PYRROLE COMPOUNDS

INCORPORATION BY REFERENCE TO ANY PRIORITY APPLICATIONS

[0001] Any and all applications for which a foreign or domestic priority claim is identified, for example, in the Application Data Sheet or Request as filed with the present application, are hereby incorporated by reference under 37 CFR 1.57, and Rules 4.18 and 20.6, including U.S. Provisional Application Nos. 62/828919, filed April 3, 2019 and 62/932686, filed November 8, 2019.

BACKGROUND

Field

[0002] The present application relates to the fields of chemistry, biochemistry and medicine. Disclosed herein are compounds of Formula (I), or pharmaceutically acceptable salts thereof, pharmaceutical compositions that include a compound described herein (including pharmaceutically acceptable salts of a compound described herein) and methods of synthesizing the same. Also disclosed herein are methods of treating diseases and/or conditions with a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

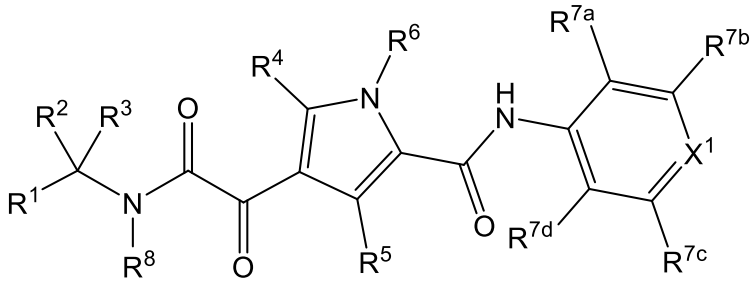
Description

[0003] The hepatitis B virus (HBV) is a DNA virus and a member of the *Hepadnaviridae* family. HBV infects more than 300 million worldwide, and is a causative agent of liver cancer and liver disease such as chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Although there are approved drugs for treating HBV, by either boosting the immune system or slowing down the replication of the HBV virus, HBV continues to be a problem due to the drawbacks associated with each of the approved drugs.

SUMMARY

[0004] Some ~~embodiments~~ examples disclosed herein relate to a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0004a] In one aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



(I)

wherein:

R^1 is an unsubstituted or a substituted C_2 alkenyl or an unsubstituted or a substituted C_2 alkynyl, wherein when the C_2 alkenyl and the C_2 alkynyl are substituted, the C_2 alkenyl and the C_2 alkynyl are independently substituted with one or more substituents independently selected from the group consisting of halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{1-4} hydroxyalkyl, an unsubstituted monocyclic C_{3-6} cycloalkyl and a hydroxy-substituted monocyclic C_{3-6} cycloalkyl;

R^2 and R^3 are independently selected from the group consisting of hydrogen, an unsubstituted or a substituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl, an unsubstituted or a substituted monocyclic 3-6 membered heterocyclyl, an unsubstituted C_{1-4} hydroxyalkyl and an unsubstituted C_{1-5} alkoxyalkyl, wherein when the monocyclic C_{3-6} cycloalkyl and the monocyclic 3-6 heterocyclyl are substituted, the monocyclic C_{3-6} cycloalkyl and the monocyclic 3-6 heterocyclyl are independently substituted with one or more substituents selected from the group consisting of halogen or hydroxy, and wherein when the C_{1-4} alkyl is substituted, the C_{1-4} alkyl is substituted with one or more substituents independently selected from the group consisting of a phosphate, an O-linked α-amino acid and an O-carboxy, and provided that at least one of R^2 and R^3 is not hydrogen; or

R^2 and R^3 are taken together along with the carbon to which R^2 and R^3 are attached to form an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl or an unsubstituted or a substituted monocyclic 3-6 membered heterocyclyl, wherein when the C_{3-6} cycloalkyl and 3-6 membered heterocyclyl are substituted, the C_{3-6} cycloalkyl and the 3-6 membered

heterocyclyl are independently substituted with 1 or 2 substituents independently selected from the group consisting of halogen and hydroxy;

R^4 and R^5 are independently hydrogen, halogen, an unsubstituted C_{1-4} alkyl, a deuterated C_{1-4} alkyl or an unsubstituted C_{2-4} alkenyl;

R^6 is hydrogen, an unsubstituted C_{1-4} alkyl, a deuterated C_{1-4} alkyl or an unsubstituted C_{3-4} alkenyl; and

provided that at least one of R^4, R^5 and R^6 is not hydrogen;

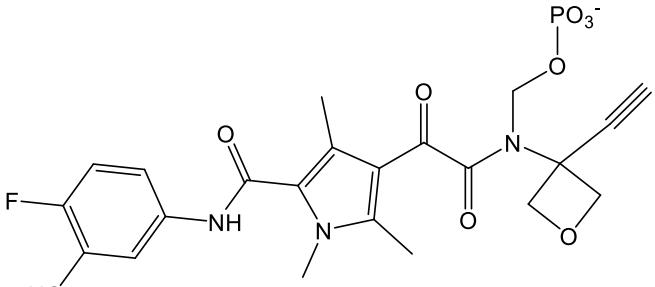
X^1 is CR^A or N;

R^{7a}, R^{7b}, R^{7c} and R^{7d} are independently hydrogen, halogen, an unsubstituted C_{1-4} haloalkyl, cyano or an unsubstituted C_{1-4} alkoxy;

R^8 is–$CH_2OC(=O)$–(an unsubstituted C_{1-4} alkyl), –$CH_2OC(=O)$–O(an unsubstituted C_{1-4} alkyl), –CH_2–(α-amino acid) or –CH_2-phosphate; and

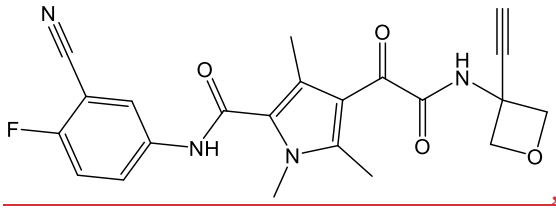
R^A is hydrogen, halogen, an unsubstituted C_{1-4} haloalkyl or cyano.

[0004b] In another aspect, there is provided a compound having the structure



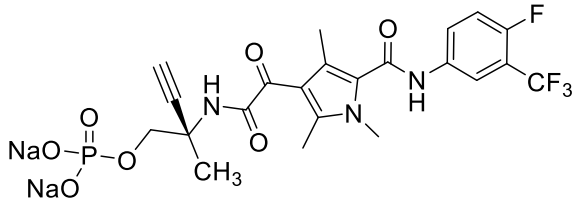
, or a pharmaceutically acceptable salt thereof.

[0004c] In another aspect, there is provided a compound having the structure



, or a pharmaceutically acceptable salt thereof.

[0004d] In another aspect, there is provided a compound having the structure



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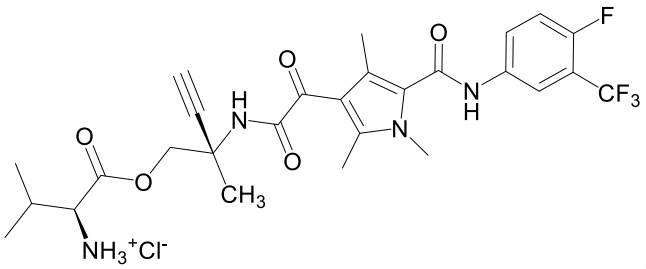
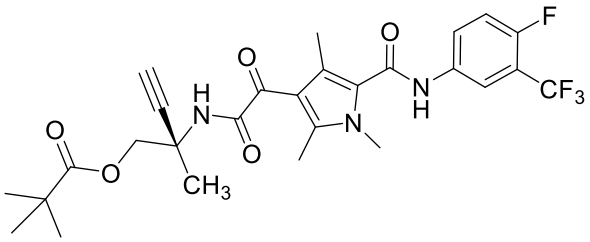
[0004e] In another aspect, there is provided a compound having the structure



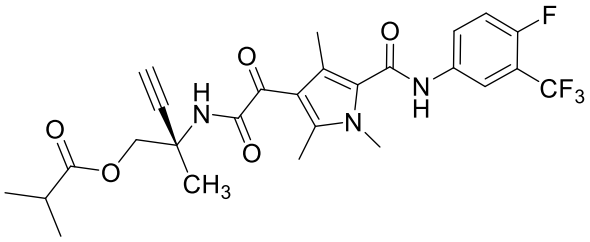
, or a pharmaceutically acceptable salt thereof.

[0004f] In another aspect, there is provided a compound having the structure



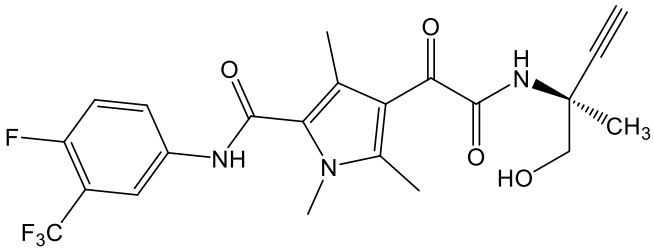
, or a pharmaceutically acceptable salt thereof.

[0004g] In another aspect, there is provided a compound having the structure



, or a pharmaceutically acceptable salt thereof.

[0004h] In another aspect, there is provided a compound having the structure



, or a pharmaceutically acceptable salt thereof.

[0005] Some examples ~~embodiments~~ disclosed herein relate to a pharmaceutical composition that can contain an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0005a] In another aspect, there is provided a pharmaceutical composition comprising an effective amount of a compound as defined herein, or a pharmaceutically acceptable salt thereof, and excipient.

[0006] Some examples ~~embodiments~~ described herein relate to a method of treating a HBV and/or HDV infection that can include administering to a subject identified as suffering from the HBV and/or HDV infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other examples ~~embodiments~~ described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of treating a HBV and/or HDV infection.

[0006a] In another aspect, there is provided use of the compound as defined herein, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of hepatitis B.

[0006b] In another aspect, there is provided use of the compound as defined herein, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of hepatitis D.

[0006c] In another aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in treating hepatitis B.

[0006d] In another aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in treating hepatitis D.

[0007] Some examples ~~embodiments~~ disclosed herein relate to a method of inhibiting replication of HBV and/or HDV that can include contacting a cell infected with the HBV and/or HDV with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein.

Other examples ~~embodiments~~ described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of inhibiting the replication HBV and/or HDV.

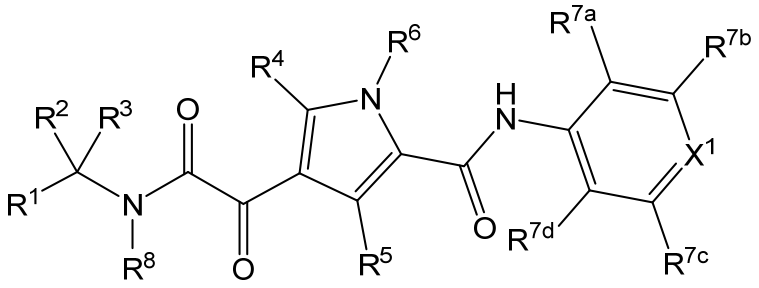
[0008] These are other examples ~~embodiments~~ are described in greater detail below

DETAILED DESCRIPTION

[0009] HBV is a partially double-stranded circular DNA of about 3.2 kilobase (kb) pairs, and is classified into eight genotypes, A to H. The HBV replication pathway has been studied in great detail. T.J. Liang, Hepatology (2009) 49(5 Suppl):S13-S21. On part of replication includes the formation of the covalently closed circular (cccDNA) form. The presence of the cccDNA gives rise to the risk of viral reemergence throughout the life of the host organism. HBV carriers can transmit the disease for many years. An estimated 300 million people are living with hepatitis B virus infection, and it is estimated that over

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



(I)

wherein:

R^1 is an unsubstituted or a substituted C_2 alkenyl~~,~~ or an unsubstituted or a substituted C_2 alkynyl, ~~an unsubstituted or a substituted monocyclic heteroaryl, an unsubstituted or a substituted bicyclic heteroaryl or an unsubstituted or a substituted monocyclic heterocyclyl,~~ wherein when the C_2 alkenyl~~,~~ and the C_2 alkynyl ~~and the monocyclic heteroaryl~~ are substituted, the C_2 alkenyl~~,~~ and the C_2 alkynyl ~~and the monocyclic heteroaryl~~ are independently substituted with one or more substituents independently selected from the group consisting of halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{1-4} hydroxyalkyl, an unsubstituted monocyclic C_{3-6} cycloalkyl and a hydroxy-substituted monocyclic C_{3-6} cycloalkyl;

R^2 and R^3 are independently selected from the group consisting of hydrogen, an unsubstituted or a substituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl, an unsubstituted or a substituted monocyclic 3-6 membered heterocyclyl, an unsubstituted C_{1-4} hydroxyalkyl and an unsubstituted C_{1-5} alkoxyalkyl, wherein when the monocyclic C_{3-6} cycloalkyl and the monocyclic 3-6 heterocyclyl are substituted, the monocyclic C_{3-6} cycloalkyl and the monocyclic 3-6 heterocyclyl are independently substituted with one or more substituents selected from the group consisting of halogen or hydroxy, and wherein when the C_{1-4} alkyl is substituted, the C_{1-4} alkyl is substituted with one or more substituents independently selected from the group consisting of a phosphate, an O-linked α–amino acid and an O-carboxy, and provided that at least one of R^2 and R^3 is not hydrogen; or

R^2 and R^3 are taken together along with the carbon to which R^2 and R^3 are attached to form an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl or an unsubstituted or a substituted monocyclic 3-6 membered heterocyclyl, wherein when the C_{3-6} cycloalkyl and 3-6 membered heterocyclyl are substituted, the C_{3-6} cycloalkyl and the 3-6 membered heterocyclyl are independently substituted with 1 or 2 substituents independently selected from the group consisting of halogen and hydroxy;

R^4 and R^5 are independently hydrogen, halogen, an unsubstituted C_{1-4} alkyl, a deuterated C_{1-4} alkyl or an unsubstituted C_{2-4} alkenyl;

R^6 is hydrogen, an unsubstituted C_{1-4} alkyl, a deuterated C_{1-4} alkyl or an unsubstituted C_{3-4} alkenyl; and

provided that at least one of R^4, R^5 and R^6 is not hydrogen;

X^1 is CR^A or N;

R^{7a}, R^{7b}, R^{7c} and R^{7d} are independently hydrogen, halogen, an unsubstituted C_{1-4} haloalkyl, cyano or an unsubstituted C_{1-4} alkoxy;

R^8 is ~~hydrogen, –~~$CH_2OC(=O)$–(an unsubstituted C_{1-4} alkyl), –$CH_2OC(=O)$–O(an unsubstituted C_{1-4} alkyl), –CH_2–(α-amino acid) or –CH_2-phosphate; and

R^A is hydrogen, halogen, an unsubstituted C_{1-4} haloalkyl or cyano.

2. The compound of Claim 1, wherein R^2 and R^3 are independently selected from the group consisting of hydrogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl, an unsubstituted or a substituted monocyclic 3-6 membered heterocyclyl, an unsubstituted C_{1-4} hydroxyalkyl and an unsubstituted C_{1-5} alkoxyalkyl, wherein when the monocyclic C_{3-6} cycloalkyl and the monocyclic 3-6 heterocyclyl are substituted, the monocyclic C_{3-6} cycloalkyl and the monocyclic 3-6 heterocyclyl are independently substituted with one or more substituents selected from the group consisting of halogen or hydroxy.

~~3. The compound of Claim 2, wherein R^2 and R^3 are each an unsubstituted C_{1-4} alkyl.~~

~~4. The compound of Claim 1, wherein R^2 and R^3 are independently selected from the group consisting of hydrogen, a substituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl, an unsubstituted or a substituted monocyclic 3-6 membered heterocyclyl, an unsubstituted C_{1-4} hydroxyalkyl and an unsubstituted C_{1-5} alkoxyalkyl, wherein the C_{1-4} alkyl is substituted with one or more substituents selected from the group consisting of a phosphate, an O-linked α-amino acid and an O-carboxy.~~

~~5. The compound of any one of Claims 1-4, wherein one of R^2 and R^3 is hydrogen.~~

~~6. The compound of Claim 5, wherein the other of R^2 and R^3 is an unsubstituted C_{1-4} alkyl.~~

~~7. The compound of Claim 5, wherein the other of R^2 and R^3 is a substituted C_{1-4} alkyl, wherein when the C_{1-4} alkyl is substituted, the C_{1-4} alkyl is substituted with one or more substituents selected from the group consisting of a phosphate, an O-linked α-amino acid and an O-carboxy.~~

~~8. The compound of Claim 5, wherein the other of R^2 and R^3 is an unsubstituted C_{1-4} haloalkyl.~~

~~9. The compound of Claim 5, wherein the other of R^2 and R^3 is an unsubstituted monocyclic C_{3-6} cycloalkyl.~~

~~10. The compound of Claim 5, wherein the other of R^2 and R^3 is a substituted monocyclic C_{3-6} cycloalkyl.~~

~~11. The compound of Claim 5, wherein the other of R^2 and R^3 is an unsubstituted monocyclic 3-6 membered heterocyclyl.~~

~~12. The compound of Claim 5, wherein the other of R^2 and R^3 is a substituted monocyclic 3-6 membered heterocyclyl.~~

~~13. The compound of Claim 5, wherein the other of R^2 and R^3 is an unsubstituted C_{1-4} hydroxyalkyl.~~

~~14. The compound of Claim 5, wherein the other of R^2 and R^3 is an unsubstituted C_{1-5} alkoxyalkyl.~~

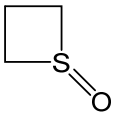
~~15.~~3. The compound of Claim 1, wherein R^2 and R^3 are taken together along with the carbon to which R^2 and R^3 are attached to form an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl or an unsubstituted or a substituted monocyclic 3-6 membered heterocyclyl, wherein when the C_{3-6} cycloalkyl and 3-6 membered heterocyclyl are substituted, the C_{3-6} cycloalkyl and the 3-6 membered heterocyclyl are independently substituted with 1 or 2 substituents selected from the group consisting of halogen and hydroxy.

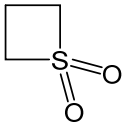
~~16. The compound of Claim 15, wherein R^2 and R^3 are taken together along with the carbon to which R^2 and R^3 are attached to form an unsubstituted monocyclic C_{3-6} cycloalkyl.~~

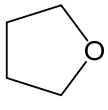
~~17. The compound of Claim 15, wherein R^2 and R^3 are taken together along with the carbon to which R^2 and R^3 are attached to form a substituted monocyclic C_{3-6} cycloalkyl~~

~~18. The compound of Claim 55, wherein R^2 and R^3 are taken together along with the carbon to which R^2 and R^3 are attached to form an unsubstituted monocyclic 3-6 membered heterocyclyl.~~

~~19. The compound of Claim 15, wherein R^2 and R^3 are taken together along with the carbon to which R^2 and R^3 are attached to form a substituted monocyclic 3-6 membered heterocyclyl.~~

~~20.~~4. The compound of Claim ~~18 or 19~~3, wherein the monocyclic 3-6 membered heterocyclyl is selected from the group consisting of an unsubstituted or substituted oxetane, an unsubstituted or substituted thietane, an unsubstituted or substituted 

, an unsubstituted or substituted 

, an unsubstituted or substituted 

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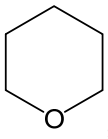
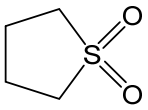
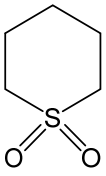
unsubstituted or substituted  , an unsubstituted or substituted  and an unsubstituted or substituted  .

~~21. The compound of any one of Claims 1-20, wherein R^4 is hydrogen.~~

~~22. The compound of any one of Claims 1-20, wherein R^4 is halogen.~~

~~23.~~5. The compound of any one of Claims 1-~~20~~4, wherein R^4 is an unsubstituted C_{1-4} alkyl; R^5 is an unsubstituted C_{1-4} alkyl; and R^6 is an unsubstituted C_{1-4} alkyl.

~~24. The compound of any one of Claims 1-20, wherein R^4 is a deuterated C_{1-4} alkyl.~~

~~25. The compound of any one of Claims 1-24, wherein R^5 is hydrogen.~~

~~26. The compound of any one of Claims 1-24, wherein R^5 is halogen.~~

~~27. The compound of any one of Claims 1-24, wherein R^5 is an unsubstituted C_{1-4} alkyl.~~

~~28. The compound of any one of Claims 1-27, wherein R^6 is an unsubstituted C_{1-4} alkyl.~~

~~29. The compound of any one of Claims 1-27, wherein R^6 is an unsubstituted C_{3-4} alkenyl.~~

~~30. The compound of any one of Claims 1-29, wherein X^1 is N.~~

~~31.~~6. The compound of any one of Claims 1-~~29~~5, wherein X^1 is CR^A.

~~32. The compound of Claim 31, wherein R^A is hydrogen.~~

~~33.~~7. The compound of Claim ~~31~~6, wherein R^A is halogen.

~~34. The compound of Claim 31, wherein R^A is an unsubstituted C_{1-4} haloalkyl.~~

~~35. The compound of Claim 31, wherein R^A is cyano.~~

~~36. The compound of Claim 31, wherein R^A is an unsubstituted C_{1-4} alkoxy.~~

~~37.~~8. The compound of any one of Claims 1-~~36~~7, wherein R^{7a} is hydrogen; and R^{7d} is hydrogen.

~~38. The compound of any one of Claims 1-36, wherein R^{7a} is halogen.~~

~~39. The compound of any one of Claims 1-36, wherein R^{7a} is an unsubstituted C_{1-4} haloalkyl.~~

~~40. The compound of any one of Claims 1-36, wherein R^{7a} is cyano.~~

~~41. The compound of any one of Claims 1-36, wherein R^{7a} is an unsubstituted C_{1-4} alkoxy.~~

~~42. The compound of any one of Claims 1-41, wherein R^{7b} is hydrogen.~~

~~43.~~9. The compound of any one of Claims 1-~~41~~8, wherein R^{7b} is halogen, an unsubstituted C_{1-4} haloalkyl, cyano or an unsubstituted C_{1-4} alkoxy.

~~44. The compound of any one of Claims 1-41, wherein R^{7b} is an unsubstituted C_{1-4} haloalkyl.~~

~~45. The compound of any one of Claims 1-41, wherein R^{7b} is cyano.~~

~~46. The compound of any one of Claims 1-41, wherein R^{7b} is an unsubstituted C_{1-4} alkoxy.~~

~~47. The compound of any one of Claims 1-46, wherein R^{7c} is hydrogen.~~

~~48.~~10. The compound of any one of Claims 1-~~46~~9, wherein R^{7c} is halogen, an unsubstituted C_{1-4} haloalkyl, cyano or an unsubstituted C_{1-4} alkoxy.

~~49. The compound of any one of Claims 1-46, wherein R^{7e} is an unsubstituted C_{1-4} haloalkyl.~~

~~50. The compound of any one of Claims 1-46, wherein R^{7e} is cyano.~~

~~51. The compound of any one of Claims 1-46, wherein R^{7e} is an unsubstituted C_{1-4} alkoxy.~~

~~52. The compound of any one of Claims 1-51, wherein R^{7d} is hydrogen.~~

~~53. The compound of any one of Claims 1-51, wherein R^{7d} is halogen.~~

~~54. The compound of any one of Claims 1-51, wherein R^{7d} is an unsubstituted C_{1-4} haloalkyl.~~

~~55. The compound of any one of Claims 1-51, wherein R^{7d} is cyano.~~

~~56. The compound of any one of Claims 1-51, wherein R^{7d} is an unsubstituted C_{1-4} alkoxy.~~

~~57.~~11. The compound of any one of Claims 1-~~56~~10, wherein R^1 is an unsubstituted C_2 alkenyl.

~~58. The compound of any one of Claims 1-56, wherein R^1 is a substituted C_2 alkenyl.~~

~~59.~~12. The compound of any one of Claims 1-~~56~~10, wherein R^1 is an unsubstituted C_2 alkynyl.

~~60. The compound of any one of Claims 1-56, wherein R^1 is a substituted C_2 alkynyl.~~

~~61. The compound of any one of Claims 1-56, wherein R^1 is an unsubstituted monocyclic heteroaryl.~~

~~62. The compound of any one of Claims 1-56, wherein R^1 is a substituted monocyclic heteroaryl.~~

~~63. The compound of any one of Claims 1-56, wherein R^1 is an unsubstituted bicyclic heteroaryl.~~

~~64. The compound of any one of Claims 1-56, wherein R^1 is a substituted bicyclic heteroaryl.~~

~~65. The compound of any one of Claims 1-56, wherein R^1 is an unsubstituted monocyclic heterocyclyl.~~

~~66. The compound of any one of Claims 1-56, wherein R^1 is a substituted monocyclic heterocyclyl.~~

~~67. The compound of any one of Claims 1-66, wherein R^8 is hydrogen.~~

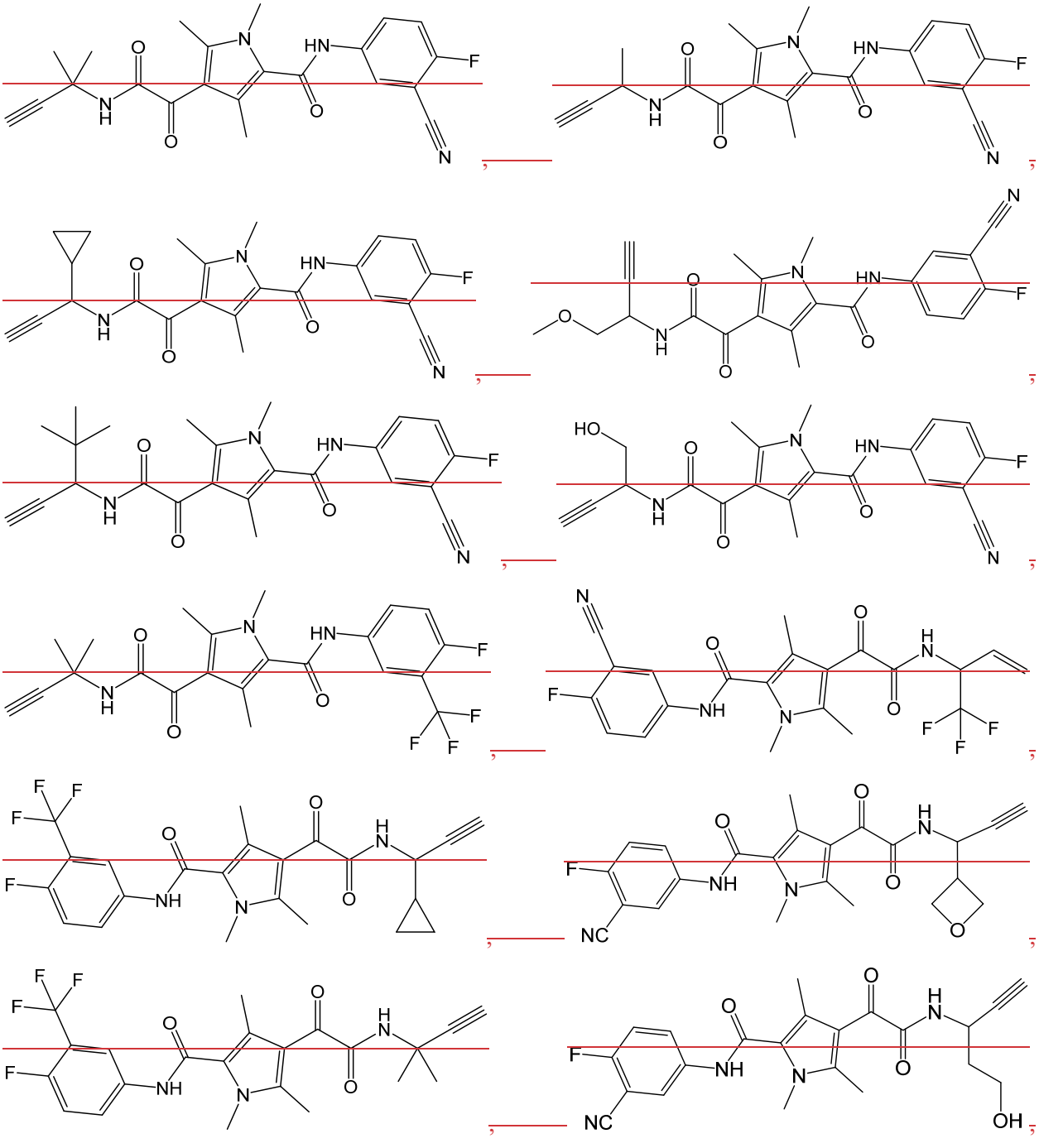
~~68.~~13. The compound of any one of Claims 1-~~66~~12, wherein R^8 is $–CH_2OC(=O)–$(an unsubstituted C_{1-4} alkyl), $–CH_2OC(=O)–O$(an unsubstituted C_{1-4} alkyl) or $–CH_2–$(α-amino acid).

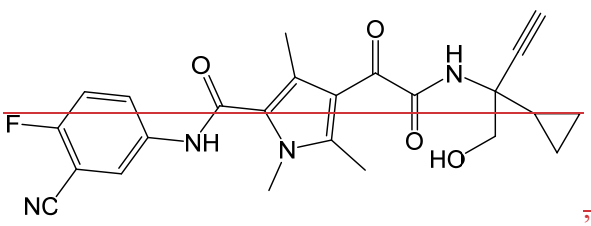
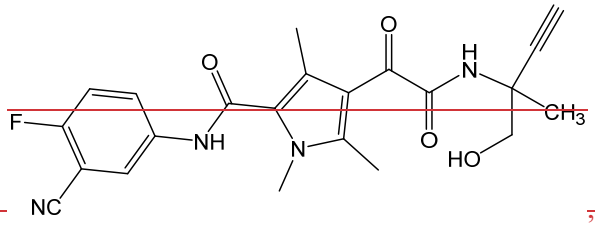
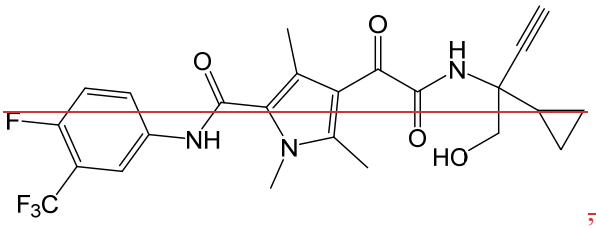
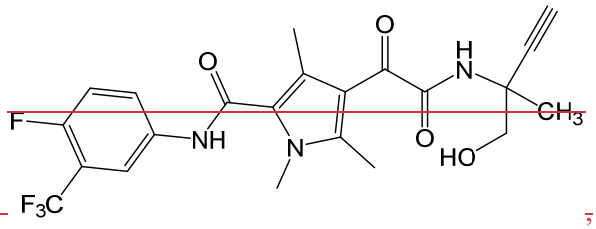
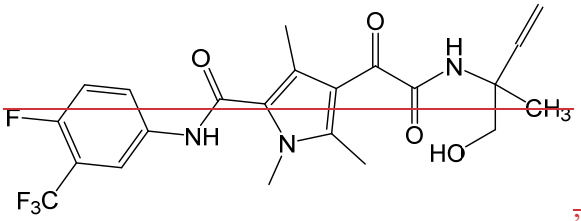
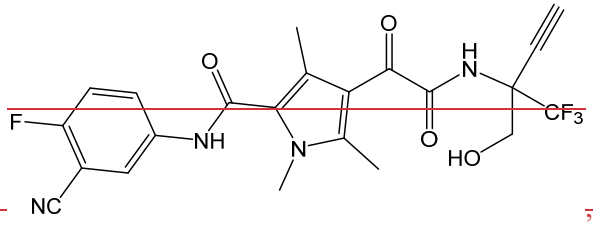
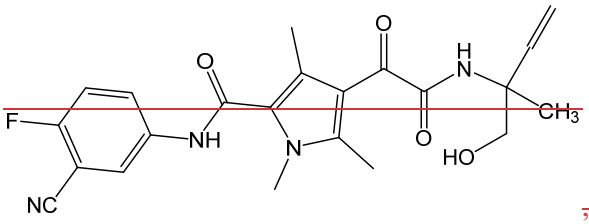
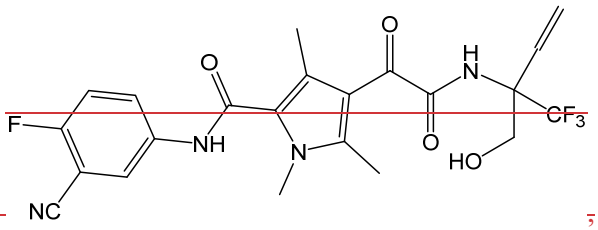
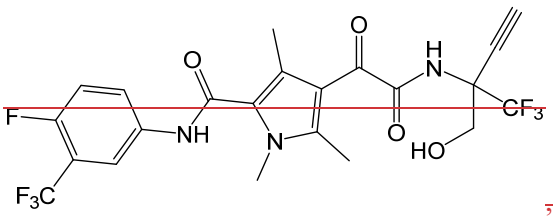
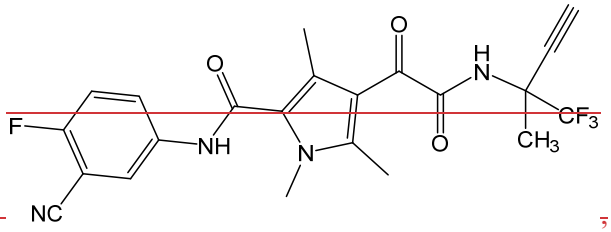
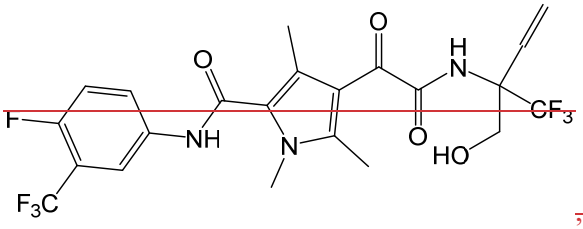
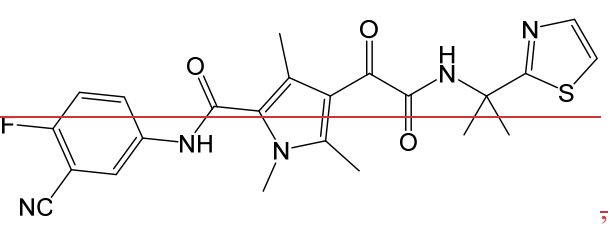
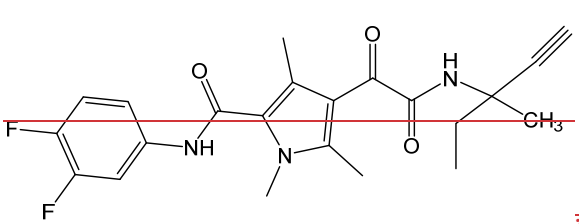
~~69. The compound of any one of Claims 1-66, wherein R^8 is $-CH_2OC(=O)-O$(an unsubstituted C_{1-4} alkyl).~~

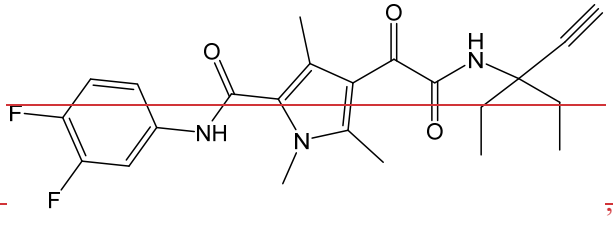
~~70. The compound of any one of Claims 1-66, wherein R^8 is $-CH_2-$(α-amino acid).~~

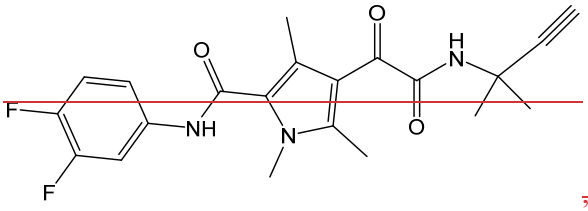
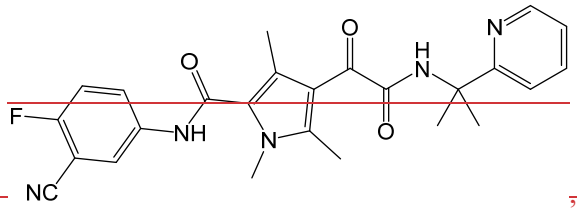
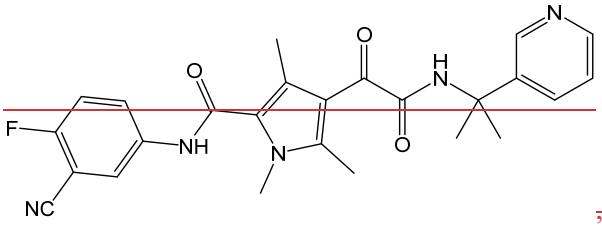
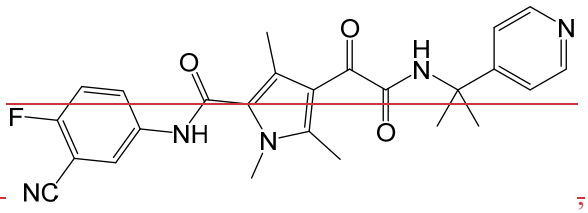
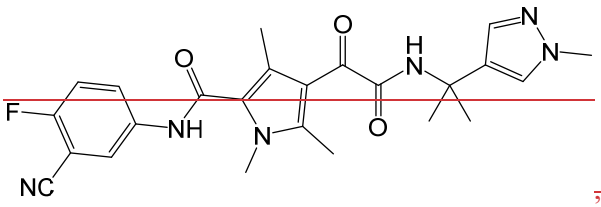
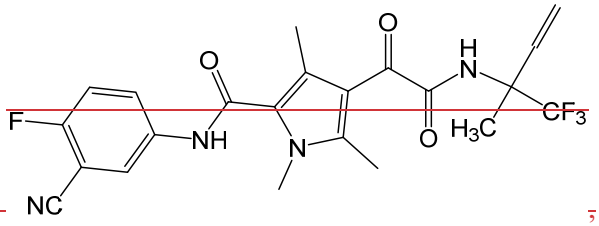
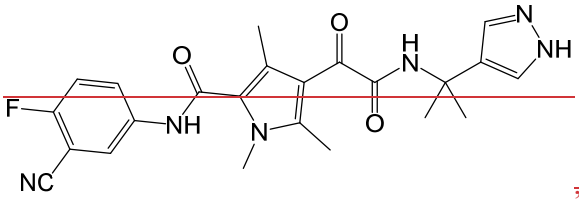
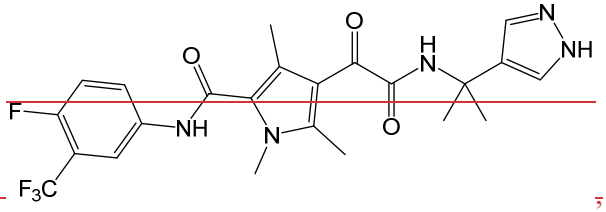
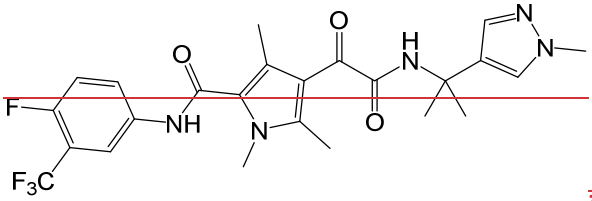
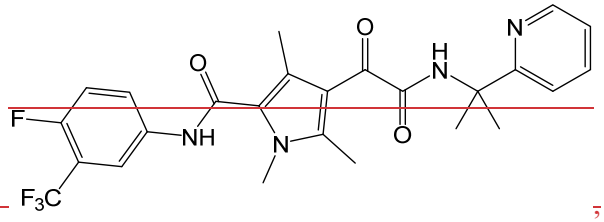
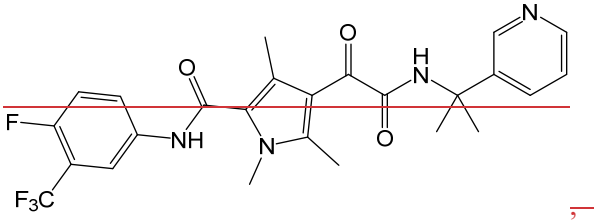
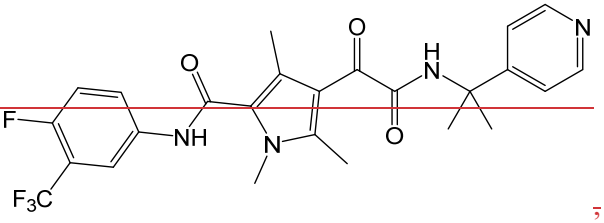
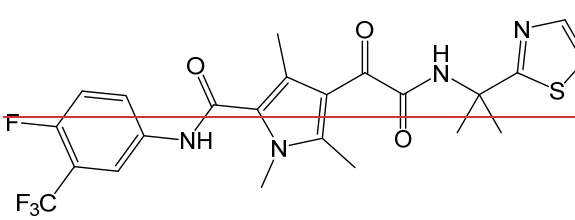
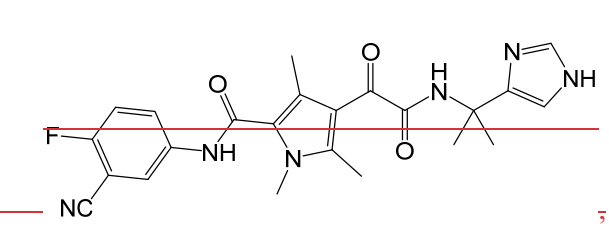
~~71.~~14. The compound of any one of Claims 1-~~66~~12, wherein R^8 is $-CH_2$-phosphate.

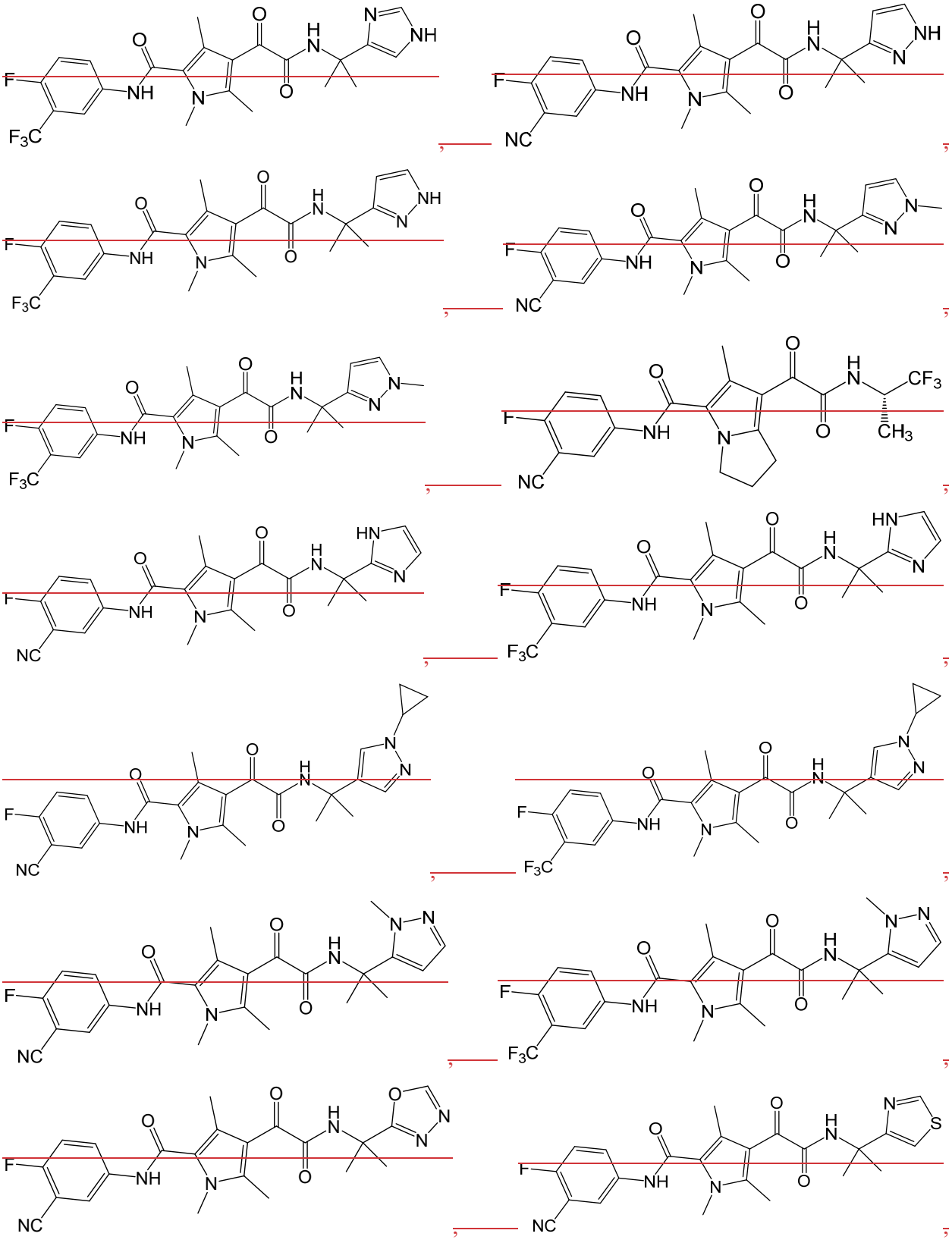
~~72. The compound of Claim 1, wherein the compound is selected from the group consisting of :~~

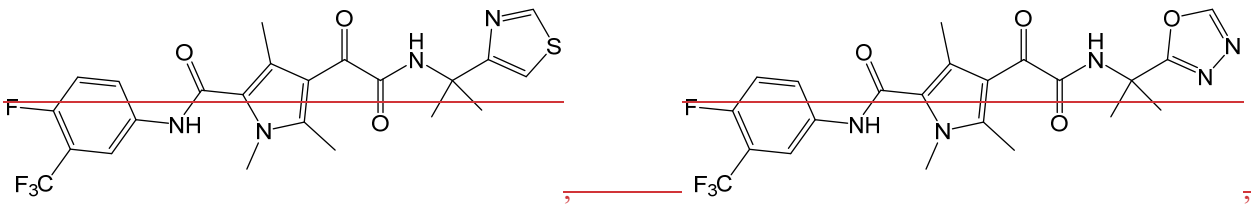


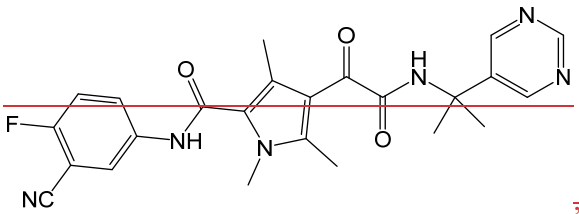
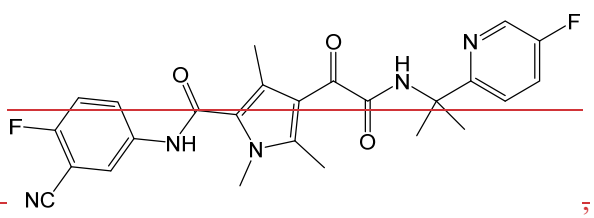
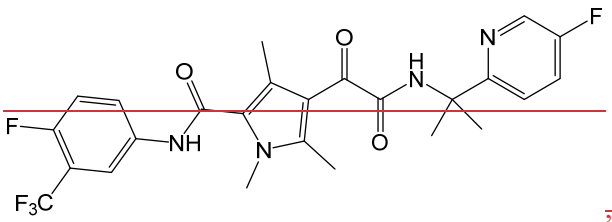
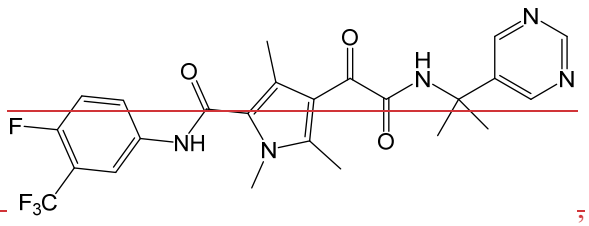
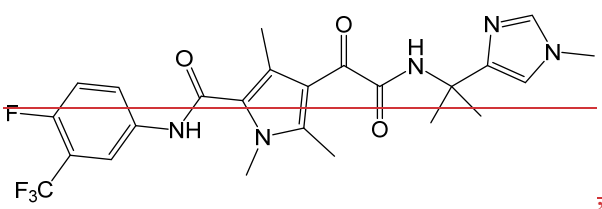
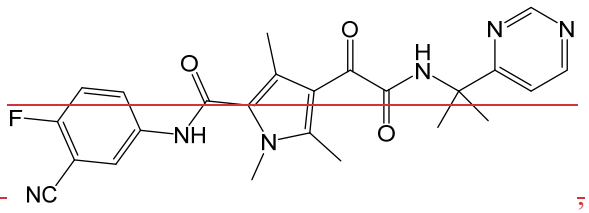
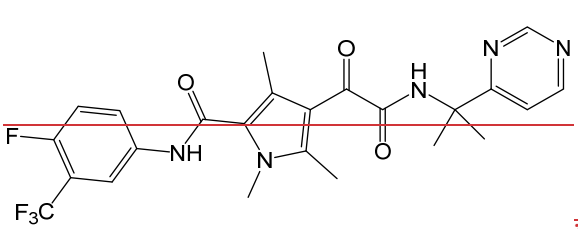
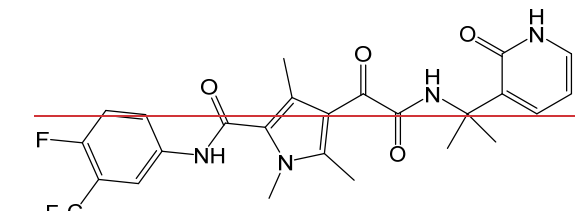
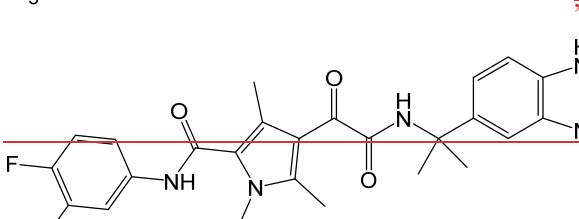
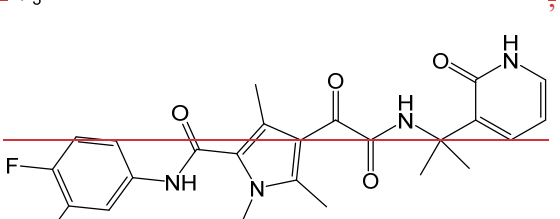
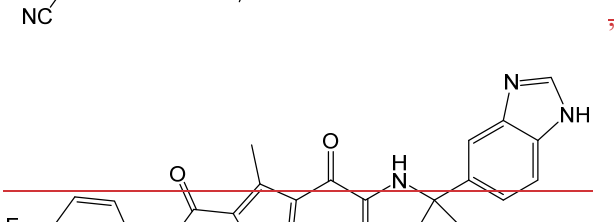
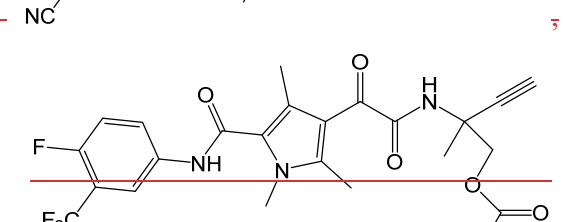
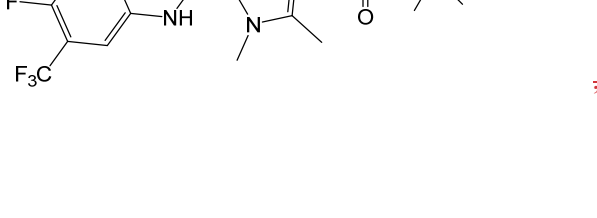














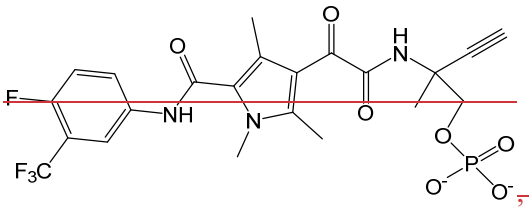
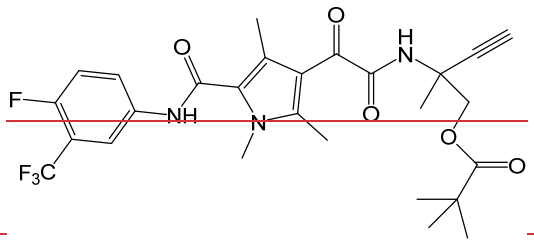




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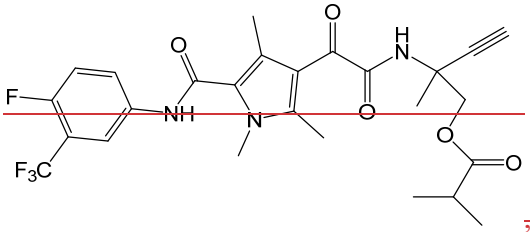
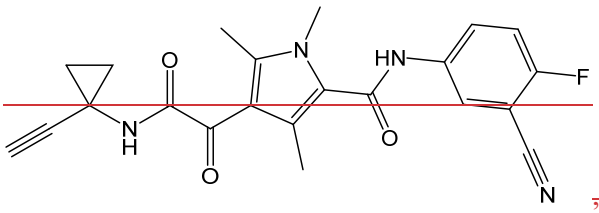

, or a pharmaceutically acceptable salt of any of the foregoing.

73. The compound of Claim 1, wherein the compound is selected from the group consisting of: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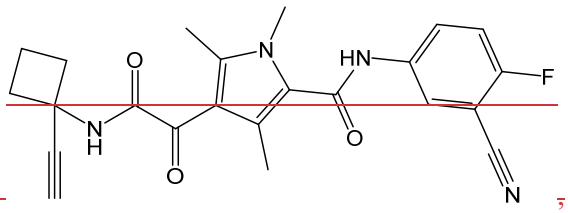
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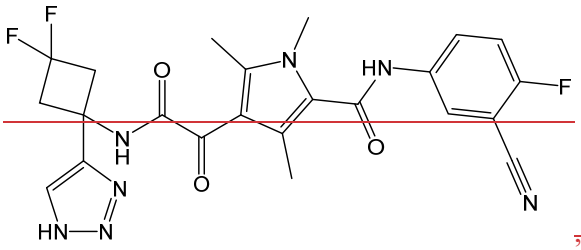
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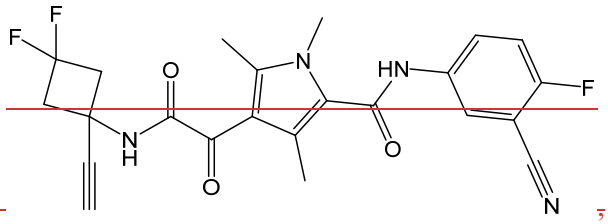
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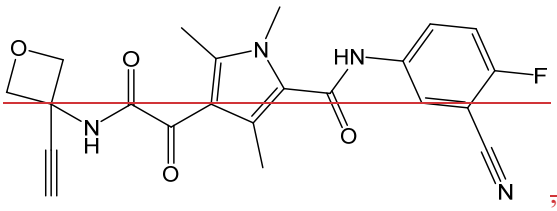
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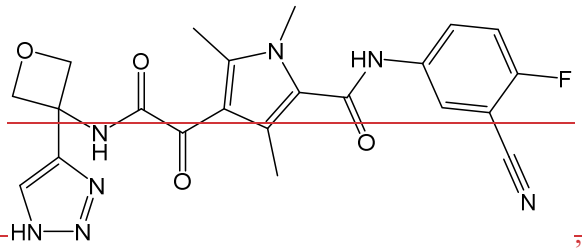
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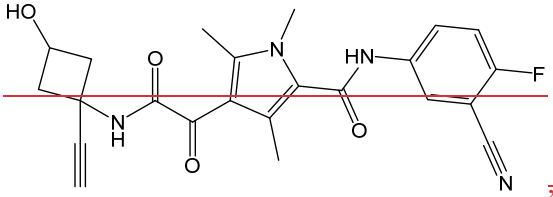
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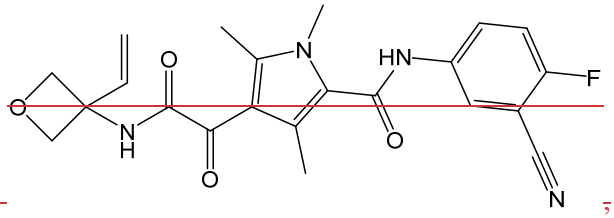
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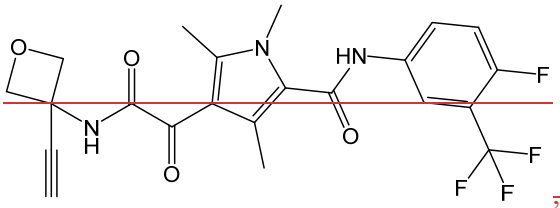
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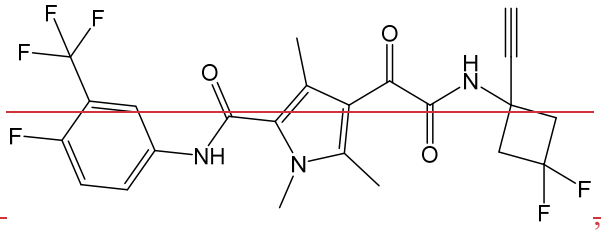
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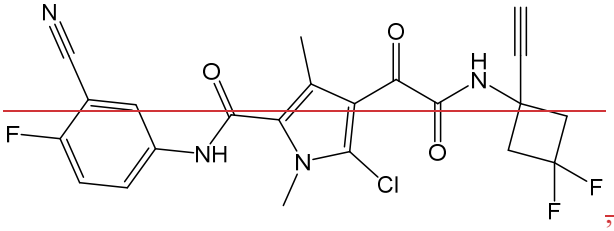
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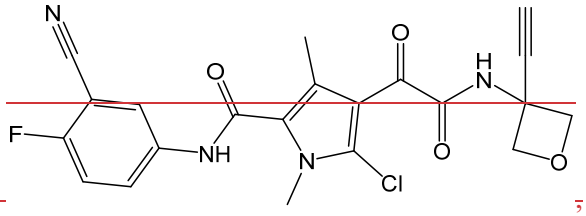
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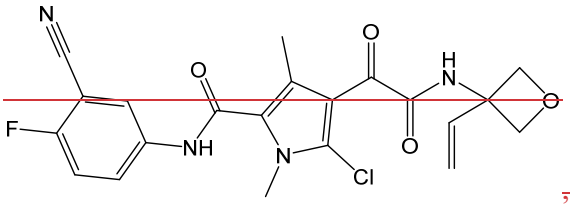
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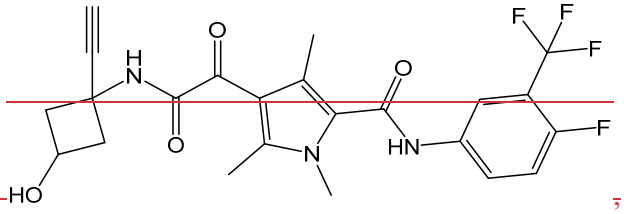
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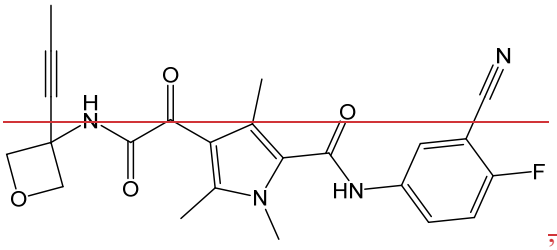
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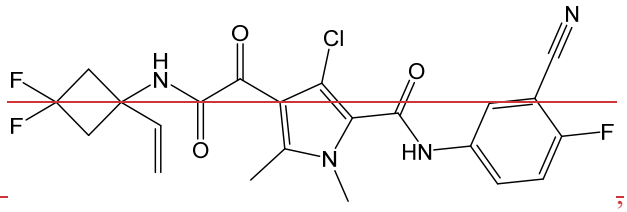
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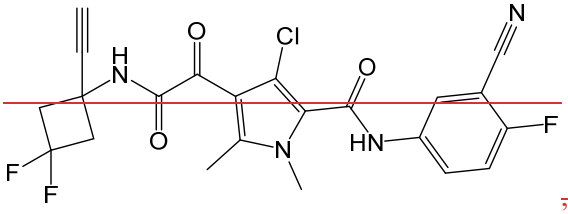
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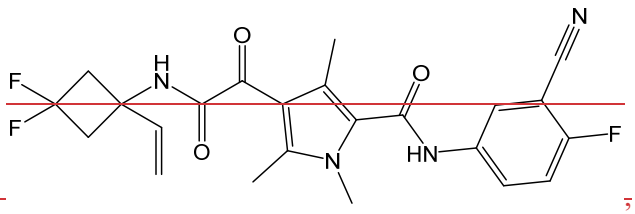
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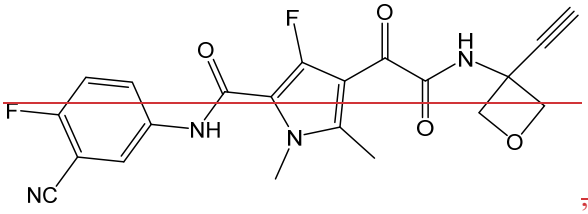
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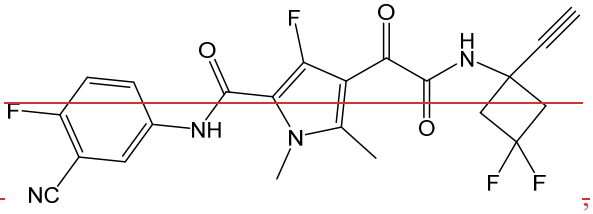
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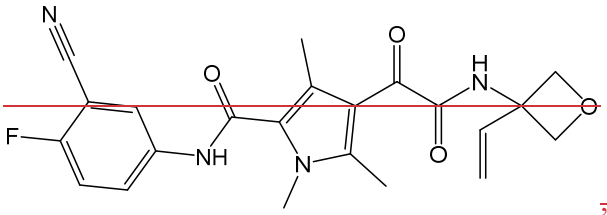
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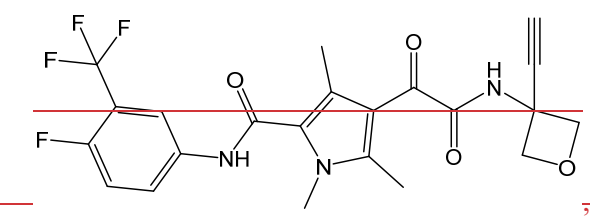
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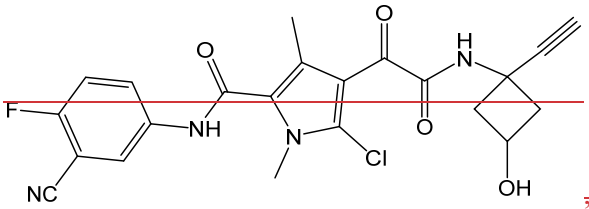
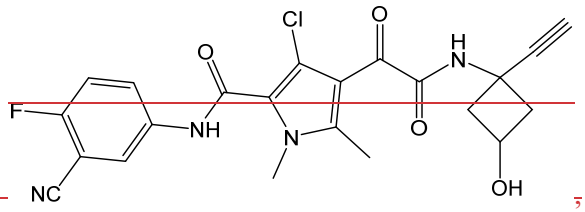

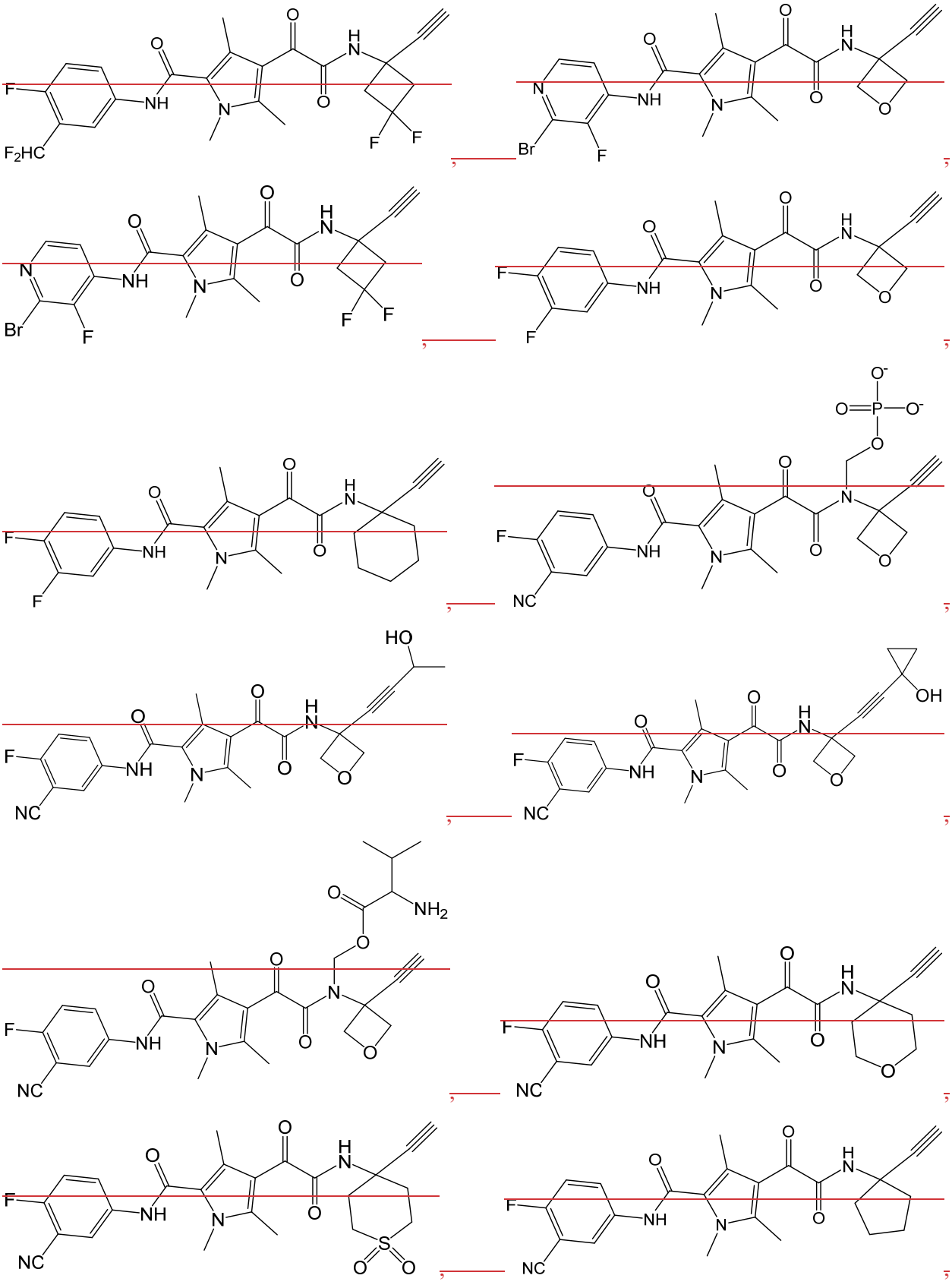

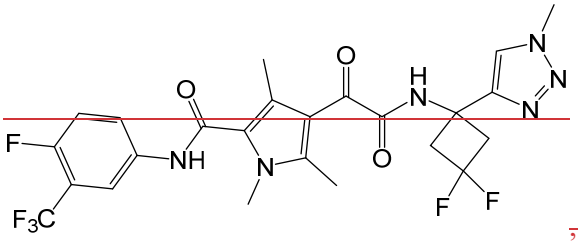
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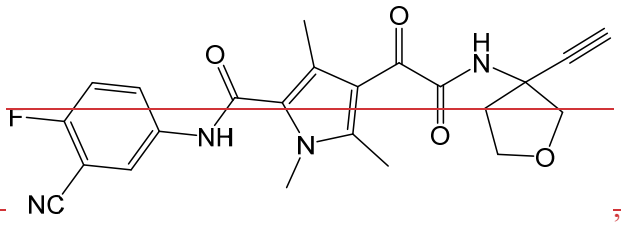
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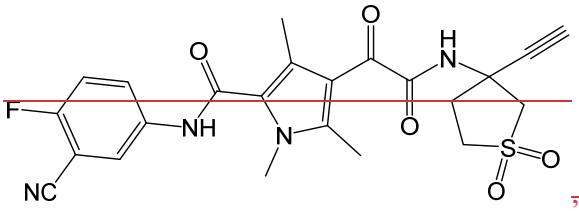
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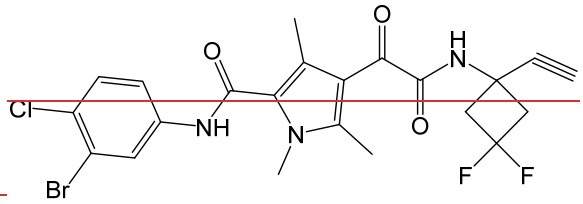
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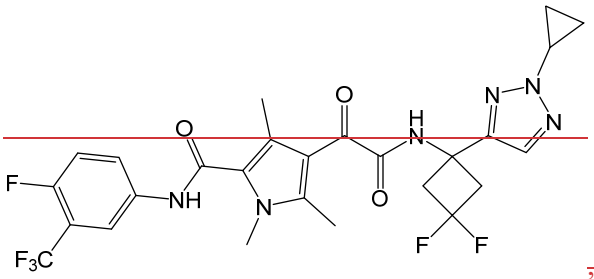
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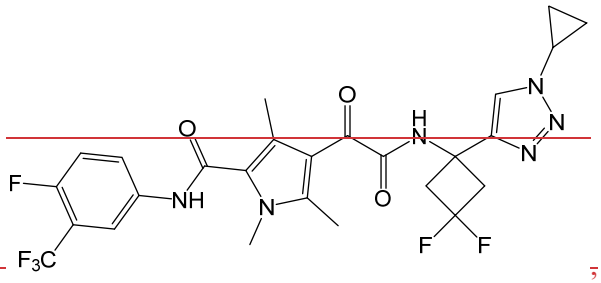
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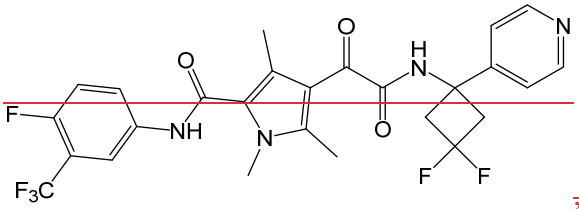
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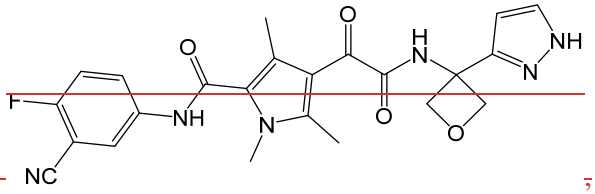
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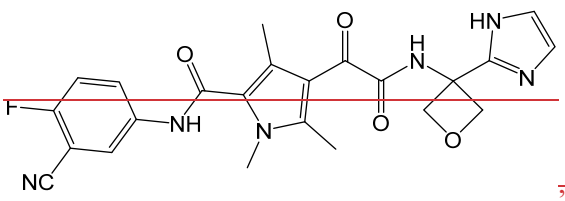
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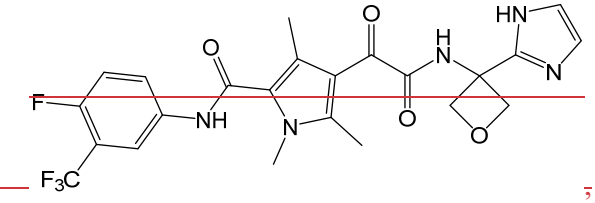
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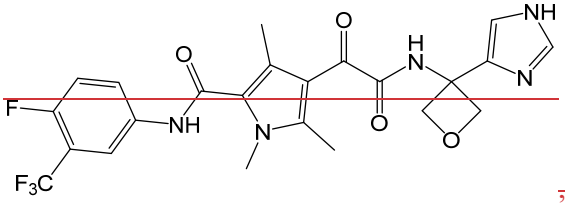
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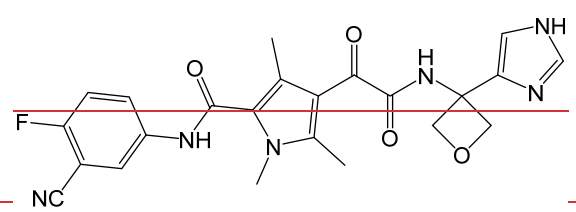
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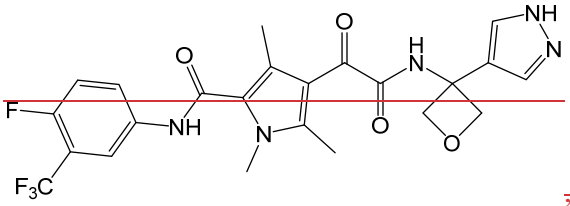
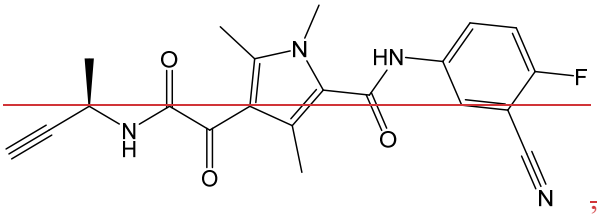

~~, or a pharmaceutically acceptable salt of any of the foregoing.~~

74. The compound of Claim 78 or 79, wherein the compound is selected from the group consisting of :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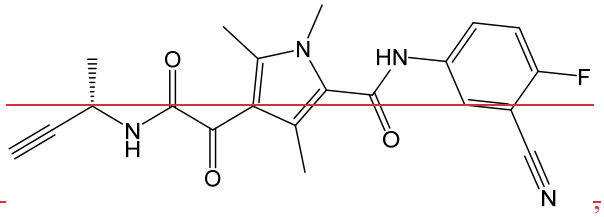
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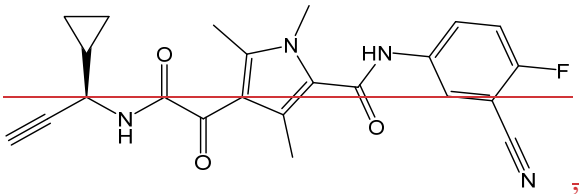
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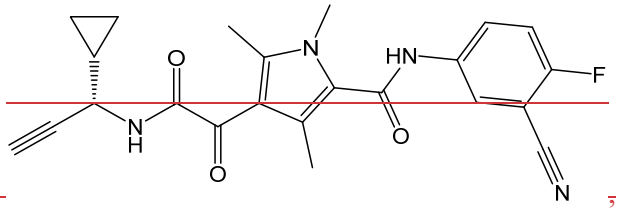
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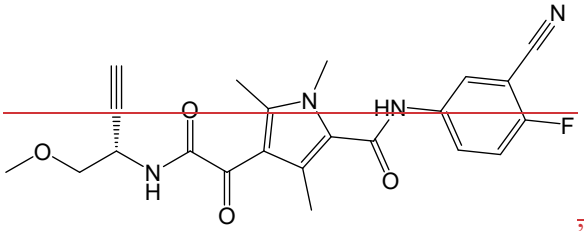
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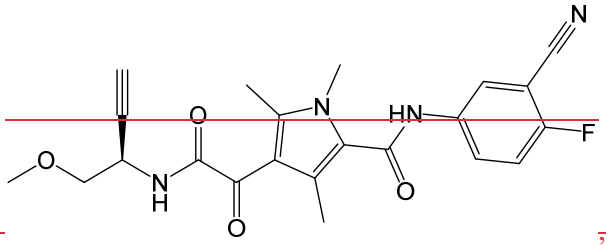
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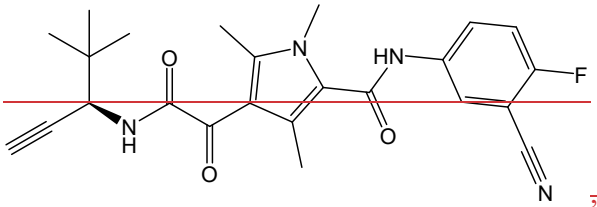
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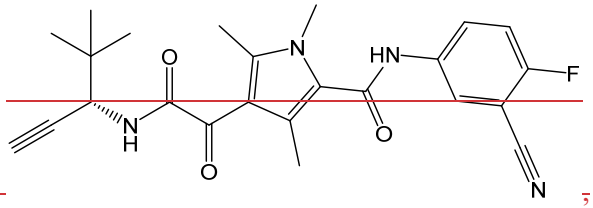
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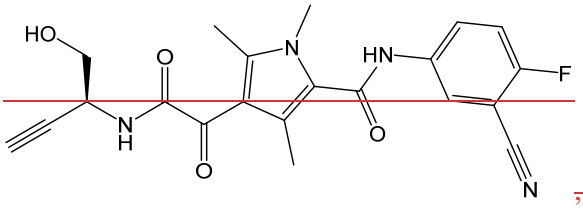
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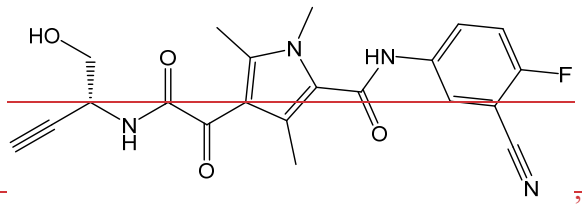
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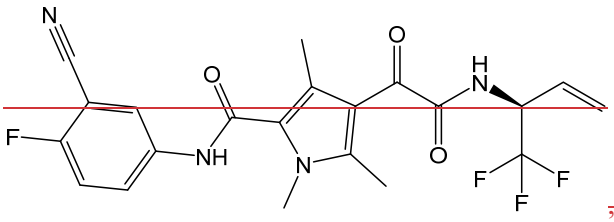
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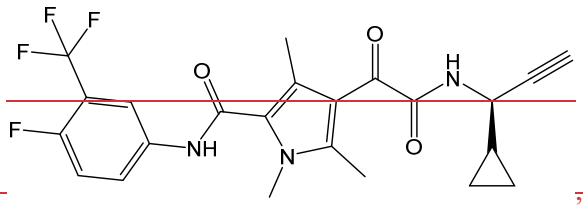
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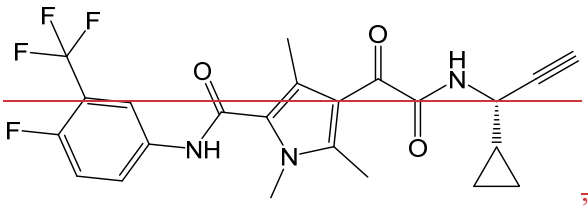
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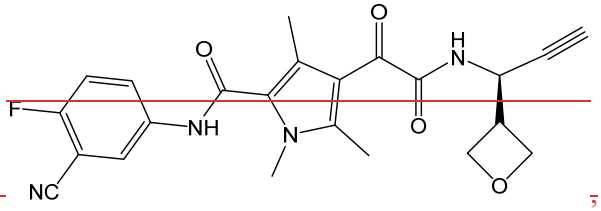
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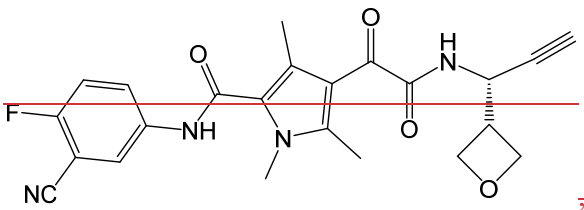
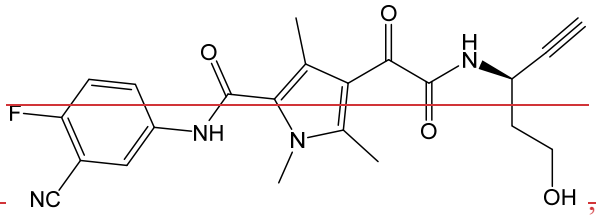
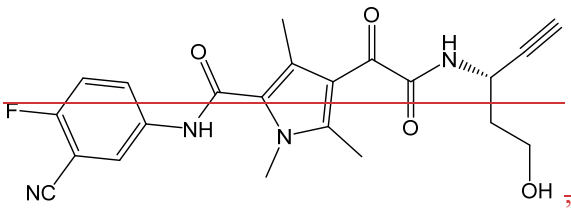
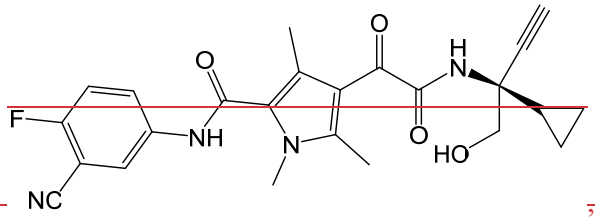
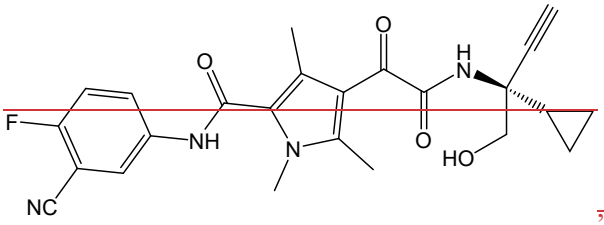
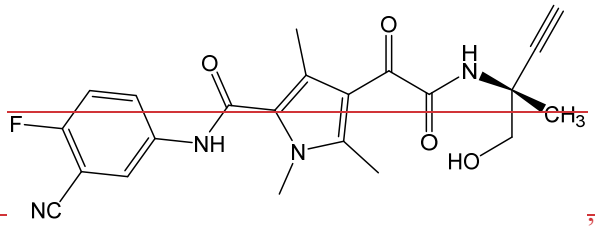
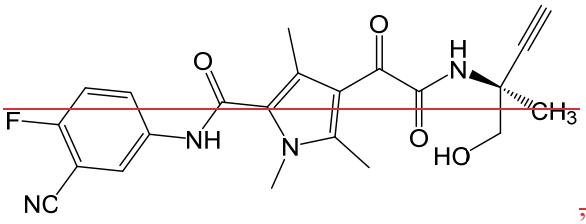
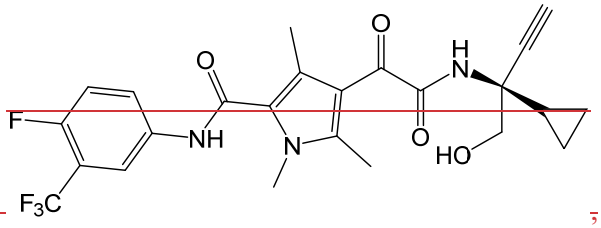
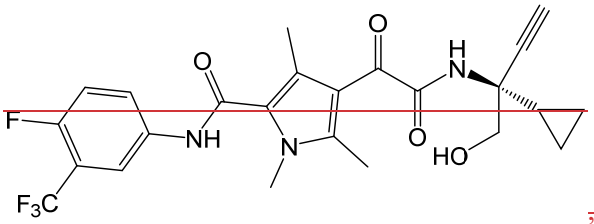
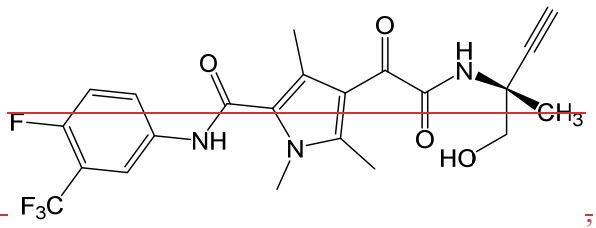
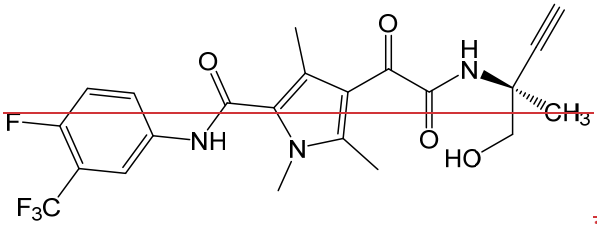
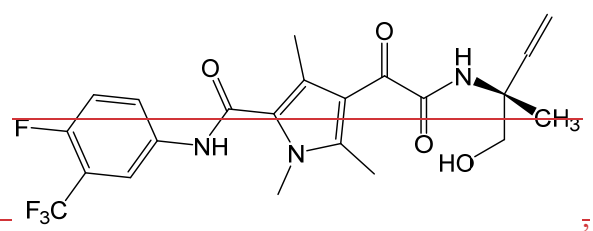
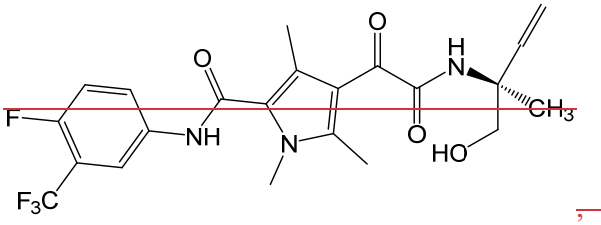
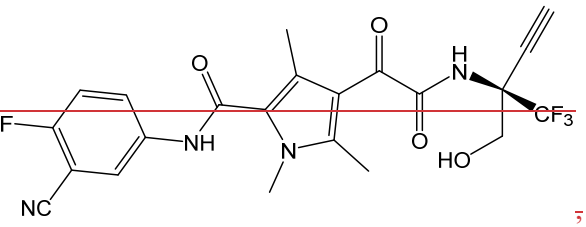

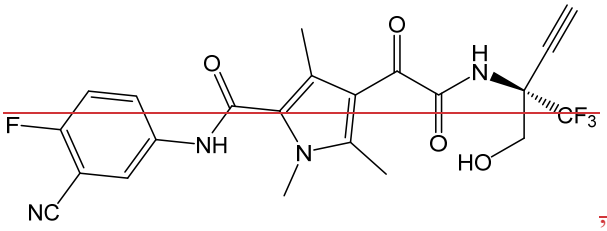
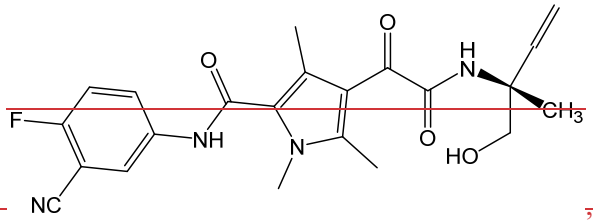
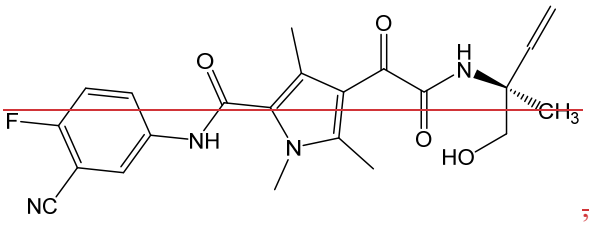
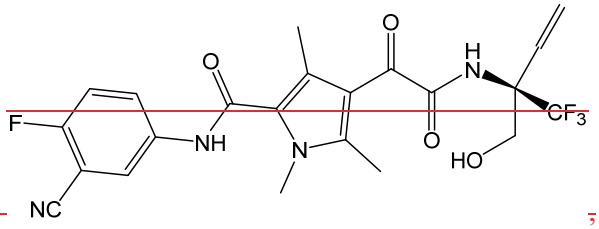
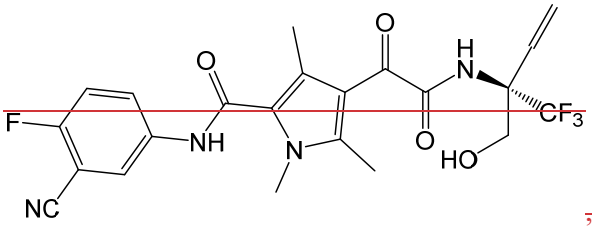
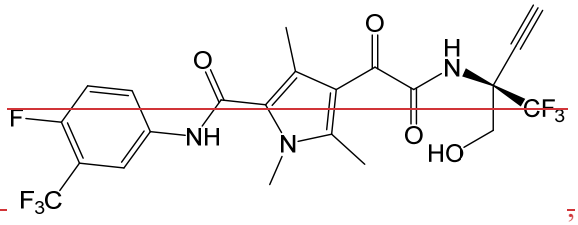
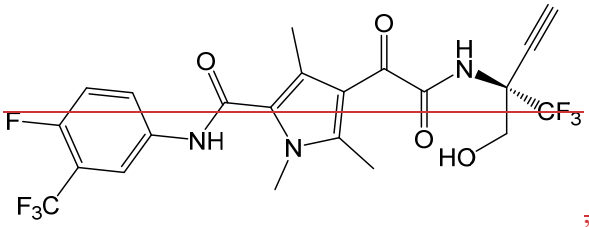
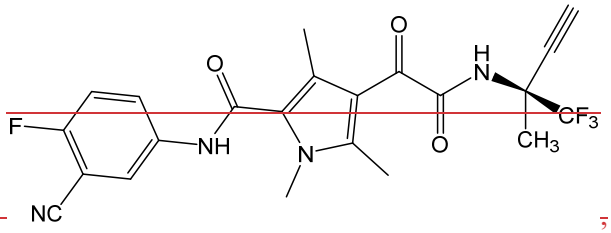
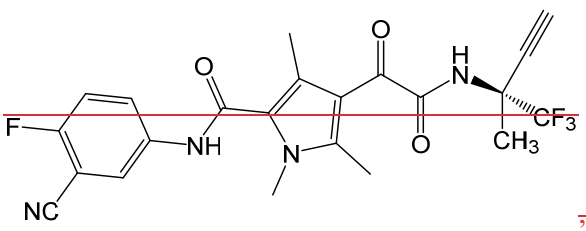
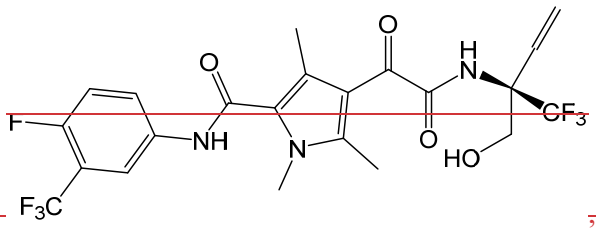
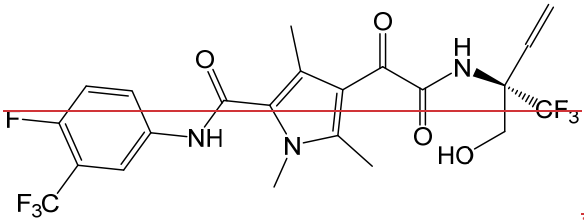
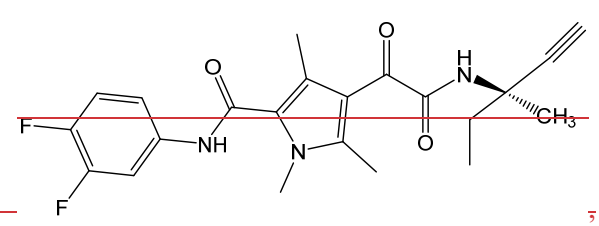
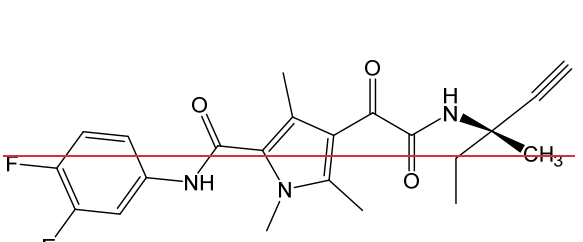
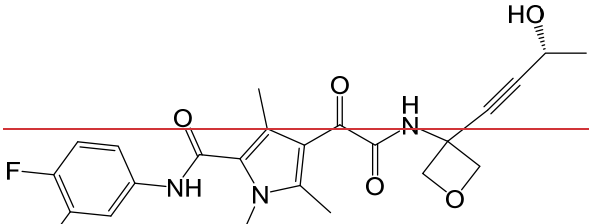



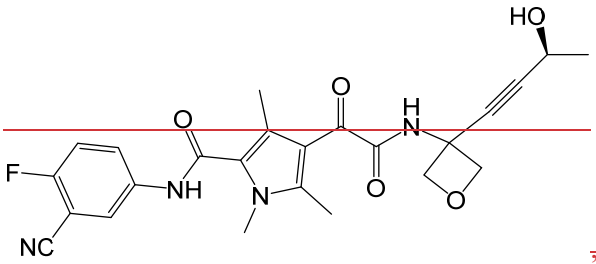
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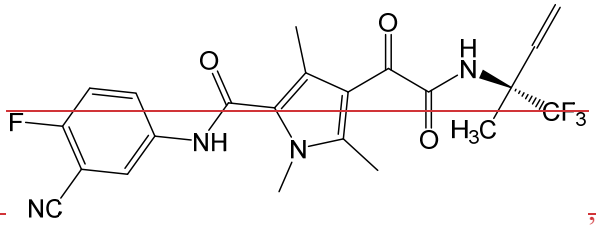
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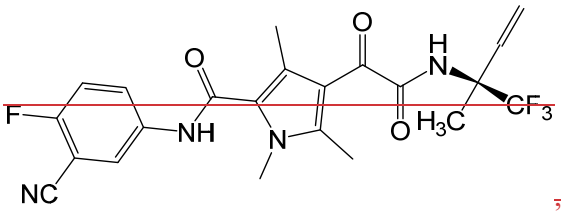
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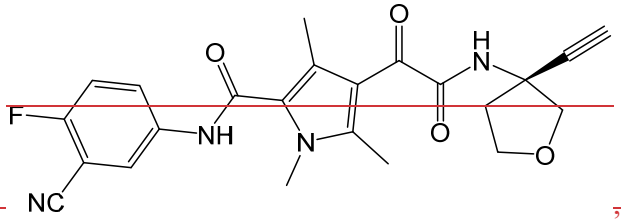
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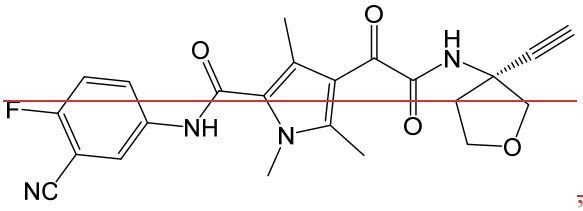
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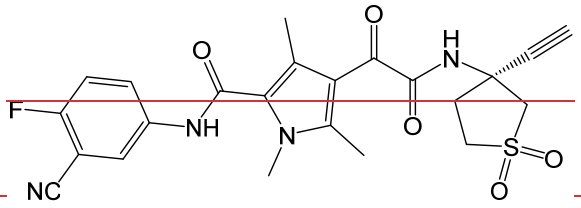
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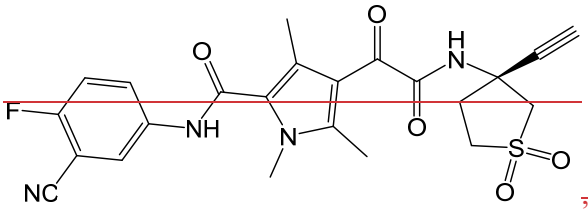
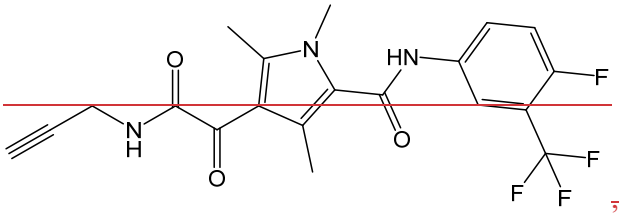

~~, or a pharmaceutically acceptable salt of any of the foregoing.~~

~~75. A compound is selected from the group consisting of :~~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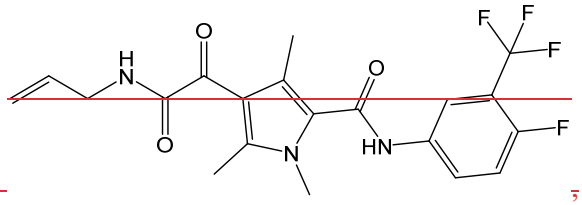
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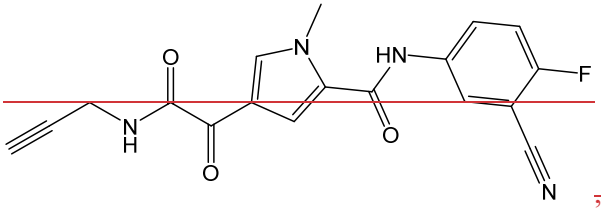
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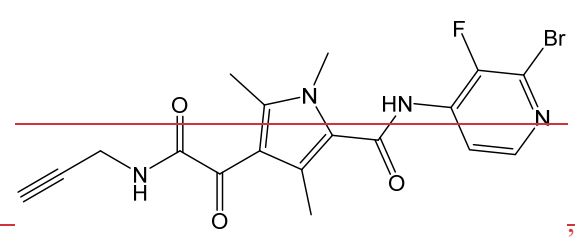
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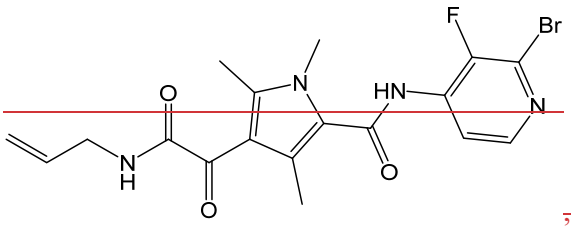
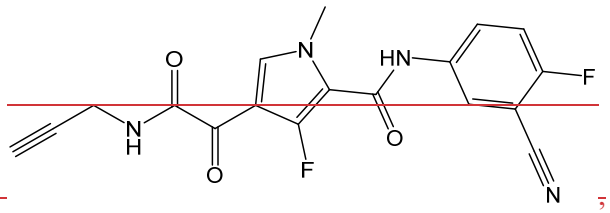
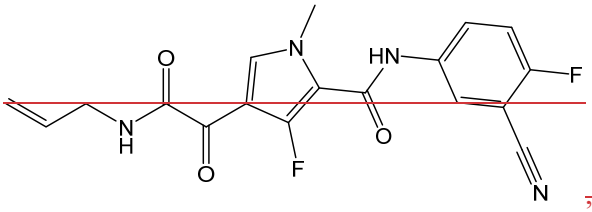
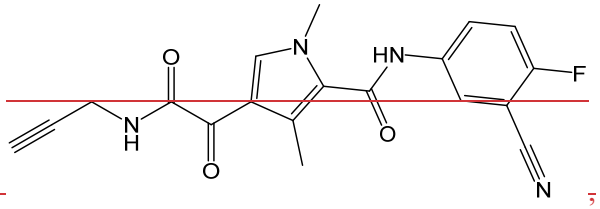
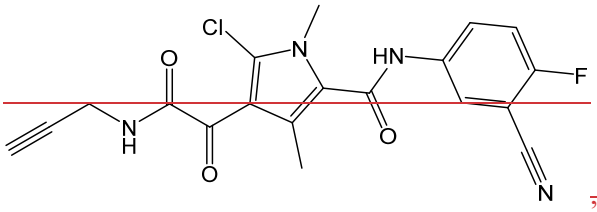
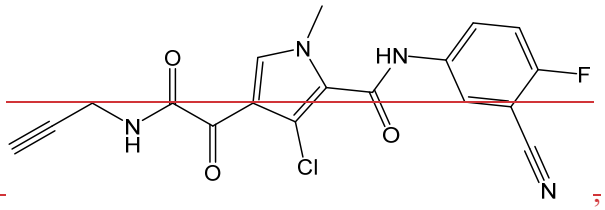
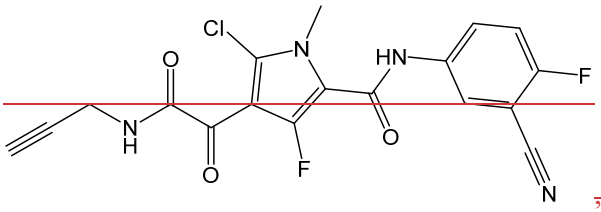
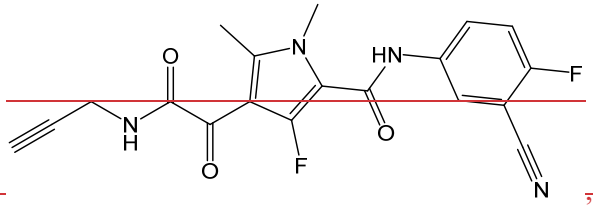
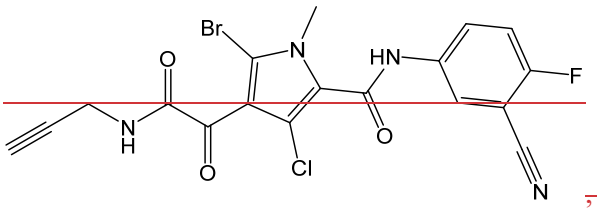
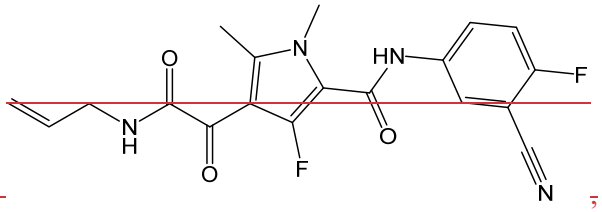
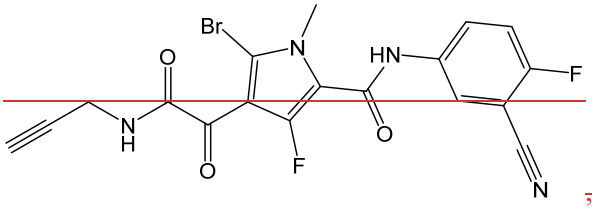
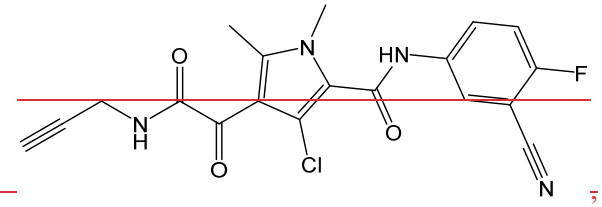
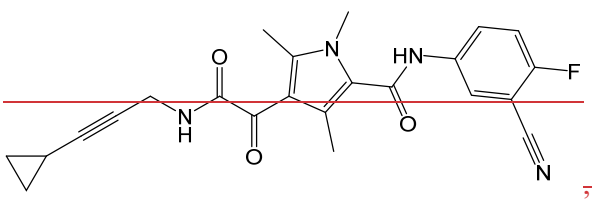
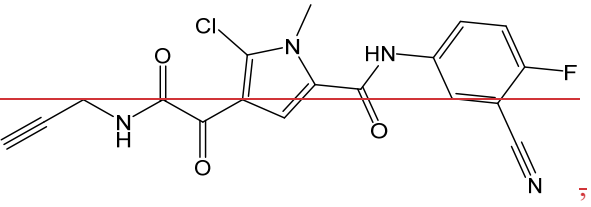

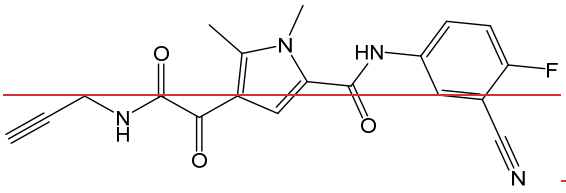

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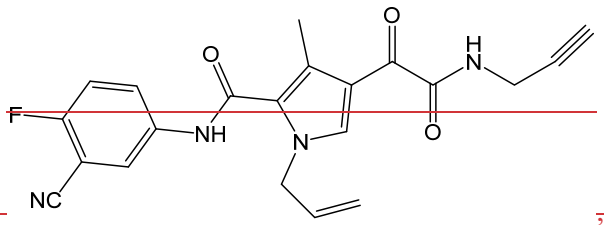


~~, or~~

~~a pharmaceutically acceptable salt of any of the foregoing.~~

~~76.~~15. A pharmaceutical composition comprising an effective amount of a compound of any one of Claims 1-~~75~~14, or a pharmaceutically acceptable salt thereof, and excipient.

~~77.~~16. Use of the compound of any one of Claims 1-~~75~~14, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of hepatitis B.

~~78.~~17. Use of the compound of any one of Claims 1-~~75~~14, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of hepatitis D.

~~79.~~18. The use of any one of Claims ~~77~~16-~~78~~17, wherein the use further comprises the use of one or more additional agents selected from the group consisting of an interferon, a nucleoside analog, a nucleotide analog, a sequence specific oligonucleotide, a nucleic acid polymer, an entry inhibitor and a small molecule immunomodulator.

~~80.~~19. The use of Claim ~~79~~18, wherein the one or more additional agents are selected from the group consisting of recombinant interferon alpha 2b, IFN-α, PEG-IFN-α-2a, lamivudine, telbivudine, adefovir dipivoxil, clevudine, entecavir, tenofovir alafenamide and tenofovir disoproxil.

~~81.~~20. A compound of any one of Claims 1-~~75~~14, or a pharmaceutically acceptable salt thereof, for use in treating hepatitis B.

~~82.~~21. A compound of any one of Claims 1-~~75~~14, or a pharmaceutically acceptable salt thereof, for use in treating hepatitis D.

~~83.~~22. The compound for use of any one of Claims ~~81~~20-~~82~~21, wherein the compound is used in combination with one or more additional agents selected from the group consisting of an interferon, a nucleoside analog, a nucleotide analog, a sequence specific oligonucleotide, a nucleic acid polymer, an entry inhibitor and a small molecule immunomodulator.

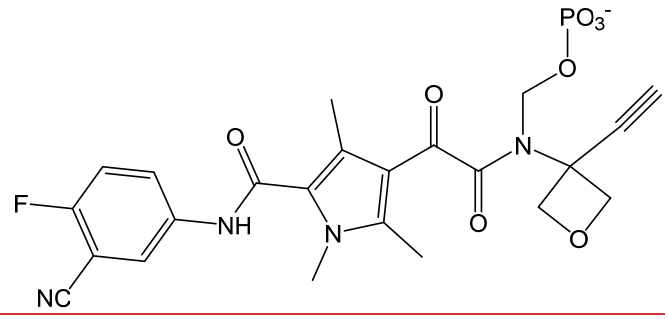
~~84.~~23. The compound for use of Claim ~~83~~22, wherein the one or more additional agents are selected from the group consisting of recombinant interferon alpha 2b, IFN-α, PEG-IFN-α-2a, lamivudine, telbivudine, adefovir dipivoxil, clevudine, entecavir, tenofovir alafenamide and tenofovir disoproxil.

~~85. A method for treating hepatitis B in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of Claims 1-75, or a pharmaceutically acceptable salt thereof, suffering from hepatitis B.~~

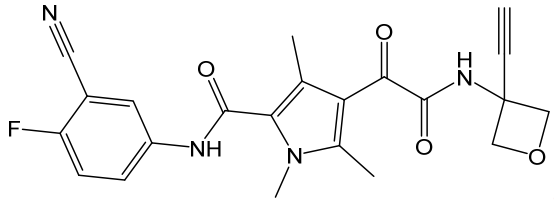
~~86. A method for treating hepatitis D in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of Claims 1-75, or a pharmaceutically acceptable salt thereof, suffering from hepatitis D.~~

~~87. The method of any one of Claims 85-86, further comprising administering an additional agent selected from the group consisting of an interferon, a nucleoside analog, a nucleotide analog, a sequence specific oligonucleotide, a nucleic acid polymer, an entry inhibitor and a small molecule immunomodulator.~~

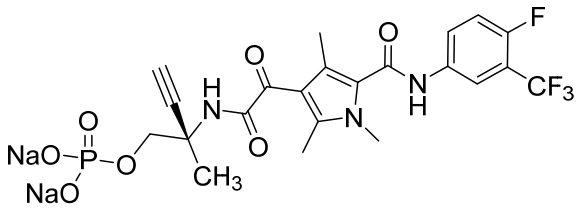
~~88. The method of Claim 87, wherein the additional agent selected from the group consisting of recombinant interferon alpha 2b, IFN α, PEG IFN α 2a, lamivudine, telbivudine, adefovir dipivoxil, clevudine, entecavir, tenofovir alafenamide and tenofovir disoproxil.~~

24. A compound having the structure 

, or a pharmaceutically acceptable salt thereof.

25. A compound having the structure 

, or a pharmaceutically acceptable salt thereof.

26. A compound having the structure 

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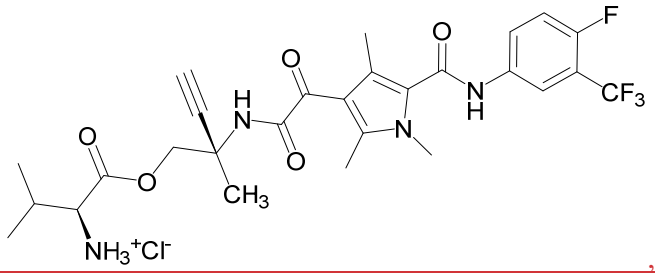
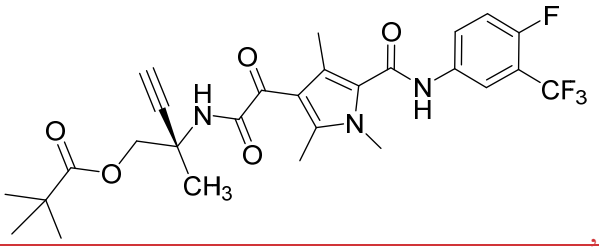
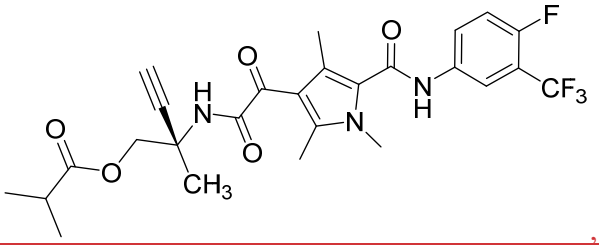
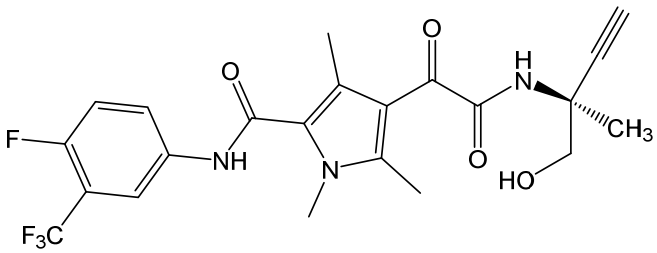
27. A compound having the structure  , or a pharmaceutically acceptable salt thereof.

28. A compound having the structure  , or a pharmaceutically acceptable salt thereof.

29. A compound having the structure  , or a pharmaceutically acceptable salt thereof.

30. A compound having the structure  , or a pharmaceutically acceptable salt thereof.

31. The compound of Claim 1, wherein:

R^1 is an unsubstituted or a substituted C_2 alkynyl, wherein when the C_2 alkynyl is substituted, the C_2 alkynyl is substituted with one or more substituents independently selected from the group consisting of halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{1-4} hydroxyalkyl, an unsubstituted monocyclic C_{3-6} cycloalkyl and a hydroxy-substituted monocyclic C_{3-6} cycloalkyl;

R^2 is an unsubstituted C_{1-4} alkyl;

R^3 is selected from the group consisting a substituted C_{1-4} alkyl and an unsubstituted C_{1-4} hydroxyalkyl, wherein when the C_{1-4} alkyl is substituted, the C_{1-4} alkyl is substituted with one or more

substituents independently selected from the group consisting of a phosphate, an O-linked α-amino acid and an O-carboxy;

R^4 and R^5 are each an unsubstituted C_{1-4} alkyl;

R^6 is an unsubstituted C_{1-4} alkyl;

X^1 is CR^A;

R^{7a}, R^{7c} and R^{7d} are each hydrogen;

R^{7b} is halogen, an unsubstituted C_{1-4} haloalkyl, cyano or an unsubstituted C_{1-4} alkoxy;

R^8 is $–CH_2OC(=O)–$(an unsubstituted C_{1-4} alkyl), $–CH_2OC(=O)–O$(an unsubstituted C_{1-4} alkyl), $–CH_2–$(α-amino acid) or $–CH_2$-phosphate; and

R^A is halogen.

32. The compound of Claim 1, wherein:

R^1 is an unsubstituted or a substituted C_2 alkynyl, wherein when the C_2 alkynyl is substituted, the C_2 alkynyl is substituted with one or more substituents independently selected from the group consisting of halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{1-4} hydroxyalkyl, an unsubstituted monocyclic C_{3-6} cycloalkyl and a hydroxy-substituted monocyclic C_{3-6} cycloalkyl;

R^2 and R^3 are taken together along with the carbon to which R^2 and R^3 are attached to form an unsubstituted or a substituted monocyclic 3-6 membered heterocyclyl, wherein when 3-6 membered heterocyclyl are substituted, the 3-6 membered heterocyclyl is substituted with 1 or 2 substituents independently selected from the group consisting of halogen and hydroxy;

R^4 and R^5 are each an unsubstituted C_{1-4} alkyl;

R^6 is an unsubstituted C_{1-4} alkyl;

X^1 is CR^A;

R^{7a}, R^{7c} and R^{7d} are each hydrogen;

R^{7b} is halogen, an unsubstituted C_{1-4} haloalkyl, cyano or an unsubstituted C_{1-4} alkoxy;

R^8 is $–CH_2OC(=O)–$(an unsubstituted C_{1-4} alkyl), $–CH_2OC(=O)–O$(an unsubstituted C_{1-4} alkyl), $–CH_2–$(α-amino acid) or $–CH_2$-phosphate; and

R^A is halogen.

33. The compound of Claim 32, wherein R^2 and R^3 are taken together along with the carbon to which R^2 and R^3 are attached to form an unsubstituted or a substituted oxetane.

34. The compound of Claim 33, wherein R^8 is $–CH_2$-phosphate.