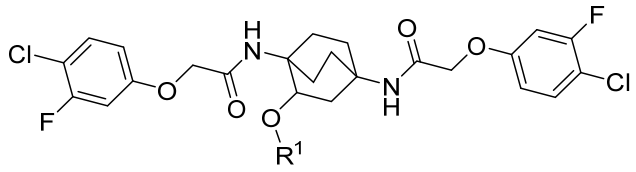
exchange of GDP with GTP in eIF2 is catalyzed by its dedicated guanine nucleotide exchange factor (GEF) eIF2B. eIF2B exists as a decamer ($B1_2\ B2_2\ B3_2\ B4_2\ B5_2$) or dimer of two pentamers in cells (Gordiyenko, Y. et al, *Nat Commun* (2014) 5:3902; Wortham, N.C. et al, *FASEB J* (2014) 28:2225-2237). Molecules such as ISRIB interact with and stabilize the eIF2B dimer conformation, thereby enhancing intrinsic GEF activity and making cells less sensitive to the cellular effects of phosphorylation of eIF2α (Sidrauski, C. et al, *eLife* (2015) e07314; Sekine, Y. et al, *Science* (2015) 348:1027-1030). As such, small molecule therapeutics that can modulate eIF2B activity may have the potential to attenuate the PERK branch of the UPR and the overall ISR, and therefore may be used in the prevention and/or treatment of various diseases, such as a neurodegenerative disease, a leukodystrophy, a cancer, an inflammatory disease, an autoimmune disease, a viral infection, a skin disease, a fibrotic disease, a hemoglobin disease, a kidney disease, a hearing loss condition, an ocular disease, a musculoskeletal disease, or a metabolic disease.

SUMMARY

[004a] In one aspect of the present disclosure, there is provided a compound represented by Formula (I):

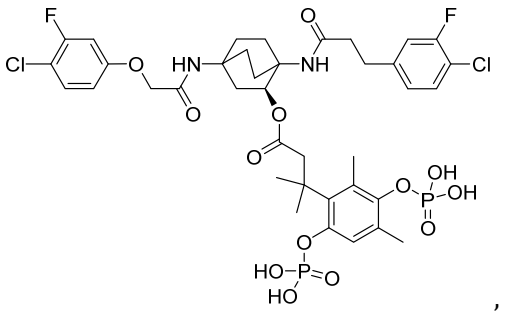
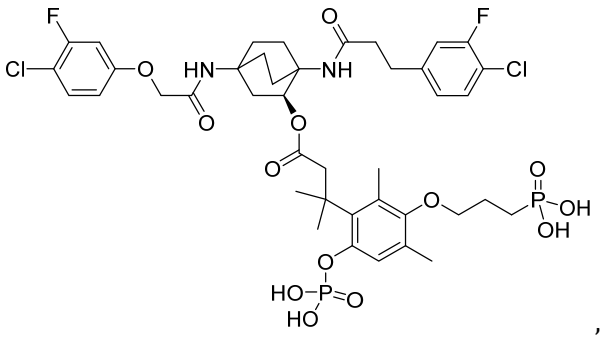
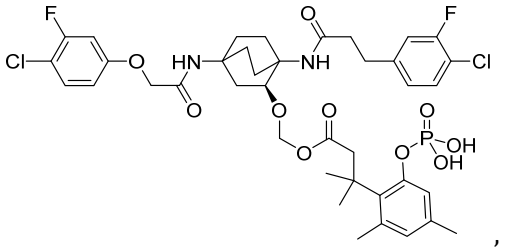
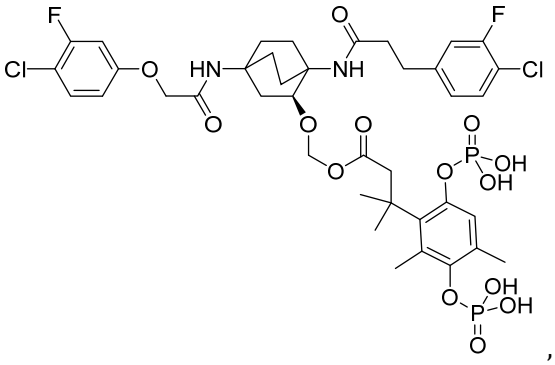


(I);

or a pharmaceutically acceptable salt thereof, wherein:

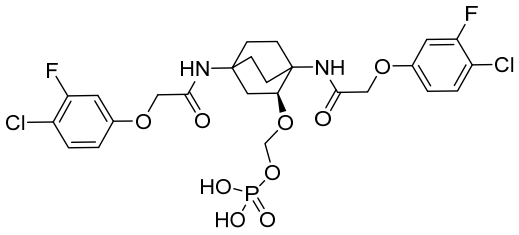
R^1 is selected from the group consisting of -C(O)-C_{1-4}alkyl, -C(O)-O-C_{1-4}alkyl, -C(O)-N(R^a)-C_{1-4}alkyl, -C(O)-C_{1-4}alkylene-C_{1-4}alkoxy, -C(O)-C_{1-4}alkylene-O-C_{1-4}alkylene-C_{1-4}alkoxy, -methylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-O-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-N(R^a)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2$)(O-C_{1-5}alkylene-P(O)$(OH)_2$), -methylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$ or -methylene-O-C(O)C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-O-C_{1-5}alkylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-N(R^a)-heteroarylene-C_{1-2}alkylene-O-P(O)$(OH)_2$, -P(O)$(OH)_2$, -SO_3H, -$SO_2NR^aR^b$, -C(O)-heteroaryl, -C(O)-C_{1-5}alkylene-O-C_{1-5}alkylene-phenyl and methylene-C_{1-5}alkoxide;

wherein -C(O)-C_{1-4}alkyl is substituted by one or two substituents each independently selected from the group consisting of –NR^aR^b and -CO_2H; and wherein -C(O)-O-C_{1-4}alkyl, -


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,

,

,

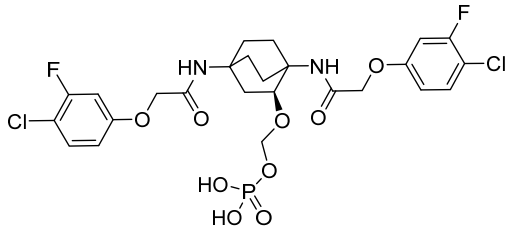
or a pharmaceutically acceptable salt thereof.

[004c] In another aspect of the present disclosure, there is provided a compound, wherein the compound is:



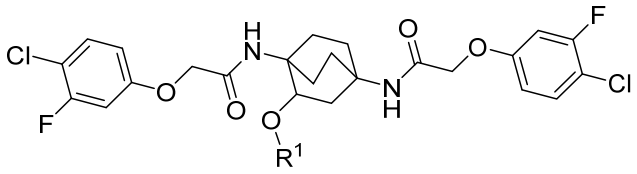
, or a pharmaceutically acceptable salt, thereof.

[004d] In a further aspect of the present disclosure, there is provided a compound, wherein the compound is



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[005] In one example, described herein is a compound represented by Formula (I):



(I);

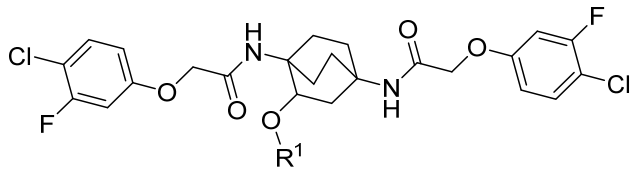
or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof, wherein:

R^1 is selected from the group consisting of -C(O)-C_{1-4}alkyl, -C(O)-O-C_{1-4}alkyl, -C(O)-N(R^a)-C_{1-4}alkyl, -C(O)-C_{1-4}alkylene-C_{1-4}alkoxy, -C(O)-C_{1-4}alkylene-O-C_{1-4}alkylene-C_{1-4}alkoxy, -methylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-O-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-N(R^a)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2$)(O-C_{1-5}alkylene-P(O)$(OH)_2$), -methylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -methylene-O-C(O)C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-O-C_{1-5}alkylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-N(R^a)-heteroarylene-C_{1-2}alkylene-O-P(O)$(OH)_2$, -P(O)$(OH)_2$, -SO_3H, -$SO_2NR^aR^b$, -C(O)-heteroaryl, -C(O)-C_{1-5}alkylene-O-C_{1-5}alkylene-phenyl and methylene-C_{1-5}alkoxide;

wherein -C(O)-C_{1-4}alkyl is substituted by one or two substituents each independently selected from the group consisting of –NR^aR^b and -CO_2H; and wherein -C(O)-O-C_{1-4}alkyl, -C(O)-N(R^a)-C_{1-4}alkyl, -C(O)-C_{1-4}alkylene-C_{1-4}alkoxy, -C(O)-C_{1-4}alkylene-O-C_{1-4}alkylene-C_{1-}

CLAIMS

1. A compound represented by Formula (I):



(I);

or a pharmaceutically acceptable salt thereof, wherein:

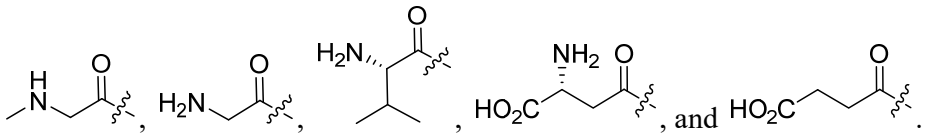
R^1 is selected from the group consisting of -C(O)-C_{1-4}alkyl, -C(O)-O-C_{1-4}alkyl, -C(O)-N(R^a)-C_{1-4}alkyl, -C(O)-C_{1-4}alkylene-C_{1-4}alkoxy, -C(O)-C_{1-4}alkylene-O-C_{1-4}alkylene-C_{1-4}alkoxy, -methylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-O-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-N(R^a)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2$)(O-C_{1-5}alkylene-P(O)$(OH)_2$), -methylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$ or -methylene-O-C(O)C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-O-C_{1-5}alkylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-N(R^a)-heteroarylene-C_{1-2}alkylene-O-P(O)$(OH)_2$, -P(O)$(OH)_2$, -SO_3H, -$SO_2NR^aR^b$, -C(O)-heteroaryl, -C(O)-C_{1-5}alkylene-O-C_{1-5}alkylene-phenyl and methylene-C_{1-5}alkoxide;

wherein -C(O)-C_{1-4}alkyl is substituted by one or two substituents each independently selected from the group consisting of –NR^aR^b and -CO_2H; and wherein -C(O)-O-C_{1-4}alkyl, -C(O)-N(R^a)-C_{1-4}alkyl, -C(O)-C_{1-4}alkylene-C_{1-4}alkoxy, -C(O)-C_{1-4}alkylene-O-C_{1-4}alkylene-C_{1-4}alkoxy, methylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-O-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-N(R^a)-C_{1-5}alkylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2$)(O-C_{1-5}alkylene-P(O)$(OH)_2$), -methylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$ or -methylene-O-C(O)C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$, -C(O)-O-C_{1-5}alkylene-O-C(O)C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$, -C(O)-heteroaryl, -C(O)-C_{1-5}alkylene-O-C_{1-5}alkylene-phenyl and -C(O)-N(R^a)-heteroarylene-C_{1-2}alkylene-O-P(O)$(OH)_2$ may optionally be substituted by one, two, three or four substituents each independently selected from the group consisting of halogen, -CO_2H, -NR^aR^b and C_{1-2}alkyl (optionally substituted by one, two or three fluorines) and aryl; and

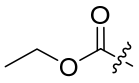
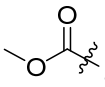
R^a and R^b are independently selected, for each occurrence, from the group consisting of hydrogen and C_{1-3}alkyl.

2. The compound of claim 1, wherein R^1 is -C(O)-C_{1-4}alkyl, wherein -C(O)-C_{1-4}alkyl is substituted by one or two substituents each independently selected from the group consisting of –NR^aR^b and -CO_2H.

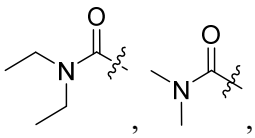
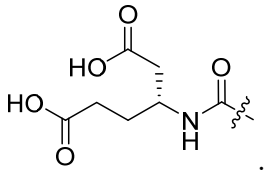
3. The compound of claim 1 or 2, wherein R^1 is selected from the group consisting of



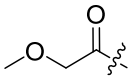
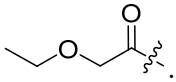
4. The compound of claim 1, wherein R^1 is -C(O)-O-C_{1-4}alkyl.

5. The compound of claim 4, wherein R^1 is selected from the group consisting of  and .

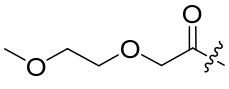
6. The compound of claim 1, wherein R^1 is -C(O)-N(R^a)-C_{1-4}alkyl, wherein -C(O)-N(R^a)-C_{1-4}alkyl may optionally be substituted by one or two $-CO_2H$ groups.

7. The compound of claim 6, wherein R^1 is represented by , and .

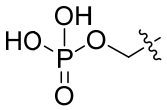
8. The compound of claim 1, wherein R^1 is -C(O)-C_{1-4}alkylene-C_{1-4}alkoxy.

9. The compound of claim 8, wherein R^1 is selected from the group consisting of  and .

10. The compound of claim 1, wherein R^1 is -C(O)-C_{1-4}alkylene-O-C_{1-4}alkylene-C_{1-4}alkoxy.

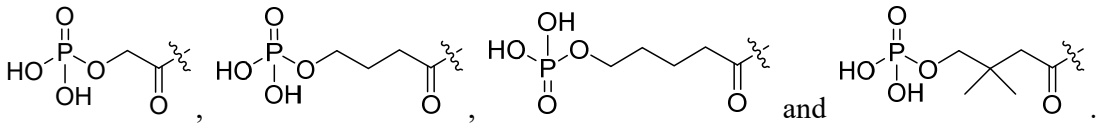
11. The compound of claim 10, wherein R^1 is represented by .

12. The compound of claim 1, wherein R^1 is -methylene-O-P(O)$(OH)_2$.

13. The compound of claim 12, wherein R^1 is represented by .

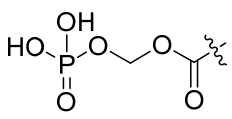
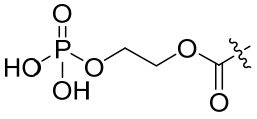
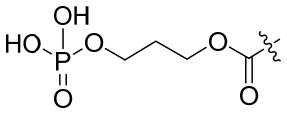
14. The compound of claim 1, wherein R^1 is -C(O)-C_{1-5}alkylene-O-P(O)$(OH)_2$.

15. The compound of claim 14, wherein R^1 is selected from the group consisting of



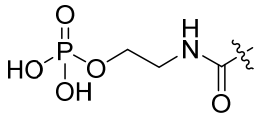
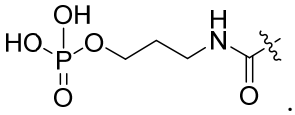
16. The compound of claim 1, wherein R^1 is -C(O)-O-C_{1-5}alkylene-O-P(O)$(OH)_2$.

17. The compound of claim 16, wherein R^1 is selected from the group consisting of

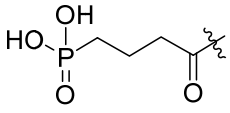
 ,  , and  .

18. The compound of claim 1,wherein R^1 is -C(O)-N(R^a)-C_{1-5}alkylene-O-P(O)$(OH)_2$.

19. The compound of claim 18, wherein R^1 is selected from the group consisting of

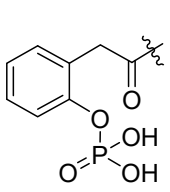
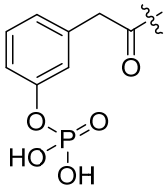
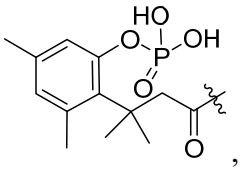
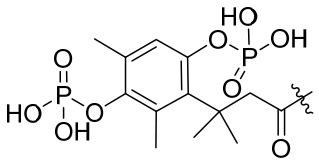
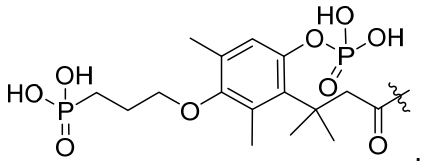
 and  .

20. The compound of claim 1, wherein R^1 is -C(O)-C_{1-5}alkylene-P(O)$(OH)_2$.

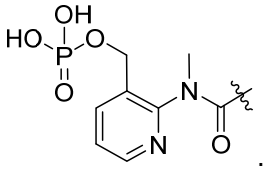
21. The compound of claim 20, wherein R^1 is represented by  .

22. The compound of claim 1, wherein R^1 is -C(O)-C_{1-5}alkylene-phenylene-O-P(O)$(OH)_2$ -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2)_2$ or -C(O)-C_{1-5}alkylene-phenylene-(O-P(O)$(OH)_2$)(O-C_{1-5}alkylene-P(O)$(OH)_2$).

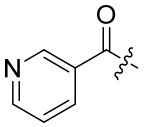
23. The compound of claim 22, wherein R^1 is selected from the group consisting of

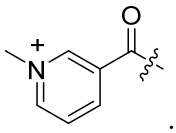
 ,  ,  ,  and  .

24. The compound of claim 1, wherein R^1 is -C(O)-N(R^a)-heteroarylene-C_{1-2}alkylene-O-P(O)$(OH)_2$.

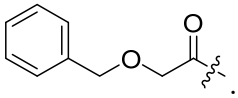
25. The compound of claim 24, wherein R^1 is represented by  .

26. The compound of claim 1, wherein R^1 is -C(O)-heteroaryl.

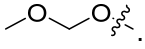
27. The compound of claim 26, wherein R^1 is selected from the group consisting of 

and .

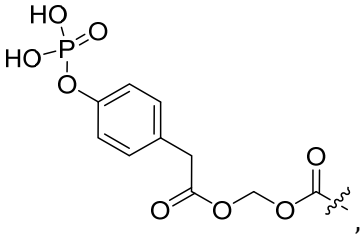
28. The compound of claim 1, wherein R^1 is -C(O)-$C_{1\text{-}5}$alkylene-O-$C_{1\text{-}5}$alkylene-phenyl.

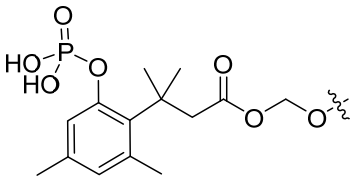
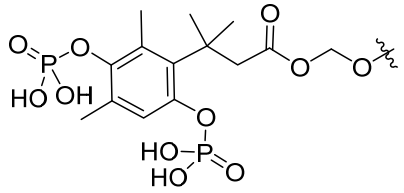
29. The compound of claim 28, wherein R^1 is represented by .

30. The compound of claim 1, wherein R^1 is methylene-$C_{1\text{-}5}$alkoxide.

31. The compound of claim 30, wherein R^1 is represented by .

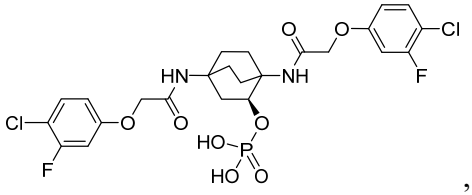
32. The compound of claim 1, wherein R^1 is -C(O)-O-$C_{1\text{-}5}$alkylene-O-C(O)$C_{1\text{-}5}$alkylene-phenylene-O-P(O)$(OH)_2$, -methylene-O-C(O)$C_{1\text{-}5}$alkylene-phenylene-O-P(O)$(OH)_2$ or -methylene-O-C(O)$C_{1\text{-}5}$alkylene-phenylene-(O-P(O)$(OH)_2)_2$.

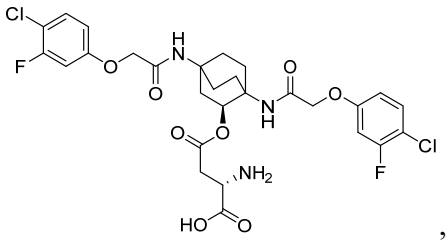
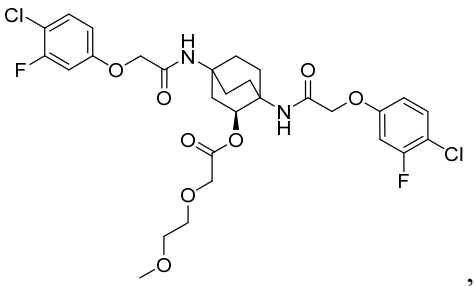
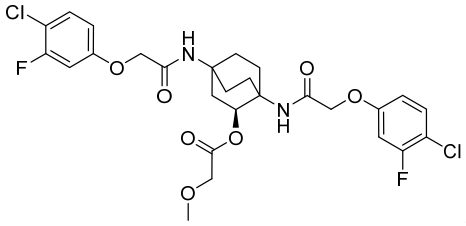
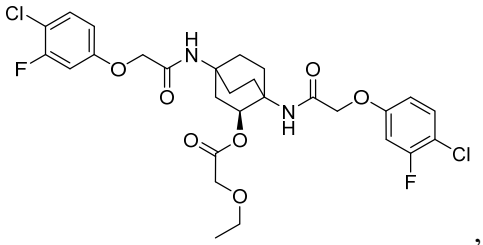
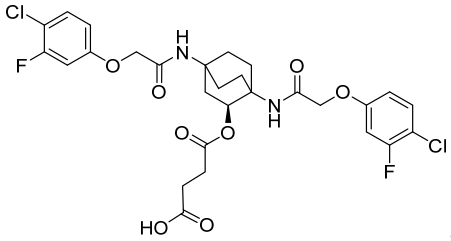
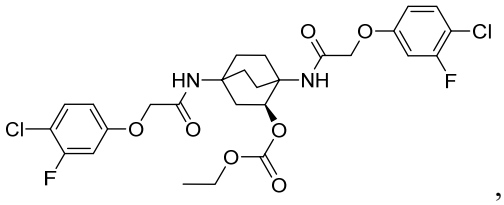
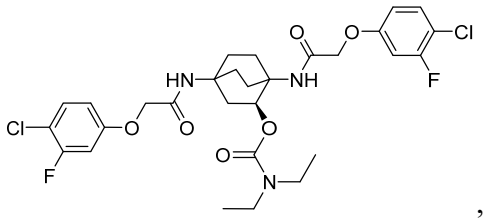
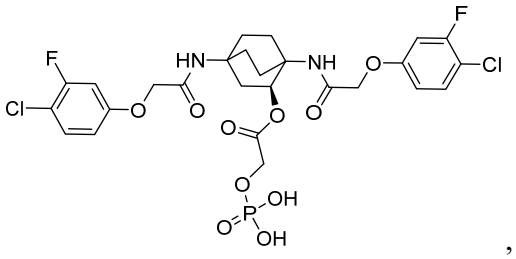
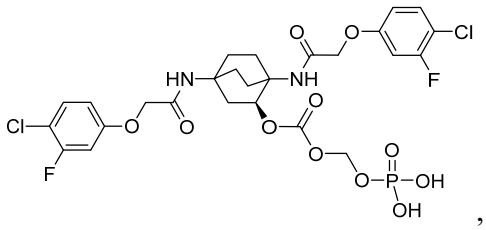
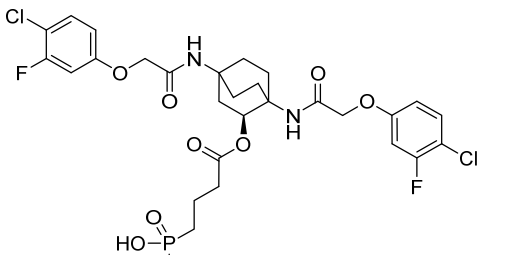
33. The compound of claim 32, wherein R^1 is represented by ,

, and .

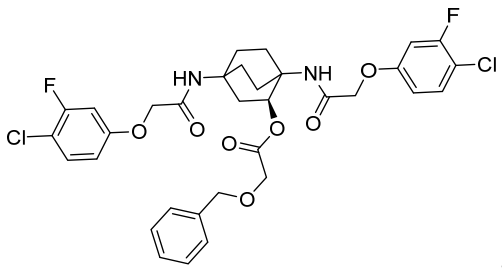
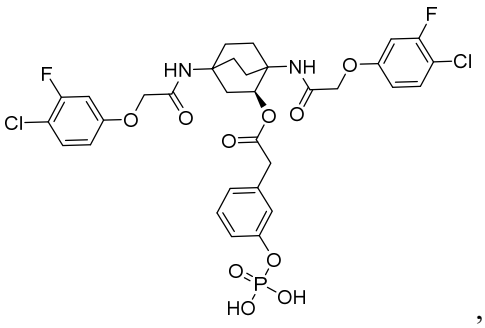
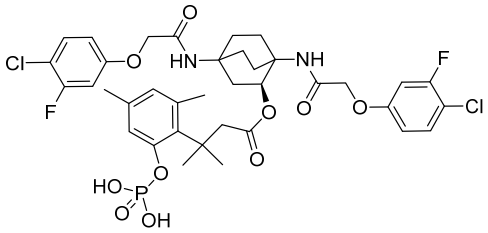
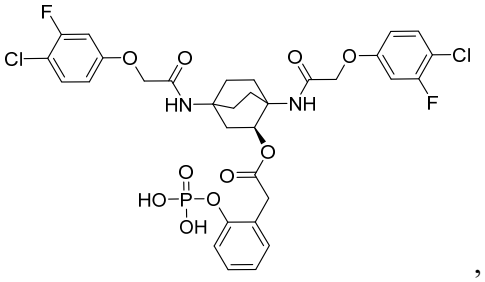
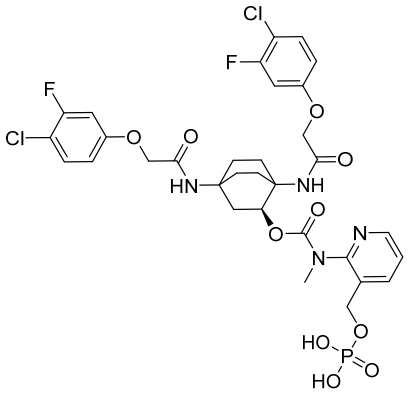
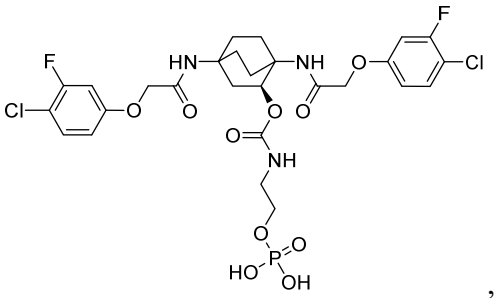
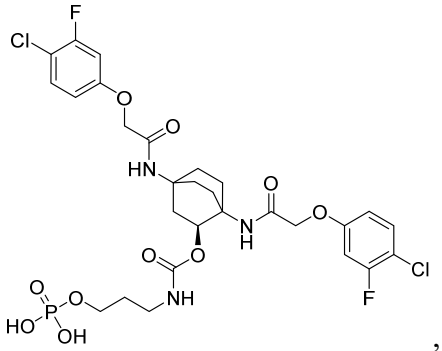
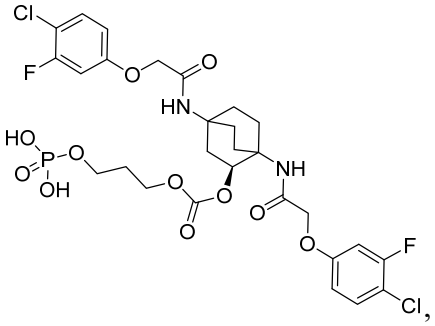
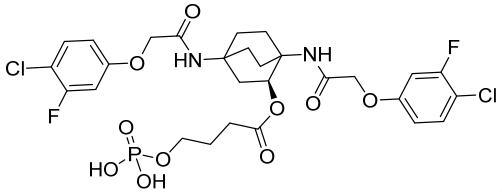
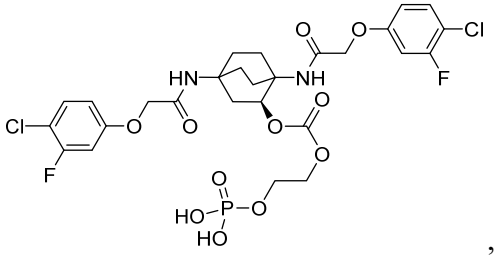
34. The compound of claim 1, wherein R^1 is selected from the group consisting of -P(O)$(OH)_2$, -SO_3H, and -SO_2NH_2.

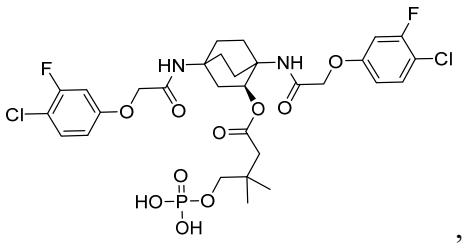
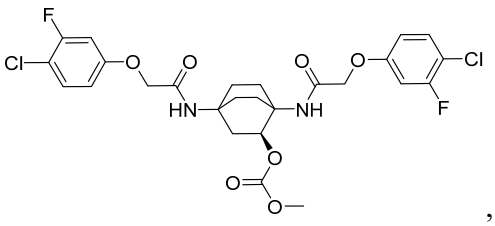
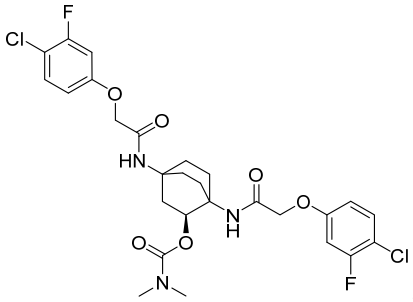
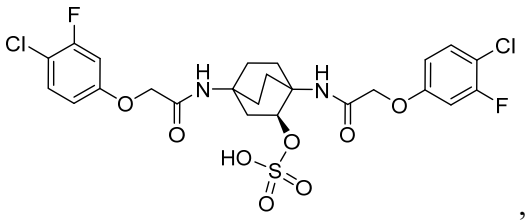
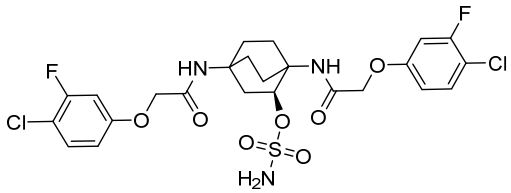
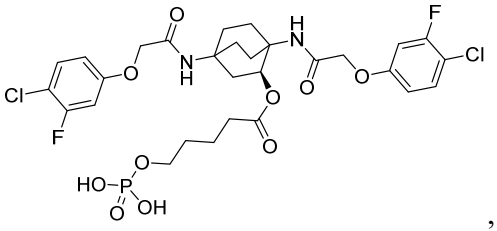
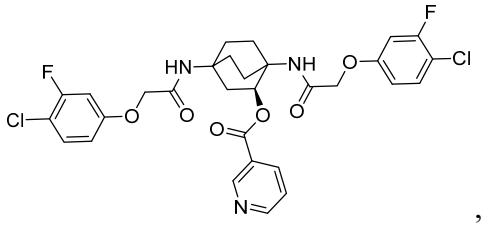
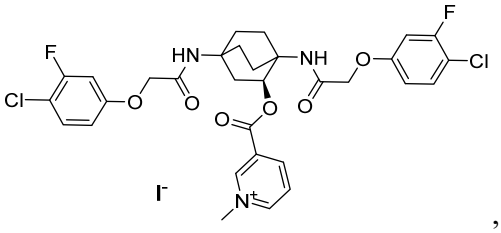
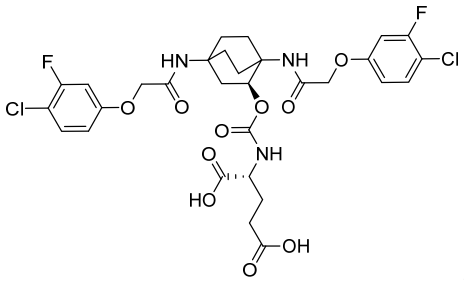
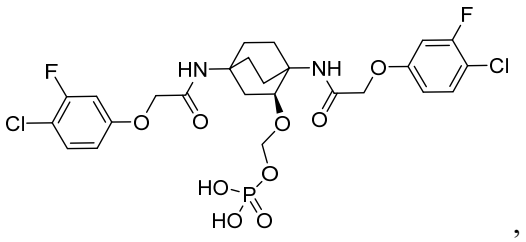
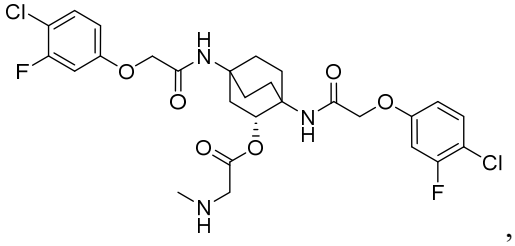
35. A compound selected from the group consisting of:

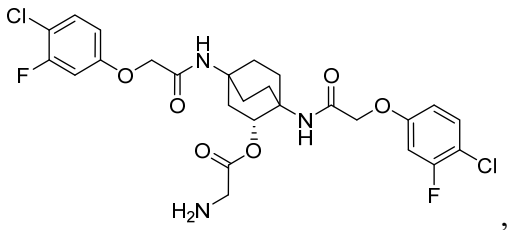
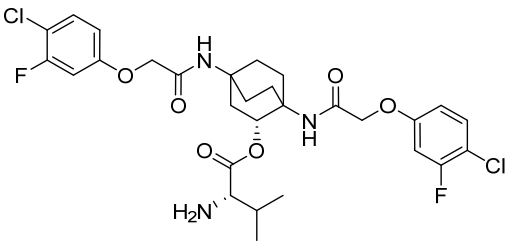
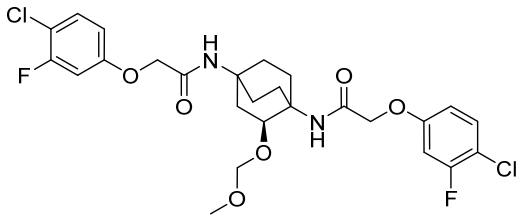
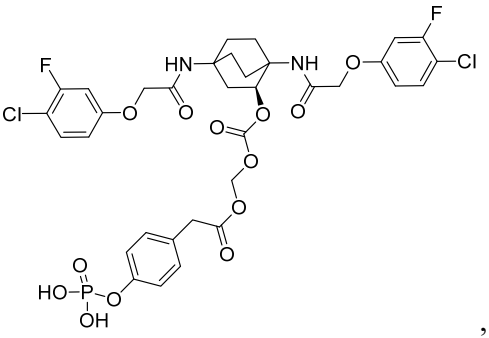
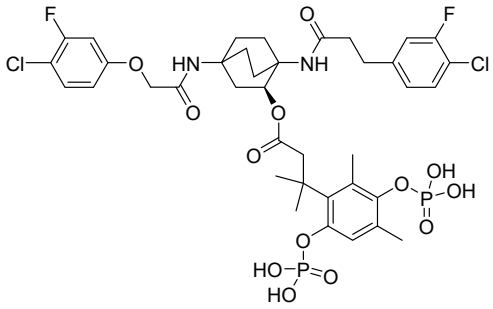
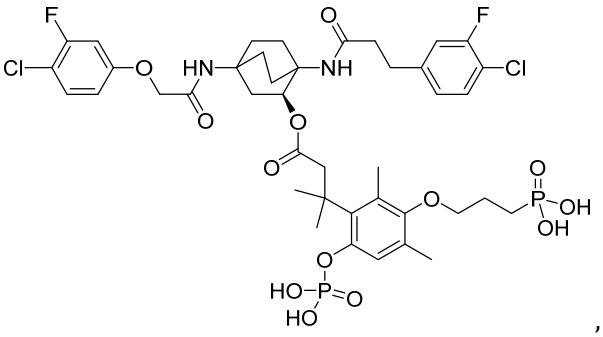
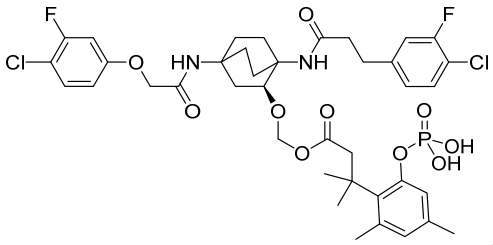
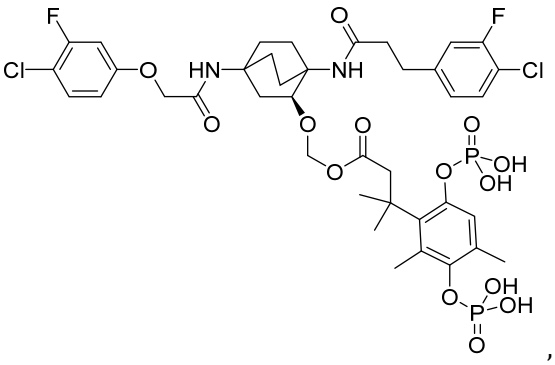
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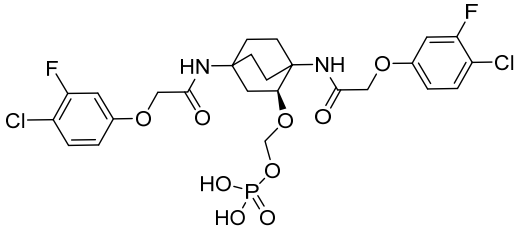

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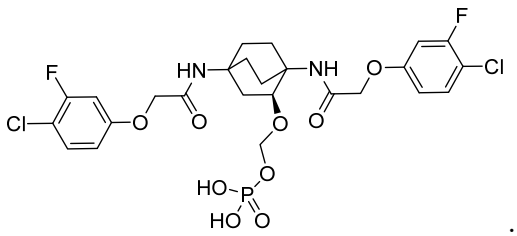

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or a pharmaceutically acceptable salt thereof.

36. A compound, wherein the compound is:


, or a pharmaceutically acceptable salt, thereof.

37. A compound, wherein the compound is 

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