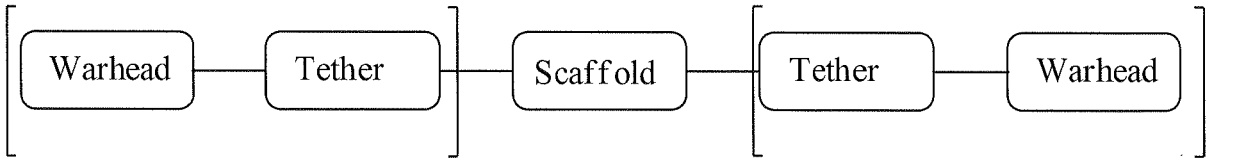
**CLAIMS**

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;

wherein the Scaffold contains a phenyl moiety;

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 a Tether connected to the phenyl moiety of the Scaffold;

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 ;

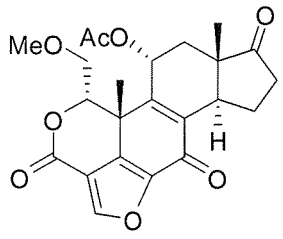
x is 0, 1, or 2;

y is 1, 2, or 3; and

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

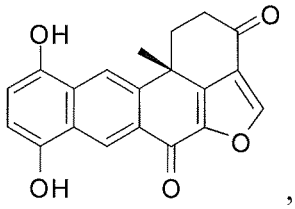
with the proviso that the compound of Formula **I** is not

wortmannin:

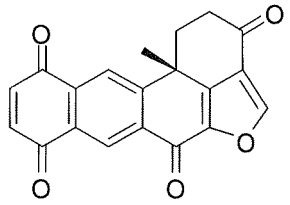


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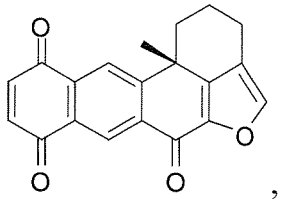
known analogues of wortmannin that covalently modify lysine through substantially the same mechanism as wortmannin:



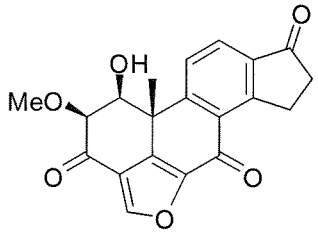
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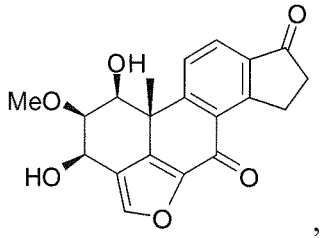
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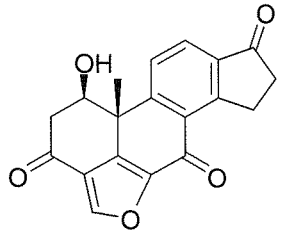
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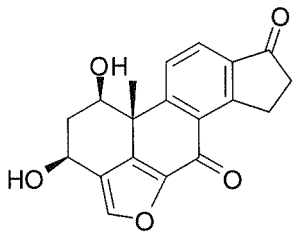
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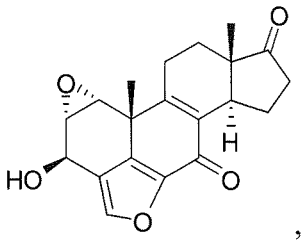
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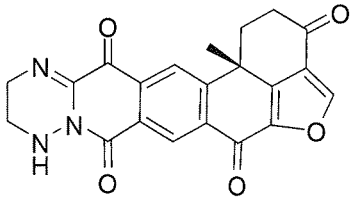
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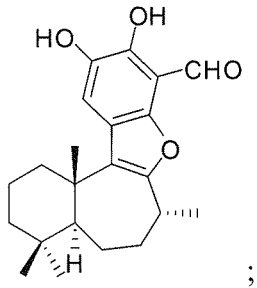
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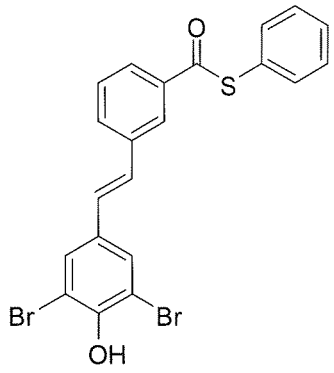
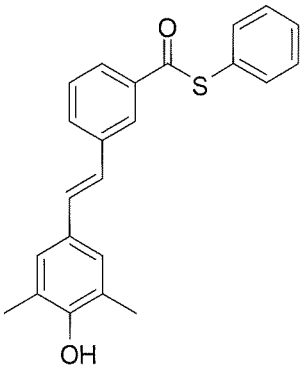
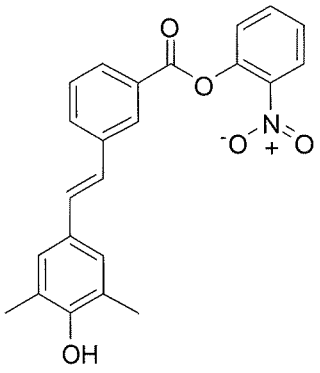


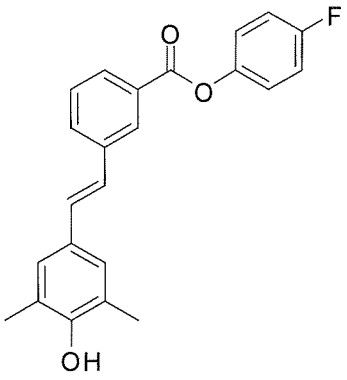
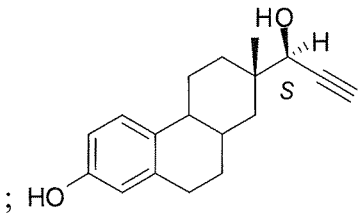
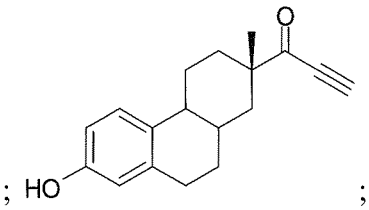
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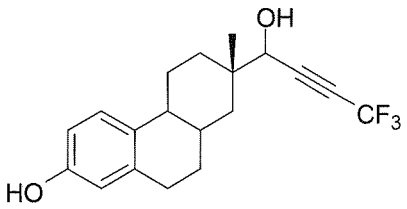
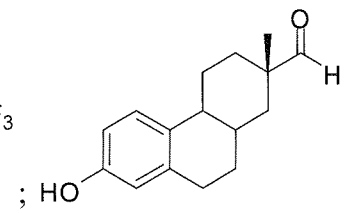


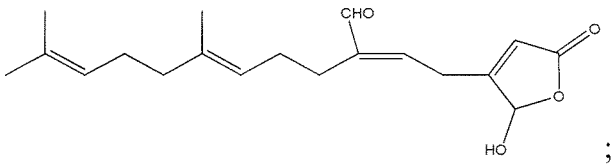
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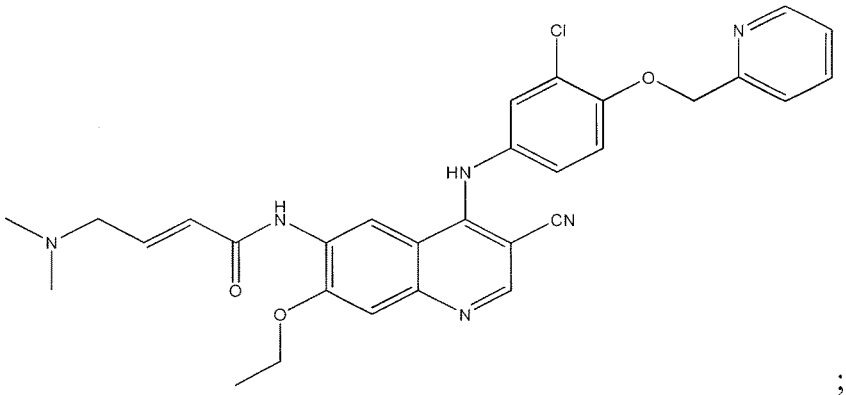

HO
OH
CHO
O
H
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O
S
Br
Br
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O
S
OH
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O
O
N
O
O
OH
;

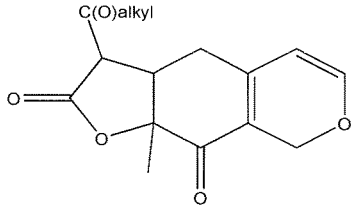

O
O
F
OH

HO
H
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HO
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O
HO
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OH
CF3
HO

O
H
HO
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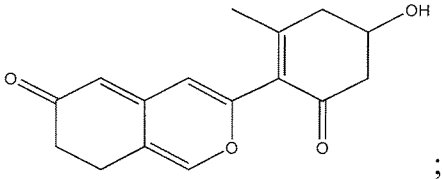

CHO
O
O
HO
;



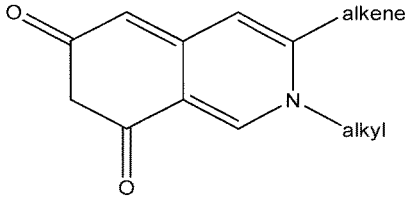

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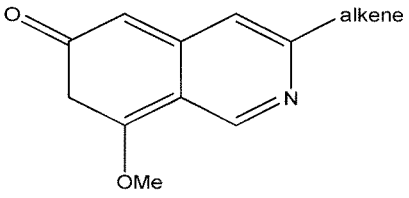

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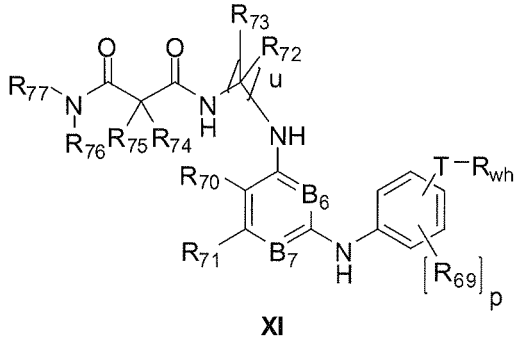



; and

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;

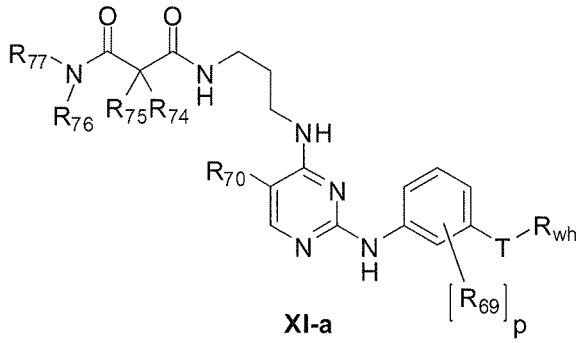
$R_7$, $R_{71}$, $R_{72}$, $R_{73}$, $R_{74}$, $R_{75}$, $R_{76}$, $R_{77}$, $R_{78}$, and $R_{79}$ are each independently hydrogen or $C_1$-$C_6$ alkyl; $R_1$ is hydrogen or $C_1$-$C_8$ alkyl; wherein one or more methylene groups of the $C_1$-$C_6$ alkyl can be replaced by -$NR_1$-, -O-, -C(O)-, -S-,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

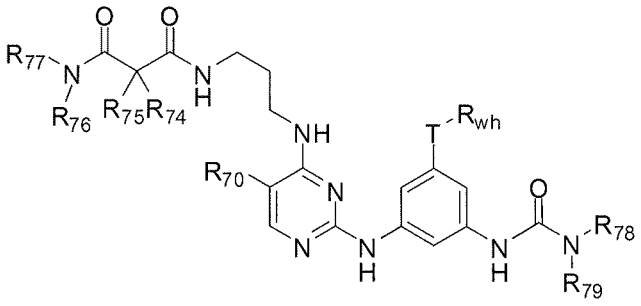
T is Tether; and

$R_{wh}$ is Warhead.

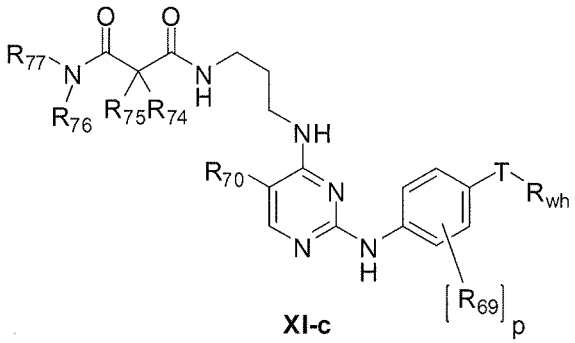
3. The compound of claim 2, wherein the compound of Formula **XI** is a compound of Formula **XI-a**, **XI-b**, or **XI-c**;



**XI-a**



**XI-b**



**XI-c**

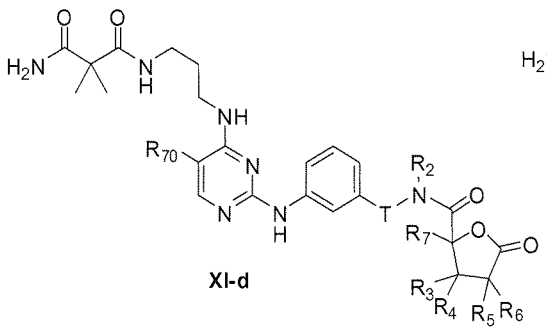
wherein

$R_{70}$ is -F, -Cl, -Br, or –I;

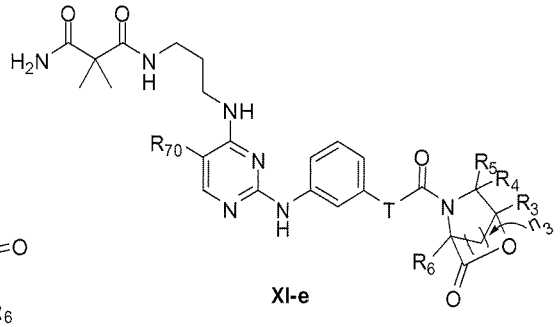
T is Tether; and

$R_{wh}$ is Warhead.

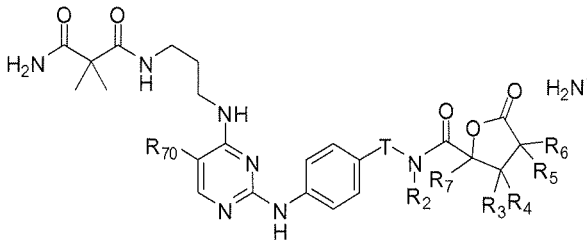
4. The compound of claim 3, wherein the compound of Formula **XI-a**, **XI-b** or **XI-c** is a compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j**:



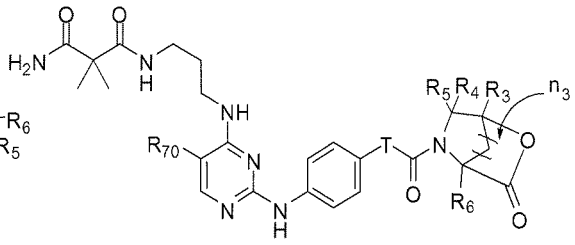
**XI-d**



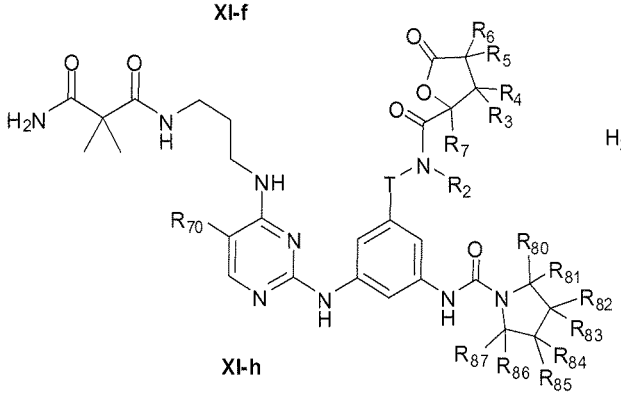
**XI-e**



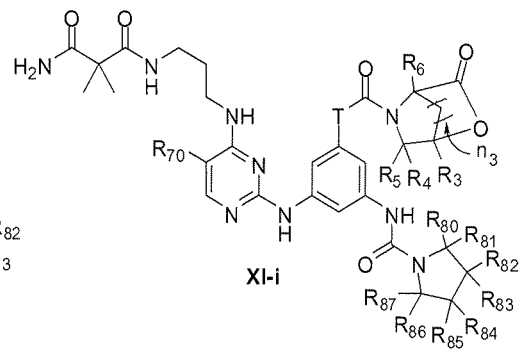
**XI-f**



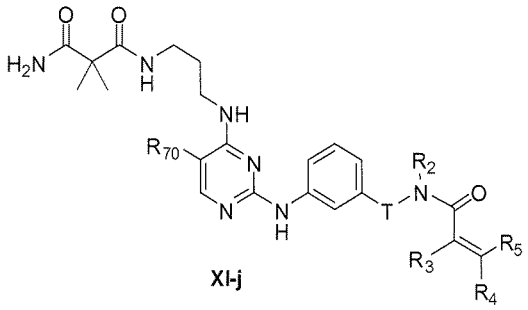
**XI-g**



**XI-h**



**XI-i**



**XI-j**

wherein

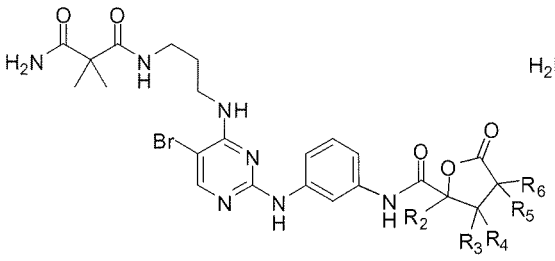
$R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_{80}$, $R_{81}$, $R_{82}$, $R_{83}$, $R_{84}$, $R_{85}$, $R_{86}$, and $R_{87}$ are each independently hydrogen or $C_1$-$C_6$ alkyl; $R_1$ is hydrogen or $C_1$-$C_8$ alkyl;

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)-;

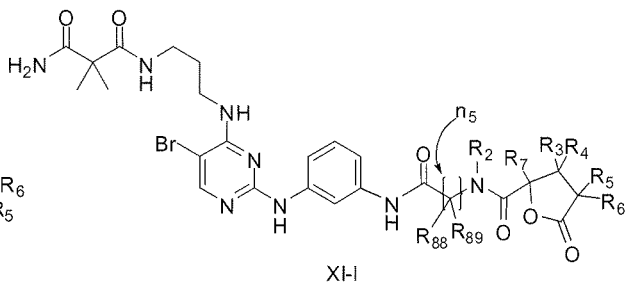
one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by .

5. The compound of claim 4, wherein

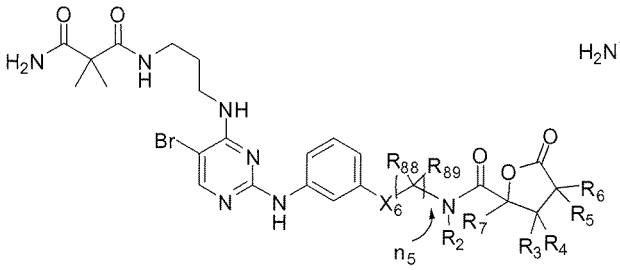
a) the compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j** is a compound of Formula **XI-k**, **XI-l**, **XI-m**, **XI-n**, **XI-o**, **XI-p**, or **XI-q**;



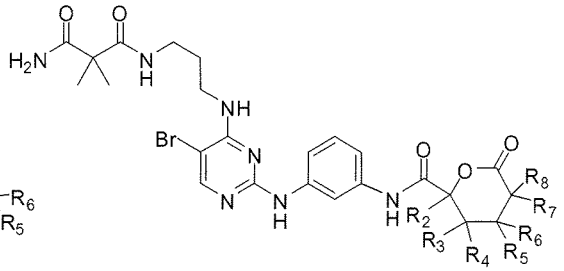
XI-k



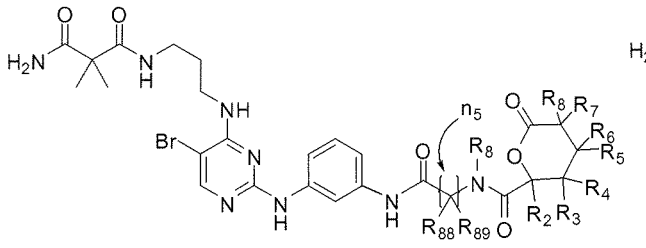
XI-l



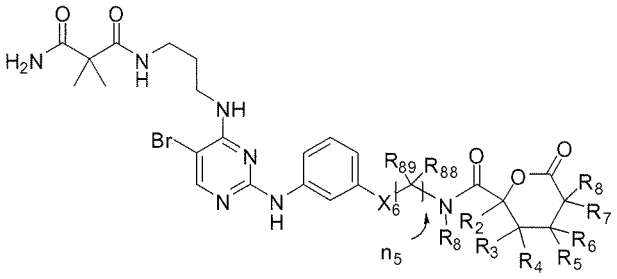
XI-m



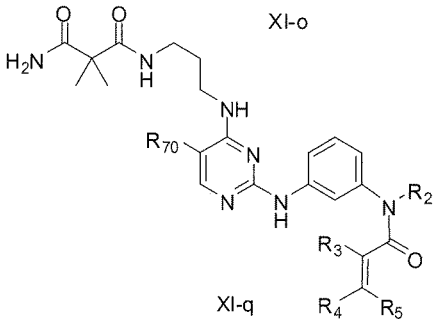
XI-n



XI-o



XI-p



XI-q

wherein

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

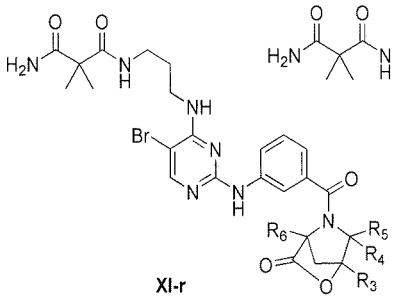
$R_{88}$ and $R_{89}$ are each independently hydrogen or $C_1$-$C_6$ alkyl; $R_1$ is hydrogen or $C_1$-$C_8$ alkyl;

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)-;

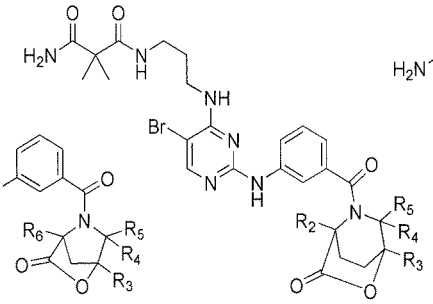
one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ; and

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

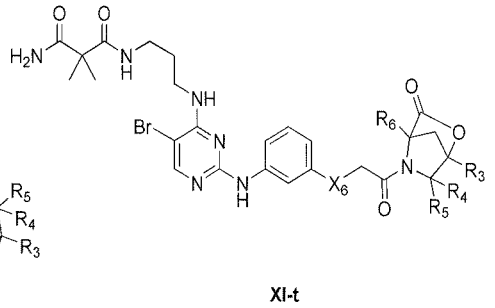
b) the compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j** is a compound of Formula **XI-r**, **XI-s**, **XI-t**, **XI-u**, **XI-v**, **XI-w**, or **XI-x**:



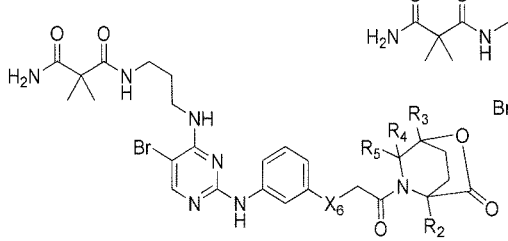
**XI-r**



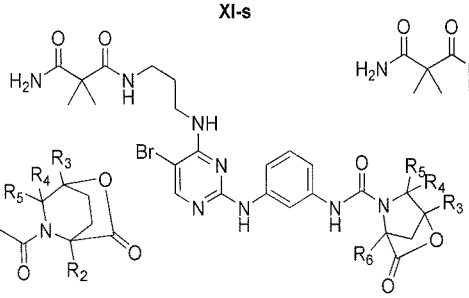
**XI-s**



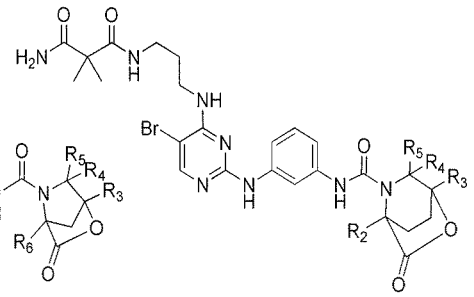
**XI-t**



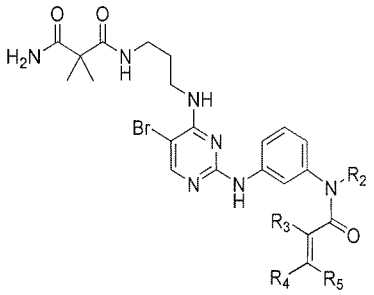
**XI-u**



**XI-v**



**XI-w**

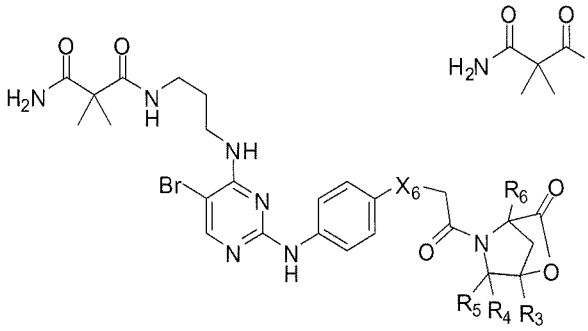


**XI-x**

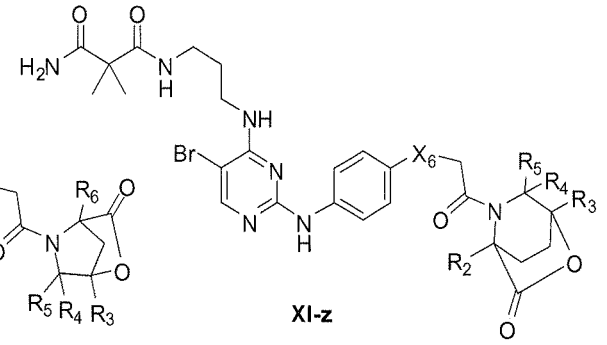
;

or

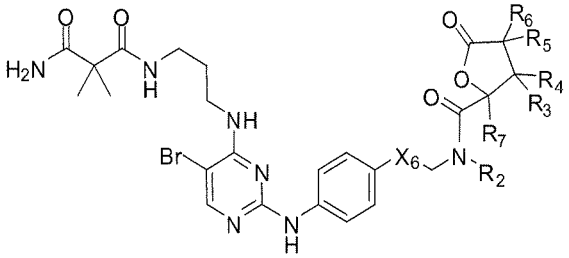
c) the compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j** is a compound of Formula **XI-y**, **XI-z**, **XI-aa**, or **XI-bb**:



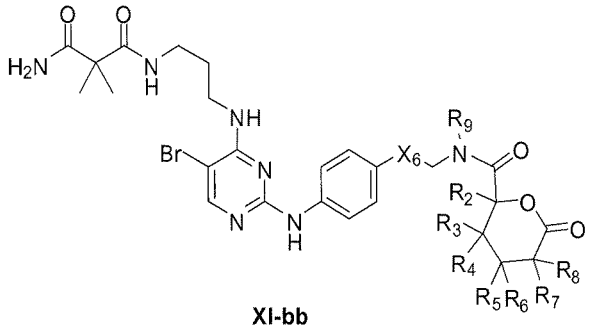
**XI-y**



**XI-z**



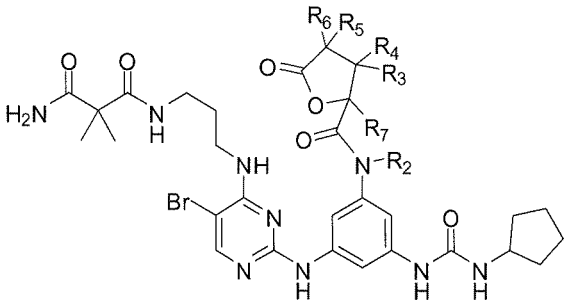
**XI-aa**



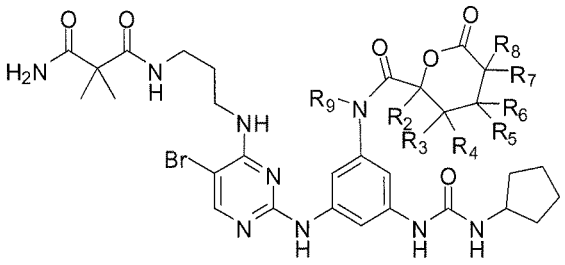
**XI-bb**

or

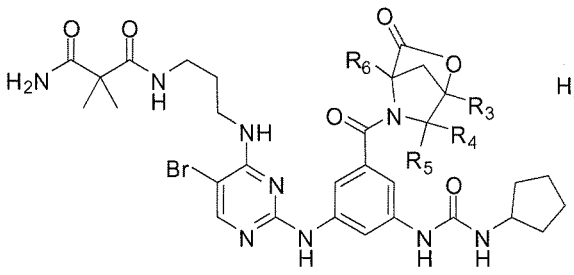
d) the compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j** is a compound of Formula **XI-cc**, **XI-dd**, **XI-ee**, or **XI-ff**:



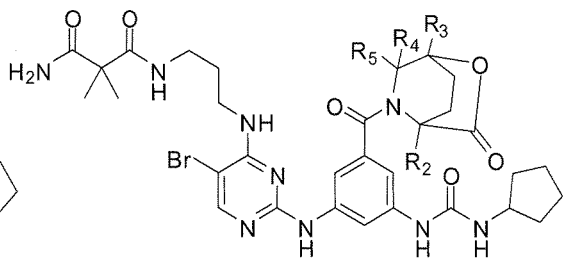
**XI-cc**



**XI-dd**

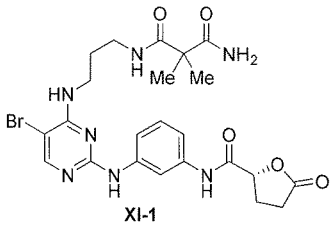


**XI-ee**

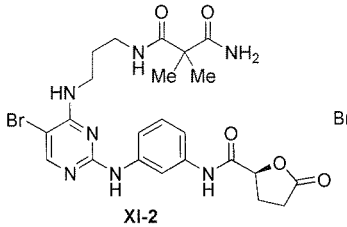


**XI-ff**

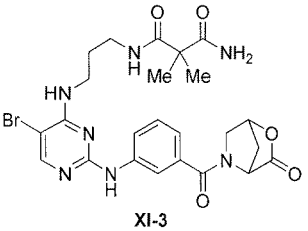
6. The compound of claim 3, wherein the compound of Formula **XI** is selected from the group consisting of:



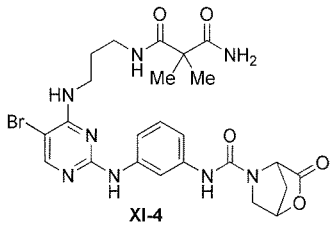
XI-1



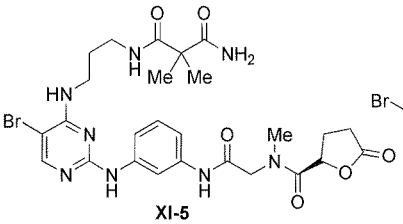
XI-2



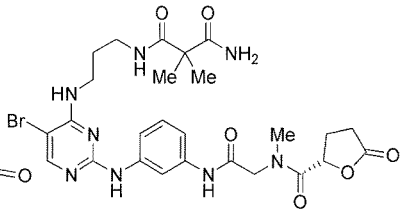
XI-3



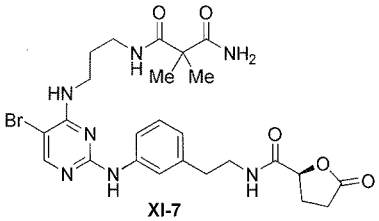
XI-4



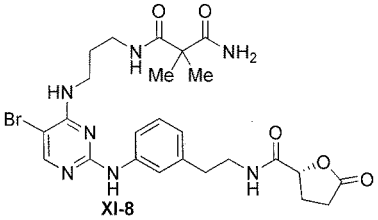
XI-5



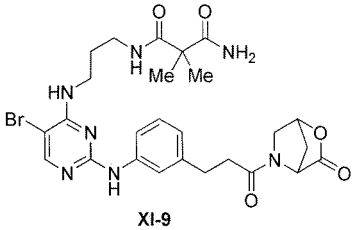
XI-6



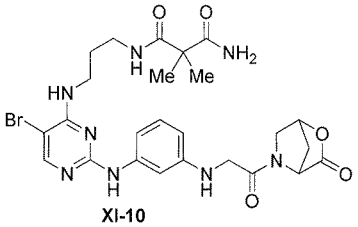
XI-7



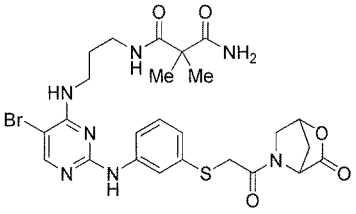
XI-8



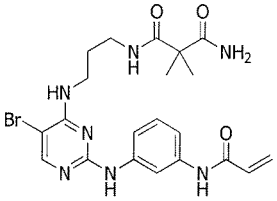
XI-9



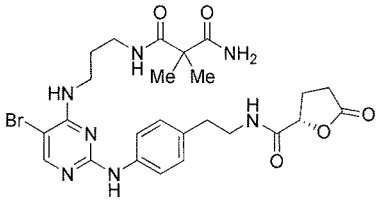
XI-10



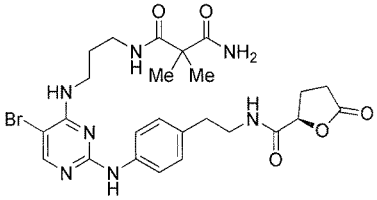
XI-11



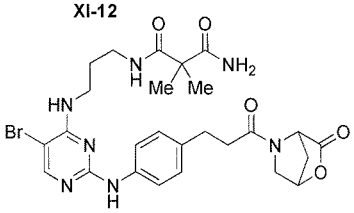
XI-12



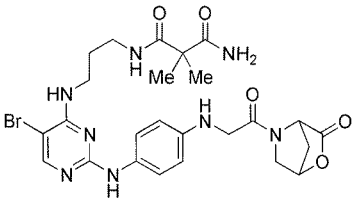
XI-13



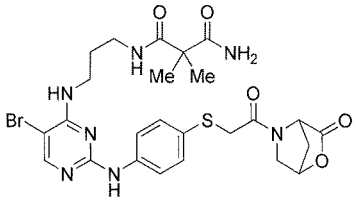
XI-14



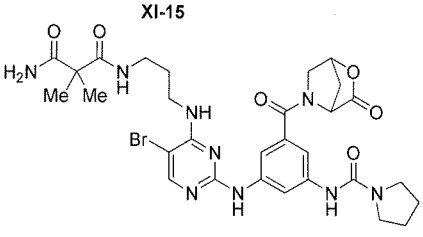
XI-15



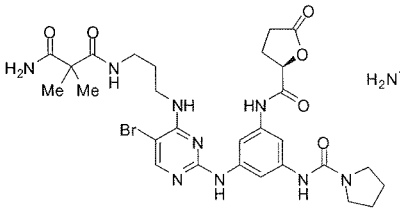
XI-16



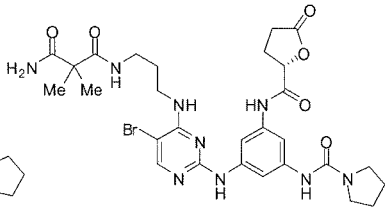
XI-17



XI-18



XI-19



XI-20

7. A compound of any one of claims 2 or 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. Use of a compound of any one of claims 2 or 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.

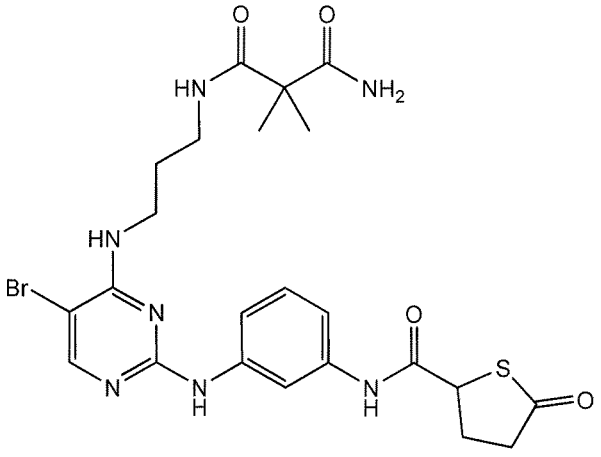
9. The use of claim 8, wherein the XIAP-mediated disorder is selected from the group consisting of proliferative disorder and an autoimmune disease.

10. The use of claim 8, 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.

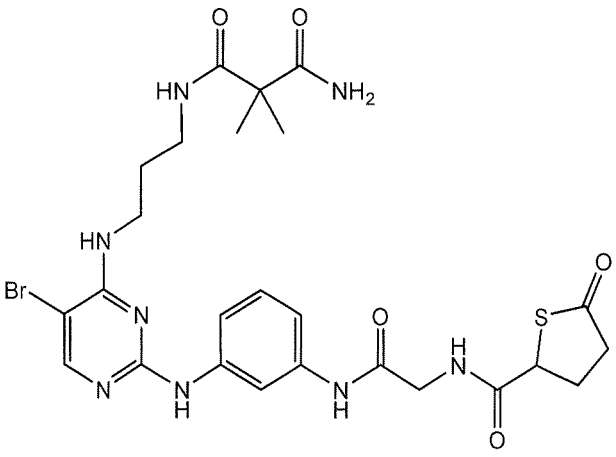
11. The use of claim 8, wherein the HCV protease-mediated disorder is hepatitis C.

12. The use of claim 8, 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.

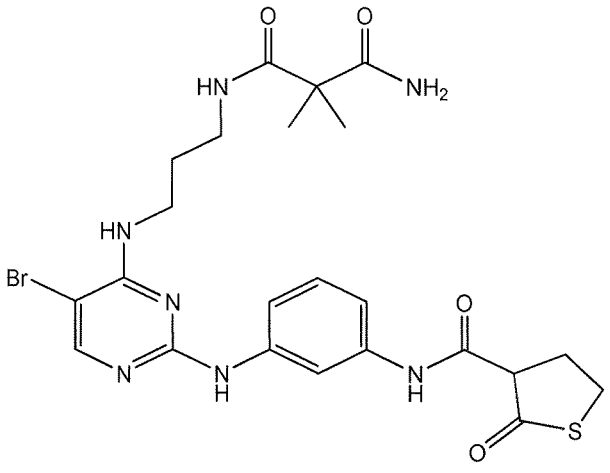
13. The compound of claim 3, wherein the compound of Formula **XI** is selected from the group consisting of:



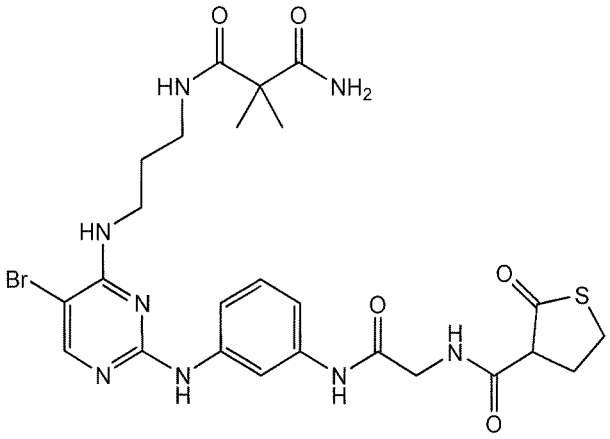
**XI-21**



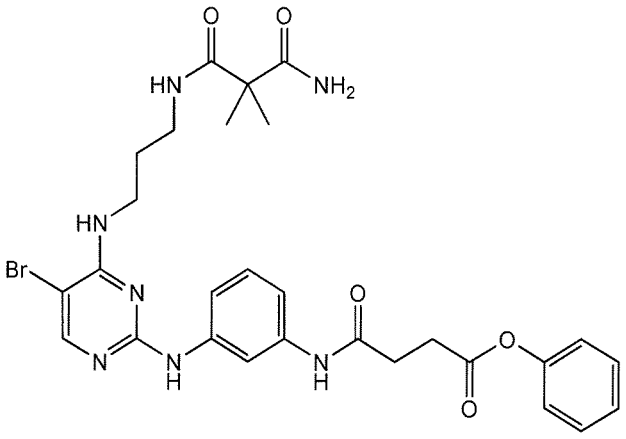
**XI-22**



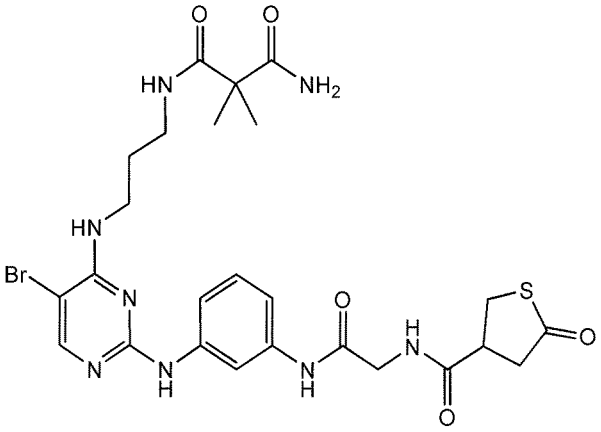
**XI-23**



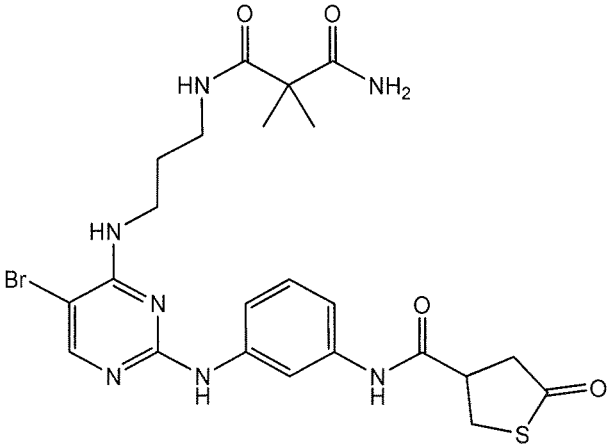
**XI-24**

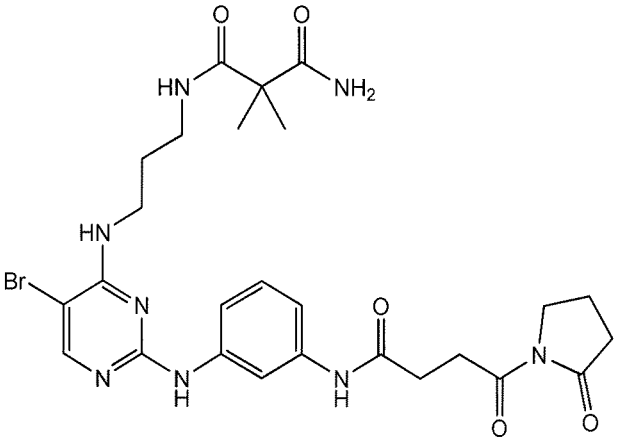


**XI-25**

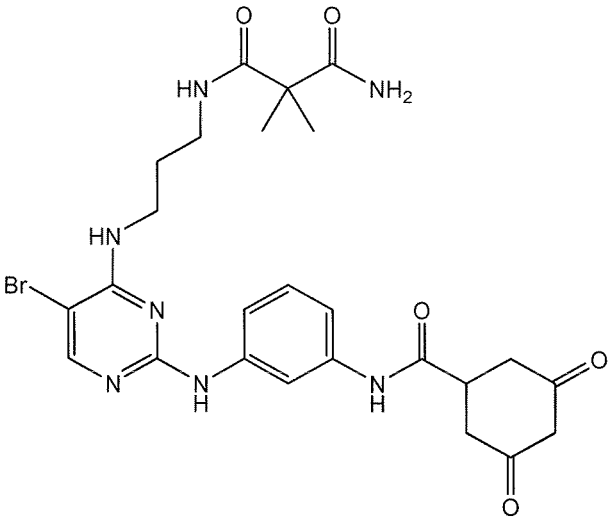


**XI-26**

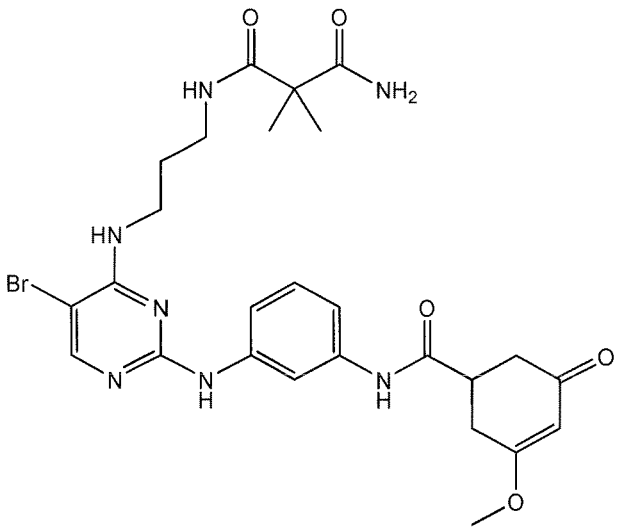




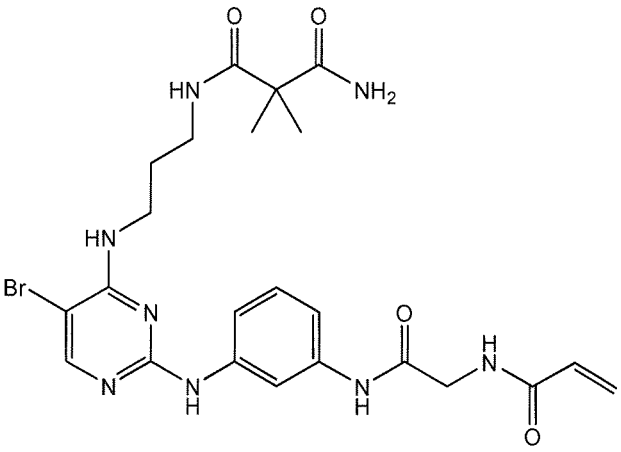
**XI-27**



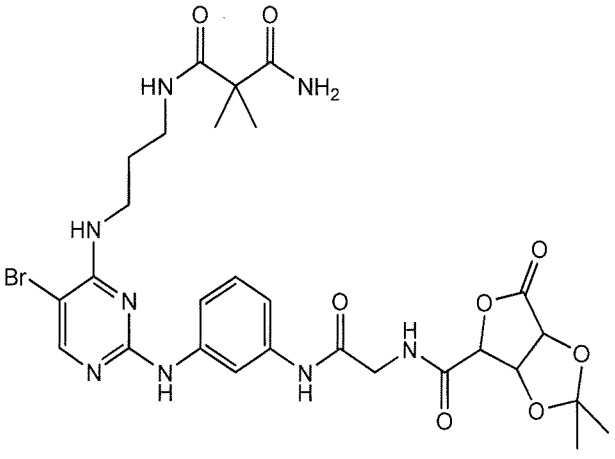
**XI-28**



**XI-29**



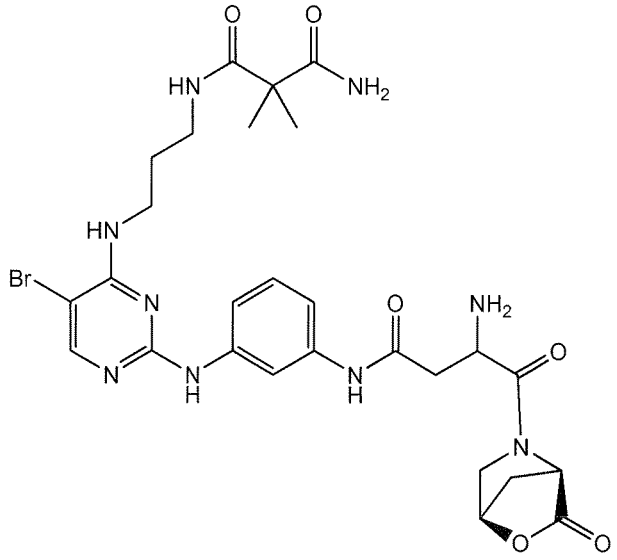
**XI-30**



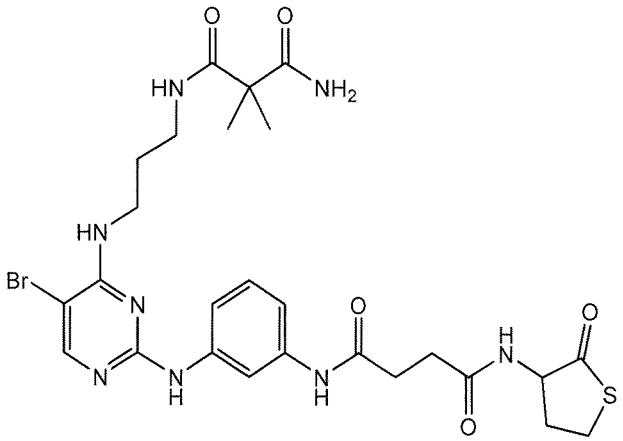
**XI-31**



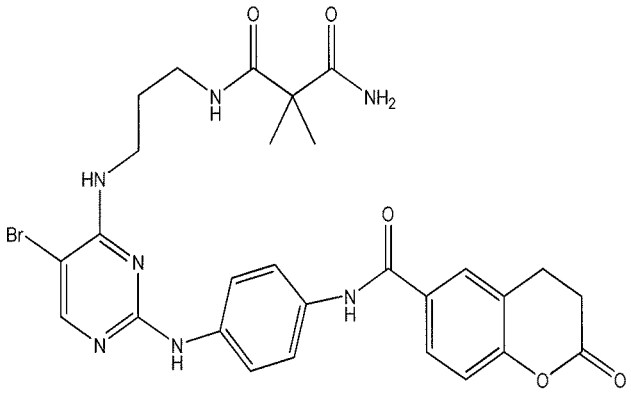
**XI-32**



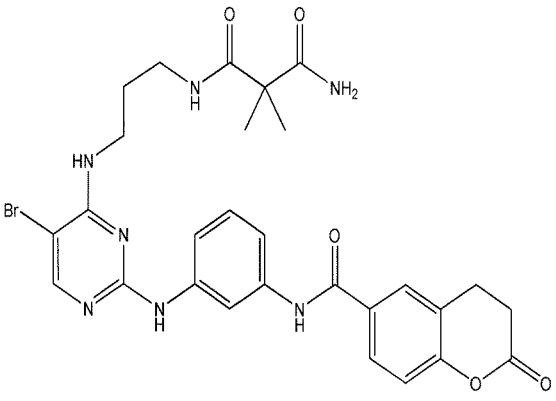
**XI-33**



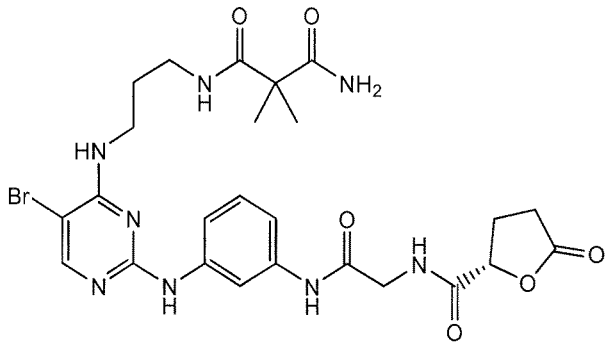
**XI-34**



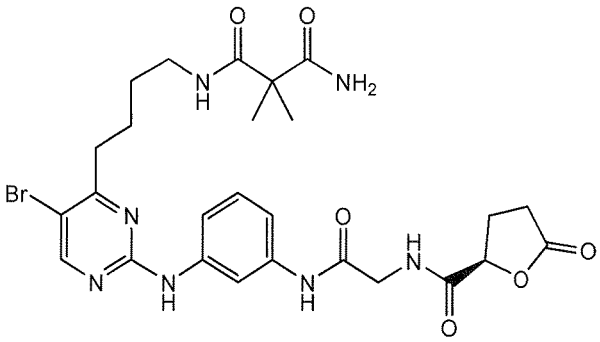
**XI-35**



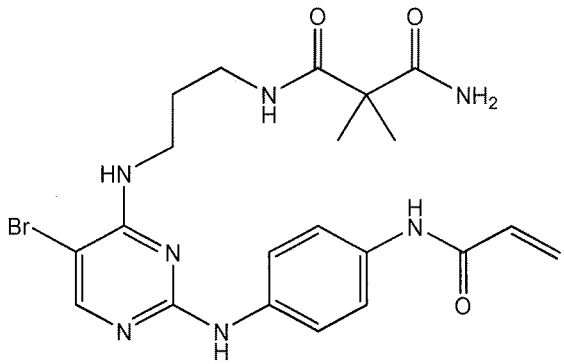
**XI-36**



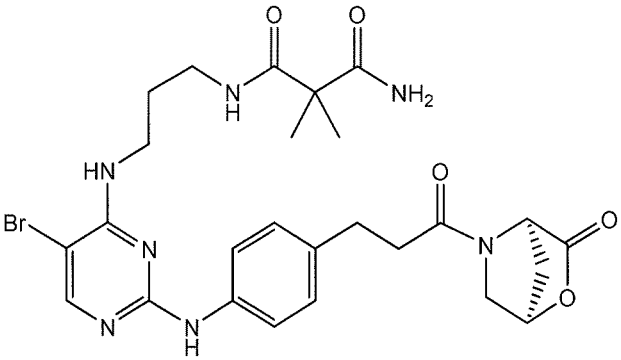
**XI-37**



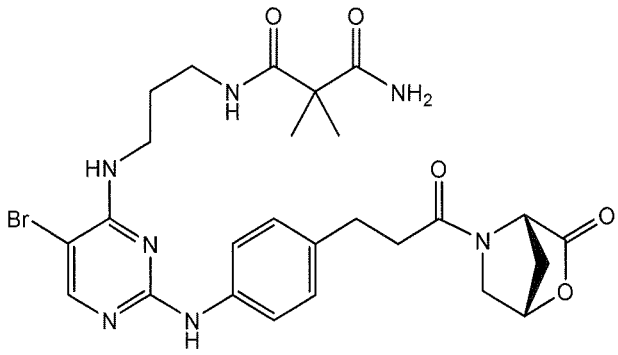
**XI-38**



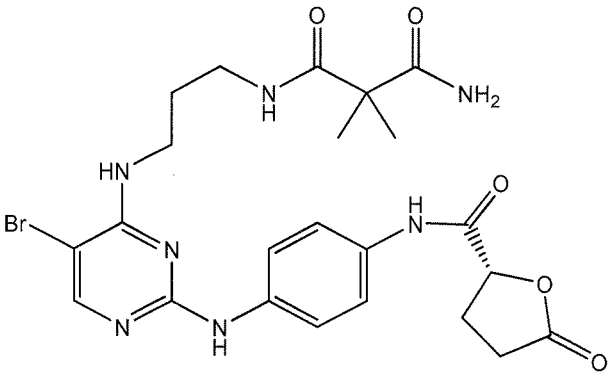
**XI-39**



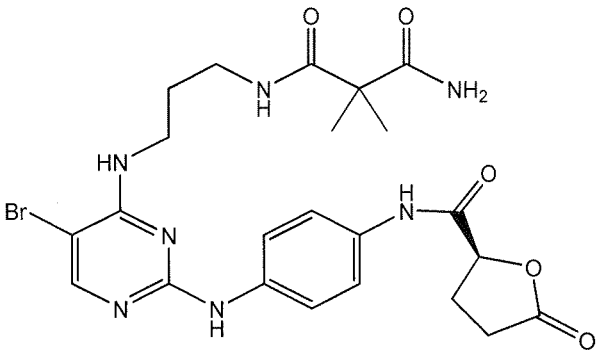
**XI-40**



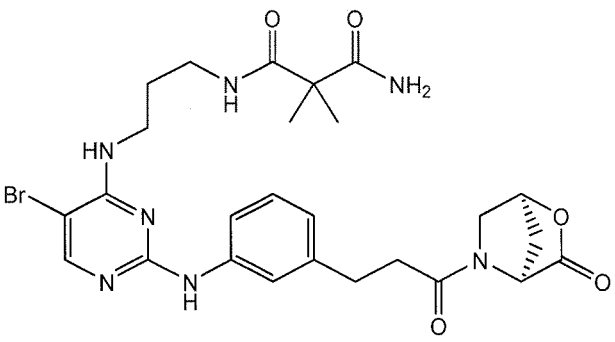
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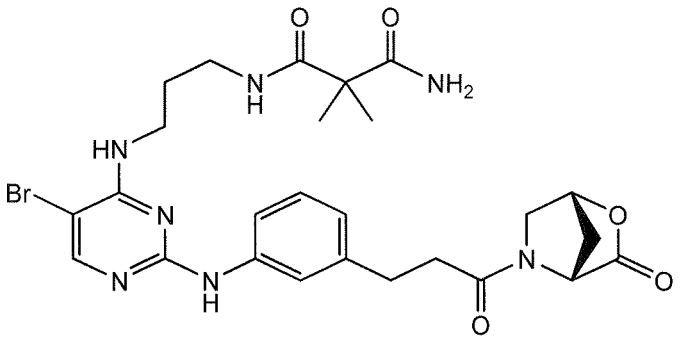
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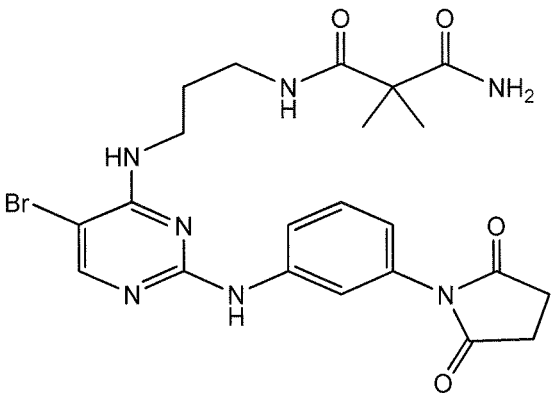
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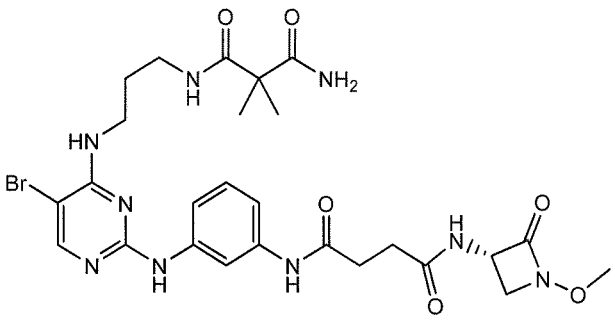
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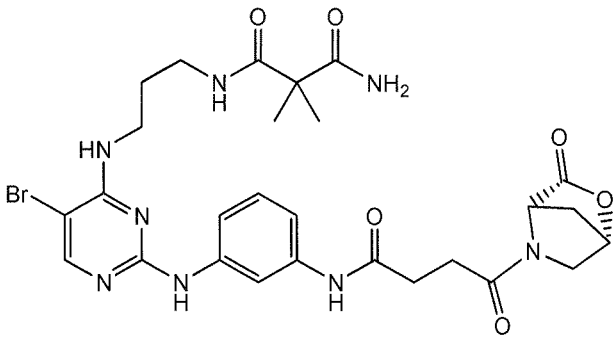
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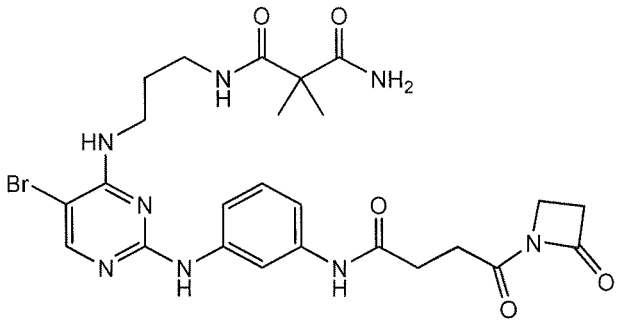
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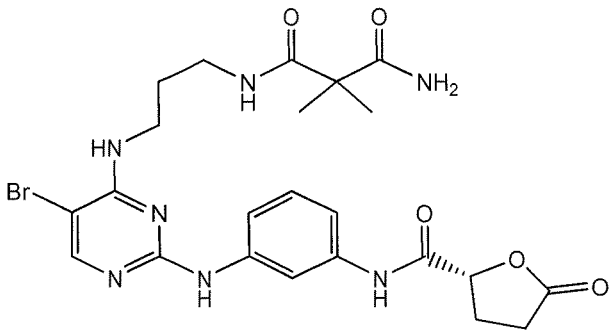
**XI-47**



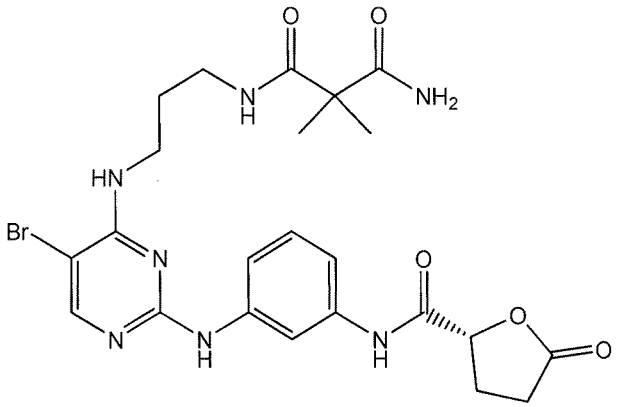
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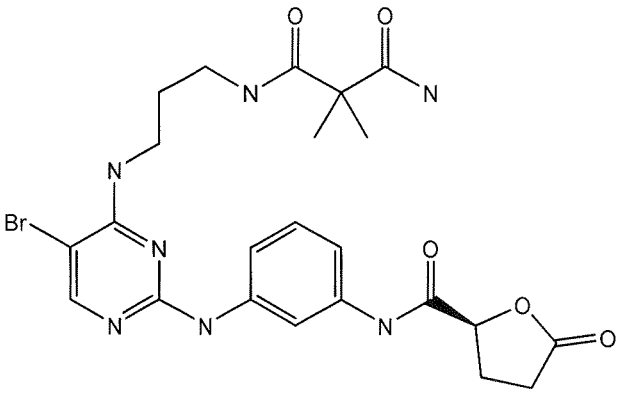
**XI-49**



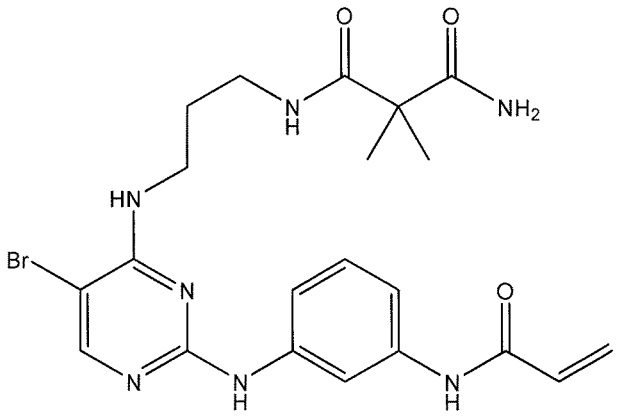
**XI-50**



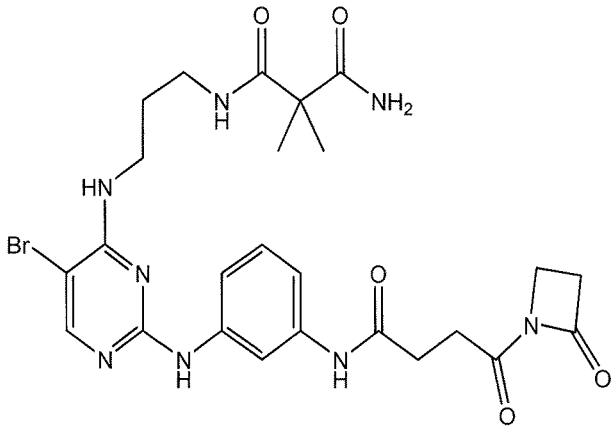
**XI-51**



**XI-52**



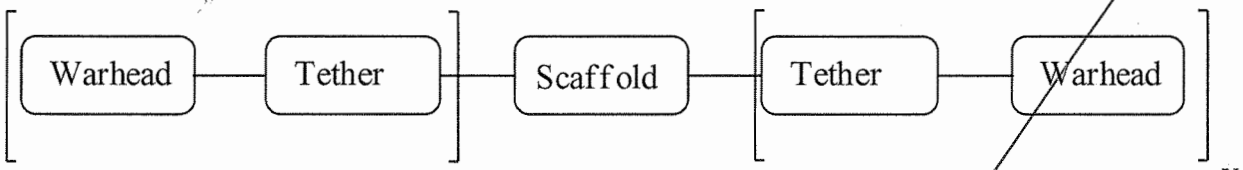
**XI-53**



**XI-55**

**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 ;

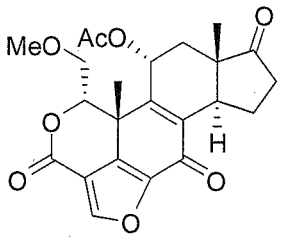
x is 0, 1, or 2;

y is 1, 2, or 3; and

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

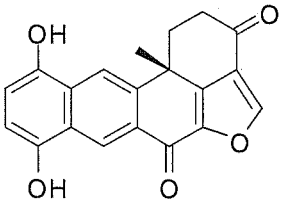
with the proviso that the compound of Formula **I** is not

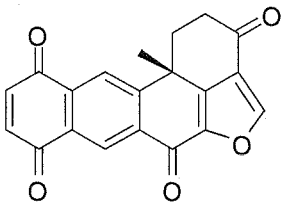
wortmannin:

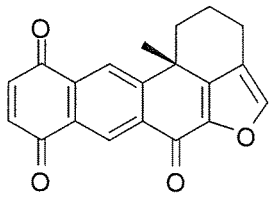


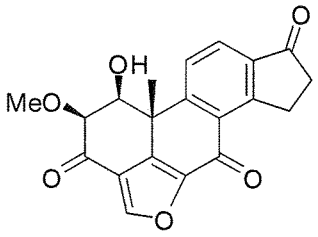
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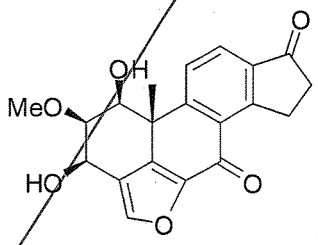
known analogues of wortmannin that covalently modify lysine through substantially the same mechanism as wortmannin:

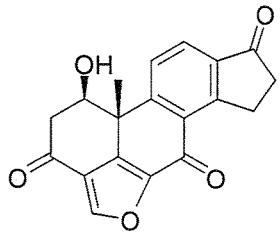


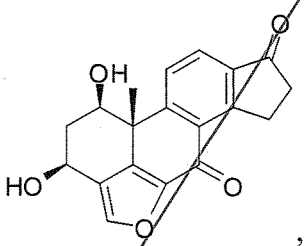
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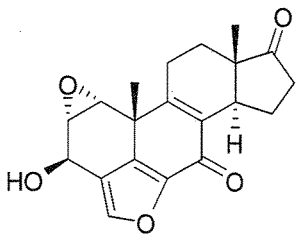
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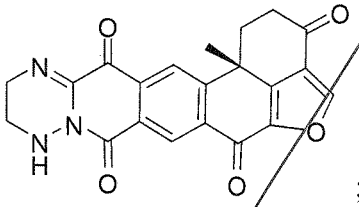
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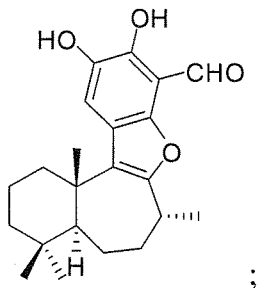
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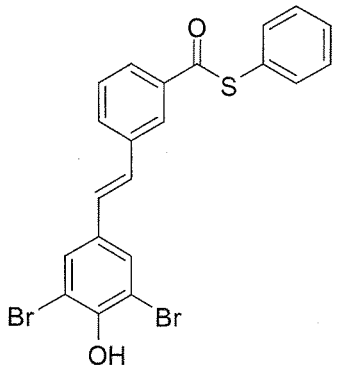
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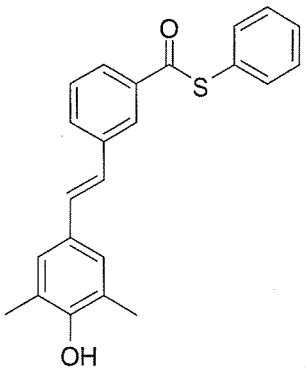
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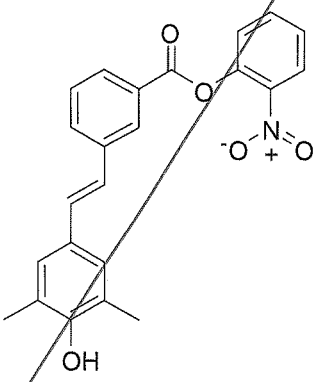
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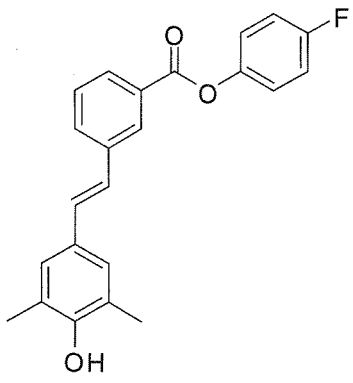
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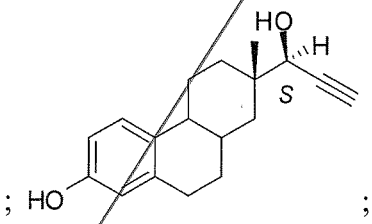

HO
OH
CHO
O
H
;

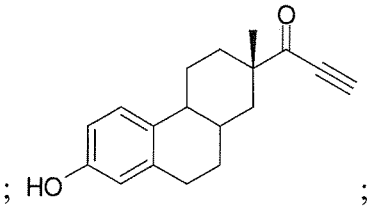

O
S
Br
Br
OH
;

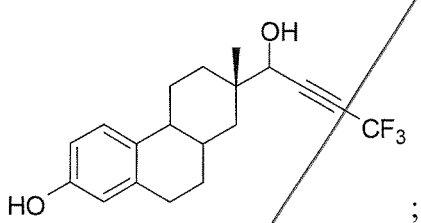

O
S
OH
;

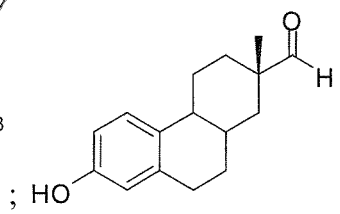

O
O
N
O
O
OH
;

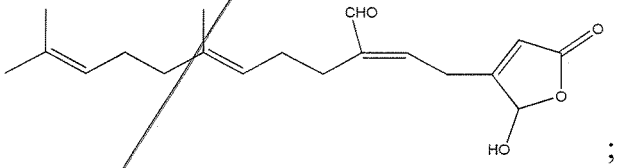

O
O
F
OH

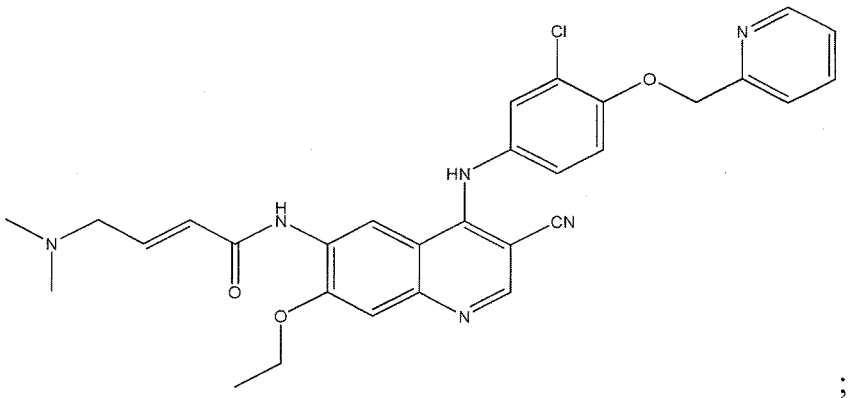

HO
H
S
HO
;


O
HO
;

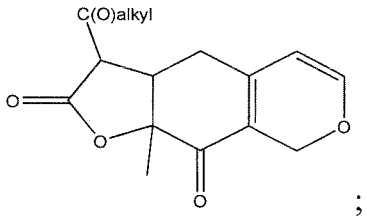

OH
CF3
HO
;


O
H
HO
;

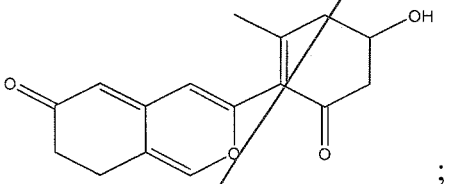

CHO
O
O
HO
;



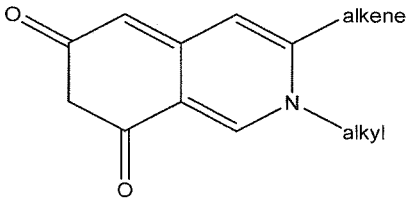

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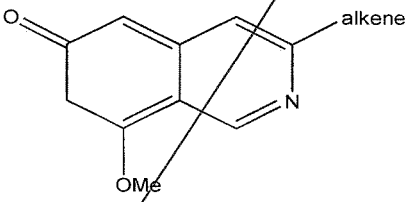

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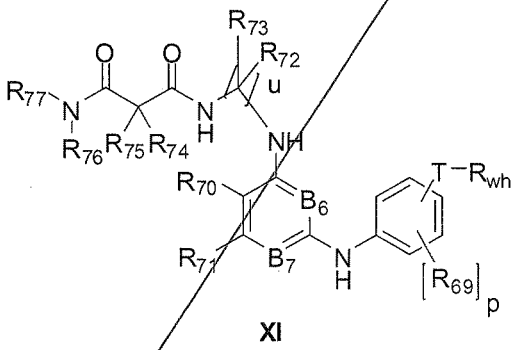



; and

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;

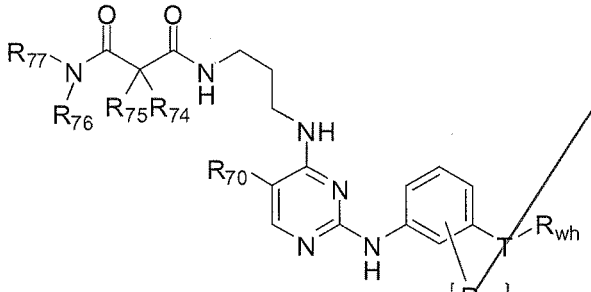
$R_7$, $R_{71}$, $R_{72}$, $R_{73}$, $R_{74}$, $R_{75}$, $R_{76}$, $R_{77}$, $R_{78}$, and $R_{79}$ are each independently hydrogen or $C_1$-$C_6$ alkyl; $R_1$ is hydrogen or $C_1$-$C_8$ alkyl; wherein one or more methylene groups of the $C_1$-$C_6$ alkyl can be replaced by -$NR_1$-, -O-, -C(O)-, -S-,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

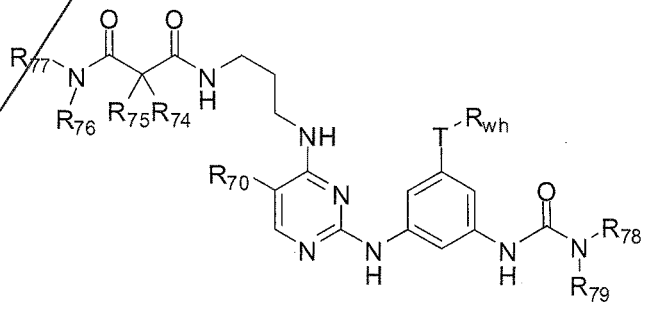
T is Tether; and

$R_{wh}$ is Warhead.

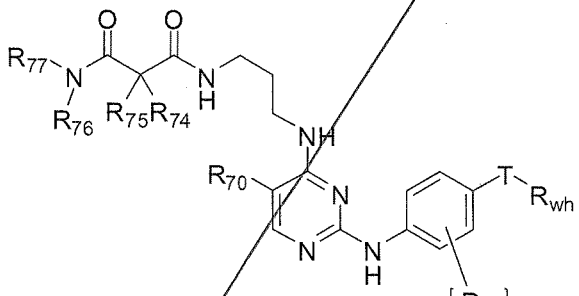
3. The compound of claim 2, wherein the compound of Formula **XI** is a compound of Formula **XI-a**, **XI-b**, or **XI-c**;



**XI-a**



**XI-b**



**XI-c**

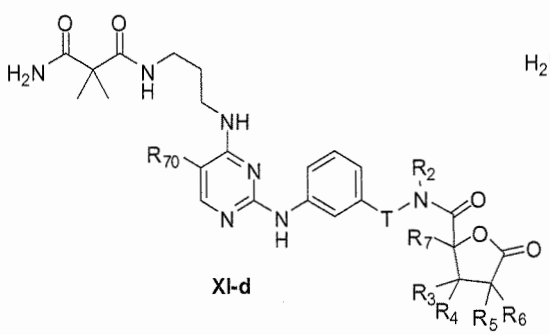
wherein

$R_{70}$ is -F, -Cl, -Br, or –I;

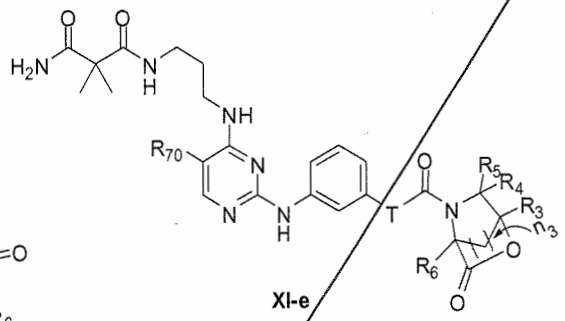
T is Tether; and

$R_{wh}$ is Warhead.

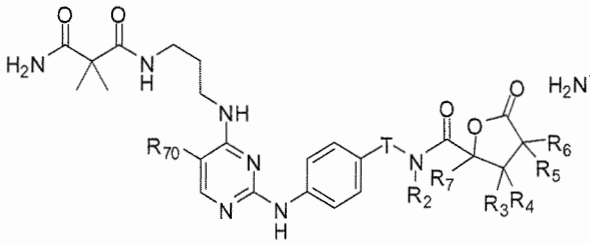
4. The compound of claim 3, wherein the compound of Formula **XI-a**, **XI-b** or **XI-c** is a compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j**:



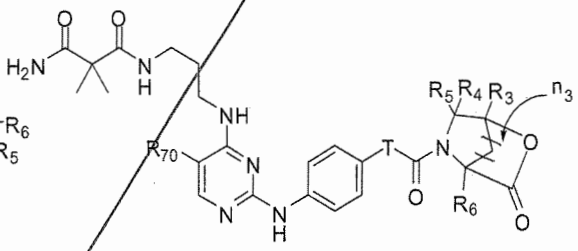
**XI-d**



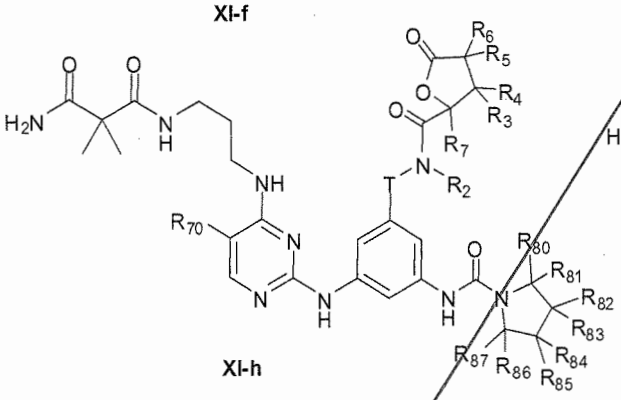
**XI-e**



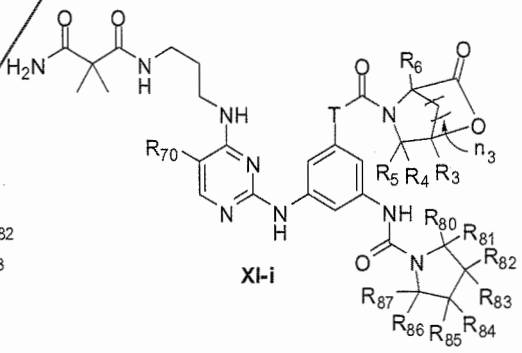
**XI-f**



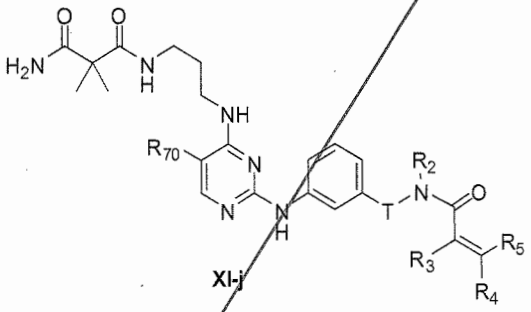
**XI-g**



**XI-h**



**XI-i**



**XI-j**

wherein

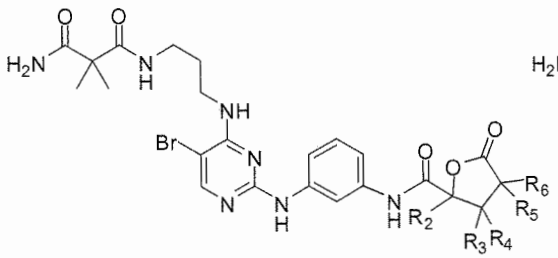
$R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_{80}$, $R_{81}$, $R_{82}$, $R_{83}$, $R_{84}$, $R_{85}$, $R_{86}$, and $R_{87}$ are each independently hydrogen or $C_1$-$C_6$ alkyl; $R_1$ is hydrogen or $C_1$-$C_8$ alkyl;

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)-;

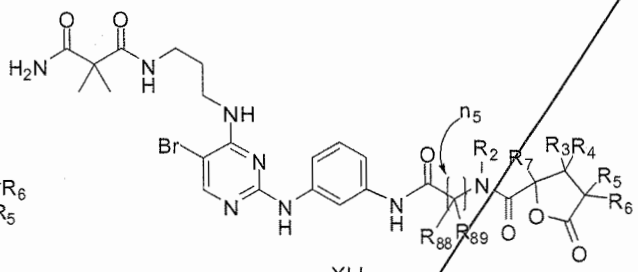
one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by .

5. The compound of claim 4, wherein

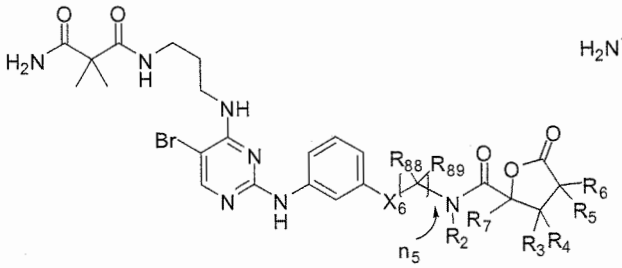
a) the compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j** is a compound of Formula **XI-k**, **XI-l**, **XI-m**, **XI-n**, **XI-o**, **XI-p**, or **XI-q**;



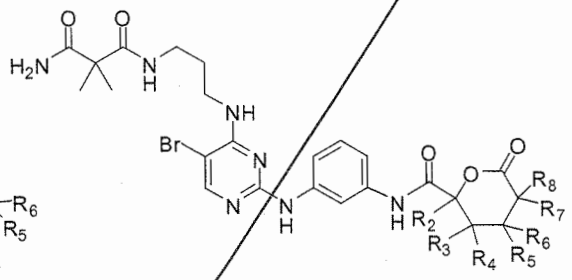
XI-k



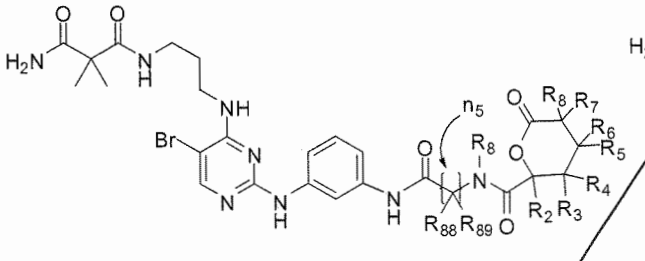
XI-l



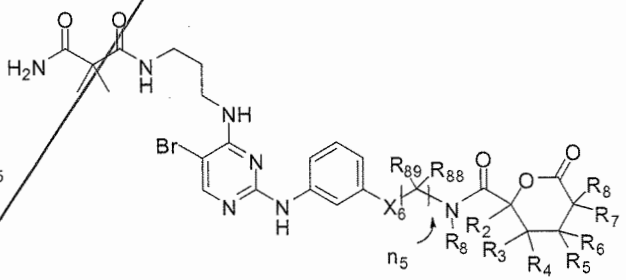
XI-m



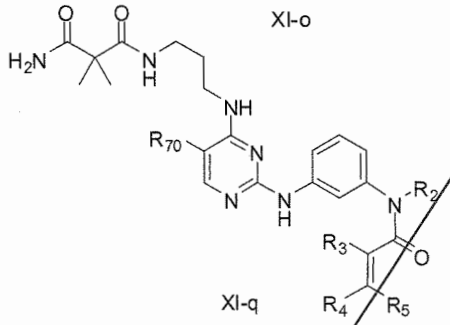
XI-n



XI-o



XI-p



XI-q

wherein

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

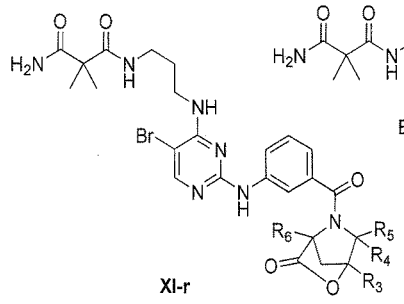
$R_{88}$ and $R_{89}$ are each independently hydrogen or $C_1$-$C_6$ alkyl; $R_1$ is hydrogen or $C_1$-$C_8$ alkyl;

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)-;

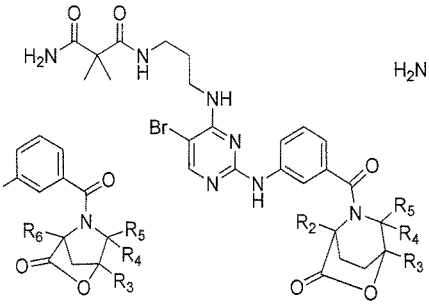
one or more methine groups of the $C_1$-$C_6$ alkyl, when present, can be independently replaced by ; and

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

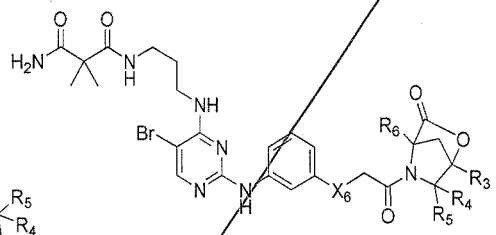
b) the compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j** is a compound of Formula **XI-r**, **XI-s**, **XI-t**, **XI-u**, **XI-v**, **XI-w**, or **XI-x**:



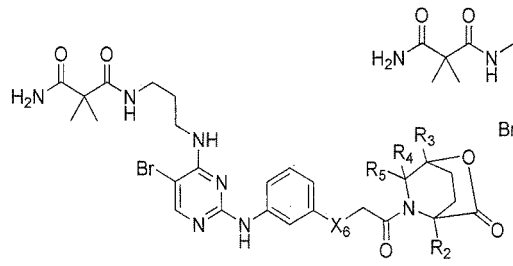
**XI-r**



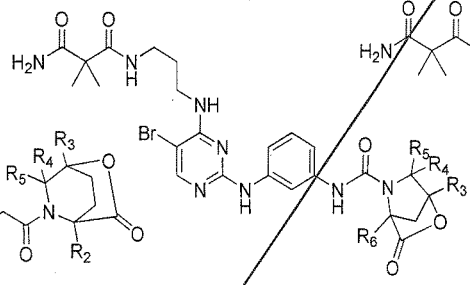
**XI-s**



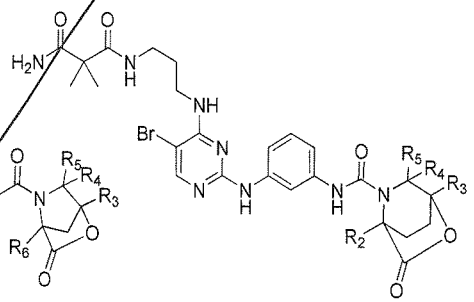
**XI-t**



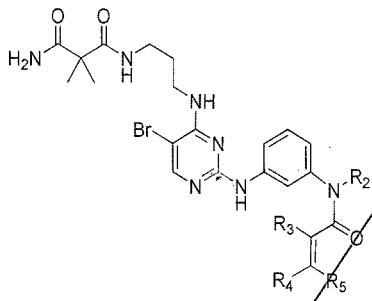
**XI-u**



**XI-v**



**XI-w**

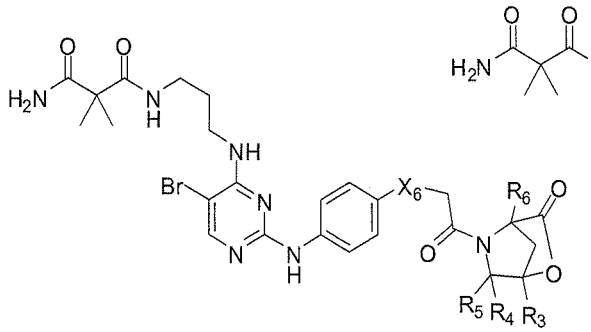


**XI-x**

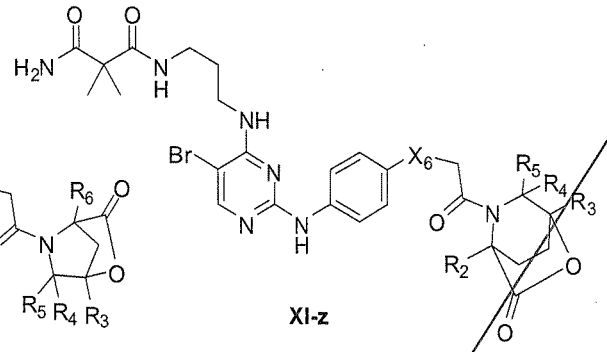
;

or

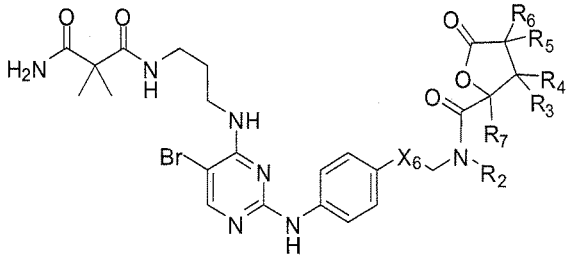
c) the compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j** is a compound of Formula **XI-y**, **XI-z**, **XI-aa**, or **XI-bb**:



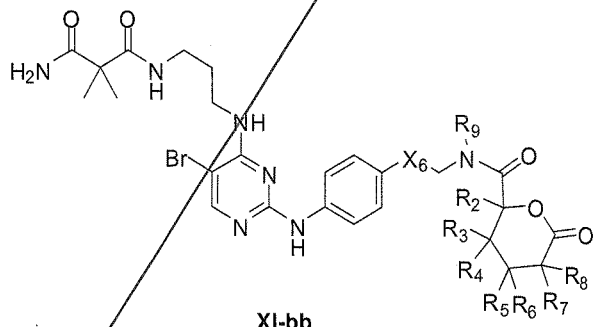
**XI-y**



**XI-z**



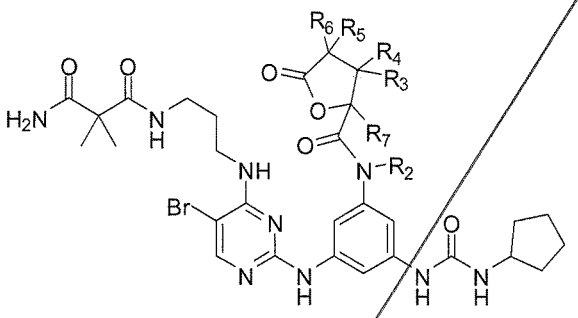
**XI-aa**



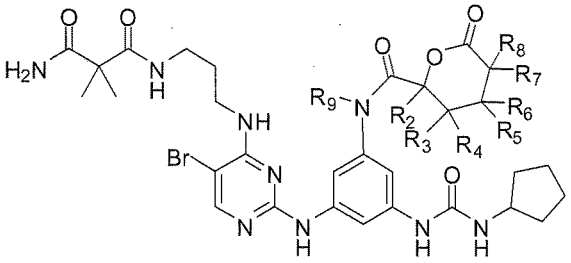
**XI-bb**

or

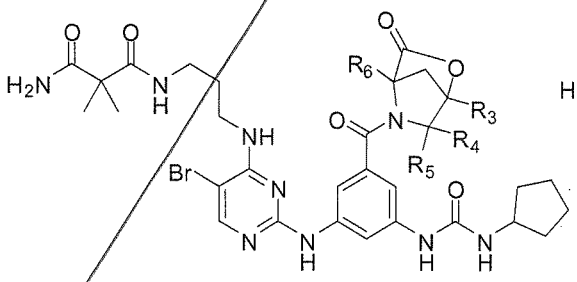
d) the compound of Formula **XI-d**, **XI-e**, **XI-f**, **XI-g**, **XI-h**, **XI-i**, or **XI-j** is a compound of Formula **XI-cc**, **XI-dd**, **XI-ee**, or **XI-ff**:



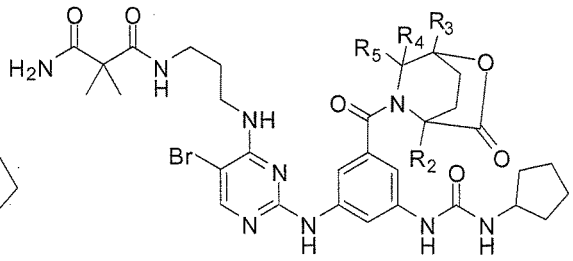
**XI-cc**



**XI-dd**

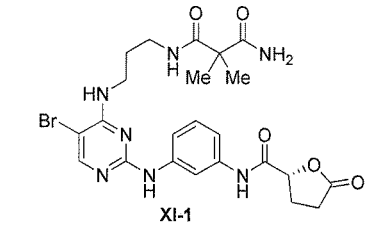


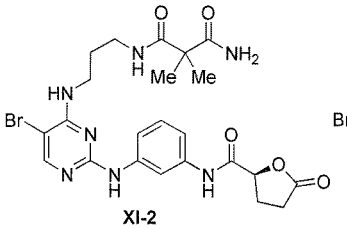
**XI-ee**

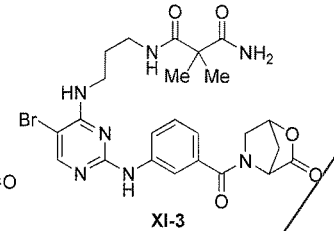


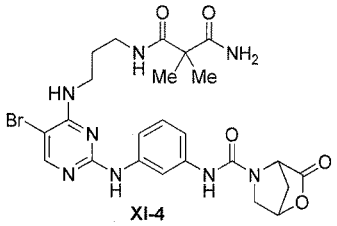
**XI-ff**

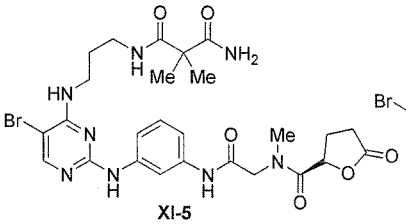
6. The compound of claim 3, wherein the compound of Formula **XI** is selected from the group consisting of:

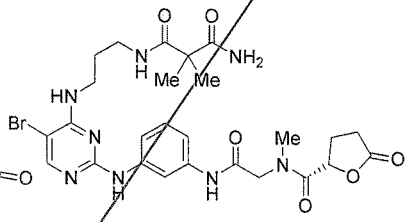

XI-1

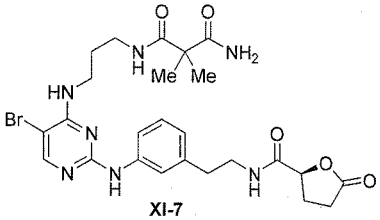

XI-2

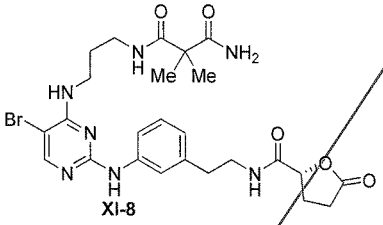

XI-3

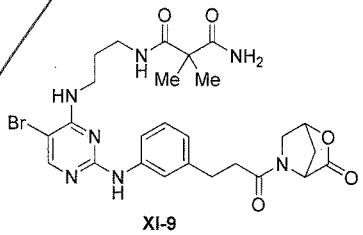

XI-4

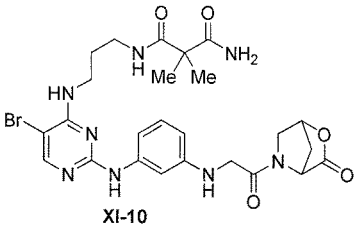

XI-5

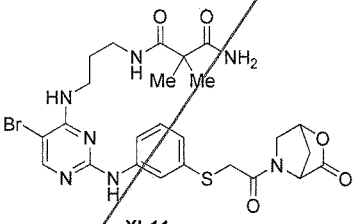

XI-6

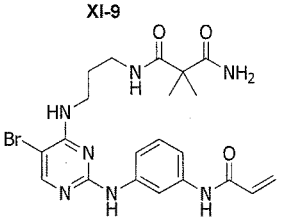

XI-7

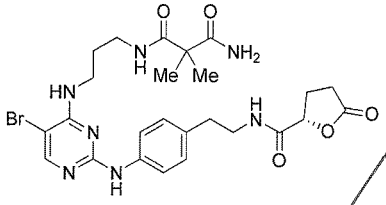

XI-8

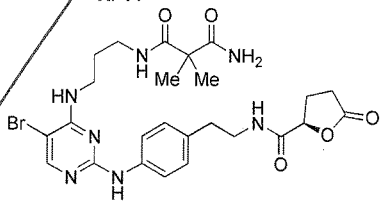

XI-9

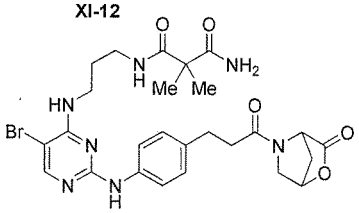

XI-10

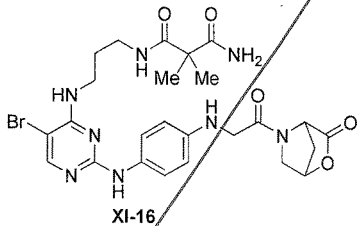

XI-11

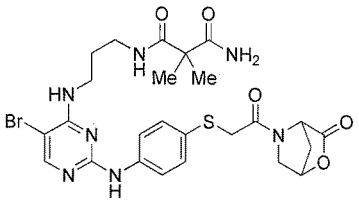

XI-12

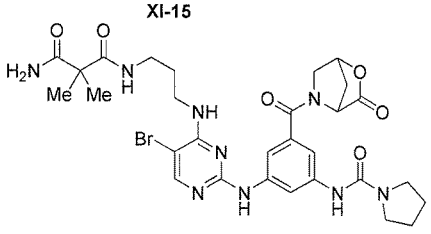

XI-13

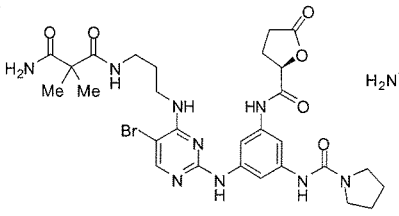

XI-14


XI-15

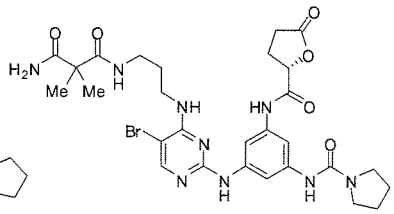

XI-16


XI-17

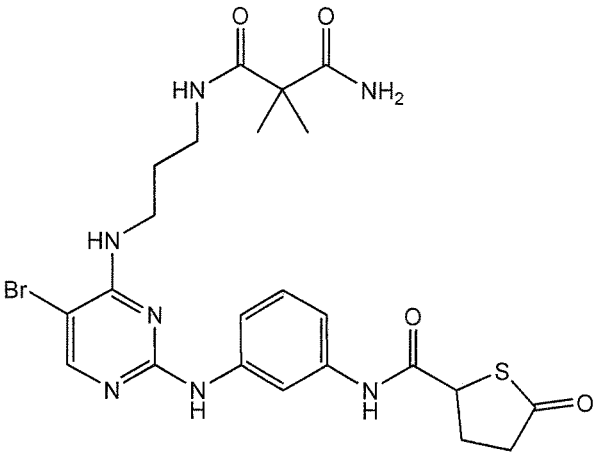

XI-18



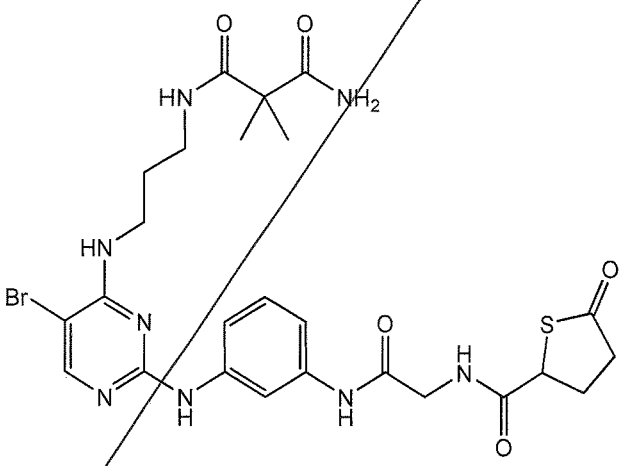
XI-19



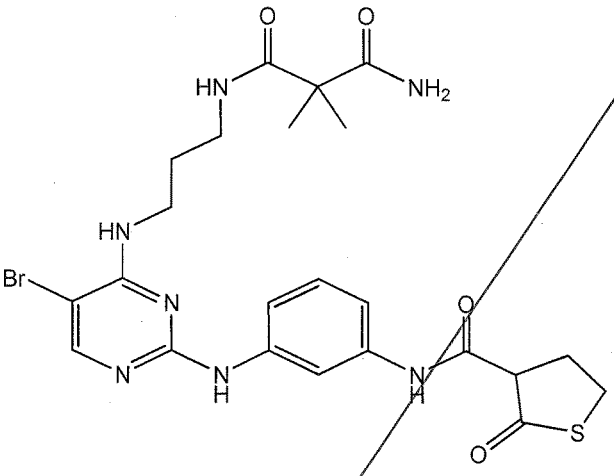
XI-20



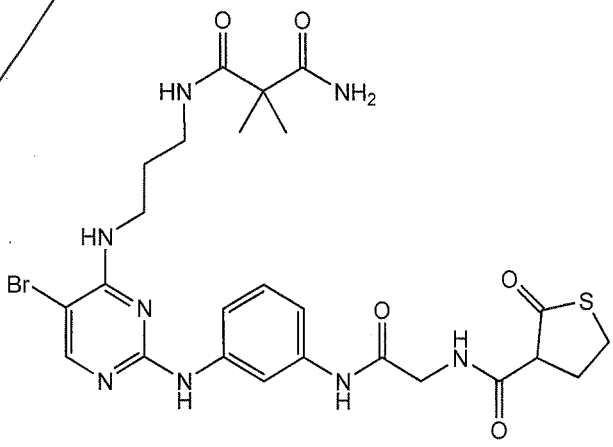
**XI-21**



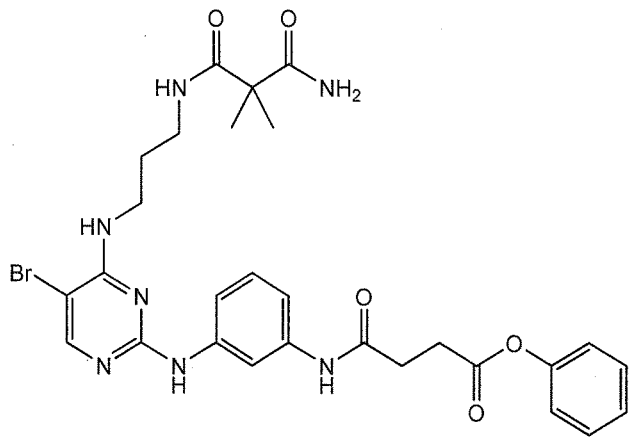
**XI-22**



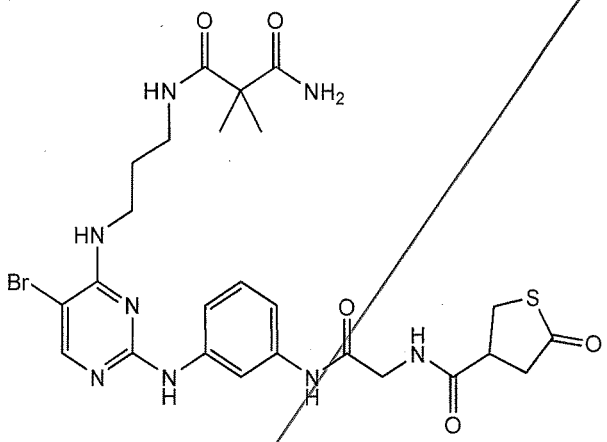
**XI-23**



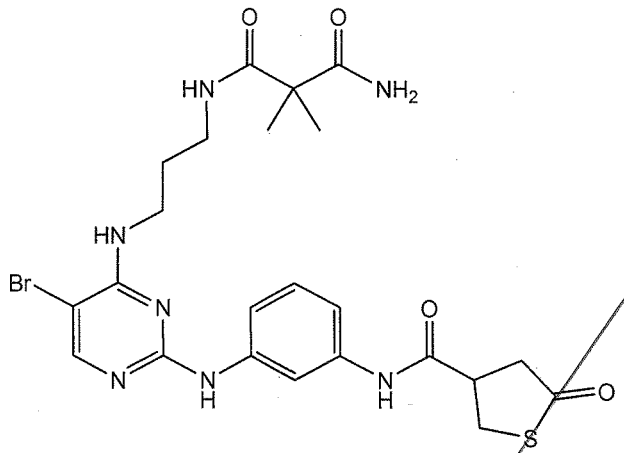
**XI-24**



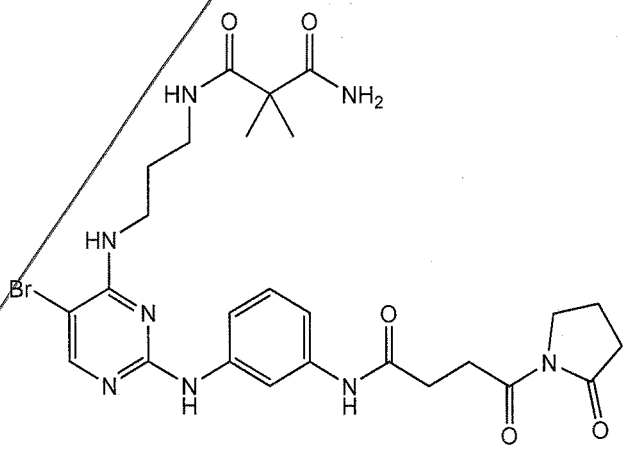
**XI-25**



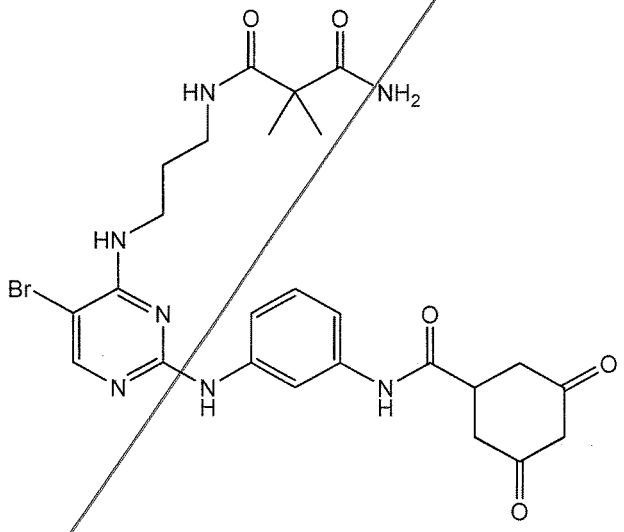
**XI-26**

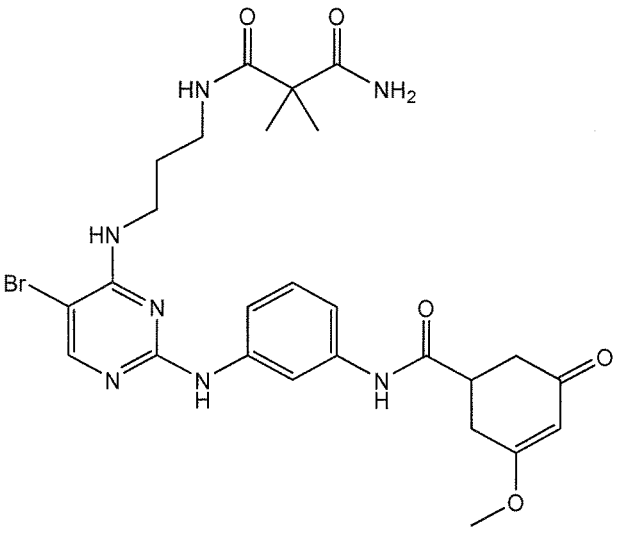


**XI-27**

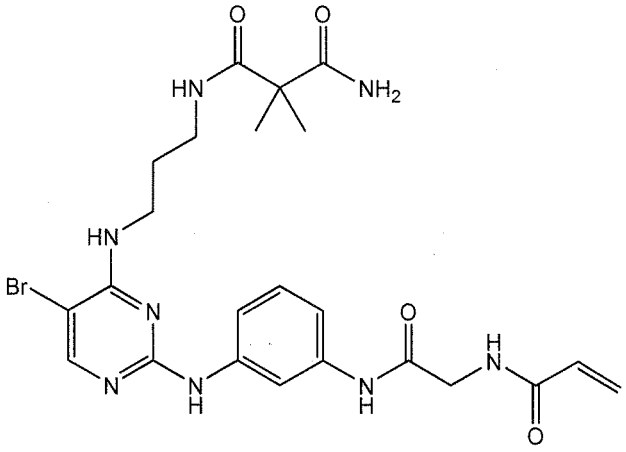


**XI-28**

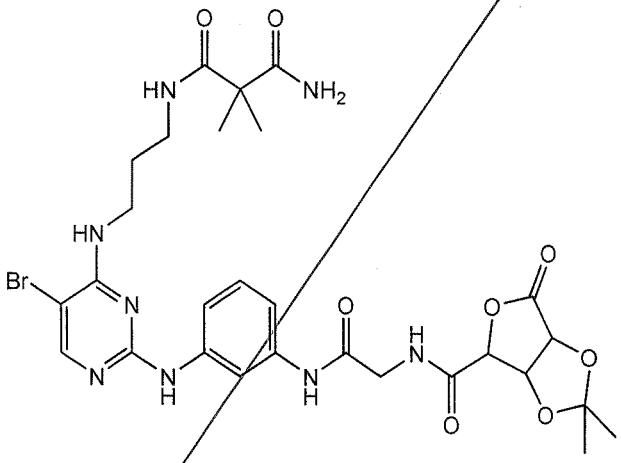




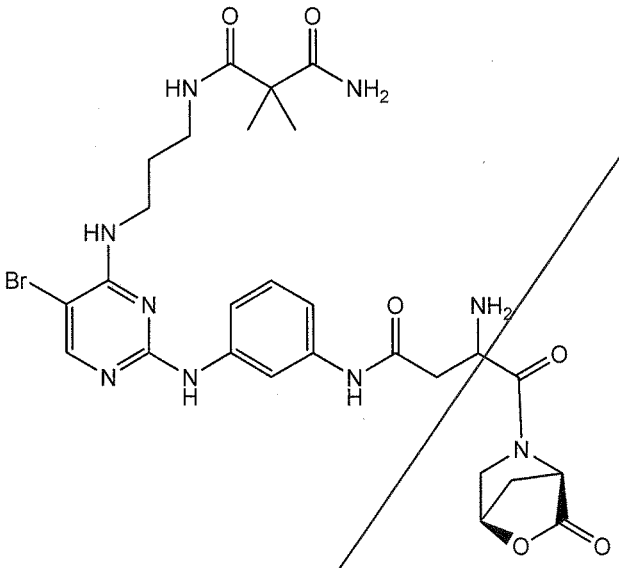
**XI-29**



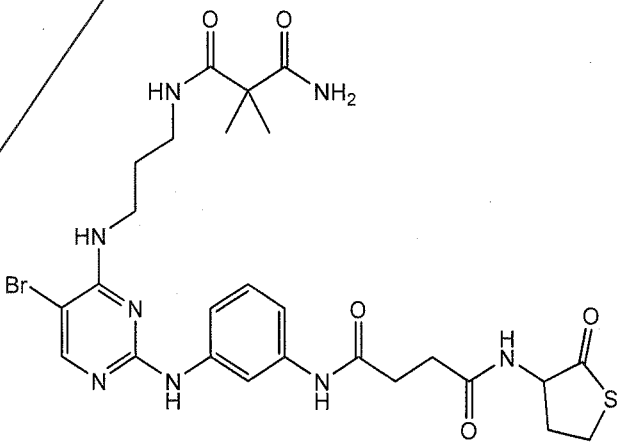
**XI-30**



**XI-31**

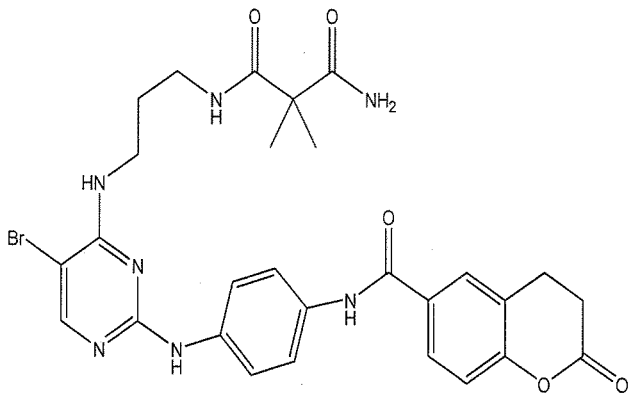


**XI-32**

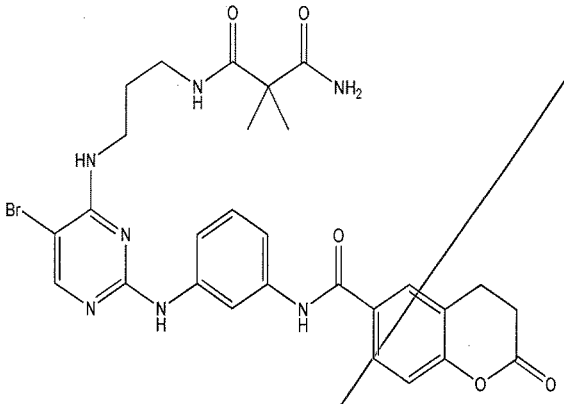


**XI-33**

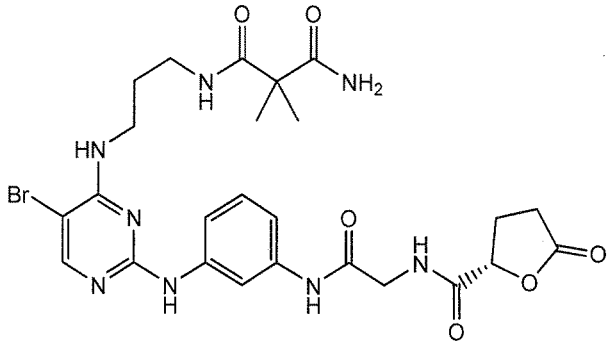
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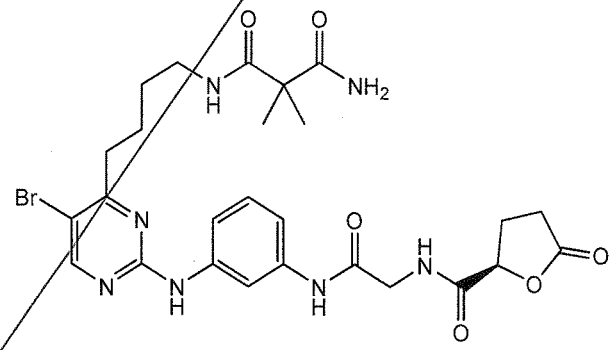
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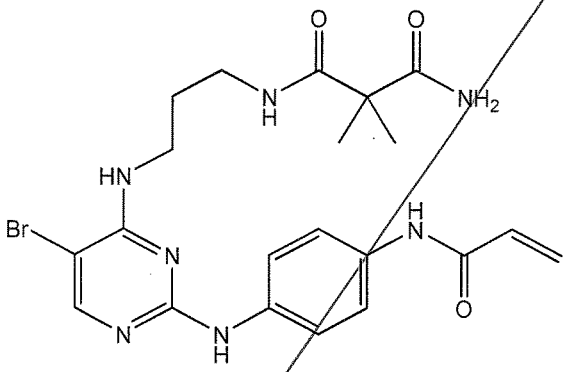
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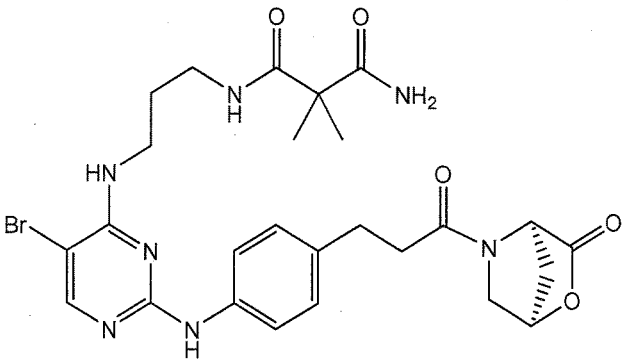
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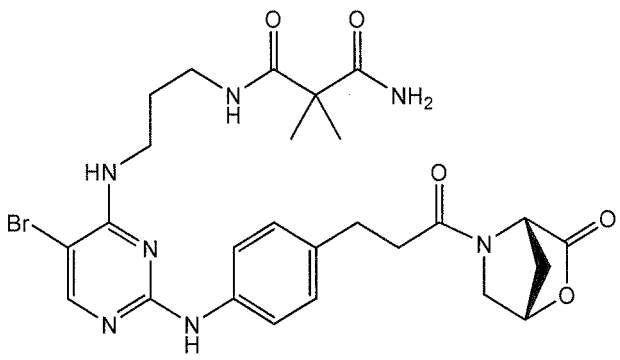
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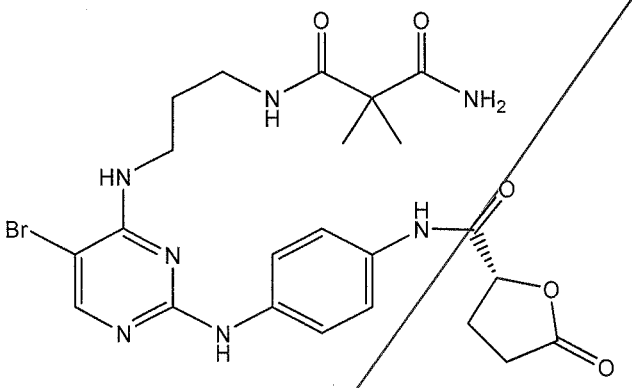
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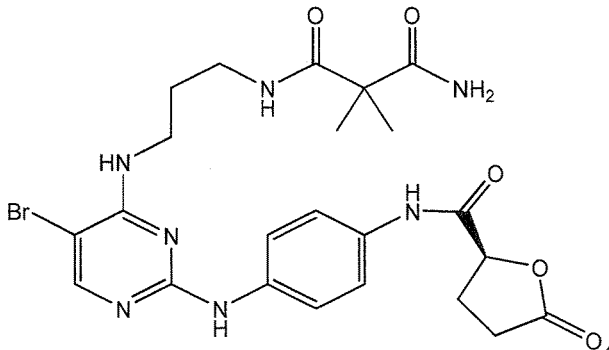
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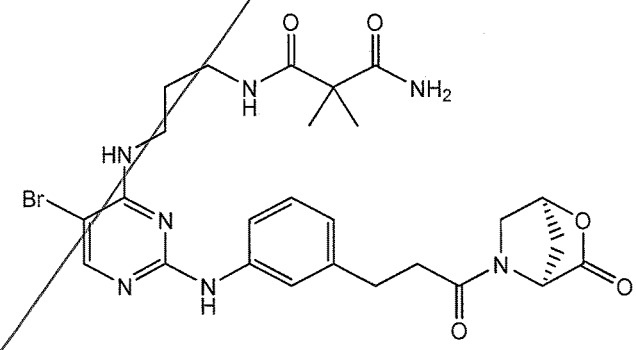
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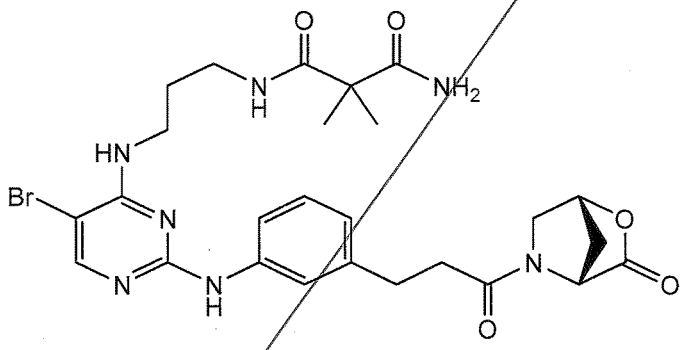
**XI-42**



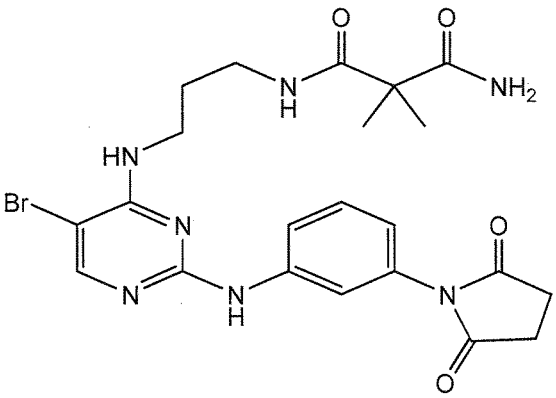
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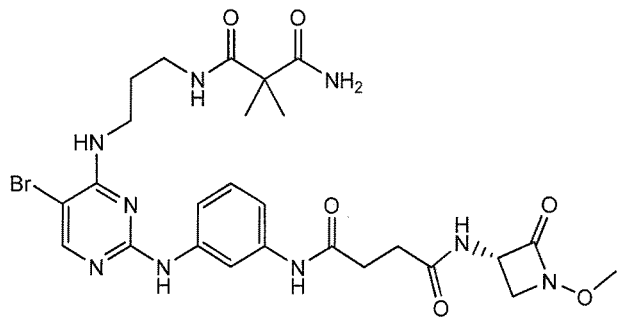
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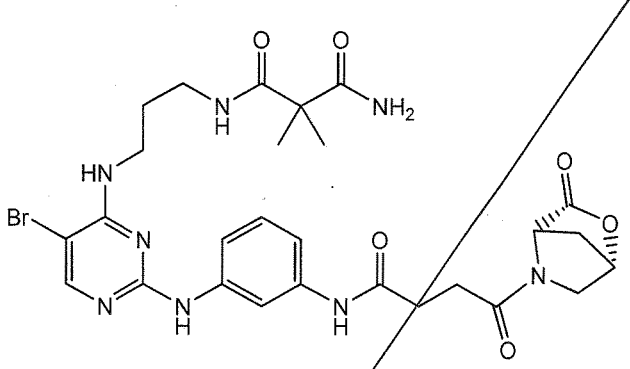
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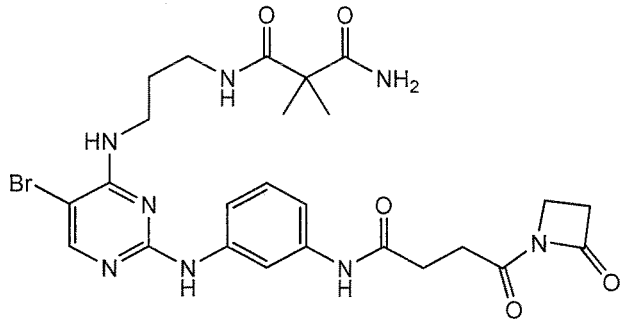
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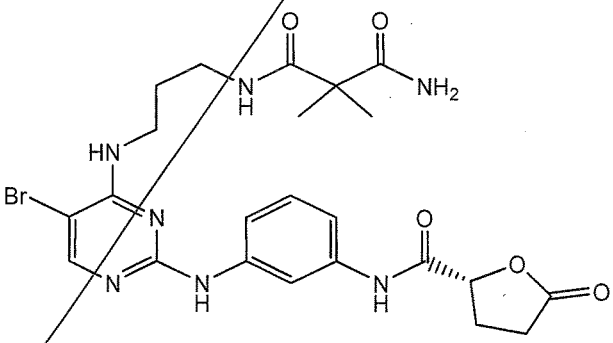
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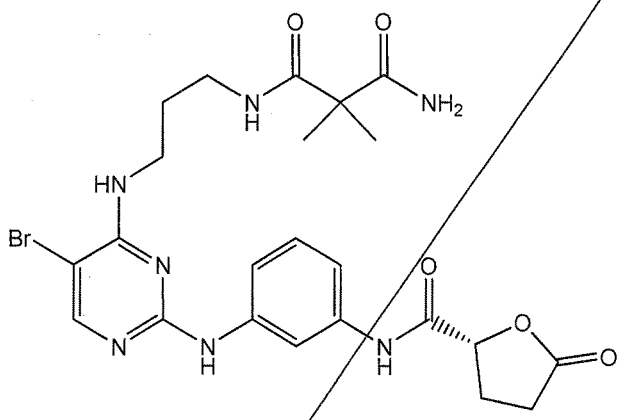
**XI-48**



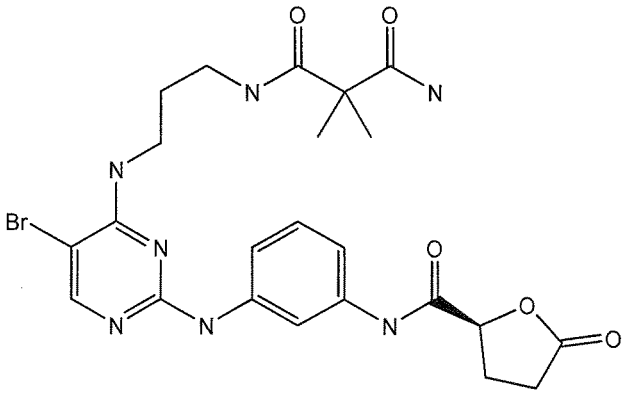
**XI-49**



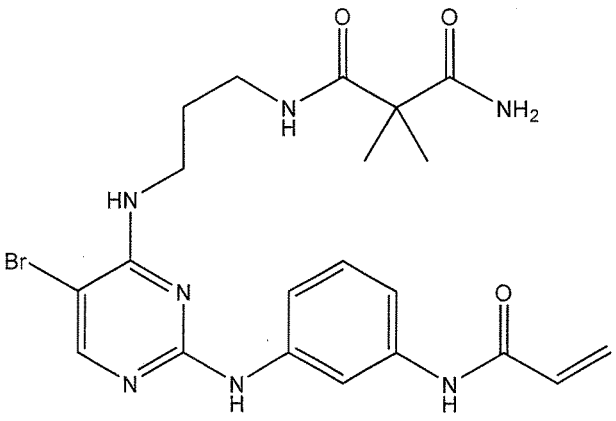
**XI-50**



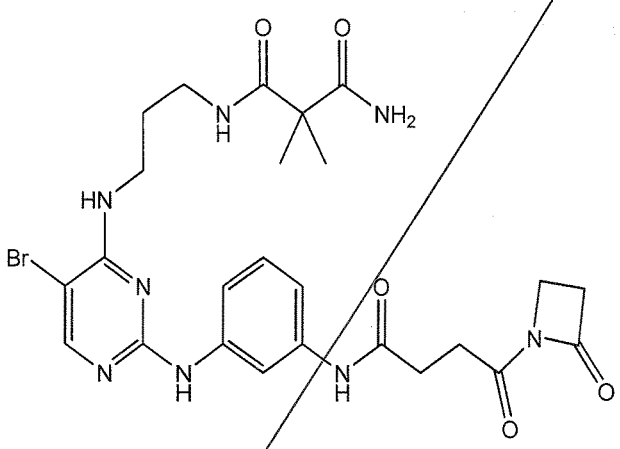
**XI-51**



**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.