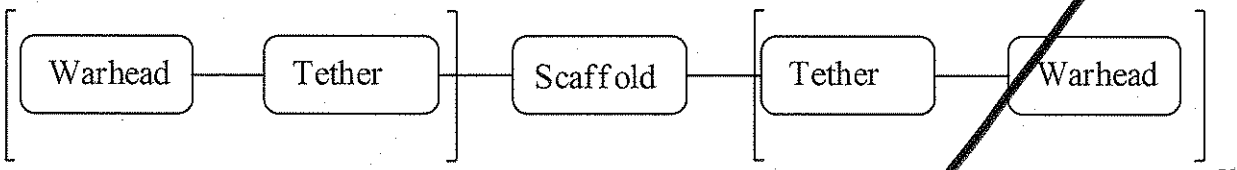
**CLAIMS**

1. A compound of Formula **I**:




**I**

wherein

Scaffold is

a) a radical resulting from the removal of a hydrogen of a ligand capable of binding to, or in proximity to, the ligand-binding site; or

b) a portion of a pharmacophore of a ligand resulting from truncation of the pharmacophore, such that the Scaffold is capable of binding to, or in proximity to, the ligand-binding site;

Warhead is an organic moiety optionally containing one or more heteroatoms selected from O, N, and S; the organic moiety having a molecular weight of about 14 daltons to about 200 daltons; Warhead being capable of reaction with a side chain primary amine group of a lysine residue; and Warhead being attached to Scaffold through Tether;

Tether is null, a bond, or a bivalent $C_1$-$C_{15}$ saturated, unsaturated, straight, branched, cyclic, bicyclic, or tricyclic hydrocarbon moiety; wherein optionally one or more methylene units of the hydrocarbon chain are independently replaced by -$NR_1$-, -O-, -C(O)-, -S-, -SO-, -$SO_2$-, -C(=S)-, or C(=$NR_1$)-; optionally one or more hydrogens are independently replaced by heteroatoms; and optionally one or more methine groups of the $C_1$-$C_{15}$ alkyl, when present, are independently replaced by ;

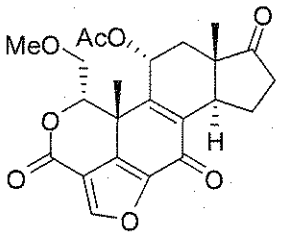
x is 0, 1, or 2;

y is 1, 2, or 3; and

$R_1$ is hydrogen or $C_1$-$C_8$ alkyl,

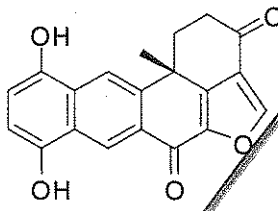
with the proviso that the compound of Formula **I** is not

wortmannin:

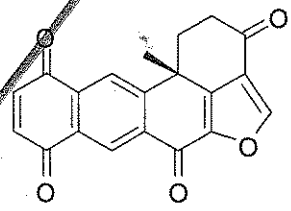


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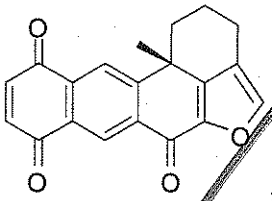
known analogues of wortmannin that covalently modify lysine through substantially the same mechanism as wortmannin:



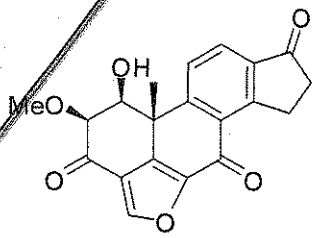
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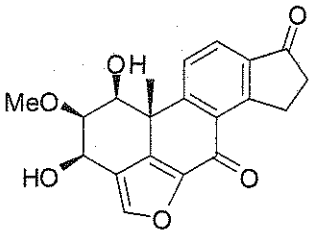
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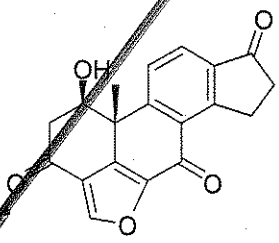
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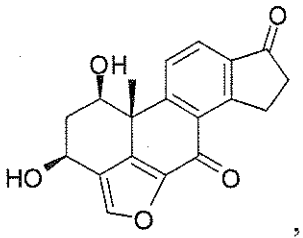
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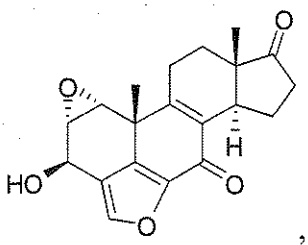
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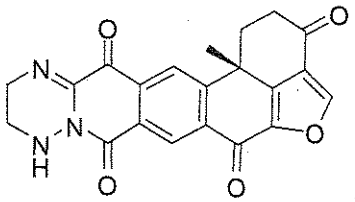
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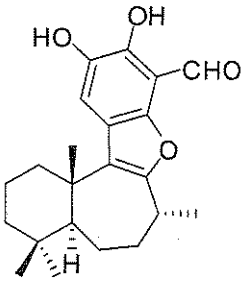
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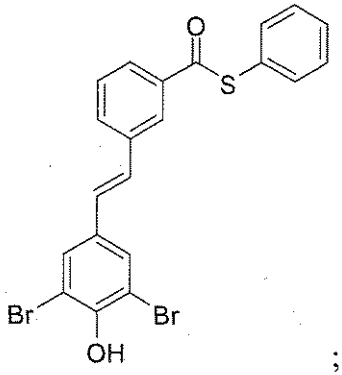


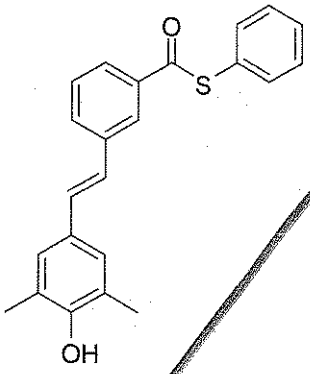
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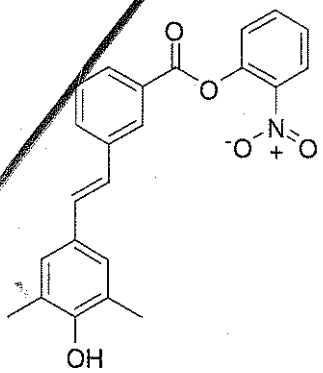


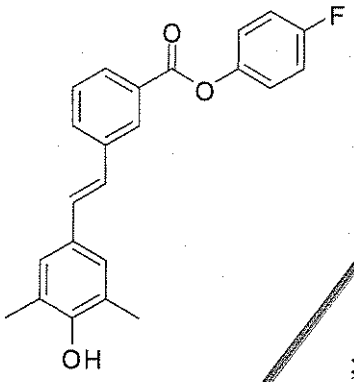
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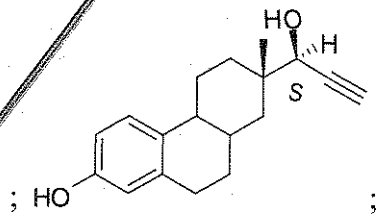

HO
OH
CHO
O
H
;

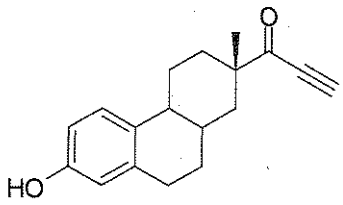

O
S
Br
Br
OH
;

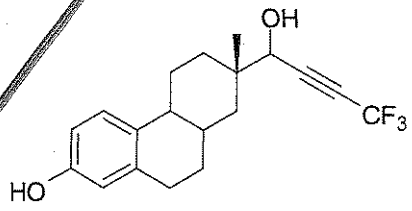

O
S
OH
;

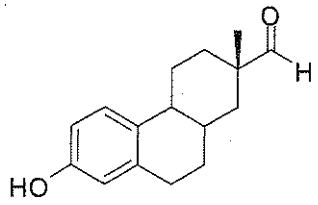

O
O
N
O
O
OH
;

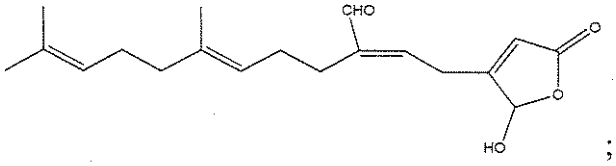

O
F
O
OH

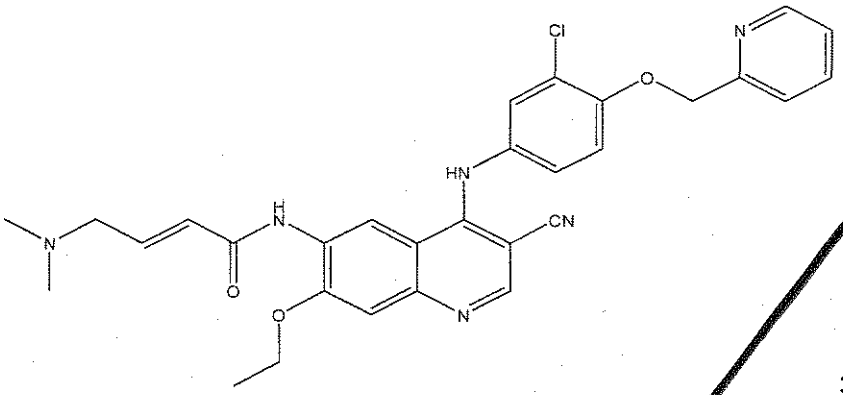

HO
H
S
HO
;


O
HO
;

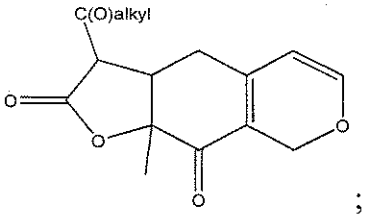

OH
CF3
HO


O
H
HO
;

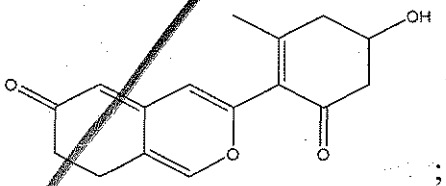

CHO
O
O
HO
;



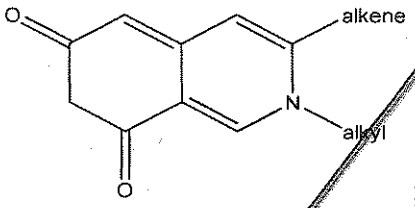

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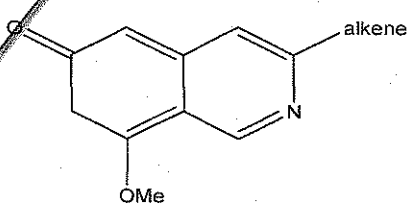

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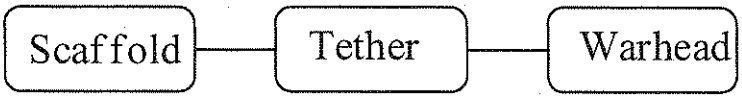

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; and

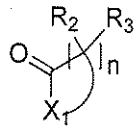
any mechanism-based irreversible inhibitors.

2. The compound of claim 1, wherein the compound of Formula **I** is compound of Formula **I'**:

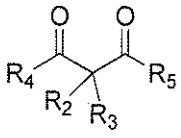



**I'**

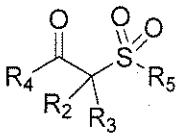
3. The compound of claim 2, wherein Warhead is a radical resulting from the removal of a hydrogen of a compound of Formula **I-a**, **I-b**, **I-c**, **I-d**, **I-e**, **I-f**, **I-g**, **I-h**, **I-i**, **I-j**, **I-k**, **I-l**, **I-m**, **I-n**, **I-o**, **I-p**, **I-q**, **I-r**, **I-s**, and **I-t**:



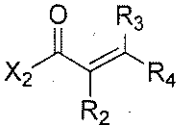
**I-a**



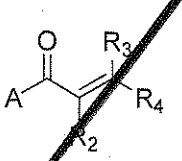
**I-b**



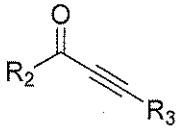
**I-c**



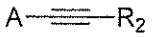
**I-d**



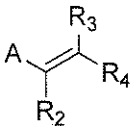
**I-e**



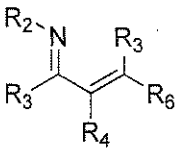
**I-f**



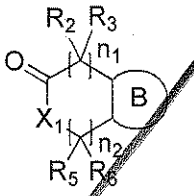
**I-g**



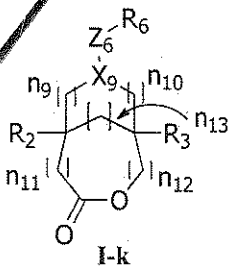
**I-h**



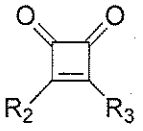
**I-i**



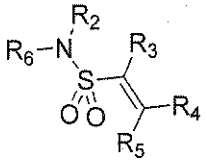
**I-j**



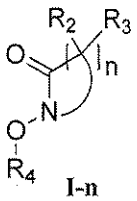
**I-k**



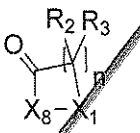
**I-l**



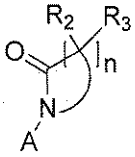
**I-m**



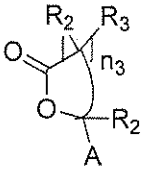
**I-n**



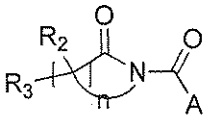
**I-o**



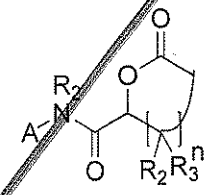
**I-p**



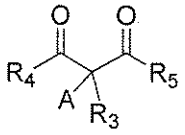
**I-q**



**I-r**



**I-s**



**I-t**

wherein

each $X_1$ and $X_8$ is independently -O-, -S-, or -$NR_6$-;

each $X_2$ is independently -$R_6$, -$OR_6$, or -$NR_6R_7$;

each $X_9$ is independently  or ;

each $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, and $R_8$ is independently hydrogen or $C_1$-$C_6$ alkyl; wherein one or more methylene groups of the $C_1$-$C_6$ alkyl can be replaced by -$NR_1$-, -O-, -C(O)-, -S-, -SO-, -$SO_2$-, or -C(=S)-; one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ;

$R_1$ is hydrogen or $C_1$-$C_8$ alkyl;

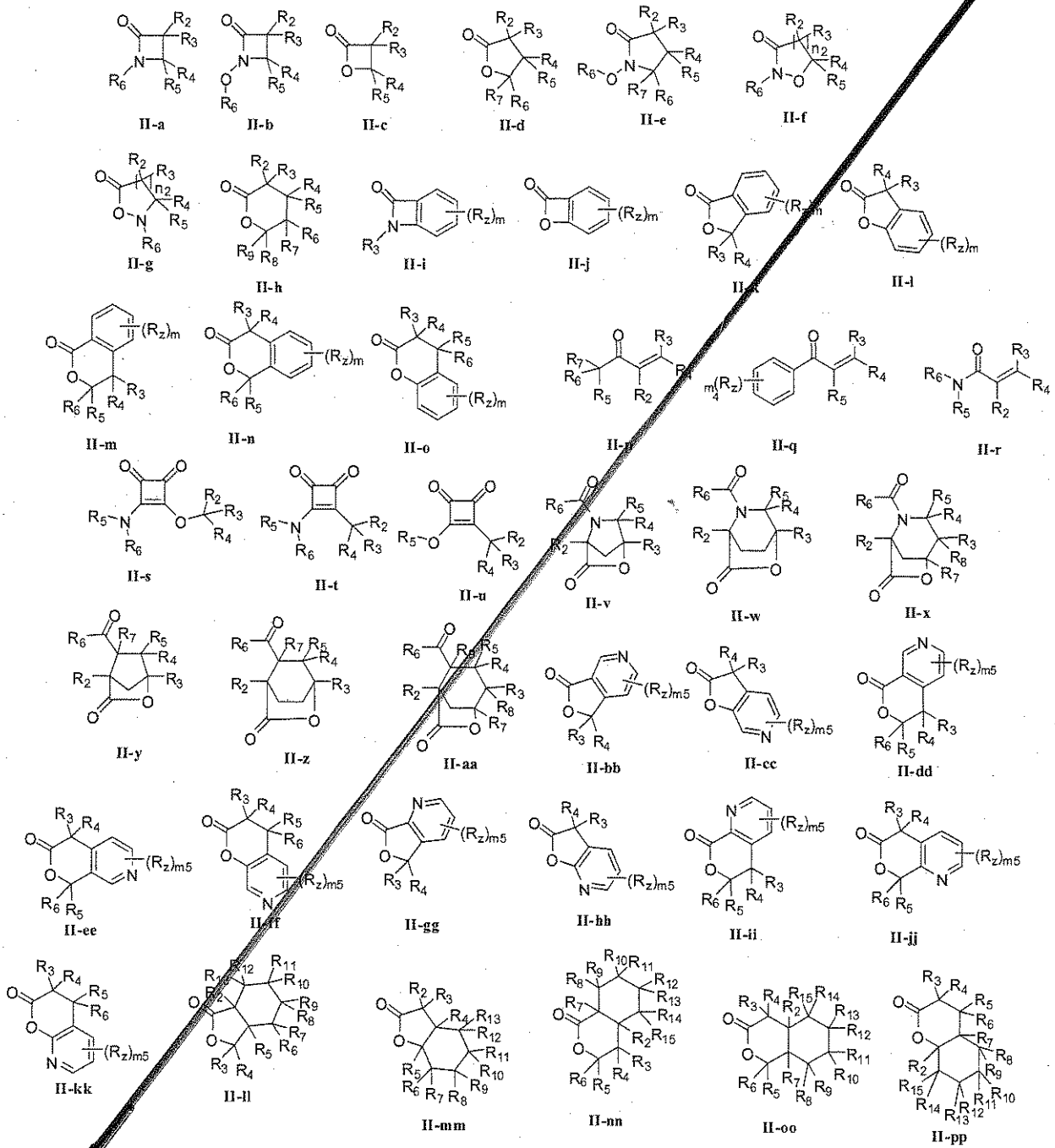
wherein optionally when proper any two of $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, and $R_8$ when taken together form a 3- to 8-membered carbocyclic or heterocyclic ring or an aryl or heteroaryl group; and optionally $X_2$ and any one of $R_2$, $R_3$, and $R_4$ when taken together form a 3- to 8-membered carbocyclic or heterocyclic ring or an aryl or heteroaryl group;

A and B are each independently an optionally substituted monocyclic, bicyclic, or tricyclic aryl or heteroaryl; and

n is an integer from 2-4; each $n_1$ and $n_2$ is independently an integer from 0-2; $n_3$ is an integer from 1-2; $n_4$ is an integer from 1-3; and each one of $n_9$, $n_{10}$, $n_{11}$, and $n_{12}$ is an integer from 0-1; and $n_{13}$ is an integer from 0-2, wherein when any one of the foregoing n integers is more than 1, the adjacent carbons represented by the integer can form a single or double bond.

4. The compound of claim 3, wherein as least one of $R_2$ and $R_3$ of the compounds of Formulas **I-b** and **I-c** is hydrogen.

5. The compound of claim 3, wherein the compound of Formula **I-a**, **I-d**, **I-e**, **I-j**, **I-k**, or **I-l** is a compound of Formula **II-a**, **II-b**, **II-c**, **II-d**, **II-e**, **II-f**, **II-g**, **II-h**, **II-i**, **II-j**, **II-k**, **II-l**, **II-m**, **II-n**, **II-o**, **II-p**, **II-q**, **II-r**, **II-s**, **II-t**, **II-u**, **II-v**, **II-w**, **II-x**, **II-y**, **II-z**, **II-aa**, **II-bb**, **II-cc**, **II-dd**, **II-ee**, **II-ff**, **II-gg**, **II-hh**, **II-ii**, **II-jj**, **II-kk**, **II-ll**, **II-mm**, **II-nn**, **II-oo**, or **II-pp**;




wherein

each m is independently an integer from 0-4;

each $m_5$ is independently an integer from 0-3;

each $m_4$ is independently an integer from 0-5;

each $n_2$ is independently an integer from 0-2;

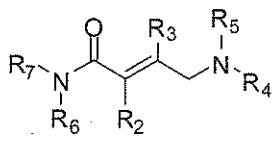
each $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, and $R_{15}$ is independently hydrogen or $C_1$-$C_6$ alkyl; $R_z$ is hydrogen, $C_1$-$C_6$ alkyl, halogen, $CF_3$, or nitro; wherein

one or more methylene groups of the $C_1$-$C_6$ alkyl can be replaced by $-NR_1-$, -O-, -C(O)-, -S-, -SO-, $-SO_2-$, or -C(=S)-; one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ;

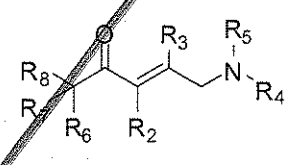
$R_1$ is hydrogen or $C_1$-$C_8$ alkyl; and

optionally when proper any two of $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$, $R_{12}$, $R_{13}$, $R_{14}$, and $R_{15}$ when taken together form a 3- to 8-membered carbocyclic or heterocyclic ring or an aryl or heteroaryl group.

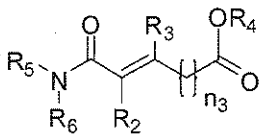
6. The compound of claim 3, wherein the compound of Formula **I-d**, or **I-h** is a compound of Formula **III-a**, **III-b**, **III-c**, **III-d**, **III-e**, **III-f**, **III-g**, **III-h**, or **III-i**;



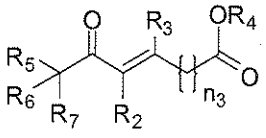
**III-a**



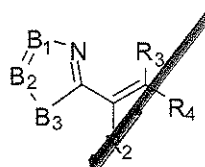
**III-b**



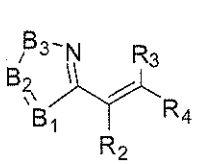
**III-c**



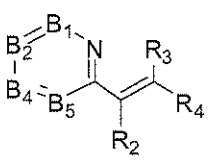
**III-d**



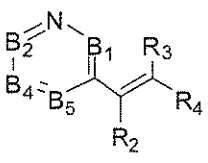
**III-e**



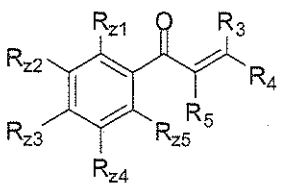
**III-f**



**III-g**



**III-h**



**III-i**

wherein

$n_3$ is an integer from 0-2;

each $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, and $R_8$ is independently hydrogen or $C_1$-$C_6$ alkyl;

each $B_1$, $B_2$, $B_4$, and $B_5$ is independently $CR_7$ or N and each $B_3$ is $NR_7$, O, or S;

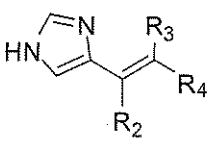
each $R_{z1}$, $R_{z2}$, $R_{z3}$, $R_{z4}$, and $R_{z5}$ is hydrogen, $C_1$-$C_6$ alkyl, halogen, $CF_3$, or nitro;

one or more methylene groups of the $C_1$-$C_6$ alkyl can be optionally replaced by $-NR_1-$, -O-, -C(O)-, -S-, -SO-, $-SO_2-$, or -C(=S)-; one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ;

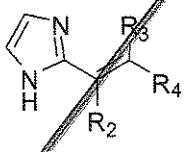
$R_1$ is hydrogen or $C_1$-$C_8$ alkyl; and

optionally when proper any two of $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, and $R_8$ when taken together form a 3- to 8-membered carbocyclic or heterocyclic ring or an aryl or heteroaryl group.

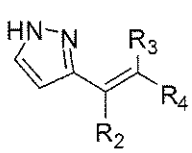
7. The compound of claim 3, wherein the compound of Formula **I-h** is a compound of Formula **IV-a**, **IV-b**, **IV-c**, **IV-d**, **IV-e**, **IV-f**, **IV-g**, **IV-h**, or **IV-i**:



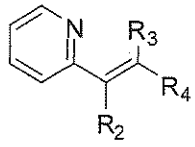
**IV-a**



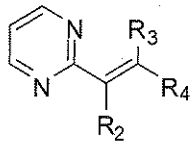
**IV-b**



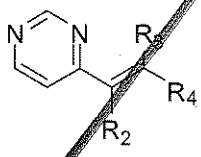
**IV-c**



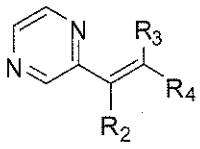
**IV-d**



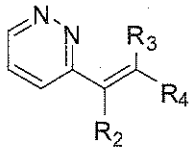
**IV-e**



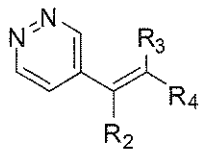
**IV-f**



**IV-g**



**IV-h**



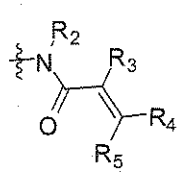
**IV-i**

;

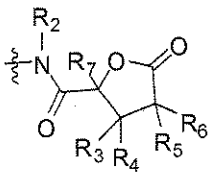
wherein any of the substitutable hydrogens on the nitrogen heterocycle of the compound can be substituted with alkyl, alkoxy, amido, acyl, acyloxy, oxoacyl, halogen.

8. The compound of claim 3, wherein

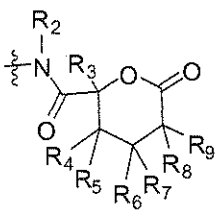
a) the radical resulting from the removal of a hydrogen of a compound of Formula **I-a**, **I-d**, **I-k**, or **I-m** is a radical of Formula **V-a**, **V-b**, **V-c**, **V-d**, **V-e**, **V-f**, **V-g**, **V-h**, **V-i**, or **V-j**;



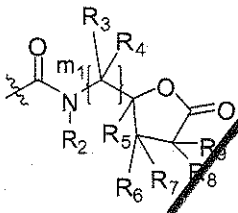
**V-a**



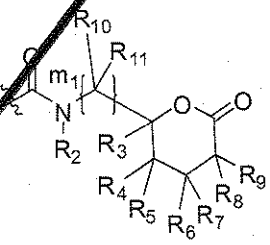
**V-b**



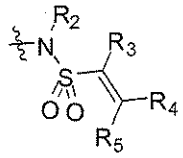
**V-c**



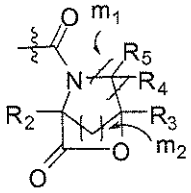
**V-d**



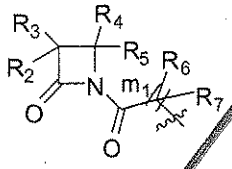
**V-e**



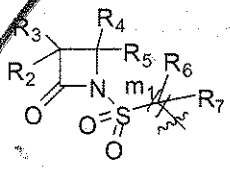
**V-f**



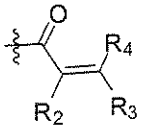
**V-g**



**V-h**



**V-i**



**V-j**

wherein

$m_1$ and $m_2$ are each independently an integer from 0 to 2;

each $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, and $R_{11}$ is independently hydrogen or $C_1$-$C_6$ alkyl;

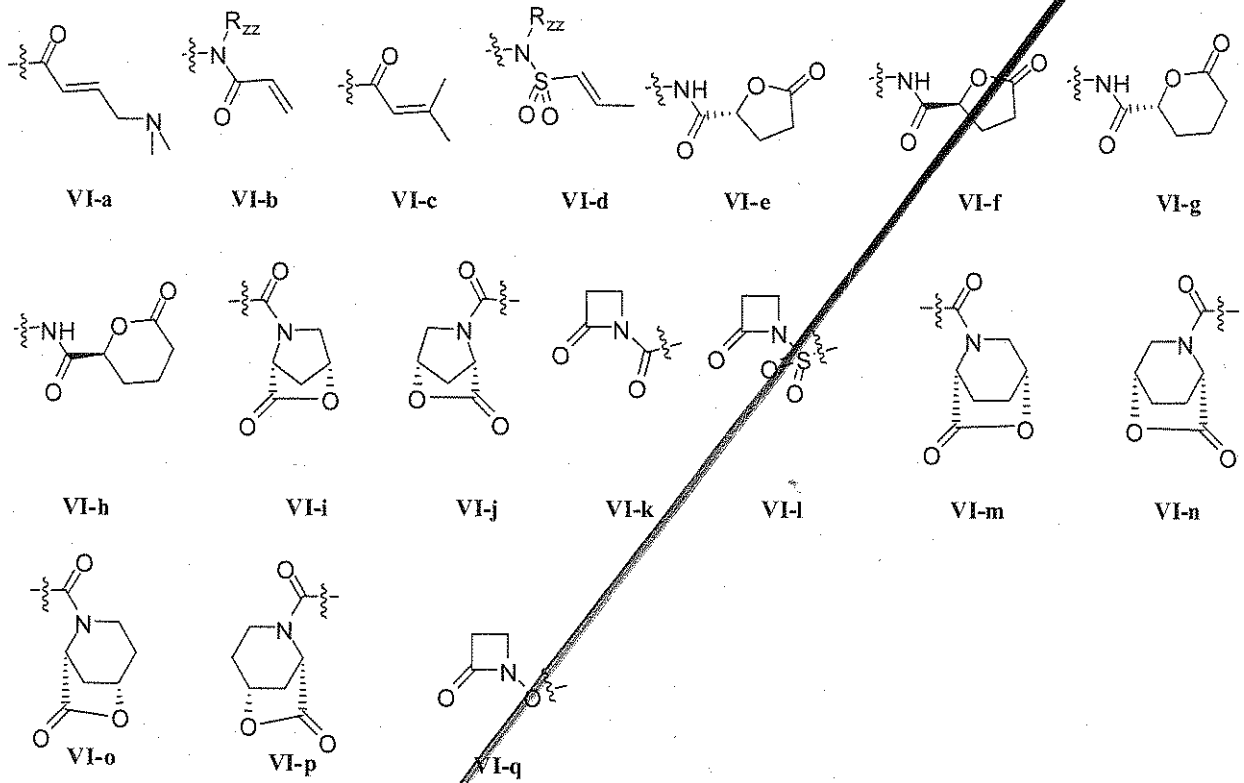
one or more methylene groups of the $C_1$-$C_6$ alkyl can be optionally replaced by $-NR_1-$, -O-, -C(O)-, -S-, -SO-, $-SO_2-$, or -C(=S)-;

one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ;

$R_1$ is hydrogen or $C_1$-$C_8$ alkyl; and

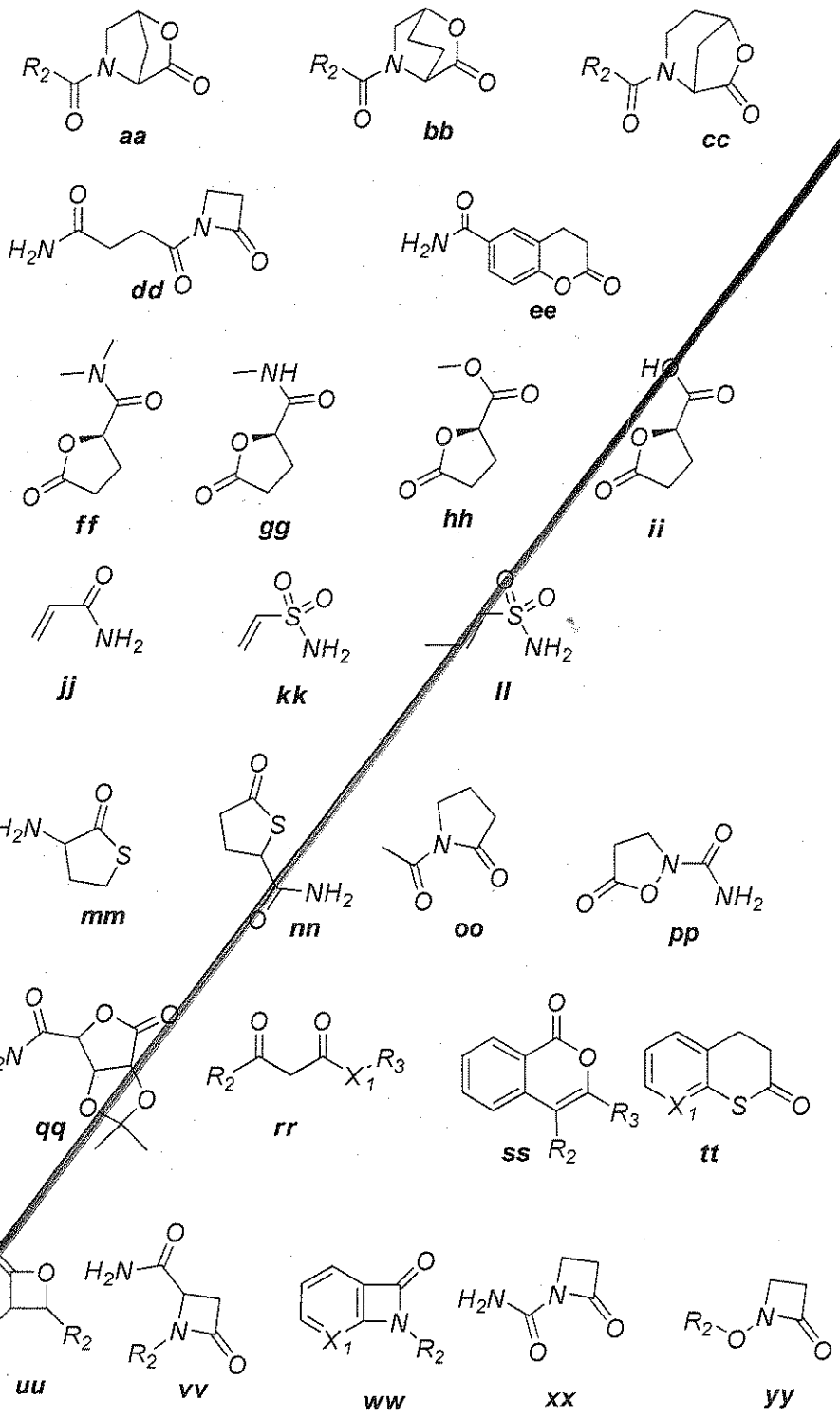
optionally when proper any two of $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, and $R_{11}$ when taken together form a 3- to 8-membered carbocyclic or heterocyclic ring or an aryl or heteroaryl group; or

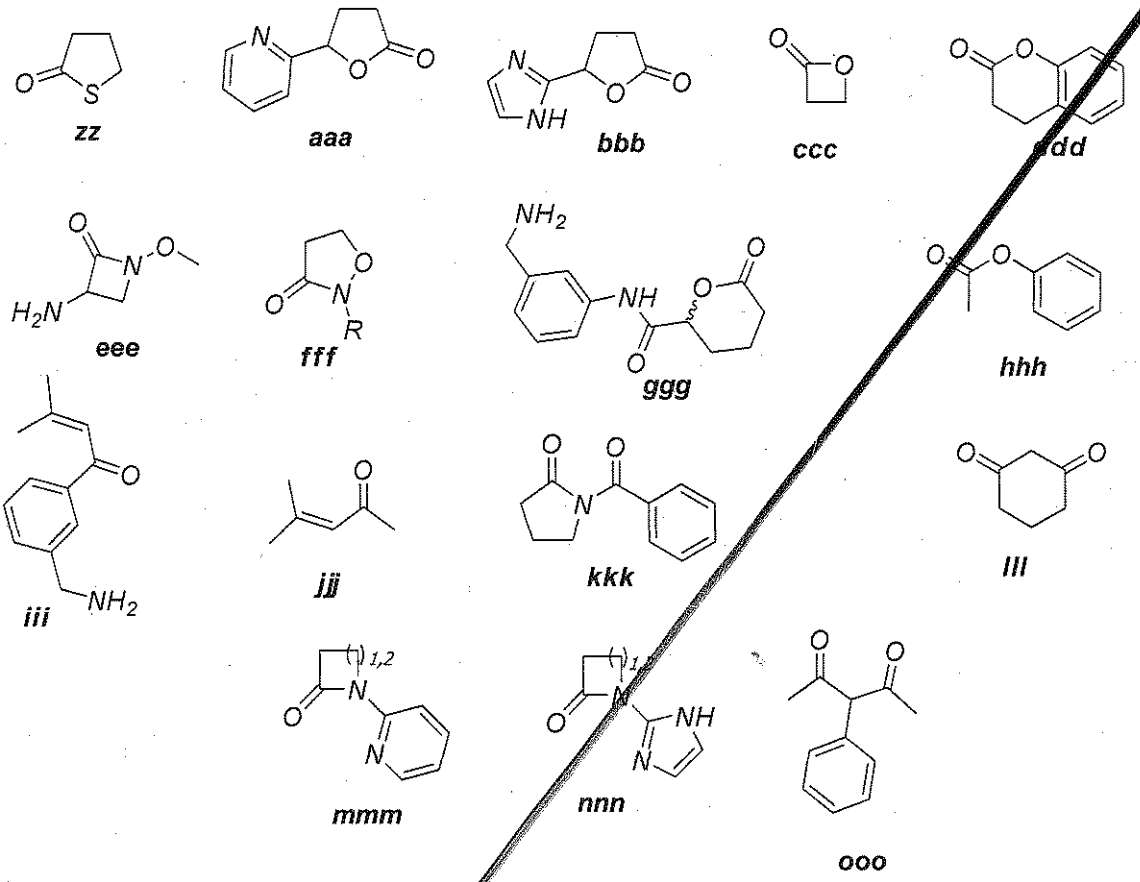
b) wherein the radical resulting from the removal of a hydrogen of a compound of Formula **I-a**, **I-d**, **I-k**, or **I-m** is a radical of Formula **VI-a**, **VI-b**, **VI-c**, **VI-d**, **VI-e**, **VI-f**, **VI-g**, **VI-h**, **VI-i**, **VI-j**, **VI-k**, **VI-l**, **VI-m**, **VI-n**, **VI-o**, **VI-p**, or **VI-q**:




wherein $R_{zz}$ is hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, $-CH_2OCH_3$, and $-CH_2CH_2OCH_3$.

9. The compound of claim 3, wherein the compounds of Formulae **I-a**, **I-b**, **I-c**, **I-d**, **I-e**, **I-f**, **I-g**, **I-h**, **I-i**, **I-j**, **I-k**, **I-l**, **I-m**, **I-n**, **I-o**, **I-p**, **I-q**, **I-r**, **I-s**, and **I-t** are selected from the group consisting of:


aa
bb
cc
dd
ee
ff
gg
hh
ii
jj
kk
ll
mm
nn
oo
pp
qq
rr
ss
tt
uu
vv
ww
xx
yy

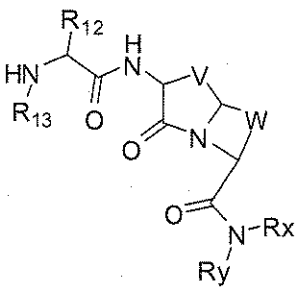



wherein any substitutable hydrogen may be substituted with the substituents as those defined by $R_2$-$R_8$ in formulas **I-a**, **I-b**, **I-c**, **I-d**, **I-e**, **I-f**, **I-g**, **I-h**, **I-i**, **I-j**, **I-k**, **I-l**, **I-m**, **I-n**, **I-o**, **I-p**, **I-q**, **I-r**, **I-s**, and **I-t**.

10. The compound of claim 2, wherein Scaffold is selected from the group consisting of Formulas **VII**, **VIII**, **IX-a**, **IX-b**, **XI**, **XII**, **XVI**, **XVII**, **XVIII**, **XIX**, **XX**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV**, **XXVI**, **XXVII**, **XXVIII**, **XXIX**, **XXXVI**, and **XXXVII**.

11. The compound of claim 3, wherein

a) Scaffold is a radical resulting from the removal of one or more hydrogens of a compound of Formula **VII**:



**VII**

wherein V and W are each independently $-(CR_{14}R_{15})_qX_3(CR_{16}R_{17})_r-$;

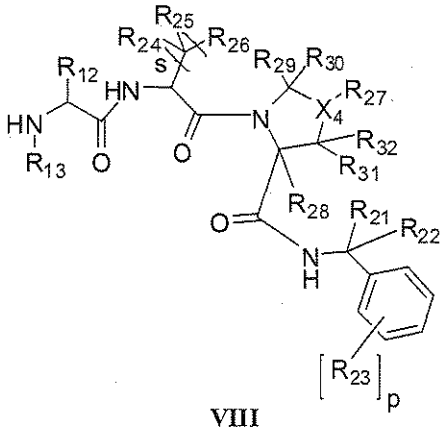
q and r are each independently 0, 1, 2, 3, or 4;

$X_3$ is $-CR_{18}R_{19}-$, or $-NR_{20}-$; and

$R_x$, $R_y$, $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{18}$, $R_{19}$, and $R_{20}$ are each independently hydrogen or $C_1$-$C_6$ alkyl; wherein one or more methylene groups of the $C_1$-$C_6$ alkyl can be replaced by $-NR_1-$, -O-, -C(O)-, -S-, -SO-, $-SO_2-$, -C(=S)-, optionally substituted aryl or heteroaryl groups; one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ; and

$R_1$ is hydrogen or $C_1$-$C_8$ alkyl; or

b) Scaffold is a radical resulting from the removal of a hydrogen of a compound of Formula **VIII**:



**VIII**

wherein

$X_4$ is $-CR_{33}-$ or -N-;

s is 0, 1, 2, 3, or 4; and

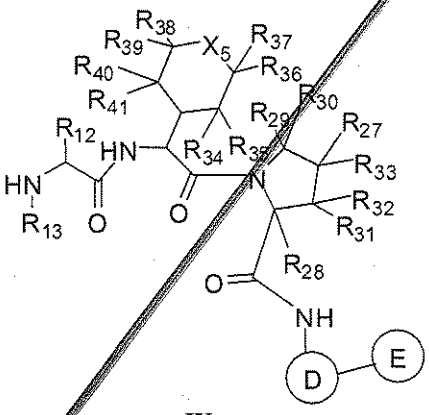
$R_{12}$, $R_{13}$, $R_{21}$, $R_{22}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, $R_{29}$, $R_{30}$, $R_{31}$, $R_{32}$, and $R_{33}$ are each independently hydrogen or $C_1$-$C_6$ alkyl;

$R_{23}$ is hydrogen, $C_1$-$C_6$ alkyl, halogen, amino, or nitro; wherein one or more methylene groups of $C_1$-$C_6$ alkyl can be optionally replaced by $-NR_1-$, -O-, -C(O)-, -S-, -SO-, $-SO_2-$, or -C(=S)-; one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ;

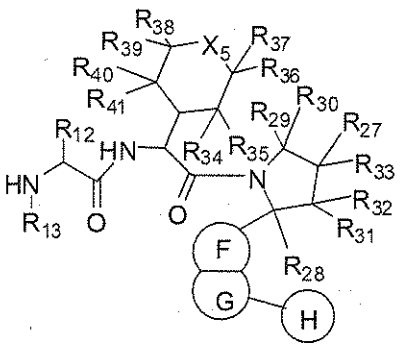
$R_1$ is hydrogen or $C_1$-$C_8$ alkyl; and

optionally $R_{21}$ and $R_{23}$ taken together can form a 4- to 8-membered carbocyclic or heterocyclic ring; or

c) Scaffold is a radical resulting from the removal of a hydrogen of a compound of Formula **IX-a** or **IX-b**:




**IX-a**




**IX-b**

wherein

$X_5$ is -O-, $-CR_{42}R_{43}-$ or $-NR_{42}-$;

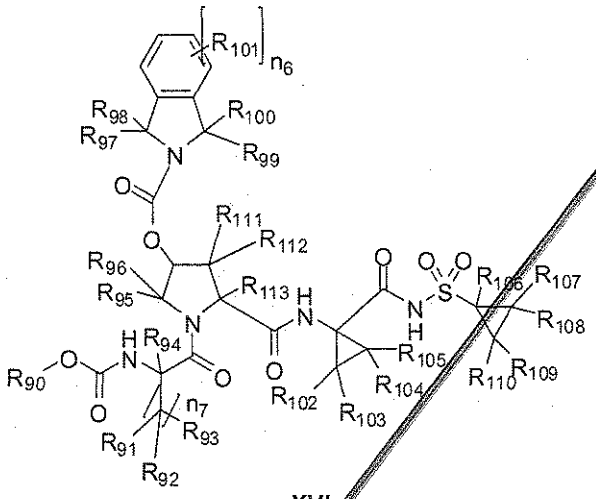
$R_{12}$, $R_{13}$, $R_{27}$, $R_{28}$, $R_{29}$, $R_{30}$, $R_{31}$, $R_{32}$, $R_{33}$, $R_{34}$, $R_{35}$, $R_{36}$, $R_{37}$, $R_{38}$, $R_{39}$, $R_{40}$, $R_{41}$, $R_{42}$, and $R_{43}$ are each independently hydrogen or $C_1$-$C_6$ alkyl; wherein one or more methylene

groups of $C_1$-$C_6$ alkyl can be optionally replaced by -$NR_1$-, -O-, -C(O)-, -S-, -SO-, -$SO_2$-, or -C(=S)-;

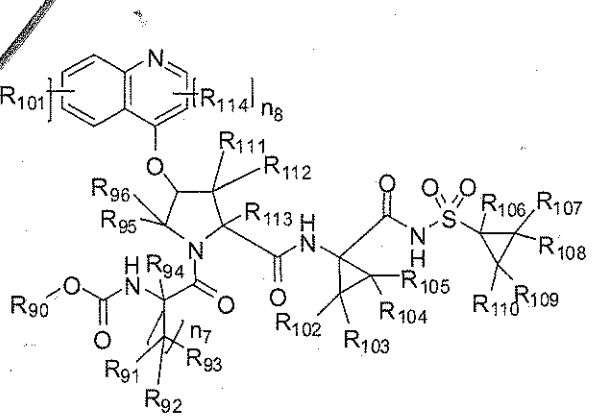
$R_1$ is hydrogen or $C_1$-$C_8$ alkyl; one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ; $R_1$ is hydrogen or $C_1$-$C_8$ alkyl;

D, E, F, G, and H are each independently optionally substituted aryl or heteroaryl; wherein F and G are fused together to form a bicyclic optionally substituted aryl or heteroaryl; or

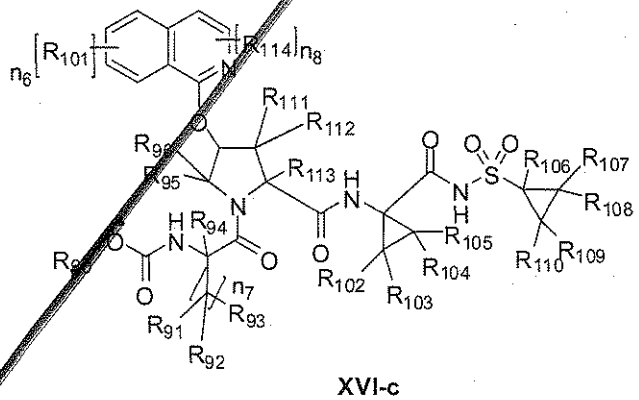
d) Scaffold is a radical resulting from the removal of a hydrogen of a compound of Formula **XVI-a**, **XVI-b**, or **XVI-c**:



**XVI-a**



**XVI-b**



**XVI-c**

wherein

$R_{90}$, $R_{91}$, $R_{92}$, $R_{93}$, $R_{94}$, $R_{95}$, $R_{96}$, $R_{97}$, $R_{98}$, $R_{99}$, $R_{100}$, $R_{102}$, $R_{104}$, $R_{105}$, $R_{106}$, $R_{107}$, $R_{108}$, $R_{109}$, $R_{110}$, $R_{111}$, $R_{112}$, $R_{113}$, and $R_{114}$ are each independently hydrogen or $C_1$-$C_6$ alkyl; wherein one or more methylene groups of $C_1$-$C_6$ alkyl can be optionally replaced by $-NR_1-$, -O-, -C(O)-, -S-, -SO-, $-SO_2-$, or -C(=S)-;

$R_{103}$ is hydrogen, $C_1$-$C_6$ alkyl, or $C_2$-$C_8$ alkenyl;

one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ;

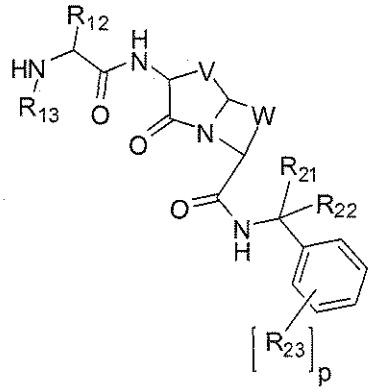
$R_1$ is hydrogen or $C_1$-$C_8$ alkyl;

each $R_{101}$ and $R_{101}$ is independently hydrogen, $C_1$-$C_6$ alkyl, $C_2$-$C_8$ alkenyl, halogen, amino, nitro, optionally substituted aryl or heteroaryl;

$n_6$ and $n_7$ are each independently integer from 0 to 4; and

$n_8$ is an integer from 0 to 2.

12. The compound of claim 11, wherein the compound of Formula **VII** is a compound of Formula **VII-a**:



**VII-a**

wherein

V and W are each independently $-(CR_{14}R_{15})_qX_3(CR_{16}R_{17})_r-$;

p, q and r are each independently 0, 1, 2, 3, or 4;

$X_3$ is $-CR_{18}R_{19}-$, or $-NR_{20}-$; and

$R_{21}$ and $R_{22}$ are each independently hydrogen or $C_1$-$C_6$ alkyl;

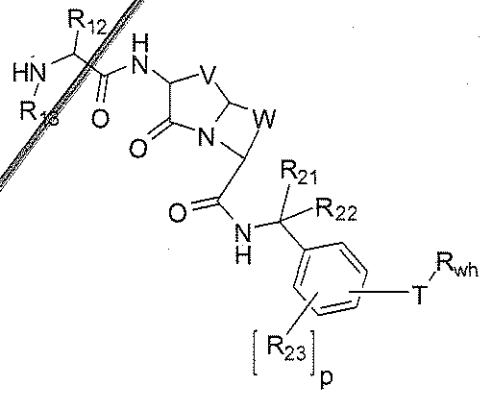
$R_{23}$ is hydrogen, $C_1$-$C_6$ alkyl, halogen, amino, or nitro; wherein one or more methylene groups of $C_1$-$C_6$ alkyl can be optionally replaced by $-NR_1-$, -O-, -C(O)-, -S-, -SO-, $-SO_2-$, or -C(=S)-; one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ;

$R_1$ is hydrogen or $C_1$-$C_8$ alkyl; and

optionally $R_{21}$ and $R_{23}$ taken together can form a 4- to 8-membered carbocyclic or heterocyclic ring.

13. The compound of claim 3, wherein

a) the compound of Formula **I'** is a compound of Formula **VII-b**:



**VII-b**

wherein

V and W are each independently $-(CR_{14}R_{15})_qX_3(CR_{16}R_{17})_r-$;

p, q and r are each independently 0, 1, 2, 3, or 4;

$X_3$ is $-CR_{18}R_{19}-$, or $-NR_{20}-$; and

$R_{21}$ and $R_{22}$ are each independently hydrogen or $C_1$-$C_6$ alkyl;

$R_{23}$ is hydrogen, $C_1$-$C_6$ alkyl, halogen, amino, or nitro; wherein one or more methylene groups of $C_1$-$C_6$ alkyl can be optionally replaced by -$NR_1$-, -O-, -C(O)-, -S-, -SO-, -$SO_2$-, or -C(=S)-; one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ;

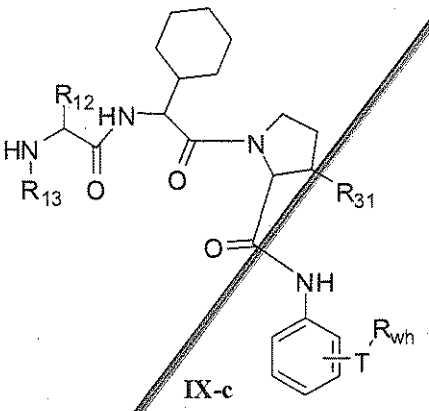
$R_1$ is hydrogen or $C_1$-$C_8$ alkyl; and

optionally $R_{21}$ and $R_{23}$ taken together can form a 4- to 8-membered carbocyclic or heterocyclic ring;

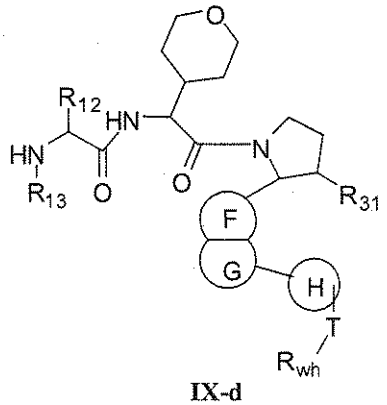
T is Tether; and

$R_{wh}$ is Warhead; or

b) the compound of Formula **I'** is a compound of Formula **IX-c** or **IX-d**:




**IX-c**




**IX-d**

wherein

$R_{12}$, $R_{13}$, and $R_{31}$ are each independently hydrogen or $C_1$-$C_6$ alkyl; wherein one or more methylene groups of $C_1$-$C_6$ alkyl can be optionally replaced by -$NR_1$-, -O-, -C(O)-, -S-, -SO-, -$SO_2$-, or -C(=S)-;

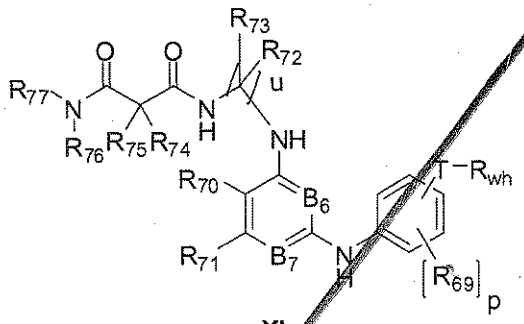
$R_1$ is hydrogen or $C_1$-$C_8$ alkyl; one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ; $R_1$ is hydrogen or $C_1$-$C_8$ alkyl;

F, G, and H are each independently optionally substituted aryl or heteroaryl; wherein F and G are fused together to form a bicyclic optionally substituted aryl or heteroaryl;

T is Tether; and

$R_{wh}$ is Warhead; or

c) the compound of Formula **I′** is a compound of Formula **XI**:



**XI**

wherein

p is an integer from 0 to 4, u is an integer from 1 to 4;

$B_6$ and $B_7$ are each independently $CR_7$ or N;

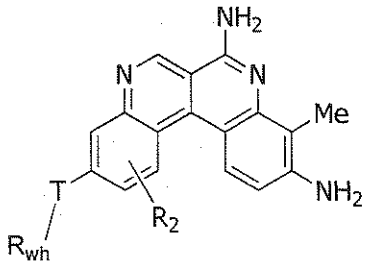
$R_{69}$ is hydrogen, $C_1$-$C_6$ alkyl, halogen, amino, nitro, or -NH(CO)$NR_{78}R_{79}$;

$R_{70}$ is hydrogen, $C_1$-$C_6$ alkyl, halogen, amino, nitro;

$R_7$, $R_{71}$, $R_{72}$, $R_{73}$, $R_{74}$, $R_{75}$, $R_{76}$, $R_{77}$, $R_{78}$, and $R_{79}$ are each independently hydrogen or $C_1$-$C_6$ alkyl; $R_1$ is hydrogen or $C_1$-$C_8$ alkyl; wherein one or more methylene groups of the $C_1$-$C_6$ alkyl can be replaced by -$NR_1$-, -O-, -C(O)-, -S-, -SO-, -$SO_2$-, or -C(=S)-; one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ;

optionally $R_{78}$, and $R_{79}$ taken together form a 4- to 8-membered carbocyclic or heterocyclic ring; or

d) the compound of Formula **I′** is a compound of Formula **XII**:



XII

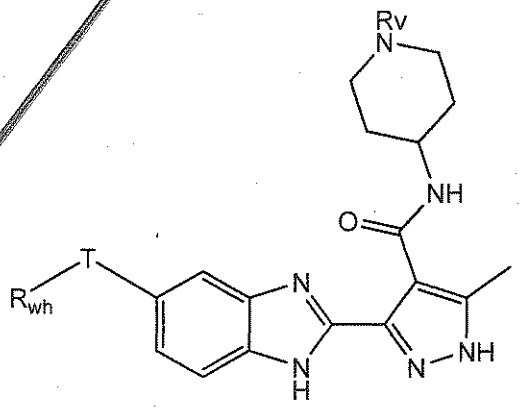
wherein

$R_1$ and $R_2$ are each independently hydrogen or $C_1$-$C_8$ alkyl; wherein one or more methylene groups of the $C_1$-$C_6$ alkyl can be replaced by -$NR_1$-, -O-, -C(O)-, -S-, -SO-, -$SO_2$-, or -C(=S)-; one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ;

T is Tether; and

$R_{wh}$ is Warhead; or

e) the compound of Formula **I′** is a compound of Formula **XXXVI**:



**XXXVI**

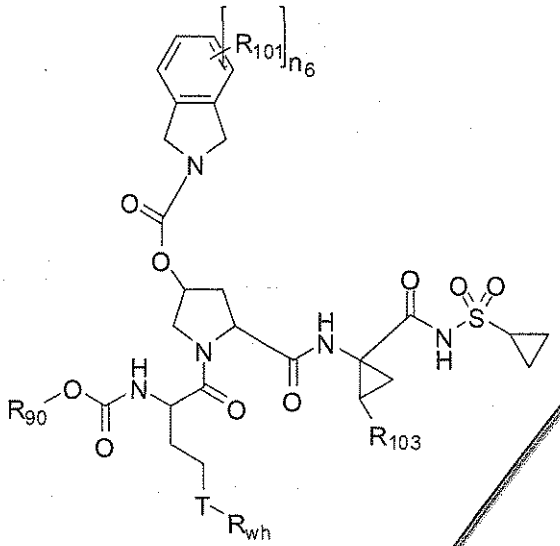
wherein

$R_v$ is H, optionally substituted $C_1$-$C_3$ branched or straight chain alkyl, or optionally substituted $C_1$-$C_3$ branched or straight chain acyl;

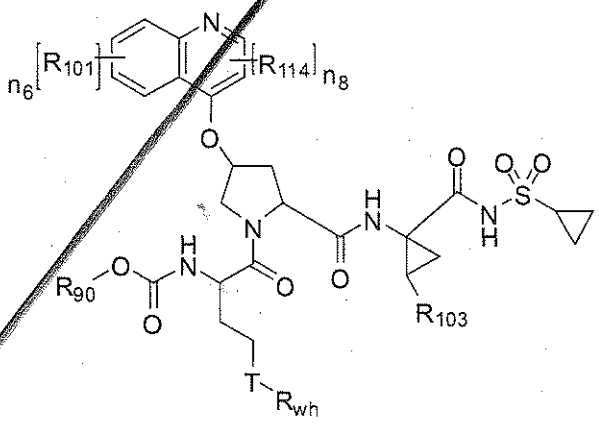
T is Tether; and

$R_{wh}$ is Warhead;

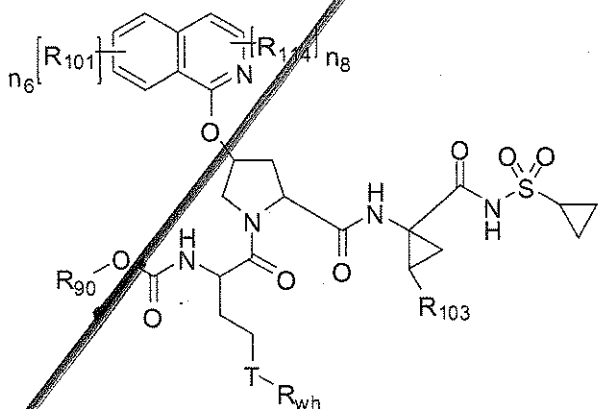
f) the compound of Formula **I'** is a compound of Formula **XVI-d**, **XVI-e**, or **XVI-f**.



**XVI-d**



**XVI-e**



**XVI-f**

wherein

$R_{90}$ and $R_{114}$ are each independently hydrogen or $C_1$-$C_6$ alkyl;

$R_{103}$ is hydrogen, $C_1$-$C_6$ alkyl, or $C_2$-$C_8$ alkenyl;

$R_1$ is hydrogen or $C_1$-$C_8$ alkyl;

$R_{101}$ is hydrogen, $C_1$-$C_6$ alkyl, $C_2$-$C_8$ alkenyl, halogen, amino, nitro, optionally substituted aryl or heteroaryl; and

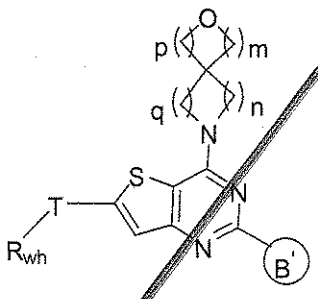
$n_6$ is an integer from 0 to 4;

$n_8$ is an integer from 0 to 2;

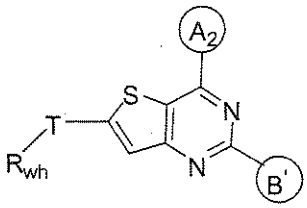
wherein one or more methylene groups of the $C_1$-$C_6$ alkyl can be replaced by -$NR_1$-, -O-, -C(O)-, -S-, -SO-, -$SO_2$-, or -C(=S)-; one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ; and

$R_1$ is hydrogen or $C_1$-$C_8$ alkyl; or

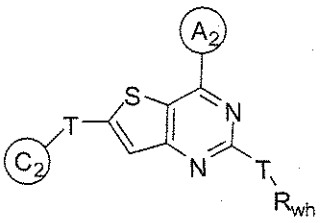
g) the compound of Formula **I'** is a compound of Formula **XXII-a**, Formula **XXII-b**, or **Formula XXII-c**:



**XXII-a**



**XXII-b**



**XXII-c**

wherein

n, m, p, and q for Formula **XXII-a** are each independently 0, 1, 2, 3; provided that n and q are not 0 at the same time, and m and q are not 0 at the same time;

$A^2$ is an optionally substituted ring selected from a 4-8 membered saturated or partially unsaturated heterocyclic ring having one or two heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-10 membered saturated or partially unsaturated

bridged bicyclic heterocyclic ring having at least one nitrogen, at least one oxygen, and optionally 1-2 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

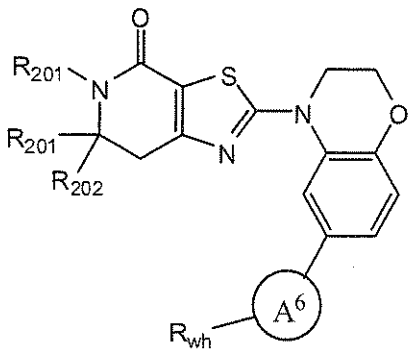
B is an optionally substituted group selected from phenyl, an 8- to 10-membered bicyclic aryl ring, a 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or –T-Rwh; and

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

T is Tether; and

$R_{wh}$ is Warhead; or

h) the compound of Formula **I'** is a compound of Formula **XXIII**:




**XXIII**

wherein:

$R_{wh}$ is Warhead;

$R_{201}$ is hydrogen or $C_{1-6}$ alkyl;

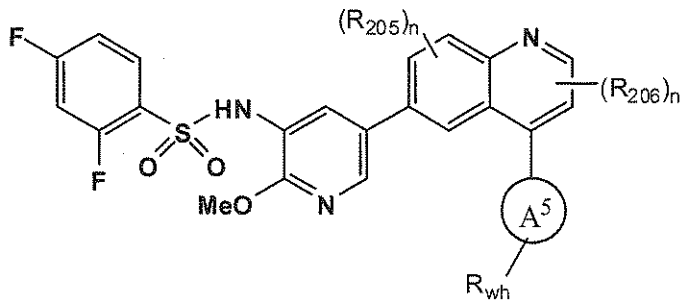
$R_{202}$ is hydrogen or an optionally substituted group selected from $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, or ($C_{1-6}$ alkylene)-$R_{203}$; or

$R_{201}$ and $R_{202}$ are taken together with the intervening carbon to form an optionally substituted ring selected from a 3- to 7-membered carbocyclic ring or a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

$R_{203}$ is a 3- to 7-membered saturated or partially unsaturated carbocyclic ring, a 7- to 10-membered saturated or partially unsaturated bicyclic carbocyclic ring, a 4- to 7-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, phenyl, a 8- to 10-membered bicyclic aryl ring, a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 8- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

Ring $A^6$ is absent or an optionally substituted group selected from a 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

i) the compound of Formula I′ is a compound of Formula **XXV**:




**XXV**

or a pharmaceutically acceptable salt thereof;

wherein

each $R_{205}$ and $R_{206}$ is independently –R", halogen, $–NO_2$, -CN, –OR", –SR", –$N(R")_2$, -C(O)R", $–CO_2R"$, –C(O)C(O)R", $–C(O)CH_2C(O)R"$, –S(O)R", $-S(O)_2R"$, $-C(O)N(R")_2$, $-SO_2N(R")_2$, –OC(O)R", –N(R")C(O)R", –$N(R")N(R")_2$, $-N(R")C(=NR")N(R")_2$, $-C(=NR")N(R")_2$, –C=NOR", $-N(R")C(O)N(R")_2$, –$N(R")SO_2N(R")_2$, $–N(R")SO_2R"$, or $-OC(O)N(R")_2$;

each R" is independently hydrogen or an optionally substituted group selected from $C_{1–6}$ aliphatic, a 3- to 7-membered saturated or partially unsaturated carbocyclic ring, a 7- to 10-membered saturated or partially unsaturated bicyclic carbocyclic ring, a 4- to 7-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, phenyl, an 8- to 10-membered bicyclic aryl ring, a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

optionally, two R" groups on the same nitrogen are taken together with the nitrogen to which they are attached to form an optionally substituted 5–8 membered saturated, partially unsaturated, or aromatic ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

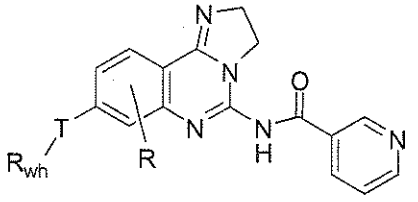
m is an integer from 0 to 6, inclusive;

each n is independently 0, 1, or 2;

Ring $A^5$ is an optionally substituted 6-membered heterocyclic or heteroaryl ring having 1-2 nitrogens; and

$R_{wh}$ is Warhead; or

j) the compound of Formula **I'** is a compound of Formula **XXVII**:



**XXVII**

or a pharmaceutically acceptable salt thereof;

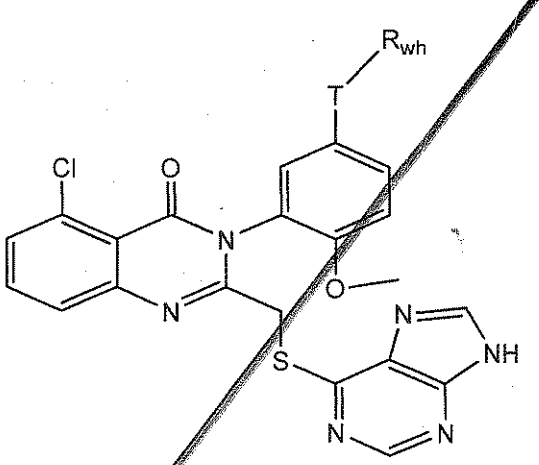
wherein:

T is Tether;

$R_{wh}$ is Warhead; and

R is H, alkyl, or alkoxy; or

k) the compound of Formula **I′** is a compound of Formula **XXXVII**:




**XXXVII**

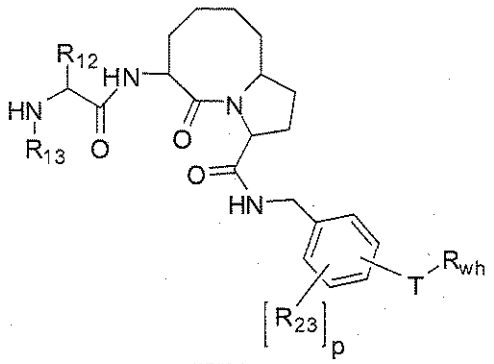
or a pharmaceutically acceptable salt thereof;

wherein

T is Tether; and

$R_{wh}$ is Warhead.

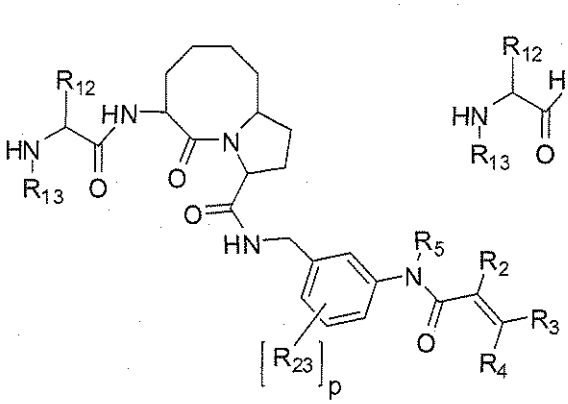
14. The compound of claim 13, wherein the compound of Formula **VII-b** is a compound of Formula **VII-h**;



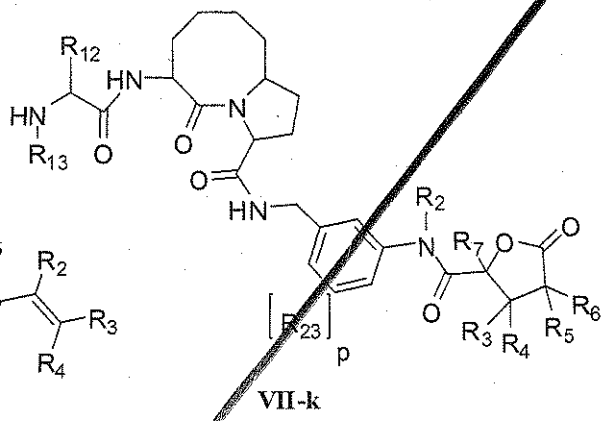
VII-h

15. The compound of claim 14, wherein

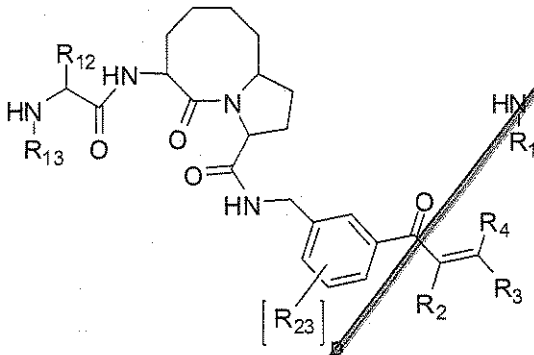
a) the compound of Formula **VII-h** is a compound of Formula **VII-j**, **VII-k**, **VII-l**, **VII-m**, **VII-n**, or **VII-o**:



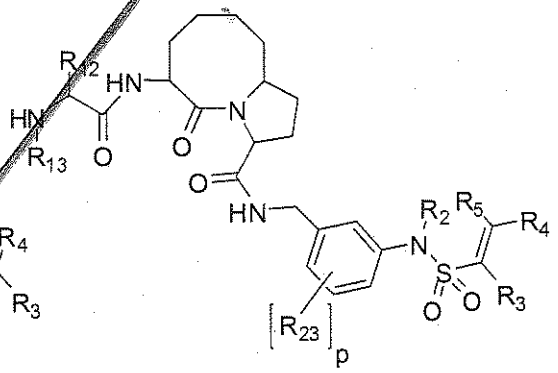
**VII-j**



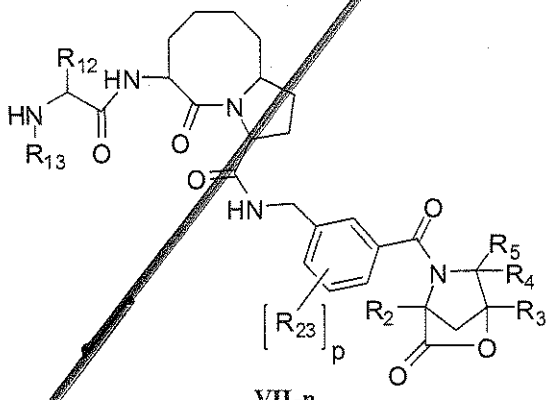
**VII-k**



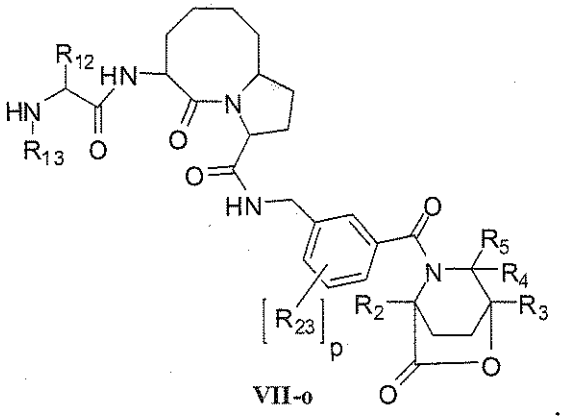
**VII-l**



**VII-m**



**VII-n**



**VII-o**

wherein

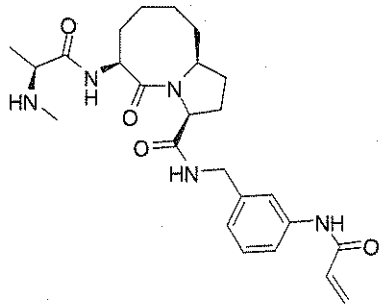
each $R_2$, $R_3$, $R_4$, and $R_5$ is independently hydrogen or $C_1$-$C_6$ alkyl;

one or more methylene groups of the $C_1$-$C_6$ alkyl can be optionally replaced by -$NR_1$-, -O-, -C(O)-, -S-, -SO-, -$SO_2$-, or -C(=S)-;

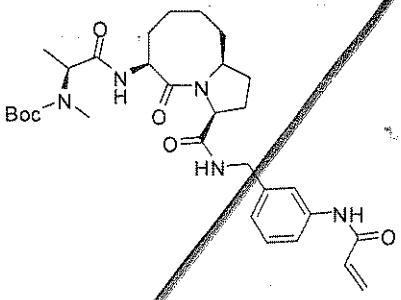
one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ;

$R_1$ is hydrogen or $C_1$-$C_8$ alkyl; or

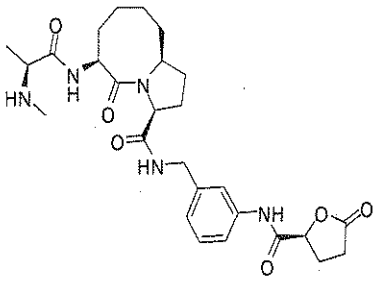
b) compound of Formula **VII-h** is selected from the group consisting of:



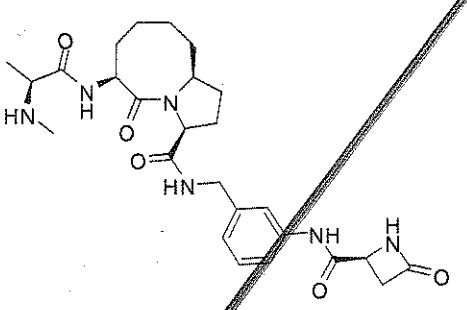
**VII-1**



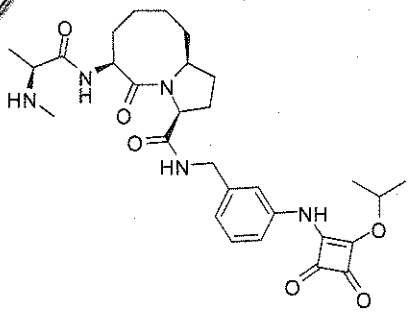
**VII-2**



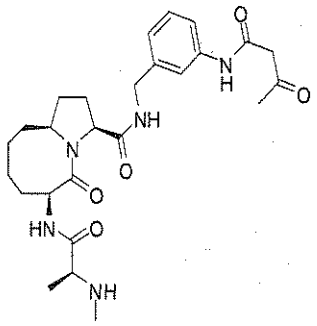
**VII-3**



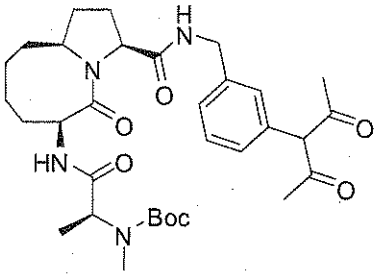
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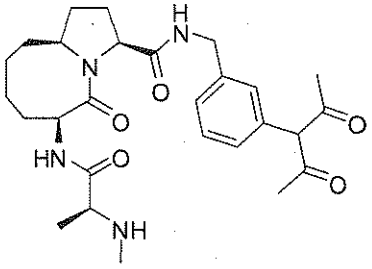
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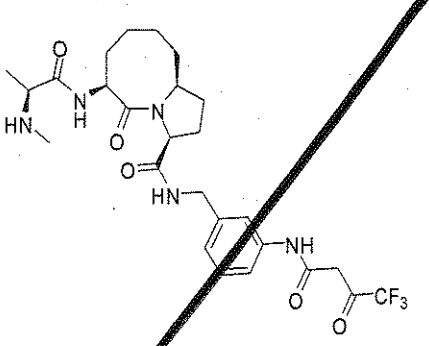
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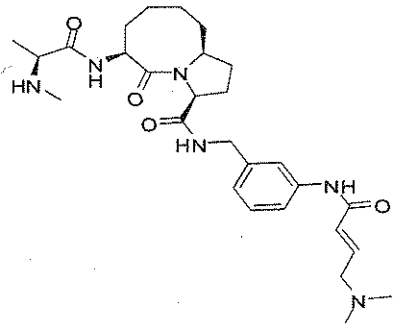
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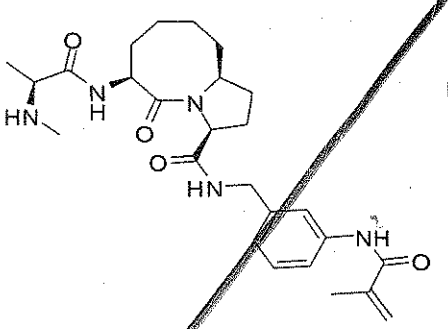
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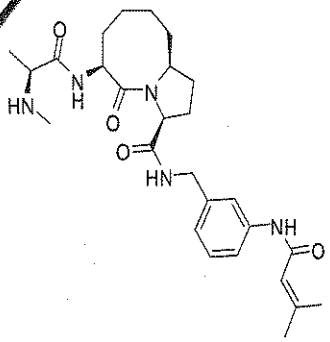
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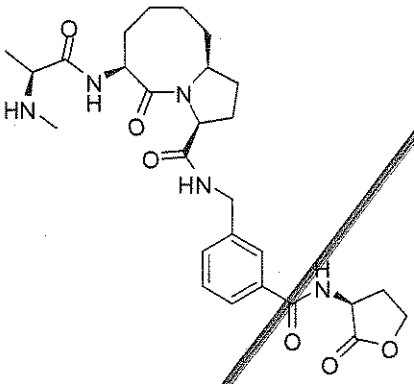
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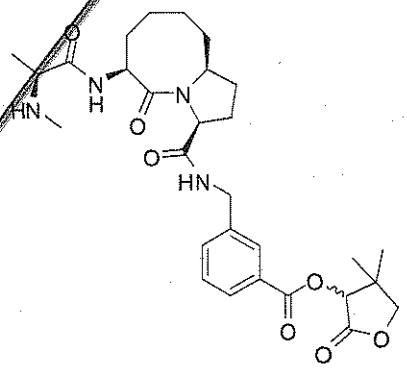
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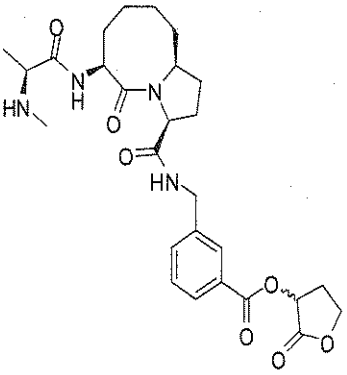
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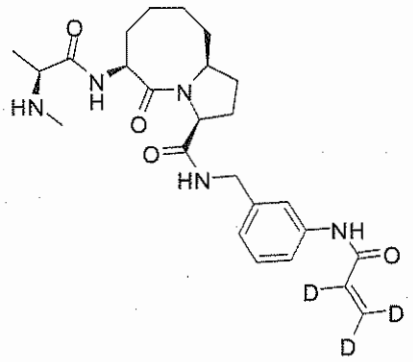
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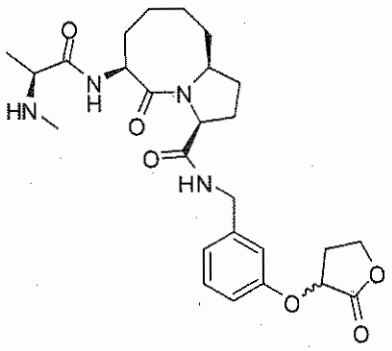
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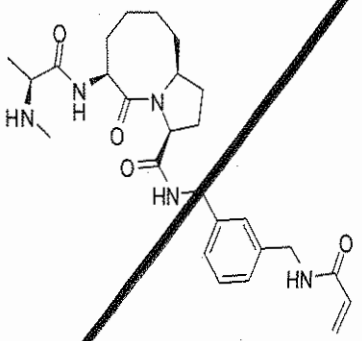
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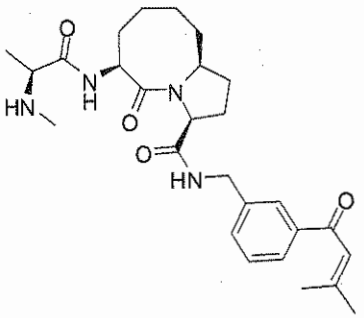
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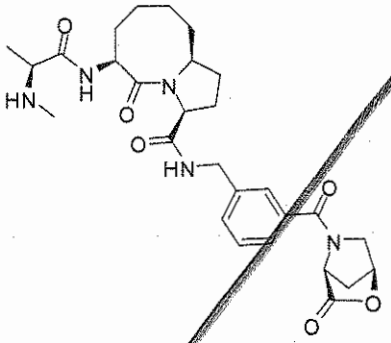
**VII-17**



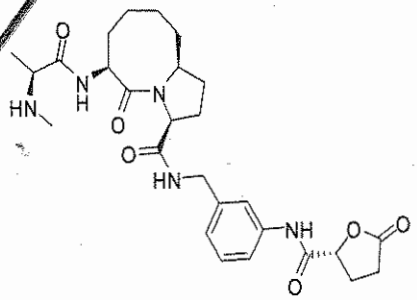
**VII-18**



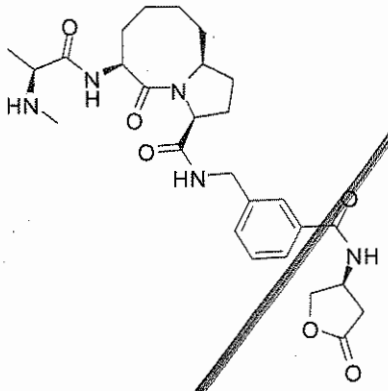
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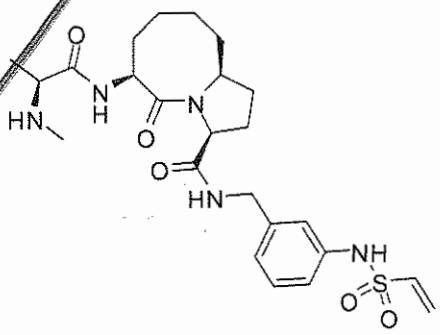
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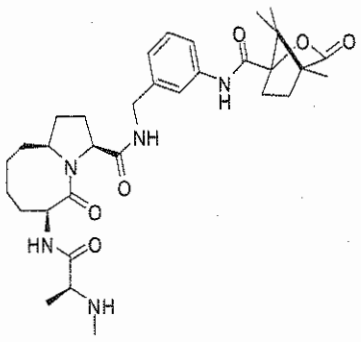
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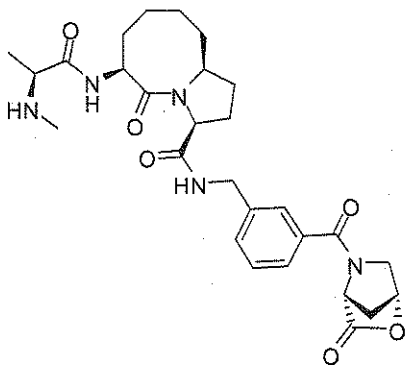
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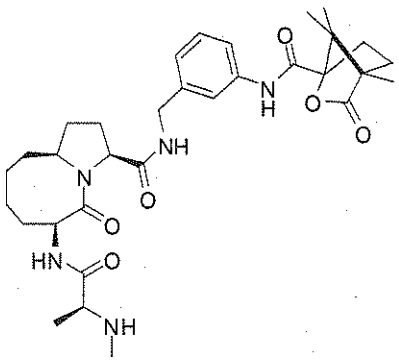
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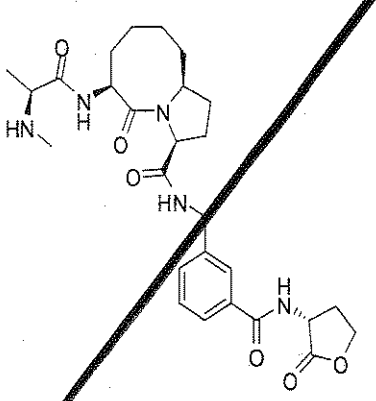
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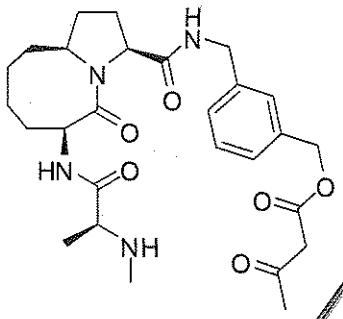
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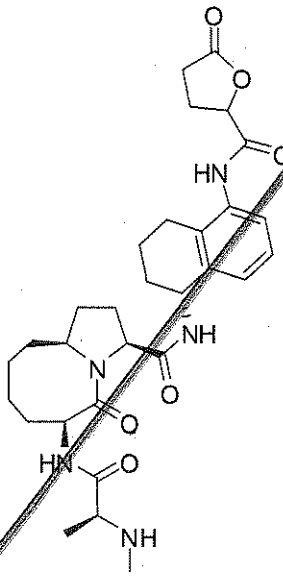
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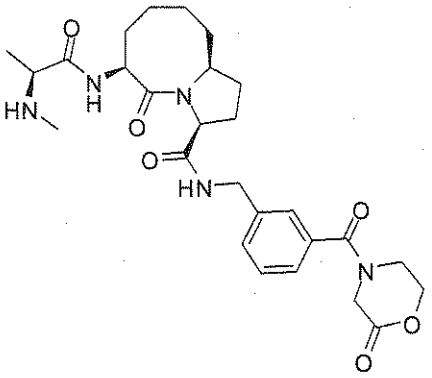
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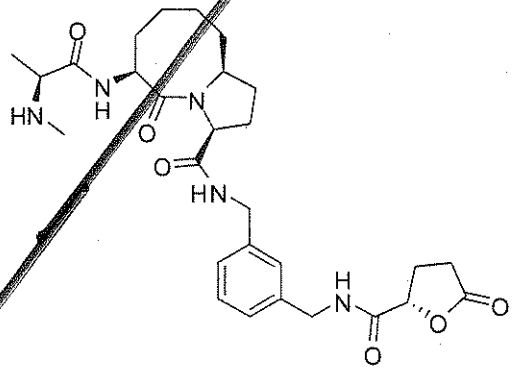
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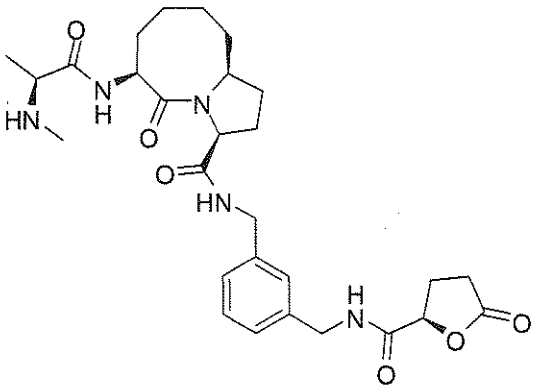
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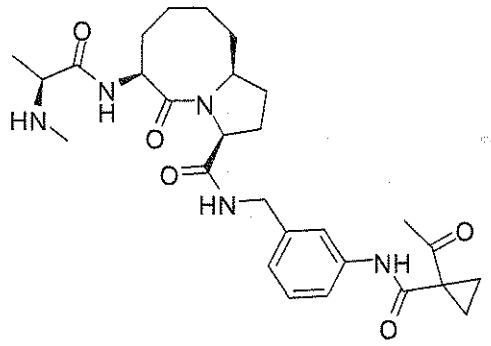
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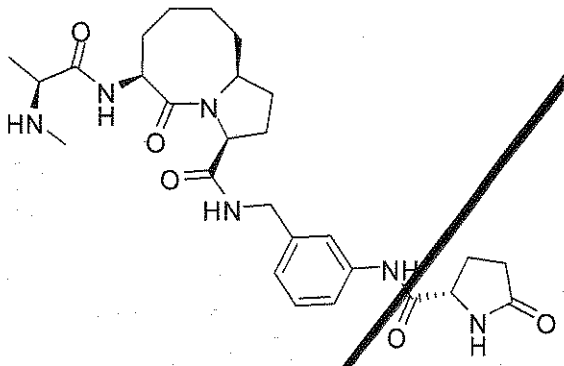
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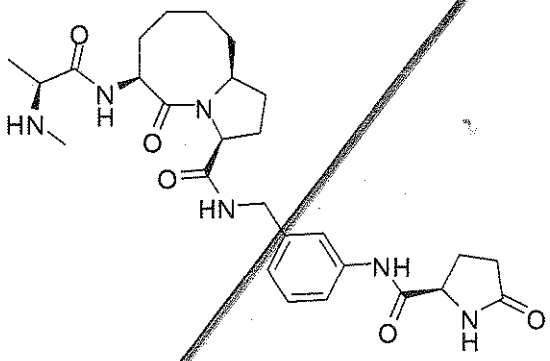
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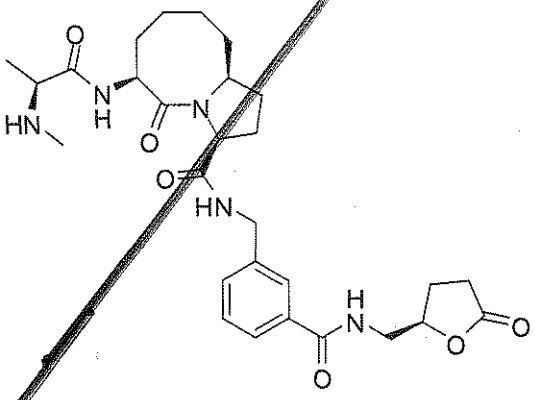
**VII-34**



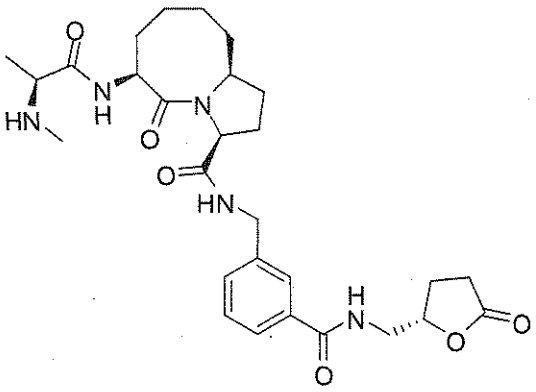
**VII-38**



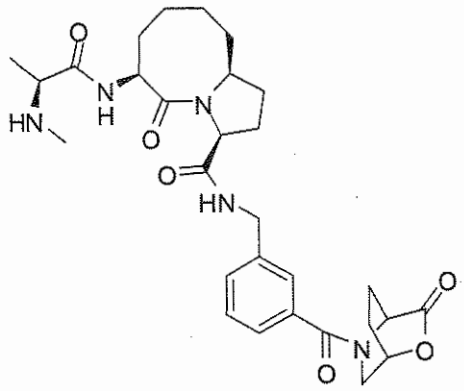
**VII-39**



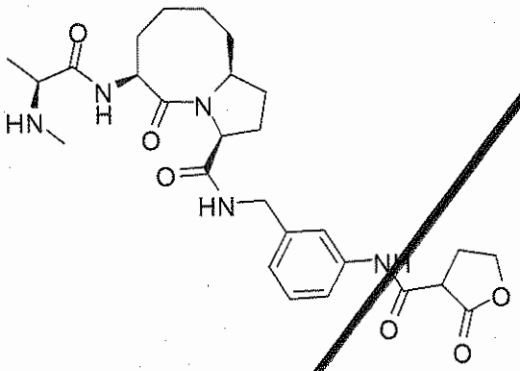
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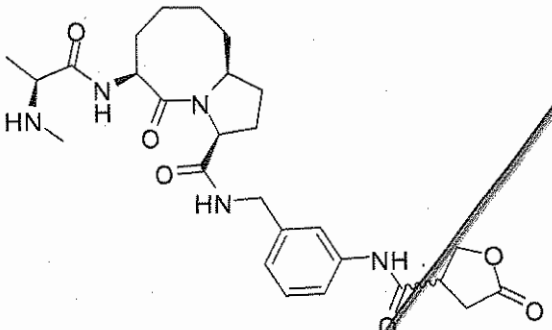
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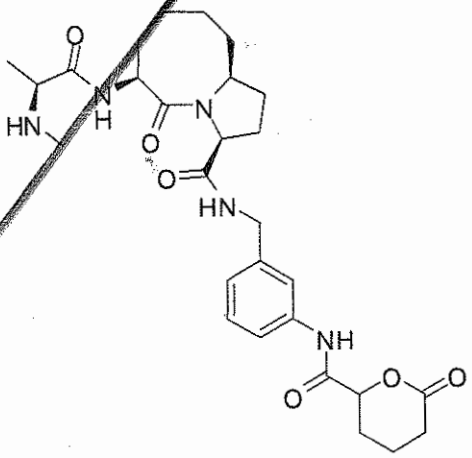
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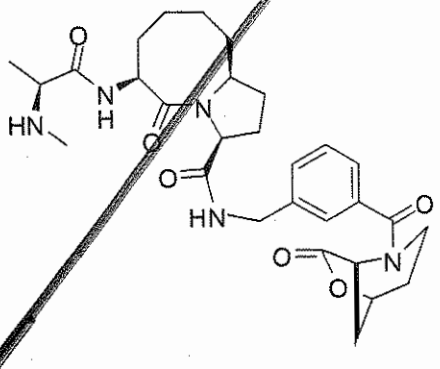
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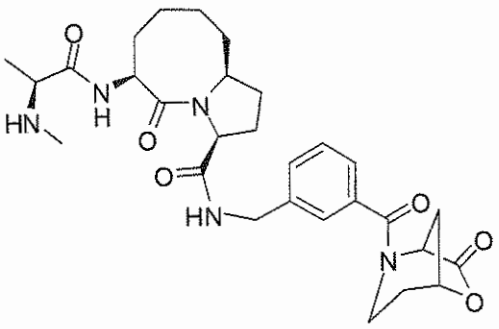
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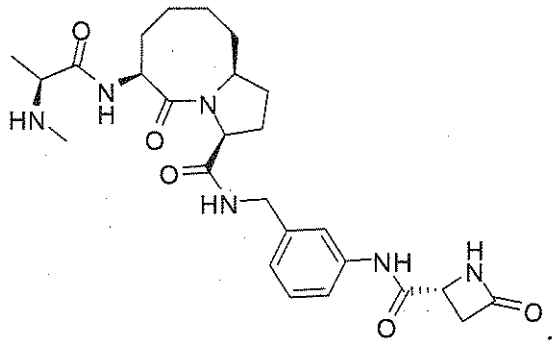
VII-46



VII-47

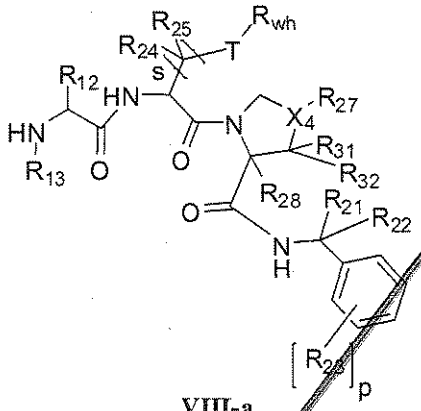


VII-48

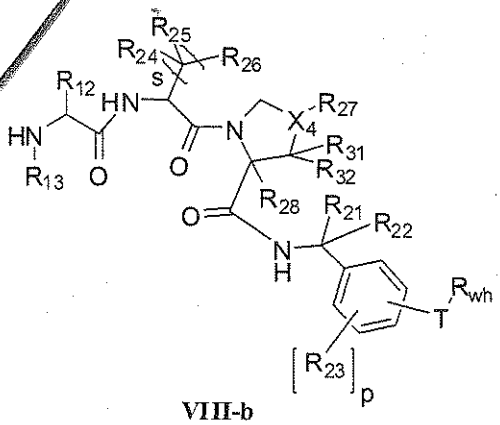
and .

**VII-49.**

16. The compound of claim 2, wherein the compound of Formula **I′** is a compound of Formula **VIII-a** or **VIII-b**:



**VIII-a**



**VIII-b**

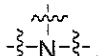
wherein

$X_4$ is $-CR_{33}-$ or -N-;

s is 0, 1, 2, 3, or 4;

$R_{12}$, $R_{13}$, $R_{21}$, $R_{22}$, $R_{24}$, $R_{25}$, $R_{26}$, $R_{27}$, $R_{28}$, $R_{29}$, $R_{30}$, $R_{31}$, $R_{32}$, and $R_{33}$ are each independently hydrogen or $C_1$-$C_6$ alkyl;

$R_{23}$ is hydrogen, $C_1$-$C_6$ alkyl, halogen, amino, or nitro; wherein one or more methylene groups of $C_1$-$C_6$ alkyl can be optionally replaced by $-NR_1-$, -O-, -C(O)-, -S-, -SO-,

$-SO_2-$, or -C(=S)-; one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ;

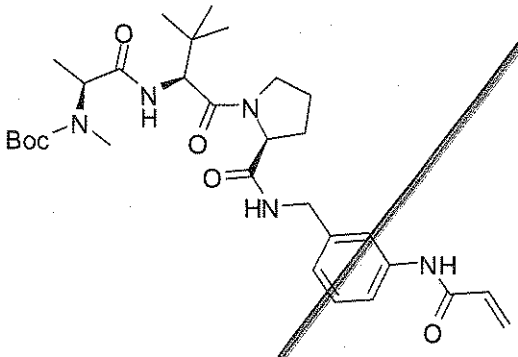
$R_1$ is hydrogen or $C_1$-$C_8$ alkyl; and

optionally $R_{21}$ and $R_{23}$ taken together can form a 4- to 8-membered carbocyclic or heterocyclic ring;

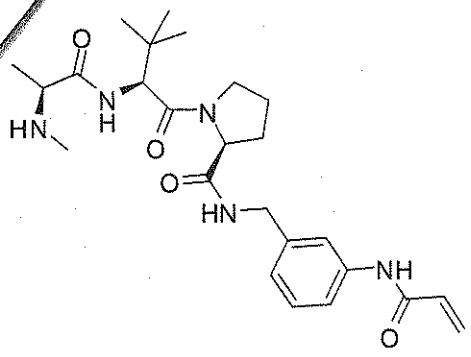
T is Tether; and

$R_{wh}$ is Warhead.

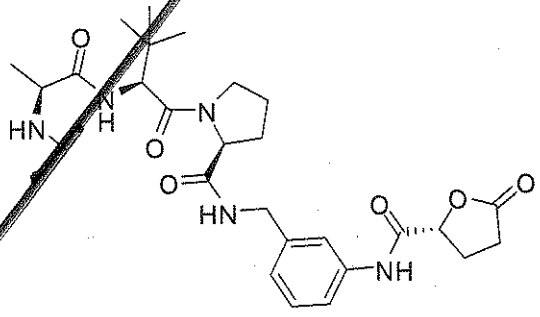
17. The compound of claim 16, wherein the compound of Formula **VIII-a** or **VIII-b** is selected from the group consisting of:



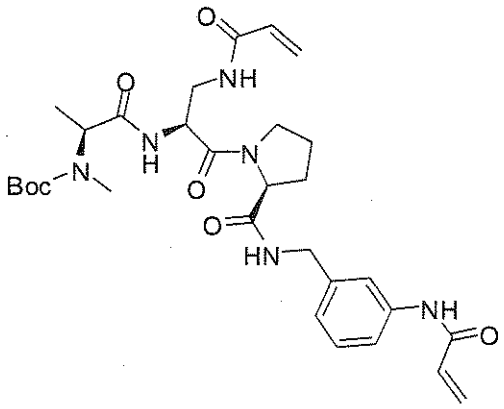
**VIII-1**



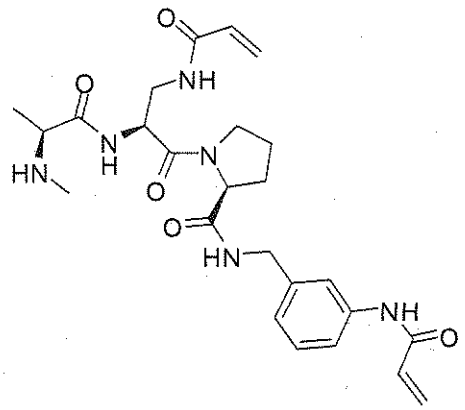
**VIII-2**



**VIII-3**

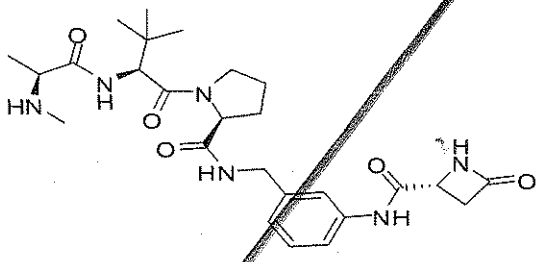


**VIII-4**



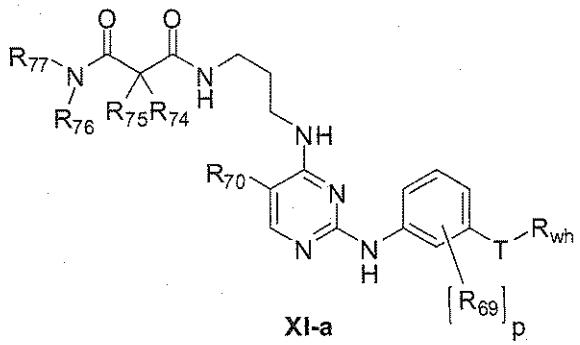
**VIII-5**

and

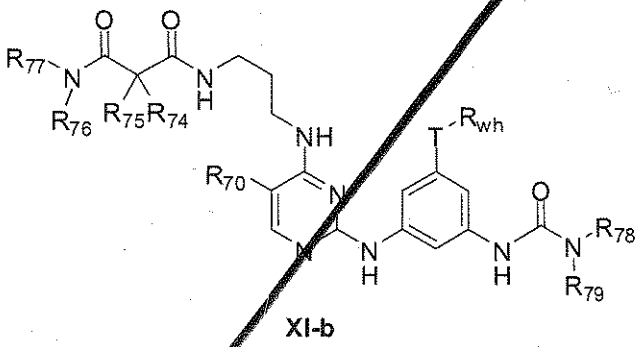


**VIII-7**

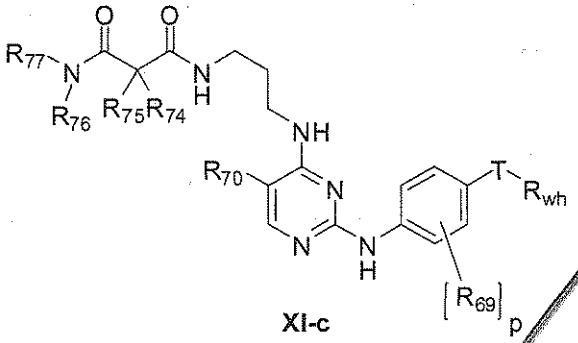
18. The compound of claim 13, wherein the compound of Formula **XI** is a compound of Formula **XI-a**, **XI-b**, or **XI-c**;



**XI-a**



**XI-b**



**XI-c**

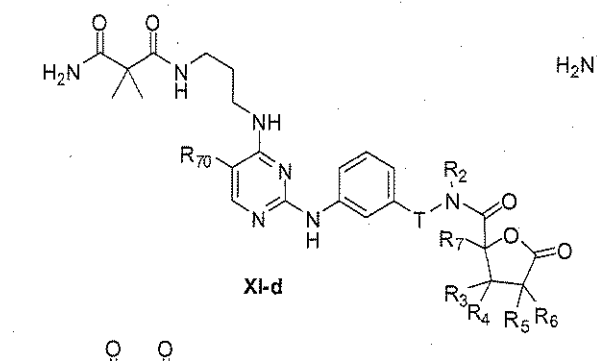
wherein

$R_{70}$ is -F, -Cl, -Br, or –I;

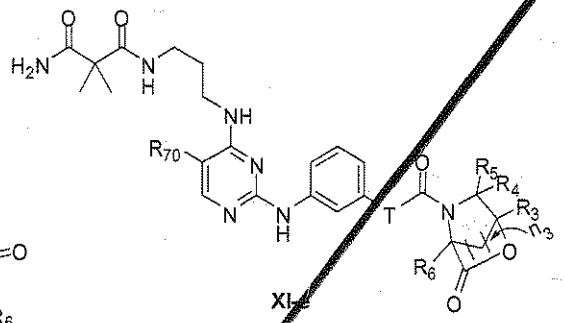
T is Tether; and

$R_{wh}$ is Warhead.

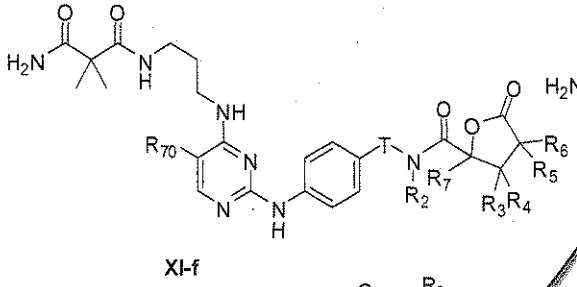
19. The compound of claim 18, wherein the compound of Formula **XI-a**, **XI-b** or **XI-c** is a compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j**:



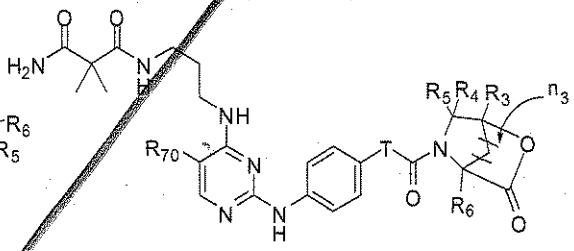
**XI-d**



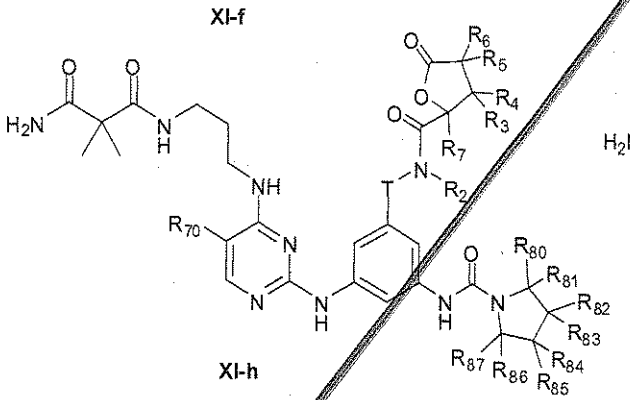
**XI-e**



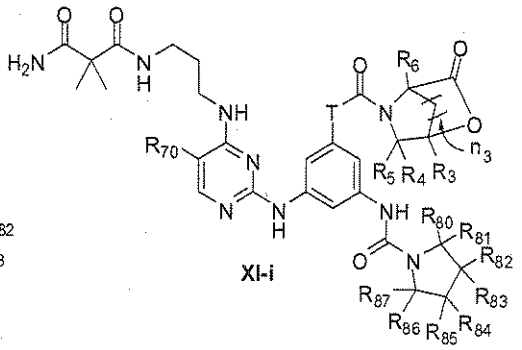
**XI-f**



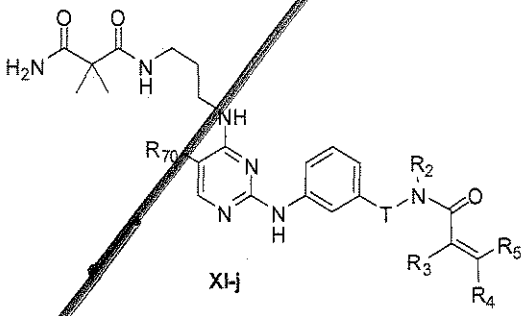
**XI-g**



**XI-h**



**XI-i**



**XI-j**

wherein

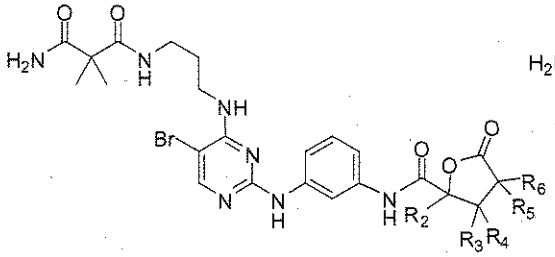
$R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_{80}$, $R_{81}$, $R_{82}$, $R_{83}$, $R_{84}$, $R_{85}$, $R_{86}$, and $R_{87}$ are each independently hydrogen or $C_1$-$C_6$ alkyl; $R_1$ is hydrogen or $C_1$-$C_8$ alkyl;

one or more methylene groups of the $C_1$-$C_6$ alkyl can be replaced by -$NR_1$-, -O-, -C(O)-, -S-, -SO-, -$SO_2$-, or -C(=S)-;

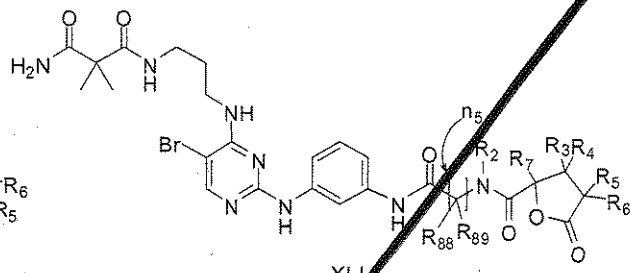
one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by .

20. The compound of claim 19, wherein

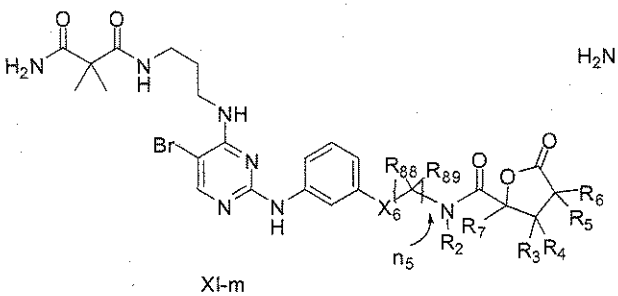
a) the compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j** is a compound of Formula **XI-k**, **XI-l**, **XI-m**, **XI-n**, **XI-o**, **XI-p**, or **XI-q**;



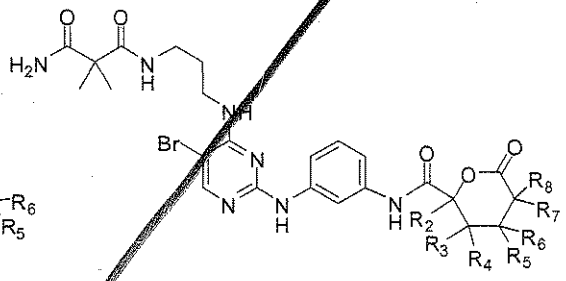
XI-k



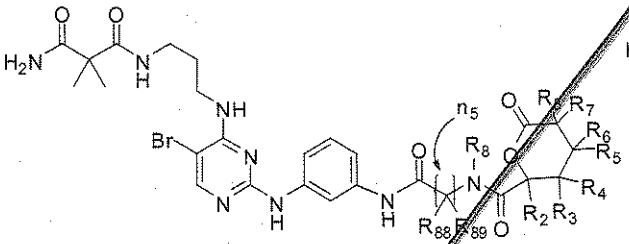
XI-l



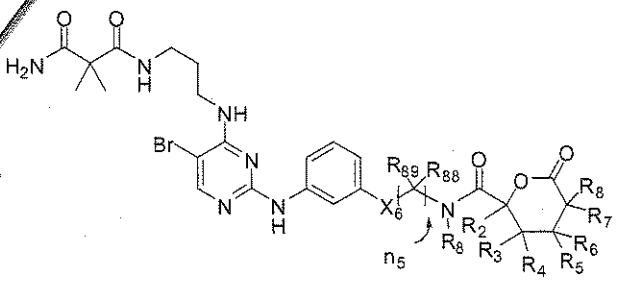
XI-m



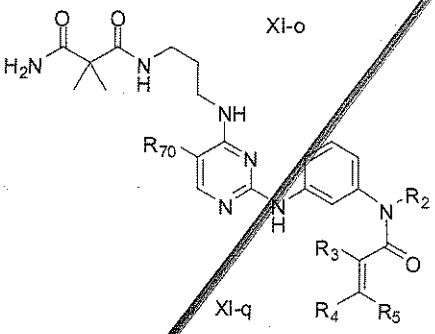
XI-n



XI-o



XI-p



XI-q

wherein

$X_6$ is $CH_2$, NH, O, or S;

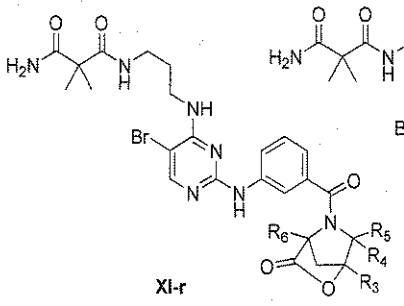
$R_{88}$ and $R_{89}$ are each independently hydrogen or $C_1$-$C_6$ alkyl; $R_1$ is hydrogen or $C_1$-$C_8$ alkyl;

one or more methylene groups of the $C_1$-$C_6$ alkyl can be replaced by -$NR_1$-, -O-, -C(O)-, -S-, -SO-, -$SO_2$-, or -C(=S)-;

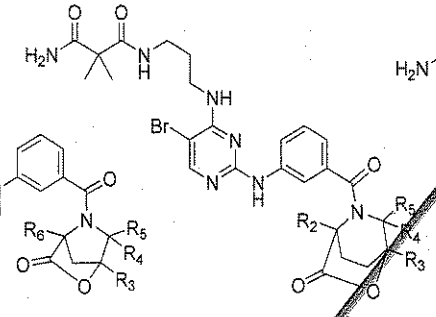
one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ; and

$n_5$ is an integer from 0 to 3; or

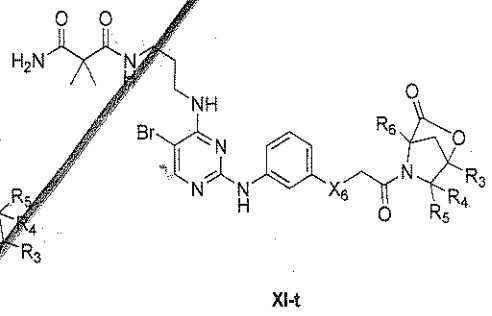
b) the compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j** is a compound of Formula **XI-r**, **XI-s**, **XI-t**, **XI-u**, **XI-v**, **XI-w**, or **XI-x**:



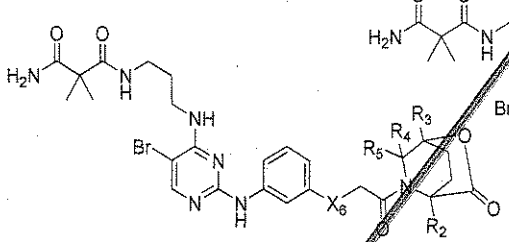
**XI-r**



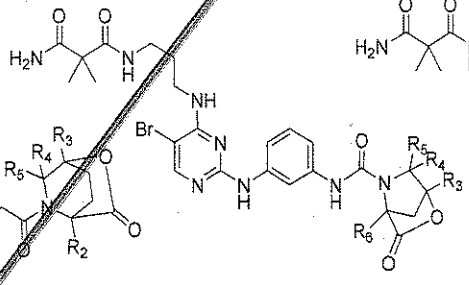
**XI-s**



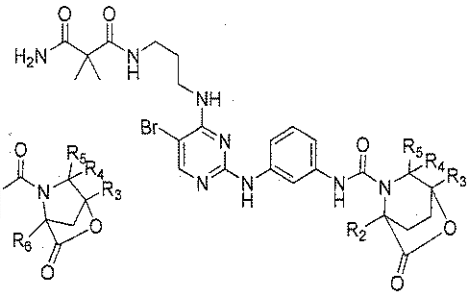
**XI-t**



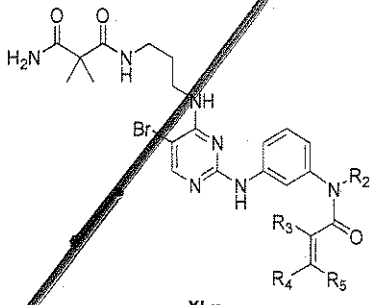
**XI-u**



**XI-v**



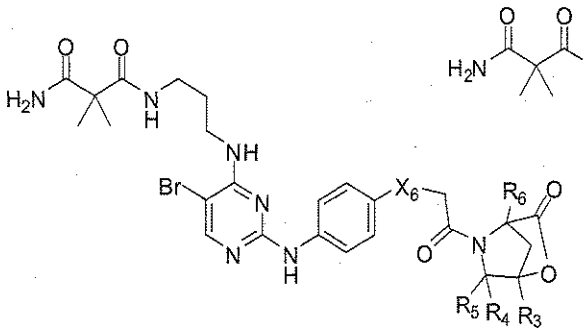
**XI-w**



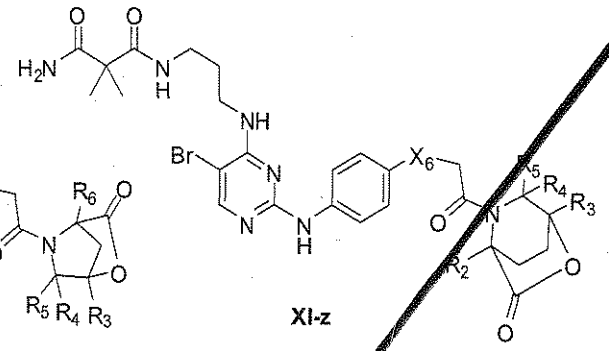
**XI-x**

;

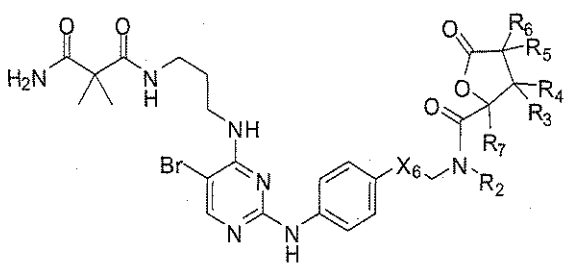
c) the compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j** is a compound of Formula **XI-y**, **XI-z**, **XI-aa**, or **XI-bb**:



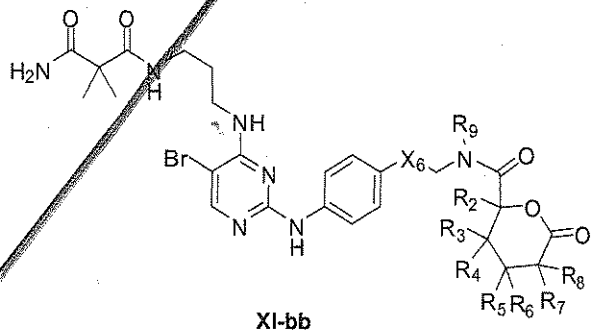
**XI-y**



**XI-z**



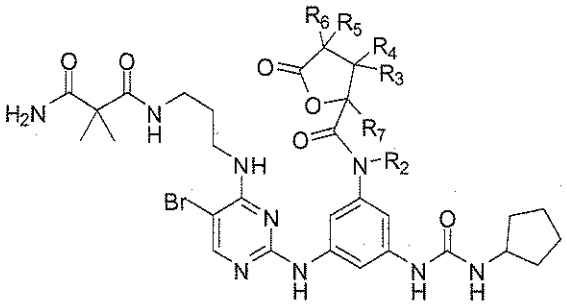
**XI-aa**



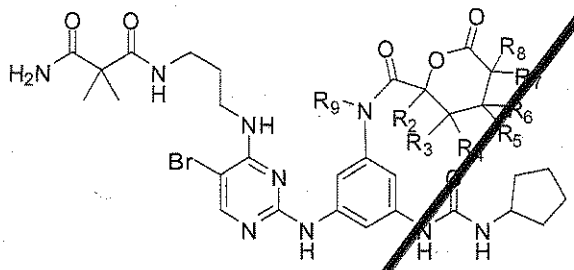
**XI-bb**

or

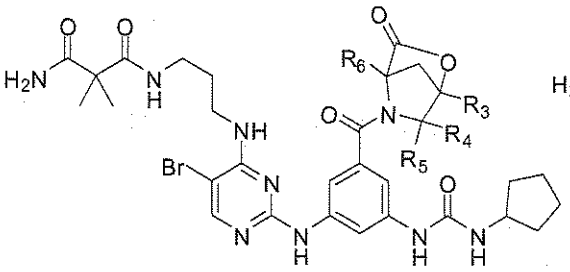
d) the compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j** is a compound of Formula **XI-cc**, **XI-dd**, **XI-ee**, or **XI-ff**:



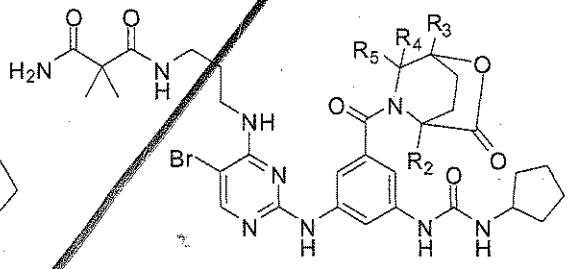
XI-cc



XI-dd

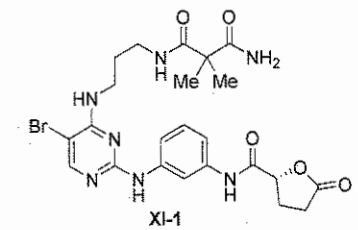


XI-ee

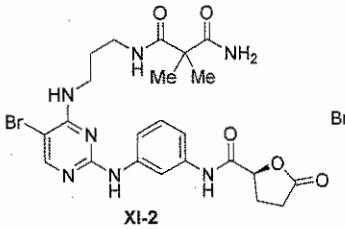


XI-ff

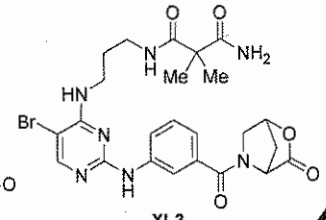
21. The compound of claim 18, wherein the compound of Formula **XI** is selected from the group consisting of:



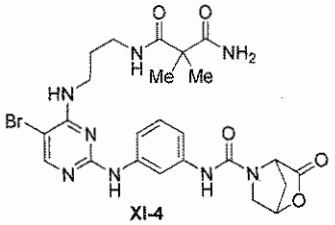
XI-1



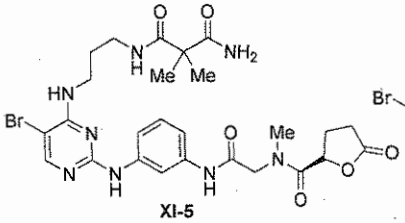
XI-2



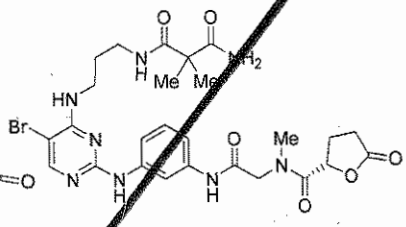
XI-3



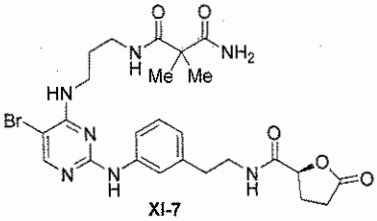
XI-4



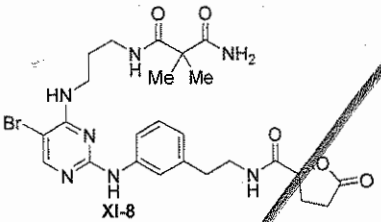
XI-5



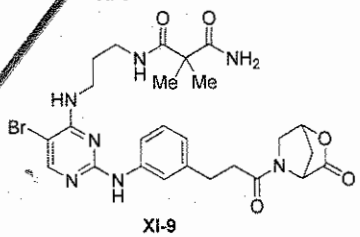
XI-6



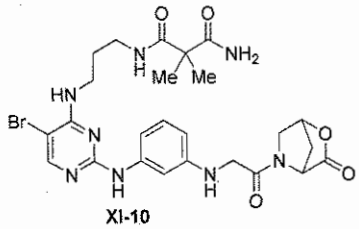
XI-7



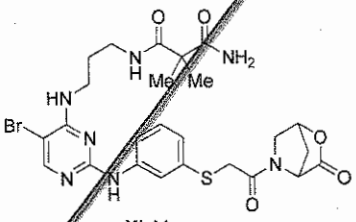
XI-8



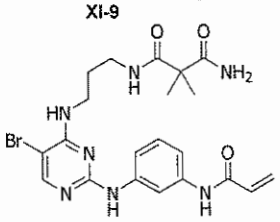
XI-9



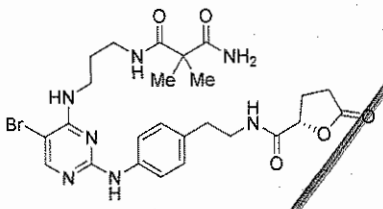
XI-10



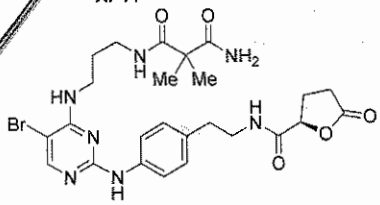
XI-11



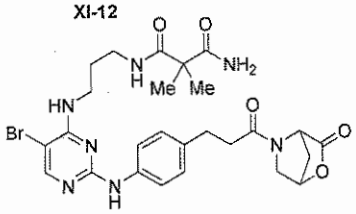
XI-12



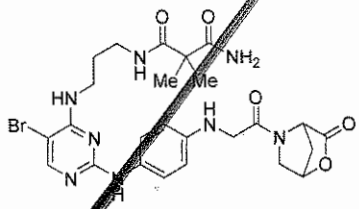
XI-13



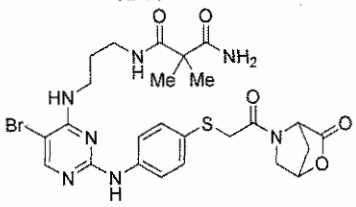
XI-14



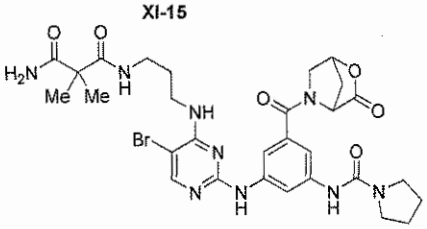
XI-15



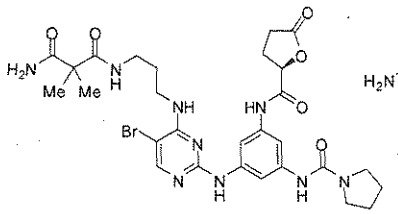
XI-16



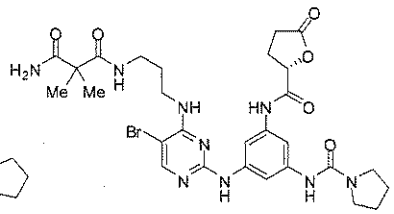
XI-17



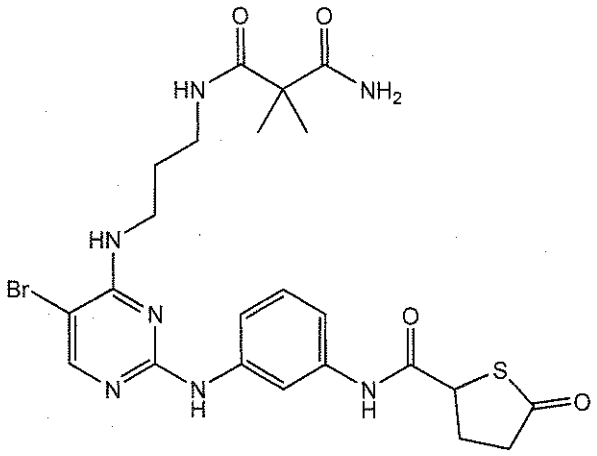
XI-18



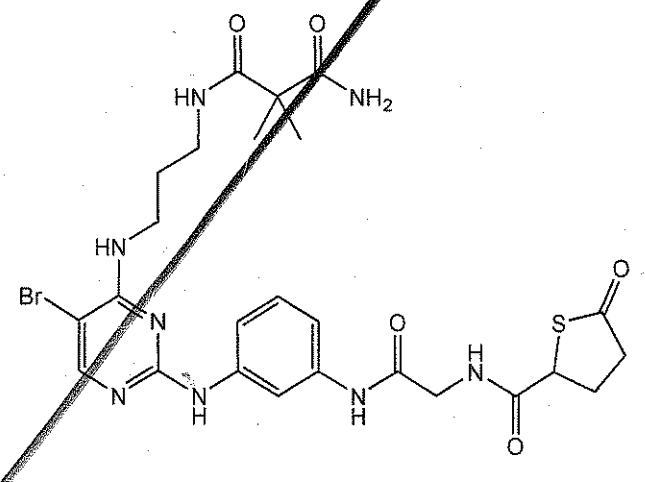
XI-19



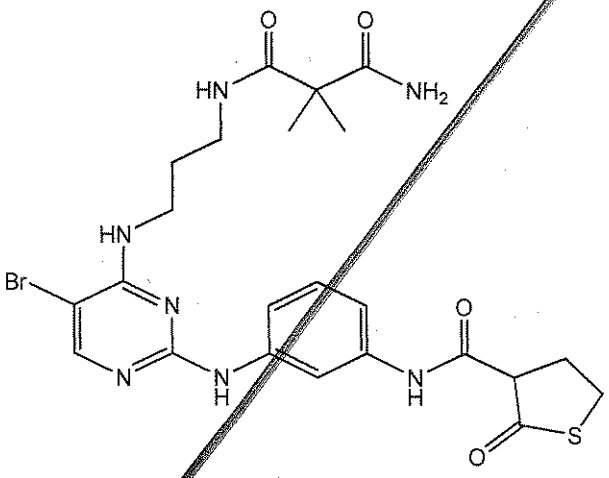
XI-20



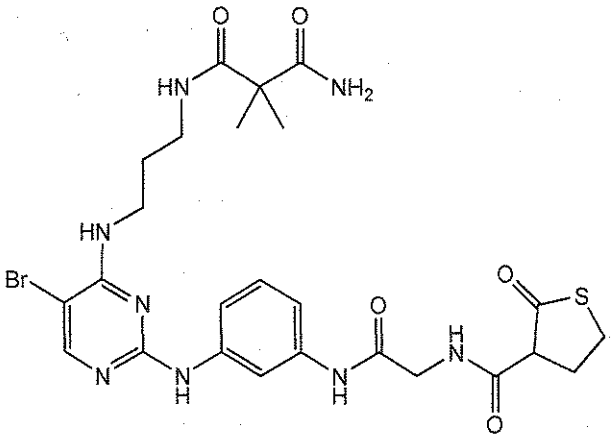
**XI-21**



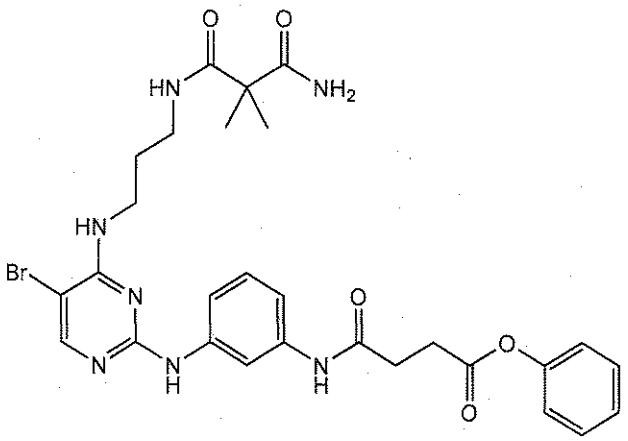
**XI-22**



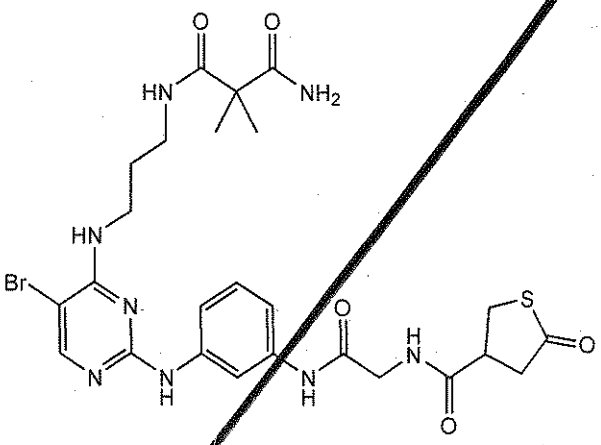
**XI-23**



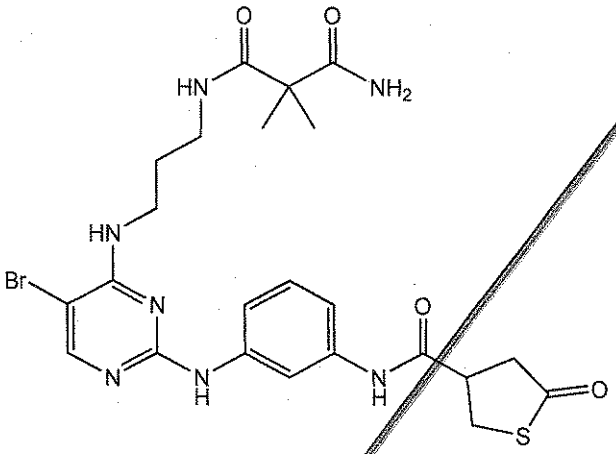
**XI-24**



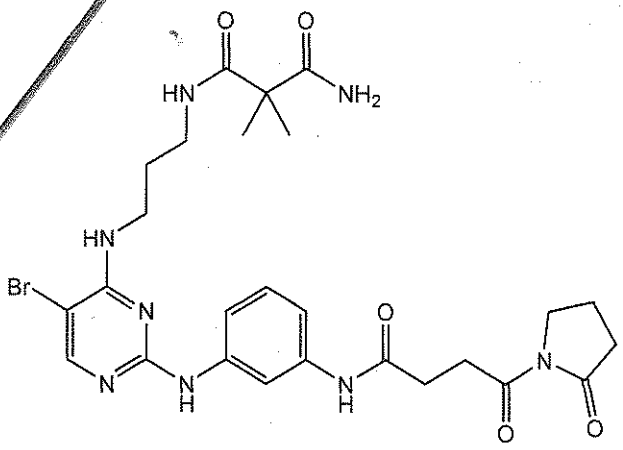
**XI-25**



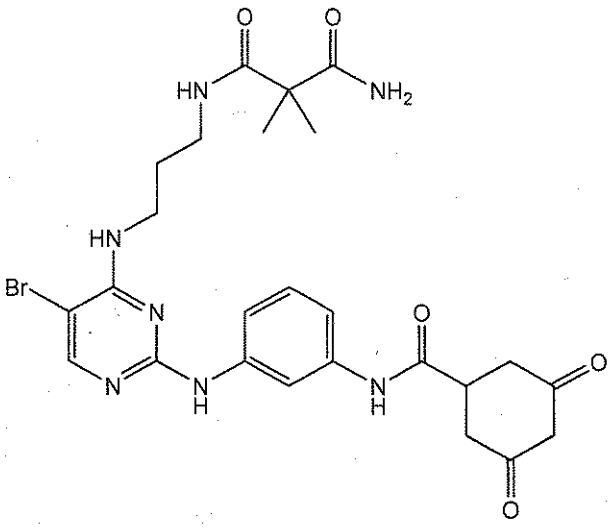
**XI-26**



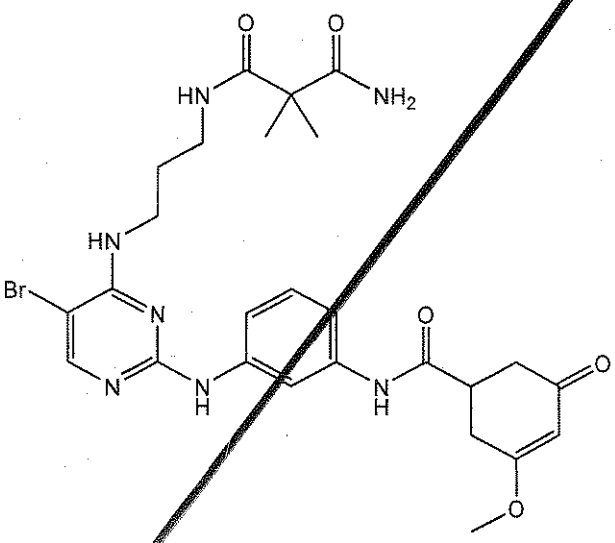
**XI-27**



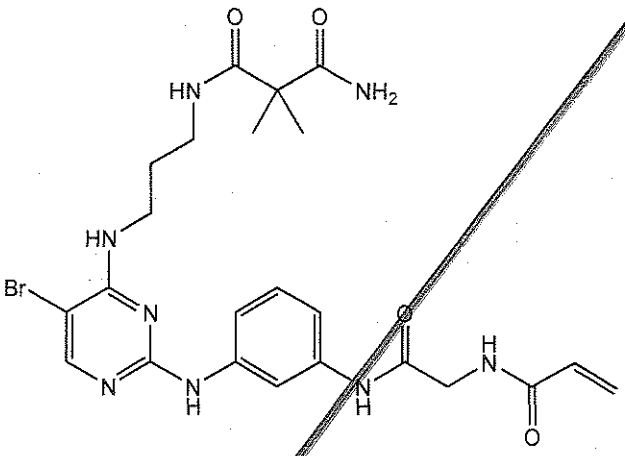
**XI-28**



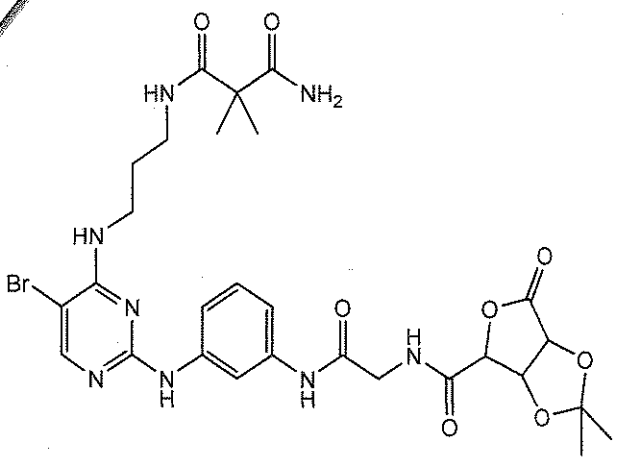
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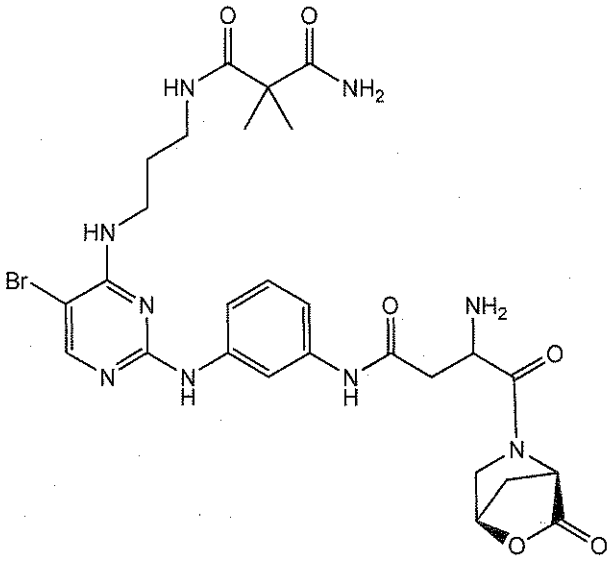
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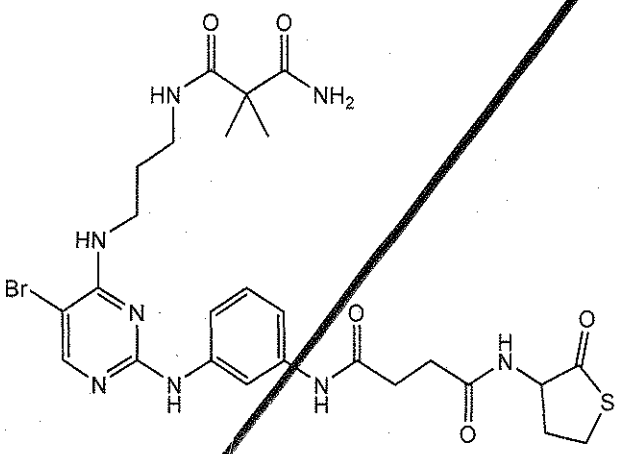
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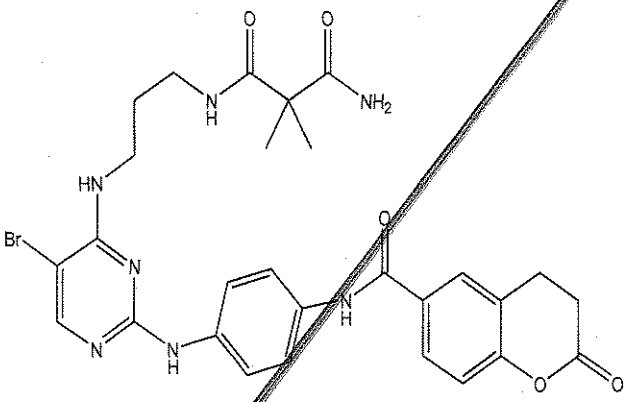
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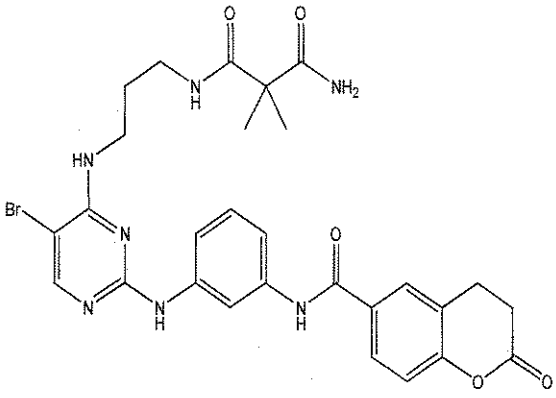
**XI-33**



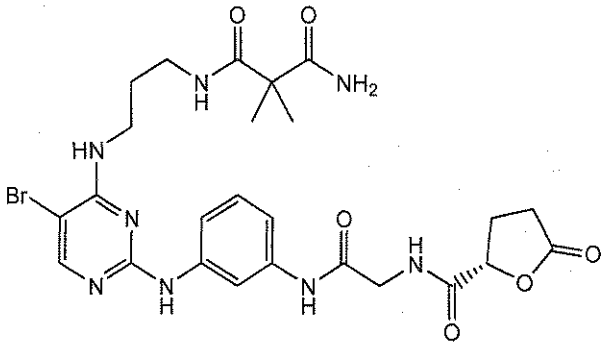
**XI-34**



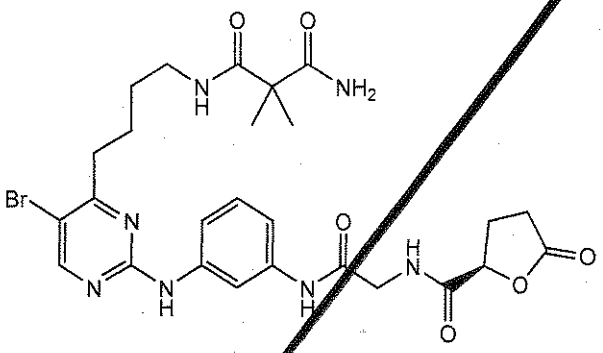
**XI-35**



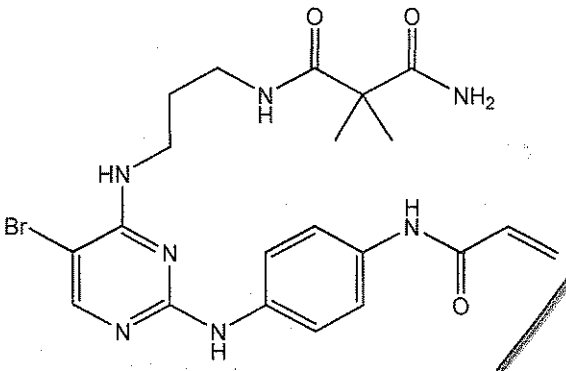
**XI-36**



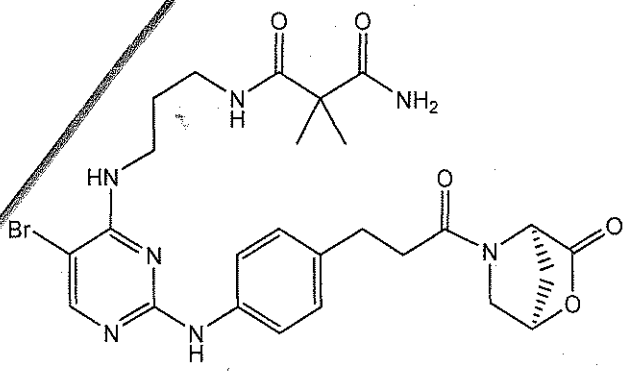
**XI-37**



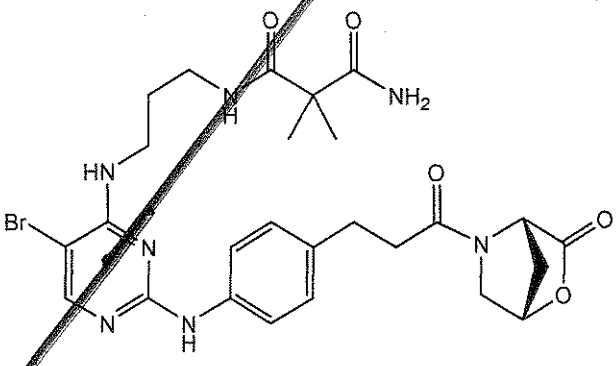
**XI-38**



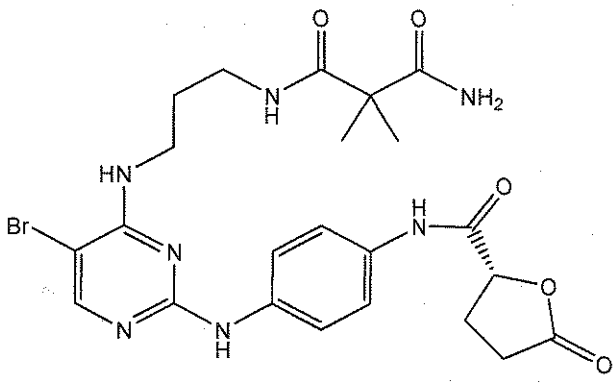
**XI-39**



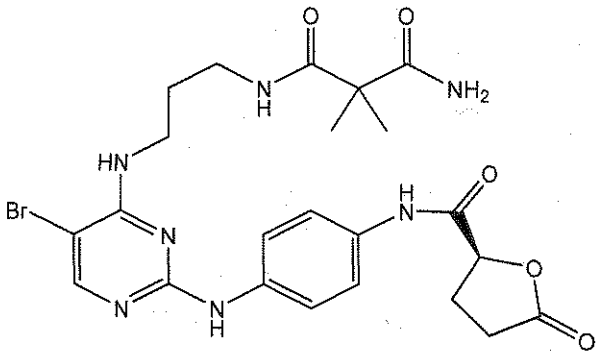
**XI-40**



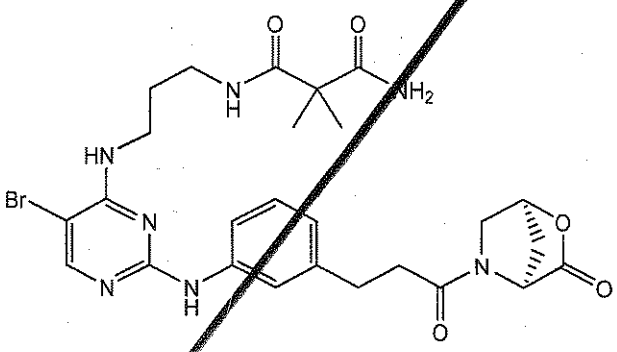
**XI-41**



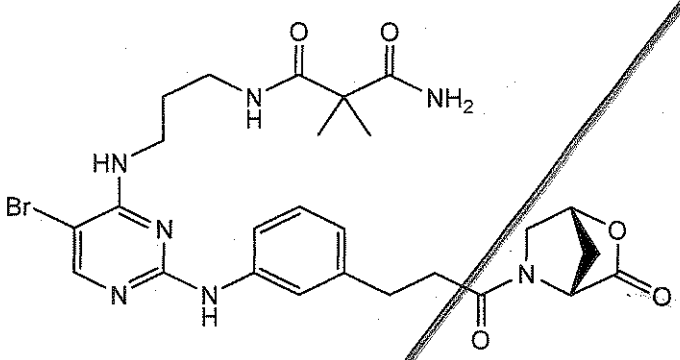
**XI-42**



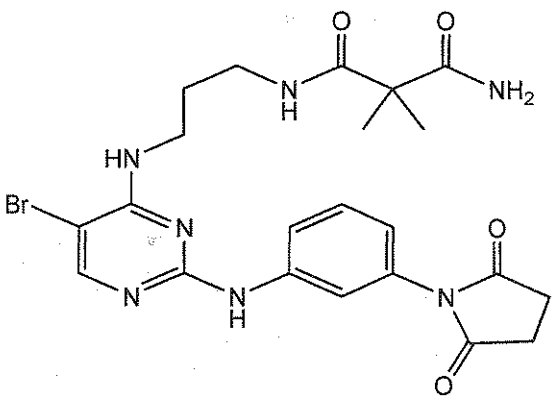
**XI-43**



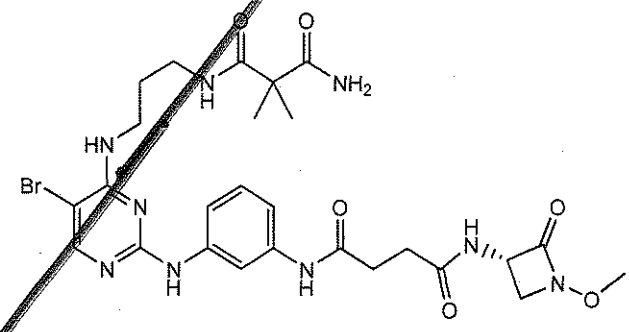
**XI-44**

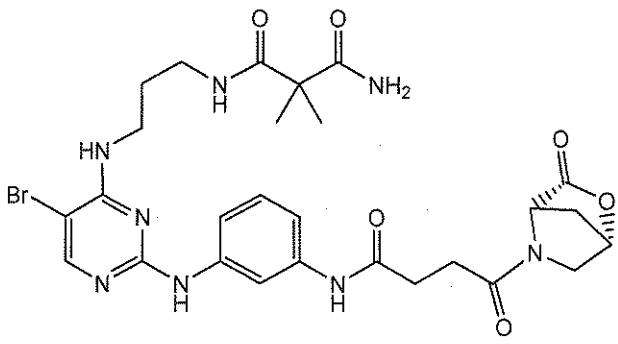


**XI-45**

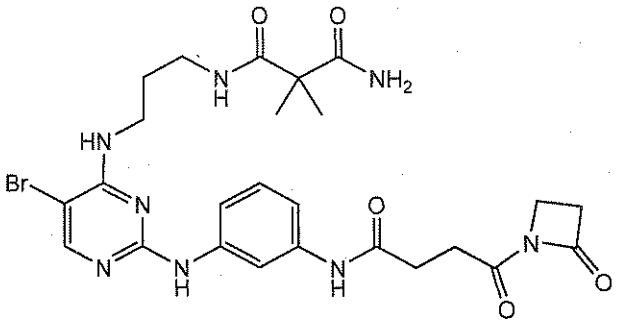


**XI-46**

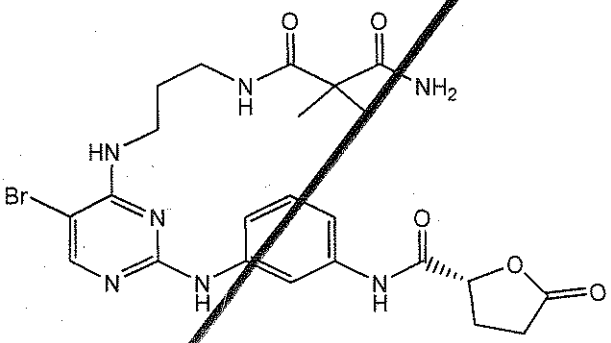




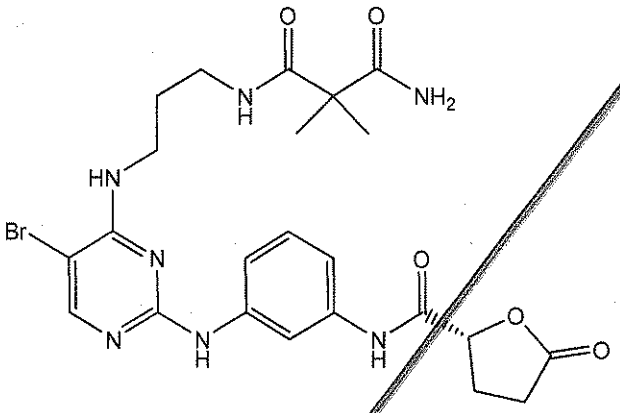
**XI-47**



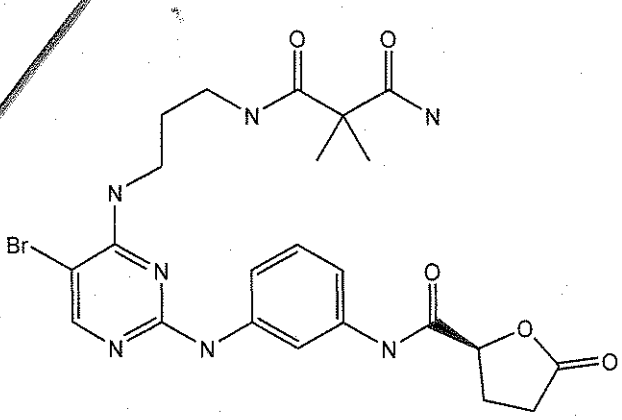
**XI-48**



**XI-49**



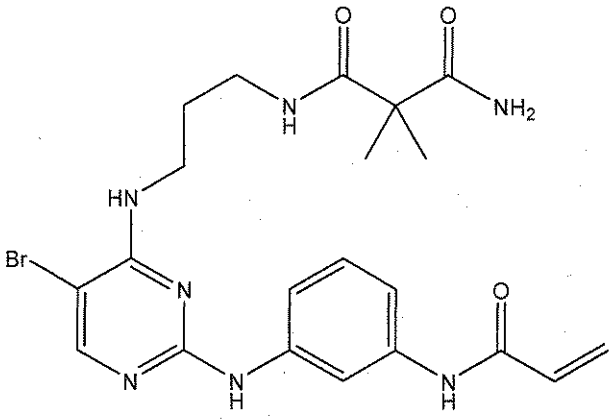
**XI-50**



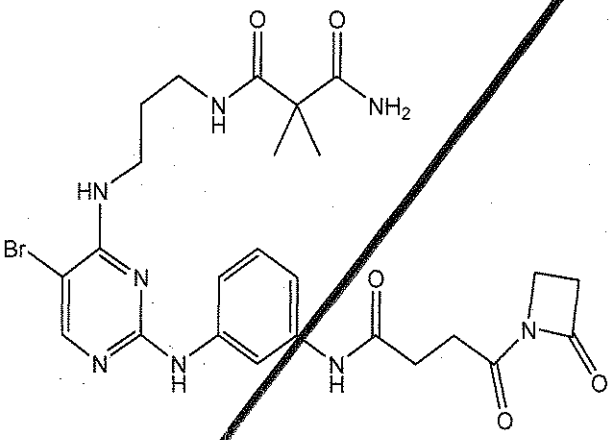
**XI-51**



**XI-52**

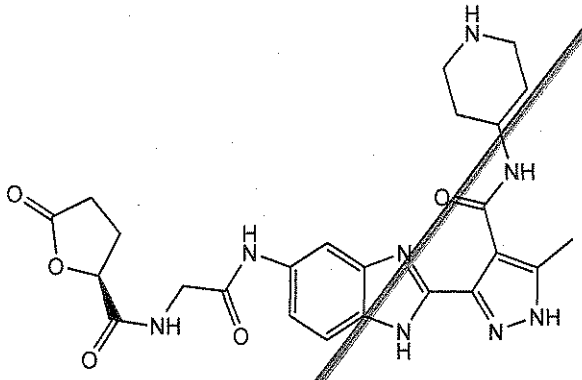


**XI-53**

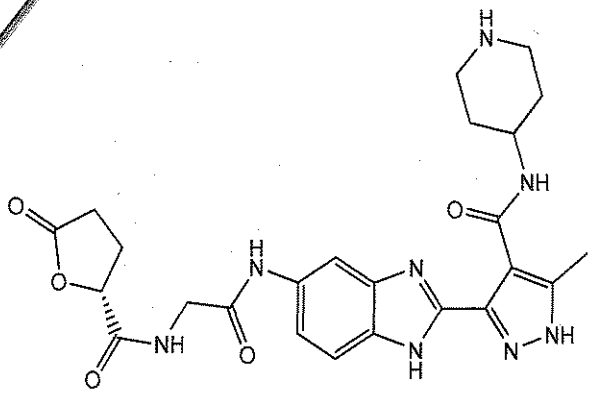


**XI-55**

22. The compound of claim 13, wherein the compound of Formula **XXXVI** is selected from the group consisting of:

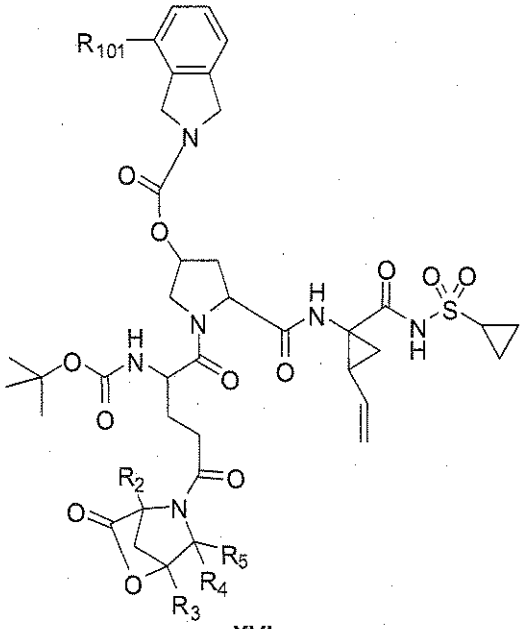


**XXXVI-1**

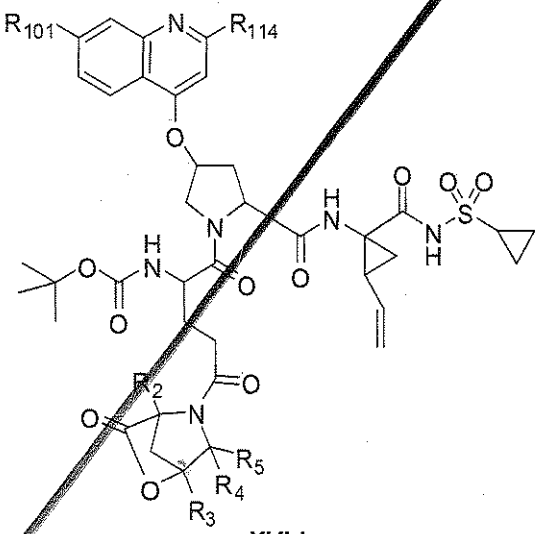


**XXXVI-2**

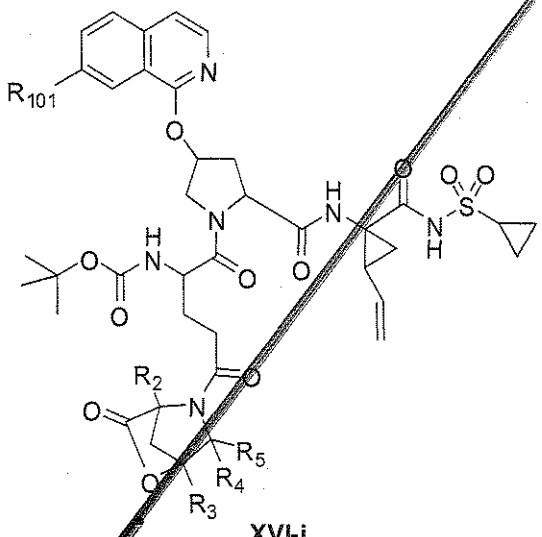
23. The compound of claim 13, wherein the compound of Formula **XVI-d**, **XVI-e**, or **XVI-f** is a compound of Formula **XVI-g**, **XVI-h**, or **XVI-i**:



**XVI-g**



**XVI-h**



**XVI-i**

wherein

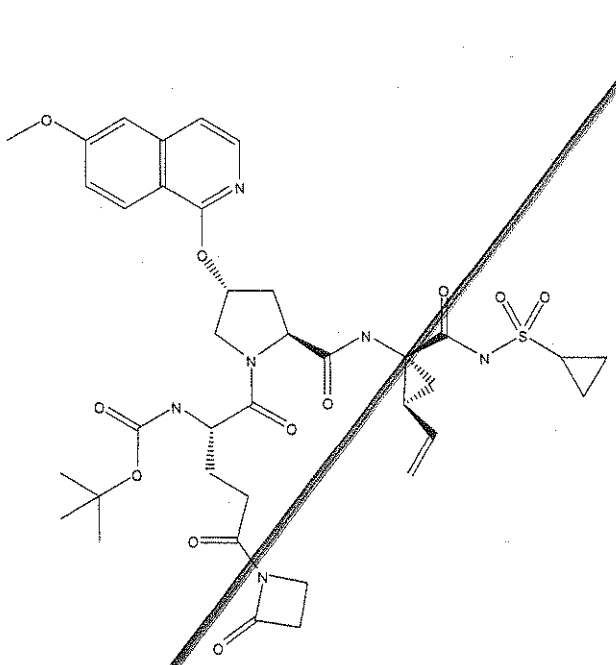
each $R_2$, $R_3$, $R_4$, and $R_5$ is independently hydrogen or $C_1$-$C_6$ alkyl; wherein one or more methylene groups of the $C_1$-$C_6$ alkyl can be replaced by -$NR_1$-, -O-, -C(O)-, -S-, -SO-,

$-SO_2-$, or -C(=S)-; one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ;

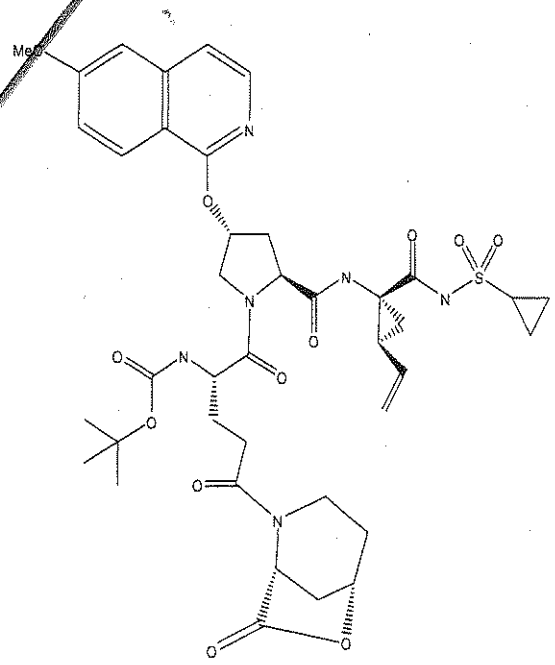
$R_1$ is hydrogen or $C_1$-$C_8$ alkyl;

wherein optionally when proper any two of $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, and $R_8$ when taken together form a 3- to 8-membered carbocyclic or heterocyclic ring or an aryl or heteroaryl group; and optionally $X_2$ and any one of $R_2$, $R_3$, and $R_4$ when taken together form a 3- to 8-membered carbocyclic or heterocyclic ring or an aryl or heteroaryl group.

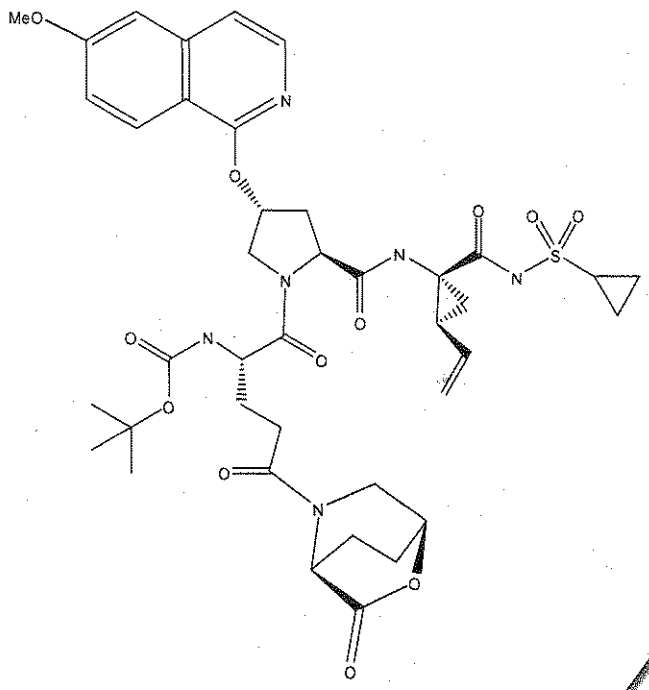
24. The compound of claim 13, wherein the compound of Formula **I'** is selected from the group consisting of:



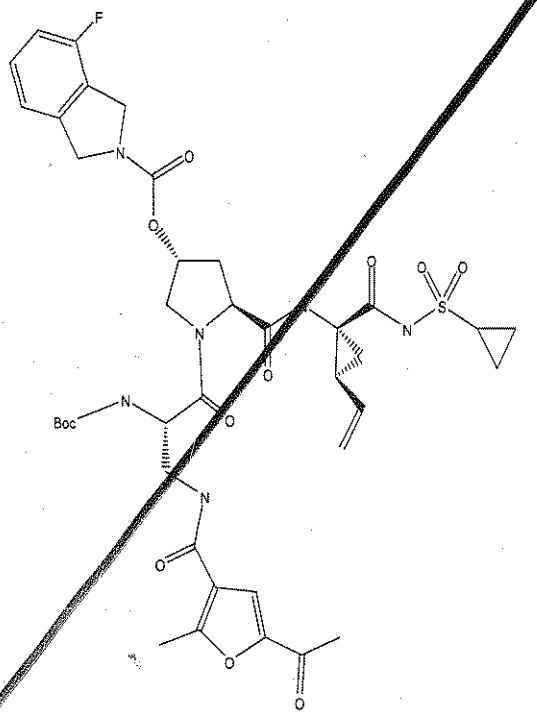
**XVI-1**



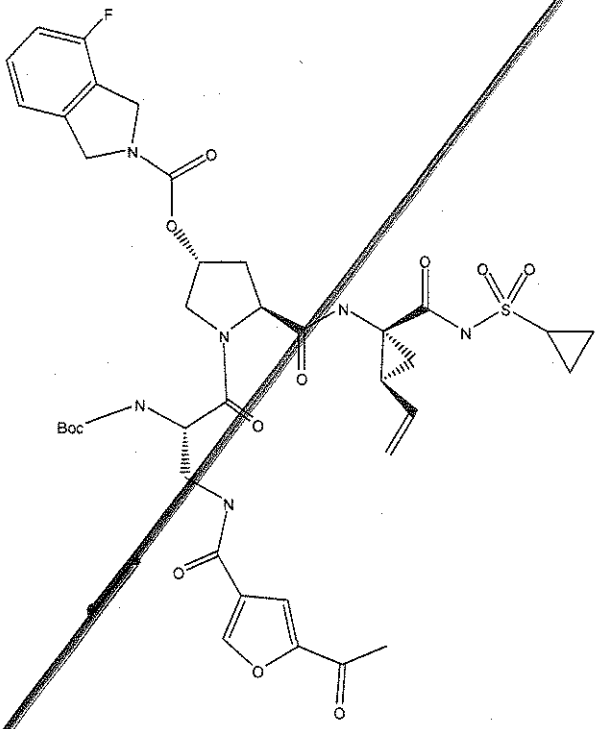
**XVI-2**



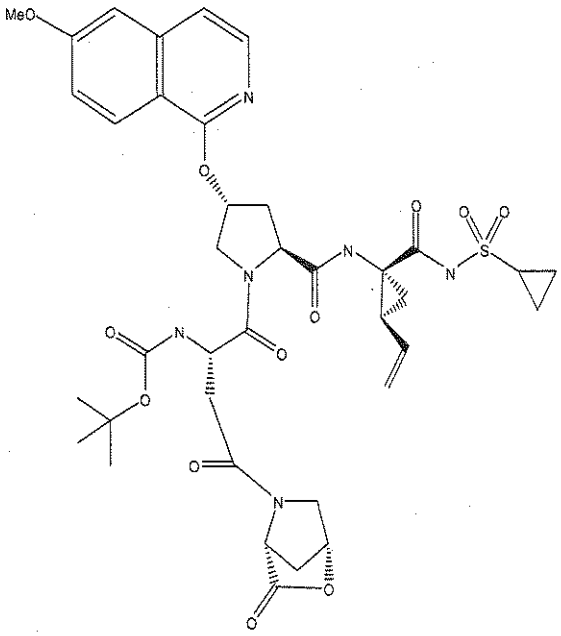
**XVI-3**



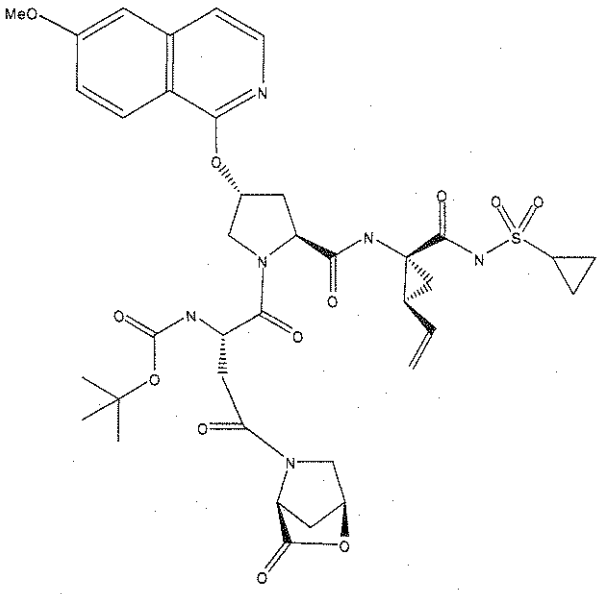
**XVI-4**



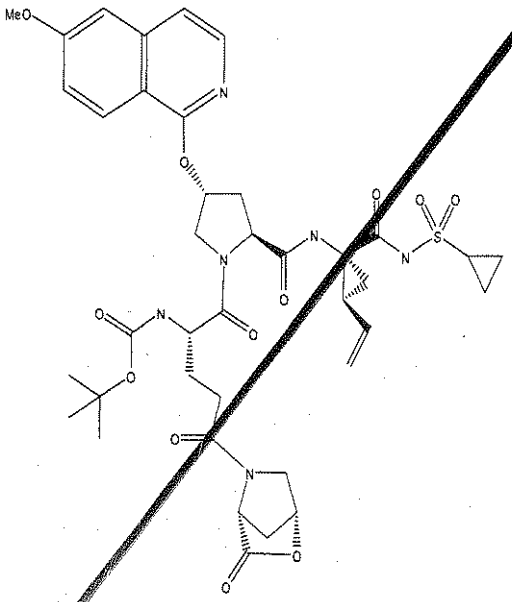
**XVI-5**



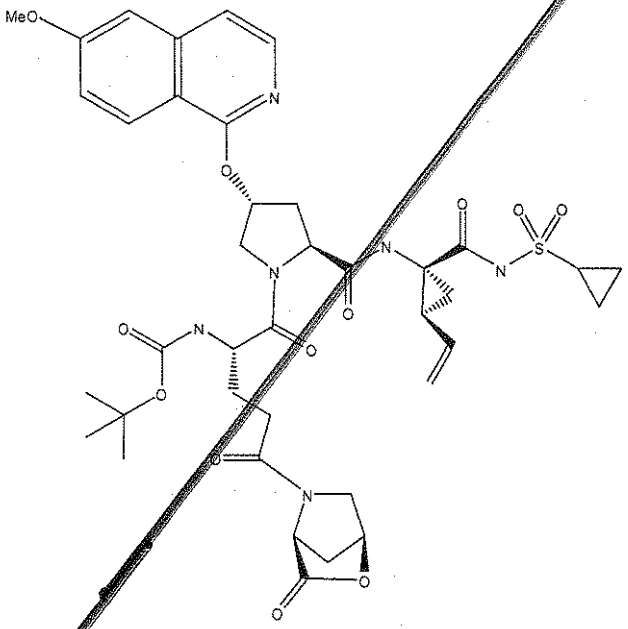
**XVI-6**



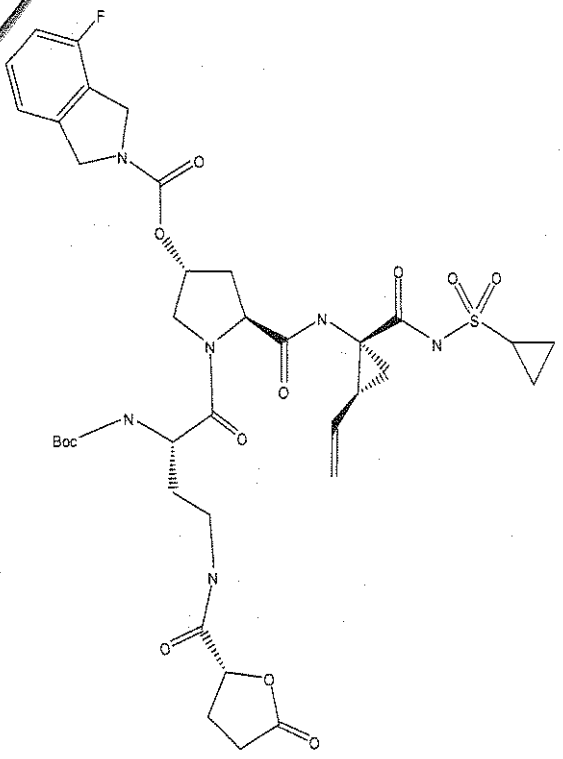
**XVI-7**



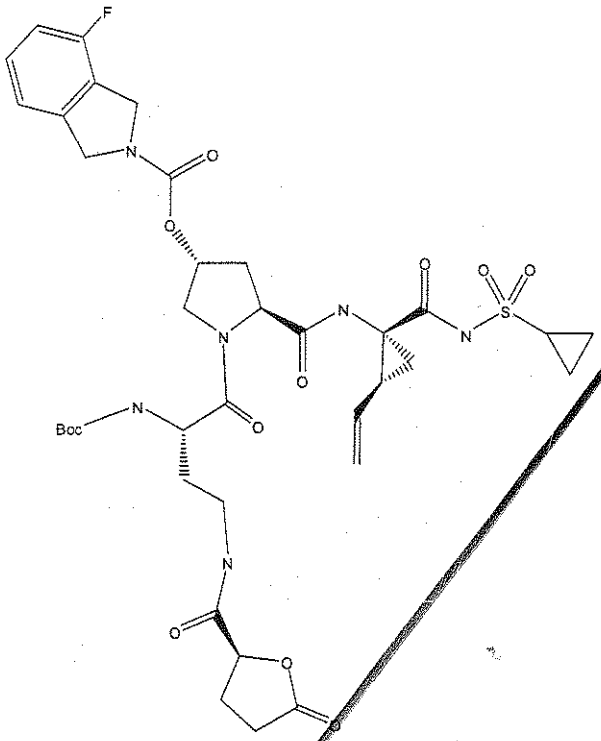
**XVI-8**

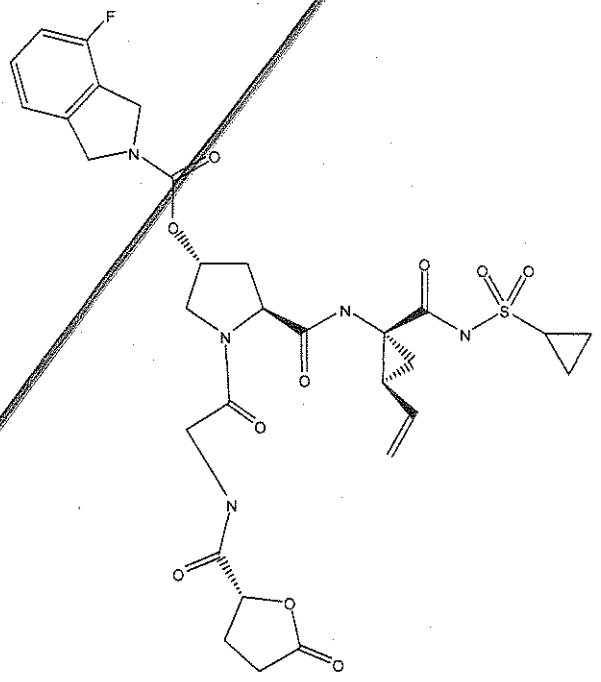


**XVI-9**

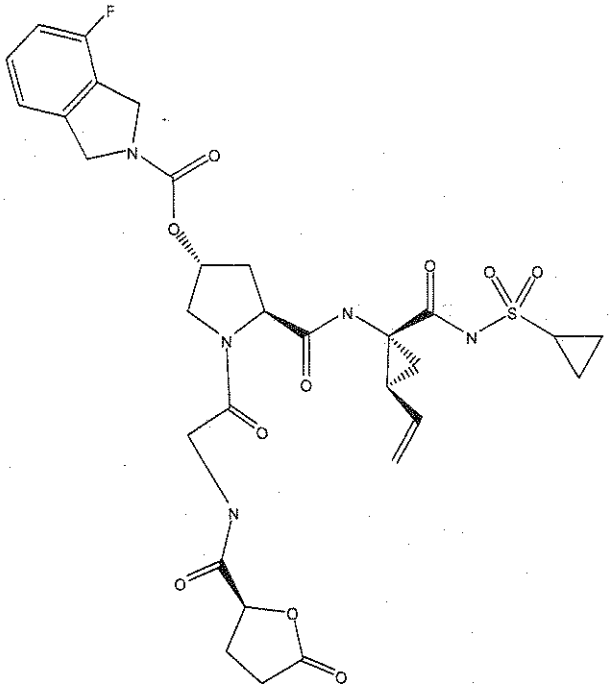


**XVI-10**

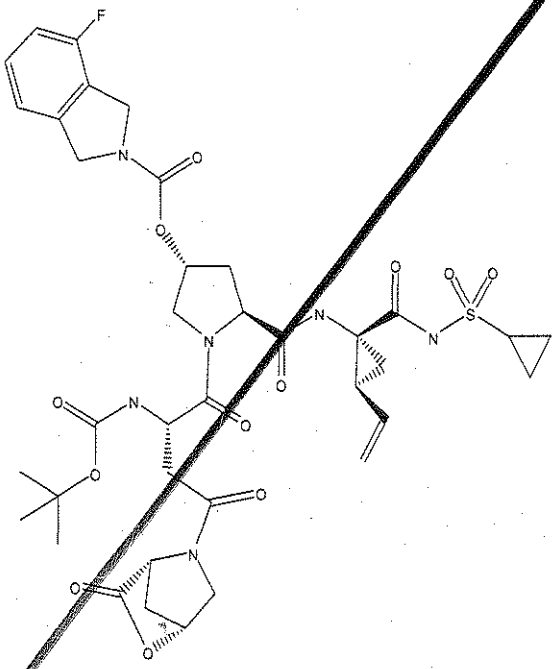




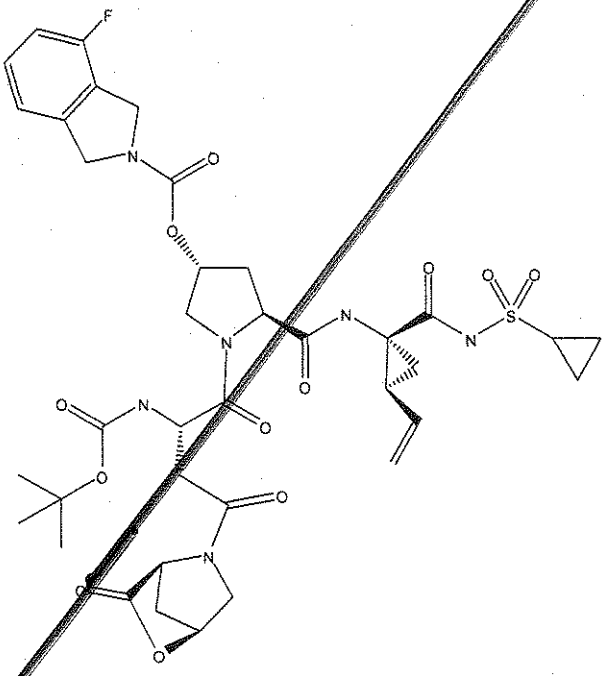
**XVI-11** **XVI-12**



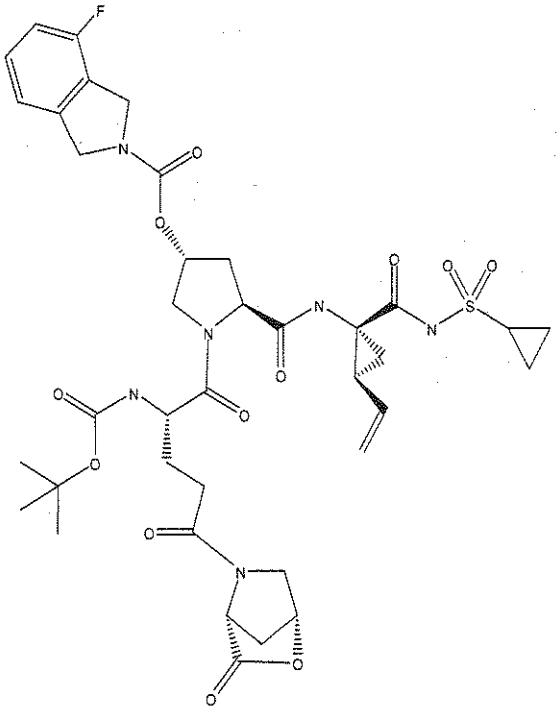
**XVI-13**



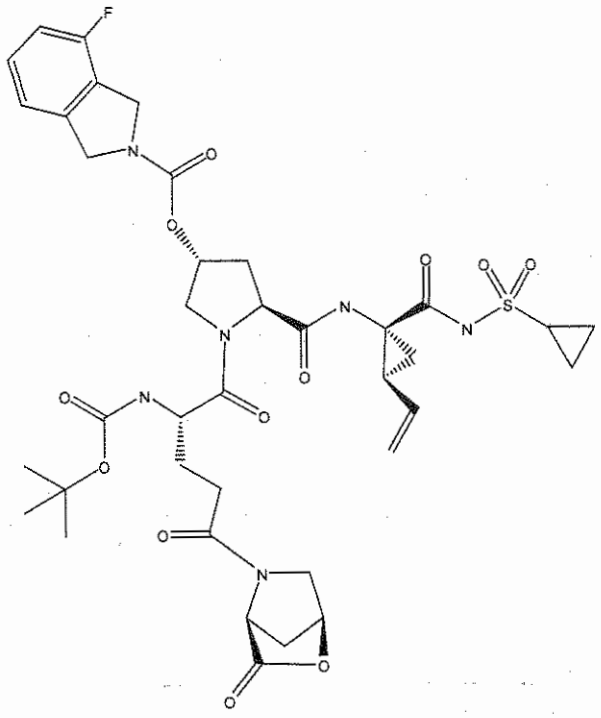
**XVI-14**



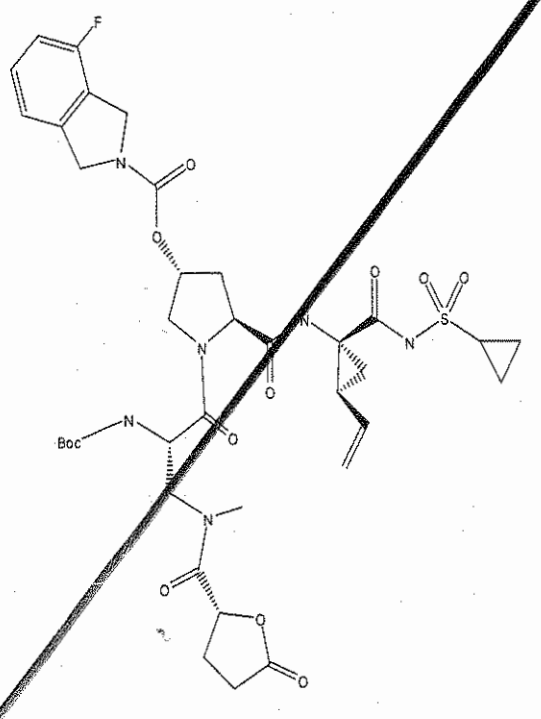
**XVI-15**



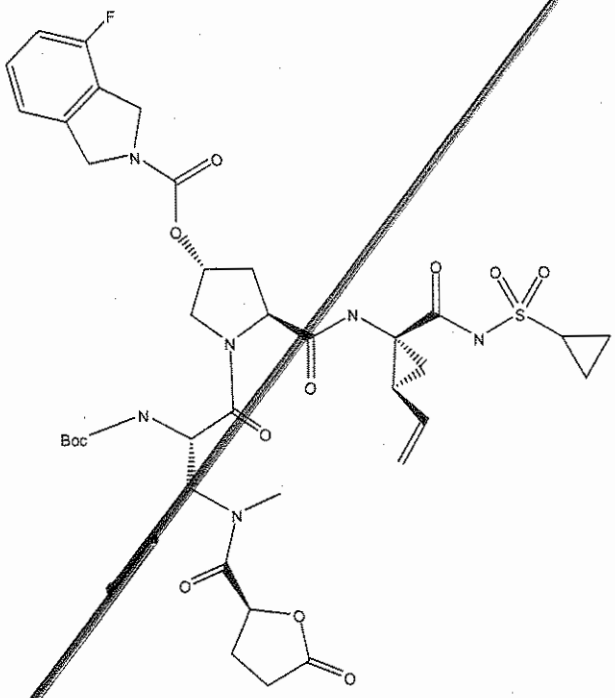
**XVI-16**



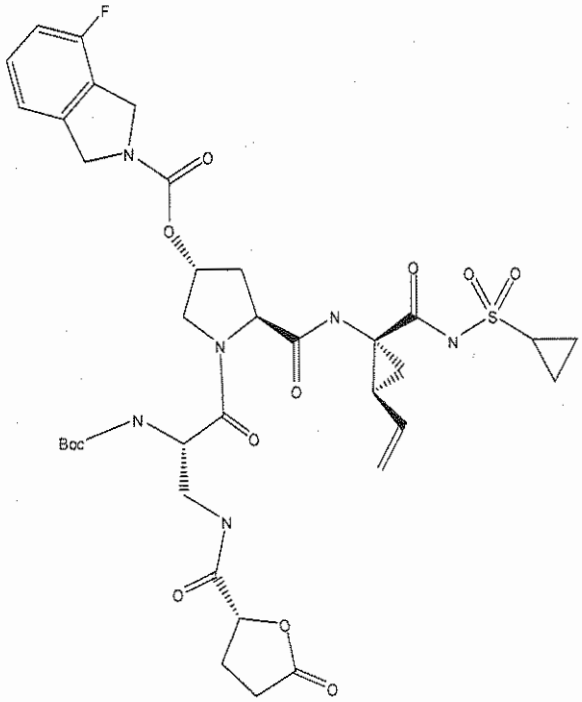
**XVI-17**



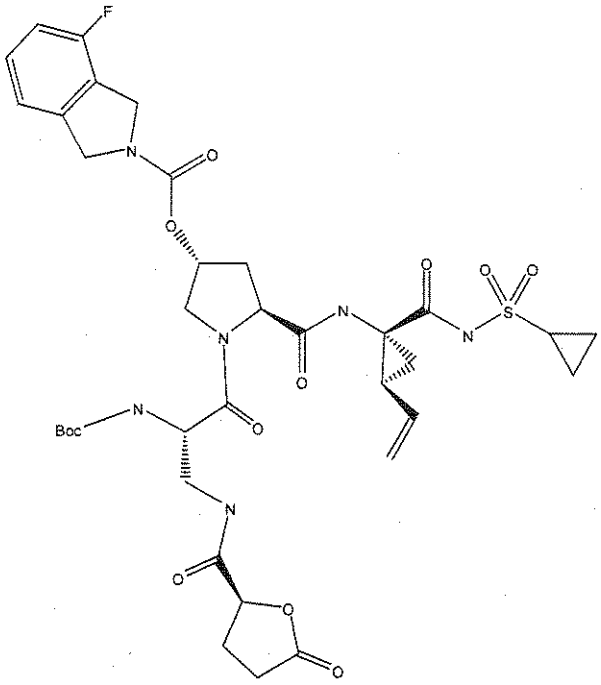
**XVI-18**



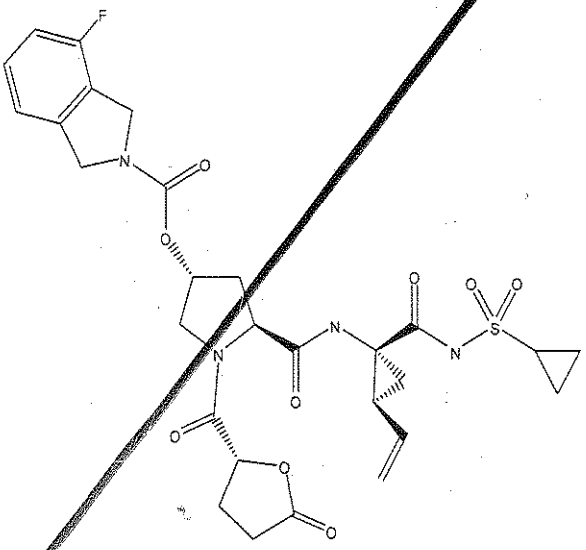
**XVI-19**



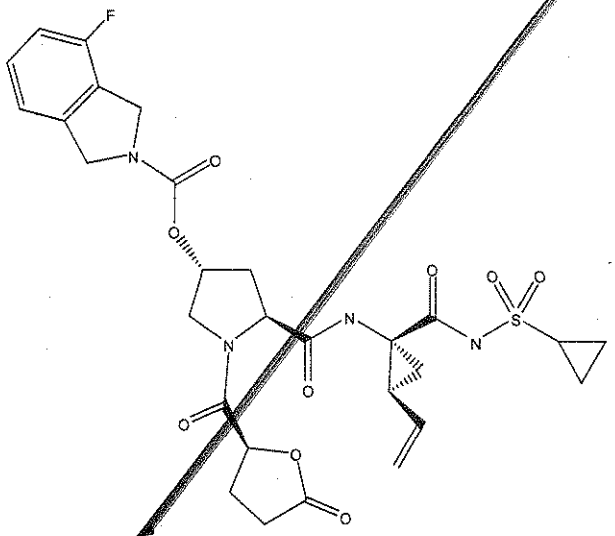
**XVI-20**



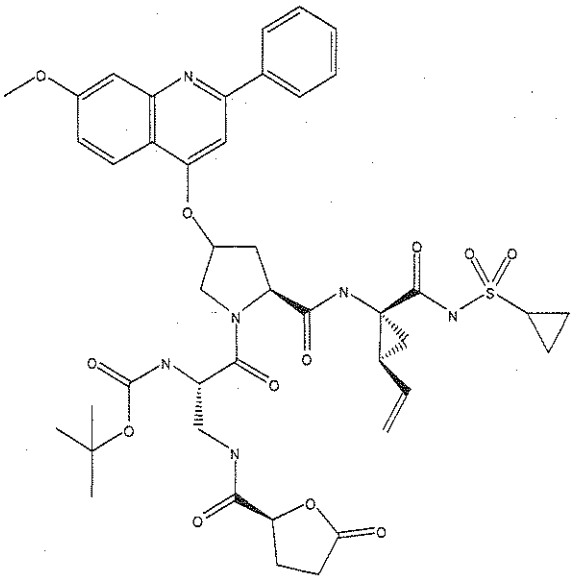
XVI-21



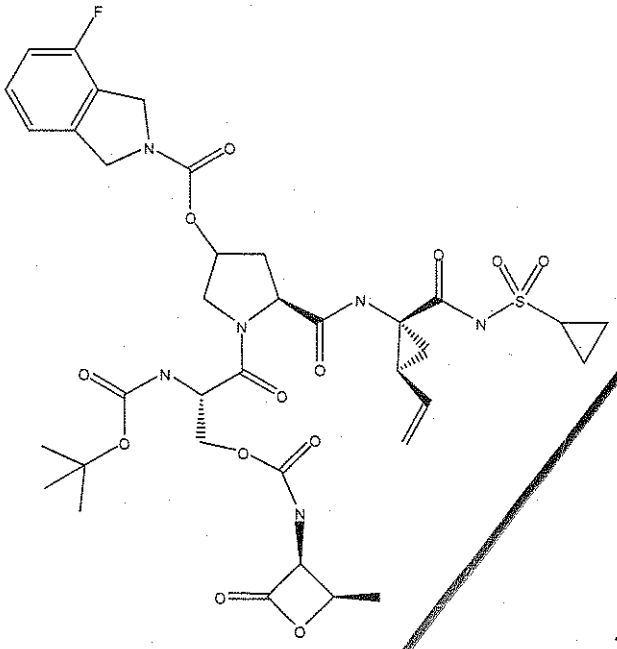
XVI-22



XVI-23

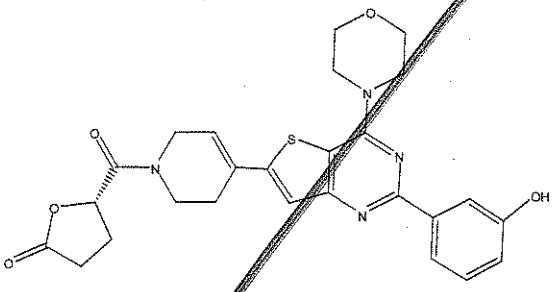


XVI-24

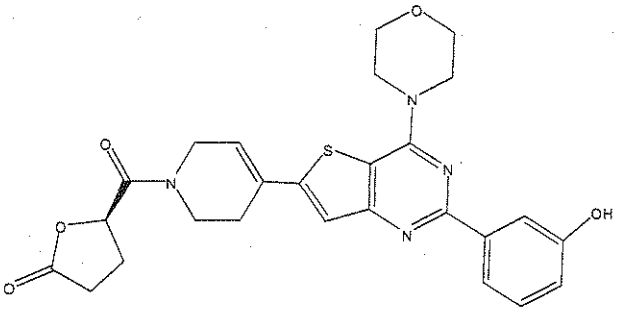


**XVI-25**

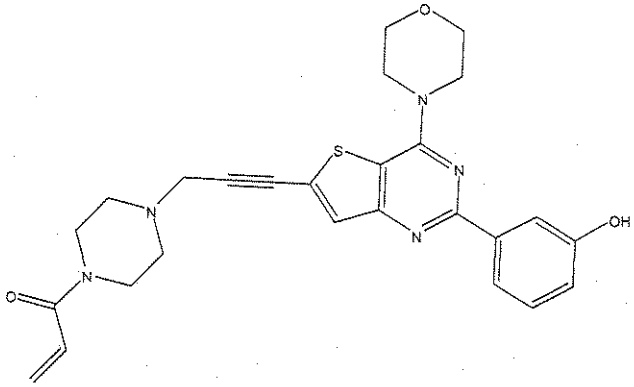
25. The compound of claim 13, wherein the compound of Formula **XXII-a**, **XXII-b**, **XXII-c** is selected from the group consisting of:



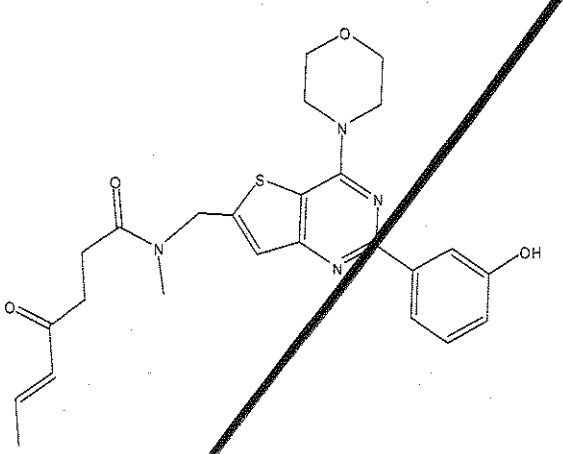
**XXII-1**



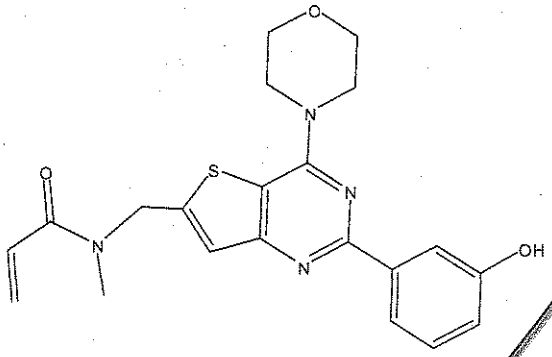
**XXII-2**



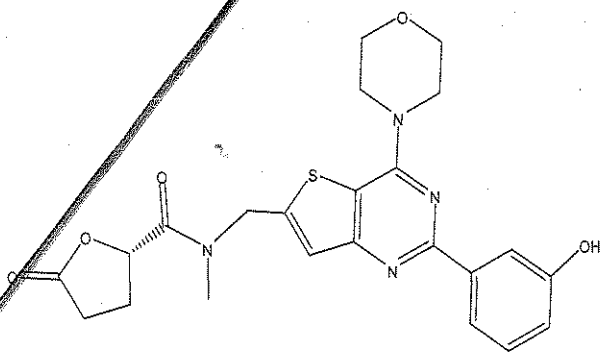
**XXII-3**



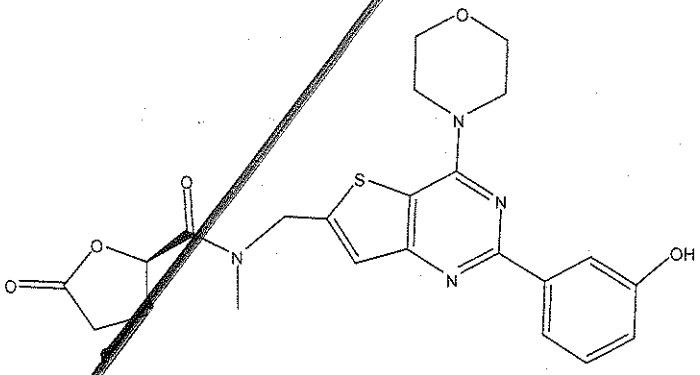
**XXII-4**



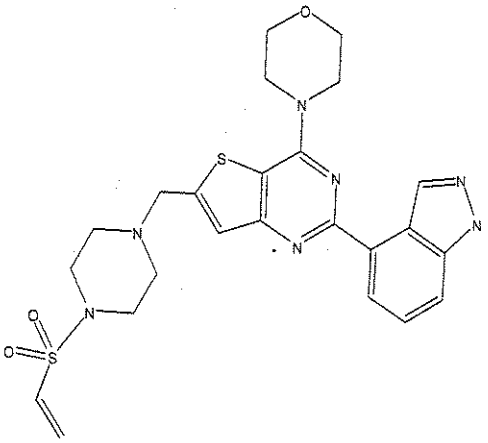
**XXII-5**



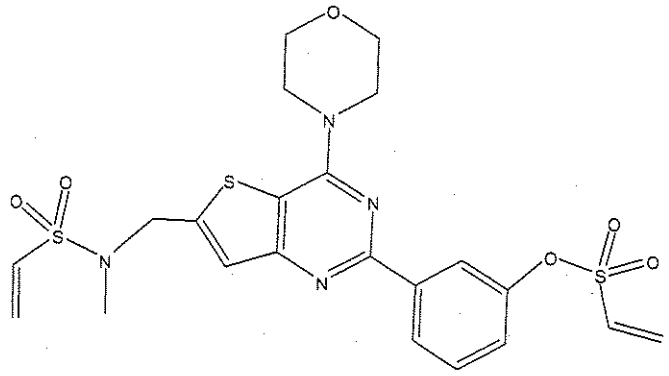
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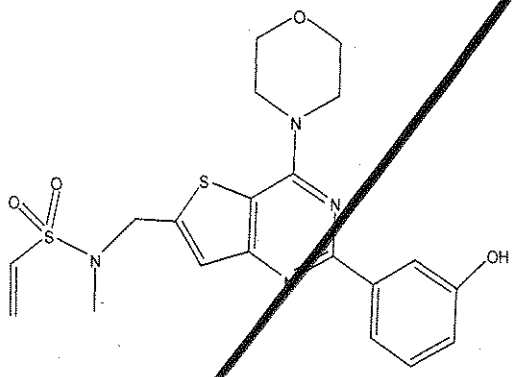
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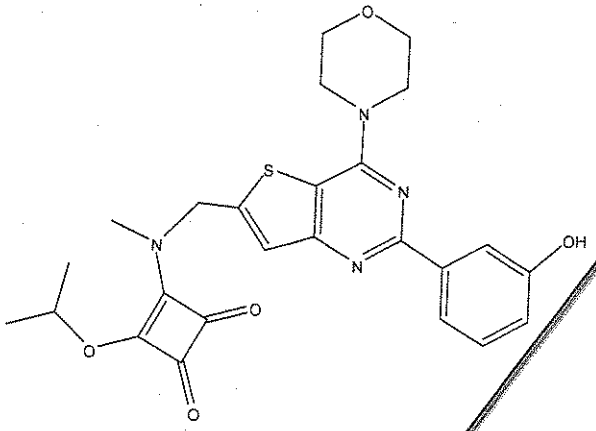
**XXII-8**



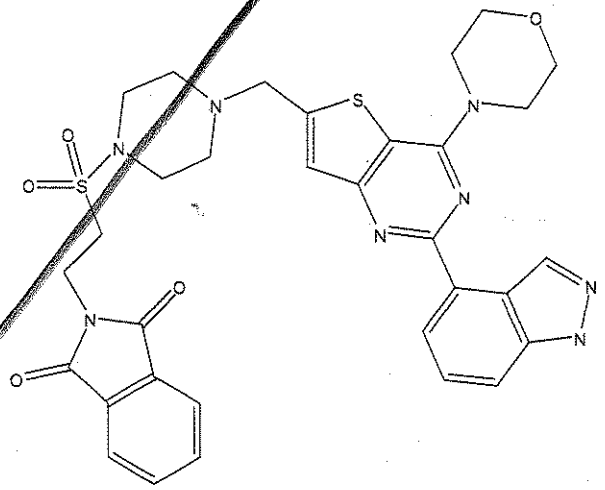
**XXII-9**



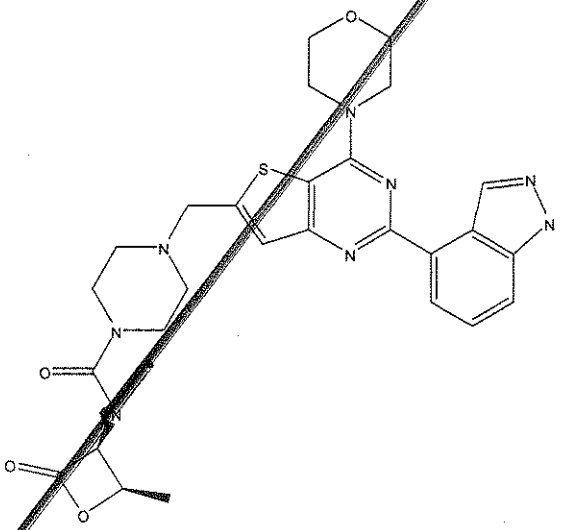
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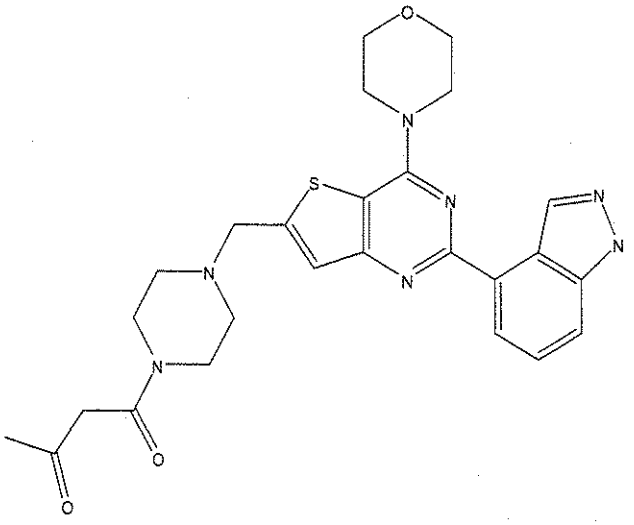
**XXII-11**



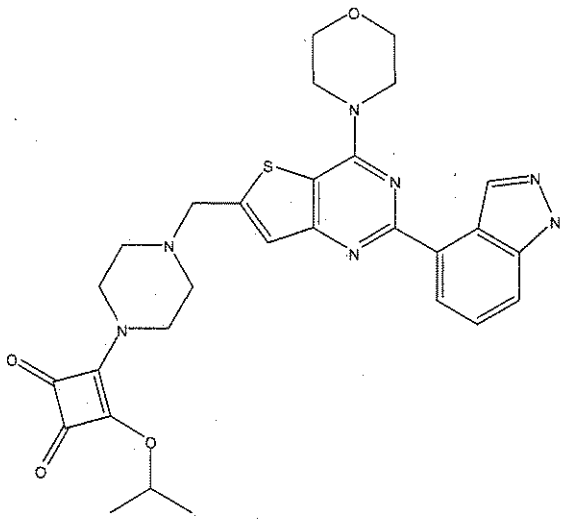
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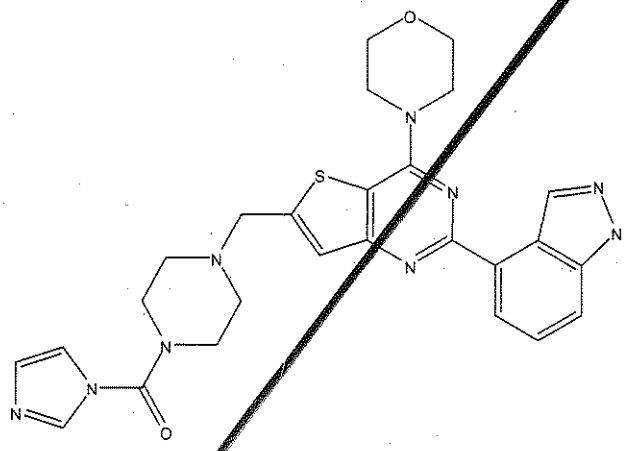
**XXII-13**



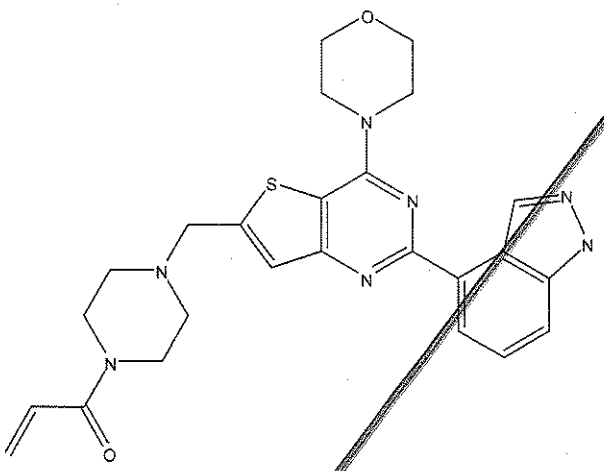
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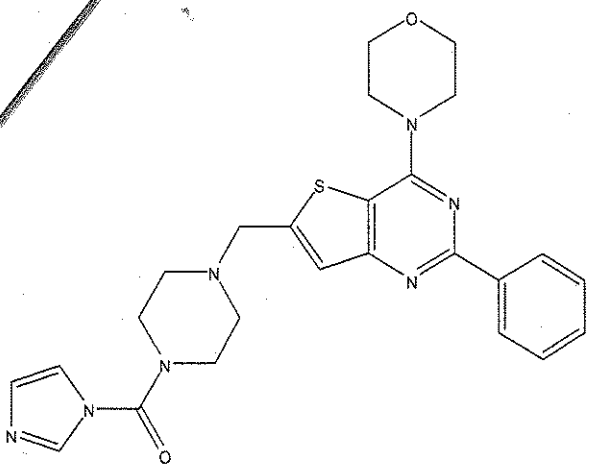
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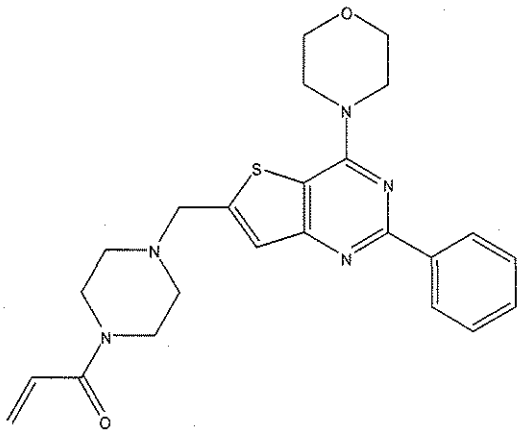
**XXII-16**



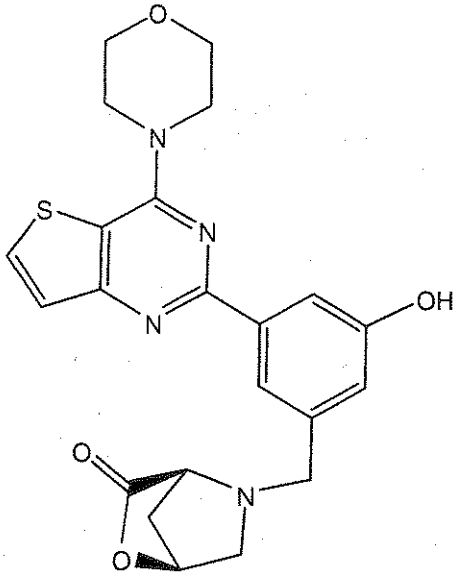
**XXII-17**



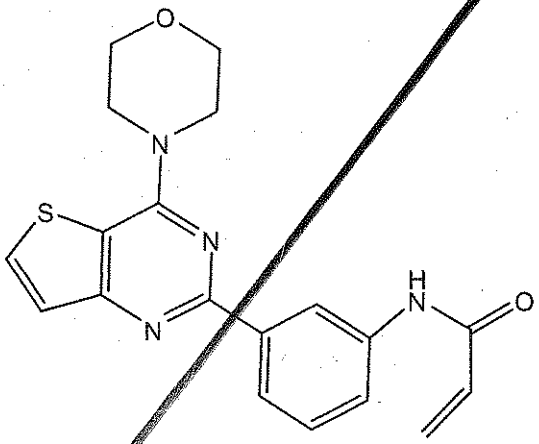
**XXII-18**



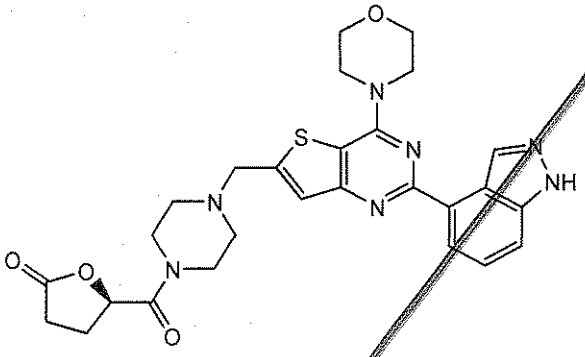
XXII-19



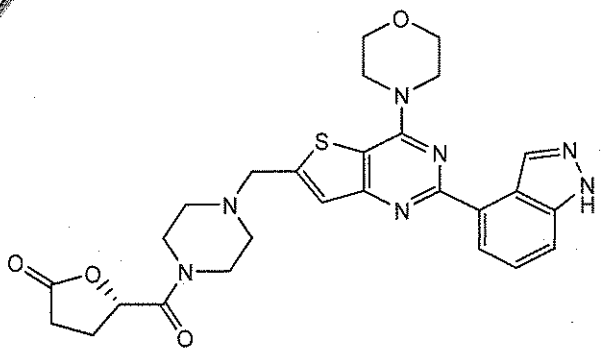
XXII-20



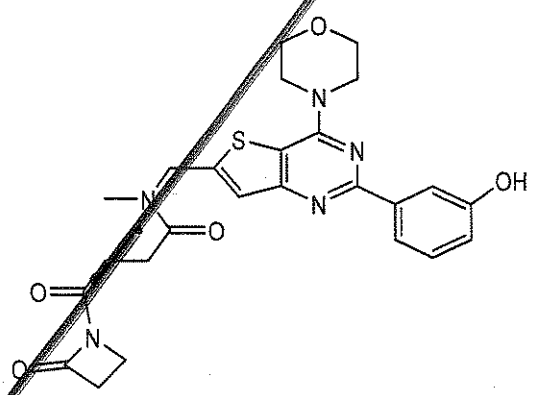
XXII-21

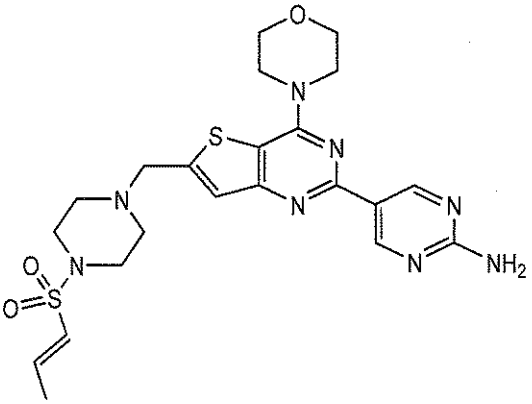


XXII-22

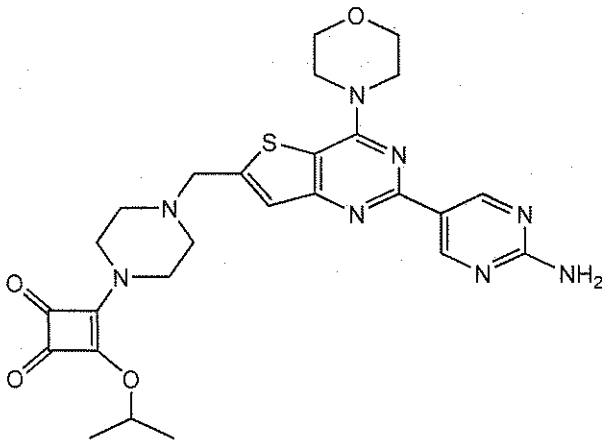


XXII-23

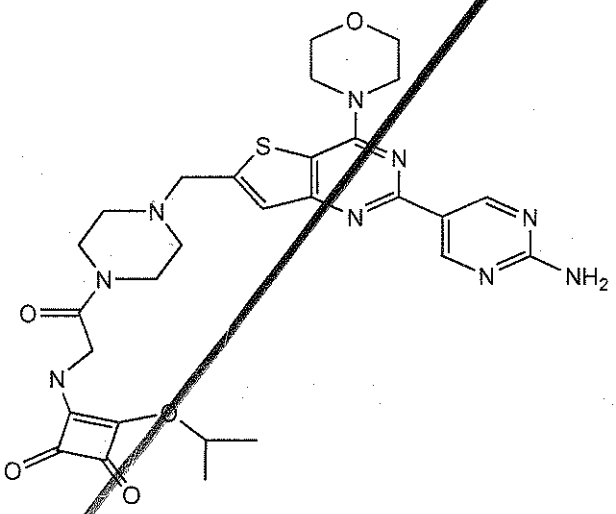




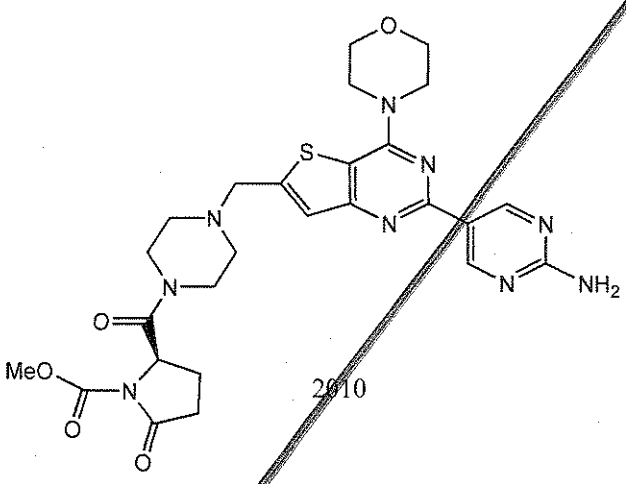
**XXII-24**



**XXII-25**

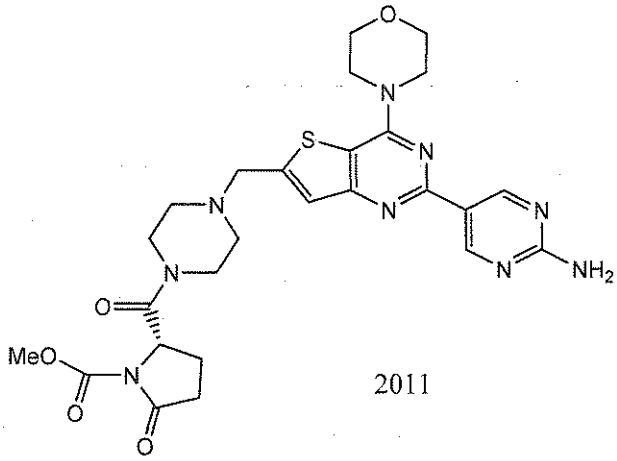


**XXII-26**



2010

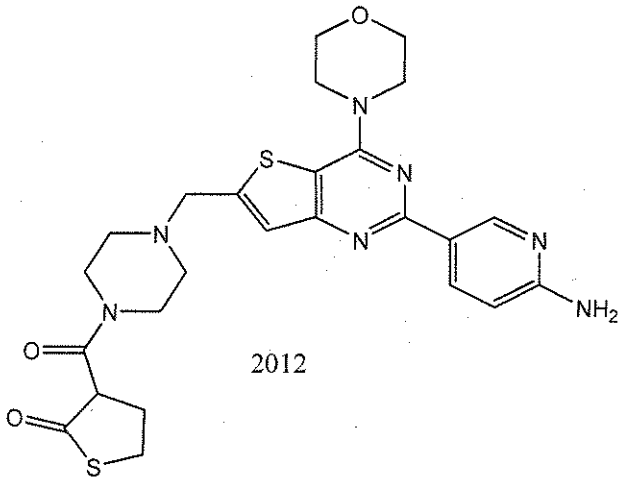
**XXII-27**



2011

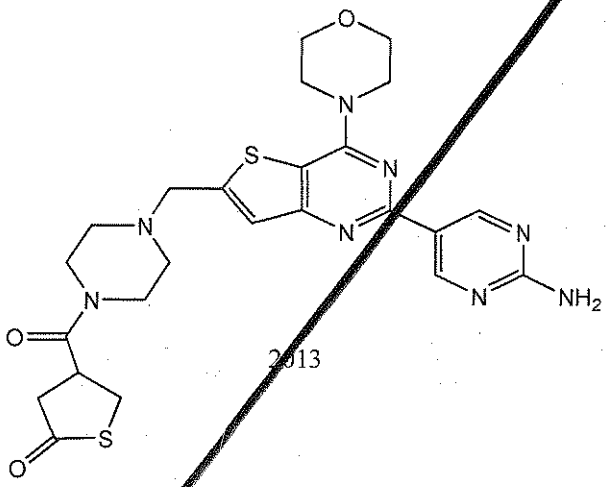
**XXII-28**

**XXII-29**



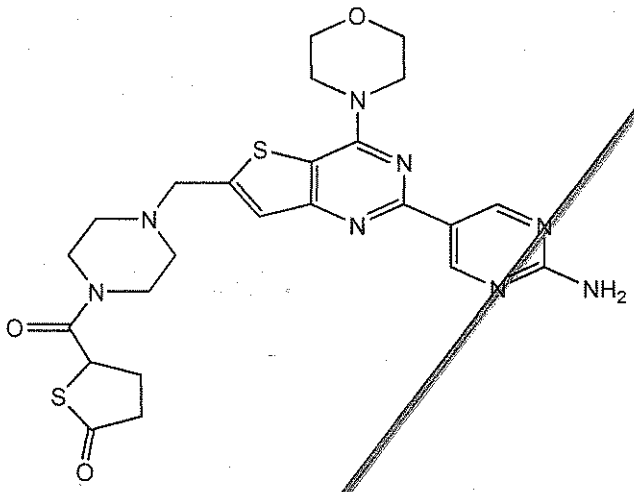
2012

**XXII-30**

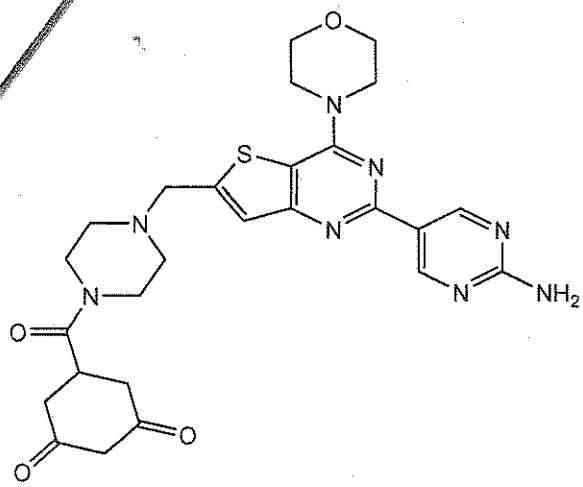


2013

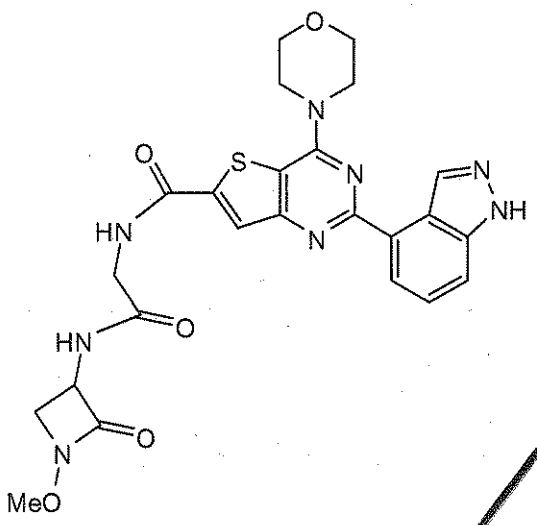
**XXII-31**



**XXII-32**

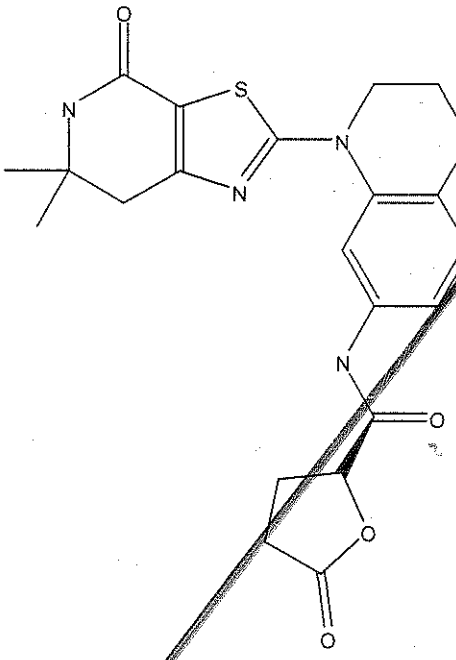


**XXII-33**

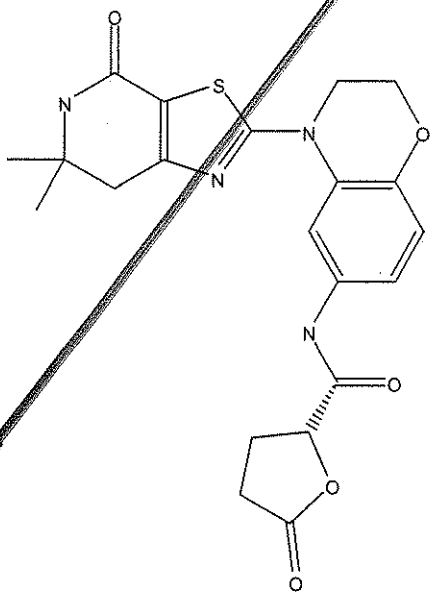



**XXII-34**

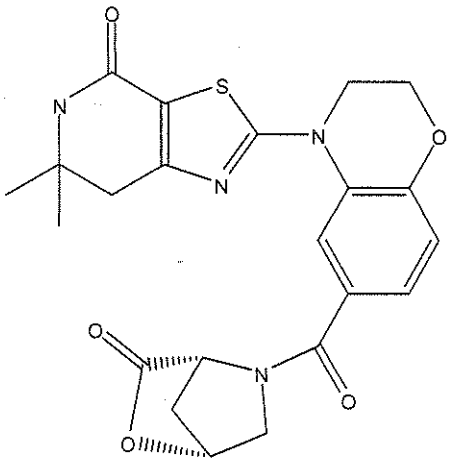
26. The compound of claim 13, where the compound of Formula **XXIII** is selected from the group consisting of:



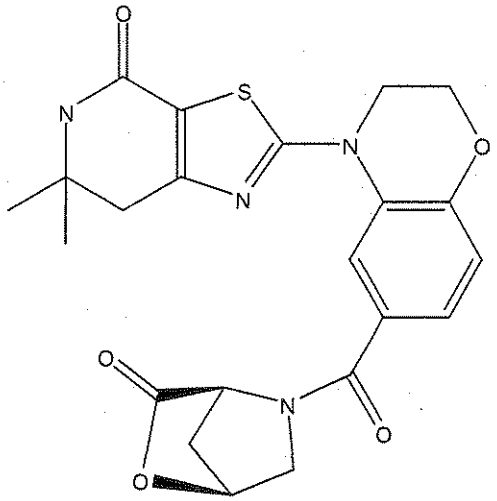
**XXIII-1**



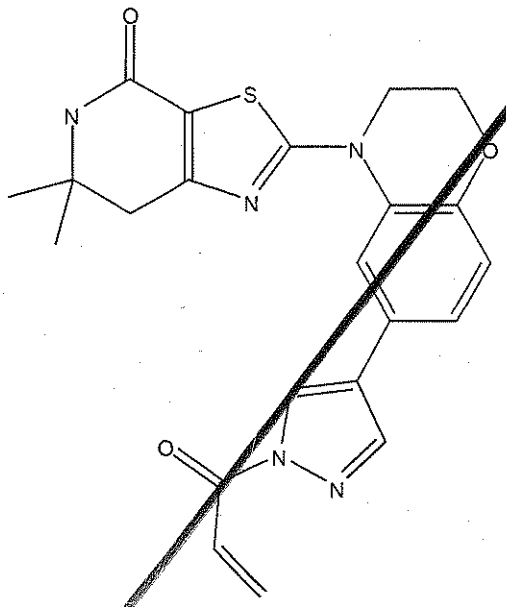
**XXIII-2**



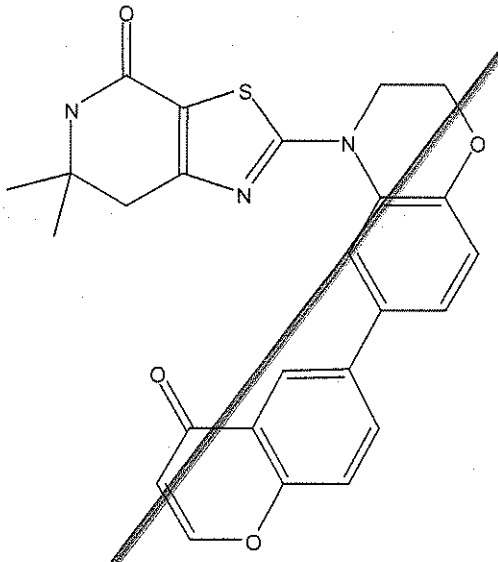
**XXIII-3**



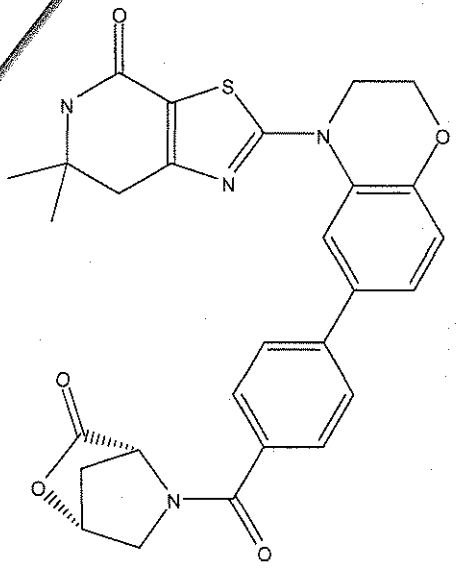
**XXIII-4**



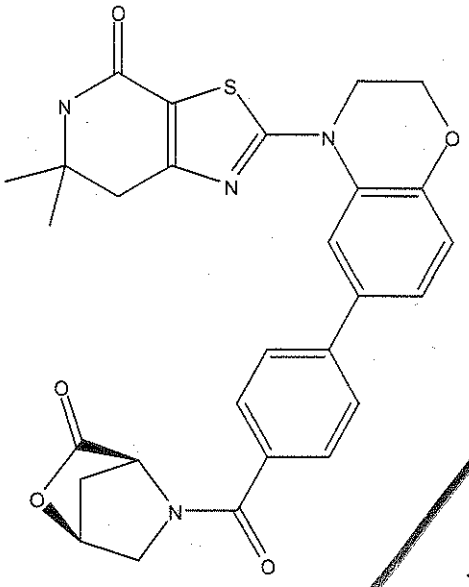
**XXIII-5**



**XXIII-6**

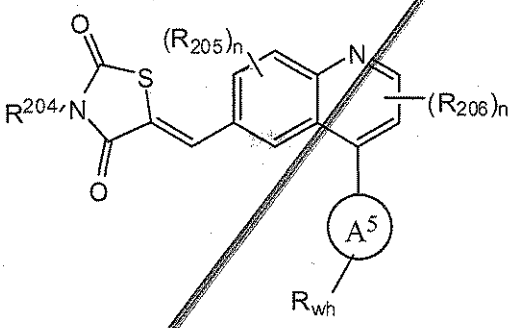


**XXIII-7**

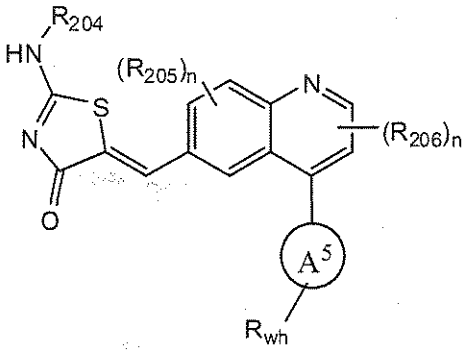


**XXIII-8**

27. The compound of claim 3, wherein the compound of Formula **I** is a compound of Formula **XXIV-a** or Formula **XXIV-b**:



**XXIV-a**



**XXIV-b**

wherein

$R_{wh}$ is Warhead;

$R_{204}$ is an hydrogen or an optionally substituted group selected from $C_{1-6}$ aliphatic, -$(CH_2)_m$-(3- to 7-membered saturated or partially unsaturated carbocyclic ring), -$(CH_2)_m$-(7- to 10-membered saturated or partially unsaturated bicyclic carbocyclic ring), -$(CH_2)_m$-(4- to 7-

membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur), -$(CH_2)_m$-(7- to 10-membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur), -$(CH_2)_m$-phenyl, -$(CH_2)_m$-(8- to 10-membered bicyclic aryl ring), -$(CH_2)_m$-(5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur), or -$(CH_2)_m$-(8- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur);

each $R_{205}$ and $R_{206}$ is independently –R", halogen, $–NO_2$, –CN, –OR", –SR", $–N(R")_2$, -C(O)R", $–CO_2R"$, –C(O)C(O)R", $–C(O)CH_2C(O)R"$, –S(O)R", $–S(O)_2R"$, $–C(O)N(R")_2$, $-SO_2N(R")_2$, –OC(O)R", –N(R")C(O)R", –N(R")N(R")$_2$, -N(R")C(=NR")N(R")$_2$, -C(=NR")N(R")$_2$, –C=NOR", –N(R")C(O)N(R")$_2$, $–N(R")SO_2N(R")_2$, $–N(R")SO_2R"$, or -OC(O)N(R")$_2$;

each R" is independently hydrogen or an optionally substituted group selected from $C_{1–6}$ aliphatic, a 3- to 7-membered saturated or partially unsaturated carbocyclic ring, a 7- to 10-membered saturated or partially unsaturated bicyclic carbocyclic ring, a 4- to 7-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, phenyl, an 8- to 10-membered bicyclic aryl ring, a 5- to 6-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

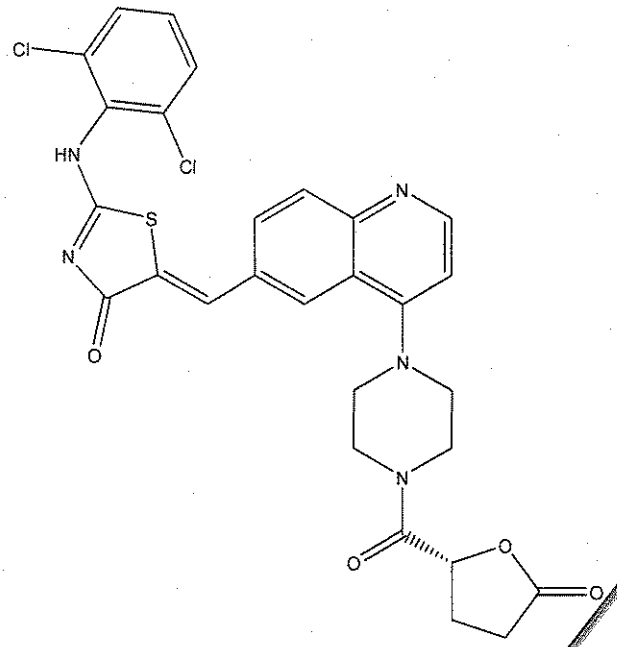
two R" groups on the same nitrogen are taken together with the nitrogen to which they are attached to form an optionally substituted 5–8 membered saturated, partially unsaturated, or aromatic ring having 1–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

m is an integer from 0 to 6, inclusive;

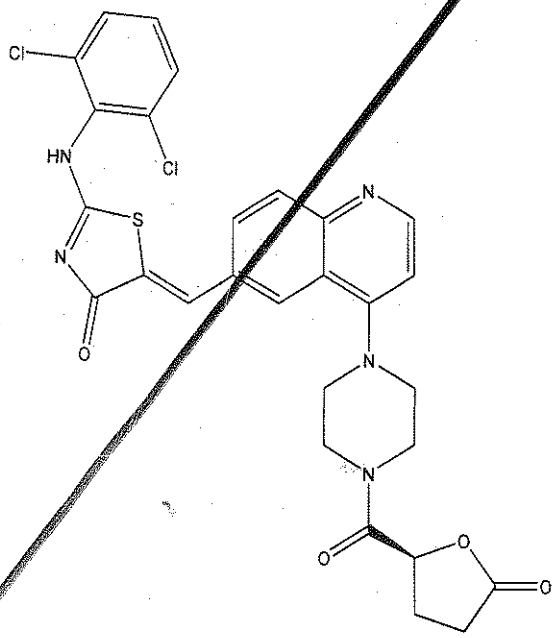
each n for Formula **XXIV-a** or Formula **XXIV-b** is independently 0, 1, or 2; and

Ring $A^5$ is an optionally substituted 6-membered heterocyclic or heteroaryl ring having 1-2 nitrogens.

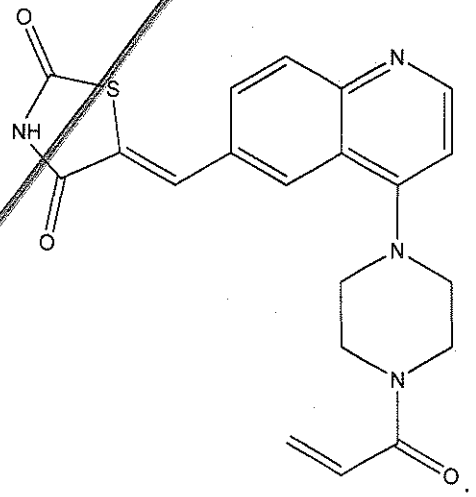
28. The compound of claim 27, wherein the compound of Formula **XXIV-a** or Formula **XXIV-b** is selected from the group consisting of:



**XXIV-1**

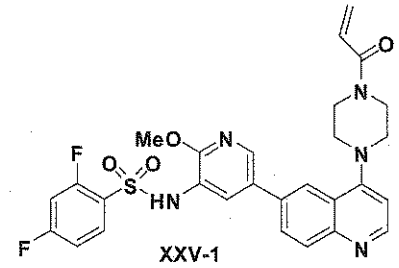


**XXIV-2**

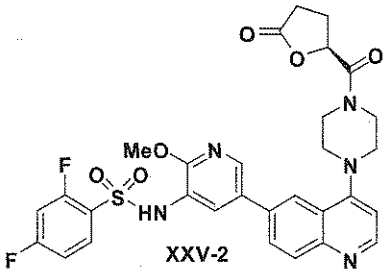


**XXIV-3**

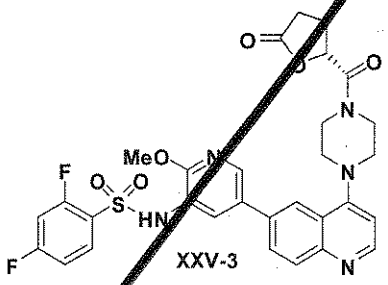
29. The compound of claim 13, wherein the compound of Formula **XXV** is selected from the group consisting of:



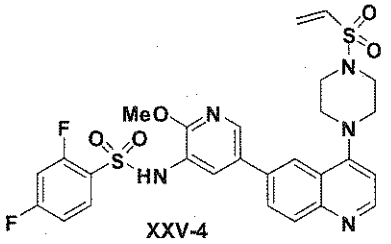
XXV-1



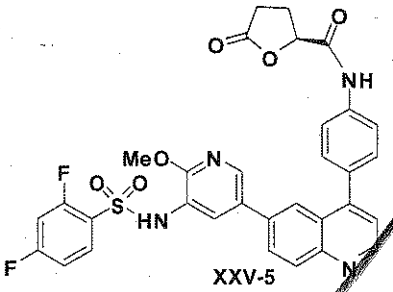
XXV-2



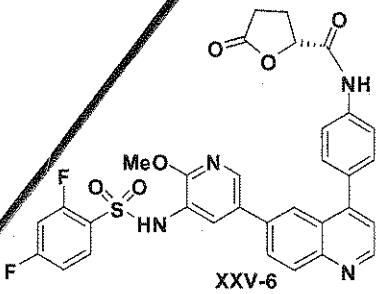
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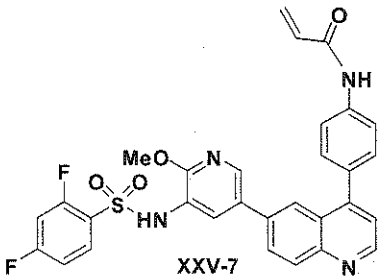
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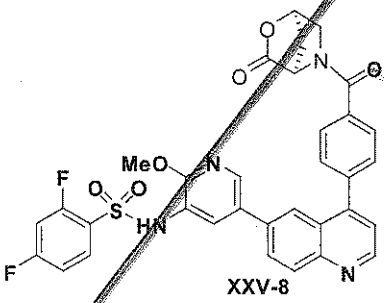
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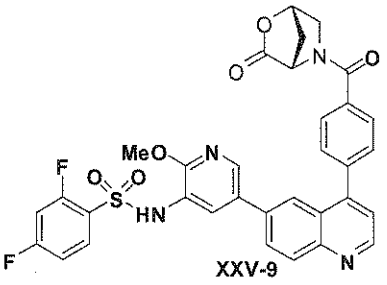
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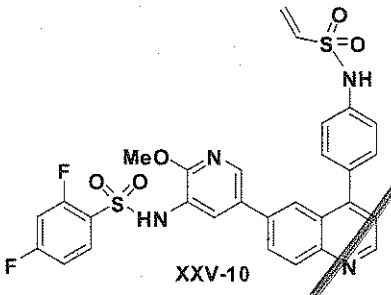
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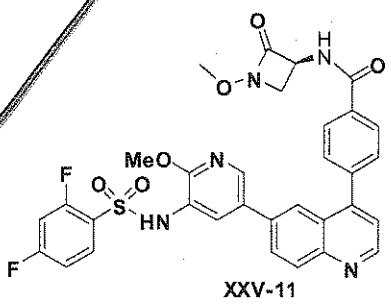
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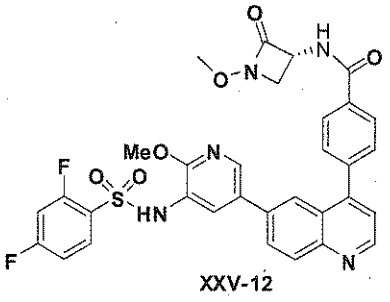
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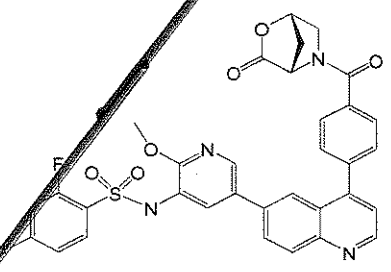
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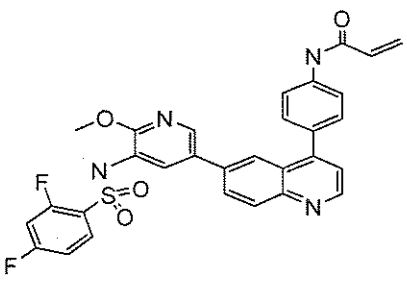
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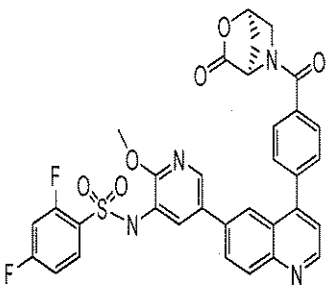
XXV-12



XXV-13

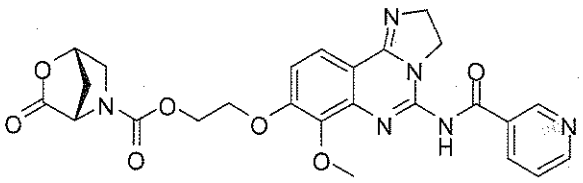


XXV-14

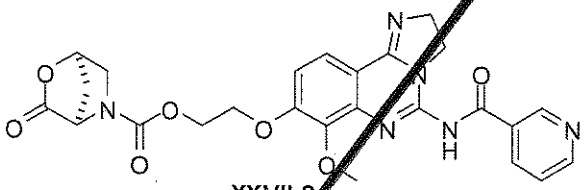


XXV-15

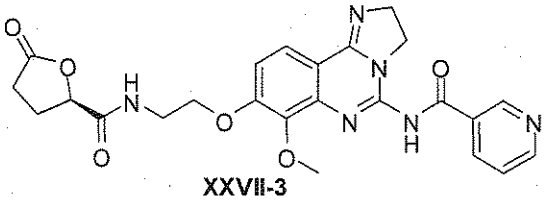
30. The compound of claim 13, wherein the compound of Formula **XXVII** is selected from the group consisting of:



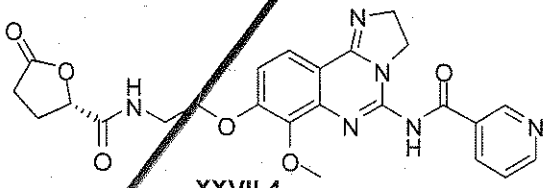
**XXVII-1**



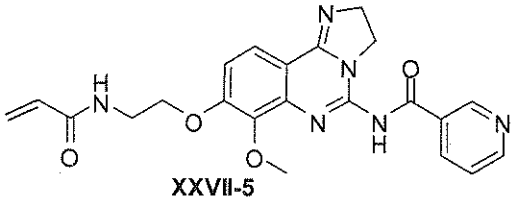
**XXVII-2**



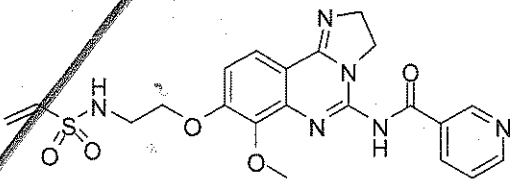
**XXVII-3**



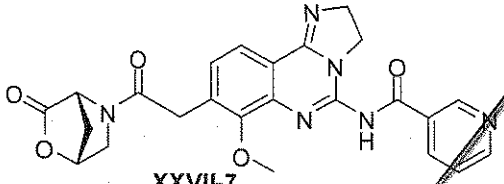
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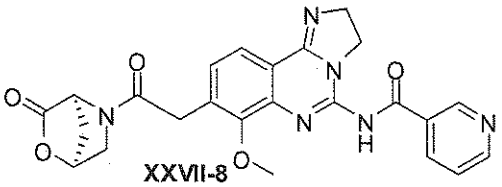
**XXVII-5**



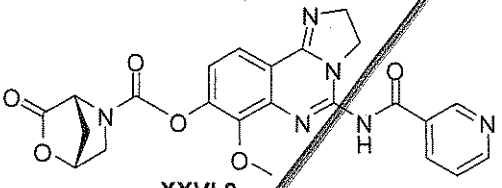
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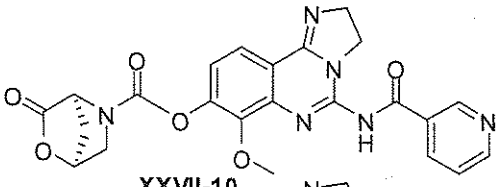
**XXVII-7**



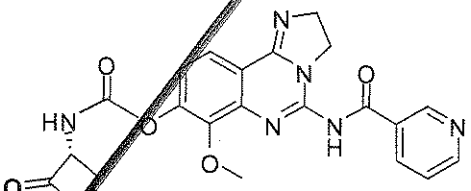
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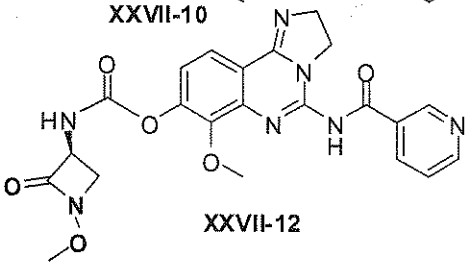
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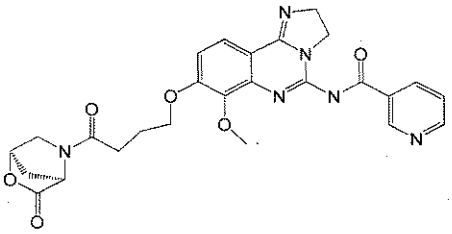
**XXVII-10**



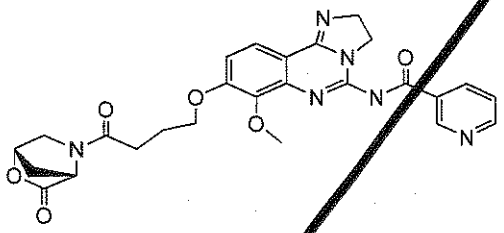
**XXVII-11**



**XXVII-12**

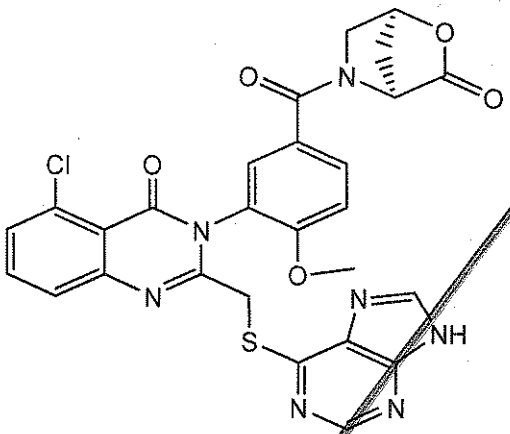


**XXVII-13**

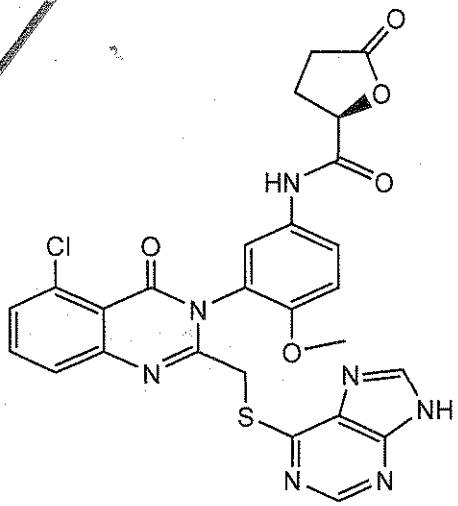


**XXVII-14**

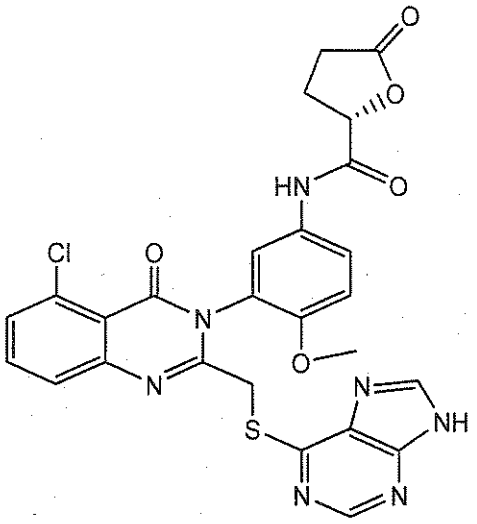
31. The compound of claim 13, wherein the compound of Formula **XXXVII** is selected from the group consisting of:



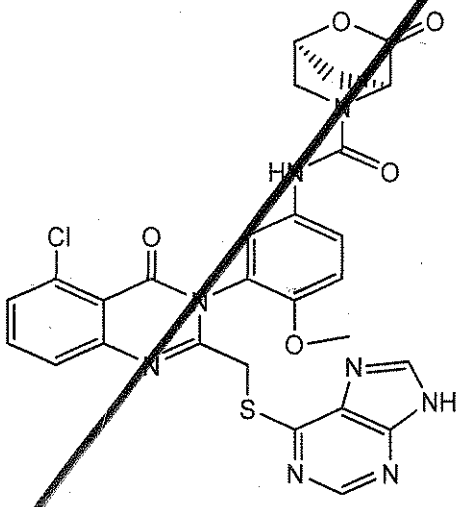
**XXXVII-1**



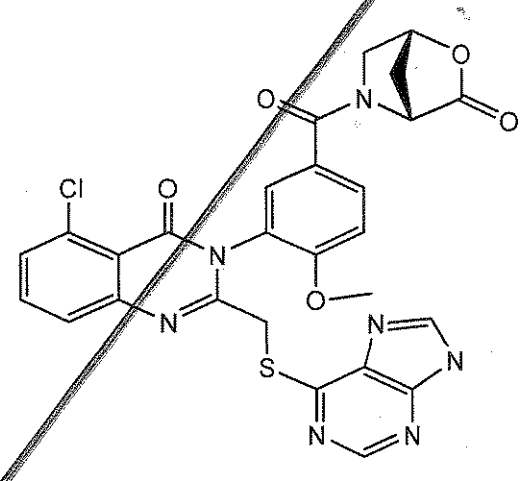
**XXXVII-2**



**XXXVII-3**



**XXXVII-4**



**XXXVII-5**

32. A compound of any one of claim 1 to 31 for use in treating:

a) an XIAP-mediated disorder wherein the compound irreversibly inhibits XIAP by covalently modifying a lysine residue conserved at an equivalent position of K297 of XIAP;

b) a PDPK1-mediated disorder wherein the compound irreversibly inhibits PDPK1 by covalently modifying a lysine residue conserved at an equivalent position of K169 or K173 or K86 of PDPK1;

c) an HCV protease-mediated disorder wherein the compound irreversibly inhibits HCV protease by covalently modifying a lysine residue conserved at an equivalent position of K136 of HCV-protease subtype of NS3/4A; or

d) a PI3K-mediated disorder wherein the compound irreversibly inhibits PI3K by covalently modifying a lysine residue conserved at an equivalent position of K777 or K802 or K890 of PI3K.

33. A method for designing a ligand that covalently binds a target protein, the method comprising:

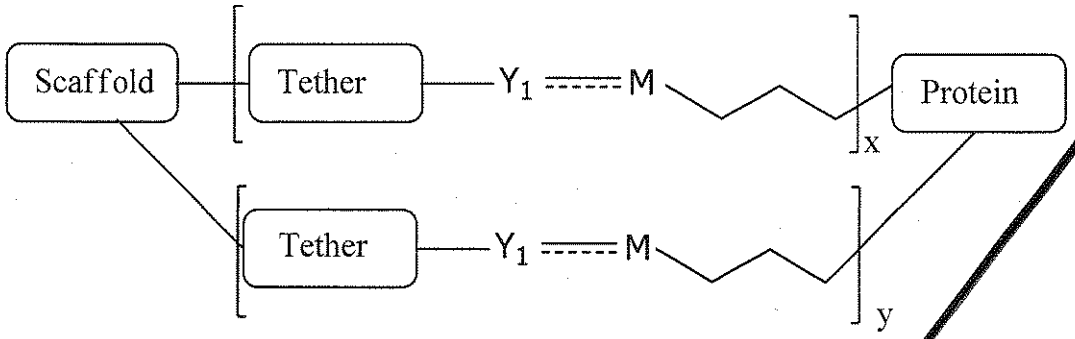
A) providing a structural model of a reversible ligand docked within, or in proximity to, a ligand-binding site in a target protein;

B) identifying a lysine residue of the target protein in, or in proximity to, the ligand-binding site that is less than about 15Å from the reversible ligand when the reversible ligand is docked in, or in proximity to, the ligand-binding site;

C) producing at least a structural model of at least one ligand-warhead compound docked within, or in proximity to, the ligand-binding site wherein the ligand-warhead compound comprises the reversible ligand in step B) or a portion thereof, a warhead comprising a reactive chemical moiety, and optionally a Tether; and

D) identifying a ligand-warhead compound whose structural model allows the lysine residue in step B) to readily assume a conformation that brings the side chain primary amine group of the lysine residue within bond-forming proximity of the warhead electrophile, wherein the ligand-warhead compound is a compound as defined in claims 1 to 31.

34. Protein-modifier-ligand conjugates of the Formula **XIII**,




**XIII**

wherein

Scaffold is

a) a radical resulting from the removal of a hydrogen of a ligand capable of binding to, or in proximity to, the ligand-binding site; or

b) a portion of a pharmacophore of a ligand resulting from truncation of the pharmacophore, such that the Scaffold is capable of binding to, or in proximity to, the ligand-binding site;

Warhead is an organic moiety optionally containing one or more heteroatoms selected from O, N, and S; the organic moiety having a molecular weight of about 14 daltons to about 200 daltons; Warhead being capable of reaction with a side chain primary amine group of a lysine residue; and Warhead being attached to Scaffold through Tether; and

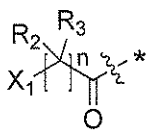
Tether is null, a bond, or a bivalent $C_1$-$C_{15}$ saturated or unsaturated, straight, branched, or cyclic hydrocarbon moiety, an aryl moiety or heteroaryl moiety, and , optionally, one or more methylene units of the hydrocarbon chain are independently replaced by $-NR_1-$, -O-, -C(O)-, -S-, -SO-, $-SO_2-$, -C(=S)-, or $-C(=NR_1)-$; and one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ;

x is 0, 1, or 2;

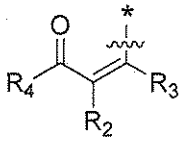
y is 1, 2, or 3;

$R_1$ is hydrogen or $C_1$-$C_8$ alkyl; and

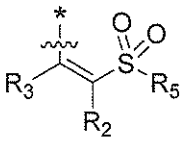
$Y_1$ is a bivalent or trivalent moiety resulting from the removal of a hydrogen of a radical of Formula **XIV-a**, **XIV-b**, **XIV-c**, **XIV-d**, **XIV-e**, **XIV-f**, **XIV-g**, **XIV-h**, or **XIV-i**,



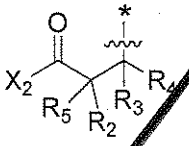
**XIV-a**



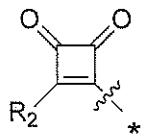
**XIV-b**



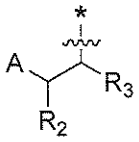
**XIV-c**



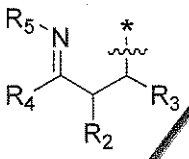
**XIV-d**



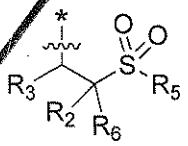
**XIV-e**



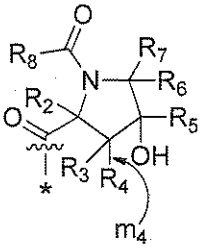
**XIV-f**



**XIV-g**



**XIV-h**



**XIV-i**

wherein

each $X_1$ and $X_2$ is independently $-CR_2R_3R_4$, $-OR_2$, or $NR_2R_3$;

each $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, and $R_8$ is independently hydrogen or $C_1$-$C_6$ alkyl;

optionally when proper any two of $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, and $R_8$ can be linked together to form a 3- to 8-membered carbocyclic or heterocyclic ring;

one or more methylene groups of the $C_1$-$C_6$ alkyl can be replaced by $-NR_1-$, -O-, -C(O)-, -S-, -SO-, $-SO_2-$, or -C(=S)-; one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ; and

n is an integer from 2-4, $m_4$ is an integer from 1 to 2;

M is connected to the position labeled as "*";

------ is a single or a double bond;

A is an optionally substituted aryl or heteroaryl;

a hydrogen of a radical of Formula **XIV-a**, **XIV-b**, **XIV-c**, **XIV-d**, **XIV-e**, **XIV-f**, **XIV-g**, **XIV-h**, or **XIV-i**, is substituted by Tether-Scaffold; and

M is –NH- or =N-, the nitrogen atom of M being a nitrogen from the side chain primary amine group of the lysine residue of the polypeptide.

35. A method for designing a ligand that covalently binds a lysine residue of a target protein, the method comprising:

A) providing a structural model of a reversible ligand docked in, or in proximity to, a ligand-binding site in a target protein, wherein the reversible ligand makes at least one non-covalent contact with the ligand-binding site;

B) identifying a lysine residue in, or in proximity to, the ligand-binding site of the target protein that is adjacent to the reversible ligand when the reversible ligand is docked in, or in proximity to, the ligand-binding site;

C) producing structural models of a plurality of ligand-warhead compounds docked in, or in proximity to, the ligand-binding site wherein each ligand-warhead compound comprises a warhead covalently attached to a substitutable position of the reversible ligand in step B), the warhead comprising a reactive chemical moiety and optionally a linker;

D) identifying among the structural models in step C) at least one ligand-warhead compound whose structural model allows the side chain primary amine group of the lysine residue in step B) to be within bonding distance of the warhead electrophile; and

E) further identifying among the structural models identified in step D) a hydrogen-bond-donor-containing amino acid residue in, or in the proximity to, the ligand-binding site, wherein the hydrogen-bond donor moiety is within hydrogen-bonding distance of the warhead electrophile, and/or within Coulombic interaction distance of the side chain primary amine group of the lysine residue identified in step D).

36. A method for identifying at least one lysine residue within at least one protein, wherein the at least one identified lysine can be modified covalently, the method comprising:

A) identifying at least one protein having a ligand-binding site;

B) providing a three-dimensional structural model for the identified protein;

C) docking a reversible ligand in, or in proximity to, the identified protein's ligand-binding site in the structural model, wherein the reversible ligand makes at least one non-covalent contact with the ligand-binding site, thereby creating a structural model of a reversible ligand bound to, or in proximity to, an identified protein's ligand-binding site; and

D) identifying in the structural model of a reversible ligand bound to, or in proximity to, an identified protein's ligand-binding site one or more lysine residues in, or in proximity to, the ligand-binding site of the identified protein which is less than about 15 Å from the reversible ligand.

37. A method for selecting a warhead that binds to a target lysine within a ligand-binding site of a protein the method comprising

(a) identifying at least one protein having a ligand-binding site;

(b) providing a three-dimensional structural model for the identified protein;

(c) identifying the location of at least one lysine in, or in proximity to, the ligand-binding site of step (a);

(d) providing at least one warhead in proximity to the at least one identified lysine;

(e) aligning the electrophilic atom of the warhead within bonding distance of the primary amine of the at least one identified lysine;

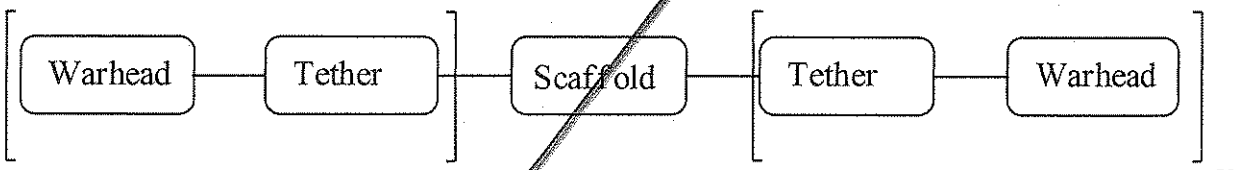
(f) forming a covalent bond between an electrophilic atom of the warhead and the primary amine of the at least one lysine;

(g) docking a reversible ligand in the identified protein's ligand-binding site within 15 Å of the covalently attached warhead of step (f), wherein the reversible ligand maintains most of its known noncovalent interactions with the ligand-binding site;

(h) aligning the closest atom of the ligand with the covalently bound warhead of step (f) and providing the geometric requirements for the design of a tether between the ligand and the covalently bound warhead of step (f), that also is complementary with the protein surface in the region between the warhead and the ligand.

38. A method of covalently modifying a lysine residue in, or in proximity to, a ligand-binding site of a protein, the method comprising:

A) contacting a compound of Formula I




I

with a protein containing a lysine residue in, or in proximity to, a ligand-binding site of a polyprotein;

B) forming a covalent bond between the side chain primary amine group of the lysine residue and Warhead of the compound;

wherein

Scaffold is

a) a radical resulting from the removal of a hydrogen of a ligand capable of binding to, or in proximity to, the ligand-binding site; or

b) a portion of a pharmacophore of a ligand resulting from truncation of the pharmacophore, such that the Scaffold is capable of binding to, or in proximity to, the ligand-binding site;

Warhead is an organic moiety optionally containing one or more heteroatoms selected from O, N, and S; the organic moiety having a molecular weight of about 14 daltons to about 200 daltons; Warhead being capable of reaction with a side chain primary amine group of a lysine residue; and Warhead being attached to Scaffold through Tether;

Tether is null, a bond, or a bivalent $C_1$-$C_{15}$ saturated, unsaturated, straight, branched, cyclic, bicyclic, or tricyclic hydrocarbon moiety; wherein optionally one or more methylene units of the hydrocarbon chain are independently replaced by -$NR_1$-, -O-, -C(O)-, -S-, -SO-, -$SO_2$-, -C(=S)-, or -C(=$NR_1$)-; optionally one or more hydrogens are independently replaced by heteroatoms; and optionally one or more methine groups of the $C_1$-$C_{15}$ alkyl, when present, are independently replaced by ;

x is 0, 1, or 2;

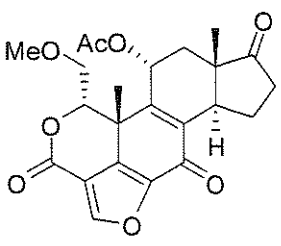
y is 1, 2, or 3; and

$R_1$ is hydrogen or $C_1$-$C_8$ alkyl;

Wherein the compound of Formula **I** is not a naturally occurring compound that exerts its biological effect through an inherent ability to covalently bind lysine; nor is the compound of Formula **I** a compound, natural or synthetic, which is based primarily on amino acids nucleoside/nucleotide derived drugs, simple lysine alkylating agents, anhydrides, steroid derived lysine alkylators, or sugar based lysine alkylators,

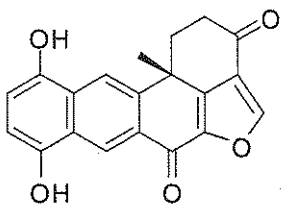
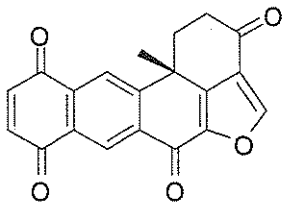
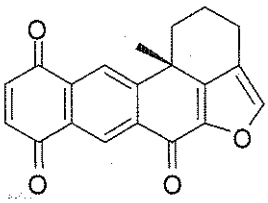
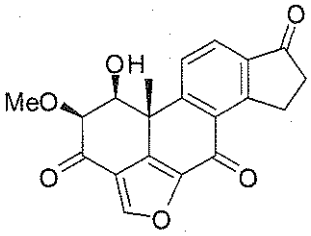
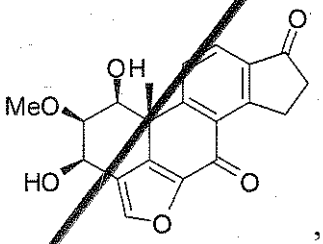
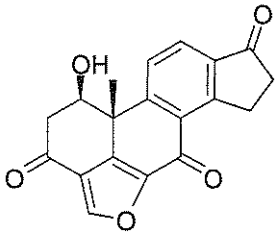
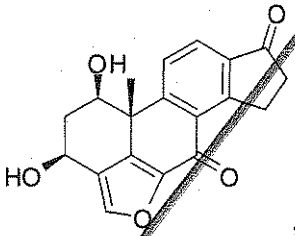
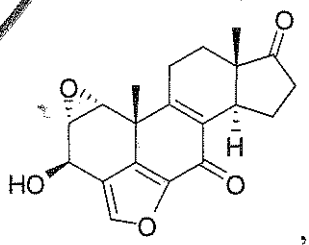
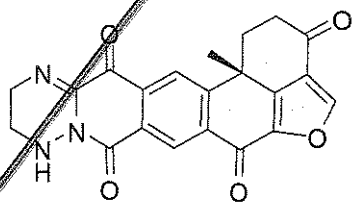
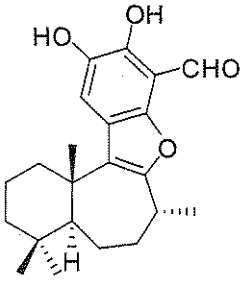
with the proviso that the compound of Formula **I** is not

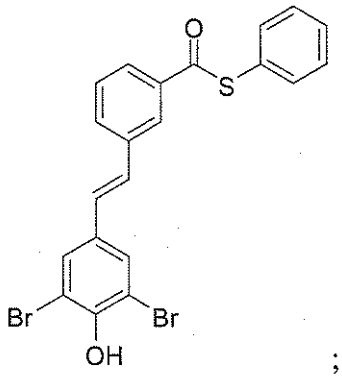
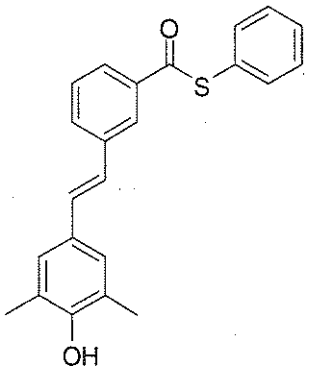
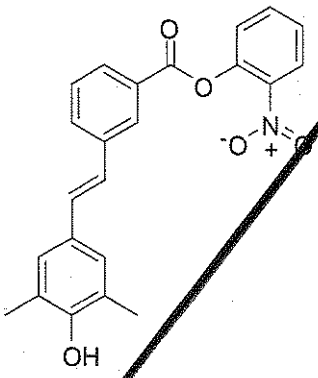
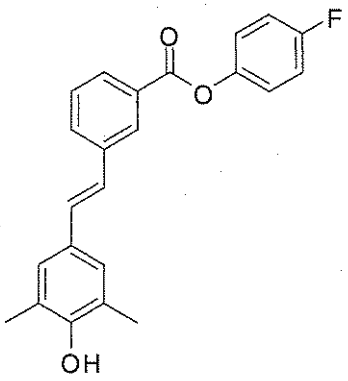
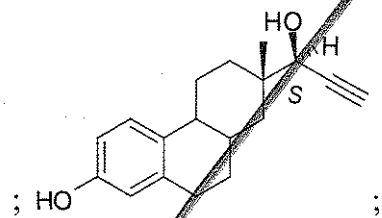
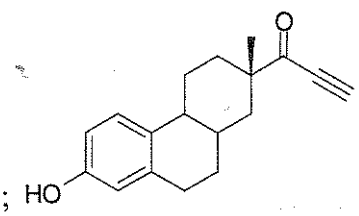
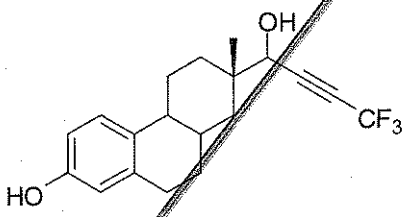
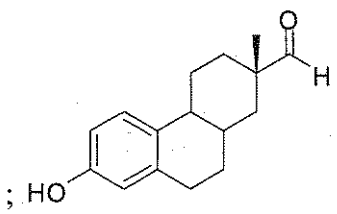
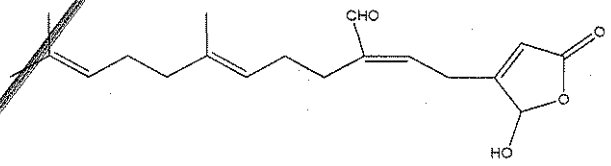
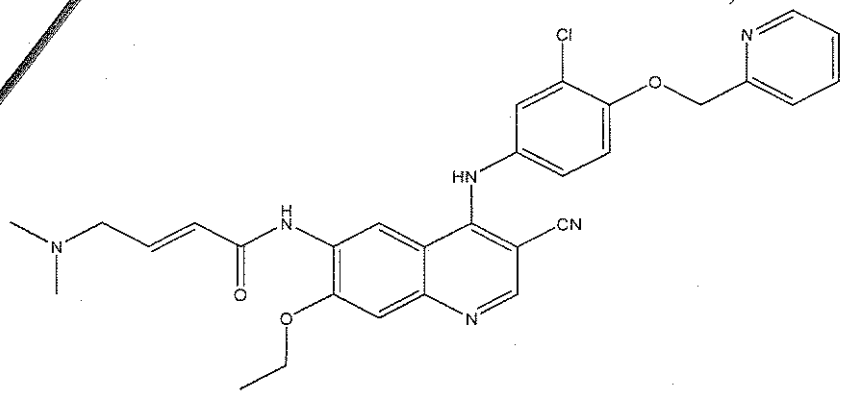
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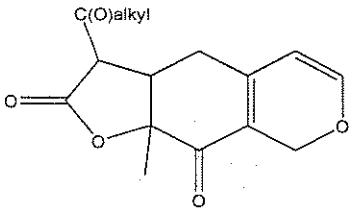


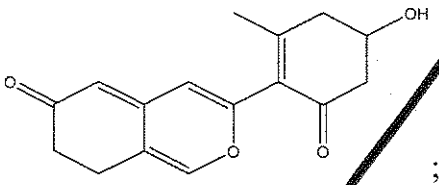
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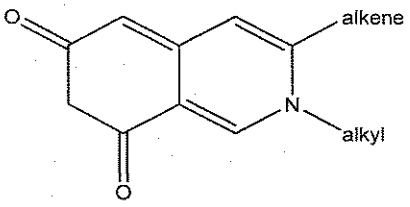
known analogues of wortmannin that covalently modify lysine through substantially the same mechanism as wortmannin:

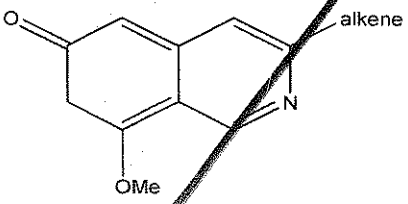

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any mechanism-based irreversible inhibitors.

39. A conjugate of claim 34 comprising:

a) a conjugate of the formula K297-linker-inhibitor moiety, wherein the K297 is K297 of XIAP; or

b) a conjugate of the formula K169-linker-inhibitor moiety, wherein the K169 is K169 of PDPK1; or

c) a conjugate of the formula K173-linker-inhibitor moiety, wherein the K173 is K173 of PDPK1; or

d) a conjugate of the formula K86-linker-inhibitor moiety, wherein the K86 is K86 of PDPK1; or

e) a conjugate of the formula K136-linker-inhibitor moiety, wherein the K136 is K136 of NS3/4A; or

f) a conjugate of the formula K777-linker-inhibitor moiety, wherein the K777 is K777 of PI3Kβ; or

g) a conjugate of the formula K802-linker-inhibitor moiety, wherein the K802 is K802 of PI3Kγ; or

h) a conjugate of the formula K890-linker-inhibitor moiety, wherein the K890 is K890 of PI3Kγ.

40. A method for testing the ability of a ligand designed by the method of claim 35 to inhibit the target protein, said method comprising:

incubating the ligand and the target protein under conditions suitable for the target protein to exert its enzymatic activity.

41. A method for testing the ability of a ligand designed using modeling data resulting from the method of claim 35 to inhibit the target protein, said method comprising:

incubating the ligand and the target protein under conditions suitable for the target protein to exert its enzymatic activity.

42. The method of claim 35, further comprising:

E) chemically bonding the warhead group, optionally through the linker, to the reversible ligand.

43.. Use of a compound of any one of claim 1 to 31 in the manufacture of a medicament for treating:

a) an XIAP-mediated disorder wherein the compound irreversibly inhibits XIAP by covalently modifying a lysine residue conserved at an equivalent position of K297 of XIAP;

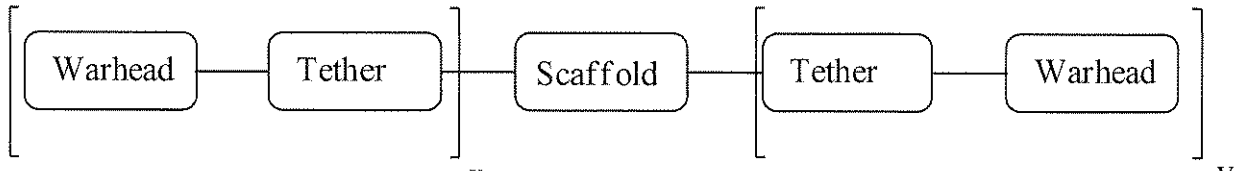
b) a PDPK1-mediated disorder wherein the compound irreversibly inhibits PDPK1 by covalently modifying a lysine residue conserved at an equivalent position of K169 or K173 or K86 of PDPK1;

c) an HCV protease-mediated disorder wherein the compound irreversibly inhibits HCV protease by covalently modifying a lysine residue conserved at an equivalent position of K136 of HCV-protease subtype of NS3/4A; or

d) a PI3K-mediated disorder wherein the compound irreversibly inhibits PI3K by covalently modifying a lysine residue conserved at an equivalent position of K777 or K802 or K890 of PI3K.

**CLAIMS**

1. A compound of Formula **I**:




**I**

wherein

Scaffold is

a) a radical resulting from the removal of a hydrogen of a ligand capable of binding to, or in proximity to, a substrate-binding site or cofactor-binding site of a protein containing a lysine residue in, or in proximity to, the substrate-binding site or cofactor-binding site; or

b) a truncated pharmacophore, such that the Scaffold is capable of binding to, or in proximity to, the substrate-binding site or cofactor-binding site;

Warhead is an organic moiety optionally containing one or more heteroatoms selected from O, N, and S; the organic moiety having a molecular weight of about 14 daltons to about 200 daltons; Warhead being capable of covalently binding to lysine; and Warhead being attached to Scaffold through Tether;

Tether is null, a bond, or a bivalent $C_1$-$C_{15}$ saturated, unsaturated, straight, branched, cyclic, bicyclic, or tricyclic hydrocarbon moiety; wherein optionally one or more methylene units of the hydrocarbon chain are independently replaced by -$NR_1$-, -O-, -C(O)-, -S-, -SO-, -$SO_2$-, -C(=S)-, or C(=$NR_1$)-; optionally one or more hydrogens are independently replaced by heteroatoms; and optionally one or more methine groups of the $C_1$-$C_{15}$ alkyl, when present, are independently replaced by ;

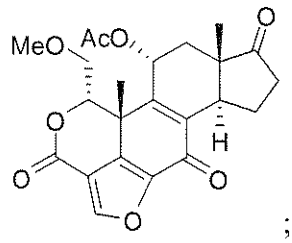
x is 0, 1, or 2;

y is 1, 2, or 3; and

$R_1$ is hydrogen or $C_1$-$C_8$ alkyl,

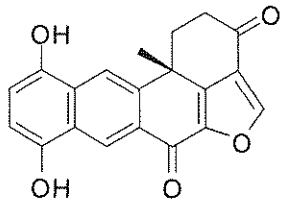
with the proviso that the compound of Formula **I** is not

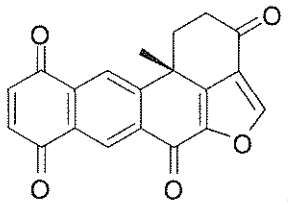
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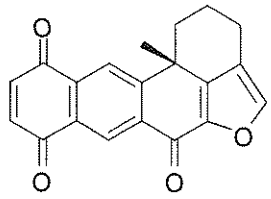


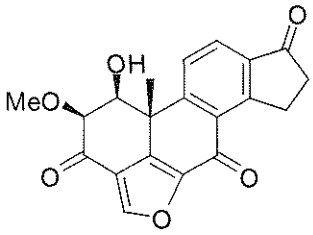
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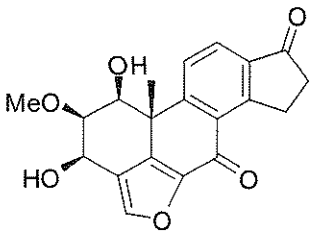
known analogues of wortmannin that covalently modify lysine through substantially the same mechanism as wortmannin:

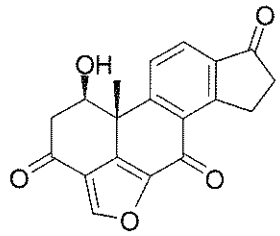


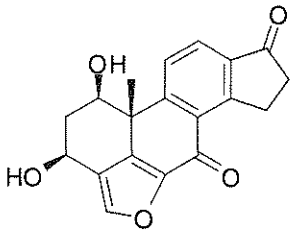
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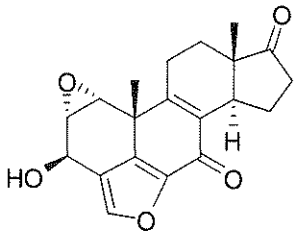
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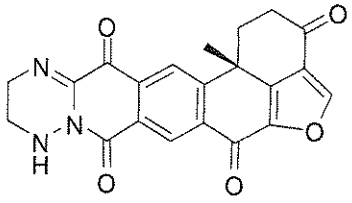
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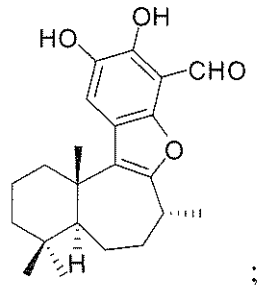
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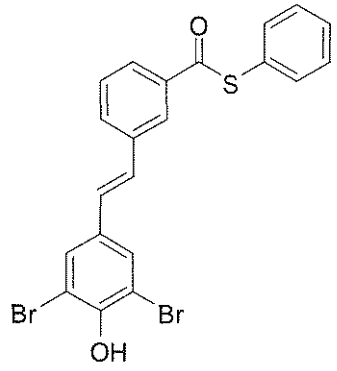
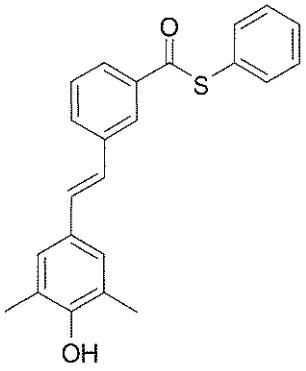
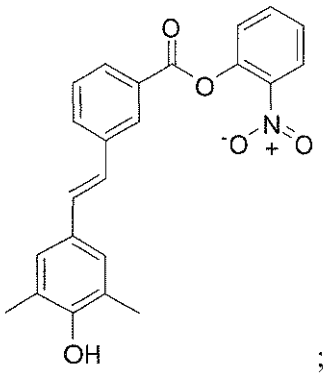
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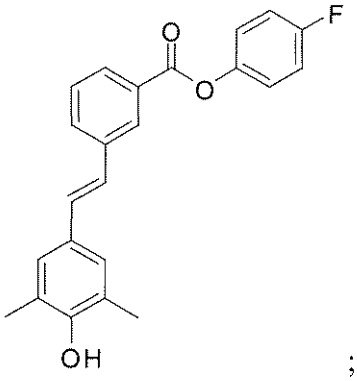
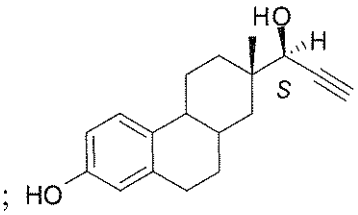
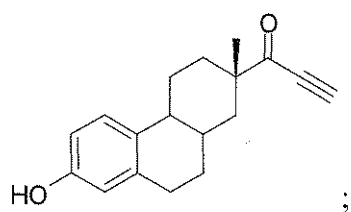
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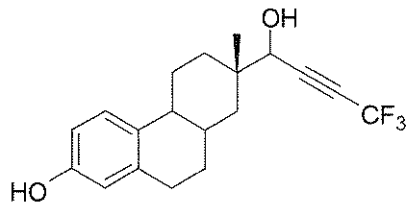
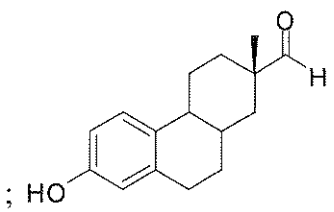
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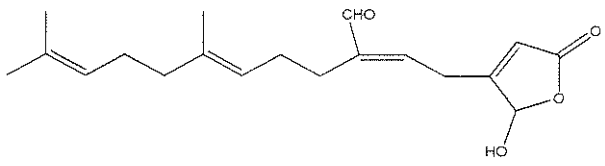
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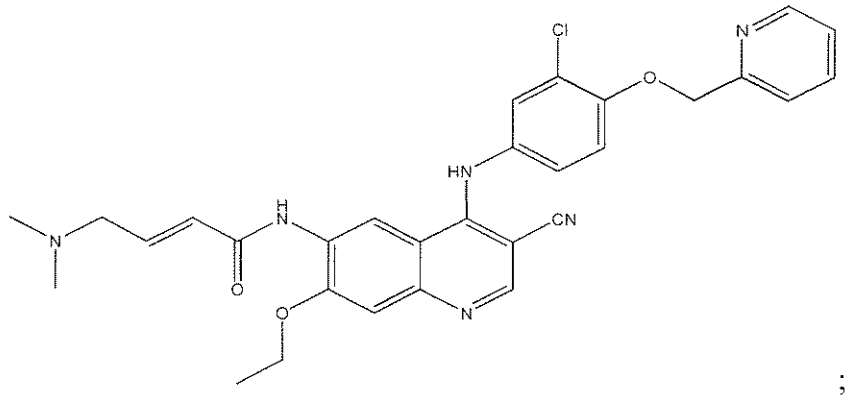

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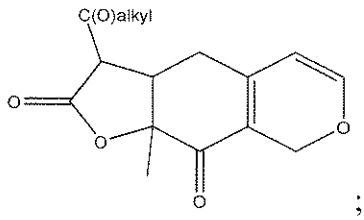

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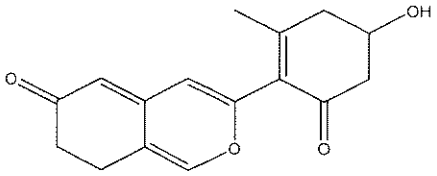

;



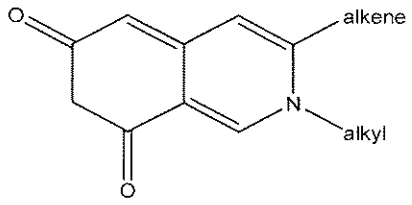
;



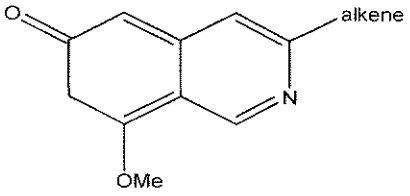
;



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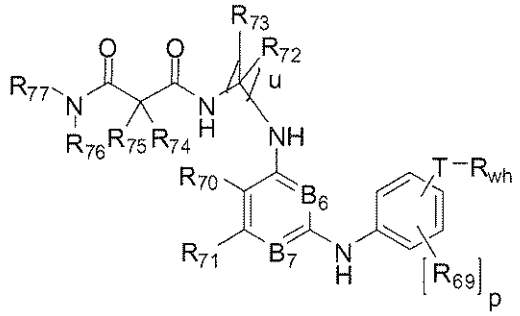


; and

any mechanism-based irreversible inhibitors.

2. The compound of claim 1, wherein

the compound of Formula **I** is a compound of Formula **XI**:




**XI**

wherein

p is an integer from 0 to 4, u is an integer from 1 to 4;

$B_6$ and $B_7$ are each independently $CR_7$ or N;

$R_{69}$ is hydrogen, $C_1$-$C_6$ alkyl, halogen, amino, nitro, or -$NH(CO)NR_{78}R_{79}$;

$R_{70}$ is hydrogen, $C_1$-$C_6$ alkyl, halogen, amino, nitro;

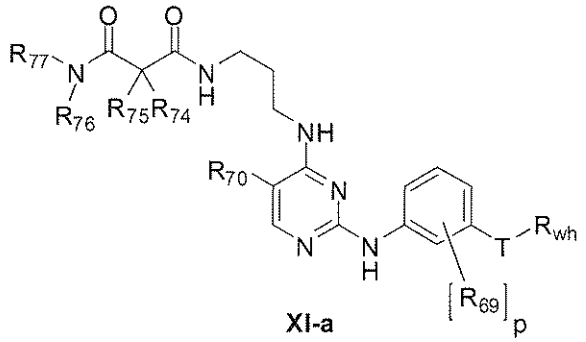
$R_7$, $R_{71}$, $R_{72}$, $R_{73}$, $R_{74}$, $R_{75}$, $R_{76}$, $R_{77}$, $R_{78}$, and $R_{79}$ are each independently hydrogen or $C_1$-$C_6$ alkyl; $R_1$ is hydrogen or $C_1$-$C_8$ alkyl; wherein one or more methylene groups of the $C_1$-$C_6$ alkyl can be replaced by -$NR_1$-, -O-, -C(O)-, -S-, -SO-, -$SO_2$-, or -C(=S)-; one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ;

optionally $R_{78}$, and $R_{79}$ taken together form a 4- to 8-membered carbocyclic or heterocyclic ring; ~~or~~

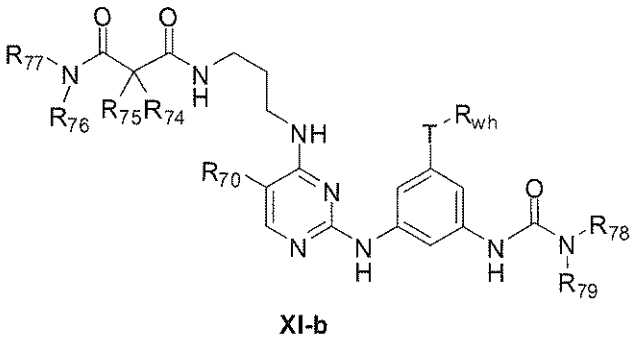
T is Tether; and

$R_{wh}$ is Warhead.

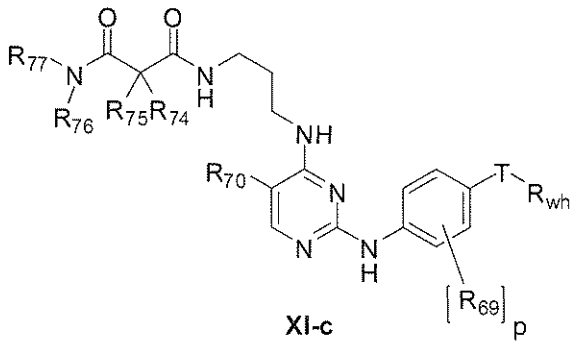
3. The compound of claim 2, wherein the compound of Formula **XI** is a compound of Formula **XI-a**, **XI-b**, or **XI-c**;



**XI-a**



**XI-b**



**XI-c**

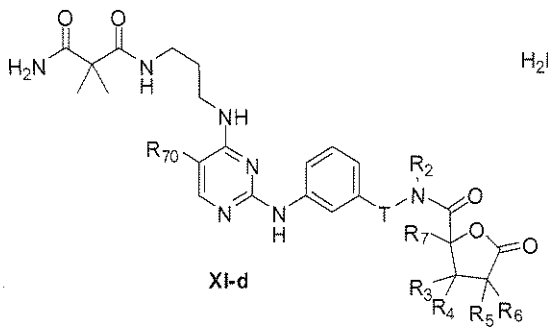
wherein

$R_{70}$ is -F, -Cl, -Br, or –I;

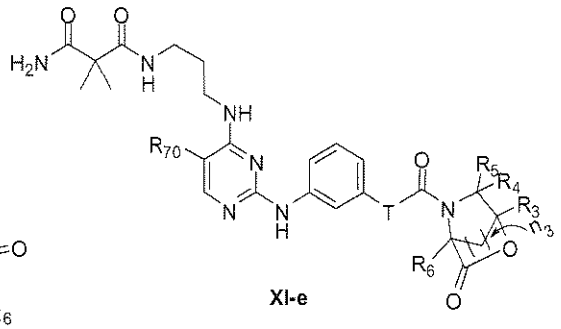
T is Tether; and

$R_{wh}$ is Warhead.

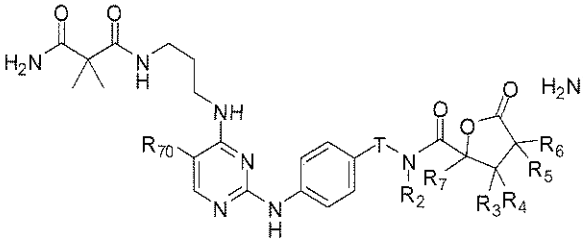
4. The compound of claim 3, wherein the compound of Formula **XI-a**, **XI-b** or **XI-c** is a compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j**:



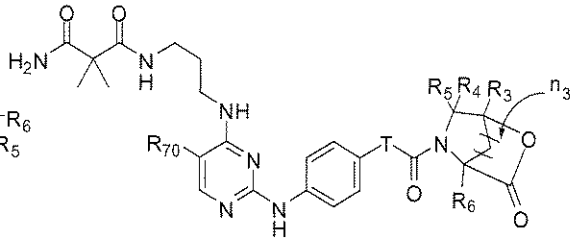
**XI-d**



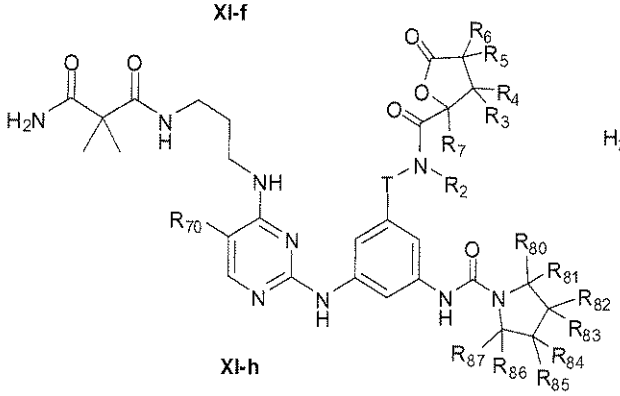
**XI-e**



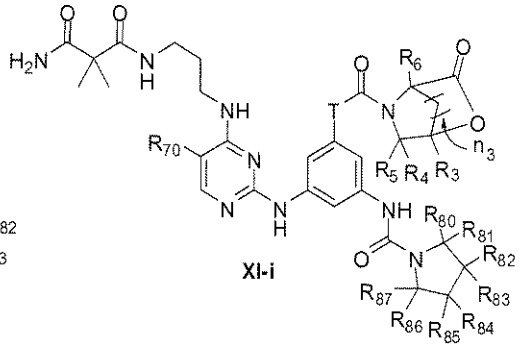
**XI-f**



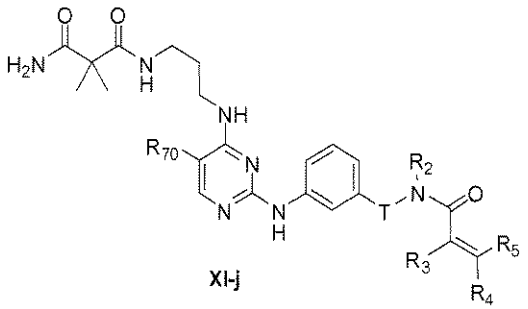
**XI-g**



**XI-h**



**XI-i**



**XI-j**

wherein

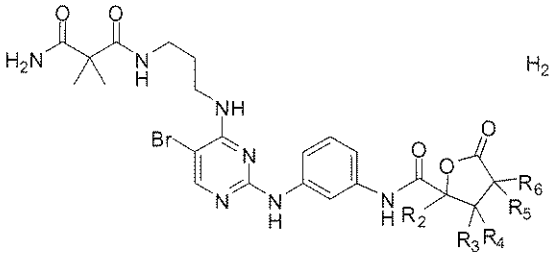
$R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_{80}$, $R_{81}$, $R_{82}$, $R_{83}$, $R_{84}$, $R_{85}$, $R_{86}$, and $R_{87}$ are each independently hydrogen or $C_1$-$C_6$ alkyl; $R_1$ is hydrogen or $C_1$-$C_8$ alkyl;

one or more methylene groups of the $C_1$-$C_6$ alkyl can be replaced by -$NR_1$-, -O-, -C(O)-, -S-, -SO-, -$SO_2$-, or -C(=S)-;

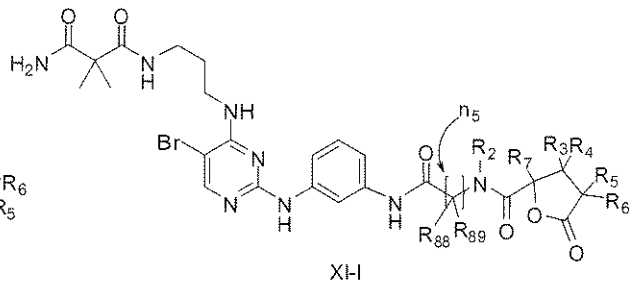
one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by .

5. The compound of claim 4, wherein

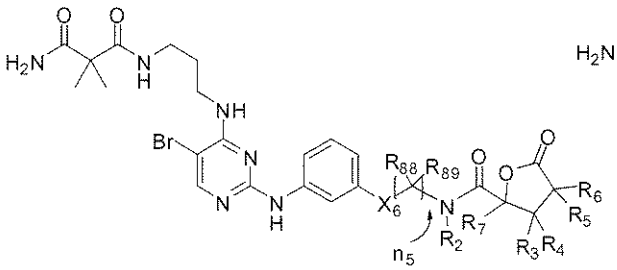
a) the compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j** is a compound of Formula **XI-k**, **XI-l**, **XI-m**, **XI-n**, **XI-o**, **XI-p**, or **XI-q**;



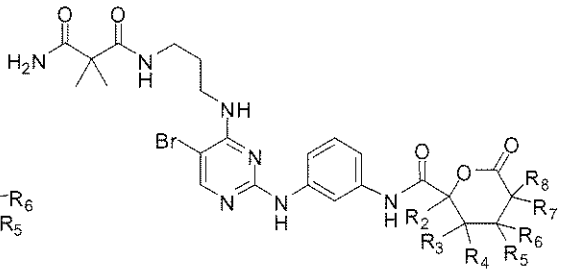
XI-k



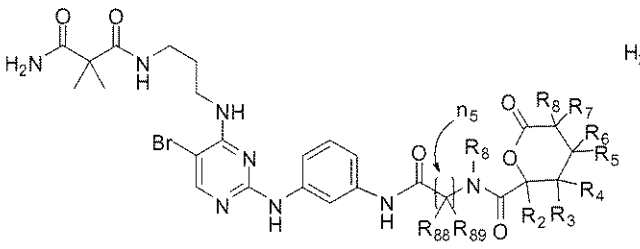
XI-l



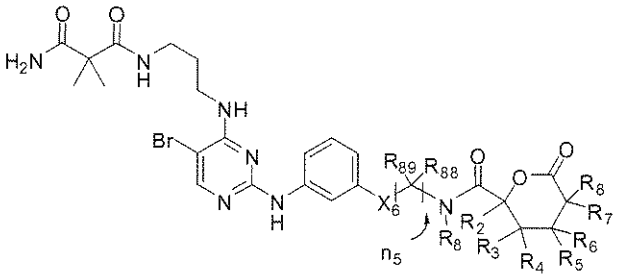
XI-m



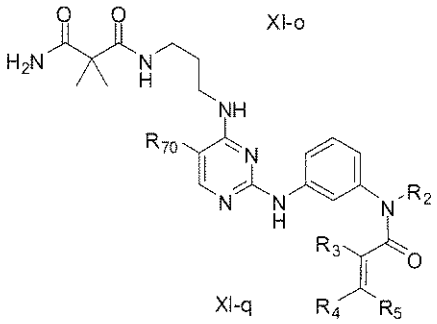
XI-n



XI-o



XI-p



XI-q

wherein

$X_6$ is $CH_2$, NH, O, or S;

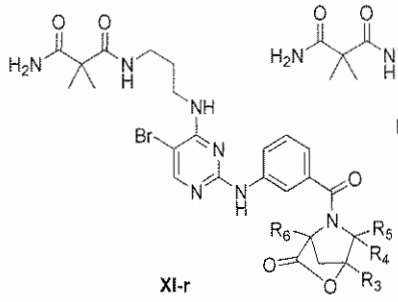
$R_{88}$ and $R_{89}$ are each independently hydrogen or $C_1$-$C_6$ alkyl; $R_1$ is hydrogen or $C_1$-$C_8$ alkyl;

one or more methylene groups of the $C_1$-$C_6$ alkyl can be replaced by -$NR_1$-, -O-, -C(O)-, -S-, -SO-, -$SO_2$-, or -C(=S)-;

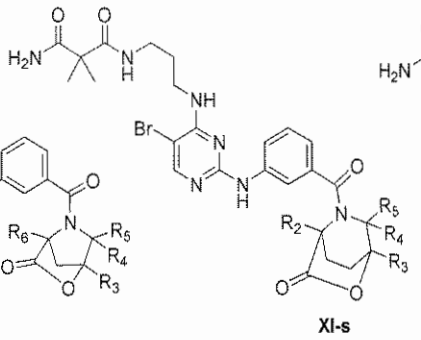
one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ; and

$n_5$ is an integer from 0 to 3; or

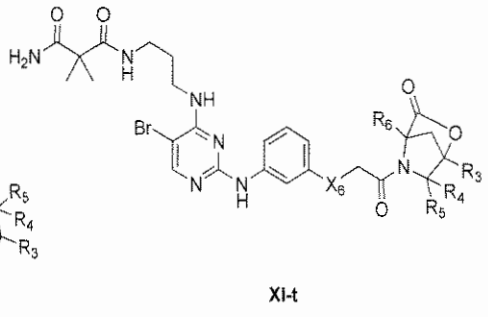
b) the compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j** is a compound of Formula **XI-r**, **XI-s**, **XI-t**, **XI-u**, **XI-v**, **XI-w**, or **XI-x**:



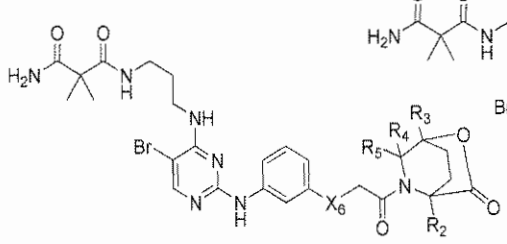
**XI-r**



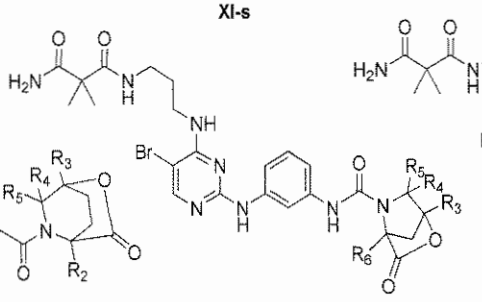
**XI-s**



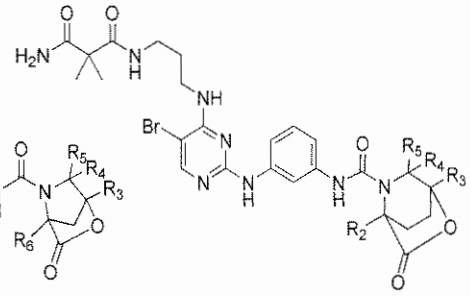
**XI-t**



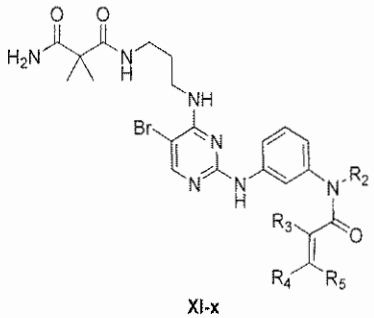
**XI-u**



**XI-v**



**XI-w**

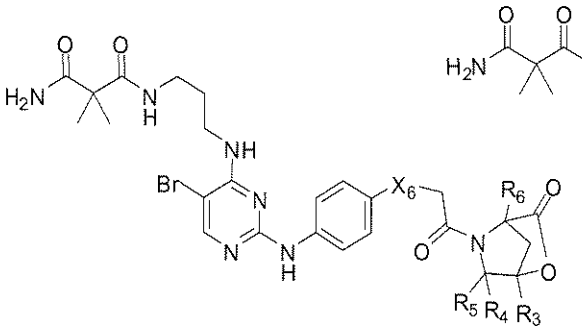


**XI-x**

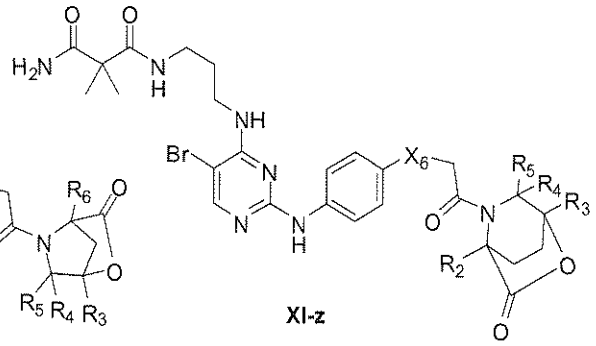
;

or

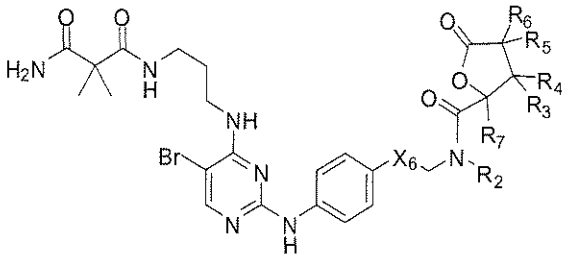
c) the compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j** is a compound of Formula **XI-y**, **XI-z**, **XI-aa**, or **XI-bb**:



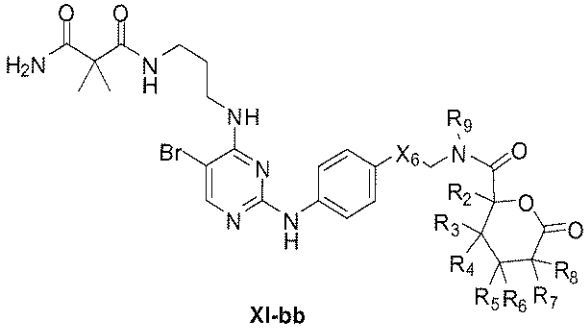
**XI-y**



**XI-z**



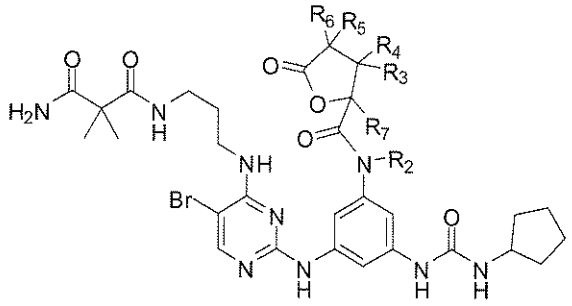
**XI-aa**



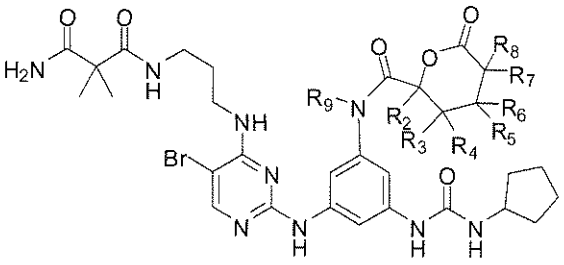
**XI-bb**

or

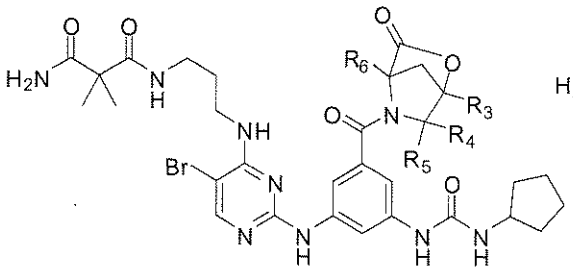
d) the compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j** is a compound of Formula **XI-cc**, **XI-dd**, **XI-ee**, or **XI-ff**:



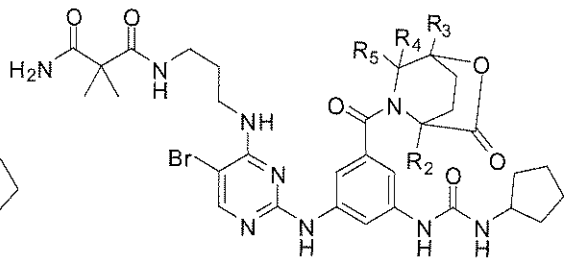
**XI-cc**



**XI-dd**

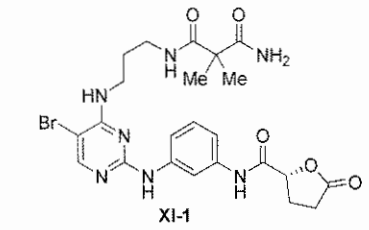


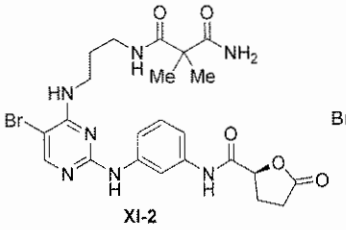
**XI-ee**

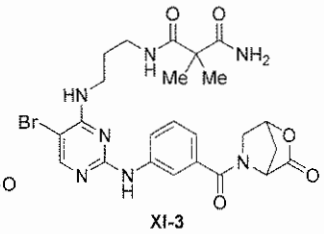


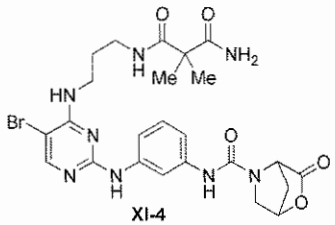
**XI-ff**

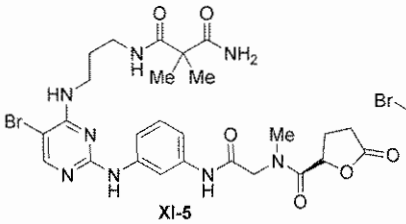
6. The compound of claim 3, wherein the compound of Formula **XI** is selected from the group consisting of:

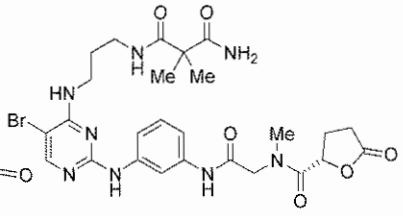

XI-1

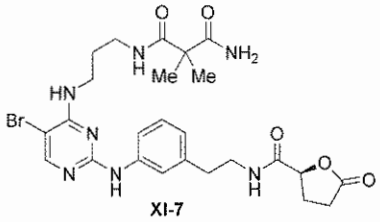

XI-2

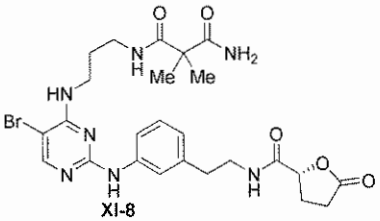

XI-3

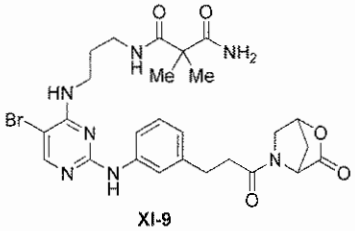

XI-4

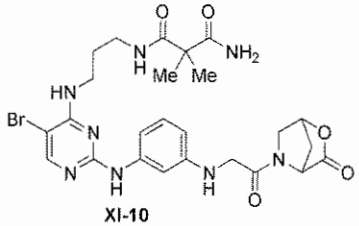

XI-5

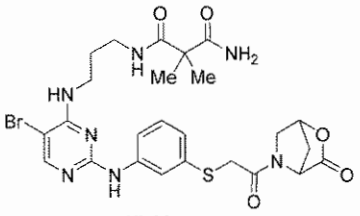

XI-6

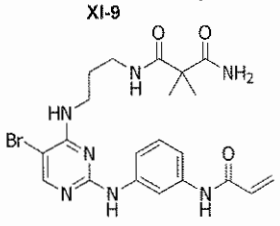

XI-7

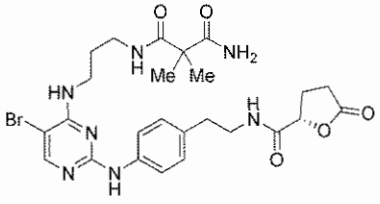

XI-8

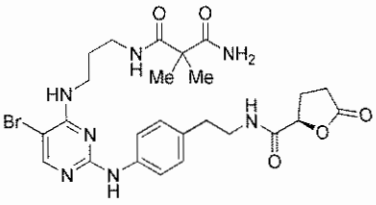

XI-9

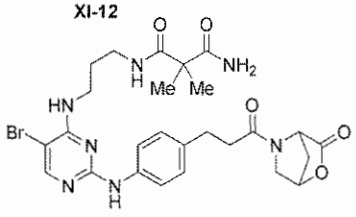

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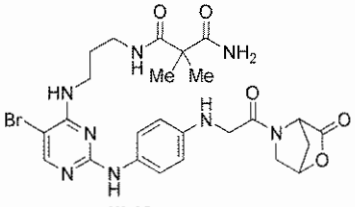

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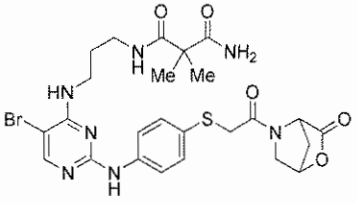

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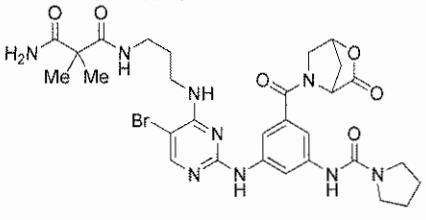

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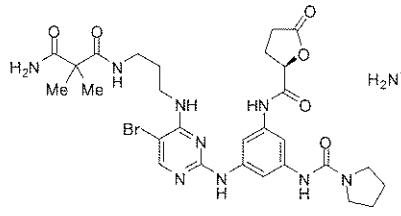

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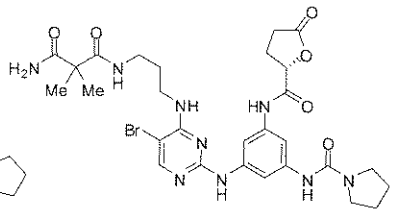

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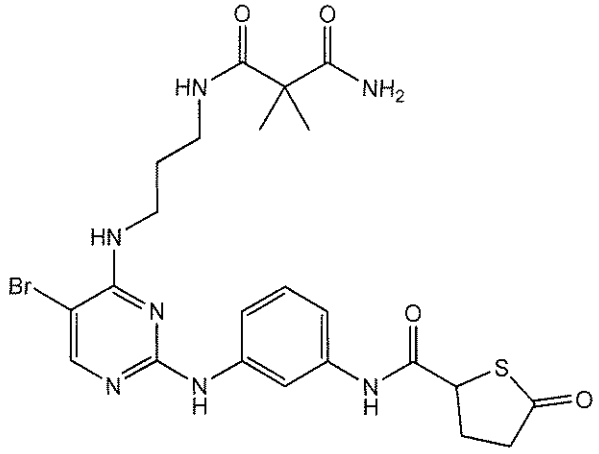

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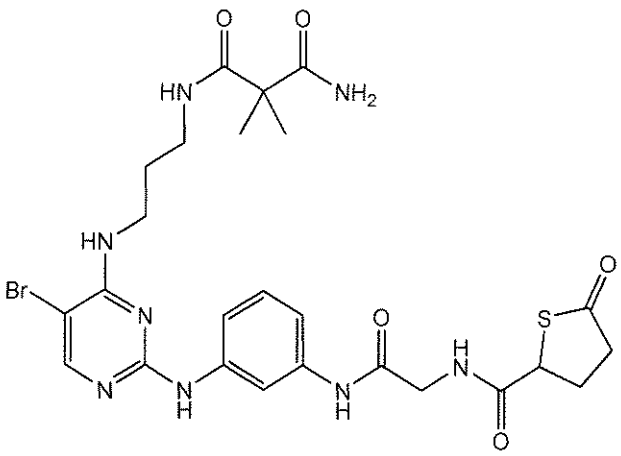
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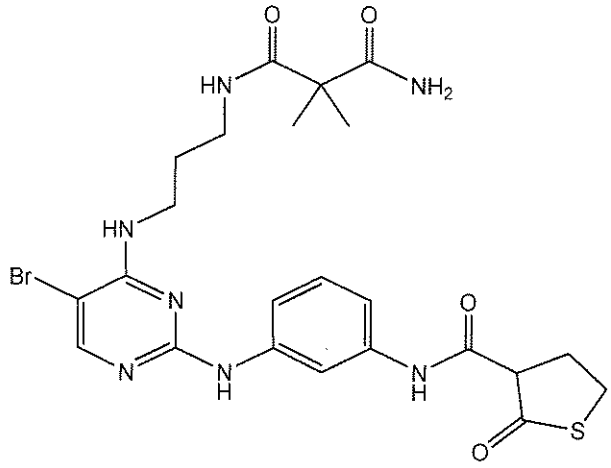
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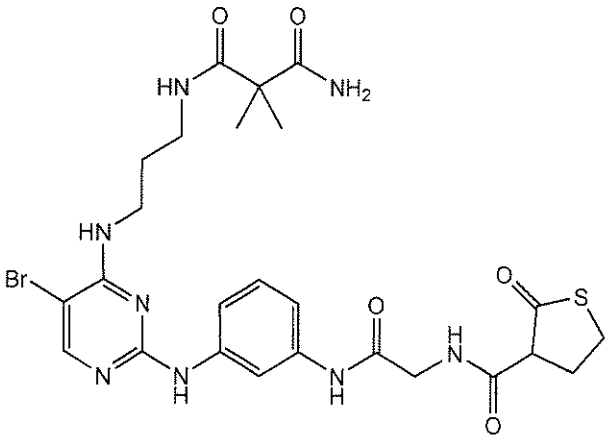
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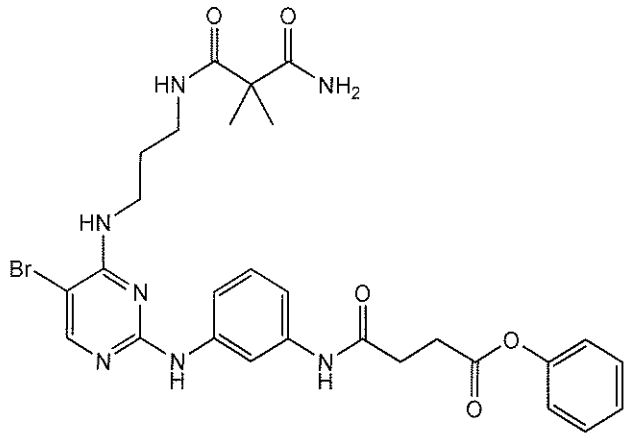
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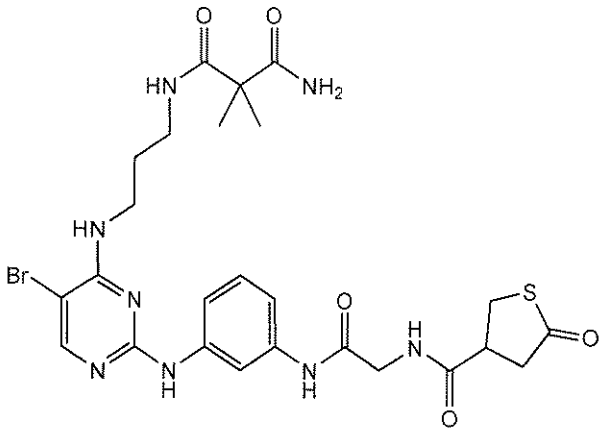
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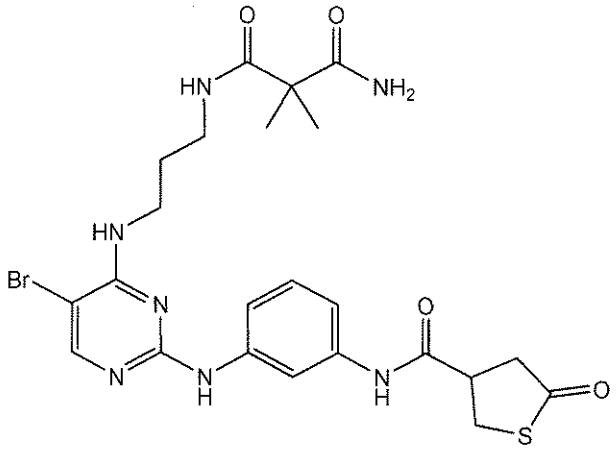
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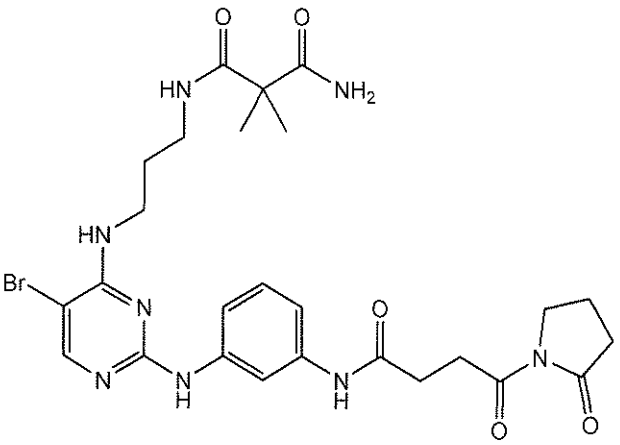
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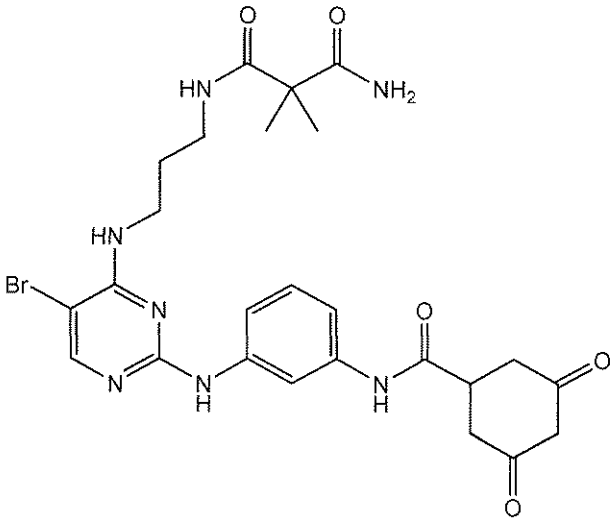
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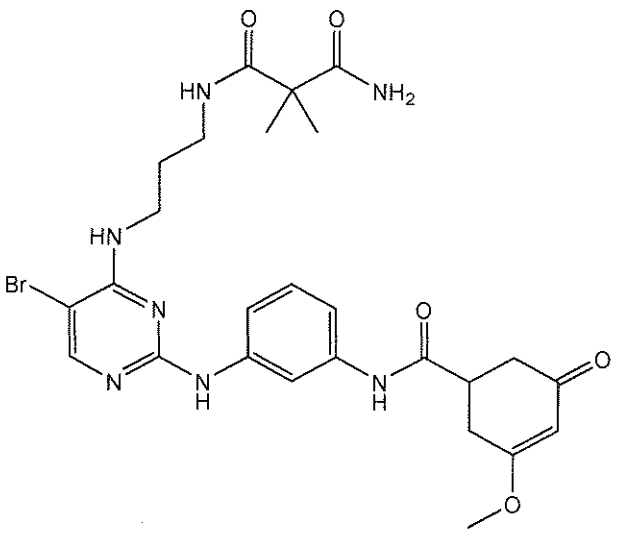


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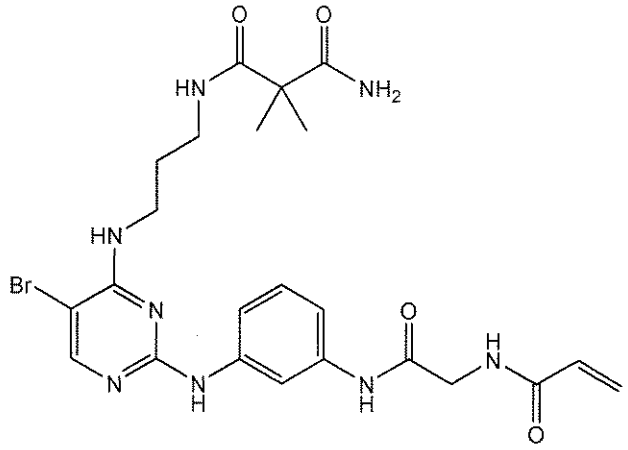


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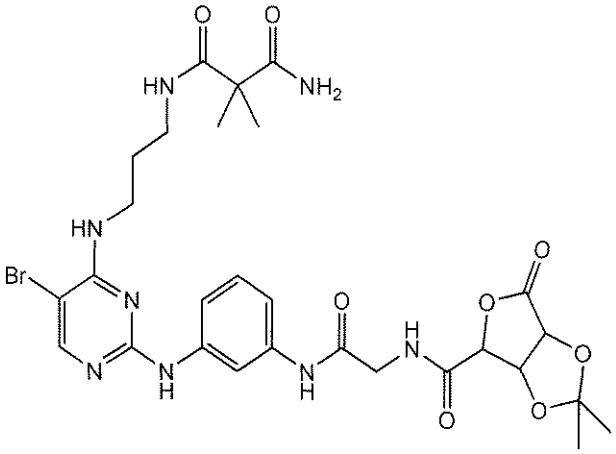




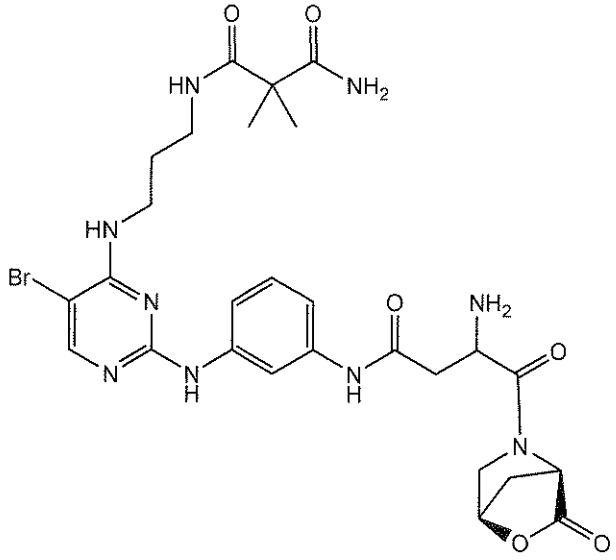
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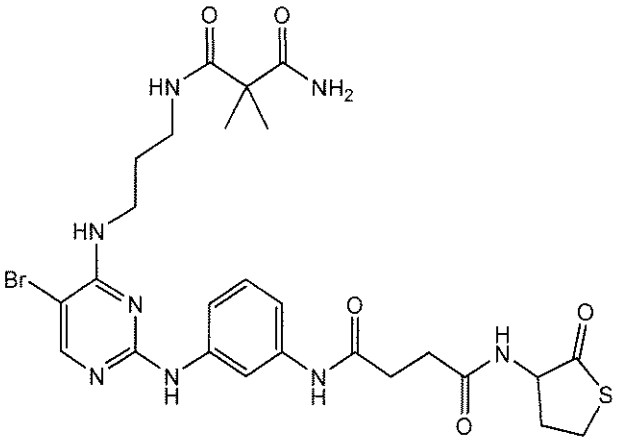
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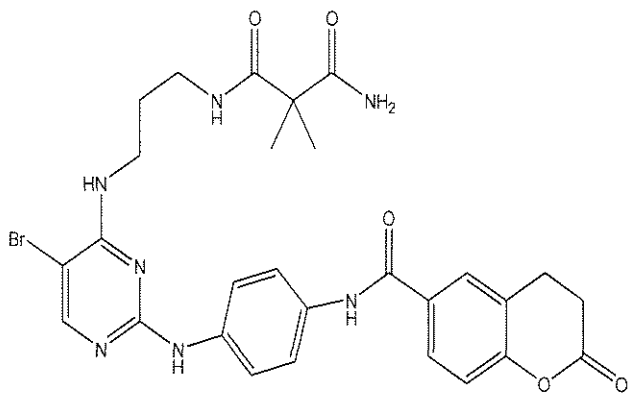
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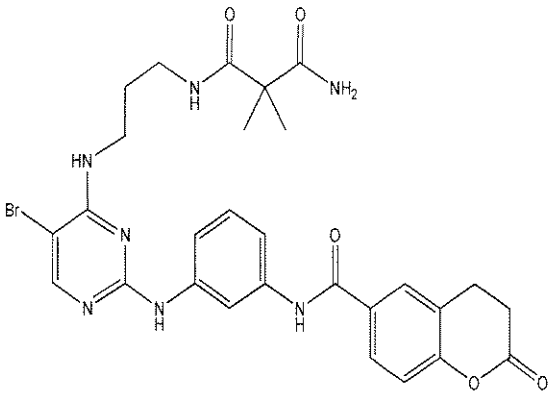
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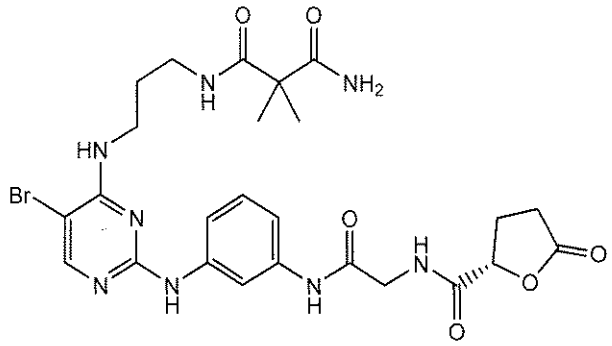
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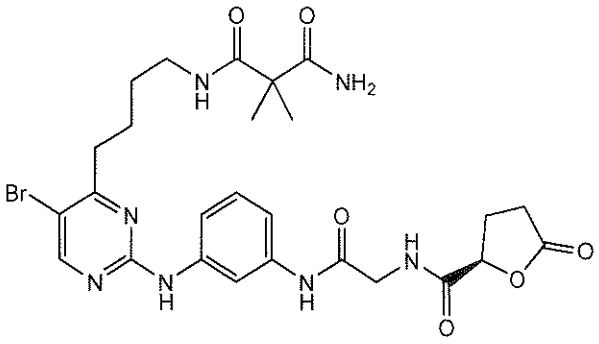
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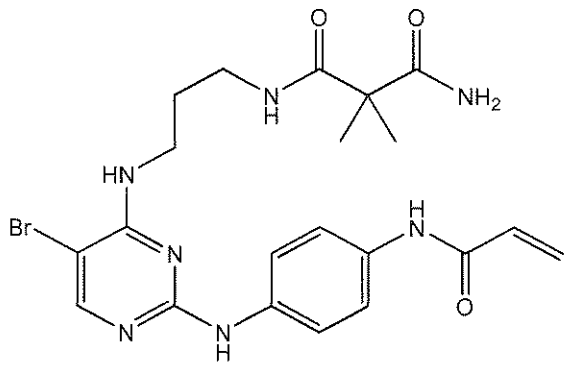
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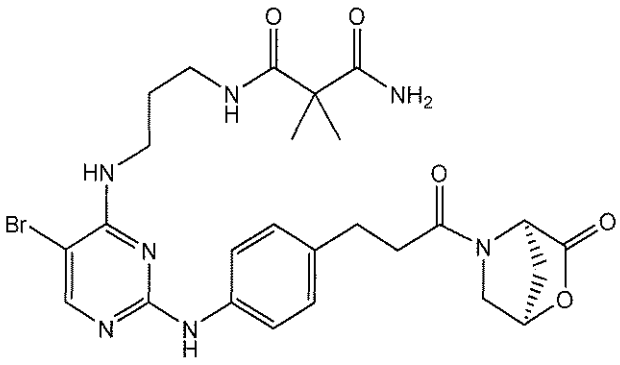
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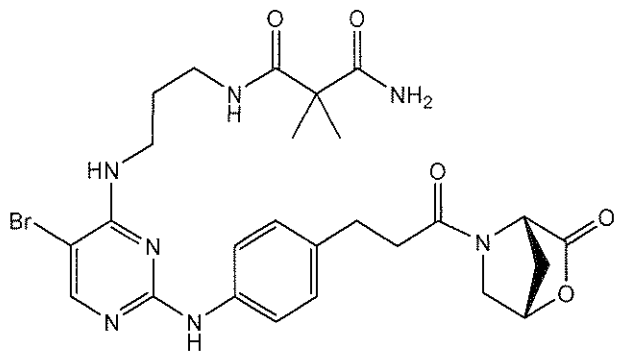
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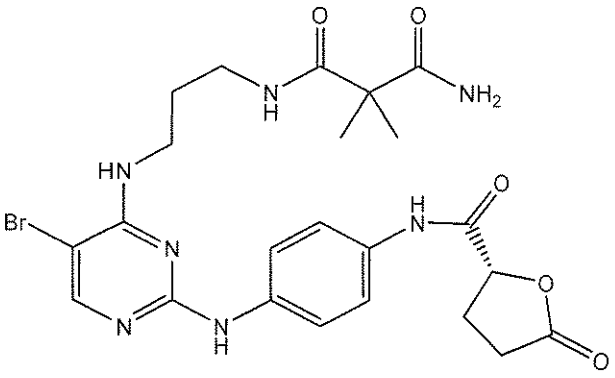
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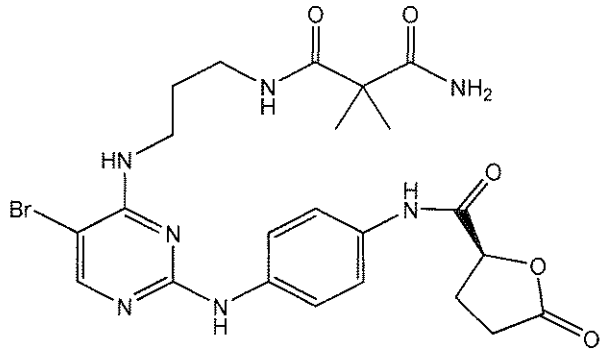
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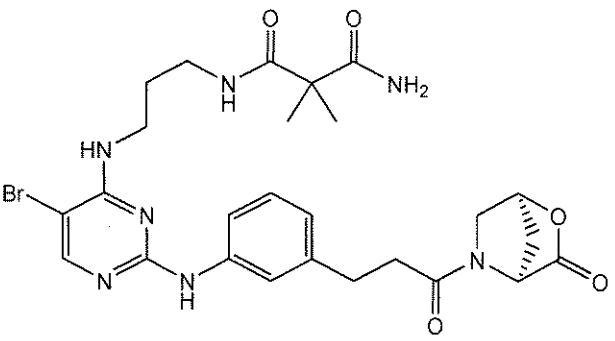
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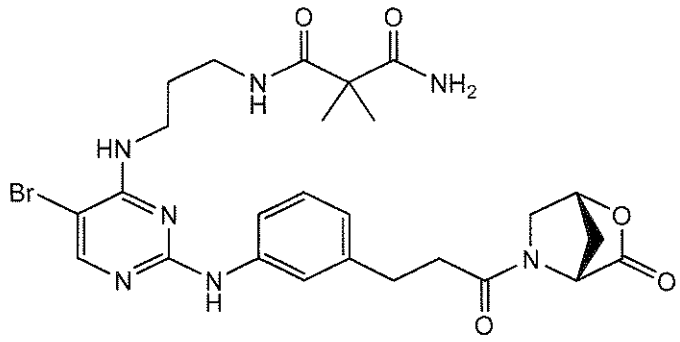
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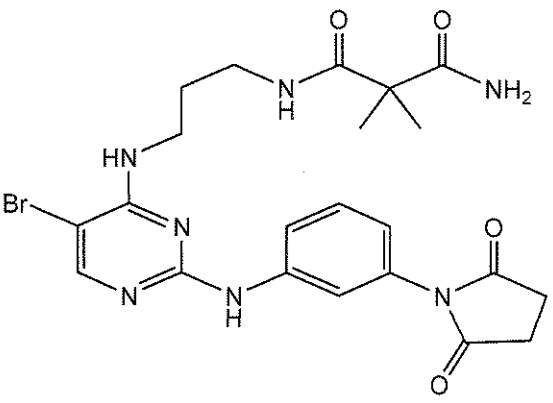
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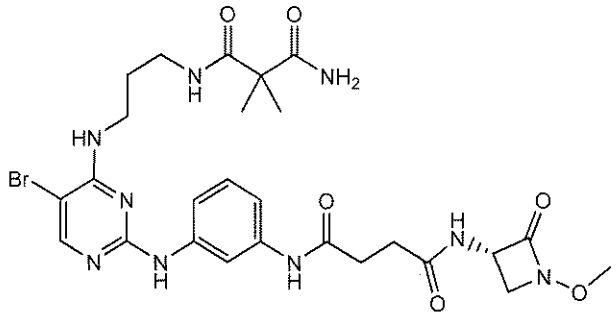
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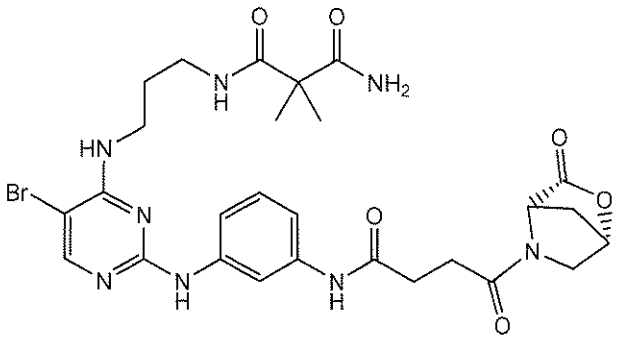
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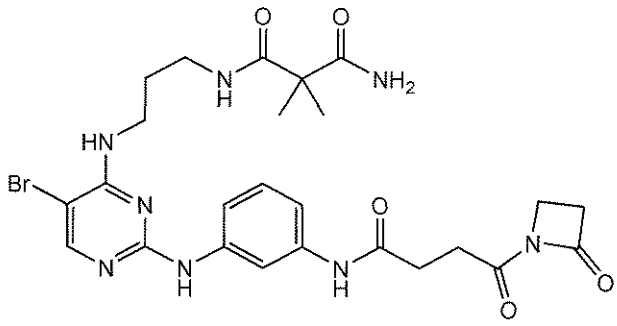
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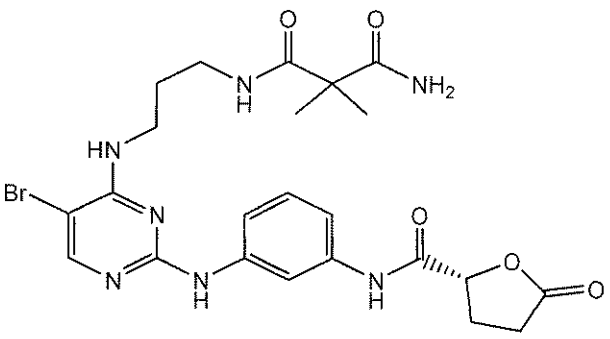
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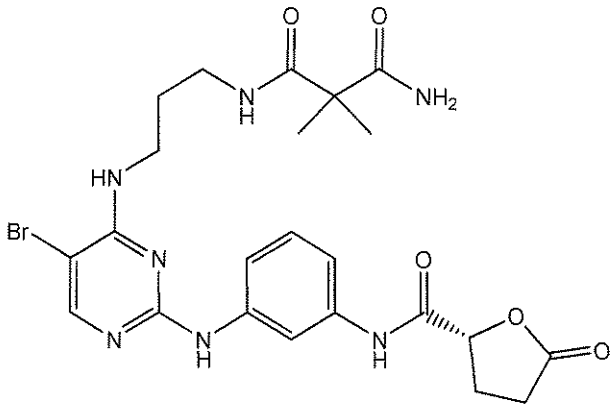
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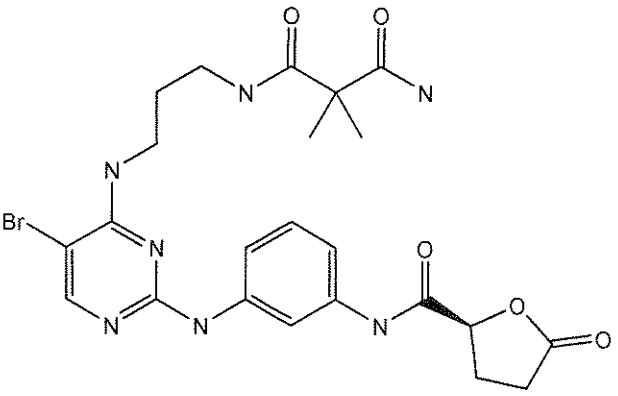
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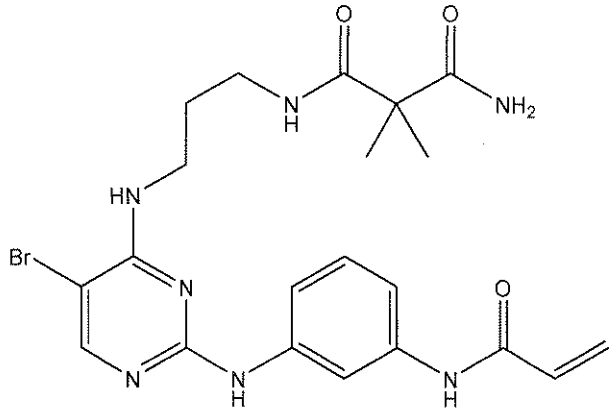
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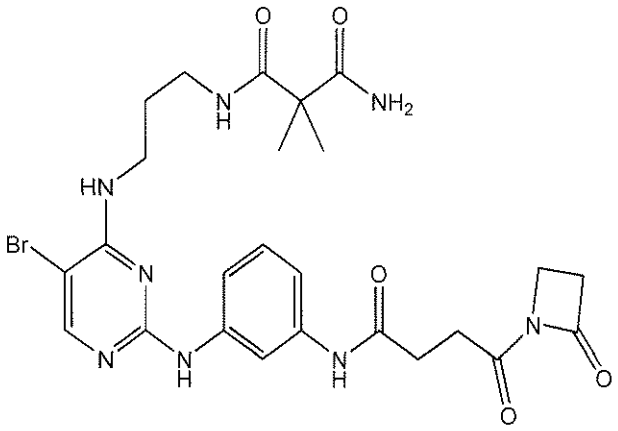
**XI-51**



**XI-52**



**XI-53**



**XI-55**

7. A compound of any one of claims 1 to 3 for use in treating:

a) an XIAP-mediated disorder wherein the compound irreversibly inhibits XIAP by covalently modifying a lysine residue conserved at an equivalent position of K297 of XIAP;

b) a PDPK1-mediated disorder wherein the compound irreversibly inhibits PDPK1 by covalently modifying a lysine residue conserved at an equivalent position of K169 or K173 or K86 of PDPK1;

c) an HCV protease-mediated disorder wherein the compound irreversibly inhibits HCV protease by covalently modifying a lysine residue conserved at an equivalent position of K136 of HCV-protease subtype of NS3/4A; or

d) a PI3K-mediated disorder wherein the compound irreversibly inhibits PI3K by covalently modifying a lysine residue conserved at an equivalent position of K777 or K802 or K890 of PI3K.

8. A method for designing a ligand that covalently binds a target protein, the method comprising:

A) providing a structural model of a reversible ligand docked within, or in proximity to, a ligand-binding site in a target protein;

B) identifying a lysine residue of the target protein in, or in proximity to, the ligand-binding site that is less than about 15Å from the reversible ligand when the reversible ligand is docked in, or in proximity to, the ligand-binding site;

C) producing at least a structural model of at least one ligand-warhead compound docked within, or in proximity to, the ligand-binding site wherein the ligand-warhead compound comprises the reversible ligand in step B) or a portion thereof, a warhead comprising a reactive chemical moiety, and optionally a Tether; and

D) identifying a ligand-warhead compound whose structural model allows the lysine residue in step B) to readily assume a conformation that brings the side chain primary amine group of the lysine residue within bond-forming proximity of the warhead electrophile, wherein the ligand-warhead compound is a compound as defined in ~~claims 1 to 31~~ claims 1, or 2 or 3; and

wherein the method is performed *in silico*.

9. Use of a compound of any one of claims 1 to 3 in the manufacture of a medicament for treating:

a) an XIAP-mediated disorder wherein the compound irreversibly inhibits XIAP by covalently modifying a lysine residue conserved at an equivalent position of K297 of XIAP;

b) a PDPK1-mediated disorder wherein the compound irreversibly inhibits PDPK1 by covalently modifying a lysine residue conserved at an equivalent position of K169 or K173 or K86 of PDPK1;

c) an HCV protease-mediated disorder wherein the compound irreversibly inhibits HCV protease by covalently modifying a lysine residue conserved at an equivalent position of K136 of HCV-protease subtype of NS3/4A; or

d) a PI3K-mediated disorder wherein the compound irreversibly inhibits PI3K by covalently modifying a lysine residue conserved at an equivalent position of K777 or K802 or K890 of PI3K.

10. The use of claim 9, wherein the XIAP-mediated disorder is selected from the group consisting of proliferative disorder and an autoimmune disease.

11. The use of claim 9, wherein the PDPK1-mediated disorder is selected from the group consisting of cancer, uterine fibroids, benign prostatic hyperplasia, familial adenomatosis polyposis, neurofibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis,

glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, an inflammatory bowel disease, transplantation rejection, endotoxic shock, and a fungal infection.

12. The use of claim 9, wherein the HCV protease-mediated disorder is hepatitis C.

13. The use of claim 9, wherein the PI3K-mediated disorder is selected from the group consisting of cancer, neurofibromatosis, ocular angiogenesis, stroke, diabetes, hepatomegaly, cardiovascular disease, Alzheimer's disease, cystic fibrosis, viral diseases, autoimmune diseases, atherosclerosis, restenosis, psoriasis, allergic disorders, inflammation, neurological disorders, angiogenic disorders, a hormone-related disease, conditions associated with organ transplantation, immunodeficiency disorders, destructive bone disorders, proliferative disorders, infectious diseases, conditions associated with cell death, thrombin-induced platelet aggregation, chronic myelogenous leukemia (CML), liver disease, pathologic immune conditions involving T cell activation, and CNS disorders.