into macrophage cells. Alternatively, conjugation to antibodies targeting a cell surface antigen (e.g., WTA, Protein A) may improve the therapeutic effects of the rifamycin analogs.

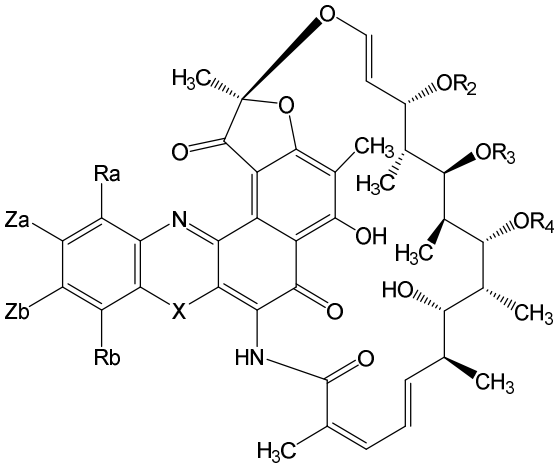
[00017] The foregoing discussion is presented solely to provide a better understanding of the nature of the problems confronting the art and should not be construed in any way as an admission as to prior art nor should the citation of any reference herein be construed as an admission that such reference constitutes "prior art" to the instant application.

SUMMARY OF THE DISCLOSURE

[00018] As discussed herein, there is a strong need to develop effective treatments for bacterial infections in general and *S. aureus* infections in particular. The present disclosure addresses these and other needs by providing new rifamycin analog compounds, intermediates and precursors thereof, antibody-drug conjugates, pharmaceutical compositions, and methods of treatment based on such compounds and pharmaceutical compositions.

[00019] Various non-limiting examples and examples are described below.

[00020] In one example, the present disclosure provides a rifamycin analog compound, intermediate or precursor thereof having a structure of formula (A):



(A)

or a pharmaceutically acceptable salt thereof, wherein:

X is selected from -O- and -NR*-;

Za and Zb are independently selected from a hydrogen, -Cl, -Br, $-OR_1$ and $-R_N$; with the proviso that at least one of Za or Zb is not a hydrogen; wherein:

R_1 is selected from a hydrogen, R_N, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, each of which further comprises 0-8

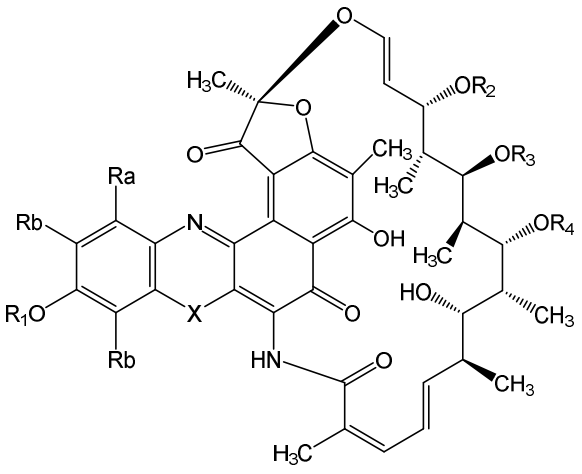
-(C=O)-R*, each of which further comprises 0-8 heteroatoms selected from halogen, O, N, and S;

R_a is selected from hydrogen, -F, -Cl, -Br, -I, -OH, -OR*, -NH_2, -NHR*, -$N(R^*)_2$, -$N(R^*)_3^+$, -(C=O)-R*, -CHO, -CO_2H, -CO_2R^*, -SR*, -SO_2R^*, and an aliphatic C_1-C_{20} hydrocarbon, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S, and wherein R_a is optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, -OR*;

R_b is selected from hydrogen, -F, -Cl, -Br, -I, -OH, -OR*, -(C=O)-R*, -CHO, -CO_2H, -CO_2R^* and an aliphatic C_1-C_{20} hydrocarbon, which further comprises 0-3 heteroatoms selected from halogen, O, and S, and wherein R_b is optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, -OR*, and

R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof.

[00021] In one example, the present disclosure provides a rifamycin analog compound having a structure of formula (I):



(I)

or a pharmaceutically acceptable salt thereof wherein:

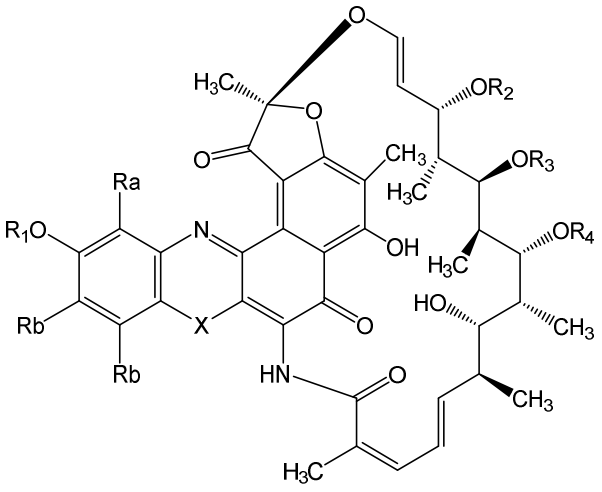
X is selected from -O- and -NR*-;

R_1 is selected from R_N, a hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, each of which further comprises 0-8 heteroatoms selected from halogen, O, N, and S, and wherein R_1 is optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, -OR*, -NO, -NO_2, -NO_3, -O-NO, -N_3, -NH_2, -NHR*, -$N(R^*)_2$,

further comprises 0-8 heteroatoms selected from halogen, O, N, and S, and wherein R_a is optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, -OR*;

R_b is selected from hydrogen, -F, -Cl, -Br, -I, -OH, -OR*, -(C=O)-R*, -CHO, -CO_2H, -CO_2R* and an aliphatic C_1-C_{20} hydrocarbon, which further comprises 0-3 heteroatoms selected from halogen, O, and S, and wherein R_b is optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, -OR*; and R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof.

[00022] In one example, the present disclosure provides a rifamycin analog compound having a structure of formula (I'):



(I')

or a pharmaceutically acceptable salt thereof wherein:

X is selected from -O- and -NR*-;

R_1 is selected from R_N, a hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, each of which further comprises 0-8 heteroatoms selected from halogen, O, N, and S, and wherein R_1 is optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, -OR*, -NO, -NO_2, -NO_3, -O-NO, -N_3, -NH_2, -NHR*, -N(R*)$_2$, -N(R*)$_3^+$, -N(R*)-OH, -O-N(R*)$_2$, -N(R*)-O-R*, -CN, -NC, -(C=O)-R*, -CHO, -CO_2H, -CO_2R*, -(C=O)-S-R*, -O-(C=O)-H, -O-(C=O)-R*, -S-(C=O)-R*, -(C=O)-NH_2, -(C=O)-N(R*)$_2$, -(C=O)-$NHNH_2$, -O-(C=O)-$NHNH_2$, -(C=S)-NH_2, -(C=S)-N(R*)$_2$, -N(R*)-CHO, -N(R*)-(C=O)-R*, -SCN, -NCS, -NSO, -SSR*, -SO_2R*, -SO_2-N(R*)$_2$, -S(=O)-OR*, -S(=O)-R*,

O, and S, and wherein R_b is optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, -OR*; and R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof.

[00023] In an example of a compound of the formulas (A), (I), or (I'), X is -O-, R_1 is an aliphatic C_1-C_3 hydrocarbon, R_2 is a methyl group, R_3 is Ac (-(C=O)-CH_3), R_4 is a hydrogen, and R_a is a hydrogen.

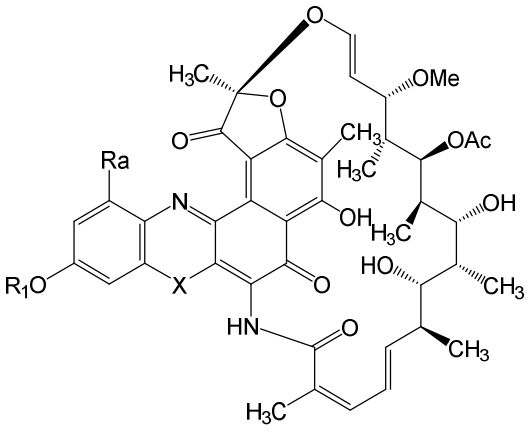
[00024] In an example of a compound of the formulas (A), (I), or (I'), X is -O-, R_1 is a benzyl group, R_2 is a methyl group, R_3 is Ac (-(C=O)-CH_3), R_4 is a hydrogen; R_a is a hydrogen and R_b is hydrogen.

[00025] In an example of a compound of the formulas (A), (I), or (I'), X is -O-, R_1 is an aliphatic C_1-C_8 hydrocarbon comprising 1-8 heteroatoms selected from O and N, R_2 is a methyl group, R_3 is Ac (-(C=O)-CH_3), R_4 is a hydrogen; R_a is a hydrogen and R_b is hydrogen.

[00026] In an example of a compound of the formulas (A), (I), or (I'), X is -O-; R_1 is an aliphatic C_1-C_8 hydrocarbon substituted with one or more of -NH_2, -NHR*, -N(R*)$_2$; R* is hydrogen or an aliphatic C_1-C_3 hydrocarbon; R_2 is a methyl group; R_3 is Ac (-(C=O)-CH_3); R_4 is a hydrogen; R_a is a hydrogen and R_b is hydrogen.

[00027] In an example of a compound of the formulas (A), (I), or (I'), X is -NCH_3-, R_1 is -OH, R_2 is a methyl group, R_3 is Ac (-(C=O)-CH_3), R_4 is a hydrogen, R_a is a hydrogen and R_b is hydrogen.

[00028] In one example, the rifamycin analog compounds of the disclosure have the structure of formula (II):

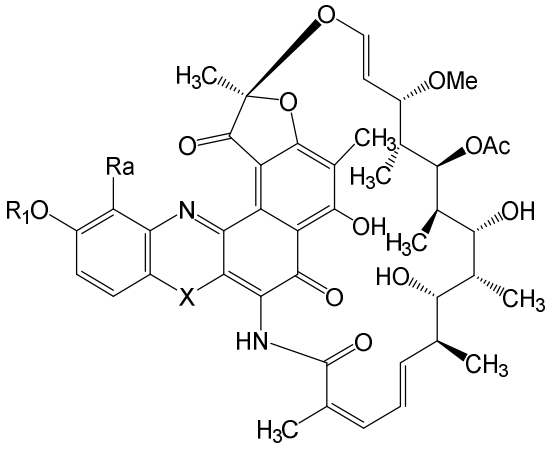


(II)

of attachment; and R', R" and R"' are selected from a hydrogen, a C_1-C_6 aliphatic hydrocarbon, and a protecting group selected from F_{MOC} and $B_{OC,}$ or wherein R' and R'' together form an aliphatic monocyclic, an aliphatic bicyclic, or an aliphatic polycyclic structure; and

R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof.

[00029] In one example, the rifamycin analog compounds of the disclosure have the structure of formula (II'):



(II')

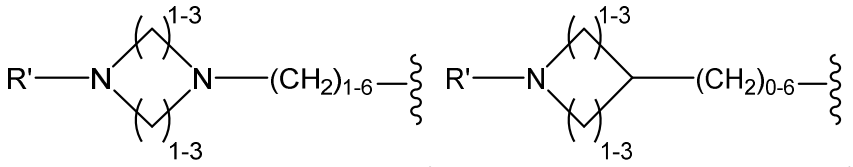
or a pharmaceutically acceptable salt thereof wherein:

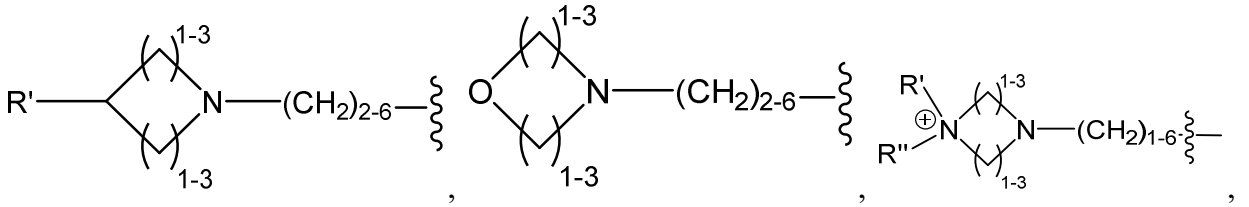
X is selected from -O- and -NR*-;

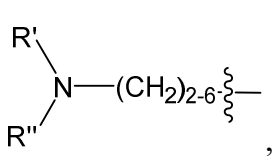
R_a is selected from hydrogen and -OR*;

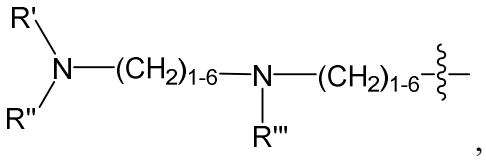
R_1 is selected from R_N, hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, each of which further comprises 0-8 heteroatoms selected from halogen, O, N, and S, and wherein R_1 is optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, -OR*, -NO, $-NO_2$, $-NO_3$, -O-NO, $-N_3$, $-NH_2$, -NHR*, $-N(R^*)_2$, $-N(R^*)_3^+$, -N(R*)-OH, $-O-N(R^*)_2$, -N(R*)-O-R*, -CN, -NC, -(C=O)-R*, -CHO, $-CO_2H$, $-CO_2R^*$, -(C=O)-S-R*, -O-(C=O)-H, -O-(C=O)-R*, -S-(C=O)-R*, $-(C=O)-NH_2$, $-(C=O)-N(R^*)_2$, $-(C=O)-NHNH_2$, $-O-(C=O)-NHNH_2$, $-(C=S)-NH_2$, $-(C=S)-N(R^*)_2$, -N(R*)-CHO, -N(R*)-(C=O)-R*, -SCN, -NCS, -NSO, -SSR*, $-SO_2R^*$, $-SO_2-N(R^*)_2$, -S(=O)-OR*, -S(=O)-R*, $-Si(R^*)_3$, $-CF_3$, $-O-CF_3$ and combinations thereof, with a proviso that R_1 is not an n-butyl group;

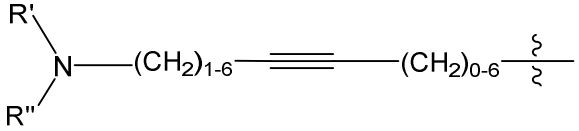
R_N is selected from:

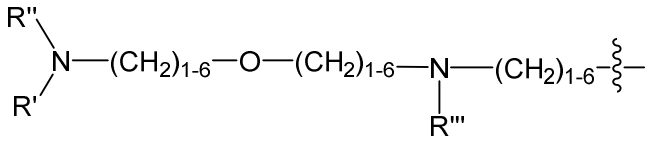


,


,


,


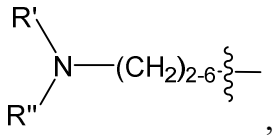
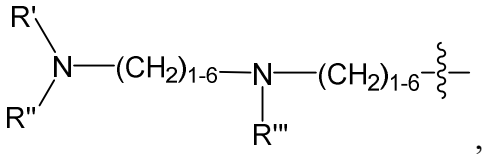
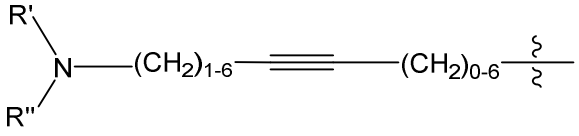
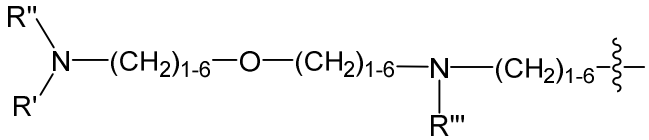
,


and


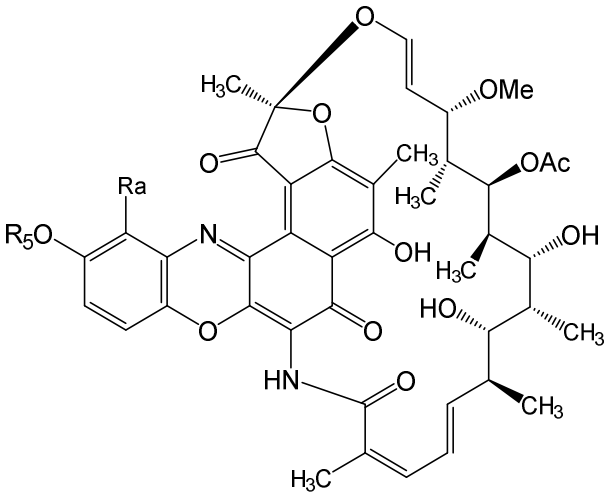
; wherein the ~~~ symbol represents the point of attachment; and R', R" and R''' are selected from a hydrogen, a C_1-C_6 aliphatic hydrocarbon, and a protecting group selected from F_{MOC} and $B_{OC,}$ or wherein R' and R'' together form an aliphatic monocyclic, an aliphatic bicyclic, or an aliphatic polycyclic structure; and

R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof.

[00030] In one example, the rifamycin analog compounds of the disclosure have the structure of formula (III):


,

,

and

; wherein the ~~~ symbol represents the point of attachment; and R', R" and R''' are selected from a hydrogen, a C_1-C_6 aliphatic hydrocarbon, and a protecting group selected from F_{MOC} and $B_{OC,}$ or wherein R' and R'' together form an aliphatic monocyclic, an aliphatic bicyclic, or an aliphatic polycyclic structure.

[00031] In one example, the rifamycin analog compounds of the disclosure have the structure of formula (III'):


(III')

or a pharmaceutically acceptable salt thereof wherein:

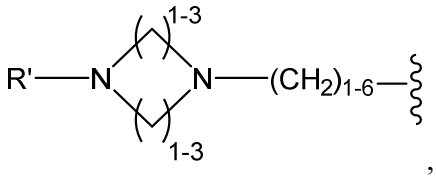
R_a is selected from hydrogen and -OR*;

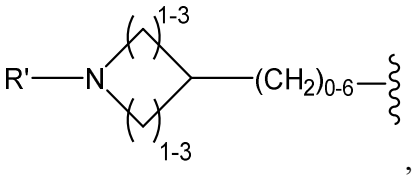
R_5 is selected from R_N, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, each of which further comprises 0-8 heteroatoms selected from halogen, O, N, and S, and wherein R_5 is optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, -OR*, -NH_2, -NHR*, -$N(R^*)_2$, -$N(R^*)_3^+$, -N(R*)-(C=O)-R*, -(C=O)-R*, -CHO,

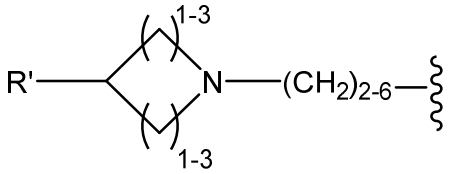
$-CO_2H$, $-CO_2R^*$ and combinations thereof, with a proviso that R_5 is not an n-butyl group;

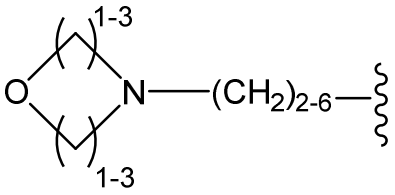
R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof; and

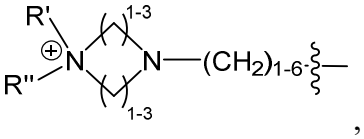
R_N is selected from:

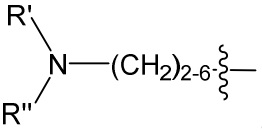


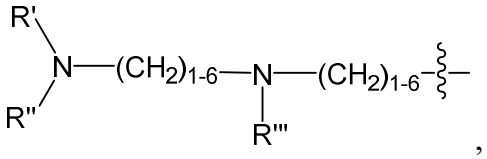
,


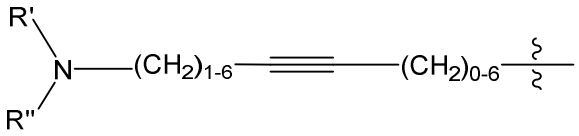
,


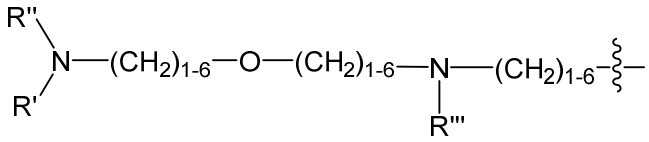
,


,


,


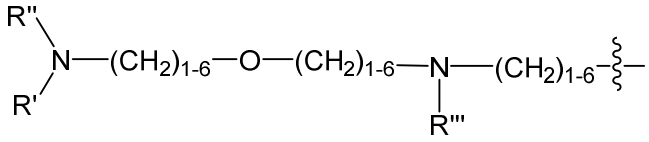
,


,


and


wherein the ~~~ symbol represents the point of attachment; and R', R" and R''' are selected from a hydrogen, a C_1-C_6 aliphatic hydrocarbon, and a protecting group selected from F_{MOC} and $B_{OC,}$ or wherein R' and R'' together form an aliphatic monocyclic, an aliphatic bicyclic, or an aliphatic polycyclic structure.

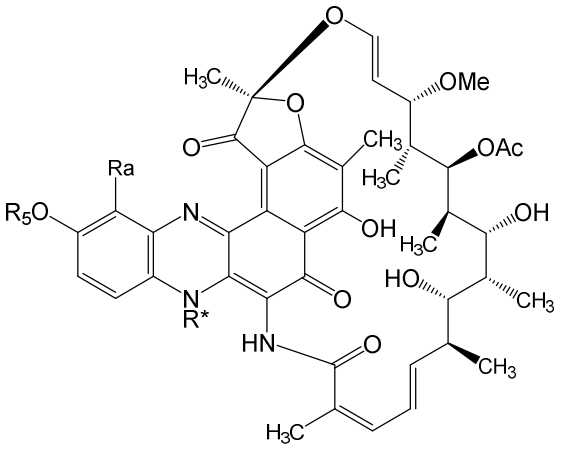
[00032] In one example, the rifamycin analog compounds of the disclosure have the structure of formula (IV):



wherein the ~~~ symbol represents the point of attachment; and R', R" and R"' are selected from a hydrogen, a C_1-C_6 aliphatic hydrocarbon, and a protecting group selected from F_{MOC} and $B_{OC,}$ or wherein R' and R'' together form an aliphatic monocyclic, an aliphatic bicyclic, or an aliphatic polycyclic structure; and

R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof.

[00033] In one example, the rifamycin analog compounds of the disclosure have the structure of formula (IV'):



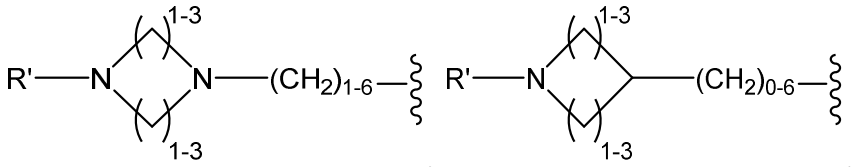
(IV')

or a pharmaceutically acceptable salt thereof wherein:

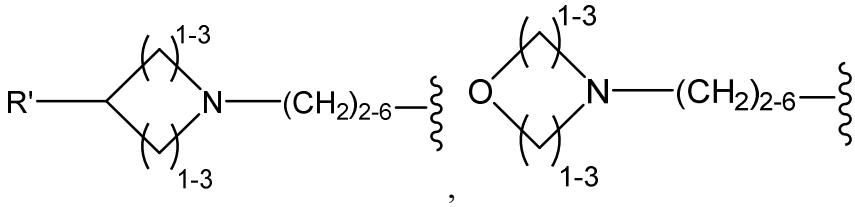
R_a is selected from hydrogen and -OR*;

R_5 is selected from R_N, hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, each of which further comprises 0-8 heteroatoms selected from halogen, O, N, and S, and wherein R_5 is optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, -OR*, -NH_2, -NHR*, -$N(R^*)_2$, -$N(R^*)_3^+$, -N(R*)-(C=O)-R*, -(C=O)-R*, -CHO, -CO_2H, -CO_2R* and combinations thereof;

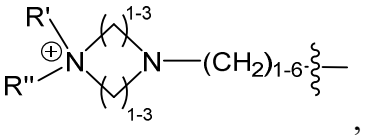
R_N is selected from:



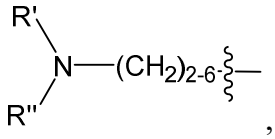
,



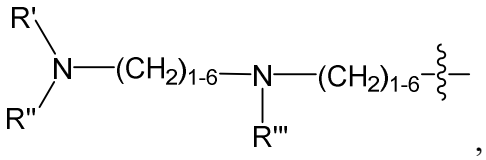
,



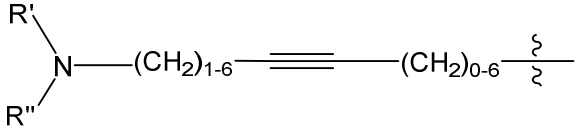
,



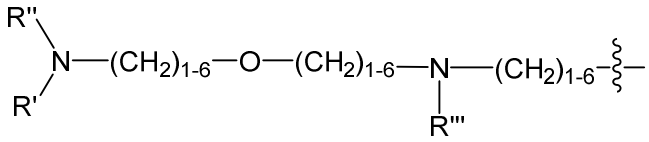
,



,



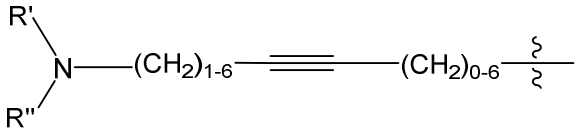
and



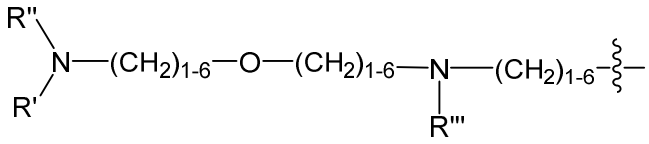
; wherein the ~~~ symbol represents the point of attachment; and R', R" and R''' are selected from a hydrogen, a C_1-C_6 aliphatic hydrocarbon, and a protecting group selected from F_{MOC} and $B_{OC,}$ or wherein R' and R'' together form an aliphatic monocyclic, an aliphatic bicyclic, or an aliphatic polycyclic structure; and

R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof.

[00034] In one example, the rifamycin analog compounds of the disclosure have the structure of formula (V):



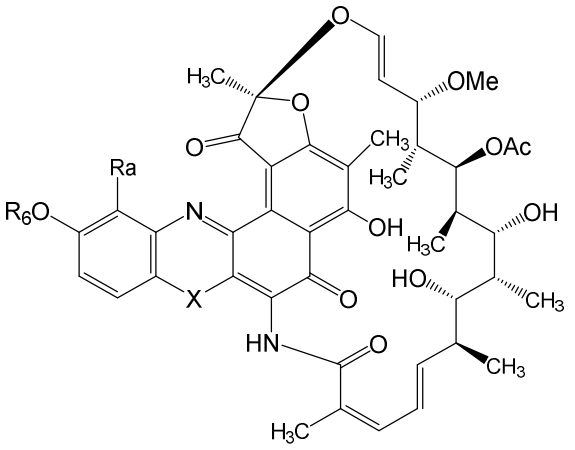
and



; wherein the ~~~ symbol represents the point of attachment; and R', R" and R''' are selected from a hydrogen, a C_1-C_6 aliphatic hydrocarbon, and a protecting group selected from F_{MOC} and $B_{OC,}$ or wherein R' and R'' together form an aliphatic monocyclic, an aliphatic bicyclic, or an aliphatic polycyclic structure; and

R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof.

[00035] In one example, the rifamycin analog compounds of the disclosure have the structure of formula (V'):



(V')

or a pharmaceutically acceptable salt thereof wherein:

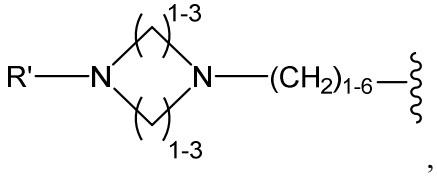
X is selected from -O- and -NR*-;

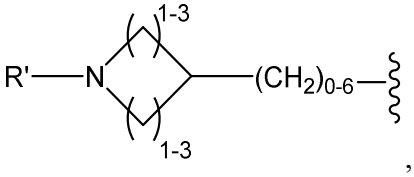
R_a is selected from hydrogen and -OR*;

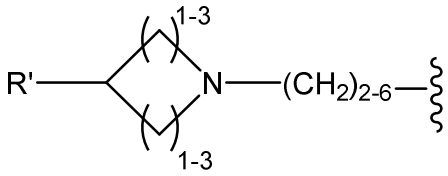
R_6 is selected from R_N, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, each of which further comprises 0-8 heteroatoms selected from halogen, O, N, and S, and wherein R_6 is optionally substituted with one or more of -OH, -OR*, $-NH_2$, -NHR*, $-N(R^*)_2$, $-N(R^*)_3^+$, -N(R*)-(C=O)-R*, -(C=O)-R*, -CHO, $-CO_2H$, $-CO_2R^*$ and

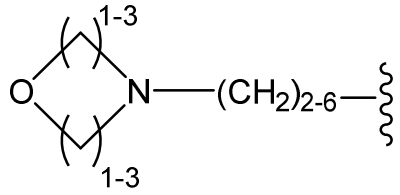
combinations thereof, with a proviso that R_6 is not an n-butyl group;

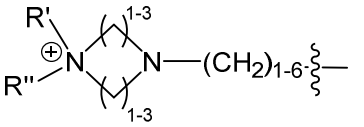
R_N is selected from:

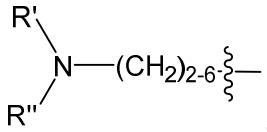


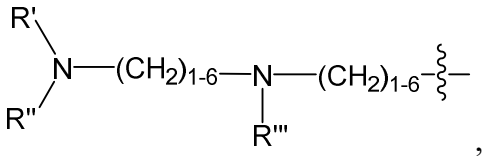
,


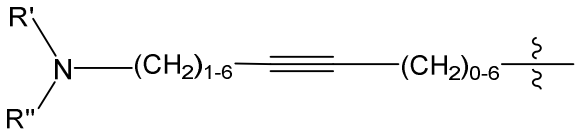
,


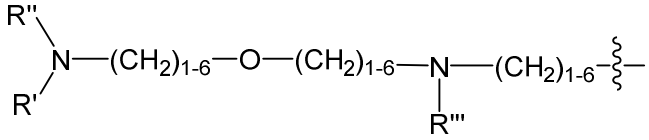
,


,


,


,


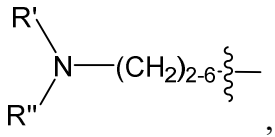
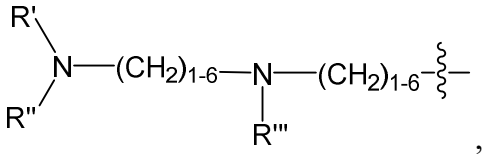
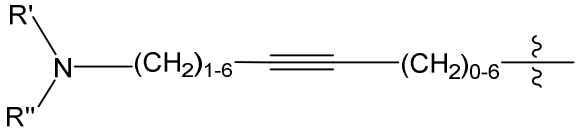
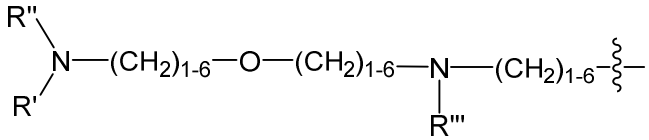
,


and


wherein the 〰 symbol represents the point of attachment; and R', R" and R''' are selected from a hydrogen, a C_1-C_6 aliphatic hydrocarbon, and a protecting group selected from F_{MOC} and $B_{OC,}$ or wherein R' and R'' together form an aliphatic monocyclic, an aliphatic bicyclic, or an aliphatic polycyclic structure; and

R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof.

[00036] In another example, the present disclosure provides a rifamycin analog compound, intermediate or precursor thereof having a structure of formula (B):


,

,

and

; wherein the ~~~ symbol represents the point of attachment; and R', R" and R''' are selected from a hydrogen, a C_1-C_6 aliphatic hydrocarbon, and a protecting group selected from Fluorenylmethyloxycarbonyl (FMOC) and *tert*-Butyloxycarbonyl (BOC), or wherein R' and R'' together form an aliphatic monocyclic, an aliphatic bicyclic, or an aliphatic polycyclic structure;

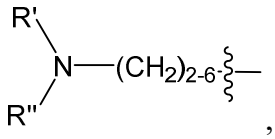
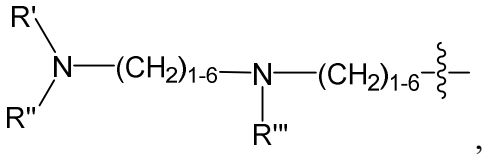
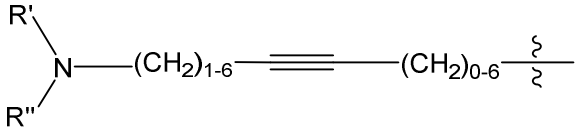
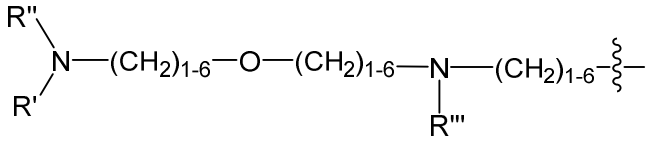
R_2, R_3, and R_4 are independently selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, and -(C=O)-R*, each of which further comprises 0-8 heteroatoms selected from halogen, O, N, and S;

R_a is selected from hydrogen, -F, -Cl, -Br, -I, -OH, -OR*, $-NH_2$, -NHR*, $-N(R^*)_2$, $-N(R^*)_3^+$, -(C=O)-R*, -CHO, $-CO_2H$, $-CO_2R^*$, -SR*, $-SO_2R^*$, and an aliphatic C_1-C_{20} hydrocarbon, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S, and wherein R_a is optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, -OR*;

R_b is selected from hydrogen, -F, -Cl, -Br, -I, -OH, -OR*, -(C=O)-R*, -CHO, $-CO_2H$, $-CO_2R^*$ and an aliphatic C_1-C_{20} hydrocarbon, which further comprises 0-3 heteroatoms selected from halogen, O, and S, and wherein R_b is optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, -OR*, and

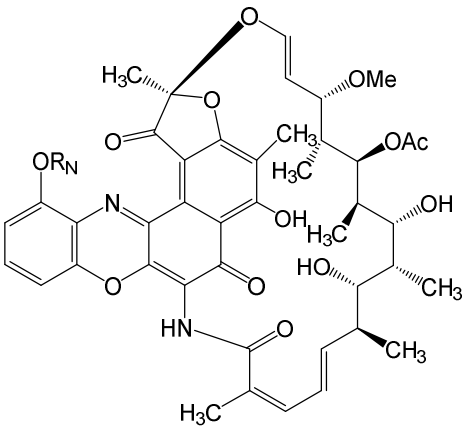
R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof.

[00037] In another example, the present disclosure provides a rifamycin analog compound having a structure of formula (B-1):


,

,

and

; wherein the ~~~ symbol represents the point of attachment; and R', R" and R''' are selected from a hydrogen, a C_1-C_6 aliphatic hydrocarbon, and a protecting group selected from F_{MOC} and $B_{OC,}$ or wherein R' and R'' together form an aliphatic monocyclic, an aliphatic bicyclic, or an aliphatic polycyclic structure; and

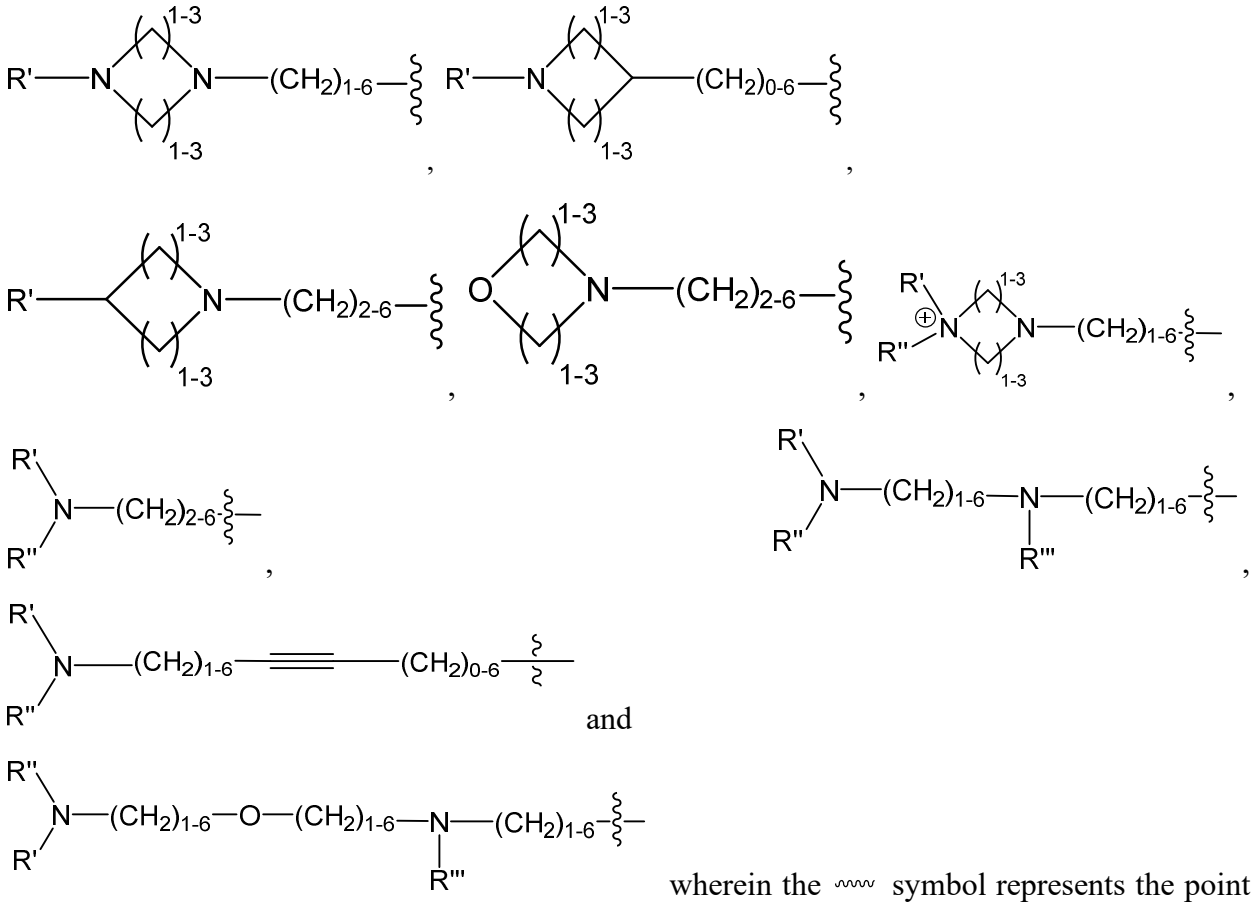
R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof.

[00038] In another example, the present disclosure provides a rifamycin analog compound having a structure of formula (B-2):


(B-2)

or a pharmaceutically acceptable salt thereof wherein:

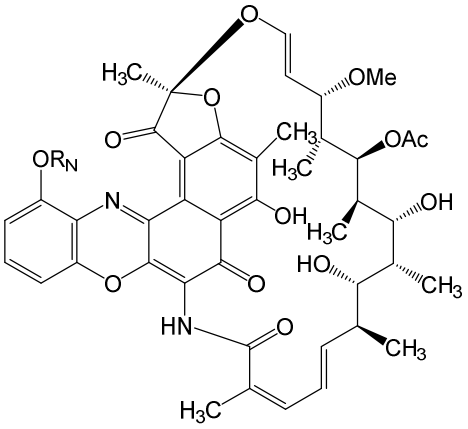
R_N is selected from:



and

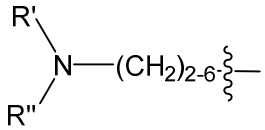
wherein the 〰 symbol represents the point of attachment; and R', R" and R''' are selected from a hydrogen, a C_1-C_6 aliphatic hydrocarbon, and a protecting group selected from F_{MOC} and $B_{OC,}$ or wherein R' and R'' together form an aliphatic monocyclic, an aliphatic bicyclic, or an aliphatic polycyclic structure.

[00039] In another example, the present disclosure provides a rifamycin analog compound having a structure of formula (B-2):

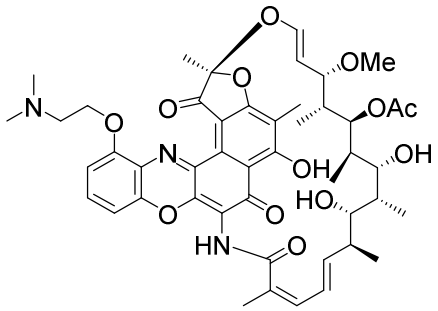


(B-2)

or a pharmaceutically acceptable salt thereof wherein:

R_N is  wherein the ~~~ symbol represents the point of attachment; and R' and R" are selected from a hydrogen and a C_1-C_6 aliphatic hydrocarbon.

[00040] In one example, a rifamycin analog compound has a structure according to the following formula:



,

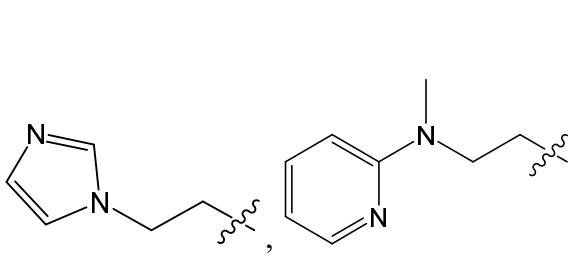
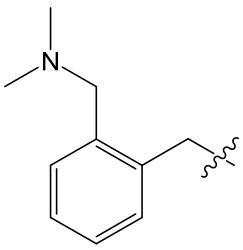
or a pharmaceutically acceptable salt thereof.

[00041] In an example of any of the preceding formulas is provided a compound wherein R_1 is selected from R_N, a hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, each of which further comprises 0-3 heteroatoms selected from O and N, and wherein R_1 is optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, C_{1-3} alkoxide, $-NH_2$, -NHR*, $-N(R^*)_2$, $-N(R^*)_3^+$, -N(R*)-OH, $-O-N(R^*)_2$, -N(R*)-O-R*, -N(R*)-(C=O)-R*, -(C=O)-R*, -CHO, $-CO_2H$, $-CO_2R^*$, -O-(C=O)-H, -O-(C=O)-R*, $-(C=O)-NH_2$, $-(C=O)-N(R^*)_2$, $-Si(R^*)_3$, $-CF_3$, $-O-CF_3$ and combinations thereof, with the provisos that R_1 is not an n-butyl group, and when X is -O-, R_1 is not hydrogen.

[00042] In an example of any of the preceding formulas is provided a compound wherein R_1 is a combination of an aliphatic C_1-C_{20} hydrocarbon and an aromatic C_1-C_{20} hydrocarbon.

[00043] In an example of any of the preceding formulas is provided a compound wherein R_1 is a combination of an aliphatic C_1-C_{20} hydrocarbon and a heteroaromatic C_1-C_{20} hydrocarbon.

[00044] In an example of any of the preceding formulas is provided a compound wherein R_1 is selected from:


,
, and 
.

[00045] In an example of any of the preceding formulas is provided a compound wherein R_1 is an aliphatic C_1-C_{20} hydrocarbon substituted with one or more of -NH_2, -NHR*, -$N(R^*)_2$, , or -N(R*)-(C=O)-R*.

[00046] In an example of any of the preceding formulas is provided a compound wherein R_1 is an aliphatic C_1-C_{20} hydrocarbon substituted with -NH-(C=O)-CH_3 or -$N(CH_3)$-(C=O)-CH_3.

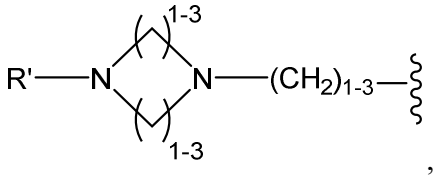
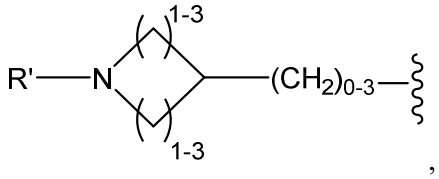
[00047] In an example of any of the preceding formulas is provided a compound wherein R_a is hydrogen.

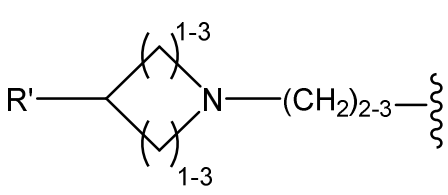
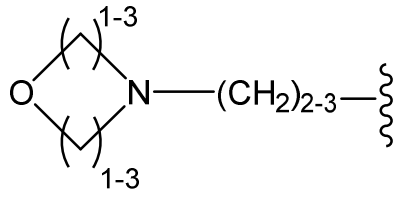
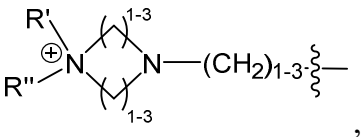
[00048] In an example of any of the preceding formulas is provided a compound wherein R_a is -OH.

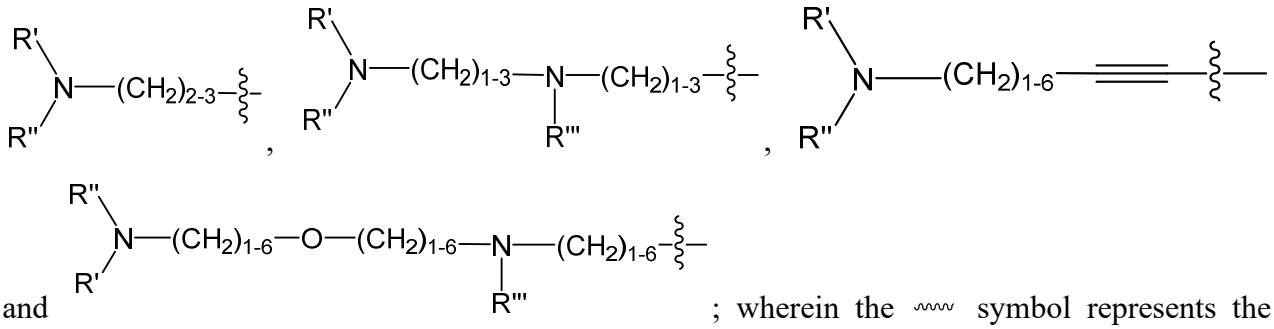
[00049] In an example of any of the preceding formulas is provided a compound wherein R_a is -Cl.

[00050] In an example of any of the preceding formulas is provided a compound wherein R_a is -OR*, and R* is selected from an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, and combinations thereof.

[00051] In an example of any of the preceding formulas is provided a compound wherein R_N is selected from:

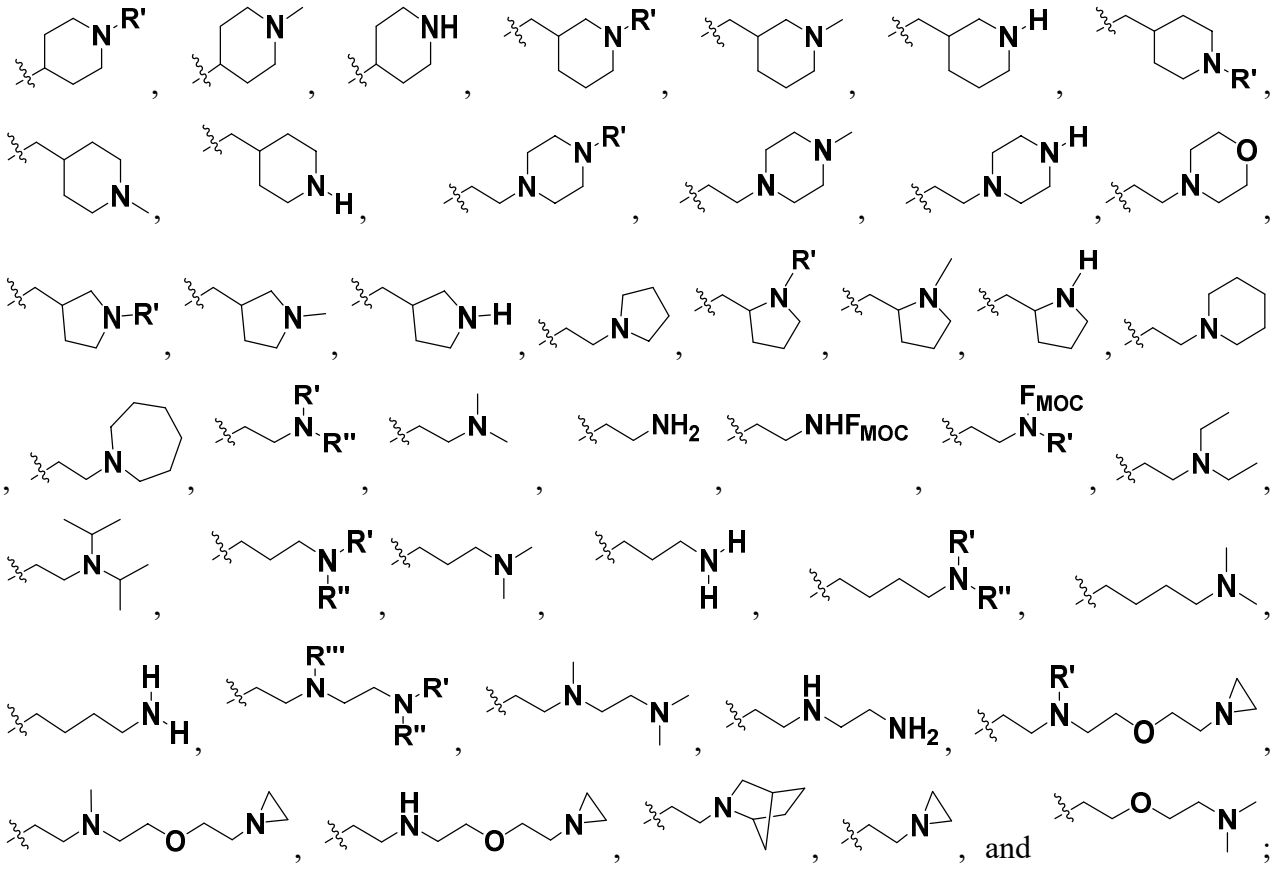

, 
,


, 
, 
,



and ; wherein the symbol represents the point of attachment; and R', R" and R''' are selected from a hydrogen, a C_1-C_6 aliphatic hydrocarbon, and a protecting group selected from F_{MOC} and $B_{OC,}$ or wherein R' and R'' together form an aliphatic monocyclic, an aliphatic bicyclic, or an aliphatic polycyclic structure.

[00052] In an example of any of the preceding formulas is provided a compound wherein R_N is selected from:

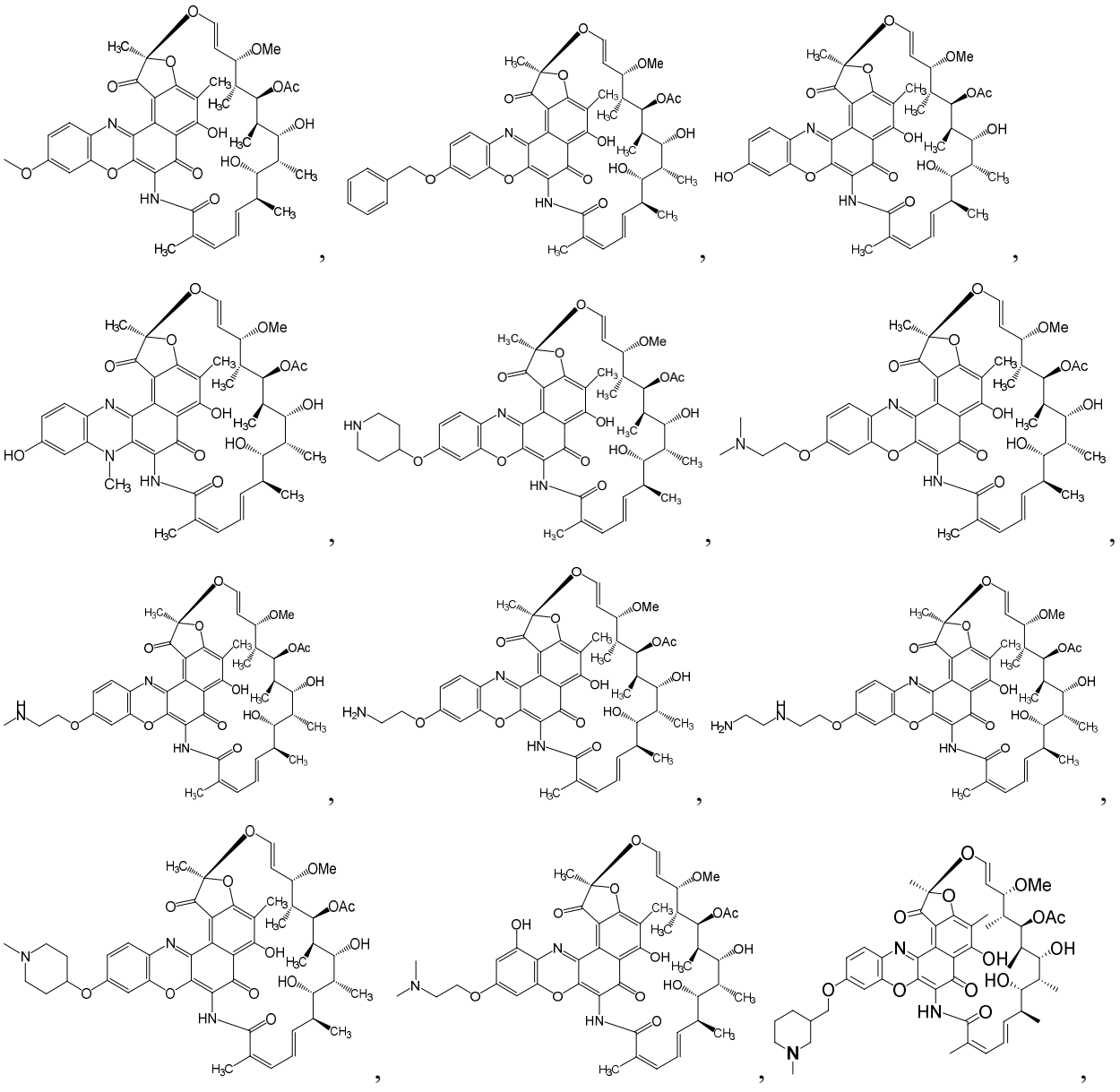


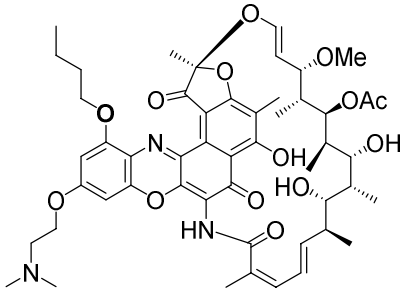
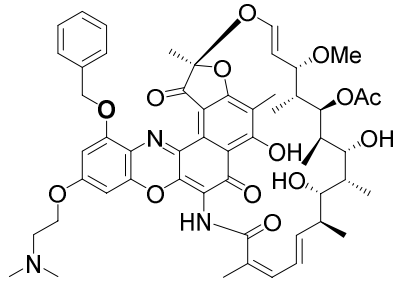
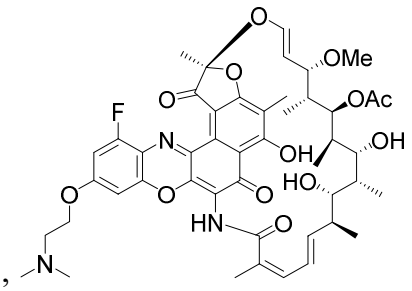
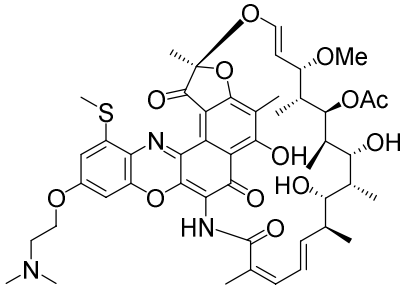
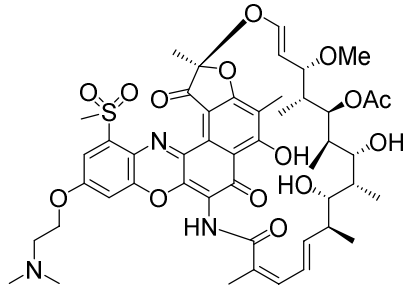
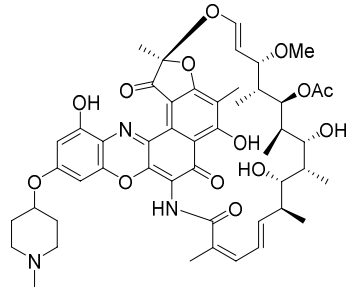
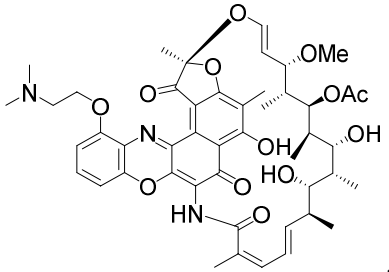
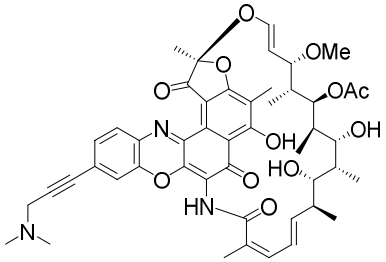
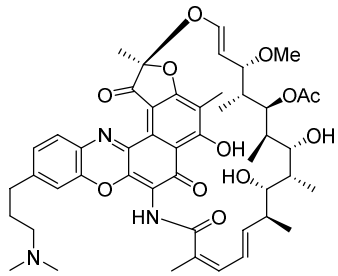
wherein R' is hydrogen, aliphatic hydrocarbon or a protecting group, and wherein the symbol represents the point of attachment.

[00053] In an example of a compound of any of the preceding formulas is provided a

compound wherein R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_6 hydrocarbon, an aromatic C_4-C_6 hydrocarbon, and combinations thereof, which optionally comprise 1-3 heteroatoms selected from O, N and combinations thereof.

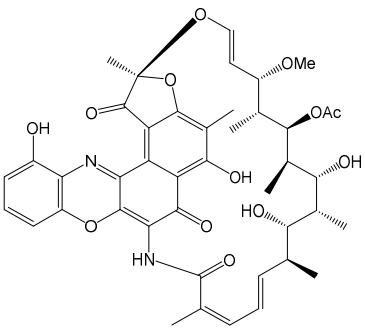
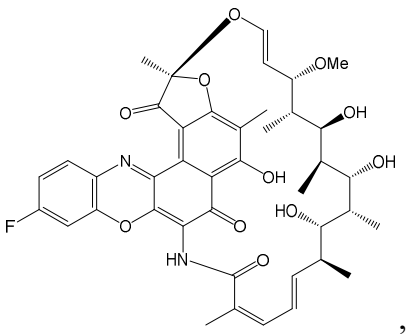
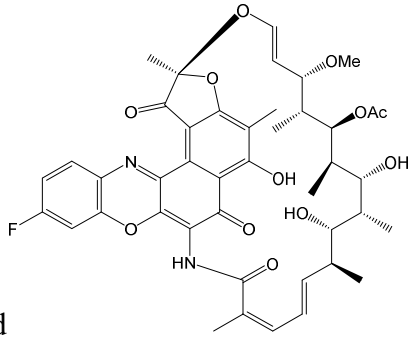
[00054] In one example, a rifamycin analog compound of the disclosure has a structure selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

[00055] In one example, a rifamycin analog compound of the disclosure has a structure selected from the group consisting of:

or a pharmaceutically acceptable salt thereof.

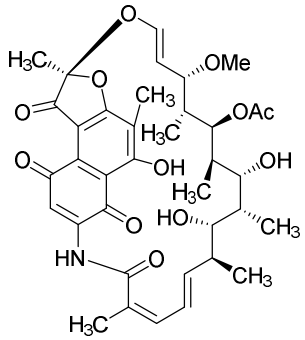
[00056] In one example, the present disclosure provides a method of manufacturing a rifamycin analog compound having the structure of formula (V):

and a protecting group selected from F_{MOC} and $B_{OC,}$ or wherein R' and R'' together form an aliphatic monocyclic, an aliphatic bicyclic, or an aliphatic polycyclic structure; and

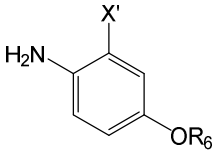
R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof,

comprising the steps of:

(a) contacting Rifamycin S having the structure:



with a compound having the structure of formula (VI):

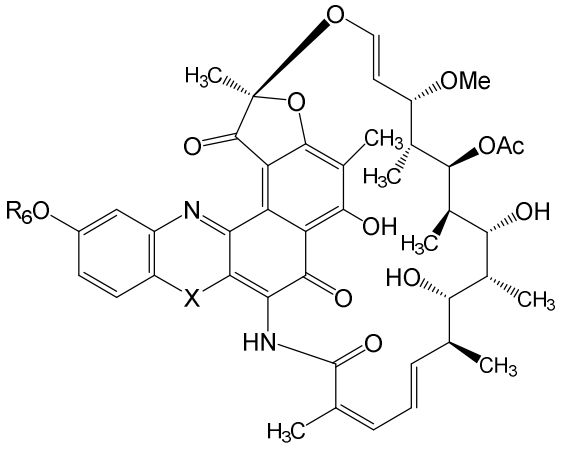


(VI),

wherein X' is selected from -OH and -NHR*, and

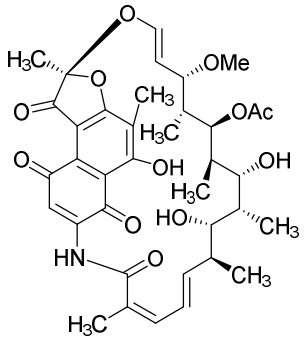
(b) treating the product of step (a) with an oxidizing agent.

[00057] In one example, the present disclosure provides a method of manufacturing a rifamycin analog compound having the structure of formula (V'):

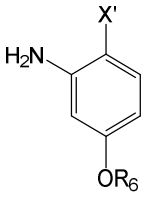


(V'),

wherein X is selected from -O- and NR*-;



with a compound having the structure of formula (VI'):

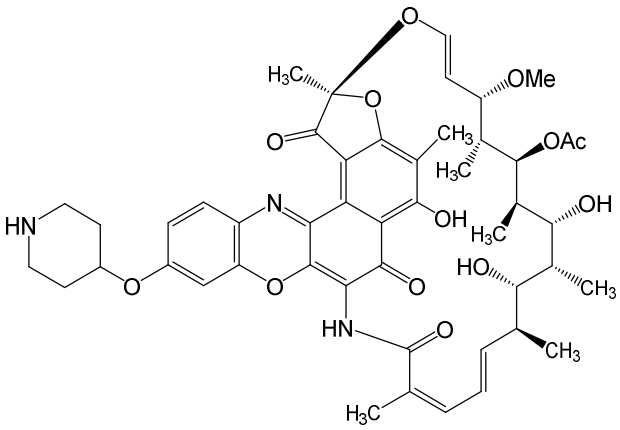


(VI'),

wherein X' is selected from -OH and -NHR*, and

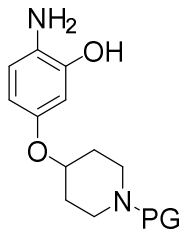
(b) treating the product of step (a) with an oxidizing agent.

[00058] In one example, the present disclosure provides a method of manufacturing a compound having the structure:



comprising the steps of:

(a) contacting Rifamycin S with a compound having the structure of formula (VII):



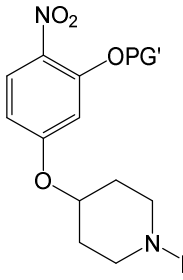
(VII),

wherein PG is a protecting group;

(b) treating the product of step (a) with an oxidizing agent, and

(c) removing the protecting group PG.

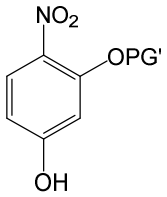
[00059] In one example, the compound of formula (VII) is prepared by removing protecting group PG' from a compound of formula (VIII):

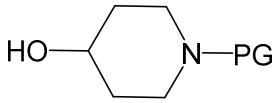


(VIII),

wherein protecting groups PG and PG' may be the same or different from each other.

[00060] In one example, the compound of formula (VIII) is prepared by contacting a compound of formula (IX):

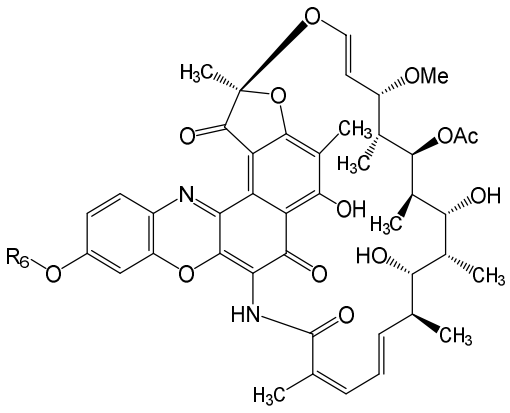


(IX) with a compound of formula (X): 

(X),

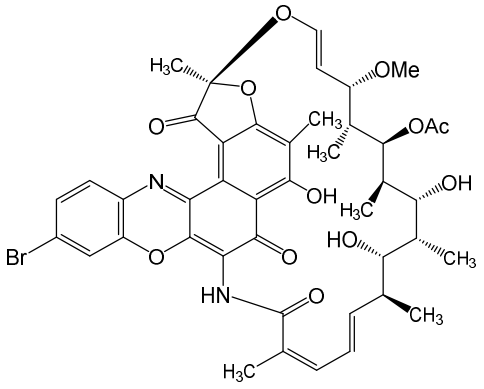
wherein protecting groups PG and PG' may be the same or different from each other.

[00061] In one example, the present disclosure provides a method of manufacturing a compound having the structure of formula (XI):



(XI)

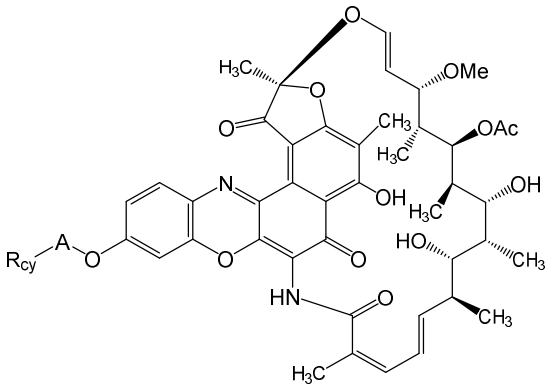
wherein R_6 is selected from R_N, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof and wherein R_6 is optionally substituted with one or more of -F-Cl, -Br, -I, -OH, -OR*, -NO, -NO_2, -NO_3, -O-NO, -N_3, -NH_2, -NHR*, -$N(R^*)_2$, -



(XII)

with an alcohol having the structure R_6-OH.

[00062] In one example, the present disclosure provides a method of manufacturing a compound having the structure of formula (XIII):



(XIII)

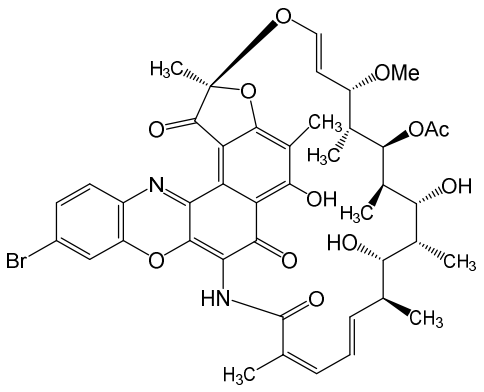
wherein A is selected from a bond (A is absent) or an aliphatic C_1-C_{20} hydrocarbon;

R_{cy} is a C_3-C_{14} cycloaliphatic hydrocarbon which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof and wherein R_{cy} is optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, -OR*, -NO, -NO_2, -NO_3, -O-NO, -N_3, -NH_2, -NHR*, -N(R*)$_2$, -N(R*)$_3^+$, -N(R*)-OH, -O-N(R*)$_2$, -N(R*)-O-R*, -CN, -NC, -(C=O)-R*, -CHO, -CO_2H, -CO_2R*, -(C=O)-S-R*, -O-(C=O)-H, -O-(C=O)-R*, -S-(C=O)-R*, -(C=O)-NH_2, -(C=O)-N(R*)$_2$, -(C=O)-$NHNH_2$, -O-(C=O)-$NHNH_2$, -(C=S)-NH_2, -(C=S)-N(R*)$_2$, -N(R*)-CHO, -N(R*)-(C=O)-R*, -SCN, -NCS, -NSO, -SSR*, -SO_2R*, -SO_2-N(R*)$_2$, -S(=O)-OR*, -S(=O)-R*, -Si(R*)$_3$, -CF_3, -O-CF_3 and combinations thereof; and

R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further

comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof;

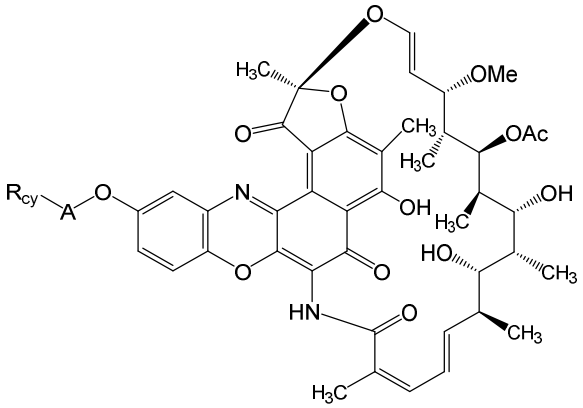
comprising contacting a compound having the structure of formula (XII):



(XII)

with an alcohol having the structure R_{cy}-A-OH.

[00063] In one example, the present disclosure provides a method of manufacturing a compound having the structure of formula (XIII'):



(XIII')

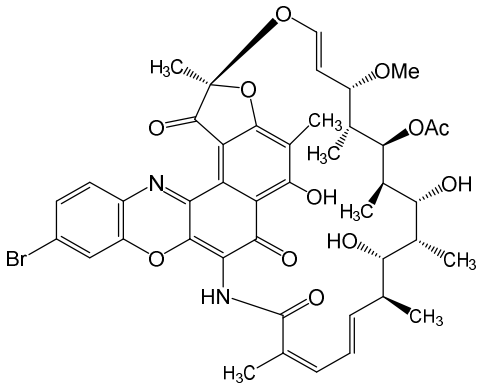
wherein A is selected from a bond (A is absent) or an aliphatic C_1-C_{20} hydrocarbon;

R_{cy} is a C_3-C_{14} cycloaliphatic hydrocarbon which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof and wherein R_{cy} is optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, -OR*, -NO, -NO_2, -NO_3, -O-NO, -N_3, -NH_2, -NHR*, -$N(R^*)_2$, -$N(R^*)_3^+$, -N(R*)-OH, -O-$N(R^*)_2$, -N(R*)-O-R*, -CN, -NC, -(C=O)-R*, -CHO, -CO_2H, -CO_2R^*, -(C=O)-S-R*, -O-(C=O)-H, -O-(C=O)-R*, -S-(C=O)-R*, -(C=O)-NH_2, -(C=O)-$N(R^*)_2$, -(C=O)-$NHNH_2$, -O-(C=O)-$NHNH_2$, -(C=S)-NH_2, -(C=S)-$N(R^*)_2$, -N(R*)-CHO, -N(R*)-(C=O)-R*, -SCN, -NCS, -NSO, -SSR*, -SO_2R^*, -SO_2-$N(R^*)_2$, -S(=O)-OR*, -S(=O)-R*, -$Si(R^*)_3$, -CF_3, -O-CF_3 and combinations thereof; and

R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon,

an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof;

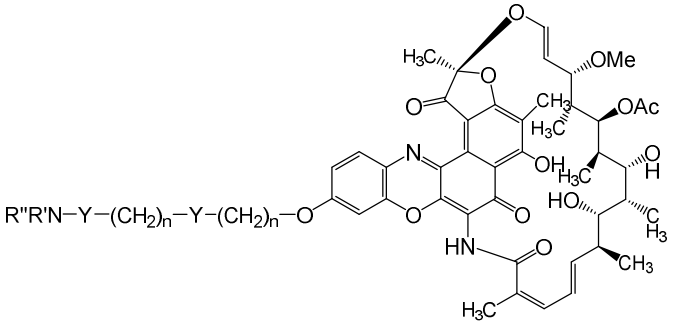
comprising contacting a compound having the structure of formula (XII):



(XII)

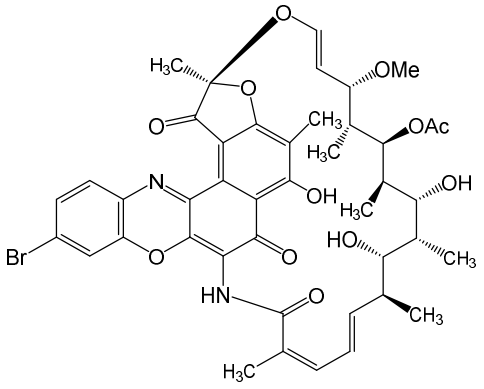
with an alcohol having the structure R_{cy}-A-OH.

[00064] In one example, the present disclosure provides a method of manufacturing a compound having the structure of formula (XIV):



(XIV),

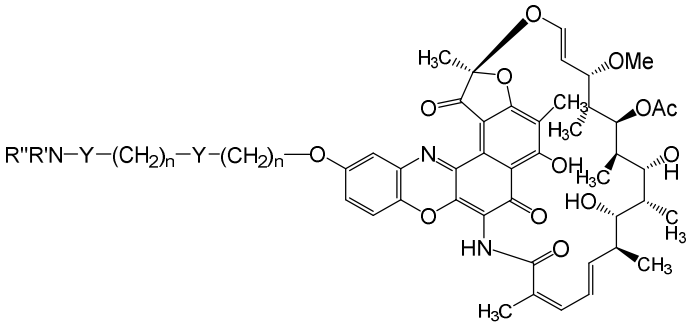
wherein Y is at each occurrence selected from -O- and -NR'R"-; n is independently at each occurrence an integer from 1-6, and R', R'', and R''' are each independently selected from a hydrogen, an aliphatic C_1-C_{20} hydrocarbon; said method comprising contacting a compound having the structure of formula (XII):



(XII)

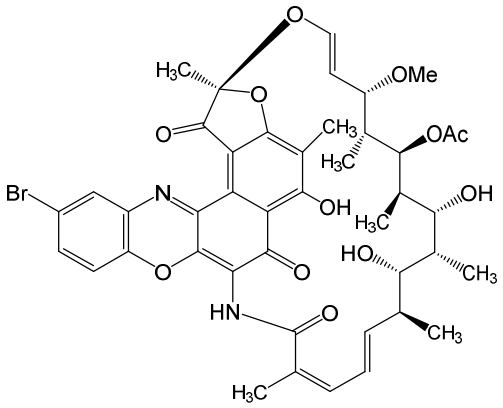
with an alcohol having the structure $R''R'N-Y-(CH_2)_n-Y-(CH_2)_n-OH$.

[00065] In one example, the present disclosure provides a method of manufacturing a compound having the structure of formula (XIV'):



(XIV'),

wherein Y is at each occurrence selected from -O- and -NR'R"-; n is independently at each occurrence an integer from 1 to 6, and R', R'', and R''' are each independently selected from a hydrogen and an aliphatic C_1-C_{20} hydrocarbon; said method comprising contacting a compound having the structure of formula (XII'):



(XII')

with an alcohol having the structure $R''R'N-Y-(CH_2)_n-Y-(CH_2)_n-OH$.

[00066] In one example, the compound of formula (XII) is prepared by contacting Rifamycin S with 2-amino-5-bromophenol, and treating the product with an oxidizing agent.

[00067] In one example, the compound of formula (XII') is prepared by contacting Rifamycin S with 2-amino-4-bromophenol, and treating the product with an oxidizing agent.

[00068] In one example, the present disclosure provides a pharmaceutical composition comprising any one or more of compounds as described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[00069] In another example, the present disclosure provides a pharmaceutical dosage form comprising any one or more of compounds as described above, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described above.

[00070] In another example, the present disclosure provides a method of preventing or inhibiting growth of a bacterium comprising administering an effective amount of a rifamycin analog compound having a structure according to any one of formula (A), (B), (I), (I'), (II), (II'), (III), (III'), (IV), (IV'), (V), (V') as provided herein.

[00071] In one example, the bacterium is a Gram-positive bacterium.

[00072] In one example, the bacterium is a penicillin-resistant bacterium.

[00073] In one example, the bacterium is *Staphylococcus aureus*.

[00074] In one example, the bacterium is methicillin-resistant *Staphylococcus aureus* (MRSA).

[00075] In one example, the bacterium is vancomycin-resistant *Staphylococcus aureus* (VRSA).

[00076] In one example, the bacterium is methicillin-susceptible *Staphylococcus aureus* (MSSA).

[00077] In yet another example, the present disclosure provides a method of treating a bacterial infection in a subject in need of such treatment comprising administering to the subject an effective amount of a rifamycin analog compound having a structure according to any one of formula (A), (B), (I), (I'), (II), (II'), (III), (III'), (IV), (IV'), (V), (V') as provided herein.

[00078] In one example, the bacterial infection is a Gram-positive bacterial infection.

[00079] In one example, the bacterial infection is a penicillin-resistant bacterial infection.

[00080] In one example, the bacterial infection is a *Staphylococcus aureus* infection.

[00081] In one example, the bacterial infection is a methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

[00082] In one example, the bacterial infection is a vancomycin-resistant *Staphylococcus aureus* (VRSA) infection.

[00083] In one example, wherein the bacterial infection is a methicillin-susceptible *Staphylococcus aureus* (MSSA) infection.

[00084] In one example, the bacterial infection is an intracellular bacterial infection.

[00085] In one example, the subject is human.

[00086] In one example, the method further comprises administering a second therapeutic agent.

[00087] In one example, the second therapeutic agent is a second antibiotic.

[00088] In one example, the second antibiotic is effective against *Staphylococcus aureus*.

[00089] In one example, the second antibiotic is selected from an aminoglycoside, a beta-lactam, a macrolide, a cyclic peptide, a tetracycline, a fluoroquinoline, a fluoroquinolone, and an oxazolidinone.

[00090] In one example, the second antibiotic is selected from clindamycin, novobiocin, retapamulin, daptomycin, sitafloxacin, teicoplanin, triclosan, napthyridone, radezolid, doxorubicin, ampicillin, vancomycin, imipenem, doripenem, gemcitabine, dalbavancin, and azithromycin.

[00091] In one example, the compound is administered to the subject orally, topically, intranasally, intravenously, intramuscularly, or subcutaneously.

[00092] In another example, provided herein are antibody-drug conjugates comprising antibodies, or antigen-binding fragments of antibodies, and further comprising a rifamycin analog. In some examplesof the antibody-drug conjugates of the present disclosure, the antibodies, or antigen-binding fragments of antibodies, bind to an infectious disease-related target. Infectious disease-related targets useful for the present disclosure include, but are not limited to, Macrophage scavenger receptor 1 (MSR1), wall teichoic acids (WTA), *S. aureus* antigens such as Protein A, IsdA, IsdB, IsdC, IsdE, IsdH, ClfA, ClfB, CP5, CP8, SdrC, SdrD, SdrE, FnBpA, FnBpB, Cna, polysaccharide poly-N-aceytlglucosamine (PNAG), and SasG.

[00093] In some examples, the antibodies, or antigen-binding fragments of antibodies bind to MSR1. In some examples, the antibodies, or antigen-binding fragments of antibodies bind to WTA. In some examples, the antibodies, or antigen-binding fragments of antibodies

bind to Protein A.

[00094] In another example, provided herein are antibody-drug conjugates comprising antibodies, or antigen-binding fragments of antibodies, that bind the membrane glycoprotein receptor known as MSR1, and further comprising a rifamycin analog. The antibodies are useful, *inter alia*, for targeting cells that express MSR1, such as macrophage cells.

[00095] In another example, provided herein are antibody-drug conjugates comprising antibodies, or antigen-binding fragments of antibodies, that bind wall teichoic acids (WTA), and further comprising a rifamycin analog.

[00096] In another example, provided herein are antibody-drug conjugates comprising antibodies, or antigen-binding fragments of antibodies, that bind Protein A, and further comprising a rifamycin analog.

[00097] In another example, provided herein is a pharmaceutical composition comprising an antibody-drug conjugate comprising a recombinant human antibody or fragment thereof, further comprising a rifamycin analog, and a pharmaceutically acceptable carrier. In some examples, the recombinant human antibody or fragment thereof specifically binds an infectious disease-related target. In some examples, the recombinant human antibody or fragment thereof specifically binds MSR1, WTA or Protein A. In a related example, example srelate to a composition which is a combination of an antibody-drug conjugate comprising antibody described herein and further comprising a rifamycin analog, and a second therapeutic agent. In one example, the second therapeutic agent is any agent that is advantageously combined with an antibody-drug conjugate comprising an antibody described herein. In one example, the second therapeutic agent is an antibody-drug conjugate comprising an antibody described herein conjugated to a second drug or a therapeutic agent. Exemplary combination therapies, co-formulations, and ADCs involving the antibodies are disclosed elsewhere herein.

[00098] Also provided herein are reactive linker-payloads comprising rifamycin analogs, for example, the compounds having a structure according to any example of formulas (A), (B), (I), (I'), (II), (II'), (III), (III'), (IV), (IV'), (V), (V'), (B-1), (B-2) as provided herein, useful for making the antibody-drug conjugates comprising an antibody. Further provided herein are modified antibodies and modified antigen-binding fragments useful for making the antibody-drug conjugates comprising rifamycin analogs. In some examples, the antibody or antigen-binding fragment thereof specifically binds an infectious disease-related target. In some examples, the

antibody or antigen-binding fragment thereof specifically binds MSR1, WTA or Protein A.

[00099] Also provided herein are methods of preventing or inhibiting growth of a bacterium comprising administration of an effective amount of an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof and a rifamycin analog. In some examples, the antibody or antigen-binding fragment thereof specifically binds an infectious disease-related target. In some examples, the antibody or antigen-binding fragment thereof specifically binds MSR1, WTA or Protein A.

[000100] Also provided herein are therapeutic methods comprising administration of an effective amount of an ADC comprising an antibody or antigen-binding fragment thereof and a rifamycin analog, to a subject in need thereof. The therapeutic methods comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an ADC comprising an antibody or antigen-binding fragment thereof and a rifamycin analog to the subject. The disorder treated is any disease or condition which is improved, ameliorated, inhibited or prevented by targeting the infectious disease-related target and/or by the administration of an antibiotic agent. In some examples, the disease or condition is a proliferative disease, a metabolic disease, inflammation, a neurodegenerative disease, or disease, disorder, or condition associated with glucocorticoid receptor signaling. In some of such examples, the side effects associated with administration of the unconjugated rifamycin analog are reduced. Provided herein is the use of an antibody, an antigen-binding portion thereof, or an ADC comprising an antibody or antigen-binding fragment thereof, described herein, for the treatment of any disease disorder or condition described herein. In some examples, the antibody or antigen-binding fragment thereof specifically binds an infectious disease-related target. In some examples, the antibody or antigen-binding fragment thereof specifically binds MSR1, WTA or Protein A.

[000101] Also provided herein are therapeutic methods for treating, attenuating, or ameliorating a disease or disorder or condition associated with Staphylococcal infection, for example, a *S. aureus* infection and/or for ameliorating at least one symptom associated with such disease, disorder or condition, comprising administration of a rifamycin analog or an ADC comprising an antibody or antigen-binding fragment thereof and a rifamycin analog, to a subject in need thereof. Such disease, disorder or condition may be cellulitis, bacteremia, dermonecrosis, eyelid infection, eye infection, neonatal conjunctivitis, osteomyelitis, impetigo, boils, scalded skin syndrome, food poisoning, pneumonia, surgical infection, urinary tract infection, burn infection,

meningitis, endocarditis, septicemia, toxic shock syndrome, or septic arthritis. In some examples, the subject has a prosthetic joint and the rifamycin analogs or ADCs comprising an antibody or antigen-binding fragment thereof and a rifamycin analog disclosed herein are used for treating and/or preventing *S. aureus* infection of the tissue surrounding the prosthetic joint. In some examples, the subject has a catheter and the rifamycin analogs or ADCs comprising an antibody or antigen-binding fragment thereof and a rifamycin analog disclosed herein are used for treating and/or preventing *S. aureus* infection of the catheter and/or the tissue surrounding the catheter. In some examples, the subject has a foreign body implanted, and the rifamycin analogs or ADCs comprising an antibody or antigen-binding fragment thereof and a rifamycin analog disclosed herein are used for treating and/or preventing *S. aureus* infection of the foreign body and/or the tissue surrounding the foreign body. In some examples, the subject has mastitis, and the antibodies disclosed herein are useful for treating mastitis. The therapeutic methods comprise administering a therapeutically effective amount of a pharmaceutical composition comprising a rifamycin analog or an ADC comprising an antibody or antigen-binding fragment thereof and a rifamycin analog, to a subject in need thereof. In some examples, the antibody or antigen-binding fragment thereof specifically binds an infectious disease-related target. In some examples, the antibody or antigen-binding fragment thereof specifically binds MSR1, WTA or Protein A.

[000102] In another example, the present disclosure provides an antibody-drug conjugate comprising an antibody, or an antigen-binding fragment thereof, conjugated to the rifamycin analog compound of any of the examplesof the disclosure via a linker or through a linker-spacer.

[000103] In various examples, the antibody, or the antigen-binding fragment thereof, binds macrophage scavenger receptor 1 (MSR1). In various examples, the antibody, or the antigen-binding fragment thereof, binds wall teichoic acids (WTA). In various examples, the antibody, or the antigen-binding fragment thereof, binds *S. aureus* Protein A.

[000104] In one example, the antibody, or the antigen-binding fragment thereof, may comprise: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) comprising an amino acid sequence as set forth in Table 9; and (b) the CDRs of a light chain variable region (LCVR) comprising an amino acid sequence as set forth in Table 9.

[000105] In one example, the anti-MSR1 antibody, or the antigen-binding fragment

thereof, may comprise:

(i) a HCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 36, 52, 92, and 284;

(ii) a HCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 38, 54, 94, and 286;

(iii) a HCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 40, 56, 96, and 288;

(iv) a LCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 44, 60, 100, and 292;

(v) a LCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 46, 62, 102, and 294; and

(vi) a LCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 48, 64, 104, and 296.

[000106] In one example, the anti-WTA antibody, or the antigen-binding fragment thereof, may comprise: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) comprising an amino acid sequence as set forth in Table 2A; and (b) the CDRs of a light chain variable region (LCVR) comprising an amino acid sequence as set forth in Table 2A.

[000107] In one example, the anti-WTA antibody, or the antigen-binding fragment thereof, may comprise:

(i) a HCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 470, 476, 482, and 488;

(ii) a HCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 471, 477, 483, and 489;

(iii) a HCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 472, 478, 484, and 490;

(iv) a LCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 467, 473, 479, and 485;

(v) a LCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 468, 474, 480, and 486; and

(vi) a LCDR3 domain comprising an amino acid sequence selected from the group

consisting of SEQ ID NOs: 469, 475, 481, and 487.

[000108] In one example, the anti-WTA antibody, or the antigen-binding fragment thereof, may comprise: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) comprising an amino acid sequence as set forth in Table 2B; and (b) the CDRs of a light chain variable region (LCVR) comprising an amino acid sequence as set forth in Table 2B.

[000109] In one example, the anti-WTA antibody, or the antigen-binding fragment thereof, may comprise:

(i) a HCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 502, 508, 514, 520, 526, 532, 538, 544, 550, 556, 562, 568, and 574;

(ii) a HCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 503, 509, 515, 521, 527, 533, 539, 545, 551, 557, 563, 569, and 575;

(iii) a HCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 504, 510, 516, 522, 528, 534, 540, 546, 552, 558, 564, 570, 576, and 584;

(iv) a LCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 499, 505, 511, 517, 523, 529, 535, 541, 547, 553, 559, 565, and 571;

(v) a LCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 500, 506, 512, 518, 524, 530, 536, 542, 548, 554, 560, 566, and 572; and

(vi) a LCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 501, 507, 513, 519, 525, 531, 537, 543, 549, 555, 561, 567, and 573.

[000110] In some examples, the anti-WTA antibody, or the antigen-binding fragment thereof, comprises a V205C mutation (EU numbering) in the light chain.

[000111] In one example, the anti-Protein A antibody, or the antigen-binding fragment thereof, may comprise: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) comprising an amino acid sequence as set forth in Table 3A; and (b) the

CDRs of a light chain variable region (LCVR) comprising an amino acid sequence as set forth in Table 3A.

[000112] In one example, the anti-Protein A antibody, or the antigen-binding fragment thereof, may comprise:

[000113] (i) a HCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 632, 652, and 672;

[000114] (ii) a HCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 634, 654, and 674;

[000115] (iii) a HCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 636, 656, and 676;

[000116] (iv) a LCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 640, 660, and 680;

[000117] (v) a LCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 642 and 662; and

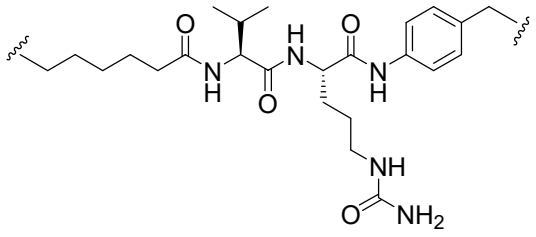
[000118] (vi) a LCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 644, 664, and 683.

[000119] In some examples, the anti-Protein A antibody, or the antigen-binding fragment thereof, comprises a H435R and a Y436F mutation (EU numbering) in the heavy chain Fc.

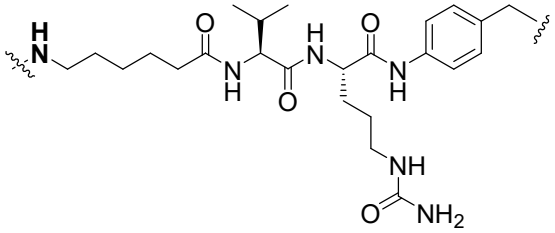
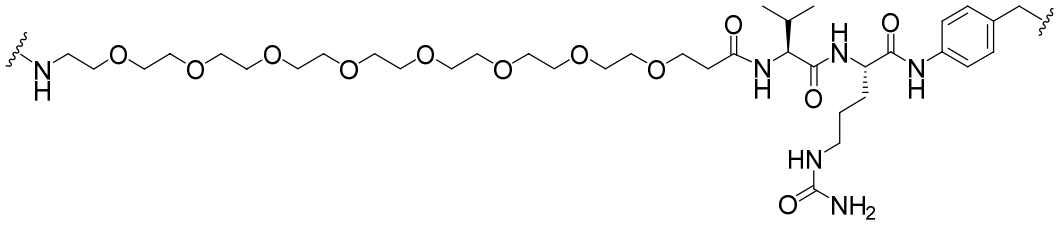
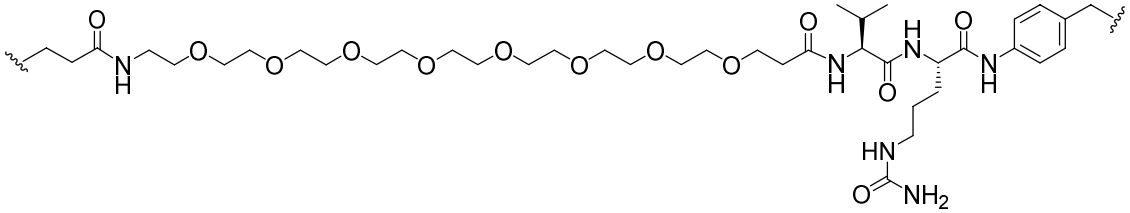
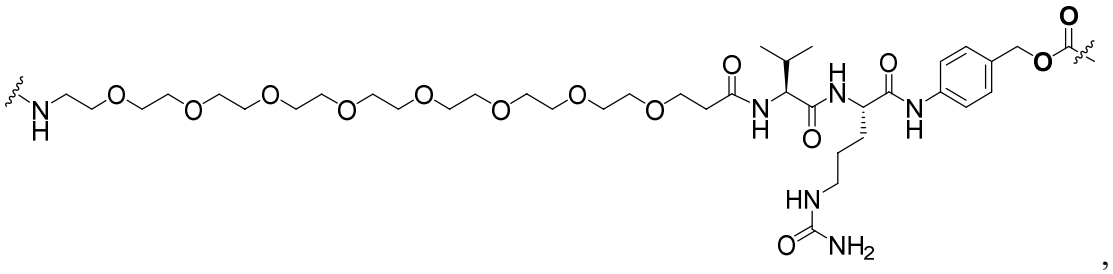
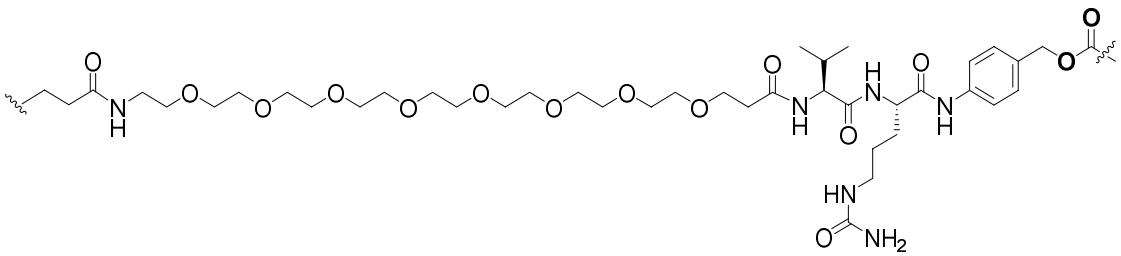
[000120] In various examples, the antibody, or antigen-binding fragment thereof, comprises a C103S mutation in the light chain.

[000121] The various examples, the antibody, or the antigen-binding fragment thereof, is conjugated to a compound of the present disclosure at position 103 of the light chain.

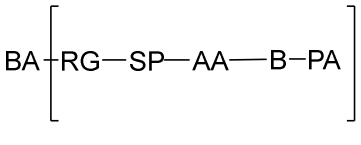
[000122] In one example, the linker or linker spacer is selected from



,


,

,

,

,
and

.

[000123] In another example, the present disclosure provides an antibody-drug conjugate having the structure according to Formula (XVIII):

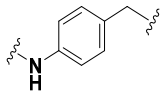

(**XVIII**), wherein

BA is an antibody, or an antigen-binding fragment thereof;

RG is a reactive group selected from a maleimide, an N-hydroxy succinimide, or a succinimide;

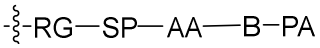
SP is absent or a spacer group residue selected from the group consisting of C_{1-6} alkyl, -NH-, -C(O)-, $-CH_2-CH_2-C(O)-NH-$, $-(CH)_u-C(O)-NH-$, $(-CH_2-CH_2-O)_e$, $-NH-CH_2-CH_2-(-O-CH_2-CH_2)_e-C(O)-$, $-C(O)-(CH_2)_u-C(O)-$, $-C(O)-NH-(CH_2)_v-$, $-(CH)_u-C(O)-NH-(CH_2-CH_2-O)_e-(CH)_u-C(O)-NH-$, $-(CH)_2-C(O)-NH-(CH_2-CH_2-O)_8-(CH)_2-C(O)-NH-$, and combinations thereof, wherein independently at each occurrence subscript **e** is an integer from 0 to 20, subscript **u** is an integer from 1 to 8, and subscript **v** is an integer from 1 to 8;

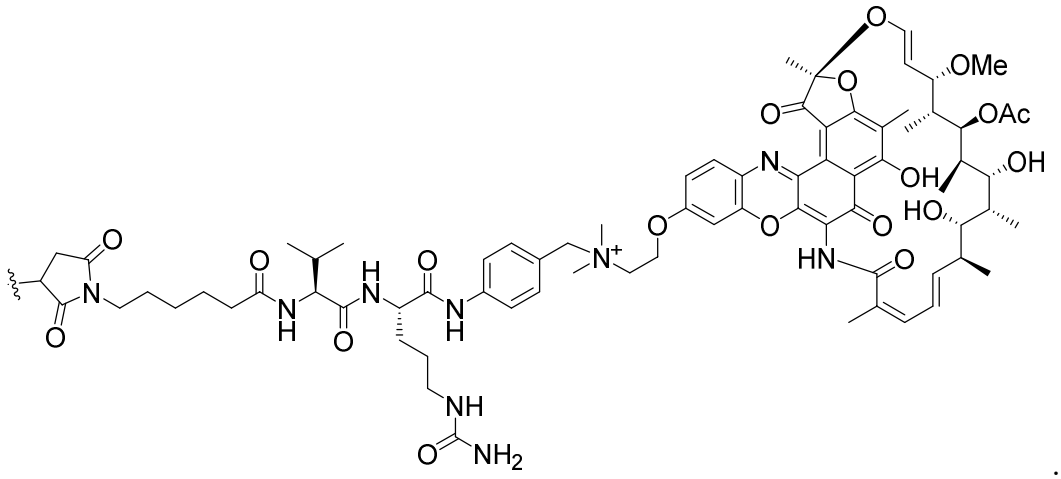
AA is a linker selected from valine-citrulline; citrulline-valine; valine-alanine; alanine-valine; valine-glycine, or glycine-valine;

B is absent or , wherein the  indicates the atom through which the **B** is bonded to the adjacent groups in the formula;

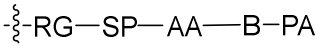
n is an integer from 1 to 30, and

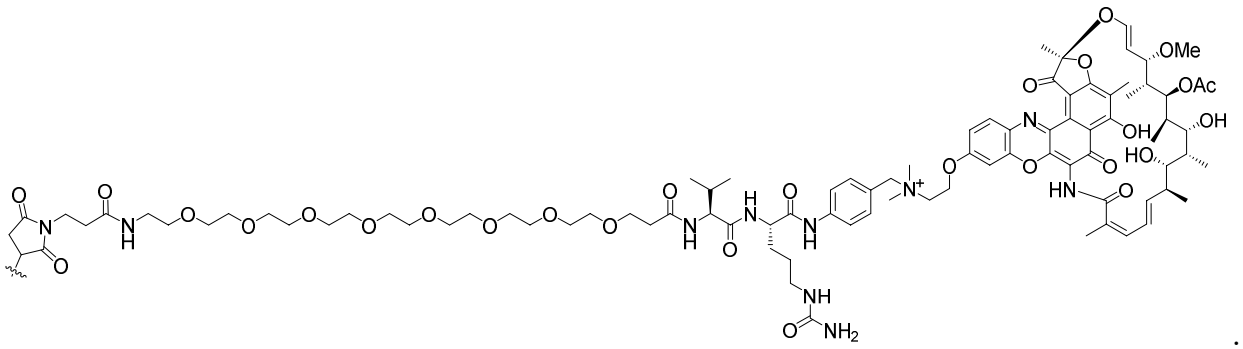
PA is a rifamycin analog according to any of the examplesof the disclosure.

[000124] In one example,  is

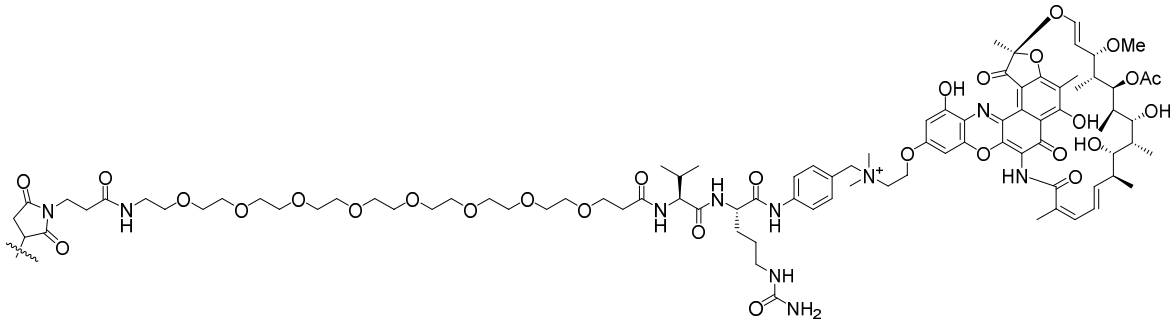


.

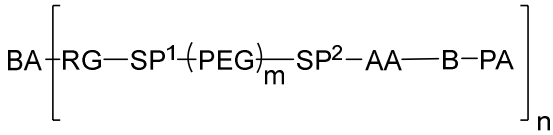
[000125] In one example,  is



[000126] In one example, -RG—SP—AA—B—PA is



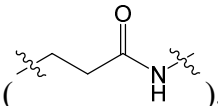
[000127] wherein the — is the bond to the antibody or the antigen-binding fragment thereof. In one example, the present disclosure provides an antibody-drug conjugate having the structure according to Formula (XIX):



(**XIX**), wherein

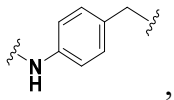
BA is an antibody, or an antigen-binding fragment thereof;

RG is selected from a maleimide, a N-hydroxy succinimide, or a succinimide;

SP^1 and **SP^2** are independently absent or a spacer group selected from the group consisting of C_{1-6} alkyl, -NH-, -C(O)-, $-CH_2-CH_2-C(O)-NH-$ (), $-(CH)_u-C(O)-NH-$, $(-CH_2-CH_2-O)_e$, $-NH-CH_2-CH_2-(-O-CH_2-CH_2)_e-C(O)-$, $-C(O)-(CH_2)_u-C(O)-$, $-C(O)-NH-(CH_2)_v-$, and combinations thereof, wherein subscript **e** is an integer from 0 to 4, subscript **u** is an integer from 1 to 8, and subscript **v** is an integer from 1 to 8;

AA is a linker selected from valine-citrulline; citrulline-valine; valine-alanine; alanine-valine; valine-glycine, or glycine-valine;

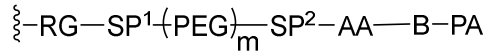
PEG is a polyethylene glycol chain comprising between 1 and 30 polyethylene glycol residues;

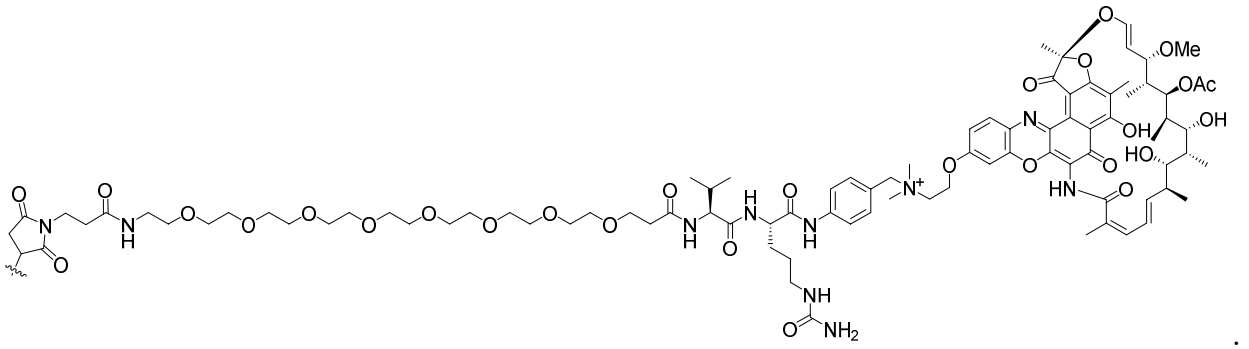
B is absent or  , wherein the  indicates the atom through which the **B** is bonded to the adjacent groups in the formula;

n is an integer from 1 to 30;

m is an integer from 0 to 20,

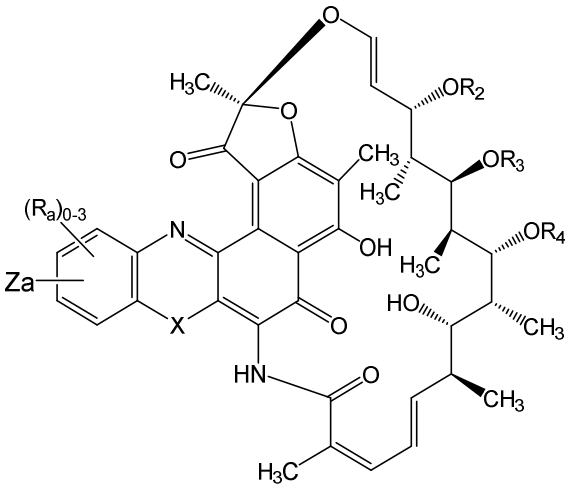
and **PA** is a rifamycin analog according to any of the examples of the disclosure.

[000128] In one example,  is



.

[000129] In one example, the present disclosure provides an antibody-drug conjugate comprising an antibody, or an antigen-binding fragment thereof, conjugated via a linker or through a linker-spacer to a rifamycin analog payload having the structure of Formula (XX):



(XX),

wherein:

X is selected from -O-, -S-, and -NR*-;

Za is selected from $-OR_1$ and $-R_N$;

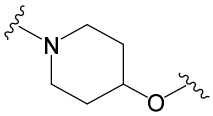
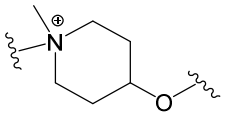
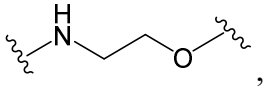
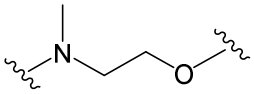
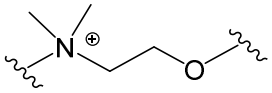
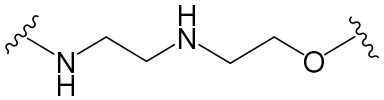
R_1 is selected from a bond; an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a

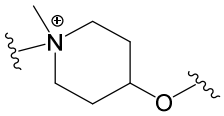
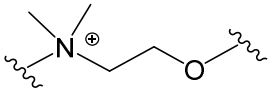
aliphatic C_1-C_{20} hydrocarbon, or -(C=O)-R*, each of which further comprises 0-8 heteroatoms selected from halogen, O, N, and S;

R_a is independently at each occurrence selected from hydrogen, -F, -Cl, -Br, -I, -OH, OR*, $-NH_2$, -NHR*, $-N(R^*)_2$, $-N(R^*)_3^+$, -(C=O)-R*, -CHO, $-CO_2H$, $-CO_2R^*$, -SR*, $-SO_2R^*$, and an aliphatic C_1-C_{20} hydrocarbon, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S, and wherein R_a is optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, -OR*;

R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_1-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_1-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof, and wherein the group Za is bonded to the linker.

[000130] It is to be understood that the group R_1 is either a bond (i.e., R_1 is absent), or a divalent group, i.e. R_1 capable of bonding to the -O- of the rifamycin analog as well as to the linker.

[000131] In one example, $-OR_1$ is –O– (i.e., R_1 is absent), , , , , , or .

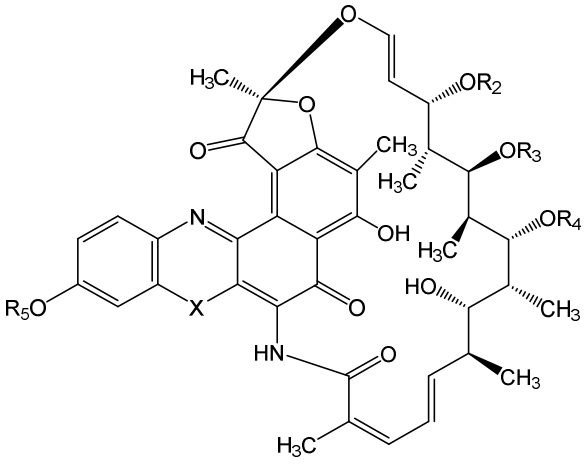
[000132] In one example, X is -O-, and $-OR_1$ comprises a tertiary amine. In some of such examples, $-OR_1$ is  or .

[000133] In some examples, antibody-drug conjugates comprising linker-rifamycin analog payloads comprise ammonium salts having one or more counterions. Any pharmaceutically acceptable counterion may be suitable. For example, in an example of the disclosure a suitable counterion may be an anion selected from F^-, Cl^-, Br^-, I^-, OH^-, $^-BF_4$, $CF_3SO_3^-$, monobasic sulfate, dibasic sulfate, monobasic phosphate, dibasic phosphate, or tribasic phosphate, NO_3^-, PF_6^-, NO_2^-, carboxylate, $C_eF_fSO_3^-$, (where in e=2-10 and f=2e+1), acetate, aspartate, benzenesulfonate, benzoate, besylate, bicarbonate, bitartrate, camsylate, carbonate, citrate, decanoate, edetate,

esylate, fumarate, gluceptate, gluconate, glutamate, glycolate, glycollyalarsanilate, hexanoate, hydrabamine, hydroxynaphthoate, isthionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, mucate, napsylate, octanoate, oleate, pamoate, pantothenate, polygalacturonate, propionate, salicylate, stearate, subacetate, succinate, tartrate, teoclate, tosylate, or triethiiodide.

[000134] In some examples, R_a is absent. In some examples, R_a is -OH and is present at one occurrence.

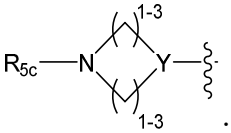
[000134a] In one aspect, there is provided an antibody-drug conjugate comprising an antibody, or an antigen-binding fragment thereof, conjugated via a linker or through a linker-spacer to a rifamycin analog having the structure of Formula (XXI):

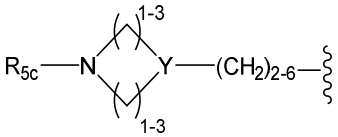


(XXI),

wherein:

X is selected from -O-, -S-, and -NR*-;

R_5 is selected from a bond; an aliphatic C_1-C_{20} hydrocarbon which further comprises 0-8 heteroatoms selected from halogen, O, N, and S; 

; or 

; wherein **Y** is C or N;

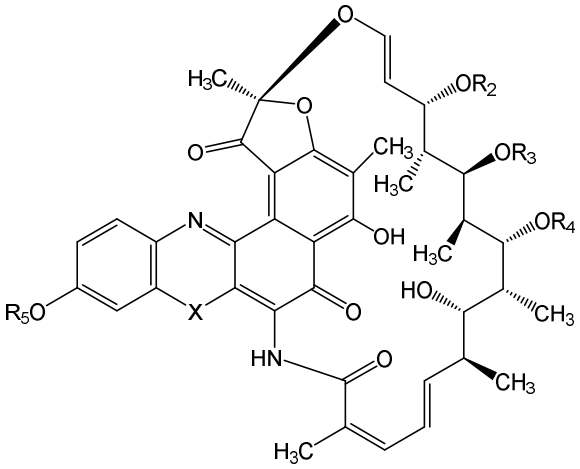
R_2, R_3, and R_4 are independently selected from a hydrogen, a straight chained, branched or cyclic aliphatic C_3-C_{20} hydrocarbon, or -(C=O)-R*, each of which further comprises 0-8 heteroatoms selected from halogen, O, N, and S,

R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_5-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_3-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof, and

R_{5c} is a bond or an aliphatic C_1-C_8 hydrocarbon,

wherein the group R_5 is bonded to the linker.

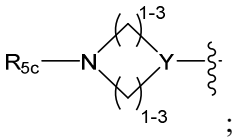
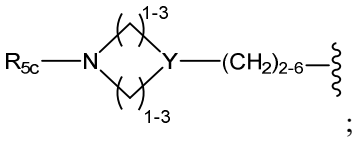
[000135] In one example, the present disclosure provides an antibody, or an antigen-binding fragment thereof, conjugated via a linker or through a linker-spacer to a rifamycin analog having the structure of Formula (XXI):



(XXI),

wherein:

X is selected from -O-, -S-, and -NR*-;

R_5 is selected from a bond; an aliphatic C_1-C_{20} hydrocarbon which further comprises 0-8 heteroatoms selected from halogen, O, N, and S;  ; or  ;

wherein **Y** is C or N;

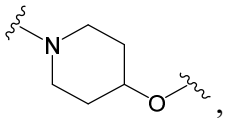
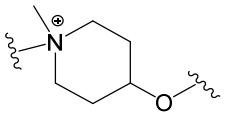
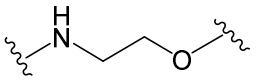
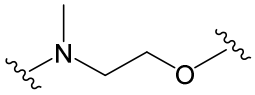
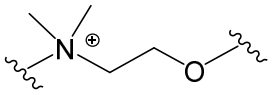
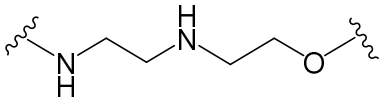
R_2, R_3, and R_4 are independently selected from a hydrogen, a straight chained, branched or cyclic aliphatic C_1-C_{20} hydrocarbon, or -(C=O)-R*, each of which further comprises 0-8 heteroatoms selected from halogen, O, N, and S, and

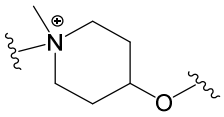
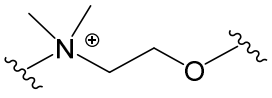
R_{5c} is a bond or an aliphatic C_1-C_8 hydrocarbon,

wherein the group R_5 is bonded to the linker.

[000136] It is to be understood that the group R_5 is either a bond (i.e., R_5 is absent), or a

divalent group, i.e. R_5 capable of bonding to the -O- of rifamycin as well as to the linker.

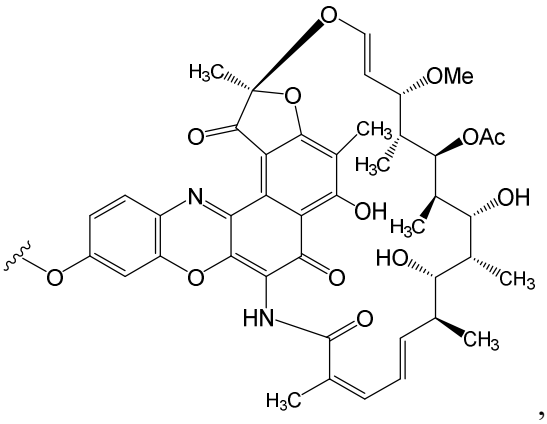
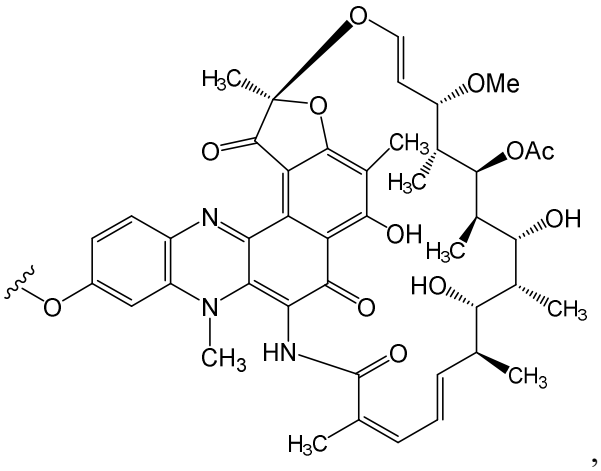
[000137] In one example, $-OR_5$ is –O– (i.e., R_5 is absent), , , , , , or .

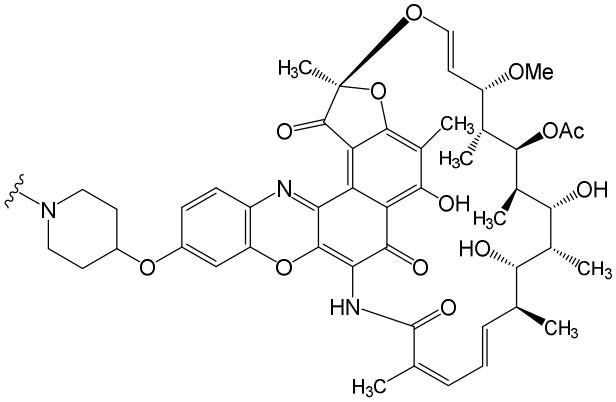
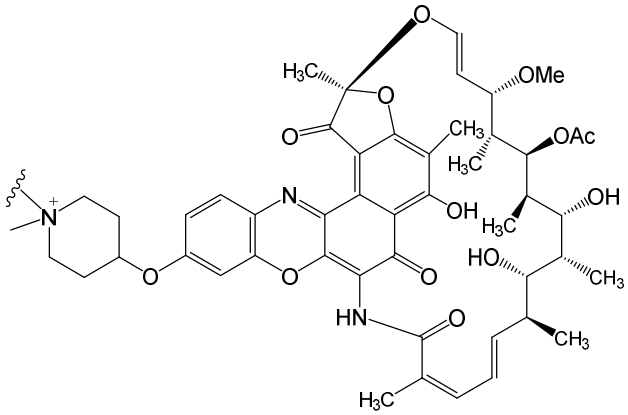
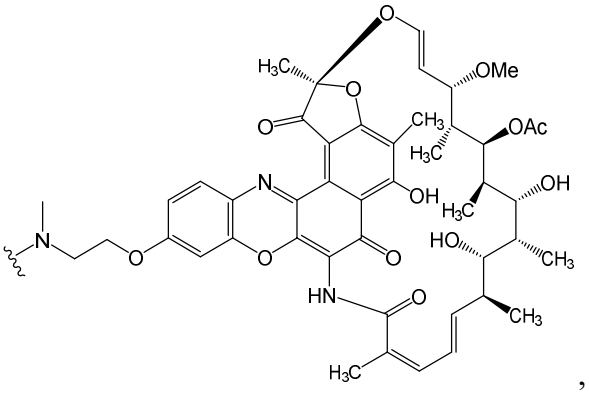
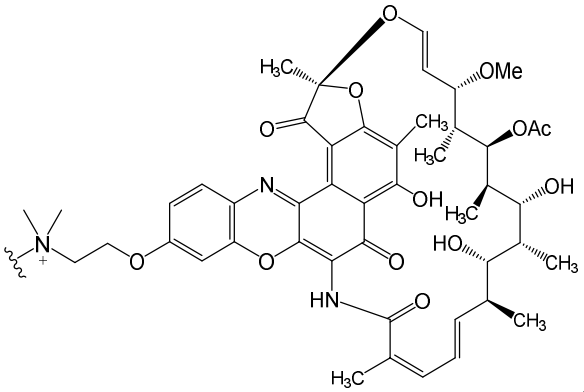
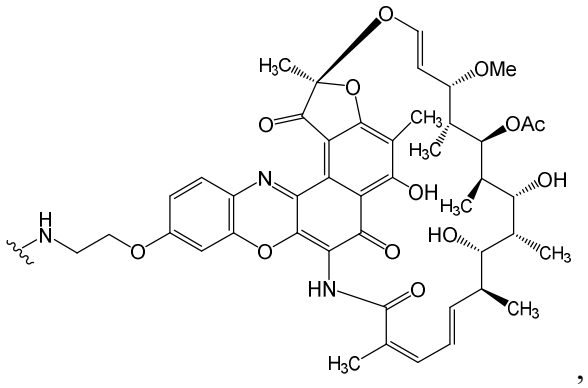
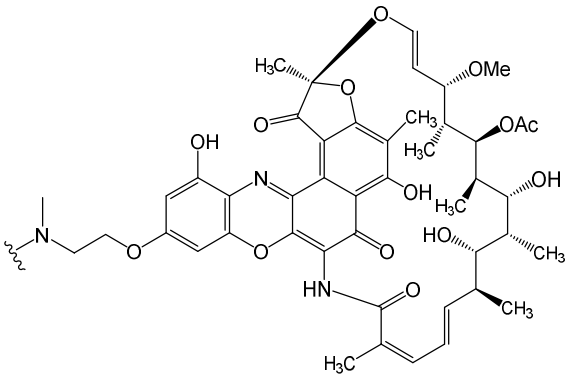
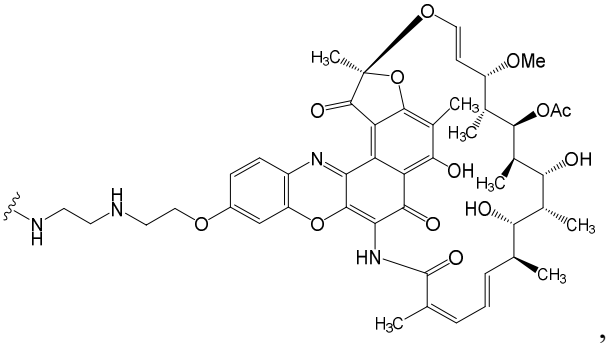
[000138] In one example, X is O, and $-OR_5$ comprises a tertiary amine. In some of such examples, $-OR_5$ is  or .

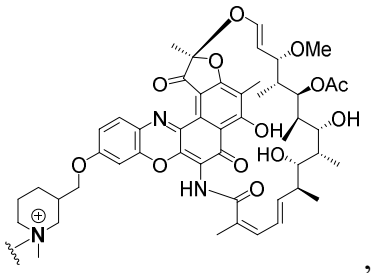
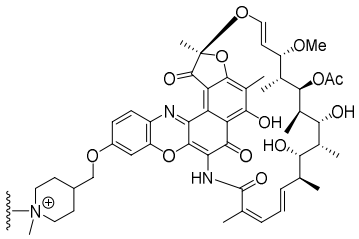
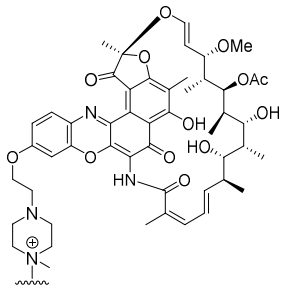
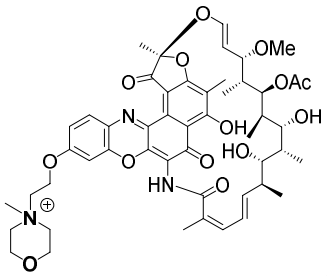
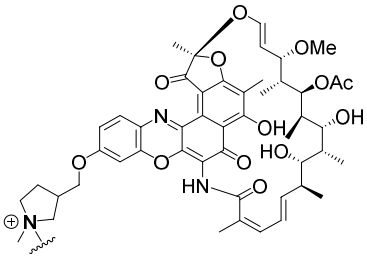
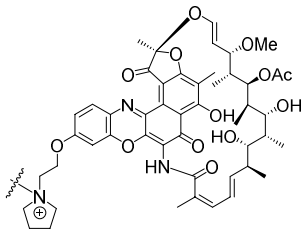
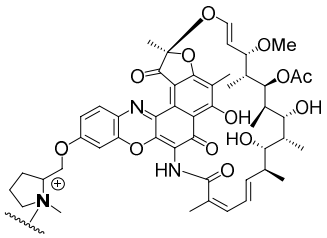
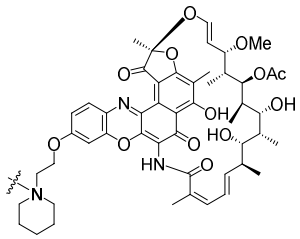
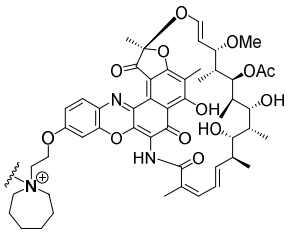
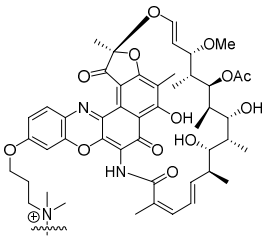
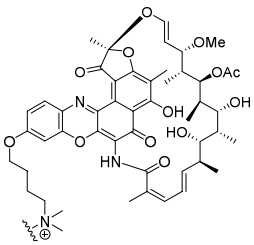
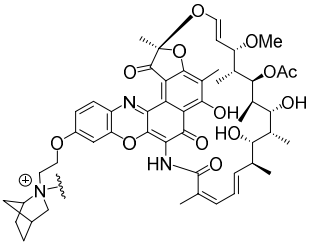
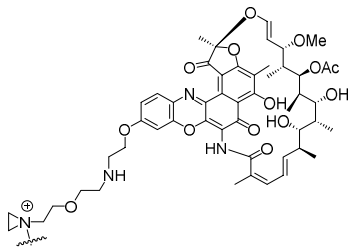
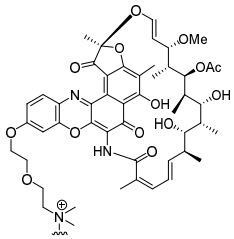
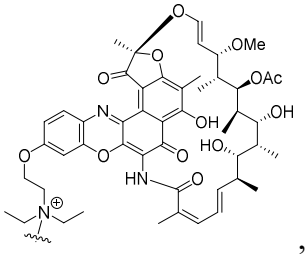
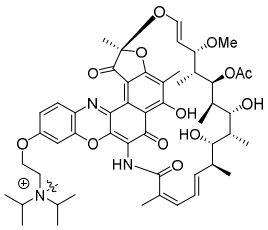
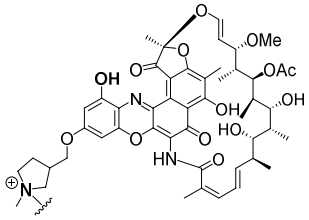
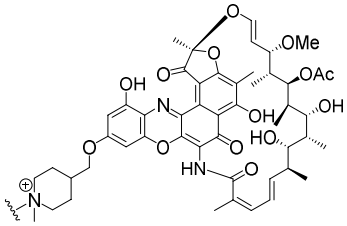
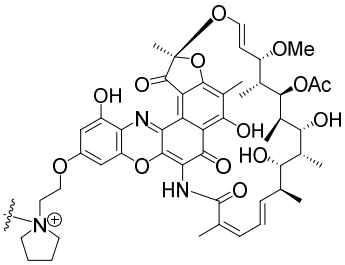
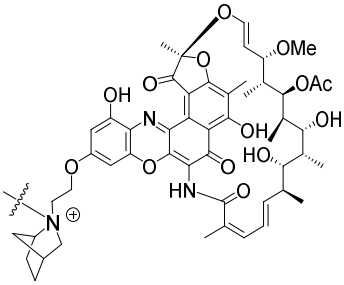
[000139] In one example of any of the above, R_2 is methyl, ethyl, propyl or isopropyl; R_3 is CH_3-(C=O)- (acetyl) group, CH_3CH_2-(C=O)-, $CH_3CH_2CH_2$-(C=O)-, or $(CH_3)_2CH$-(C=O)-, and R_4 is hydrogen.

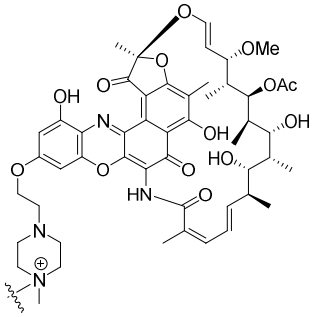
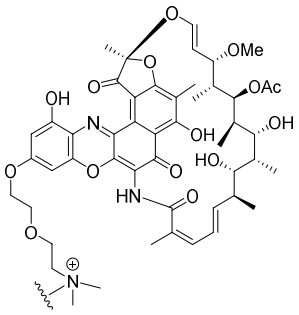
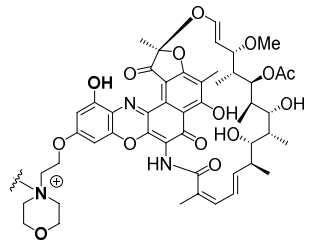
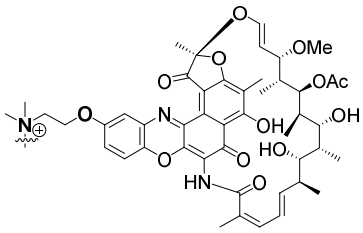
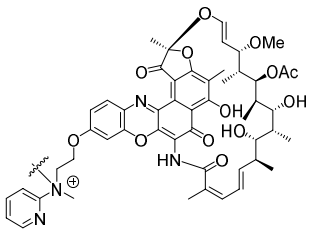
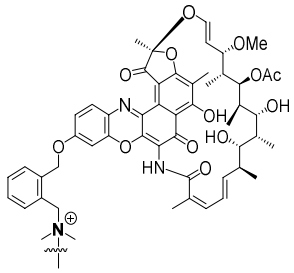
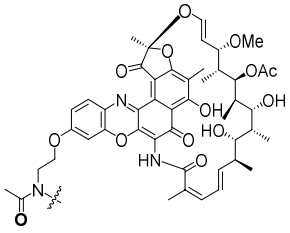
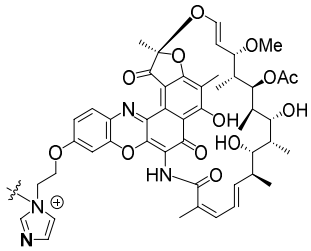
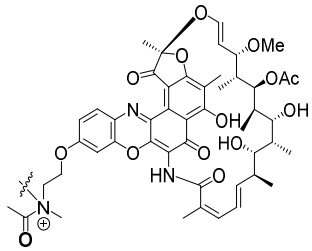
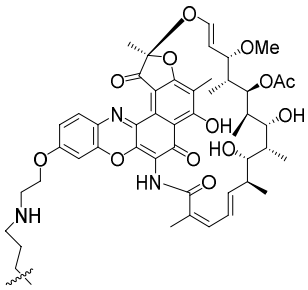
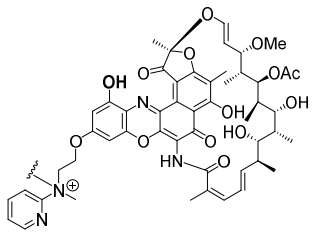
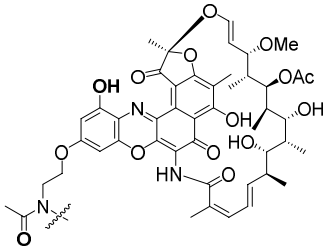
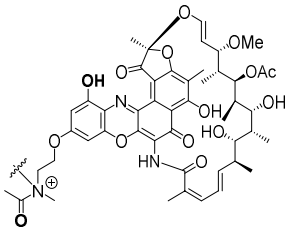
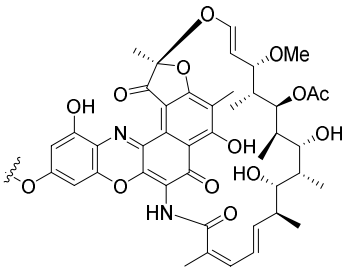
[000140] In one example of any of the above, R_2 is methyl, R_3 is acetyl, and R_4 is hydrogen.

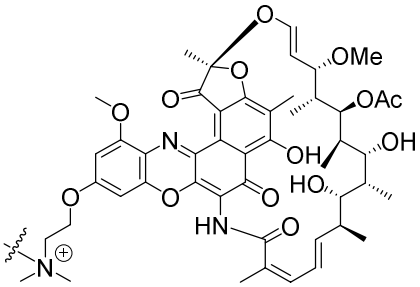
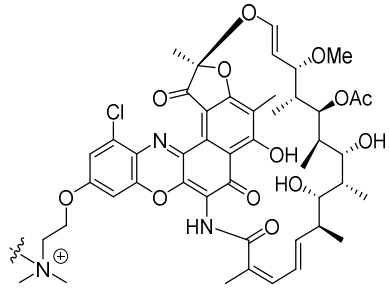
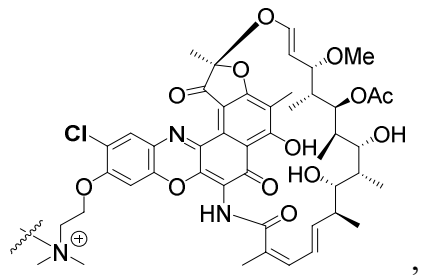
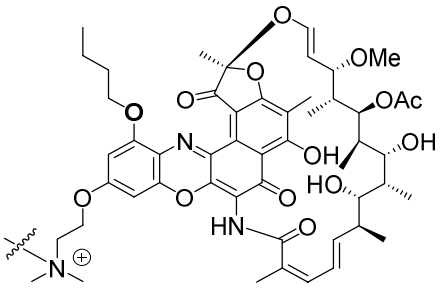
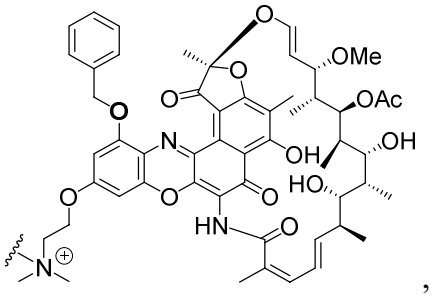
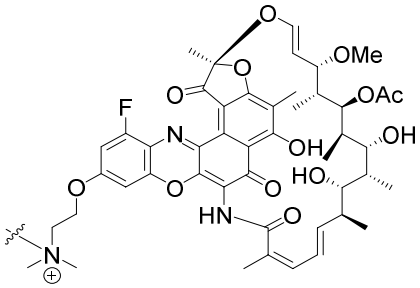
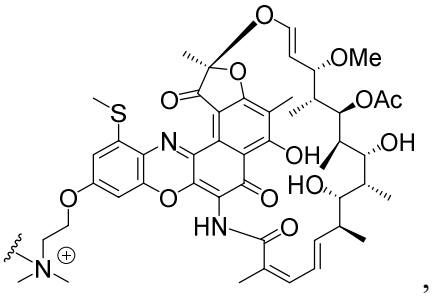
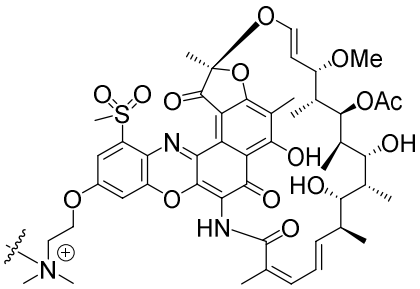
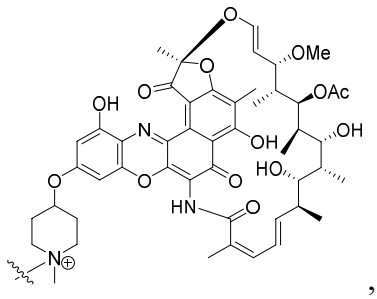
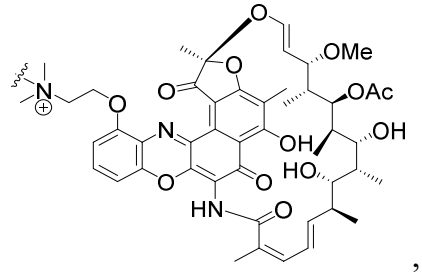
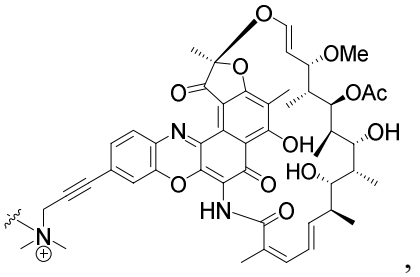
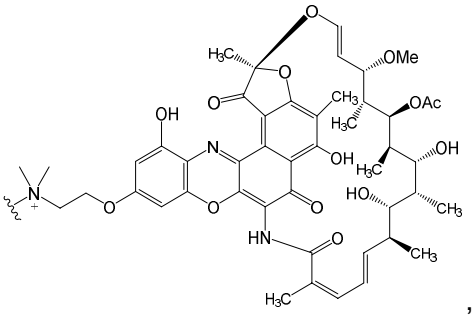
[000140a] In another aspect, there is provided an antibody-drug conjugate comprising an antibody, or an antigen-binding fragment thereof, conjugated via a linker or through a linker-spacer to a compound selected from the group consisting of:

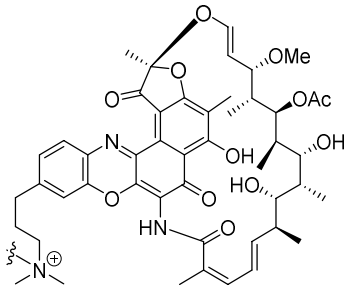
, ,


,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

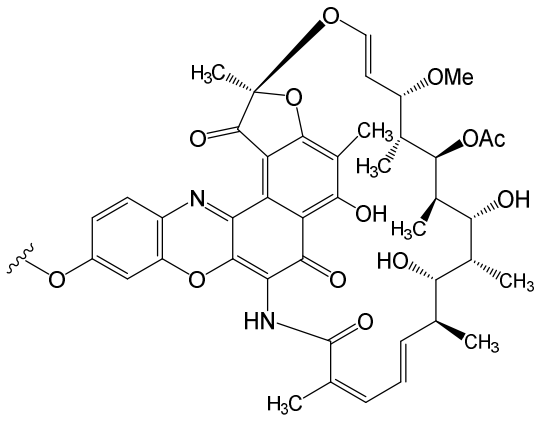

,

,

,

,

,


,

,

,

,

,

, and



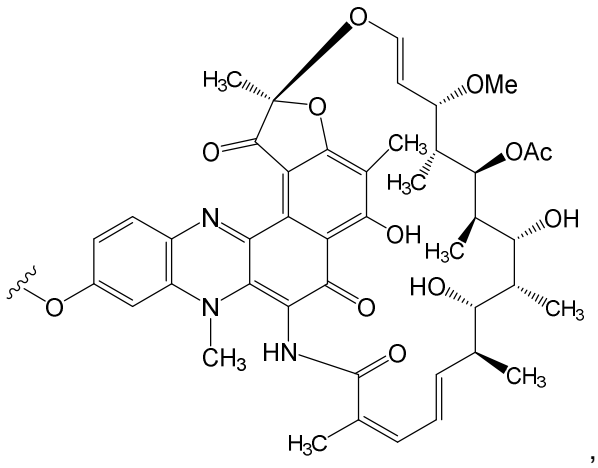
,

wherein the ~— is the bond to the linker, and when the compound comprises an ammonium salt, the counterion is an anion selected from F^-, Cl^-, Br^-, I^-, OH^-, $^-BF_4$, $CF_3SO_3^-$, monobasic sulfate, dibasic sulfate, monobasic phosphate, dibasic phosphate, or tribasic phosphate, NO_3^-, PF_6^-, NO_2^-, carboxylate, $C_eF_fSO_3^-$, where in e=2-10 and f=2e+1, acetate, aspartate, benzenesulfonate, benzoate, besylate, bicarbonate, bitartrate, camsylate, carbonate, citrate, decanoate, edetate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolate, glycollyalarsanilate, hexanoate, hydrabamine, hydroxynaphthoate, isthionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, mucate, napsylate, octanoate, oleate, pamoate, pantothenate, polygalacturonate, propionate, salicylate, stearate, subacetate, succinate, tartrate, teoclate, tosylate, or triethiiodide.

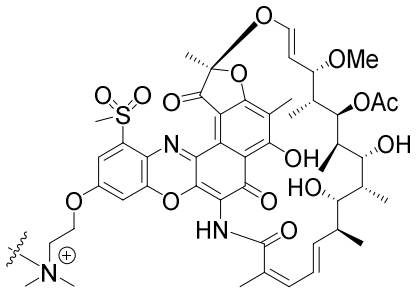
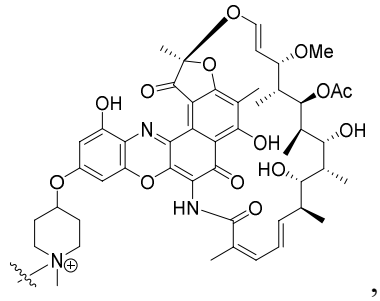
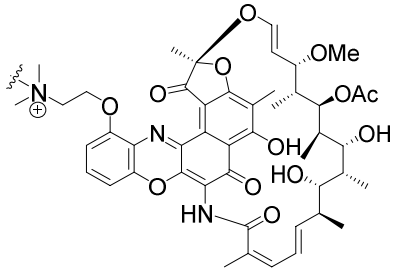
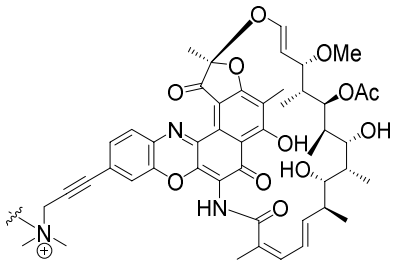
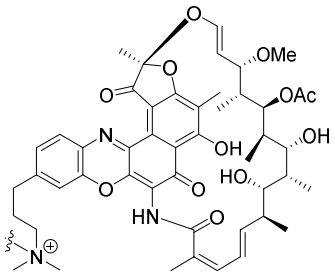
[000141] In one example of any of the above, the compound is selected from the group consisting of:



,

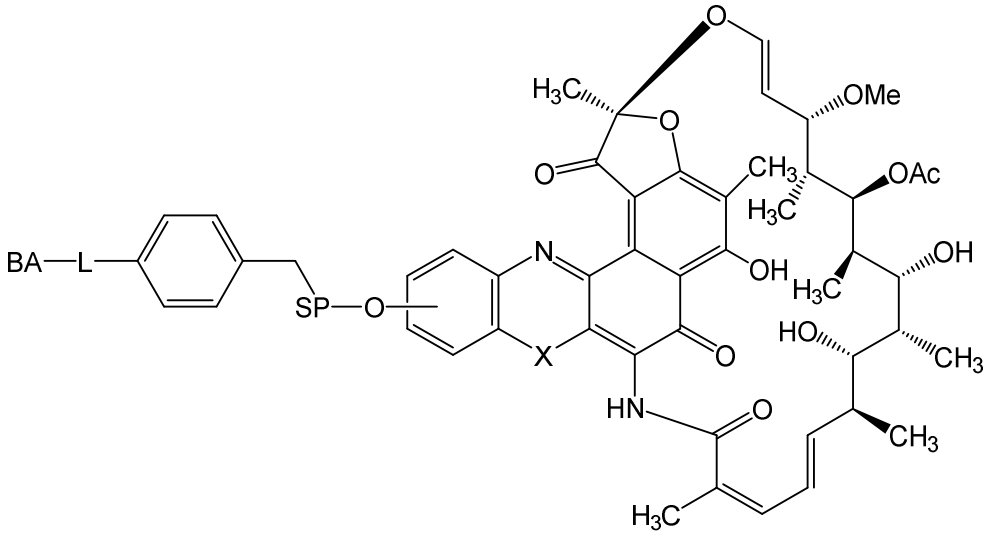


,

wherein the ⟆— is the bond to the linker.

[000141a] In another aspect, there is provided an antibody-drug conjugate having the structure of Formula (XXII):



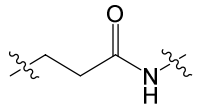
(XXII),

wherein:

BA is an antibody, or an antigen-binding fragment thereof;

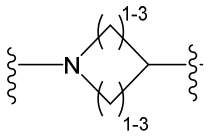
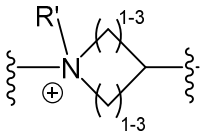
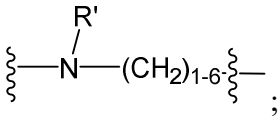
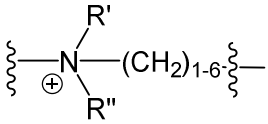
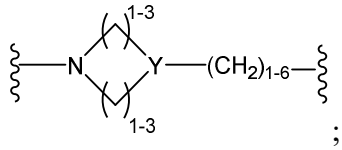
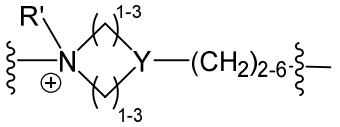
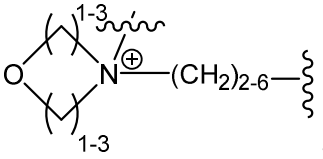
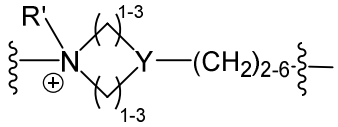
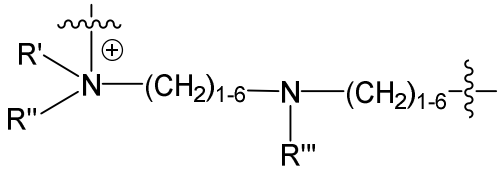
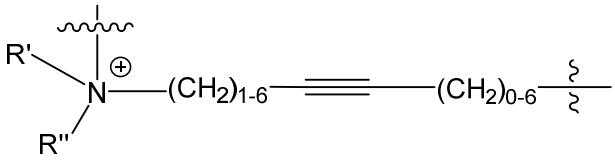
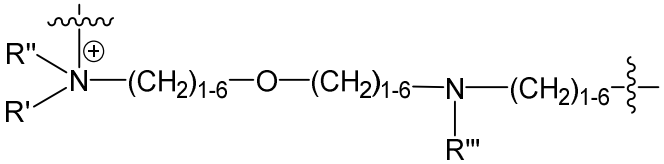
L is a linker having the formula ⟆—RG—SP^1—PEG—SP^2—AA_{2-4}—⟆, wherein

RG is selected from a maleimide, a N-hydroxysuccinimide, or a succinimide;

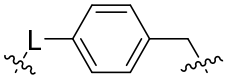
SP^1 and SP^2 are independently absent or a spacer group selected from the group consisting of  ; $C_{1\text{-}6}$ alkyl, -NH-, -C(O)-, $-CH_2-CH_2-C(O)-NH-$, $-(CH)_u-C(O)-NH-$, $(-CH_2-CH_2-O)_e$, $-NH-CH_2-CH_2-(-O-CH_2-CH_2)_e-C(O)-$, $-C(O)-(CH_2)_u-C(O)-$, $-C(O)-NH-(CH_2)_v-$, and combinations thereof, wherein subscript **e** is an integer from 0 to 4, subscript **u** is an integer from 1 to 8, and subscript **v** is an integer from 1 to 8;

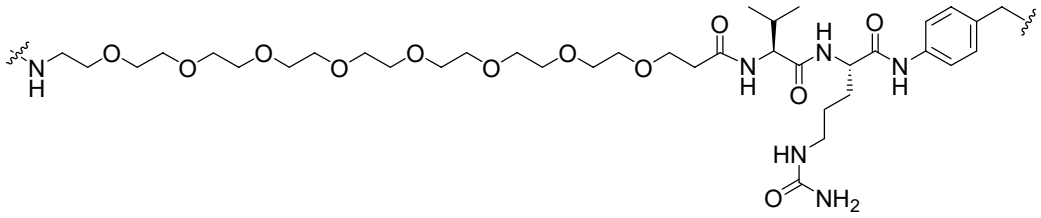
$AA_{2\text{-}4}$ is a dipeptide selected from valine-citrulline; citrulline-valine; valine-alanine; alanine-valine; valine-glycine, or glycine-valine, and

PEG is a polyethylene glycol chain comprising between 1 and 30 polyethylene glycol residues;

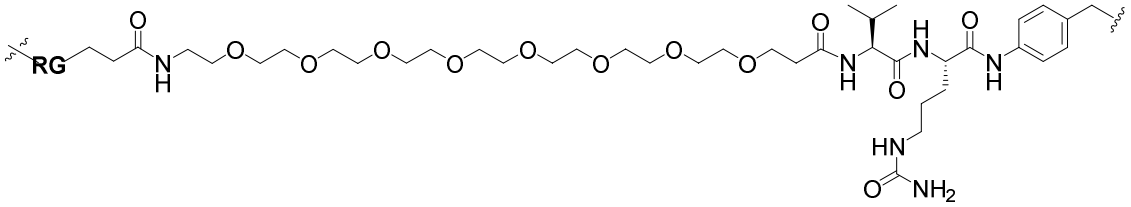
SP is a spacer group selected from  ;  ;  ;  ;  ;  ;  ;  ;  ,  and  ;

Y is C or N; wherein the 〰 symbol represents the point of attachment; and R', R" and R''' are selected from a hydrogen, a C_1-C_6 aliphatic hydrocarbon, and a protecting group selected from Fluorenylmethyloxycarbonyl (F_{MOC}) and *tert*-Butyloxycarbonyl (B_{OC}), or

wherein R' and R'' together form an aliphatic monocyclic, an aliphatic bicyclic, or an aliphatic polycyclic structure; or wherein the  has a structure:



or,



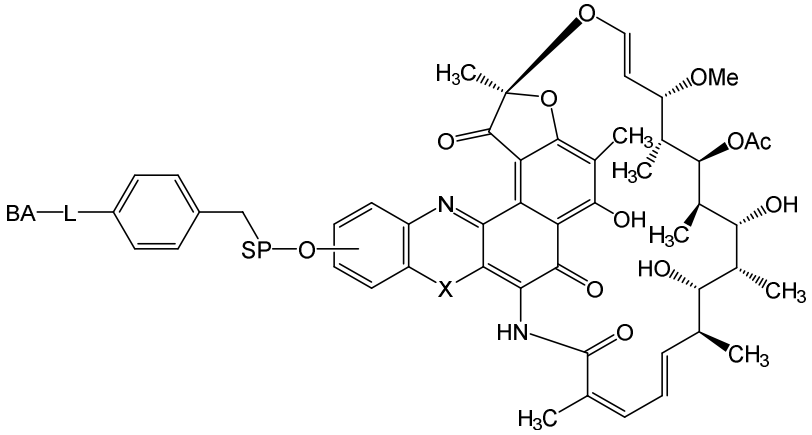
,

R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_5-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_3-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof,

and

X is selected from -O-, -S-, and -NR*.

[000142] In one example, the present disclosure provides an antibody-drug conjugate having the structure of Formula (XXII):

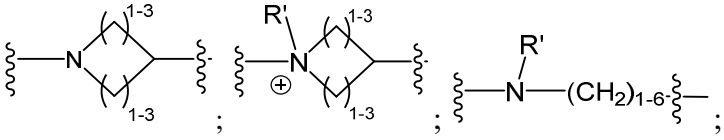


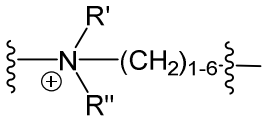
(XXII)

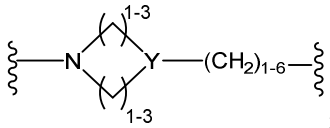
wherein:

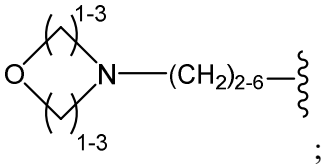
BA is an antibody, or an antigen-binding fragment thereof;

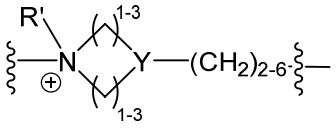
L is a linker;

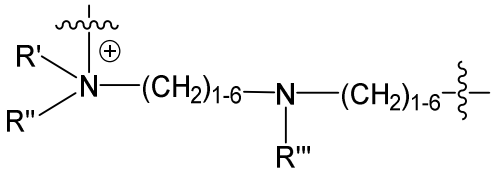
SP is a spacer group selected from 

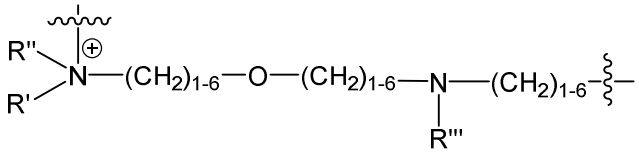


;


;


;


;


, and


wherein the 〰 symbol represents the point of attachment; and R', R" and R''' are selected from a hydrogen, a C_1-C_6 aliphatic hydrocarbon, and a protecting group selected from Fluorenylmethyloxycarbonyl (FMOC) and *tert*-Butyloxycarbonyl (BOC), or wherein R' and R'' together form an aliphatic monocyclic, an aliphatic bicyclic, or an aliphatic polycyclic structure;

Y is C or N;

R' and R" are independently at each occurrence selected from a hydrogen and a C_{1-6} alkyl, and

X is selected from -O-, -S-, and -NR*.

[000143] In one example, the antibody is an anti-MSR1 antibody, or the antigen-binding fragment thereof, comprises: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) comprising an amino acid sequence as set forth in Table 9; and (b) the CDRs of a light chain variable region (LCVR) comprising an amino acid sequence as set forth in Table 9.

[000144] In one example, the anti-MSR1 antibody, or the antigen-binding fragment thereof, comprises:

(i) a HCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 36, 52, 92, and 284;

(ii) a HCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 38, 54, 94, and 286;

(iii) a HCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 40, 56, 96, and 288;

(iv) a LCDR1 domain comprising an amino acid sequence selected from the group

consisting of SEQ ID NOs: 12, 44, 60, 100, and 292;

(v) a LCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 46, 62, 102, and 294; and

(vi) a LCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 48, 64, 104, and 296.

[000145] In one example, the anti-MSR1 antibody, or the antigen-binding fragment thereof, comprises

(i) a HCDR1 domain comprising an amino acid sequence of SEQ ID NO: 52;

(ii) a HCDR2 domain comprising an amino acid sequence of SEQ ID NO: 54;

(iii) a HCDR3 domain comprising an amino acid sequence of SEQ ID NO: 56;

(iv) a LCDR1 domain comprising an amino acid sequence of SEQ ID NO: 60;

(v) a LCDR2 domain comprising an amino acid sequence of SEQ ID NO: 62; and

(vi) a LCDR3 domain comprising an amino acid sequence of SEQ ID NO: 64.

[000146] In one example, the anti-MSR1 antibody, or the antigen-binding fragment thereof, comprises a N297Q mutation.

[000147] In one example, the anti-WTA antibody, or the antigen-binding fragment thereof, may comprise: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) comprising an amino acid sequence as set forth in Table 2A; and (b) the CDRs of a light chain variable region (LCVR) comprising an amino acid sequence as set forth in Table 2A.

[000148] In one example, the anti-WTA antibody, or the antigen-binding fragment thereof, may comprise:

(i) a HCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 470, 476, 482, and 488;

(ii) a HCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 471, 477, 483, and 489;

(iii) a HCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 472, 478, 484, and 490;

(iv) a LCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 467, 473, 479, and 485;

(v) a LCDR2 domain comprising an amino acid sequence selected from the group

consisting of SEQ ID NOs: 468, 474, 480, and 486; and

(vi) a LCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 469, 475, 481, and 487.

[000149] In one example, the anti-WTA antibody, or the antigen-binding fragment thereof, may comprise: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) comprising an amino acid sequence as set forth in Table 2B; and (b) the CDRs of a light chain variable region (LCVR) comprising an amino acid sequence as set forth in Table 2B.

[000150] In one example, the anti-WTA antibody, or the antigen-binding fragment thereof, may comprise:

(i) a HCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 502, 508, 514, 520, 526, 532, 538, 544, 550, 556, 562, 568, and 574;

(ii) a HCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 503, 509, 515, 521, 527, 533, 539, 545, 551, 557, 563, 569, and 575;

(iii) a HCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 504, 510, 516, 522, 528, 534, 540, 546, 552, 558, 564, 570, 576, and 584;

(iv) a LCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 499, 505, 511, 517, 523, 529, 535, 541, 547, 553, 559, 565, and 571;

(v) a LCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 500, 506, 512, 518, 524, 530, 536, 542, 548, 554, 560, 566, and 572; and

(vi) a LCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 501, 507, 513, 519, 525, 531, 537, 543, 549, 555, 561, 567, and 573.

[000151] In some examples, the anti-WTA antibody, or the antigen-binding fragment thereof, comprises a V205C mutation (EU numbering) in the light chain.

[000152] In one example, the anti-WTA antibody, or the antigen-binding fragment

thereof, is derived from antibody 4497 described in US Patent Application Publication 20140356375 (which is incorporated herein by reference in its entirety). In one example, the anti-WTA antibody is derived from antibody 4497 and further comprises a V205C mutation in the light chain.

[000153] In one example, the anti-WTA antibody, or the antigen-binding fragment thereof, comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 of SEQ ID Nos: 568-569-570-565-566-567.

[000154] In some examples, the anti-WTA antibody or antigen binding fragment thereof comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NOs: 586; and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 585.

[000155] In some examples, the anti-WTA antibody or antigen binding fragment thereof comprises an HCVR amino acid sequence of SEQ ID NOs: 586, and an LCVR amino acid sequence of SEQ ID NO: 585.

[000156] In some example, the anti-WTA antibody comprises a heavy chain amino acid sequence of SEQ ID NOs: 602 and a light chain amino acid sequence of SEQ ID NO: 587 or SEQ ID NO: 589. In some examples, the anti-WTA antibody, or the antigen-binding fragment thereof comprises a V205C mutation in the light chain.

[000157] In one example, the anti-Protein A antibody, or the antigen-binding fragment thereof, may comprise: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) comprising an amino acid sequence as set forth in Table 3A; and (b) the CDRs of a light chain variable region (LCVR) comprising an amino acid sequence as set forth in Table 3A.

[000158] In one example, the anti-Protein A antibody, or the antigen-binding fragment thereof, may comprise:

[000159] (i) a HCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 632, 652, and 672;

[000160] (ii) a HCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 634, 654, and 674;

[000161] (iii) a HCDR3 domain comprising an amino acid sequence selected from the

group consisting of SEQ ID NOs: 636, 656, and 676;

[000162] (iv) a LCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 640, 660, and 680;

[000163] (v) a LCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 642 and 662; and

[000164] (vi) a LCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 644, 664, and 683.

[000165] In some examples, the anti-Protein A antibody, or the antigen-binding fragment thereof, comprises a H435R and a Y436F mutation (EU numbering) in the heavy chain Fc.

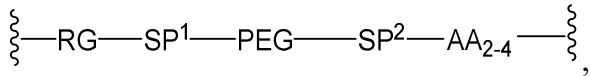
[000166] In one example, the anti-Protein A antibody or antigen binding fragment thereof comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NOs: 630; and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 638. In one example, the anti-Protein A antibody or antigen binding fragment thereof comprises a set of six CDRs (HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) comprising SEQ ID NOs: 632-634-636-640-642-644.

[000167] In one example, the anti-Protein A antibody or antigen binding fragment thereof comprises an HCVR amino acid sequence of SEQ ID NOs: 630; and an LCVR amino acid sequence of SEQ ID NO: 638.

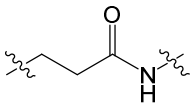
[000168] In one example, the anti-Protein A antibody comprises a heavy chain amino acid sequence of SEQ ID NOs: 666 and a light chain amino acid sequence of SEQ ID NO: 668. In one examples, the anti-Protein A antibody, further comprises a H435R and a Y436F mutation (EU numbering) in the heavy chain Fc. In one example, anti-Protein A antibody further comprises a C103S mutation in the light chain. In one example, the anti-Protein A antibody, or antigen-binding fragment thereof, is conjugated to a compound of the present disclosure at light chain position 103.

[000169] In various examples, the antibody, or antigen-binding fragment thereof, comprises a C103S mutation in the light chain.

[000170] The various examples, the antibody, or the antigen-binding fragment thereof, is conjugated to a compound of the present disclosure at position 103 of the light chain.

[000171] In one example, L is a linker having the formula , wherein

RG is selected from a maleimide, a N-hydroxy succinimide, or a succinimide;

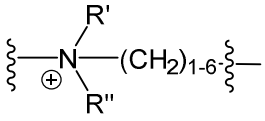
SP^1 and SP^2 are independently absent or a spacer group selected from the group consisting of ; C_{1-6} alkyl, -NH-, -C(O)-, $-CH_2-CH_2-C(O)-NH-$, $-(CH)_u-C(O)-NH-$, $(-CH_2-CH_2-O)_e$, $-NH-CH_2-CH_2-(-O-CH_2-CH_2)_e-C(O)-$, $-C(O)-(CH_2)_u-C(O)-$, $-C(O)-NH-(CH_2)_v-$, and combinations thereof, wherein subscript **e** is an integer from 0 to 4, subscript **u** is an integer from 1 to 8, and subscript **v** is an integer from 1 to 8;

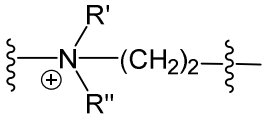
AA_{2-4} is a peptide unit comprising from 2 to 4 amino acids, and

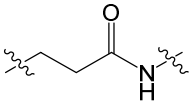
PEG is a polyethylene glycol chain comprising between 1 and 30 polyethylene glycol residues.

[000172] In one example, AA_{2-4} is a dipeptide selected from valine-citrulline; citrulline-valine; valine-alanine; alanine-valine; valine-glycine, glycine-valine, or alanine-glycine, alanine-alanine.

[000173] In one example, AA_{2-4} is valine-citrulline.

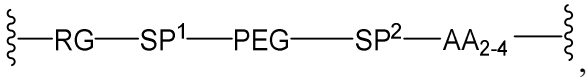
[000174] In one example, SP is  and R' and R" are each a C_{1-6} alkyl.

[000175] In one example, SP is  and R' and R" are each methyl.

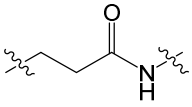
[000176] In one example, SP^1 and SP^2 are each .

[000177] In one example, PEG comprises 8 polyethylene glycol units.

[000178] In one example, BA is an antibody, or an antigen-binding fragment thereof;

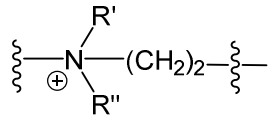
L is a linker having the formula , wherein

RG is selected from a maleimide or a succinimide;

SP^1 and SP^2 are each ;

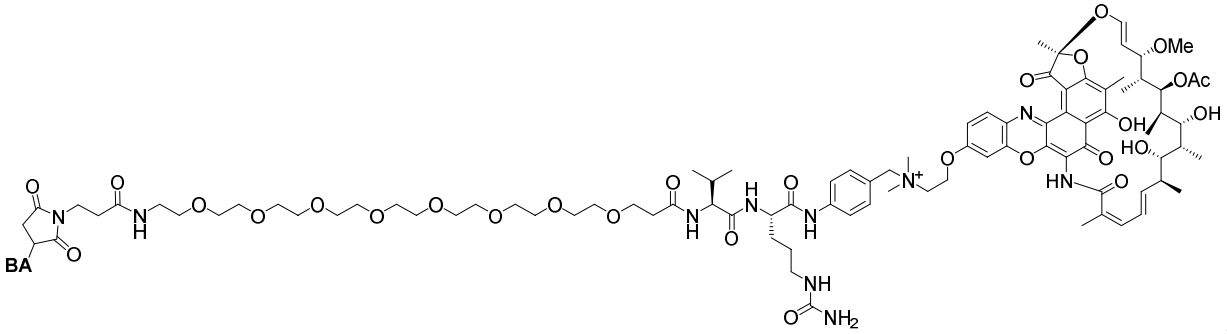
AA_{2-4} is valine-citrulline;

PEG is a polyethylene glycol chain comprising 8 polyethylene glycol residues

SP is  and R' and R" are each methyl, and

X is -O-.

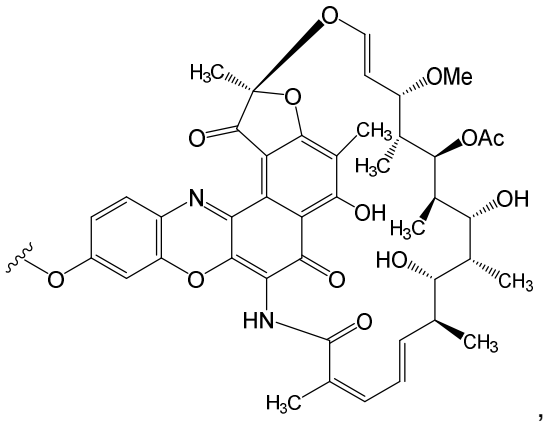
[000179] In one example, the antibody-drug conjugate has a structure:



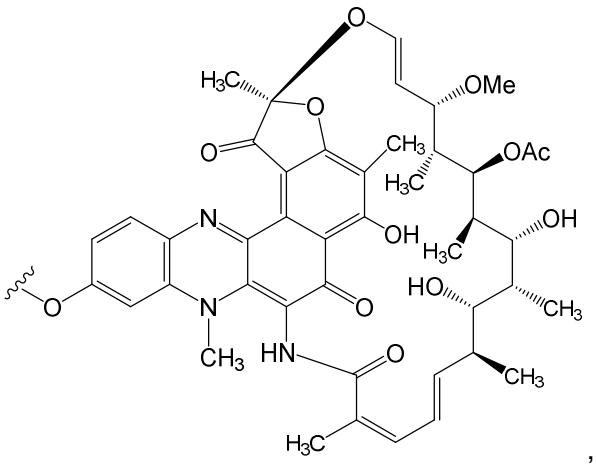
,

wherein BA is an antibody, or an antigen-binding fragment thereof.

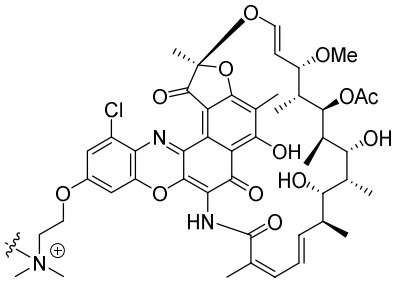
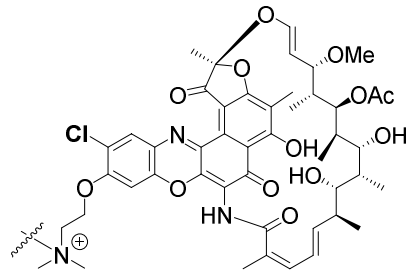
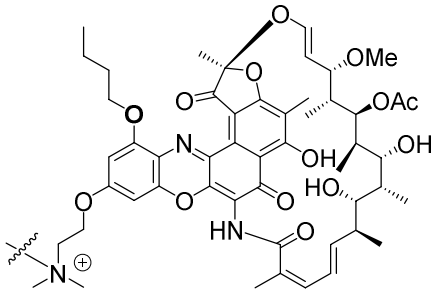
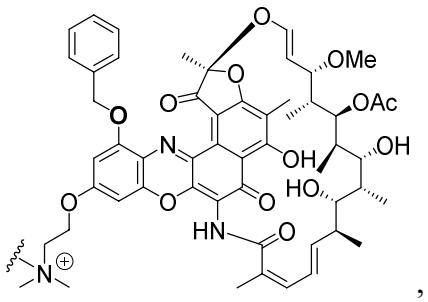
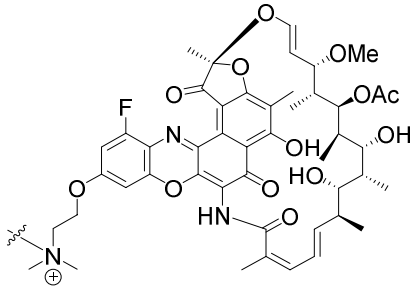
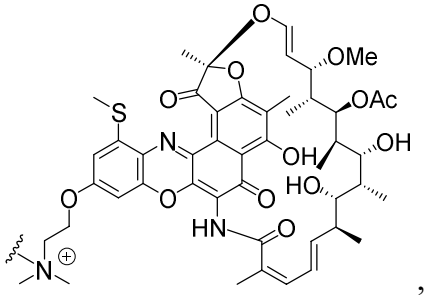
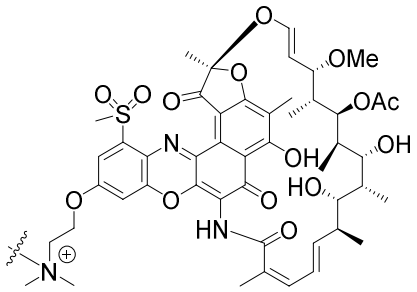
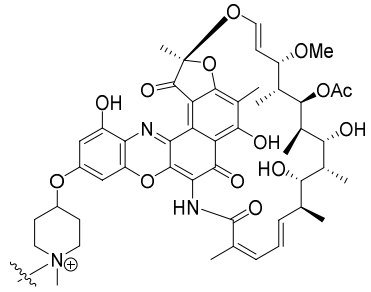
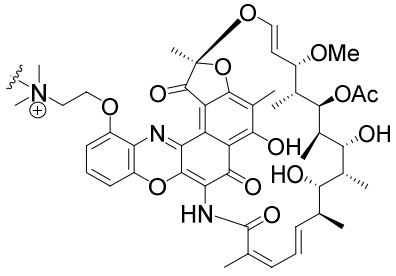
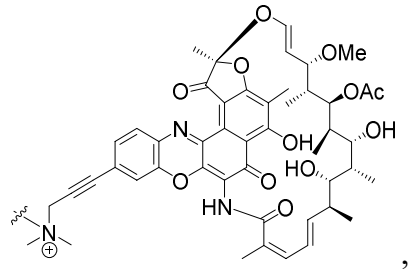
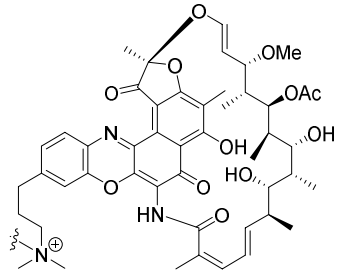
[000180] In another example, the present disclosure provides an isolated antibody or antigen binding fragment thereof, wherein the antibody or antigen binding fragment thereof is conjugated, directly or through a linker or a linker-spacer, to a payload having the structure selected from the group consisting of:



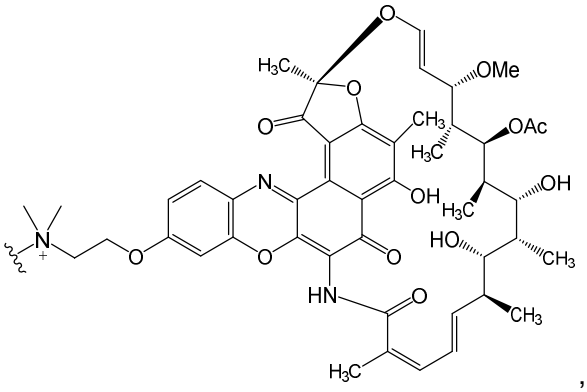
,



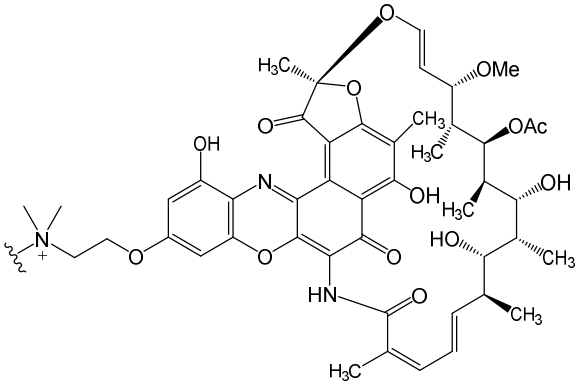
,

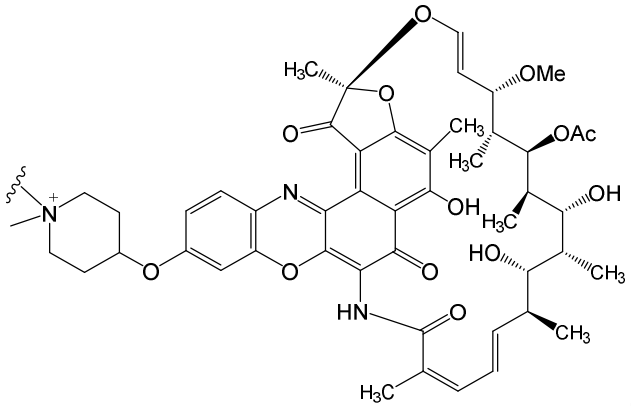
[000181] In one example, the payload has the structure selected from:



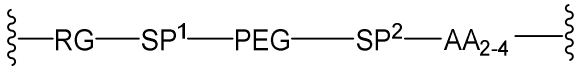
,



and

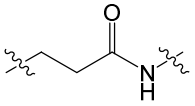


.

[000182] In one example, the payload is conjugated through a linker, the linker having the structure: 

, wherein

RG is selected from a maleimide or a succinimide;

SP^1 and SP^2 are independently absent or a spacer group selected from the group consisting of 

; $C_{1\text{-}6}$ alkyl, -NH-, -C(O)-, $-CH_2-CH_2-C(O)-NH-$, $-(CH)_u-C(O)-NH-$, $(-CH_2-CH_2-O)_e$, $-NH-CH_2-CH_2-(-O-CH_2-CH_2)_e-C(O)-$, $-C(O)-(CH_2)_u-C(O)-$, $-C(O)-NH-(CH_2)_v-$, and

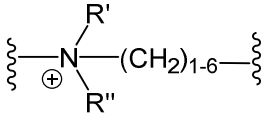
combinations thereof, wherein subscript **e** is an integer from 0 to 4, subscript **u** is an integer from 1 to 8, and subscript **v** is an integer from 1 to 8;

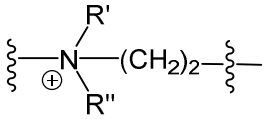
AA_{2-4} is a peptide unit comprising from 2 to 4 amino acids, and

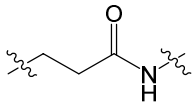
PEG is a polyethylene glycol chain comprising between 1 and 30 polyethylene glycol residues.

[000183] In one example, AA_{2-4} is a dipeptide selected from valine-citrulline; citrulline-valine; valine-alanine; alanine-valine; valine-glycine, or glycine-valine.

[000184] In one example, AA_{2-4} is valine-citrulline.

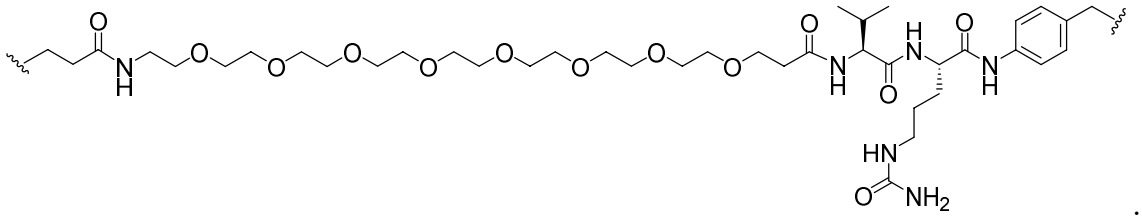
[000185] In one example, SP is  and R' and R" are each a C_{1-6} alkyl.

[000186] In one example, SP is  and R' and R" are each methyl.

[000187] In one example, SP^1 and SP^2 are each .

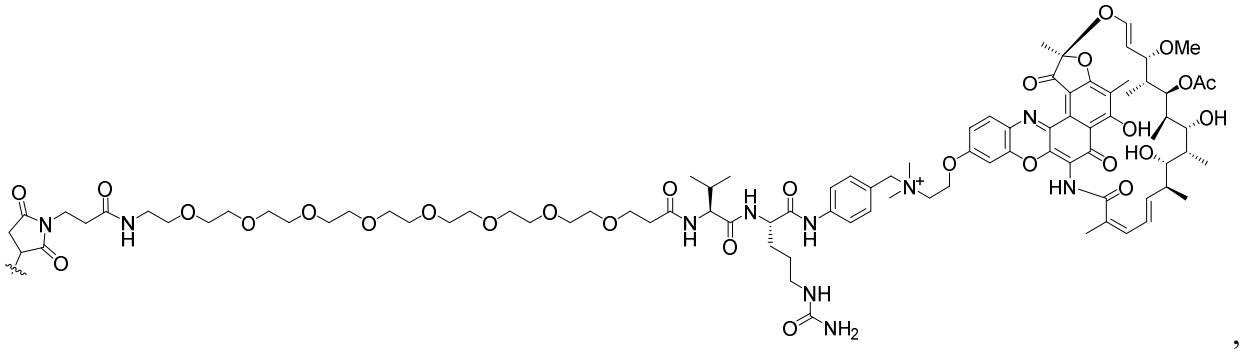
[000188] In one example, PEG comprises 8 polyethylene glycol units.

[000189] In one example, the payload is conjugated through a linker having the structure:



.

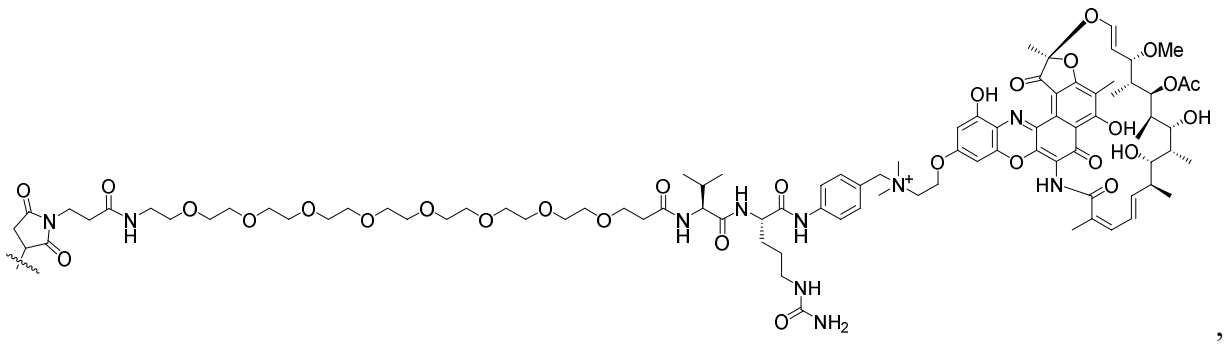
[000190] In one example, the payload is conjugated through a linker, the linker-payload having the structure:



,

wherein the is the bond to the antibody or the antigen-binding fragment thereof.

[000191] In one example, the payload is conjugated through a linker, the linker-payload having the structure:



wherein the ≈— is the bond to the antibody or the antigen-binding fragment thereof.

[000192] In one example, the antibody, or the antigen-binding fragment thereof, that binds macrophage scavenger receptor 1 (MSR1) comprises: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) comprising an amino acid sequence as set forth in Table 9; and (b) the CDRs of a light chain variable region (LCVR) comprising an amino acid sequence as set forth in Table 9.

[000193] In one example, the anti-MSR1 antibody, or the antigen-binding fragment thereof, comprises:

(i) a HCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 36, 52, 92, and 284;

(ii) a HCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 38, 54, 94, and 286;

(iii) a HCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 40, 56, 96, and 288;

(iv) a LCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 44, 60, 100, and 292;

(v) a LCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 46, 62, 102, and 294; and

(vi) a LCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 48, 64, 104, and 296.

[000194] In one example, the anti-MSR1 antibody, or the antigen-binding fragment thereof, comprises

(i) a HCDR1 domain comprising an amino acid sequence of SEQ ID NO: 52;

(ii) a HCDR2 domain comprising an amino acid sequence of SEQ ID NO: 54;

(iii) a HCDR3 domain comprising an amino acid sequence of SEQ ID NO: 56;

(iv) a LCDR1 domain comprising an amino acid sequence of SEQ ID NO: 60;

(v) a LCDR2 domain comprising an amino acid sequence of SEQ ID NO: 62; and

(vi) a LCDR3 domain comprising an amino acid sequence of SEQ ID NO: 64.

[000195] In one example, the anti-MSR1 antibody, or the antigen-binding fragment thereof, comprises a N297Q mutation.

[000196] In one example, the anti-WTA antibody, or the antigen-binding fragment thereof, may comprise: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) comprising an amino acid sequence as set forth in Table 2A; and (b) the CDRs of a light chain variable region (LCVR) comprising an amino acid sequence as set forth in Table 2A.

[000197] In one example, the anti-WTA antibody, or the antigen-binding fragment thereof, may comprise:

(i) a HCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 470, 476, 482, and 488;

(ii) a HCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 471, 477, 483, and 489;

(iii) a HCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 472, 478, 484, and 490;

(iv) a LCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 467, 473, 479, and 485;

(v) a LCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 468, 474, 480, and 486; and

(vi) a LCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 469, 475, 481, and 487.

[000198] In one example, the anti-WTA antibody, or the antigen-binding fragment thereof, may comprise: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) comprising an amino acid sequence as set forth in Table 2B; and (b) the CDRs of a light chain variable region (LCVR) comprising an amino acid sequence as set forth in

Table 2B.

[000199] In one example, the anti-WTA antibody, or the antigen-binding fragment thereof, may comprise:

(i) a HCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 502, 508, 514, 520, 526, 532, 538, 544, 550, 556, 562, 568, and 574;

(ii) a HCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 503, 509, 515, 521, 527, 533, 539, 545, 551, 557, 563, 569, and 575;

(iii) a HCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 504, 510, 516, 522, 528, 534, 540, 546, 552, 558, 564, 570, 576, and 584;

(iv) a LCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 499, 505, 511, 517, 523, 529, 535, 541, 547, 553, 559, 565, and 571;

(v) a LCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 500, 506, 512, 518, 524, 530, 536, 542, 548, 554, 560, 566, and 572; and

(vi) a LCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 501, 507, 513, 519, 525, 531, 537, 543, 549, 555, 561, 567, and 573.

[000200] In some examples, the anti-WTA antibody, or the antigen-binding fragment thereof, comprises a V205C mutation (EU numbering) in the light chain.

[000201] In one example, the anti-WTA antibody, or the antigen-binding fragment thereof, is derived from antibody 4497 described in US Patent Application Publication 20140356375 (which is incorporated herein by reference in its entirety). In one example, the anti-WTA antibody is derived from antibody 4497 and further comprises a V205C mutation in the light chain.

[000202] In one example, the anti-WTA antibody, or the antigen-binding fragment thereof, comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 of SEQ ID Nos: 568-569-570-565-566-567.

[000203] In some examples, the anti-WTA antibody or antigen binding fragment thereof comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NOs: 586; and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 585.

[000204] In some examples, the anti-WTA antibody or antigen binding fragment thereof comprises an HCVR amino acid sequence of SEQ ID NOs: 586, and an LCVR amino acid sequence of SEQ ID NO: 585.

[000205] In some examples, the anti-WTA antibody comprises a heavy chain amino acid sequence of SEQ ID NOs: 602 and a light chain amino acid sequence of SEQ ID NO: 587 or SEQ ID NO: 589. In some examples, the anti-WTA antibody, or the antigen-binding fragment thereof comprises a V205C mutation in the light chain.

[000206] In one example, the anti-Protein A antibody, or the antigen-binding fragment thereof, may comprise: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) comprising an amino acid sequence as set forth in Table 3A; and (b) the CDRs of a light chain variable region (LCVR) comprising an amino acid sequence as set forth in Table 3A.

[000207] In one example, the anti-Protein A antibody, or the antigen-binding fragment thereof, may comprise:

[000208] (i) a HCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 632, 652, and 672;

[000209] (ii) a HCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 634, 654, and 674;

[000210] (iii) a HCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 636, 656, and 676;

[000211] (iv) a LCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 640, 660, and 680;

[000212] (v) a LCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 642 and 662; and

[000213] (vi) a LCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 644, 664, and 683.

[000214] In some examples, the anti-Protein A antibody, or the antigen-binding fragment thereof, comprises a H435R and a Y436F mutation (EU numbering) in the heavy chain Fc.

[000215] In some examples, the anti-Protein A antibody, or the antigen-binding fragment thereof, comprises a H435R and a Y436F mutation (EU numbering) in the heavy chain Fc.

[000216] In one example, the anti-Protein A antibody or antigen binding fragment thereof comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NOs: 630; and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 638. In one example, the anti-Protein A antibody or antigen binding fragment thereof comprises a set of six CDRs (HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) comprising SEQ ID NOs: 632-634-636-640-642-644.

[000217] In one example, the anti-Protein A antibody or antigen binding fragment thereof comprises an HCVR amino acid sequence of SEQ ID NOs: 630; and an LCVR amino acid sequence of SEQ ID NO: 638.

[000218] In one example, the anti-Protein A antibody comprises a heavy chain amino acid sequence of SEQ ID NOs: 666 and a light chain amino acid sequence of SEQ ID NO: 668. In one examples, the anti-Protein A antibody, further comprises a H435R and a Y436F mutation (EU numbering) in the heavy chain Fc. In one example, anti-Protein A antibody further comprises a C103S mutation in the light chain. In one example, the anti-Protein A antibody, or antigen-binding fragment thereof, is conjugated to a compound of the present disclosure at light chain position 103.

[000219] In various examples, the antibody, or antigen-binding fragment thereof, comprises a C103S mutation in the light chain.

[000220] The various examples, the antibody, or the antigen-binding fragment thereof, is conjugated to a compound of the present disclosure at position 103 of the light chain.

[000221] In one example, the present disclosure provides a method of preventing or inhibiting growth of a bacterium comprising administering an effective amount of an antibody-drug conjugate as described herein.

[000222] In one example, the bacterium is a Gram-positive bacterium.

[000223] In one example, the bacterium is a penicillin-resistant bacterium.

[000224] In one example, the bacterium is *Staphylococcus aureus*.

[000225] In one example, the bacterium is selected from methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Staphylococcus aureus* (VRSA), and methicillin-susceptible *Staphylococcus aureus* (MSSA).

[000226] In one example, the present disclosure provides a method of treating a bacterial infection in a subject in need of such treatment comprising administering to the subject an effective amount of an antibody-drug conjugate as described herein.

[000227] In one example, the bacterial infection is a Gram-positive bacterial infection.

[000228] In one example, the bacterial infection is a penicillin-resistant bacterial infection.

[000229] In one example, the bacterial infection is a *Staphylococcus aureus* infection.

[000230] In one example, the bacterial infection is selected from a methicillin-resistant *Staphylococcus aureus* (MRSA) infection, a vancomycin-resistant *Staphylococcus aureus* (VRSA) infection, and a methicillin-susceptible *Staphylococcus aureus* (MSSA) infection.

[000231] In one example, the bacterial infection is an intracellular bacterial infection.

[000232] In one example, the subject is human.

[000233] In one example, the method further comprises administering a second therapeutic agent.

[000234] In one example, the second therapeutic agent is a second antibiotic.

[000235] In one example, the second antibiotic is effective against *Staphylococcus aureus*.

[000236] In one example, the second antibiotic is selected from an aminoglycoside, a beta-lactam, a macrolide, a cyclic peptide, a tetracycline, a fluoroquinoline, a fluoroquinolone, and an oxazolidinone.

[000237] In one example, the second antibiotic is selected from clindamycin, novobiocin, retapamulin, daptomycin, sitafloxacin, teicoplanin, triclosan, napthyridone, radezolid, doxorubicin, ampicillin, vancomycin, imipenem, doripenem, gemcitabine, dalbavancin, and azithromycin.

[000238] In one example, the antibody-drug conjugate is administered to the subject orally, topically, intranasally, intravenously, intramuscularly, or subcutaneously.

[000238a] In another aspect, there is provided a pharmaceutical composition comprising the

antibody-drug conjugate as described above or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[000238b] In another aspect, there is provided a pharmaceutical dosage form comprising the antibody-drug conjugate as described above or a pharmaceutically acceptable salt thereof.

[000238c] In another aspect, there is provided a use of the antibody-drug conjugate as described above, or the pharmaceutical composition as described above or the pharmaceutical dosage form as described above in the manufacture of a medicament for inhibiting growth of a bacterium.

[000238d] In another aspect, there is provided a use of the antibody-drug conjugate as described above, or the pharmaceutical composition as described above, or the pharmaceutical dosage form as described above in the manufacture of a medicament for treating a bacterial infection in a subject in need of such treatment.

[000238e] In another aspect, there is provided a use of the antibody-drug conjugate as described above, or the pharmaceutical composition as described above, or the pharmaceutical dosage form as described above in the manufacture of a medicament for preventing or treating cellulitis, bacteremia, dermonecrosis, eyelid infection, eye infection, neonatal conjunctivitis, osteomyelitis, impetigo, boils, scalded skin syndrome, food poisoning, pneumonia, surgical infection, urinary tract infection, burn infection, meningitis, endocarditis, septicemia, toxic shock syndrome, septic arthritis, mastitis, infection associated with a prosthetic joint, infection associated with a catheter, or infection associated with an implant.

[000239] In yet another example, the present disclosure provides a method of preventing or

treating cellulitis, bacteremia, dermonecrosis, eyelid infection, eye infection, neonatal conjunctivitis, osteomyelitis, impetigo, boils, scalded skin syndrome, food poisoning, pneumonia, surgical infection, urinary tract infection, burn infection, meningitis, endocarditis, septicemia, toxic shock syndrome, septic arthritis, mastitis, infection associated with a prosthetic joint, infection associated with a catheter, or infection associated with an implant, in a subject comprising administering to the subject an effective treatment amount of the compounds, the antibody-drug conjugates, or the pharmaceutical compositions as described herein.

[000240] These and other example sof the present disclosure will become apparent to those skilled in the art after a reading of the following detailed description of the disclosure, including the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[000241] **Figure 1** is a plot of the results of the *S. aureus* growth inhibition assay conducted with rifamycin analogs according to the disclosure.

[000242] **Figure 2** is a bar graph of the results of the *S. aureus* intracellular killing assay conducted with rifamycin analogs according to the disclosure.

[000243] **Figure 3** is a plot of the results of the *S. aureus* intracellular killing assay conducted with rifamycin analogs according to the disclosure.

[000244] **Figure 4** is a schematic of four day *S. aureus* infection model.

[000245] **Figure 5** is a plot of colony forming units of Anti-*Staphylococcus aureus* ADCs according to the disclosure in an intracellular killing assay using THP cells.

[000246] **Figure 6** depicts the average *S. aureus* kidney burden in mice treated with isotype control and anti-WTA Ab-Antibiotic ncADC (antibody-drug conjugates) according to the disclosure at 2 mg/kg in combination with vancomycin.

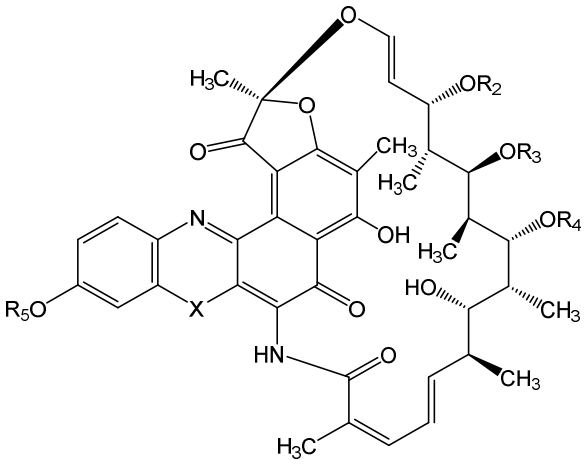
[000247] **Figure 7** depicts the average *S. aureus* kidney burden in mice treated with isotype control and anti-Protein A Ab-Antibiotic ncADC according to the disclosure at 2 mg/kg in combination with vancomycin.

[000248] **Figure 8** depicts the average *S. aureus* kidney burden in mice treated with isotype control and anti-WTA Ab-Antibiotic ncADC according to the disclosure at 5 mg/kg in combination with vancomycin.

DETAILED DESCRIPTION

WHAT IS CLAIMED IS:

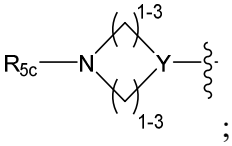
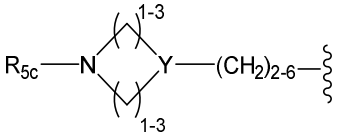
1. An antibody-drug conjugate comprising an antibody, or an antigen-binding fragment thereof, conjugated via a linker or through a linker-spacer to a rifamycin analog having the structure of Formula (XXI):



(XXI),

wherein:

X is selected from -O-, -S-, and -NR*-;

R_5 is selected from a bond; an aliphatic C_1-C_{20} hydrocarbon which further comprises 0-8 heteroatoms selected from halogen, O, N, and S;  ; or  ; wherein **Y** is C or N;

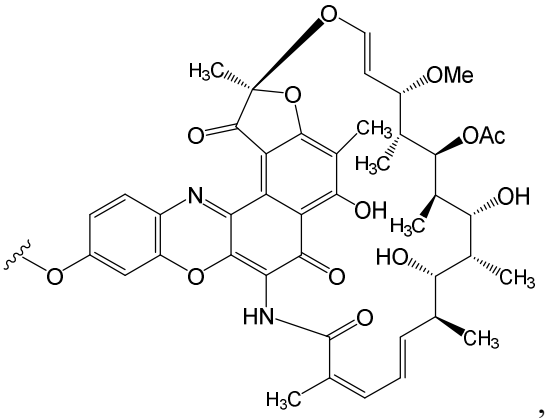
R_2, R_3, and R_4 are independently selected from a hydrogen, a straight chained, branched or cyclic aliphatic C_3-C_{20} hydrocarbon, or -(C=O)-R*, each of which further comprises 0-8 heteroatoms selected from halogen, O, N, and S,

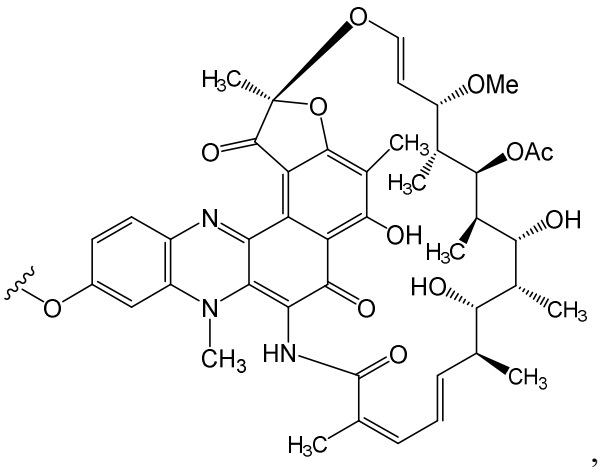
R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_5-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_3-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof, and

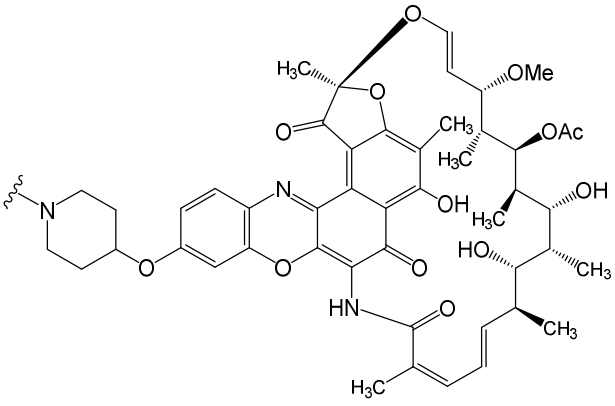
R_{5c} is a bond or an aliphatic C_1-C_8 hydrocarbon,

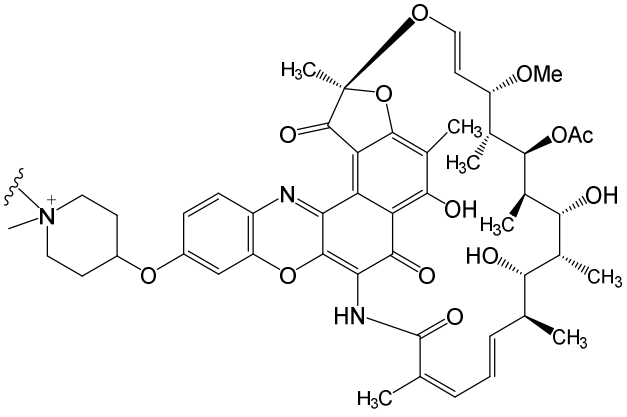
wherein the group R_5 is bonded to the linker.

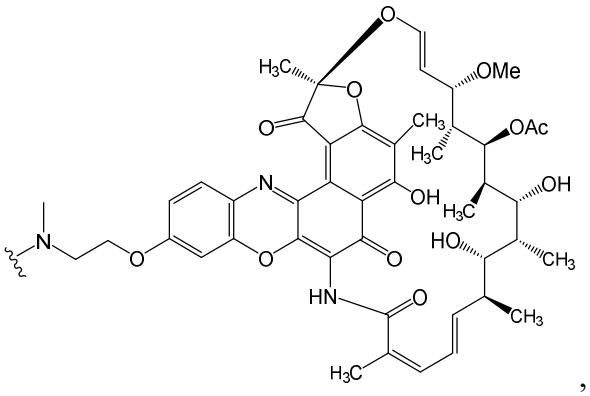
2. An antibody-drug conjugate comprising an antibody, or an antigen-binding fragment thereof, conjugated via a linker or through a linker-spacer to a compound selected from the group consisting of:

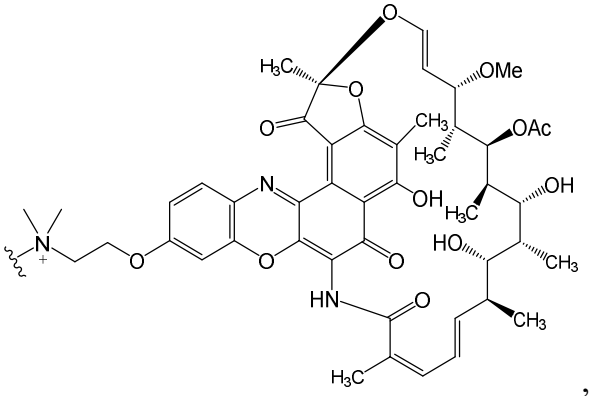
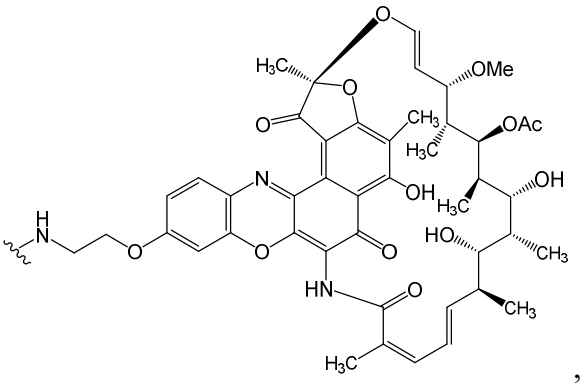
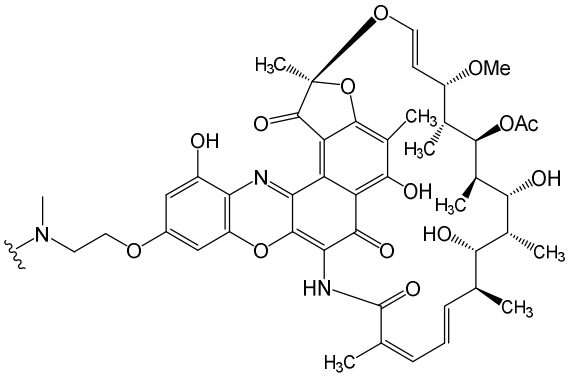
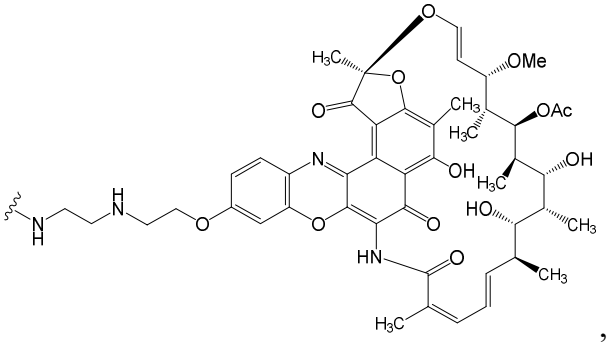
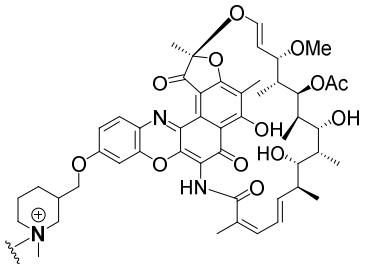
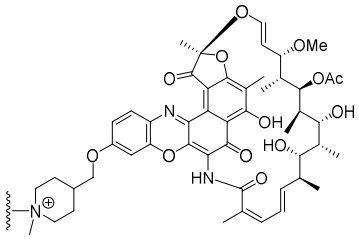
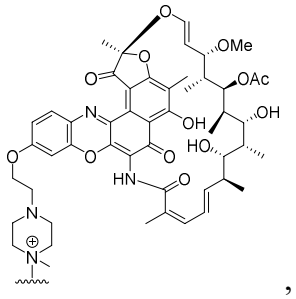
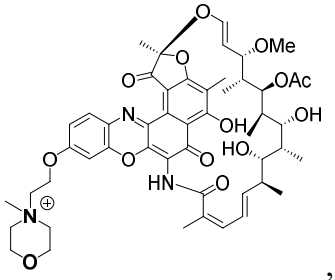
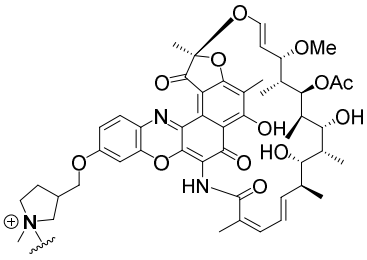
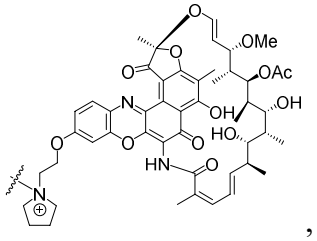
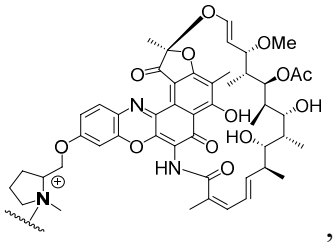
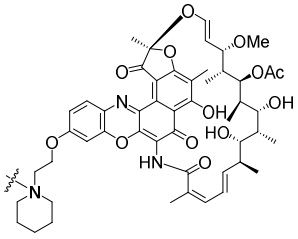
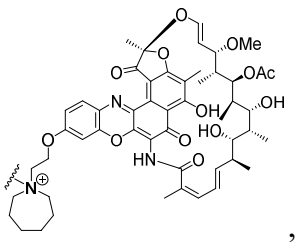
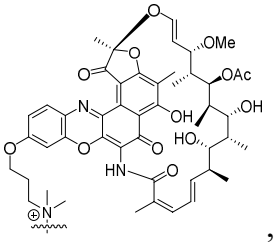

,

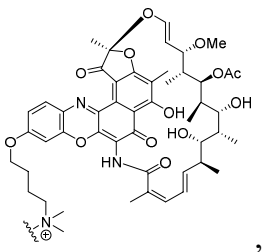
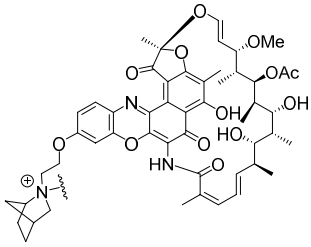
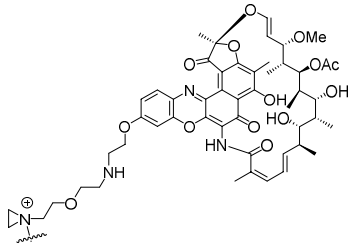

,

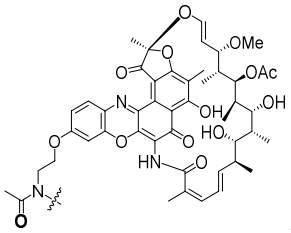
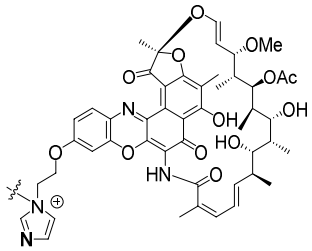
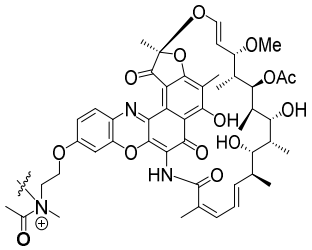
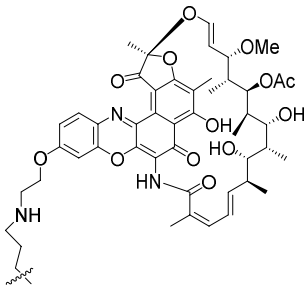
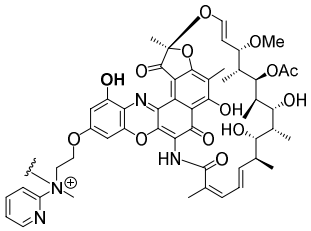
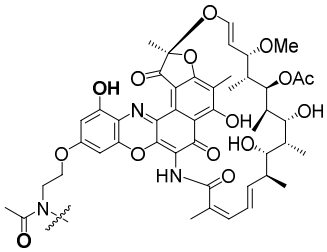
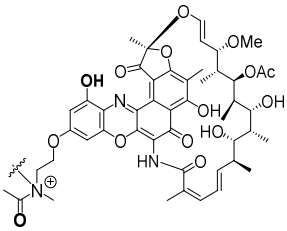
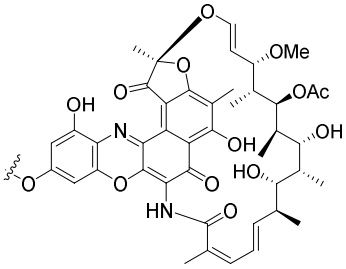
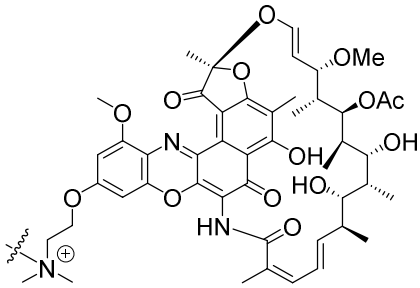
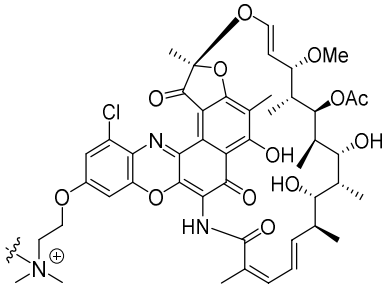
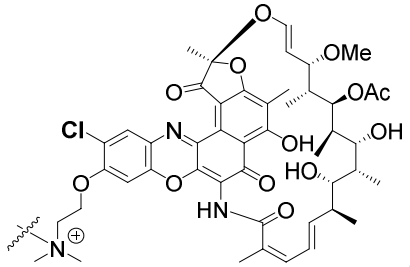
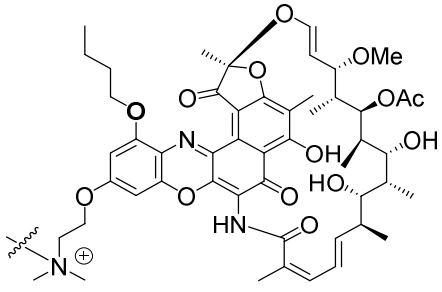
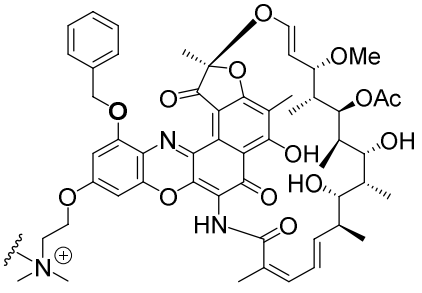

,

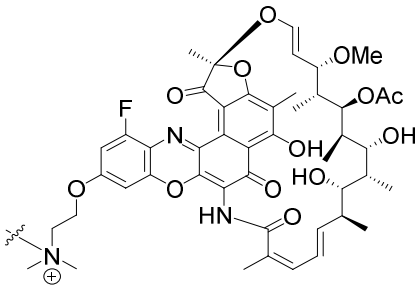
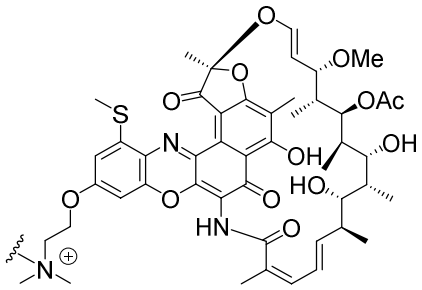
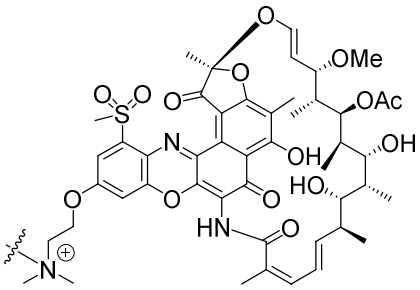
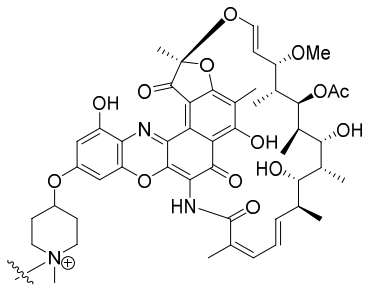
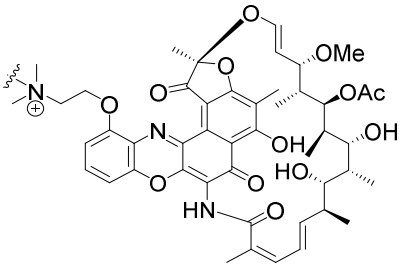
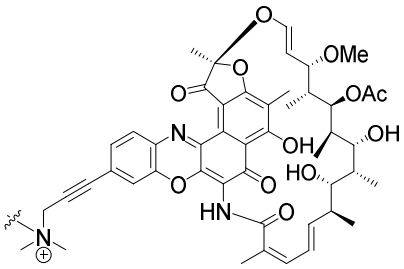
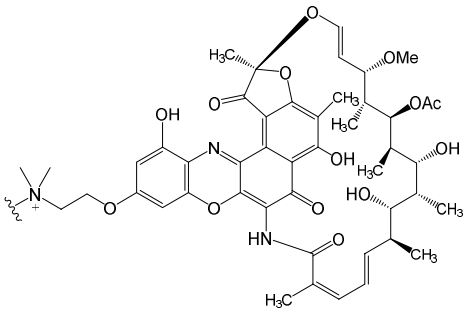
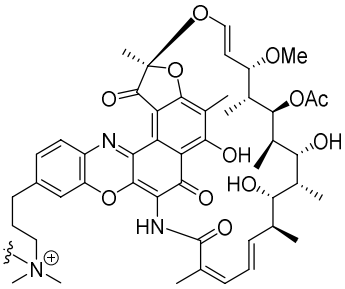

,


,


,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

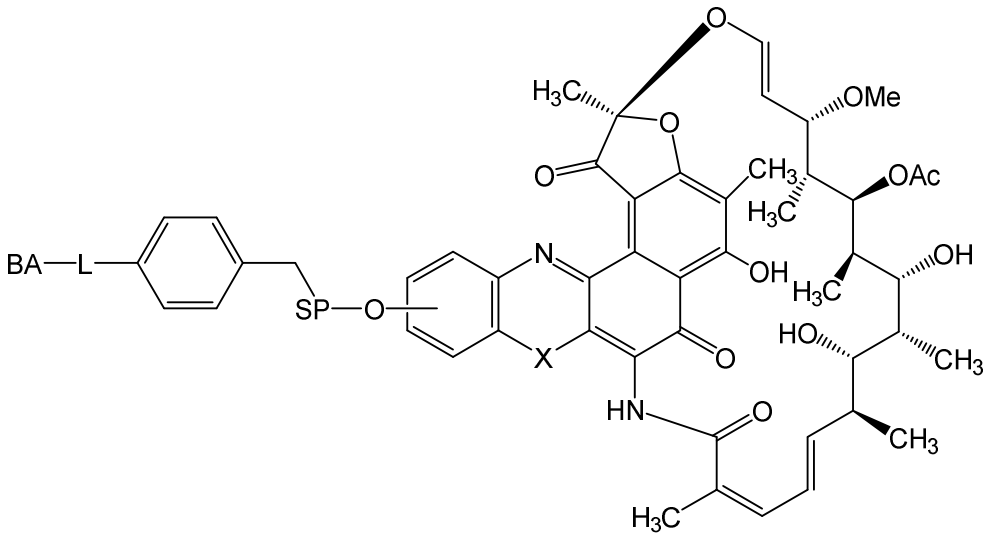

,

,

,

,

,

,

,

,

,

,

,

,

,



,

,

,

,

,

, and

,

wherein the ~ is the bond to the linker, and when the compound comprises an ammonium salt, the counterion is an anion selected from F^-, Cl^-, Br^-, I^-, OH^-, $^-BF_4$, $CF_3SO_3^-$, monobasic sulfate, dibasic sulfate, monobasic phosphate, dibasic phosphate, or tribasic phosphate, NO_3^-, PF_6^-, NO_2^-, carboxylate, $C_eF_fSO_3^-$, where in e=2-10 and f=2e+1, acetate, aspartate, benzenesulfonate, benzoate, besylate, bicarbonate, bitartrate, camsylate, carbonate, citrate, decanoate, edetate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolate, glycollyalarsanilate, hexanoate, hydrabamine, hydroxynaphthoate, isthionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate,

mucate, napsylate, octanoate, oleate, pamoate, pantothenate, polygalacturonate, propionate, salicylate, stearate, subacetate, succinate, tartrate, teoclate, tosylate, or triethiiodide.

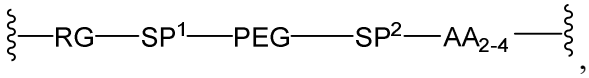
3. An antibody-drug conjugate having the structure of Formula (XXII):



(XXII),

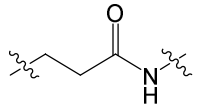
wherein:

BA is an antibody, or an antigen-binding fragment thereof;

L is a linker having the formula 

, wherein

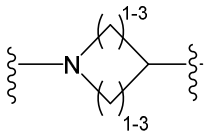
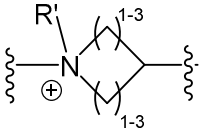
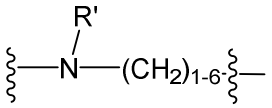
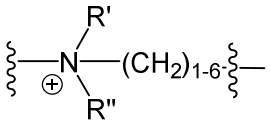
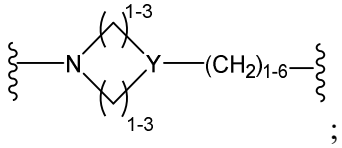
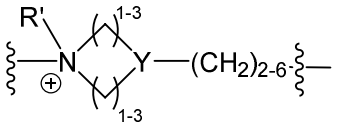
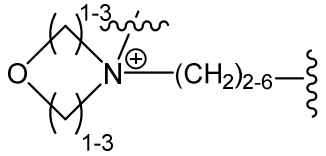
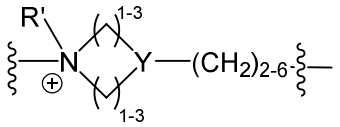
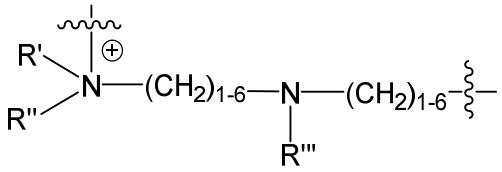
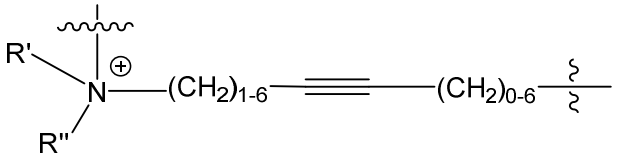
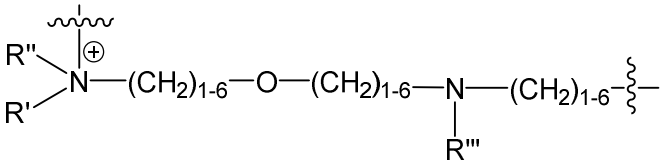
RG is selected from a maleimide, a N-hydroxysuccinimide, or a succinimide;

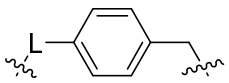
SP^1 and SP^2 are independently absent or a spacer group selected from the group consisting of 

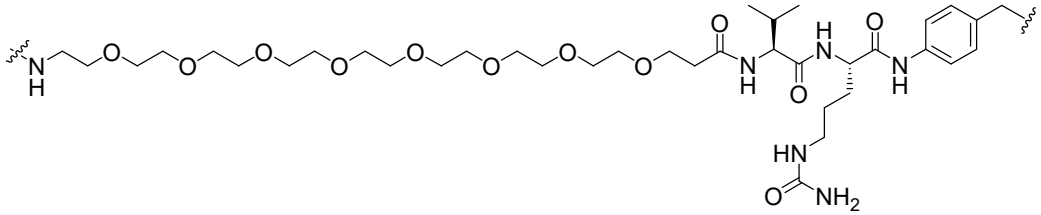
; C_{1-6} alkyl, -NH-, -C(O)-, $-CH_2-CH_2-C(O)-NH-$, $-(CH)_u-C(O)-NH-$, $(-CH_2-CH_2-O)_e$, $-NH-CH_2-CH_2-(-O-CH_2-CH_2)_e-C(O)-$, $-C(O)-(CH_2)_u-C(O)-$, $-C(O)-NH-(CH_2)_v-$, and combinations thereof, wherein subscript **e** is an integer from 0 to 4, subscript **u** is an integer from 1 to 8, and subscript **v** is an integer from 1 to 8;

AA_{2-4} is a dipeptide selected from valine-citrulline; citrulline-valine; valine-alanine; alanine-valine; valine-glycine, or glycine-valine, and

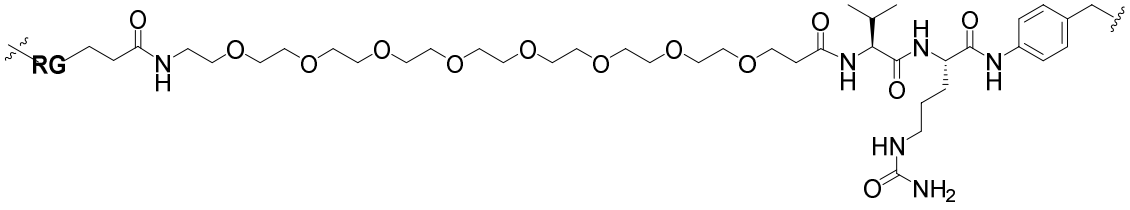
PEG is a polyethylene glycol chain comprising between 1 and 30 polyethylene glycol residues;

SP is a spacer group selected from ; ; ; ; ; ; ; ; , ;  and ;

Y is C or N; wherein the 〰 symbol represents the point of attachment; and R', R" and R''' are selected from a hydrogen, a C_1-C_6 aliphatic hydrocarbon, and a protecting group selected from Fluorenylmethyloxycarbonyl (F_{MOC}) and *tert*-Butyloxycarbonyl (B_{OC}), or wherein R' and R'' together form an aliphatic monocyclic, an aliphatic bicyclic, or an aliphatic polycyclic structure; or wherein the  has a structure:



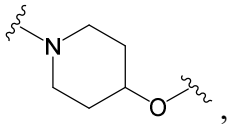
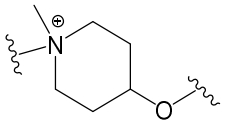
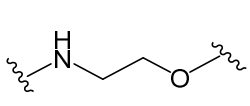
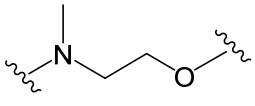
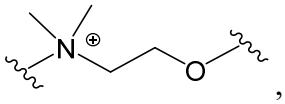
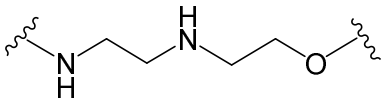
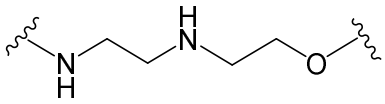
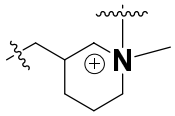
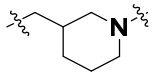
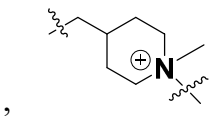
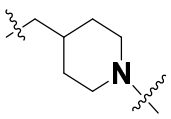
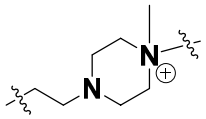
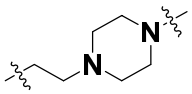
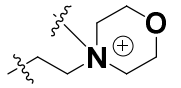
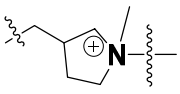
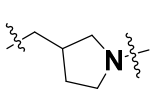
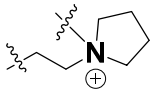
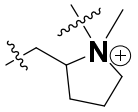
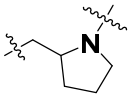
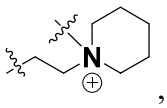
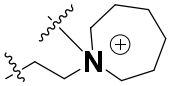
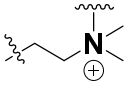
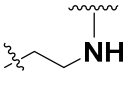
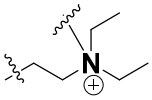
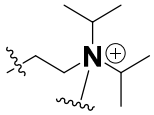
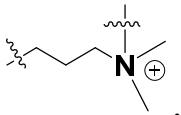
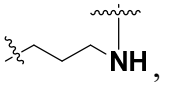
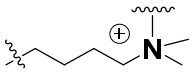
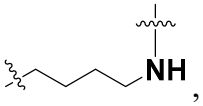
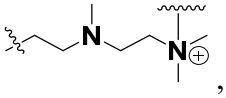
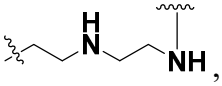
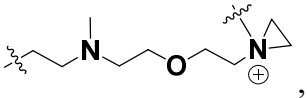
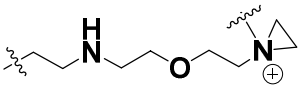
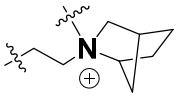
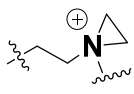
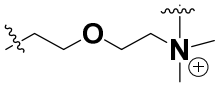
or,

,

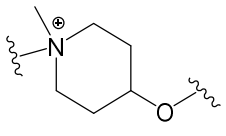
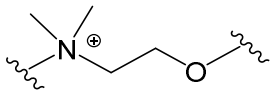
R* is independently at each occurrence selected from hydrogen, an aliphatic C_1-C_{20} hydrocarbon, an aromatic C_5-C_{20} hydrocarbon, a heteroaromatic C_1-C_{20} hydrocarbon, a cyclic aliphatic C_3-C_{20} hydrocarbon, a heterocyclic C_1-C_{20} hydrocarbon, and combinations thereof, which further comprises 0-8 heteroatoms selected from halogen, O, N, and S and combinations thereof,

and

X is selected from -O-, -S-, and -NR*.

4. The antibody-drug conjugate of claim 1, wherein $-OR_5$ is –O–, , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , or .

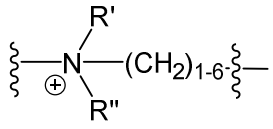
5. The antibody-drug conjugate of claim 1, wherein X is O, and -OR_5 comprises a tertiary amine.

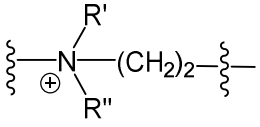
6. The antibody-drug conjugate of claim 1, wherein -OR_5 is  or .

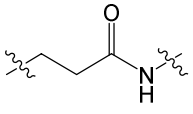
7. The antibody-drug conjugate of claim 1, wherein R_2 is methyl, ethyl, propyl or isopropyl; R_3 is CH_3-(C=O)- (acetyl), CH_3CH_2-(C=O)-, $CH_3CH_2CH_2$-(C=O)-, or $(CH_3)_2CH$-(C=O)-, and R_4 is hydrogen.

8. The antibody-drug conjugate of claim 1, wherein R_2 is methyl, R_3 is acetyl, and R_4 is hydrogen.

9. The antibody-drug conjugate of claim 3, wherein AA_{2-4} is valine-citrulline.

10. The antibody-drug conjugate of claim 3, wherein SP is  and R' and R" are each a C_{1-6} alkyl.

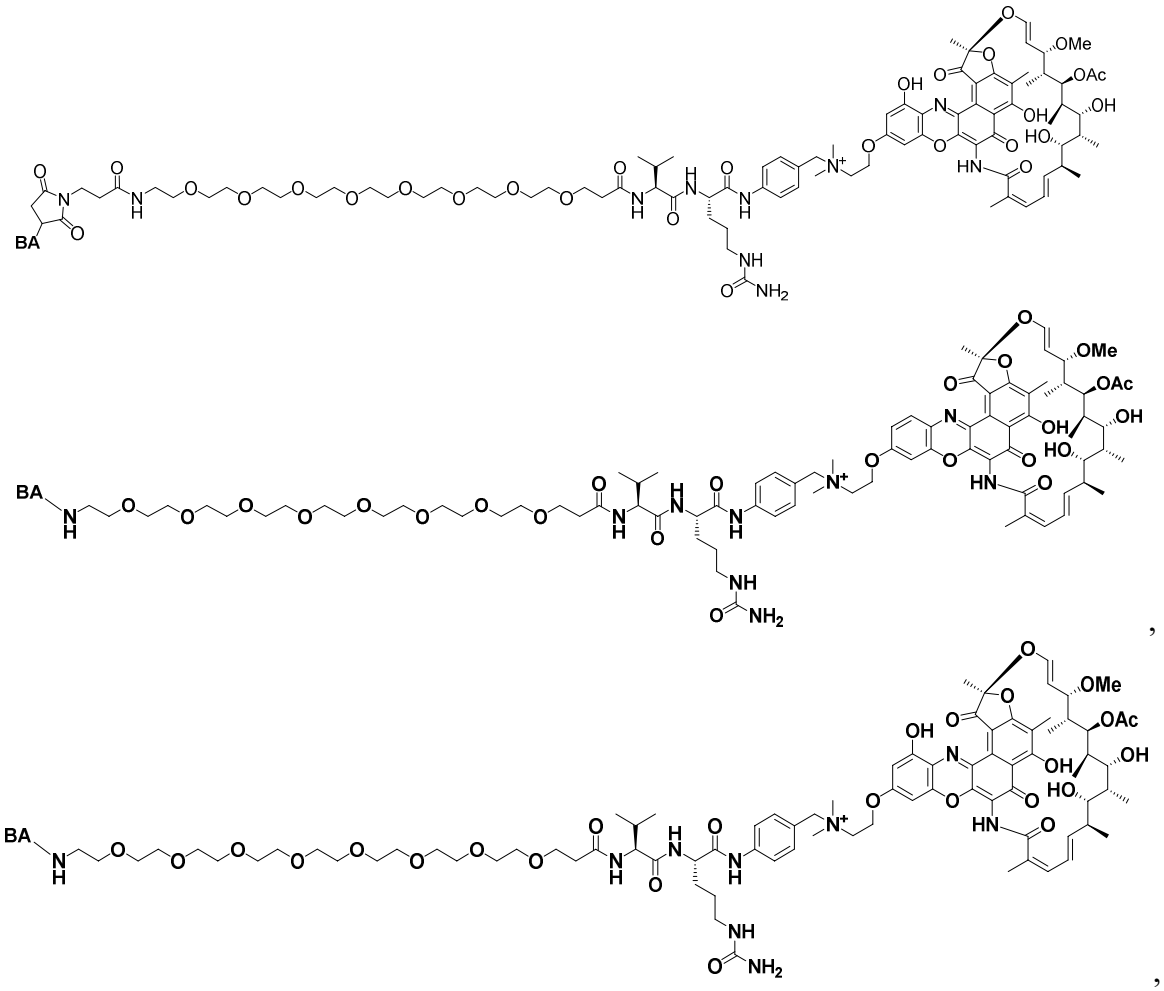
11. The antibody-drug conjugate of claim 3, wherein SP is  and R' and R" are each methyl.

12. The antibody-drug conjugate of claim 3, wherein SP^1 and SP^2 are each .

13. The antibody-drug conjugate of claim 3, wherein PEG comprises 8 polyethylene glycol

units.

14. The antibody-drug conjugate of claim 3, wherein the antibody-drug conjugate has a structure selected from the group consisting of:



wherein BA is an antibody, or an antigen-binding fragment thereof.

15. The antibody-drug conjugate of any one of claims 1 and 4-8, wherein the antibody, or an antigen-binding fragment thereof, binds an infectious disease-related target.

16. A pharmaceutical composition comprising the antibody-drug conjugate of any one of claims 1 and 4-8 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

17. A pharmaceutical dosage form comprising the antibody-drug conjugate of any one of claims 1 and 4-8 or a pharmaceutically acceptable salt thereof.

18. Use of the antibody-drug conjugate of any one of claims 1 and 4-8, or the pharmaceutical composition of claim 16, or the pharmaceutical dosage form of claim 17 in the manufacture of a medicament for inhibiting growth of a bacterium.

19. Use of the antibody-drug conjugate of any one of claims 1 and 4-8, or the pharmaceutical composition of claim 16, or the pharmaceutical dosage form of claim 17 in the manufacture of a medicament for treating a bacterial infection in a subject in need of such treatment.

20. Use of the antibody-drug conjugate of any one of claims 1 and 4-8, or the pharmaceutical composition of claim 16, or the pharmaceutical dosage form of claim 17 in the manufacture of a medicament for preventing or treating cellulitis, bacteremia, dermonecrosis, eyelid infection, eye infection, neonatal conjunctivitis, osteomyelitis, impetigo, boils, scalded skin syndrome, food poisoning, pneumonia, surgical infection, urinary tract infection, burn infection, meningitis, endocarditis, septicemia, toxic shock syndrome, septic arthritis, mastitis, infection associated with a prosthetic joint, infection associated with a catheter, or infection associated with an implant.

21. The antibody-drug conjugate of any one of claims 2-14, wherein the antibody, or an antigen-binding fragment thereof, binds an infectious disease-related target.

22. A pharmaceutical composition comprising the antibody-drug conjugate of any one of claims 2-14 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

23. A pharmaceutical dosage form comprising the antibody-drug conjugate of any one of claims 2-14 or a pharmaceutically acceptable salt thereof.

24. Use of the antibody-drug conjugate of any one of claims 2-14, or the pharmaceutical

composition of claim 22, or the pharmaceutical dosage form of claim 23 in the manufacture of a medicament for inhibiting growth of a bacterium.

25. Use of the antibody-drug conjugate of any one of claims 2-14, or the pharmaceutical composition of claim 22, or the pharmaceutical dosage form of claim 23 in the manufacture of a medicament for treating a bacterial infection in a subject.

26. Use of the antibody-drug conjugate of any one of claims 2-14, or the pharmaceutical composition of claim 22, or the pharmaceutical dosage form of claim 23 in the manufacture of a medicament for preventing or treating cellulitis, bacteremia, dermonecrosis, eyelid infection, eye infection, neonatal conjunctivitis, osteomyelitis, impetigo, boils, scalded skin syndrome, food poisoning, pneumonia, surgical infection, urinary tract infection, burn infection, meningitis, endocarditis, septicemia, toxic shock syndrome, septic arthritis, mastitis, infection associated with a prosthetic joint, infection associated with a catheter, or infection associated with an implant.