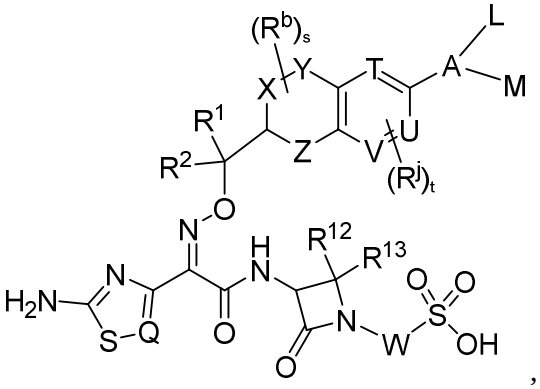
strains. Because monobactams are inherently resistant to hydrolysis by MBLs, several companies have begun developing novel monobactam compounds for the treatment of infections caused by Gram-negative bacteria. Monobactam compounds comprising a siderophore moiety are disclosed in WO 2007/065288, WO2012/073138, *J. Medicinal Chemistry* 56: 5541-5552 (2013), and *Bioorganic and Medicinal Chemstry Letters* 22:5989 (2012).

WO2017/106064 discloses biaryl monobactam compounds and their use to treat bacterial infections. U.S. Patent Application Publication No US 2015/0045340 and No. US 2014/0275007 disclose oxamazin monobactams and their use as antibacterial agents. U.S. Patent Application Publication No. US 2015/0266867 discloses novel monobactam compounds for the use as antibacterial agents. WO 2013/110643 discloses novel amidine substituted monobactam derivatives and their use as antimicrobial reagents. WO 2015/103583 discloses monobactam derivatives useful for treating infectious disease which is bacterial infection.

The need for new antibiotics to overcome multidrug resistance continues. Compounds disclosed in this invention are designed to fill this medical need, through administration either on their own or in combination with a suitable β-lactamase inhibitor.

SUMMARY

The disclosure relates to the design and synthesis of monobactam analogs, a novel class of highly potent antibiotics effective against a broad range of Gram-negative bacteria. These compounds and their pharmaceutically acceptable salts may be useful as therapeutic agents for clinical treatment of various infections caused by Gram-negative bacteria, including strains that are multidrug resistant. The compounds can be used alone or in combination with a suitable β-lactamase inhibitor. The present disclosure~~, in one aspect,~~ includes compounds of Formula I:



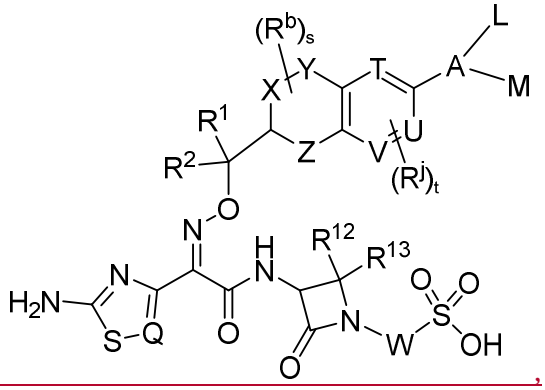
(I)

or a pharmaceutically acceptable salt thereof, wherein:

wherein C1-C3 alkyl unsubstituted or substituted with one to three Rb;

each n is independently 0, 1, 2, 3, 4, 5 or 6;
each m is independently 0, 1 or 2;
each p is independently 1 or 2;
each q is independently 0, 1, 2, 3, 4, 5 or 6;
each s is independently 0, 1, 2 or 3;
each t is independently 0, 1, 2 or 3;
each u is independently 0, 1, 2, 3, 4, 5 or 6; and
each v is independently 0, 1, or 2.

In one aspect, the present disclosure relates to a compound of Formula I



(I)

or a pharmaceutically acceptable salt thereof, wherein:

T, U and V are each CH;

W is O;

Q is CR3;

X is CH2;

Y is O or CH2;

Z is O or CH2;

A is
–C(=NH)-NH,

AryC, or
HetC,
wherein A is unsubstituted or substituted with one to four Ri;

AryC is a 5- to 6-membered monocyclic aromatic ring with 0, 1, 2, or 3 ring atoms independently selected from N, N as a quaternary salt, O and S, unsubstituted or substituted with one to four Ri, wherein AryC is optionally fused to a 4- to 7- membered heterocycloalkyl ring containing one to two heteroatoms selected from O, S and –NRg;

HetC is a 4- to 7-membered saturated or monounsaturated monocyclic ring with 1, 2, or 3 heteroatom ring atoms independently selected from N, N as a quaternary salt, O and S, unsubstituted or substituted with one to four Ri;

L is
absent,
R4,
-NHR4,
-N(R4)2,
-OR4,
-(CH2)nR4,
-C(O)R4 ,
-C(NH)R4, or
-S(O)mR4,
wherein L is unsubstituted or substituted with 1-4 substituents selected from Re ;

M is
R5,
-NHR5,
-N(R5)2,
-OR5,
-(CH2)uR5,
-C(O)R5,
-C(NH)R5, or
-S(O)vR5,
wherein M is unsubstituted or substituted with 1 - 4 substituents selected from R6;

R1 and R2 are independently selected from:
hydrogen,

-C1-C8 alkyl, and
-C(O)ORe,
wherein -C1-C8 alkyl is unsubstituted or substituted with one to three Ra,

provided that if R1 is -C(O)ORe, then R2 is not -C(O)ORe;

R3 is hydrogen;

each occurrence of R4 is independently:
hydrogen,
-C1-C10 alkyl,
-C2-C8 alkenyl,
-(CH2)nORe,
-S(O)mRe,
-S(O)mNRcRd,
-(CH2)nNRcRd,
-OC(O)Re,
-C(O)ORe,
-CN,
-C(O)NRcRd,
-NRcC(O)Re,
-NRcC(O)ORe,
-NRcC(O)NRcRd,
-NRcS(O)mRe,
=NR11,
-C3-C7 cycloalkyl,
-O-C3-C6cycloalkyl,
-C1-C10alkylene-C3-C6cycloalkyl,
-O-C1-C10alkylene-C3-C6cycloalkyl,
HetB,
-O-HetB,
-C1-C10alkylene-HetB,
-O-C1-C10alkylene-HetB,
AryB,
-O-AryB,
-C1-C10alkylene-AryB, or
-O-C1-C10alkylene-AryB,
wherein R4 is unsubstituted or substituted with one to four R6;

AryB is a 5- to 6-membered monocyclic aromatic ring with 0, 1, 2, or 3 ring atoms independently selected from N, O and S, unsubstituted or substituted with one to four Rc;

HetB is a 4- to 7-membered saturated or monounsaturated monocyclic ring with 1, 2, or 3 heteroatom ring atoms independently selected from N, N as a quaternary salt, O and S, unsubstituted or substituted with one to three Ra;

R5 is
hydrogen,
C1-C10 alkyl,
-C2-C8 alkenyl,
-(CH2)uORe,
-S(O)vRe,
-S(O)vNRcRd,
-(CH2)uNRcRd,
-OC(O)Re,
-C(O)ORe,
-CN,
-C(O)NRcRd,
-NRcC(O)Re,
-NRcC(O)ORe,
-NRcC(O)NRcRd,
-NRcS(O)vRe,
=NR11,
-C3-C7 cycloalkyl,
-O-C3-C6cycloalkyl,
-C1-C10alkylene-C3-C6cycloalkyl,
-O-C1-C10 alkylene-C3-C6cycloalkyl,
HetB,
-O-HetB,
-C1-C10alkylene-HetB,
-O-C1-C10 alkylene-HetB,
AryB,
-O-AryB,
-C1-C10alkylene-AryB, or
-O-C1-C10alkylene-AryB,
wherein R5 is unsubstituted or substituted with one to four R6;

each occurrence of R6 is independently:
halogen,
-C1-C6alkyl,
-ORe,
-S(O)vRe,
-S(O)vNRcRd,
-C(O)Re,
-OC(O)Re,
-C(O)ORe,
-CN,
-C(O)NRcRd,
-C(NH)NRcRd,
-(CH2)uNRcRd,
-(CH2)uNRcRd,
-N(Rc)(C(O)Re),
-N(Rc)(C(O)ORe),
-N(Rc)(C(O)NRcRd),
-N(Rc)(S(O)vRe), or
HetB;

R9 is
hydrogen,
C1-C4 alkyl, or
C3-C7 cycloalkyl;

R10 is
hydrogen,
C1-C4 alkyl, or
C3-C7 cycloalkyl;

R11 is
hydrogen,
C1-C4 alkyl, or
C3-C7 cycloalkyl;

R12 and R13 are independently C1-C3 alkyl, wherein C1-C3 alkyl is unsubstituted or substituted with one to seven fluorines,

or alternatively R12 and R13 together with the carbon to which they are attached form a monocyclic C4-C6 cycloalkyl unsubstituted or substituted with one to three substituents independently selected from -F, -OH and -OC1-C3alkyl;

each occurrence of Ra is independently:
hydrogen,
halogen,
C1-C3alkyl,
-NRcRd, or
-ORe;

each occurrence of Rb is independently:
hydrogen,
-C1-C6 alkyl,
-OC1-C6 alkyl,
OH,
N(R9)2, or
halogen,
wherein -C1-C3 alkyl is unsubstituted or substituted with one to three Ra;

Rc and Rd are independently selected from:
hydrogen,
-C1-C10 alkyl, and
-C2-C10 alkenyl,
wherein each Rc and Rd is unsubstituted or substituted with one to three Rf;

each occurrence of Re is independently hydrogen, or -C1-C10alkyl, wherein each Re is unsubstituted or substituted with one to three Rh;

each occurrence of Rf is independently:
halogen,
-C1-C10 alkyl,
-OH,
-OC1-C4 alkyl,
-S(O)mC1-C4 alkyl,
-CN,
-CF3,
-OCHF2,

-OCF3, or
NH2,
wherein -C1-C10 alkyl is unsubstituted or substituted with one to three substituents independently selected from –OH, halogen, cyano, and -S(O)2CH3;

each occurrence of Rg is independently:
hydrogen,
-C(O)Re, or
-C1-C10 alkyl,
wherein -C1-C10alkyl is unsubstituted or substituted with one to five fluorines;

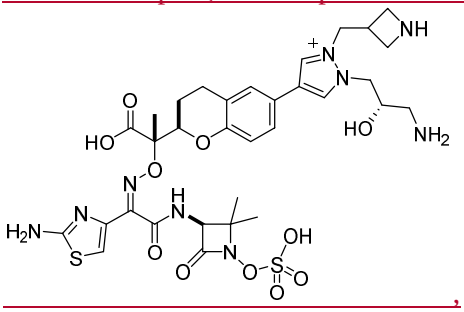
each occurrence of Rh is independently:
halogen,
-C1-C10alkyl,
-OH,
-OC1-C4 alkyl,
-S(O)mC1-C4 alkyl,
-CN,
-CF3,
-OCHF2, or
-OCF3,
wherein -C1-C10 alkyl is unsubstituted or substituted with one to three substituents independently selected from: -OH, halogen, cyano, or–S(O)2CH3;

each occurrence of Ri is independently:
-C1-C8 alkyl,
-C2-C8 alkenyl,
-C2-C8 alkynyl,
halogen,
-ORe ,
-S(O)mRe,
-S(O)mNRcRd,
-C(O)Re,
-OC(O)Re,
-C(O)ORe,
-CN,
-C(O)NRcRd,
-NRcRd,

-(CH2)nNRcRd,
-NRcC(O)Re,
-NRcC(O)ORe,
-NRcC(O)NRcRd,
-NRcS(O)mRe,
=NH,
-CF3,
-OCF3, or
-OCHF2;

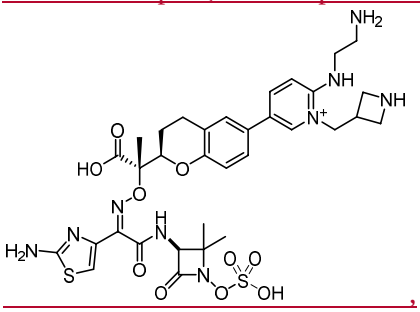
each occurrence of Rj is independently:
hydrogen,
C1-C3 alkyl,
OR10,
=NR10,
N(R10) 2, or
halogen,
wherein C1-C3 alkyl unsubstituted or substituted with one to three Rb;

each n is independently 0, 1, 2, 3, 4, 5 or 6;
each m is independently 0, 1 or 2;
each s is independently 0, 1, 2 or 3;
each t is independently 0, 1, 2 or 3;
each u is independently 0, 1, 2, 3, 4, 5 or 6; and
each v is independently 0, 1, or 2.
In another aspect, there is provided a compound which is:



,
or a pharmaceutically acceptable salt thereof.

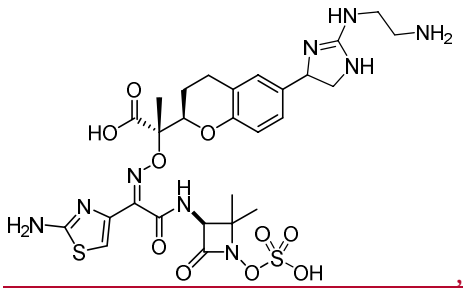
In another aspect, there is provided a compound which is:



,

or a pharmaceutically acceptable salt thereof.

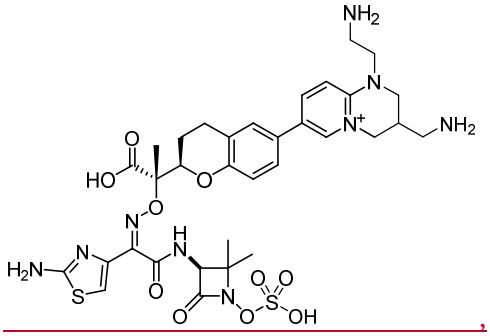
In yet another aspect, there is provided a compound which is:



,

or a pharmaceutically acceptable salt thereof.

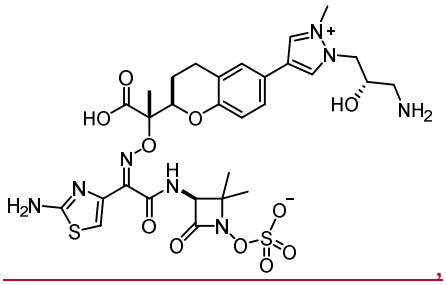
In another aspect, there is provided a compound which is:



,

or a pharmaceutically acceptable salt thereof.

In yet another aspect, there is provided a compound which is:



,

or a pharmaceutically acceptable salt thereof.

The present disclosure also relates to a pharmaceutical composition for treating a bacterial infection in a subject, including infection with multidrug resistant Gram-negative bacterial strains, comprising a monobactam compound of the disclosure and a pharmaceutically acceptable carrier, diluent or excipient.

In another aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The Compounds of Formula (I), also referred to herein as the "monobactam compounds", and pharmaceutically acceptable salts thereof can be useful, for example, for inhibiting the growth of Gram-negative bacterial strains, including but not limited to, Pseudomonas, Klebsiella and Acinetobacter strains, including Pseudomonas aeruginosa, Klebsiella pneumoniae and Acinetobacter baumannii, and/or for treating or preventing the clinical maifestations thereof in a patient.

The present disclosure is also directed to methods of treating Gram-negative bacterial infections in a subject in need of treatment thereof, comprising administering to the subject an effective amount of a monobactam compound of the disclosure. In specific examples of the disclosure, the method includes administration of a beta lactamase inhibitor compound.

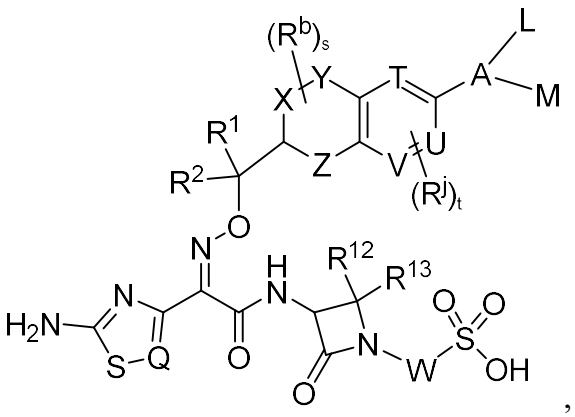
In another aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, optionally in combination with a beta-lactamase inhibitor compound or a pharmaceutical composition as defined herein for use in treating a bacterial infection.

In another aspect, there is provided use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, optionally in combination with a beta-lactamase inhibitor compound or a pharmaceutical composition as defined herein in the manufacture of a medicament for treating a bacterial infection. In another aspect, there is provided use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a bacterial infection, in combination with a beta-lactamase inhibitor compound for treating a bacterial infection, or in combination with a beta-lactamase inhibitor compound in the manufacture of a medicament for treating a bacterial infection.

Embodiments, sub-embodiments, examples and features of the present disclosure are either further described in or will be apparent from the ensuing description, examples and appended claims.

WHAT IS CLAIMED

1. A compound of Formula I



(I)

or a pharmaceutically acceptable salt thereof, wherein:

~~T is CH or N, provided that no more than two of T, U and V is N;~~
~~U is CH or N;~~
~~V is CH or N;~~

T, U and V are each CH;

W is
~~a bond, or~~
O;

Q is
~~N, or~~
CR^3;

X is
~~O, or~~
CH_2;

Y is

~~1) O ,~~
~~2) NR^8;~~
~~3) S, or~~
~~4)~~ CH_2;~~,~~
~~provided that when Y is O, NR^8 or S then X is not O;~~

Z is
~~1)~~ O~~,~~
~~2) S,~~ or
~~3)~~ CH_2;~~ or~~
~~4) NH,~~
~~provided that when Z is O, S or NH, then X is not O;~~

A is
1) –C(=NH)-NH,
~~2) $-(CH_2)_qN(R^7)$-AryC,~~
~~3) $-(CH_2)_qO$-AryC,~~
~~4)~~2) AryC, or
~~5) $-(CH_2)_qN(R^7)$-HetC,~~
~~6) $-(CH_2)_qO$-HetC,~~
~~7)~~3) HetC, ~~or~~
~~8) C_3-C_7 cycloalkyl,~~
wherein A is~~CH_2 and C_3-C_7 cycloalkyl are~~ unsubstituted or substituted with one to four R^i;

AryC is a 5- to 6-membered monocyclic aromatic ring with 0, 1, 2, or 3 ring atoms independently selected from N, N as a quaternary salt, O and S, unsubstituted or substituted with one to four R^i, wherein AryC is optionally fused to a 4- to 7- membered heterocycloalkyl ring containing one to two heteroatoms selected from O, S and –NR^g;

HetC is a 4- to 7-membered saturated or monounsaturated monocyclic ring with 1, 2, or 3 heteroatom ring atoms independently selected from N, N as a quaternary salt, O and S, unsubstituted or substituted with one to four R^i;

L is
1) absent,
2) R^4,
3) -NHR^4,

4) -$N(R^4)_2$,
5) -OR^4,
6) -$(CH_2)_nR^4$,
7) -$C(O)R^4$,
8) -$C(NH)R^4$, or
9) -$S(O)_mR^4$,

wherein L is unsubstituted or substituted with 1-4 substituents selected from R^e ;

M is

1) R^5,
2) -NHR^5,
3) -$N(R^5)_2$,
4) -OR^5,
5) -$(CH_2)_uR^5$,
6) -$C(O)R^5$,
7) -$C(NH)R^5$, or
8) -$S(O)_vR^5$,

wherein M is unsubstituted or substituted with 1 - 4 substituents selected from R^6;

R^1 and R^2 are independently selected from:~~is~~

1) hydrogen,
2) -C_1-C_8 alkyl, and
~~3) -C_3-C_7 cycloalkyl,~~
~~4)~~3) -C(O)OR^e,
~~5) -C(O)NR^eR^d,~~
~~6) tetrazolyl,~~
~~7) oxadiazolonyl,~~
~~8) HetA,~~
~~9) AryA,~~
~~10) -$S(O)_mR^e$,~~
~~11) -$S(O)_mNR^eR^d$, or~~
~~-$P(O)(R^e)_p$,~~

wherein -C_1-C_8 alkyl ~~and -C_3-C_7 cycloalkyl are~~is unsubstituted or substituted with one to three R^a~~,~~;

~~R^2 is~~
~~1) hydrogen,~~

~~2) -C_1-C_8 alkyl,~~
~~3) -C_3-C_7 cycloalkyl,~~
~~4) -C(O)OR^e,~~
~~5) -C(O)NR^eR^d,~~
~~6) tetrazolyl,~~
~~7) oxadiazolonyl,~~
~~8) HetA,~~
~~9) AryA,~~
~~10) -S(O)$_m$$R^e$,~~
~~11) -S(O)$_m$$NR^eR^d$, or~~
~~12) -P(O)$(R^e)_p$,~~
~~wherein -C_1-C_8 alkyl and -C_3-C_7 cycloalkyl are unsubstituted or substituted with one to three R^a,~~
provided that ~~when~~ if R^1 is -C(O)OR^e, ~~-C(O)NR^eR^d, -S(O)$_m$$R^e$, -S(O)$_m$$NR^eR^d$, or -P(O)$(R^e)_p$,~~ then R^2 is not -C(O)OR^e, ~~-C(O)NR^eR^d, -S(O)$_m$$R^e$, -S(O)$_m$$NR^eR^d$, or -P(O)$(R^e)_p$~~;

~~HetA is a 4- to 7- membered saturated or monounsaturated monocyclic ring with 1, 2, or 3 heteroatom ring atoms independently selected from N, N as a quaternary salt, O and S, unsubstituted or substituted with one to four R^e;~~

~~AryA is a 5- to 6-membered monocyclic aromatic ring with 0, 1, 2, or 3 ring atoms independently selected from N, N as a quaternary salt, O and S, unsubstituted or substituted with one to four R^e;~~

R^3 is
hydrogen;~~,~~

~~1) C_1-C_4 alkyl,~~
~~2) halogen, or~~
~~3) C_3-C_7cycloalkyl,~~
~~wherein C_1-C_4 alkyl and C_3-C_7cycloalkyl are unsubstituted or substituted with one to three R^a;~~

each occurrence of R^4 is independently:
1) hydrogen,
2) -C_1-C_{10} alkyl,
3) -C_2-C_8 alkenyl,

4) -$(CH_2)_nOR^e$,
5) -$S(O)_mR^e$,
6) -$S(O)_mNR^cR^d$,
7) -$(CH_2)_nNR^cR^d$,
8) -$OC(O)R^e$,
9) -$C(O)OR^e$,
10) -CN,
11) -$C(O)NR^cR^d$,
12) -$NR^cC(O)R^e$,
13) -$NR^cC(O)OR^e$,
14) -$NR^cC(O)NR^cR^d$,
15) -$NR^cS(O)_mR^e$,
16) =NR^{11},
17) -C_3-C_7 cycloalkyl,
18) -O-C_3-C_6cycloalkyl,
19) -C_1-C_{10}alkylene-C_3-C_6cycloalkyl,
20) -O-C_1-C_{10}alkylene-C_3-C_6cycloalkyl,
21) HetB,
22) -O-HetB,
23) -C_1-C_{10}alkylene-HetB,
24) -O-C_1-C_{10}alkylene-HetB,
25) AryB,
26) -O-AryB,
27) -C_1-C_{10}alkylene-AryB, or
28) -O-C_1-C_{10}alkylene-AryB,

wherein R^4 is unsubstituted or substituted with one to four R^6;

AryB is a 5- to 6-membered monocyclic aromatic ring with 0, 1, 2, or 3 ring atoms independently selected from N, O and S, unsubstituted or substituted with one to four R^c;

HetB is a 4- to 7-membered saturated or monounsaturated monocyclic ring with 1, 2, or 3 heteroatom ring atoms independently selected from N, N as a quaternary salt, O and S, unsubstituted or substituted with one to three R^a;

R^5 is

1) hydrogen,
2) C_1-C_{10} alkyl,

3) -C_2-C_8 alkenyl,
4) -$(CH_2)_u OR^e$,
5) -$S(O)_v R^e$,
6) -$S(O)_v NR^c R^d$,
7) -$(CH_2)_u NR^c R^d$,
8) -$OC(O)R^e$,
9) -$C(O)OR^e$,
10) -CN,
11) -$C(O)NR^c R^d$,
12) -$NR^c C(O)R^e$,
13) -$NR^c C(O)OR^e$,
14) -$NR^c C(O)NR^c R^d$,
15) -$NR^c S(O)_v R^e$,
16) $=NR^{11}$,
17) -C_3-C_7 cycloalkyl,
18) -O-C_3-C_6cycloalkyl,
19) -C_1-C_{10}alkylene-C_3-C_6cycloalkyl,
20) -O-C_1-C_{10} alkylene-C_3-C_6cycloalkyl,
21) HetB,
22) -O-HetB,
23) -C_1-C_{10}alkylene-HetB,
24) -O-C_1-C_{10} alkylene-HetB,
25) AryB,
26) -O-AryB,
27) -C_1-C_{10}alkylene-AryB, or
28) -O-C_1-C_{10}alkylene-AryB,

wherein R^5 is unsubstituted or substituted with one to four R^6;

each occurrence of R^6 is independently:

1) halogen,
2) -C_1-C_6alkyl,
3) -OR^e,
4) -$S(O)_v R^e$,
5) -$S(O)_v NR^c R^d$,
6) -$C(O)R^e$,
7) -$OC(O)R^e$,
8) -$C(O)OR^e$,

9) -CN,
10) -C(O)NR^{c}R^d,
11) -C(NH)NR^{c}R^d,
12) -$(CH_2)_u$NR^{c}R^d,
13) -$(CH_2)_u$NR^{c}R^d,
14) -N(R^c)(C(O)R^e),
15) -N(R^c)(C(O)OR^e),
16) -N(R^c)(C(O)NR^{c}R^d),
17) -N(R^c)$(S(O)_vR^e)$, or
18) HetB;

~~R^7 is~~
~~1) hydrogen,~~
~~2) C_1-C_3 alkyl, or~~
~~3) C_3-C_7 cycloalkyl,~~
~~wherein C_1-C_3 alkyl and C_3-C_7 cycloalkyl are unsubstituted or substituted with one to three R^a;~~

~~R^8 is~~
~~1) hydrogen,~~
~~2) C_1-C_4 alkyl, or~~
~~3) C_3-C_7 cycloalkyl;~~

R^9 is
1) hydrogen,
2) C_1-C_4 alkyl, or
3) C_3-C_7 cycloalkyl;

R^{10} is
1) hydrogen,
2) C_1-C_4 alkyl, or
3) C_3-C_7 cycloalkyl;

R^{11} is
1) hydrogen,
2) C_1-C_4 alkyl, or
3) C_3-C_7 cycloalkyl;

R^{12} and R^{13} are independently~~:~~

~~1) hydrogen,~~

~~2) -SC_1-C_3alkyl,~~

~~3)~~ C_1-C_3 alkyl,

~~4) -(C_1-C_3alkylene)$_n$$OC_1$-$C_3$alkyl, or~~

~~5) -(C_1-C_3alkylene)$_n$$NC_1$-$C_3$alkyl,~~

wherein ~~-SC_1-C_3alkyl,~~ C_1-C_3 alkyl~~, -(C_1-C_3alkylene)$_n$$OC_1$-$C_3$alkyl and -($C_1$-$C_3$alkylene)$_n$$NC_1$-$C_3$alkyl are~~is unsubstituted or substituted with one to seven fluorines, or~~, alternatively~~,~~ R^{12} and R^{13} together with the carbon to which they are attached~~,~~ form a monocyclic C_4-C_{6}~~7~~ cycloalkyl ~~or a monocyclic C_4-C_7 heterocycloalkyl with 1, 2, or 3 heteroatom ring atoms independently selected from N, O and S, wherein C_4-C_7 cycloalkyl and C_4-C_7 heterocycloalkyl are~~ unsubstituted or substituted with one to three substituents independently selected from -F, -OH and -OC_1-C_3alkyl;

~~R^{14} is~~

~~1) hydrogen,~~

~~2) C_1-C_4 alkyl, or~~

~~3) C_3-C_7 cycloalkyl;~~

each occurrence of R^a is independently:

1) hydrogen,
2) halogen,
3) C_1-C_3alkyl,
4) -NR^cR^d, or
5) -OR^e;

each occurrence of R^b is independently:

1) hydrogen,
2) -C_1-C_6 alkyl,
3) -OC_1-C_6 alkyl,
4) OH,
5) $N(R^9)_2$, or
6) halogen,

wherein -C_1-C_3 alkyl is unsubstituted or substituted with one to three R^a;

~~each occurrence of~~ R^c and R^d are~~is~~ independently selected from:

1) hydrogen,
2) -C_1-C_{10} alkyl, and
3) -C_2-C_{10} alkenyl,
~~4) -C_3-C_6 cycloalkyl,~~
~~5) -C_1-C_{10} alkylene-C_3-C_6 cycloalkyl,~~
~~6) HetA,~~
~~7) -C_1-C_{10}alkylene-HetB,~~
~~8) AryB,~~
~~9) -C_1-C_{10} alkylene-AryB, or~~
~~10) -C_1-C_{10} alkylene-HetB,~~

~~or, alternatively, R^e and R^d together with the nitrogen atom to which they are attached, form a 4- to 7-membered heterocycloalkyl optionally containing one to two additional heteroatoms independently selected from O, S and -NR^g, and~~ wherein each R^c and R^d is unsubstituted or substituted with one to three R^f;

each occurrence of R^e is independently~~:~~

~~1)~~ hydrogen, or
~~2)~~ -C_1-C_{10}alkyl,
~~3) -C_2-C_{10} alkenyl,~~
~~4) -OH,~~
~~5) -OC_1-C_4 alkyl,~~
~~6) -C_3-C_6 cycloalkyl,~~
~~7) -C_1-C_{10} alkylene-C_3-C_6 cycloalkyl,~~
~~8) HetB,~~
~~9) -C_1-C_{10} alkylene-HetB,~~
~~10) AryB,~~
~~11) -C_1-C_{10} alkylene-AryB,~~
~~12) -C_1-C_{10} alkylene- HetB, or~~
~~13) halogen,~~

wherein each R^e is unsubstituted or substituted with one to three R^h;

each occurrence of R^f is independently:
1) halogen,
2) -C_1-C_{10} alkyl,
3) -OH,
4) -OC_1-C_4 alkyl,
5) -$S(O)_m$$C_1$-$C_4$ alkyl,

6) -CN,
7) $-CF_3$,
8) $-OCHF_2$,
9) $-OCF_3$, or
10) NH_2,

wherein $-C_1$-C_{10} alkyl is unsubstituted or substituted with one to three substituents independently selected from –OH, halogen, cyano, and $-S(O)_2CH_3$;

each occurrence of R^g is independently:

1) hydrogen,
2) $-C(O)R^e$, or
3) $-C_1$-C_{10} alkyl,

wherein $-C_1$-C_{10}alkyl is unsubstituted or substituted with one to five fluorines;

each occurrence of R^h is independently:

1) halogen,
2) $-C_1$-C_{10}alkyl,
3) -OH,
4) $-OC_1$-C_4 alkyl,
5) $-S(O)_mC_1$-C_4 alkyl,
6) -CN,
7) $-CF_3$,
8) $-OCHF_2$, or
9) $-OCF_3$,

wherein $-C_1$-C_{10} alkyl is unsubstituted or substituted with one to three substituents independently selected from: -OH, halogen, cyano, or–$S(O)_2CH_3$;

each occurrence of R^i is independently:

1) $-C_1$-C_8 alkyl,
2) $-C_2$-C_8 alkenyl,
3) $-C_2$-C_8 alkynyl,
4) halogen,
5) $-OR^e$,
6) $-S(O)_mR^e$,
7) $-S(O)_mNR^cR^d$,
8) $-C(O)R^e$,
9) $-OC(O)R^e$,

10) -C(O)OR^e,
11) -CN,
12) -C(O)NR^{c}R^d,
13) -NR^{c}R^d,
14) -$(CH_2)_n$NR^{c}R^d,
15) -NR^{c}C(O)R^e,
16) -NR^{c}C(O)OR^e,
17) -NR^{c}C(O)NR^{c}R^d,
18) -NR^{c}S(O)$_m$R^e,
19) =NH,
20) -CF_3,
21) -OCF_3, or
22) -$OCHF_2$;

each occurrence of R^j is independently:
1) hydrogen,
2) C_1-C_3 alkyl,
3) OR^{10},
4) =NR^{10},
5) N(R^{10})$_2$, or
6) halogen,
wherein C_1-C_3 alkyl unsubstituted or substituted with one to three R^b;

each n is independently 0, 1, 2, 3, 4, 5 or 6;
each m is independently 0, 1 or 2;
~~each p is independently 1 or 2;~~
~~each q is independently 0, 1, 2, 3, 4, 5 or 6;~~
each s is independently 0, 1, 2 or 3;
each t is independently 0, 1, 2 or 3;
each u is independently 0, 1, 2, 3, 4, 5 or 6; and
each v is independently 0, 1, or 2.

~~2. A compound of Claim 1 wherein~~
~~T, U and V are each CH;~~
~~or a pharmaceutically acceptable salt thereof.~~

~~3. The compound of Claim 1 wherein~~

~~W is O;~~

~~or a pharmaceutically acceptable salt thereof.~~

~~4. The compound of Claim 1 wherein~~

~~Q is CR^3; and~~

~~R^3 is hydrogen;~~

~~or a pharmaceutically acceptable salt thereof.~~

~~5. The compound of Claim 1 wherein~~

~~X is CH_2;~~

~~or a pharmaceutically acceptable salt thereof.~~

~~6. The compound of Claim 5 wherein~~

~~Y is O or CH_2; and~~

~~Z is O or CH_2;~~

~~or a pharmaceutically acceptable salt thereof.~~

~~7.~~2. The compound of Claim 1 wherein

Y is CH_2; and

Z is O;

or a pharmaceutically acceptable salt thereof.

~~8. The compound of Claim 1 wherein R^1 and R^2 are independently selected from:~~

~~1) hydrogen,~~

~~2) -C_1-C_8 alkyl, and~~

~~3) -C(O)OR^e,~~

~~wherein -C_1-C_8 alkyl is unsubstituted or substituted with one to three R^a,~~

~~provided that if R^1 is -C(O)OR^e, then R^2 is not -C(O)OR^e;~~

~~or a pharmaceutically acceptable salt thereof.~~

~~9.~~3. The compound of Claim 1 wherein

R^1 and R^2 are independently selected from

1) -C_1-C_8 alkyl, and

2) -C(O)OR^{e},

provided if R^{1} is -C(O)OR^{e}, then R^{2} is -C$_{1}$-C$_{8}$ alkyl, and if R^{2} is -C(O)OR^{e}, then R^{1} is -C$_{1}$-C$_{8}$ alkyl; or a pharmaceutically acceptable salt thereof.

~~10. The compound of Claim 1 wherein~~

~~R^{12} and R^{13} are independently C$_{1}$-C$_{3}$ alkyl, wherein C$_{1}$-C$_{3}$ alkyl is unsubstituted or substituted with one to seven fluorines,~~

~~or alternatively R^{12} and R^{13} together with the carbon to which they are attached form a monocyclic C$_{4}$-C$_{6}$ cycloalkyl unsubstituted or substituted with one to three substituents independently selected from -F, -OH and -OC$_{1}$-C$_{3}$alkyl;~~

~~or a pharmaceutically acceptable salt thereof.~~

~~11. The compound of Claim 1 wherein~~

~~A is~~

~~1) C(=NH)-NH,~~

~~2) AryC, or~~

~~3) HetC,~~

~~wherein A is unsubstituted or substituted with one to four R^{i};~~

~~or a pharmaceutically acceptable salt thereof.~~

~~12.~~4. The compound of Claim 1 wherein

A is

1) AryC, or

2) HetC,

wherein A is unsubstituted or substituted with one to four R^{i};

or a pharmaceutically acceptable salt thereof.

5. The compound of Claim 1 wherein

A is –C(=NH)-NH, wherein A is unsubstituted or substituted with one to four R^{i};

or a pharmaceutically acceptable salt thereof.

6. The compound of Claim 1 wherein

A is AryC, wherein A is unsubstituted or substituted with one to four R^{i};

or a pharmaceutically acceptable salt thereof.

~~13.~~7. The compound of Claim 1 wherein

L is

1) absent, or
2) R^4,

wherein L is unsubstituted or substituted with 1-4 substituents selected from R^e; and

each occurrence of R^4 is independently:

1) hydrogen,
2) -C_1-C_{10} alkyl,
3) -$(CH_2)_nOR^e$,
4) -$(CH_2)_nNR^cR^d$, or
5) -C_1-C_{10}alkylene-HetB,

wherein R^4 is unsubstituted or substituted with one to four R^6;

or a pharmaceutically acceptable salt thereof.

~~14.~~8. The compound of Claim 7~~13~~ wherein

each occurrence of R^4 is independently:

1) -C_1-C_{10} alkyl,
2) ~~-~~-$(CH_2)_nNR^cR^d$, or
3) -C_1-C_{10}alkylene-HetB,

wherein R^4 is unsubstituted or substituted with one to four R^6;

or a pharmaceutically acceptable salt thereof.

~~15.~~9. The compound of Claim 1 wherein

M is

1) R^5, or
2) -NHR^5,

wherein M is unsubstituted or substituted with 1 – 4 substituents selected from R^6; and

R^5 is

1) hydrogen,
2) C_1-C_6 alkyl,
3) -C_1-C_4alkyl-$(NR^cR^d)_2$,
4) ~~-~~-$(CH_2)_uNR^cR^d$, or
5) -C_1-C_{10}alkylene-HetB,

wherein R^5 is unsubstituted or substituted with one to four R^6;
or a pharmaceutically acceptable salt thereof.

~~16.~~10. The compound of Claim ~~15~~ 9 wherein
R^5 is
1) $-C_1$-C_4alkyl-$(NR^cR^d)_2$, or
2) $-(CH_2)_uNR^cR^d$,
wherein R^5 is unsubstituted or substituted with one to four R^6;
or a pharmaceutically acceptable salt thereof.

~~17.~~11. The compound of Claim 1 wherein
T, U and V are CH;
W is O;
Q is CR^3;
X is CH_2;
Y is O or CH_2;
Z is O or CH_2;

R^1 and R^2 are independently selected from:
1) hydrogen,
2) $-C_1$-C_8 alkyl, and
3) $–C(O)OR^e$,
wherein $-C_1$-C_8 alkyl is unsubstituted or substituted with one to three R^a, provided that if R^1 is $–C(O)OR^e$, then R^2 is independently selected from hydrogen and $-C_1$-C_8 alkyl;

R^3 is hydrogen;

R^{12} and R^{13} are independently C_1-C_3 alkyl, wherein C_1-C_3 alkyl is unsubstituted or substituted with one to seven fluorines,
or alternatively R^{12} and R^{13} together with the carbon to which they are attached form a monocyclic C_4-C_6 cycloalkyl unsubstituted or substituted with one to three substituents independently selected from -F, -OH and $-OC_1$-C_3alkyl;

A is

1) –C(=NH)-NH,
2) AryC, or
3) HetC,

wherein A is unsubstituted or substituted with one to four R^i;

L is

1) absent, or
2) R^4,

wherein L is unsubstituted or substituted with 1-4 substituents selected from R^e;

each occurrence of R^4 is independently:

1) hydrogen,
2) -C_1-C_{10} alkyl,
3) -$(CH_2)_nOR^e$,
4) -$(CH_2)_nNR^cR^d$, or
5) –C_1-C_{10}alkylene-HetB,

wherein R^4 is unsubstituted or substituted with one to four R^6;

M is

1) R^5, or
2) -NHR^5,

wherein M is unsubstituted or substituted with 1 – 4 substituents selected from R^6; and

R^5 is

1) hydrogen,
2) -C_1-C_6 alkyl,
3) -C_1-C_4alkyl-$(NR^cR^d)_2$,
4) -$(CH_2)_uNR^cR^d$, or
5) –C_1-C_{10}alkylene-HetB,

wherein R^5 is unsubstituted or substituted with one to four R^6;

or a pharmaceutically acceptable salt thereof.

~~18.~~12. The compound of Claim 1 wherein

T, U and V are CH;

W is O;

Q is CR^3;

R^3 is hydrogen;

X is CH_2;

Y is CH_2;

Z is O;

R^1 and R^2 are independently selected from

1) -C_1-C_6 alkyl, and
2) -C(O)OR^e,

wherein -C_1-C_6 alkyl is unsubstituted or substituted with one to three R^a, provided that if R^1 is –C(O)OR^e, then R^2 is -C_1-C_6 alkyl;

R^{12} and R^{13} are independently C_1-C_3 alkyl, wherein C_1-C_3 alkyl is unsubstituted or substituted with one to seven fluorines;

A is

1) AryC, or
2) HetC,

wherein A is unsubstituted or substituted with one to four R^i;

L is

1) absent, or
2) R^4,

wherein L is unsubstituted or substituted with 1-4 substituents selected from R^e;

each occurrence of R^4 is independently:

1) -C_1-C_{10} alkyl,
2) -$(CH_2)_n NR^c R^d$, or
3) -C_1-C_{10}alkylene-HetB,

wherein R^4 is unsubstituted or substituted with one to four R^6;

M is

1) R^5, or
2) -NHR^5,

wherein M is unsubstituted or substituted with 1 – 4 substituents selected from R^6;

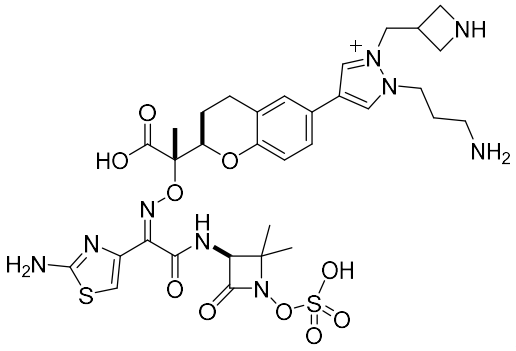
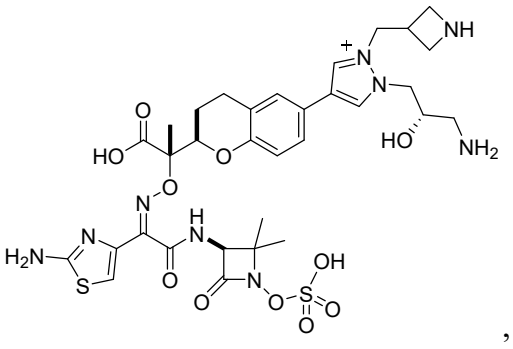
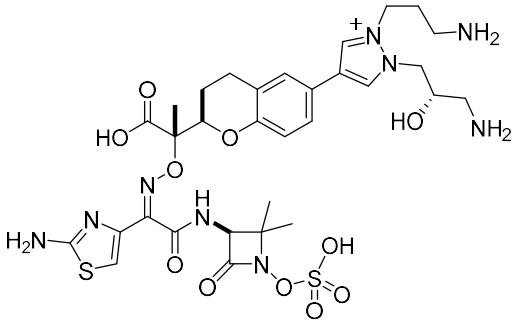
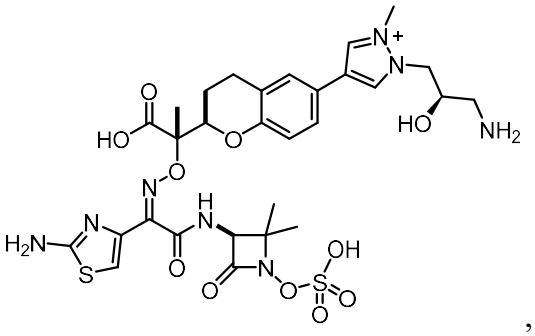
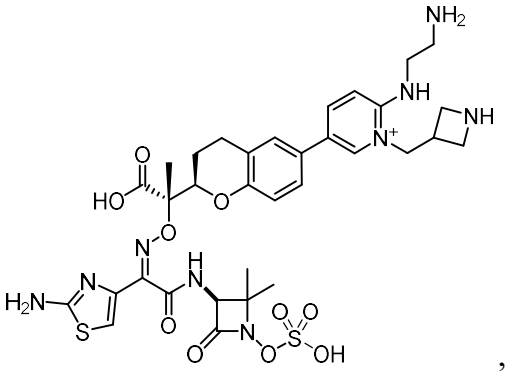
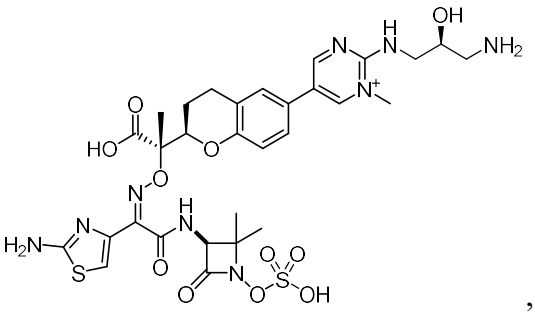
R^5 is

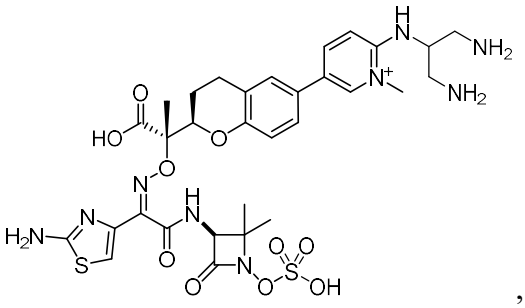
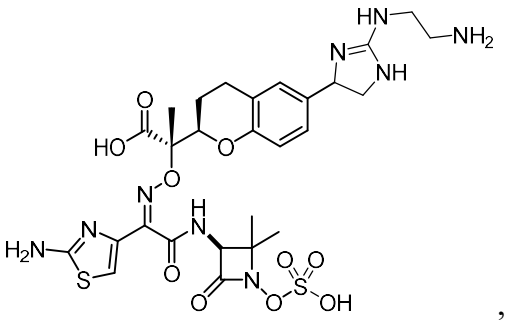
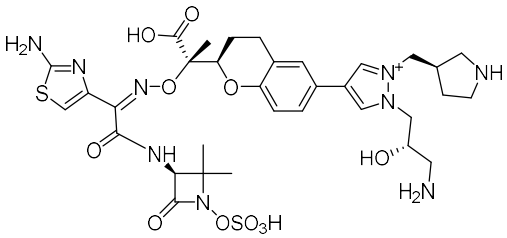
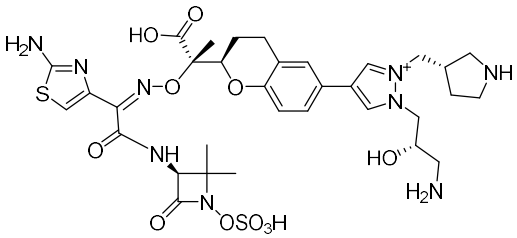
1) $-C_1$-C_4alkyl-$(NR^cR^d)_2$, or
2) $-(CH_2)_uNR^cR^d$,

wherein R^5 is unsubstituted or substituted with one to four R^6;

or a pharmaceutically acceptable salt thereof.

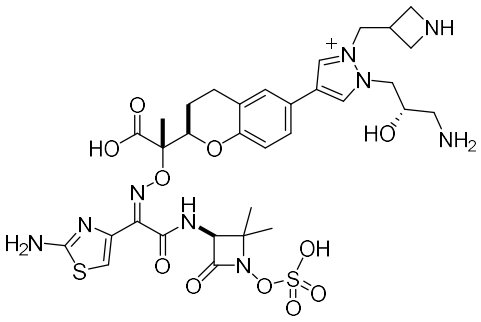
~~19~~13. The compound of Claim 1 ~~which is~~ selected from:


,

,

,

,

,

,


,

,

, and


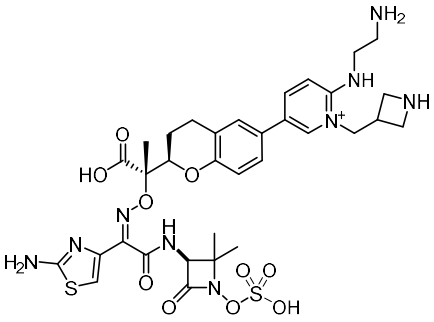
or a pharmaceutically acceptable salt thereof.

2014. ~~The~~ A compound ~~of Claim 1~~ which is:


,

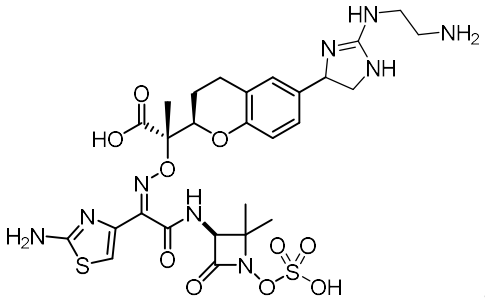
or a pharmaceutically acceptable salt thereof.

2115. ~~The~~ A compound ~~of Claim 1~~ which is:


,

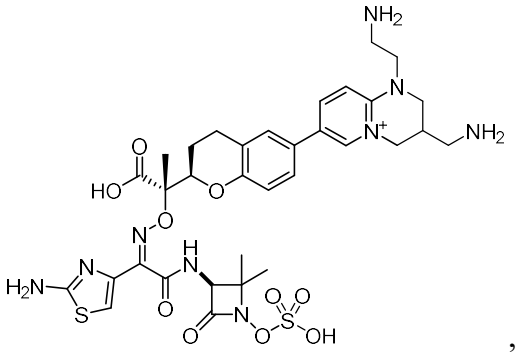
or a pharmaceutically acceptable salt thereof.

2216. ~~The~~ A compound ~~of Claim 1~~ which is:



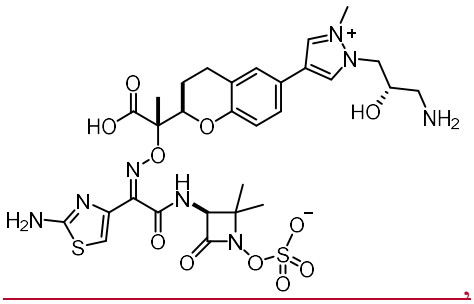
or a pharmaceutically acceptable salt thereof.

~~23~~17. ~~The~~ A compound ~~of Claim 1~~ which is:



or a pharmaceutically acceptable salt thereof.

18. A compound which is:



or a pharmaceutically acceptable salt thereof.

~~24~~19. A pharmaceutical composition comprising a therapeutically effective amount of a compound ~~accordingaccording~~ to any one of Claims 1 to ~~23~~18, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

~~25~~20. A pharmaceutical composition according to Claim ~~24~~19, which further comprises a therapeutically effective amount of a beta-lactamase inhibitor compound.

~~26.~~ 21. A pharmaceutical composition according to Claim ~~25~~20, wherein the beta-lactamase inhibitor compound is selected from the group consisting of relebactam, tazobactam, clavulanic acid, sulbactam, and avibactam.

~~27~~22. A compound according to any one of Claims 1 to ~~23~~18, or a pharmaceutically acceptable salt thereof, optionally in combination with a beta-lactamase inhibitor compound or a pharmaceutical composition according to any one of claims ~~24~~ 19 to ~~26~~ 21 for use in treating a bacterial infection.

~~28~~23. Use of a compound according to any one of Claims 1 to ~~23~~18, or a pharmaceutically acceptable salt thereof, optionally in combination with a beta-lactamase inhibitor compound or a pharmaceutical composition according to any one of claims ~~24~~ 19 to ~~26~~ 21 in the manufacture of a medicament for treating a bacterial infection.

~~29~~24. Use of a compound according to any one of Claims 1 to ~~23~~18, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a bacterial infection, in combination with a beta-lactamase inhibitor compound for treating a bacterial infection, or in combination with a beta-lactamase inhibitor compound in the manufacture of a medicament for treating a bacterial infection.

~~30~~25. The compound or the pharmaceutical composition of Claim ~~27~~ 22 or the use of claim ~~28~~ 23 or ~~29~~24, wherein the beta-lactamase inhibitor compound is selected from the group consisting of relebactam, tazobactam, clavulanic acid, sulbactam, and avibactam.

~~31~~26. The compound or the pharmaceutical composition of claim ~~27~~ 22 or ~~30~~ 25 or the use of claim ~~28~~ 23 or ~~29~~24, wherein the bacterial infection is due to Pseudomonas spp., Klebsiella spp., Enterobacter spp., Escherichia spp., Morganella spp., Citrobacter spp., Serratia spp. or Acintetobacter spp.