DI-CYCLOPROPYL BASED IL-17A MODULATORS AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of priority of U.S. Provisional Patent Application No. 63/314,257 filed on February 25, 2022, which is incorporated herein by reference in its entirety.

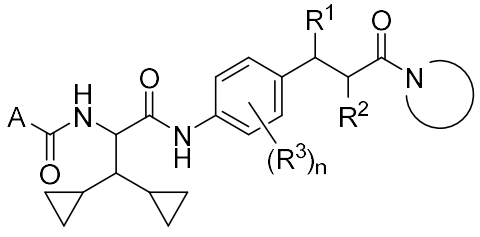
BACKGROUND OF THE INVENTION

[0002] The IL-17 family consists of six cytokines (IL-17A through IL-17F). Interleukin-17A (IL-17A), is an established pro-inflammatory cytokine, which is involved in the induction of IL-6, IL-8, G-CSF, TNF-α, IL-1β, PGE2, and IFN-γ, as well as numerous chemokines and other effectors. IL-17A can form homodimers or heterodimers with its family member, IL-17F and can bind to both IL-17 receptors, IL-17 RA and IL-17 RC, in order to mediate signaling. IL-17A is a major pathological cytokine expressed by Th17 cells, which are involved in the pathology of inflammation and autoimmunity, and also CD8+ T cells, γδ cells, NK cells, NKT cells, macrophages and dendritic cells. Additionally, IL-17A and Th17 are necessary for defense against various microbes despite their involvement in inflammation and autoimmune disorders. Further, IL-17A can act in cooperation with other inflammatory cytokines such as TNF-α, IFN-γ, and IL-1β to mediate pro-inflammatory effects.

[0003] To date, there are a few biologics (Secukinumab and Ixekizumab) that have been approved to modulate IL-17A for the treatment of inflammatory diseases, such as psoriasis, ankylosing spondylitis, and psoriatic arthritis. These treatments require injection to a patient as they are not readily absorbed by the gut when orally ingested. Further, these approved biologic treatments have a high cost of entry for patients, limiting the availability to the patient population in need thereof. There are a few small molecule modulators of IL-17A that have been approved for oral administration. However, while these have the convenience of oral administration and a lower cost of entry for patients, they lack the efficacy of approved biologics. Therefore, there exists a need for the development of potent small molecule IL-17A modulators for the treatment of inflammatory diseases and other associated disorders.

SUMMARY

[0004] In certain aspects the present disclosure provides a compound represented by the structure of Formula

(I):  (I),

or a pharmaceutically acceptable salt thereof, wherein:

C_{3-6} carbocycle and 5- to 6-membered heterocycle, any of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-NO_2$, and -CN; and

C_{3-6} carbocycle or 4- to 6-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from:

halogen, $-OR^{13}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-NO_2$, -CN, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-NO_2$, and -CN;

R^C is selected from hydrogen and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from: halogen, $-OR^{17}$, $-N(R^{17})_2$, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-NO_2$, and -CN;

R^D is selected from C_{1-6} alkyl and C_{3-6} carbocycle, any of which is optionally substituted with one or more substituents independently selected from: halogen, $-OR^{18}$, $-N(R^{18})_2$, $-C(O)R^{18}$, $-C(O)OR^{18}$, $-NO_2$, and -CN;

R^E is selected from hydrogen, C_{1-6} alkyl and C_{3-6}carbocycle, any of which is optionally substituted with one or more substituents independently selected from: halogen, $-OR^{19}$, $-N(R^{19})_2$, $-C(O)R^{19}$, $-C(O)OR^{19}$, $-NO_2$, and -CN;

R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, and R^{19} are each independently selected at each occurrence from:

hydrogen;

C_{1-6} alkyl optionally substituted with one more substituents independently selected from halogen, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, $-NH_2$, $-NO_2$, =O, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle, wherein each C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one or more substituents independently selected from: halogen, -OH, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, $-NH_2$, $-NO_2$, =O, and -CN; and

C_{3-10} carbocycle and 3- to 10-membered heterocycle optionally substituted with one or more substituents independently selected from: halogen, -OH, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, $-NH_2$, $-NO_2$, =O, and -CN; and

n is selected from 0, 1, 2, 3, and 4.

[0005] In certain examples, the present disclosure provides a pharmaceutical composition comprising a compound or salt of Formula (I), and a pharmaceutically acceptable excipient.

[0006] In certain examples the present disclosure provides a method of modulating IL-17A in a subject in need thereof, comprising administering to the subject a compound or salt of Formula (I) or a pharmaceutical composition thereof.

[0007] In certain examples the present disclosure provides a method of treating an inflammatory disease or condition comprising administering to a subject in need thereof a compound or salt of Formula (I) or a pharmaceutical composition thereof. In some examples, the inflammatory disease or condition is selected from plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa, rheumatoid arthritis, Palmoplantar Psoriasis, Spondyloarthritis, and Non-infectious Uveitis.

[0007a] In certain aspects, the present disclosure provides a compound or salt as defined herein or a pharmaceutical composition as defined herein for use in modulating IL-17A.

[0007b] In certain aspects, the present disclosure provides use of a compound or salt as defined herein or a pharmaceutical composition as defined herein in the manufacture of a medicament for treating an inflammatory disease or condition.

[0007c] In certain aspects, the present disclosure provides use of a compound or salt as defined herein, or a pharmaceutical composition as defined herein in the manufacture of a medicament for treating an inflammatory disease or condition, wherein the inflammatory disease or condition is selected from plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa, rheumatoid arthritis, Palmoplantar Psoriasis, Spondyloarthritis, and Non-infectious Uveitis.

[0007d] In certain aspects, the present disclosure provides a pharmaceutical composition comprising a compound or salt as defined herein, and a pharmaceutically acceptable excipient.

[0007e] In certain aspects, the present disclosure provides a pharmaceutical composition comprising a compound as defined herein, and a pharmaceutically acceptable excipient.

[0007f] In certain aspects, the present disclosure provides a compound or salt as defined herein or a pharmaceutical composition as defined herein for use in therapy.

INCORPORATION BY REFERENCE

[0008] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

DETAILED DESCRIPTION OF THE INVENTION

[0009] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope

of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Definitions

[0010] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference.

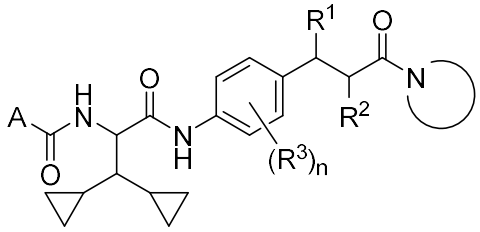
[0011] As used in the specification and claims, the singular form “a”, “an” and “the” includes plural references unless the context clearly dictates otherwise.

[0012] "Alkyl" refers to a straight or branched hydrocarbon chain monovalent radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, and preferably having from one to twelve carbon atoms (*i.e.*, C_1-C_{12} alkyl). The alkyl is attached to the remainder of the molecule through a single bond. In certain embodiments, an alkyl comprises one to twelve carbon atoms (*i.e.*,

CLAIMS

WHAT IS CLAIMED IS:

1. A compound represented by the structure of Formula I:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

A is selected from a C_{3-6} carbocycle and 5- to 6-membered heterocycle, any one of which is optionally substituted with one or more substituents independently selected from (a), (b), and (c):

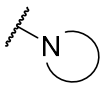
(a) halogen, $-OR^{11}$, $-N(R^{11})_2$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-NO_2$, and -CN;

(b) C_{1-6} alkyl optionally substituted with one or more substituents independently selected from: halogen, $-OR^{11}$, $-N(R^{11})_2$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-NO_2$, -CN, C_{3-6} carbocycle and 3- to 6-membered heterocycle, wherein each C_{3-6} carbocycle and 3- to 6-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, $-OR^{11}$, $-N(R^{11})_2$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-NO_2$, and -CN; and

(c) C_{3-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, $-OR^{11}$, $-N(R^{11})_2$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-NO_2$, and -CN;

R^1 is selected from hydrogen, halogen, $-OR^{12}$, $-N(R^{12})_2$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NO_2$, -CN, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{12}$, $-N(R^{12})_2$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NO_2$, and -CN;

R^2 is selected from $-N(R^A)C(O)(R^B)$ and $-N(R^C)C(O)N(R^D)(R^E)$;



is selected from a 4- to 12-membered heterocycle optionally substituted with one or more substituents independently selected from:

halogen, $-OR^{13}$, $-N(R^{13})_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-NO_2$, -CN, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{13}$, $-N(R^{13})_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-NO_2$, and -CN;

R^3 is selected from halogen, $-OR^{14}$, $-N(R^{14})_2$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-NO_2$, -CN, C_{1-6} alkyl and C_{3-6} carbocycle, wherein each C_{1-6} alkyl and C_{3-6} carbocycle of which is optionally substituted

with one or more substituents independently selected from halogen, $-OR^{14}$, $-N(R^{14})_2$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-NO_2$, and -CN;

R^A is selected from hydrogen and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{15}$, $-N(R^{15})_2$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-NO_2$, and -CN;

R^B is selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from:

halogen, $-OR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-N(R^{16})C(O)OR^{16}$, $-NO_2$, -CN;

C_{3-6} carbocycle and 5- to 6-membered heterocycle, any of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-NO_2$, and -CN; and

C_{3-6} carbocycle or 4- to 6-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from:

halogen, $-OR^{13}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-NO_2$, -CN, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-NO_2$, and -CN;

R^C is selected from hydrogen and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from: halogen, $-OR^{17}$, $-N(R^{17})_2$, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-NO_2$, and -CN;

R^D is selected from C_{1-6} alkyl and C_{3-6} carbocycle, any of which is optionally substituted with one or more substituents independently selected from: halogen, $-OR^{18}$, $-N(R^{18})_2$, $-C(O)R^{18}$, $-C(O)OR^{18}$, $-NO_2$, and -CN;

R^E is selected from hydrogen, C_{1-6} alkyl and C_{3-6}carbocycle, any of which is optionally substituted with one or more substituents independently selected from: halogen, $-OR^{19}$, $-N(R^{19})_2$, $-C(O)R^{19}$, $-C(O)OR^{19}$, $-NO_2$, and -CN;

R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, and R^{19} are each independently selected at each occurrence from:

hydrogen;

C_{1-6} alkyl optionally substituted with one more substituents independently selected from halogen, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, $-NH_2$, $-NO_2$, =O, -CN, C_{3-10} carbocycle and 3- to 10-membered heterocycle, wherein each C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one or more substituents independently selected from: halogen, -OH, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, $-NH_2$, $-NO_2$, =O, and -CN; and

C_{3-10} carbocycle and 3- to 10-membered heterocycle optionally substituted with one or more substituents independently selected from: halogen, -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -NH_2, -NO_2, =O, and -CN; and

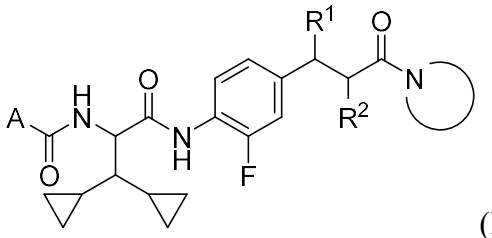
n is selected from 0, 1, 2, 3, and 4.

2. The compound or salt of claim 1, wherein n is 1.

3. The compound or salt of claim 1 or claim 2, wherein each R^3 is independently selected from fluorine, chlorine, -OR^{14}, -$N(R^{14})_2$, -CN, C_{1-3} alkyl and C_{1-3} haloalkyl.

4. The compound or salt of claim 3, wherein each R^3 is selected from fluorine.

5. The compound or salt of any one of claims 1 to 4, wherein Formula (I) is represented by Formula (I-A):



(I-A).

6. The compound or salt of any one of claims 1 to 5, wherein R^1 is selected from selected from hydrogen, halogen, -OR^{12}, -$N(R^{12})_2$, -CN, C_{1-3} alkyl and C_{1-3} haloalkyl.

7. The compound or salt of claim 6, wherein R^1 is selected from methyl, ethyl, propyl, and trifluoromethyl.

8. The compound or salt of claim 7, wherein R^1 is selected from selected from methyl.

9. The compound or salt of claim 7, wherein R^1 is selected from selected from trifluoromethyl.

10. The compound or salt of any one of claims 1 to 9, wherein A is selected from a saturated C_{3-6} carbocycle and a 5-membered heteroaryl, any of which is optionally substituted with one or more substituents independently selected from: from (a), (b), and (c):

(a) halogen, -OR^{11}, -$N(R^{11})_2$, -$C(O)R^{11}$, -$C(O)OR^{11}$, -NO_2, and -CN;

(b) C_{1-3} alkyl optionally substituted with one or more substituents independently selected from halogen, -OR^{11}, -$N(R^{11})_2$, -$C(O)R^{11}$, -$C(O)OR^{11}$, -NO_2, -CN, C_{3-6} carbocycle and 5- to 6-membered heterocycle, wherein each C_{3-6} carbocycle and 5- to 6-membered

heterocycle is optionally substituted with one or more substituents independently selected from: halogen, -OR^{11}, -$N(R^{11})_2$, -$C(O)R^{11}$, -$C(O)OR^{11}$, -NO_2, and -CN; and

(c) C_{3-6} carbocycle each of which is optionally substituted with one or more substituents selected from: halogen, -OR^{11}, -$N(R^{11})_2$, -$C(O)R^{11}$, -$C(O)OR^{11}$, -NO_2, and -CN.

11. The compound or salt of claim 10, wherein A is selected saturated C_{3-6} carbocycle, any one of which is optionally substituted with one or more substituents independently selected from halogen, -OR^{11}, -$N(R^{11})_2$, -CN, C_{1-3} alkyl, and C_{1-3} haloalkyl.

12. The compound or salt of claim 11, wherein A is cyclopropyl optionally substituted with halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl.

13. The compound or salt of claim 12, wherein A is 

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14. The compound or salt of claim 10, wherein A is a 5-membered heteroaryl optionally substituted with one or more substituents independently selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from: halogen, -OR^{11}, -$N(R^{11})_2$, -$C(O)R^{11}$, -$C(O)OR^{11}$, -NO_2, -CN; and 5- to 6-membered heterocycle each of which is optionally substituted with one or more substituents selected from: halogen, -OR^{11}, -$N(R^{11})_2$, -$C(O)R^{11}$, -$C(O)OR^{11}$, -NO_2, and -CN; and

C_{3-6} carbocycle each of which is optionally substituted with one or more substituents selected from: halogen, -OR^{11}, -$N(R^{11})_2$, -$C(O)R^{11}$, -$C(O)OR^{11}$, -NO_2, and -CN.

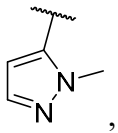
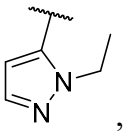
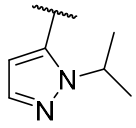
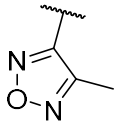
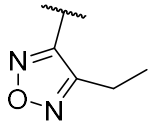
15. The compound or salt of claim 14, wherein A is selected from pyrazole, imidazole, oxazole, isoxazole, oxadiazole, triazole, tetrazole, any one of which is optionally substituted with one or more substituents independently selected from:

C_{1-3} alkyl optionally substituted with one or more substituents independently selected from: halogen, -OR^{11}, and 5- to 6-membered saturated heterocycle each of which is optionally substituted with one or more substituents selected from: halogen, -OR^{11}, -$N(R^{11})_2$, -$C(O)R^{11}$, -$C(O)OR^{11}$, -NO_2, and -CN; and

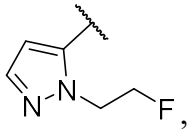
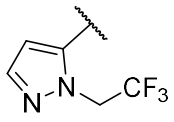
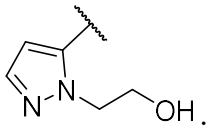
saturated C_{3-6} carbocycle optionally substituted with one or more substituents selected from: halogen, -OR^{11}, -$N(R^{11})_2$, -$C(O)R^{11}$, -$C(O)OR^{11}$, -NO_2, and -CN.

16. The compound or salt of claim 15, wherein A is selected from pyrazole and oxadiazole, each of which is optionally substituted with one or more substituents independently selected from C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkyl-OR^{11}, and C_{1-3} alkyl substituted with 5- to 6-membered saturated heterocycle.

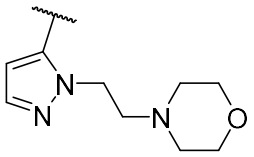
17. The compound or salt of claim 16, wherein A is selected from pyrazole and oxadiazole, each of which is optionally substituted with methyl, ethyl, propyl, and isopropyl.

18. The compound or salt of claim 17, wherein A is selected from: , , , , and .

19. The compound or salt of claim 16, wherein A is selected from pyrazole and oxadiazole, each of which is optionally substituted with C_{1-3} haloalkyl, and C_{1-3} alkyl-OR^{11}.

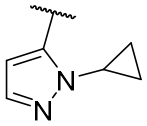
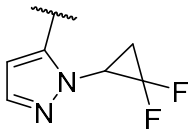
20. The compound or salt of claim 19, wherein A is selected from: , , , and .

21. The compound or salt of claim 16, wherein A is from pyrazole and oxadiazole, each of which is optionally substituted with C_{1-3} alkyl substituted with 5- to 6-membered saturated heterocycle.

22. The compound or salt of claim 21, wherein A is .

23. The compound or salt of claim 15, wherein A is selected from pyrazole and oxadiazole, each of which is optionally substituted with one or more substituents independently selected from saturated C_{3-6} carbocycle optionally substituted with one or more substituents selected from: halogen, -OR^{11}, -$N(R^{11})_2$, -$C(O)R^{11}$, -$C(O)OR^{11}$, -NO_2, and -CN.

24. The compound or salt of claim 23, wherein A is selected from pyrazole and oxadiazole, each of which is optionally substituted by cyclopropyl, wherein the cyclopropyl is optionally substituted with fluorine or chlorine.

25. The compound or salt of claim 24, wherein A is selected from:  and .

26. The compound or salt of any one of claims 1 to 25, wherein R^2 is selected from -$N(R^C)C(O)N(R^D)(R^E)$, wherein:

R^C is selected from hydrogen;

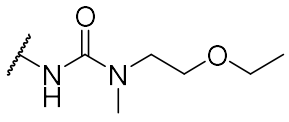
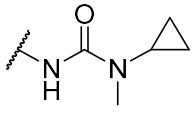
R^D is selected from C_{1-6} alkyl and saturated C_{3-6} carbocycle, any of which is optionally substituted with one or more substituents independently selected from: halogen, -OR^{18}, -$N(R^{18})_2$, -$C(O)R^{18}$, -$C(O)OR^{18}$, -NO_2, and -CN; and

R^E is selected from C_{1-6} alkyl and saturated C_{3-6}carbocycle, any of which is optionally substituted with one or more substituents independently selected from: halogen, -OR^{19}, -$N(R^{19})_2$, -$C(O)R^{19}$, -$C(O)OR^{19}$, -NO_2, and -CN.

27. The compound or salt of claim 26, wherein

R^D is selected from C_{1-3} alkyl and cyclopropyl, any of which is optionally substituted with one or more substituents independently selected from: halogen, -OR^{18}, -$N(R^{18})_2$, -NO_2, and -CN; and

R^E is selected from C_{1-3} alkyl.

28. The compound or salt of claim 27, wherein R^2 is selected from:  and .

29. The compound or salt of any one of claims 1 to 25, wherein R^2 is selected from -$N(R^A)C(O)(R^B)$, wherein:

R^A is selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^B is selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -OR^{16}, -$N(R^{16})_2$, -$C(O)R^{16}$, -$C(O)OR^{16}$, -$N(R^{16})C(O)OR^{16}$, -NO_2, -CN; C_{3-6} carbocycle and 5- to 6-membered heterocycle, any of which is

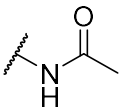
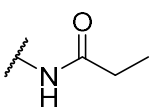
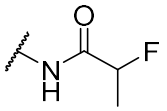
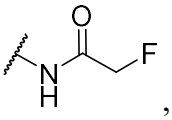
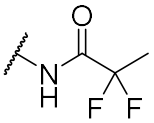
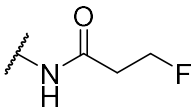
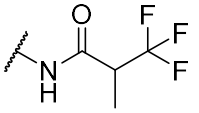
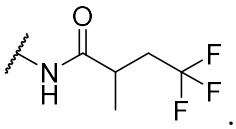
optionally substituted with one or more substituents independently selected from: halogen, -OR^{16}, -$N(R^{16})_2$, -$C(O)R^{16}$, -$C(O)OR^{16}$, -NO_2, and -CN; and

4- to 6-membered heterocycle optionally substituted with one or more substituents independently selected from: halogen, -OR^{13}, -$N(R^{16})_2$, -$C(O)R^{16}$, -$C(O)OR^{16}$, -NO_2, -CN, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from: halogen, -OR^{16}, -$N(R^{16})_2$, -$C(O)R^{16}$, -$C(O)OR^{16}$, -NO_2, and -CN.

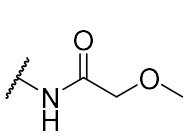
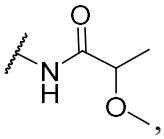
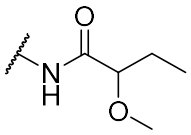
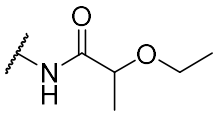
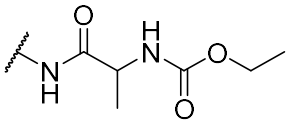
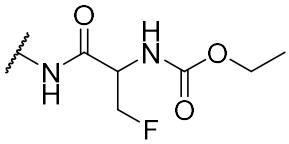
30. The compound or salt of claim 29, wherein R^A is hydrogen; and R^B is selected from: C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -OR^{16}, -$N(R^{16})_2$, -$C(O)R^{16}$, -$C(O)OR^{16}$, -$N(R^{16})C(O)OR^{16}$, -NO_2, -CN, C_{3-6} carbocycle and 5- to 6-membered heterocycle, wherein each C_{3-6} carbocycle and 5- to 6-membered heterocycle is optionally substituted with one or more substituents independently selected from: halogen, -OR^{16}, -$N(R^{16})_2$, -$C(O)R^{16}$, -$C(O)OR^{16}$, -NO_2, and -CN.

31. The compound or salt of claim 30, wherein R^A is hydrogen; and R^B is selected from: C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -OR^{16}, -$N(R^{16})_2$, -$C(O)R^{16}$, -$C(O)OR^{16}$, -$N(R^{16})C(O)OR^{16}$, -NO_2, and -CN.

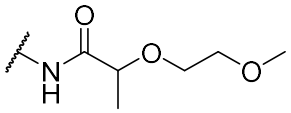
32. The compound or salt of claim 31, wherein R^A is hydrogen; and R^B is selected from C_{1-6} alkyl and C_{1-6} haloalkyl.

33. The compound or salt of claim 32, wherein R^2 is selected from: , , , , , , , and .

34. The compound or salt of claim 31, wherein R^A is hydrogen; and R^B is selected from: C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -OR^{16} and $N(R^{16})C(O)OR^{16}$.

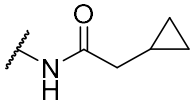
35. The compound or salt of claim 34, wherein R^2 is selected from: , , , , , and .

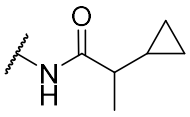
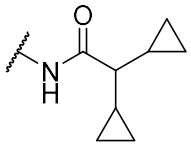
36. The compound or salt of claim 31, wherein R^A is hydrogen; and R^B is C_{1-6} alkyl optionally substituted with $-OR^{16}$, wherein R^{16} is C_{1-6} alkyl substituted with -O-C_{1-6} alkyl.

37. The compound or salt of claim 36, wherein R^2 is .

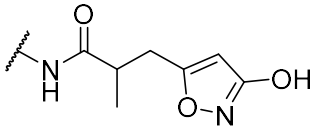
38. The compound or salt of claim 30, wherein R^A is hydrogen; and R^B is selected from: C_{1-6} alkyl optionally substituted with one or more substituents independently selected from C_{3-6} carbocycle and 5- to 6-membered heterocycle, any one of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{16}$, $-N(R^{16})_2$, $-NO_2$, and -CN.

39. The compound or salt of claim 38, wherein R^A is hydrogen; and R^B is selected from: C_{1-6} alkyl optionally substituted with one or more substituents independently selected from optionally substituted C_{3-6} carbocycle.

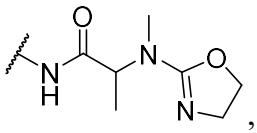
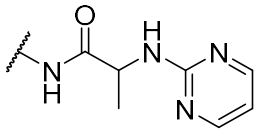
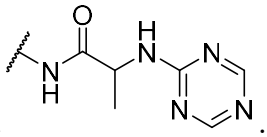
40. The compound or salt of claim 39, wherein R^2 is selected from: ,

, and .

41. The compound or salt of claim 38, wherein R^A is hydrogen; and R^B is selected from: C_{1-6} alkyl optionally substituted with one or more substituents independently selected from 5-membered heterocycle optionally substituted with one or more substituents independently selected from halogen, $-OR^{16}$, $-N(R^{16})_2$, $-NO_2$, and -CN.

42. The compound or salt of claim 41, wherein R^2 is .

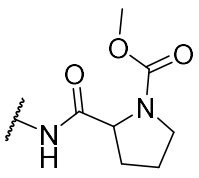
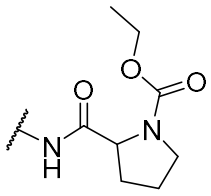
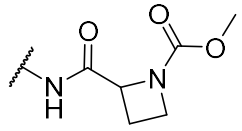
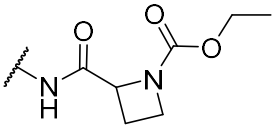
43. The compound or salt of claim 29, wherein R^A is hydrogen; and R^B is selected from: C_{1-6} alkyl optionally substituted with $-N(R^{16})_2$; wherein R^{16} is selected at each occurrence from hydrogen, C_{1-3} alkyl, and 3- to 6-membered heterocycle, where each C_{1-3} alkyl and 3- to 6-membered heterocycle is optionally substituted.

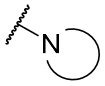
44. The compound or salt of claim 43, wherein R^2 is selected from: , , and .

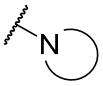
45. The compound or salt of claim 29, wherein R^A is hydrogen; and R^B is selected from a 4- to 6-membered heterocycle optionally substituted with one or more substituents independently selected from halogen, $-OR^{13}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-NO_2$, -CN, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-NO_2$, and -CN.

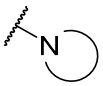
46. The compound or salt of claim 45, wherein R^A is hydrogen; and R^B is selected from a 4- to 6-membered saturated heterocycle, any one of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{13}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-NO_2$, -CN, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{16}$, $-N(R^{16})_2$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-NO_2$, and -CN.

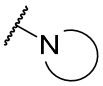
47. The compound or salt of claim 46, wherein R^A is hydrogen; and R^B is selected from azetidine and pyrrolidine, each of which is optionally substituted with halogen, $-OR^{13}$, $-C(O)R^{16}$, $-C(O)OR^{16}$.

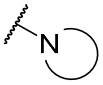
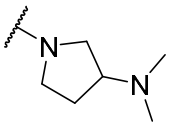
48. The compound or salt of claim 47, wherein R^2 is selected from: , , , and .

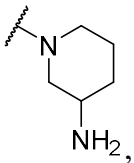
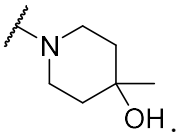
49. The compound or salt of any one of claims 1 to 48, wherein  is selected from a 4- to 6-membered monocyclic heterocycle and 5- to 10-membered bicyclic fused heterocycle each of which is optionally substituted with one or more substituents independently selected from: halogen, $-OR^{13}$, $-N(R^{13})_2$, $-NO_2$, -CN, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^{13}$, $-N(R^{13})_2$, $-NO_2$, and -CN.

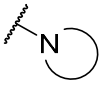
50. The compound or salt of claim 49, wherein  is selected from 4- to 6-membered monocyclic heterocycle, any of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{13}$, $-N(R^{13})_2$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from: halogen, and $-OR^{13}$.

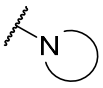
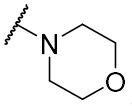
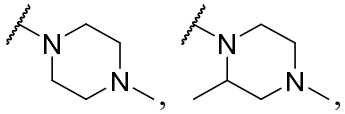
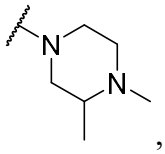
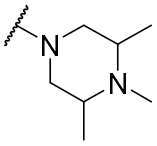
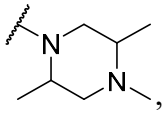
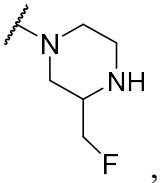
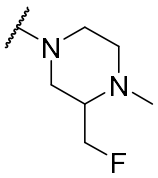
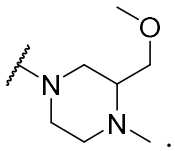
51. The compound or salt of claim 50, wherein  is selected from azetidine, pyrrolidine, pyrazolidine, imidazolidine, piperidine, morpholine, and piperazine, each of which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{13}$, $-N(R^{13})_2$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from: halogen, and $-OR^{13}$.

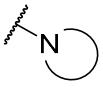
52. The compound or salt of claim 51, wherein  is selected from pyrrolidine, piperidine, morpholine, and piperazine, each of which is optionally substituted with one or more substituents selected from $-OR^{13}$, $-N(R^{13})_2$, and C_{1-3} alkyl.

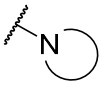
53. The compound or salt of claim 52, wherein  is selected from: ,

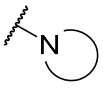
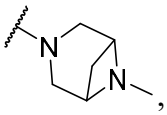
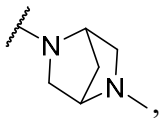
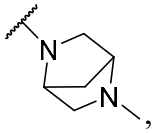
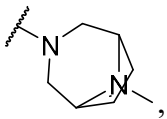
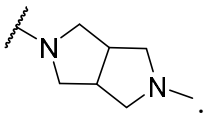
, and .

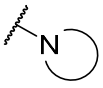
54. The compound or salt of claim 51, wherein  is selected from pyrrolidine, piperidine, morpholine, and piperazine, each of which is optionally substituted with one or more substituents selected from C_{1-3} alkyl optionally substituted with one or more substituents independently selected from: halogen and $-OR^{13}$.

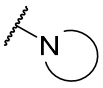
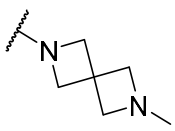
55. The compound or salt of claim 54, wherein  is selected from: , , , , , , , and .

56. The compound or salt of claim 49, wherein  is selected from 7- to 10-membered bicyclic heterocycle, any one of which is optionally substituted with one or more substituents independently selected from $C_{1\text{-}6}$ alkyl optionally substituted with halogen, $-OR^{13}$, $-N(R^{13})_2$, $-NO_2$, and -CN.

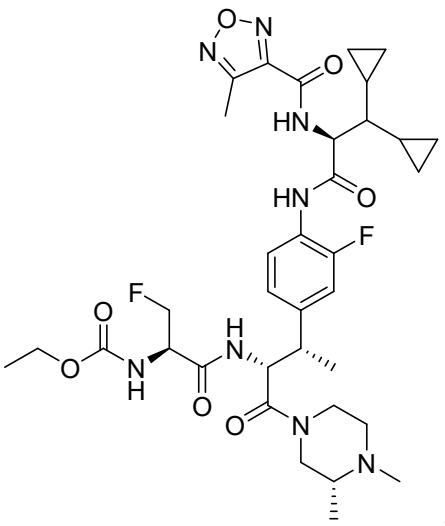
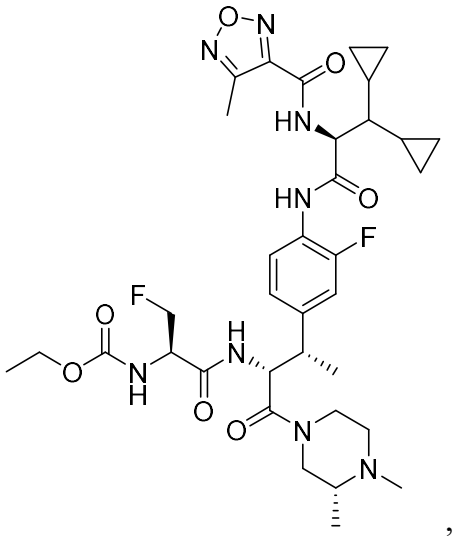
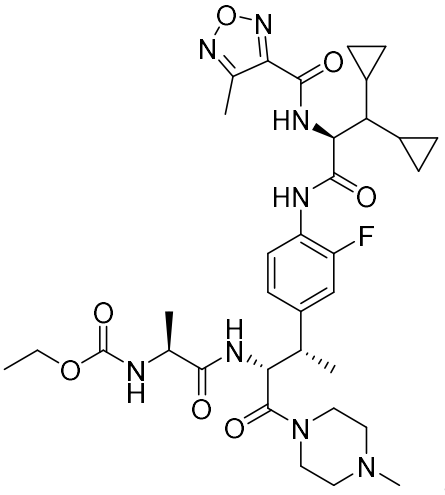
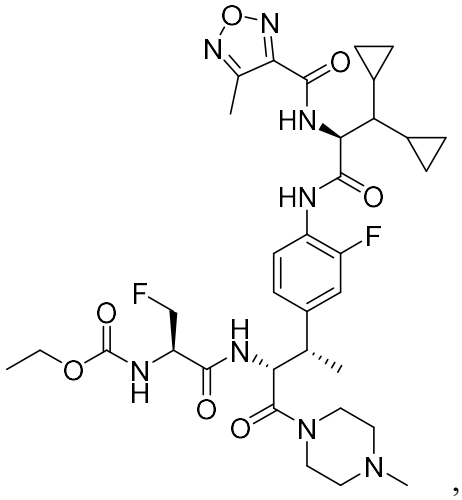
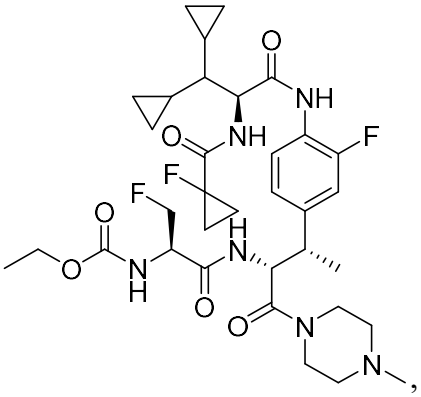
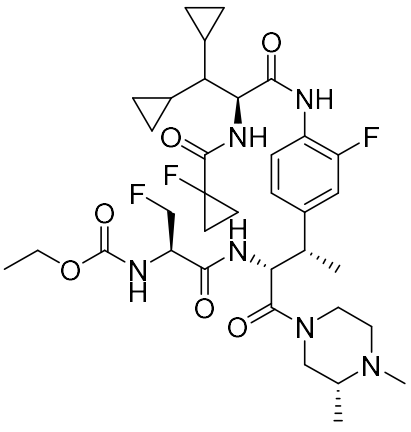
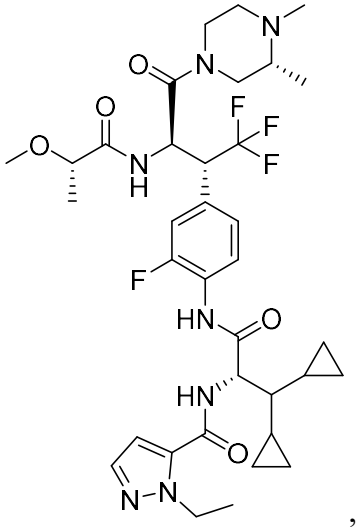
57. The compound or salt of claim 56, wherein  is selected from 7- to 10-membered bicyclic heterocycle, any one of which is optionally substituted with $C_{1\text{-}3}$ alkyl.

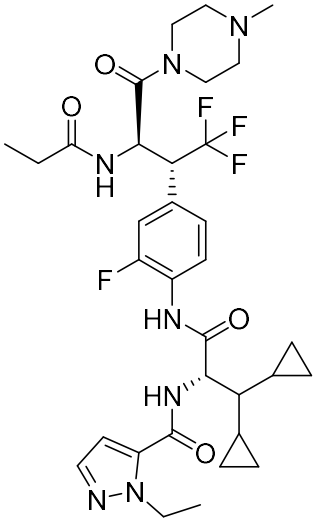
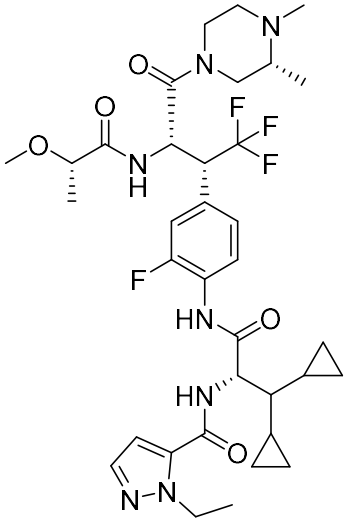
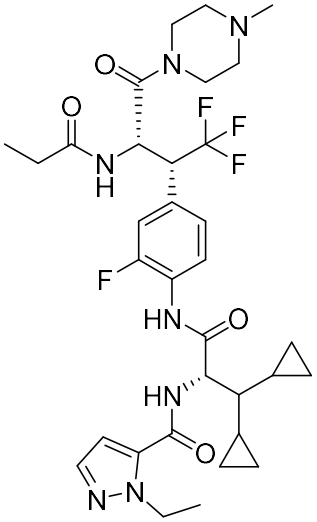
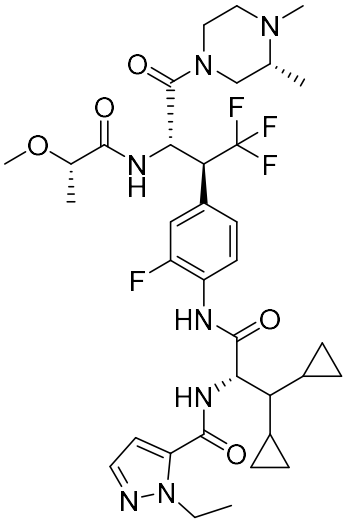
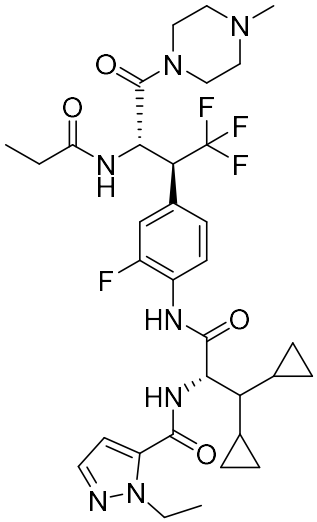
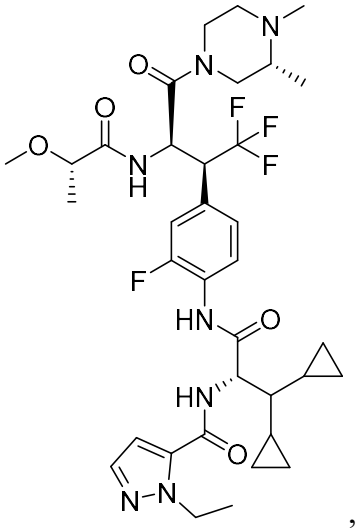
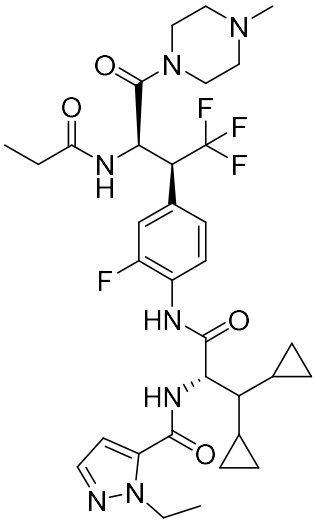
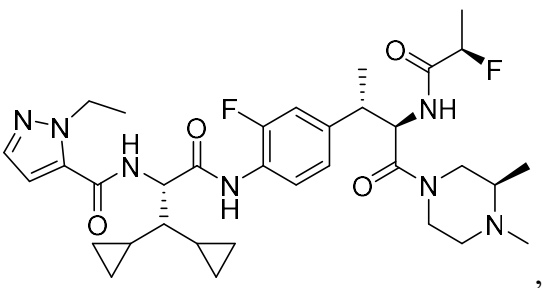
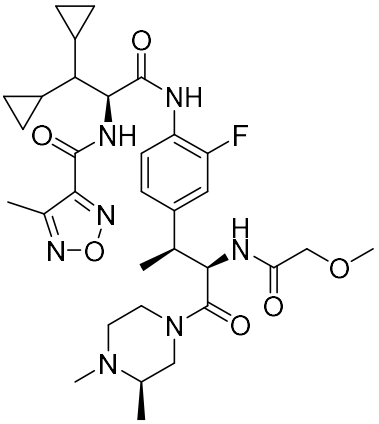
58. The compound or salt of claim 57, wherein  is selected from: , , , , and .

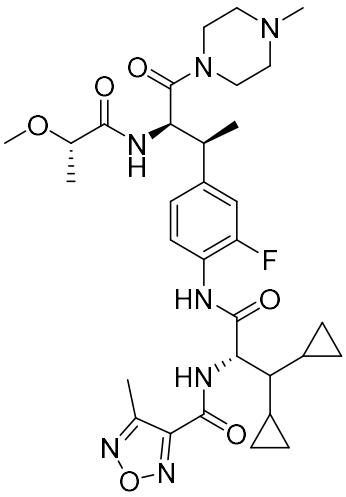
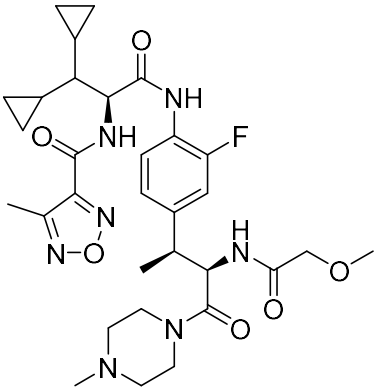
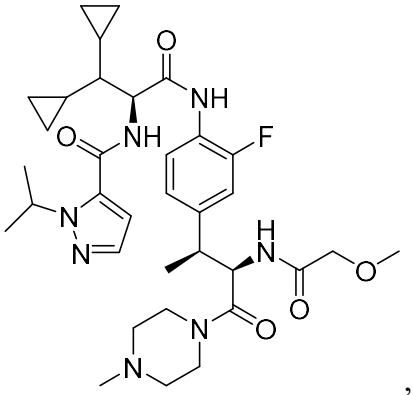
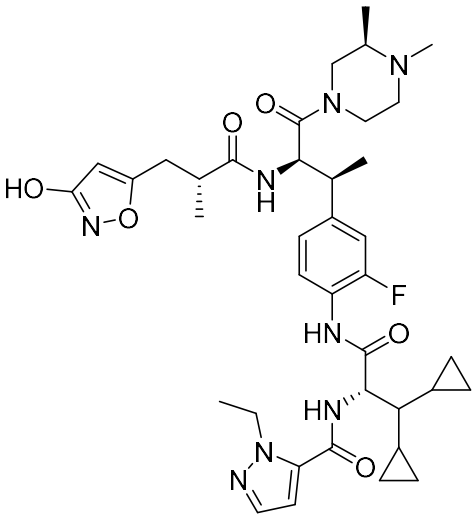
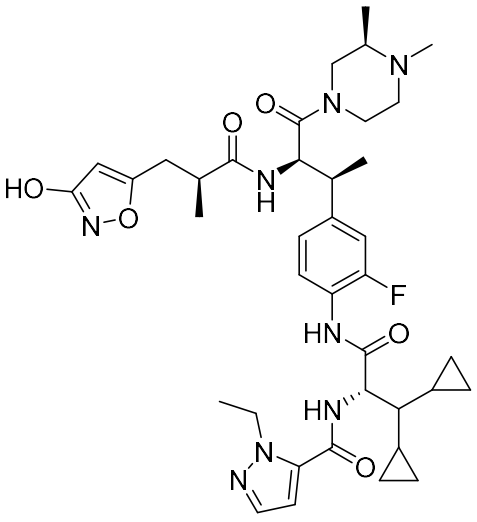
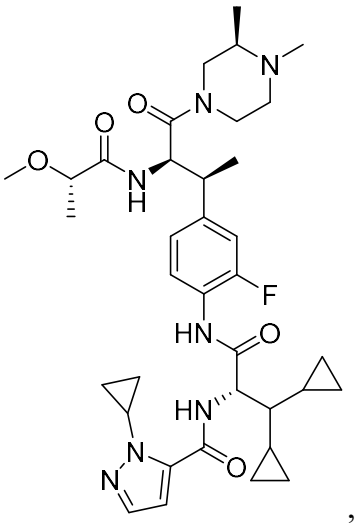
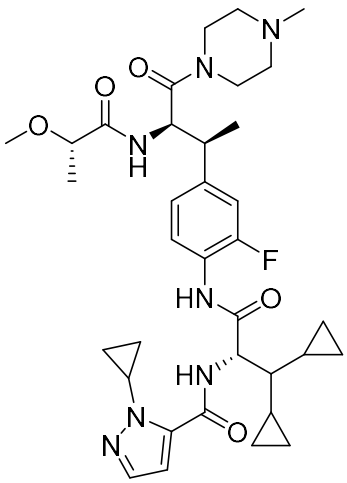
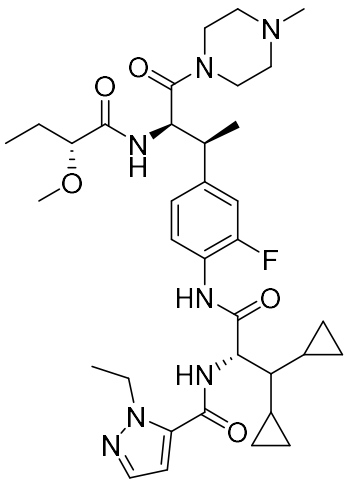
59. The compound or salt of claim 49, wherein  is selected from 5- to 8-membered spirocyclic heterocycle, any one of which is optionally substituted with one or more substituents independently selected from $C_{1\text{-}6}$ alkyl optionally substituted with halogen, $-OR^{13}$, $-N(R^{13})_2$, $-NO_2$, and -CN.

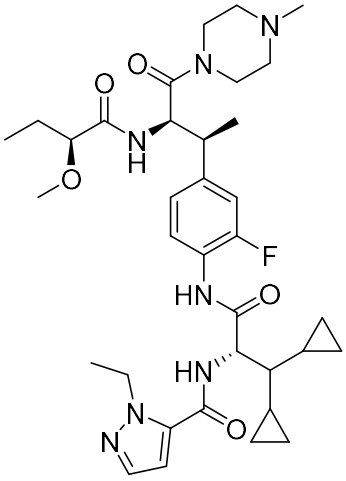
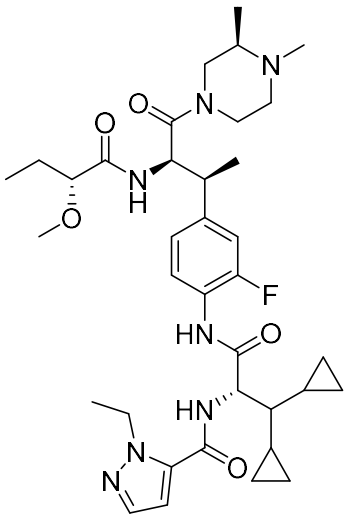
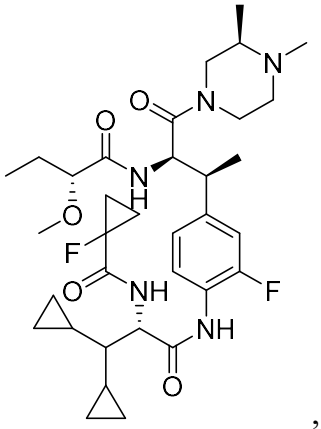
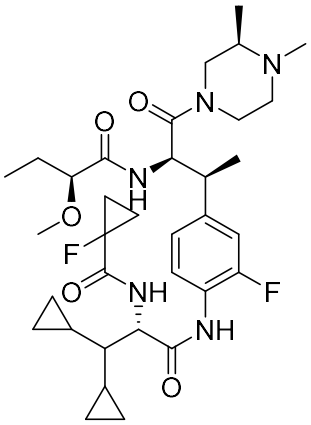
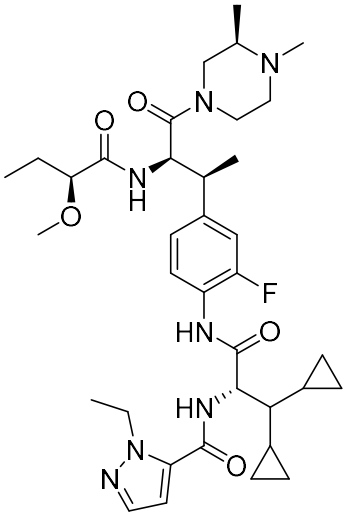
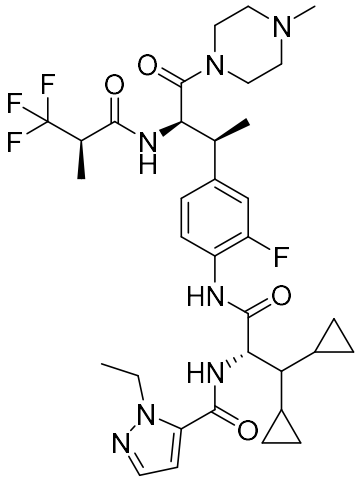
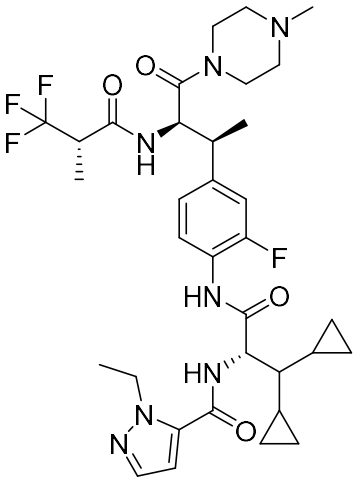
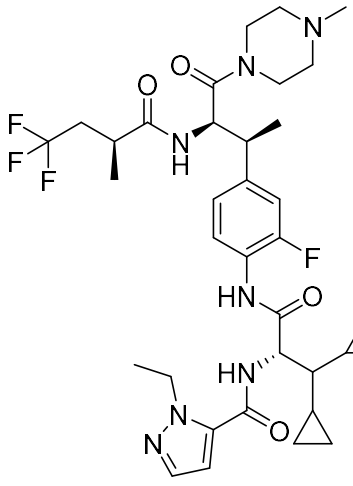
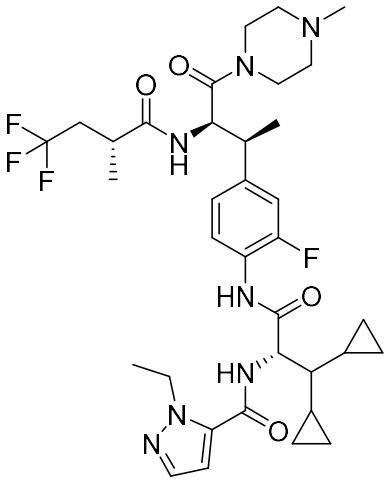
60. The compound or salt of claim 59, wherein  is .

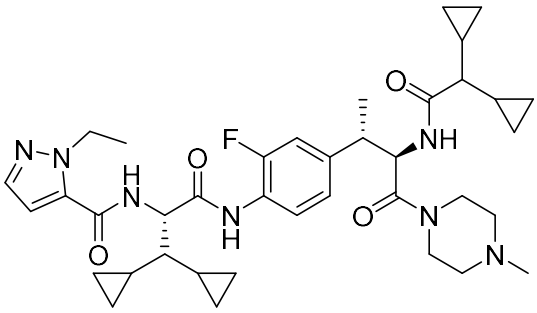
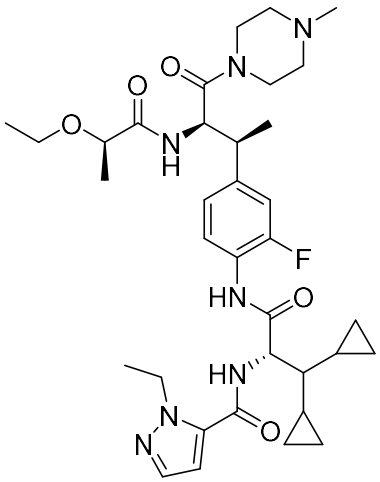
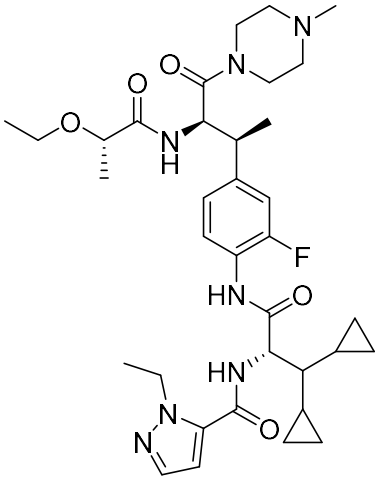
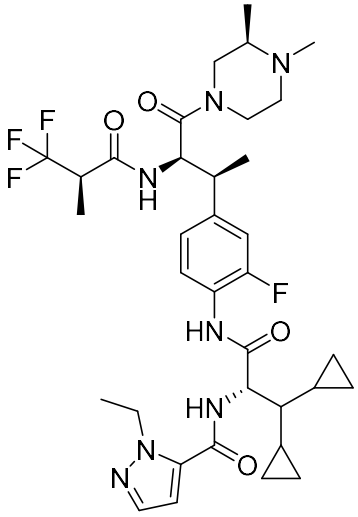
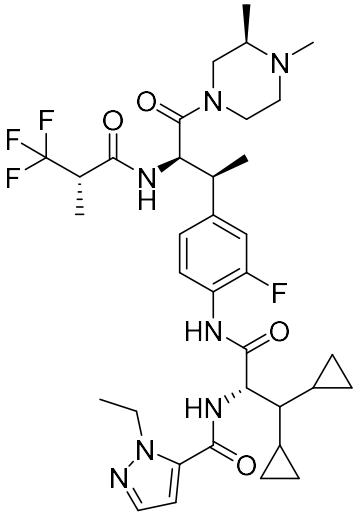
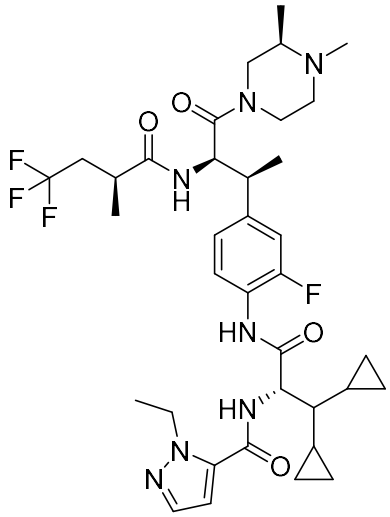
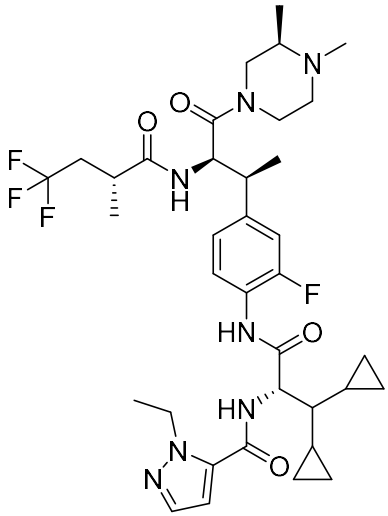
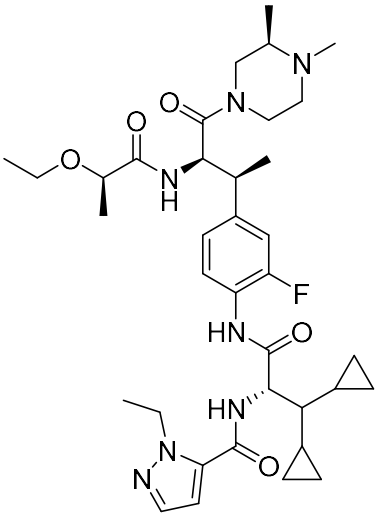
61. The compound or salt of claim 1, wherein Formula (I) is selected from:

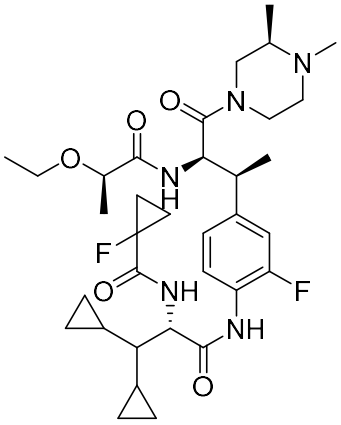
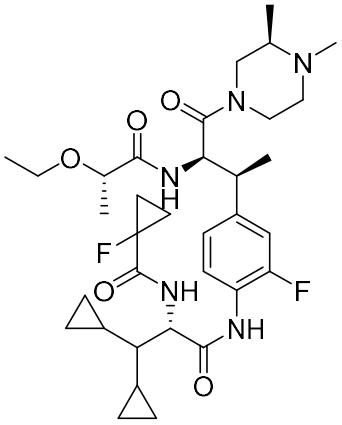
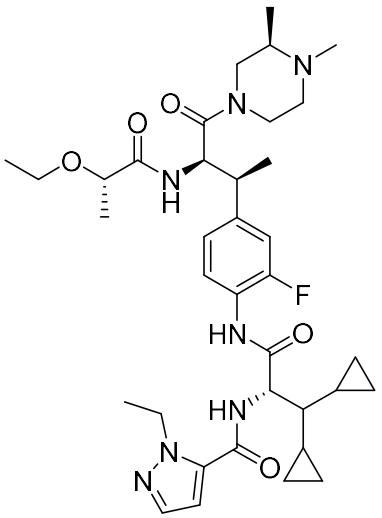
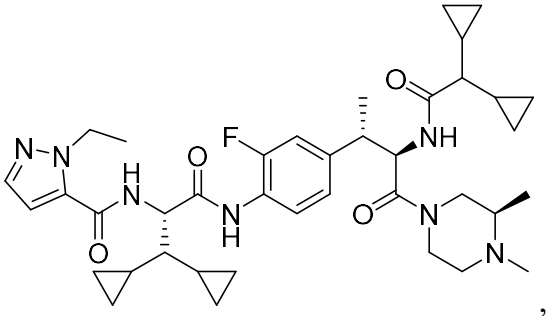
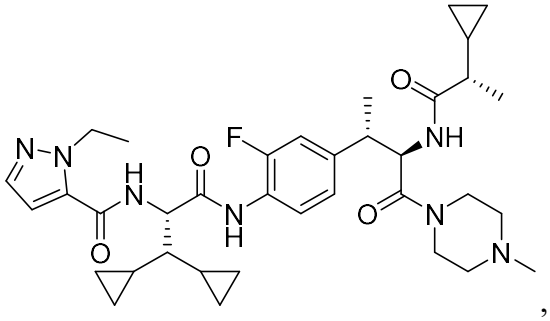
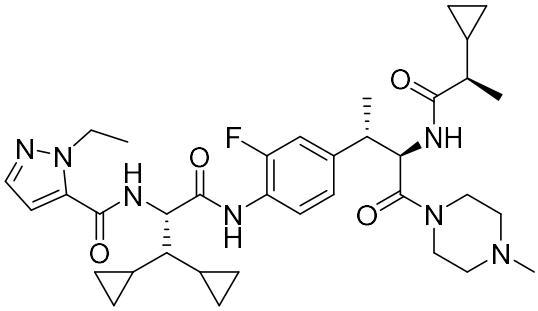
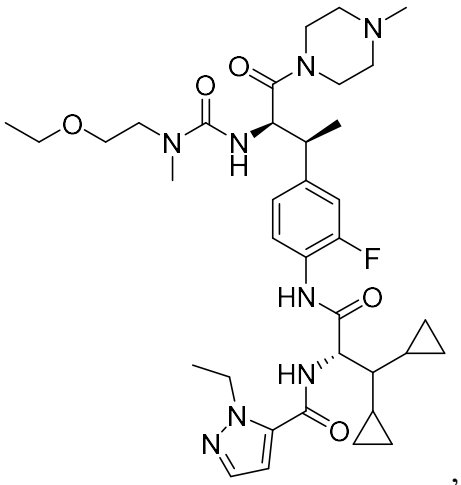
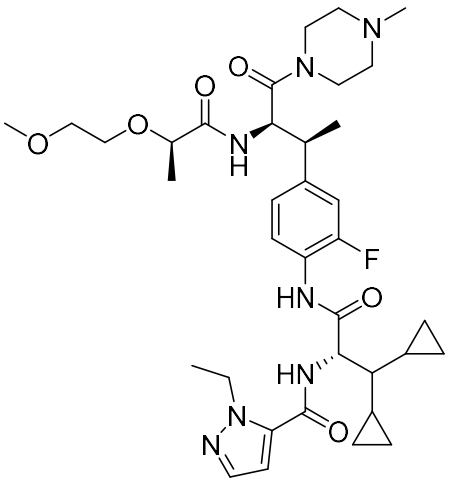
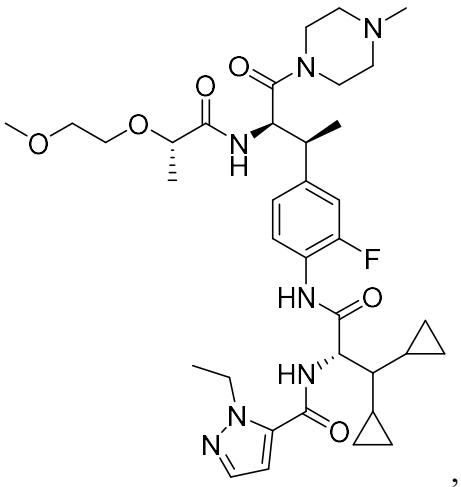

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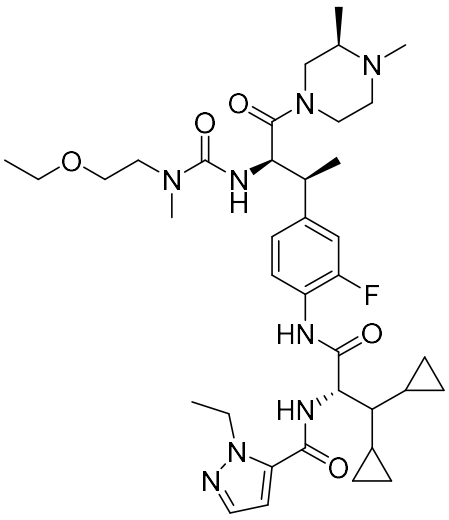
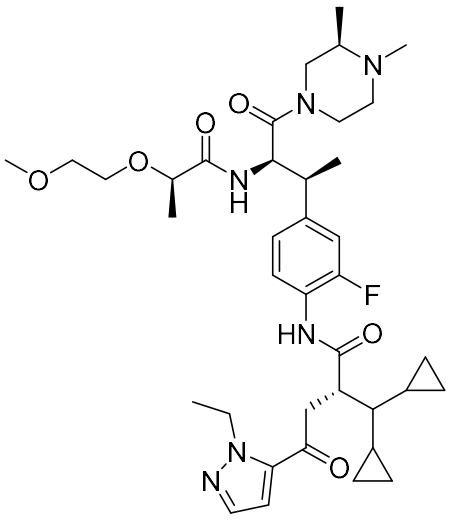
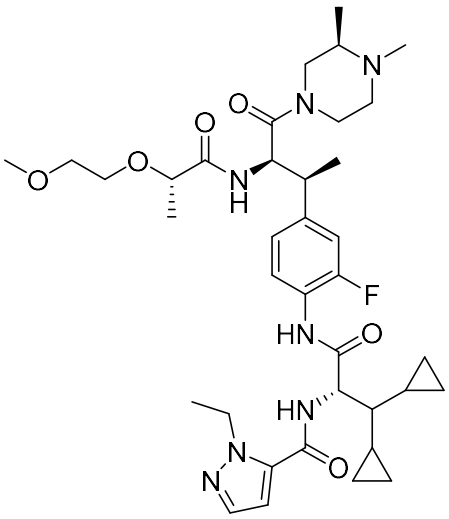
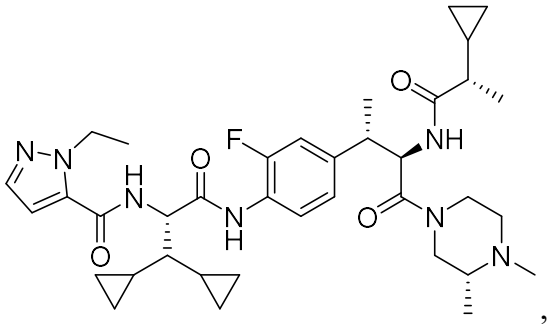
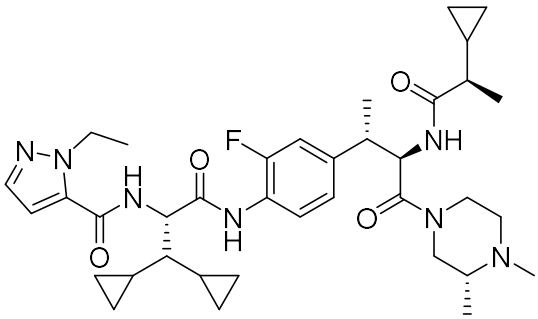
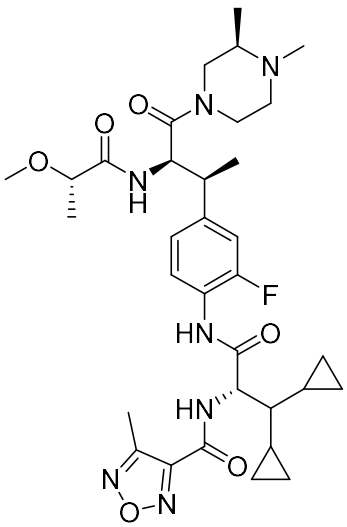
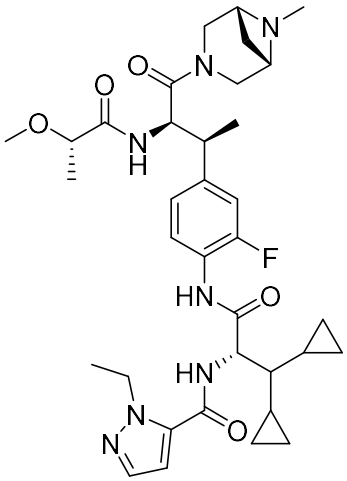

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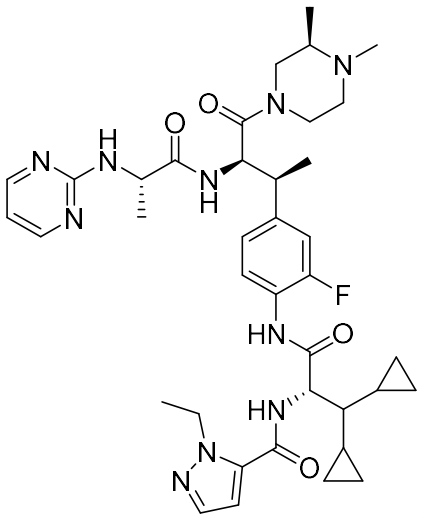
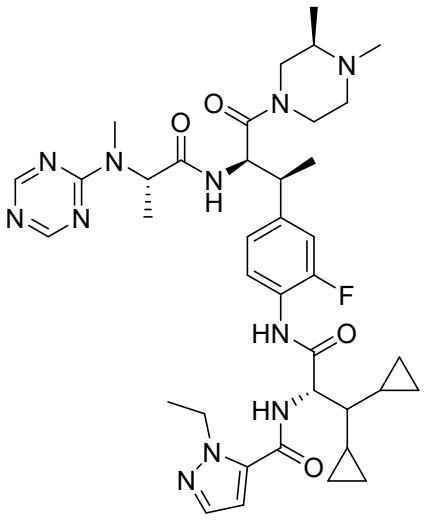
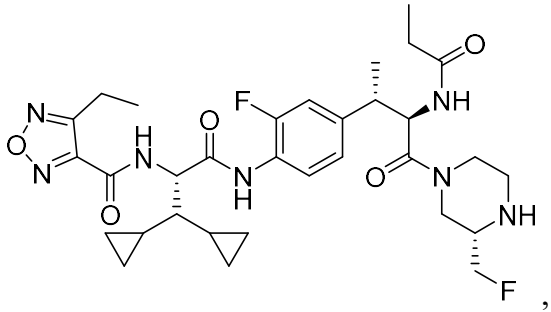
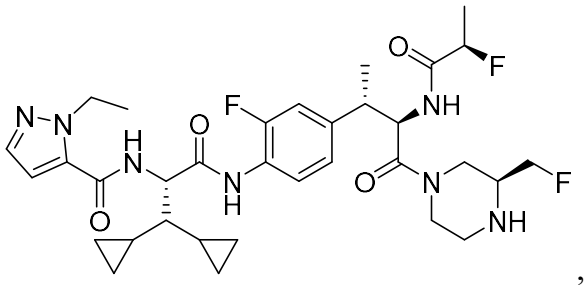
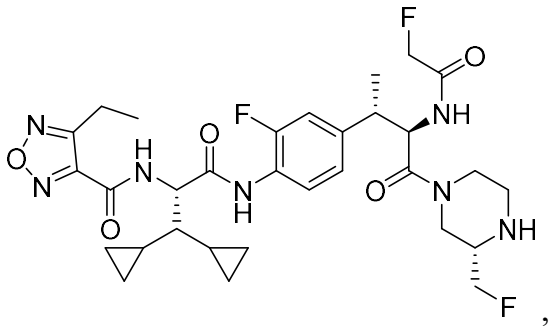
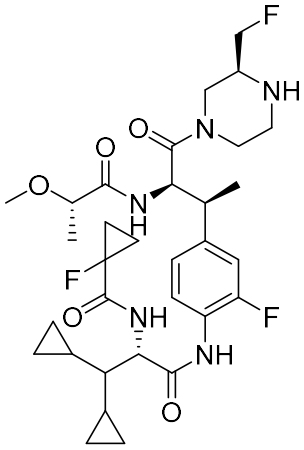
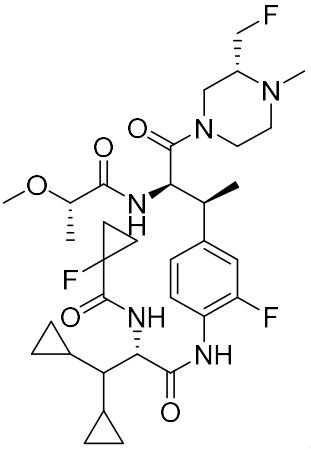

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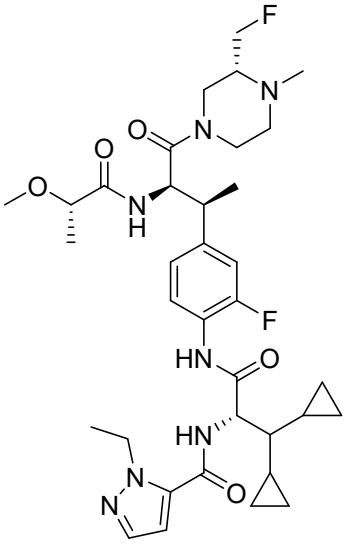
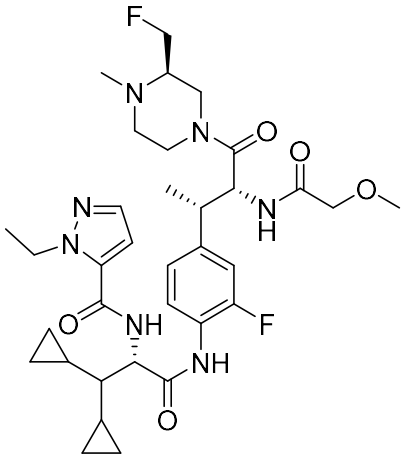
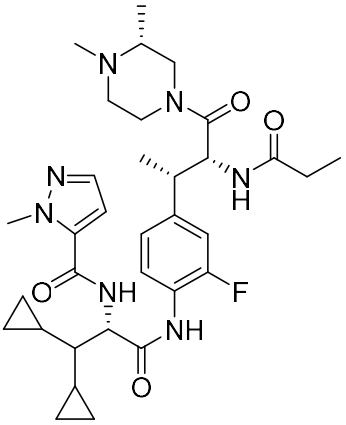
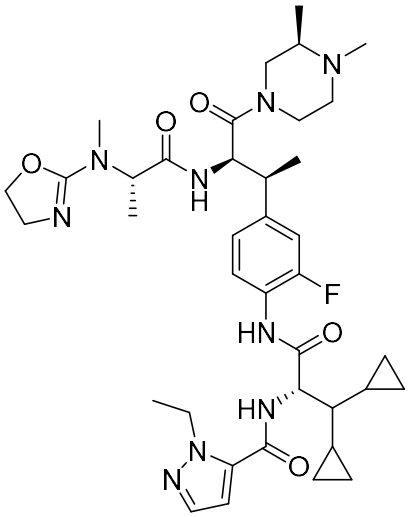
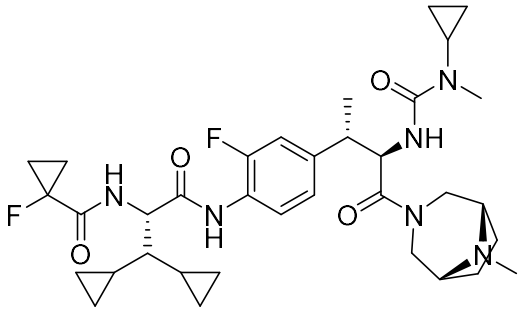
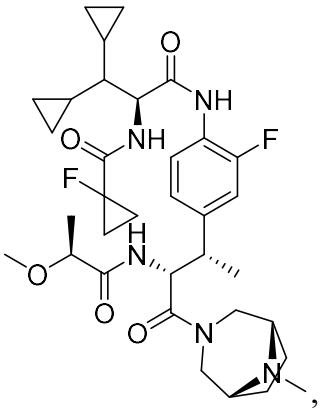
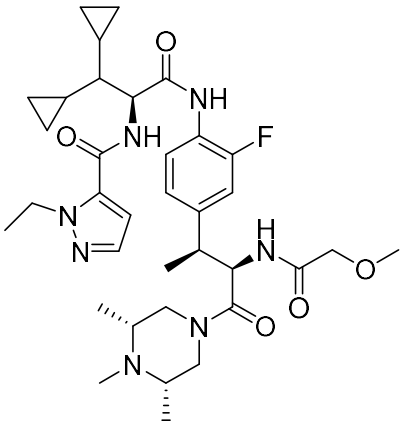
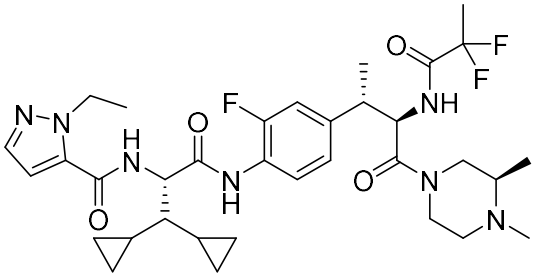
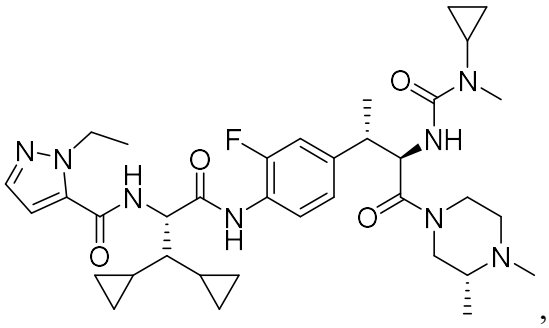

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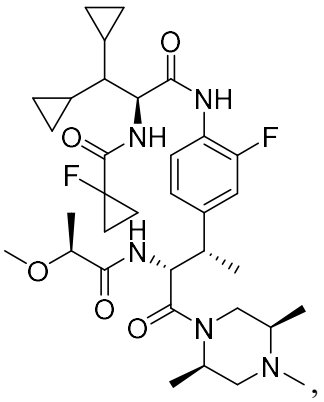
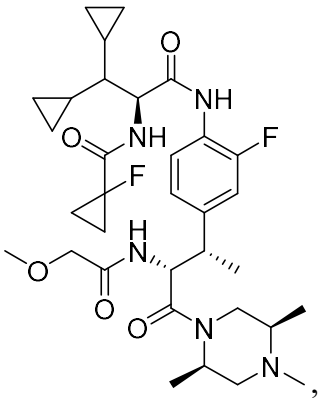
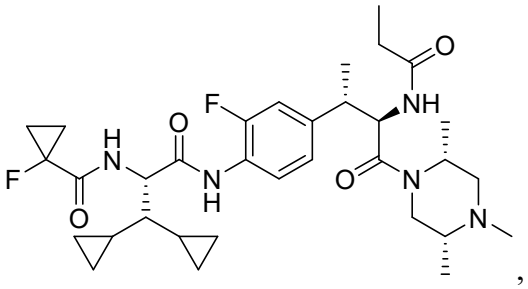
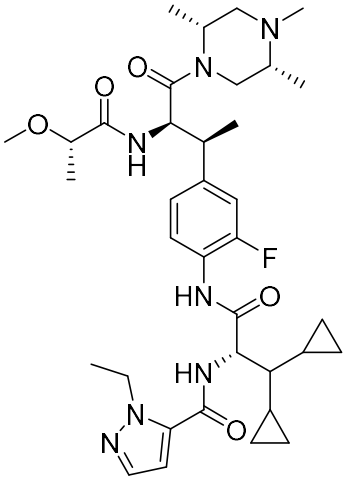
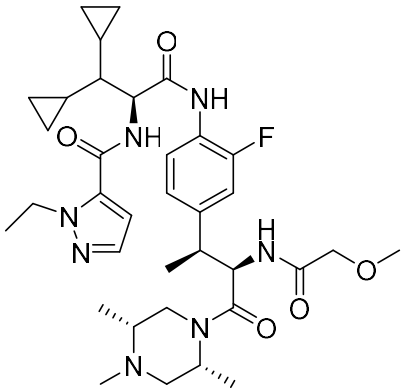
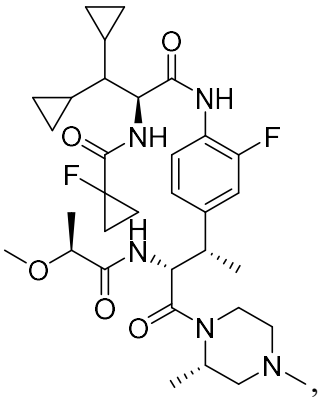
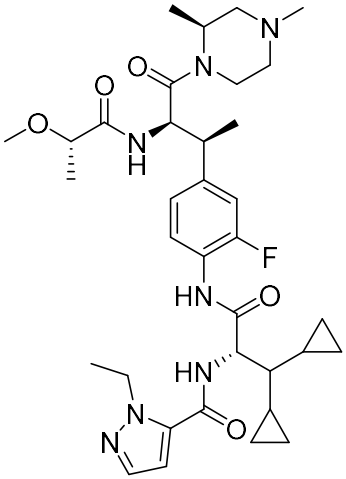
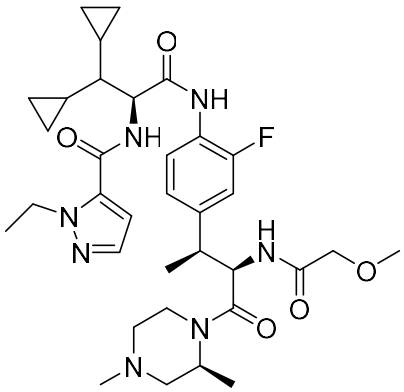
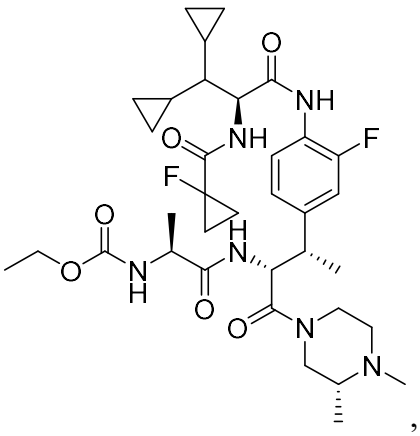
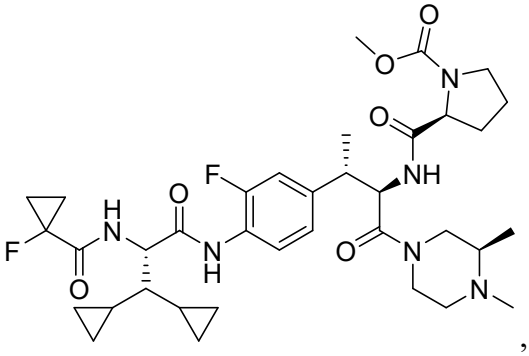
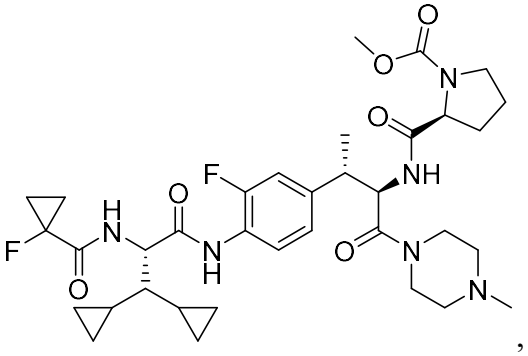

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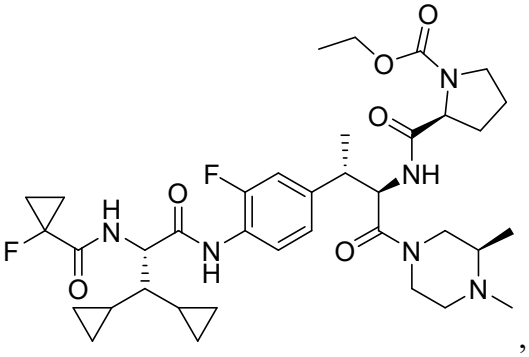
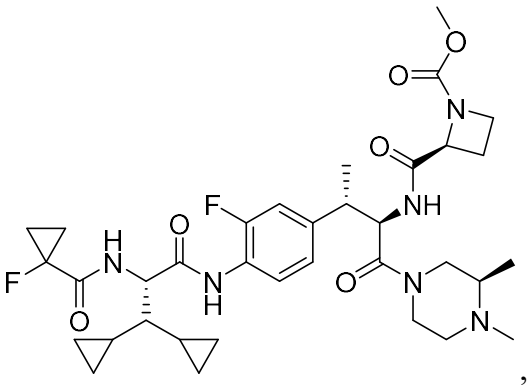
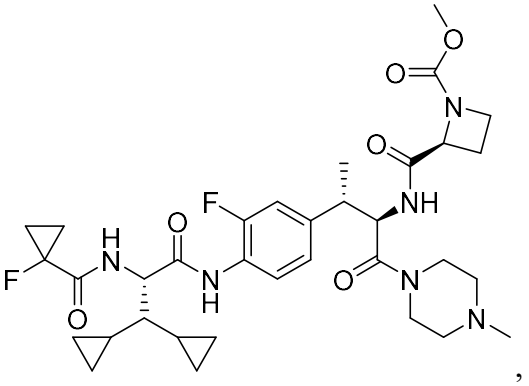
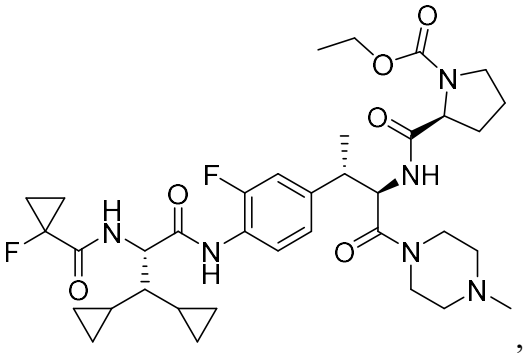
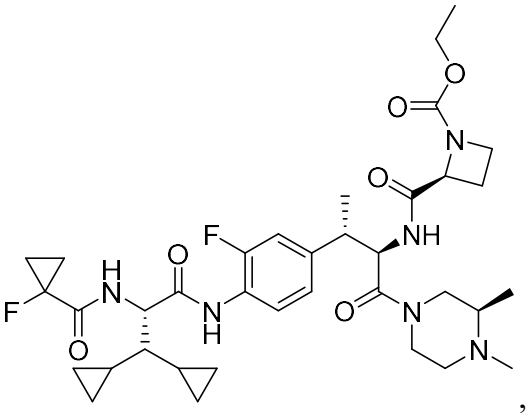
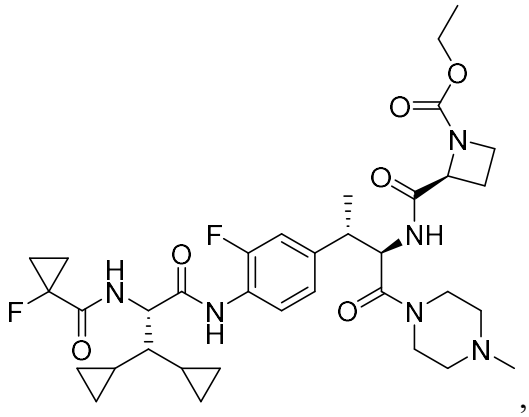
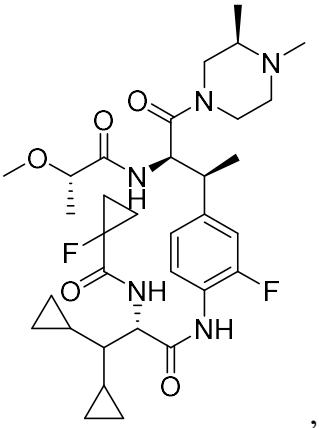
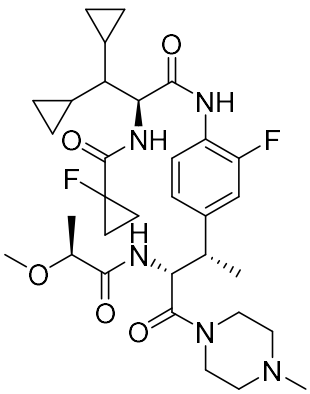
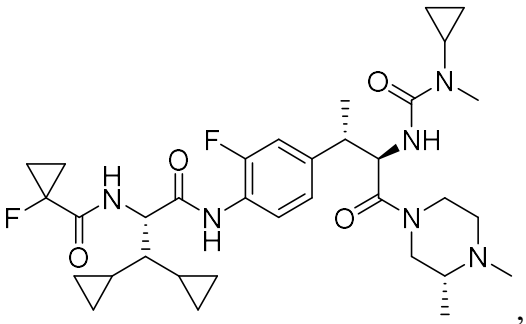

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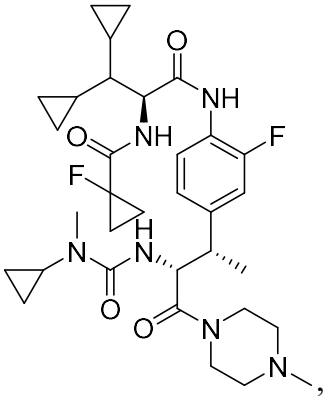
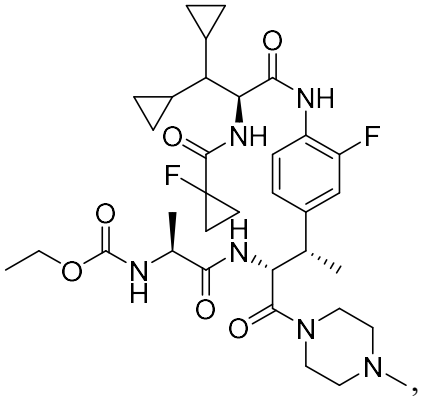
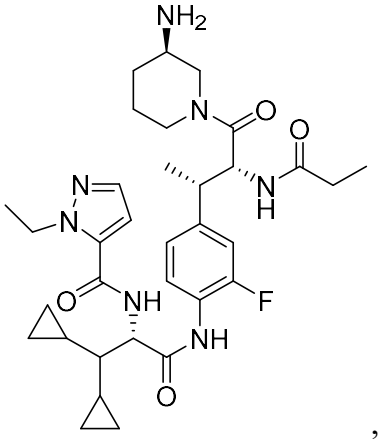
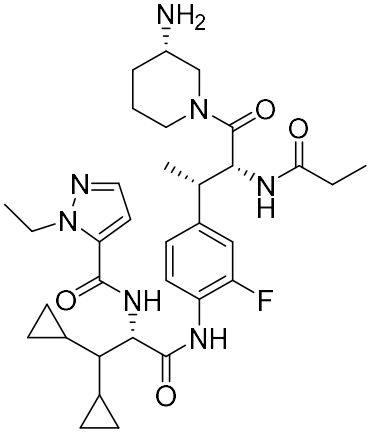
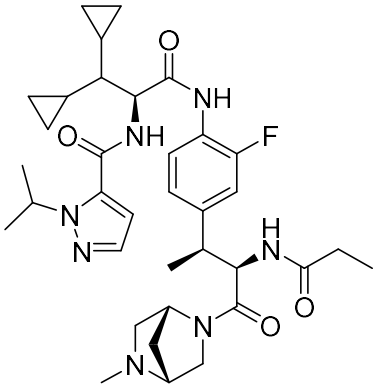
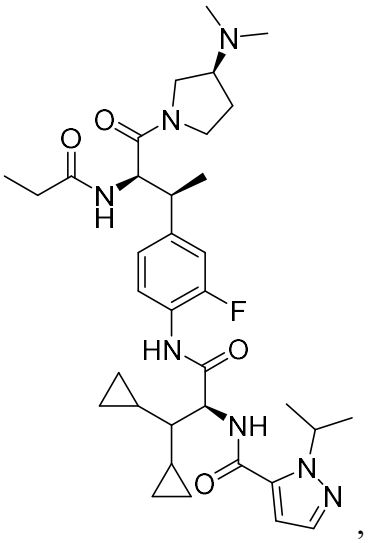
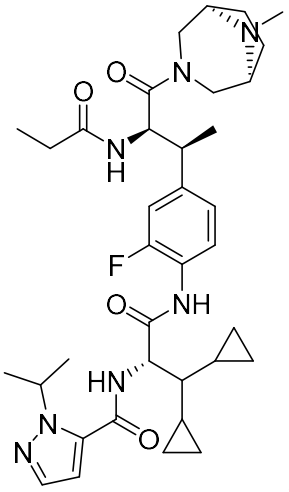
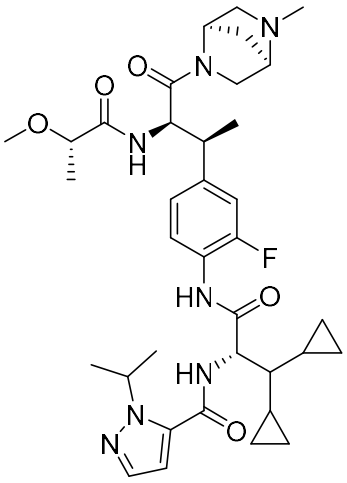
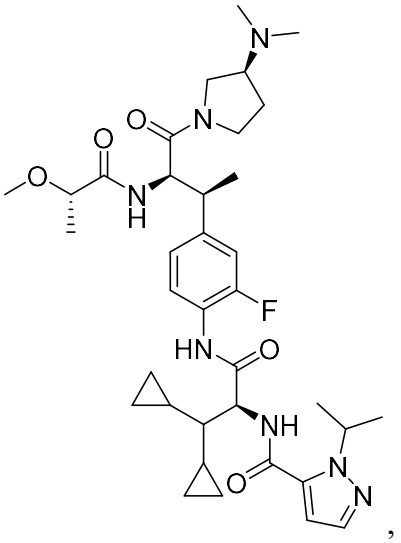

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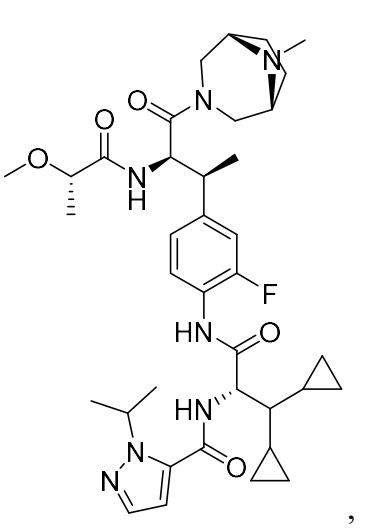
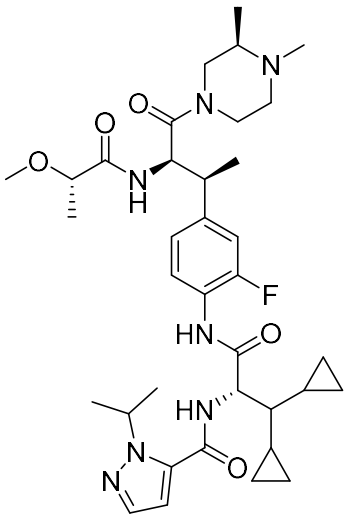
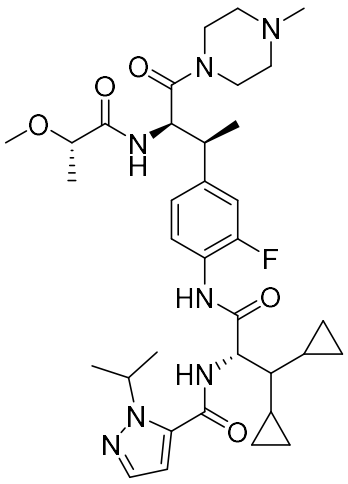
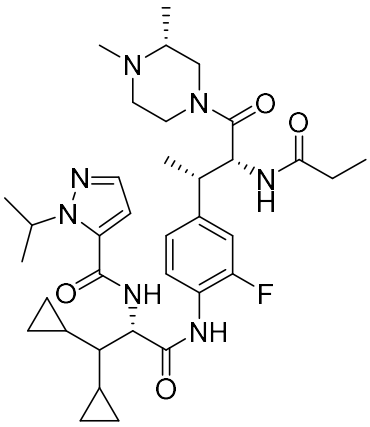
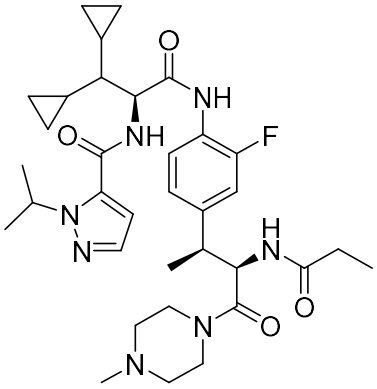
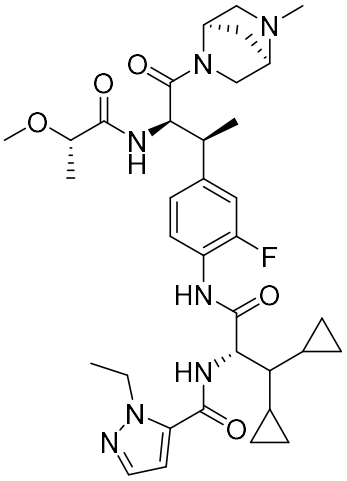
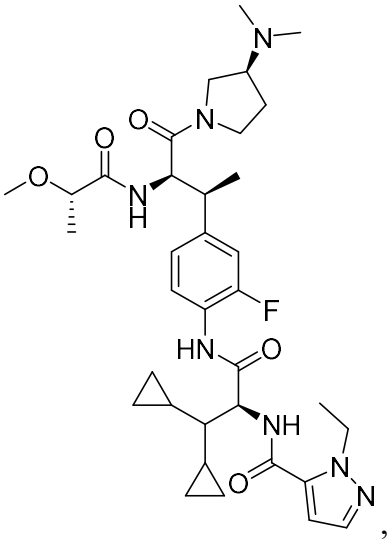
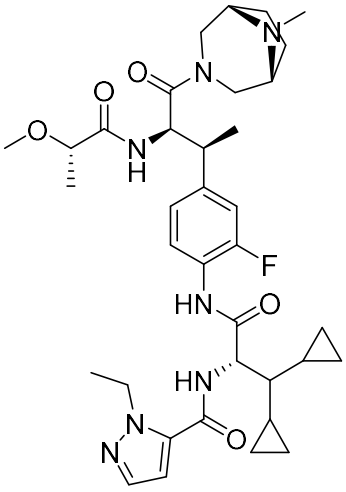
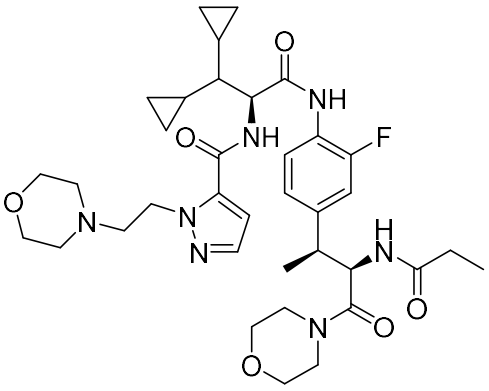

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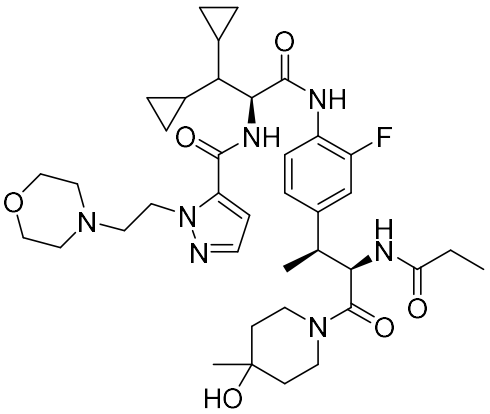
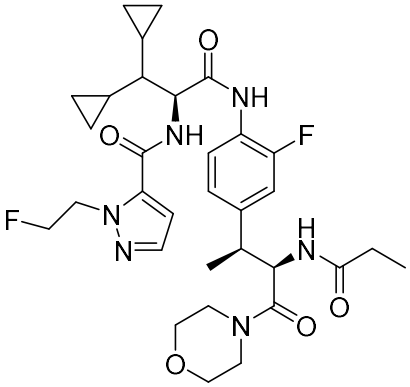
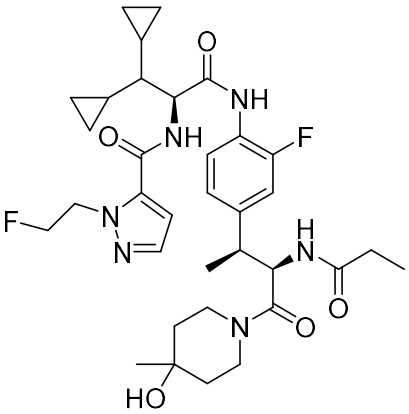
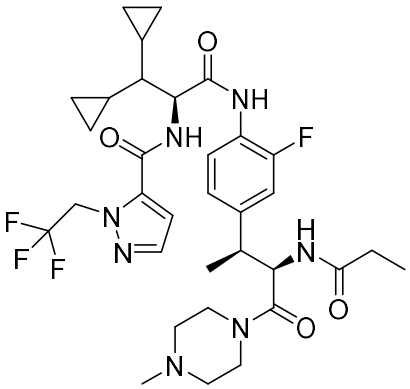
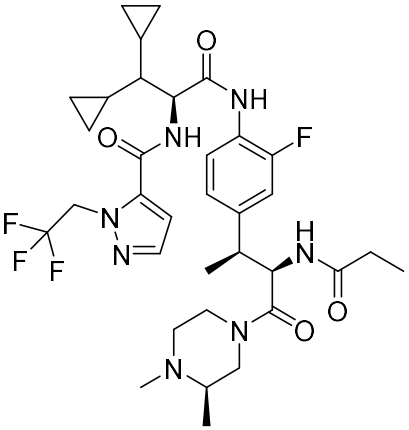
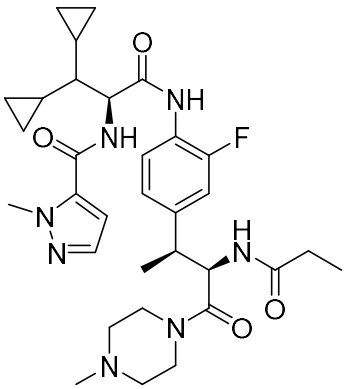
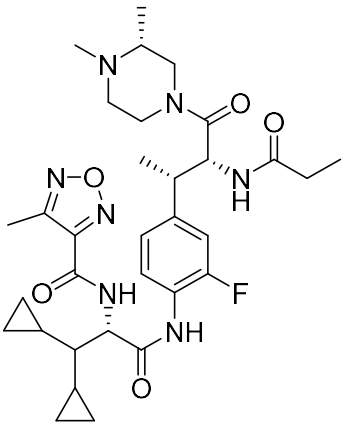
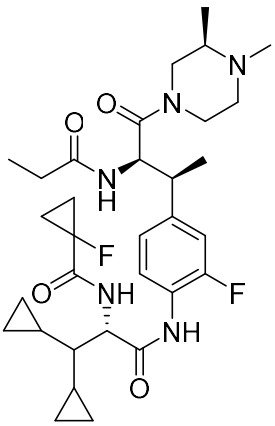
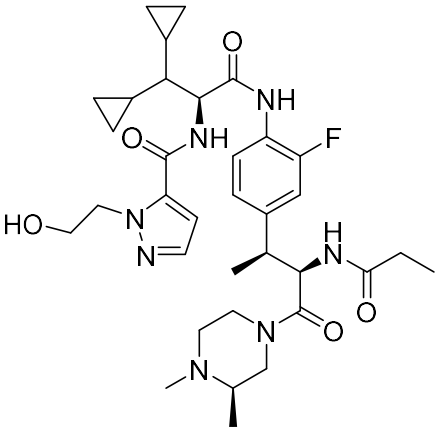
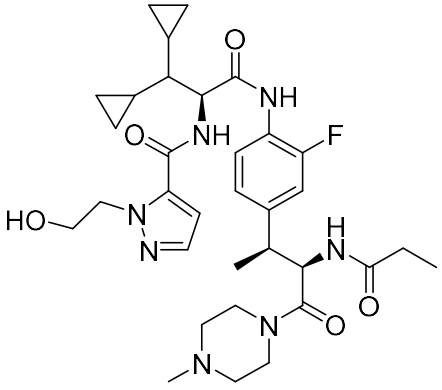
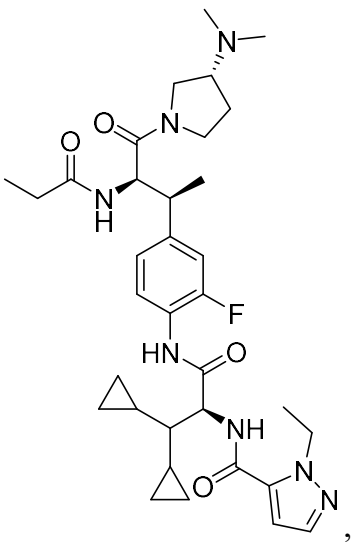

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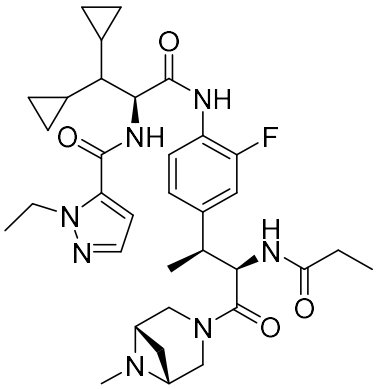
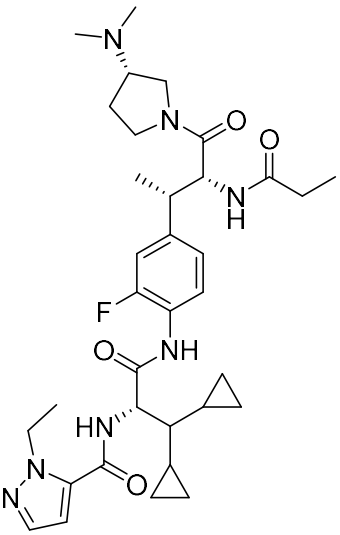
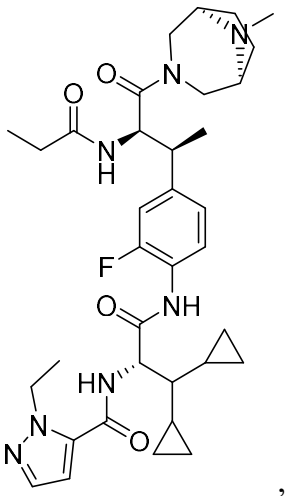
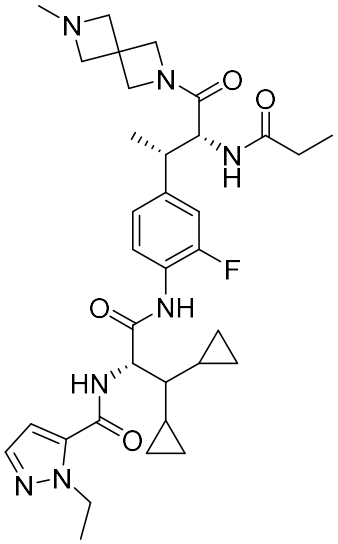
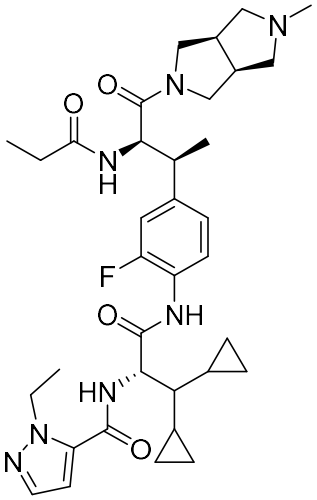
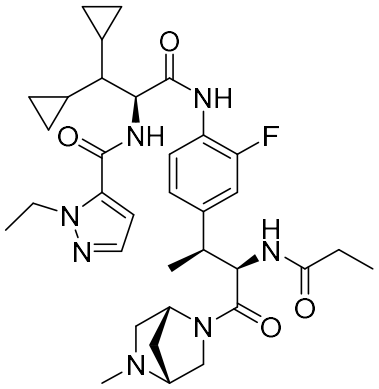
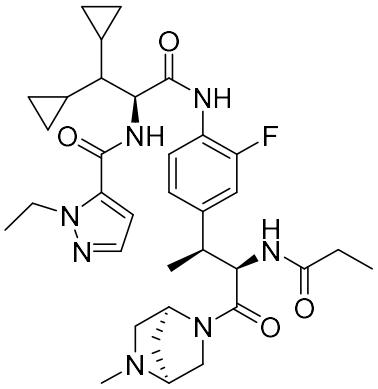
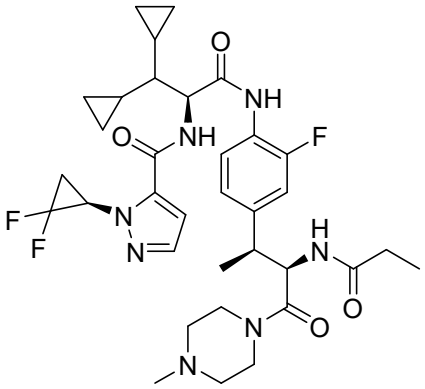
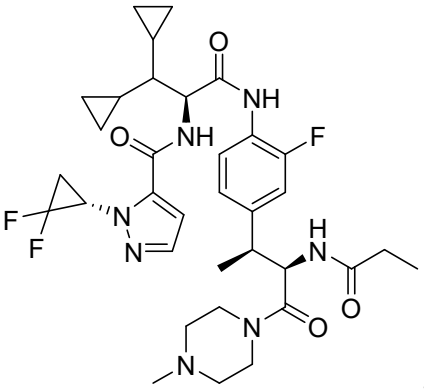

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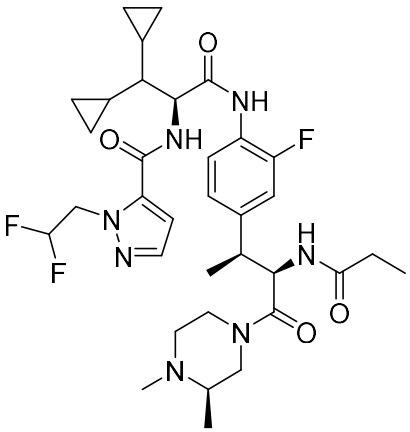
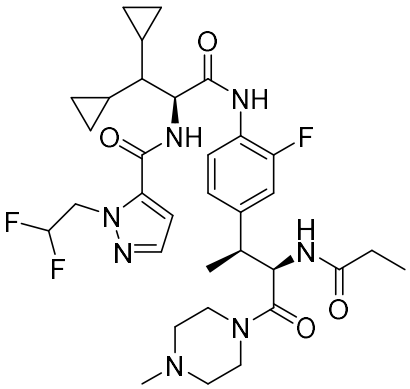
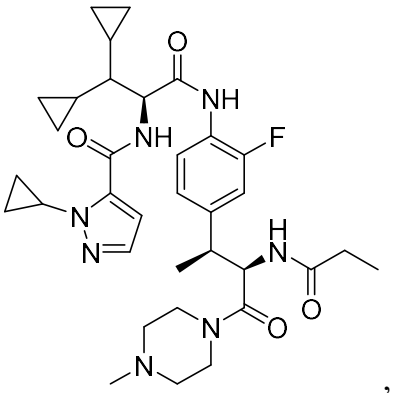
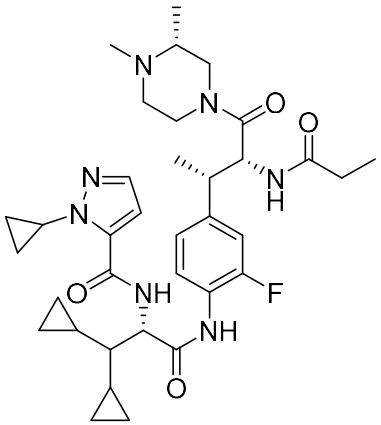
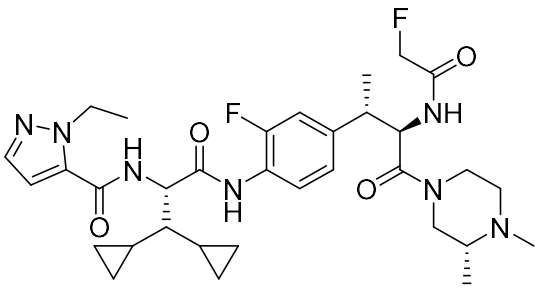
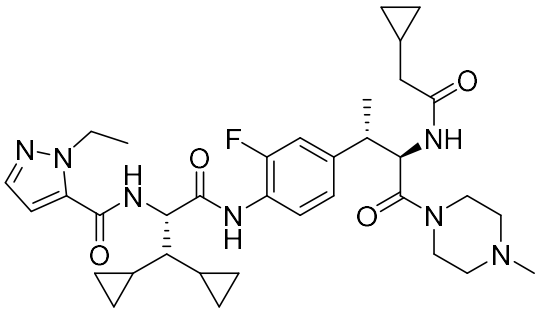
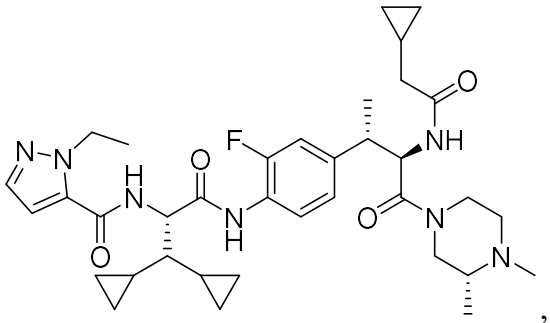
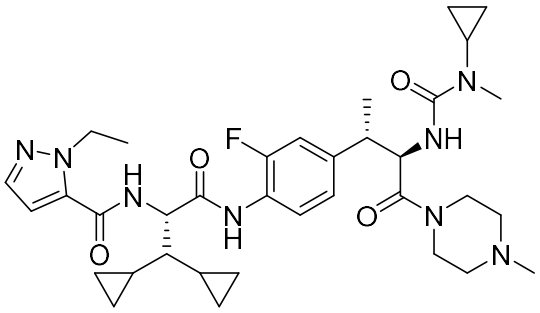
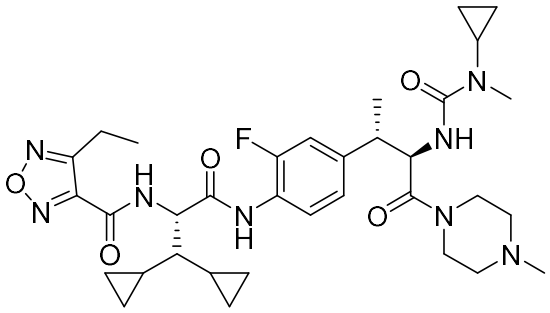

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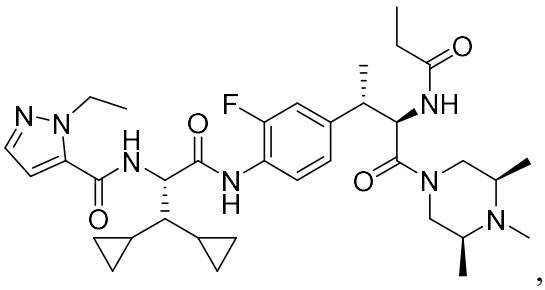
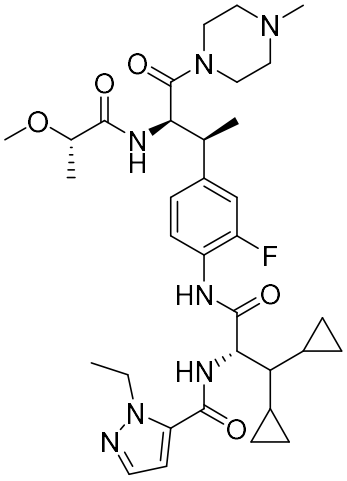
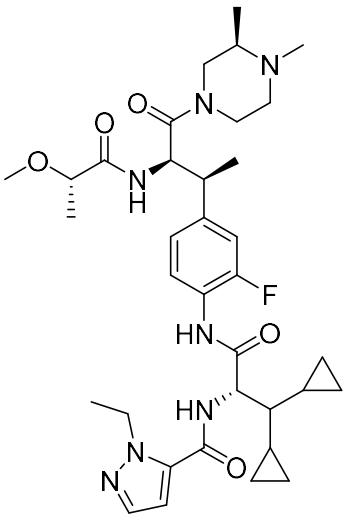
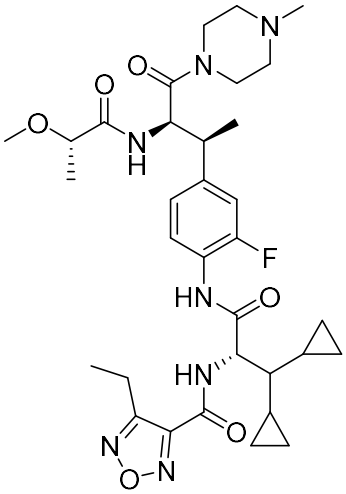
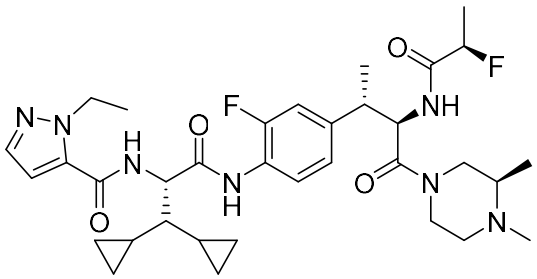
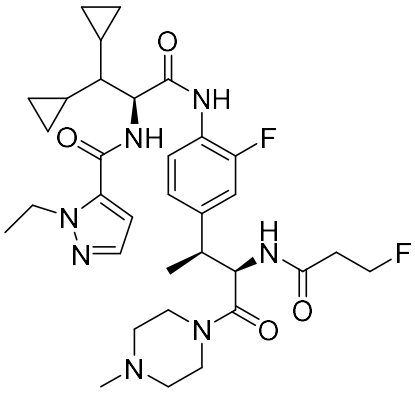
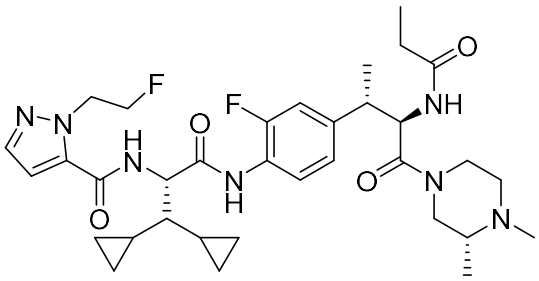
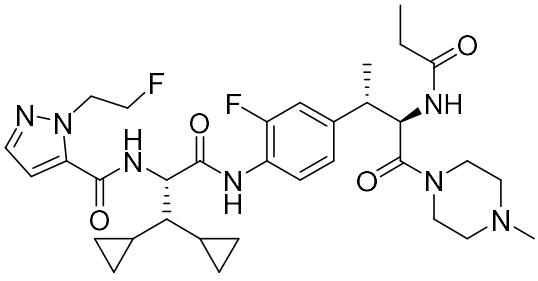
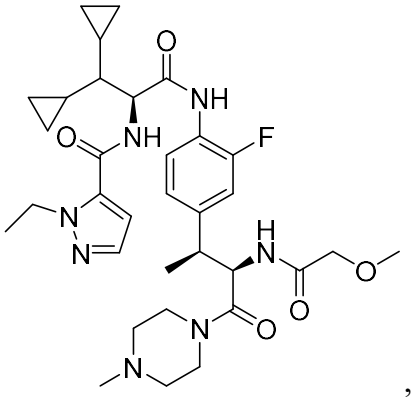

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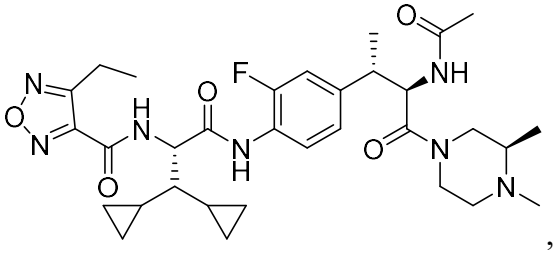
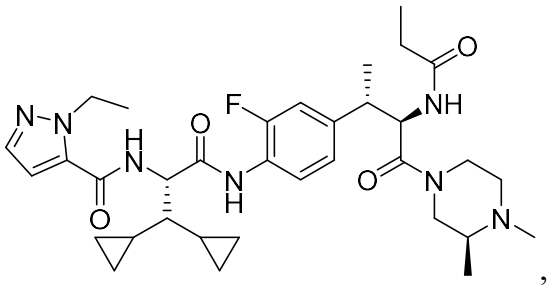
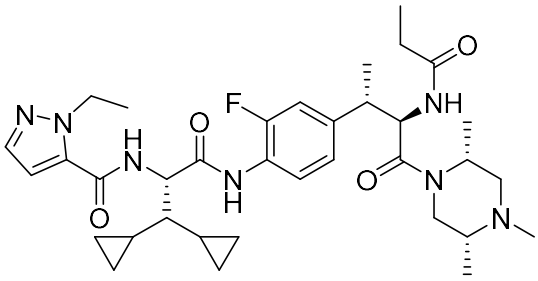
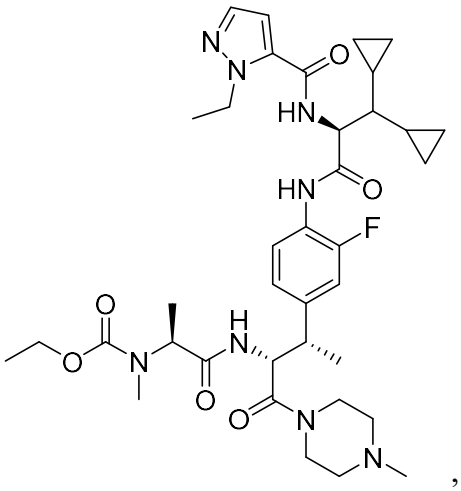
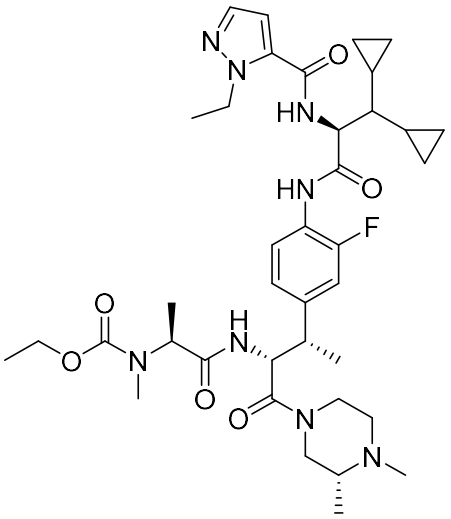
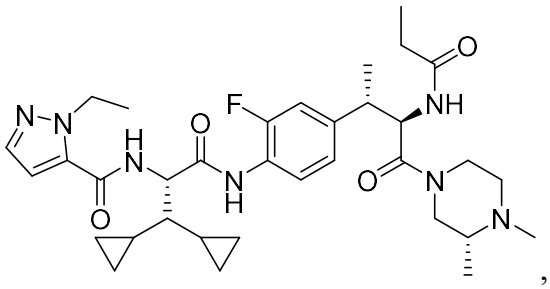
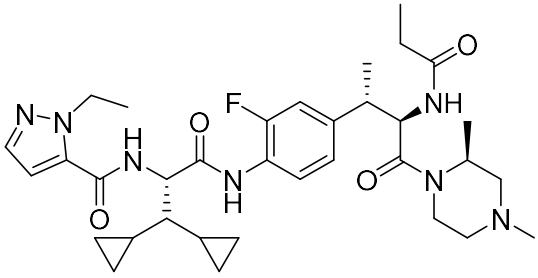
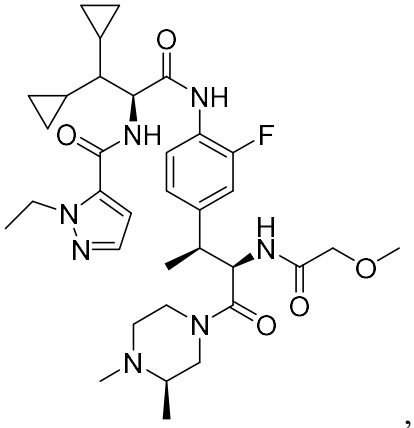

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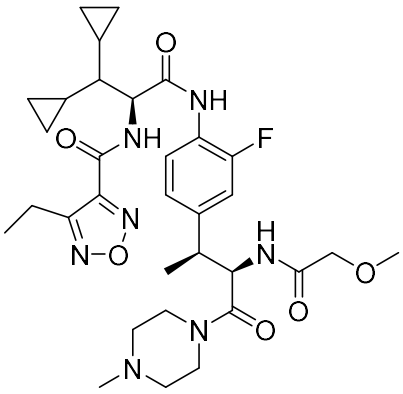
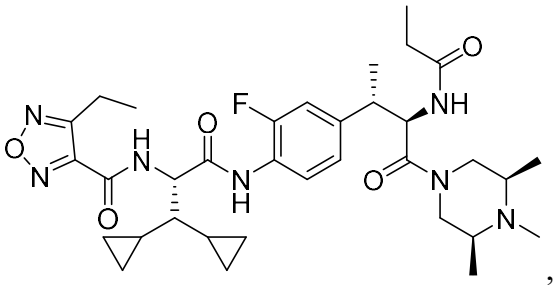
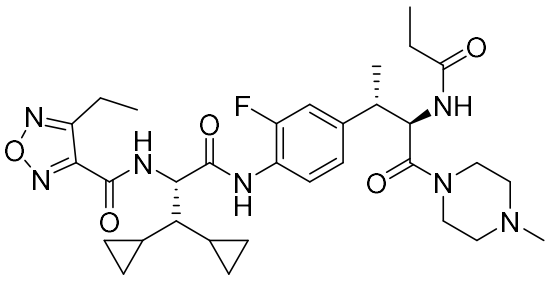
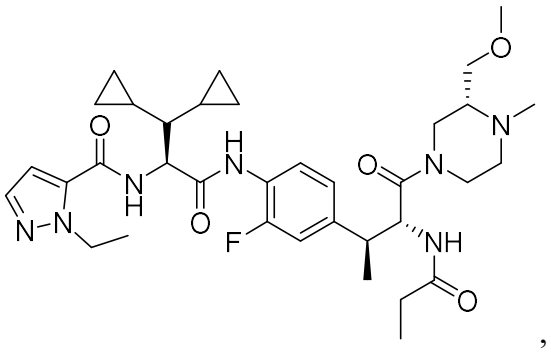
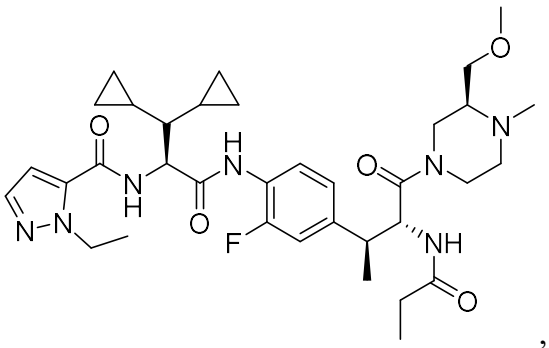
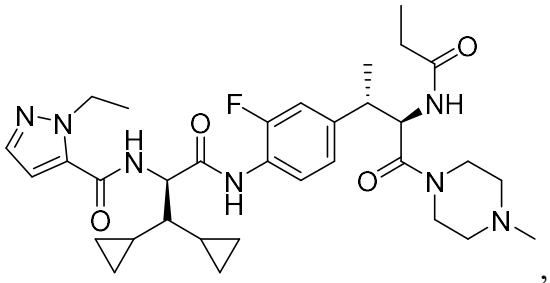
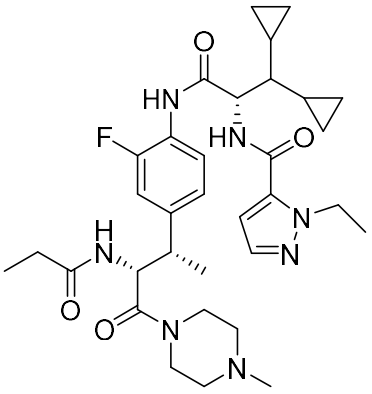

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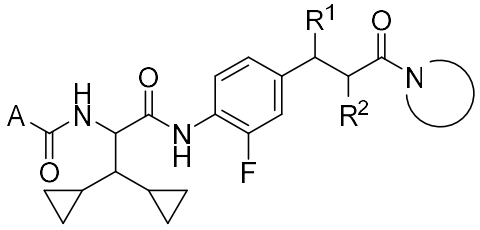
62. A pharmaceutical composition comprising a compound or salt of any one of claims 1 to 61, and a pharmaceutically acceptable excipient.

63. A compound or salt of any one of claims 1 to 61 or a pharmaceutical composition of claim 62 for use in modulating IL-17A.

64. Use of a compound or salt of any one of claims 1 to 61 or a pharmaceutical composition of claim 62 in the manufacture of a medicament for treating an inflammatory disease or condition.

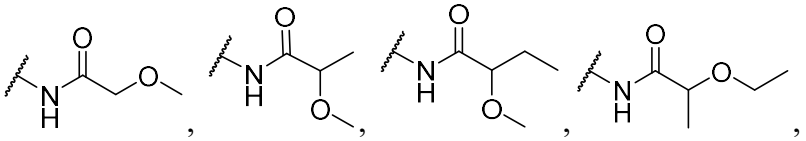
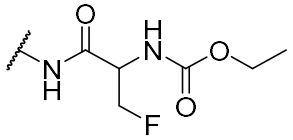
65. The use of claim 64, wherein the inflammatory disease or condition is selected from plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa, rheumatoid arthritis, Palmoplantar Psoriasis, Spondyloarthritis, and Non-infectious Uveitis.

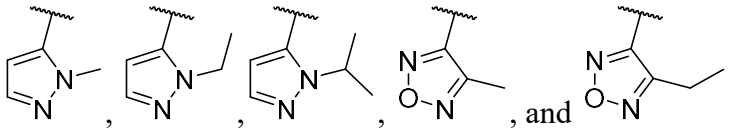
66. The compound or salt of claim 5, of the formula:

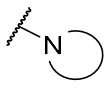
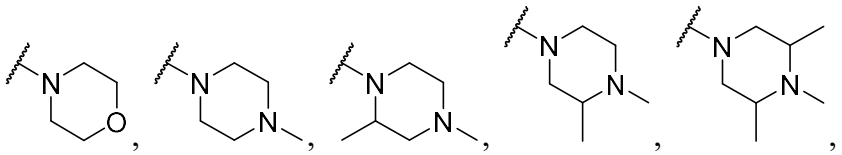
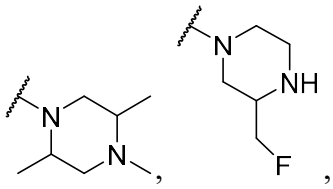
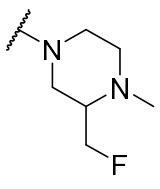
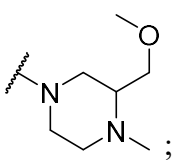

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wherein:

R^1 is methyl;

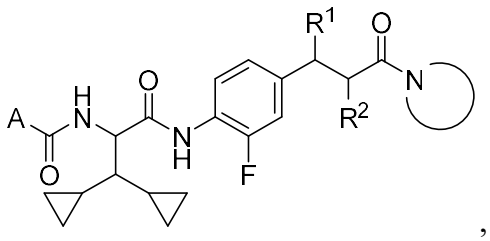
R^2 is selected from: 
, and 
;

A is selected from: 
, and
; and


is selected from: 
, 
, 
, and 
;

or a pharmaceutically acceptable salt thereof.

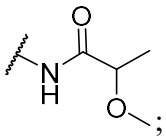
67. The compound or salt of claim 66, of the formula:

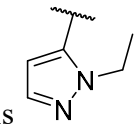


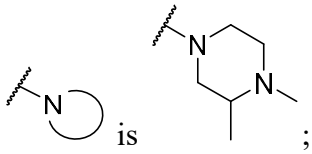
,

wherein:

R^1 is methyl;

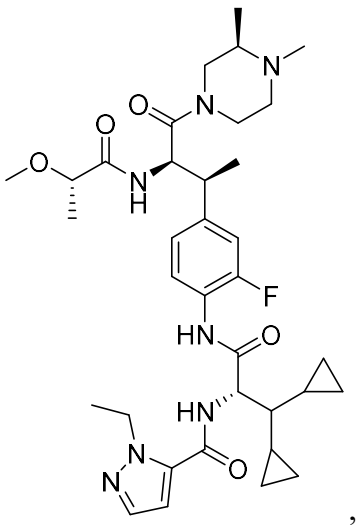
R^2 is ;

A is ; and

 is ;

or a pharmaceutically acceptable salt thereof.

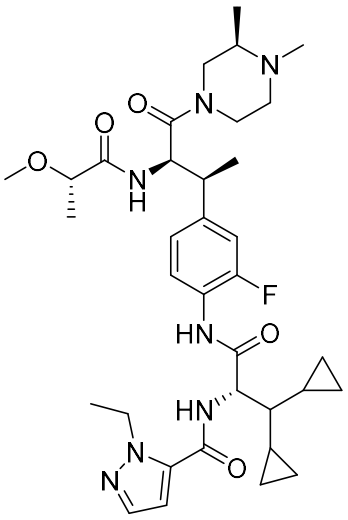
68. The compound or salt of claim 67, of the formula:



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or a pharmaceutically acceptable salt thereof.

69. The compound of claim 68 which is:



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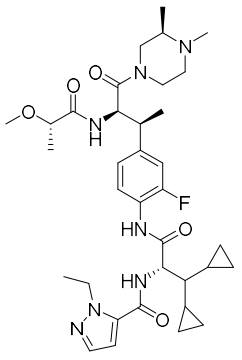
70. A pharmaceutical composition comprising a compound or salt of claim 67, and a pharmaceutically acceptable excipient.

71. A pharmaceutical composition comprising a compound or salt of claim 68, and a pharmaceutically acceptable excipient.

72. A pharmaceutical composition comprising a compound of claim 69, and a pharmaceutically acceptable excipient.

73. Use of a compound or salt of any one of claims 66 to 69, or a pharmaceutical composition of any one of claims 70 to 72 in the manufacture of a medicament for treating an inflammatory disease or condition, wherein the inflammatory disease or condition is selected from plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa, rheumatoid arthritis, Palmoplantar Psoriasis, Spondyloarthritis, and Non-infectious Uveitis.

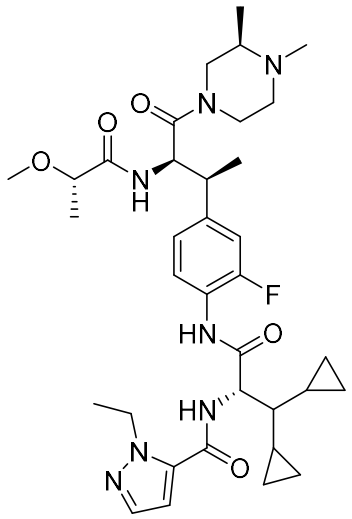
74. The use of claim 73 wherein the compound is:



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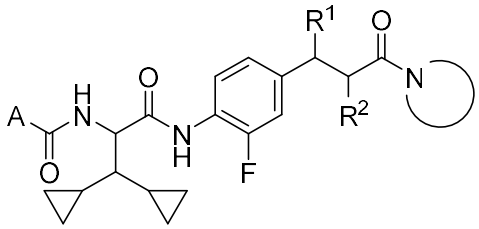
and wherein the inflammatory disease or condition is plaque psoriasis.

75. The use of claim 74 wherein the compound is:



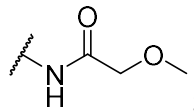
and wherein the inflammatory disease or condition is selected from psoriatic arthritis, ankylosing spondylitis, or spondyloarthritis.

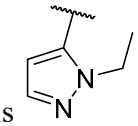
76. The compound or salt of claim 66, of the formula:

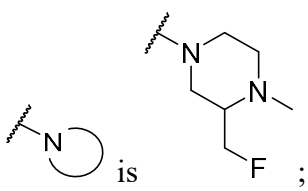


wherein:

R^1 is methyl;

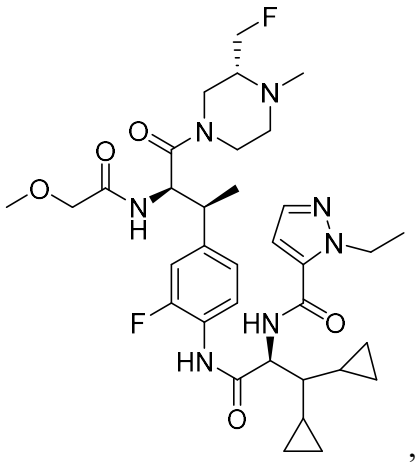
R^2 is ;

A is ; and

 is ;

or a pharmaceutically acceptable salt thereof.

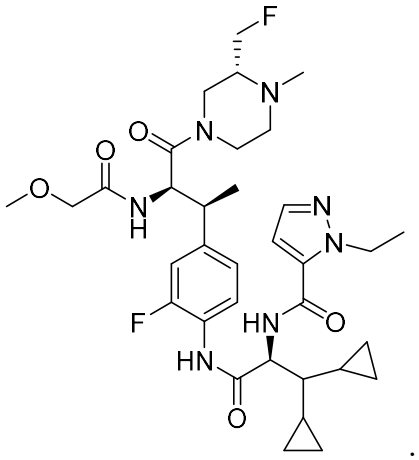
77. The compound or salt of claim 76, of the formula:



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or a pharmaceutically acceptable salt thereof.

78. The compound of claim 77 which is:



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79. A pharmaceutical composition comprising a compound or salt of claim 76, and a pharmaceutically acceptable excipient.

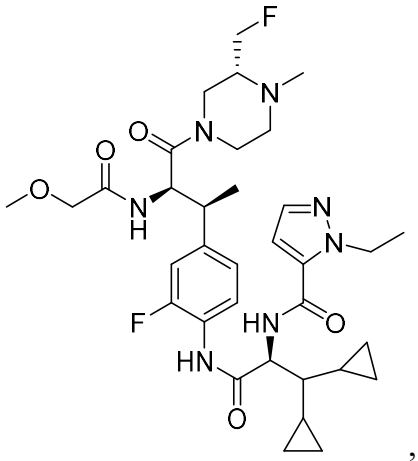
80. A pharmaceutical composition comprising a compound or salt of claim 77, and a pharmaceutically acceptable excipient.

81. A pharmaceutical composition comprising a compound of claim 78, and a pharmaceutically acceptable excipient.

82. Use of a compound or salt of any one of claims 76 to 78, or a pharmaceutical composition of any one of claims 79 to 81 in the manufacture of a medicament for treating an inflammatory disease or condition, wherein the inflammatory disease or condition is selected from plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis,

erythrodermic psoriasis, psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa, rheumatoid arthritis, Palmoplantar Psoriasis, Spondyloarthritis, and Non-infectious Uveitis.

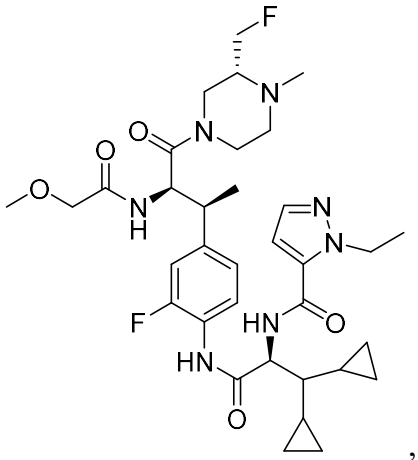
83. The use of claim 82 wherein the compound is:



,

and wherein the inflammatory disease or condition is plaque psoriasis.

84. The use of claim 82 wherein the compound is:



,

and wherein the inflammatory disease or condition is selected from psoriatic arthritis, ankylosing spondylitis, or spondyloarthritis.

85. A compound or salt of any one of claims 1 to 61, 66 to 69, 76 to 78 or a pharmaceutical composition of any one of claims 62, 70 to 72 or 79 to 81 for use in therapy.