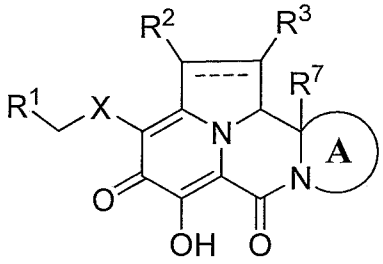
US 2007/0111984 discloses a series of bicyclic pyrimidinone compounds useful as HIV integrase inhibitors.

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.

US7462608 and US7649015 each disclose phosphate and phosphonate substituted heterocycles useful as HIV nNRTI inhibitors and HIV protease inhibitors, respectively.

## SUMMARY

In one aspect, the present disclosure provides Compounds of Formula (I):



(I)

or pharmaceutically acceptable salts thereof,

wherein:

----- represents an optional double bond;

ring A, inclusive of the carbon atom and nitrogen atom to which ring A is fused, is a 5- to 8-membered monocyclic or bicyclic heterocycloalkyl group, which can be optionally and independently substituted on ring A carbon atom with a group selected from $C_1$-$C_6$ alkyl, -O-($C_1$-$C_6$ alkyl) and $C_3$-$C_7$ cycloalkyl, and which can be optionally and independently substituted on a ring nitrogen atom with a group selected from $C_1$-$C_6$ alkyl, -C(O)-($C_1$-$C_6$ alkyl) and -$S(O)_2$-($C_1$-$C_6$ alkyl);

X is selected from 5 or 6-membered monocyclic heteroaryl and -$N(R^4)C(O)$-;

$R^1$ is a phenyl group which is optionally substituted with from 1 to 3 groups, each independently selected from $C_1$-$C_6$ alkyl, halo, -O-($C_1$-$C_6$ alkyl), $C_1$-$C_6$ haloalkyl, -O-($C_1$-$C_6$ haloalkyl), -CN, -$NO_2$, -$N(R^4)_2$, -$C(O)OR^6$, -$C(O)N(R^4)_2$ and -$NHC(O)R^6$;

$R^2$ is selected from H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, halo, $C_1$-$C_6$ haloalkyl, -$OR^5$, -$N(R^4)_2$, -$C(O)R^5$, -$C(O)N(R^4)_2$ and -$NHC(O)R^5$, wherein said $C_1$-$C_6$ alkyl group is optionally substituted with one or more groups, each independently selected from halo, -OH, -O($C_1$-$C_6$ alkyl) and -$N(R^4)_2$;

$R^3$ is selected from H, $C_1$-$C_6$ alkyl and -O-($C_1$-$C_6$ alkyl), -N($R^4$)$_2$;

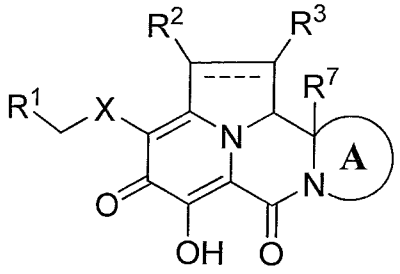
each occurrence of $R^4$ is independently selected from H and $C_1$-$C_6$ alkyl;

each occurrence of $R^5$ is independently selected from H, $C_1$-$C_6$ alkyl and $C_3$-$C_7$ cycloalkyl;

each occurrence of $R^6$ is independently selected from H and $C_1$-$C_6$ alkyl; and

$R^7$ is selected from H and $C_1$-$C_6$ alkyl.

The present disclosure provides Compounds of Formula (I):




(I)

or pharmaceutically acceptable salts thereof,

wherein:

----- represents an optional double bond;

ring A, inclusive of the carbon atom and nitrogen atom to which ring A is fused, is a 5- to 7-membered monocyclic or bicyclic heterocycloalkyl group, which can be optionally and independently substituted on ring A carbon atom with a group selected from $C_1$-$C_6$ alkyl, -O-($C_1$-$C_6$ alkyl) and $C_3$-$C_7$ cycloalkyl, and which can be optionally and independently substituted on a ring nitrogen atom with a group selected from $C_1$-$C_6$ alkyl, -C(O)-($C_1$-$C_6$ alkyl) and -S(O)$_2$-($C_1$-$C_6$ alkyl);

X is selected from 5 or 6-membered monocyclic heteroaryl and -N($R^4$)C(O)-;

$R^1$ is a phenyl group which is optionally substituted with from 1 to 3 groups, each independently selected from $C_1$-$C_6$ alkyl, halo, -O-($C_1$-$C_6$ alkyl), $C_1$-$C_6$ haloalkyl, -O-($C_1$-$C_6$ haloalkyl), -CN, -NO$_2$, -N($R^4$)$_2$, -C(O)O$R^6$, -C(O)N($R^4$)$_2$ and -NHC(O)$R^6$;

$R^2$ is selected from H, $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, halo, $C_1$-$C_6$ haloalkyl, -O$R^5$, -N($R^4$)$_2$, -C(O)$R^5$, -C(O)N($R^4$)$_2$ and -NHC(O)$R^5$, wherein said $C_1$-$C_6$ alkyl group is optionally substituted with one or more groups, each independently selected from halo, -OH, -O($C_1$-$C_6$ alkyl) and -N($R^4$)$_2$;

$R^3$ is selected from H, $C_1$-$C_6$ alkyl and -O-($C_1$-$C_6$ alkyl), -N($R^4$)$_2$;

each occurrence of $R^4$ is independently selected from H and $C_1$-$C_6$ alkyl;

each occurrence of R5 is independently selected from H, C1-C6 alkyl and C3-C7 cycloalkyl;

each occurrence of $R^6$ is independently selected from H and $C_1$-$C_6$ alkyl; and

$R^7$ is selected from H and $C_1$-$C_6$ alkyl.

The Compounds of Formula (I) (also referred to herein as the "Tetracyclic Heterocycle Compounds") and pharmaceutically acceptable salts or prodrugs thereof may 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 Tetracyclic Heterocycle Compounds inhibit HIV viral replication by inhibiting HIV Integrase.

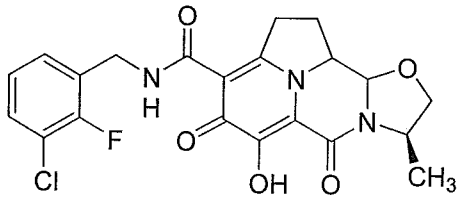
In another aspect, the present disclosure provides a pharmaceutical composition comprising an effective amount of a compound as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

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 Tetracyclic Heterocycle Compound.

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

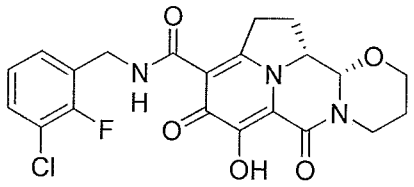
In another aspect, the present disclosure provides use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the inhibition of HIV integrase, for the treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis, or delay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

In another aspect, the present disclosure provides a compound having the structure:



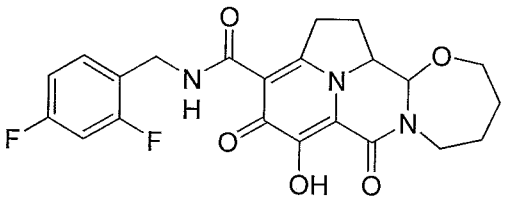

or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides a compound having the structure:



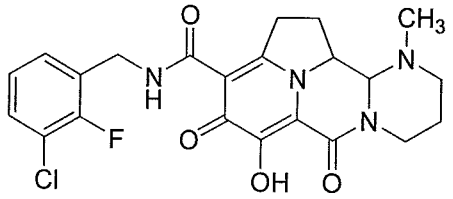
or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides a compound having the structure:



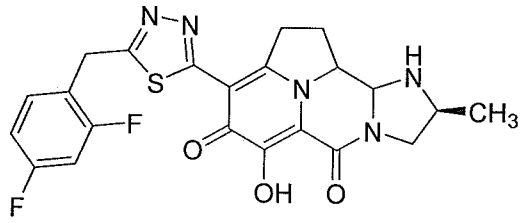
or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides a compound having the structure:



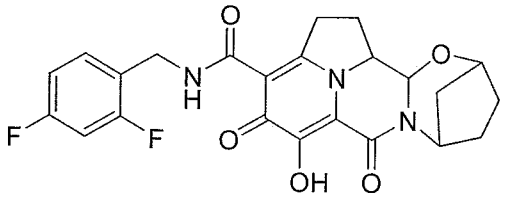
or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides a compound having the structure:



or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides a compound having the structure:



or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides a pharmaceutically acceptable salt of the compound as defined herein.

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

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

## DETAILED DESCRIPTION OF THE INVENTION

The present invention includes Tetracyclic Heterocycle Compounds, compositions comprising at least one Tetracyclic Heterocycle Compound, and methods of using the Tetracyclic Heterocycle Compounds for treating or preventing HIV infection in a subject.

### Definitions and Abbreviations

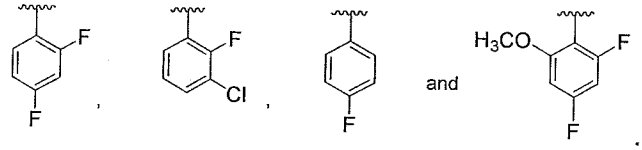
The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "hydroxyalkyl," "haloalkyl," "-O-alkyl," etc.

$R^1$ is a phenyl group which is optionally substituted with from 1 to 3 groups, each independently selected from $C_1$-$C_6$ alkyl, halo and -O-($C_1$-$C_6$ alkyl);

$R^2$ is selected from H and –O-($C_1$-$C_6$ alkyl); and

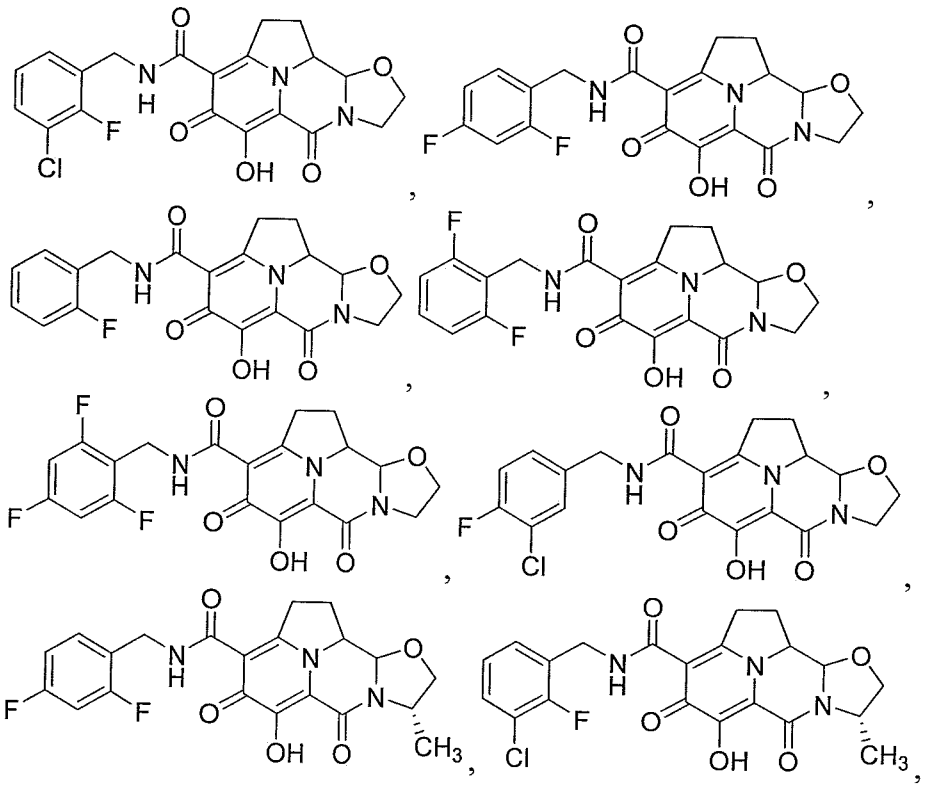
$R^7$ is selected from H and $C_1$-$C_6$ alkyl.

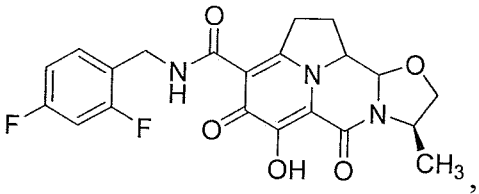
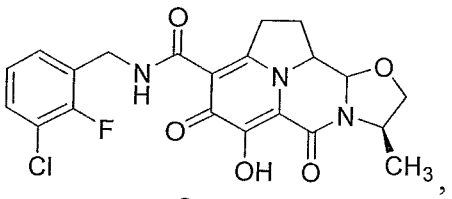
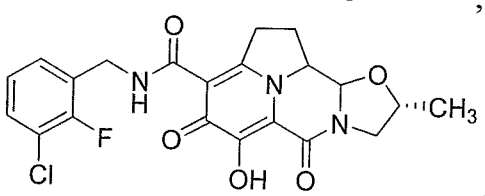
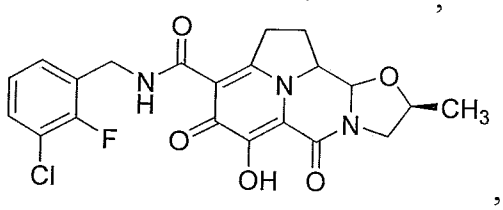
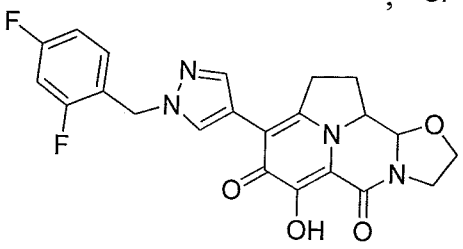
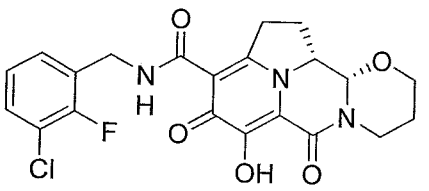
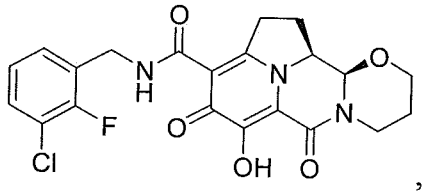
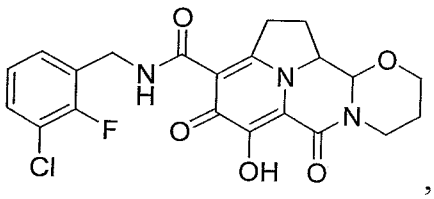
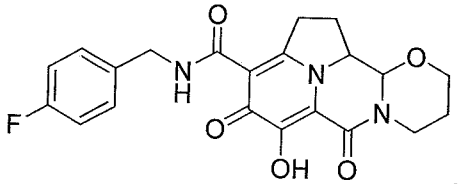
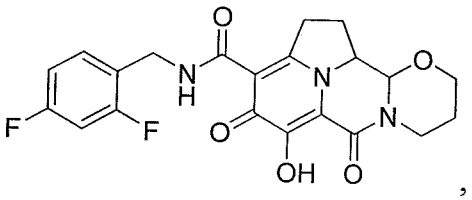
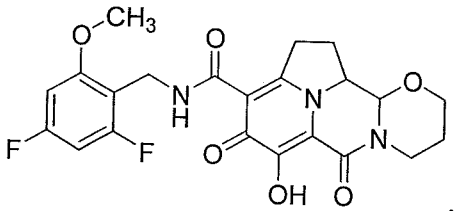
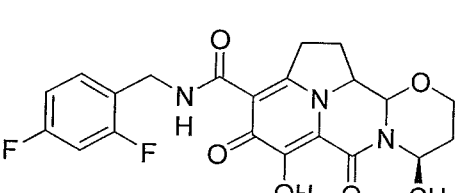
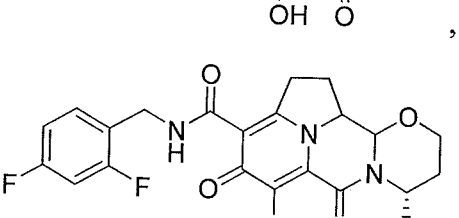
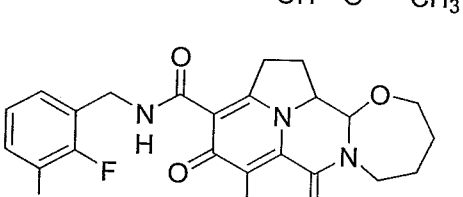
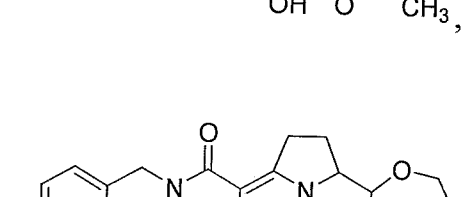
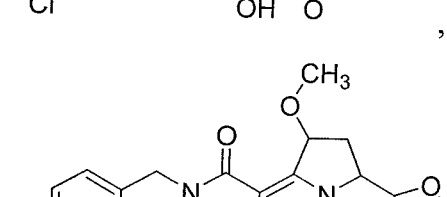
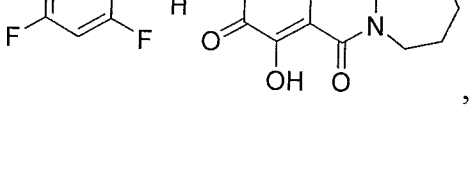
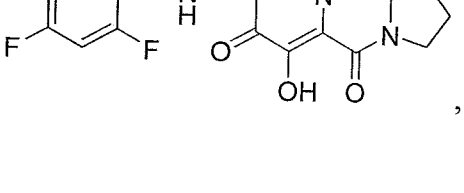
8. The compound of any of claims 1-7, wherein $R^1$ is selected from:

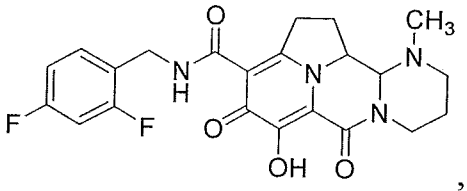
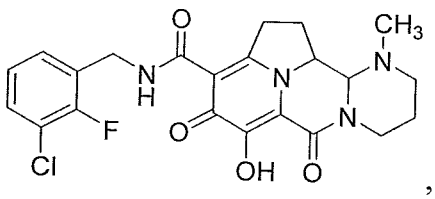
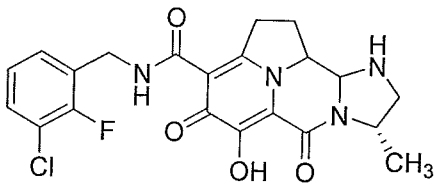
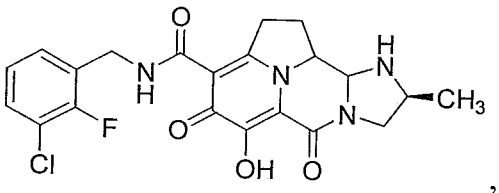
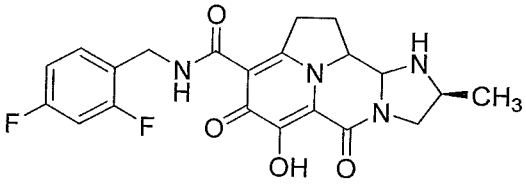
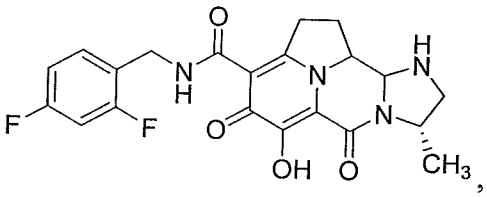
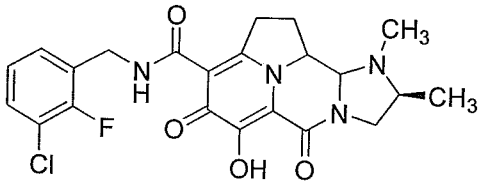
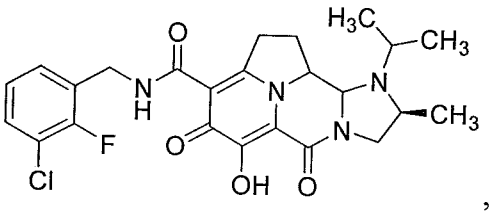
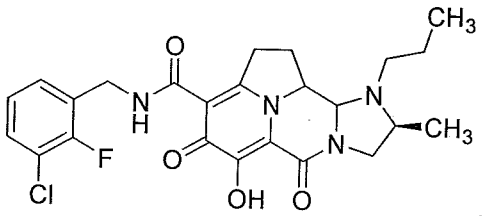
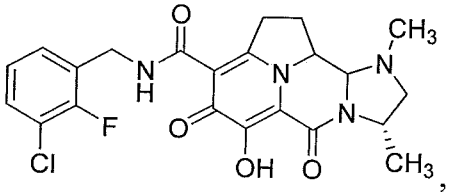
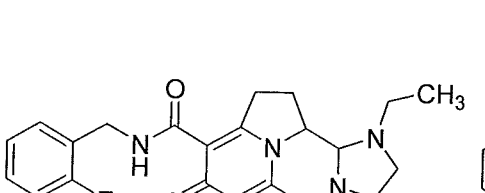
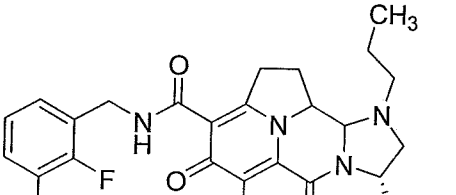
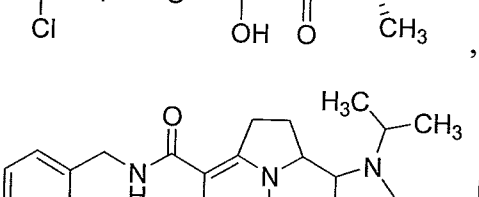


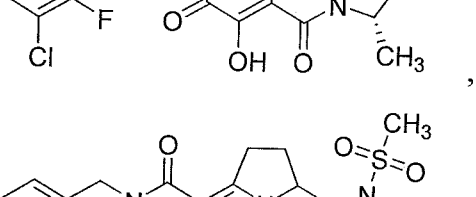
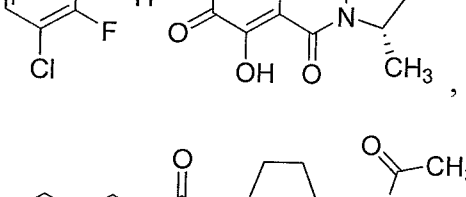
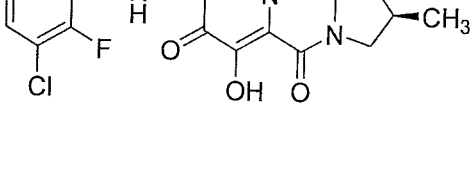
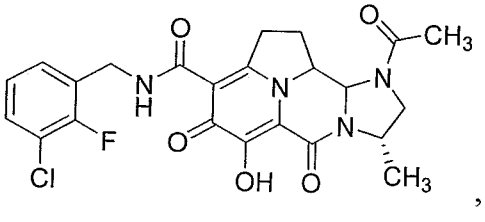

9. The compound of any of claims 1-8, wherein $R^7$ is H.

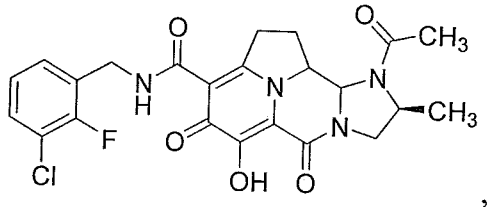
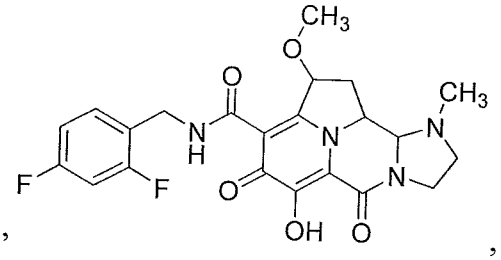
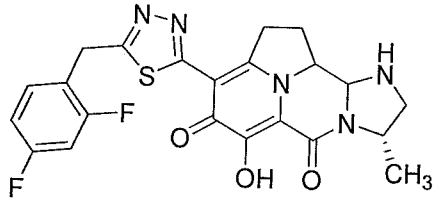
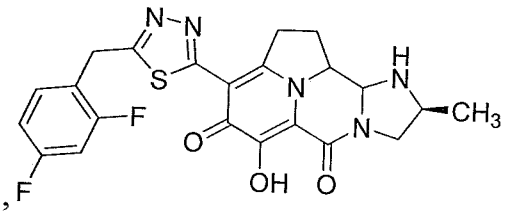
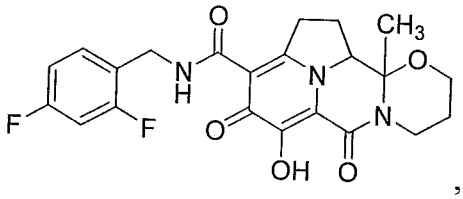
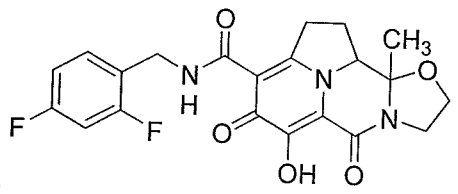
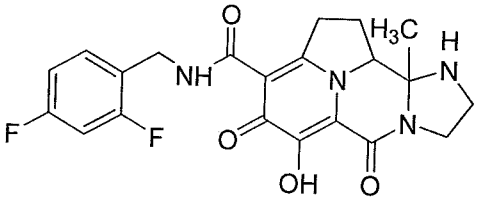
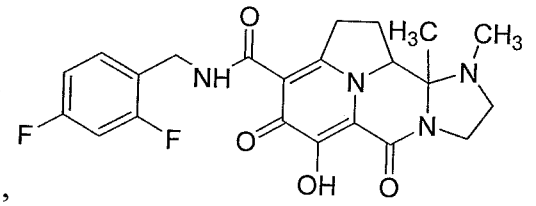
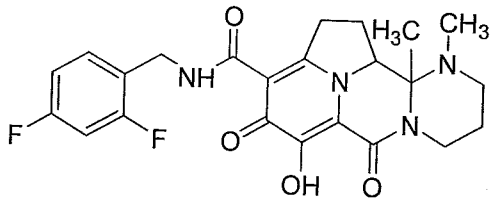
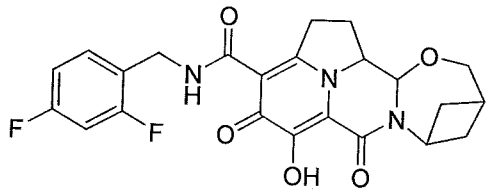
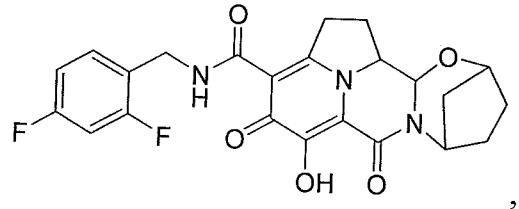
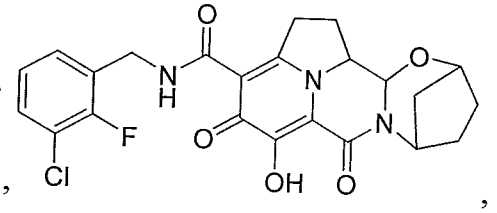
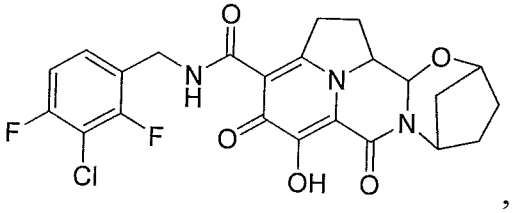
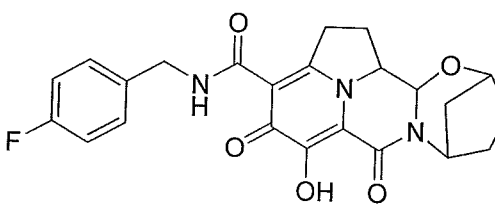
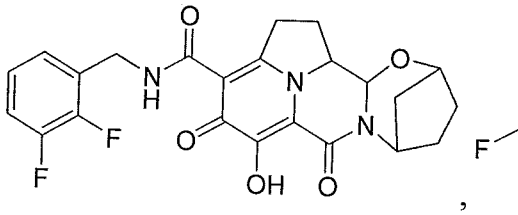
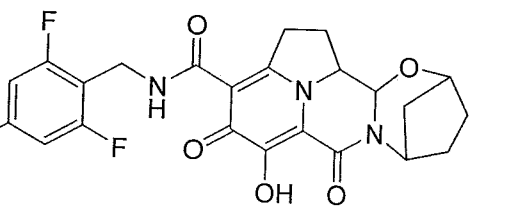
10. A compound of claim 1 selected from




,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

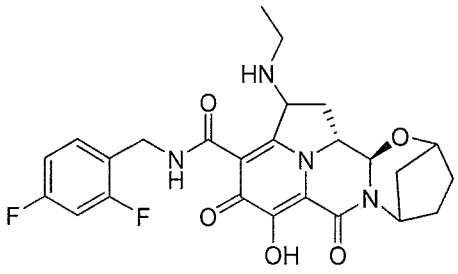
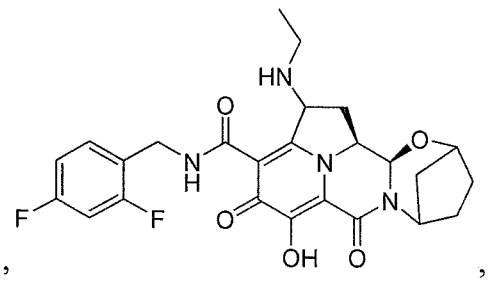
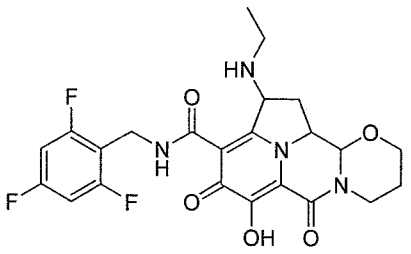
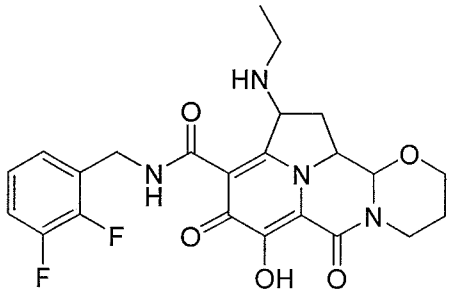
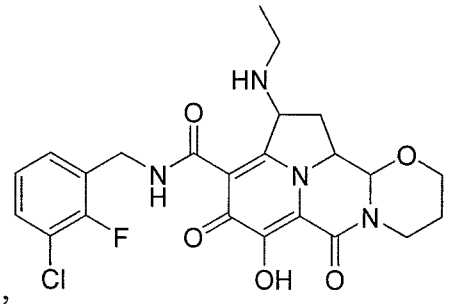
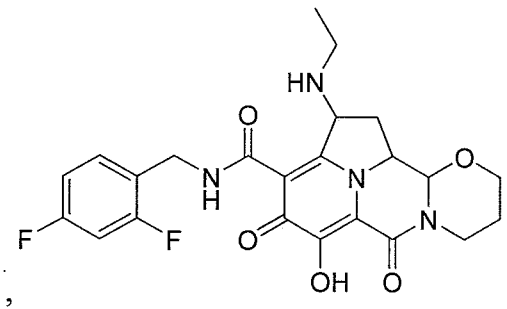

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

, or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising an effective amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

12. A compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use as a medicament.

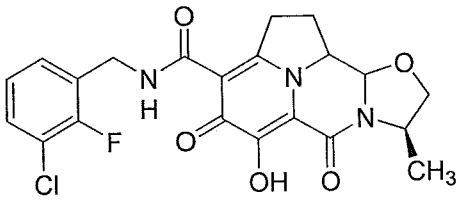
13. Use of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the inhibition of HIV integrase, for the treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in a subject in need thereof.

5

14. The pharmaceutical composition of claim 11, further comprising one or more additional therapeutic agents selected from: lamivudine, abacavir, ritonavir, darunavir, atazanavir, emtricitabine, tenofovir, rilpivirine and lopinavir.

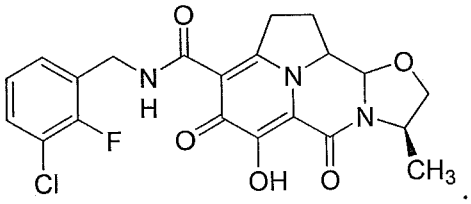
15. The use of claim 13, further comprising one or more additional therapeutic agents selected from: abacavir, lamivudine, ritonavir and lopinavir.

16. A compound having the structure:



or a pharmaceutically acceptable salt thereof.

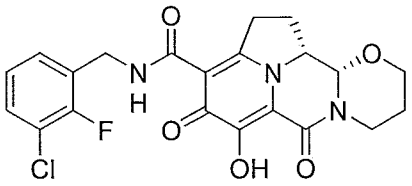
17. The compound of claim 16 having the structure:



18. A pharmaceutically acceptable salt of the compound of claim 16.

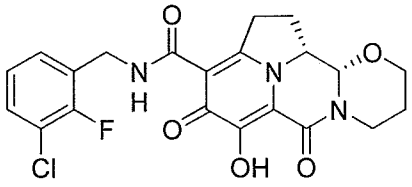
19. A pharmaceutical composition comprising the compound of claim 16 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

20. A compound having the structure:



or a pharmaceutically acceptable salt thereof.

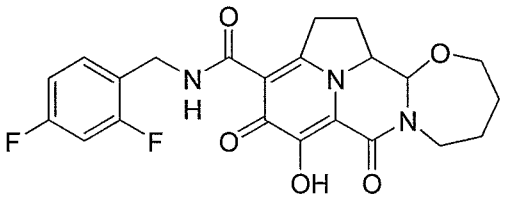
21. The compound of claim 20 having the structure:



22. A pharmaceutically acceptable salt of the compound of claim 20.

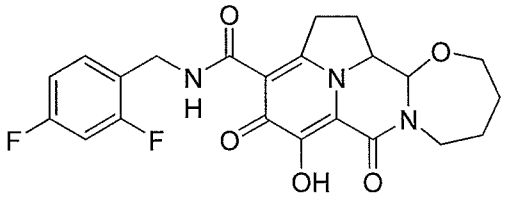
23. A pharmaceutical composition comprising the compound of claim 20 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

24. A compound having the structure:



or a pharmaceutically acceptable salt thereof.

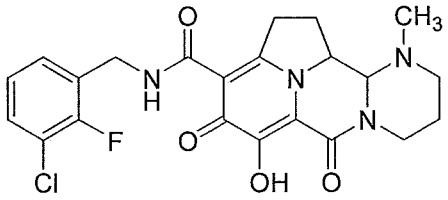
25. The compound of claim 24 having the structure:



26. A pharmaceutically acceptable salt of the compound of claim 24.

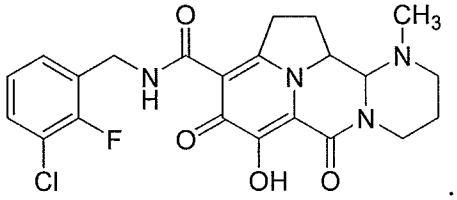
27. A pharmaceutical composition comprising the compound of claim 24 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

28. A compound having the structure:



or a pharmaceutically acceptable salt thereof.

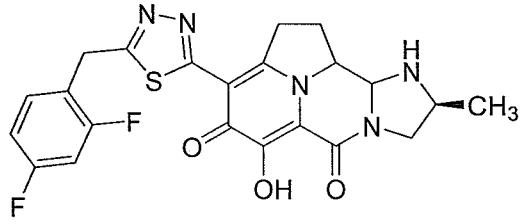
29. The compound of claim 28 having the structure:



30. A pharmaceutically acceptable salt of the compound of claim 28.

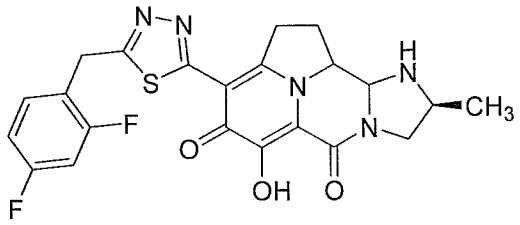
31. A pharmaceutical composition comprising the compound of claim 28 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

32. A compound having the structure:



or a pharmaceutically acceptable salt thereof.

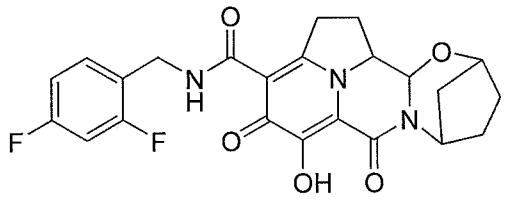
33. The compound of claim 32 having the structure:



34. A pharmaceutically acceptable salt of the compound of claim 32.

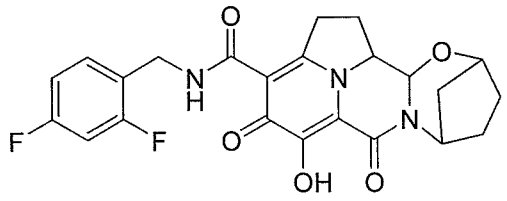
35. A pharmaceutical composition comprising the compound of claim 32 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

36. A compound having the structure:



or a pharmaceutically acceptable salt thereof.

37. The compound of claim 36 having the structure:



38. A pharmaceutically acceptable salt of the compound of claim 36.

39. A pharmaceutical composition comprising the compound of claim 36 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.