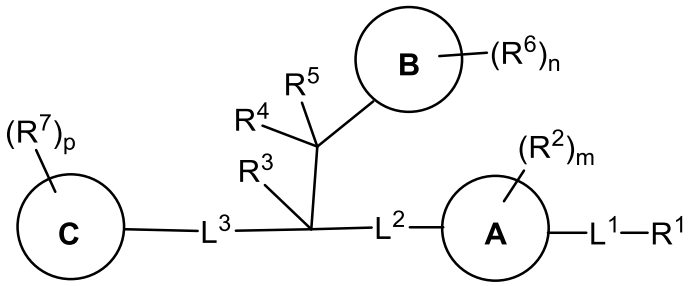
SUMMARY

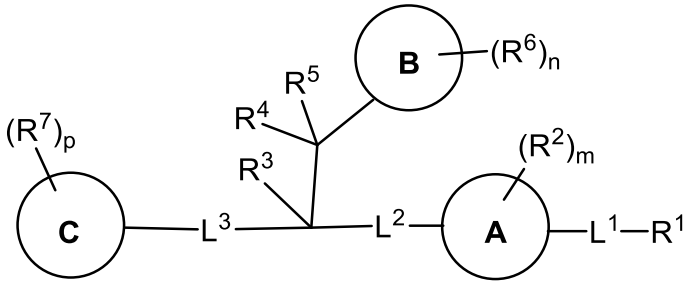
[0007] It has now been found that compounds of this present disclosure, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of USP30. Such compounds have the general formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

[0007a] In an aspect of the present disclosure, there is provided a compound of formula **I'**:



I'

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic aryl or heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

L^1 is $-S(O)_2NH-$, $-S(O)NH-$, $-S(O)-$, $-S(O)(N\text{-}t\text{-}Bu)-$, or $-C(CF_3)(H)NH-$;

each R is independently hydrogen or an optionally substituted C_{1-3} aliphatic group;

R^1 is an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered saturated or partially unsaturated bridged bicyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^2 is independently halogen, $–CF_3$, –CN, –C(O)NHR, $–NO_2$, –NHR, –NHC(O)R, $–NHS(O)_2R$, $–N(R)_2$, or –OR, or a C_{1-6} aliphatic group; or

L^2 is–C(O)N(R')–;

R' is hydrogen or a C_{1-3} aliphatic group;

L^3 is–C(O)N(R")–;

R" is hydrogen or a C_{1-3} aliphatic group;

R^3 is hydrogen or a C_{1-3} aliphatic;

R^4 is hydrogen;

R^5 is hydrogen;

Ring B is phenyl;

each R^6 is independently halogen, –CN, $–NO_2$, –NHR, $–N(R)_2$, –OR, or an optionally substituted C_{1-6} aliphatic group;

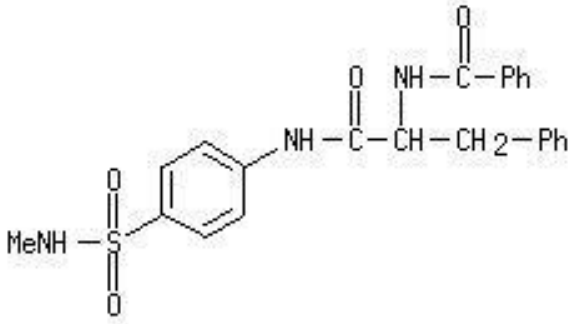
Ring C is phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen and oxygen, or an 8-10 membered bicyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^7 is independently halogen, –CN, $–NO_2$, –NHR, $–N(R)_2$, –OR, or a C_{1-6} aliphatic group; and

each of m, n, and p is independently 0, 1, 2, 3 or 4;

provided that R^1 is other than isopropyl, t-butyl, 1-methylcyclopropyl, 1-fluoromethylcyclopropyl, 1-difluoromethylcyclopropyl, 1-trifluoromethylcyclopropyl, or 3-methyl-3-oxetanyl when L^1 is $–S(O)_2N(H)$-;

R^1 is other than ethyl when L^1 is $–S(O)_2N(H)$- and Ring A is naphthyl; and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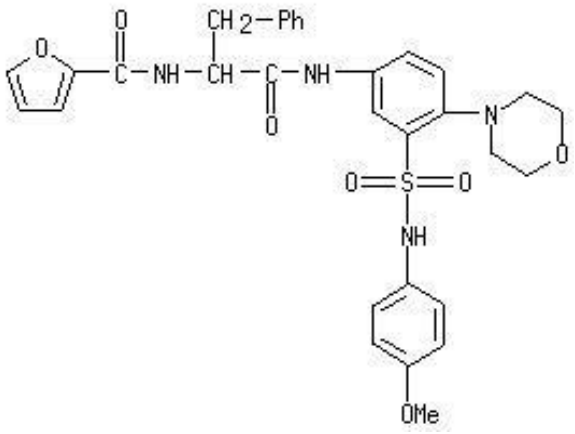
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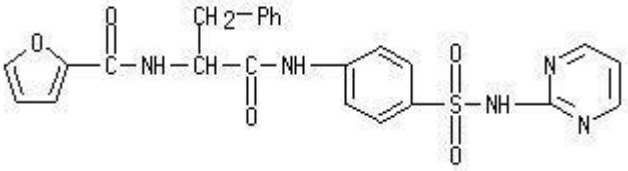
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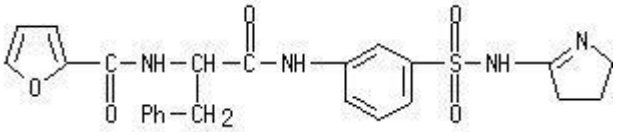
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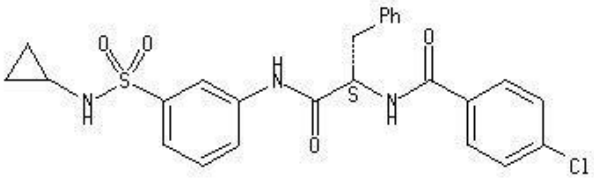
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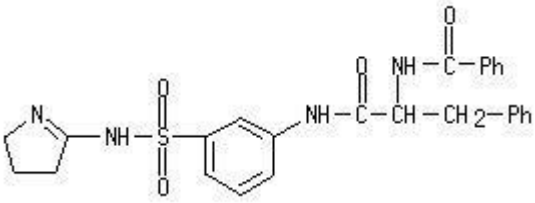
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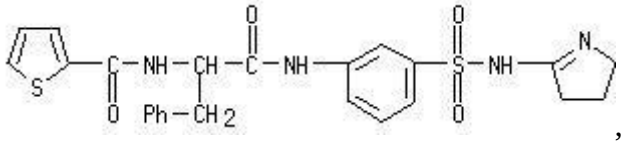
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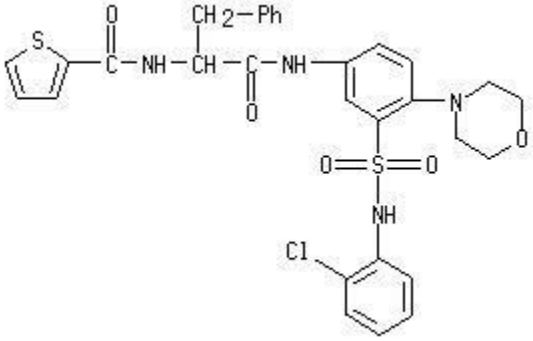
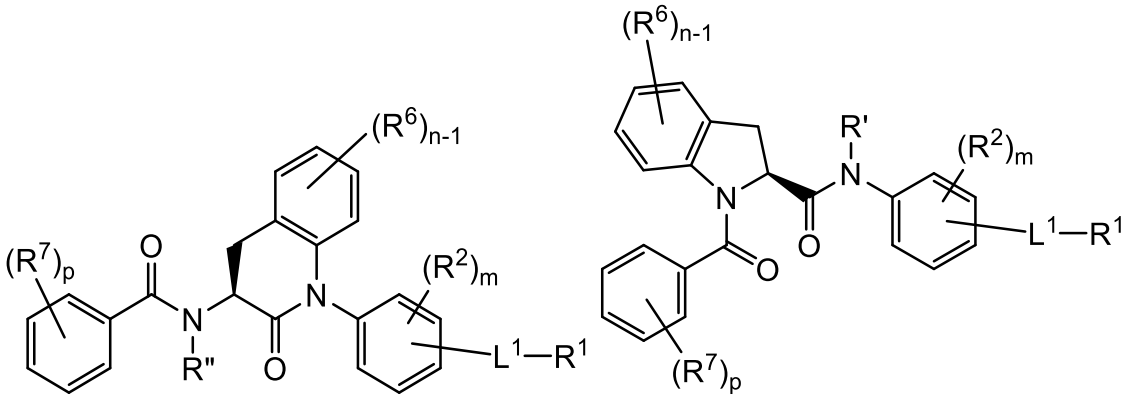
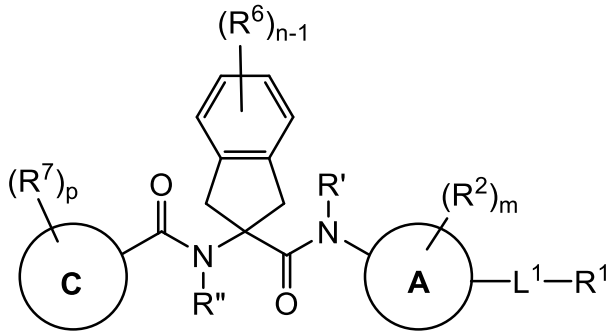

and .

[0007b] In another aspect of the present disclosure, there is provided a compound that is one of the following formulae or a pharmaceutically acceptable salt thereof:

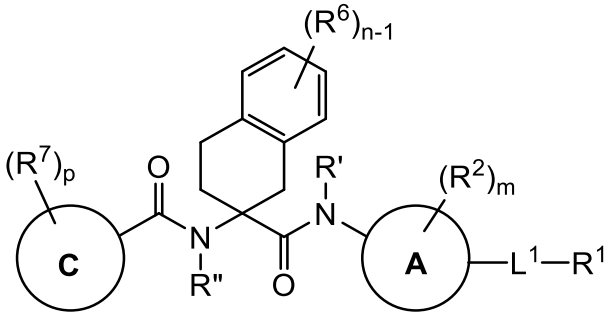


5e

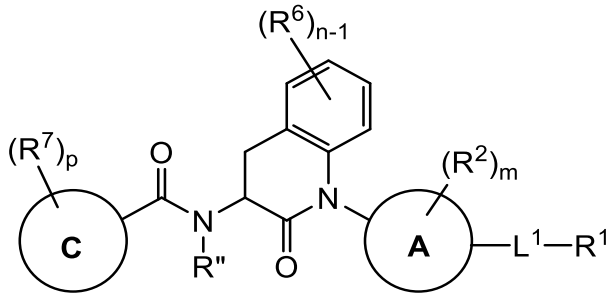
VII-a



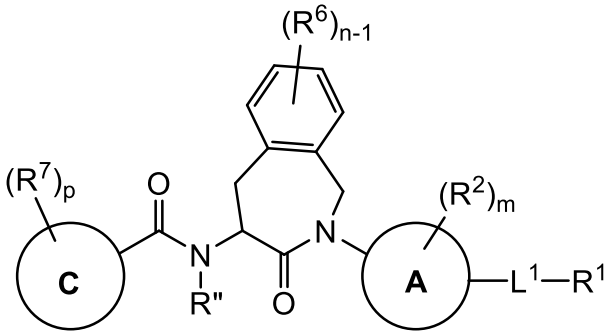
VII-b



VIII



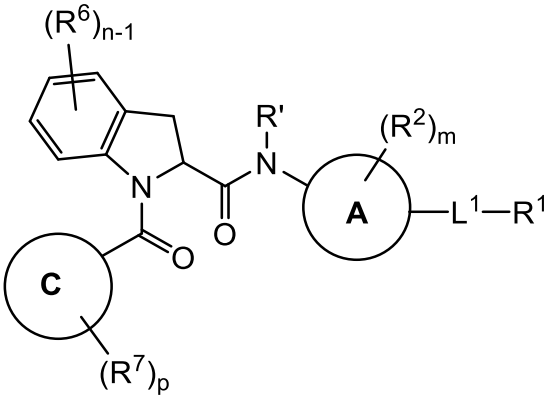
IX

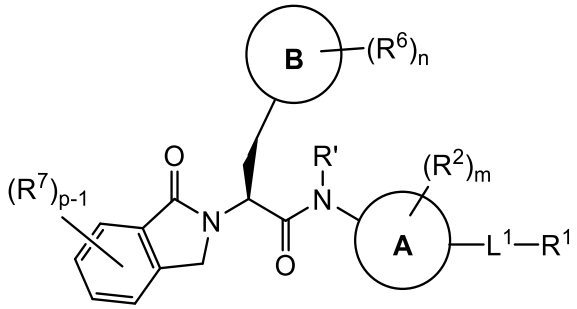


X

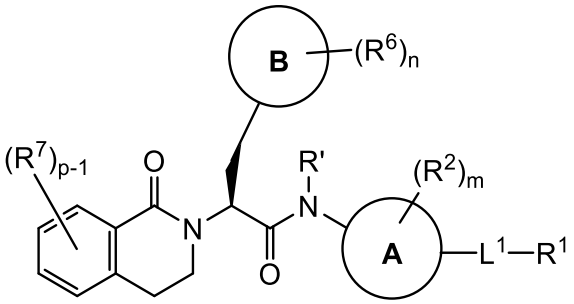
XI

XII





or



XIV-a **XIV-b**

wherein:

L^1 is–N(R)C(O)–, –S(O)–,–S(O)N(R)–, or –$S(O)_2$N(R)–;

each R is independently hydrogen or an optionally substituted C_{1-3} aliphatic group;

R^1 is an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered saturated or partially unsaturated bridged bicyclic carbocyclic ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^2 is independently halogen, –CF_3, –CN, –C(O)NHR, –NO_2, –NHR, –NHC(O)R, –$NHS(O)_2R$, –$N(R)_2$, or –OR, or a C_{1-6} aliphatic group;

R' is hydrogen or a C_{1-3} aliphatic group;

R" is hydrogen or a C_{1-3} aliphatic group;

each R^6 is independently halogen, –CN, –NO_2, –NHR, –$N(R)_2$, –OR, or an optionally substituted C_{1-6} aliphatic group;

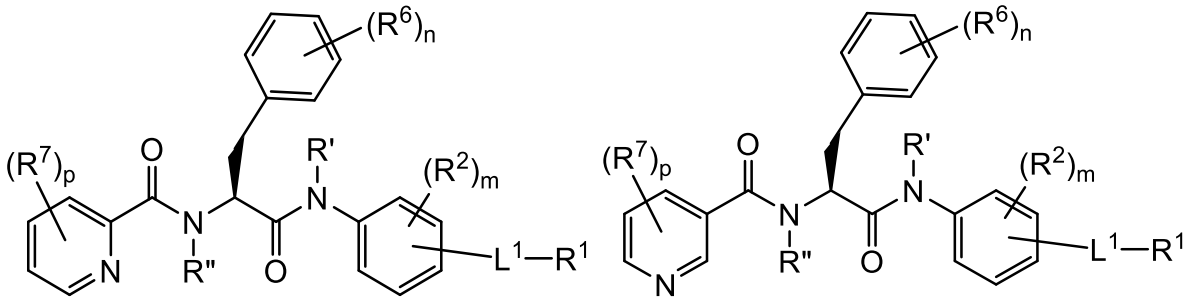
each R^7 is independently halogen, –CN, –NO_2, –NHR, –$N(R)_2$, –OR, or a C_{1-6} aliphatic group;

each of m and p is independently 0, 1, 2, 3, or 4; and

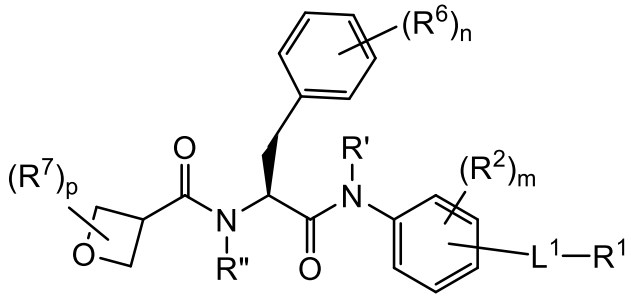
n is 0;

provided that R^1 is other than isopropyl, *t*-butyl, 1-methylcyclopropyl, 1-fluoromethylcyclopropyl, 1-difluoromethylcyclopropyl, 1-trifluoromethylcyclopropyl, or 3-methyl-3-oxetanyl when L^1 is –$S(O)_2$N(R)-.

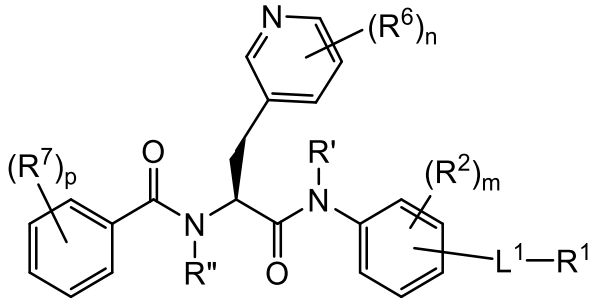
[0007c] In a further aspect of the present disclosure, there is provided a compound of any one of formulas **XV-a**, **XV-b**, **XV-c**, **XV-d**, **XVII-a**, **XVII-b**, **XVII-c**, **XVII-d**, **XIX-a**, **XIX-b**, **XIX-c**, **XIX-d**, **XXI**, **XXIII-a**, **XXIII-b**, **XXV-a**, **XXV-b**, **XXV-c**, or **XXV-d**:



XV-a



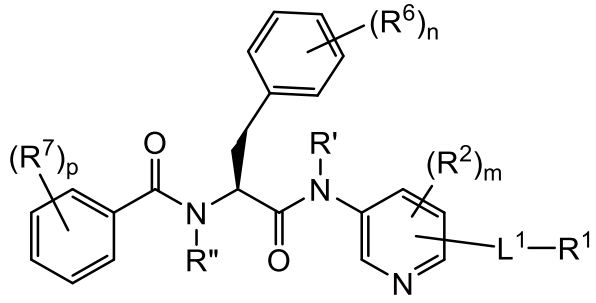
XV-b



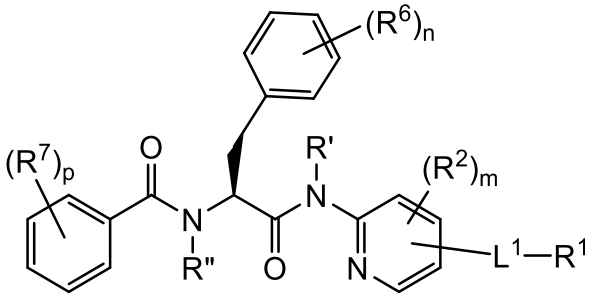
XV-c

XV-d

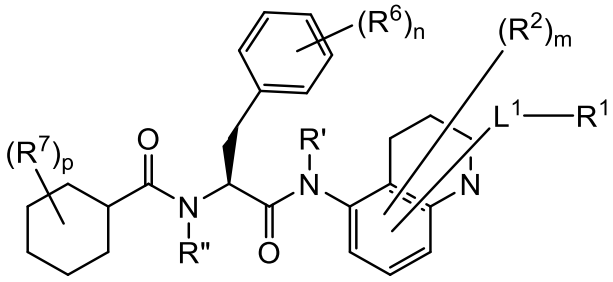
XVII-a



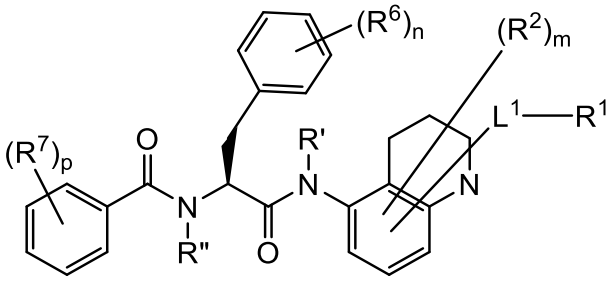
XVII-b



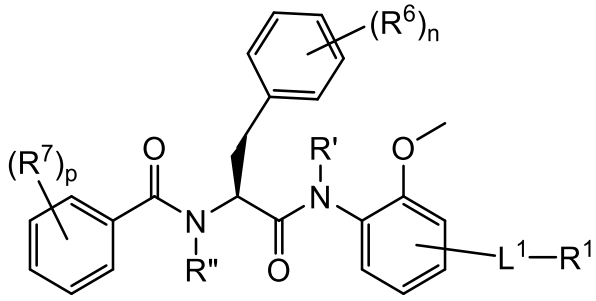
XVII-c



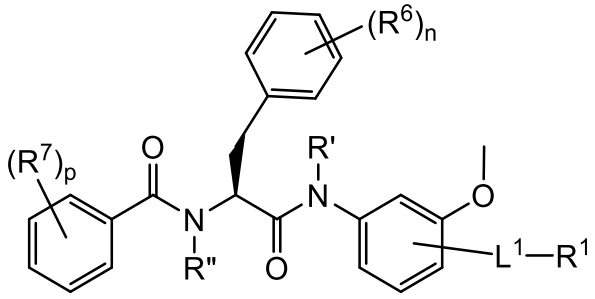
XVII-d

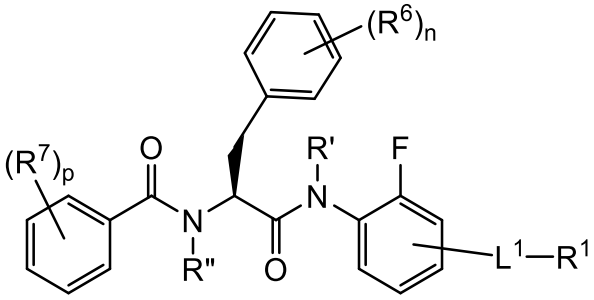


XIX-a

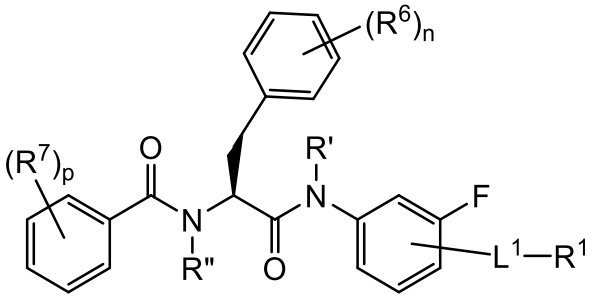


XIX-b

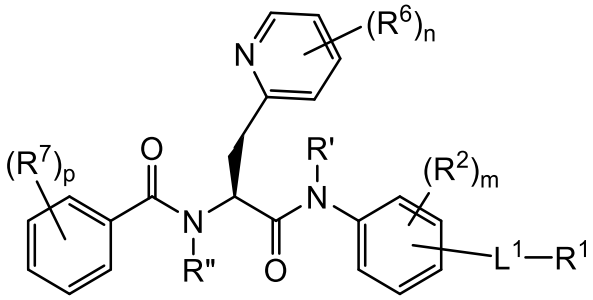




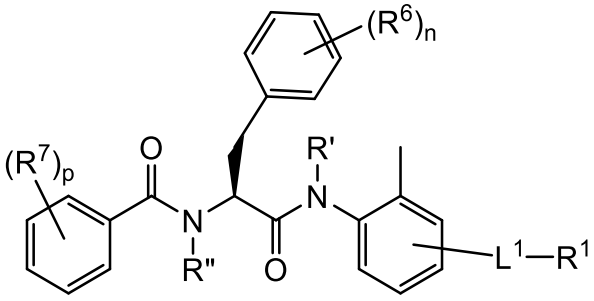
XIX-c



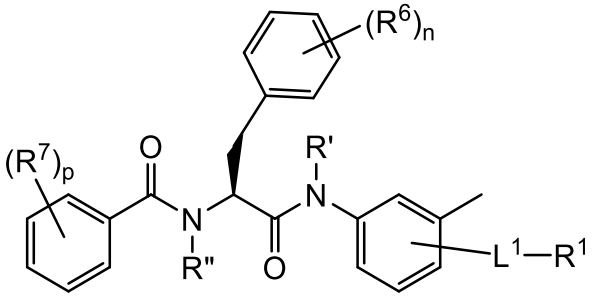
XIX-d



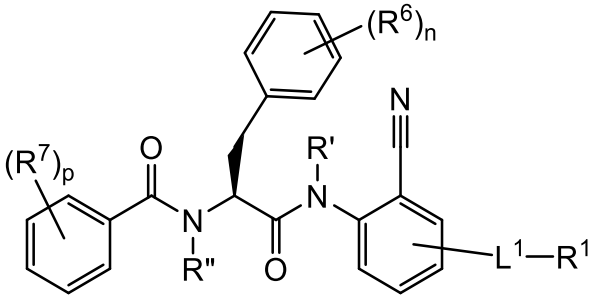
XXI



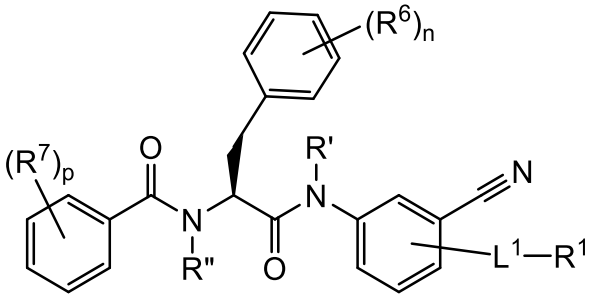
XXIII-a



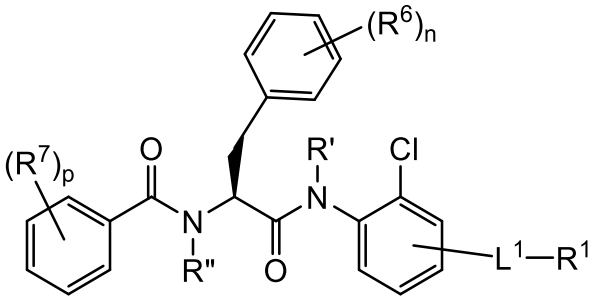
XXIII-b



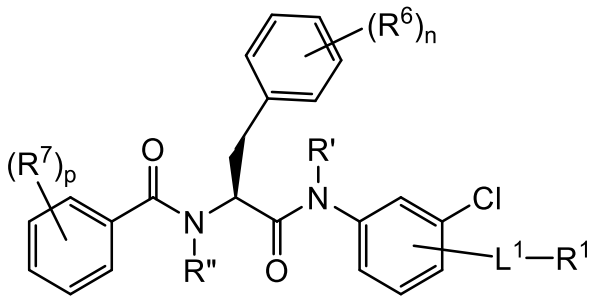
XXV-a



XXV-b



XXV-c



XXV-d

or a pharmaceutically acceptable salt thereof, wherein:

L^1 is–N(R)C(O)–, –S(O)–, –S(O)N(R)–, or $–S(O)_2N(R)–$;

each R is independently hydrogen or an optionally substituted C_{1-3} aliphatic group;

R^1 is an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered saturated or partially unsaturated bridged bicyclic carbocyclic ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^2 is independently halogen, $–CF_3$, –CN, –C(O)NHR, $–NO_2$, –NHR, –NHC(O)R, $–NHS(O)_2R$, $–N(R)_2$, or –OR, or a C_{1-6} aliphatic group;

R' is hydrogen or a C_{1-3} aliphatic group;

R" is hydrogen or a C_{1-3} aliphatic group;

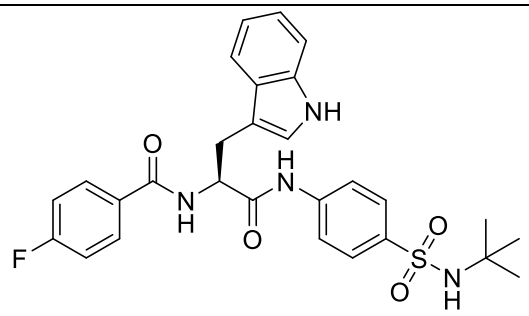
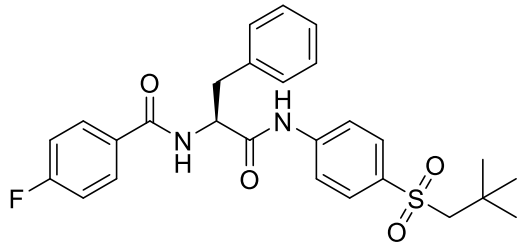
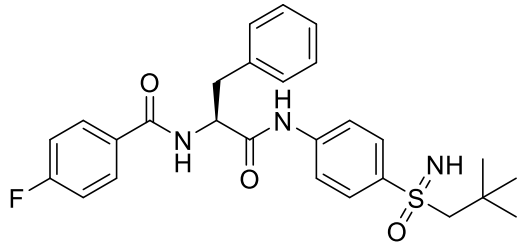
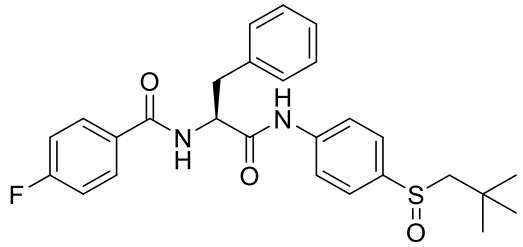
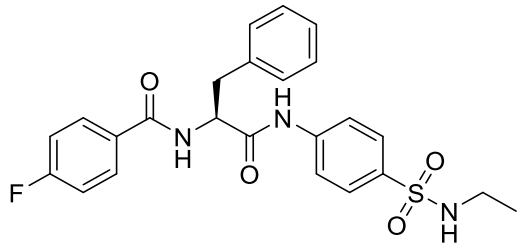
each R^6 is independently halogen, –CN, $–NO_2$, –NHR, $–N(R)_2$, –OR, or an optionally substituted C_{1-6} aliphatic group;

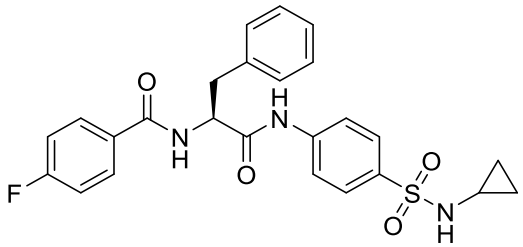
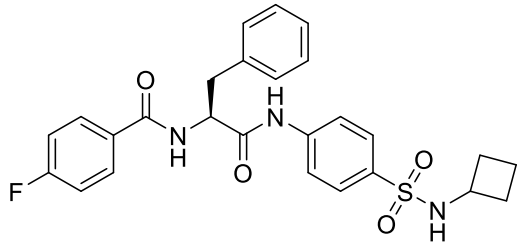
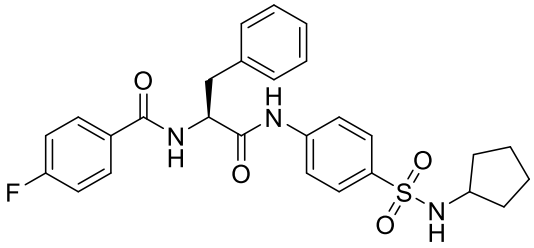
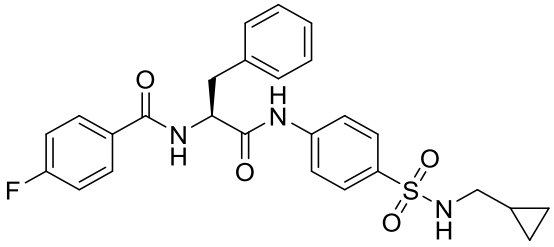
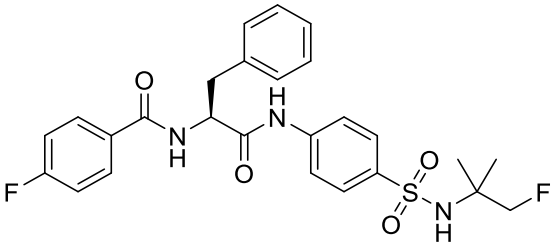
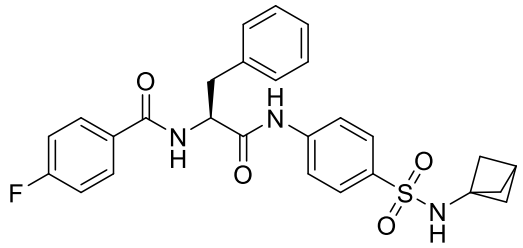
each R^7 is independently halogen, –CN, $–NO_2$, –NHR, $–N(R)_2$, –OR, or a C_{1-6} aliphatic group; and

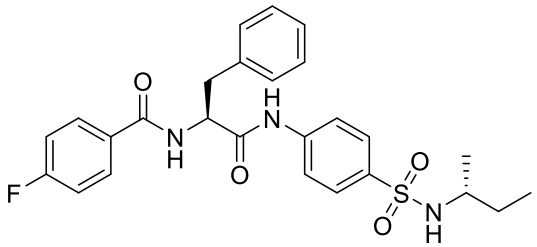
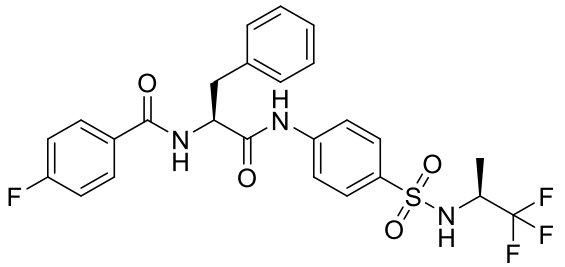
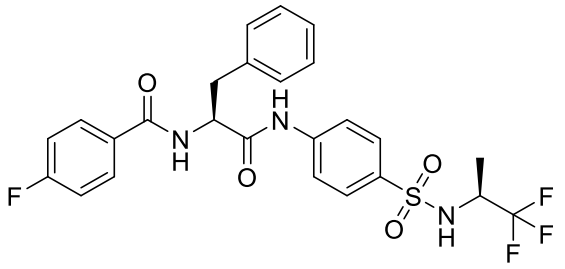
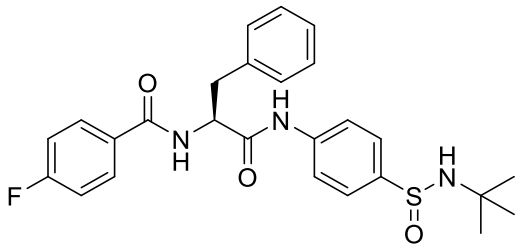
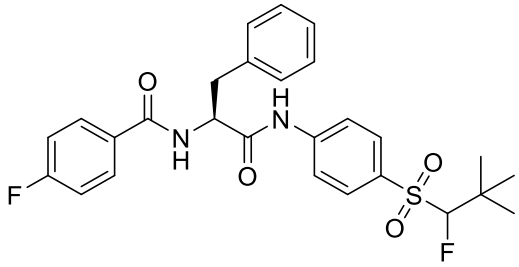
each of m, n, and p is independently 0, 1, 2, 3 or 4;

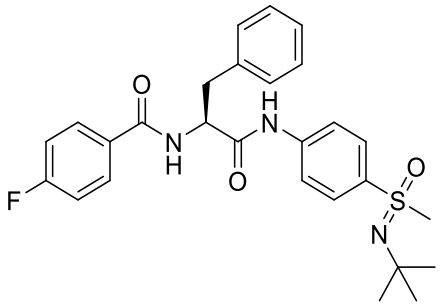
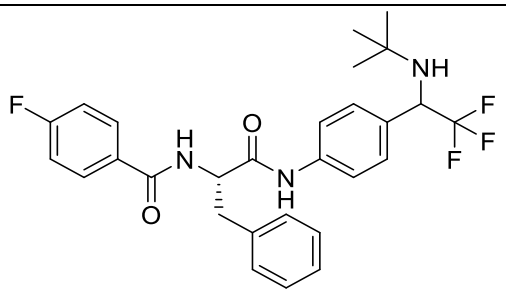
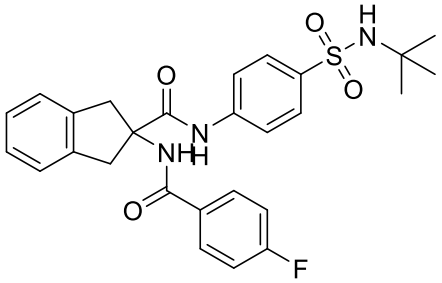
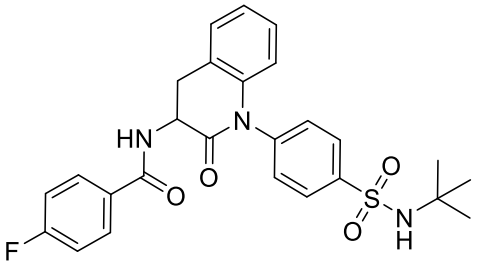
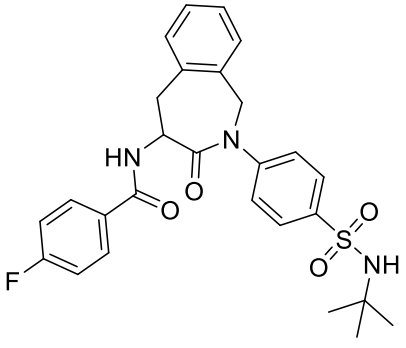
provided that R^1 is other than isopropyl, t-butyl, 1-methylcyclopropyl, 1-fluoromethylcyclopropyl, 1-difluoromethylcyclopropyl, 1-trifluoromethylcyclopropyl, or 3-methyl-3-oxetanyl when L^1 is $–S(O)_2N(R)$-.

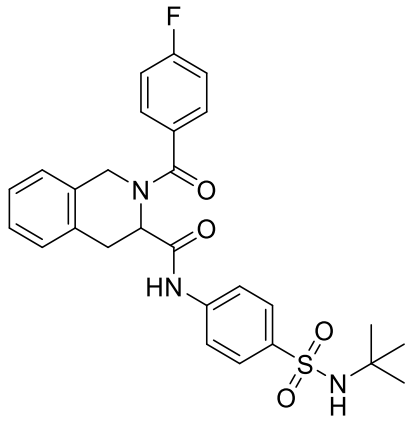
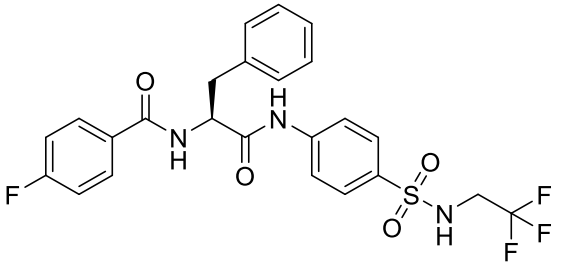
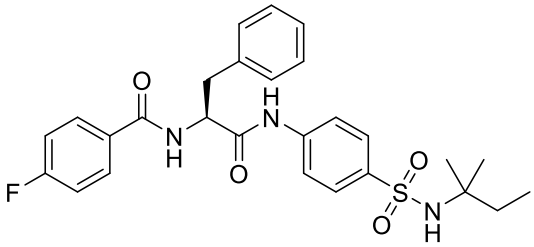
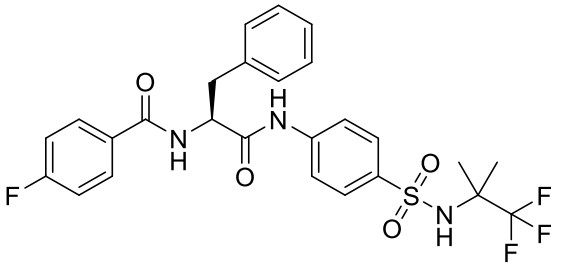
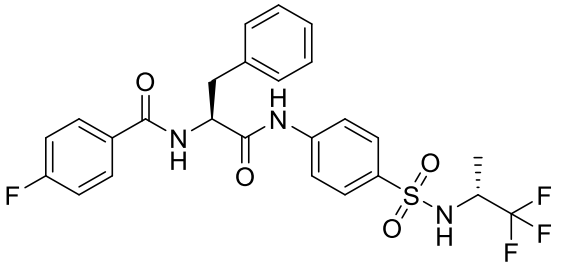
[0007d] In another aspect of the present disclosure, there is provided a compound selected from:

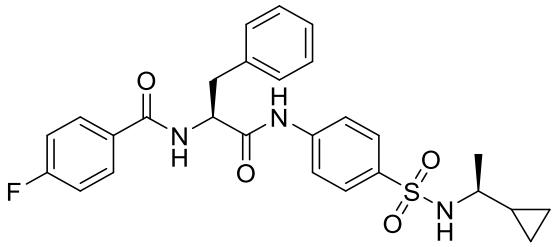
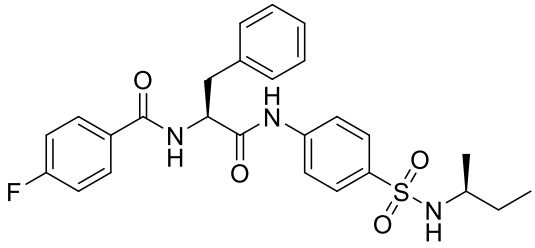
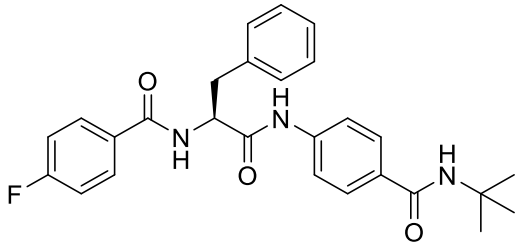
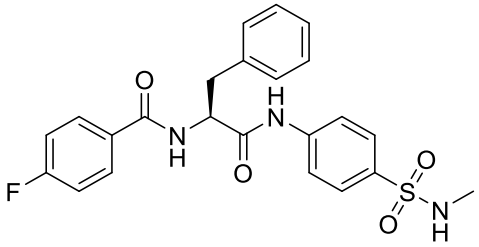
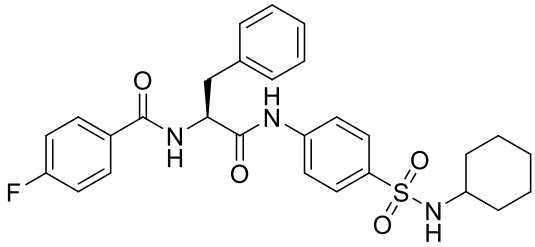
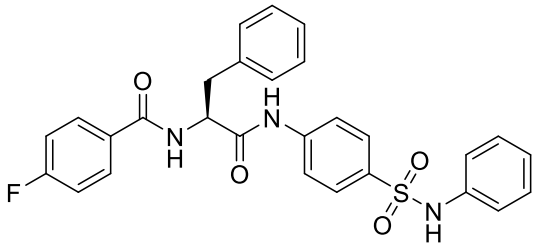
Compound	Structure
I-1	
I-2	
I-3	
I-4	
I-5	

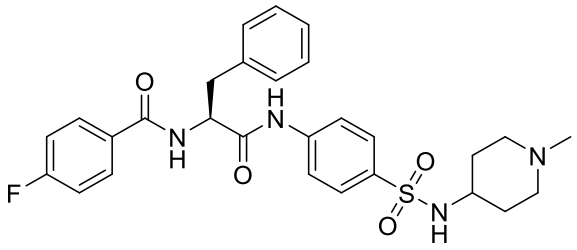
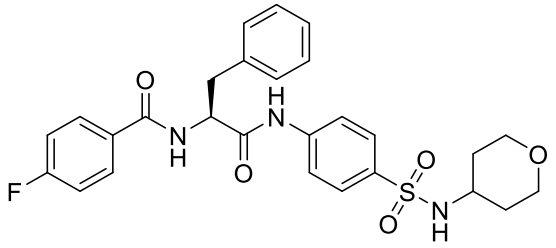
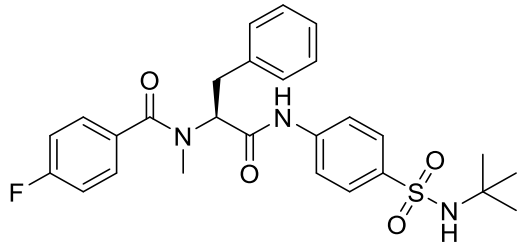
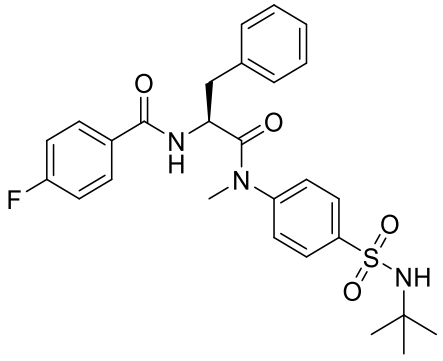
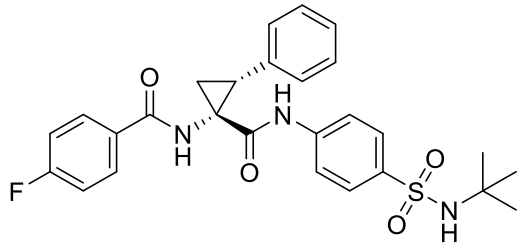
I-6	
I-7	
I-8	
I-9	
I-10	
I-11	

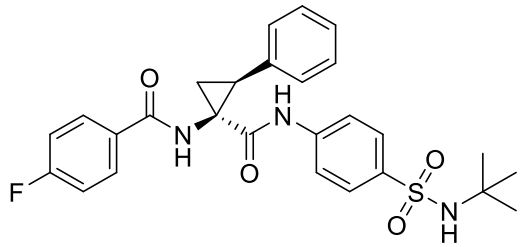
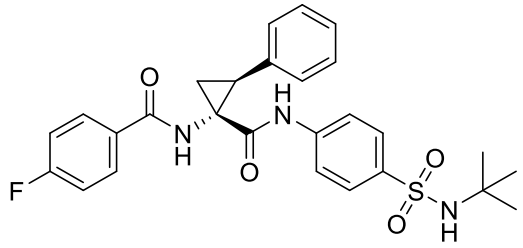
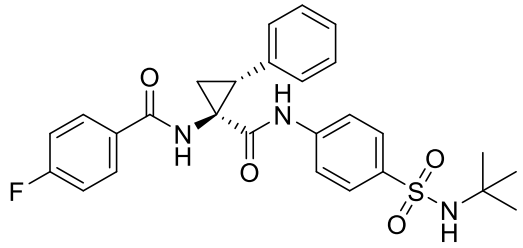
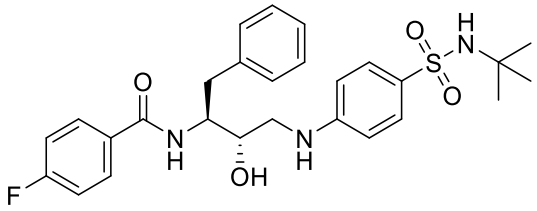
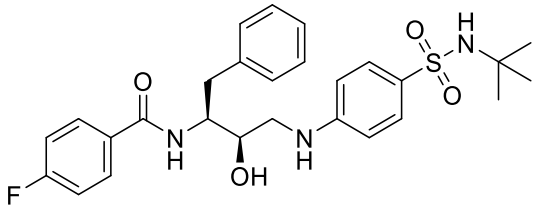
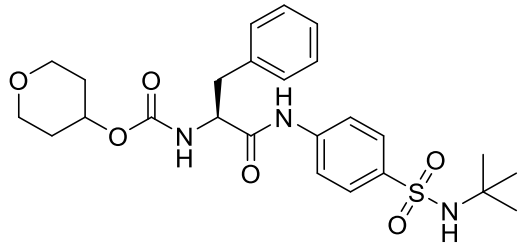
I-12	
I-13	
I-14	
I-15	
I-16	

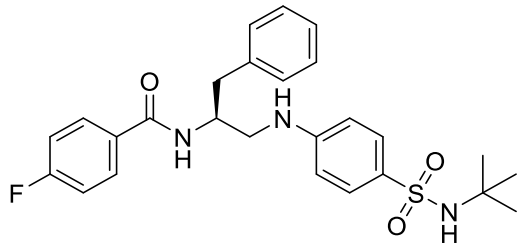
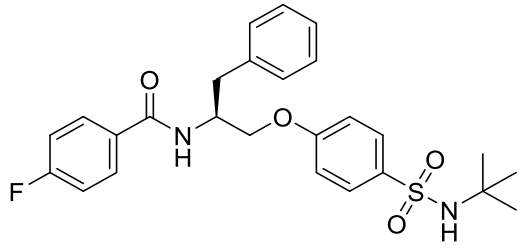
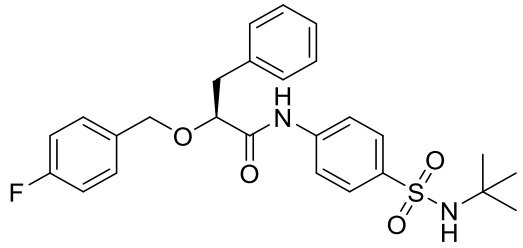
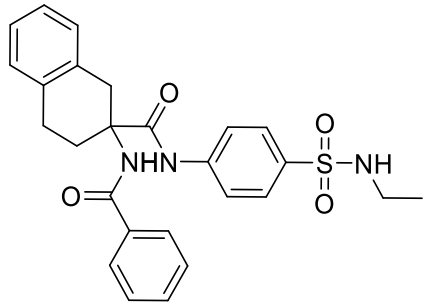
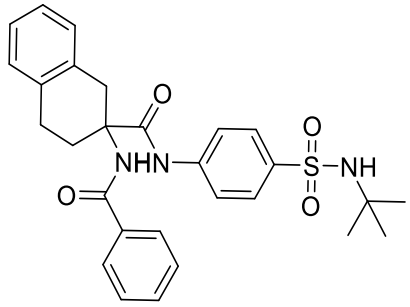
I-17	
I-18	
I-19	
I-20	
I-21	

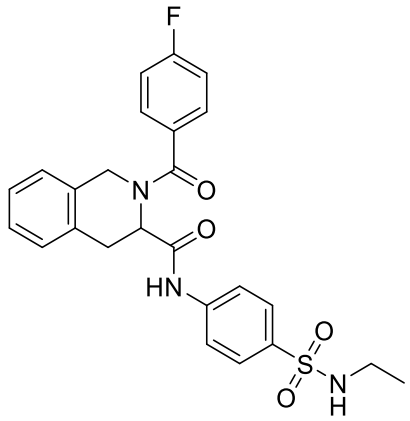
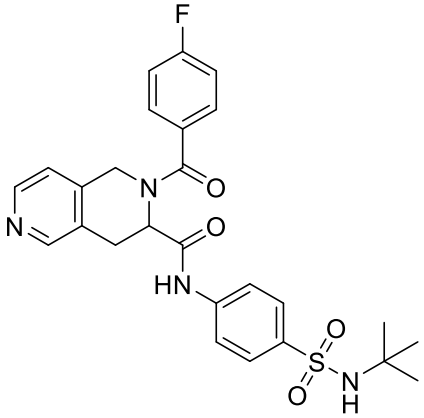
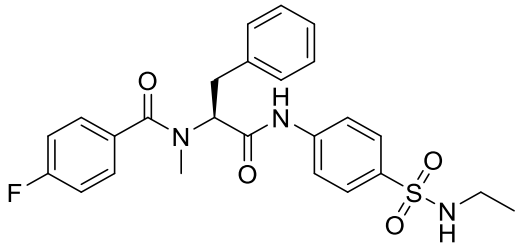
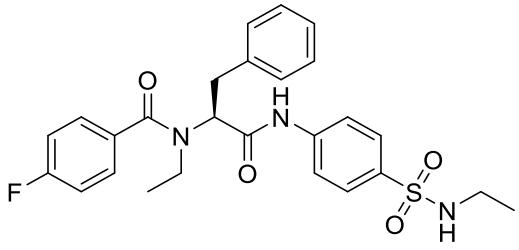
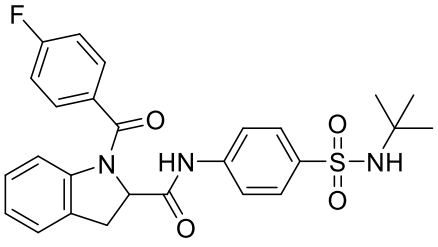
I-22	
I-23	
I-24	
I-25	
I-26	

I-27	
I-28	
I-29	
I-30	
I-31	
I-32	

I-33	
I-34	
I-35	
I-36	
I-37	

I-38	
I-39	
I-40	
I-41	
I-42	
I-43	

I-44	
I-45	
I-46	
I-47	
I-48	

I-49	
I-50	
I-51	
I-52	
I-53	

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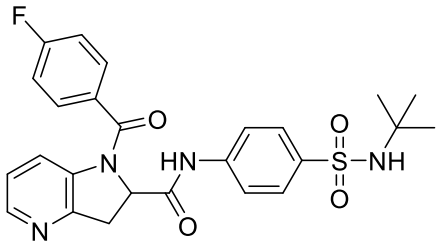
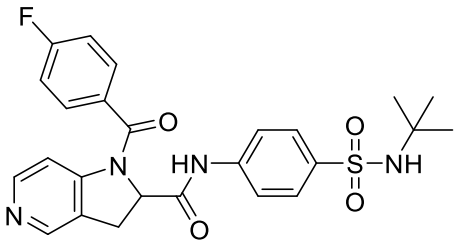
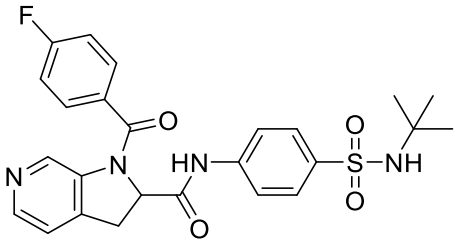
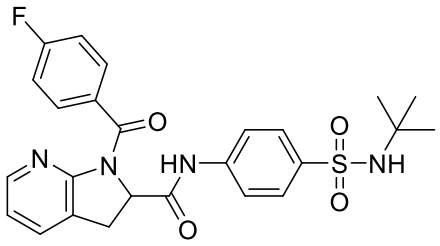
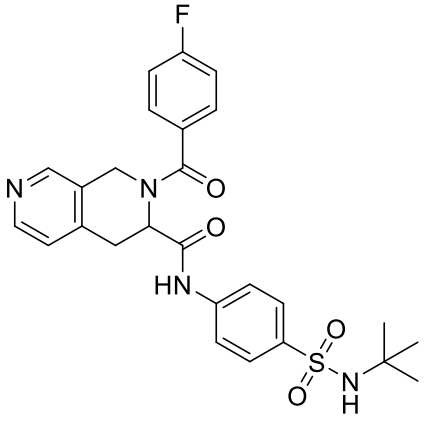
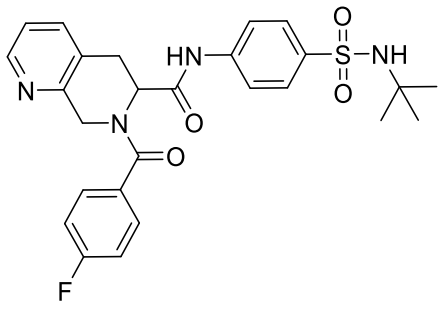
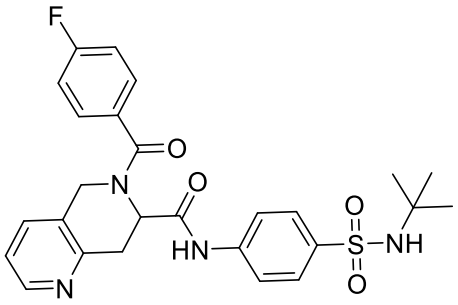
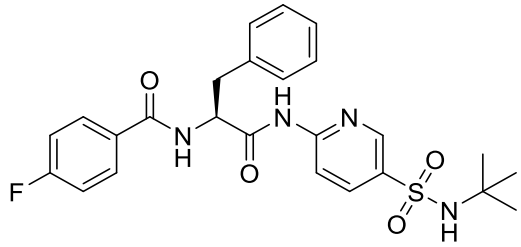
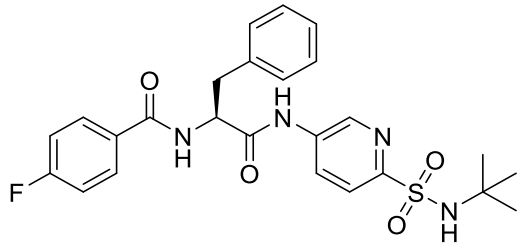
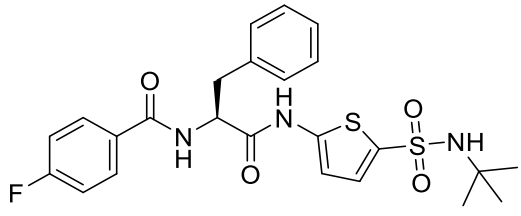
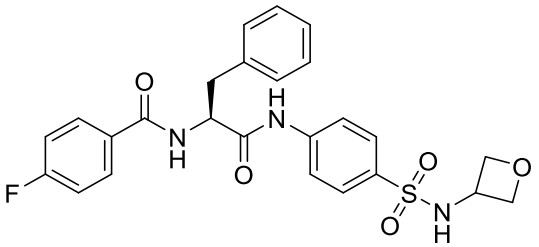
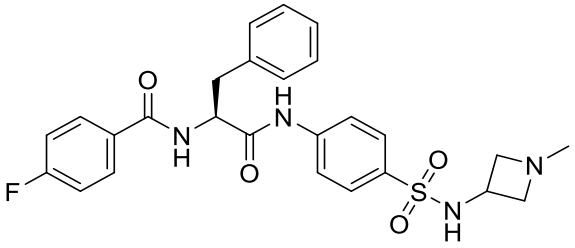
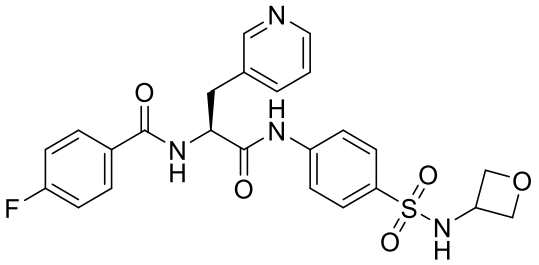
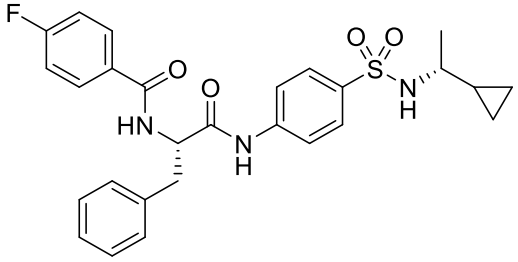
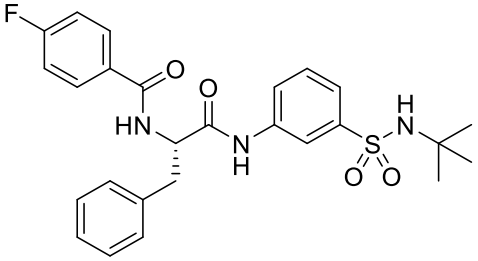
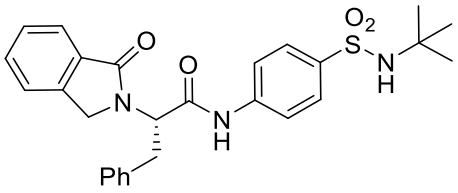
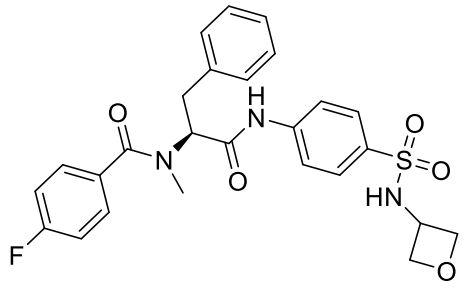
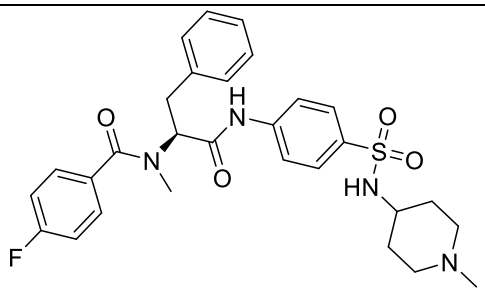
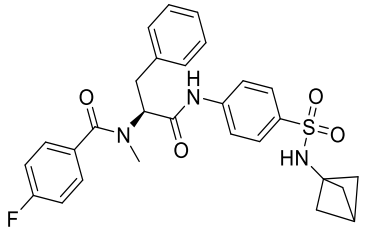
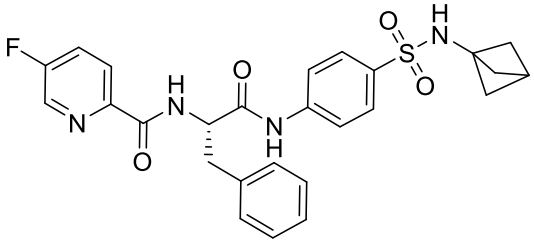
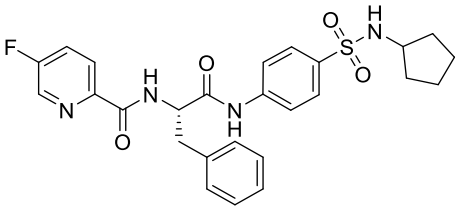
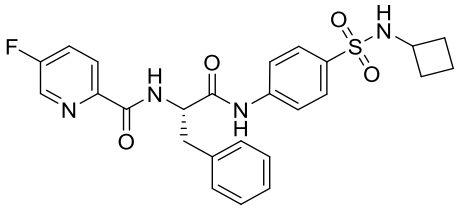
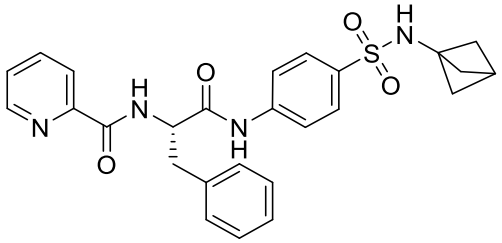
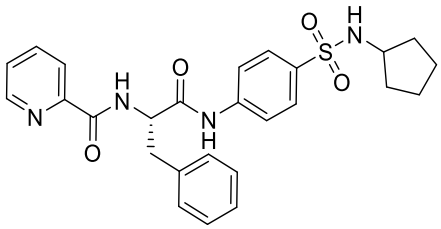
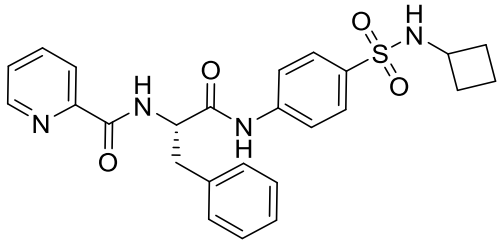
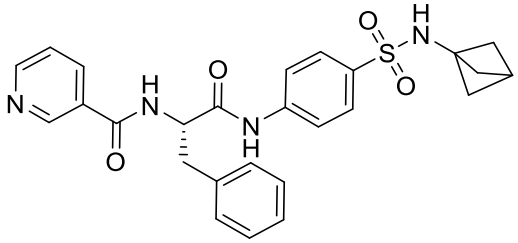
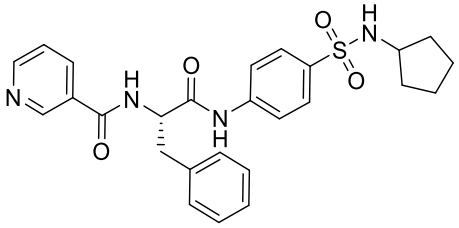
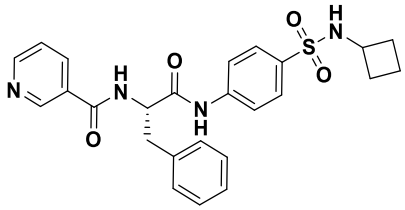
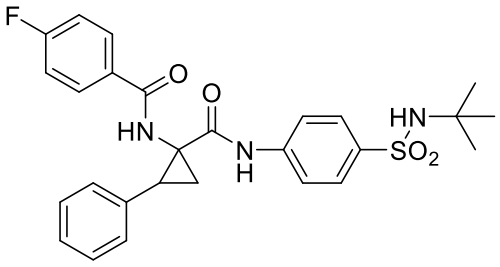
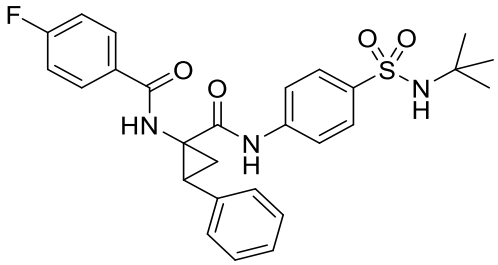
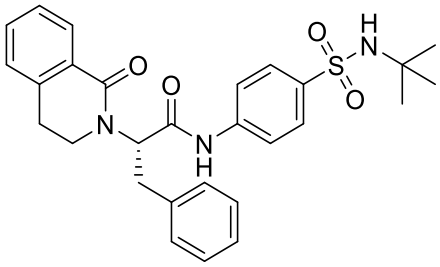
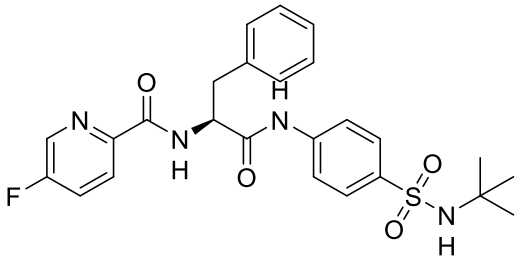
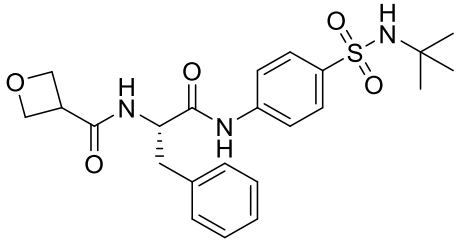
I-54	
I-55	
I-56	
I-57	
I-58	

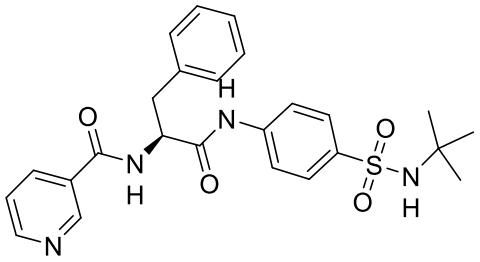
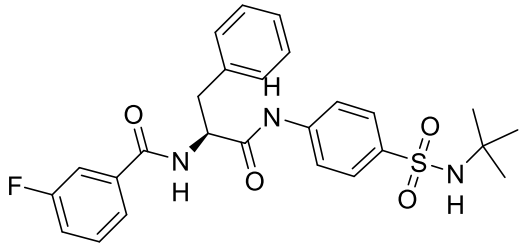
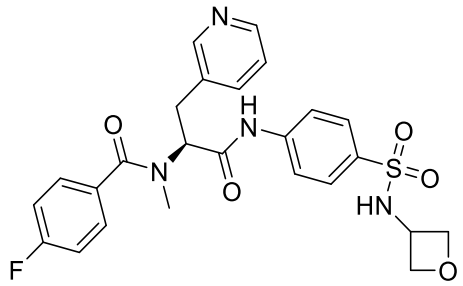
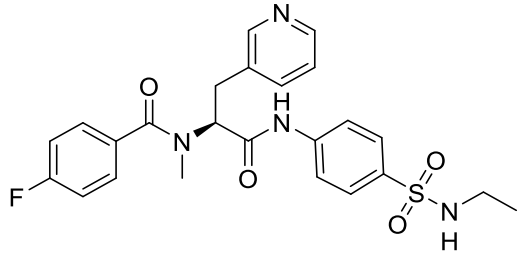
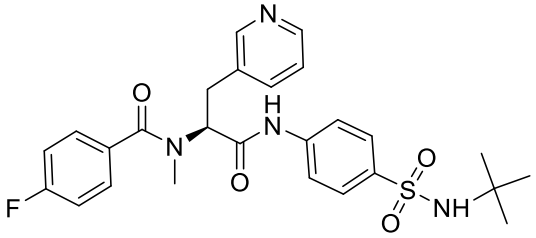
I-59	
I-60	
I-61	
I-62	
I-63	

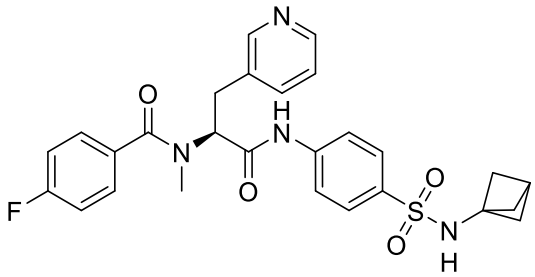
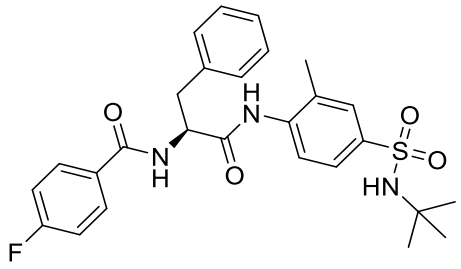
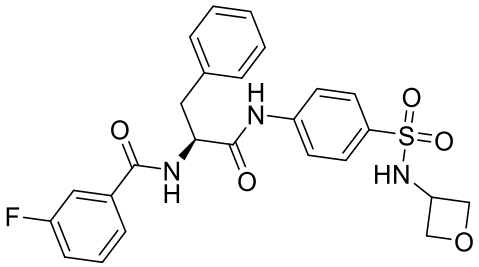
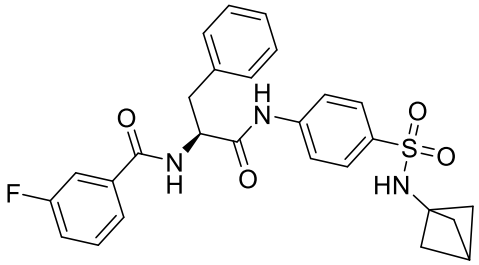
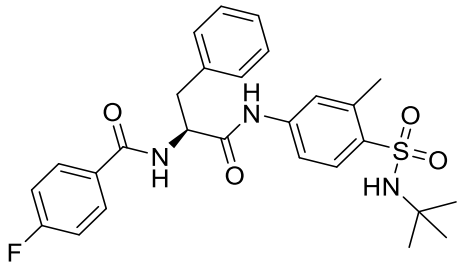
I-64	
I-65	
I-66	
I-67	
I-68	
I-69	

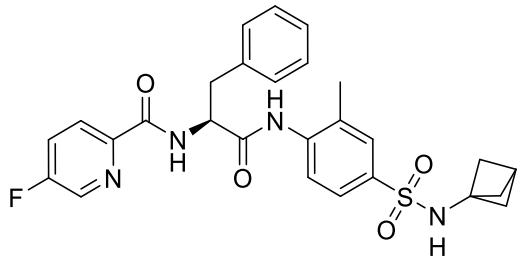
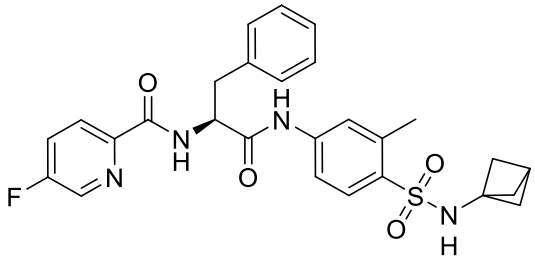
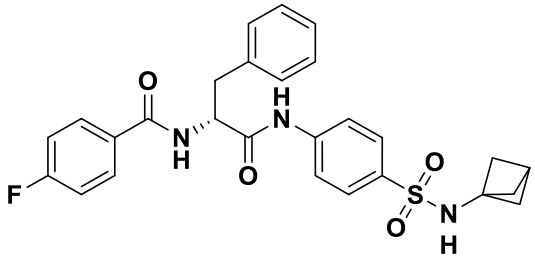
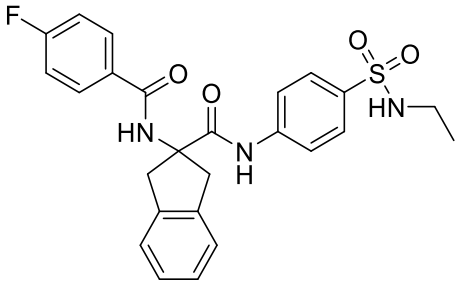
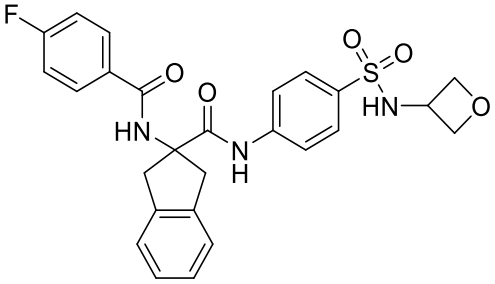
I-70	
I-71	
I-72	
I-73	
I-74	
I-75	

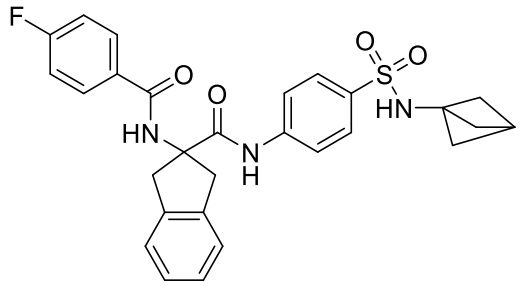
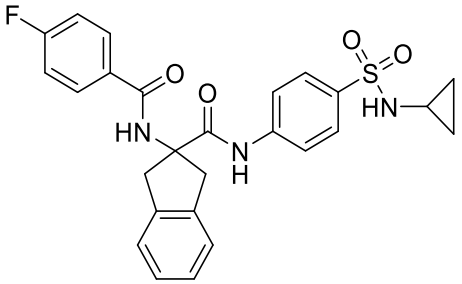
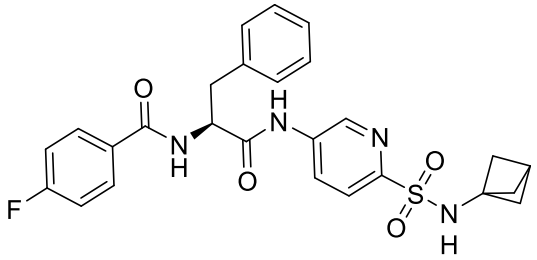
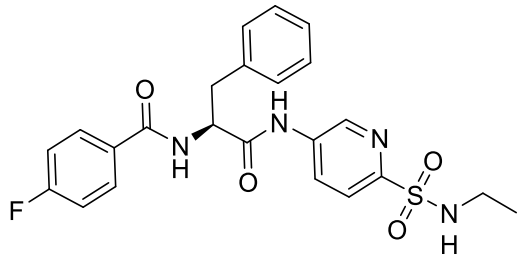
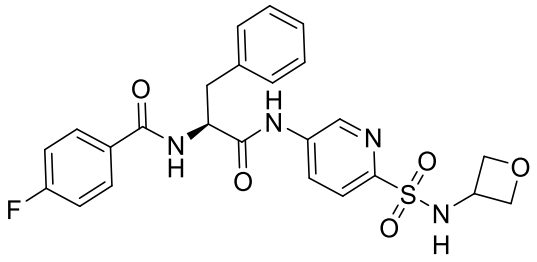
I-76	
I-77	
I-78	
I-79	
I-80	
I-81	

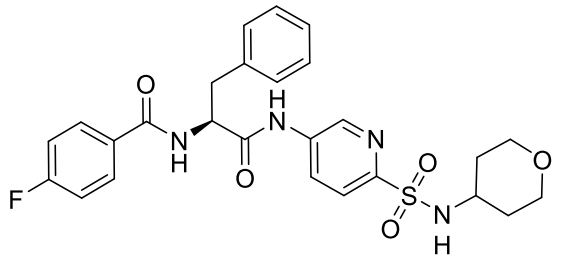
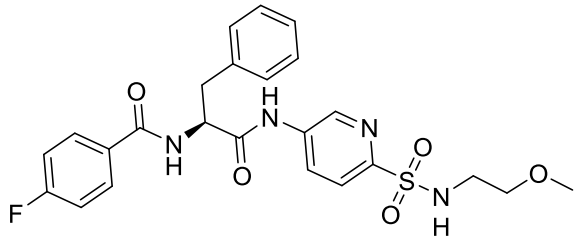
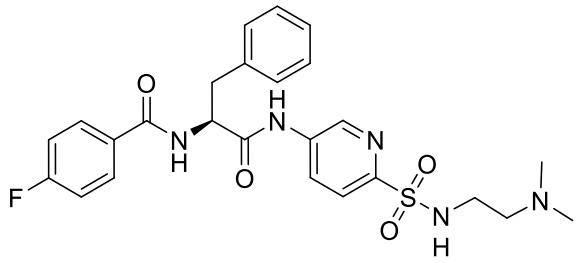
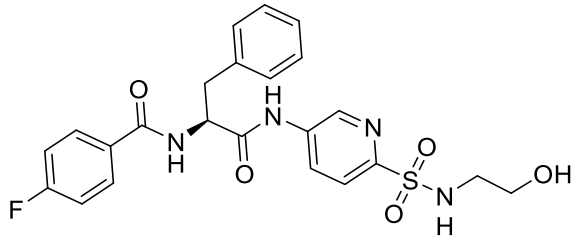
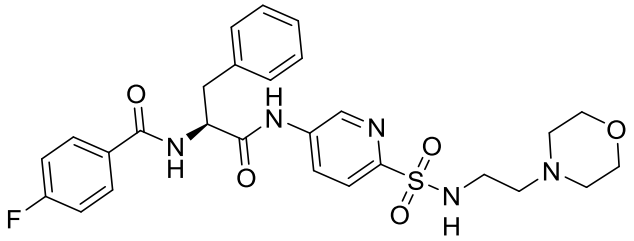
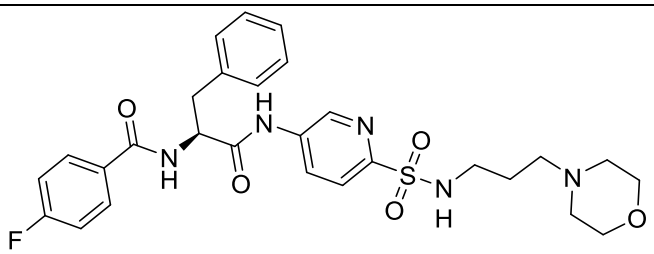
I-82	
I-83	
I-84	
I-85	
I-86	

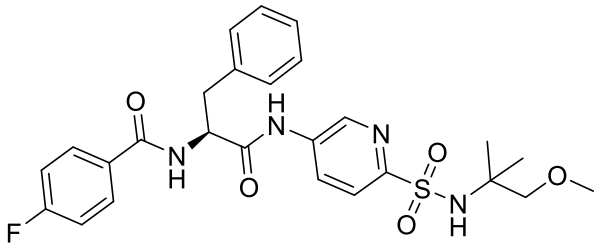
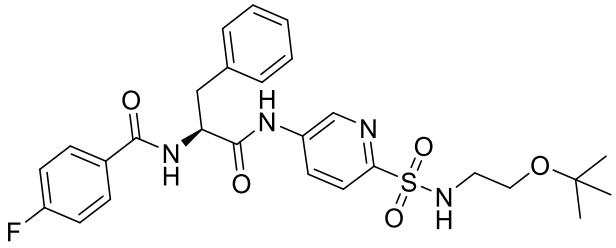
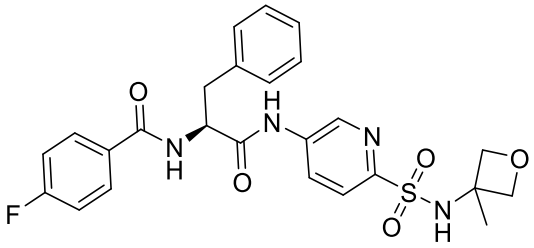
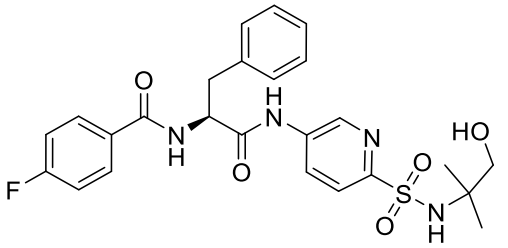
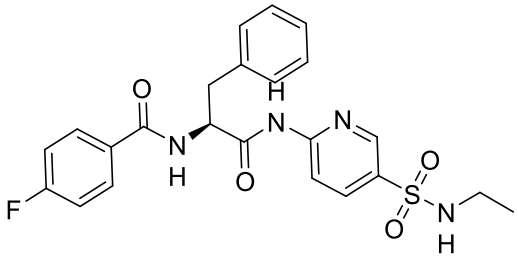
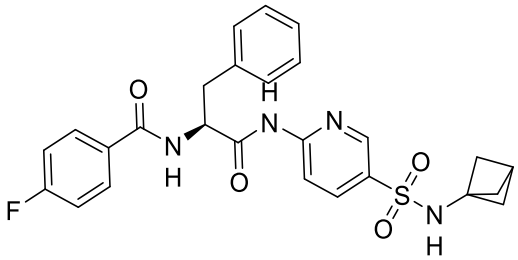
I-87	
I-88	
I-89	
I-90	
I-91	

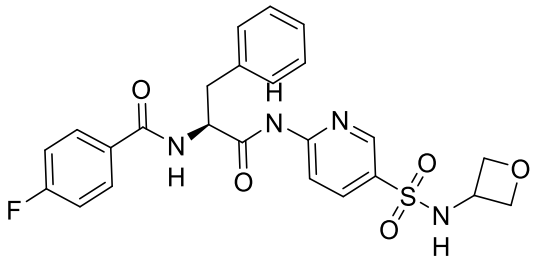
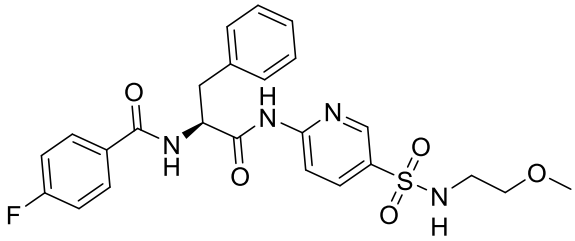
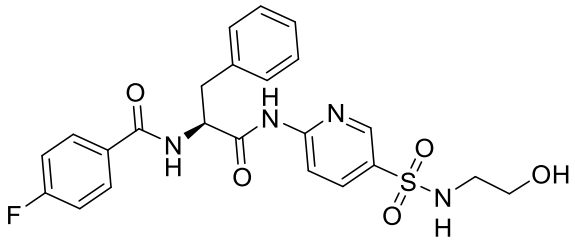
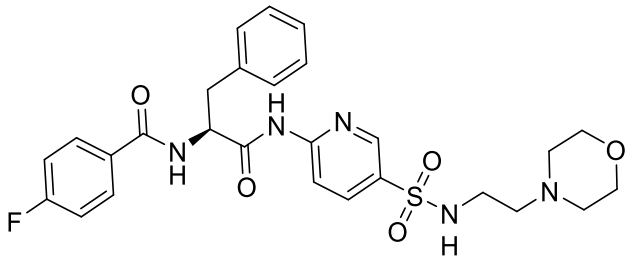
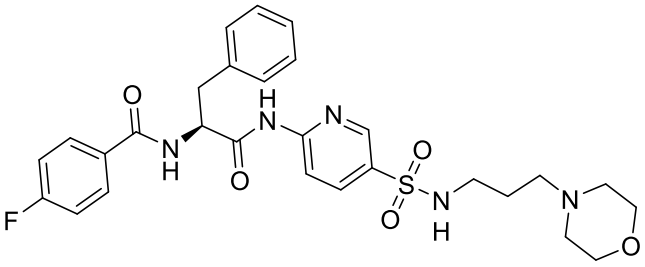
I-92	
I-93	
I-94	
I-95	
I-96	

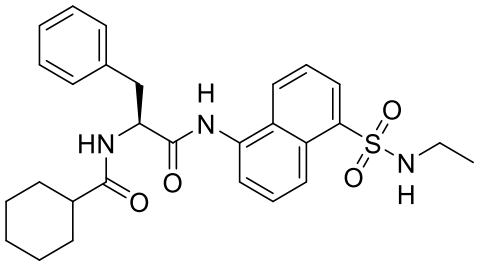
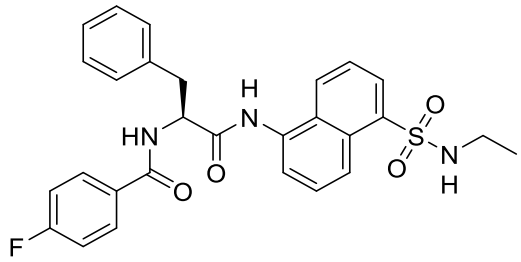
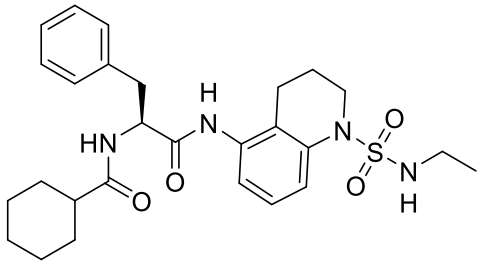
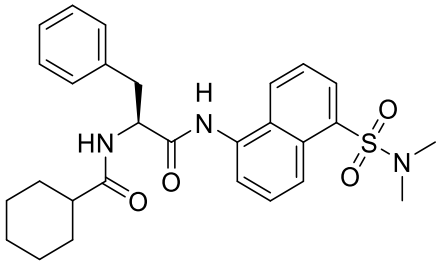
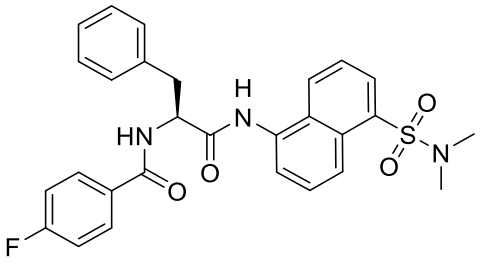
I-97	
I-98	
I-99	
I-100	
I-101	

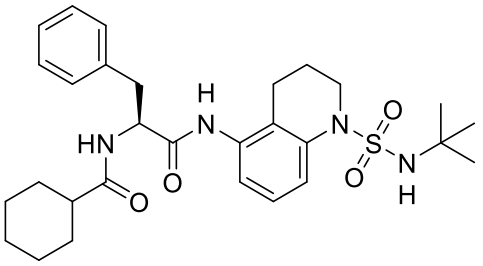
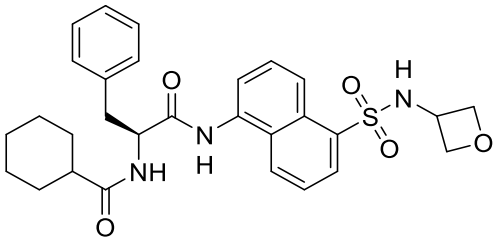
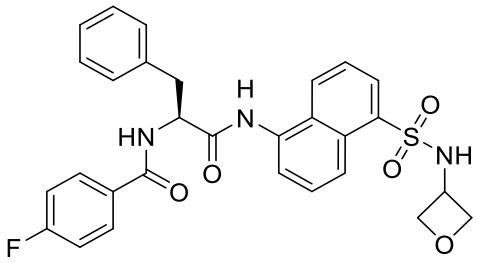
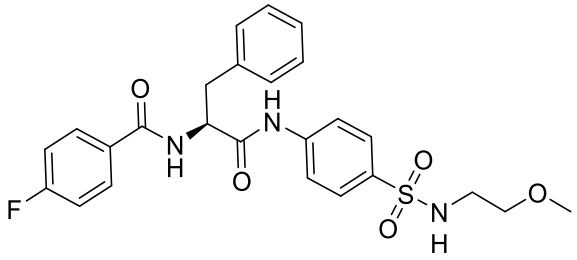
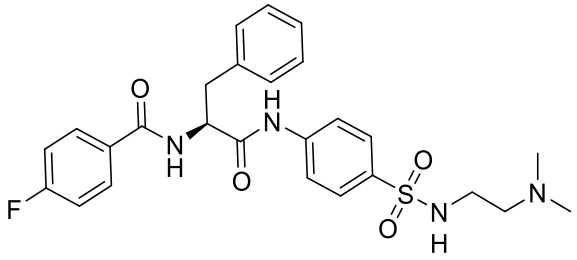
I-102	
I-103	
I-104	
I-105	
I-106	

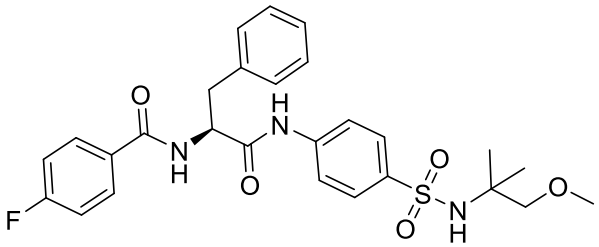
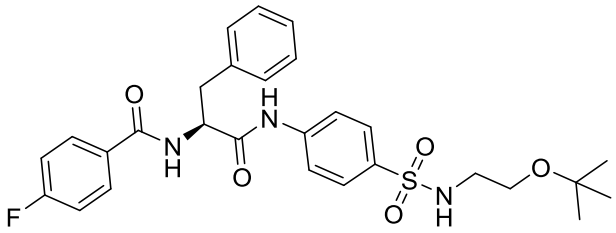
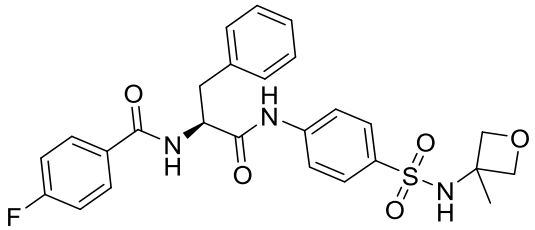
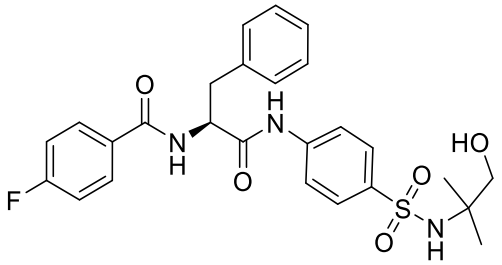
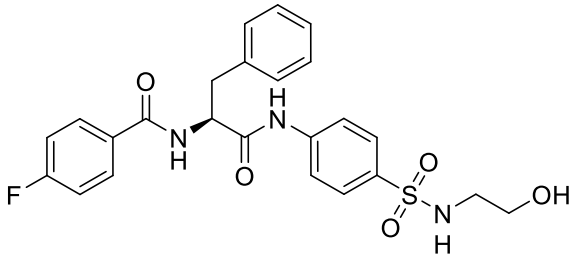
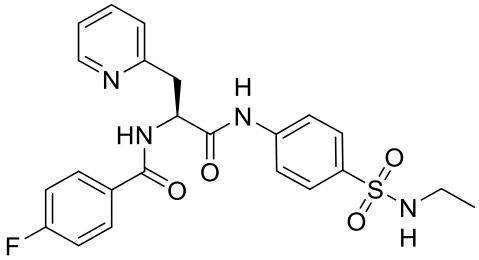
I-107	
I-108	
I-109	
I-110	
I-111	
I-112	

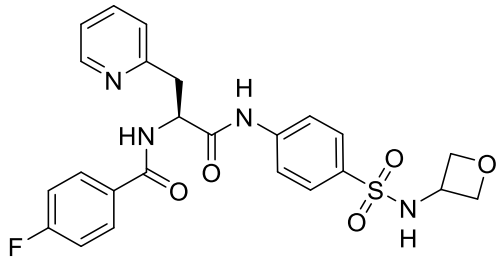
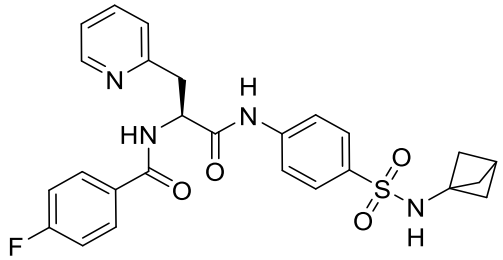
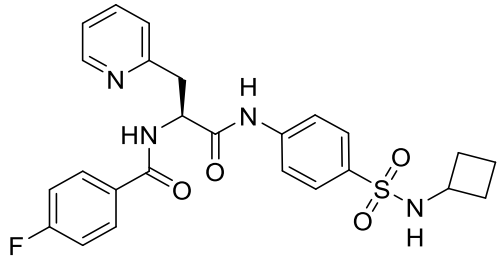
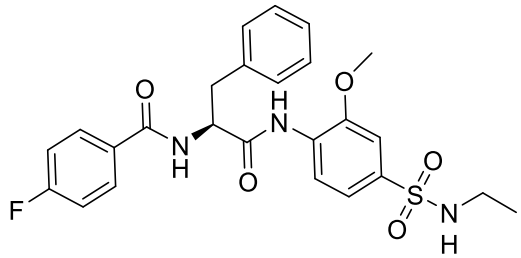
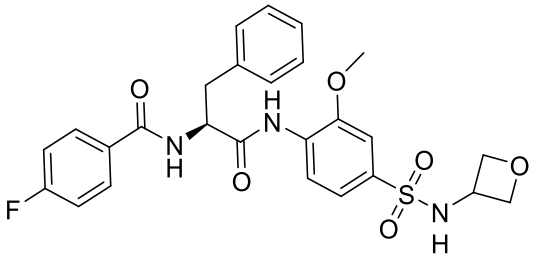
I-113	
I-114	
I-115	
I-116	
I-117	
I-118	

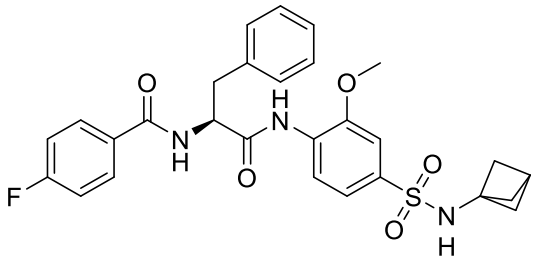
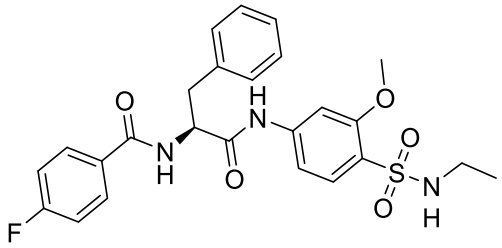
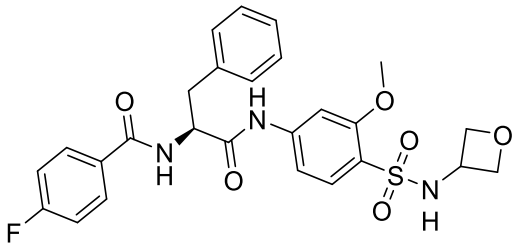
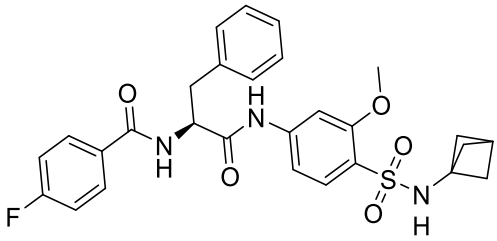
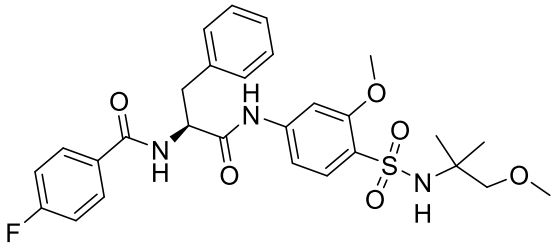
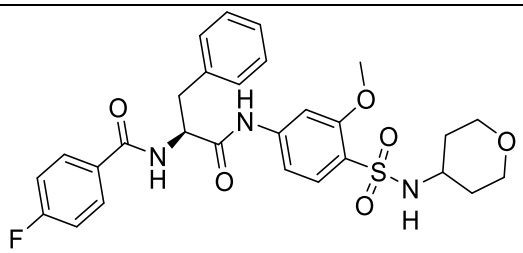
I-119	
I-120	
I-121	
I-122	
I-123	

1-124	
I-125	
I-126	
I-127	
I-128	

I-129	
I-130	
I-131	
I-132	
I-133	

I-134	
I-135	
I-136	
I-137	
I-138	
I-139	

I-140	
I-141	
I-142	
I-143	
I-144	

I-145	
I-146	
I-147	
I-148	
I-149	
I-150	

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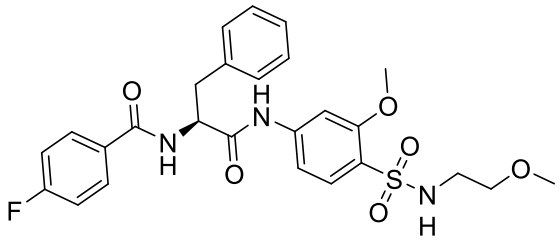
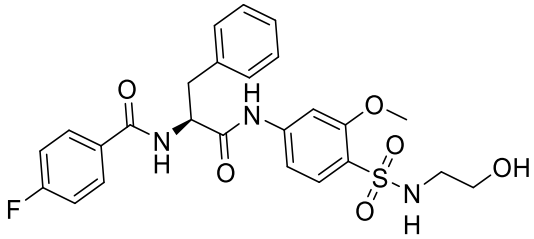
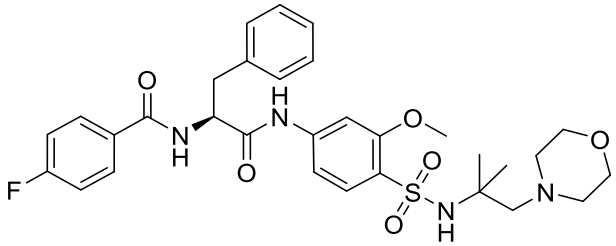
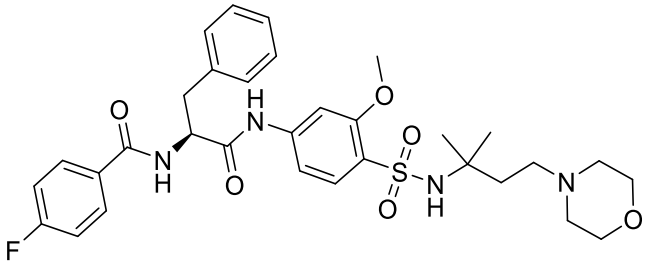
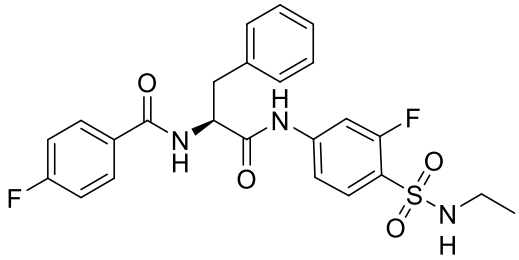
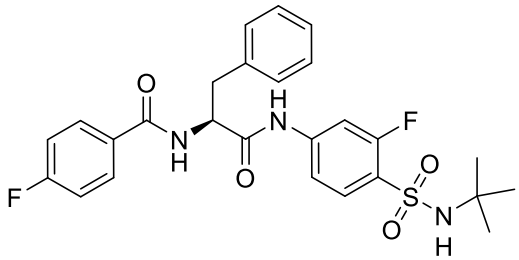
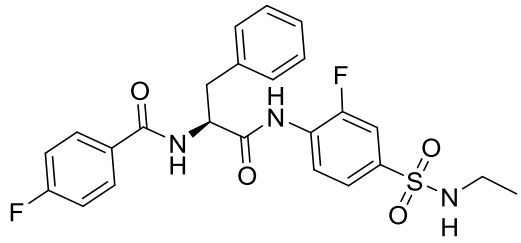
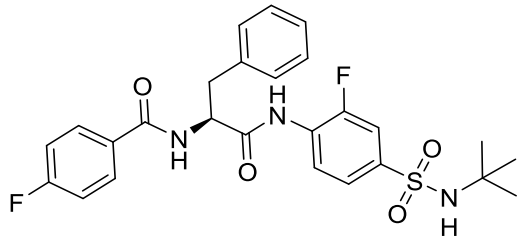
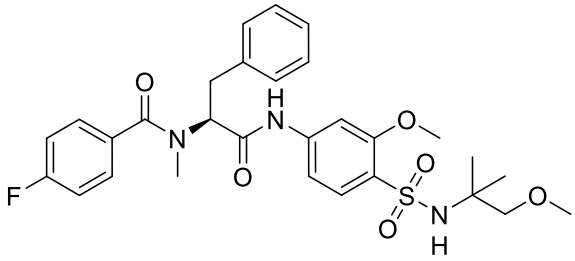
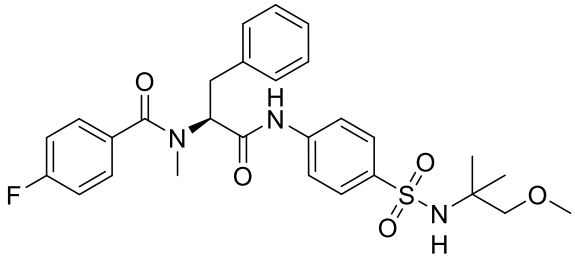
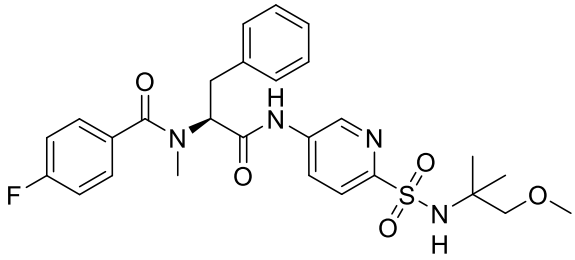
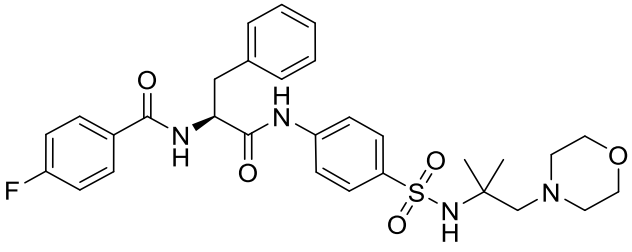
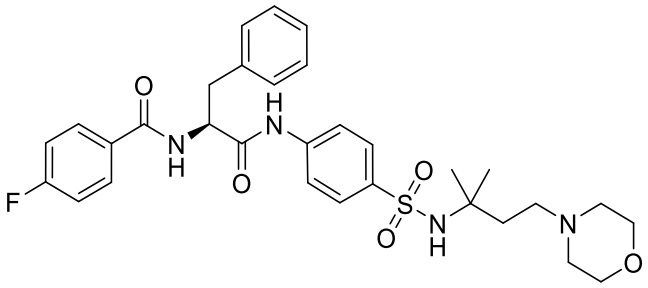
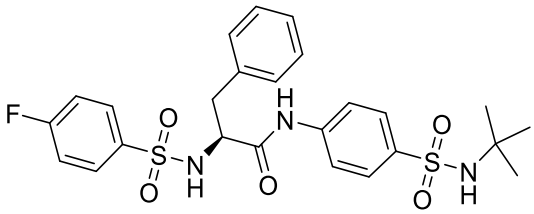
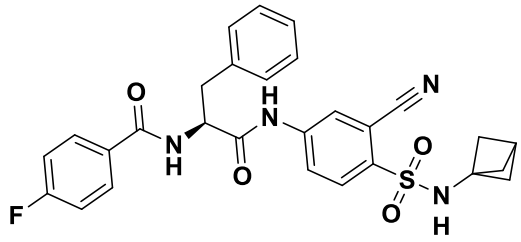
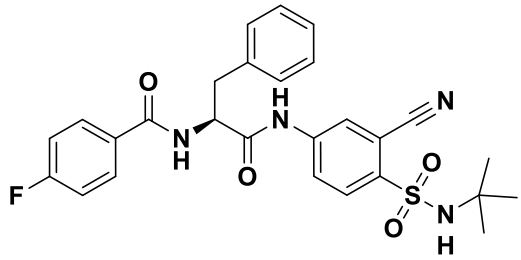
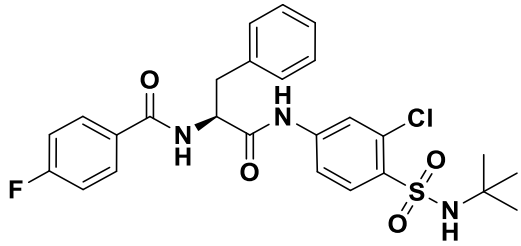
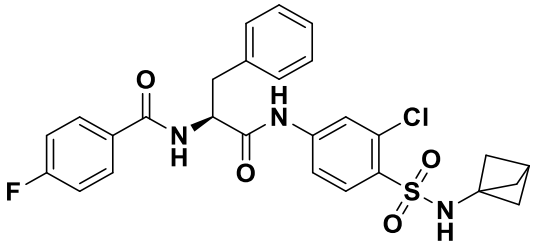
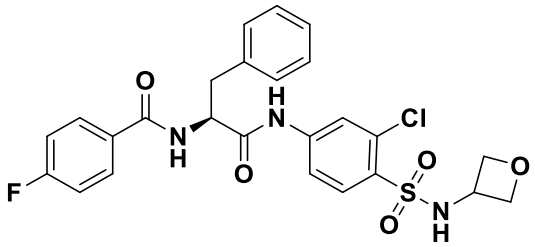
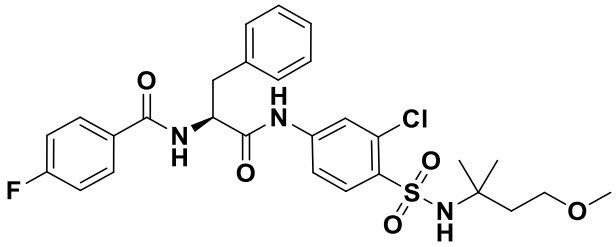
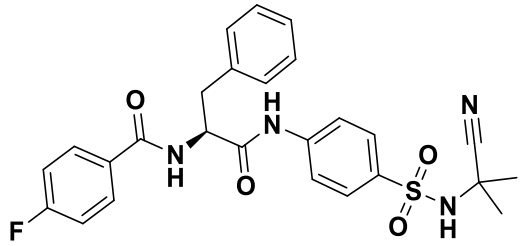
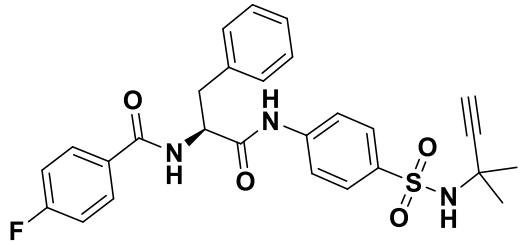
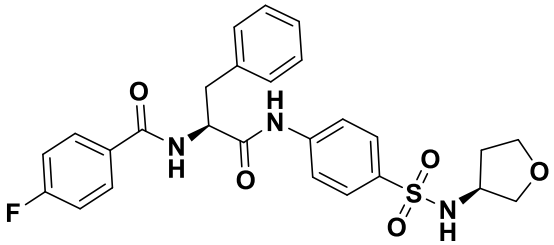
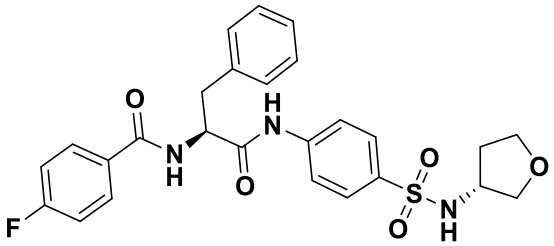
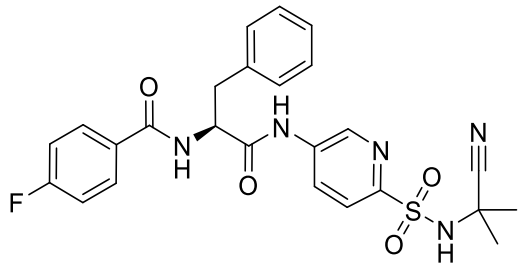
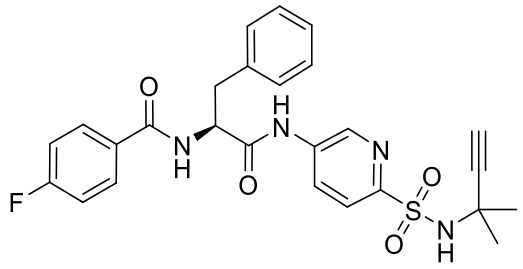
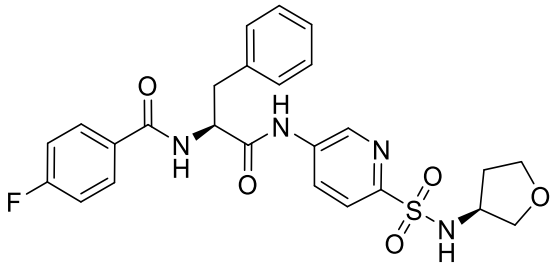
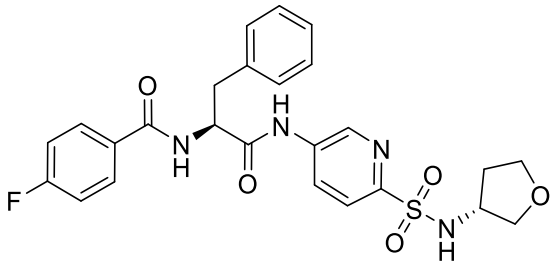
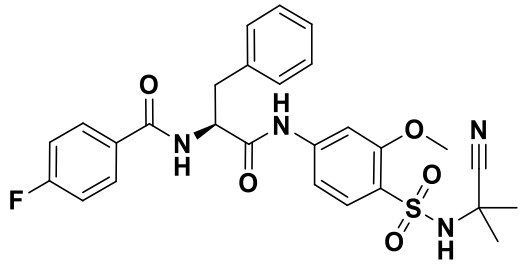
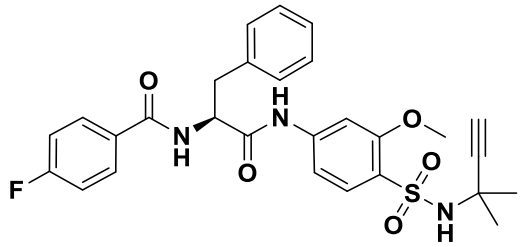
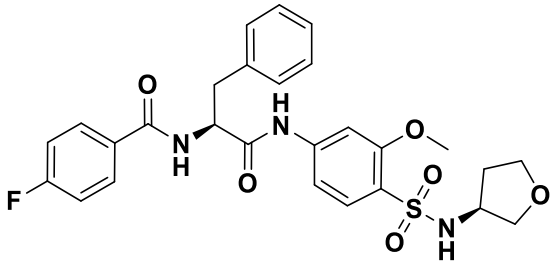
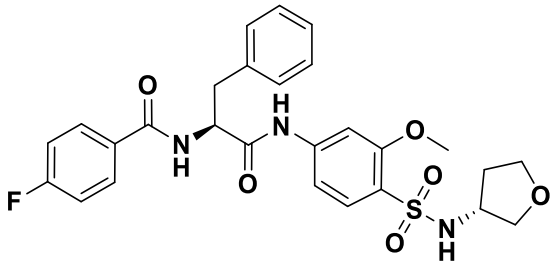
I-151	
I-152	
I-153	
I-154	
I-155	
I-156	

I-157	
I-158	
I-159	
I-160	
I-161	
I-162	

I-163	
I-165	
I-166	
I-167	
I-168	
I-169	

I-170	
I-171	
I-172	
I-173	
I-174	
I-175	

I-176	
I-177	
I-178	
I-179	
I-180	

I-181	
I-182	
I-183	

, or a pharmaceutically acceptable salt thereof.

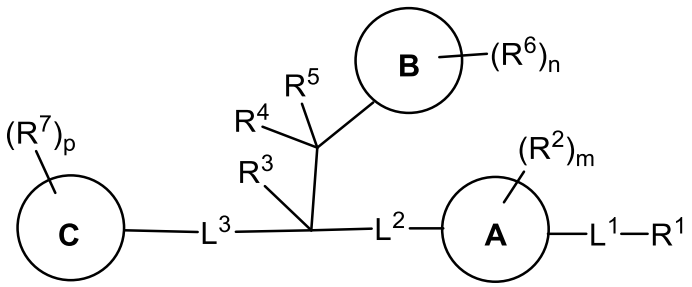
[0007e] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0007f] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein in the preparation of a medicament for inhibiting USP30, wherein the inhibiting regulates mitochondrial homeostasis.

[0007g] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein in the preparation of a medicament for treating an USP30-mediated disorder, disease, or condition selected from the group consisting of a neurodegenerative disease; mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome; Leber's hereditary optic neuropathy (LHON); neuropathy, ataxia, retinitis pigmentosa- maternally inherited Leigh syndrome (NARP-MILS); Danon disease; ischemic heart disease leading to myocardial infarction; multiple sulfatase deficiency (MSD); mucolipidosis II (ML II); mucolipidosis III (ML III); mucolipidosis IV (ML IV); GM1 - gangliosidosis (GM1); neuronal ceroid- lipofuscinoses (NCL1); Alpers disease; Barth syndrome; Beta-oxidation defects; carnitine- acyl-carnitine deficiency; carnitine deficiency; creatine deficiency syndromes; coenzyme Q10 deficiency; complex I deficiency; complex II deficiency; complex III deficiency; complex IV deficiency; complex V deficiency; COX deficiency; chronic progressive external ophthalmoplegia syndrome (CPEO); CPT I deficiency; CPT II deficiency; glutaric aciduria type II; Kearns-Sayre syndrome; lactic acidosis; long-chain acyl-CoA dehydrongenase deficiency (LCHAD); Leigh disease or syndrome; lethal infantile cardiomyopathy (LIC); Luft disease; glutaric aciduria type II; medium-chain acyl-CoA dehydrongenase deficiency (MCAD); myoclonic epilepsy and ragged-red fiber (MERRF) syndrome; mitochondrial recessive ataxia syndrome; mitochondrial cytopathy; mitochondrial DNA depletion syndrome; myoneurogastointestinal disorder and encephalopathy; Pearson syndrome; pyruvate carboxylase deficiency; pyruvate dehydrogenase deficiency; POLG mutations; medium/short-chain 3-hydroxyacyl-CoA dehydrogenase (M/SCHAD) deficiency; and very long-chain acyl-CoA dehydrongenase (VLCAD) deficiency.

[0007h] In another aspect of the present disclosure, there is provided a compound disclosed herein, for use in therapy.

[0008] In some examples, such compounds have the general formula **I'**:



I'

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

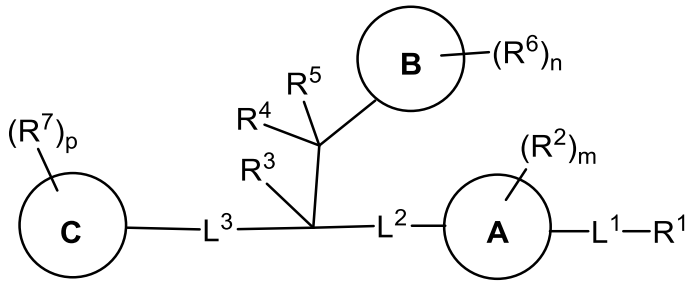
[0009] Compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with mitochondrial homeostasis implicating USP30. Such diseases, disorders, or conditions include those described herein.

[0010] Compounds provided by this present disclosure are also useful for the study of USP30 in biological and pathological phenomena; the study of mitochondrial homeostasis occurring in bodily tissues; and the comparative evaluation of new USP30 inhibitors or other regulators of mitochondrial homeostasis *in vitro* or *in vivo*.

CLAIMS

We claim:

1. A compound of formula **I'**:



I'

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

L^1 is $-S(O)_2NH-$, -S(O)NH-, -S(O)-, -S(O)(N-*t*-Bu)-, or $-C(CF_3)(H)NH-$;

each R is independently hydrogen or an optionally substituted C_{1-3} aliphatic group;

R^1 is an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered saturated or partially unsaturated bridged bicyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^2 is independently halogen, $–CF_3$, –CN, –C(O)NHR, $–NO_2$, –NHR, –NHC(O)R, $–NHS(O)_2R$, $–N(R)_2$, or –OR, or a C_{1-6} aliphatic group;

L^2 is $–C(O)N(R')–$;

R' is hydrogen or a C_{1-3} aliphatic group;

L^3 is –C(O)N(R")–;

R" is hydrogen or a C_{1-3} aliphatic group;

R^3 is hydrogen or a C_{1-3} aliphatic;

R^4 is hydrogen;

R^5 is hydrogen;

Ring B is phenyl;

each R^6 is independently halogen, –CN, –NO_2, –NHR, –$N(R)_2$, –OR, or an optionally substituted C_{1-6} aliphatic group;

Ring C is phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen and oxygen, or an 8-10 membered bicyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

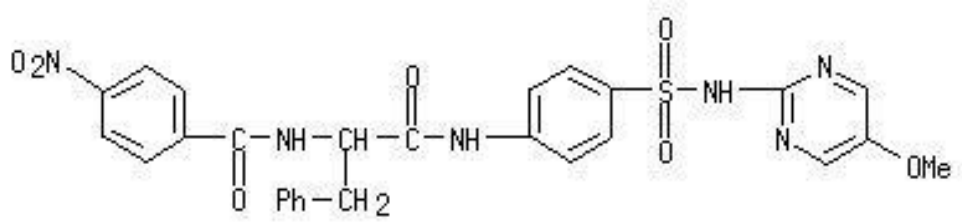
each R^7 is independently halogen, –CN, –NO_2, –NHR, –$N(R)_2$, –OR, or a C_{1-6} aliphatic group; and

each of m, n, and p is independently 0, 1, 2, 3 or 4;

provided that R^1 is other than isopropyl, t-butyl, 1-methylcyclopropyl, 1-fluoromethylcyclopropyl, 1-difluoromethylcyclopropyl, 1-trifluoromethylcyclopropyl, or 3-methyl-3-oxetanyl when L^1 is –$S(O)_2N(H)$-;

R^1 is other than ethyl when L^1 is –$S(O)_2N(H)$- and Ring A is naphthyl; and

the compound is other than:



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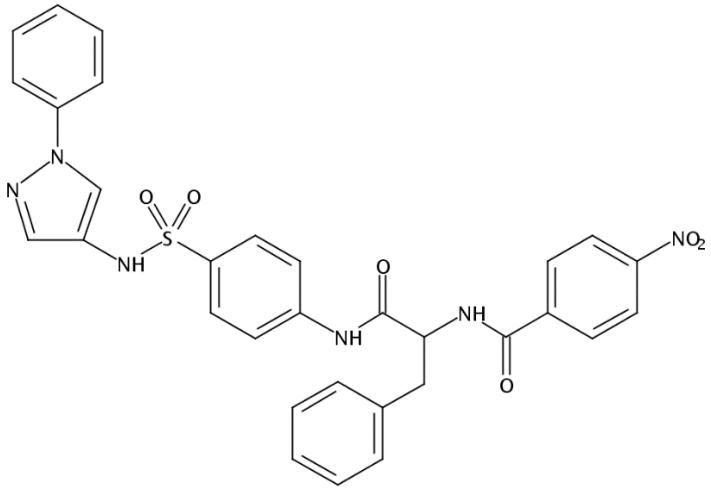

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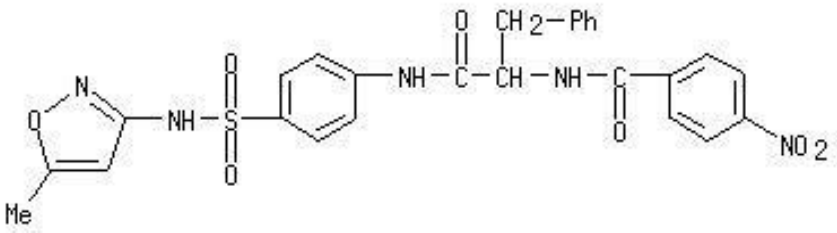

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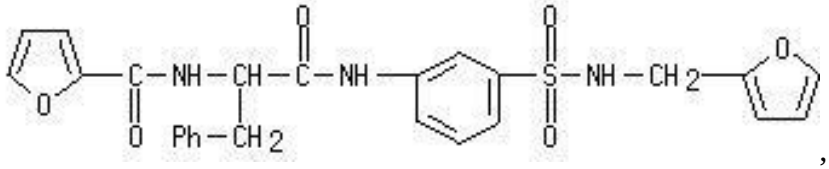

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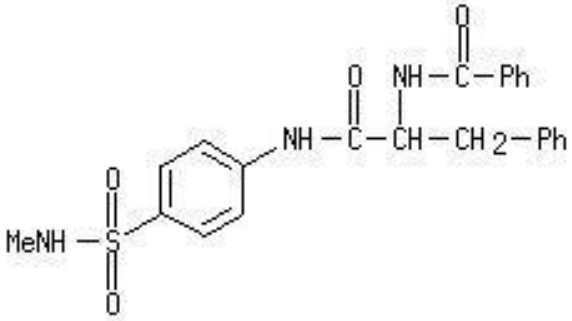

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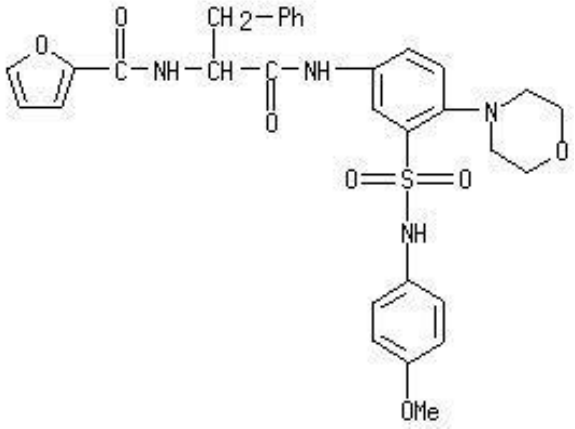

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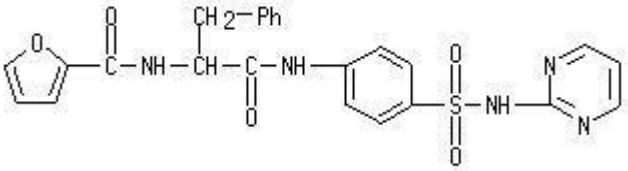

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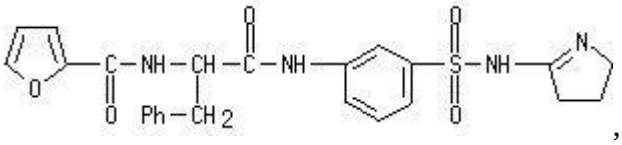

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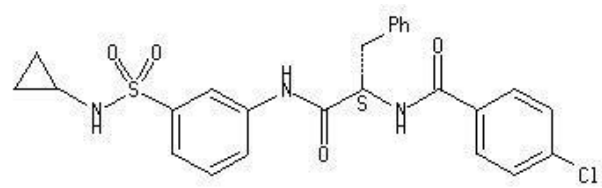

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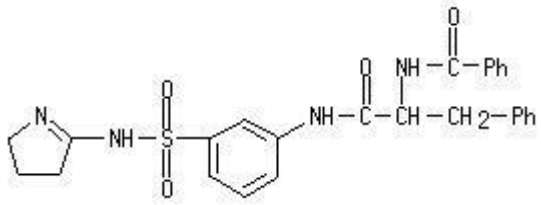
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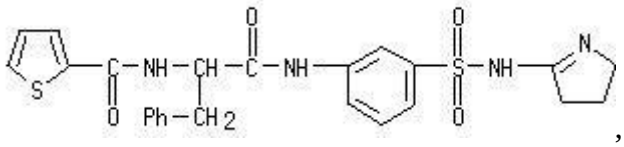
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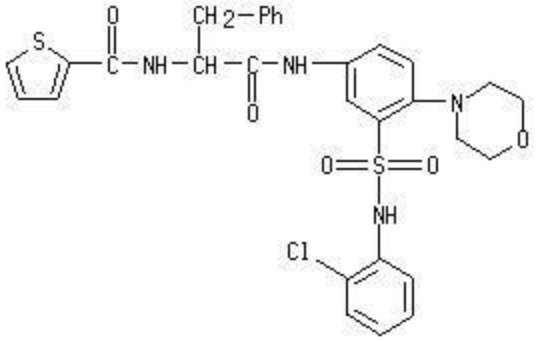
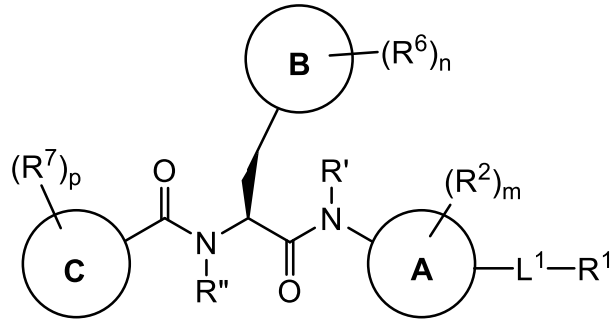

and .

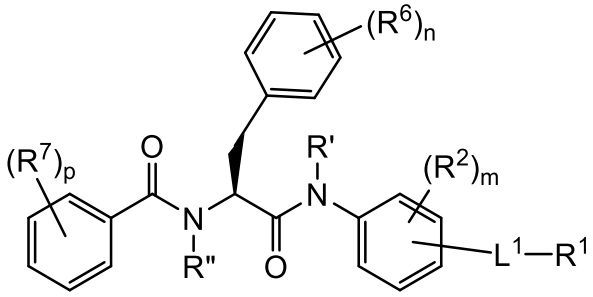
2. The compound of claim 1 of formula **II**:



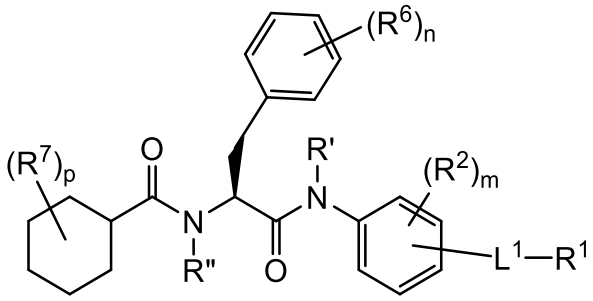
II

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 of one of formulas **III-a** or **III-c**:



III-a

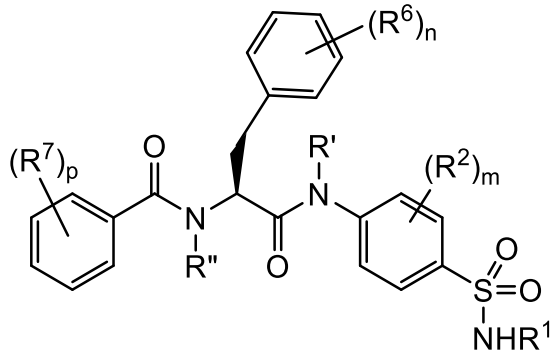


III-c

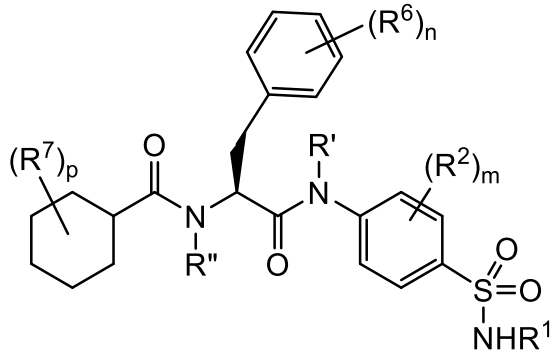
or a pharmaceutically acceptable salt thereof.

4. The compound of any one of the preceding claims where L^1 is $–S(O)_2NH-$.

5. The compound of claim 1 of one of formulas **IV-a** or **IV-c**:



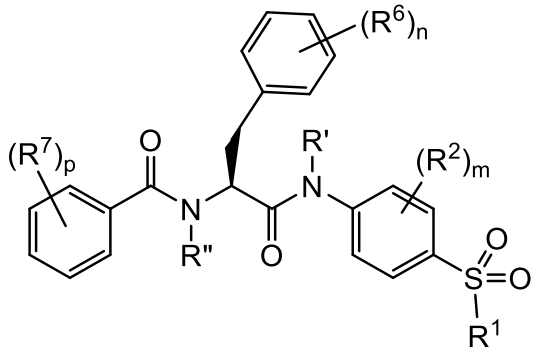
IV-a



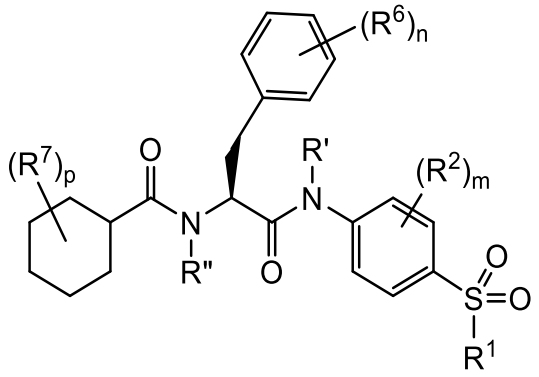
IV-c

or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1 of one of formulas **V-a** or **V-c**:



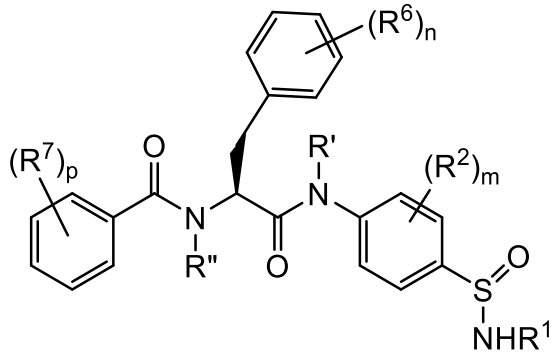
V-a



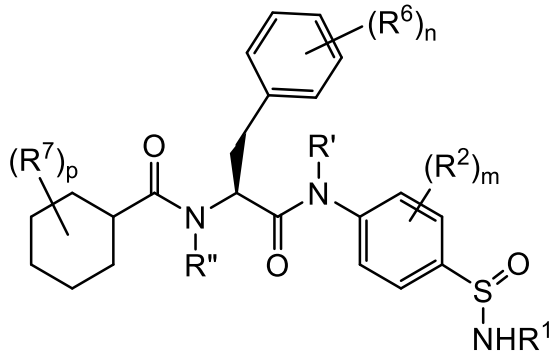
V-c

or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1 of one of formulas **VI-a** or **VI-c**:



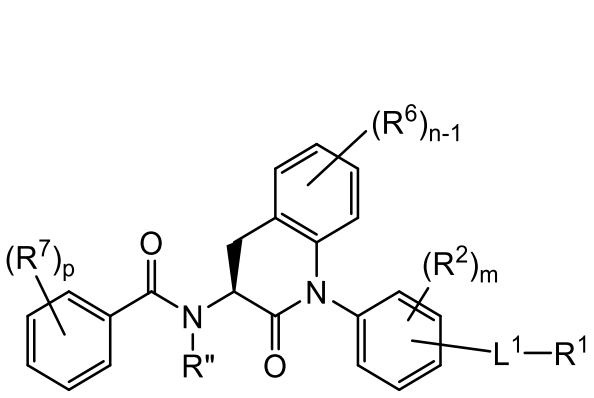
VI-a



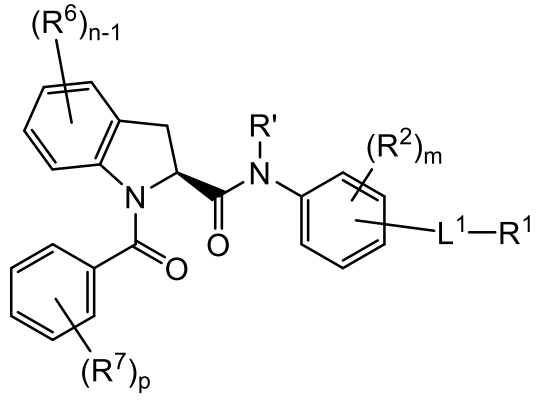
VI-c

or a pharmaceutically acceptable salt thereof.

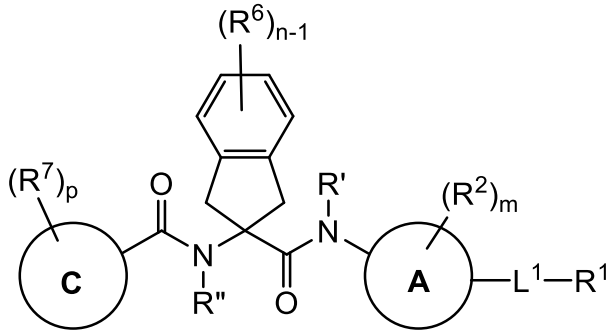
8. A compound that is one of the following formulae or a pharmaceutically acceptable salt thereof:



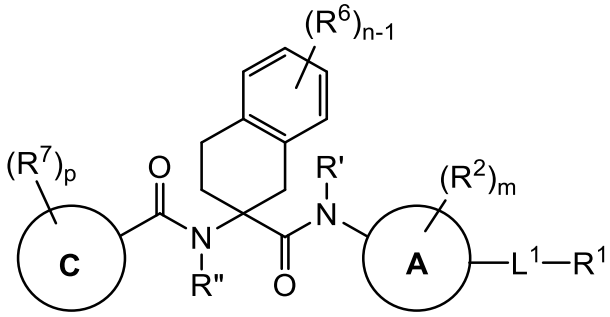
VII-a



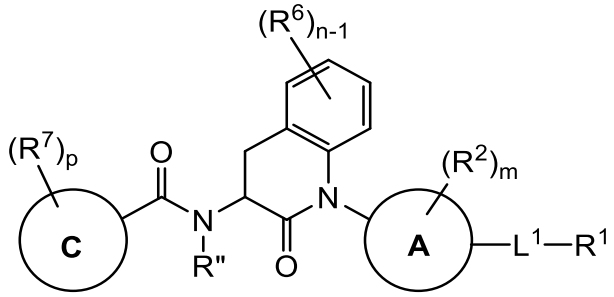
VII-b



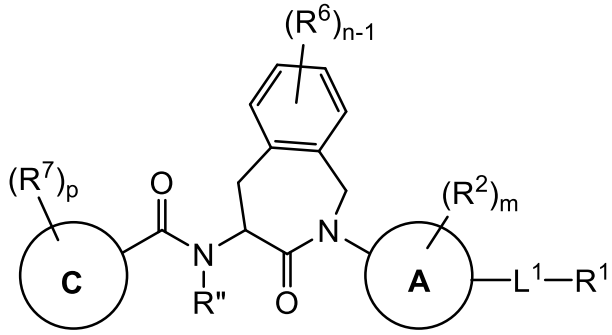
VIII



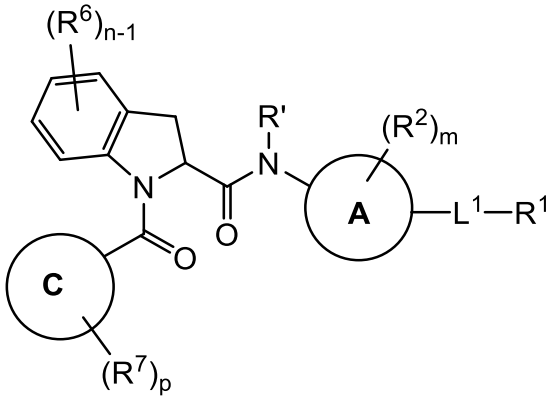
IX



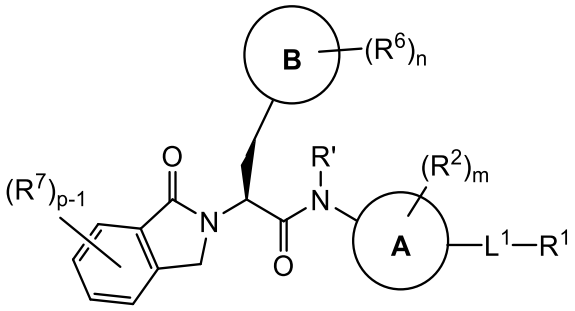
X



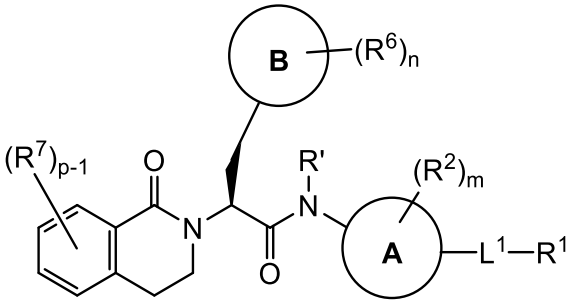
XI



XII



or



XIV-a **XIV-b**

wherein:

L^1 is–N(R)C(O)–, –S(O)–,–S(O)N(R)–, or –$S(O)_2$N(R)–;

each R is independently hydrogen or an optionally substituted C_{1-3} aliphatic group;

R^1 is an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered saturated or partially unsaturated bridged bicyclic carbocyclic ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen,

oxygen, or sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^2 is independently halogen, $–CF_3$, –CN, –C(O)NHR, $–NO_2$, –NHR, –NHC(O)R, $–NHS(O)_2R$, $–N(R)_2$, or –OR, or a C_{1-6} aliphatic group;

R' is hydrogen or a C_{1-3} aliphatic group;

R" is hydrogen or a C_{1-3} aliphatic group;

each R^6 is independently halogen, –CN, $–NO_2$, –NHR, $–N(R)_2$, –OR, or an optionally substituted C_{1-6} aliphatic group;

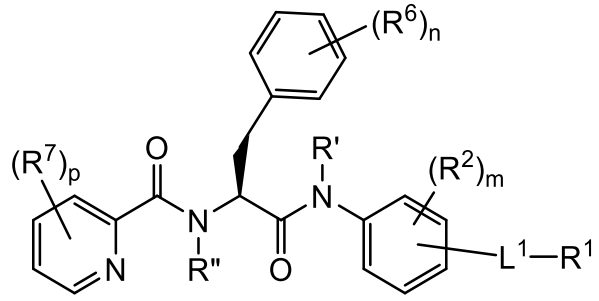
each R^7 is independently halogen, –CN, $–NO_2$, –NHR, $–N(R)_2$, –OR, or a C_{1-6} aliphatic group;

each of m and p is independently 0, 1, 2, 3, or 4; and

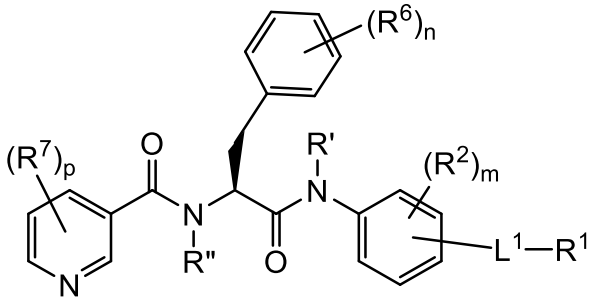
n is 0;

provided that R^1 is other than isopropyl, *t*-butyl, 1-methylcyclopropyl, 1-fluoromethylcyclopropyl, 1-difluoromethylcyclopropyl, 1-trifluoromethylcyclopropyl, or 3-methyl-3-oxetanyl when L^1 is $–S(O)_2N(R)$-.

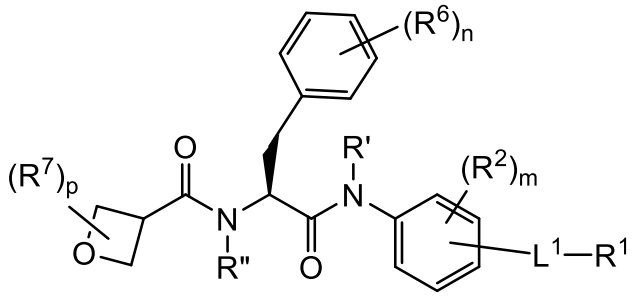
9. A compound of any one of formulas **XV-a**, **XV-b**, **XV-c**, **XV-d**, **XVII-a**, **XVII-b**, **XVII-c**, **XVII-d**, **XIX-a**, **XIX-b**, **XIX-c**, **XIX-d**, **XXI**, **XXIII-a**, **XXIII-b**, **XXV-a**, **XXV-b**, **XXV-c**, or **XXV-d**:

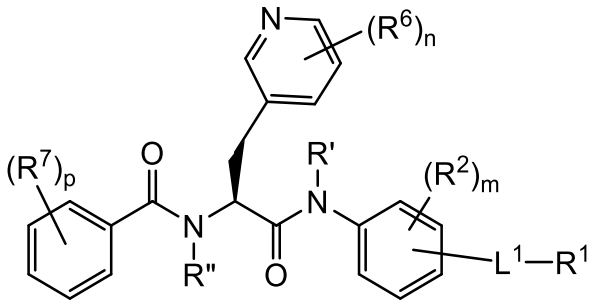


XV-a

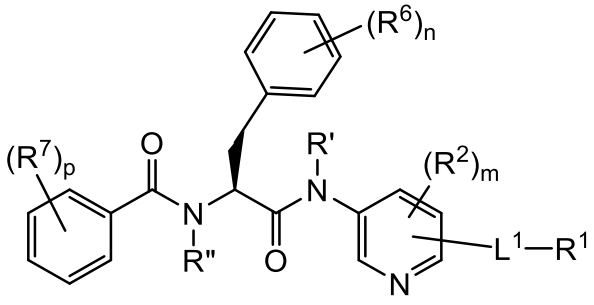


XV-b

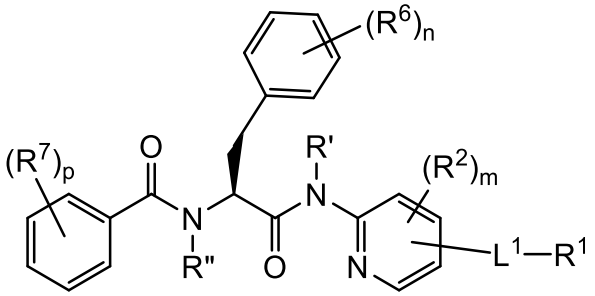




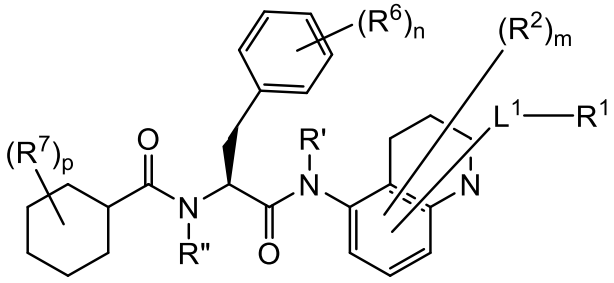
XV-c



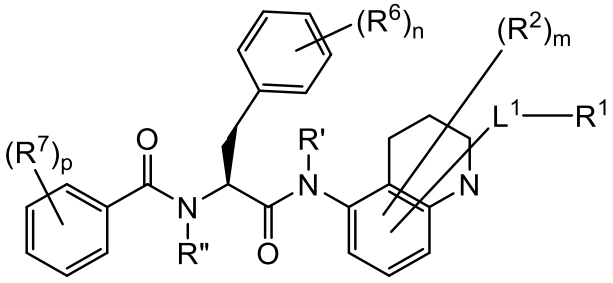
XV-d



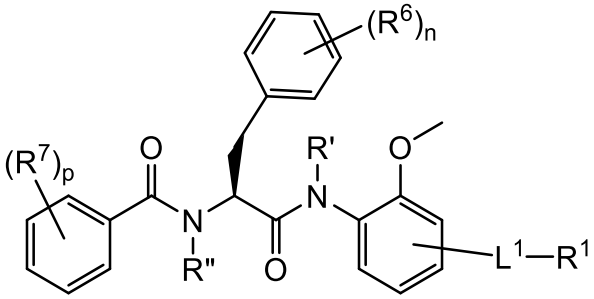
XVII-a



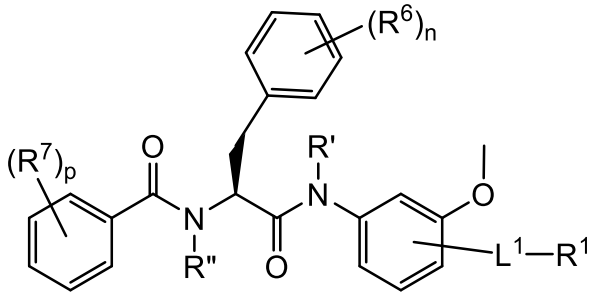
XVII-b



XVII-c



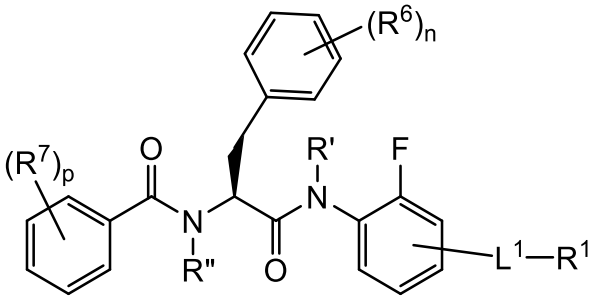
XVII-d



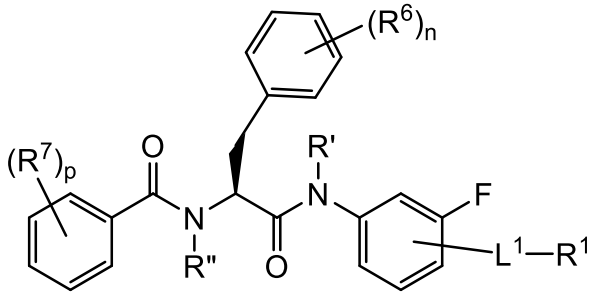
XIX-a

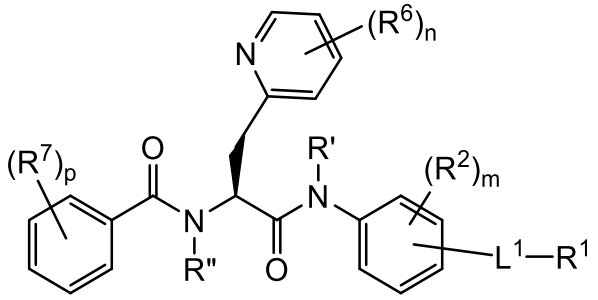
XIX-b

XIX-c

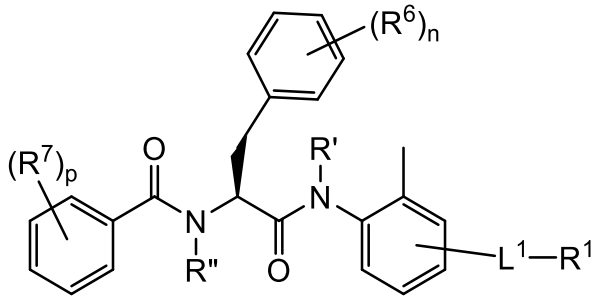


XIX-d

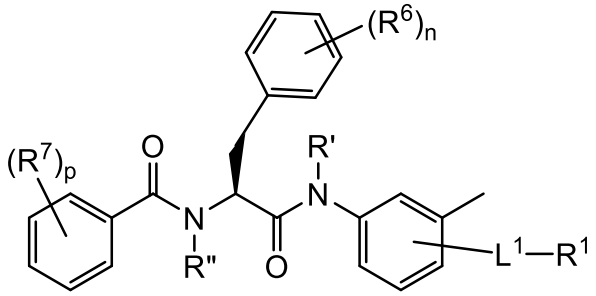




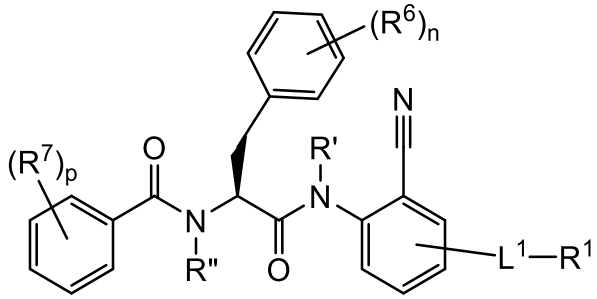
XXI



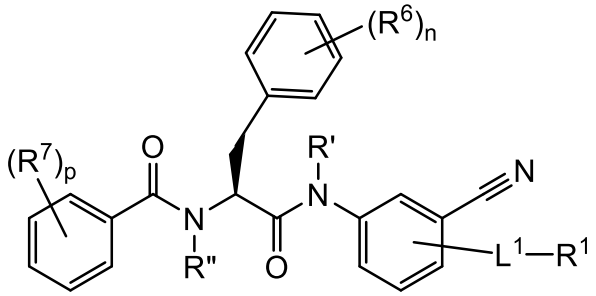
XXIII-a



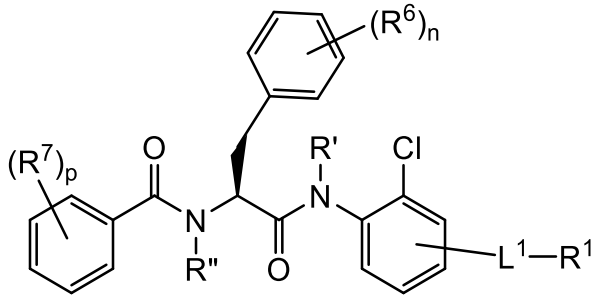
XXIII-b



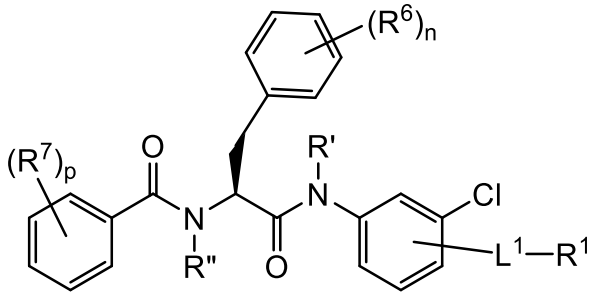
XXV-a



XXV-b



XXV-c



XXV-d

or a pharmaceutically acceptable salt thereof, wherein:

L^1 is –N(R)C(O)–, –S(O)–, –S(O)N(R)–, or $–S(O)_2N(R)–$;

each R is independently hydrogen or an optionally substituted C_{1-3} aliphatic group;

R^1 is an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered saturated or partially unsaturated bridged bicyclic carbocyclic ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^2 is independently halogen, $–CF_3$, –CN, –C(O)NHR, $–NO_2$, –NHR, –NHC(O)R, $–NHS(O)_2R$, $–N(R)_2$, or –OR, or a C_{1-6} aliphatic group;

R' is hydrogen or a C_{1-3} aliphatic group;

R" is hydrogen or a C_{1-3} aliphatic group;

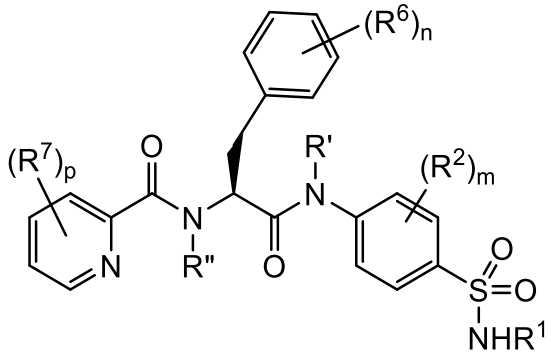
each R^6 is independently halogen, –CN, $–NO_2$, –NHR, $–N(R)_2$, –OR, or an optionally substituted C_{1-6} aliphatic group;

each R^7 is independently halogen, –CN, $–NO_2$, –NHR, $–N(R)_2$, –OR, or a C_{1-6} aliphatic group; and

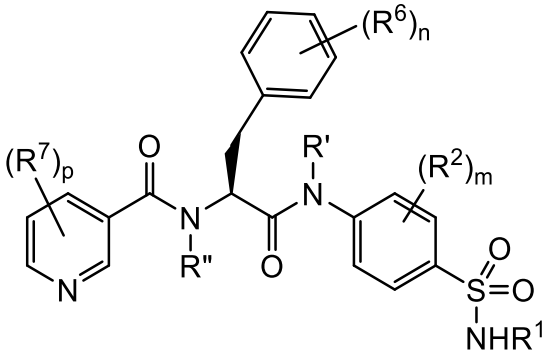
each of m, n, and p is independently 0, 1, 2, 3 or 4;

provided that R^1 is other than isopropyl, t-butyl, 1-methylcyclopropyl, 1-fluoromethylcyclopropyl, 1-difluoromethylcyclopropyl, 1-trifluoromethylcyclopropyl, or 3-methyl-3-oxetanyl when L^1 is $–S(O)_2N(R)$-.

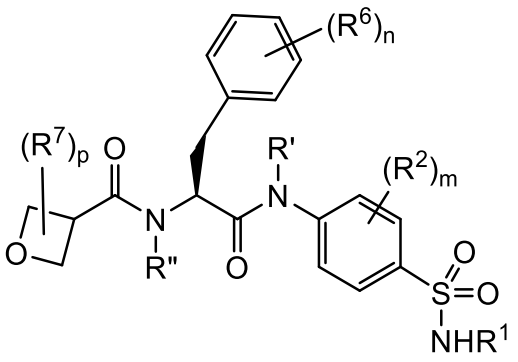
10. The compound of claim 9 of any one of formulas **XVI-a**, **XVI-b**, **XVI-c**, **XVI-d**, **XVIII-a**, **XVIII-b**, **XVIII-c**, **XVIII-d**, **XX-a**, **XX-b**, **XX-c**, **XX-d**, **XXII**, **XXIV-a**, **XXIV-b**, **XXVI-a**, **XXVI-b**, **XXVI-c**, or **XXVI-d**:



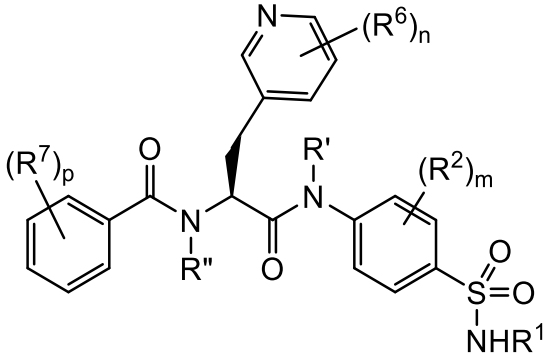
XVI-a



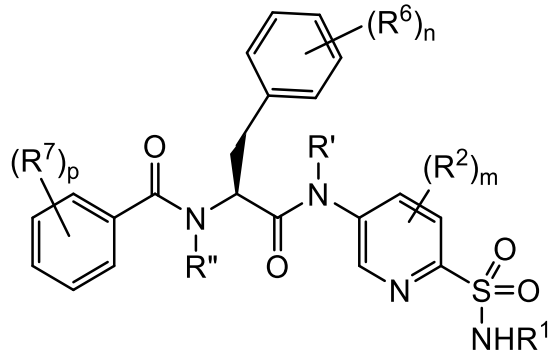
XVI-b



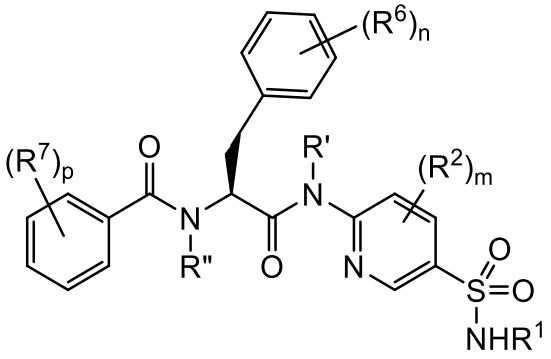
XVI-c



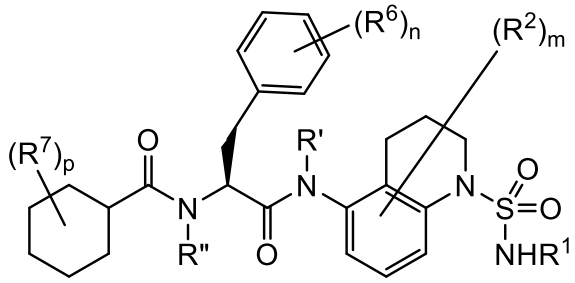
XVI-d



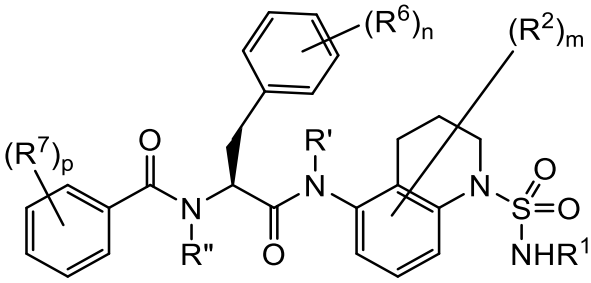
XVIII-a



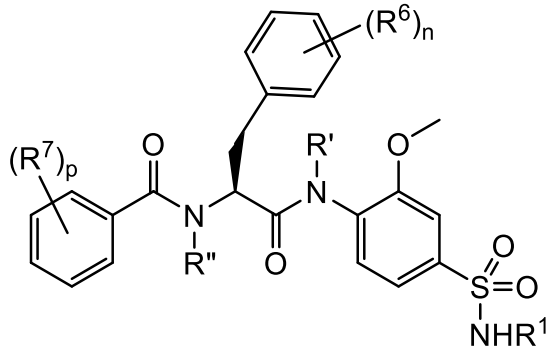
XVIII-b



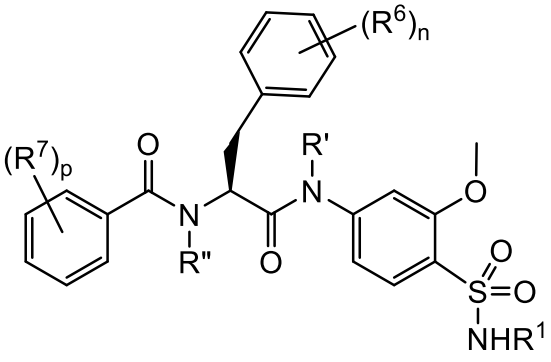
XVIII-c



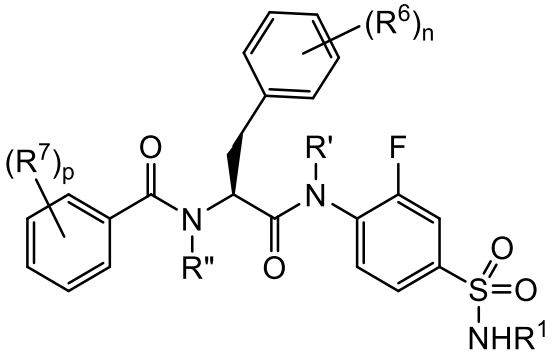
XVIII-d



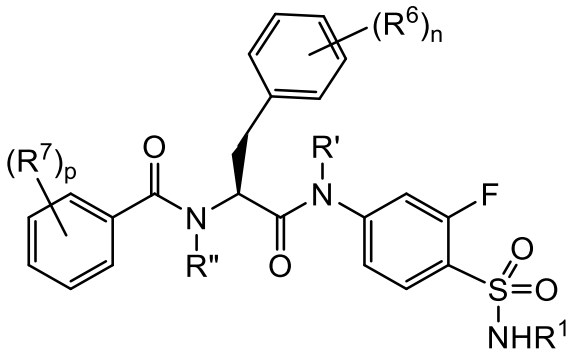
XX-a



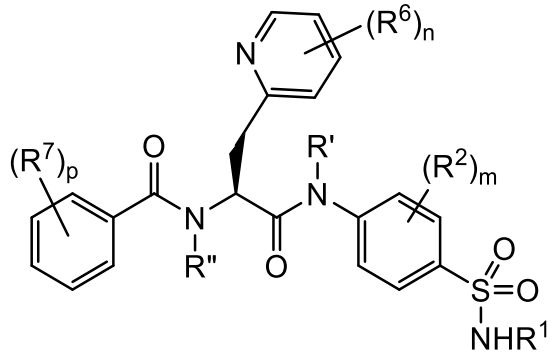
XX-b



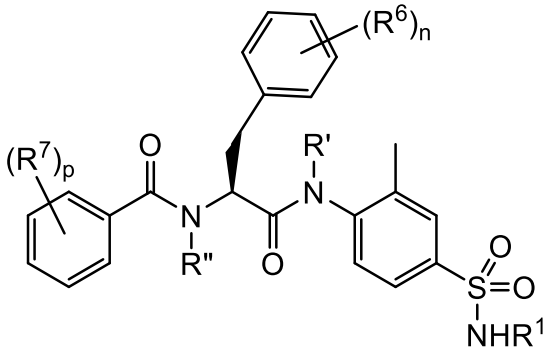
XX-c



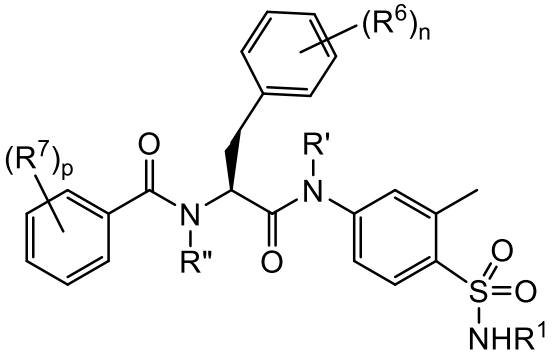
XX-d



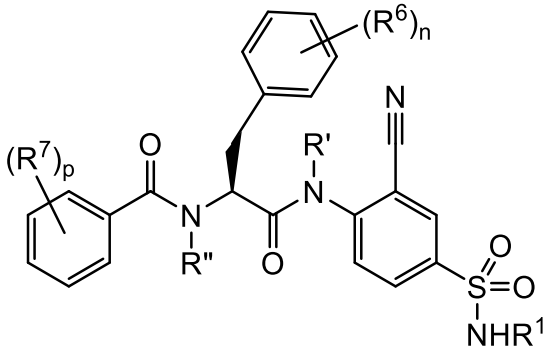
XXII

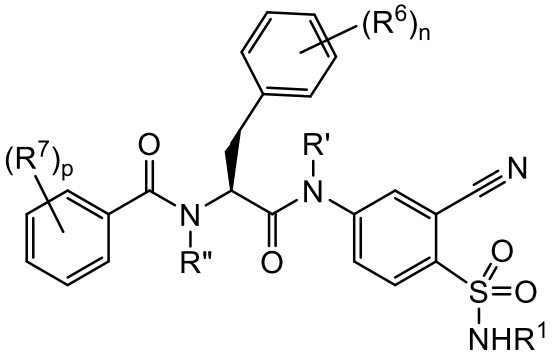


XXIV-a

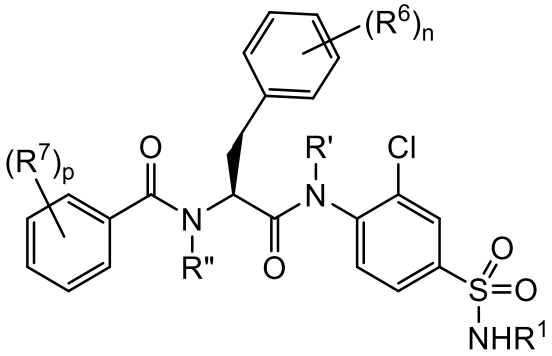


XXIV-b

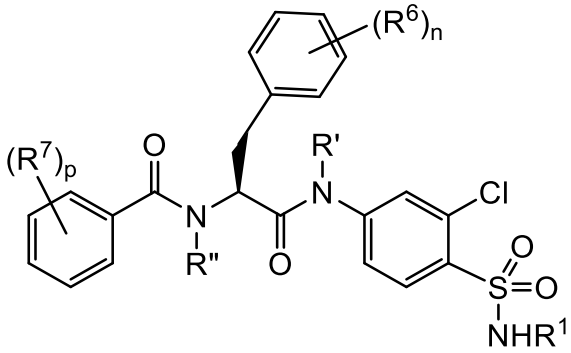




XXVI-a



XXVI-b



XXVI-c

XXVI-d

or a pharmaceutically acceptable salt thereof.

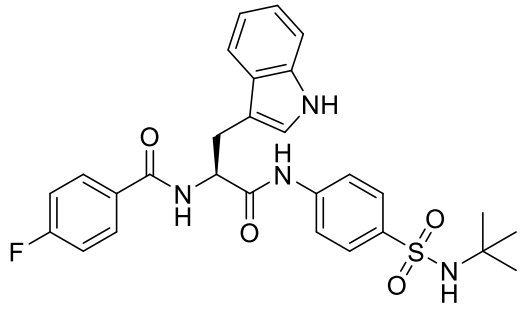
11. The compound of any one of claims 1-9, wherein at least one R^2 is fluoro, methyl, or methoxy.

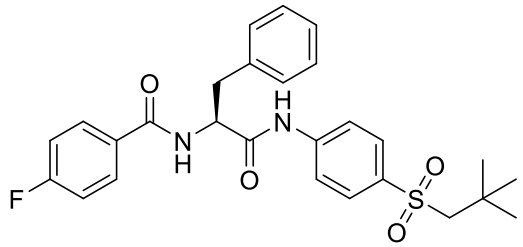
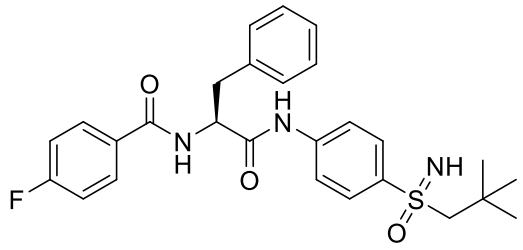
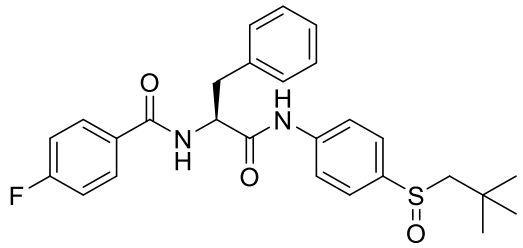
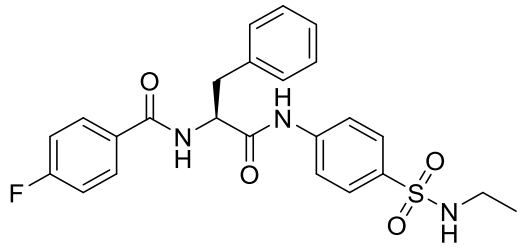
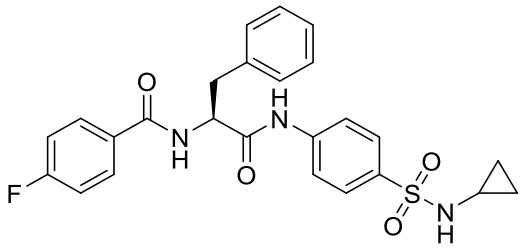
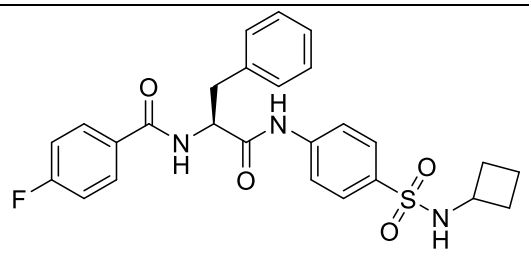
12. The compound of any one of the preceding claims, wherein m is 0, 1, 2, or 3.

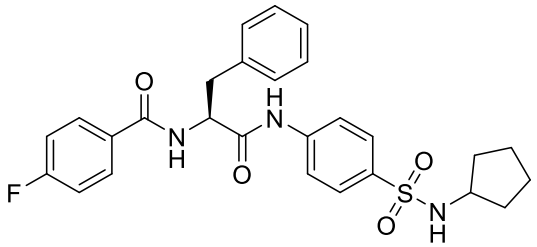
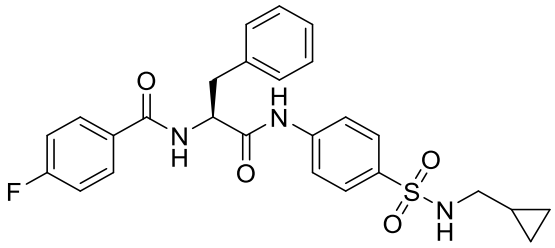
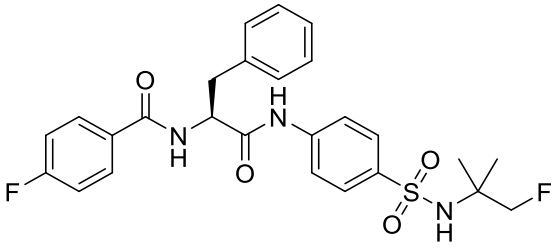
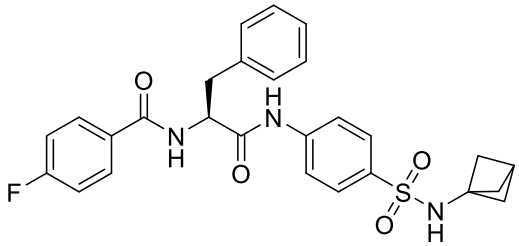
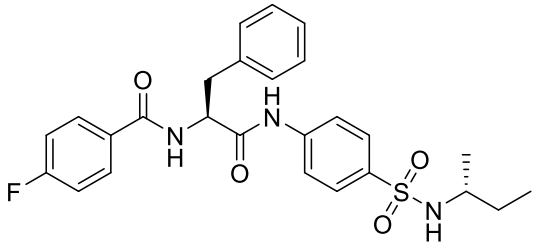
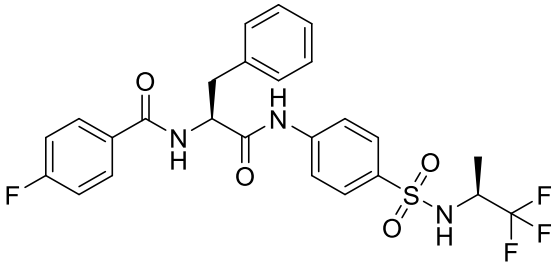
13. The compound of any one of the preceding claims, wherein p is 0, 1, 2, or 3.

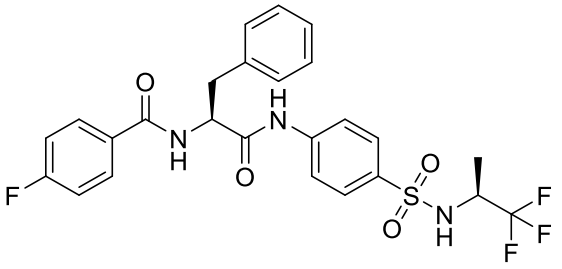
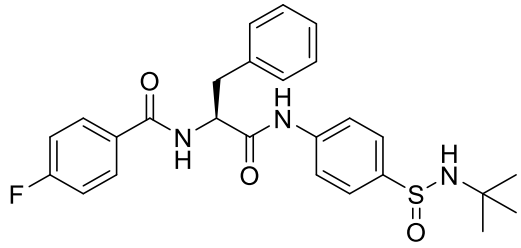
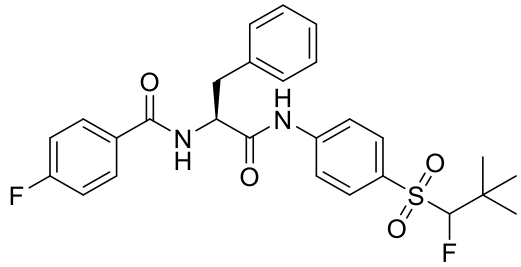
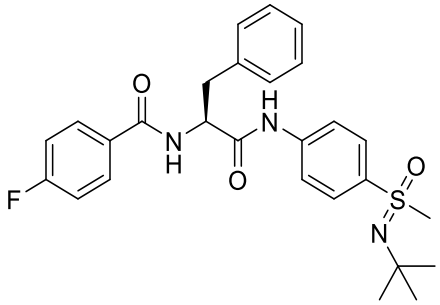
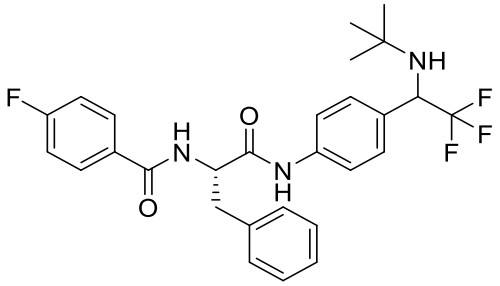
14. The compound of any one of the preceding claims, wherein at least one R^7 is fluoro.

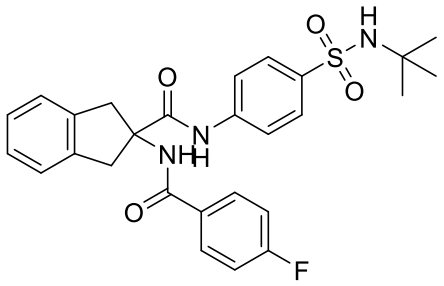
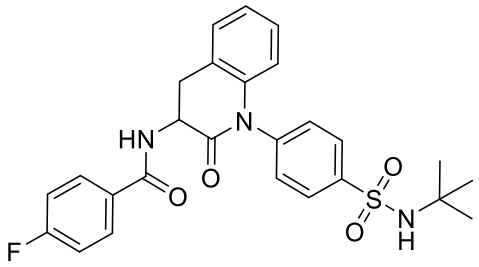
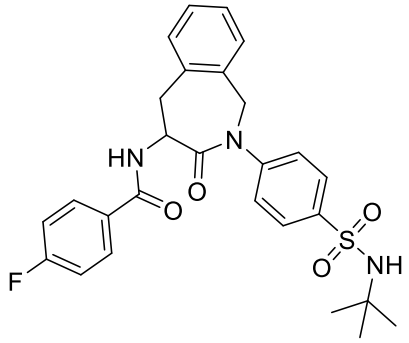
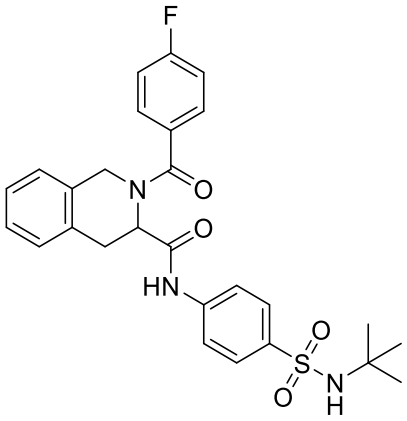
15. A compound selected from:

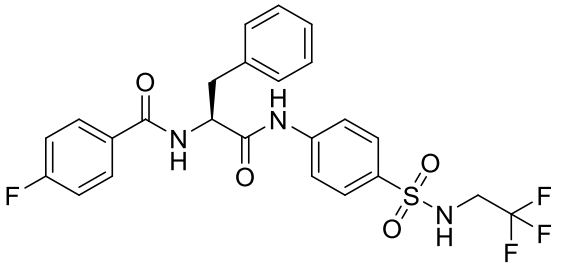
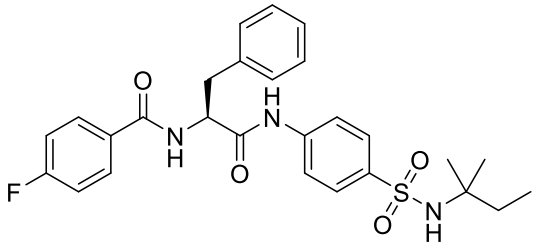
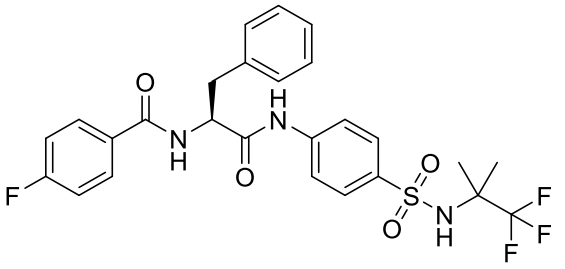
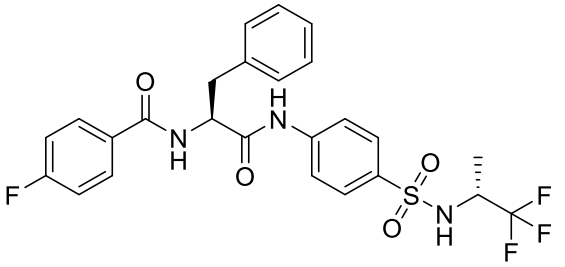
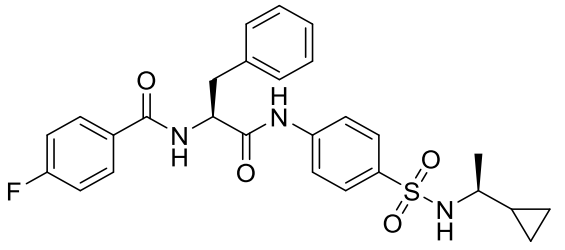
Compound	Structure
I-1	

Compound	Structure
I-2	
I-3	
I-4	
I-5	
I-6	
I-7	

Compound	Structure
I-8	
I-9	
I-10	
I-11	
I-12	
I-13	

Compound	Structure
I-14	
I-15	
I-16	
I-17	
I-18	

Compound	Structure
I-19	
I-20	
I-21	
I-22	

Compound	Structure
I-23	
I-24	
I-25	
I-26	
I-27	

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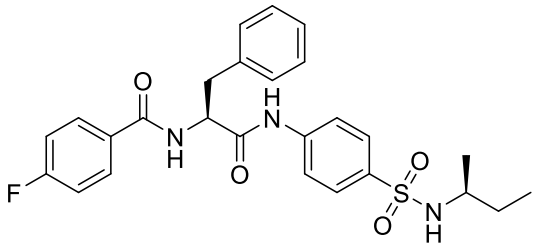
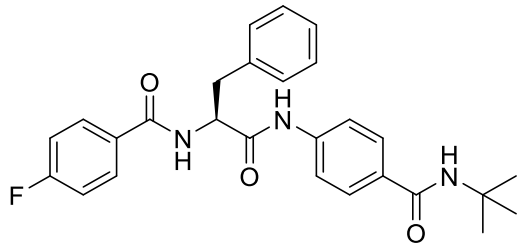
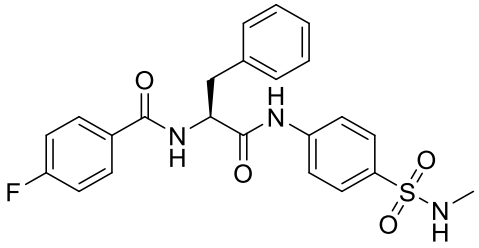
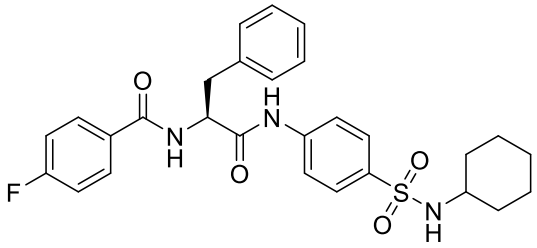
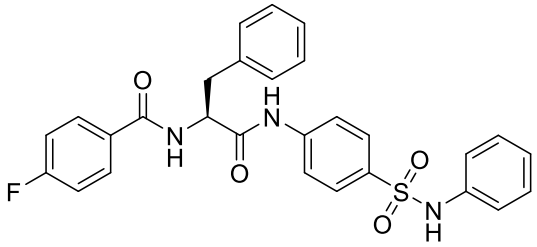
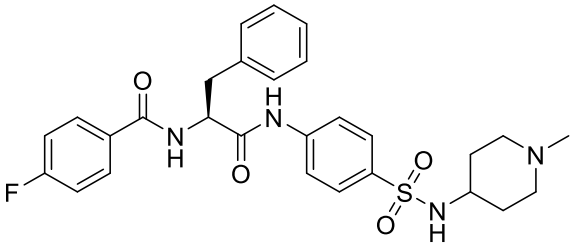
I-28	
I-29	
I-30	
I-31	
I-32	
I-33	

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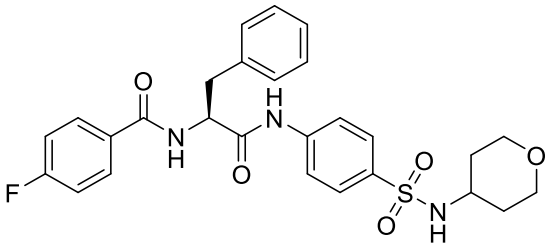
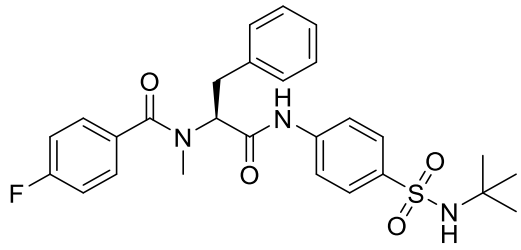
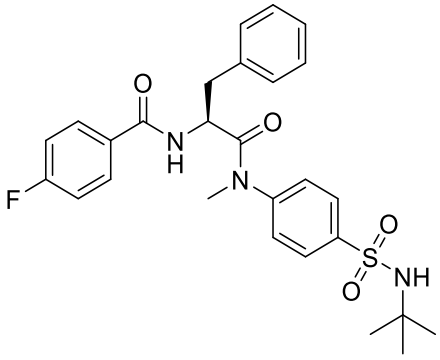
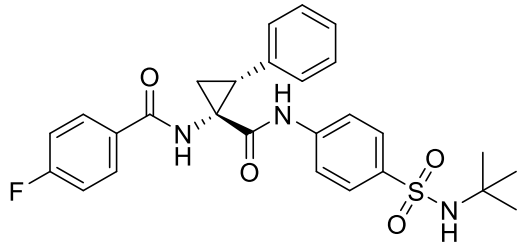
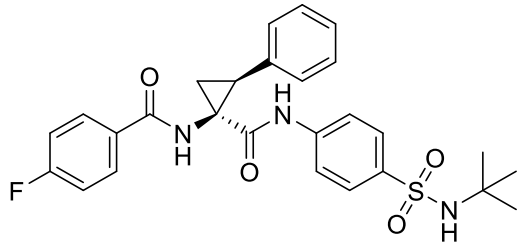
I-34	
I-35	
I-36	
I-37	
I-38	

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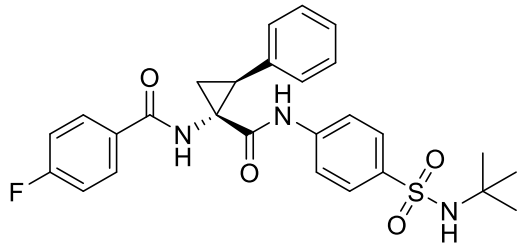
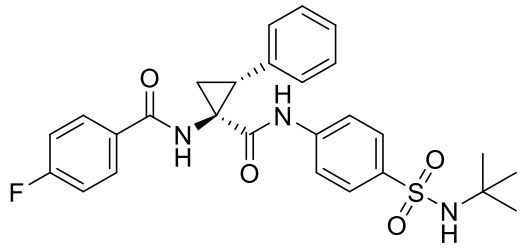
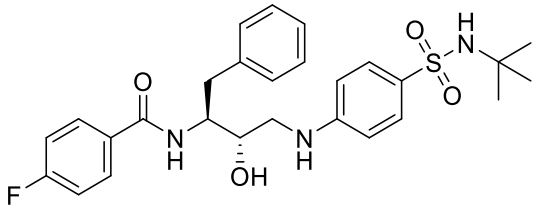
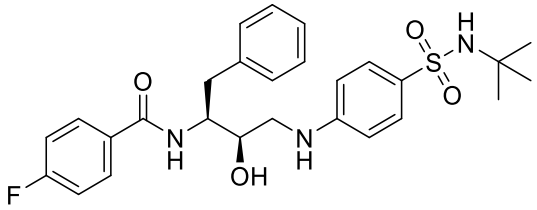
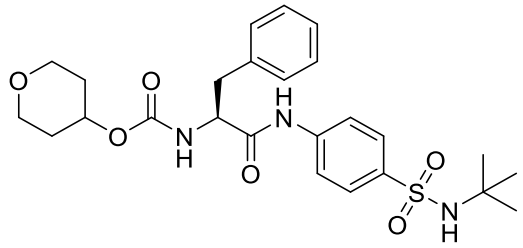
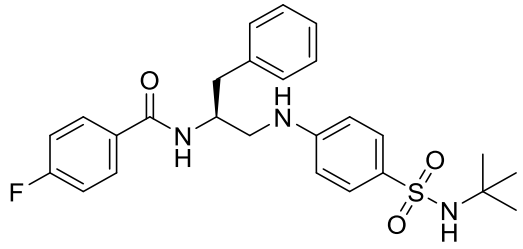
I-39	
I-40	
I-41	
I-42	
I-43	
I-44	

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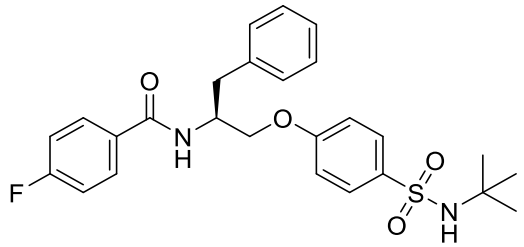
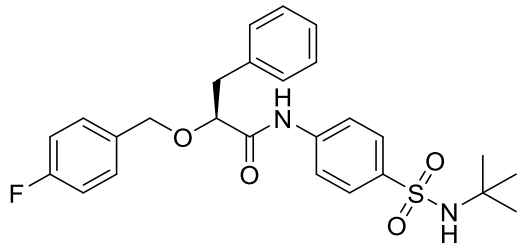
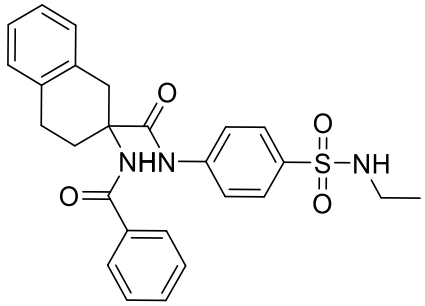
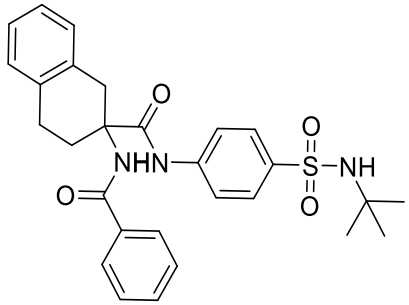
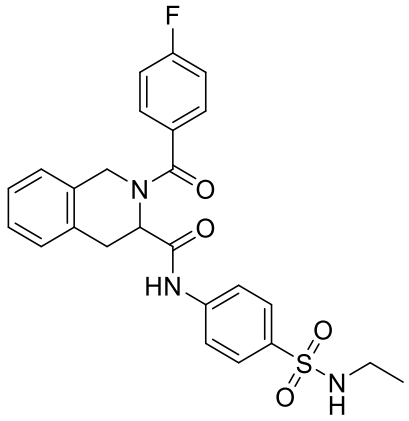
I-45	
I-46	
I-47	
I-48	
I-49	

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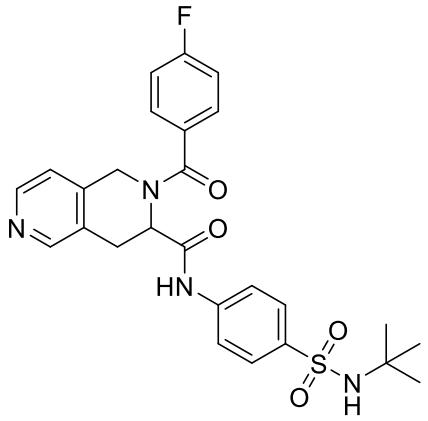
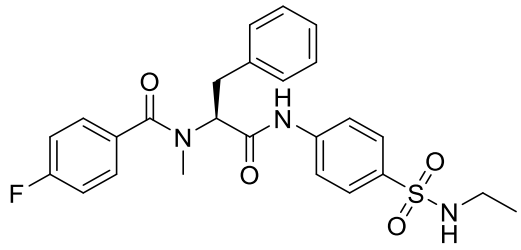
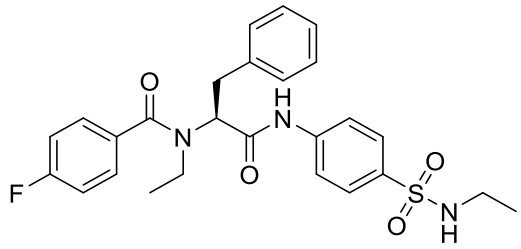
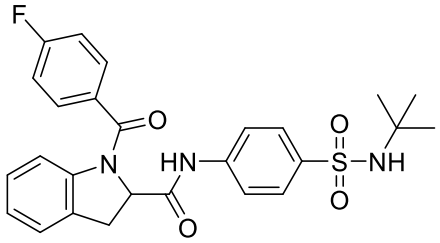
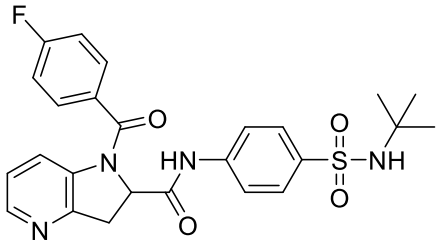
I-50	
I-51	
I-52	
I-53	
I-54	

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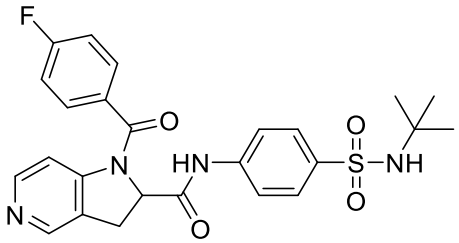
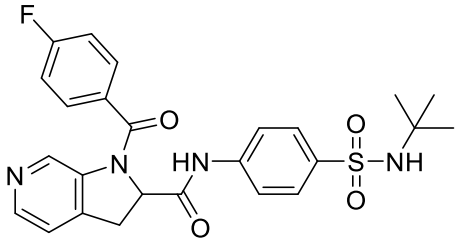
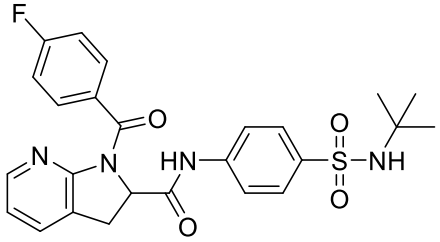
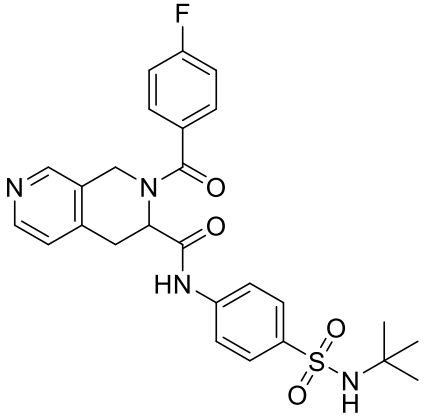
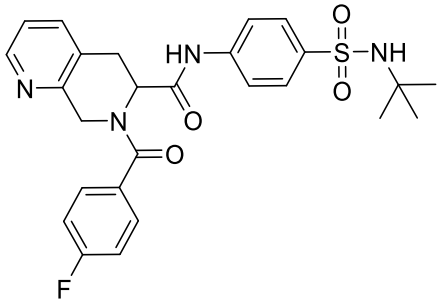
I-55	
I-56	
I-57	
I-58	
I-59	

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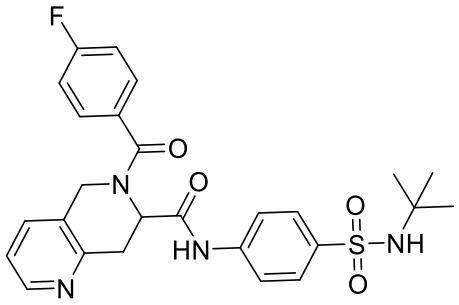
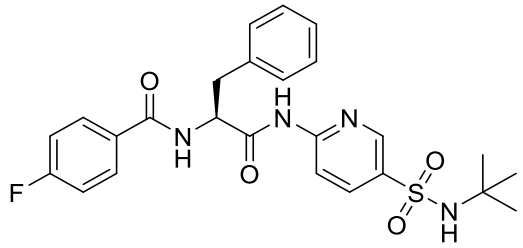
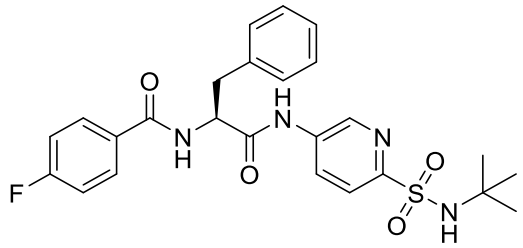
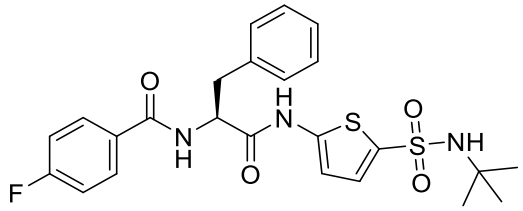
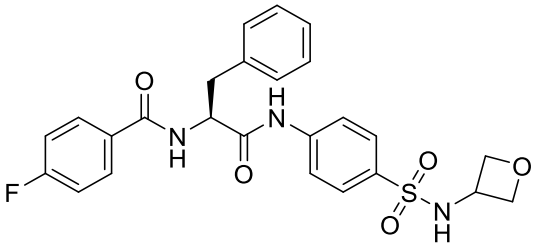
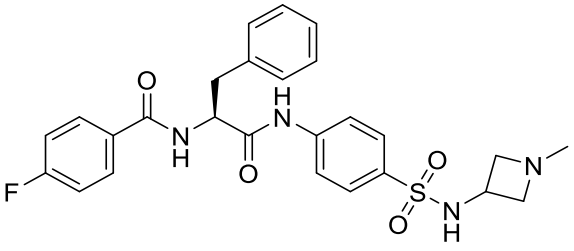
I-60	
I-61	
I-62	
I-63	
I-64	
I-65	

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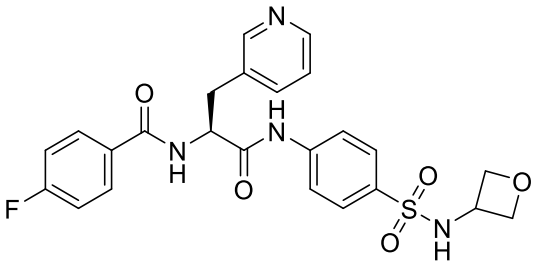
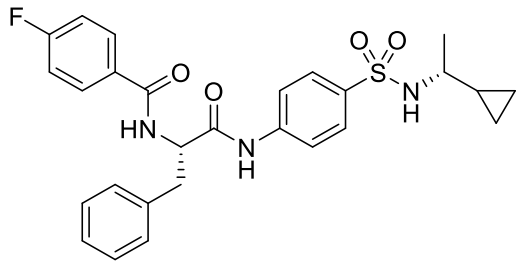
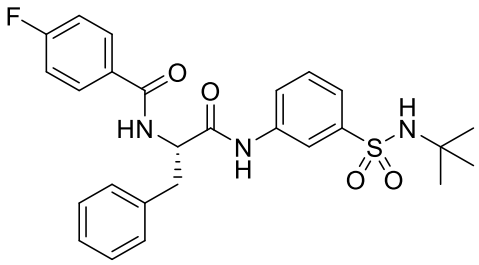
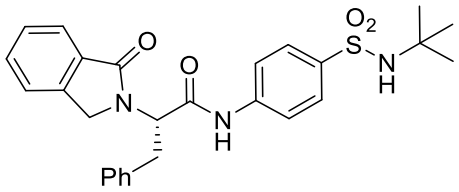
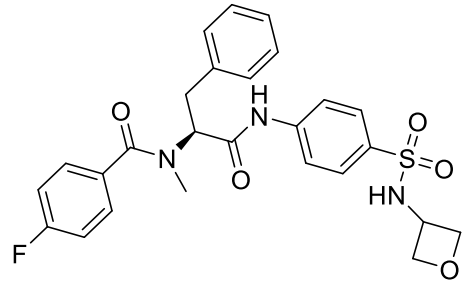
I-66	
I-67	
I-68	
I-69	
I-70	

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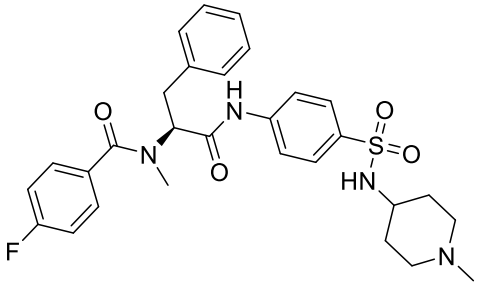
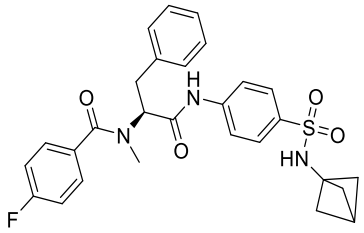
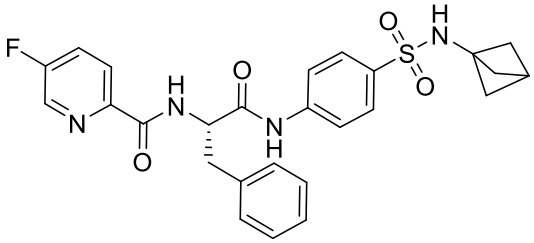
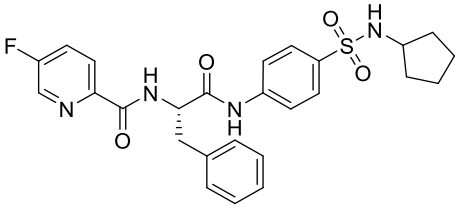
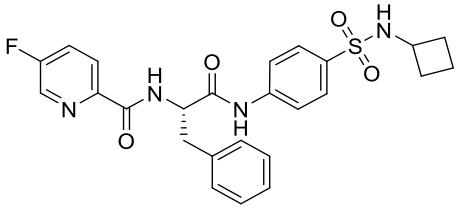
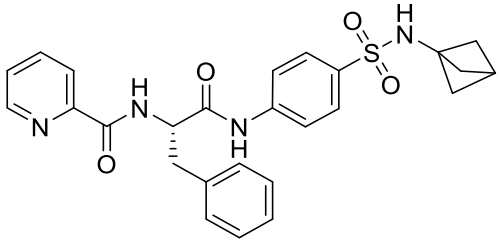
I-71	
I-72	
I-73	
I-74	
I-75	
I-76	

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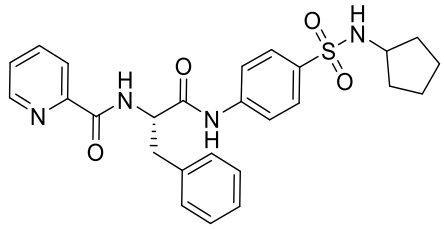
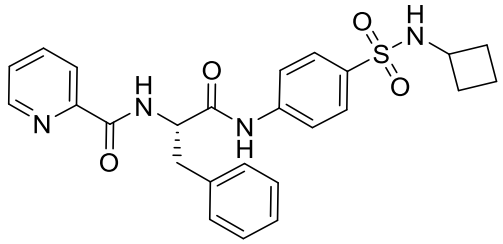
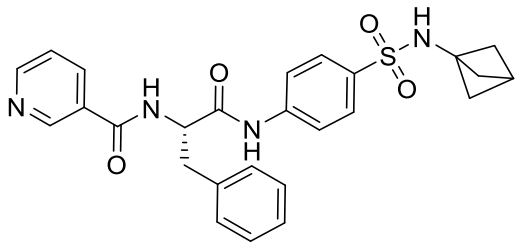
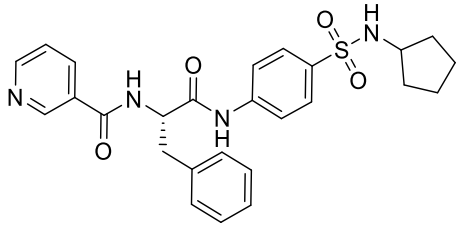
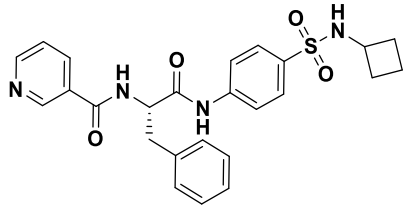
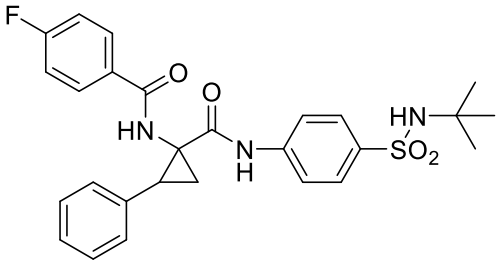
I-77	
I-78	
I-79	
I-80	
I-81	
I-82	

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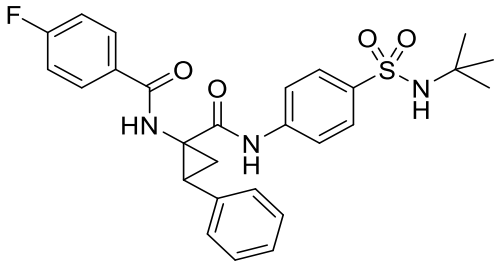
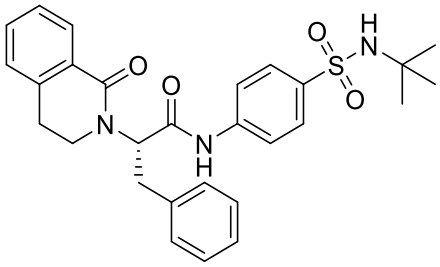
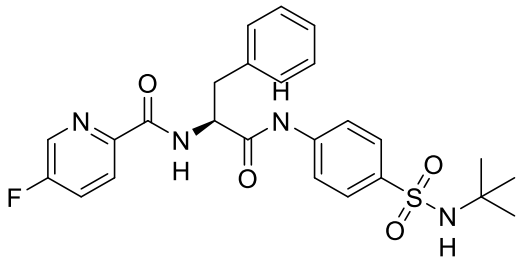
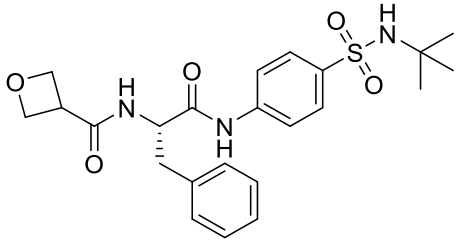
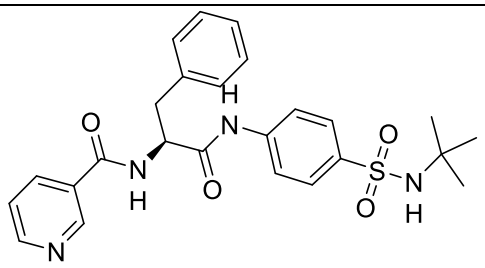
I-83	
I-84	
I-85	
I-86	
I-87	

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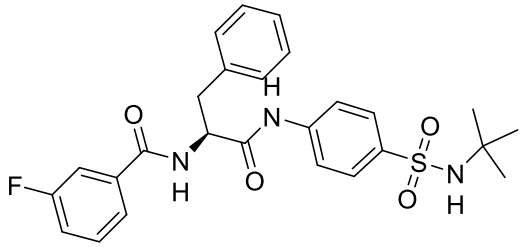
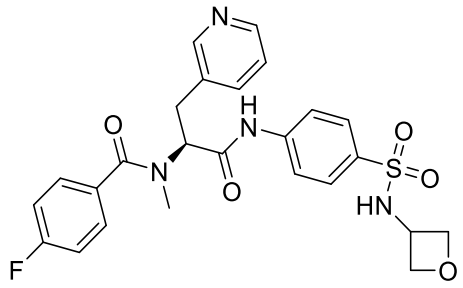
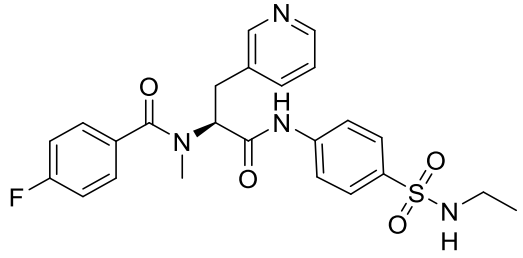
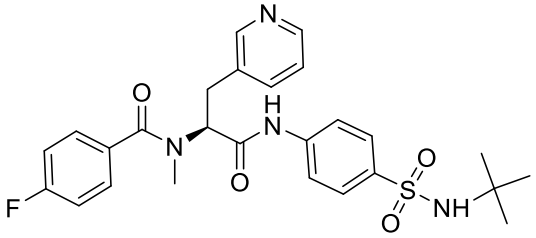
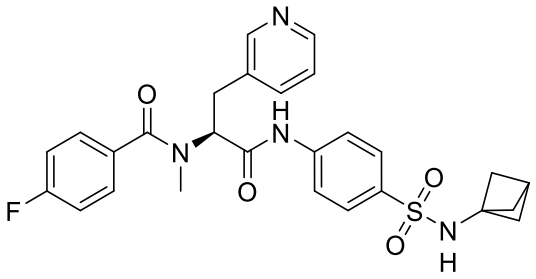
I-88	
I-89	
I-90	
I-91	
I-92	

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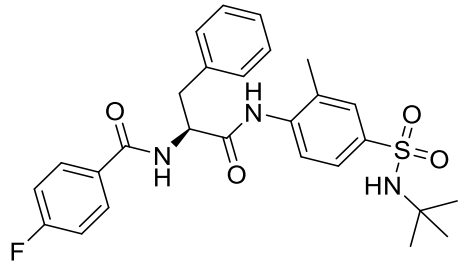
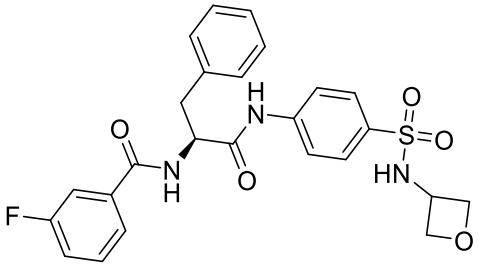
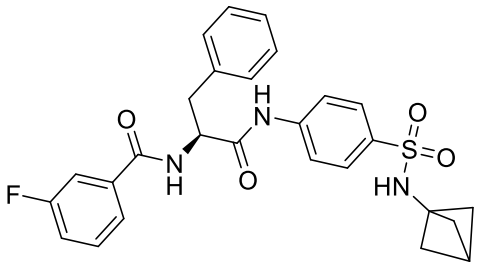
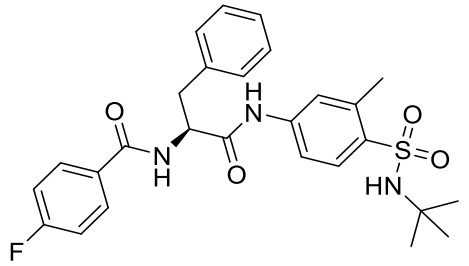
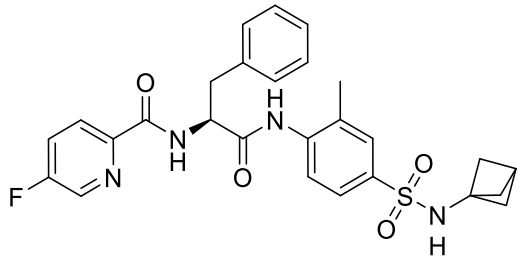
I-93	
I-94	
I-95	
I-96	
I-97	

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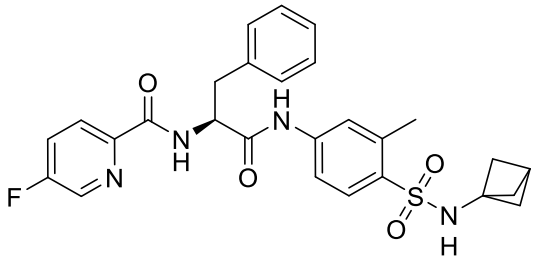
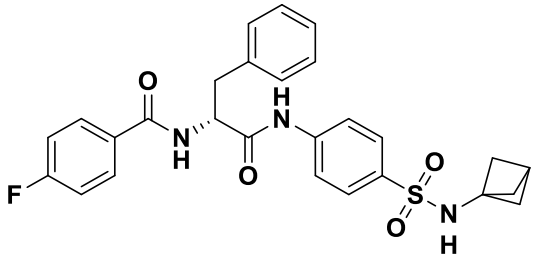
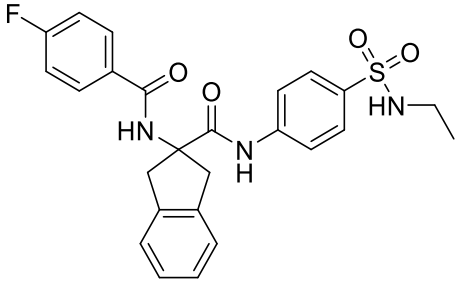
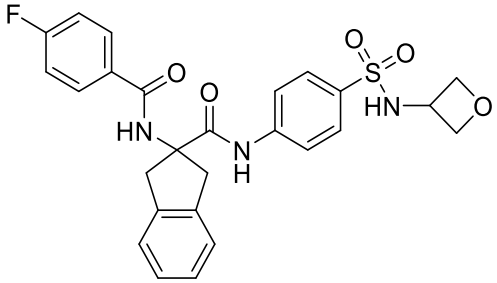
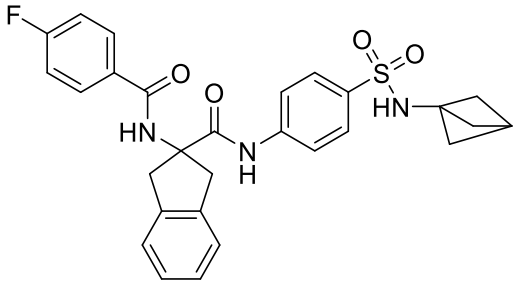
I-98	
I-99	
I-100	
I-101	
I-102	

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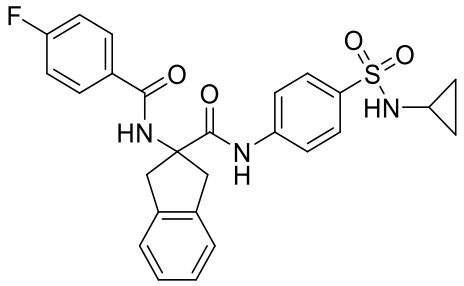
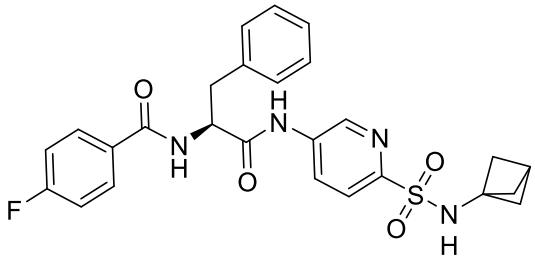
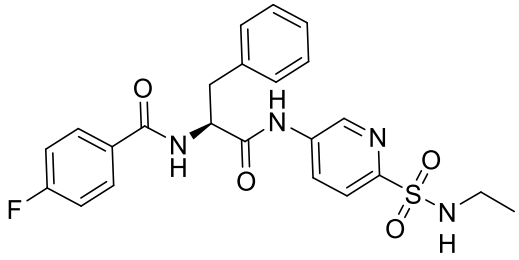
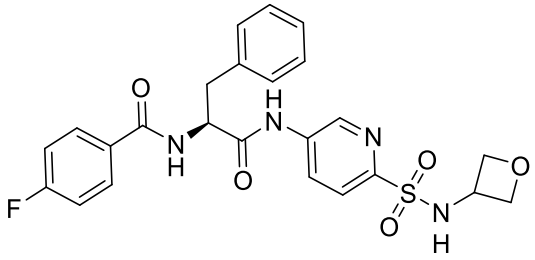
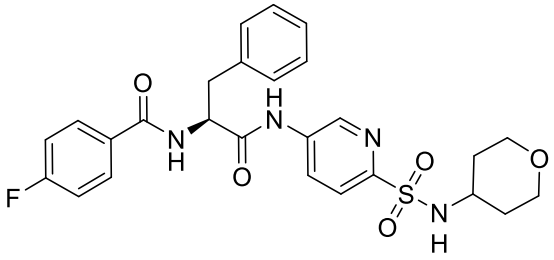
I-103	
I-104	
I-105	
I-106	
I-107	

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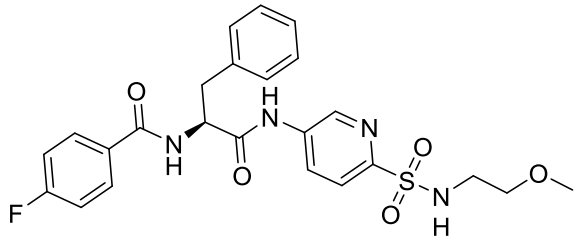
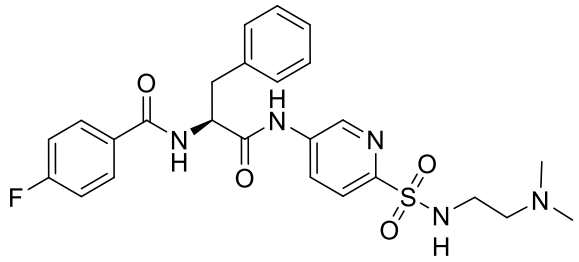
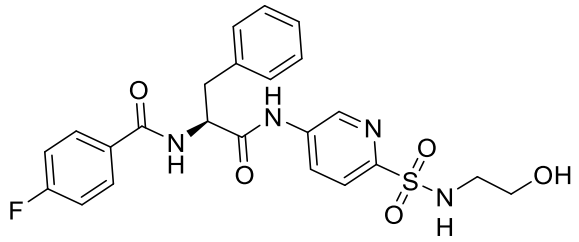
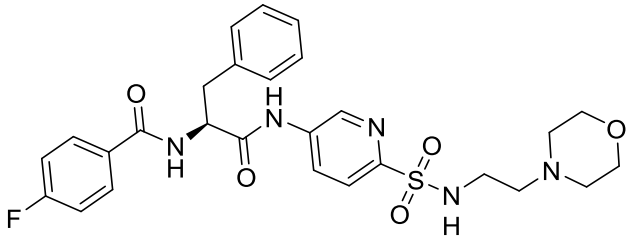
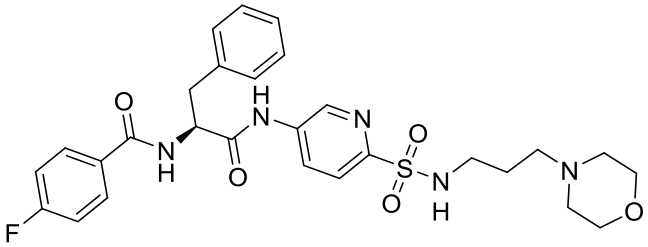
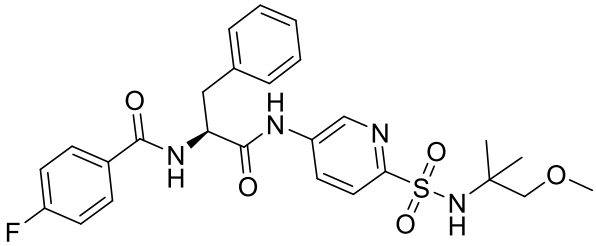
I-108	
I-109	
I-110	
I-111	
I-112	
I-113	

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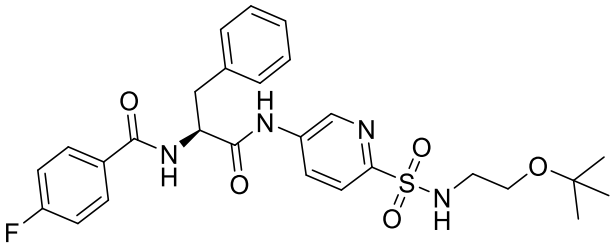
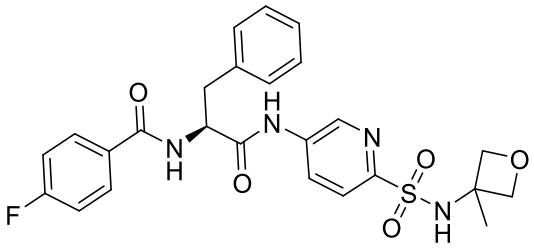
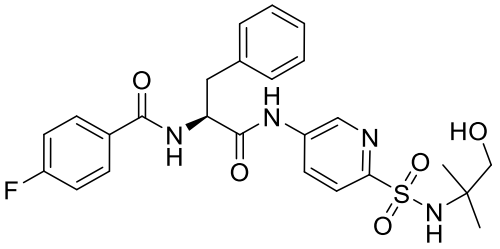
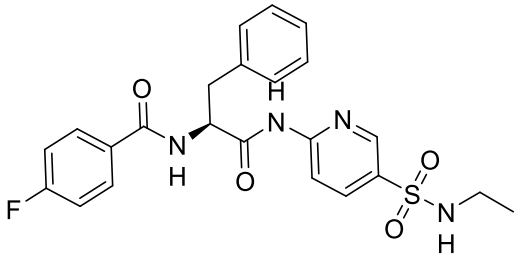
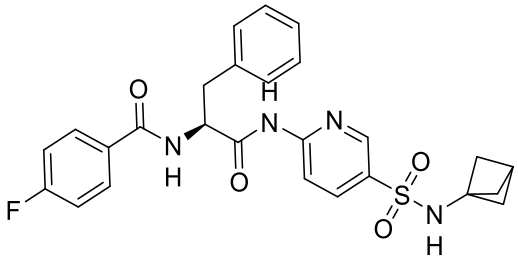
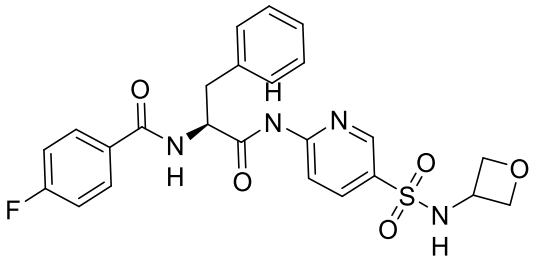
I-114	
I-115	
I-116	
I-117	
I-118	
I-119	

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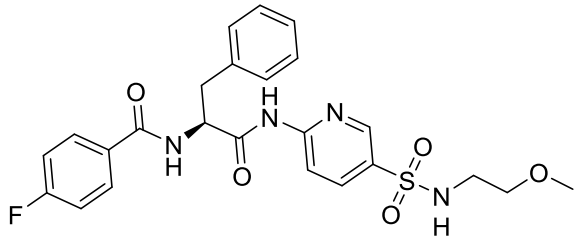
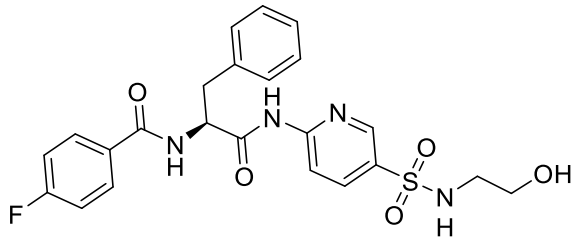
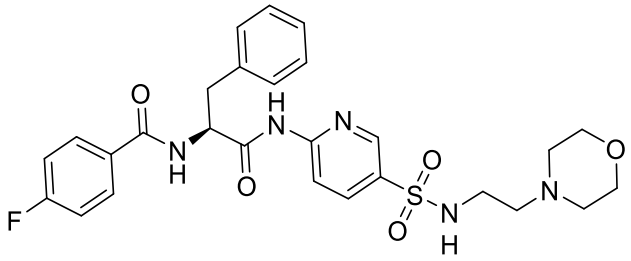
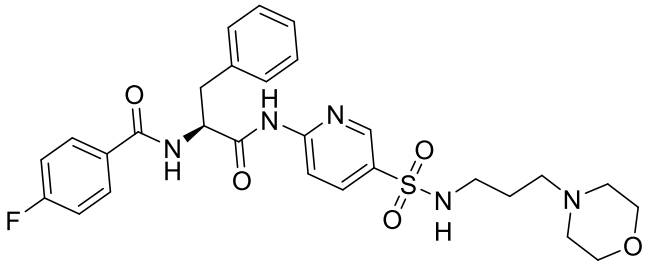
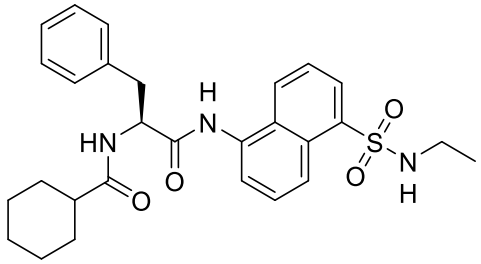
I-120	
I-121	
I-122	
I-123	
1-124	

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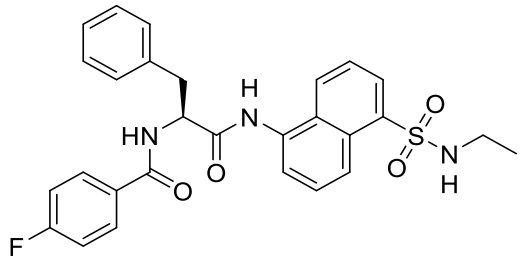
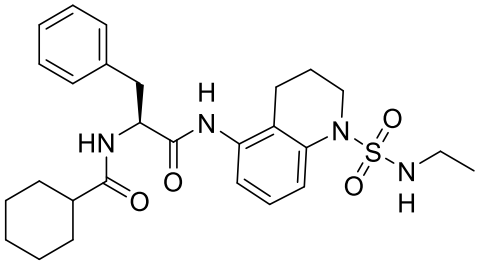
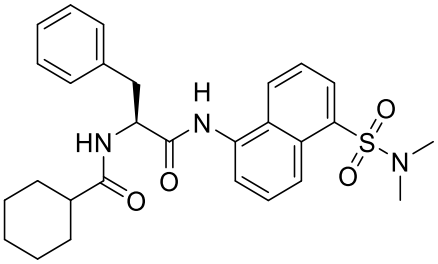
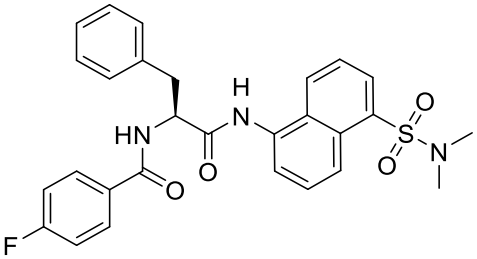
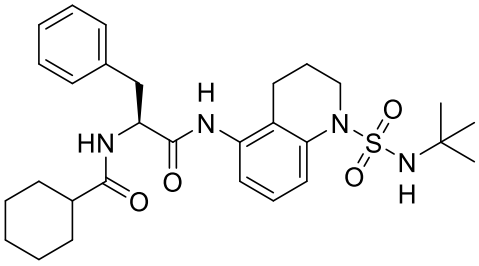
I-125	
I-126	
I-127	
I-128	
I-129	

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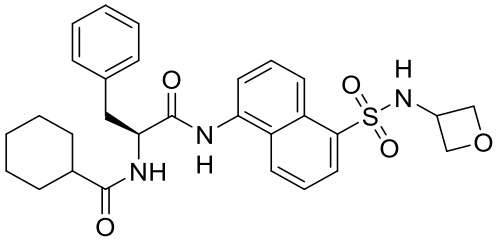
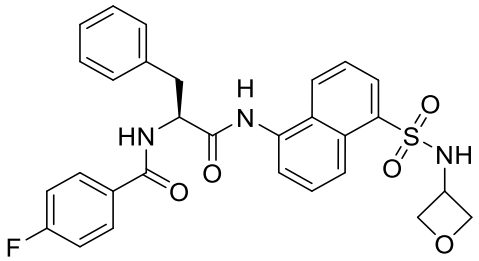
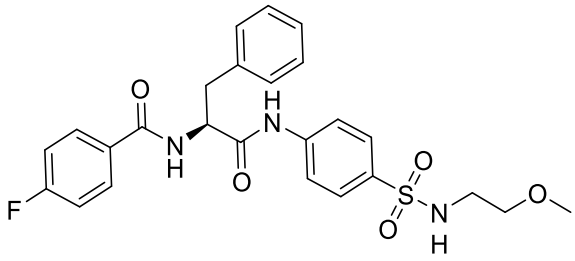
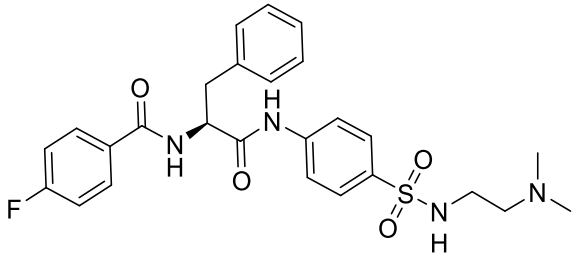
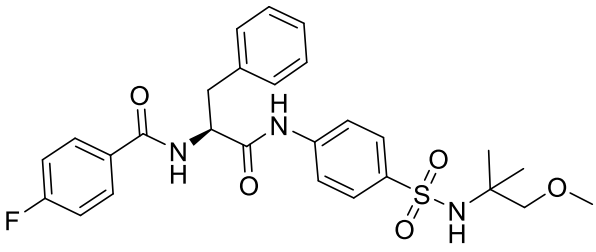
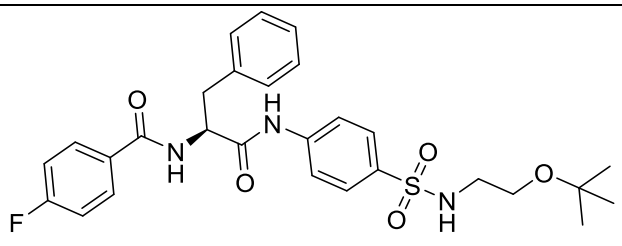
I-130	
I-131	
I-132	
I-133	
I-134	
I-135	

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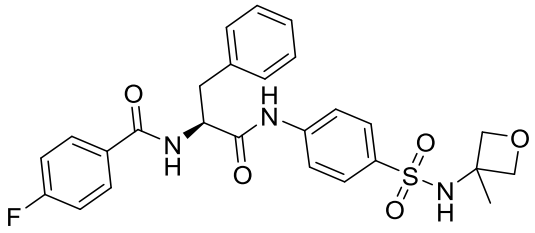
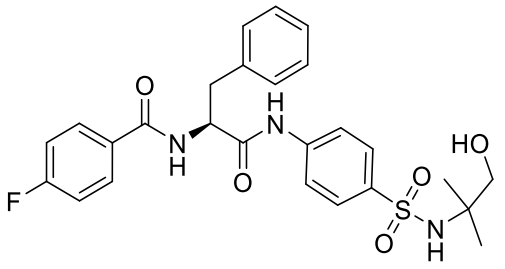
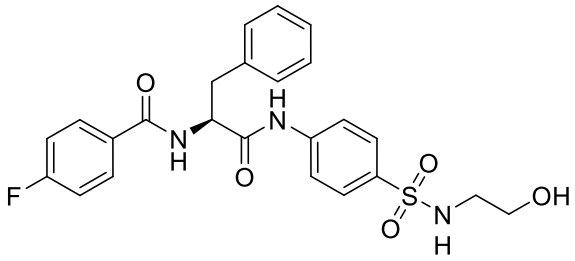
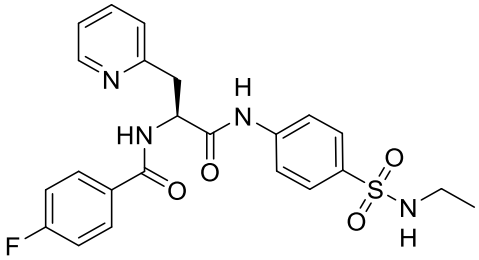
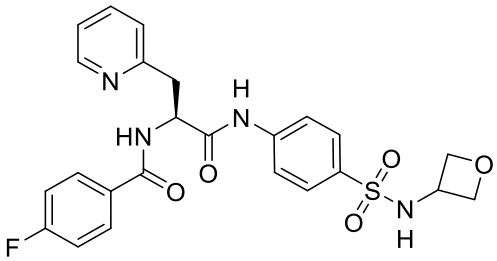
I-136	
I-137	
I-138	
I-139	
I-140	

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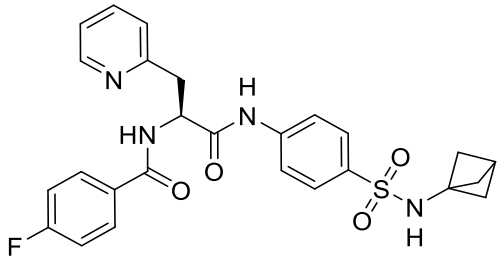
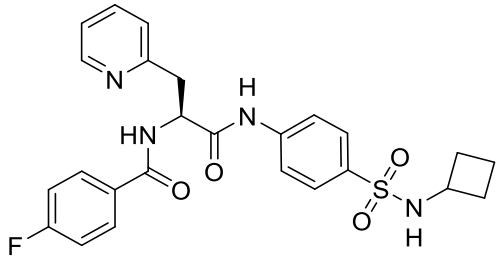
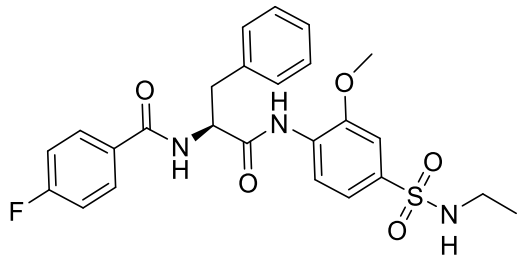
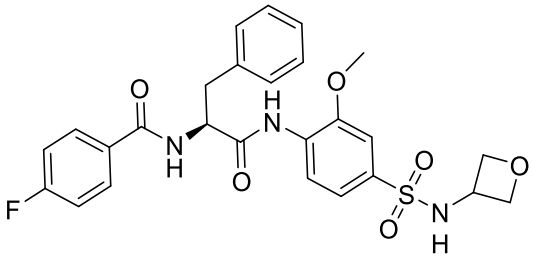
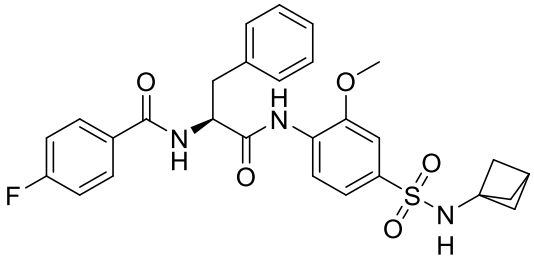
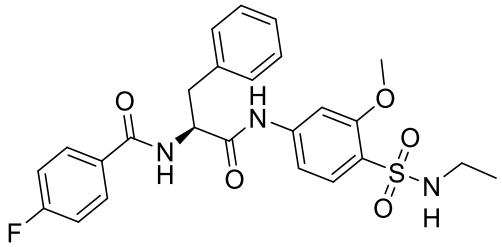
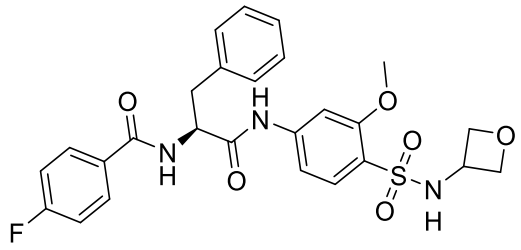
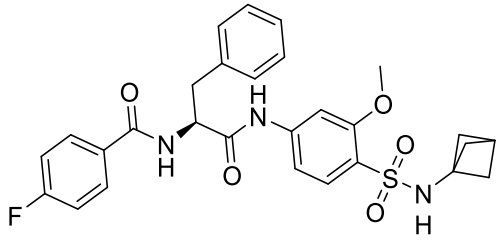
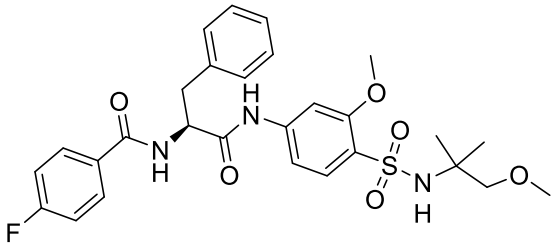
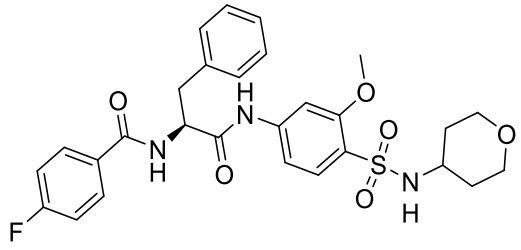
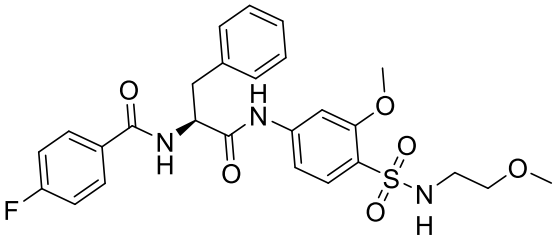
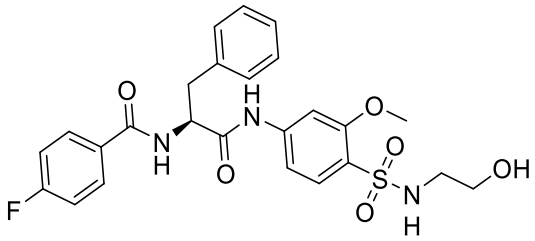
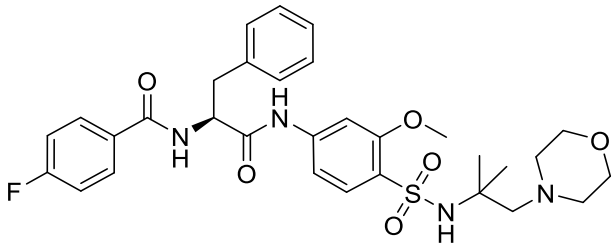
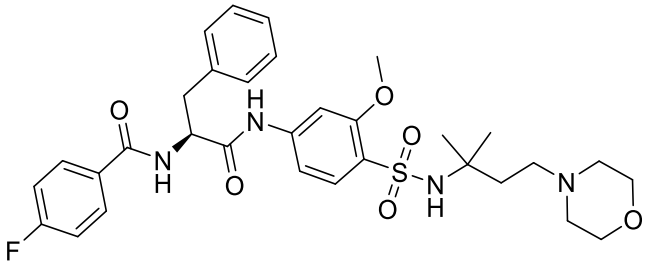
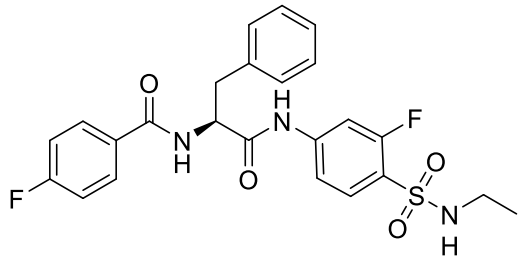
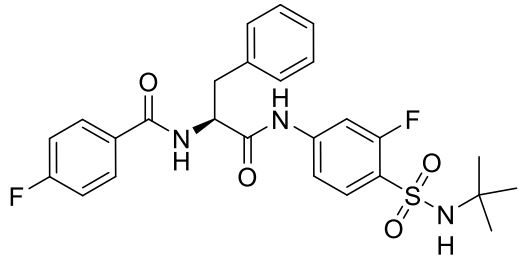
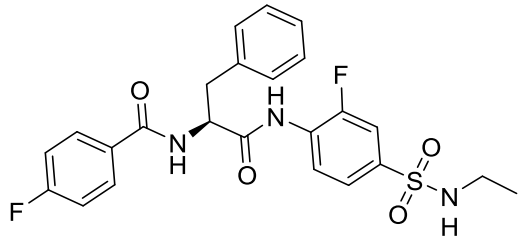
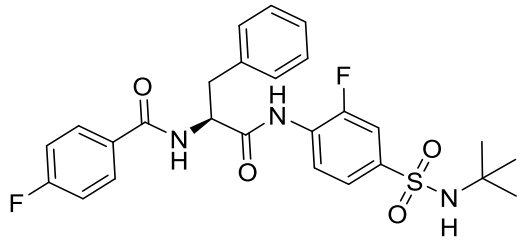
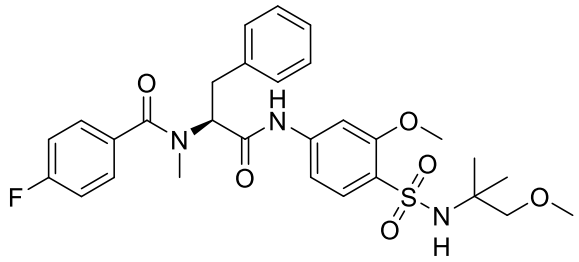
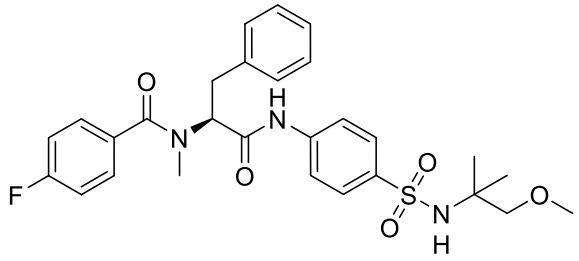
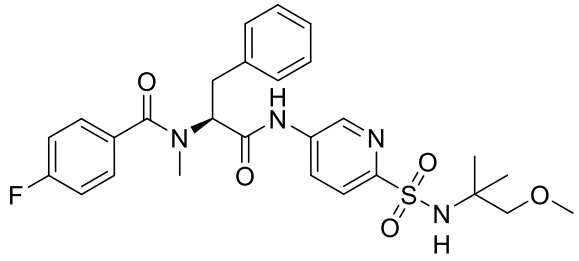
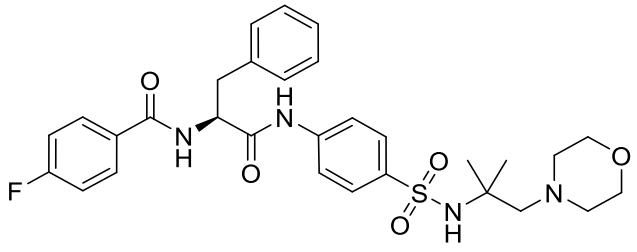
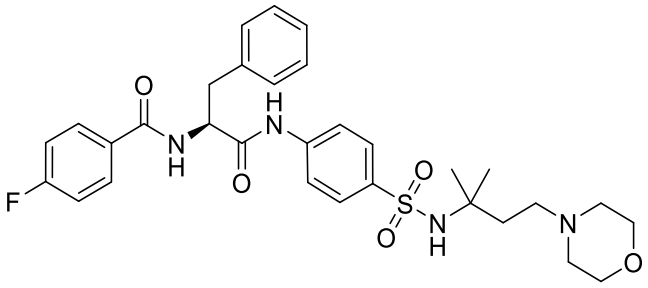
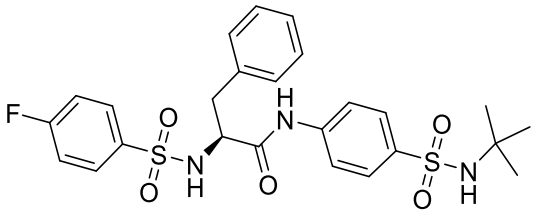
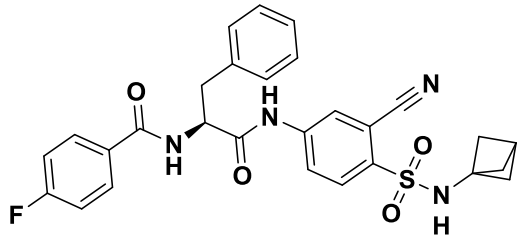
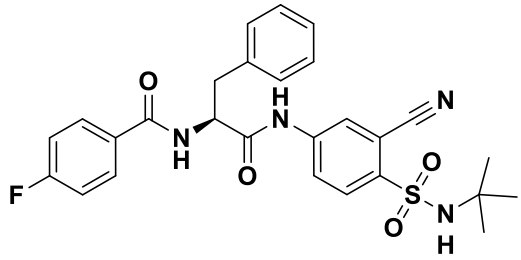
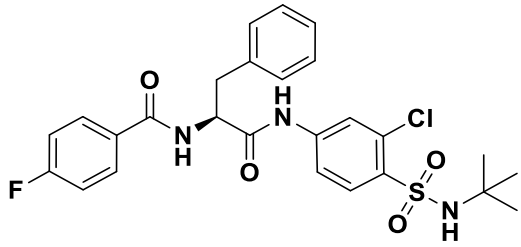
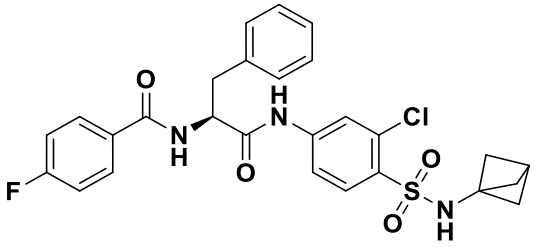
I-141	
I-142	
I-143	
I-144	
I-145	

Compound	Structure
I-146	
I-147	
I-148	
I-149	
I-150	
I-151	

Compound	Structure
I-152	
I-153	
I-154	
I-155	
I-156	
I-157	

Compound	Structure
I-158	
I-159	
I-160	
I-161	
I-162	

Compound	Structure
I-163	
I-165	
I-166	
I-167	
I-168	
I-169	

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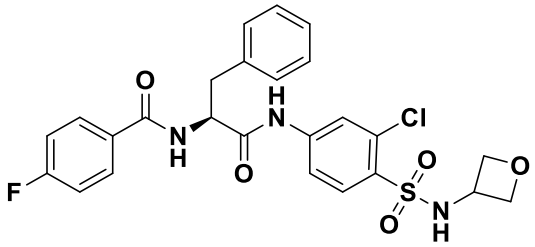
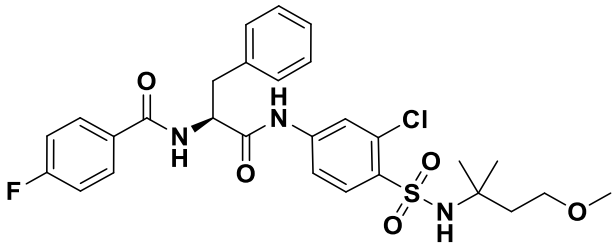
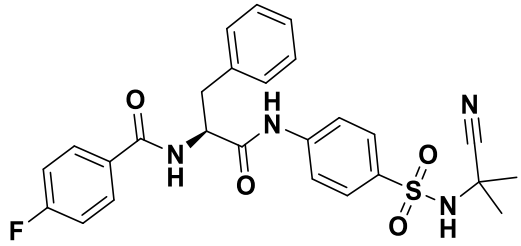
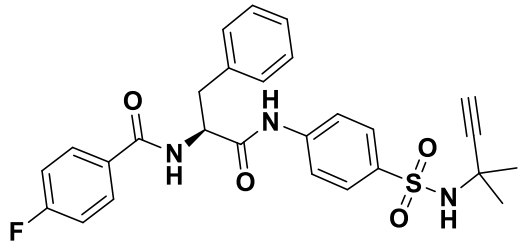
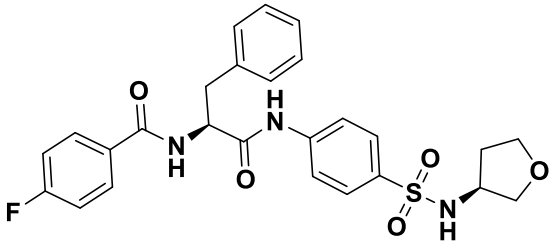
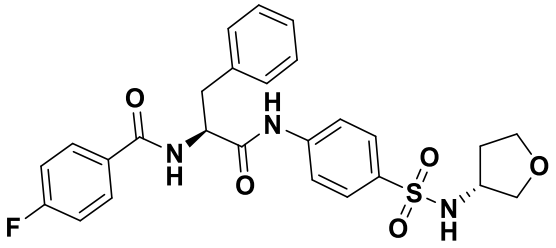
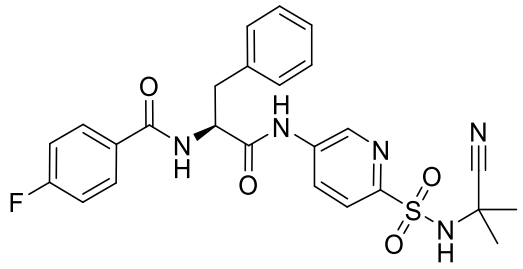
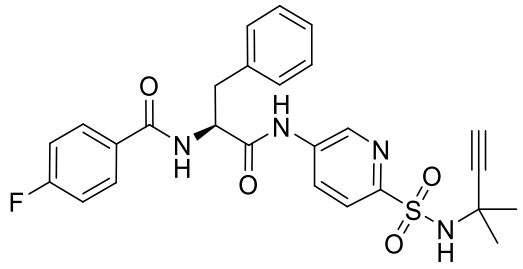
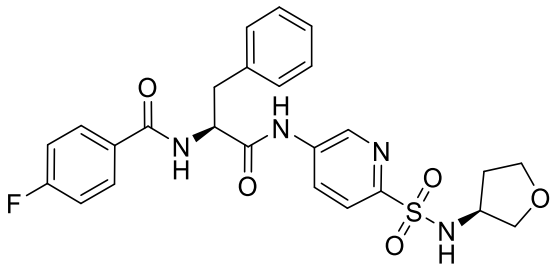
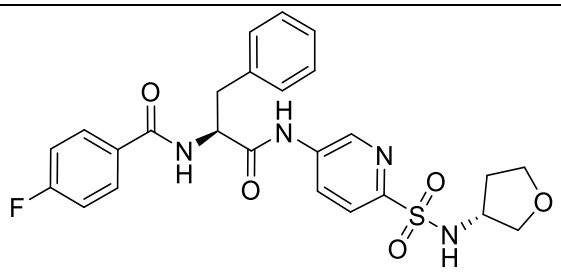
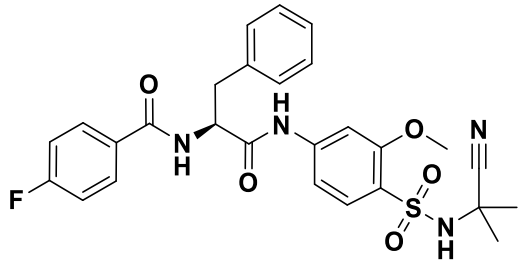
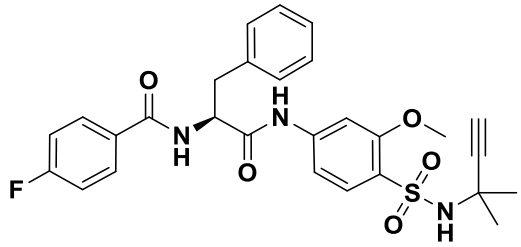
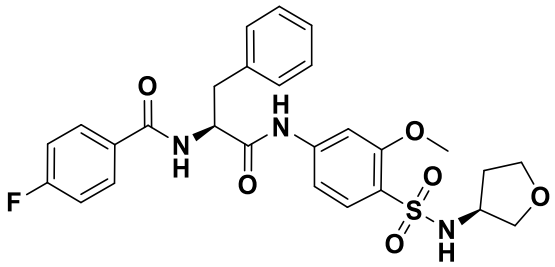
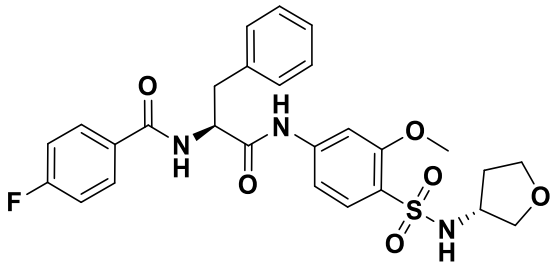
I-170	
I-171	
I-172	
I-173	
I-174	
I-175	

Compound	Structure
I-176	
I-177	
I-178	
I-179	
I-180	

Compound	Structure
I-181	
I-182	
I-183	

, or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising a compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

17. Use of a compound of any one of claims 1-15 in the preparation of a medicament for inhibiting USP30, wherein the inhibiting regulates mitochondrial homeostasis.

18. Use of a compound of any one of claims 1-15 in the preparation of a medicament for treating an USP30-mediated disorder, disease, or condition selected from the group consisting of a neurodegenerative disease; mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome; Leber's hereditary optic neuropathy (LHON); neuropathy, ataxia, retinitis pigmentosa- maternally inherited Leigh syndrome (NARP-MILS); Danon disease; ischemic heart disease leading to myocardial infarction; multiple sulfatase

deficiency (MSD); mucolipidosis II (ML II); mucolipidosis III (ML III); mucolipidosis IV (ML IV); GM1 -gangliosidosis (GM1); neuronal ceroid- lipofuscinoses (NCL1); Alpers disease; Barth syndrome; Beta-oxidation defects; carnitine- acyl-carnitine deficiency; carnitine deficiency; creatine deficiency syndromes; coenzyme Q10 deficiency; complex I deficiency; complex II deficiency; complex III deficiency; complex IV deficiency; complex V deficiency; COX deficiency; chronic progressive external ophthalmoplegia syndrome (CPEO); CPT I deficiency; CPT II deficiency; glutaric aciduria type II; Kearns-Sayre syndrome; lactic acidosis; long-chain acyl-CoA dehydrongenase deficiency (LCHAD); Leigh disease or syndrome; lethal infantile cardiomyopathy (LIC); Luft disease; glutaric aciduria type II; medium-chain acyl-CoA dehydrongenase deficiency (MCAD); myoclonic epilepsy and ragged-red fiber (MERRF) syndrome; mitochondrial recessive ataxia syndrome; mitochondrial cytopathy; mitochondrial DNA depletion syndrome; myoneurogastointestinal disorder and encephalopathy; Pearson syndrome; pyruvate carboxylase deficiency; pyruvate dehydrogenase deficiency; POLG mutations; medium/short-chain 3-hydroxyacyl-CoA dehydrogenase (M/SCHAD) deficiency; and very long-chain acyl-CoA dehydrongenase (VLCAD) deficiency.

19. The use of claim 18, wherein the neurodegenerative disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, ischemia, stroke, dementia with Lewy bodies, and frontotemporal dementia.

20. The use of claim 18, wherein the neurodegenerative disease is Alzheimer's disease or Parkinson's disease.

21. The use of claim 18, wherein the disorder is a neoplastic disease selected from the group consisting of metastatic carcinoma, multiple myeloma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, nasopharyngeal carcinoma, and leukemia.

22. The use of claim 18, wherein the disease is cardiovascular disease, kidney disease, pulmonary fibrosis, ophthalmic conditions, cancer, cognitive disease, peroxisome related disease, natural aging, or an age-related disease.

23. The use of claim 22, wherein the peroxisome related disease is selected from the group consisting of Ataxia-telangiectasia mutated, Heimler syndrome, Infantile refsum disease, Neonatal adrenoleukodystrophy, Rhizomelic chondrodysplasia punctate, White matter dementia, Zellweger syndrome, and Zellweger spectrum disorder.

24. A compound of any one of claims 1-15, for use in therapy.