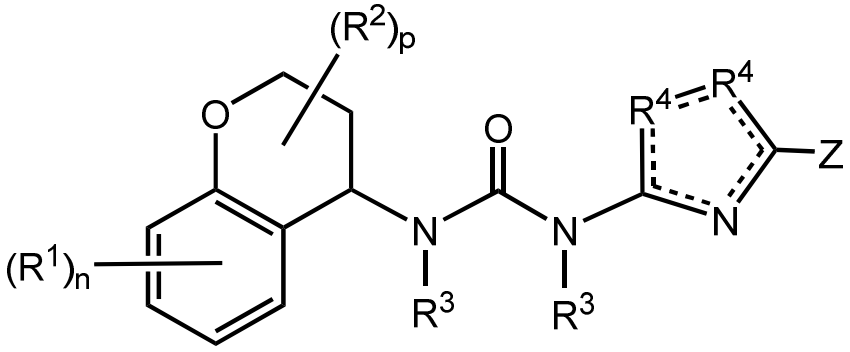
[0006] There are over 300 POLγ mutations correlated to a broad clinical spectrum of neurodegenerative and mitochondrial diseases. *See, e.g.*, Rahman, S., *et al.*, "POLG-related disorders and their neurological manifestations," *Nat. Rev. Neurol.*, 15:40-52 (2019) (Rahman 2019). Many disease-causing variants of POLγ are associated with decreased replication processivity of the mtDNA replication machinery, leading to replication stalling.

[0007] In view of the numerous and varied roles of POLγ, the need exists for potent and specific compounds that increase the processivity of POLγ.

SUMMARY

[0008] Provided are compounds, pharmaceutically acceptable salts of the compounds, and pharmaceutical compositions comprising the compounds or their salts for increasing the processivity of POLγ.

[0009] In examples, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, represented by formula (I):



(I)

wherein:

R^1 is selected from the group consisting of H, C_1-C_3 alkyl, Cl, F, CN, and O-C_1-C_6 alkyl optionally substituted with one or more halogen;

R^2 is H or C_1-C_3 alkyl optionally substituted with OR^5;

R^3 is each independently H or C_1-C_4 alkyl optionally substituted with one or more halogen or OH;

R^4 is C-R^5 or S, wherein one R^4 is C-R^5 and the other R^4 is S;

independently selected from the group consisting of F, Cl, OR^5, CN, C_1-C_4 alkyl, oxo, and NR^5R^6,

wherein heteroaryl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more OH or F, CN, $C(O)NR^5R^6$, OR^5, NR^5R^6, oxo, SO_2R^6, a 4- to 6-membered heterocyclic ring, and C_1-C_4 alkyl optionally substituted with one or more groups each independently selected from the group consisting of F, NR^5R^6, OR^5, and $C(O)NR^5R^6$;

wherein the aryl-heterocyclyl is optionally substituted with one or more groups each independently selected from the group consisting of Cl, F, and C1-C4 alkyl that is optionally substituted with a group selected from the group consisting of OR^5, Cl, and F;

wherein the aryl-heteroaryl is optionally substituted with C1-C3 alkyl that is optionally substituted with OR^5;

R^5 is independently H or C_1-C_5 alkyl;

R^6 is selected from the group consisting of H, cyclopropyl, and C_1-C_5 alkyl optionally substituted with one or more groups selected from the group consisting of NR^5R^5, OR^5, and halogen;

R^7 is cycloalkyl optionally substituted with one or more halogens;

n is 1-4;

p is 1-2;

with the proviso that a compound selected from the group consisting of:

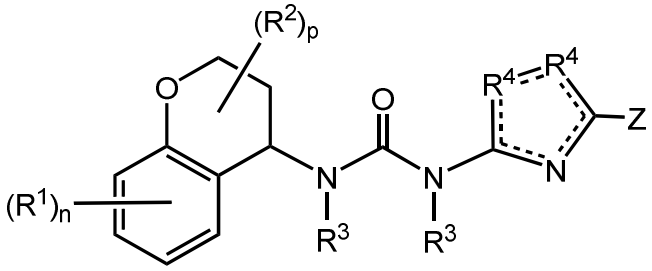
(*S*)-1-(8-fluorochroman-4-yl)-3-(5-(tetrahydro-2*H*-pyran-4-yl)thiazol-2-yl)urea,

1-(chroman-4-yl)-3-(4-cyclobutylthiazol-2-yl)urea,

1-((3*R*,4*R*)-3-(hydroxymethyl)chroman-4-yl)-3-(4-(methoxymethyl)thiazol-2-yl)urea, and

1-(5-cyclopropylthiazol-4-yl)-3-((3*R*,4*R*)-3-(hydroxymethyl)chroman-4-yl)urea, is excluded.

[0009a] In one aspect, the present disclosure relates to a compound having the structure of formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein:

R^1 is selected from the group consisting of H, C_1-C_3 alkyl, Cl, F, CN, and O-C_1-C_6 alkyl optionally substituted with one or more halogen;

R^2 is H or C_1-C_3 alkyl optionally substituted with OR^5;

R^3 is each independently H or C_1-C_4 alkyl optionally substituted with one or more halogen or OH;

R^4 is C-R^5 or S, wherein one R^4 is C-R^5 and the other R^4 is S;

Z is selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkene, NR^5R^6, SR^5, $C(O)R^5$, $C(O)R^7$, $C(O)OR^5$, $C(O)NR^5R^6$, , cycloalkyl, heterocyclyl, aryl, heteroaryl, heteroaryl-cycloalkyl, aryl-heterocyclyl, aryl-heteroaryl, and sulfonamide,

wherein the C_1-C_6 alkyl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more halogen, phenyl, OR^5, halogen, $C(O)NR^5R^6$, NR^5R^6, NR^5-$C(O)CH_3$, SO_2R^5, NH-SO_2R^5, heterocyclyl, aryl, heteroaryl, and aryl-heteroaryl,

wherein cycloalkyl is optionally substituted with one or more groups each independently selected from the group consisting of F, C_1-C_3 alkyl-OH, C_1-C_3 alkyl-O-C_1-C_3 alkyl, $C(O)OR^5$, $C(O)NR^5R^5$, NR^5R^5, and NR^5-$C(O)CH_3$,

wherein heterocyclyl optionally contains another heteroatom that is N or O, and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR^5, keto, C_3-C_6 cycloalkyl, $C(O)CH_3$, $C(O)NR^5R^5$, NH-$C(O)R^5$, NH-SO_2R^5, and C_1-C_4 alkyl that is optionally substituted with one or more F or OH,

wherein aryl is optionally substituted with one or more groups selected from the group consisting of:

C_1-C_4 alkyl that is optionally substituted with one or more groups each independently selected from the group consisting of F, OH, and NR^5R^6,

C_3-C_6 cycloalkyl that is substituted with NR^5R^6,

halogen,

CN,

OR^5,

$C(O)NR^5R^6$,

NR^5R^6,

SO_2R^6,

$SO_2NR^5R^6$,

SO(NH)R,

S(NR)(NH)R,

$P(O)R^5R^5$, and

4- or 5,6-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is optionally substituted with one or more groups independently selected from the group consisting of F, Cl, OR^5, CN, C_1-C_4 alkyl, oxo, and NR^5R^6,

wherein heteroaryl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more OH or F, CN, $C(O)NR^5R^6$, OR^5, NR^5R^6, oxo, SO_2R^6, a 4- to 6-membered heterocyclic ring, and C_1-C_4 alkyl optionally substituted with one or more groups each independently selected from the group consisting of F, NR^5R^6, OR^5, and $C(O)NR^5R^6$;

wherein the aryl-heterocyclyl is optionally substituted with one or more groups each independently selected from the group consisting of Cl, F, and C1-C4 alkyl that is optionally substituted with a group selected from the group consisting of OR^5, Cl, and F;

wherein the aryl-heteroaryl is optionally substituted with C1-C3 alkyl that is optionally substituted with OR^5;

R^5 is independently H or C_1-C_5 alkyl;

R^6 is selected from the group consisting of H, cyclopropyl, and C_1-C_5 alkyl optionally substituted with one or more groups selected from the group consisting of NR^5R^5, OR^5, and halogen;

R^7 is cycloalkyl optionally substituted with one or more halogens;

n is 1-4;

p is 1-2;

with the proviso that a compound selected from the group consisting of:

(*S*)-1-(8-fluorochroman-4-yl)-3-(5-(tetrahydro-2*H*-pyran-4-yl)thiazol-2-yl)urea,

1-(chroman-4-yl)-3-(4-cyclobutylthiazol-2-yl)urea,

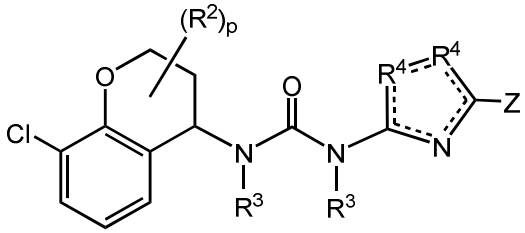
1-((3*R*,4*R*)-3-(hydroxymethyl)chroman-4-yl)-3-(4-(methoxymethyl)thiazol-2-yl)urea, and

1-(5-cyclopropylthiazol-4-yl)-3-((3*R*,4*R*)-3-(hydroxymethyl)chroman-4-yl)urea, is excluded.

[0010] Further examples of the present invention are compounds of formula (I) and their pharmaceutically acceptable salts wherein one or more hydrogen is substituted with a deuterium atom.

[0011] Additional examples of the invention are pharmaceutical compositions comprising a compound of the invention, a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.

[0011a] In one aspect, the present disclosure relates to a compound having the structure of formula (II), or a pharmaceutically acceptable salt thereof,



(II)

wherein:

R^2 is H or C_1-C_3 alkyl optionally substituted with OR^5;

R^3 is each independently H or C_1-C_4 alkyl optionally substituted with one or more halogen or OH;

R^4 is C-R^5 or S, wherein one R^3 is C-R^5 and the other R^3 is S;

Z is selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkene, NR^5R^6, SR^5, $C(O)OR^5$, $C(O)R^7$, $C(O)OR^5$, $C(O)NR^5R^6$, cycloalkyl, heterocyclyl, aryl, heteroaryl, aryl-heterocyclyl, aryl-heteroaryl, and sulfonamide,

wherein the C_1-C_6 alkyl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more halogen, phenyl, OR^5, halogen, heterocyclyl, $C(O)NR^5R^6$, NR^5R^6, NR^5-$C(O)CH_3$, SO_2R^5, NH-SO_2R^5, aryl, heteroaryl, and aryl-heteroaryl,

wherein cycloalkyl is optionally substituted with one or more groups each independently selected from the group consisting of F, C_1-C_3 alkyl-OH, C_1-C_3 alkyl-O-C_1-C_3 alkyl, $C(O)OR^5$, $C(O)NR^5R^5$, NR^5R^5, and NR^5-$C(O)CH_3$,

wherein heterocyclyl optionally contains another heteroatom that is N or O, and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR^5, keto, C_3-C_6 cycloalkyl, $C(O)CH_3$, $C(O)NR^5R^5$, NH-$C(O)R^5$, NH-SO_2R^5, and C_1-C_4 alkyl that is optionally substituted with one or more F or OH,

wherein aryl is optionally substituted with one or more groups selected from the group consisting of:

C_1-C_4 alkyl that is optionally substituted with one or more groups each independently selected from the group consisting of F, OH, and NR^5R^6,

C_3-C_6 cycloalkyl that is substituted with NR^5R^6,

halogen,

CN,

OR^5,

$C(O)NR^5R^6$,

NR^5R^6,

SO_2R^6,

$SO_2NR^5R^6$,

SO(NH)R,

S(NR)(NH)R,

$P(O)R^5R^5$, and

4- or 5,6-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is optionally substituted with one or more groups independently selected from the group consisting of F, Cl, OR^5, CN, C_1-C_4 alkyl, oxo, and NR^5R^6,

wherein heteroaryl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more OH or F, CN,

$C(O)NR^5R^6$, OR^5, NR^5R^6, oxo, SO_2R^6, a 4- to 6-membered heterocyclic ring, and C_1-C_3 alkyl optionally substituted with one or more groups each independently selected from the group consisting of F, NR^5R^6, OR^5, and $C(O)NR^5R^6$;

wherein the aryl-heterocyclyl is optionally substituted with one or more groups each independently selected from the group consisting of Cl, F, and C1-C4 alkyl that is optionally substituted with a group selected from the group consisting of OR^5, Cl, and F;

wherein the aryl-heteroaryl is optionally substituted with C1-C3 alkyl that is optionally substituted with OR^5;

R^5 is independently H or C_1-C_5 alkyl;

R^6 is selected from the group consisting of H, cyclopropyl, and C_1-C_5 alkyl optionally substituted with one or more groups selected from the group consisting of NR^5R^5, OR^5, and halogen;

R^7 is cycloalkyl optionally substituted with one or more halogens;

p is 1-2;

with the proviso that a compound selected from the group consisting of:

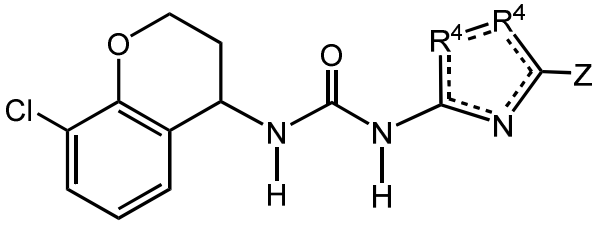
(*S*)-1-(8-fluorochroman-4-yl)-3-(5-(tetrahydro-2*H*-pyran-4-yl)thiazol-2-yl)urea,

1-(chroman-4-yl)-3-(4-cyclobutylthiazol-2-yl)urea,

1-((3*R*,4*R*)-3-(hydroxymethyl)chroman-4-yl)-3-(4-(methoxymethyl)thiazol-2-yl)urea, and

1-(5-cyclopropylthiazol-4-yl)-3-((3*R*,4*R*)-3-(hydroxymethyl)chroman-4-yl)urea, is excluded.

[0011b] In one aspect, the present disclosure refers to a compound having the structure of formula (III), or a pharmaceutically acceptable salt thereof,



(III)

wherein:

R^4 is C-R^5 or S, wherein one R^4 is C-R^5 and the other R^4 is S;

Z is selected from the group consisting of C_1-C_3 alkyl, C_1-C_6 alkene, NR^5R^6, SR^5, $C(O)R^5$, $C(O)R^7$, $C(O)OR^5$, $C(O)NR^5R^6$, cycloalkyl, heterocyclyl, aryl, heteroaryl, heteroaryl-cycloalkyl, and sulfonamide,

wherein the C_1-C_3 alkyl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more halogen, OR^5, halogen, NR^5R^6, and NH-SO_2R^5,

wherein cycloalkyl is optionally substituted with one or more F, C_1-C_3 alkyl-OH, C_1-C_3 alkyl-O-C_1-C_3 alkyl, $C(O)OR^5$,

wherein heterocyclyl optionally contains another heteroatom that is N or O, and is optionally substituted with one or more groups each independently selected from the group consisting of F, OR^5, and C_1 alkyl optionally substituted with one or more F,

wherein aryl is optionally substituted with one or more groups selected from the group consisting of:

C_1-C_3 alkyl that is optionally substituted with NR^5R^6,

halogen,

CN,

OR^5,

$C(O)NR^5R^6$,

SO_2R^6,

$SO_2NR^5R^6$,

SO(NH)R,

S(NR)(NH)R,

$P(O)R^5R^5$, and

5-membered heterocyclic ring optionally containing one or more additional heteroatoms that is S or N, and is optionally substituted with one or more oxo,

wherein heteroaryl is optionally substituted with one or more groups each independently selected from the group consisting of cycloalkyl optionally substituted with one or more OH or F, CN, $C(O)NR^5R^6$, SO_2R^6, a 4- to 6-membered heterocyclic ring, and C_1-C_3 alkyl optionally substituted with one or more groups each independently selected from the group consisting of F, NR^5R^6, and OR^5;

wherein the aryl-heterocyclyl is optionally substituted with one or more groups each independently selected from the group consisting of Cl, F, and C1-C4 alkyl that is optionally substituted with one or more groups selected from the group consisting of OR^5, Cl, and F;

wherein the aryl-heteroaryl is optionally substituted with C1-C3 alkyl that is optionally substituted with OR^5;

R^5 is independently H or C_1 alkyl;

R^6 is selected from the group consisting of H, cyclopropyl, and C_1-C_3 alkyl optionally substituted with one or more groups selected from the group consisting of NR^5R^5, OR^5, and halogen;

R^7 is cycloalkyl optionally substituted with one or more halogens;

with the proviso that a compound selected from the group consisting of:

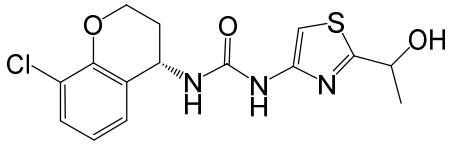
(*S*)-1-(8-fluorochroman-4-yl)-3-(5-(tetrahydro-2*H*-pyran-4-yl)thiazol-2-yl)urea,

1-(chroman-4-yl)-3-(4-cyclobutylthiazol-2-yl)urea,

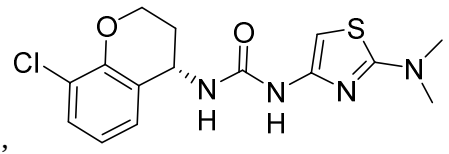
1-((3*R*,4*R*)-3-(hydroxymethyl)chroman-4-yl)-3-(4-(methoxymethyl)thiazol-2-yl)urea, and

1-(5-cyclopropylthiazol-4-yl)-3-((3*R*,4*R*)-3-(hydroxymethyl)chroman-4-yl)urea, is excluded.

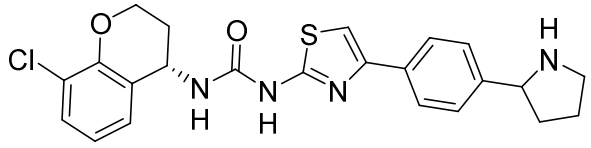
[0011c] In one aspect, the present disclosure refers to a compound, or pharmaceutically acceptable salt thereof, selected from the group consisting of:



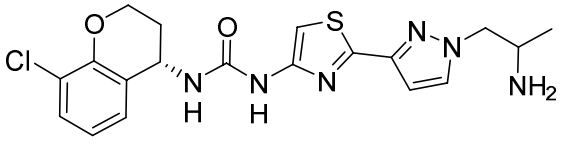
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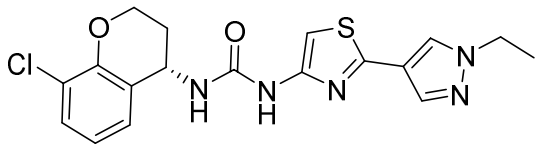
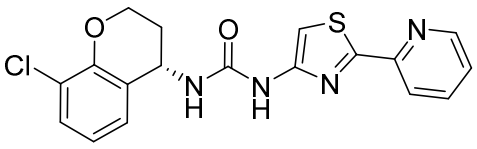
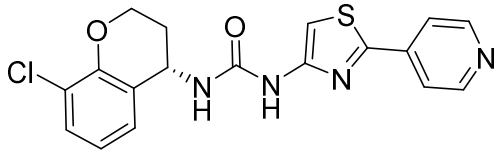
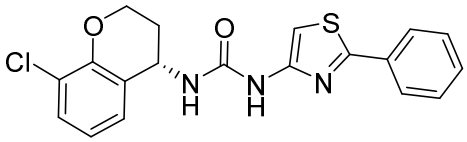
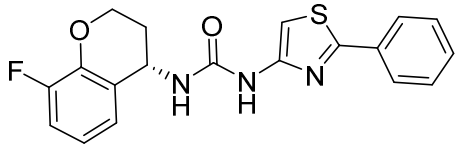
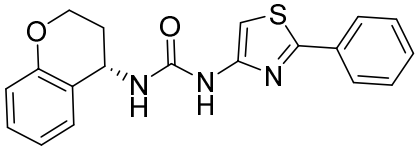
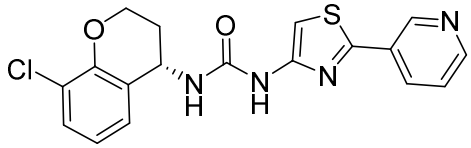
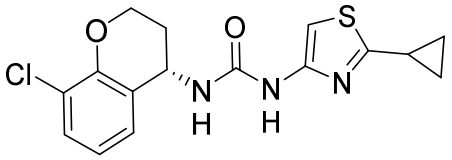
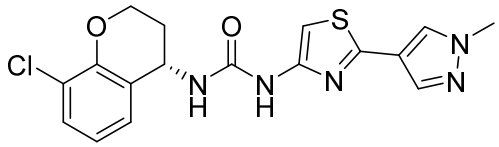
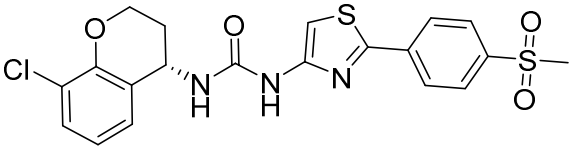
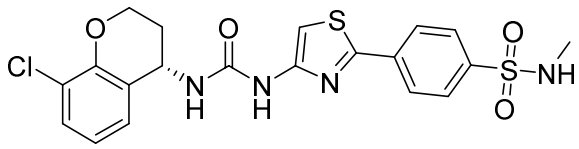
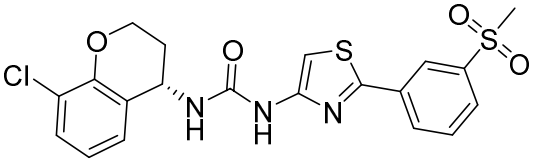
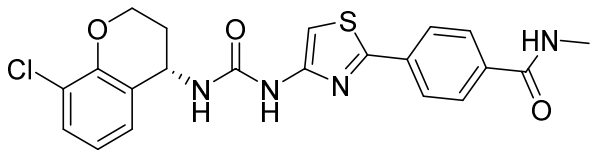
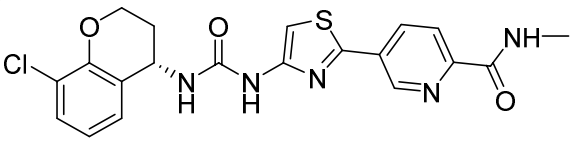
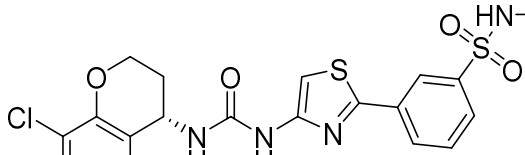
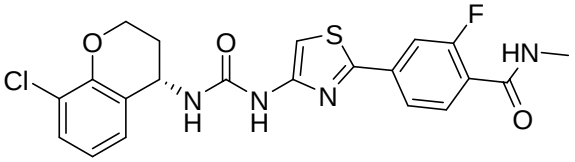
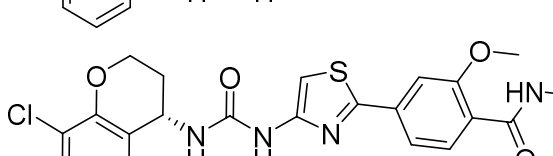
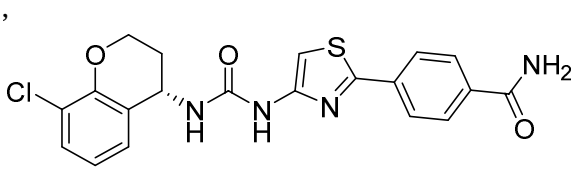
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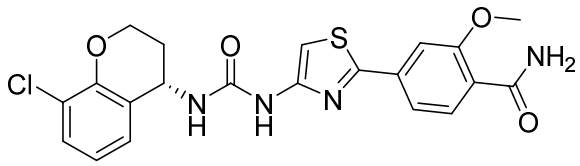
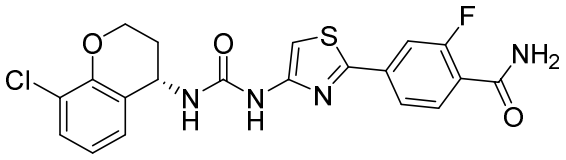
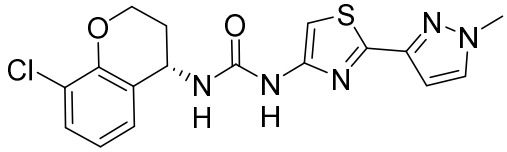
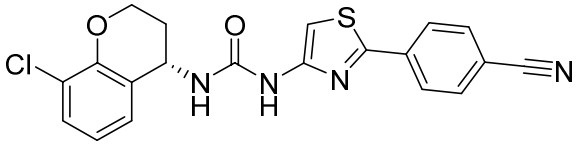
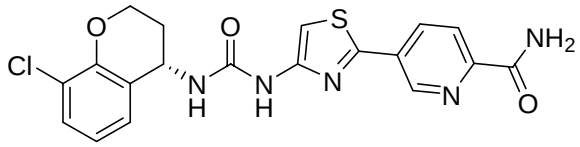
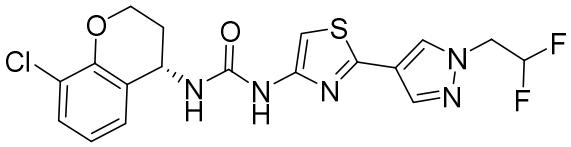
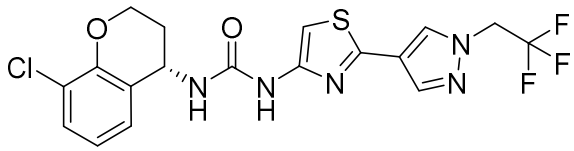
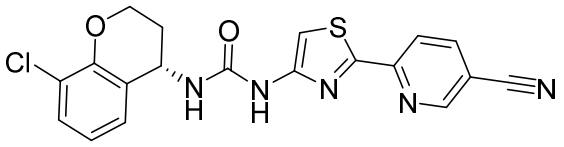
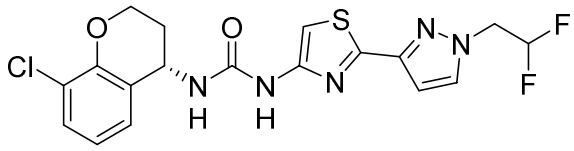
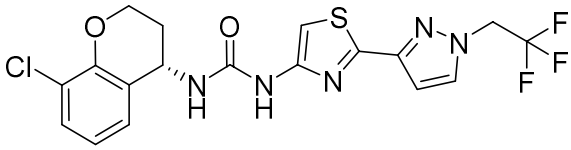
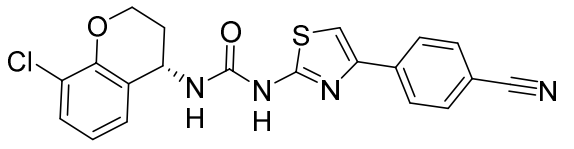
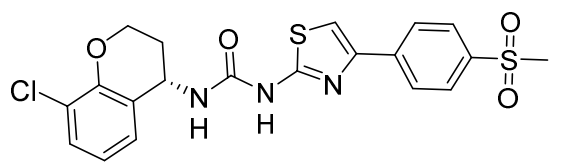
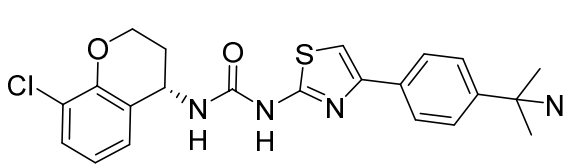
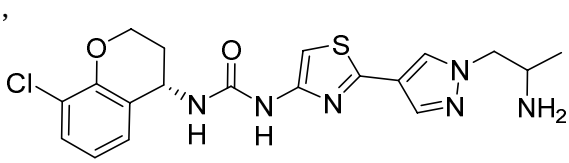
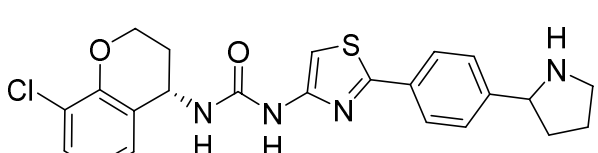
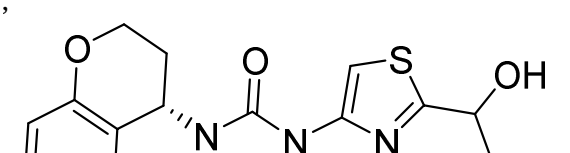
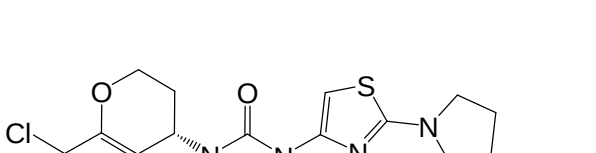
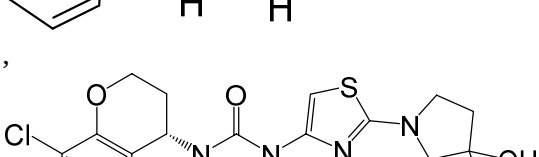
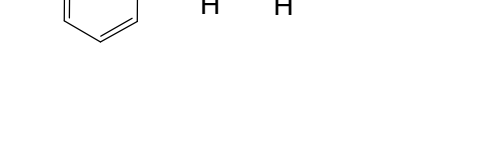
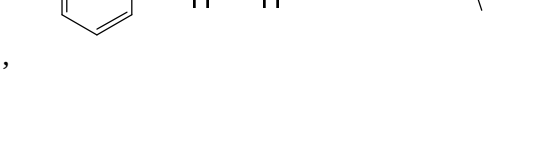
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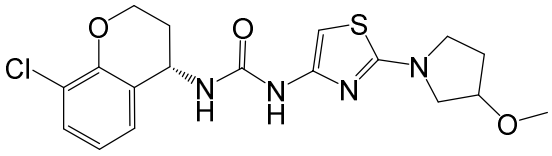
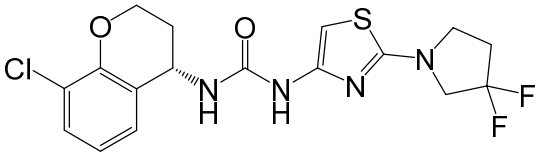
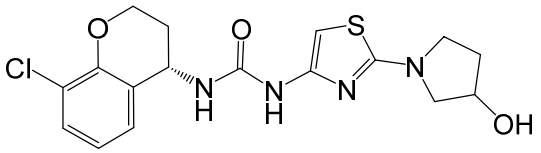
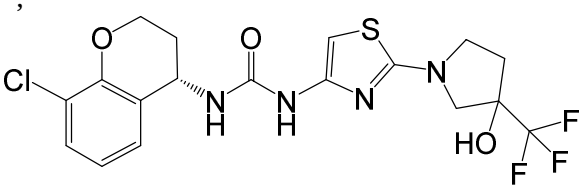
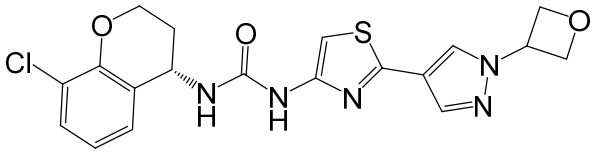
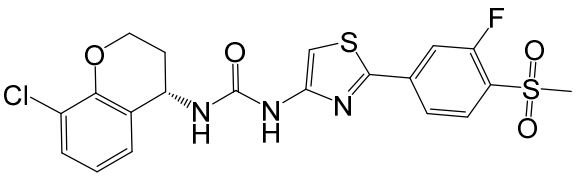
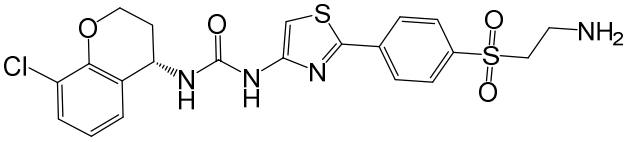
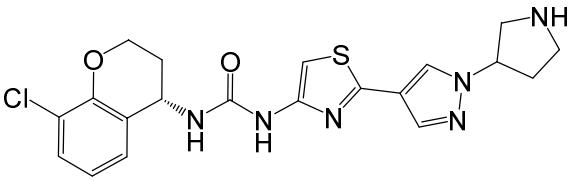
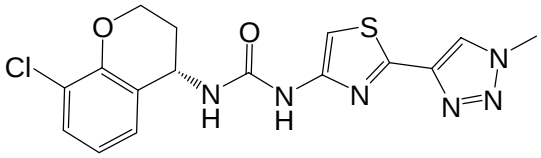
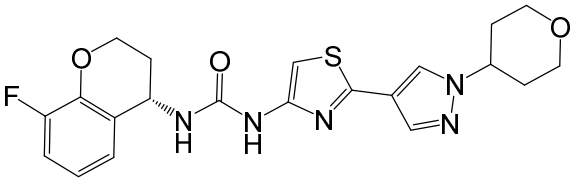
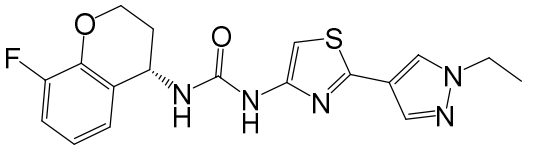
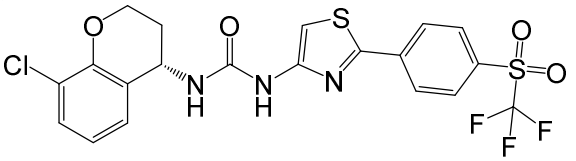
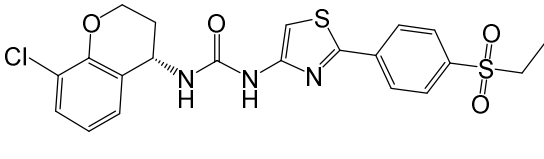
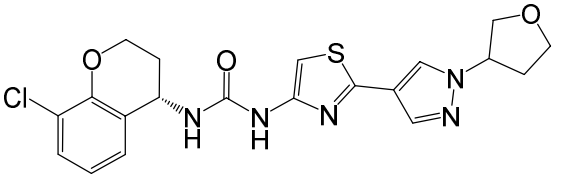
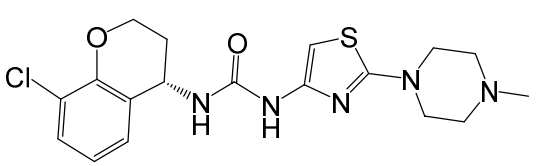
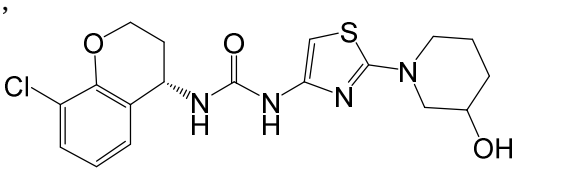
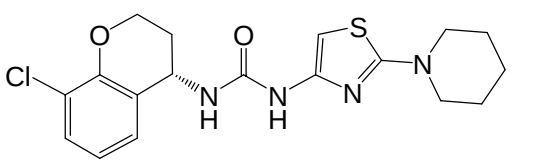
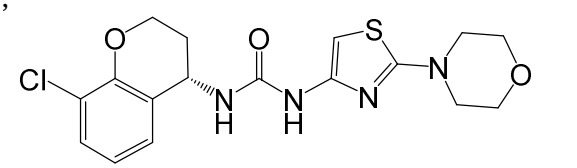


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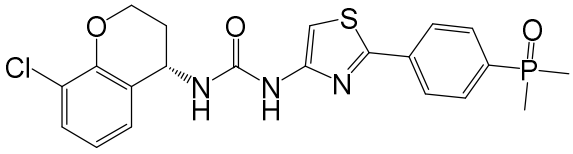


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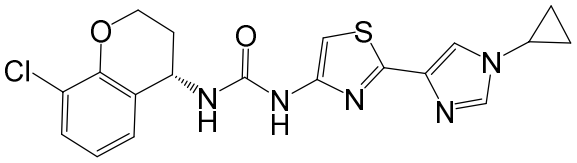

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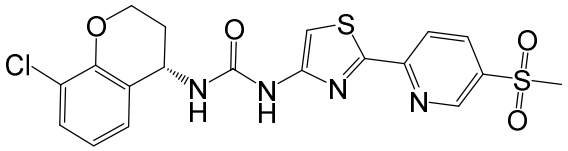


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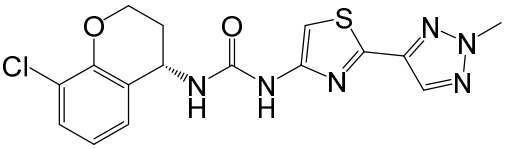

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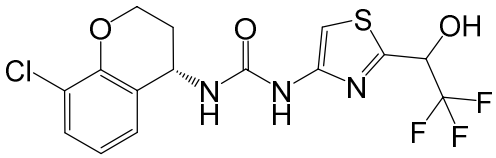


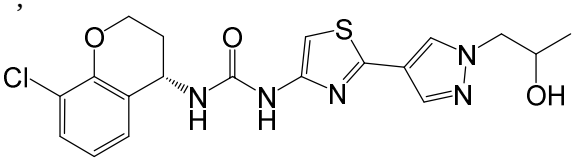
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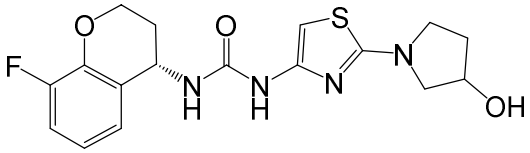


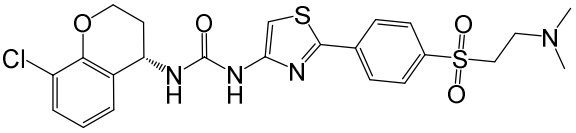
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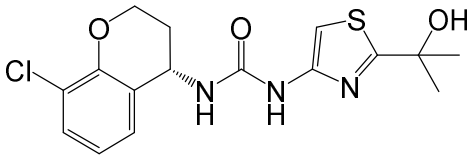


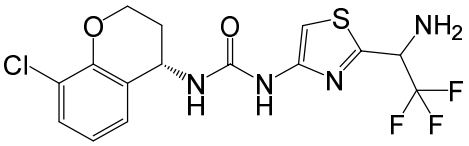
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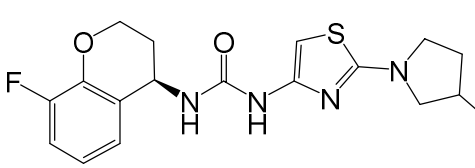


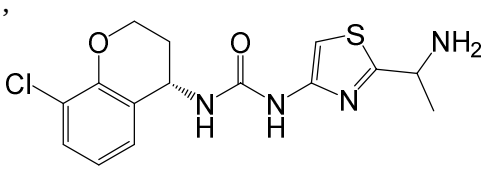
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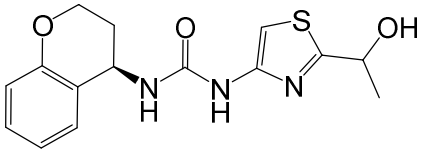


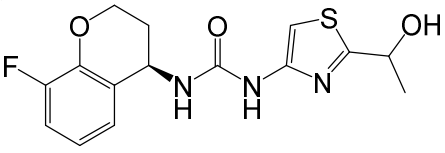
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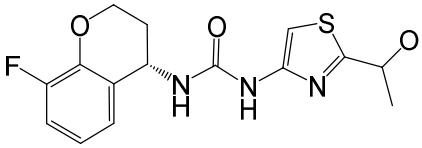


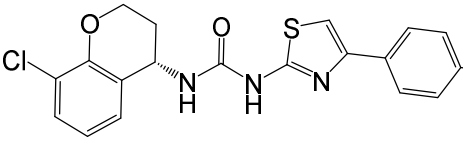
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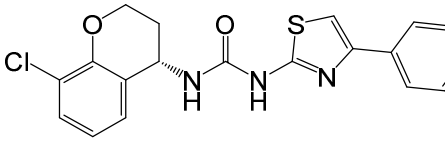


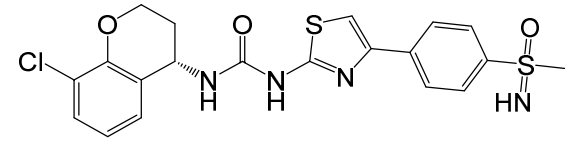
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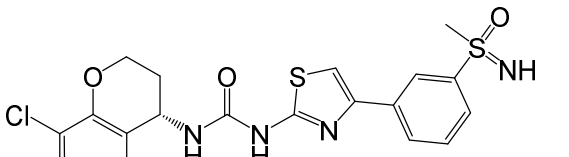


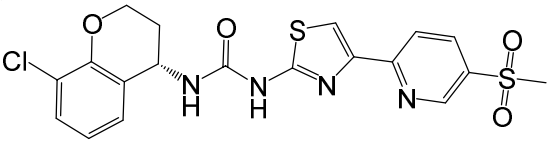
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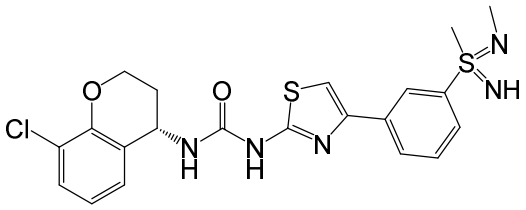


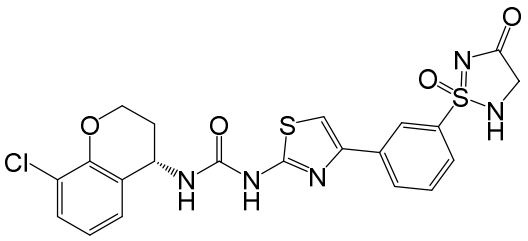


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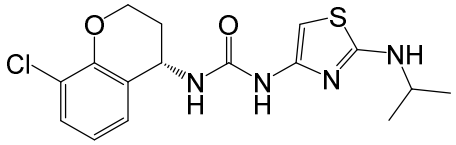


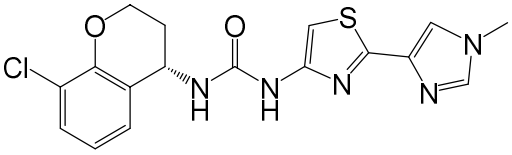
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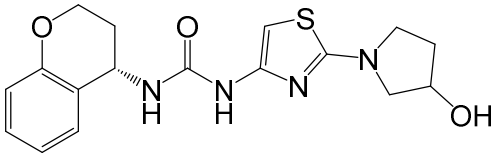


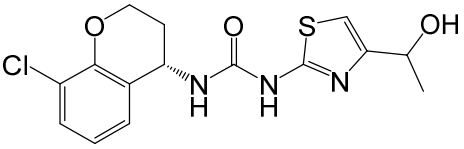
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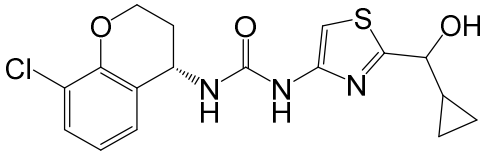


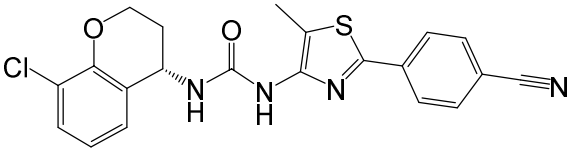
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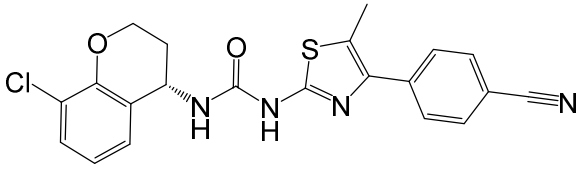


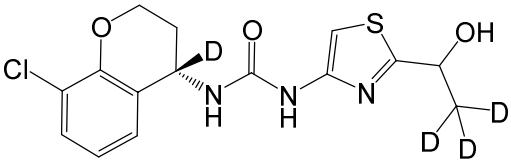
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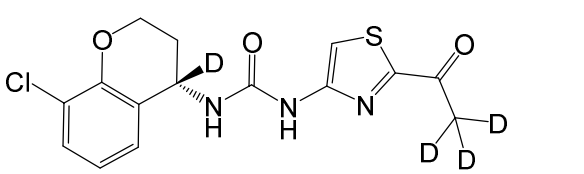


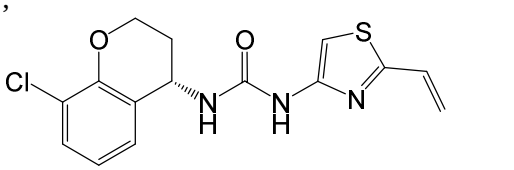
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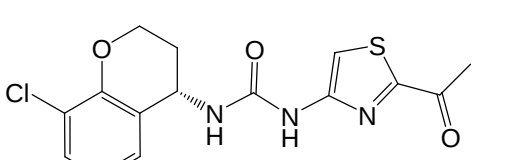


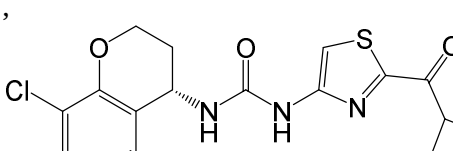
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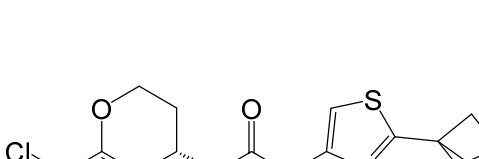


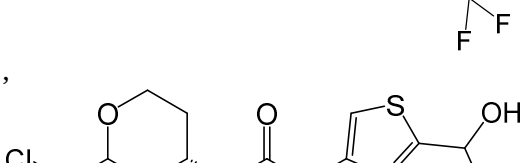
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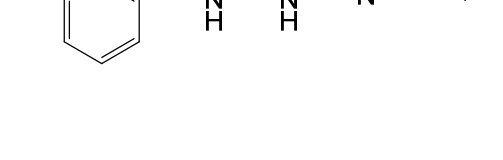


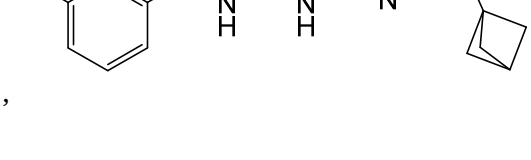
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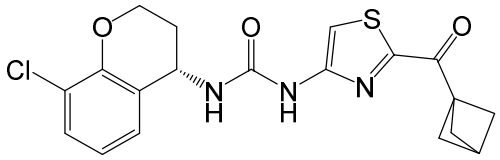


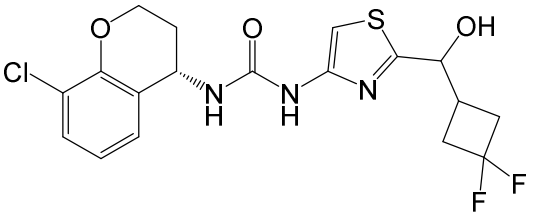
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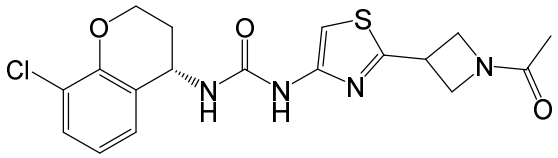


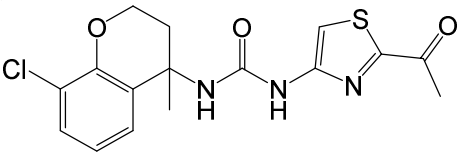
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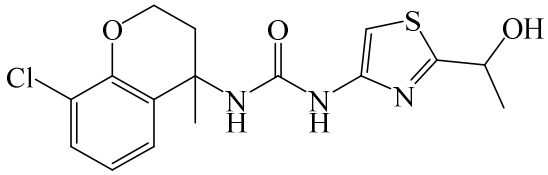


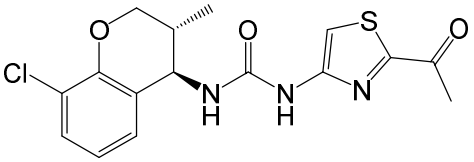
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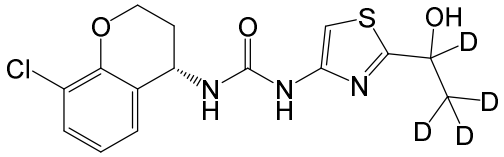


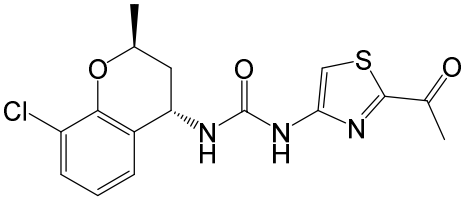
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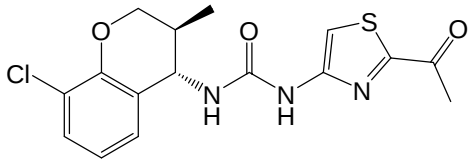


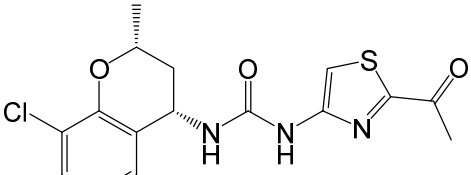
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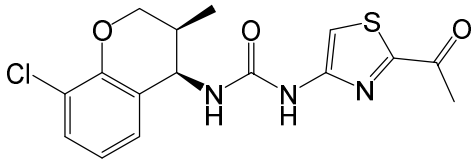


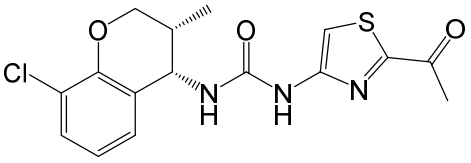
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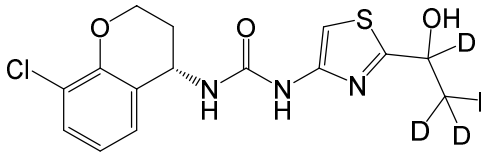


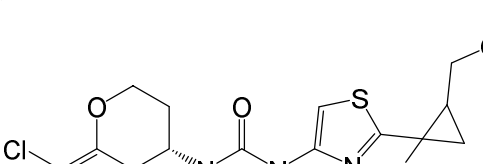
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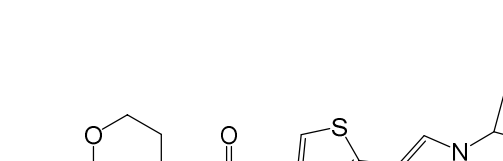


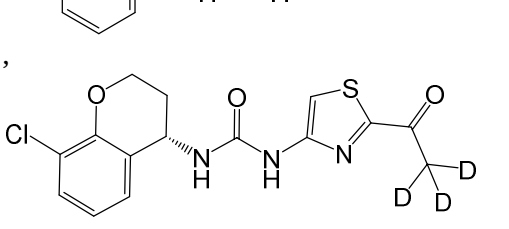
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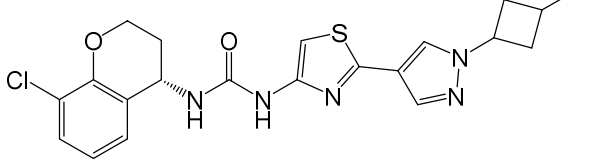


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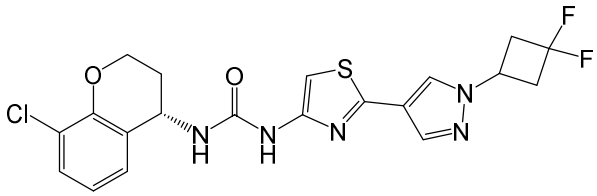
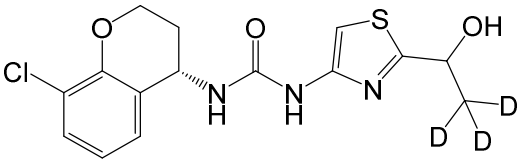
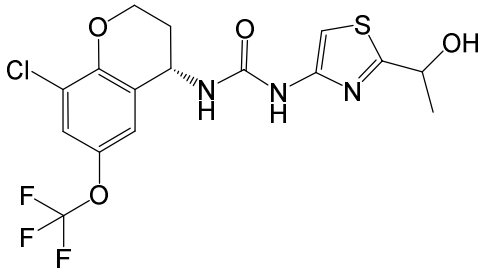
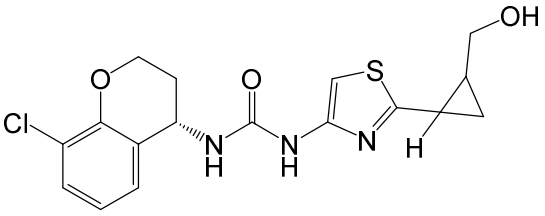
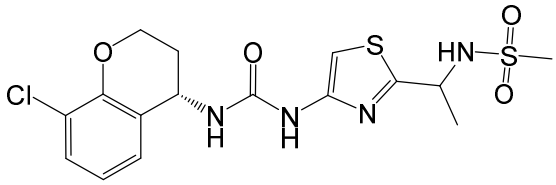
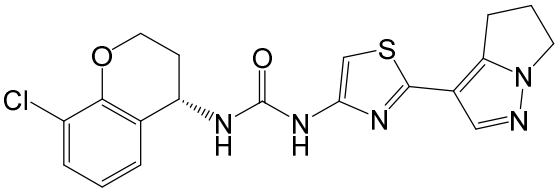
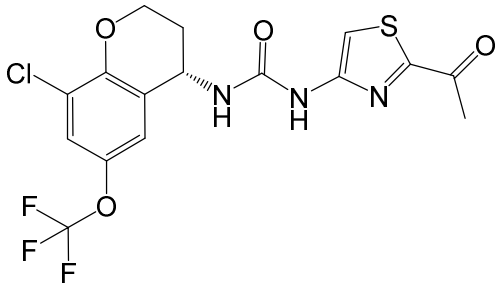
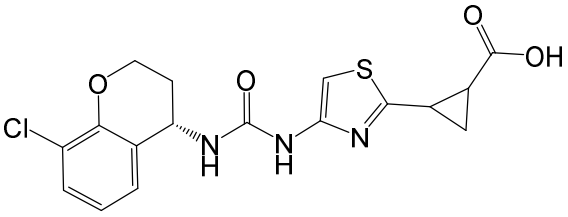
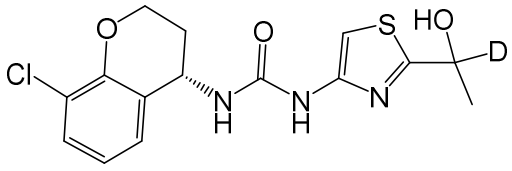
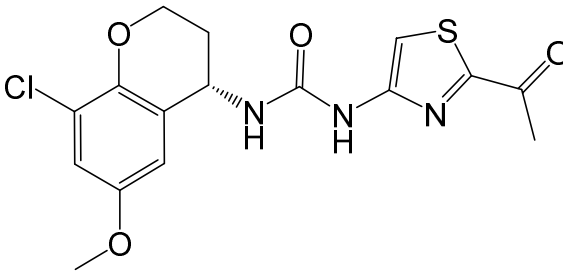
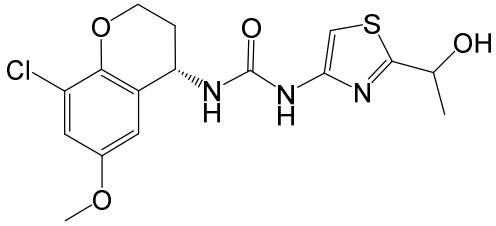
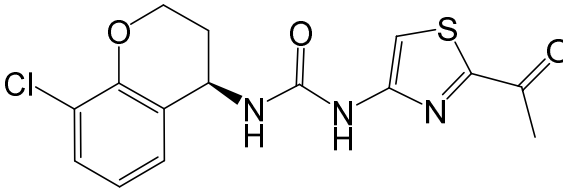
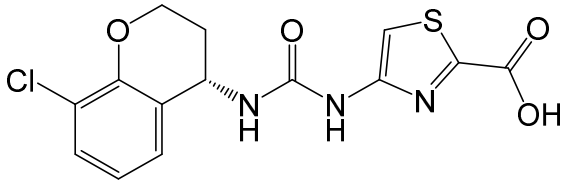
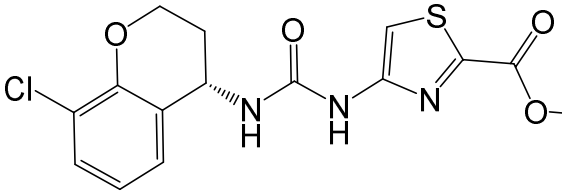


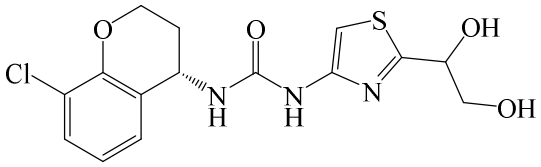


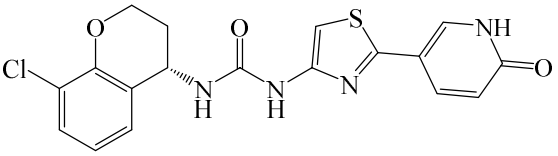
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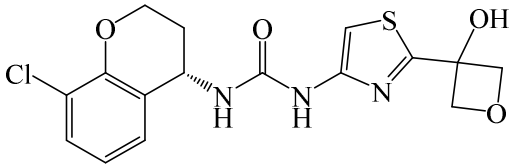
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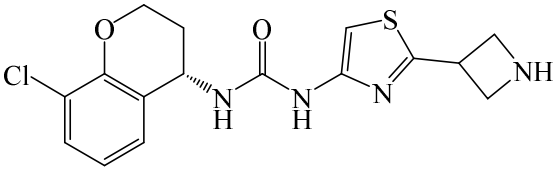

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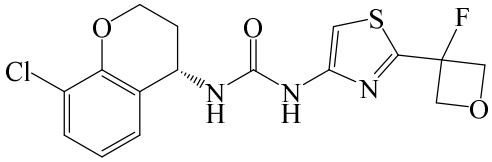


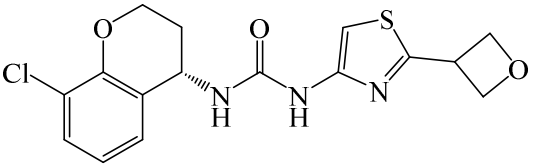
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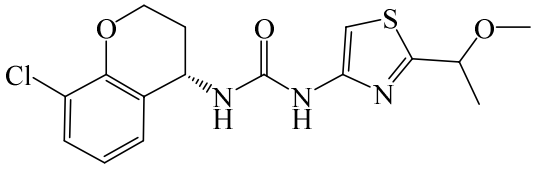


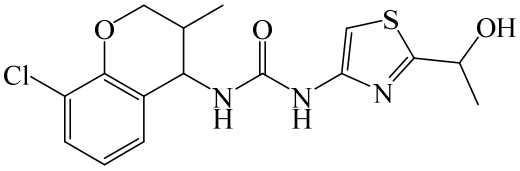
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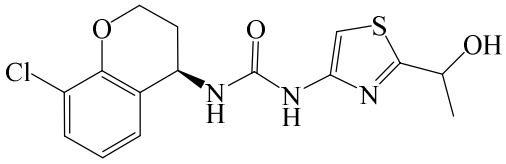


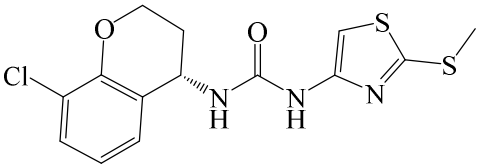
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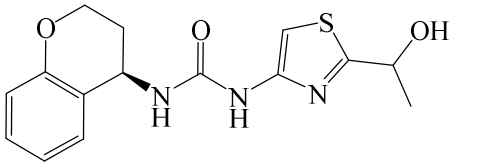


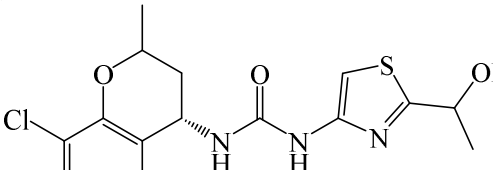
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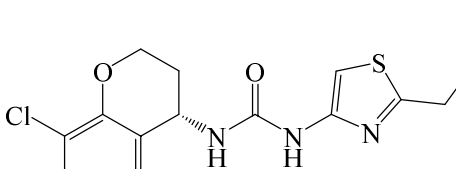


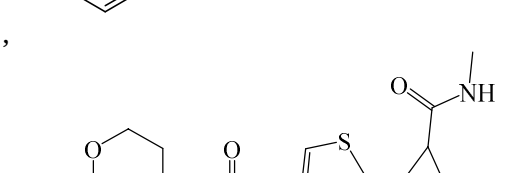
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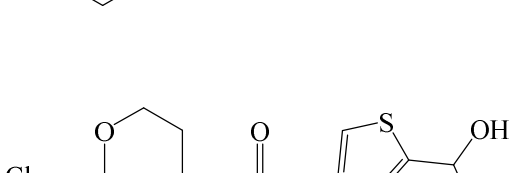


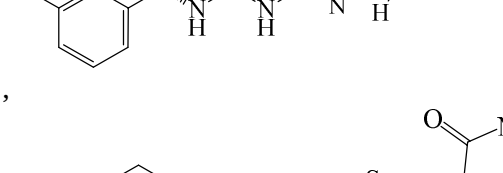
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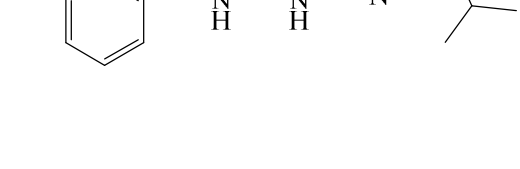


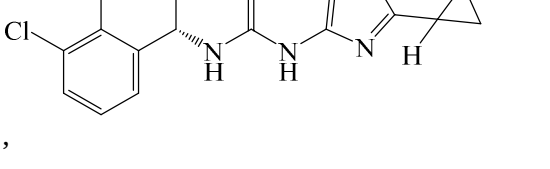
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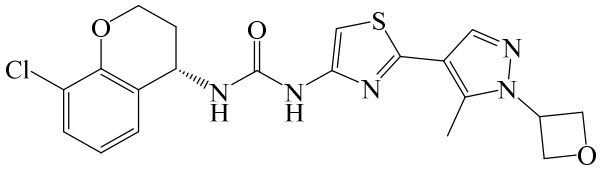
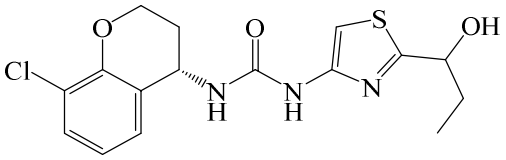
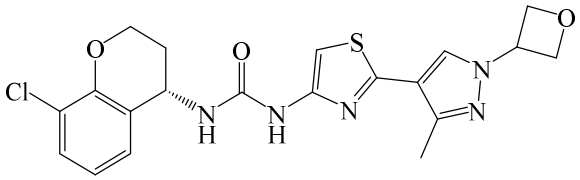
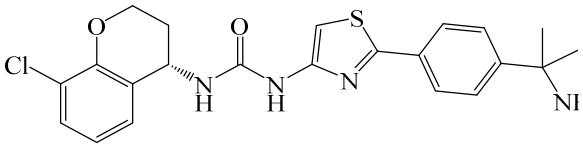
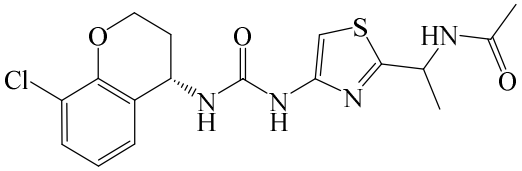
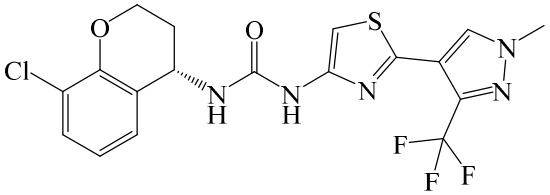
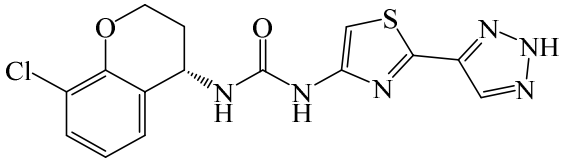
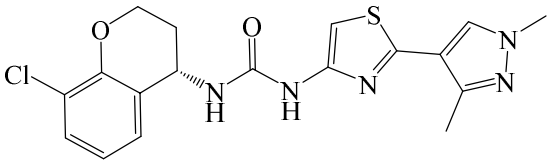
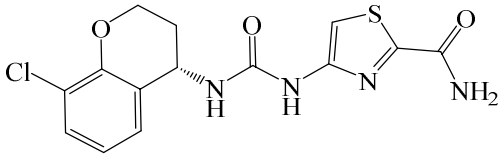
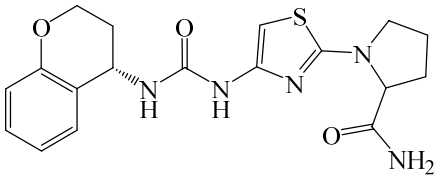
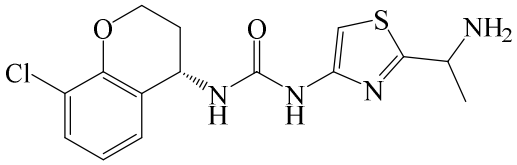
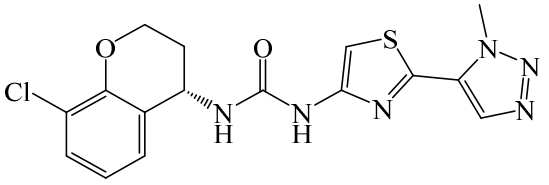
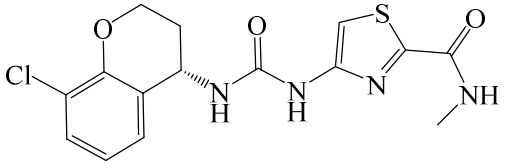
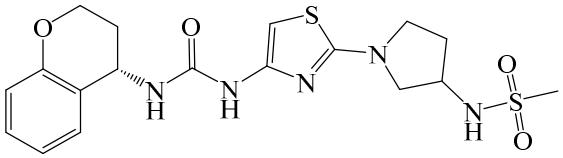
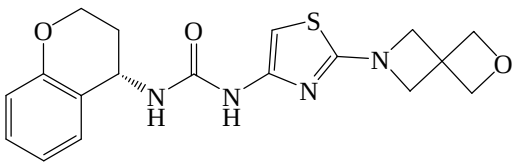
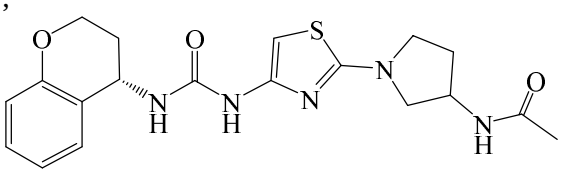
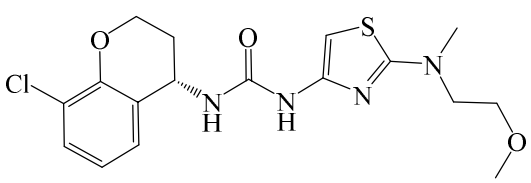
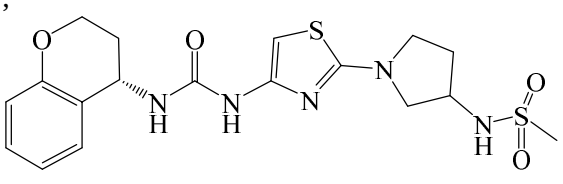


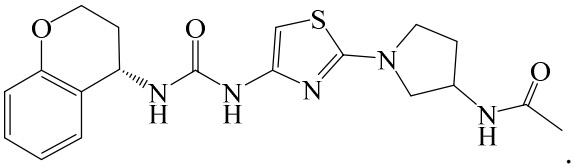
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DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0012] The term “alkyl” as used herein refers to both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms in a specified range. For example the term “C_1-C_7 alkyl” means linear or branched chain alkyl groups, including all possible isomers, having 1, 2, 3, 4, 5, 6, or 7 carbon atoms. Furthermore, alkyl groups allow for substituents to be located on any of the carbon atoms. For example, a substituted C_3 alkyl group allows for the substituent to be located on any one, or more, of the three carbon atoms.

[0013] The term “alkoxy” or “alkoxyl” as used herein refers to an -O-alkyl group. For example, the term “C_1-C_4 alkoxyl” means -O-C_1-C_4 alkyl. In certain embodiments, alkoxy may be represented by “OR” wherein R is an optionally substituted alkyl group. Examples of alkoxyl include methoxyl, ethoxyl, propoxyl (*e.g.*, *n*-propoxyl and isopropoxyl), and the like.

[0014] The term “azole” as used herein refers to a class of five-membered heterocyclic compounds containing a nitrogen atom and at least one other non-carbon atom (i.e., nitrogen, sulfur, or oxygen) as part of the ring. Examples of azole rings include, but not limited to, pyrrole, furazan, pyrazole, thiazole, oxazole, triazole, thiadiazole, oxadiazole, imidazole, 1,2 pyrazole, 2,3 thiazole, 2,4 thiazole, 2,3 oxazole, 1,2,4 triazole, 1,2,4 thiadiazole, and 1,2,4 oxadiazole.

[0015] The term “halogen” or “halo” as used herein refers any of the six nonmetallic elements that constitute Group 17 (Group VIIa) of the periodic table. The halogen elements include, but are not limited to, fluorine or fluoro (F), chlorine or chloro (Cl), bromine or bromo (Br), and iodine or iodo (I).

[0016] The term “cycloalkyl” as used herein refers to a completely saturated or partially unsaturated cyclic group that includes monocyclic or multicyclic ring system. In certain embodiments, cycloalkyl groups contain 3 to 14 carbon atoms in the ring system (“C_4-C_{14} cycloalkyl”). In certain embodiments, each of the cycloalkyl rings may contain one or more