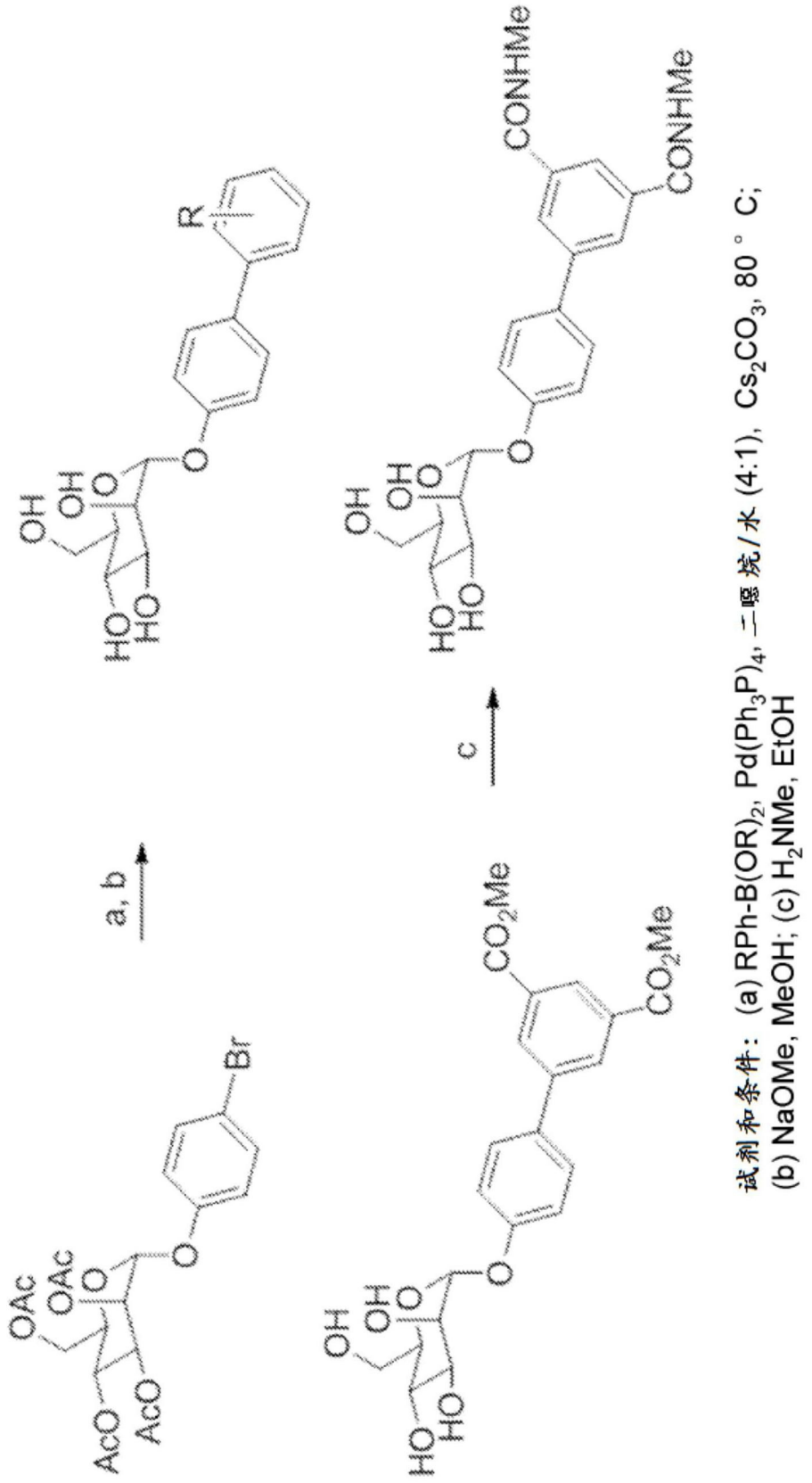

a, b
c
试剂和条件：(a) RPh-B(OR)2, Pd(Ph3P)4, 二噁烷/水 (4:1), Cs2CO3, 80 ° C;
(b) NaOMe, MeOH; (c) H2NMe, EtOH

图35

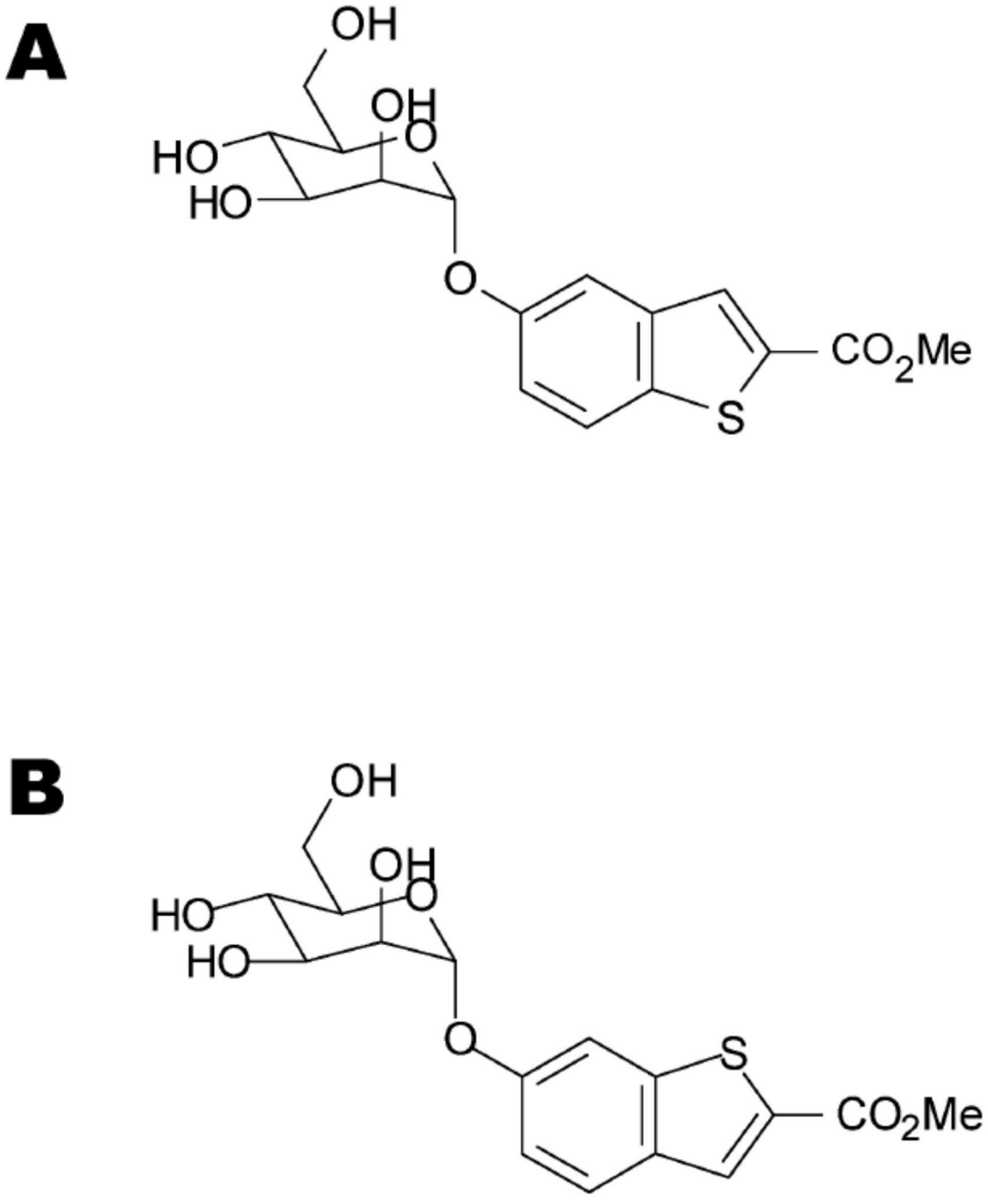


图36

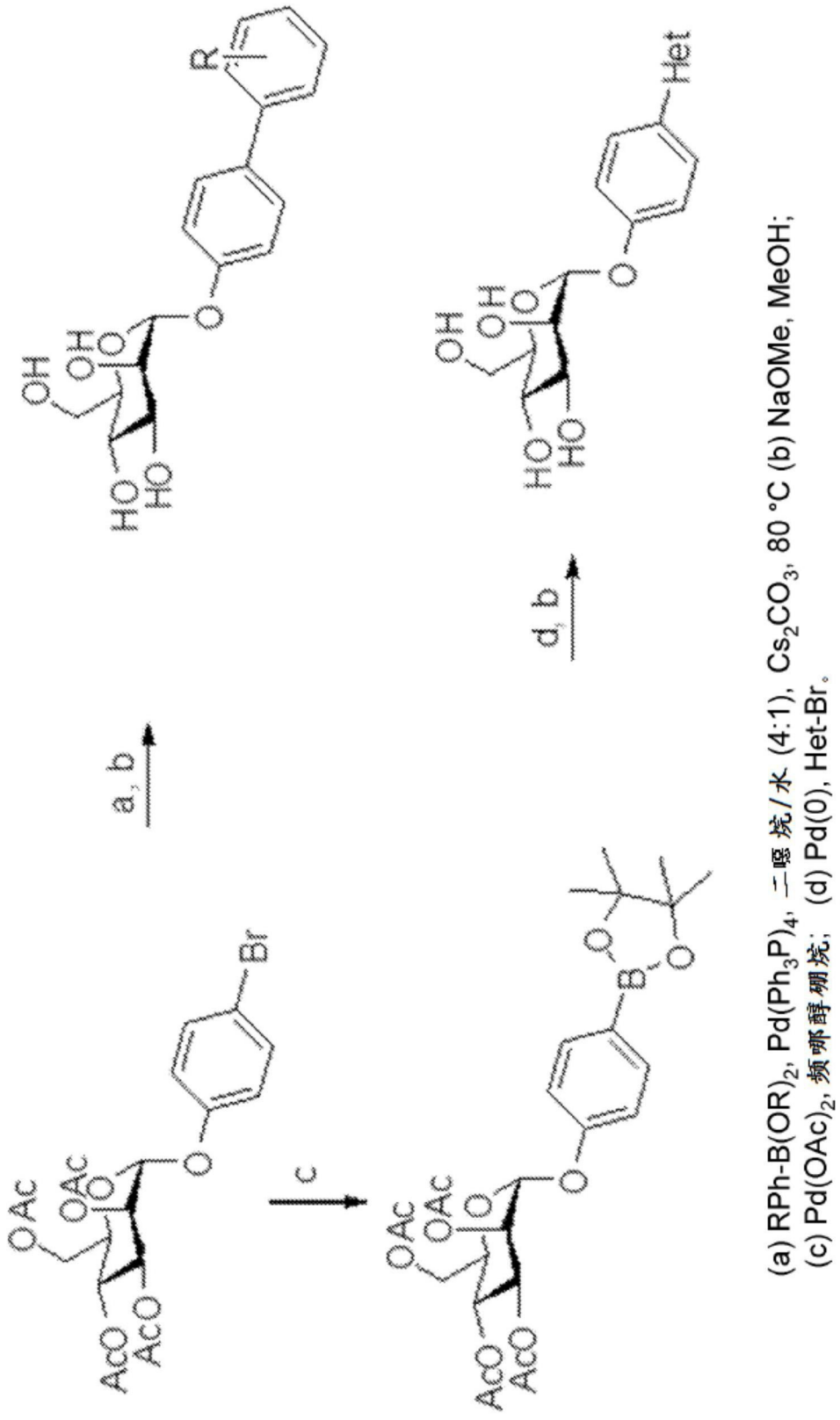

R
OH
OH
O
HO
HO
a, b
Br
OAc
OAc
O
AcO
AcO
c
B
O
O
d, b
Het
(a) RPh-B(OR)2, Pd(Ph3P)4, 二噁烷/水 (4:1), Cs2CO3, 80 °C (b) NaOMe, MeOH;
(c) Pd(OAc)2, 频哪酵硼烷; (d) Pd(0), Het-Br。

图36C