

ANTIVIRAL COMPOUNDS

This application claims priority to U.S. Application No. 13/831,116, filed on March 14, 2013, and U.S. Provisional Application No. 61/647,966, filed on May 16, 2012, both of which are hereby incorporated by reference in their entirety.

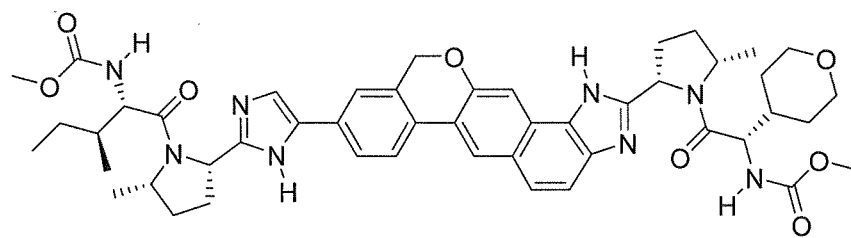
BACKGROUND

Hepatitis C is recognized as a chronic viral disease of the liver which is characterized by liver disease. Although drugs targeting the liver are in wide use and have shown effectiveness, toxicity and other side effects have limited their usefulness. Inhibitors of hepatitis C virus (HCV) are useful to limit the establishment and progression of infection by HCV as well as in diagnostic assays for HCV.

There is a need for new HCV therapeutic agents. In particular, there is a need for HCV therapeutic agents that have broad activity against HCV genotypes (e.g. genotypes 1a, 1b, 2a, 3a, 4a). There is also a particular need for agents that are less susceptible to viral resistance. Resistance mutations to inhibitors have been described for HCV NS5A for genotypes 1a and 1b in Antimicrobial Agents and Chemotherapy, September 2010, Volume 54, p. 3641-3650.

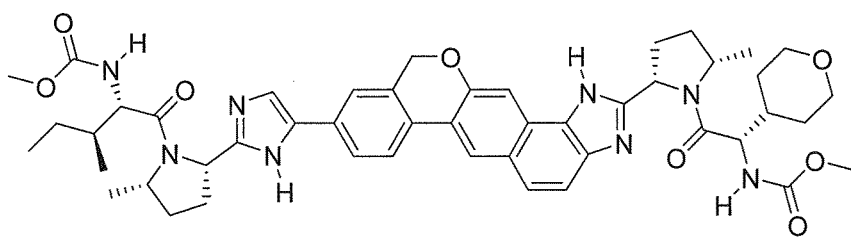
SUMMARY

In one aspect, there is provided a compound of formula:

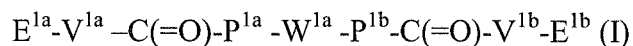


or a pharmaceutically acceptable salt thereof.

In one aspect, there is provided a compound of formula:

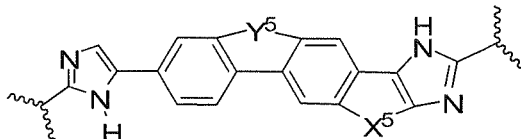


In one embodiment the disclosure provides a compound of formula (I):



wherein:

W^{1a} is



and W^{1a} is optionally substituted with one or more groups independently selected from halo, alkyl, haloalkyl, optionally substituted aryl, optionally substituted heterocycle, and cyano;

Y^5 is $-O-CH_2-$, $-CH_2-O-$, $-O-C(=O)-$, or $-C(=O)-O-$; X^5 is $-CH_2-CH_2-$ or $-CH=CH-$;

E^{1a} is $-N(H)(alkoxycarbonyl)$, $-N(H)(cycloalkylcarbonyl)$

or $-N(H)(cycloalkyloxycarbonyl)$; or $E^{1a}-V^{1a}$ taken together are R^{9a} ;

or a pharmaceutically acceptable salt or prodrug thereof;

provided that when Y⁵ is -O-CH₂-, or -CH₂O-, then at least one of the following occurs:

(1) at least one of V^{1a} and V^{1b} is selected from (af), (ag), (ah), (ai), (aj), (ak), (al), (am), (an), (ao), (ap) or (aq); or

(2) P^{1a} is selected from (be), (bf), (bg), (bh), (bi), (bj), (bk), (bl), (bm), (bn), (bo), (bq) or (br); or

(3) P^{1b} is selected from (be), (bf), (bg), (bh), (bi), (bj), (bk), (bl), (bm), (bn), (bo), (bp), (bq) or (br).

The disclosure also provides isotopically enriched compounds that are compounds of the disclosure that comprise an enriched isotope at one or more positions in the compound.

In one aspect, there is provided a pharmaceutical composition comprising the compound described herein and a pharmaceutically acceptable diluent or carrier, or combination thereof.

The present disclosure also provides a pharmaceutical composition comprising a compound of the disclosure or a pharmaceutically acceptable salt or prodrug thereof and at least one pharmaceutically acceptable carrier.

In one aspect, there is provided the compound described herein for use in the prophylactic or therapeutic treatment of hepatitis C.

In one aspect, there is provided use of the compound described herein in the manufacture of a medicament for the treatment of hepatitis C.

In one aspect, there is provided the pharmaceutical composition described herein for use in the prophylactic or therapeutic treatment of hepatitis C.

The present disclosure also provides a pharmaceutical composition for use in treating hepatitis C (HCV). In one embodiment the composition comprises at least one additional therapeutic agent for treating HCV. In one embodiment, the therapeutic agent is selected from ribavirin, an NS3 protease inhibitor, a nucleoside or nucleotide inhibitor of HCV NS5B polymerase, an alpha-glucosidase 1 inhibitor, a hepatoprotectant, a non-nucleoside inhibitor of HCV polymerase, or combinations thereof. In one embodiment, the composition further comprises a nucleoside or nucleotide inhibitor of HCV NS5B polymerase. In one embodiment, the nucleoside or nucleotide inhibitor of HCV NS5B polymerase is selected from ribavirin, viremide, levovirin, a L-nucleoside, or isatoribine.

In one embodiment, provided is a pharmaceutical composition comprising a compound as described herein and at least one nucleoside or nucleotide inhibitor of HCV NS5B polymerase, and at least one pharmaceutically acceptable carrier. In one embodiment, the composition further comprises an interferon, a pegylated interferon, ribavirin or combinations thereof. In one embodiment, the nucleoside or nucleotide inhibitor of HCV NS5B polymerase is sofosbuvir. In one embodiment, provided is a pharmaceutical composition comprising a compound as described herein and at least one NS3 protease inhibitor, and at least one pharmaceutically acceptable carrier. In one embodiment, the composition further comprises sofosbuvir.

The present disclosure also provides a pharmaceutical composition further comprising an interferon or pegylated interferon.

The present disclosure also provides a pharmaceutical composition further comprising a nucleoside analog.

The present disclosure also provides for a pharmaceutical composition wherein said nucleoside analogue is selected from ribavirin, viramidine, levovirin, an L-nucleoside, and isatoribine and said interferon is α -interferon or pegylated α -interferon.

The present disclosure also provides for a method of treating hepatitis C, said method comprising administering to a human patient a pharmaceutical composition which comprises a therapeutically effective amount of a compound of the disclosure.

The present disclosure also provides a method of inhibiting HCV, comprising administering to a mammal afflicted with a condition associated with HCV activity, an amount of a compound of the disclosure, effective to inhibit HCV.

The present disclosure also provides a compound of the disclosure for use in medical therapy (e.g. for use in inhibiting HCV activity or treating a condition associated with HCV activity), as well as the use of a compound of the disclosure for the manufacture of a medicament useful for inhibiting HCV or the treatment of a condition associated with HCV activity in a mammal.

The present disclosure also provides synthetic processes and novel intermediates disclosed herein which are useful for preparing compounds of the disclosure. Some of the compounds of the disclosure are useful to prepare other compounds of the disclosure.

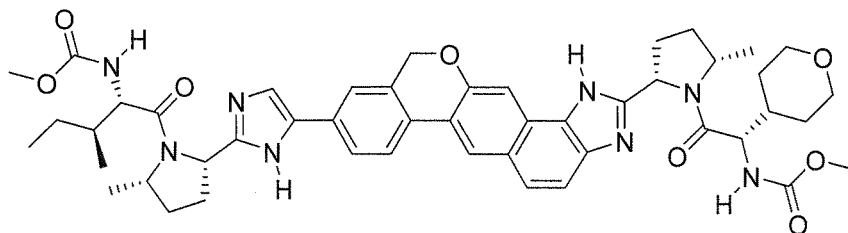
In another ~~aspect~~ embodiment the disclosure provides a compound of the disclosure, or a pharmaceutically acceptable salt or prodrug thereof, for use in the prophylactic or therapeutic treatment of hepatitis C or a hepatitis C associated disorder.

In another ~~aspect~~ embodiment the disclosure provides a method of inhibiting HCV activity in a sample comprising treating the sample with a compound of the disclosure.

Compounds of formula (I) have been found to possess useful activity against several HCV genotypes. Additionally certain compounds of formula (I) exhibit significant potency against resistant variants in, e.g., GT1.

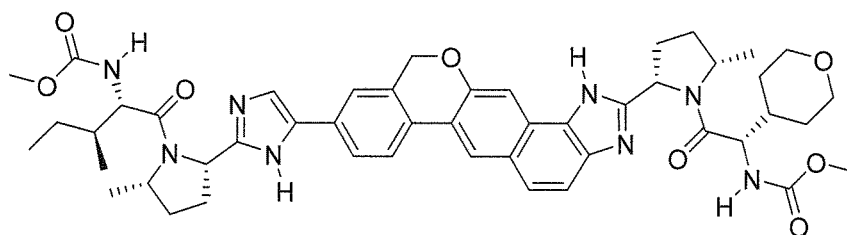
Claims

1. A compound of formula:



or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable diluent or carrier, or combination thereof.
3. The pharmaceutical composition of claim 2, formulated for oral administration.
4. The pharmaceutical composition of claim 2, formulated in tablet form.
5. The compound of claim 1 for use in the prophylactic or therapeutic treatment of hepatitis C.
6. Use of the compound of claim 1 in the manufacture of a medicament for the treatment of hepatitis C.
7. The pharmaceutical composition of claim 2 for use in the prophylactic or therapeutic treatment of hepatitis C.
8. A compound of formula:

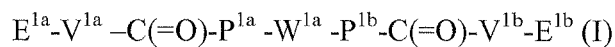


9. A pharmaceutical composition comprising the compound of claim 8 and a pharmaceutically acceptable diluent or carrier, or combination thereof.
10. The pharmaceutical composition of claim 9, formulated for oral administration.
11. The pharmaceutical composition of claim 9, formulated in tablet form.

12. The compound of claim 8 for use in the prophylactic or therapeutic treatment of hepatitis C.
13. Use of the compound of claim 8 in the manufacture of a medicament for the treatment of hepatitis C.
14. The pharmaceutical composition of claim 9 for use in the prophylactic or therapeutic treatment of hepatitis C.

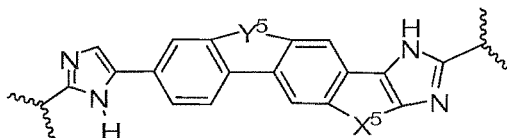
Claims

1. A compound of formula (I):



wherein:

W^{1a} is



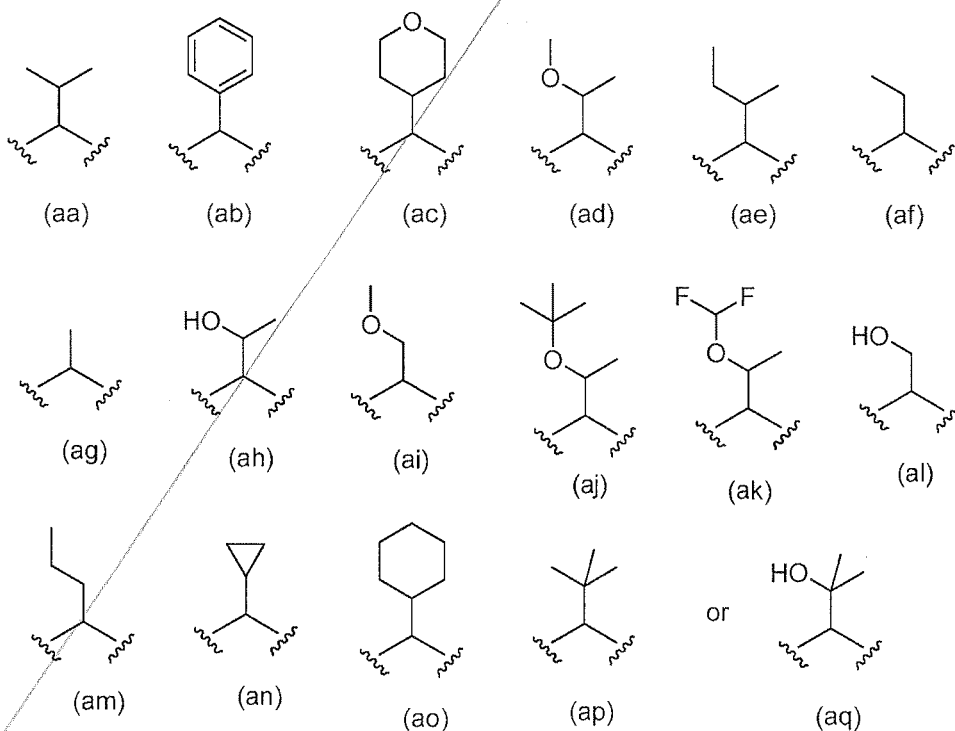
and W^{1a} is optionally substituted with one or more groups independently selected from halo, alkyl, haloalkyl, optionally substituted aryl, optionally substituted heterocycle, and cyano;

Y^5 is $-O-CH_2-$, $-CH_2-O-$, $-O-C(=O)-$, or $-C(=O)-O-$; X^5 is $-CH_2-CH_2-$ or $-CH=CH-$;

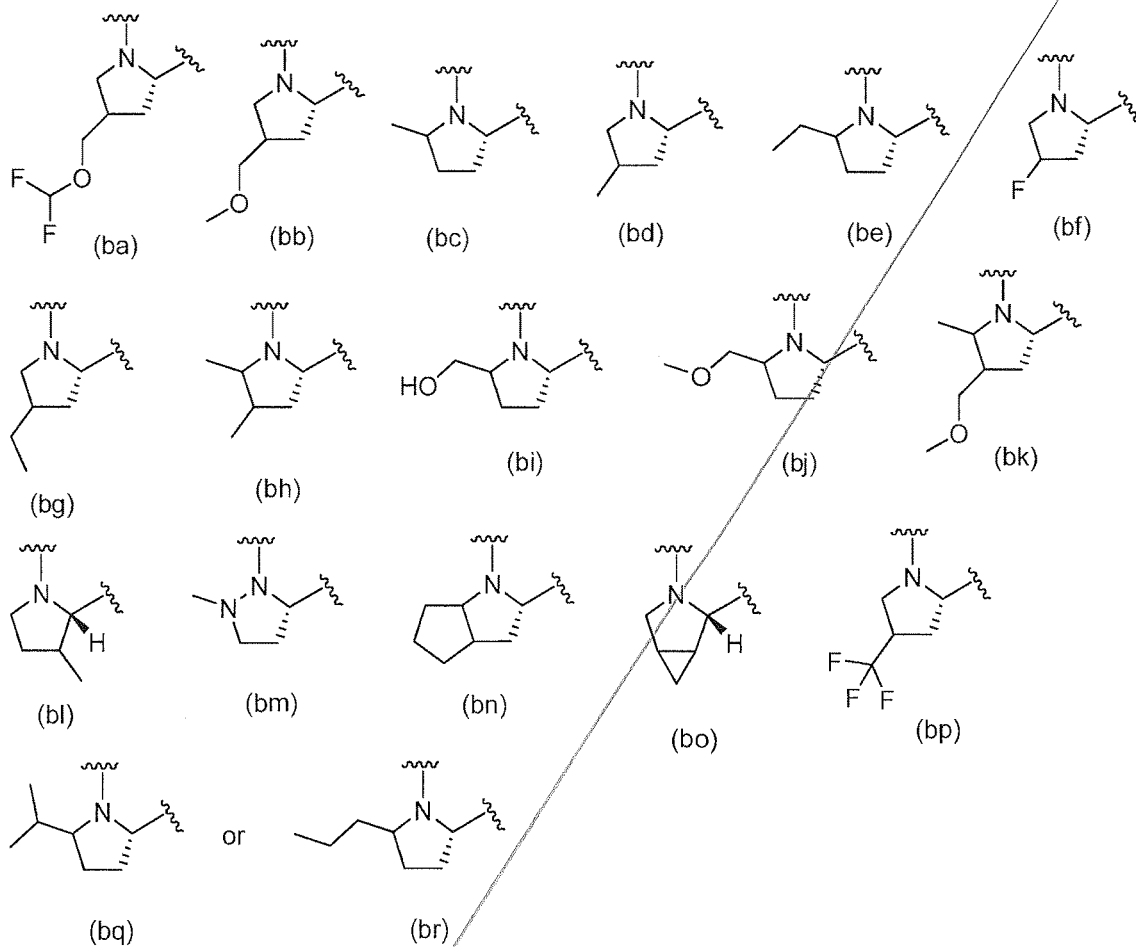
E^{1a} is $-N(H)(\text{alkoxycarbonyl})$, $-N(H)(\text{cycloalkylcarbonyl})$ or $-N(H)(\text{cycloalkyloxycarbonyl})$; or $E^{1a}-V^{1a}$ taken together are R^{9a} ;

E^{1b} is $-N(H)(\text{alkoxycarbonyl})$, $-N(H)(\text{cycloalkylcarbonyl})$ or $-N(H)(\text{cycloalkyloxycarbonyl})$; or $E^{1b}-V^{1b}$ taken together are R^{9b} ;

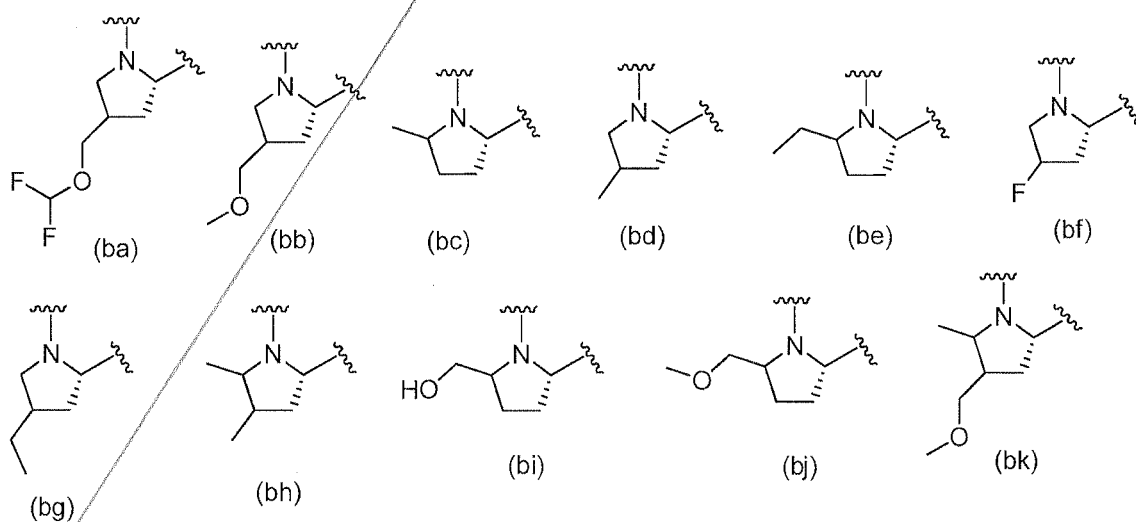
V^{1a} and V^{1b} are each independently selected from:

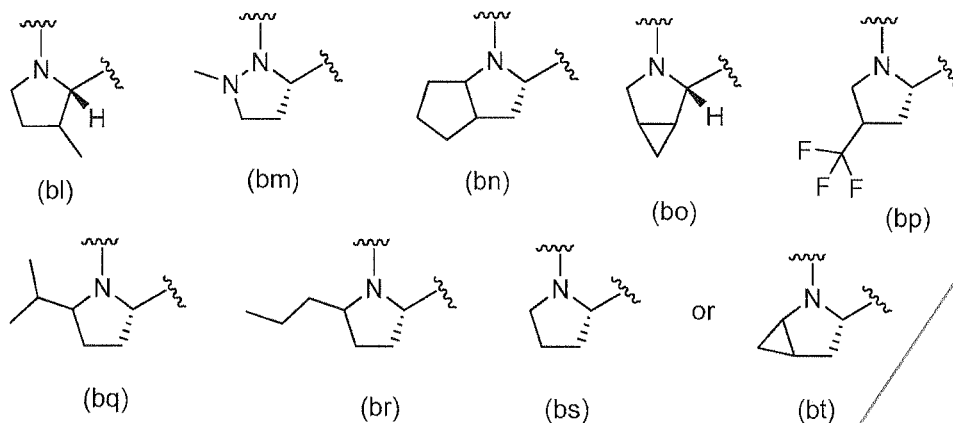


P^{1a} is selected from:



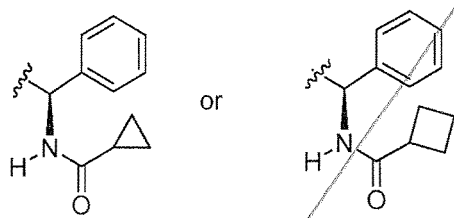
P^{1b} is selected from:





and

R^{9a} and R^{9b} are each independently selected from:

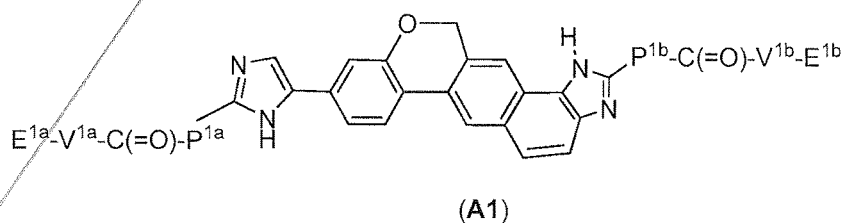


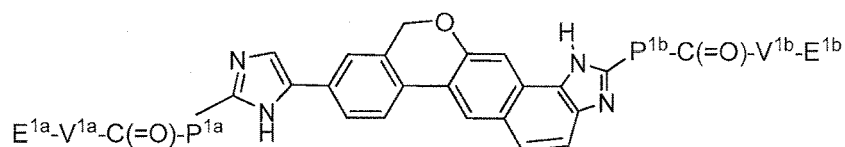
or a pharmaceutically acceptable salt or prodrug thereof;

provided that when Y^5 is $-O-CH_2-$, or $-CH_2-O-$, then at least one of the following occurs:

- (1) at least one of V^{1a} and V^{1b} is selected from (af), (ag), (ah), (ai), (aj), (ak), (al), (am), (an), (ao), (ap) or (aq); or
- (2) P^{1a} is selected from (be), (bf), (bg), (bh), (bi), (bj), (bk), (bl), (bm), (bn), (bo), (bq) or (br); or
- (3) P^{1b} is selected from (be), (bf), (bg), (bh), (bi), (bj), (bk), (bl), (bm), (bn), (bo), (bp), (bq) or (br).

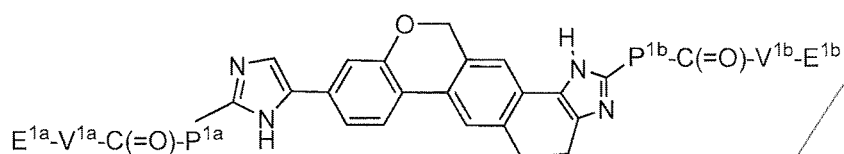
2. The compound of claim 1, wherein the compound of formula (I) is represented by formula:





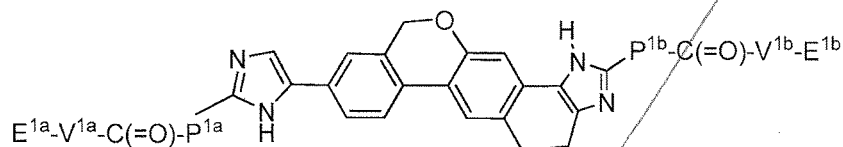
(A2)

;



(A3)

; or

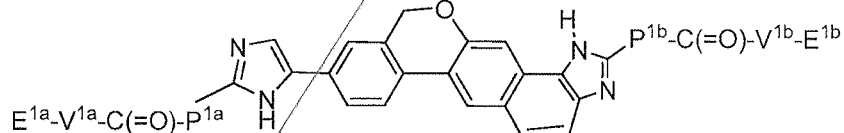


(A4)

wherein the imidazole ring shown in formula (A1), (A2), (A3) and (A4) is optionally substituted with one or more groups independently selected from halo, haloalkyl, cyano, and alkyl;

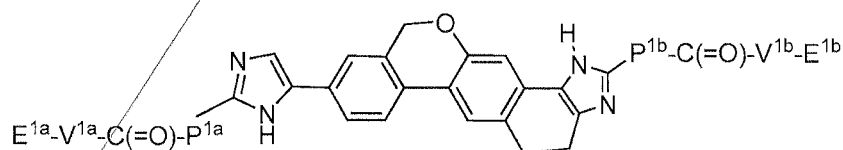
or a pharmaceutically acceptable salt or prodrug thereof.

3. The compound of claim 1, wherein the compound of formula (I) is represented by formula:



(A2)

; or



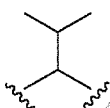
(A4)

wherein the imidazole ring shown in formula (A2) and (A4) is optionally substituted with one or more groups independently selected from halo, haloalkyl, cyano, and alkyl;

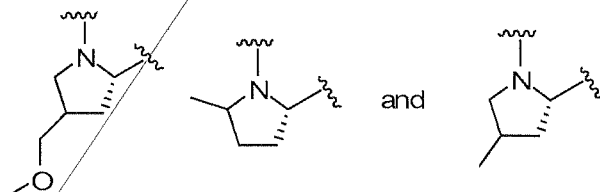
or a pharmaceutically acceptable salt or prodrug thereof.

4. The compound of any one of claims 1-3, wherein at least one of E^{1a} and E^{1b} is -N(H)(alkoxycarbonyl).

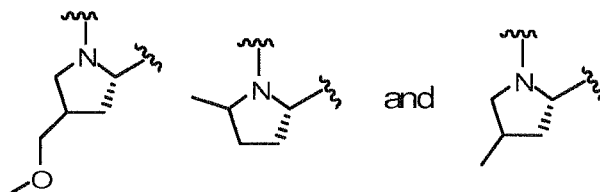
5. The compound of any one of claims 1-3, wherein at least one of E^{1a} and E^{1b} is $-N(H)C(=O)OMe$.
6. The compound of any one of claims 1-3, wherein both of E^{1a} and E^{1b} are $-N(H)C(=O)OMe$.
7. The compound of any one of claims 1-3, wherein at least one of E^{1a} and E^{1b} is $-N(H)(cycloalkylcarbonyl)$ or $-N(H)(cycloalkyloxycarbonyl)$.
8. The compound of any one of claims 1-3, wherein at least one of E^{1a} and E^{1b} is cyclopropylcarbonylamino, cyclobutylcarbonylamino, cyclopropyloxycarbonylamino or cyclobutyloxycarbonylamino.
9. The compound of any one of claims 1-3, wherein E^{1a} and E^{1b} are each independently selected from cyclopropylcarbonylamino, cyclobutylcarbonylamino, cyclopropyloxycarbonylamino and methoxycarbonylamino.
10. The compound of any one of claims 1-9, wherein at least one of V^{1a} and V^{1b} is:



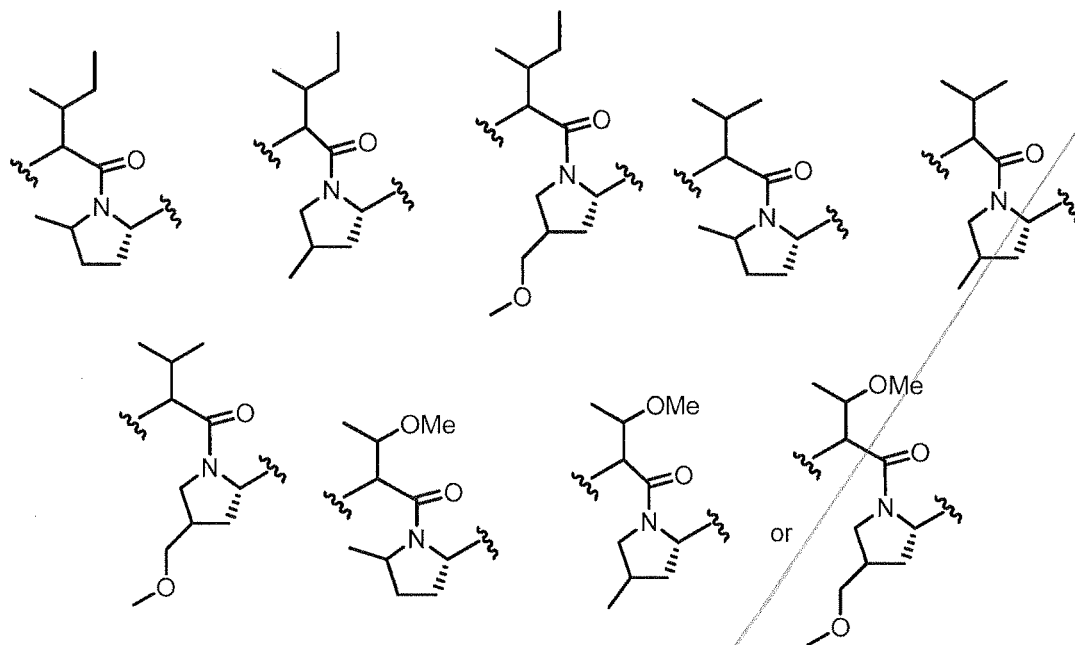
11. The compound of any one of claims 1-10, wherein $E^{1a}-V^{1a}$ taken together are R^{9a} or wherein $E^{1b}-V^{1b}$ taken together are R^{9b} .
12. The compound of any one of claims 1-11, wherein at least one of P^{1a} and P^{1b} is selected from:



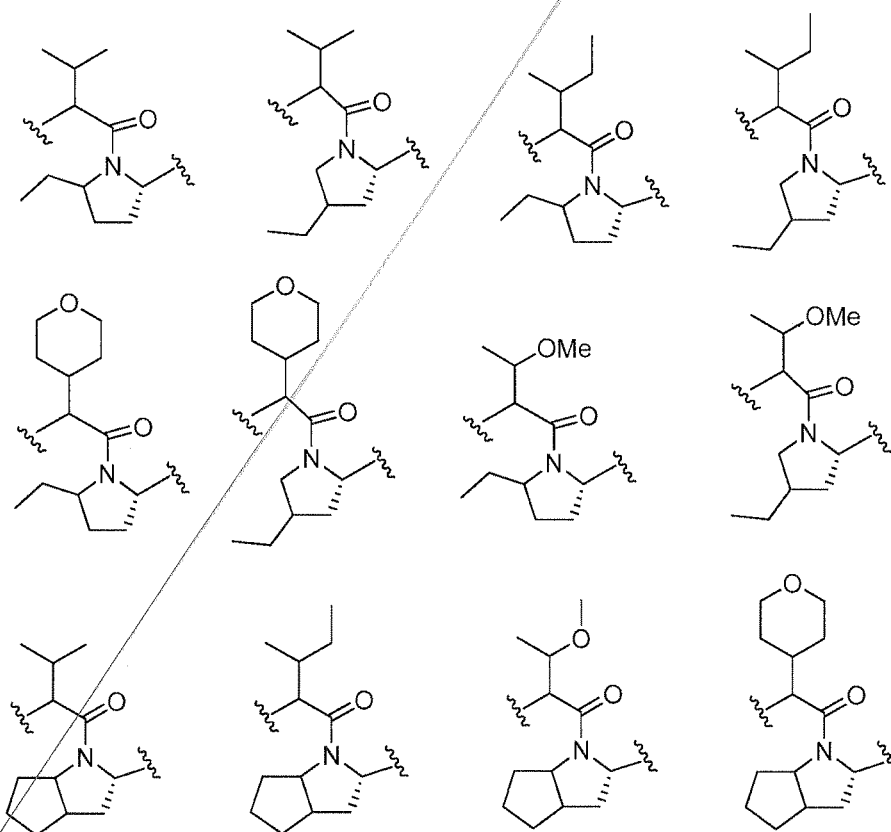
13. The compound of any one of claims 1-11, wherein P^{1a} and P^{1b} are each independently selected from:

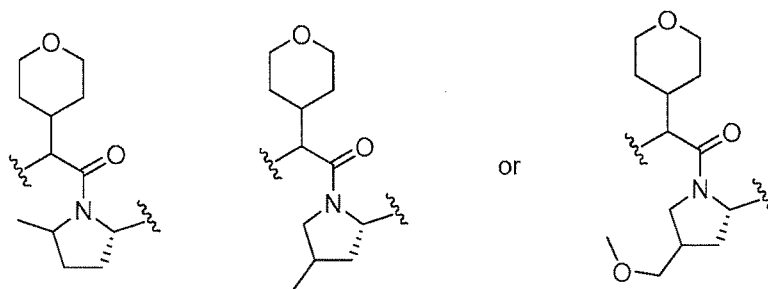


14. The compound of any one of claims 1-11, wherein at least one of $-V^{1a}-C(=O)-P^{1a}-$ and $-P^{1b}-C(=O)-V^{1b}-$ is:

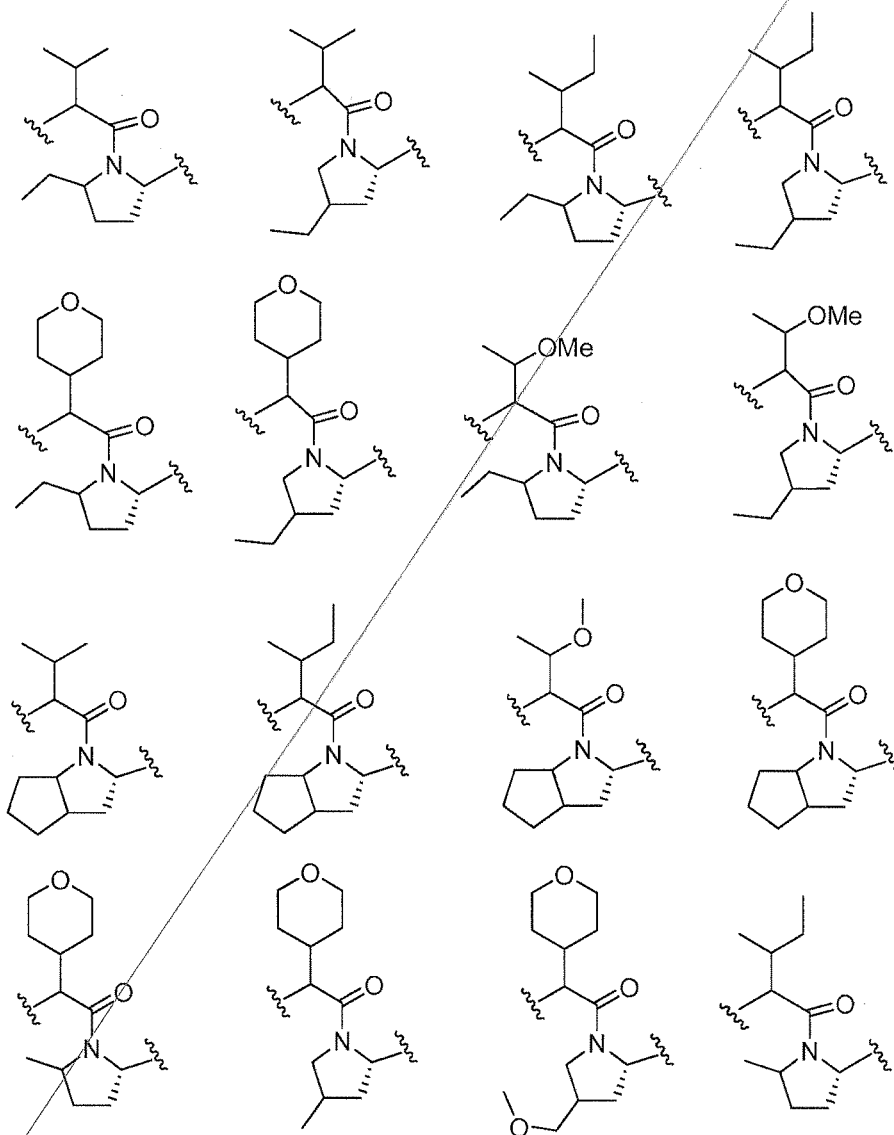


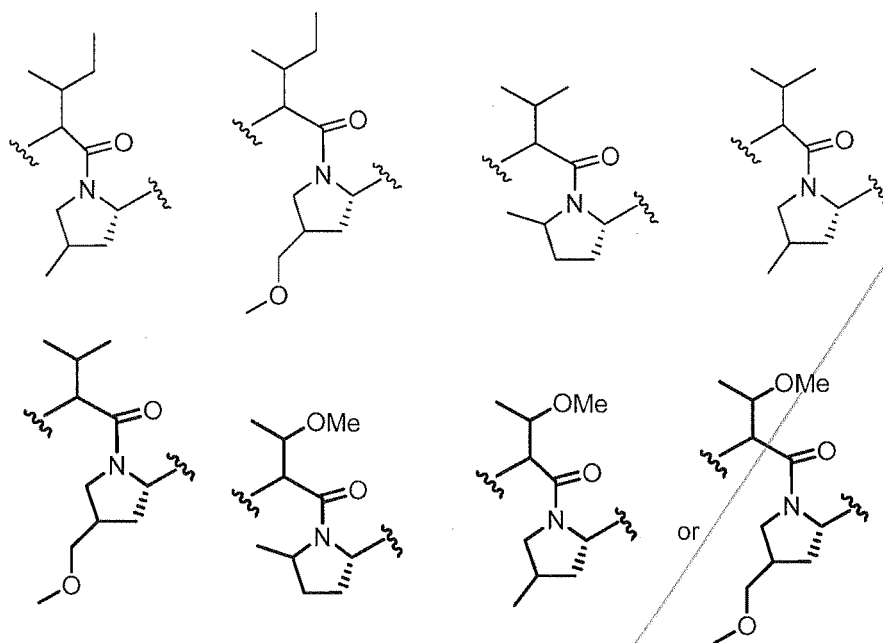
15. The compound of any one of claims 1-11, wherein at least one of $-V^{1a}-C(=O)-P^{1a}-$ and $-P^{1b}-C(=O)-V^{1b}-$ is:



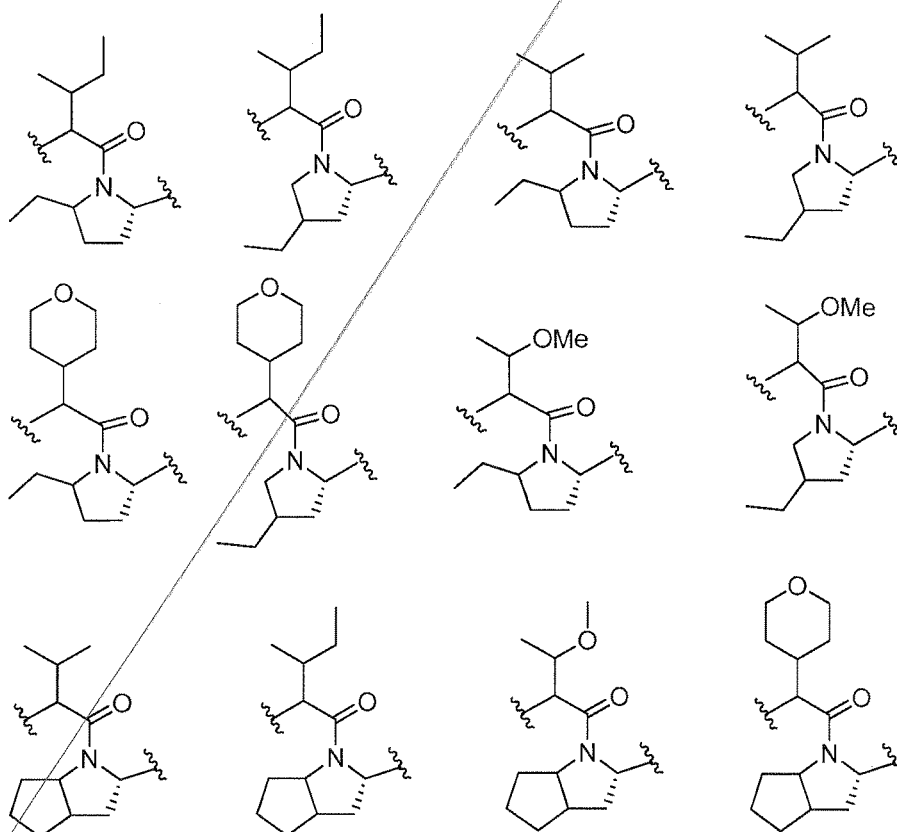


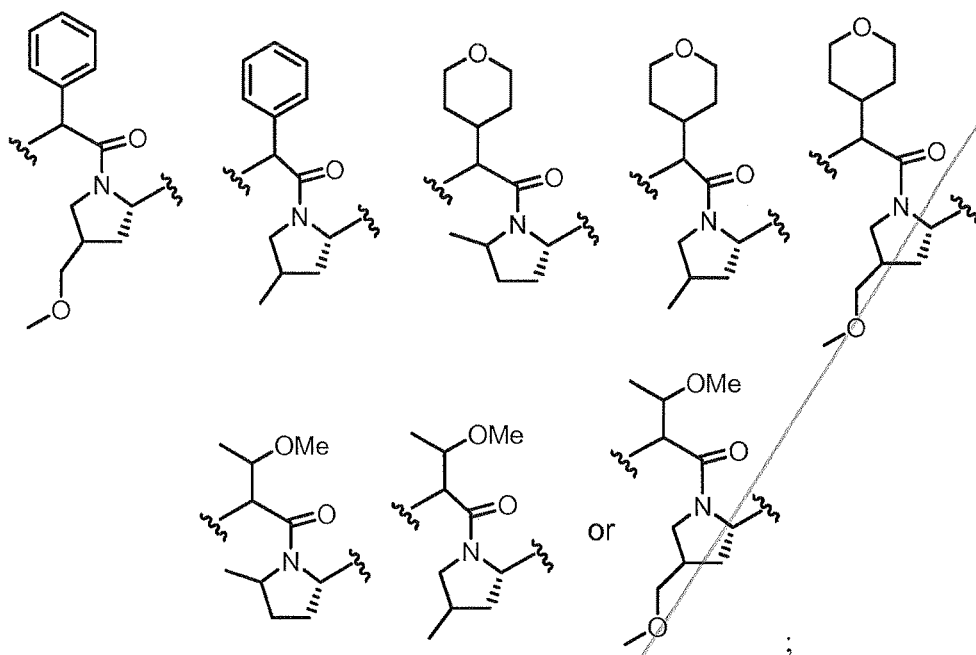
16. The compound of any one of claims 1-11, wherein $-V^{1a}-C(=O)-P^{1a}-$ and $-P^{1b}-C(=O)-V^{1b}-$ are each independently:



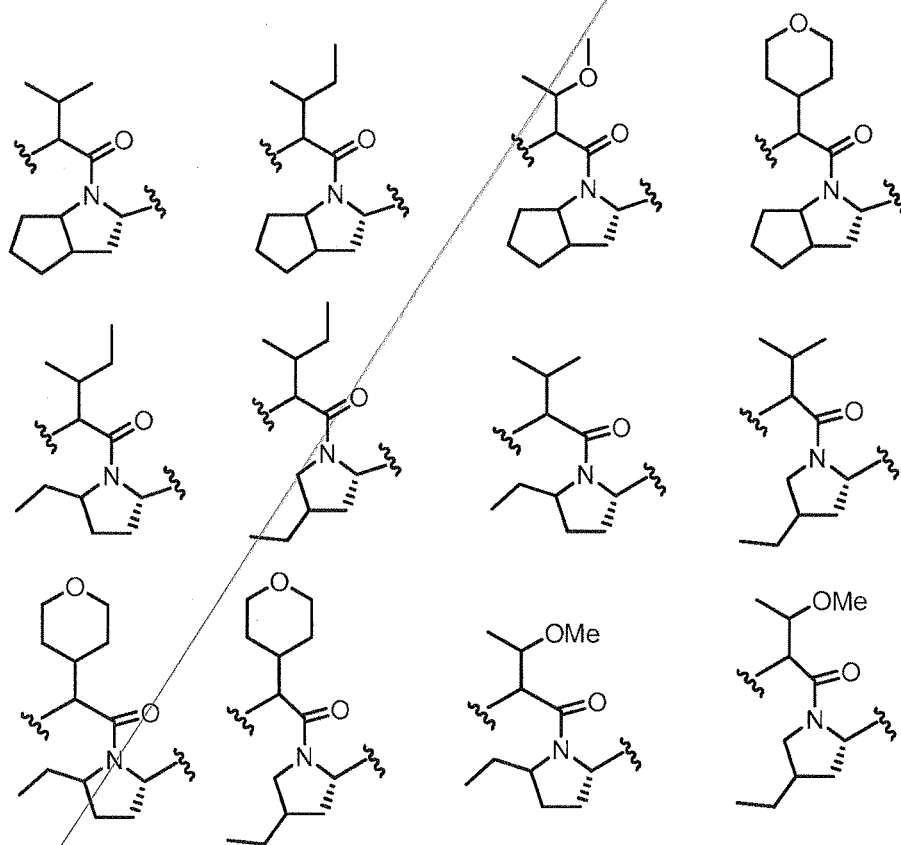


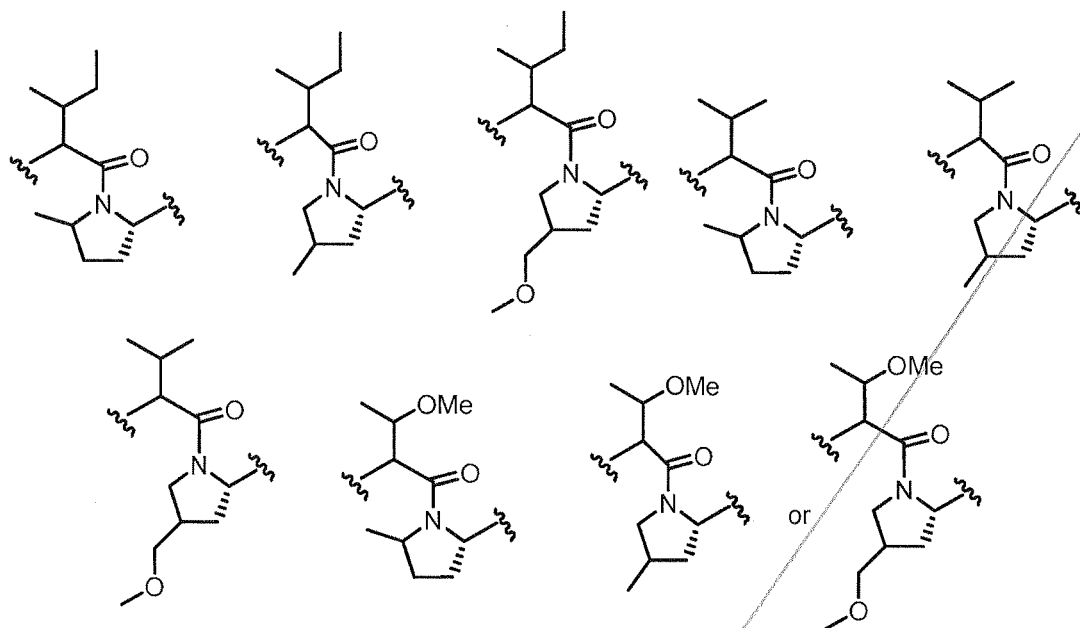
17. The compound of any one of claims 1-11, wherein one of $-V^{1a}-C(=O)-P^{1a}-$ and $-P^{1b}-C(=O)-V^{1b}-$ is:



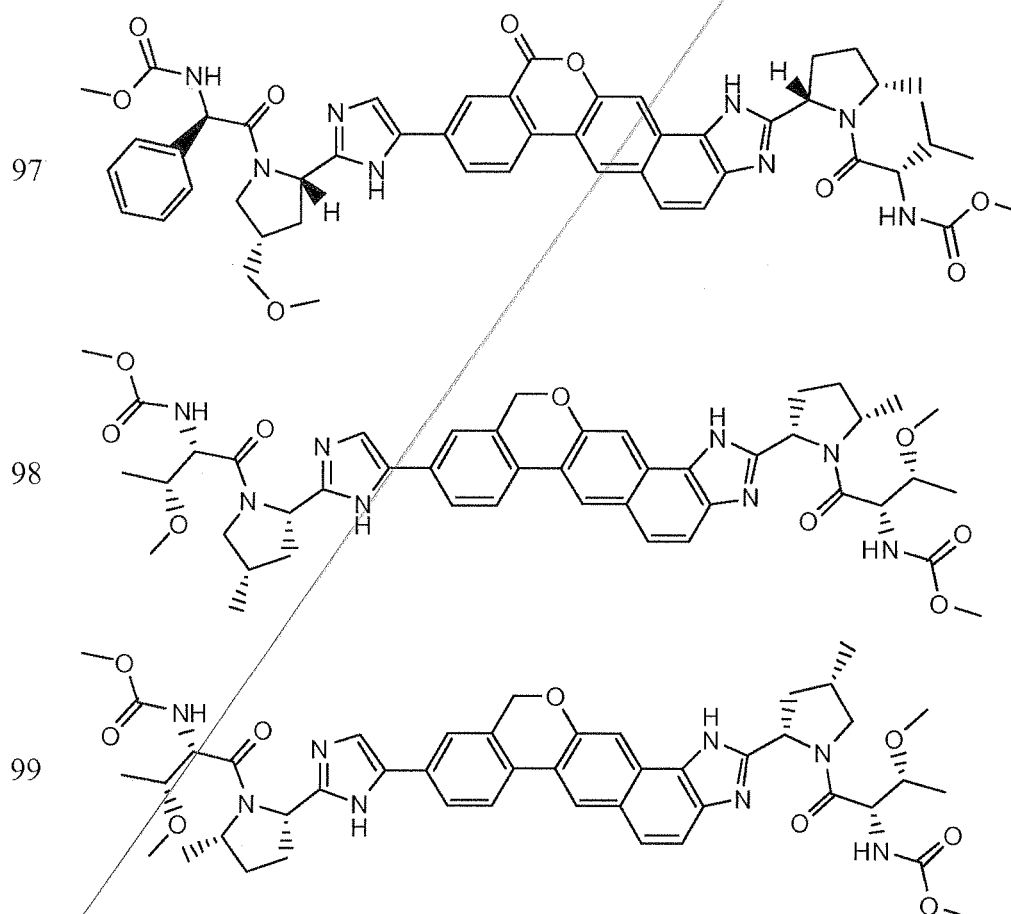


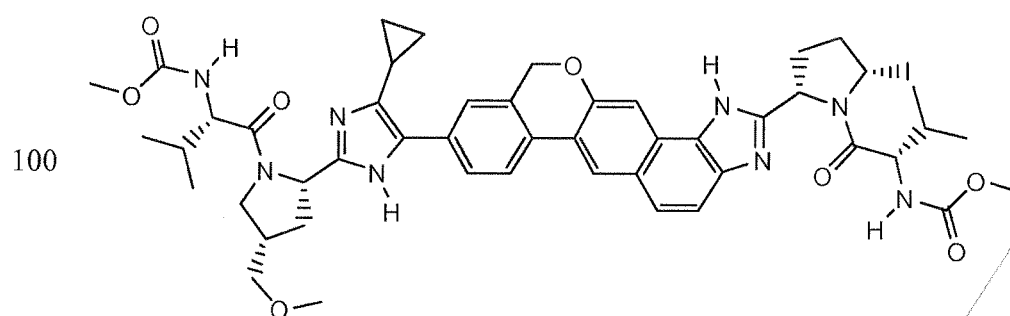
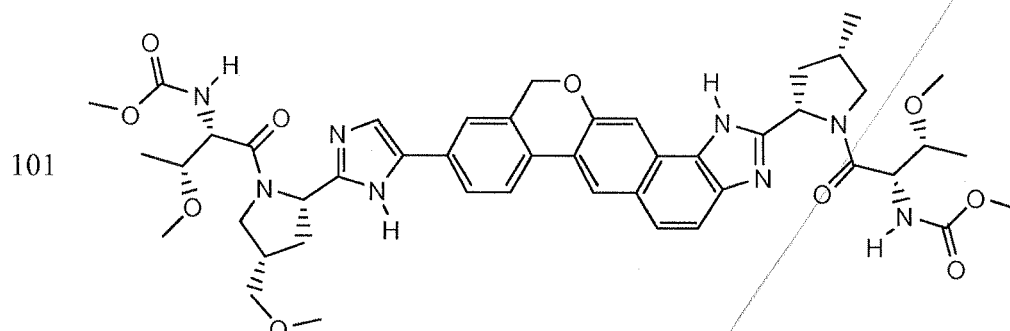
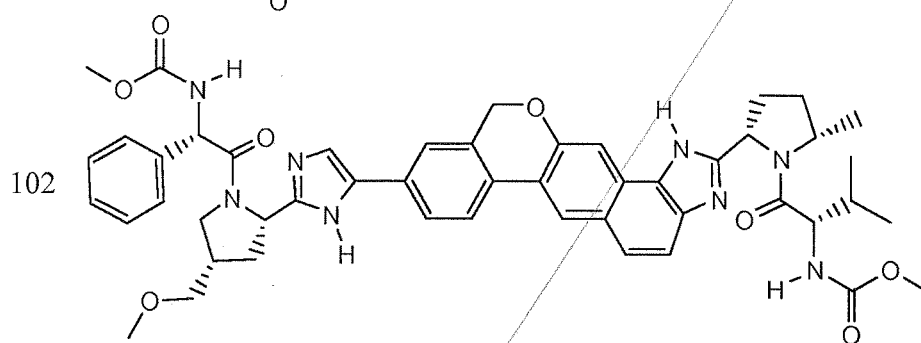
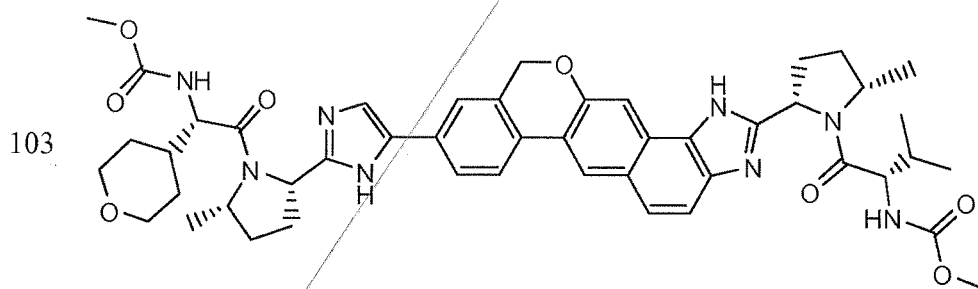
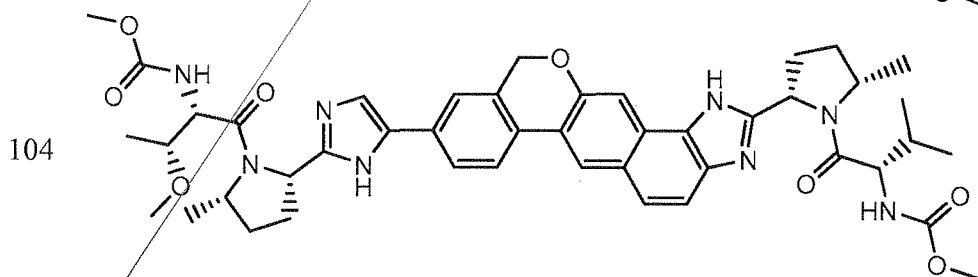
and the other of $-V^{1a}-C(=O)-P^{1a}-$ and $-P^{1b}-C(=O)-V^{1b}-$ is:

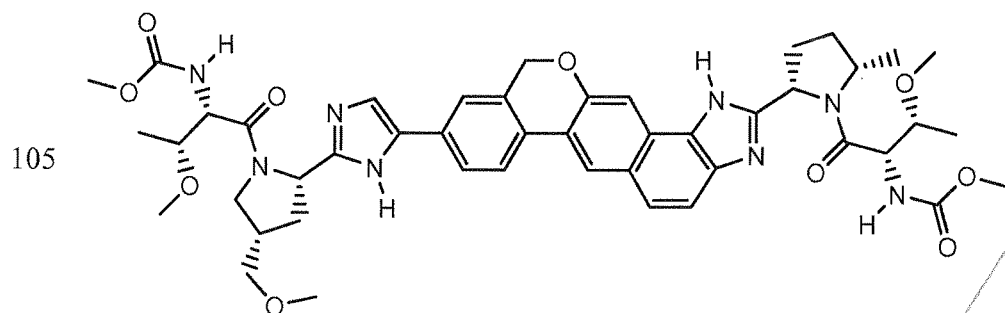
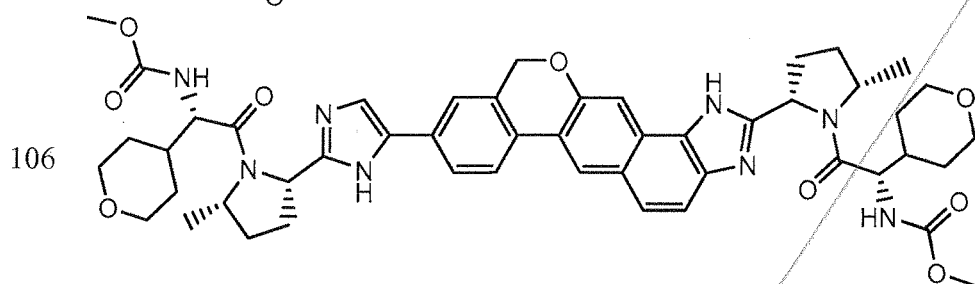
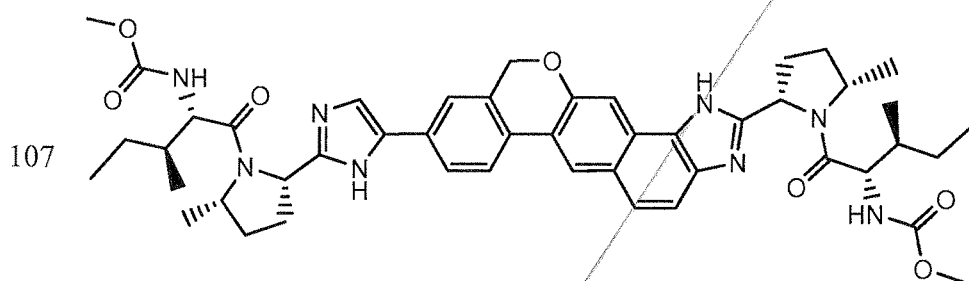
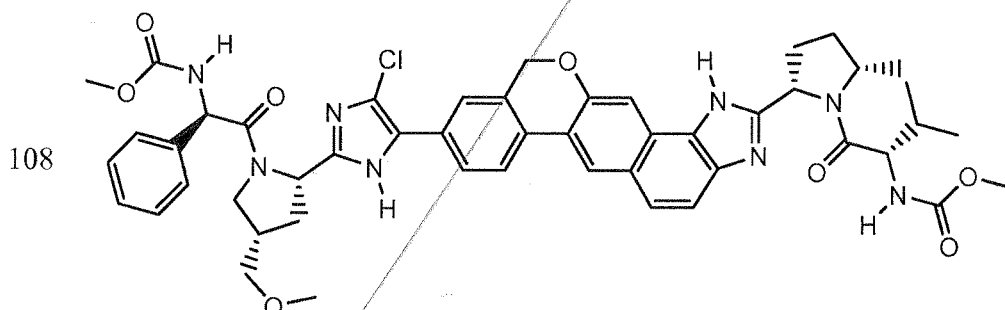
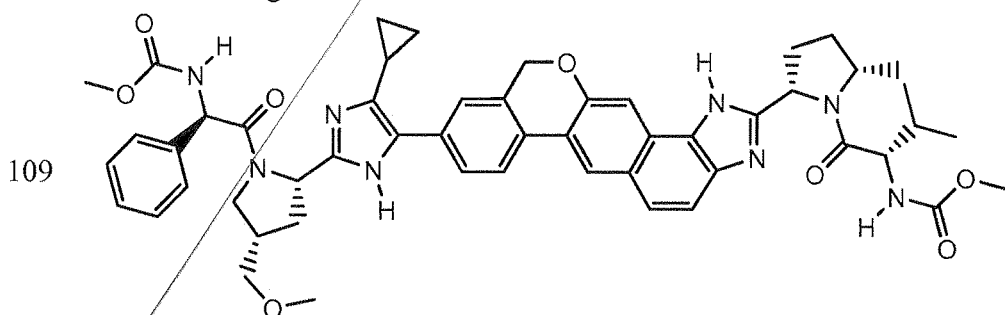


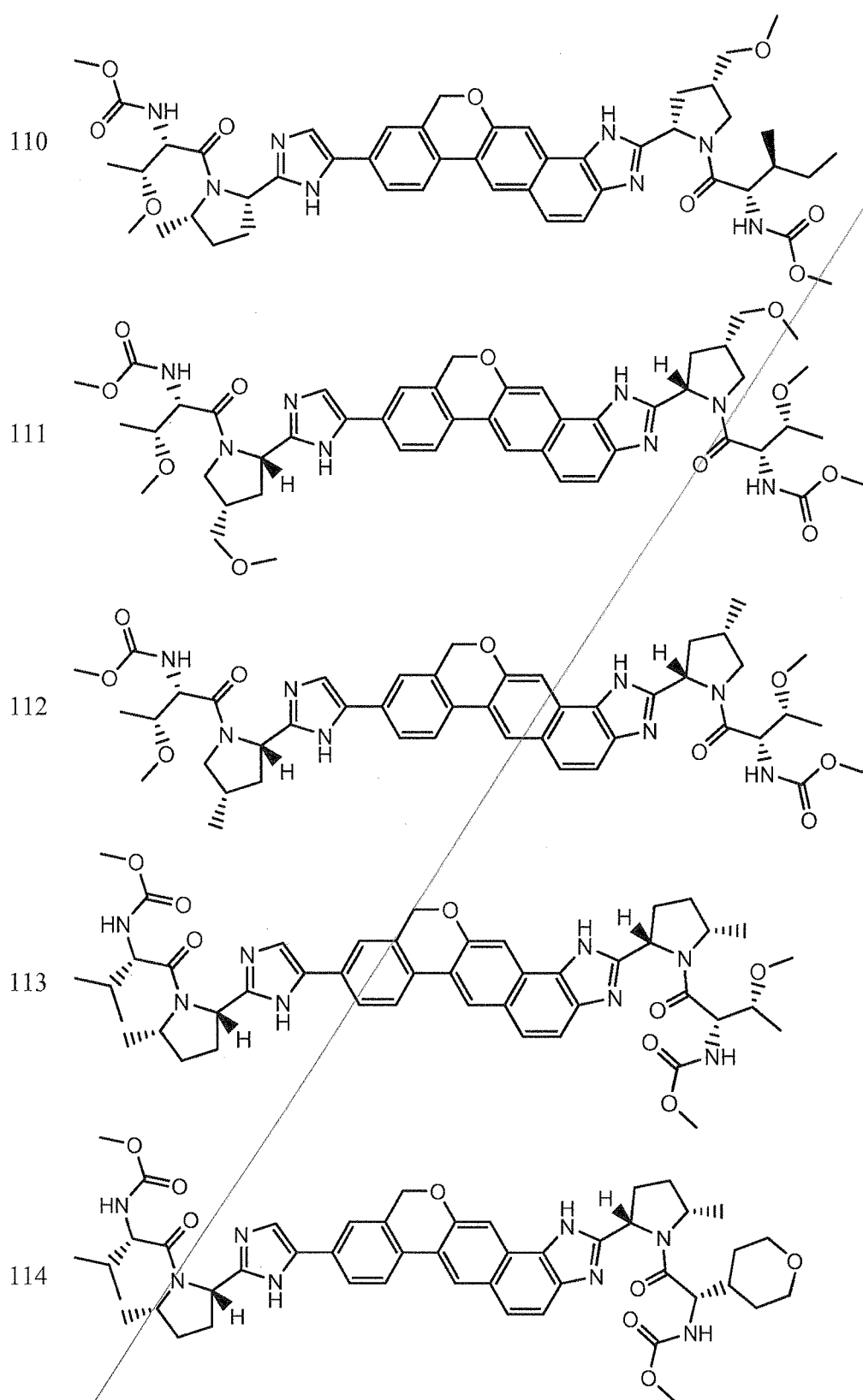


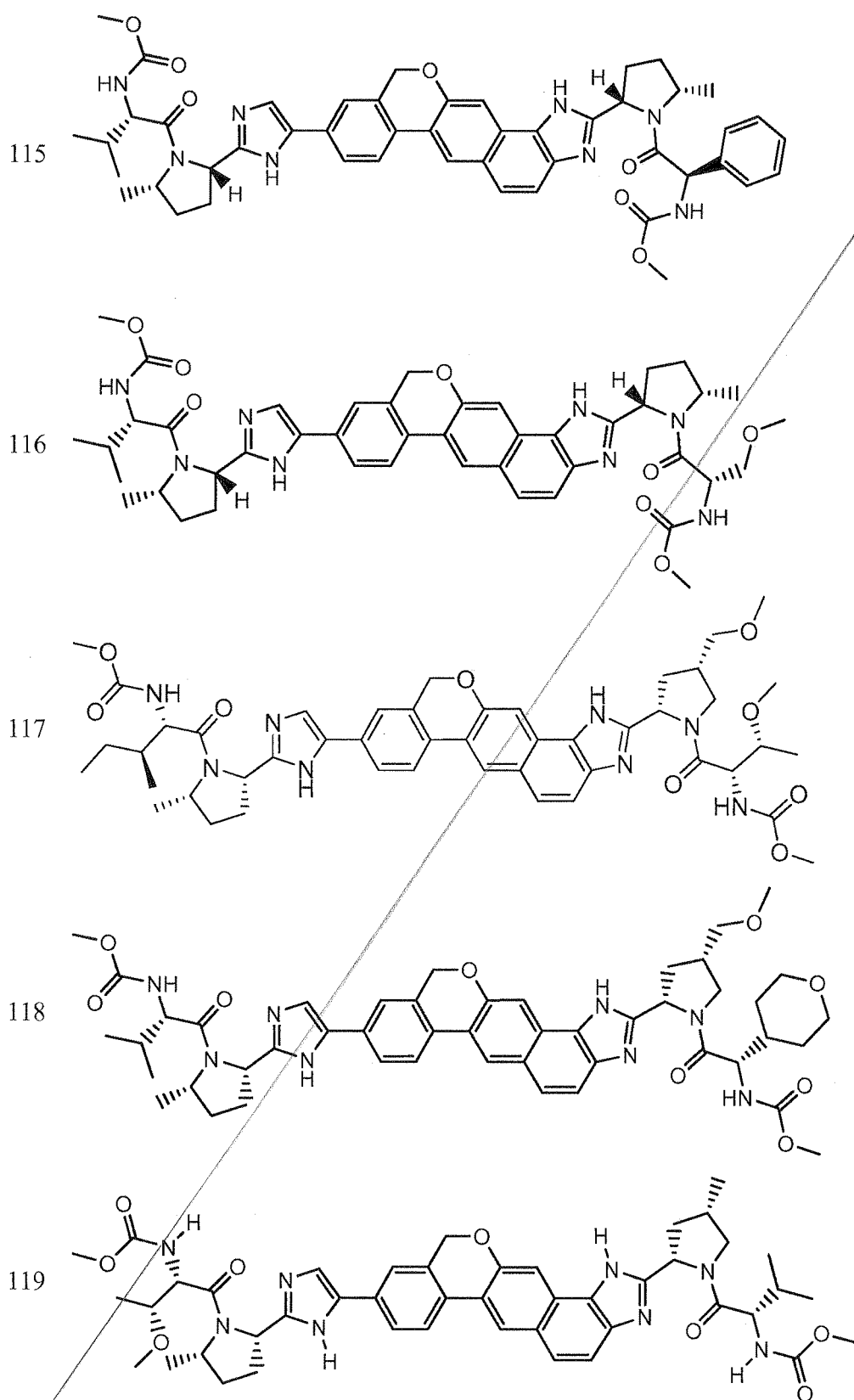
18. A compound selected from:



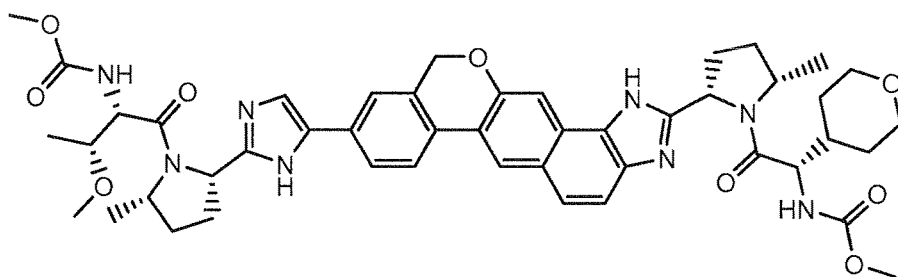




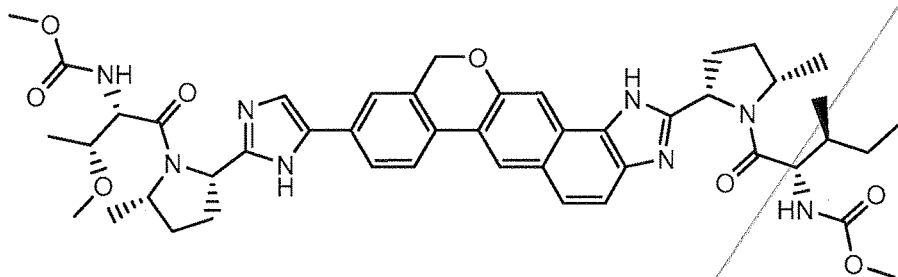




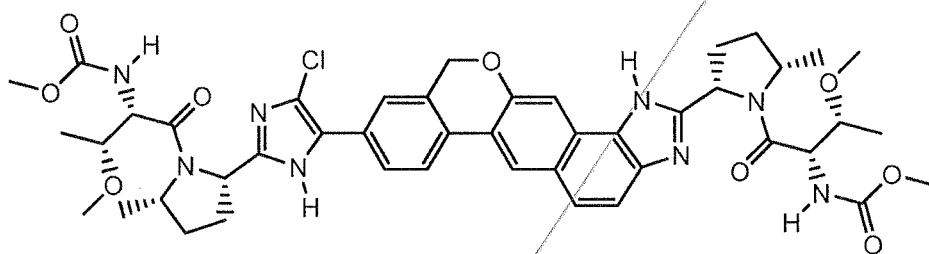
120



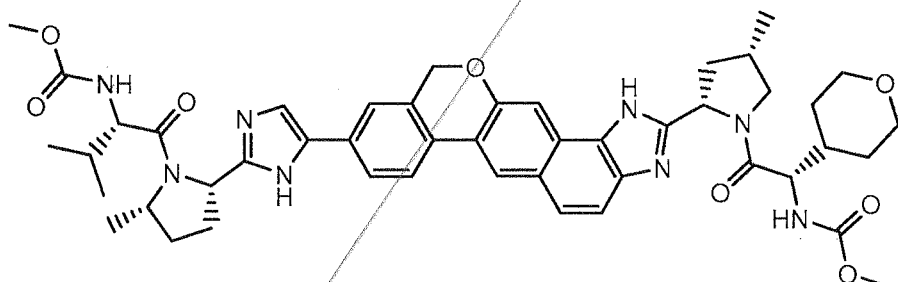
121



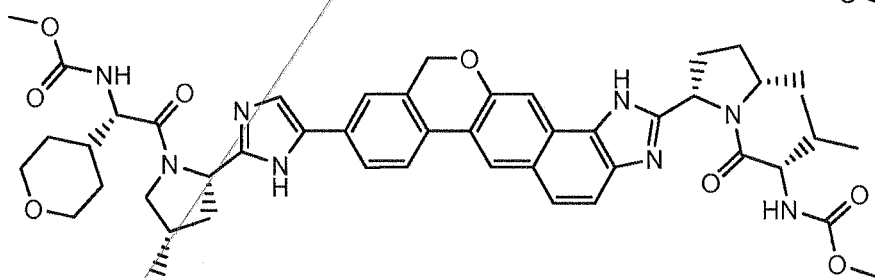
122



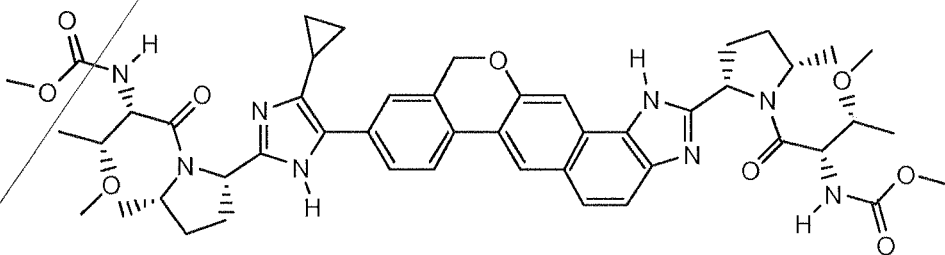
123



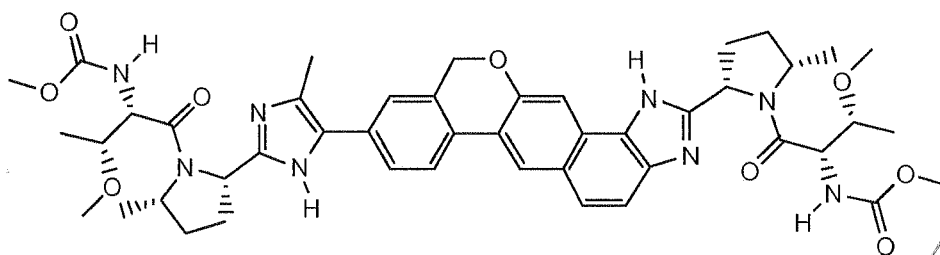
124



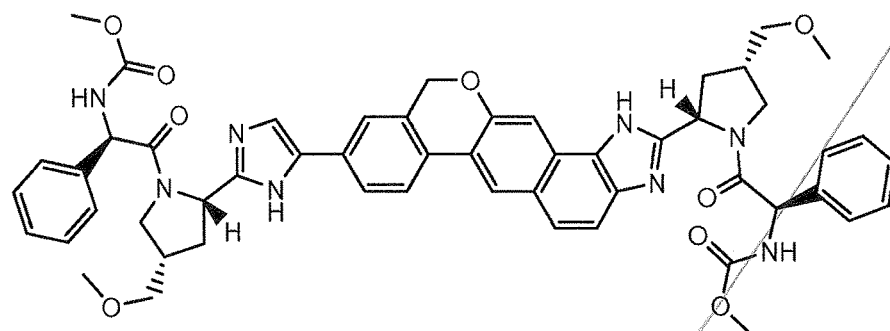
125



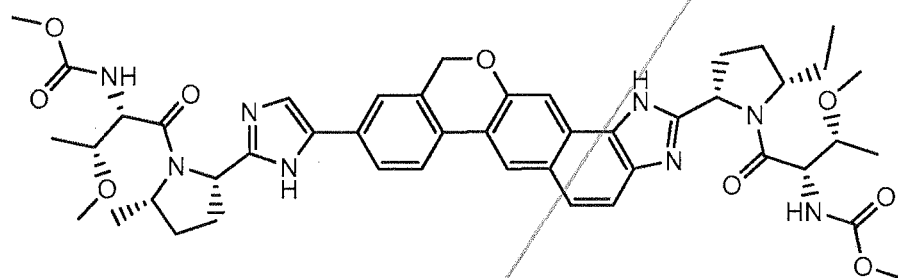
126



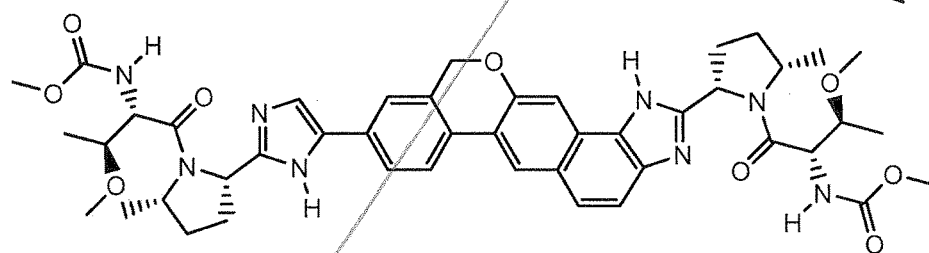
127



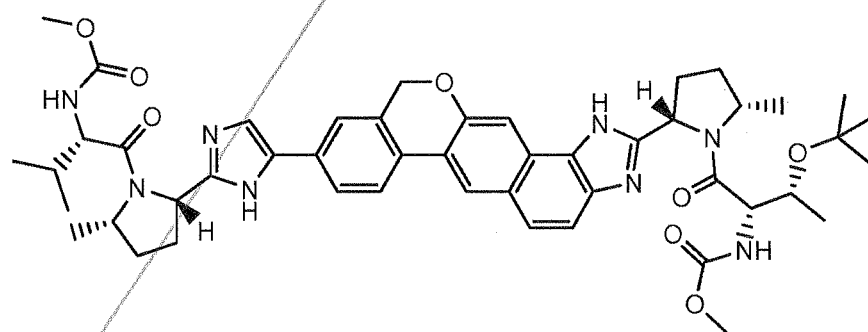
128

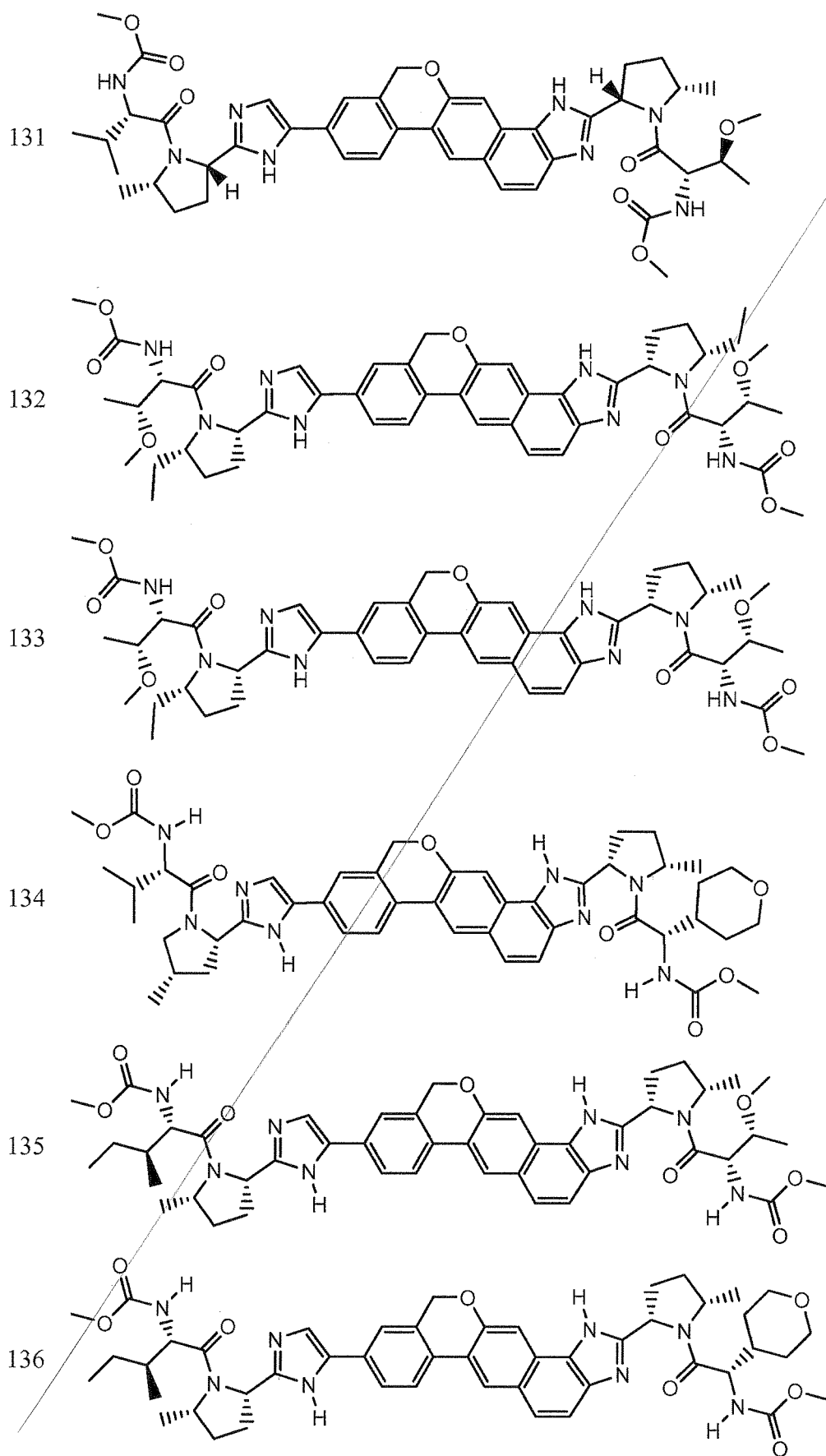


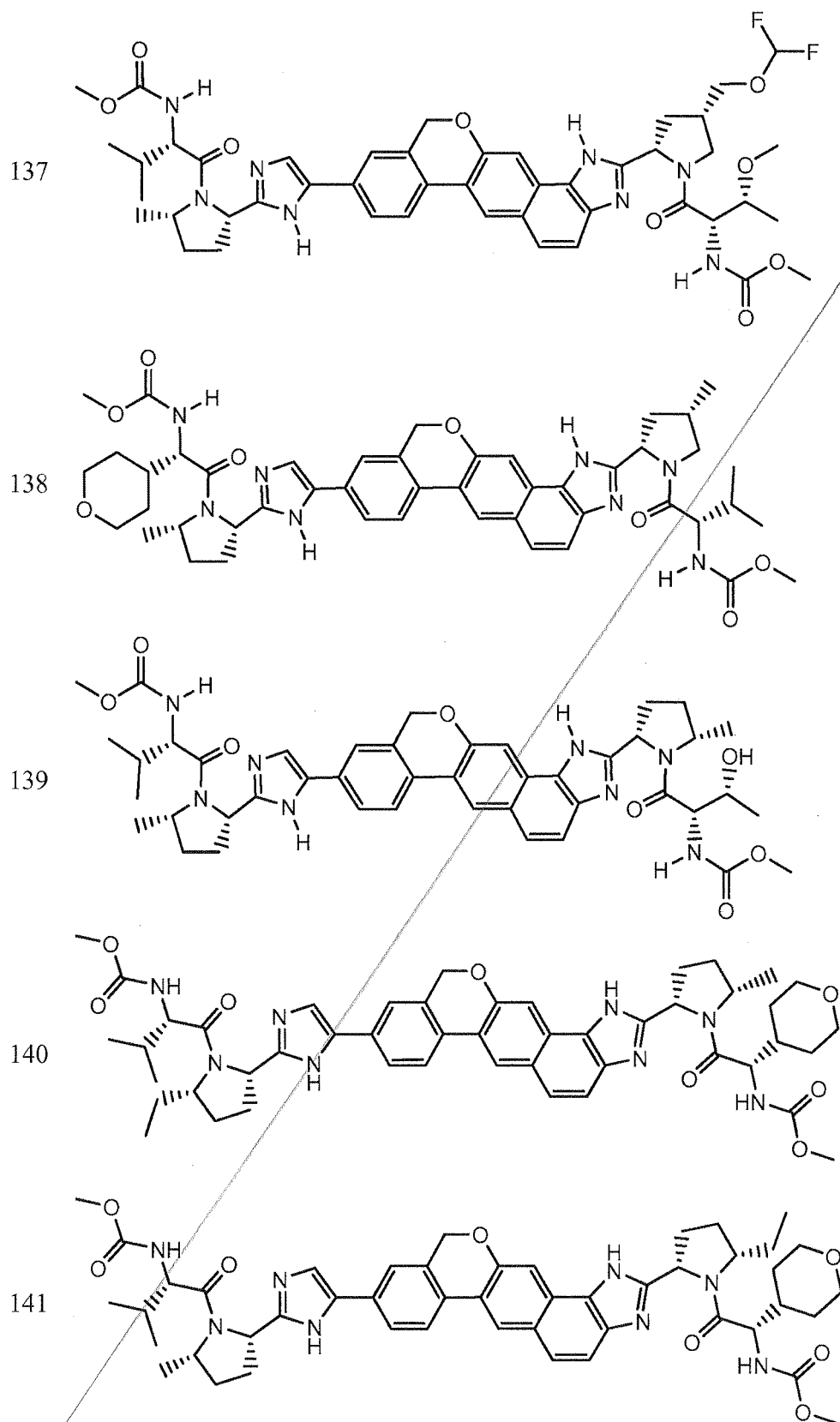
129

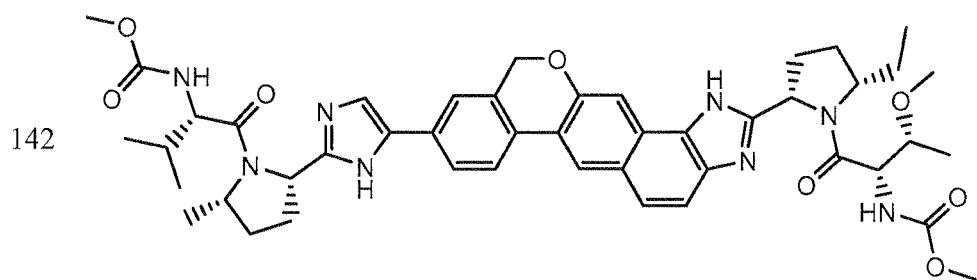
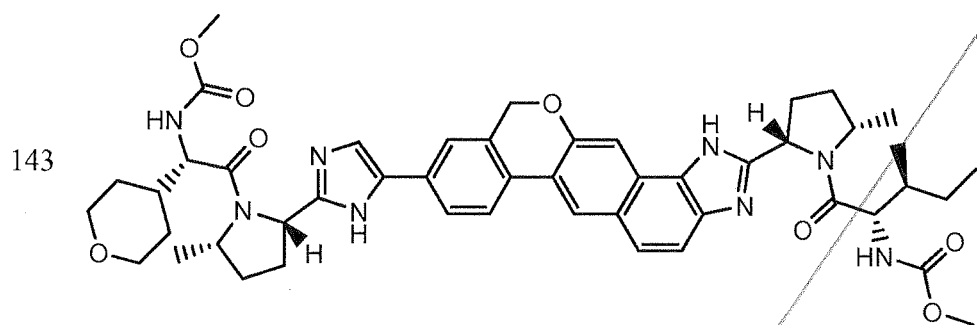
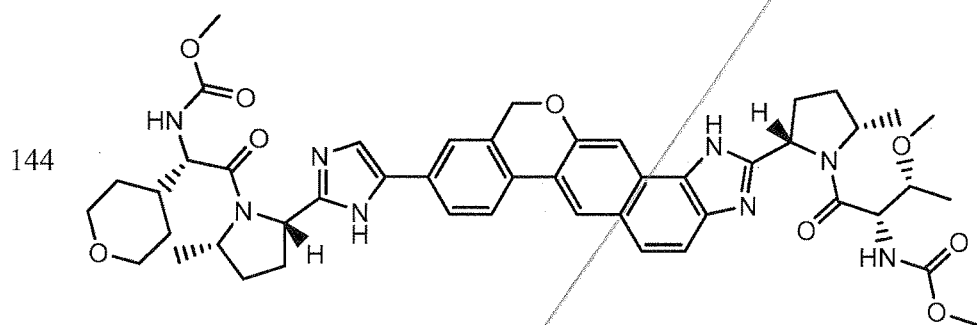
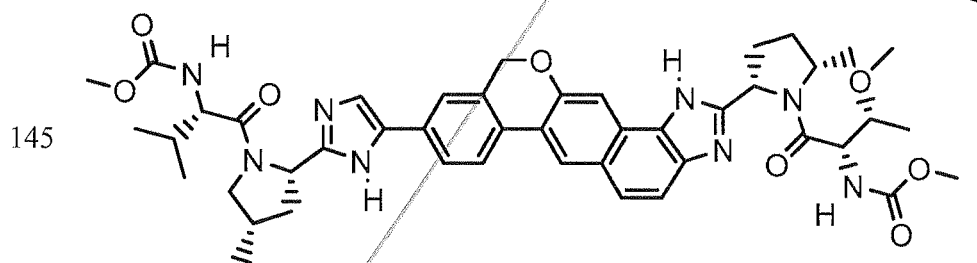
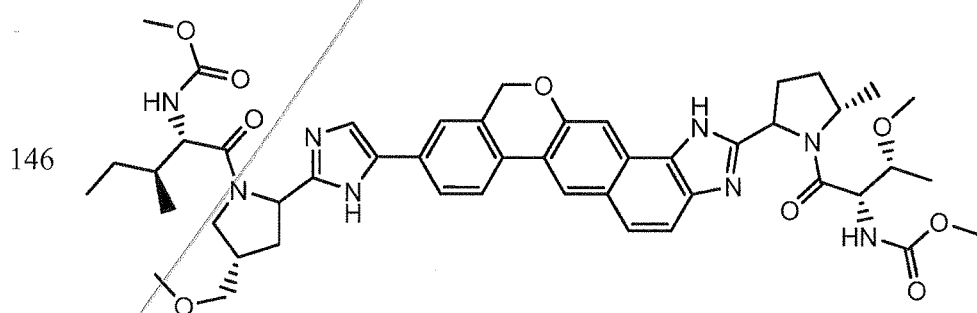


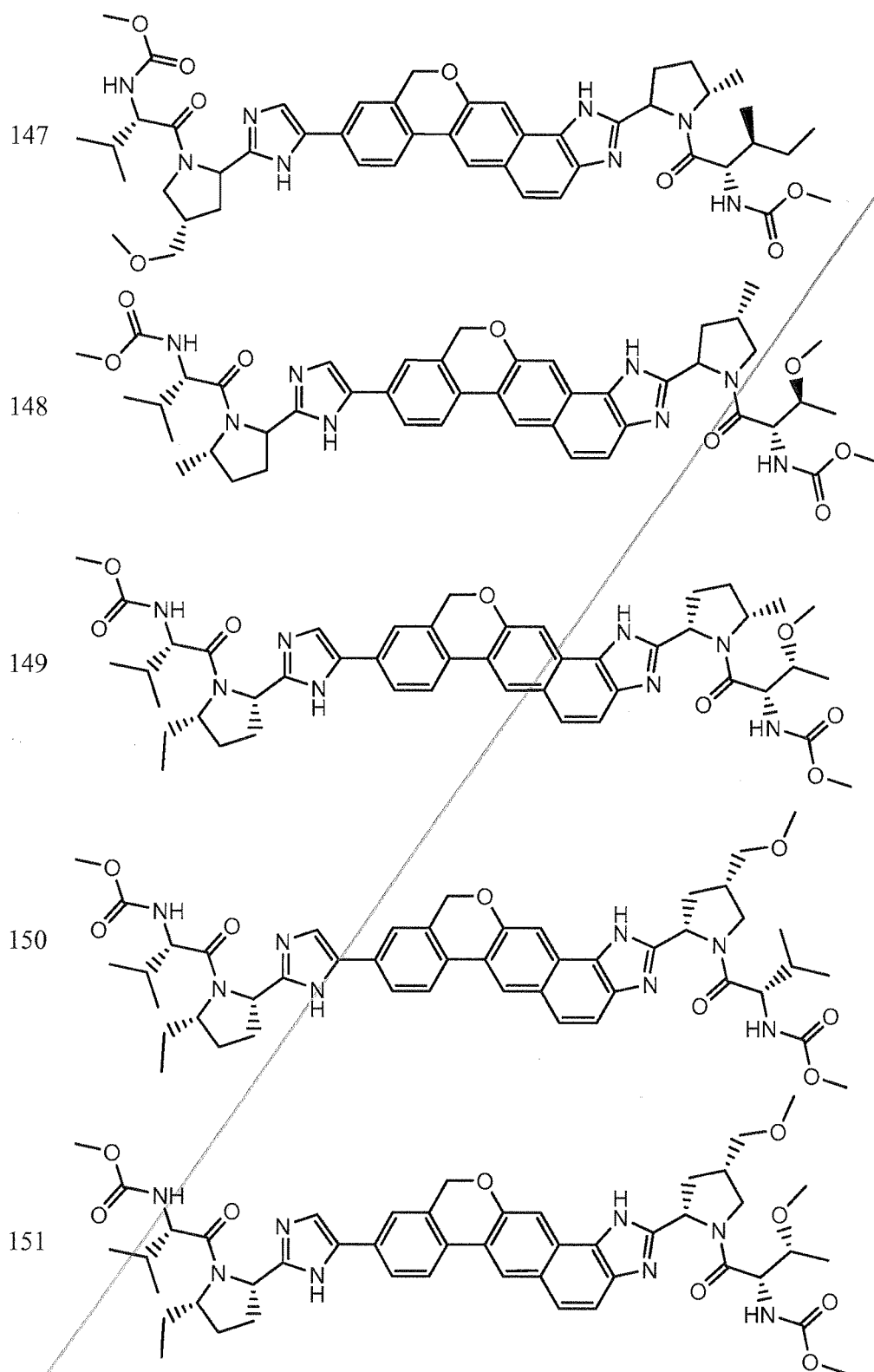
130

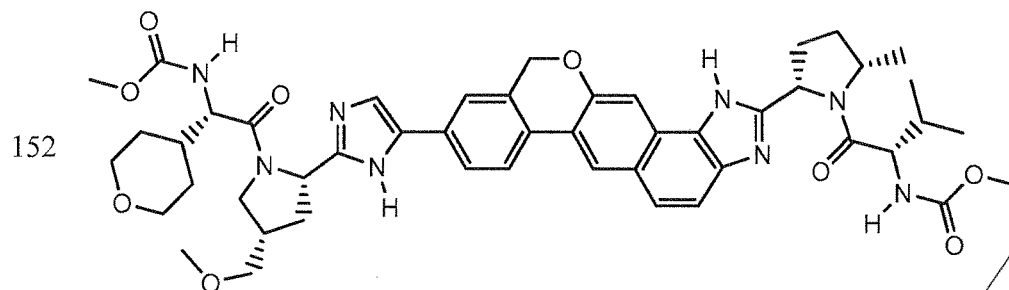
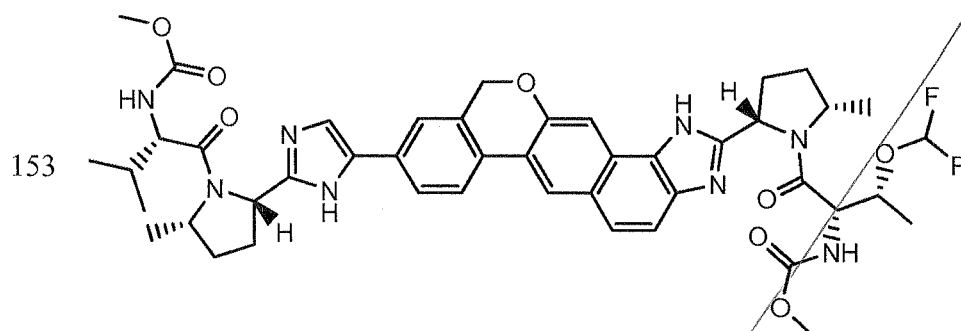
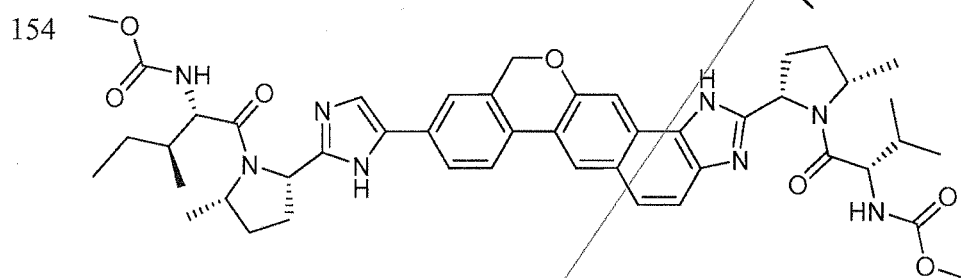
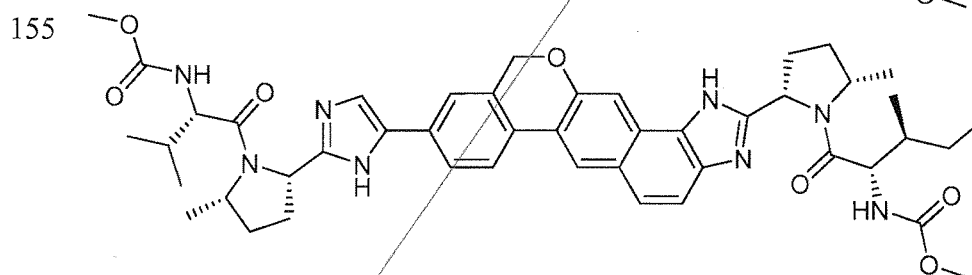
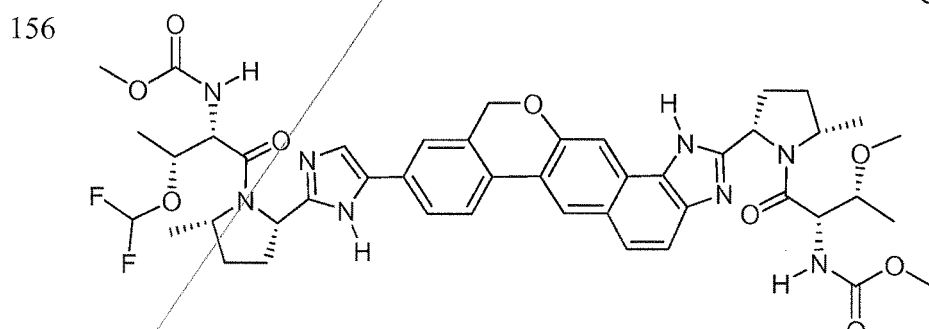
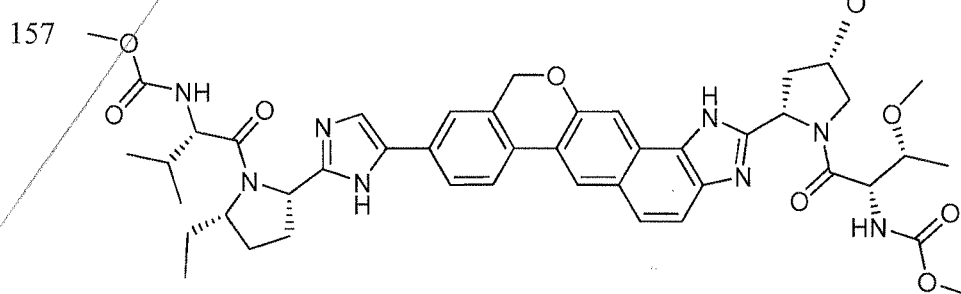


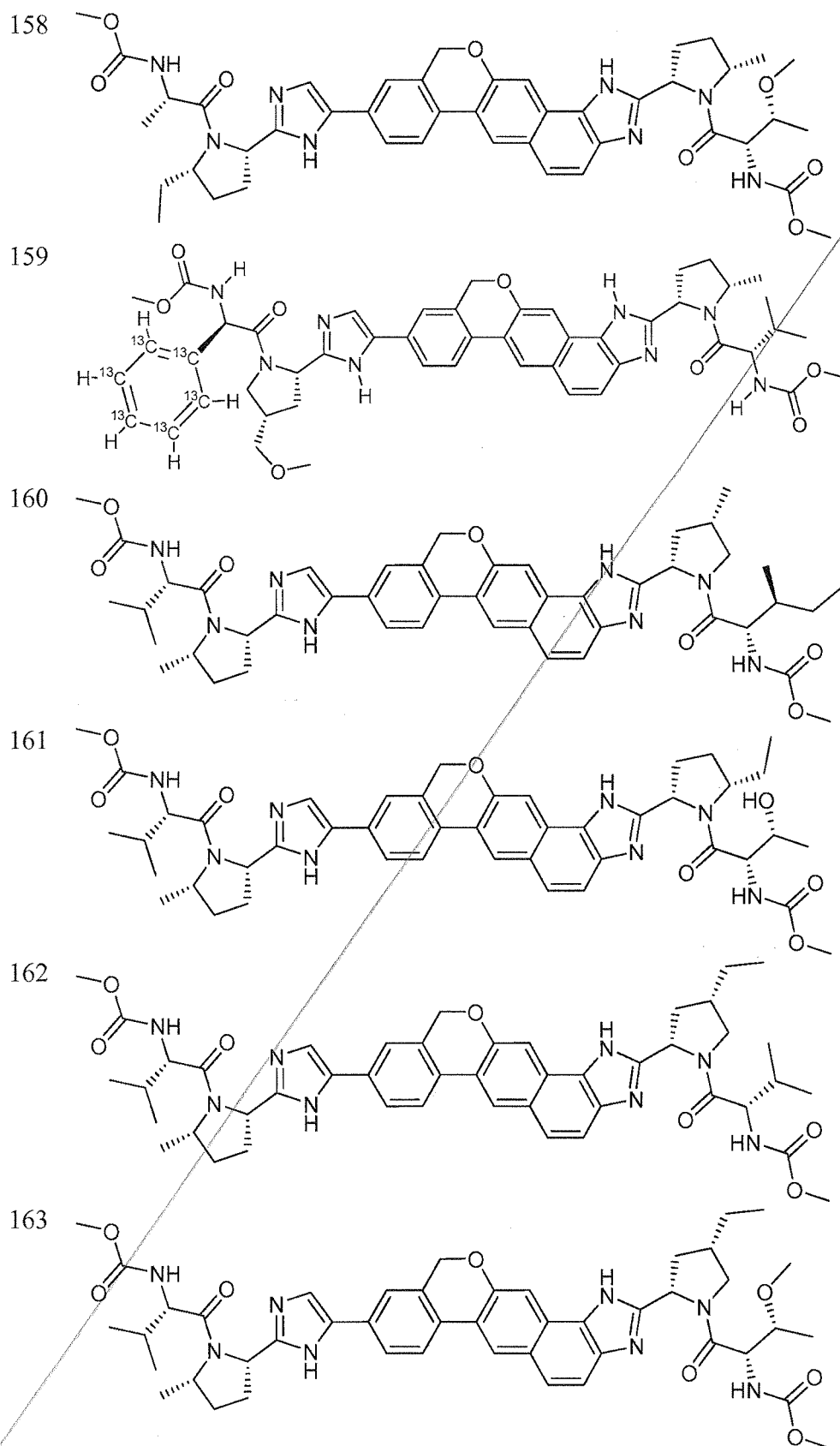


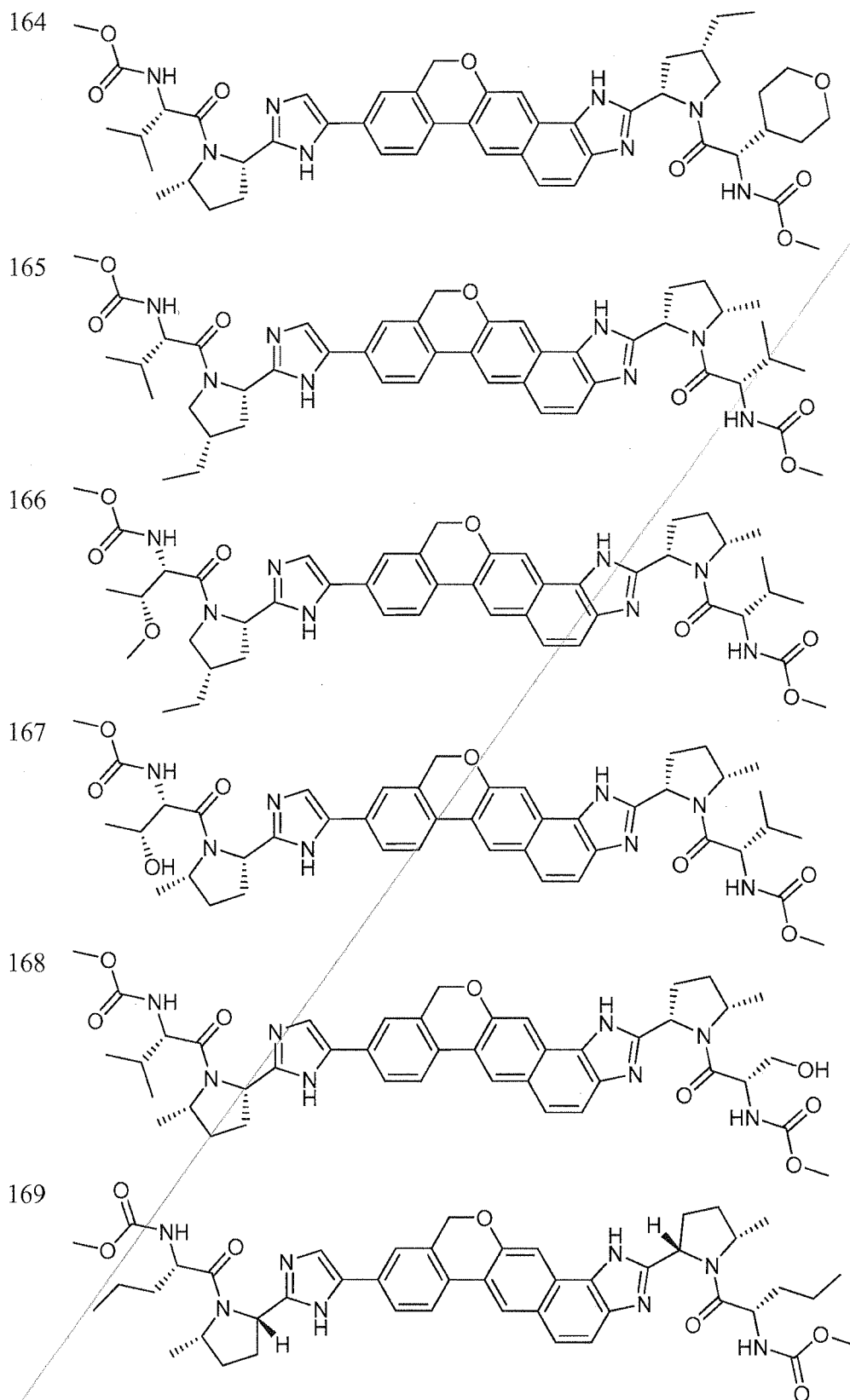




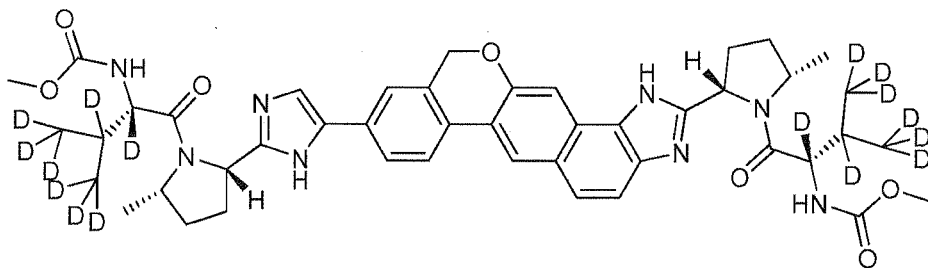




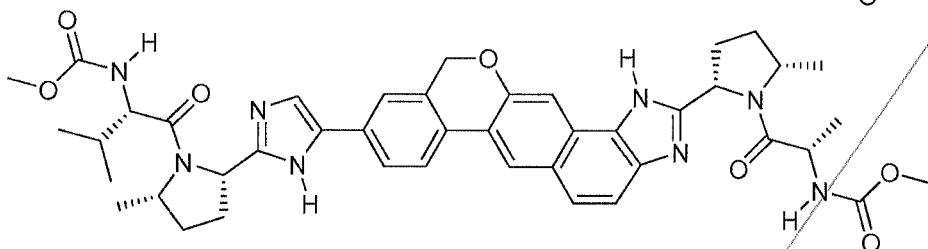




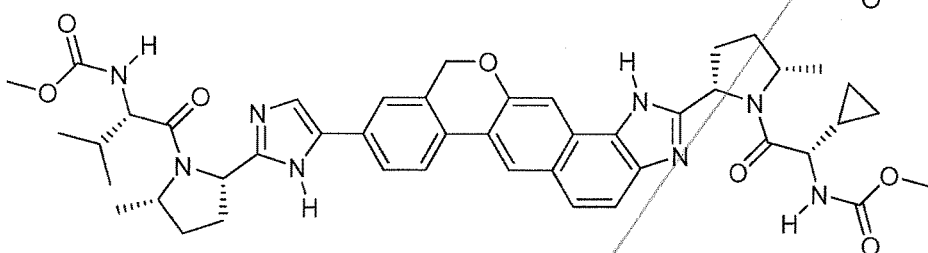
170



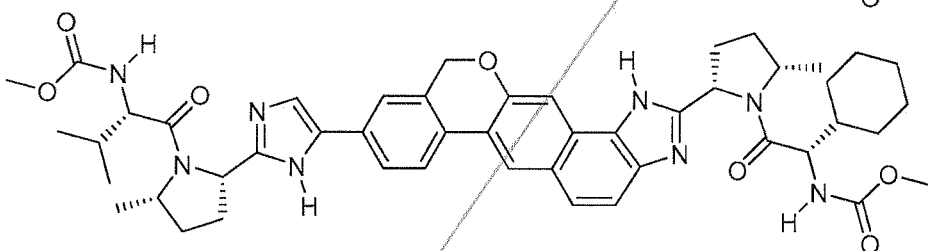
171



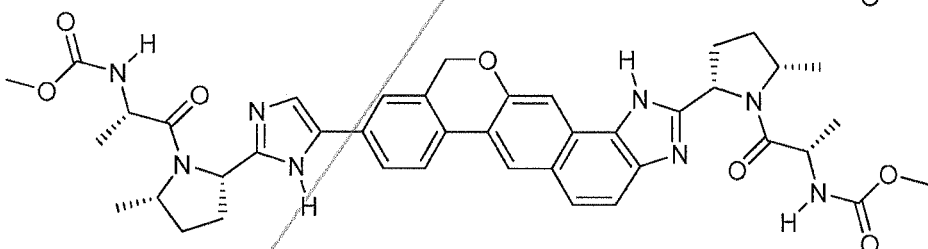
172



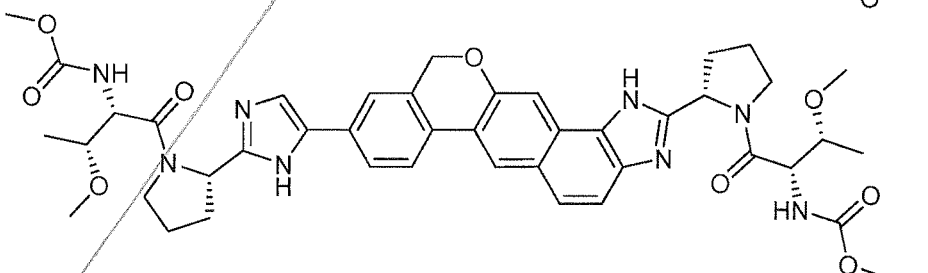
173



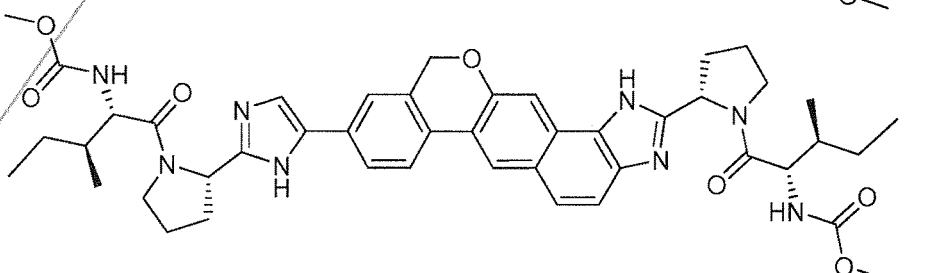
174

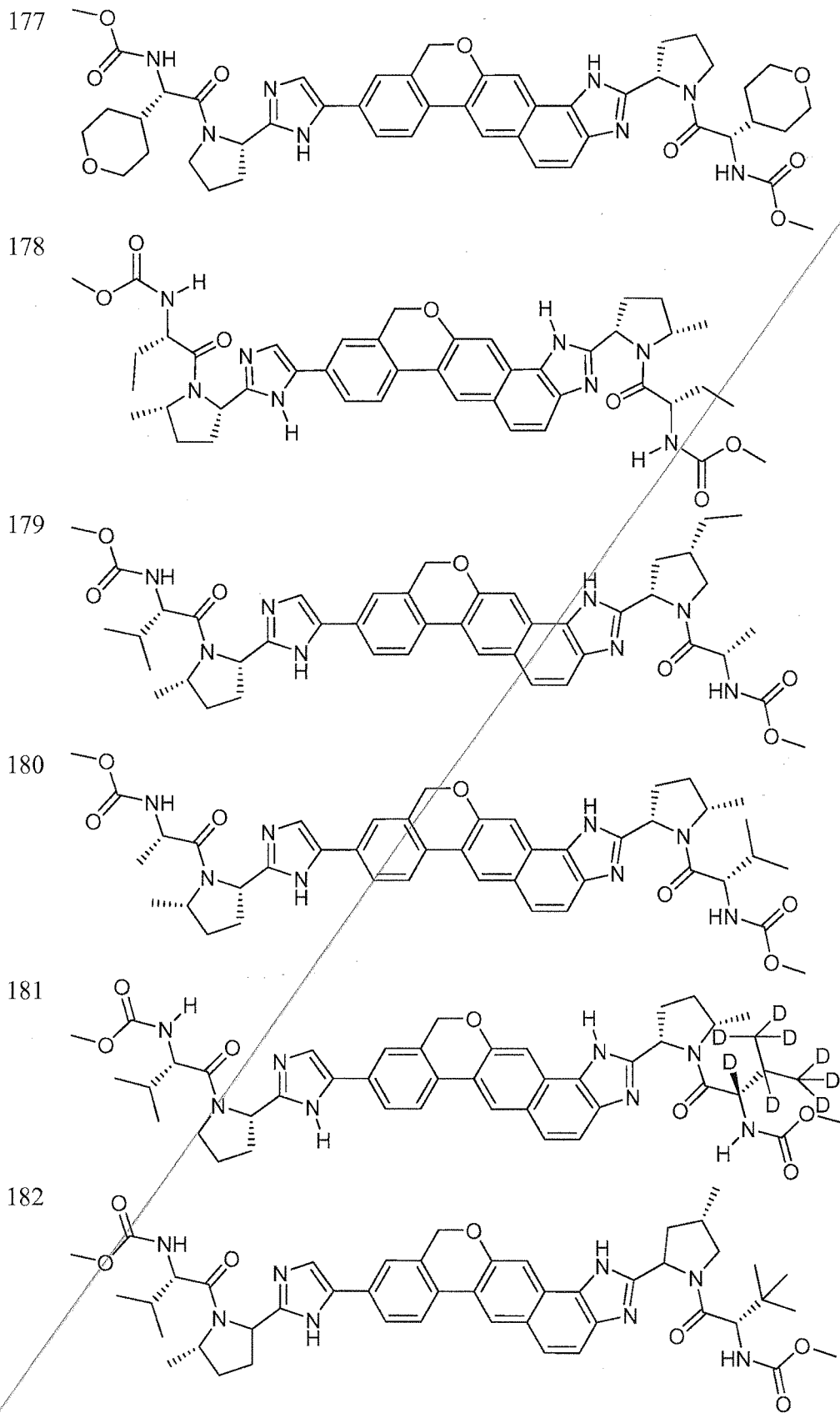


175

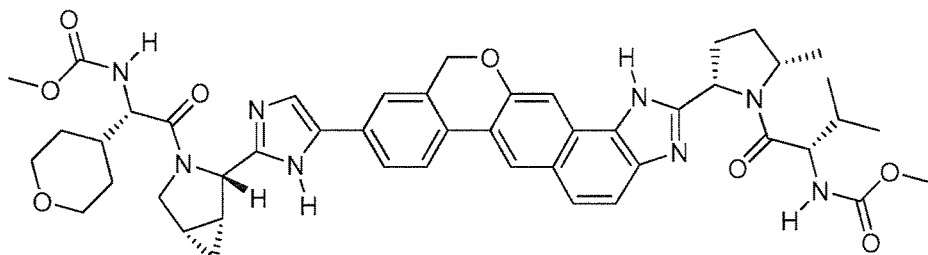


176

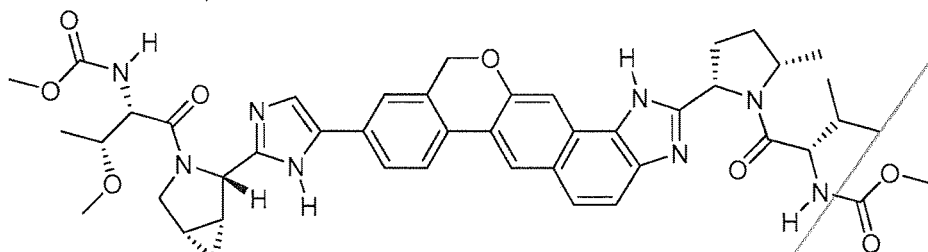




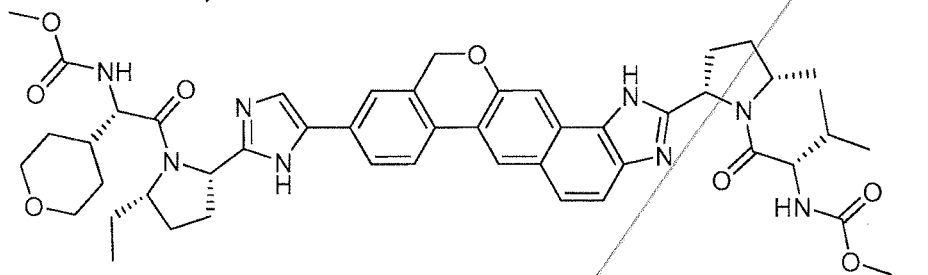
183



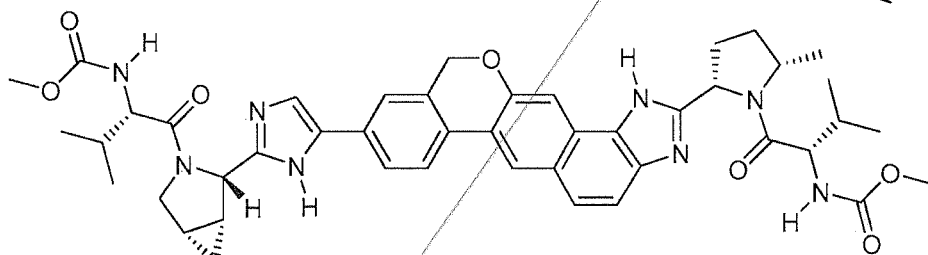
184



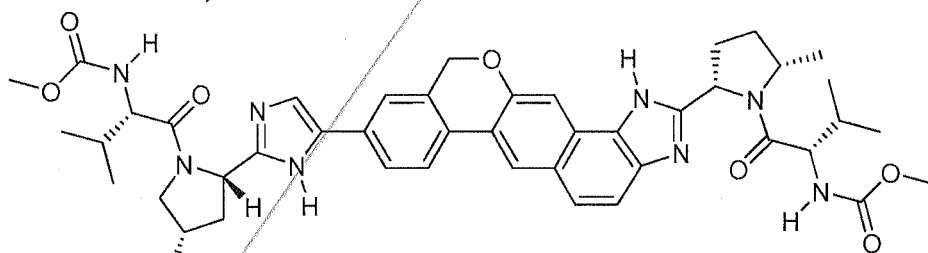
185



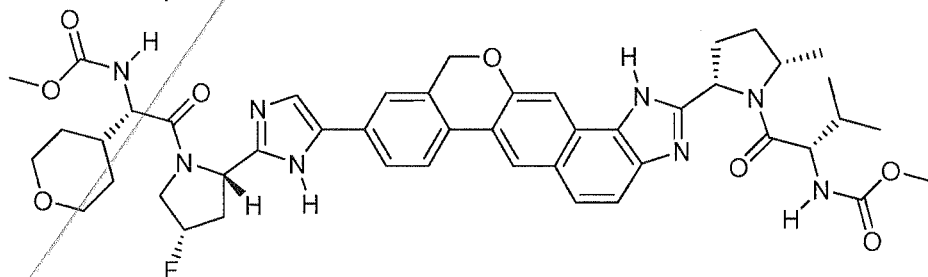
186

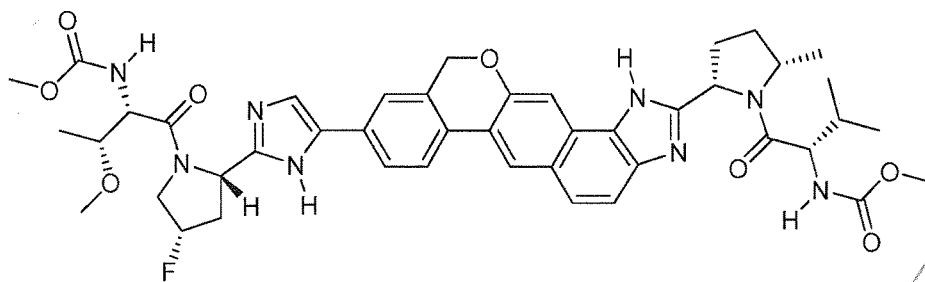
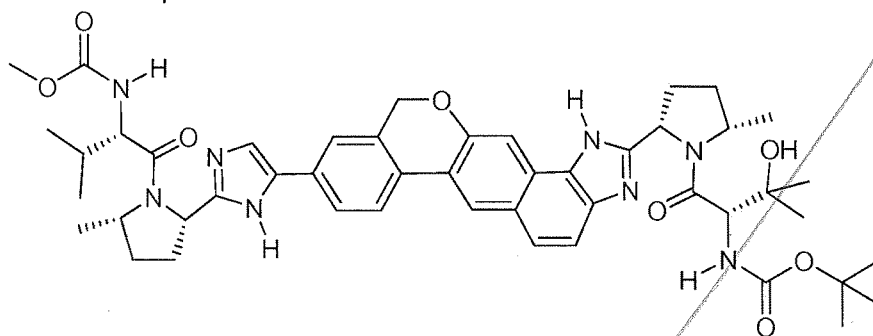
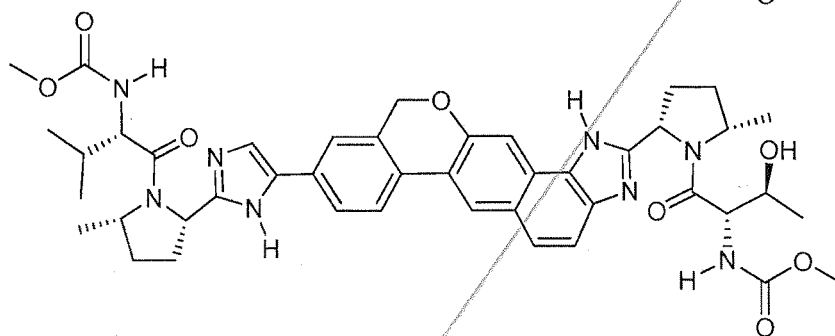
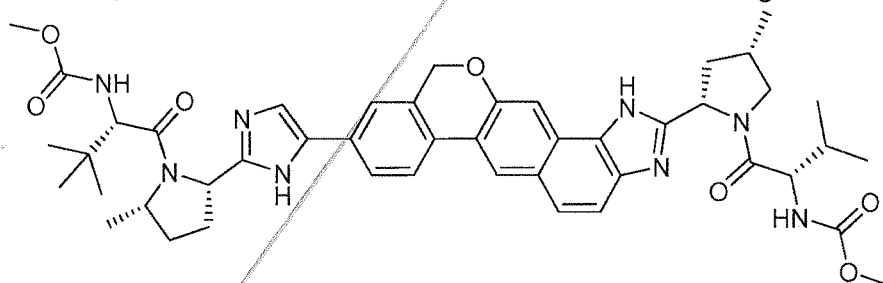
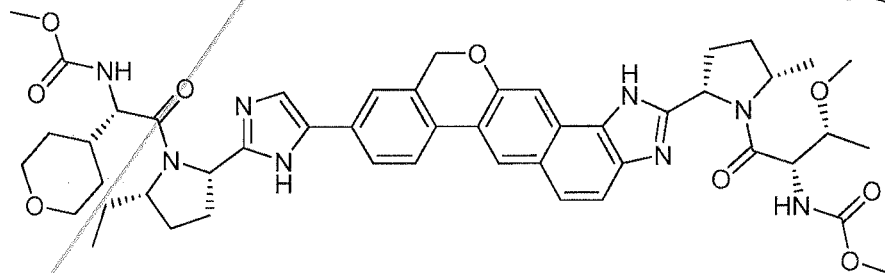
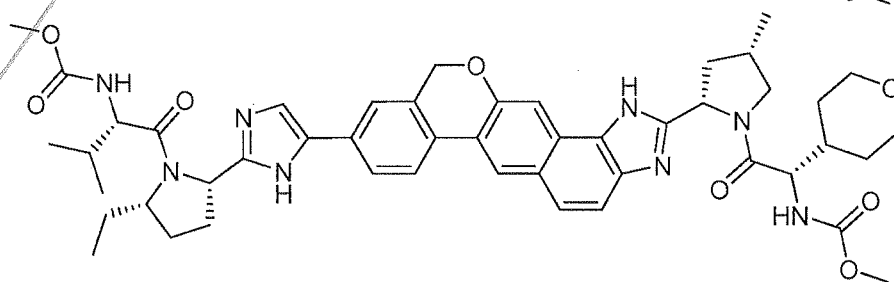


187

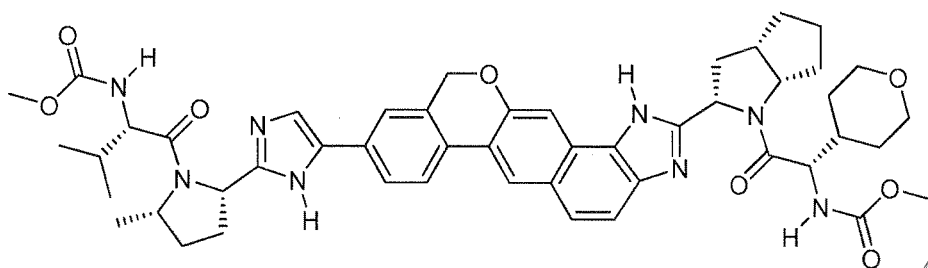


188

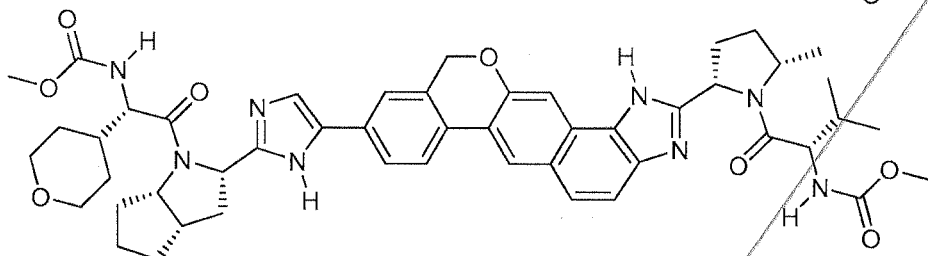




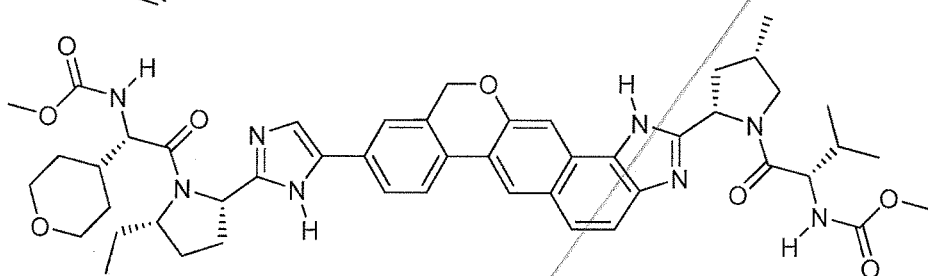
195



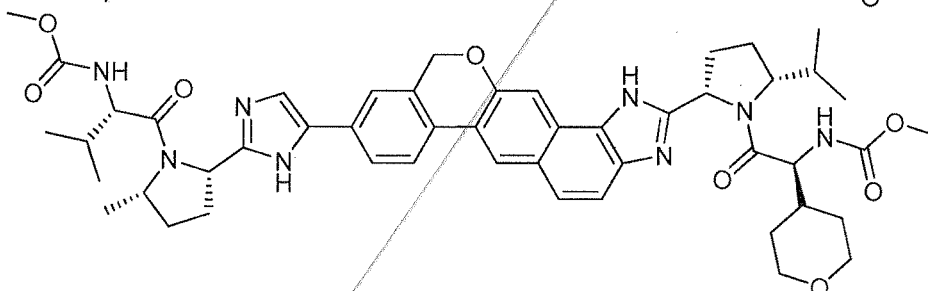
196



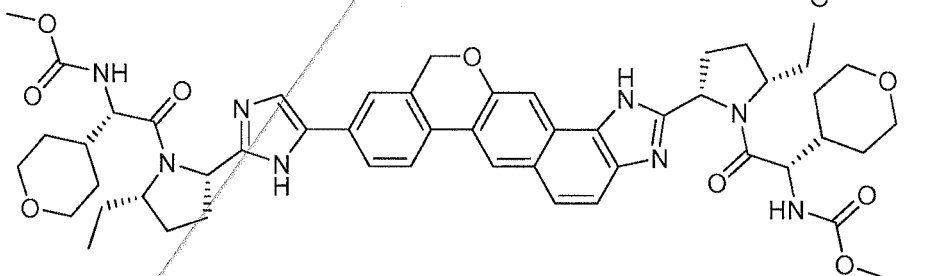
197



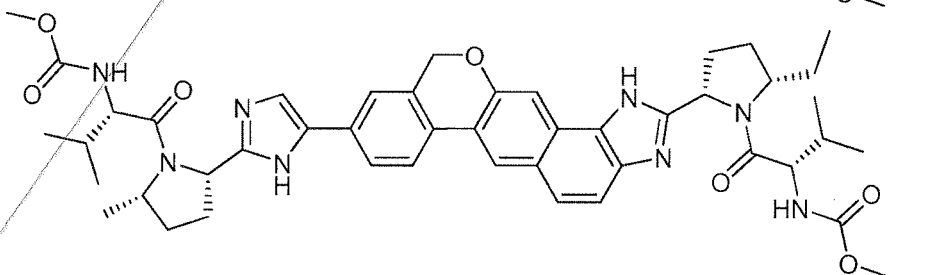
198

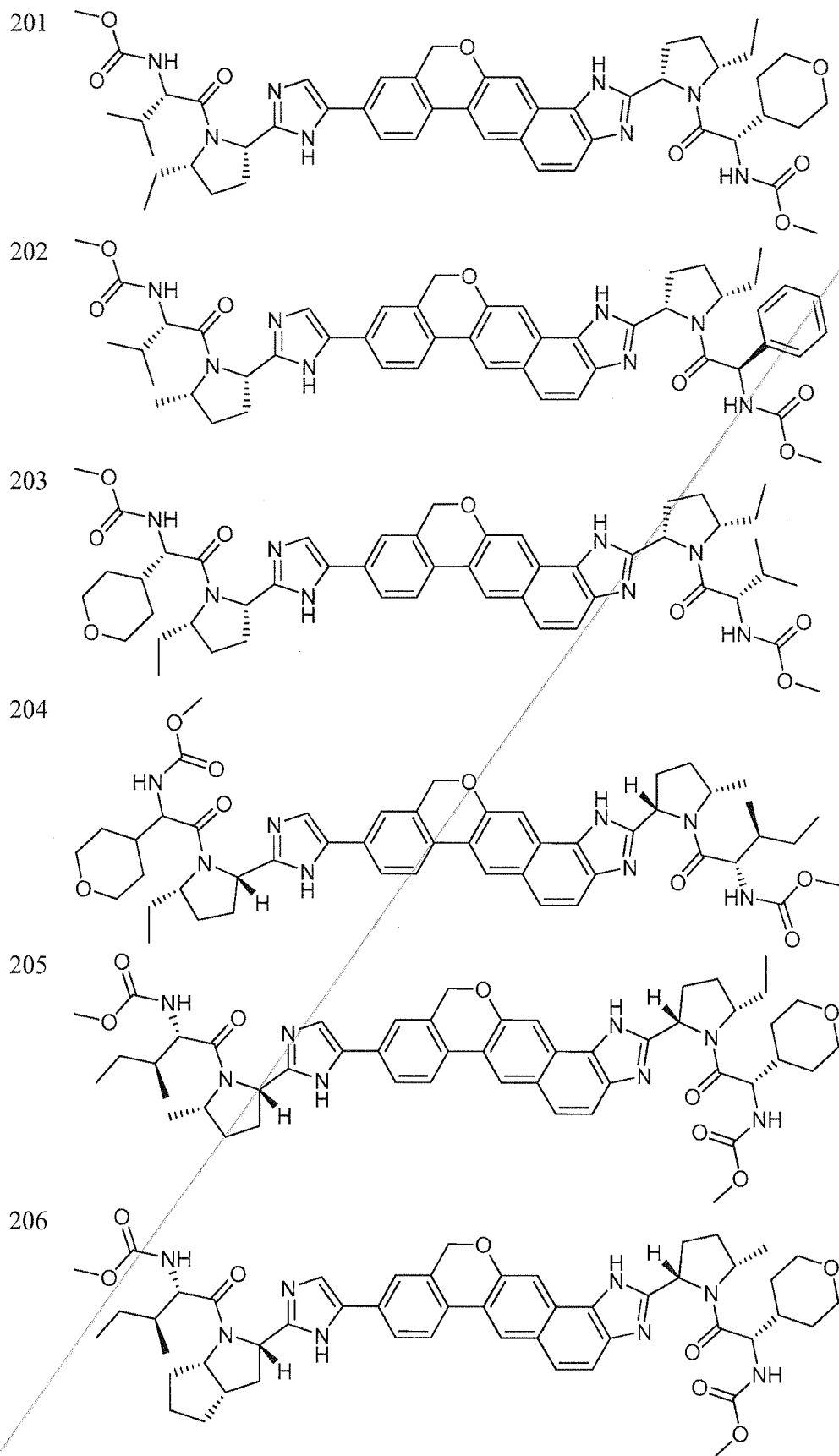


199

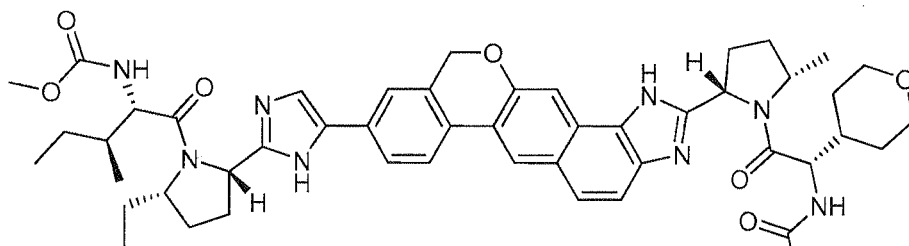


200

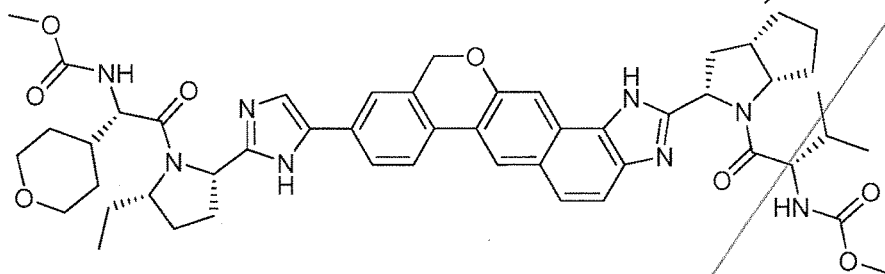




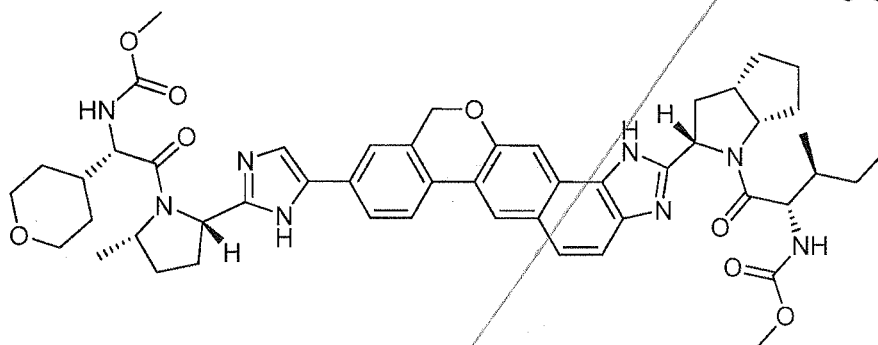
207



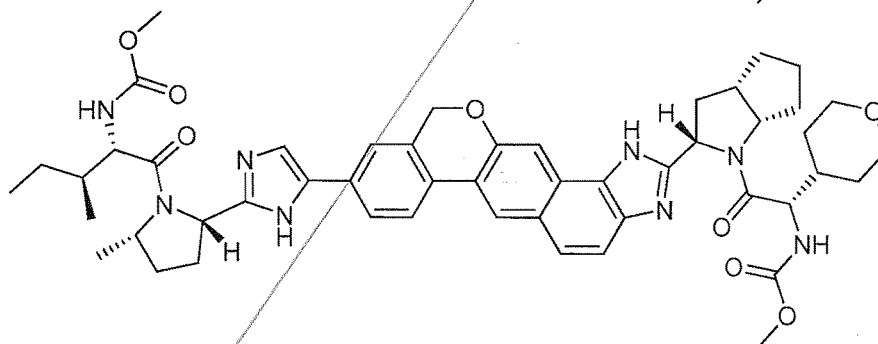
208



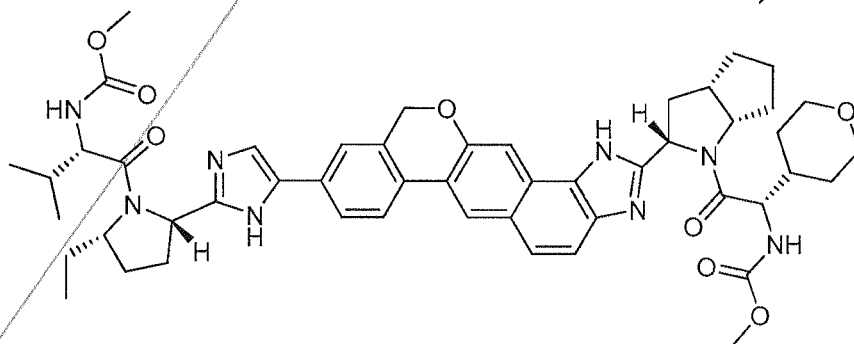
209

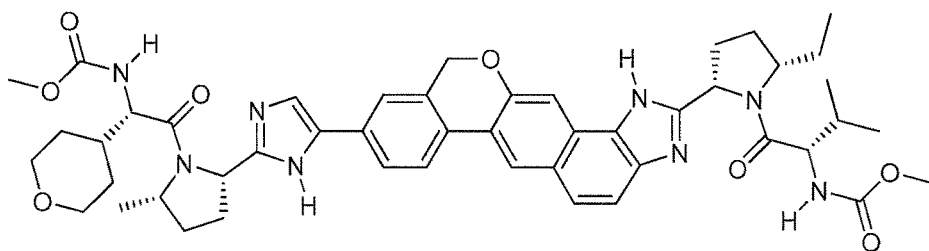
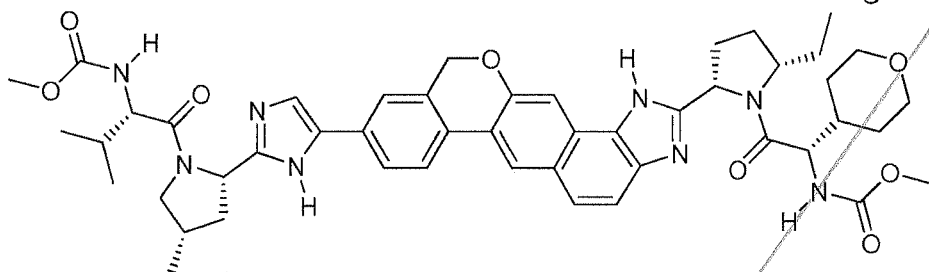
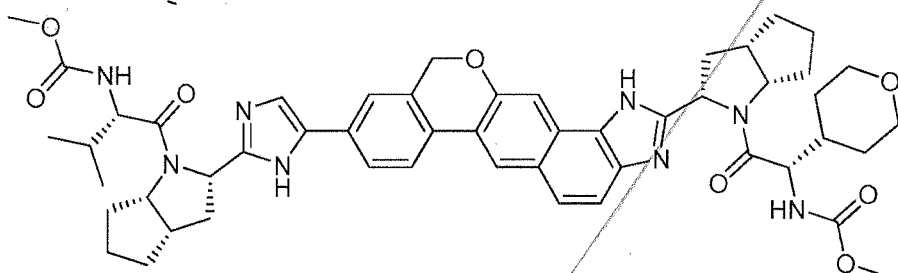
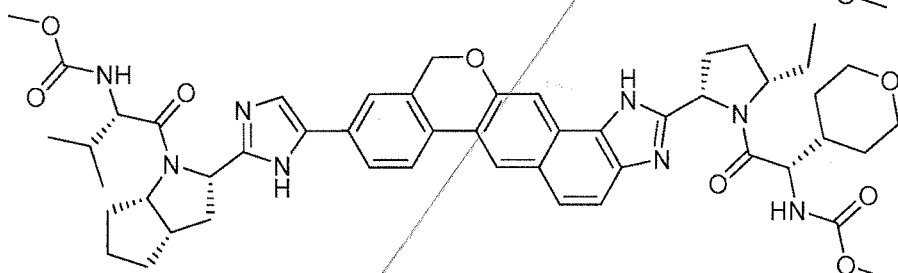
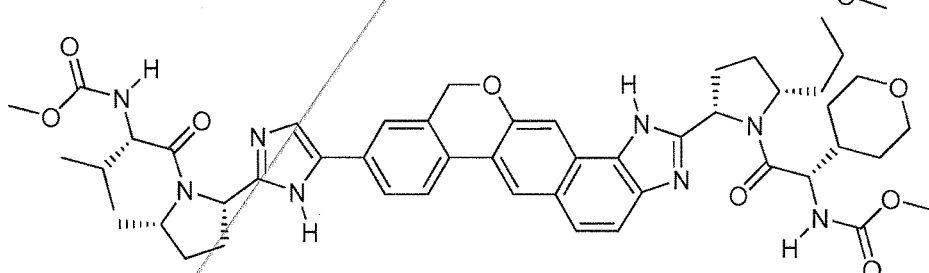
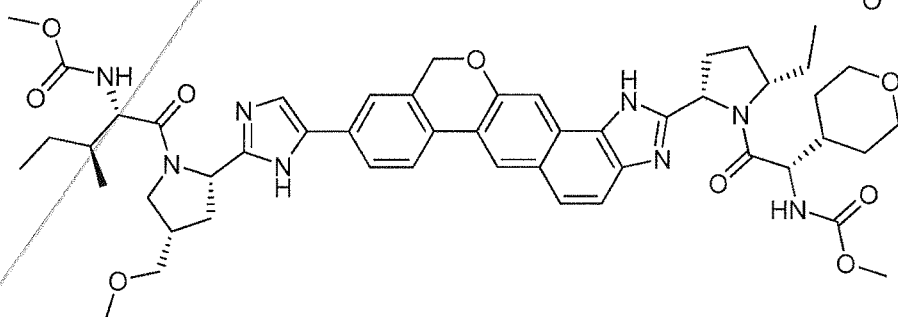


210

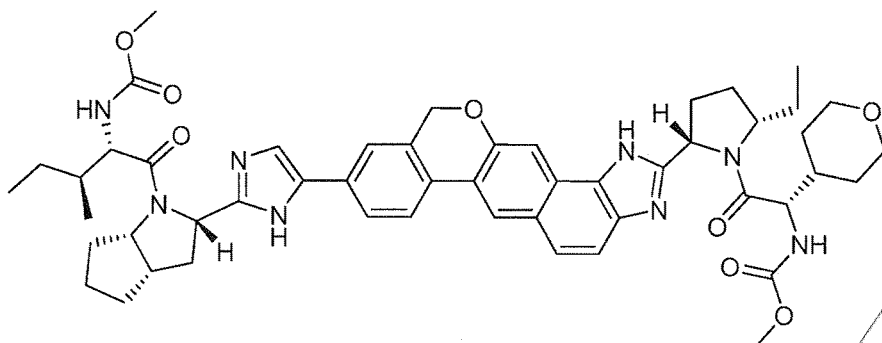


211

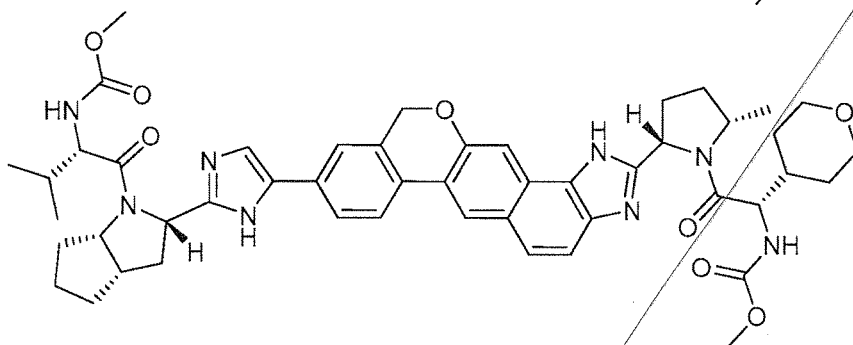




218

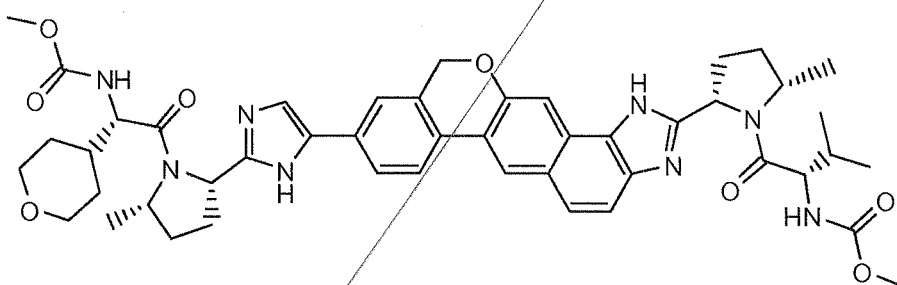


219



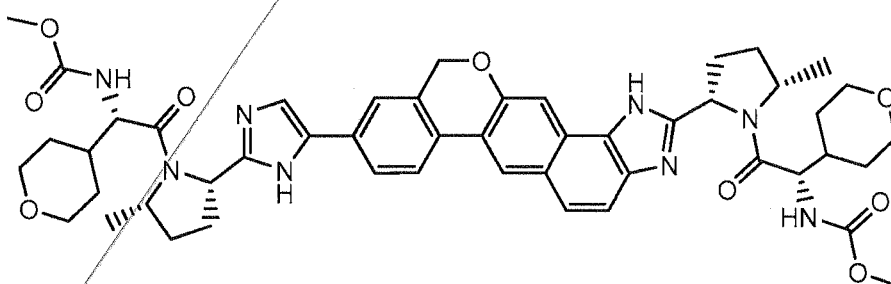
or a pharmaceutically acceptable salt or prodrug thereof.

19. A compound of formula:



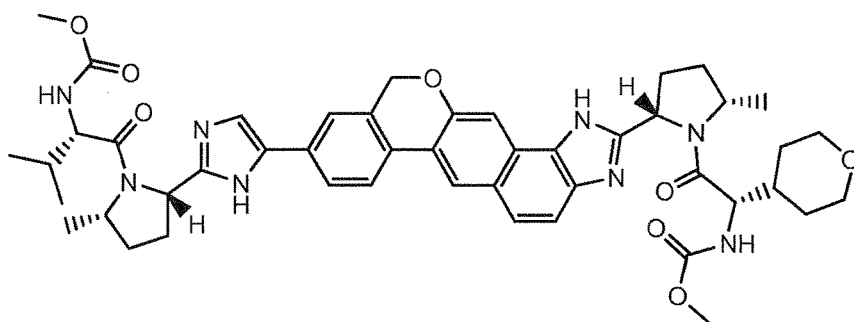
or a pharmaceutically acceptable salt or prodrug thereof.

20. A compound of formula:



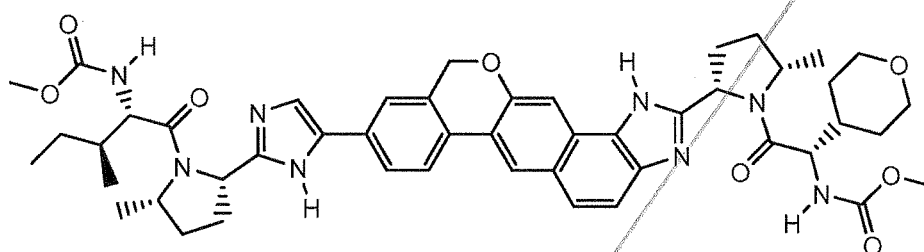
or a pharmaceutically acceptable salt or prodrug thereof.

21. A compound of formula:



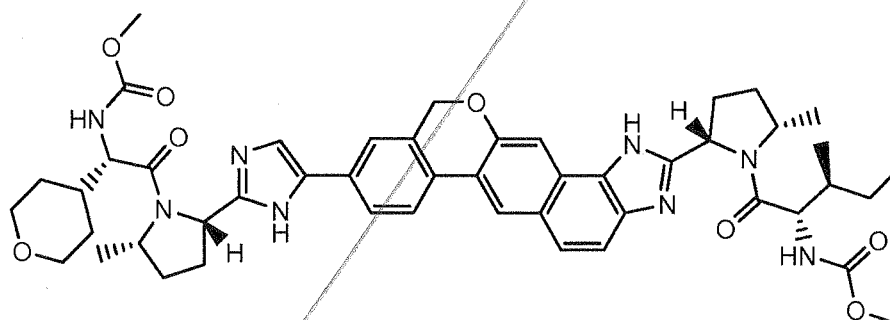
or a pharmaceutically acceptable salt or prodrug thereof.

22. A compound of formula:



or a pharmaceutically acceptable salt or prodrug thereof.

23. A compound of formula:



or a pharmaceutically acceptable salt or prodrug thereof.

24. A pharmaceutical composition comprising the compound of any one of claims 1-23 or a pharmaceutically acceptable salt or prodrug thereof, and at least one pharmaceutically acceptable carrier.

25. The pharmaceutical composition of claim 24, further comprising at least one additional therapeutic agent for treating HCV.

26. The pharmaceutical composition of claim 25, wherein said additional therapeutic agent is selected from ribavirin, an NS3 protease inhibitor, a nucleoside or nucleotide inhibitor of HCV NS5B polymerase, an alpha-glucosidase 1 inhibitor, a hepatoprotectant, a non-nucleoside inhibitor of HCV polymerase, or combinations thereof.

27. The pharmaceutical composition according to claim 24, further comprising a nucleoside or nucleotide inhibitor of HCV NS5B polymerase.
28. The pharmaceutical composition according to claim 27, wherein said nucleoside or nucleotide inhibitor of HCV NS5B polymerase is selected from ribavirin, viremagine, levovirin, a L-nucleoside, or isatoribine.
29. The pharmaceutical composition according to claim 27, further comprising an interferon or pegylated interferon.
30. The pharmaceutical composition of claim 27, wherein the nucleoside or nucleotide inhibitor of HCV NS5B polymerase is sofosbuvir.
31. A method of treating disorders associated with hepatitis C, said method comprising administering to an individual a pharmaceutical composition which comprises a therapeutically effective amount of the compound of any one of claims 1-23 or a pharmaceutically acceptable salt or prodrug thereof.
32. The method of claim 31, further comprising administering to the patient an interferon or pegylated interferon.
33. The method of claim 31, further comprising administering to the patient ribavirin.