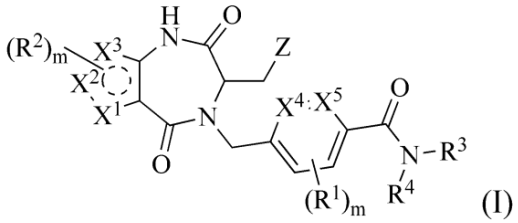
are not without significant cost and risks such as transmission of drug-resistant E coli (DeFilipp et al. 2019). Antitoxin antibody therapies are also under active investigation and development. Active vaccination strategies have demonstrated robust immune responses towards the C. difficile toxins, however, data on the ability of the vaccines to suppress the pathology of infection is limited, and no vaccine has been approved for the prevention of CDAD (Henderson et al. 2017). Monoclonal antibodies targeted to Toxin B were shown to reduce recurrence from to 8% from 32% (Wilcox et al. 2017). However, the burden of intravenous infusion combined with the high cost of monoclonal antibody therapy can limit its use while competing against other more inexpensive medications, especially for non-hospitalized patients.

Inhibitors of the toxin virulence factors that disrupt barrier function are actively being explored as another option for the treatment of CDAD (Stroke et al. 2018; Bender et al. 2015; Savidge et al. 2011). Such anti virulence strategies have the potential to suppress the pathology without further disrupting the normal flora and providing a selection pressure to promote antibiotic resistance as additional antibiotic therapy prone to do (Fleitas Martínez et al. 2019). The identification of a compound that suppresses the pathology of C. difficile infection while preserving and allowing for reconstitution of the normal flora would thus be a highly impactful therapeutic intervention.

SUMMARY

In a first aspect of the present disclosure, there is provided a compound of Formula (I):



(I)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof; wherein

X^1, X^2, and X^3 are each independently CR^2, N, NR^5, O, or S;

X^4 and X^5 are each independently C or N;

m is an integer of 0, 1, or 2;

Z is a 6- to 10-membered aryl or, 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms independently selected from N, O, and S.

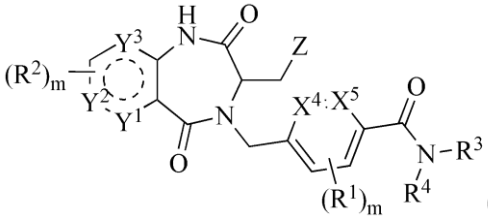
R^1 and R^2 are each independently hydrogen, halo, cyano, hydroxyl, amino, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy;

R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, alkylamino, haloalkyl, alkoxy, haloalkoxy, 6- to 10-membered aryl, 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms independently selected from N, O, and S, 3- to 10-membered carbocyclyl, or 4- to 10-membered heterocyclyl containing 1 to 3 heteroatoms independently selected from N, O, and S, wherein the aryl, heteroaryl, carbocyclyl, and heterocyclyl are independently substituted with 0 to 5 R^5;

R^5 is hydrogen, halo, cyano, hydroxyl, amino, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, hydroxycycloalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, haloalkoxy or -C(O)OR^6; and

R^6 is hydrogen or C_{1-6} alkyl.

In another aspect of the present disclosure, there is provided a compound which is represented by Formula (II):


(II), wherein

Y^1, Y^2, and X^3 are each independently CR^2, or N, provided that at least one Y^1, Y^2, and Y^3 is N;

X^4 and X^5 are each independently C or N;

m is an integer of 0, 1, or 2;

Z is a 6- to 10-membered aryl or, 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms independently selected from N, O, and S.

R^1 and R^2 are each independently hydrogen, halo, cyano, hydroxyl, amino, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy;

R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, alkylamino, haloalkyl, alkoxy, or haloalkoxy, 6- to 10-membered aryl, 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms independently selected from N, O, and S, 3- to 10-membered carbocyclyl, or 4- to 10-membered heterocyclyl containing 1 to 3 heteroatoms independently selected from N,

O, and S, wherein the aryl, heteroaryl, carbocyclyl, and heterocyclyl are independently substituted with 0 to 5 R^5; and

R^5 is hydrogen, halo, cyano, hydroxyl, amino, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, hydroxycycloalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, haloalkoxy or

-C(O)OR^6; and

R^6 is hydrogen or C_{1-6} alkyl.

In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound as disclosed herein, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof.

In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition as disclosed herein, for use in therapy.

In another aspect of the present disclosure, there is provided a compound as disclosed herein or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition as disclosed herein, for use in treating a *C. difficile* infection.

In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition as disclosed herein for the manufacture of a medicament for therapy.

In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition as disclosed herein for the manufacture of a medicament for treating a *C. difficile* infection.

In another aspect of the present disclosure, there is provided a method of making a compound as disclosed herein or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition as disclosed herein according to the synthetic routes disclosed herein.

In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for inhibiting a *C. difficile* bacterial toxin in a cell.

In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for reducing glucosylation of Rho GTPase proteins in a cell.

In one example, the present disclosure provides compounds of Formula (I), and Formula (II) as well as the subgenera as species thereof, including stereoisomers, tautomers, pharmaceutically acceptable salts, and solvates thereof. In certain examples, the compounds are useful to treat *C. difficile* bacterial infections.

In another example, the present disclosure also provides processes and intermediates for making the compounds of the present disclosure.

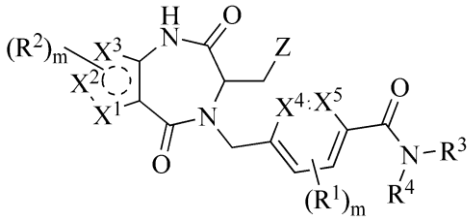
In another example, the present disclosure also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present disclosure or stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

In another example, the compounds of the disclosure may be used in therapy, either alone or in combination with one or more additional therapeutic agents.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



(I)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof; wherein

X^1, X^2, and X^3 are each independently CR^2, N, NR^5, O, or S;

X^4 and X^5 are each independently C or N;

m is an integer of 0, 1, or 2;

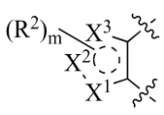
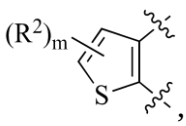
Z is a 6- to 10-membered aryl or, 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms independently selected from N, O, and S.

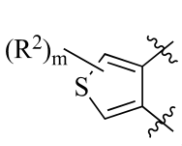
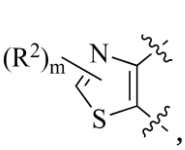
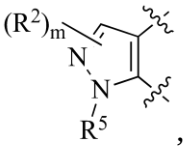
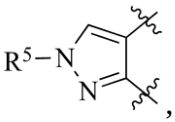
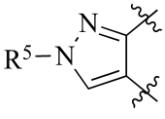
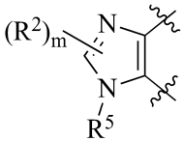
R^1 and R^2 are each independently hydrogen, halo, cyano, hydroxyl, amino, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy;

R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, alkylamino, haloalkyl, alkoxy, haloalkoxy, 6- to 10-membered aryl, 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms independently selected from N, O, and S, 3- to 10-membered carbocyclyl, or 4- to 10-membered heterocyclyl containing 1 to 3 heteroatoms independently selected from N, O, and S, wherein the aryl, heteroaryl, carbocyclyl, and heterocyclyl are independently substituted with 0 to 5 R^5;

R^5 is hydrogen, halo, cyano, hydroxyl, amino, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, hydroxycycloalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, haloalkoxy or -C(O)OR^6; and

R^6 is hydrogen or C_{1-6} alkyl.

2. The compound according to claim 1, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof; wherein the  moiety is  ,

 ,  ,  ,  ,  , and 

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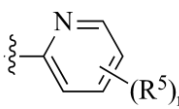
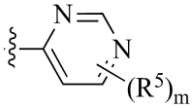
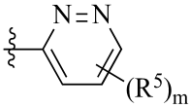
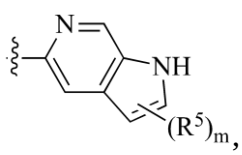
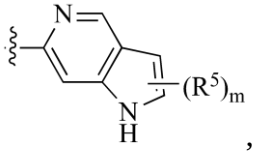
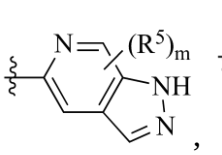
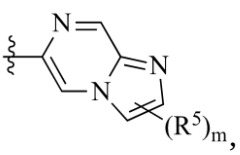
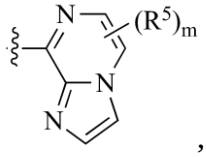
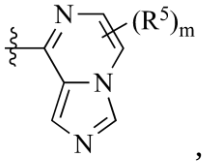
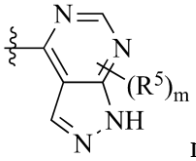
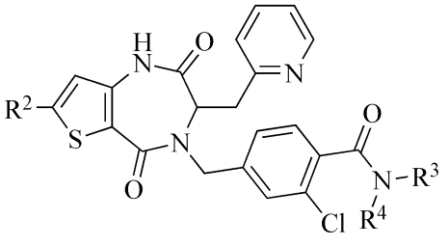
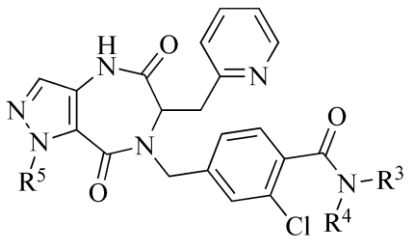
3. The compound according to claim 1 or 2, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof; wherein:

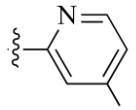
R^3 is hydrogen and R^4 is selected from  ,  ,  ,  ,  ,  ,  ,  ,  , and  m is an integer of 0, 1 or 2 and R^5 is the same as defined above.

4. The compound of claim 1, which is represented by Formula (Ia):

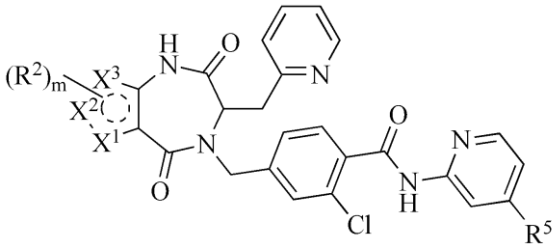
 (Ia).

5. The compound of claim 1, which is represented by Formula (Ib):

 (Ib).

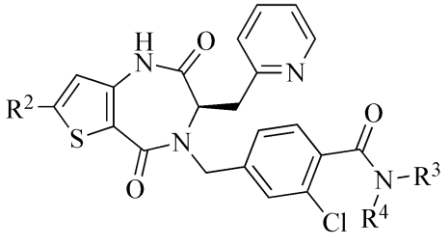
6. The compound according to claim 1, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof; wherein: R^3 is hydrogen and R^4 may be selected from  , where R^5 is as defined above.

7. The compound of claim 1, which is represented by Formula (Ic):



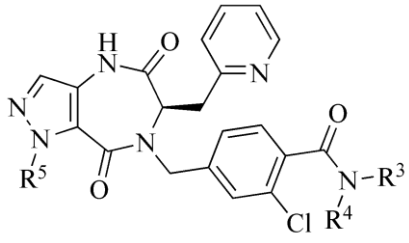
(Ic)

8. The compound of claim 1, which is represented by Formula (Id):



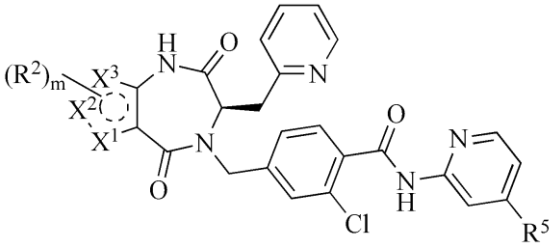
(Id)

9. The compound of claim 1, which is represented by Formula (Ie):



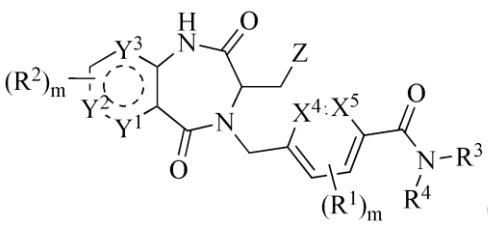
(Ie)

10. The compound of claim 1, which is represented by Formula (If):



(If)

11. A compound which is represented by Formula (II):



(II), wherein

Y^1, Y^2, and X^3 are each independently CR^2, or N, provided that at least one Y^1, Y^2, and Y^3 is N;

X^4 and X^5 are each independently C or N;

m is an integer of 0, 1, or 2;

Z is a 6- to 10-membered aryl or, 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms independently selected from N, O, and S.

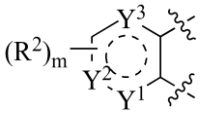
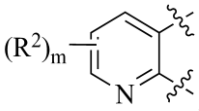
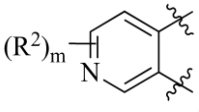
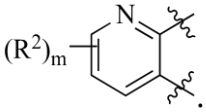
R^1 and R^2 are each independently hydrogen, halo, cyano, hydroxyl, amino, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, or haloalkoxy;

R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, alkylamino, haloalkyl, alkoxy, or haloalkoxy, 6- to 10-membered aryl, 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms independently selected from N, O, and S, 3- to 10-membered carbocyclyl, or 4- to 10-membered heterocyclyl containing 1 to 3 heteroatoms independently selected from N, O, and S, wherein the aryl, heteroaryl, carbocyclyl, and heterocyclyl are independently substituted with 0 to 5 R^5; and

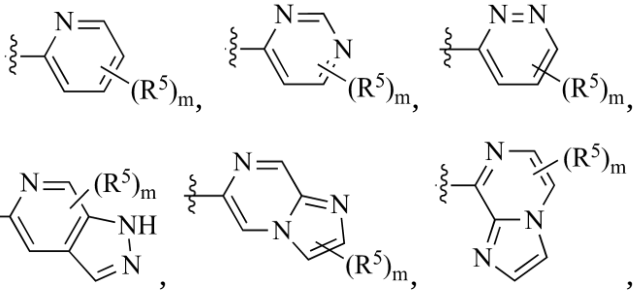
R^5 is hydrogen, halo, cyano, hydroxyl, amino, C_{1-6} alkyl, alkylamino, haloalkyl, hydroxyalkyl, hydroxycycloalkyl, aminoalkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, haloalkoxy or

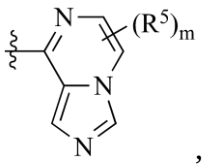
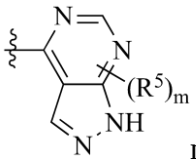
$-C(O)OR^6$; and

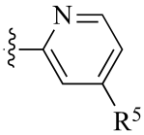
R^6 is hydrogen or C_{1-6} alkyl.

12. The compound according to claim 11, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof; wherein the  moiety is  ,  , and  .

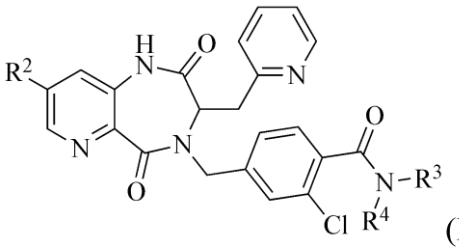
13. The compound according to claim 11 or 12, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof; wherein:

R^3 is hydrogen and R^4 is selected from  ,

 , and  m is an integer of 0, 1 or 2 and R^5 is the same as defined above.

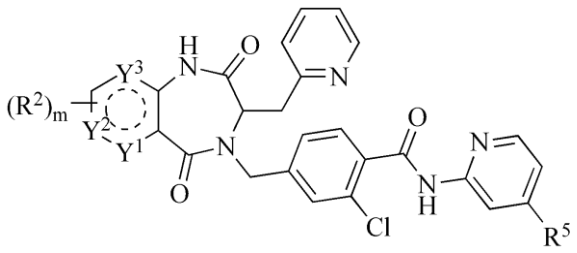
14. The compound according to claim 11, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof; wherein: R^3 is hydrogen and R^4 may be selected from  , where R^5 is as defined above.

15. The compound of claim 11, which is represented by Formula (IIa):



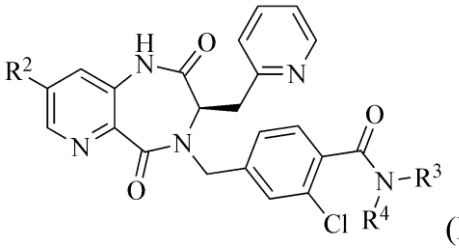
(IIa)

16. The compound of claim 11, which is represented by Formula (IIb):



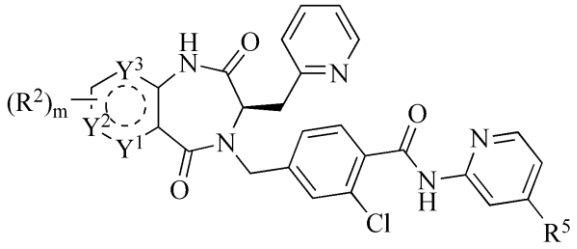
(IIb)

17. The compound of claim 11, which is represented by Formula (IIc):



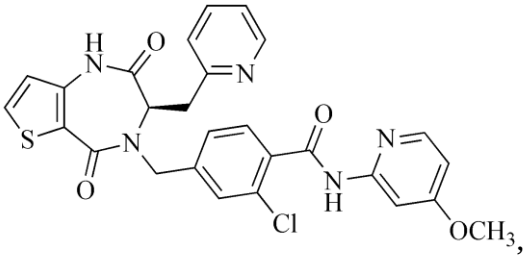
(IIc)

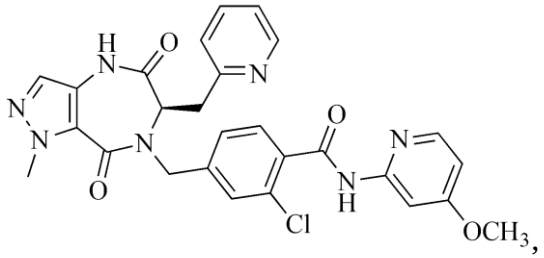
18. The compound of claim 11, which is represented by Formula (IId):

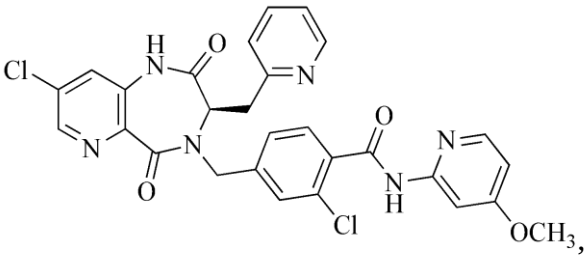


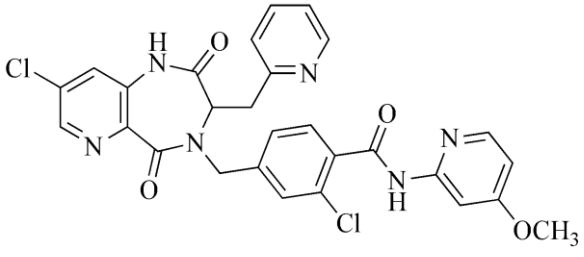
(IId)

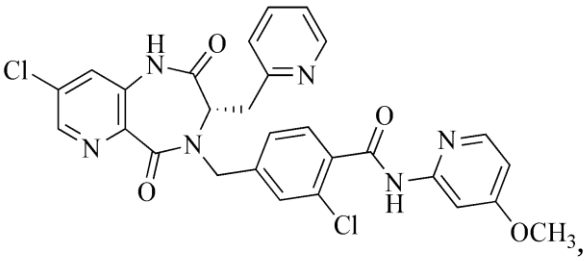
19. The compound according to claim 1 or claim 11, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof, selected from:

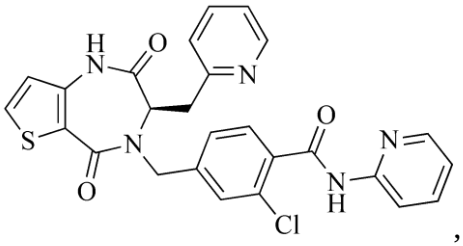


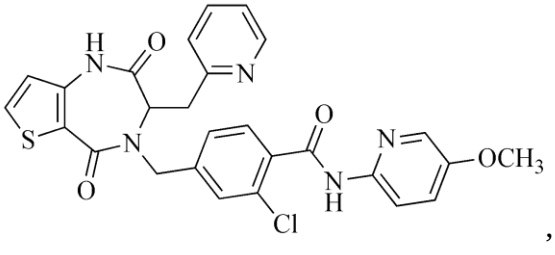


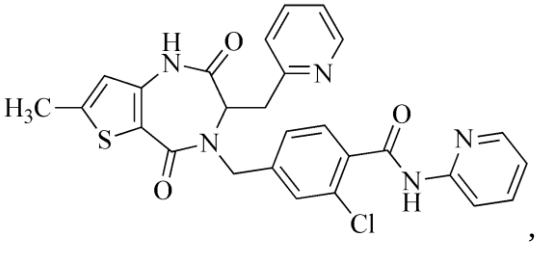


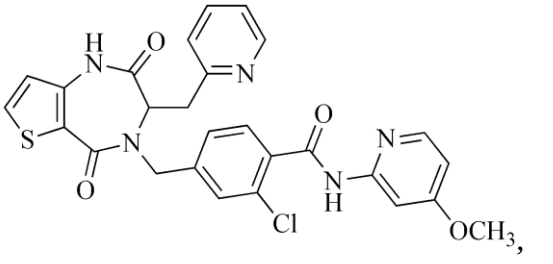


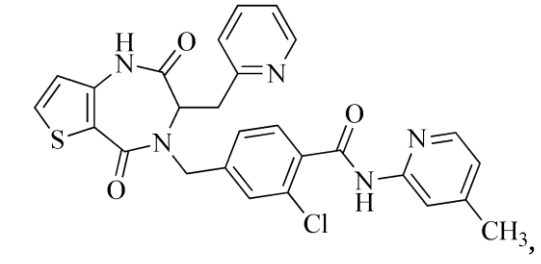


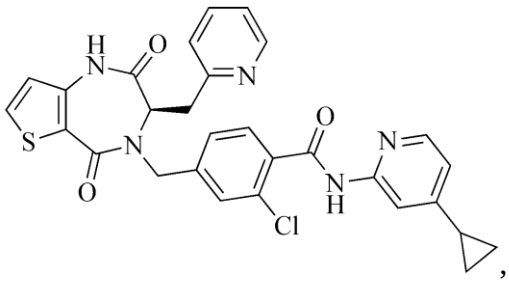
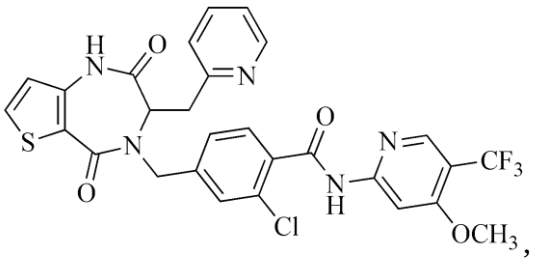
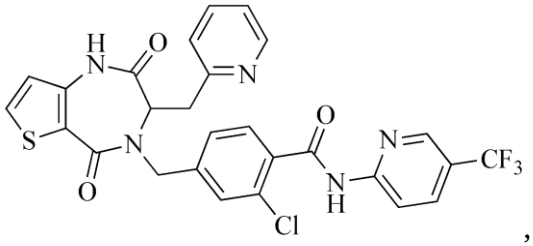
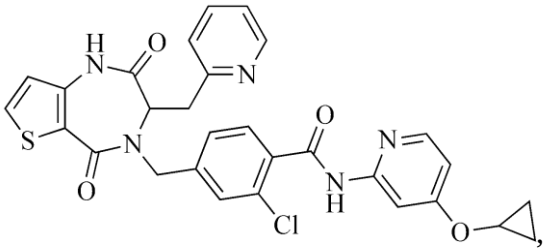
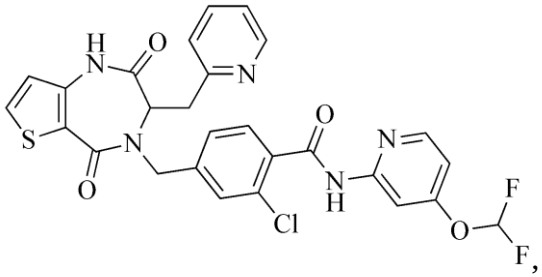
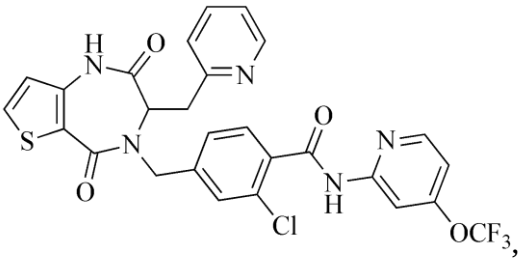
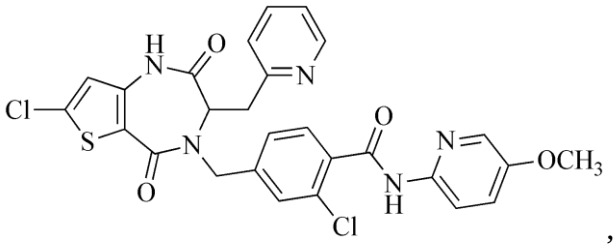
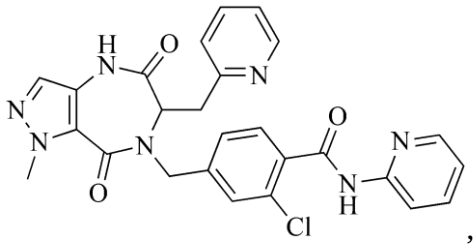
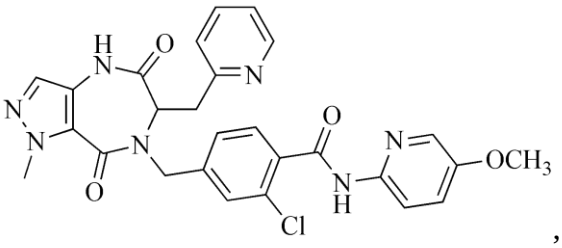
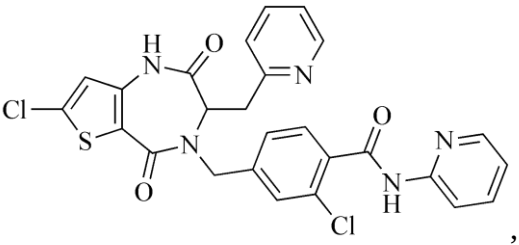
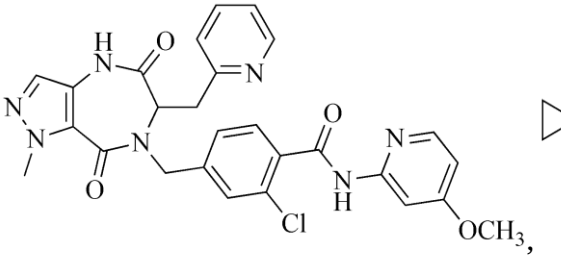
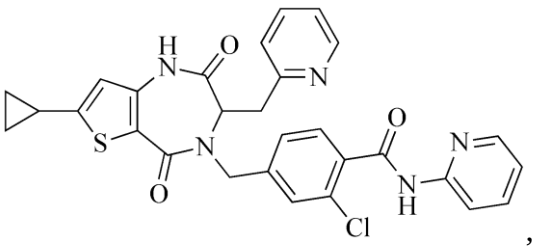


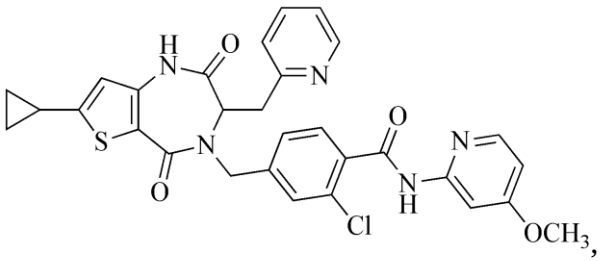


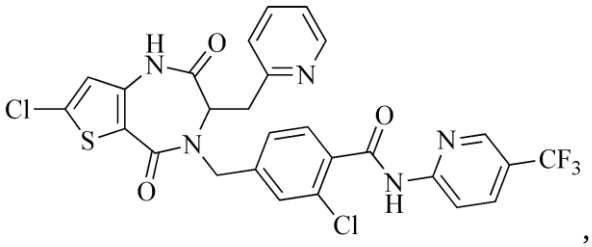


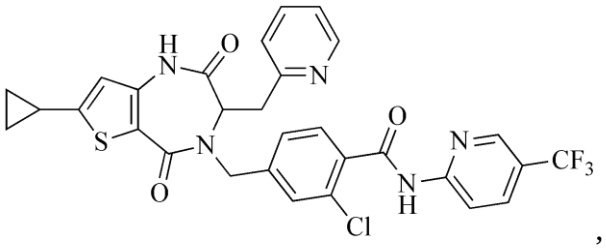


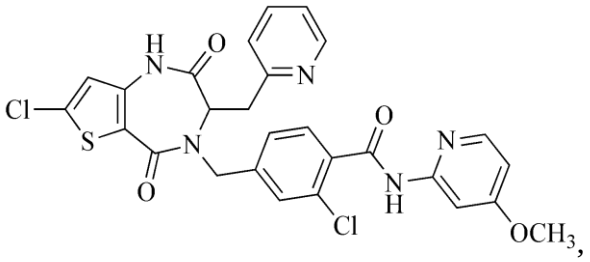


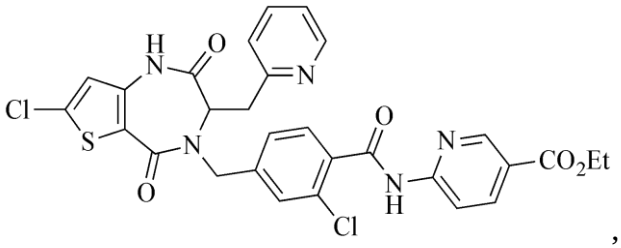
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,

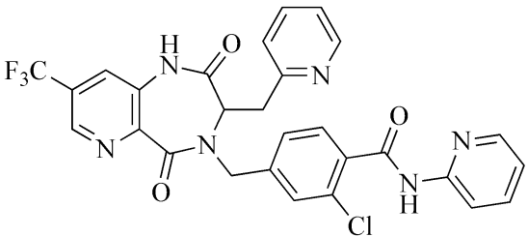
 ,

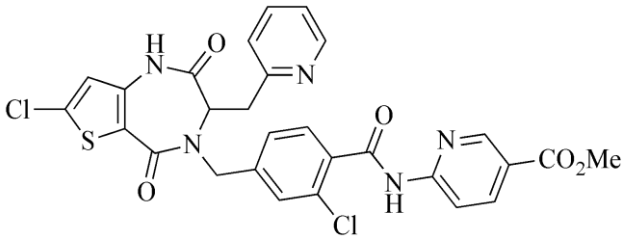
 ,

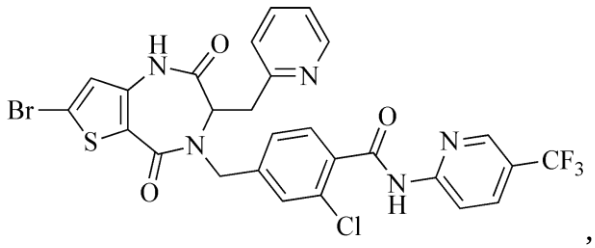
 ,

 ,

 ,



 ,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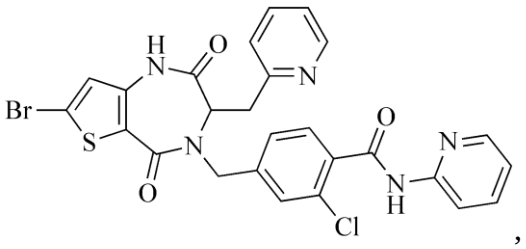
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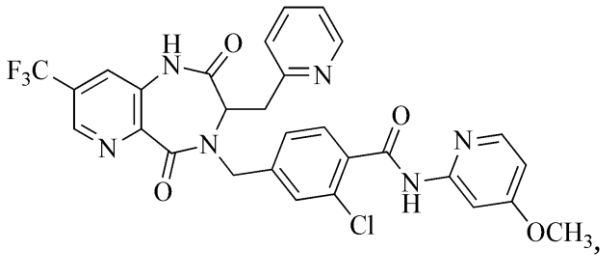
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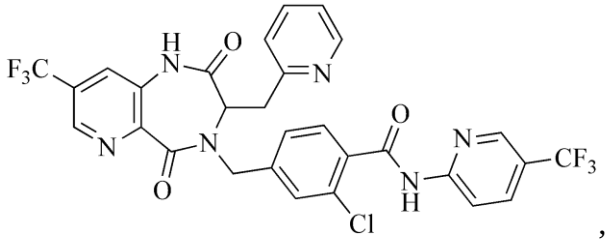
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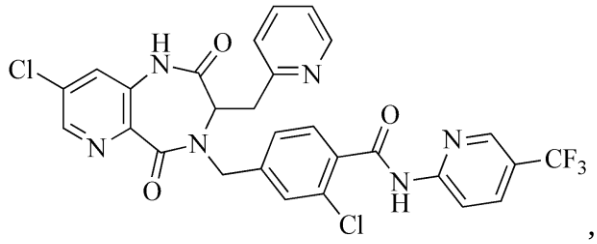
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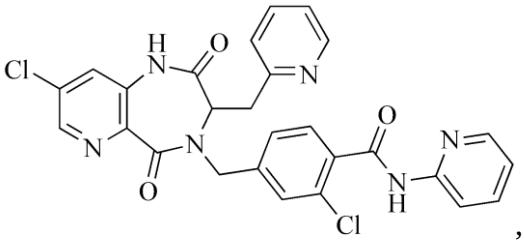
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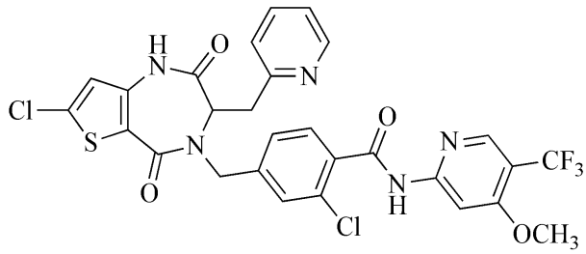
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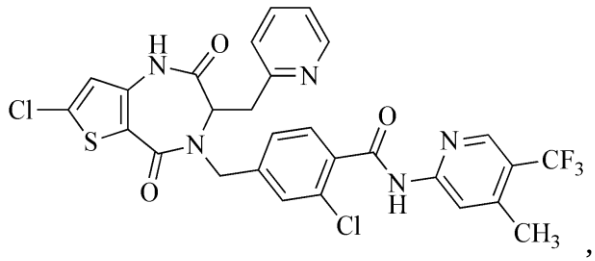

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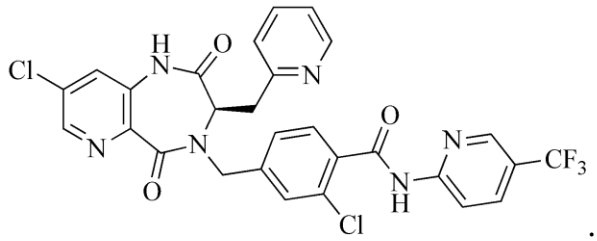

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20. The compound of claim 1 or claim 11, which is selected from any one of the Examples as described in the specification, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof.

21. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to any one of claims 1 to 20, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof.

22. A compound according to any one of claims 1 to 20, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition of claim 21, for use in therapy.

23. A compound according to any one of claims 1 to 20 or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition of claim 21, for use in treating a *C. difficile* infection.

24. Use of a compound according to any one of claims 1 to 20 or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition of claim 21 for the manufacture of a medicament for therapy.

25. Use of a compound according to any one of claims 1 to 20 or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition of claim 21 for the manufacture of a medicament for treating a *C. difficile* infection.

26. A method of making a compound according to any one of claims 1 to 20 or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition of claim 21 according to the synthetic routes disclosed herein.

27. The use of claim 25, wherein the medicament is to be administered to a subject, and wherein a therapeutically-effective amount of a second therapeutic agent is to be further administered to the subject.

28. The use of claim 27, wherein the second therapeutic agent comprises an antibiotic.

29. Use of a compound according to any one of claims 1 to 20, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition of claim 21, in the manufacture of a medicament for inhibiting a *C. difficile* bacterial toxin in a cell.

30. Use of a compound according to any one of claims 1 to 20, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition of claim 21, in the manufacture of a medicament for reducing glucosylation of Rho GTPase proteins in a cell.