[13] Nucleoside analogue compounds (NI), which bind at the enzyme active site and compete with natural nucleoside triphosphates, interfere with viral RNA synthesis. A number of these compounds have entered clinical trials. Nucleoside inhibitors include, for example, IDX184 (Idenix), RG7128 (RO5024048; Pharmasset/Roche), and most notably the recently-approved sofosbuvir (SOVALDI®, PSI-7977; Gilead/Pharmasset).

[14] Non-nucleoside inhibitors, by contrast, appear to bind at allosteric sites on NS5B—of which about 4 are well characterized. *Id.* NNI compounds include, for example, filibuvir (Pfizer), tegobuvir (GS 9190; Gilead), VX-222 (Vertex), A-837093 (Abbott), ABT-072 (Abbott), ABT-333 (Abbott), and PF-868554 (Pfizer).

[15] Also among the non-nucleoside inhibitors of NS5B are a series of thiophene-2-carboxylic acids and derivatives thereof. See, e.g., Chan et al., *Bioorg Med Chem Lett*, 2004, 14, 793-96; International patent publications WO 02/100846 A1, WO 02/100851 A2, WO 2004/052879 A2, WO 2004/052885 A1, WO 2006/072347 A2, WO 2006/119646 A1, WO 2008/017688 A1, WO 2008/043791 A2, WO 2008/058393 A1, WO 2008/059042 A1, WO 2008/125599 A1, and WO 2009/000818 A1. See also US Patents 6,881,741 B2, 7,402,608 B2, and 7,569,600 B2. See also, Yang et al., *Bioorg Med Chem Lett* 2010, 20, 4614-19, relating to some bioisosteres of such compounds. Other similar compounds are described, for example, in US Patents 6,887,877 B2 and 6,936,629 B2.

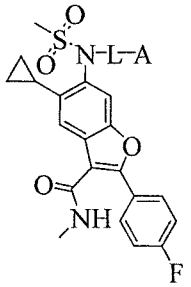
[16] Pyrophosphate compounds (PPi) mimic natural pyrophosphates released during nucleotidyl transfer reactions.

[17] Various NI and NNI compounds have shown safety or efficacy in clinical trials, but few have yet reached approval for use in treating humans. PPi compounds, by contrast, are generally in the investigational stage.

[18] There remains a profound need for more effective pharmaceutical therapies, including medicaments that are useful as single agents or in combination with other active agents, for the treatment of hepatitis C infection in humans.

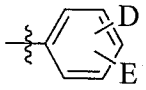
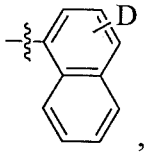
SUMMARY OF THE INVENTION

[19] In one aspect, there is provided a compound having the structure:

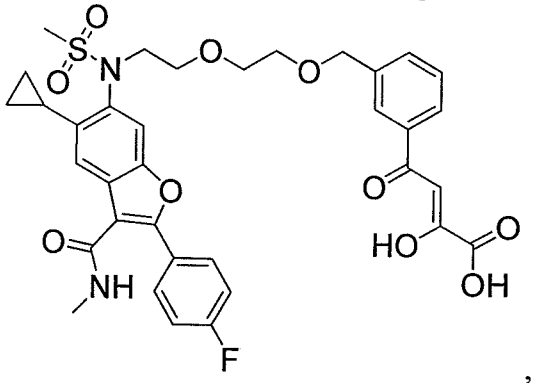


I

, or a pharmaceutically acceptable salt thereof, wherein: L is (a): $-(CH_2)_x-[O(CH_2)_w]_y-O-(CR^d_2)_z-$, in which each R^d is selected from hydrogen, methyl, and phenyl, or both R^d together with the carbon to which they are attached form C_{3-5}cycloalkyl;

w is 2 to 4; x is 2 to 6; and y and z are each independently 0 to 5, with the proviso that when y is 0, then (x+z) is 4 to 11; and A is selected from CO_2H, –CONHOH, $–CO_2–C_{1-4}$alkyl, $–C(O)NH_2$, chloropyridinyl, $–OC_{1-2}$alkylene$–CO_2H$, $–OC_{1-2}$alkylene$–CO_2C_{1-4}$alkyl, $–SC(O)CH_3$,  and , in which D is $–(C_{0-3}$alkylene$)–CO_2H$, $–(C_{0-3}$alkylene$)–CO_2C_{1-5}$alkyl, $–(C_{0-3}$alkylene$)–$CONHOH, $–C(O)CH=C(OH)CO_2H$, $–C(O)CH=C(OH)CO_2C_{1-4}$alkyl, $–CO_2CH_2C(O)NH_2$, $–CO_2CH_2SC_{1-4}$alkyl, $–CO_2Bn$, or $–CO_2CH_2CO_2C_{1-4}$alkyl, and E is null, halo, C_{1-4}alkyl, $–OC_{1-4}$alkyl , $–NH–C_{1-4}$alkyl , $–C_{0-3}$alkylene$–NH_2$, or NO_2.

In another aspect, there is provided a compound, or pharmaceutically acceptable salt thereof, selected from:



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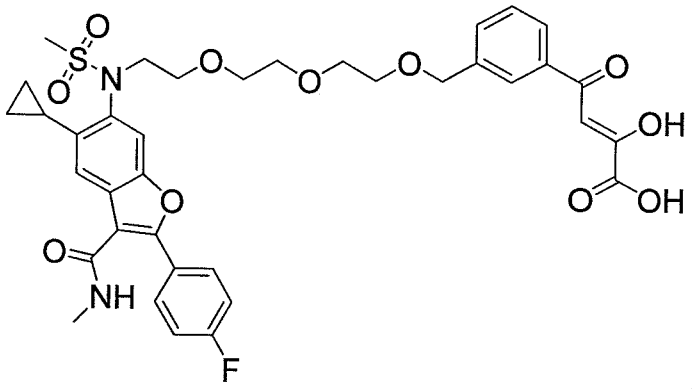

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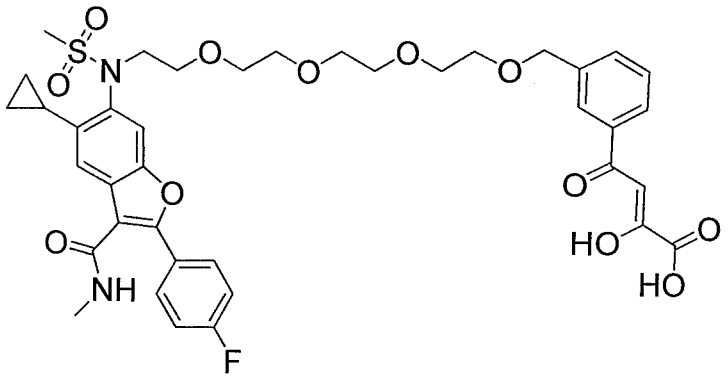

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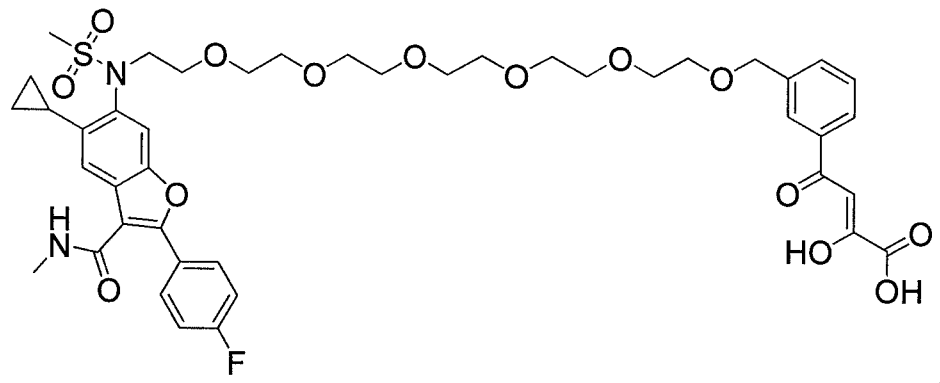

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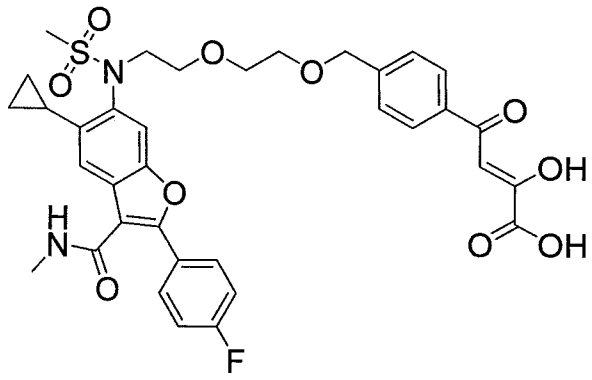

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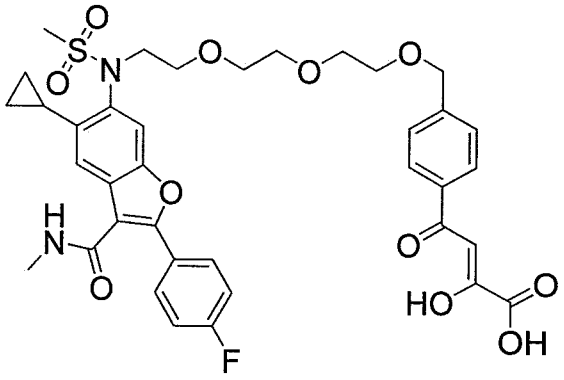

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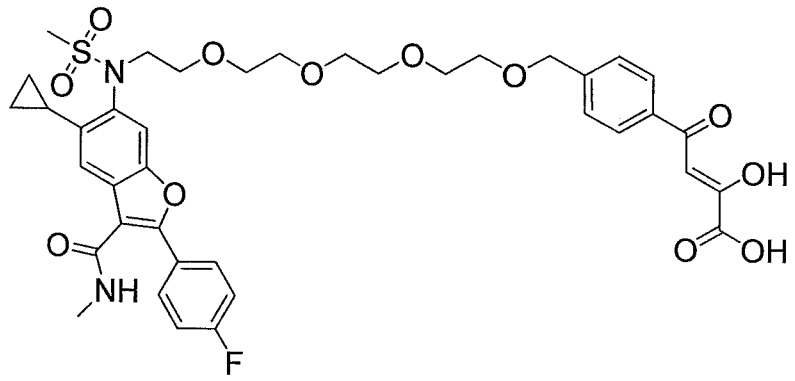

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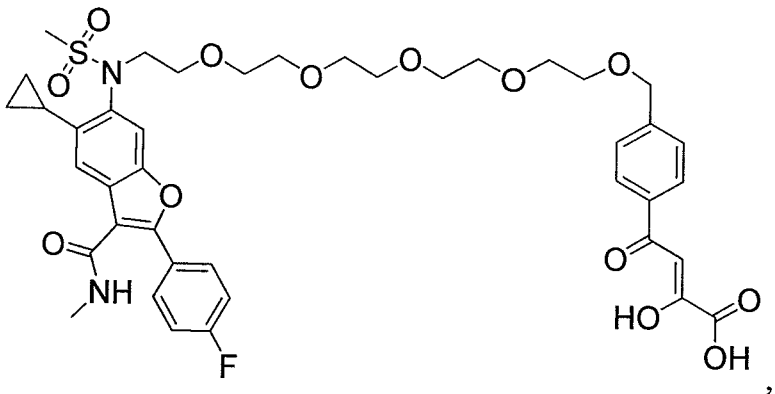
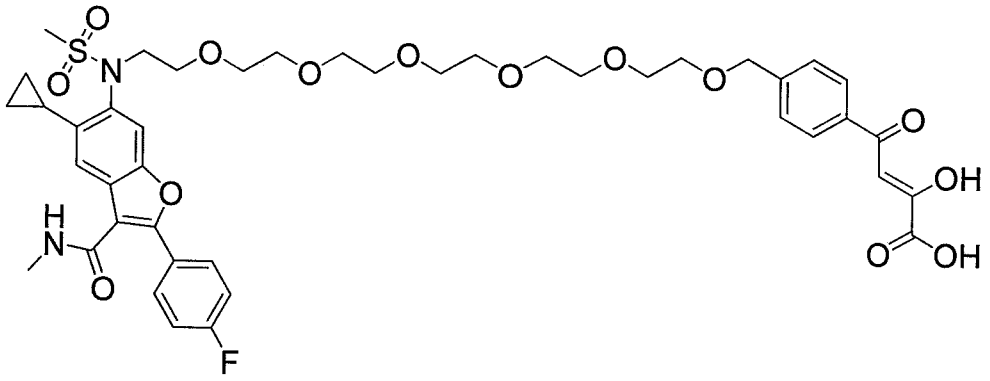
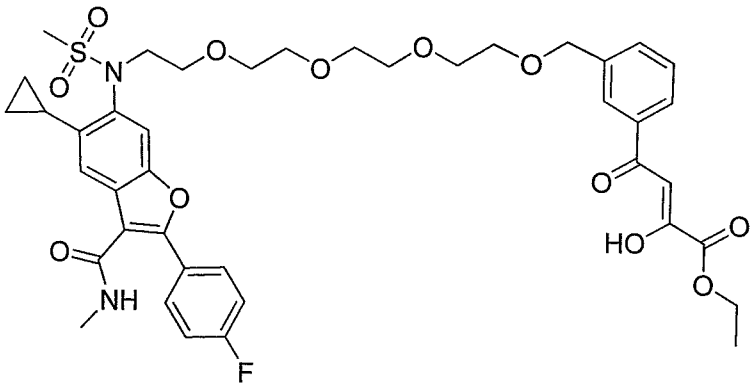
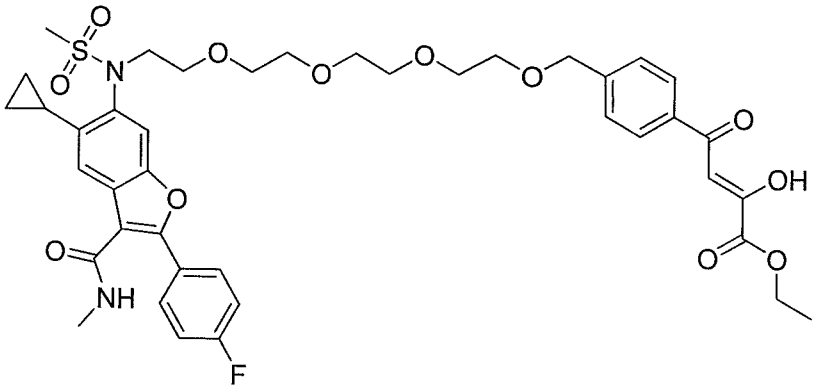
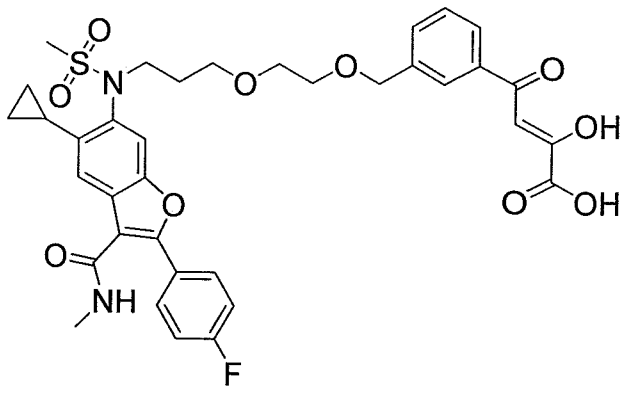
02-10I ,

02-10J ,

02-9C ,

02-9H ,



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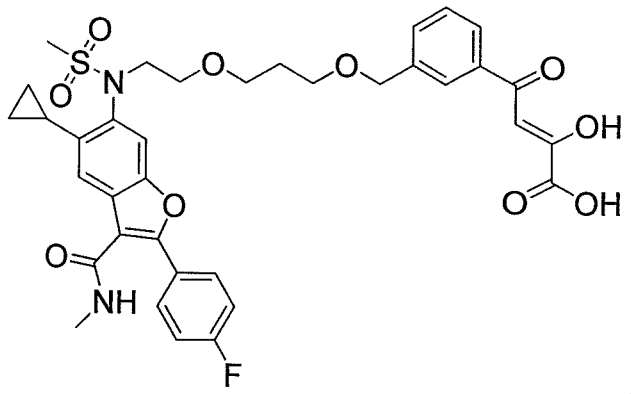

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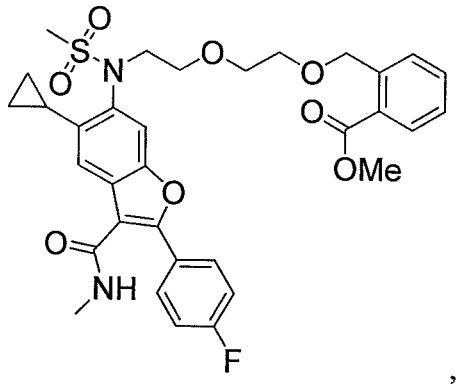

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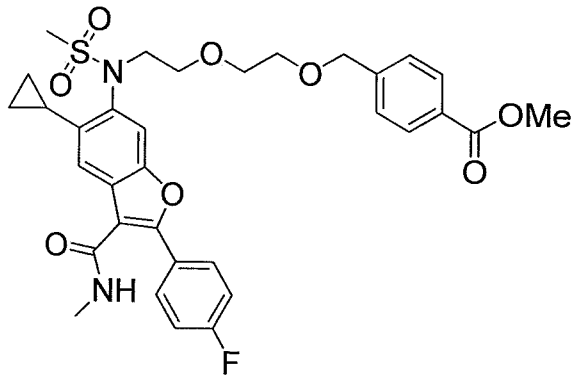

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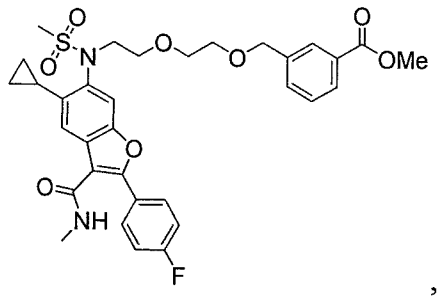

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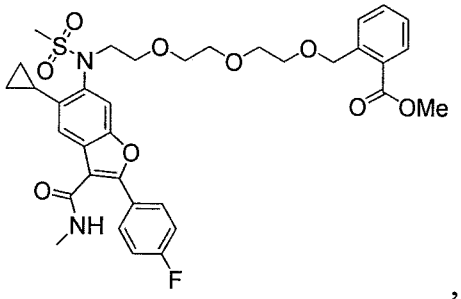

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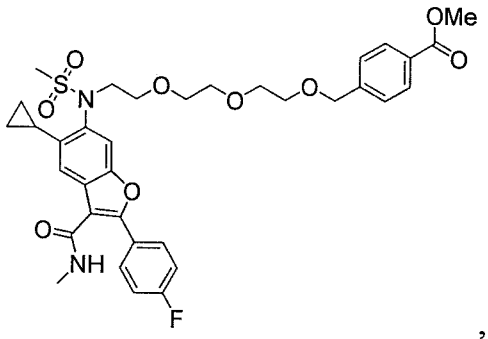

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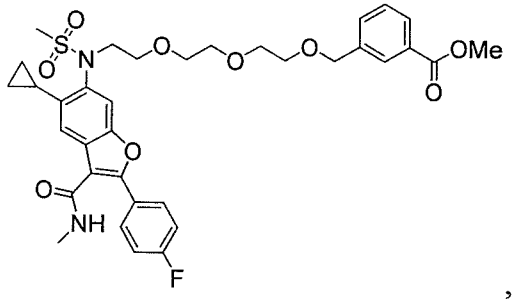

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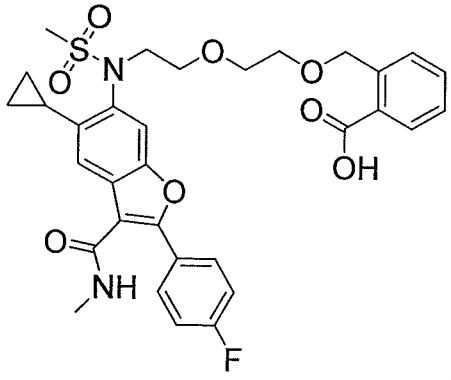

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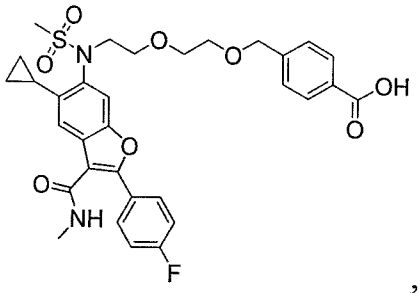

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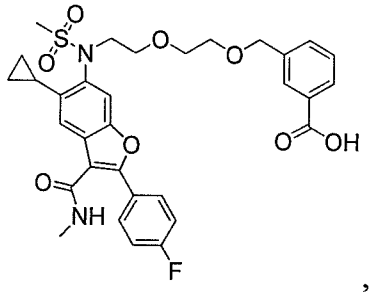

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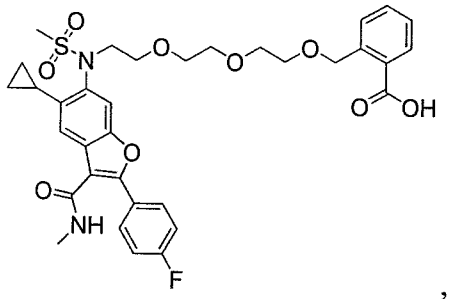

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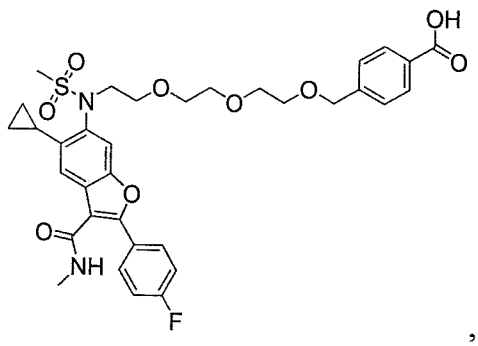

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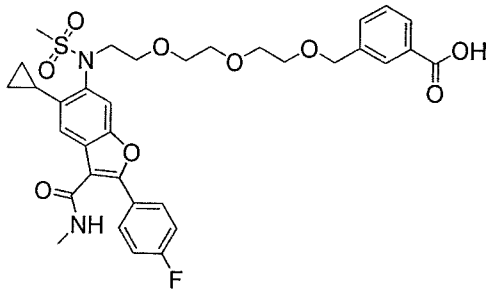

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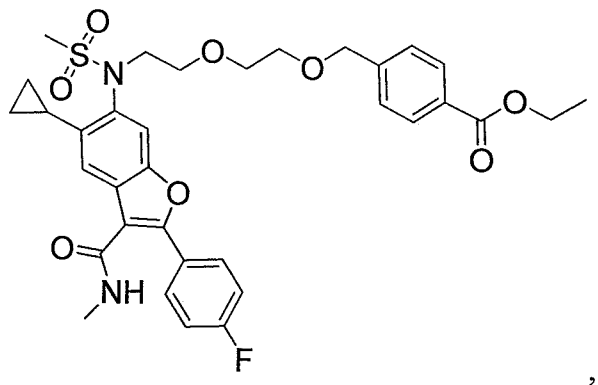

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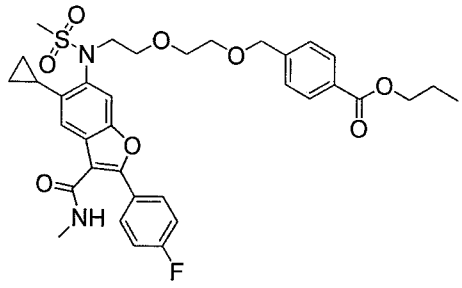

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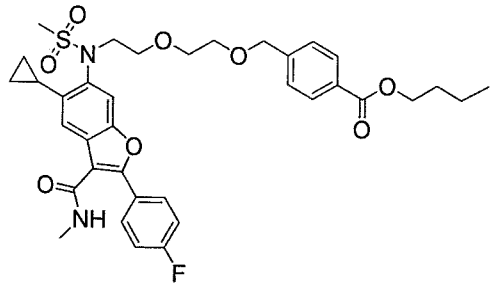

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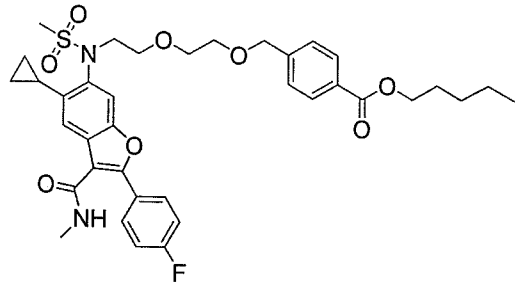

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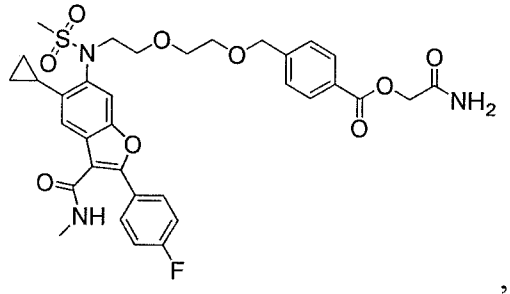

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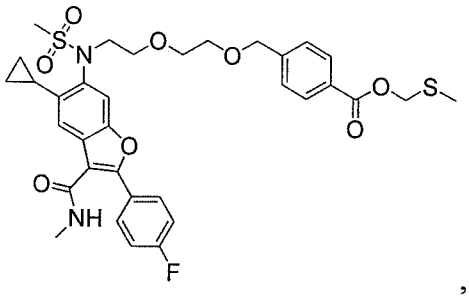

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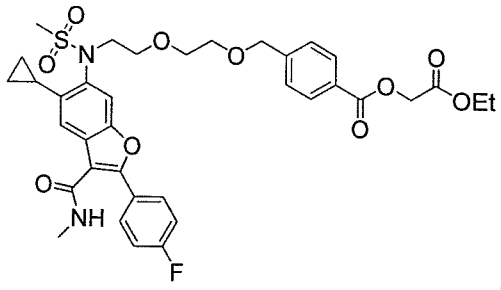

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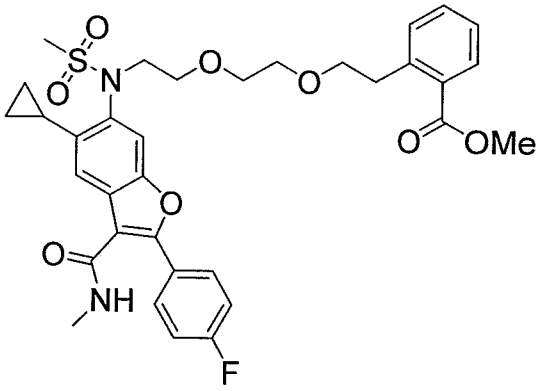

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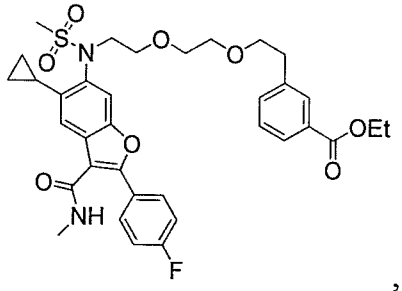

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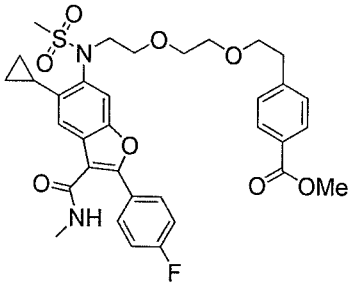

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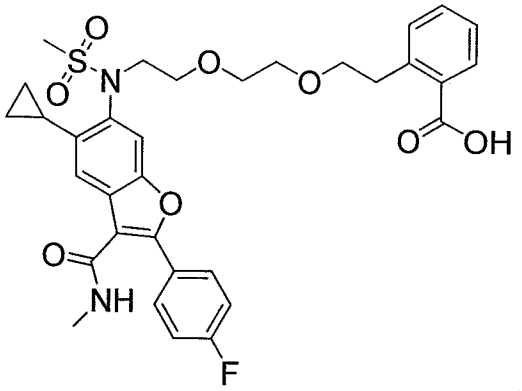

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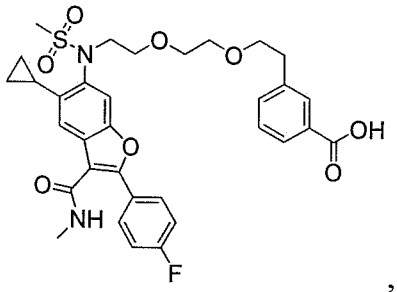

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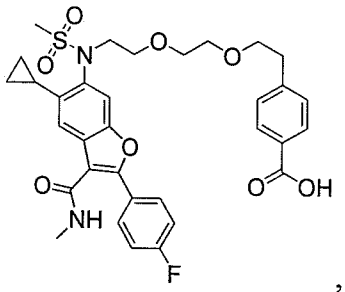

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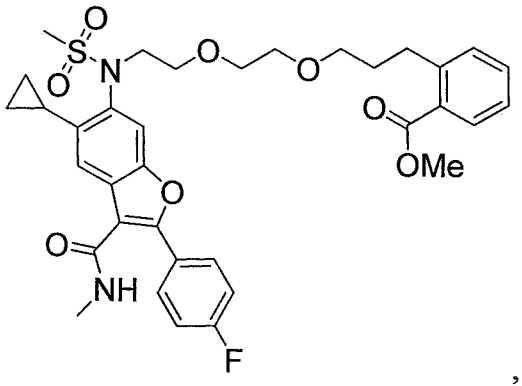

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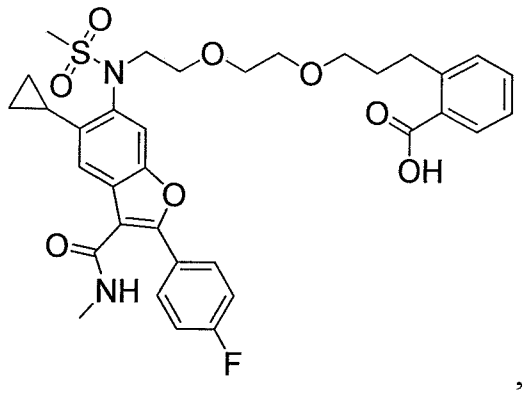

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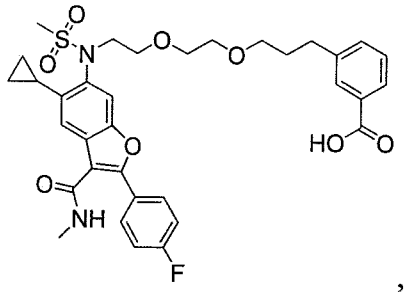

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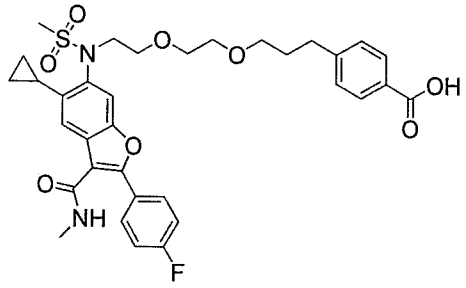

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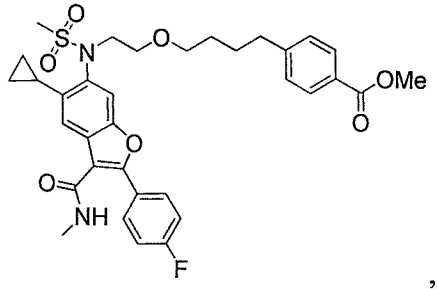

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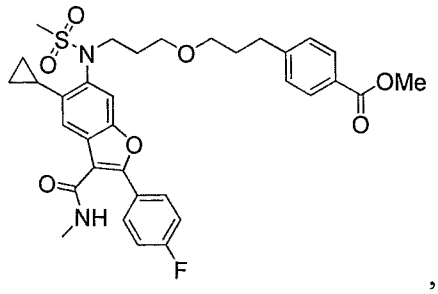

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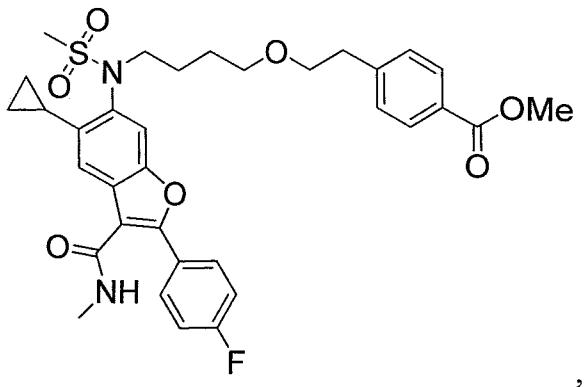

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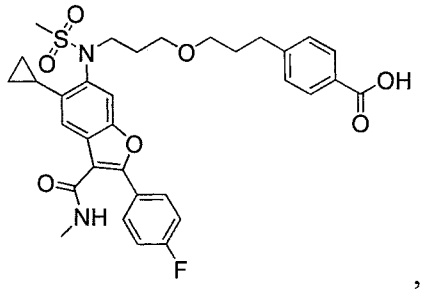

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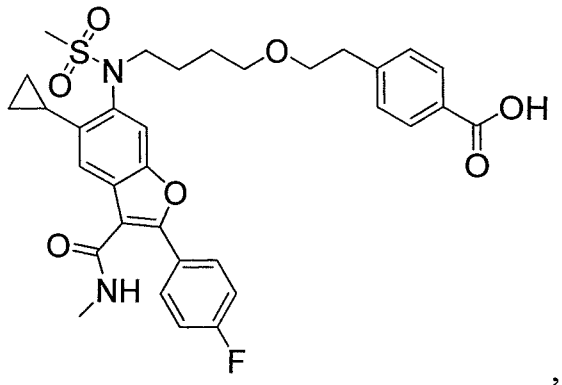

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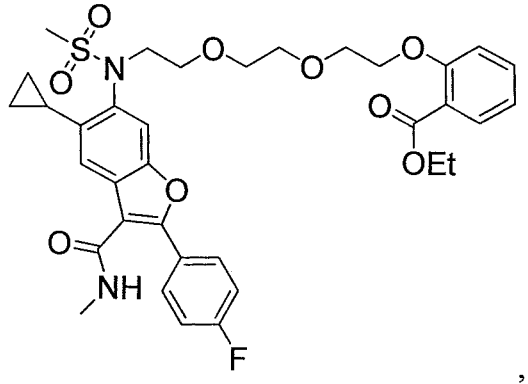

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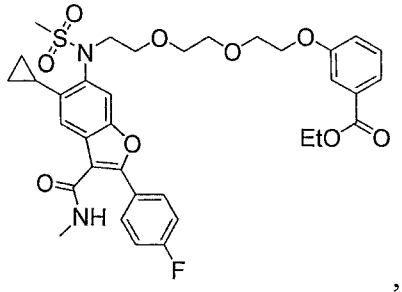

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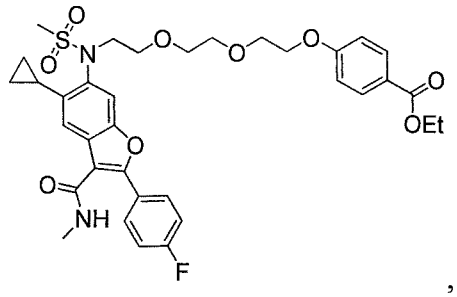
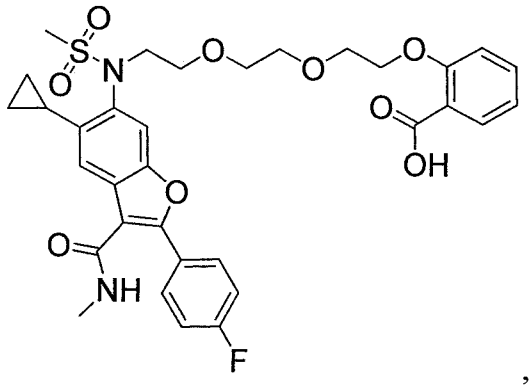
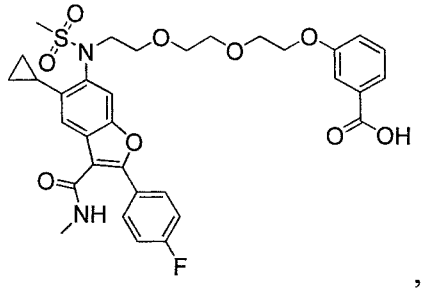


14-6C ,



14-7A ,



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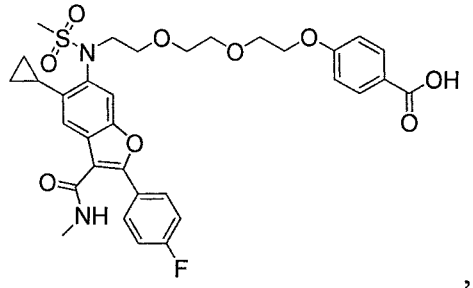

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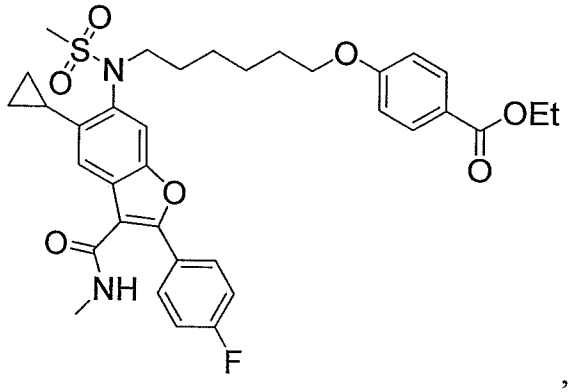

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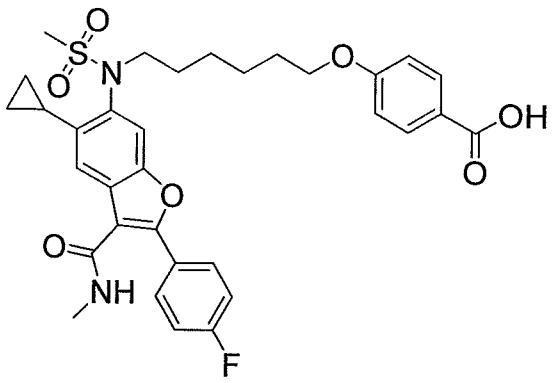
15-8 

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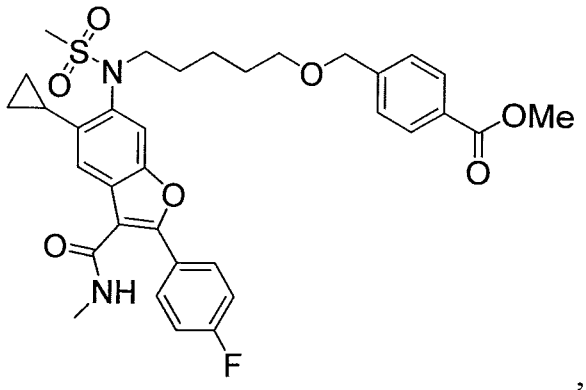
16-6 

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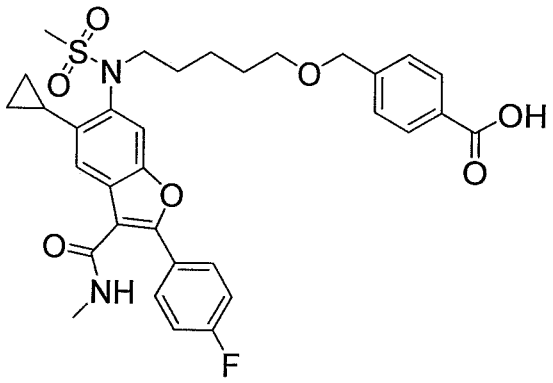
16-7 

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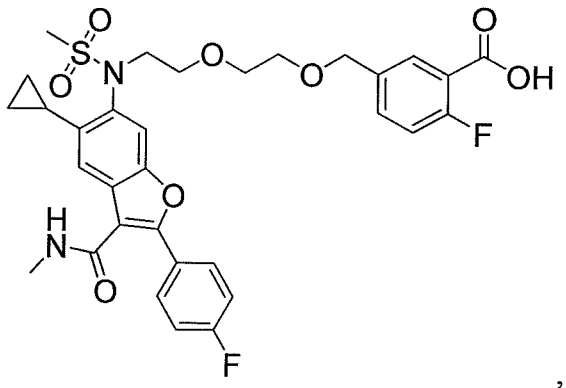
17A-8A 

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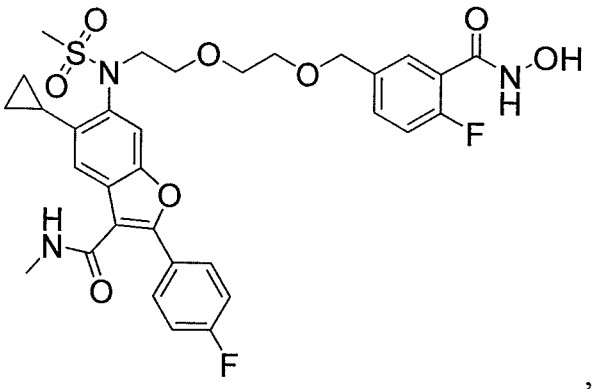

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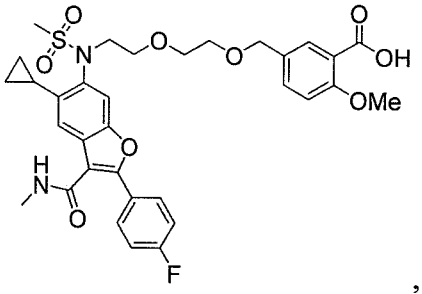
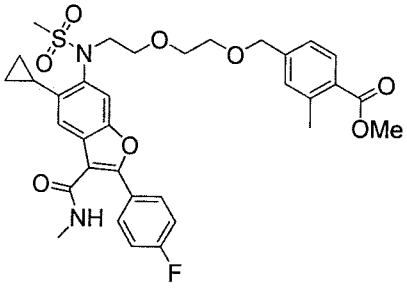


17B-8 ,



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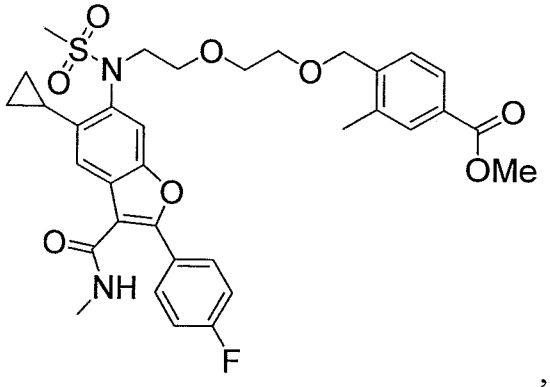

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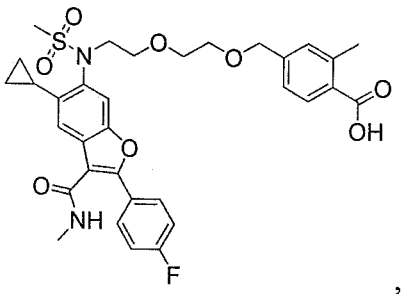

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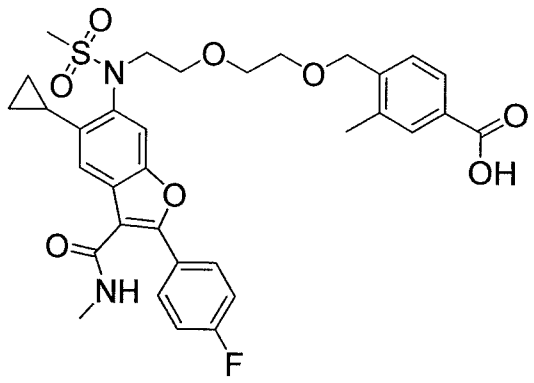

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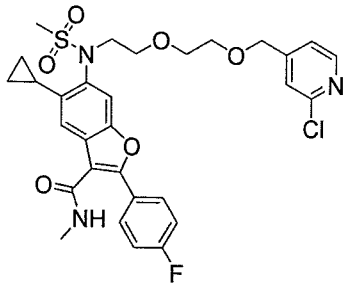

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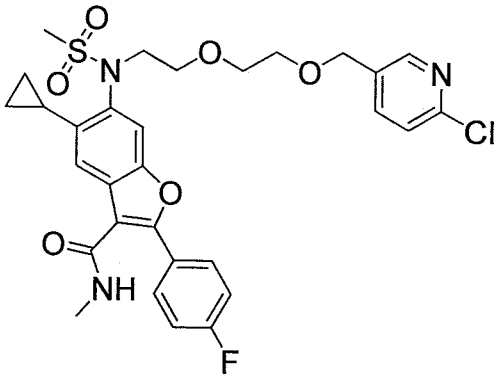

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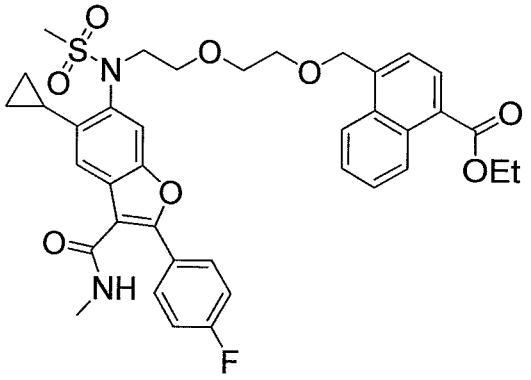

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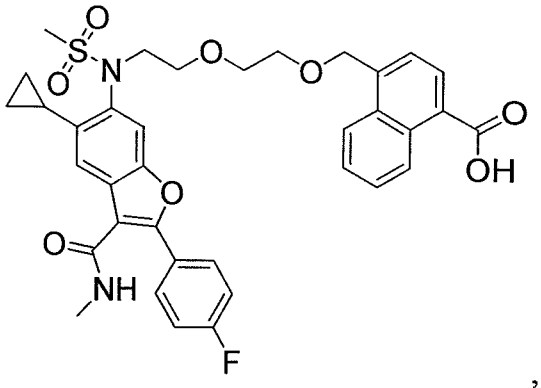

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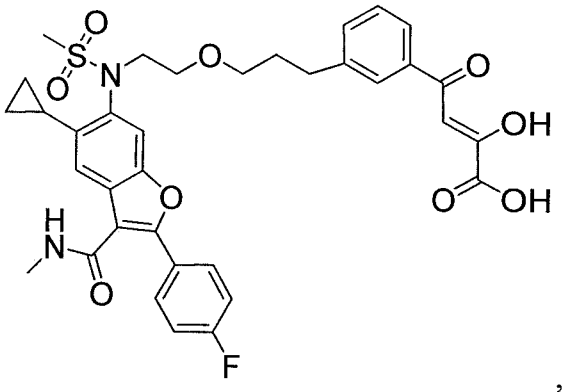

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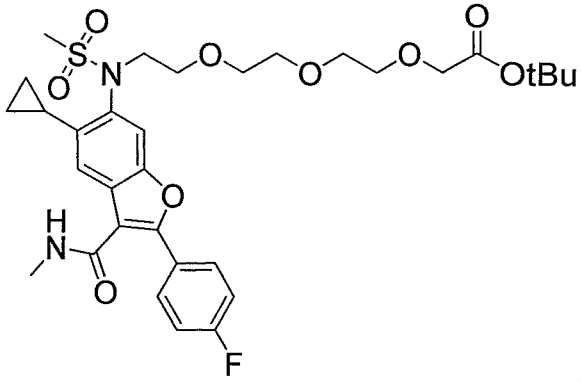

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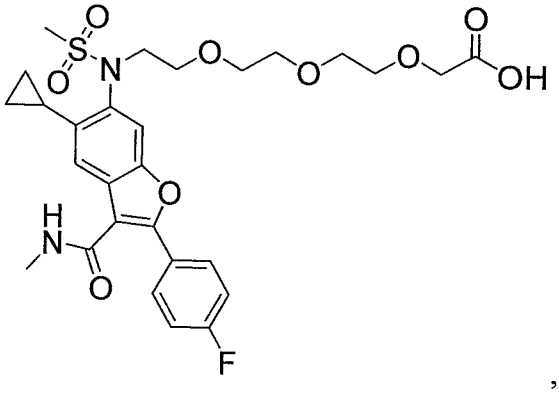

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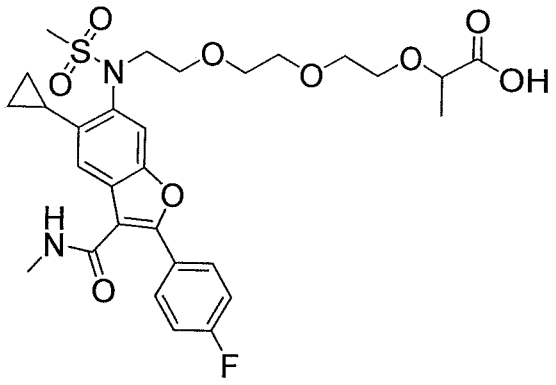

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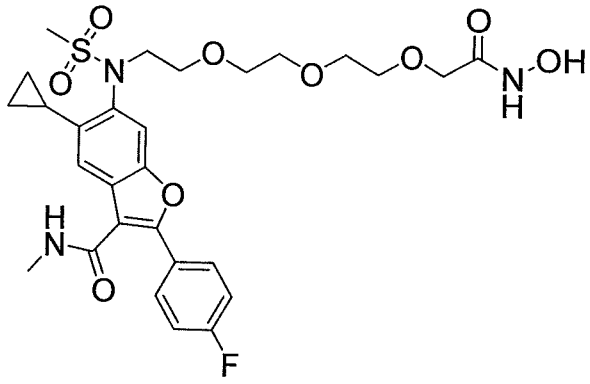

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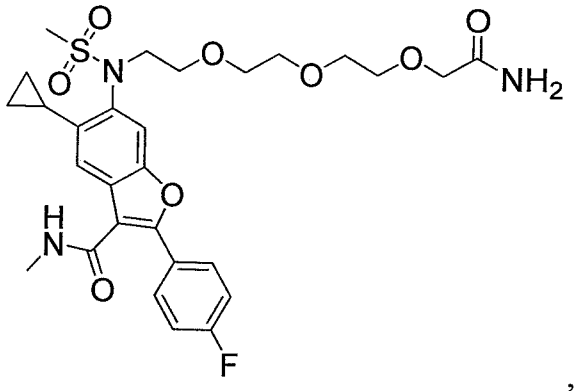

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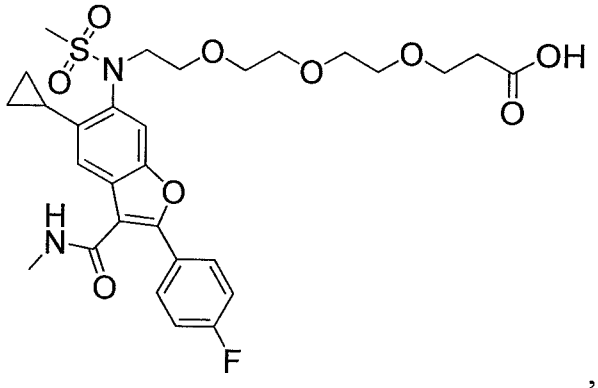

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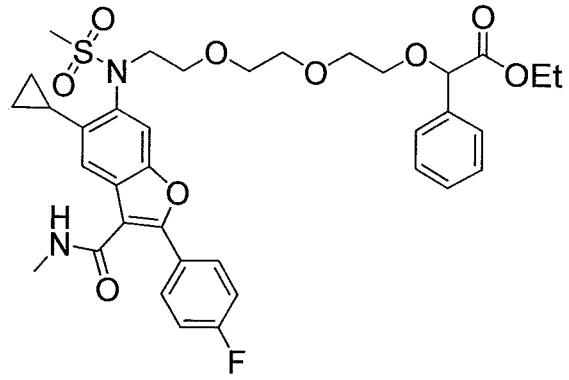

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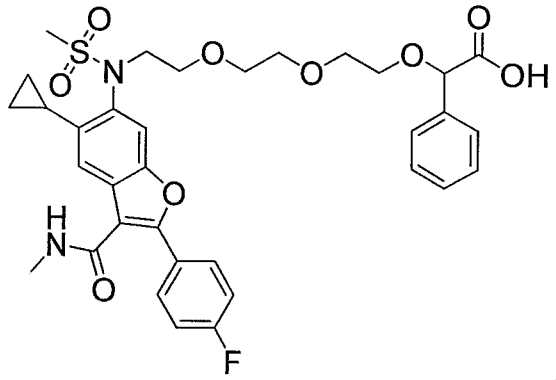

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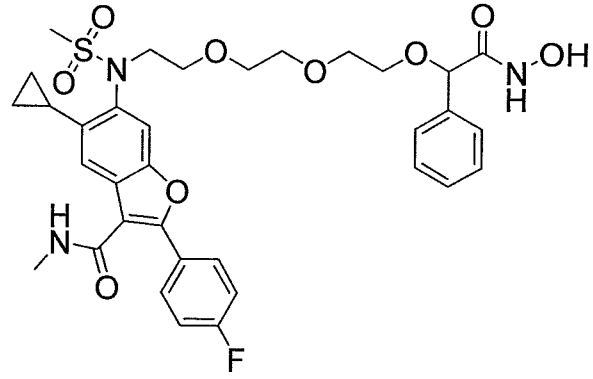

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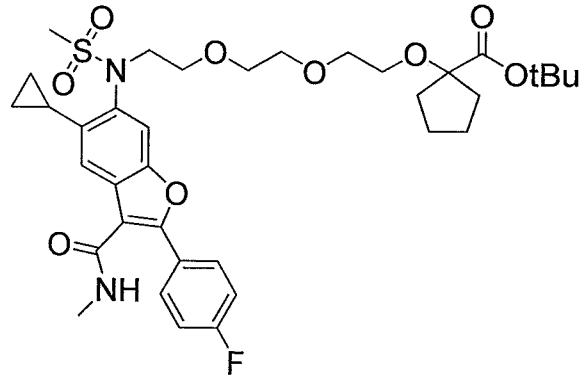
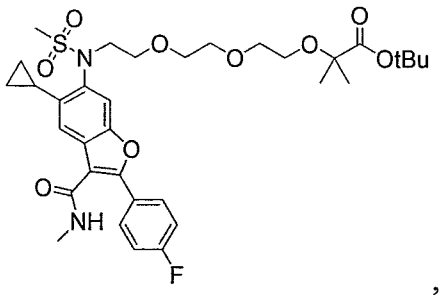
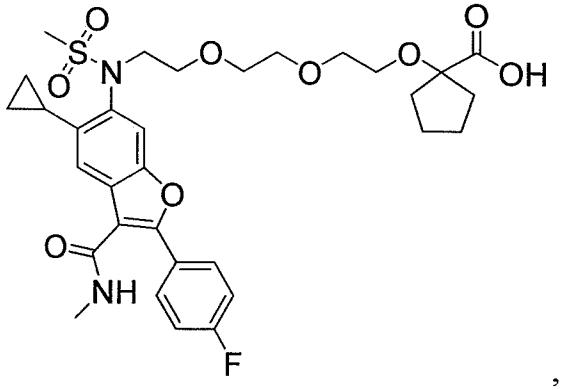
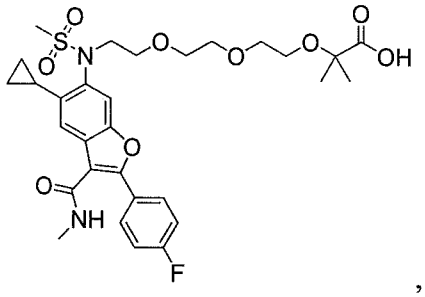
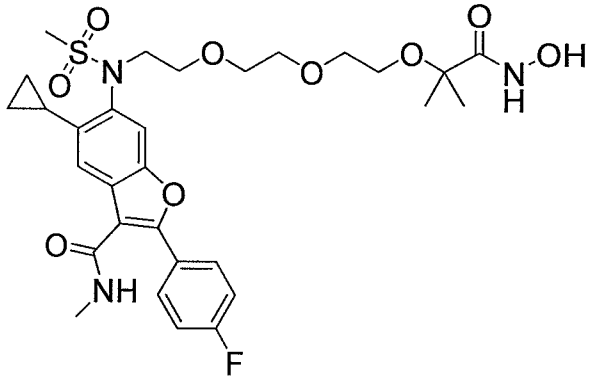


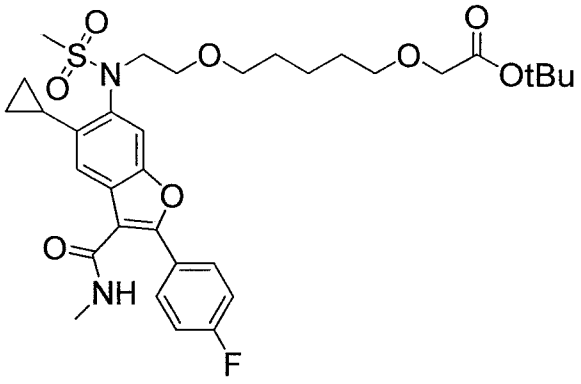
26-6A ,

26-6B ,

26-7A ,

26-7B ,

26-8B ,

27-8A 

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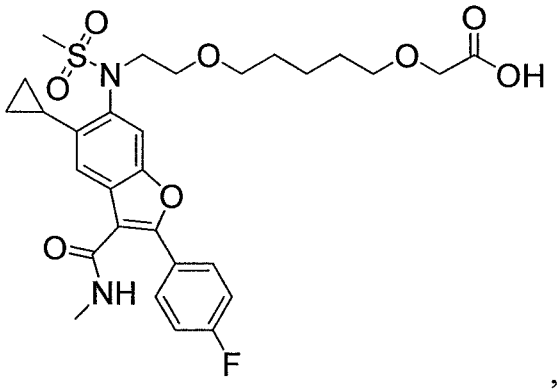
27-9A 

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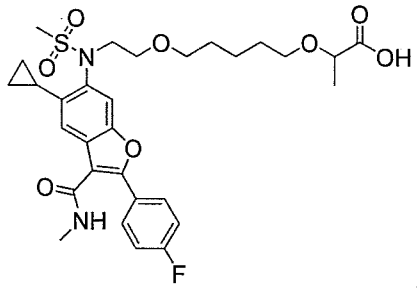
27-9B 

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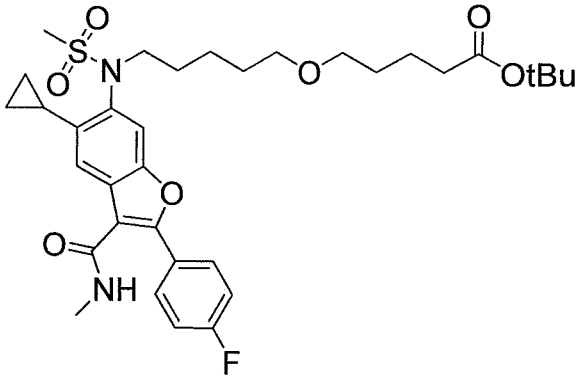
28-7A 

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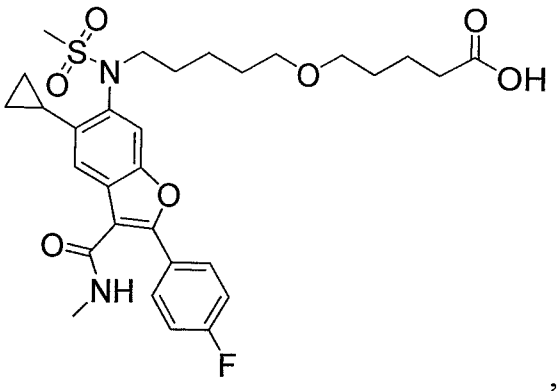

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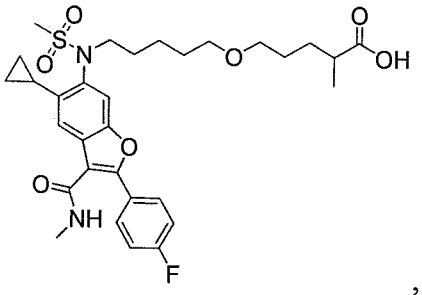

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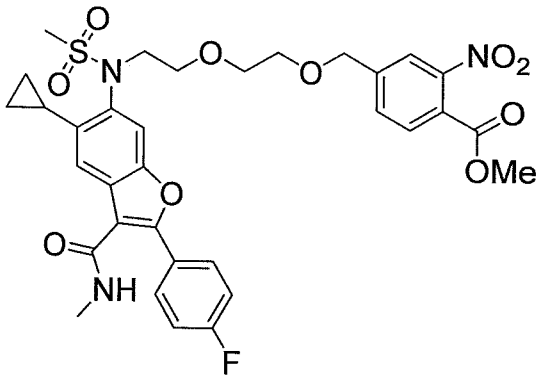

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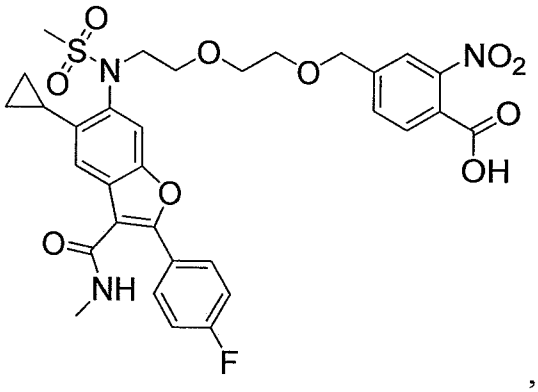

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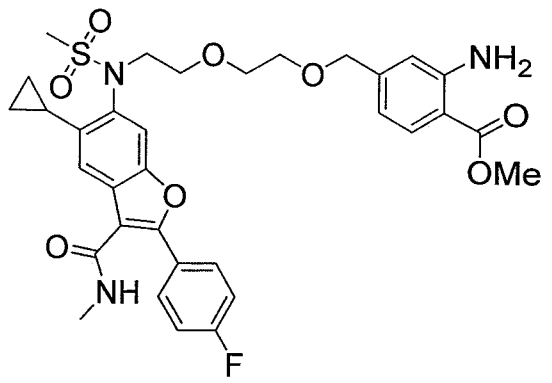
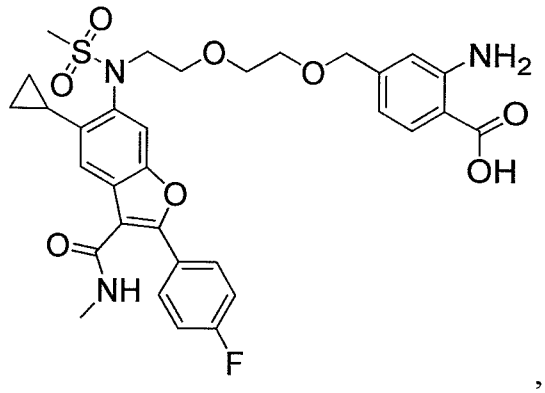
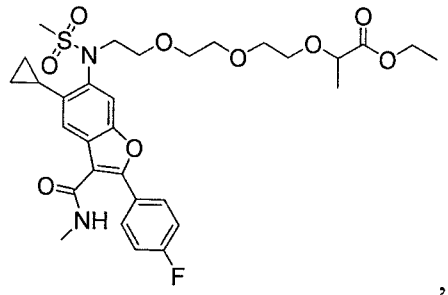
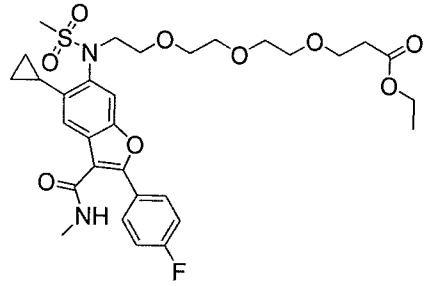
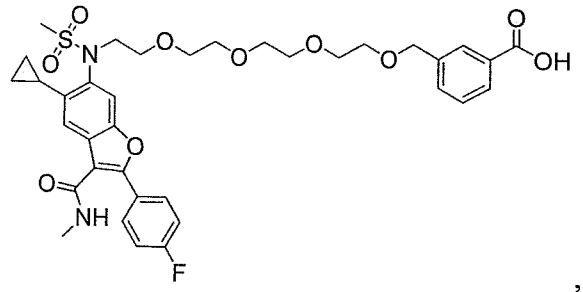
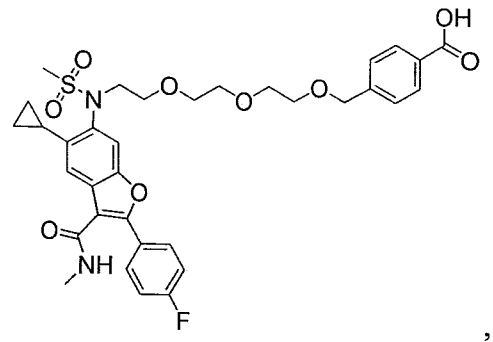
29-9 ,

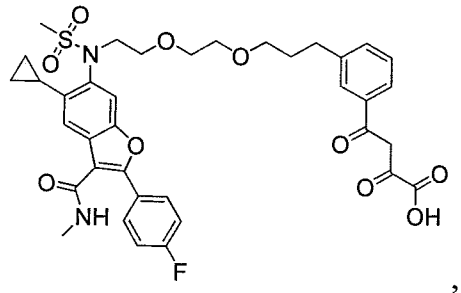
29-10 ,

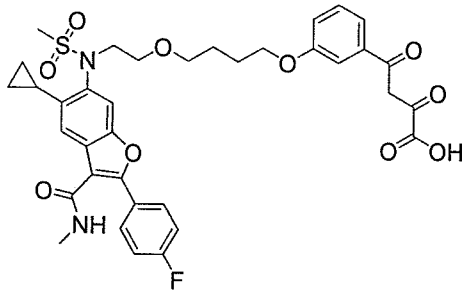
30-2 ,

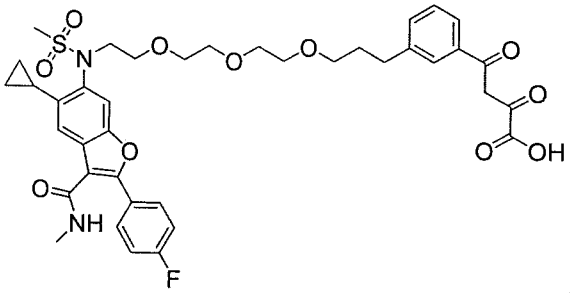
30-3 ,

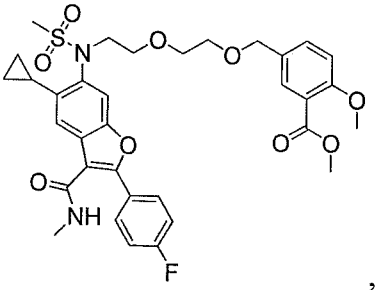
30-4 ,

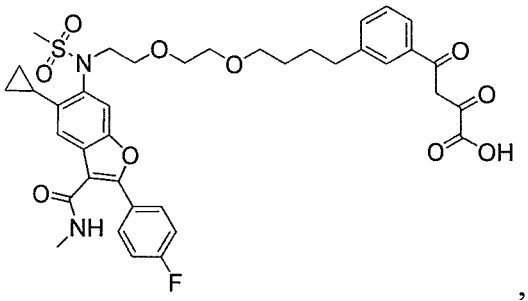
30-7 ,

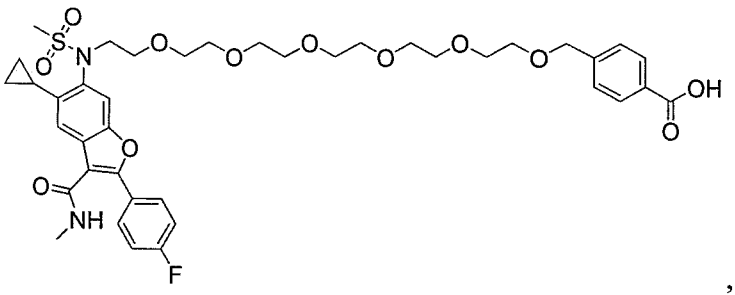
30-8 ,

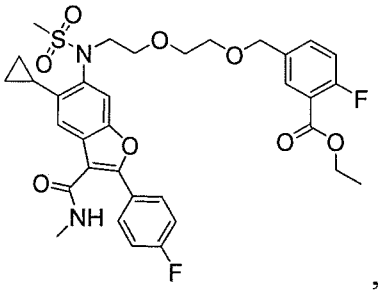
30-9 ,

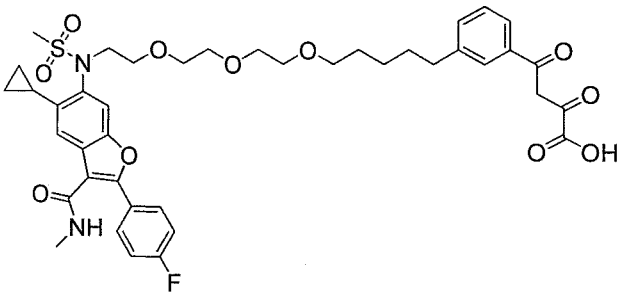
30-10 ,

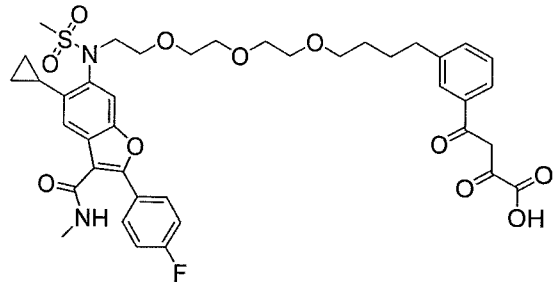
30-11 ,

30-12  ,

30-13  ,

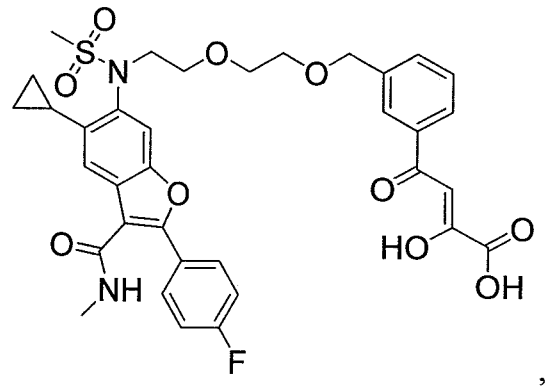
30-14  ,

30-15  , and



30-16 .

In another aspect, there is provided a compound, or pharmaceutically acceptable salt thereof, selected



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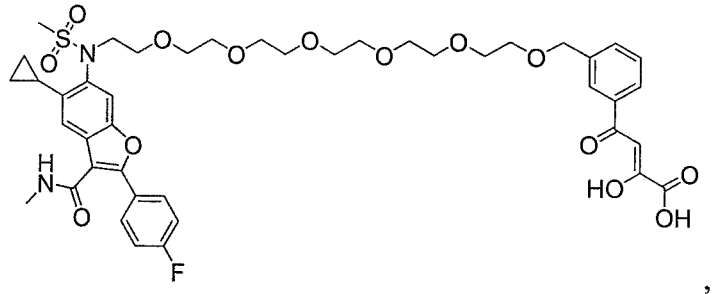
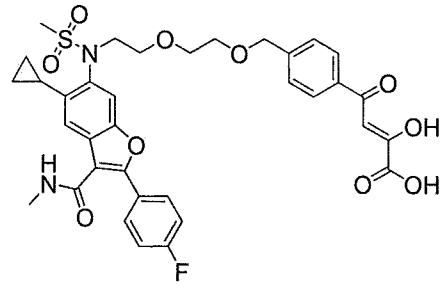


2-10E ,



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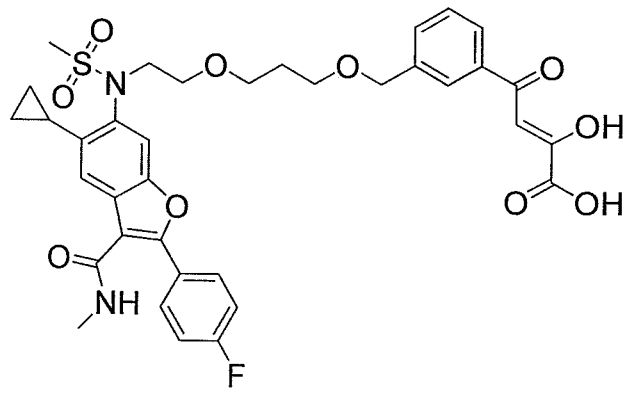

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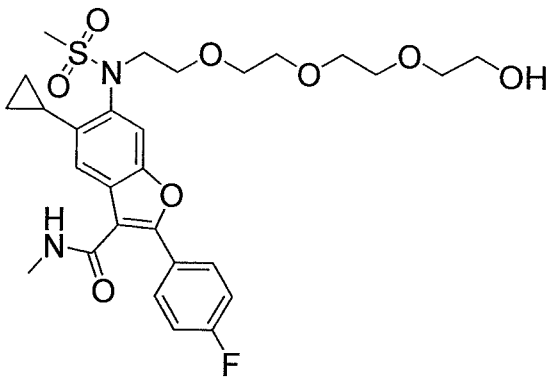

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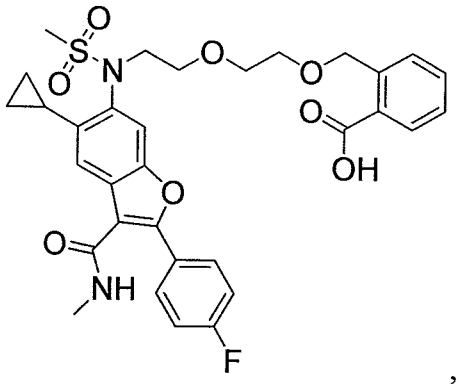

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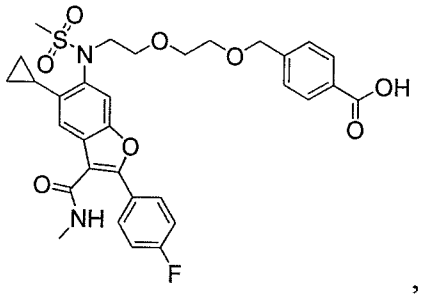

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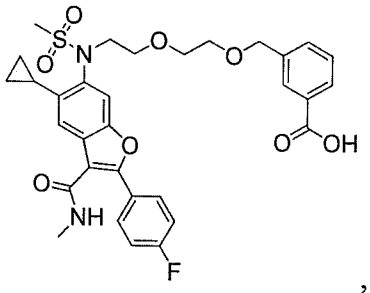

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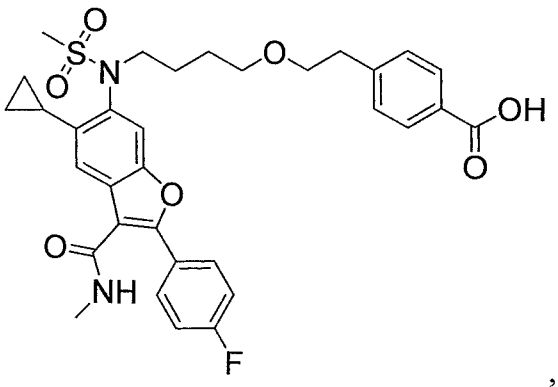

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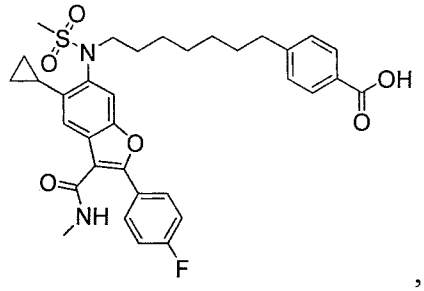
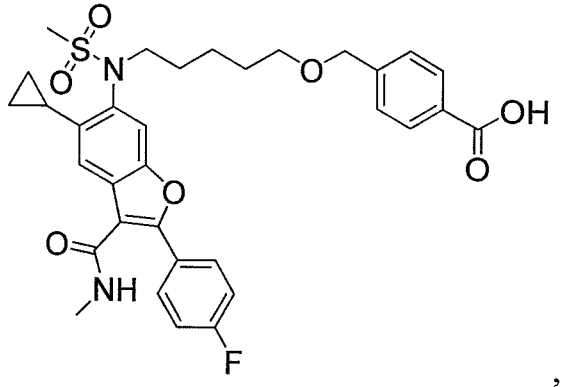
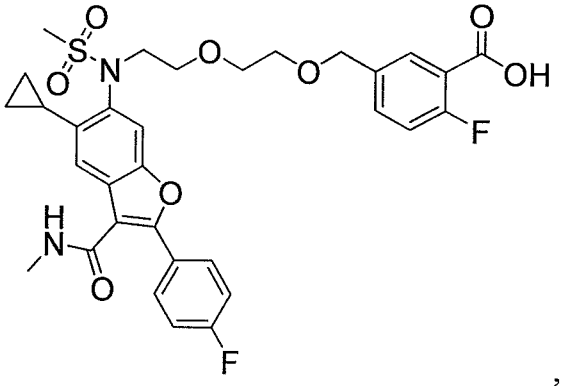
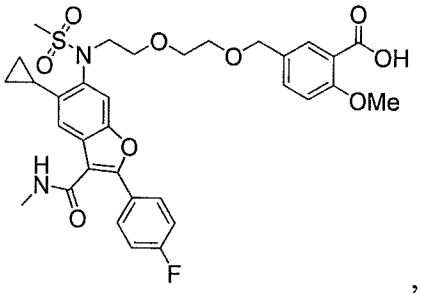
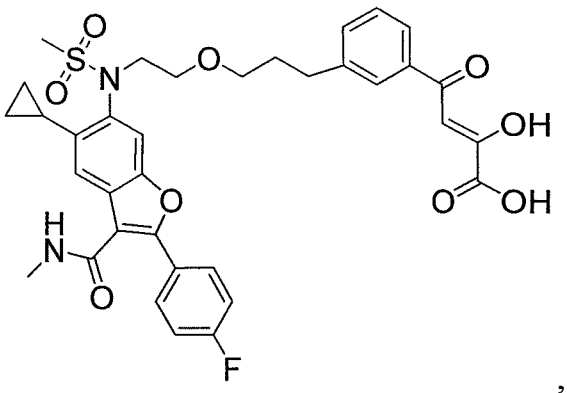
13-8D  ,

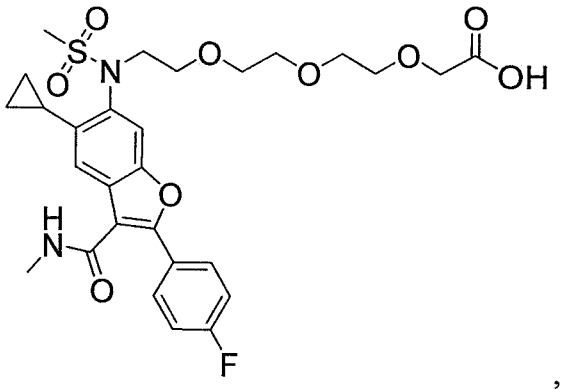
16-7  ,

17A-8A  ,

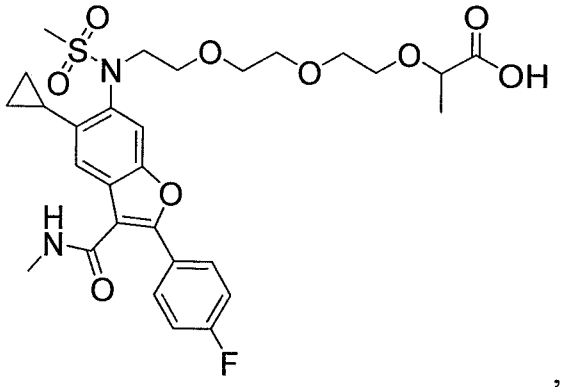
17B-8  ,



22-12 ,



23-6A ,



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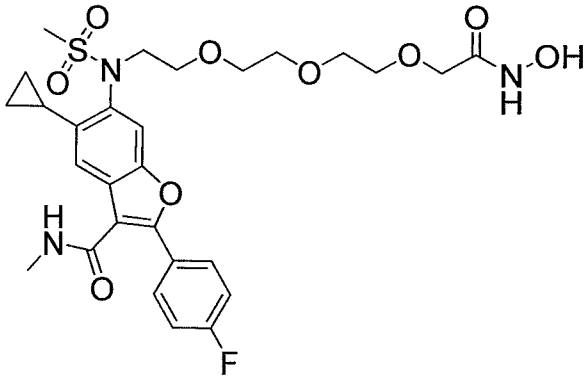
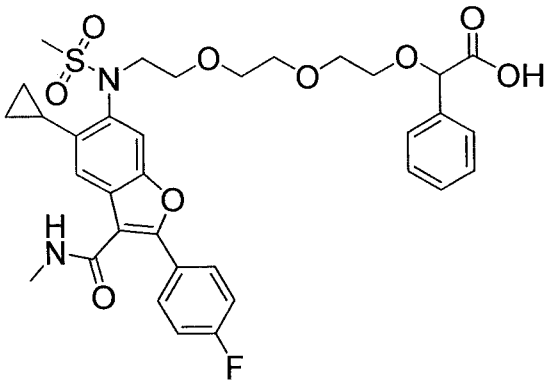


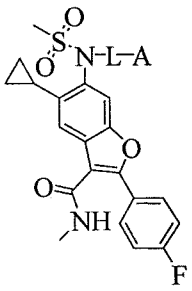
23-6C , and



25-5

In another aspect, there is provided a composition comprising a compound according to the present invention and at least one pharmaceutically acceptable excipient. In another aspect, there is provided the use of a compound according to the present invention, or a composition according to the present invention, in the manufacture of a medicament for treating or preventing hepatitis C virus infection or reactivation in a host. In another aspect, there is provided a combination, comprising a compound of the present invention, together with at least one active agent selected from interferons, ribavirin, nucleoside HCV NS5B polymerase inhibitors, non-nucleoside HCV NS5B polymerase inhibitors, HCV NS3-4A protease inhibitors, HCV NS5A inhibitors, HCV entry inhibitors, HCV NS3 inhibitors, HCV NS3 helicase inhibitors, HCV NS4B inhibitors, and human cyclophilin inhibitors. In another aspect, there is provided a combination, comprising a composition of the present invention, together with a composition comprising at least one active agent selected from interferons, ribavirin, nucleoside HCV NS5B polymerase inhibitors, non-nucleoside HCV NS5B polymerase inhibitors, HCV NS3-4A protease inhibitors, HCV NS5A inhibitors, HCV entry inhibitors, HCV NS3 inhibitors, HCV NS3 helicase inhibitors, HCV NS4B inhibitors, and human cyclophilin inhibitors and a pharmaceutically acceptable excipient.

The present disclosure provides compounds represented by the general Formula I:



I

and salts (e.g., pharmaceutically acceptable salts) thereof, wherein L, A, D, and E are as defined in classes and subclasses herein, and compositions (e.g., pharmaceutical compositions) comprising such

compounds, which compounds are useful as inhibitors of hepatitis C virus polymerase, and thus are useful, for example, as medicaments for the treatment of HCV infection and diseases associated with or consequent to such infection.

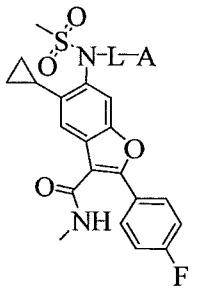
[20] In certain other examples, the disclosure provides pharmaceutical compositions comprising a compound of the invention, wherein the compound is present in an amount effective to inhibit HCV polymerase activity. In certain other examples, the disclosure provides pharmaceutical compositions comprising a compound of Formula I and optionally further comprising an additional active agent to achieve therapeutic effect. In yet other examples, the additional active agent is an agent that has anti-HCV activity or function.

[21] In yet another example, the present disclosure provides methods for inhibiting HCV polymerase activity in a subject (or optionally in a biological sample ex vivo or in vitro), comprising administering to the subject (or contacting the biological sample) with an effective inhibitory amount of a compound of Formula I.

[22] In still another example, the present disclosure provides methods for treating any disorder constitutively associated with HCV infection or replication or involving HCV polymerase activity, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I.

DETAILED DESCRIPTION

[23] In one aspect, the invention provides compounds having the structure given as Formula I:



I

or a pharmaceutically acceptable salt thereof,

in which:

L is (a): $-(CH_2)_x-[O(CH_2)_w]_y-O-(CR^d_2)_z-$

each R^d is selected from hydrogen, methyl, and phenyl, or both R^d together with the carbon to which they are attached form C_{3-5}cycloalkyl;

w is 2 to 4;

x is 2 to 6; and

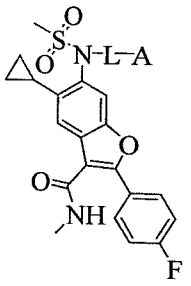
y and z are each independently 0 to 5, with the proviso that when y is 0, then (x+z) is 4 to 11;

or

(b): $-(CH_2)_m-G^1-C(O)-G^2-C(R^b)_2-G^3-C(O)-G^4-(CR^c_2)_n-$, in which

WHAT IS CLAIMED IS:

1. A compound having the structure:



I

or a pharmaceutically acceptable salt thereof,

wherein:

L is (a): $-(CH_2)_x-[O(CH_2)_w]_y-O-(CR^d{}_2)_z-$, in which

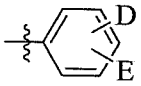
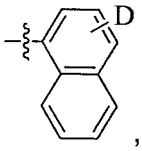
each R^d is selected from hydrogen, methyl, and phenyl, or both R^d together with the carbon to which they are attached form C_{3-5}cycloalkyl;

w is 2 to 4;

x is 2 to 6; and

y and z are each independently 0 to 5, with the proviso that when y is 0, then (x+z) is 4 to 11;

and

A is selected from $-CO_2H$, $-CONHOH$, $-CO_2-C_{1-4}$alkyl, $-C(O)NH_2$, chloropyridinyl, $-OC_{1-2}$alkylene$-CO_2H$, $-OC_{1-2}$alkylene$-CO_2C_{1-4}$alkyl, $-SC(O)CH_3$,  and ,

in which D is $-(C_{0-3}$alkylene$)-CO_2H$, $-(C_{0-3}$alkylene$)-CO_2C_{1-5}$alkyl, $-(C_{0-3}$alkylene$)-CONHOH$, $-C(O)CH=C(OH)CO_2H$, $-C(O)CH=C(OH)CO_2C_{1-4}$alkyl,

$-CO_2CH_2C(O)NH_2$, $-CO_2CH_2SC_{1-4}$alkyl, $-CO_2Bn$, or $-CO_2CH_2CO_2C_{1-4}$alkyl, and

E is null, halo, C_{1-4}alkyl, $-OC_{1-4}$alkyl , $-NH-C_{1-4}$alkyl , $-C_{0-3}$alkylene$-NH_2$, or NO_2.

2. A compound according to claim 1, wherein E is null, fluoro, methyl, NH_2 or NO_2.

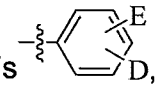
3. A compound according to claim 1 or 2, in which x = 2, w=2, y = 1, and z = 1.

4. A compound according to claim 1 or 2, in which x = 3, y = 1, and z = 1.

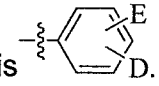
5. A compound according to claim 1 or 2, wherein y is 1 to 4.

6. A compound according to claim 1 or 2, wherein L is $-(CH_2)_x-(OCH_2CH_2)_y-O-(CH_2)_z-$.

7. A compound according to any one of claims 1 to 6, wherein A is $-CO_2H$, -CONHOH, $-CO_2-C_{1-4}$alkyl, $-C(O)NH_2$, $-OC_{1-2}$alkylene$-CO_2H$, or $-OC_{1-2}$alkylene$-CO_2C_{1-4}$alkyl.

8. A compound according to any one of claims 1 to 6, wherein A is , D is $-(C_{0-3}$alkylene$)-CO_2H$, $-(C_{0-3}$alkylene$)-CO_2C_{1-5}$alkyl, or $-(C_{0-3}$alkylene$)$-CONHOH, and E is null.

9. A compound according to claim 8, in which D is at the *para* or *meta* position on the phenyl group.

10. A compound according to claim 9, wherein A is .

11. A compound according to claim 9 or 10, wherein D is $-CO_2H$, $-CO_2C_{1-5}$alkyl, or –CONHOH.

12. A compound according to claim 10 or 11, wherein D is $-CO_2H$.

13. A compound according to any one of claims 10-12, wherein E is null.

14. A compound according to any one of claims 10-13, wherein x is 4 to 6.

15. A compound according to any one of claims 10-14, wherein y is 0 to 1 and w is 2.

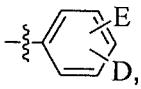
16. A compound according to any one of claims 10-15, wherein z is 0 to 2.

17. A compound according to any one of claims 10-16, wherein x is 5.

18. A compound according to any one of claims 10-17, wherein y is 0.

19. A compound according to any one of claims 10-18, wherein z is 1.

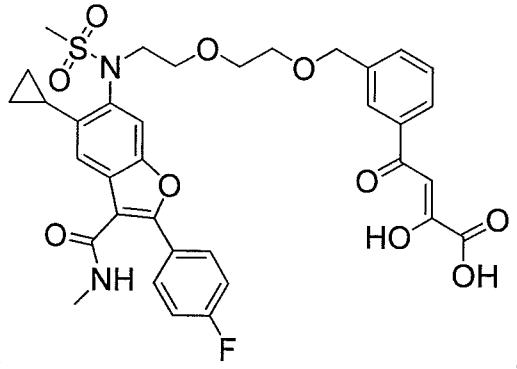
20. A compound according to any one of claims 10-19, wherein both R^d are hydrogen.

21. A compound according to claim 1, wherein x = 5, y = 0, z = 1, both R^d are hydrogen, A is 

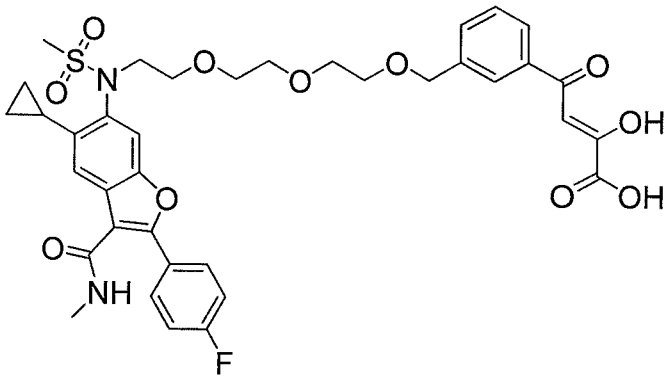
, D is $-CO_2H$, and E is null.

22. A compound according to claim 21, wherein D is at the *para* position on the phenyl group.

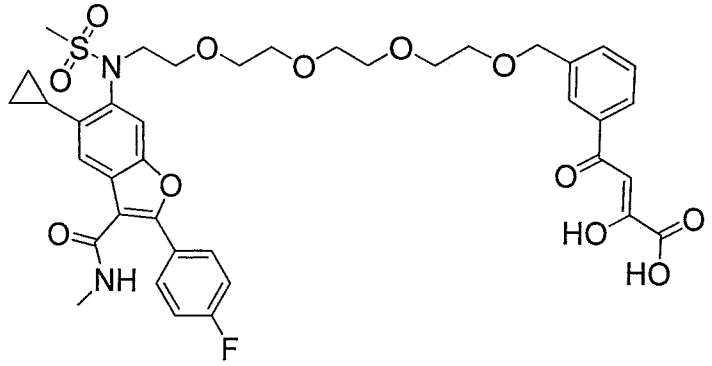
23. A compound, or pharmaceutically acceptable salt thereof, selected from:



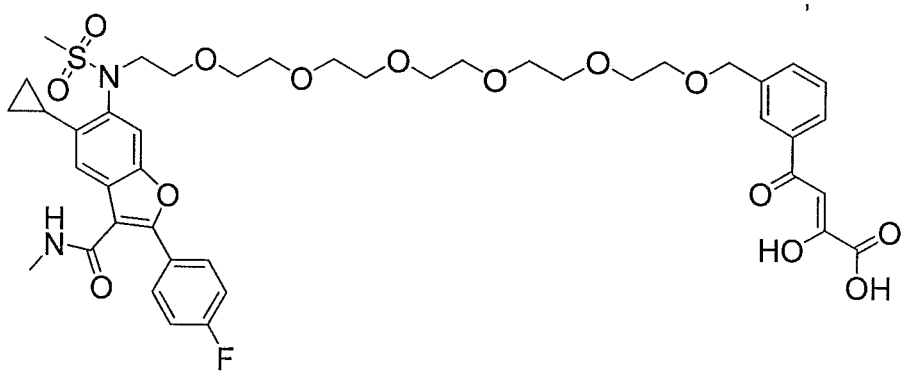
02-10A



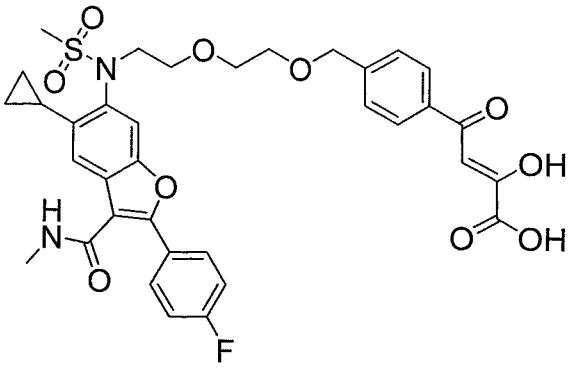
02-10B



02-10C



02-10E



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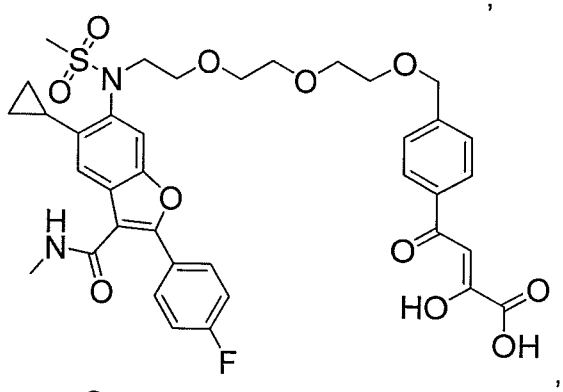

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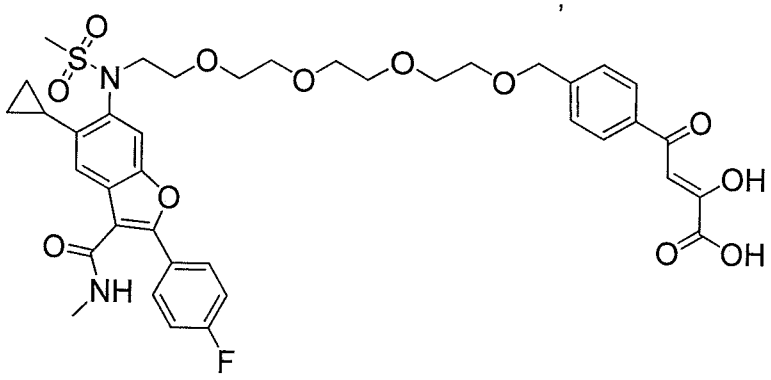

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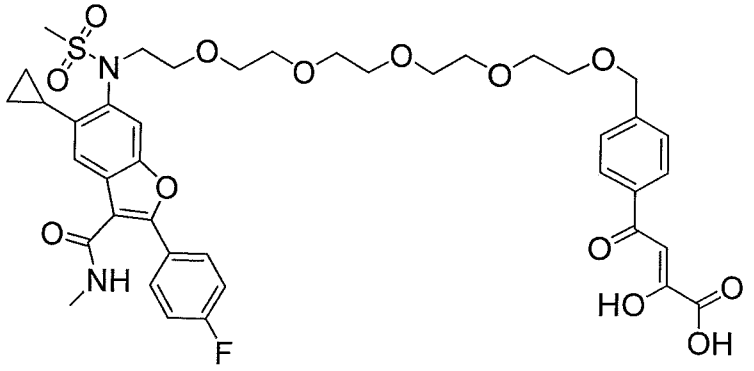
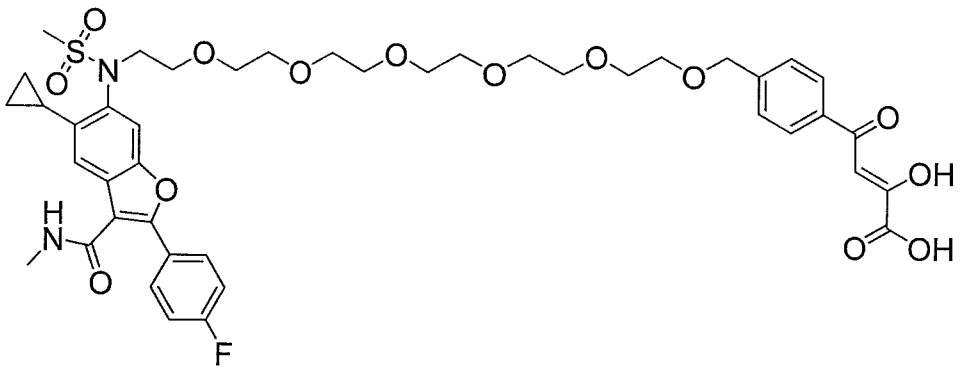


02-10I ,



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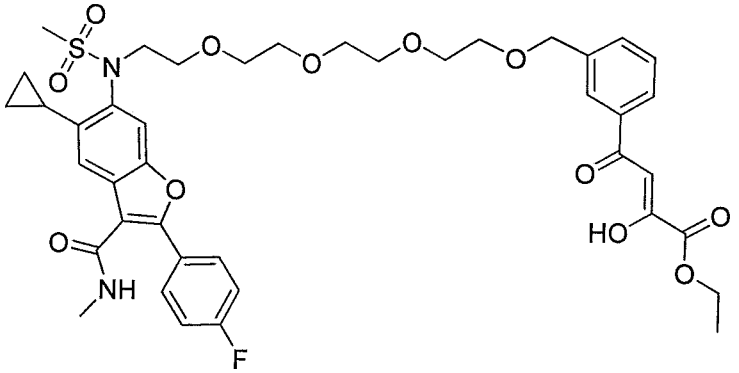
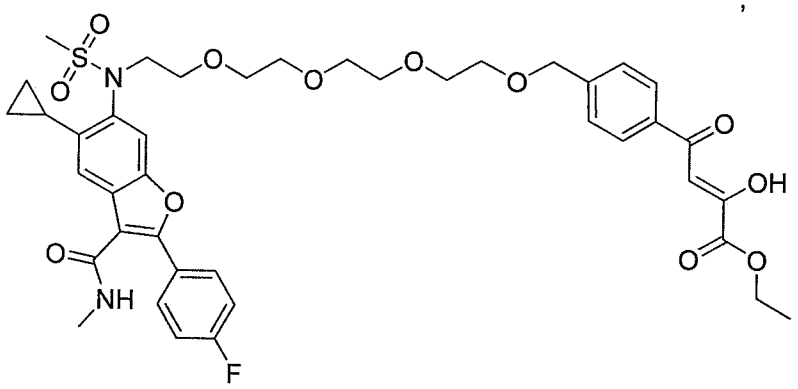


02-9C ,



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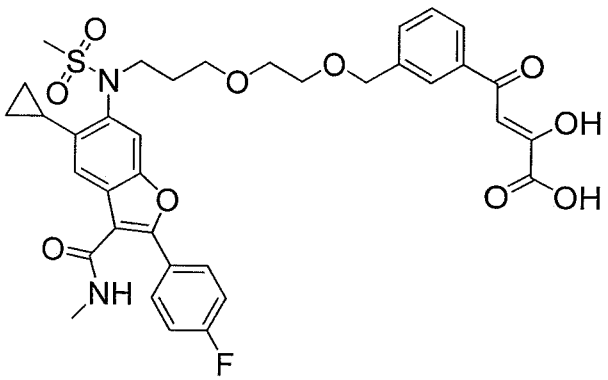

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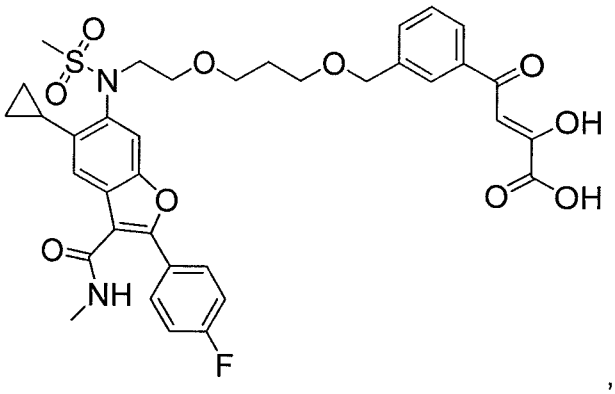
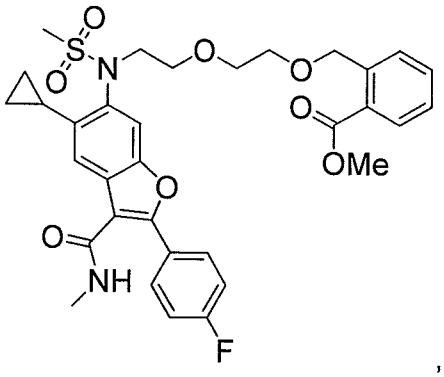
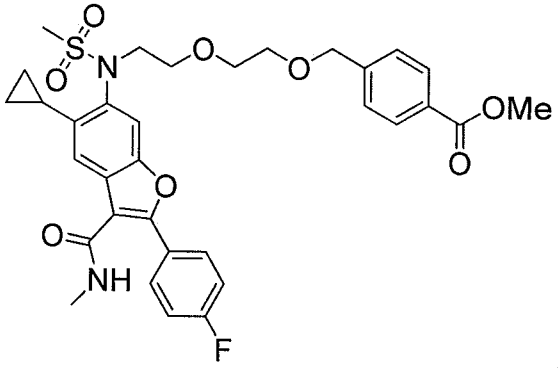


03-8B ,



06-6A ,



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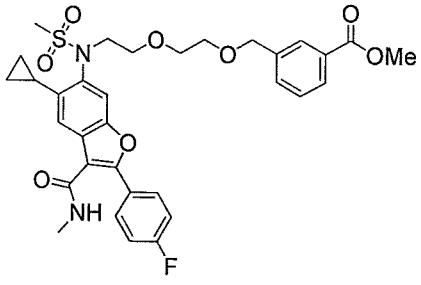

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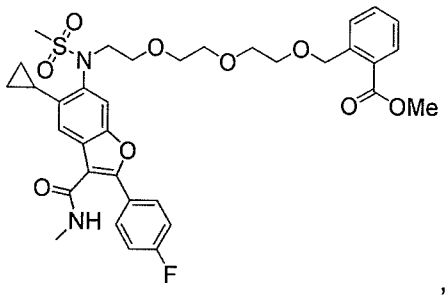

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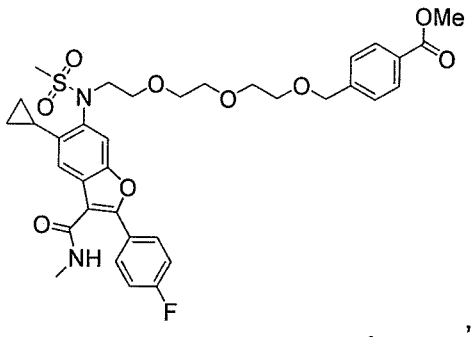
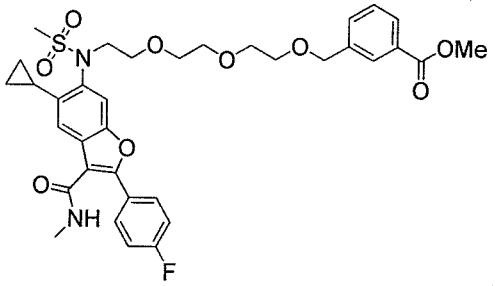
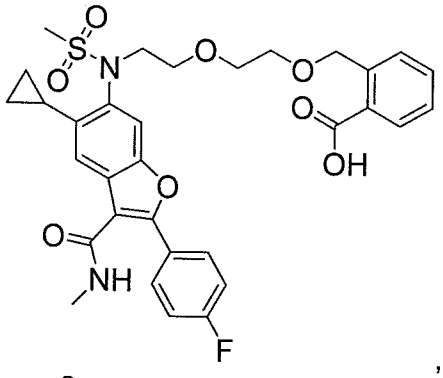


06-6E ,



06-6F ,



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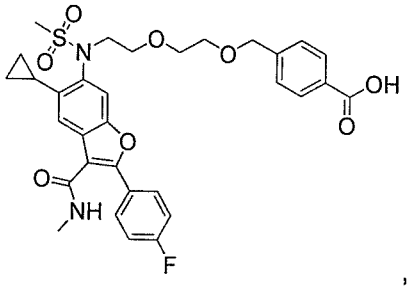

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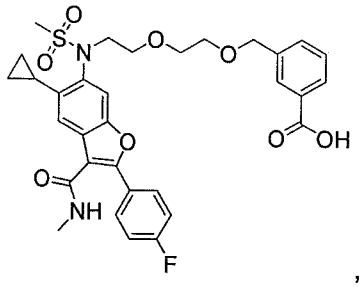

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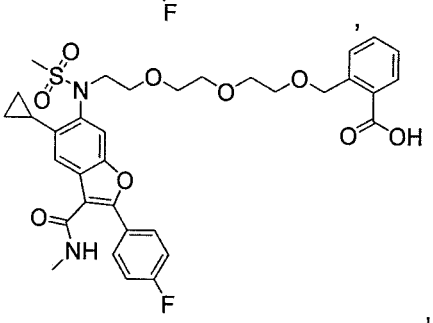

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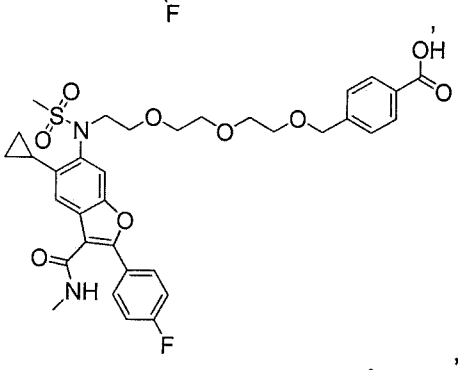

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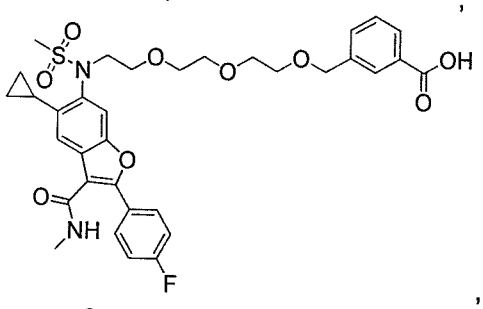

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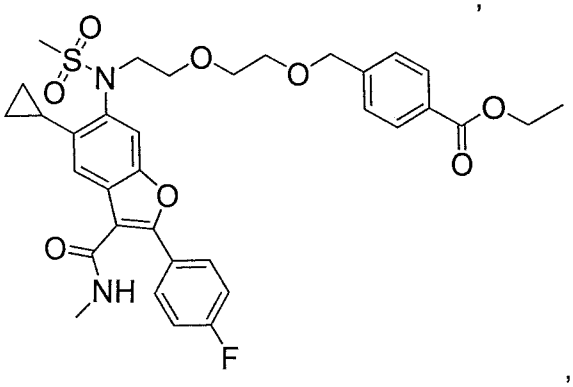

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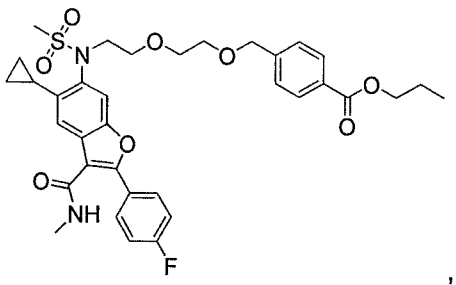

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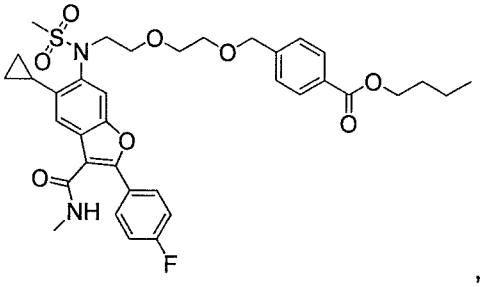

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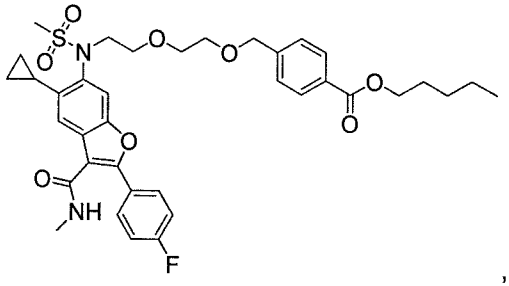

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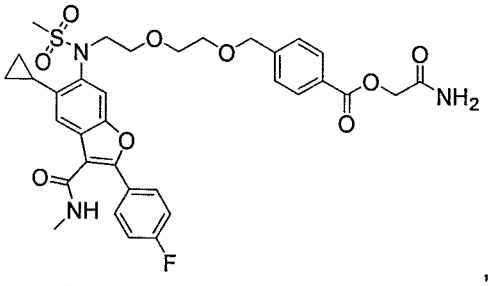

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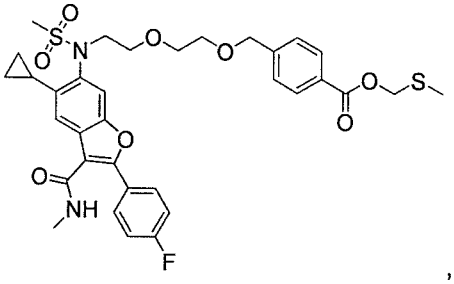

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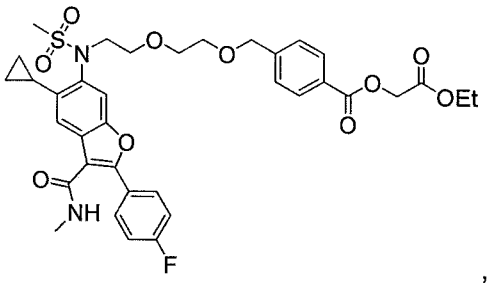

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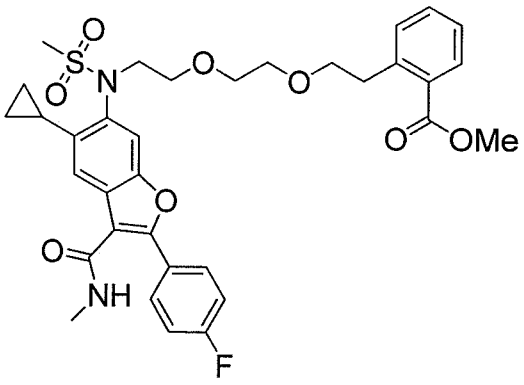

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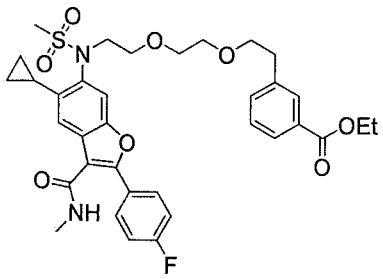

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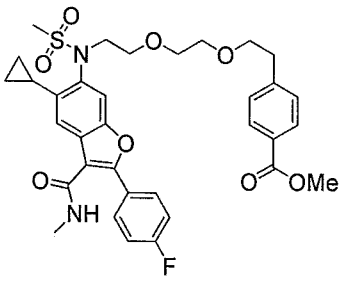

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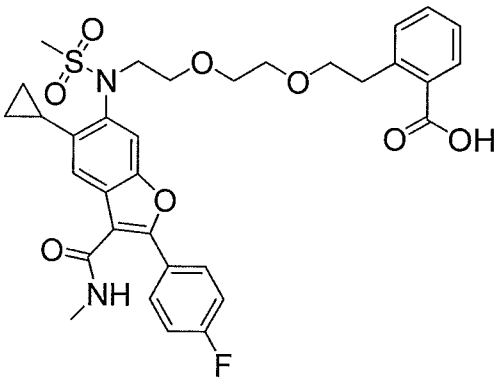

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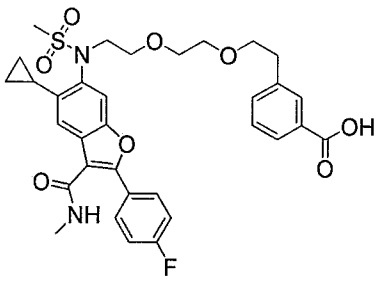

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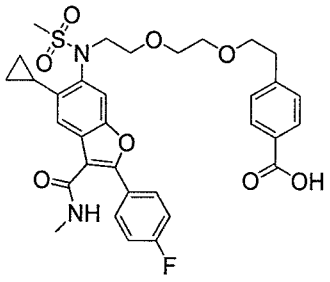

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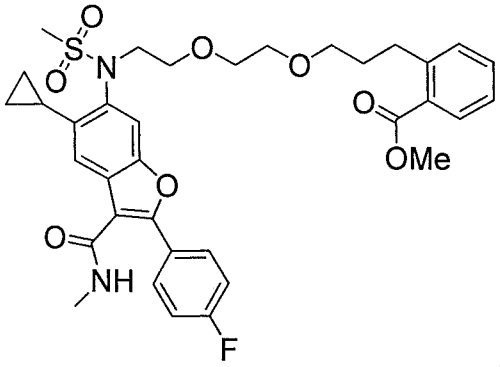

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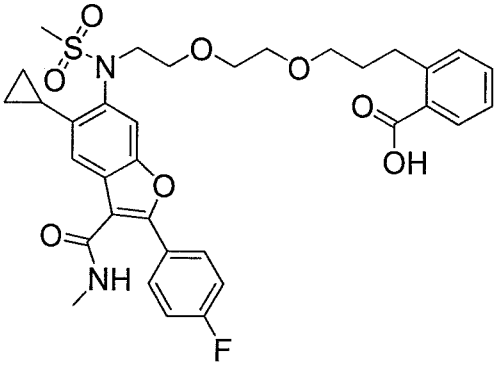

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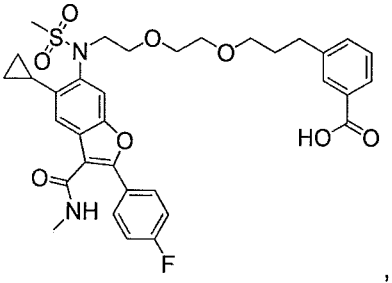

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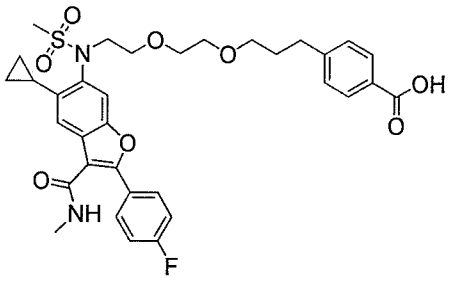

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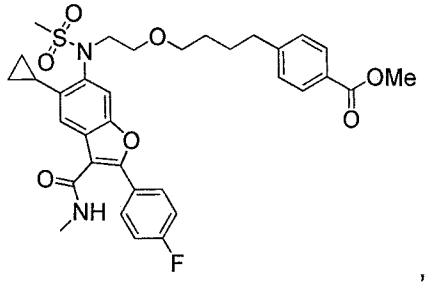

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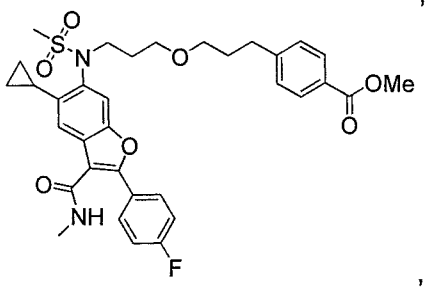

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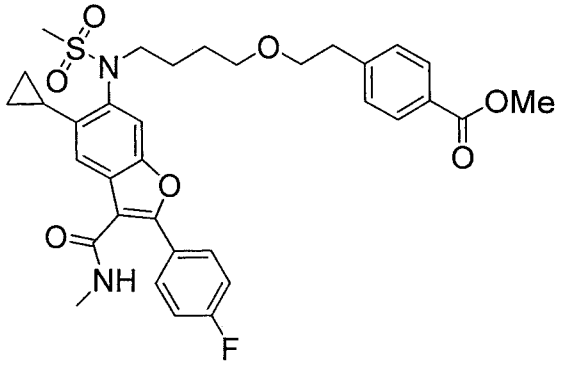

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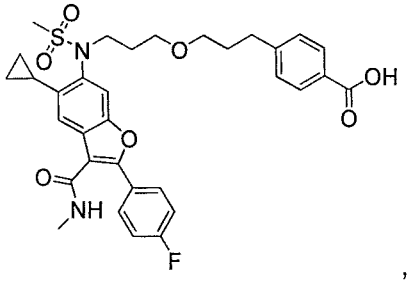

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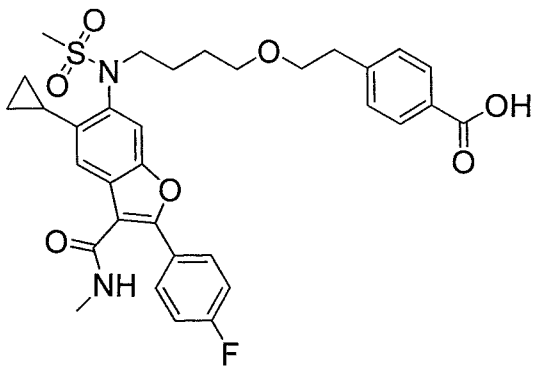

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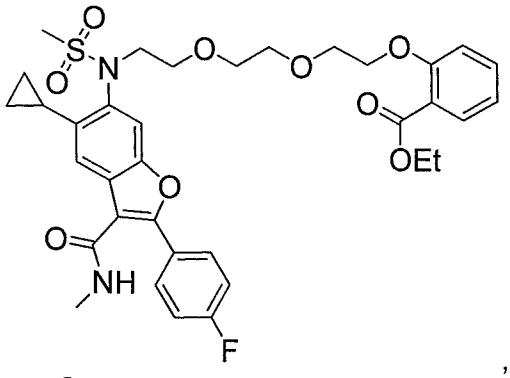

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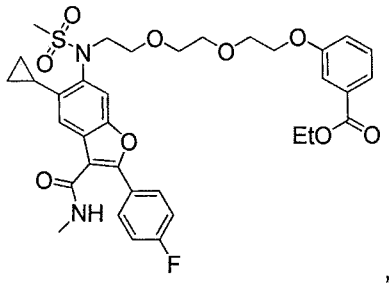

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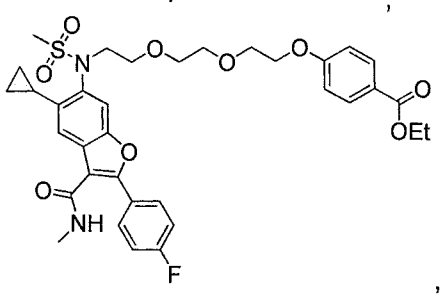

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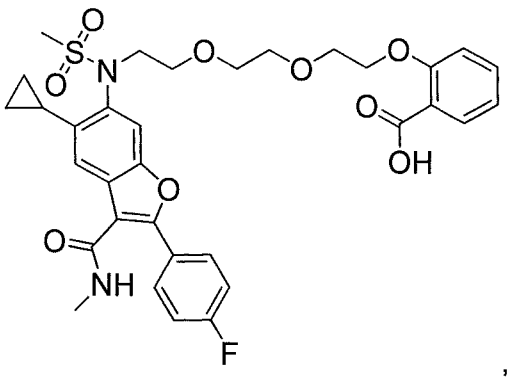

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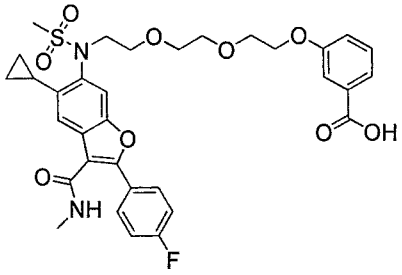

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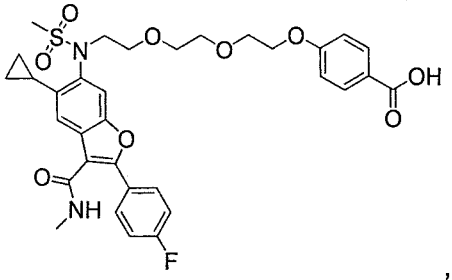

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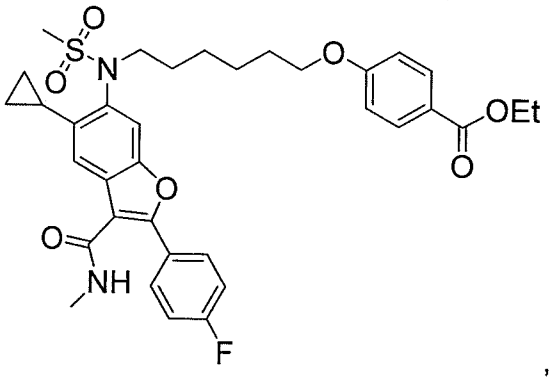

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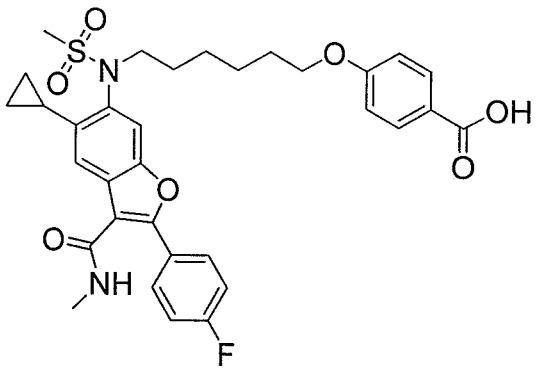
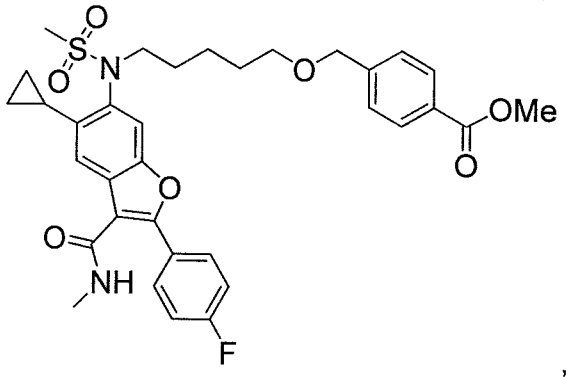
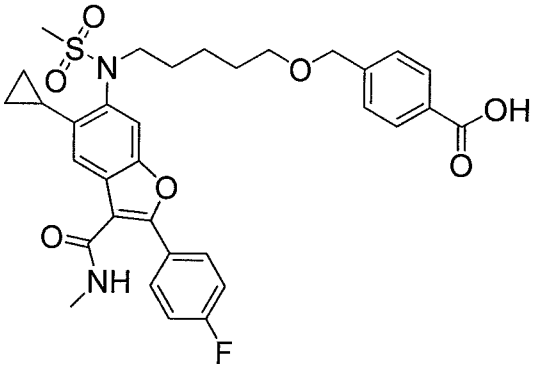
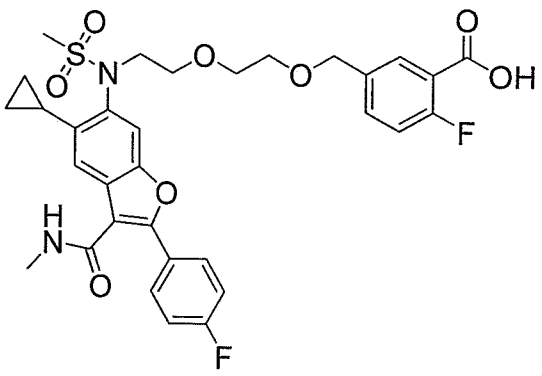
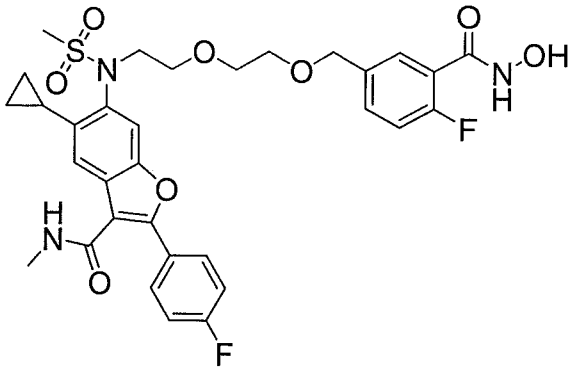
15-8 

16-6 

16-7 

17A-8A 



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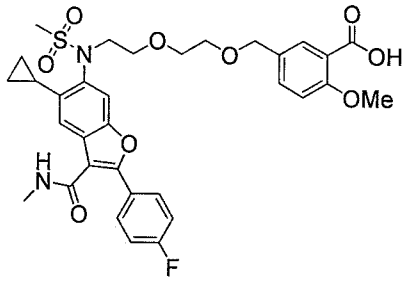

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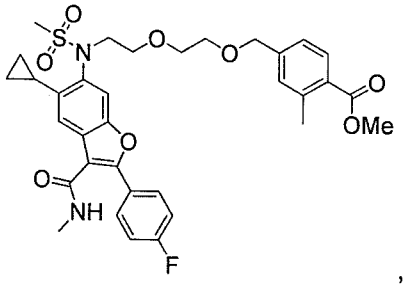

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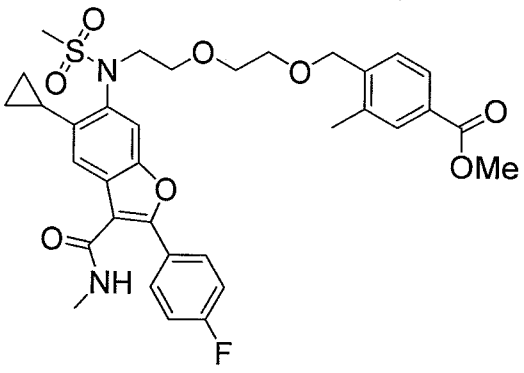

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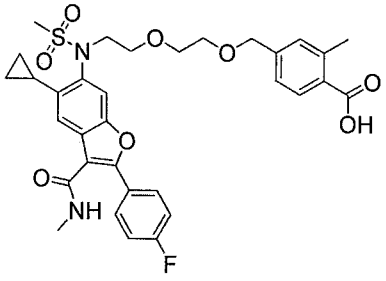

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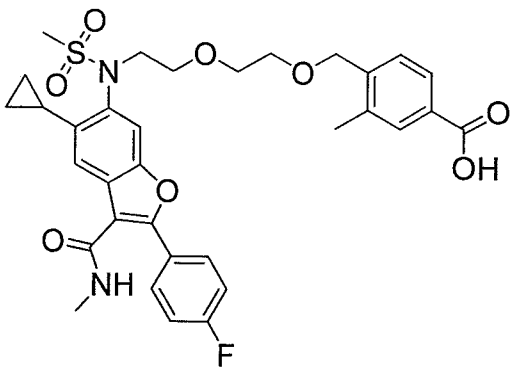

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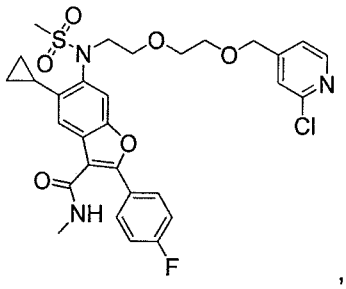

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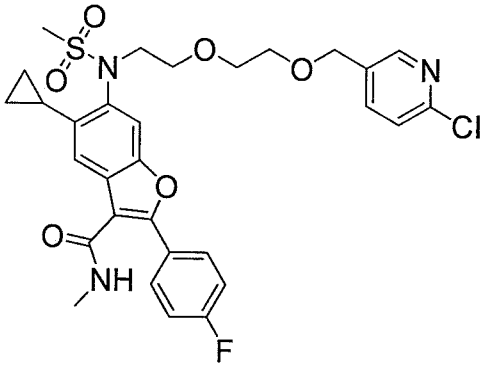

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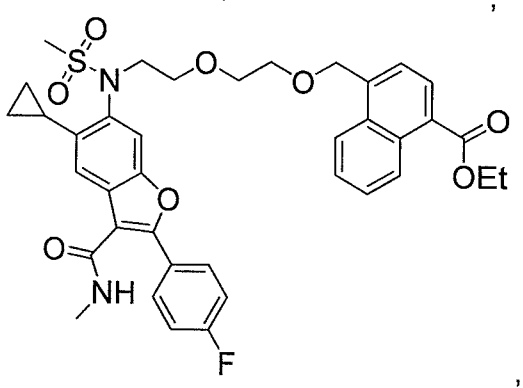

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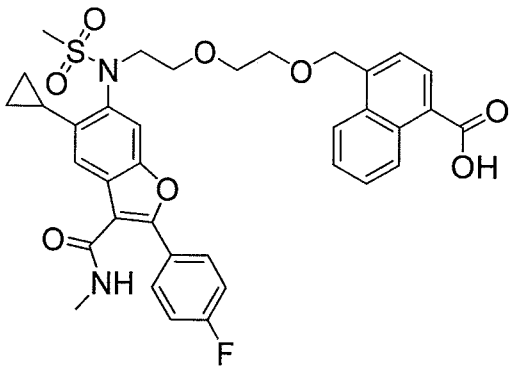

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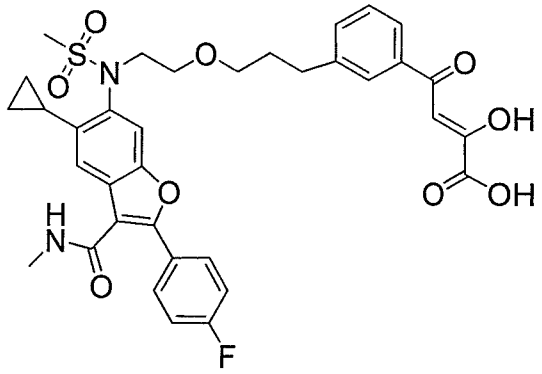

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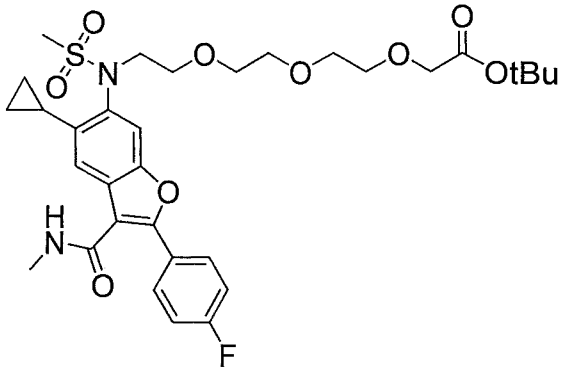

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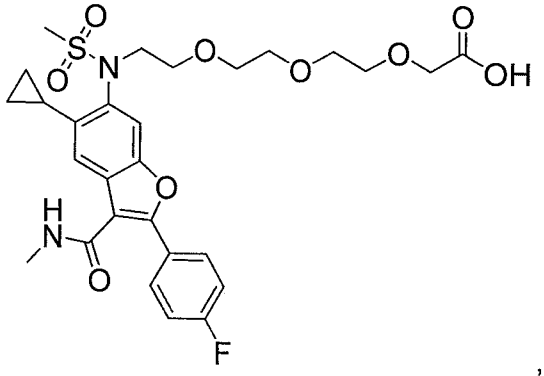

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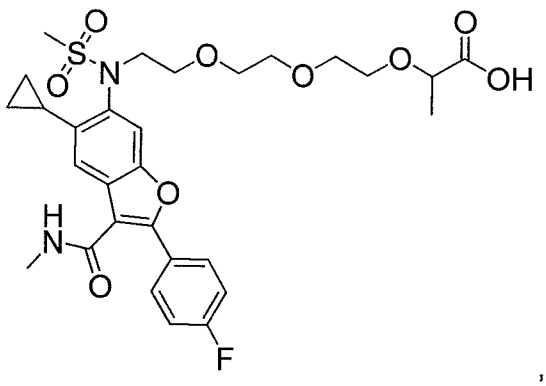

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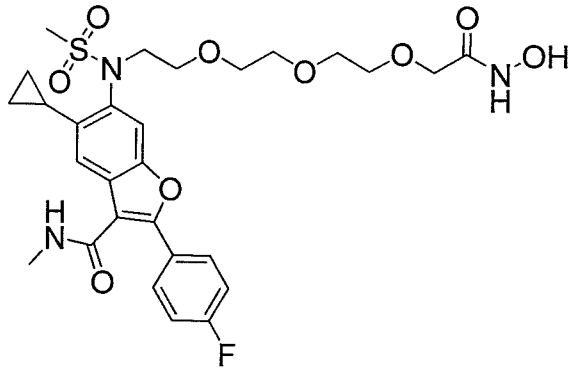

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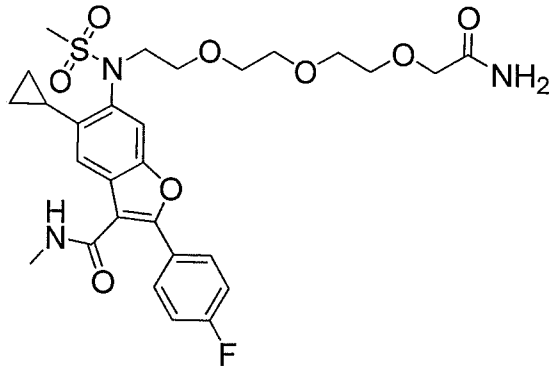

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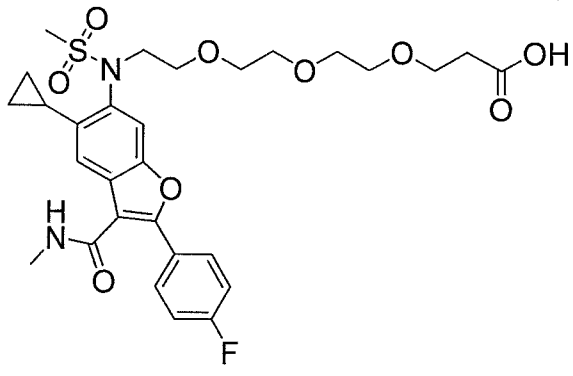

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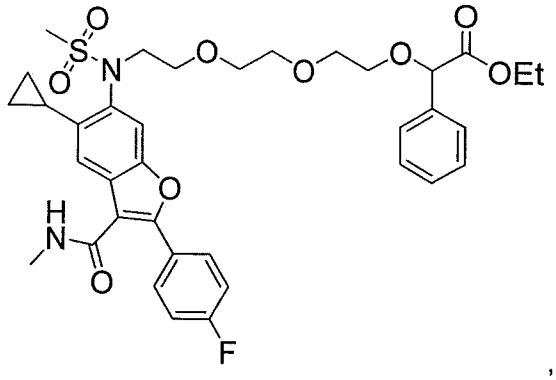

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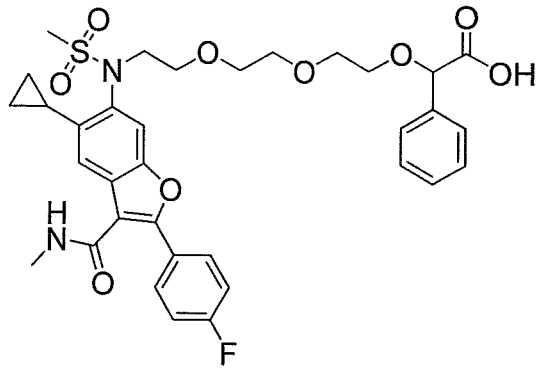

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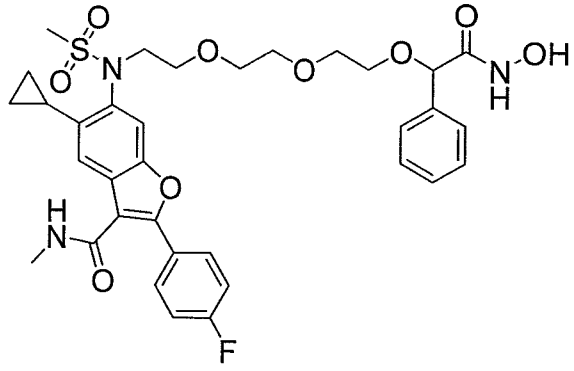

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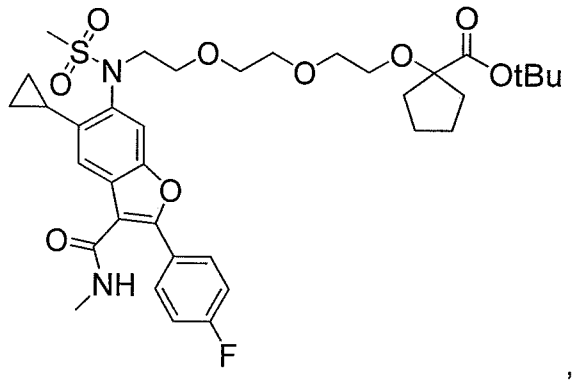
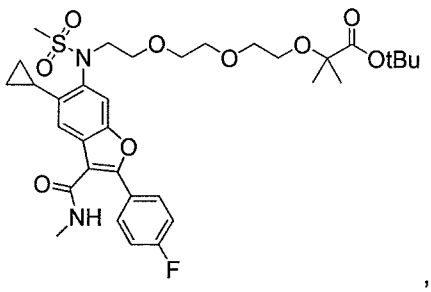


26-6A ,



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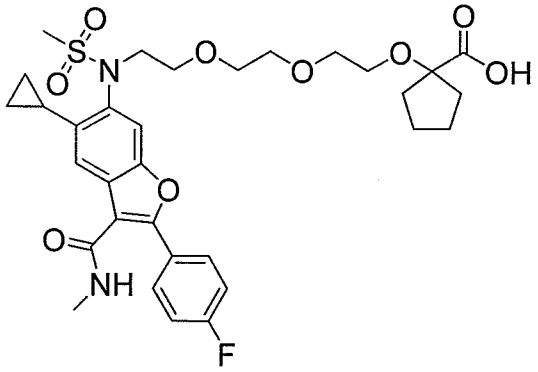

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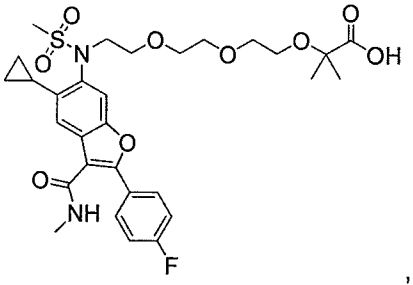

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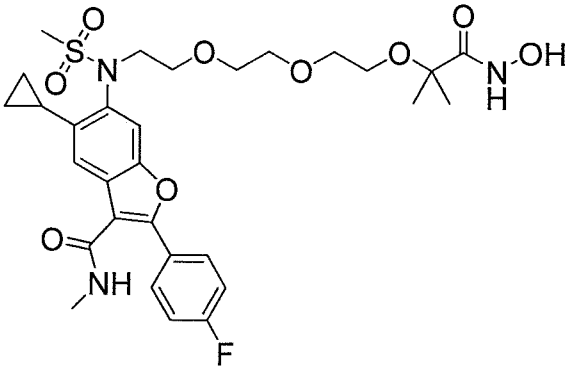

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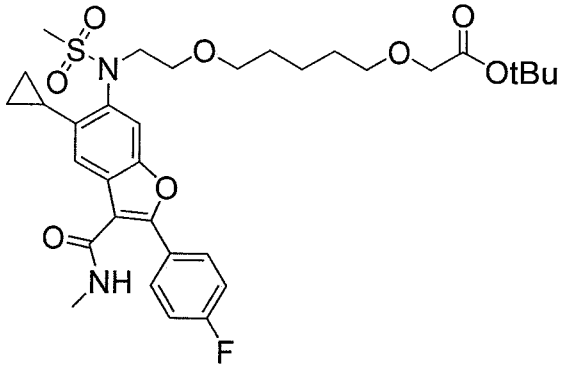

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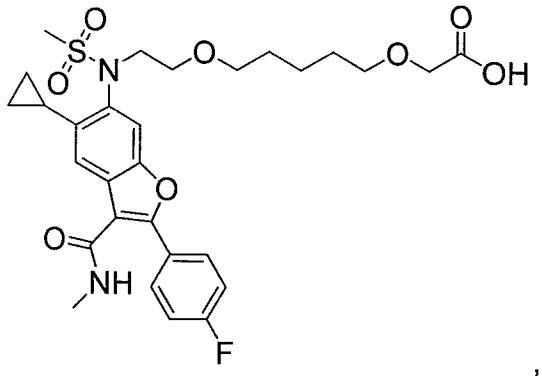

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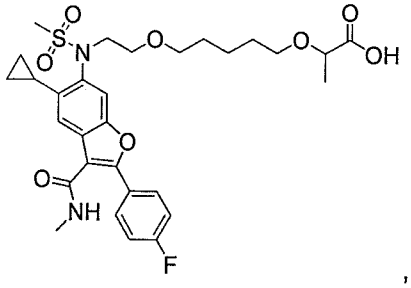

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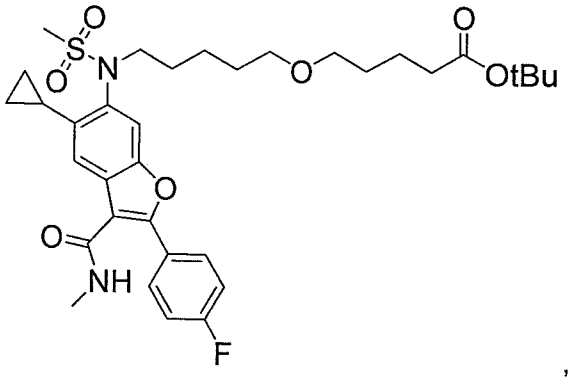

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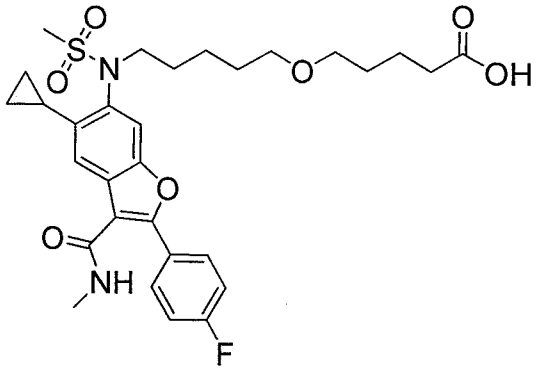

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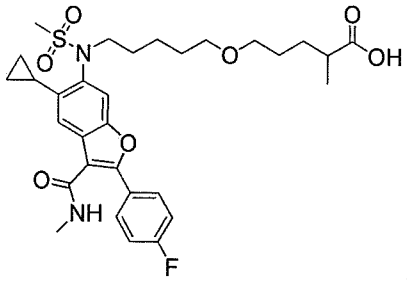

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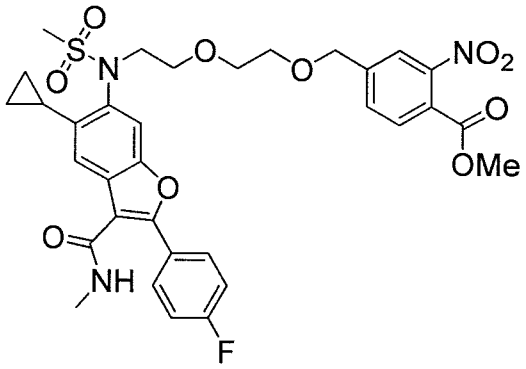

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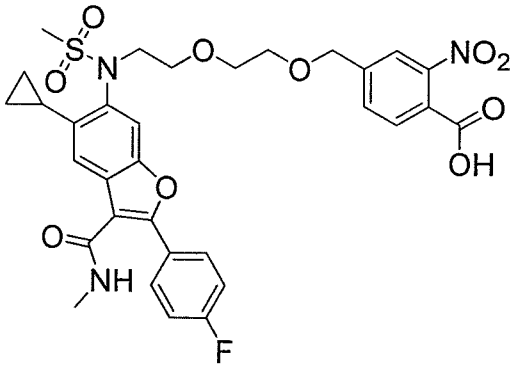

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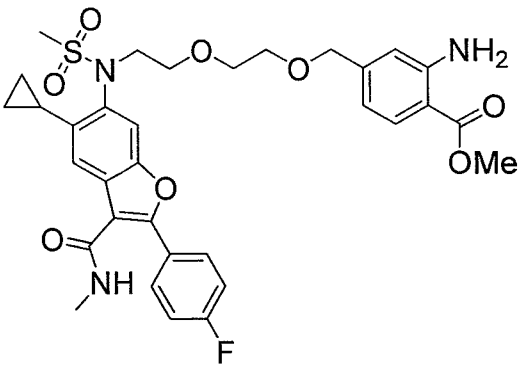
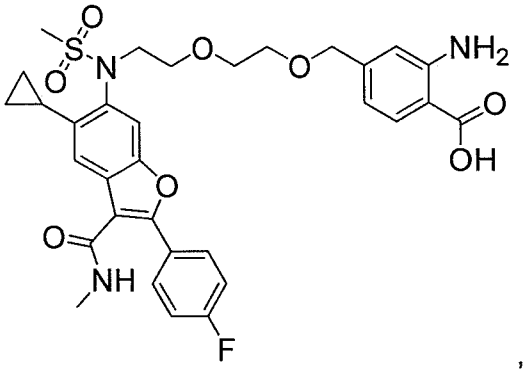
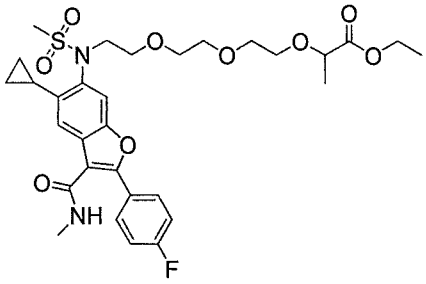
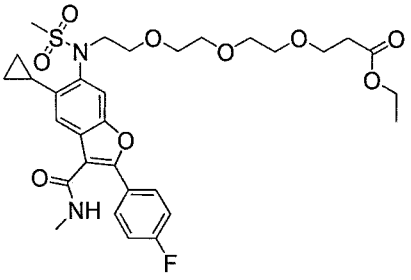
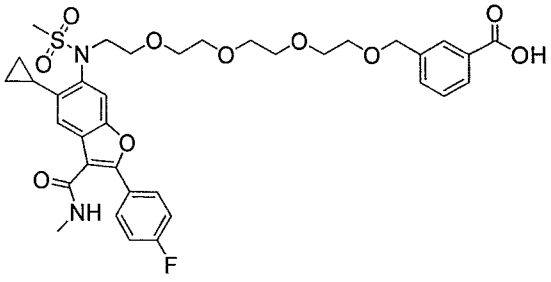
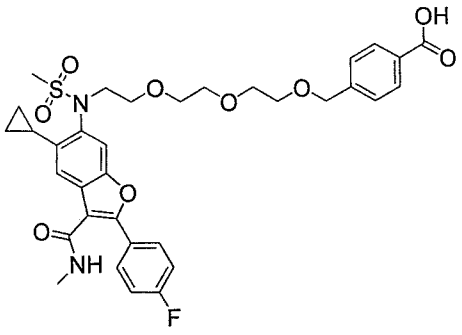
29-9  ,

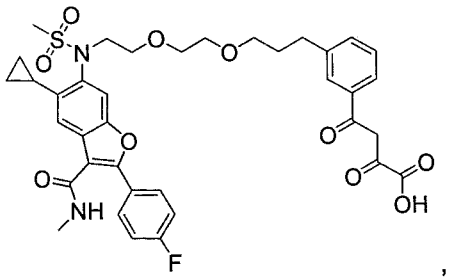
29-10  ,

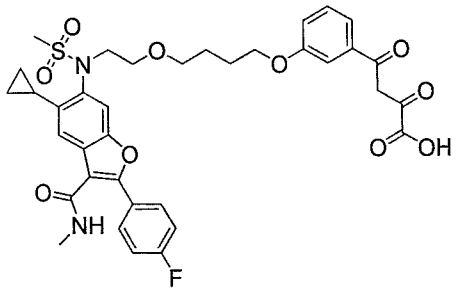
30-2  ,

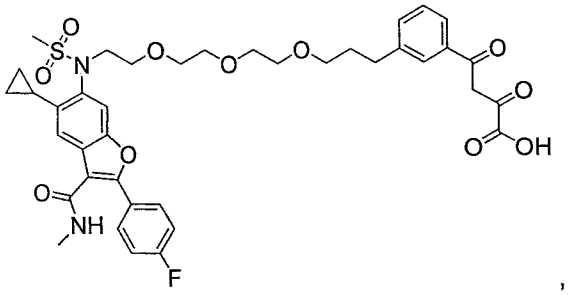
30-3  ,

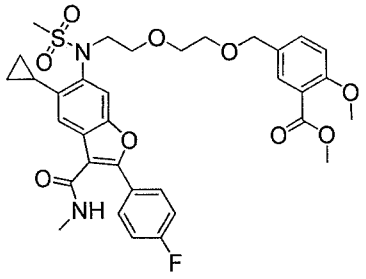
30-4  ,

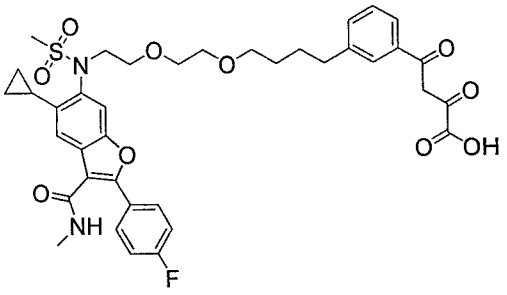
30-7 ,

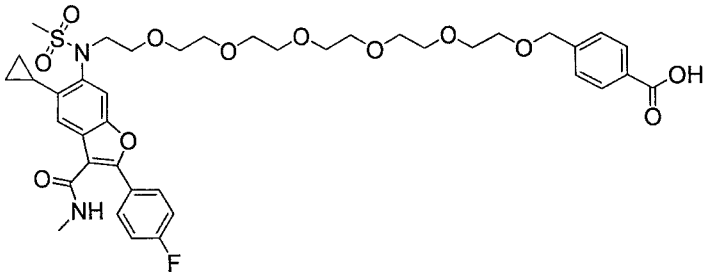
30-8 ,

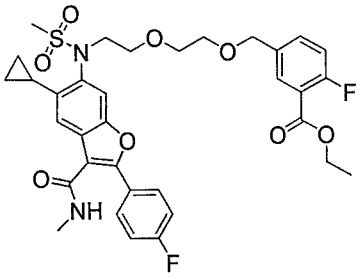
30-9 ,

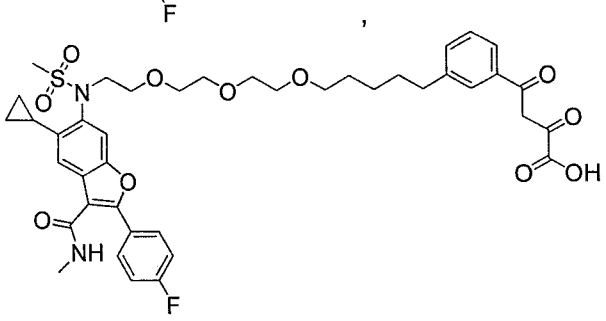
30-10 ,

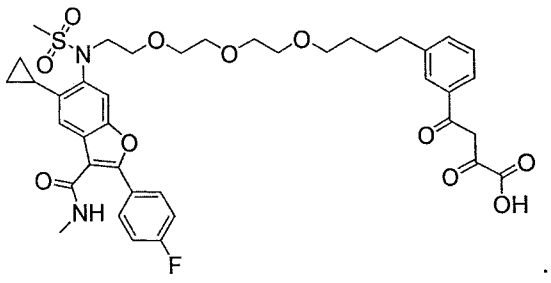
30-11 ,

30-12  ,

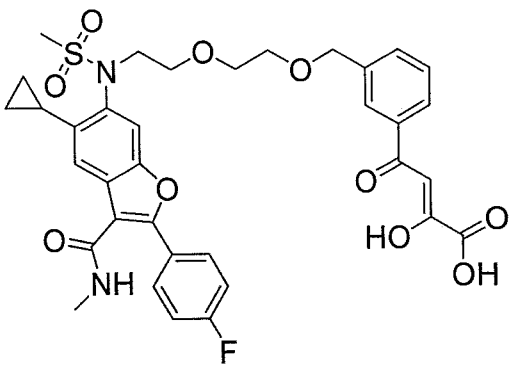
30-13  ,

30-14  ,

30-15  , and

30-16  .

24. A compound, or pharmaceutically acceptable salt thereof, selected from:



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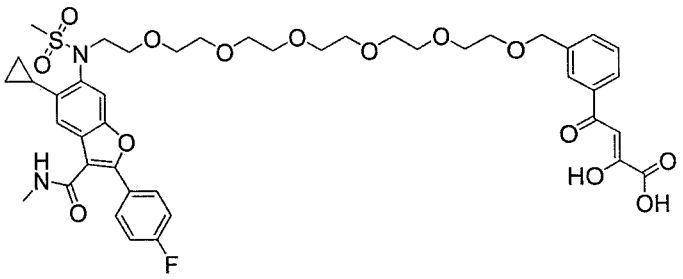
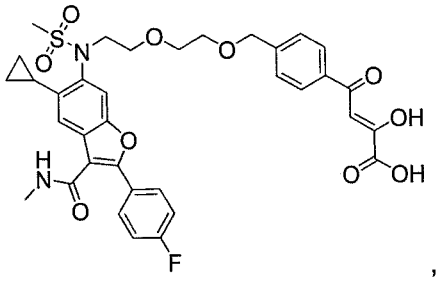


2-10E ,



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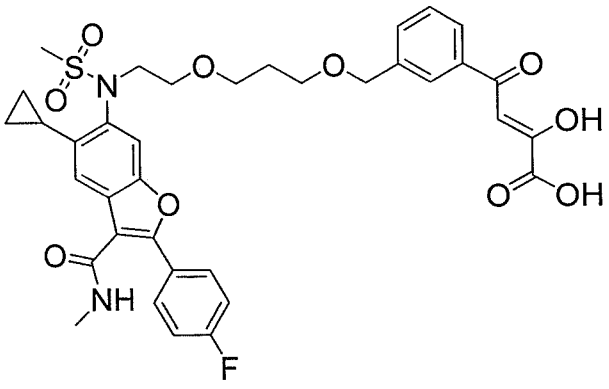
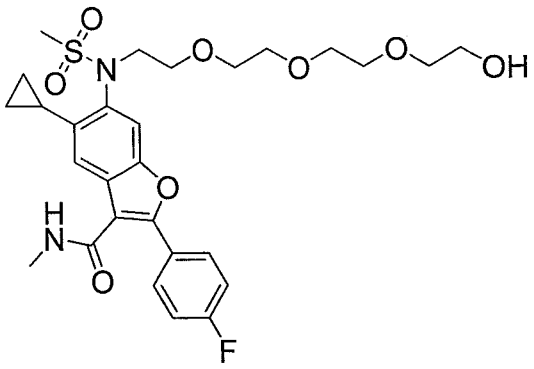
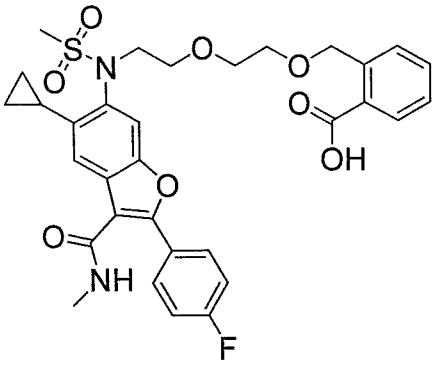


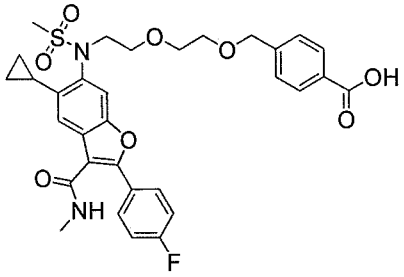
3-8B ,



04-5 ,



06-7A ,



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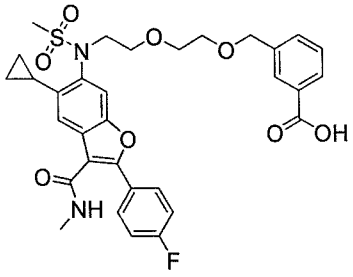

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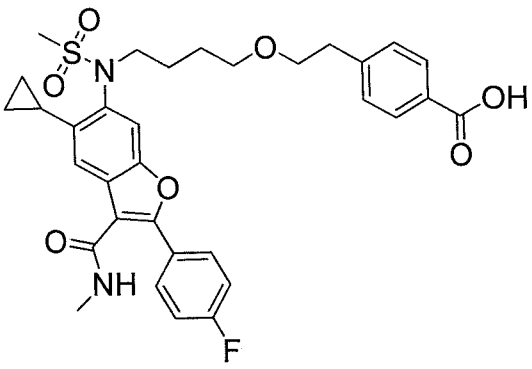

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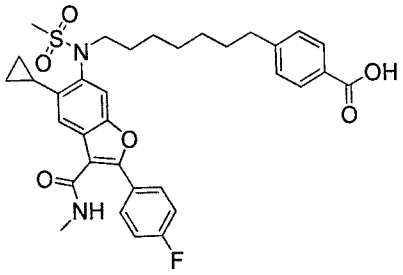

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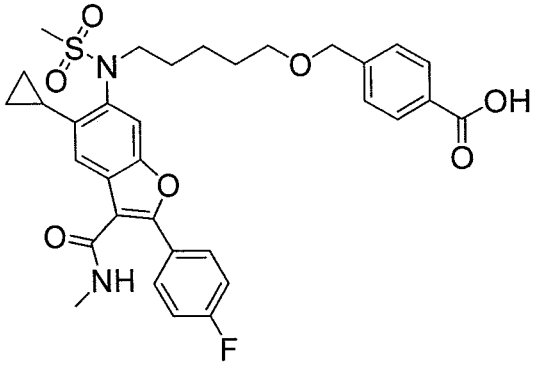

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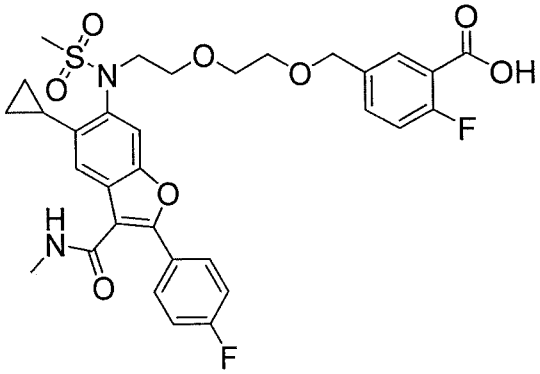
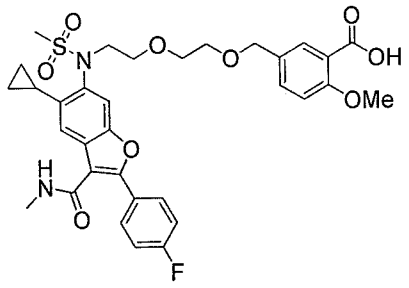
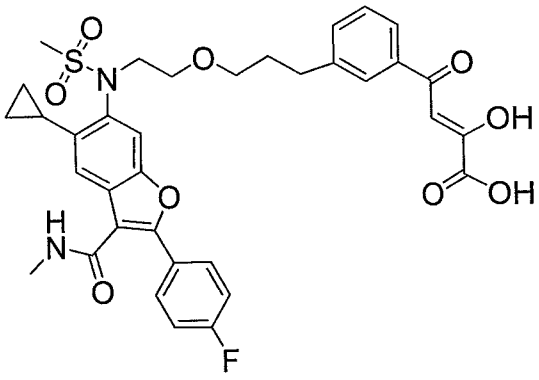


17A-8A ,



17B-8 ,



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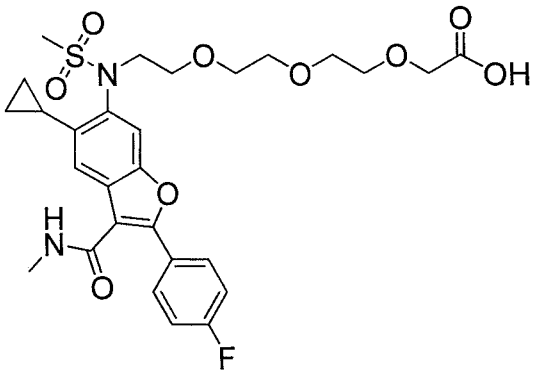

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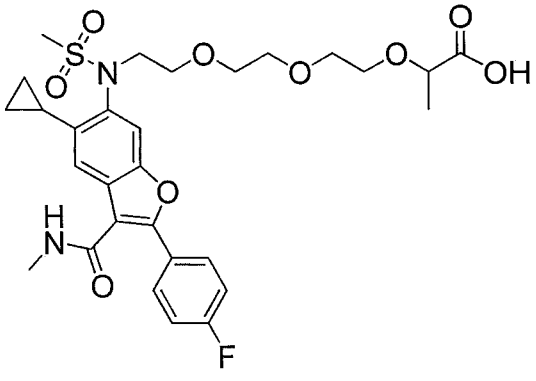

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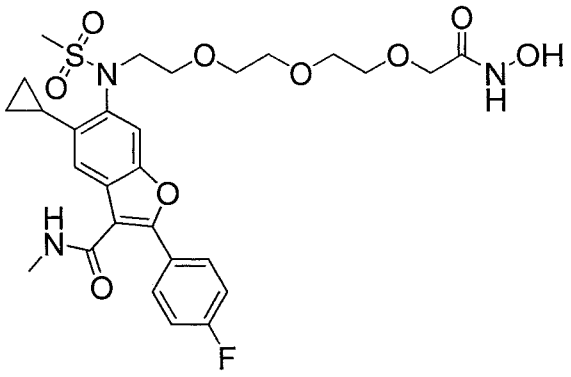
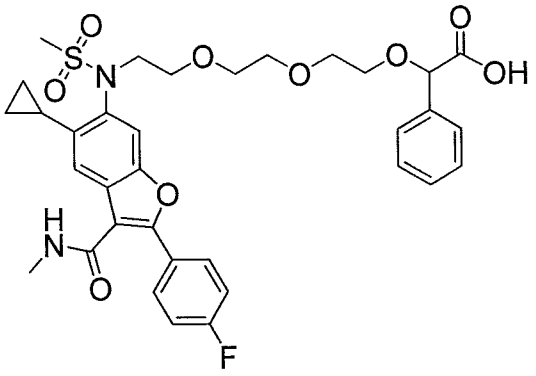
23-6C  , and

25-5  .

25. A composition comprising a compound according to any one of claims 1 to 24 and at least one pharmaceutically acceptable excipient.

26. The use of a compound according to any one of claims 1 to 24, or a composition according to claim 25 in the manufacture of a medicament for treating or preventing hepatitis C virus infection or reactivation in a host.

27. The use according to claim 26, wherein the host is to be further administered with at least one active agent selected from the group consisting of interferons, ribavirin, nucleoside HCV NS5B polymerase inhibitors, non-nucleoside HCV NS5B polymerase inhibitors, HCV NS3-4A protease inhibitors, HCV NS5A inhibitors, HCV entry inhibitors, HCV NS3 inhibitors, HCV NS3 helicase inhibitors, HCV NS4B inhibitors, and human cyclophilin inhibitors.

28. A combination, comprising a compound of any of claims 1-24, together with at least one active agent selected from interferons, ribavirin, nucleoside HCV NS5B polymerase inhibitors, non-nucleoside HCV NS5B polymerase inhibitors, HCV NS3-4A protease inhibitors, HCV NS5A inhibitors, HCV entry inhibitors, HCV NS3 inhibitors, HCV NS3 helicase inhibitors, HCV NS4B inhibitors, and human cyclophilin inhibitors.

29. A combination, comprising a composition of claim 25, together with a composition comprising at least one active agent selected from interferons, ribavirin, nucleoside HCV NS5B polymerase inhibitors, non-nucleoside HCV NS5B polymerase inhibitors, HCV NS3-4A protease inhibitors, HCV NS5A inhibitors, HCV entry inhibitors, HCV NS3 inhibitors, HCV NS3 helicase inhibitors, HCV NS4B inhibitors, and human cyclophilin inhibitors and a pharmaceutically acceptable excipient.