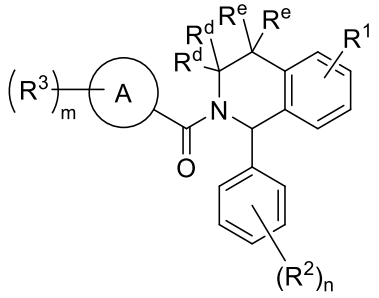
is associated with cytosolic chaperones such as the signal recognition particle (SRP), auxiliary components such as translocating chain-associating membrane (TRAM), translocon-associated protein (TRAP) and modifying enzymes such as oligosaccharyltransferase (OST). The latter is responsible for proper glycosylation of proteins and binds to the ribosome-Sec61-TRAP complex in near stoichiometric ratio. The importance of this complex is highlighted by mutations found in one of the TRAP components of the complex that lead to glycosylation disorders.

[0005] The lysosome is an organelle containing over 60 different enzymes such as lipases, proteases and hydrolases that are mainly involved in the breakdown of proteins, lipids and carbohydrates. Mutations found in multiple lysosomal proteins are the underlying cause of multiple different disease grouped under the classification of neuronal ceroid lipofuscinosis (NCL) also known as Batten disease. In some cases, certain lysosomal proteins act as co-factors of lysosomal enzymes. Their distribution and/or level of expression can modulate the activity of the lysosomal enzymes and as such, have regulatory downstream function on the overall function of the lysosome.

SUMMARY

[0005a] In a first aspect of the present disclosure, there is provided a compound, or pharmaceutically acceptable salt thereof, having a structure of Formula (I):



(I)

wherein

ring A is a 4- to 12-membered heterocycle comprising a ring O or S atom, further comprising 0-3 additional ring heteroatoms selected from O, N, and S;

R^1 is hydrogen, C_{1-6}alkyl, halo, C_{1-3}haloalkyl, O-C_{1-3}haloalkyl,C_{0-3}alkylene-CN, C_{0-3}alkylene-NR^N_2, C_{0-6}alkylene-OR^N, C_{0-6}alkylene- $C(O)OR^N$, C_{0-6}alkylene-$C(O)N(R^N)_2$, or C_{0-6}alkylene-SO_pR^N; each R^N is independently hydrogen or C_{1-6}alkyl, and p is 0-2;

each R^2 is independently halo;

each R^3 is independently hydrogen, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{0-6}alkylene-OH, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{1-6}alkylene-O-C_{1-6}alkyl, C_{0-6}alkylene-NR^aR^b, S-C_{1-6}alkyl, C_{2-6}alkenyl, C(O)-C_{1-6}haloalkyl, SO_2-C_{1-6}alkyl, $S^{2+}(O)^-(NR^a)^-C_{1-6}$alkyl, OR^4, 5- to 8- membered heteroaryl comprising 1-4 ring N atoms, or 4- to 6-membered heterocycle comprising 1-4 ring heteroatoms selected from O, N, and S with at least 1 ring heteroatom being N, and the heteroaryl or heterocycle is optionally substituted with 1 or 2 substituents independently selected from halo, C_{1-6}alkyl, OH, and C_{1-6}alkoxy, or

two geminal R^3 together with the atom to which they are attached form an oxo group, and

when ring A comprises a ring N atom, the N is substituted with R^a, and if ring A does not comprise a ring N atom, then at least one R^3 is C_{0-6}alkylene-NR^aR^b;

R^a and R^b are each independently hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-OH, C_{1-6}alkylene-O-C_{1-6}alkyl, C(O)-C_{1-6}alkyl, C(O)-C_{1-6}haloalkyl, $S(O)_2$-C_{1-6}alkyl, $S(O)_2$-C_{1-6}haloalkyl; or

R^a and R^b together with the nitrogen to which they are attached form a 3- to 12-membered monocyclic or bicyclic heterocycle optionally further comprising 1-3 additional ring heteroatoms selected from O, N, and S;

R^4 is C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylene-C_{3-8}cycloalkyl, or C_{0-6}alkylene-C_{6-10}aryl;

each R^d is independently H or D;

each R^e is independently H, D, halo, OH, methyl, or methoxy, or

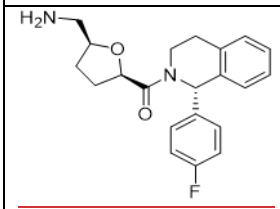
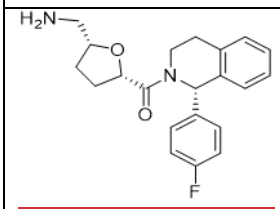
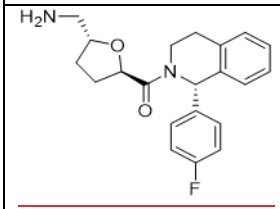
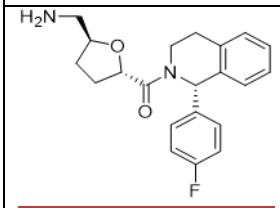
two geminal R^e together with the atom to which they are attached form an oxo group or a spiro C_{3-5}cycloalkyl;

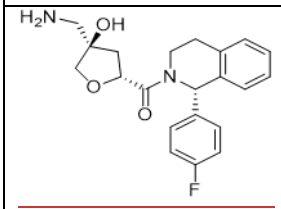
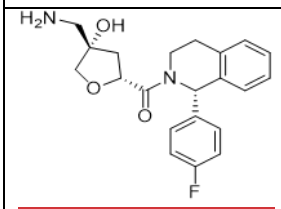
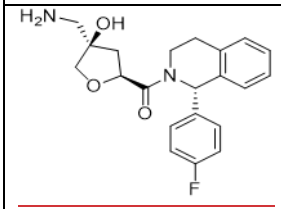
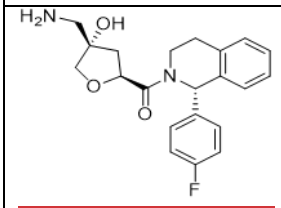
m is 1-4; and

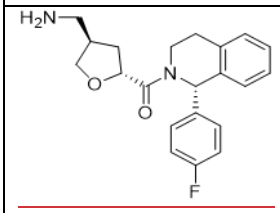
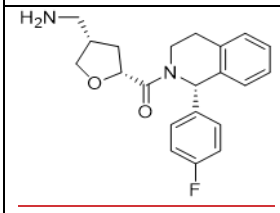
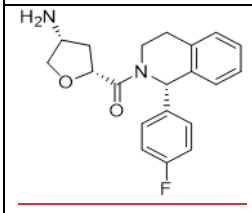
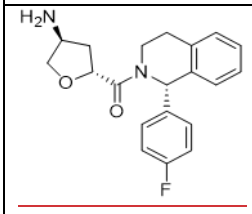
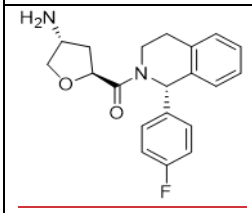
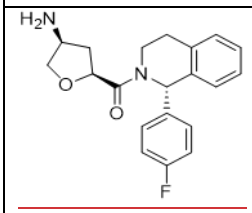
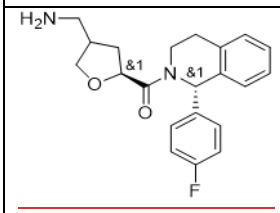
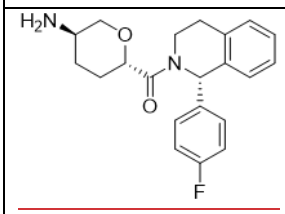
n is 0-2.

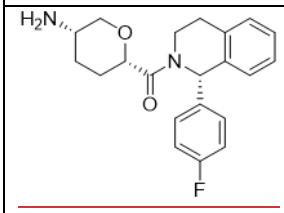
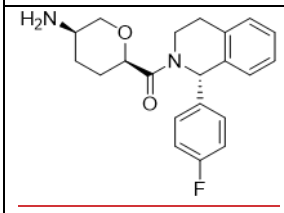
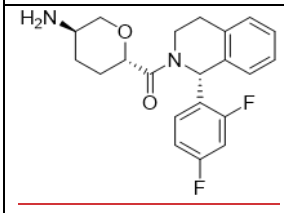
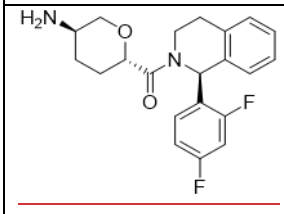
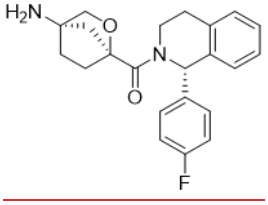
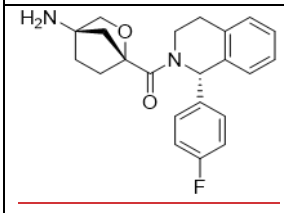
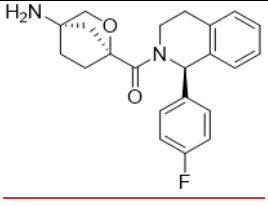
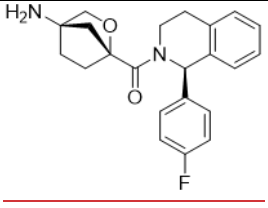
[0005b] In another aspect of the present disclosure, there is provided a compound, or pharmaceutically acceptable salt thereof, having a structure as shown in Table A:

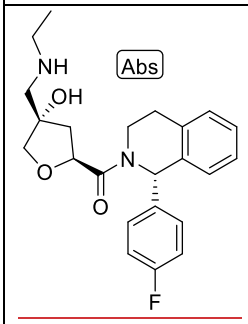
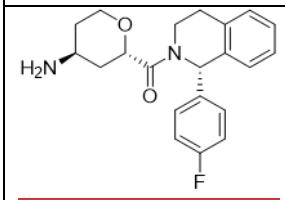
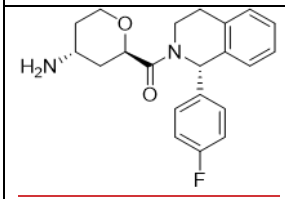
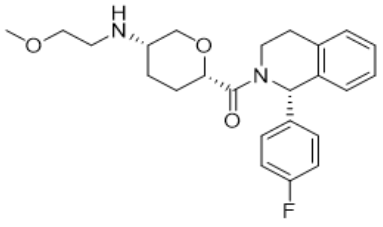
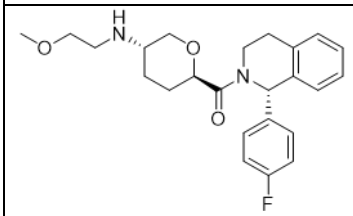
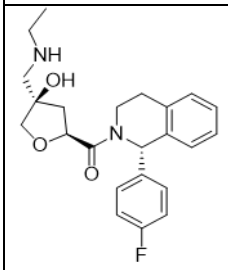
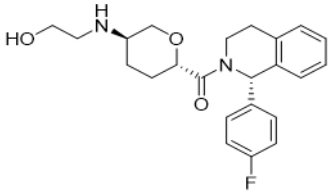
Table A

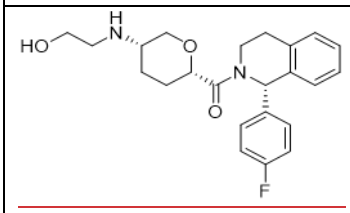
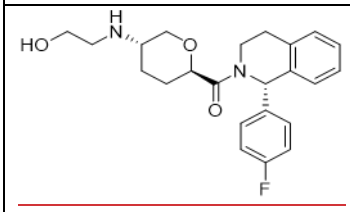
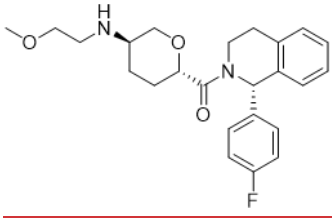
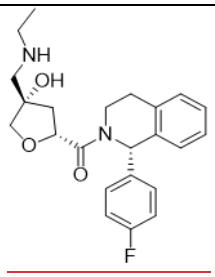
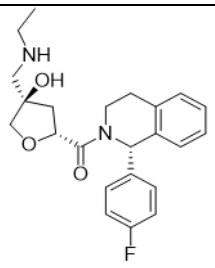
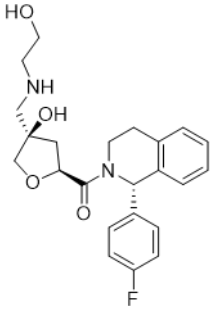
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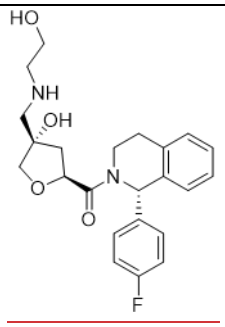
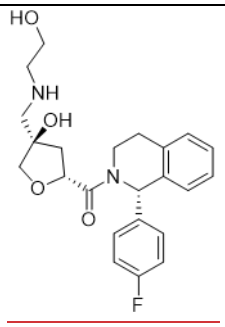
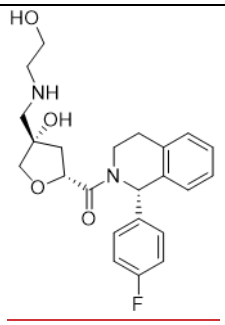
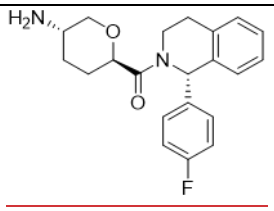
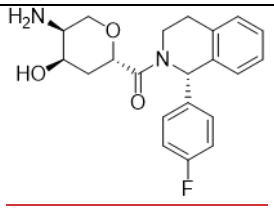
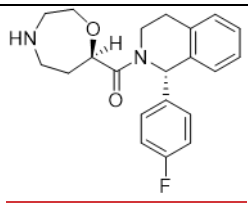
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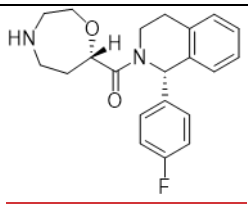
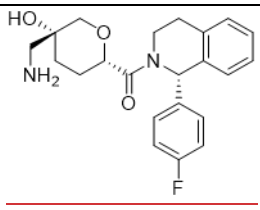
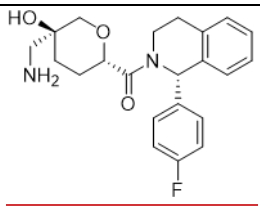
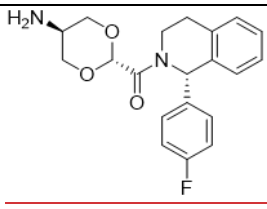
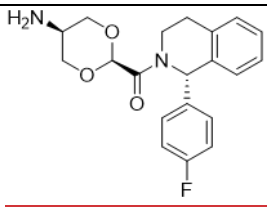
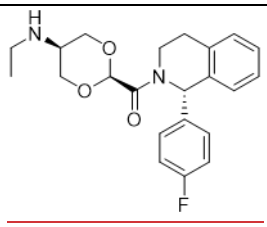
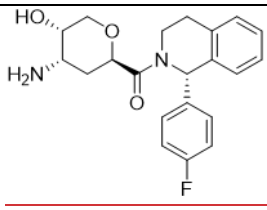
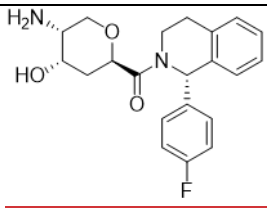
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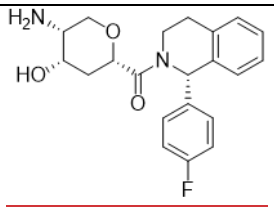
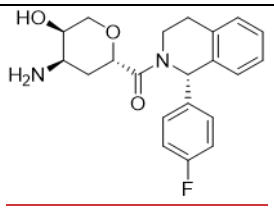
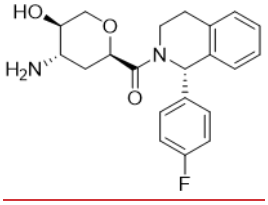
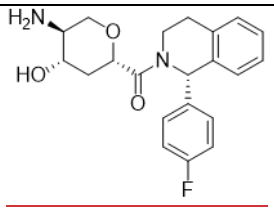
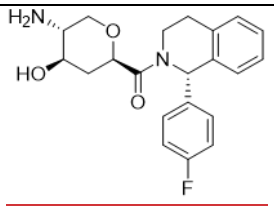
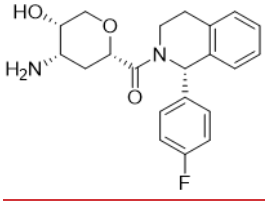
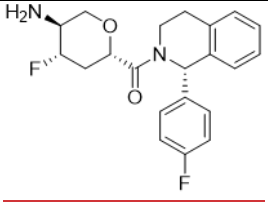
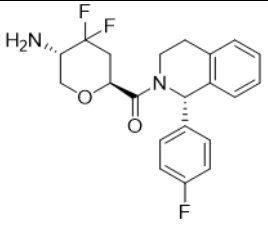
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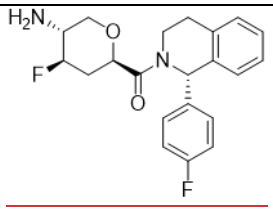
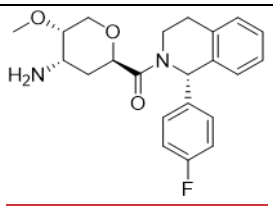
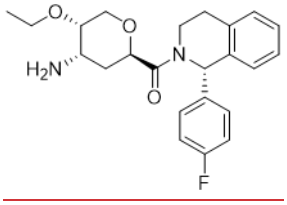
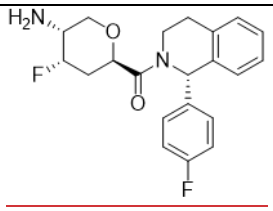
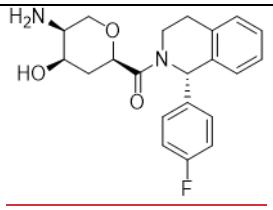
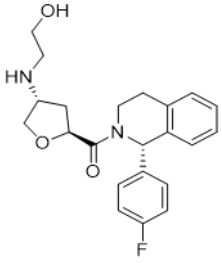
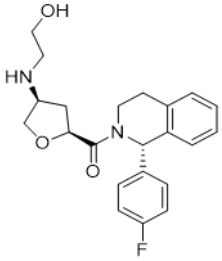
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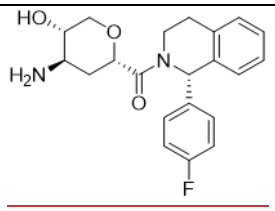
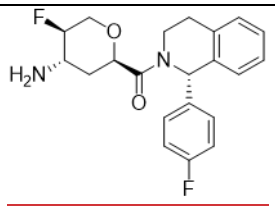
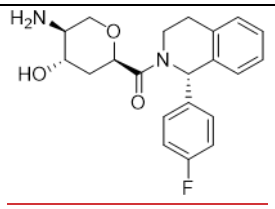
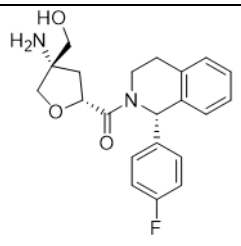
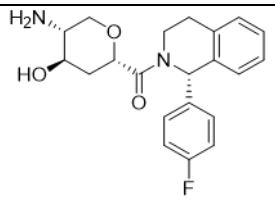
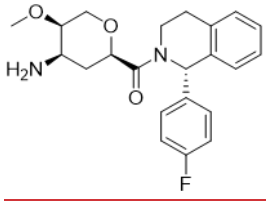
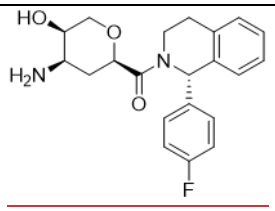
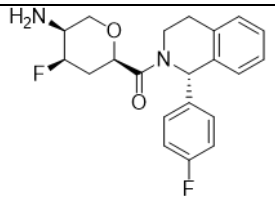
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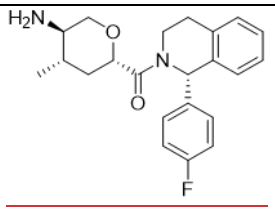
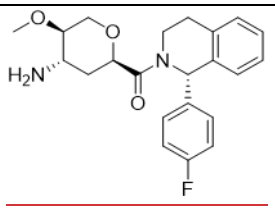
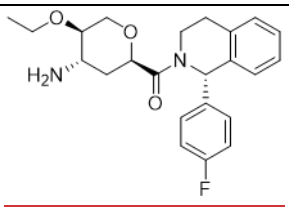
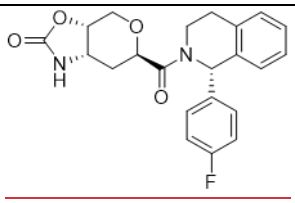
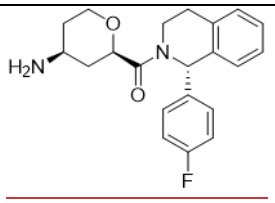
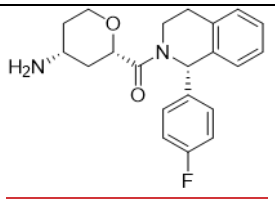
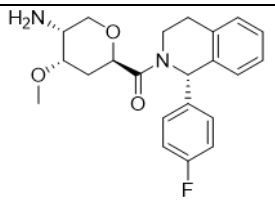
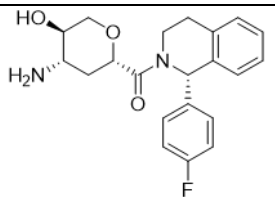
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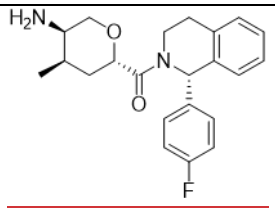
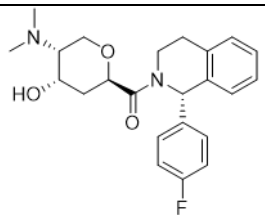
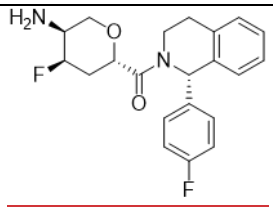
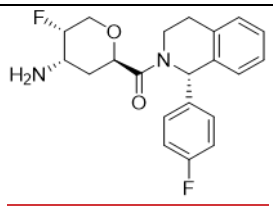
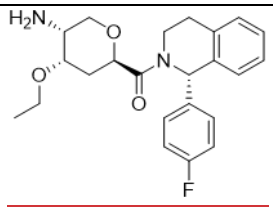
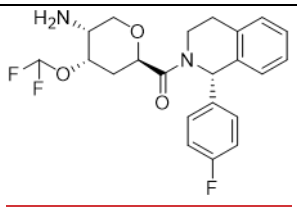
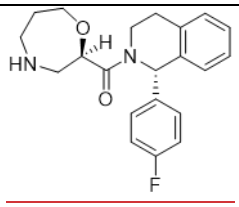
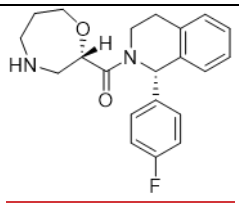
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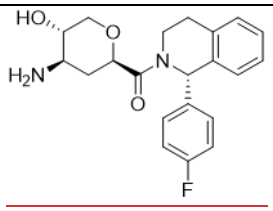
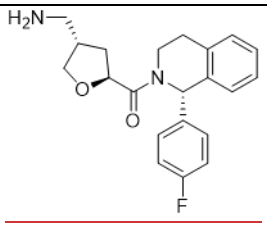
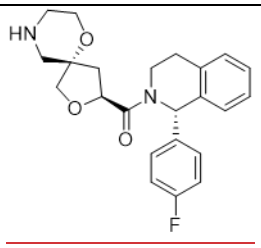
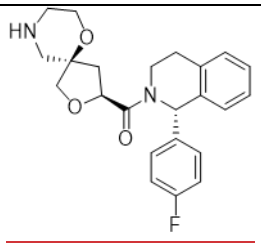
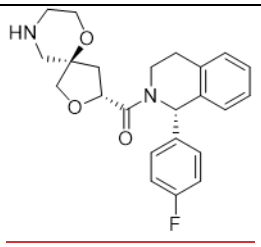
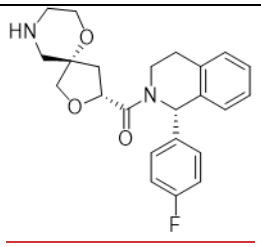
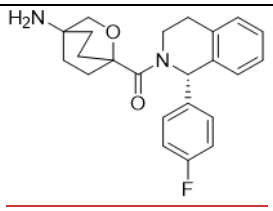
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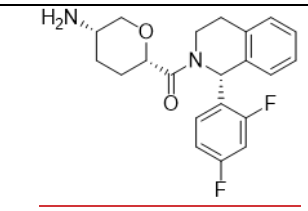
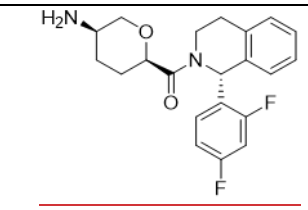
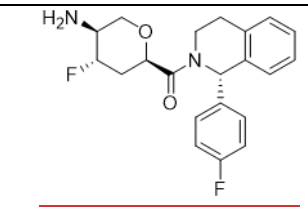
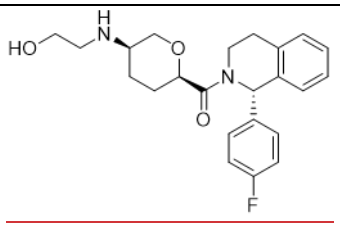
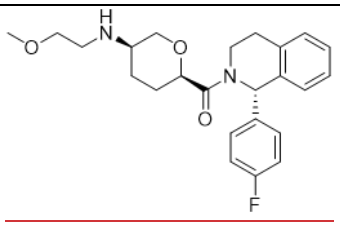
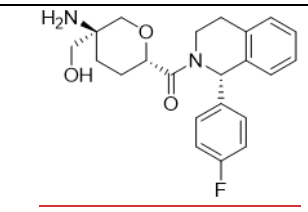
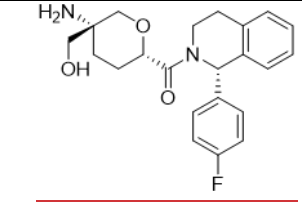
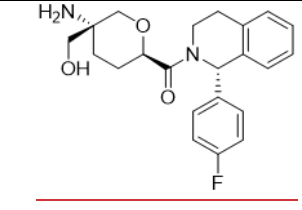
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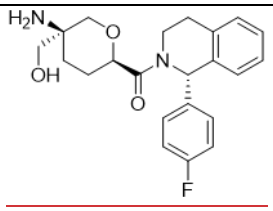
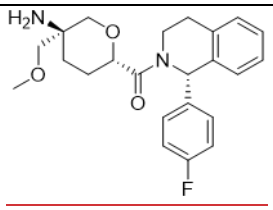
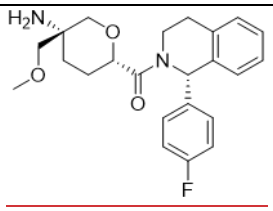
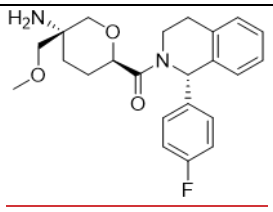
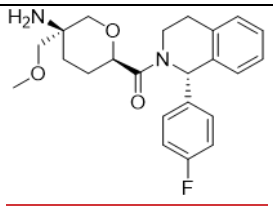
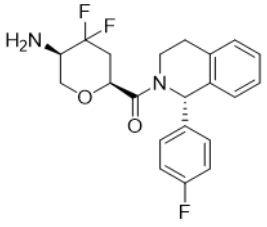
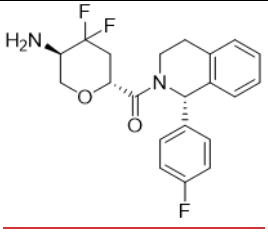
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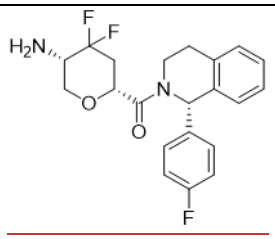
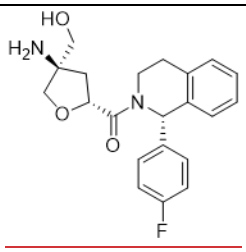
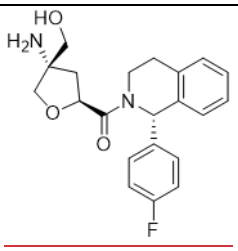
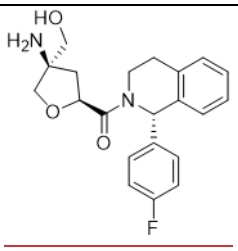
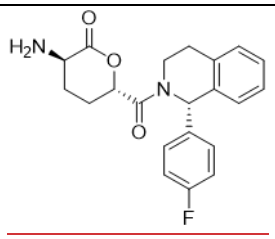
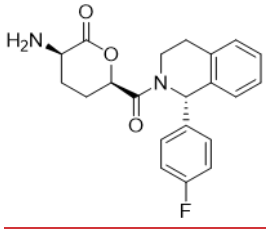
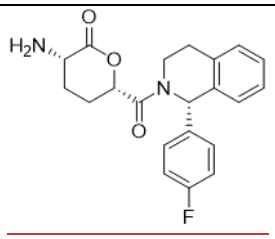
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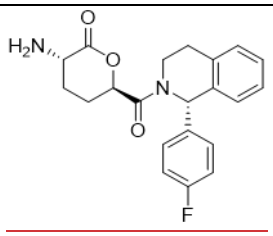
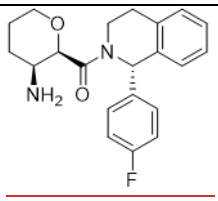
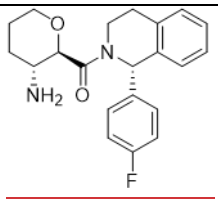
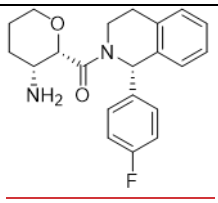
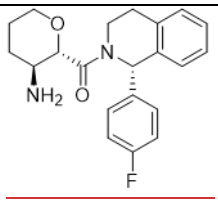
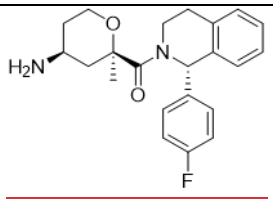
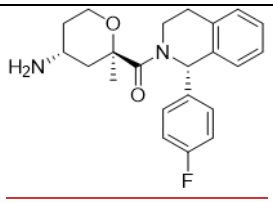
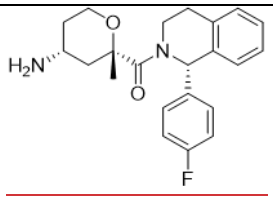
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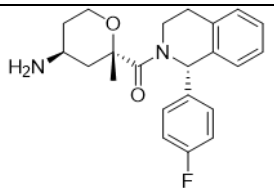
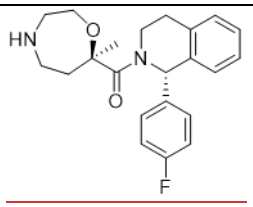
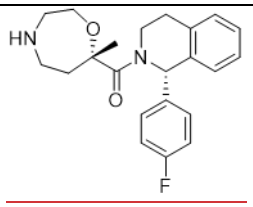
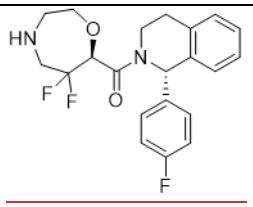
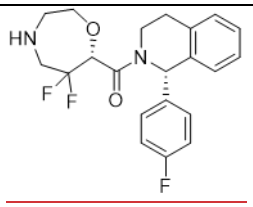
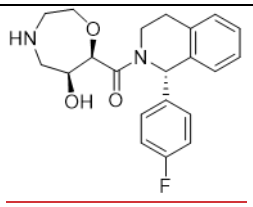
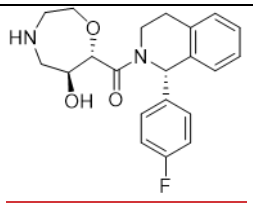
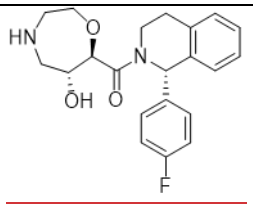
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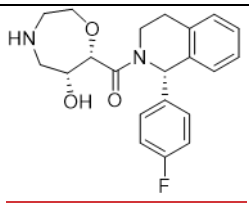
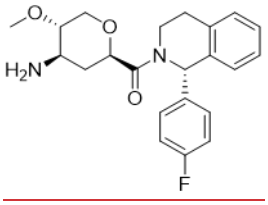
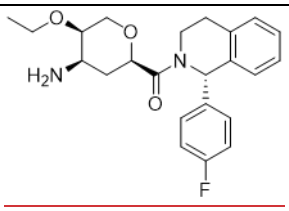
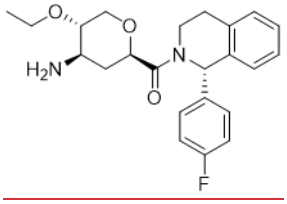
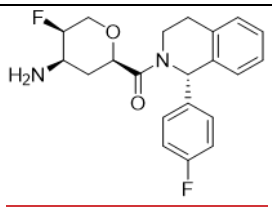
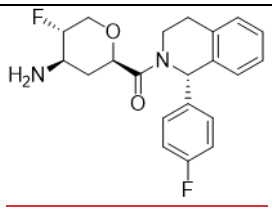
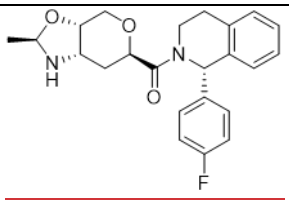
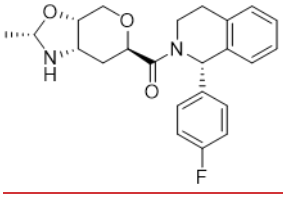
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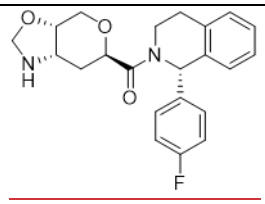
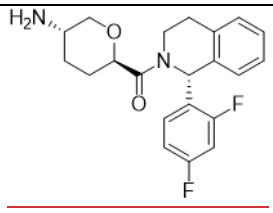
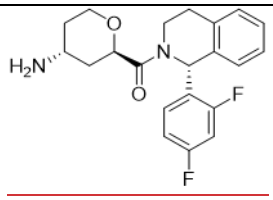
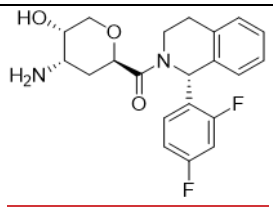
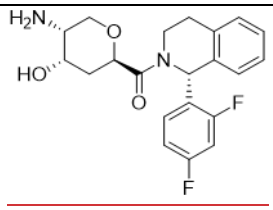
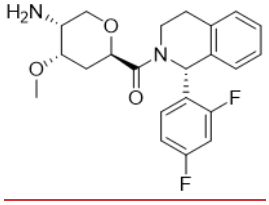
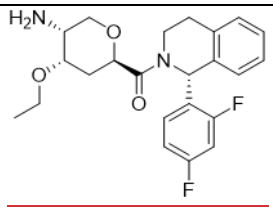
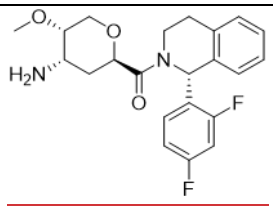
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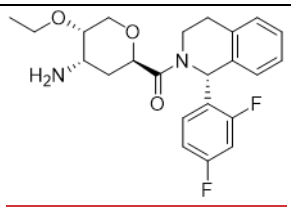
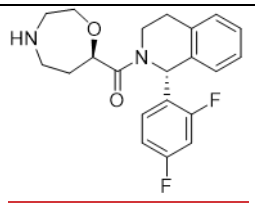
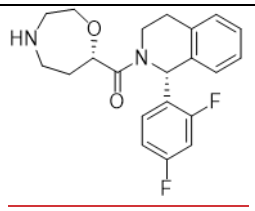
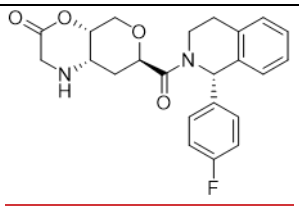
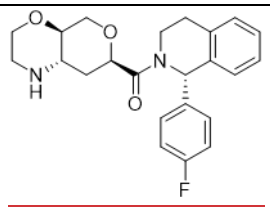
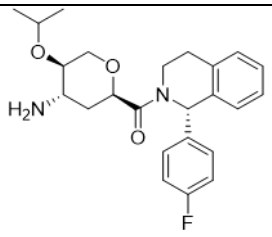
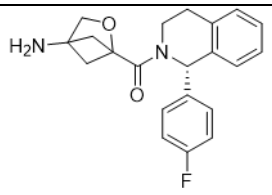
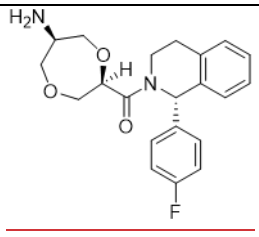
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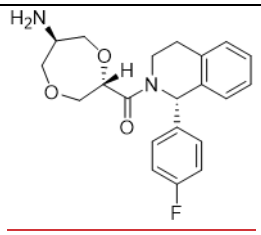
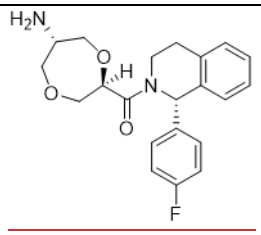
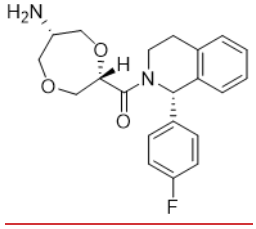
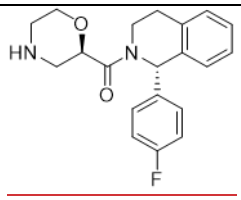
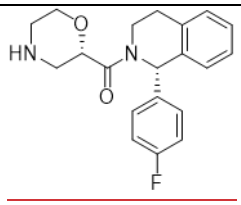
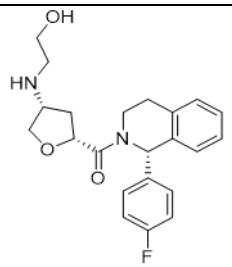
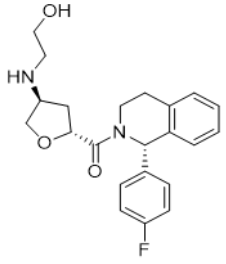
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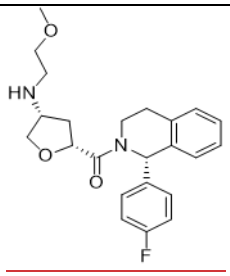
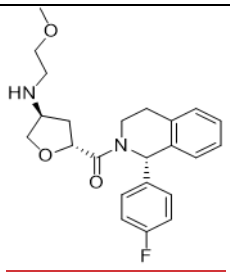
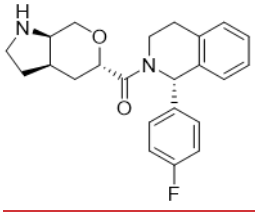
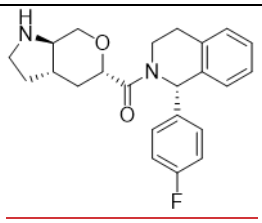
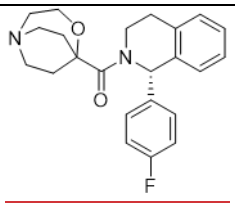
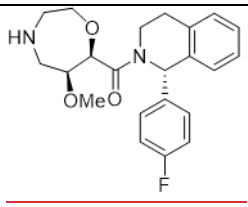
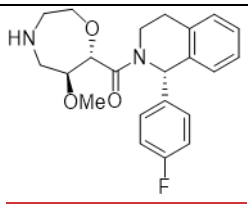
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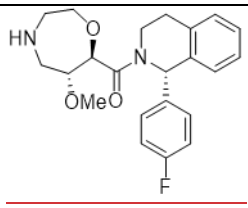
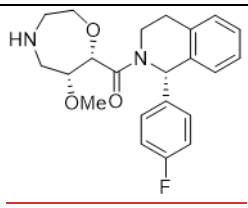
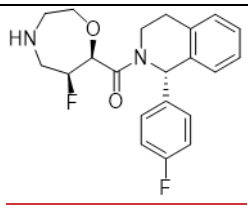
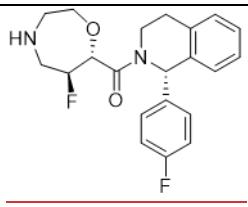
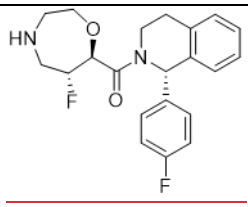
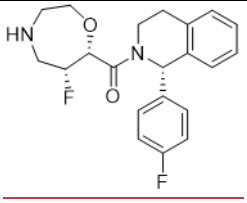
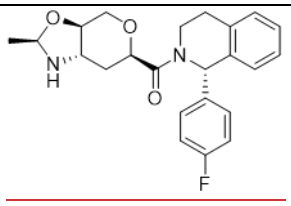
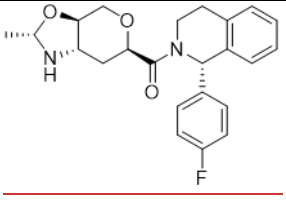
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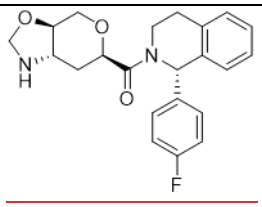
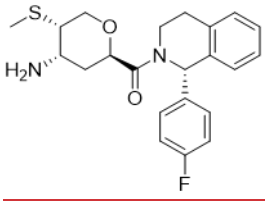
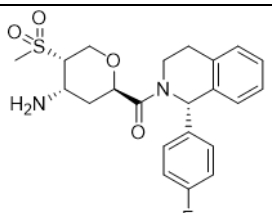
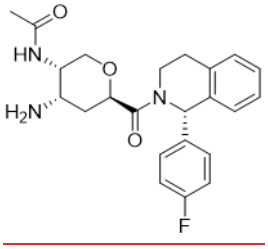
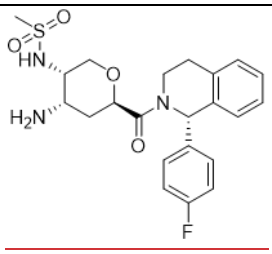
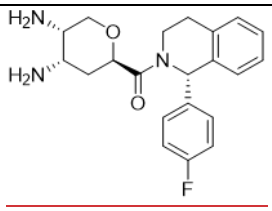
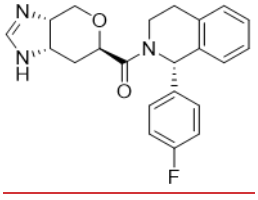
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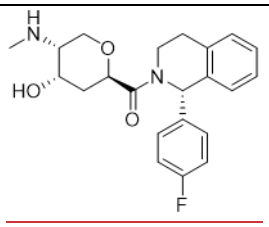
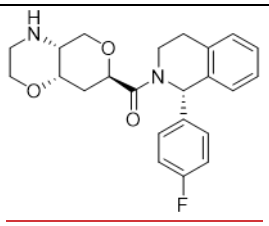
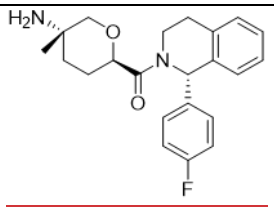
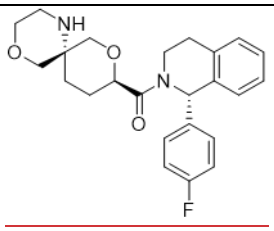
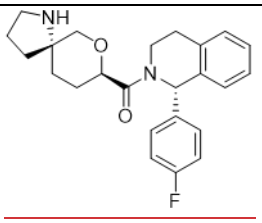
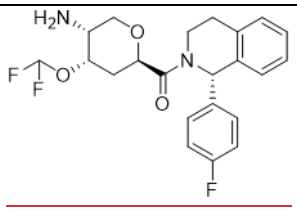
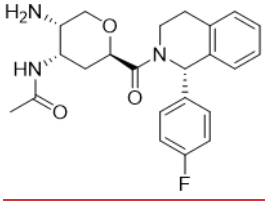
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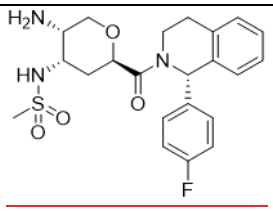
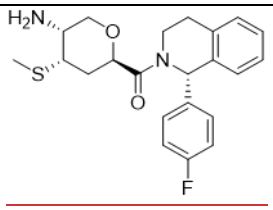
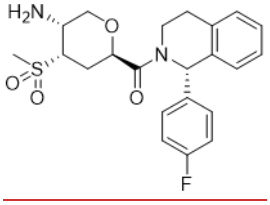
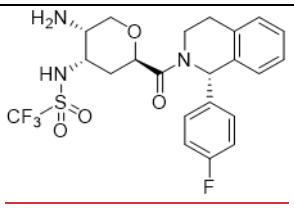
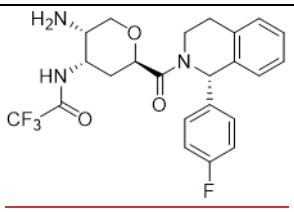
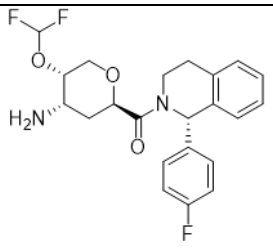
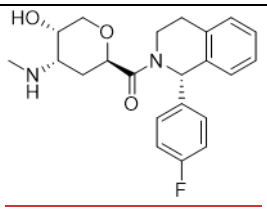
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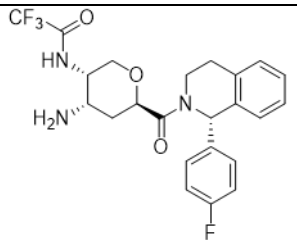
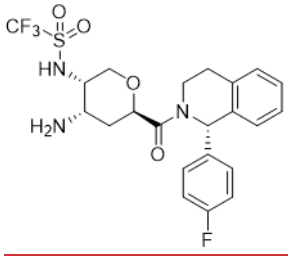
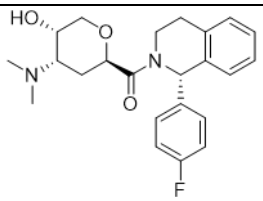
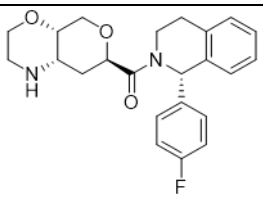
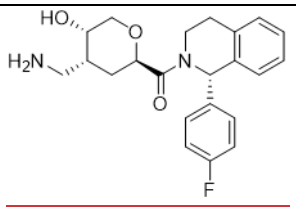
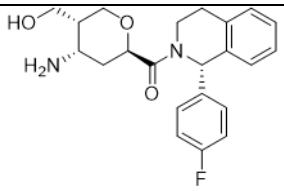
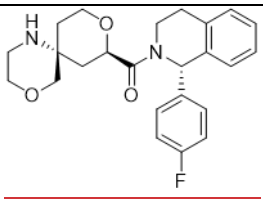
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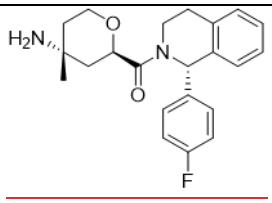
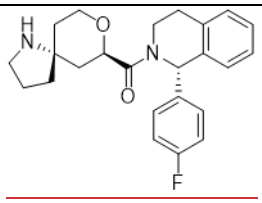
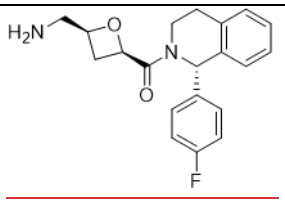
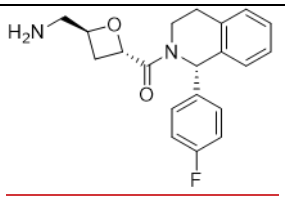
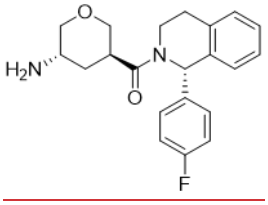
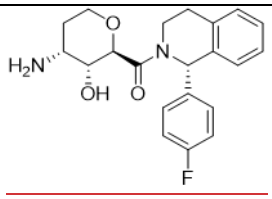
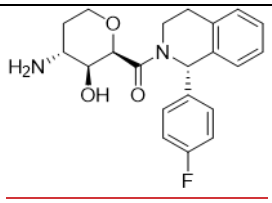
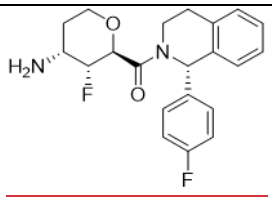
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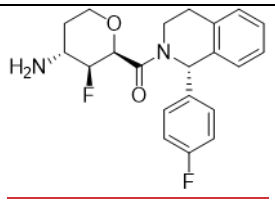
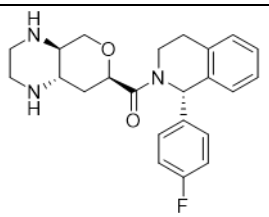
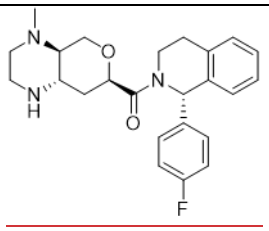
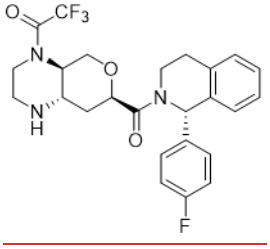
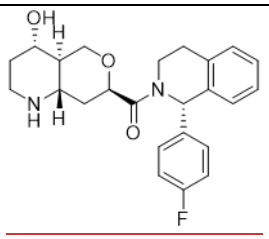
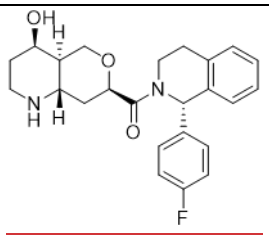
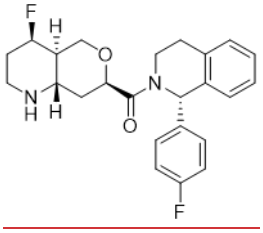
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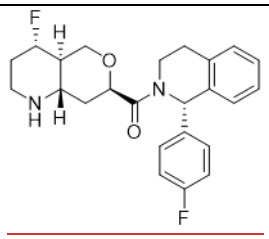
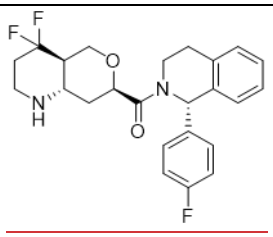
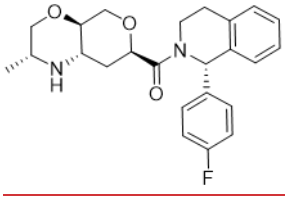
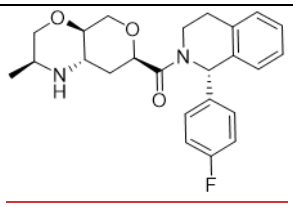
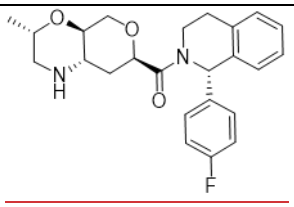
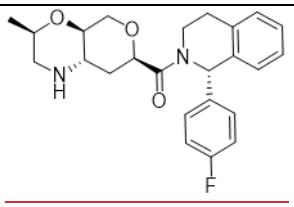
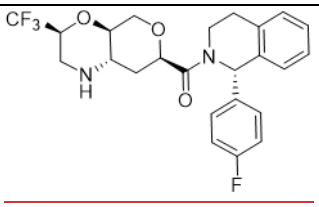
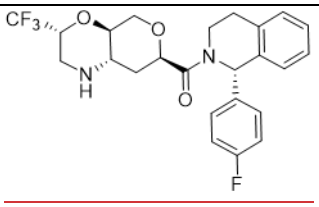
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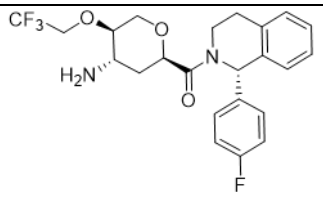
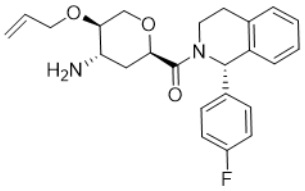
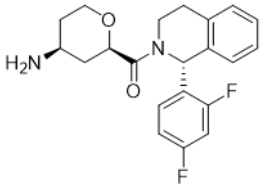
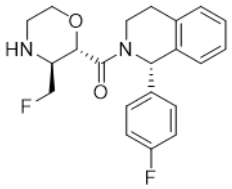
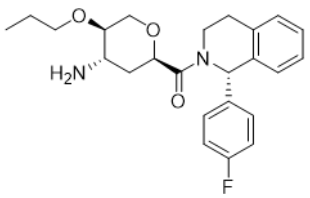
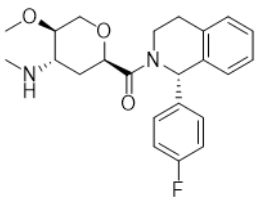
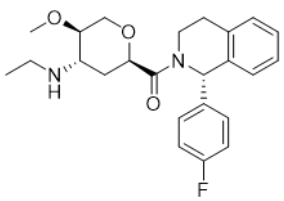
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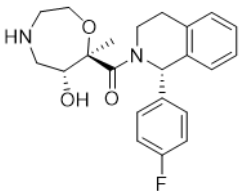
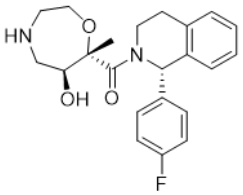
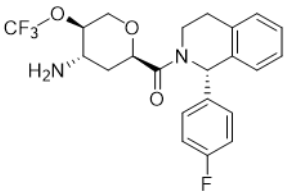
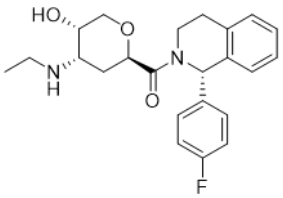
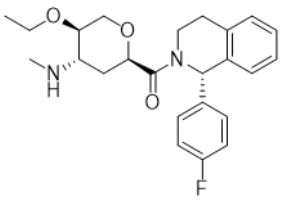
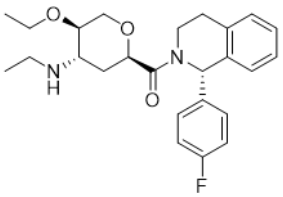
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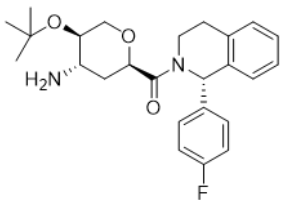
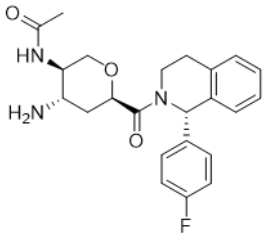
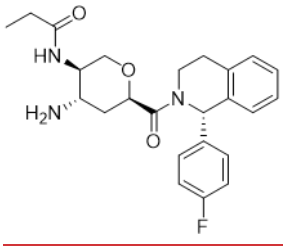
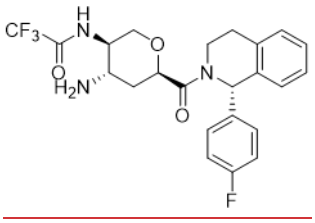
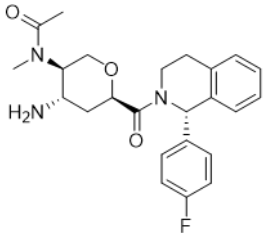
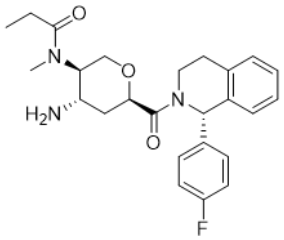
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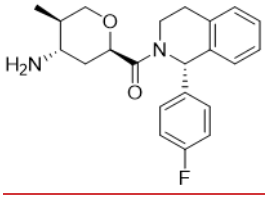
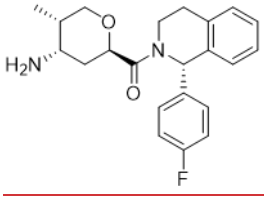
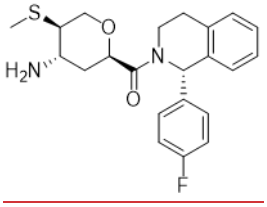
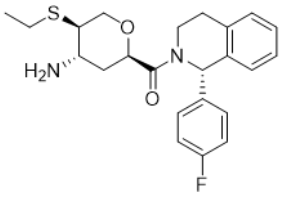
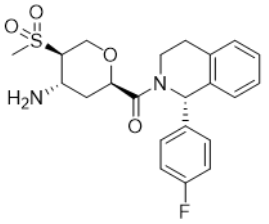
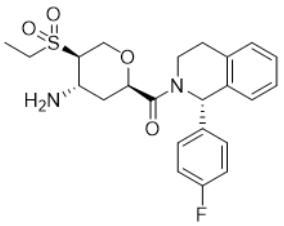
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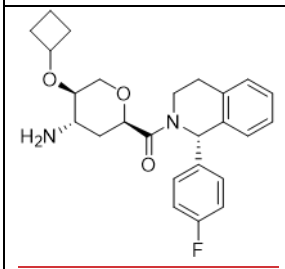
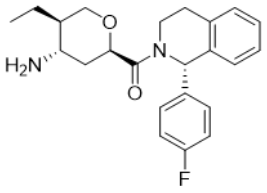
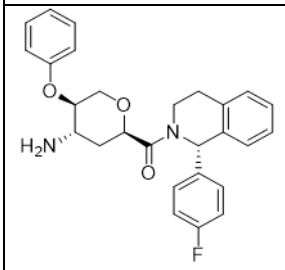
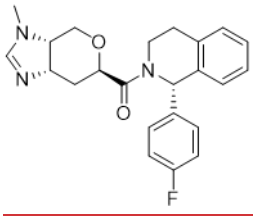
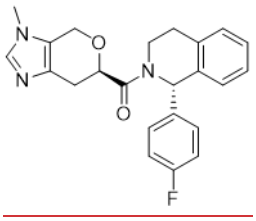
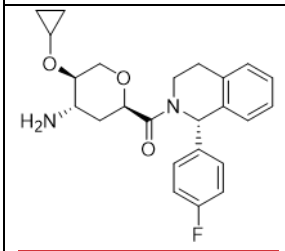
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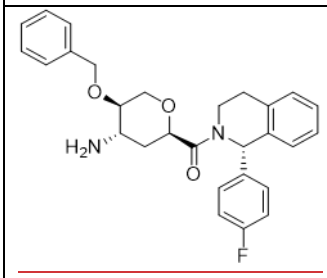
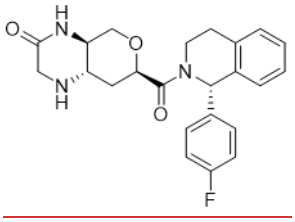
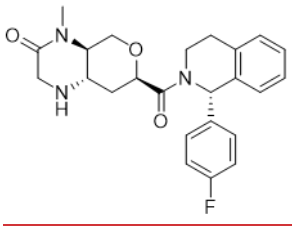
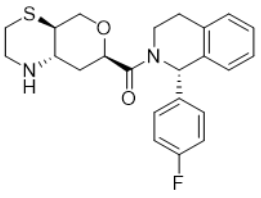
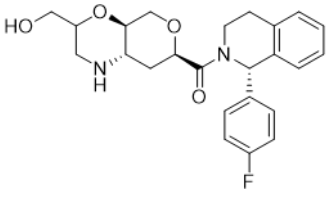
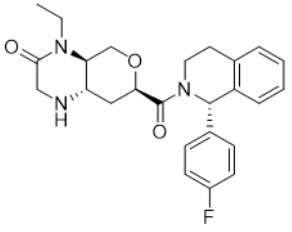
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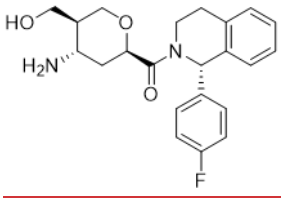
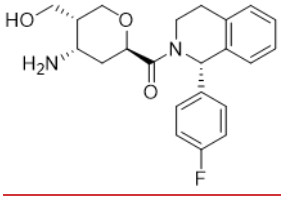
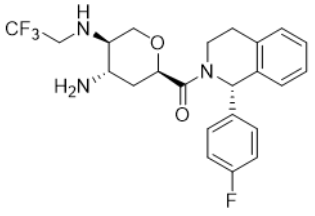
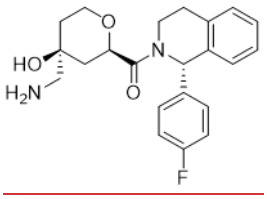
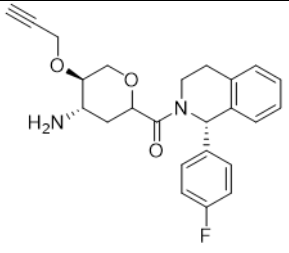
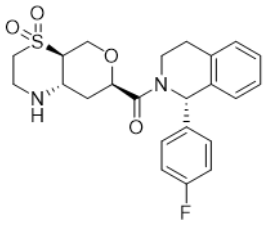
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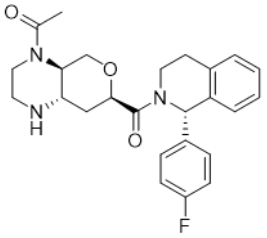
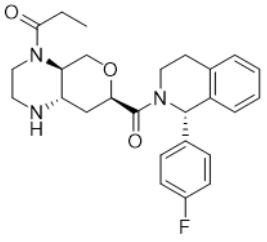
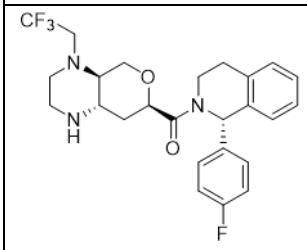
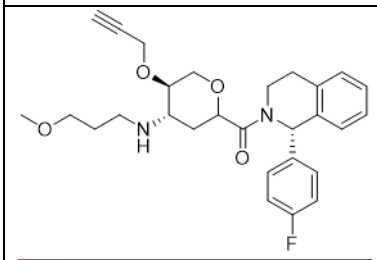
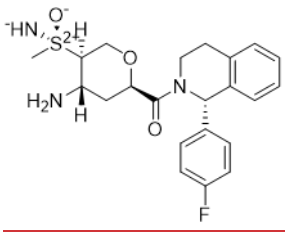
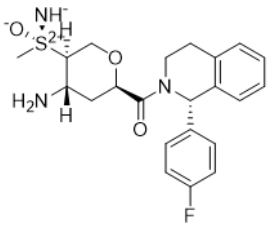
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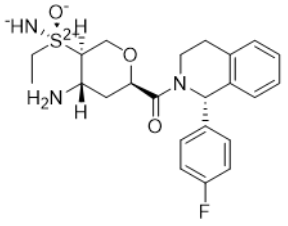
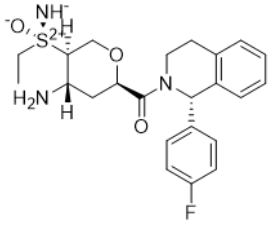
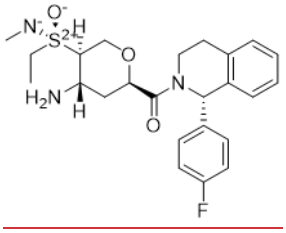
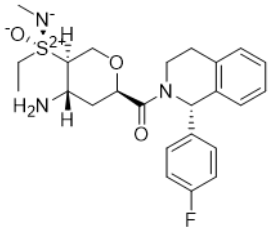
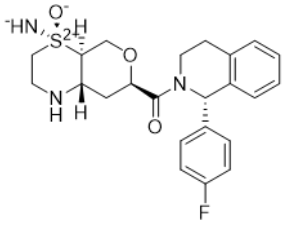
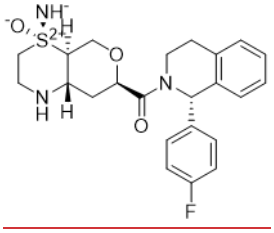
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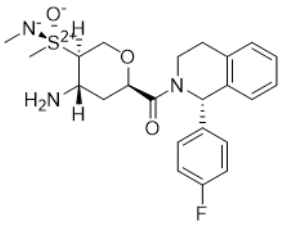
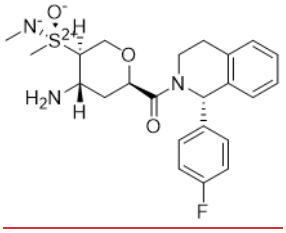
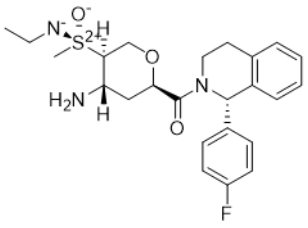
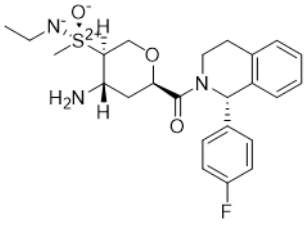
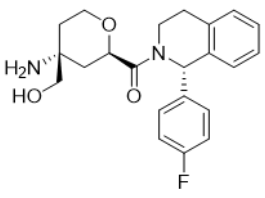
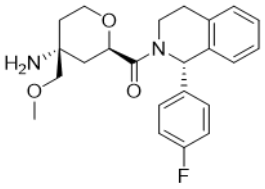
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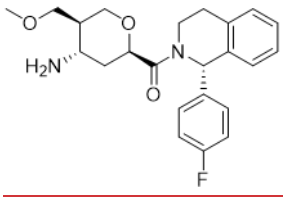
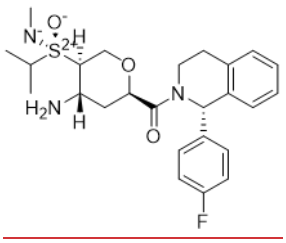
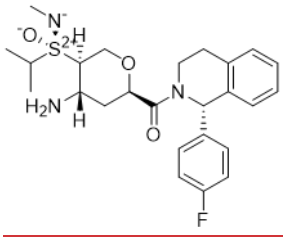
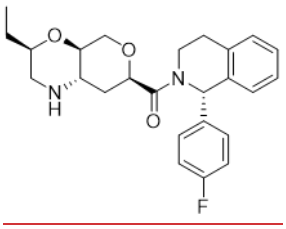
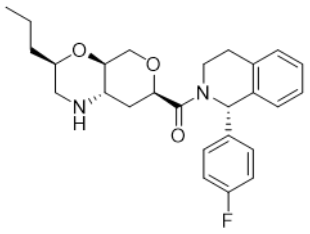
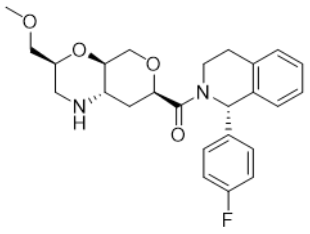
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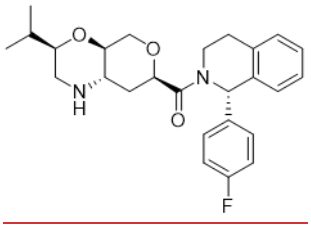
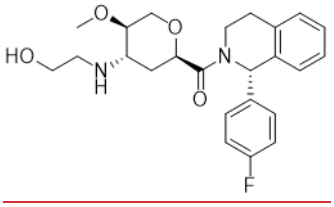
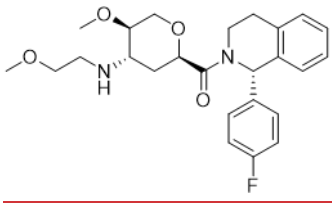
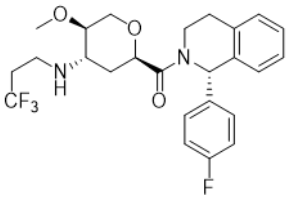
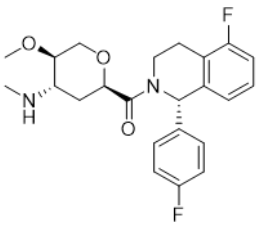
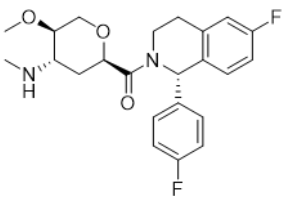
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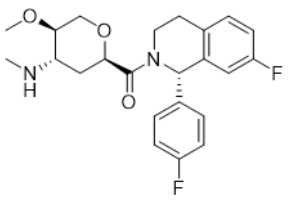
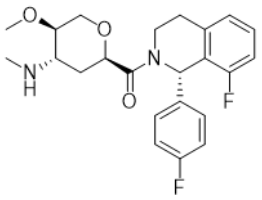
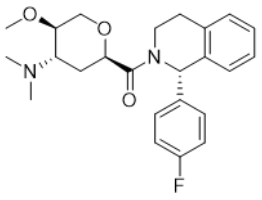
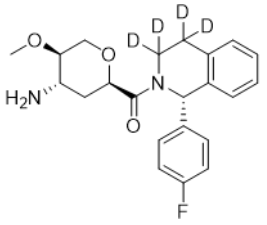
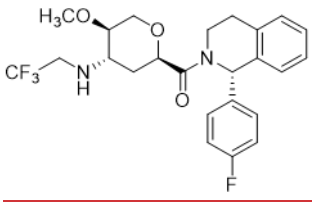
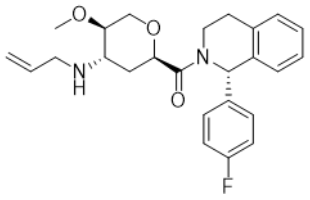
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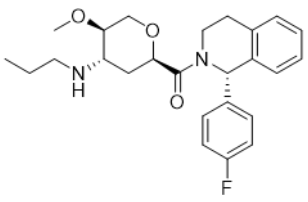
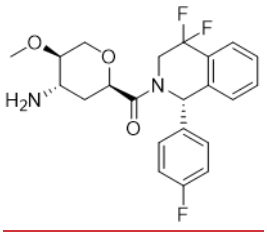
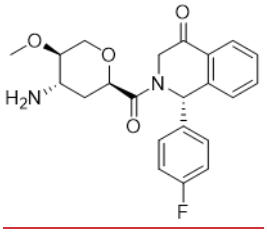
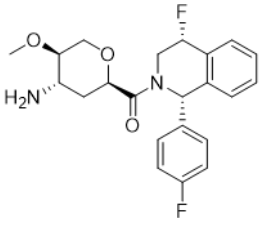
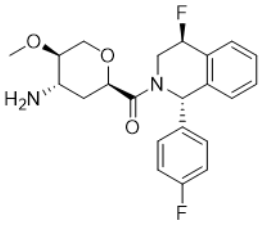
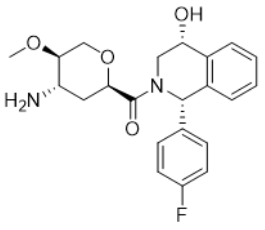
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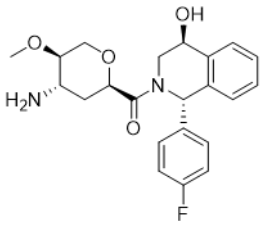
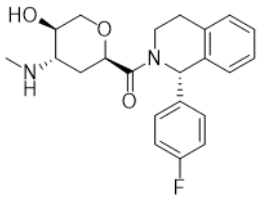
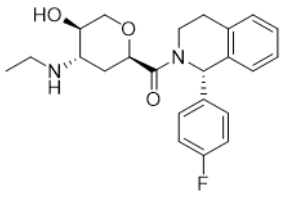
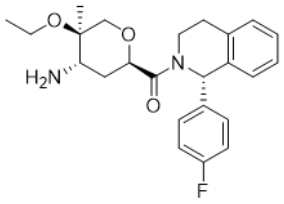
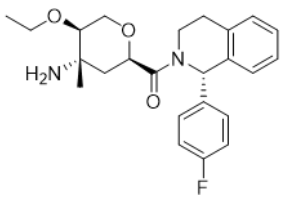
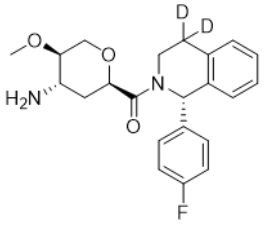
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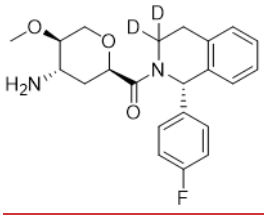
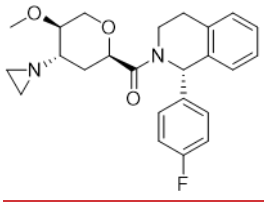
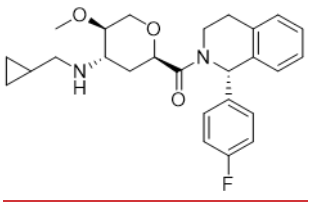
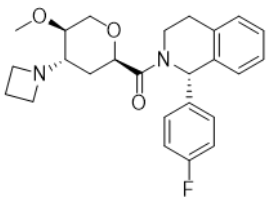
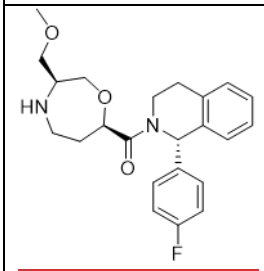
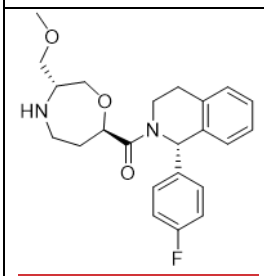
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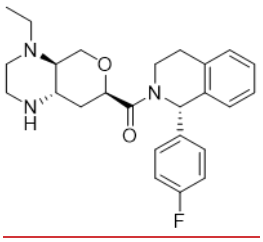
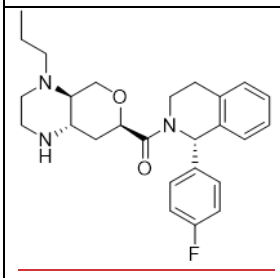
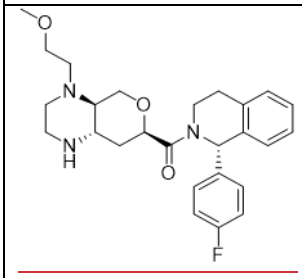
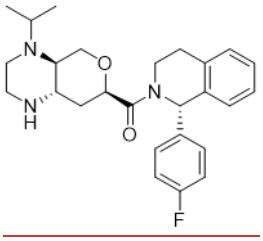
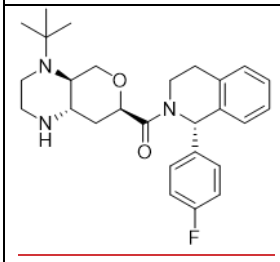
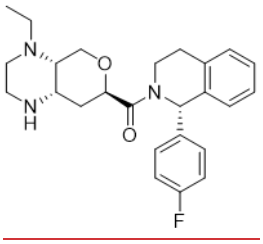
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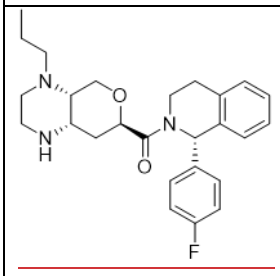
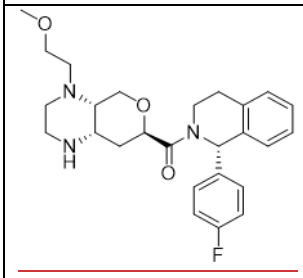
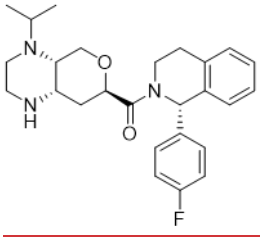
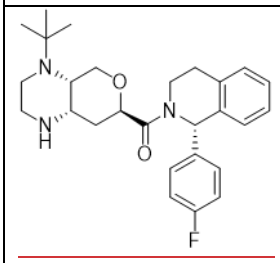
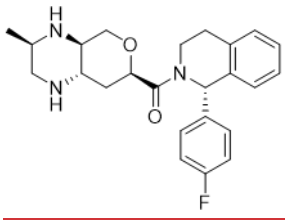
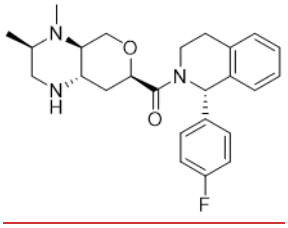
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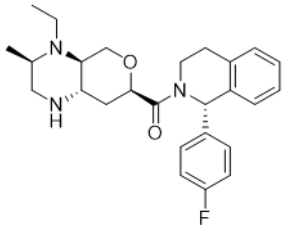
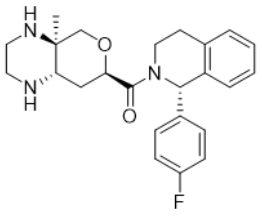
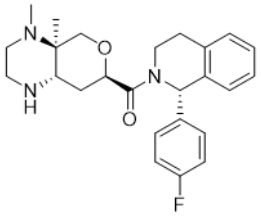
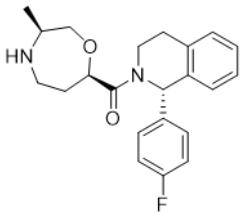
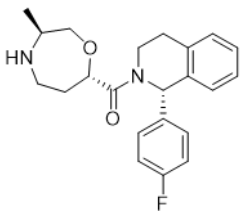
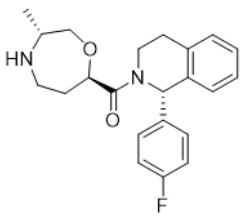
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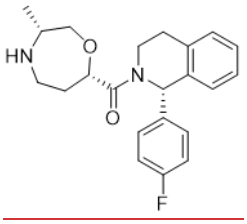
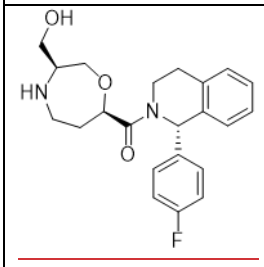
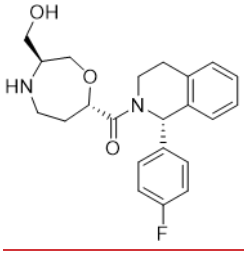
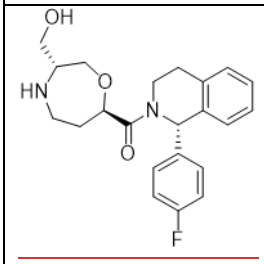
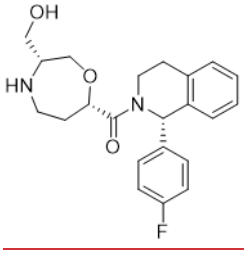
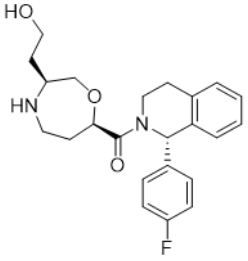
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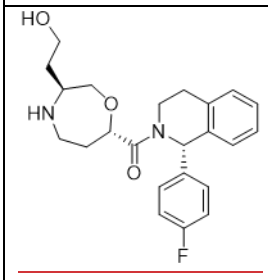
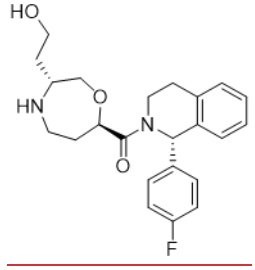
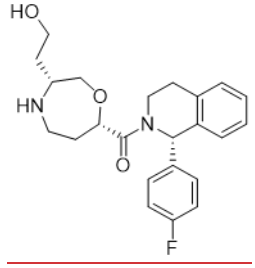
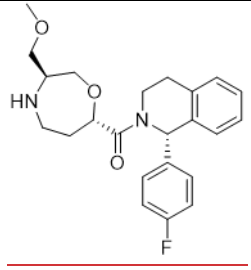
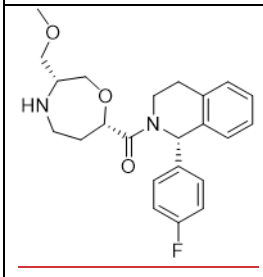
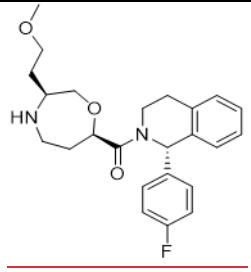
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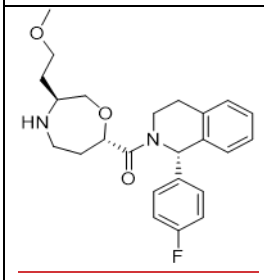
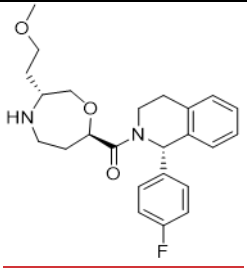
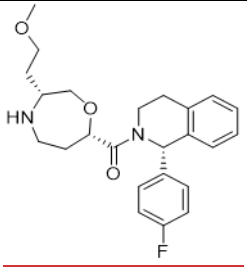
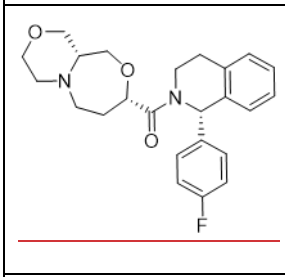
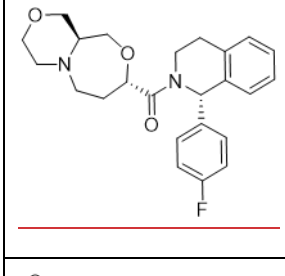
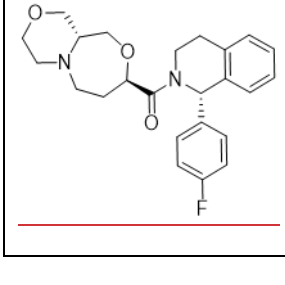
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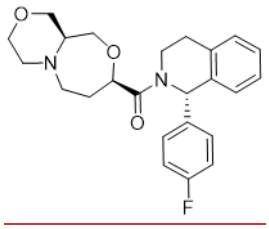
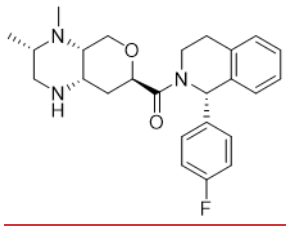
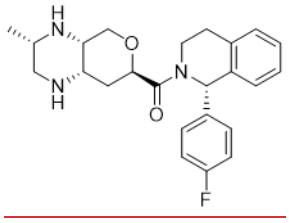
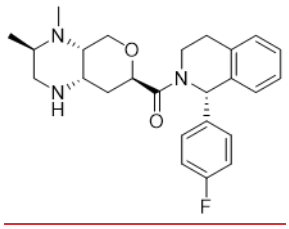
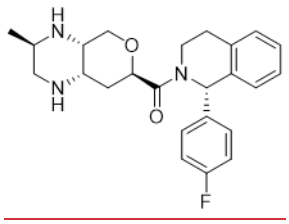
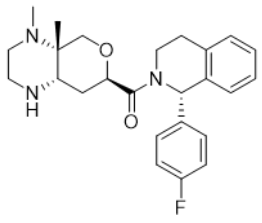
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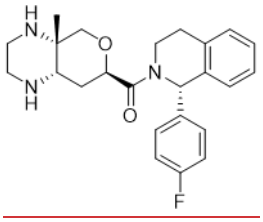
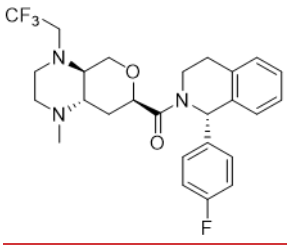
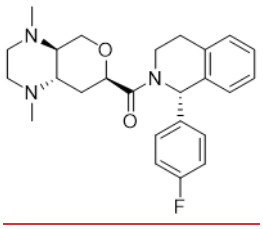
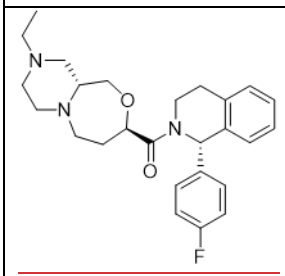
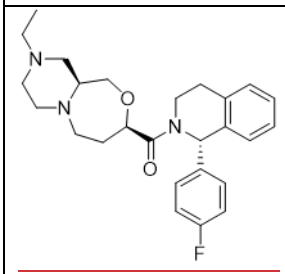
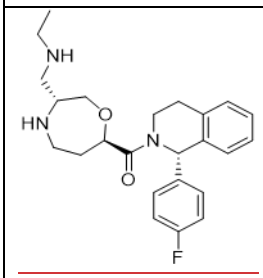
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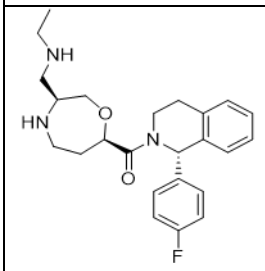
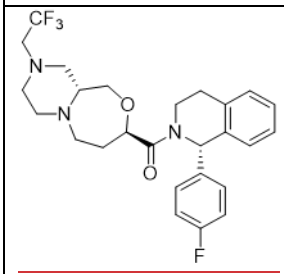
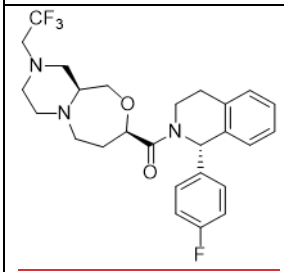
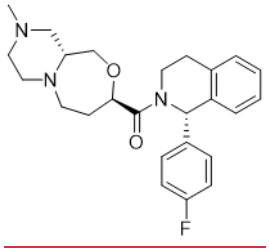
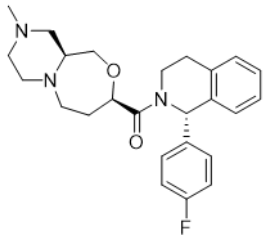
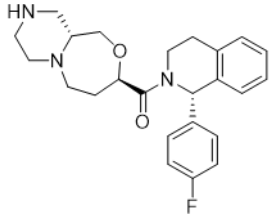
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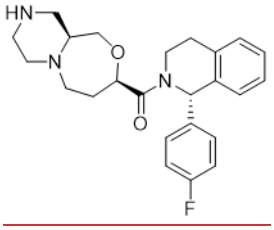
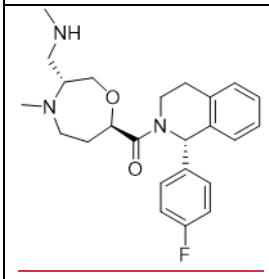
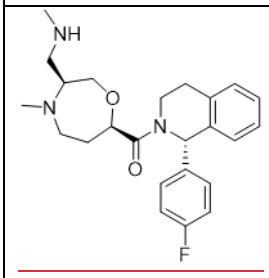
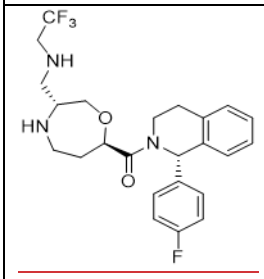
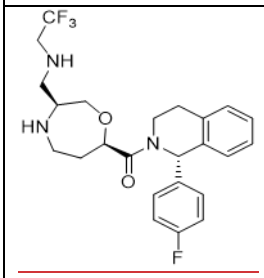
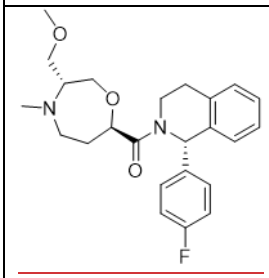
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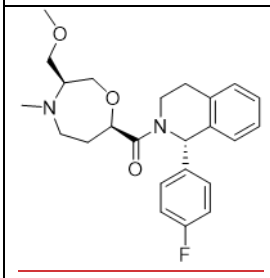
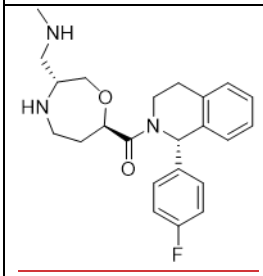
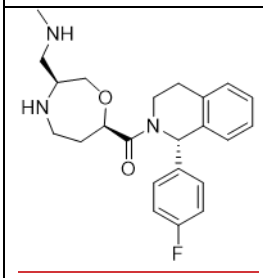
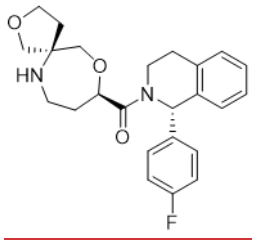
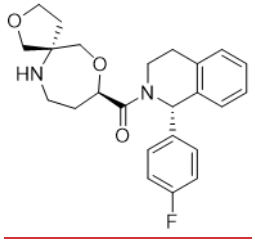
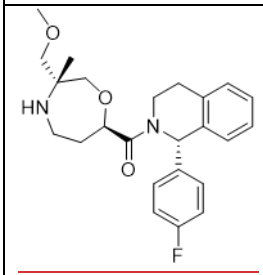
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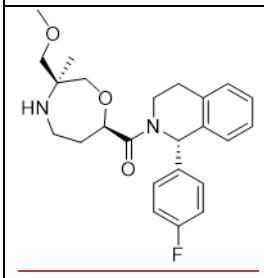
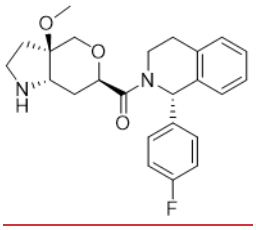
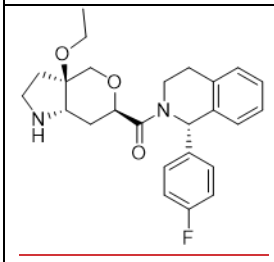
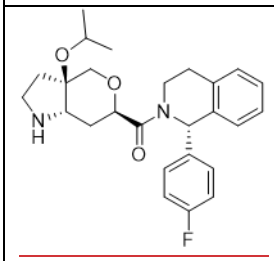
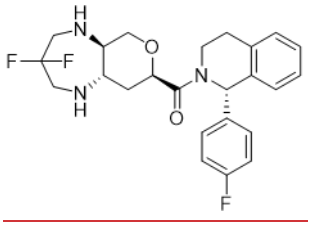
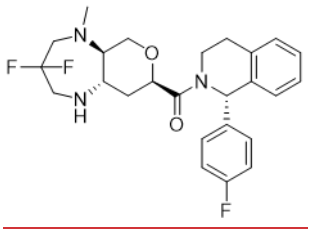
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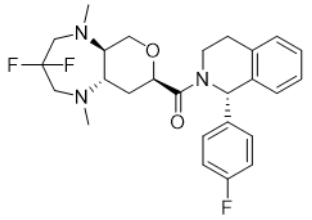
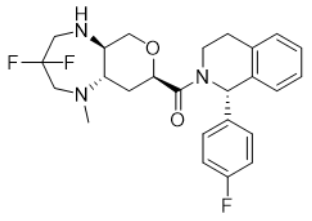
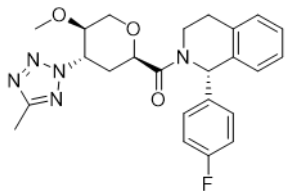
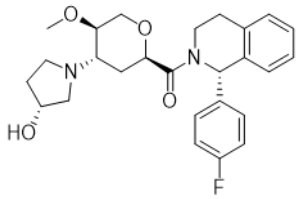
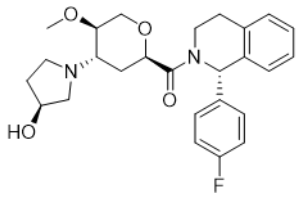
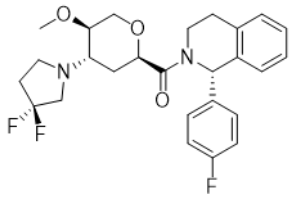
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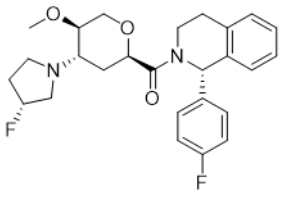
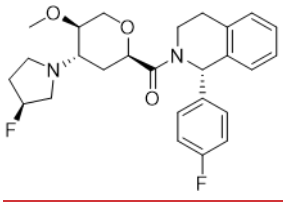
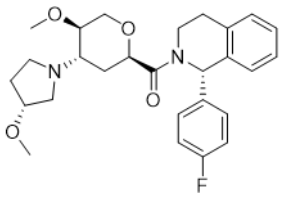
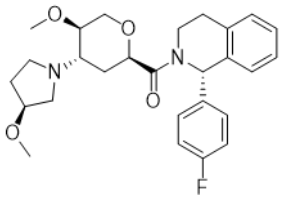
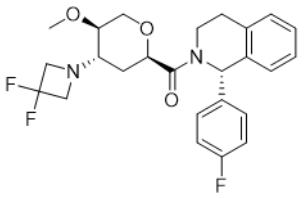
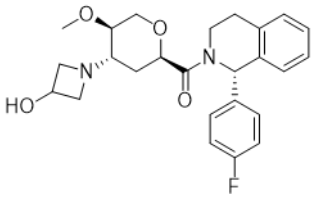
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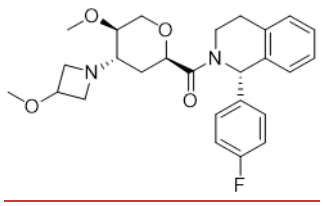
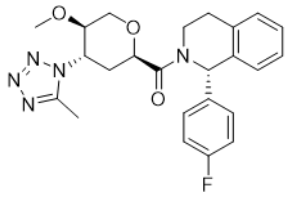
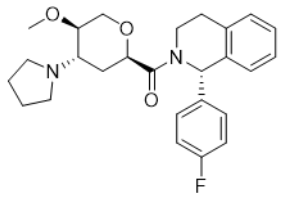
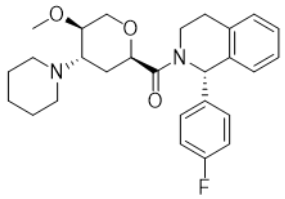
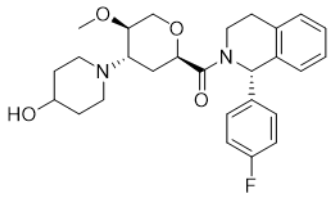
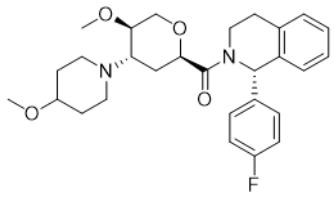
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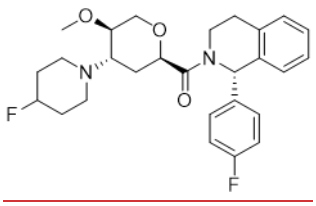
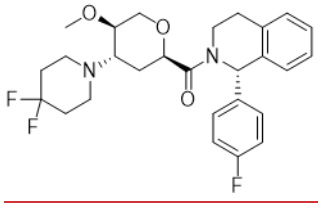
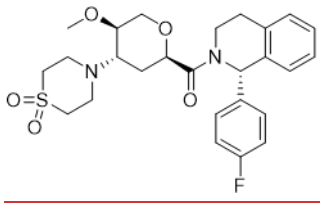
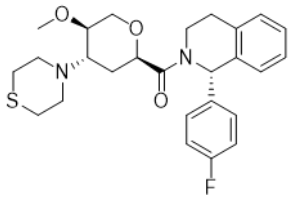
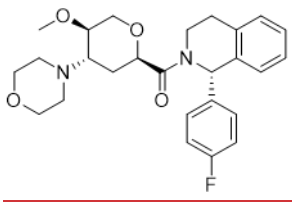
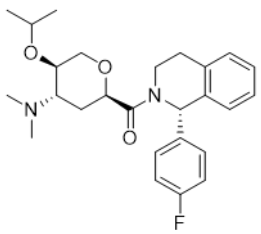
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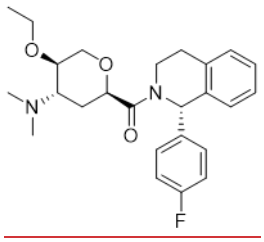
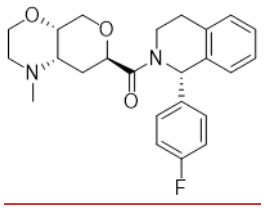
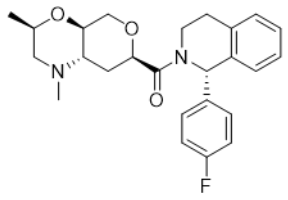
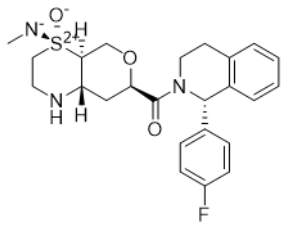
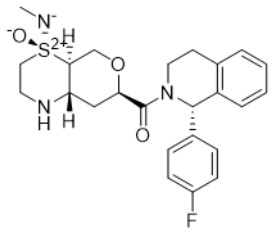
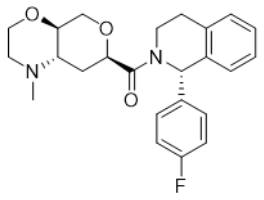
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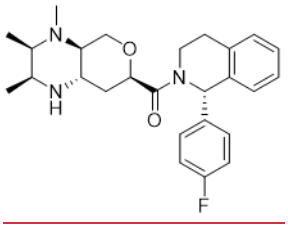
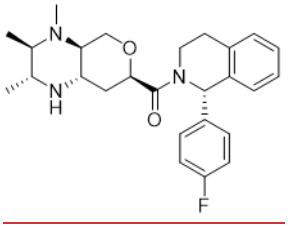
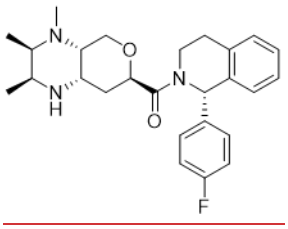
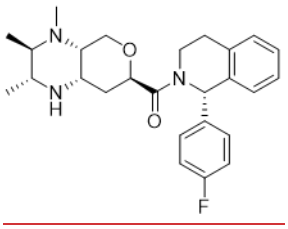
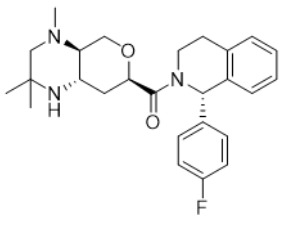
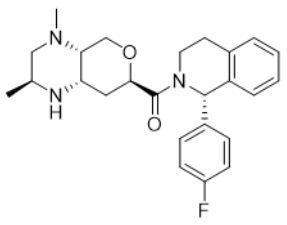
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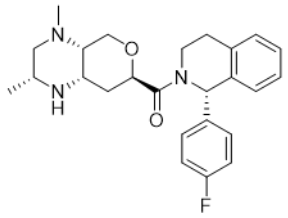
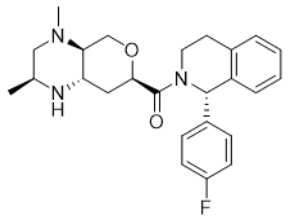
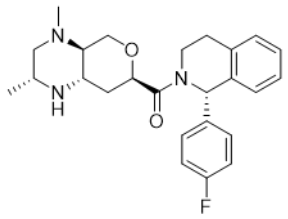
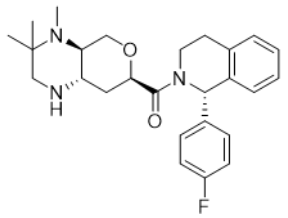
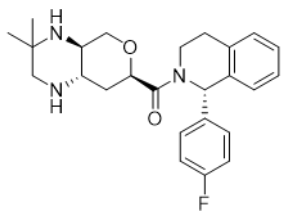
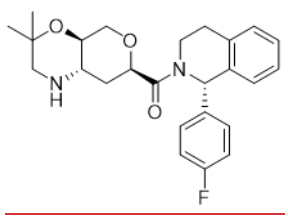
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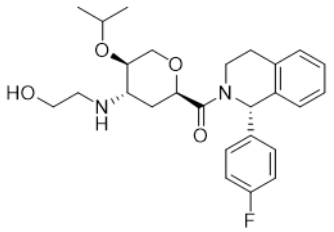
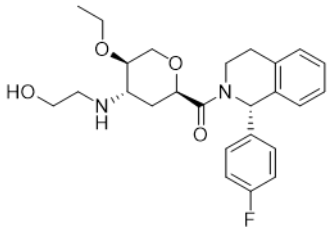
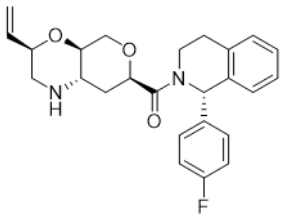
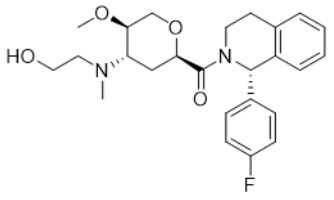
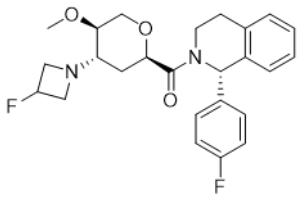
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[0005c] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound or salt as disclosed herein and a pharmaceutically acceptable excipient.

[0005d] In a further aspect of the present disclosure, there is provided a use of the compound or salt as disclosed herein in the manufacture of a medicament for treating a progranulin-associated disorder in a subject.

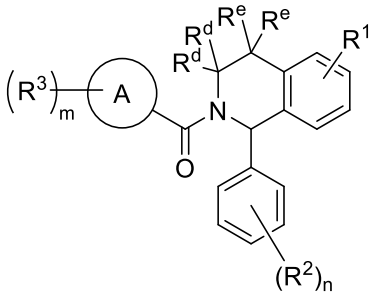
[0005e] In another aspect of the present disclosure, there is provided a use of the compound or salt as disclosed herein in the manufacture of a medicament for treating:

(i) a lysosomal storage disorder;
(ii) an inflammatory disorder;
(iii) stroke, Down syndrome, congenital heart disease, diabetes, common variable immune deficiency (CVID), tubulo-interstitial kidney disease (TKD), polycystic liver disease, myocarditis, dermatitis hyperhomocysteinemia, endo-toxic shock, lung injury, bone defect (e.g., inflammatory periodontal bone defect), or osteolysis; or
(iv) a neurodegenerative disease in a subject.

[0005f] In yet another aspect of the present disclosure, there is provided the compound or salt as disclosed herein, for use in therapy.

[0006] Provided herein are compounds and methods for modulating progranulin, e.g., increasing the level of progranulin or granulin in a subject. More particularly, provided are modulators of progranulin and the uses of such modulators in treating progranulin-associated disorders, e.g., Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), Frontotemporal dementia (FTD), Frontotemporal dementia - Granulin subtype (FTD-GRN), Lewy body dementia (LBD), Prion disease, Motor neuron diseases (MND), Huntington's disease (HD), Spinocerebellar ataxia (SCA), Spinal muscular atrophy (SMA), lysosomal storage diseases, diseases associated with inclusions and/or misfunction of C9orf72, TDP-43, FUS, UBQLN2, VCP, CHMP28, and/or MAPT, acute neurological disorders, glioblastoma, or neuroblastoma.

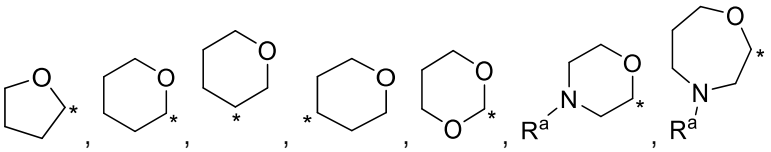
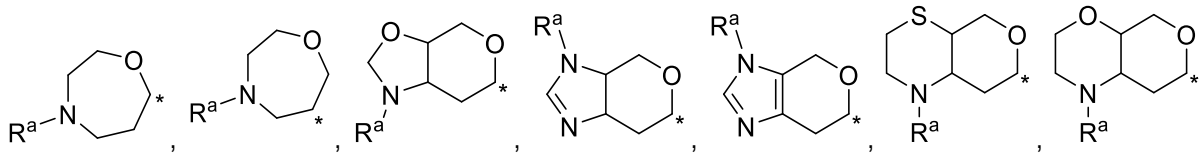
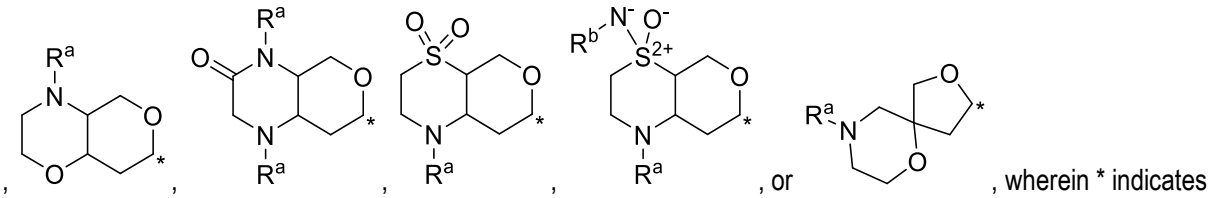
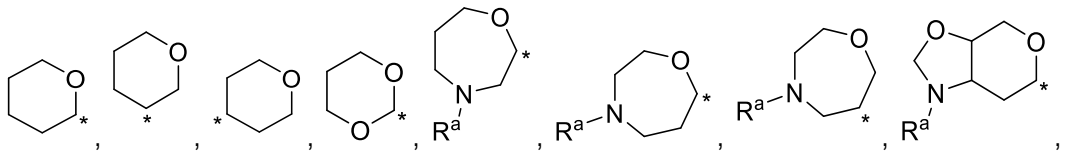
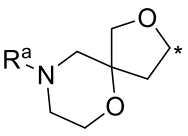
[0007] The present disclosure provides compounds of Formula (I):



(I)

wherein ring A is a 4- to 12-membered heterocycle comprising a ring O or S atom, further comprising 0-3 additional ring heteroatoms selected from O, N, and S; R^1 is hydrogen, C_{1-6}alkyl, halo, C_{1-3} haloalkyl, O-C_{1-3} haloalkyl,C_{0-3} alkylene-CN, C_{0-3} alkylene-NR^N_2, C_{0-6} alkylene-OR^N, C_{0-6} alkylene- $C(O)OR^N$, C_{0-6} alkylene-$C(O)N(R^N)_2$, or C_{0-6} alkylene-SO_pR^N; each R^N is independently hydrogen or C_{1-6}alkyl, and p is 0-2; each R^2 is

independently halo; each R^3 is independently hydrogen, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{0-6}alkylene-OH, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{1-6}alkylene-O-C_{1-6}alkyl, C_{0-6}alkylene-NR^aR^b, S-C_{1-6}alkyl, C_{2-6}alkenyl, C(O)-C_{1-6}haloalkyl,

[0009] In some cases, ring A is , , , , , , , , , , , , or , wherein * indicates the point of attachment of ring A to the adjacent carbonyl moiety of Formula I. In some cases, ring A is , , , , , , , , , , , , or , wherein * indicates the point of attachment of ring A to the adjacent carbonyl moiety of Formula I. In some cases, ring A is .

[0010] Further provided are methods of modulating progranulin in a subject. In some ~~embodiments~~examples, provided are methods of treating a progranulin-associated disorder in a subject.

[0011] Other ~~aspects~~ examples of the present disclosure include a compound as disclosed herein for use in the preparation of a medicament for the modulation of progranulin, and the use of a compound as disclosed herein in a method of treating or preventing a progranulin-associated disorder in a subject.

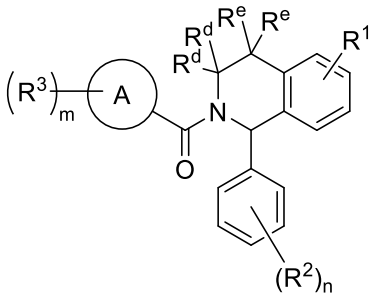
DETAILED DESCRIPTION

Compounds as Progranulin Modulators

[0012] Provided herein are compounds that can modulate progranulin production and/or secretion. In some cases, the compounds can increase the level of progranulin or granulin in a subject. Also provided are methods of modulating the translocon complex using compounds as disclosed herein to increase lysosomal protein levels.

What is Claimed:

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



(I)

wherein

ring A is a 4- to 12-membered heterocycle comprising a ring O or S atom, further comprising 0-3 additional ring heteroatoms selected from O, N, and S;

R^1 is hydrogen, C_{1-6}alkyl, halo, C_{1-3} haloalkyl, O-C_{1-3} haloalkyl,C_{0-3} alkylene-CN, C_{0-3} alkylene-NR^N_2, C_{0-6} alkylene-OR^N, C_{0-6} alkylene- $C(O)OR^N$, C_{0-6} alkylene-$C(O)N(R^N)_2$, or C_{0-6} alkylene-SO_pR^N; each R^N is independently hydrogen or C_{1-6}alkyl, and p is 0-2;

each R^2 is independently halo;

each R^3 is independently hydrogen, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{0-6}alkylene-OH, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{1-6}alkylene-O-C_{1-6}alkyl, C_{0-6}alkylene-NR^aR^b, S-C_{1-6}alkyl, C_{2-6}alkenyl, C(O)-C_{1-6}haloalkyl, SO_2-C_{1-6}alkyl, $S^{2+}(O)^-(NR^a)^-C_{1-6}$alkyl, OR^4,, 5- to 8- membered heteroaryl comprising 1-4 ring N atoms, or 4- to 6-membered heterocycle comprising 1-4 ring heteroatoms selected from O, N, and S with at least 1 ring heteroatom being N, and the heteroaryl or heterocycle is optionally substituted with 1 or 2 substituents independently selected from halo, C_{1-6}alkyl, OH, and C_{1-6}alkoxy, or

two geminal R^3 together with the atom to which they are attached form an oxo group, and

when ring A comprises a ring N atom, the N is substituted with R^a, and if ring A does not comprise a ring N atom, then at least one R^3 is C_{0-6}alkylene-NR^aR^b;

R^a and R^b are each independently hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-OH, C_{1-6}alkylene-O-C_{1-6}alkyl, C(O)-C_{1-6}alkyl, C(O)-C_{1-6}haloalkyl, $S(O)_2$-C_{1-6}alkyl, $S(O)_2$-C_{1-6}haloalkyl; or

R^a and R^b together with the nitrogen to which they are attached form a 3- to 12-membered monocyclic or bicyclic heterocycle optionally further comprising 1-3 additional ring heteroatoms selected from O, N, and S;

R^4 is C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylene-C_{3-8}cycloalkyl, or C_{0-6}alkylene-C_{6-10}aryl;

each R^d is independently H or D;

each R^e is independently H, D, halo, OH, methyl, or methoxy, or

two geminal R^e together with the atom to which they are attached form an oxo group or a spiro C_{3-5}cycloalkyl;

m is 1-4; and

n is 0-2.

2. The compound or salt of claim 1, wherein ring A is a 4- to 6-membered heterocycle.

~~3. The compound or salt of claim 1 or 2, wherein ring A is a 6- to 8-membered heterocycle.~~

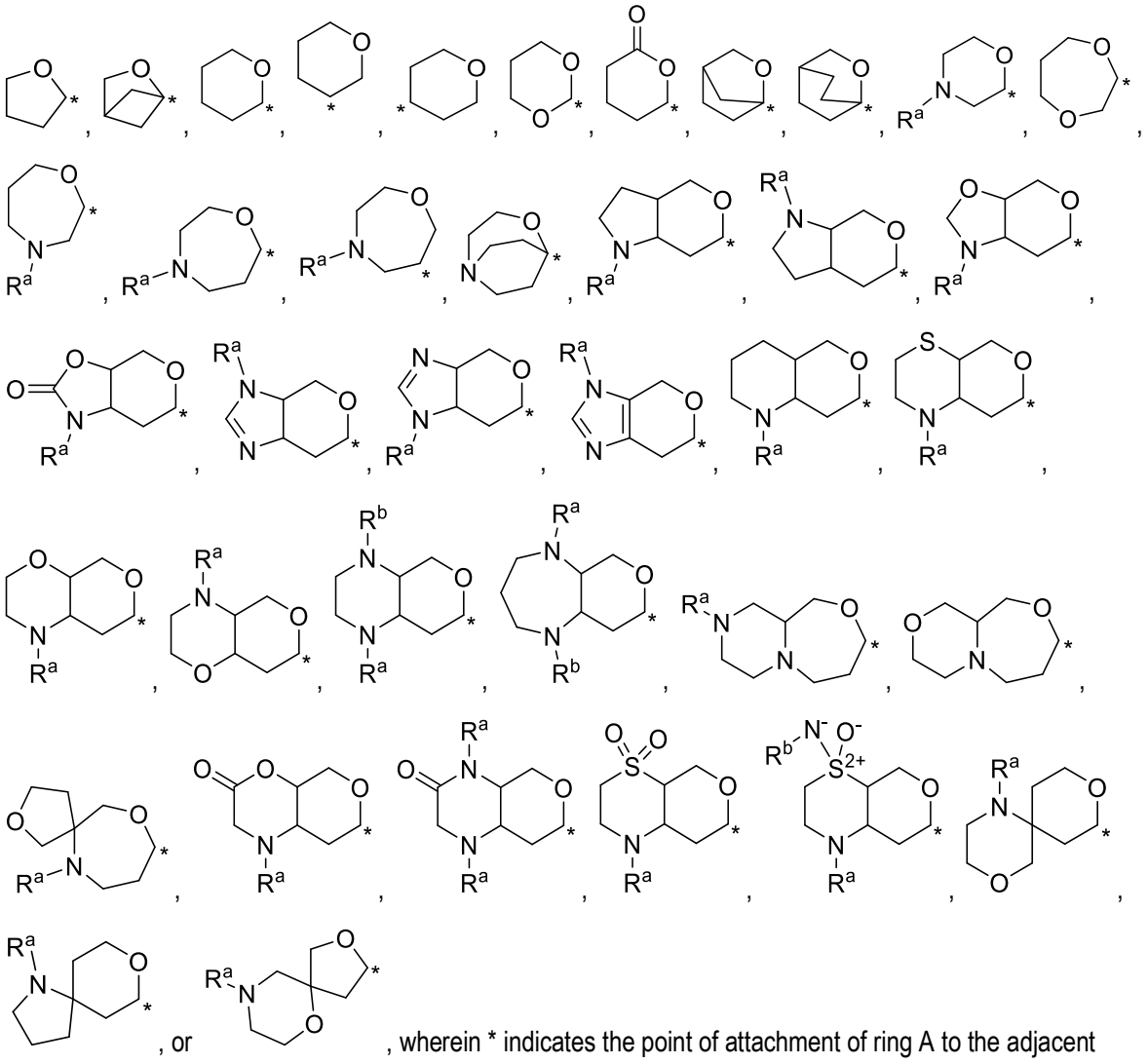
~~4.~~3. The compound or salt of ~~any one of claims 1 to 3~~claim 1 or 2, wherein ring A comprises a ring O atom and 0-3 additional ring heteroatoms selected from O, N, and S.

~~5. The compound or salt of claim 4, wherein ring A comprises a tetrahydropyranyl ring.~~

~~6.~~4. The compound or salt of ~~any one of claims 1 to 3~~claim 1 or 2, wherein ring A comprises a ring O and N atom.

~~7.~~5. The compound or salt of ~~any one of claims 1 to 3~~claim 1 or 2, wherein ring A comprises a ring S atom and 0-3 additional ring heteroatoms selected from O, N, and S.

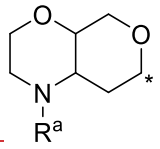
~~8.~~6. The compound or salt of ~~any one of claims 1 to 3~~claim 1 or 2, wherein ring A is ,

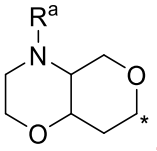
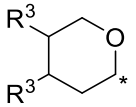


, wherein * indicates the point of attachment of ring A to the adjacent carbonyl moiety of Formula I.

~~9.~~7. The compound or salt of claim ~~6~~8, wherein ring A is ,

~~10. The compound or salt of claim 8, wherein ring A is~~ ,

~~11. The compound or salt of claim 8, wherein ring A is~~  ~~or~~

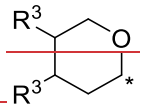
 , or .

~~12. The compound or salt of any one of claims 1 to 11, wherein m is 1.~~

~~13. The compound or salt of claim 12, wherein R^3 is hydrogen.~~

~~14. The compound or salt of any one of claims 1 to 11, wherein m is 3.~~

~~15. The compound or salt of any one of claims 1 to 11, wherein m is 2.~~

~~16. The compound or salt of claim 15, wherein ring A is~~ 

~~17.~~8. The compound or salt of any one of claims 1 to ~~12 and 14 to 16~~7, wherein: (i) at least one R^3 is $C_{0\text{-}6}$alkylene-NR^aR^b;

~~18. The compound or salt of claim 17, wherein at least one R^3 is NH_2.~~

~~19. The compound or salt of claim 17, wherein at least one R^3 is NHMe.~~

~~20. The compound or salt of any one of claims 1 to 12, and 14 to 19, wherein~~ (ii) at least one R^3 is halo;

~~21. The compound or salt of claim 20, wherein at least one R^3 is F.~~

~~22. The compound or salt of any one of claims 1 to 12 and 14 to 21, wherein~~ (iii) at least one R^3 is $C_{1\text{-}6}$alkoxy;

~~23. The compound or salt of claim 22, wherein at least one R^3 is methoxy.~~

~~24. The compound or salt of claim 22, wherein at least one R^3 is ethoxy.~~

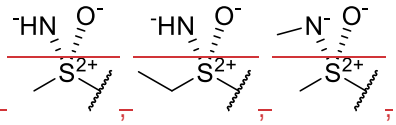
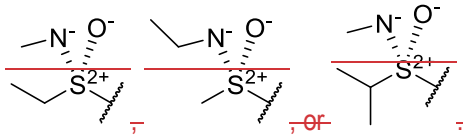
~~25. The compound or salt of claim 21, wherein one R^3 is F and one R^3 is NH_2.~~

~~26. The compound or salt of claim 23, wherein one R^3 is methoxy and one R^3 is NH_2.~~

~~27. The compound or salt of claim 23, wherein one R^3 is methoxy and one R^3 is NHMe.~~

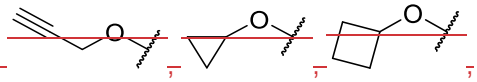
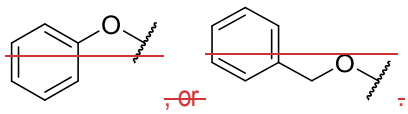
~~28. The compound or salt of claim 24, wherein one R^3 is ethoxy and one R^3 is NH_2.~~

~~29. The compound or salt of any one of claims 1 to 12, wherein~~ (iv) R^3 is $S^{2+}(O)^-(NR^a)^-C_{1-6}$alkyl;~~.~~

~~30. The compound or salt of claim 29, wherein R^3 is~~  ~~,~~  ~~, or~~ ~~.~~

~~31. The compound or salt of any one of claims 1 to 12, wherein~~ or (v) R^3 is OR^4.

~~32. The compound or salt of claim 31, wherein R^4 is C_{2-6}alkynyl, C_{0-6}alkylene-C_{3-8}cycloalkyl, or C_{0-6}alkylene-C_{6-10}aryl.~~

~~33. The compound or salt of claim 33, wherein R^3 is~~  ~~,~~  ~~, or~~ ~~.~~

9. The compound or salt of claim 8, wherein:

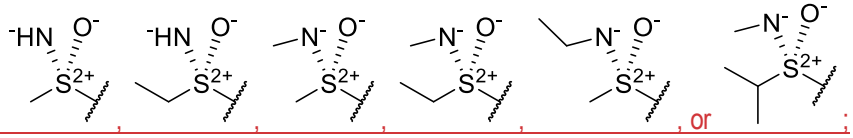
(i) at least one R^3 is NH_2;

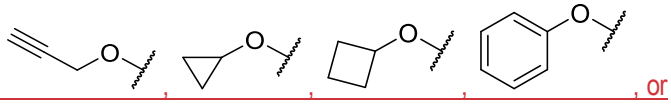
(ii) at least one R^3 is NHMe;

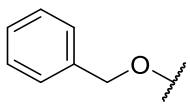
(iii) at least one R^3 is F;

(iv) at least one R^3 is methoxy;

(v) at least one R^3 is ethoxy;

(vi) R^3 is  ; or

(vii) R^3 is  , or

 .

10. The compound or salt of any one of claims 1 to 9, wherein:

(i) one R^3 is F and one R^3 is NH_2;

(ii) one R^3 is methoxy and one R^3 is NH_2;

(iii) one R^3 is methoxy and one R^3 is NHMe; or

(iv) one R^3 is NH_2.

~~34. The compound or salt of any one of claims 1 to 33, wherein n is 0.~~

~~35. The compound or salt of any one of claims 1 to 33, wherein n is 1.~~

~~36. The compound or salt of any one of claims 1 to 33, wherein n is 2.~~

~~37.~~11. The compound or salt of any one of claims 1 to ~~28, 35 and 36~~10, wherein R^2 is F or Cl.

~~38. The compound or salt of claim 37, wherein R^2 is F.~~

~~39.~~12. The compound or salt of any one of claims 1 to 11~~38~~, wherein R^1 is hydrogen or halo.

~~40. The compound or salt of claim 39, wherein R^1 is F.~~

~~41. The compound or salt of any one of claims 1 to 38, wherein R^1 is hydrogen.~~

~~42. The compound or salt of any one of claims 1 to 41, wherein at least one R^d is H.~~

~~43. The compound or salt of claim 42, wherein each R^d is H.~~

~~44. The compound or salt of any one of claims 1 to 41, wherein at least wherein at least one R^d is D.~~

~~45.~~13. The compound or salt of any one of claims 1 to ~~44~~12, wherein at least one R^e is H, D, OH, or halo, or~~.~~

~~46. The compound or salt of claim 45, wherein each R^e is H.~~

~~47. The compound or salt of any one of claims 1 to 44, wherein at least one R^e is D.~~

~~48. The compound or salt of any one of claims 1 to 44, wherein each R^e is D.~~

~~49. The compound or salt of any one of claims 1 to 44, wherein at least one R^e is OH.~~

~~50. The compound or salt of any one of claims 1 to 44, wherein at least one R^e is halo.~~

~~51. The compound or salt of any one of claims 1 to 44, wherein at least one R^e is F.~~

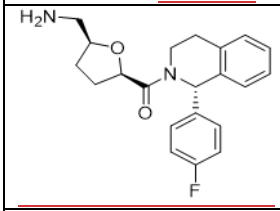
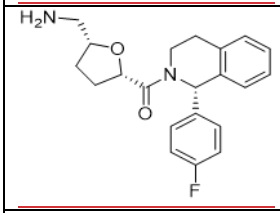
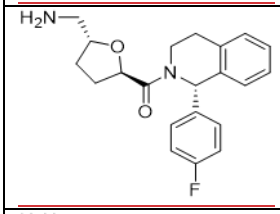
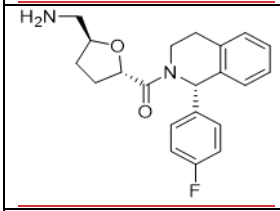
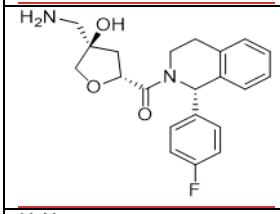
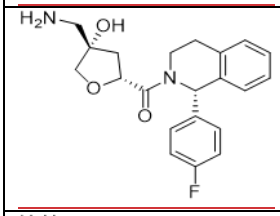
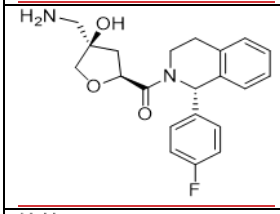
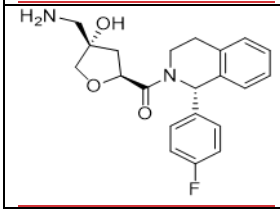
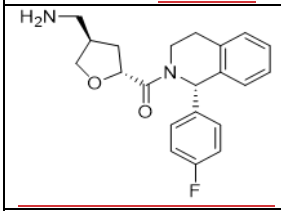
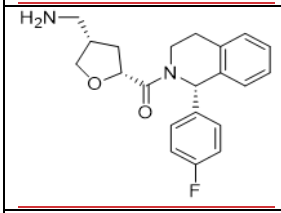
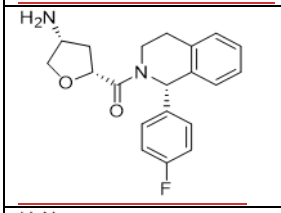
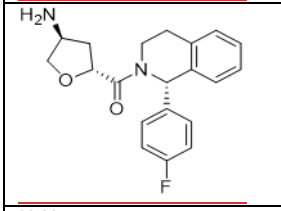
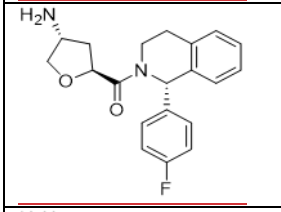
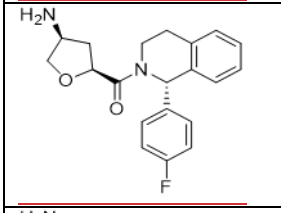
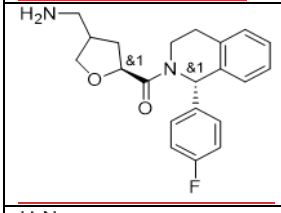
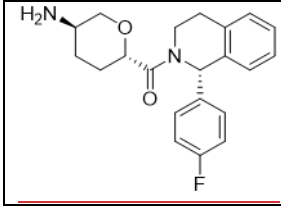
~~52. The compound or salt of any one of claims 1 to 44, wherein each R^e is halo.~~

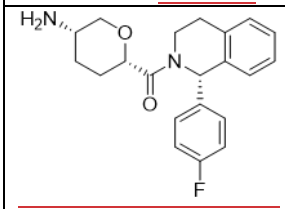
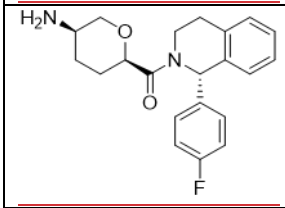
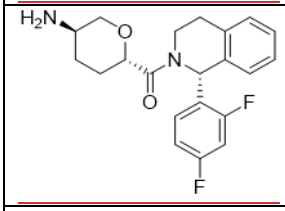
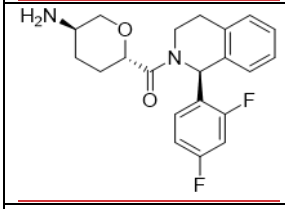
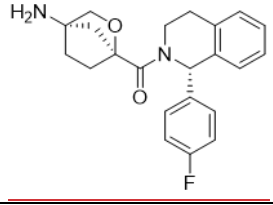
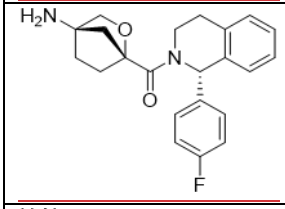
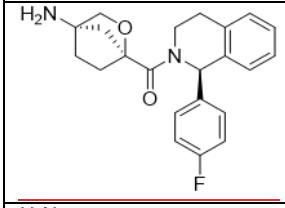
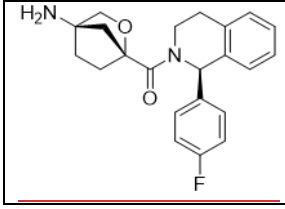
~~53. The compound or salt of any one of claims 1 to 44, wherein each R^e is F.~~

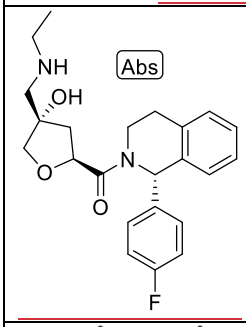
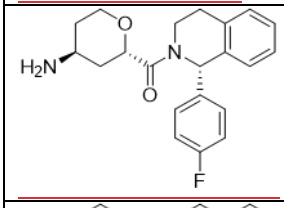
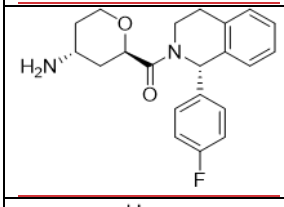
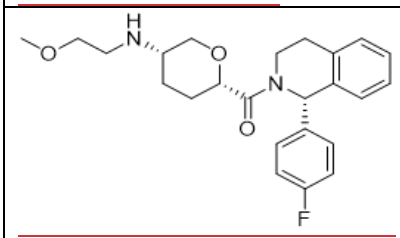
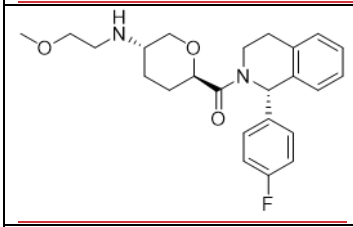
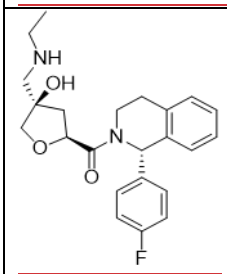
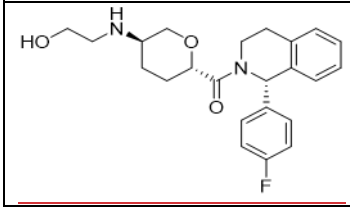
~~54. The compound or salt of any one of claims 1 to 44,~~ wherein two geminal R^e together with the atom to which they are attached form an oxo group.

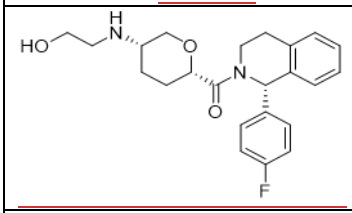
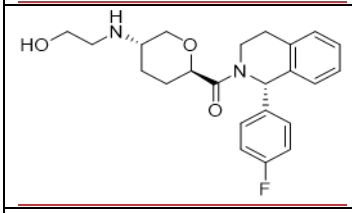
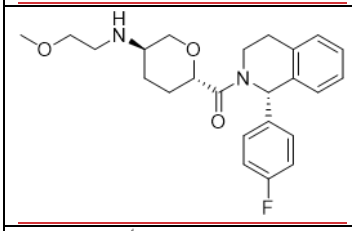
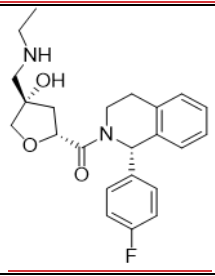
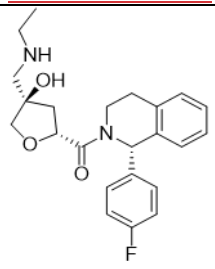
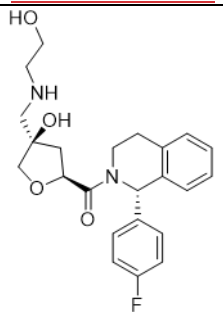
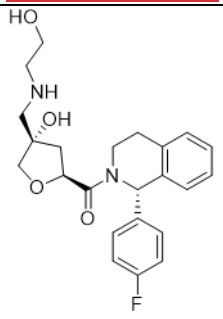
~~55.~~14. A compound, or pharmaceutically acceptable salt thereof, having a structure as shown in Table A:-

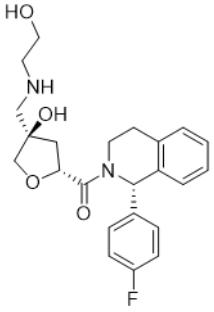
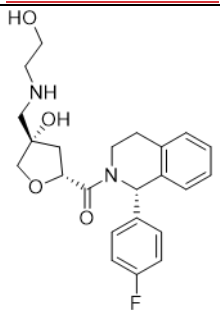
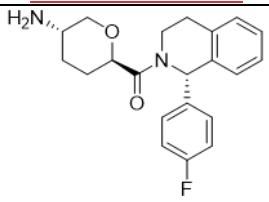
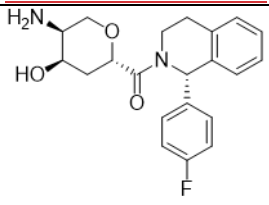
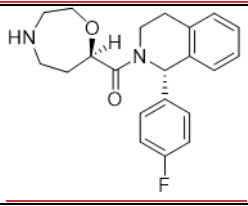
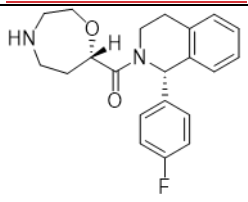
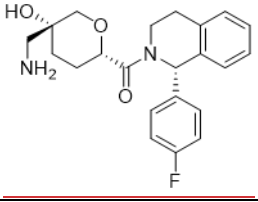
Table A

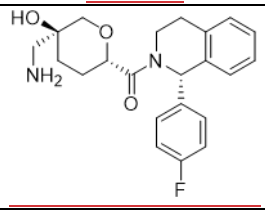
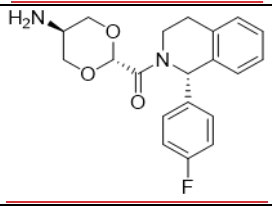
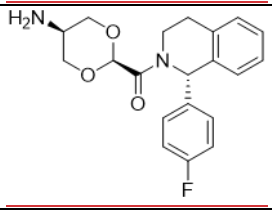
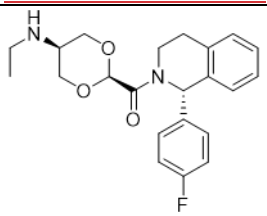
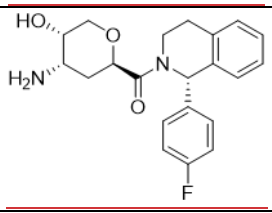
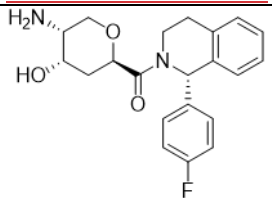
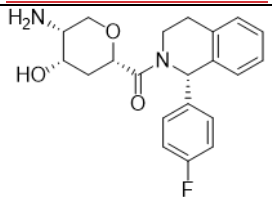
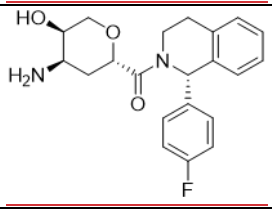
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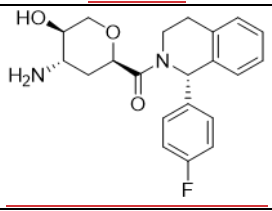
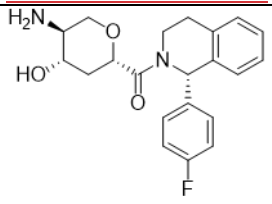
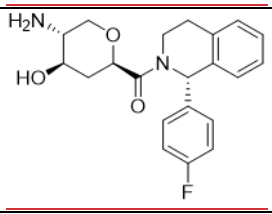
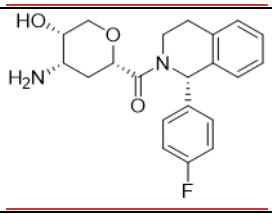
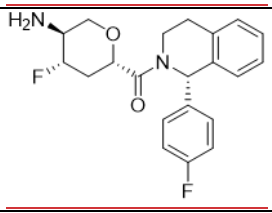
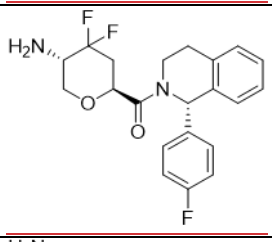
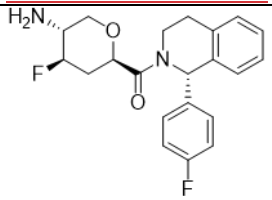
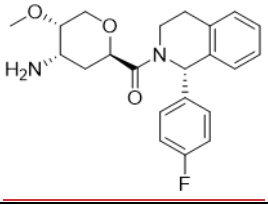
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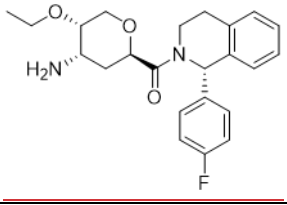
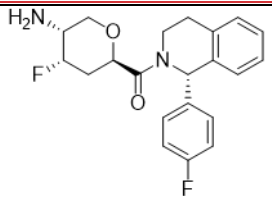
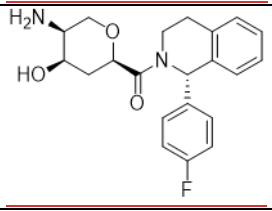
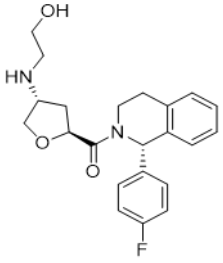
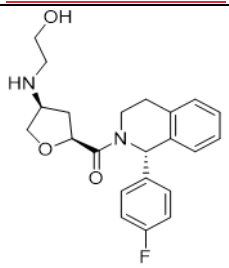
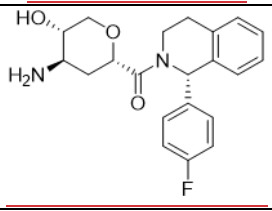
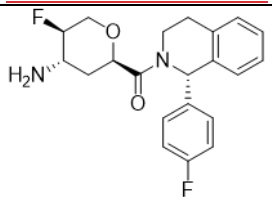
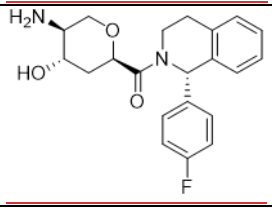
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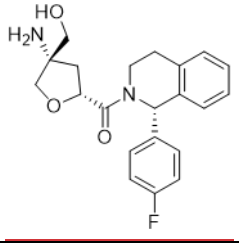
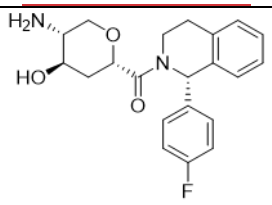
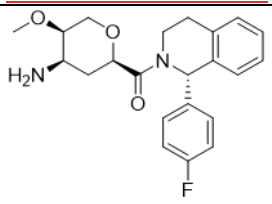
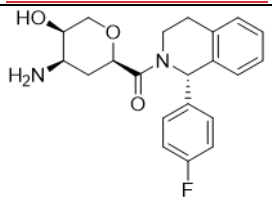
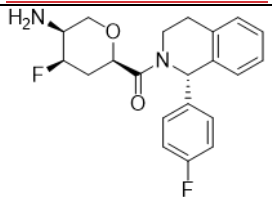
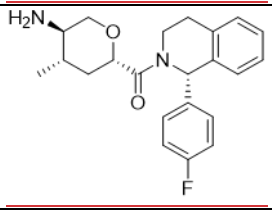
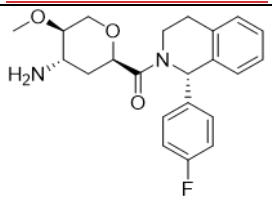
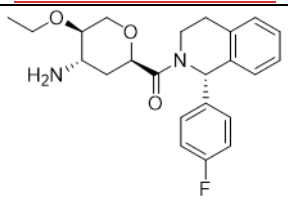
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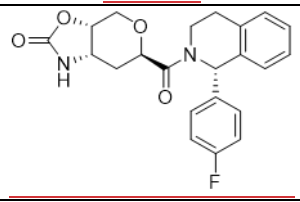
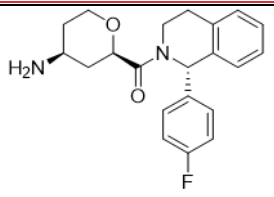
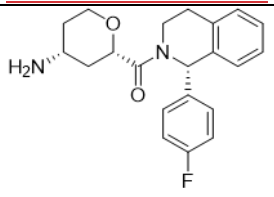
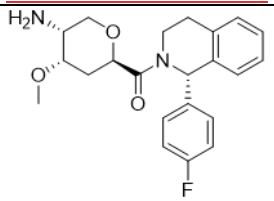
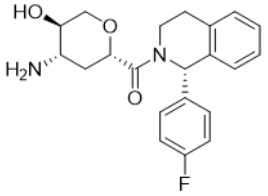
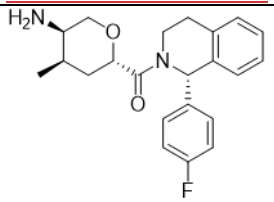
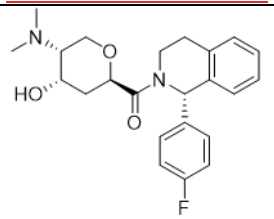
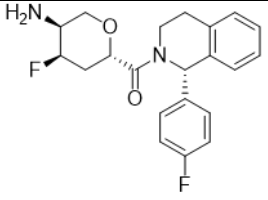
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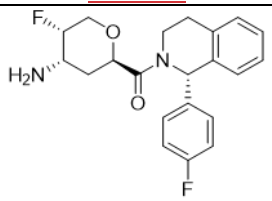
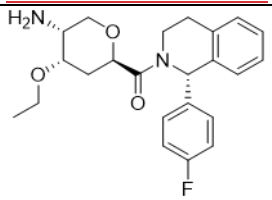
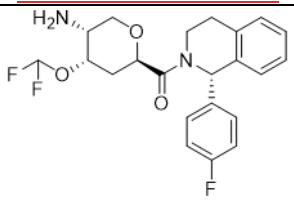
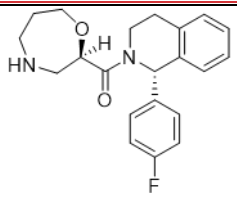
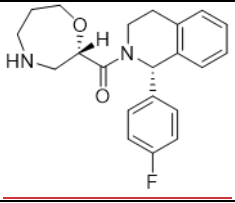
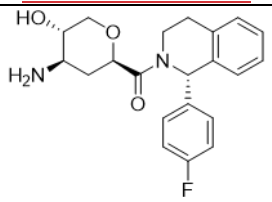
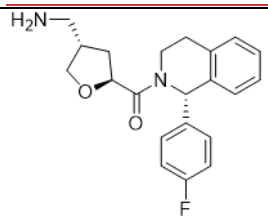
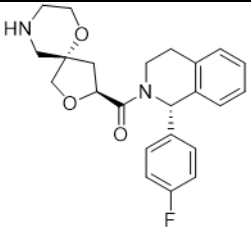
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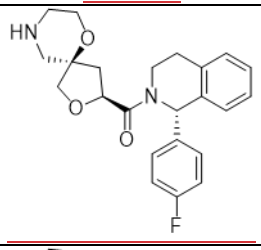
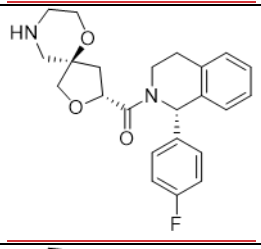
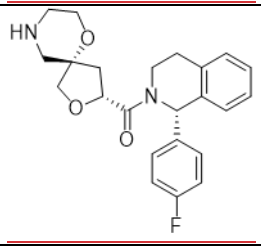
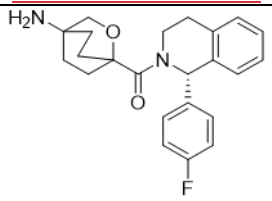
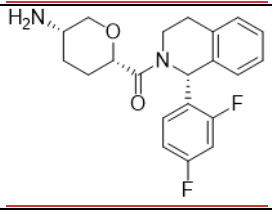
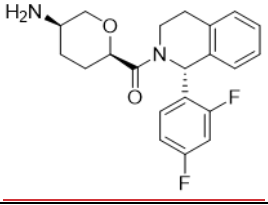
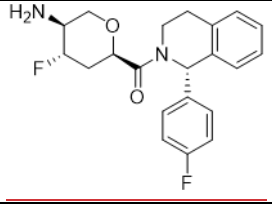
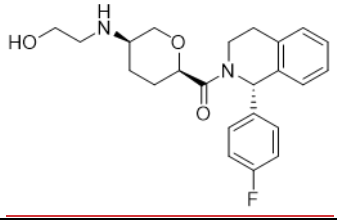
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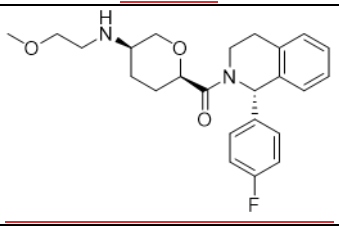
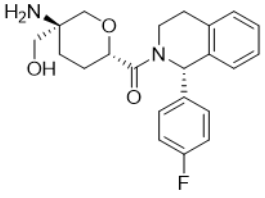
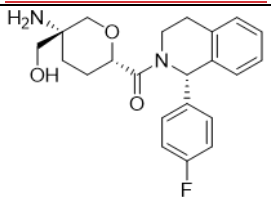
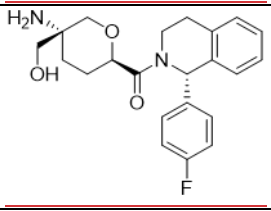
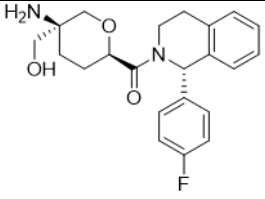
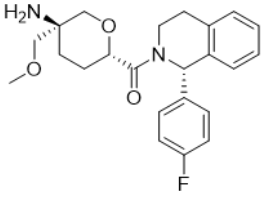
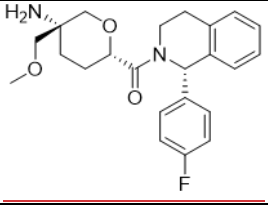
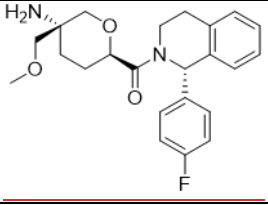
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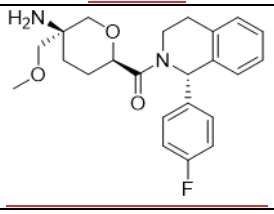
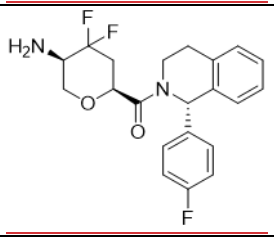
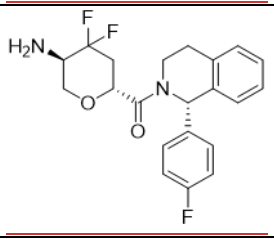
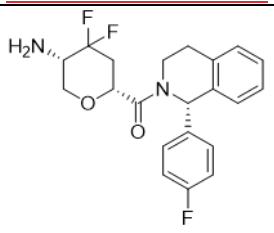
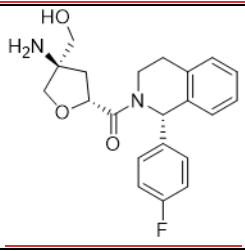
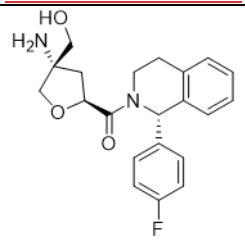
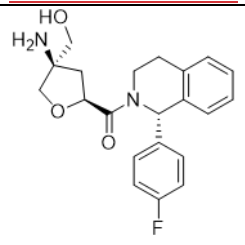
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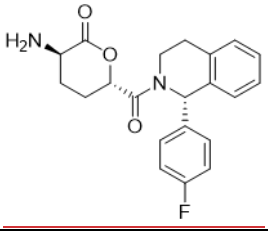
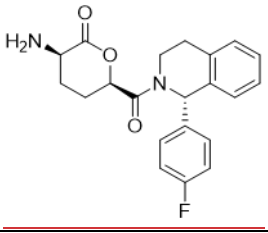
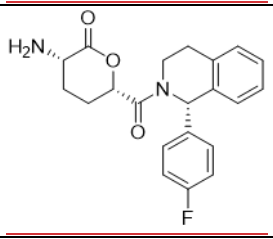
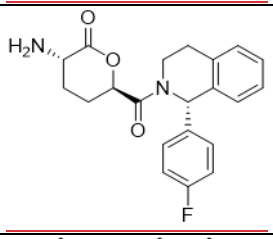
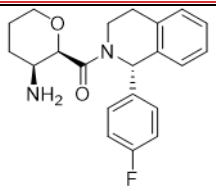
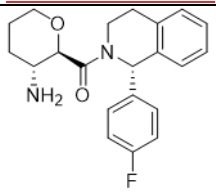
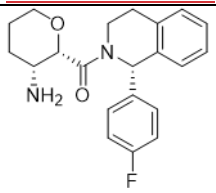
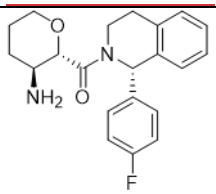
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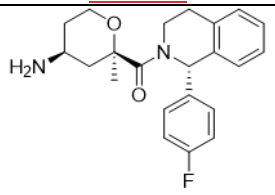
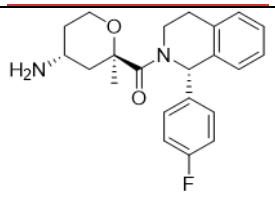
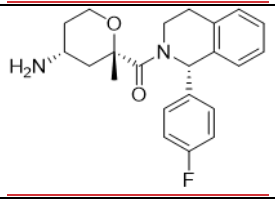
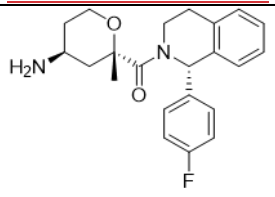
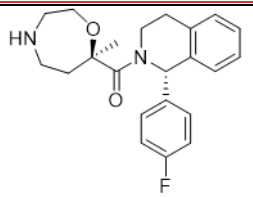
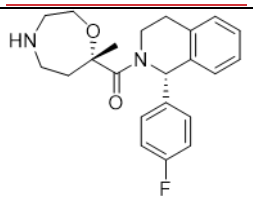
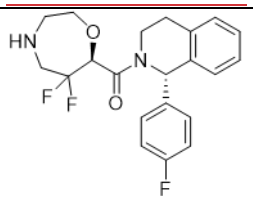
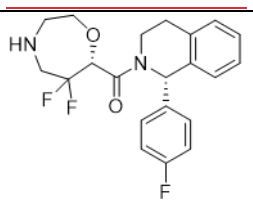
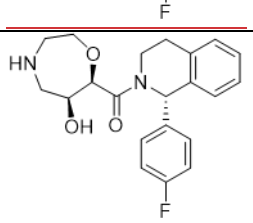
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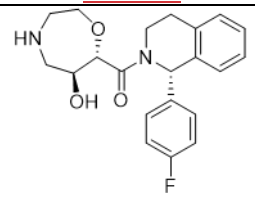
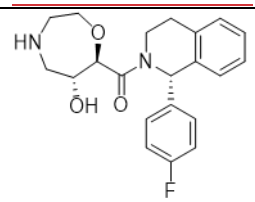
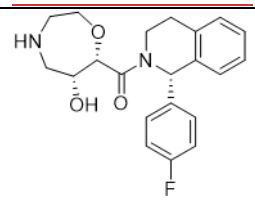
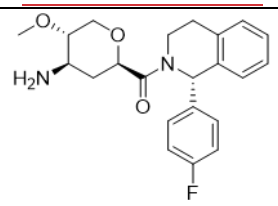
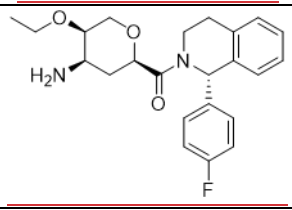
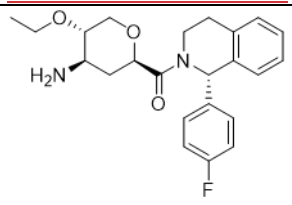
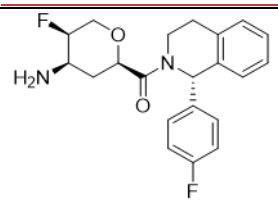
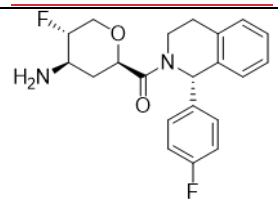
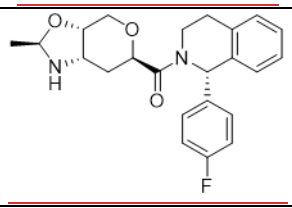
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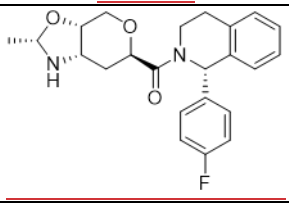
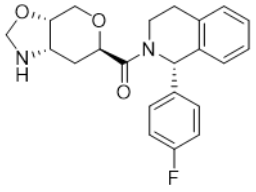
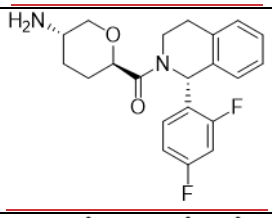
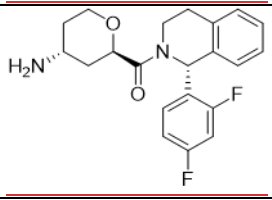
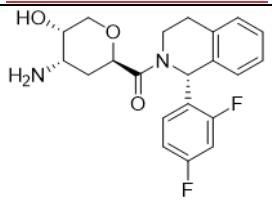
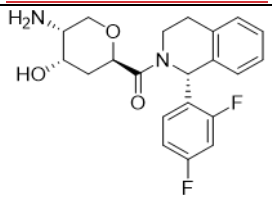
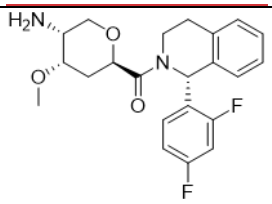
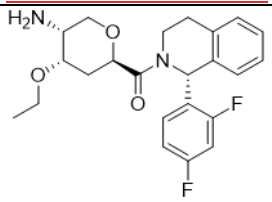
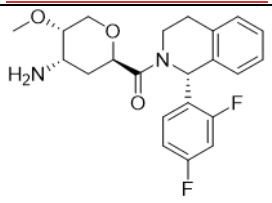
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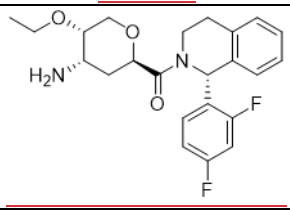
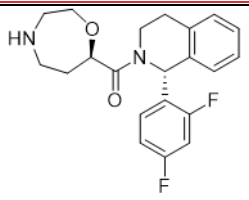
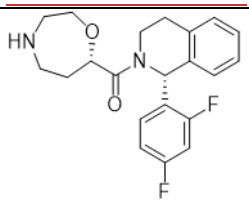
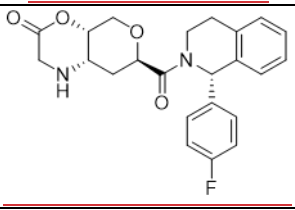
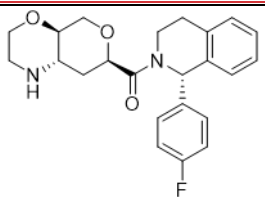
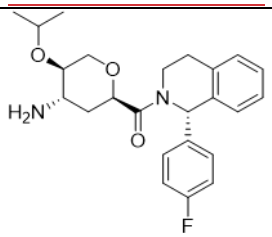
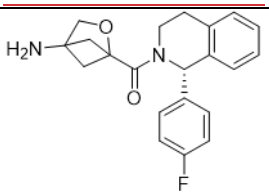
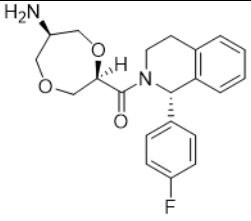
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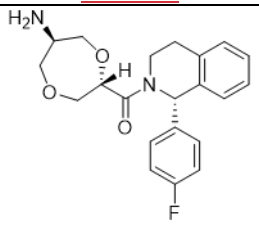
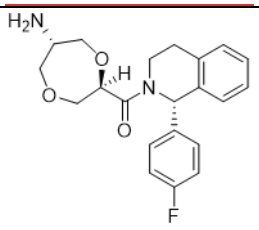
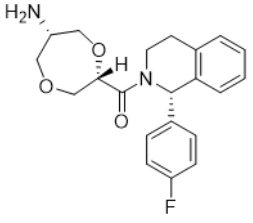
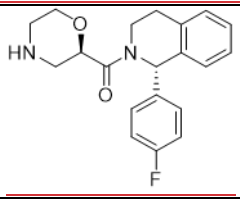
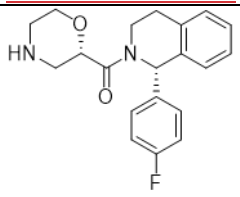
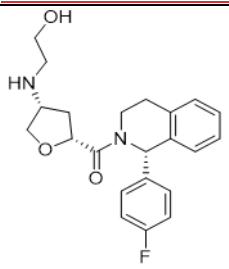
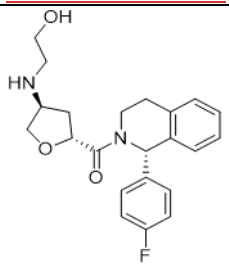
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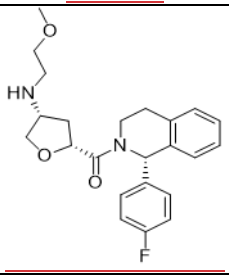
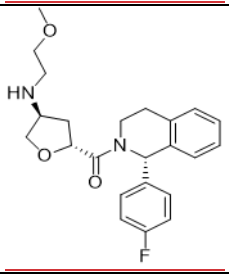
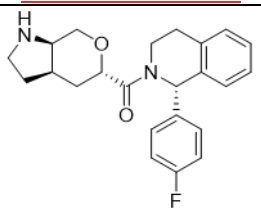
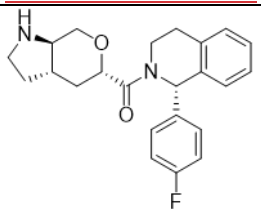
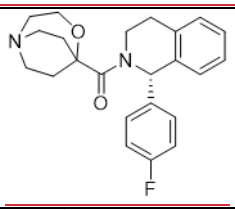
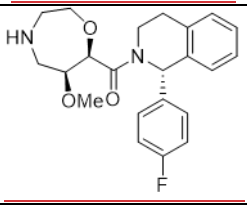
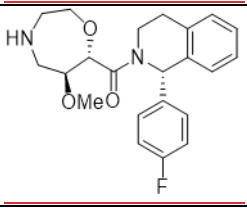
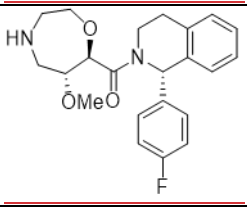
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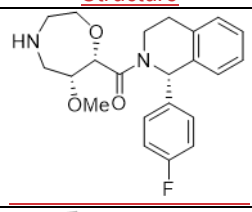
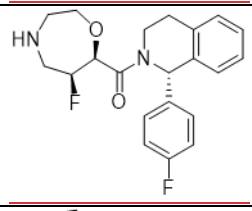
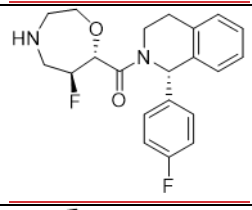
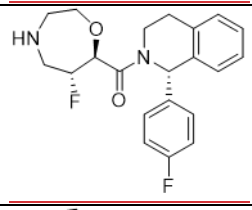
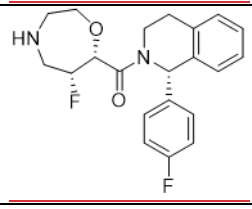
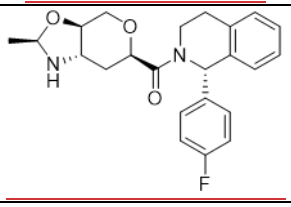
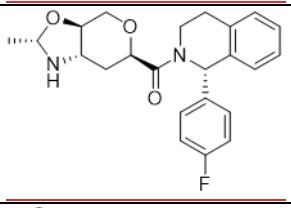
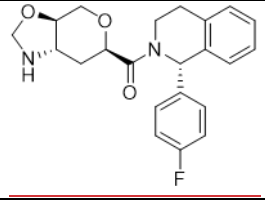
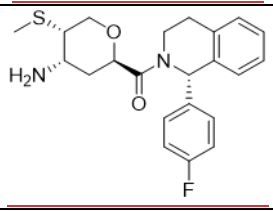
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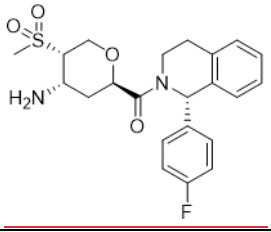
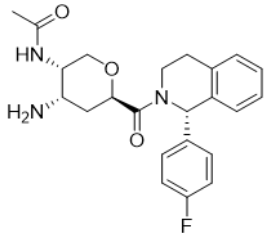
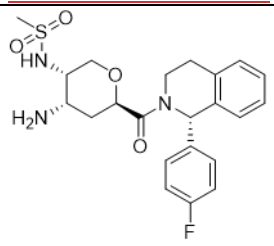
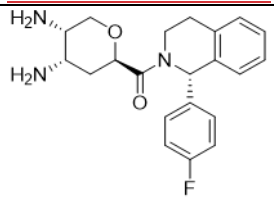
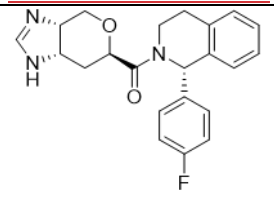
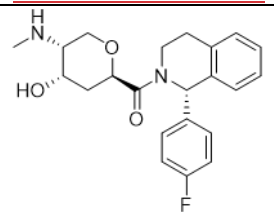
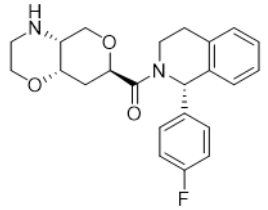
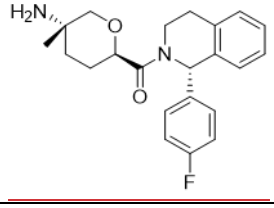
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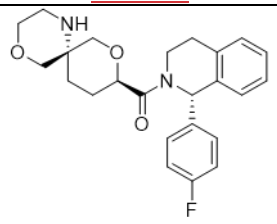
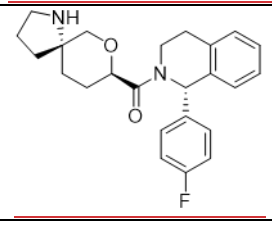
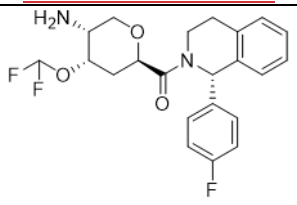
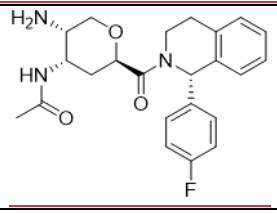
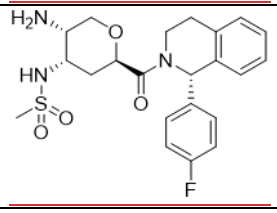
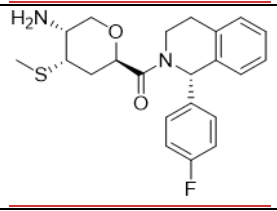
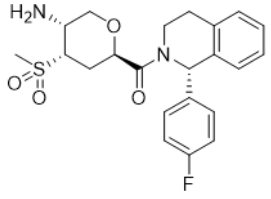
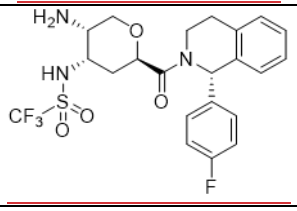
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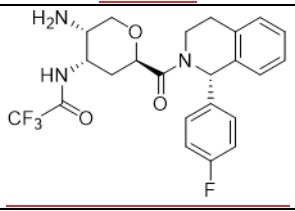
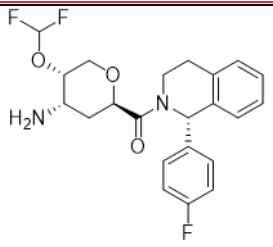
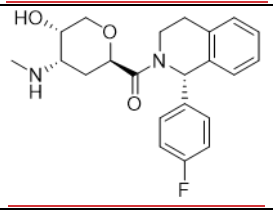
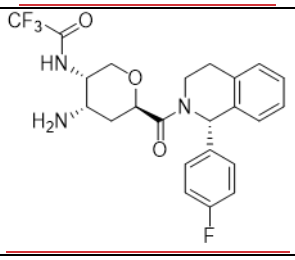
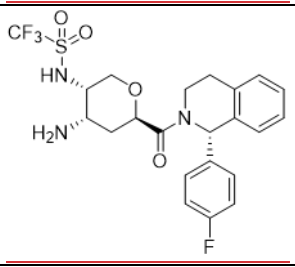
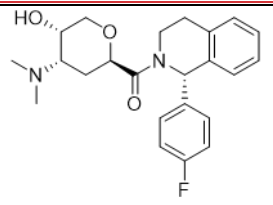
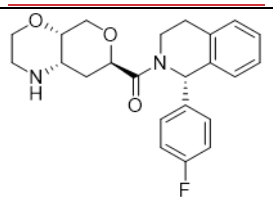
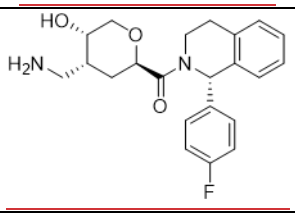
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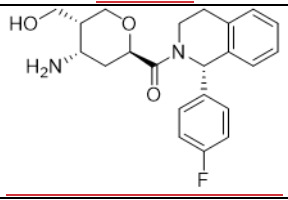
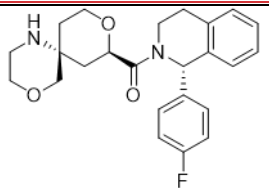
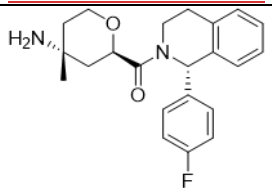
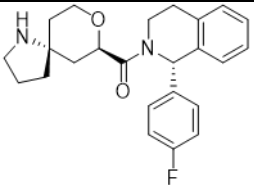
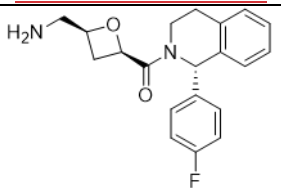
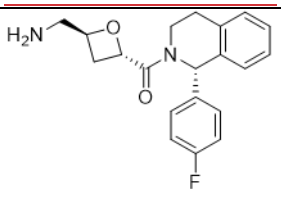
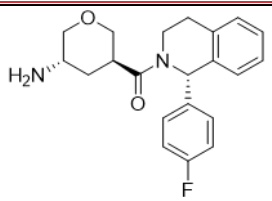
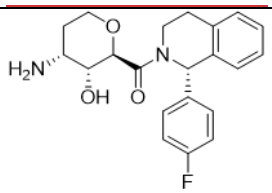
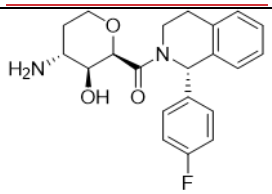
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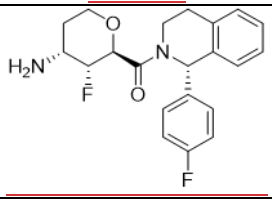
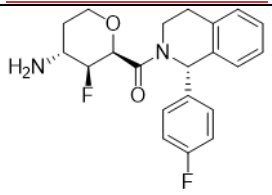
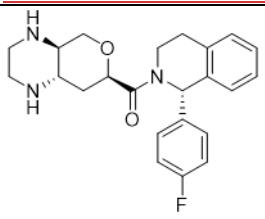
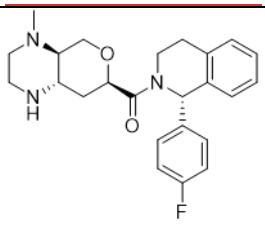
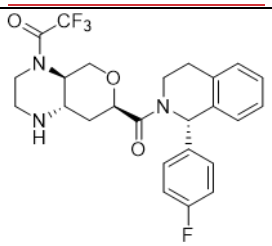
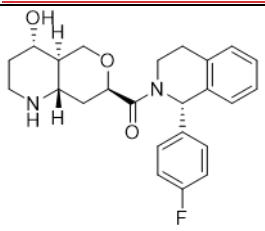
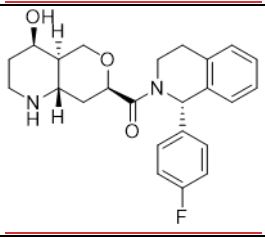
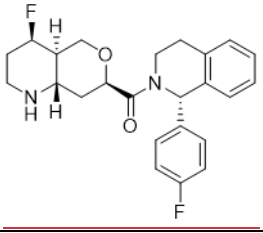
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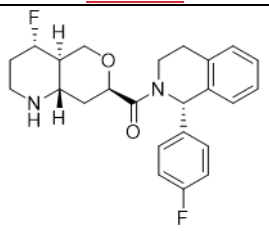
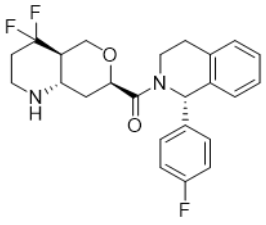
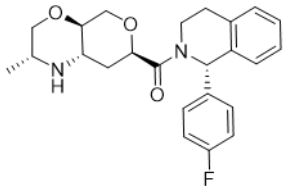
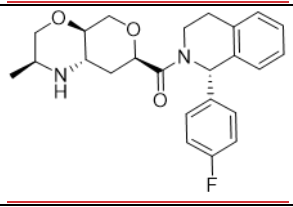
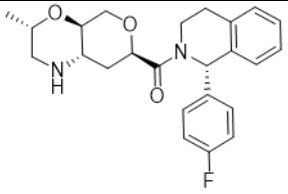
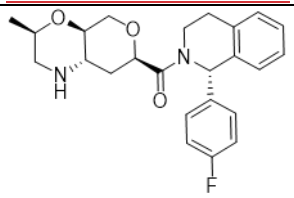
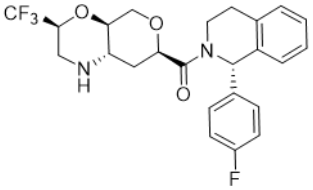
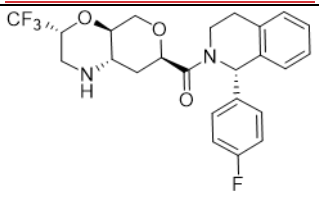
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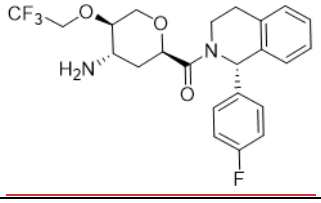
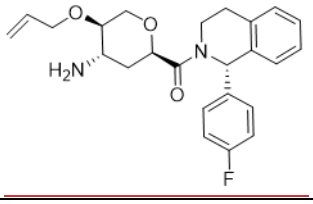
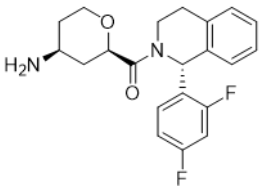
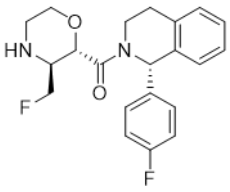
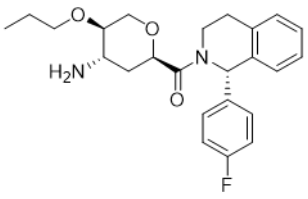
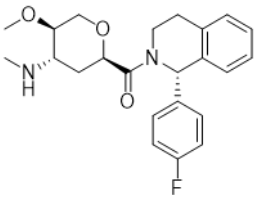
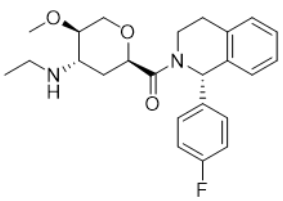
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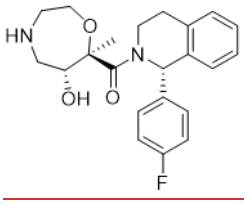
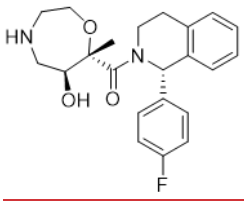
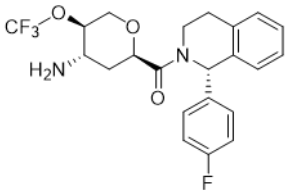
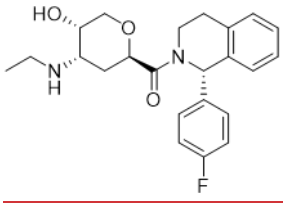
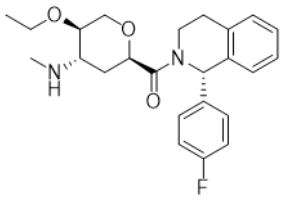
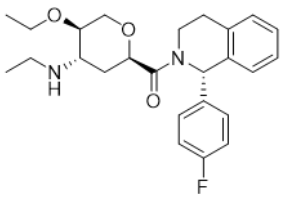
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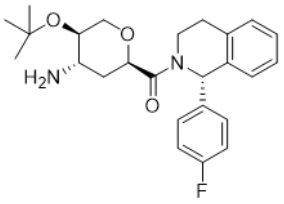
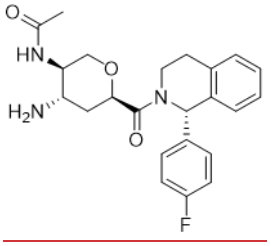
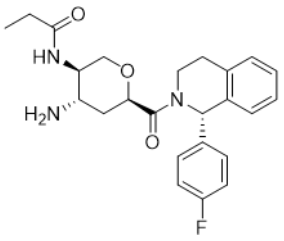
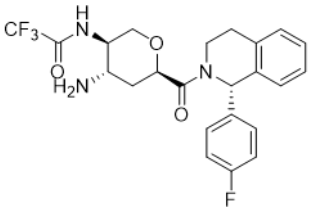
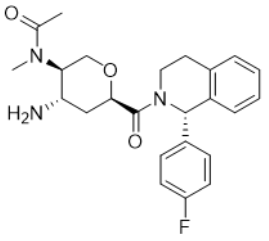
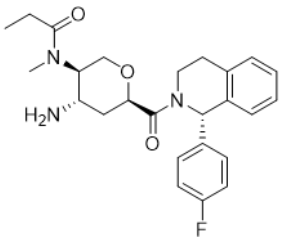
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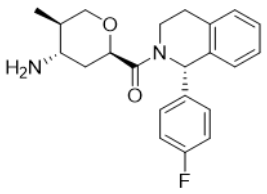
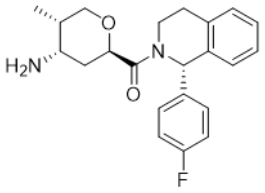
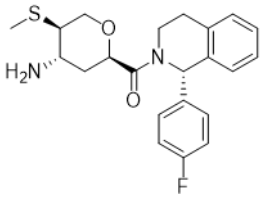
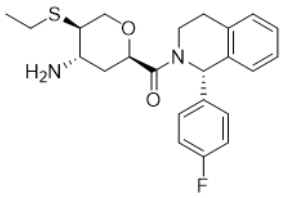
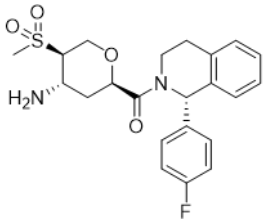
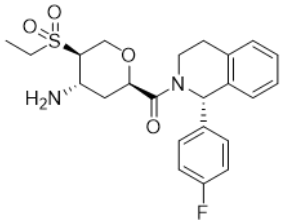
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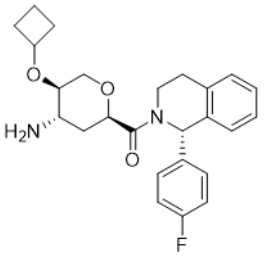
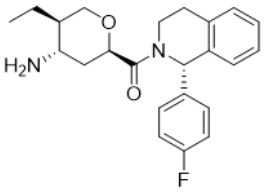
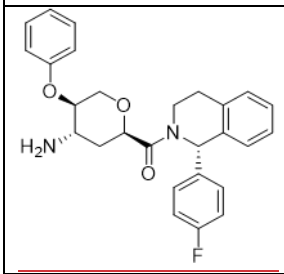
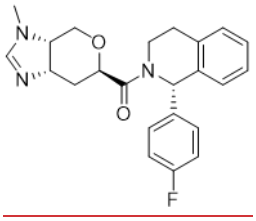
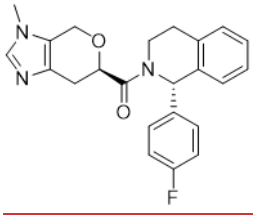
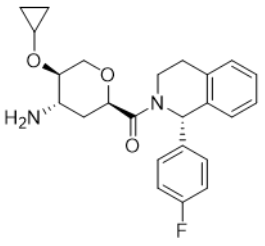
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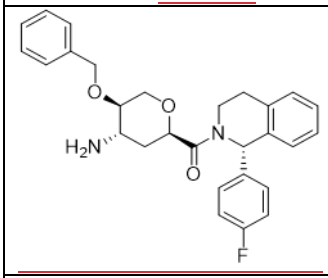
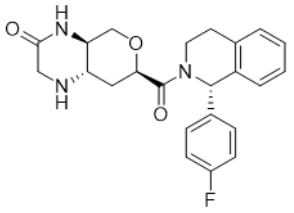
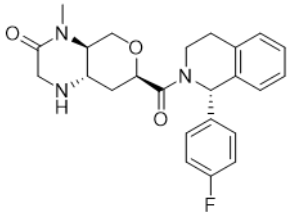
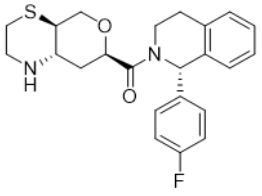
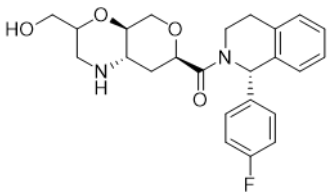
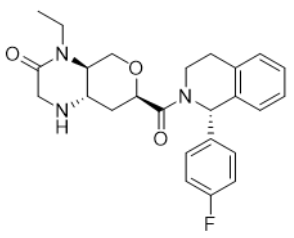
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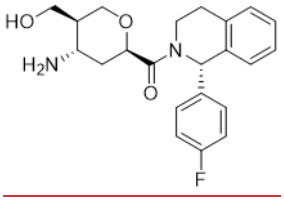
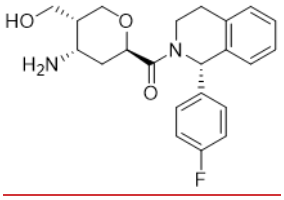
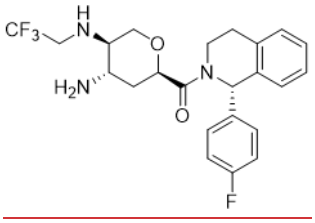
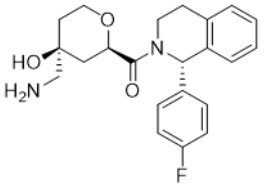
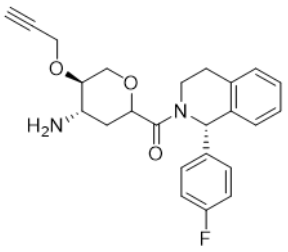
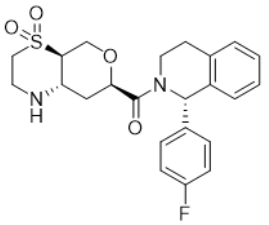
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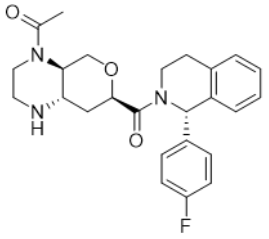
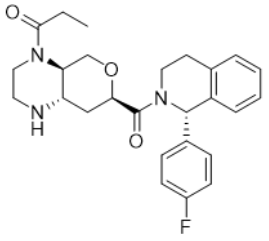
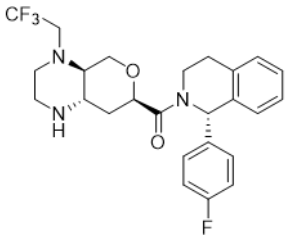
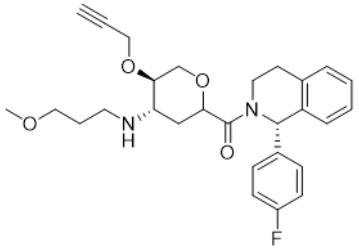
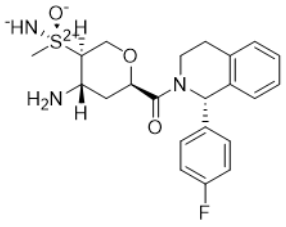
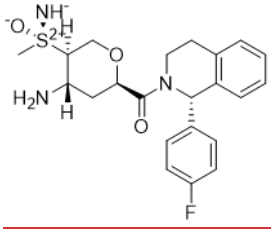
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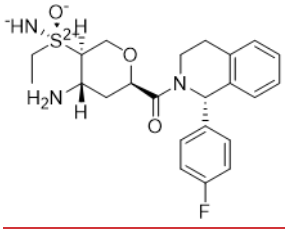
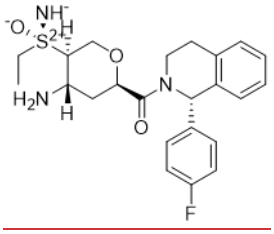
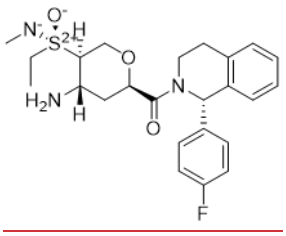
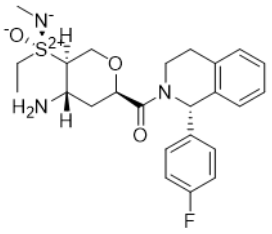
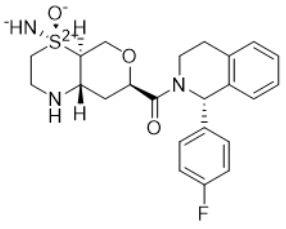
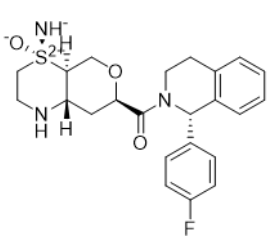
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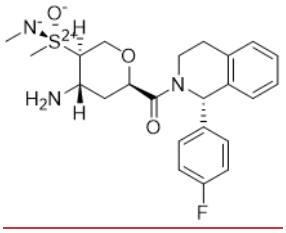
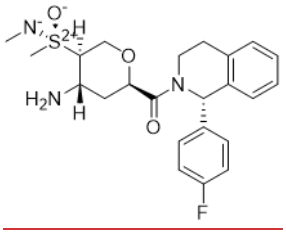
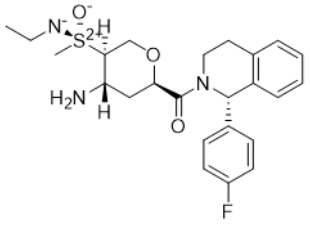
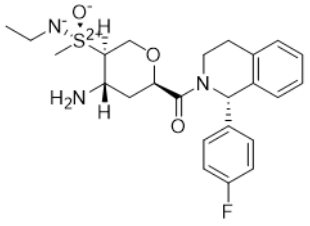
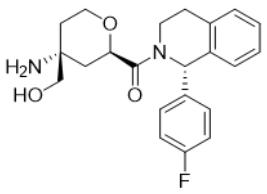
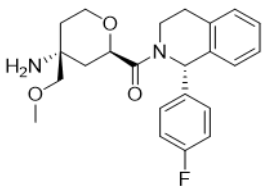
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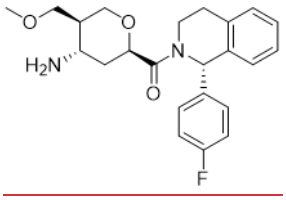
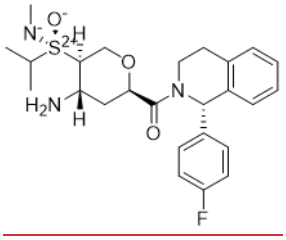
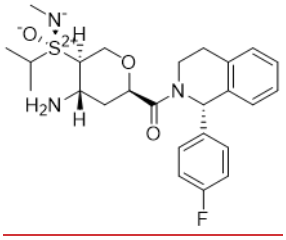
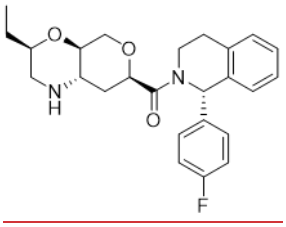
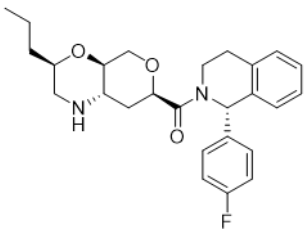
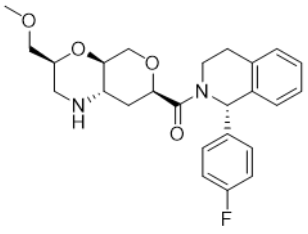
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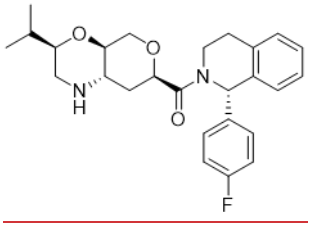
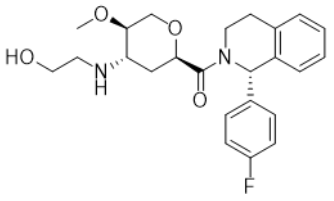
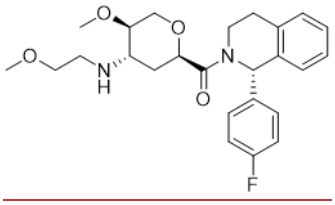
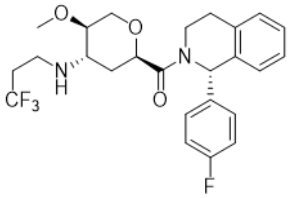
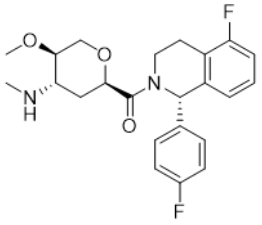
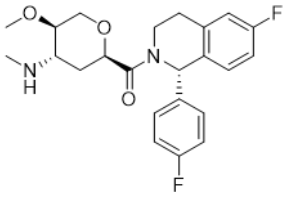
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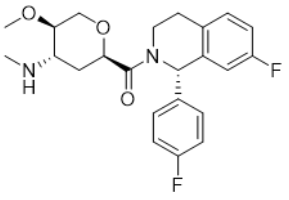
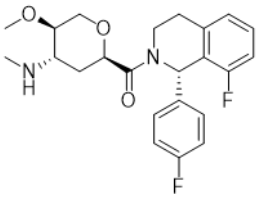
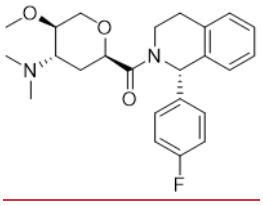
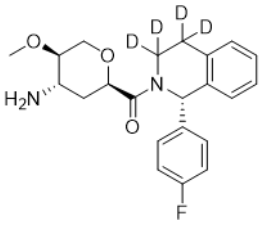
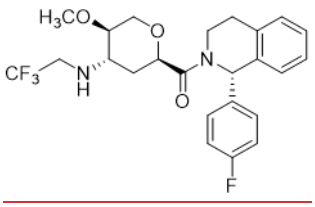
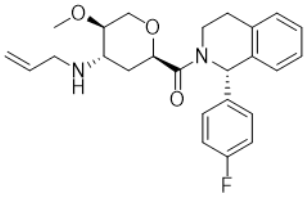
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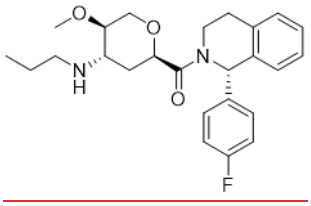
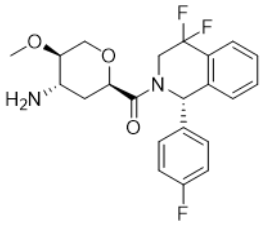
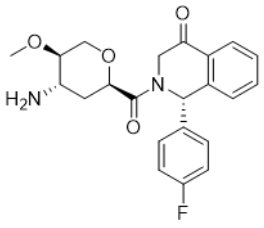
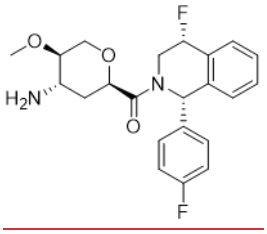
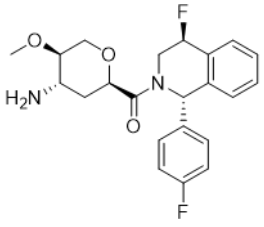
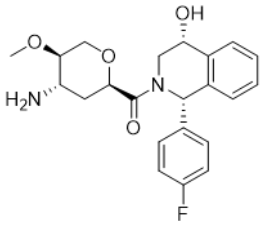
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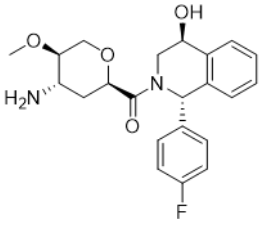
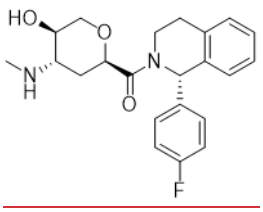
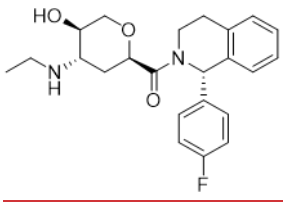
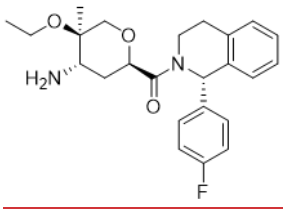
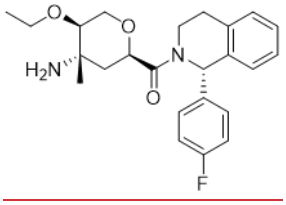
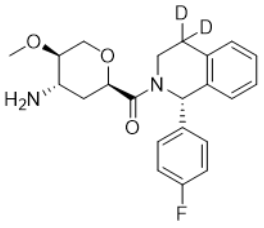
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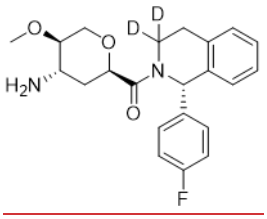
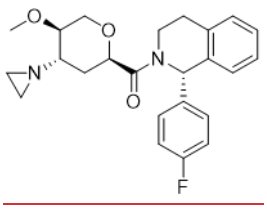
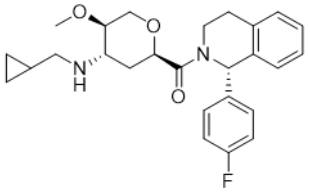
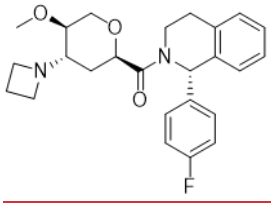
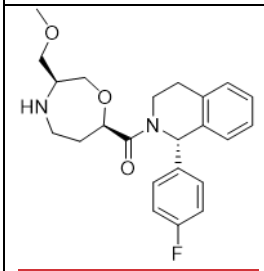
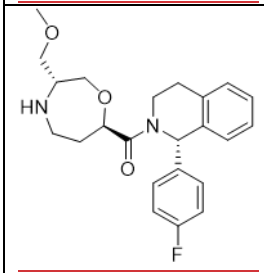
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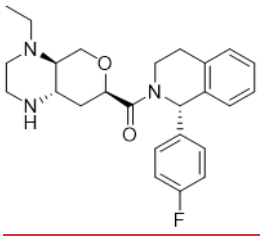
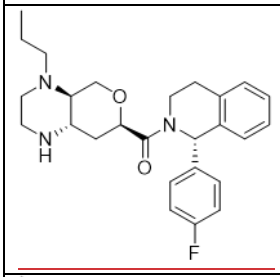
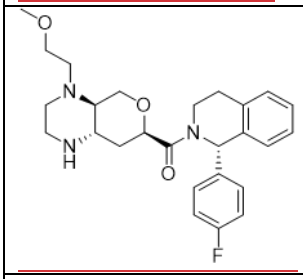
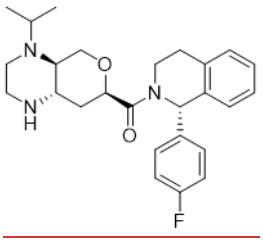
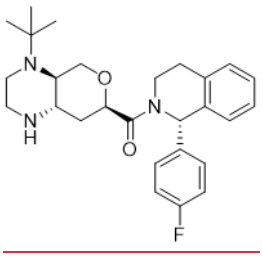
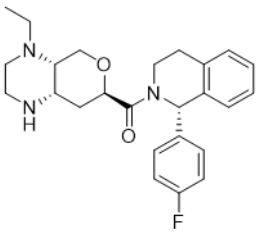
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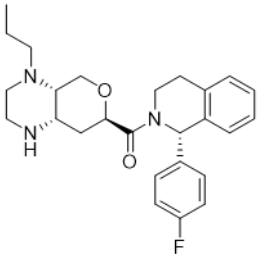
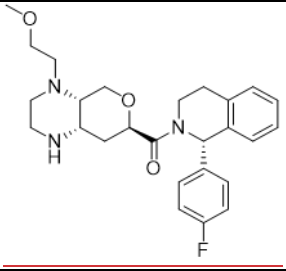
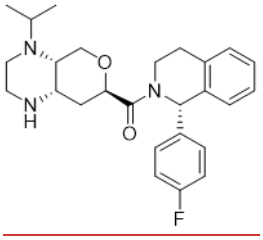
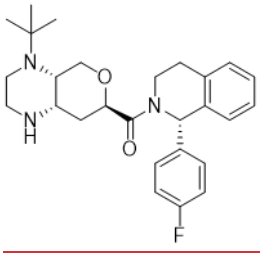
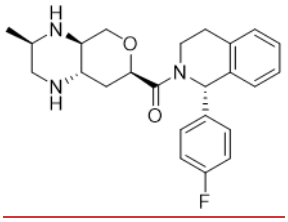
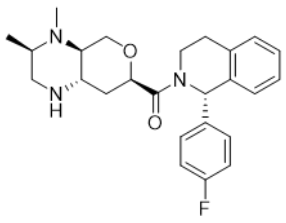
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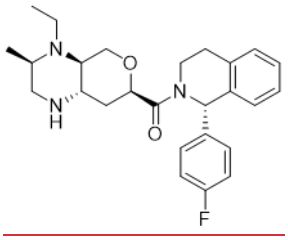
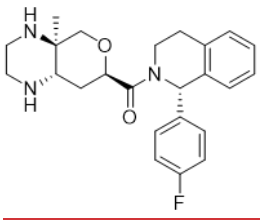
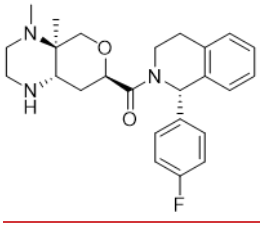
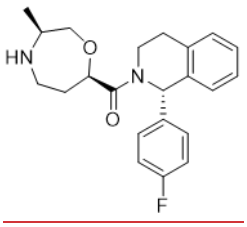
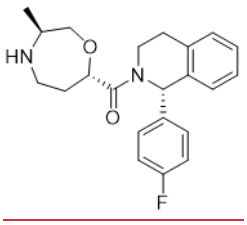
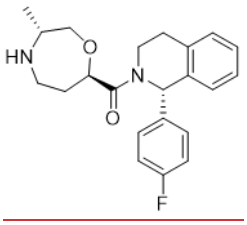
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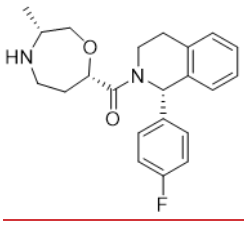
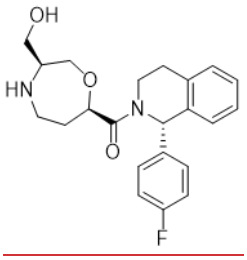
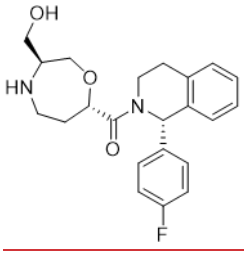
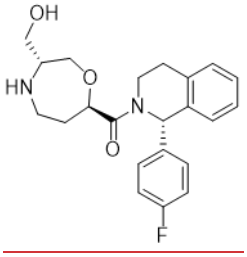
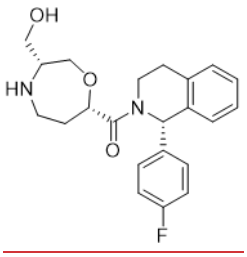
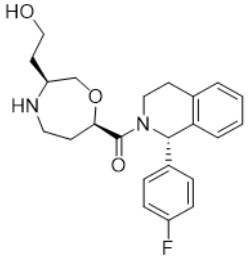
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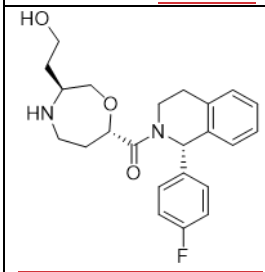
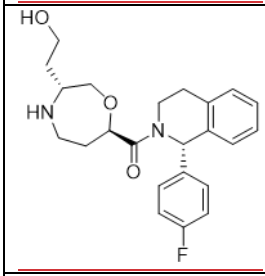
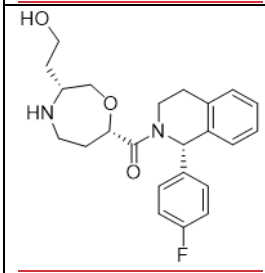
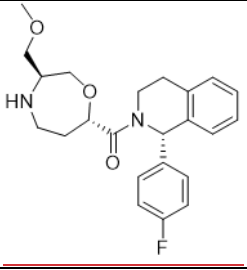
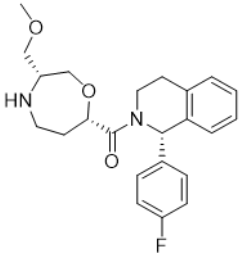
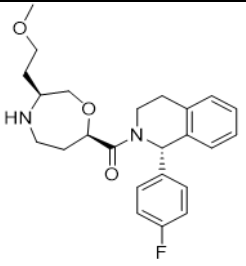
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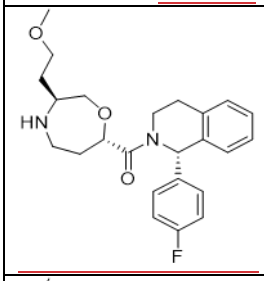
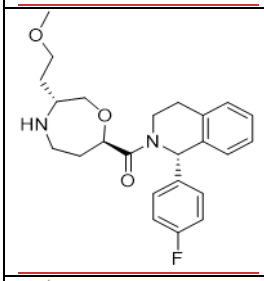
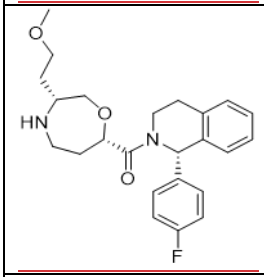
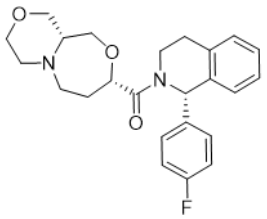
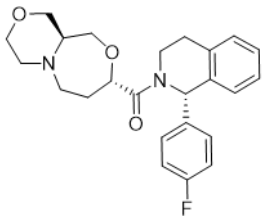
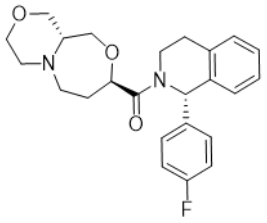
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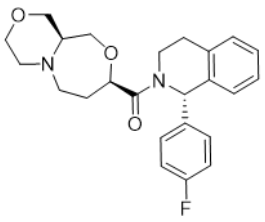
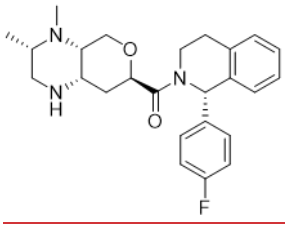
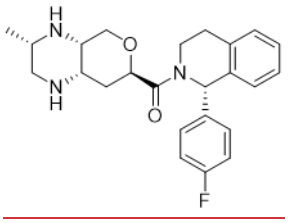
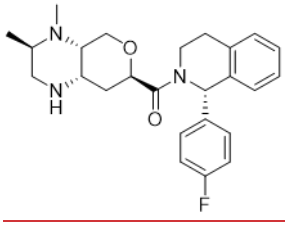
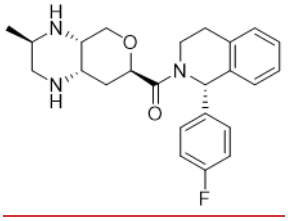
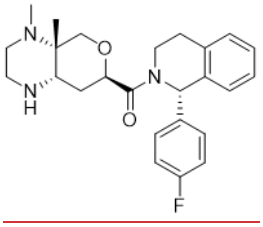
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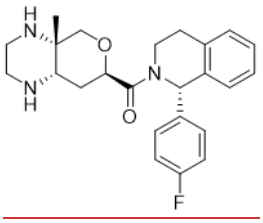
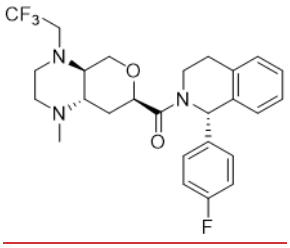
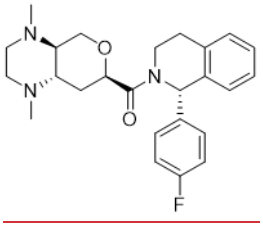
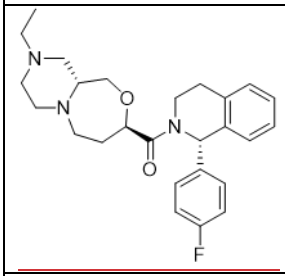
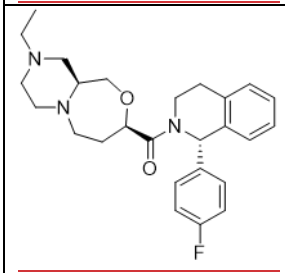
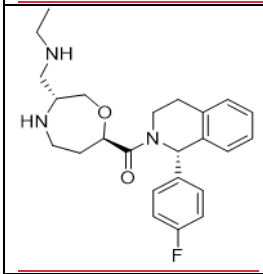
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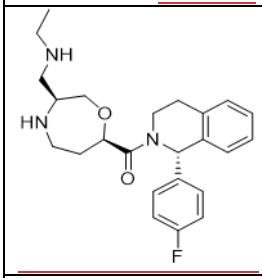
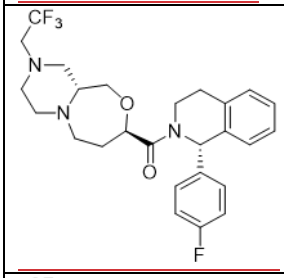
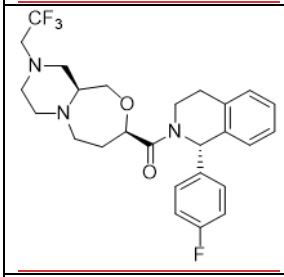
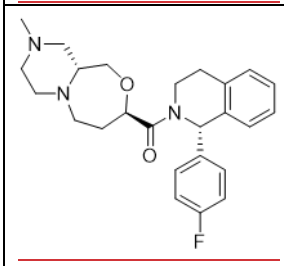
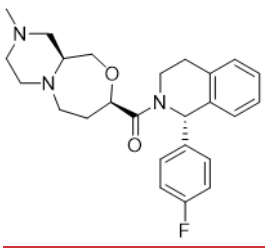
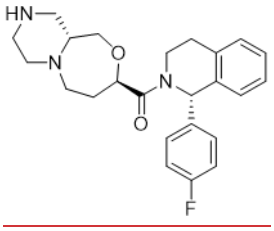
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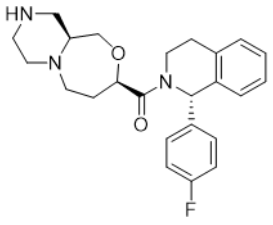
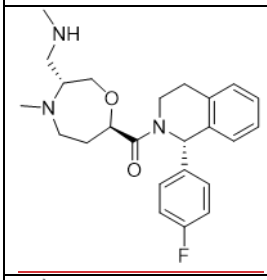
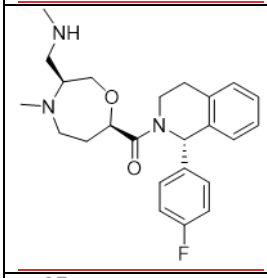
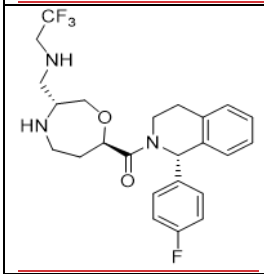
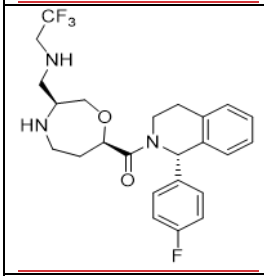
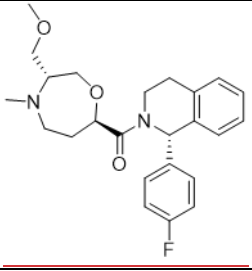
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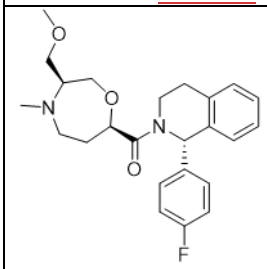
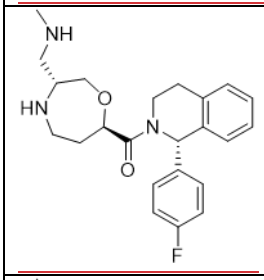
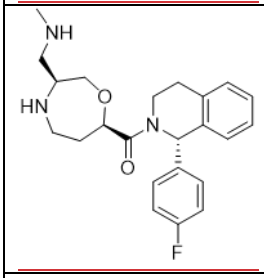
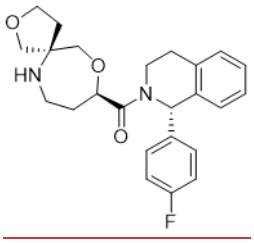
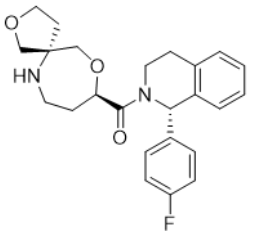
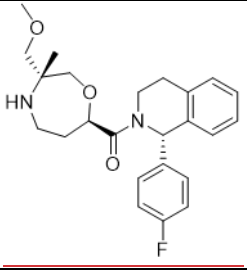
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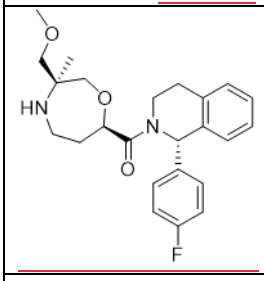
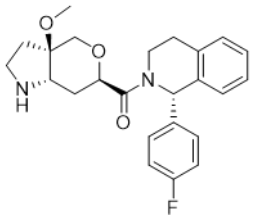
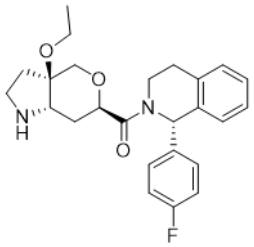
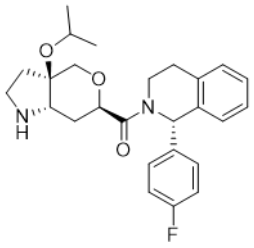
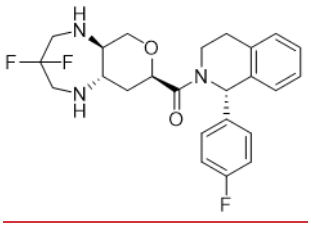
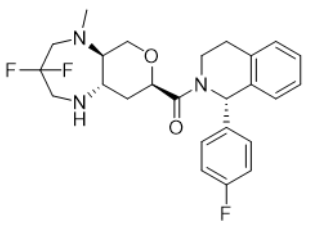
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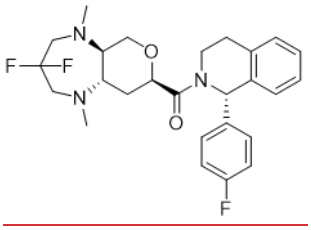
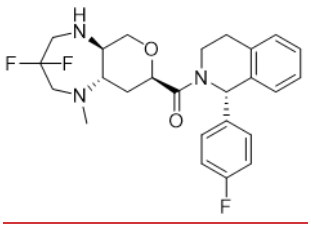
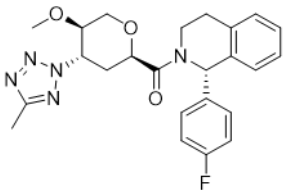
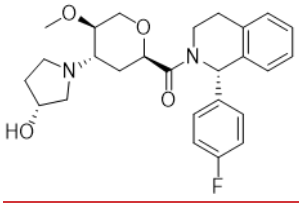
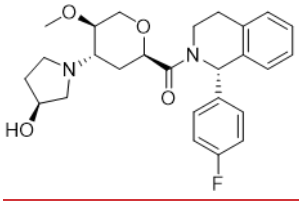
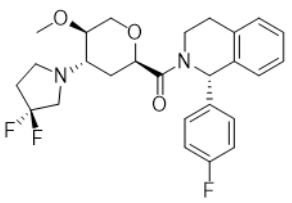
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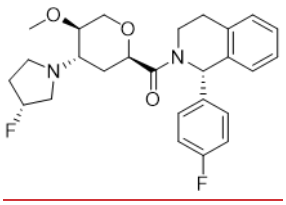
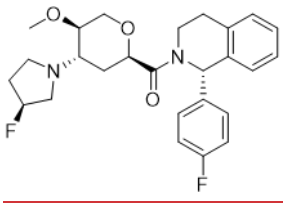
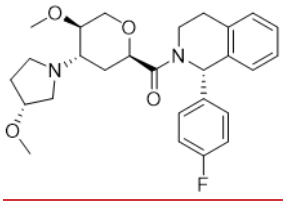
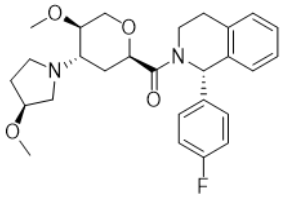
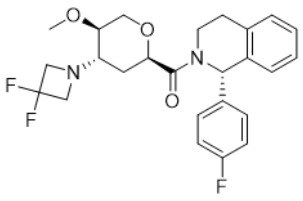
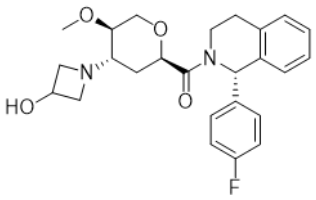
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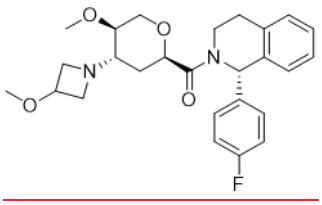
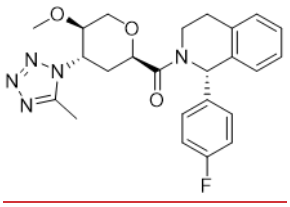
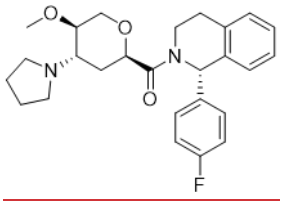
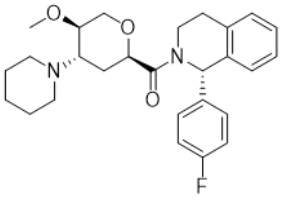
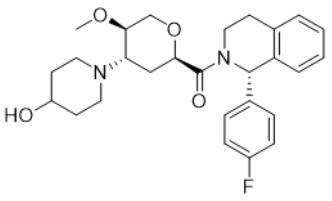
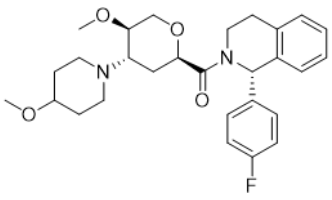
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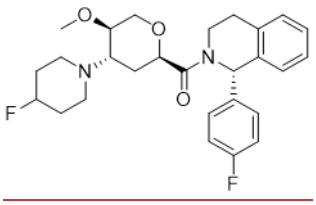
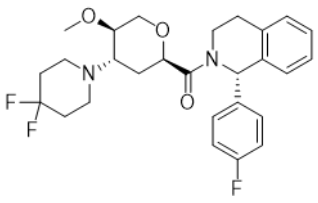
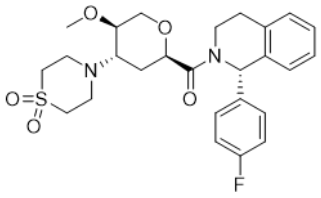
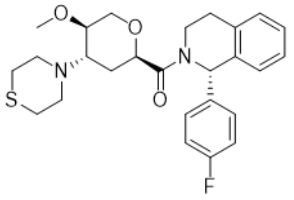
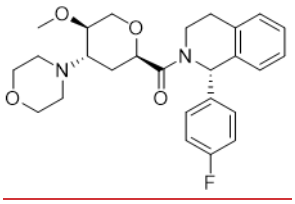
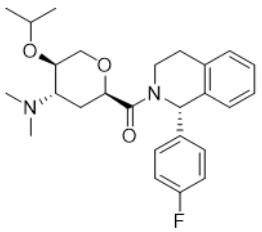
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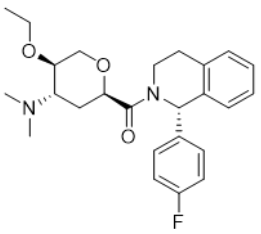
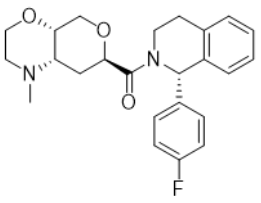
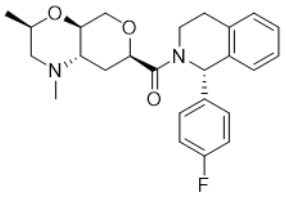
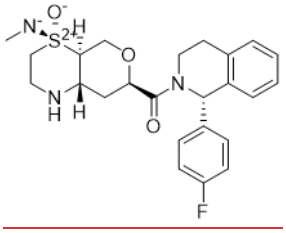
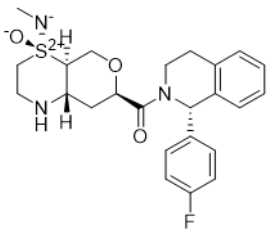
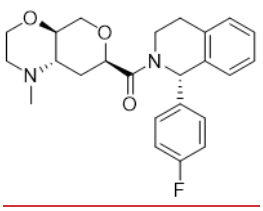
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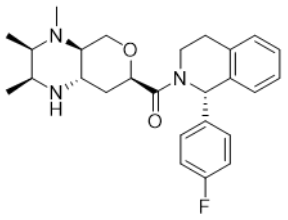
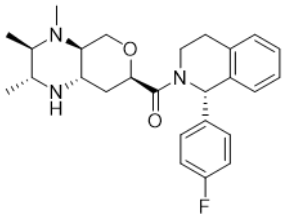
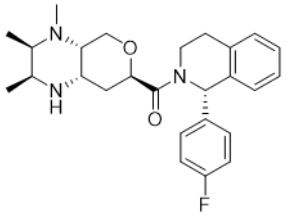
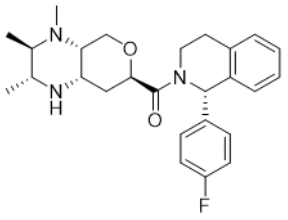
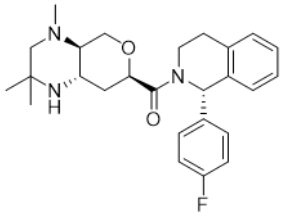
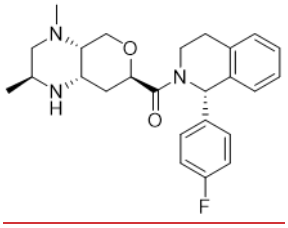
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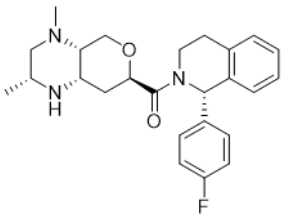
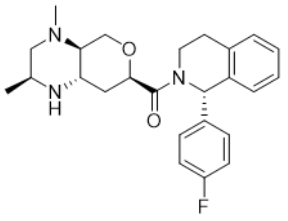
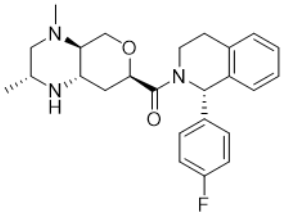
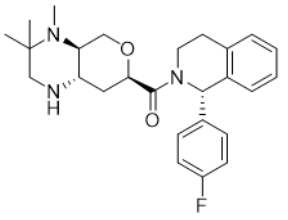
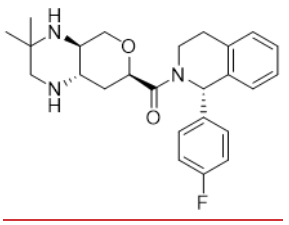
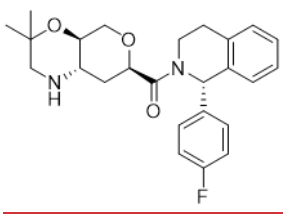
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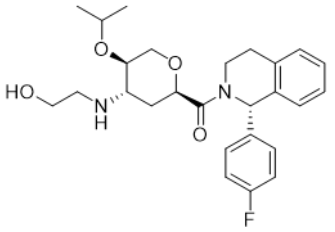
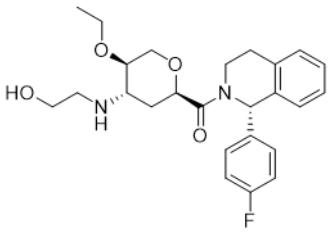
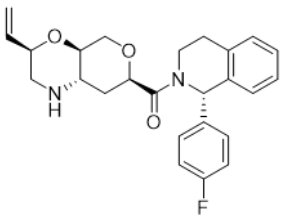
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	5782

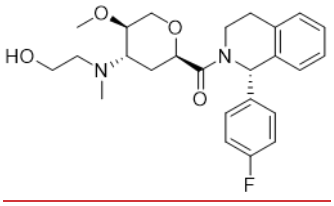
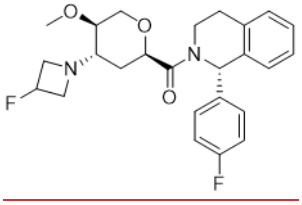
Structure	Cpd No.
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Structure	Cpd No.
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	5793
	5800

Structure	Cpd No.
	5801
	5802
	5803
	5804
	5805
	5806

Structure	Cpd No.
	5807
	5808
	5809
	5810
	5812
	5814

Structure	Cpd No.
	5815
	5816
	5817

Structure	Cpd No.
	5818
	5819

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~~56. The compound or salt of claim 55, selected from compound 5605, 5602, 5599, 5575, 5564, 5550, 5472, 5545, 5543, 5461, 5267, 5448, 5475, 5087, 5077, 5051, 5045, 5042, 5021, and 5012, and pharmaceutically acceptable salts thereof.~~

~~57. The compound or salt of claim 56, selected from compound 5599, 5564, 5472, 5077, and 5087, and pharmaceutically acceptable salts thereof.~~

~~58. The compound or salt of any one of claims 1 to 57 in the form of a salt.~~

~~59.~~15. A pharmaceutical composition comprising the compound or salt of any one of claims 1 to 14~~58~~ and a pharmaceutically acceptable excipient.

~~60. Use of the compound or salt of any one of claims 1 to 58 as a medicament for the modulation of progranulin.~~

~~61. The use of claim 60, wherein progranulin secretion is increased.~~

~~62. A method of modulating progranulin in a subject in need thereof comprising administering to the subject the compound or salt of any one of claims 1 to 58 in an amount effective to increase the level of progranulin or granulin in the subject.~~

~~63.~~16. Use of the compound or salt of any one of claims 1 to 15 in the manufacture of a medicament for ~~A method of~~ treating a progranulin-associated disorder in a subject ~~in need thereof comprising administering a therapeutically effective amount of the compound or salt of any one of claims 1 to 58 to the subject~~.

~~64.~~17. The ~~method~~ use of claim 16~~63~~, wherein the progranulin-associated disorder is Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), Frontotemporal dementia (FTD), Frontotemporal dementia -Granulin subtype (FTD-GRN), Lewy body dementia (LBD), Prion disease, Motor neuron diseases (MND), Huntington's disease (HD), Spinocerebellar ataxia (SCA), Spinal muscular atrophy (SMA), a lysosomal storage disease, nephropathy, a disease associated with inclusions and/or misfunction of C9orf72, TDP-43, FUS, UBQLN2, VCP, CHMP28, and/or MAPT, an acute neurological disorder, glioblastoma, or neuroblastoma.

~~65. The method of claim 64, wherein the Parkinson's disease is Parkinson's disease with GBA mutation.~~

~~66. The method of claim 64, wherein the lysosomal storage disease is Paget's disease, Gaucher's disease, Nieman's Pick disease, Tay-Sachs Disease, Fabry Disease, Pompes disease, or Naso-Hakula disease.~~

~~67. The method of claim 64, wherein the acute neurological disorder is stroke, cerebral hemorrhage, traumatic brain injury or head trauma.~~

~~68. The method of claim 64, wherein the progranulin-associated disorder is Frontotemporal dementia (FTD).~~

~~69. The method of claim 64, wherein the progranulin-associated disorder is Frontotemporal dementia -Granulin subtype (FTD-GRN).~~

~~70. A method of increasing lysosomal protein levels in a cell comprising contacting the cell with an effective amount of the compound or salt of any one of claims 1 to 58.~~

~~71. A method of increasing lysosomal protein levels in a subject comprising administering a therapeutically effective amount of the compound or salt of any one of claims 1 to 58 to the subject.~~

~~72. The method of claim 70 or 71, wherein the lysosomal protein is progranulin, prosaposin, β-glucocerebrosidase, galactosidase alpha, cathepsin B, cathepsin Z, neuraminidase 1, tripeptidyl peptidase, alpha-L-fucosidase 2, mannosidase alpha class 2B member 2, mannosidase beta, serine carboxypeptidase 1, acid ceramidase, GM2 ganglioside activator, cathepsin D, cathepsin S, cathepsin K, cathepsin L, or hexosaminidase.~~

~~73.~~18. Use of the compound or salt of any one of claims 1 to 15 in the manufacture of a medicament for~~A method of~~ treating: (i) a lysosomal storage disorder;
(ii) an inflammatory disorder;
(iii) stroke, Down syndrome, congenital heart disease, diabetes, common variable immune deficiency (CVID), tubulo-interstitial kidney disease (TKD), polycystic liver disease, myocarditis, dermatitis hyperhomocysteinemia,

endo-toxic shock, lung injury, bone defect (e.g., inflammatory periodontal bone defect), or osteolysis; or (iv) a neurodegenerative disease in a subject ~~suffering therefrom comprising administering a therapeutically effective amount of the compound or salt of any one of claims 1 to 58 to the subject~~.

~~74.~~19. The ~~method~~ use of claim 18~~73~~, wherein: (i) the lysosomal storage disorder is mucopolysaccharidosis, sphingolipidosis, glycogen storage disease type II, glycoprotein storage disease, Hurler disease, Scheie disease, Hunter disease, Sanfilippo disease A, Sanfilippo disease B, Sanfilippo disease C, Sanfilippo disease D, Morquio disease A, Morquio disease B, Maroteaux-Lamy disease, Sly disease, mucopolysaccharidosis type IX, mucopolysaccharidosis-plus syndrome, Fabry disease, Gaucher disease, Tay-Sachs disease, sialidosis, Niemann Pick type A, Niemann Pick type B, galactosialidosis, Niemann pick type C, I-cell disease, mucolipidosis type III, GM1 gangliosidosis, β-galactosidase deficiency, α-mannosidosis, GM2 gangliosidosis, β-mannosidosis, Krabbe, fucosidosis, metachromatic leukodystrophy, aspartylglucosaminuria, multiple sulfatase deficiency, Schindler, Farber lipogranulomatosis, Pompe disease, Wolman disease, Danon disease, free sialic acid storage disease, ceroid lipofuscinosis, β-glucuronidase hypoactivity disease, Sandhoff disease, or cholesterol ester storage disease;~~.~~

~~75. A method of treating an inflammatory disorder in a subject suffering therefrom comprising administering a therapeutically effective amount of the compound or salt of any one of claims 1 to 58 to the subject.~~

~~76. The method of claim 75, wherein~~ (ii) the inflammatory disorder is Sjogren disease, inflammatory arthritis, osteoarthritis, inflammatory bowel disease, or immune thrombocytopenia; or~~.~~

~~77. A method of treating a disorder in a subject suffering therefrom comprising administering a therapeutically effective amount of the compound or salt of any one of claims 1 to 58 to the subject, wherein the disorder is stroke, Down syndrome, congenital heart disease, diabetes, common variable immune deficiency (CVID), tubulo-interstitial kidney disease (TKD), polycystic liver disease, myocarditis, dermatitis hyperhomocysteinemia, endo-toxic shock, lung injury, bone defect (e.g., inflammatory periodontal bone defect), or osteolysis.~~

~~78. A method of treating a neurodegenerative disease in a subject suffering therefrom comprising administering a therapeutically effective amount of the compound or salt of any one of claims 1 to 58 to the subject.~~

~~79. The method of claim 78, wherein~~ (iii) the neurodegenerative disease is Parkinson's disease, frontotemporal dementia, Alzheimer's disease, Huntington's disease, traumatic brain injury, neuronal ceroid lipofuscinosis (NCL), multiple sclerosis, amyotrophic lateral sclerosis (ALS), aigyrophilic grain dementia, Alexander's disease, Alper's disease, cerebral palsy, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, dementia pugilistica, diffuse neurofibrillary tangles with calcification, HIV-associated dementia, lewy body dementia, Kennedy's disease, neuroborreliosis, primary lateral sclerosis, Refsum's disease, Gerstmann-Straussler-Scheinker disease, Hallevorden-

Spatz disease, hereditary diffuse leukoencepholopathy with spheroids (HDLS), inclusion body myositis, multiple system atrophy, myotonic dystrophy, Nasu-Hakola disease, Schilder's disease, Wobbly Hedgehog Syndrome (WHS), Duchenne-Aran muscular atrophy, progressive bulbar palsy, pseudobulbar palsy, HIV-associated neurocognitive disorder (HAND), tauopathy, chronic traumatic encephalopathy, or cerebellar downbeat nystagmus.

20. The compound or salt of any one of claims 1 to 15, for use in therapy.