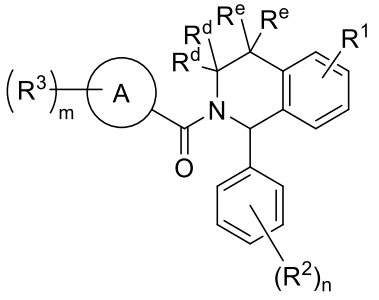
is associated with cytosolic chaperones such as the signal recognition particle (SRP), auxiliary components such as translocating chain-associating membrane (TRAM), translocon-associated protein (TRAP) and modifying enzymes such as oligosaccharyltransferase (OST). The latter is responsible for proper 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

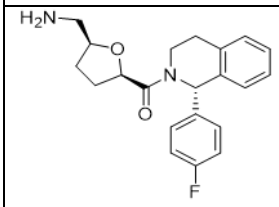
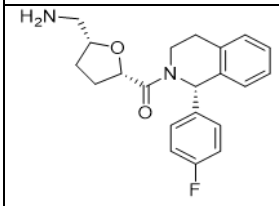
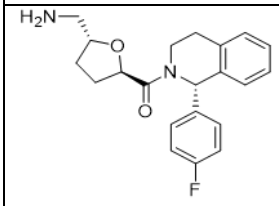
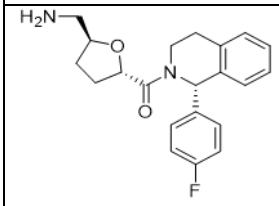
two geminal R^e together with the atom to which they are attached form an oxo group or a spiro C_{3-5}cycloalkyl;

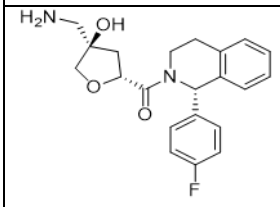
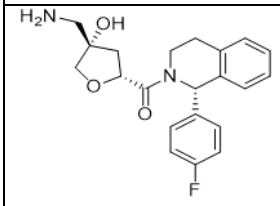
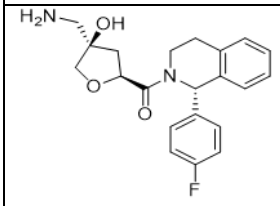
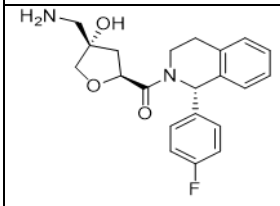
m is 1-4; and

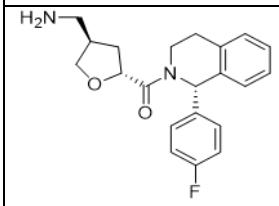
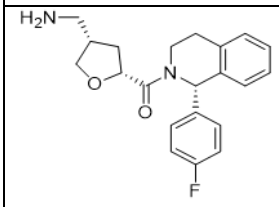
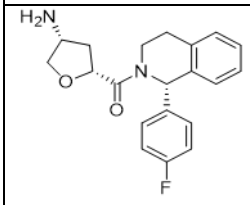
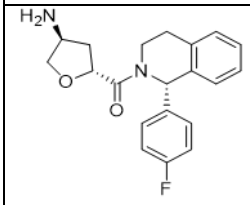
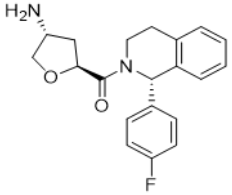
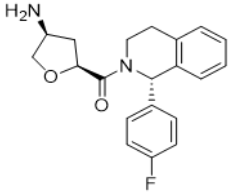
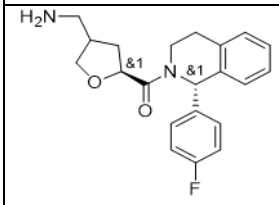
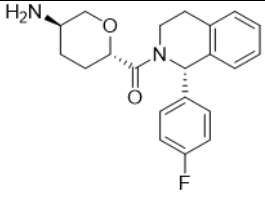
n is 0-2.

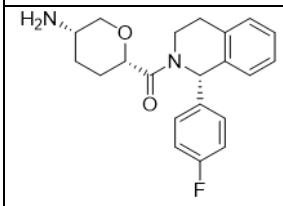
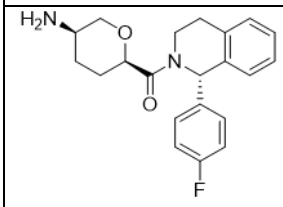
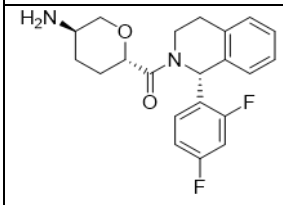
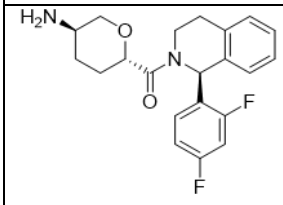
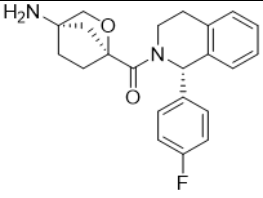
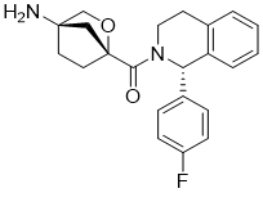
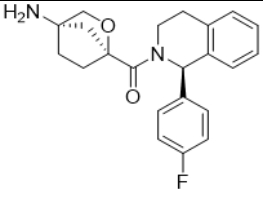
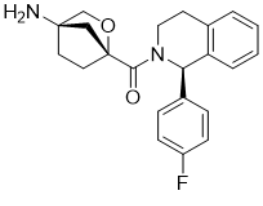
[0005b] In another aspect of the present disclosure, there is provided a compound, or pharmaceutically acceptable salt thereof, having a structure as shown in Table A:

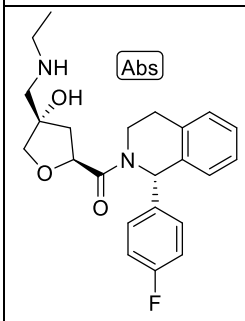
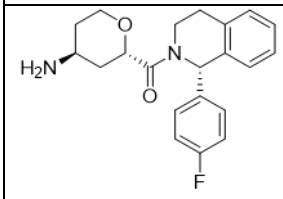
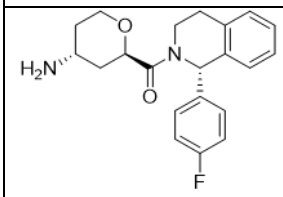
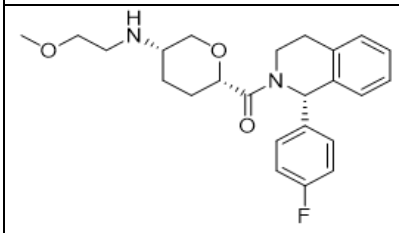
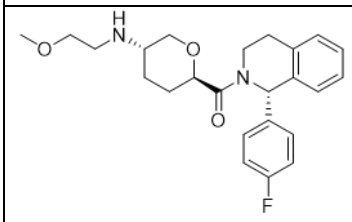
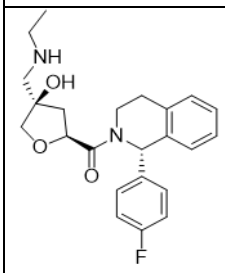
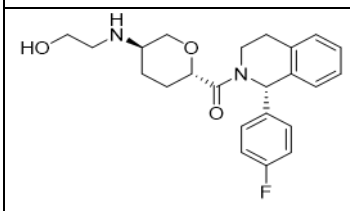
Table A

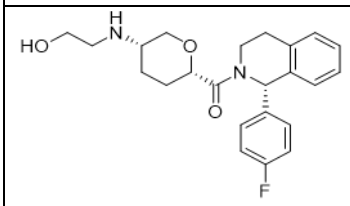
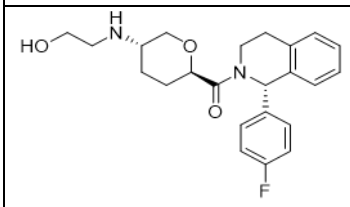
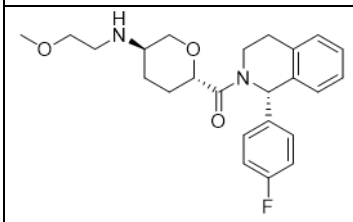
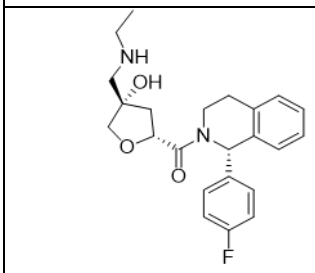
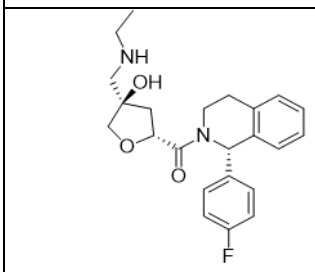
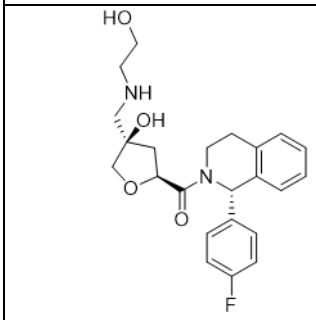
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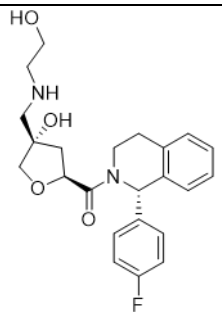
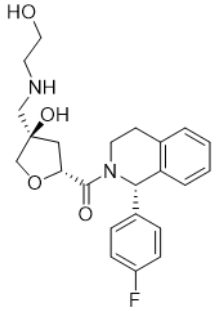
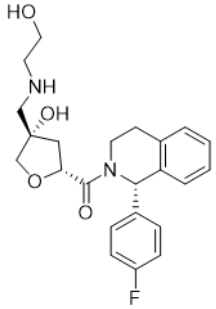
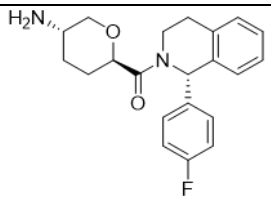
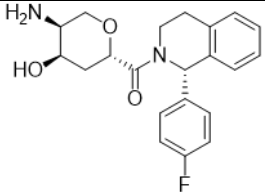
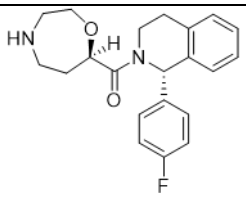
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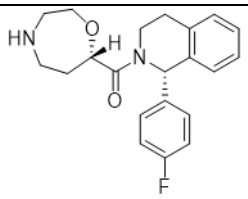
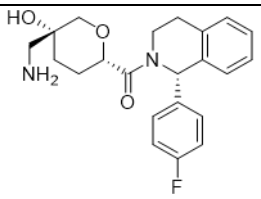
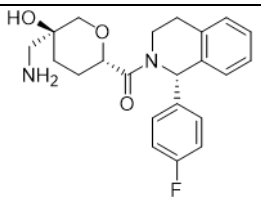
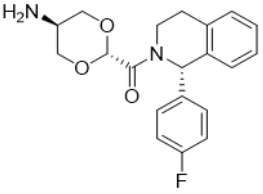
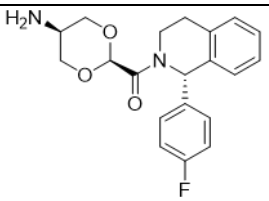
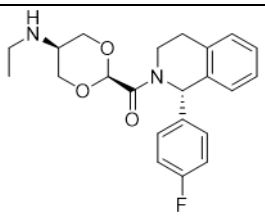
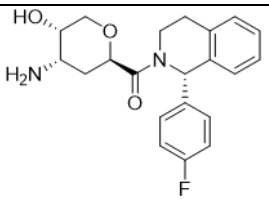
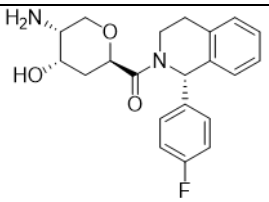
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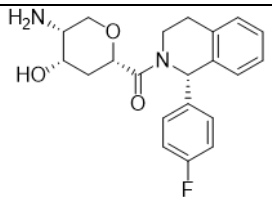
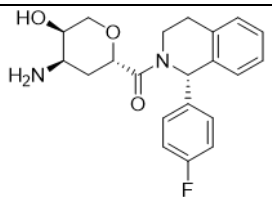
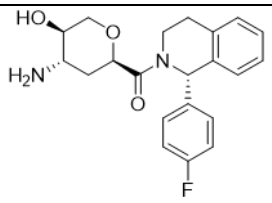
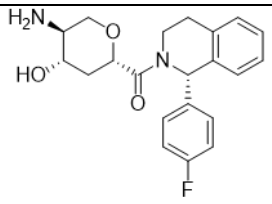
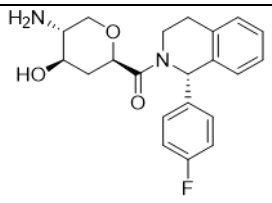
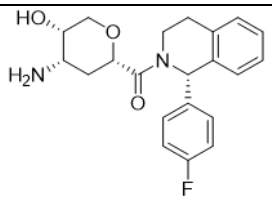
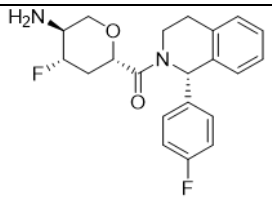
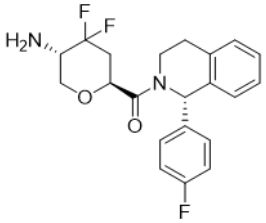
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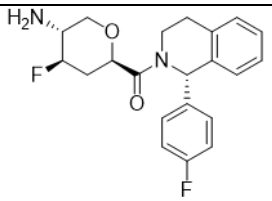
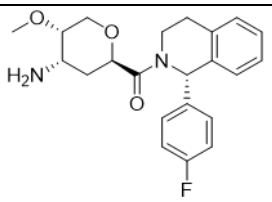
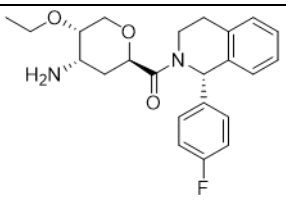
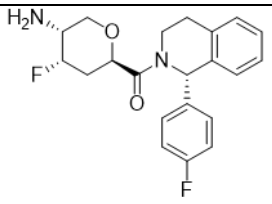
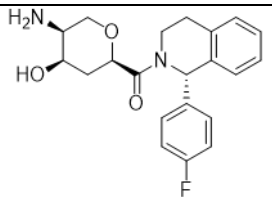
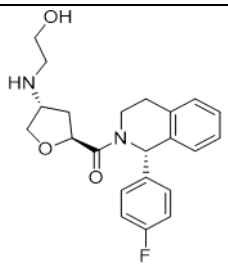
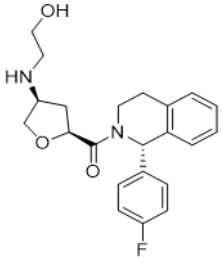
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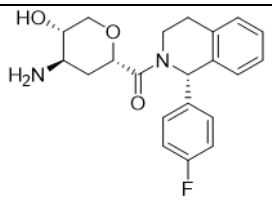
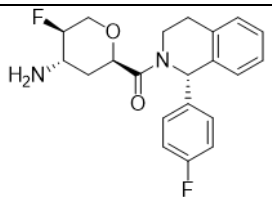
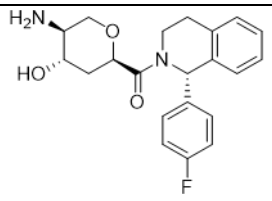
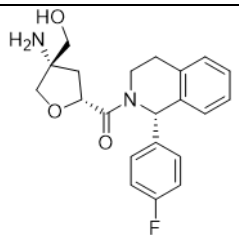
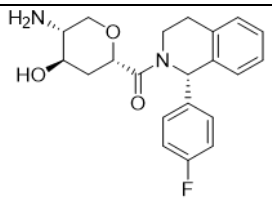
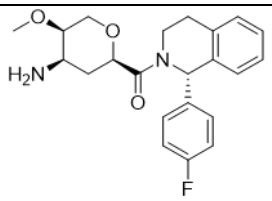
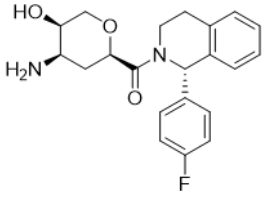
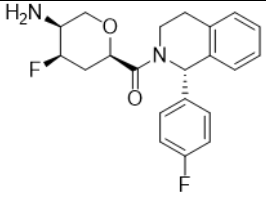
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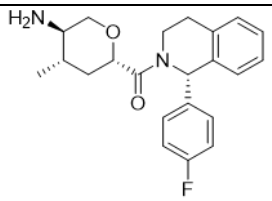
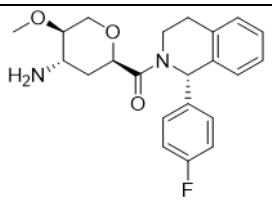
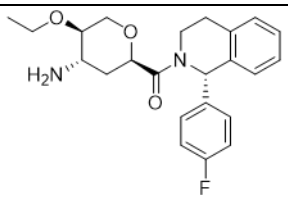
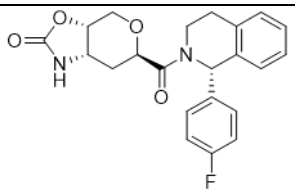
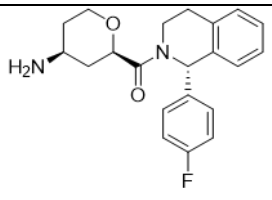
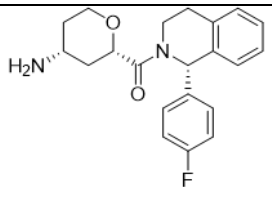
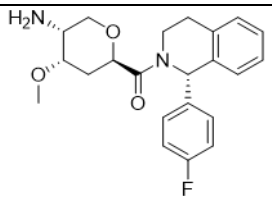
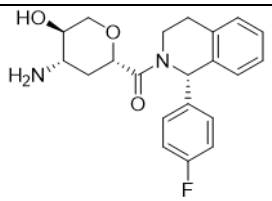
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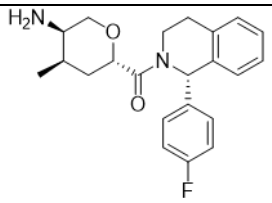
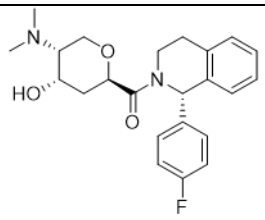
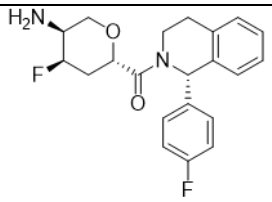
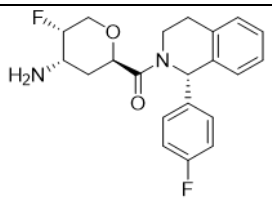
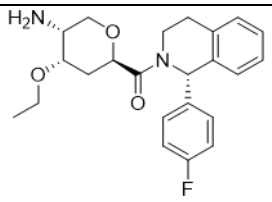
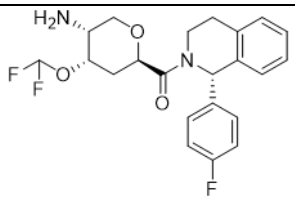
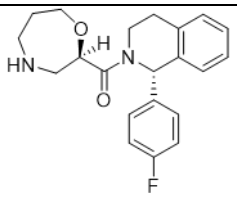
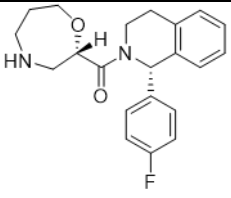
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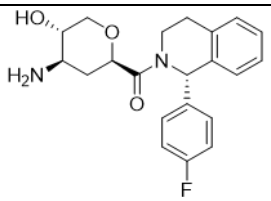
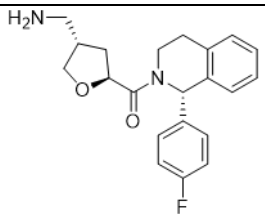
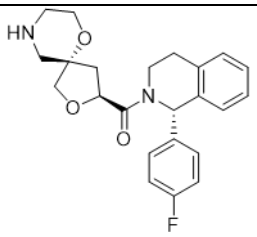
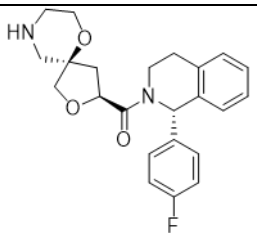
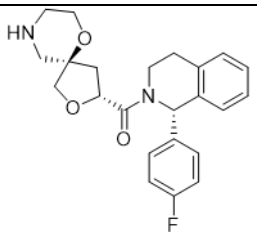
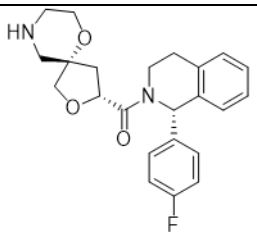
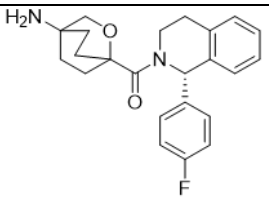
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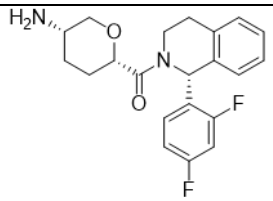
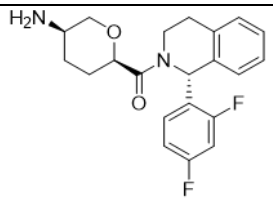
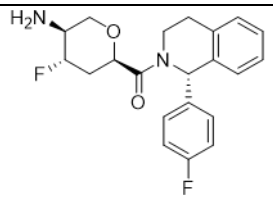
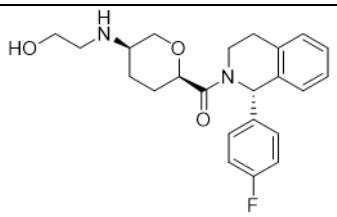
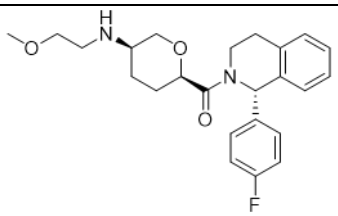
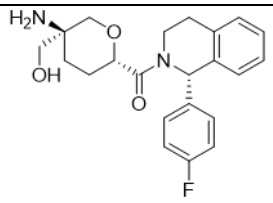
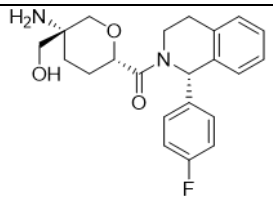
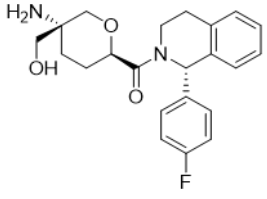
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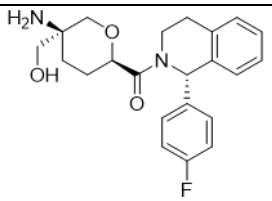
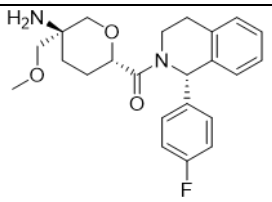
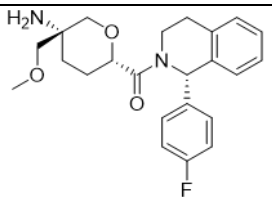
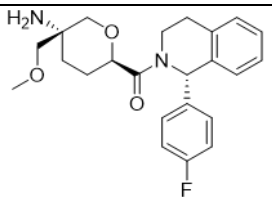
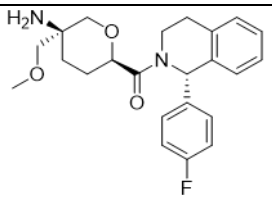
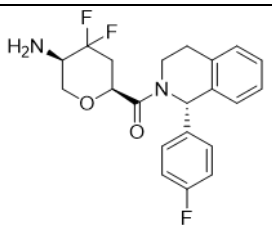
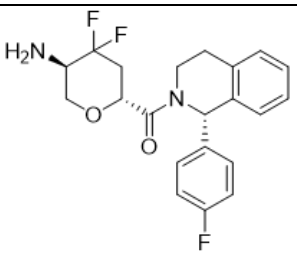
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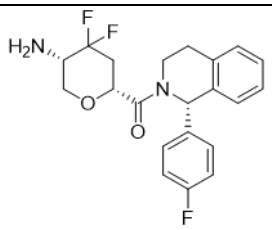
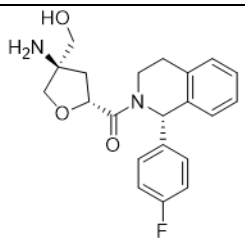
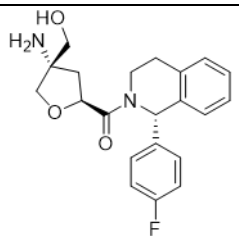
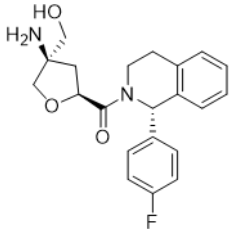
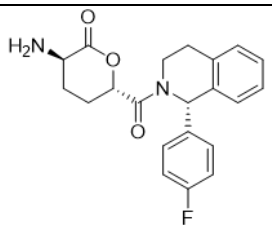
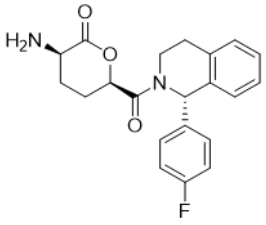
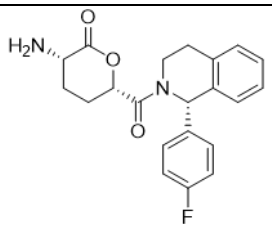
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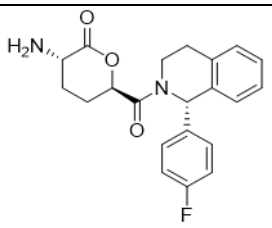
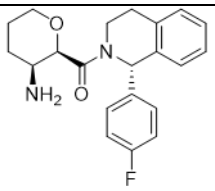
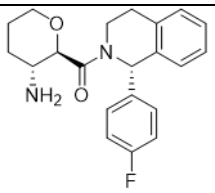
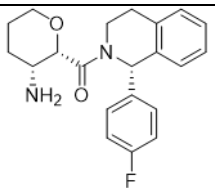
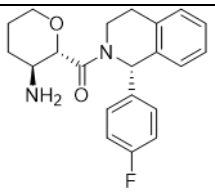
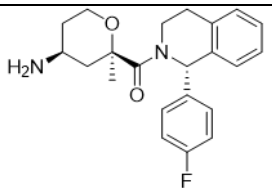
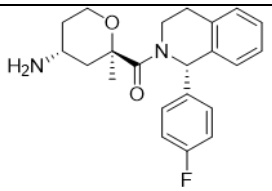
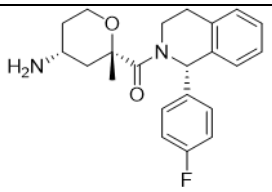
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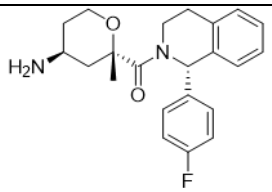
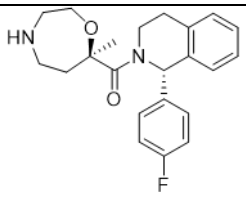
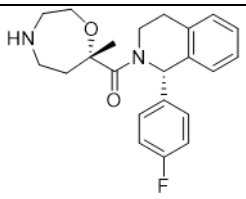
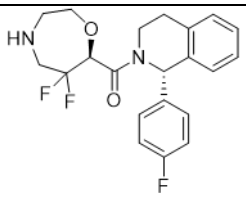
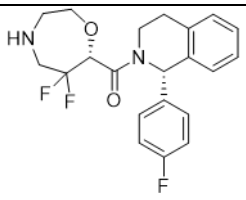
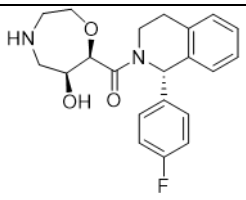
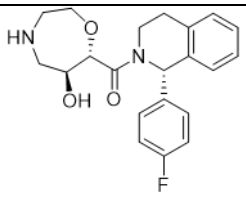
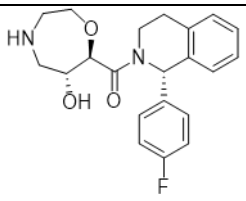
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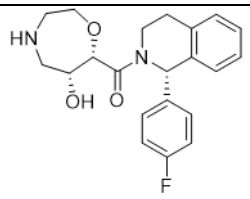
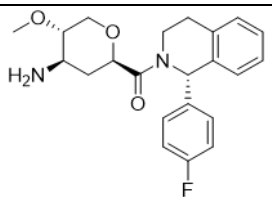
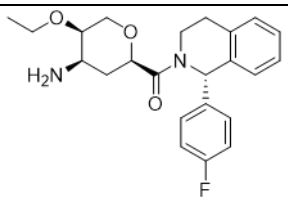
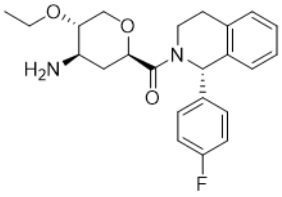
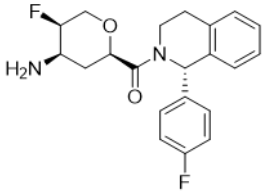
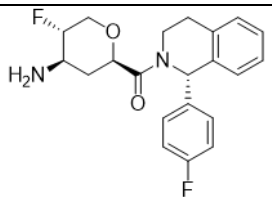
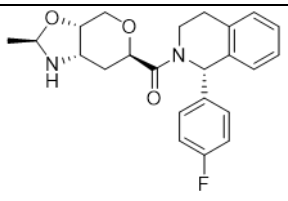
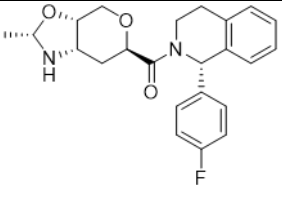
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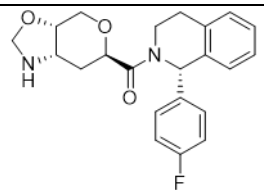
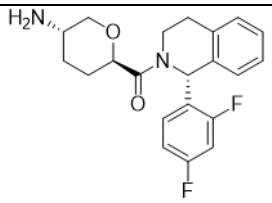
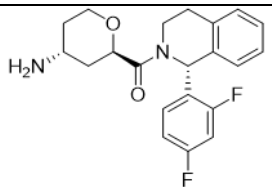
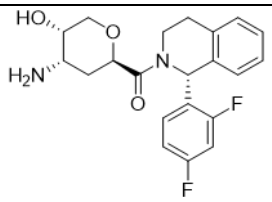
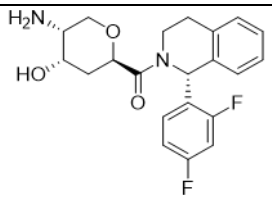
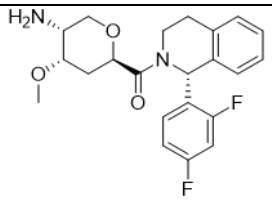
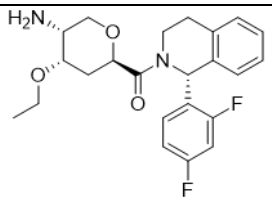
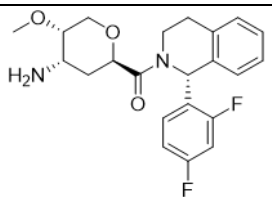
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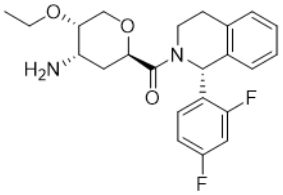
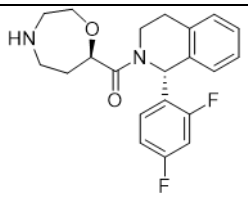
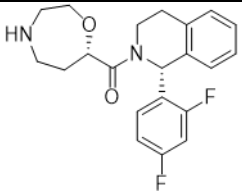
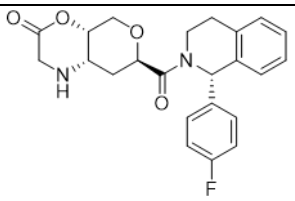
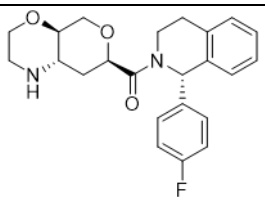
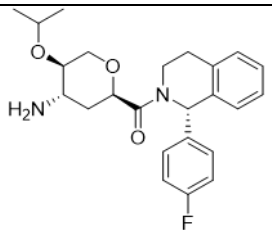
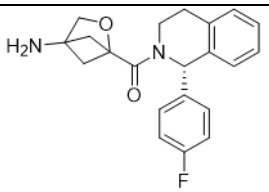
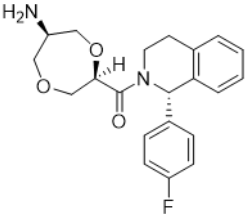
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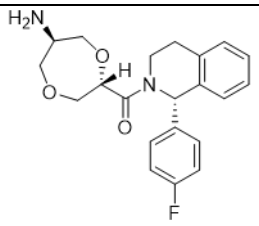
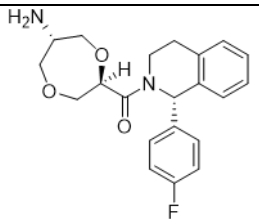
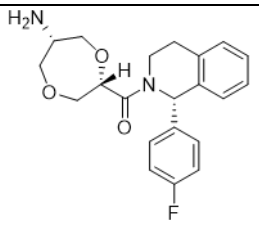
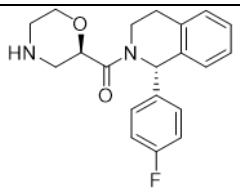
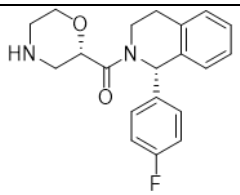
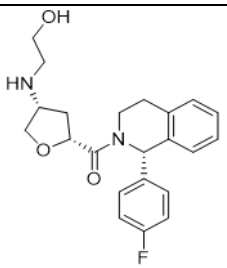
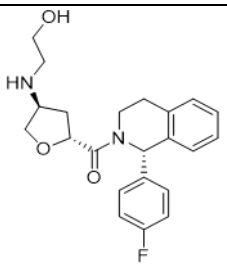
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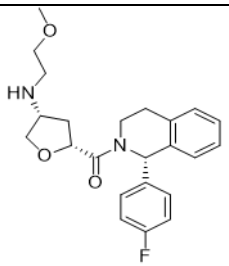
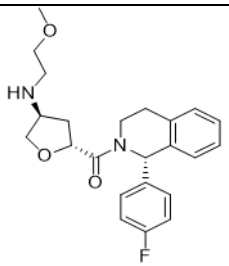
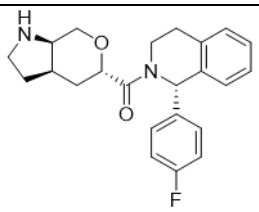
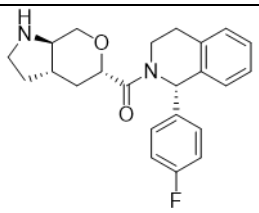
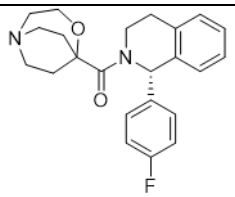
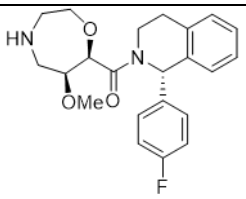
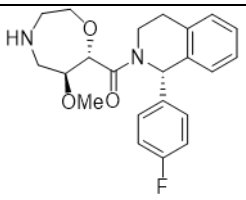
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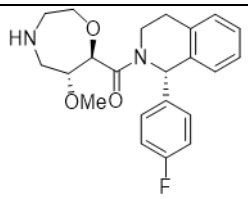
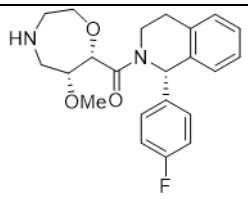
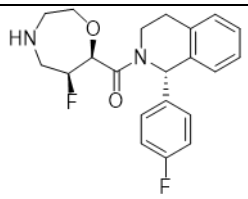
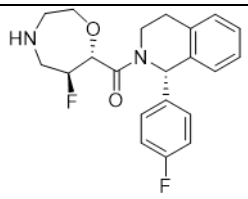
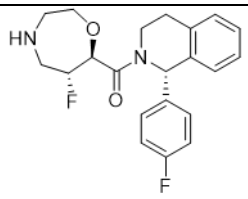
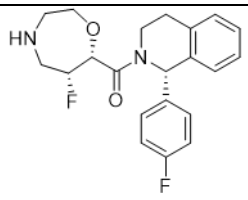
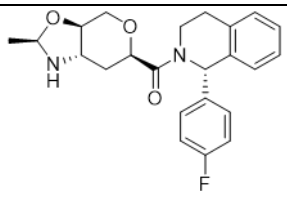
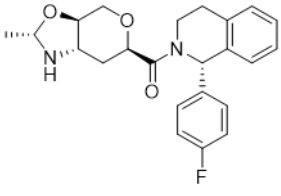
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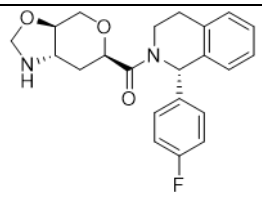
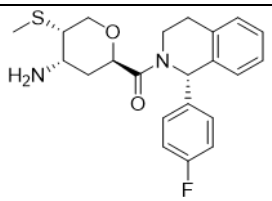
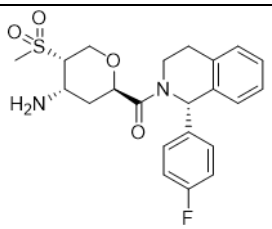
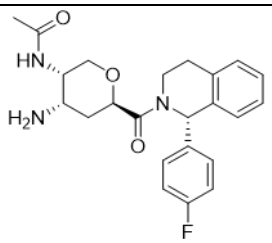
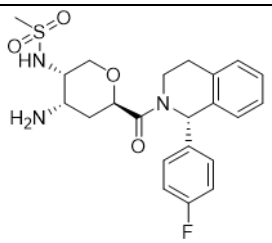
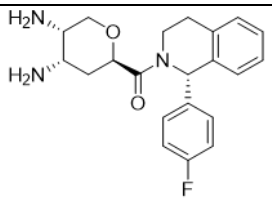
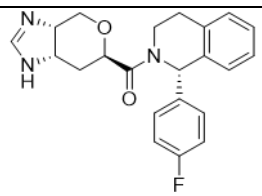
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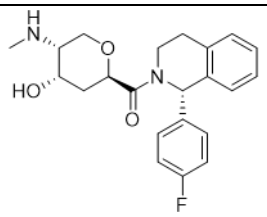
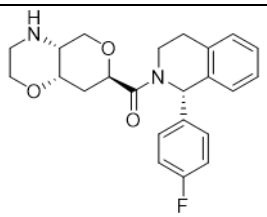
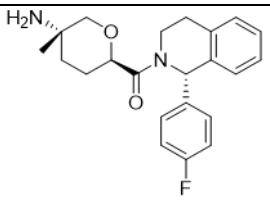
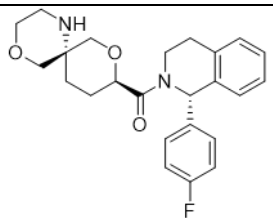
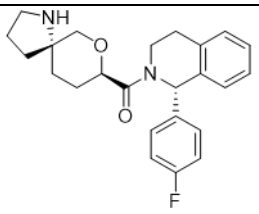
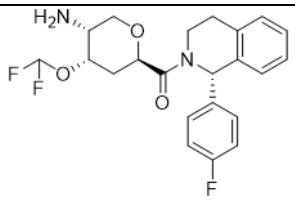
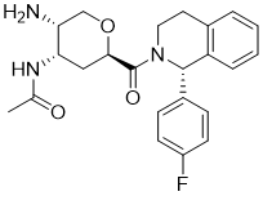
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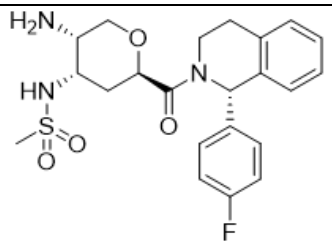
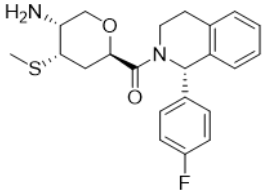
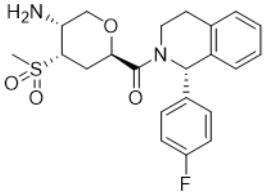
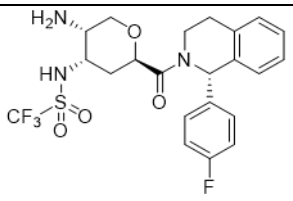
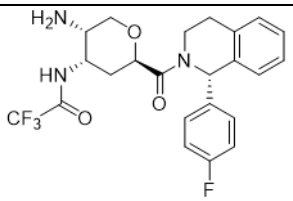
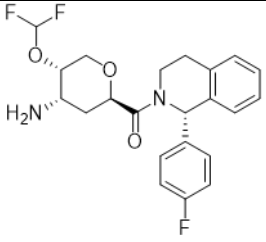
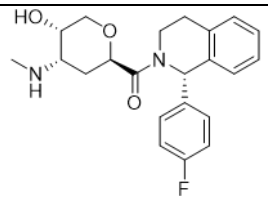
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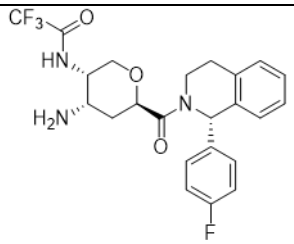
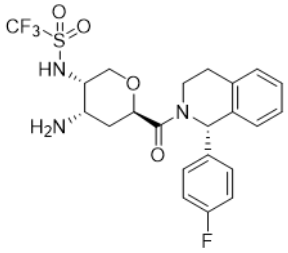
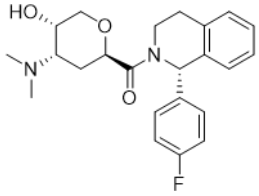
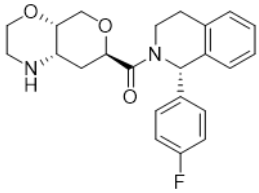
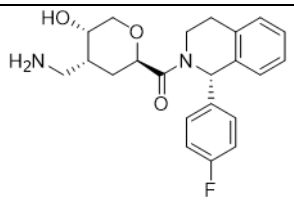
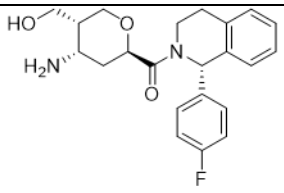
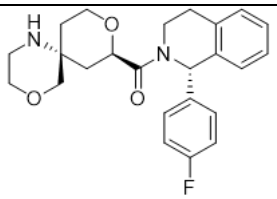
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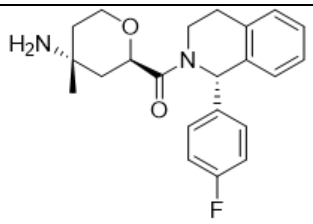
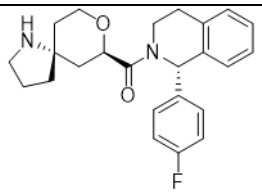
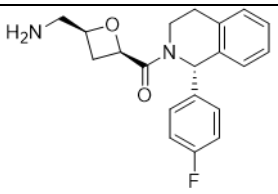
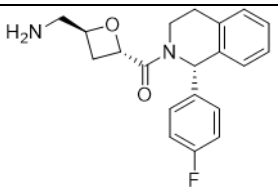
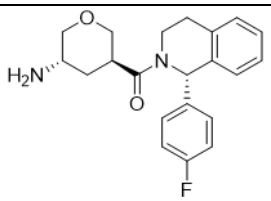
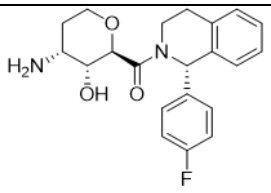
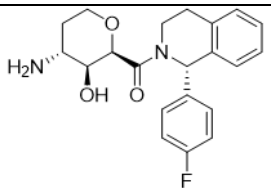
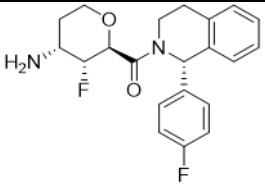
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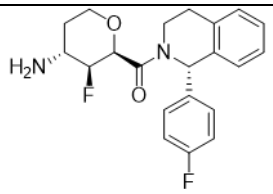
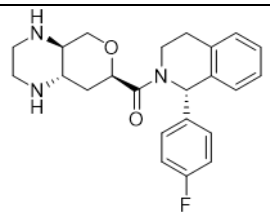
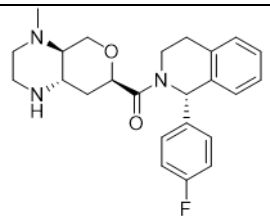
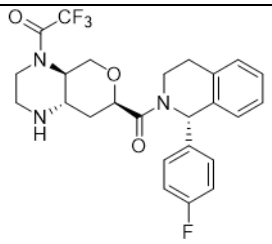
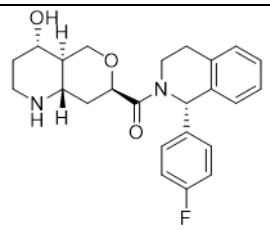
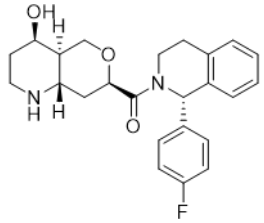
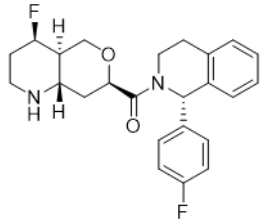
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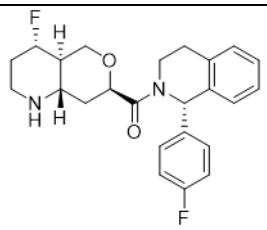
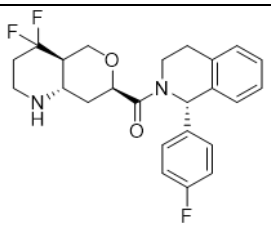
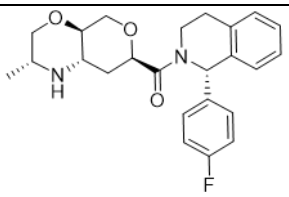
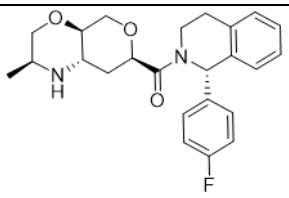
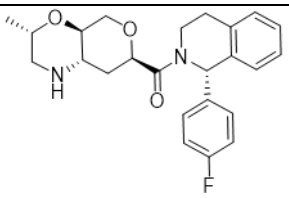
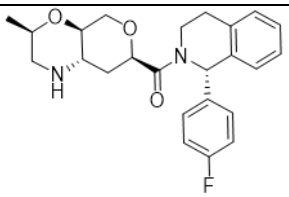
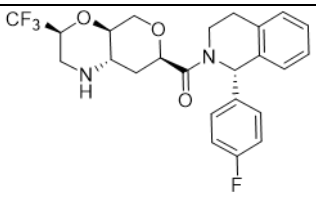
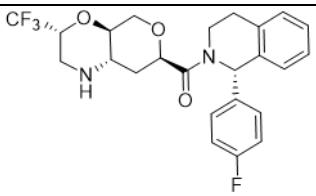
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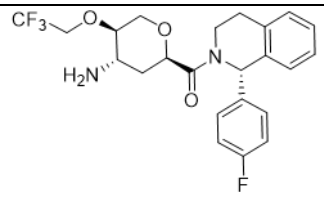
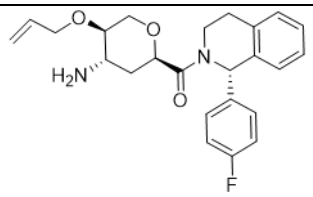
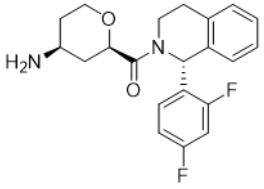
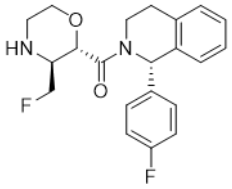
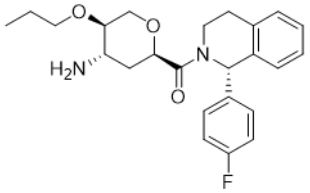
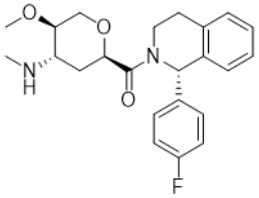
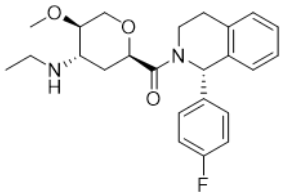
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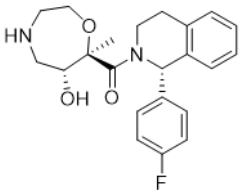
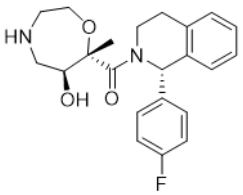
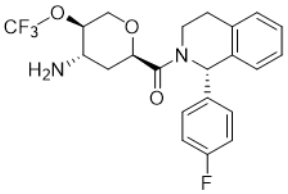
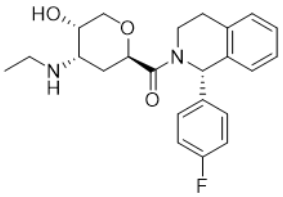
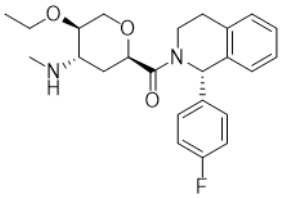
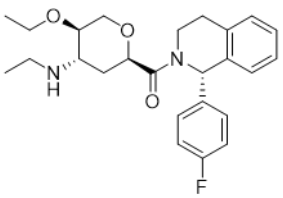
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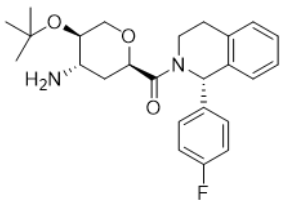
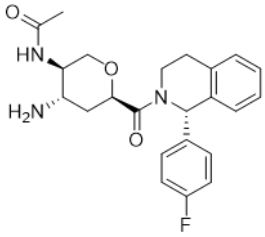
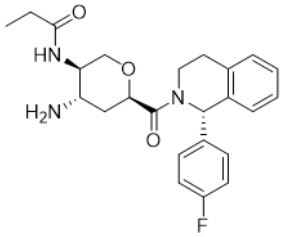
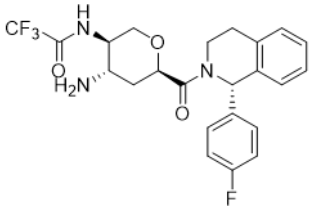
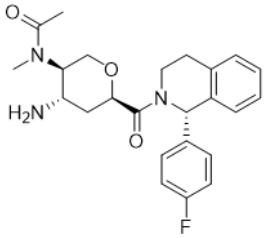
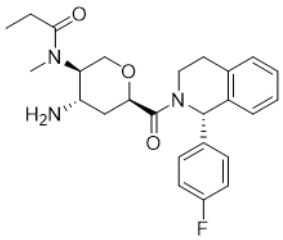
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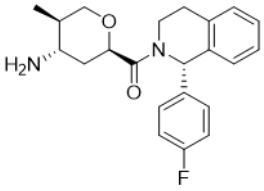
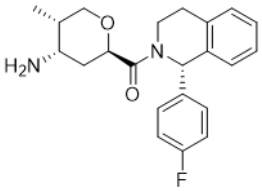
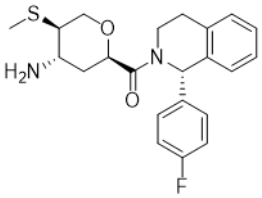
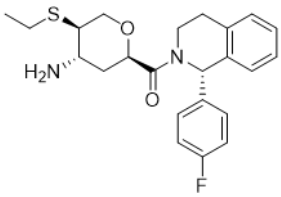
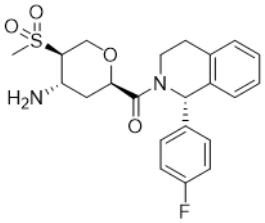
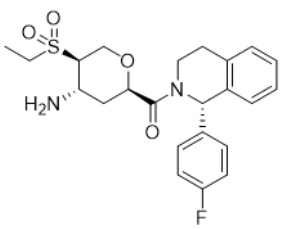
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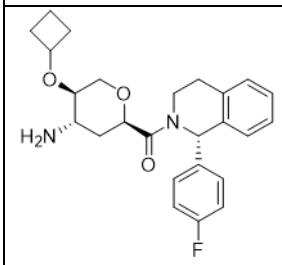
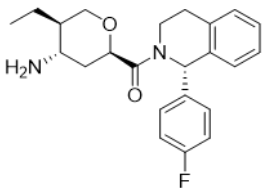
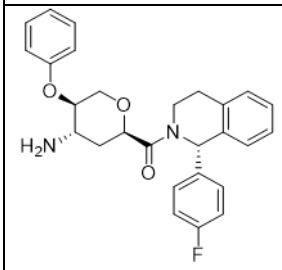
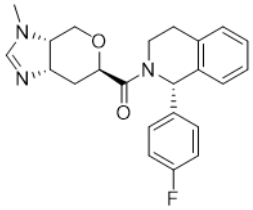
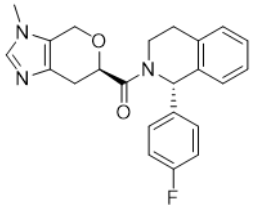
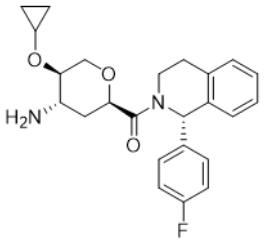
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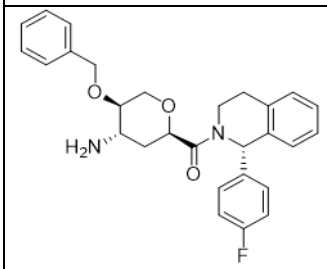
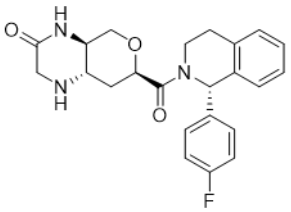
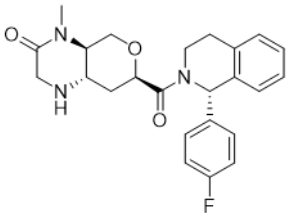
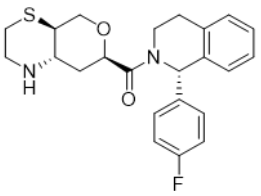
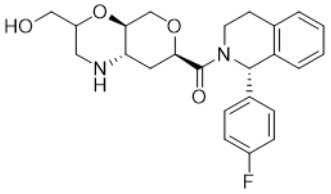
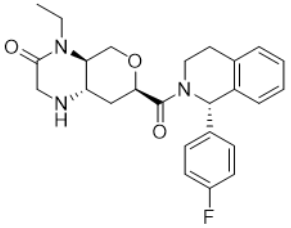
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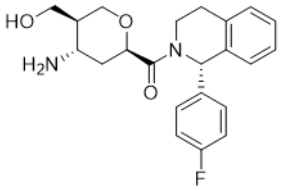
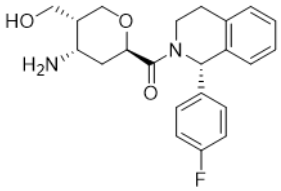
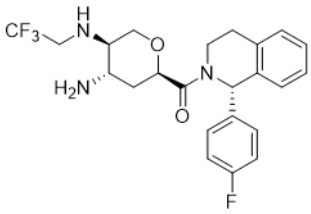
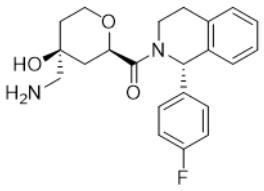
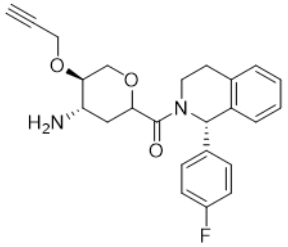
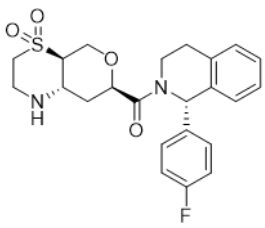
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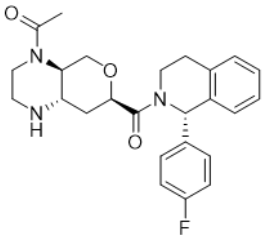
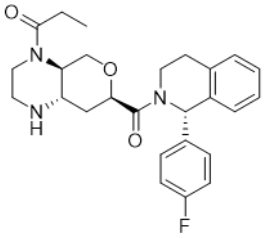
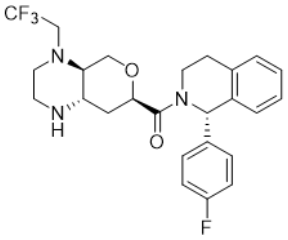
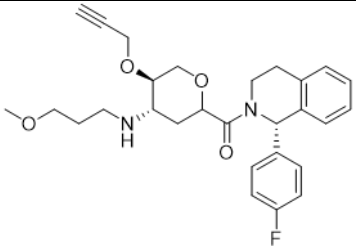
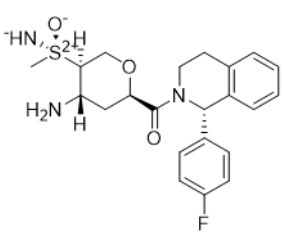
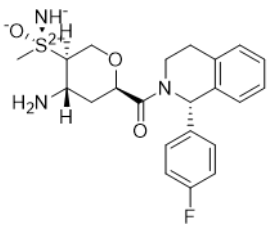
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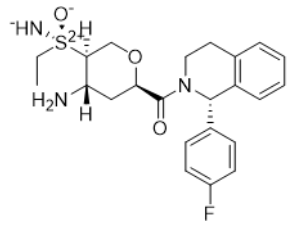
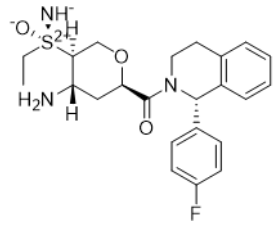
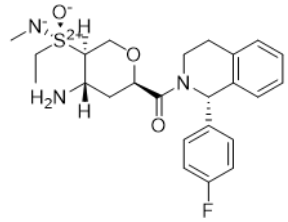
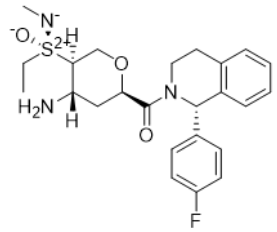
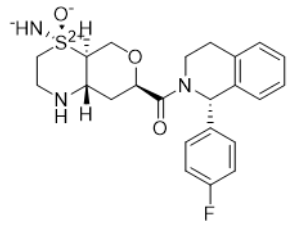
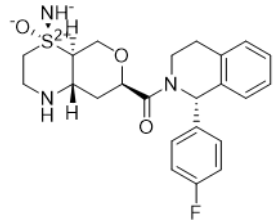
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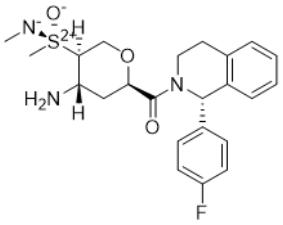
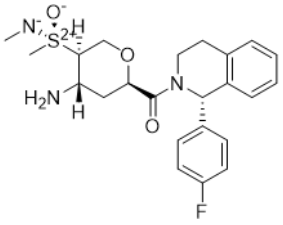
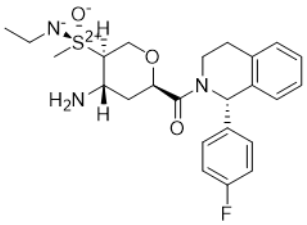
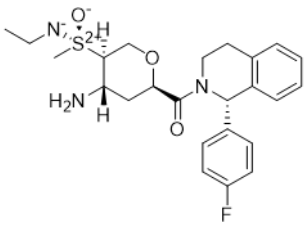
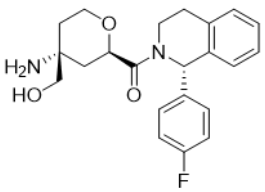
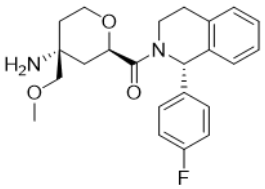
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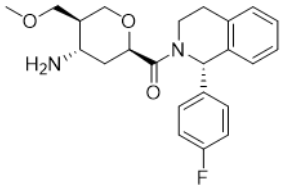
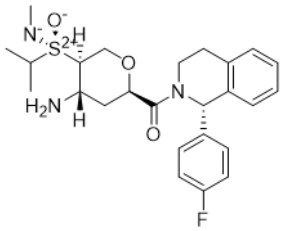
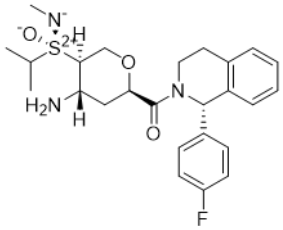
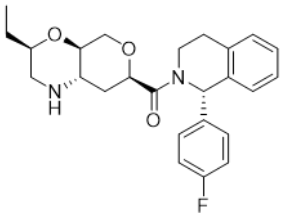
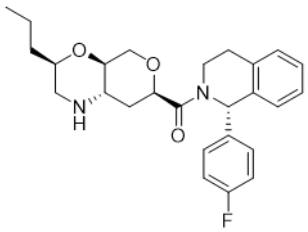
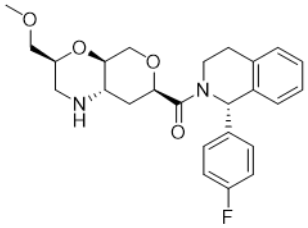
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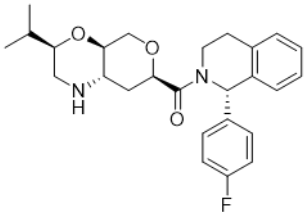
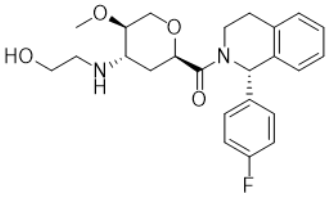
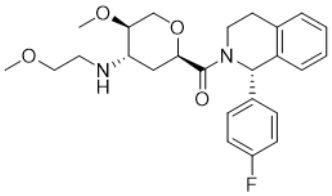
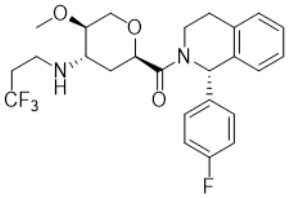
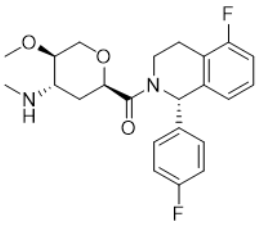
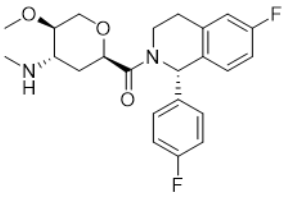
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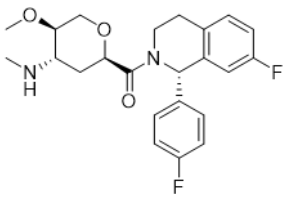
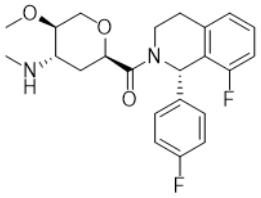
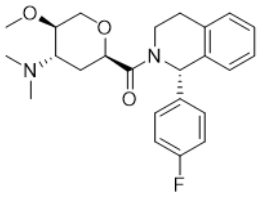
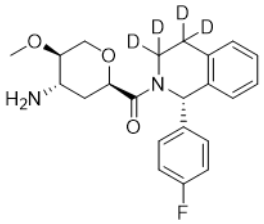
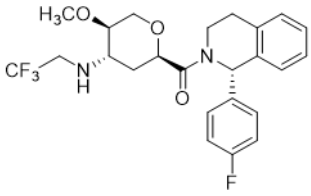
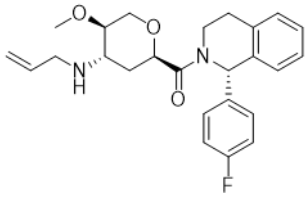
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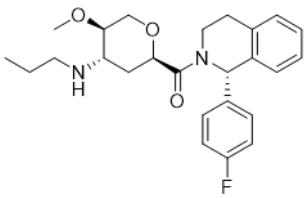
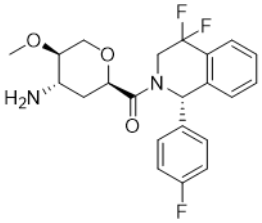
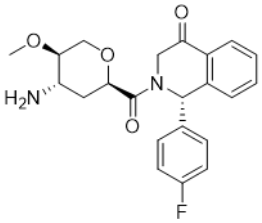
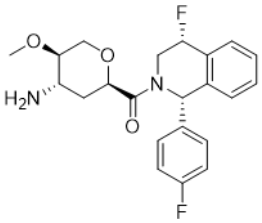
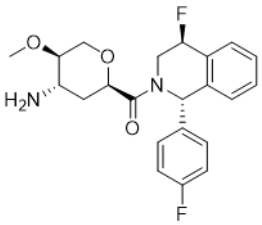
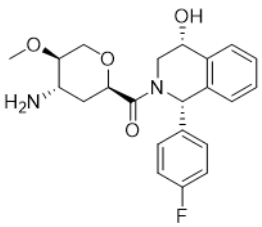
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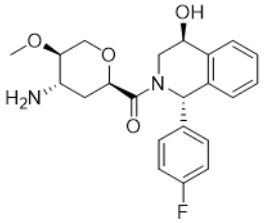
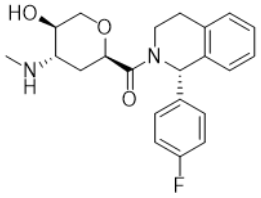
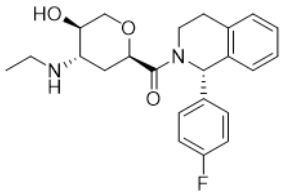
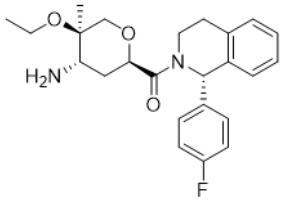
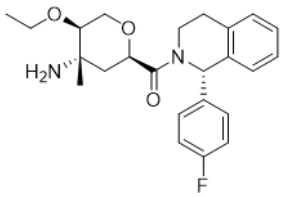
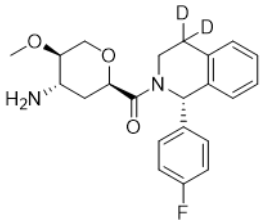
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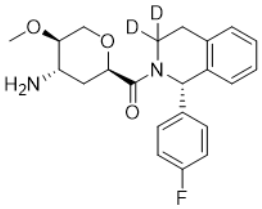
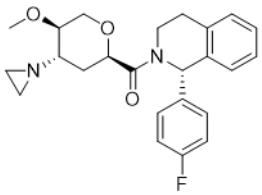
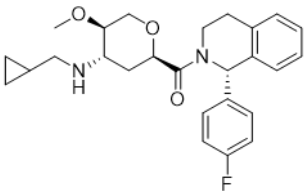
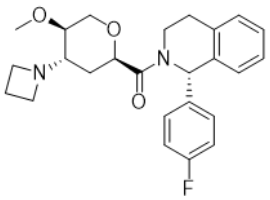
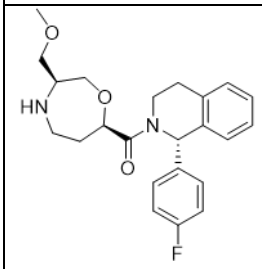
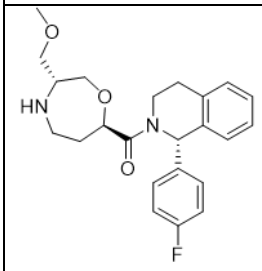
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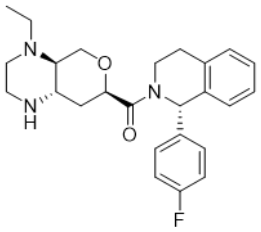
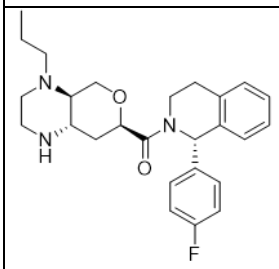
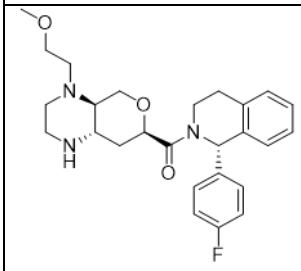
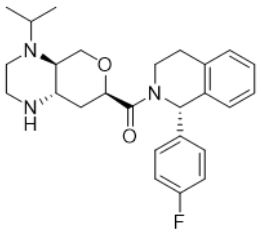
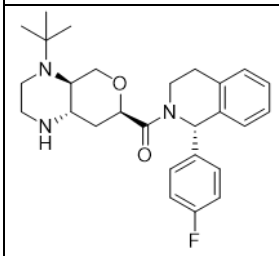
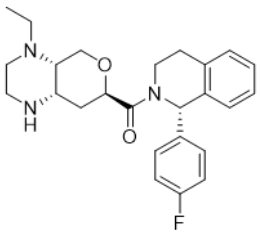
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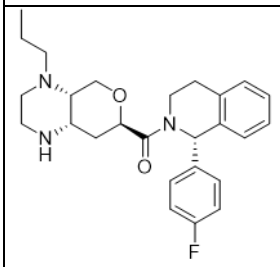
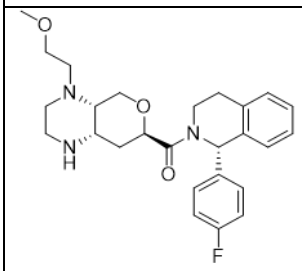
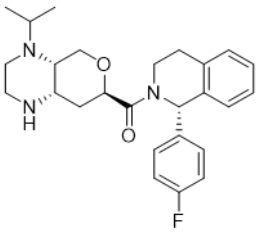
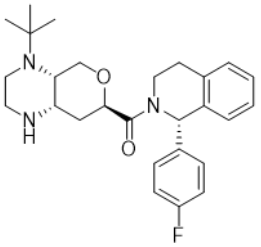
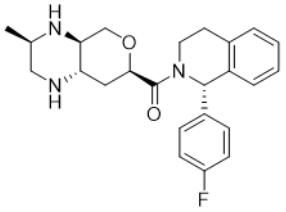
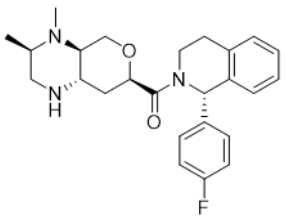
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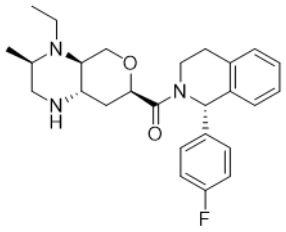
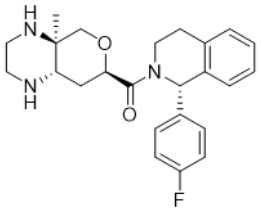
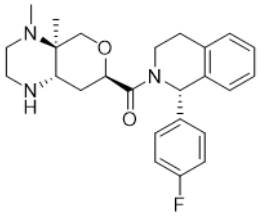
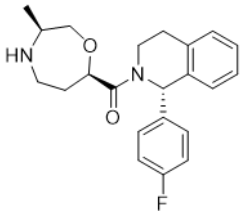
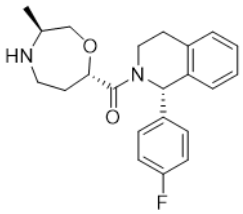
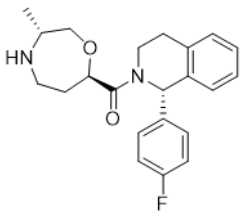
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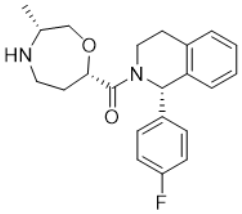
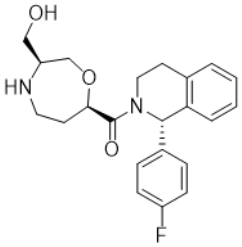
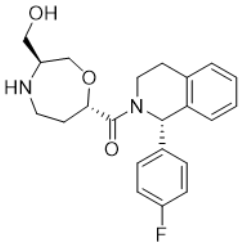
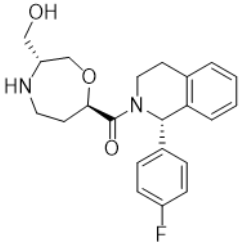
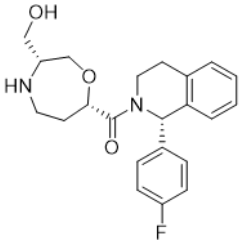
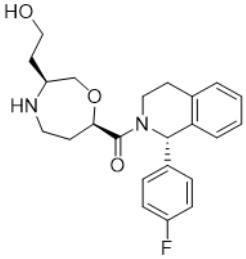
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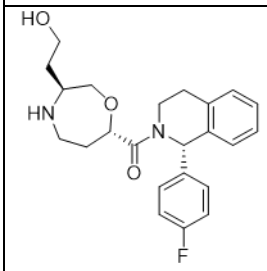
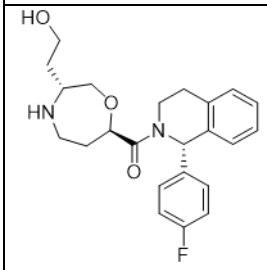
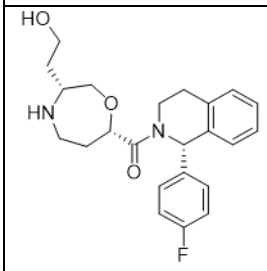
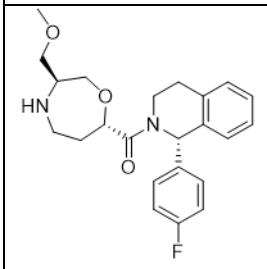
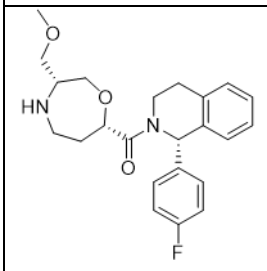
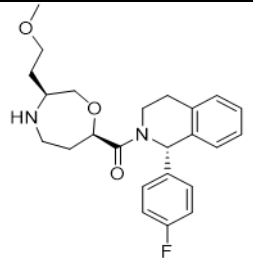
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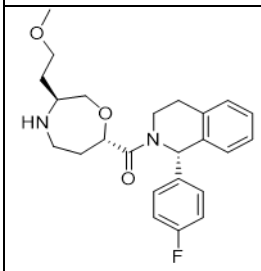
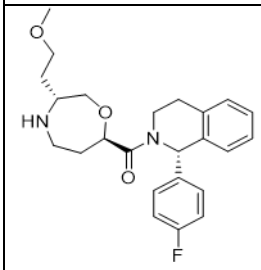
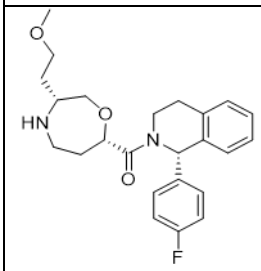
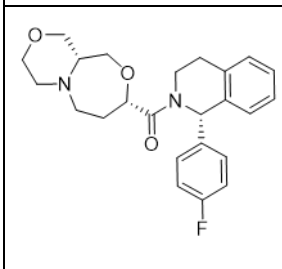
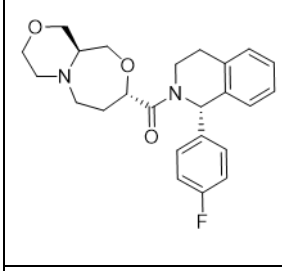
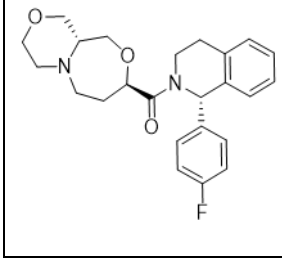
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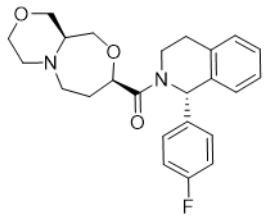
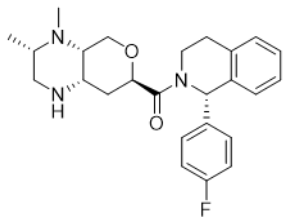
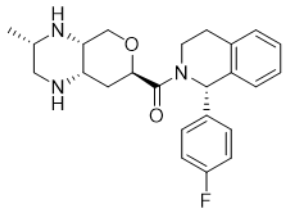
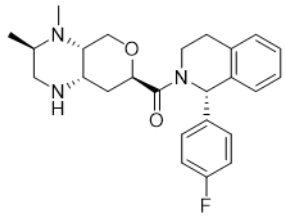
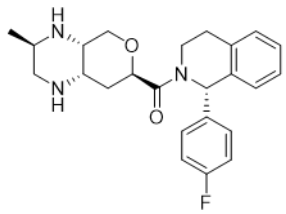
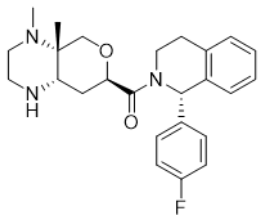
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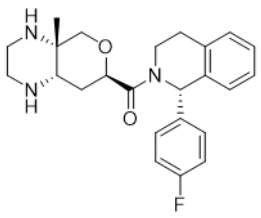
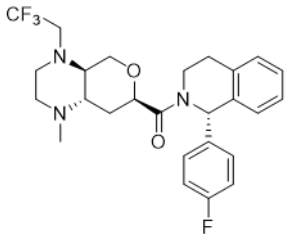
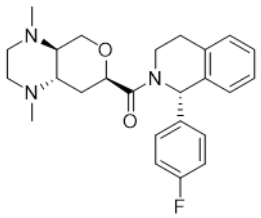
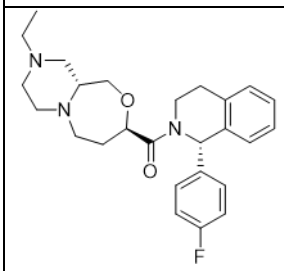
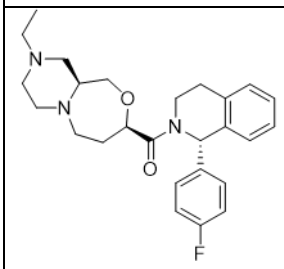
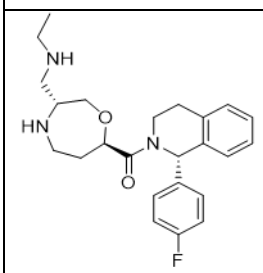
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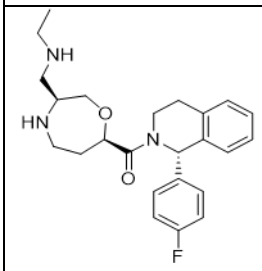
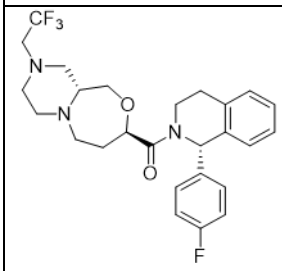
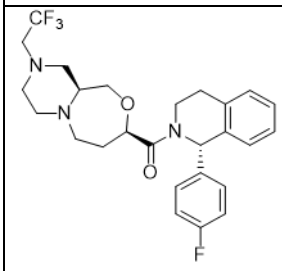
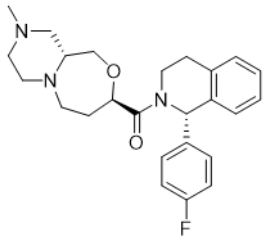
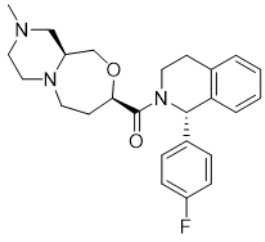
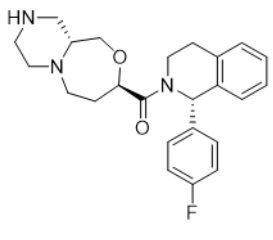
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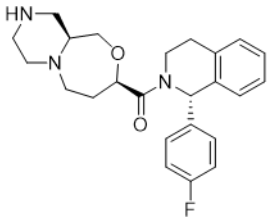
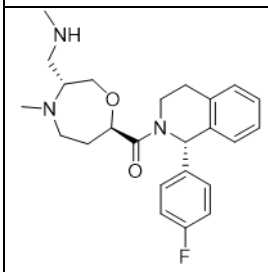
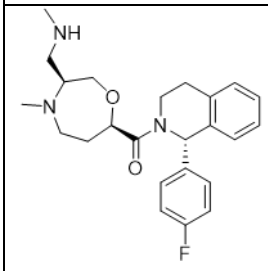
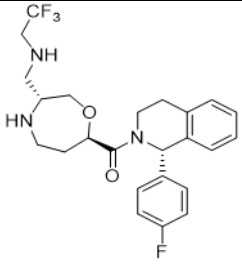
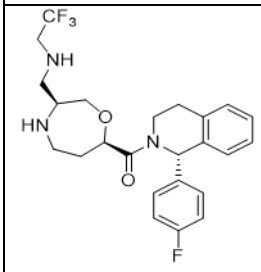
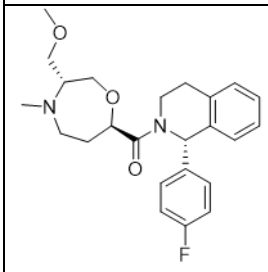
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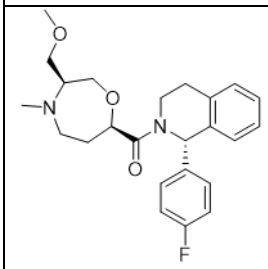
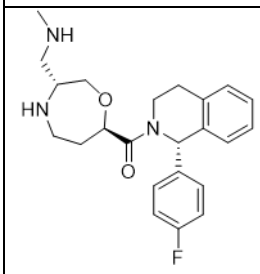
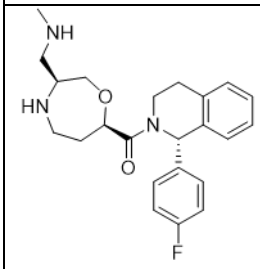
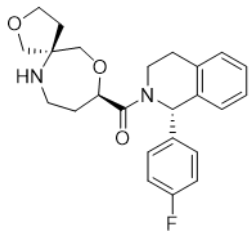
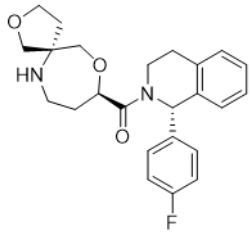
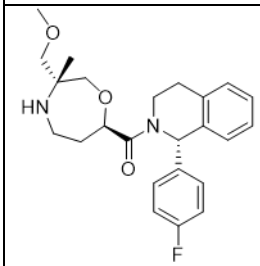
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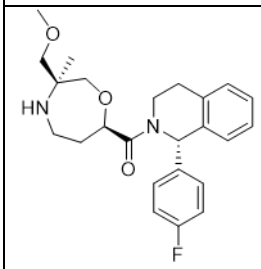
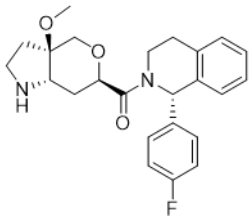
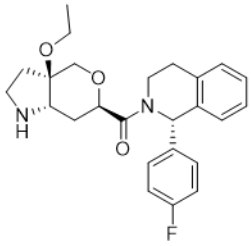
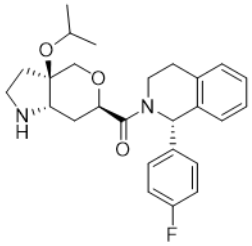
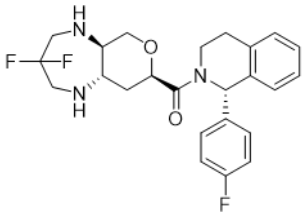
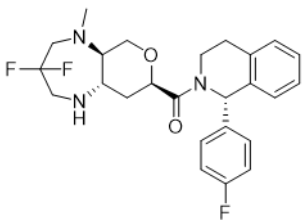
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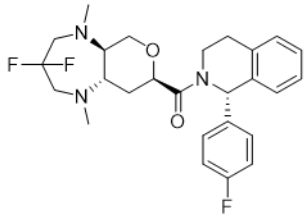
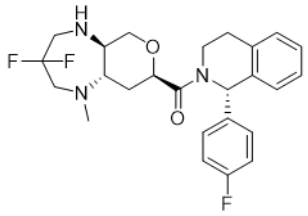
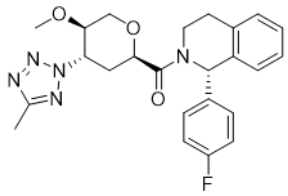
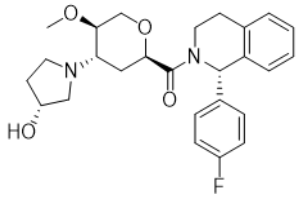
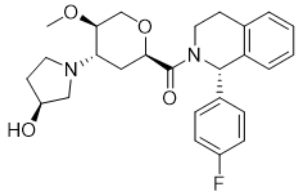
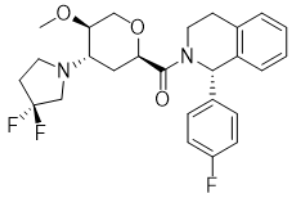
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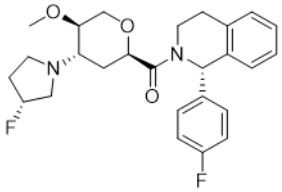
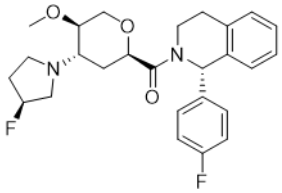
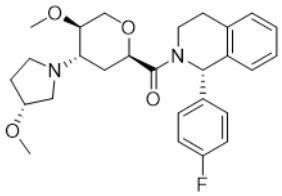
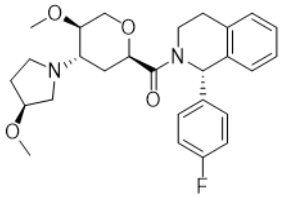
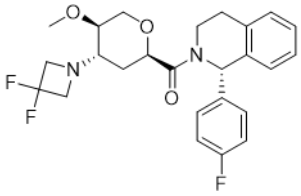
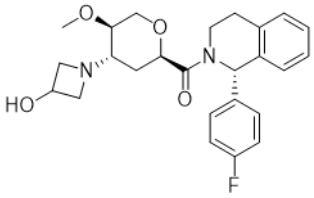
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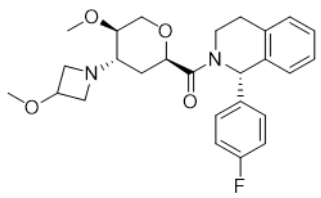
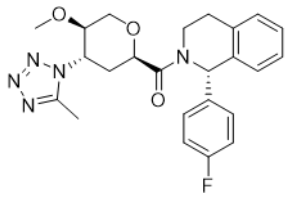
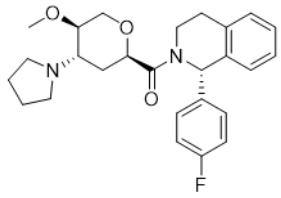
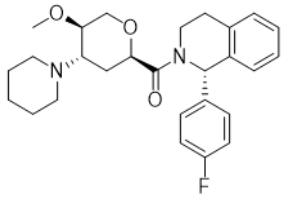
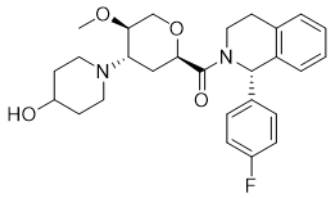
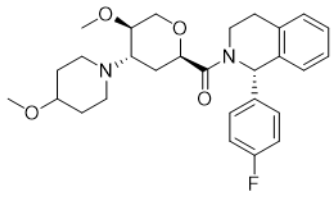
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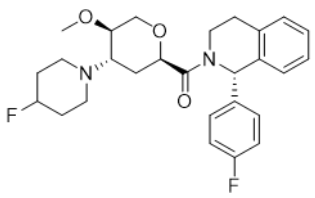
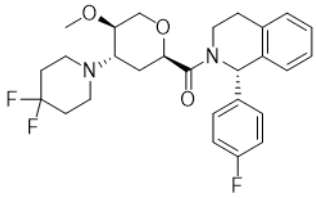
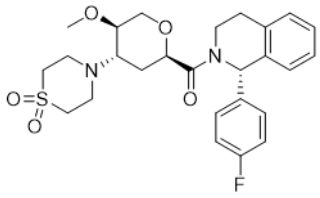
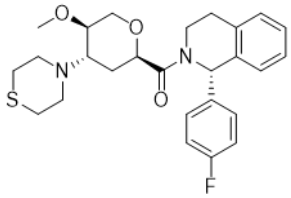
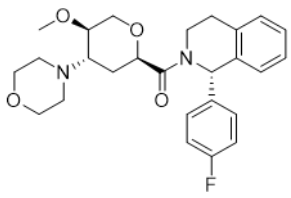
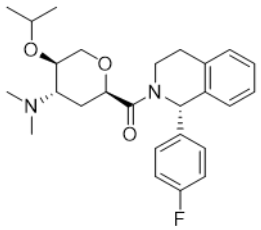
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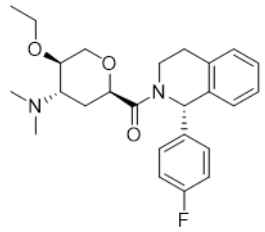
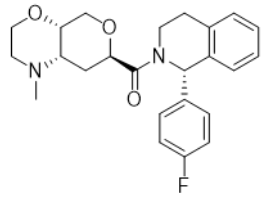
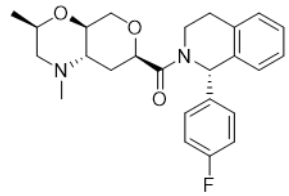
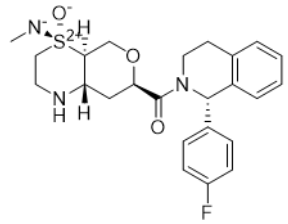
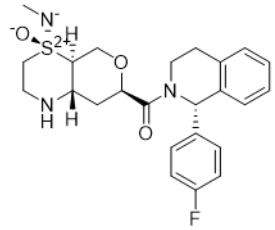
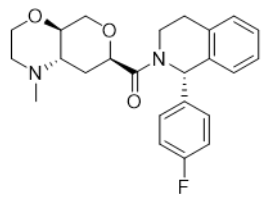
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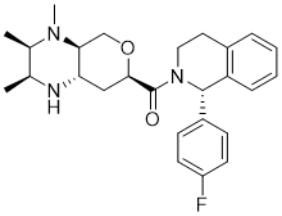
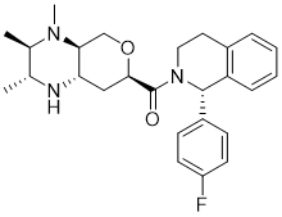
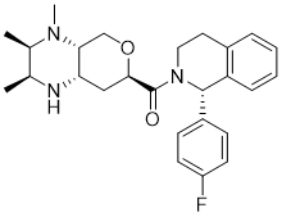
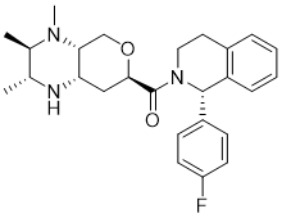
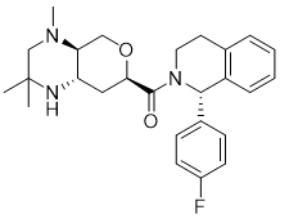
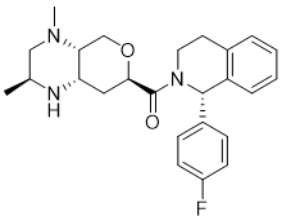
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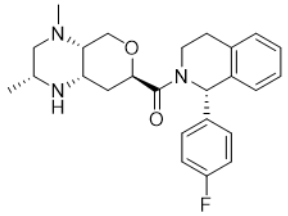
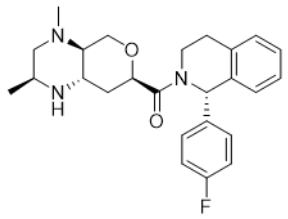
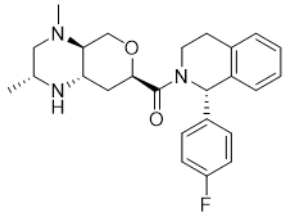
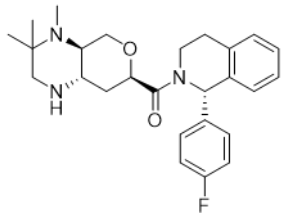
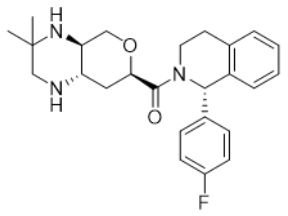
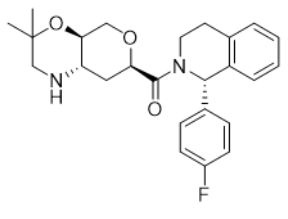
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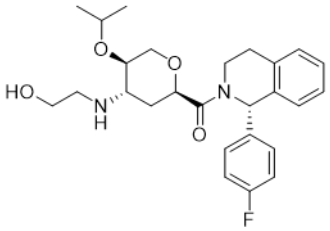
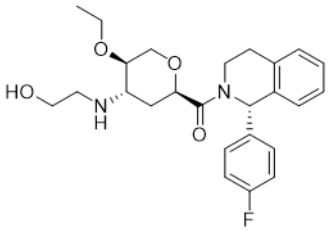
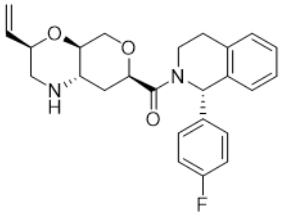
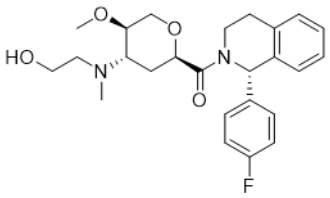
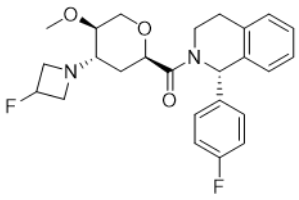
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[0005c] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound or salt as disclosed herein and a pharmaceutically acceptable excipient.

[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;

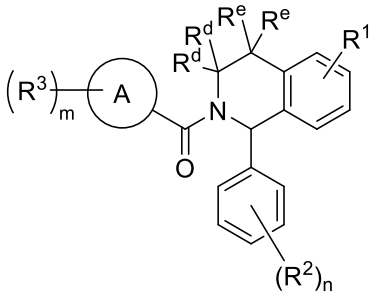
(iii) stroke, Down syndrome, congenital heart disease, diabetes, common variable immune deficiency (CVID), tubulo-interstitial kidney disease (TKD), polycystic liver disease, myocarditis, dermatitis hyperhomocysteinemia, endo-toxic shock, lung injury, bone defect (e.g., inflammatory periodontal bone 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.

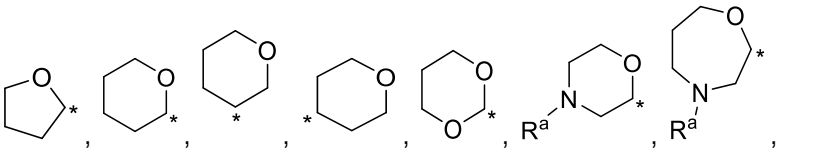
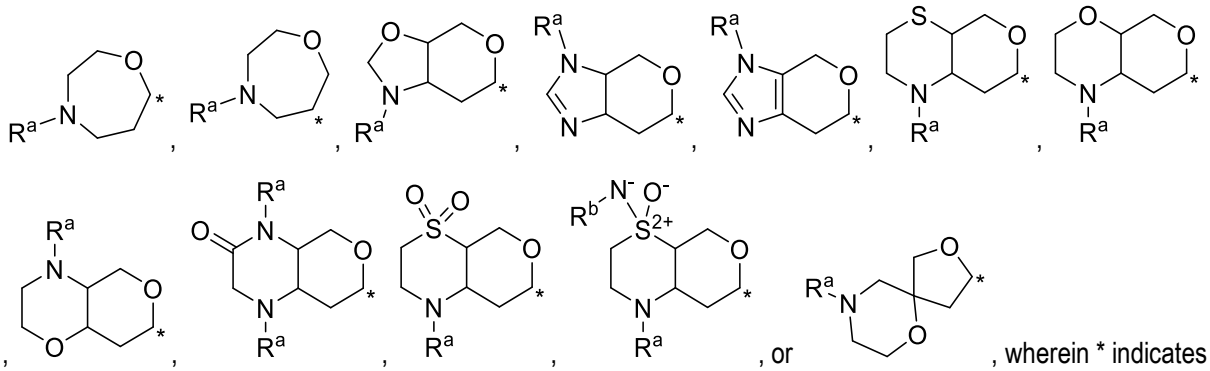
[0007] The present disclosure provides compounds of Formula (I):



(I)

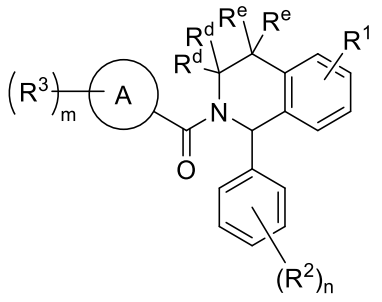
wherein ring A is a 4- to 12-membered heterocycle comprising a ring O or S atom, further comprising 0-3 additional ring heteroatoms selected from O, N, and S; R^1 is hydrogen, C_{1-6}alkyl, halo, C_{1-3} haloalkyl, O-C_{1-3} haloalkyl,C_{0-3} alkylene-CN, C_{0-3} alkylene-NR^N_2, C_{0-6} alkylene-OR^N,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

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

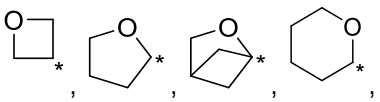
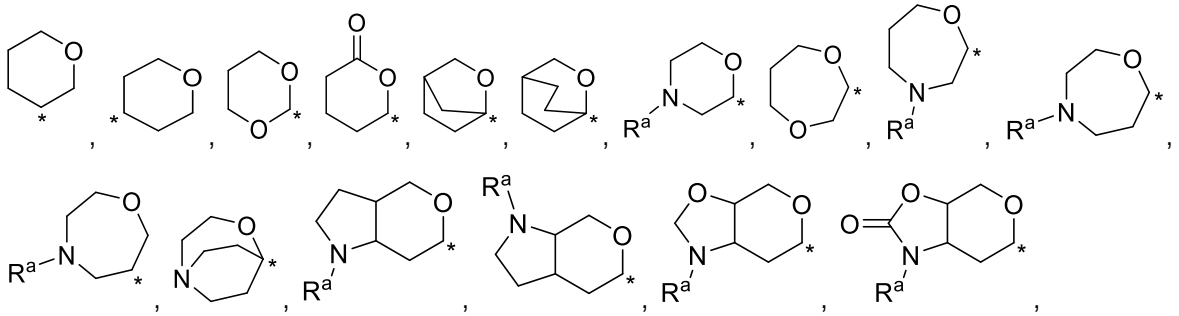
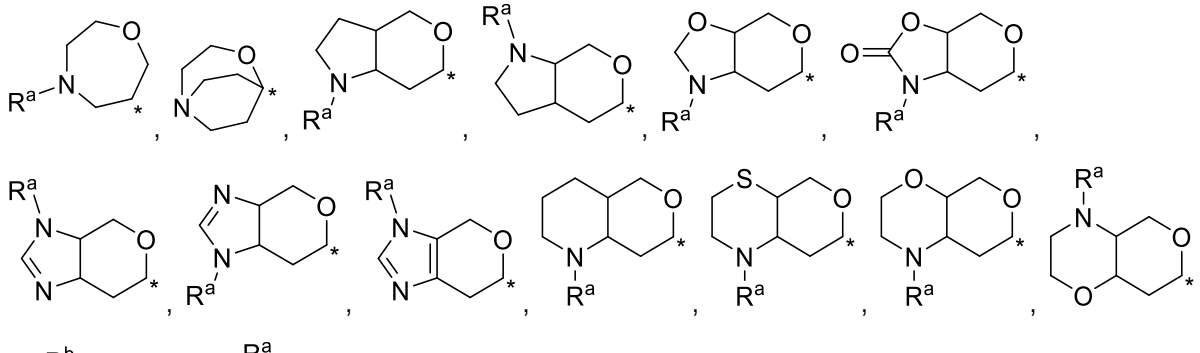
n is 0-2.

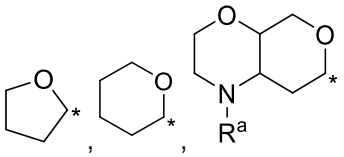
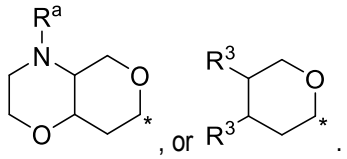
2. The compound or salt of claim 1, wherein ring A is a 4- to 6-membered heterocycle.

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

4. The compound or salt of claim 1 or 2, wherein ring A comprises a ring O and N atom.

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

6. The compound or salt of claim 1 or 2, wherein ring A is , , , , , , or , wherein * indicates the point of attachment of ring A to the adjacent carbonyl moiety of Formula I.

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

8. The compound or salt of any one of claims 1 to 7, wherein:

(i) at least one R^3 is C_{0-6}alkylene-NR^aR^b;

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

(iii) at least one R^3 is C_{1-6}alkoxy;

(iv) R^3 is $S^{2+}(O)^-(NR^a)^-C_{1-6}$alkyl; or

(v) R^3 is OR^4.

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

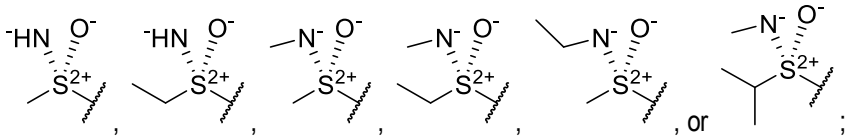
(i) at least one R^3 is NH_2;

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

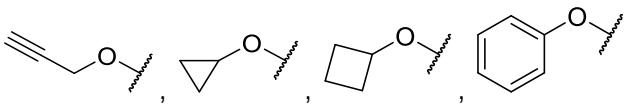
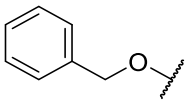
(iii) at least one R^3 is F;

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

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

(vi) R^3 is , or ;

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.

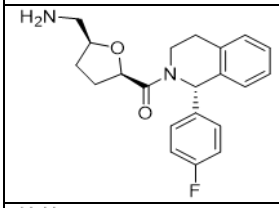
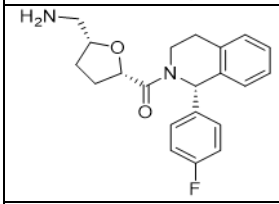
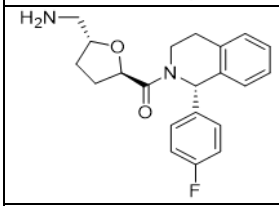
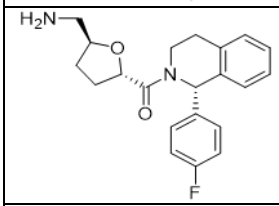
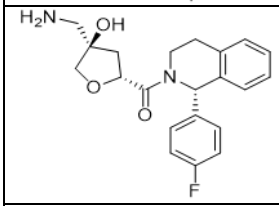
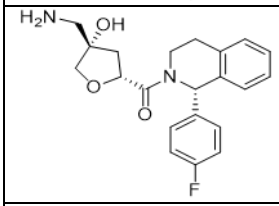
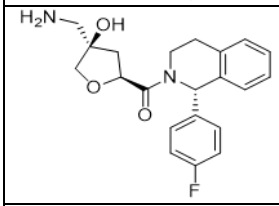
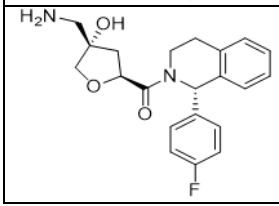
11. The compound or salt of any one of claims 1 to 10, wherein R^2 is F or Cl.

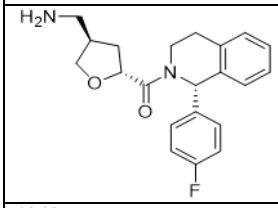
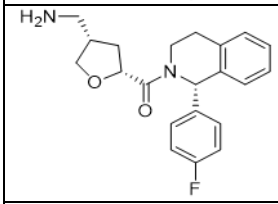
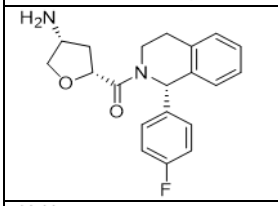
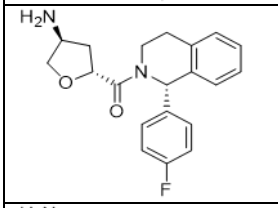
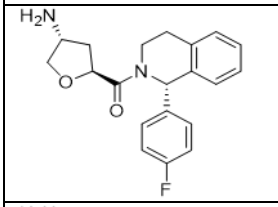
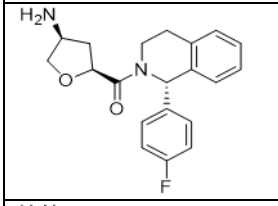
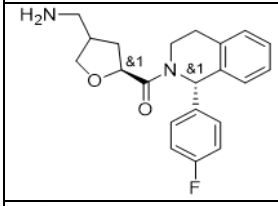
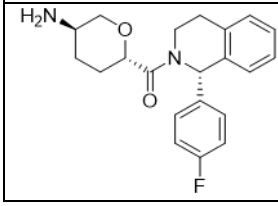
12. The compound or salt of any one of claims 1 to 11, wherein R^1 is hydrogen or halo.

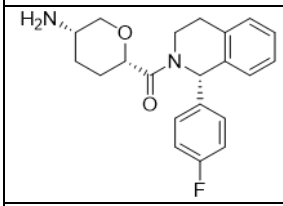
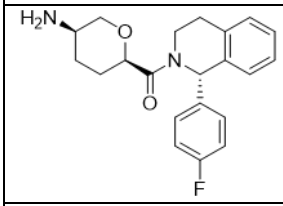
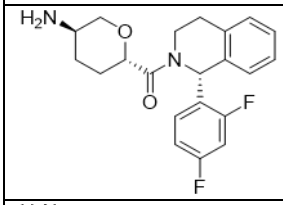
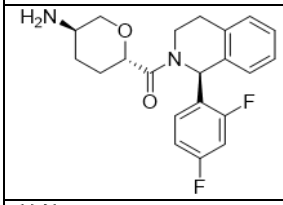
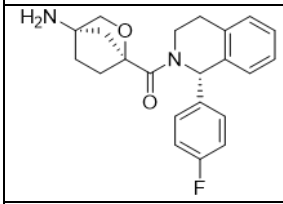
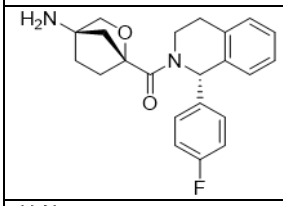
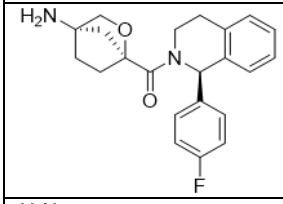
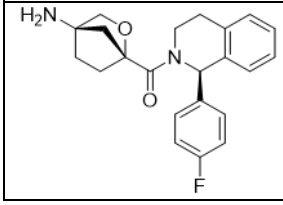
13. The compound or salt of any one of claims 1 to 12, wherein at least one R^e is H, D, OH, or halo, or wherein two geminal R^e together with the atom to which they are attached form an oxo group.

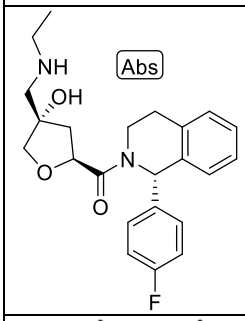
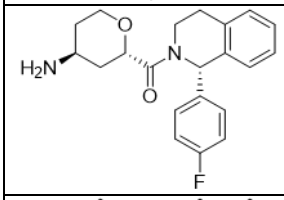
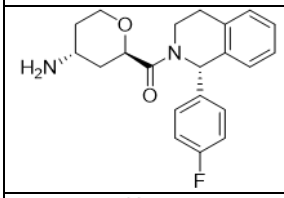
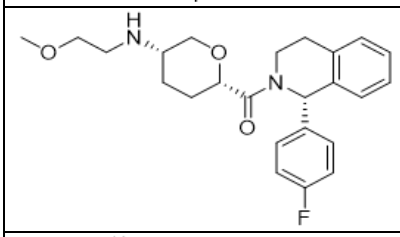
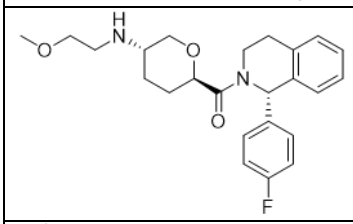
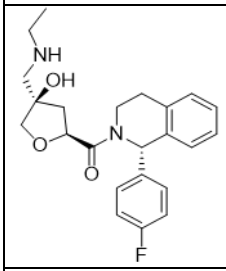
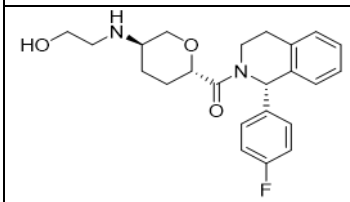
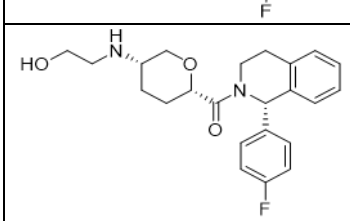
14. A compound, or pharmaceutically acceptable salt thereof, having a structure as shown in Table A:

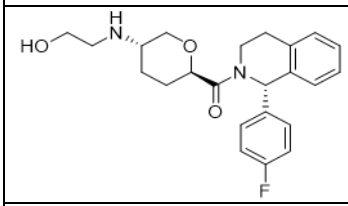
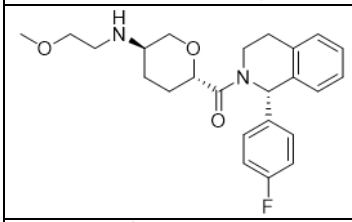
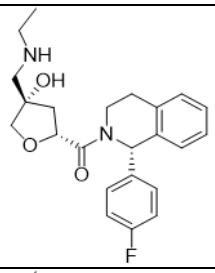
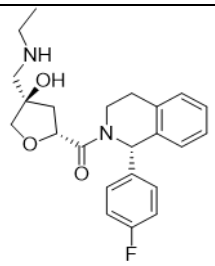
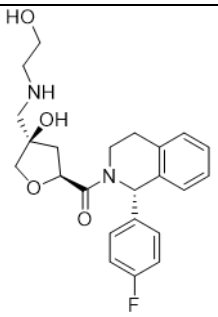
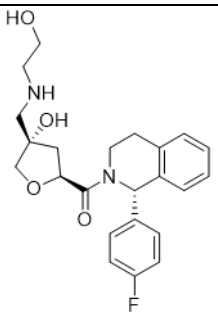
Table A

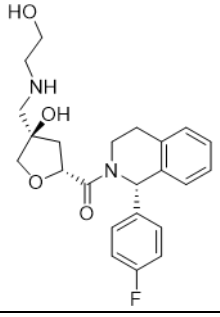
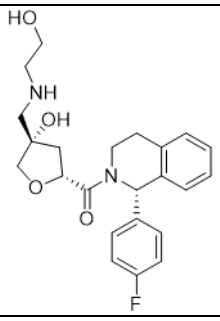
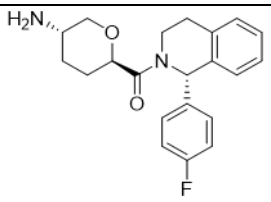
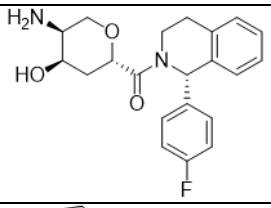
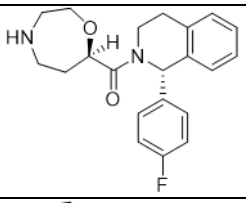
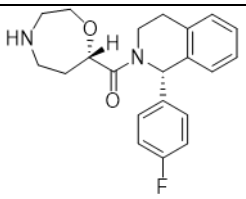
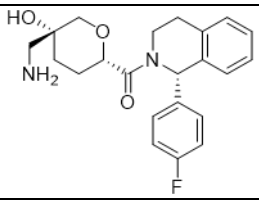
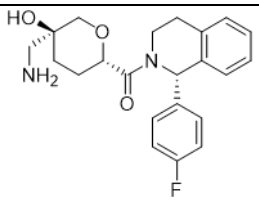
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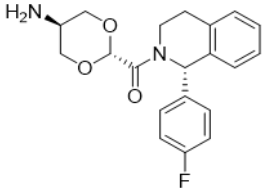
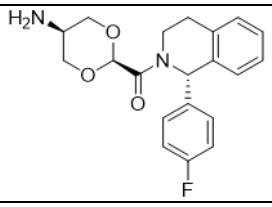
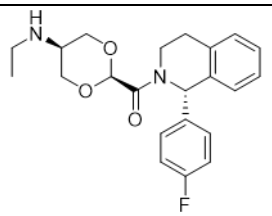
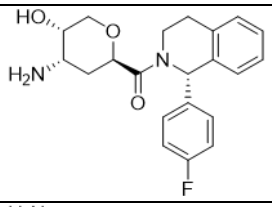
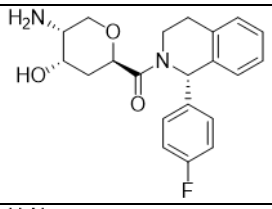
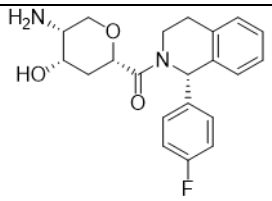
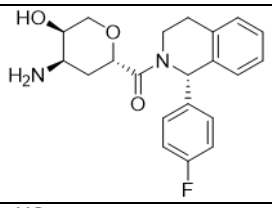
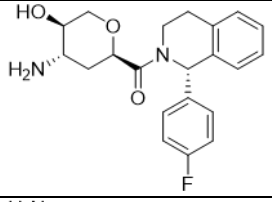
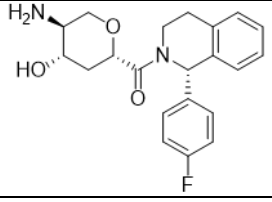
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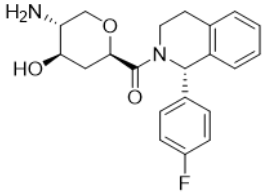
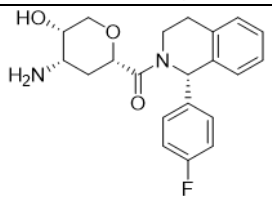
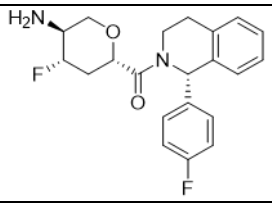
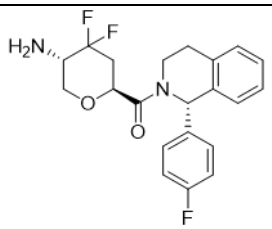
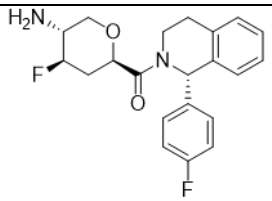
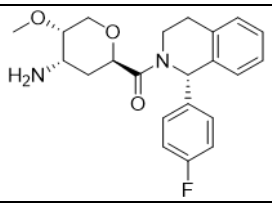
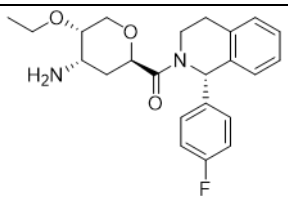
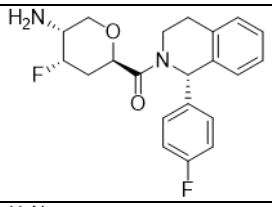
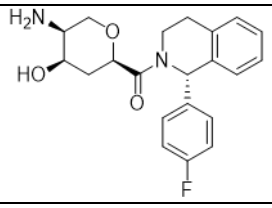
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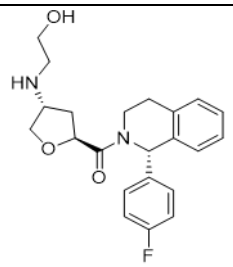
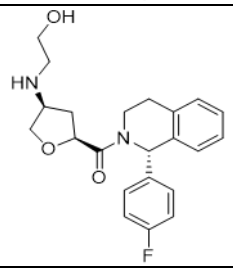
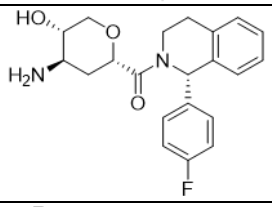
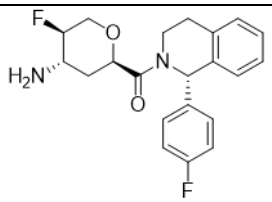
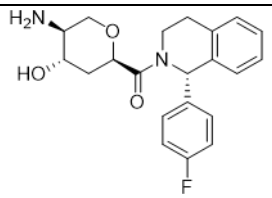
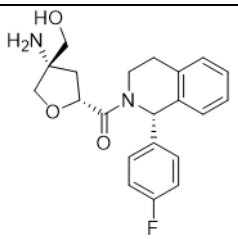
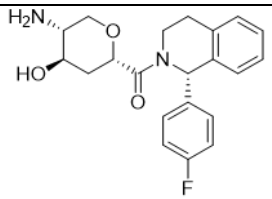
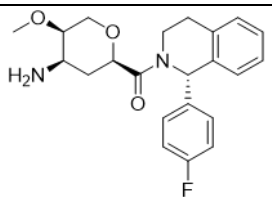
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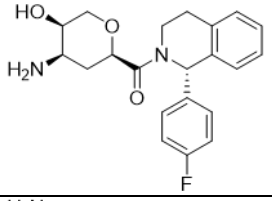
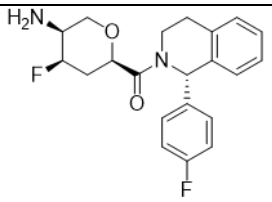
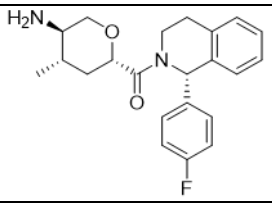
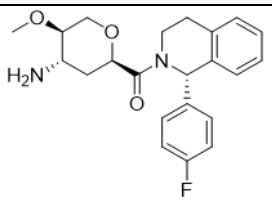
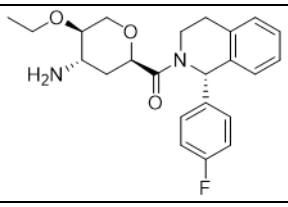
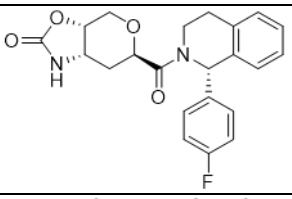
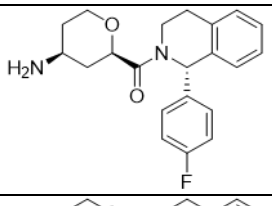
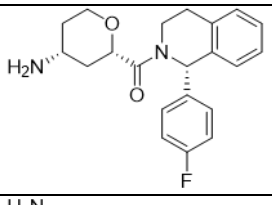
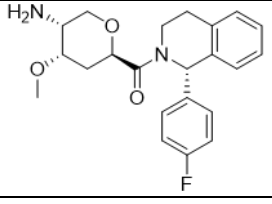
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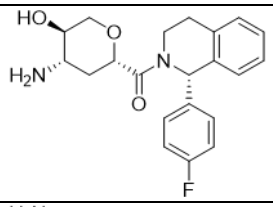
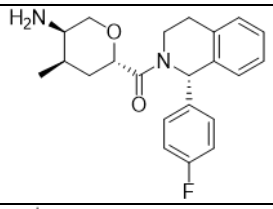
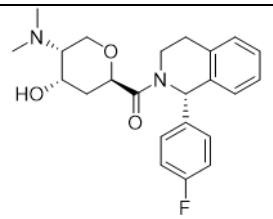
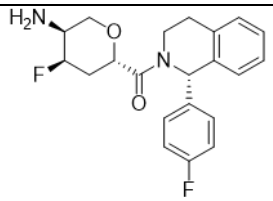
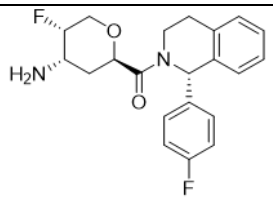
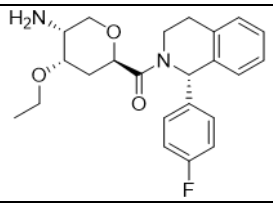
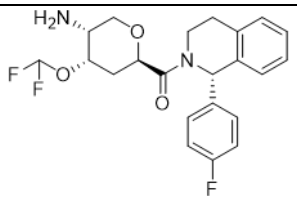
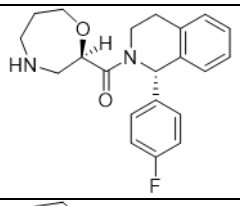
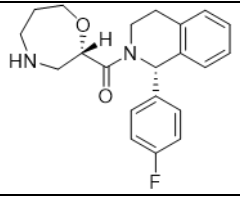
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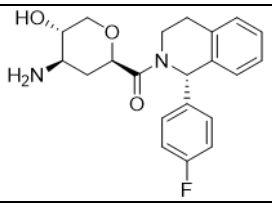
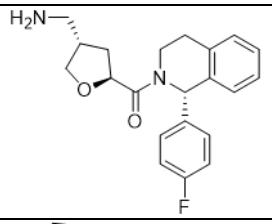
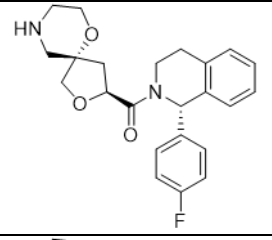
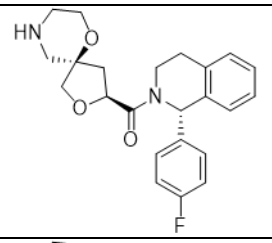
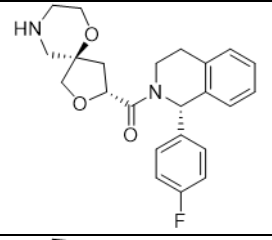
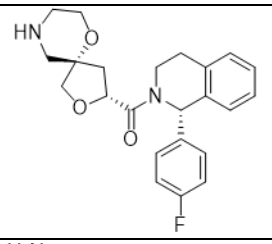
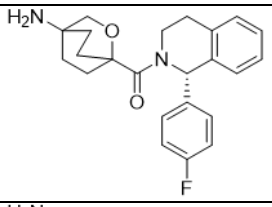
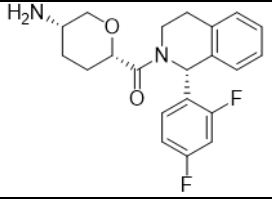
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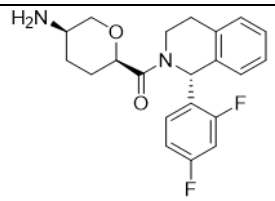
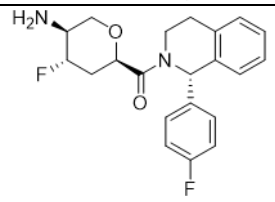
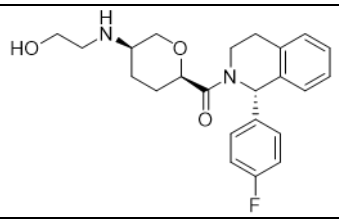
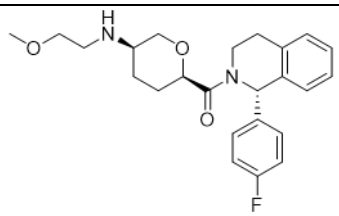
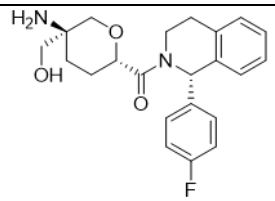
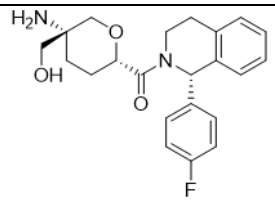
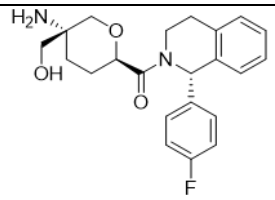
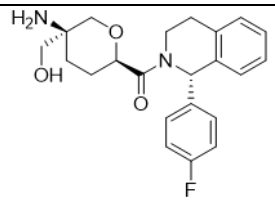
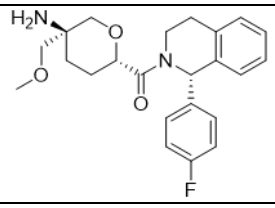
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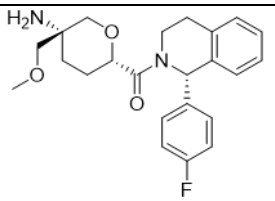
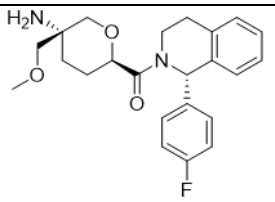
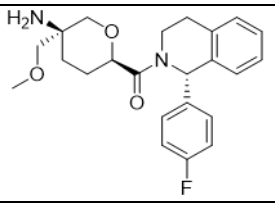
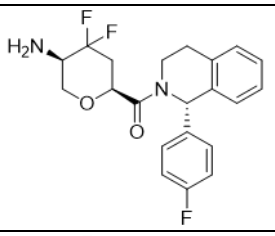
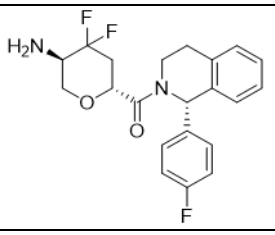
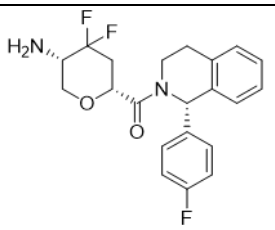
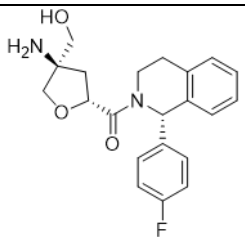
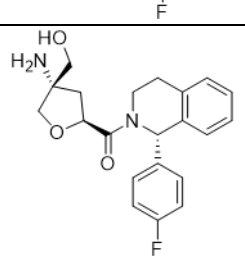
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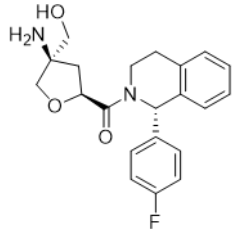
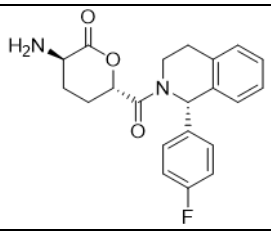
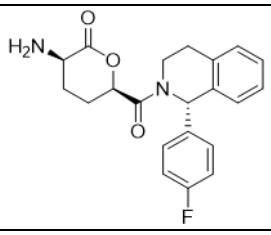
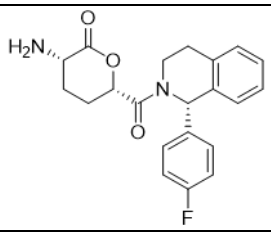
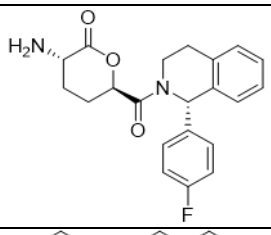
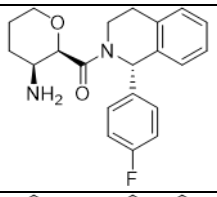
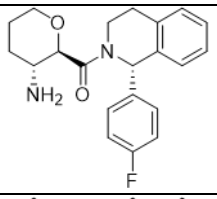
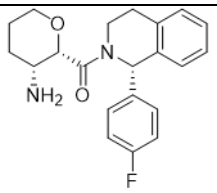
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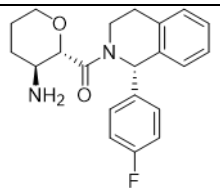
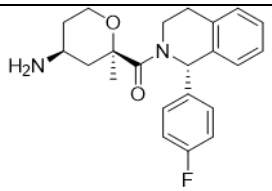
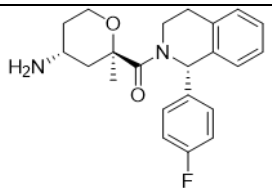
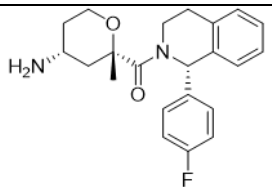
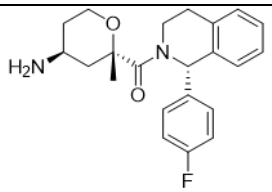
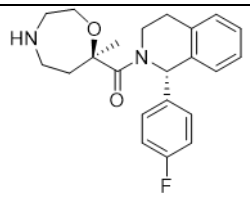
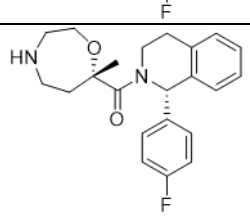
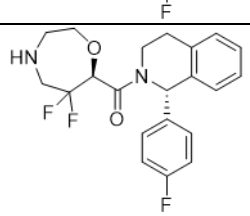
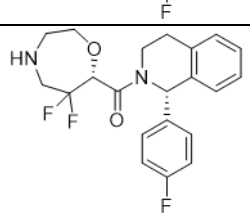
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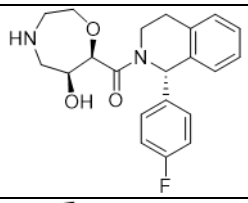
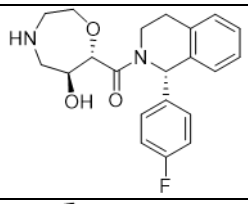
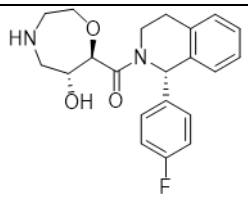
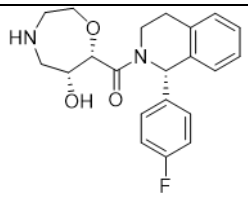
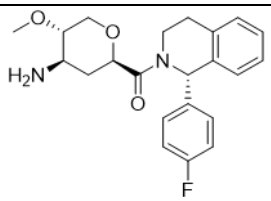
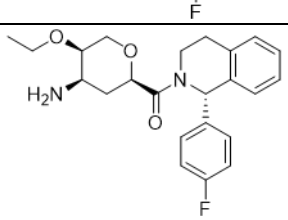
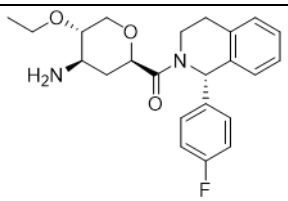
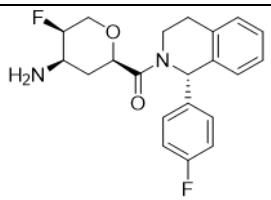
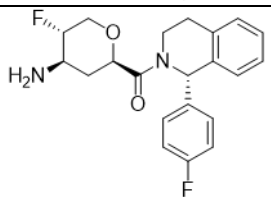
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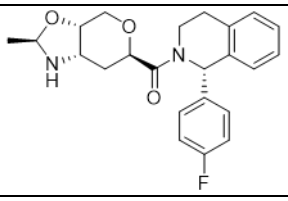
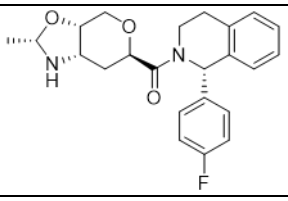
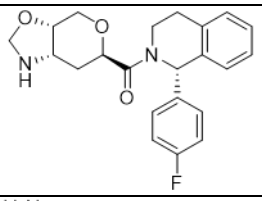
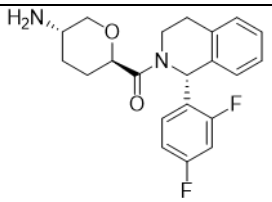
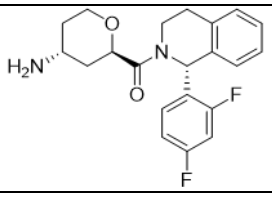
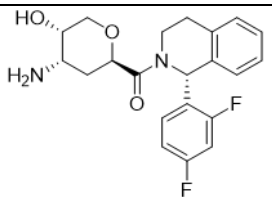
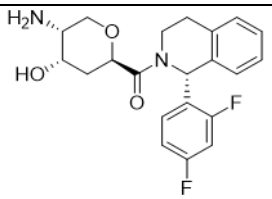
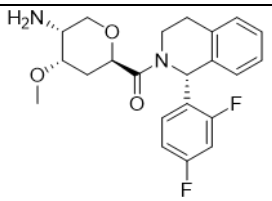
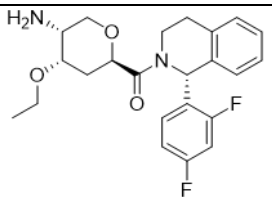
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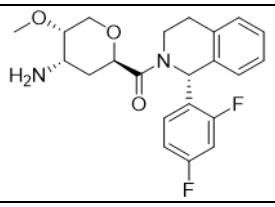
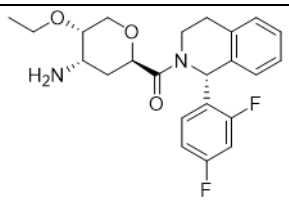
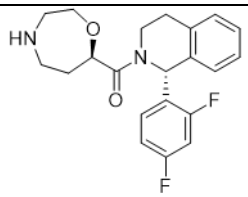
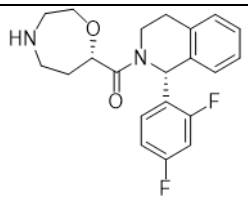
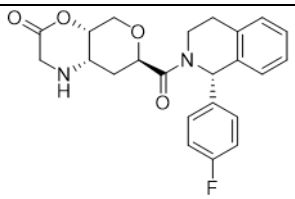
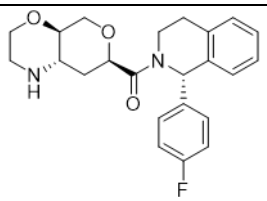
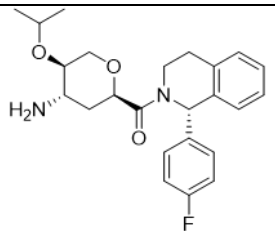
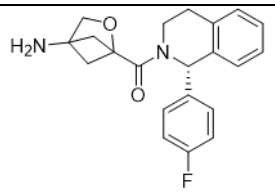
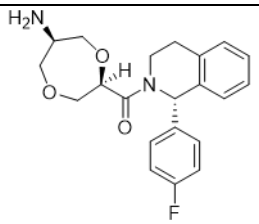
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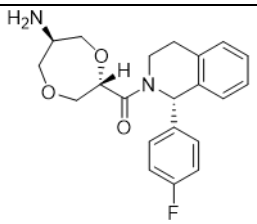
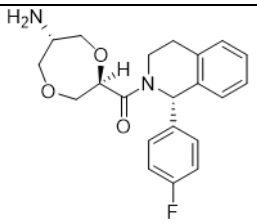
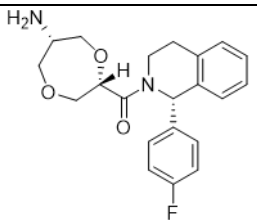
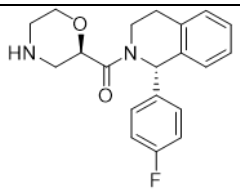
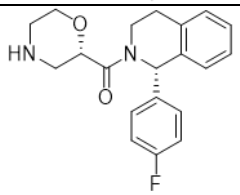
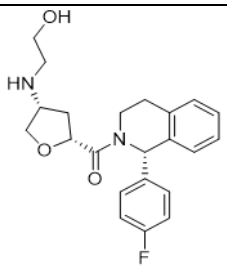
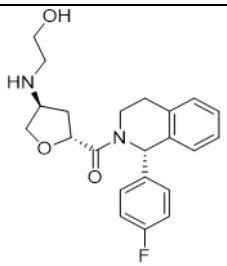
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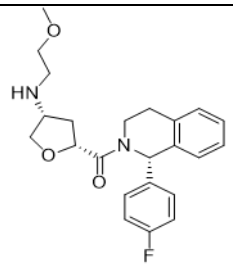
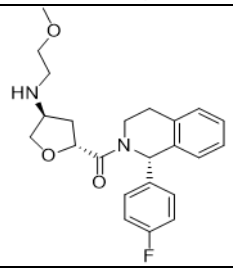
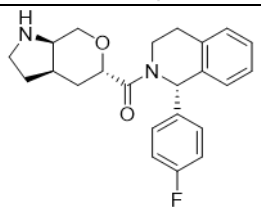
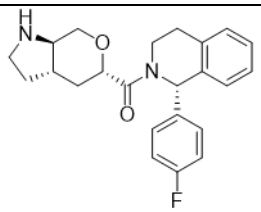
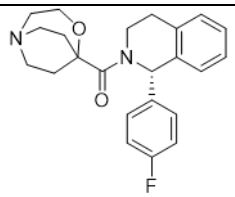
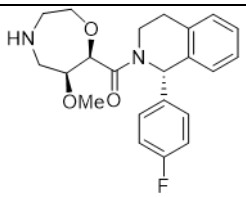
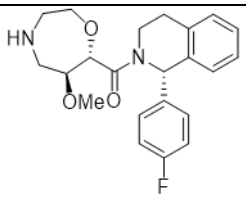
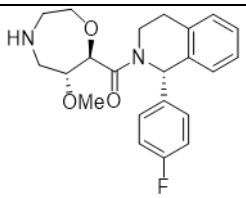
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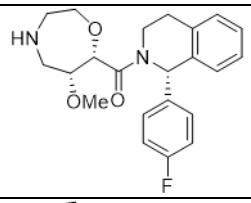
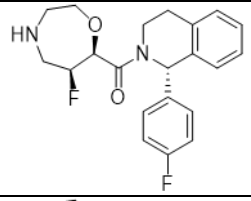
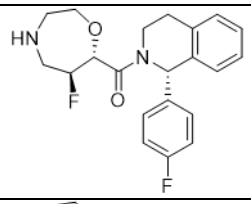
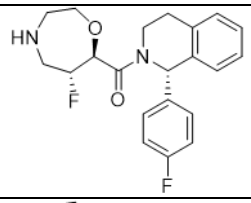
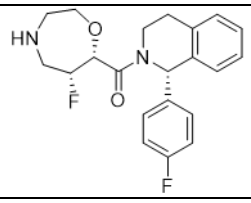
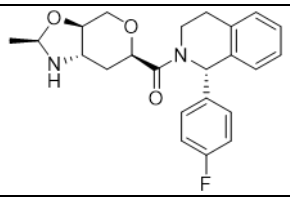
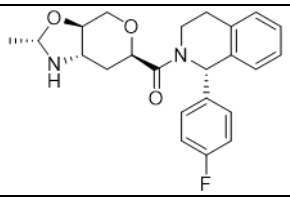
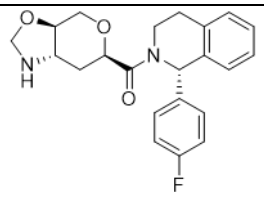
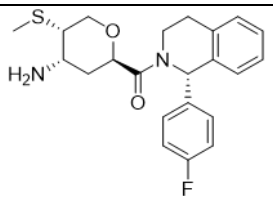
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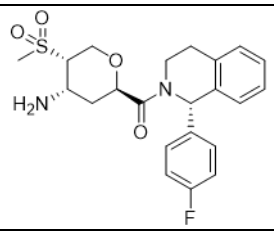
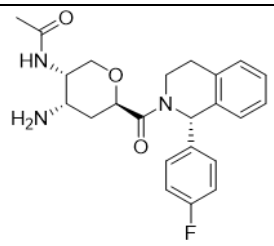
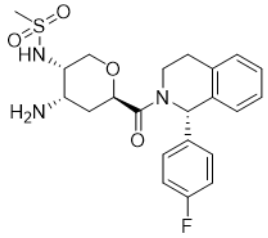
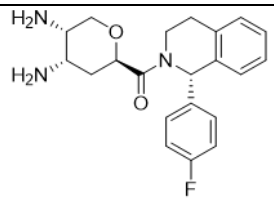
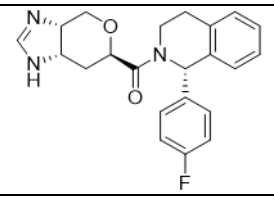
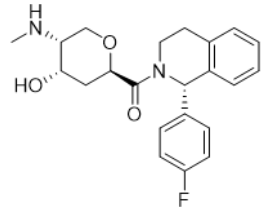
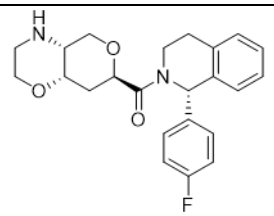
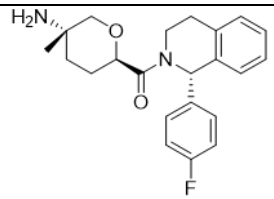
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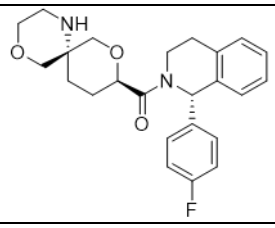
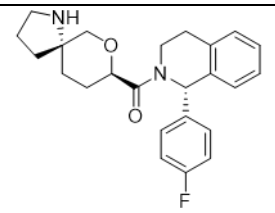
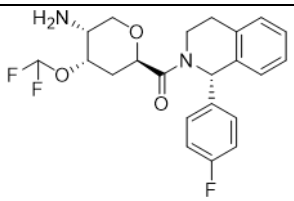
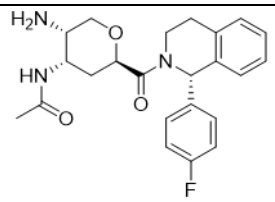
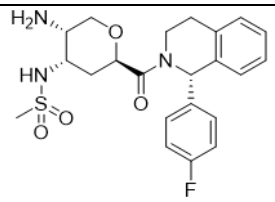
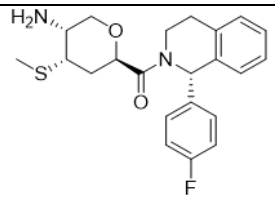
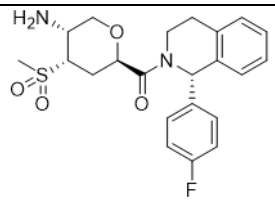
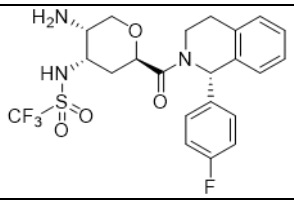
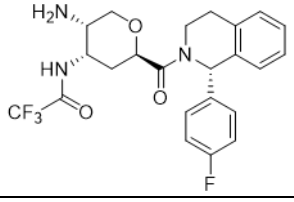
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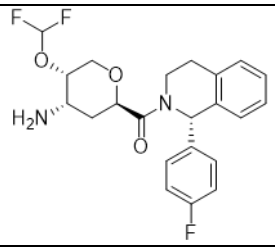
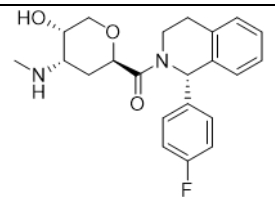
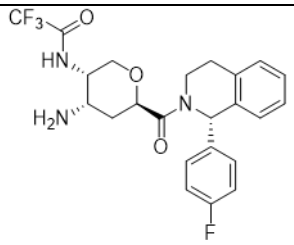
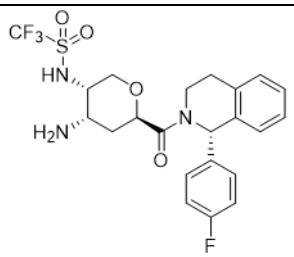
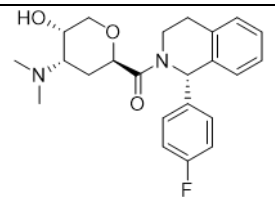
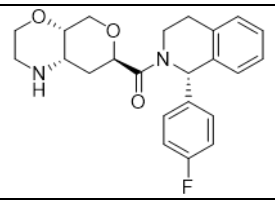
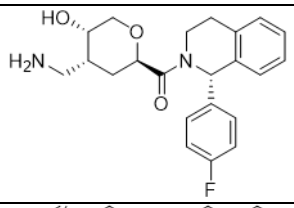
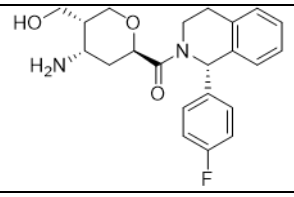
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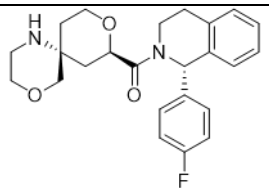
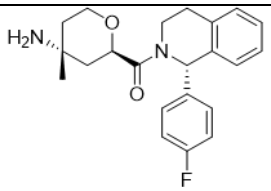
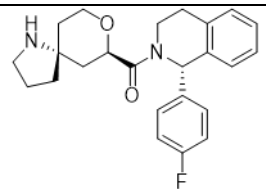
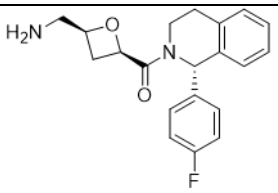
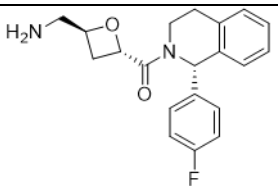
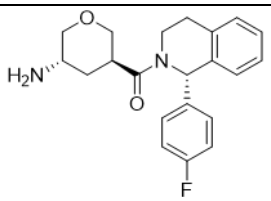
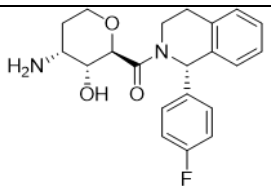
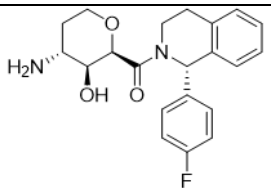
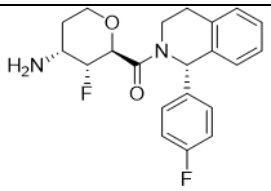
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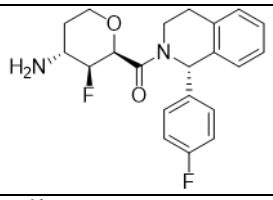
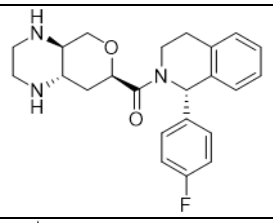
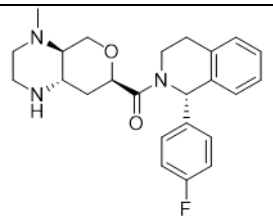
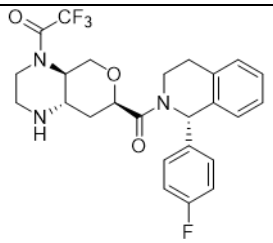
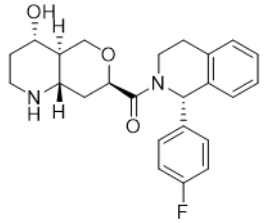
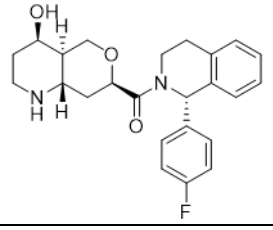
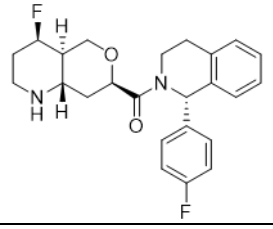
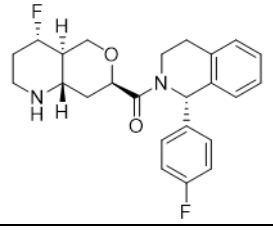
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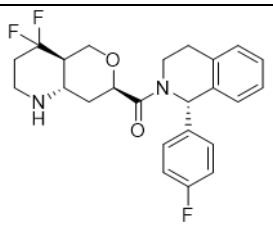
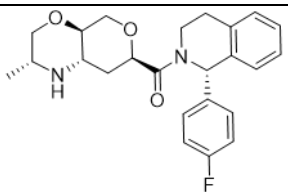
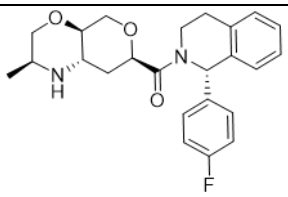
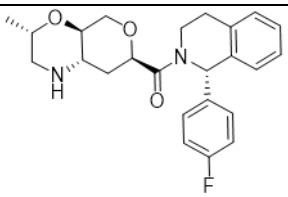
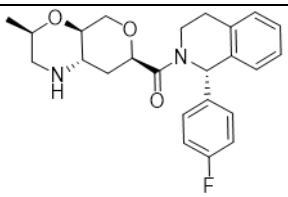
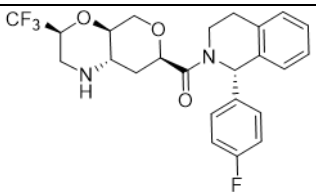
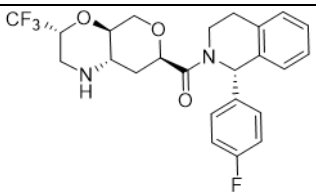
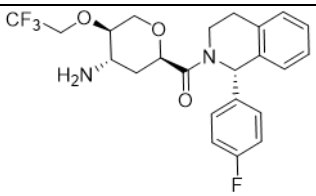
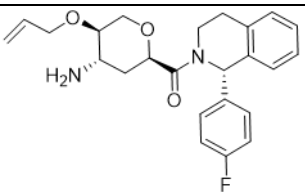
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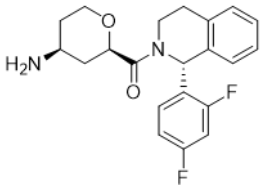
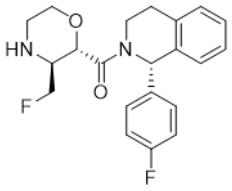
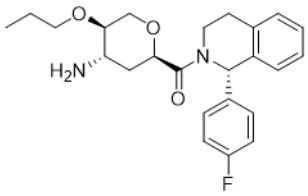
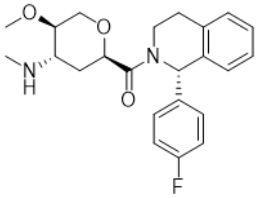
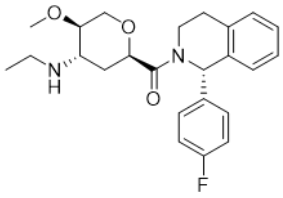
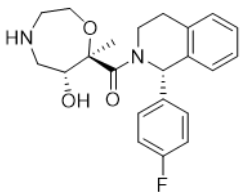
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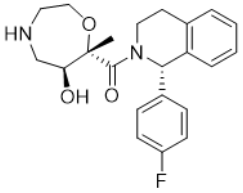
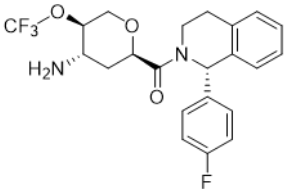
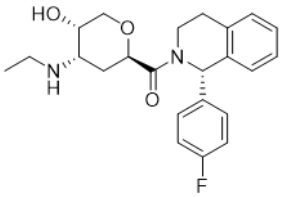
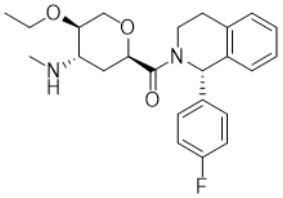
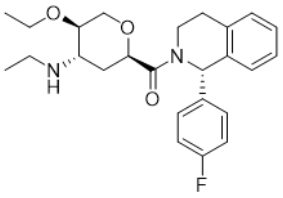
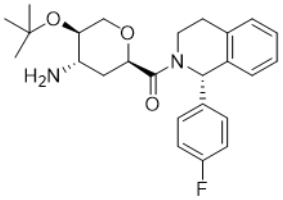
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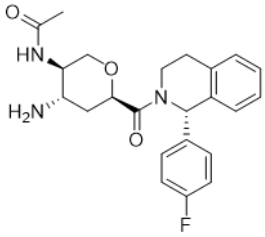
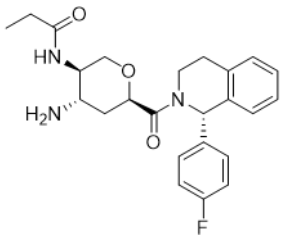
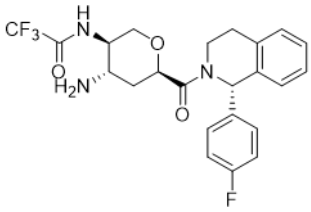
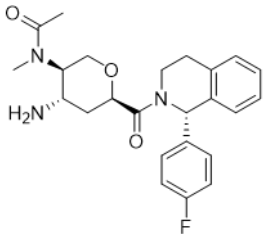
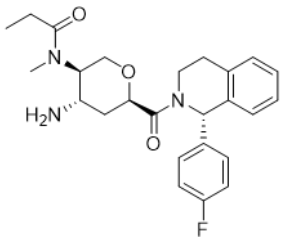
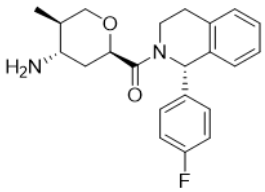
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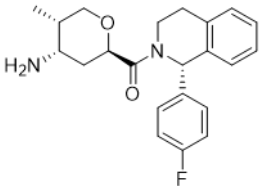
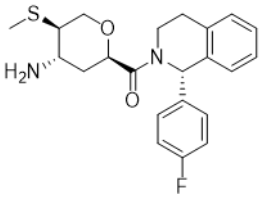
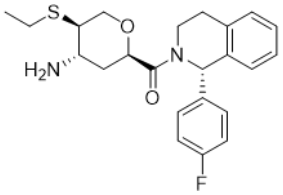
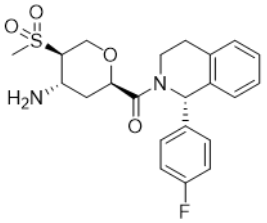
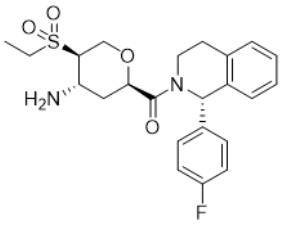
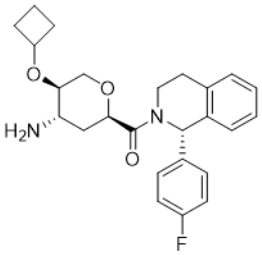
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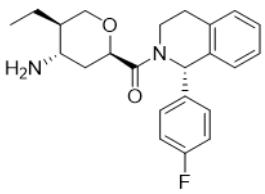
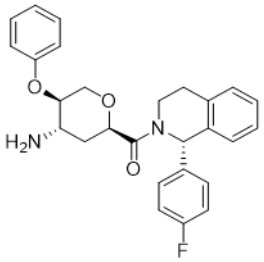
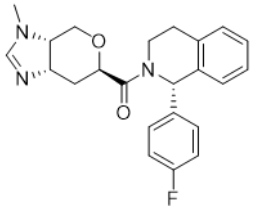
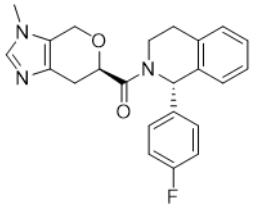
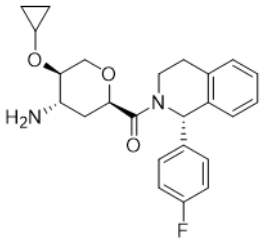
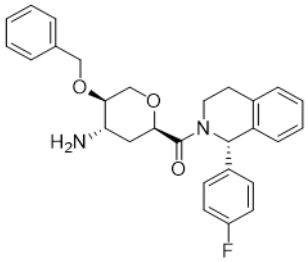
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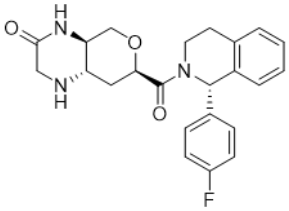
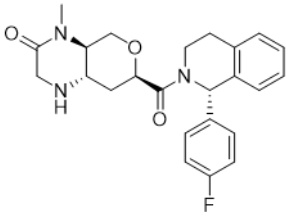
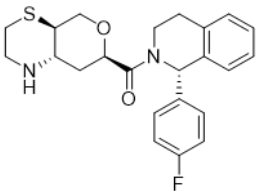
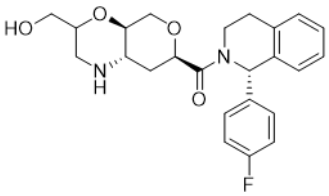
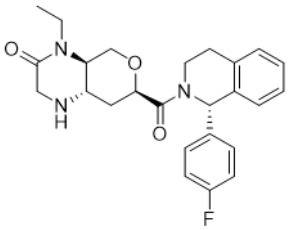
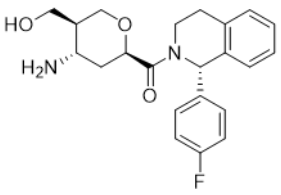
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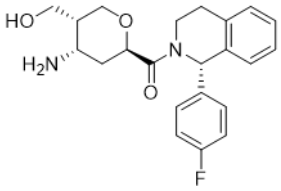
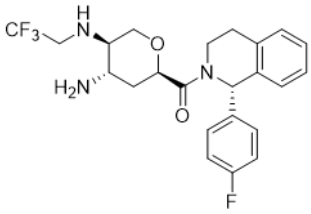
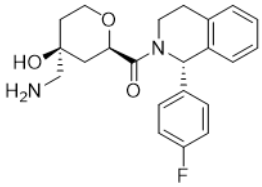
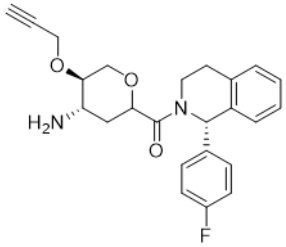
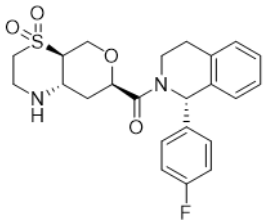
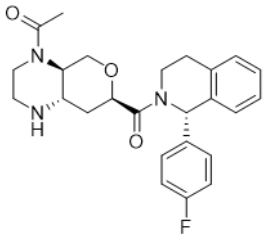
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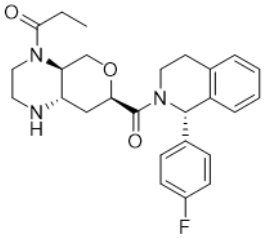
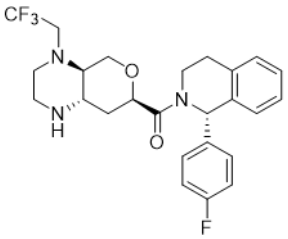
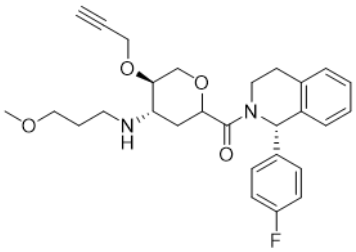
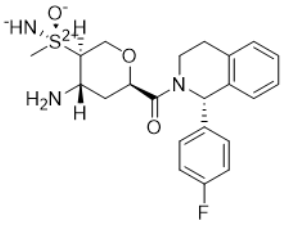
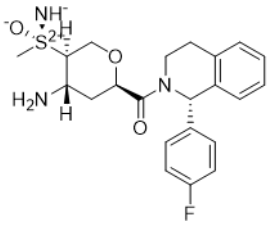
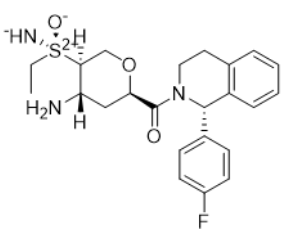
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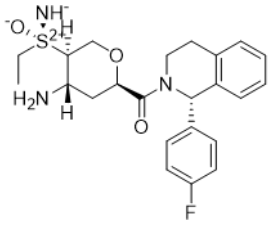
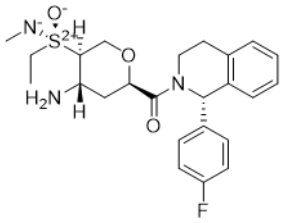
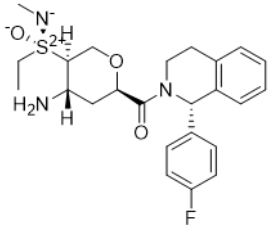
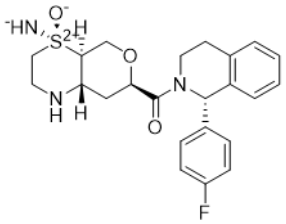
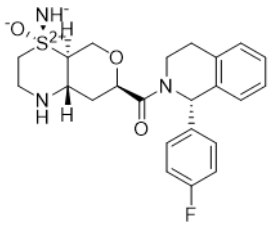
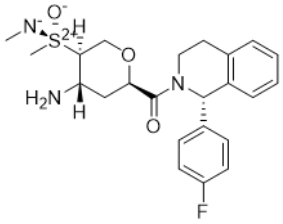
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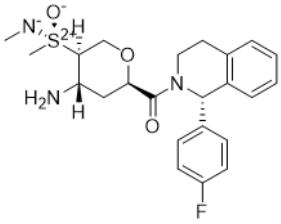
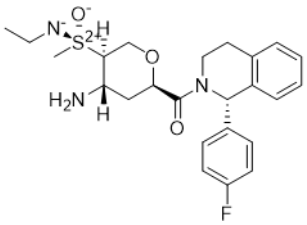
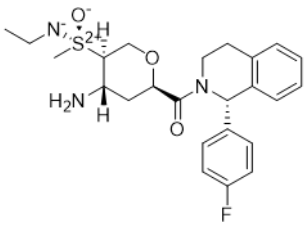
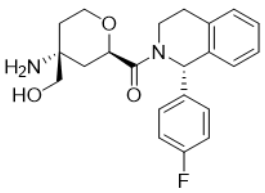
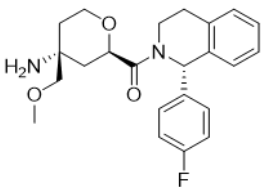
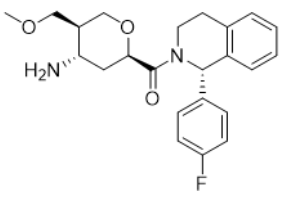
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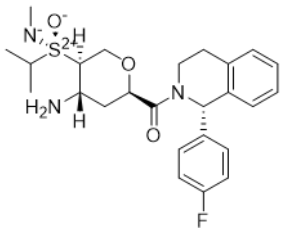
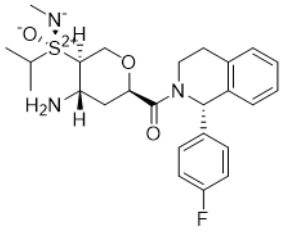
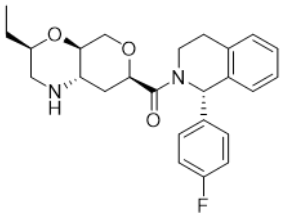
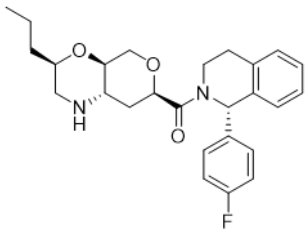
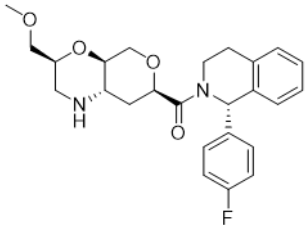
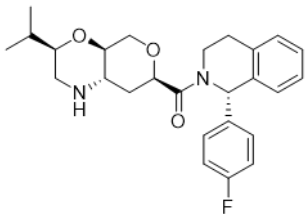
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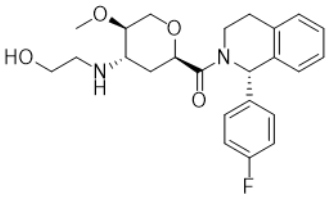
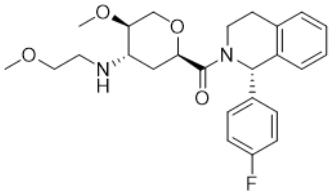
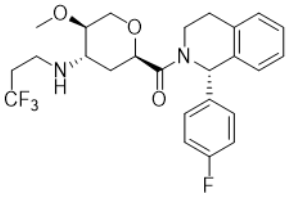
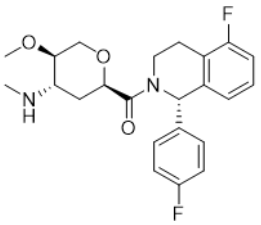
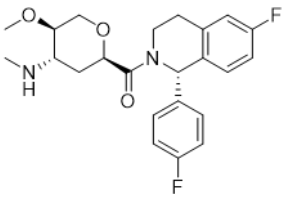
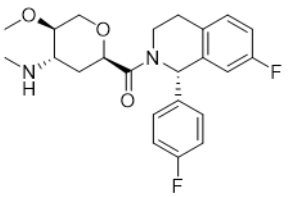
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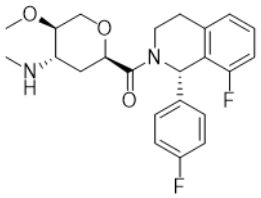
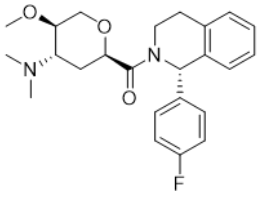
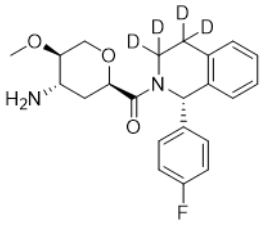
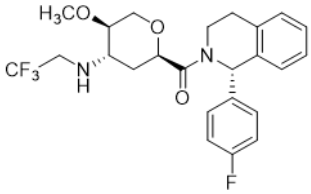
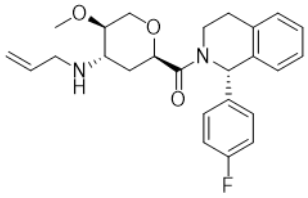
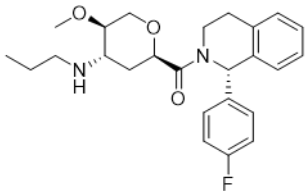
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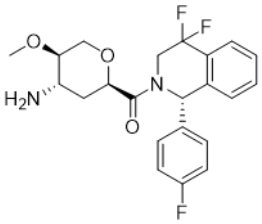
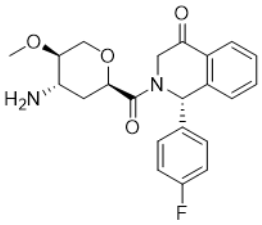
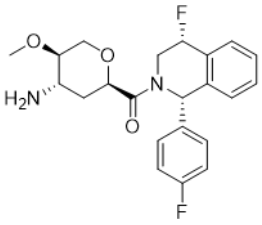
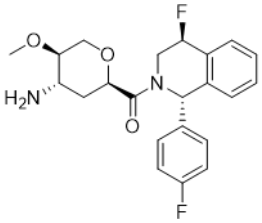
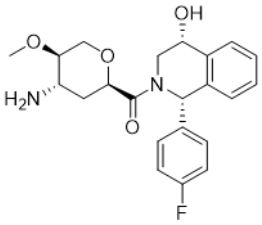
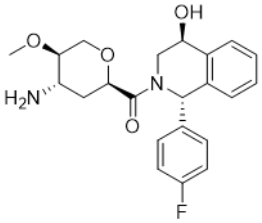
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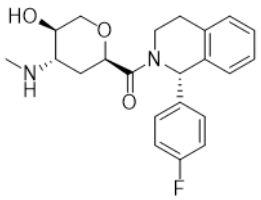
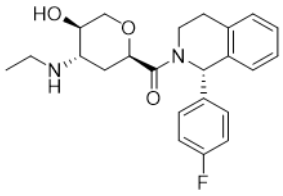
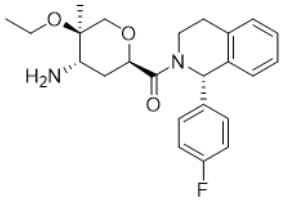
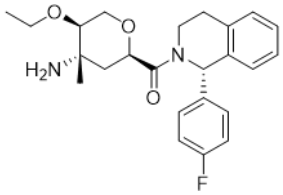
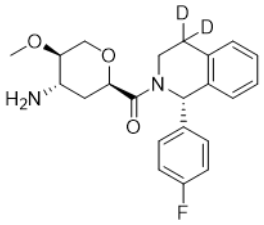
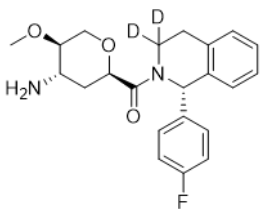
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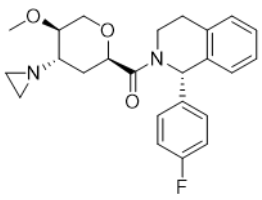
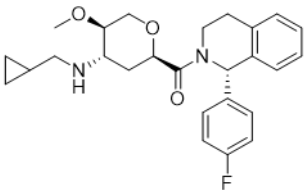
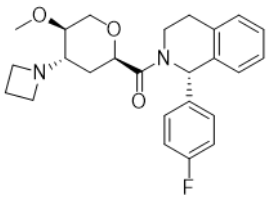
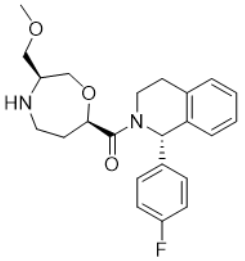
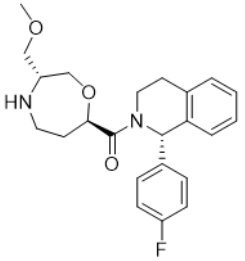
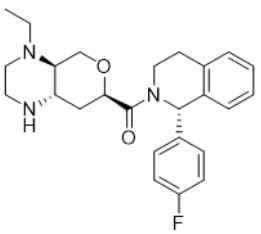
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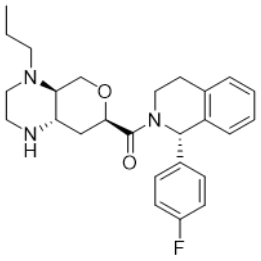
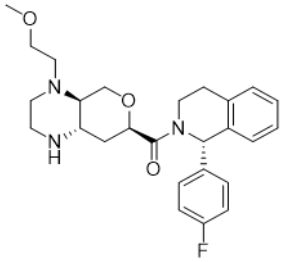
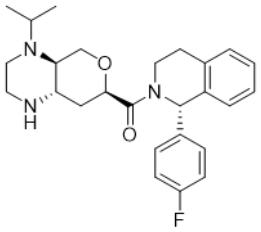
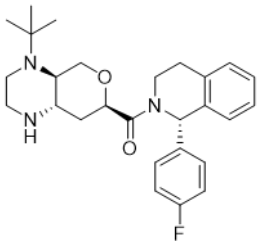
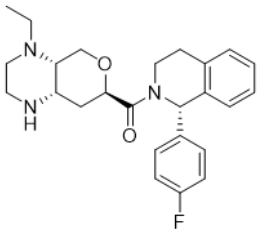
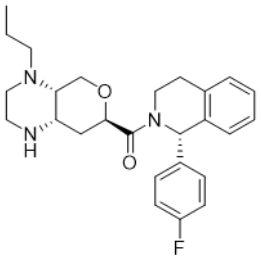
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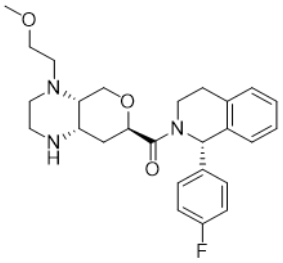
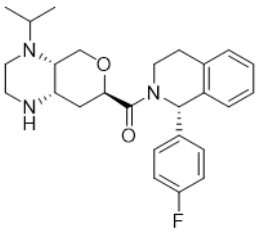
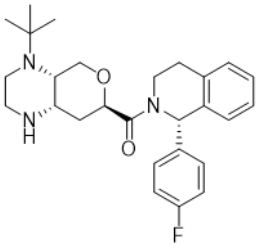
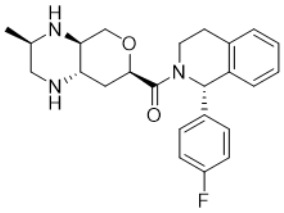
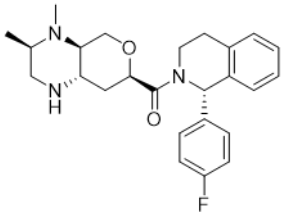
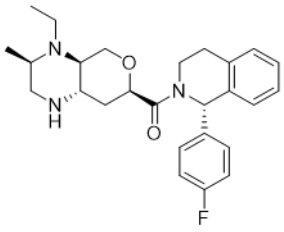
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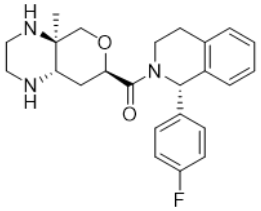
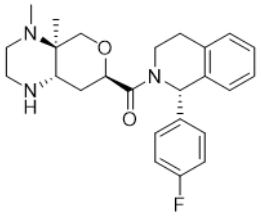
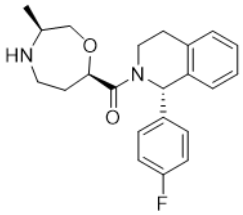
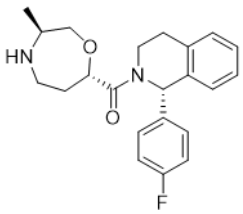
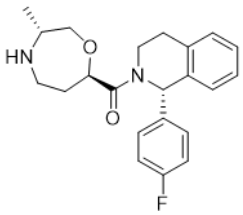
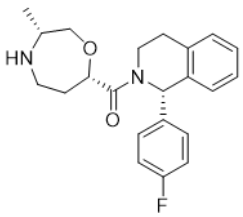
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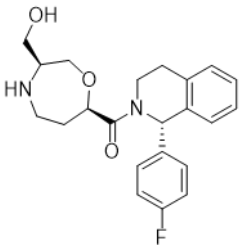
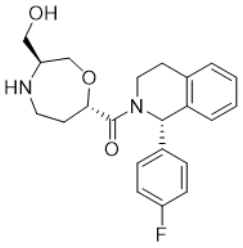
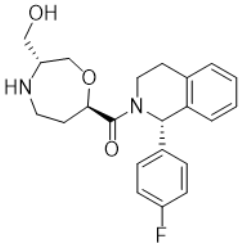
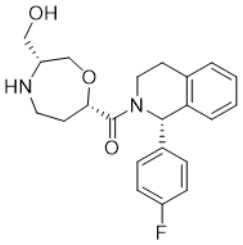
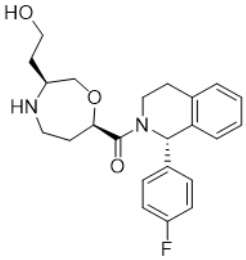
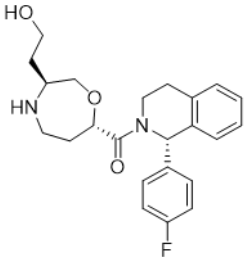
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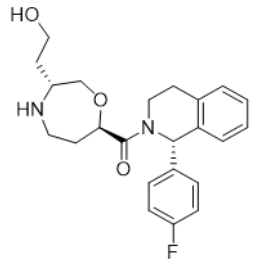
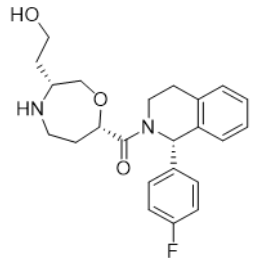
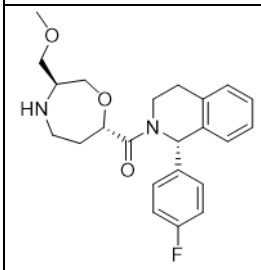
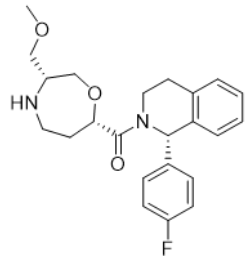
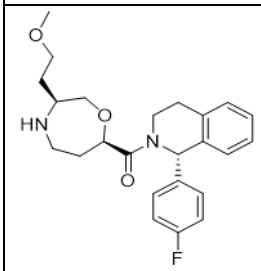
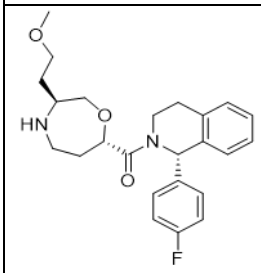
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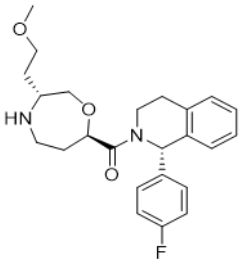
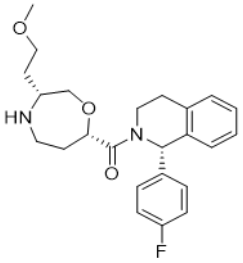
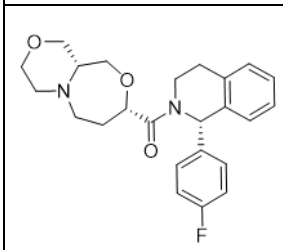
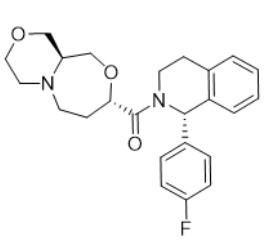
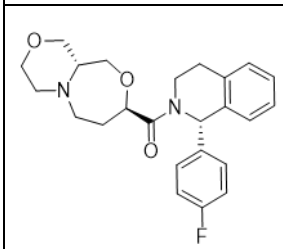
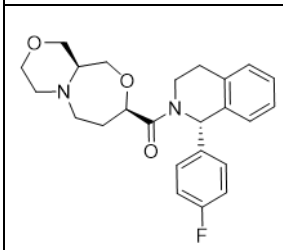
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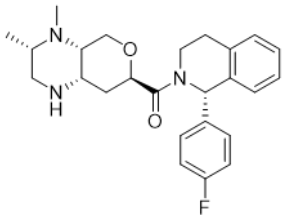
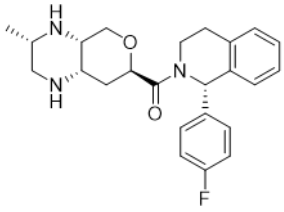
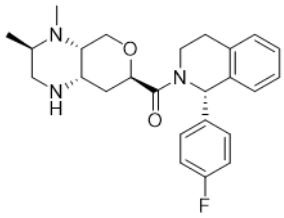
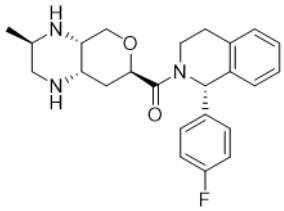
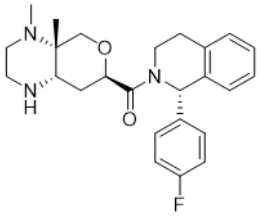
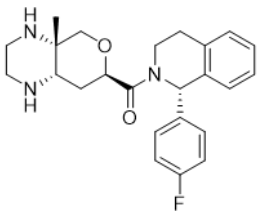
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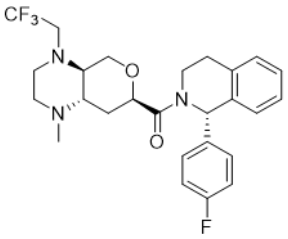
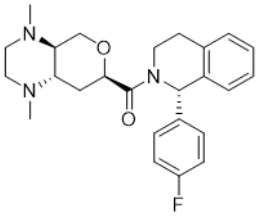
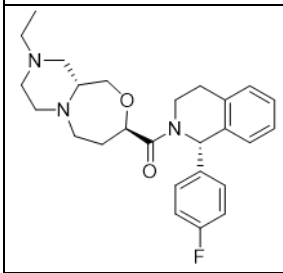
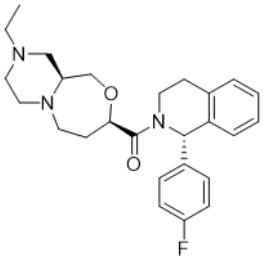
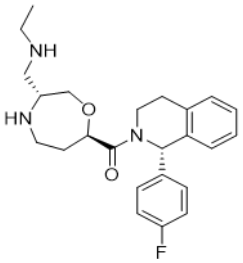
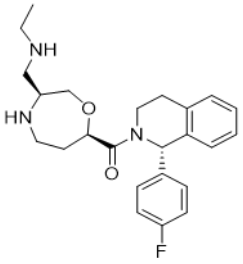
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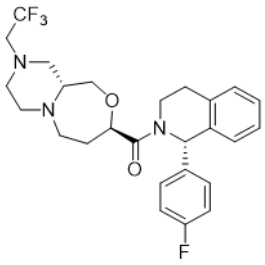
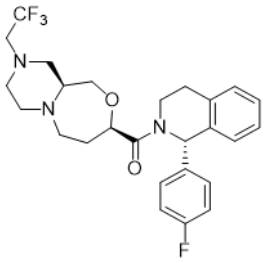
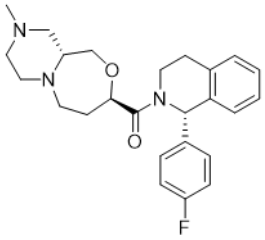
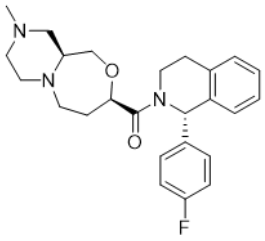
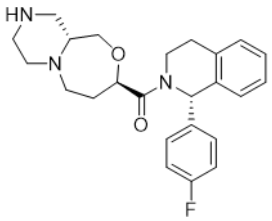
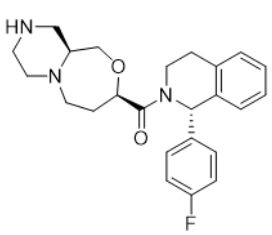
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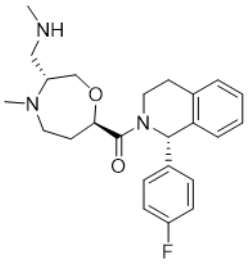
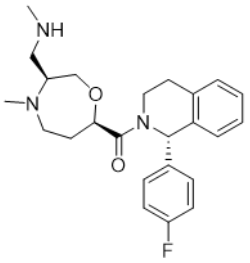
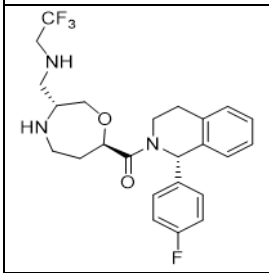
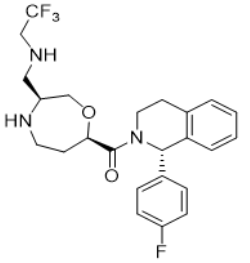
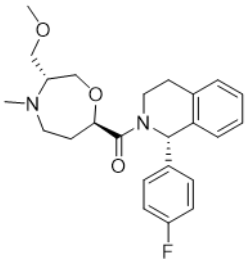
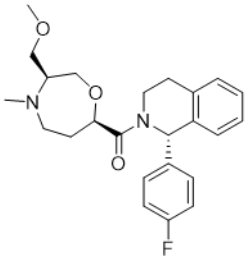
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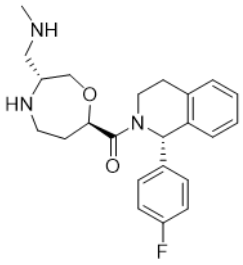
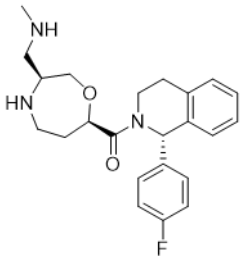
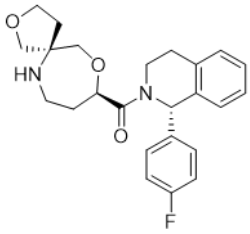
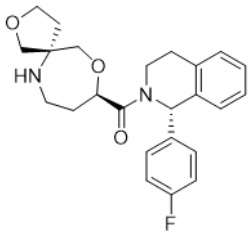
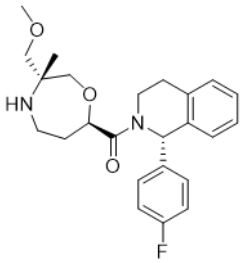
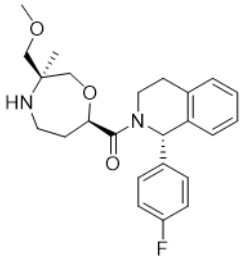
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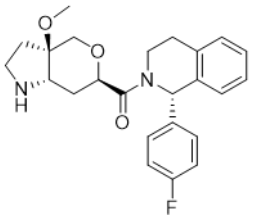
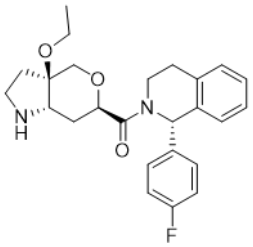
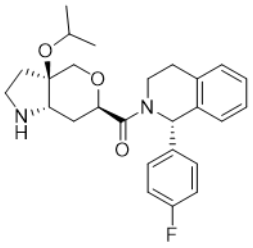
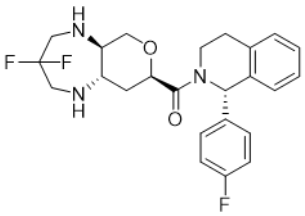
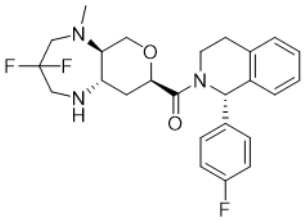
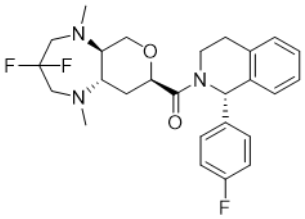
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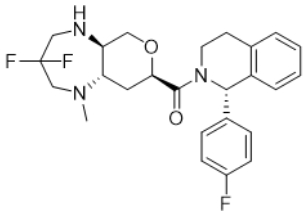
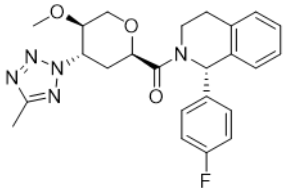
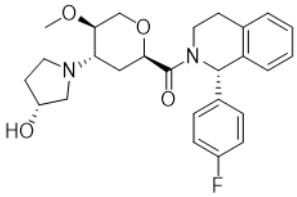
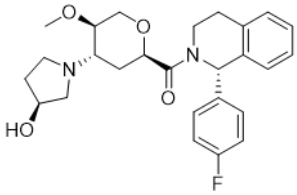
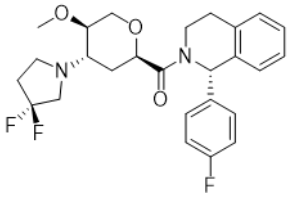
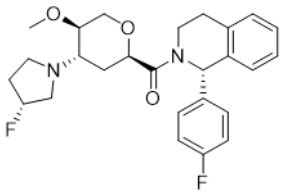
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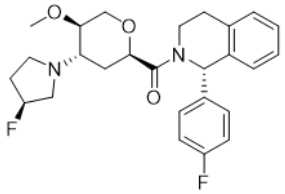
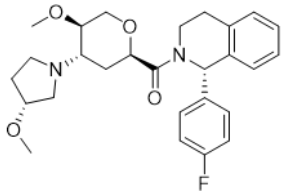
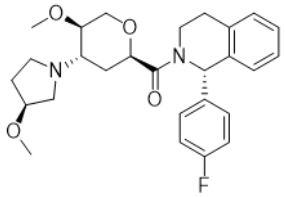
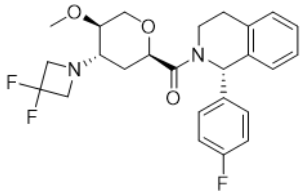
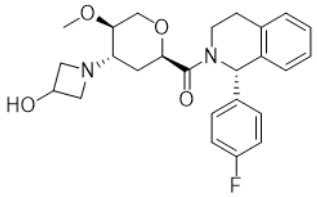
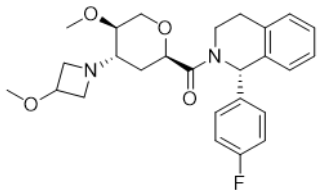
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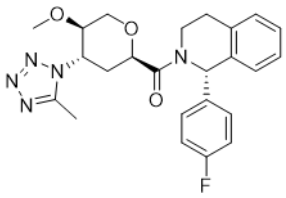
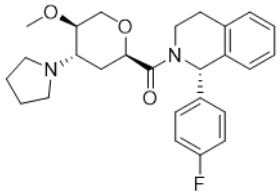
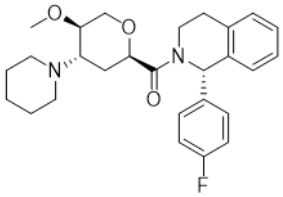
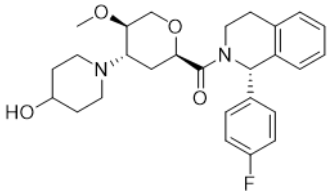
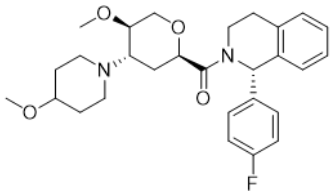
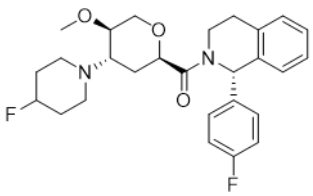
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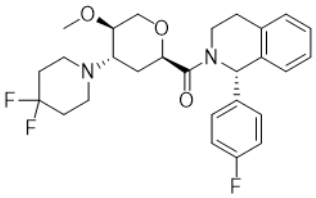
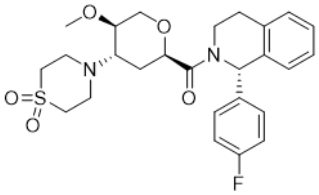
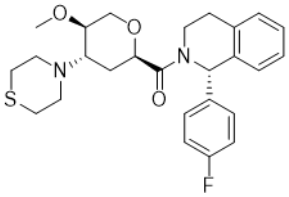
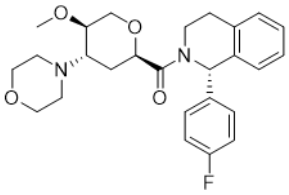
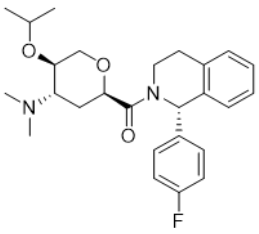
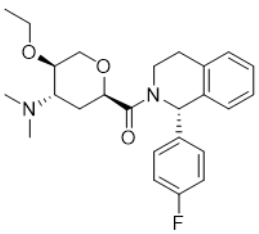
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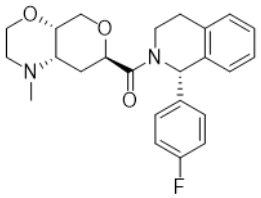
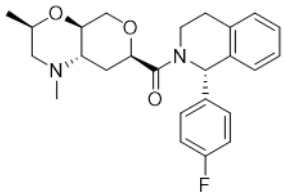
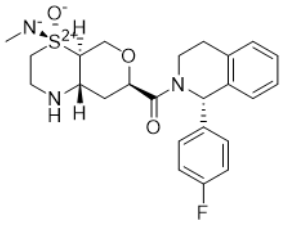
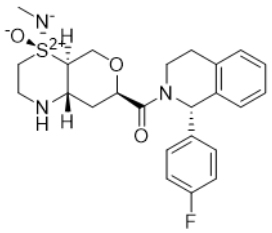
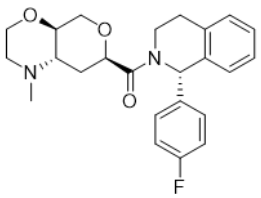
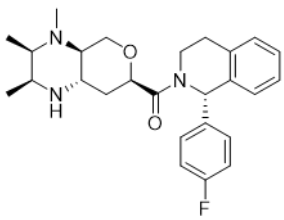
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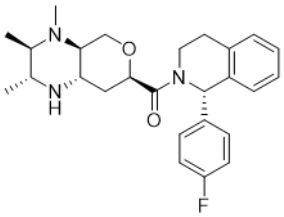
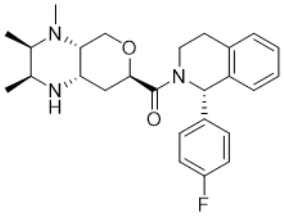
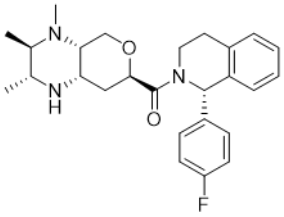
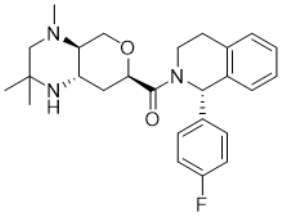
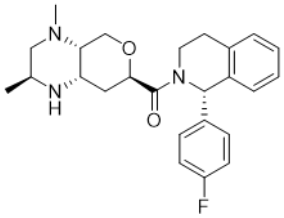
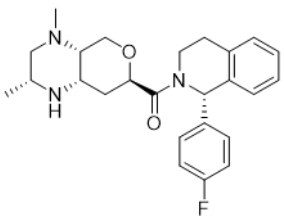
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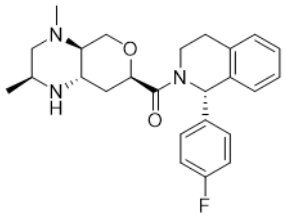
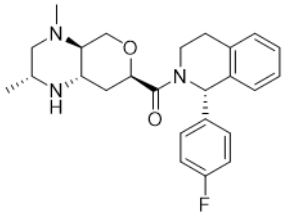
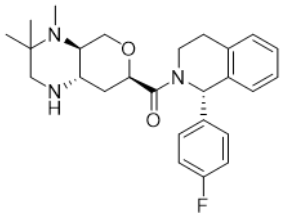
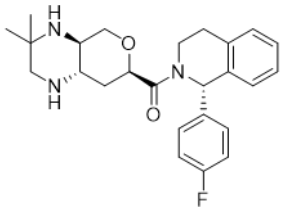
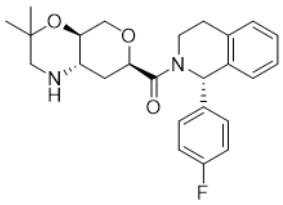
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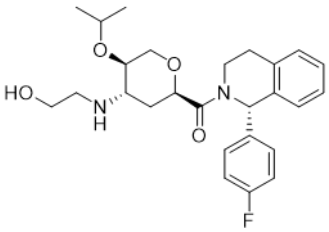
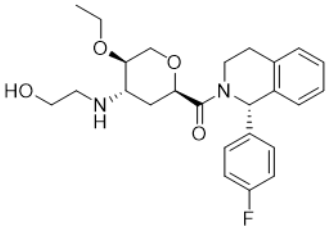
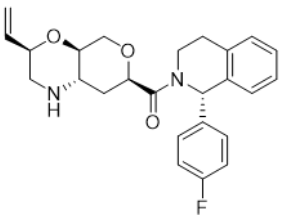
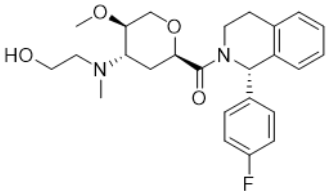
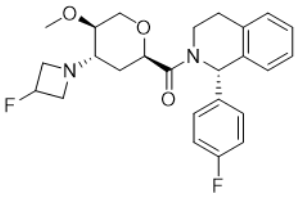
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15. A pharmaceutical composition comprising the compound or salt of any one of claims 1 to 14 and a pharmaceutically acceptable excipient.

16. Use of the compound or salt of any one of claims 1 to 15 in the manufacture of a medicament for treating a progranulin-associated disorder in a subject.

17. The use of claim 16, 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.

18. Use of the compound or salt of any one of claims 1 to 15 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.

19. The use of claim 18, 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;

(ii) the inflammatory disorder is Sjogren disease, inflammatory arthritis, osteoarthritis, inflammatory bowel disease, or immune thrombocytopenia; or

(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.