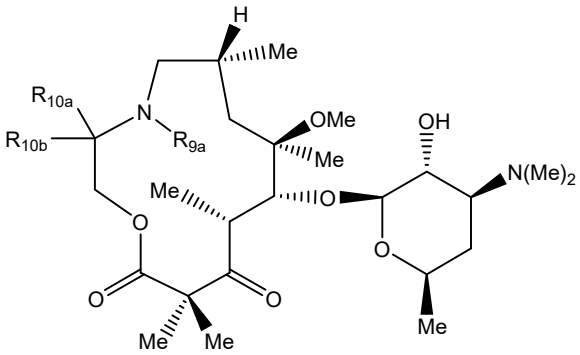
and the ribosome. See, *e.g.*, Ma *et al.*, *Curr. Med. Chem.* (2011) 18:1993-2015; Ma *et al.*, *Mini-Rev. Med. Chem.* (2010) 10:272-286. Despite greatly improved ribosomal binding, ketolides such as telithromycin and solithromycin have not addressed several of the newest forms of macrolide resistance that have evolved in nosocomial settings, especially ribosome methylation and RNA point mutations.

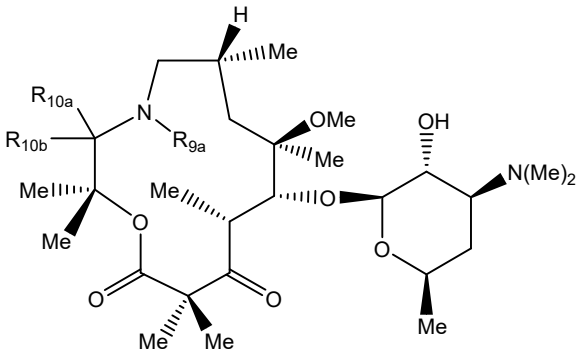
[0005] Accordingly, the discovery and development of new antibiotics effective against drug-resistant bacteria, especially Gram-negative bacteria, represents a currently unmet medical need.

SUMMARY

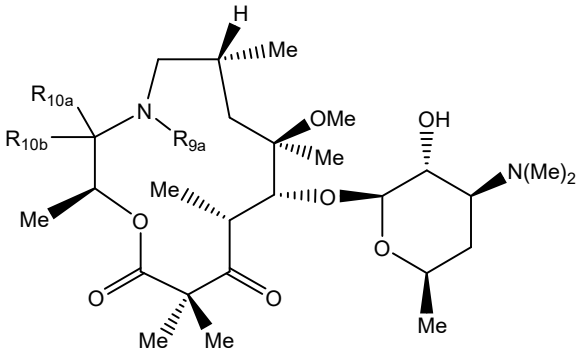
[0005a] In an aspect of the present disclosure, there is provided a compound of formula IIA, IIB, IIC, or IID:



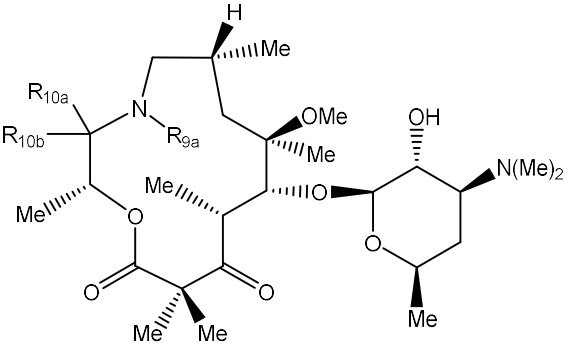
IIA;



IIB;



IIC;



IID;

or a pharmaceutically acceptable salt thereof, wherein:

R_{9a} is selected from the group consisting of H, optionally substituted C_{1-10} alkyl, hydroxyalkyl, optionally substituted C_{1-10} alkylene-$NR_TR_{T'}$, optionally substituted C_{1-10} alkylene-cycloalkyl-$NR_TR_{T'}$, and optionally substituted alkoxyalkyl; wherein R_T and $R_{T'}$ are

each independently selected from the group consisting of H, optionally substituted alkyl, and optionally substituted C_{1-10} alkylene-heterocycloalkyl;

R_{10b} is selected from the group consisting of H and optionally substituted C_{1-10} alkyl; and

R_{10a} is selected from the group consisting of $-CO_2H$, $–CO_2$-optionally substituted alkyl, $–CON(R_{z'})(R_{z''})$, and optionally substituted C_{1-10} alkylene-R_{101}, C_{2-10} alkenylene-R_{101}, and C_{2-10} alkynylene-R_{101}; wherein

R_{101} is selected from the group consisting of (C_{1-6} alkyl)-S-, (C_{1-6} alkyl)-SO-, (C_{1-6} alkyl)-SO_2-, -OH, -O-alkyl, $-NR_xR_{x'}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R_x and $R_{x'}$ are each independently selected from the group consisting of -H, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkylene-cycloalkyl, optionally substituted alkylene-heterocycloalkyl, optionally substituted alkylene-aryl, optionally substituted alkylene-heteroaryl, -C(=O)-alkyl, and -C(=O)-alkylene-$N(R_{y'})(R_{y''})$; or

R_x and $R_{x'}$ together with the atom to which they are attached form an optionally substituted 3-, 4-, 5-, 6-, or 7-membered ring optionally containing an additional heteroatom selected from the group consisting of O, S, SO, SO_2, NR_y, and N-C_1-C_{10} alkyl; and wherein:

each R_y is independently selected from the group consisting of H and optionally substituted C_{1-10} alkyl, and

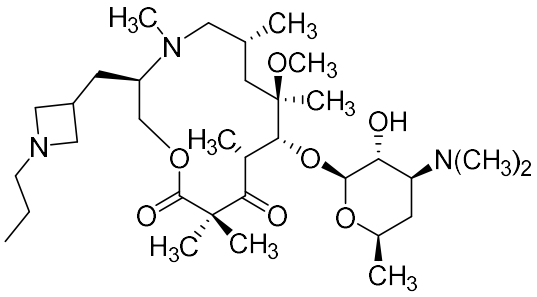
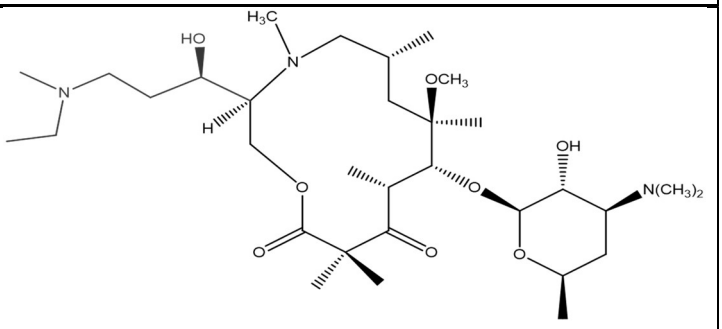
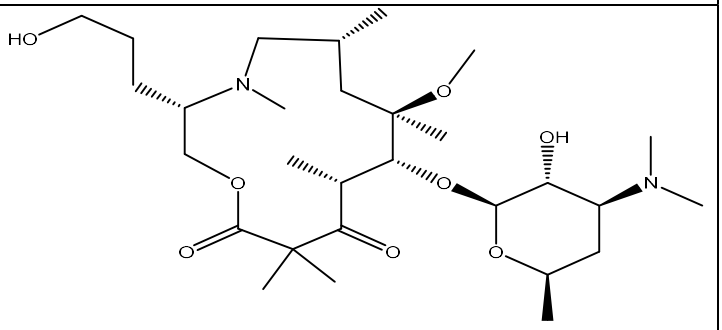
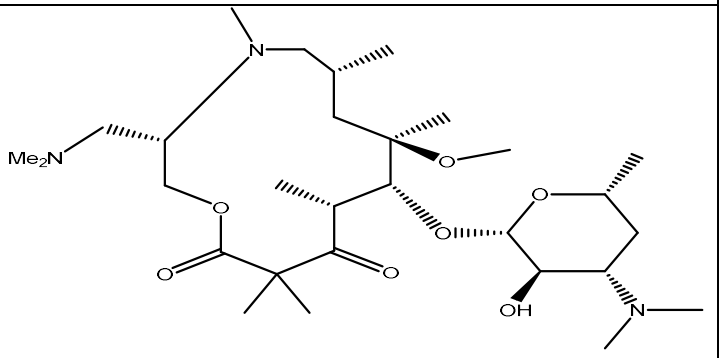
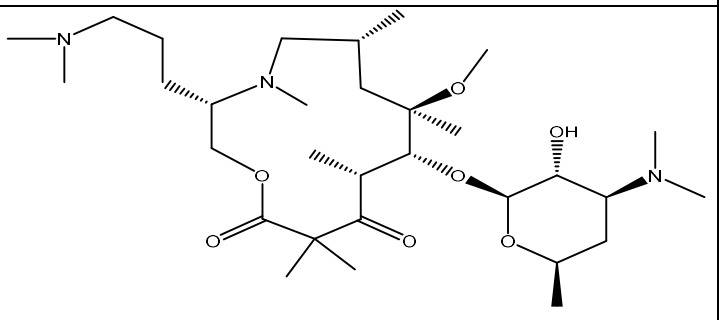
$R_{z'}$ and $R_{z''}$ are each independently H or optionally substituted alkyl.

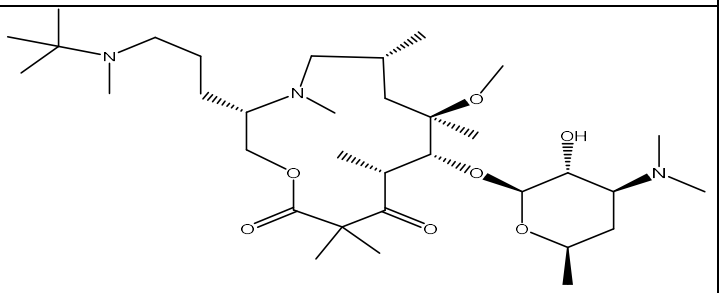
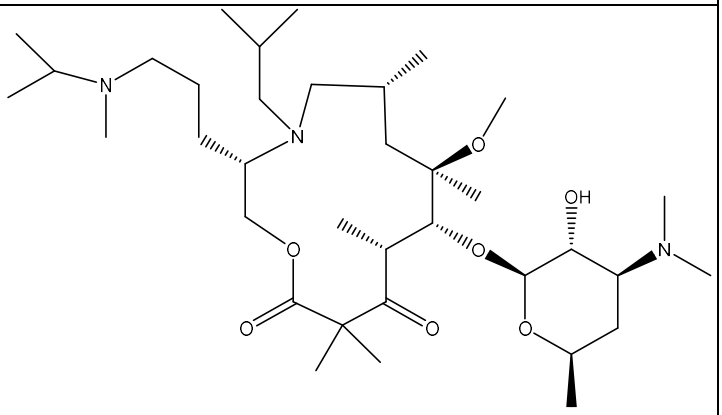
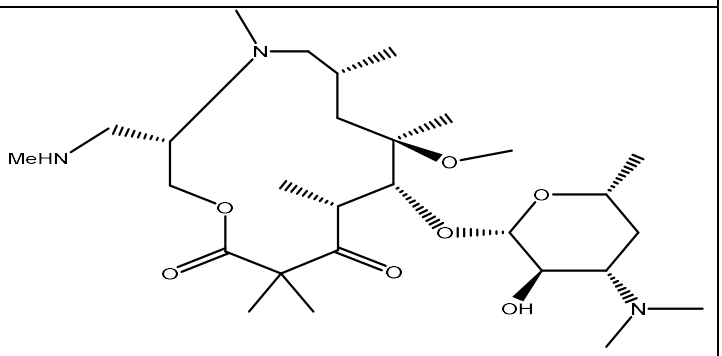
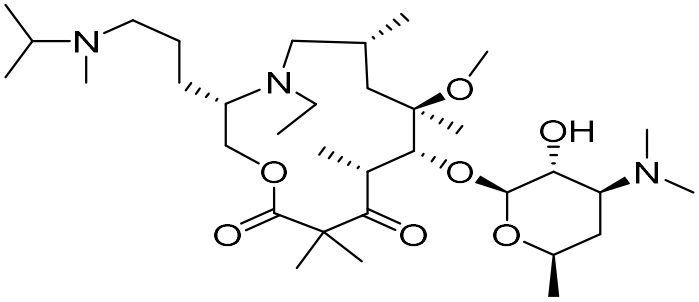
[0005b] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

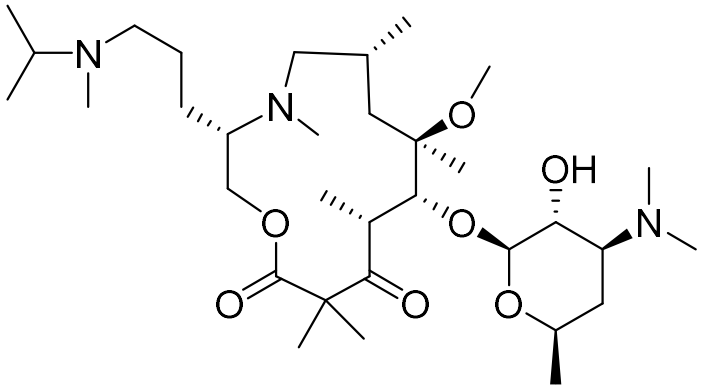
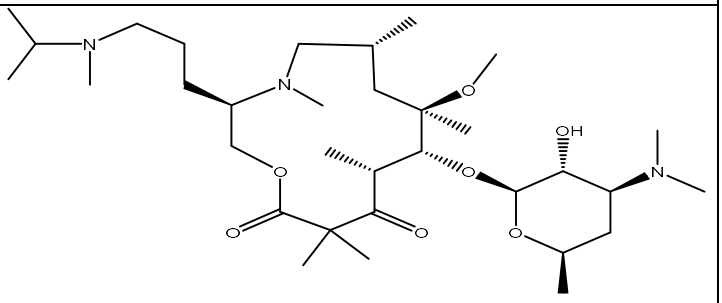
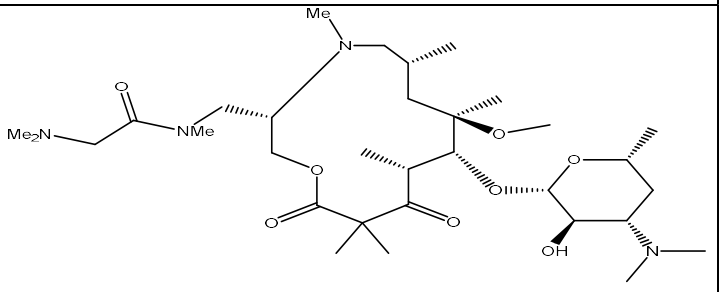
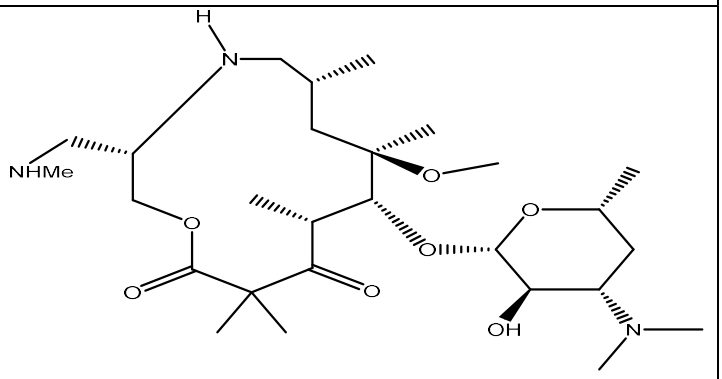
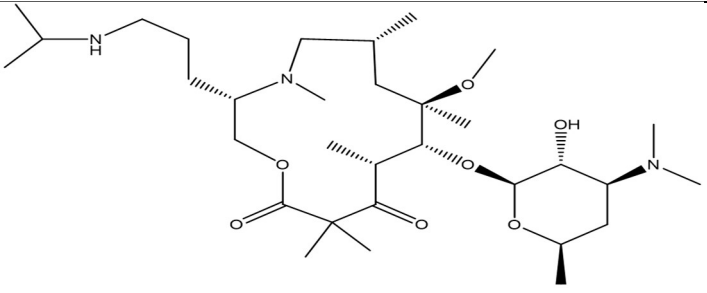
[0005c] In a further aspect of the present disclosure, there is provided a use of a compound of disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition also disclosed herein, in the manufacture of a medicament for treating an infectious disease, wherein the infectious disease is a Gram-positive or Gram-negative bacterial infection, or a parasitic infection.

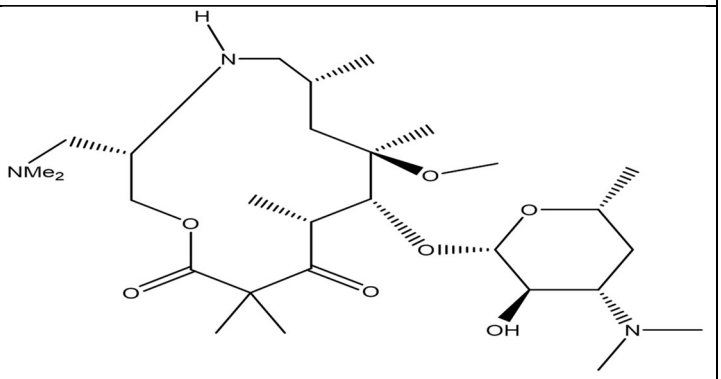
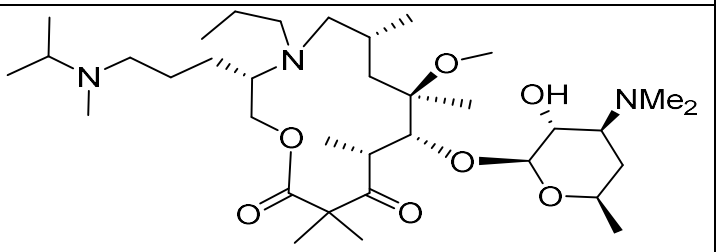
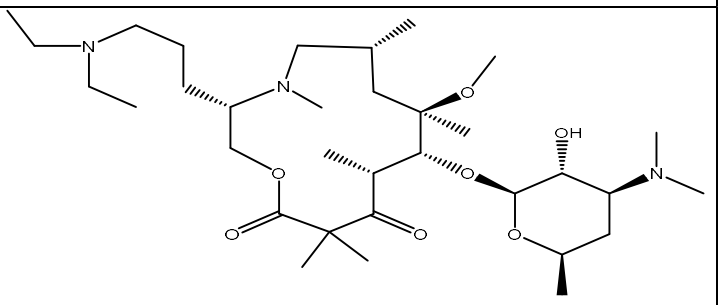
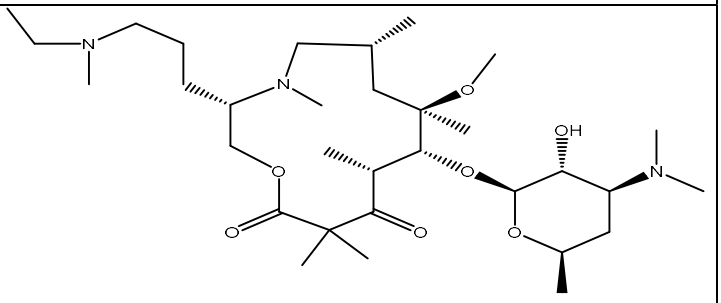
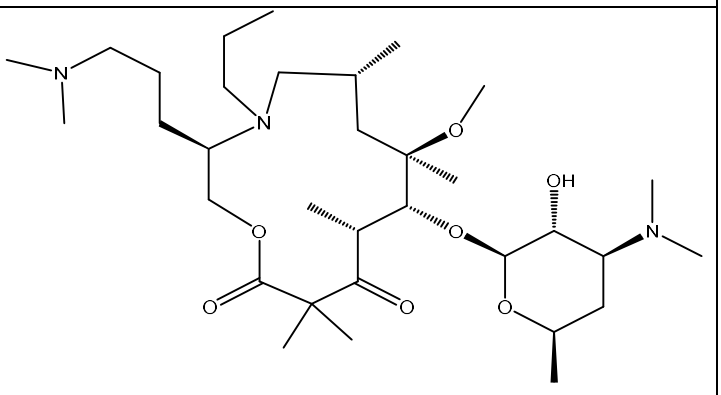
[0005d] In another aspect of the present disclosure, there is provided a compound disclosed herein, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition also disclosed herein, for use in the treatment of an infectious disease, wherein the infectious disease is a Gram-positive or Gram-negative bacterial infection, or a parasitic infection.

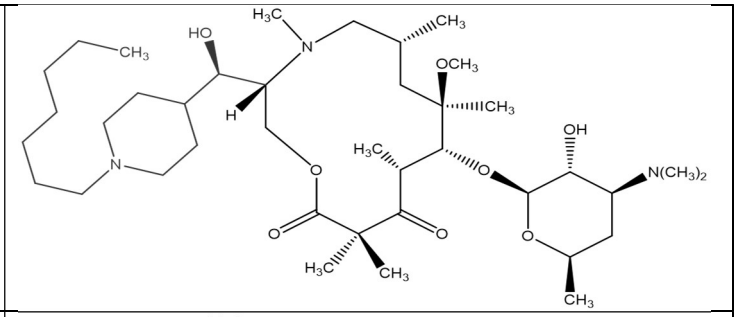
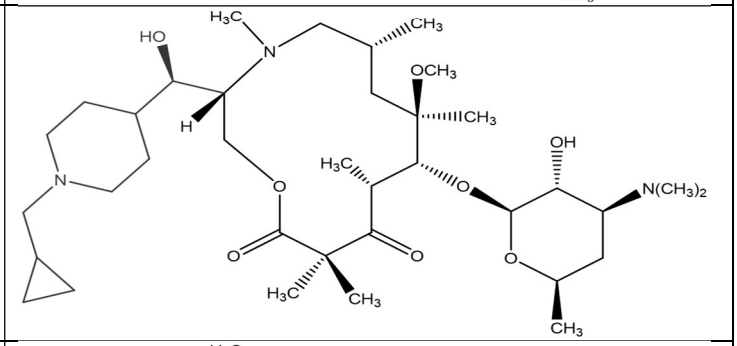
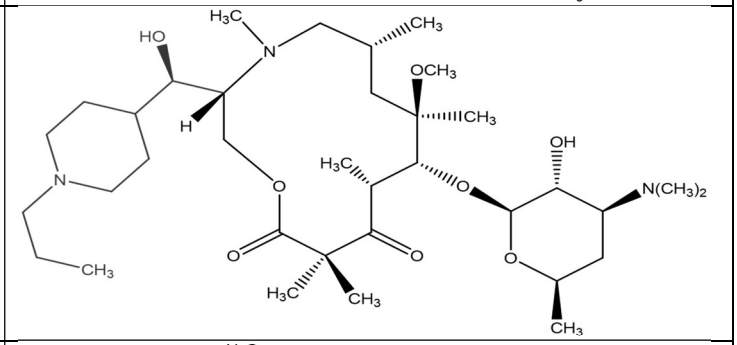
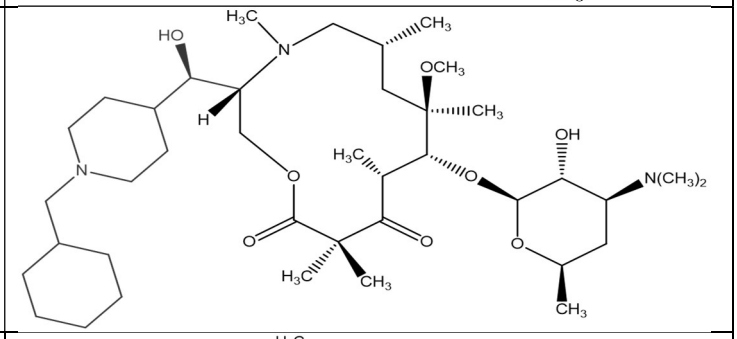
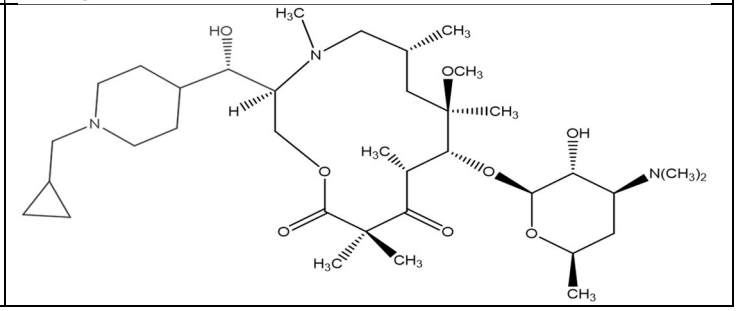
[0005e] In a further aspect of the present disclosure, there is provided a compound which is selected from:

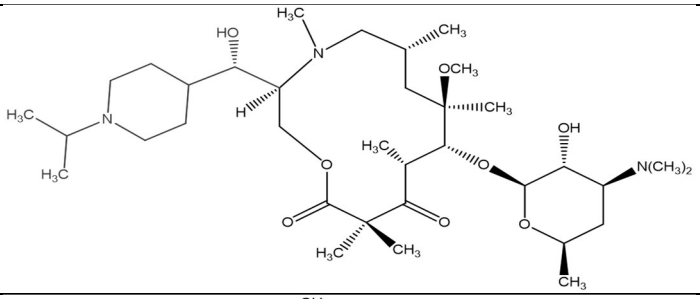
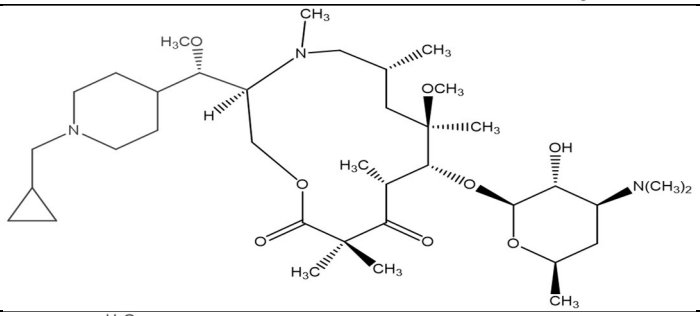
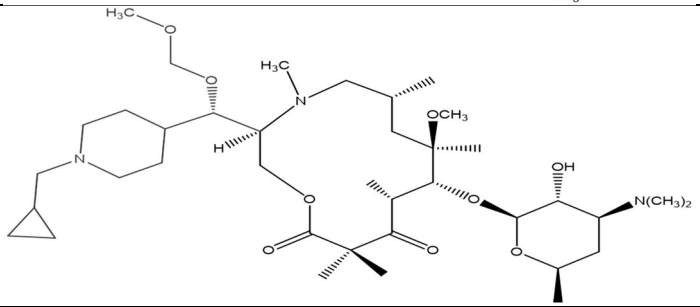
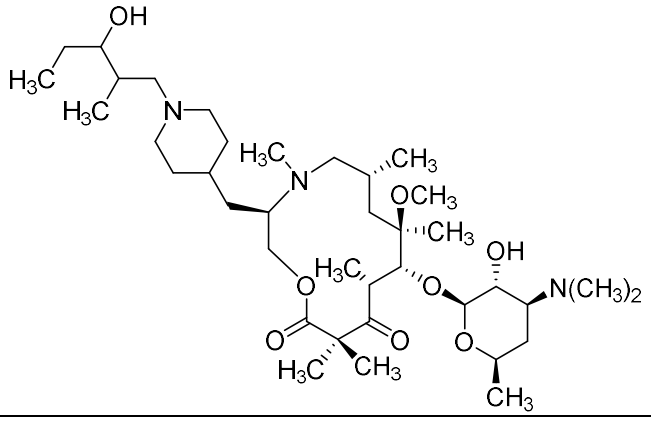
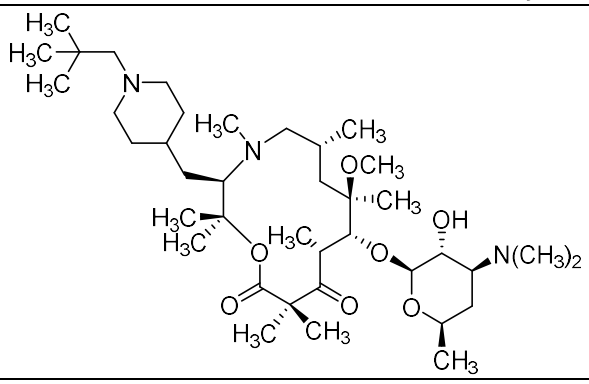
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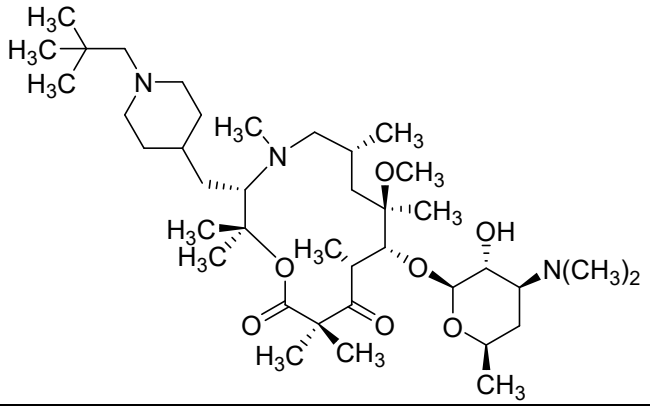
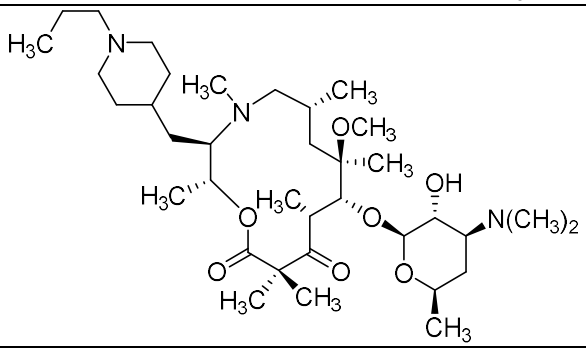
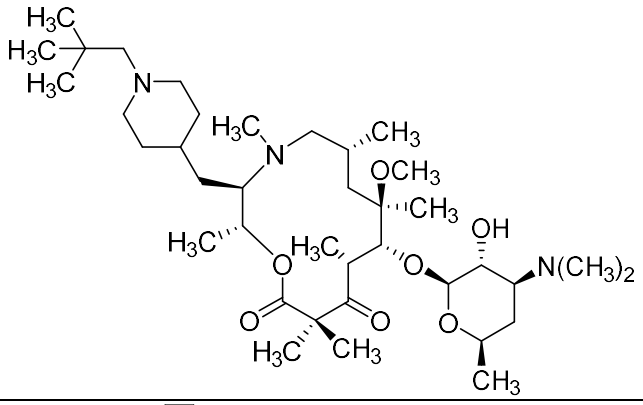
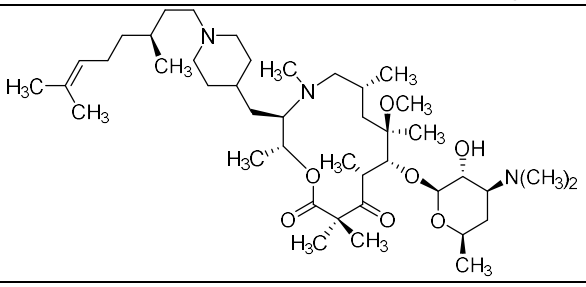
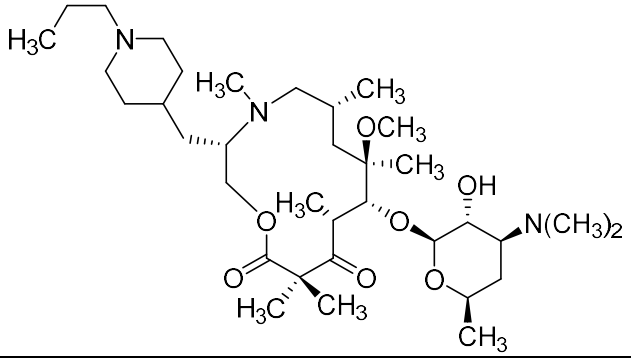
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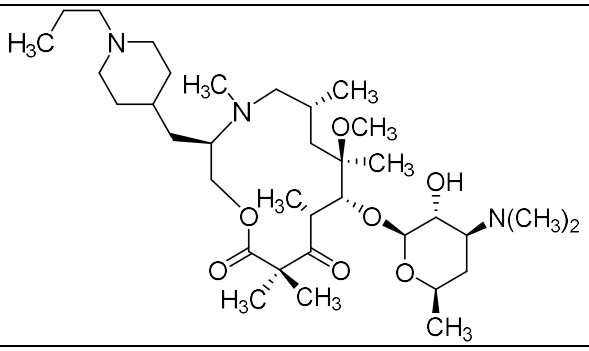
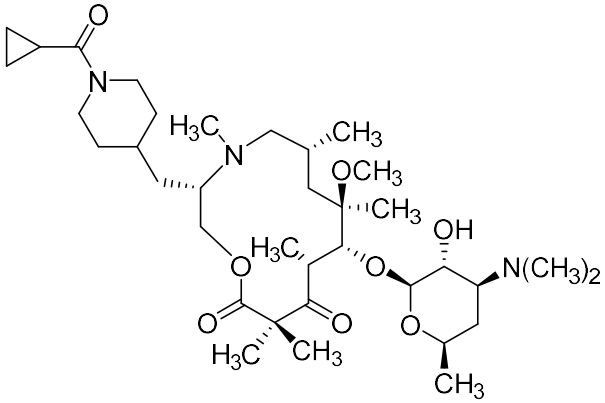
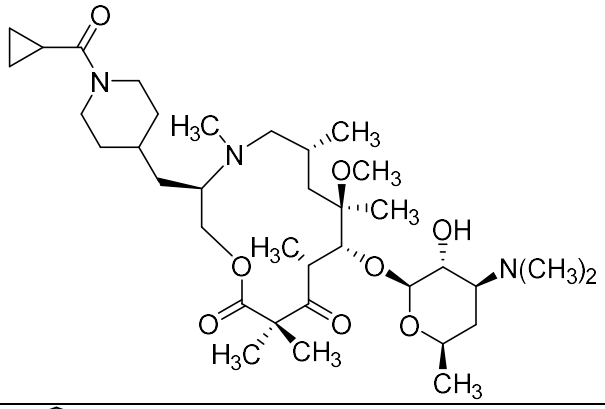
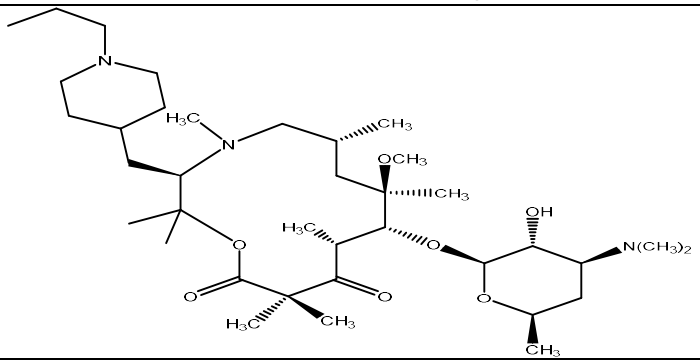
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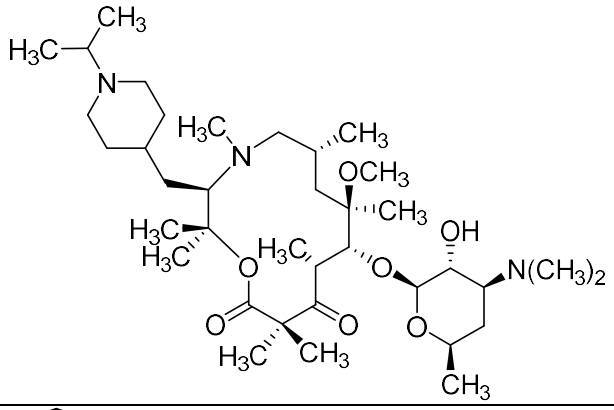
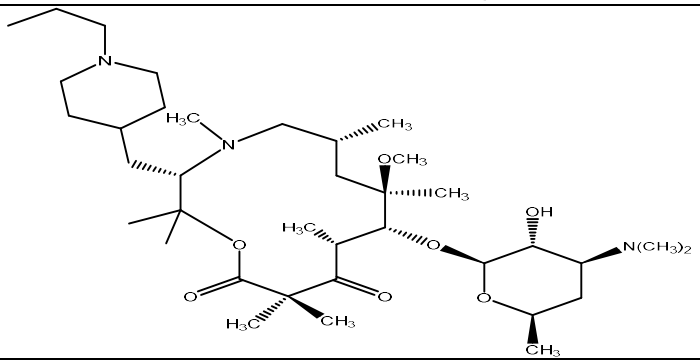
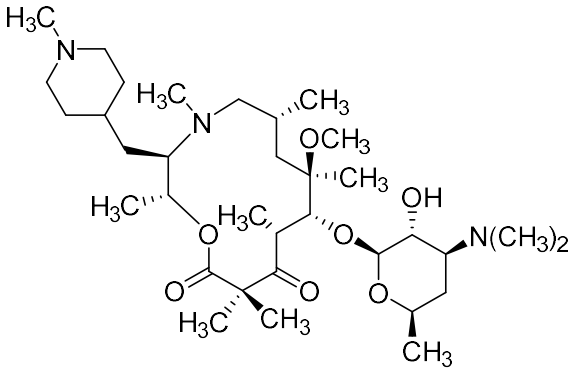
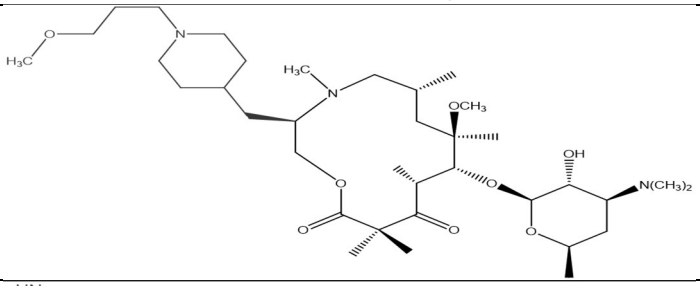
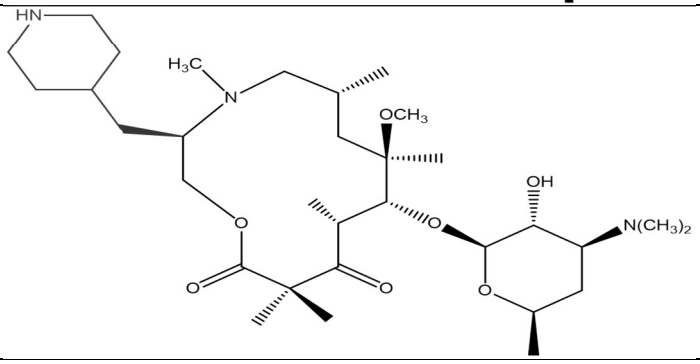
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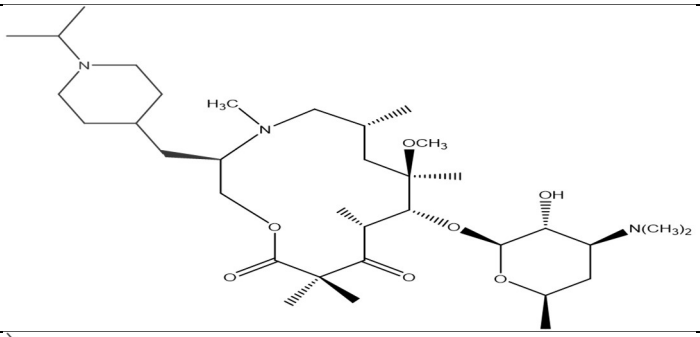
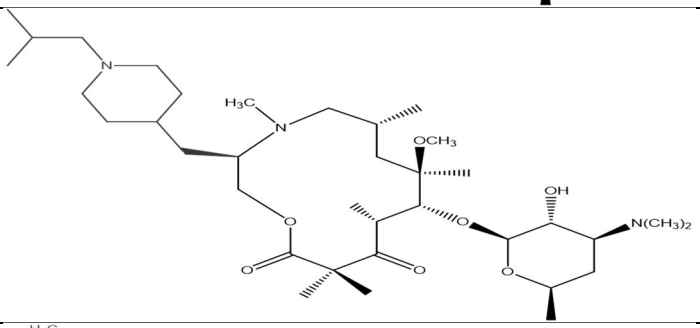
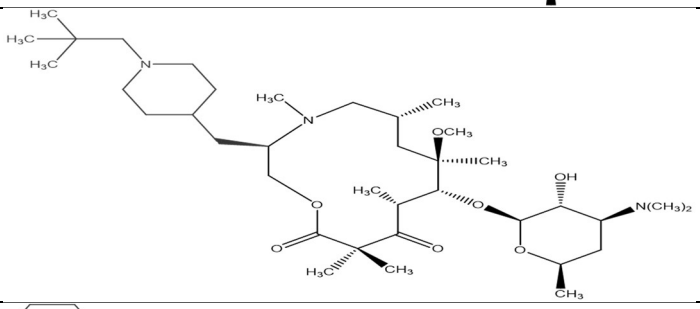
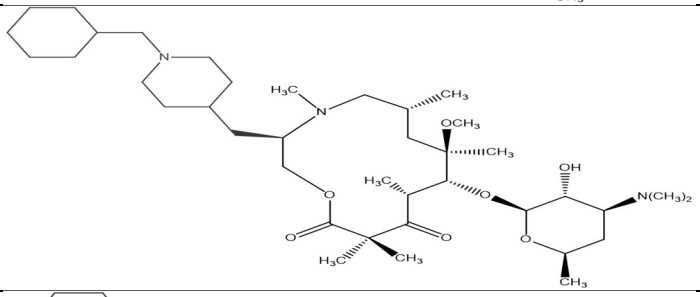
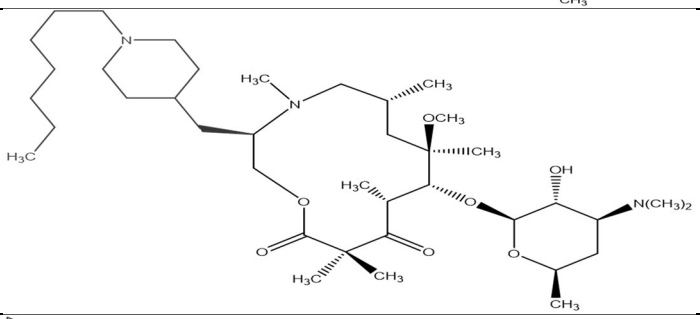
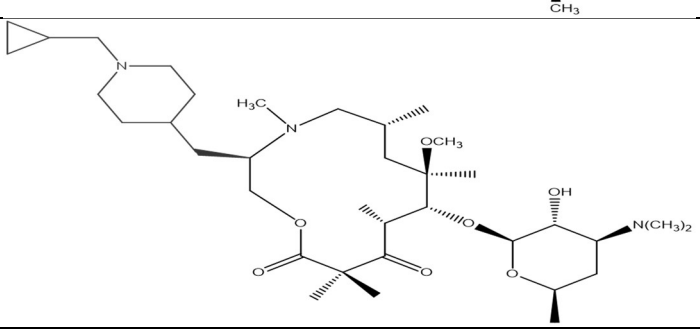
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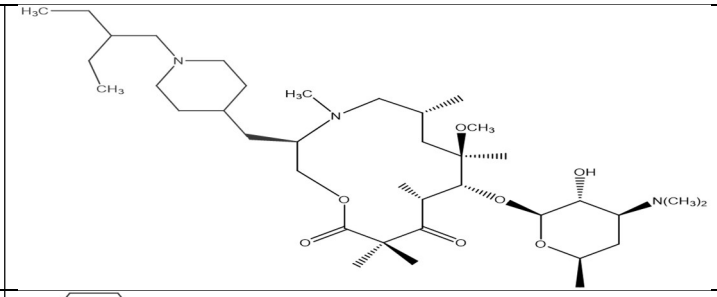
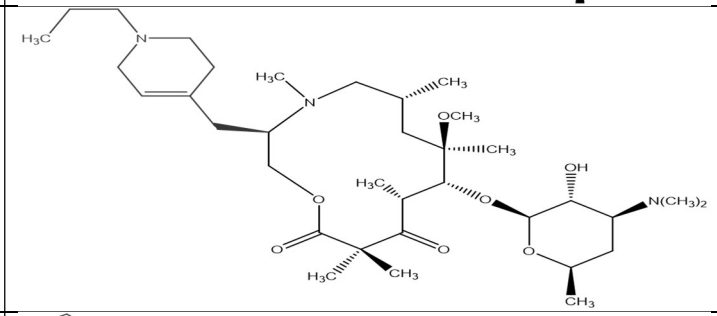
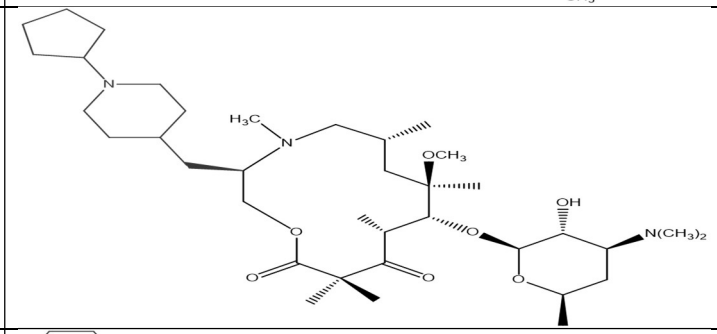
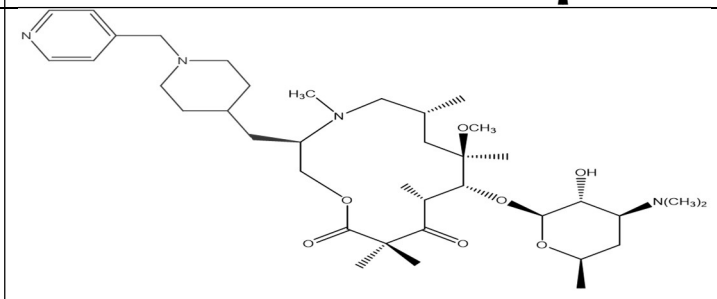
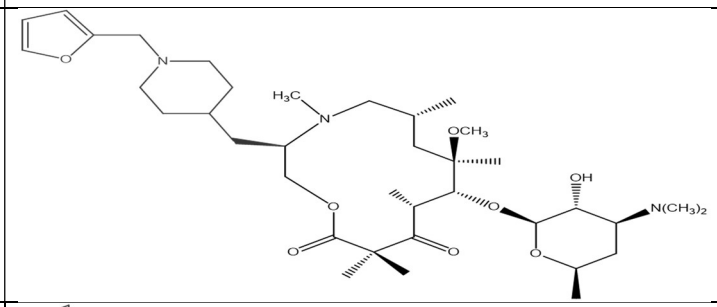
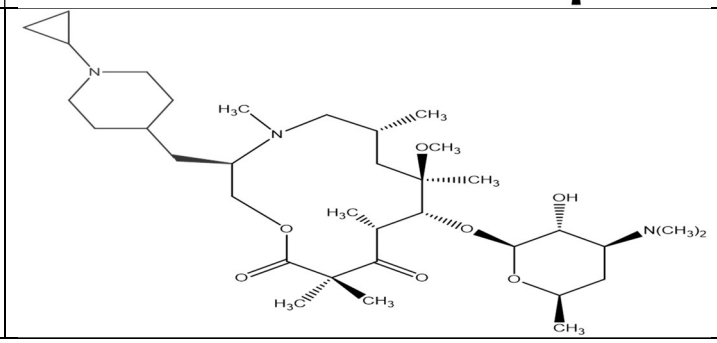
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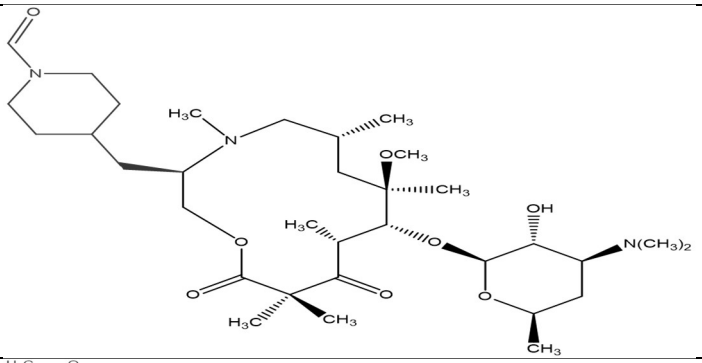
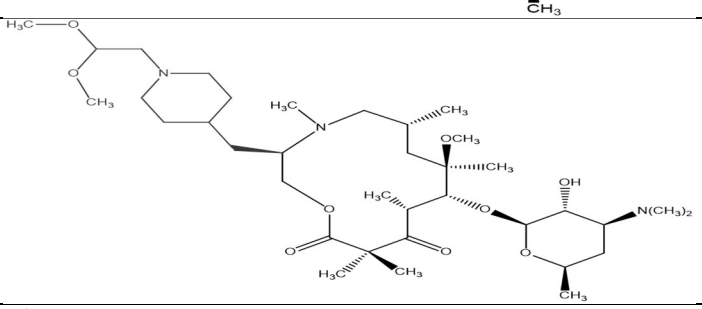
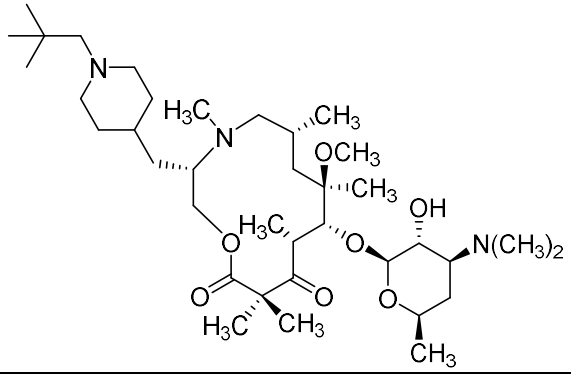
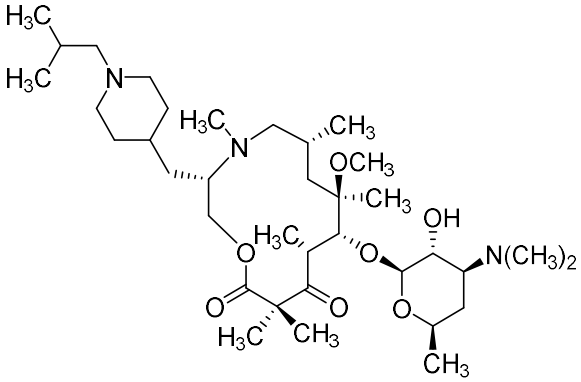
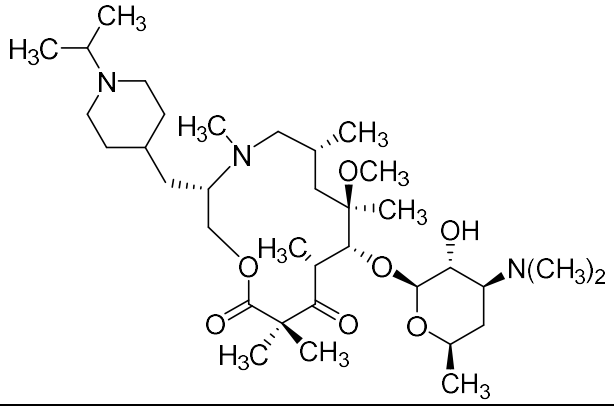
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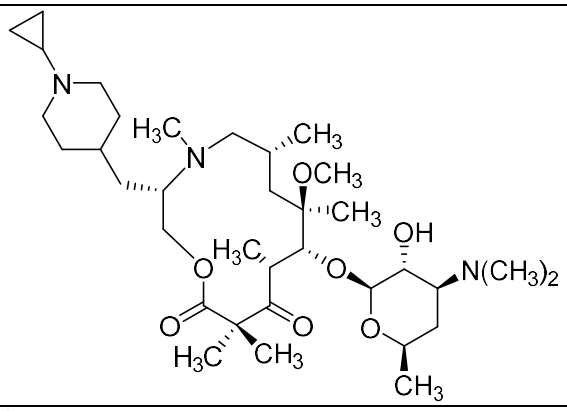
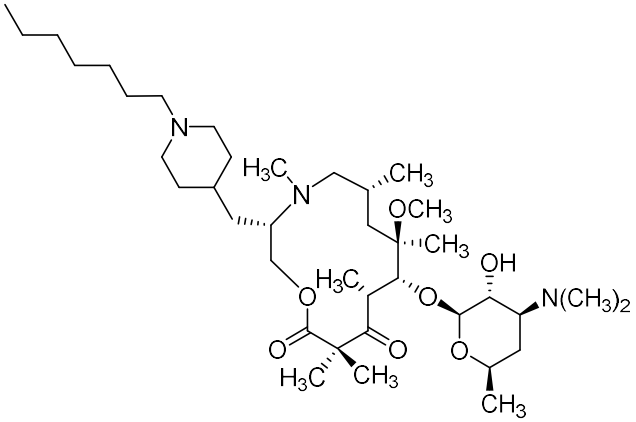
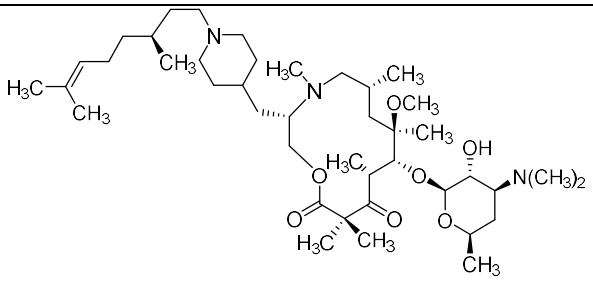
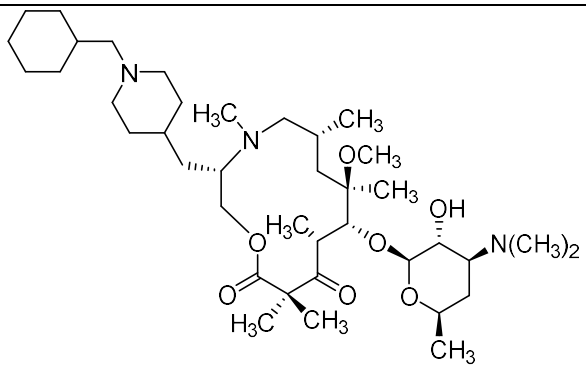
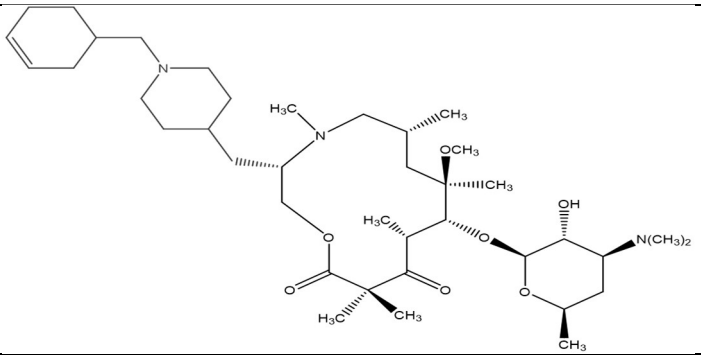
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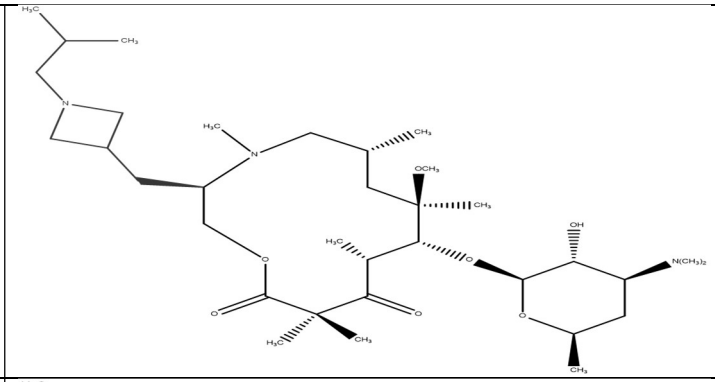
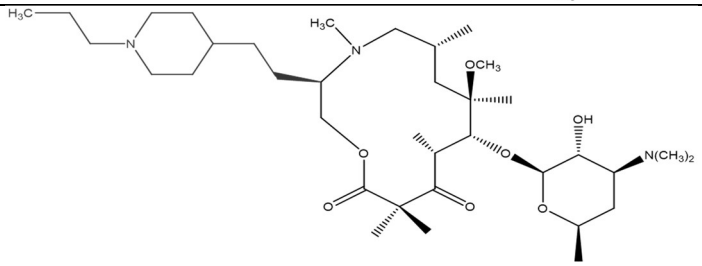
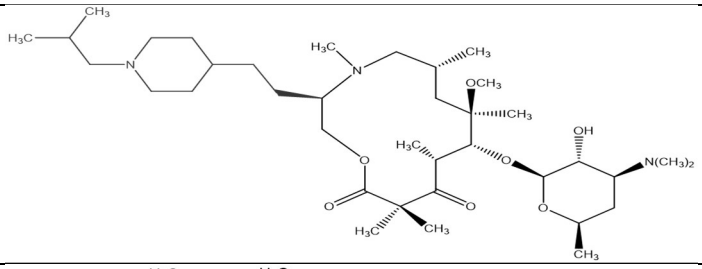
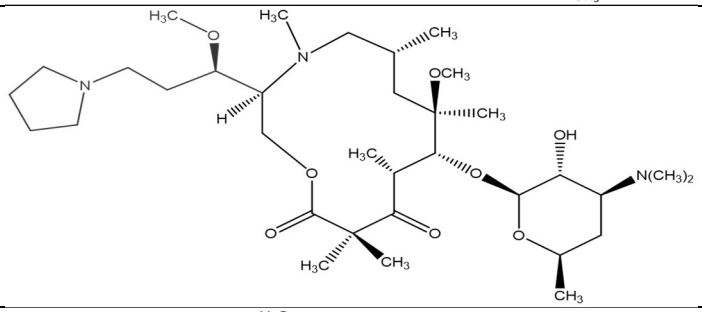
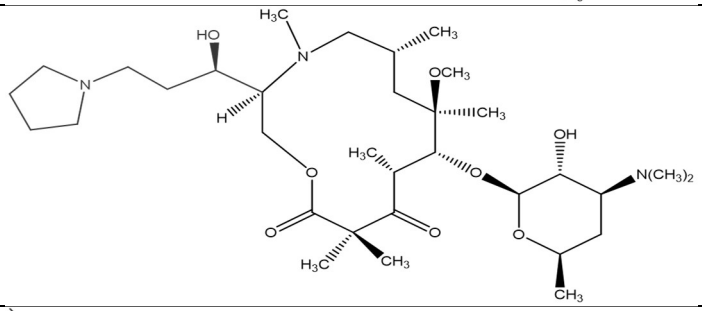
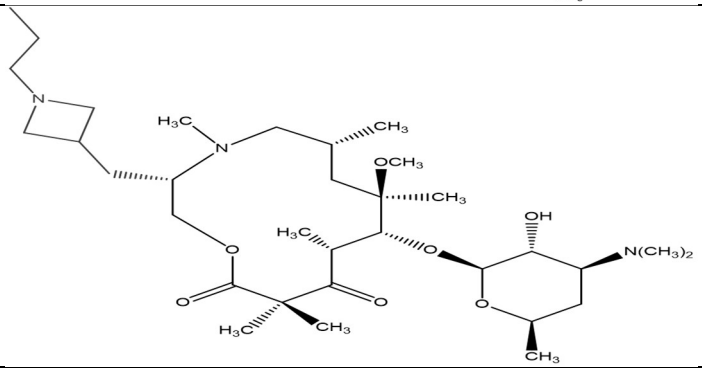
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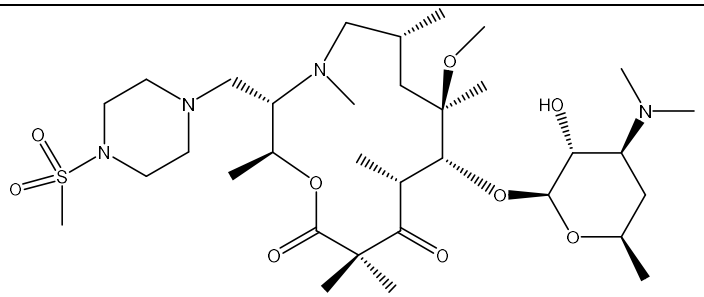
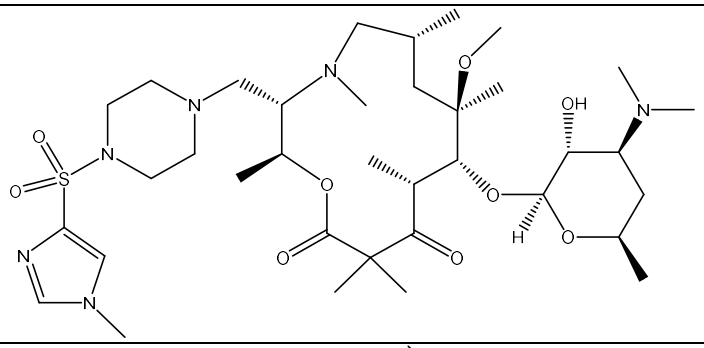
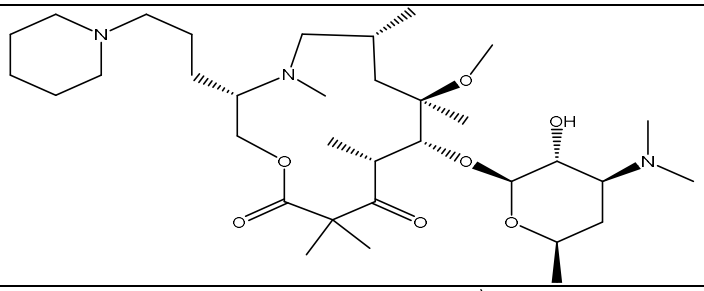
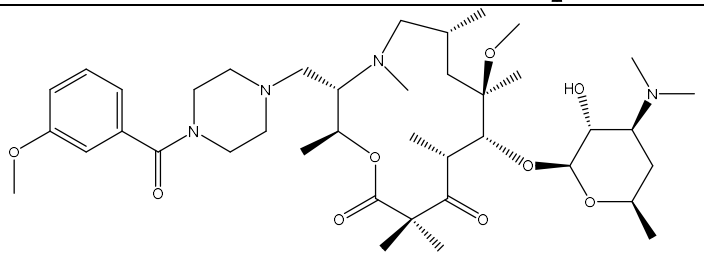
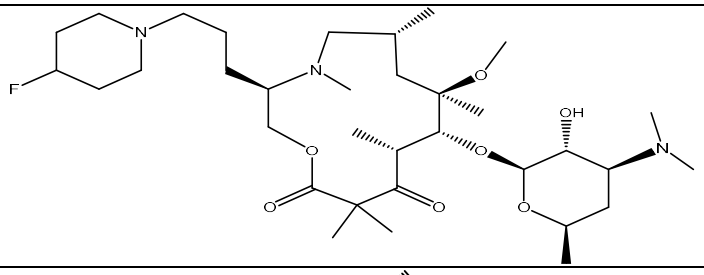
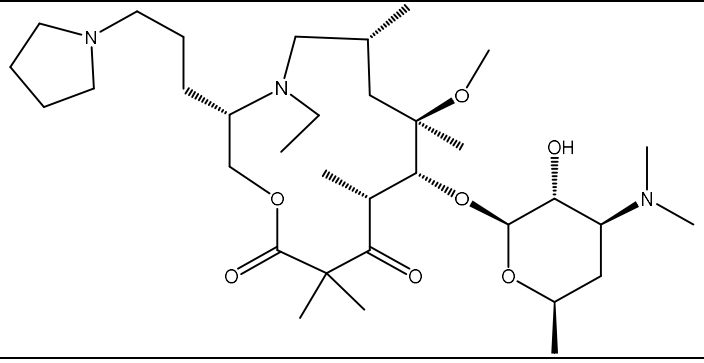
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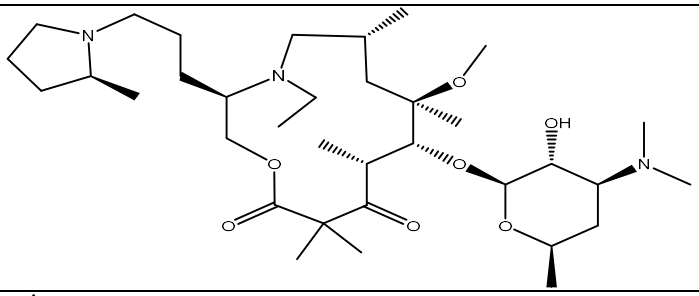
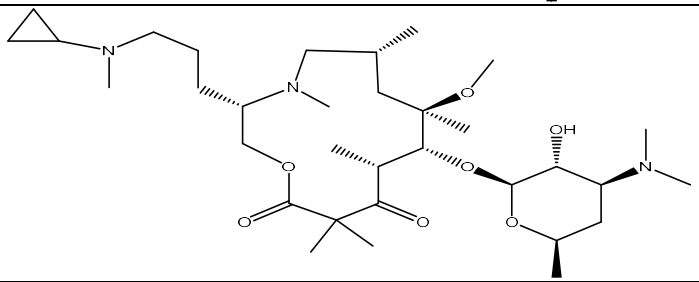
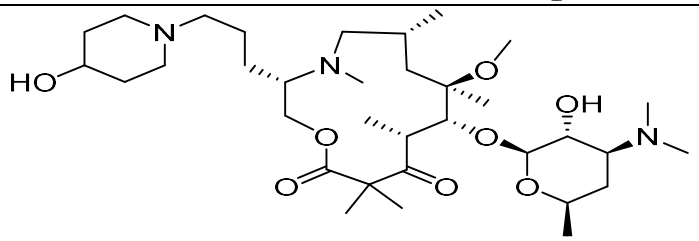
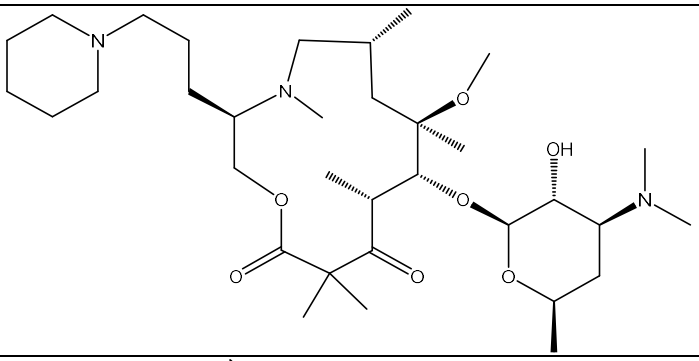
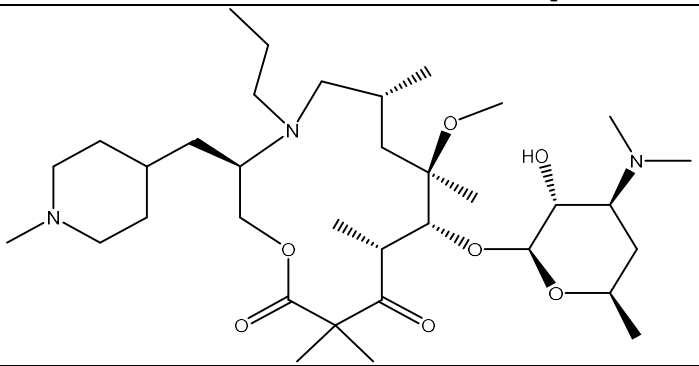
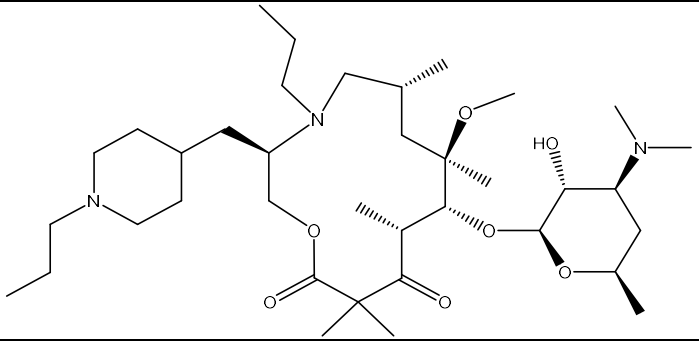
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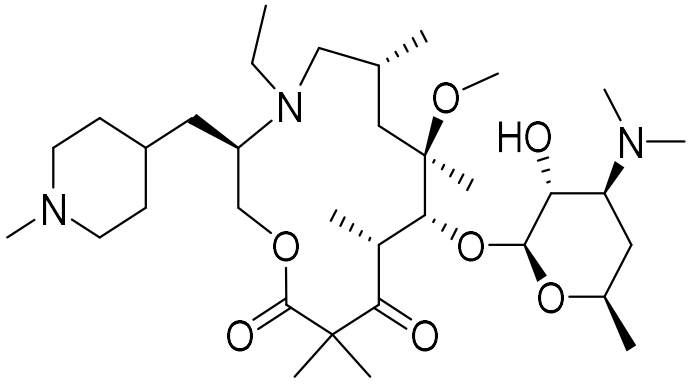
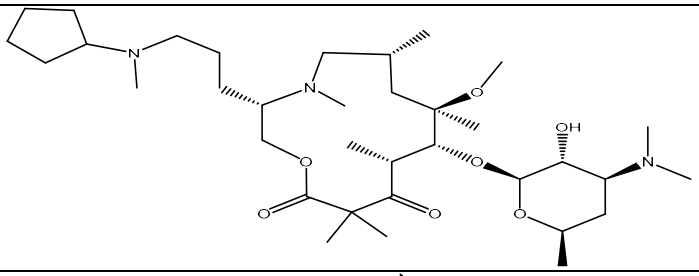
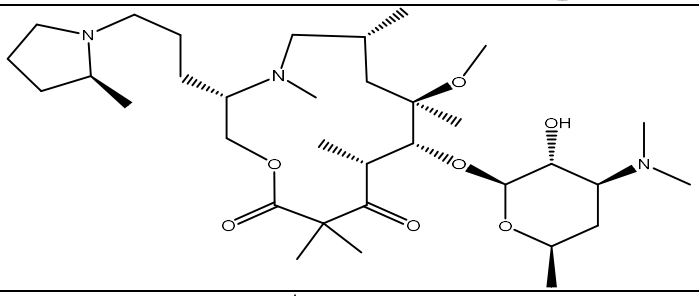
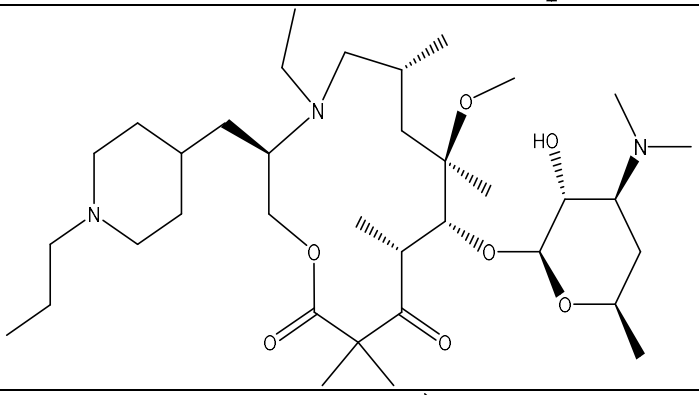
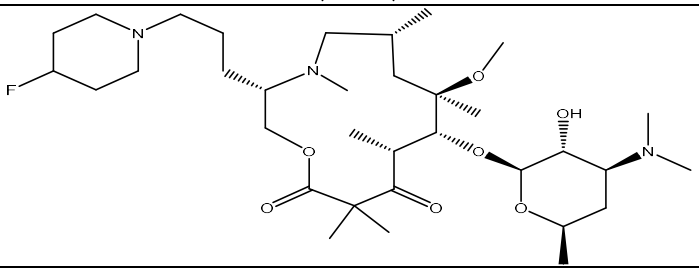
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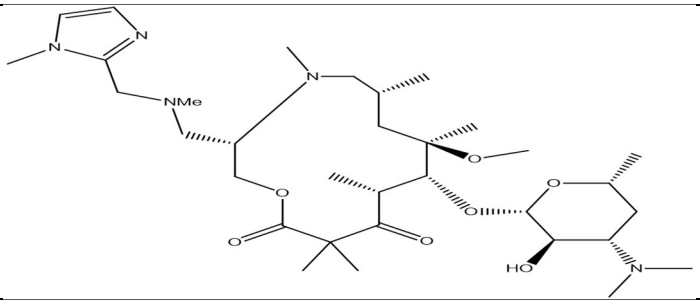
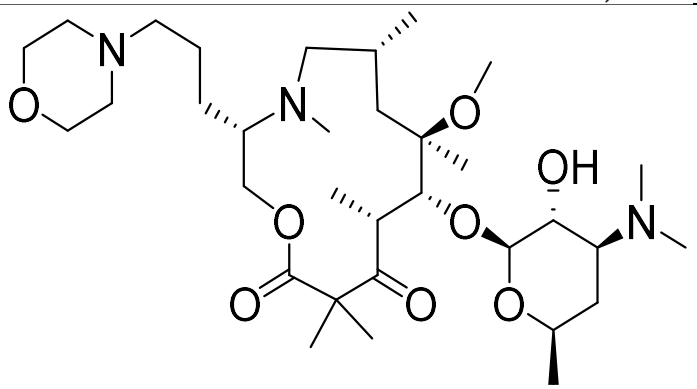
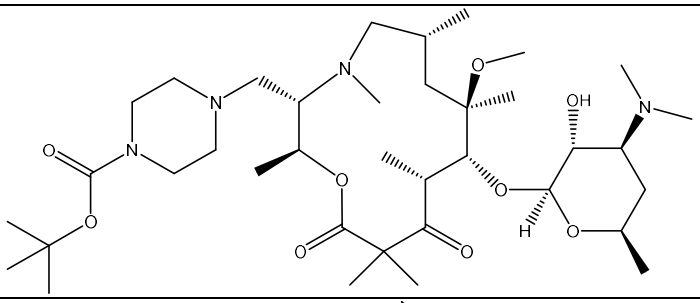
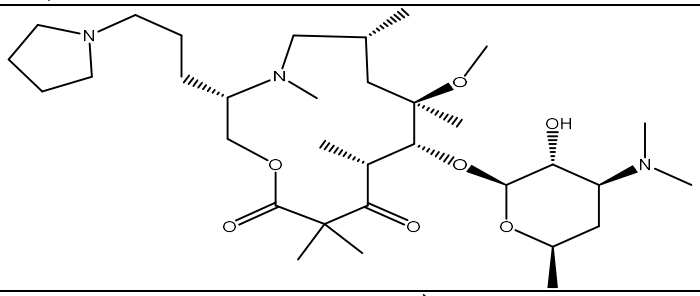
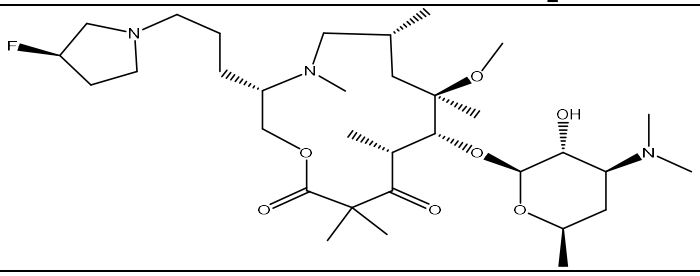
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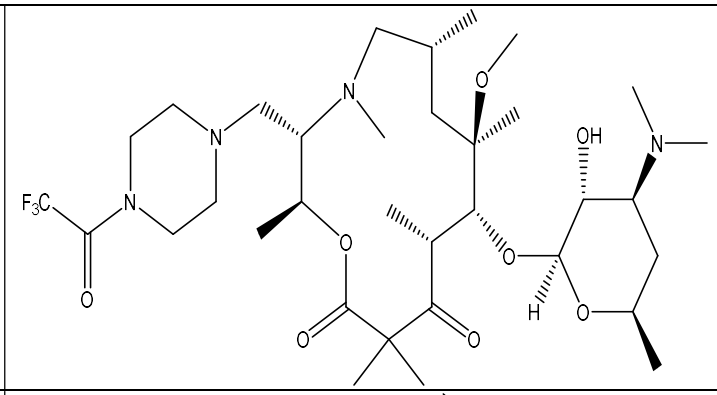
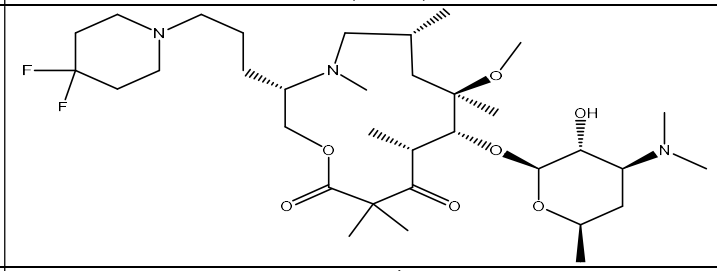
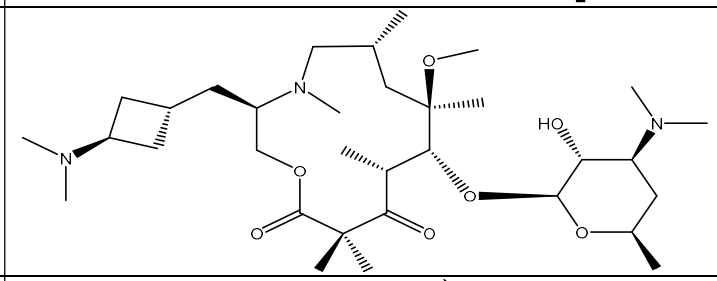
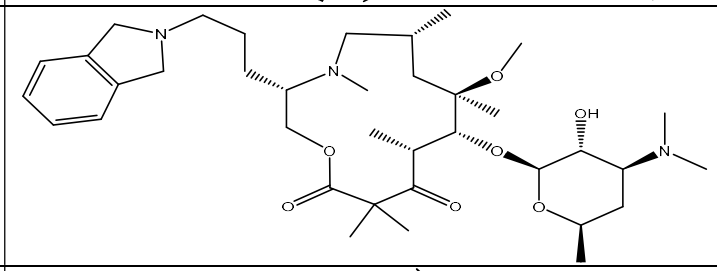
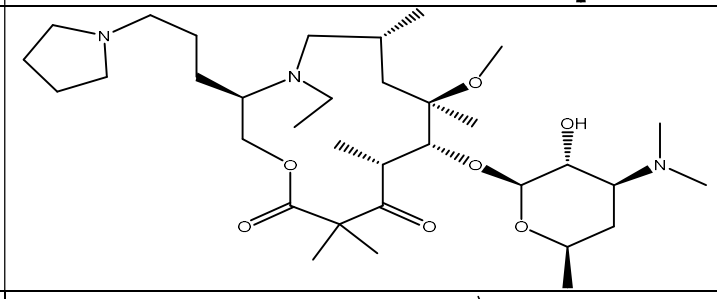
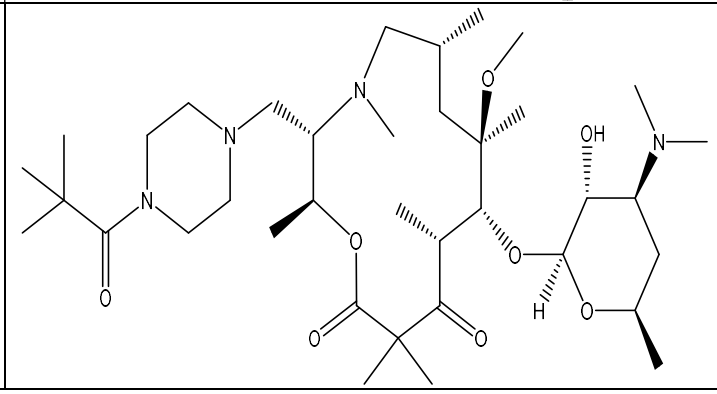
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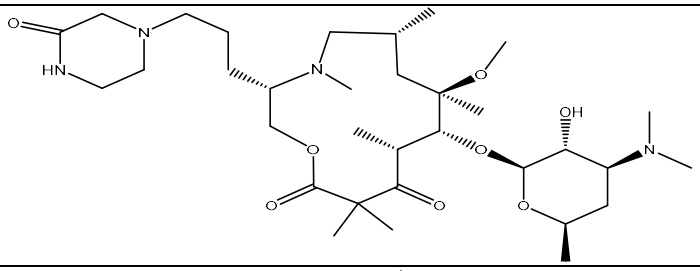
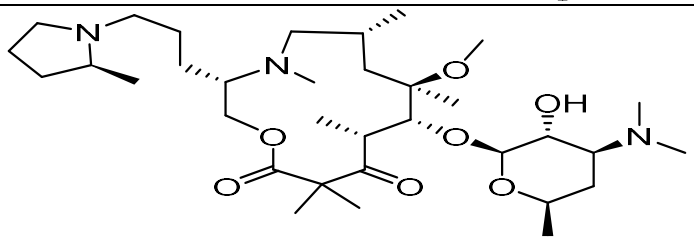
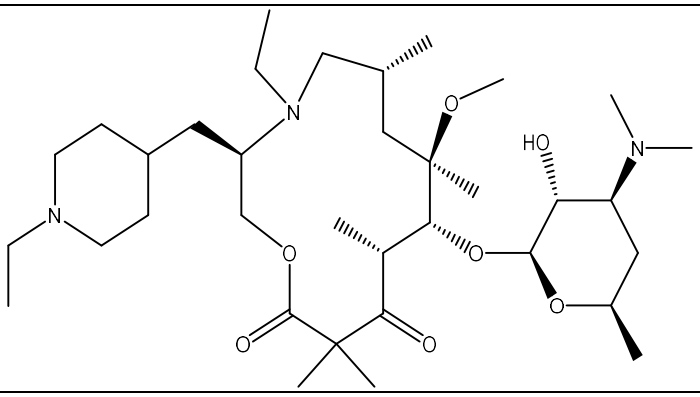
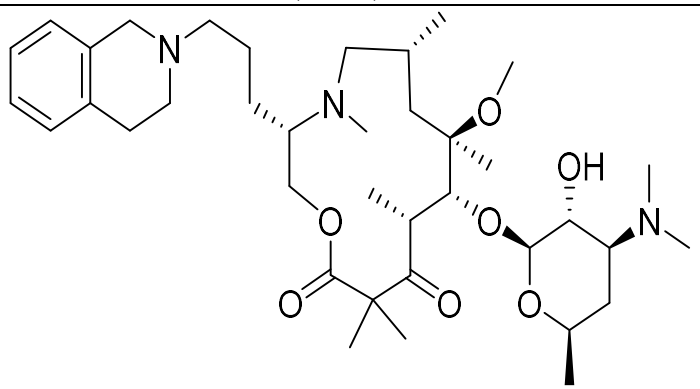
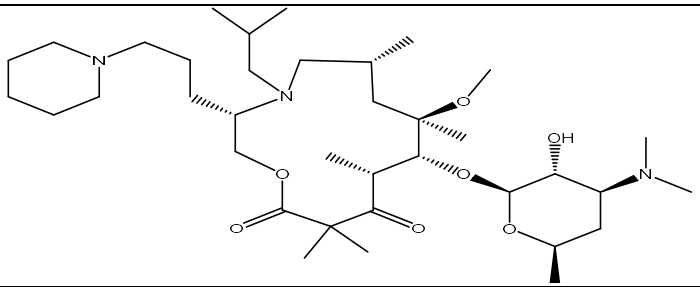
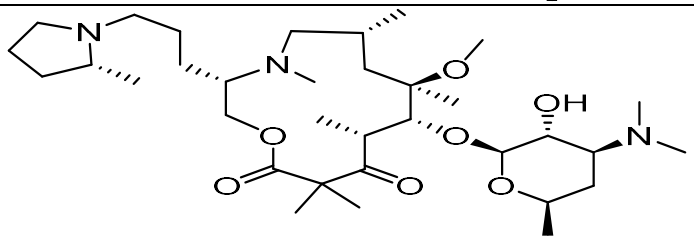
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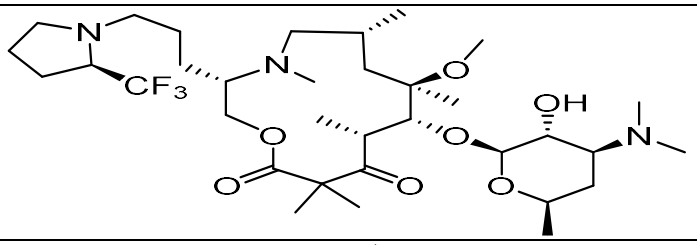
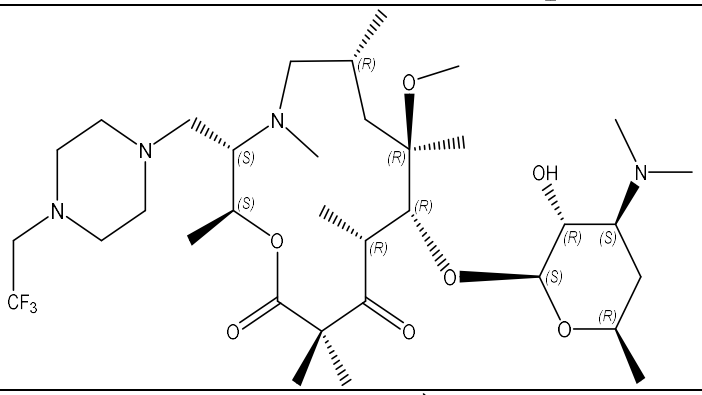
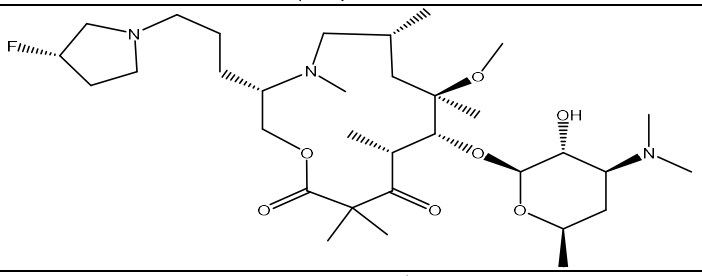
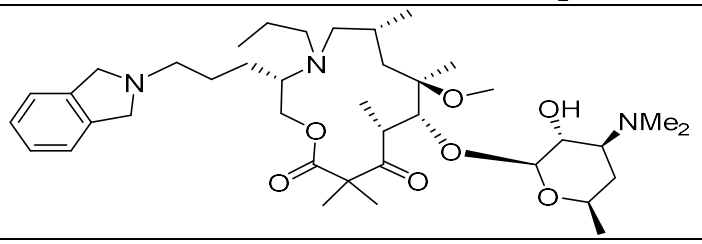
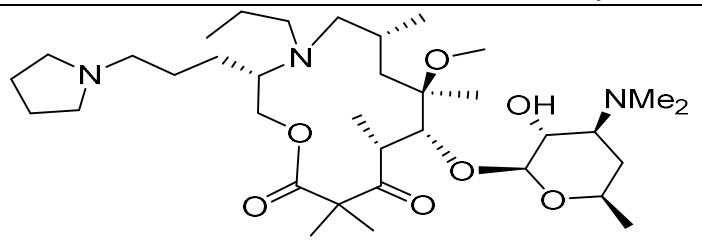
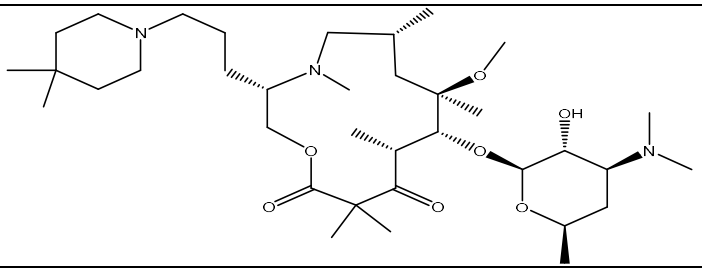
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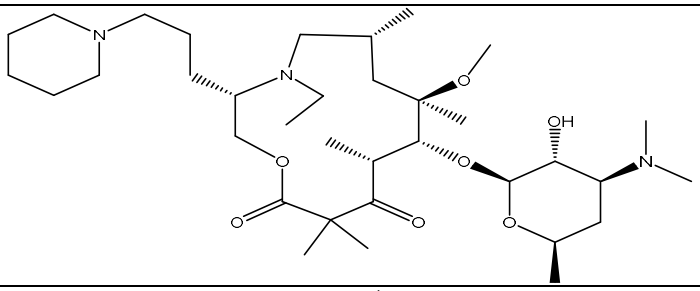
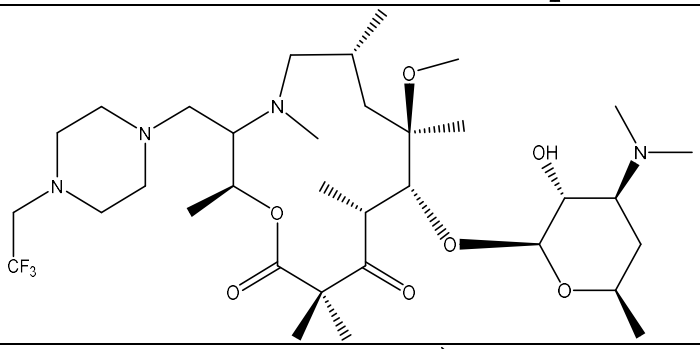
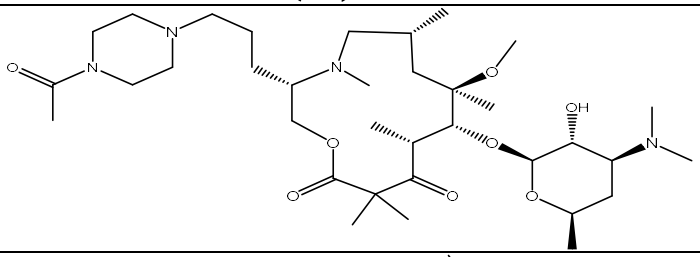
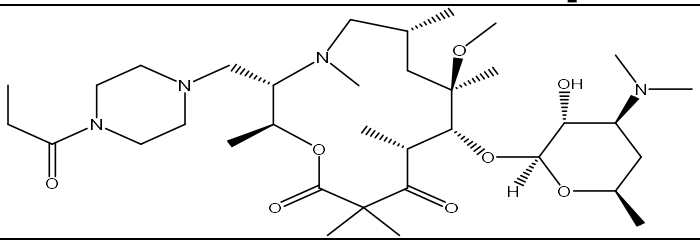
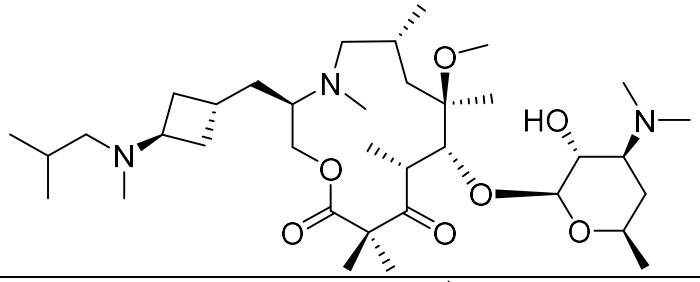
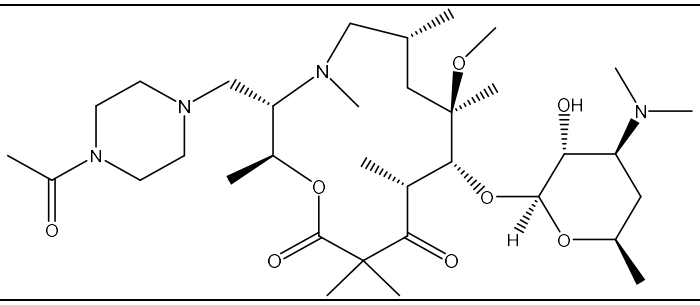
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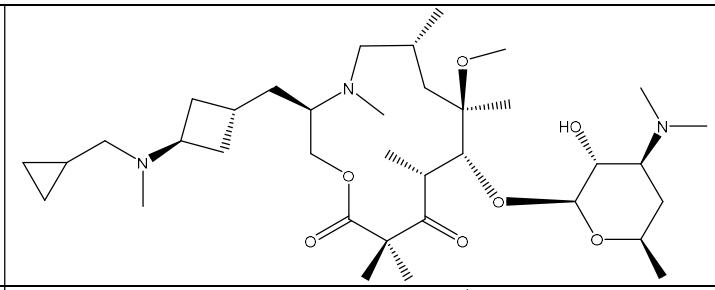
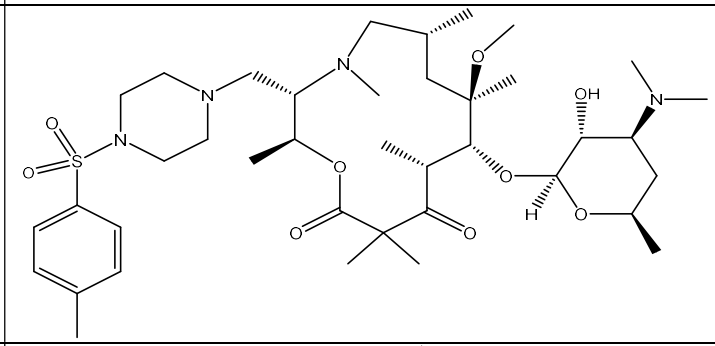
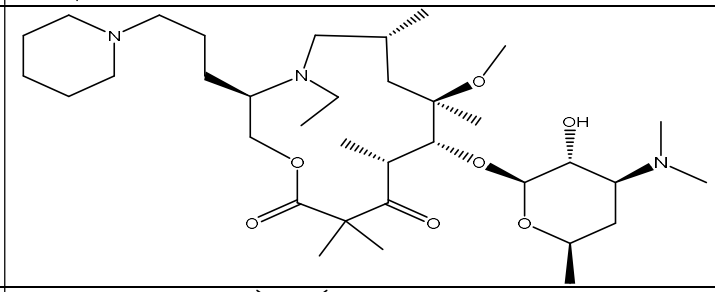
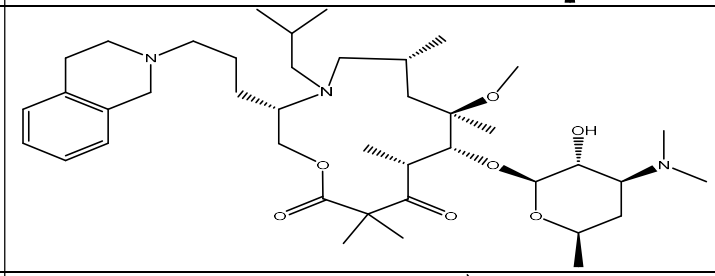
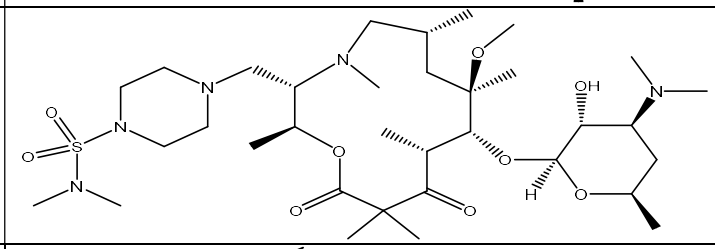
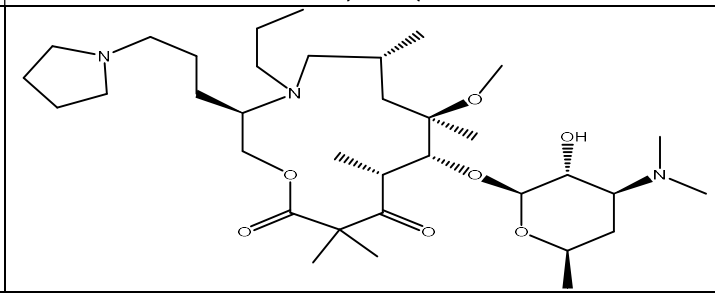
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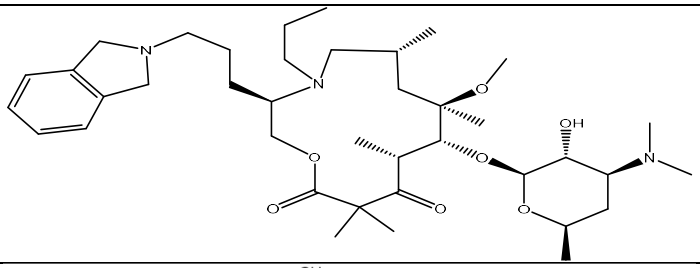
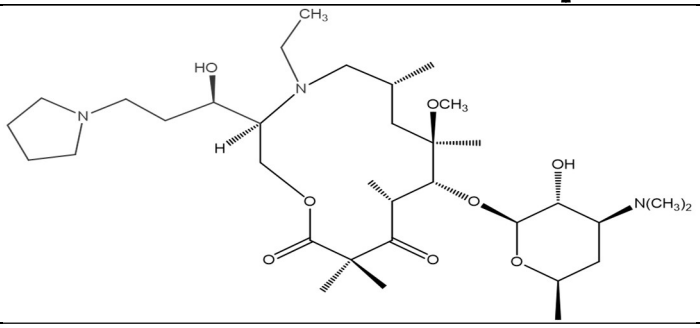
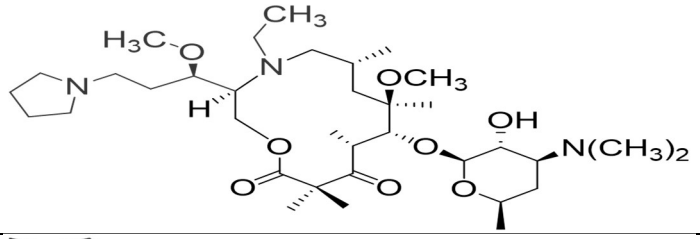
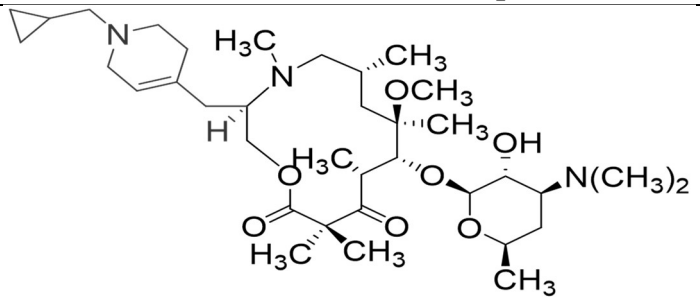
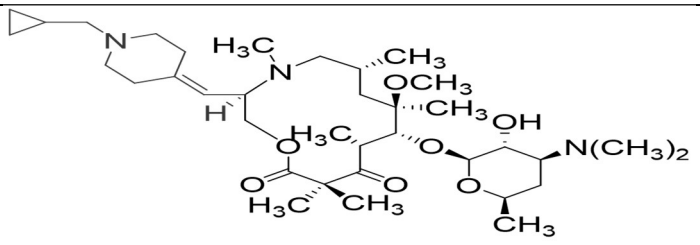
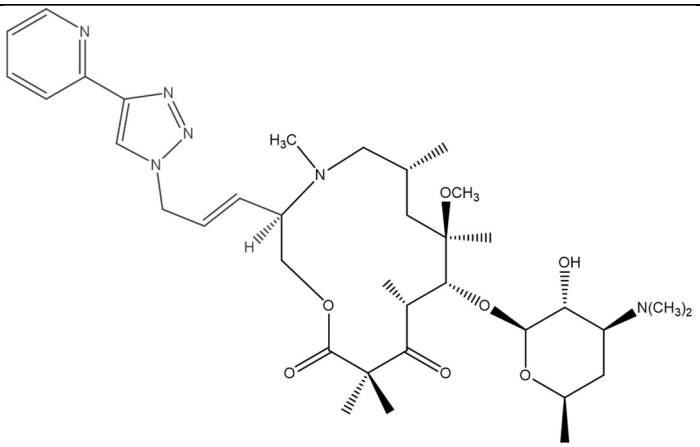
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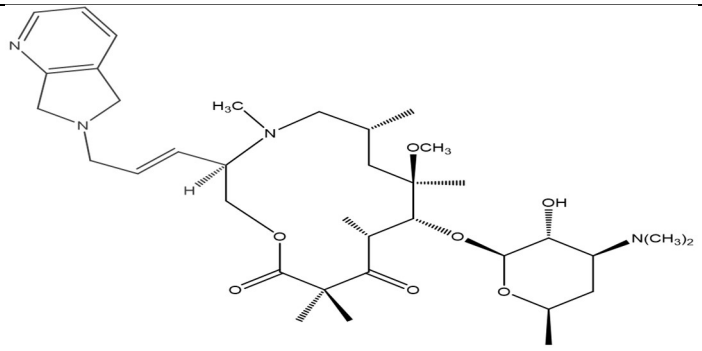
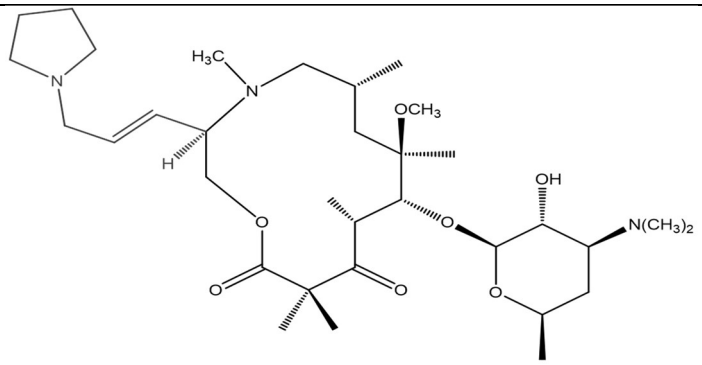
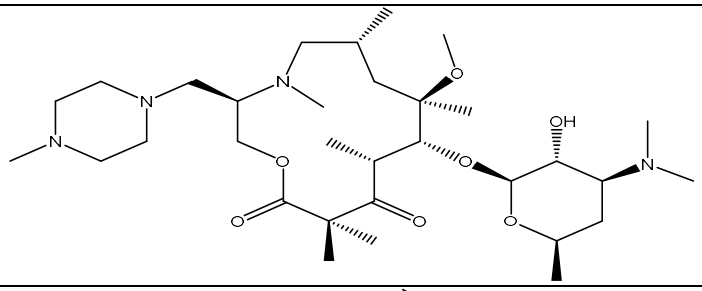
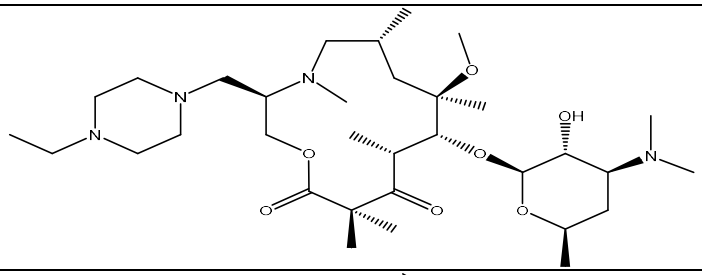
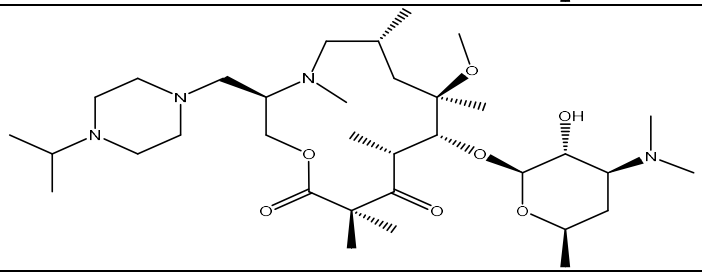
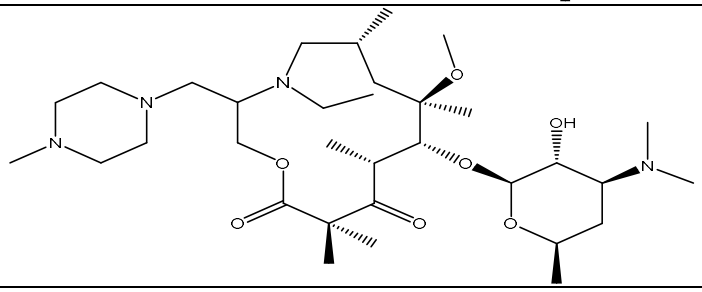
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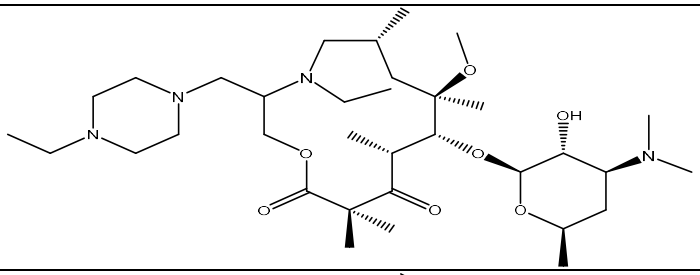
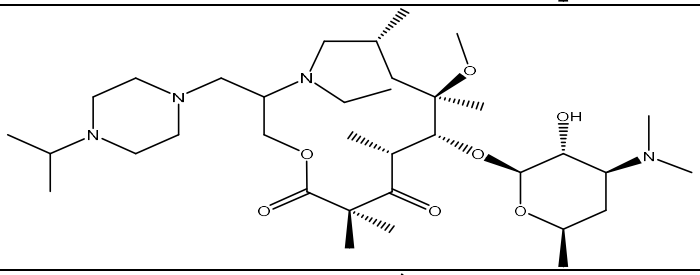
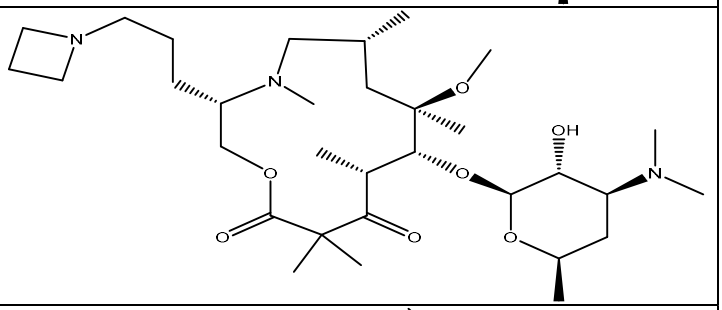
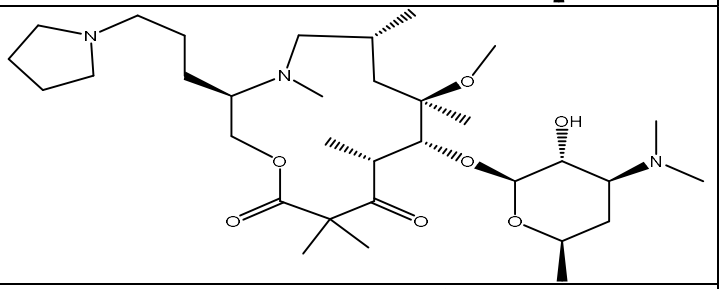
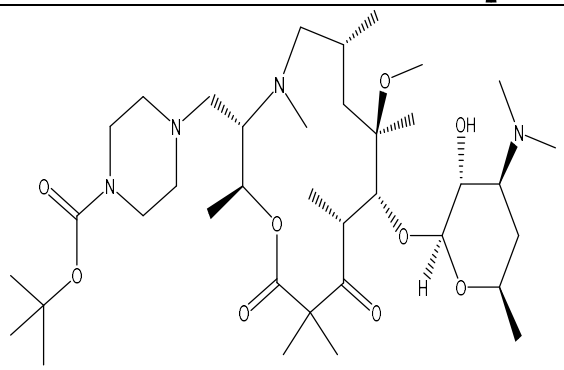
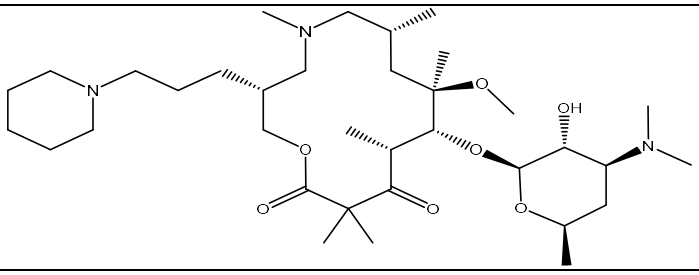
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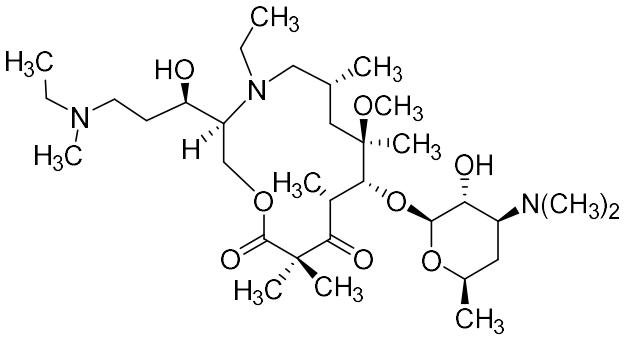
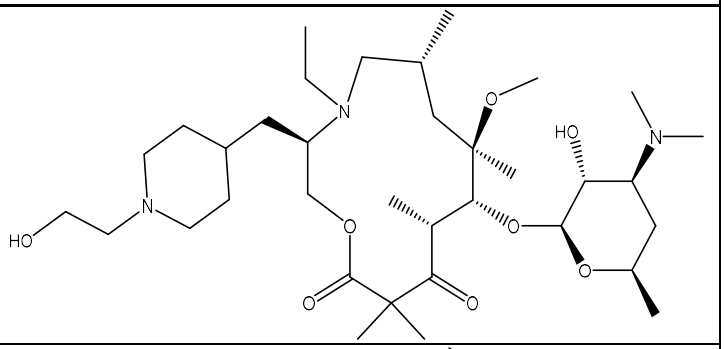
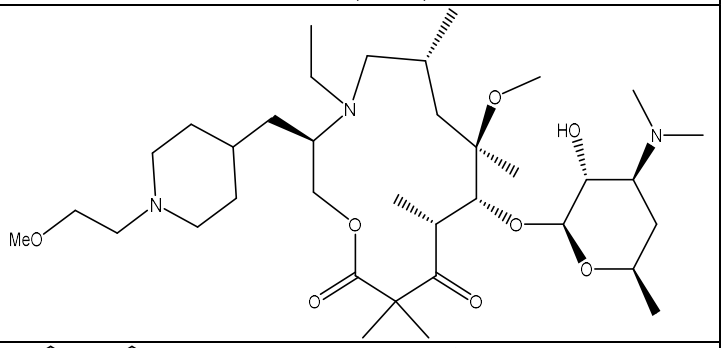
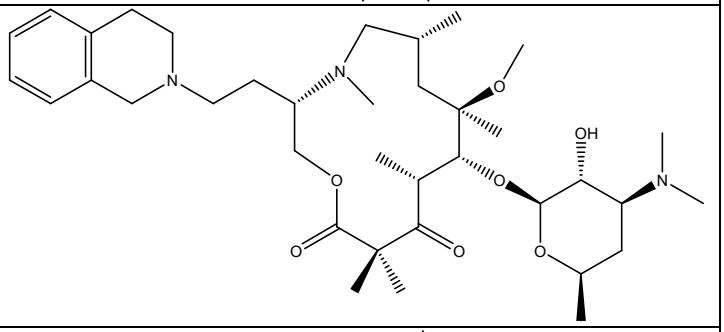
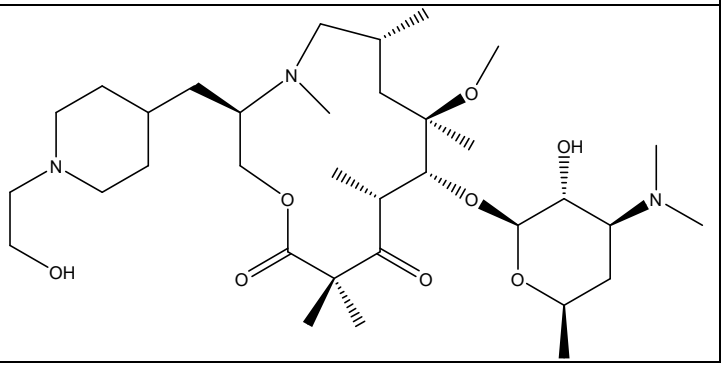
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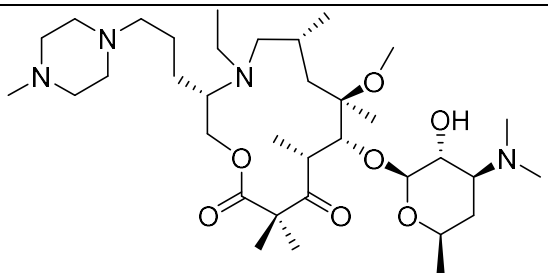
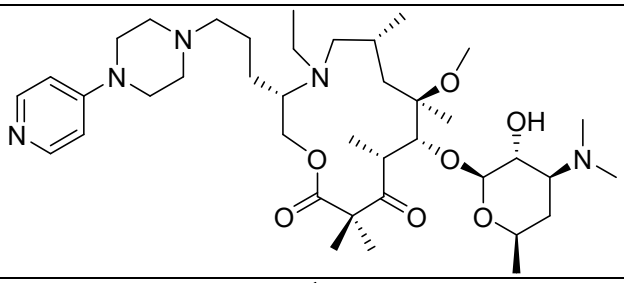
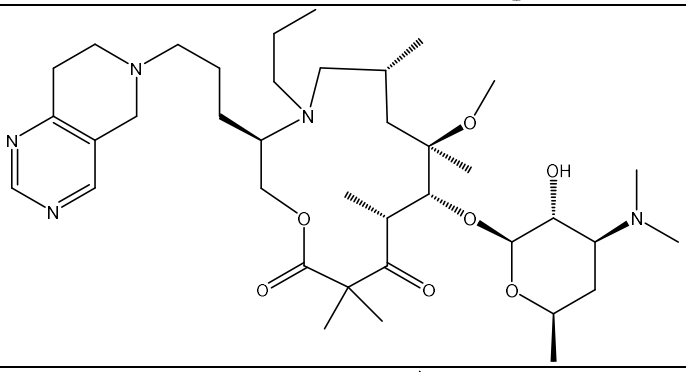
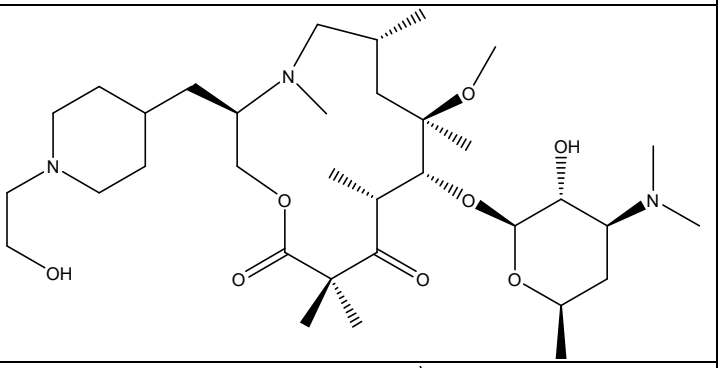
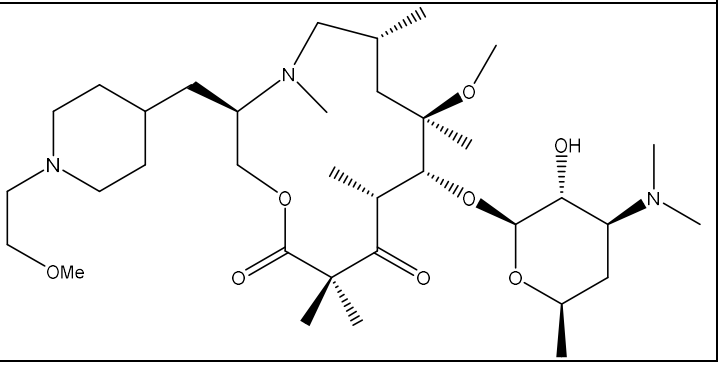
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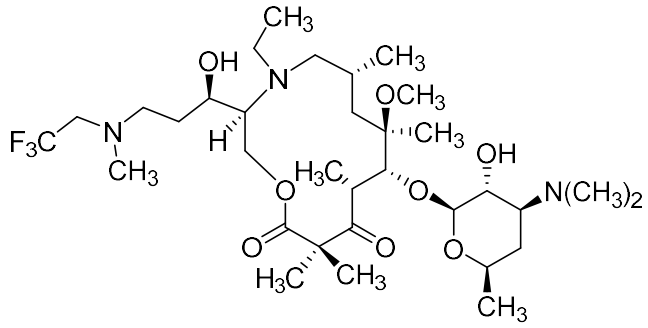
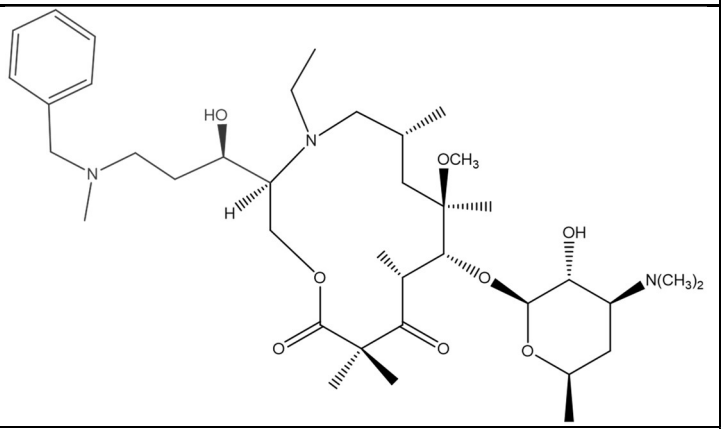
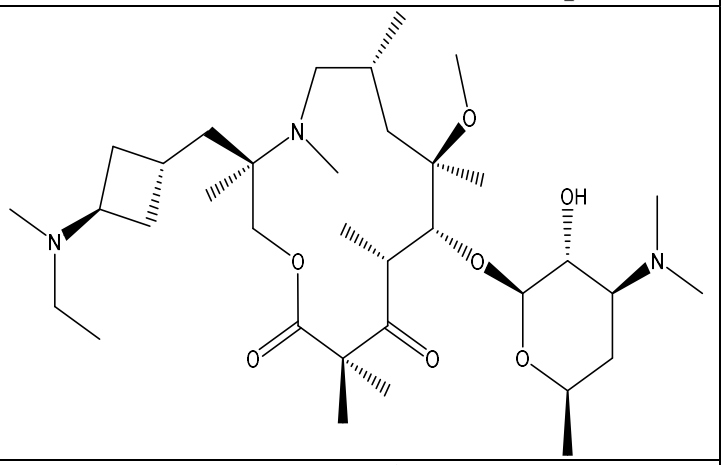
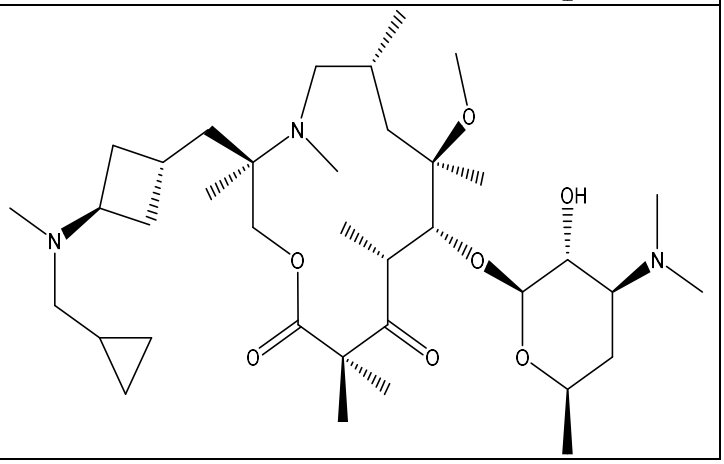
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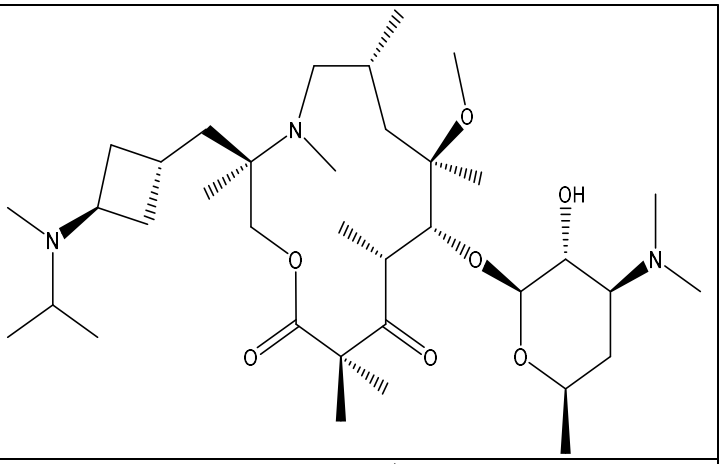
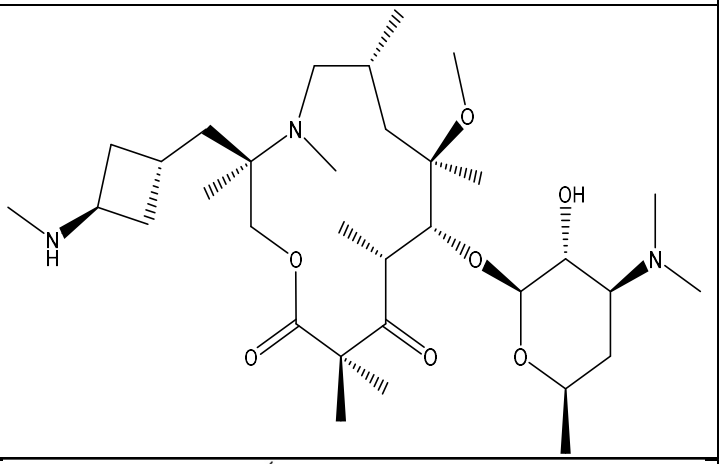
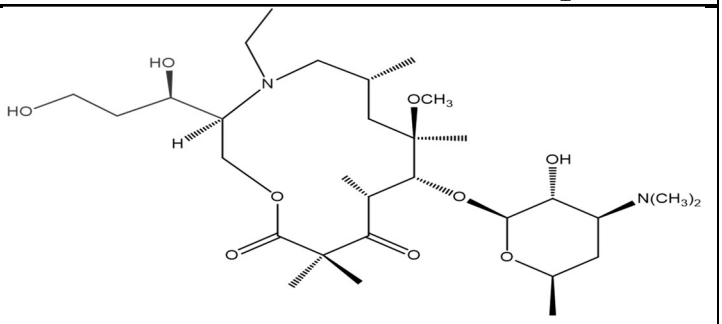
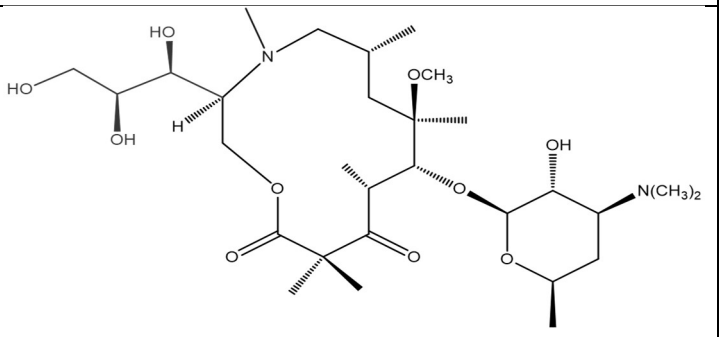
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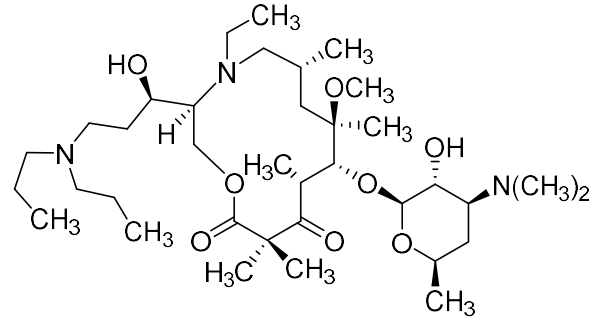
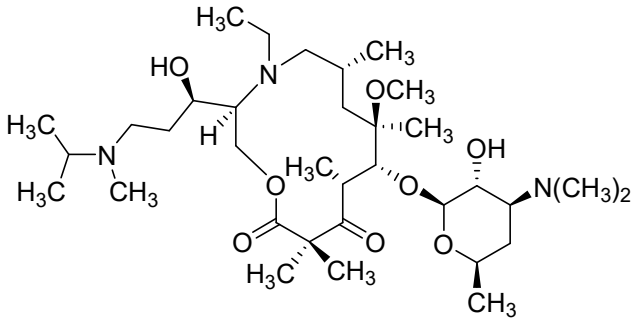
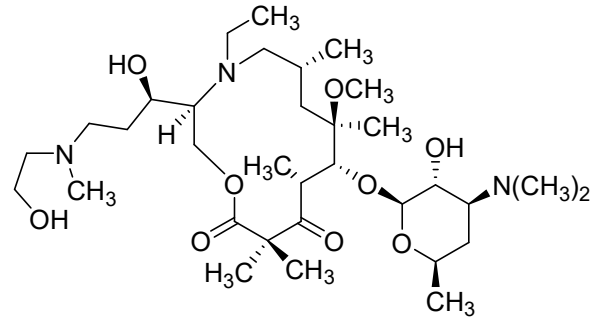
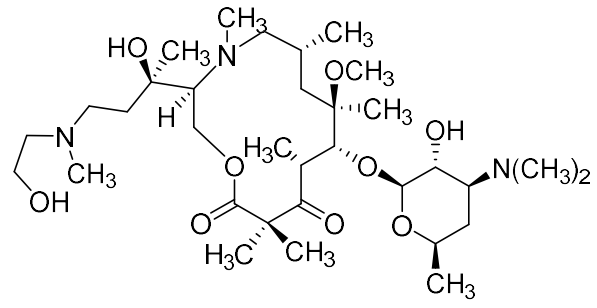
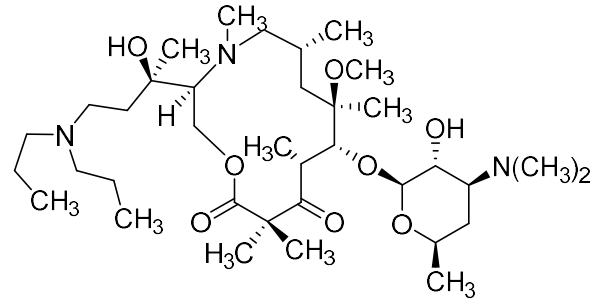
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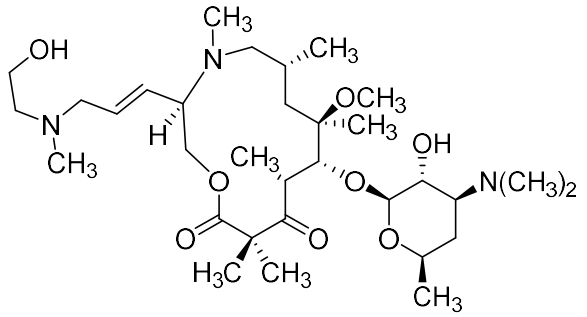
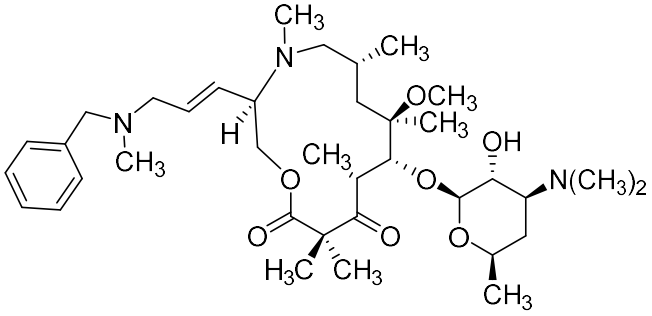
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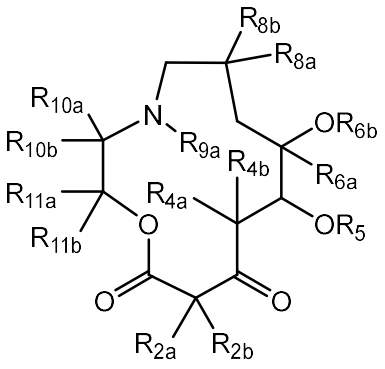
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or a pharmaceutically acceptable salt thereof.

[0006] Disclosed herein are compounds that are novel, synthetically accessible 13-membered macrolides. The compounds are novel antibiotics with unexpectedly potent antimicrobial activity.

[0007] In one example, the present disclosure provides compounds of Formula (**I**):



I

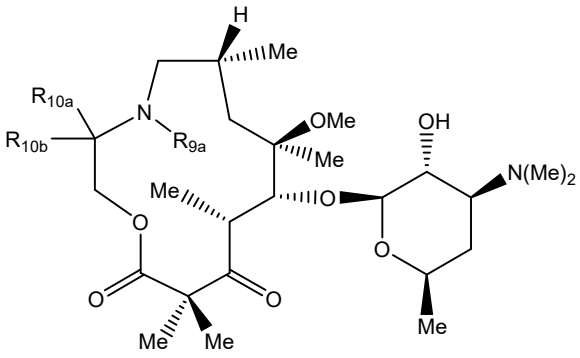
or a pharmaceutically acceptable salt thereof, wherein:

one of R_{2a} and R_{2b} is selected from the group consisting of H, halo, optionally substituted C_{1-10} alkyl, optionally substituted C_{1-10} alkoxy, and optionally substituted C_{1-10} alkenyl, wherein C_{1-10} alkyl, C_{1-10} alkoxy, and C_{1-10} alkenyl are optionally substituted with one or more groups selected from the group consisting of halo, aryl, amino, alkyl, heteroalkyl, heteroalkenyl, heterocycloalkyl, and heteroaryl; and

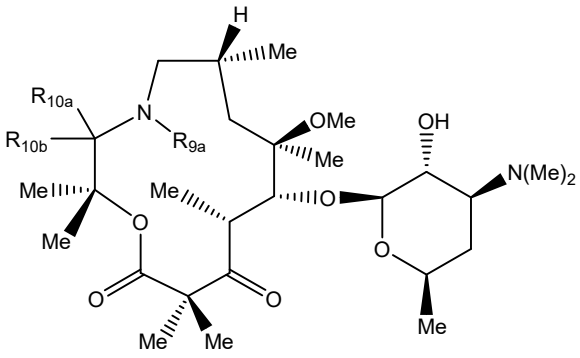
the other of R_{2a} and R_{2b} is selected from the group consisting of halo, optionally substituted C_{1-10} alkyl, optionally substituted C_{1-10} alkoxy, and optionally substituted C_{1-10} alkenyl, wherein C_{1-10} alkyl, C_{1-10} alkoxy, and C_{1-10} alkenyl are optionally substituted with one or more groups selected from the group consisting of halo, aryl, amino, substituted amino, alkyl, heteroalkyl, heteroalkenyl, heterocycloalkyl, and heteroaryl;

CLAIMS

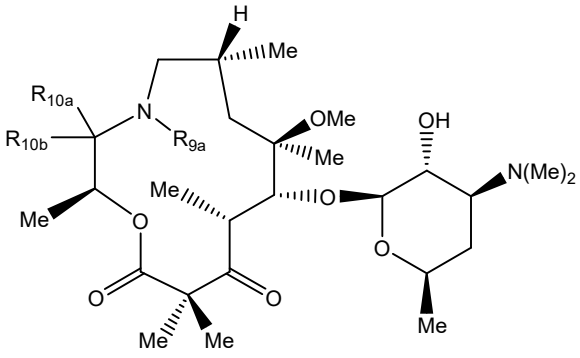
1. A compound of formula IIA, IIB, IIC, or IID:



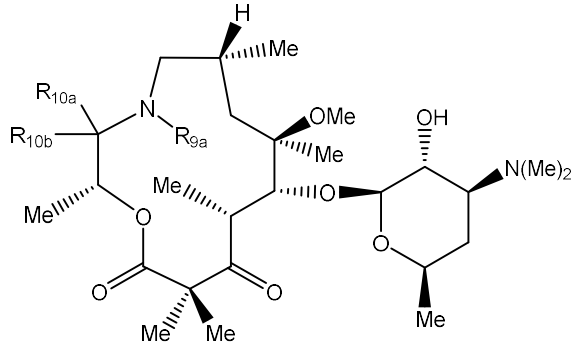
IIA;



IIB;



IIC;



IID;

or a pharmaceutically acceptable salt thereof, wherein:

R_{9a} is selected from the group consisting of H, optionally substituted C_{1-10} alkyl, hydroxyalkyl, optionally substituted C_{1-10} alkylene-$NR_TR_{T'}$, optionally substituted C_{1-10} alkylene-cycloalkyl-$NR_TR_{T'}$, and optionally substituted alkoxyalkyl; wherein R_T and $R_{T'}$ are each independently selected from the group consisting of H, optionally substituted alkyl, and optionally substituted C_{1-10} alkylene-heterocycloalkyl;

R_{10b} is selected from the group consisting of H and optionally substituted C_{1-10} alkyl; and

R_{10a} is selected from the group consisting of $-CO_2H$, $–CO_2$-optionally substituted alkyl, $–CON(R_{z'})(R_{z''})$, and optionally substituted C_{1-10} alkylene-R_{101}, C_{2-10} alkenylene-R_{101}, and C_{2-10} alkynylene-R_{101}; wherein

R_{101} is selected from the group consisting of (C_{1-6} alkyl)-S-, (C_{1-6} alkyl)-SO-, (C_{1-6} alkyl)-SO_2-, -OH, -O-alkyl, $-NR_xR_{x'}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R_x and $R_{x'}$ are each independently selected from the group consisting of -H, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocycloalkyl,

optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkylene-cycloalkyl, optionally substituted alkylene-heterocycloalkyl, optionally substituted alkylene-aryl, optionally substituted alkylene-heteroaryl, -C(=O)-alkyl, and -C(=O)-alkylene-$N(R_{y'})(R_{y''})$; or

R_x and $R_{x'}$ together with the atom to which they are attached form an optionally substituted 3-, 4-, 5-, 6-, or 7-membered ring optionally containing an additional heteroatom selected from the group consisting of O, S, SO, SO_2, NR_y, and N-C_1-C_{10} alkyl; and wherein:

each R_y is independently selected from the group consisting of H and optionally substituted C_{1-10} alkyl, and

$R_{z'}$ and $R_{z''}$ are each independently H or optionally substituted alkyl.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R_{10b} is H; and

(a) R_{10a} is an optionally substituted C_3 alkylene-R_{101}, or an optionally substituted C_2 alkylene-R_{101a1}; wherein

R_{101} is selected from the group consisting of -H, -OH, -O-alkyl, -$NR_xR_{x'}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R_{101a1} is selected from the group consisting of (C_{1-6} alkyl)-S-, (C_{1-6} alkyl)-SO-, (C_{1-6} alkyl)-SO_2-, -OH, -O-alkyl, -$NR_xR_{x'}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl, wherein

R_x and $R_{x'}$ are each independently selected from the group consisting of -H, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkylene-cycloalkyl, optionally substituted alkylene-heterocycloalkyl, optionally substituted alkylene-aryl, optionally substituted alkylene-heteroaryl, -C(=O)-alkyl, and -C(=O)-alkylene-$N(R_{y'})(R_{y''})$; or

R_x and $R_{x'}$ together with the atom to which they are attached form an optionally substituted 3-, 4-, 5-, 6-, or 7-membered ring optionally containing an additional heteroatom selected from the group consisting of O, S, SO, SO_2, NR_y, and N-C_1-C_{10} alkyl; and wherein:

each R_y is independently selected from the group consisting of H and optionally substituted C_{1-10} alkyl; or

(b) R_{10a} is R_{101a2}-CH_2-; and

R_{101a2} is $NR_xR_{x'}$, wherein R_x and $R_{x'}$ are each independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkylene-cycloalkyl, optionally substituted alkylene-heterocycloalkyl, optionally substituted alkylene-aryl, and optionally substituted alkylene-heteroaryl group and -C(=O)-alkylene-$N(R_{y'})(R_{y''})$; or

R_{101a2} is selected from the group consisting of optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; and wherein

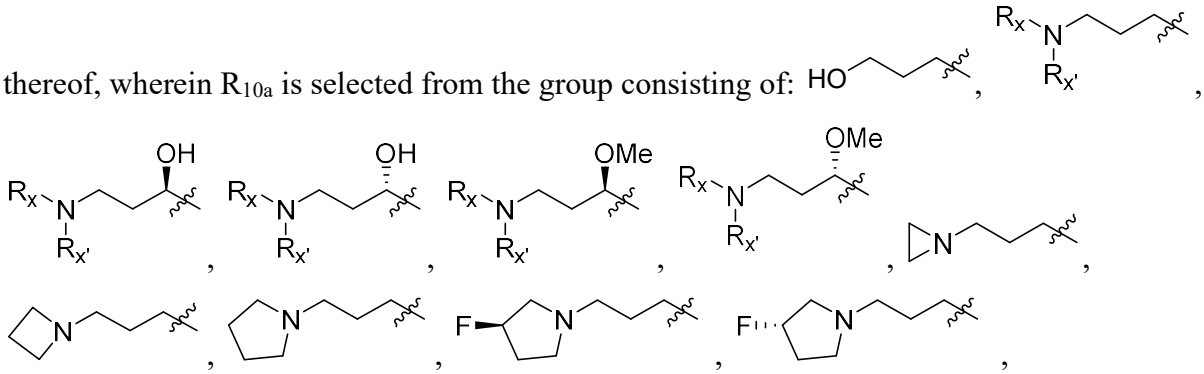
each R_y is independently selected from the group consisting of -H and optionally substituted $C_{1\text{-}10}$ alkyl.

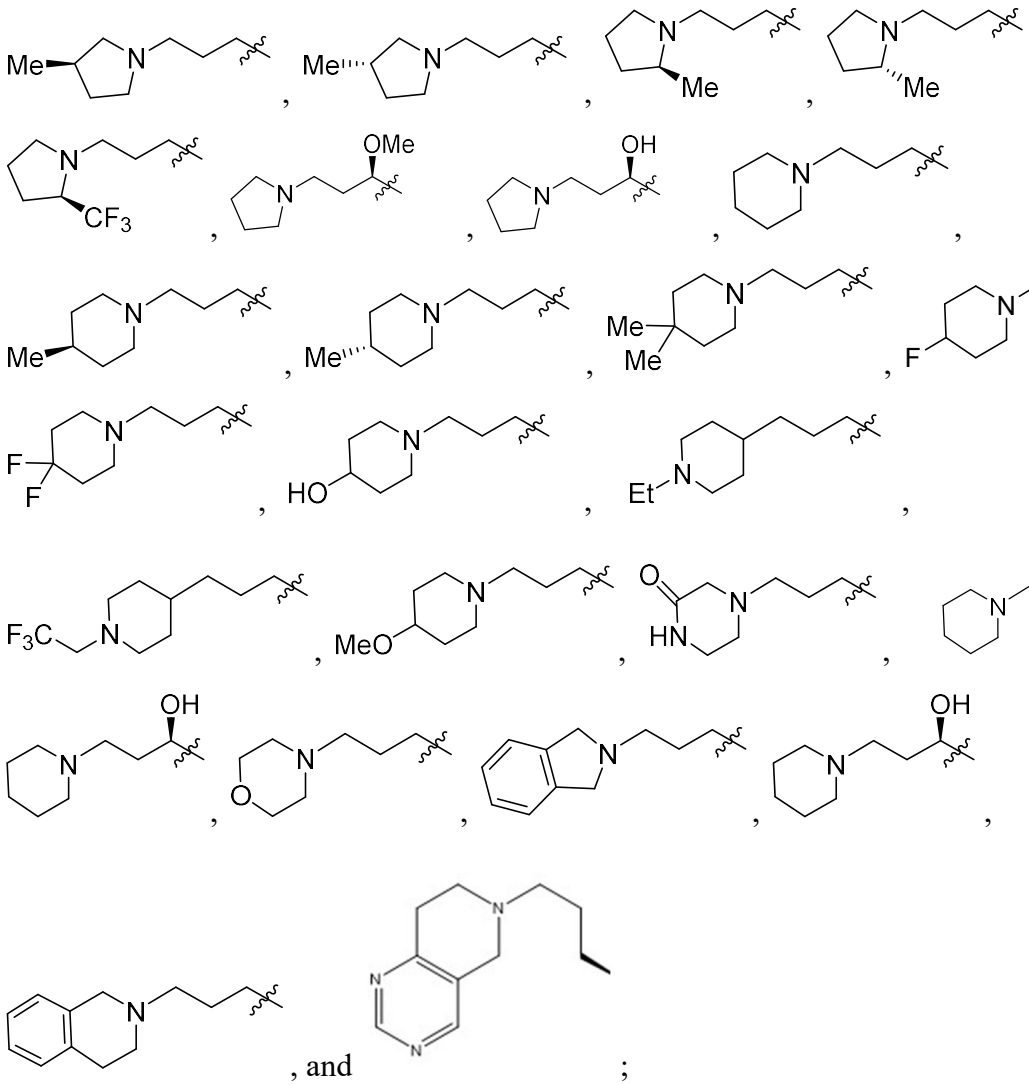
3. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein:

R_{10a} is selected from the group consisting of an optionally substituted R_{101}-$CH_2CH_2CH_2$-, optionally substituted R_{101}-CH_2CH_2CH-OH-, and optionally substituted R_{101}-CH_2CH_2CH-OMe- and

R_{101} is selected from the group consisting of -H, -OH, -O-alkyl, -N(Me)(Et), $-N(Me)_2$, -N(Me)(t-Bu), -N(Me)(iPr), -NH(Me), -NH(iPr), $-N(Et)_2$, -N(Me)(cyclopropyl), -NH(cyclopropyl), -N(Me)(cyclobutyl), -NH(cyclobutyl), -N(Me)(cyclopentyl), -NH(cyclopentyl), -N(Me)(cyclohexyl), -NH(cyclohexyl), optionally substituted aziridinyl, optionally substituted azetidinyl, optionally substituted pyrollidinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted morpholinyl, optionally substituted piperazinyl-2-one, optionally substituted tetrahydroisoquinolinyl, optionally substituted indolinyl, and optionally substituted isoindolinyl.

4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R_{10a} is selected from the group consisting of:



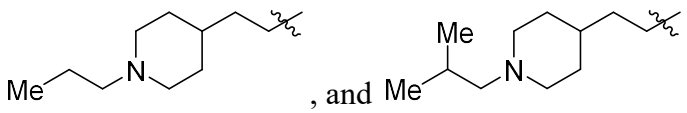


wherein

$NR_xR_{x'}$ is selected from the group consisting of -N(Me)(Et), -$N(Me)_2$, -N(Me)(t-Bu), -N(Me)(iPr), -NH(Me), -NH(iPr), -$N(Et)_2$, -N(Me)(cyclopropyl), -NH(cyclopropyl), -N(Me)(cyclobutyl), -NH(cyclobutyl), -N(Me)(cyclopentyl), -NH(cyclopentyl), -N(Me)(cyclohexyl), and -NH(cyclohexyl);

and wherein "〰" indicates a point of attachment.

5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R_{10a} is selected from the group consisting of: $MeSCH_2CH_2$-, $MeSOCH_2CH_2$-, $MeSO_2CH_2CH_2$-,



, and wherein "〰" indicates a point of attachment.

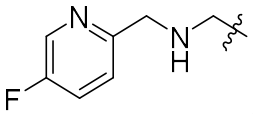
6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

R_{101a2} is selected from the group consisting of -NHR_z, and -$NMeR_z$, wherein:

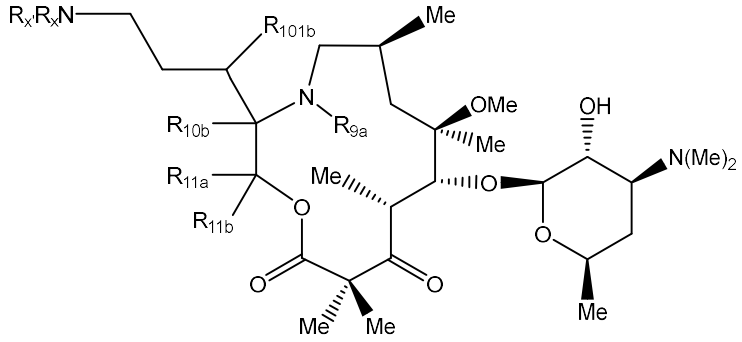
R_z is optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted –CH_2-cycloalkyl, optionally substituted –CH_2-heterocycloalkyl, optionally substituted –CH_2-aryl, optionally substituted –CH_2-heteroaryl, –(C=O)-cycloalkyl or –(C=O)-alkylene-$NR_{Z'}R_{Z''}$; wherein $R_{z'}$ and $R_{z''}$ are each independently H or alkyl; or

R_z is –optionally substituted alkylene-$R_{101a2'}$, wherein $R_{101a2'}$ is optionally substituted heteroaryl.

7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein:

R_{101a2}-CH_2- is selected from -CH_2NHMe, -$CH_2N(Me)_2$, -$CH_2N(Me)$(cyclopropyl), -CH_2NH(oxetanyl), -CH_2NHCH_2(cyclopropyl), or , wherein " ~~~ " indicates a point of attachment.

8. The compound of claim 1, which is a compound of formula III:



III

or a pharmaceutically acceptable salt thereof, wherein:

R_{101b} is -H, methyl, or methoxy;

R_{10b} is -H;

R_{11a} and R_{11b} are independently selected from the group consisting of -H and methyl;

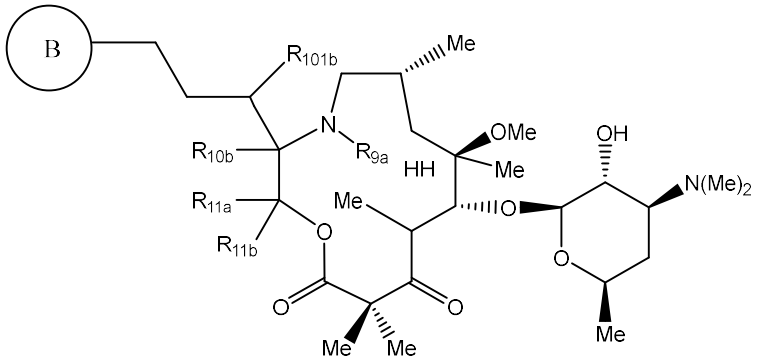
R_x and $R_{x'}$ are each independently selected from the group consisting of -H, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkylene-cycloalkyl, optionally substituted alkylene-heterocycloalkyl, optionally substituted alkylene-aryl, optionally substituted alkylene-heteroaryl, -C(=O)-alkyl, and -C(=O)-alkylene-$N(R_y)_2$; or

R_x and $R_{x'}$ together with the atom to which they are attached form an optionally substituted 3-, 4-, 5-, 6-, or 7-membered ring optionally containing an additional heteroatom selected from the group consisting of O, S, SO, SO_2, NR_y, and N-C_1-C_{10} alkyl; and wherein

each R_y is independently selected from the group consisting of -H and optionally substituted $C_{1\text{-}10}$ alkyl.

9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein $NR_xR_{x'}$ is selected from the group consisting of -N(Me)(Et), -$N(Me)_2$, -N(Me)(t-Bu), -N(Me)(iPr), -NH(Me), -NH(iPr), -$N(Et)_2$, -N(Me)(cyclopropyl), -NH(cyclopropyl), -N(Me)(cyclobutyl), -NH(cyclobutyl), -N(Me)(cyclopentyl), -NH(cyclopentyl), -N(Me)(cyclohexyl), and NH(cyclohexyl).

10. The compound of claim 1, which is a compound of formula IV:



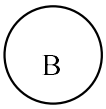
IV

or a pharmaceutically acceptable salt thereof, wherein:

R_{101b} is -H, methyl, or methoxy;

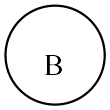
R_{10b} is -H;

R_{11a} and R_{11b} are independently selected from the group consisting of -H and methyl; and



is selected from the group consisting of optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl.

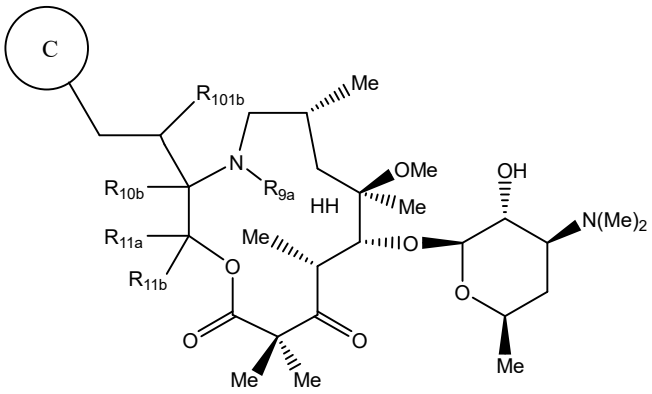
11. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein



is selected from the group consisting of optionally substituted aziridinyl, optionally

substituted azetidinyl, optionally substituted pyrollidinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted morpholinyl, optionally substituted piperazinyl-2-one, optionally substituted tetrahydroisoquinolinyl, optionally substituted indolinyl, and optionally substituted isoindolinyl.

12. The compound of claim 1, which is a compound of formula V:



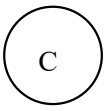
V

or a pharmaceutically acceptable salt thereof, wherein:

R_{101b} is -H, methyl, or methoxy;

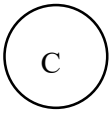
R_{10b} is -H;

R_{11a} and R_{11b} are independently selected from the group consisting of -H and methyl; and



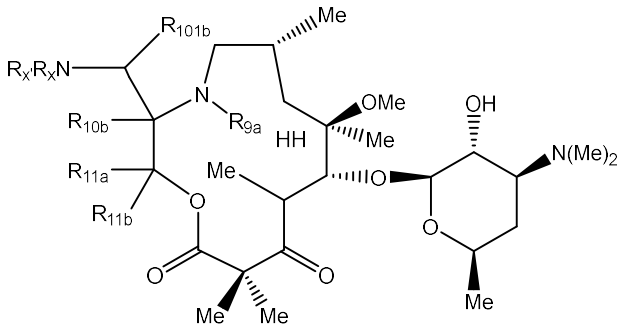
is selected from the group consisting of optionally substituted heterocycloalkyl.

13. The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein



is optionally substituted piperidinyl.

14. The compound of claim 1, which is a compound of formula VI:



VI

or a pharmaceutically acceptable salt thereof, wherein:

R_{101b} is -H;

R_{10b} is -H;

R_{11a} and R_{11b} are independently selected from the group consisting of -H and methyl; and

R_x and $R_{x'}$ are each independently selected from the group consisting of -H, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkylene-cycloalkyl, optionally substituted alkylene-heterocycloalkyl, optionally substituted alkylene-aryl, optionally substituted alkylene-heteroaryl, -C(=O)-alkyl, and -C(=O)-alkylene-$N(R_{y'})(R_{y''})$; or

R_x and $R_{x'}$ together with the atom to which they are attached form an optionally substituted 3-, 4-, 5-, 6-, or 7-membered ring optionally containing an additional heteroatom selected from the group consisting of O, S, SO, SO_2, NR_y, and N-C_1-C_{10} alkyl; and wherein

each R_y is independently selected from the group consisting of -H and optionally substituted C_{1-10} alkyl; or

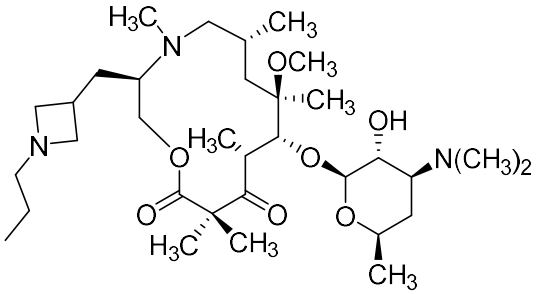
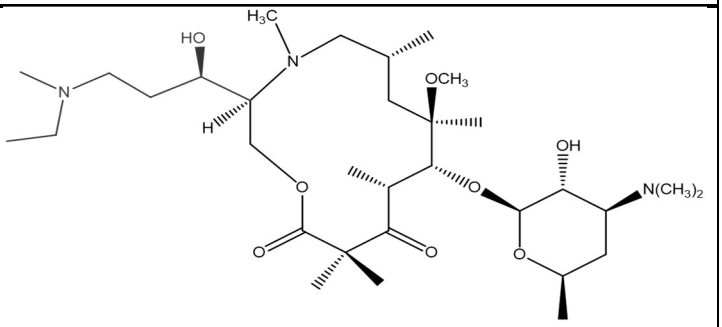
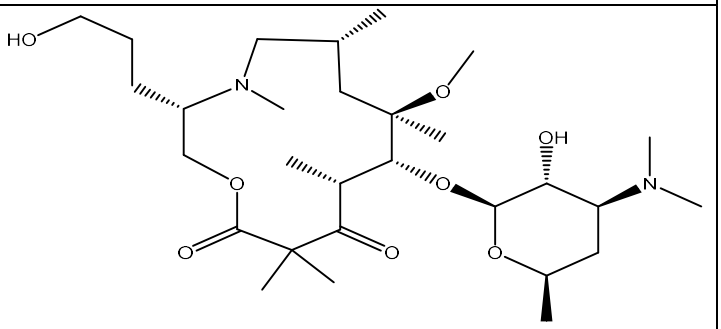
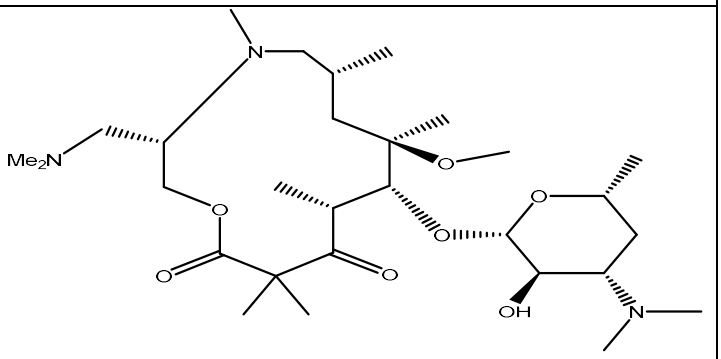
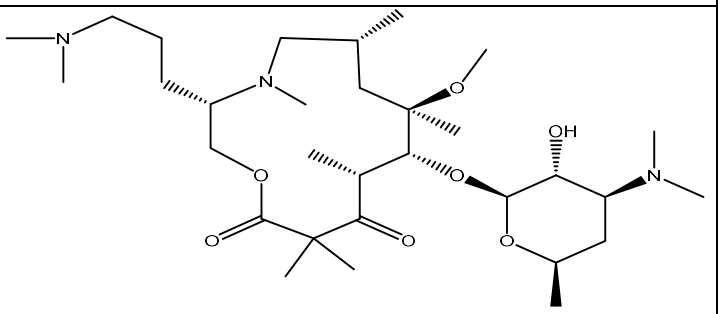
one of R_x and $R_{x'}$ is -H or alkyl and the other is R_z, wherein

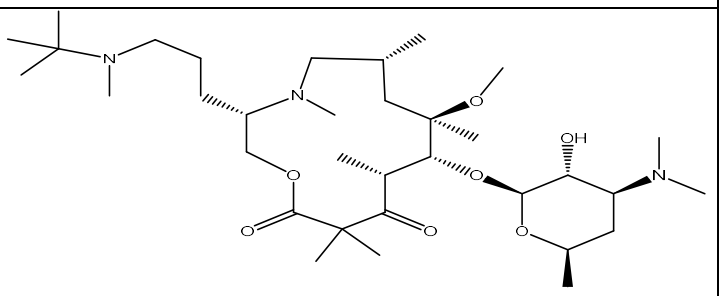
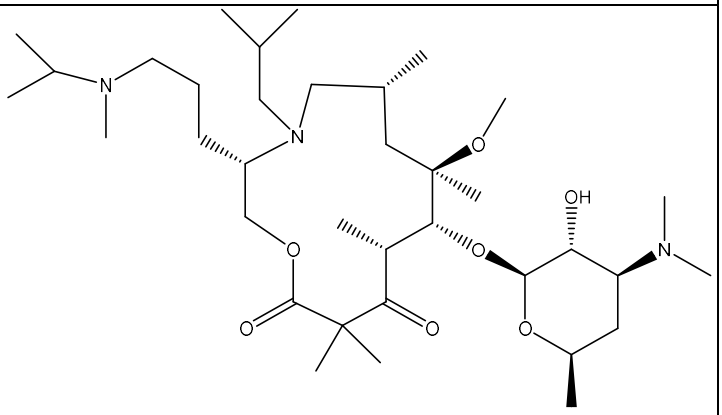
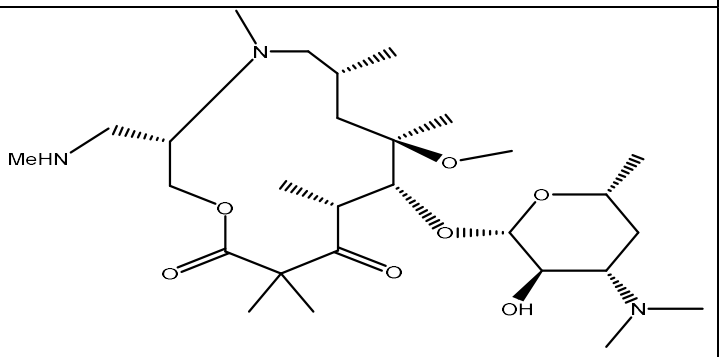
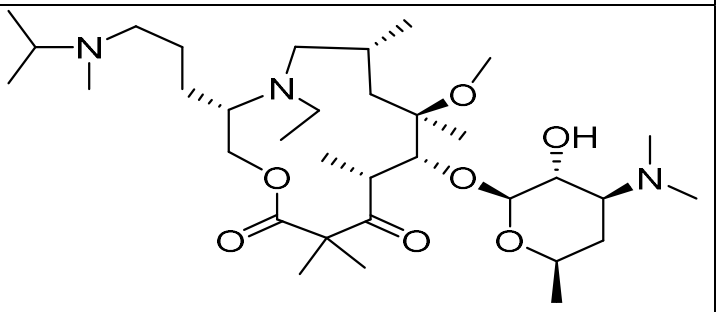
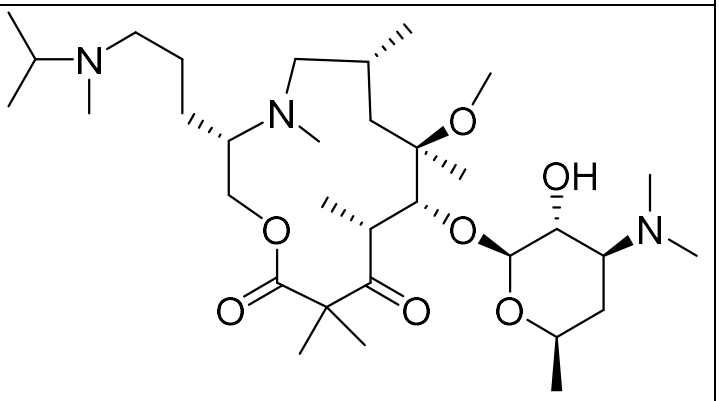
R_z is –(C=O)-cycloalkyl or –(C=O)-alkylene-$NR_{z''}R_{z'''}$; wherein $R_{z''}$ and $R_{z'''}$ are each independently -H or alkyl; or

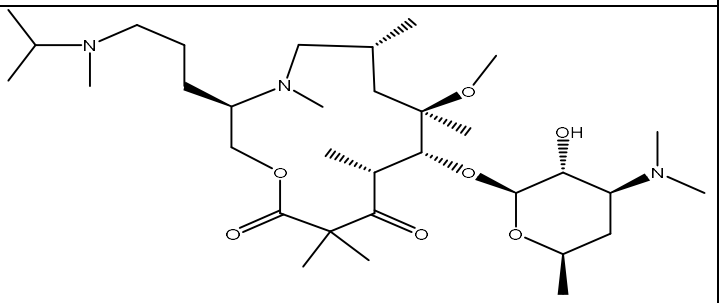
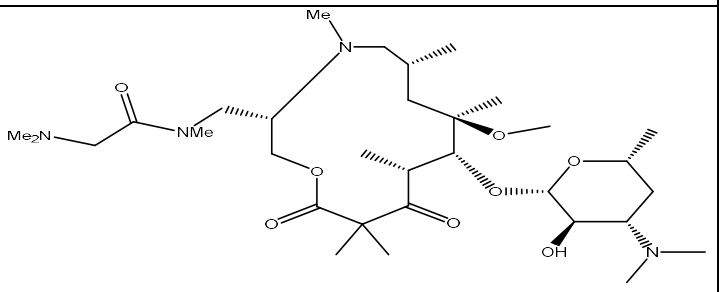
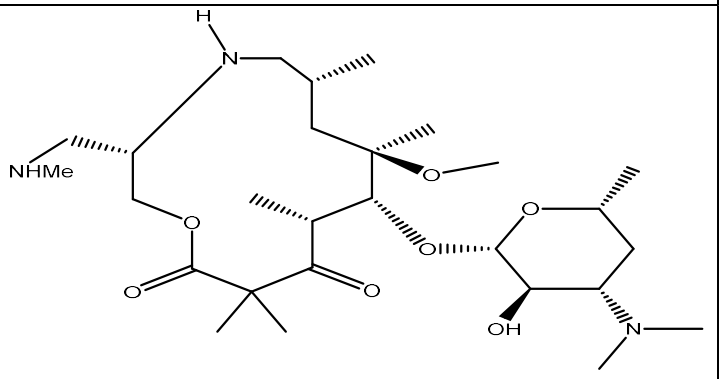
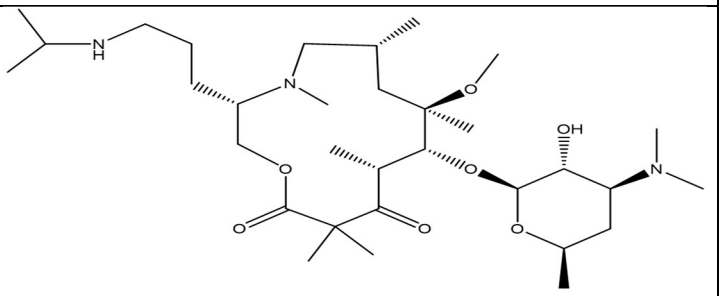
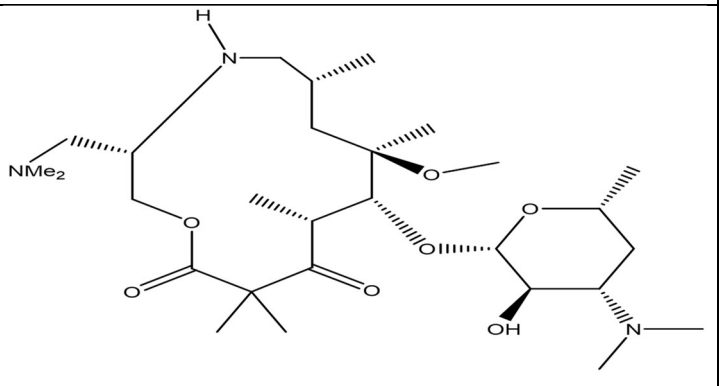
R_z is –alkylene-R_{101a} wherein R_{101a} is optionally substituted heteroaryl.

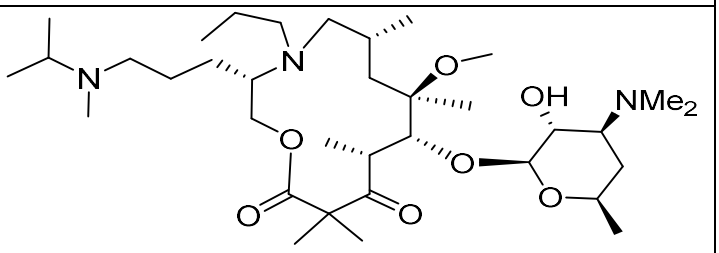
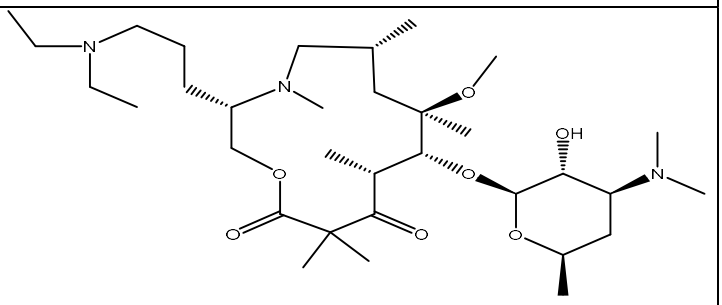
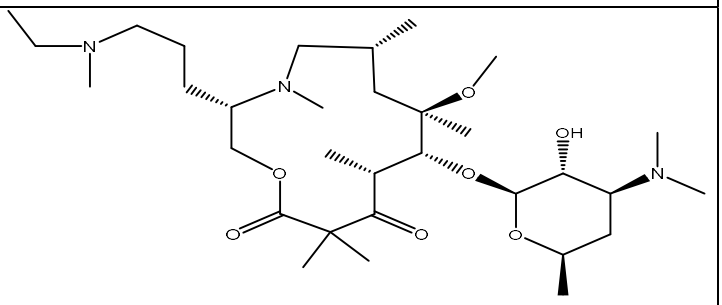
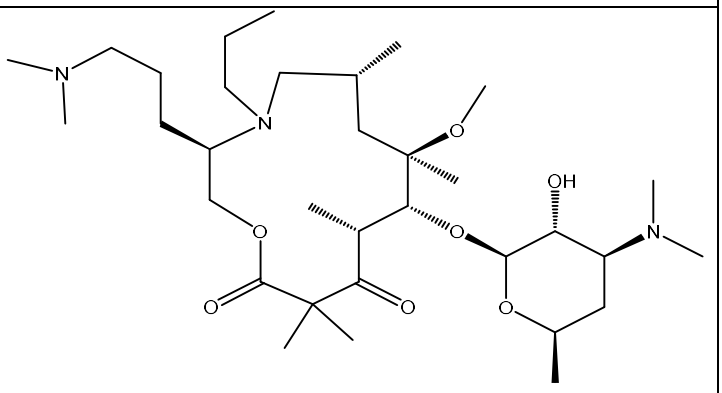
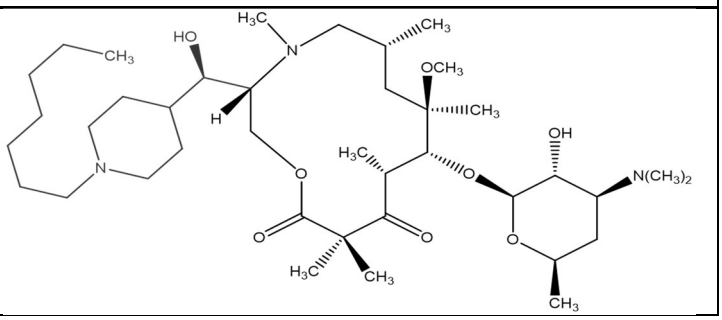
15. The compound of any of claims 7 to 14, or a pharmaceutically acceptable salt thereof, wherein R_{9a} is -H or C_{1-4} alkyl; R_{10b} is H; and R_{11a} and R_{11b} are each independently H or methyl.

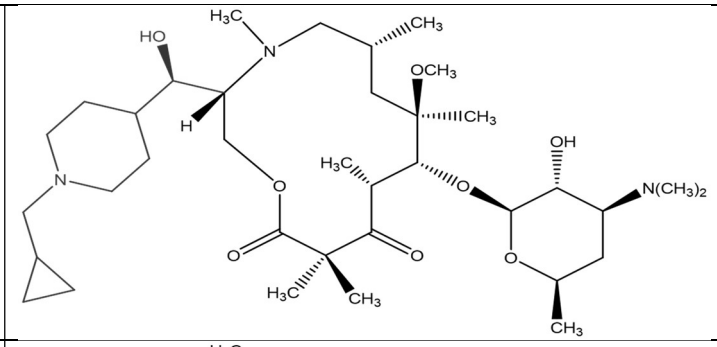
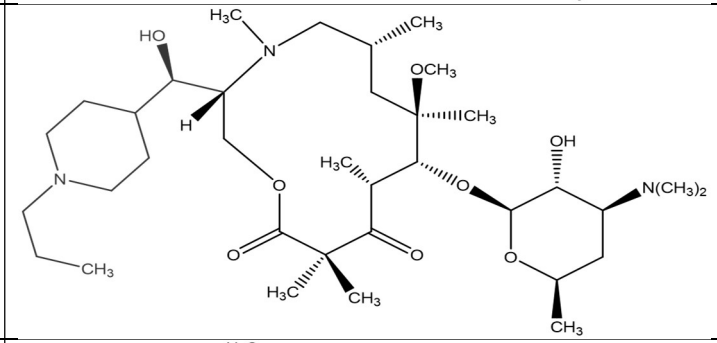
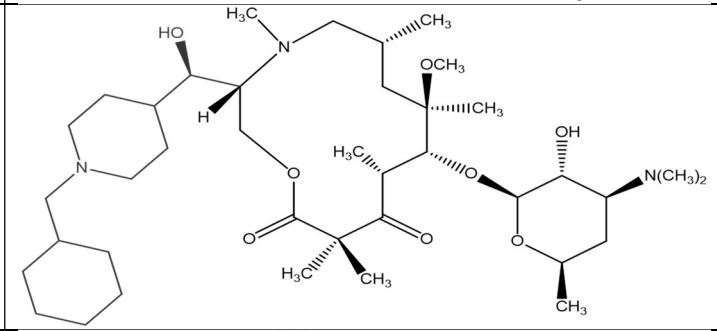
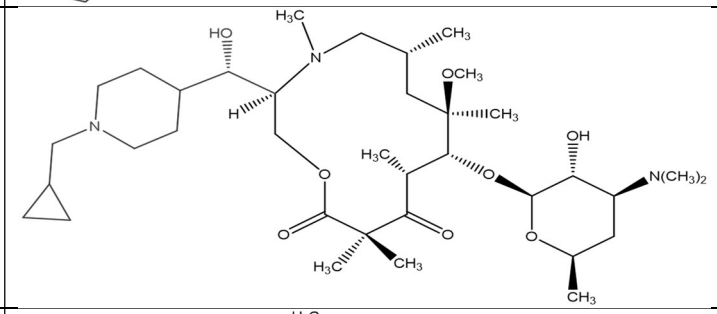
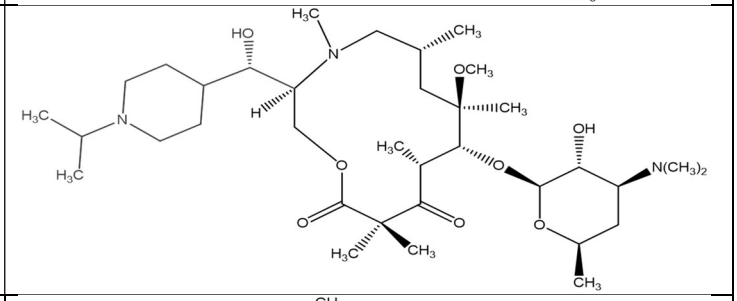
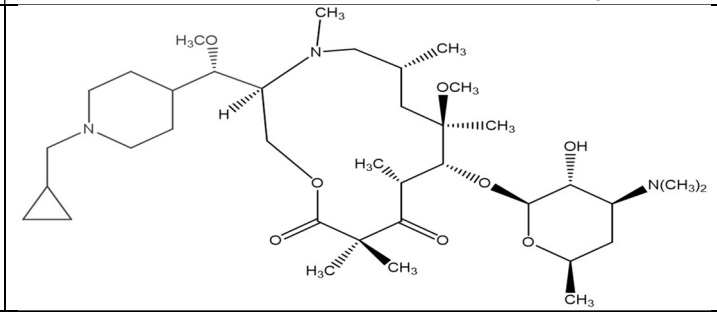
16. A compound which is selected from:

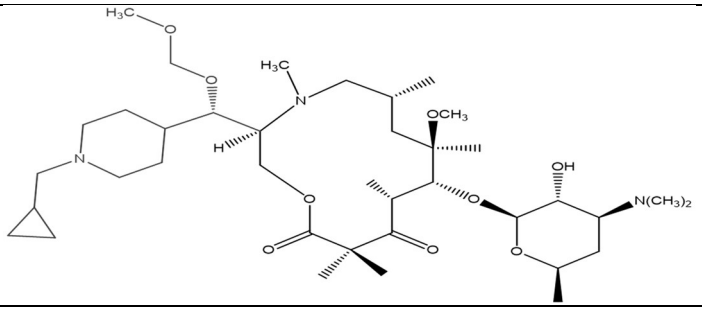
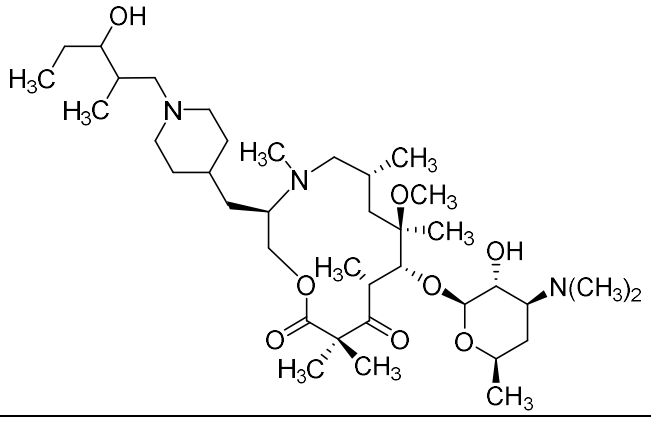
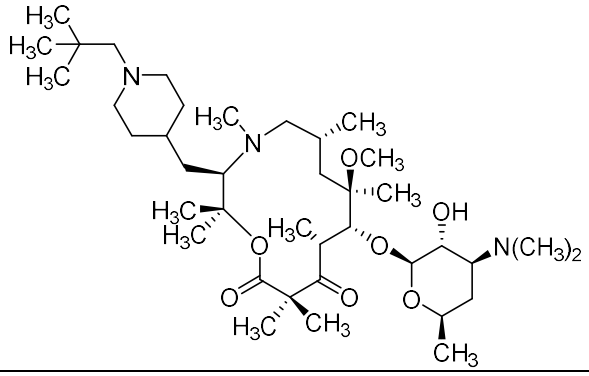
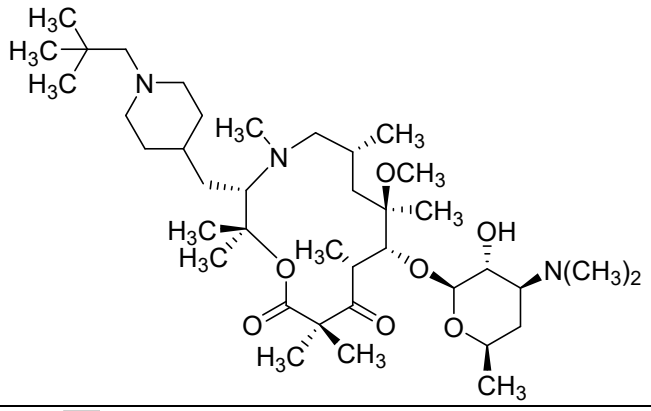
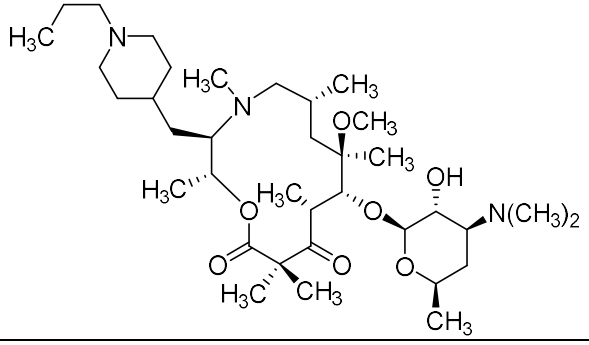
Compound #	Structure
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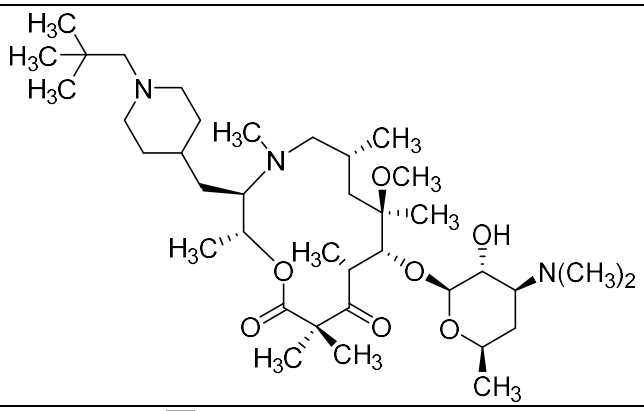
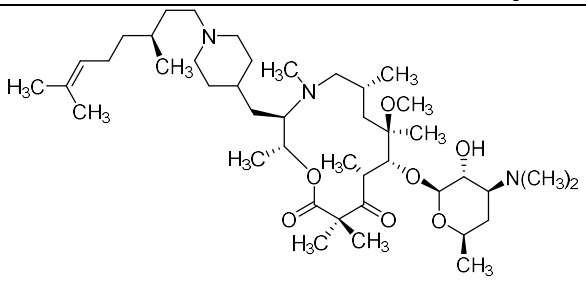
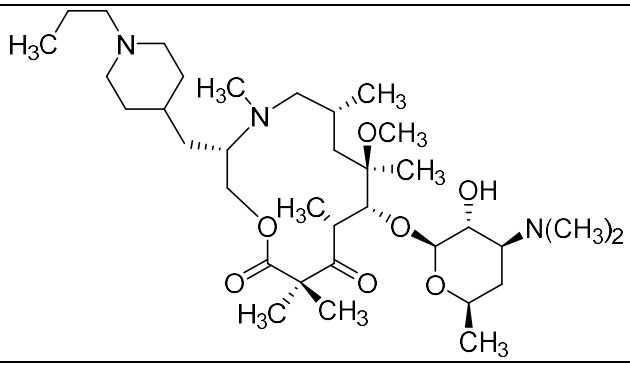
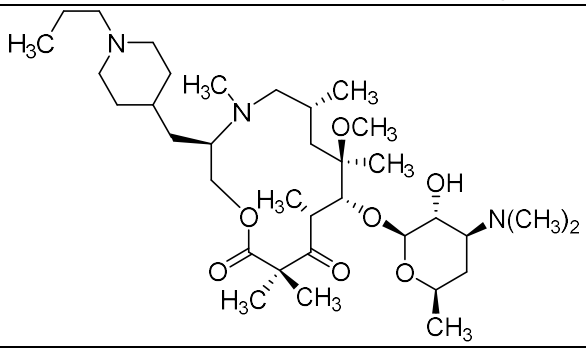
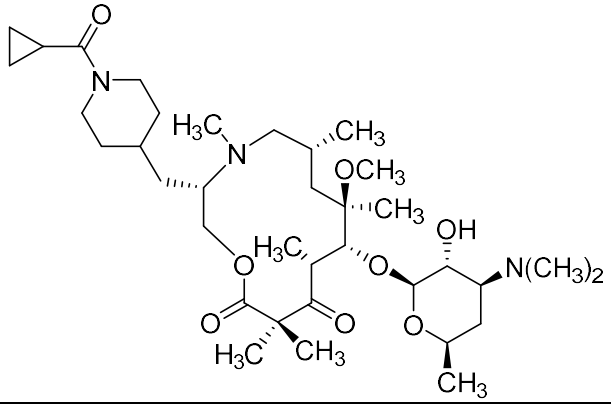
Compound #	Structure
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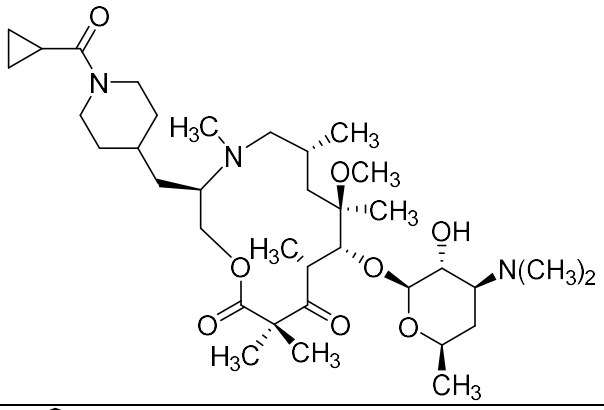
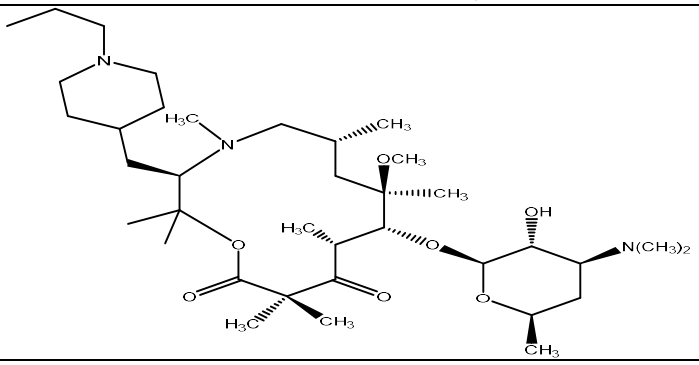
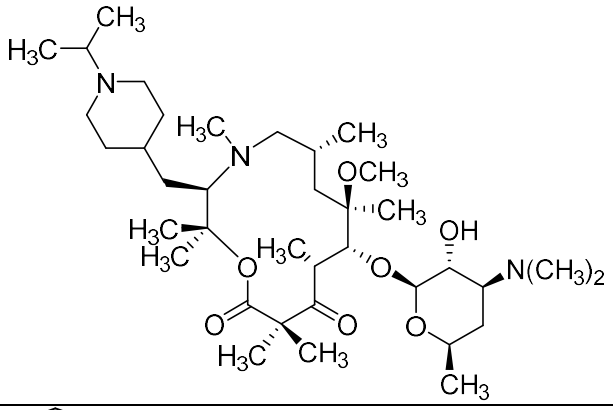
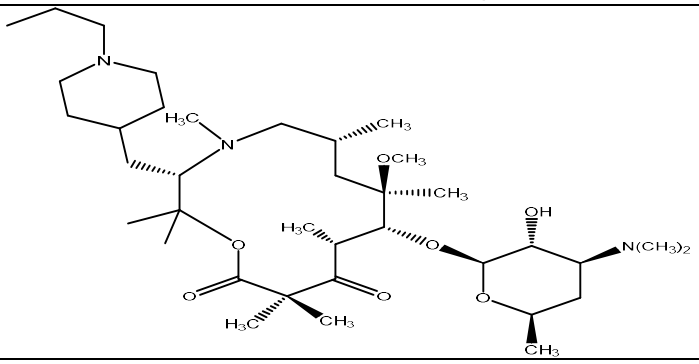
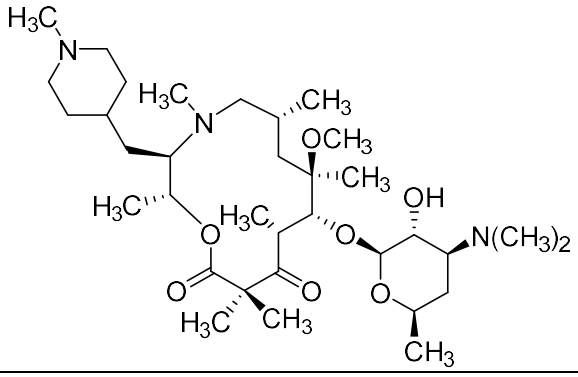
Compound #	Structure
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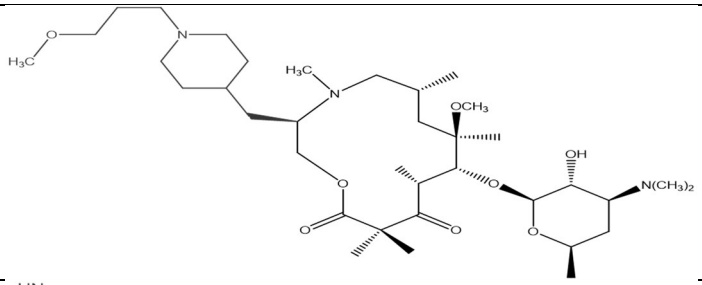
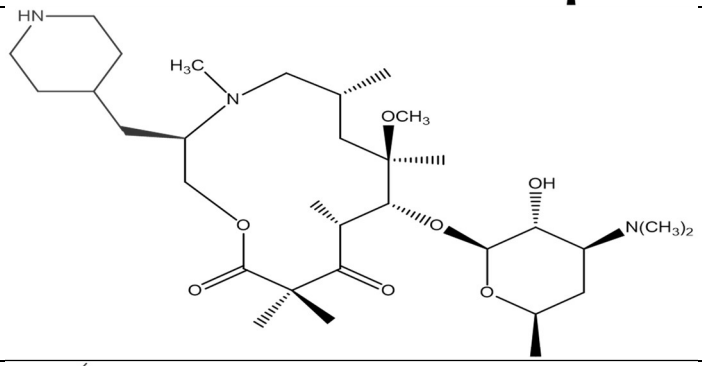
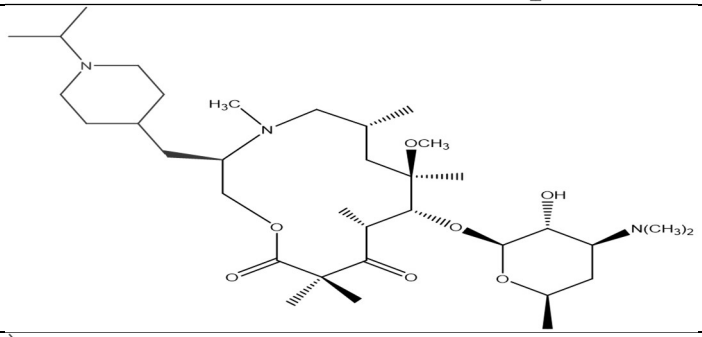
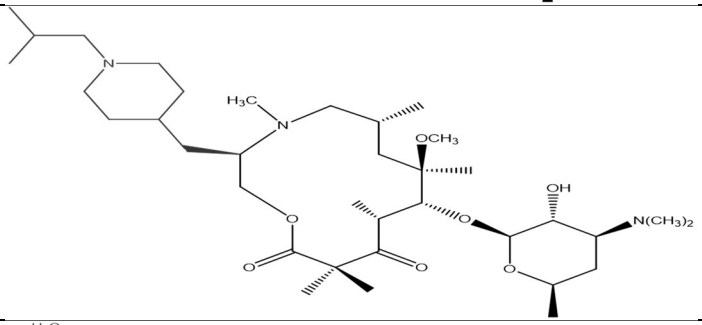
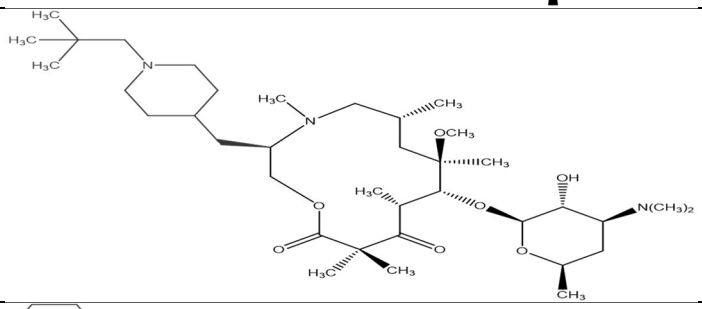
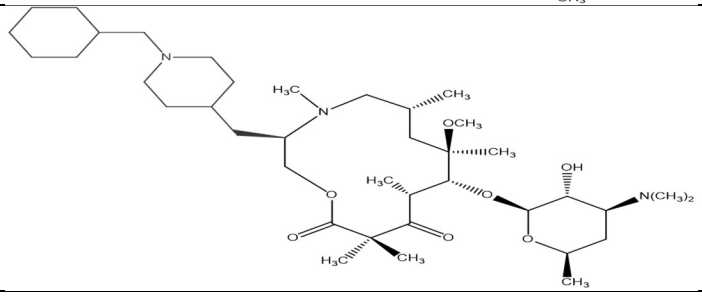
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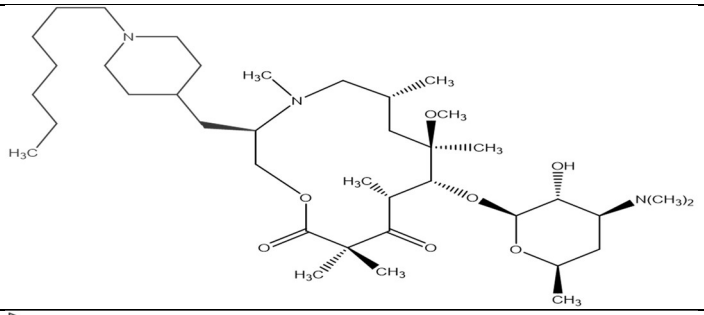
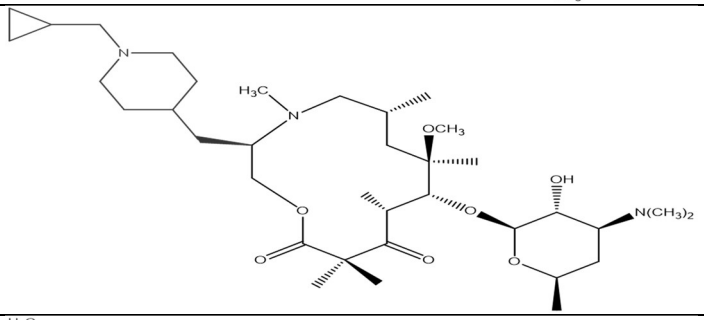
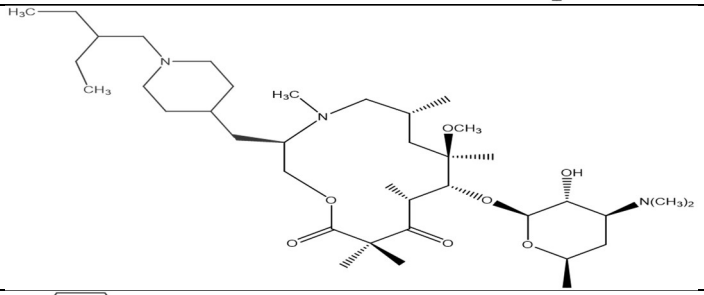
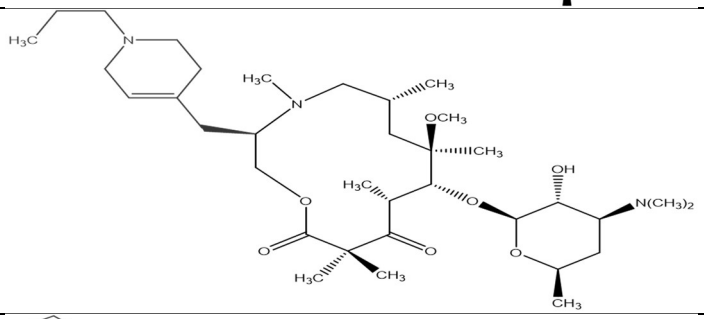
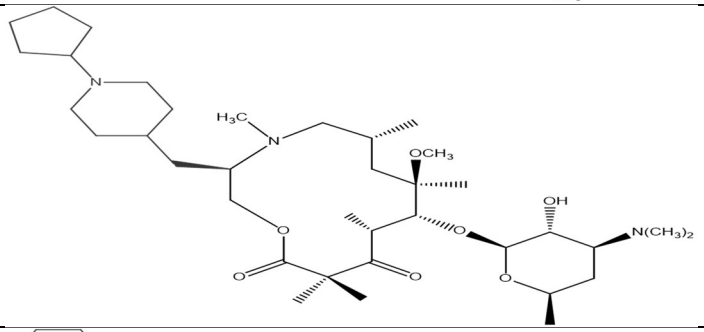
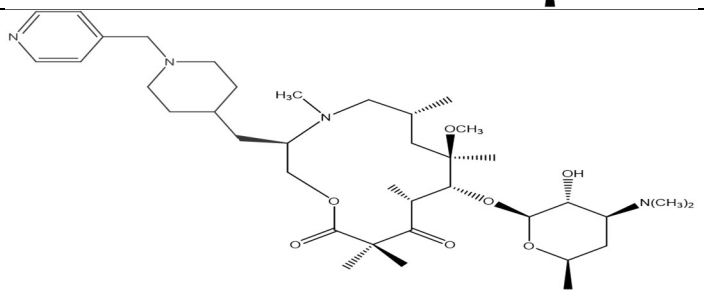
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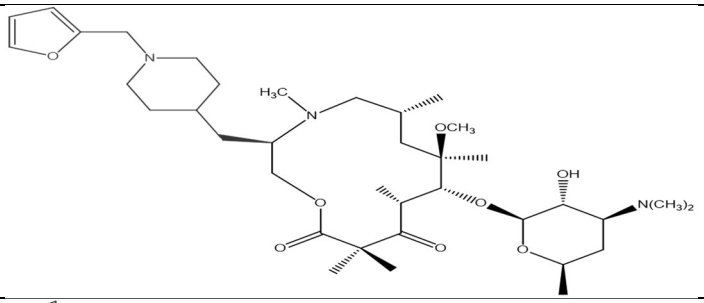
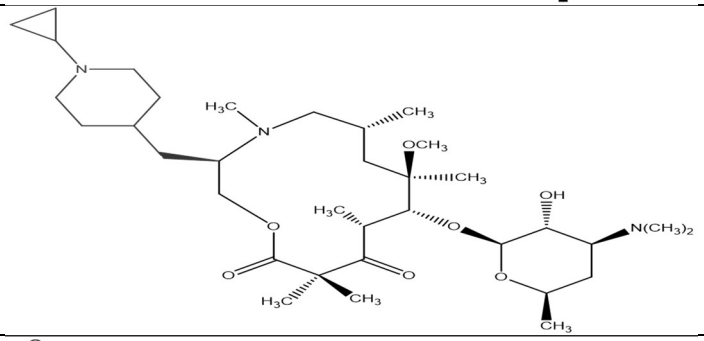
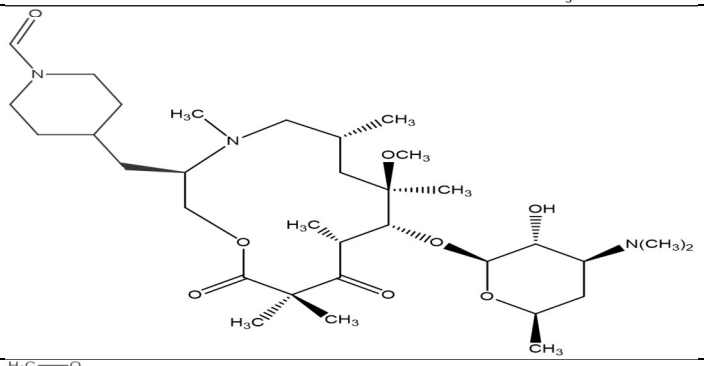
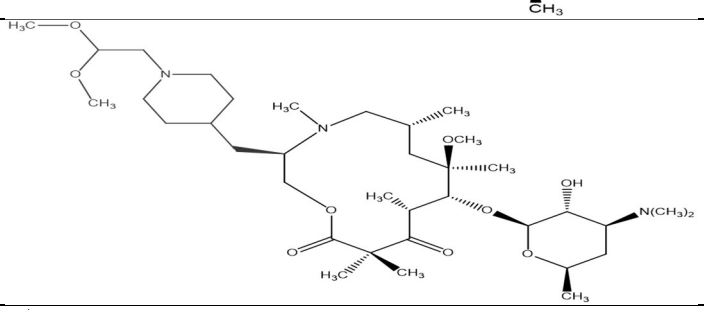
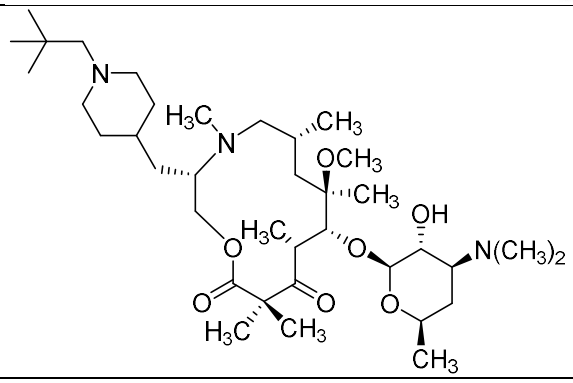
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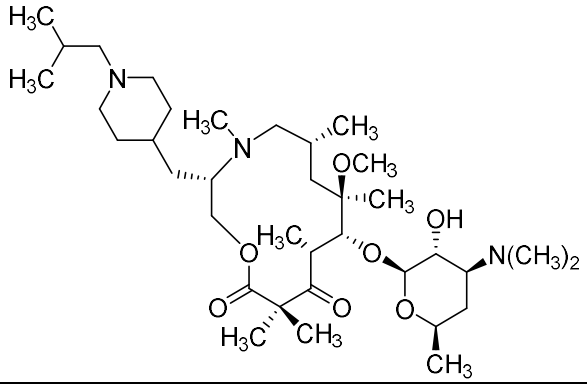
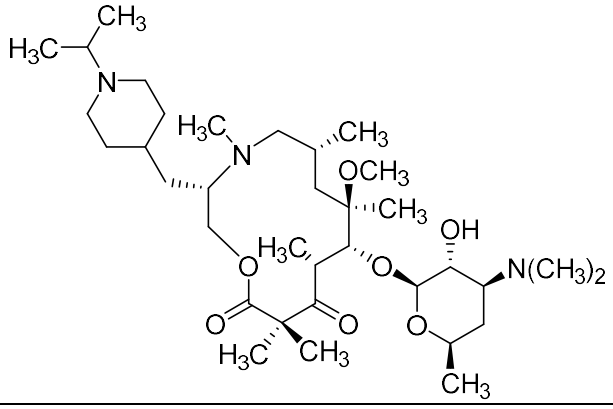
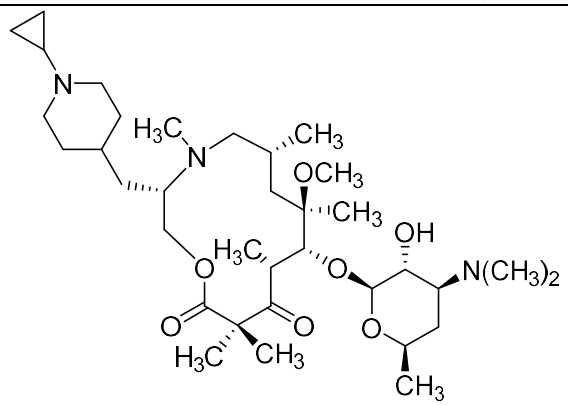
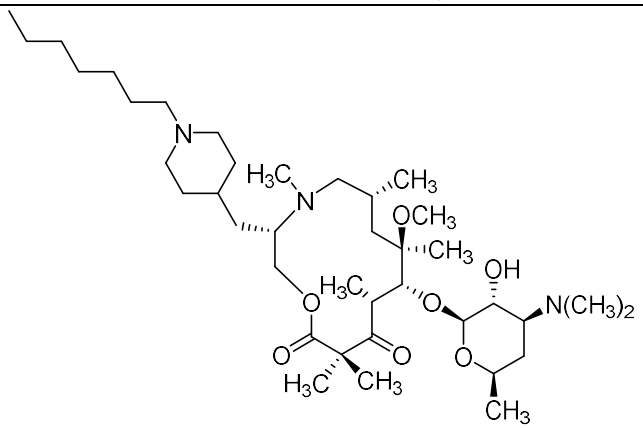
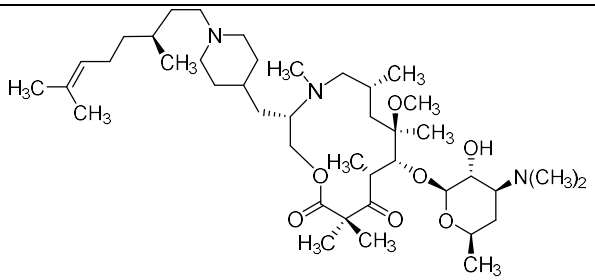
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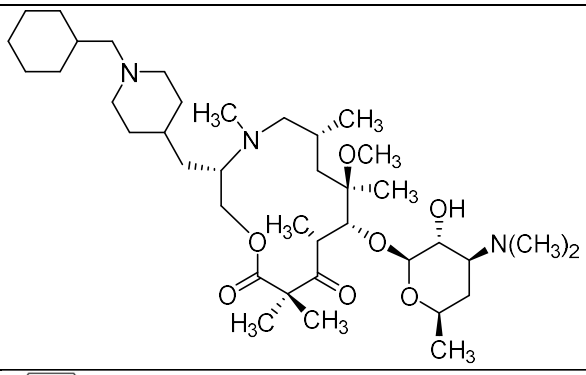
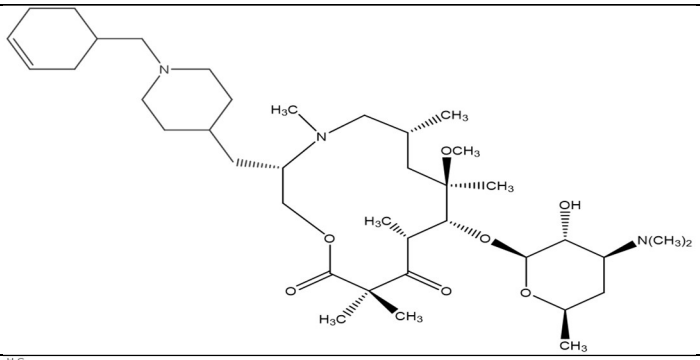
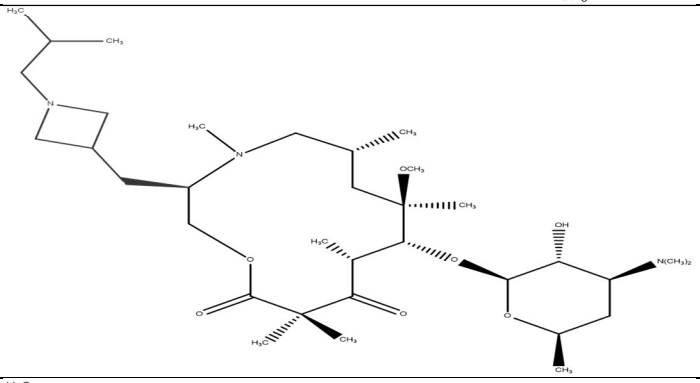
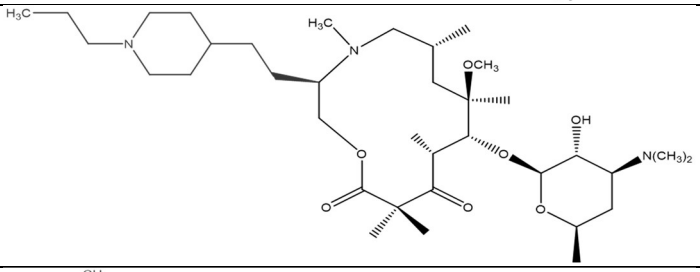
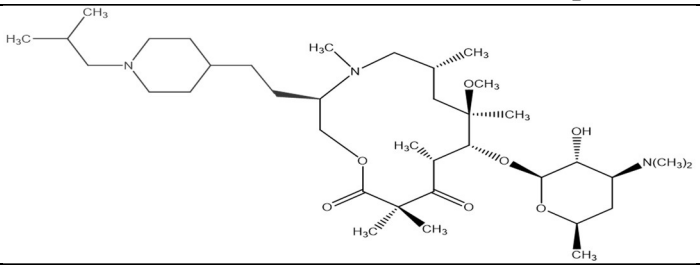
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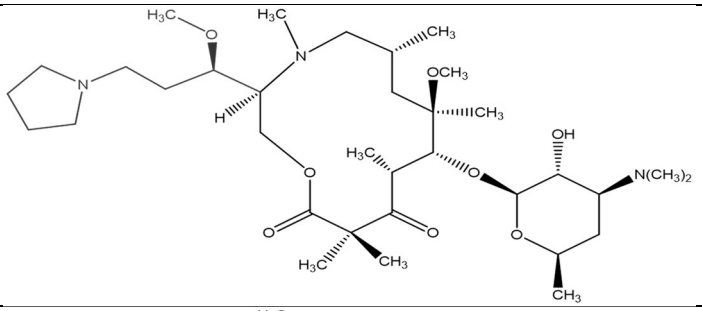
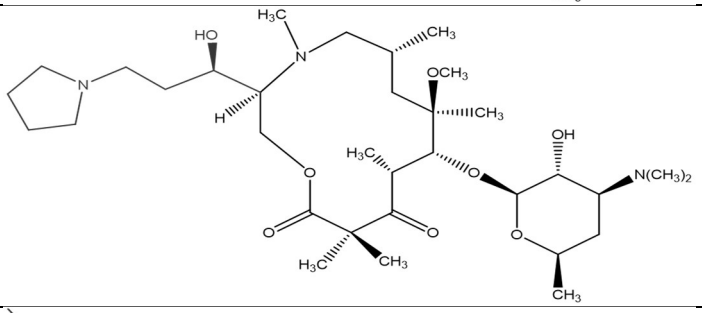
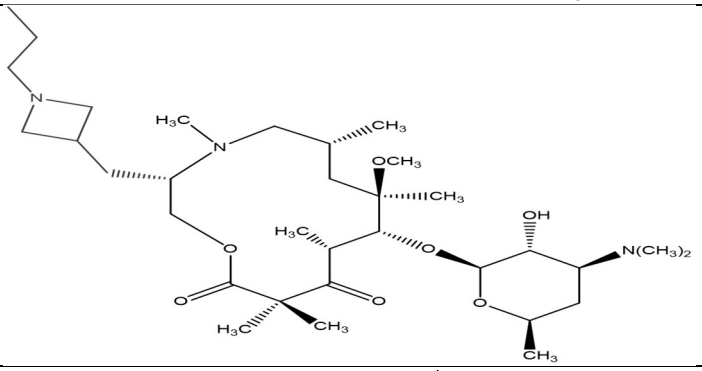
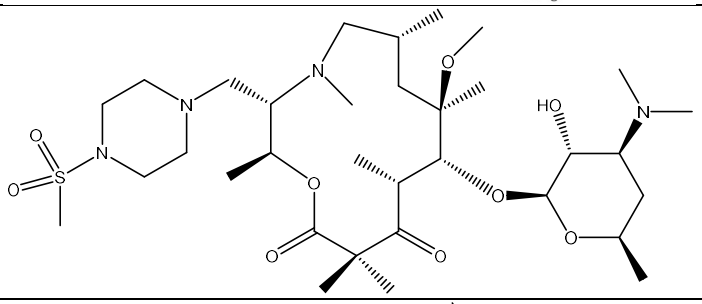
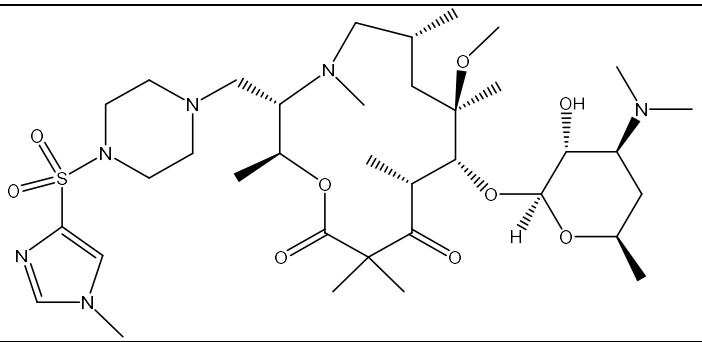
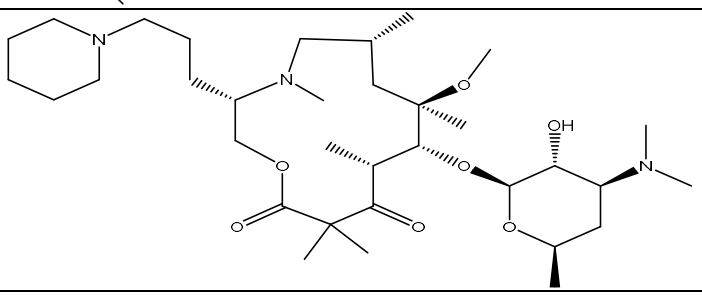
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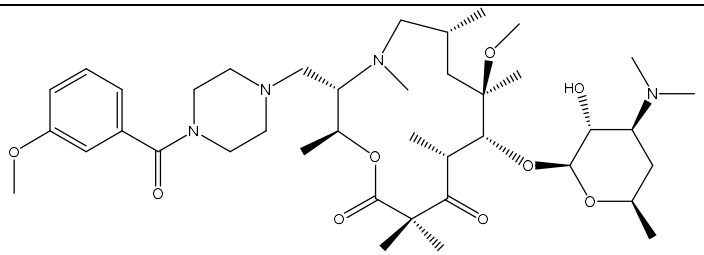
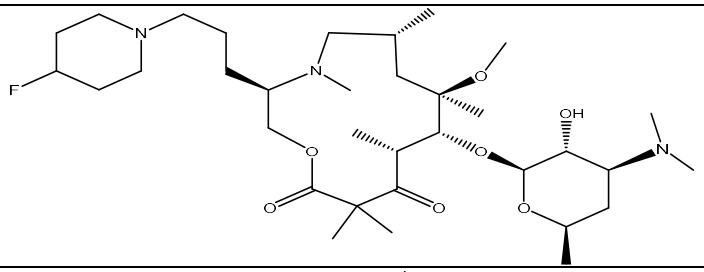
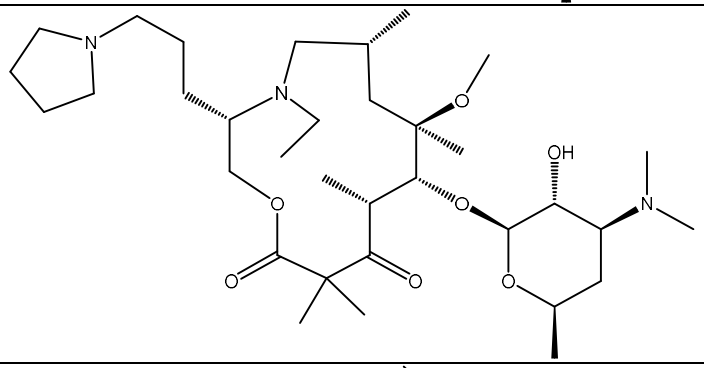
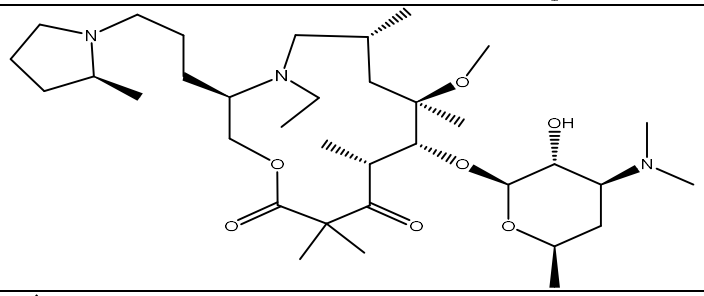
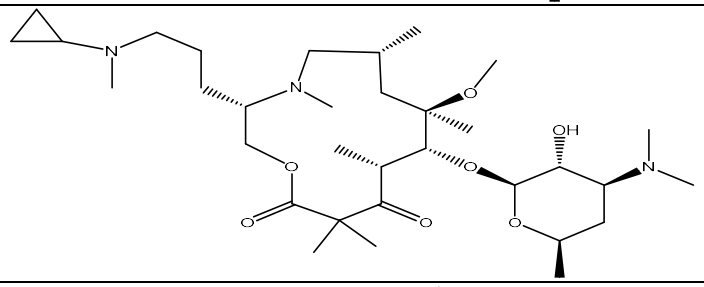
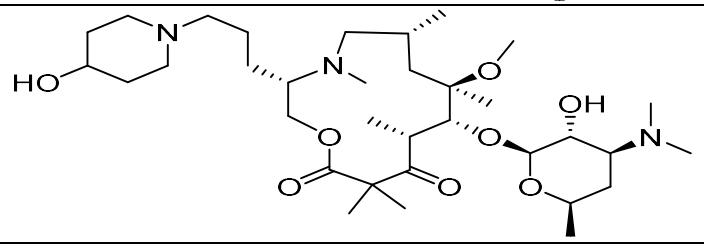
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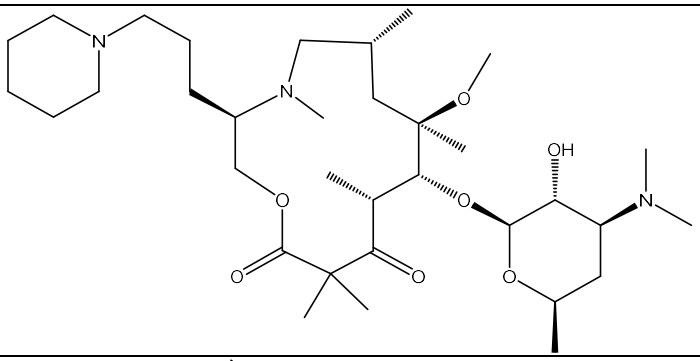
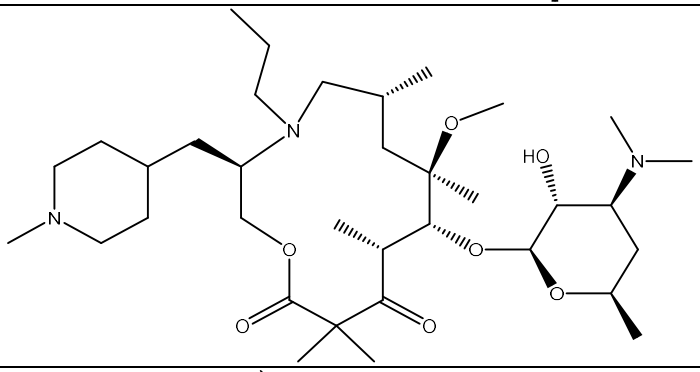
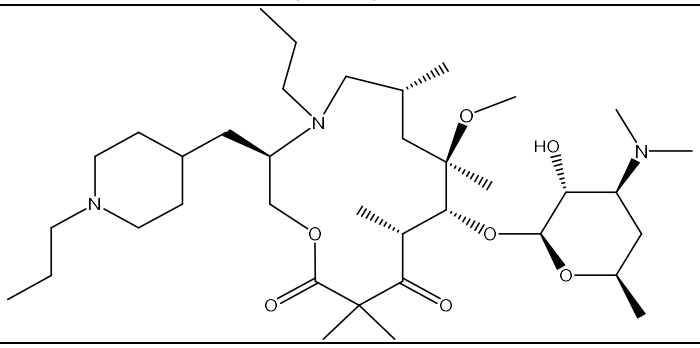
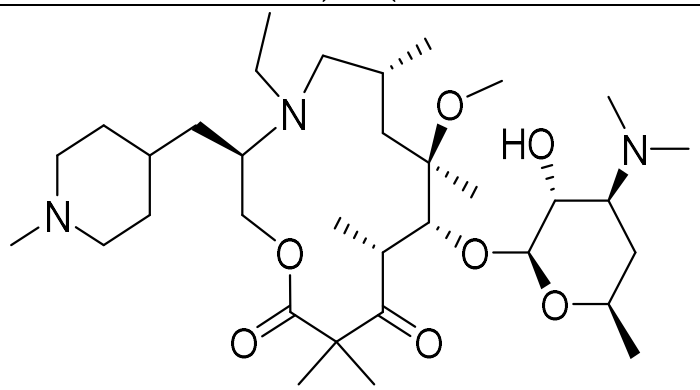
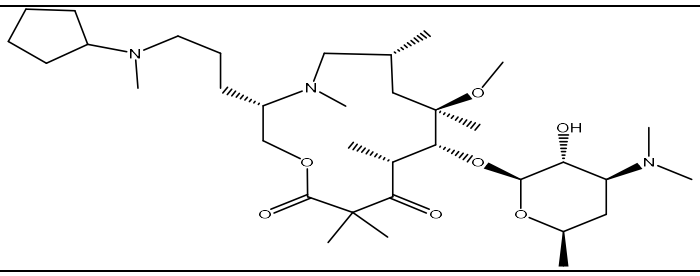
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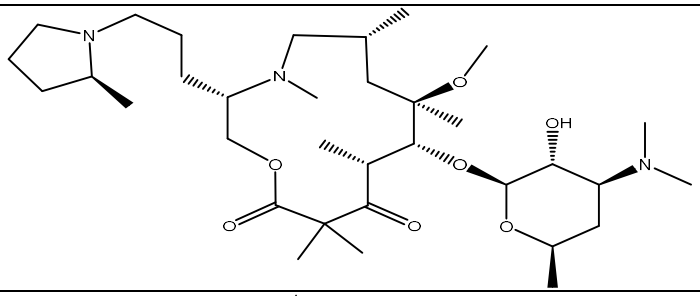
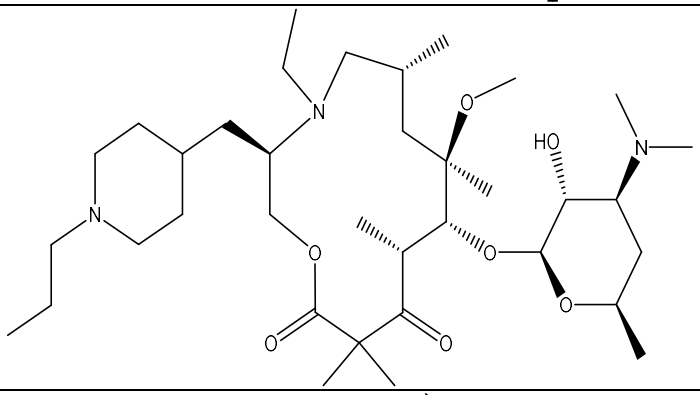
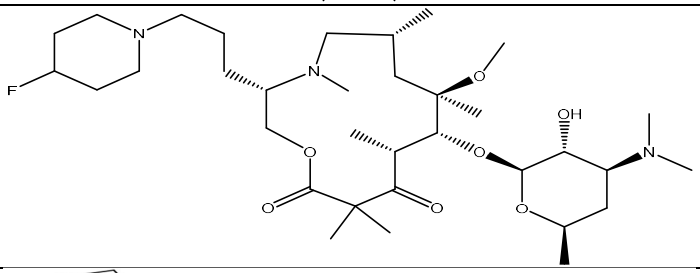
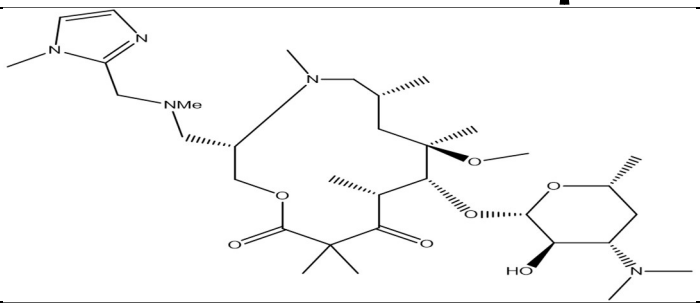
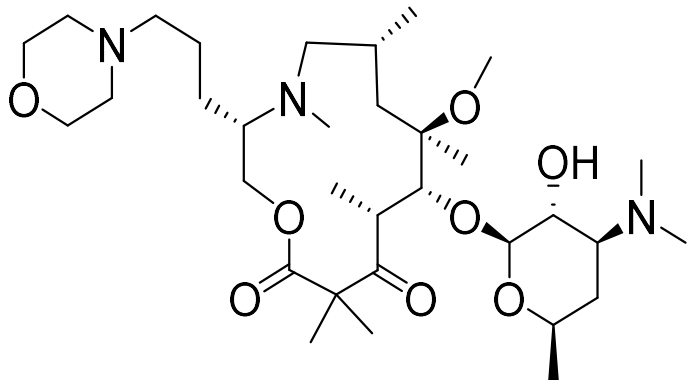
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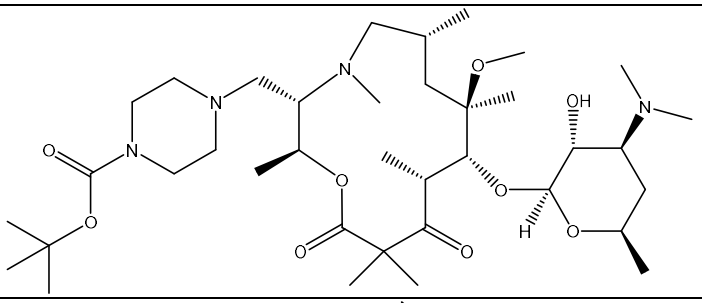
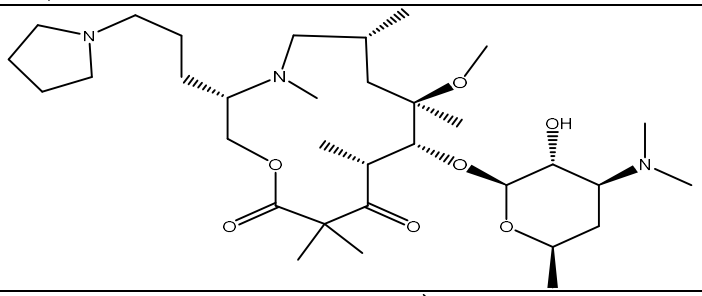
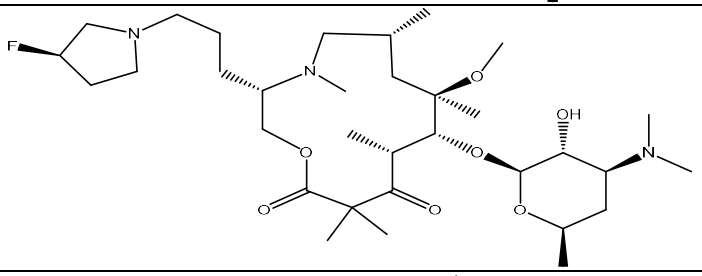
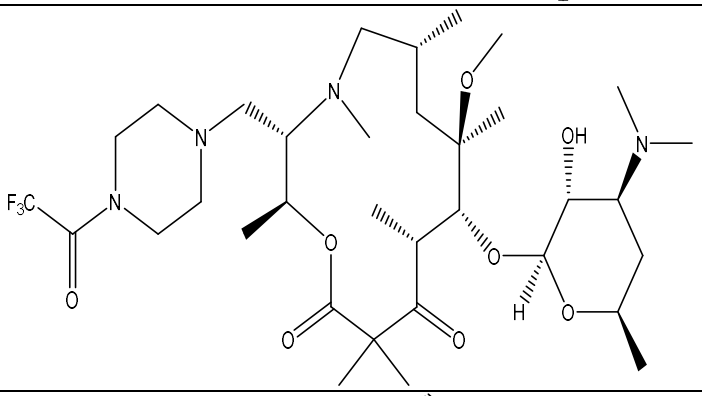
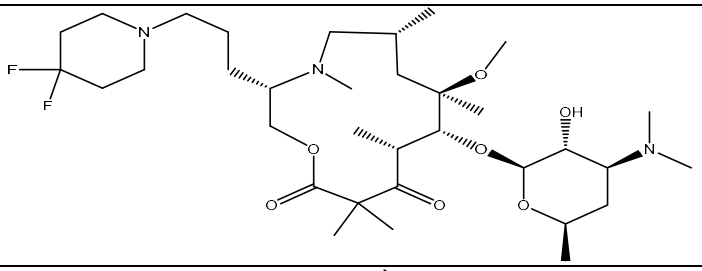
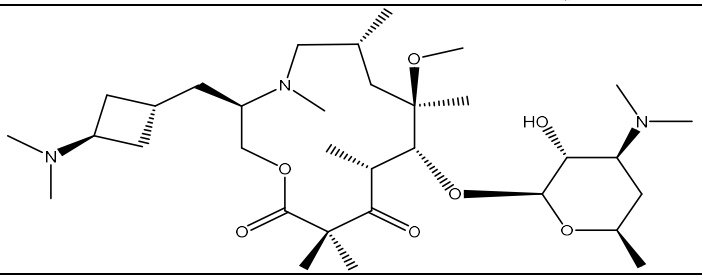
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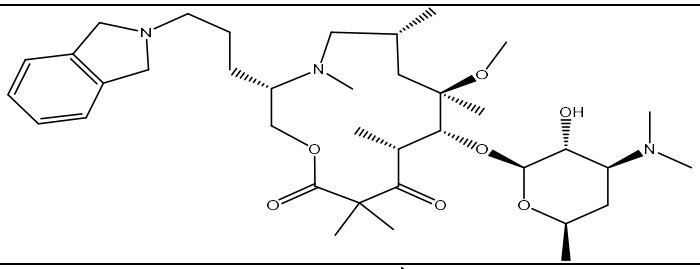
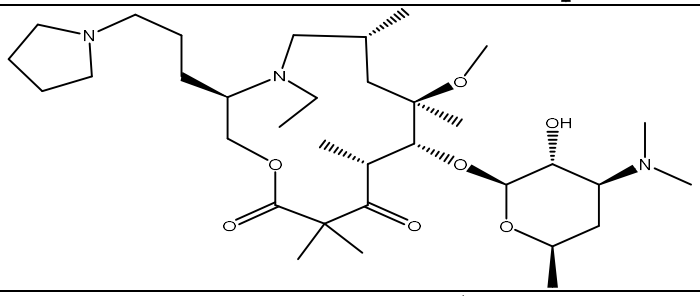
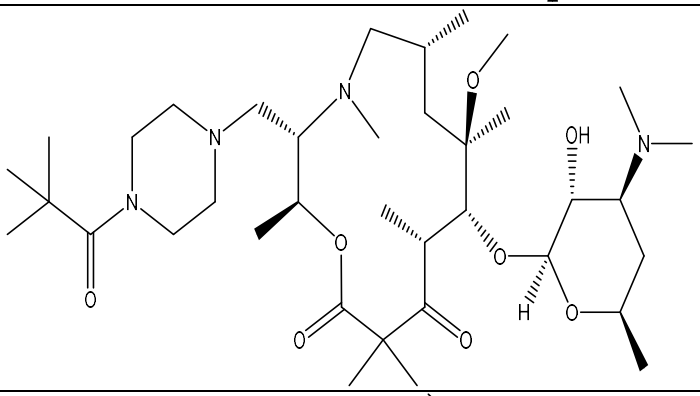
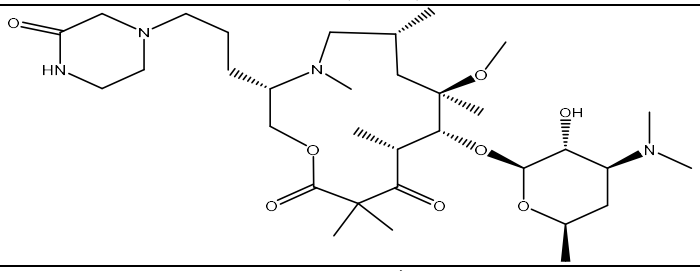
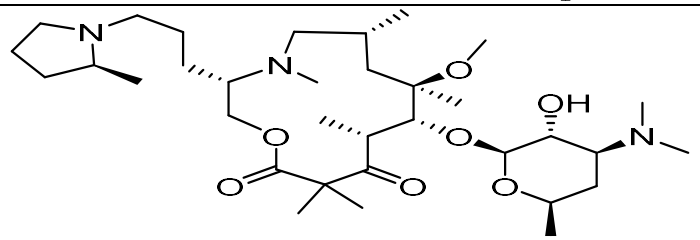
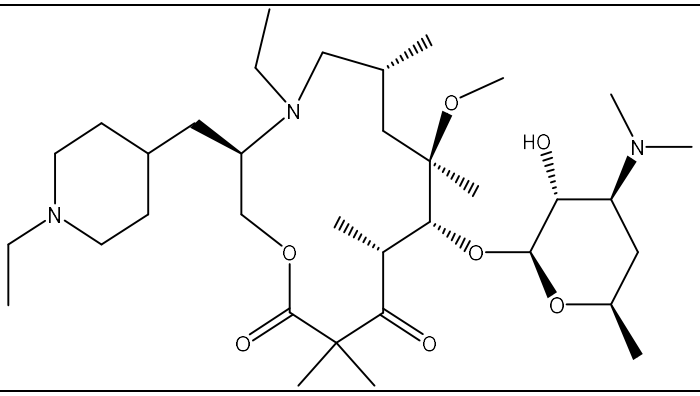
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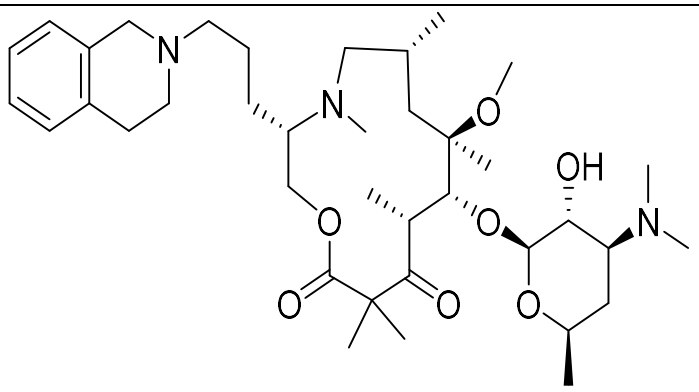
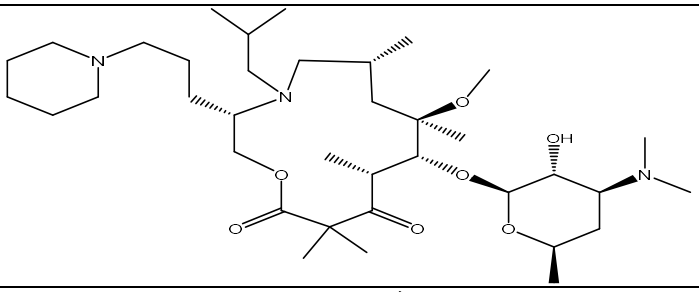
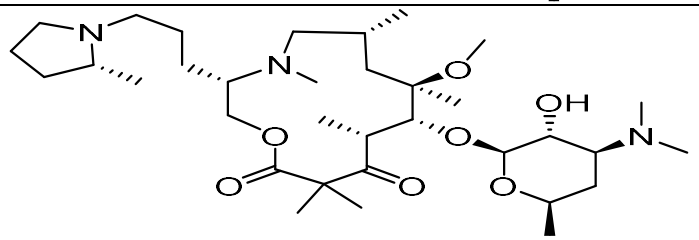
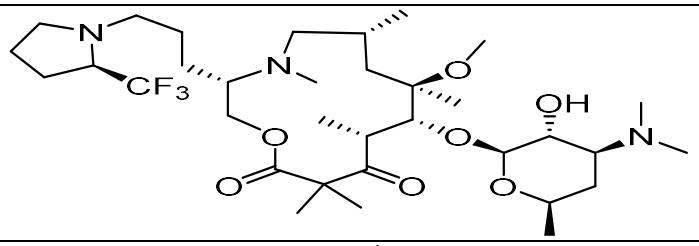
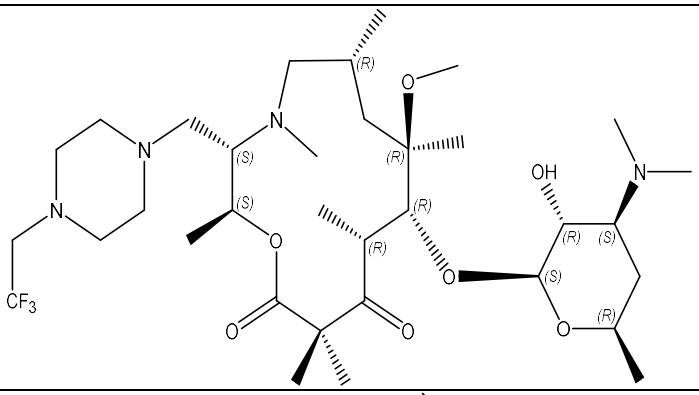
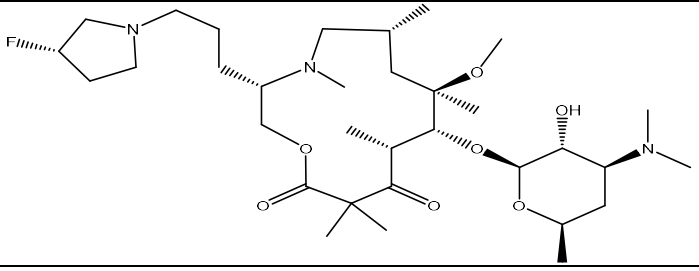
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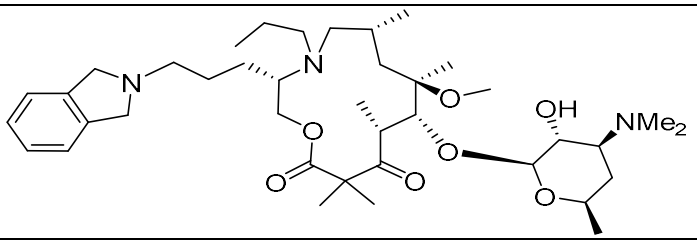
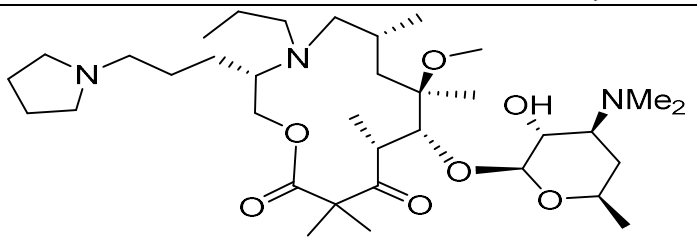
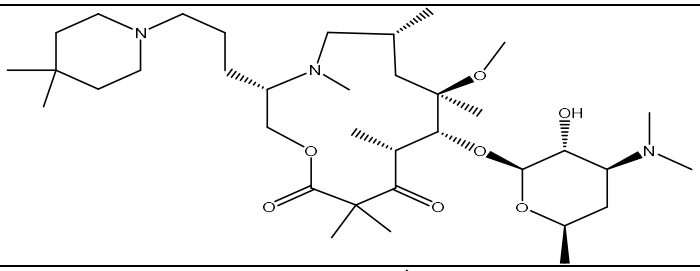
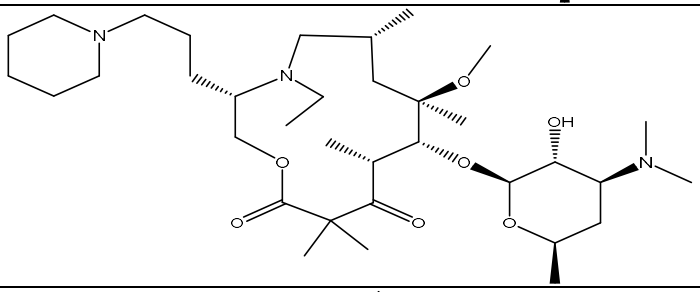
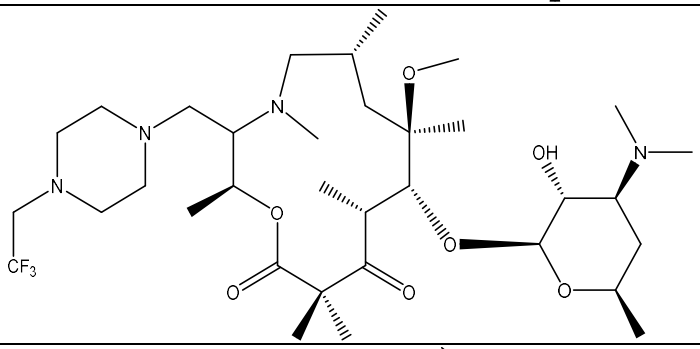
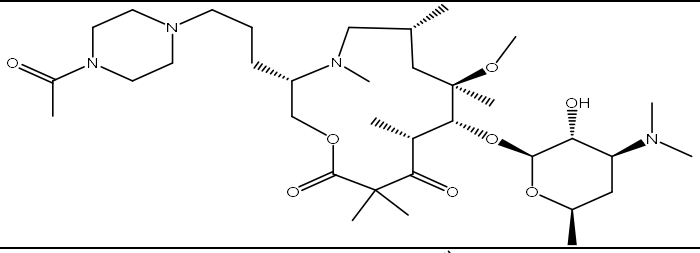
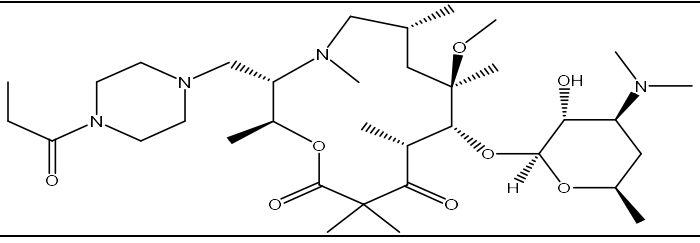
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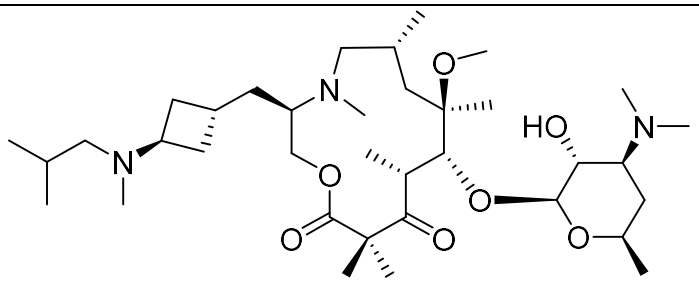
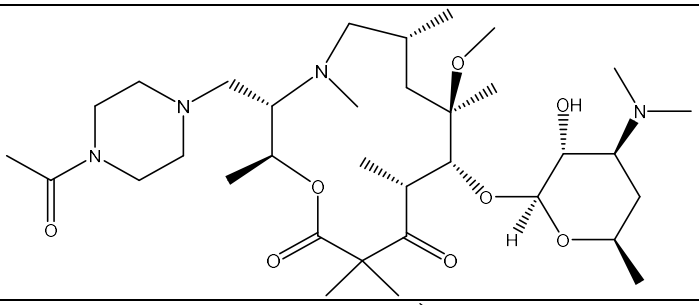
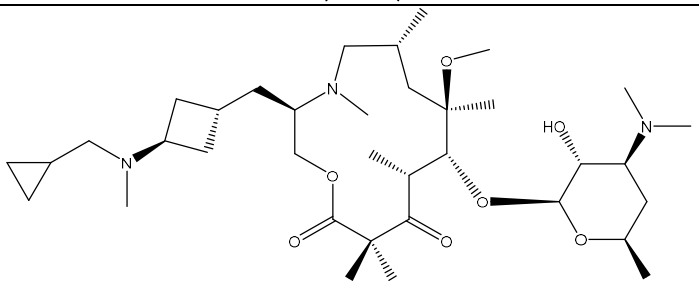
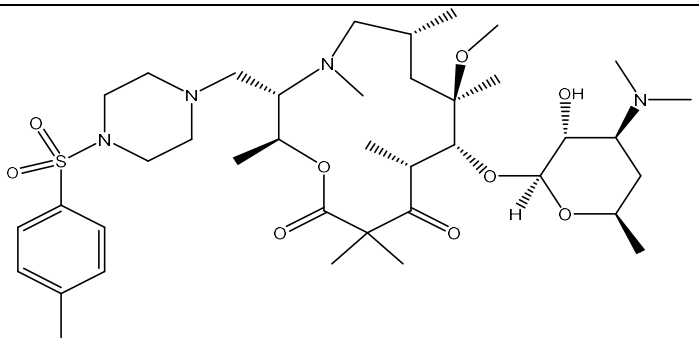
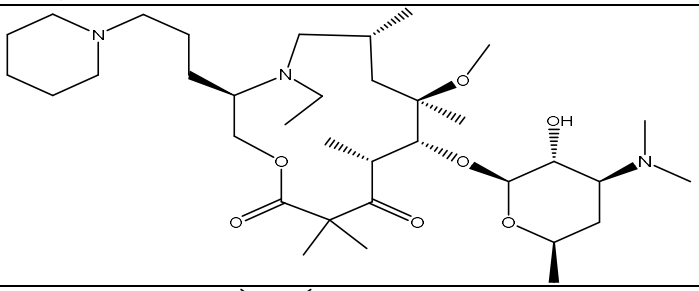
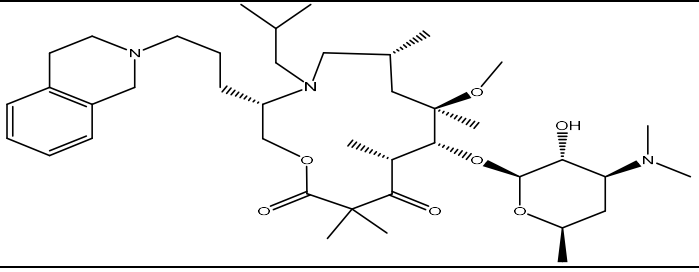
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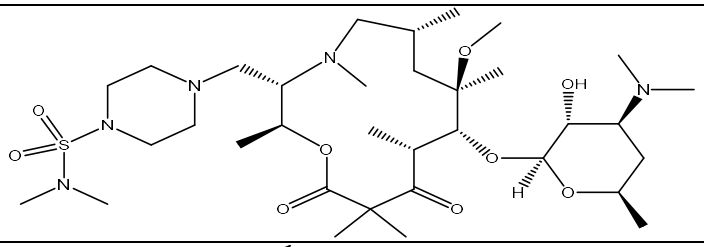
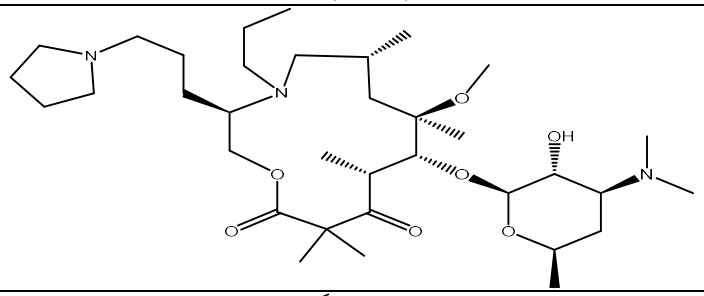
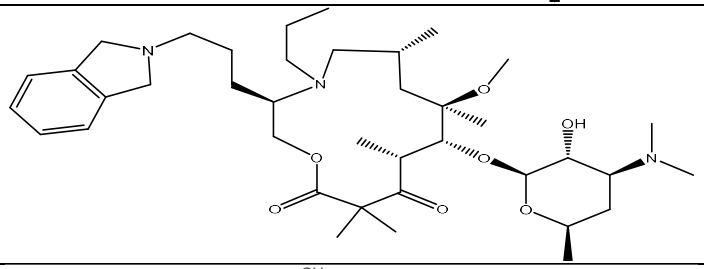
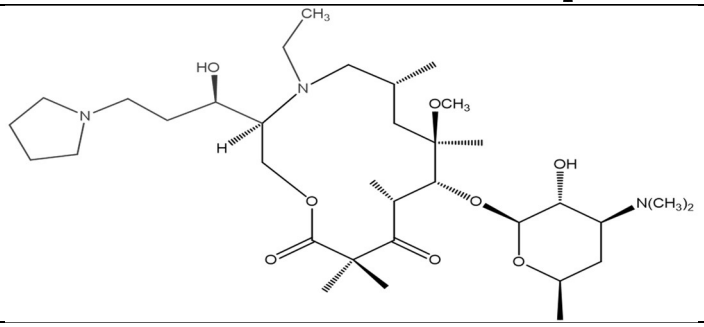
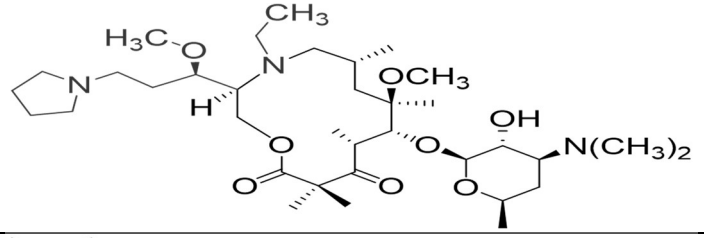
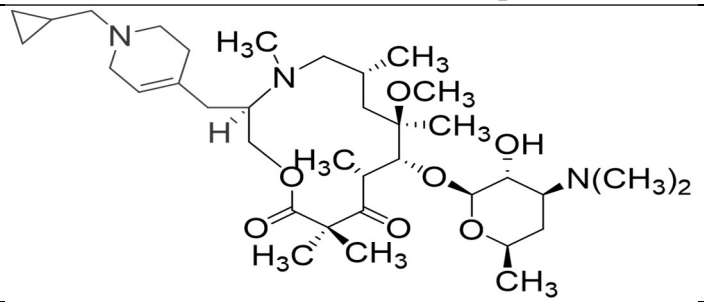
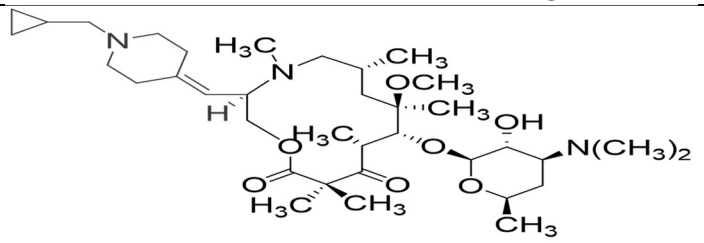
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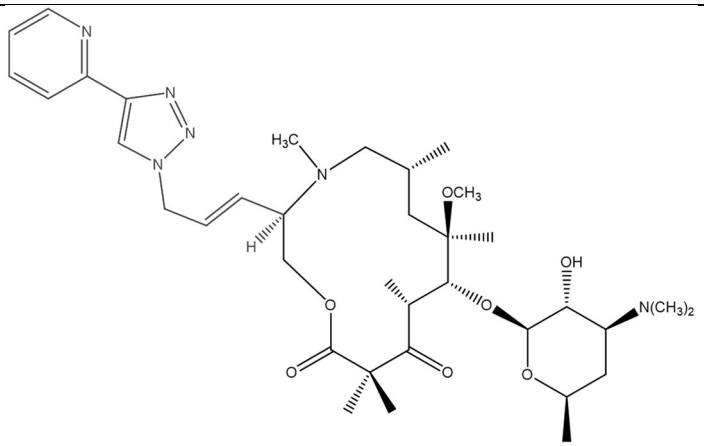
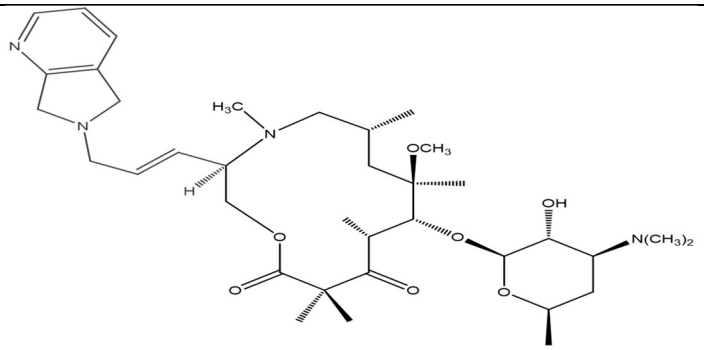
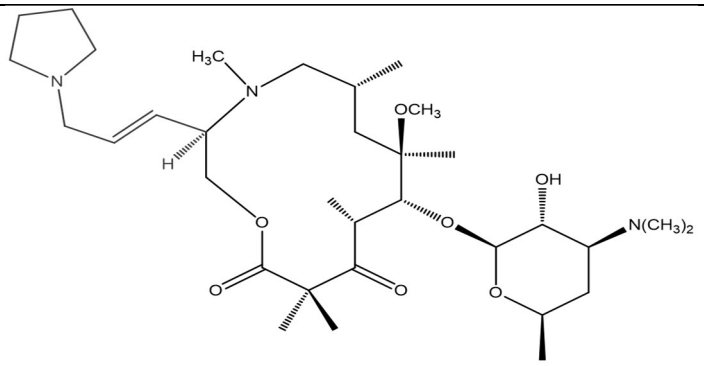
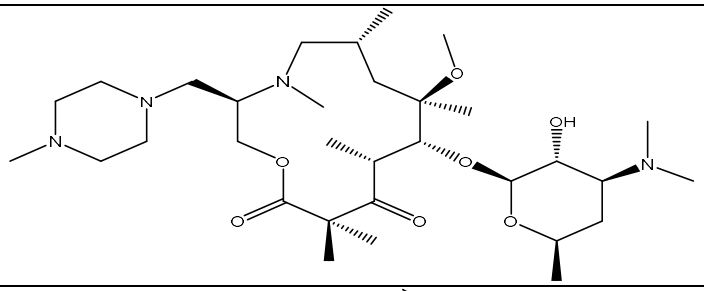
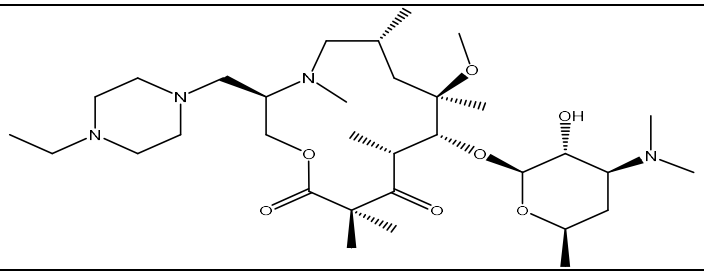
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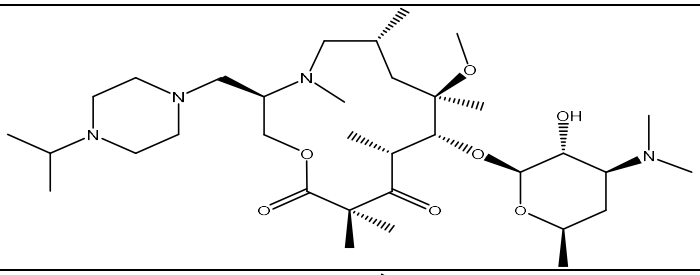
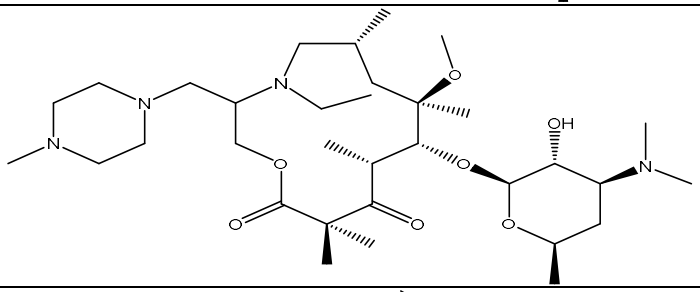
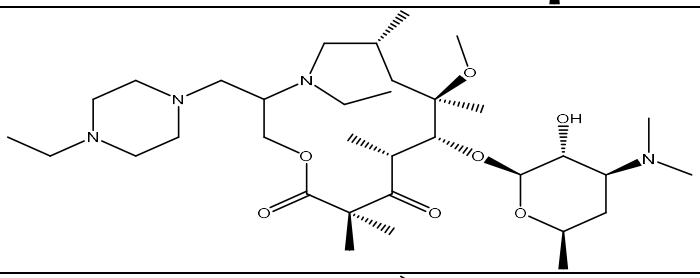
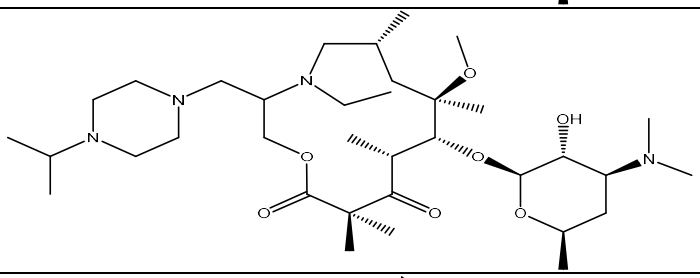
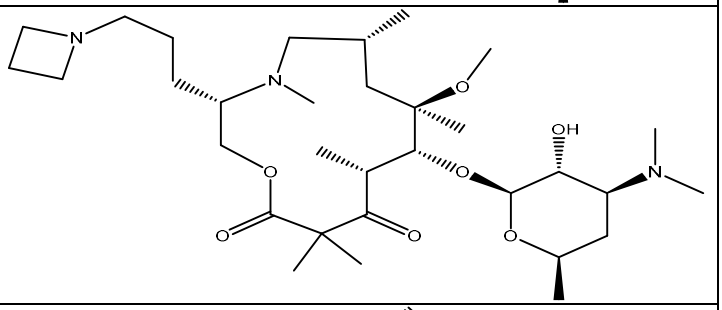
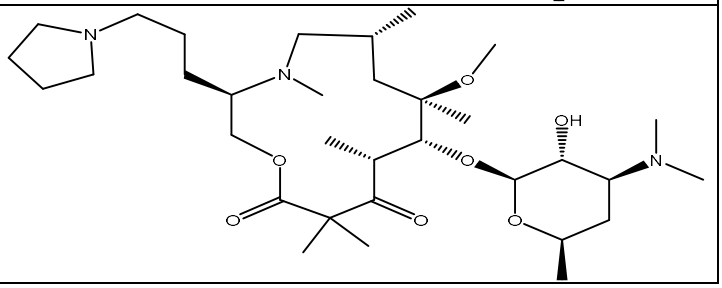
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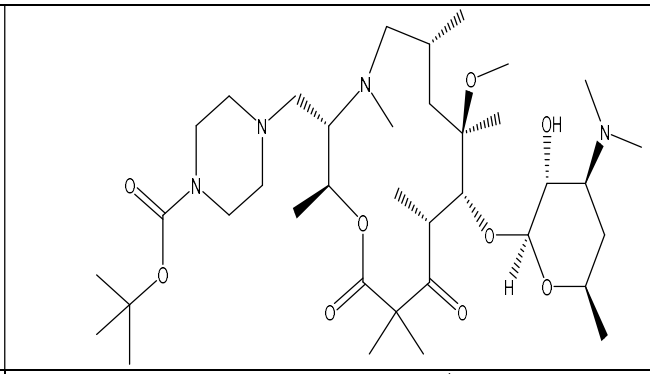
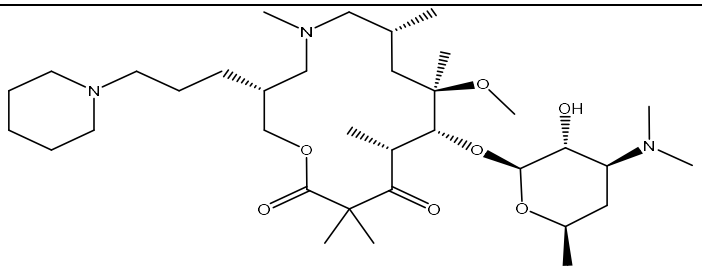
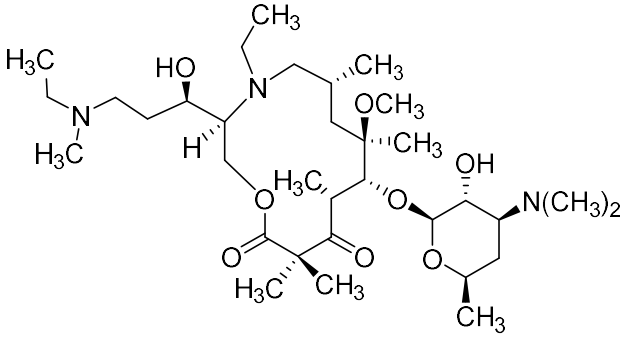
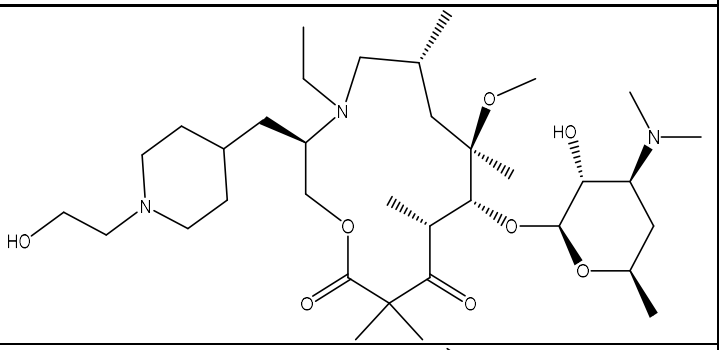
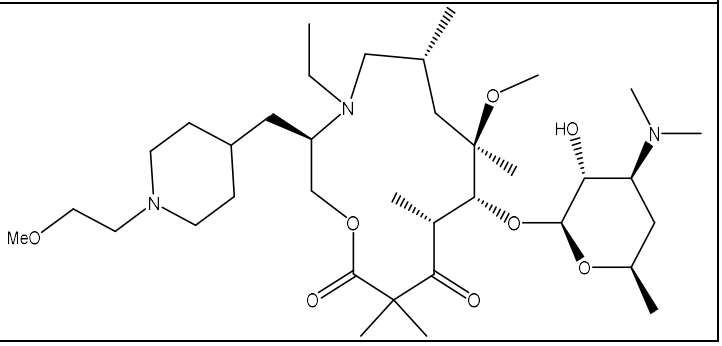
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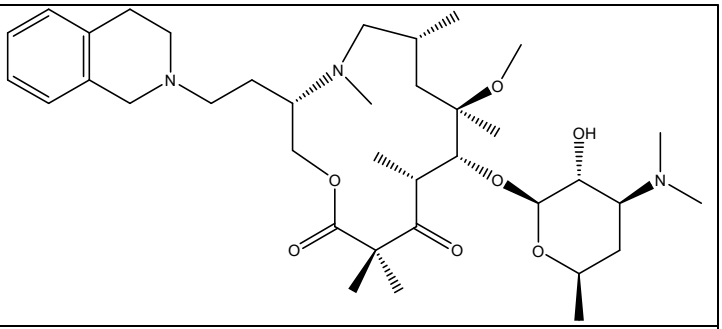
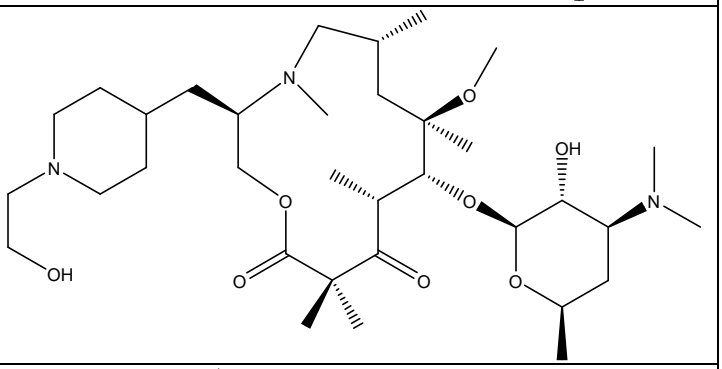
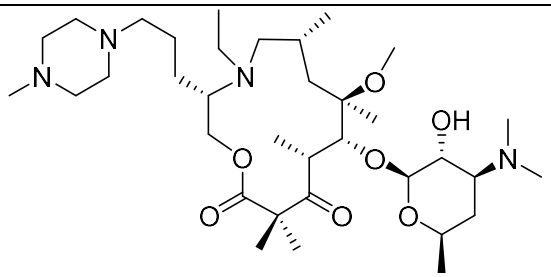
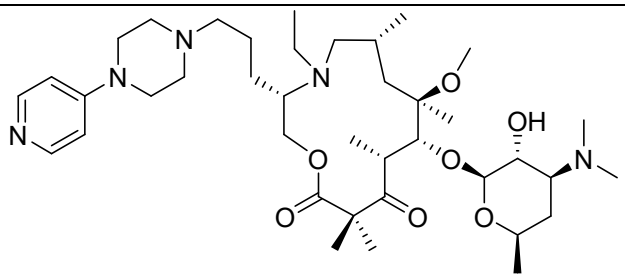
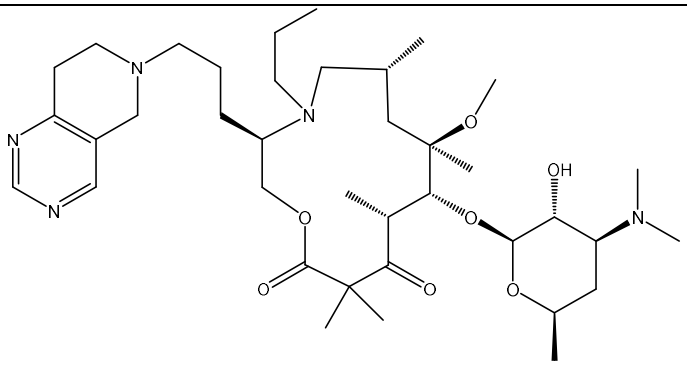
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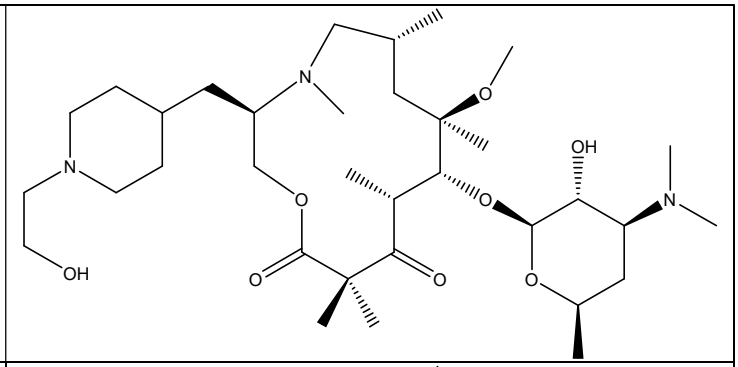
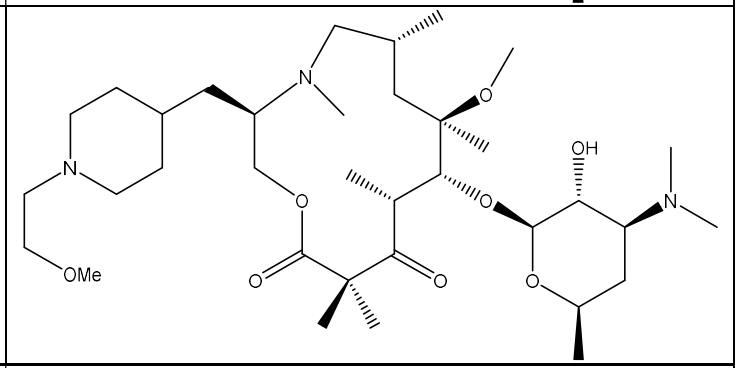
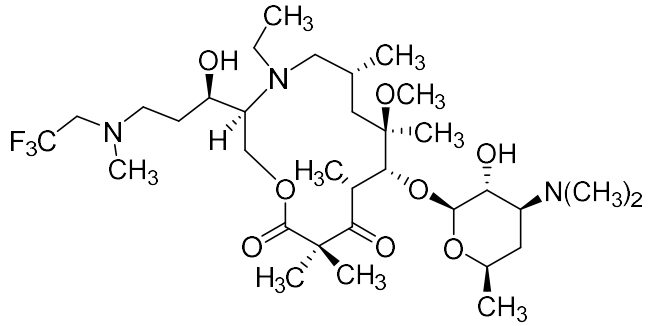
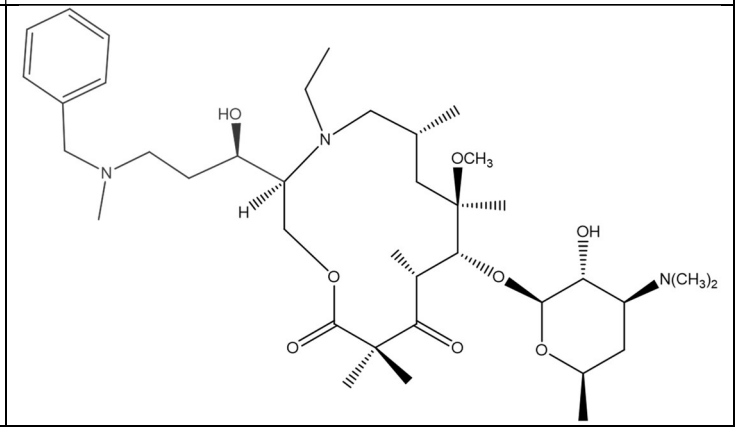
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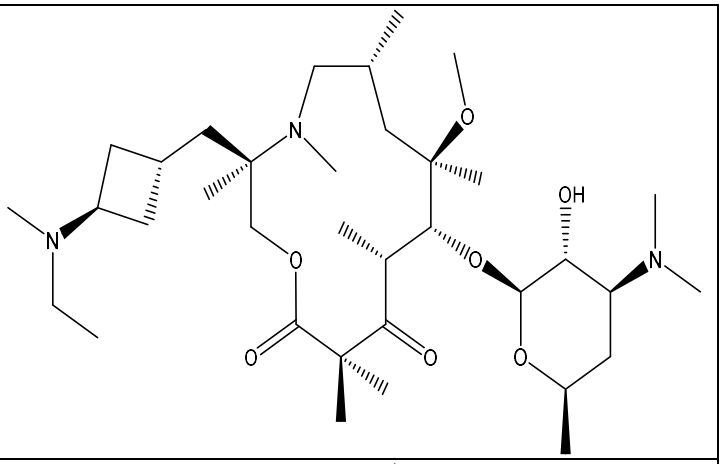
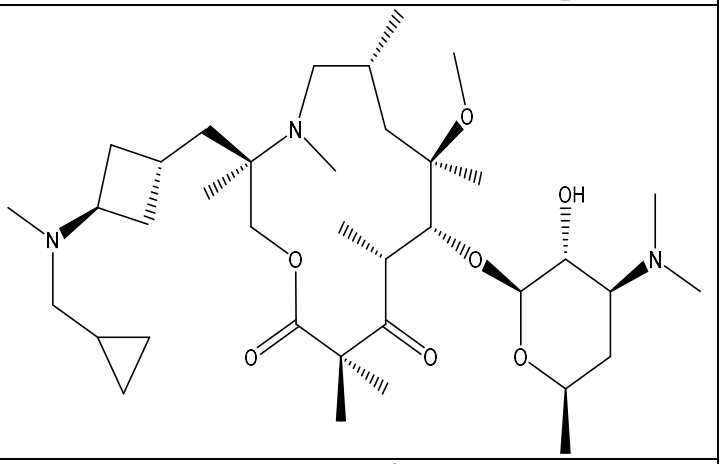
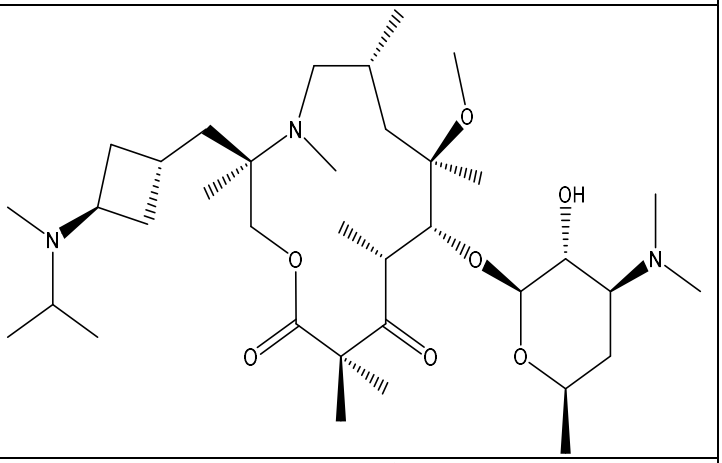
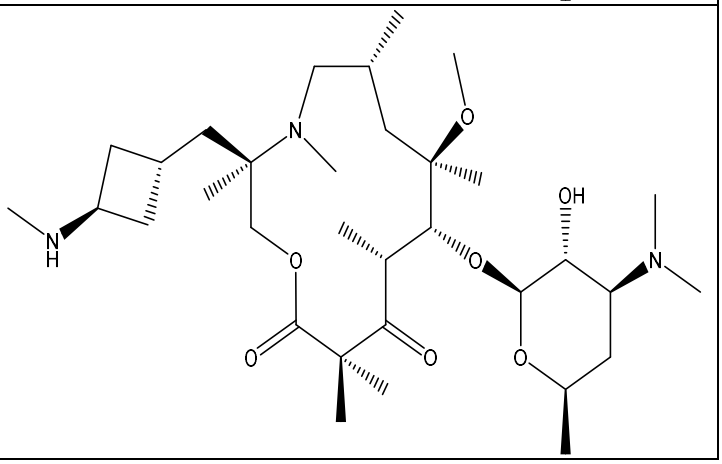
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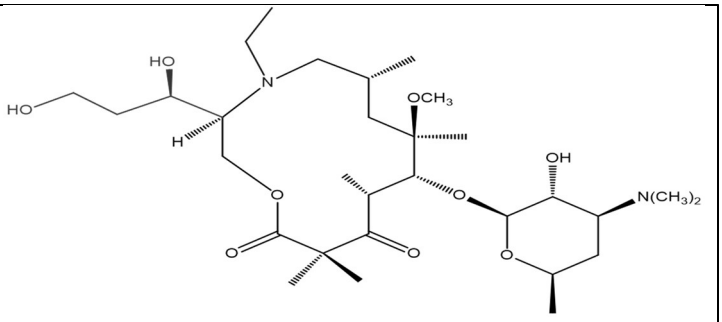
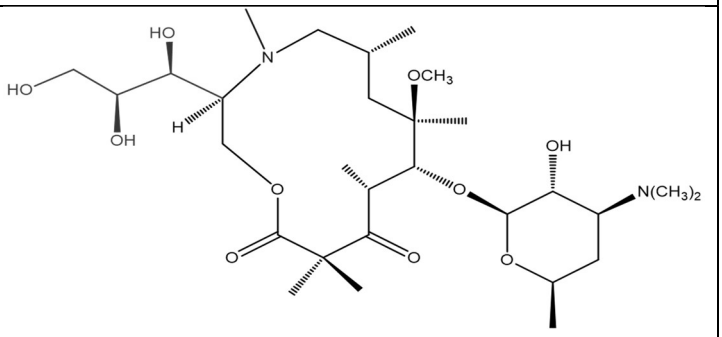
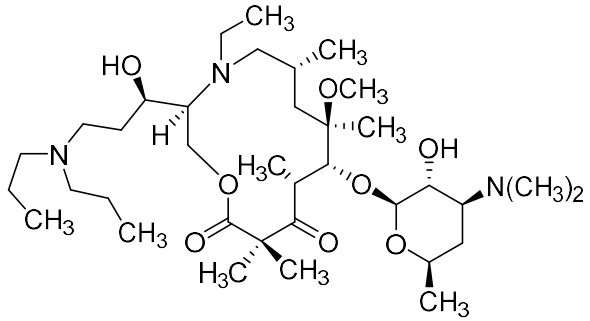
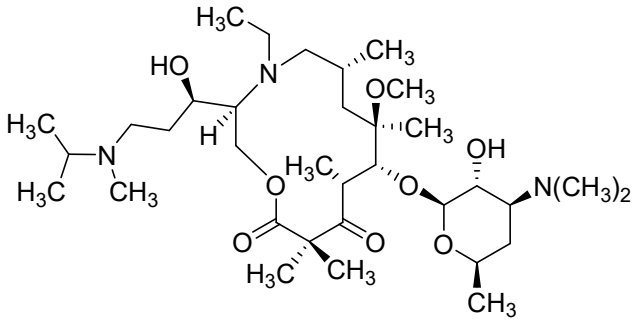
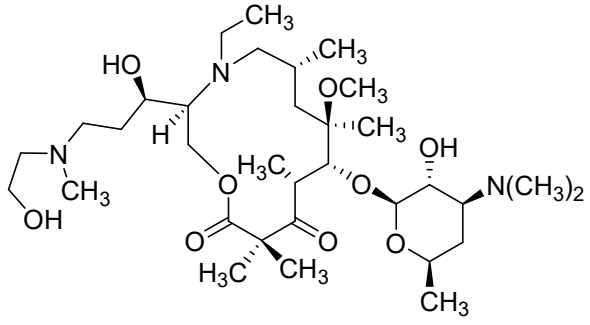
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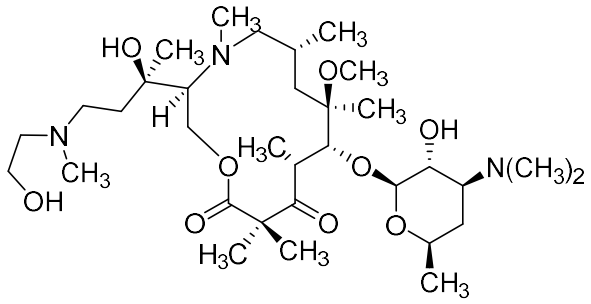
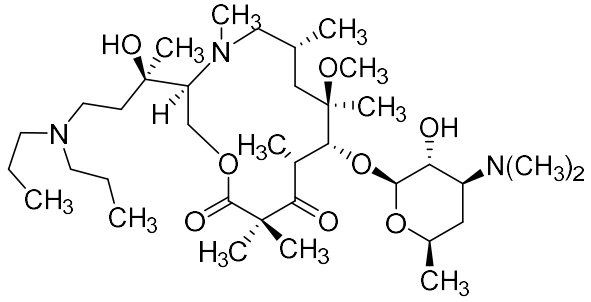
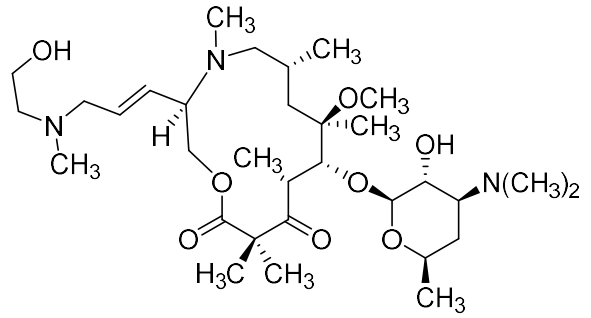
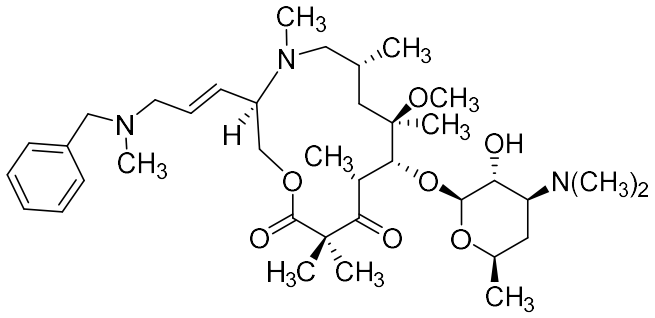
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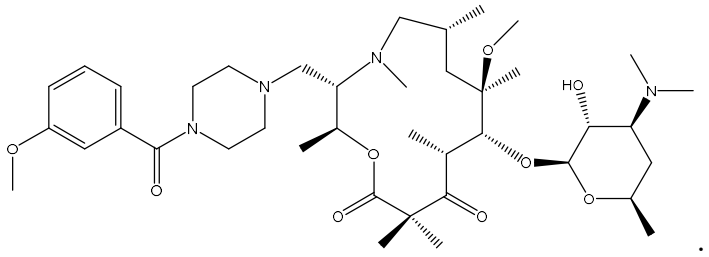
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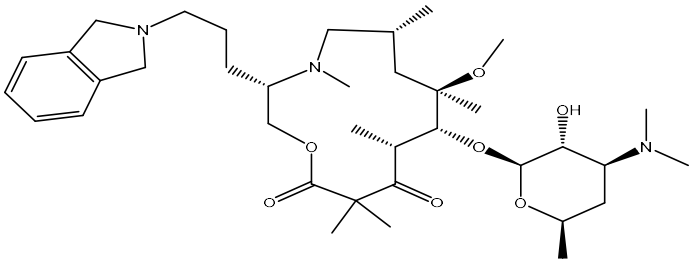
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or a pharmaceutically acceptable salt thereof.

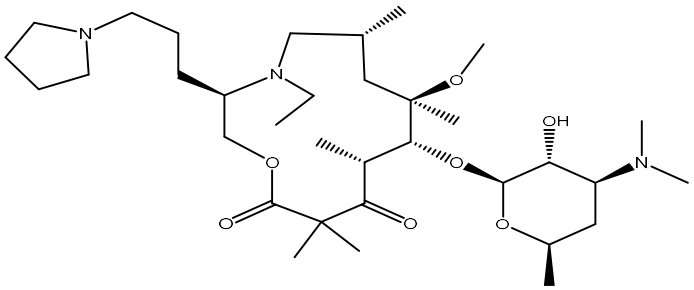
17. A compound according to claim 1 which is



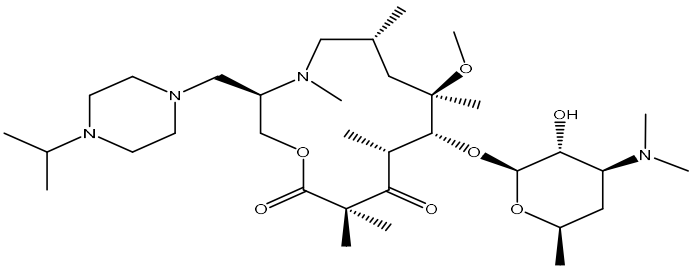
18. A compound according to claim 1 which is



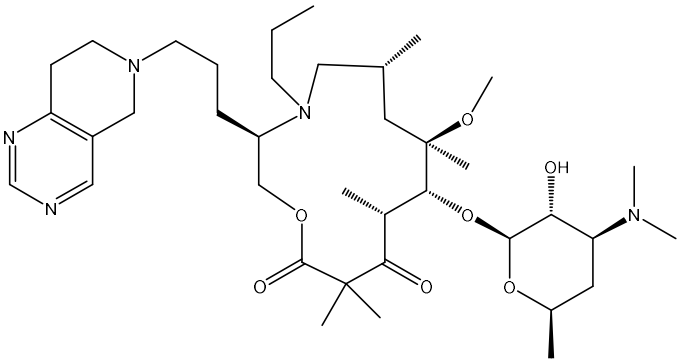
19. A compound according to claim 1 which is



20. A compound according to claim 1 which is



21. A compound according to claim 1 which is



22. A pharmaceutical composition comprising a compound of any one of claims 1 to 21, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

23. Use of a compound of any one of claims 1 to 21, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 22, in the manufacture of a medicament for treating an infectious disease, wherein the infectious disease is a Gram-negative or Gram-positive bacterial infection, or a parasitic infection.

24. A compound of any one of claims 1 to 21, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 22, for use in the treatment of an infectious disease, wherein the infectious disease is a Gram-positive or Gram-negative bacterial infection, or a parasitic infection.

25. The use of claim 23, or the compound or composition for use of claim 24, wherein the bacterial infection is a *Staphylococcus* infection, an *Acinetobacter* infection, a *Klebsiella* infection, an *Escherichia* infection, or a *Pseudomonas* infection.