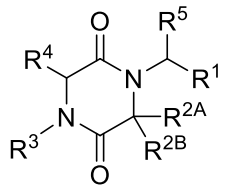
[0005] Current agents that target the cardiac sarcomere, such as inotropes (drugs that increase the contractile ability of the heart) are poorly selective for cardiac tissue, which leads to recognized adverse effects that limit their use. These adverse effects include cell damage caused by an increased rate of energy expenditure, exacerbation of relaxation abnormalities, and potential arrhythmogenic side effects that may result from increased cytosolic Ca^{2+} and cyclic AMP concentrations in the inotropically stimulated myocardium. Given the limitations of current agents, new approaches are needed to improve cardiac function in HCM and HFpEF.

[0006] There remains a great need for agents that exploit new mechanisms of action and may have better outcomes in terms of relief of symptoms, safety, and patient mortality, both short-term and long-term. New agents with an improved therapeutic index over current agents will provide a means to achieve these clinical outcomes. The selectivity of agents directed at the cardiac sarcomere (for example, by targeting cardiac myosin) has been identified as an important means to achieve this improved therapeutic index. The present disclosure provides such agents (particularly cardiac sarcomere inhibitors) and methods for their use. These agents are allosteric inhibitors of cardiac myosin. Benefits of these compounds include a wider therapeutic index, less impact on cardiac relaxation, better pharmacokinetics, and better safety.

[0007] The present disclosure provides chemical entities, pharmaceutical compositions and methods for the treatment of heart failure including HCM and HFpEF. The compositions are inhibitors of the cardiac sarcomere, for example, inhibitors of cardiac myosin.

BRIEF SUMMARY

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



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of substituted or unsubstituted phenyl and substituted or unsubstituted pyridyl;

R^{2A}, R^{2B}, R^3, and R^4 are defined by any one of (i) – (iii):

(i) R^{2A} is H or substituted or unsubstituted alkyl;

R^{2B} is selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^3 is phenyl substituted with two or more substituents, or substituted or unsubstituted pyridyl; and

R^4 is H or substituted or unsubstituted alkyl;

or

(ii) R^{2A} is H or substituted or unsubstituted alkyl;

R^{2B} is substituted or unsubstituted phenyl or substituted or unsubstituted pyridyl;

R^3 is unsubstituted C_2-C_4 alkyl; and

R^4 is H or substituted or unsubstituted alkyl;

or

(iii) R^{2A} and R^{2B} are taken together with the carbon atom to which they are attached to form G^1, wherein G^1 is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, or substituted or unsubstituted heterocyclyl ring, each of which is optionally fused to a phenyl ring;

R^3 is selected from the group consisting of unsubstituted C_2-C_6 alkyl, alkyl substituted with alkoxy, cyano, or halo, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl; and

R^4 is H or unsubstituted alkyl; and

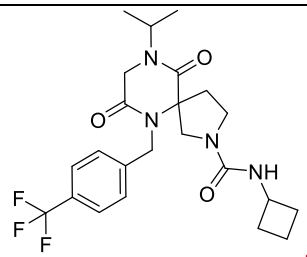
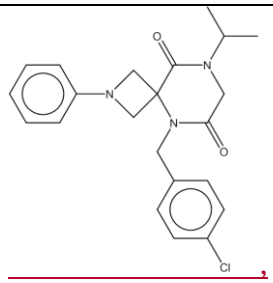
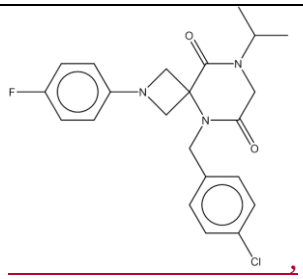
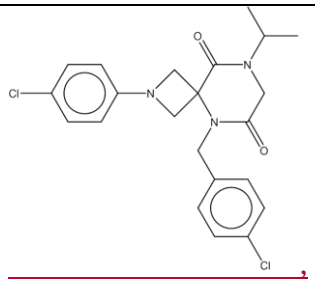
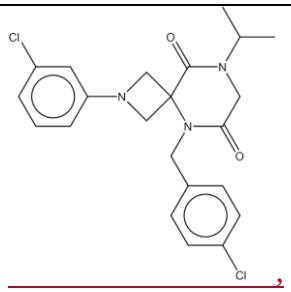
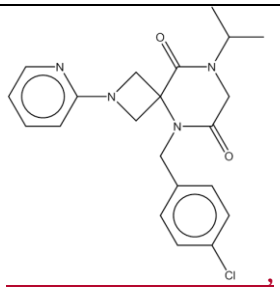
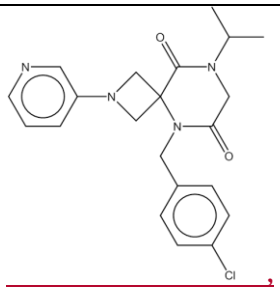
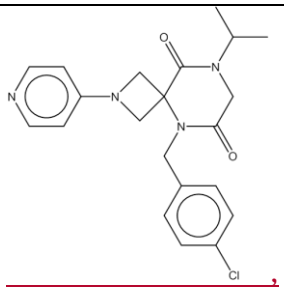
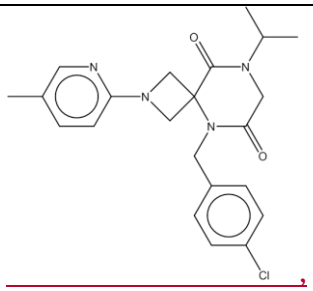
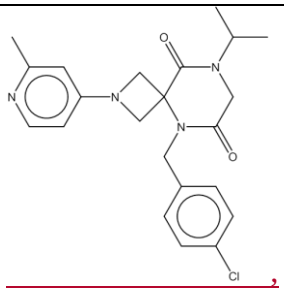
R^5 is H or substituted or unsubstituted alkyl;

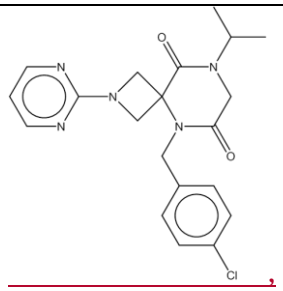
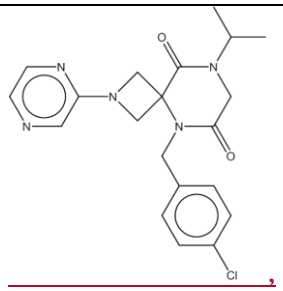
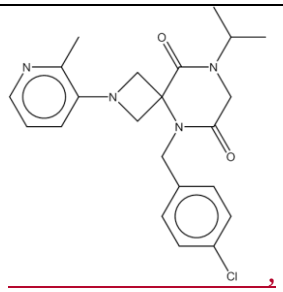
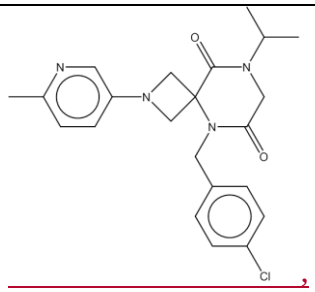
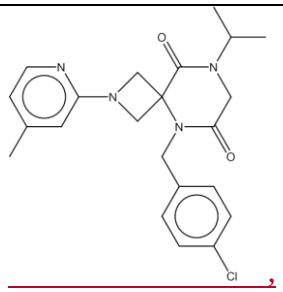
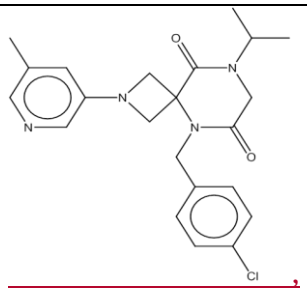
wherein, when one or more of provisions (a) – (b) apply, then R^1 is substituted or unsubstituted pyridyl or phenyl substituted with at least one substituent other than methyl or methoxy:

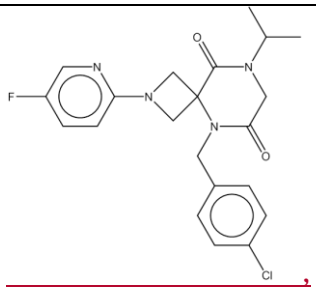
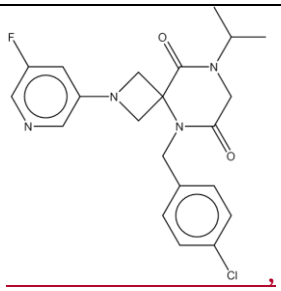
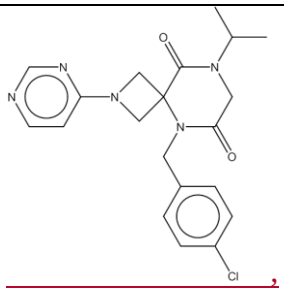
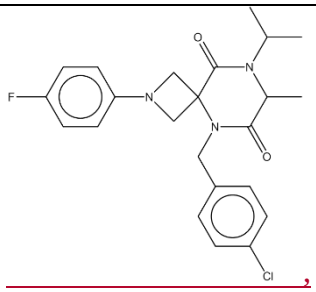
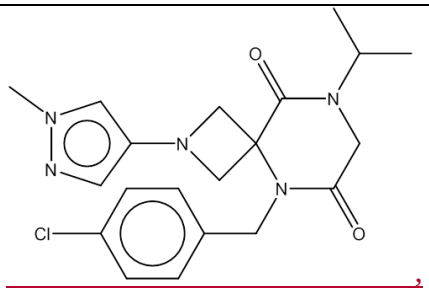
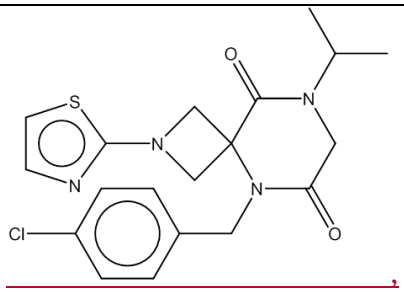
(a) R^{2A} and R^{2B} are as defined by (i) and R^3 is phenyl substituted with two or more substituents;

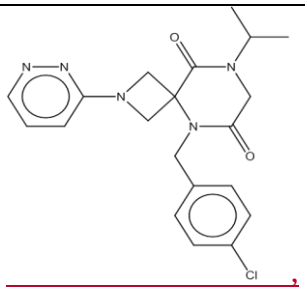
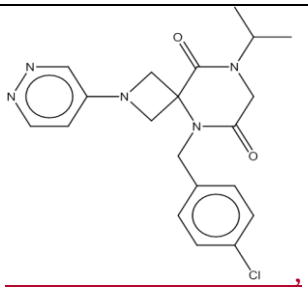
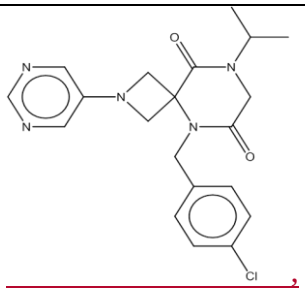
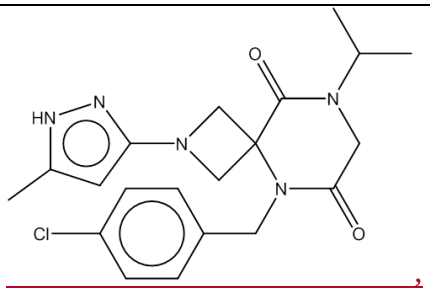
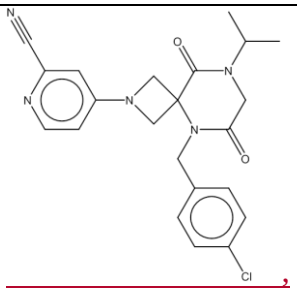
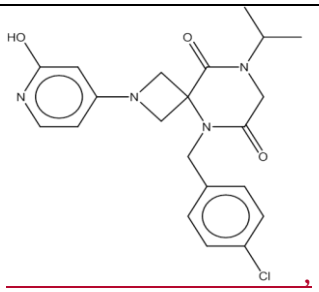
(b) R^{2A} and R^3 are as defined by (ii) and R^{2B} is 4-methoxyphenyl.

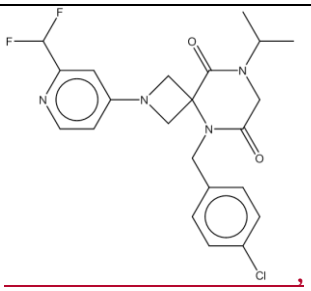
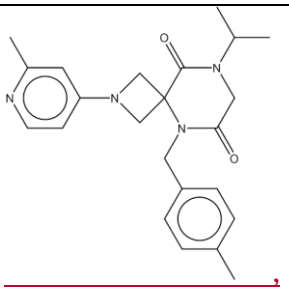
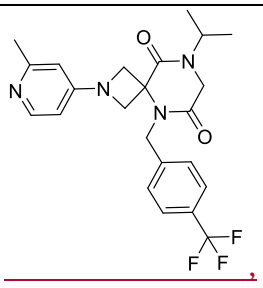
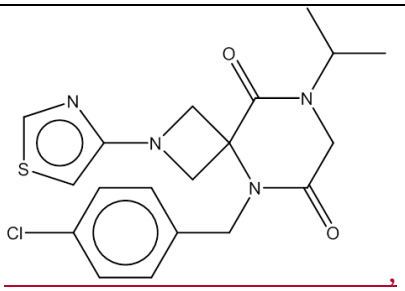
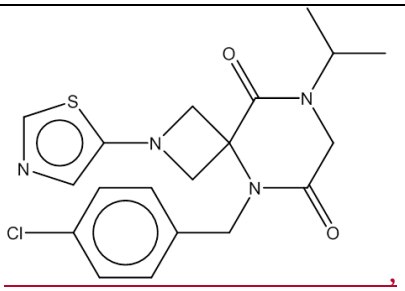
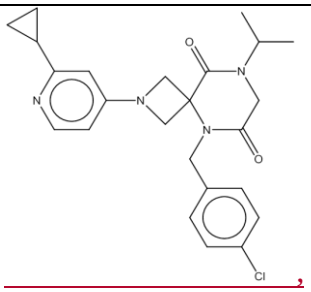
[0007b] In another aspect of the present disclosure, there is provided a compound selected from the group consisting of :

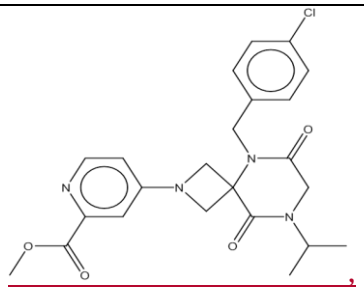
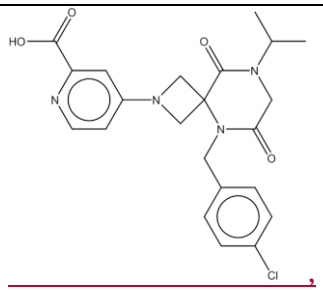
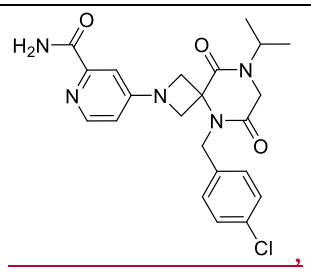
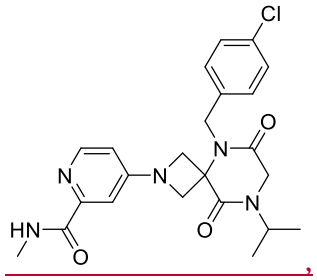
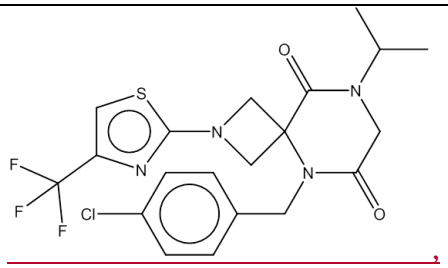
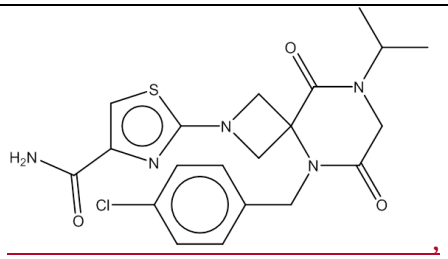
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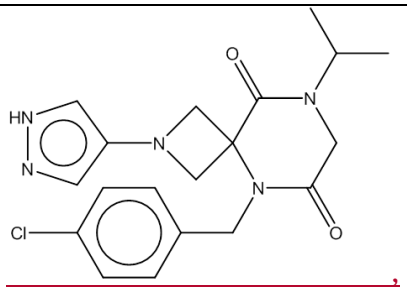
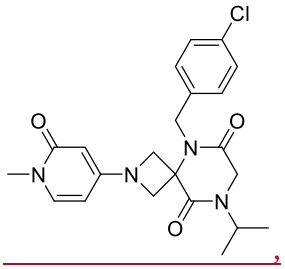
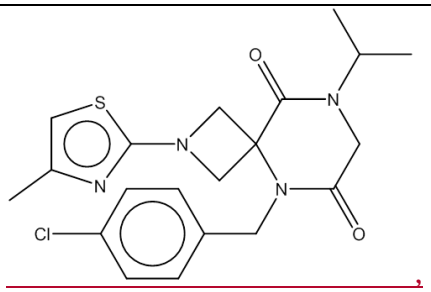
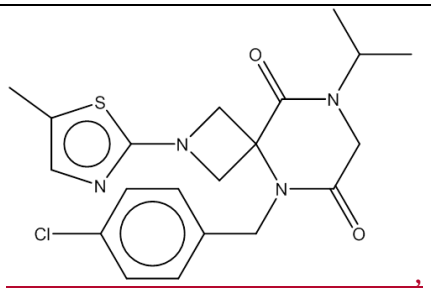
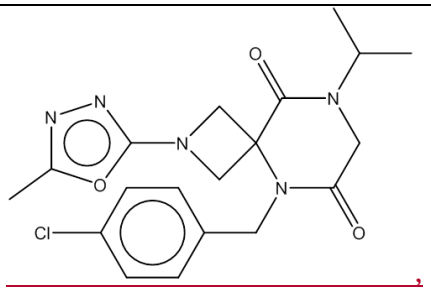
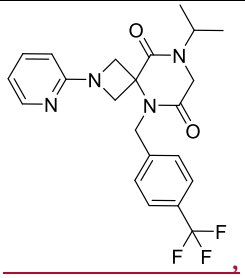
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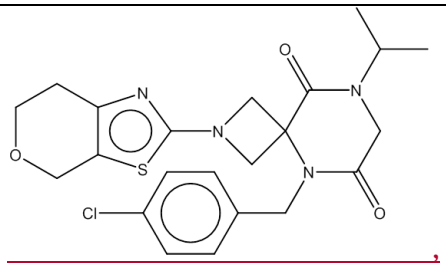
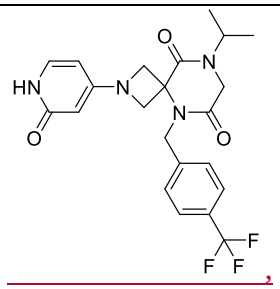
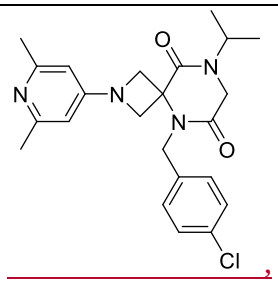
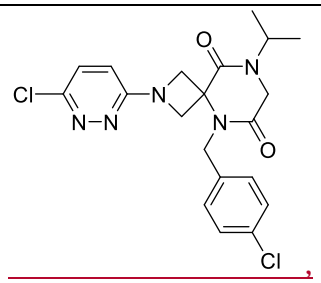
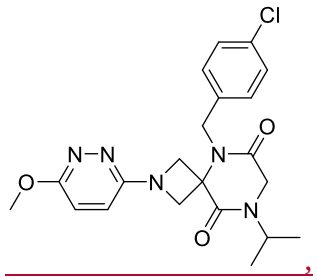
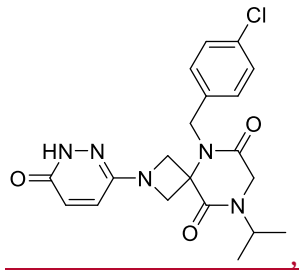
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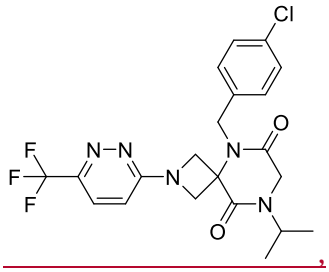
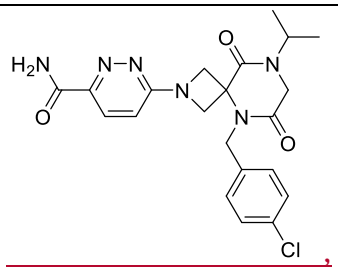
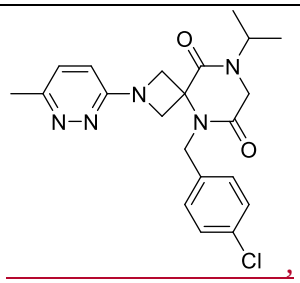
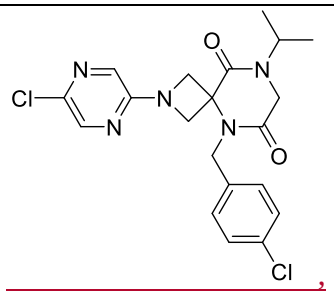
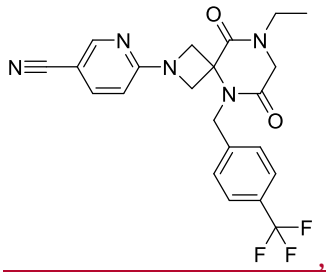
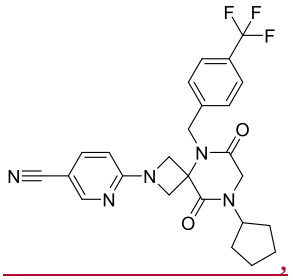
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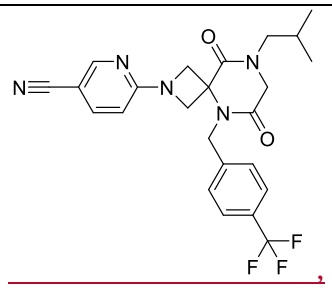
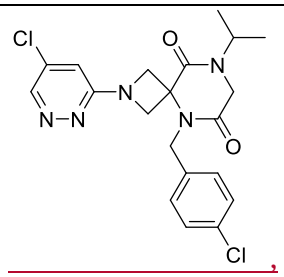
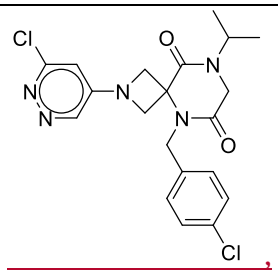
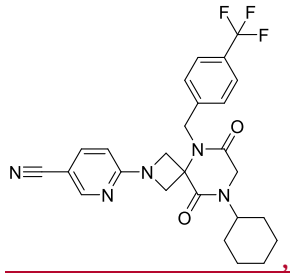
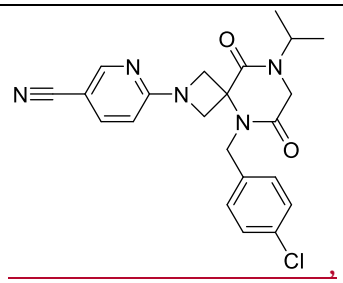
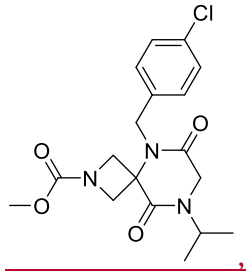
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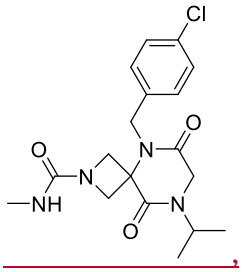
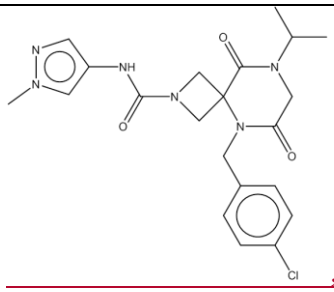
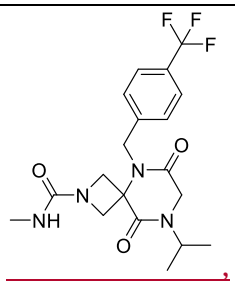
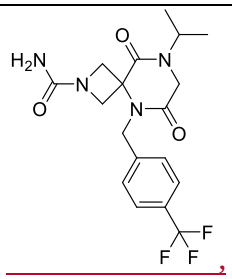
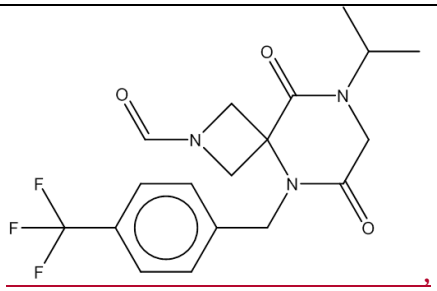
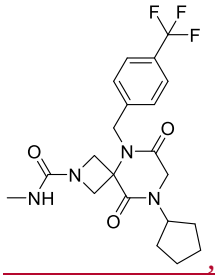
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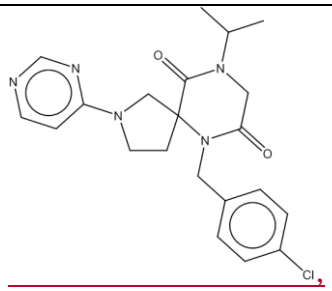
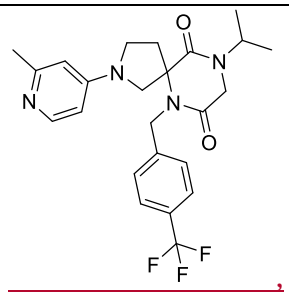
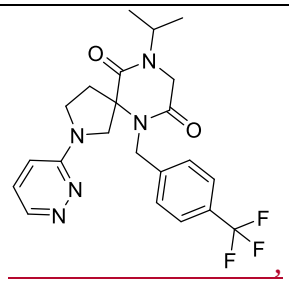
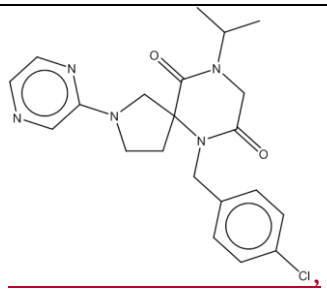
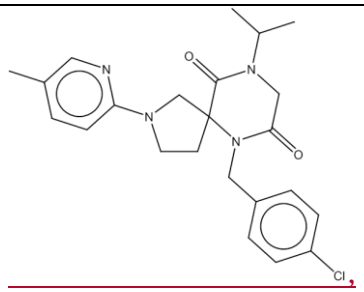
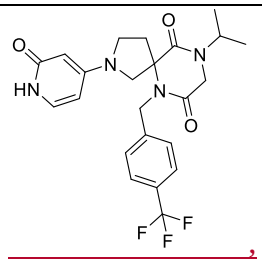
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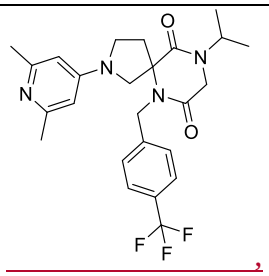
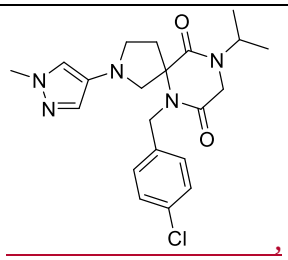
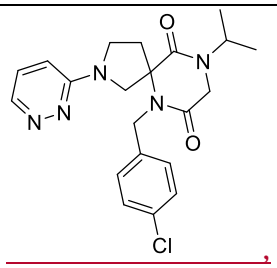
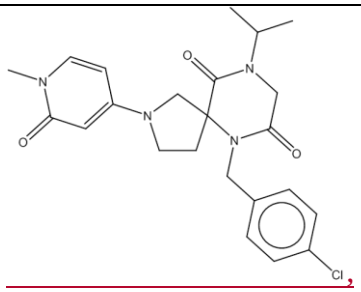
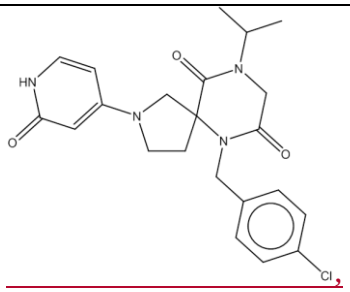
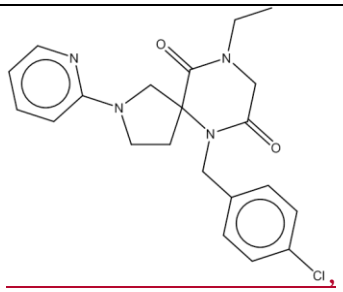
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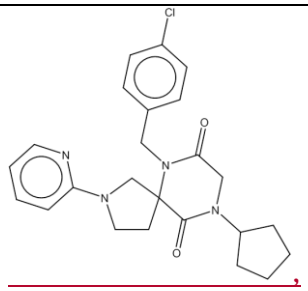
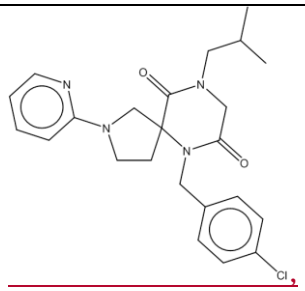
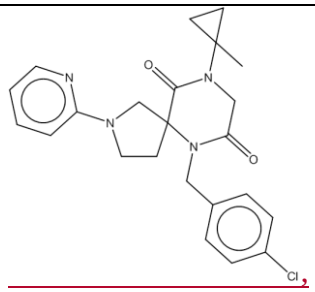
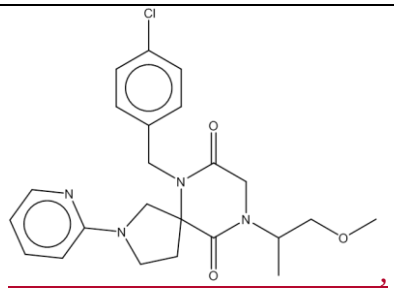
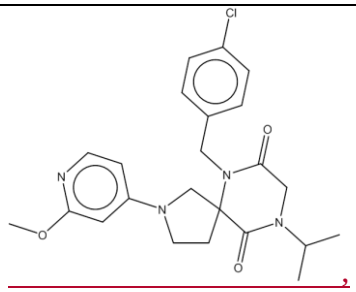
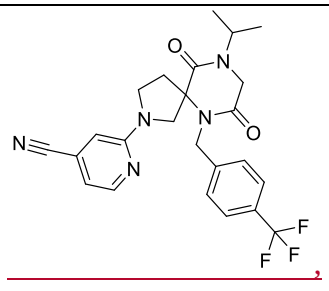
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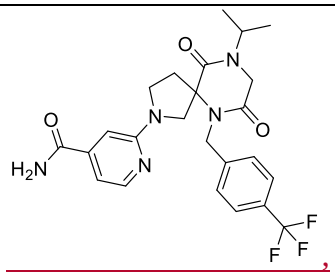
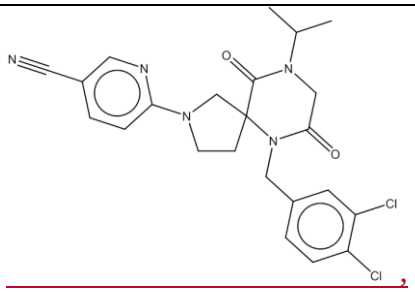
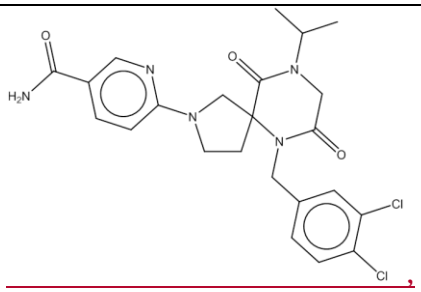
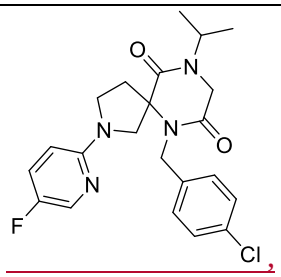
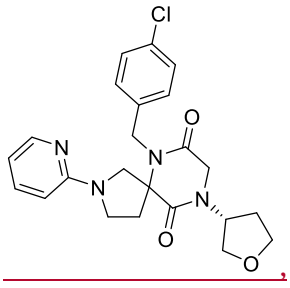
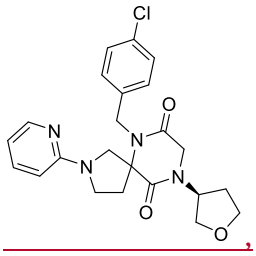
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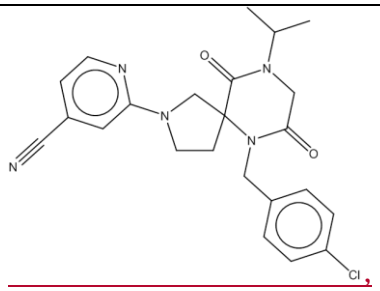
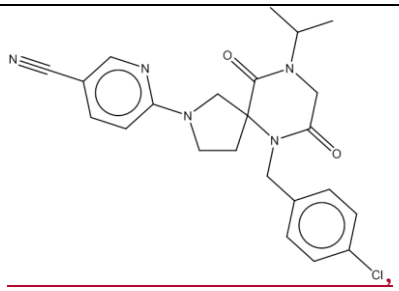
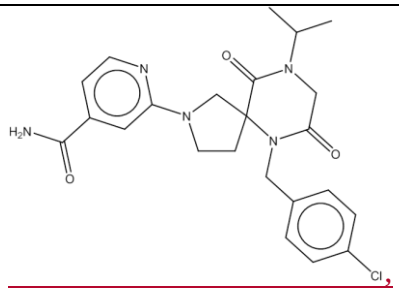
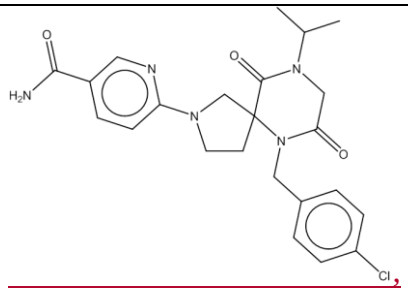
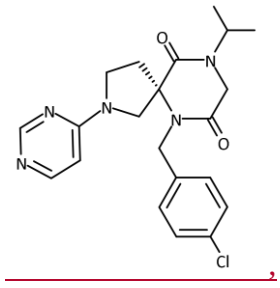
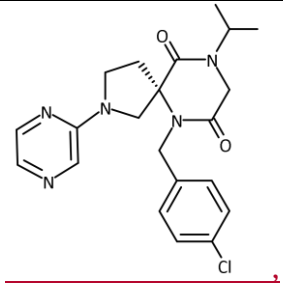
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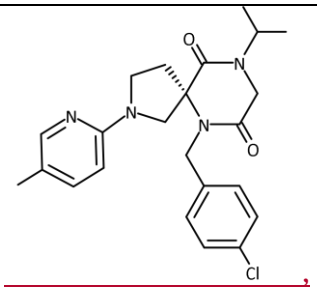
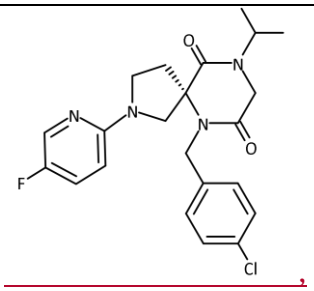
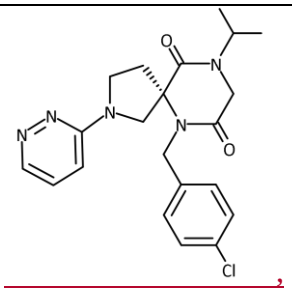
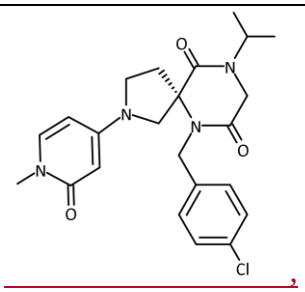
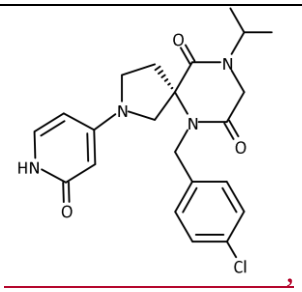
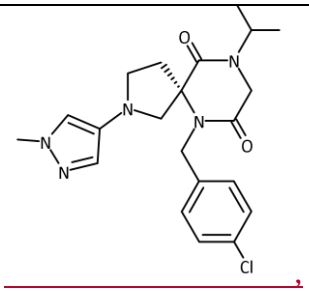
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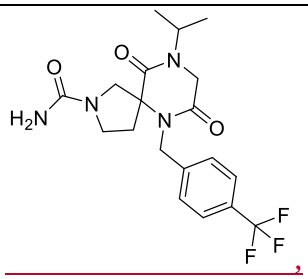
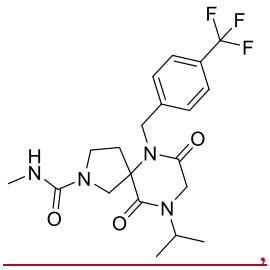
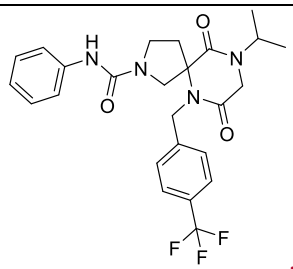
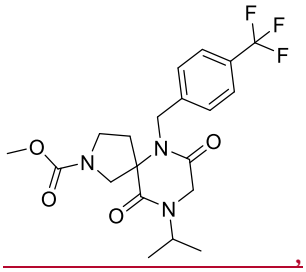
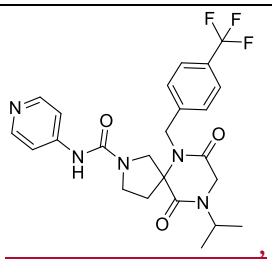
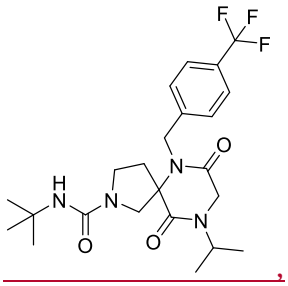
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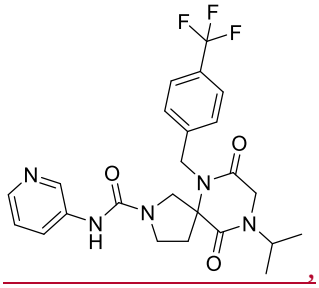
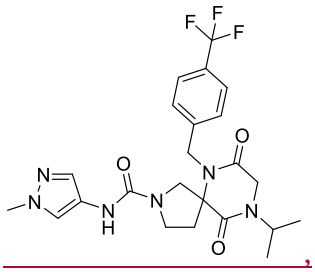
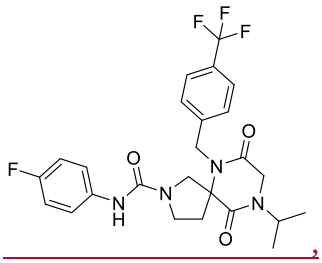
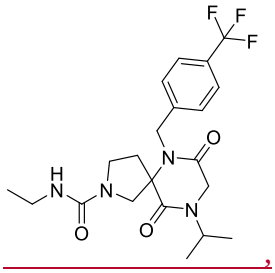
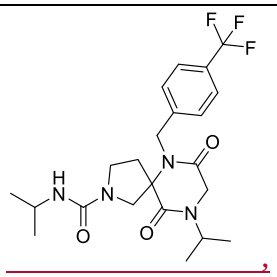
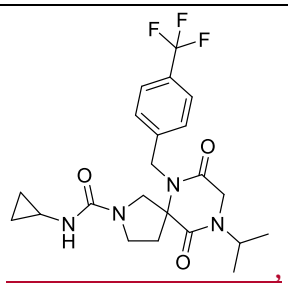
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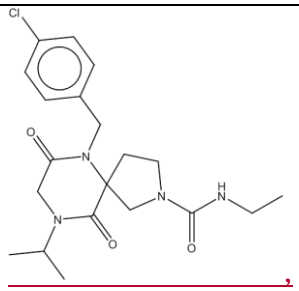
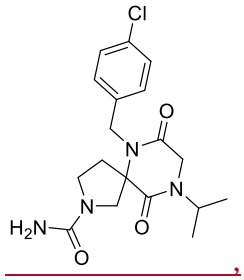
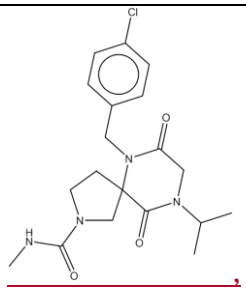
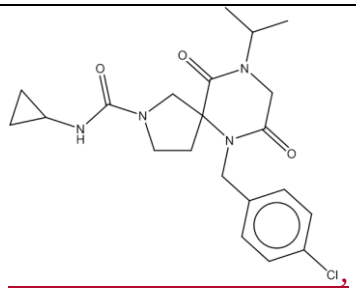
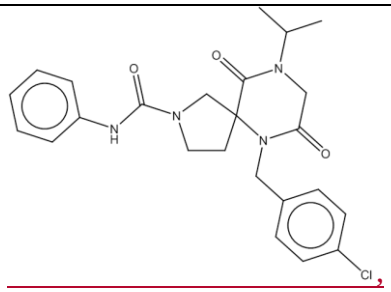
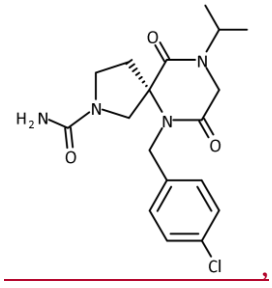
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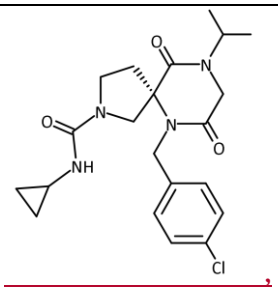
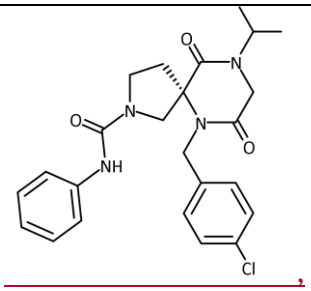
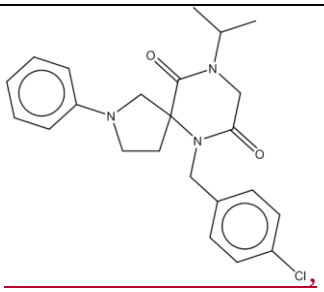
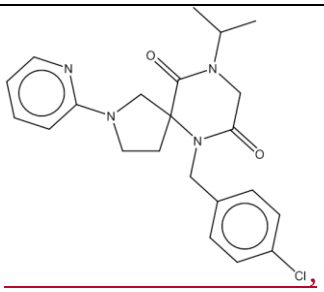
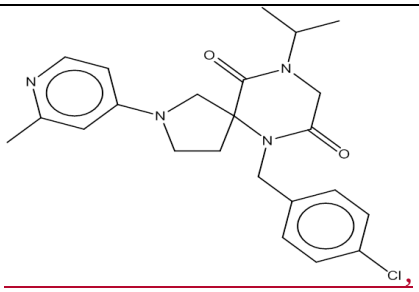
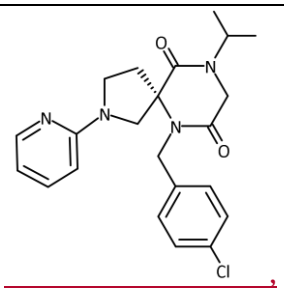
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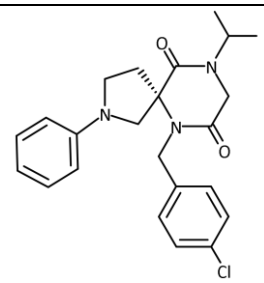
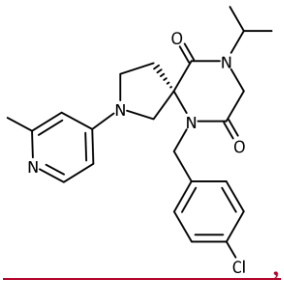
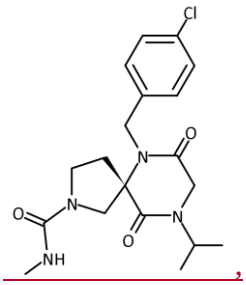
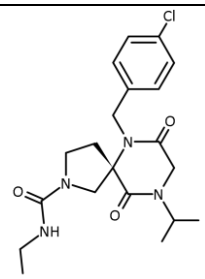
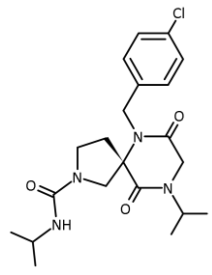
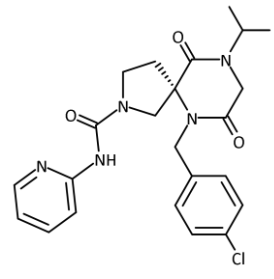
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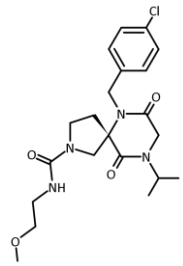
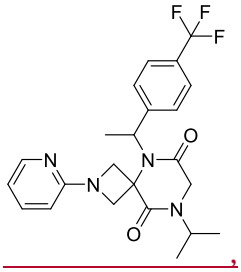
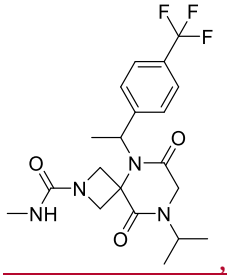
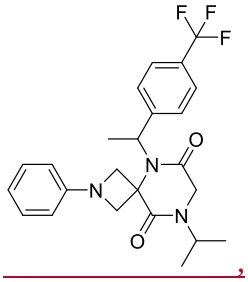
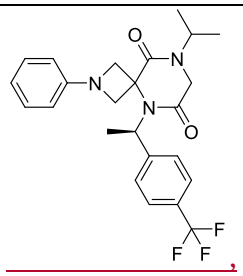
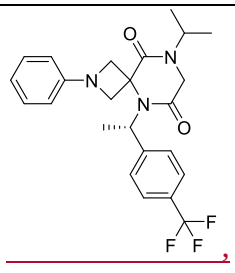
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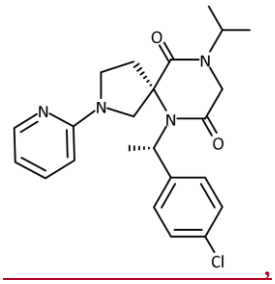
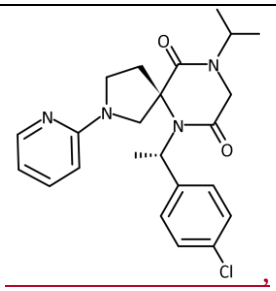
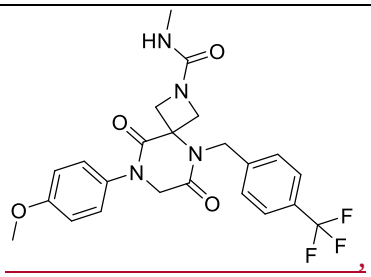
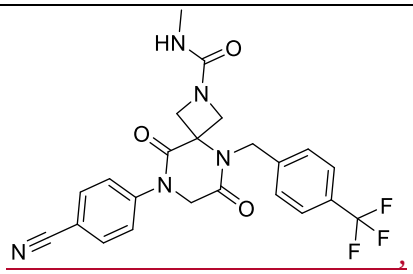
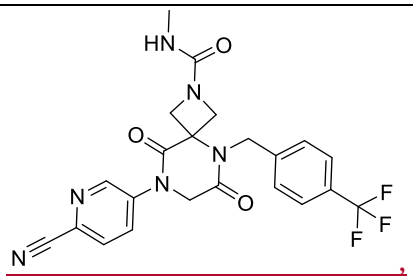
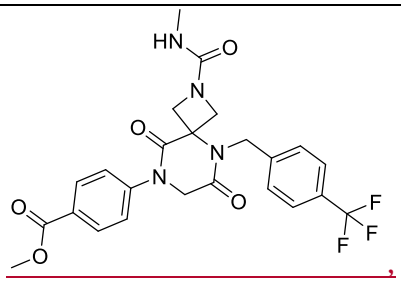
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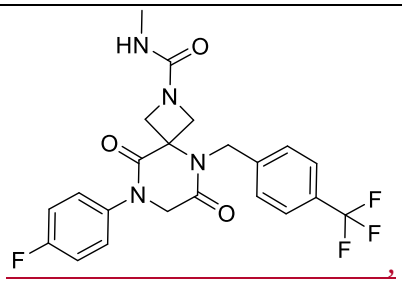
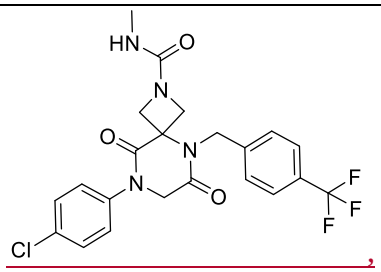
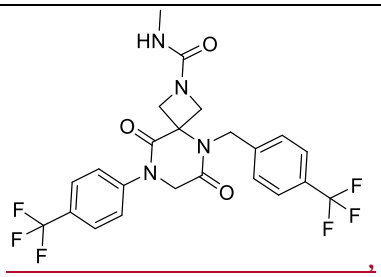
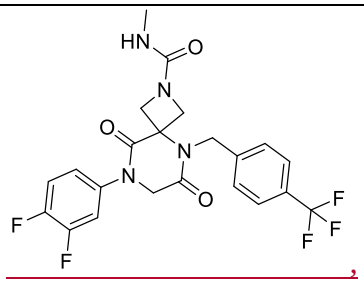
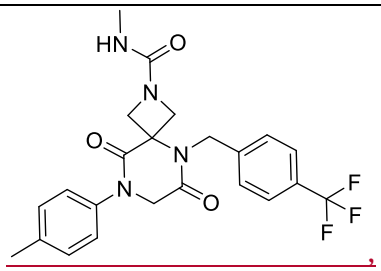
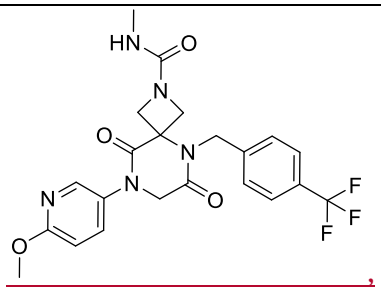
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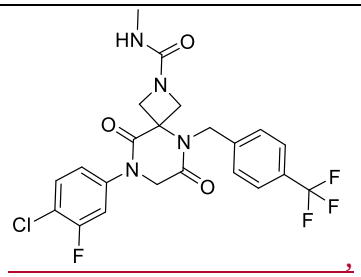
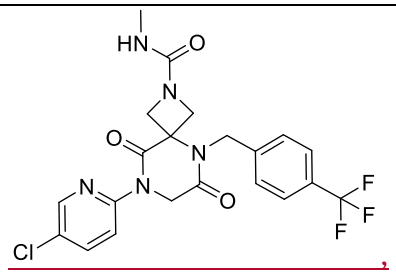
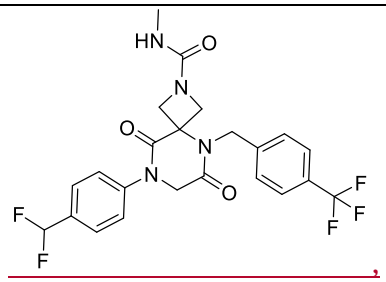
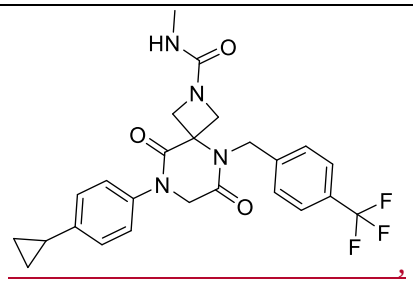
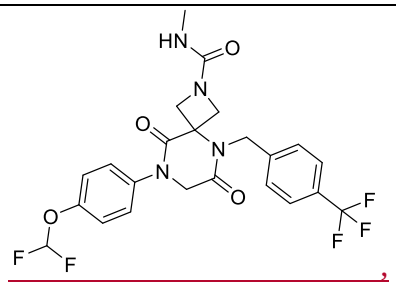
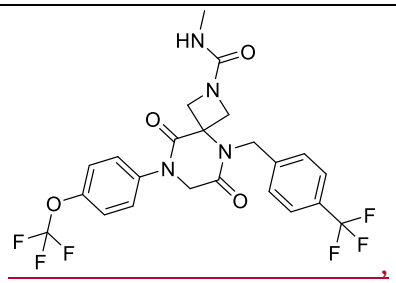
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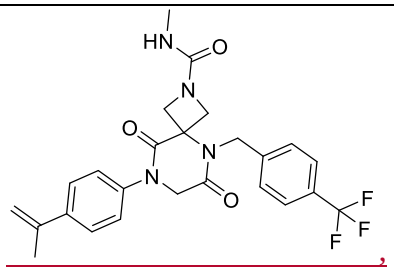
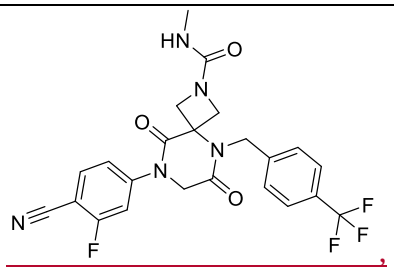
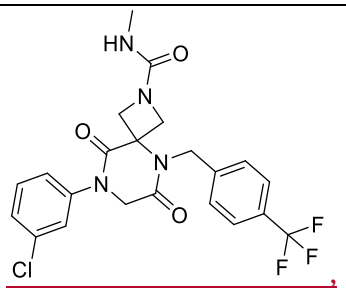
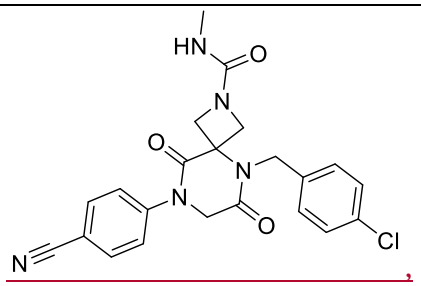
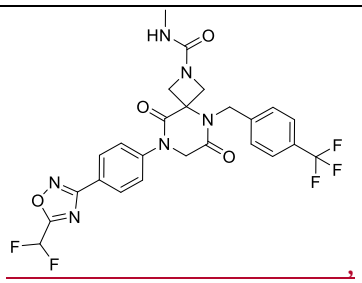
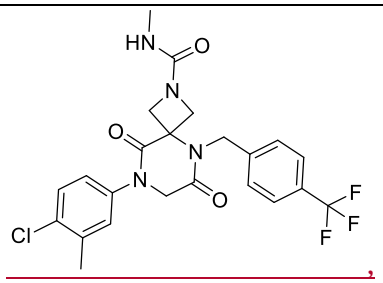
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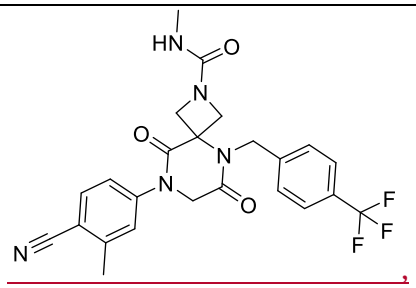
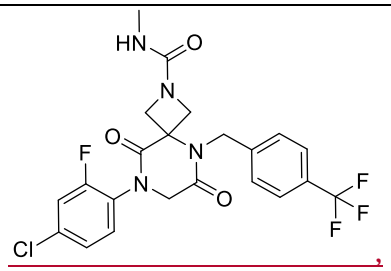
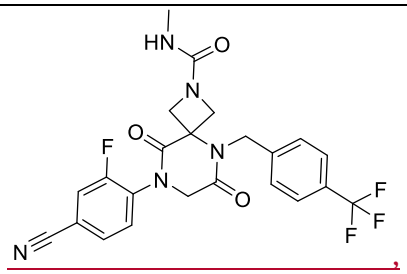
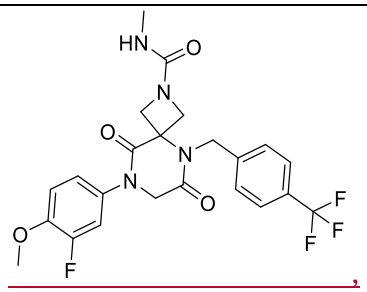
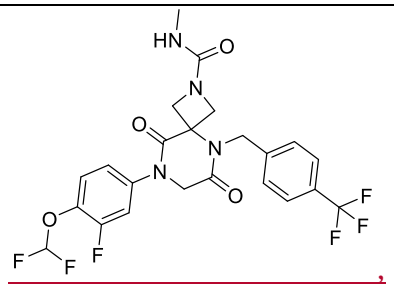
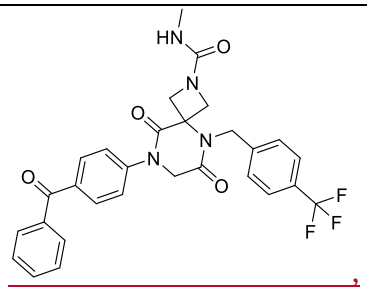
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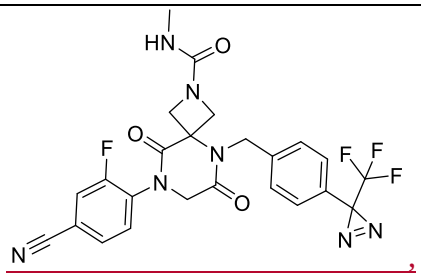
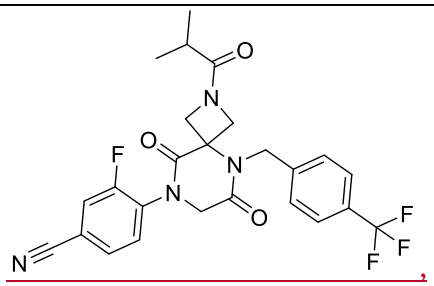
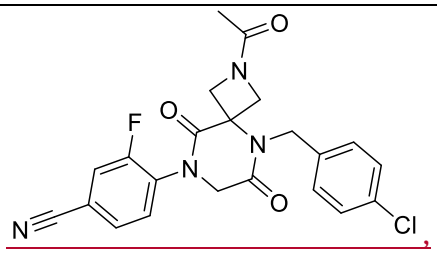
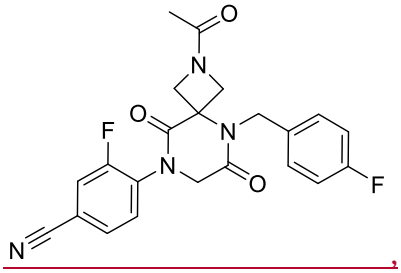
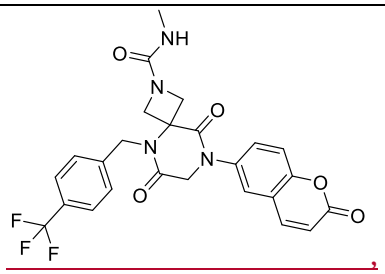
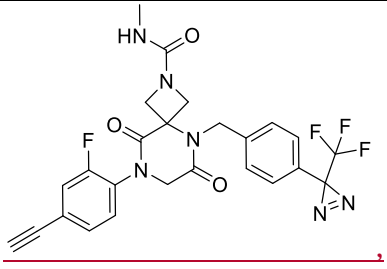
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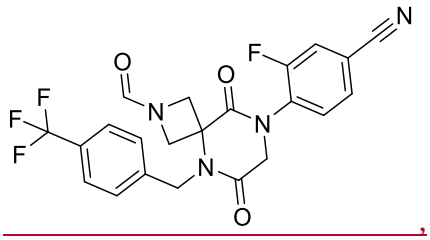
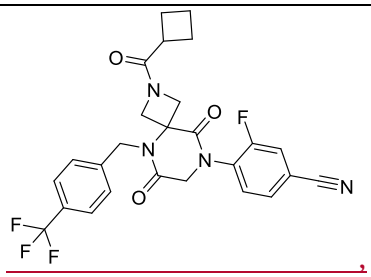
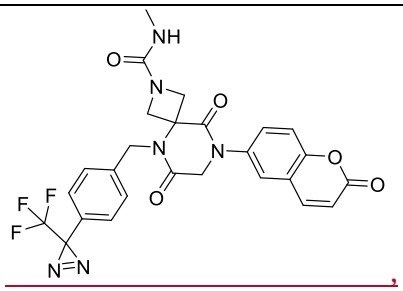
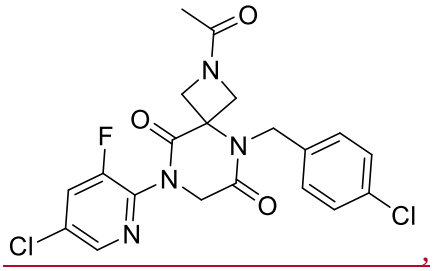
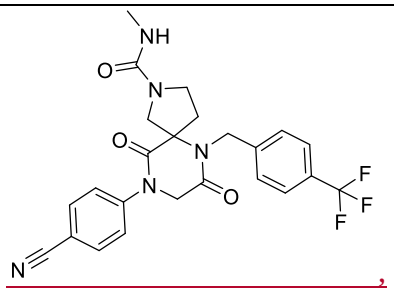
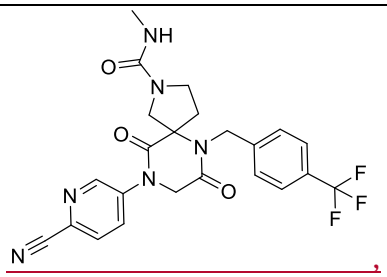
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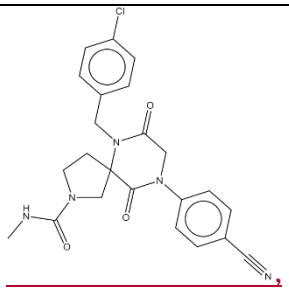
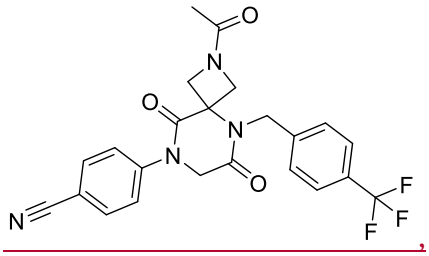
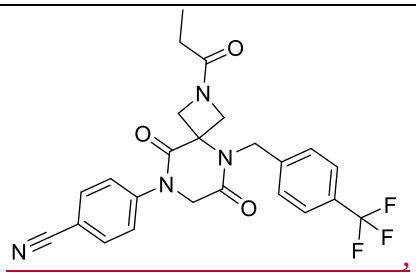
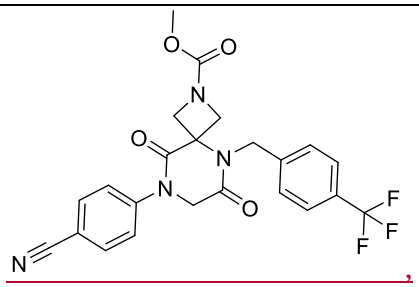
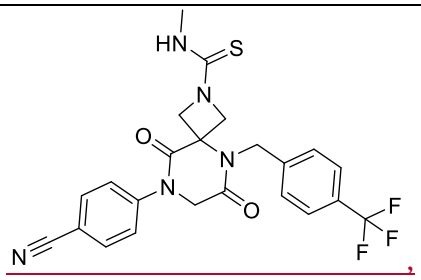
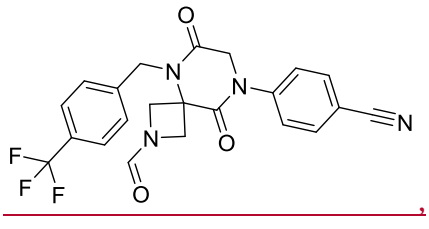
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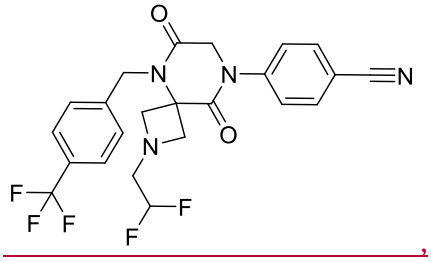
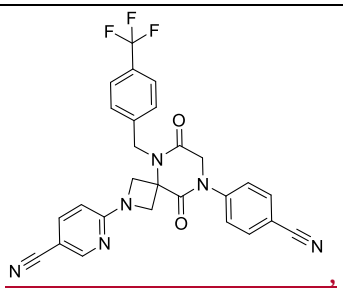
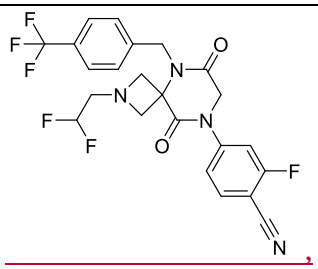
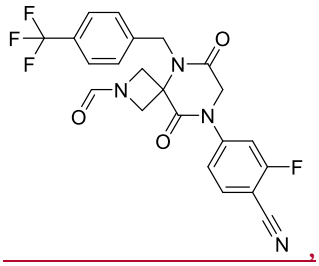
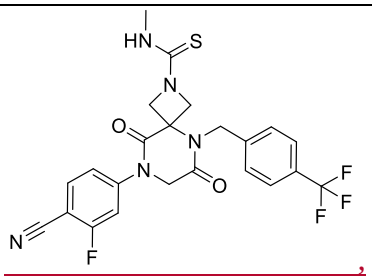
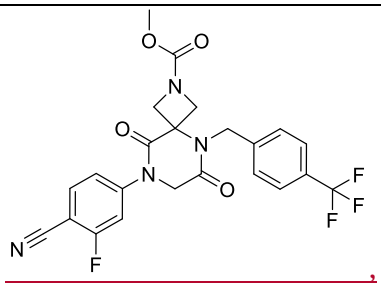
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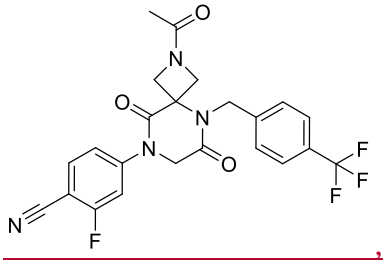
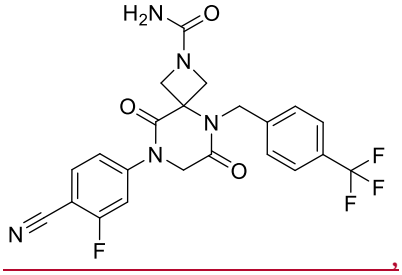
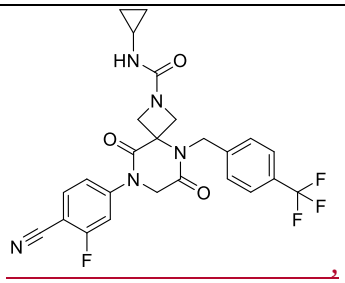
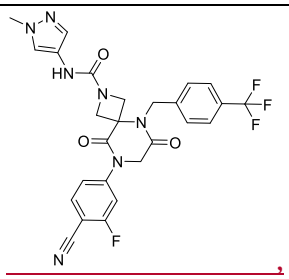
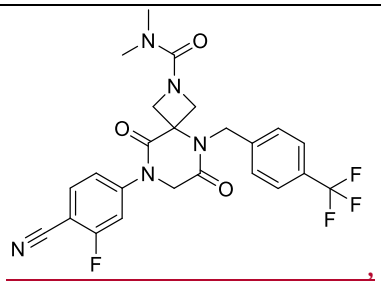
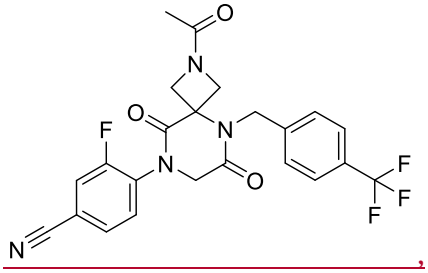
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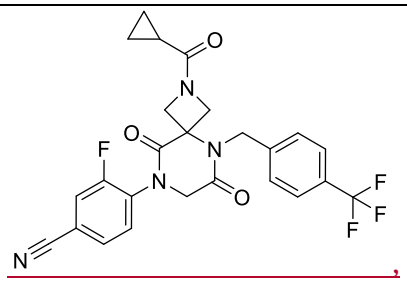
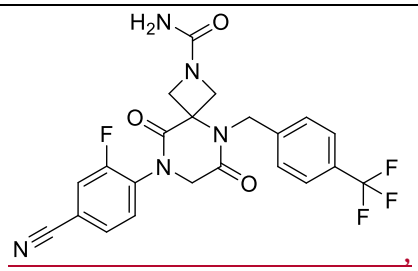
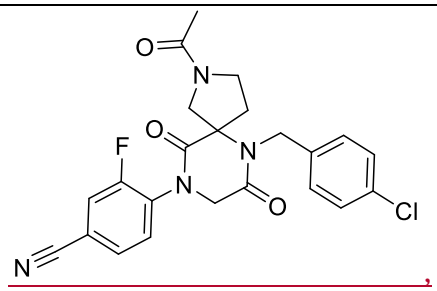
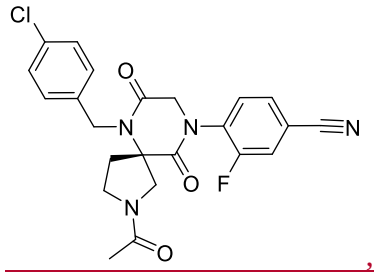
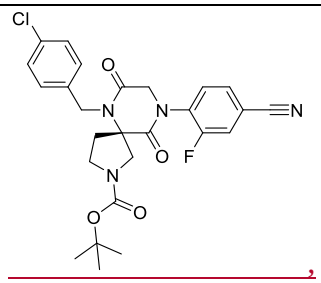
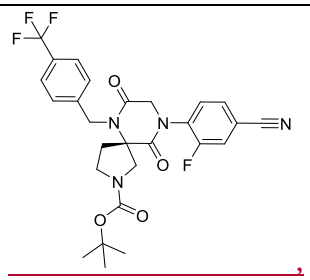
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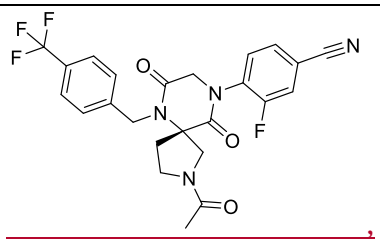
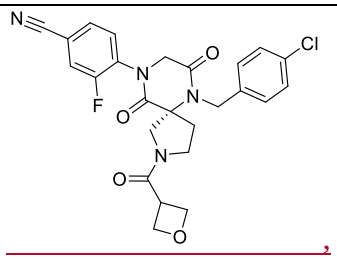
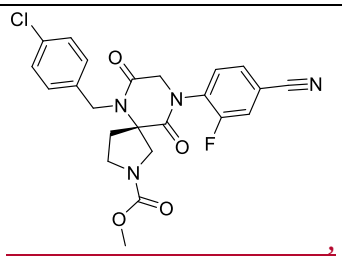
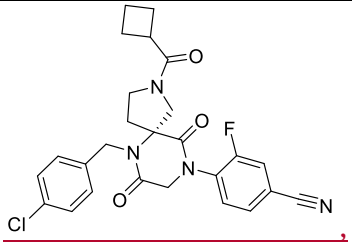
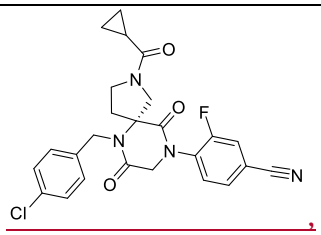
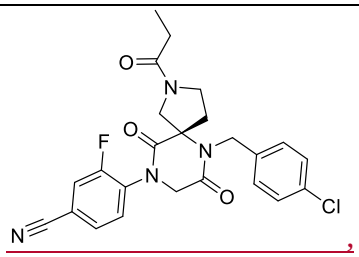
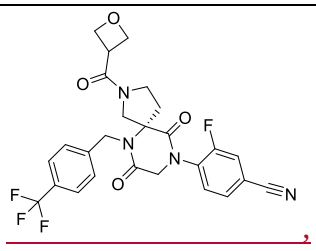
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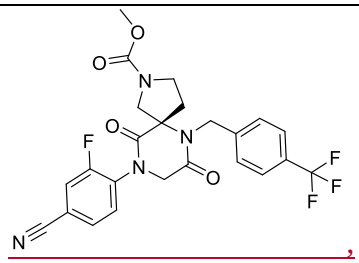
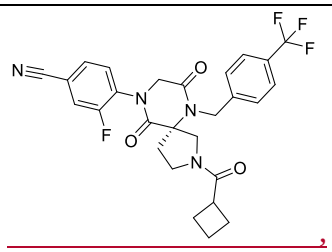
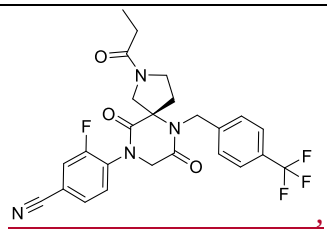
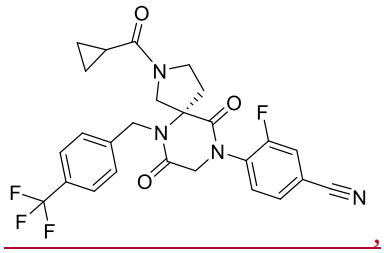
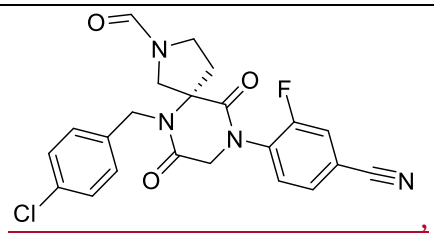
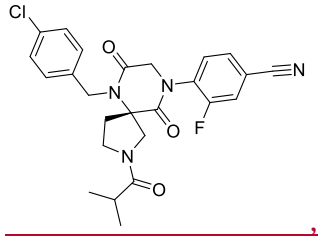
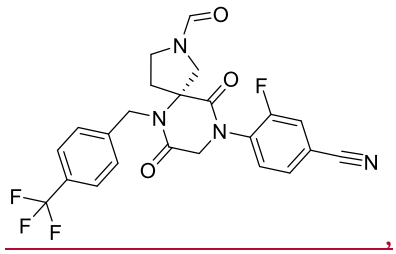
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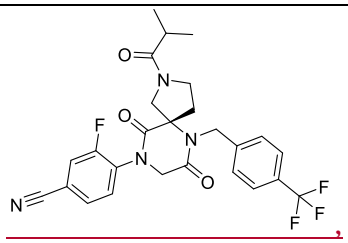
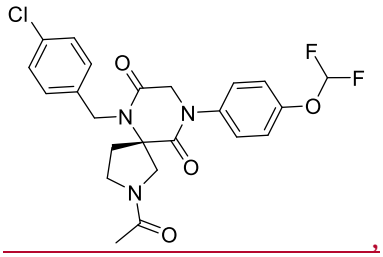
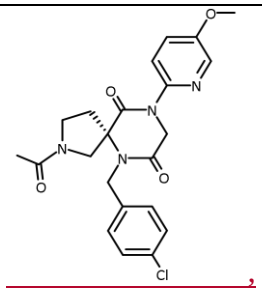
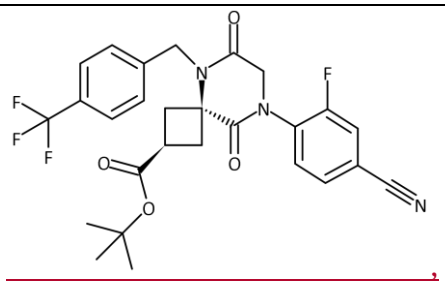
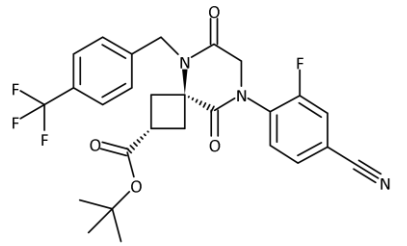
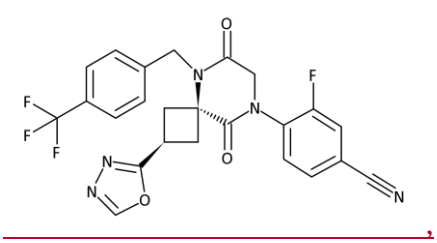
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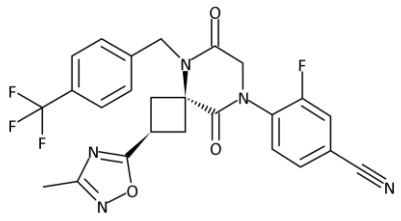
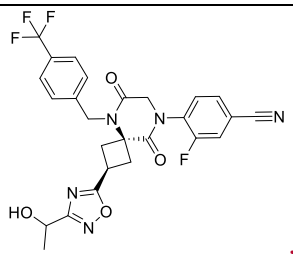
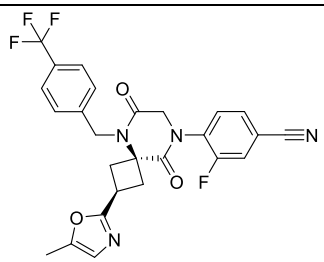
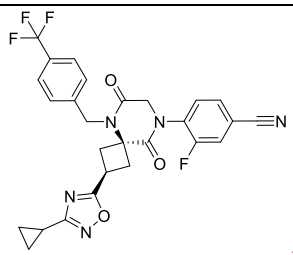
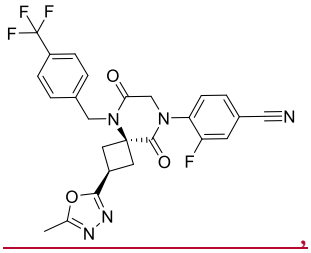
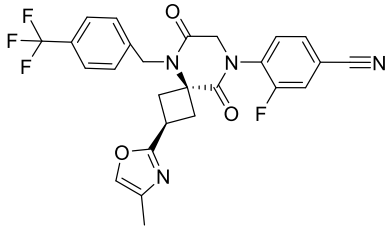
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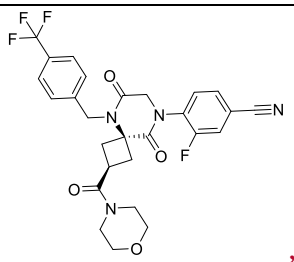
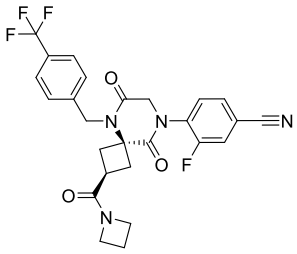
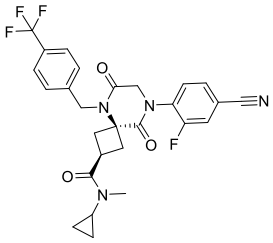
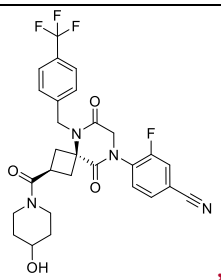
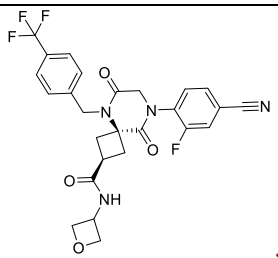
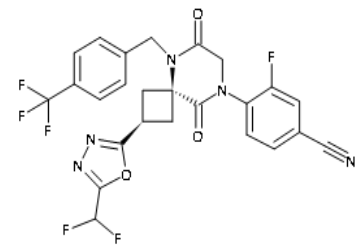
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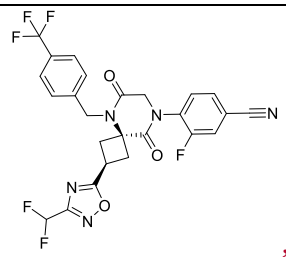
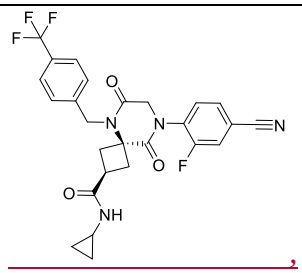
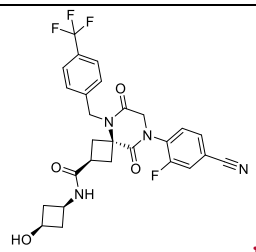
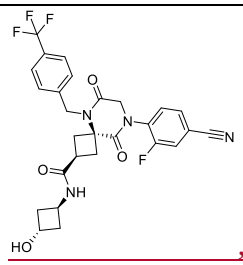
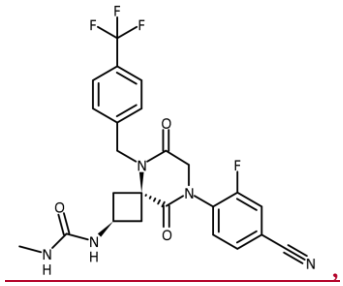
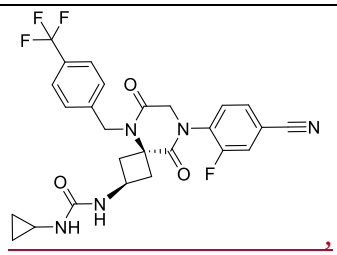
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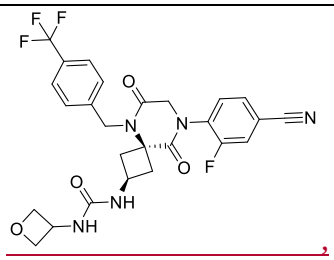
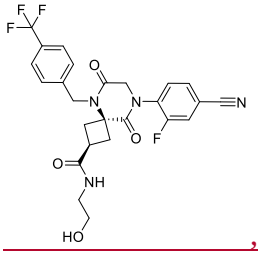
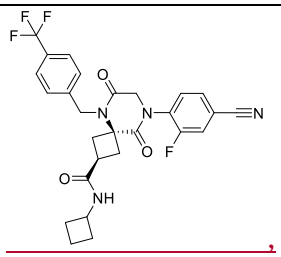
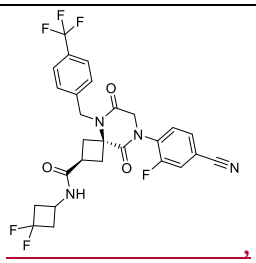
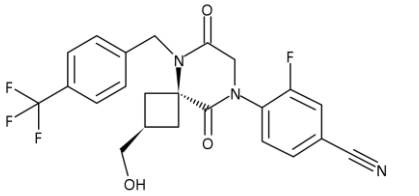
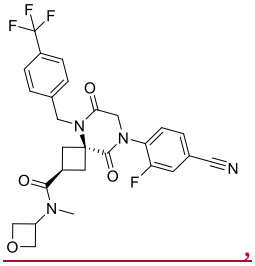
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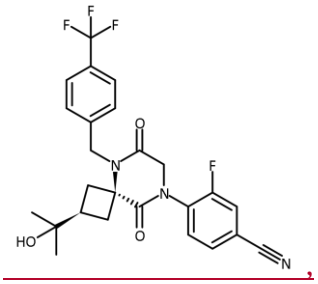
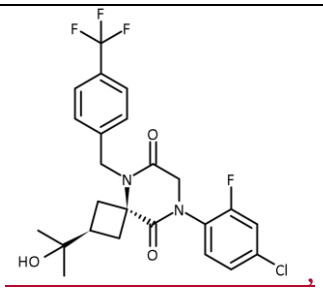
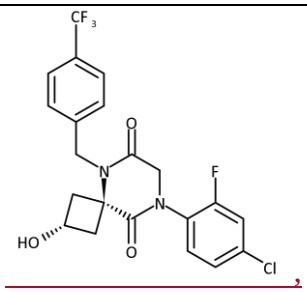
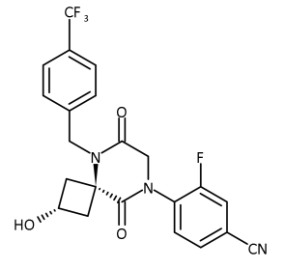
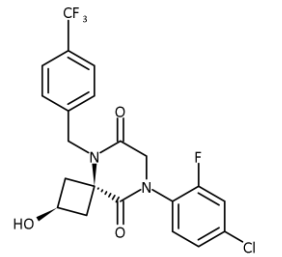
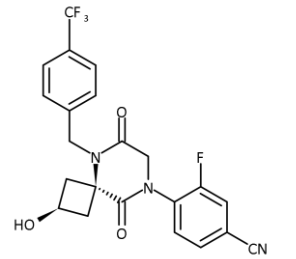
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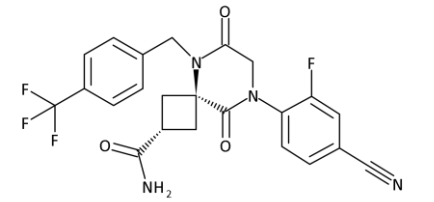
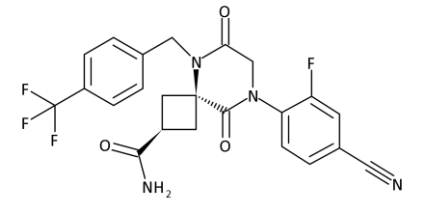
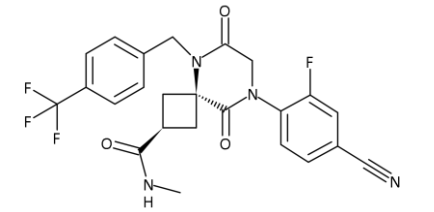
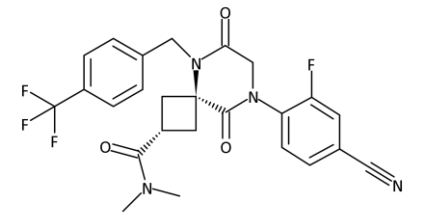
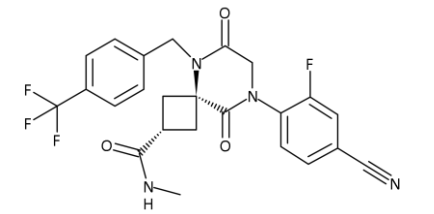
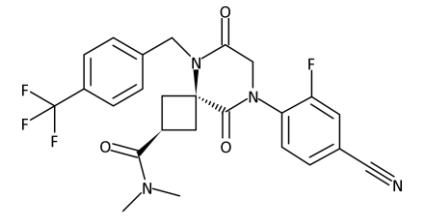
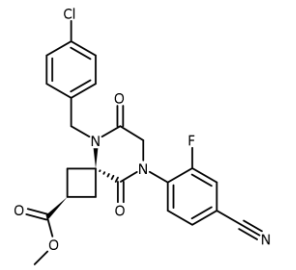
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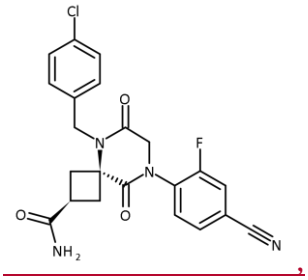
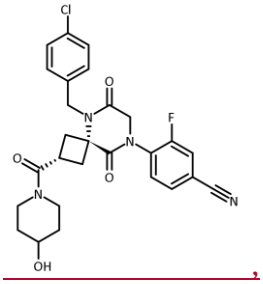
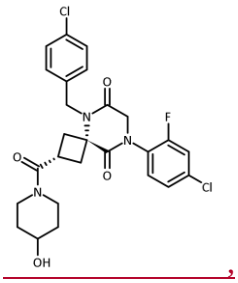
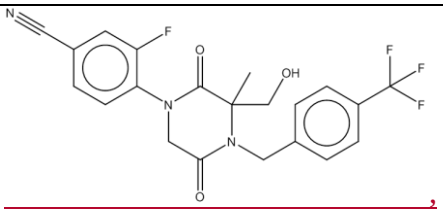
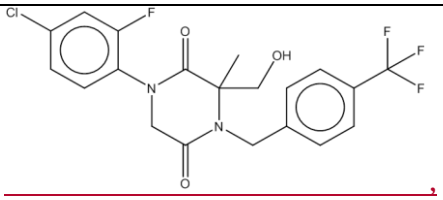
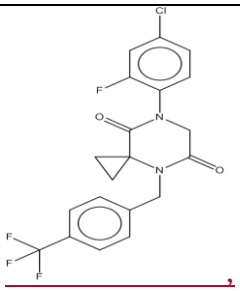
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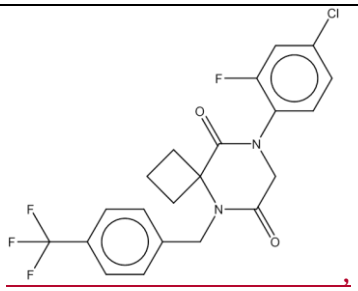
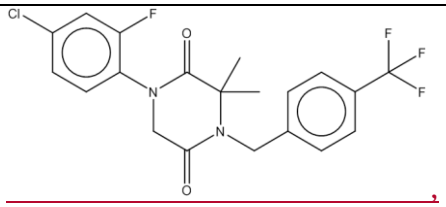
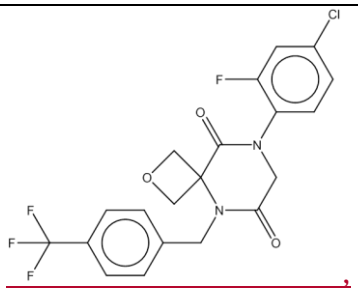
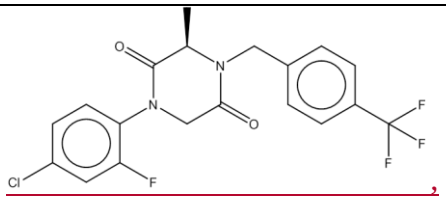
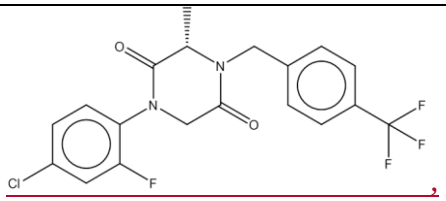
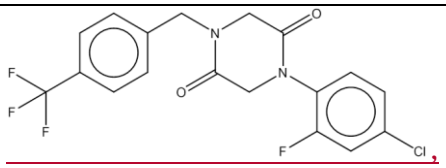
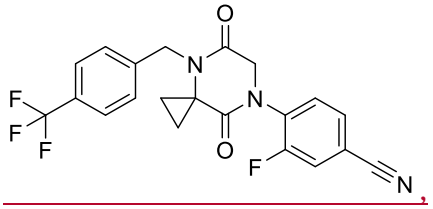
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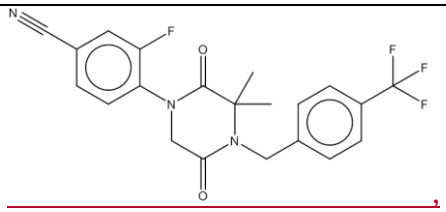
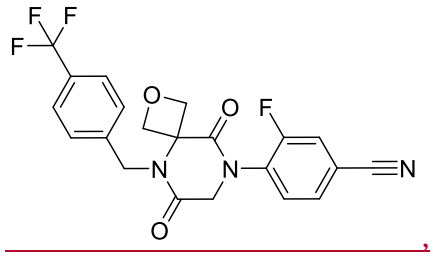
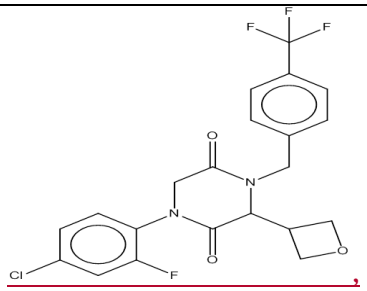
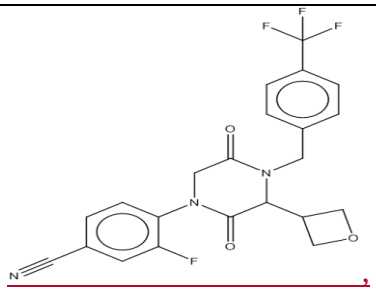
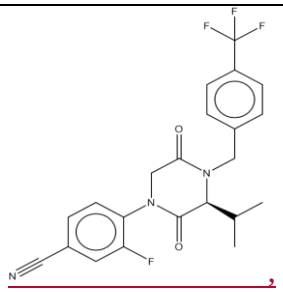
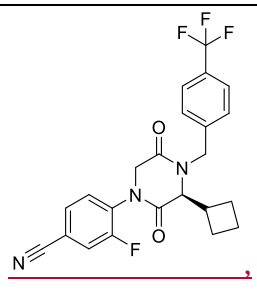
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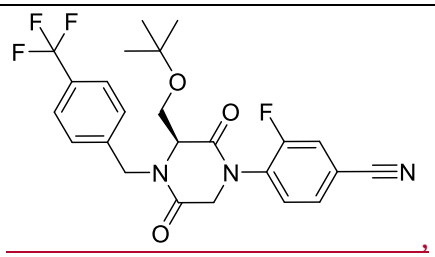
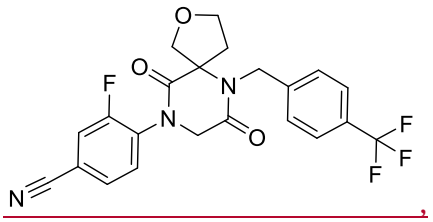
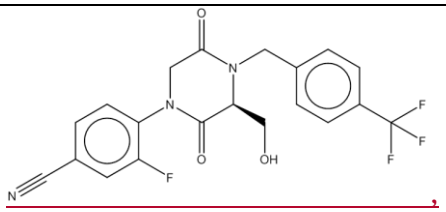
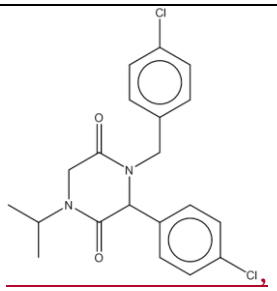
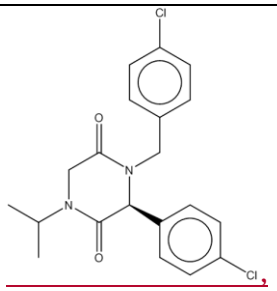
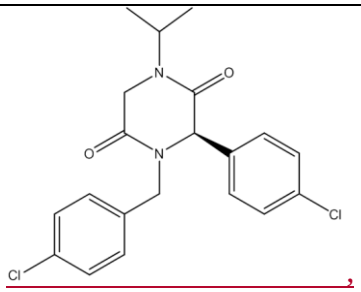
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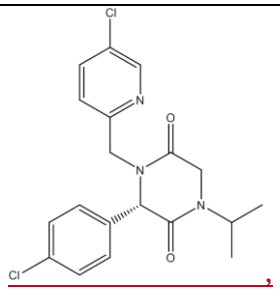
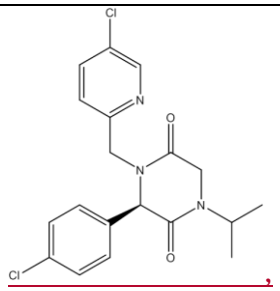
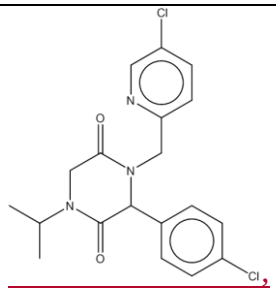
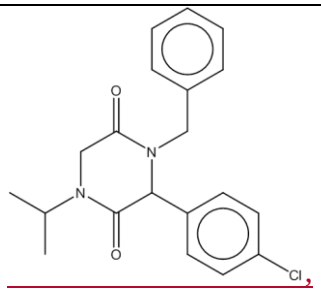
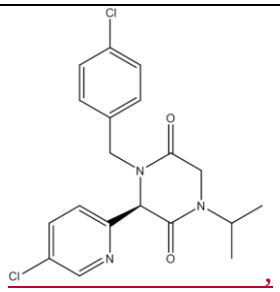
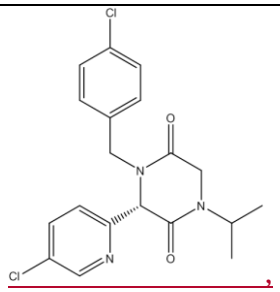
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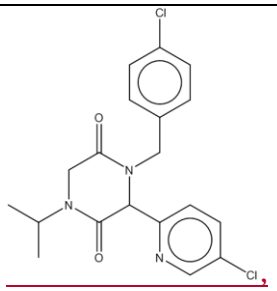
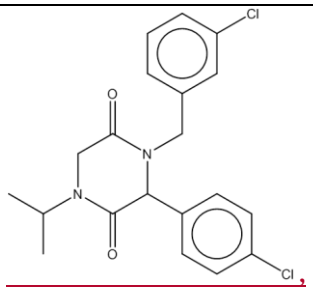
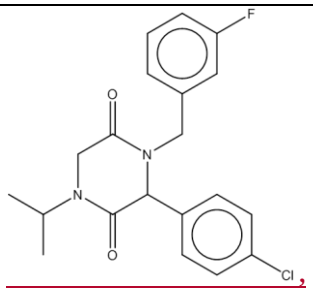
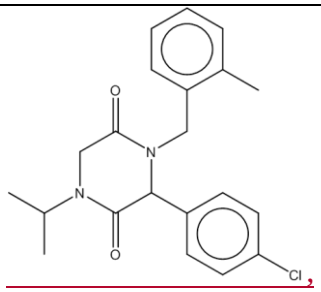
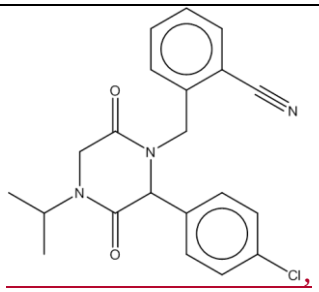
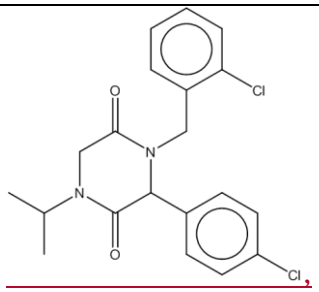
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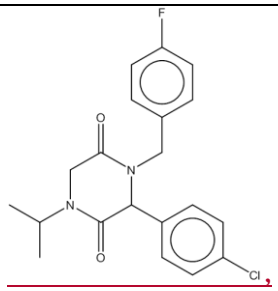
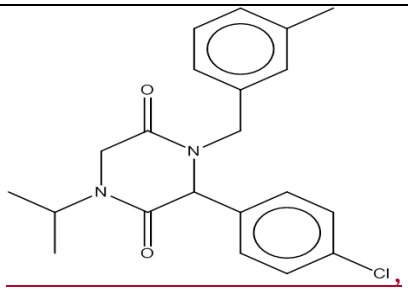
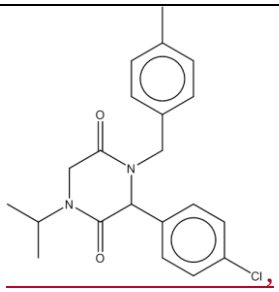
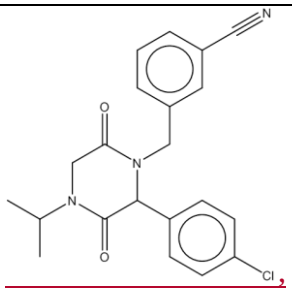
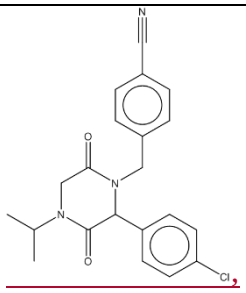
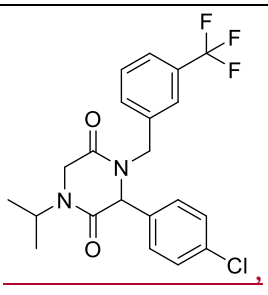
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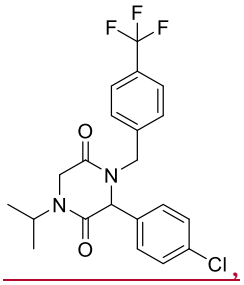
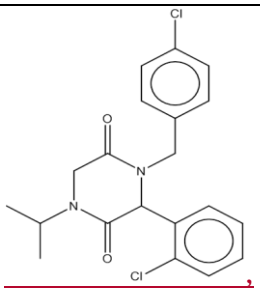
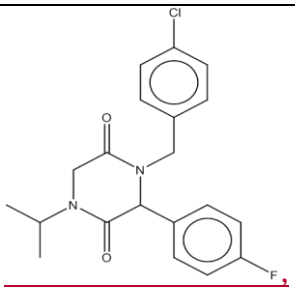
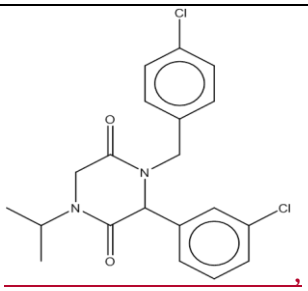
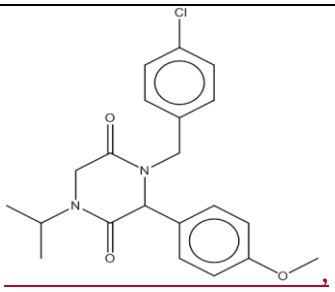
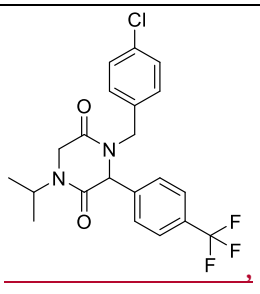
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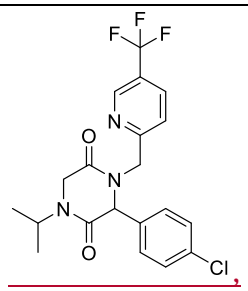
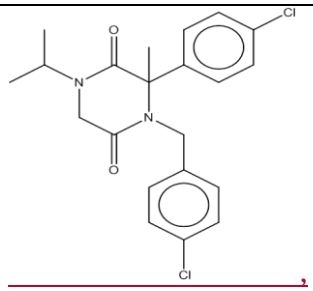
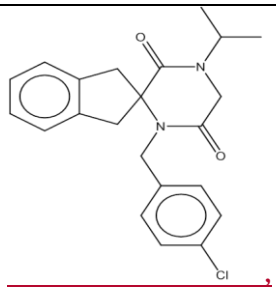
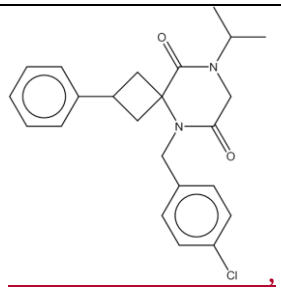
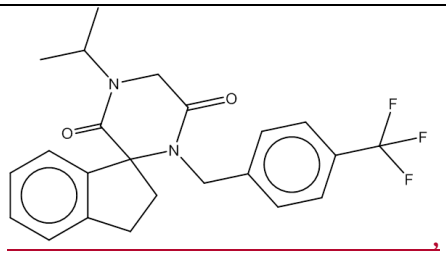
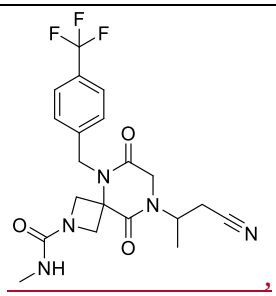
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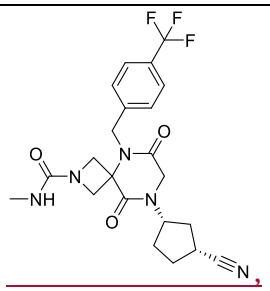
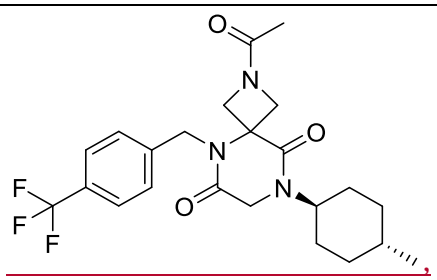
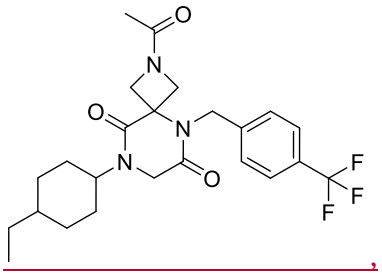
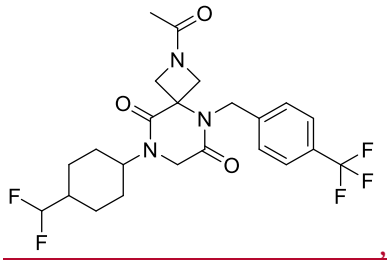
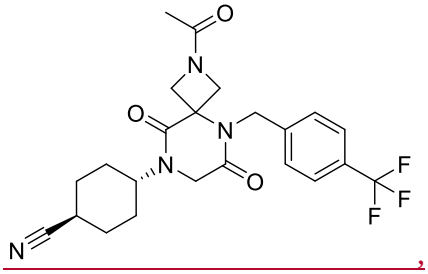
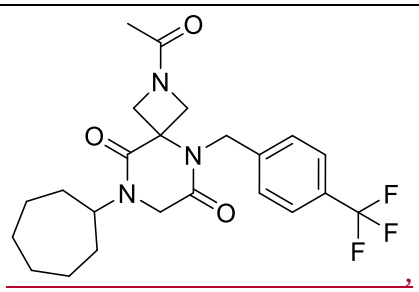
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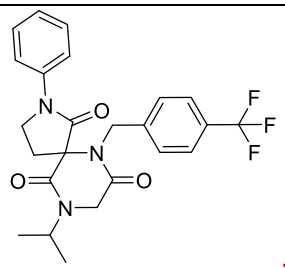
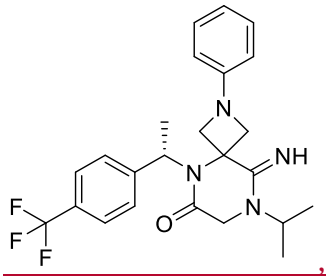
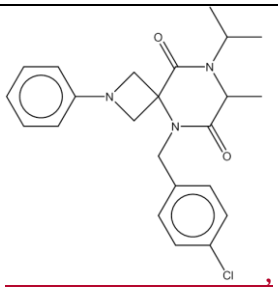
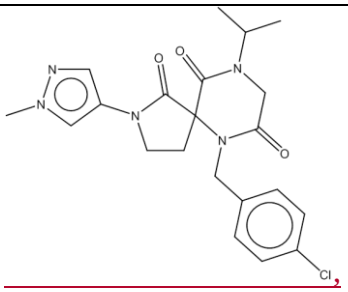
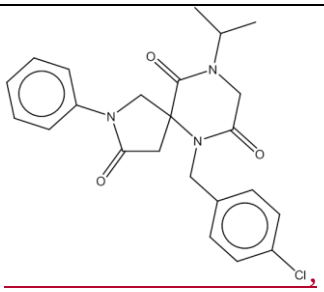
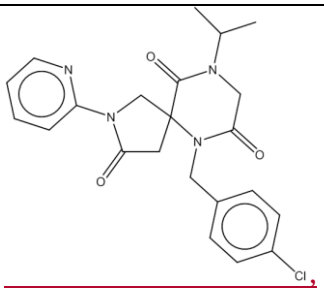
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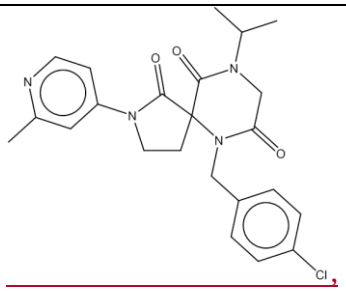
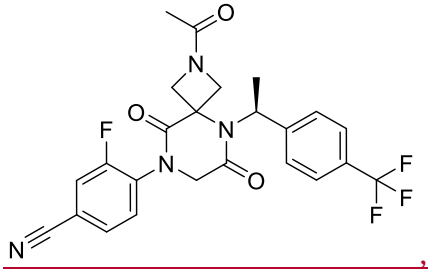
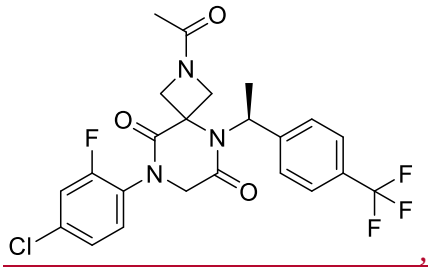
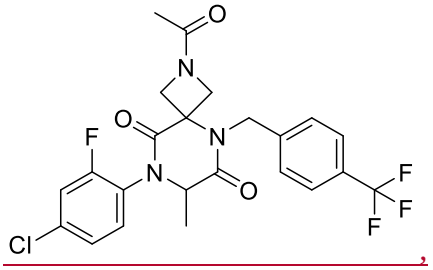
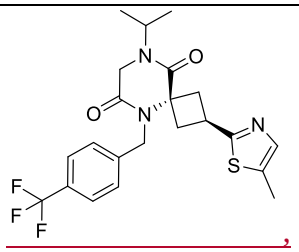
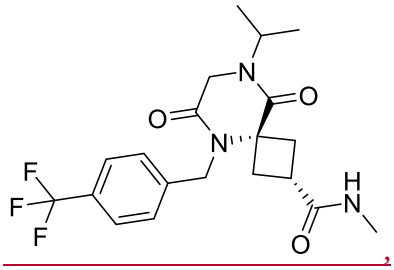
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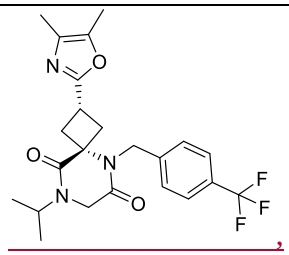
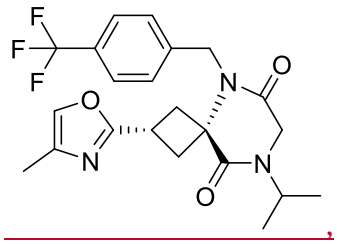
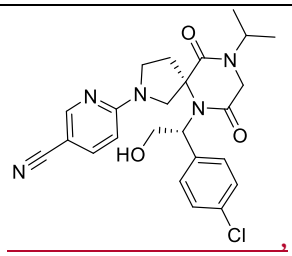
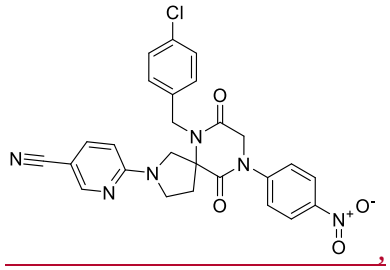
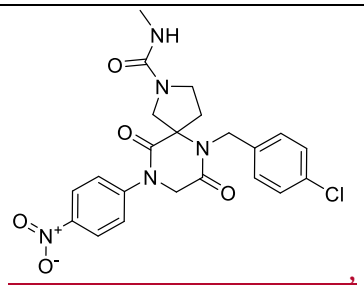
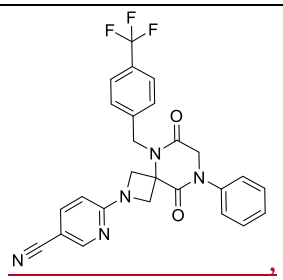
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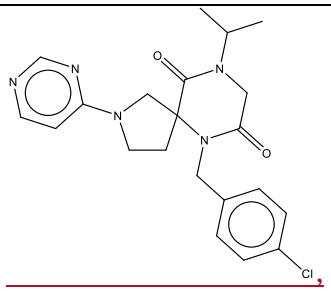
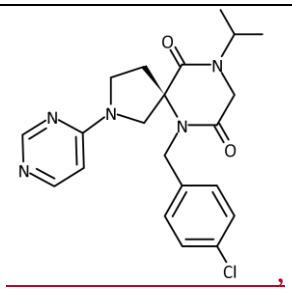
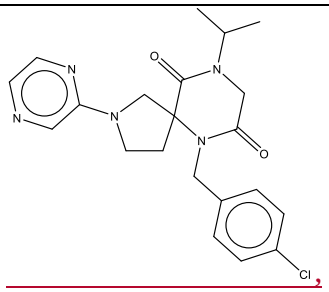
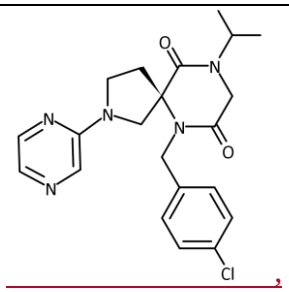
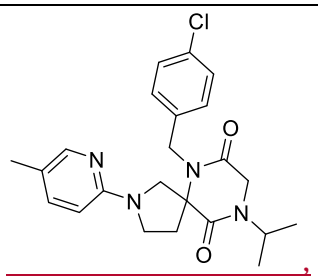
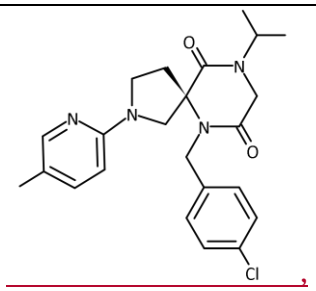
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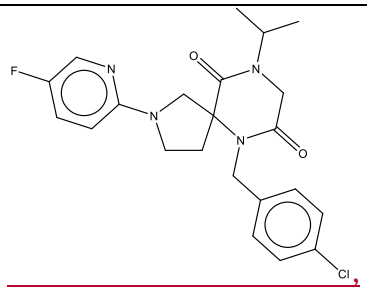
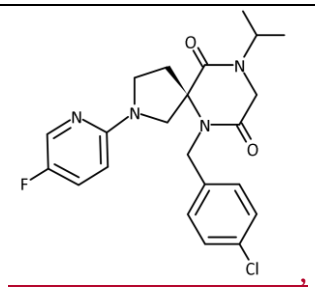
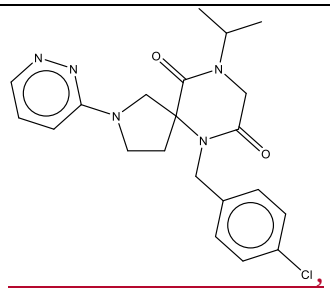
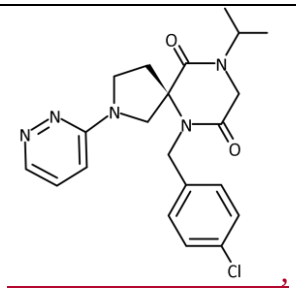
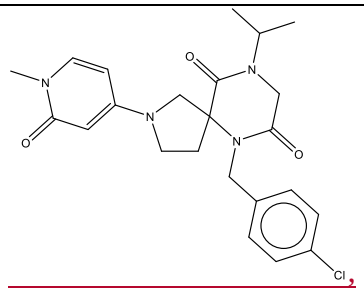
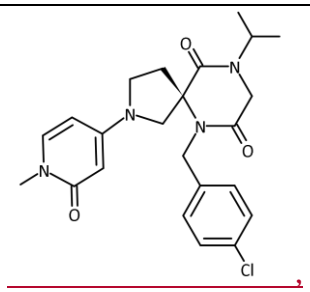
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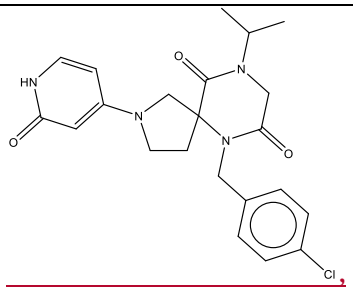
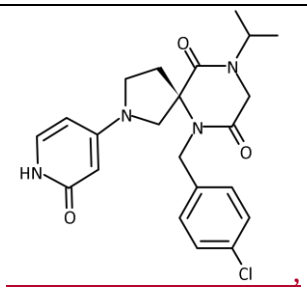
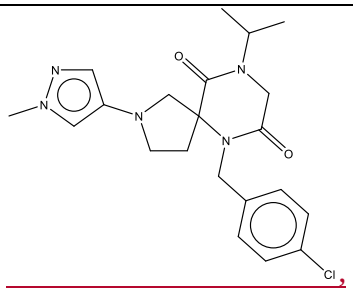
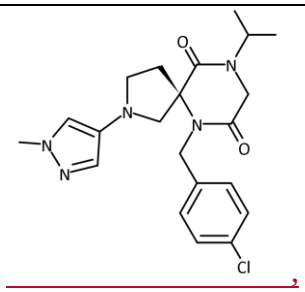
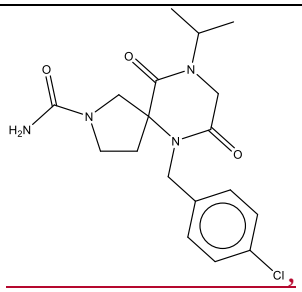
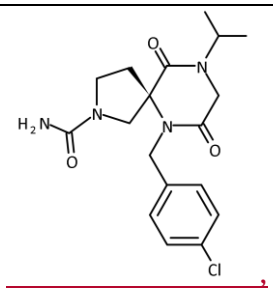
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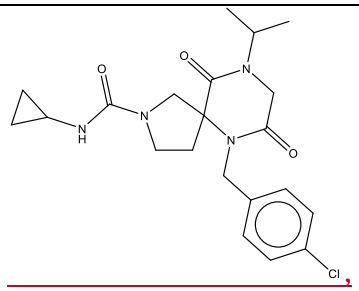
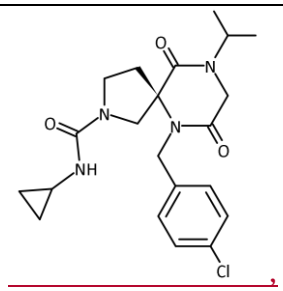
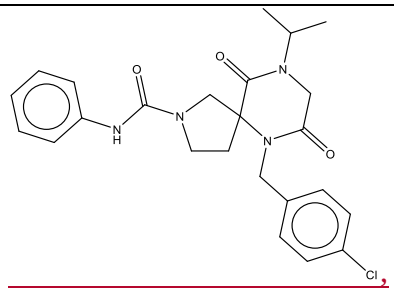
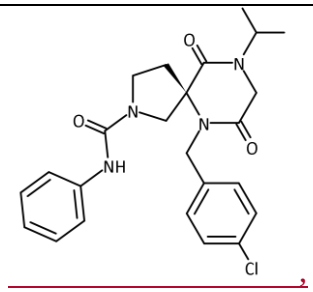
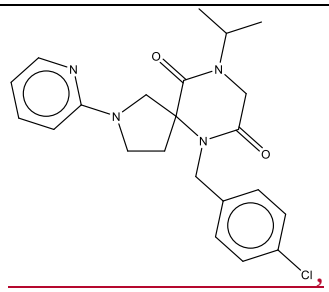
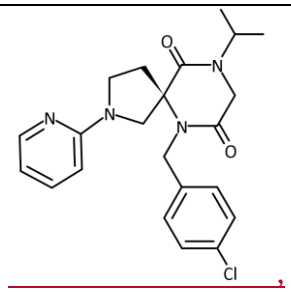
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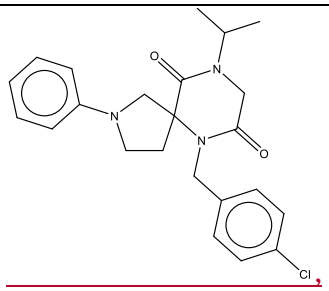
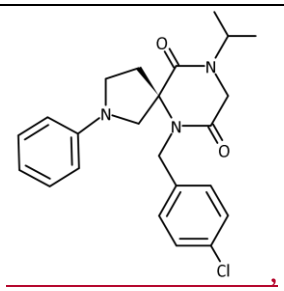
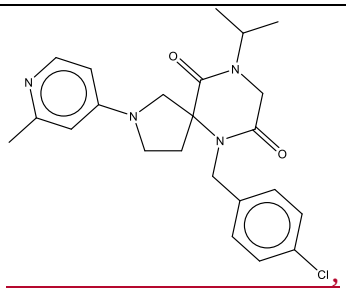
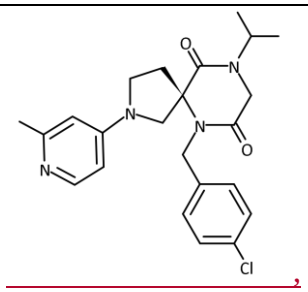
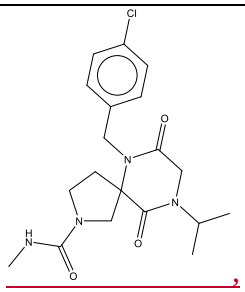
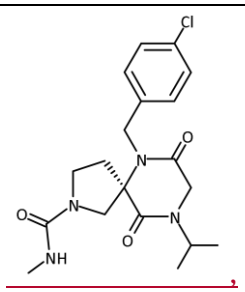
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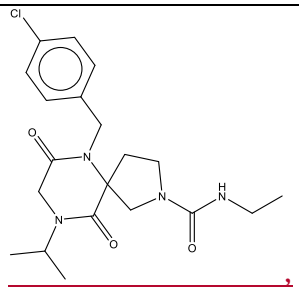
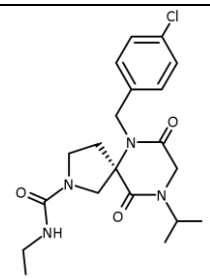
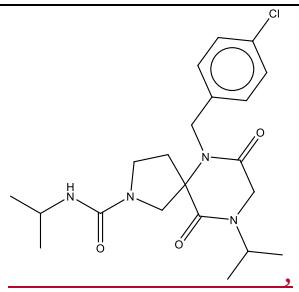
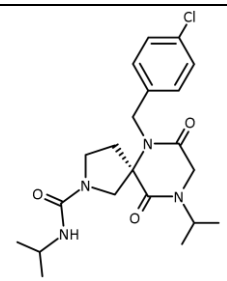
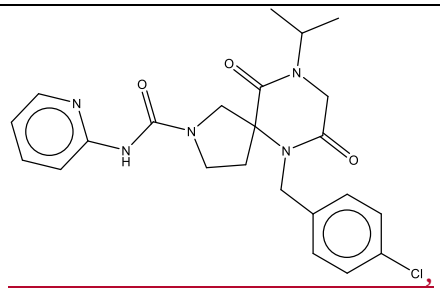
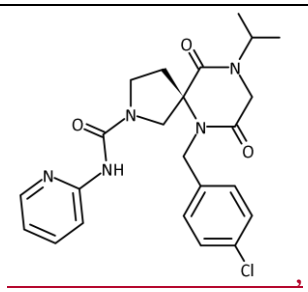
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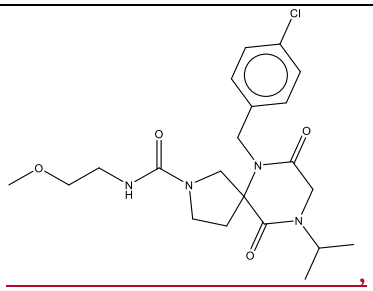
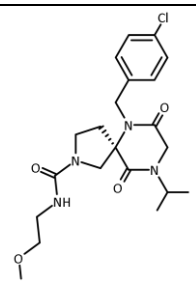
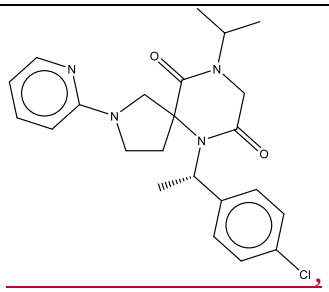
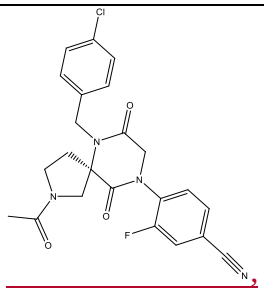
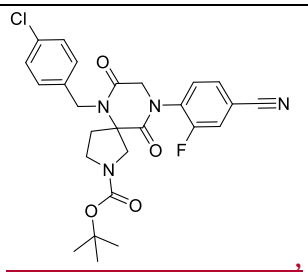
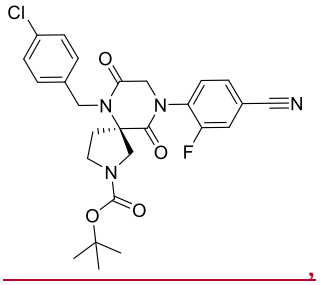
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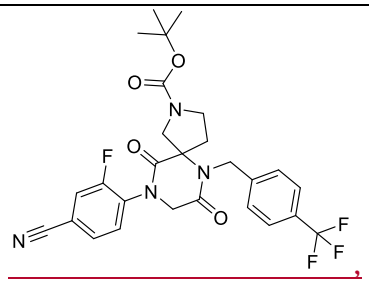
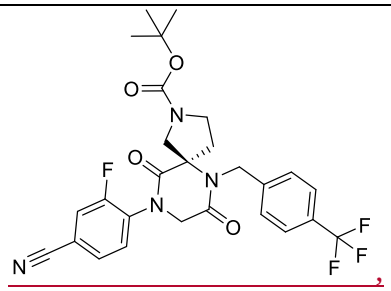
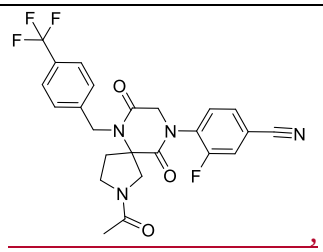
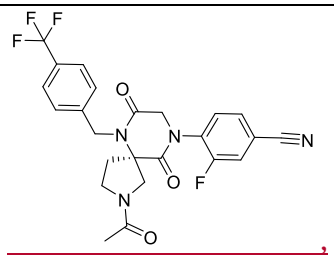
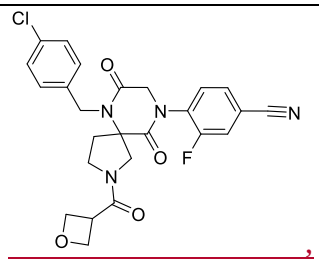
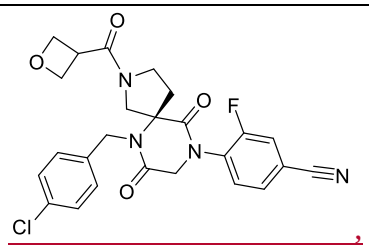
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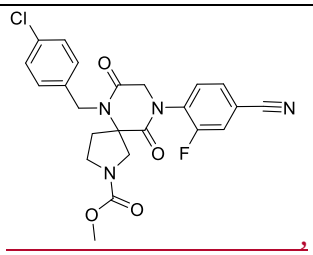
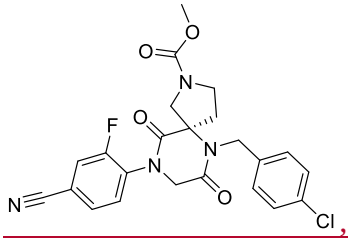
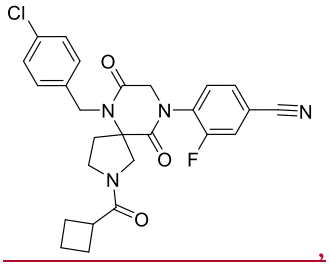
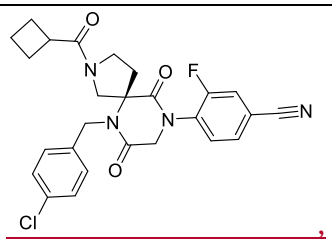
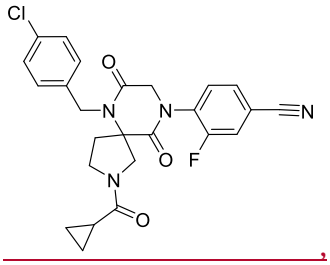
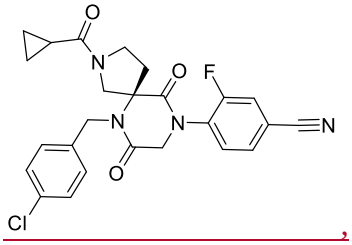
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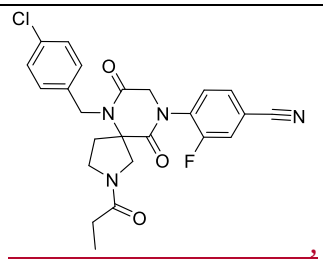
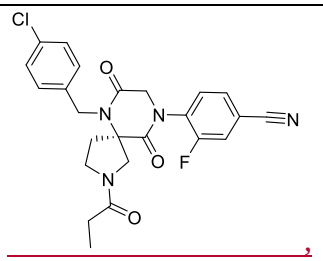
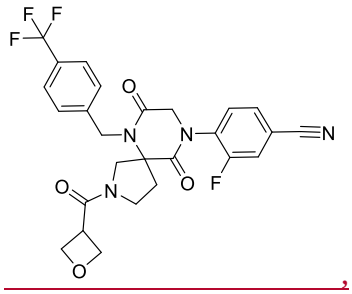
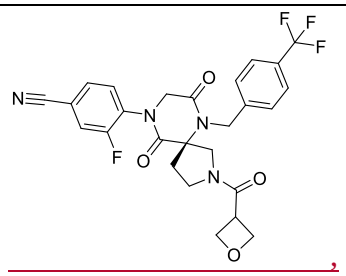
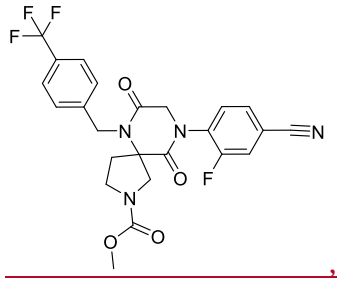
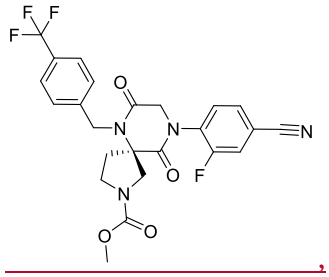
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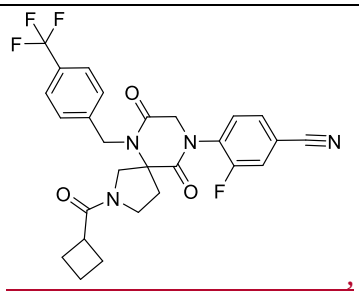
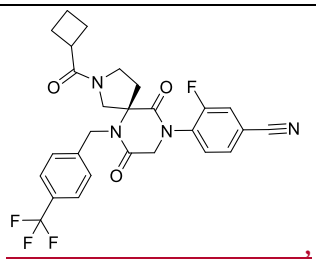
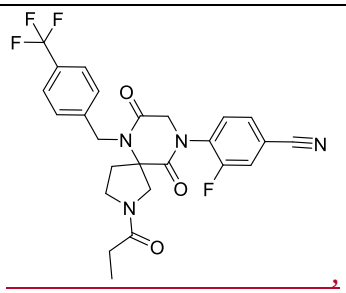
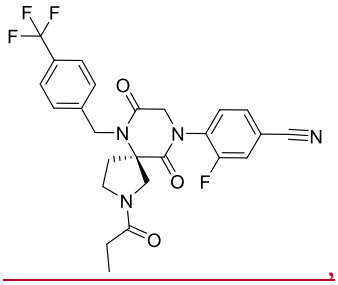
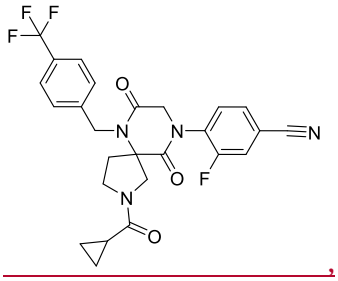
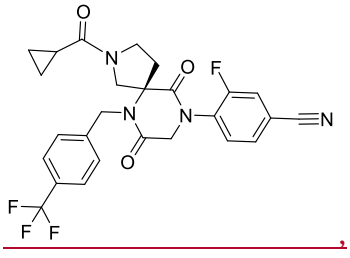
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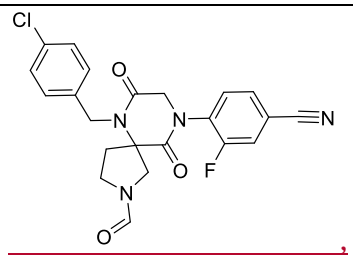
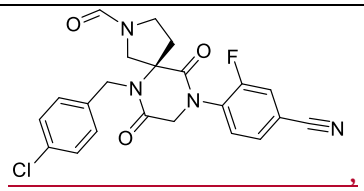
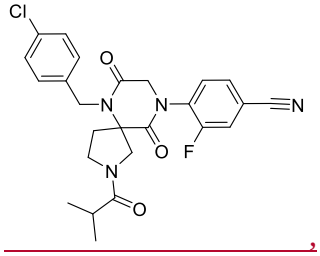
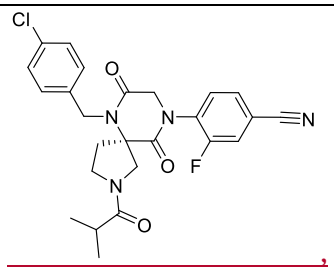
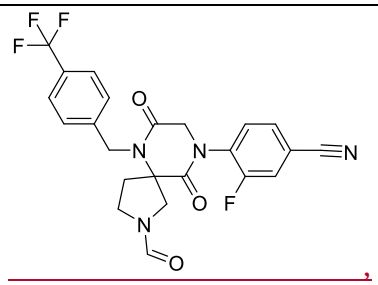
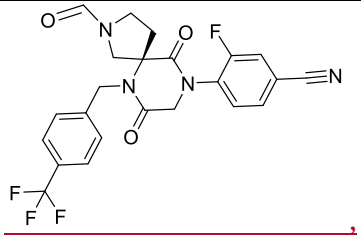
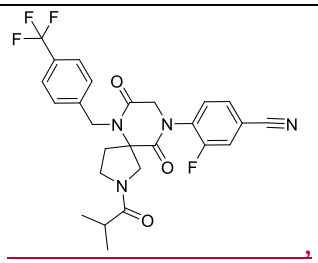
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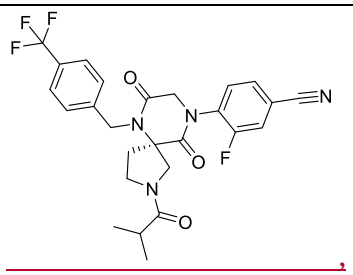
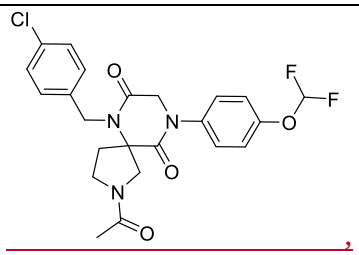
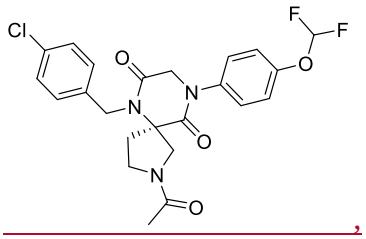
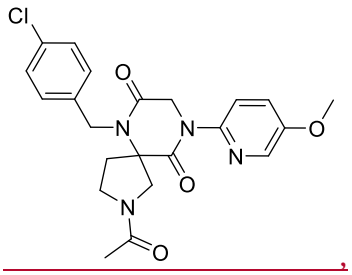
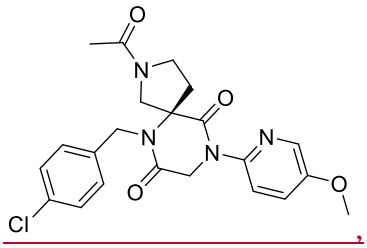
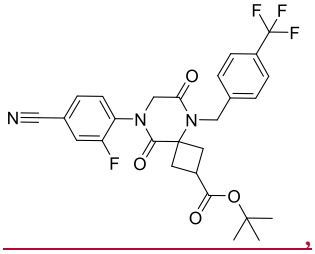
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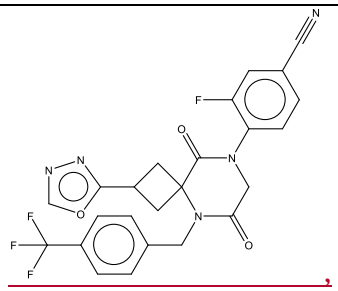
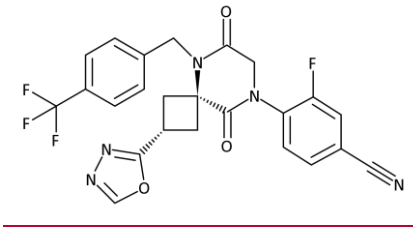
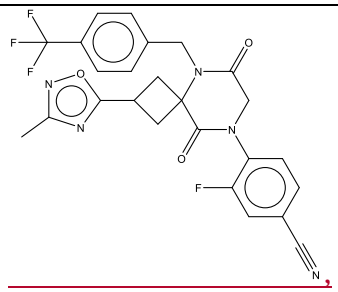
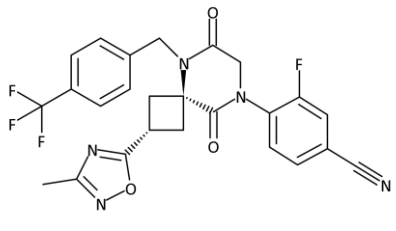
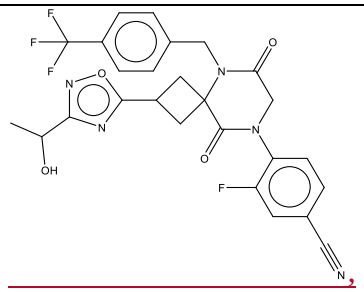
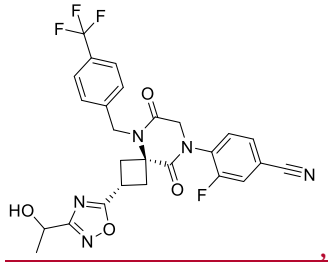
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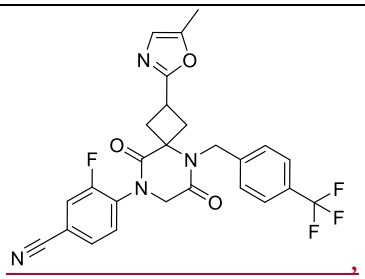
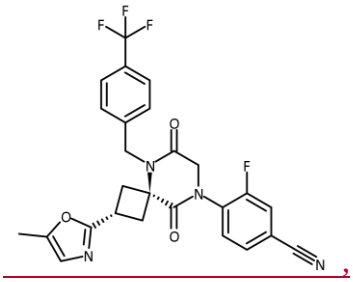
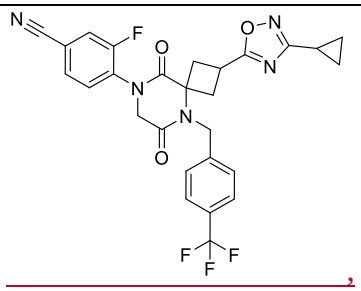
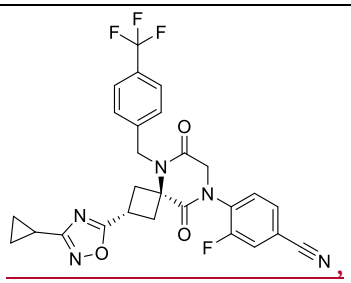
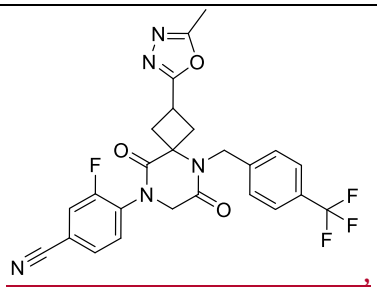
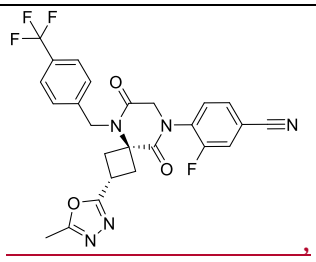
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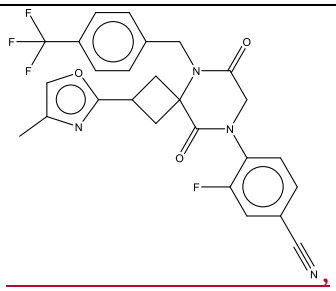
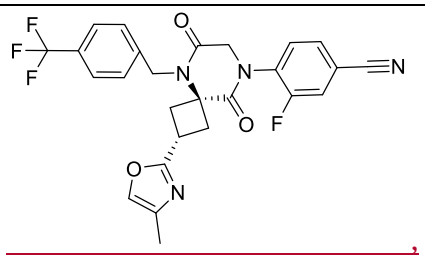
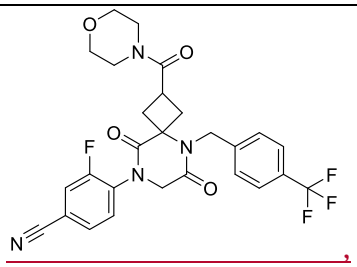
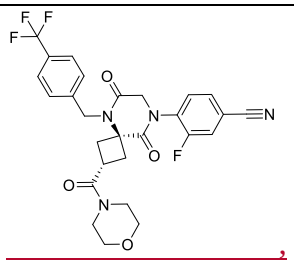
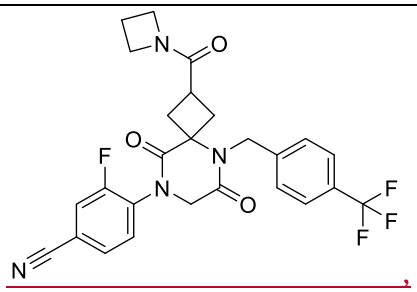
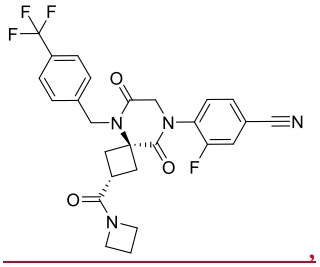
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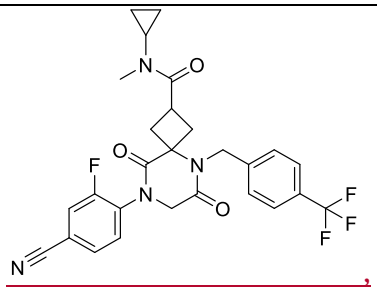
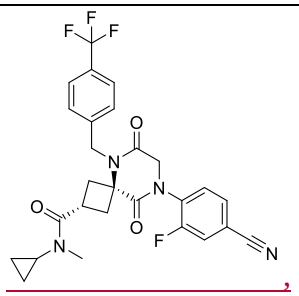
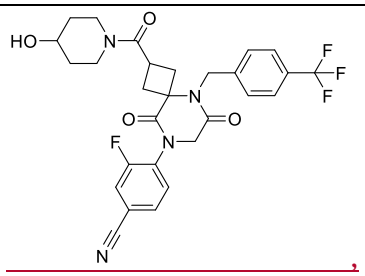
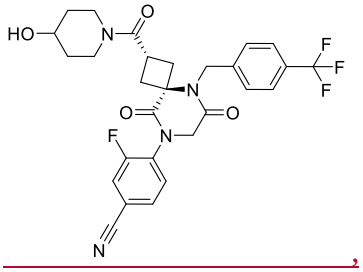
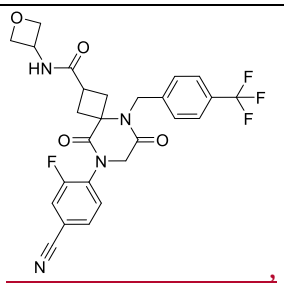
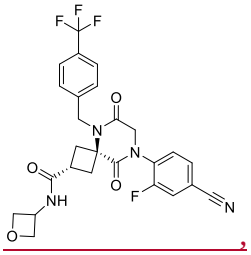
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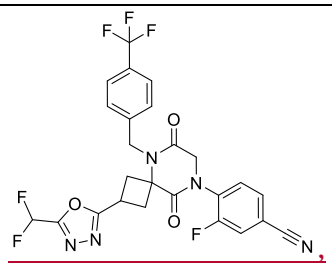
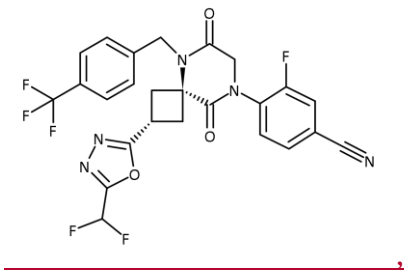
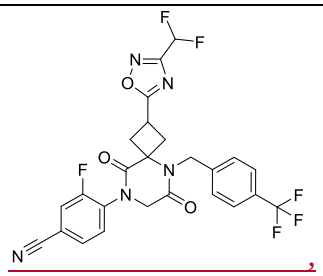
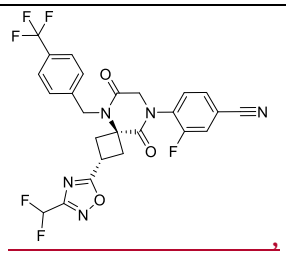
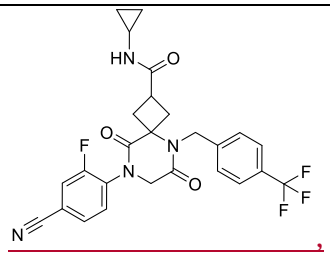
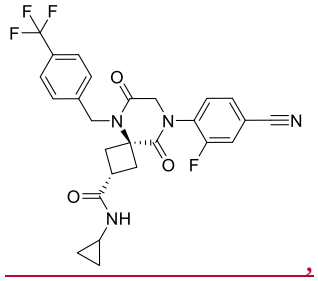
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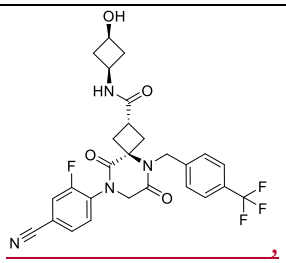
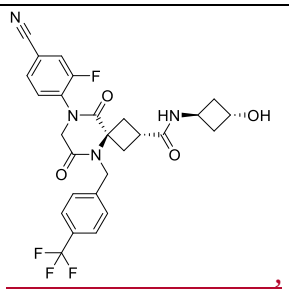
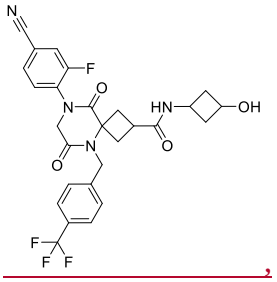
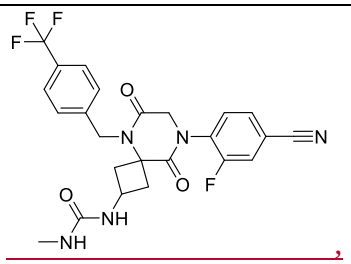
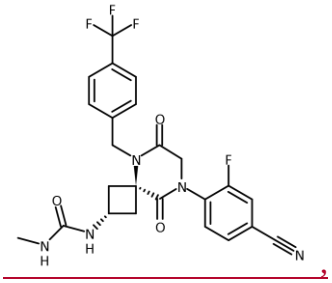
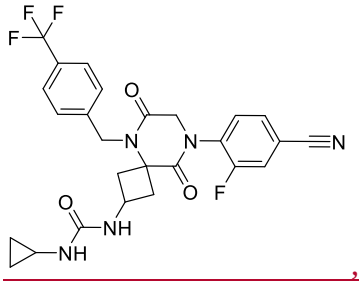
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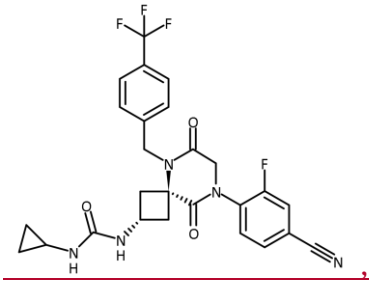
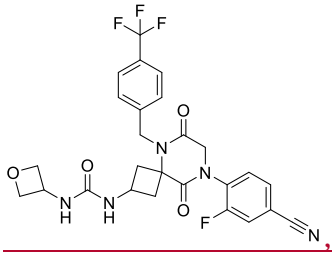
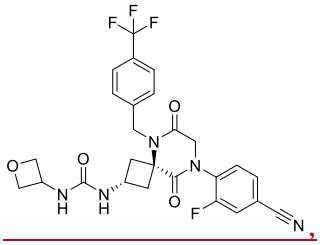
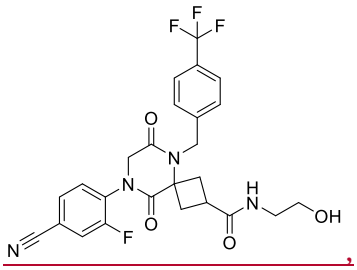
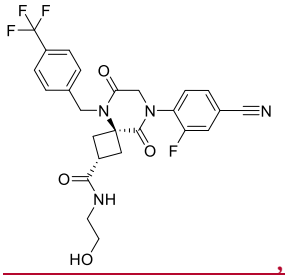
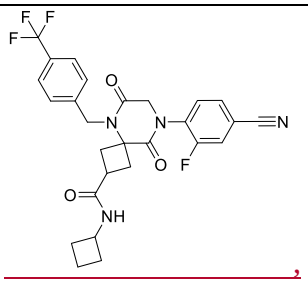
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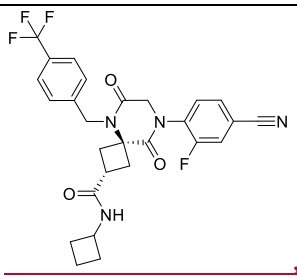
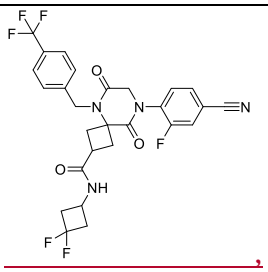
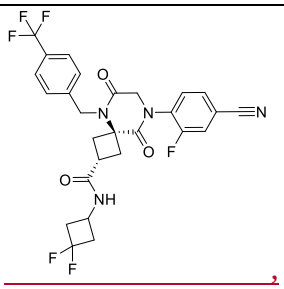
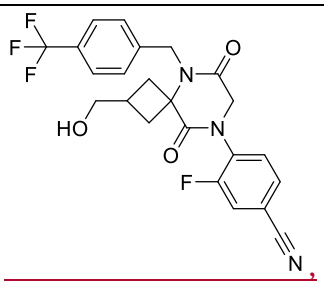
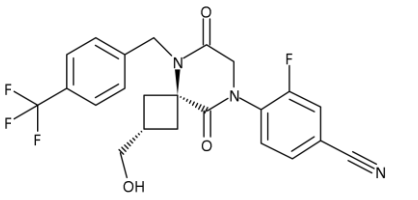
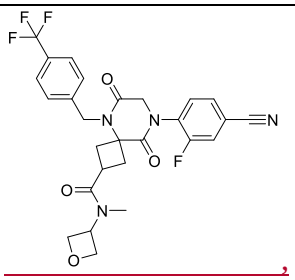
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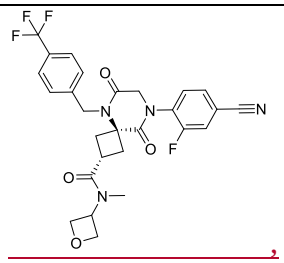
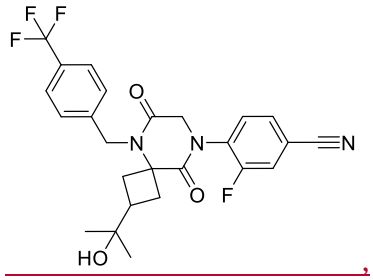
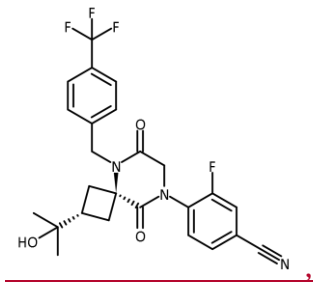
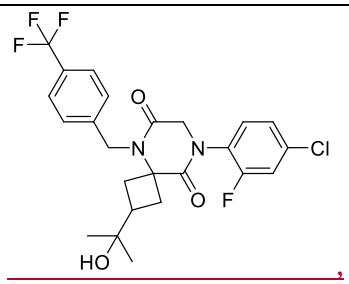
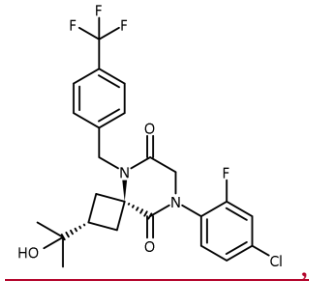
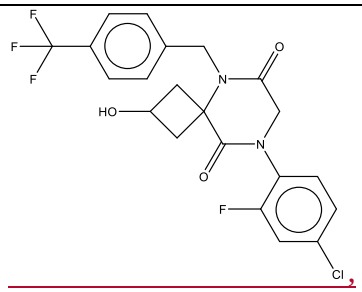
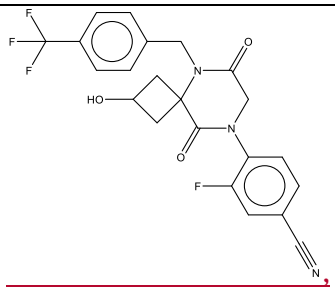
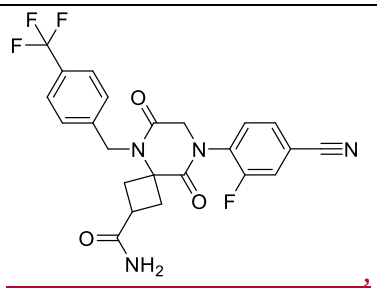
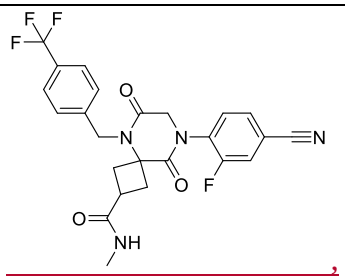
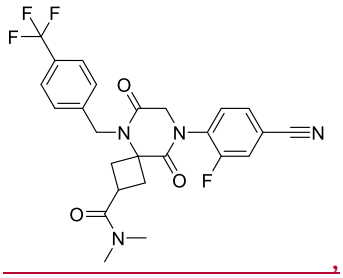
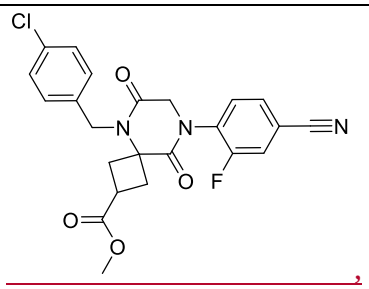
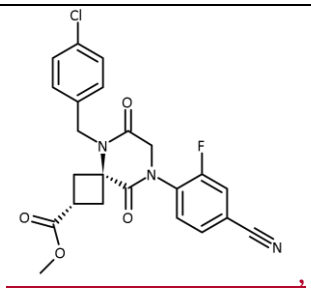
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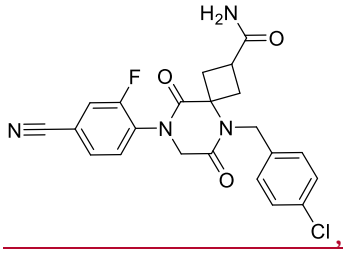
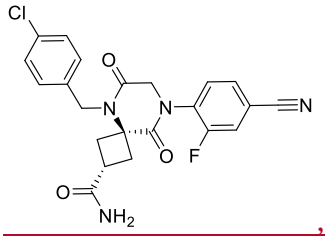
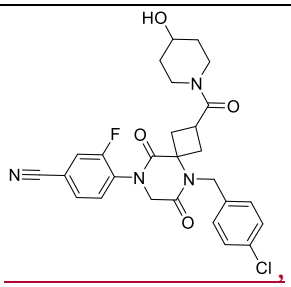
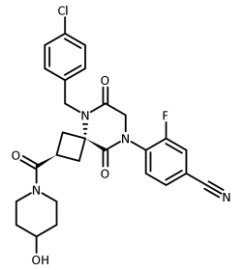
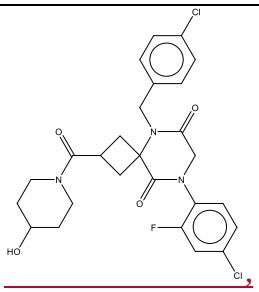
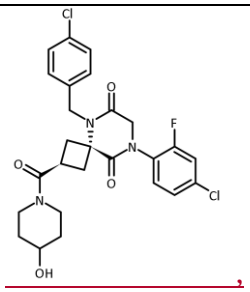
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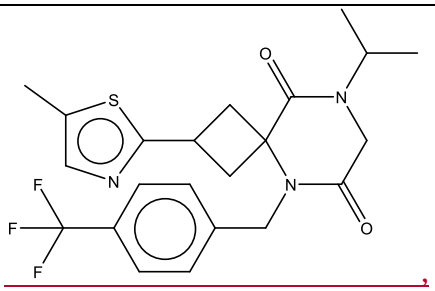
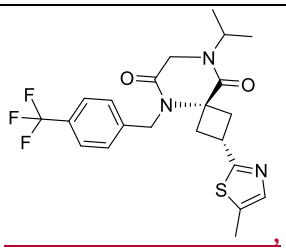
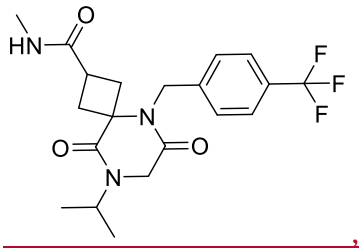
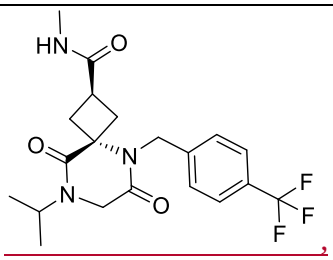
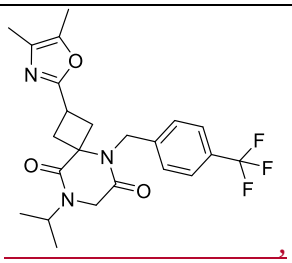
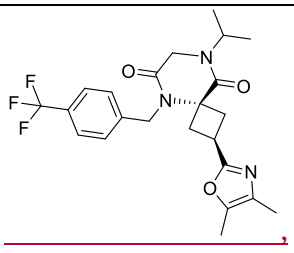
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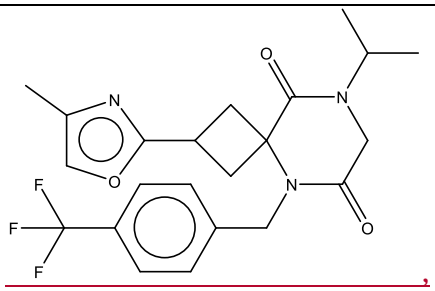
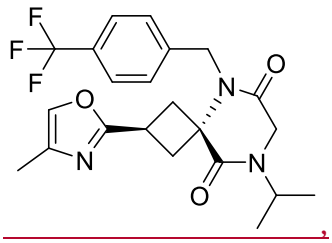
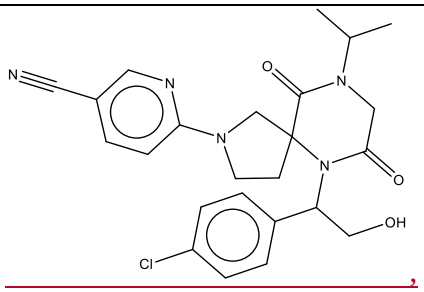
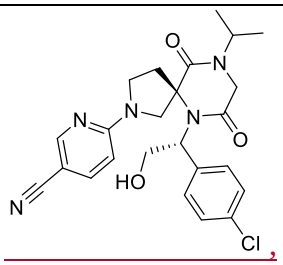
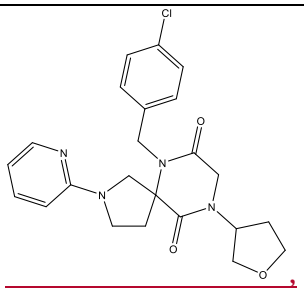
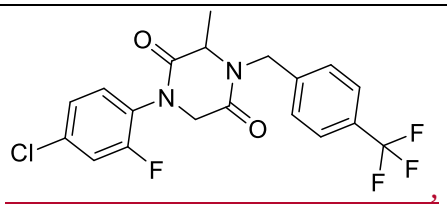
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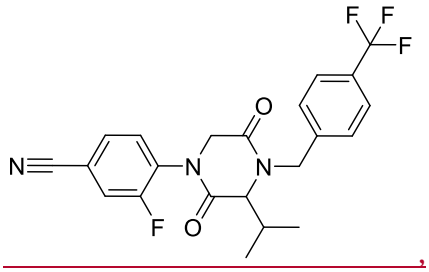
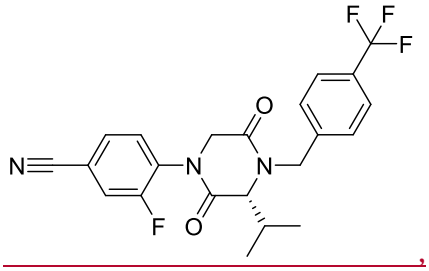
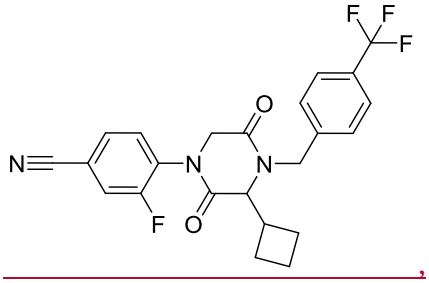
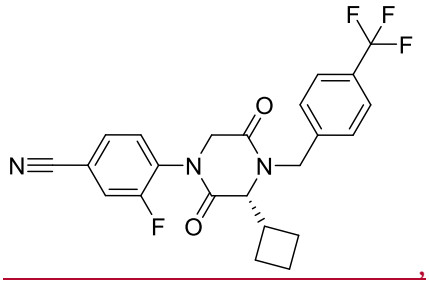
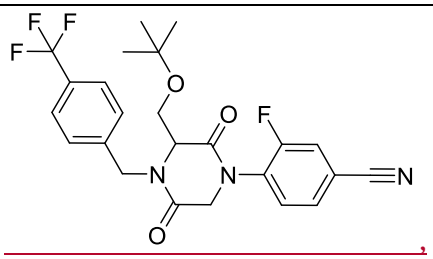
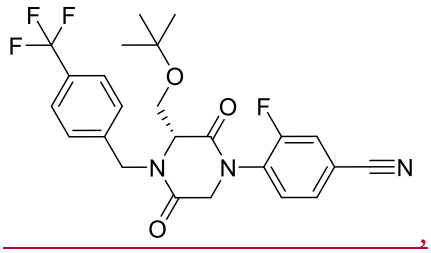
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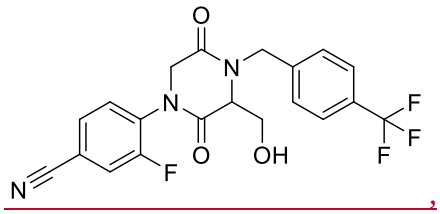
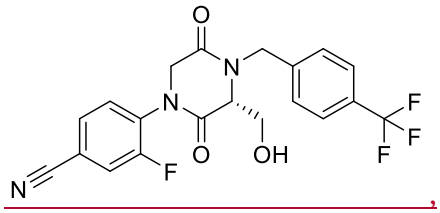
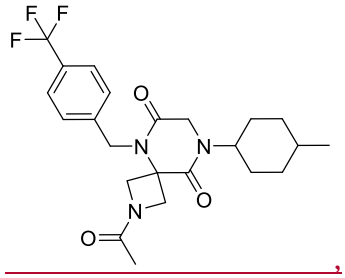
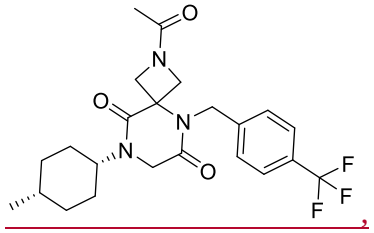
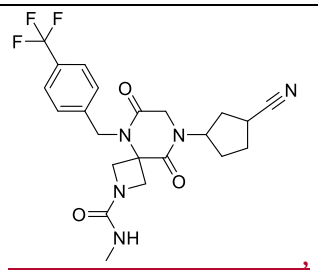
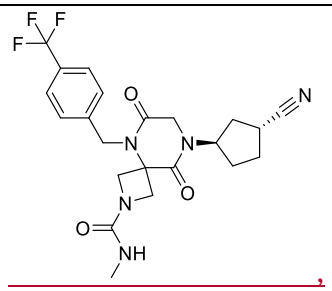
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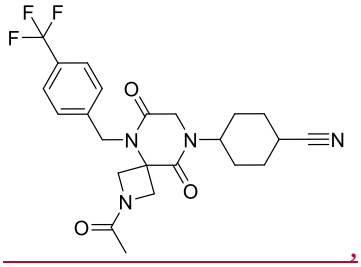
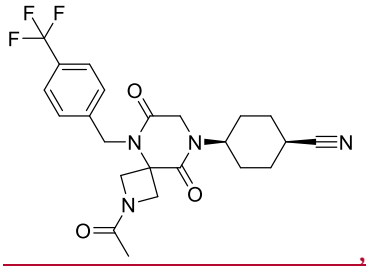
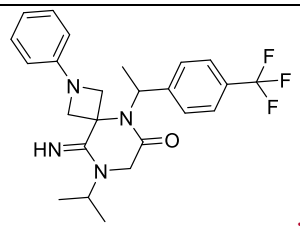
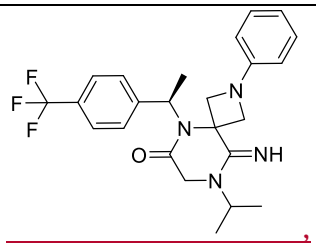
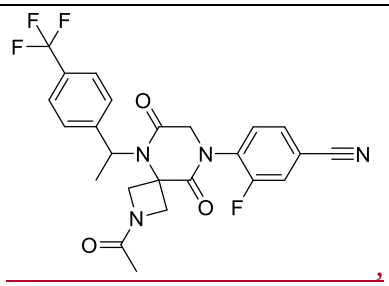
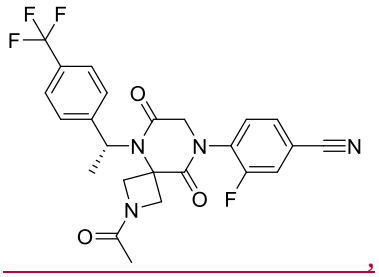
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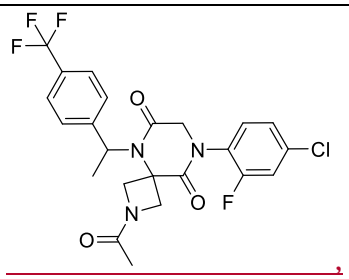
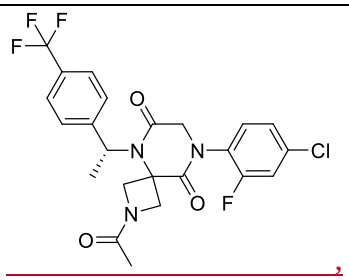
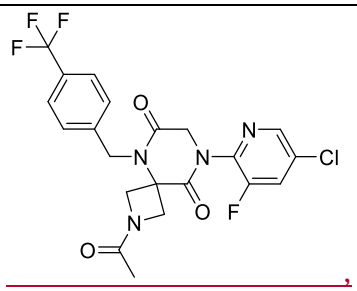
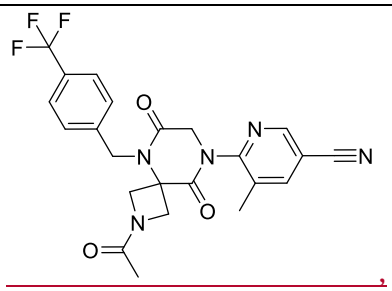
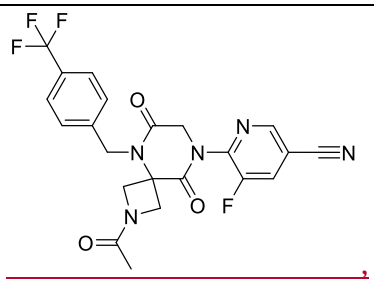
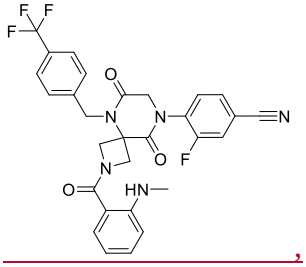
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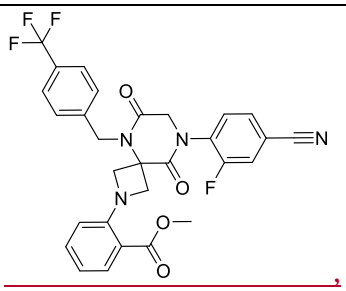
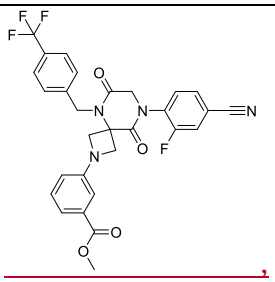
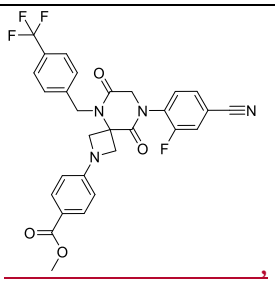
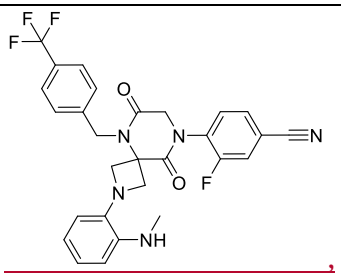
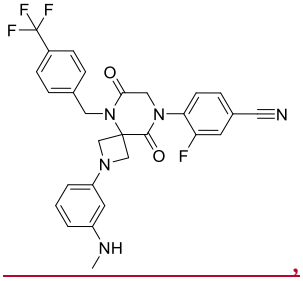
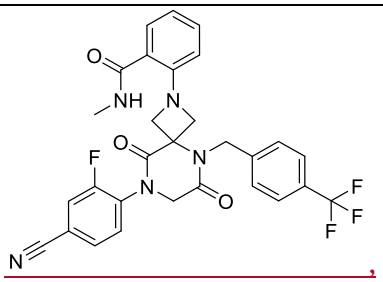
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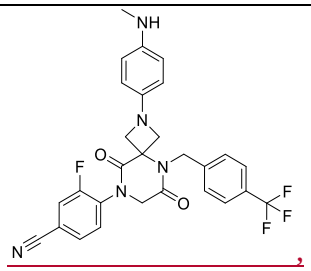
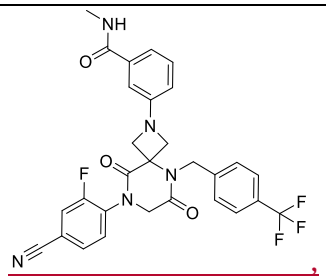
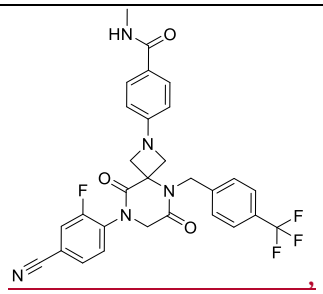
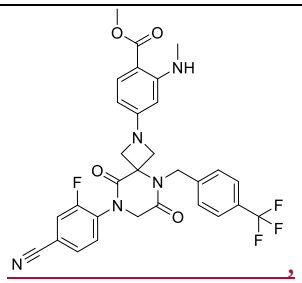
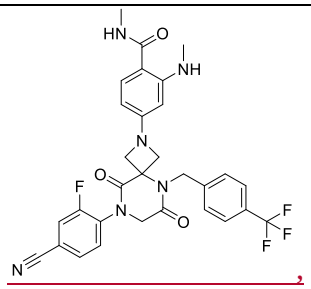
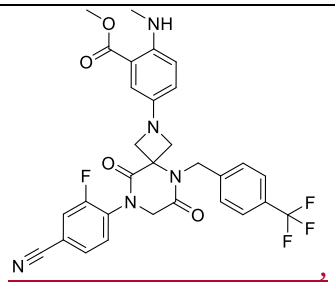
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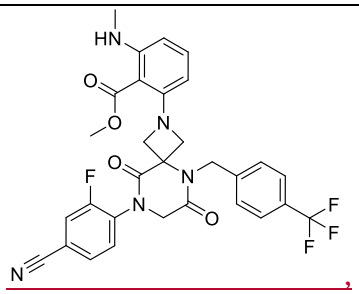
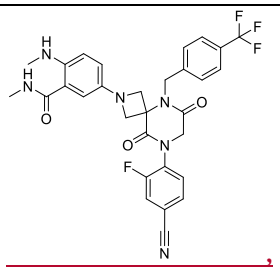
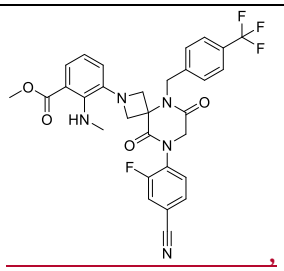
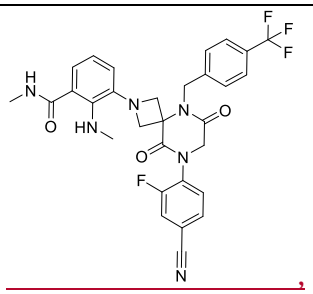
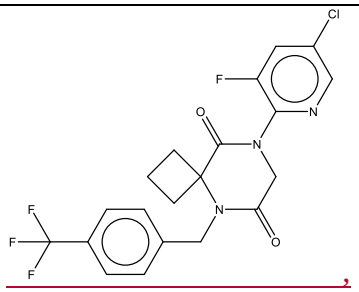
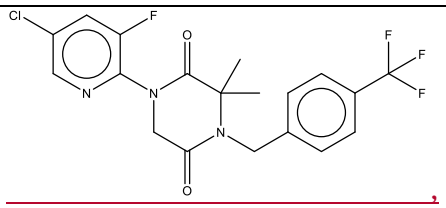
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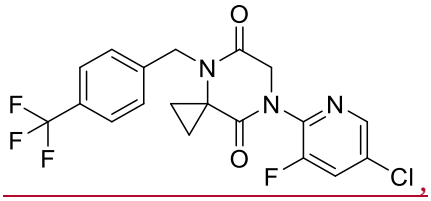
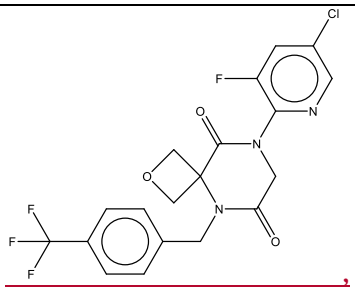
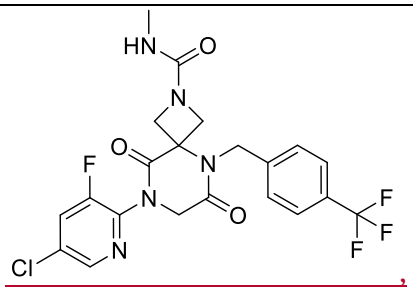
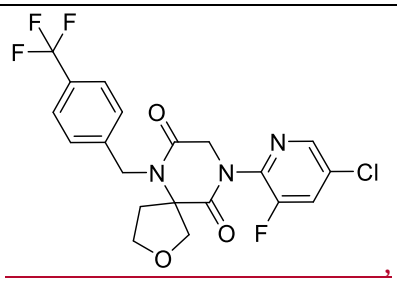
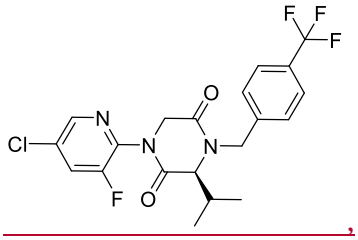
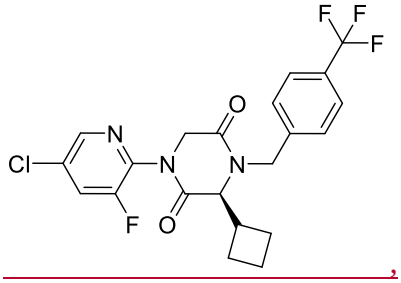
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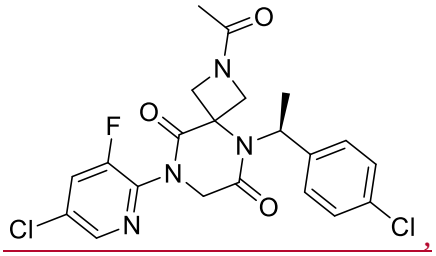
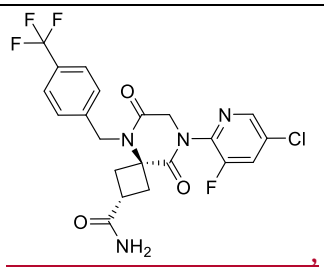
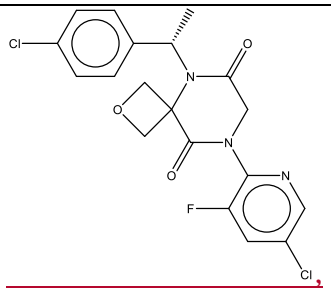
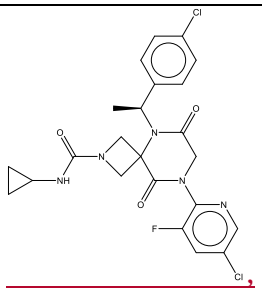
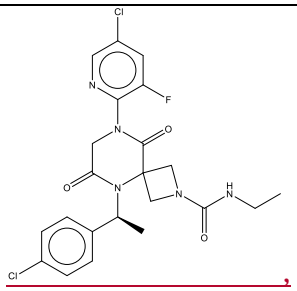
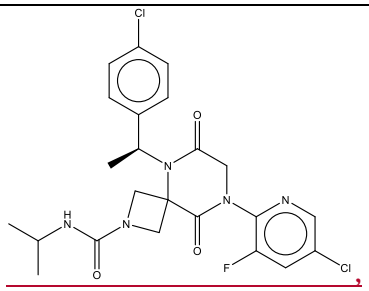
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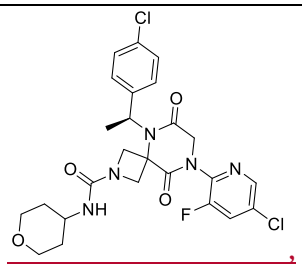
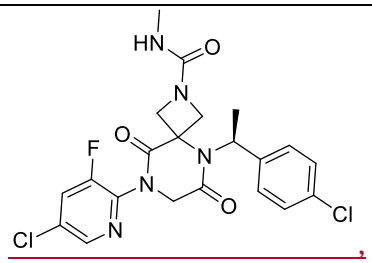
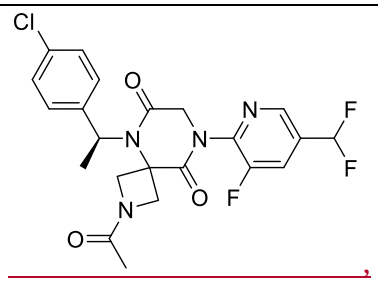
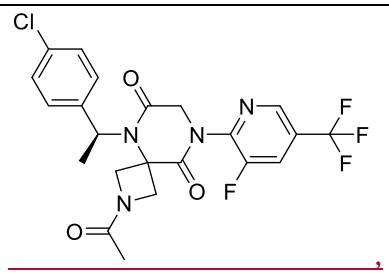
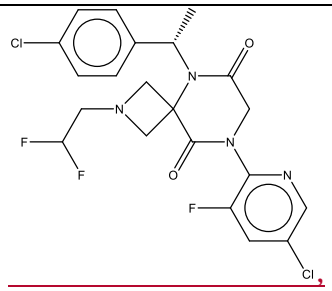
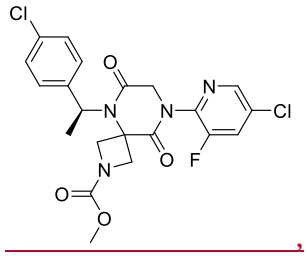
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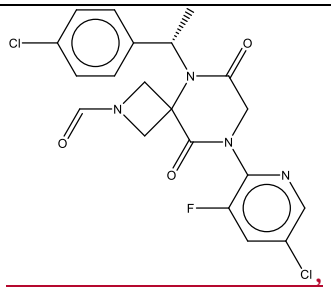
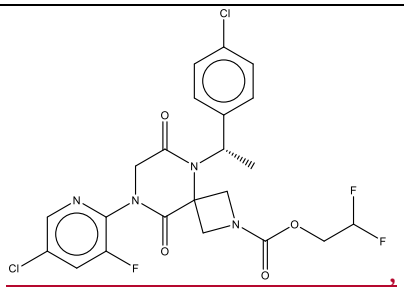
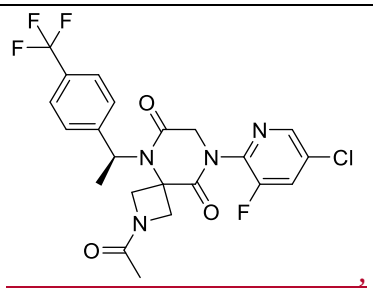
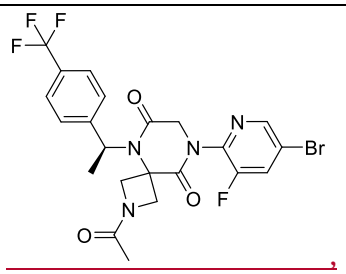
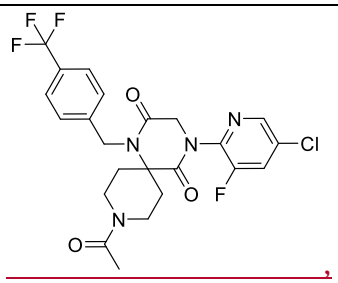
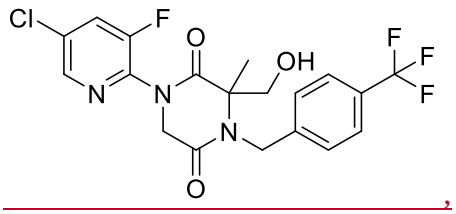
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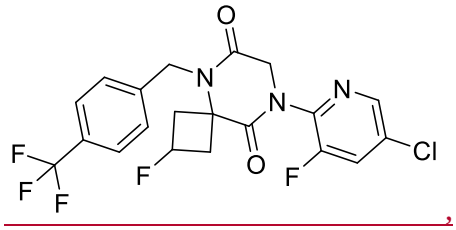
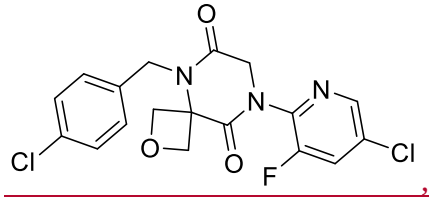
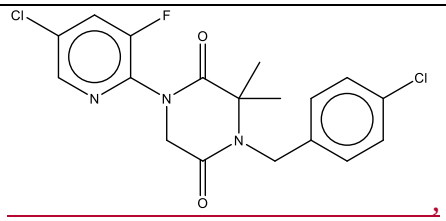
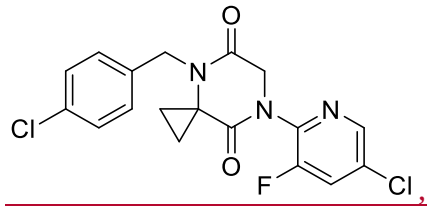
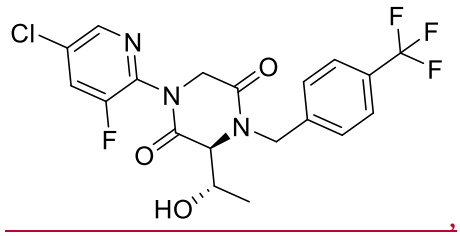
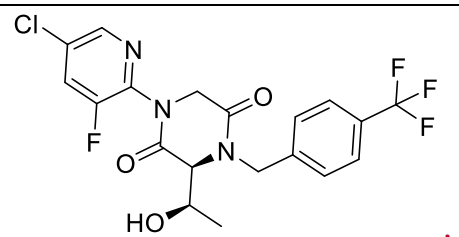
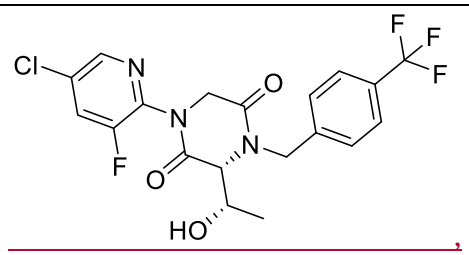
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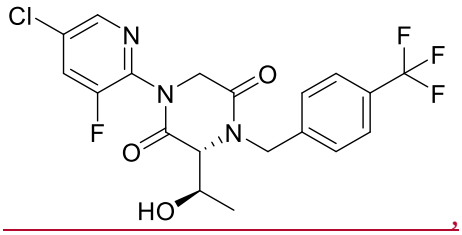
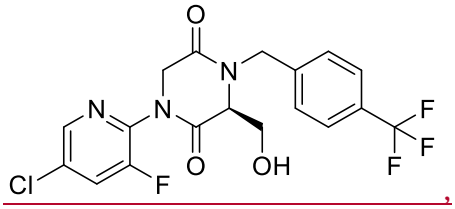
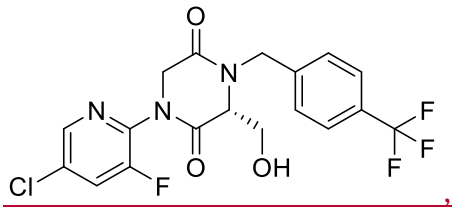
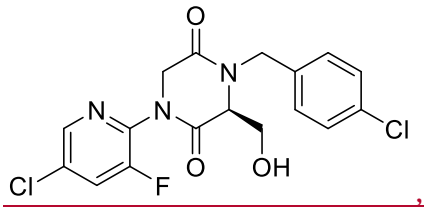
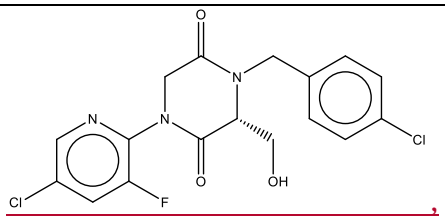
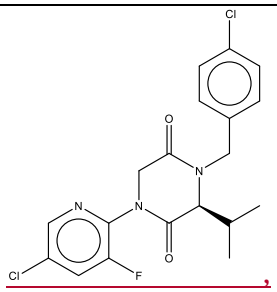
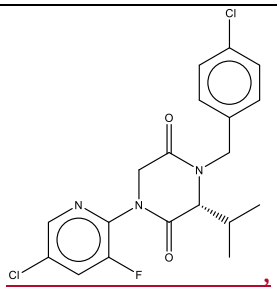
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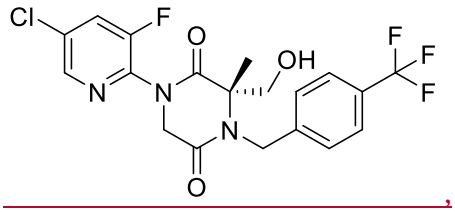
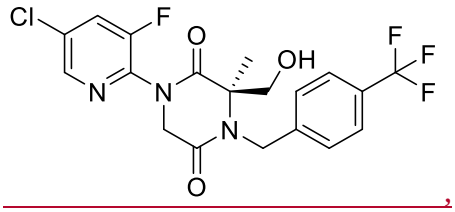
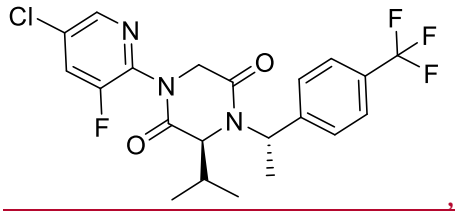
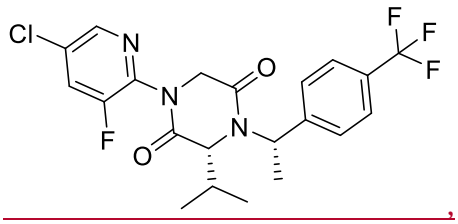
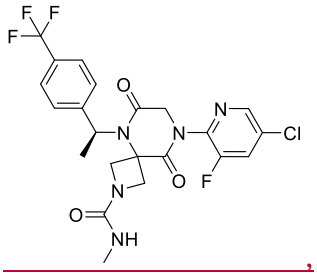
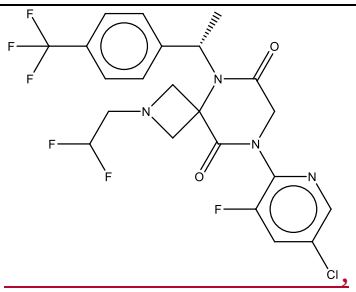
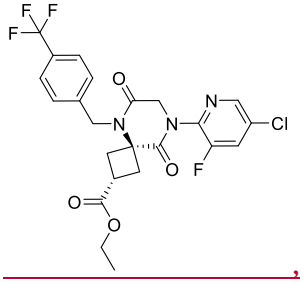
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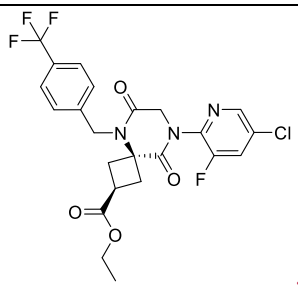
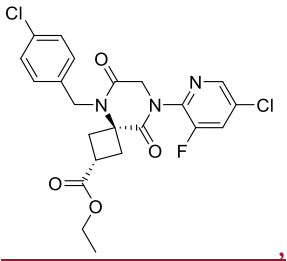
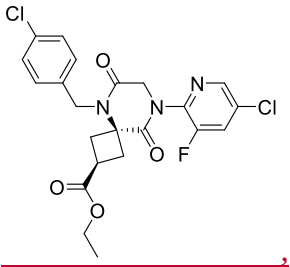
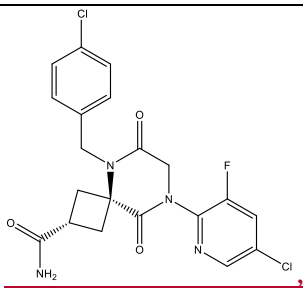
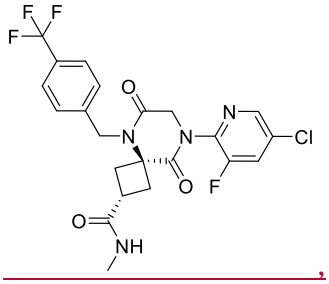
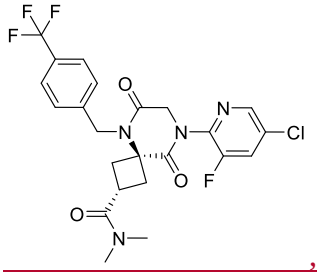
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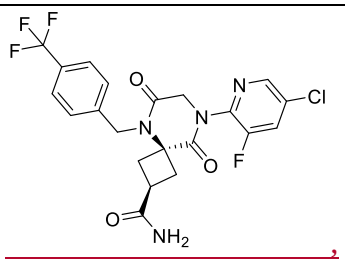
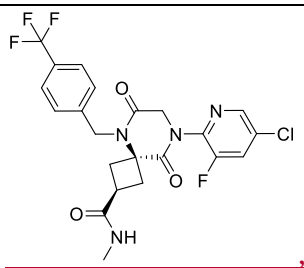
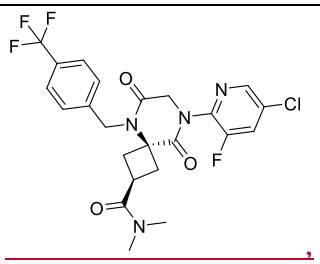
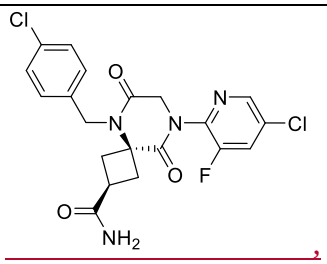
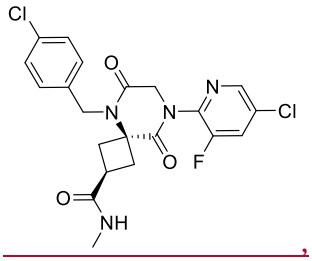
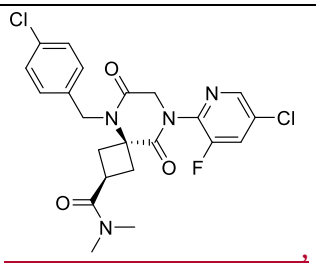
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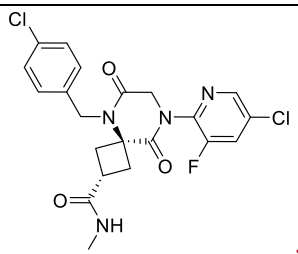
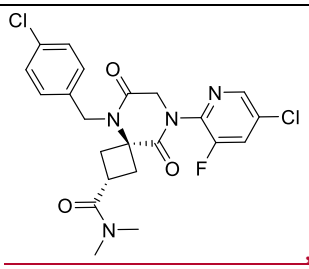
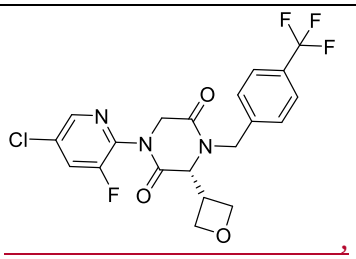
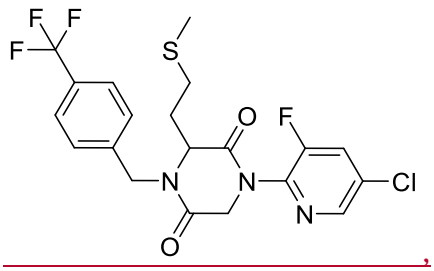
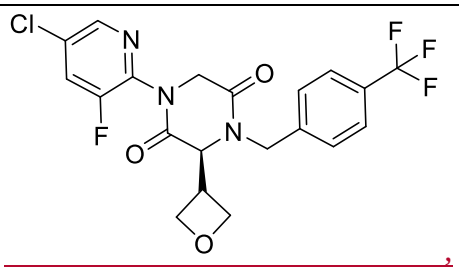
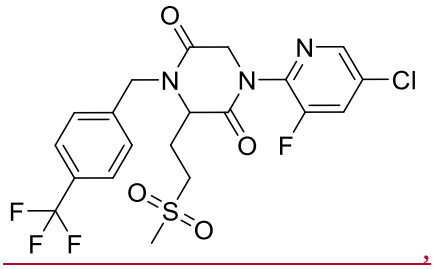
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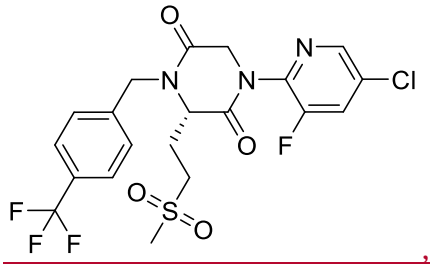
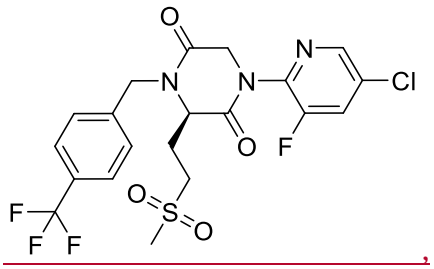
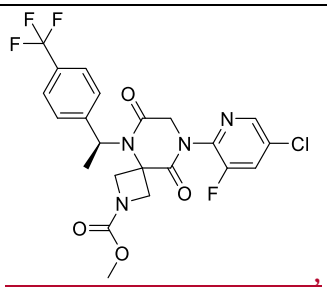
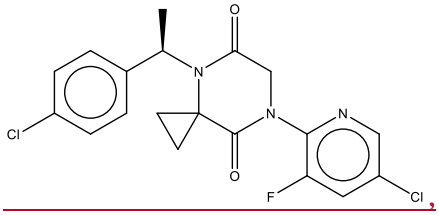
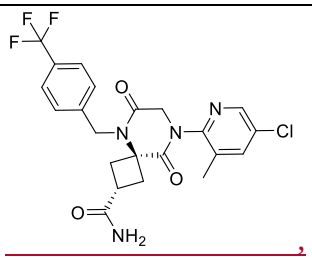
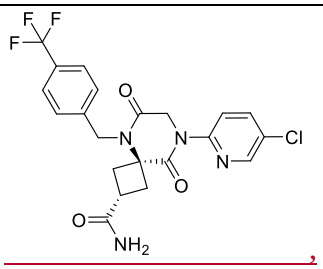
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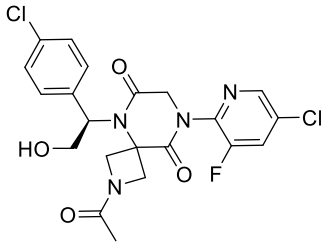
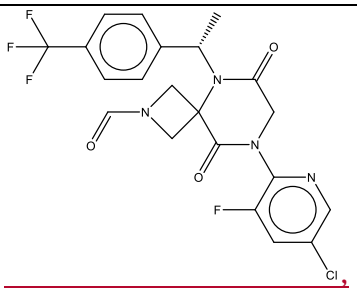
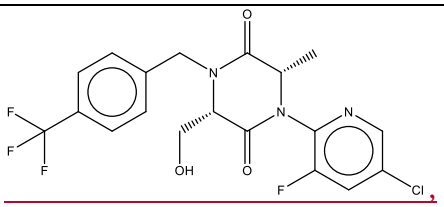
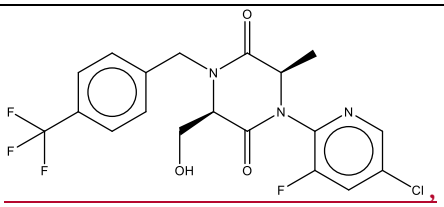
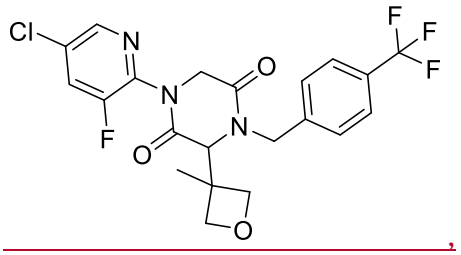
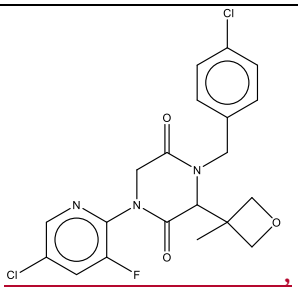
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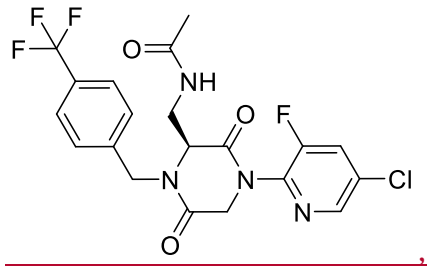
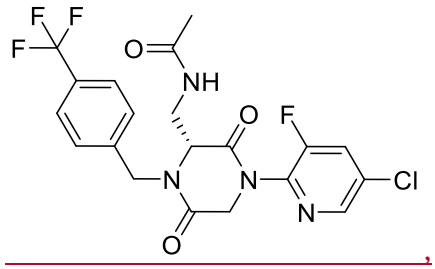
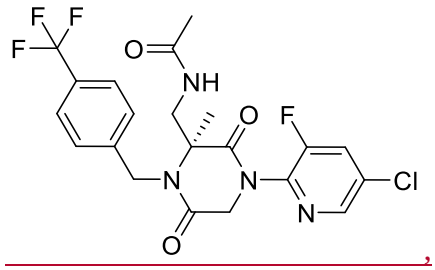
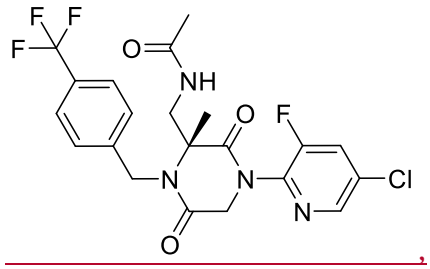
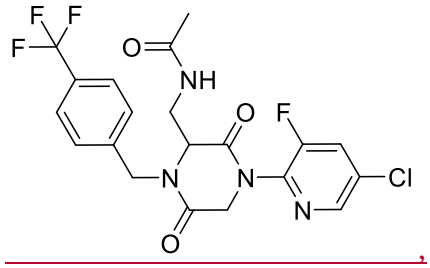
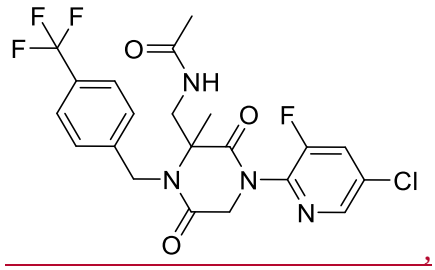
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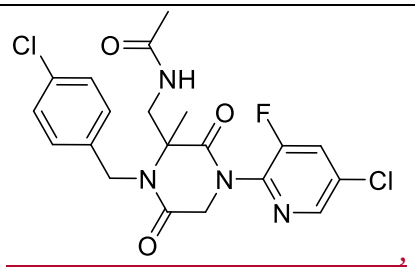
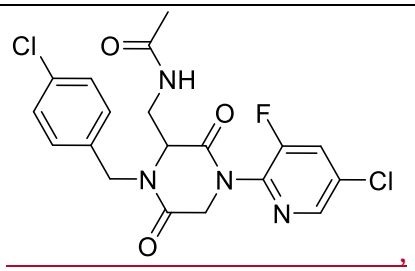
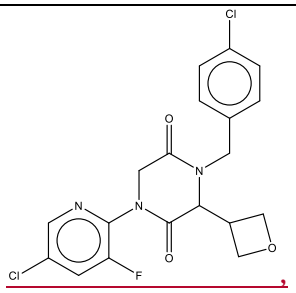
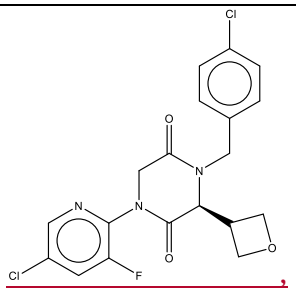
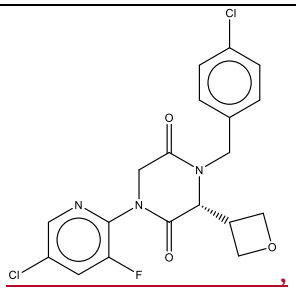
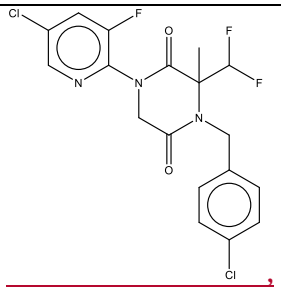
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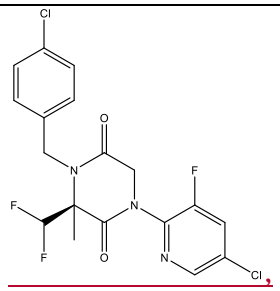
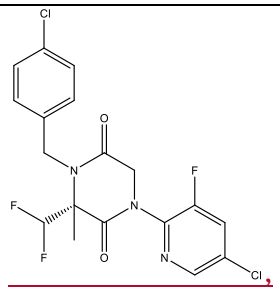
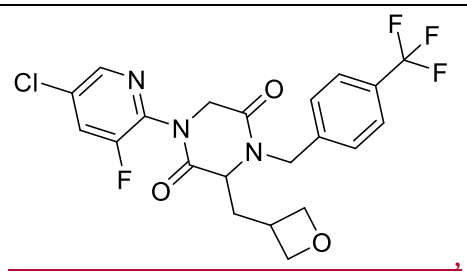
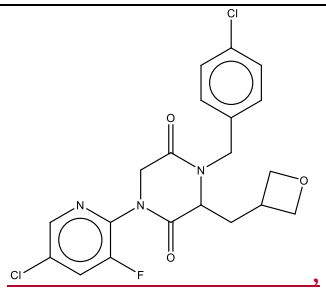
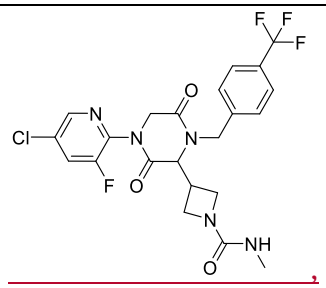
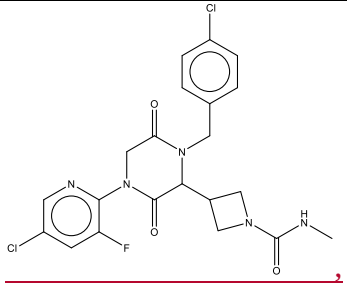
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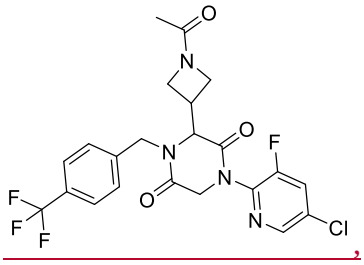
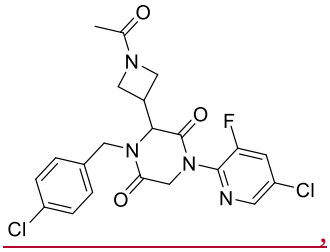
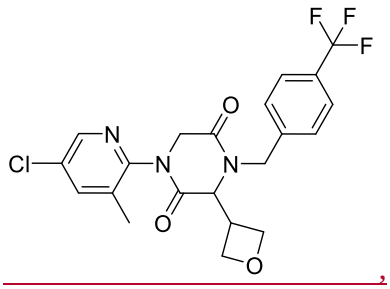
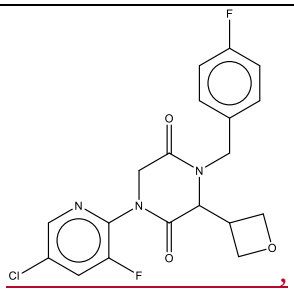
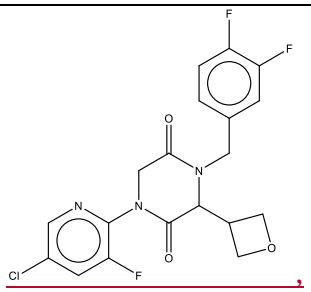
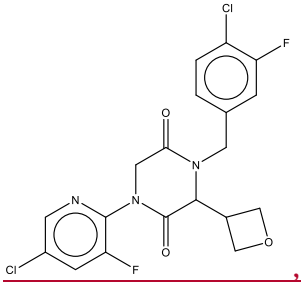
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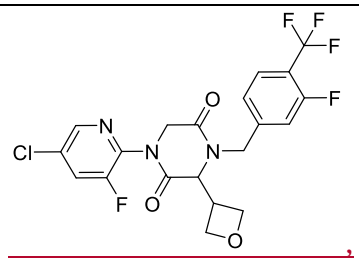
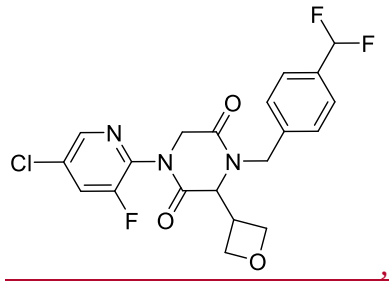
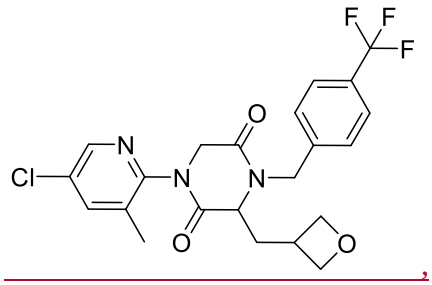
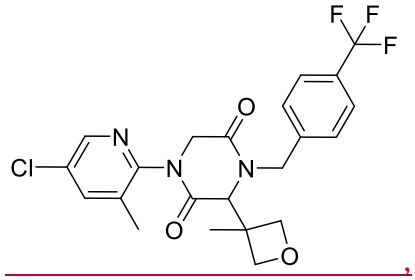
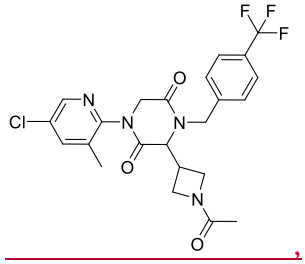
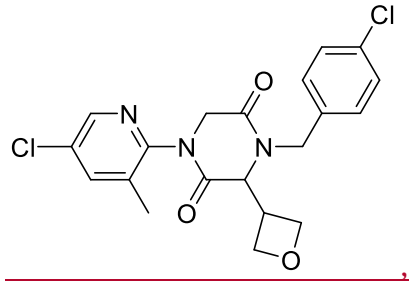
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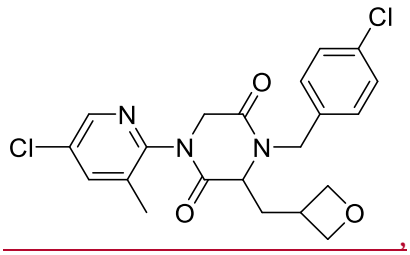
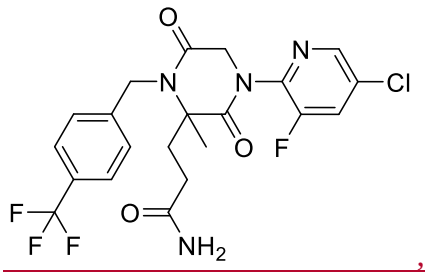
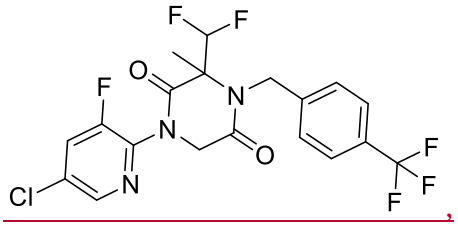
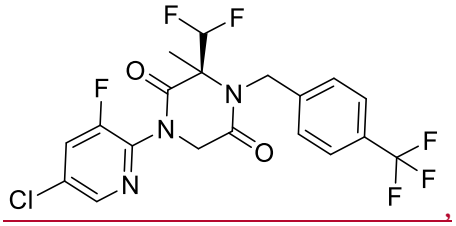
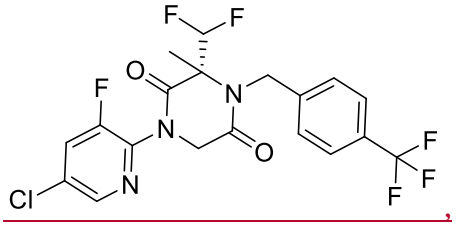
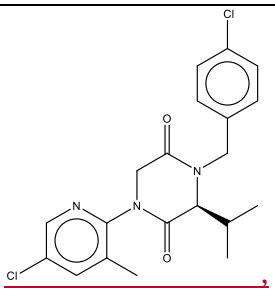
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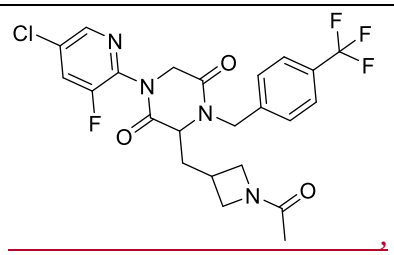
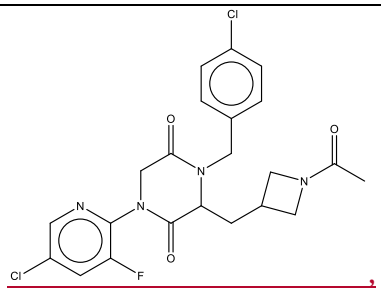
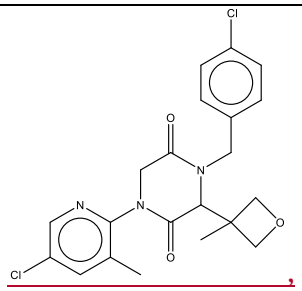
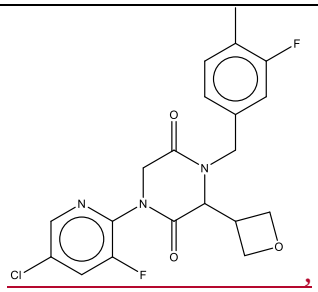
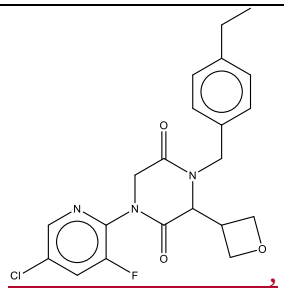
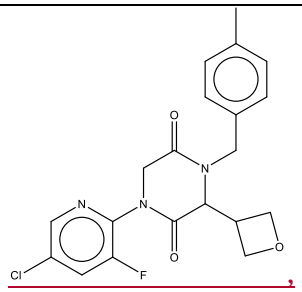
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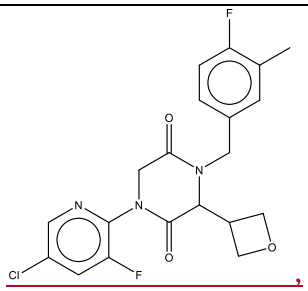
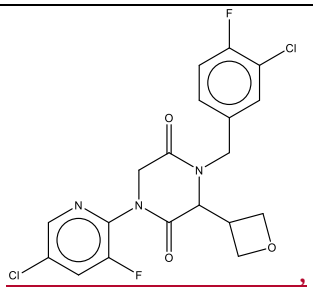
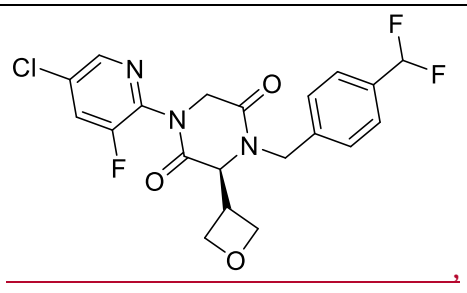
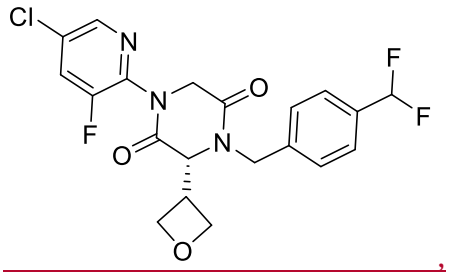
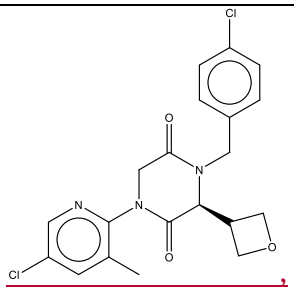
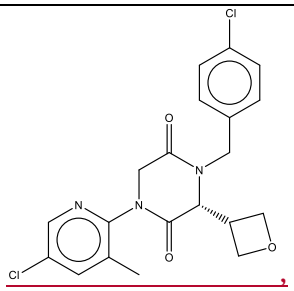
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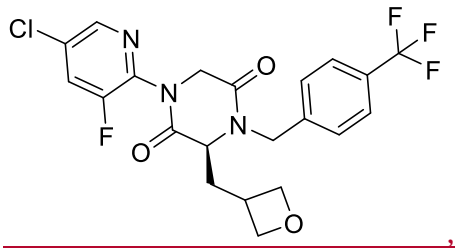
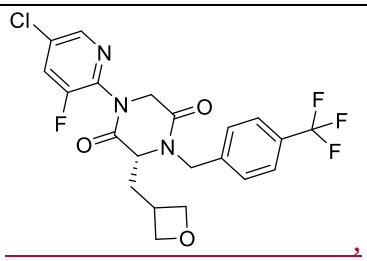
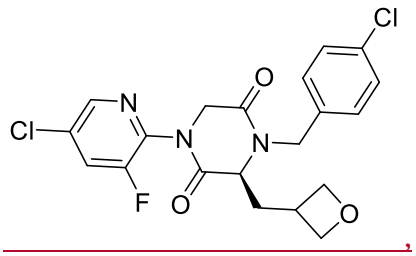
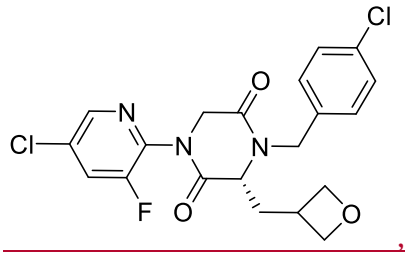
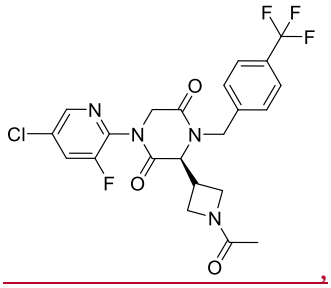
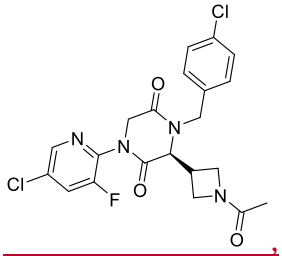
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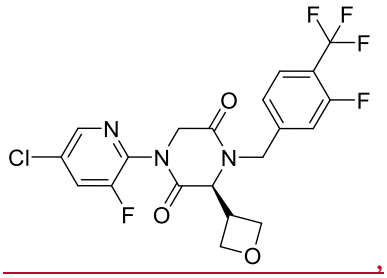
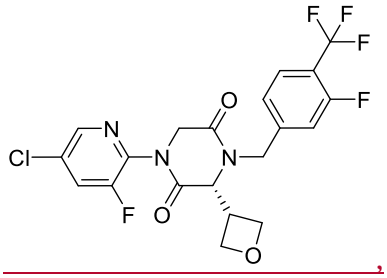
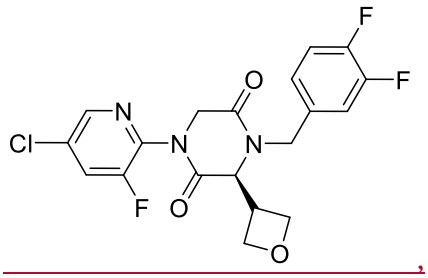
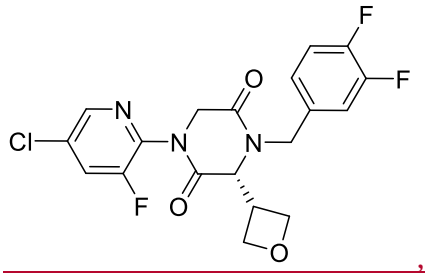
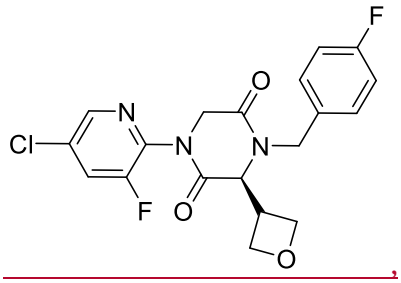
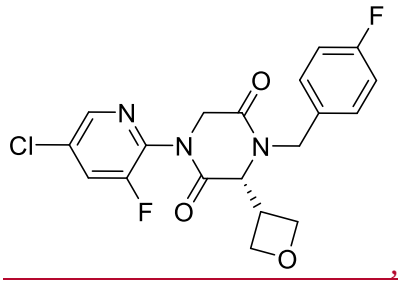
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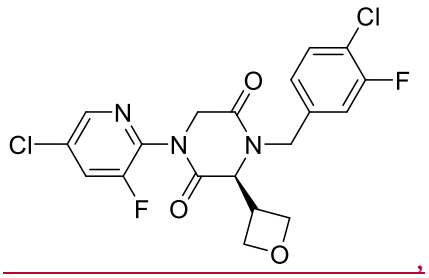
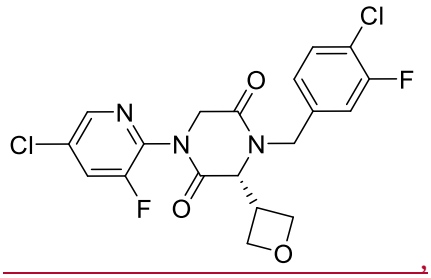
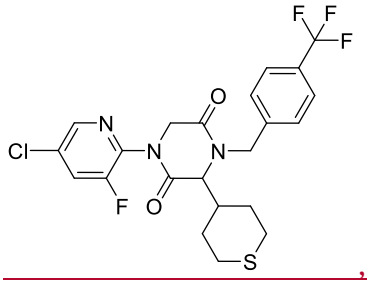
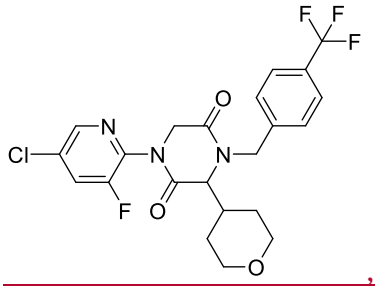
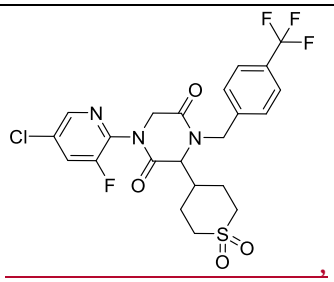
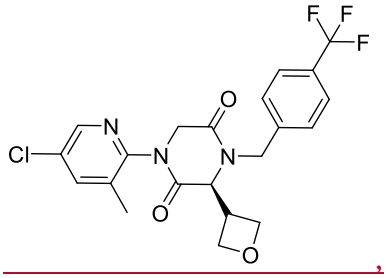
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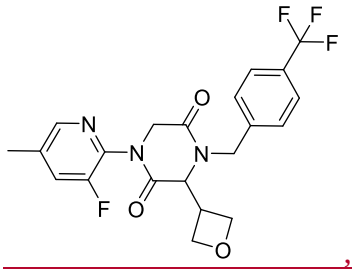
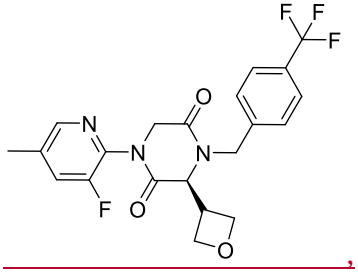
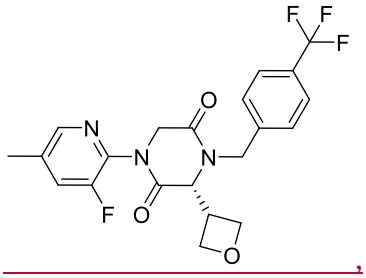
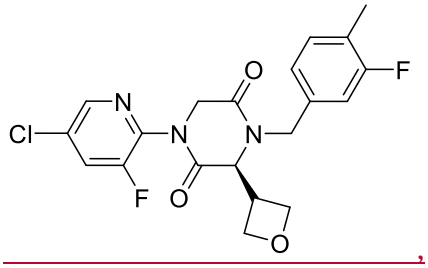
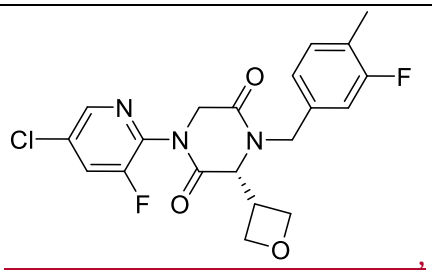
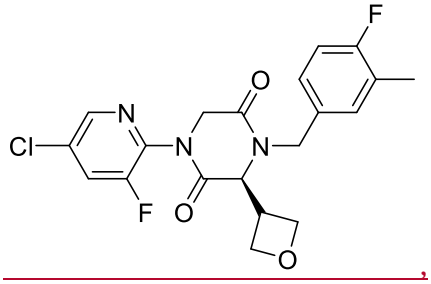
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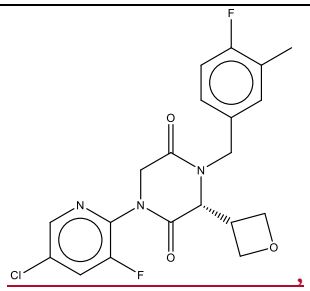
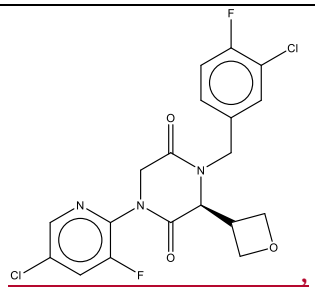
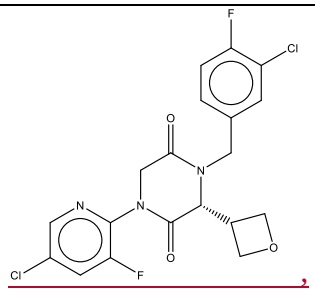
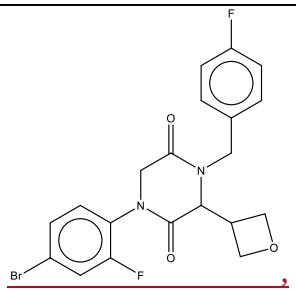
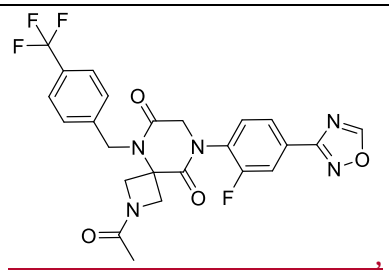
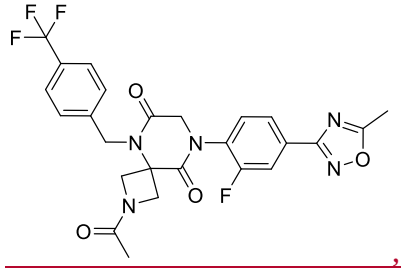
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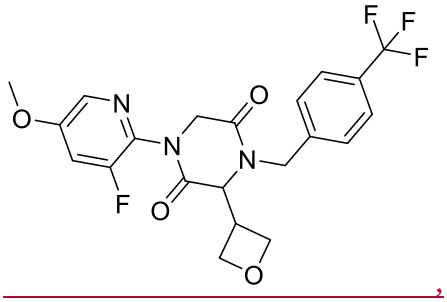
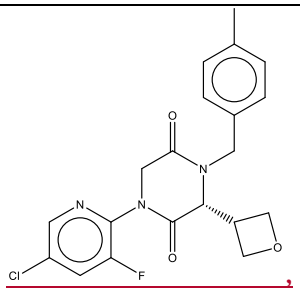
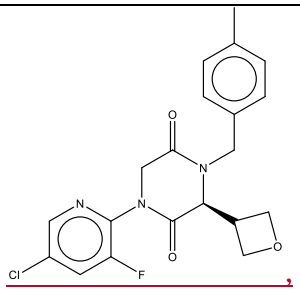
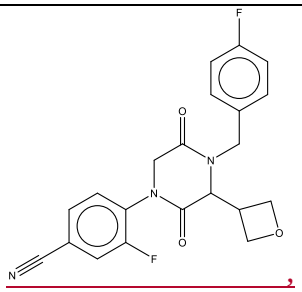
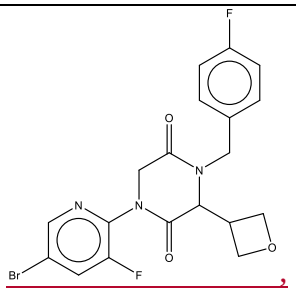
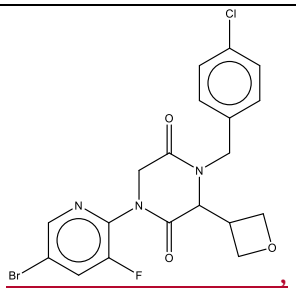
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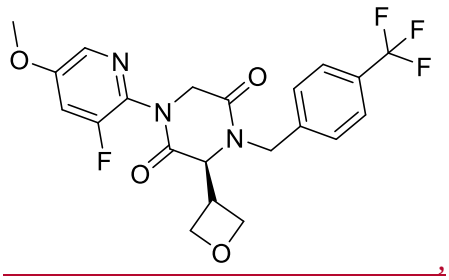
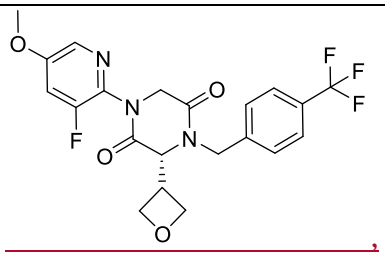
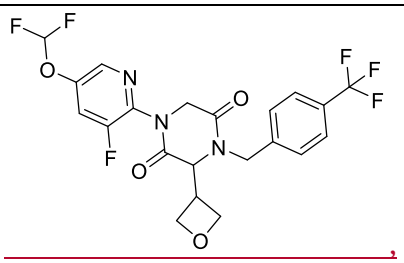
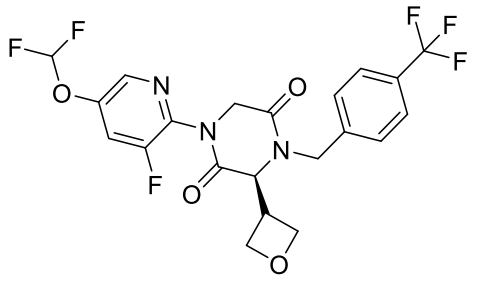
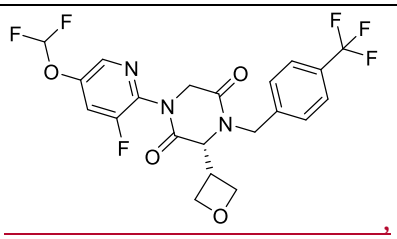
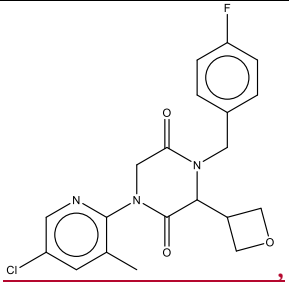
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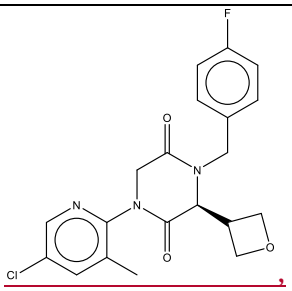
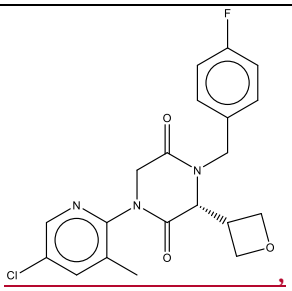
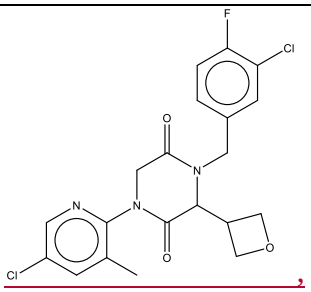
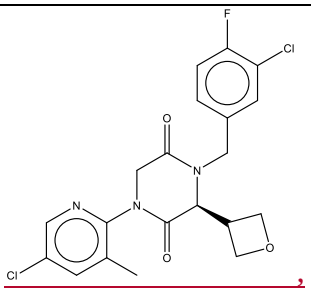
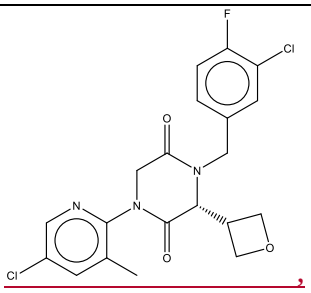
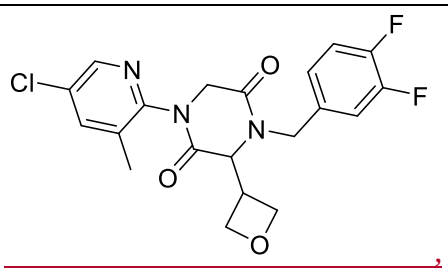
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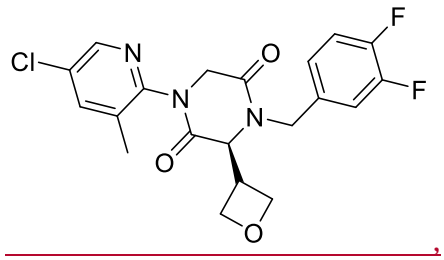
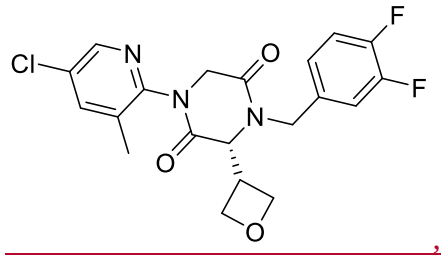
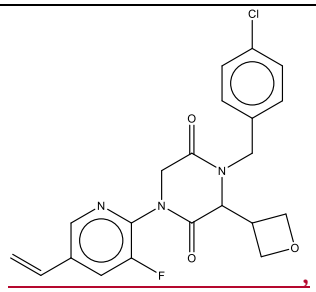
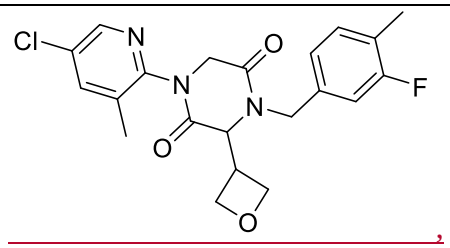
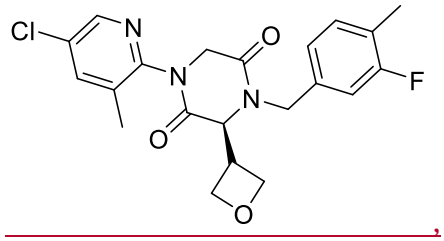
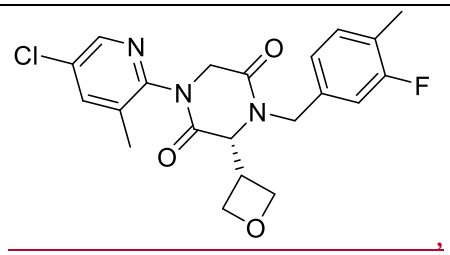
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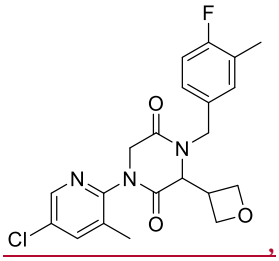
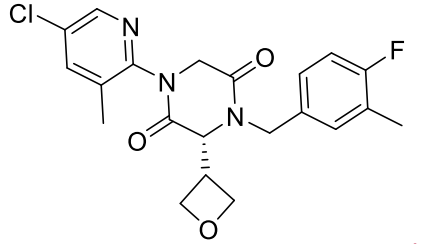
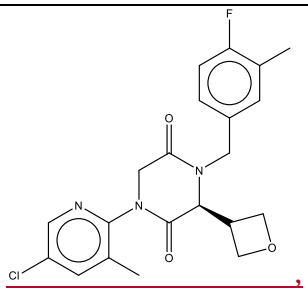
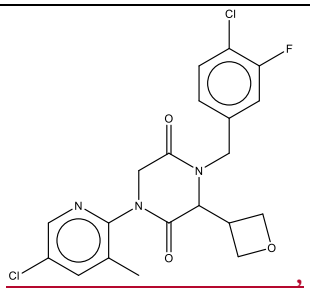
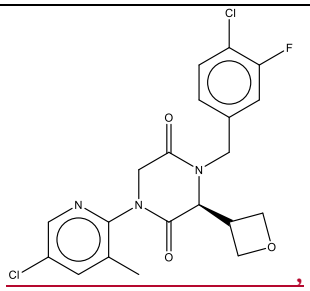
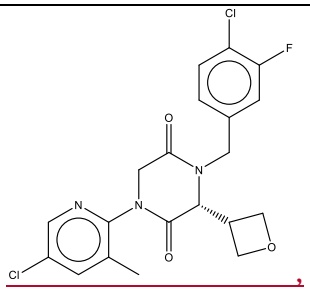
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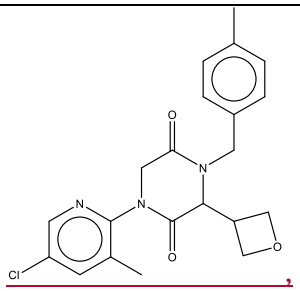
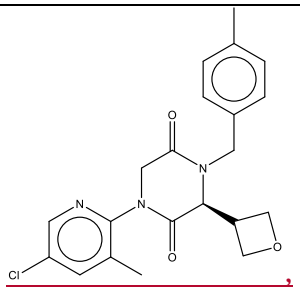
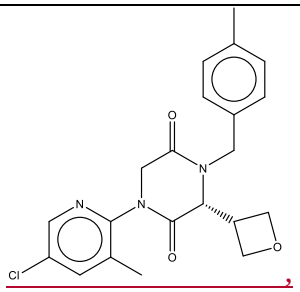
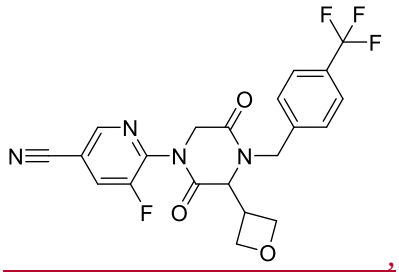
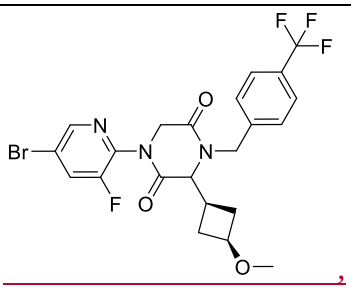
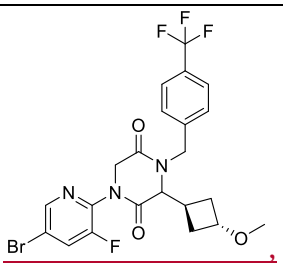
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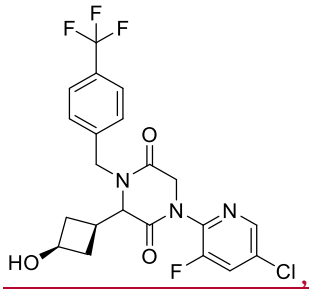
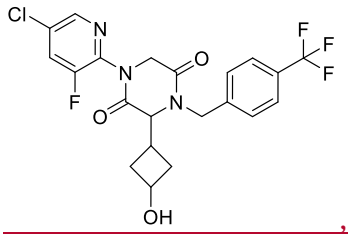
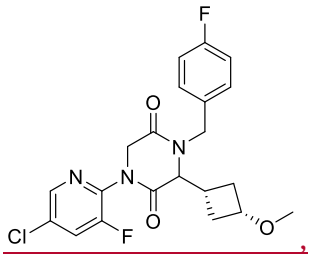
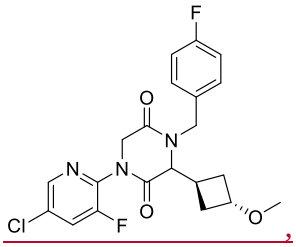
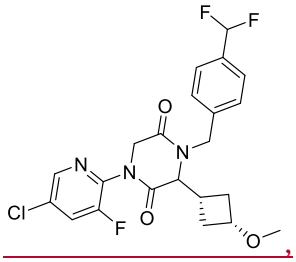
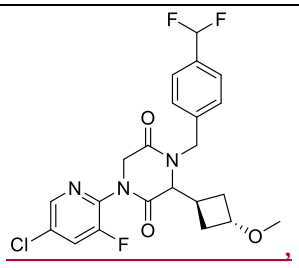
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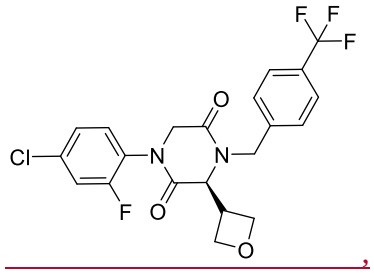
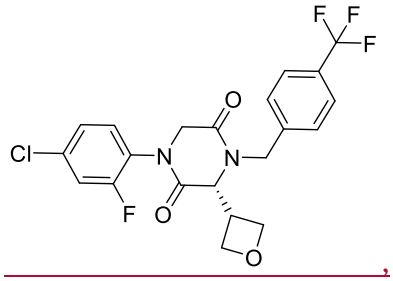
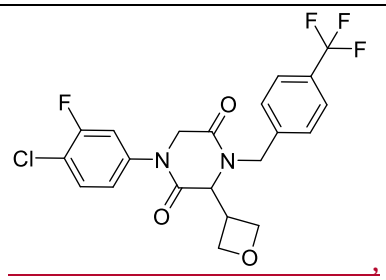
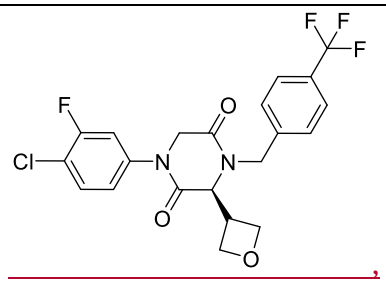
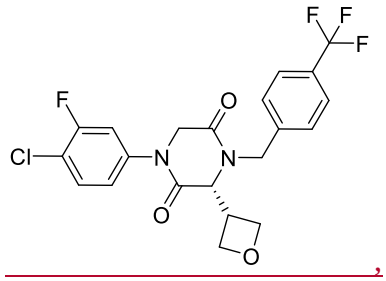
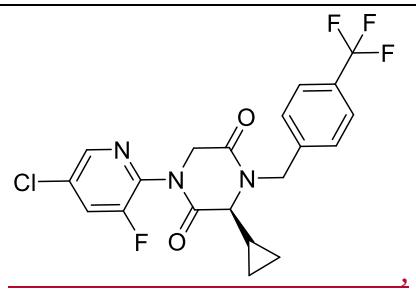
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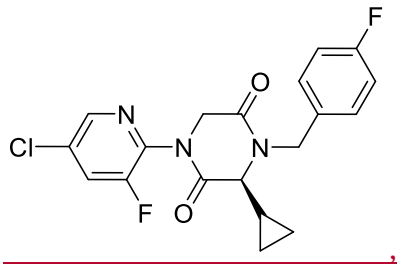
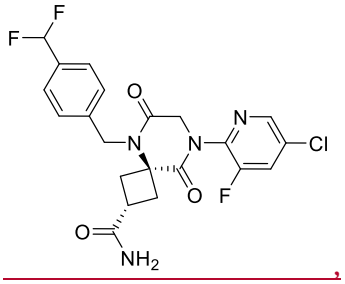
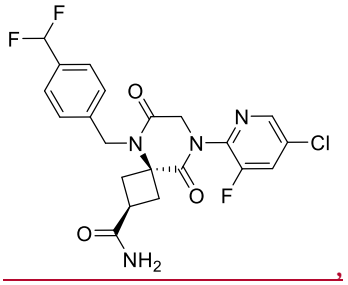
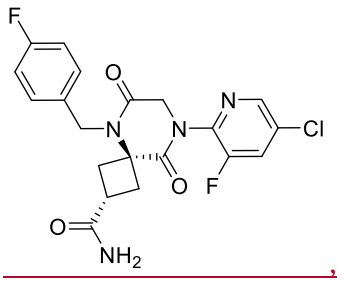
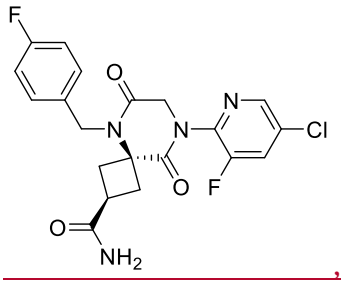
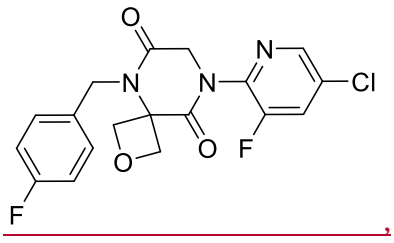
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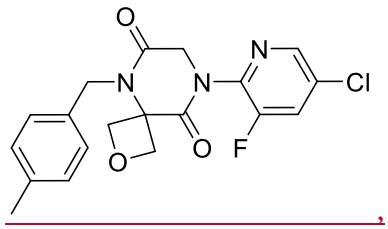
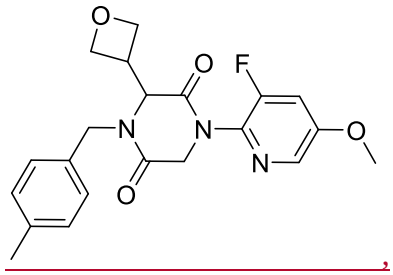
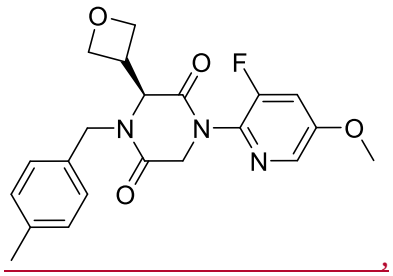
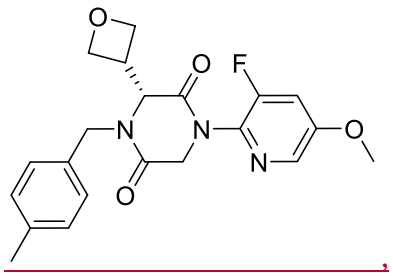
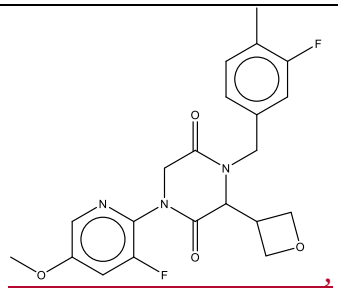
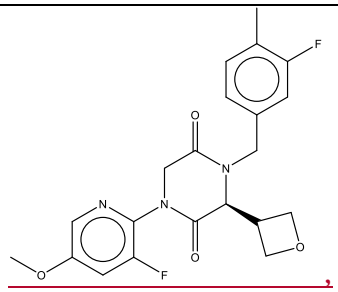
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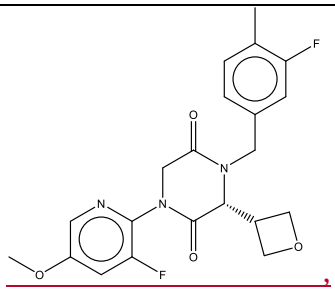
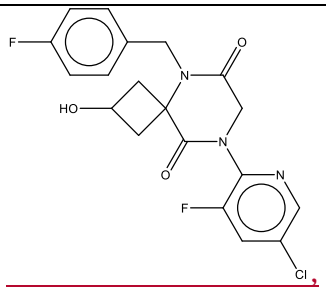
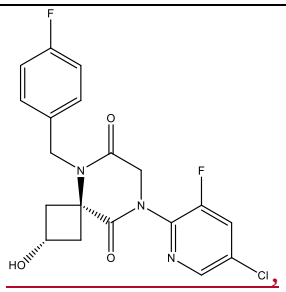
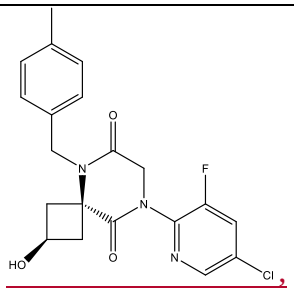
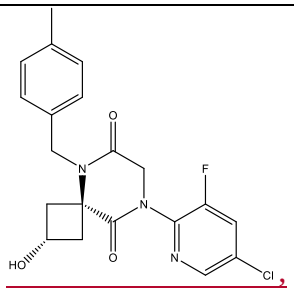
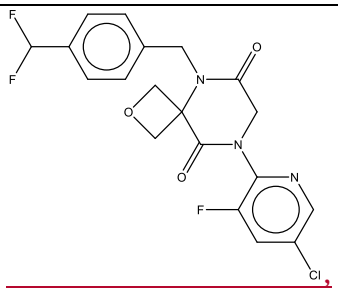
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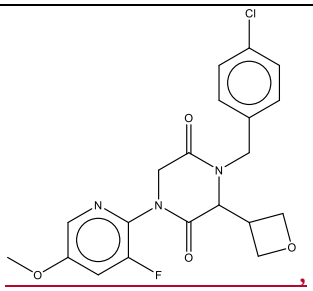
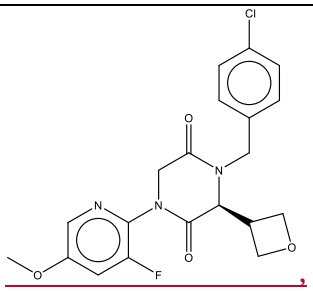
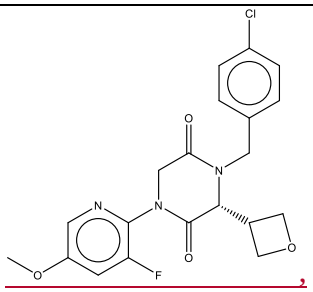
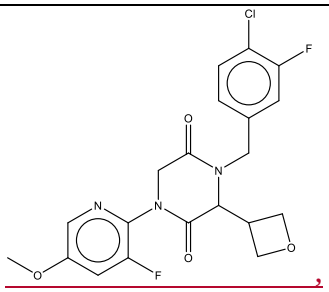
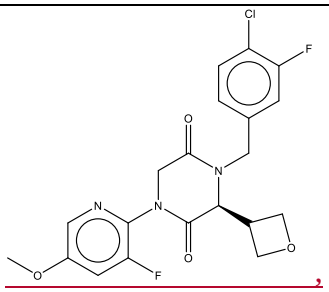
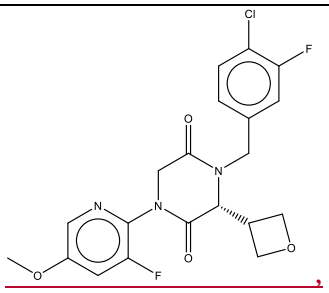
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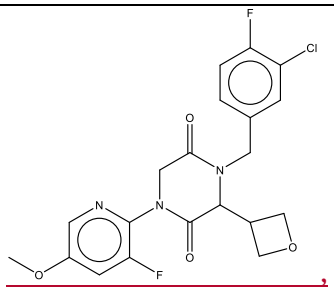
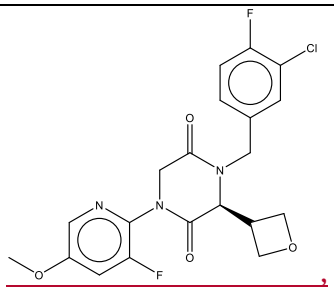
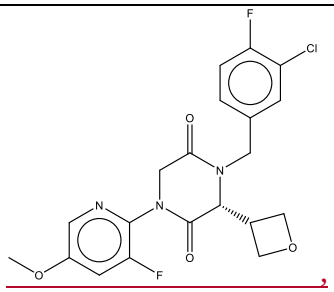
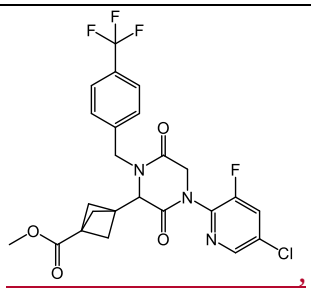
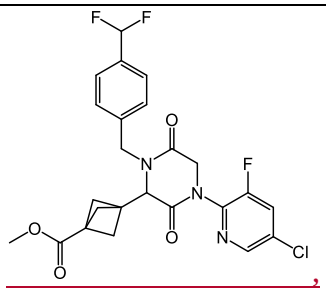
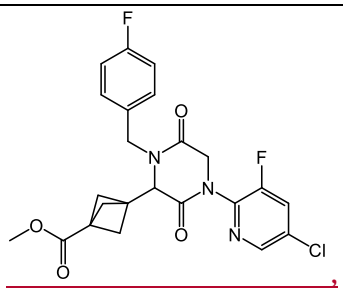
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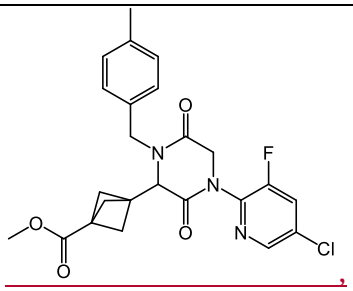
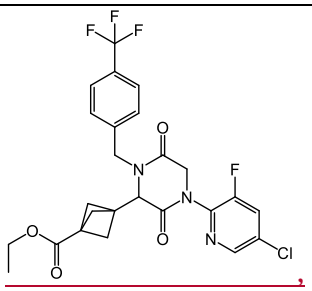
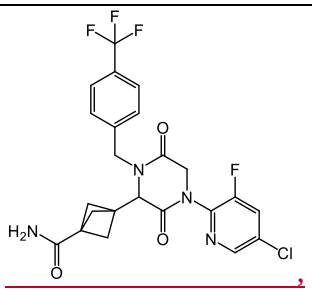
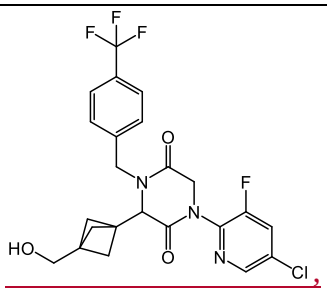
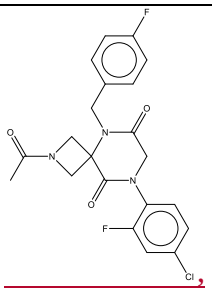
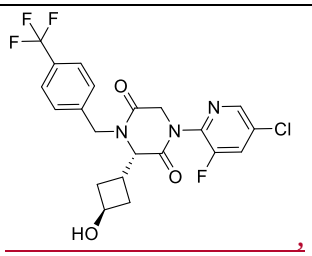
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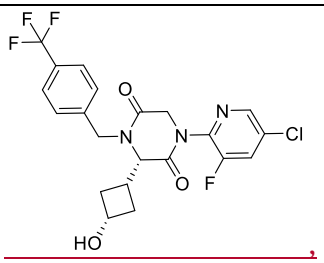
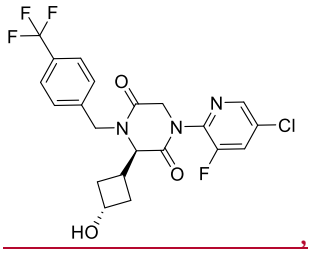
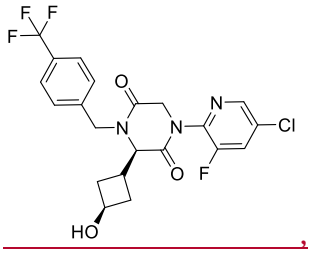
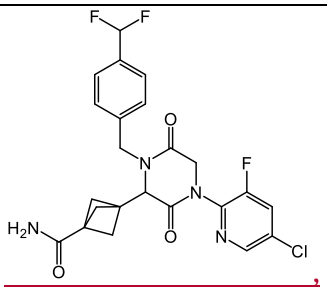
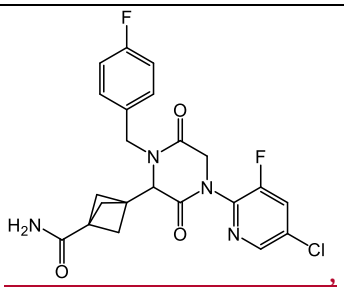
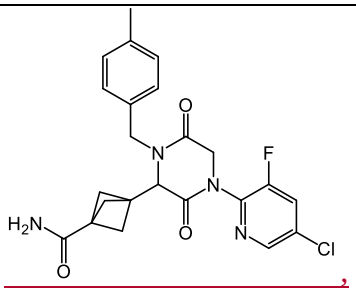
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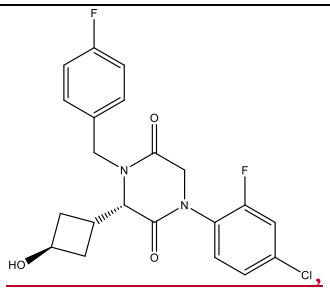
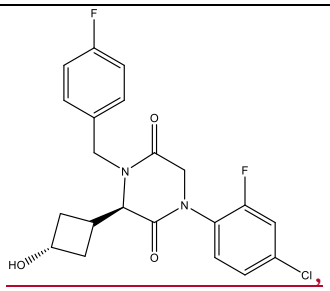
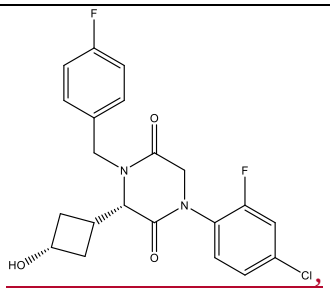
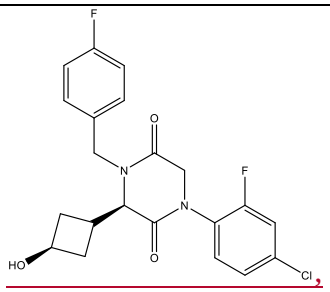
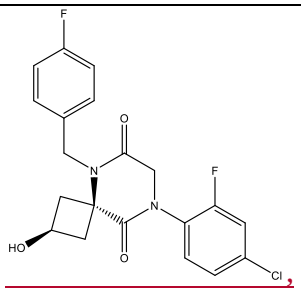
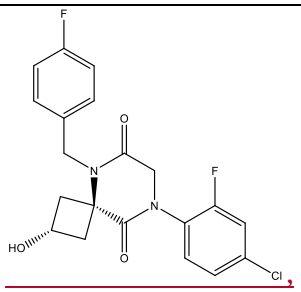
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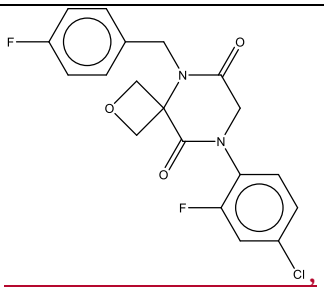
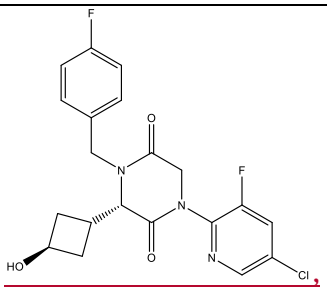
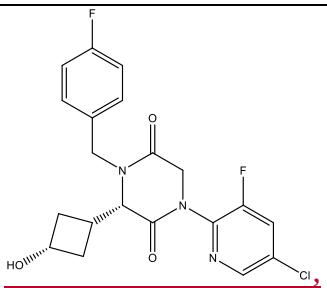
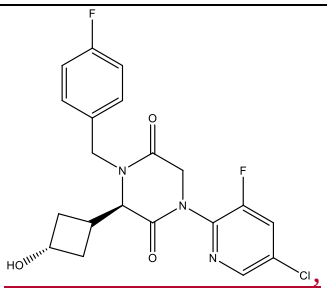
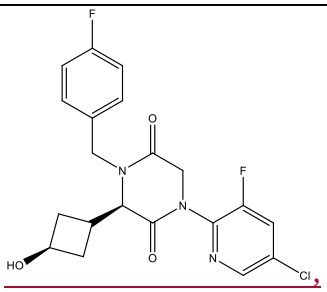
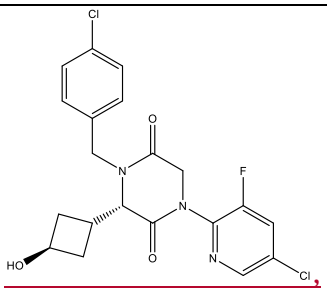
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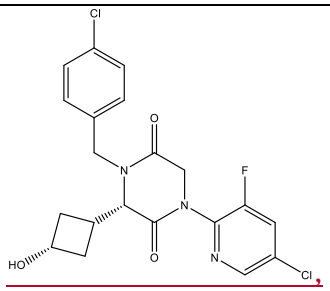
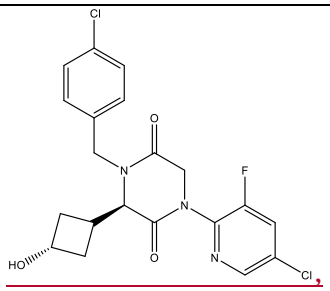
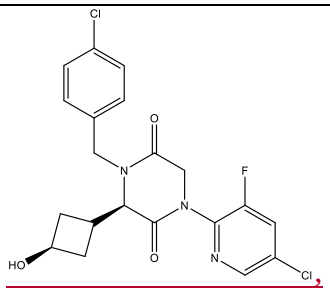
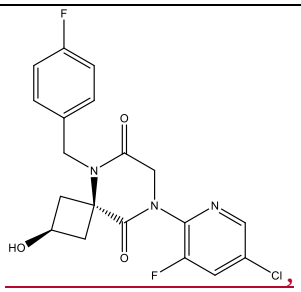
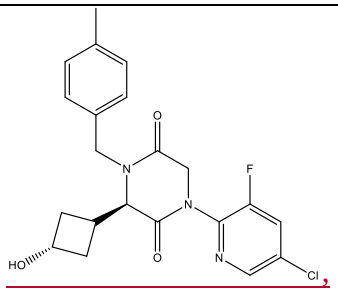
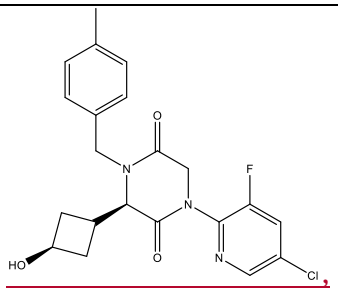
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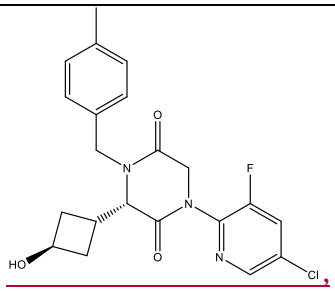
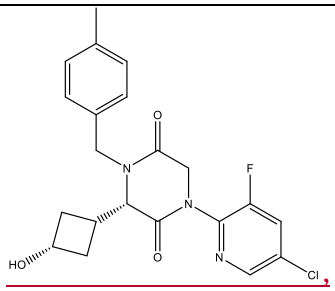
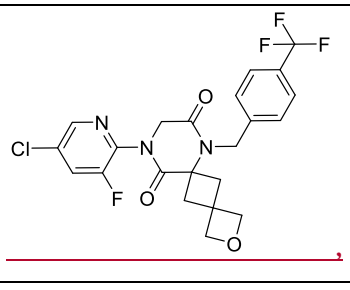
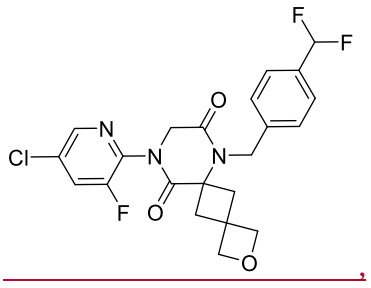
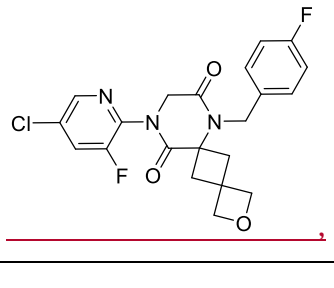
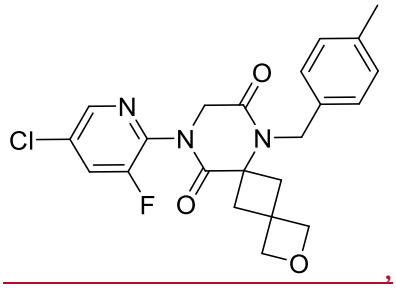
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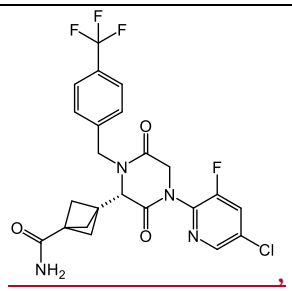
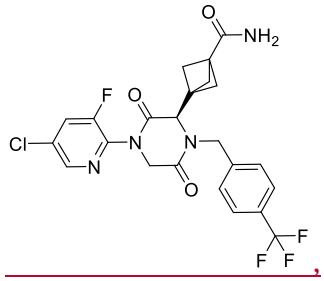
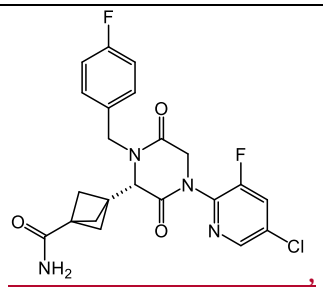
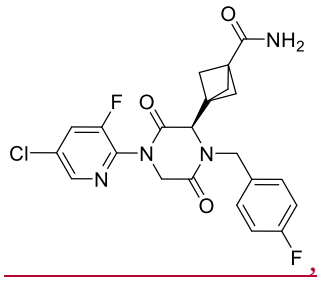
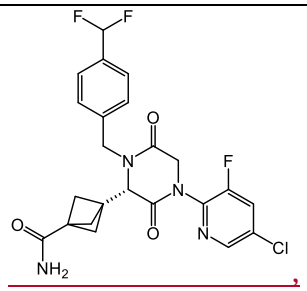
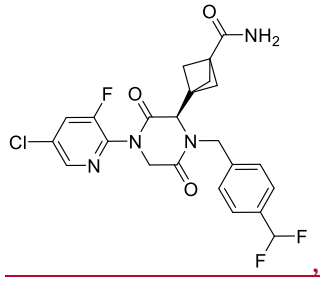
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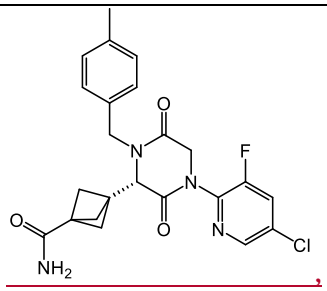
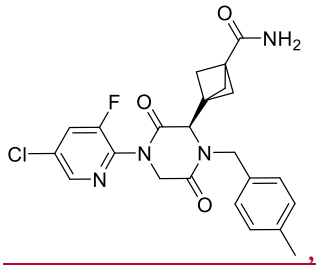
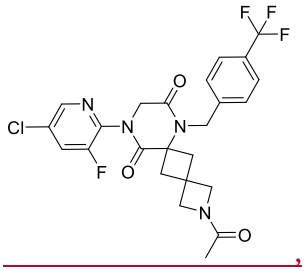
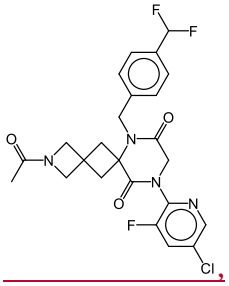
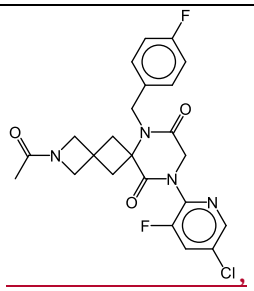
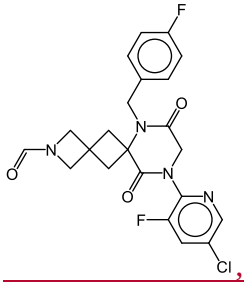
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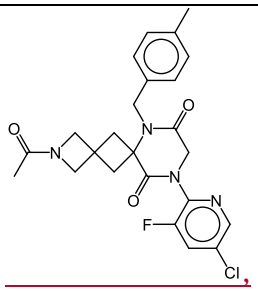
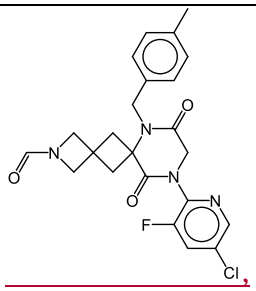
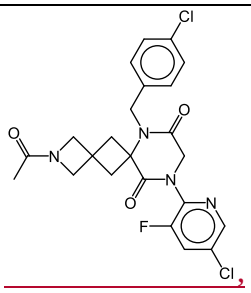
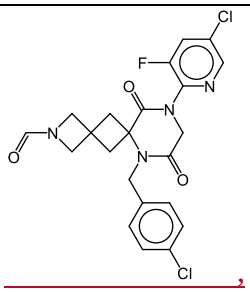
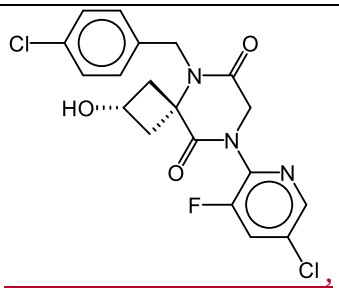
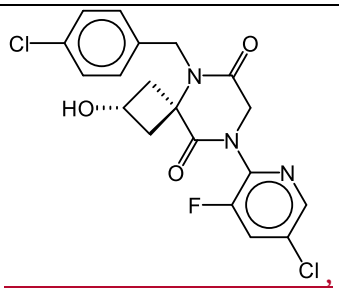
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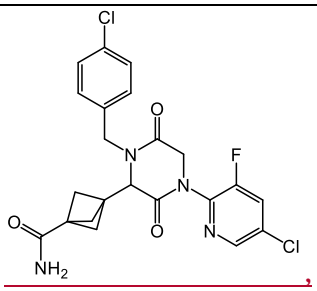
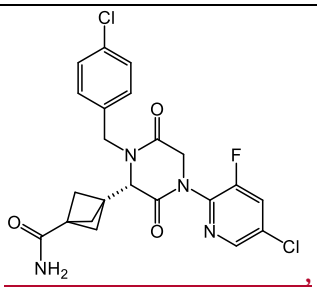
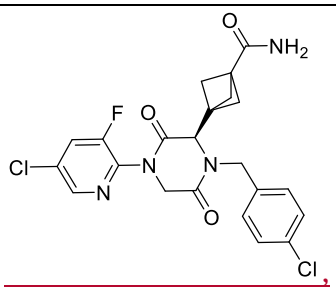
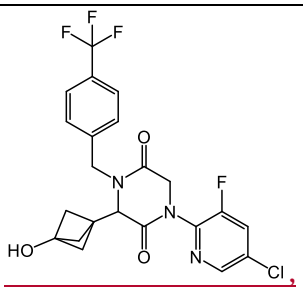
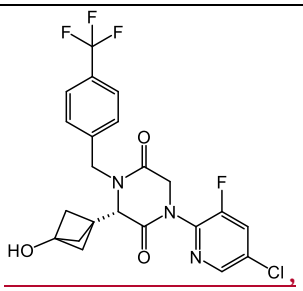
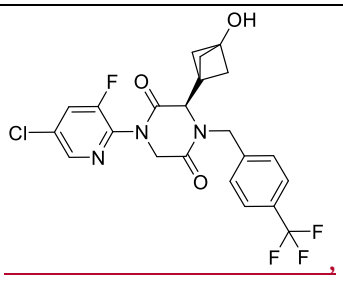
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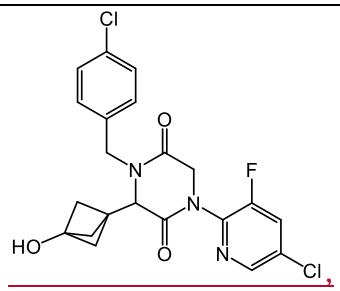
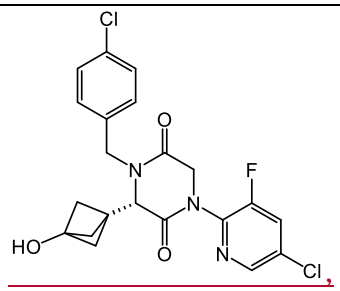
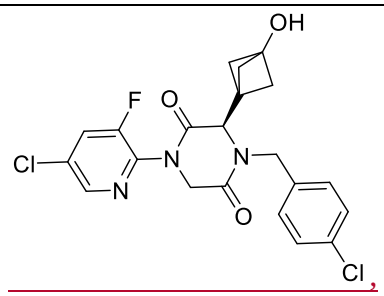
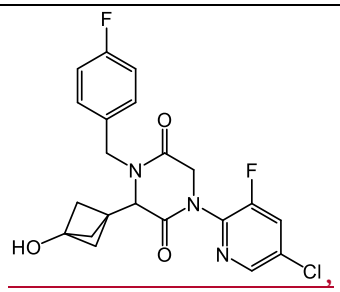
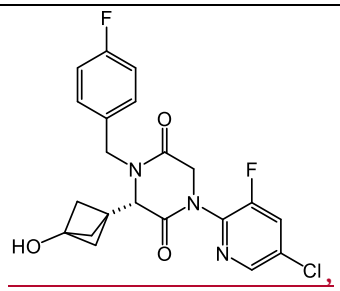
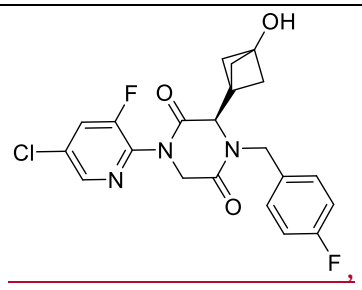
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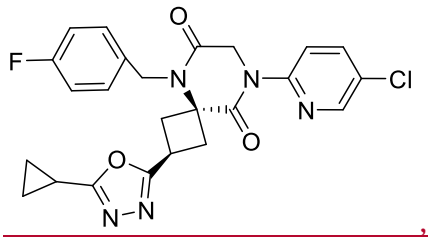
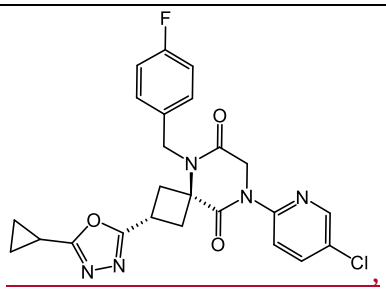
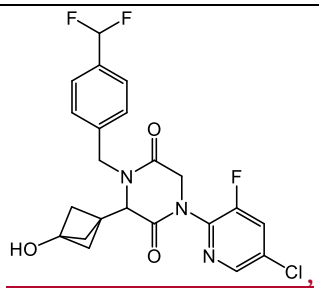
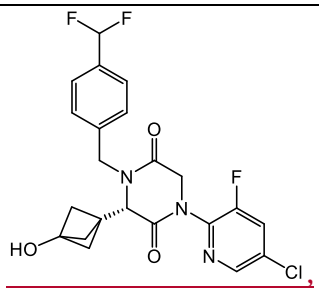
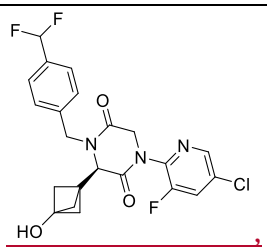
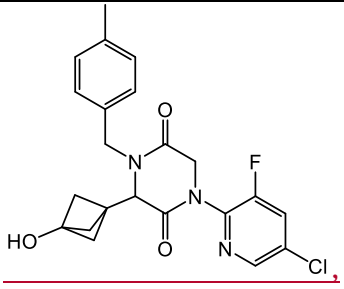
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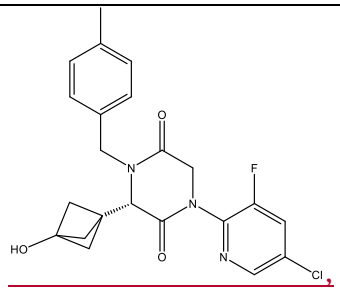
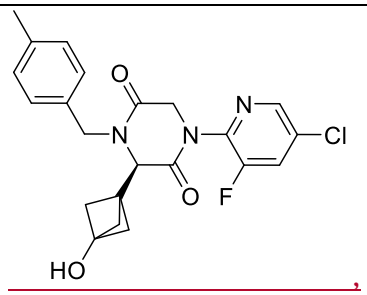
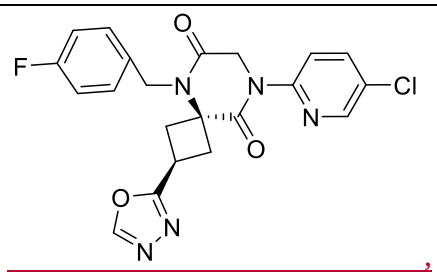
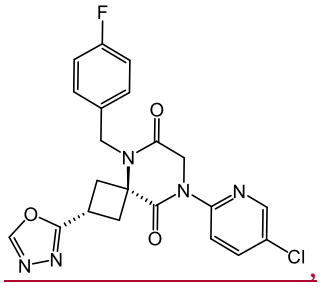
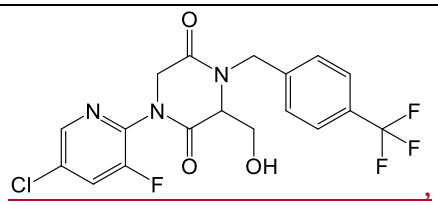
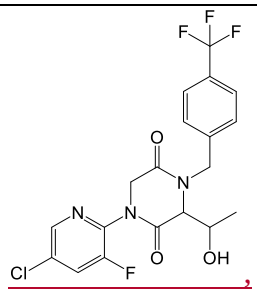
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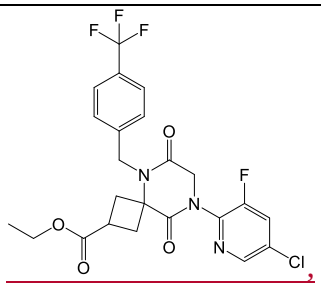
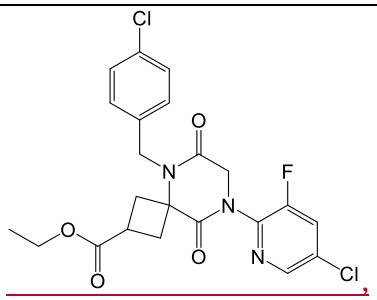
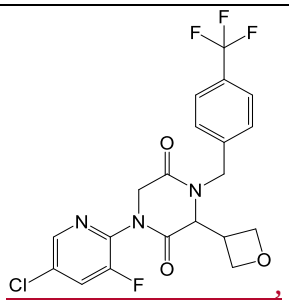
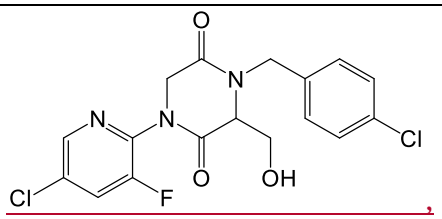
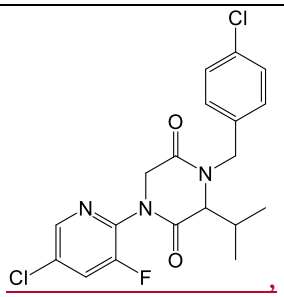
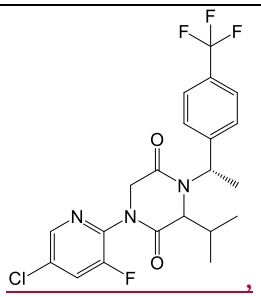
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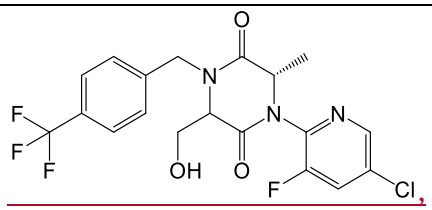
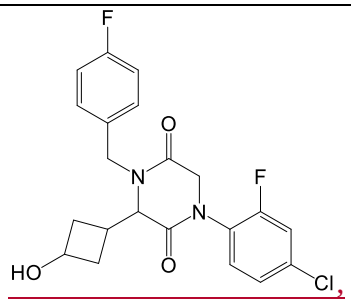
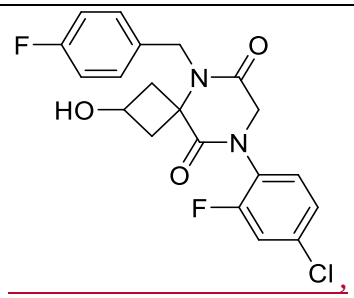
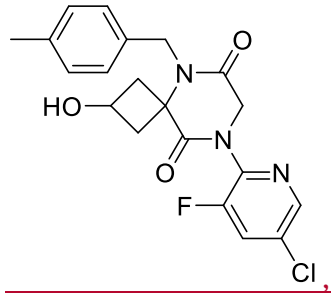
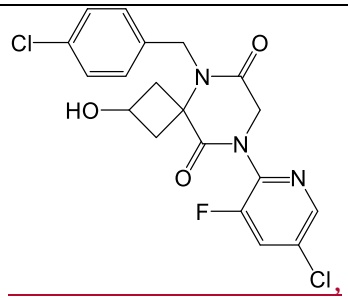
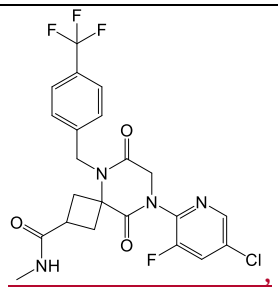
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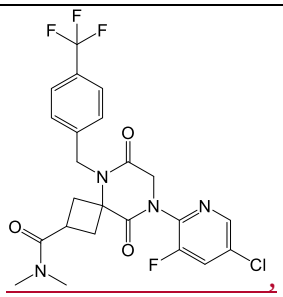
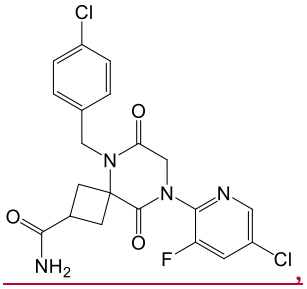
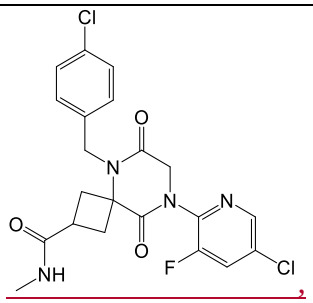
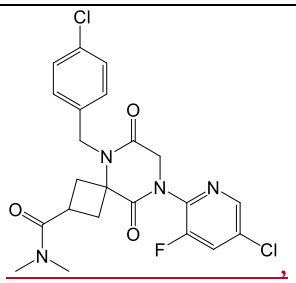
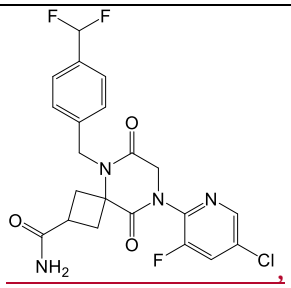
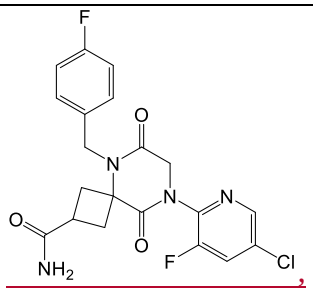
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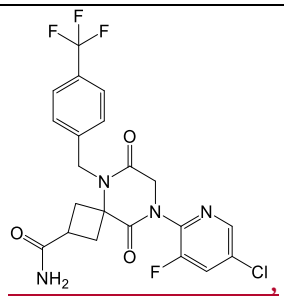
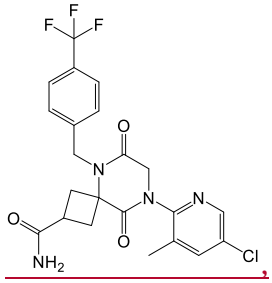
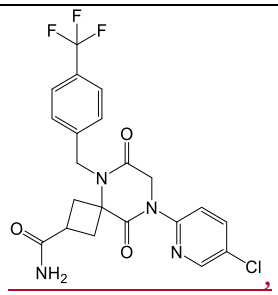
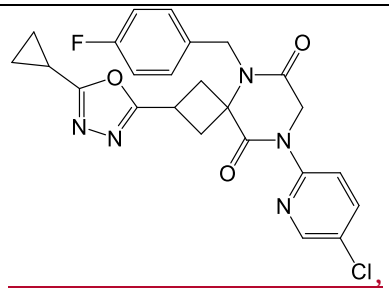
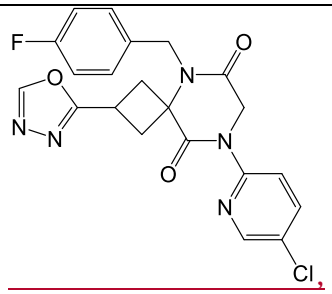
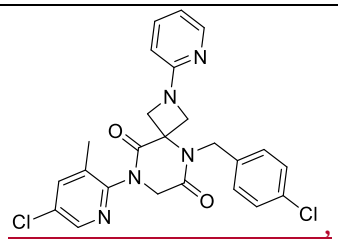
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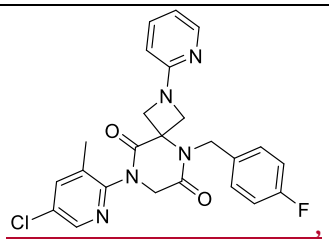
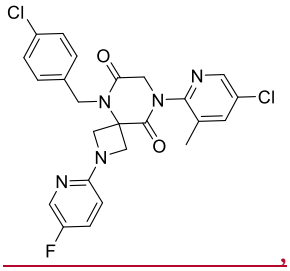
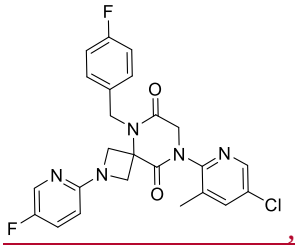
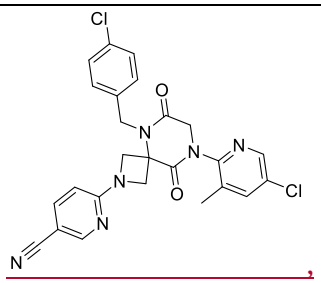
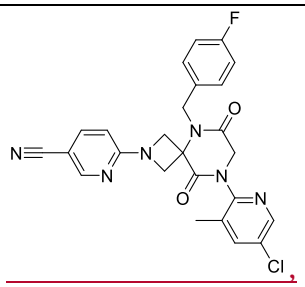
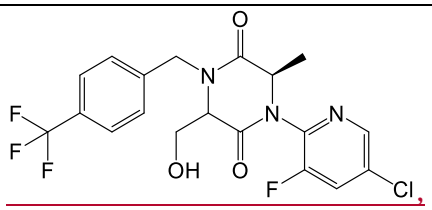
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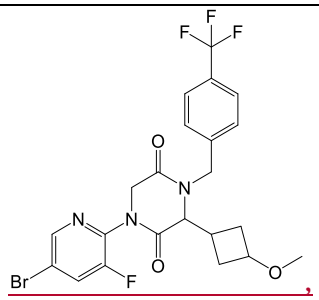
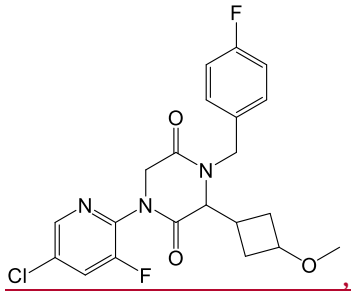
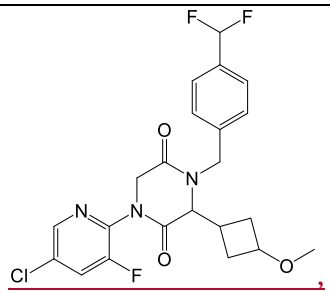
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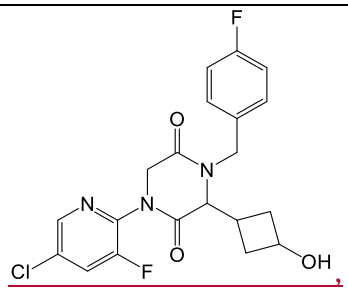
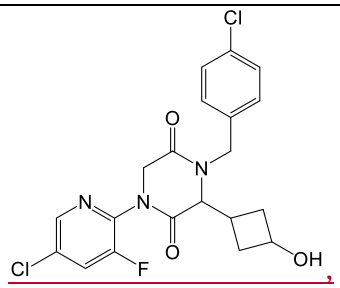
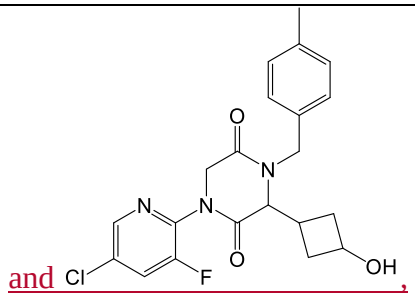
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or a pharmaceutically acceptable salt thereof.

[0007c] 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 excipient.

[0007d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating heart disease.

[0007e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition associated with hypertrophic cardiomyopathy.

[0007f] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a

medicament for treating a disease or condition that is associated with secondary left ventricular wall thickening.

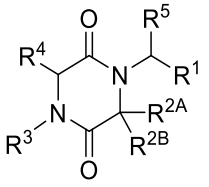
[0007g] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition that is associated with small left ventricular cavity and cavity obliteration, hyperdynamic left ventricular contraction, myocardial ischemia, or cardiac fibrosis.

[0007h] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or condition selected from muscular dystrophies and glycogen storage diseases.

[0007i] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting the cardiac sarcomere.

[0007j] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

[0008] In one ~~aspect~~example, provided is a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from the group consisting of substituted or unsubstituted phenyl and substituted or unsubstituted pyridyl;

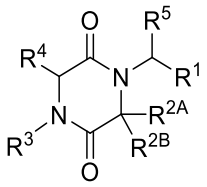
wherein, when one or more of provisions (a) – (c) apply, then R^1 is substituted or unsubstituted pyridyl or phenyl substituted with at least one substituent other than methyl or methoxy:

(a) R^{2A} and R^{2B} are as defined by (i) and R^3 is substituted or unsubstituted phenyl;

(b) R^{2A} and R^3 are as defined by (ii) and R^{2B} is 4-methoxyphenyl;

(c) R^{2A}, and R^{2B} are as defined by (iii) and R^3 is 4-methoxyphenylmethyl.

[0009] In another ~~aspect~~example, provided is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof:



(Ia)

wherein:

R^1 is selected from the group consisting of substituted or unsubstituted phenyl and substituted or unsubstituted pyridyl;

R^{2A} is H or substituted or unsubstituted alkyl;

R^{2B} is selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

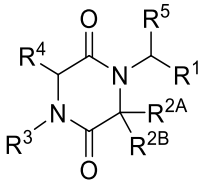
R^3 is substituted or unsubstituted phenyl or substituted or unsubstituted pyridyl;

R^4 is H or substituted or unsubstituted alkyl; and

R^5 is H or substituted or unsubstituted alkyl;

wherein, when R^3 is substituted or unsubstituted phenyl, R^1 is substituted or unsubstituted pyridyl or phenyl substituted with at least one substituent other than methyl or methoxy.

[0010] In another ~~aspect~~example, provided is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof:



(Ib)

wherein:

R^1 is selected from the group consisting of substituted or unsubstituted phenyl and substituted or unsubstituted pyridyl;

R^{2A} is H or substituted or unsubstituted alkyl;

R^{2B} is substituted or unsubstituted phenyl or substituted or unsubstituted pyridyl;

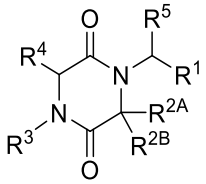
R^3 is substituted or unsubstituted alkyl;

R^4 is H or substituted or unsubstituted alkyl; and

R^5 is H or substituted or unsubstituted alkyl;

wherein, when R^{2B} is 4-methoxyphenyl, R^1 is substituted or unsubstituted pyridyl or phenyl substituted with at least one substituent other than methyl or methoxy.

[0011] In another ~~aspect~~example, provided is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof:



(Ic)

wherein:

R^1 is selected from the group consisting of substituted or unsubstituted pyridyl and substituted or unsubstituted pyridyl;

R^{2A} and R^{2B} are taken together with the carbon atom to which they are attached to form G^1, wherein G^1 is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, or substituted or unsubstituted heterocyclyl ring, each of which is optionally fused to a phenyl ring;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or

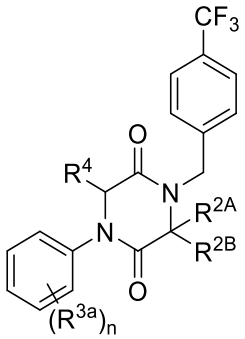
unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^4 is H or substituted or unsubstituted alkyl; and

R^5 is H or substituted or unsubstituted alkyl;

wherein, when R^3 is 4-methoxyphenylmethyl, R^1 is substituted or unsubstituted pyridyl or phenyl substituted with at least one substituent other than methyl or methoxy.

[0012] In another ~~aspect~~example, provided is a compound of Formula (Id), or a pharmaceutically acceptable salt thereof:



(Id)

wherein:

R^{2A} is H or substituted or unsubstituted alkyl;

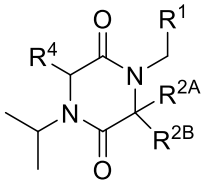
R^{2B} is selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

n is 0, 1, or 2;

R^{3a} is selected from the group consisting of halo and cyano; and

R^4 is H.

[0013] In another ~~aspect~~example, provided is a compound of Formula (Ie), or a pharmaceutically acceptable salt thereof:



(Ie)

wherein:

R^1 is selected from the group consisting of substituted or unsubstituted phenyl and substituted or unsubstituted pyridyl;

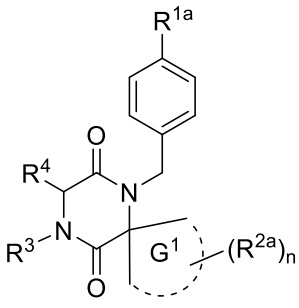
R^{2A} is H or substituted or unsubstituted alkyl;

R^{2B} is substituted or unsubstituted phenyl or substituted or unsubstituted pyridyl; and

R^4 is H;

wherein, when R^{2B} is 4-methoxyphenyl, R^1 is substituted or unsubstituted pyridyl or phenyl substituted with at least one substituent other than methyl or methoxy.

[0014] In another ~~aspect~~example, provided is a compound of Formula (If), or a pharmaceutically acceptable salt thereof:



(If)

wherein:

G^1 is selected from the group consisting of substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, and substituted or unsubstituted heterocyclyl ring, each of which is optionally fused to a phenyl ring;

R^{1a} is selected from the group consisting of cyano, halo, substituted or unsubstituted alkoxy, substituted or unsubstituted alkyl, and substituted or unsubstituted heterocyclyl;

R^{2a} is selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted aminoacyl, substituted or unsubstituted acyl, substituted or

unsubstituted aminosulfonyl, substituted or unsubstituted aminocarbonylamino, and substituted or unsubstituted alkyl;

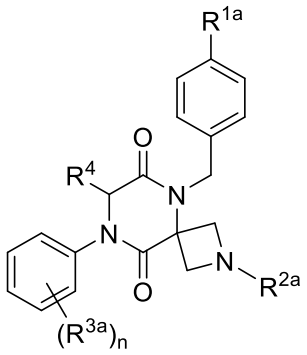
n is 0, 1, 2, or 3;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted aryl; and

R^4 is H;

wherein, when R^3 is 4-methoxyphenylmethyl, R^{1a} is not methyl or methoxy.

[0015] In another ~~aspect~~example, provided is a compound of Formula (Ig), or a pharmaceutically acceptable salt thereof:



(Ig)

wherein:

R^{1a} is selected from the group consisting of cyano, halo, substituted or unsubstituted alkoxy, substituted or unsubstituted alkyl, and substituted or unsubstituted heterocyclyl;

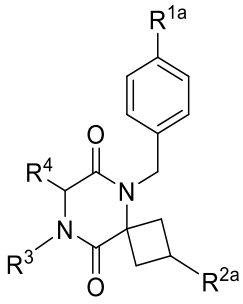
R^{2a} is selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted aminoacyl, substituted or unsubstituted acyl, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted aminocarbonylamino, and substituted or unsubstituted alkyl;

n is 0, 1, 2, or 3;

R^{3a} is selected from the group consisting of halo and cyano; and

R^4 is H.

[0016] In another ~~aspect~~example, provided is a compound of Formula (Ih), or a pharmaceutically acceptable salt thereof:



(Ih)

wherein:

R^{1a} is selected from the group consisting of cyano, halo, substituted or unsubstituted alkoxy, substituted or unsubstituted alkyl, and substituted or unsubstituted heterocyclyl;

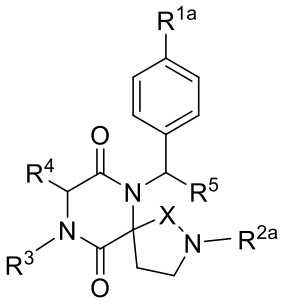
R^{2a} is selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted aminoacyl, substituted or unsubstituted acyl, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted aminocarbonylamino, and substituted or unsubstituted alkyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted aryl; and

R^4 is H;

wherein, when R^3 is 4-methoxyphenylmethyl, R^{1a} is not methyl or methoxy.

[0017] In another ~~aspect~~example, provided is a compound of Formula (Ii), or a pharmaceutically acceptable salt thereof:



(Ii)

[0018] wherein:

R^{1a} is selected from the group consisting of cyano, halo, substituted or unsubstituted alkoxy, substituted or unsubstituted alkyl, and substituted or unsubstituted heterocyclyl;

R^{2a} is selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted aminoacyl, substituted or unsubstituted acyl, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted aminocarbonylamino, and substituted or unsubstituted alkyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted aryl;

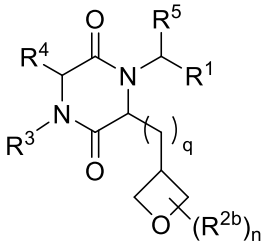
R^4 is H;

R^5 is H or substituted or unsubstituted alkyl; and

X is $-CH_2-$ or -C(O)-;

wherein, when R^3 is 4-methoxyphenylmethyl, R^{1a} is not methyl or methoxy.

[0019] In another ~~aspect~~example, provided is a compound of Formula (Ij), or a pharmaceutically acceptable salt thereof:



(Ij)

wherein:

R^1 is substituted or unsubstituted phenyl;

each R^{2b} is independently substituted or unsubstituted alkyl;

R^3 is substituted or unsubstituted phenyl or substituted or unsubstituted pyridyl;

R^4 is H;

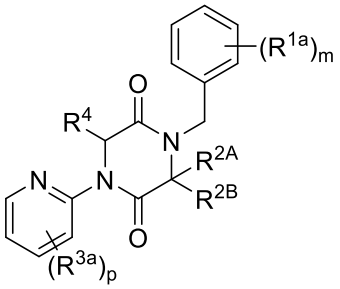
R^5 is H or substituted or unsubstituted alkyl;

n is 0, 1, or 2; and

q is 0 or 1,

wherein, when R^3 is substituted or unsubstituted phenyl, then R^1 is phenyl substituted with at least one substituent other than methyl or methoxy.

[0020] In another ~~aspect~~example, provided is a compound of Formula (Ik-1), or a pharmaceutically acceptable salt thereof:



(Ik-1)

wherein:

R^{2A} is H or substituted or unsubstituted alkyl;

R^{2B} is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, and substituted or unsubstituted heterocyclyl;

m is 0, 1, or 2;

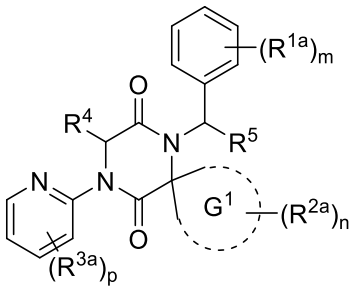
p is 0, 1, or 2;

each R^{1a} is independently selected from the group consisting of halo and substituted or unsubstituted alkyl;

each R^{3a} is independently selected from the group consisting of halo, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkoxy; and

R^4 is H.

[0021] In another ~~aspect~~example, provided is a compound of Formula (Ik-2), or a pharmaceutically acceptable salt thereof:



(Ik-2)

wherein:

G^1 is selected from the group consisting of substituted or unsubstituted cycloalkyl and substituted or unsubstituted heterocyclyl;

each R^{1a} is independently selected from the group consisting of halo and substituted or unsubstituted alkyl;

each R^{2a} is independently selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted aminoacyl, substituted or unsubstituted acyl, substituted or unsubstituted aminothionyl, substituted or unsubstituted aminocarbonylamino, and substituted or unsubstituted alkyl;

each R^{3a} is independently selected from the group consisting of halo, cyano, and substituted or unsubstituted alkyl,

R^4 is H;

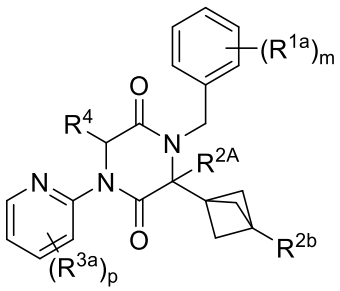
R^5 is H or substituted or unsubstituted alkyl;

m is 0, 1, or 2;

n is 0, 1, or 2; and

p is 0, 1, or 2.

[0022] In another ~~aspect~~example, provided is a compound of Formula (Il), or a pharmaceutically acceptable salt thereof:



(Il)

wherein:

R^{2A} is H or substituted or unsubstituted alkyl;

R^{2b} is selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted aminoacyl, and hydroxy;

m is 0, 1, or 2;

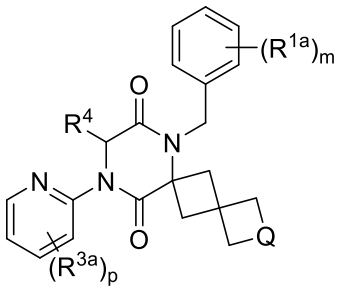
p is 0, 1, or 2;

each R^{1a} is independently selected from the group consisting of halo and substituted or unsubstituted alkyl;

each R^{3a} is independently halo; and

R^4 is H.

[0023] In another ~~aspect~~example, provided is a compound of Formula (Im), or a pharmaceutically acceptable salt thereof:



(Im)

wherein:

Q is -O- or -N(R^{2b})-;

R^{2b} is selected from the group consisting of H and substituted or unsubstituted acyl;

m is 0, 1, or 2;

p is 0, 1, or 2;

each R^{1a} is independently selected from the group consisting of halo and substituted or unsubstituted alkyl;

each R^{3a} is independently halo; and

R^4 is H.

[0024] In another ~~aspect~~example, provided is a compound of Formula (In-1), or a pharmaceutically acceptable salt thereof:

or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^4 is H or substituted or unsubstituted alkyl; and

R^5 is H or substituted or unsubstituted alkyl;

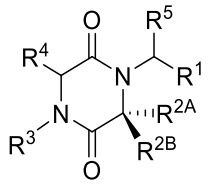
wherein, when one or more of provisions (a) – (c) apply, then R^1 is substituted or unsubstituted pyridyl or phenyl substituted with at least one substituent other than methyl or methoxy:

(a) R^{2A} and R^{2B} are as defined by (i) and R^3 is substituted or unsubstituted phenyl;

(b) R^{2A} and R^3 are as defined by (ii) and R^{2B} is 4-methoxyphenyl;

(c) R^{2A}, and R^{2B} are as defined by (iii) and R^3 is 4-methoxyphenylmethyl.

[0025] In another ~~aspect~~example, provided is a compound of Formula (In-2), or a pharmaceutically acceptable salt thereof:



(In-2)

wherein:

R^1 is selected from the group consisting of substituted or unsubstituted phenyl and substituted or unsubstituted pyridyl;

R^{2A}, R^{2B}, and R^3 are defined by any one of (i) – (iii):

(i) R^{2A} is H or substituted or unsubstituted alkyl;

R^{2B} is selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl; and

R^3 is substituted or unsubstituted phenyl or substituted or unsubstituted pyridyl;

or

(ii) R^{2A} is H or substituted or unsubstituted alkyl;

R^{2B} is substituted or unsubstituted phenyl or substituted or unsubstituted pyridyl; and

R^3 is substituted or unsubstituted alkyl;

or

(iii) R^{2A} and R^{2B} are taken together with the carbon atom to which they are attached to form G^1, wherein G^1 is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, or substituted or unsubstituted heterocyclyl ring, each of which is optionally fused to a phenyl ring; and

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^4 is H or substituted or unsubstituted alkyl; and

R^5 is H or substituted or unsubstituted alkyl;

wherein, when one or more of provisions (a) – (c) apply, then R^1 is substituted or unsubstituted pyridyl or phenyl substituted with at least one substituent other than methyl or methoxy:

(a) R^{2A} and R^{2B} are as defined by (i) and R^3 is substituted or unsubstituted phenyl;

(b) R^{2A} and R^3 are as defined by (ii) and R^{2B} is 4-methoxyphenyl;

(c) R^{2A}, and R^{2B}-are as defined by (iii) and R^3 is 4-methoxyphenylmethyl.

[0026] Provided in some ~~embodiment~~examples are compounds selected from the group consisting of compounds of Table 1, or a pharmaceutically acceptable salt thereof.

[0027] Provided in some ~~aspect~~examples is a pharmaceutical composition containing a compound of Formula (I) or any variation thereof, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0028] Provided in some ~~aspect~~examples are methods of treating heart disease in a subject in need thereof, the method comprising administering to the subject a compound of Formula (I) or any variation thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing a compound of Formula (I) or any variation thereof or a pharmaceutically acceptable salt thereof. In some ~~embodiment~~examples, the heart disease is hypertrophic cardiomyopathy (HCM). In some ~~embodiment~~examples, the HCM is obstructive or nonobstructive or is caused by sarcomeric and/or non-sarcomeric mutations. In some ~~embodiment~~examples, the heart disease is heart failure with preserved ejection fraction (HFpEF). In some ~~embodiment~~examples, the heart disease is selected from the group consisting of diastolic dysfunction, primary or secondary restrictive cardiomyopathy, myocardial infarction, angina pectoris, and left ventricular outflow tract obstruction. In some ~~embodiment~~examples, the heart disease is hypertensive heart disease, congenital heart disease, cardiac ischemia, coronary heart disease, diabetic heart disease, congestive heart failure, right heart failure, cardiorenal syndrome, or infiltrative cardiomyopathy. In some ~~embodiment~~examples, the heart disease is a condition that is or is related to cardiac senescence and/or diastolic dysfunction due to aging. In some ~~embodiment~~examples, the heart disease is a condition that is or is related to left ventricular hypertrophy and/or concentric left ventricular remodeling.

[0029] Provided in other ~~aspect~~examples are methods of treating a disease or condition associated with HCM in a subject in need thereof, wherein the method comprises administering to the subject a compound of Formula (I) or any variation thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing a compound of Formula (I) or any variation thereof or a pharmaceutically acceptable salt thereof. In some ~~embodiment~~examples, the disease or condition is selected from the group consisting of Fabry's Disease, Danon Disease, mitochondrial cardiomyopathies, and Noonan Syndrome.

[0030] Provided in some ~~aspect~~examples are methods of treating a disease or condition that is associated with secondary left ventricular wall thickening in a subject in need thereof, wherein the method comprises administering to the subject a compound of Formula (I) or any variation thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing a compound of Formula (I) or any variation thereof or a

pharmaceutically acceptable salt thereof. In some ~~embodiment~~examples, the disease or condition is selected from the group consisting of hypertension, valvular heart diseases (such as aortic stenosis and Mitral valve regurgitation), metabolic syndromes (such as diabetes and obesity), end stage renal disease, scleroderma, sleep apnea, amyloidosis, Fabry's disease, Friedreich Ataxia, Danon disease, Noonan syndrome, and Pompe disease.

[0031] Provided in other ~~aspect~~examples are methods of treating a disease or condition that is associated with small left ventricular cavity and cavity obliteration, hyperdynamic left ventricular contraction, myocardial ischemia, or cardiac fibrosis. Also provided are methods of treating muscular dystrophies (e.g., Duchenne muscular dystrophy) or glycogen storage diseases.

[0032] Also provided are methods of inhibiting the cardiac sarcomere, wherein the method involves contacting the cardiac sarcomere with a compound of Formula (I) or any variation thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing a compound of Formula (I) or any variation thereof or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION

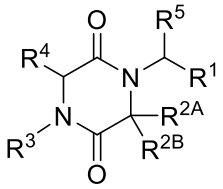
Definitions

[0033] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0034] Throughout this application, unless the context indicates otherwise, references to a compound of Formula (I) includes all subgroups of Formula (I) defined herein, such as Formula (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik-1), (Ik-2), (Il), (Im), (In-1), and (In-2), including all substructures, subgenera, preferences, embodiments, examples and particular compounds defined and/or described herein. References to a compound of Formula (I) and subgroups thereof, such as Formula (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik-1), (Ik-2), (Il), (Im), (In-1), and (In-2), include ionic forms, polymorphs, pseudopolymorphs, amorphous forms, solvates, co-crystals, chelates, isomers, tautomers, oxides (e.g., N-oxides, S-oxides), esters, prodrugs, isotopes and/or protected forms thereof. In some embodiments, references to a compound of Formula (I) and subgroups thereof, such as Formula (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik-1), (Ik-2), (Il), (Im), (In-1),

CLAIMS

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of substituted or unsubstituted phenyl and substituted or unsubstituted pyridyl;

R^{2A}, R^{2B}, R^3, and R^4~~R^3~~ are defined by any one of (i) – (iii):

(i) R^{2A} is H or substituted or unsubstituted alkyl;

R^{2B} is selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl; ~~and~~

R^3 is ~~substituted or unsubstituted~~ phenyl substituted with two or more substituents, or substituted or unsubstituted pyridyl; and

R^4 is H or substituted or unsubstituted alkyl;

or

(ii) R^{2A} is H or substituted or unsubstituted alkyl;

R^{2B} is substituted or unsubstituted phenyl or substituted or unsubstituted pyridyl; ~~and~~

R^3 is unsubstituted C_2-C_4 alkyl; and

R^4 is H or substituted or unsubstituted alkyl;

or

(iii) R^{2A} and R^{2B} are taken together with the carbon atom to which they are attached to form G^1, wherein G^1 is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, or substituted or unsubstituted heterocyclyl ring, each of which is optionally fused to a phenyl ring; ~~and~~

R^3 is selected from the group consisting of ~~substituted or~~ unsubstituted C_2-C_6 alkyl, alkyl substituted with alkoxy, cyano, or halo, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl; and

R^4 is H ~~or substituted~~ or unsubstituted alkyl; and

R^5 is H or substituted or unsubstituted alkyl;

wherein, when one or more of provisions (a) – (b~~c~~) apply, then R^1 is substituted or unsubstituted pyridyl or phenyl substituted with at least one substituent other than methyl or methoxy:

(a) R^{2A} and R^{2B} are as defined by (i) and R^3 is phenyl substituted with two or more substituents~~unsubstituted phenyl~~;

(b) R^{2A} and R^3 are as defined by (ii) and R^{2B} is 4-methoxyphenyl~~;~~

~~(c) R^{2A} and R^{2B} are as defined by (iii) and R^3 is 4-methoxyphenylmethyl~~.

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

R^{2A} is H or substituted or unsubstituted alkyl;

R^{2B} is selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl; and

R^3 is ~~substituted or unsubstituted~~ phenyl substituted with two or more substituents, or substituted or unsubstituted pyridyl.

3. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein R^3 is phenyl substituted with two or more substituents~~unsubstituted phenyl~~.

4. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein R^3 is substituted or unsubstituted pyridyl.

5. The compound of claim~~any one of claims~~ 2~~-4~~, or a pharmaceutically acceptable salt thereof, wherein R^3 is phenyl substituted with two~~one~~ or more halo substituents selected from the group consisting of F and Cl.

6. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein R^3 is further substituted with one, two, or three –CN substituents.

7. The compound of claim~~any one of claims~~ 2~~-6~~, or a pharmaceutically acceptable salt thereof, wherein R^{2A} is substituted or unsubstituted alkyl.

8. The compound of claim~~any one of claims~~ 2~~-6~~, or a pharmaceutically acceptable salt thereof, wherein R^{2A} is H.

9. The compound of claim~~any one of claims~~ 2~~-8~~, or a pharmaceutically acceptable salt thereof, wherein R^{2B} is substituted or unsubstituted alkyl.

10. The compound of claim~~any one of claims~~ 2~~-9~~, or a pharmaceutically acceptable salt thereof, wherein R^{2B} is selected from the group consisting of methyl, hydroxymethyl, and isopropyl.

11. The compound of claim~~any one of claims~~ 2~~-9~~, or a pharmaceutically acceptable salt thereof, wherein R^{2B} is alkyl substituted with substituted or unsubstituted alkoxy.

12. The compound of claim~~any one of claims~~ 2~~-9~~, or a pharmaceutically acceptable salt thereof, wherein R^{2B} is alkyl substituted with substituted or unsubstituted oxetanyl.

13. The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein R^{2B} is methyl substituted with unsubstituted 3-oxetanyl.

14. The compound of claim~~any one of claims~~ 2~~-8~~, or a pharmaceutically acceptable salt thereof, wherein R^{2B} is substituted or unsubstituted cycloalkyl.

15. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein R^{2B} is cyclobutanyl.

16. The compound of claim~~any one of claims~~ 2~~-8~~, or a pharmaceutically acceptable salt thereof, wherein R^{2B} is substituted or unsubstituted heterocyclyl.

17. The compound of claim 16, or a pharmaceutically acceptable salt thereof, wherein R^{2B} is oxetanyl.

18. The compound of claim 17, or a pharmaceutically acceptable salt thereof, wherein R^{2B} is 3-oxetanyl.

19. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

R^{2A} is H or substituted or unsubstituted alkyl;

R^{2B} is substituted or unsubstituted phenyl or substituted or unsubstituted pyridyl; and

R^3 is ~~substituted or~~ unsubstituted C_2-C_4 alkyl.

20. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein R^{2A} is unsubstituted alkyl.

21. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein R^{2A} is H.

22. The compound of claim~~any one of claims~~ 19~~-21~~, or a pharmaceutically acceptable salt thereof, wherein R^{2B} is substituted phenyl or substituted pyridyl.

23. The compound of claim~~any one of claims~~ 19~~-22~~, or a pharmaceutically acceptable salt thereof, wherein R^{2B} is phenyl or pyridyl, each of which is substituted with one or more substituents independently selected from the group consisting of halo, alkoxy, and substituted alkyl.

24. The compound of claim~~any one of claims~~ 19~~-23~~, or a pharmaceutically acceptable salt thereof, wherein R^{2B} is phenyl or pyridyl, each of which is substituted with -CF_3.

25. The compound of claim~~any one of claims~~ 19~~-23~~, or a pharmaceutically acceptable salt thereof, wherein the R^{2B} is phenyl or pyridyl, each of which is substituted with methoxy.

~~26. The compound of any one of claims 19-25, or a pharmaceutically acceptable salt thereof, wherein R^3 is unsubstituted alkyl.~~

~~27.~~26. The compound of ~~any one of~~ claim~~s~~ 19~~-26~~, or a pharmaceutically acceptable salt thereof, wherein R^3 is isopropyl.

~~28.~~27. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

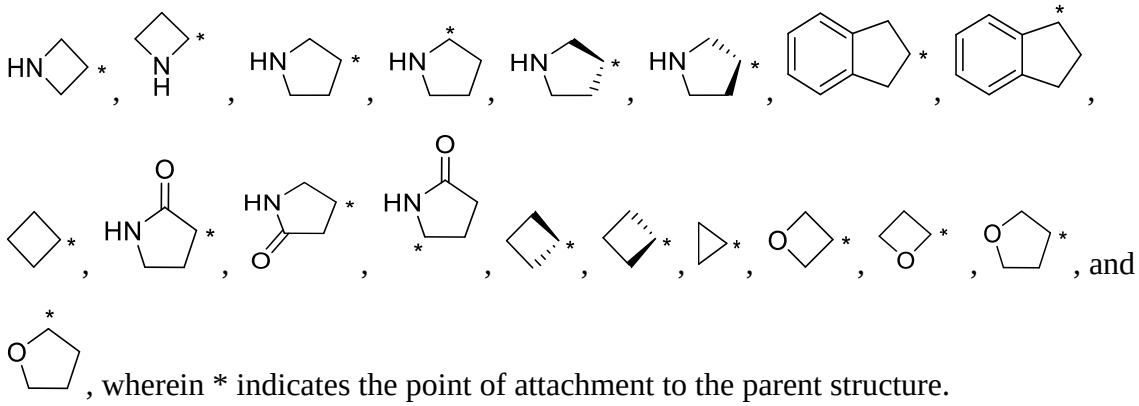
R^{2A} and R^{2B} are taken together with the carbon atom to which they are attached to form G^1, wherein G^1 is a substituted or unsubstituted cycloalkyl, substituted or

unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, or substituted or unsubstituted heterocyclyl ring, each of which is optionally fused to a phenyl ring; and

R^3 is selected from the group consisting of ~~substituted or~~ unsubstituted C_2-C_6 alkyl, alkyl substituted with alkoxy, cyano, or halo, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

~~29.~~28. The compound of claim 27~~28~~ or a pharmaceutically acceptable salt thereof, wherein G^1 is selected from the group consisting of substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted 2,3-dihydro-1H-indene.

~~30.~~29. The compound of claim 27~~28 or claim 29~~, or a pharmaceutically acceptable salt thereof, wherein G^1 is a substituted or unsubstituted cycloalkyl or heterocyclyl selected from the group consisting of:



, and

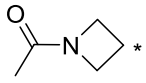
, wherein * indicates the point of attachment to the parent structure.

~~31.~~30. The compound of claim 27~~any one of claims 28-30~~, or a pharmaceutically acceptable salt thereof, wherein G^1 is substituted or unsubstituted 

.

~~32.~~31. The compound of claim 27~~any one of claims 28-31~~, or a pharmaceutically acceptable salt thereof, wherein G^1 is substituted with one, two, or three substituents selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted

aminoacyl, substituted or unsubstituted acyl, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted aminocarbonylamino, and substituted or unsubstituted alkyl.

~~33.~~32. The compound of claim 27~~any one of claims 28-32~~, or a pharmaceutically acceptable salt thereof, wherein G^1 is .

~~34.~~33. The compound of claim 27~~any one of claims 28-33~~, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from the group consisting of ~~substituted or~~ unsubstituted C_2-C_6 alkyl, alkyl substituted with alkoxy, cyano, or halo, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted aryl.

~~35.~~34. The compound of claim 27~~any one of claims 28-34~~, or a pharmaceutically acceptable salt thereof, wherein R^3 is phenyl substituted with one or more substituents selected from the group consisting of nitro, alkoxy, halo, cycloalkyl, cyano, alkenyl, alkoxycarbonyl, phenylcarbonyl, and alkyl.

~~36.~~35. The compound of claim 27~~any one of claims 28-35~~, or a pharmaceutically acceptable salt thereof, wherein R^3 is phenyl substituted with F and CN.

~~37.~~36. The compound of claim 27~~any one of claims 28-34~~, or a pharmaceutically acceptable salt thereof, wherein R^3 is cycloalkyl substituted with one or more substituents selected from the group consisting of alkyl, cyano, and halo.

~~38.~~37. The compound of claim 27~~any one of claims 28-34~~, or a pharmaceutically acceptable salt thereof, wherein R^3 is alkyl substituted with one or more substituents selected from the group consisting of alkoxy, cyano, and halo.

~~39.~~38. The compound of claim~~any one of claims~~ 1~~-38~~ or a pharmaceutically acceptable salt thereof, wherein R^4 is H.

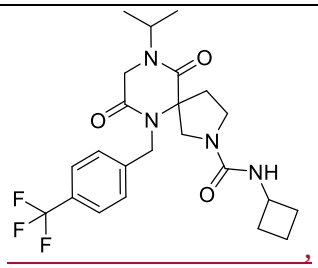
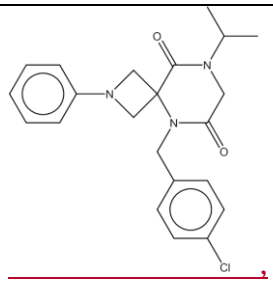
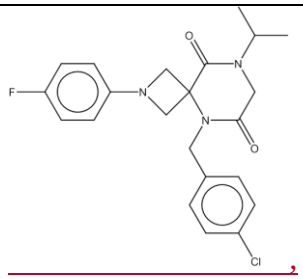
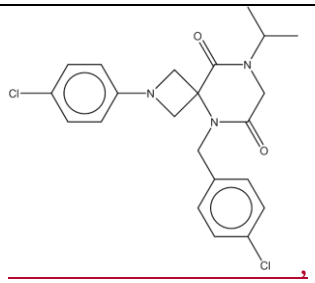
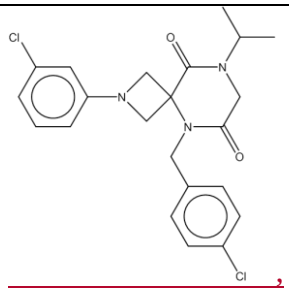
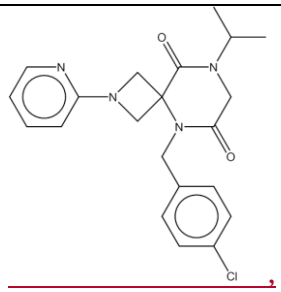
~~40.~~39. The compound of claim~~any one of claims~~ 1~~-38~~ or a pharmaceutically acceptable salt thereof, wherein R^4 is alkyl substituted with substituted or unsubstituted alkoxy.

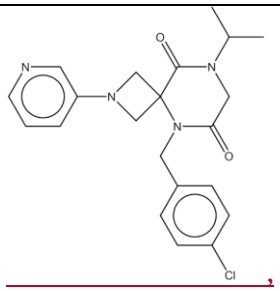
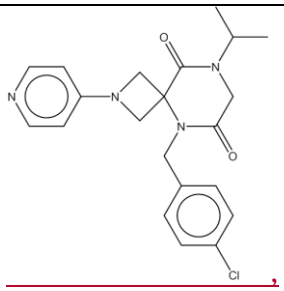
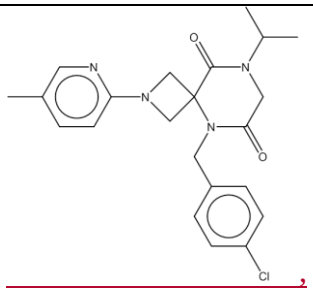
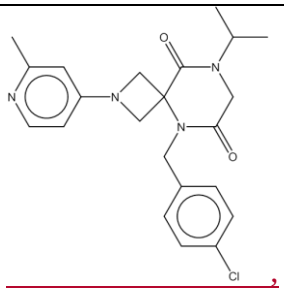
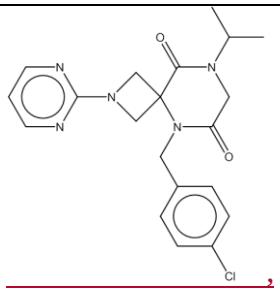
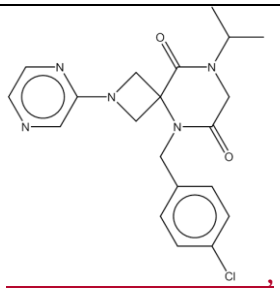
~~41.~~40. The compound of claim~~any one of claims~~ 1~~-40~~ or a pharmaceutically acceptable salt thereof, wherein R^5 is H.

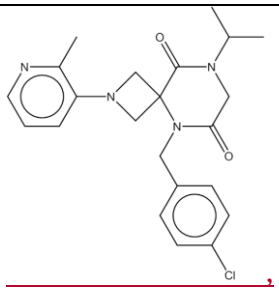
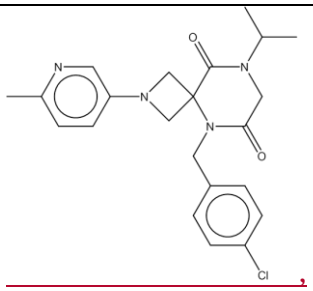
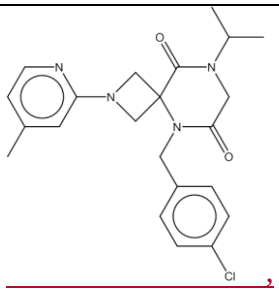
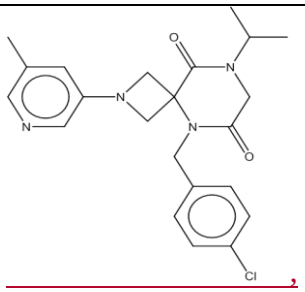
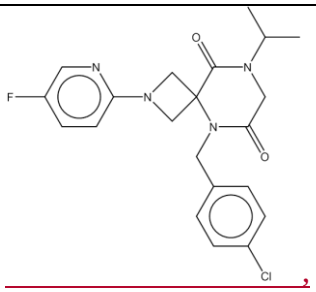
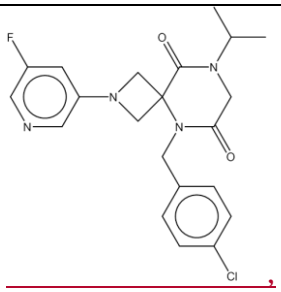
~~42.~~41. The compound of claim~~any one of claims~~ 1~~-41~~ or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl or pyridinyl, each of which is substituted with one or more substituents independently selected from the group consisting of cyano, halo, substituted or unsubstituted alkoxy, substituted or unsubstituted alkyl, and substituted or unsubstituted heterocyclyl.

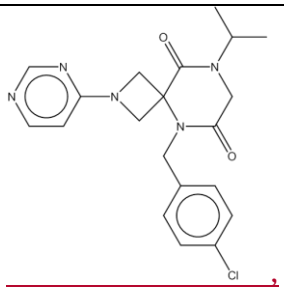
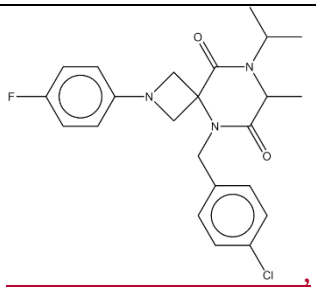
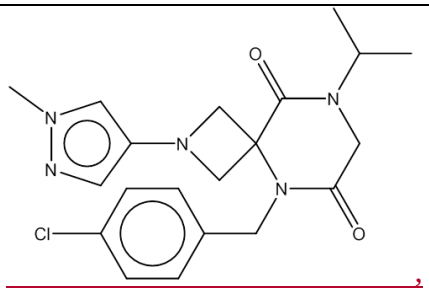
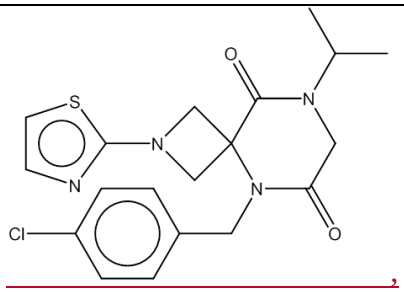
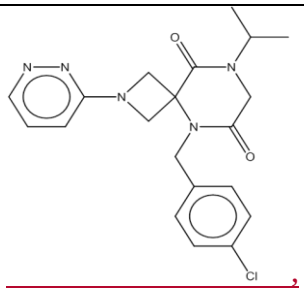
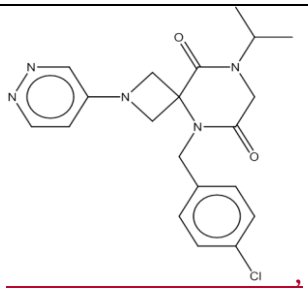
~~43.~~42. The compound of claim~~any one of claims~~ 1~~-42~~ or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl substituted with trifluoromethyl.

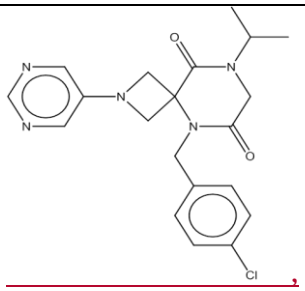
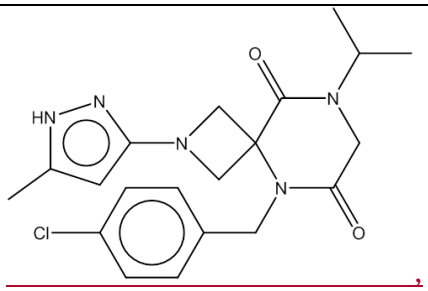
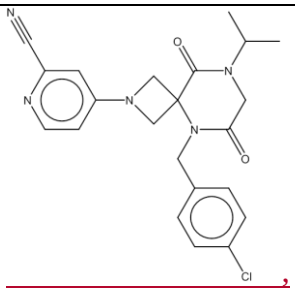
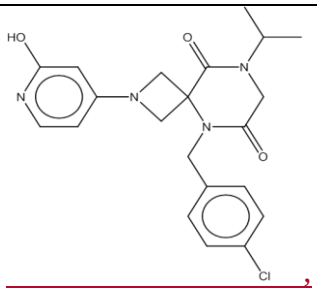
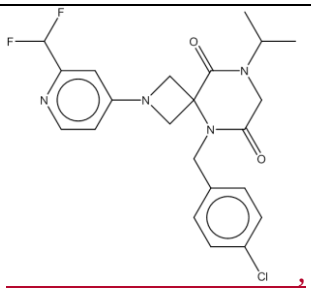
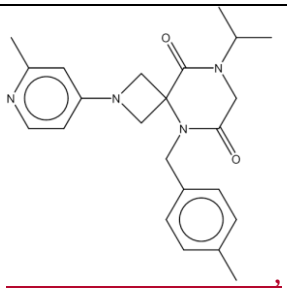
~~44.~~43. A compound selected from the group consisting of ~~compounds of Table 1,~~;

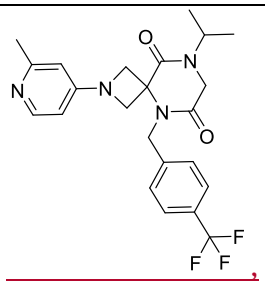
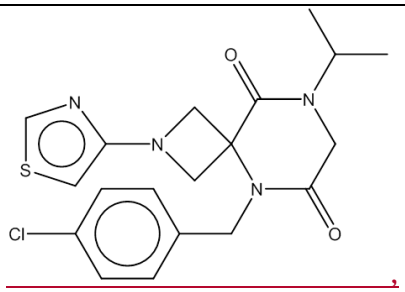
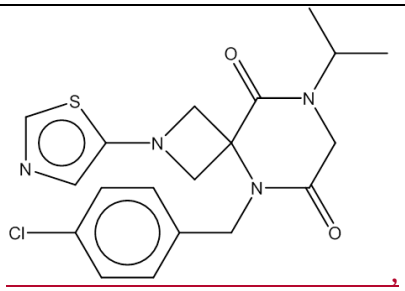
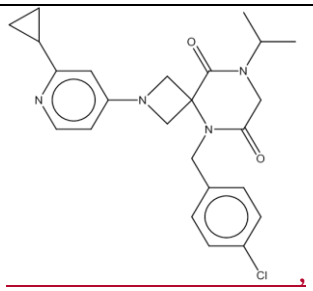
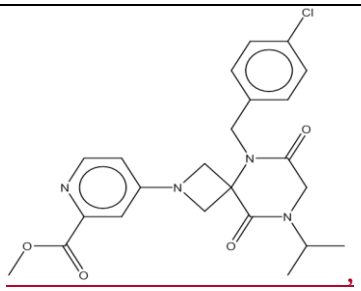
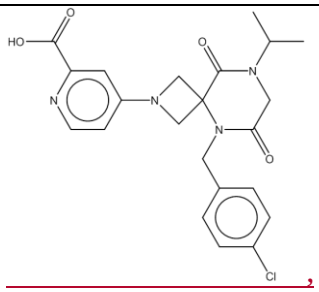
No.	Structure
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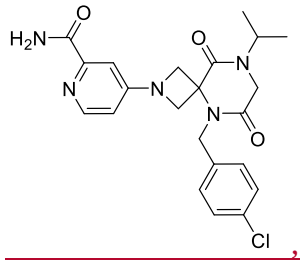
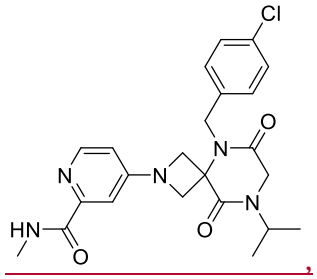
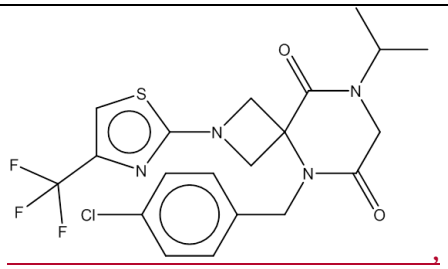
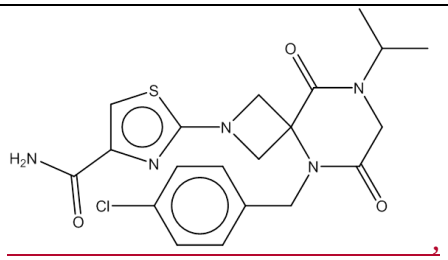
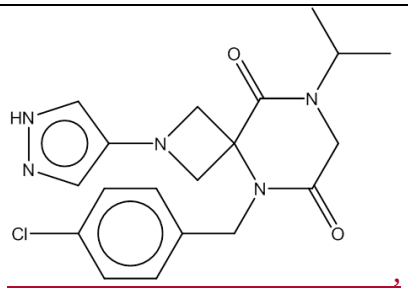
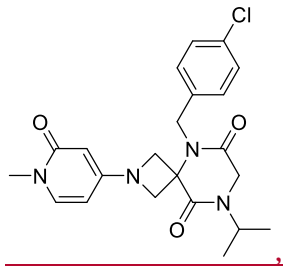
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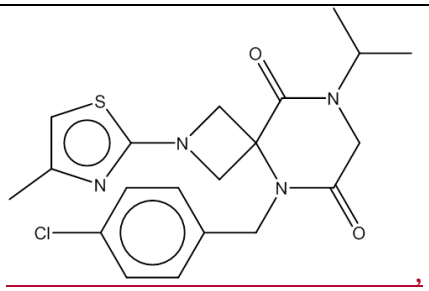
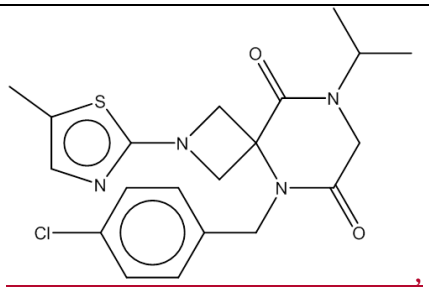
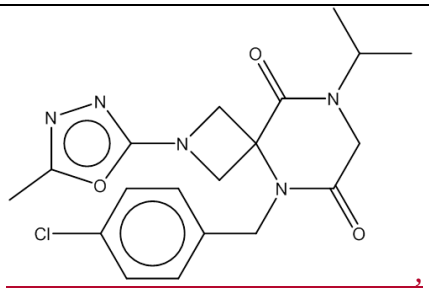
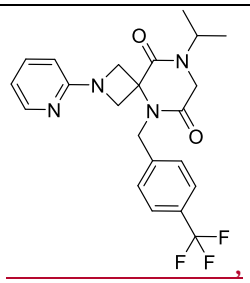
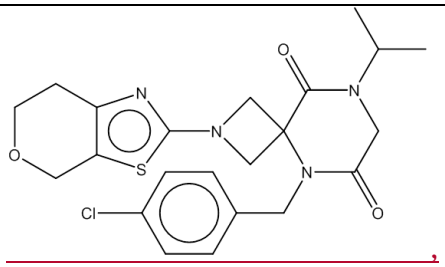
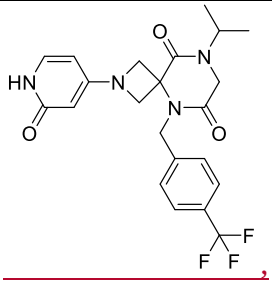
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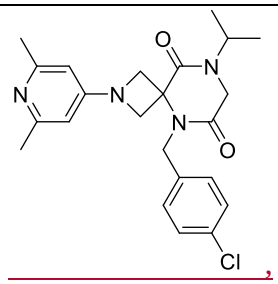
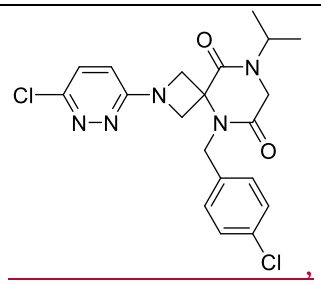
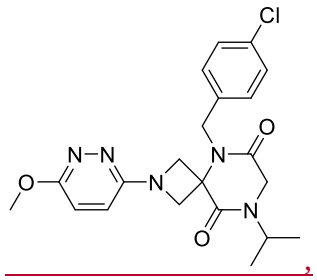
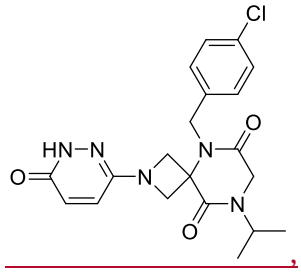
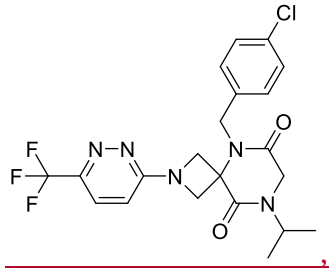
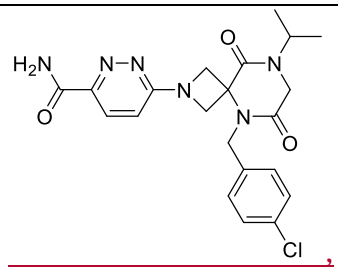
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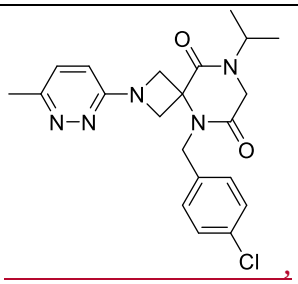
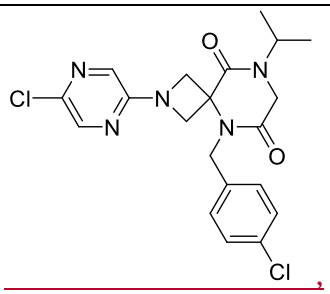
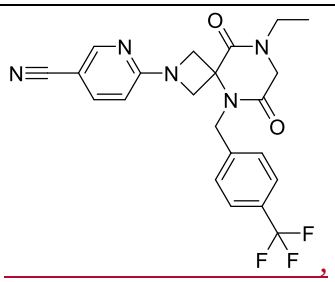
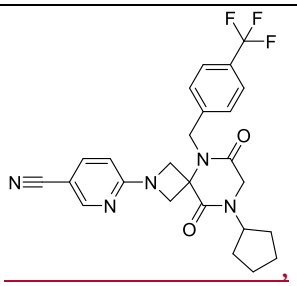
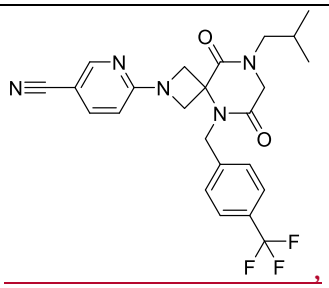
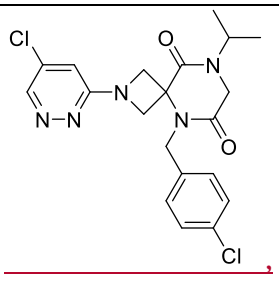
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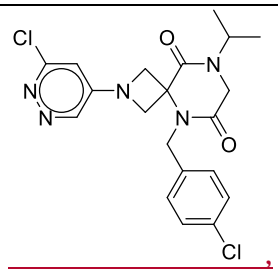
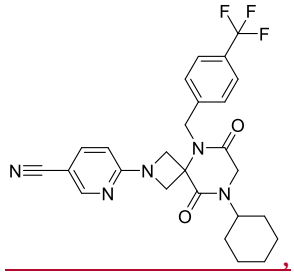
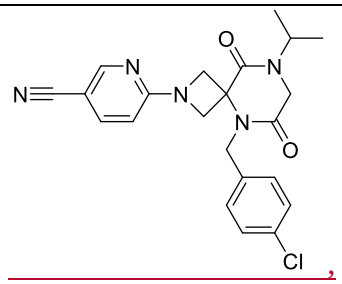
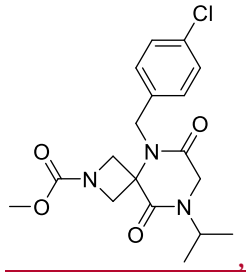
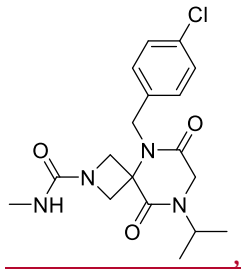
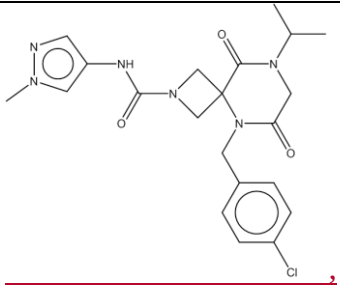
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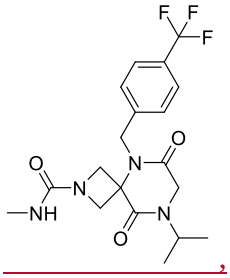
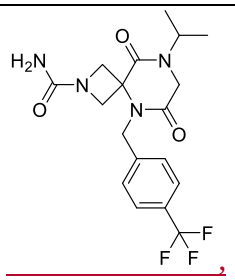
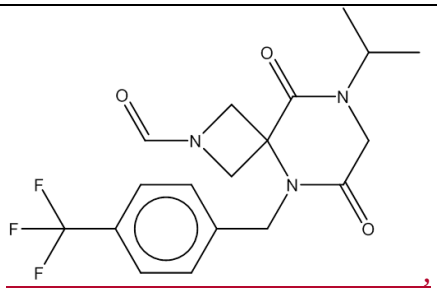
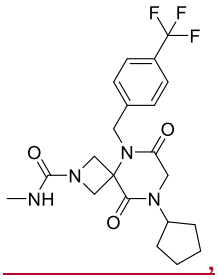
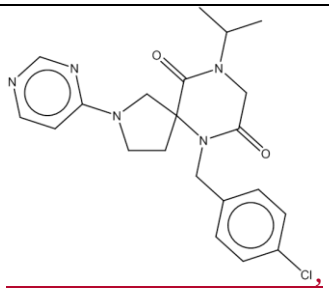
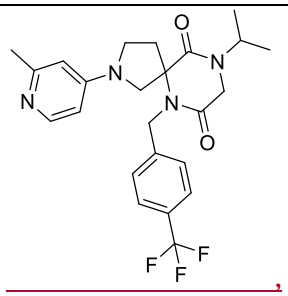
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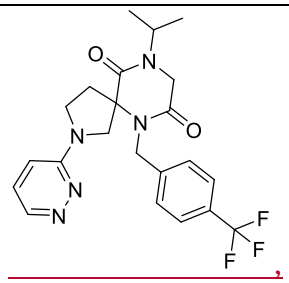
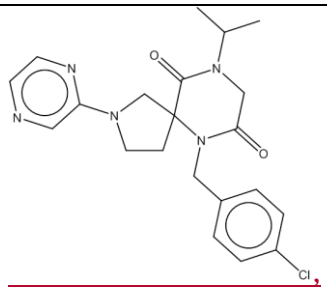
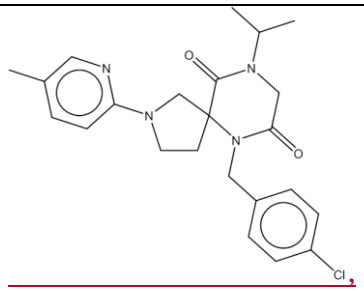
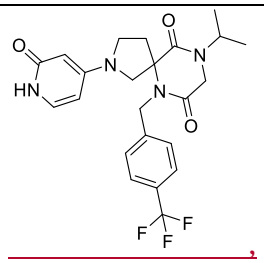
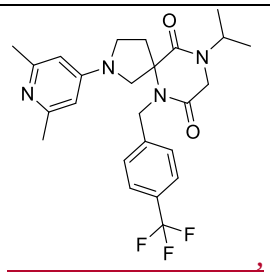
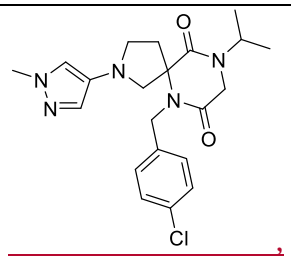
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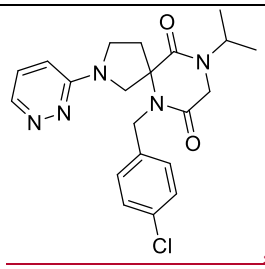
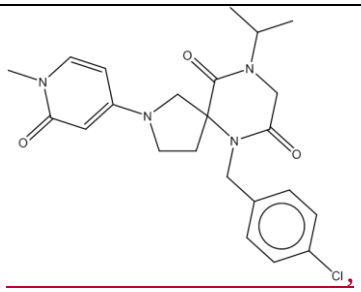
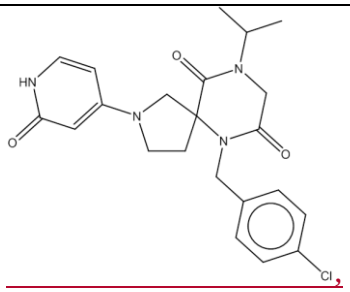
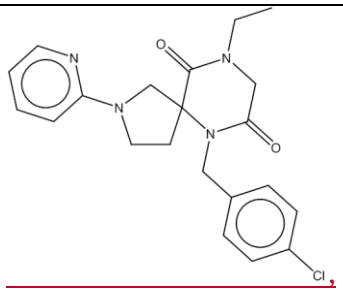
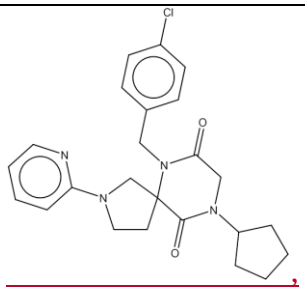
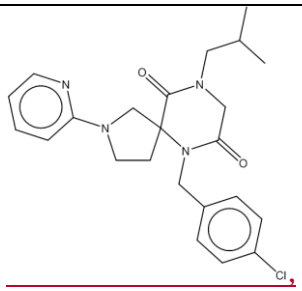
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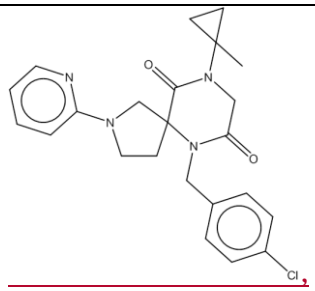
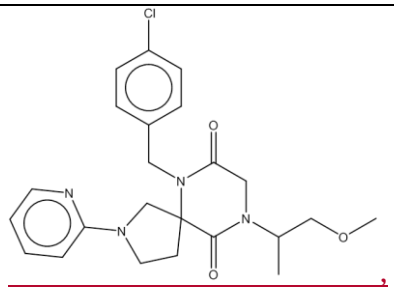
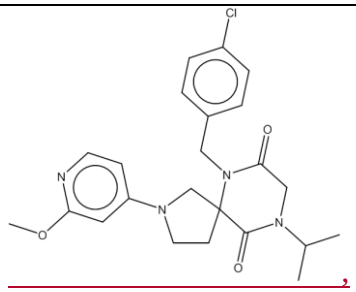
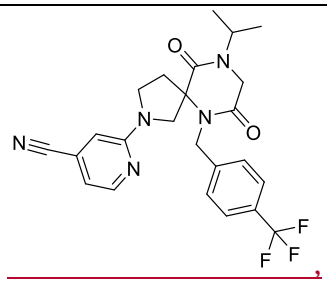
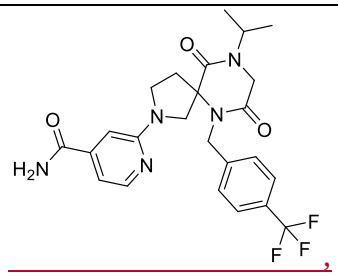
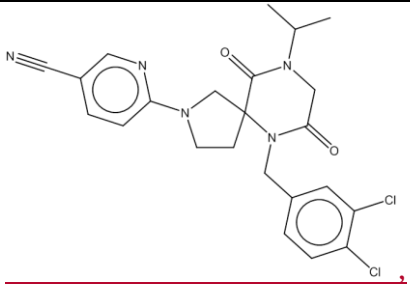
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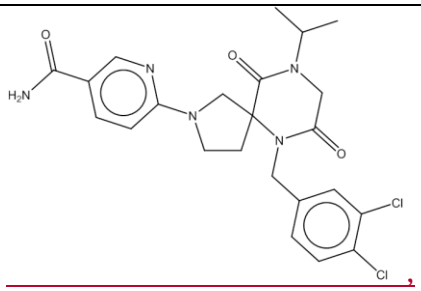
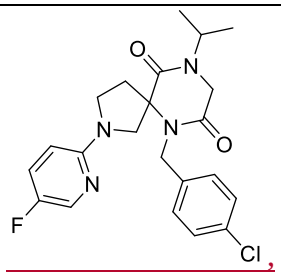
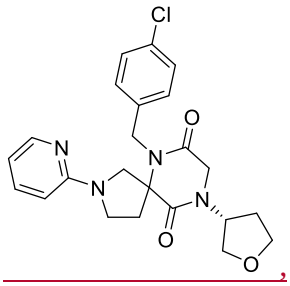
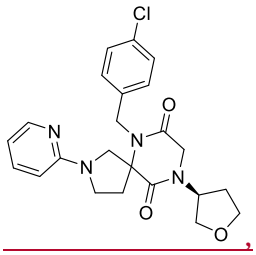
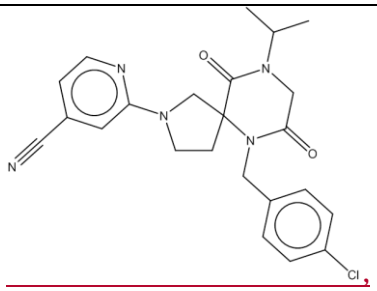
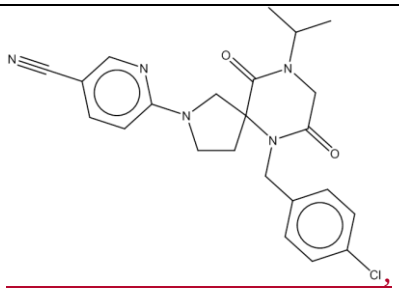
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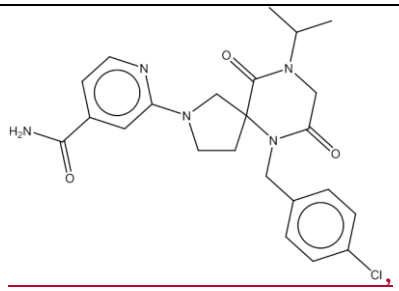
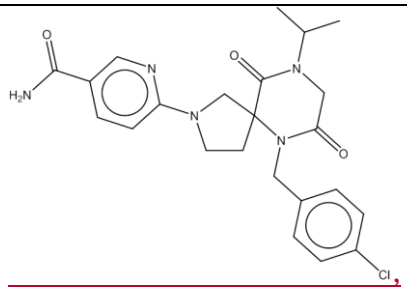
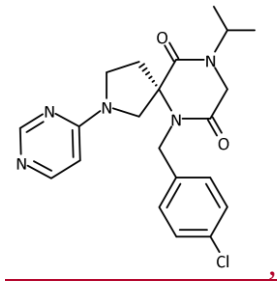
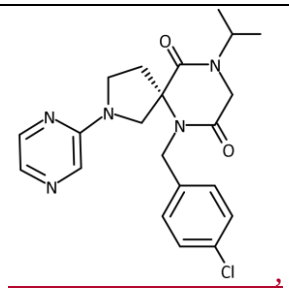
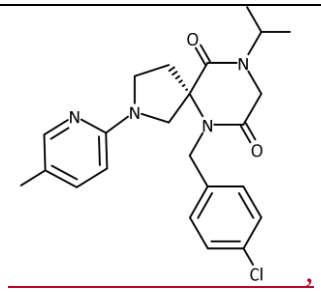
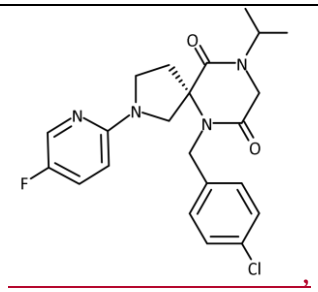
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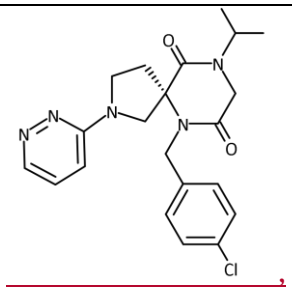
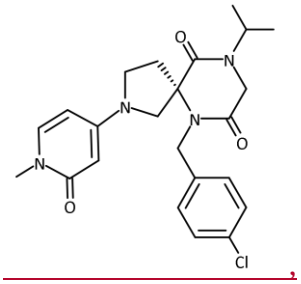
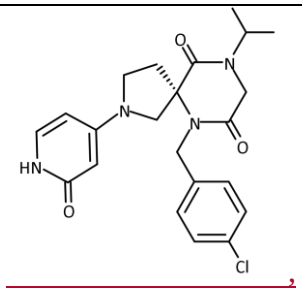
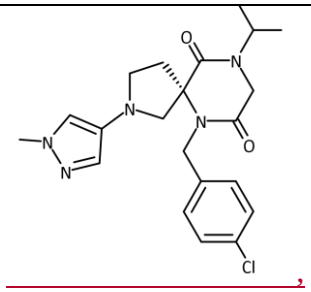
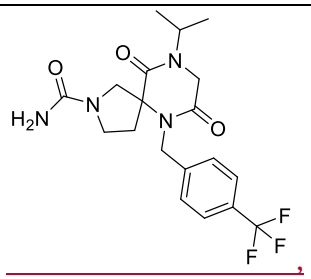
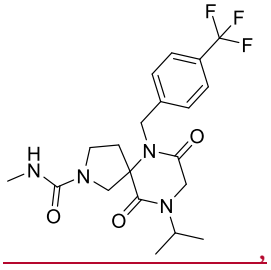
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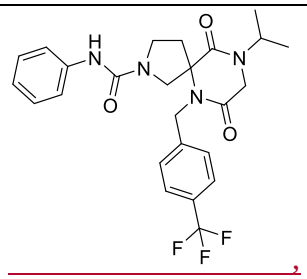
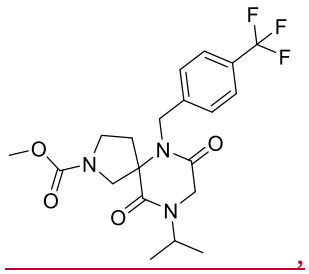
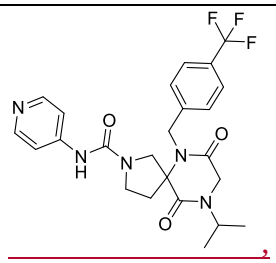
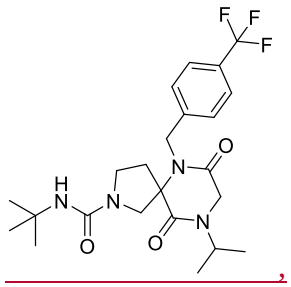
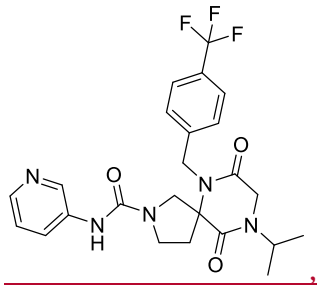
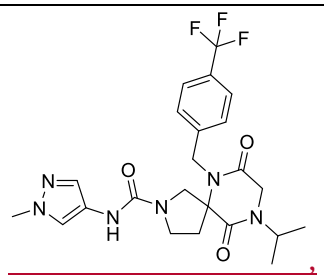
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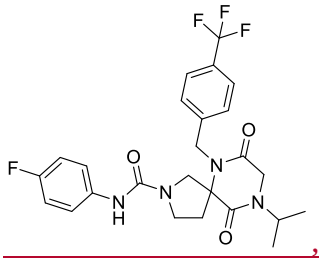
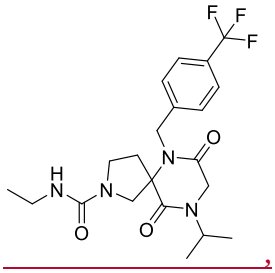
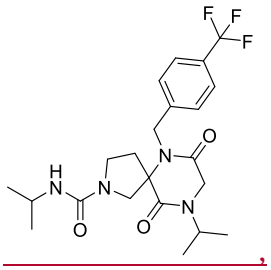
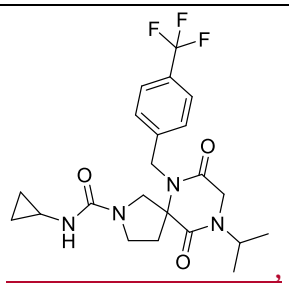
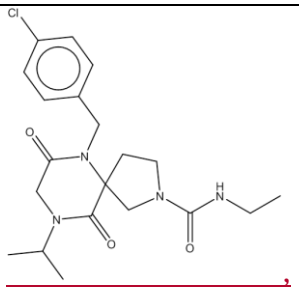
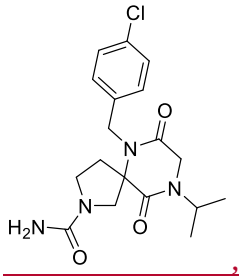
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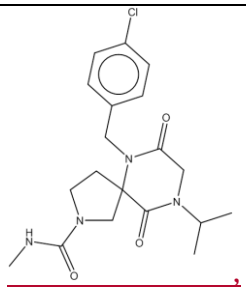
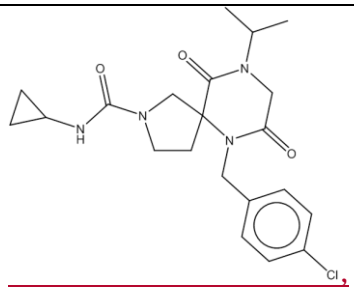
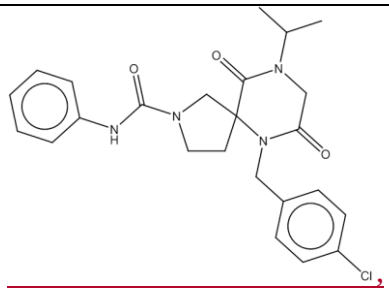
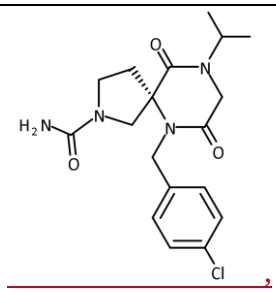
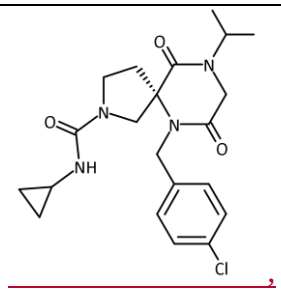
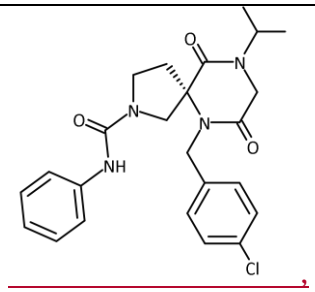
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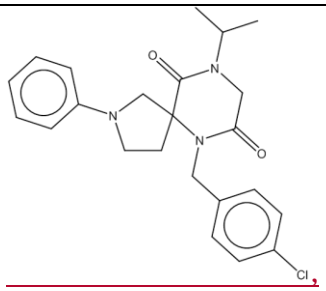
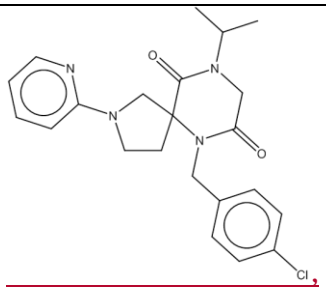
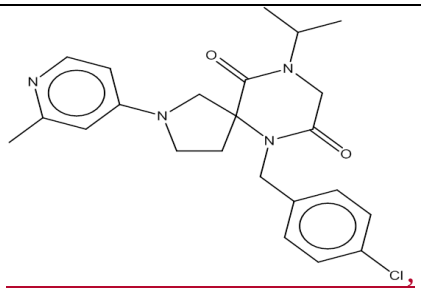
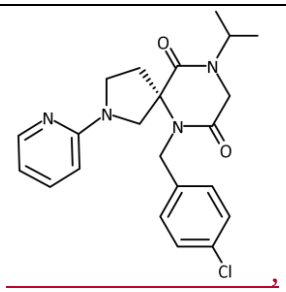
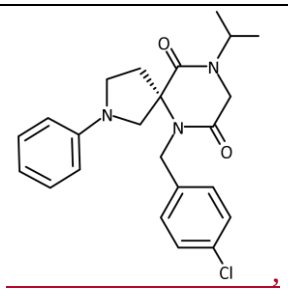
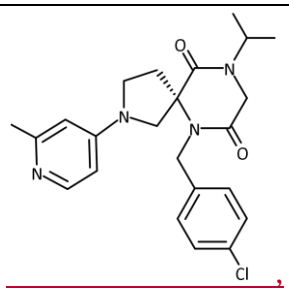
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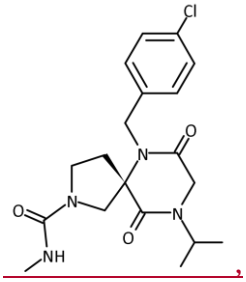
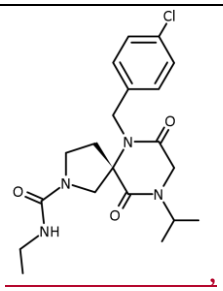
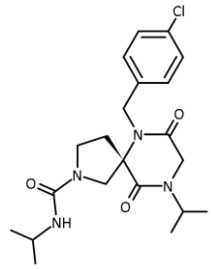
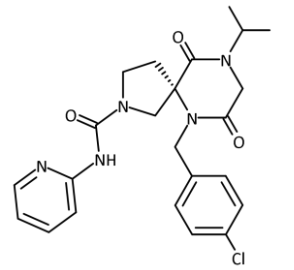
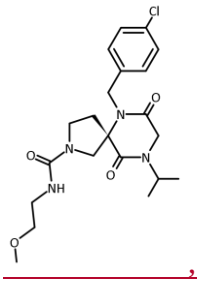
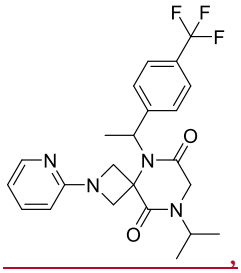
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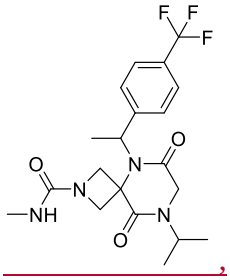
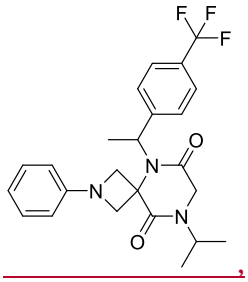
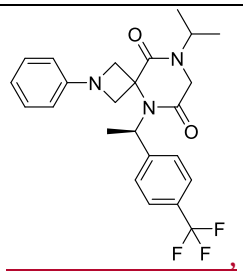
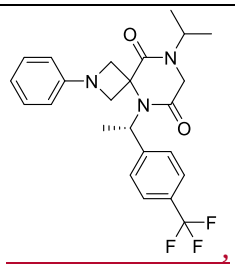
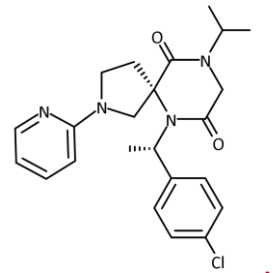
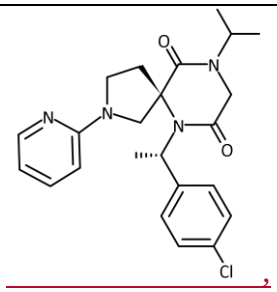
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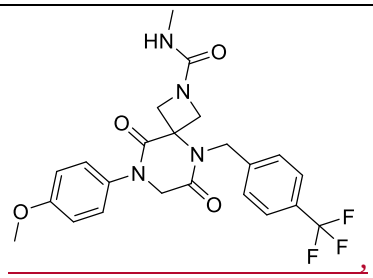
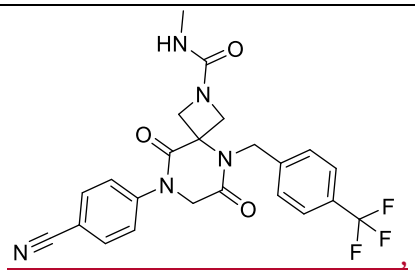
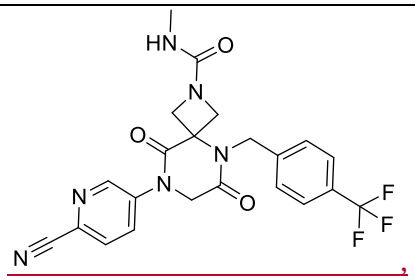
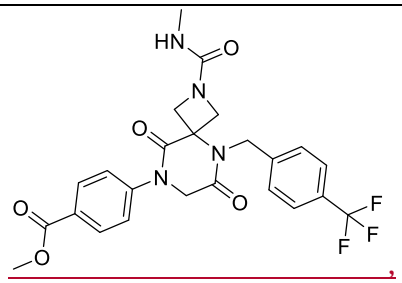
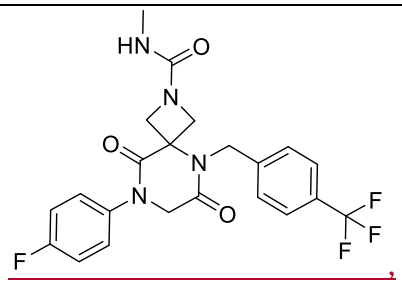
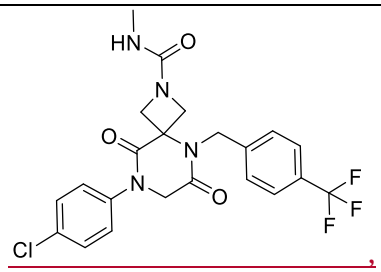
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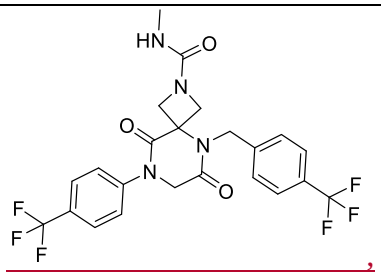
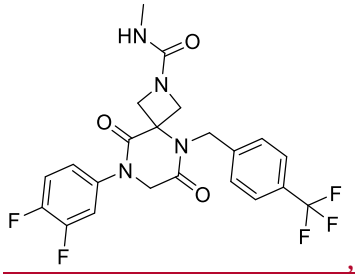
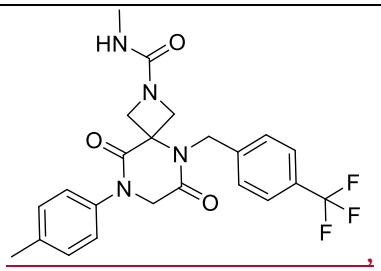
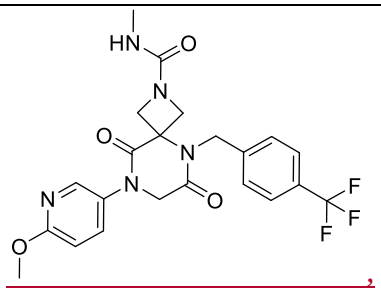
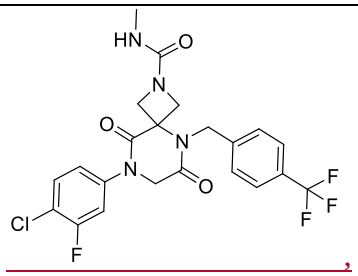
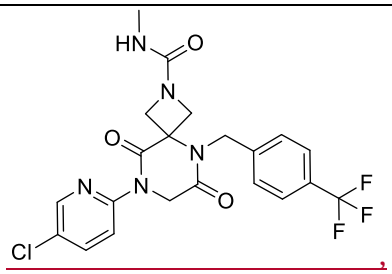
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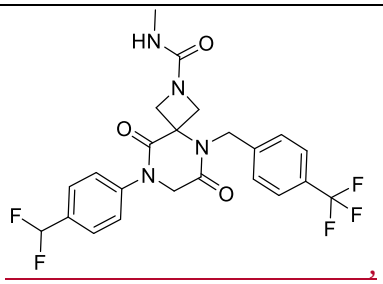
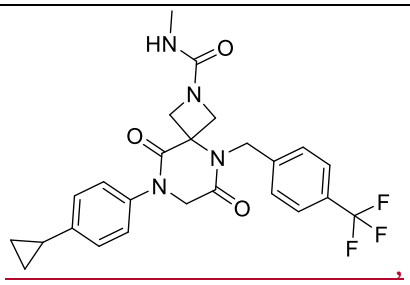
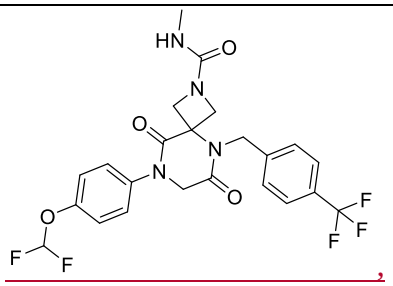
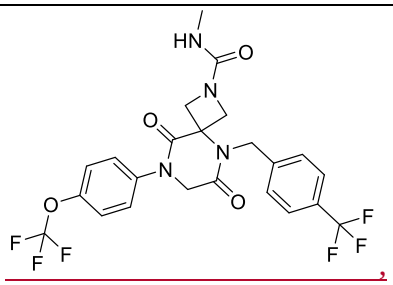
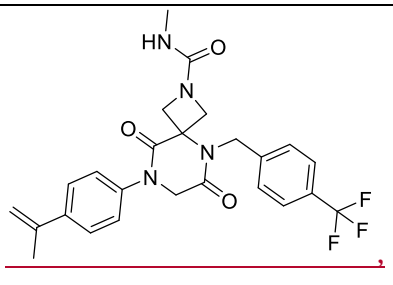
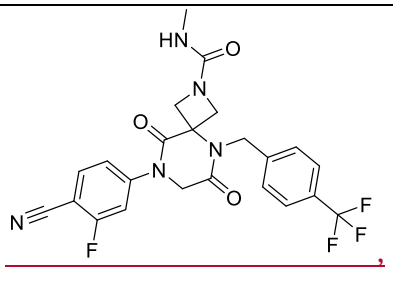
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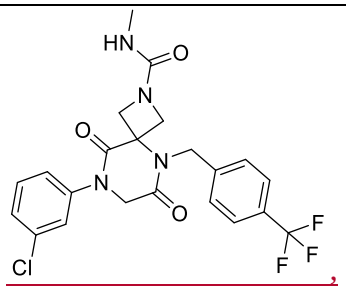
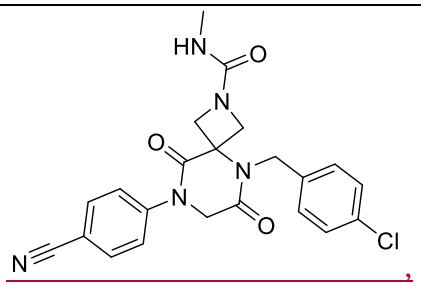
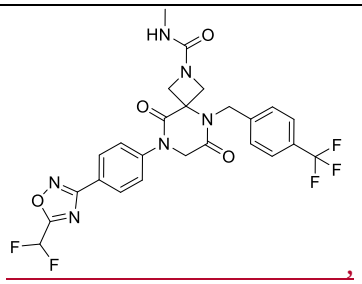
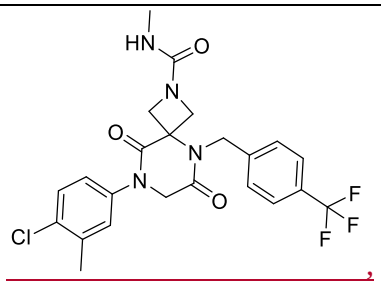
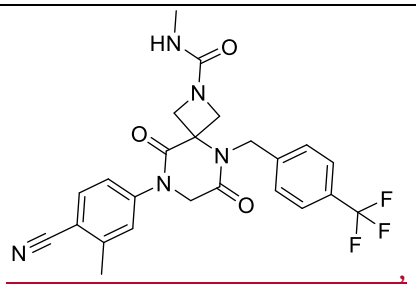
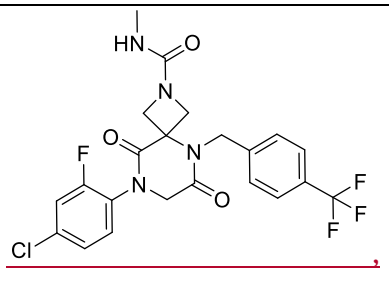
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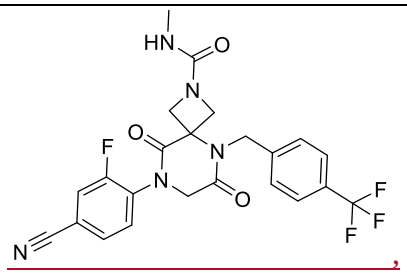
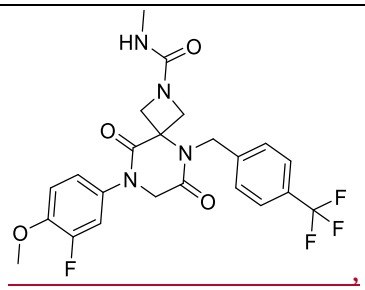
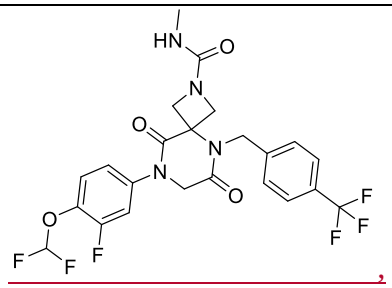
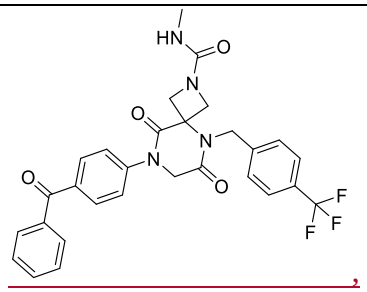
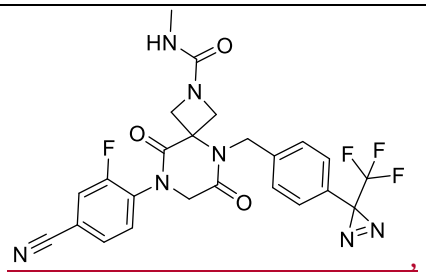
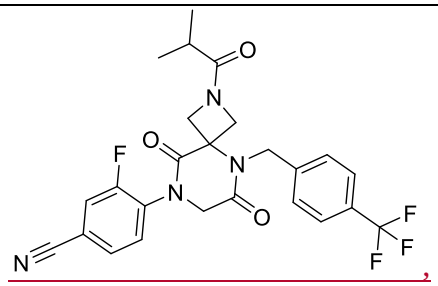
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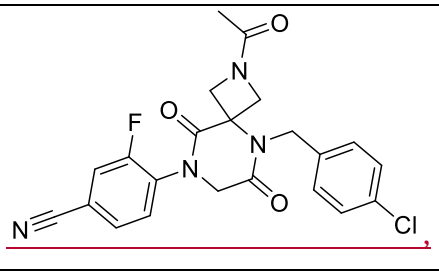
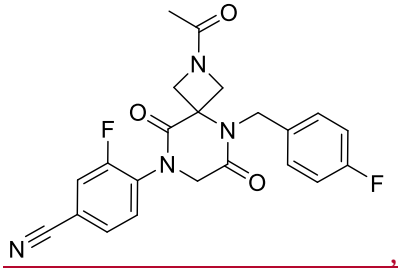
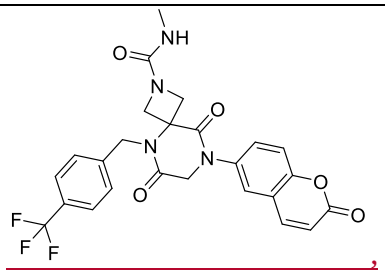
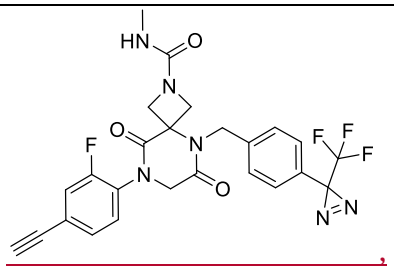
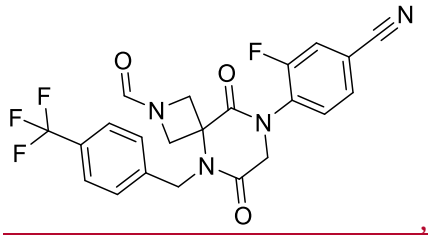
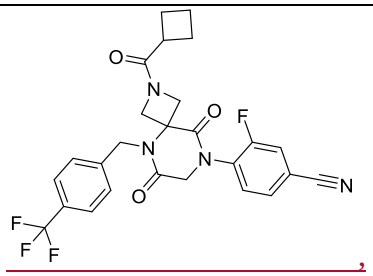
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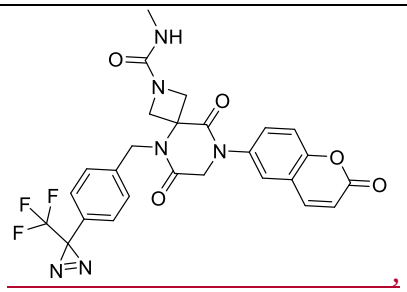
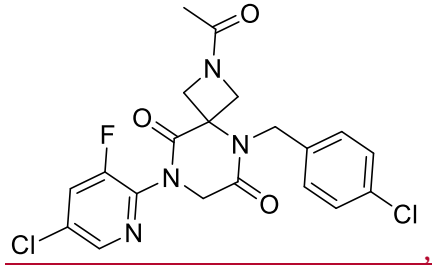
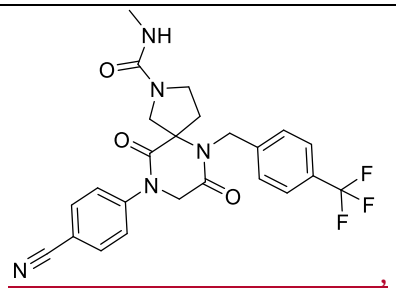
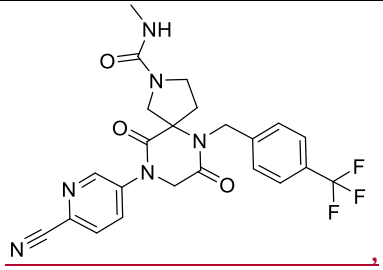
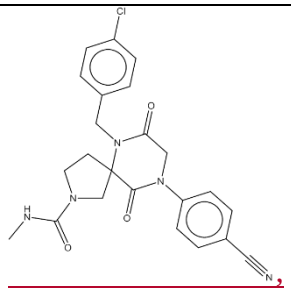
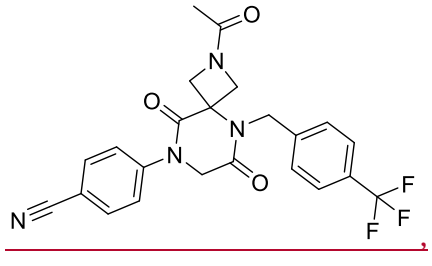
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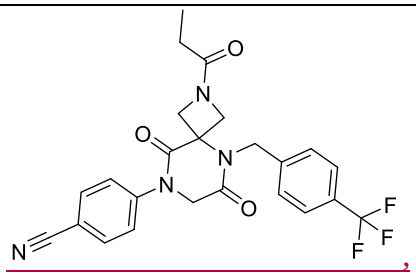
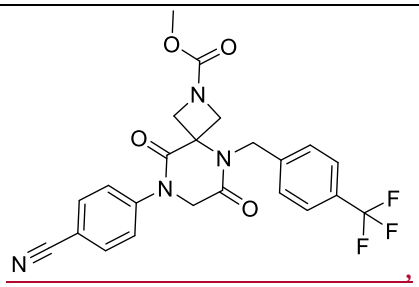
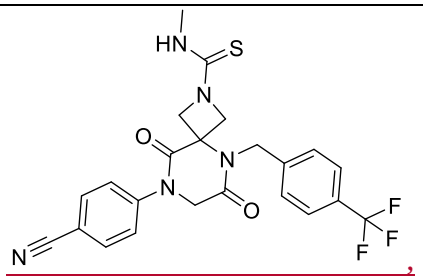
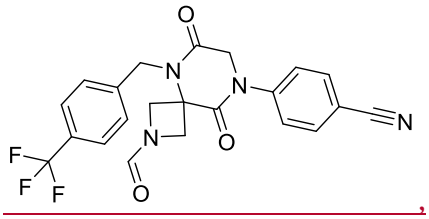
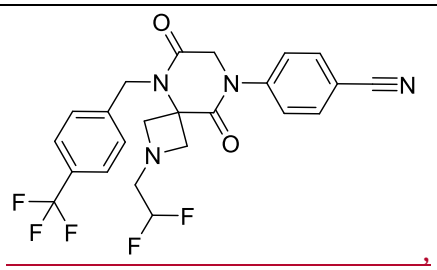
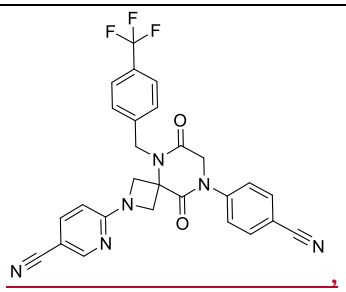
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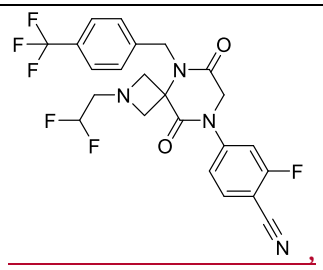
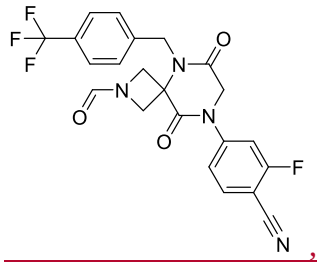
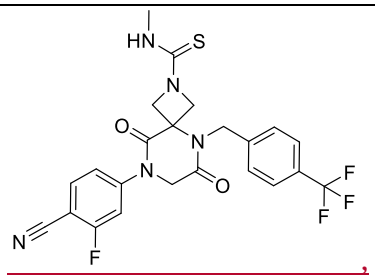
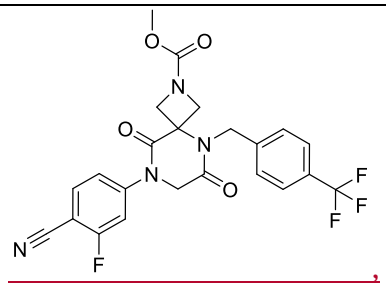
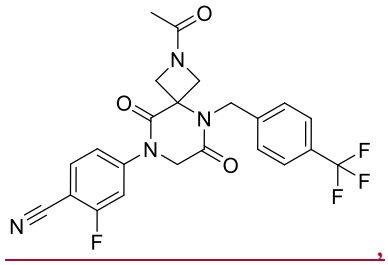
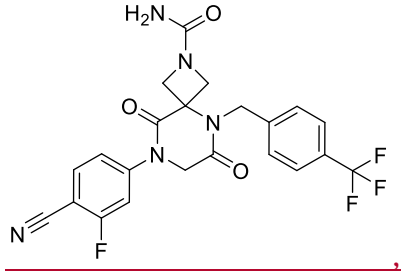
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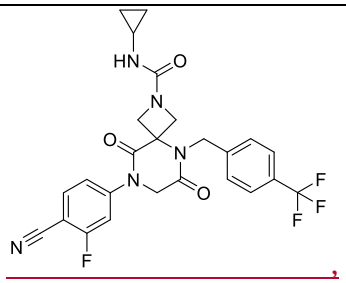
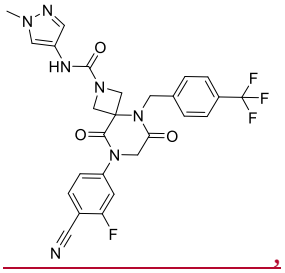
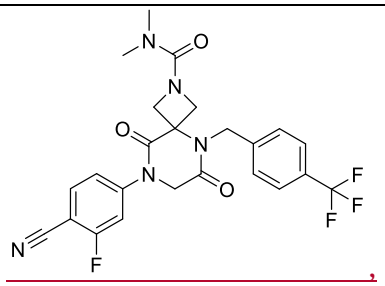
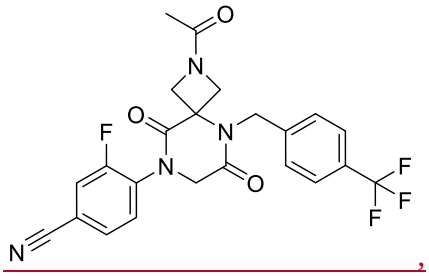
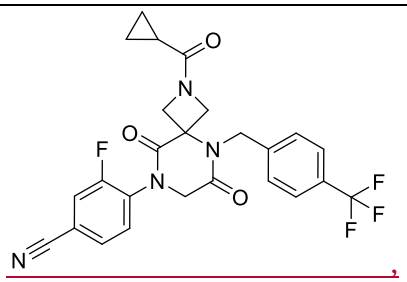
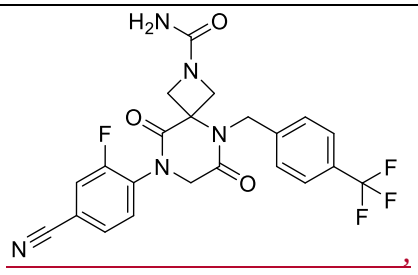
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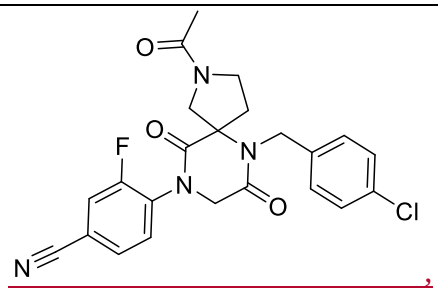
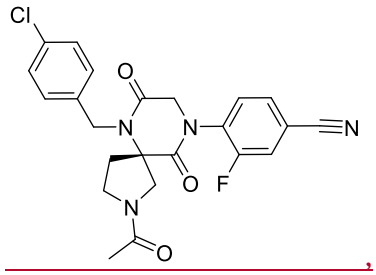
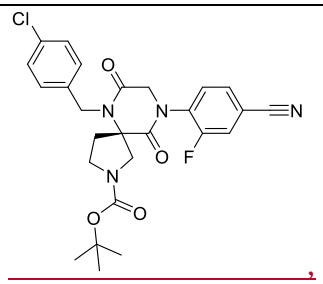
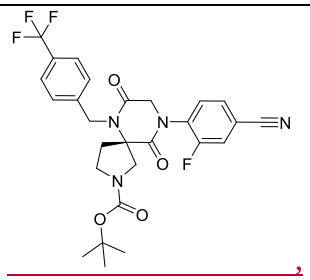
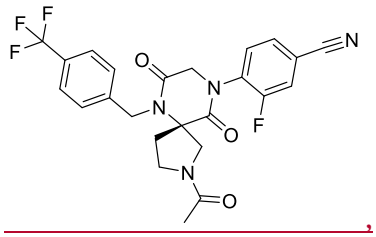
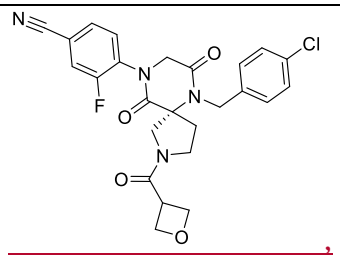
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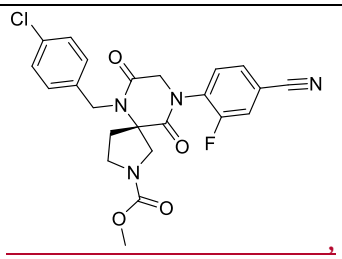
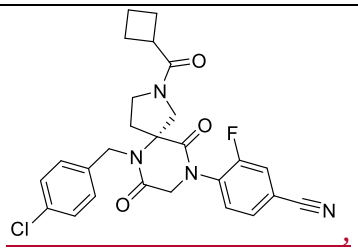
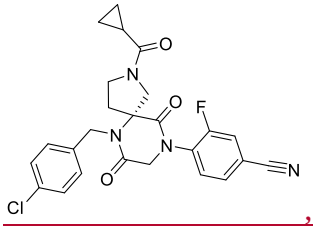
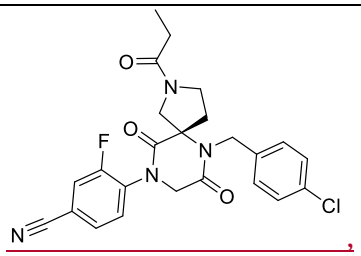
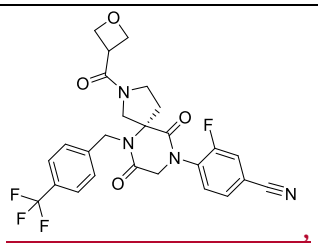
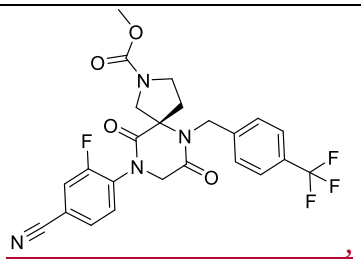
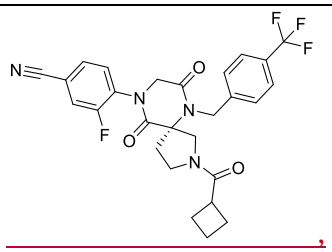
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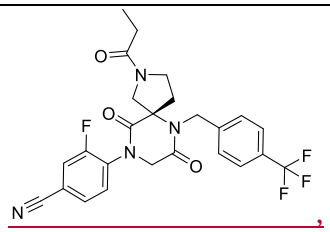
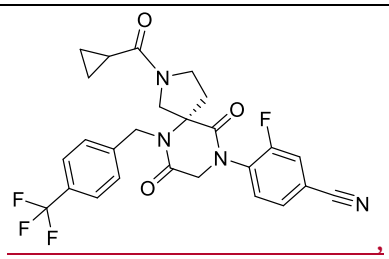
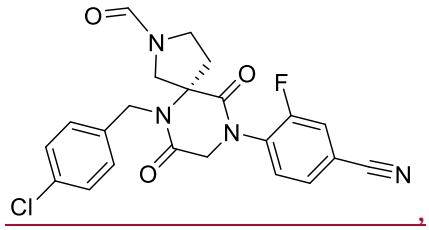
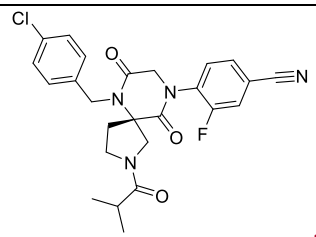
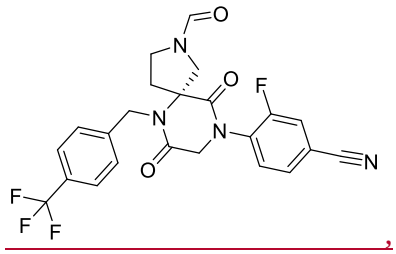
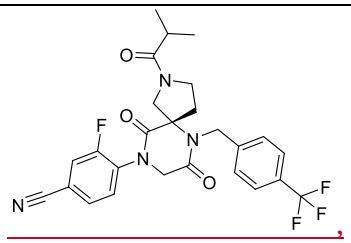
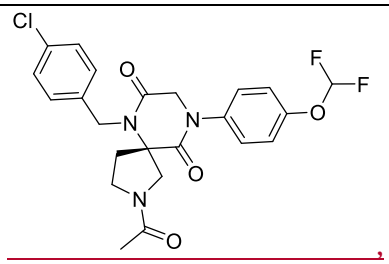
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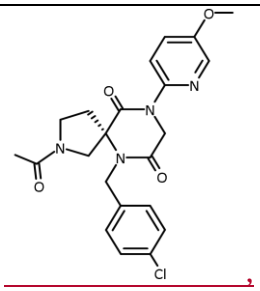
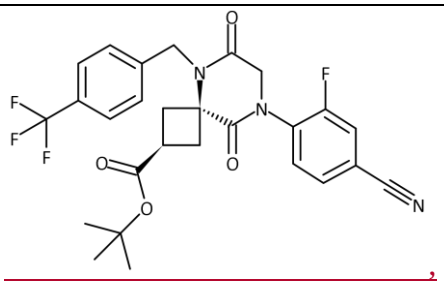
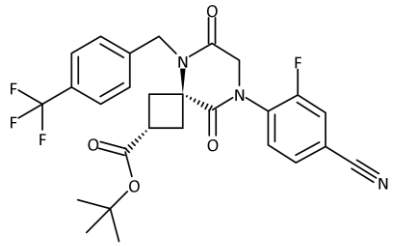
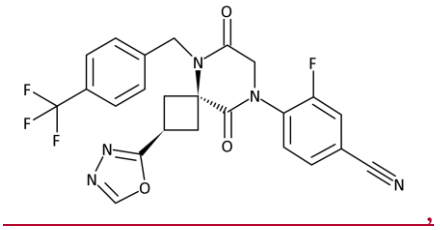
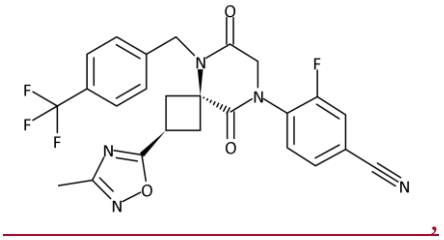
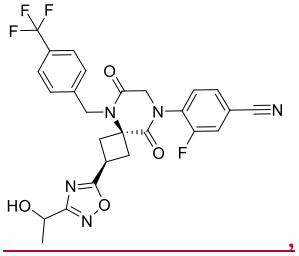
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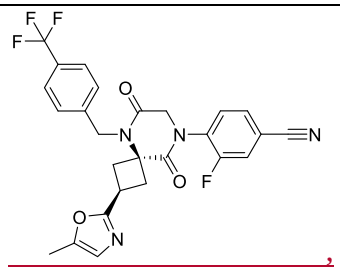
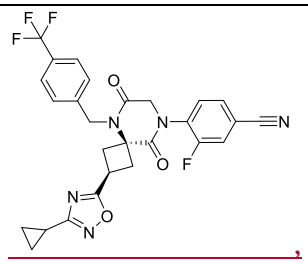
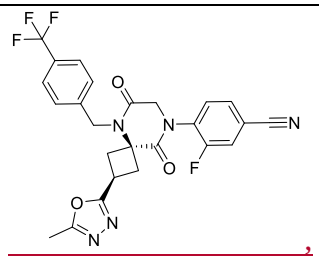
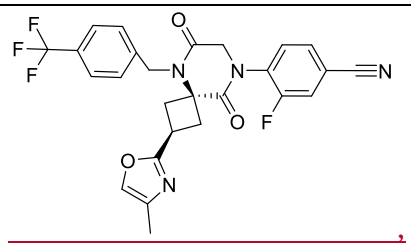
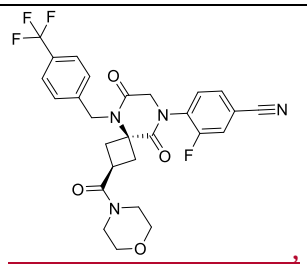
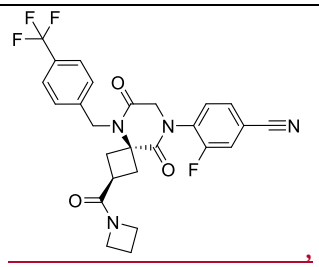
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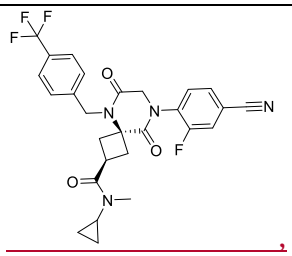
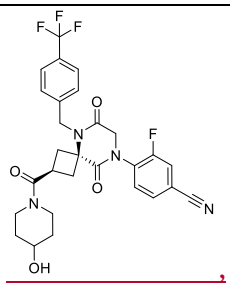
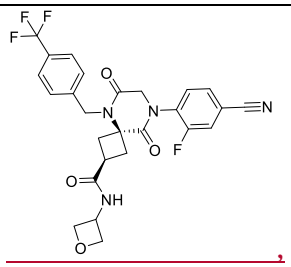
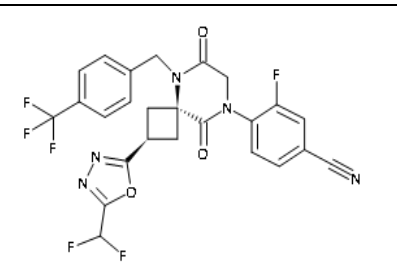
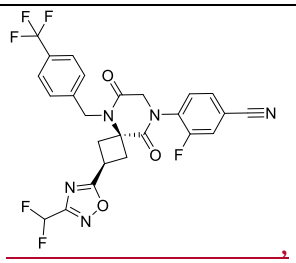
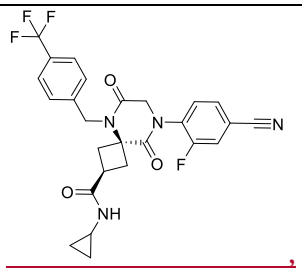
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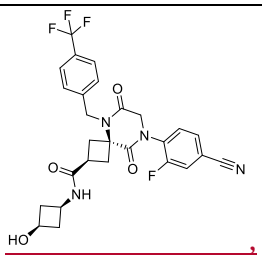
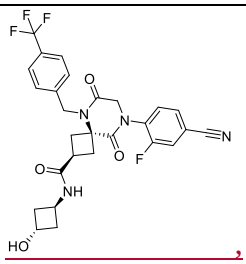
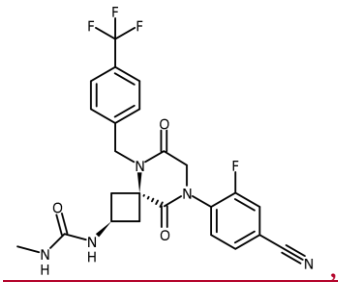
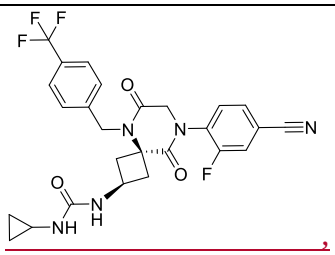
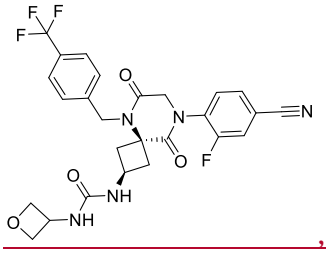
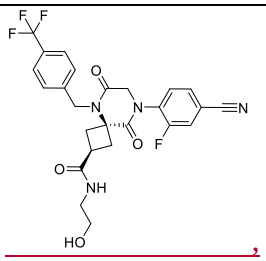
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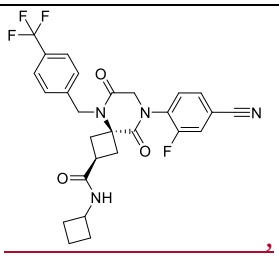
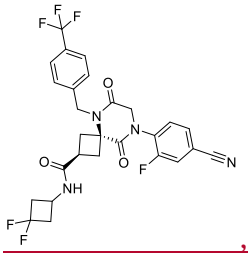
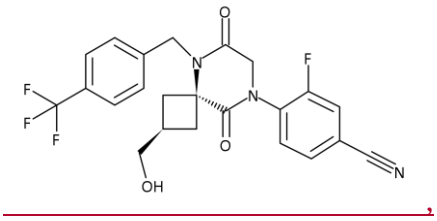
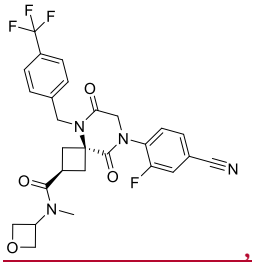
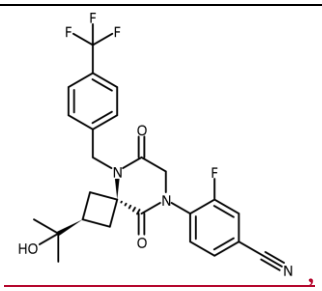
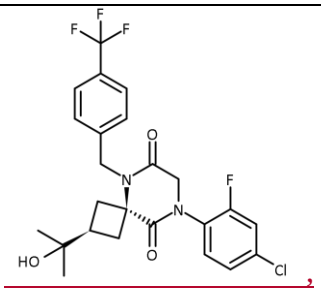
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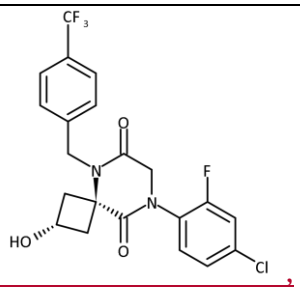
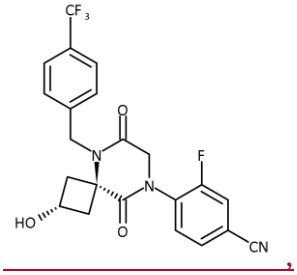
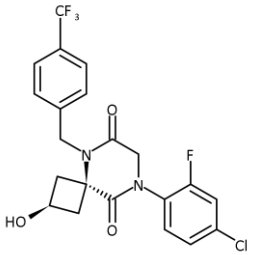
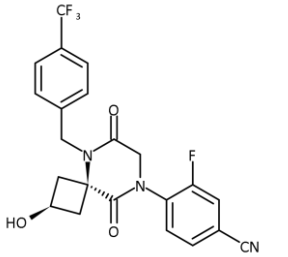
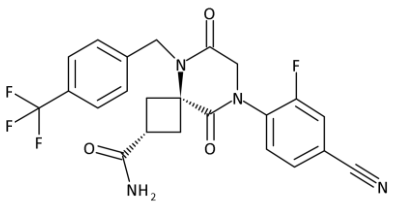
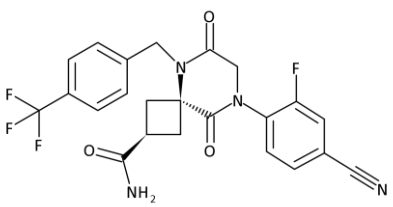
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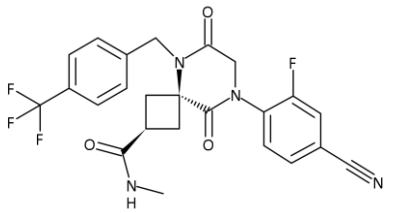
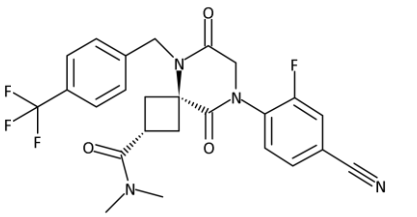
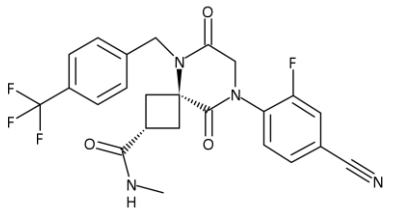
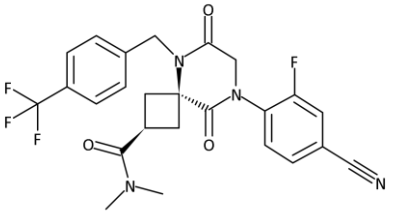
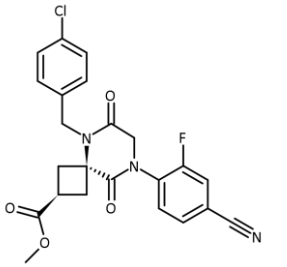
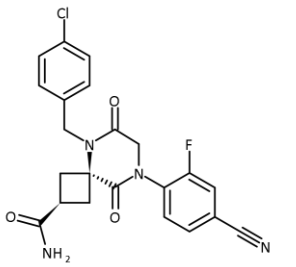
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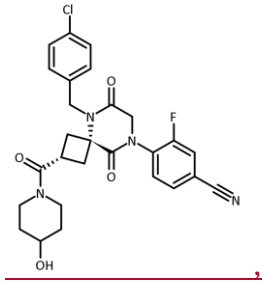
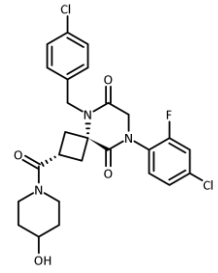
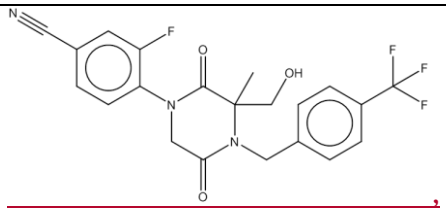
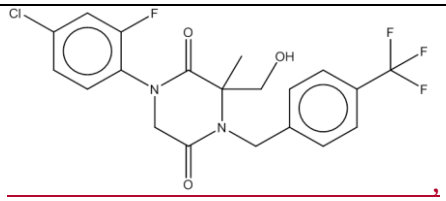
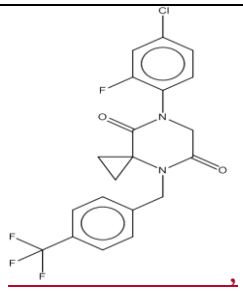
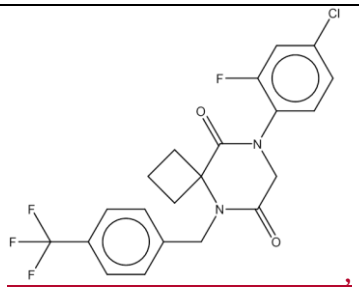
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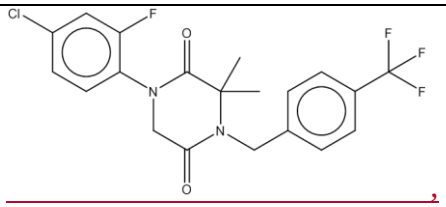
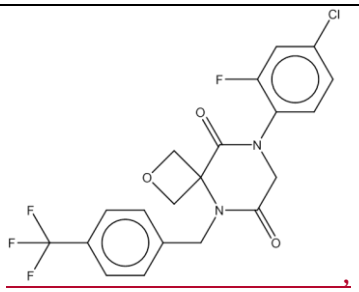
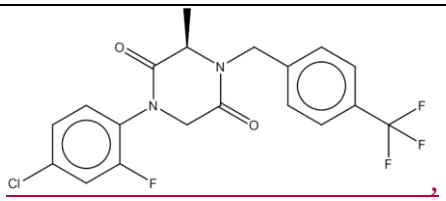
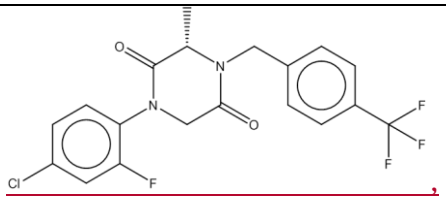
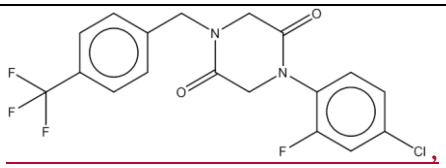
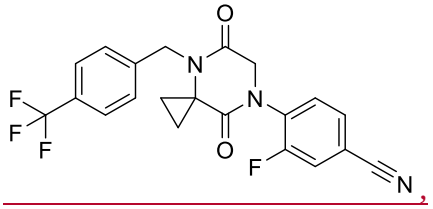
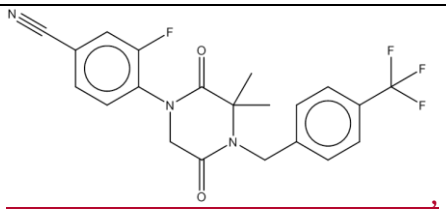
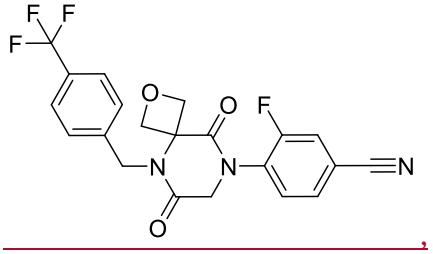
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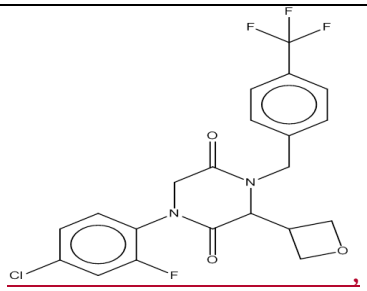
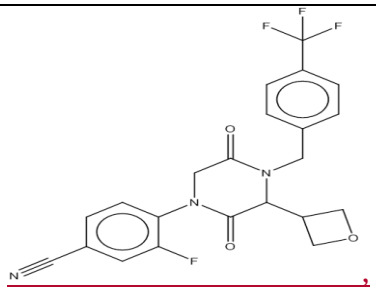
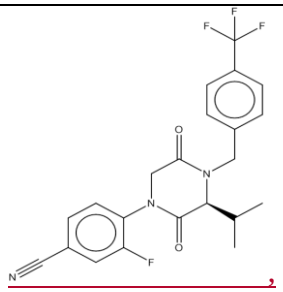
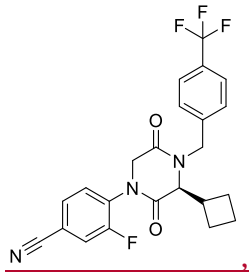
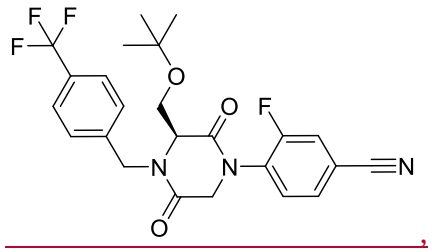
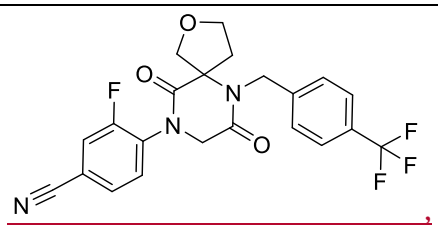
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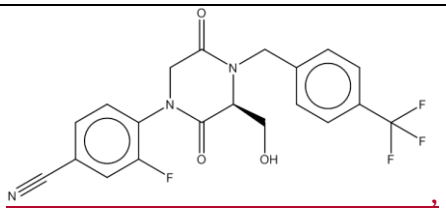
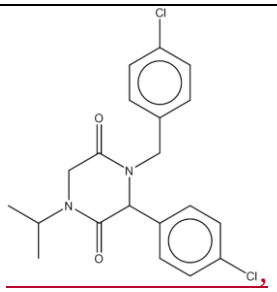
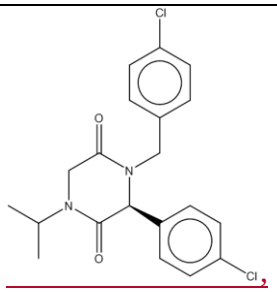
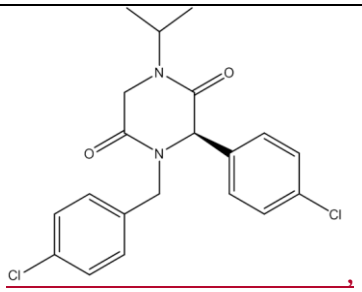
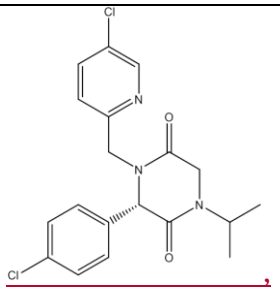
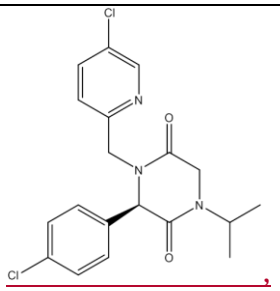
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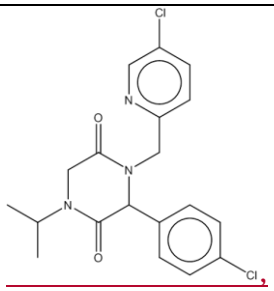
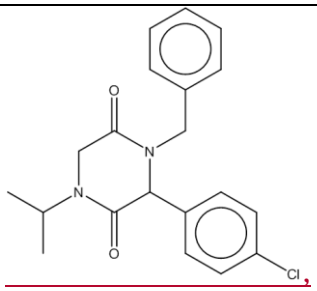
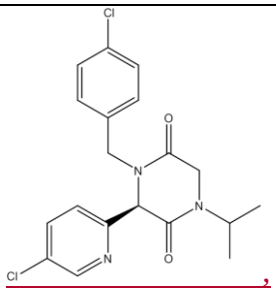
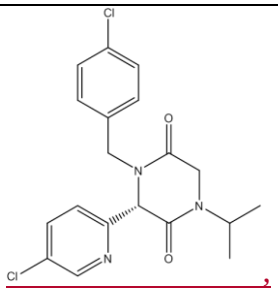
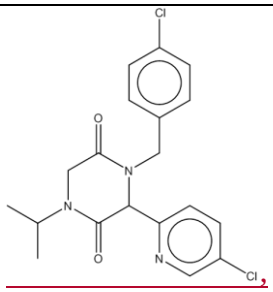
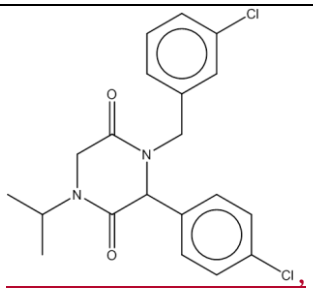
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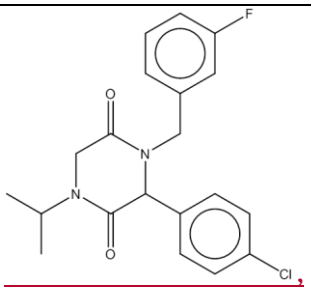
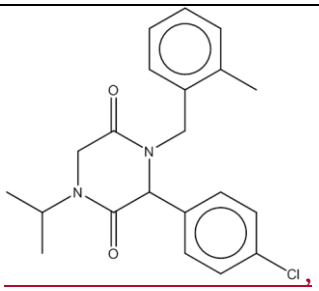
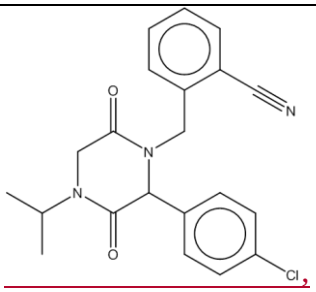
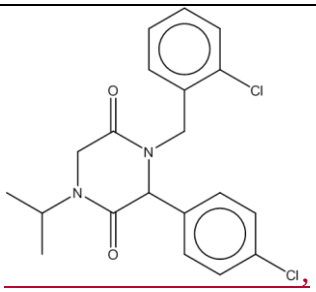
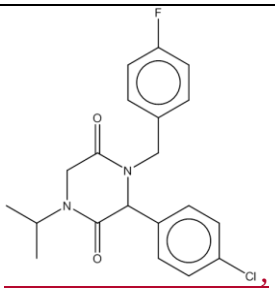
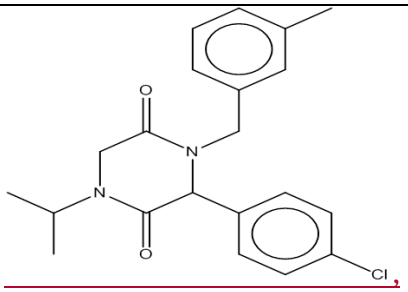
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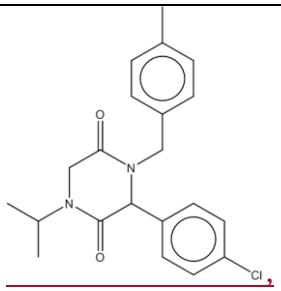
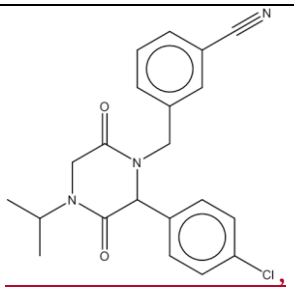
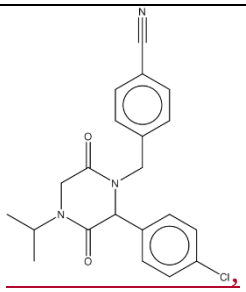
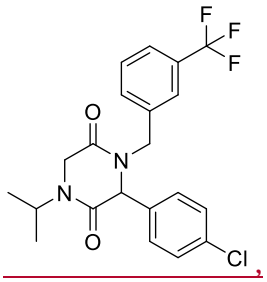
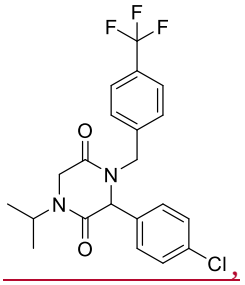
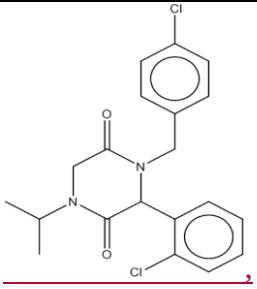
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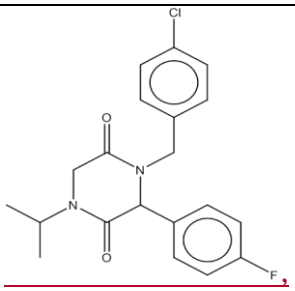
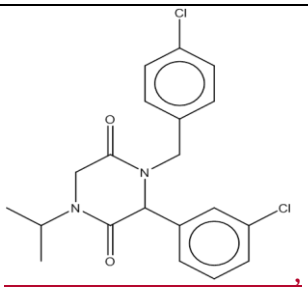
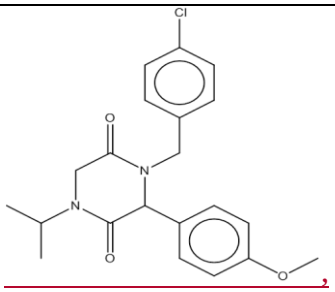
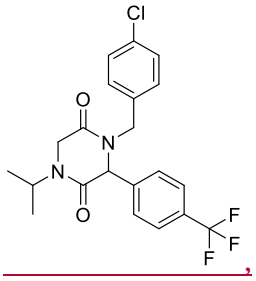
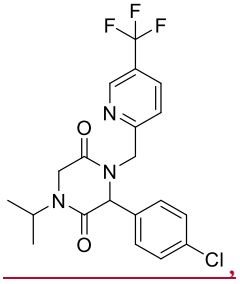
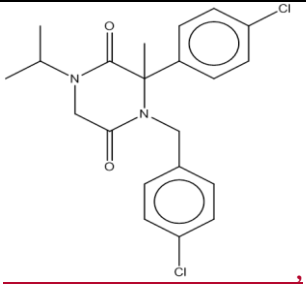
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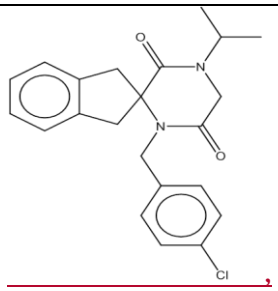
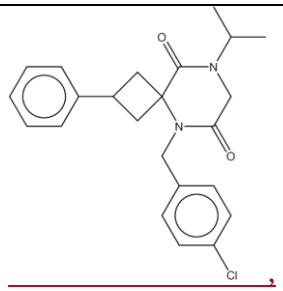
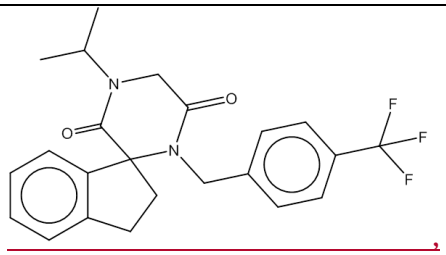
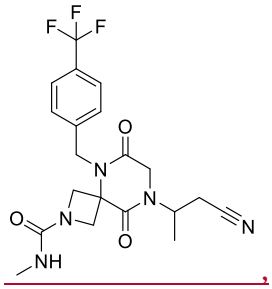
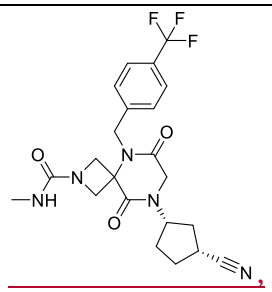
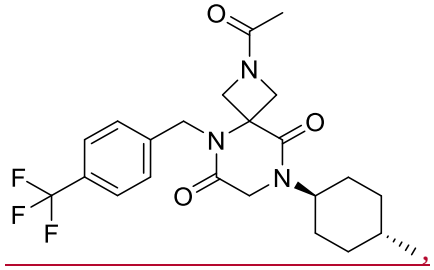
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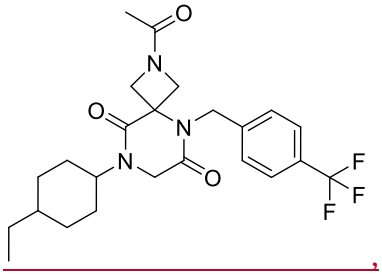
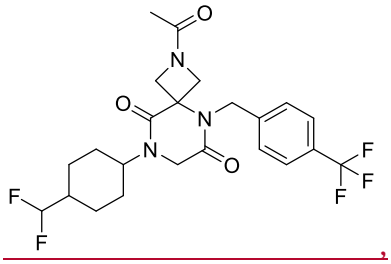
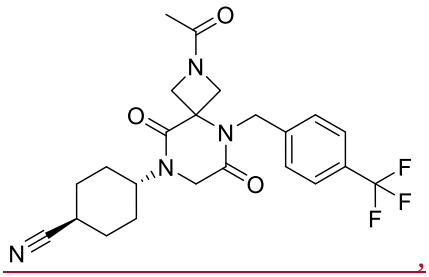
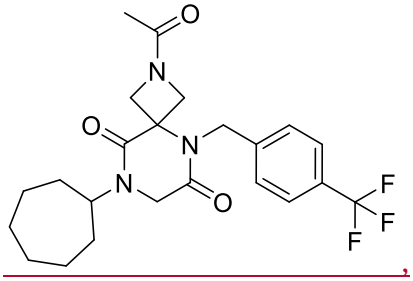
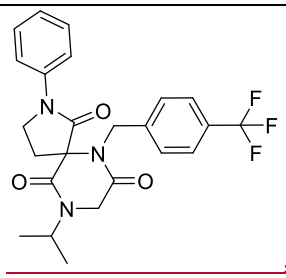
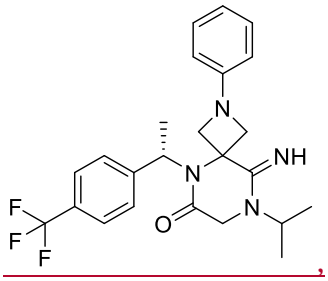
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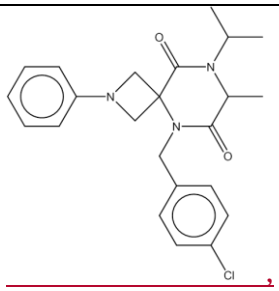
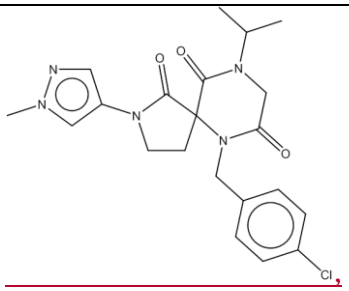
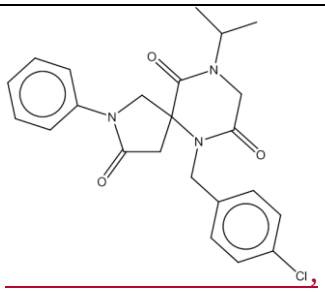
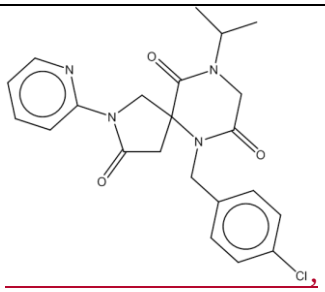
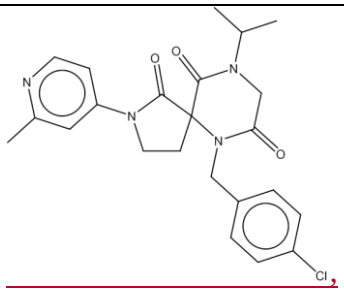
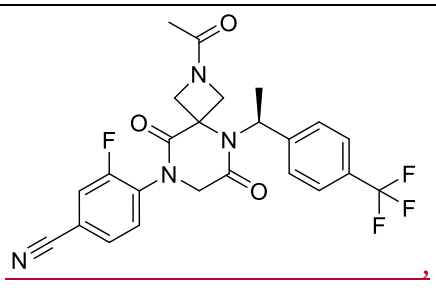
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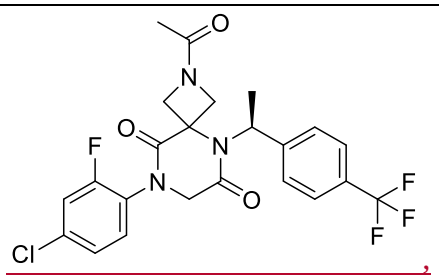
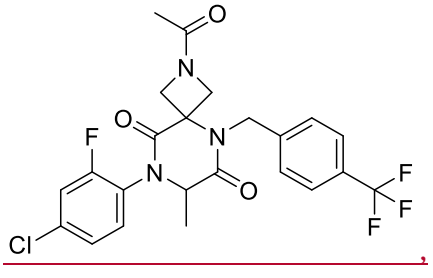
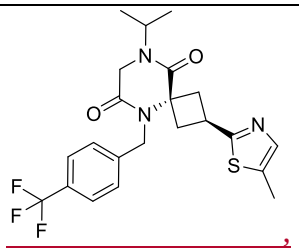
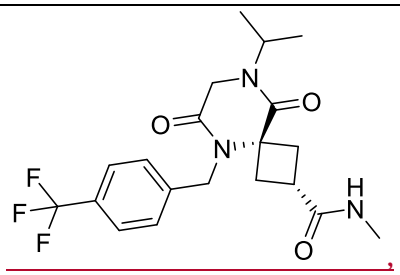
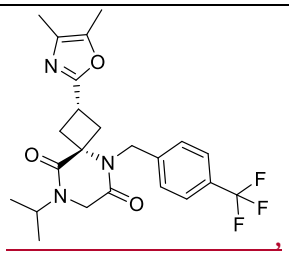
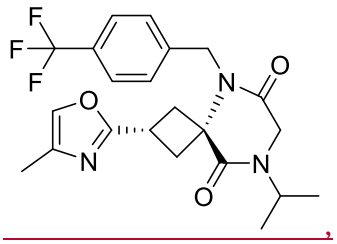
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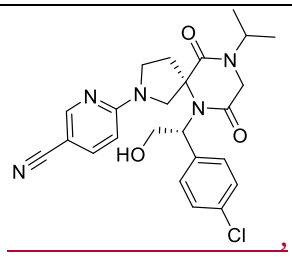
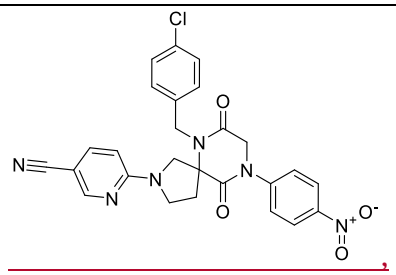
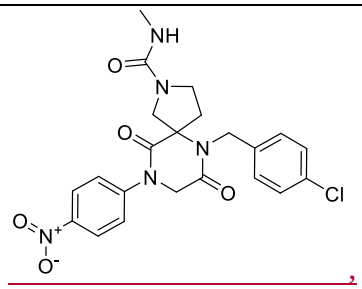
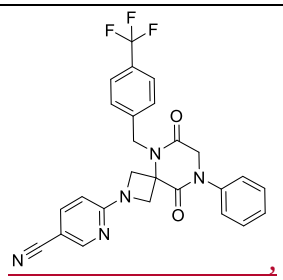
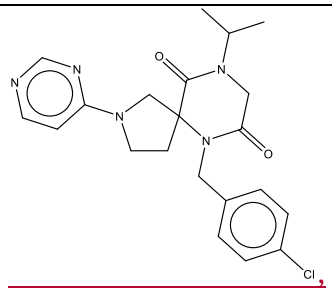
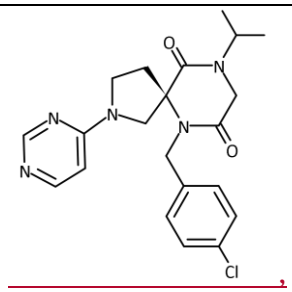
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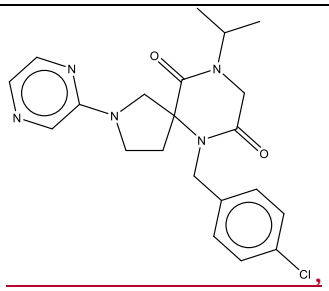
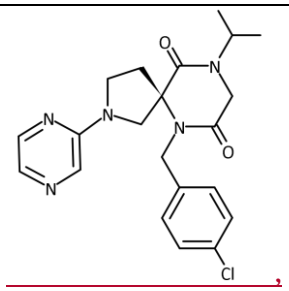
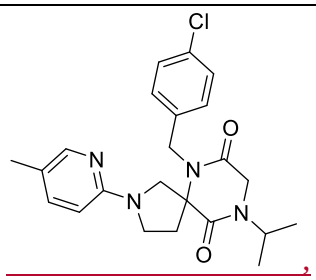
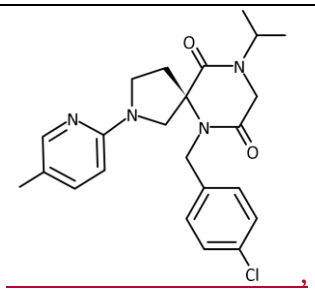
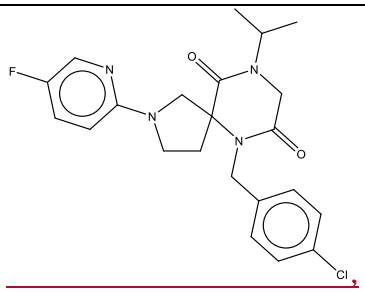
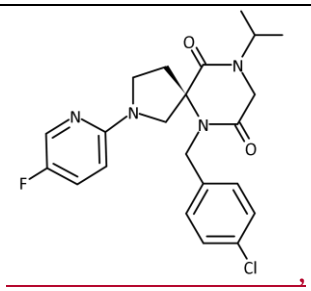
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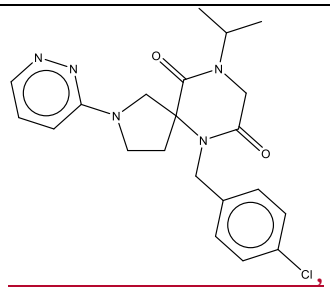
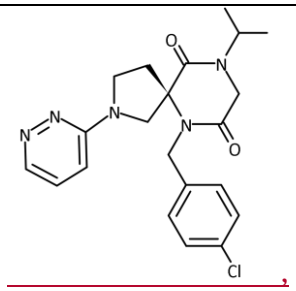
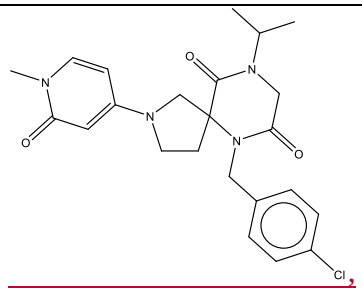
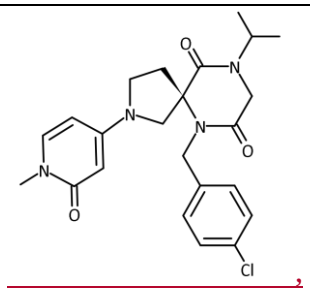
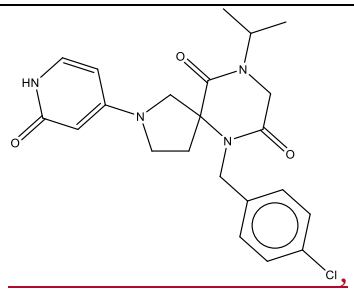
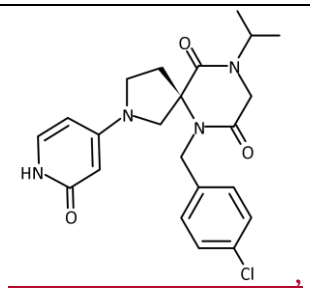
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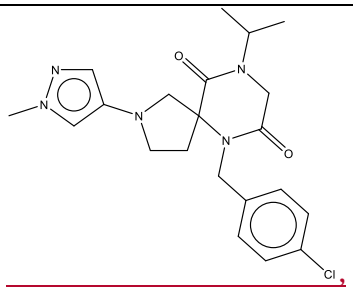
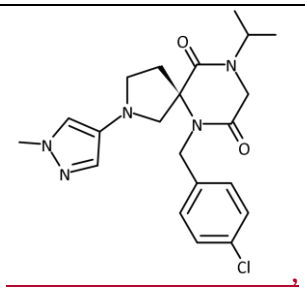
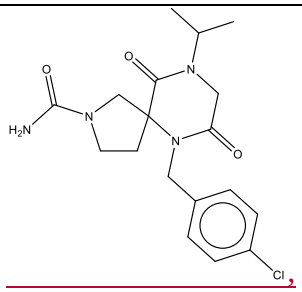
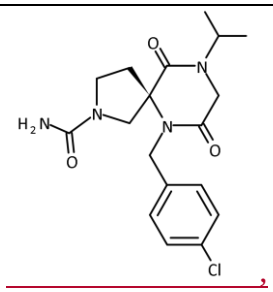
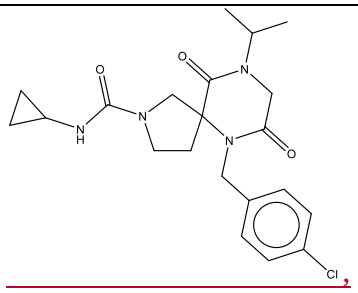
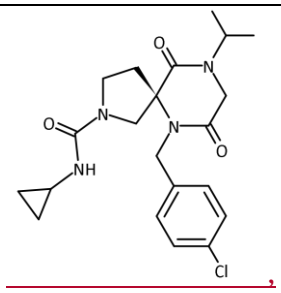
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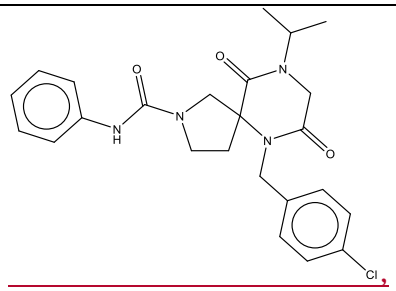
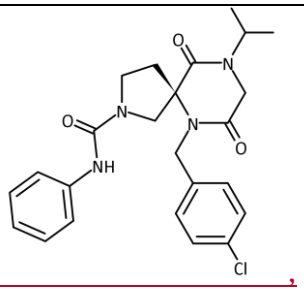
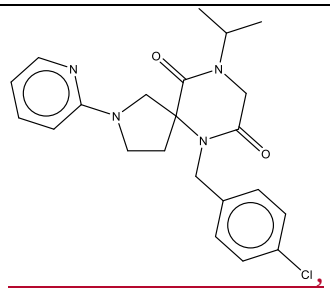
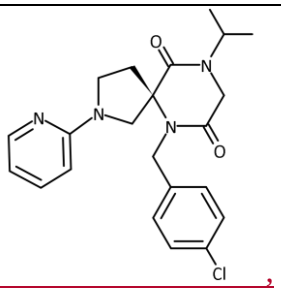
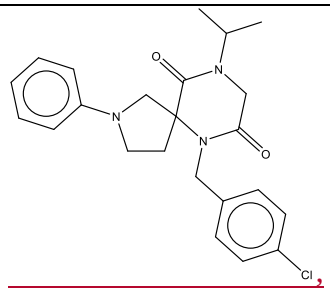
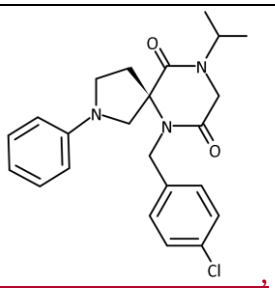
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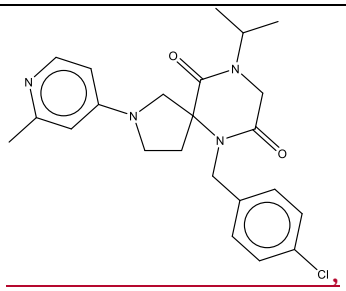
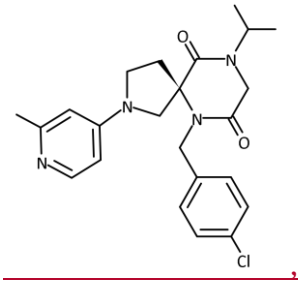
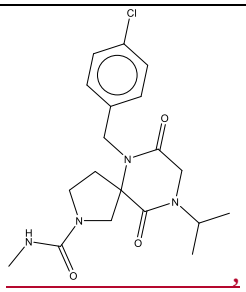
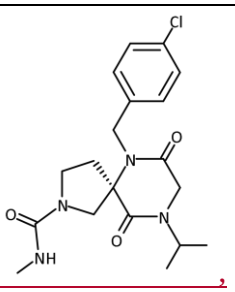
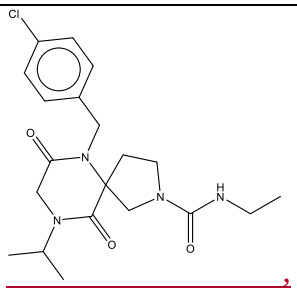
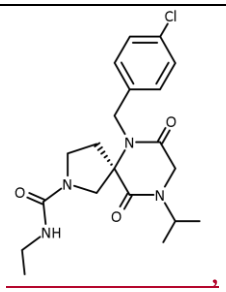
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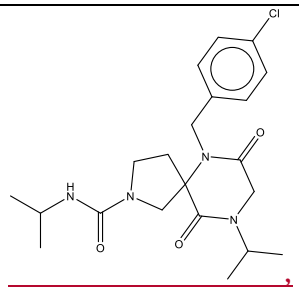
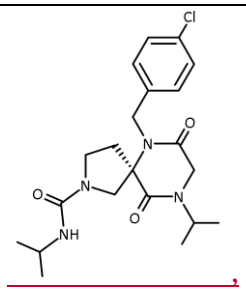
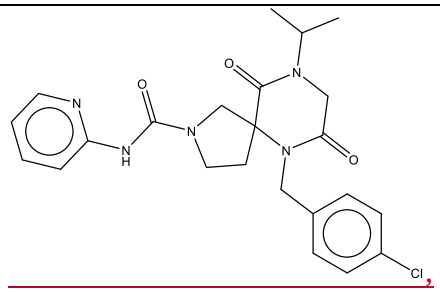
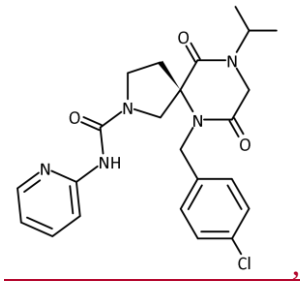
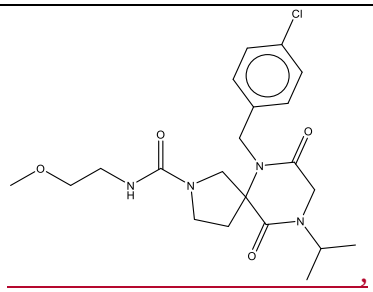
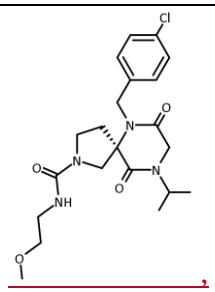
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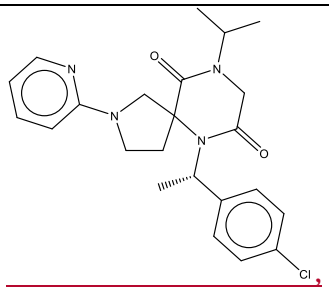
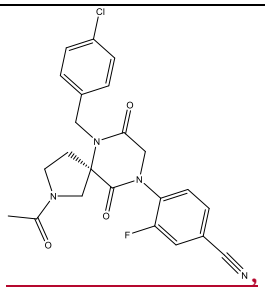
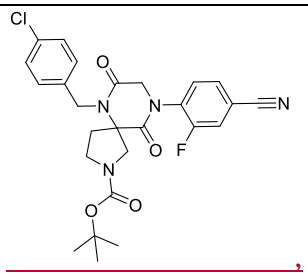
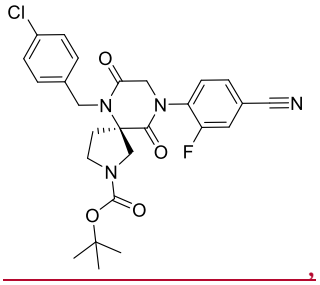
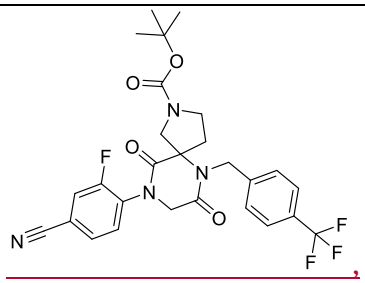
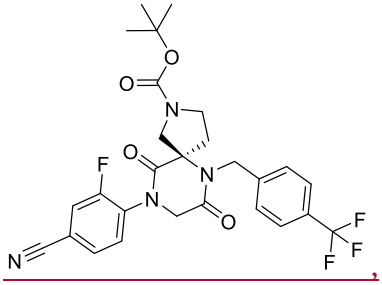
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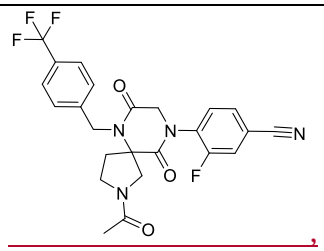
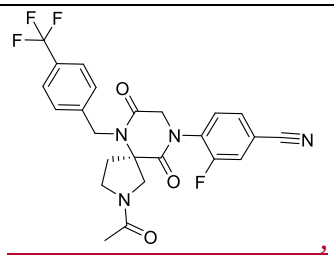
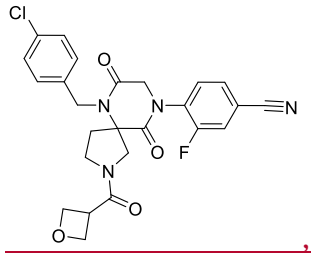
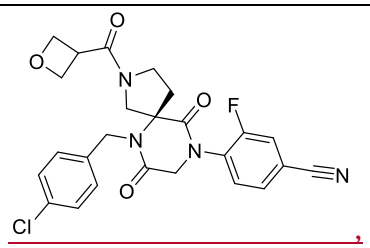
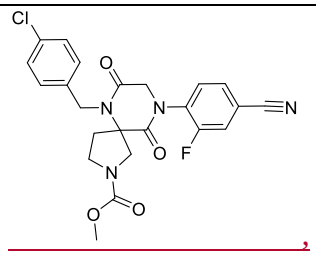
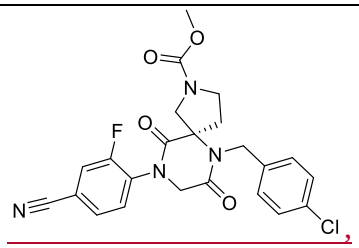
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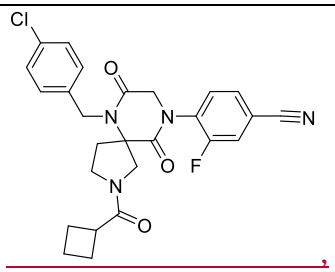
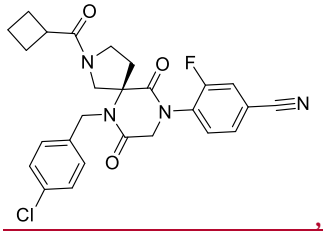
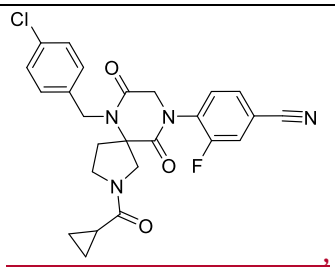
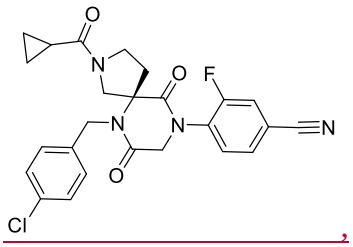
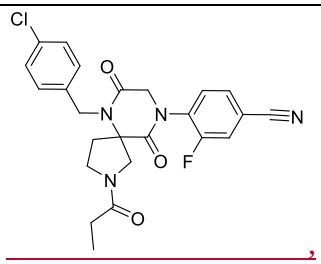
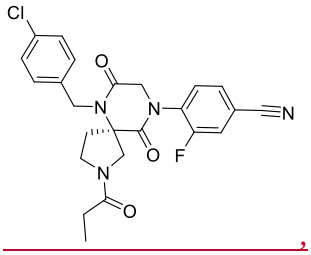
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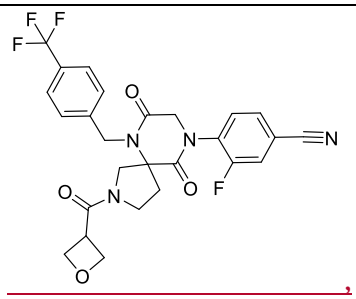
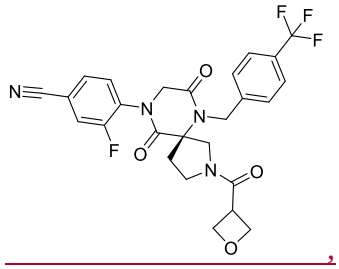
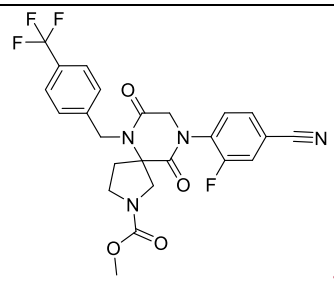
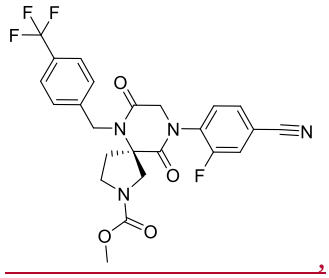
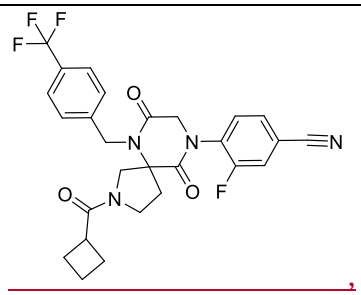
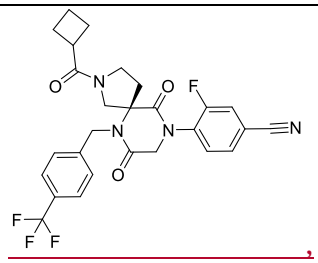
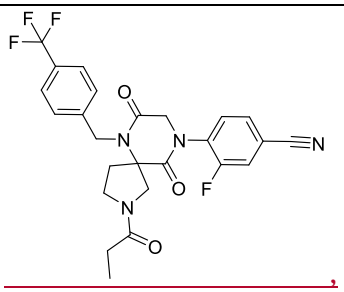
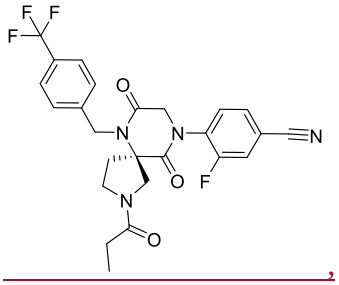
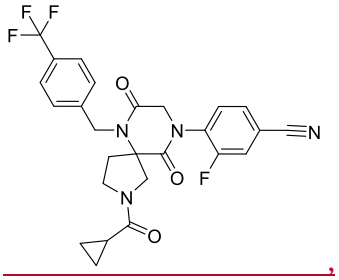
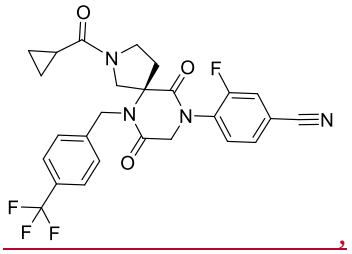
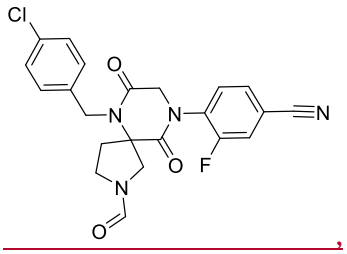
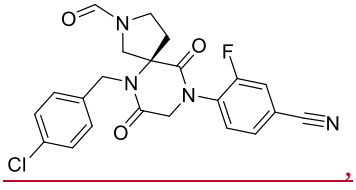
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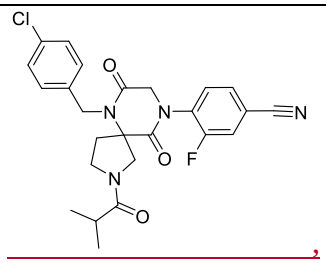
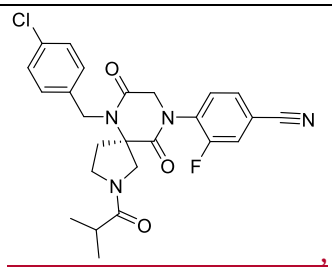
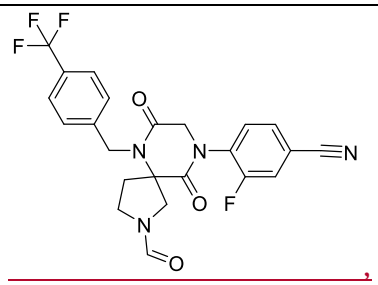
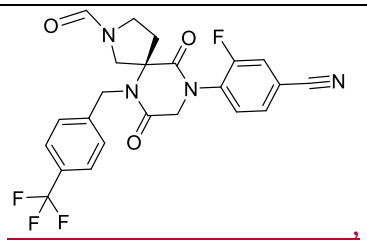
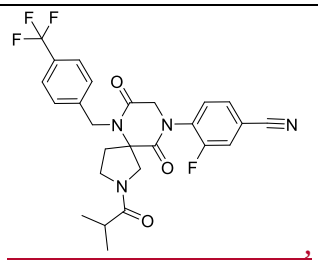
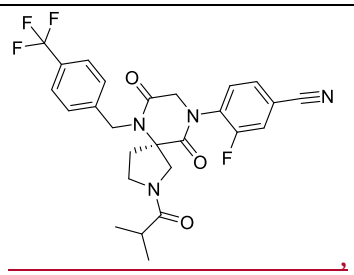
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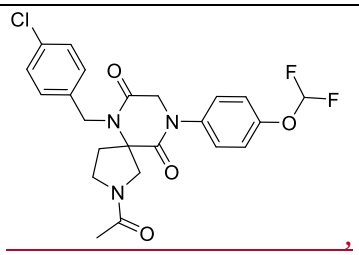
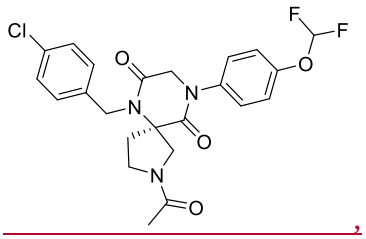
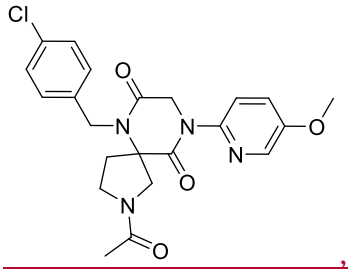
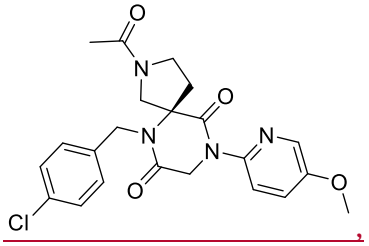
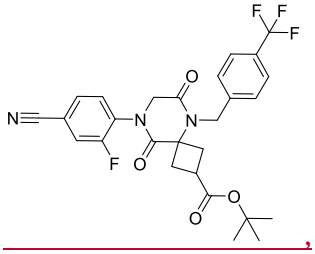
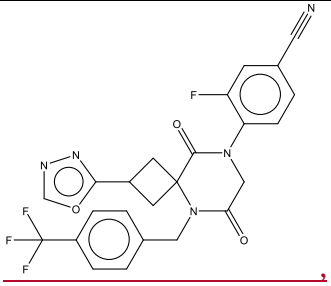
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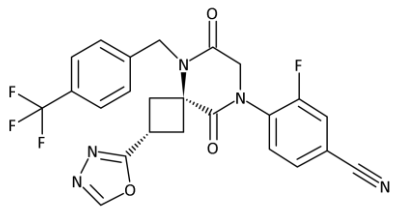
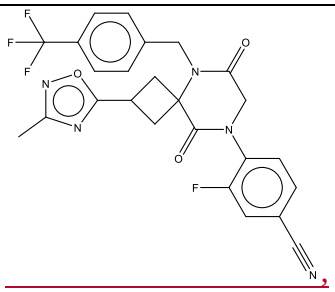
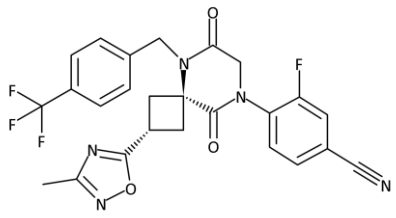
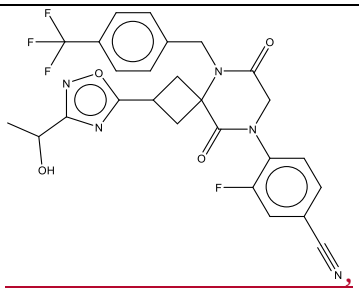
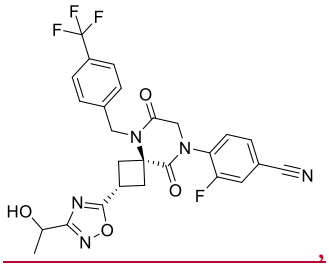
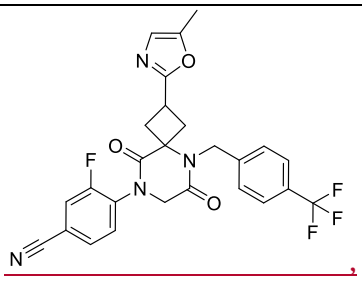
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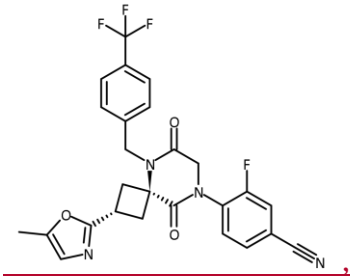
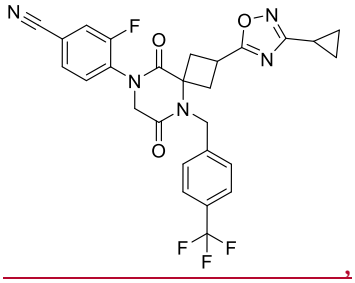
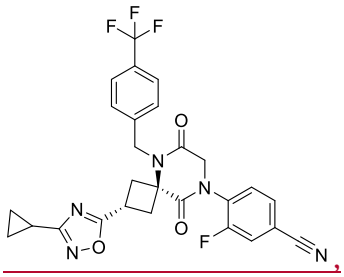
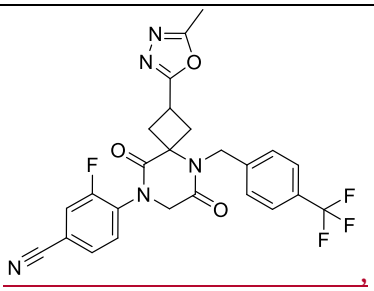
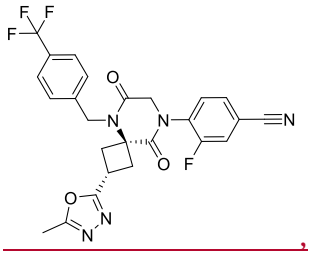
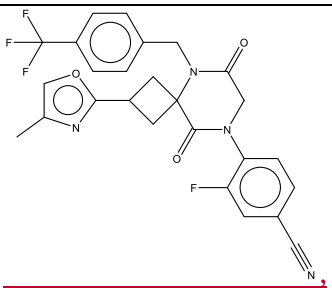
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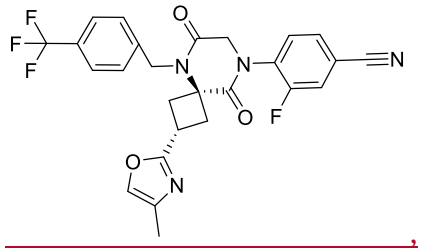
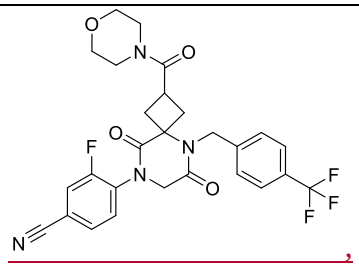
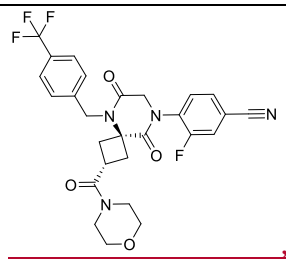
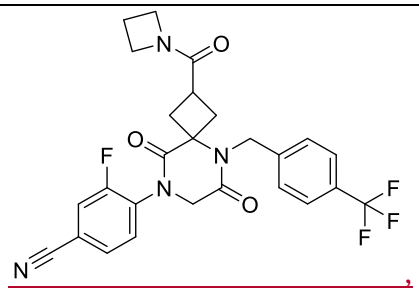
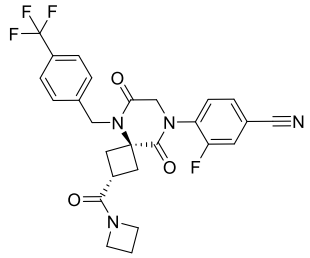
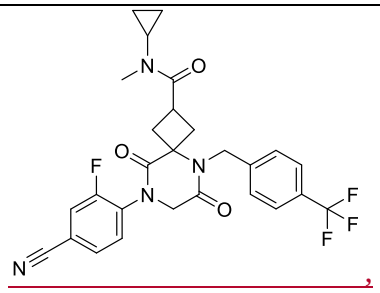
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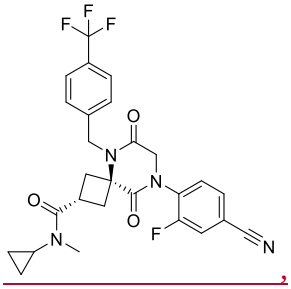
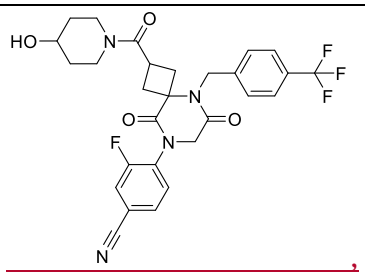
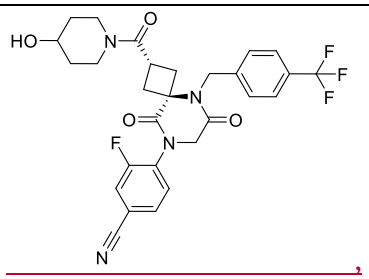
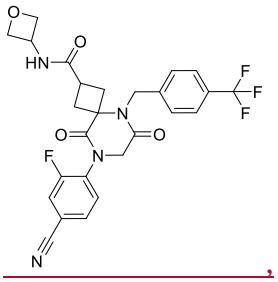
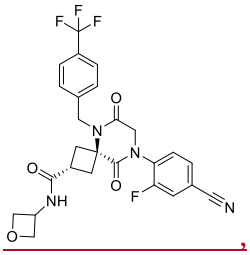
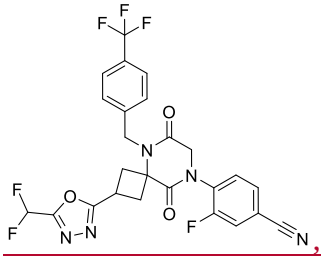
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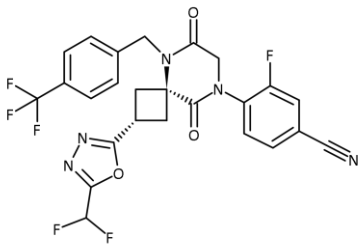
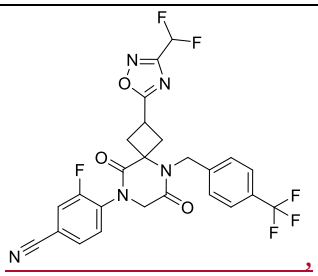
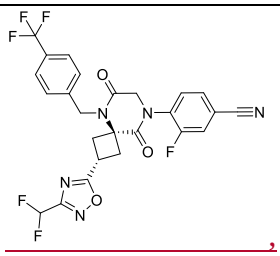
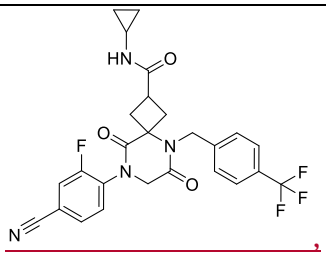
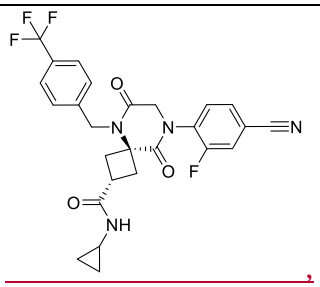
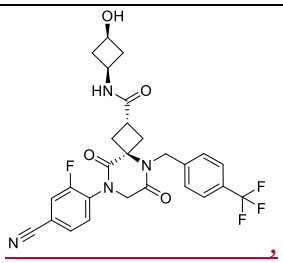
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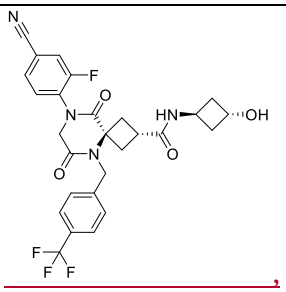
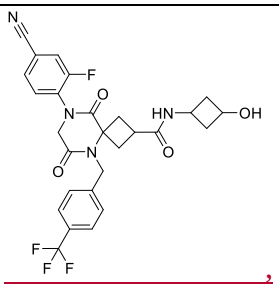
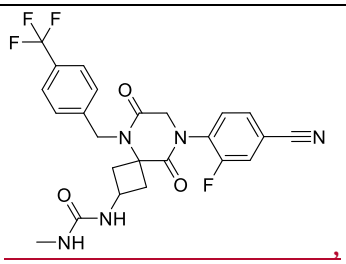
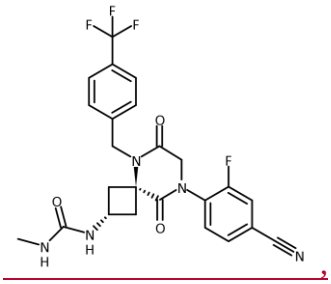
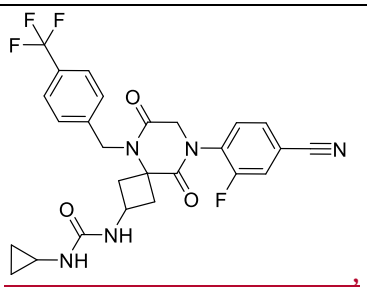
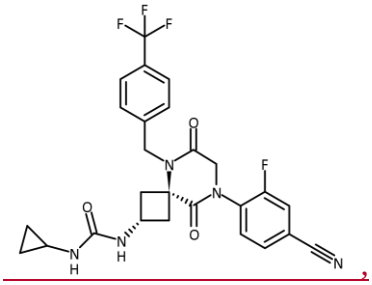
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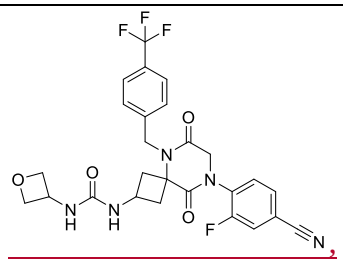
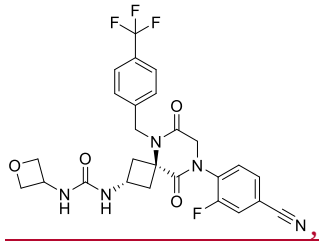
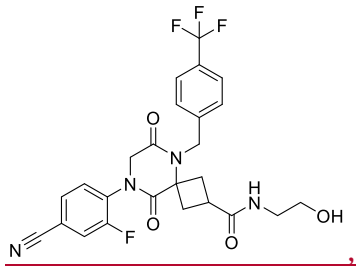
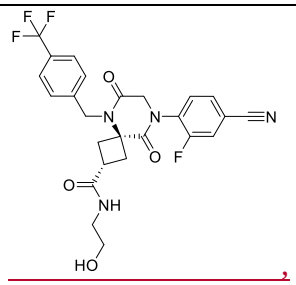
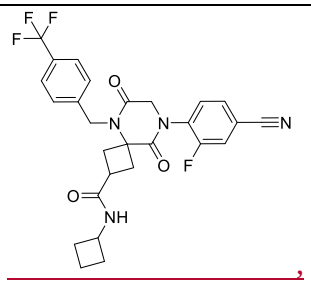
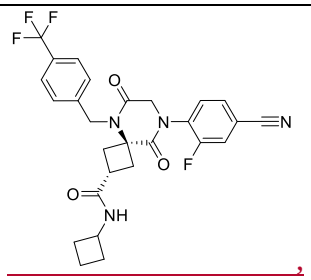
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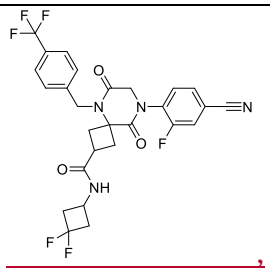
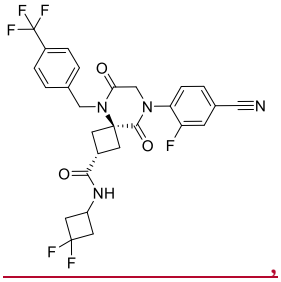
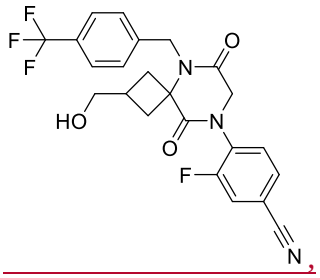
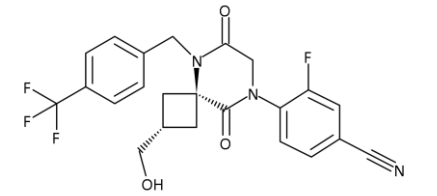
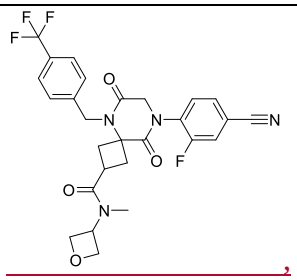
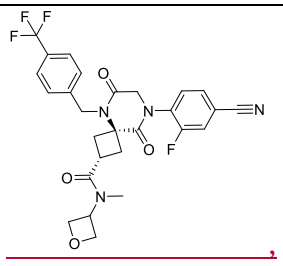
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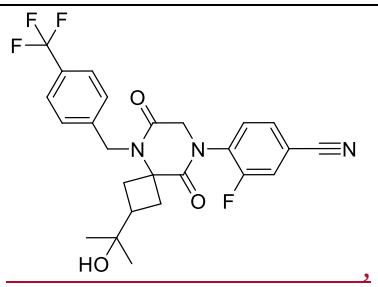
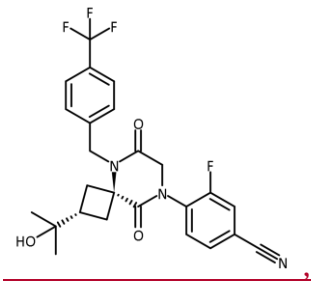
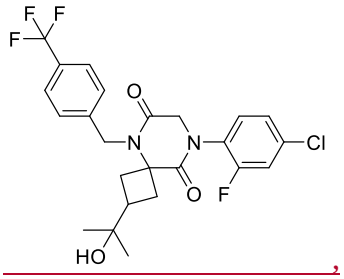
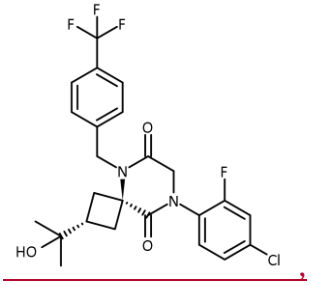
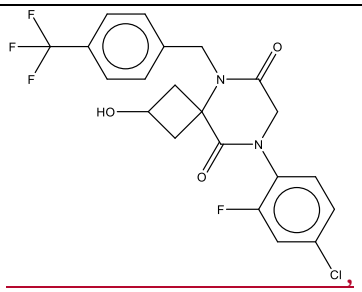
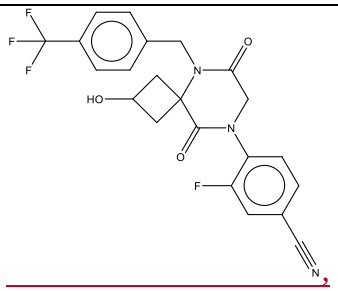
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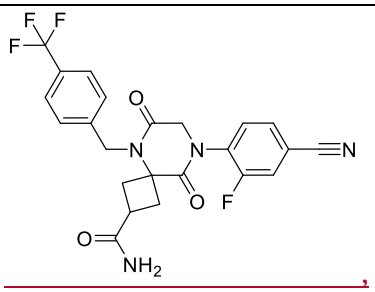
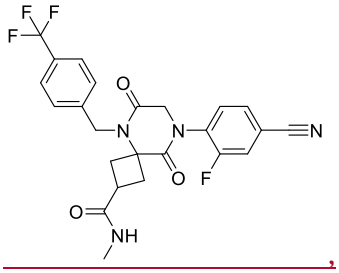
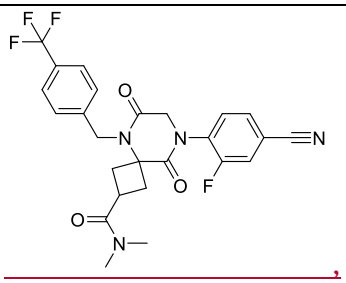
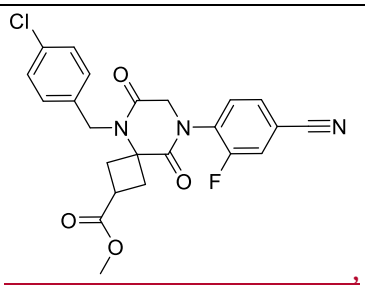
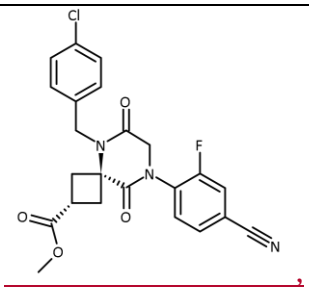
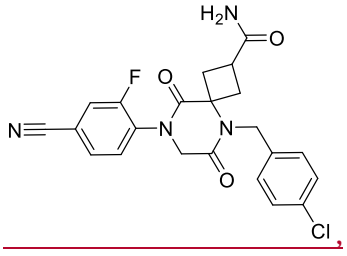
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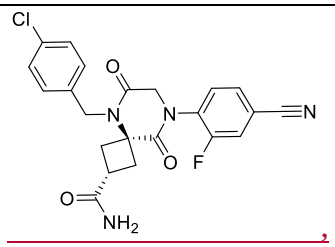
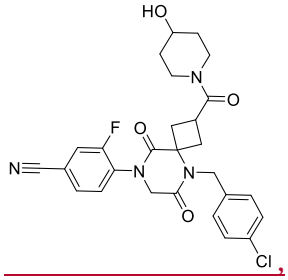
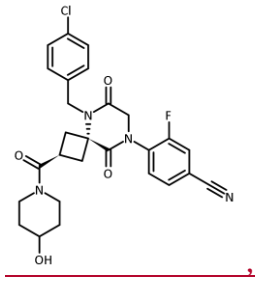
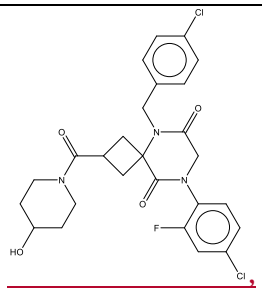
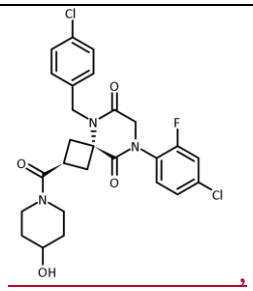
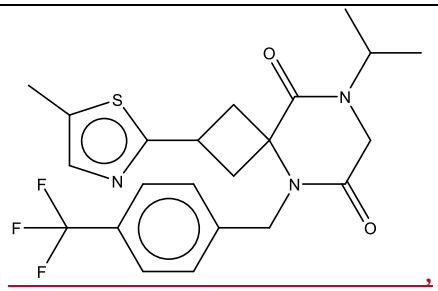
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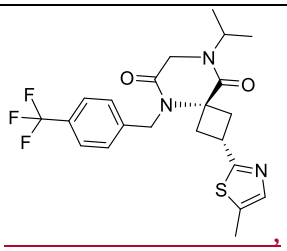
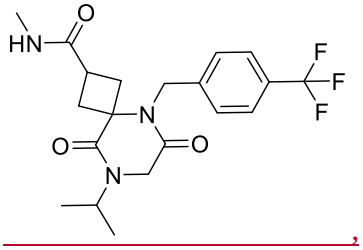
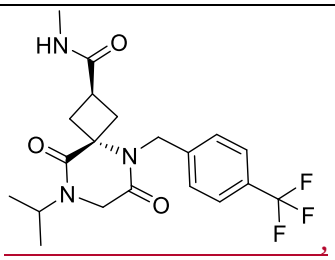
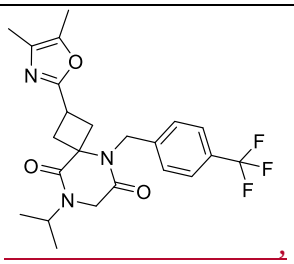
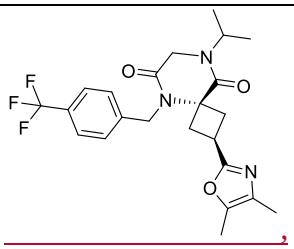
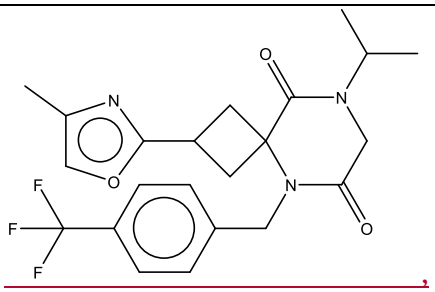
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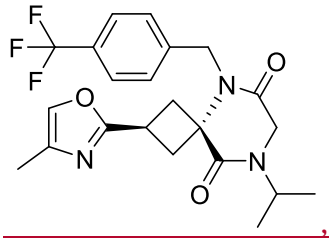
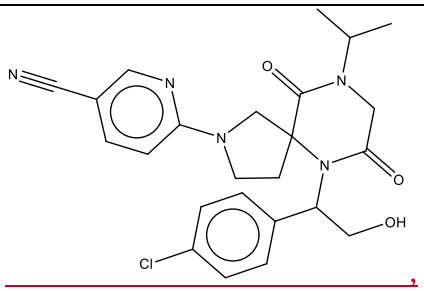
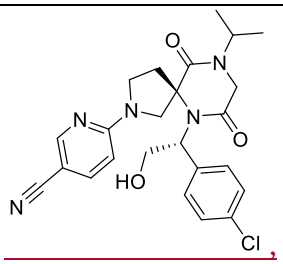
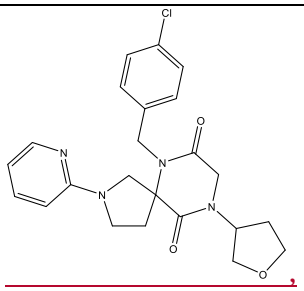
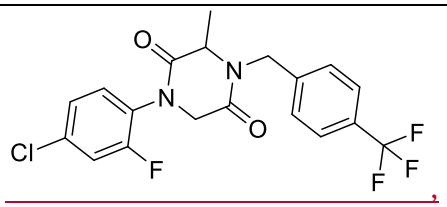
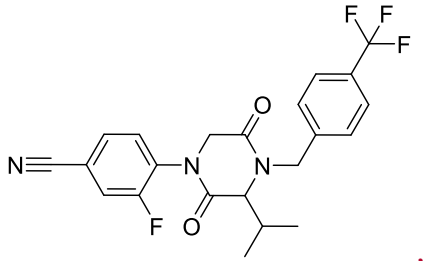
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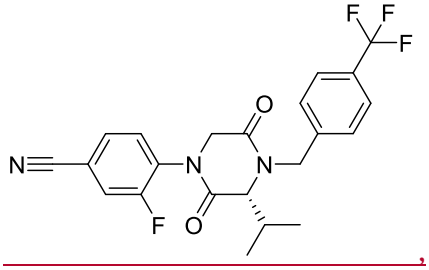
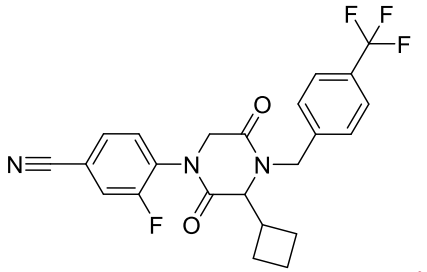
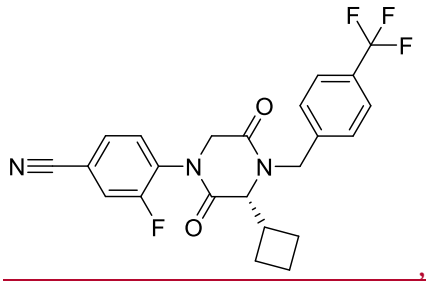
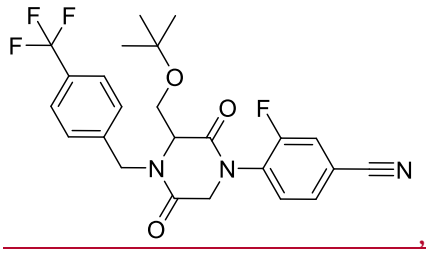
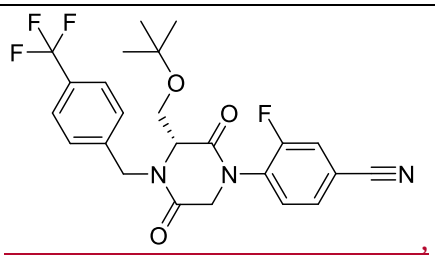
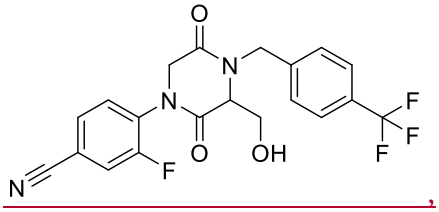
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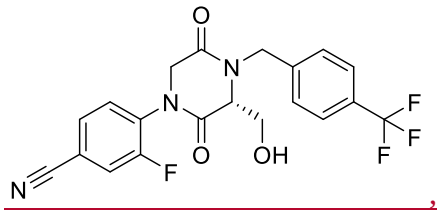
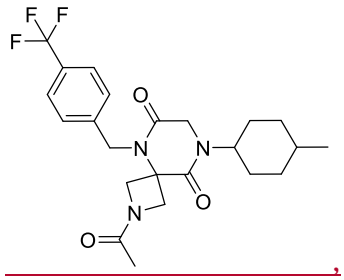
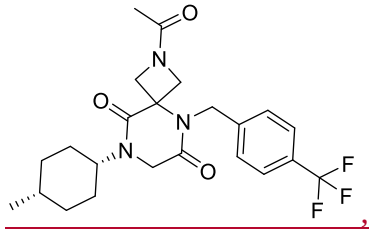
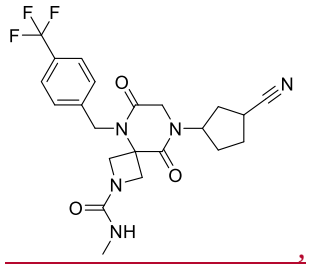
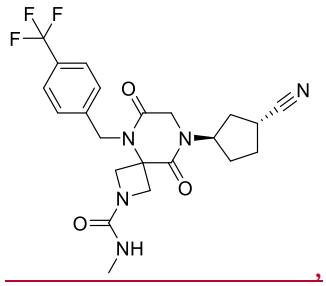
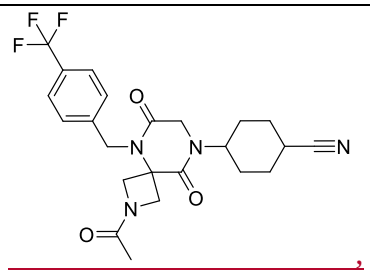
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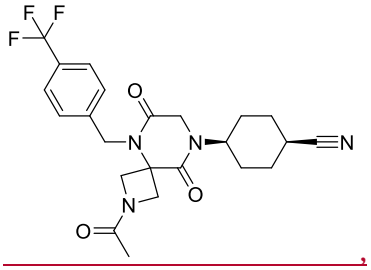
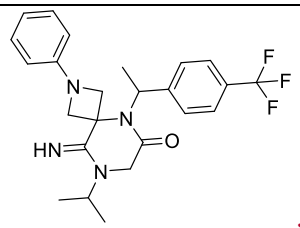
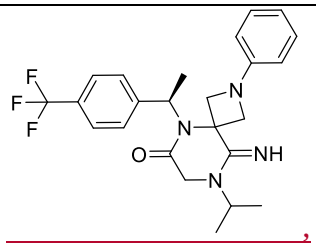
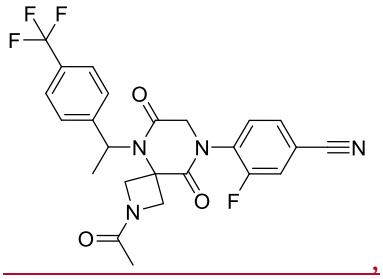
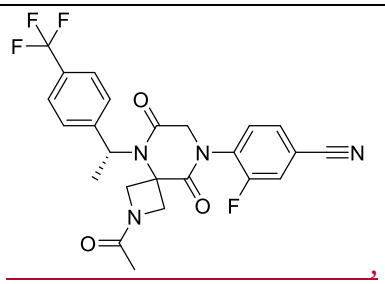
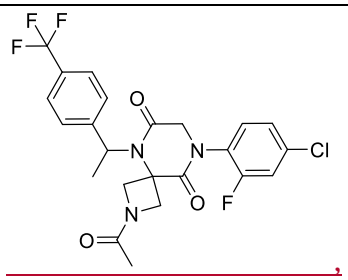
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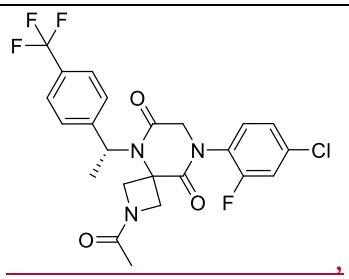
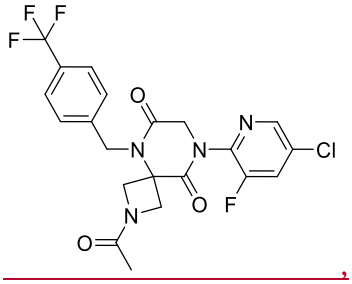
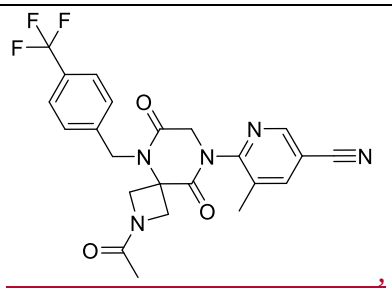
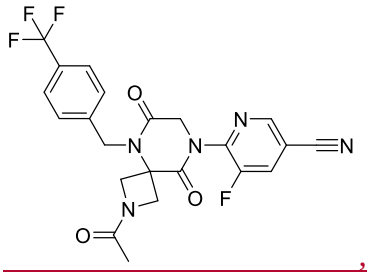
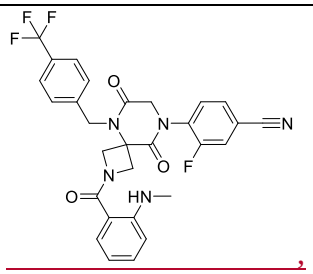
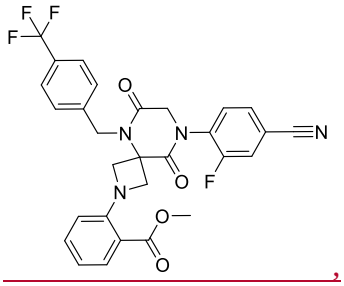
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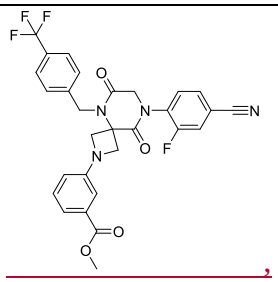
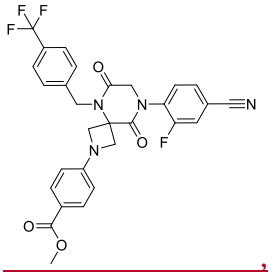
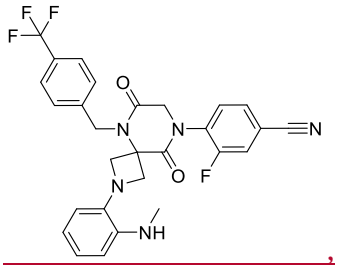
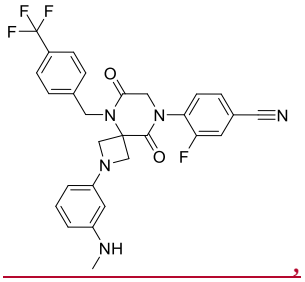
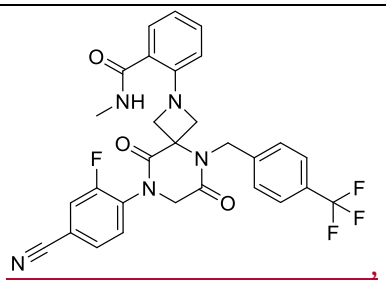
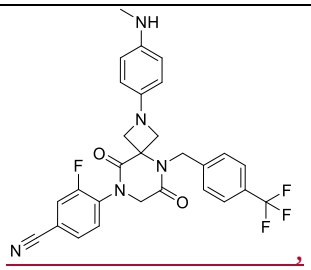
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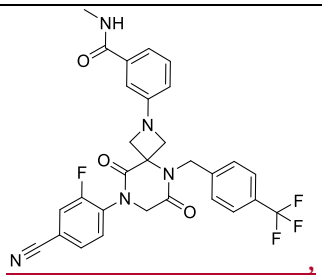
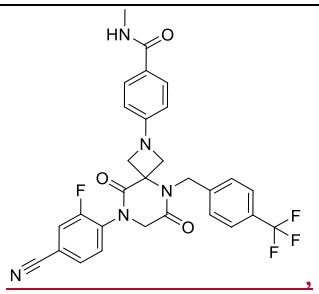
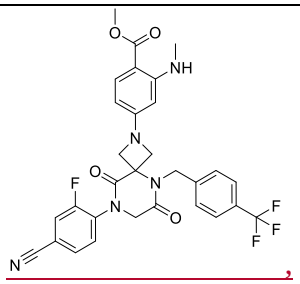
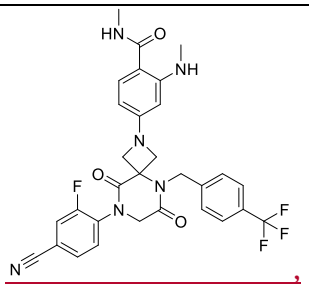
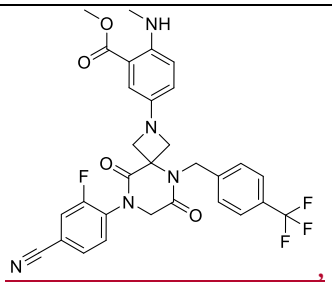
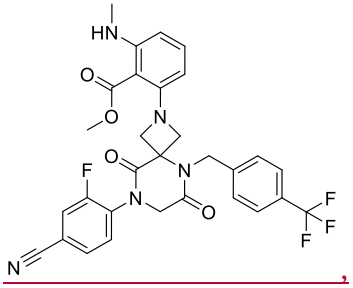
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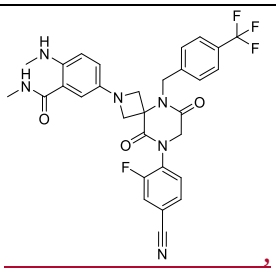
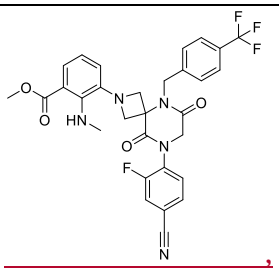
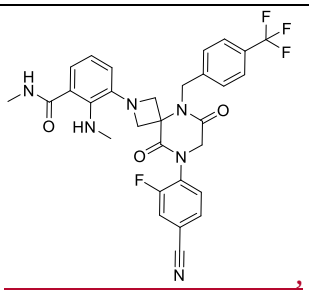
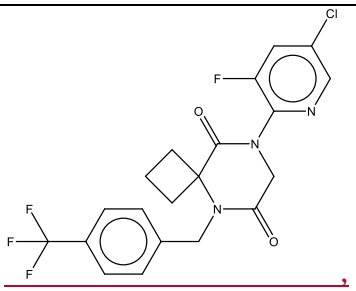
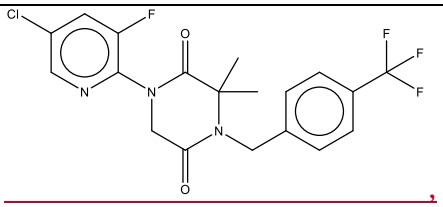
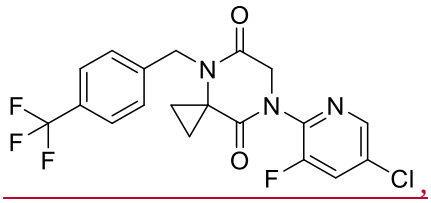
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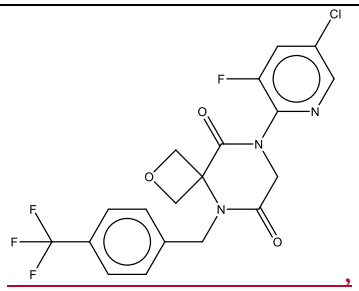
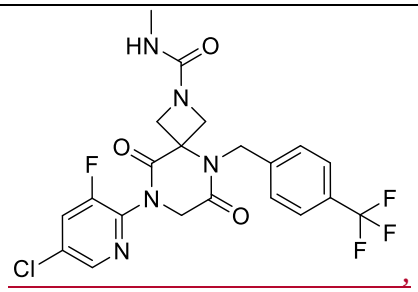
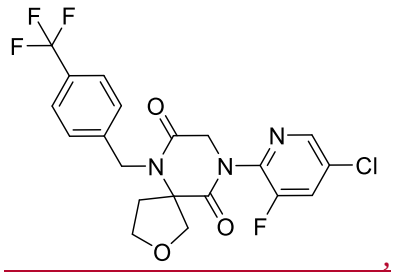
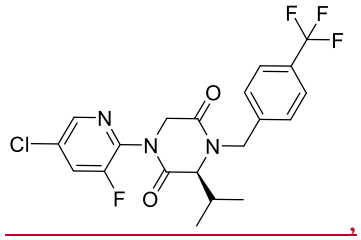
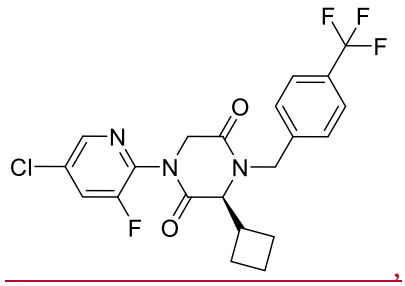
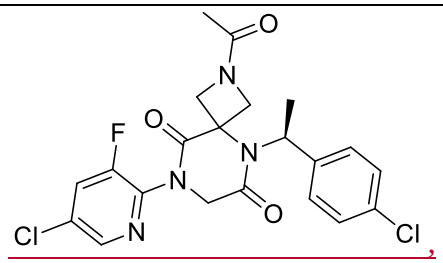
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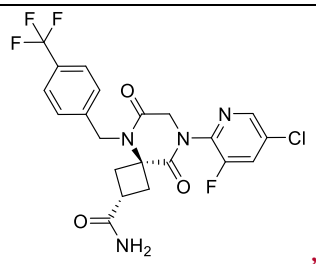
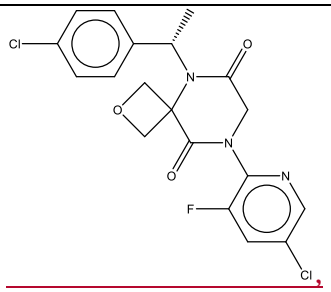
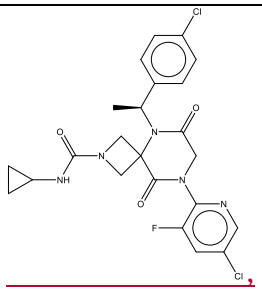
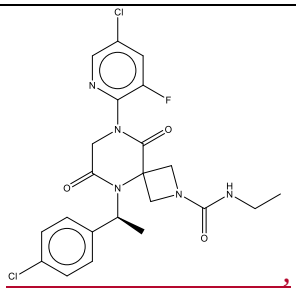
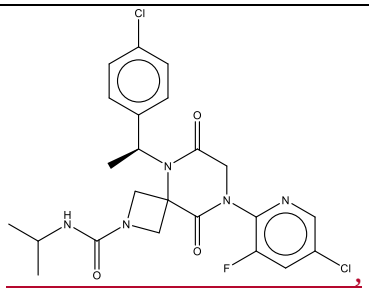
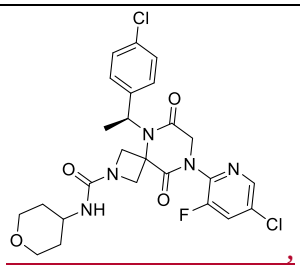
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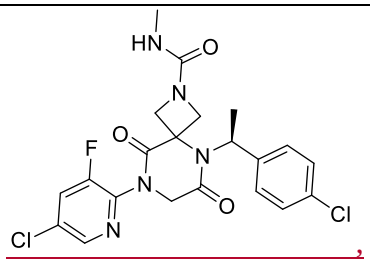
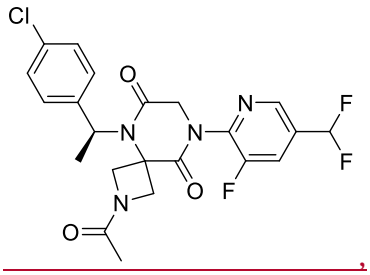
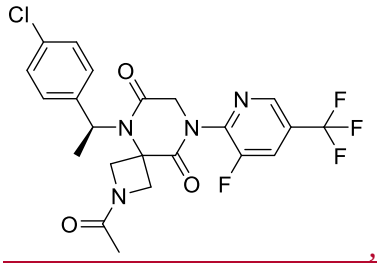
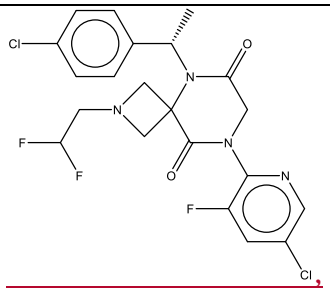
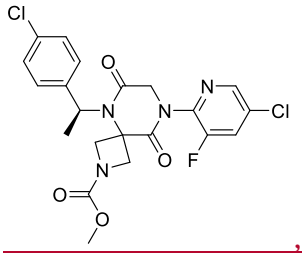
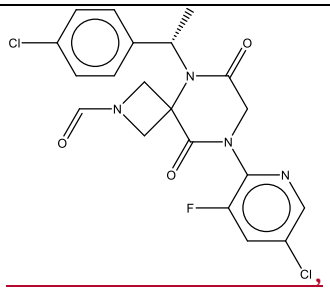
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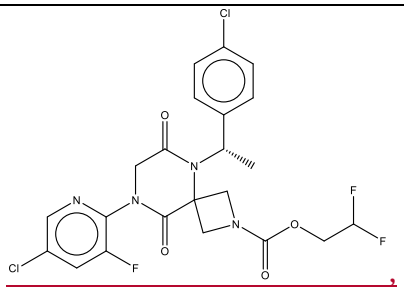
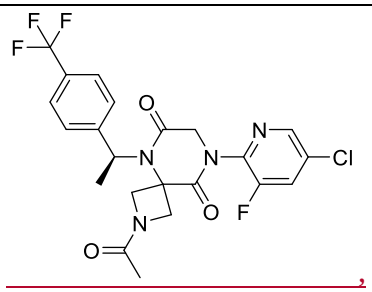
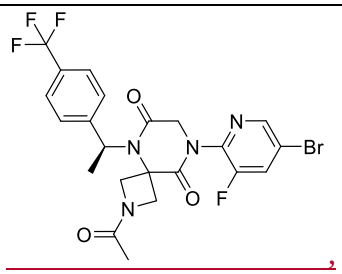
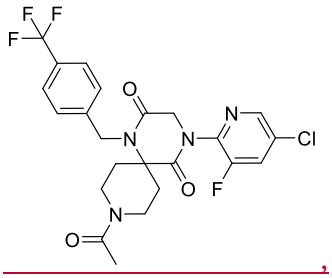
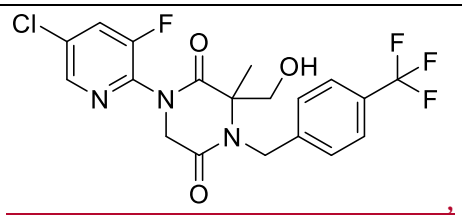
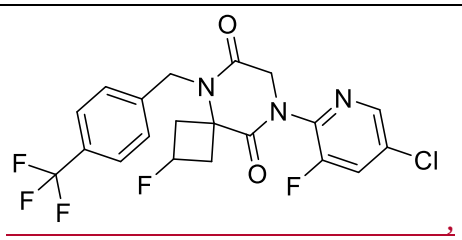
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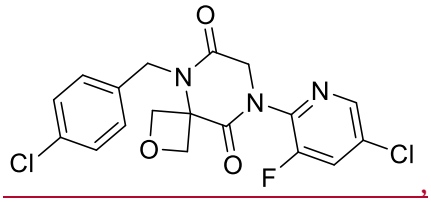
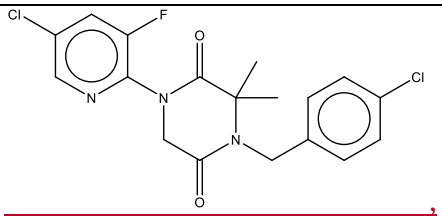
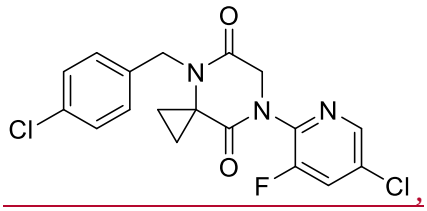
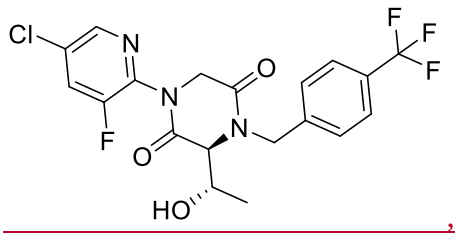
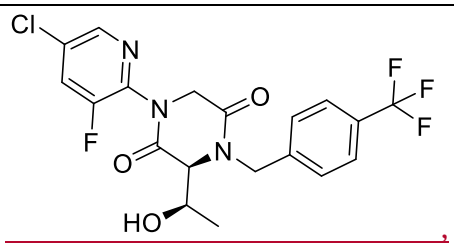
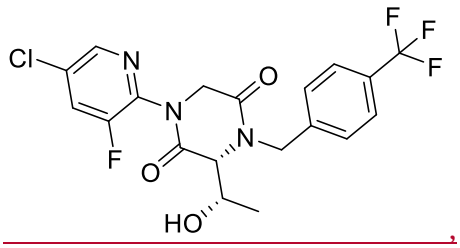
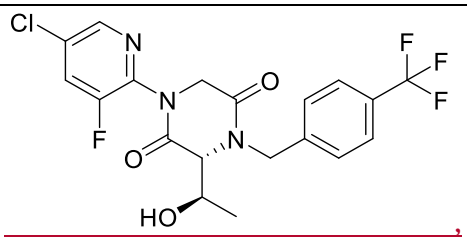
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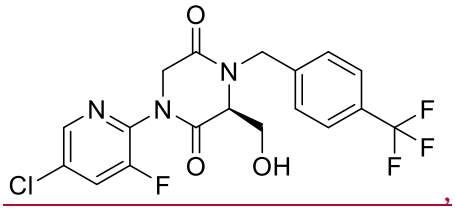
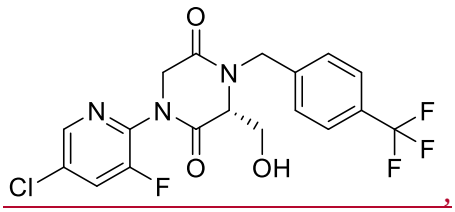
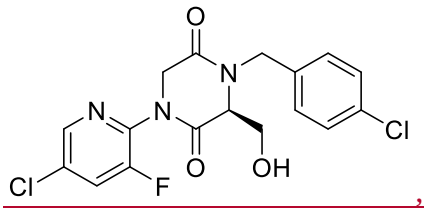
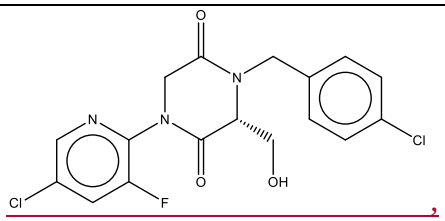
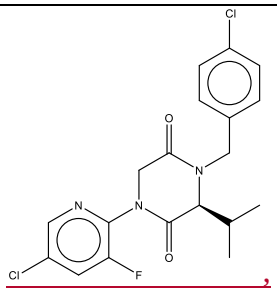
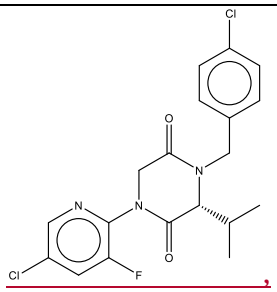
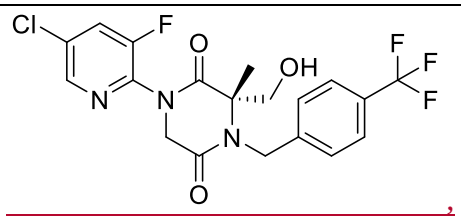
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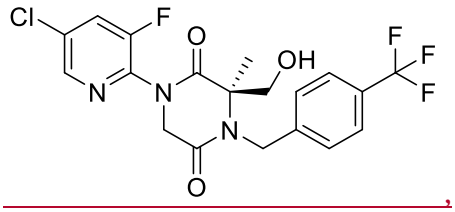
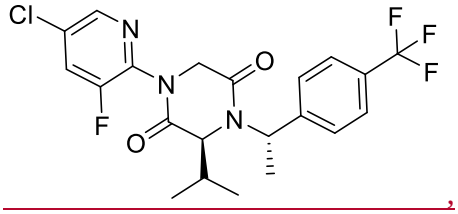
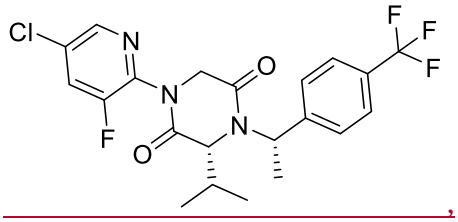
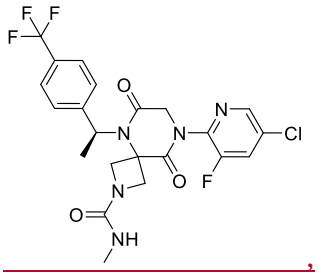
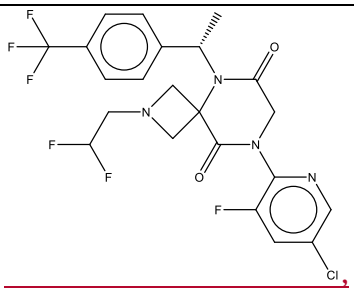
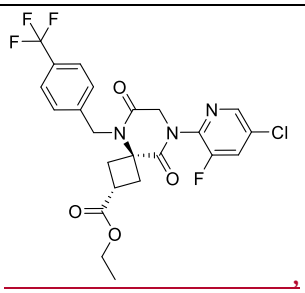
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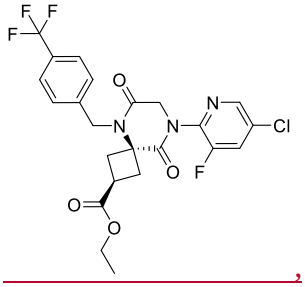
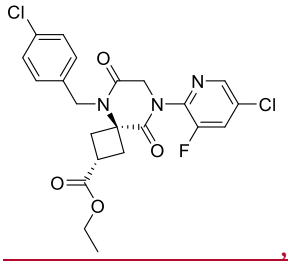
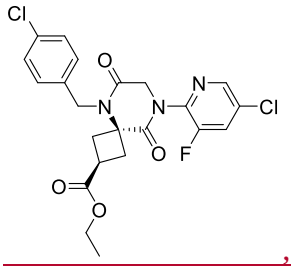
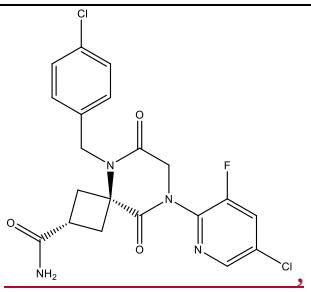
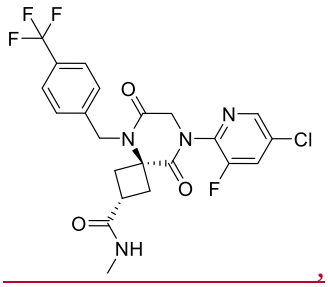
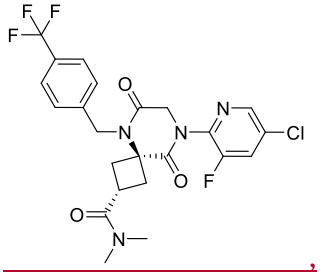
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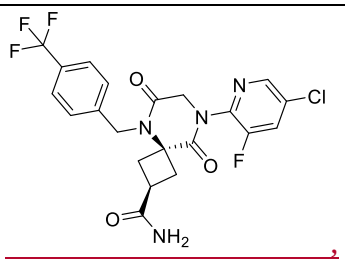
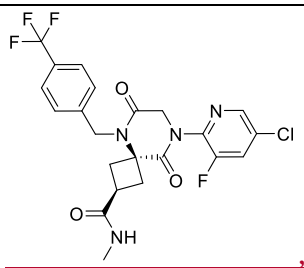
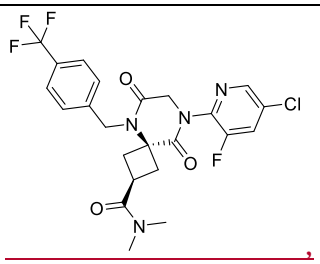
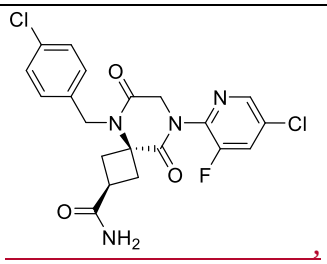
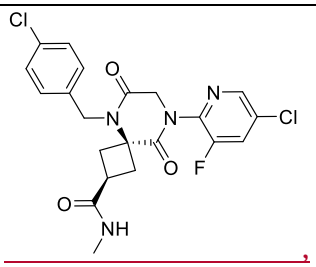
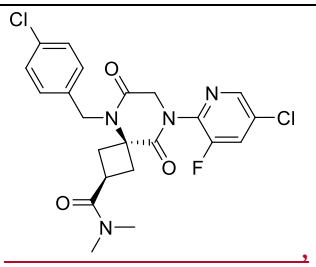
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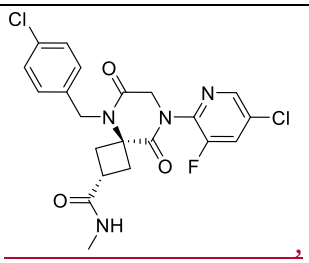
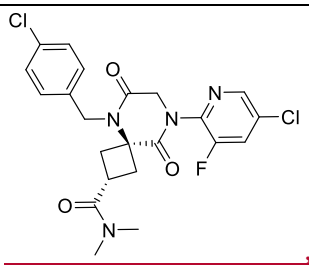
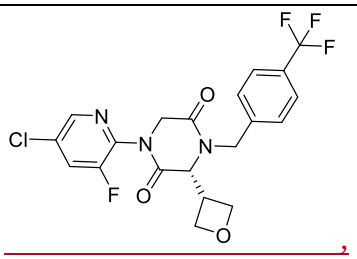
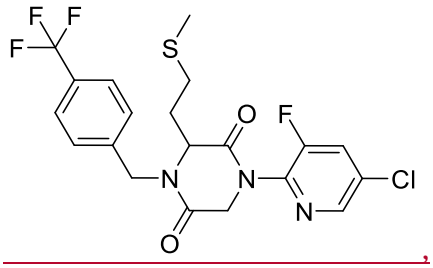
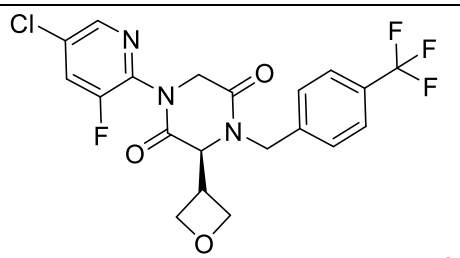
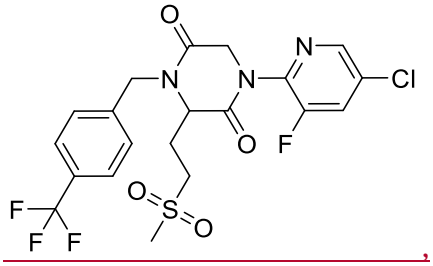
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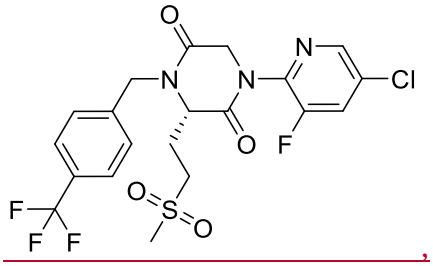
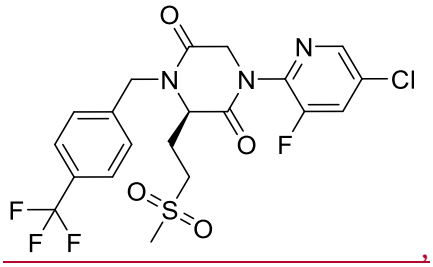
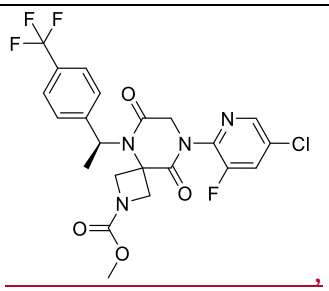
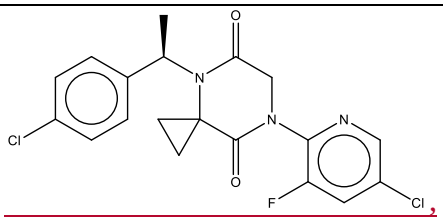
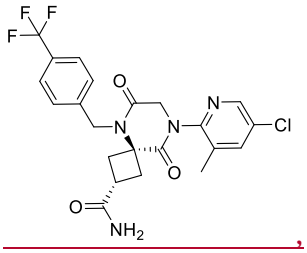
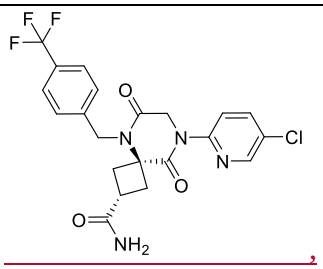
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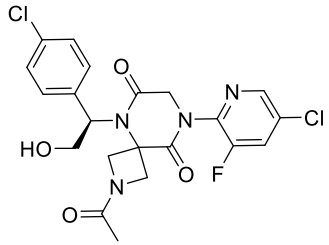
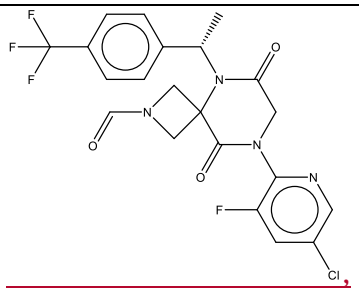
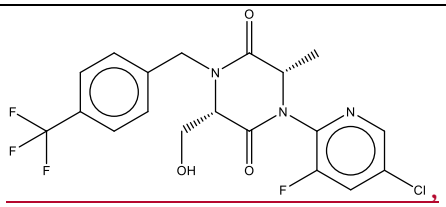
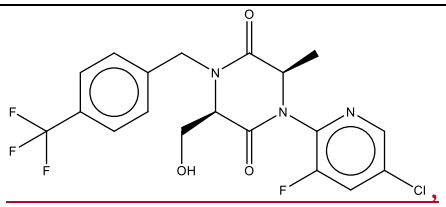
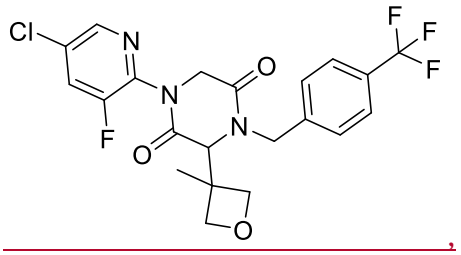
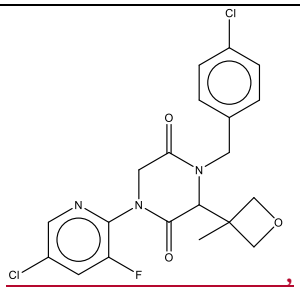
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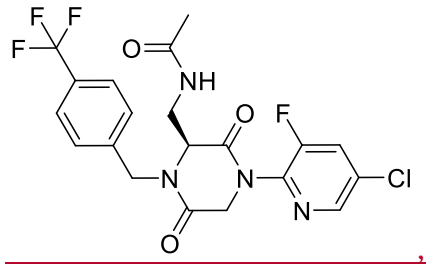
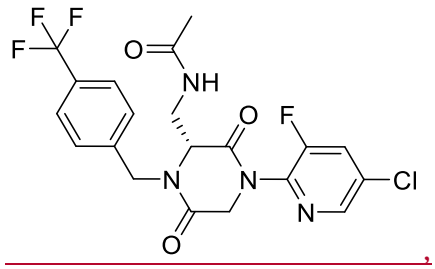
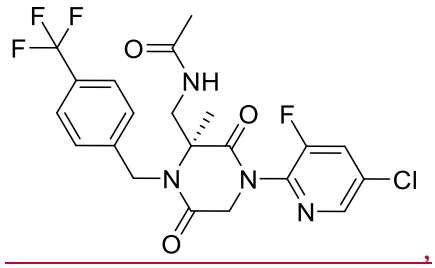
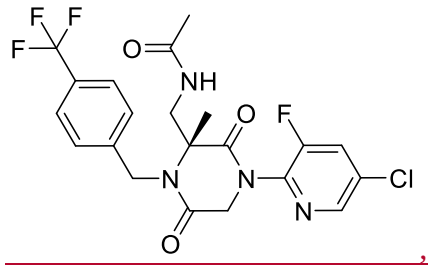
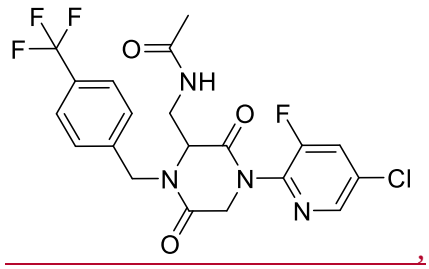
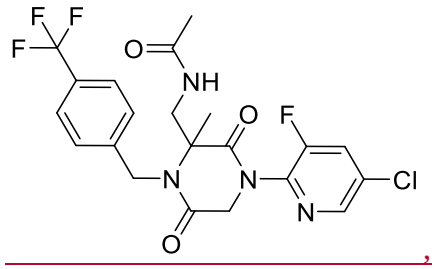
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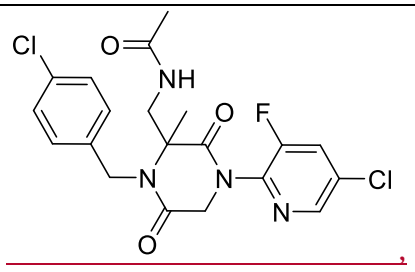
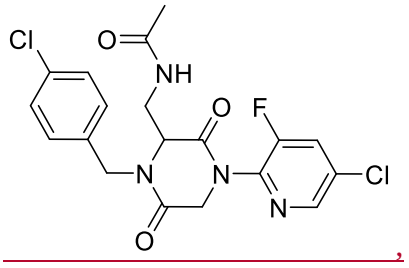
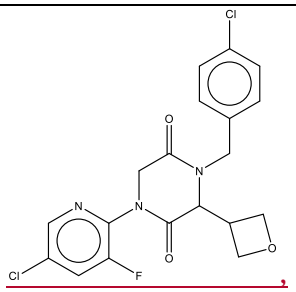
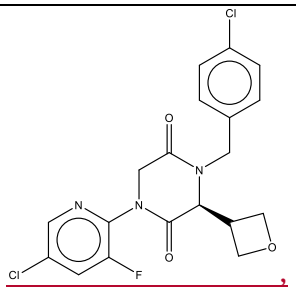
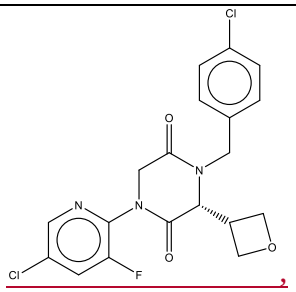
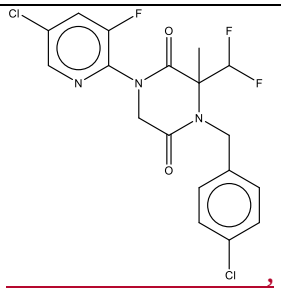
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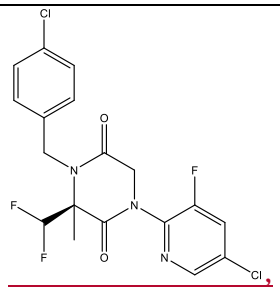
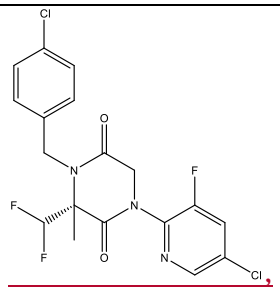
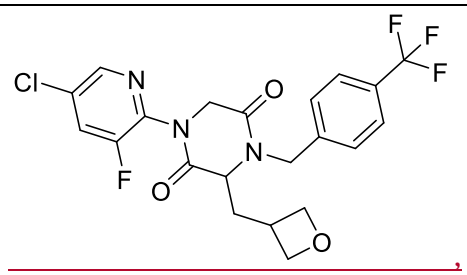
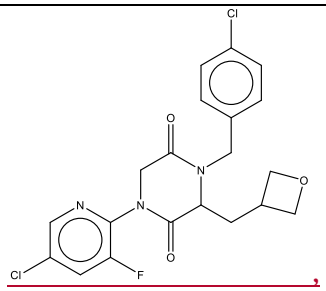
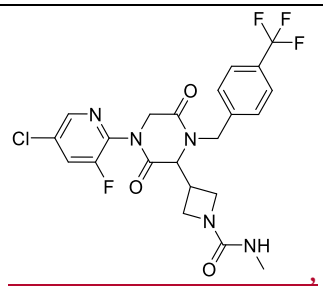
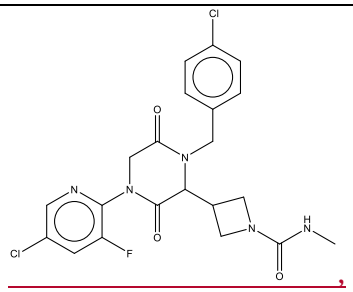
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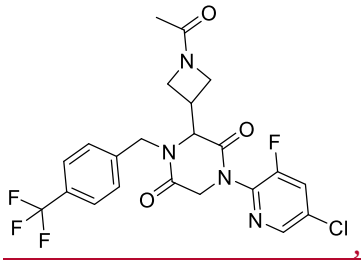
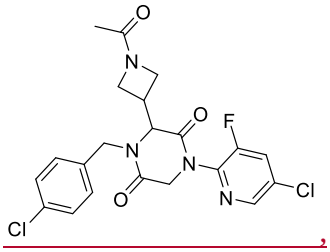
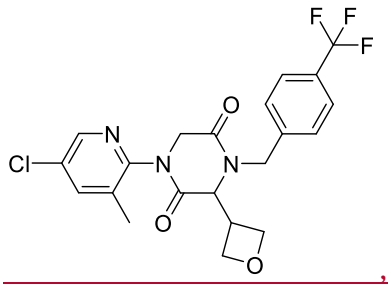
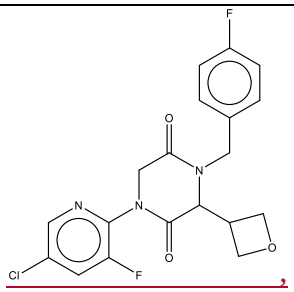
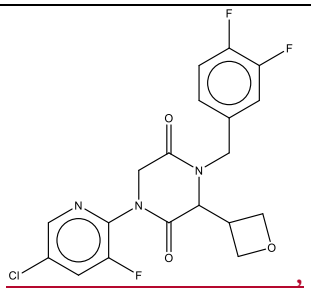
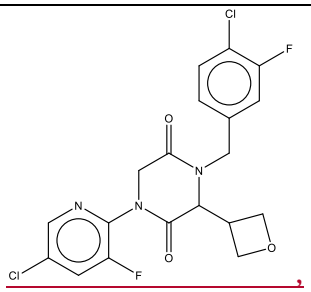
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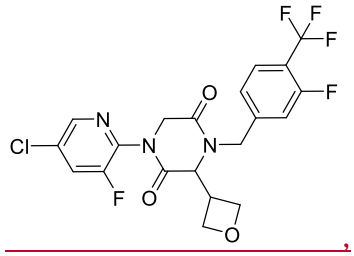
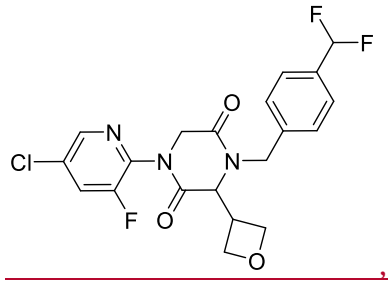
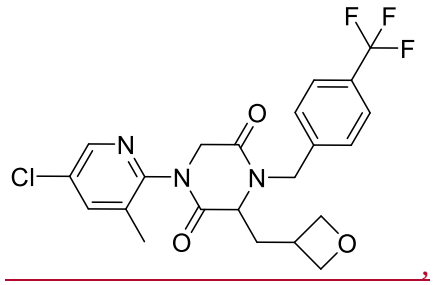
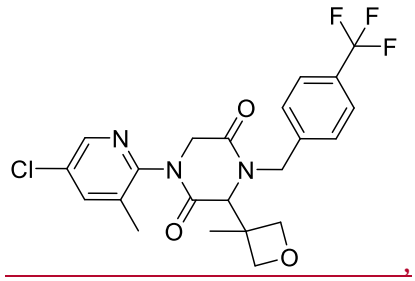
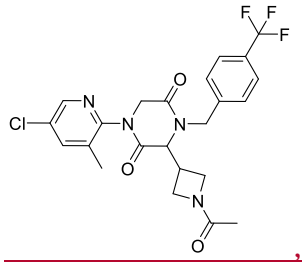
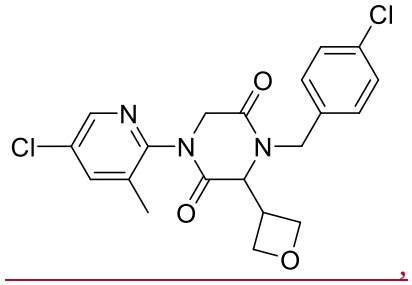
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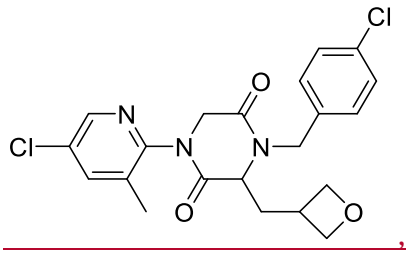
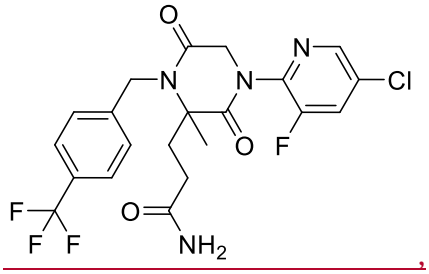
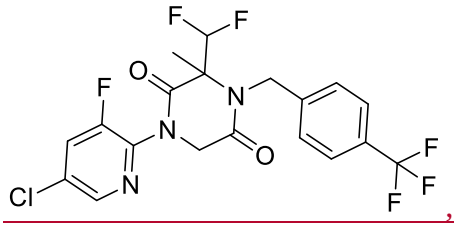
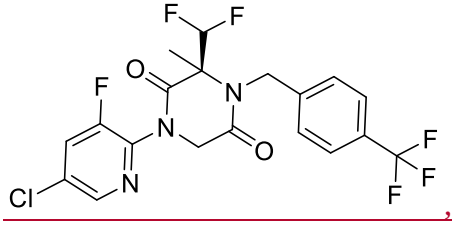
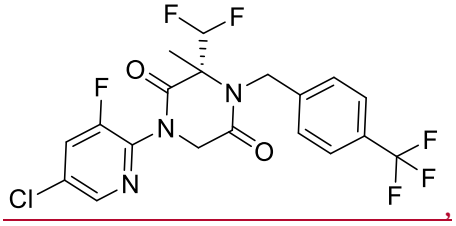
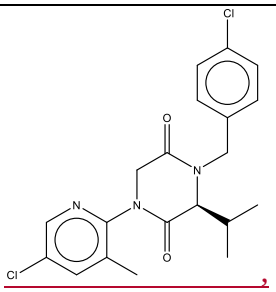
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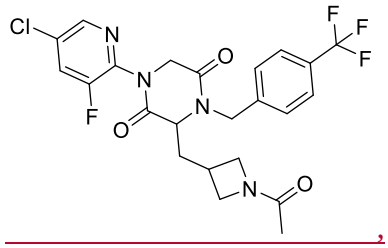
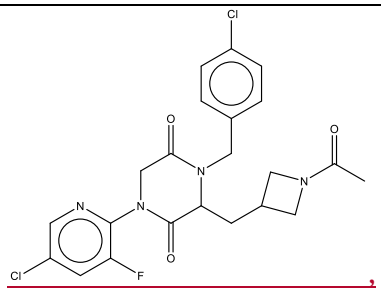
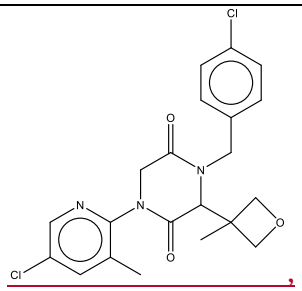
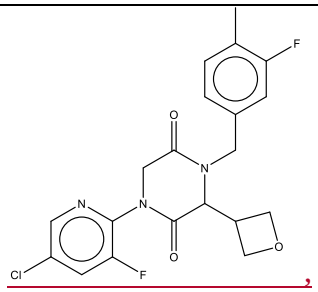
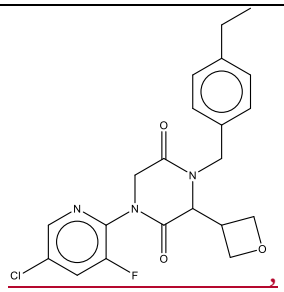
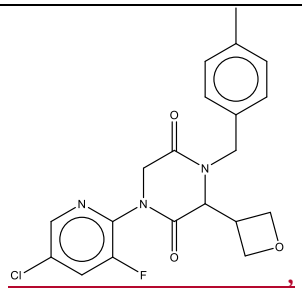
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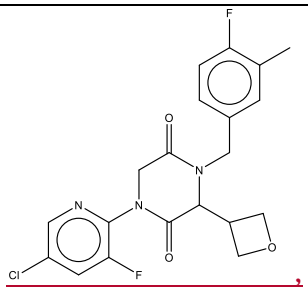
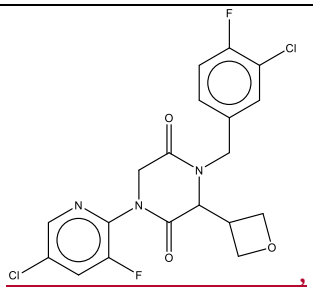
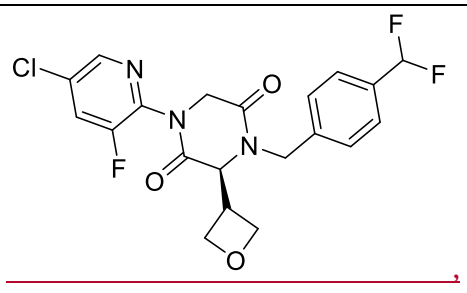
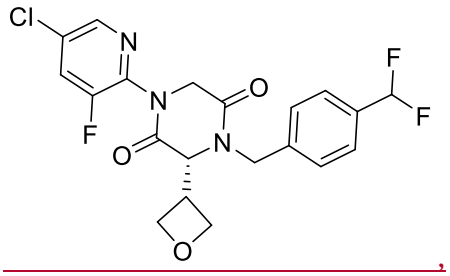
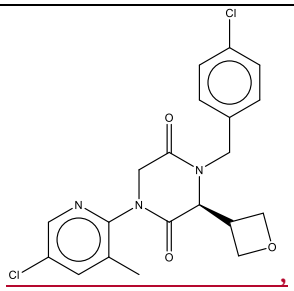
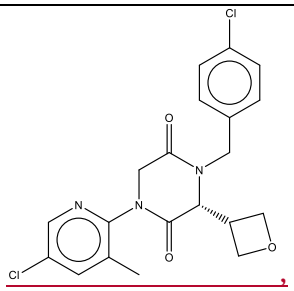
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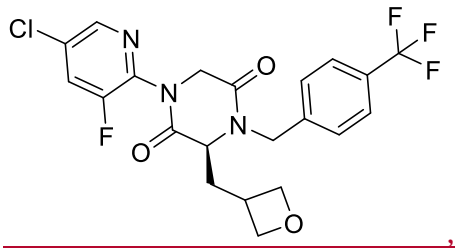
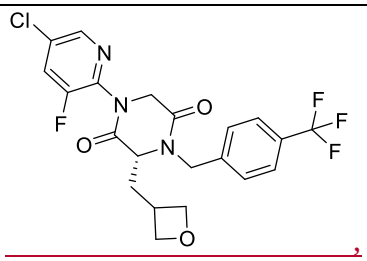
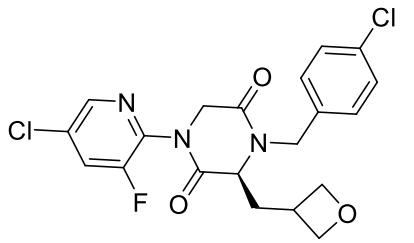
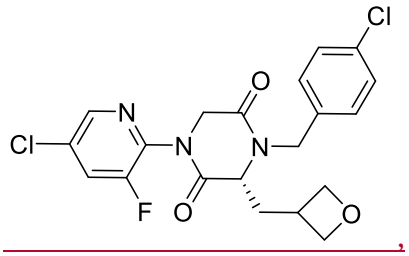
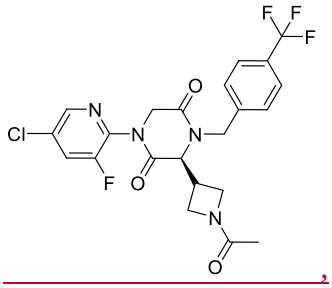
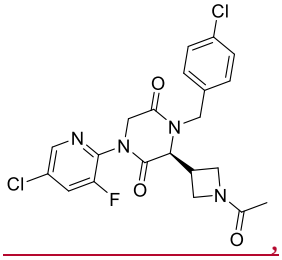
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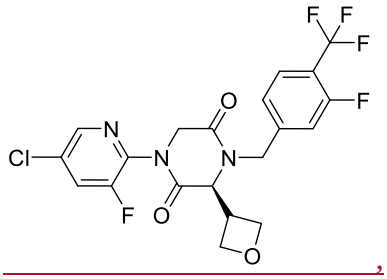
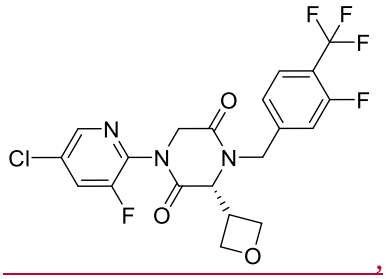
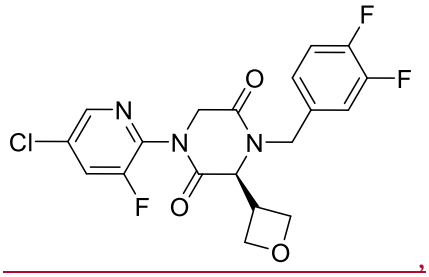
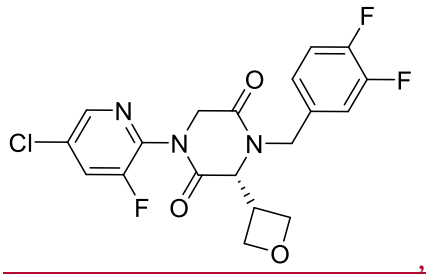
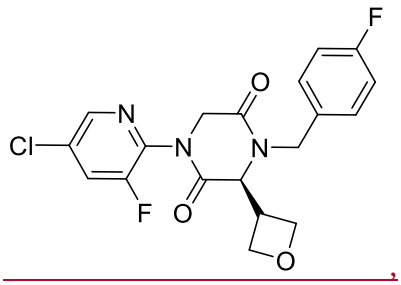
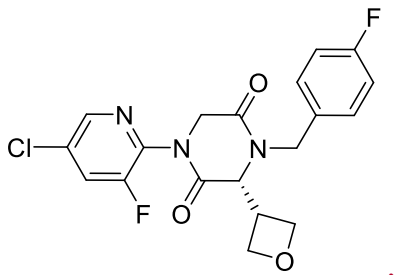
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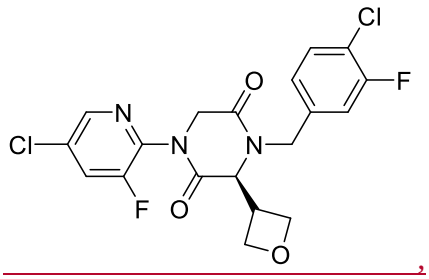
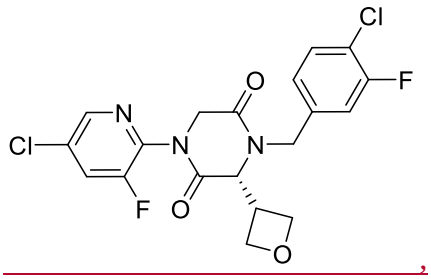
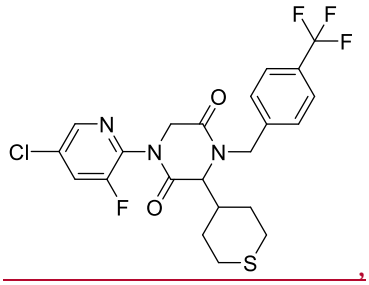
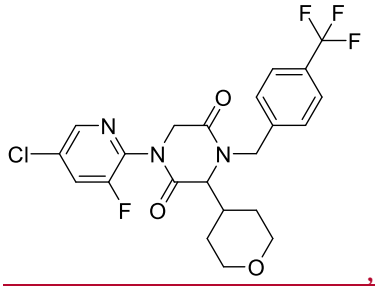
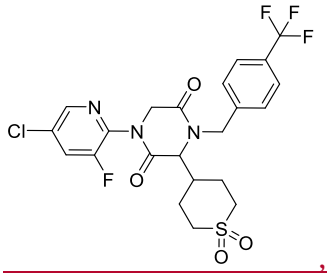
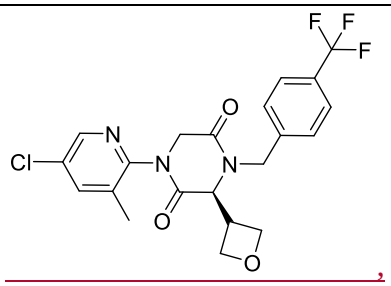
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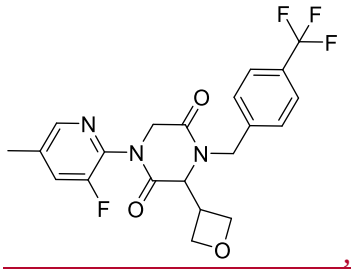
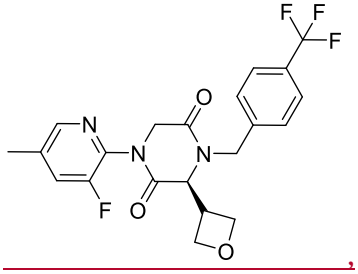
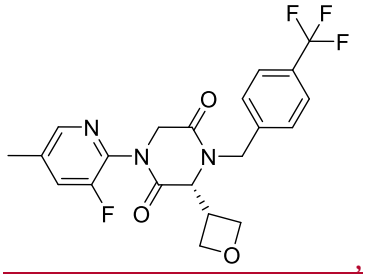
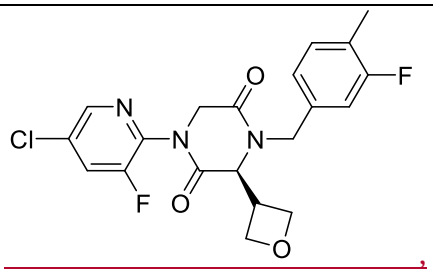
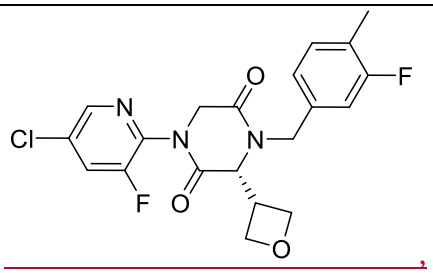
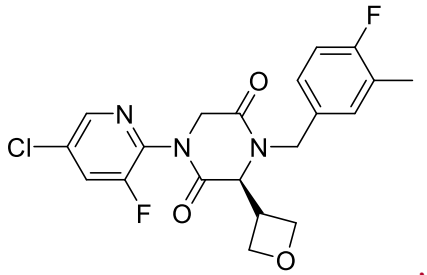
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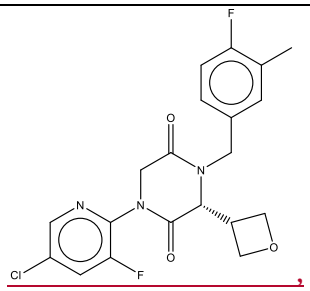
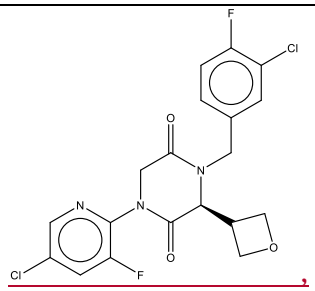
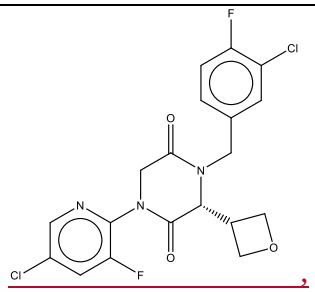
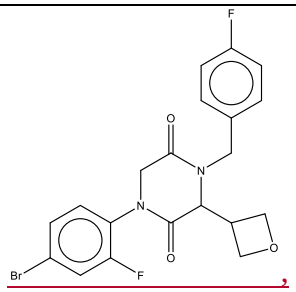
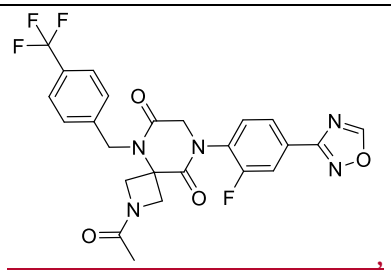
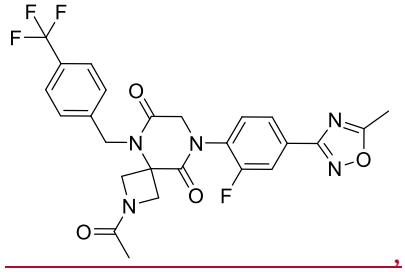
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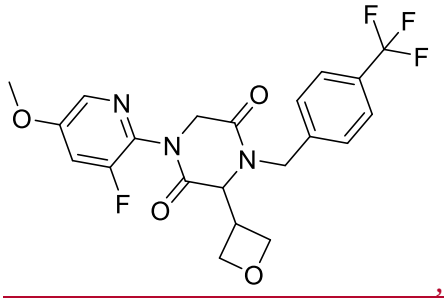
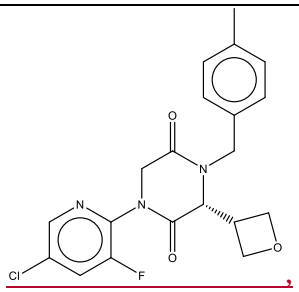
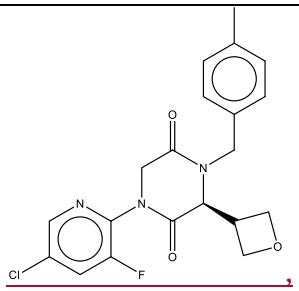
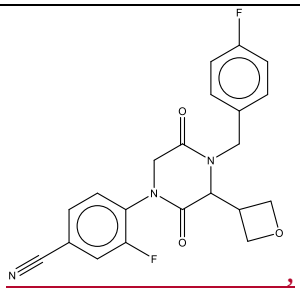
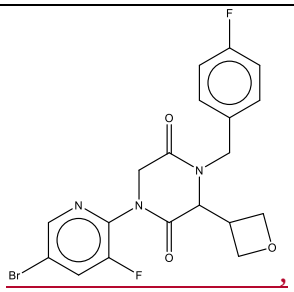
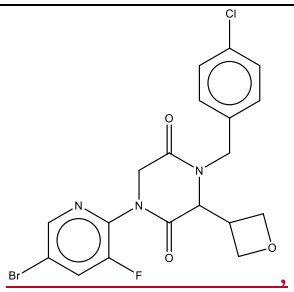
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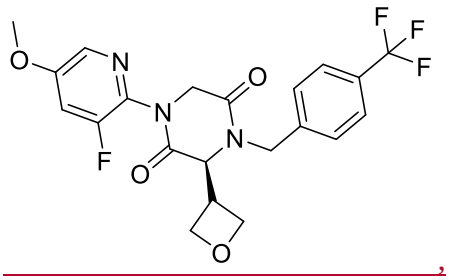
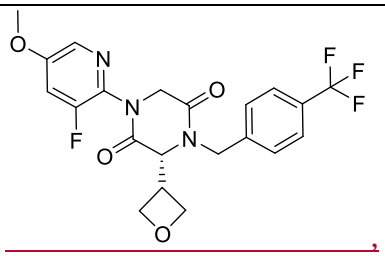
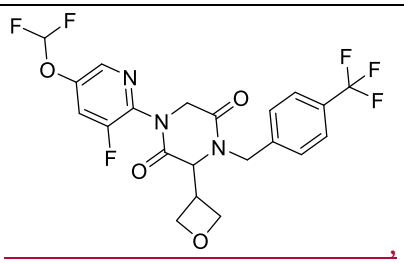
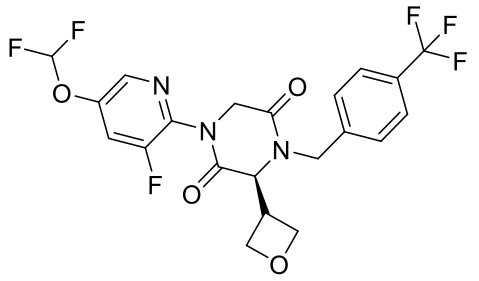
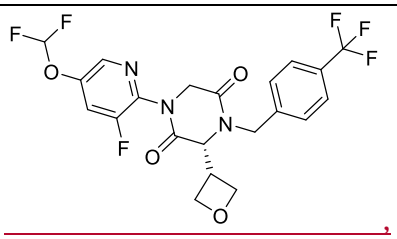
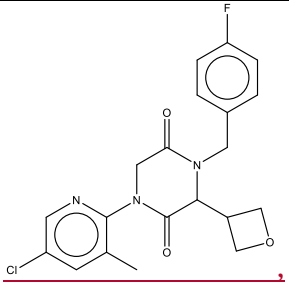
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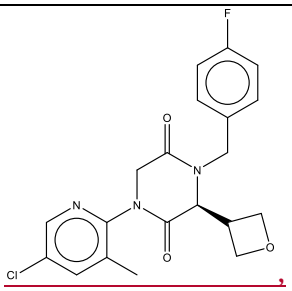
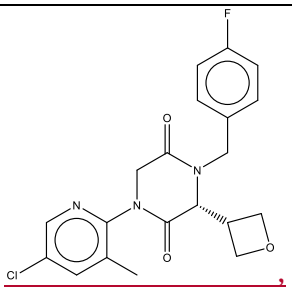
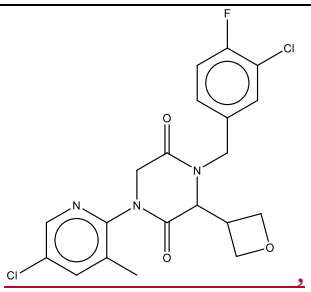
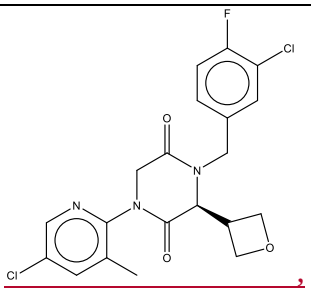
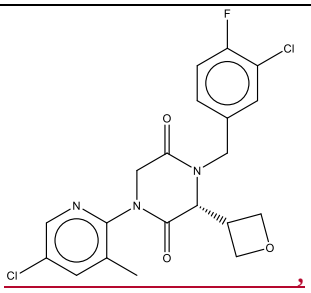
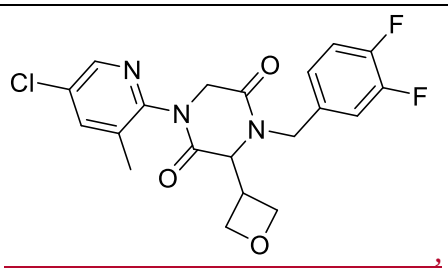
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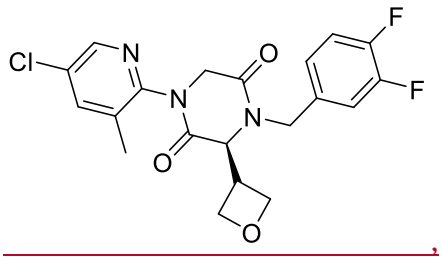
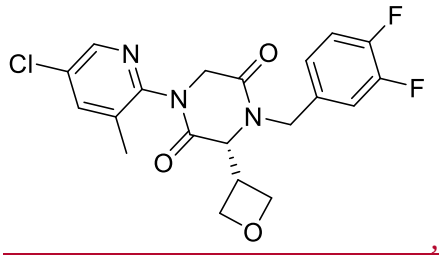
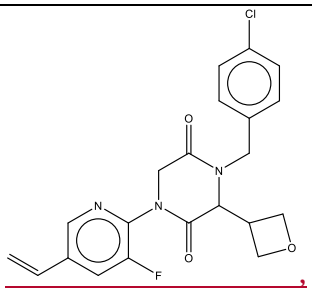
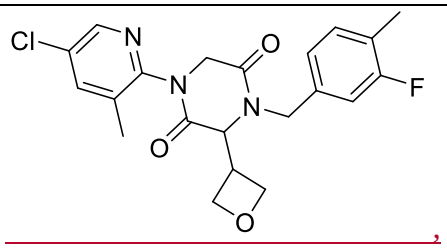
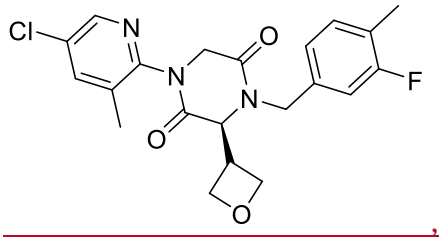
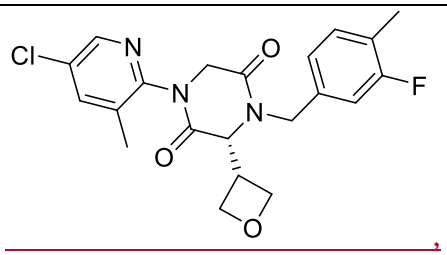
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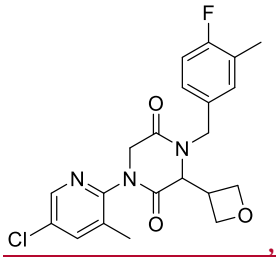
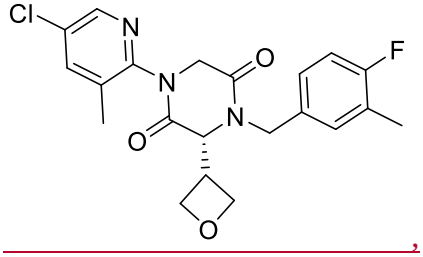
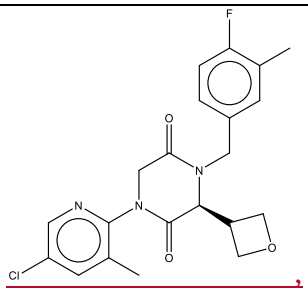
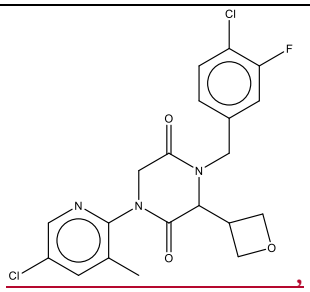
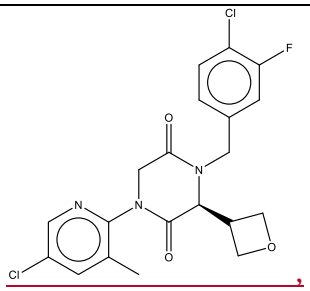
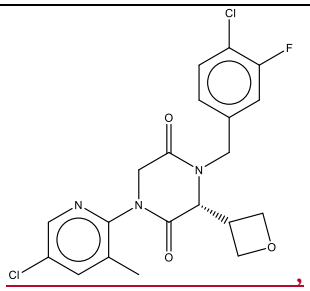
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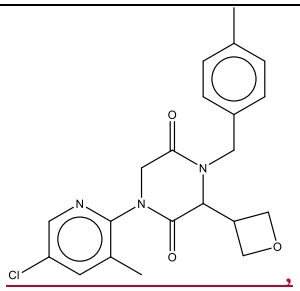
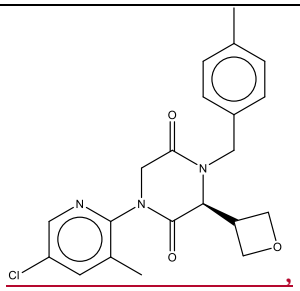
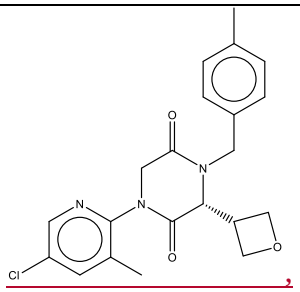
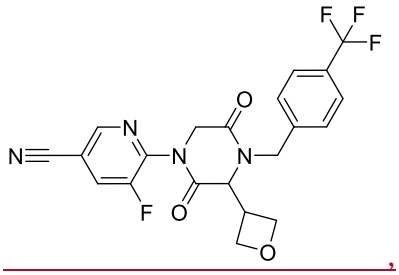
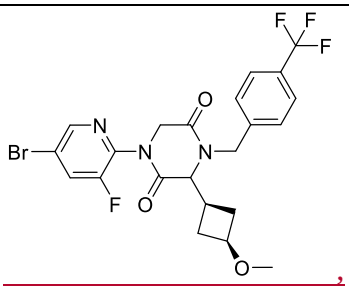
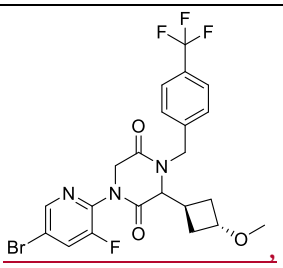
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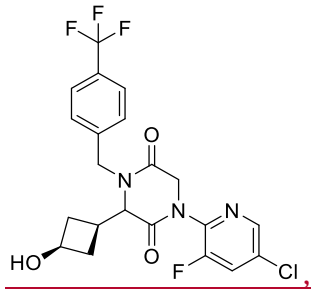
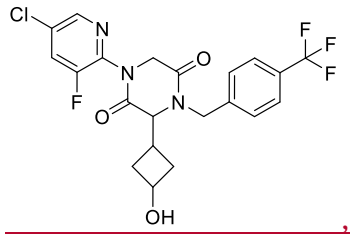
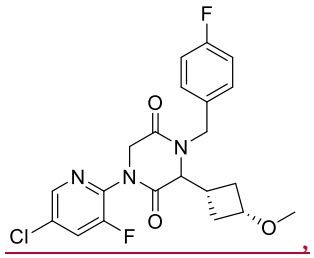
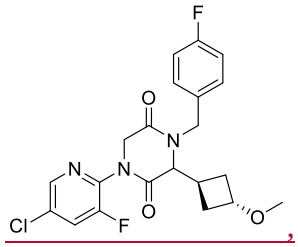
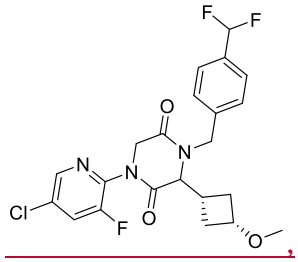
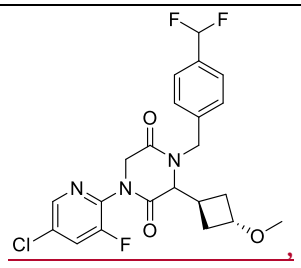
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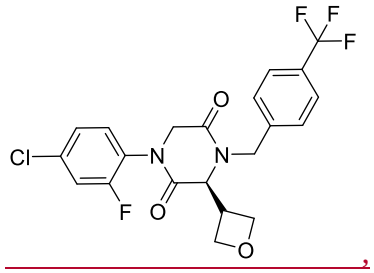
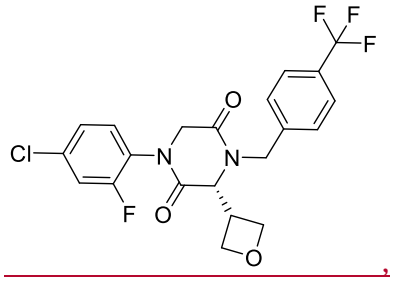
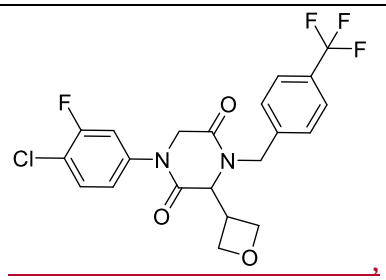
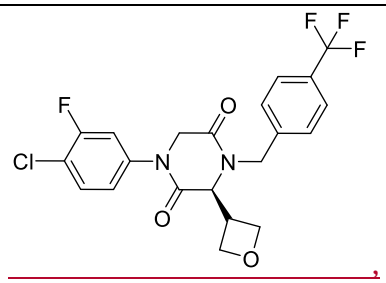
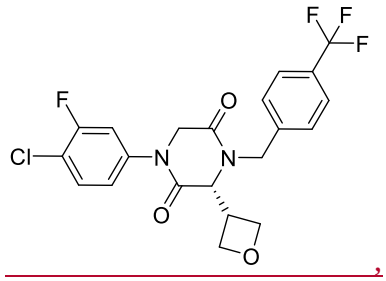
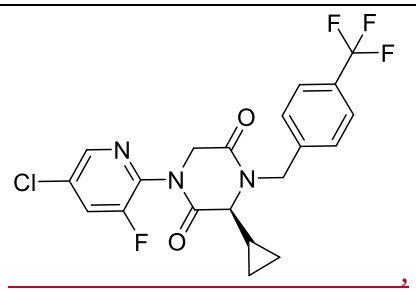
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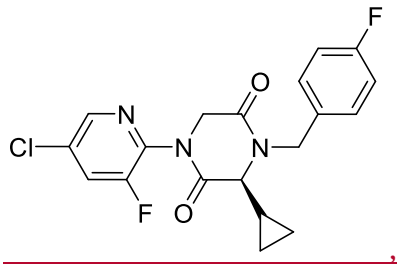
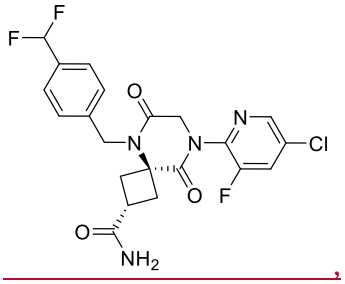
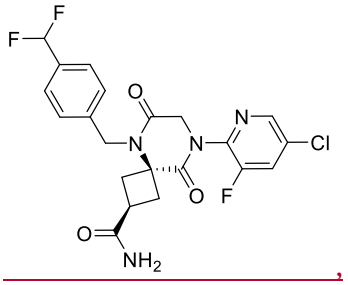
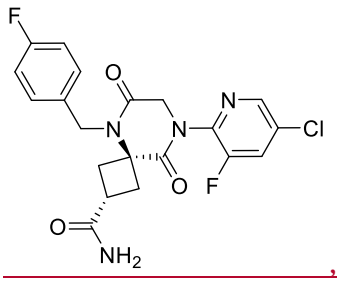
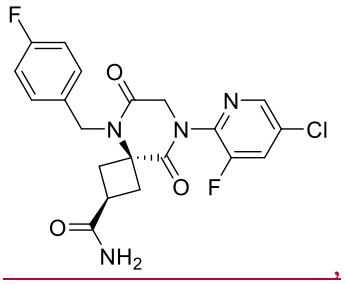
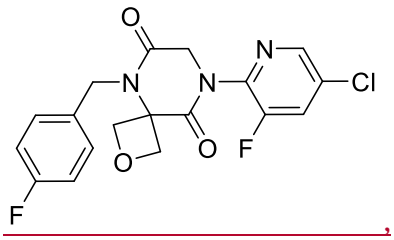
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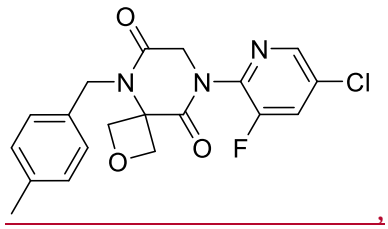
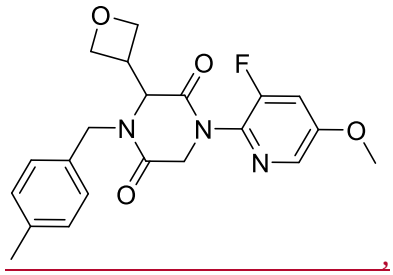
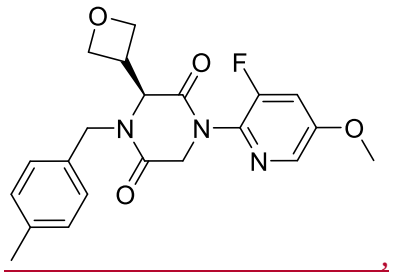
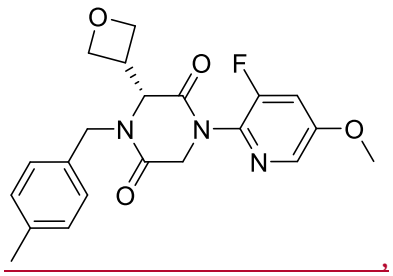
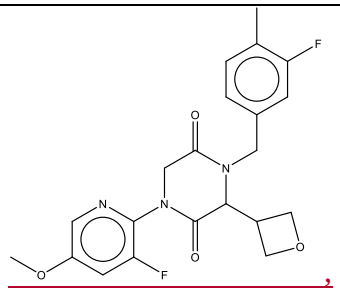
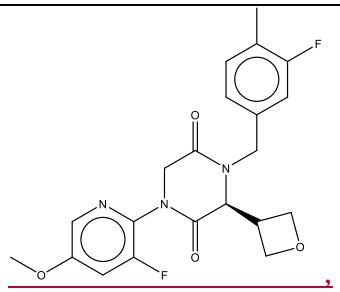
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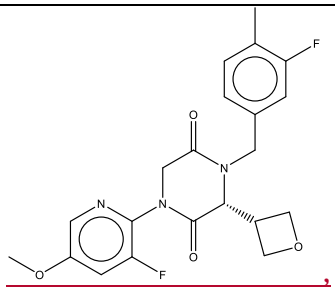
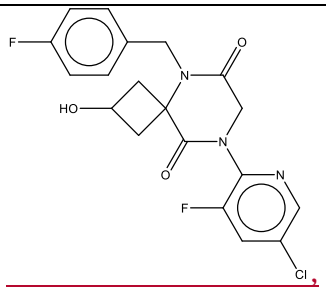
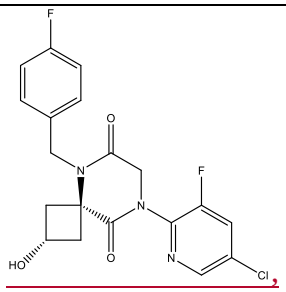
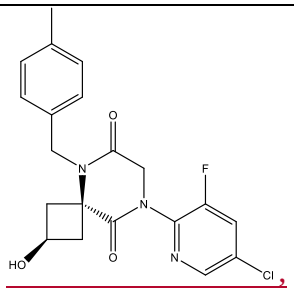
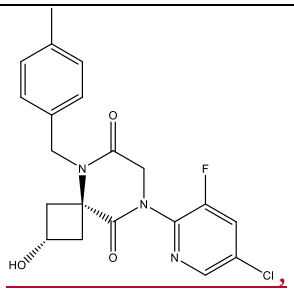
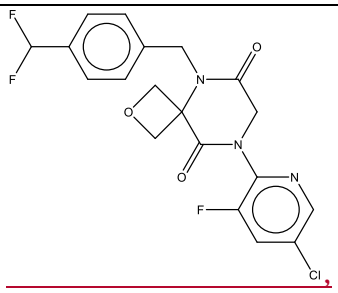
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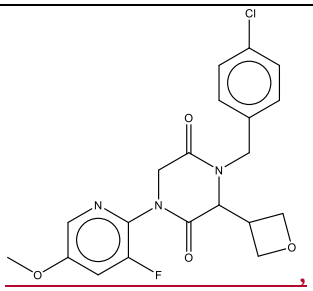
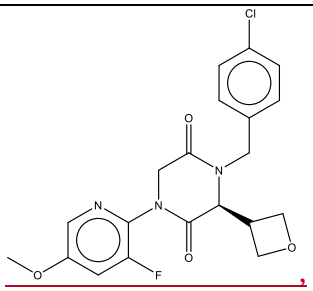
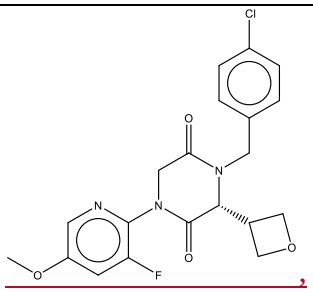
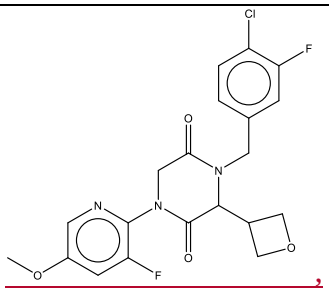
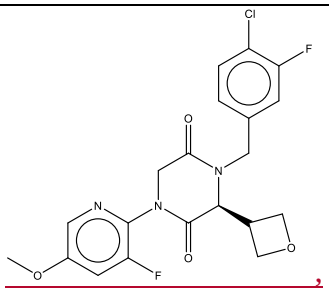
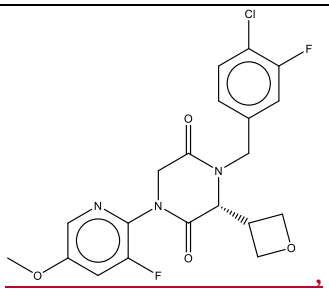
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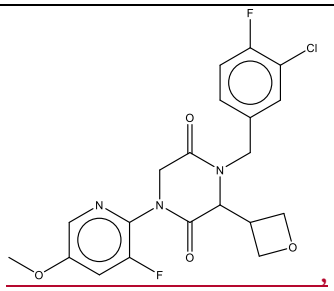
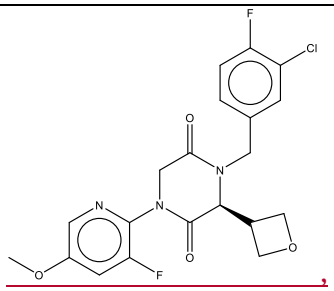
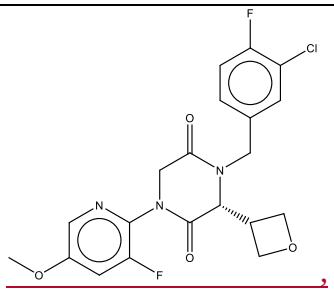
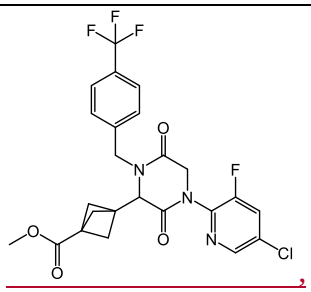
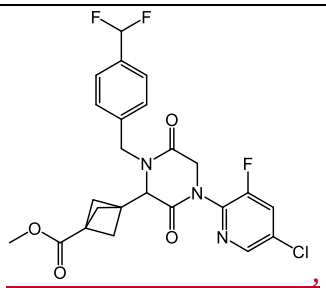
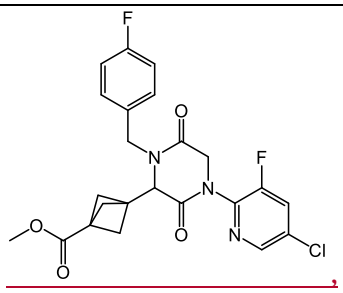
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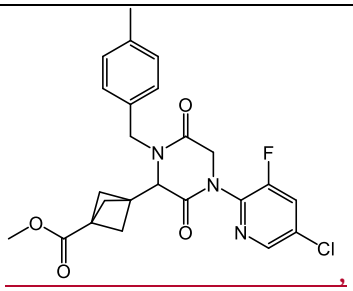
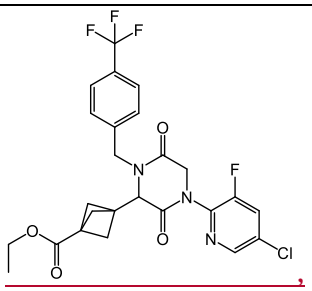
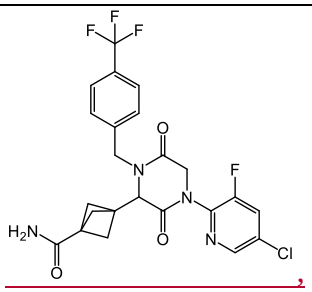
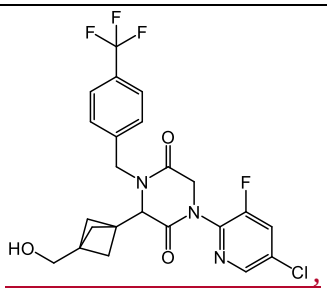
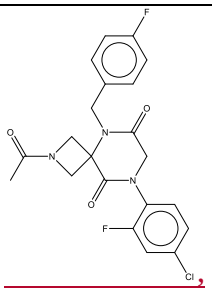
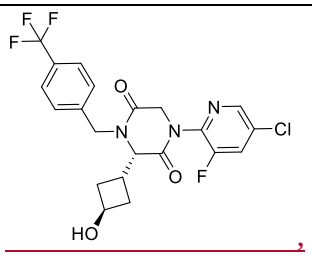
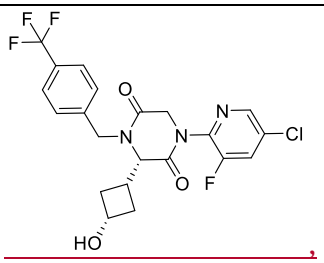
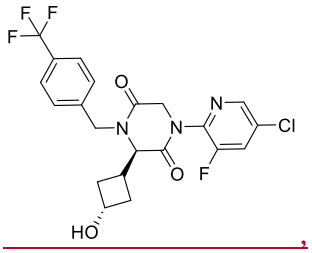
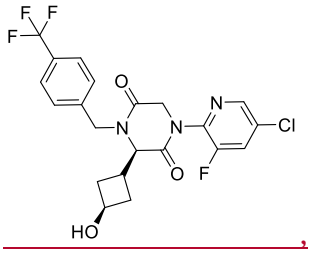
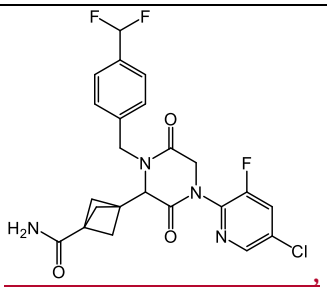
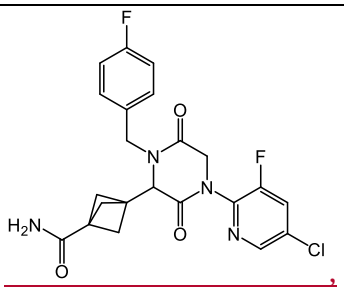
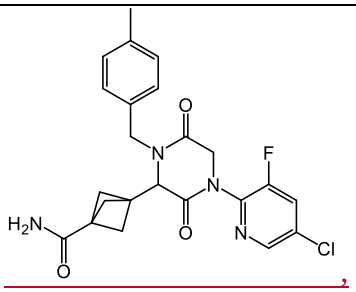
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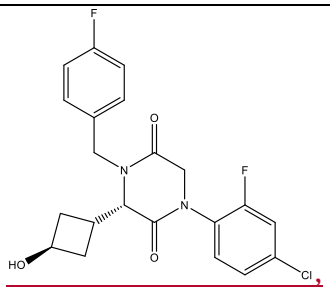
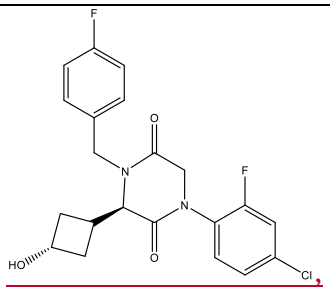
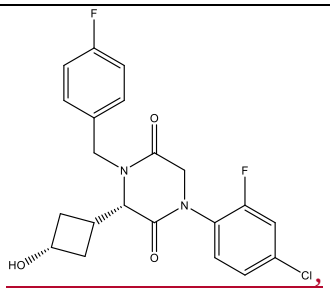
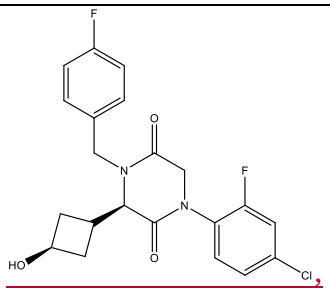
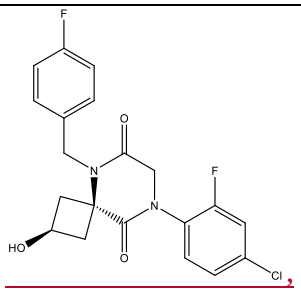
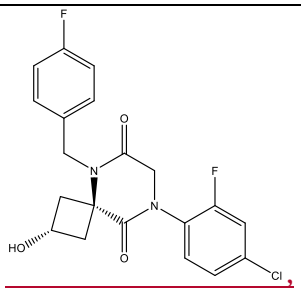
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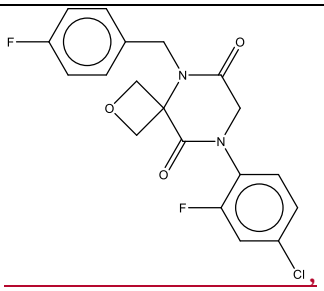
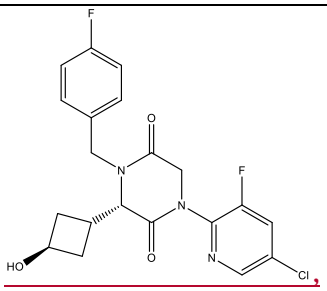
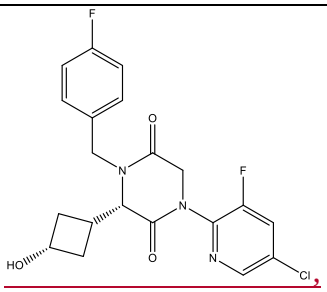
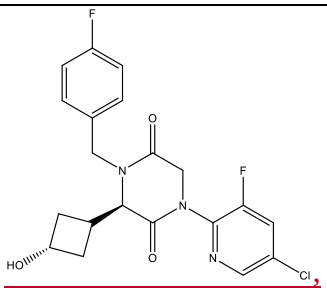
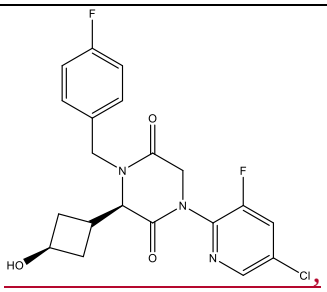
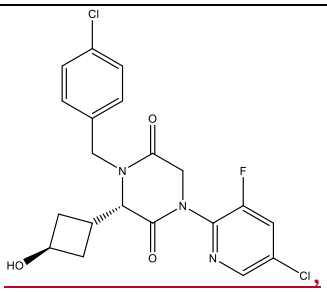
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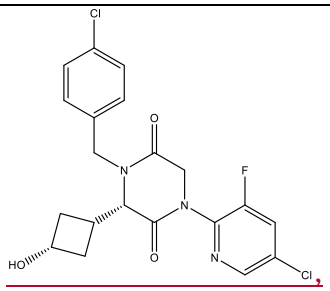
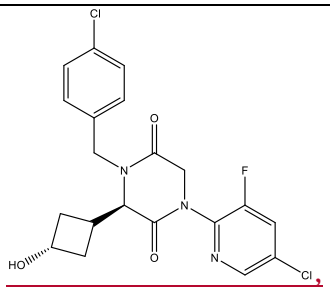
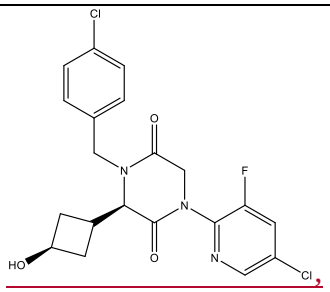
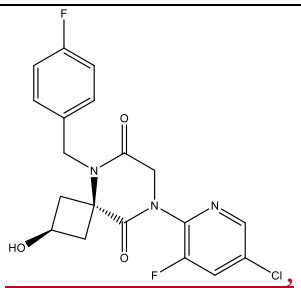
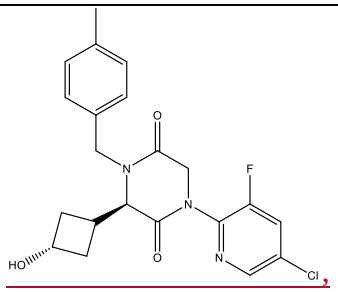
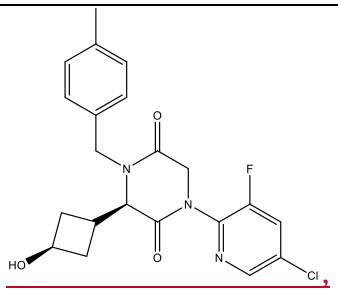
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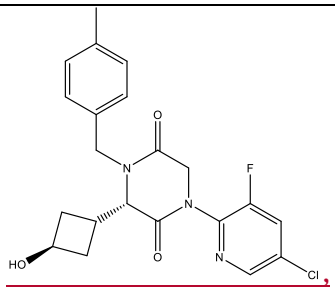
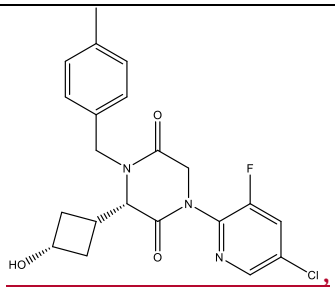
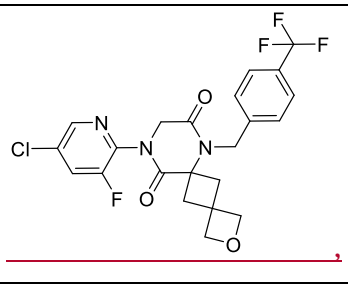
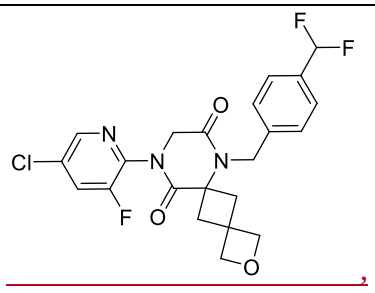
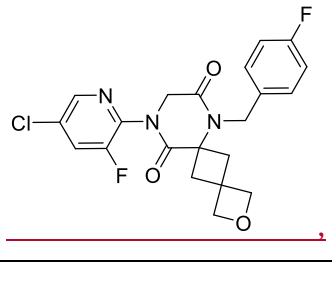
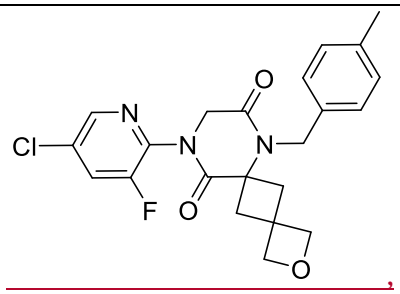
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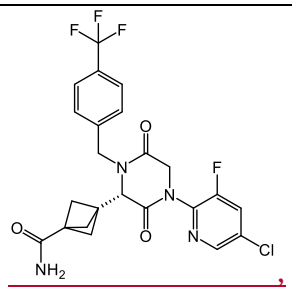
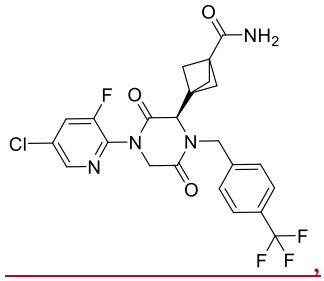
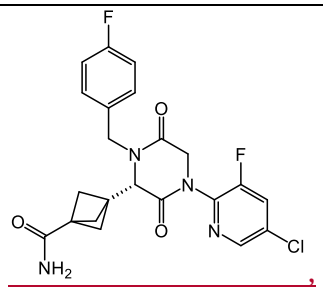
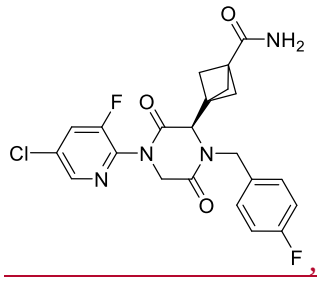
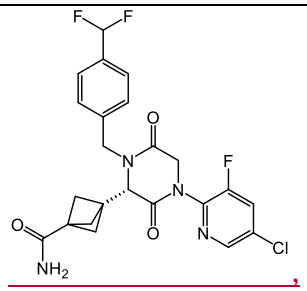
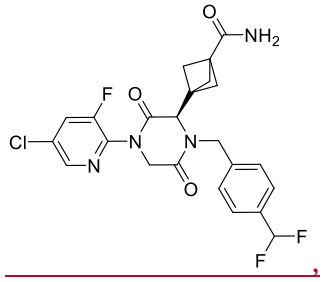
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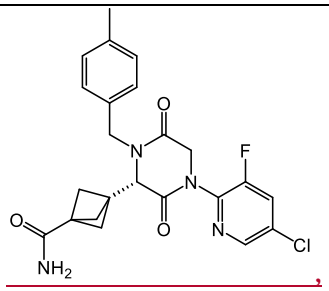
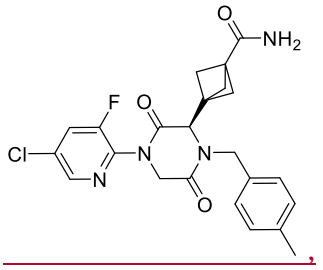
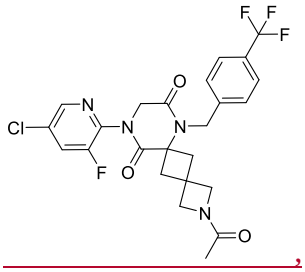
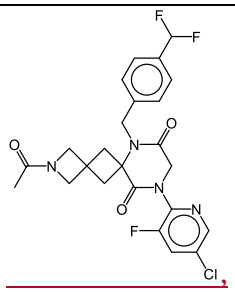
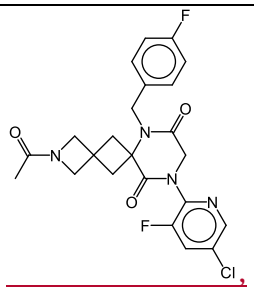
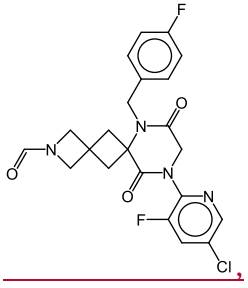
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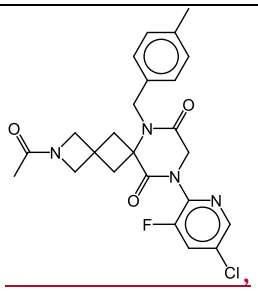
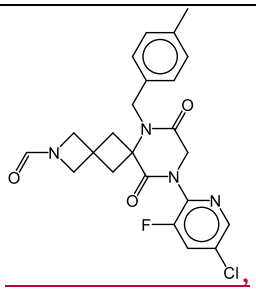
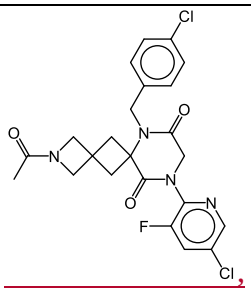
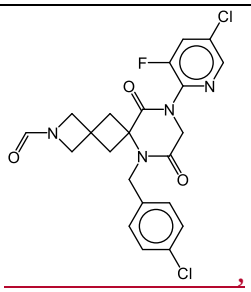
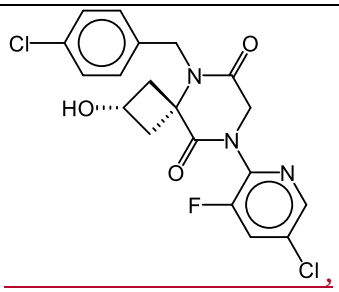
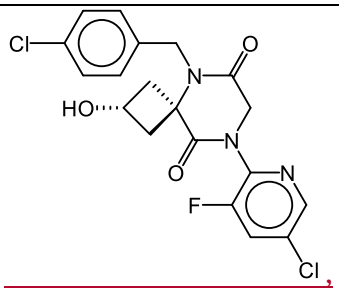
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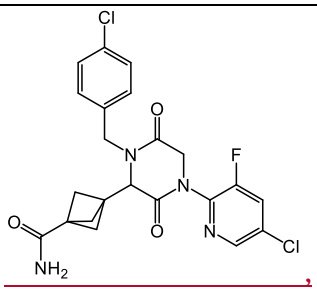
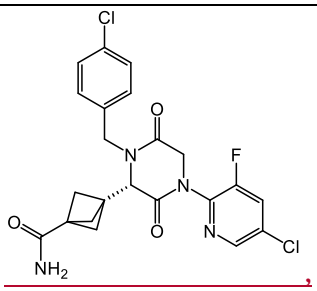
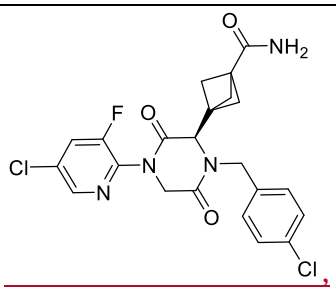
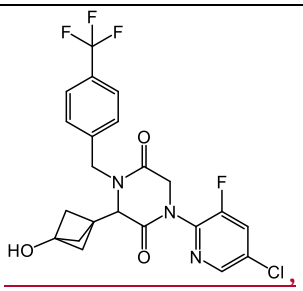
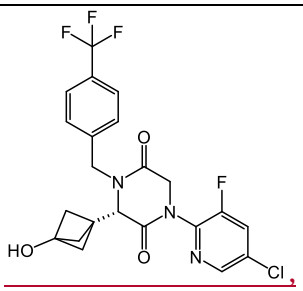
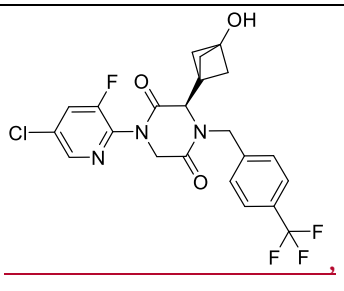
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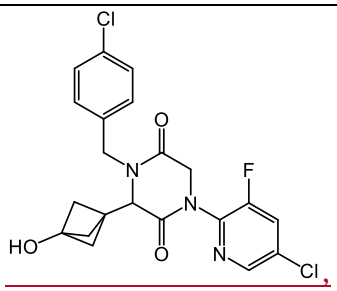
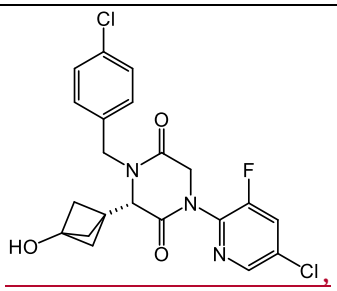
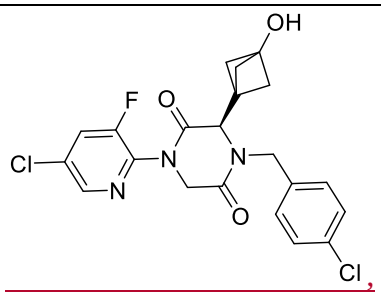
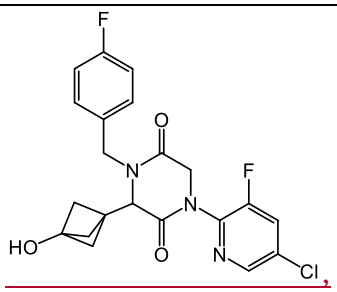
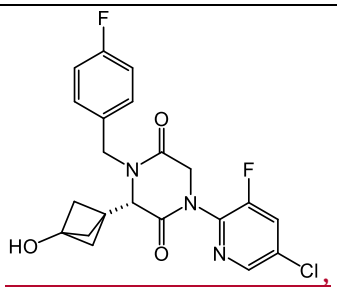
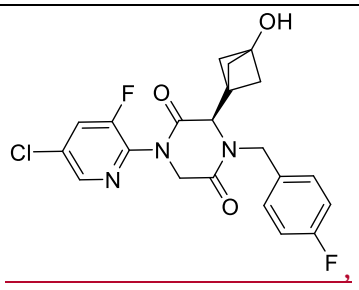
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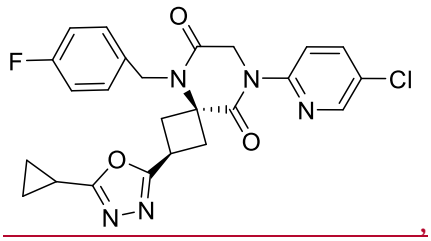
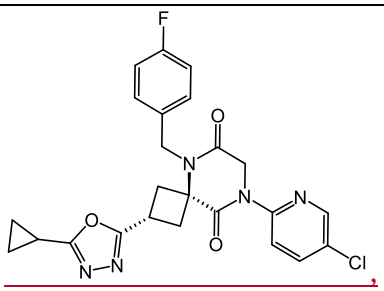
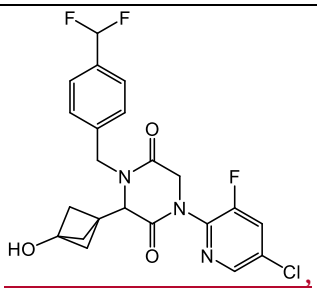
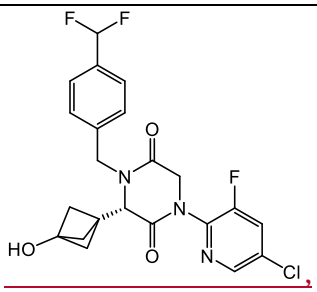
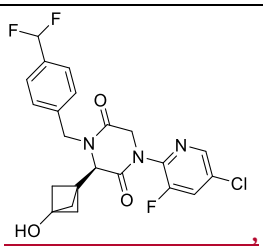
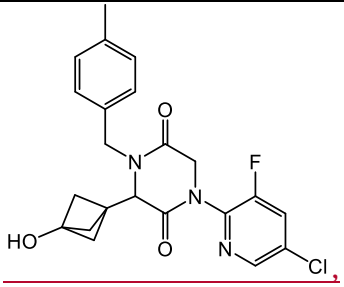
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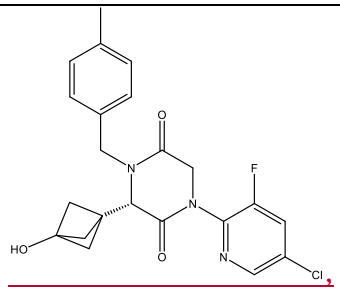
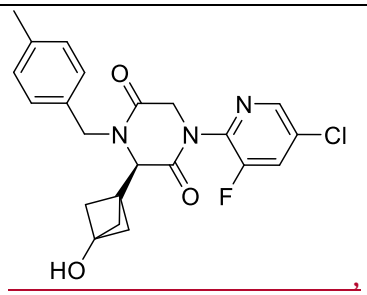
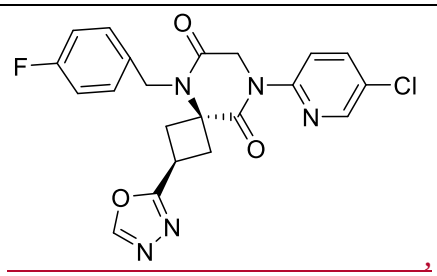
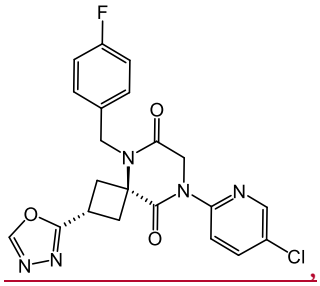
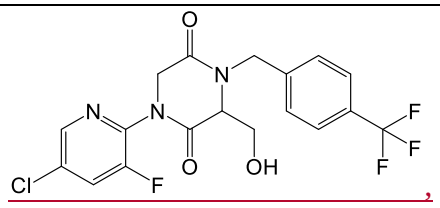
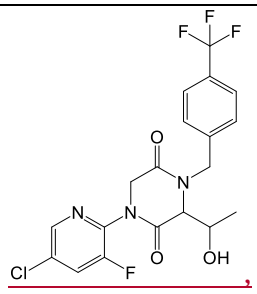
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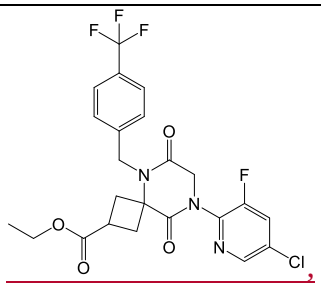
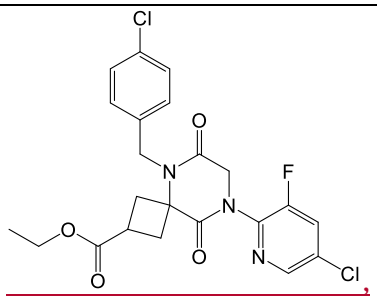
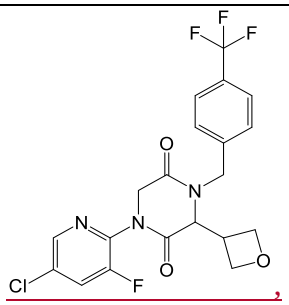
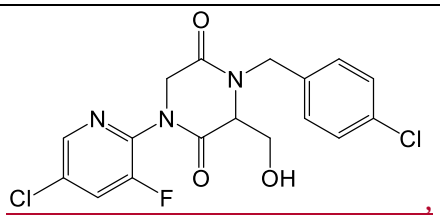
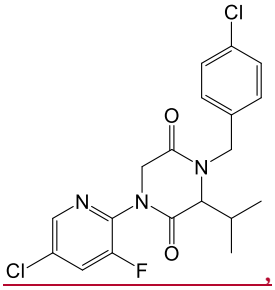
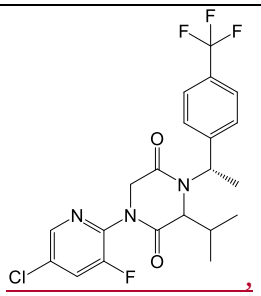
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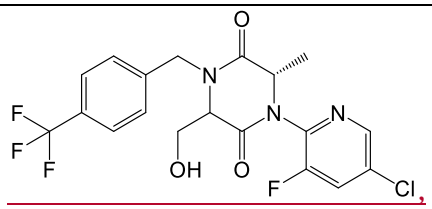
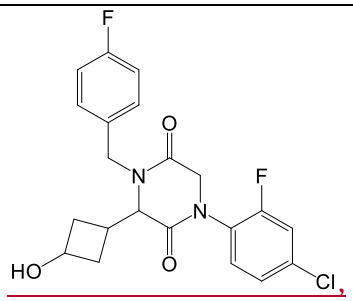
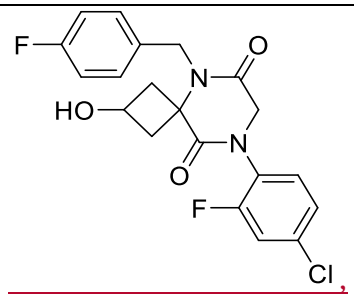
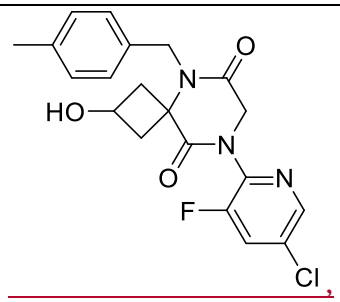
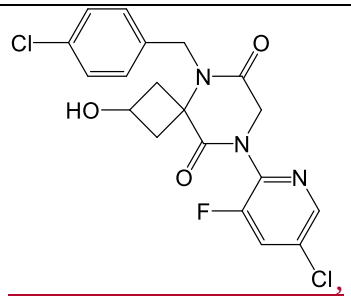
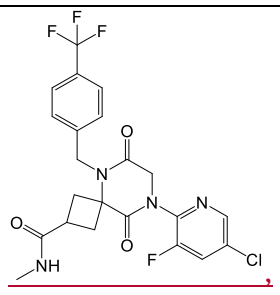
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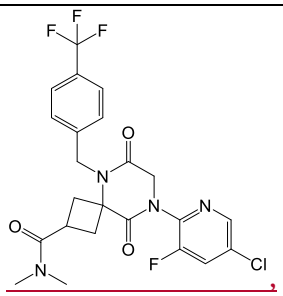
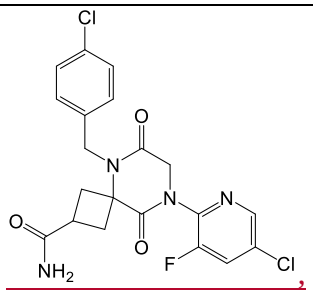
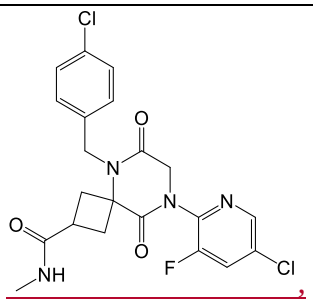
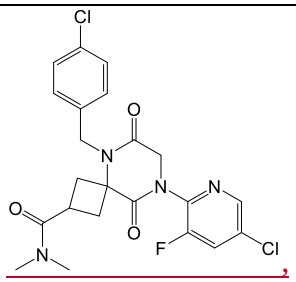
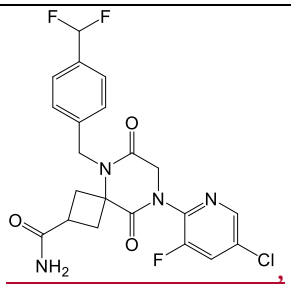
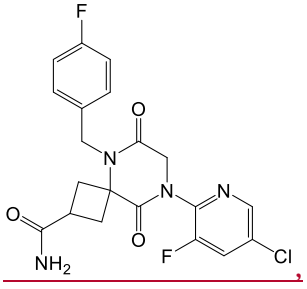
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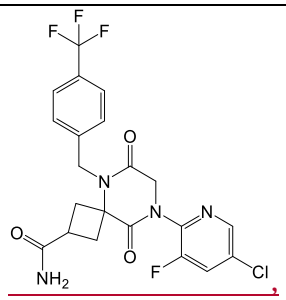
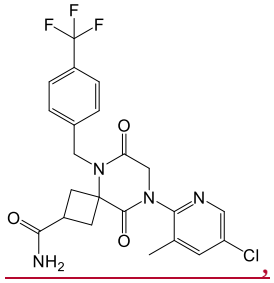
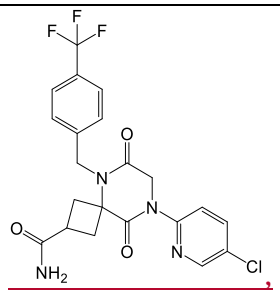
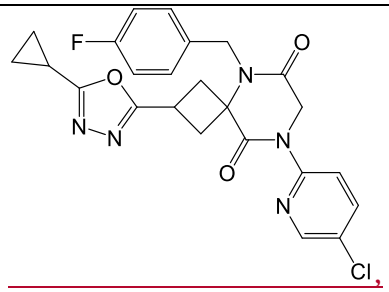
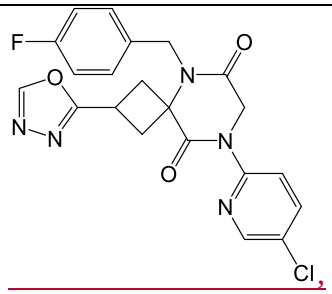
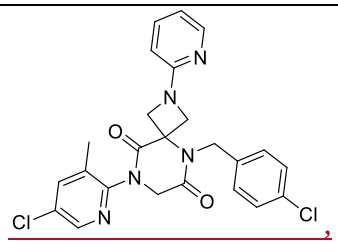
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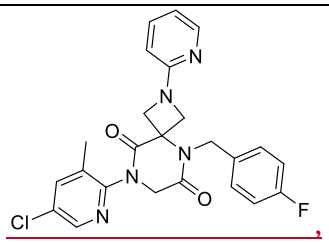
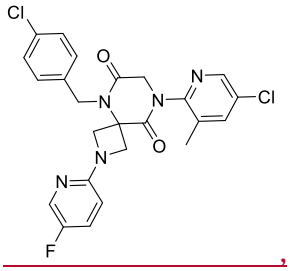
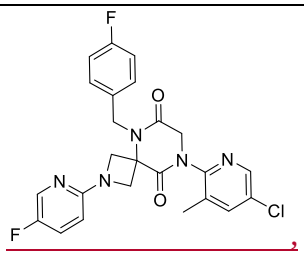
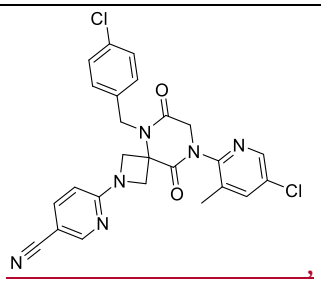
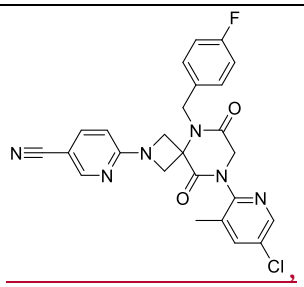
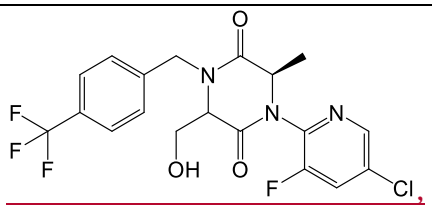
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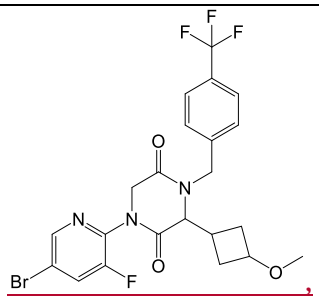
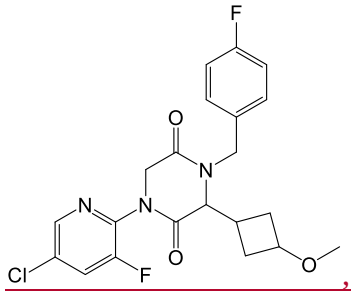
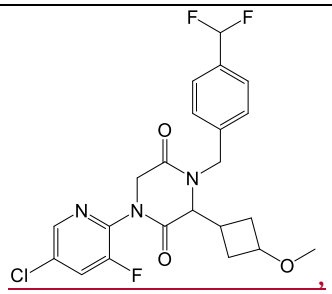
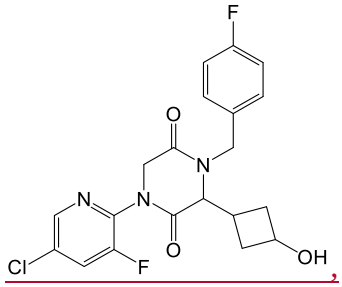
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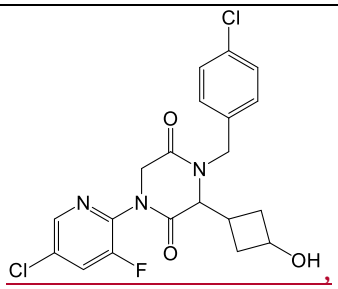
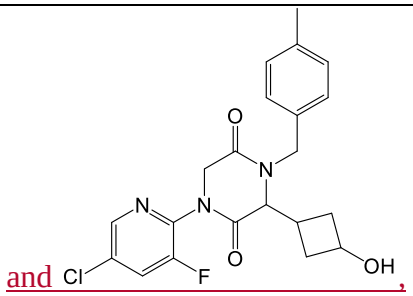
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or a pharmaceutically acceptable salt thereof.

~~45.~~44. A pharmaceutical composition comprising a compound according to claim~~any one of claims~~ 1~~ to 44~~, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

~~46.~~45. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~A method of~~ treating heart disease ~~in a subject in need thereof, comprising administering to the subject a compound of any one of claims 11-44, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 45~~.

~~47.~~46. The ~~method~~ use of claim 45~~46~~, wherein the heart disease is hypertrophic cardiomyopathy.

~~48.~~47. The use ~~method~~ of claim 46~~47~~, wherein the hypertrophic cardiomyopathy is obstructive or nonobstructive or is caused by sarcomeric and/or non-sarcomeric mutations.

~~49.~~48. The use ~~method~~ of claim 45~~46~~, wherein the heart disease is heart failure with preserved ejection fraction.

~~50.~~49. The use ~~method~~ of claim 45~~46~~, wherein the heart disease is selected from the group consisting of diastolic dysfunction, primary or secondary restrictive cardiomyopathy, myocardial infarction and angina pectoris, left ventricular outflow tract obstruction, hypertensive heart disease, congenital heart disease, cardiac ischemia, coronary heart disease, diabetic heart disease, congestive heart failure, right heart failure, cardiorenal syndrome, and infiltrative cardiomyopathy.

~~51.~~50. The use ~~method~~ of claim 45~~46~~, wherein the heart disease is or is related to one or more conditions selected from the group consisting of cardiac senescence, diastolic dysfunction due to aging, left ventricular hypertrophy and concentric left ventricular remodeling.

~~52.~~51. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~A method of~~ treating a disease or condition associated with hypertrophic cardiomyopathy ~~in a subject in need thereof, comprising administering to the subject a compound of any one of claims 1-44, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 45~~.

~~53.~~52. The ~~method~~ use of claim 51~~52~~, wherein the disease or condition is selected from the group consisting of Fabry's Disease, Danon Disease, mitochondrial cardiomyopathies, and Noonan Syndrome.

~~54.~~53. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~A method of~~ treating a disease or condition that is associated with secondary left ventricular wall thickening ~~in a subject in need thereof, comprising administering to the subject a compound of any one of claims 1-44, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 45~~.

~~55.~~54. The use ~~method~~ of claim 53~~54~~, wherein the disease or condition is selected from the group consisting of hypertension, valvular heart diseases, aortic stenosis, Mitral valve regurgitation, metabolic syndromes, diabetes, obesity, end stage renal disease, scleroderma, sleep apnea, amyloidosis, Fabry's disease, Friedreich Ataxia, Danon disease, Noonan syndrome, and Pompe disease.

~~56.~~55. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~A method of~~ treating a disease or condition that is associated with small left ventricular cavity and cavity obliteration, hyperdynamic left ventricular contraction, myocardial ischemia, or cardiac fibrosis ~~in a subject in need thereof, comprising administering to the subject a compound of any one of claims 1-44, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 45~~.

~~57.~~56. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~A method of~~ treating a disease or condition selected from muscular dystrophies and glycogen storage diseases ~~in a subject in need thereof, comprising administering to the subject a compound of any one of claims 1-44, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 45~~.

~~58.~~57. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~A method of~~ inhibiting the cardiac sarcomere~~,~~ ~~comprising contacting the cardiac sarcomere with a compound of any one of claims 1-44, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 45~~.

58. A compound of claim 1, or a pharmaceutically acceptable salt thereof, for use in therapy.