US2004/229909 discloses certain compounds having integrase inhibitory activity.

US 7232819 and US 2007/0083045 disclose certain 5,6-dihydroxypyrimidine-4-carboxamides as HIV integrase inhibitors.

US 7169780, US 7217713, and US 2007/0123524 disclose certain N-substituted 5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxamides as HIV integrase inhibitors.

US 7279487 discloses certain hydroxynaphthyridinone carboxamides that are useful as HIV integrase inhibitors.

US 7135467 and US 7037908 disclose certain pyrimidine carboxamides that are useful as HIV integrase inhibitors.

US 7211572 discloses certain nitrogenous condensed ring compounds that are HIV integrase inhibitors.

US 7414045 discloses certain tetrahydro-4H-pyrido[1,2-a]pyrimidine carboxamides, hexahydropyrimido[1,2-*a*]azepine carboxamides, and related compounds that are useful as HIV integrase inhibitors.

US 8129385 discloses certain hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazine-9-carboxamides, and related compounds that are useful as HIV integrase inhibitors.

WO 2006/103399 discloses certain tetrahydro-4H-pyrimidooxazepine carboaxmides, tetrahydropyrazinopyrimidine carboxamides, hexahydropyrimidodiazepine carboxamides, and related compounds that are useful as HIV integrase inhibitors.

US 2007/0142635 discloses processes for preparing hexahydropyrimido[1,2-a]azepine-2-carboxylates and related compounds.

US 2007/0149556 discloses certain hydroxypyrimidinone derivatives having HIV integrase inhibitory activity.

Various pyrimidinone compounds useful as HIV integrase inhibitors are also disclosed in US 7115601, US 7157447, US 7173022, US 7176196, US 7192948, US 7273859, and US 7419969.

US 2007/0111984 discloses a series of bicyclic pyrimidinone compounds useful as HIV integrase inhibitors.

US 2006/0276466, US 2007/0049606, US 2007/0111985, US 2007/0112190, US 2007/0281917, US 2008/0004265 each disclose a series of bicyclic pyrimidinone compounds useful as HIV integrase inhibitors.

SUMMARY

The present disclosure provides Compounds of Formula

each occurrence of R^8 is independently selected from C_1-C_6 alkyl, halo, -OR^6, -SR^6, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -O-(C_1-C_6 haloalkyl), -CN, -NO_2, -$N(R^6)_2$, -$C(O)OR^7$, -$C(O)N(R^7)_2$ and -$NHC(O)R^7$;

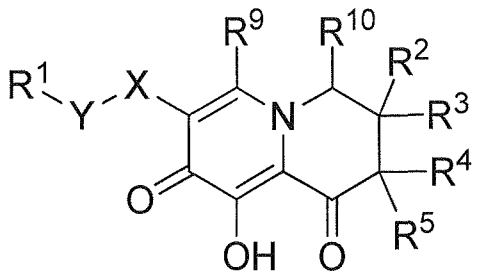
R^9 is selected from H, C_1-C_6 alkyl, -C_1-C_6 alkyl-O-C_1-C_6 alkyl,-C_1-C_6 alkyl-NR^6-C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_1-C_6 hydroxyalkyl;

R^{10} is selected from H, C_1-C_6 alkyl, -C_1-C_6 alkyl-O-C_1-C_6 alkyl,-C_1-C_6 alkyl-NR^6-C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_1-C_6 hydroxyalkyl;

each occurrence of R^{11} is independently selected from H, C_1-C_6 alkyl, -$S(O)_2R_{12}$ and –$C(O)R^{12}$; and

each occurrence of R^{12} is independently selected from C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_6-C_{10} aryl, 4 to 7-membered monocyclic heterocycloalkyl, 8 to 11-membered bicyclic heterocycloalkyl, 5 or 6-membered monocyclic heteroaryl and 9 or 10-membered bicyclic heteroaryl, wherein said C_3-C_7 cycloalkyl group, said C_6-C_{10} aryl group, 4 to 7-membered monocyclic heterocycloalkyl, said 8 to 11-membered bicyclic heterocycloalkyl group, said 5 or 6-membered monocyclic heteroaryl group and said 9 or 10-membered bicyclic heteroaryl group can each be optionally substituted with up to three R^8 groups.

In one aspect, the present disclosure provides a compound having the formula:



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

X is selected from a 5-membered monocyclic heteroaryl and-$N(R^6)C(O)$-;

Y is C_1-C_3 alkylene;

R^1 is selected from phenyl, 5 or 6-membered monocyclic heteroaryl and 9-membered bicyclic heteroaryl, wherein said phenyl group, said 5 or 6-membered monocyclic heteroaryl group and said 9-membered bicyclic heteroaryl group can each be optionally substituted with up to three R^8 groups;

R^2 is H, methyl, or -OR^7 or R^2 and R^4, together with the carbon atoms to which they are attached, can join to form a 5 to 7-membered monocyclic cycloalkyl group, 5 to 7-membered monocyclic heterocycloalkyl group, or a 5 to 7-membered monocyclic heterocycloalkenyl group, wherein said 5 to 7-membered monocyclic cycloalkyl group, said 5 to 7-membered monocyclic heterocycloalkyl group, and said 5 to 7-membered monocyclic heterocycloalkenyl group can be optionally substituted with up to three R^8 groups, which can be the same or different;

R^3 is H, methyl, or -OR^7;

R^4 is selected from methyl, ethyl, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), and -OR^7;

R^5 is selected from methyl, ethyl, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), and -OR^7;

each occurrence of R^6 is independently H or C_1-C_6 alkyl;

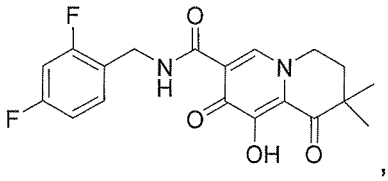
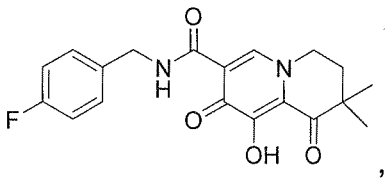
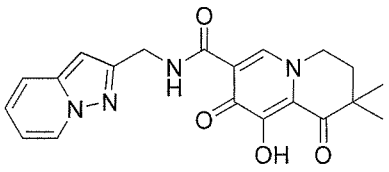
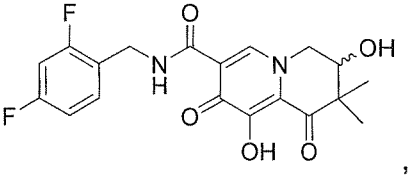
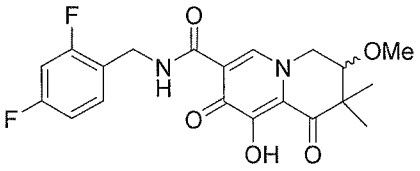
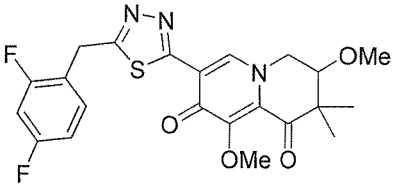
each occurrence of R^7 is independently selected from H, C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl) and C_3-C_7 cycloalkyl;

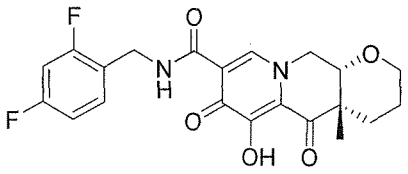
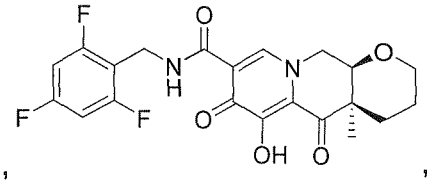
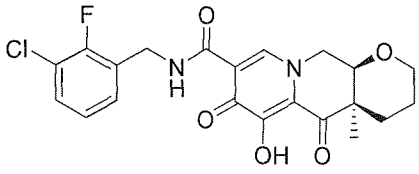
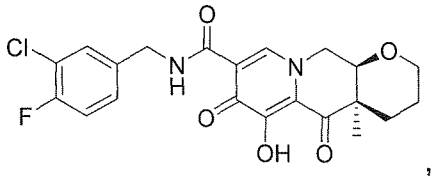
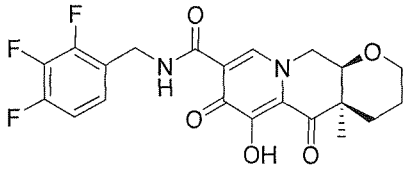
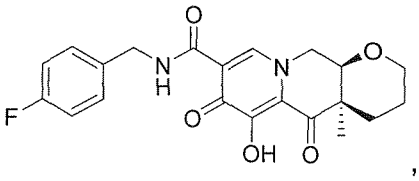
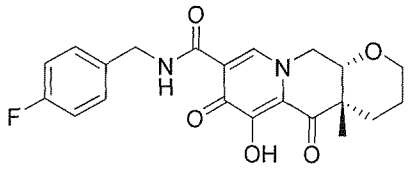
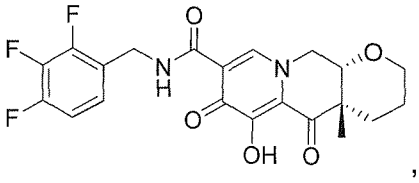
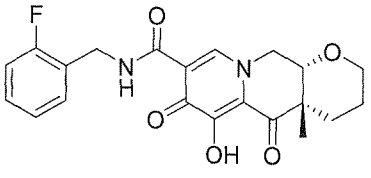
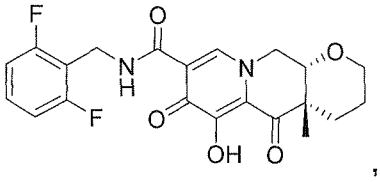
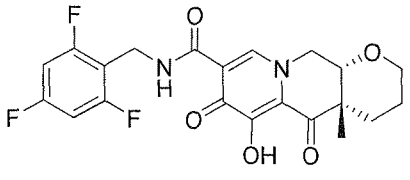
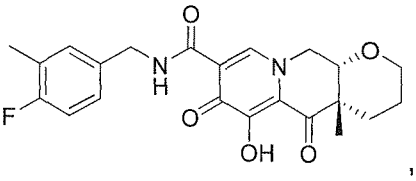
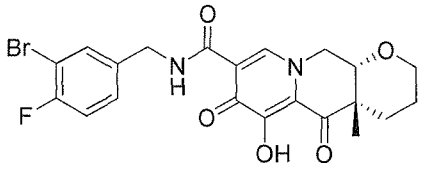
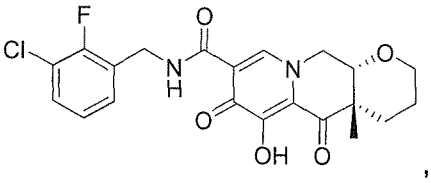
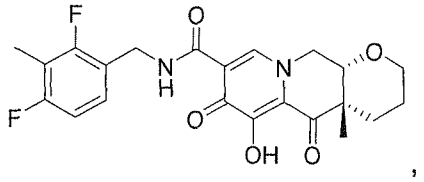
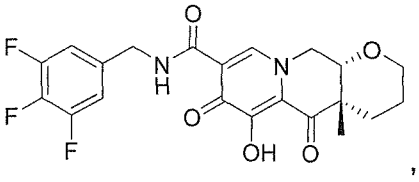
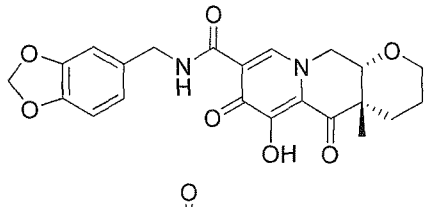
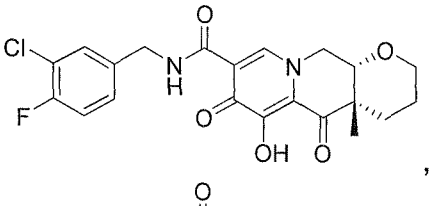
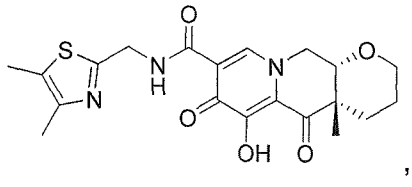
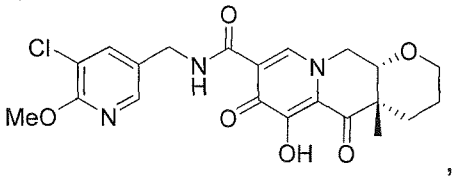
each occurrence of R^8 is independently selected from C_1-C_6 alkyl, halo and -OR^6;

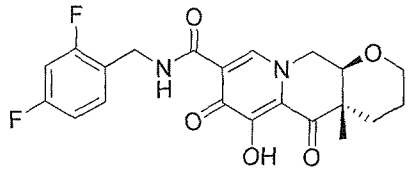
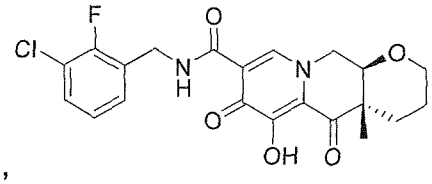
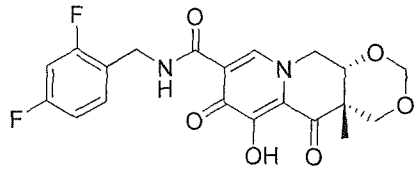
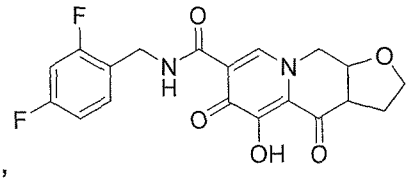
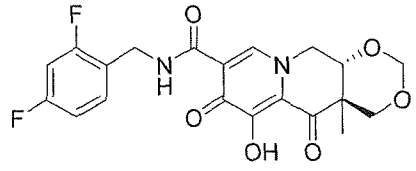
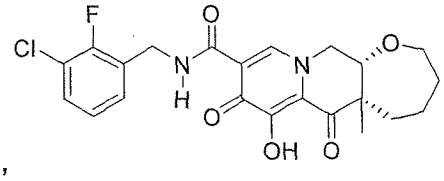
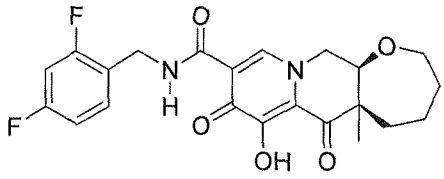
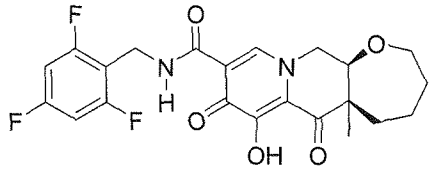
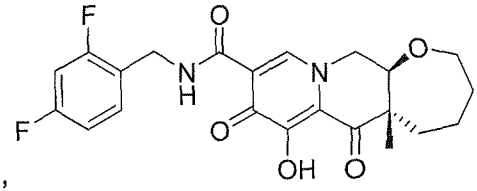
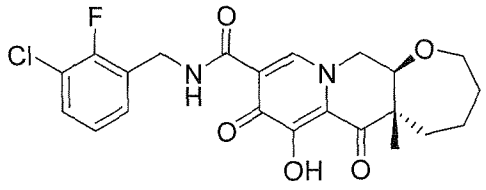
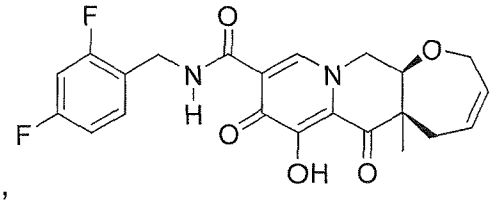
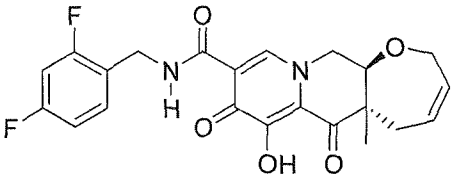
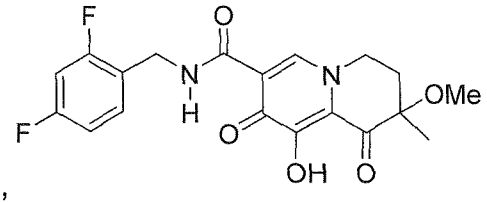
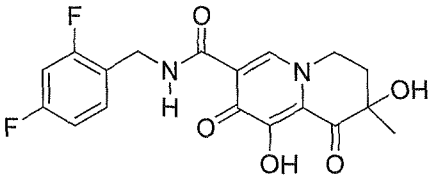
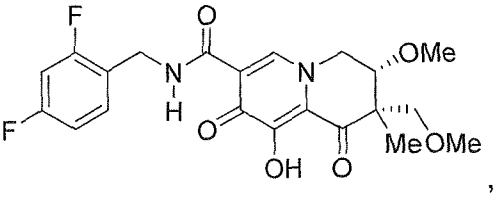
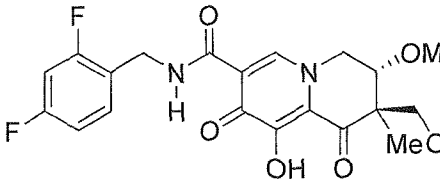
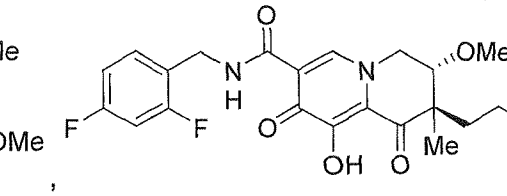
R^9 is H; and

R^{10} is H.

In another aspect, the present disclosure provides a compound selected from

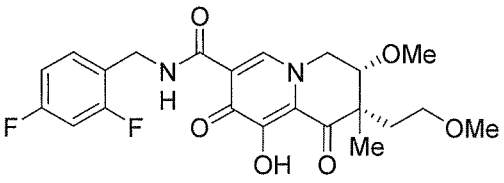
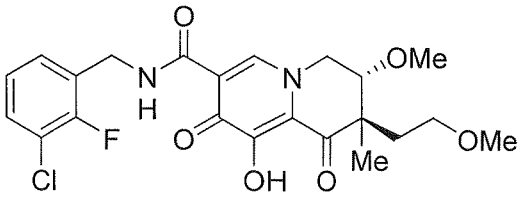
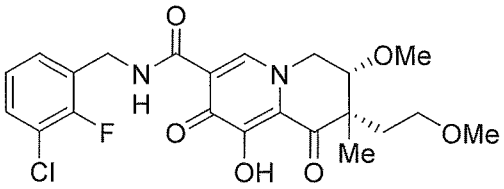
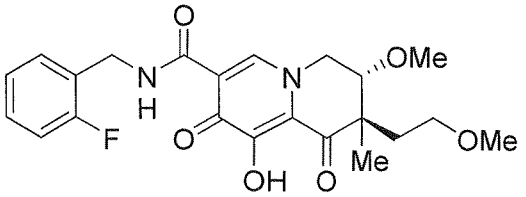
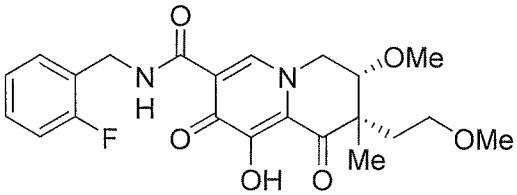
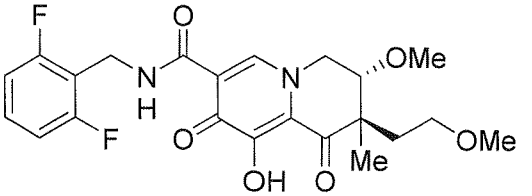
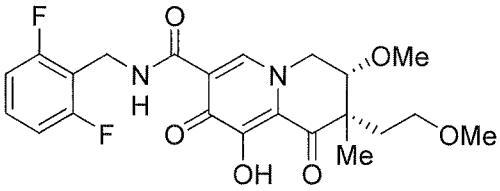
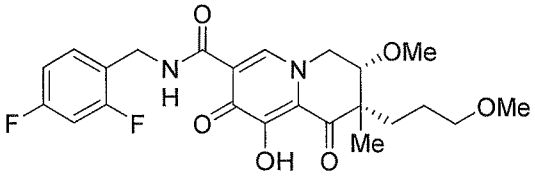
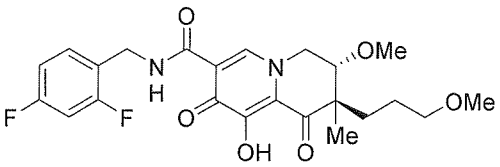
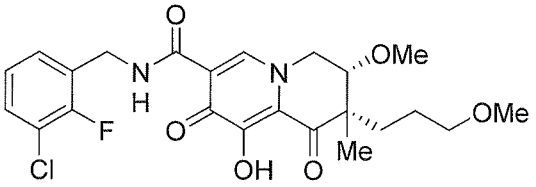
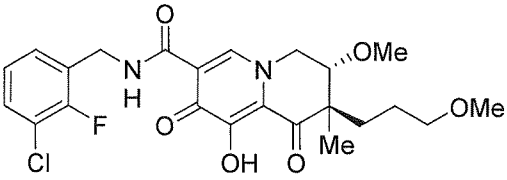
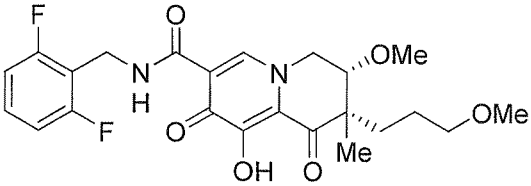
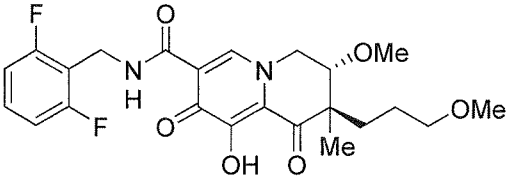
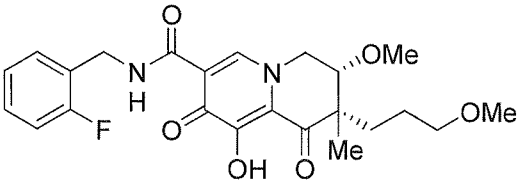
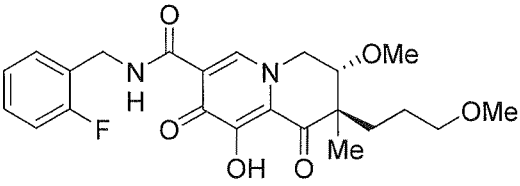
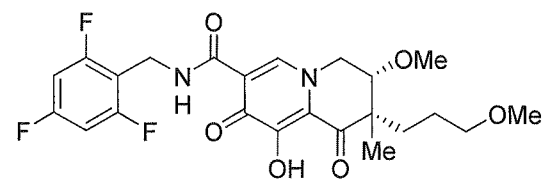
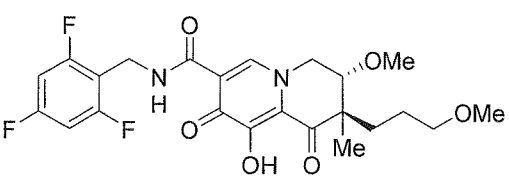
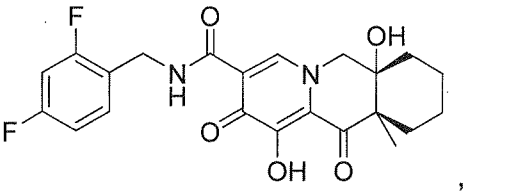

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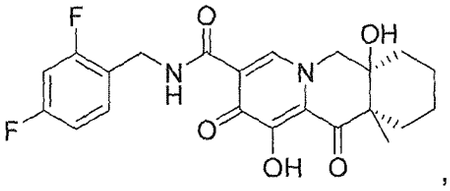
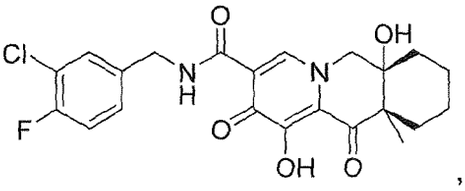
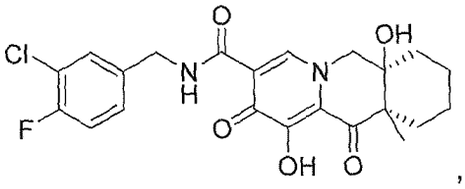
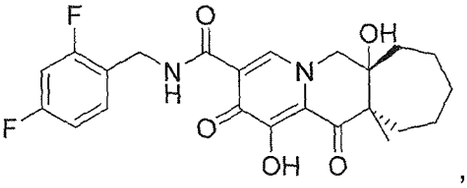
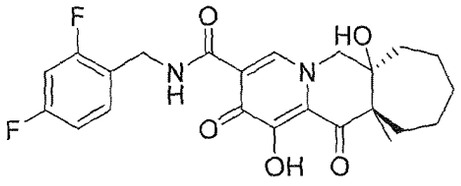
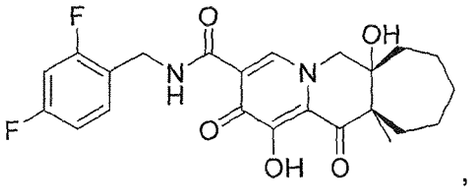
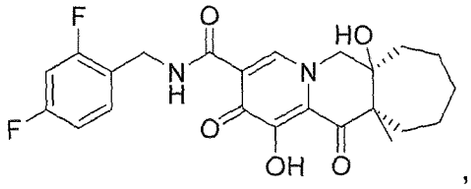
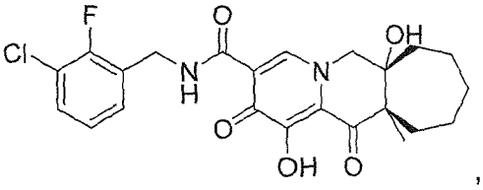
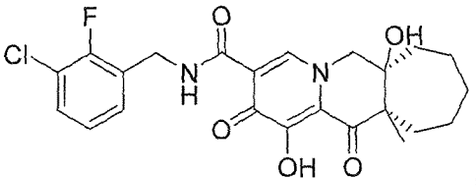
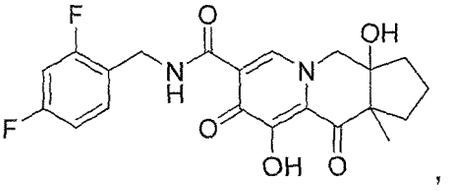
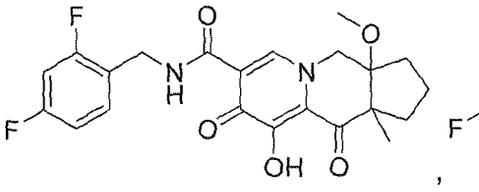
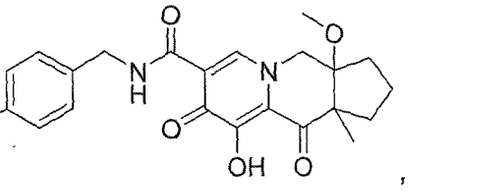
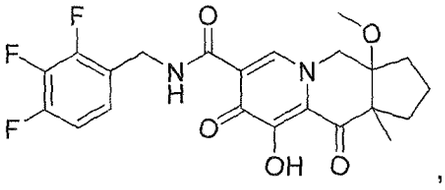
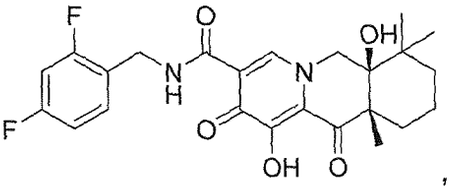
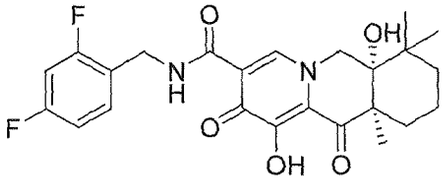
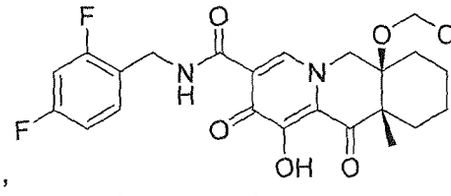
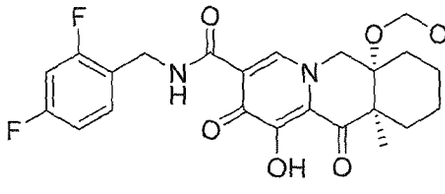
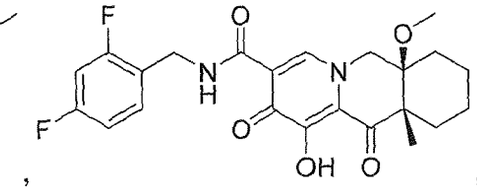
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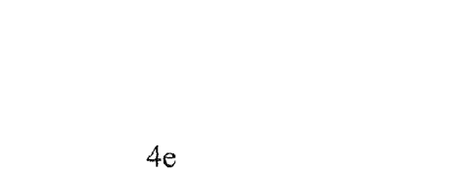
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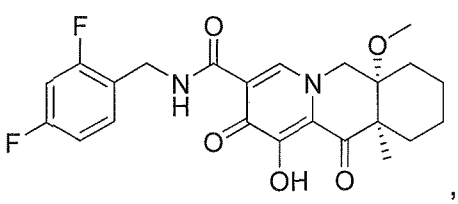
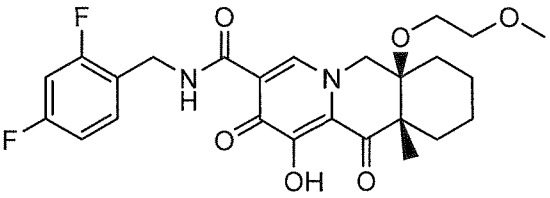
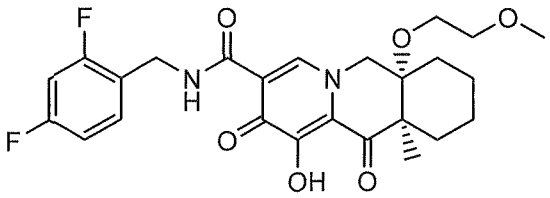
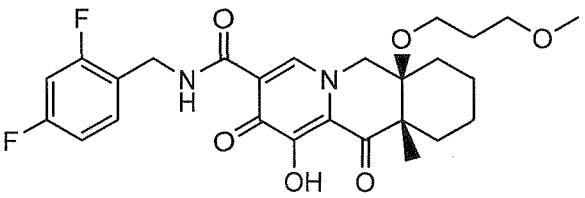
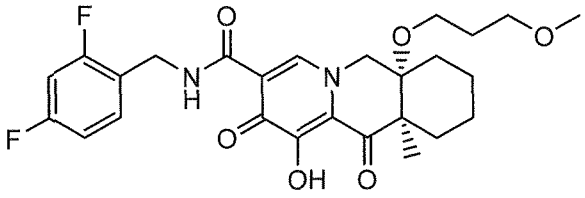
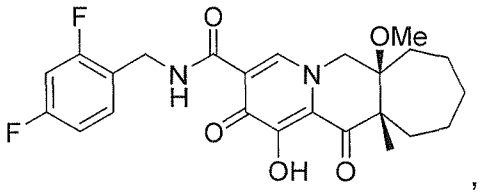
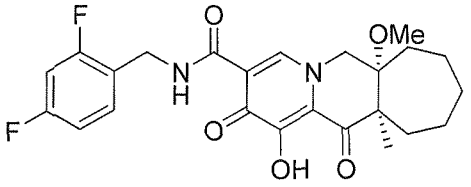
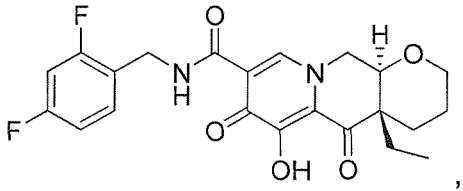
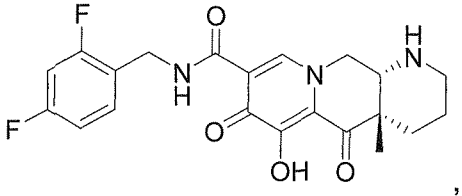
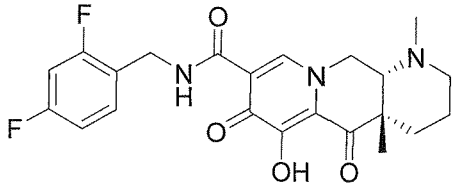

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or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides a pharmaceutical composition comprising an effective amount of a compound as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The Compounds of Formula (I) (also referred to herein as the "Substituted Quinolizine Derivatives") and pharmaceutically acceptable salts or prodrugs thereof can be useful, for example, for inhibiting HIV viral replication or replicon activity, or for treating or preventing HIV infection in a subject. Without being bound by any specific theory, it is believed that the Substituted Quinolizine Derivatives inhibit HIV viral replication by inhibiting HIV Integrase.

Accordingly, the present disclosure provides methods for treating or preventing HIV infection in a subject, comprising administering to the subject an effective amount of at least one Substituted Quinolizine Derivative.

In another aspect, the present disclosure provides a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

In another aspect, the present disclosure provides use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the inhibition of HIV integrase in a subject in need thereof.

In another aspect, the present disclosure provides use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of infection by HIV or for the treatment of AIDS in a subject in need thereof.

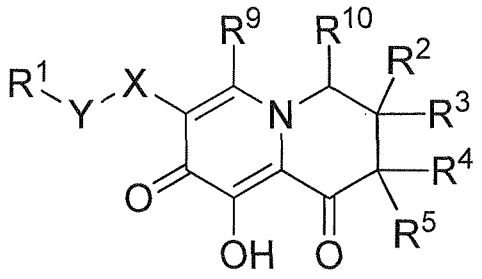
In another aspect, the present disclosure provides use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment or prophylaxis of infection by HIV, or for the prophylaxis, or delay in the onset or progression of AIDS in a subject in need thereof.

The details of the disclosure are set forth in the accompanying detailed description below.

Although any methods and materials similar to those described herein can be used in the practice or testing of the present disclosure, illustrative methods and materials are now described. Other embodiments, aspects and features of the present disclosure are either further described in or will be apparent from the ensuing description, examples and appended claims.

WHAT IS CLAIMED IS:

1. A compound having the formula:



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

X is selected from a 5-membered monocyclic heteroaryl and-N(R^6)C(O)-;

Y is C_1-C_3 alkylene;

R^1 is selected from phenyl, 5 or 6-membered monocyclic heteroaryl and 9-membered bicyclic heteroaryl, wherein said phenyl group, said 5 or 6-membered monocyclic heteroaryl group and said 9-membered bicyclic heteroaryl group can each be optionally substituted with up to three R^8 groups;

R^2 is H, methyl, or -OR^7 or R^2 and R^4, together with the carbon atoms to which they are attached, can join to form a 5 to 7-membered monocyclic cycloalkyl group, 5 to 7-membered monocyclic heterocycloalkyl group, or a 5 to 7-membered monocyclic heterocycloalkenyl group, wherein said 5 to 7-membered monocyclic cycloalkyl group, said 5 to 7-membered monocyclic heterocycloalkyl group, and said 5 to 7-membered monocyclic heterocycloalkenyl group can be optionally substituted with up to three R^8 groups, which can be the same or different;

R^3 is H, methyl, or -OR^7;

R^4 is selected from methyl, ethyl, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), and -OR^7;

R^5 is selected from methyl, ethyl, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), and -OR^7;

each occurrence of R^6 is independently H or C_1-C_6 alkyl;

each occurrence of R^7 is independently selected from H, C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl) and C_3-C_7 cycloalkyl;

each occurrence of R^8 is independently selected from C_1-C_6 alkyl, halo and -OR^6;

R^9 is H; and

R^{10} is H.

2. The compound of claim 1, wherein X is -NHC(O)-, or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein X is 5-membered monocyclic heteroaryl, or a pharmaceutically acceptable salt thereof.

4. The compound of any of claims 1-3, wherein Y is CH_2, or a pharmaceutically acceptable salt thereof.

5. The compound of any of claims 1-4, wherein R^1 is phenyl or 9-membered bicyclic heteroaryl, wherein said phenyl and said 9-membered bicyclic heteroaryl groups can each be optionally substituted with up to three R^8 groups, or a pharmaceutically acceptable salt thereof.

6. The compound of claim 5, wherein R^1 is phenyl, which is substituted by 1 to 3 halo groups, which can be the same or different, or a pharmaceutically acceptable salt thereof.

7. The compound of claim 5, wherein R^1 is 2,4-difluorophenyl or 3-chloro-2-fluorophenyl, or a pharmaceutically acceptable salt thereof.

8. The compound of any of claims 1-7, wherein R^2 and R^3 are each independently selected from H, –OH and –O-(C_1-C_6 alkyl), or a pharmaceutically acceptable salt thereof.

9. The compound of any of claims 1-8, wherein one of R^2 is H and R^3 is –OH or –O-(C_1-C_6 alkyl), or a pharmaceutically acceptable salt thereof.

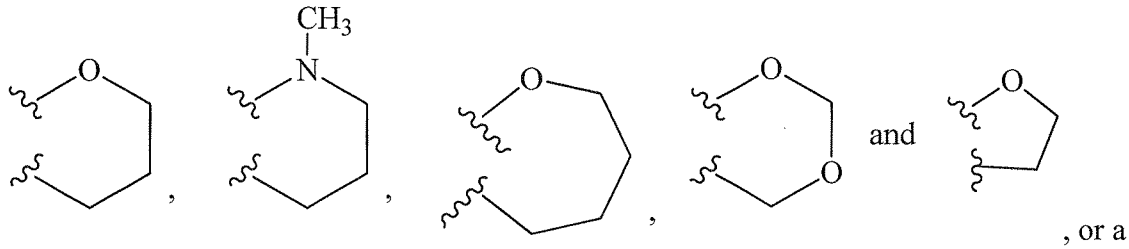
10. The compound of any of claims 1-9, wherein R^4 and R^5 are each independently selected from methyl, ethyl, and –(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), or a pharmaceutically acceptable salt thereof.

11. The compound of claim 10, wherein R^4 and R^5 are each independently selected from methyl and $–CH_2CH_2OCH_3$, or a pharmaceutically acceptable salt thereof.

12. The compound of any of claims 1-7, wherein R^2 and R^4, together with the carbon atoms to which they are attached, join to form a 5 to 7-membered monocyclic heterocycloalkyl group, or a pharmaceutically acceptable salt thereof.

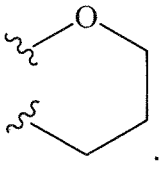
13. The compound of any of claims 1-12, wherein R^5 is methyl, or a pharmaceutically acceptable salt thereof.

14. The compound of claim 5 wherein R^3 is H; R^5 is methyl; and R^2 and R^4, together with the carbon atoms to which they are attached, join to form a group selected from:



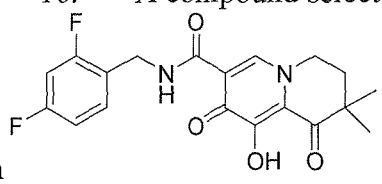
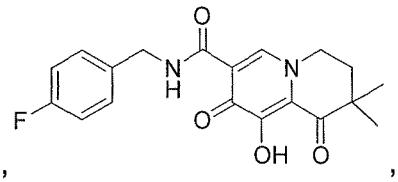
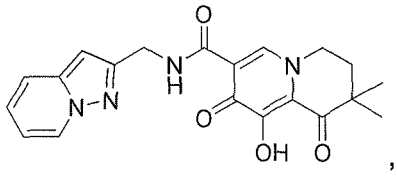
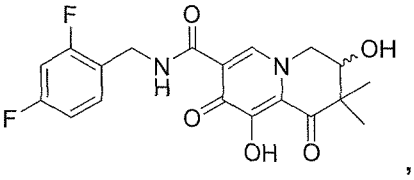
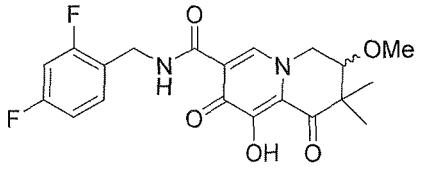
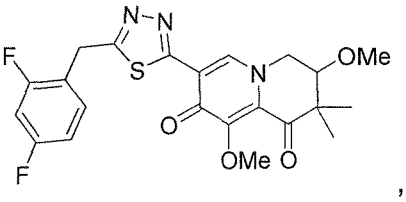
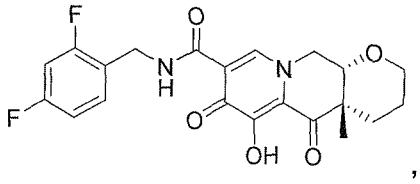
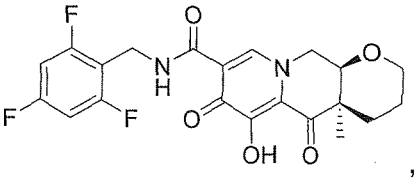
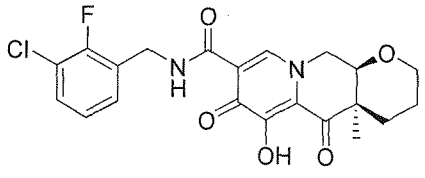
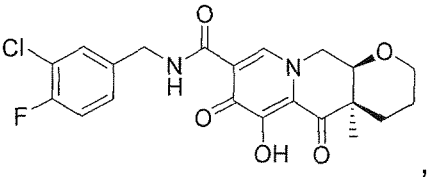
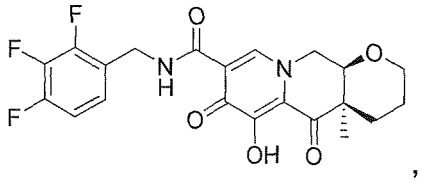
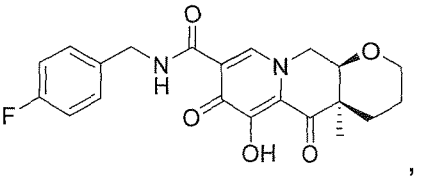
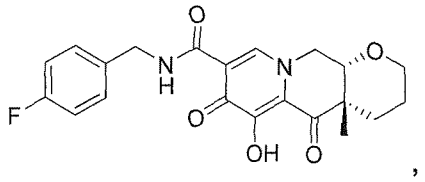
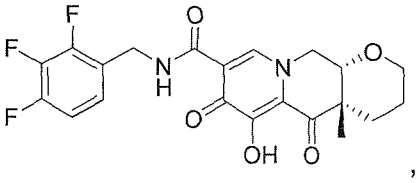
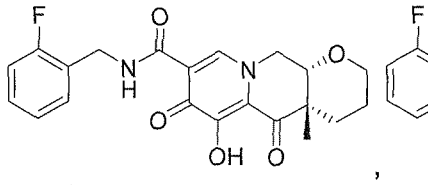
, or a pharmaceutically acceptable salt thereof.

15. The compound of any of claims 1-7 and 12-14, wherein R^2 and R^4, together with the carbon atoms to which they are attached, join to form:



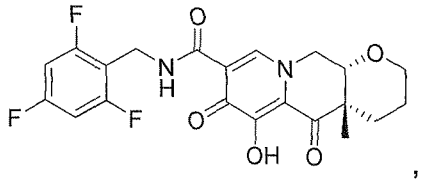
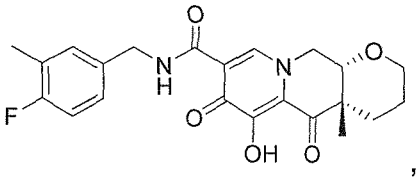
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16. A compound selected from


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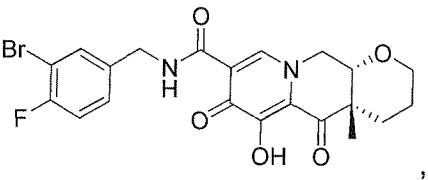
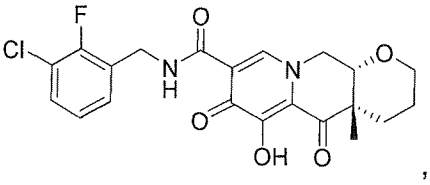
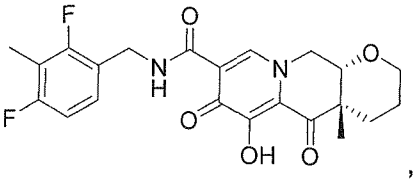
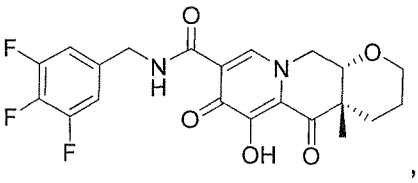
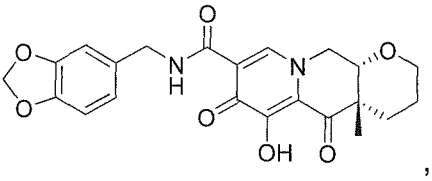
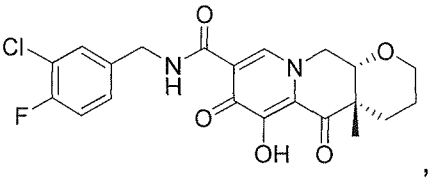
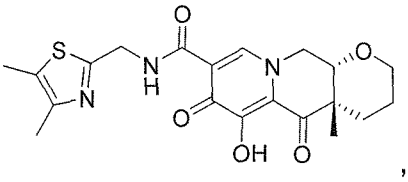
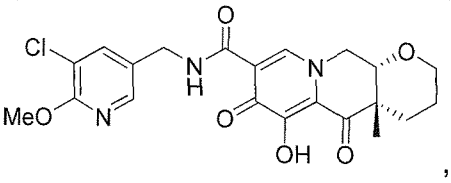
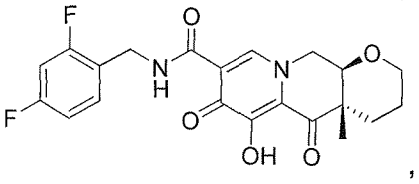
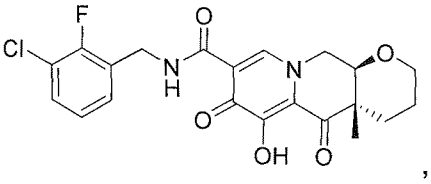
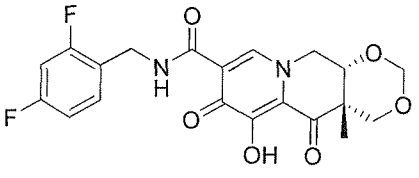
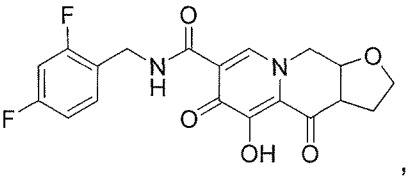
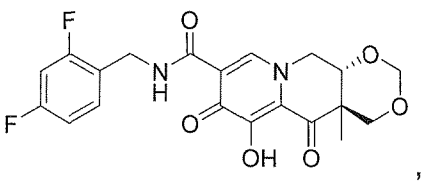
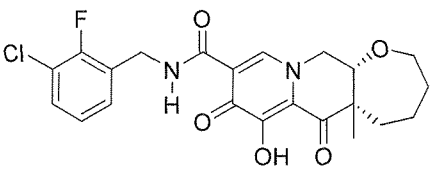
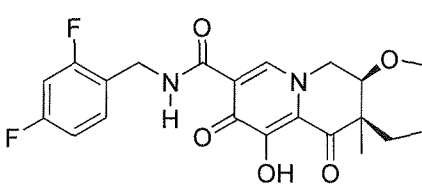
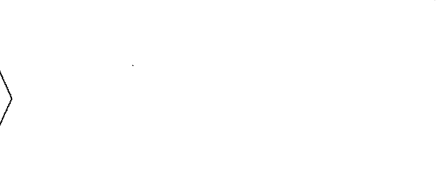
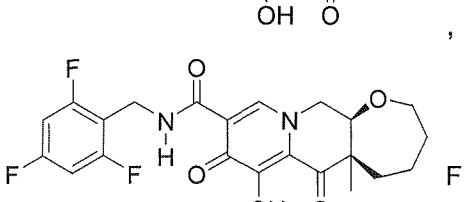
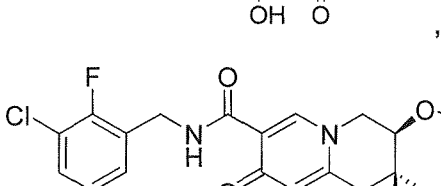
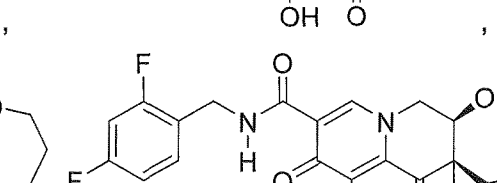
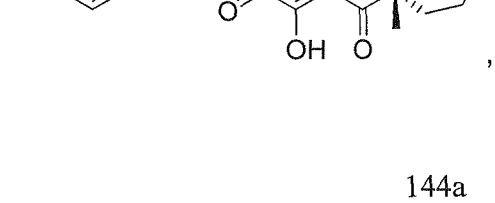
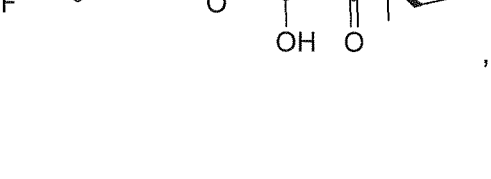
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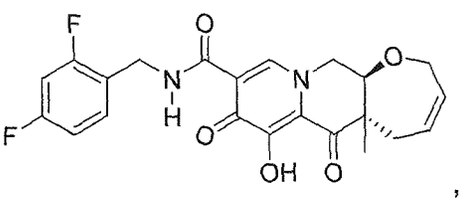
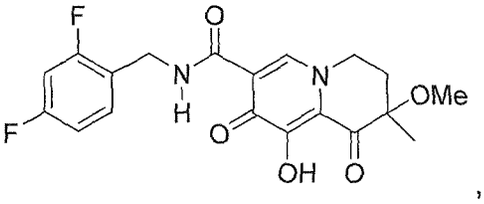
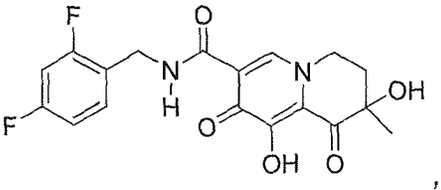
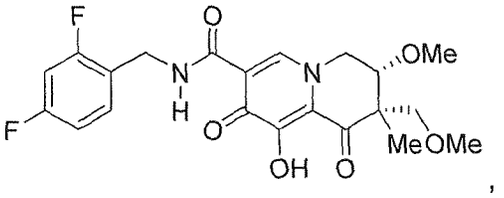
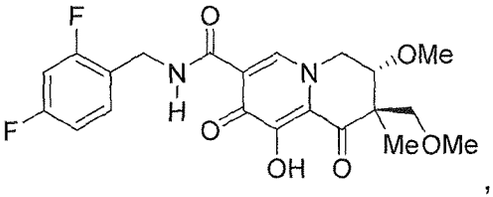
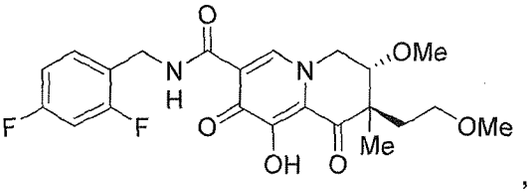
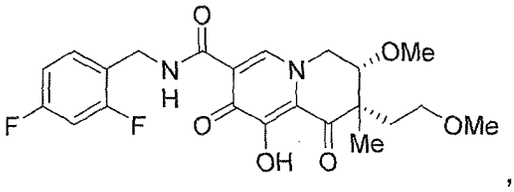
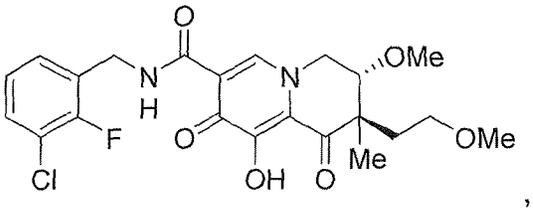
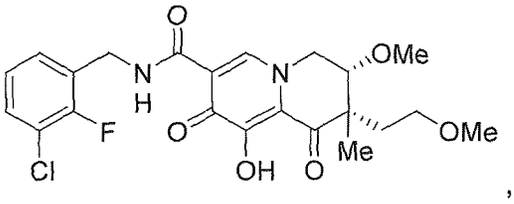
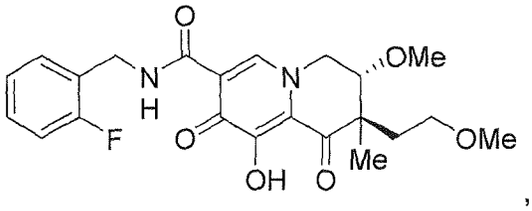
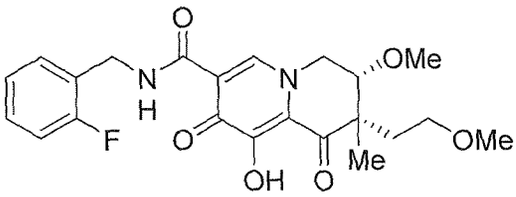
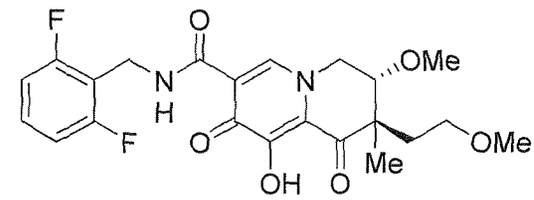
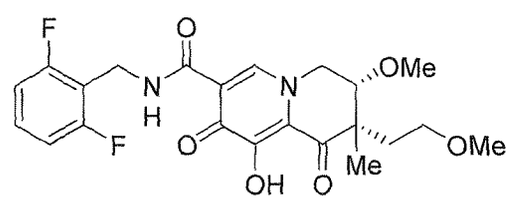
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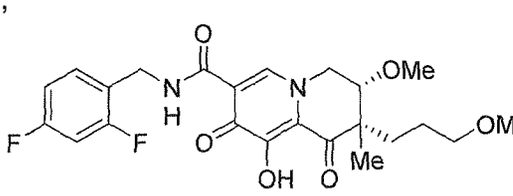
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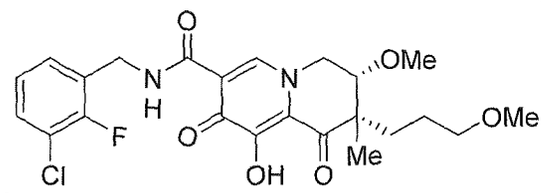
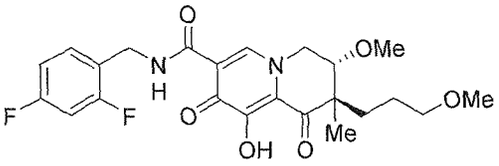

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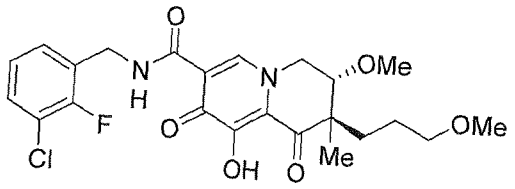
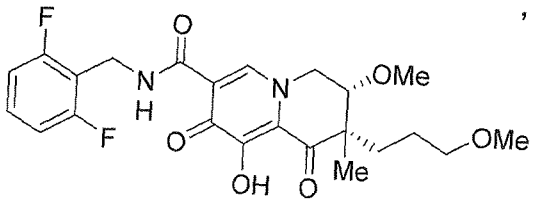
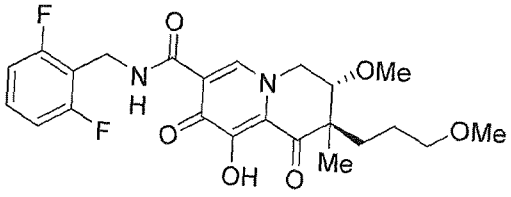
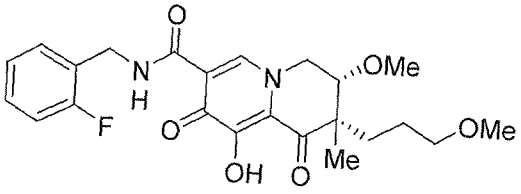
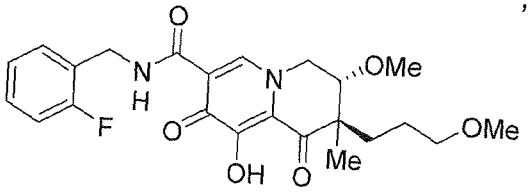
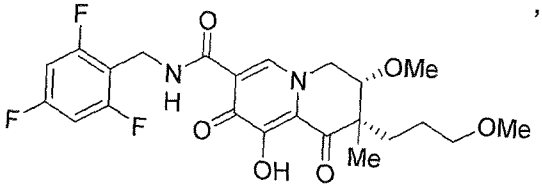
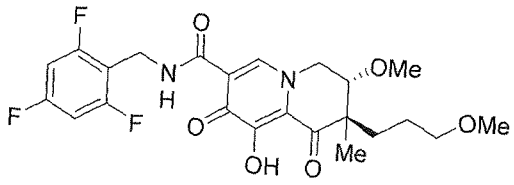
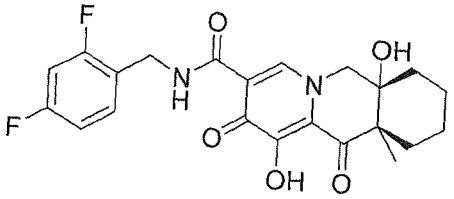
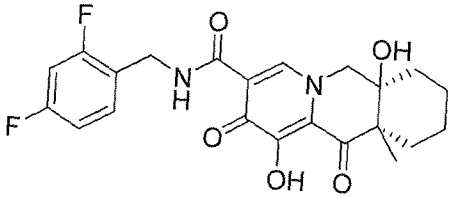
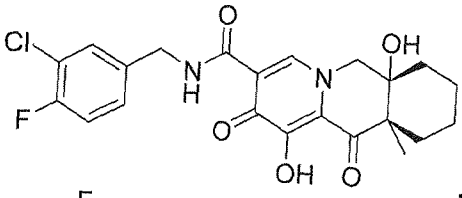
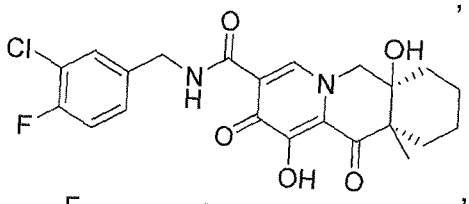
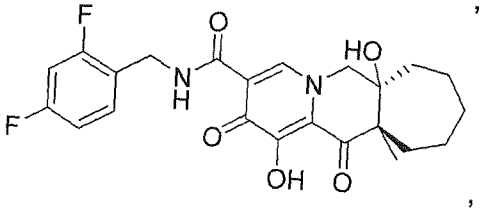
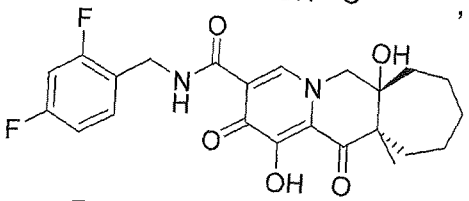

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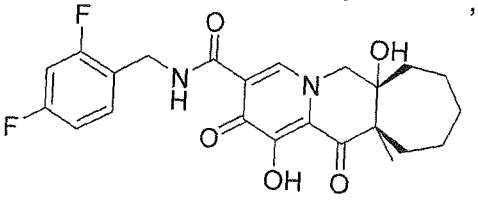
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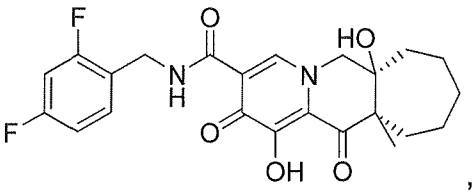
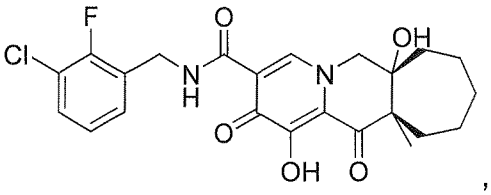
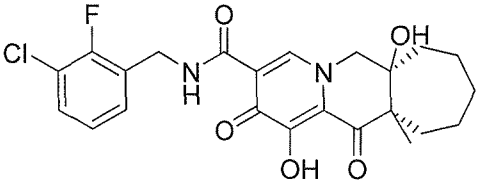
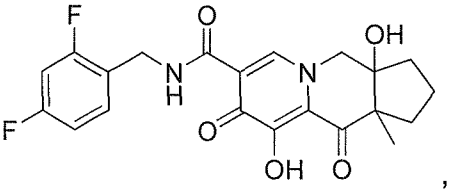
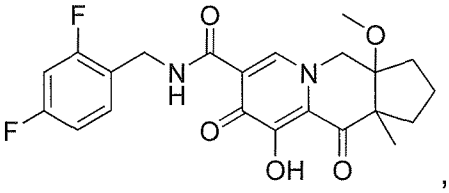
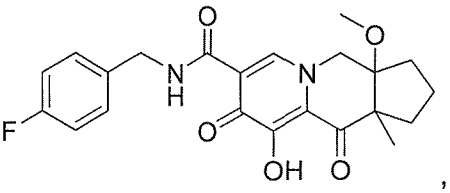
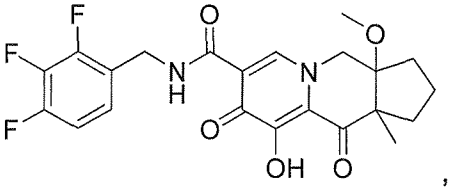
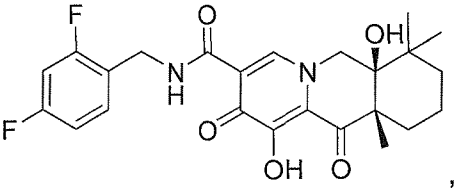
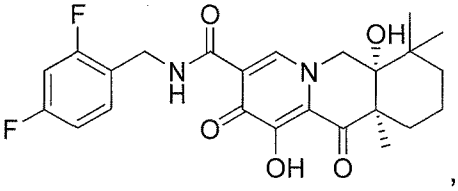
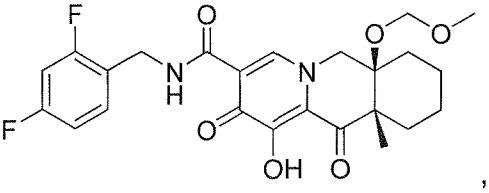
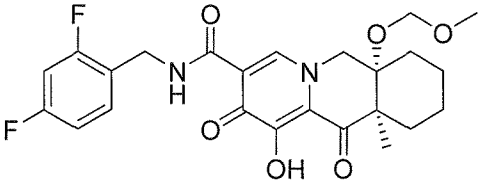
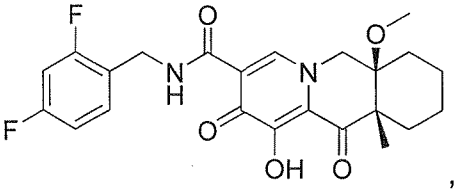
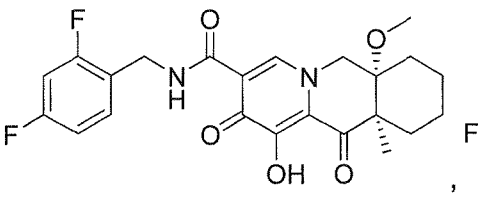
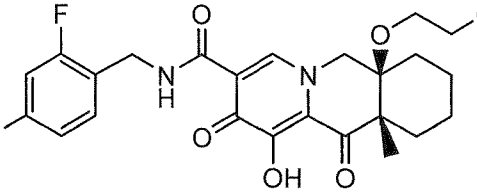
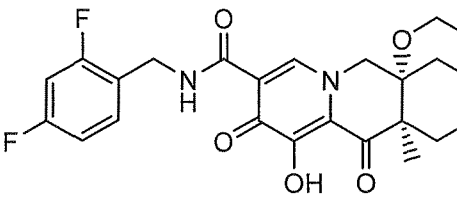
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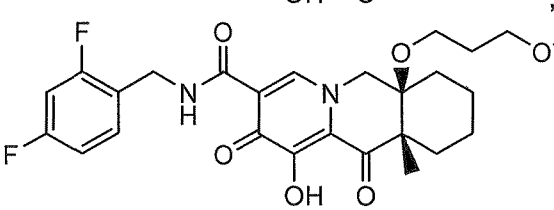
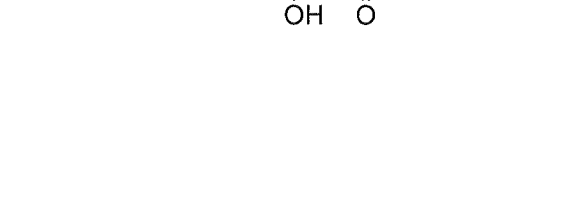
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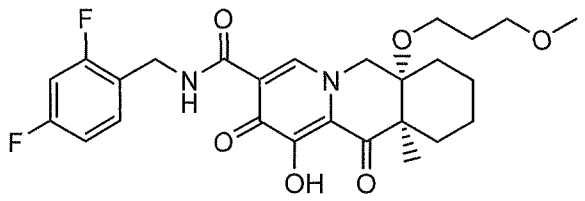
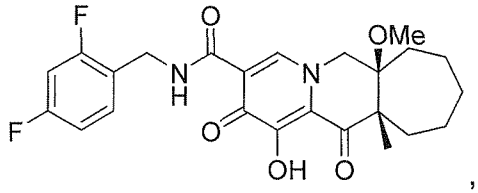
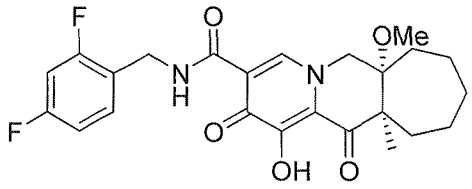
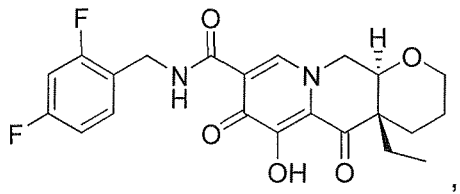
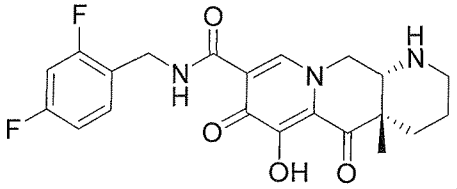
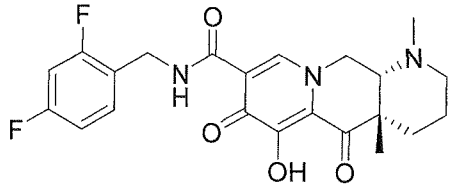

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or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition comprising an effective amount of a compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

18. A compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, for use in therapy.

19. Use of a compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the inhibition of HIV integrase in a subject in need thereof.

20. Use of a compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of infection by HIV or for the treatment of AIDS in a subject in need thereof.

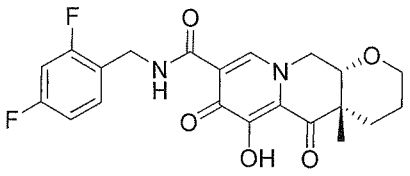
21. Use of a compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment or prophylaxis of

infection by HIV, or for the prophylaxis, or delay in the onset or progression of AIDS in a subject in need thereof.

22. The pharmaceutical composition of claim 17, further comprising one or more additional therapeutic agents selected from, lamivudine, abacavir, ritonavir, darunavir, atazanavir, emtricitabine, tenofovir, rilpivirine and lopinavir.

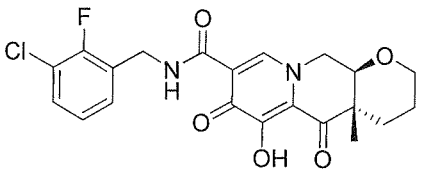
23. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, and one or more additional therapeutic agents selected from lamivudine, abacavir, ritonavir, darunavir, atazanavir, emtricitabine, tenofovir, rilpivirine and lopinavir for use in the inhibition of HIV integrase, for use in the treatment or prophylaxis of infection by HIV, or for use in the treatment, prophylaxis, or for use in delay in the onset or progression of AIDS in a subject in need thereof.

24. The compound of the formula



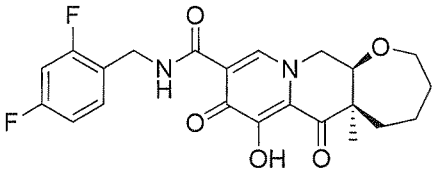
or a pharmaceutically acceptable salt thereof.

25. The compound of the formula



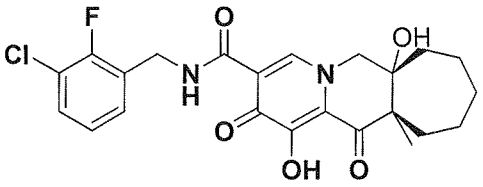
or a pharmaceutically acceptable salt thereof.

26. The compound of the formula



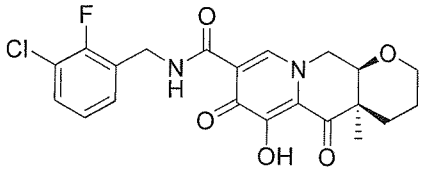
or a pharmaceutically acceptable salt thereof.

27. The compound of the formula



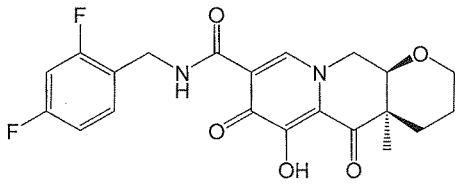
or a pharmaceutically acceptable salt thereof.

28. The compound of the formula



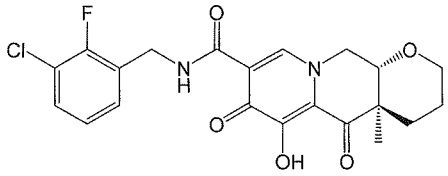
or a pharmaceutically acceptable salt thereof.

29. A compound of the formula



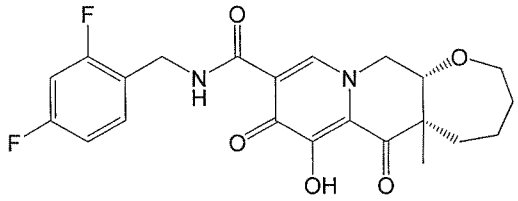
or a pharmaceutically acceptable salt thereof.

30. A compound of the formula



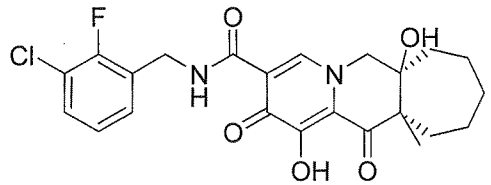
or a pharmaceutically acceptable salt thereof.

31. A compound of the formula



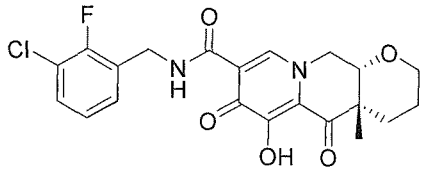
or a pharmaceutically acceptable salt thereof.

32. A compound of the formula



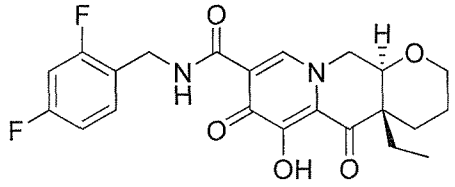
or a pharmaceutically acceptable salt thereof.

33. A compound of the formula



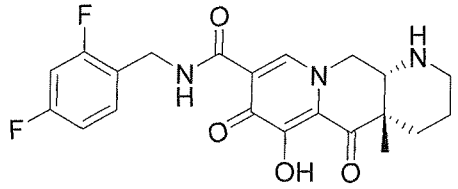
or a pharmaceutically acceptable salt thereof.

34. A compound of the formula



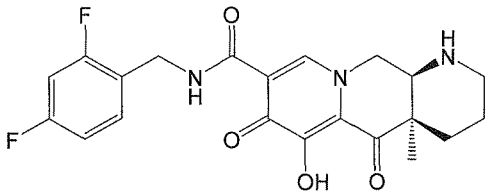
or a pharmaceutically acceptable salt thereof.

35. A compound of the formula



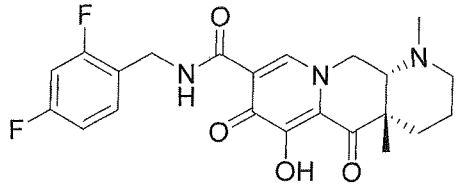
or a pharmaceutically acceptable salt thereof.

36. A compound of the formula



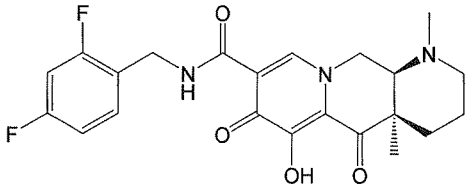
or a pharmaceutically acceptable salt thereof.

37. A compound of the formula



or a pharmaceutically acceptable salt thereof.

38. A compound of the formula



or a pharmaceutically acceptable salt thereof.