MACROCYCLIC BROAD SPECTRUM ANTIBIOTICS

CROSS-REFERENCE

[0001] This patent application claims the benefit of PCT Application No. PCT/CN2017/073575, filed February 15, 2017; and PCT Application No. PCT/CN2017/085075, filed May 19, 2017; each of which is incorporated herein by reference in their entirety.

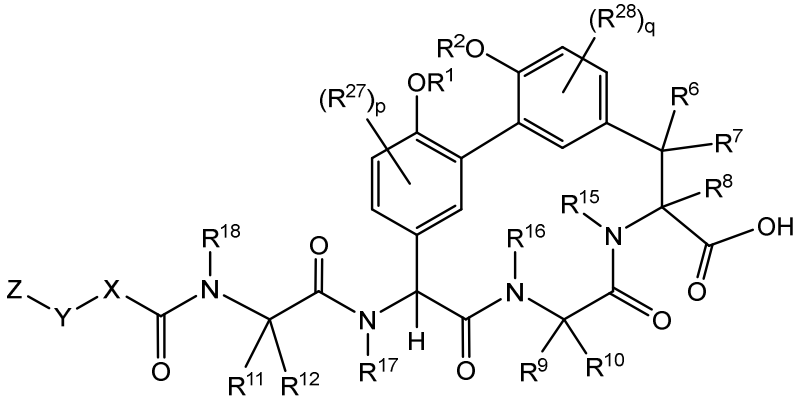
BACKGROUND OF THE INVENTION

[0001] Antibiotic resistance is a serious and growing phenomenon in contemporary medicine and has emerged as a major public health concern of the 21st century. Therefore, novel classes of broad-spectrum antibiotics, especially those that target novel mechanisms of action, are needed to treat multidrug-resistant pathogens.

SUMMARY OF THE INVENTION

[0002] Described herein are novel macrocyclic compounds for the treatment of microbial infections, such as for the treatment of bacterial infections. In various embodiments, the present disclosure provides lipopeptide macrocyclic compounds for the treatment of bacterial infections. In various embodiments, the present disclosure provides classes and subclasses of chemical compounds structurally related to arylomycin for the treatment of bacterial infections. In various embodiments, the macrocyclic compounds act by inhibition of bacterial type 1 signal peptidase (SpsB), an essential protein in bacteria. In some embodiments, the signal peptidase is a Gram-negative signal peptidase. In some embodiments, the signal peptidase is LepB.

[0002a] In one aspect, described herein is a compound of Formula (V):



Formula (V);

wherein:

R^1 and R^2 are each independently H, -(C_1-C_6)alkyl, -(C_1-C_6)alkyl-OR^{23}, -$CH_2CH(OH)CH_2NH_2$, -CH_2CH(heterocycloalkyl)CH_2NH_2, -$CH_2C(O)NH_2$, -$CH_2C(O)N(H)CH_2CN$, -(C_1-C_6)alkyl-$C(O)OR^{23}$, -(C_1-C_6)alkyl-$NR^{21}R^{22}$, -(C_1-C_6)alkyl-$C(O)NR^{25}R^{26}$, -(C_1-C_6)alkyl-$N(R^{23})C(O)$(C_1-C_6)alkyl$NR^{21}R^{22}$, -(C_1-C_6)alkyl-$N(R^{23})C(O)$(C_1-C_6)alkyl, -(C_1-C_6)alkyl-$C(O)N(R^{23})$(C_1-C_6)alkyl, -(C_1-C_6)alkyl-

$C(O)N(R^{23})(C_1\text{-}C_6)$alkyl-heterocycloalkyl, -$(C_1\text{-}C_6)$alkyl-$NR^{23}C(=NH)NR^{21}R^{22}$, -$(C_1\text{-}C_6)$alkyl-$NR^{23}C(=NH)R^{23}$, -$(C_1\text{-}C_6)$alkyl-$[(C_1\text{-}C_6)$alkyl-$NR^{21}R^{22}]_2$, -$(C_1\text{-}C_6)$heteroalkyl, or optionally substituted heterocycloalkyl;

or R^1 and R^2 and the atoms to which they are attached form an optionally substituted heterocycloalkyl ring;

R^6, R^7, and R^8 are each independently H, fluoro, hydroxyl, amino, optionally substituted alkyl, heteroalkyl, or -$(C_1\text{-}C_6)$alkyl;

R^9 is H, -$(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$haloalkyl, or -$(C_3\text{-}C_6)$cycloalkyl;

R^{10} is H, -$(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$haloalkyl, or -$(C_3\text{-}C_6)$cycloalkyl;

or R^9 and R^{10} are combined to form a heterocycloalkyl or cycloalkyl ring

R^{11} and R^{12} are each independently H, -NH_2, -$(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$alkyl-OR^{23}, -$(C_1\text{-}C_6)$alkyl-SR^{23}, -$(C_1\text{-}C_6)$alkyl-$C(O)OR^{23}$, -$(C_1\text{-}C_6)$alkyl-$NR^{21}R^{22}$, -$(C_1\text{-}C_6)$alkyl-$NR^{23}OR^{23}$, -$(C_1\text{-}C_6)$alkyl-$NHC(O)NR^{23}OR^{23}$, -$(C_1\text{-}C_6)$alkyl-O-$(C_1\text{-}C_6)$alkyl-$NR^{25}R^{26}$, -$(C_1\text{-}C_6)$alkyl-CN, -$(C_1\text{-}C_6)$alkyl-$NR^{23}C(O)R^{23}$, -$(C_1\text{-}C_6)$alkyl-$C(O)NR^{25}R^{26}$, -$(C_1\text{-}C_6)$heteroalkyl-CO_2H, -$(C_1\text{-}C_6)$alkyl-$S(O)(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$alkyl-N(H)CH=NH, -$(C_1\text{-}C_6)$alkyl-$C(NH_2)$=NH, -$(C_1\text{-}C_6)$alkyl-$N(H)C(=NH)NH_2$, -$(C_1\text{-}C_6)$alkyl-$N(H)S(O)_2NR^{25}R^{26}$, -$(C_1\text{-}C_6)$alkyl-$N(H)S(O)_2(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$alkyl-N(H)-$C(O)NR^{25}R^{26}$, -$(C_1\text{-}C_6)$alkyl$C(O)N(H)$[optionally substituted$(C_2\text{-}C_6)$alkyl]-$OR^{23}$, -$(C_1\text{-}C_6)$alkyl$N(H)C(O)(C_1\text{-}C_6)$alkyl-$OR^{23}$, -$(C_1\text{-}C_6)$alkyl$C(O)N(H)$heterocycloalkyl, -$(C_1\text{-}C_6)$alkyl$C(O)NR^{25}R^{26}$, -$(C_1\text{-}C_6)$alkyl-N(H)-C(O)-$(C_1\text{-}C_6)$alkyl-$NR^{25}R^{26}$, -$(C_1\text{-}C_6)$alkyl-N(H)-$(C_1\text{-}C_6)$alkyl$C(O)NR^{25}R^{26}$, -$(C_1\text{-}C_6)$alkyl-heterocycloalkyl, optionally substituted -$(C_1\text{-}C_6)$alkyl-N(H)heterocycloalkyl, or -$(C_1\text{-}C_6)$alkyl-heteroaryl;

or R^{11} and R^{18} are combined to form an optionally substituted heterocycloalkyl ring; and R^{12} is H;

R^{15}, R^{16}, R^{17}, and R^{18} are each independently H, -$(C_1\text{-}C_6)$alkyl, -$(C_3\text{-}C_6)$cycloalkyl, -$(C_1\text{-}C_6)$alkyl-OR^{23}, -$(C_1\text{-}C_6)$alkyl-$C(O)OR^{23}$, or -$(C_1\text{-}C_6)$alkyl-$NR^{21}R^{22}$;

X is optionally substituted heteroaryl;

Y is a bond, -O-, -S-, optionally substituted -$(C_1\text{-}C_6)$alkyl-, -$(C_2\text{-}C_6)$alkenyl-, -$(C_2\text{-}C_6)$alkynyl, -$(C_1\text{-}C_6)$alkyl-$N(R^{24})(C_1\text{-}C_6)$alkyl-, -O-$(C_1\text{-}C_6)$alkyl-, -O$(C_6\text{-}C_{10})$aryl-, -$N(R^{24})(C_1\text{-}C_6)$alkyl-, -$N(R^{24})SO_2(C_1\text{-}C_6)$alkyl-, -$N(R^{24})C(O)(C_1\text{-}C_6)$alkyl-, -$C(O)(C_1\text{-}C_6)$alkyl-, -$S(C_1\text{-}C_6)$alkyl-, -$SO_2(C_1\text{-}C_6)$alkyl-, -$C(O)NH(C_1\text{-}C_6)$alkyl-, optionally substituted -$(C_3\text{-}C_7)$cycloalkyl-, optionally substituted -$C(O)N(R^{24})$aryl-, optionally substituted -$N(R^{24})C(O)$aryl-, optionally substituted -$N(R^{24})SO_2$aryl-, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

Z is H, halogen, -NH_2, -CN, -CF_3, -CO_2H, -$(C_1\text{-}C_{12})$alkyl, -$(C_2\text{-}C_{12})$alkenyl, -CH=$((C_3\text{-}C_7)$cycloalkyl), -$(C_2\text{-}C_{12})$alkynyl, -$C(O)NR^{25}R^{26}$, -O-$(C_1\text{-}C_{12})$alkyl, -S-$(C_1\text{-}C_{12})$alkyl, -O-[optionally substituted $(C_3\text{-}C_7)$cycloalkyl], -O-$(C_1\text{-}C_6)$alkyl-OR^{23}, -$(C_1\text{-}C_{12})$alkyl-OR^{23}, -$(C_1\text{-}C_{12})$alkyl-CN, -S-$(C_1\text{-}C_{12})$alkyl, -$N(R^{24})(C_1\text{-}C_{12})$alkyl, -$N(R^{24})C(O)(C_1\text{-}C_{12})$alkyl, optionally substituted -$(C_3\text{-}C_7)$cycloalkyl, -$(C_1\text{-}C_6)$alkyl-$(C_3\text{-}C_7)$cycloalkyl, -$(C_1\text{-}C_6)$alkyl-heterocycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R^{21} and R^{22} is independently H, -(C_1-C_6)alkyl, -(C_1-C_6)heteroalkyl, -(C_1-C_6)alkyl-CO_2H, -C(O)(C_1-C_6)alkyl, -C(O)O(C_1-C_6)alkyl, -C(O)O(C_1-C_6)haloalkyl, -C(=NH)(C_1-C_6)alkyl, -C(=NH)N(R^{31})$_2$, -C(O)N(R^{31})$_2$, or -SO_2N(R^{31})$_2$; or R^{21} and R^{22} and the nitrogen atom to which they are attached form a heterocycloalkyl ring;

each R^{31} is independently H or -(C_1-C_6)alkyl; or two R^{31} and the nitrogen atom to which they are attached form a heterocycloalkyl ring;

each R^{23} is independently H or -(C_1-C_6)alkyl;

each R^{24} is independently H or -(C_1-C_6)alkyl;

each R^{25} and R^{26} is independently H or optionally substituted -(C_1-C_6)alkyl;

or R^{25} and R^{26} and the nitrogen atom to which they are attached form a heterocycloalkyl ring;

each R^{27} is independently halogen, -$NR^{23}R^{24}$, -NHC(O)R^{23}, -NHC(O)$NR^{23}R^{24}$, nitro, hydroxyl, optionally substituted -(C_1-C_6)alkyl, optionally substituted -(C_1-C_6)heteroalkyl, optionally substituted -(C_1-C_6)heteroalkyloxy, optionally substituted -(C_1-C_6)heteroalkylamino, -(C_1-C_6)alkoxy, -C(O)(C_1-C_6)alkyl, or -$S(O)_2$(C_1-C_6)alkyl;

or R^1 and R^{27} and the atoms to which they are attached form an optionally substituted 5- or 6-membered heterocycloalkyl ring;

each R^{28} is independently halogen, -$NR^{23}R^{24}$, -NHC(O)R^{23}, -NHC(O)$NR^{23}R^{24}$, nitro, hydroxyl, optionally substituted -(C_1-C_6)alkyl, optionally substituted -(C_1-C_6)heteroalkyl, optionally substituted -(C_1-C_6)heteroalkyloxy, optionally substituted -(C_1-C_6)heteroalkylamino, -(C_1-C_6)alkoxy, -C(O)(C_1-C_6)alkyl, or -$S(O)_2$(C_1-C_6)alkyl;

or R^2 and R^{28} and the atoms to which they are attached form an optionally substituted 5- or 6-membered heterocycloalkyl ring;

p is 0, 1, or 2; and

q is 0, 1, or 2;

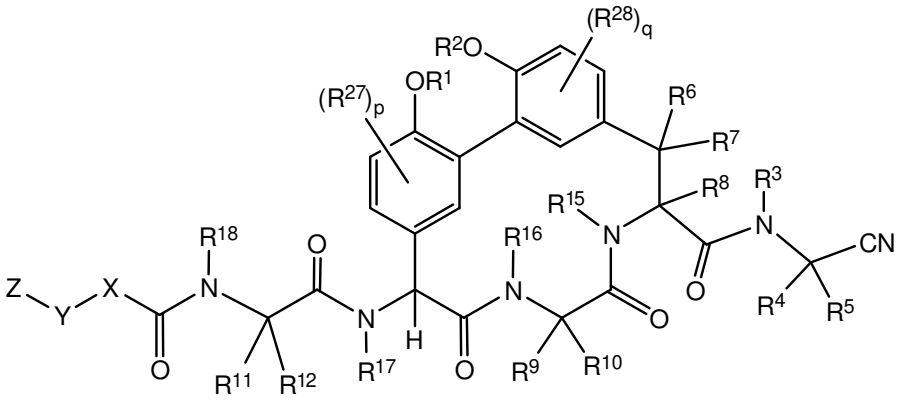
or a pharmaceutically acceptable salt or solvate thereof.

[0002b] In another aspect, described herein is a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[0002c] In another aspect, described herein is the use of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for treatment of a bacterial infection in a patient.

[0002d] In another aspect, described herein is a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

[0003] In one aspect described herein is a compound of Formula (I):



Formula (I);

wherein:

R^1 and R^2 are each independently H, -(C_1-C_6)alkyl, -(C_1-C_6)alkyl-OR^{23}, -$CH_2CH(OH)CH_2NH_2$, -CH_2CH(heterocycloalkyl)CH_2NH_2, -$CH_2C(O)NH_2$, -$CH_2C(O)N(H)CH_2CN$, -(C_1-C_6)alkyl-$C(O)OR^{23}$, -(C_1-C_6)alkyl-$NR^{21}R^{22}$, -(C_1-C_6)alkyl-$C(O)NR^{25}R^{26}$, -(C_1-C_6)alkyl-$N(R^{23})C(O)(C_1$-C_6)alkyl$NR^{21}R^{22}$, -(C_1-C_6)alkyl-$N(R^{23})C(O)(C_1$-C_6)alkyl, -(C_1-C_6)alkyl-$C(O)N(R^{23})(C_1$-C_6)alkyl, -(C_1-C_6)alkyl-