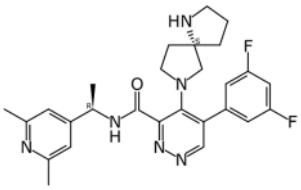
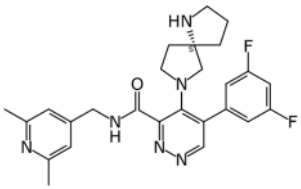
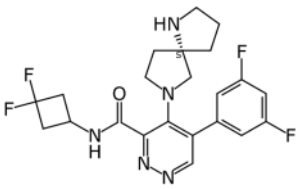
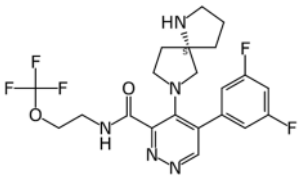
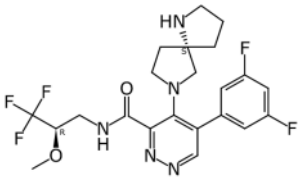
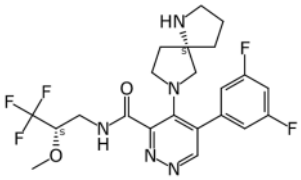
[0059] In one aspect, the compound is selected from:


,

,

,

,

, and

.

[0060] In another aspect, also disclosed herein, is a method of treating a disorder selected from polycystic kidney disease, polycystic liver disease, and ciliopathies, comprising administering to a subject in need thereof a compound of any one Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), or Formula (IIa), or a pharmaceutically acceptable salt thereof. In some embodiments, the disorder is polycystic kidney disease. In some embodiments, the polycystic kidney disease is autosomal dominant polycystic kidney disease (ADPKD).

[0060a] In yet another aspect, there is provided a use of a compound as described herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disorder selected from the group consisting of polycystic kidney disease, polycystic liver disease, and ciliopathies.

[0061] In another aspect, also disclosed herein, is a pharmaceutical composition including a compound of any one Formula (I), Formula (Ia), Formula (Ib), Formula (Ic), Formula (Id), Formula (II), or Formula (IIa), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0062] FIG. 1 depicts how abnormal primary cilia function triggers cystogenesis in autosomal dominant polycystic kidney disease (ADPKD).

[0063] FIG. 2 depicts interplay of calcium ions and cAMP ciliary signaling pathways in renal tissue of (A) healthy individuals and (B) individuals with ADPKD.

[0064] FIG. 3 depicts the mechanism of action by which SSTR3 activation can inhibit adenylyl cyclase activity and decrease cilio-plasma cAMP levels.

[0065] FIG. 4 depicts an analysis of the mRNA expression of SSTR2, SSTR3, SSTR5, and vasopressin receptor 2 (AVPR2) in healthy and cystic tissue.

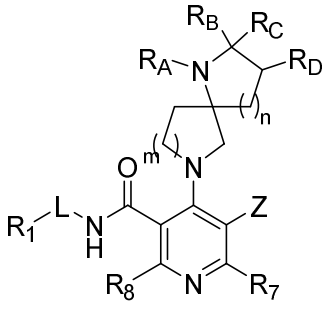
[0066] FIG. 5 depicts the effect of (A) compound 105 and (B) compound 108 in an *in vitro* 3D cystogenesis model.

[0067] FIG. 6 depicts the effect of oral administration of compound 108 on (A) left kidney weight and (B) kidney cystic index in ADPKD mice.

CLAIMS

We Claim:

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

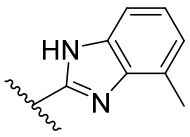


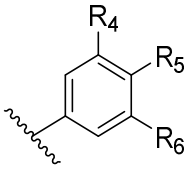
(I)

wherein:

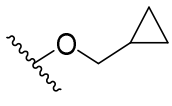
R_1 is unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted 6-membered heterocycloalkyl, unsubstituted or substituted C_{5-7} bicycloalkyl, unsubstituted or substituted aryl, or unsubstituted or substituted 6-membered heteroaryl; wherein if R_1 is substituted then R_1 is substituted with 1-3 X, wherein each X is independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} fluoroalkyl, C_{1-6} fluoroalkoxy, C_{3-6} cycloalkoxy, CN, and OH;

L is a bond or CR_2R_3, wherein R_2 is H or C_{1-6} alkyl, and R_3 is H, C_{1-6} alkyl, C_{1-6} alkoxy, CH_2OCH_3, or C_{1-6} fluoroalkyl; or R_2 and R_3 together with the carbon to which they are attached form a C_{3-6} cycloalkyl;

Z is 

or 

wherein R_4 is H or halogen; R_5 is H or halogen; and R_6 is H, halogen, CN, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_7 is H, D, CN, or 

;

R_8 is H, D, OH, C_{1-6} alkyl, C_{1-6} alkoxy, NH_2, or $-NH(CH_2)_2OH$;

R_A is H, $C(O)OC_{1-6}$ alkyl, or $C(O)C_{1-6}$ alkyl;

R_B is H, D, or C_{1-6} alkyl;

R_C is H or D;

R_D is H or halogen;

m is an integer selected from 0 and 1; and

n is an integer selected from 0, 1, and 2.

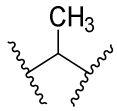
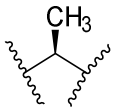
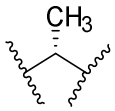
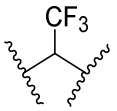
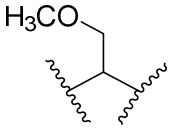
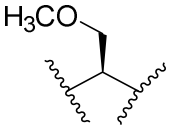
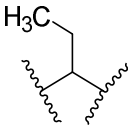
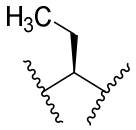
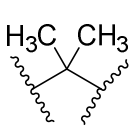
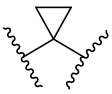
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L is a bond.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L is CR_2R_3.

4. The compound of any one of claims 1 and 3, or a pharmaceutically acceptable salt thereof, wherein R_2 is H or methyl.

5. The compound of any one of claims 1, 3, and 4, or a pharmaceutically acceptable salt thereof, wherein R_3 is H, methyl, ethyl, trifluoromethyl, or CH_2OCH_3.

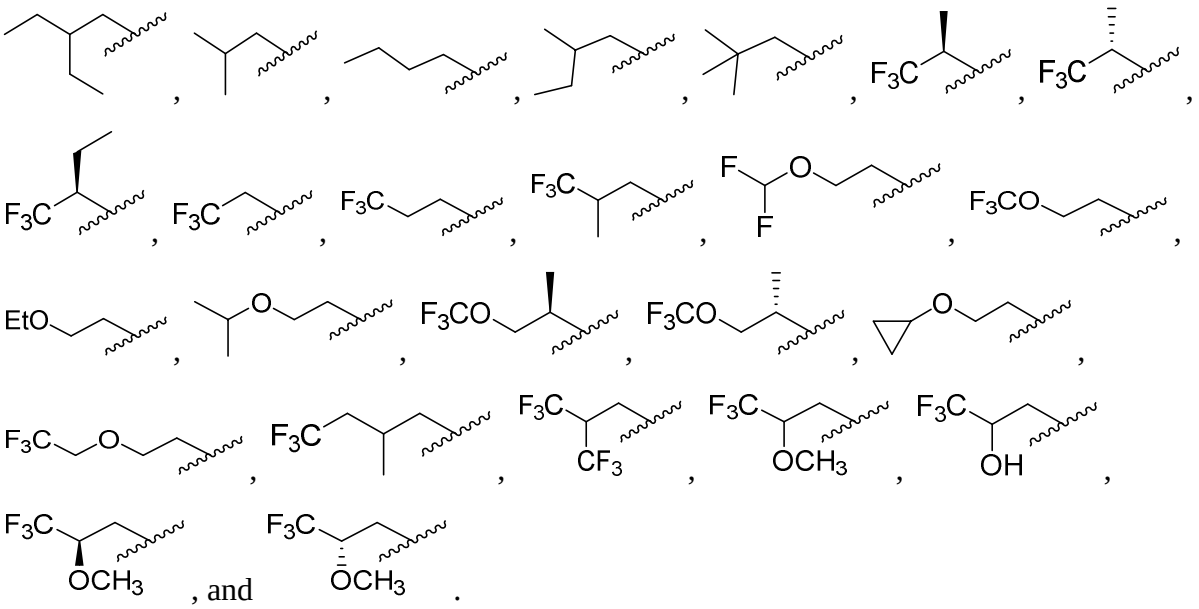
6. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein L is selected from the group consisting of:

CH_2, , , , , , , , , , and .

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R_1 is unsubstituted or substituted C_{1-4} alkyl.

8. The compound of claim 7, or a pharmaceutically acceptable salt thereof, wherein if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from the group consisting of methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, cyclopropoxy, and OH.

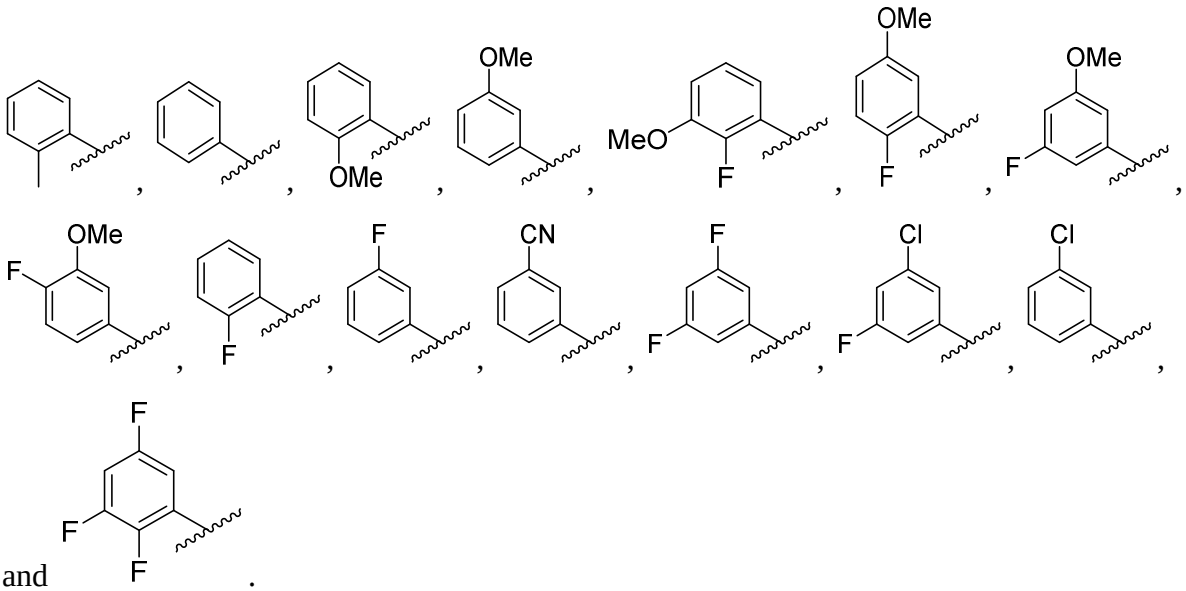
9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of:


F3C
F3C
F3C

13. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R_1 is unsubstituted or substituted phenyl.

14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein if R_1 is substituted then R_1 is substituted with 1-3 X, wherein each X is independently selected from the group consisting of fluoro, chloro, methyl, methoxy, and CN.

15. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of:

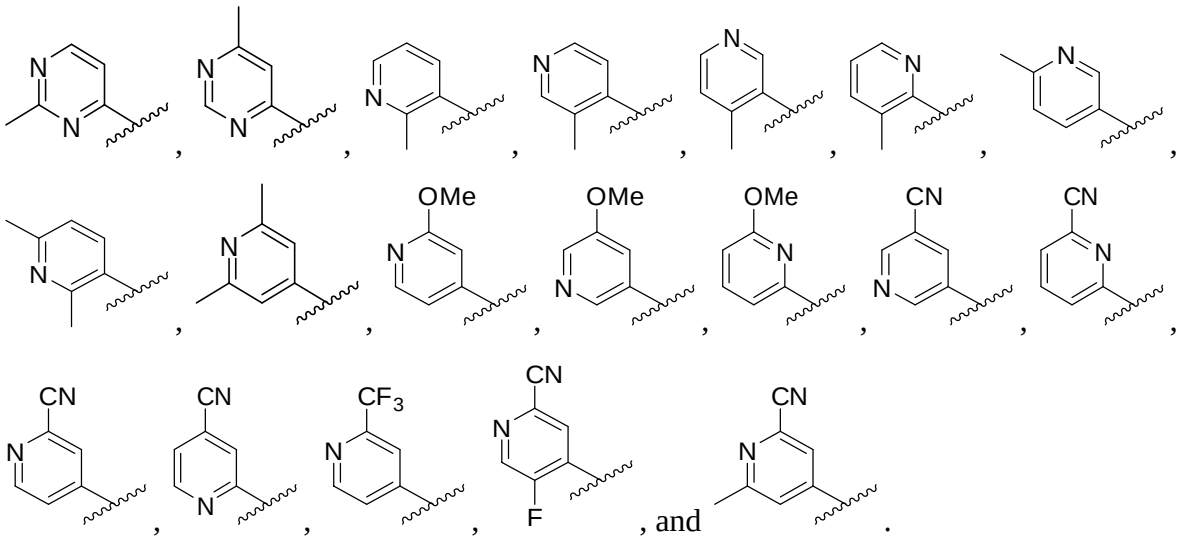


and .

16. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R_1 is unsubstituted or substituted pyridinyl, or unsubstituted or substituted pyrimidinyl.

17. The compound of claim 16, or a pharmaceutically acceptable salt thereof, wherein if R_1 is substituted then R_1 is substituted with 1-2 X, wherein each X is independently selected from the group consisting of fluoro, methyl, trifluoromethyl, methoxy, and CN.

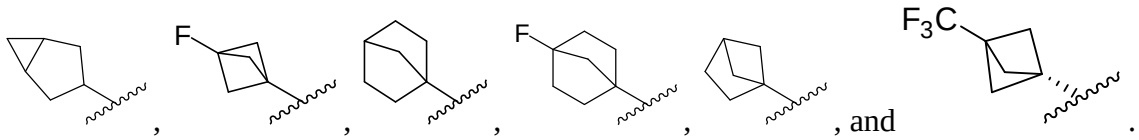
18. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of:



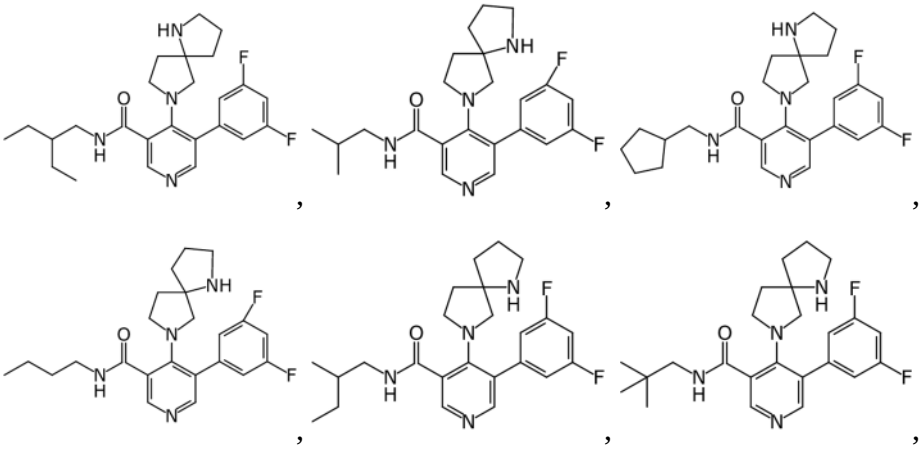
19. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R_1 is unsubstituted or substituted C_{5-7} bicycloalkyl.

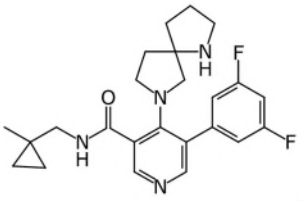
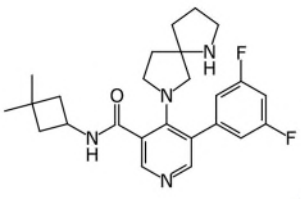
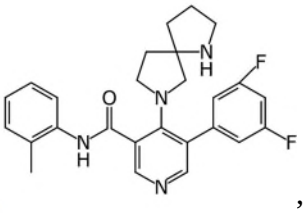
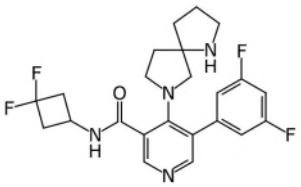
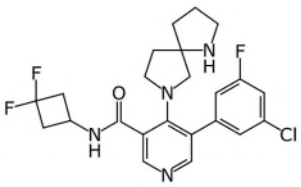
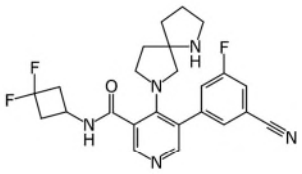
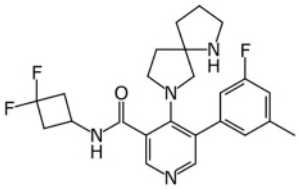
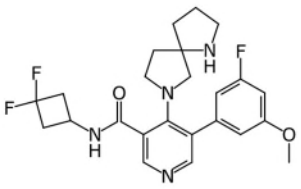
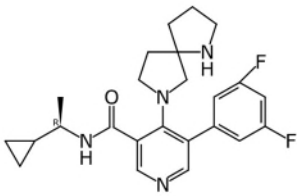
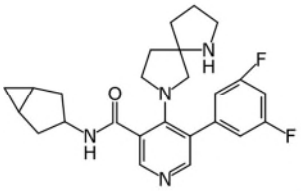
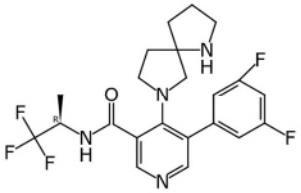
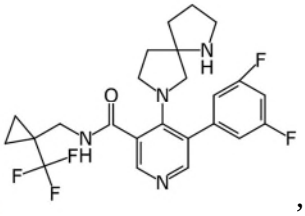
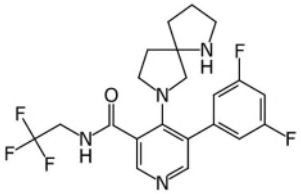
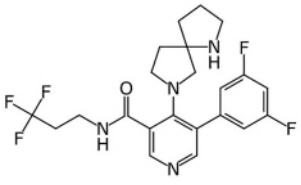
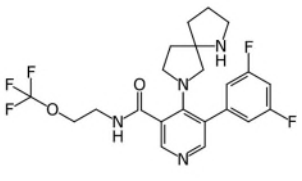
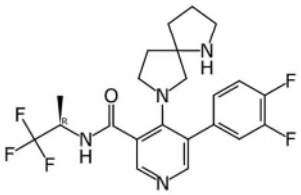
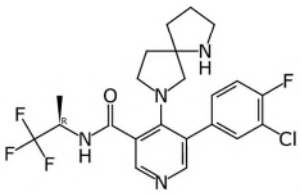
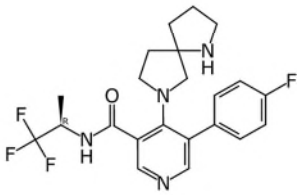
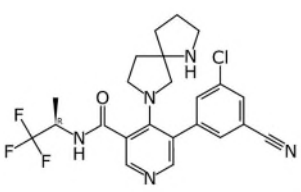
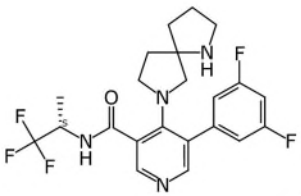
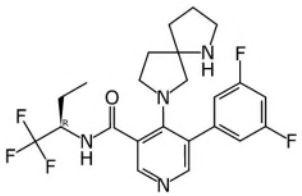
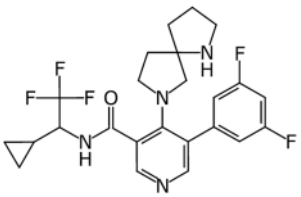
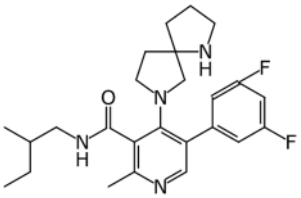
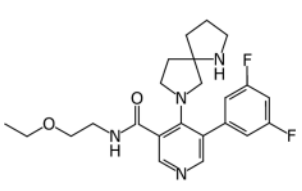
20. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein if R_1 is substituted then R_1 is substituted with fluoro or trifluoromethyl.

21. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from the group consisting of:



22. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

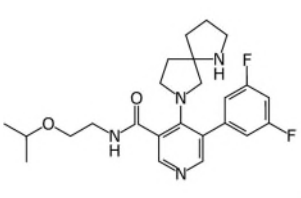
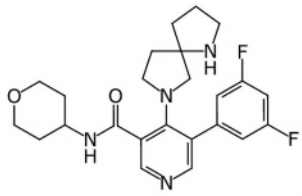
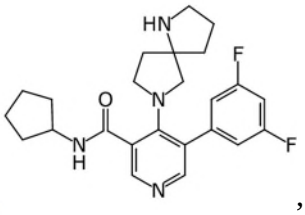
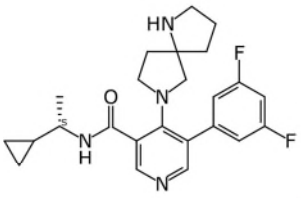
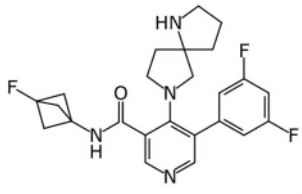
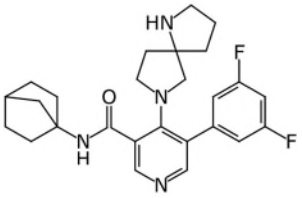
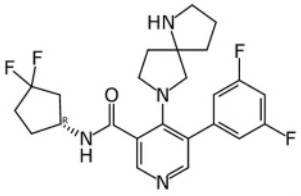
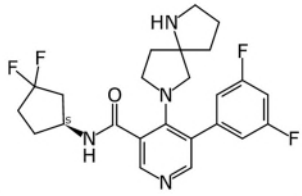
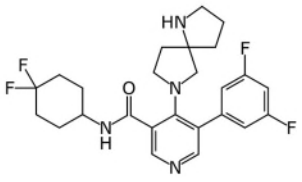
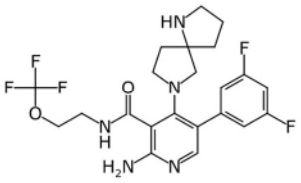
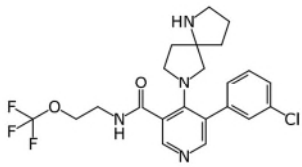
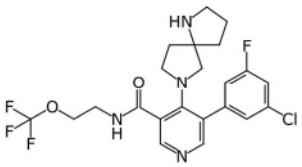
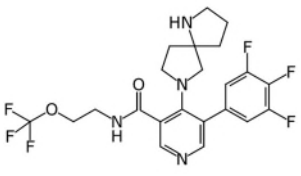
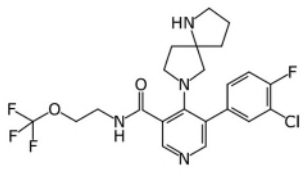
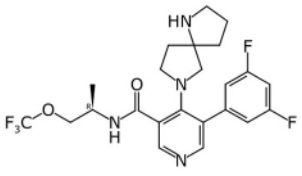
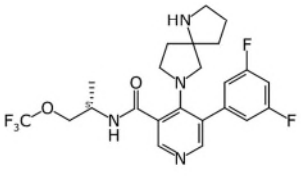
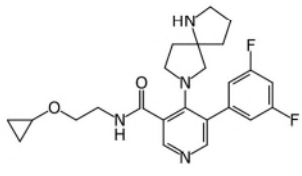
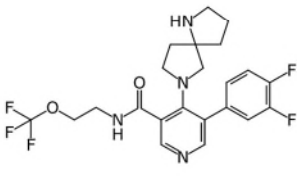
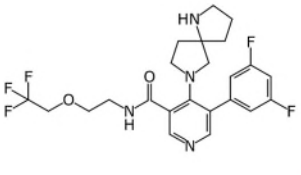
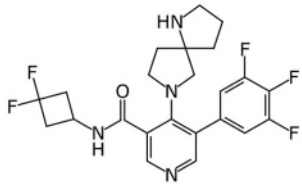
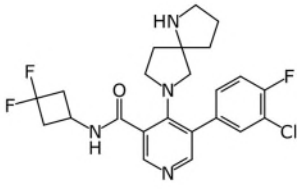
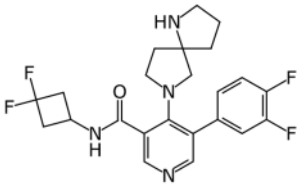
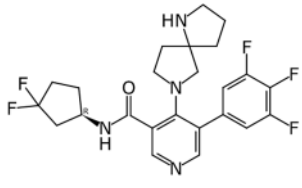
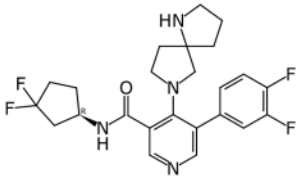


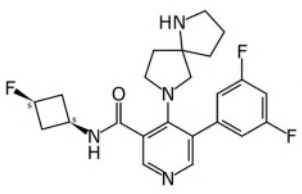
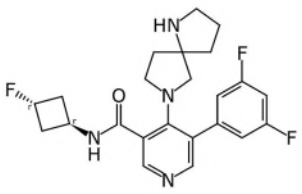
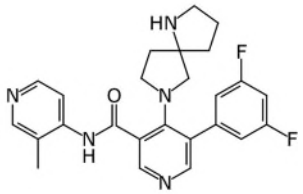
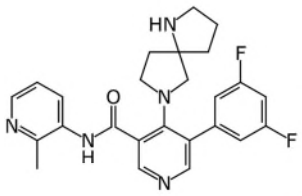
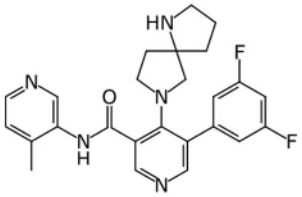
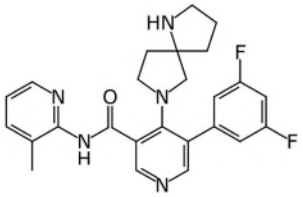
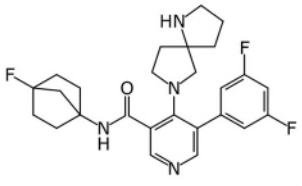
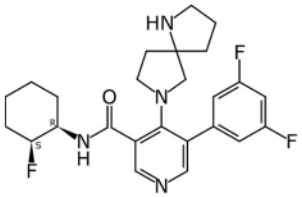
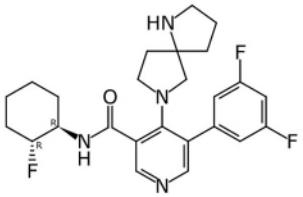
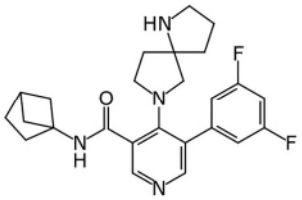
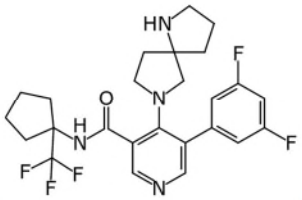
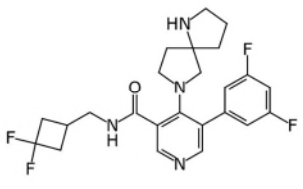
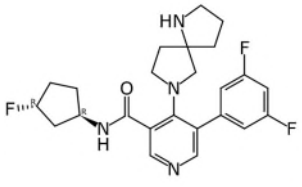
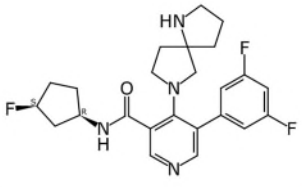
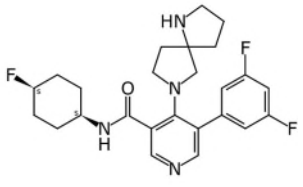
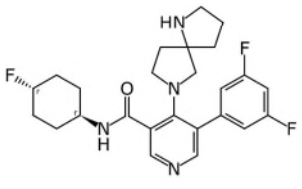
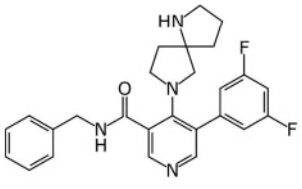
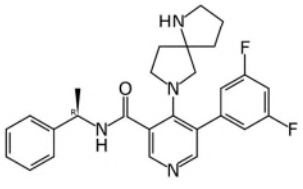
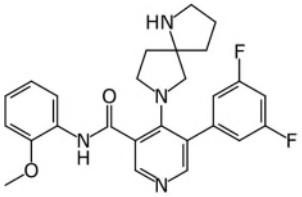
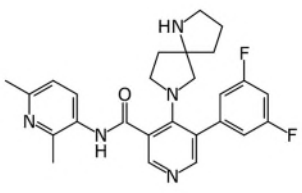
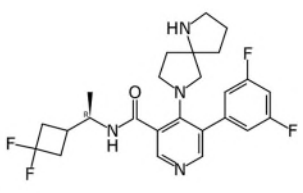
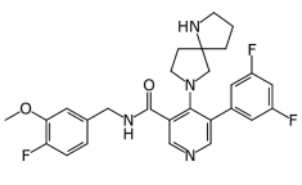
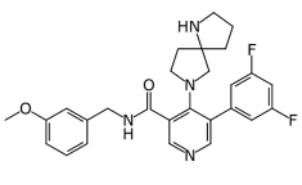
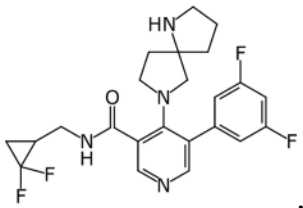

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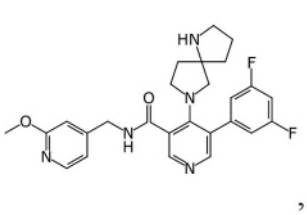
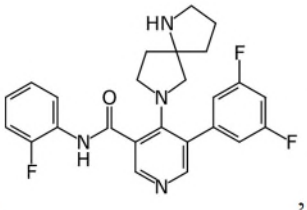
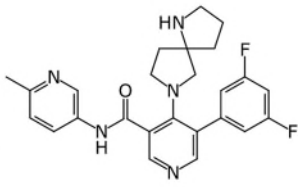
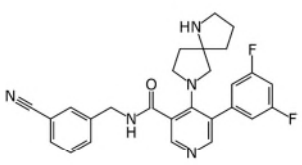
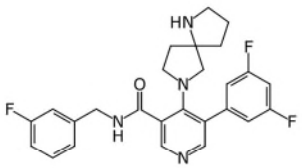
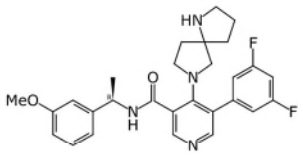
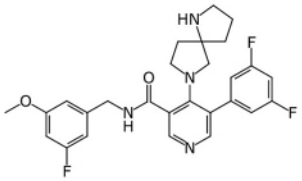
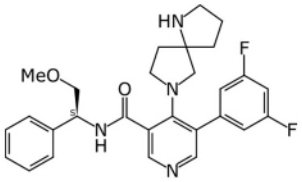
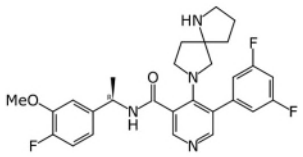
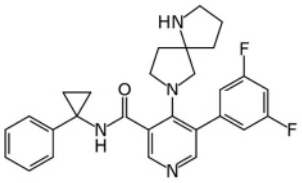
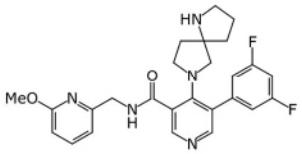
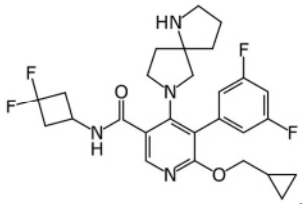
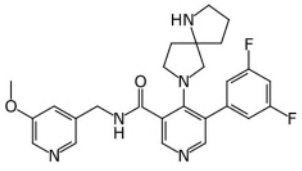
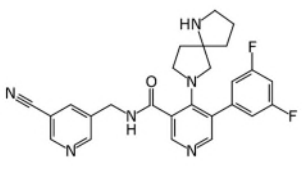
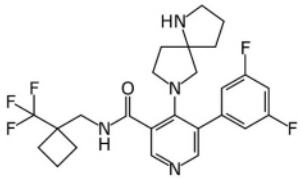
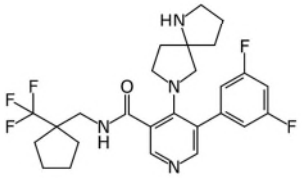
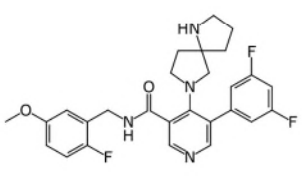
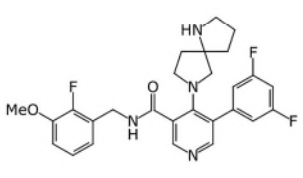
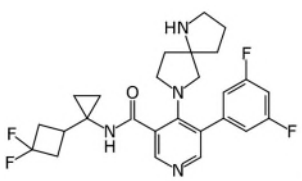
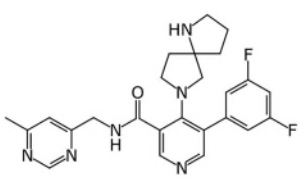
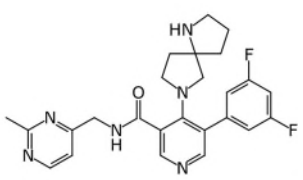
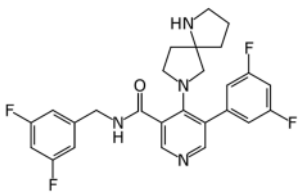
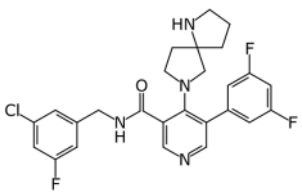
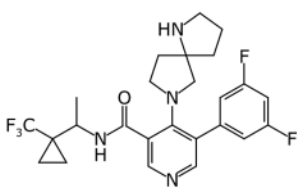
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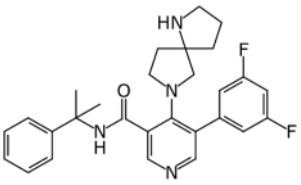
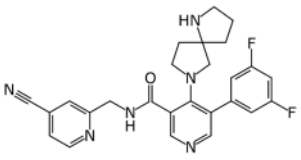
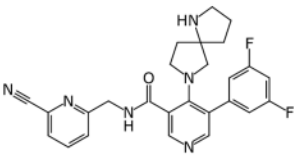
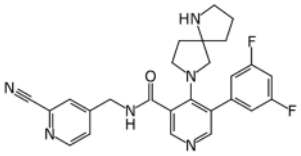
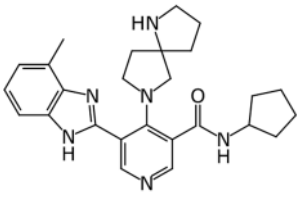

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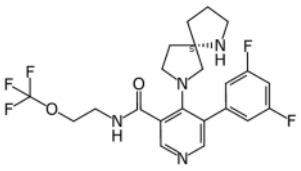
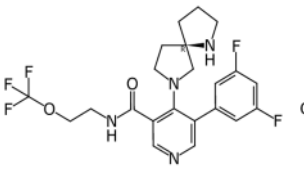
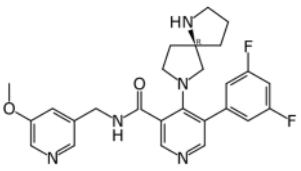
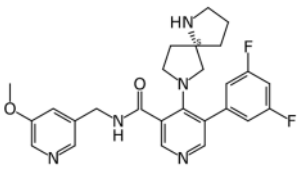
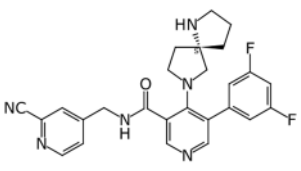
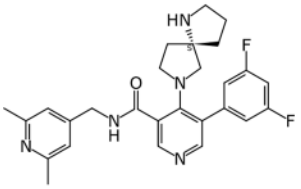
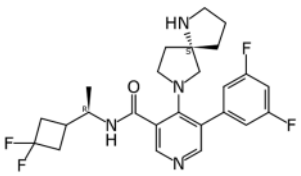
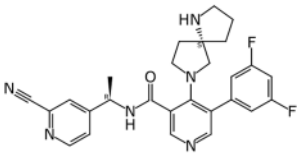
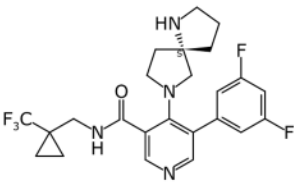
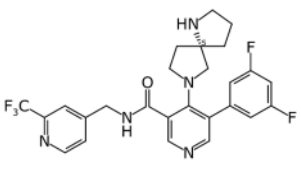
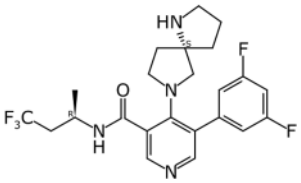
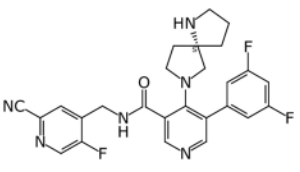
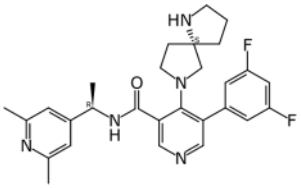
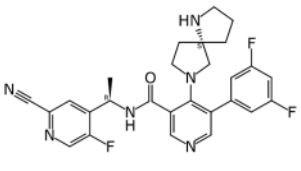
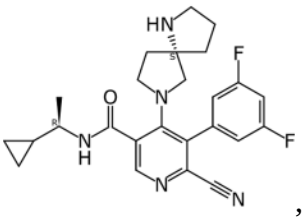
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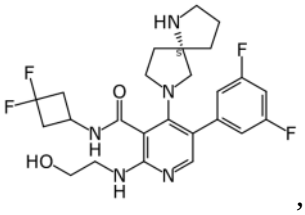
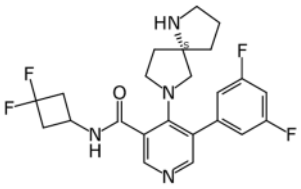
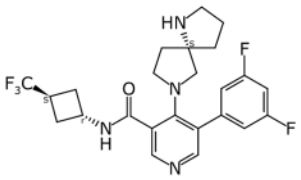
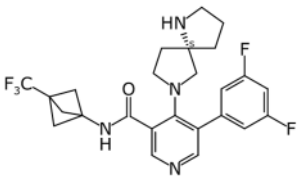
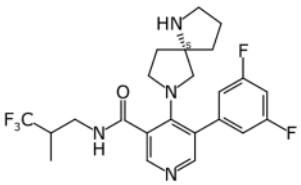
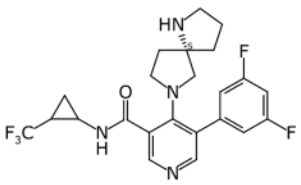
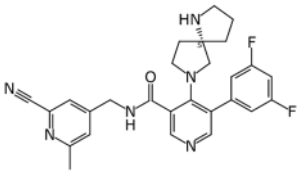
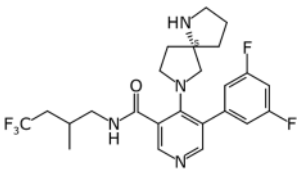
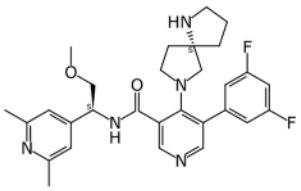
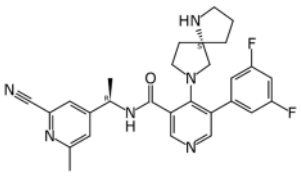
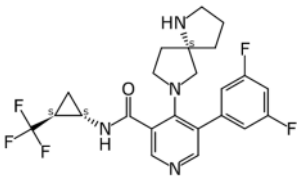
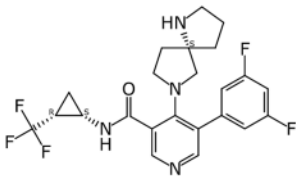
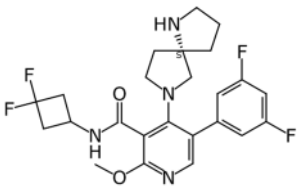
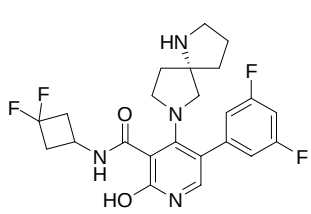
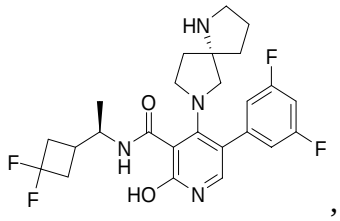
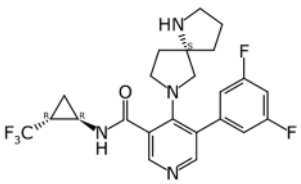
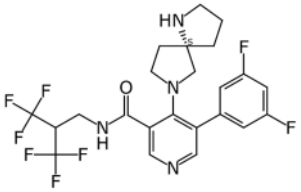
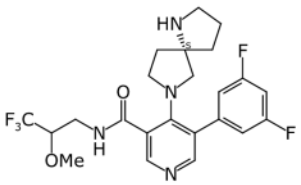
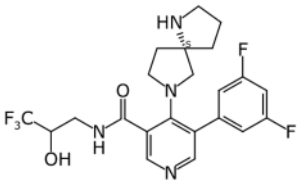
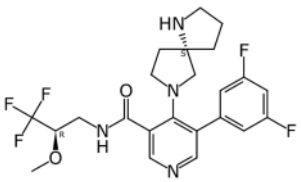
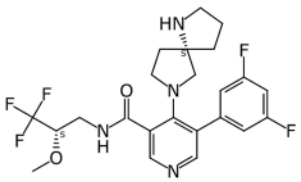
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23. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

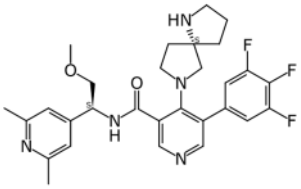
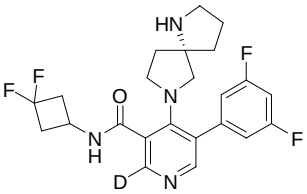
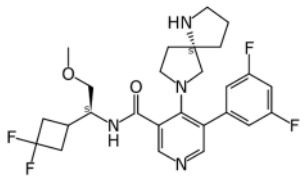
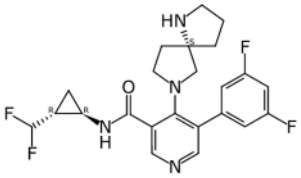
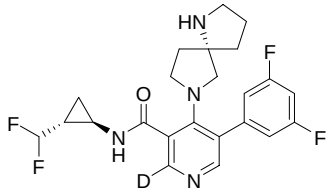
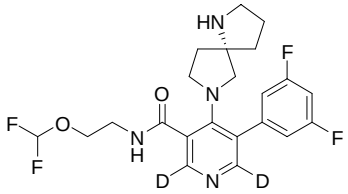

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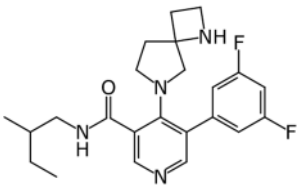
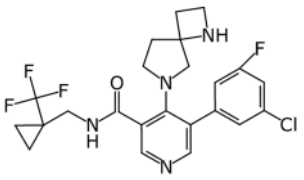
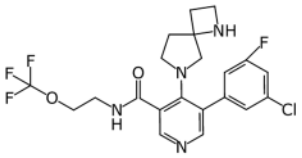
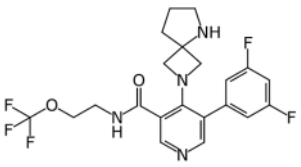
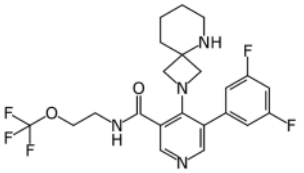
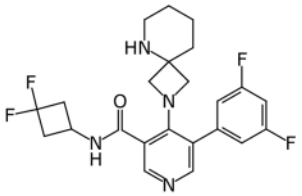
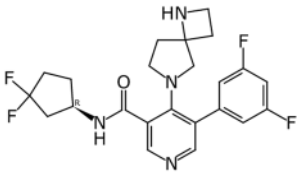
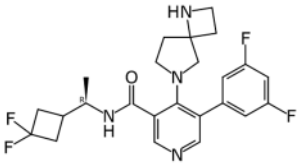
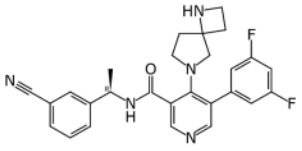
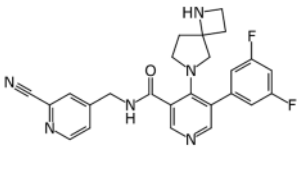
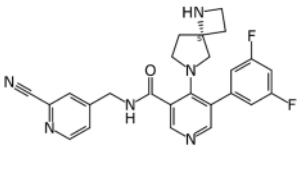
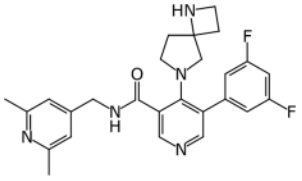
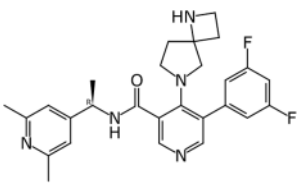
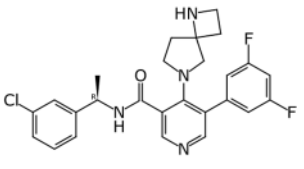
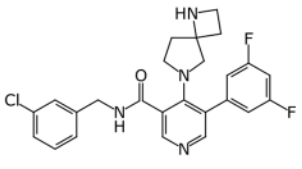
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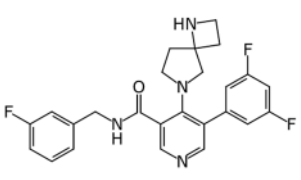
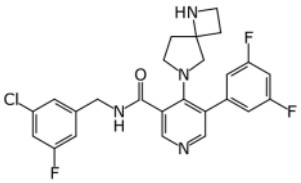
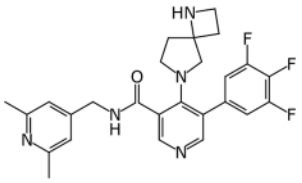
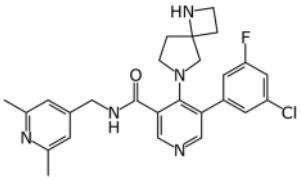
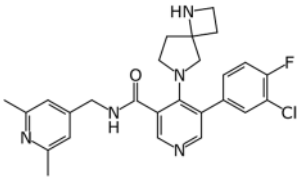
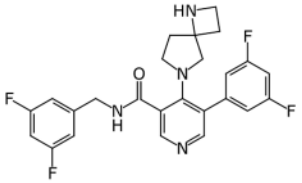
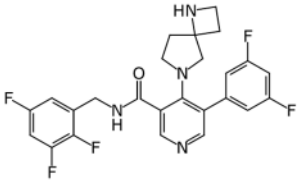
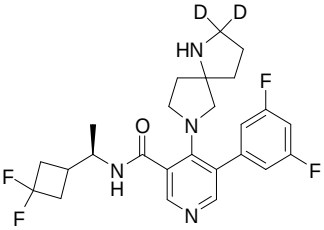
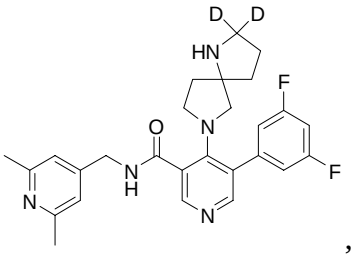
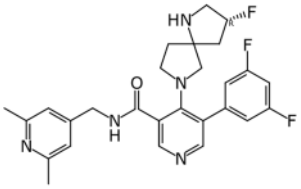
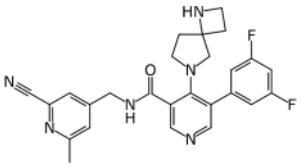
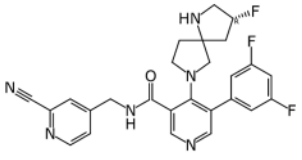
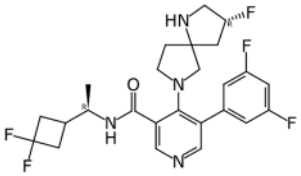
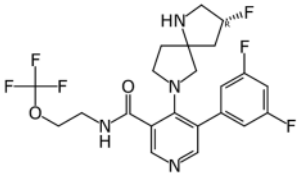
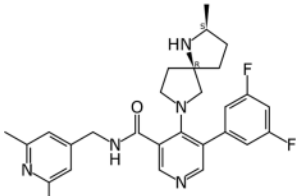
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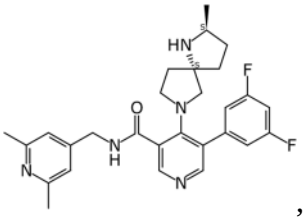
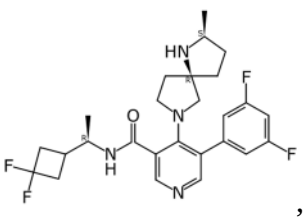
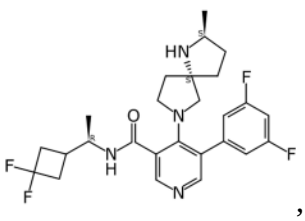
24. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

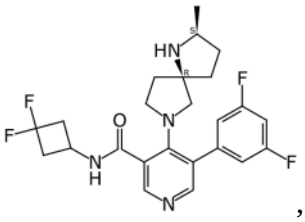
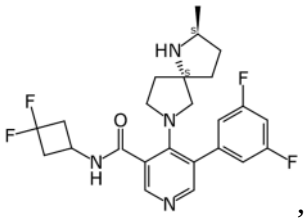
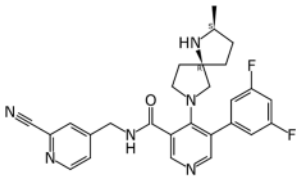

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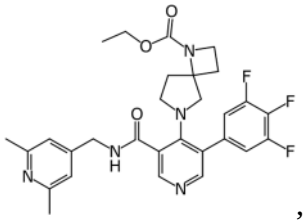
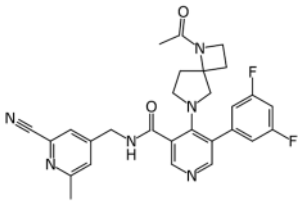
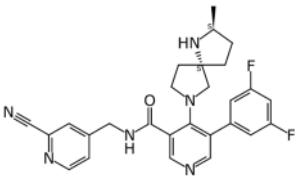

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25. Use of a compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disorder selected from the group consisting of polycystic kidney disease, polycystic liver disease, and ciliopathies.

26. A pharmaceutical composition comprising a compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.