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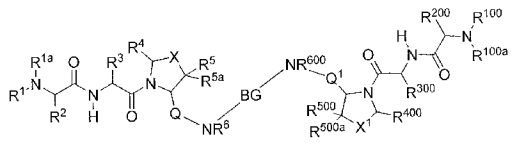

1.1A

(57) Abstract: A compound of Formula 1.1A: 1.1A or salt thereof, as well as methods of making compounds of Formula 1.1A, methods of using compounds of Formula 1.1A to treat proliferative disorders such as cancer, and related compounds, composition, and methods.

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BRIDGED SECONDARY AMINES AND USE THEREOF AS IAP BIR DOMAIN BINDING COMPOUNDS

BACKGROUND OF THE INVENTION

[0001] Apoptosis, or programmed cell death, typically occurs in the normal development and maintenance of healthy tissues in multicellular organisms. It is a complex process which results in the removal of damaged, diseased or developmentally redundant cells, in the absence of signs of inflammation or necrosis.

[0002] Intrinsic apoptotic pathways are known to be dysregulated in cancer and lymphoproliferative syndromes, as well as autoimmune disorders such as multiple sclerosis and rheumatoid arthritis, as well as in neurodegenerative diseases and inflammation. Additionally, alterations in a host apoptotic response have been described in the development or maintenance of viral and bacterial infections.

[0003] Apoptosis is the ordered dismantling of cellular components leading to cell death, which occurs as a normal part of development, the maintenance of normal cellular homeostasis, or as a consequence of injurious stimuli such as chemotherapy and radiation. Cancer cells, however, gain the ability to overcome or circumvent apoptosis and continue with inappropriate proliferation despite strong pro-apoptotic signals such as hypoxia, endogenous cytokines, radiation treatments and chemotherapy. In autoimmune disease, pathogenic effector cells can become resistant to normal apoptotic cues. Resistance results from numerous mechanisms, including alterations in the apoptotic machinery due to increased activity of anti-apoptotic pathways or expression of anti-apoptotic genes. Thus, approaches that reduce the threshold of apoptotic induction in cancer cells by overcoming innate resistance mechanisms may be of significant clinical utility.

[0004] The caspases are a family of proteolytic enzymes from the class of cysteine proteases which are known to initiate and execute apoptosis. In normal cells, the caspases are present as inactive zymogens, which are catalytically activated following external signals, for example those resulting from ligand driven Death Receptor activation, such as cytokines or immunological agents, or by release of mitochondrial factors, such as cytochrome C following genotoxic, chemotoxic, or radiation-induced cellular injury. The Inhibitors of Apoptosis Proteins

(IAPs) constitute a family of proteins which are capable of binding to and inhibiting the caspases, thereby suppressing cellular apoptosis. Because of their central role in regulating caspase activity, the IAPs are capable of inhibiting programmed cell death from a wide variety of triggers, which include loss of homeostatic, or endogenous cellular growth control mechanisms, as well as chemotherapeutic drugs and irradiation.

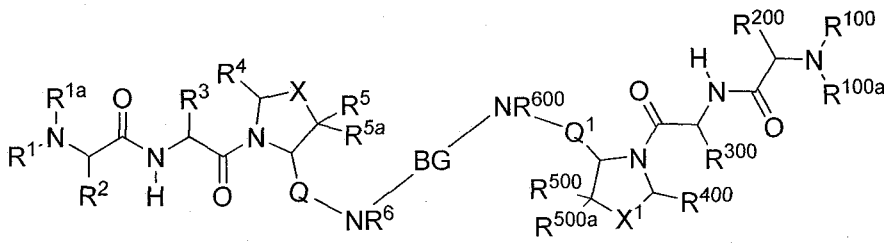
[0005] The IAPs contain one to three homologous structural domains known as baculovirus IAP repeat (BIR) domains. They may also contain a RING zinc finger domain at the C-terminus, with a capability of inducing ubiquitinylation of IAP-binding molecules via its E3 ligase function. The human IAPs, XIAP, HIAP1 (also referred to as cIAP2), and HIAP2 (cIAP1) each have three BIR domains, and a carboxy terminal RING zinc finger. Another IAP, NAIP, has three BIR domains (BIR1, BIR2 and BIR3), but no RING domain, whereas Livin, TsIAP and MLIAP have a single BIR domain and a RING domain. The X chromosome-linked inhibitor of apoptosis (XIAP) is an example of an IAP which can inhibit the initiator caspase, known as caspase-9, and the effector caspases, Caspase-3 and Caspase-7, by direct binding. It can also induce the removal of caspases through the ubiquitylation-mediated proteasome pathway via the E3 ligase activity of a RING zinc finger domain. It is via the BIR3 domain that XIAP binds to and inhibits caspase-9. The linker-BIR2 domain of XIAP inhibits the activity of caspases-3 and -7. The BIR domains have also been associated with the interactions of IAPs with tumor necrosis factor-receptor associated factor (TRAFs)-1 and -2, and to TAB1, as adaptor proteins effecting survival signaling through NFkB activation. The IAPs thus function as a direct brake on the apoptosis cascade, by preventing the action of, or inhibiting active caspases and by re-directing cellular signaling to a pro-survival mode.

[0006] Cancer cells and cells involved in autoimmune disease may avoid apoptosis by the sustained over-expression of one or more members of the IAP family of proteins. For example, IAP overexpression has been demonstrated to be prognostic of poor clinical outcome in multiple cancers, and decreased IAP expression through RNA antisense or siRNA strategies sensitizes tumor cells to a wide variety of apoptotic insults including chemotherapy, radiotherapy and death receptor ligands. For XIAP this is shown in cancers as diverse as leukemia and ovarian cancer. Over expression of HIAP1 and HIAP2 resulting from the frequent chromosome amplification of the 11q21-q23 region, which encompasses both, has been observed in a variety of malignancies, including medulloblastomas, renal cell carcinomas,

glioblastomas, and gastric carcinomas. Also, abnormally apoptotic resistant T-cells have been demonstrated in autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, idiopathic thrombocytopenic purpura, and alopecia areata. Other abnormally apoptotic resistant cells also have been linked to autoimmune disease, such as fibroblast-like synoviocytes in rheumatoid arthritis (RA) and keratinocytes in psoriasis. Thus, IAPs are valid therapeutic targets and compounds that inhibit their expression or function may have significant utility in the treatment of proliferative diseases associated with dysregulated apoptosis, including cancer and autoimmune diseases.

SUMMARY OF THE INVENTION

[0007] The invention provides a compound of Formula 1.1A:



1.1A

or a salt thereof,

wherein X is C_1-C_3 alkylene or heteroalkylene optionally substituted with one or more R^{11} substituents; or X is –C(O)-;

[0008] Q and Q^1 are independently

–CH_2–,

–CH_2CH_2–,

–CH(C_1–C_6 alkyl)–,

–CH(C_3–C_7 cycloalkyl)–,

–C_3–C_7 cycloalkyl–,

–CH(C_1–C_6 alkyl–C_3–C_7 cycloalkyl)–; *or*

–C(O) –

[0009] BG is

–L–;

$-Y^1-L-Y^{100}-$;

$-L^1-Z-L^{100}-$; or

$-Y^1-L^1-Z-L^{100}-Y^{100}-$.

wherein Y^1 and Y^{100} are equal or Y^1 and Y^{100} are different, L^1 and L^{100} are equal or L^1 and L^{100} are different;

[0010] Y is O, NR^8, or S;

[0011] Y^1 and Y^{100} are independently

$-C(O)-$,

$-S(O)_2-$,

$-C(O)N(R^8)-$,or

$-C(O)O-$,

[0012] L, L^1 and L^{100} are :

$-C_1$-C_{12} alkyl–,

$-C_2$-C_{12} alkenyl–,

$-C_2-C_{12}$ alkynyl–,

$-C_3$-C_7 cycloalkyl–,

$-C_3$-C_7 cycloalkenyl–,

–aryl–,

–biphenyl–,

–heteroaryl–,

–biheteroaryl–,

–heterocyclyl–,

$-C_1$-C_6 alkyl–(C_2-C_6 alkenyl)– C_1-C_6 alkyl–,

$-C_1$-C_6 alkyl–(C_2-C_4 alkynyl)–C_1-C_6 alkyl–,

$-C_1$-C_6 alkyl–(C_3-C_7 cycloalkyl)–C_1-C_6 alkyl–,

$-C_1$-C_6 alkyl–aryl–C_1-C_6 alkyl–,

$-C_1$-C_6 alkyl–biphenyl–C_1-C_6 alkyl–,

$-C_1$-C_6 alkyl–heteroaryl–C_1-C_6 alkyl–,

$-C_1$-C_6 alkyl–biheteroaryl–C_1-C_6 alkyl–,

$-C_1$-C_6 alkyl heterocycyl–C_1-C_6 alkyl–,

–C_1-C_6 alkyl-Y-C_1-C_6 alkyl–; or

–C_1-C_6 alkyl–Z– C_1-C_6 alkyl–.

wherein the alkyl, alkenyl, alkynyl, cycloalkyenyl and cycloalkyl are optionally substituted with one or more R^7 substituents; and the aryl, heteroaryl, biphenyl and heterocyclyl are optionally substituted with one or more R^{11} substituents;

[0013] Z is :

–C(O)–,

–$S(O)_2$–,

–$N(R^8)C(O)$–,

–$C(O)N(R^8)$–,

–$OC(O)N(R^8)$–,

–$S(O)_2N(R^8)$–,

–$N(R^8)CON(R^8)$–,

–$N(R^8)$-C_1-C_{12}-alkyl-$N(R^8)$–,

–$N(R^8)$-C_3-C_{12}-cycloalkyl-$N(R^8)$–,

–$N(R^8)$-C(O)C(O)-$N(R^8)$–,

–$N(R^8)$-C(O)-C_1-C_{12}-alkyl-C(O)-$N(R^8)$–,

-$N(R^8)$-C(O)-C_3-C_{12}-cycloalkyl-C(O)-$N(R^8)$–

–$N(R^8)$-C(O)-aryl-C(O)-$N(R^8)$–,

–$N(R^8)$-C(O)-aryl-O-aryl-C(O)-$N(R^8)$–,

–$N(R^8)$-C(O)-heteroaryl-C(O)-$N(R^8)$–,

–$N(R^8)$-C(O)-biheteroaryl-C(O)-$N(R^8)$–,

–$N(R^8)$-C(O)-biphenyl-C(O)-$N(R^8)$–,

–$N(R^8)$-$S(O)_2$-C_1-C_{12}-alkyl-$S(O)_2$-$N(R^8)$–,

–$N(R^8)$-$S(O)_2$-aryl-$S(O)_2$-$N(R^8)$–,

–$N(R^8)$-$S(O)_2$-heteroaryl-$S(O)_2$-$N(R^8)$–,

–$N(R^8)$-$S(O)_2$-biheteroaryl-$S(O)_2$-$N(R^8)$–,

–$N(R^8)$-$S(O)_2$-biphenyl-$S(O)_2$-$N(R^8)$–,

–$N(R^8)$-C_1-C_{12}-alkyl-$N(R^8)$–,

–$N(R^8)$-aryl-$N(R^8)$–,

–$N(R^8)$-heteroaryl-$N(R^8)$–,

–$N(R^8)$-biheteroaryl-$N(R^8)$–, or

–N(R^8)-biphenyl-N(R^8)–;

wherein the alkyl and cycloalkyl are optionally substituted with one or more R^7 substituents, and the aryl, heteroaryl and heterocyclyl are optionally substituted with one or more R^{11} substituents;

[0014] R^1 ,R^{100} , R^{1a} and R^{100a} are independently

H, or

C_1–C_6 alkyl optionally substituted with one or more R^7 substituents;

[0015] R^2 and R^{200} are independently

H,

C_1–C_6 alkyl optionally substituted with one or more R^7 substituents, or

C_3-C_7 cycloalkyl optionally substituted with one or more R^7 substituents;

[0016] R^3 and R^{300} are independently

cycloalkyl,

cycloalkenyl,

aryl,

biphenyl,

heteroaryl,

heterocyclyl, or

heterobicyclyl,

wherein the cycloalkyl and cycloalkenyl are optionally substituted with one or more R^7 substituents; and the aryl, heteroaryl, heterocyclyl, and heterobicyclyl are optionally substituted with one or more R^{11} substituents;

[0017] R^4, R^{400}, R^5, R^{5a}, R^{500} and R^{500a} are each independently :

H

halogen,

NO_2,

-CN,

haloalkyl,

C_1–C_6 alkyl,
C_2-C_6 alkenyl,
C_2-C_4 alkynyl,
C_3–C_7 cycloalkyl,
C_3-C_7 cycloalkenyl,
aryl,
biphenyl,
heteroaryl,
heterocyclyl,
heterobicyclyl,
-OR^8,
-$S(O)_m R^8$,
-NR^9R^{10} ,
-$NR^9S(O)_2R^{12}$,
-$C(O)O_nR^8$,
-$CONR^9R^{10}$,
-$S(O)_2NR^9R^{10}$,
-$OC(O)R^8$,
-$OC(O)Y$-R^{12},
-$SC(O)R^8$, or
-$NC(Y)$ R^9R^{10},

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl are optionally substituted with one or more R^7 substitutents; the aryl, heteroaryl, heterocyclyl, and heterobicyclyl are optionally substituted with one or more R^{11} substituents; R^5 and R^{5a} may together be a carbonyl oxygen atom; and R^{500} and R^{500a} may together be a carbonyl oxygen atom;

[0018] R^6 and R^{600} are each independently
H,
haloalkyl,
C_1–C_6 alkyl,
C_2-C_6 alkenyl,
C_2-C_4 alkynyl,
C_3–C_7 cycloalkyl,

C_3-C_7 cycloalkenyl,
aryl,
biphenyl,
heteroaryl,
heterocyclyl,
heterobicyclyl,
$-C(O)(O)_n-R^{12}$,
$-C(=Y)NR^9R^{10}$, or
$-S(O)_2-R^{12}$,

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl are optionally substituted with one or more R^7 substitutents; and the aryl, heteroaryl, heterocyclyl, and heterobicyclyl are optionally substituted with one or more R^{11} substituents;

[0019] R^7 is
halogen,
NO_2,
CN,
haloalkyl,
C_1–C_6 alkyl,
C_2-C_6 alkenyl,
C_2-C_4 alkynyl,
C_3–C_7 cycloalkyl,
C_3-C_7 cycloalkenyl,
aryl,
biphenyl,
heteroaryl,
heterocyclyl,
heterobicyclyl,
$-OR^8$,
$-S(O)_m R^8$,
$-NR^9R^{10}$,
$-NR^9S(O)_2R^{12}$,
$-C(O)O_nR^8$,

$-CONR^9R^{10}$,
$-S(O)_2NR^9R^{10}$,
$-OC(O)R^8$,
$-OC(O)Y-R^{12}$,
$-SC(O)R^8$, or
$-NC(Y)\ R^9R^{10}$.

wherein the aryl, heteroaryl, heterocyclyl, and heterobicyclyl are optionally substituted with one or more R^{11} substituents;

[0020] R^8 is

H,
haloalkyl,
C_1–C_6 alkyl,
C_2-C_6 alkenyl,
C_2-C_4 alkynyl,
C_3–C_7 cycloalkyl,
C_3-C_7 cycloalkenyl,
aryl,
biphenyl,
heteroaryl,
heterocyclyl,
heterobicyclyl,
$-C(Y)NR^9R^{10}$,
$-C_1$-C_6 alkyl-C_2-C_4 alkenyl, or
$-C_1$-C_6 alkyl-C_2-C_4 alkynyl,

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl are optionally substituted with one or more R^7 substituents; and the aryl, heteroaryl, heterocyclyl, and heterobicyclyl are optionally substituted with one or more R^{11} substituents;

[0021] R^9 and R^{10} are each independently

H,
haloalkyl,
C_1–C_6 alkyl,

C_2-C_6 alkenyl,
C_2-C_4 alkynyl,
C_3–C_7 cycloalkyl,
C_3-C_7 cycloalkenyl,
aryl,
biphenyl,
heteroaryl,
heterocyclyl,
heterobicyclyl,
-C(O)R^{12},
-C(O)YR^{12}, or
-S(O)$_2$$R^{12}$.

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl are optionally substituted with one or more R^7 substituents; and the aryl, heteroaryl, heterocyclyl, and heterobicyclyl are optionally substituted with one or more R^{11} substituents;

[0022] or R^9 and R^{10} together with the nitrogen atom to which they are bonded form a five, six or seven membered heterocyclic ring optionally substituted with one or more R^7 substituents;

[0023] R^{11} is
halogen,
-NO_2,
-CN,
-B(OR^{13})(OR^{14}),
C_1-C_6 alkyl,
C_2-C_6 alkenyl,
C_2-C_4 alkynyl,
C_3-C_7 cycloalkyl,
C_3-C_7 cycloalkenyl,
haloalkyl,
-OR^8,
-NR^9R^{10},

$-SR^8$,
$-C(O)O_nR^8$,
$-S(O)_mR^8$,
$-CONR^9R^{10}$,
$-S(O)_2NR^9R^{10}$,
aryl,
biphenyl,
heteroaryl,
heterocyclyl, or
heterobicyclyl.

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl are optionally substituted with one or more R^7 substituents;

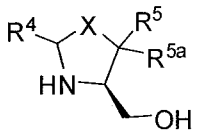
[0024] R^{12} is
haloalkyl,
C_1–C_6 alkyl,
C_2-C_6 alkenyl,
C_2-C_4 alkynyl,
C_3–C_7 cycloalkyl,
C_3-C_7 cycloalkenyl,
aryl,
biphenyl,
heteroaryl,
heterocyclyl, or
heterobicyclyl.

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl are optionally substituted with one or more R^7 substituents; and the aryl, heteroaryl, heterocyclyl, and heterobicyclyl are optionally substituted with one or more R^{11} substituents;

[0025] and R^{13} and R^{14} are each independently
H, or
C_1-C_6 alkyl,

or R^{13} and R^{14} are combined to form a ring system.

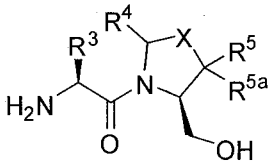
[0026] In another aspect of the present invention, there is provided compounds useful as intermediates in the preparation of compounds of Formula 1.1A. In one aspect, there is provided an compound of Formula 2:



2

wherein R^4, R^5, R^{5a} and X are as defined herein.

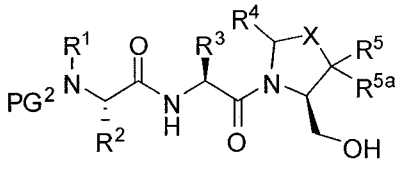
[0027] In another aspect of the present invention, there is provided a compound of Formula 3:



3

wherein R^3, R^4, R^5, R^{5a} and X are as defined herein.

[0028] In another aspect of the present invention, there is provided a compound of Formula 4:

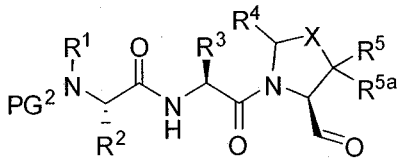


4

wherein R^1, R^2, R^3, R^4, R^5, R^{5a} and X are as defined herein and PG^2 is a suitable protective group, such as, but not limited to Boc, Fmoc, CBz and Bn.

[0029] Similarly, as used herein PG^2 , PG^3 ,PG^4 is a suitable protective group, such as, but not limited to Boc, Fmoc, CBz and Bn.

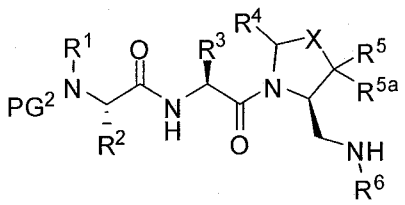
[0030] In another aspect of the present invention, there is provided a compound of Formula 5:



5

wherein PG^2, R^1, R^2, R^3, R^4, R^5, R^{5a} and X are as defined herein.

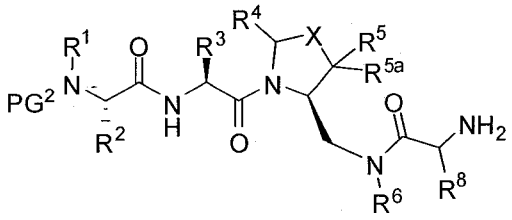
[0031] In another aspect of the present invention, there is provided a compound of Formula 6:



6

wherein PG^2, R^1, R^2, R^3, R^4, R^5, R^{5a}, X, and R^6 are as defined herein.

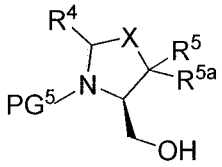
[0032] In another aspect of the present invention, there is provided a compound of Formula 7:



7

wherein PG^2, R^1, R^2, R^3, R^4, R^5, R^{5a}, X, R^6 and R^8 are as defined herein.

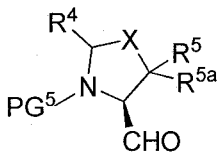
[0033] In another aspect of the present invention, there is provided a compound of Formula 16:



16

wherein PG^5, R^4, R^5, R^{5a} and X are as defined herein.

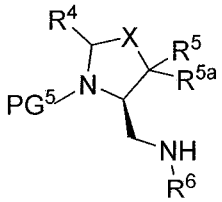
[0034] In another aspect of the present invention, there is provided a compound of Formula 17:



17

wherein PG^5, R^4, R^5, R^{5a} and X are as defined herein.

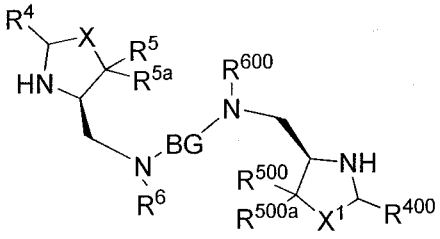
[0035] In another aspect of the present invention, there is provided a compound of Formula 18:



18

wherein PG^5, R^4, R^5, R^{5a}, R^6 and X are as defined herein.

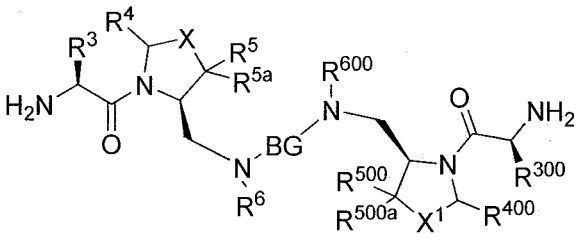
[0036] In another aspect of the present invention, there is provided a compound of Formula 19:



19

wherein R^4, R^{400}, R^5, R^{500}, R^{5a}, R^{500a}, R^6, R^{600}, X, X^1 and BG are as defined herein.

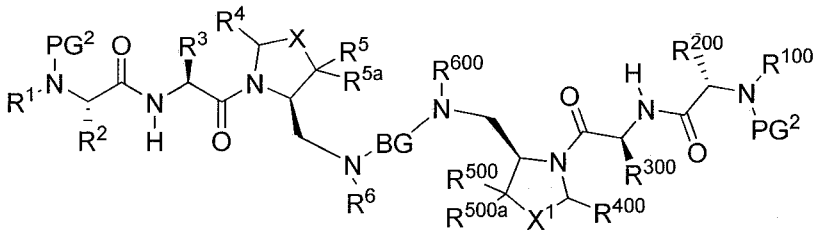
[0037] In another aspect of the present invention, there is provided a compound of Formula 24:



24

wherein R^3, R^{300}, R^4, R^{400}, R^5, R^{500}, R^{5a}, R^{500a}, R^6, R^{600}, X, X^1 and BG are as defined herein.

[0038] In another aspect of the present invention, there is provided a compound of Formula 25:

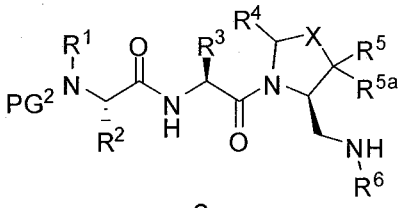


25

wherein PG^2, R^1, R^{100}, R^2, R^{200}, R^3, R^{300}, R^4, R^{400}, R^5, R^{500}, R^{5a}, R^{500a}, R^6, R^{600}, X, X^1 and BG are as defined herein.

[0039] In another aspect of the present invention, there is provided a process for producing a compound, the process comprising:

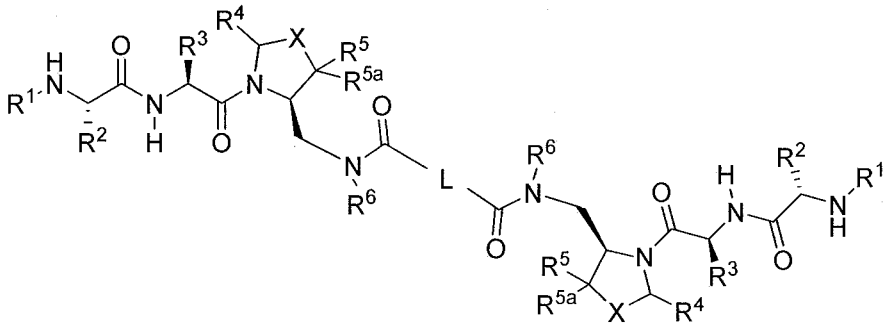
a) combining two compounds of Formula 6:



6

and LG-C(O)-L-C(O)-LG in a solvent with a base; and

b) deprotecting PG^2 to provide a compound of Formula 8:

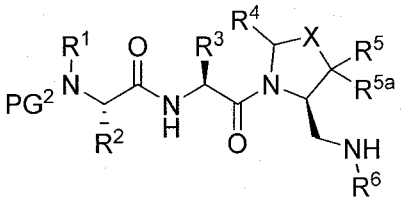


8

wherein R^1, R^2, R^3, R^4, R^5, R^{5a}, R^6, X, and L are as defined herein.

[0040] In another aspect of the present invention, there is provided a process for producing a compound, the process comprising:

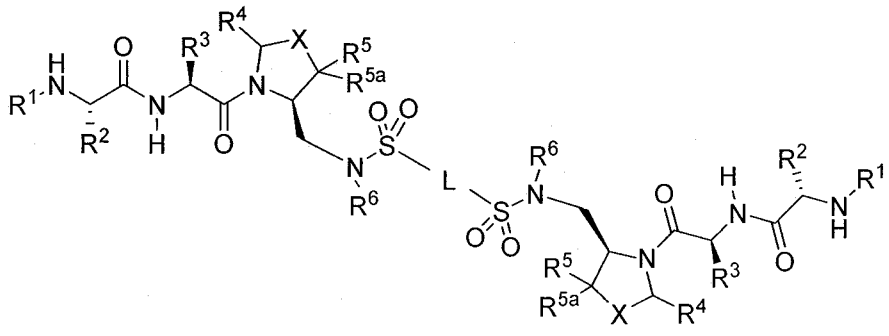
a) combining two compounds of Formula 6:



6

and LG-$S(O)_2$-L-$S(O)_2$-LG in a solvent with a base; and

b) deprotecting PG^2 to provide a compound of Formula 9:

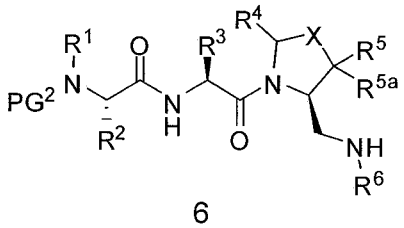


9

wherein R^1, R^2, R^3, R^4, R^5, R^{5a}, R^6, X and L are as defined herein.

[0041] In another aspect of the present invention, there is provided a process for producing a compound, the process comprising:

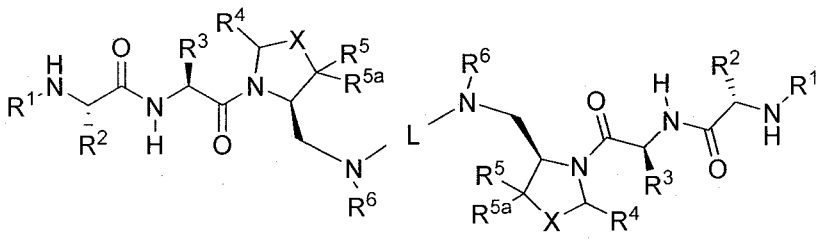
a) combining two compounds of Formula 6:



6

and LG-L-LG in a solvent with a base; and

b) deprotecting PG^2 to provide a compound of Formula 10:

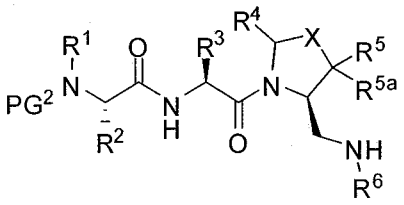


10

wherein R^1, R^2, R^3, R^4, R^5, R^{5a}, R^6, X and L are as defined herein.

[0042] In another aspect of the present invention, there is provided a process for producing a compound, the process comprising:

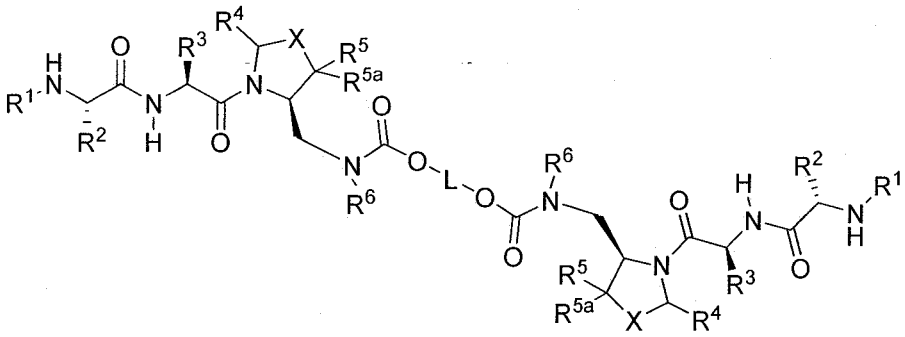
a) combining two compounds of Formula 6:



6

and LG-C(O)O-L-OC(O)-LG in a solvent with a base; and

b) deprotecting PG^2 to provide a compound of Formula 11:

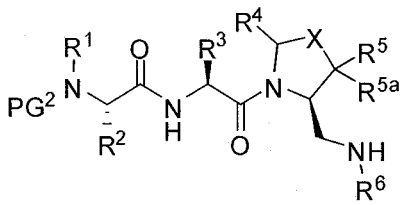


11

wherein R^1, R^2, R^3, R^4, R^5, R^{5a}, R^6, X, and L are as defined herein.

[0043] In another aspect of the present invention, there is provided a process for producing a compound, the process comprising:

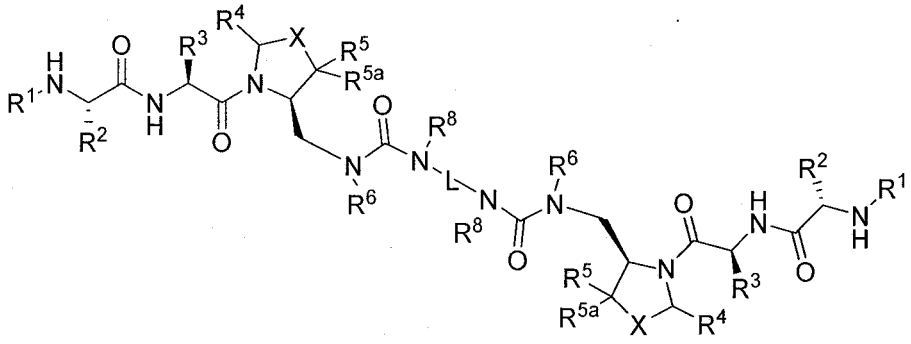
a) combining two compounds of Formula 6:



6

and LG-C(O)N(R^8)-L-(R^8)NC(O)-LG in a solvent with a base; and

b) deprotecting PG^2 to provide a compound of Formula 12:

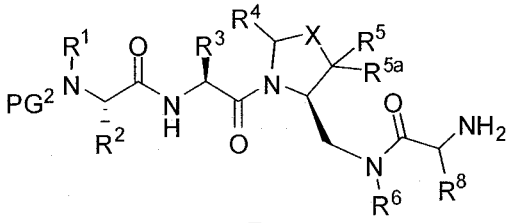


12

wherein R^1, R^2, R^3, R^4, R^5, R^{5a}, R^6, R^8, X and L are as defined herein.

[0044] In another aspect of the present invention, there is provided a process for producing a compound, the process comprising:

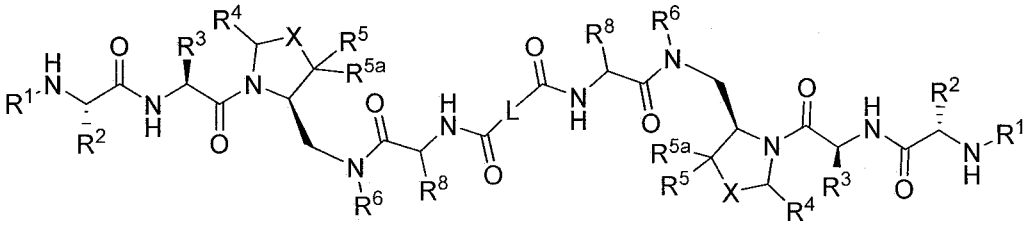
a) combining two compounds of Formula 7:



7

and LG-C(O)-L-C(O)-LG in a solvent with a base; and

b) deprotecting PG^2 to provide a compound of Formula 13:

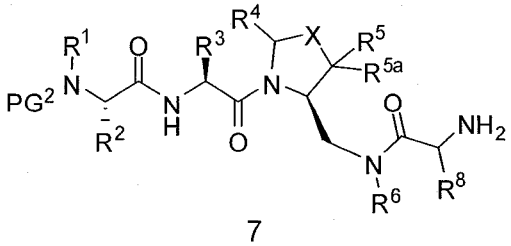


13

wherein R^1, R^2, R^3, R^4, R^5, R^{5a}, R^6, R^8, X, and L are as defined herein.

[0045] In another aspect of the present invention, there is provided a process for producing a compound, the process comprising:

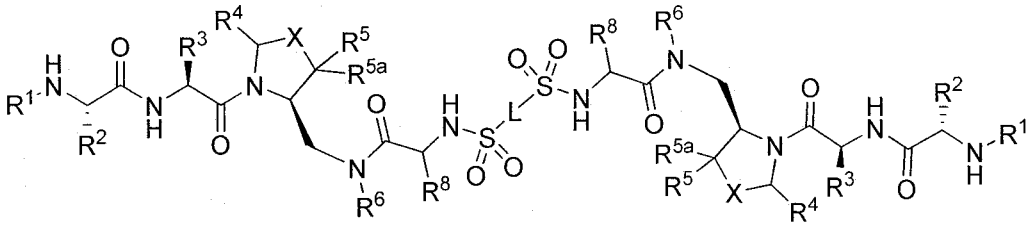
a) combining two compounds of Formula 7:



7

and LG-$S(O)_2$-L-$S(O)_2$-LG in a solvent with a base; and

b) deprotecting PG^2 to provide a compound of Formula 14:

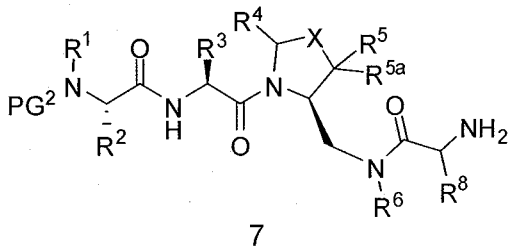


14

wherein R^1, R^2, R^3, R^4, R^5, R^{5a}, R^6, R^8, X, and L are as defined herein.

[0046] In another aspect of the present invention, there is provided a process for producing a compound, the process comprising:

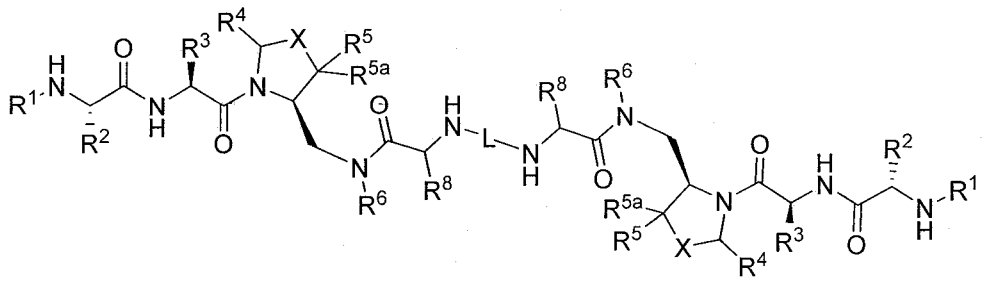
a) combining two compounds of Formula 7:



7

and LG-L-LG in a solvent with a base; and

b) deprotecting PG^2 to provide a compound of Formula 15:

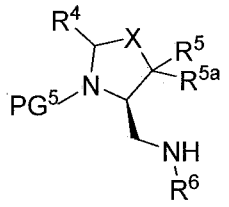


15

wherein R^1, R^2, R^3, R^4, R^5, R^{5a}, R^6, R^8, X, and L are as defined herein.

[0047] In another aspect of the present invention, there is provided a process for producing a compound, the process comprising:

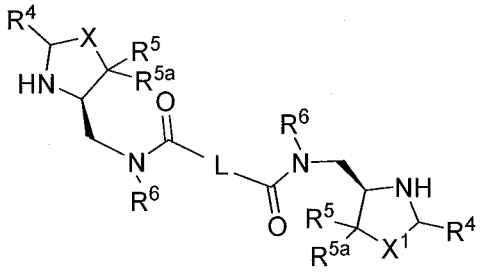
a) combining two compounds of Formula 18:



18

and LG-C(O)-L-C(O)-LG in a solvent with a base; and

b) deprotecting PG^5 to provide a compound of Formula 20:

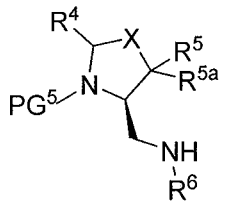


20

wherein R^4, R^5, R^{5a}, R^6, X and L are as defined herein.

[0048] In another aspect of the present invention, there is provided a process for producing a compound, the process comprising:

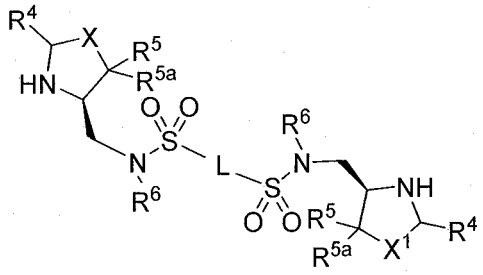
a) combining two compounds of Formula 18:



18

and LG-$S(O)_2$-L-$S(O)_2$-LG in a solvent with a base; and

b) deprotecting PG^5 to provide a compound of Formula 21:

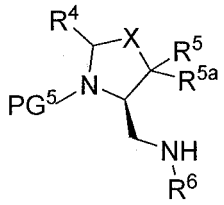


21

wherein R^4, R^5, R^{5a}, R^6, X, and L are as defined herein.

[0049] In another aspect of the present invention, there is provided a process for producing a compound, the process comprising:

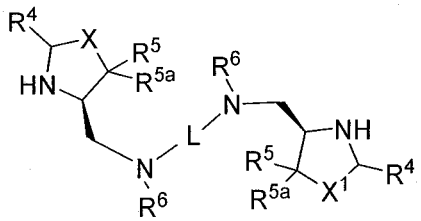
a) combining two compounds of Formula 18:



18

and LG-L-LG in a solvent with a base; and

b) deprotecting PG^5 to provide a compound of Formula 22:



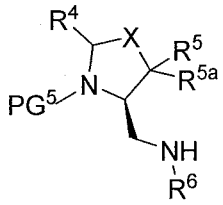
22

23

wherein R^4, R^5, R^{5a}, R^6, X and L are as defined herein.

[0050] In another aspect of the present invention, there is provided a process for producing a compound, the process comprising:

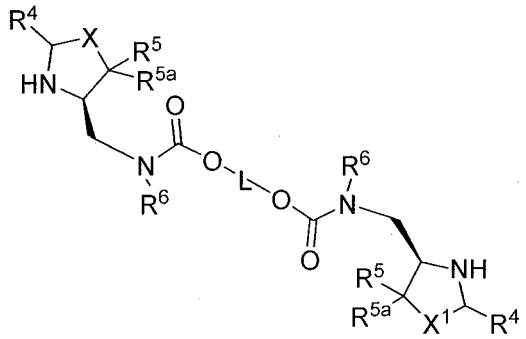
a) combining two compounds of Formula 18:



18

and LG-C(O)O-L-OC(O)-LG in a solvent with a base; and

b) deprotecting PG^5 to provide a compound of Formula 23:

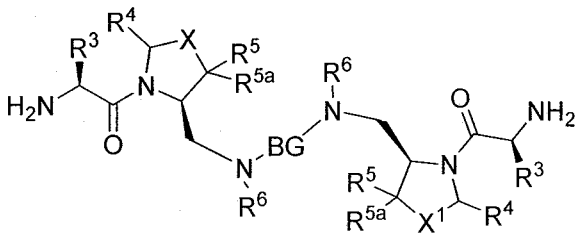


23

wherein R^4, R^5, R^{5a}, R^6, X, and L are as defined herein.

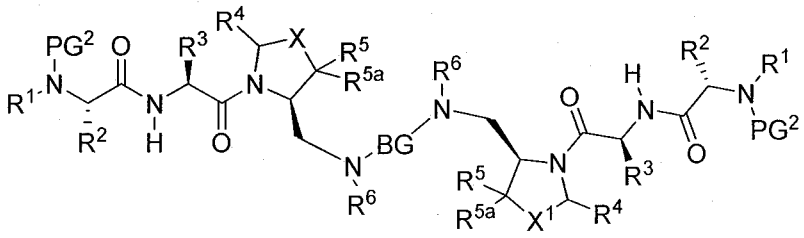
[0051] In another aspect of the present invention, there is provided a process for producing a compound, the process comprising:

a) combining a compound of Formula 24:



24

and $PG^2(R^1)NCH(R^2)CO_2H$ with the appropriate amino acid coupling agent(s) in a solvent with a base; to provide compound 25:



25

wherein PG^2, R^1, R^2, R^3, R^4, R^5, R^{5a}, R^6, X and BG are as defined herein.

[0052] In another aspect of the present invention, there is provided a method for the preparation of a pharmaceutically acceptable salt of a compound of Formula 1.1A (or Formula 1 or Formula 1A described herein). The method can comprise treating a compound of the invention with a pharmaceutically acceptable acid (e.g., 1 to 2 equivalents of a pharmaceutically acceptable acid), so as to form a pharmaceutically acceptable salt of a compound of Formula 1.1A (or Formula 1 or Formula 1A described herein). Alternatively, the method can comprise treating an intermediate compound of formula 25 with a pharmaceutically acceptable acid so as to provide a pharmaceutically acceptable salt of a compound of Formula 1.1A (or Formula 1 or Formula 1A described herein).

[0053] In another aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of Formula 1.1A (or Formula 1 or Formula 1A described herein) and a pharmaceutically acceptable carrier, diluent or excipient, as well as a method of

preparing same comprising combining a compound of Formula 1.1A (or Formula 1 or Formula 1A described herein) with a pharmaceutically acceptable carrier, diluents, or excipient.

[0054] In another aspect of the present invention, there is provided a method of treating a proliferative disorder or a disease state characterized by insufficient apoptosis, the method comprising: administering to a subject in need thereof, a therapeutically effective amount of a compound or pharmaceutical composition, as described above, so as to treat the proliferative disorder or disease state.

[0055] In another aspect of the present invention, there is provided a method of modulating IAP function, the method comprising: contacting a cell with a compound of the present invention so as to prevent binding of a BIR binding protein to an IAP BIR domain thereby modulating the IAP function.

[0056] In another aspect of the present invention, there is provided a probe, the probe being a compound of Formula 1.1A (or Formula 1 or Formula 1A described herein) labeled with a detectable label or an affinity tag. In other words, the probe comprises a compound of Formula 1.1A (or Formula 1 or Formula 1A described herein) and a detectable label.

[0057] In another aspect of the present invention, there is provided a method of identifying compounds that bind to an IAP BIR domain, the assay comprising:

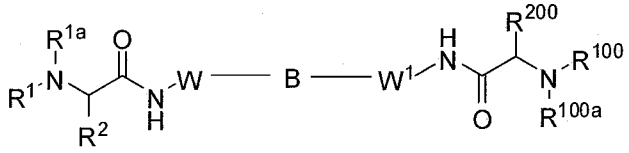
a) contacting an IAP BIR domain with a probe, as described herein, to form a probe:BIR domain complex, the probe being displaceable by a test compound;
b) measuring a signal from the probe so as to establish a reference level;
c) incubating the probe:BIR domain complex with the test compound;
d) measuring the signal from the probe; and
e) comparing the signal from step d) with the reference level, a modulation of the signal (e.g., an increase or decrease in the signal relative to the reference level) being an indication that the test compound binds to the BIR domain.

[0058] In another aspect of the present invention, there is provided a method of detecting loss of function or suppression of IAPs in vivo, the method comprising: a) administering to a subject, a therapeutically effective amount of a pharmaceutical composition, as defined above;

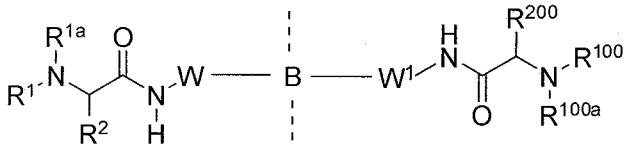
b) isolating a tissue sample from the subject; and c) detecting a loss of function or suppression of IAPs from the sample.

DETAILED DESCRIPTION OF THE INVENTION

[0059] Provided herein is a compound of Formula 1:



or a salt thereof. Compounds of Formula 1 also can be represented by the following formula, in which M1 and M2 represent independent BIR binding domains:

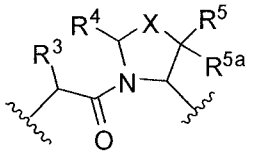
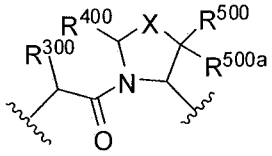


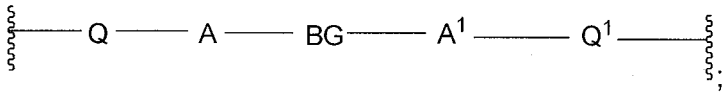
M1 M2

[0060] In one subset of compounds of Formula 1, M1 is the same as M2 and the dotted line denotes a line of symmetry. In another subset, M1 is different from M2.

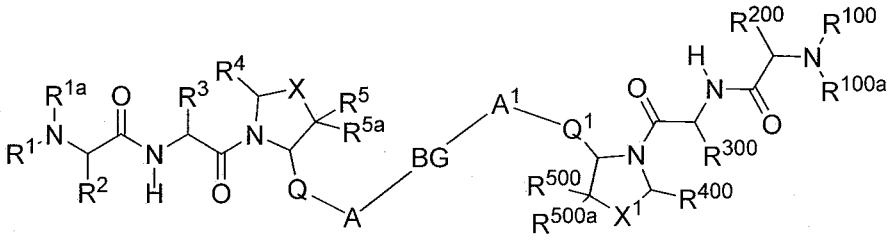
[0061] One skilled in the art will recognize that when M1 and M2 are the same, the R^1, R^{1a}, R^2, R^3, R^4, R^5, R^{5a}, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, Y^1, Q, and X substituents in M1 have the same meaning as the R^{100}, R^{100a}, R^{200}, R^{300}, R^{400}, R^{500}, R^{600}, R^{700}, R^{800}, R^{900}, R^{1000}, R^{1100}, R^{1200}, R^{1300}, R^{1400}, Y^{100}, Q^1, and X^1 substituents respectively in M2. When M1 and M2 are different, at least one of the aforesaid substituents is different in either of M1 or M2.

[0062] Alternatively the substituents in M1 can be defined as R^1, R^{1a}, R^2, R^3, R^4, R^5, R^{5a}, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, Y^1, Q, and X ,and those in M2 can be defined as R^{100}, R^{100a}, R^{200}, R^{300}, R^{400}, R^{500}, R^{600}, R^{700}, R^{800}, R^{900}, R^{1000}, R^{1100},R^{1200}, R^{1300}, R^{1400}, n, m, Y^{100}, Q^1, and X^1 respectively. In the case where M1 and M2 are the same, the R^1, R^{1a}, R^2, R^3, R^4, R^5, R^{5a}, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, Y^1, Q, and X substituents in M1 have the same meanings as R^{100}, R^{100a}, R^{200}, R^{300}, R^{400}, R^{500}, R^{600}, R^{700}, R^{800}, R^{900}, R^{1000}, R^{1100}, R^{1200},R^{1300}, R^{1400}, n, m, Y^{100}, Q^1, and X^1 respectively in M2. In the case where M1 and M2 are different, at least one of the aforesaid substituents is different.

[0063] According to Formula 1, W is  and W^1 is  , and B is

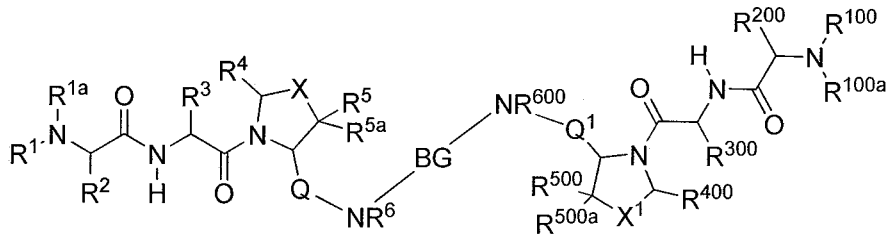


wherein A, A^1 are NR^6 and NR^{600}. When the structures for W, B, and/or A are included in Formula 1, Formula 1 also can be presented as Formula 1A or Formula 1.1A, and these Formulae are used interchangeably in describing the invention:



1A

or

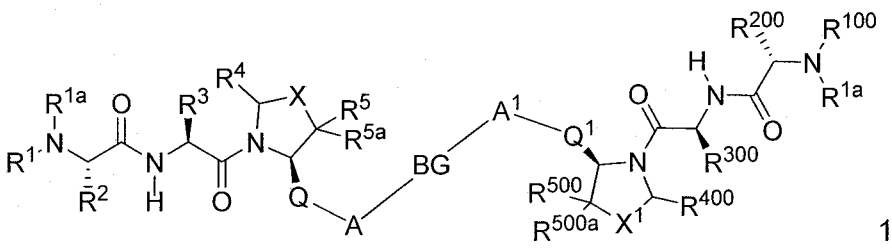


1.1A

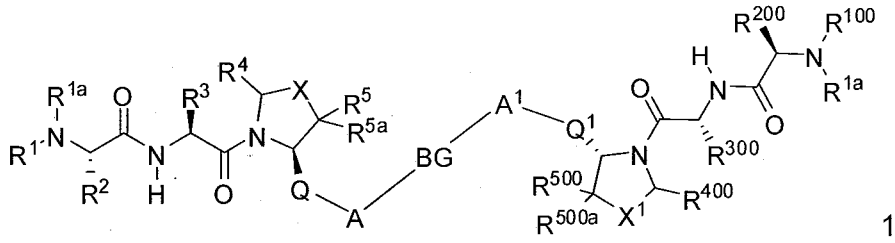
[0064] In a preferred aspect, the compounds of the present invention are useful as BIR domain binding compounds in mammalian IAPs. The following embodiments further illustrate compounds of Formula 1.

Core

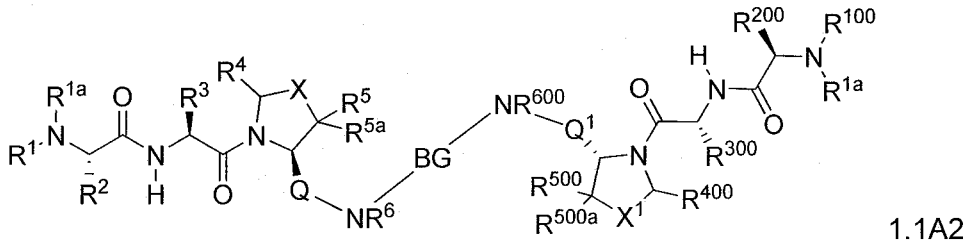
[0065] The compounds of Formula 1 can have any configuration about the core. For example, such compounds can include compounds of any of Formulas 1A1, 1A2, 1.1A2, and 1A3:



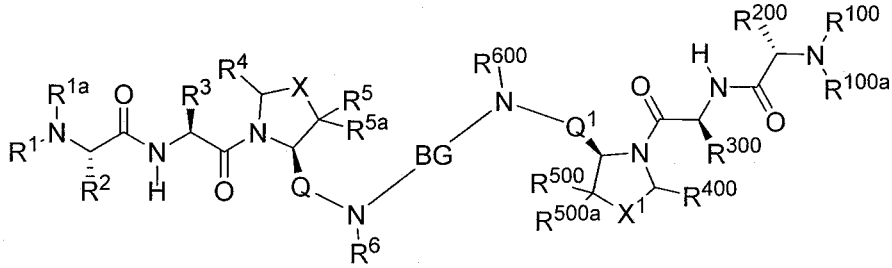
1A1



1A2



1.1A2



1A3

wherein R^1, R^{1a}, R^2, R^3, R^4, R^5, R^{5a}, R^6, Q, Q^1, BG, X, X^1, R^{100}, R^{100a}, R^{200}, R^{300}, R^{400}, R^{500}, R^{500a} and R^{600} are as defined herein.

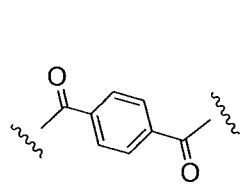
Q and Q^1:

[0066] Q and Q1 can be any moiety as previously defined herein, without limitation. In one subset of compounds of Formula 1, Q and Q^1 are both $-CH_2-$. In an alternative subset of compounds of Formula 1, Q and Q^1 are both –C(O)–.

[0067] Any and each individual definition of Q and Q^1 as set out herein may be combined with any and each individual definition of the other substituent groups of Formula 1 (e.g., R^1, R^{1a}, R^2, R^{100}, R^{100a}, R^{200}, etc.) as set out herein.

BG:

[0068] BG can be –L–; $-Y^1-L-Y^{100}-$; $-L^1-Z-L^{100}-$; or $-Y^1-L^1-Z-L^{100}-Y^{100}-$. Furthermore, Y^1, Y^{100}, L^1, L^{100}, and Z can each be any moiety as previously defined herein, without limitation. Thus, BG includes, for example, the following: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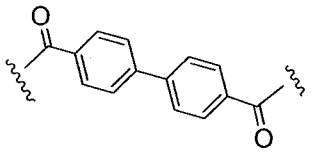
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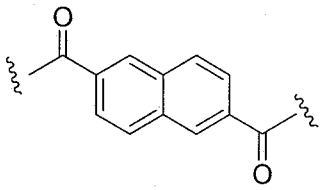
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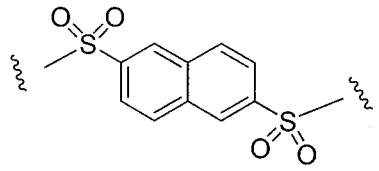
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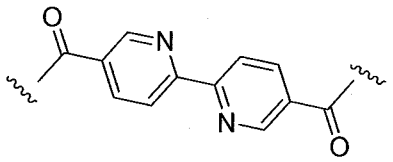
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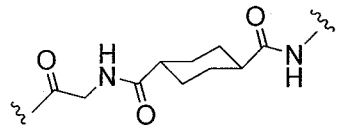
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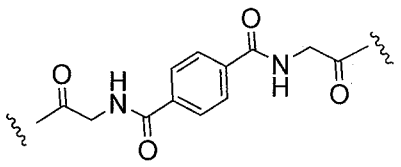
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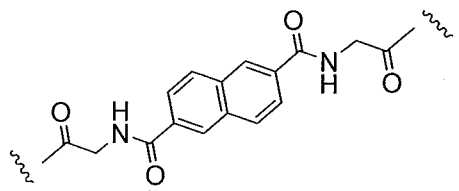
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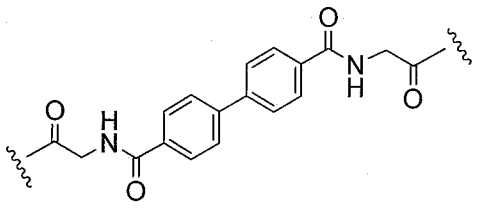
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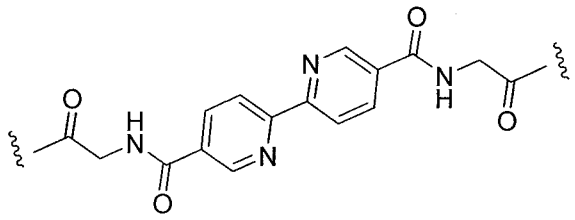
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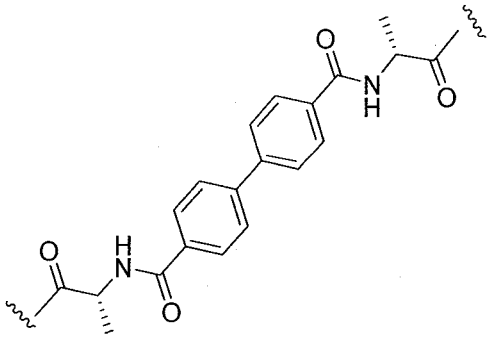
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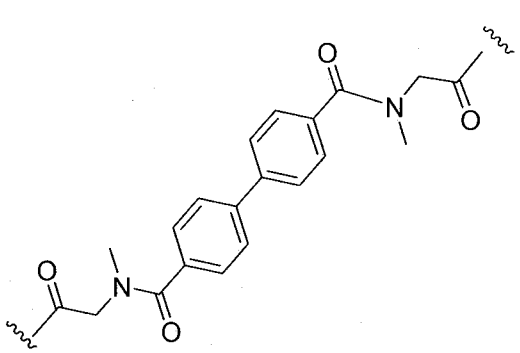
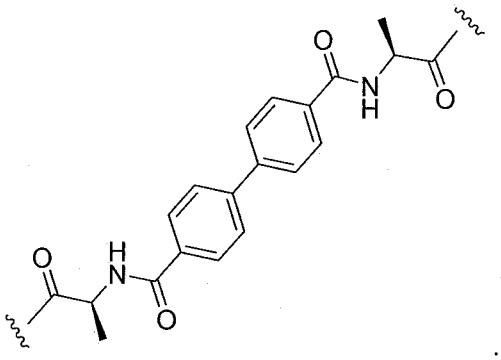
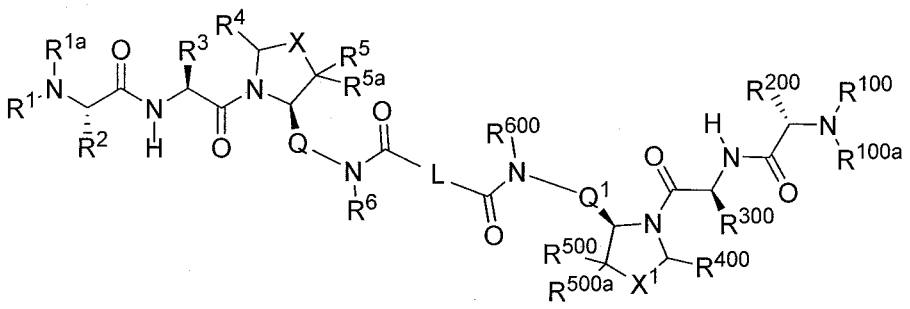
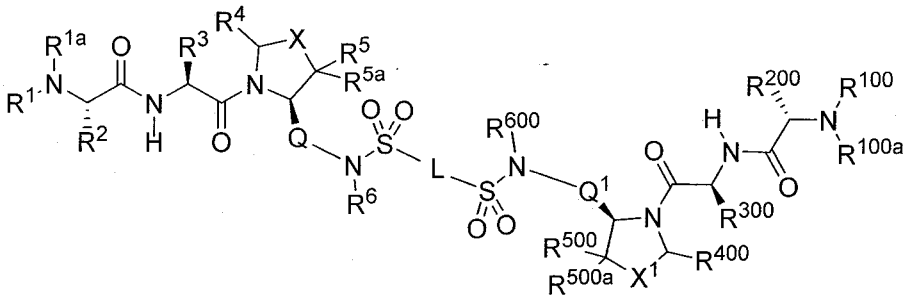



[0069] Any and each individual definition of BG, Y^1, Y^{100}, L^1, L^{100}, and Z as set out herein may be combined with any and each individual definition of the other substituent groups of Formula 1 (e.g., R^1, R^{1a}, R^2, R^3, R^4, R^5, R^{5a}, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, n, m, A, Q, X R^{100}, R^{100a}, R^{200}, R^{300}, R^{400}, R^{500}, R^{600}, R^{700}, R^{800}, R^{900}, R^{1000}, R^{1100},R^{1200}, R^{1300}, R^{1400}, n, m, A^1, Q^1, and X^1) as set out herein.

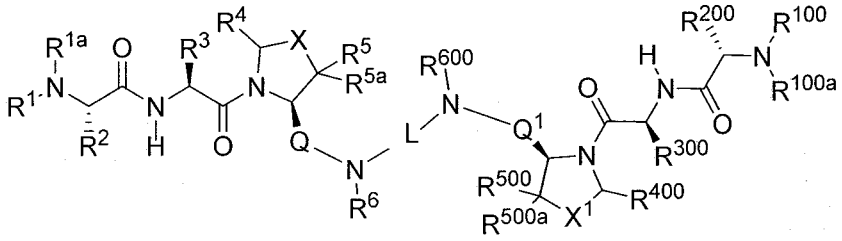
[0070] By way of further illustration, the compounds of Formula 1 can include compounds of any of Formulas 1A4-1A8:



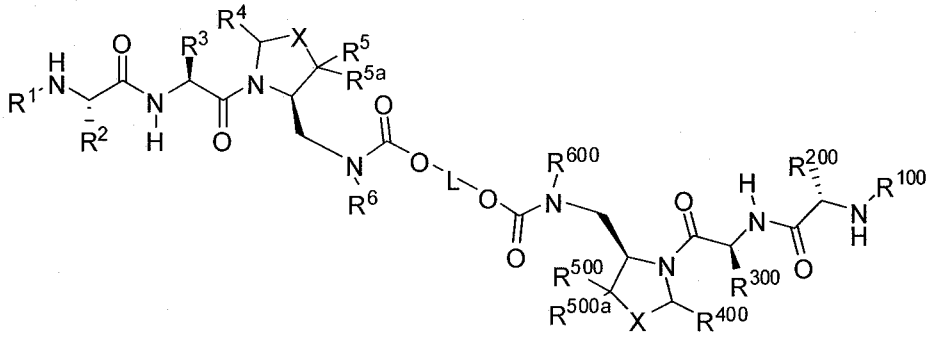
1A4



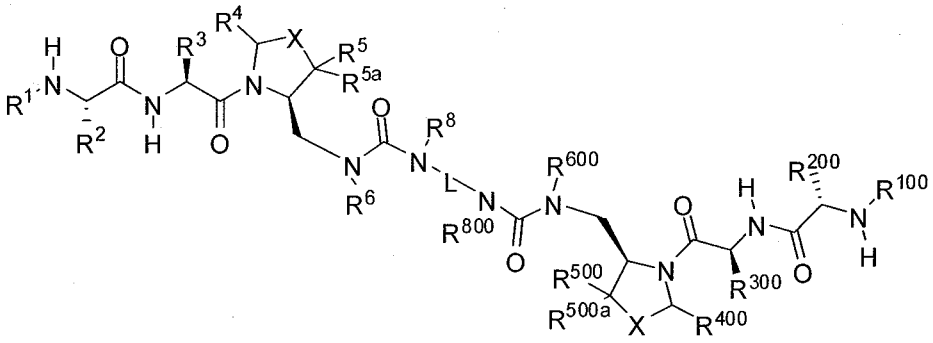
1A5



1A6



1A7



1A8

wherein R^1, R^{1a}, R^2, R^2, R^3, R^4, R^5, R^{5a}, R^6, R^8, X, X^1, L, R^{100}, R^{100a}, R^{200}, R^{300}, R^{400}, R^{500}, R^{500a}, R^{600} and R^{800} are as defined herein.

R^1, R^{1a}, R^{100} and R^{100a}:

[0071] R^1, R^{1a}, R^{100} and R^{100a} can be any group as previously defined herein, without limitation. In one subset of compounds, R^1, R^{1a}, R^{100} and R^{100a} are independently selected from H or CH_3.

[0072] Any and each individual definition of R^1, R^{1a}, R^{100}, R^{100a} as set out herein may be combined with any and each individual definition of the other substituent groups of Formula 1 (e.g., L, L^1, L^{100}, R^2, R^3, R^4, R^5, R^{5a}, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, A, Y^1, Q, X, R^{200}, R^{300},

R^{400}, R^{500}, R^{600}, R^{700}, R^{800}, R^{900}, R^{1000}, R^{1100}, R^{1200},R^{1300}, R^{1400}, A^1, Y^{100}, Q^1, and X^1) as set out herein.

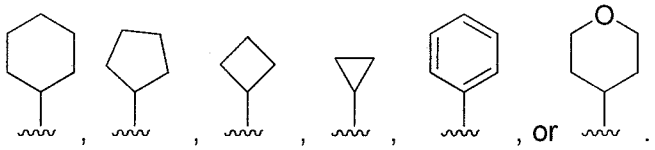
R^2 and R^{200}:

[0073] R^2 and R^{200} can be any group as previously defined herein, without limitation. In one subset of compounds of Formula 1, both R^2 and R^{200} display (S)-stereochemistry.

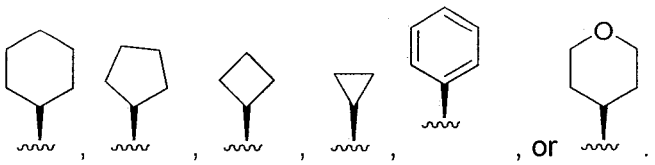
[0074] Any and each individual definition of R^2 and R^{200} as set out herein may be combined with any and each individual definition of the other substituent groups of Formula 1 (e.g., L, L^1, L^{100}, R^1, R^{1a}, R^3, R^4, R^5, R^{5a}, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, A, Y^1, Q, X, R^{100}, R^{100a}, R^{300}, R^{400}, R^{500}, R^{600}, R^{700}, R^{800}, R^{900}, R^{1000}, R^{1100}, R^{1200},R^{1300}, R^{1400}, A^1, Y^{100}, Q^1, and X^1) as set out herein.

R^3 and R^{300}:

[0075] R^3 and R^{300} can be any group as previously defined herein, without limitation. In one subset of compounds of Formula 1, R^3 and R^{300} are both C_1–C_6 cycloalkyl optionally substituted with an R^7 substituent. Typical examples of suitable R^3 and R^{300} include cyclohexyl, cyclopropyl, and tetrahydro-2H-pyranyl. For example, R^3 and R^{300} can be, independently:



[0076] While R^3 and R^{300} can have any stereochemistry, desirably R^3 and/or R^{300} display (S)- stereochemistry, as illustrated, for example, by the following:



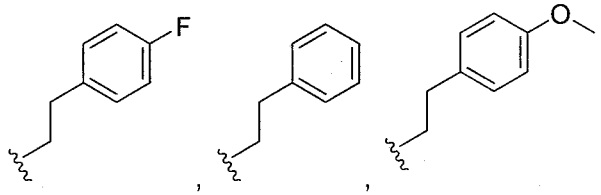
[0077] Any and each individual definition of R^3 and R^{300} as set out herein may be combined with any and each individual definition of the other substituent groups of Formula 1 (e.g., L, L^1, L^{100}, R^1, R^{1a}, R^2, R^4, R^5, R^{5a}, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, A, Y^1, Q, X, R^{100}, R^{100a}, R^{200}, R^{400}, R^{500}, R^{600}, R^{700}, R^{800}, R^{900}, R^{1000}, R^{1100},R^{1200}, R^{1300}, R^{1400}, A^1, Y^{100}, Q^1, and X^1) as set out herein.

R^6 and R^{600}:

[0078] R^6 and R^{600} can be any group as previously defined herein, without limitation. In one subset of compounds of the invention, R^6 and R^{600} are each independently

1) H,
2) C_1–C_6 alkyl, or
3) aryl

wherein the alkyl is optionally substituted with one or more R^7 substituents; and wherein the aryl is optionally substituted with one or more R^{11} substituents. Typical examples of R^6 and R^{600} include



[0079] Any and each individual definition of R^6 and R^{600} as set out herein may be combined with any and each individual definition of the other substituent groups of Formula 1 (e.g., L, L^1, L^{100}, R^1, R^{1a}, R^2, R^3, R^4, R^5, R^{5a}, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, A, Y^1, Q, X · R^{100}, R^{100a}, R^{200}, R^{300}, R^{400}, R^{500}, R^{700}, R^{800}, R^{900}, R^{1000}, R^{1100},R^{1200}, R^{1300}, R^{1400}, A^1, Y^{100}, Q^1, and X^1) as set out herein.

R^7:

[0080] R^7 can be any group as previously defined herein, without limitation. In one subset of compounds of the invention, R^7 is

1) C_3–C_7 cycloalkyl,
2) aryl,
3) heteroaryl, or
4) NHC(O)OCH_2-phenyl,

wherein the aryl and the heteroaryl are optionally substituted with one or more R^{11} substituents; and wherein R^9 and R^{10} are as defined herein.

[0081] Any and each individual definition of R^7 as set out herein may be combined with any and each individual definition of the other substituent groups of Formula 1 (e.g., L, L^1, L^{100}, R^1,

R^{1a}, R^2, R^3, R^4, R^5, R^{5a}, R^6, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, A, Y^1, Q, X, R^{100}, R^{100a}, R^{200}, R^{300}, R^{400}, R^{500}, R^{600}, R^{700}, R^{800}, R^{900}, R^{1000}, R^{1100},R^{1200}, R^{1300}, R^{1400}, A^1, Y^{100}, Q^1, and X^1) as set out herein.

R^8:

[0082] R^8 can be any group as previously defined herein, without limitation. In one subset, R^8 is selected from

1) H,
2) haloalkyl,
3) C_1–C_6 alkyl,
4) C_3–C_7 cycloalkyl,
5) aryl,
6) heteroaryl,
7) heterocyclyl, or
8) heterobicyclyl,

wherein the alkyl and the cycloalkyl, are optionally substituted with one or more R^7 substituents; and wherein the aryl, the heteroaryl, the heterocyclyl, and the heterobicyclyl are optionally substituted with one or more R^{11} substituents.

[0083] Any and each individual definition of R^8 as set out herein may be combined with any and each individual definition of the other substituent groups of Formula 1 (e.g., L, L^1, L^{100}, R^1, R^{1a}, R^2, R^3, R^4, R^5, R^{5a}, R^6, R^7, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, A, Y^1, Q, X, R^{100}, R^{100a}, R^{200}, R^{300}, R^{400}, R^{500}, R^{600}, R^{700}, R^{800}, R^{900}, R^{1000}, R^{1100}, R^{1200},R^{1300}, R^{1400}, A^1, Y^{100}, Q^1, and X^1) as set out herein.

R^{11}:

[0084] R^{11} can be any group as previously defined herein, without limitation. In one subset of compounds of the invention, R^{11} is

1) halogen,
2) CF_3,
3) OH,
4) OMe,

5) aryl, or

6) heteroaryl.

More specific examples of R^{11} include F, Cl, Br, OH, OMe, CF_3, phenyl and tetrazole.

[0085] Any and each individual definition of R^{11} as set out herein may be combined with any and each individual definition of the other substituent groups of Formula 1 (e.g., L, L^1, L^{100}, R^1, R^{1a}, R^2, R^3, R^4, R^5, R^{5a}, R^6, R^7, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, A, Y^1, Q, X, R^{100}, R^{100a}, R^{200}, R^{300}, R^{400}, R^{500}, R^{600}, R^{700}, R^{800}, R^{900}, R^{1000}, R^{1100},R^{1200}, R^{1300}, R^{1400}, A^1, Y^{100}, Q^1, and X^1) as set out herein.

X and X^1

[0086] X can be a carbonyl group, or a C_1-C_3 alkylene which forms part of a ring system, the ring system being optionally substituted with one or more R^{11} substituents; or X can be part of a 5, 6, or 7 membered heterocyclic ring system optionally including one, two or three heteroatoms selected from O, N or S, the ring system being optionally substituted with one or more R^{11}. In other words, X can be -C(O)-, a heteroatom (e.g., O, S, or N), or a C_1-C_3 arylene or heteroarylene, optionally substituted with one or more R^{11} groups. By way of further illustration, X can be:

a) $-CH_2-$

b) $-CH(OH)-$

c) $-CH(OCH_3)-$

d) $-CF_2-$

e) $-CHF-$

f) $-CHNH_2-$

g) $-CH(NHC(O)CH_3)-$

h) $-CH_2CH_2-$

i) $-CH_2O-$

j) $-CH_2NH-$

k) $-CH_2CF_2-$

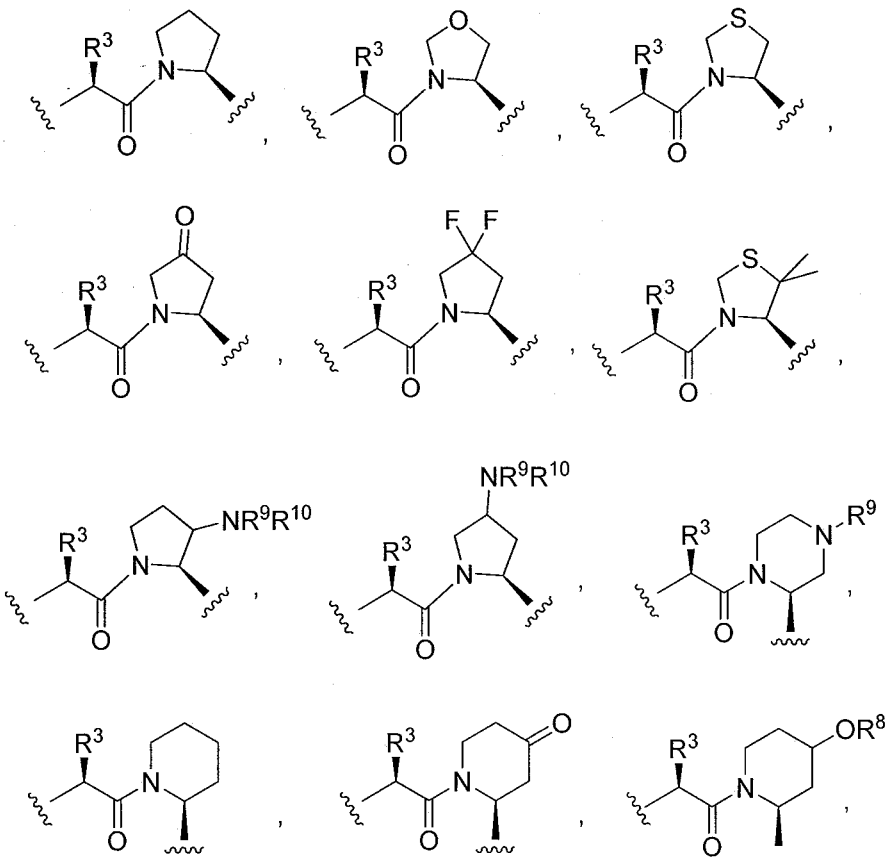
l) $-CH_2N(C(O)CH_3)-$

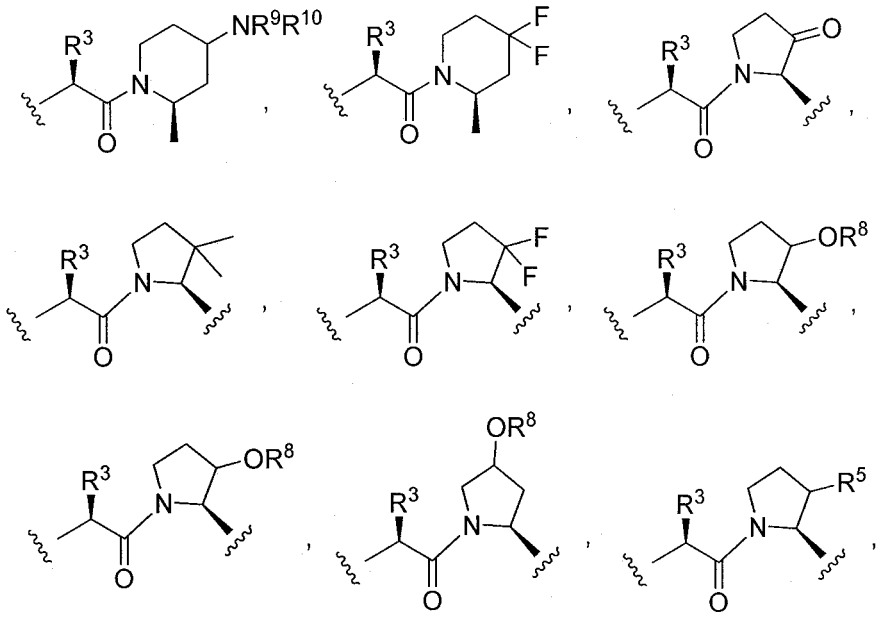
m) $-CH_2CH(OH)-$

n) $-CH_2CH(NH_2)-$, or

o) $-CH_2CH(NHC(O)CH_3)-$.

[0087] In one subset of compounds of the present invention, X, R^5 and R^{5a} (and R^{500} and ^{500a}) are selected so as to provide compounds of Formula 1 wherein W and W^1 (and the corresponding moieties of Formula 1A and 1.1A) have the structure:





[0088] Any and each individual definition of X, R^5, R^{5a}, R^{500}, R^{500a}, W, and W^1 as set out herein may be combined with any and each individual definition of the other substituent groups of Formula 1 as set out herein.

[0089] If any variable, such as R^3, R^4 and the like, occurs more than one time in any constituent structure, the definition of the variable at each occurrence is independent at every other occurrence. If a substituent is itself substituted with one or more substituents, it is to be understood that that the one or more substituents may be attached to the same carbon atom or different carbon atoms. Combinations of substituents and variables defined herein are allowed only if they produce chemically stable compounds.

[0090] One skilled in the art will understand that substitution patterns and substituents on compounds of the present invention may be selected to provide compounds that are chemically stable and can be readily synthesized using the chemistry set forth in the examples and chemistry techniques well known in the art using readily available starting materials.

[0091] It is to be understood that many substituents or groups described herein have functional group equivalents, which means that the group or substituent may be replaced by another group or substituent that has similar electronic, hybridization or bonding properties.

[0092] The invention further includes an isomer, enantiomer, diastereoisomer or tautomer of a compound represented by Formula 1, 1A, 1.1A, or any other compound depicted or described herein.

Definitions

[0093] Unless otherwise specified, the following definitions apply:

[0094] The singular forms "a", "an" and "the" include corresponding plural references unless the context clearly dictates otherwise.

[0095] As used herein, the term "comprising" is intended to mean that the list of elements following the word "comprising" are included but that other elements are optional and may or may not be present .

[0096] As used herein, the term "consisting of" is intended to mean including and limited to whatever follows the phrase "consisting of." Thus the phrase "consisting of" indicates that the listed elements are included and that no other elements may be present.

[0097] As used herein, the term "alkyl" is intended to include both branched and straight chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, for example, C_1-C_6 as in C_1-C_6 - alkyl is defined as including groups having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement, and C_1-C_4 as in C_1-C_4 alkyl is defined as including groups having 1, 2, 3, or 4 carbons in a linear or branched arrangement, and for example, C_1-C_{20} as in C_1-C_{20} - alkyl is defined as including groups having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbons in a linear or branched arrangement, Examples of C_1-C_6-alkyl and C_1-C_4 alkyl as defined above include, but are not limited to, methyl, ethyl, n-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *i*-butyl, pentyl and hexyl. For the purposes of describing the invention, the term "alkyl" encompasses an "alkylene."

[0098] As used herein, the term, "alkenyl" is intended to mean unsaturated straight or branched chain hydrocarbon groups having the specified number of carbon atoms therein, and in which at least two of the carbon atoms are bonded to each other by a double bond, and having either E or Z regeochemistry and combinations thereof. For example, C_2-C_6 as in C_2-C_6 alkenyl is defined as including groups having 2, 3, 4, 5, or 6 carbons in a linear or branched arrangement, at least two of the carbon atoms being bonded together by a double bond.

Examples of C_2-C_6 alkenyl include ethenyl (vinyl), 1-propenyl, 2-propenyl, 1- butenyl and the like. For the purposes of describing the invention, the term "alkenyl" encompasses an "alkenylene."

[0099] As used herein, the term "alkynyl" is intended to mean unsaturated, straight chain hydrocarbon groups having the specified number of carbon atoms therein and in which at least two carbon atoms are bonded together by a triple bond. For example C_2-C_4 as in C_2-C_4 alkynyl is defined as including groups having 2, 3, or 4 carbon atoms in a chain, at least two of the carbon atoms being bonded together by a triple bond. Examples of such alkynyls include ethynyl, 1-propynyl, 2-propynyl and the like. For the purposes of describing the invention, the term "alkynyl" encompasses an "alkynylene."

[0100] As used herein, the term "cycloalkyl" is intended to mean a monocyclic saturated aliphatic hydrocarbon group having the specified number of carbon atoms therein, for example, C_3-C_7 as in C_3-C_7 cycloalkyl is defined as including groups having 3, 4, 5, 6, or 7 carbons in a monocyclic arrangement. Examples of C_3-C_7 cycloalkyl as defined above include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. For the purposes of describing the invention, the term "cycloalkyl" encompasses a "cycloalkylene."

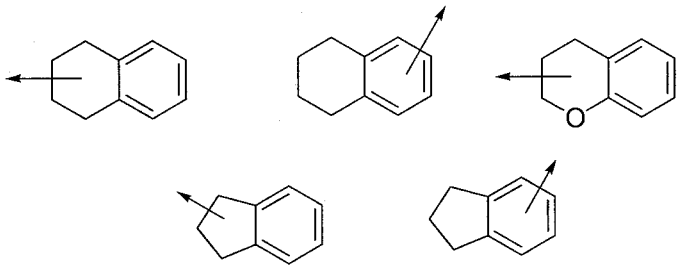
[0101] As used herein, the term "cycloalkenyl" is intended to mean a monocyclic unsaturated aliphatic hydrocarbon group having the specified number of carbon atoms therein, for example, C_3-C_7 as in C_3-C_7 cycloalkenyl is defined as including groups having 3, 4, 5, 6, or 7 carbons in a monocyclic arrangement. Examples of C_3-C_7 cycloalkenyl as defined above include, but are not limited to, cyclopentenyl, and cyclohexenyl. For the purposes of describing the invention, the term "cycloalkenyl" encompasses a "cycloalkenylene."

[0102] As used herein, the term "halo" or "halogen" is intended to mean fluorine, chlorine, bromine and iodine.

[0103] As used herein, the term "haloalkyl" is intended to mean an alkyl as defined above, in which each hydrogen atom may be successively replaced by a halogen atom. Examples of haloalkyls include, but are not limited to, CH_2F, CHF_2 and CF_3.

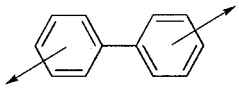
[0104] As used herein, the term "aryl", either alone or in combination with another radical, means a carbocyclic aromatic monocyclic group containing 6 carbon atoms which may be

further fused to a second or a third 5- or 6-membered carbocyclic group which may be aromatic, saturated or unsaturated. Aryl includes, but is not limited to, phenyl, indanyl, 1-naphthyl, 2-naphthyl, tetrahydronaphthyl, 1-anthracenyl, 2-anthracenyl, 9-anthracenyl, 1-phenanthryl, 2-phenanthryl, 3-phenanthryl, 4-phenanthryl, and 5-phenanthryl. The aryls may be connected to another group either at a suitable position on the cycloalkyl ring or the aromatic ring. For example:

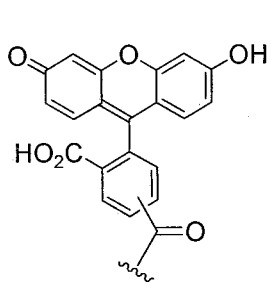
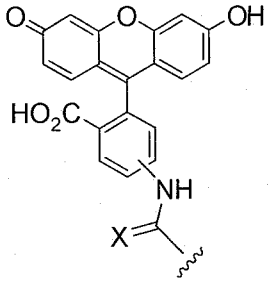


[0105] Arrowed lines drawn from the ring system indicate that the bond may be attached to any of the suitable ring atoms. For the purposes of describing the invention, the term "aryl" encompasses an "arylene."

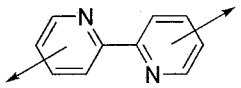
[0106] As used herein, the term "biphenyl" is intended to mean two phenyl groups bonded together at any one of the available sites on the phenyl ring. For example:

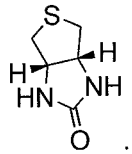


[0107] As used herein, the term "heteroaryl" is intended to mean a monocyclic or bicyclic ring system of up to ten atoms, wherein at least one ring is aromatic, and contains from 1 to 4 hetero atoms selected from the group consisting of O, N, and S. The heteroaryl substituent may be attached either via a ring carbon atom or one of the heteroatoms. Examples of heteroaryl groups include, but are not limited to thienyl, benzimidazolyl, benzo[b]thienyl, furyl, benzofuranyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, 2H-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, napthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, isothiazolyl, isochromanyl, chromanyl, isoxazolyl, furazanyl, indolinyl, isoindolinyl, thiazolo[4,5-b]-pyridine, and

fluoroscein derivatives such as:  or  . For the purposes of describing the invention, the term "heteroaryl" encompasses a "heteroarylene."

[0108] As used herein, the term "biheteroaryl" is intended to mean a heteroaryl group substituted with another heteroaryl group at any one of the available sites on the heteroaryl ring. Biheteroaryl includes, for example:



[0109] As used herein, the term "heterocyclyl" is intended to mean a 5, 6, or 7 membered non-aromatic ring system containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Examples of heterocycles include, but are not limited to pyrrolidinyl, tetrahydrofuranyl, piperidyl, pyrrolinyl, piperazinyl, imidazolidinyl, morpholinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, and  . For the purposes of describing the invention, the term "heterocyclyl" encompasses a "heterocyclylene."

[0110] As used herein, the term "heterobicycle" either alone or in combination with another radical, is intended to mean a heterocycle as defined above fused to another cycle, be it a heterocycle, an aryl or any other cycle defined herein. Examples of such heterobicycles include, but are not limited to, coumarin, benzo[d][1,3]dioxole, 2,3-dihydrobenzo[b][1,4]dioxine and 3,4-dihydro-2H-benzo[b][1,4]dioxepine.

[0111] As used herein, the term "heteroatom" is intended to mean O, S or N.

[0112] As used herein, the term "activated diacid" is intended to mean a diacid wherein the carboxylic acid moieties have been transformed to, for example, but not limited to, acid halides, a succinate esters, or HOBt esters, either in situ or in a separate synthetic step. For example,

succinyl chloride and terephthaloyl chloride are examples of "diacid chlorides". HOBt esters can be formed in situ by the treatment of a diacid with a dehydrating agent such as DCC, EDC, HBTU, or others, a base such as DIPEA, and HOBt in an appropriate solvent. The reaction of an activated diacid with an amine will result in the conversion of the acid functionality to amide functionality.

[0113] As used herein, the term "detectable label" is intended to mean a group that may be linked to a compound of the present invention to produce a probe or to an IAP BIR domain, such that when the probe is associated with the BIR domain, the label allows either direct or indirect recognition of the probe so that it may be detected, measured and quantified.

[0114] As used herein, the term "affinity tag" is intended to mean a ligand or group, which is linked to either a compound of the present invention or to an IAP BIR domain to allow another compound to be extracted from a solution to which the ligand or group is attached.

[0115] As used herein, the term "probe" is intended to mean a compound of Formula 1 which is labeled with either a detectable label or an affinity tag, and which is capable of binding, either covalently or non-covalently, to an IAP BIR domain. When, for example, the probe is non-covalently bound, it may be displaced by a test compound. When, for example, the probe is bound covalently, it may be used to form cross-linked adducts, which may be quantified and inhibited by a test compound.

[0116] As used herein, the term "optionally substituted with one or more substituents" or its equivalent term "optionally substituted with at least one substituent" is intended to mean that the subsequently described event of circumstances may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. The definition is intended to mean from zero to five substituents.

[0117] If the substituents themselves are incompatible with the synthetic methods of the present invention, the substituent may be protected with a suitable protecting group (PG) that is stable to the reaction conditions used in these methods. The protecting group may be removed at a suitable point in the reaction sequence of the method to provide a desired intermediate or target compound. Suitable protecting groups and the methods for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, Protecting Groups in

Chemical Synthesis (3rd ed.), John Wiley & Sons, NY (1999), which is incorporated herein by reference in its entirety. Examples of protecting groups used throughout include, but are not limited to Fmoc, Bn, Boc, CBz and $COCF_3$. In some instances, a substituent may be specifically selected to be reactive under the reaction conditions used in the methods of this invention. Under these circumstances, the reaction conditions convert the selected substituent into another substituent that is either useful in an intermediate compound in the methods of this invention or is a desired substituent in a target compound.

[0118] As used herein, the term "subject" is intended to mean humans and non-human mammals such as primates, cats, dogs, swine, cattle, sheep, goats, horses, rabbits, rats, mice and the like.

[0119] As used herein, the term "prodrug" is intended to mean a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound of the present invention. Thus, the term "prodrug" refers to a precursor of a compound of the invention that is pharmaceutically acceptable. A prodrug may be inactive or display limited activity when administered to a subject in need thereof, but is converted in vivo to an active compound of the present invention. Typically, prodrugs are transformed in vivo to yield the compound of the invention, for example, by hydrolysis in blood or other organs by enzymatic processing. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in the subject (see, Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam). The definition of prodrug includes any covalently bonded carriers which release the active compound of the invention in vivo when such prodrug is administered to a subject. Prodrugs of a compound of the present invention may be prepared by modifying functional groups present in the compound of the invention in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to a parent compound of the invention.

[0120] As used herein, the term "pharmaceutically acceptable carrier, diluent or excipient" is intended to mean, without limitation, any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, emulsifier, or encapsulating agent, such as a liposome, cyclodextrins, encapsulating polymeric delivery systems or polyethyleneglycol matrix, which is acceptable for use in the subject, preferably humans.

[0121] As used herein, the term "pharmaceutically acceptable salt" is intended to mean both acid and base addition salts.

[0122] As used herein, the term "pharmaceutically acceptable acid addition salt" is intended to mean those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

[0123] As used herein, the term "pharmaceutically acceptable base addition salt" is intended to mean those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like.

[0124] As used herein, the term “BIR domain binding” is intended to mean the action of a compound of the present invention upon an IAP BIR domain, which blocks or diminishes the binding of IAPs to BIR binding proteins or is involved in displacing BIR binding proteins from an IAP. Examples of BIR binding proteins include, but are not limited to, caspases and mitochondrially derived BIR binding proteins such as Smac, Omi/WTR2A and the like.

[0125] As used herein, the term “insufficient apoptosis” is intended to mean a state wherein a disease is caused or continues because cells deleterious to the subject have not apoptosed.

This includes, but is not limited to, cancer cells that survive in a subject without treatment, cancer cells that survive in a subject during or following anti-cancer treatment, or immune cells whose action is deleterious to the subject, and includes, neutrophils, monocytes, B-cells and auto-reactive T-cells.

[0126] As used herein, the term "therapeutically effective amount" is intended to mean an amount of a compound of Formula 1 which, when administered to a subject is sufficient to effect treatment for a disease-state associated with insufficient apoptosis. The amount of the compound of Formula 1 will vary depending on the compound, the condition and its severity, and the age of the subject to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

[0127] As used herein, the term "treating" or "treatment" is intended to mean treatment of a disease-state associated with insufficient apoptosis, as disclosed herein, in a subject, and includes: (i) preventing a disease or condition associated with insufficient apoptosis from occurring in a subject, in particular, when such mammal is predisposed to the disease or condition but has not yet been diagnosed as having it; (ii) inhibiting a disease or condition associated with insufficient apoptosis, i.e., arresting its development; or (iii) relieving a disease or condition associated with insufficient apoptosis, i.e., causing regression or alleviation of the condition or any symptom thereof.

[0128] As used herein, the term "treating cancer" is intended to mean the administration of a pharmaceutical composition of the present invention to a subject, preferably a human, which is afflicted with cancer to cause an alleviation of the cancer (i.e., any symptom of the cancer) by killing, inhibiting the growth, or inhibiting the metastasis of the cancer cells.

[0129] As used herein, the term "preventing disease" is intended to mean, in the case of cancer, the post-surgical, post-chemotherapy or post-radiotherapy administration of a pharmaceutical composition of the present invention to a subject, preferably a human, which was afflicted with cancer to prevent the regrowth of the cancer by killing, inhibiting the growth, or inhibiting the metastasis of any remaining cancer cells. Also included in this definition is the prevention of pathogenic-cell survivial in conditions that lead to diseases such as asthma, MS and the like.

[0130] As used herein, the term "synergistic effect" is intended to mean that the effect achieved with the combination of the compounds of the present invention and either the chemotherapeutic agents or death receptor agonists of the invention is greater than the effect which is obtained with only one of the compounds, agents or agonists, or advantageously the effect which is obtained with the combination of the above compounds, agents or agonists is greater than the addition of the effects obtained with each of the compounds, agents or agonists used separately. Such synergy enables smaller doses to be given.

[0131] As used herein, the term "apoptosis" or "programmed cell death" is intended to mean the regulated process of cell death wherein a dying cell displays a set of well-characterized biochemical hallmarks that include cell membrane blebbing, cell soma shrinkage, chromatin condensation, and DNA laddering, as well as any caspase-mediated cell death.

[0132] As used herein, the term "BIR domain" or "BIR" are used interchangeably throughout and are intended to mean a domain which is characterized by a number of invariant amino acid residue including conserved cysteines and one conserved hisitidine residue within the sequence Cys-$(Xaa1)_2$Cys-$(Xaa1)_{16}$His-$(Xaa1)_{6-8}$Cys. The BIR domain residues are listed below (see Genome Biology (2001) 1-10):

	XIAP	HIAP-1	HIAP-2
BIR1	21-93	41-113	24-96
BIR2	159-230	179-250	164-235
BIR3	258-330	264-336	250-322
Seq. #	P98170	XP-006266	XP-006267

[0133] As used herein, the term "ring zinc finger" or "RZF" is intended to mean a domain having the amino acid sequence of the consensus sequence: Glu-Xaa1-Xaa1-Xaa1-Xaa1-Xaa1-Xaa- 1-Xaa2-Xaa1-Xaa1-Xaa1-Cys-Lys-Xaa3-Cys-Met-Xaa1-Xaa1-Xaa1-Xaa1-Xaa1-Xaa3-X- aa1-Phe-Xaa1-Pro-Cys-Gly-His-Xaa1-Xaa1-Xaa1-Cys-Xaa1-Xaa1-Cys-Ala-Xaa1-Xaa-1-Xaa1-Xaa1-Xaa1-Cys-Pro-Xaa1-Cys, wherein Xaa1 is any amino acid, Xaa2 is Glu or Asp, and Xaa3 is Val or Ile.

[0134] As used herein, the term "IAP" is intended to mean a polypeptide or protein, or fragment thereof, encoded by an IAP gene. Examples of IAPs include, but are not limited to

human or mouse NAIP (Birc 1), HIAP-1 (cIAP2, Birc 3), HIAP-2 (cIAP1, Birc 2), XIAP (Birc 4), survivin (Birc 5), livin (ML-IAP, Birc 7), ILP-2 (Birc 8) and Apollon/BRUCE (Birc 6) (see for example US Patent Numbers 6,107,041; 6,133,437; 6,156,535; 6,541,457; 6,656,704; 6,689,562; Deveraux and Reed, Genes Dev. 13, 239-252, 1999; Kasof and Gomes, J. Biol. Chem., 276, 3238-3246, 2001; Vucic et al., Curr. Biol. 10, 1359-1366, 2000; Ashab et al. FEBS Lett., 495, 56-60, 2001, the contents of which are hereby incorporated by reference).

[0135] As used herein, the term "IAP gene" is intended to mean a gene encoding a polypeptide having at least one BIR domain and which is capable of modulating (inhibiting or enhancing) apoptosis in a cell or tissue. The IAP gene is a gene having about 50% or greater nucleotide sequence identity (preferably 95% or greater sequence identity or 100% sequence identity) to at least one of human or mouse NAIP (Birc 1), HIAP-1 (cIAP2, Birc 3), HIAP-2 (cIAP1, Birc 2), XIAP (Birc 4), survivin (Birc 5), livin (ML-IAP, Birc 7), ILP-2 (Birc 8) and Apollon/BRUCE (Birc 6). The region of sequence over which identity is measured is a region encoding at least one BIR domain and a ring zinc finger domain. Mammalian IAP genes include nucleotide sequences isolated from any mammalian source.

[0136] As used herein, the term "IC_{50}" is intended to mean an amount, concentration or dosage of a particular compound of the present invention that achieves a 50% inhibition of a maximal response, such as displacement of maximal fluorescent probe binding in an assay that measures such response.

[0137] As used herein, the term "EC_{50}" is intended to mean an amount, concentration or dosage of a particular compound of the present invention that achieves a 50% inhibition of cell survival.

[0138] As used herein, the term "modulate" or "modulating" is intended to mean the treatment, prevention, suppression, enhancement or induction of a function or condition using the compounds of the present invention. For example, the compounds of the present invention can modulate IAP function in a subject, thereby enhancing apoptosis by significantly reducing, or essentially eliminating the interaction of activated apoptotic proteins, such as caspase-3, 7 and 9, with the BIR domains of mammalian IAPs or by inducing the loss of XIAP protein in a cell.

[0139] As used herein, the term "enhancing apoptosis" is intended to mean increasing the number of cells that apoptose in a given cell population either in vitro or in vivo. Examples of cell populations include, but are not limited to, ovarian cancer cells, colon cancer cells, breast cancer cells, lung cancer cells, pancreatic cancer cells, or T cells and the like. It will be appreciated that the degree of apoptosis enhancement provided by an apoptosis-enhancing compound of the present invention in a given assay will vary, but that one skilled in the art can determine the statistically significant change in the level of apoptosis that identifies a compound that enhances apoptosis otherwise limited by an IAP. Preferably "enhancing apoptosis" means that the increase in the number of cells undergoing apoptosis is at least 25%, more preferably the increase is 50%, and most preferably the increase is at least one-fold. Preferably the sample monitored is a sample of cells that normally undergo insufficient apoptosis (i.e., cancer cells). Methods for detecting the changes in the level of apoptosis (i.e., enhancement or reduction) are described in the Examples and include methods that quantitate the fragmentation of DNA, methods that quantitate the translocation phosphatoylserine from the cytoplasmic to the extracellular side of the membrane, determination of activation of the caspases and methods quantitate the release of cytochrome C and the apoptosis inhibitory factor into the cytoplasm by mitochondria.

[0140] As used herein, the term "proliferative disease" or “proliferative disorder” is intended to mean a disease that is caused by or results in inappropriately high levels of cell division, inappropriately low levels of apoptosis, or both. For example, cancers and autoimmune disorders are all examples of proliferative diseases.

[0141] As used herein, the term "death receptor agonist" is intended to mean an agent capable of stimulating by direct or indirect contact the pro apoptotic response mediated by the death-receptors. For example, an agonist TRAIL receptor antibody would bind to TRAIL receptor (S) and trigger an apoptotic response. On the other hand, other agents such as interferon-α could trigger the release of endogeneous TRAIL and/or up regulate the TRAIL receptors in such a way that the cell pro-apoptotic response is amplified.

[0142] The compounds of the present invention, or their pharmaceutically acceptable salts, may contain one or more asymmetric centers, chiral axes and chiral planes. These compounds may, thus, give rise to enantiomers, diastereomers, and other stereoisomeric forms and may be defined in terms of absolute stereochemistry, such as (R)- or (S)- or, as (D)- or (L)- for amino

acids. The present invention is intended to include all such possible isomers, as well as, their racemic and optically pure forms. Optically active (+) and (-), (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as reverse phase HPLC. The racemic mixtures may be prepared and thereafter separated into individual optical isomers or these optical isomers may be prepared by chiral synthesis. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may then be separated by crystallization, gas-liquid or liquid chromatography, selective reaction of one enantiomer with an enantiomer specific reagent. It will also be appreciated by those skilled in the art that where the desired enantiomer is converted into another chemical entity by a separation technique, an additional step is then required to form the desired enantiomeric form. Alternatively specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts, or solvents or by converting one enantiomer to another by asymmetric transformation.

[0143] Certain compounds of the present invention may exist in Zwitterionic form and the present invention includes Zwitterionic forms of these compounds and mixtures thereof.

Utilities

[0144] The compounds of the present invention can be used for any purpose. However, compounds of Formula 1 as provided herein are believed to be especially useful as IAP BIR domain binding compounds. As such the compounds, compositions and method of the present invention include application to the cells or subjects afflicted with or having a predisposition towards developing a particular disease state, which is characterized by insufficient apoptosis. Thus, the compounds, compositions and methods of the present invention can be used to treat cellular proliferative diseases/disorders, which include, but are not limited to, i) cancer, ii) autoimmune disease, iii) inflammatory disorders, iv) proliferation induced post medical procedures, including, but not limited to, surgery, angioplasty, and the like. Accordingly, the invention provides a method of treating a proliferative disorder or other disease state characterized by insufficient apoptosis comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the invention (e.g., a compound of Formula 1) or pharmaceutical composition comprising same, so as to treat the proliferative disorder or disease state characterized by insufficient apoptosis.

[0145] The compounds of the present invention may be particularly useful in the treatment of diseases in which there is a defect in the programmed cell-death or the apoptotic machinery (TRAIL, FAS, apoptosome), such as multiple sclerosis, artherosclerosis, inflammation, autoimmunity, rheumatoid arthritis (RA) and the like. Without wishing to be bound by any particular theory, it is believed that the compounds of the present invention act in combination with endogenous cell-death ligands, such as Fas, to induce apoptosis in synoviocytes (e.g., human synoviocytes). Thus, in another aspect, the invention provides a method of inducing apoptosis in a synoviocyte, especially human synoviocytes, comprising administering to the synoviocyte a compound of the invention alone or in combination, simultaneously or sequentially, with a cell-death ligand including, but not limited to, Fas. The synoviocyte can be in a tissue or a subject, for example, a tissue or subject afflicted with a disease associated with a defect in the programmed cell-death or the apoptotic machinery (TRAIL, FAS, apoptosome) of a synoviocyte, especially an autoimmune disease such as RA.

[0146] In particular, the compounds, compositions and methods of the present invention can be used for the treatment of cancer including solid tumors such as skin, breast, brain, lung, testicular carcinomas, and the like. Cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to the following:

Tissue	Example
Adrenal gland	neuroblastoma
Bone	osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors
Cardiac	sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma
Gastrointestinal	esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma,

Tissue	Example
	leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma)
Genitourinary tract	kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma)
Gynecological	uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma)
Hematologic	blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]
Liver	hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma
Lung	bronchogenic carcinoma (squamous cell, undifferentiated small

Tissue	Example
	cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma
Nervous system	skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma)
Skin	malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids

[0147] The compounds of the present invention, or their pharmaceutically acceptable salts or their prodrugs, may be administered in pure form or in an appropriate pharmaceutical composition, and can be carried out via any of the accepted modes of Galenic pharmaceutical practice.

[0148] The pharmaceutical compositions of the present invention can be prepared by mixing a compound of the present invention with an appropriate pharmaceutically acceptable carrier, diluent or excipient, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. Typical routes of administering such pharmaceutical compositions include, without limitation, oral, topical, transdermal, inhalation, parenteral (subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), sublingual, ocular, rectal, vaginal, and intranasal. Pharmaceutical compositions of the present invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a subject. Compositions that will be administered to a subject or patient take the form of one or more dosage units, where for example, a tablet may be a single dosage unit, and a container of a compound of the present invention in aerosol form may hold a plurality of dosage units.

Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state as described above.

[0149] A pharmaceutical composition of the present invention may be in the form of a solid or liquid. In one aspect, the carrier(s) are particulate, so that the compositions are, for example, in tablet or powder form. The carrier(s) may be liquid, with the compositions being, for example, an oral syrup, injectable liquid or an aerosol, which is useful in, for example inhalatory administration.

[0150] For oral administration, the pharmaceutical composition is preferably in either solid or liquid form, where semi-solid, semi-liquid, suspension and gel forms are included within the forms considered herein as either solid or liquid.

[0151] As a solid composition for oral administration, the pharmaceutical composition may be formulated into a powder, granule, compressed tablet, pill, capsule, chewing gum, wafer or the like form. Such a solid composition will typically contain one or more inert diluents or edible carriers. In addition, one or more of the following may be present: binders such as carboxymethylcellulose, ethyl cellulose, microcrystalline cellulose, gum tragacanth or gelatin; excipients such as starch, lactose or dextrins, disintegrating agents such as alginic acid, sodium alginate, Primogel, corn starch and the like; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; sweetening agents such as sucrose or saccharin; a flavoring agent such as peppermint, methyl salicylate or orange flavoring; and a coloring agent.

[0152] When the pharmaceutical composition is in the form of a capsule, e.g., a gelatin capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or oil such as soybean or vegetable oil.

[0153] The pharmaceutical composition may be in the form of a liquid, e.g., an elixir, syrup, solution, emulsion or suspension. The liquid may be for oral administration or for delivery by injection, as two examples. When intended for oral administration, preferred composition contain, in addition to the present compounds, one or more of a sweetening agent,

preservatives, dye/colorant and flavor enhancer. In a composition intended to be administered by injection, one or more of a surfactant, preservative, wetting agent, dispersing agent, suspending agent, buffer, stabilizer and isotonic agent may be included.

[0154] The liquid pharmaceutical compositions of the present invention, whether they be solutions, suspensions or other like form, may include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or diglycerides which may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; encapsulating agents such as cyclodextrins or functionalized cyclodextrins, including, but not limited to, α, β, or δ-hydroxypropylcyclodextins hydroxypropylcyclodextins or Captisol; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediamine tetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. An injectable pharmaceutical composition is preferably sterile.

[0155] A liquid pharmaceutical composition of the present invention used for either parenteral or oral administration should contain an amount of a compound of the present invention such that a suitable dosage will be obtained. Typically, this amount is at least 0.01% of a compound of the present invention in the composition. When intended for oral administration, this amount may be varied to be between 0.1 and about 70% of the weight of the composition. For parenteral usage, compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 0.01 to 10% by weight of the compound of the present invention. Pharmaceutical compositions may be further diluted at the time of administration; for example a parenteral formulation may be further diluted with a sterile, isotonic solution for injection such as 0.9 % saline, 5 wt % dextrose (D5W), Ringer`s solution, or others.

[0156] The pharmaceutical composition of the present invention may be used for topical administration, in which case the carrier may suitably comprise a solution, emulsion, ointment or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, bee wax, mineral oil, diluents such as water and alcohol, and

emulsifiers and stabilizers. Thickening agents may be present in a pharmaceutical composition for topical administration. If intended for transdermal administration, the composition may include a transdermal patch or iontophoresis device. Topical formulations may contain a concentration of the compound of the present invention from about 0.1 to about 10% w/v (weight per unit volume).

[0157] The pharmaceutical composition of the present invention may be used for rectal administration to treat for example, colon cancer, in the form, e.g., of a suppository, which will melt in the rectum and release the drug. The composition for rectal administration may contain an oleaginous base as a suitable nonirritating excipient. Such bases include, without limitation, lanolin, cocoa butter and polyethylene glycol.

[0158] The pharmaceutical composition of the present invention may include various materials, which modify the physical form of a solid or liquid dosage unit. For example, the composition may include materials that form a coating shell around the active ingredients. The materials that form the coating shell are typically inert, and may be selected from, for example, sugar, shellac, and other enteric coating agents. Alternatively, the active ingredients may be encased in a gelatin capsule.

[0159] The pharmaceutical composition of the present invention in solid or liquid form may include an agent that binds to the compound of the present invention and thereby assists in the delivery of the compound. Suitable agents that may act in this capacity include, but are not limited to, a monoclonal or polyclonal antibody, a protein or a liposome.

[0160] The pharmaceutical composition of the present invention may consist of dosage units that can be administered as an aerosol. The term aerosol is used to denote a variety of systems ranging from those of colloidal nature to systems consisting of pressurized packages. Delivery may be by a liquefied or compressed gas or by a suitable pump system that dispenses the active ingredients. Aerosols of compounds of the present invention may be delivered in single phase, bi-phasic, or tri-phasic systems in order to deliver the active ingredient(s). Delivery of the aerosol includes the necessary container, activators, valves, subcontainers, and the like, which together may form a kit. One skilled in the art, without undue experimentation may determine preferred aerosols.

[0161] The pharmaceutical compositions of the present invention may be prepared by methodology well known in the pharmaceutical art. For example, a pharmaceutical composition intended to be administered by injection can be prepared by admixing a compound of the present invention with sterile, distilled water so as to form a solution. A surfactant may be added to facilitate the formation of a homogeneous solution or suspension. Surfactants are compounds that non-covalently interact with the compound of the present invention so as to facilitate dissolution or homogeneous suspension of the compound in the aqueous delivery system.

[0162] The compounds of the present invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount, which will vary depending upon a variety of factors including the activity of the specific compound employed; the metabolic stability and length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disorder or condition; and the subject undergoing therapy. Generally, a therapeutically effective daily dose may be from about 0.1 mg to about 40 mg/kg of body weight per day or twice per day of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

Combination therapy

[0163] The compounds of the present invention, or pharmaceutically acceptable salts thereof, may also be administered simultaneously with, prior to, or after administration of one or more additional therapeutic agents described herein. Such combination therapy may include administration of a single pharmaceutical dosage formulation which contains a compound of the present invention and one or more additional agents given below, as well as administration of the compound of the present invention in a pharmaceutical dosage formulation separate from one or more additional therapeutic agents. For example, a compound of the present invention and a chemotherapeutic agent, such as taxol (paclitaxel), taxotere, etoposide, cisplatin, vincristine, vinblastine, and the like, can be administered to the patient either together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations or via intravenous injection. Where separate dosage formulations are used, the compounds of the present invention and one or more additional agents can be administered at essentially the same time, i.e., concurrently, or at separately

staggered times, i.e., sequentially; combination therapy is understood to include all these regimens. In addition, these compounds may synergize with molecules that may stimulate the death receptor apoptotic pathway through a direct or indirect manner. Accordingly, the compounds of the present invention may be used in combination with soluble TRAIL, an anti-TRAIL receptor antibody, or any agent or procedure that can cause an increase in circulating level of TRAIL, such as interferon-alpha or radiation.

[0164] Thus, the present invention also encompasses the use of the compounds of the present invention in combination with radiation therapy and/or one or more additional agents such as those described in WO 03/099211 (PCT/US03/15861), which is hereby incorporated by reference. Examples of such additional agents include, but are not limited to the following:

a) an estrogen receptor modulator,

b) an androgen receptor modulator,

c) retinoid receptor modulator,

d) a cytotoxic agent,

e) an antiproliferative agent,

f) a prenyl-protein transferase inhibitor,

g) an HMG-CoA reductase inhibitor,

h) an HIV protease inhibitor,

i) a reverse transcriptase inhibitor,

k) an angiogenesis inhibitor,

l) a PPAR-γ agonist,

m) a PPAR-δ agonist,

n) an inhibitor of inherent multidrug resistance,

o) an anti-emetic agent,

p) an agent useful in the treatment of anemia,

q) agents useful in the treatment of neutropenia,

r) an immunologic-enhancing drug,

s) a proteasome inhibitor such as Velcade and MG132 (7-Leu-Leu-aldehyde) (see He at al. in Oncogene (2004) 23, 2554-2558),

t) an HDAC inhibitor, such as sodium butyrate, phenyl butyrate, hydroamic acids, cyclin tetrapeptide and the like (see Rosato et al,. Molecular Cancer Therapeutics 2003, 1273-1284),

u) an inhibitor of the chymotrypsin-like activity in the proteasome,

v) E3 ligase inhibitors,
w) a modulator of the immune system such as interferon-alpha and ionizing radiation (UVB) that can induce the release of cytokines, such as the interleukins, TNF, or induce release of Death receptor Ligands such as TRAIL,
x) a modulator of death receptors, includingTRAIL and TRAIL receptor agonists such as the humanized antibodies HGS-ETR1 and HGS-ETR2.

[0165] Additional combinations may also include agents which reduce the toxicity of the aforesaid agents, such as hepatic toxicity, neuronal toxicity, nephrotoxicity and the like.

TRAIL Receptor Agonists

[0166] In one example, co-administration of one of the compounds of Formula 1 of the present invention with a death receptor agonist such as TRAIL, such as a small molecule or an antibody that mimics TRAIL may cause an advantageous synergistic effect. Moreover, the compounds of the present invention may be used in combination with any compounds that cause an increase in circulating levels of TRAIL. Agonist antibodies directed against the death receptors TRAIL-R1 and/or TRAIL-R2 can be used in combination with compounds of the invention. Exemplary agonist antibodies that may be used in combination with compounds of the invention include those described in U.S. Pat. No. 7,244,429; in U.S. Patent Application Publication Nos. 2007/0179086, 2002/0004227, 2006/0269554 , 2005/0079172, 2007/0292411, 2006/0270837, 2006/0269555, 2004/0214235, and 2007/0298039; and in International Patent Publications WO2006/017961 and WO98/51793. Each of these publications is hereby incorporated by reference in its entirety. In preferred embodiments, compounds of the invention are used in combination with one or more of these TRAIL receptor agonist antibodies for the treatment of cancer and other neoplasms.

Vinca Alkaloids and Related Compounds

[0167] Vinca alkaloids that can be used in combination with the nucleobase oligomers of the invention to treat cancer and other neoplasms include vincristine, vinblastine, vindesine, vinflunine, vinorelbine, and anhydrovinblastine.

[0168] Dolastatins are oligopeptides that primarily interfere with tubulin at the vinca alkaloid binding domain. These compounds can also be used in combination with the compounds of the

invention to treat cancer and other neoplasms. Dolastatins include dolastatin-10 (NCS 376128), dolastatin-15, ILX651, TZT-1027, symplostatin 1, symplostatin 3, and LU103793 (cemadotin).

[0169] Cryptophycins (e.g., cryptophycin 1 and cryptophycin 52 (LY355703)) bind tubulin within the vinca alkaloid-binding domain and induce G2/M arrest and apoptosis. Any of these compounds can be used in combination with the compounds of the invention to treat cancer and other neoplasms.

[0170] Other microtubule disrupting compounds that can be used in conjunction with the compounds of the invention to treat cancer and other neoplasms are described in U.S. Pat. Nos. 6,458,765; 6,433,187; 6,323,315; 6,258,841; 6,143,721; 6,127,377; 6,103,698; 6,023,626; 5,985,837; 5,965,537; 5,955,423; 5,952,298; 5,939,527; 5,886,025; 5,831,002; 5,741,892; 5,665,860; 5,654,399; 5,635,483; 5,599,902; 5,530,097; 5,521,284; 5,504,191; 4,879,278; and 4,816,444, and U.S. patent application Publication Nos. 2003/0153505 A1; 2003/0083263 A1; and 2003/0055002 A1, each of which is hereby incorporated by reference.

Taxanes and Other Microtubule Stabilizing Compounds

[0171] Taxanes such as paclitaxel, doxetaxel, RPR 109881A, SB-T-1213, SB-T-1250, SB-T-101187, BMS-275183, BRT 216, DJ-927, MAC-321, IDN5109, and IDN5390 can be used in combination with the compounds of the invention to treat cancer and other neoplasms. Taxane analogs (e.g., BMS-184476, BMS-188797) and functionally related non-taxanes (e.g., epothilones (e.g., epothilone A, epothilone B (EPO906), deoxyepothilone B, and epothilone B lactam (BMS-247550)), eleutherobin, discodermolide, 2-epi-discodermolide, 2-des-methyldiscodermolide, 5-hydroxymethyldiscoder- molide, 19-des-aminocarbonyldiscodermolide, 9(13)-cyclodiscodermolide, and laulimalide) can also be used in the methods and compositions of the invention.

[0172] Other microtubule stabilizing compounds that can be used in combination with the compounds of the invention to treat cancer and other neoplasms are described in U.S. Pat. Nos. 6,624,317; 6,610,736; 6,605,599; 6,589,968; 6,583,290; 6,576,658; 6,515,017; 6,531,497; 6,500,858; 6,498,257; 6,495,594; 6,489,314; 6,458,976; 6,441,186; 6,441,025; 6,414,015; 6,387,927; 6,380,395; 6,380,394; 6,362,217; 6,359,140; 6,306,893; 6,302,838; 6,300,355; 6,291,690; 6,291,684; 6,268,381; 6,262,107; 6,262,094; 6,147,234; 6,136,808; 6,127,406; 6,100,411; 6,096,909; 6,025,385; 6,011,056; 5,965,718; 5,955,489; 5,919,815; 5,912,263;

5,840,750; 5,821,263; 5,767,297; 5,728,725; 5,721,268; 5,719,177; 5,714,513; 5,587,489; 5,473,057; 5,407,674; 5,250,722; 5,010,099; and 4,939,168; and U.S. patent application Publication Nos. 2003/0186965 A1; 2003/0176710 A1; 2003/0176473 A1; 2003/0144523 A1; 2003/0134883 A1; 2003/0087888 A1; 2003/0060623 A1; 2003/0045711 A1; 2003/0023082 A1; 2002/0198256 A1; 2002/0193361 A1; 2002/0188014 A1; 2002/0165257 A1; 2002/0156110 A1; 2002/0128471 A1; 2002/0045609 A1; 2002/0022651 A1; 2002/0016356 A1; 2002/0002292 A1, each of which is hereby incorporated by reference.

[0173] Other chemotherapeutic agents that may be administered with a compound of the present invention are listed in the following Table:

Alkylating agents	cyclophosphamide lomustine busulfan procarbazine ifosfamide altretamine melphalan estramustine phosphate hexamethylmelamine	mechlorethamine thiotepa streptozocin chlorambucil temozolomide dacarbazine semustine carmustine
Platinum agents	cisplatin carboplatinum oxaliplatin ZD-0473 (AnorMED) spiroplatinum lobaplatin (Aeterna) carboxyphthalatoplatinum satraplatin (Johnson Matthey)	tetraplatin BBR-3464 (Hoffmann-La Roche) Ormiplatin SM-11355 (Sumitomo) iproplatin AP-5280 (Access)
Antimetabolites	azacytidine tomudex gemcitabine trimetrexate capecitabine deoxycoformycin 5-fluorouracil fludarabine floxuridine pentostatin 2-chlorodeoxyadenosine raltitrexed	6-mercaptopurine hydroxyurea 6-thioguanine decitabine (SuperGen) cytarabin clofarabine (Bioenvision) 2-fluorodeoxy cytidine irofulven (MGI Pharma) methotrexate DMDC (Hoffmann-La Roche) idatrexate ethynylcytidine (Taiho)

Topoisomerase inhibitors	amsacrine rubitecan (SuperGen) epirubicin exatecan mesylate (Daiichi) etoposide quinamed (ChemGenex) teniposide or mitoxantrone gimatecan (Sigma-Tau) irinotecan (CPT-11) diflomotecan (Beaufour-Ipsen) 7-ethyl-10-hydroxy-camptothecin	TAS-103 (Taiho) Topotecan elsamitrucin (Spectrum) dexrazoxanet (TopoTarget) J-107088 (Merck & Co) pixantrone (Novuspharma) BNP-1350 (BioNumerik) rebeccamycin analogue (Exelixis) CKD-602 (Chong Kun Dang) BBR-3576 (Novuspharma) KW-2170 (Kyowa Hakko)
Antitumor antibiotics	dactinomycin (actinomycin D) amonafide doxorubicin (adriamycin) azonafide deoxyrubicin anthrapyrazole valrubicin oxantrazole daunorubicin (daunomycin) losoxantrone epirubicin bleomycin sulfate (blenoxane) therarubicin	bleomycinic acid idarubicin bleomycin A rubidazone bleomycin B plicamycinp mitomycin C porfiromycin MEN-10755 (Menarini) cyanomorpholinodoxorubicin GPX-100 (Gem Pharmaceuticals) mitoxantrone (novantrone)
Antimitotic agents	paclitaxel SB 408075 (GlaxoSmithKline) docetaxel E7010 (Abbott) Colchicines PG-TXL (Cell Therapeutics) vinblastine IDN 5109 (Bayer) Vincristine A 105972 (Abbott) Vinorelbine A 204197 (Abbott) Vindesine LU 223651 (BASF) dolastatin 10 (NCI) D 24851 (ASTAMedica) rhizoxin (Fujisawa) ER-86526 (Eisai) mivobulin (Warner-Lambert) combretastatin A4 (BMS) cemadotin (BASF) isohomohalichondrin-B (PharmaMar)	RPR 109881A (Aventis) ZD 6126 (AstraZeneca) TXD 258 (Aventis) PEG-paclitaxel (Enzon) epothilone B (Novartis) AZ10992 (Asahi) T 900607 (Tularik) IDN-5109 (Indena) T 138067 (Tularik) AVLB (Prescient NeuroPharma) cryptophycin 52 (Eli Lilly) azaepothilone B (BMS) vinflunine (Fabre) BNP-7787 (BioNumerik) auristatin PE (Teikoku Hormone) CA-4 prodrug (OXiGENE) BMS 247550 (BMS) dolastatin-10 (NIH) BMS 184476(BMS) CA-4 (OXiGENE) BMS 188797 (BMS) taxoprexin (Protarga)

Aromatase inhibitors	Aminoglutethimide Exemestane Letrozole atamestane (BioMedicines)	anastrazole YM-511 (Yamanouchi) formestane
Thymidylate synthase inhibitors	pemetrexed (Eli Lilly) nolatrexed (Eximias)	ZD-9331 (BTG) CoFactor™ (BioKeys)
DNA antagonists	trabectedin (PharmaMar) mafosfamide (Baxter International) glufosfamide (Baxter International) apaziquone (Spectrum Pharmaceuticals)	albumin + 32P (Isotope Solutions) O6 benzyl guanine (Paligent) thymectacin (NewBiotics) edotreotide (Novartis)
Farnesyl-transferase inhibitors	arglabin (NuOncology Labs) tipifarnib (Johnson & Johnson) lonafarnib (Schering-Plough)	perillyl alcohol (DOR BioPharma) BAY-43-9006 (Bayer)
Pump inhibitors	CBT-1 (CBA Pharma) zosuquidar trihydrochloride (Eli Lilly)	tariquidar (Xenova) biricodar dicitrate (Vertex) MS-209 (Schering AG)
Histone acetyltransferase inhibitors	tacedinaline (Pfizer) pivaloyloxymethyl butyrate (Titan) SAHA (Aton Pharma)	depsipeptide (Fujisawa) MS-275 (Schering AG)
Metallo-proteinase inhibitors	Neovastat (Aeterna Laboratories) CMT-3 (CollaGenex)	marimastat (British Biotech) BMS-275291 (Celltech)
Ribonucleoside reductase inhibitors	gallium maltolate (Titan) tezacitabine (Aventis)	triapine (Vion) didox (Molecules for Health)
TNF alpha agonists/ antagonists	virulizin (Lorus Therapeutics) revimid (Celgene)	CDC-394 (Celgene)
Endothelin A receptor antagonist	atrasentan (Abbott) YM-598 (Yamanouchi)	ZD-4054 (AstraZeneca)
Retinoic acid receptor agonists	fenretinide (Johnson & Johnson) alitretinoin (Ligand)	LGD-1550 (Ligand)
Immuno-modulators	Interferon dexosome therapy (Anosys) oncophage (Antigenics)	norelin (Biostar) IRX-2 (Immuno-Rx) BLP-25 (Biomira)

	pentrix (Australian Cancer Technology) GMK (Progenics) ISF-154 (Tragen) adenocarcinoma vaccine (Biomira) cancer vaccine (Intercell) CTP-37 (A VI BioPharma)	PEP-005 (Peplin Biotech) MGV (Progenics) synchrovax vaccines (CTL Immuno) beta.-alethine (Dovetail) melanoma vaccine (CTL Immuno) CLL therapy (Vasogen) p21 RAS vaccine (GemVax)
Hormonal and antihormonal agents	estrogens Prednisone conjugated estrogens methylprednisolone ethinyl estradiol prednisolone chlortrianisen aminoglutethimide idenestrol leuprolide hydroxyprogesterone caproate goserelin medroxyprogesterone leuporelin testosterone	bicalutamide testosterone propionate; fluoxymesterone flutamide methyltestosterone octreotide diethylstilbestrol nilutamide megestrol mitotane tamoxifen P-04 (Novogen) Toremofine 2-methoxyestradiol (EntreMed) dexamethasone arzoxifene (Eli Lilly)
Photodynamic agents	talaporfin (Light Sciences) Pd-bacteriopheophorbide (Yeda) Theralux (Theratechnologies) lutetium texaphyrin (Pharmacyclics)	motexafin gadolinium (Pharmacyclics) hypericin
Tyrosine Kinase Inhibitors	imatinib (Novartis) kahalide F (PharmaMar) leflunomide (Sugen/Pharmacia) CEP-701 (Cephalon) ZD1839 (AstraZeneca) CEP-751 (Cephalon) erlotinib (Oncogene Science) MLN518 (Millenium) canertinib (Pfizer) PKC412 (Novartis) squalamine (Genaera) phenoxodiol SU5416 (Pharmacia) trastuzumab (Genentech) SU6668 (Pharmacia) Sorafenib Herceptin Cetuximab	C225 (ImClone) ZD4190 (AstraZeneca) rhu-Mab (Genentech) ZD6474 (AstraZeneca) MDX-H210 (Medarex) vatalanib (Novartis) 2C4 (Genentech) PKI166 (Novartis) MDX-447 (Medarex) GW2016 (GlaxoSmithKline) ABX-EGF (Abgenix) EKB-509 (Wyeth) IMC-1C11 (ImClone) EKB-569 (Wyeth) CI-1033 EKB-569 Semaxanib ZD6474

	ZD1839 PKI 166	PTK-787 INC-1C11
Miscellaneous agents		
SR-27897 (CCK A inhibitor, Sanofi-Synthelabo) BCX-1777 (PNP inhibitor, BioCryst) tocladesine (cyclic AMP agonist, Ribapharm) ranpirnase (ribonuclease stimulant, Alfacell) alvocidib (CDK inhibitor, Aventis) galarubicin (RNA synthesis inhibitor, Dong-A) CV-247 (COX-2 inhibitor, Ivy Medical) tirapazamine (reducing agent, SRI International) P54 (COX-2 inhibitor, Phytopharm) N-acetylcysteine (reducing agent, Zambon) CapCell™ (CYP450 stimulant, Bavarian Nordic) R-flurbiprofen (NF-kappaB inhibitor, Encore) GCS-100 (gal3 antagonist, GlycoGenesys) 3CPA (NF-kappaB inhibitor, Active Biotech) G17DT immunogen (gastrin inhibitor, Aphton) seocalcitol (vitamin D receptor agonist, Leo) efaproxiral (oxygenator, Allos Therapeutics) 131-I-TM-601 (DNA antagonist, TransMolecular) PI-88 (heparanase inhibitor, Progen) eflornithine (ODC inhibitor, ILEX Oncology) tesmilifene (histamine antagonist, YM BioSciences) minodronic acid (osteoclast inhibitor, Yamanouchi) histamine (histamine H2 receptor agonist, Maxim) indisulam (p53 stimulant, Eisai) tiazofurin (IMPDH inhibitor, Ribapharm) aplidine (PPT inhibitor, PharmaMar) cilengitide (integrin antagonist, Merck KGaA) rituximab (CD20 antibody, Genentech) SR-31747 (IL-1 antagonist, Sanofi-Synthelabo)	gemtuzumab (CD33 antibody, Wyeth Ayerst) CCI-779 (mTOR kinase inhibitor, Wyeth) PG2 (hematopoiesis enhancer, Pharmagenesis) exisulind (PDE V inhibitor, Cell Pathways) Immunol™ (triclosan oral rinse, Endo) CP-461 (PDE V inhibitor, Cell Pathways) triacetyluridine (uridine prodrug, Wellstat) AG-2037 (GART inhibitor, Pfizer) SN-4071 (sarcoma agent, Signature BioScience) WX-UK1 (plasminogen activator inhibitor, Wilex) TransMID-107 .TM. (immunotoxin, KS Biomedix) PBI-1402 (PMN stimulant, ProMetic LifeSciences) PCK-3145 (apoptosis promotor, Procyon) bortezomib (proteasome inhibitor, Millennium) doranidazole (apoptosis promotor, Pola) SRL-172 (T cell stimulant, SR Pharma) CHS-828 (cytotoxic agent, Leo) TLK-286 (glutathione S transferase inhibitor, Telik) trans-retinoic acid (differentiator, NIH) PT-100 (growth factor agonist, Point Therapeutics) MX6 (apoptosis promotor, MAXIA) midostaurin (PKC inhibitor, Novartis) apomine (apoptosis promotor, ILEX Oncology) bryostatin-1 (PKC stimulant, GPC Biotech) urocidin (apoptosis promotor, Bioniche) CDA-II (apoptosis promotor, Everlife) Ro-31-7453 (apoptosis promotor, La Roche) SDX-101 (apoptosis promotor, Salmedix) brostallicin (apoptosis promotor, Pharmacia) ceflatonin (apoptosis promotor, ChemGenex)	

[0174] Additional combinations may also include agents which reduce the toxicity of the aforesaid agents, such as hepatic toxicity, neuronal toxicity, nephrotoxicity and the like.

[0175] Additional combinations may be used in the treatment of RA such as non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids and disease-modifying antirheumatic drugs. Further combinations may include Kineret, Actemra, Hydroxychloroquine (Plaquenil™), Sulfasalazine (Azulfidine™), Leflunomide (Arava™), Tumor Necrosis Factor Inhibitors such as etanercept (Enbrel™, adalimumab (Humira™), and infliximab (Remicade™), T-cell costimulatory blocking agents such as abatacept (Orencia™), B cell depleting agents such as rituximab (Rituxan™), Interleukin-1 (IL-1) receptor antagonist therapy such as anakinra (Kineret™), intramuscular gold and other immunomodulatory and cytotoxic agents such as azathioprine (Imuran™), cyclophosphamide and cyclosporine A (Neoral™, Sandimmune™).

[0176] Other cotherapies for the treatment of RA include Methotrexate, Campath (alemtuzumab), anti-RANKL MAb (denosumab), anti-Blys MAb LymphoStat-B™ (belimumab), Cimzia (certolizumab pegol), p38 inhibitors, JAK inhibitors, anti-TNF agents, anti-CD20 MAbs, anti-IL/ILR targeting agents such as those which target IL-1, IL-5, IL-6 (toclizumab), Il-4, IL-13, and IL-23.

[0177] Additional combinations may be used in the treatment of MS such as Remicade™, Enbrel™, Humaira™, Kineret™, Orencia™, Rituxan™ and TYSABRI™ (natalizumab).

Screening assays

[0178] The compounds of the present invention may also be used in a method to screen for other compounds that bind to an IAP BIR domain. Generally speaking, to use the compounds of the invention in a method of identifying compounds that bind to an IAP BIR domain, the IAP is bound to a support, and a compound of the invention is added to the assay. Alternatively, the compound of the invention may be bound to the support and the IAP is added.

[0179] There are a number of ways in which to determine the binding of a compound of the present invention to the BIR domain. In one way, the compound of the invention, for example, may be fluorescently or radioactively labeled and binding determined directly. For example, this may be done by attaching the IAP to a solid support, adding a detectably labeled compound of the invention, washing off excess reagent, and determining whether the amount of the detectable label is that present on the solid support. Numerous blocking and washing steps may be used, which are known to those skilled in the art.

[0180] In some cases, only one of the components is labeled. For example, specific residues in the BIR domain may be labeled. Alternatively, more than one component may be labeled with different labels; for example, using I^{125} for the BIR domain, and a fluorescent label for the probe.

[0181] The compounds of the invention may also be used as competitors to screen for additional drug candidates or test compounds. As used herein, the terms "drug candidate" or "test compounds" are used interchangeably and describe any molecule, for example, protein, oligopeptide, small organic molecule, polysaccharide, polynucleotide, and the like, to be tested for bioactivity. The compounds may be capable of directly or indirectly altering the IAP biological activity.

[0182] Drug candidates can include various chemical classes, although typically they are small organic molecules having a molecular weight of more than 100 and less than about 2,500 Daltons. Candidate agents typically include functional groups necessary for structural interaction with proteins, for example, hydrogen bonding and lipophilic binding, and typically include at least an amine, carbonyl, hydroxyl, ether, or carboxyl group. The drug candidates often include cyclical carbon or heterocyclic structures and/or aromatic or polyaromatic structures substituted with one or more functional groups.

[0183] Drug candidates can be obtained from any number of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means.

[0184] Competitive screening assays may be done by combining an IAP BIR domain and a probe to form a probe:BIR domain complex in a first sample followed by adding a test compound from a second sample. The binding of the test is determined, and a change or difference in binding between the two samples indicates the presence of a test compound capable of binding to the BIR domain and potentially modulating the IAP's activity.

[0185] In one case, the binding of the test compound is determined through the use of competitive binding assays. In this embodiment, the probe is labeled with a fluorescent label. Under certain circumstances, there may be competitive binding between the test compound and the probe. Test compounds which display the probe, resulting in a change in fluorescence as compared to control, are considered to bind to the BIR region.

[0186] In one case, the test compound may be labeled. Either the test compound, or a compound of the present invention, or both, is added first to the IAP BIR domain for a time sufficient to allow binding to form a complex.

[0187] Formation of the probe:BIR domain complex typically require Incubations of between 4 °C and 40 °C for between 10 minutes to about 1 hour to allow for high-throughput screening. Any excess of reagents are generally removed or washed away. The test compound is then added, and the presence or absence of the labeled component is followed, to indicate binding to the BIR domain.

[0188] In one case, the probe is added first, followed by the test compound. Displacement of the probe is an indication the test compound is binding to the BIR domain and thus is capable of binding to, and potentially modulating, the activity of IAP. Either component can be labeled. For example, the presence of probe in the wash solution indicates displacement by the test compound. Alternatively, if the test compound is labeled, the presence of the probe on the support indicates displacement.

[0189] In one case, the test compound may be added first, with incubation and washing, followed by the probe. The absence of binding by the probe may indicate the test compound is bound to the BIR domain with a higher affinity. Thus, if the probe is detected on the support, coupled with a lack of test compound binding, may indicate the test compound is capable of binding to the BIR domain.

[0190] Modulation is tested by screening for a test compound's ability to modulate the activity of IAP and includes combining a test compound with an IAP BIR domain, as described above, and determining an alteration in the biological activity of the IAP. Therefore in this case, the test compound should both bind to the BIR domain (although this may not be necessary), and alter its biological activity as defined herein.

[0191] Positive controls and negative controls may be used in the assays. All control and test samples are performed multiple times to obtain statistically significant results. Following incubation, all samples are washed free of non-specifically bound material and the amount of bound probe determined. For example, where a radiolabel is employed, the samples may be counted in a scintillation counter to determine the amount of bound compound.

[0192] Typically, the signals that are detected in the assay may include fluorescence, resonance energy transfer, time resolved fluorescence, radioactivity, fluorescence polarization, plasma resonance, or chemiluminescence and the like, depending on the nature of the label. Detectable labels useful in performing screening assays in this invention include a fluorescent label such as Fluorescein, Oregon green, dansyl, rhodamine, tetramethyl rhodamine, texas red, Eu^{3+}; a chemiluminescent label such as luciferase; colorimetric labels; enzymatic markers; or radioisotopes such as tritium, I^{125} and the like. Affinity tags, which may be useful in performing the screening assays of the present invention include be biotin, polyhistidine and the like.

SYNTHESIS AND METHODOLOGY

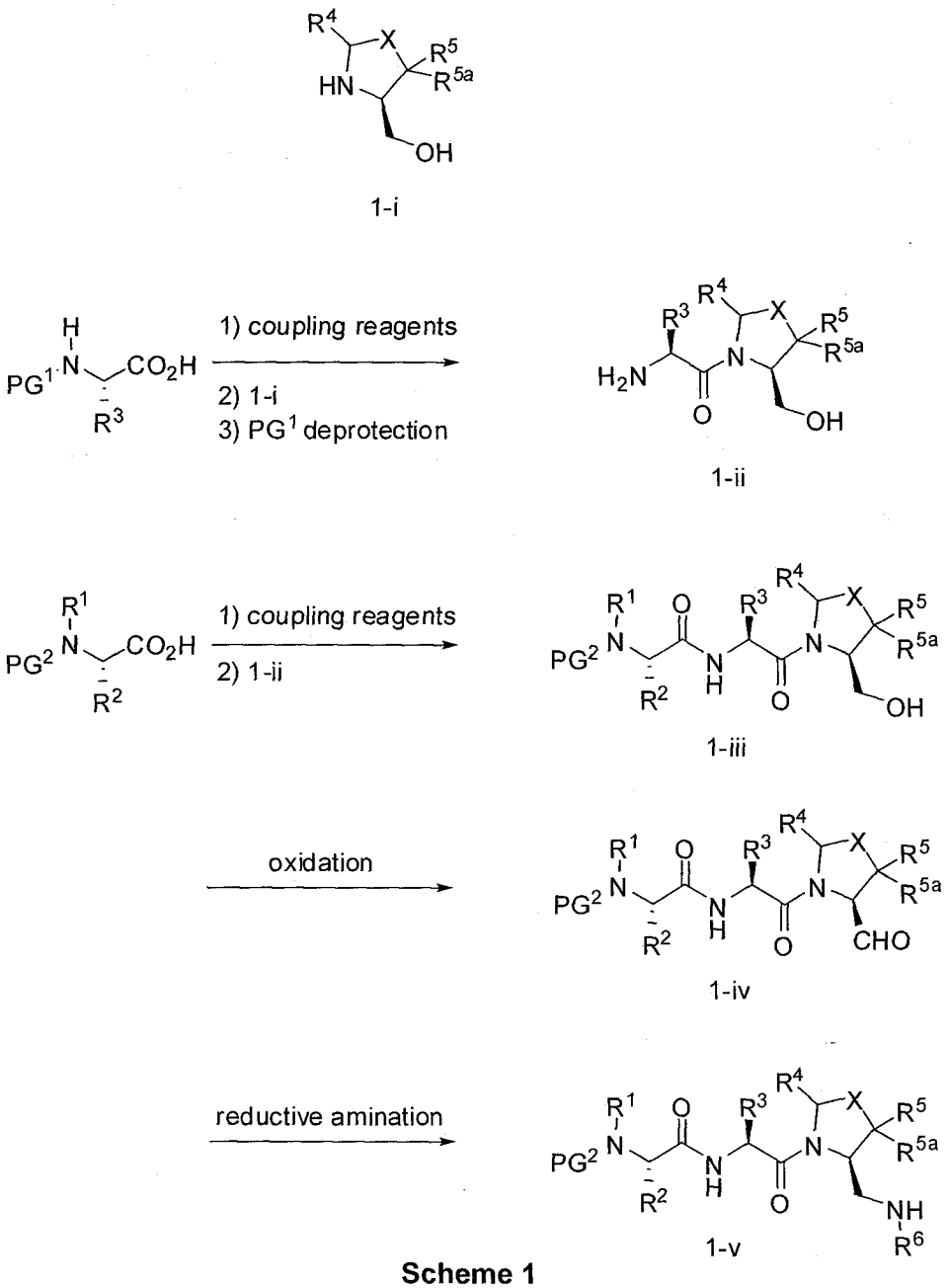
[0193] General methods for the synthesis of the compounds of the present invention are shown below and are disclosed merely for the purpose of illustration and are not meant to be interpreted as limiting the processes to make the compounds by any other methods. Those skilled in the art will readily appreciate that a number of methods are available for the preparation of the compounds of the present invention. General Method A describes the bridging of two BIR binding units, such as intermediates 1-v or 7-i, while General Method B involves preparation of the compound starting with the bridging moiety and sequential addition of amino acid moieties. Thus, the invention provides a method of preparing a compound comprising the steps of Method A or Method B. Furthermore, each of the individual steps of Method A and Method B, the intermediates involved, and methods of preparing the intermediate compounds used, are considered to be additional aspects of the invention.

General Procedures

General Method A:

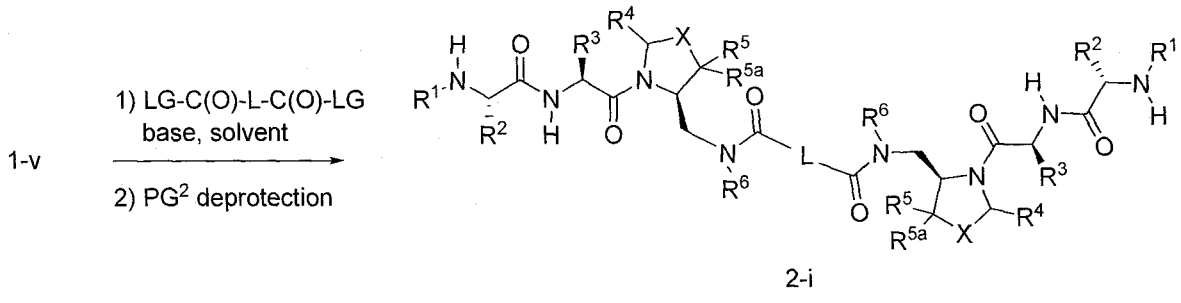
[0194] Scheme 1 illustrates a general procedure for the preparation of intermediates of general formula 1-v. Intermediate 1-v is obtained from a prolinol derivative of general formula 1-i by first coupling $PG^1(H)N(R^3)CHCO_2H$ using amino acid coupling agents, followed by deprotection of PG^1. Similarly, $PG^2(R^1)N(R^2)CHCO_2H$ is coupled to 1-ii to yield 1-iii which was

then oxidized to the corresponding aldehyde 1-iv. Intermediate 1-v was then prepared by a reductive amination sequence. As such, 1-iv was treated with amine R^6NH_2, followed by reduction with an appropriate hydride.



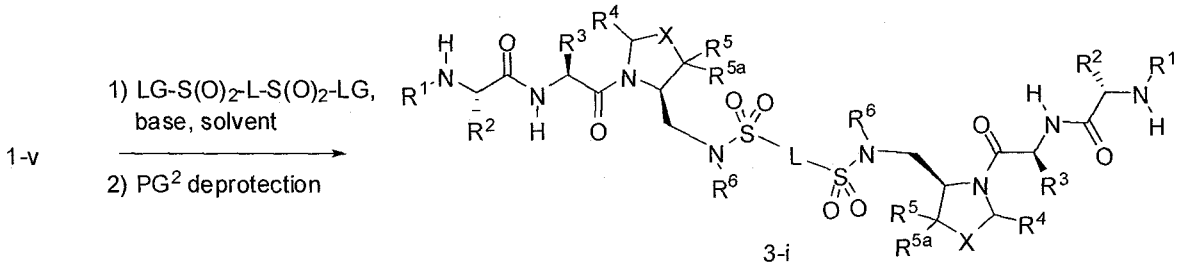
Scheme 1

[0195] Scheme 2 illustrates general procedures for the preparation of bis-amide bridged compound of the instant invention. Treatment of intermediate 1-v with LG-C(O)-L-C(O)-LG and deprotection of PG^2 provides compounds of formula 2-i.



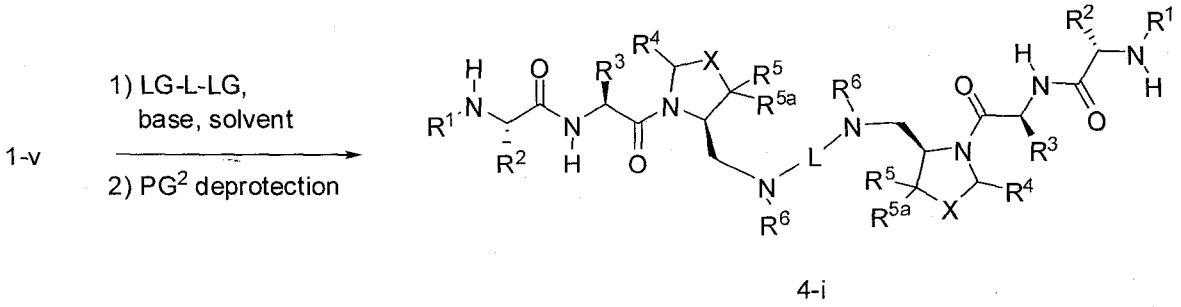
Scheme 2

[0196] Scheme 3 illustrates general procedures for the preparation of bis-sulfonamide bridged compounds of the instant invention. Treatment of intermediate 1-v with LG-$S(O)_2$-L-$S(O)_2$-LG and deprotection of PG^2 provides compounds of formula 3-i.



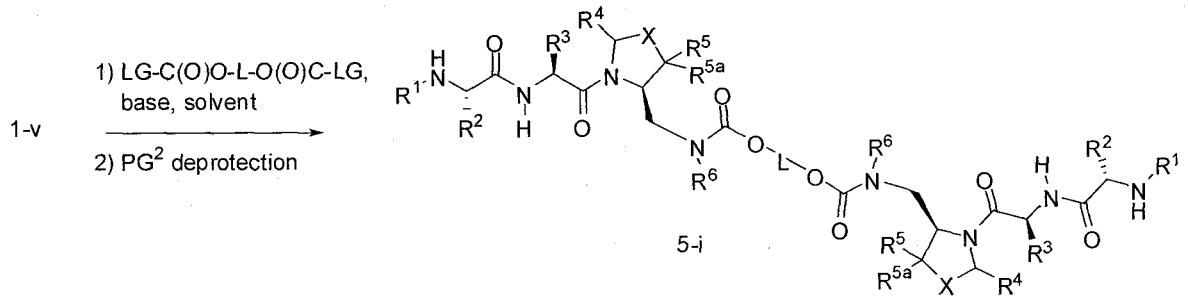
Scheme 3

[0197] Scheme 4 illustrates general procedures for the preparation of alkyl bridged compounds of the instant invention. Treatment of intermediate 1-v with LG-L-LG and deprotection of PG^2 provides compounds of formula 4-i.



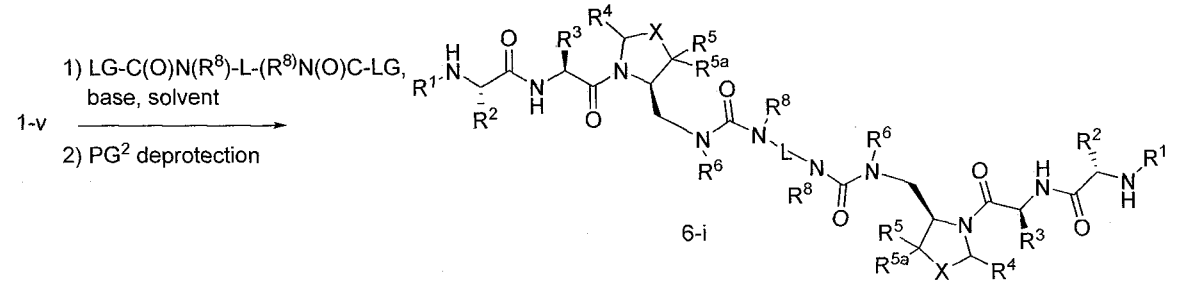
Scheme 4

[0198] Scheme 5 illustrates general procedures for the preparation of bis-carbamate bridged compounds of the instant invention. Treatment of intermediate 1-v with LG-C(O)O-L-O(O) C-LG and deprotection of PG^2 provides compounds of formula 5-i.



Scheme 5

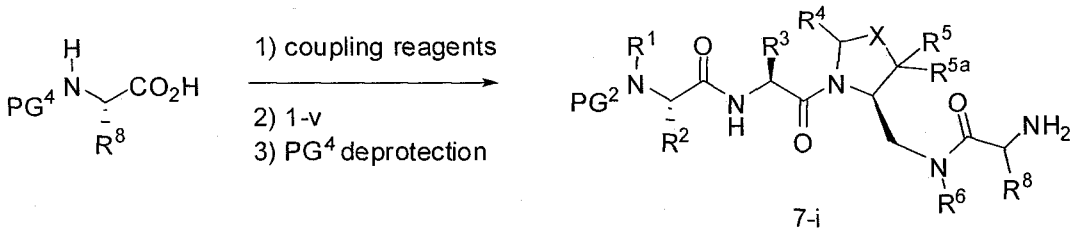
[0199] Scheme 6 illustrates general procedures for the preparation of bis-urea bridged compounds of the instant invention. Treatment of intermediate 1-v with LG-C(O)N(R^8)-L-(R^8)N(O)C-LG and deprotection of PG^2 provides compounds of formula 6-i.



Scheme 6

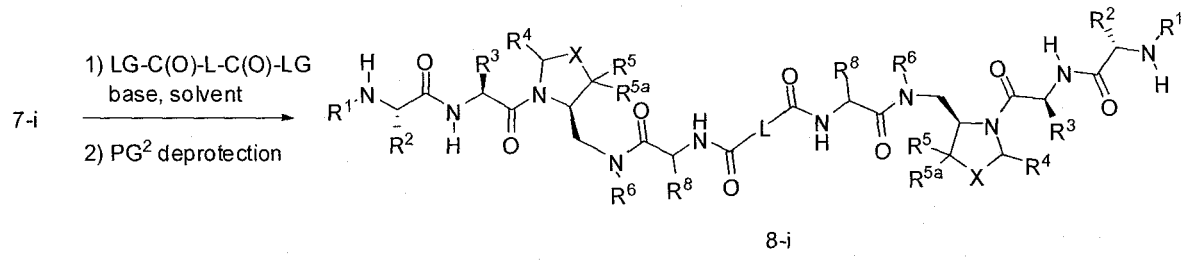
[0200] Scheme 7, 8, 9 and 10 illustrates the use of functionalized amino acids as bridging groups.

[0201] Scheme 7 illustrates a general procedure for the preparation of intermediates of general formula 7-i. $PG^4(H)N(R^8)CHCO_2H$ is coupled to 1-v using amino acid coupling agents, followed by deprotection of PG^4 provides intermediates of formula 7-i.



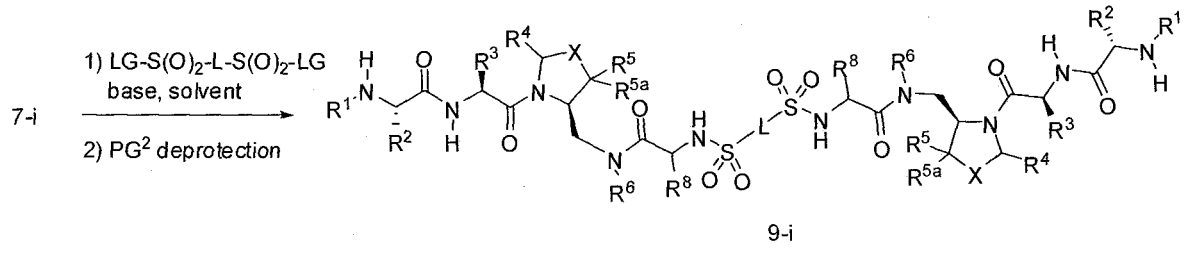
Scheme 7

[0202] Treatment of intermediate 7-i with LG-C(O)-L-C(O)-LG followed by deprotection of PG^2 provides compounds of formula 8-i.



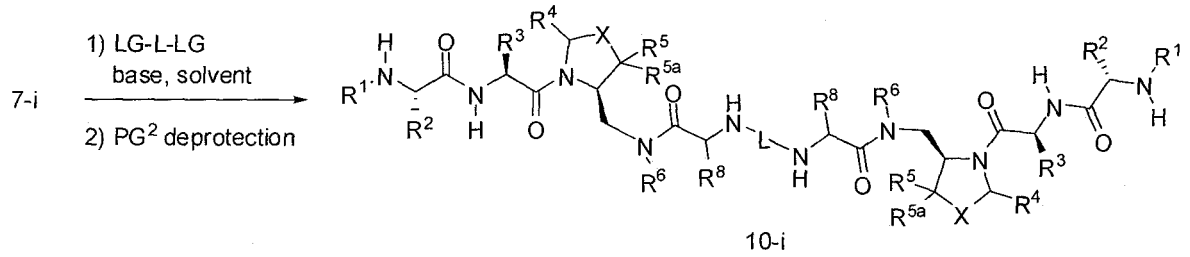
Scheme 8

[0203] Treatment of intermediate 7-i with LG-$S(O)_2$-L-$S(O)_2$-LG followed by deprotection of PG^2 provides compounds of formula 9-i.



Scheme 9

[0204] Treatment of intermediate 7-i with LG-L-LG followed by deprotection of PG^2 provides compounds of formula 10-i.

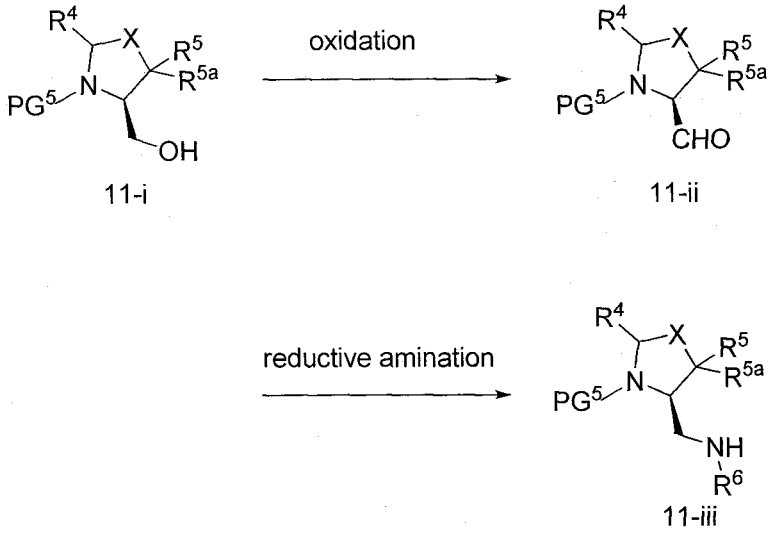


Scheme 10

[0205] Accordingly, the invention provides, as an additional aspect of the invention, a method for preparing a compound of Formula 1 (or Formulas 1A or 1.1A) comprising any one or more of the steps illustrated by Schemes 1-10, above.

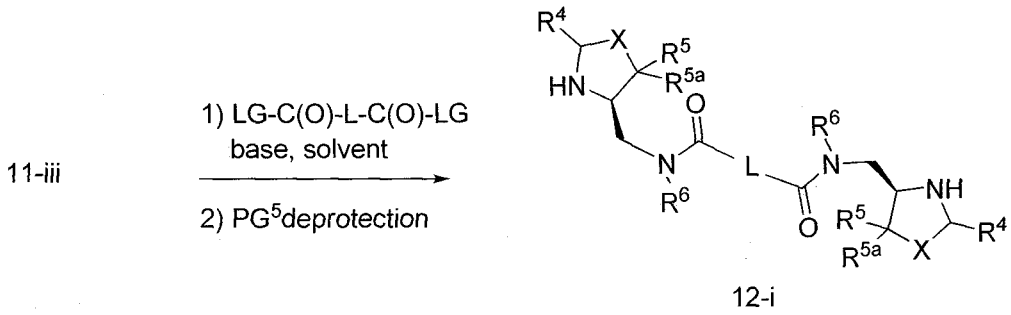
General Method B:

[0206] Scheme 11 illustrates a general procedure for the preparation of intermediates of general formula 11-iii. Alcohol 11-i was oxidized to the corresponding aldehyde 11-ii. Intermediate 11-iii was then prepared by a reductive amination sequence; 11-ii was treated with amine R^6NH_2, followed by reduction by an appropriated hydride.



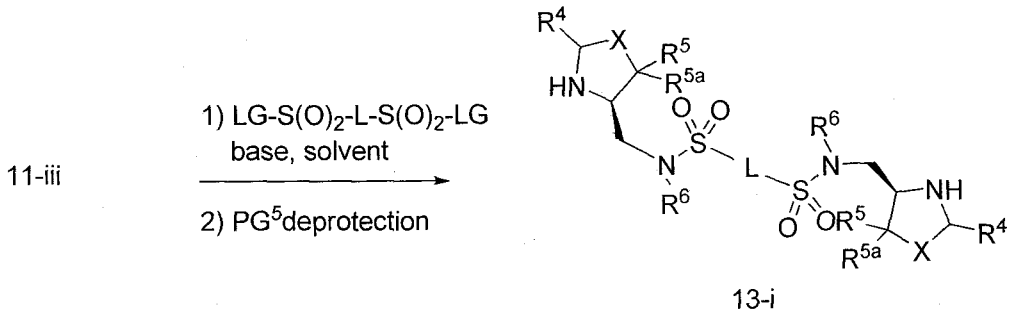
Scheme 11

[0207] Scheme 12 illustrates general procedures for the preparation of bis-amide bridged intermediates. Treatment of intermediate 11-iii with LG-C(O)-L-C(O)-LG and deprotection of PG^5 provides intermediates of formula 12-i.



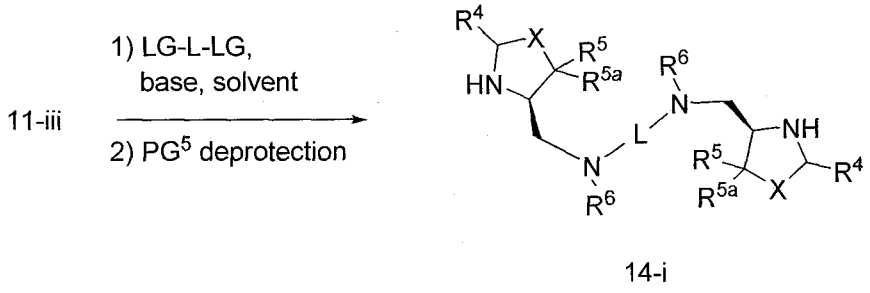
Scheme 12

[0208] Scheme 13 illustrates general procedures for the preparation of bis-sulfonamide bridged intermediates. Treatment of intermediate 11-iii with LG-$S(O)_2$-L-$S(O)_2$-LG and deprotection of PG^5 provides intermediates of formula 13-i.



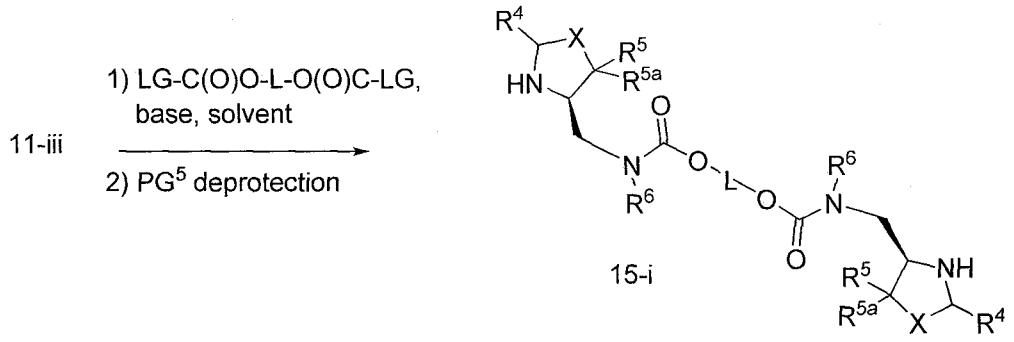
Scheme 13

[0209] Scheme 14 illustrates general procedures for the preparation of alkyl bridged intermediates. Treatment of intermediate 11-iii with LG-L-LG and deprotection of PG^5 provides intermediates of formula 14-i.



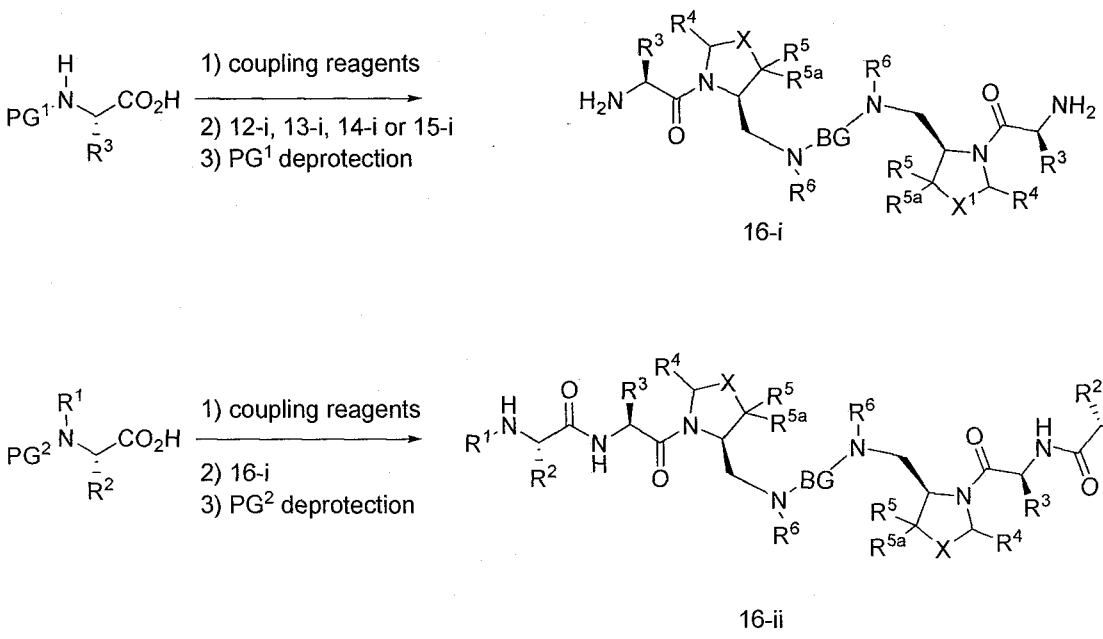
Scheme 14

[0210] Scheme 15 illustrates general procedures for the preparation of bis-carbamate bridged intermediates. Treatment of intermediate 11-iii with LG-C(O)O-L-O(O)C-LG and deprotection of PG^5 provides intermediates of formula 15-i.



Scheme 15

[0211] Scheme 16 illustrates a general procedure for the preparation of compounds of the instant invention. Compounds of general formula 16-ii are obtained from intermediate 12-i, 13-i, 14-i or 15-i by first coupling $PG^1(H)N(R^3)CHCO_2H$ using amino acid coupling agents, followed by deprotection of PG^1. Similarly, $PG^2(R^1)N(R^2)CHCO_2H$ is coupled to 16-i and deprotection of PG^2 provides compounds of formula 16-ii.



Scheme 16

[0212] LG is a leaving group such as, for example, Cl, Br, I, OTs or OMs. PG is a protecting group such as, for example, Boc, Cbz, Fmoc.

[0213] Accordingly, the invention provides, as an additional aspect of the invention, a method for preparing a compound of Formula 1 (or Formulas 1A or 1.1A) comprising any one or more of the steps illustrated by Schemes 11-16, above. Thus, the method can comprise any one or more of the following steps:

(a) oxidizing a compound of Formula 11-i to provide a compound of Formula 11-ii; (b) treating a compound of 11-ii with an amine (R6NH2) followed by reduction with a hydride to provide a compound of Formula 11-iii;

(c) combining the compound of Formula 11-iii with (1) LG-C(O)-L-C(O)-LG followed by deprotecting PG5 to provide a compound of Formula 12-i; (2) LG-S(O)2-L-S(O)2-LG followed by deprotecting PG5 to provide a compound of Formula 13-i; (3) LG-L-LG followed by deprotecting PG5 to provide a compound of Formula 14-i; or (4) LG-C(O)O-L-O(O)C-LG

followed by deprotecting PG5 to provide a compound of Formula 15-i; and/or

(d) combining (e.g., coupling) the compound of Formula 12-i, 13-i, 14-i, or 15-i with PG1(H)N(R3)CHCO2H using an amino acid coupling agent, followed by deprotection of PG1 to provide a compound of Formula 16-i.

EXAMPLES

[0214] The following abbreviations are used throughout:

Boc: *t*-butoxycarbonyl;
Boc-Chg-OH: Boc-L-2(cyclohexyl)glycine
Boc-N-MeAla-OH: N-Boc-N-methylalanine
CBz: benzyloxycarbonyl;
DCM: dichloromethane, CH_2Cl_2;
DIPEA: diisopropylethylamine;
DMAP: 4-(dimethylamino)pyridine;
DMF: N,N-dimethylformamide;
DTT: dithiothreitol;
EDC: 3-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride;
EDTA: ethylenediaminetetracetic acid;
Fmoc: N-(9-fluorenylmethoxycarbonyl);
HBTU: *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate;
HCl: hydrochloric acid;
HOAc: acetic acid;
HOBt: 1-hydroxybenzotriazole;
HPLC: high performance liquid chromatography;
LCMS: liquid chromatography-mass spectrometer;
MeOH: methanol;
$MgSO_4$: magnesium sulfate;
MS: mass spectrum;
Ms: methanesulfonyl;
$NaHCO_3$: sodium hydrogen carbonate;
Pd/C: palladium on carbon;
TEA: triethylamine;

TFA: trifluoroacetic acid;
THF: tetrahydrofuran;
TMEDA: N,N,N,N-tetramethylethylenediamine;
Ts: para-toluenesulfonyl.

SYNTHETIC METHODS

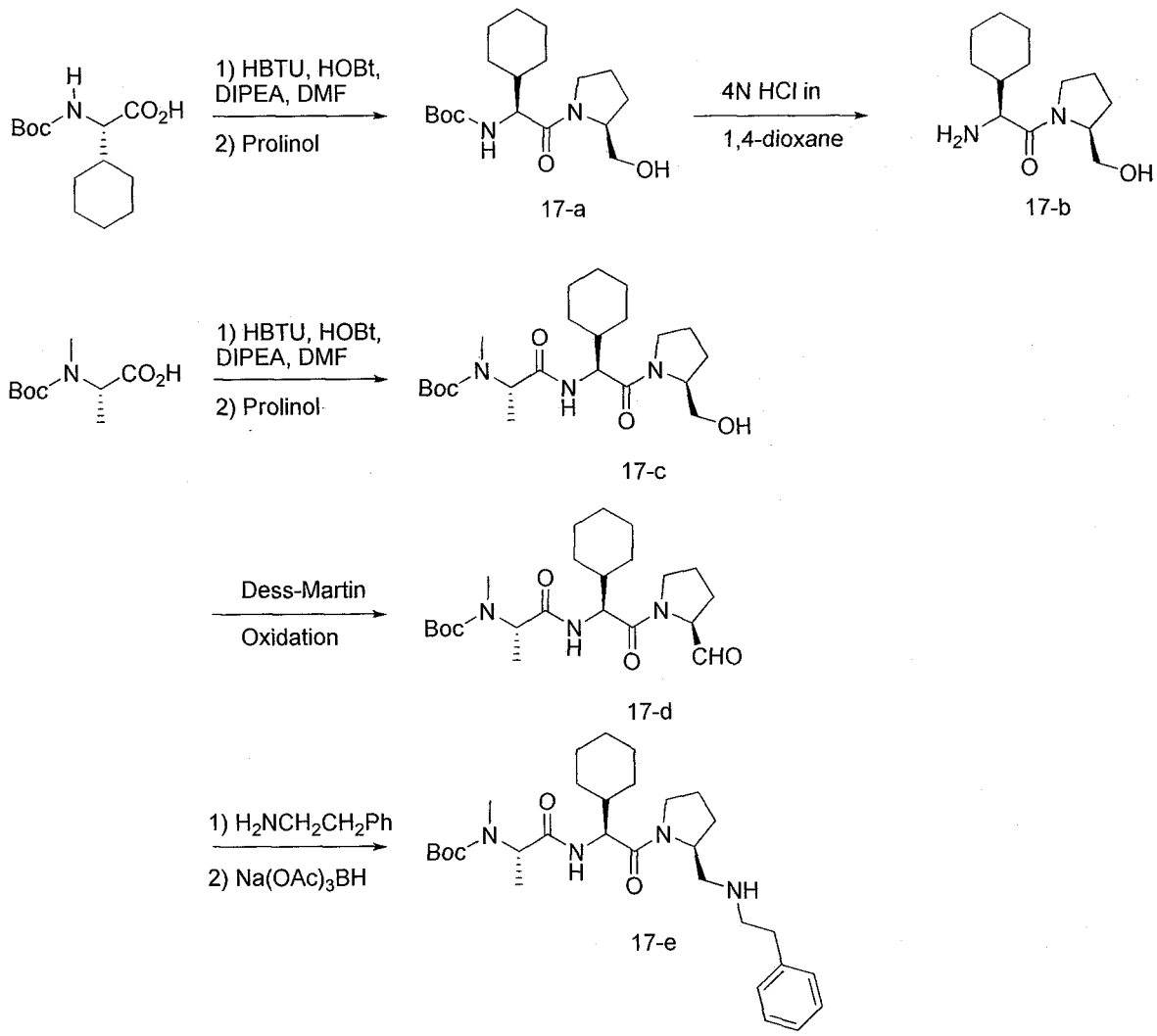
[0215] The following section summarizes synthetic methods used in the synthesis of compounds of the instant invention.

Preparation of representative examples:

[0216] General Method A is illustrated in Schemes 17-20 for the preparation of compounds 1 and 12. General Method B is illustrated in Schemes 21-23 for the preparation of compounds 27 and 36. Compounds of the instant invention may be prepared using variation of these methods using the appropriate starting materials and reagents.

Synthesis of Intermediate 17-e

[0217] Activation of the carboxyl group of Boc-Chg-Gly-OH by treatment with the amide coupling agent HBTU, HOBt, and DIPEA in DMF followed by addition of (S)-prolinol provides intermediate 17-a. Boc deprotection using 4N HCl in 1,4-dioxane provides intermediate 17-b. Under similar conditions activation of the carboxyl group of Boc-NMe-Ala-OH was followed by the addition of intermediate 17-b to provide intermediate 17-c. Dess-Martin oxidation of intermediate 17-c provides the corresponding aldehyde 17-d. Reductive amination of intermediate 17-d using phenethylamine and sodium triacethoxy borohydride provides intermediate 17-e.



Scheme 17

Step 1

[0218] To a solution of Boc-Chg-OH (9.16 g, 35.6 mmol) in DMF cooled to 0 °C were sequentially added DIPEA (10.33 mL, 59.3 mmol), HOBt (4.81 g, 35.6 mmol) and HBTU (13.50 g, 35.6 mmol). After stirring for 10 minutes (S)-Prolinol (3.0 g, 29.7 mmol) was added and the reaction mixture was stirred overnight at room temperature. Water and ethyl acetate were added, the organic layer was separated, washed with 10 % citric acid, aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by silica gel chromatography, eluting with a hexane/THF gradient, provided intermediate 17-a as colorless oil.

Step 2

[0219] 4N HCl in 1,4 dioxane (30 mL) was added to intermediate 17-a (10.10 g, 29.7 mmol) and the solution was stirred for 1 hour at room temperature. Volatiles were removed under reduced pressure and the residue was triturated with diethyl ether to provide intermediate 17-b·HCl as a white solid. MS (m/z) M+1= 240.2

Step 3

[0220] To a solution of Boc-N-Me-Ala-OH (6.02 g, 29.6 mmol) in DMF cooled to 0 °C were sequentially added DIPEA (20.70 mL, 118 mmol), HOBt (6.35 g, 41.5 mmol) and HBTU (14.61 g, 38.5 mmol). After stirring for 10 minutes intermediate 17-b·HCl (8.20 g, 29.6 mmol) was added and the reaction mixture was stirred overnight at room temperature. Water and ethyl acetate were added, the organic layer was separated, washed with 10 % citric acid, aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by silica gel chromatography, eluting with a THF/Hexane gradient provided intermediate 17-c as colorless oil.

Step 4

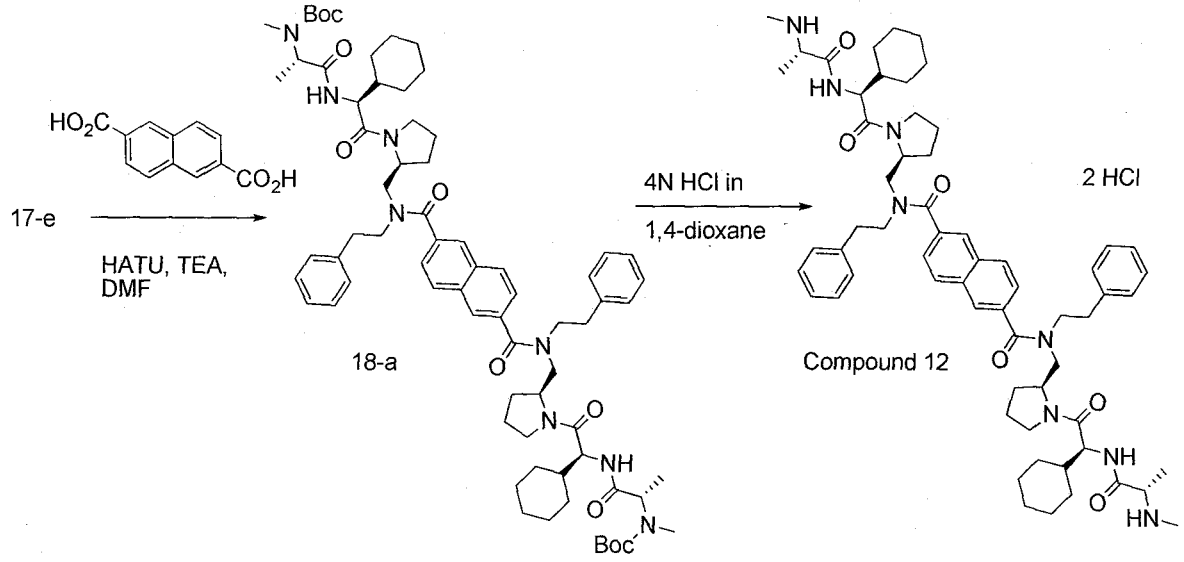
[0221] To a solution of intermediate 17-c (1.20 g, 2.82 mmol) in CH_2Cl_2 cooled to 0°C were sequentially added sodium hydrogencarbonate (2.36 g, 28.2 mmol) and Dess-Martin Periodinane (1.49 g, 3.52 mmol) and the reaction was then stirred for 2 hours at 10°C. Aqueous $NaHCO_3$ and ethyl acetate were added, the organic layer was separated, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to provide intermediate 17-d as colorless oil.

Step 5

[0222] To a solution of intermediate 17-d (500 mg, 1.18 mmol) in CH_2Cl_2 was added phenethylamine (283 uL, 1.88 mmol). After stirring for 2 hours at room temperature sodium triacetoxyborohydride (300 mg, 1.41 mmol) and methanol were added and the reaction was stirred at room temperature overnight. Saturated aqueous $NaHCO_3$ and ethyl acetate were added, the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to provide intermediate 17-e as colorless oil. MS (m/z) M+1=528.4

Synthesis of Compound 12

[0223] Activation of carboxyl groups of naphthalene-2,6-dicarboxylic acid using HATU, followed by addition of 17-e provides intermediate 18-a. Boc-deprotection of intermediate 18-a using 4N HCl in 1,4-dioxane yields compound 12 as its bis-hydrochloride salt.



Scheme 18

Step 1

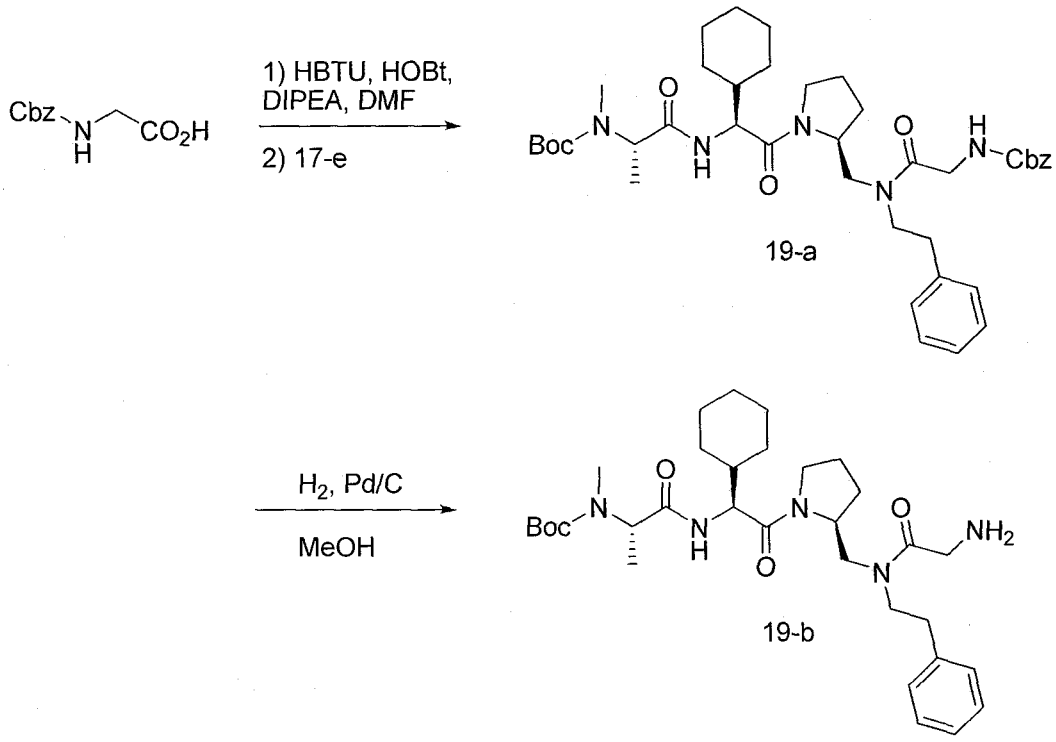
[0224] To a solution of naphthalene-2,6-dicarboxylic acid (62 mg, 0.28 mmol) in DMF cooled to 0°C were sequentially added DIPEA (151 uL, 0.86 mmol) and HATU (241 mg, 0.63 mmol). After stirring for 10 minutes intermediate 17-e (320 g, 0.60 mmol) was added and the reaction was stirred overnight at room temperature. Water and ethyl acetate were added, the organic layer was separated, washed with 10 % citric acid, aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by silica gel chromatography, eluting with a hexane/THF gradient, provided intermediate 18-a as a white solid.

Step 2

[0225] 4N HCl in 1,4-dioxane (2.0 mL) was added to intermediate 18-a (156 mg, 0.12 mmol) and the solution was stirred for 1 hour at room temperature. Volatiles were removed under reduced pressure and the residue was triturated with diethyl ether to provide compound 12·2HCl as a white solid. MS (m/z) M+1= 1037.7

Synthesis of Intermediate 19-b

[0226] Activation of the carboxyl group of Cbz-Gly-OH by treatment with the amide coupling agent HBTU and DIPEA in DMF solvent was followed by the addition of 11-e to provide intermediate 13-a. Cbz deprotection using Pd/C under a hydrogen atmosphere in MeOH provided intermediate 13-b.



Scheme 19

Step 1

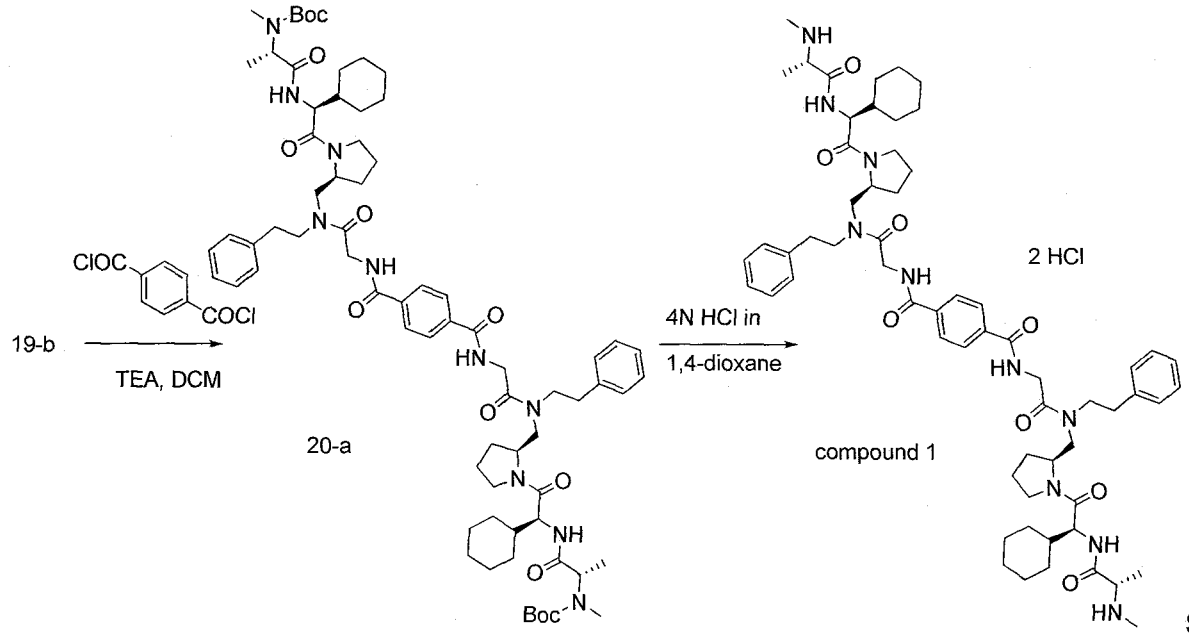
[0227] To a solution of Cbz-Gly-OH (1.04 g, 5.0 mmol) in DMF cooled to 0 °C were sequentially added DIPEA (2.91 mL, 16.64 mmol) and HBTU (2.05 g, 5.41 mmol). After stirring for 10 minutes intermediate 17-e (2.20 g, 4.16 mmol) was added and the reaction mixture was stirred overnight at room temperature. Water and ethyl acetate were added, the organic layer was separated, washed with 10 % citric acid, aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by silica gel chromatography, eluting with a hexane/THF gradient, provided intermediate 19-a as a white solid.

Step 2

[0228] To a solution of intermediate 19-a (2.47 g, 3.43 mmol) in anhydrous MeOH and stirred under N_2 was added 10% Pd/C (73 mg). The reaction mixture was purged with H_2 and stirred for 1 hour. The reaction was then filtered through celite and the filtrates were concentrated in vacuo to provide intermediate 19-b as a white solid. MS (m/z) M+1= 585.4

Synthesis of compound 1

[0229] Treatment of a solution of 19-b with terephthaloyl dichloride and TEA in CH_2Cl_2 provided intermediate 20-a. Boc-deprotection of intermediate 20-a using 4N HCl in 1,4-dioxane yields compound 1 as its bis-hydrochloride salt.



Sch eme 20

Step 1

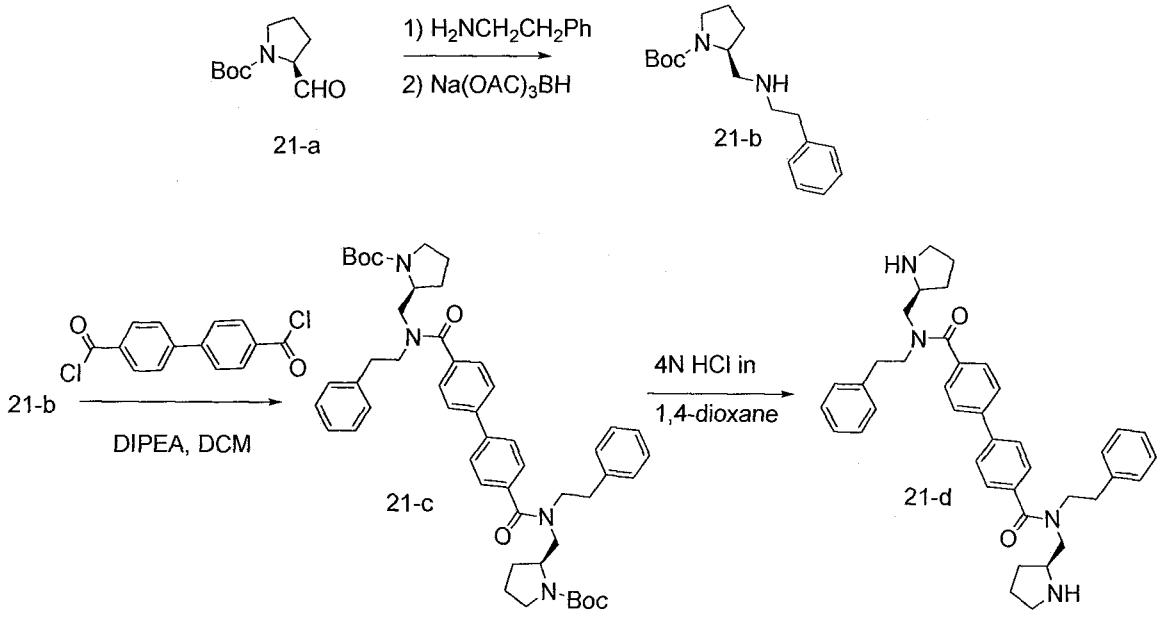
[0230] To a solution of intermediate 19-b (200 mg, 0.34 mmol) in CH_2Cl_2 cooled to 0°C were sequentially added DIPEA (71.0 uL, 0.40 mmol), DMAP (Catalytic) and terephthaloyl dichloride (33 mg, 0.16 mmol) and the reaction was stirred overnight at room temperature. Water and ethyl acetate were added, the organic layer was separated, washed with 10 % citric acid, aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by silica gel chromatography, eluting with a hexane/THF gradient, provided intermediate 20-a as a white solid.

Step 2

[0231] 4N HCl in 1,4-dioxane (2.0 mL) was added to intermediate 20-a (190 mg, 0.14 mmol) and the solution was stirred for 1 hour at room temperature. Volatiles were removed under reduced pressure and the residue was triturated with diethyl ether to provide compound 1·2HCl as a white solid. MS (m/z) M+1= 1101.7

Synthesis of intermediate 21-d

[0232] Reductive amination of Boc-(S)-Prolinal, 21-a, using phenethylamine and sodium triacethoxy borohydride provides intermediate 21-b. Treatment of a solution of intermediate 21-b with biphenyl-4,4'-dicarbonyl dichloride and DIPEA in DCM provided intermediate 21-c. Boc-deprotection of intermediate 21-c using 4N HCl in 1,4-dioxane provided intermediate 21-d.



Scheme 21

Step1

[0233] To a solution of intermediate 21-a (5.00 g, 25.09 mmol) in CH_2Cl_2 was added phenethylamine (3.04 g, 25.09 mmol). After stirring for 2 hours at room temperature sodium triacetoxyborohydride (6.38 g, 30.10 mmol) and methanol were added and the reaction was stirred at room temperature overnight. Saturated aqueous $NaHCO_3$ and ethyl acetate were added, the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to provide intermediate 21-b as colorless oil. MS (m/z) M+1=305.2.

Step2

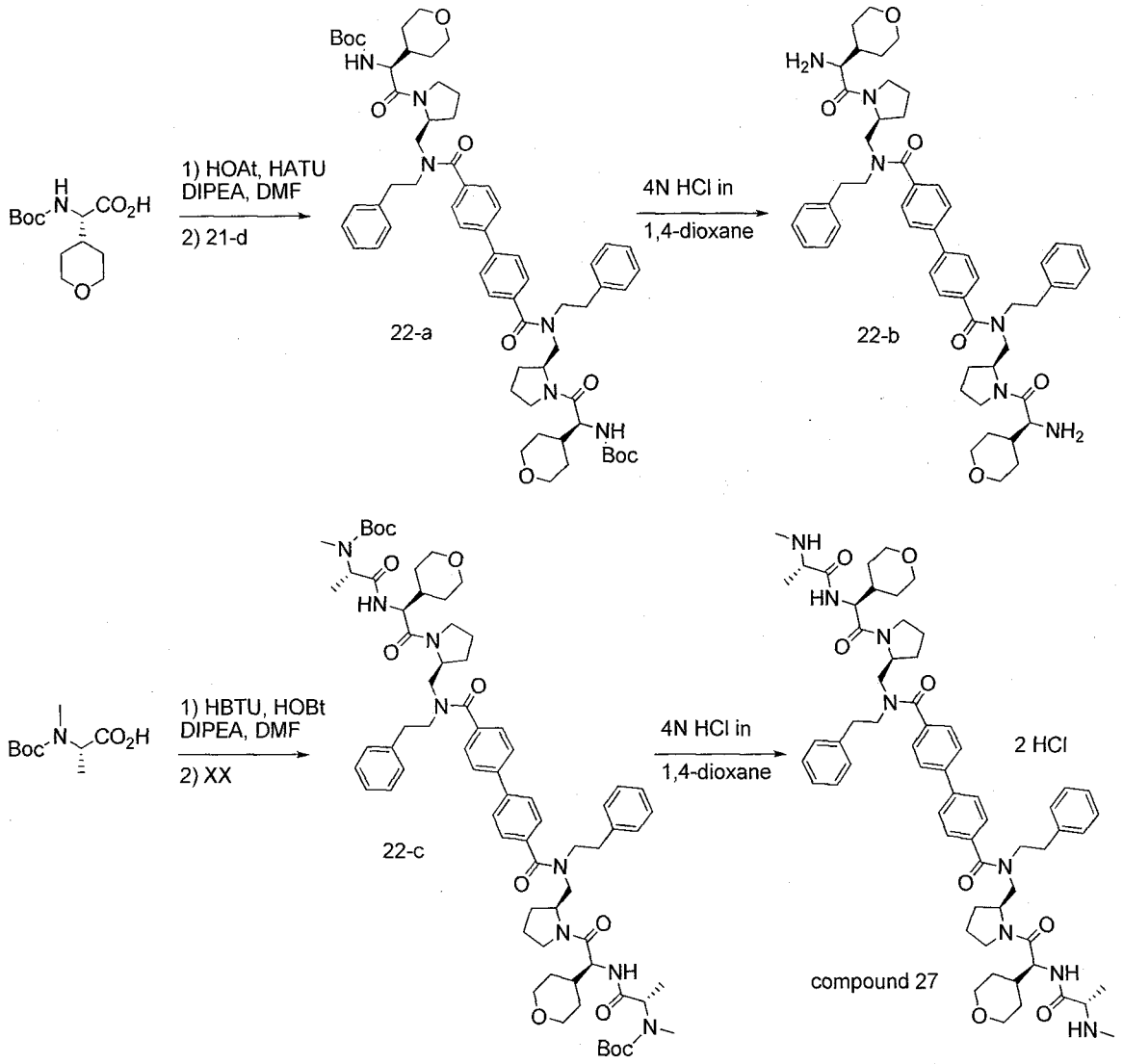
[0234] To a solution of intermediate 21-b (3.00 g, 9.85 mmol) in CH_2Cl_2 cooled to 0°C were sequentially added DIPEA (3.44 mL, 19.71 mmol), DMAP (Catalytic) and biphenyl-4,4'-dicarbonyl dichloride (1.37 g, 4.93 mmol) and the reaction was stirred overnight at room temperature. Water and ethyl acetate were added, the organic layer was separated, washed with 10 % citric acid, aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by silica gel chromatography, eluting with a hexane/THF gradient, provided intermediate 21-c as a white solid.

Step3

[0235] 4N HCl in 1,4-dioxane (1.18 mL) was added to intermediate 21-c (3.85 g, 4.72 mmol) in MeOH (0.5 mL) and the solution was stirred for 1 hour at 0°C. Volatiles were removed under reduced pressure and the residue was triturated with diethyl ether to provide intermediate 21-d as a white solid. MS (m/z) M+1= 615.5

Synthesis of compound 27

[0236] Activation of the carboxyl group of (S)-2-(tert-butoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid by treatment with the amide coupling agent HATU, HOAt, and DIPEA in DMF followed by addition of intermediate 21-d provides intermediate 22-a. Boc deprotection using 4N HCl in 1,4-dioxane provides intermediate 22-b. Under similar conditions activation of the carboxyl group of Boc-NMe-Ala-OH with the amide coupling agent HBTU, HOBt, and DIPEA in DMF was followed by the addition of intermediate 22-b to provide intermediate 22-c. Boc-deprotection of intermediate 22-c using 4N HCl in 1,4-dioxane yields compound 27 as its bis-hydrochloride salt.



Scheme 22

Step1

[0237] To a solution of 21-d (222 mg, 0.32 mmol) in DMF cooled to 0 °C were sequentially added DIPEA (226 uL, 1.29 mmol), HOAt (1.07 mL, 0.64 mmol) (S)-2-(tert-butoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (251 mg, 0.96 mmol) and HATU (491 mg, 1.29 mmol) and the reaction mixture was stirred overnight at room temperature. Water and ethyl acetate were added, the organic layer was separated, washed with 1M HCl, aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by silica gel chromatography, eluting with a hexane/THF gradient, provided intermediate 22-a as a white solid.

Step2

[0238] 4N HCl in 1,4 dioxane (4.0 mL) was added to intermediate 22-a (285 mg, 0.24 mmol) and the solution was stirred for 1 hour at 0°C. Volatiles were removed under reduced pressure and the residue was triturated with diethyl ether to provide intermediate 22-b as a white solid. MS (m/z) M+1= 897.4

Step3

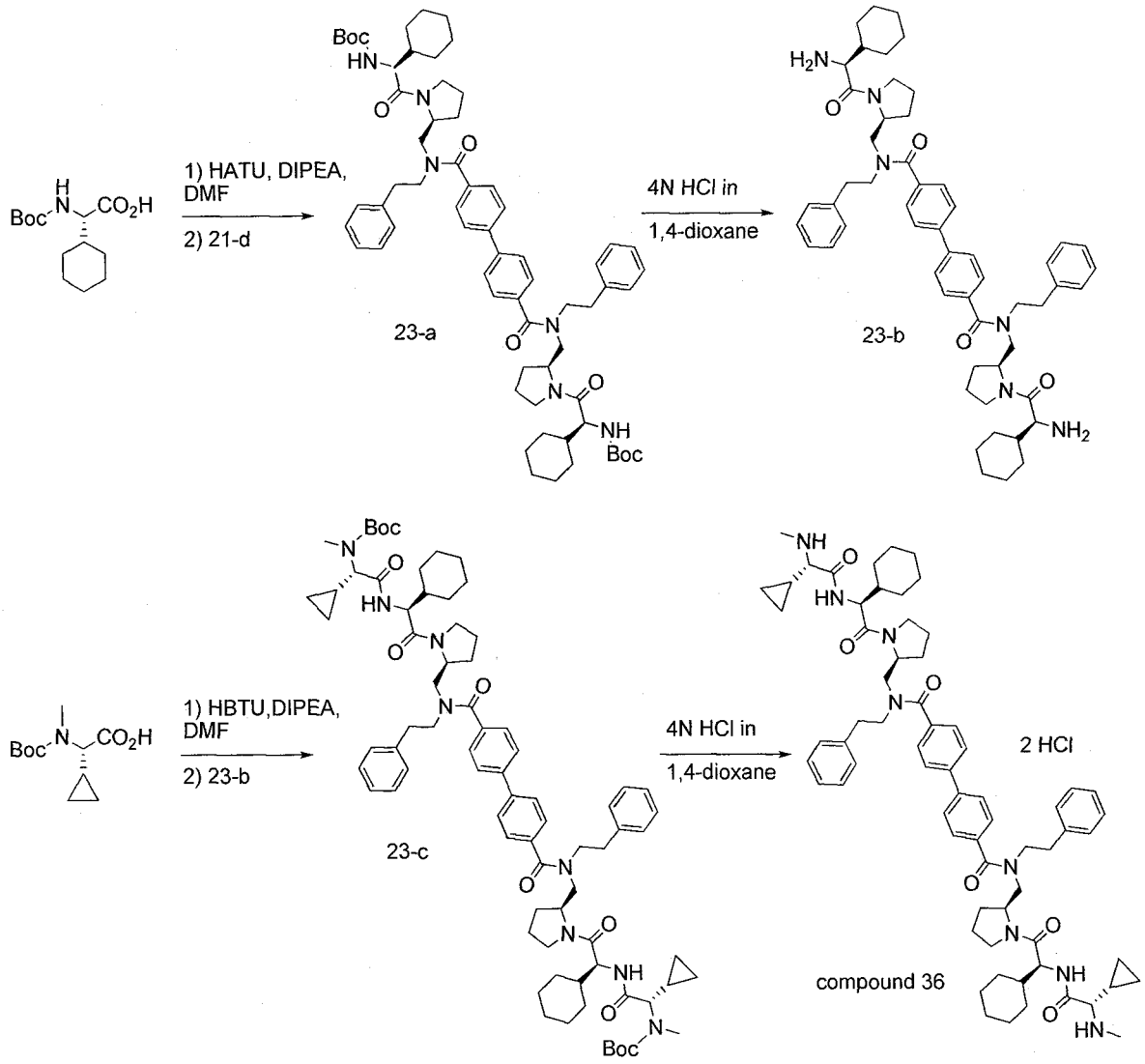
[0239] To a solution of Boc-N-Me-Ala-OH (148 mg, 0.73 mmol) in DMF cooled to 0 °C were sequentially added DIPEA (255 uL, 1.46 mmol), HOBt (187 mg, 0.73 mmol) and HBTU (277 mg, 0.73 mmol). After stirring for 10 minutes intermediate 22-b (236 mg, 0.24 mmol) was added and the reaction mixture was stirred overnight at room temperature. Water and ethyl acetate were added, the organic layer was separated, washed with 10 % citric acid, aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by silica gel chromatography, eluting with a THF/Hexane gradient provided intermediate 22-c as a white solid.

Step4

[0240] 4N HCl in 1,4 dioxane (4.0 mL) was added to intermediate 22-c (199 mg, 0.15 mmol) and the solution was stirred for 1 hour at 0°C. Volatiles were removed under reduced pressure and the residue was triturated with diethyl ether to provide compound 27·2HCl as a white solid. MS (m/z) M+1= 1067.7

Synthesis of compound 36

[0241] Activation of the carboxyl group of Boc-Chg-OH by treatment with the amide coupling agent HATU, and DIPEA in DMF followed by addition of intermediate 21-d provides intermediate 23-a. Boc deprotection using 4N HCl in 1,4-dioxane provides intermediate 23-b. Under similar conditions activation of the carboxyl group of (S)-2-(tert-butoxycarbonyl(methyl)amino)-2-cyclpropylacetic acid with the amide coupling agent HBTU, and DIPEA in DMF was followed by the addition of intermediate 23-b to provide intermediate 23-c. Boc-deprotection of intermediate 23-c using 4N HCl in 1,4-dioxane yields compound 36 as its bis-hydrochloride salt.



Scheme 23

Step1

[0242] To a solution of 21-d (5.20 g, 7.56 mmol) in DMF cooled to 0 °C were sequentially added DIPEA (10.0 mL, 53.7 mmol), Boc-Chg-OH (4.28 g, 16.63 mmol) and HATU (7.19 g, 18.90 mmol and the reaction mixture was stirred overnight at room temperature. Water and ethyl acetate were added, the organic layer was separated, washed with 1M HCl, aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by silica gel chromatography, eluting with a hexane/THF gradient, provided intermediate 23-a as a white solid.

Step2

[0243] 4N HCl in 1,4 dioxane (20.0 mL) was added to intermediate 23-a (6.46 g, 5.91 mmol) at 0°C and the solution was stirred for 3 hours at room temperature. Volatiles were removed under reduced pressure and the residue was triturated with diethyl ether to provide intermediate 23-b as a white solid. MS (m/z) M+1= 893.5

Step3

[0244] To a solution of intermediate 23-b (493 mg, 0.44 mmol) in DMF cooled to 0 °C were sequentially added DIPEA (1.0 mL, 5.74 mmol), (S)-2-(tert-butoxycarbonyl(methyl)amino)-2-cyclopropylacetic acid (222 mg, 0.96 mmol) and HBTU (417 mg, 1.10 mmol) and the reaction mixture was stirred overnight at room temperature. Water and ethyl acetate were added, the organic layer was separated, washed with 1M HCl, aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by silica gel chromatography, eluting with a THF/Hexane gradient provided intermediate 23-c as a white solid.

Step4

[0245] 4N HCl in 1,4 dioxane (1.0 mL) was added to intermediate 23-c (317 mg, 0.24 mmol) in MeOH at 0°C and the solution was stirred for 3 hours at room temperature. Volatiles were removed under reduced pressure and the residue was triturated with diethyl ether to provide compound 36·2HCl as a white solid. MS (m/z) M+1= 1115.6

[0246] Representative compounds of the present invention were prepared according to the above procedures and are illustrated in Table 1.

[0247] Compounds 1-17, 29 and 31-33 were prepared using similar procedures as described in General Method A, using the appropriate starting materials and reagents. Compounds 18-28, 30 and 34-39 were prepared using similar procedures as described in General Method B, using the appropriate starting materials and reagents.

TABLE 1

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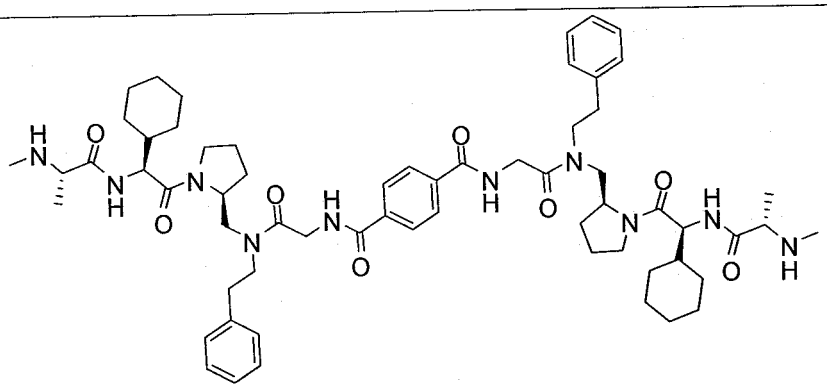
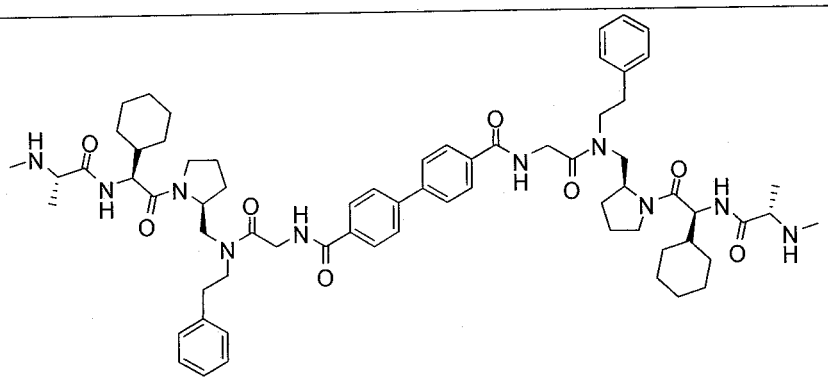
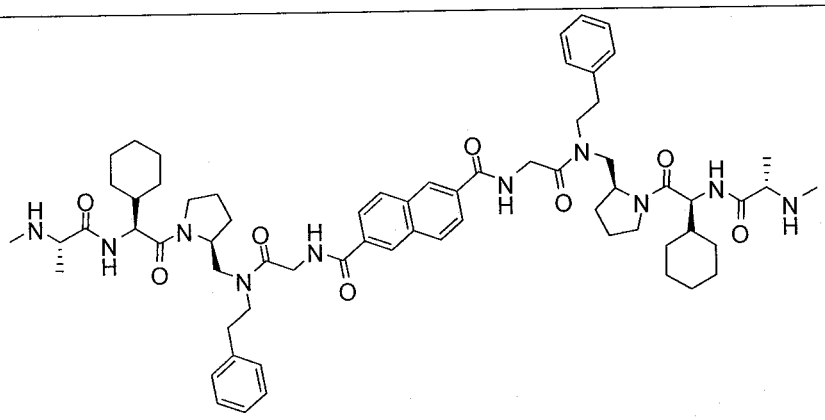
1		M+1=1101.7
2		M+1=1177.8
3		M+1=1151.8

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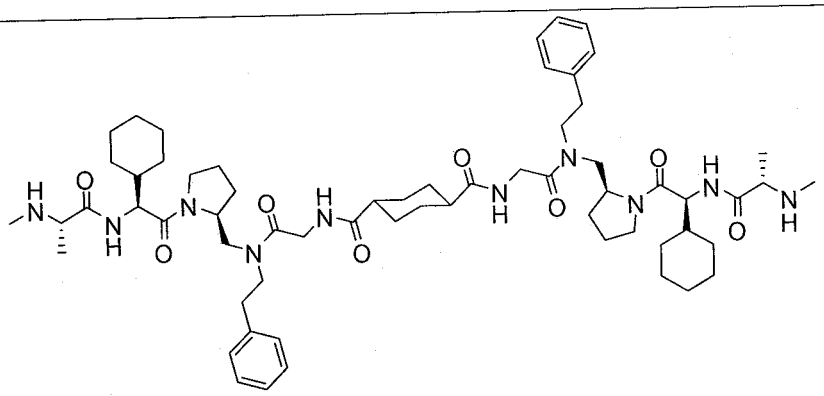
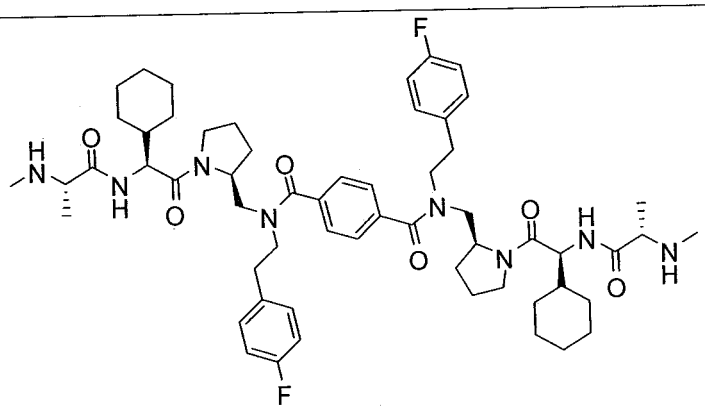
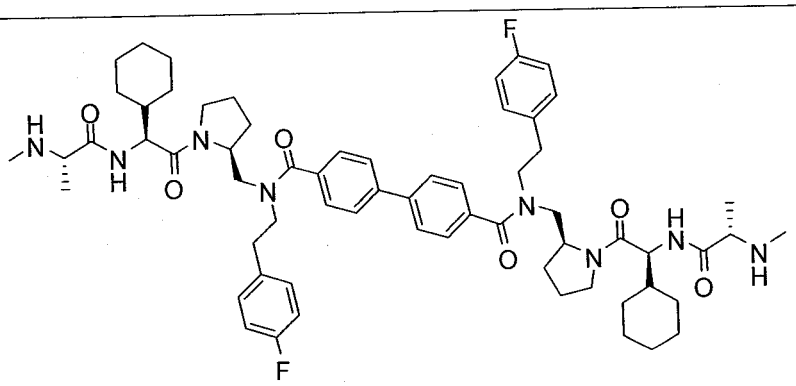
4		M+1=1107.8
5		M+1=1023.6
6		M+1=1099.6

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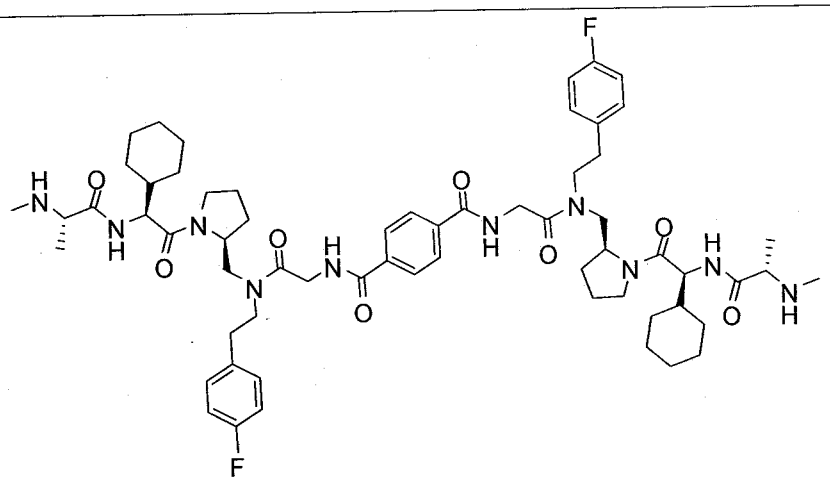
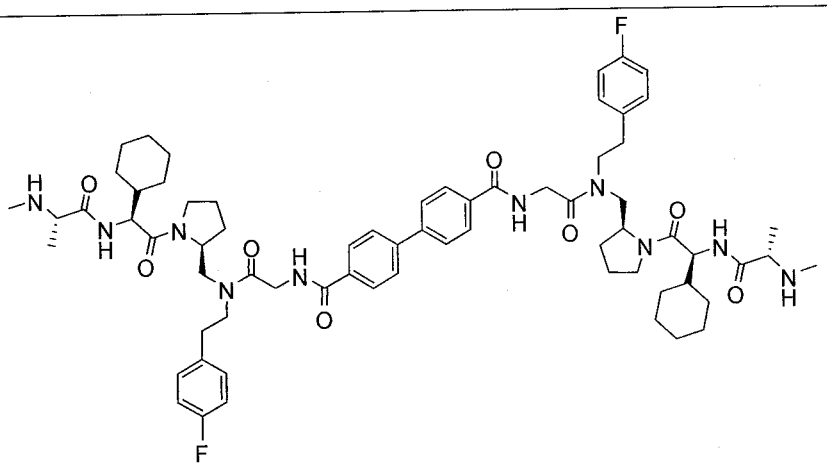
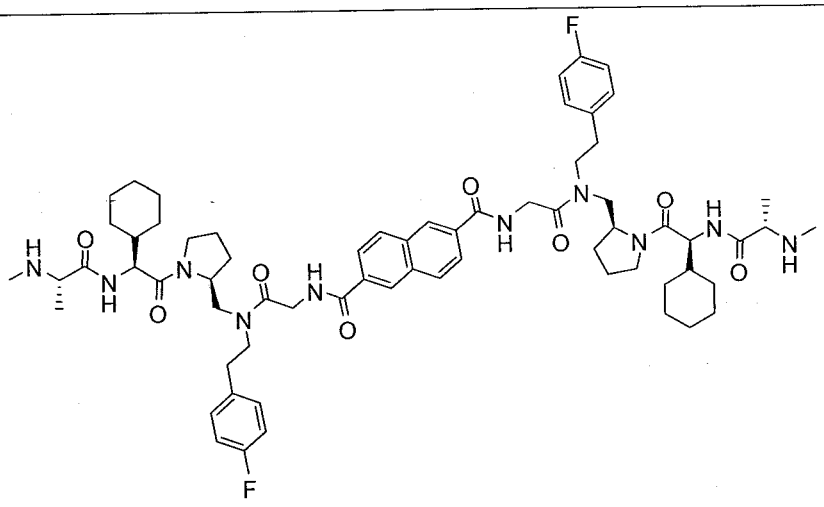
7		M+1=1137.8
8		M+1=1213.7
9		M+1=1187.8

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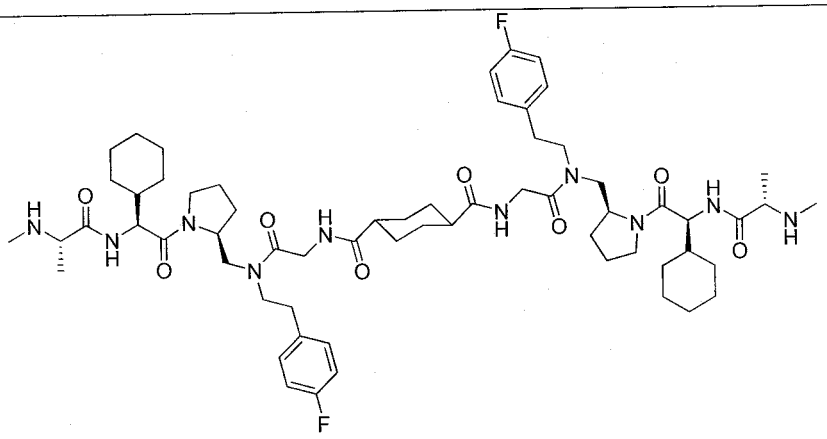
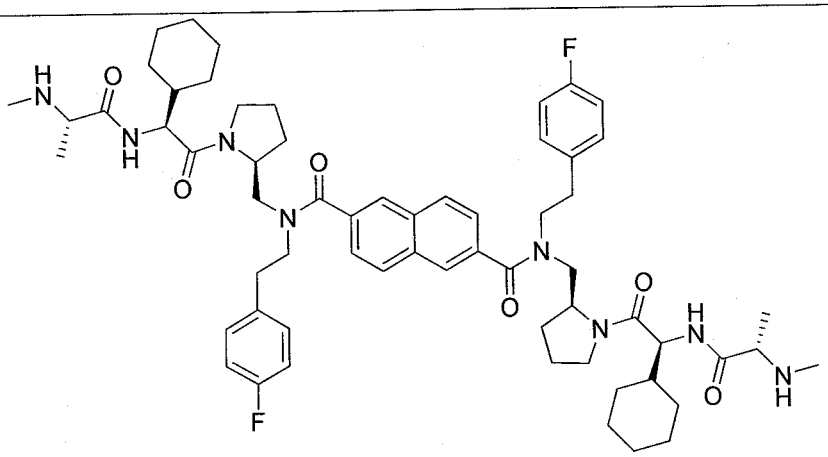
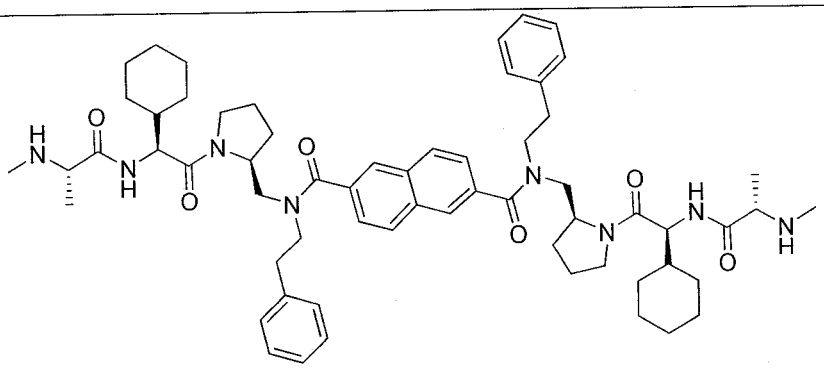
10		M+1=1143.9
11		M+1=1073.8
12		M+1=1037.7

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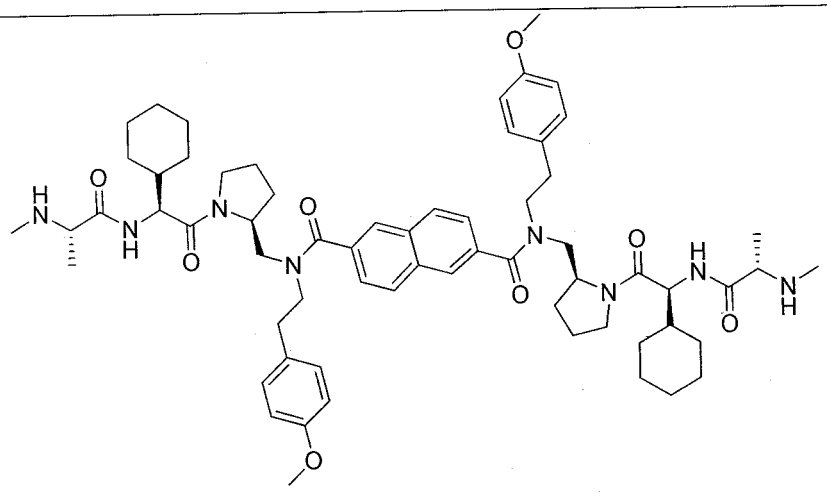
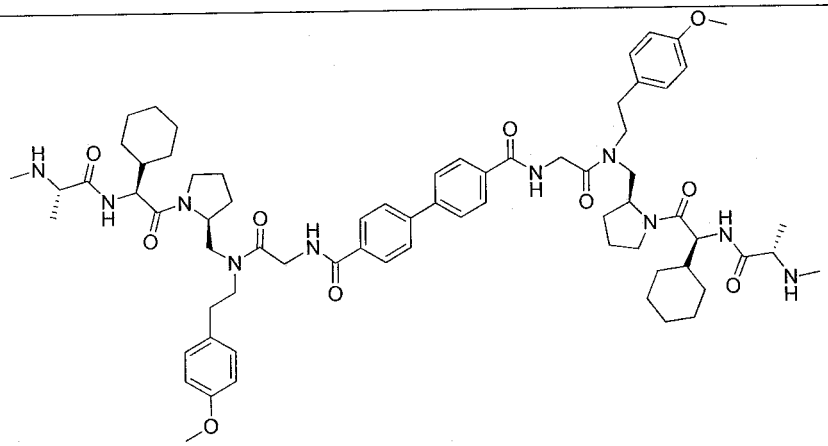
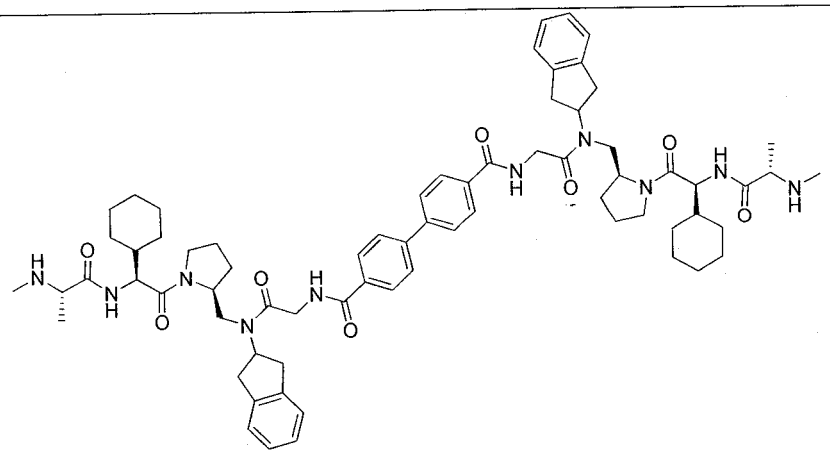
13		M+1=1097.9
14		M+1=1237.9
15		M+1=1201.9

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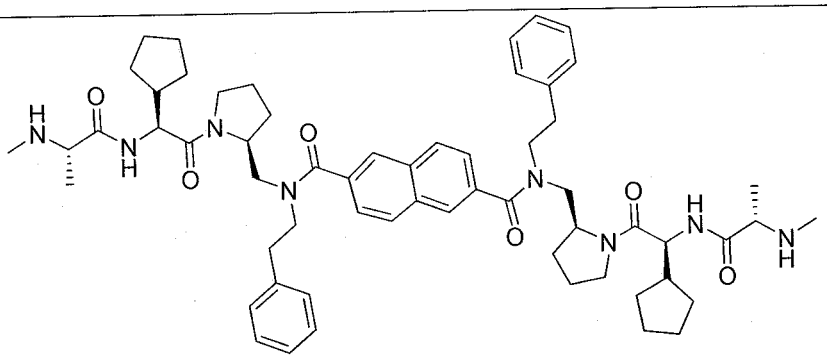
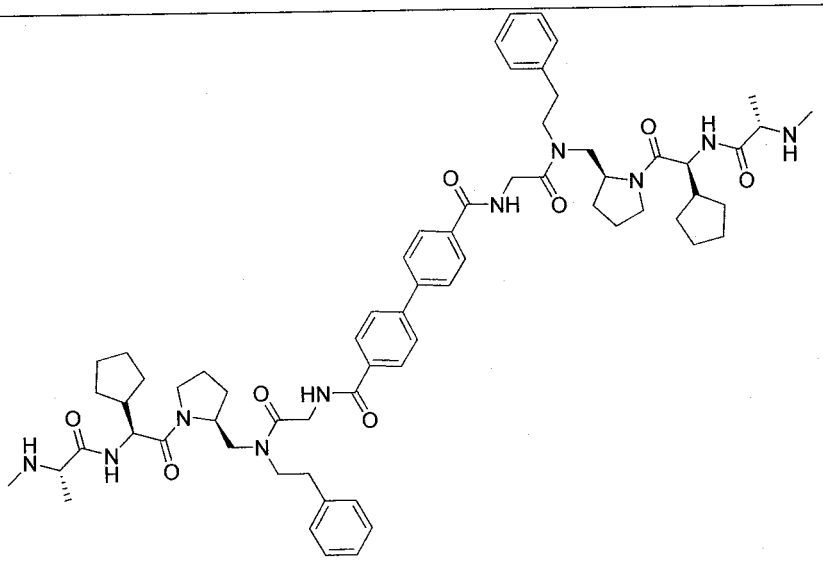
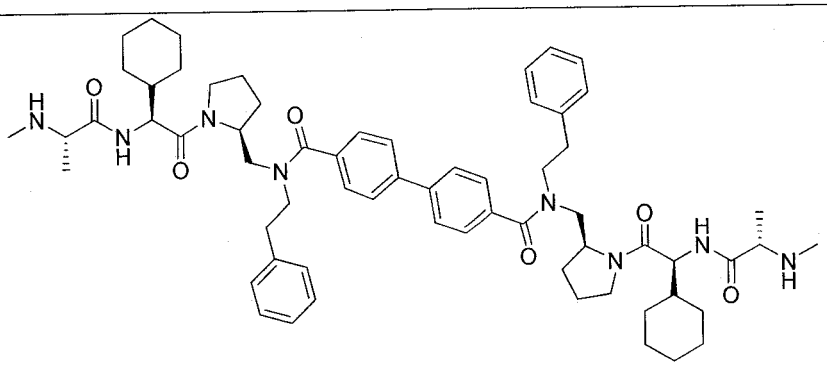
16		M+1=1009.7
17		M+1=1149.8
18		M+1=1063.7

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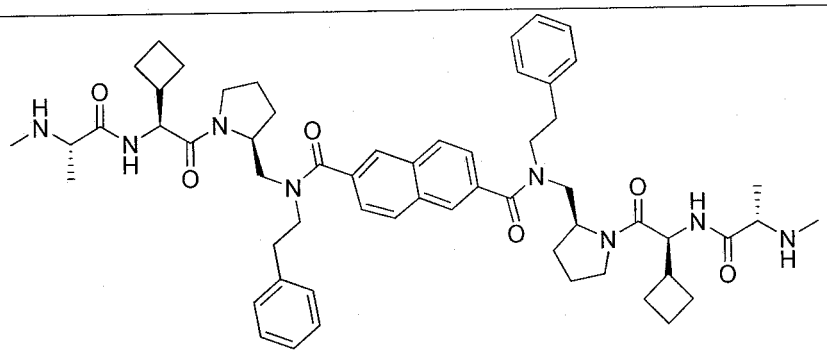
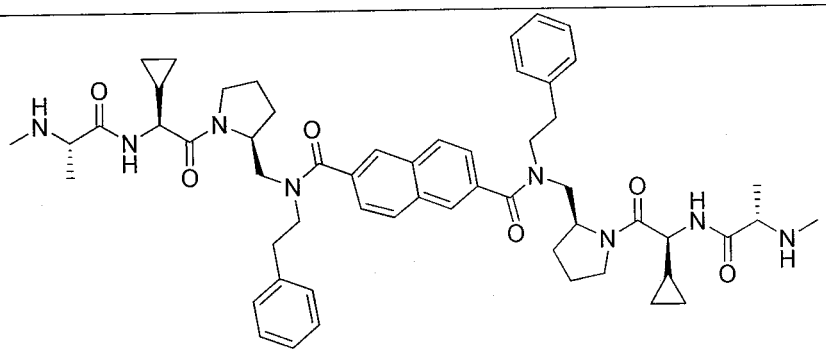
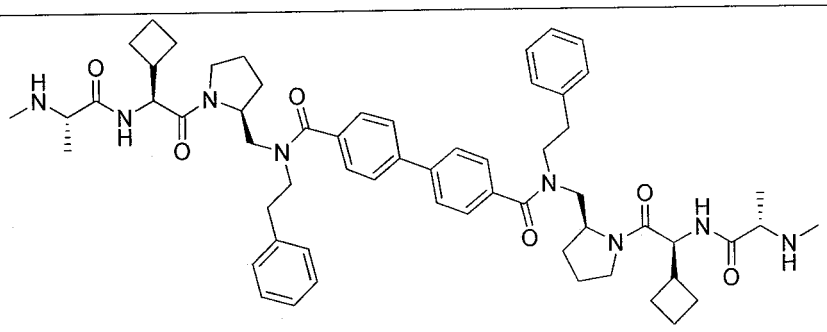
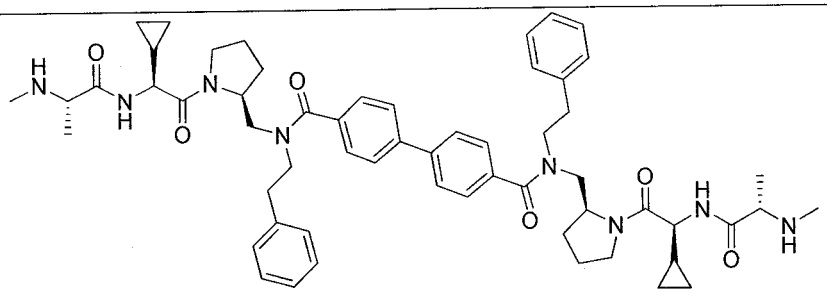
19		M+1=981.7
20		M+1=953.7
21		M+1=1007.6
22		M+1=979.6

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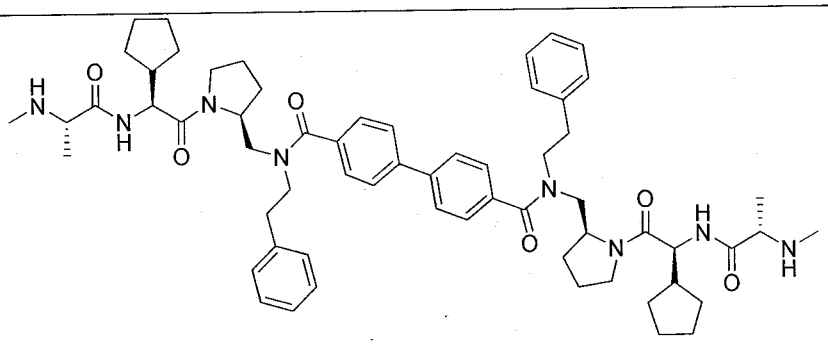
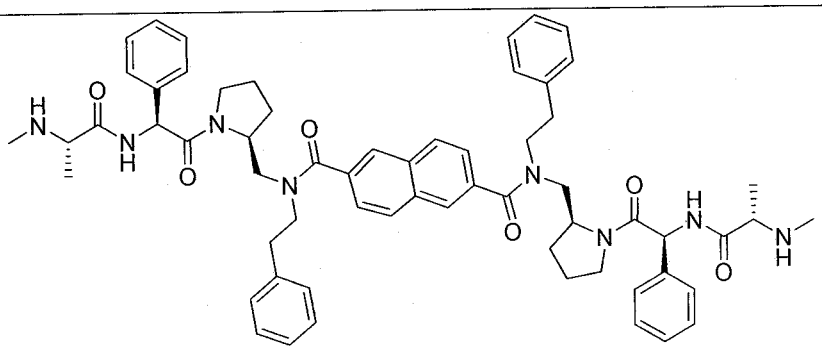
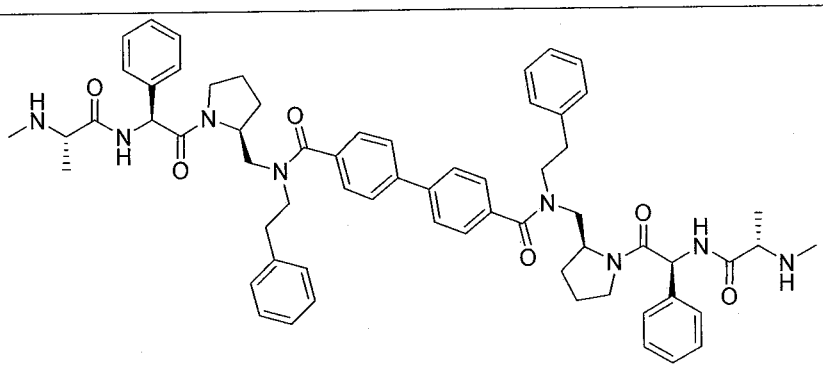
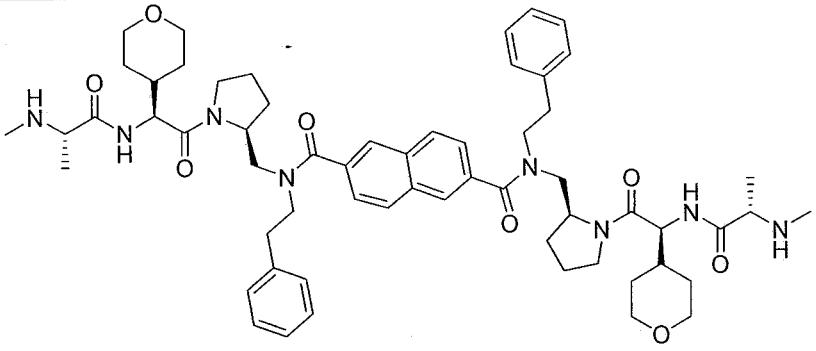
23		M+1=1035.6
24		M+1=1025.7
25		M+1=1051.8
26		M+1=1041.7

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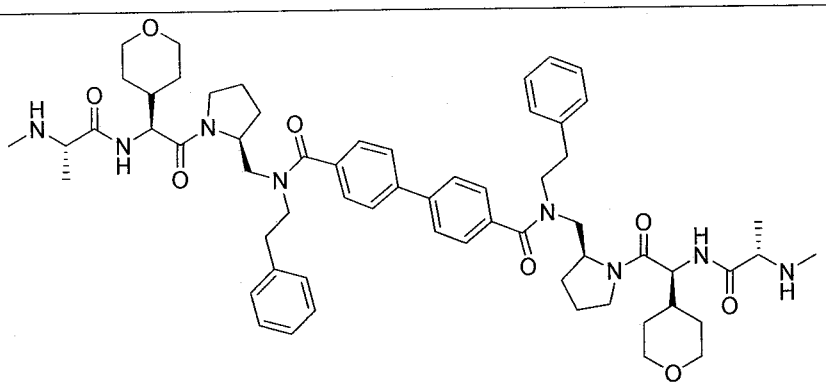
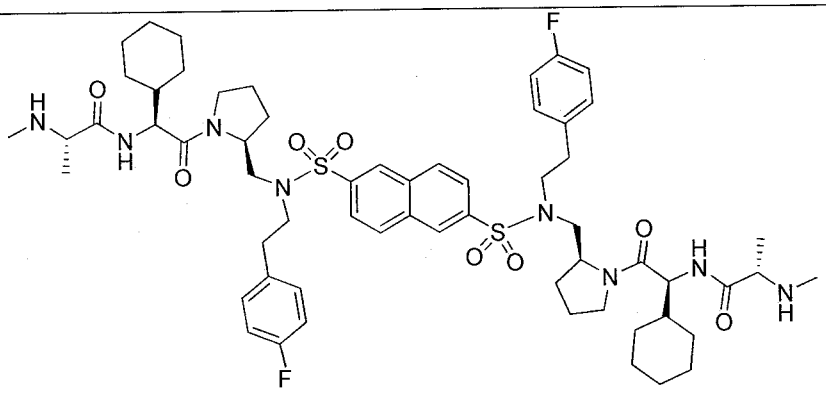
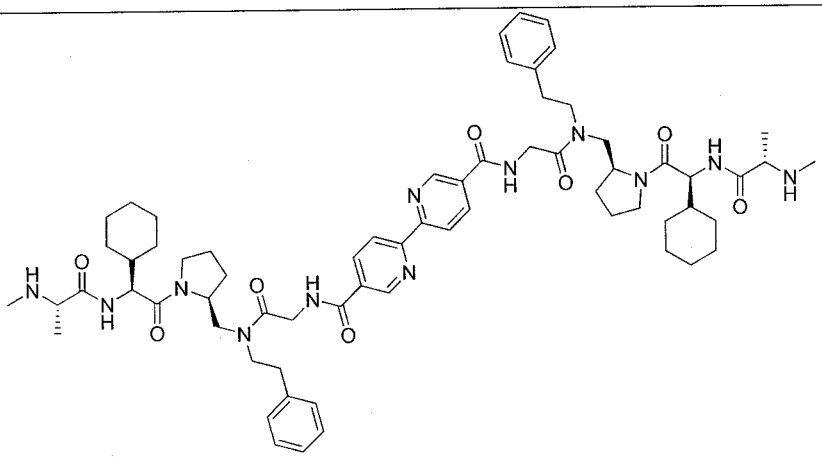
27		M+1=1067.7
28		M+1=1145.7
29		M+1=1179.7

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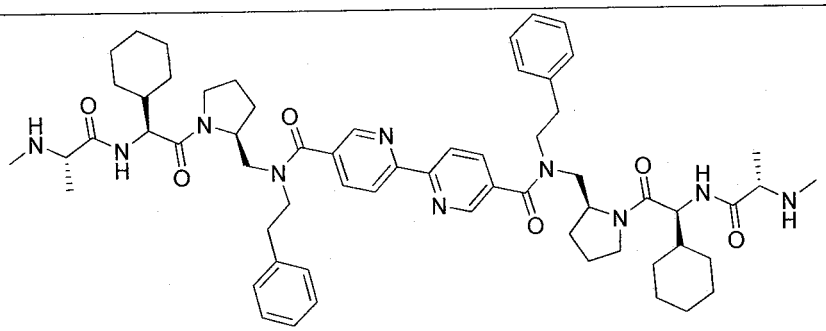
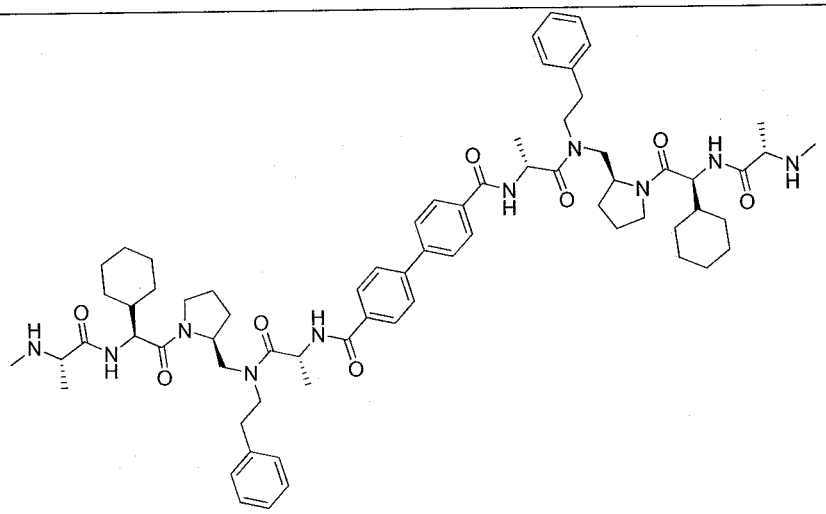
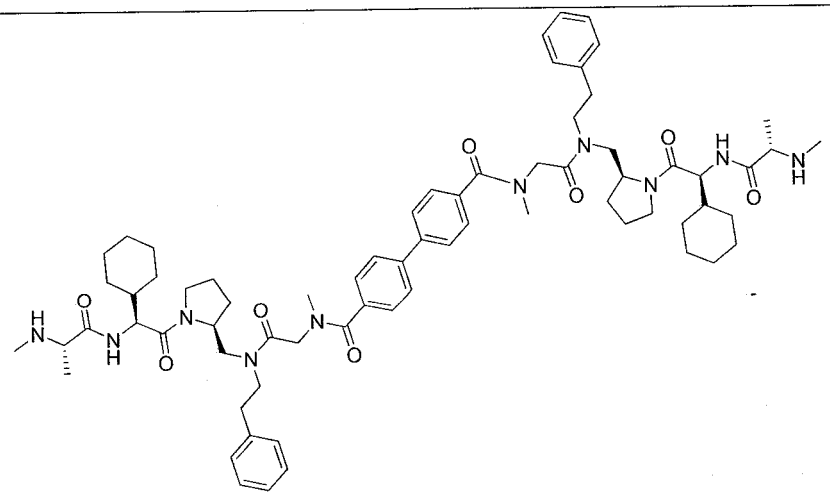
30		M+1=1065.7
31		M+1=1205.7
32		M+1=1205.7

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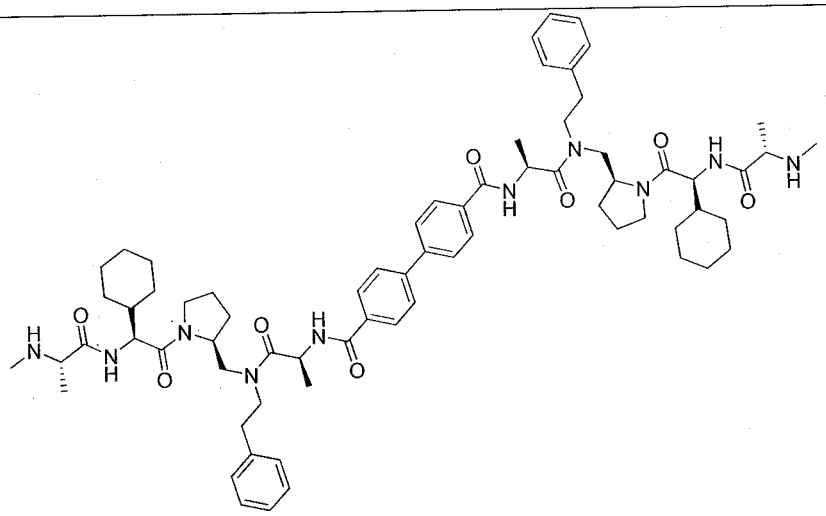
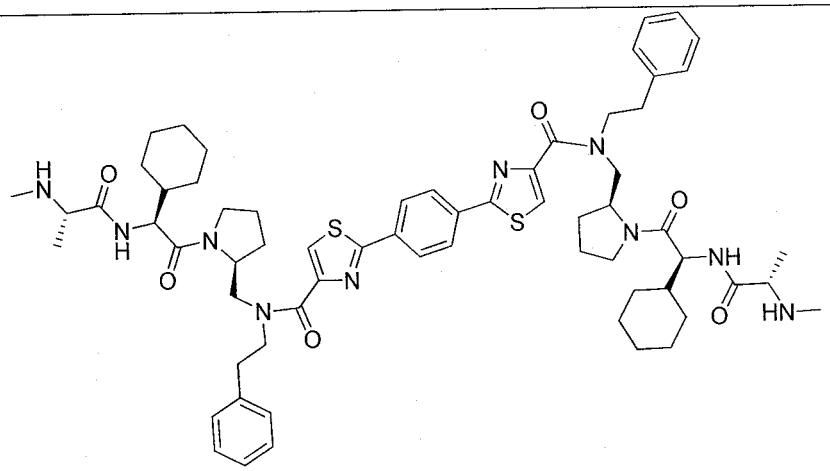
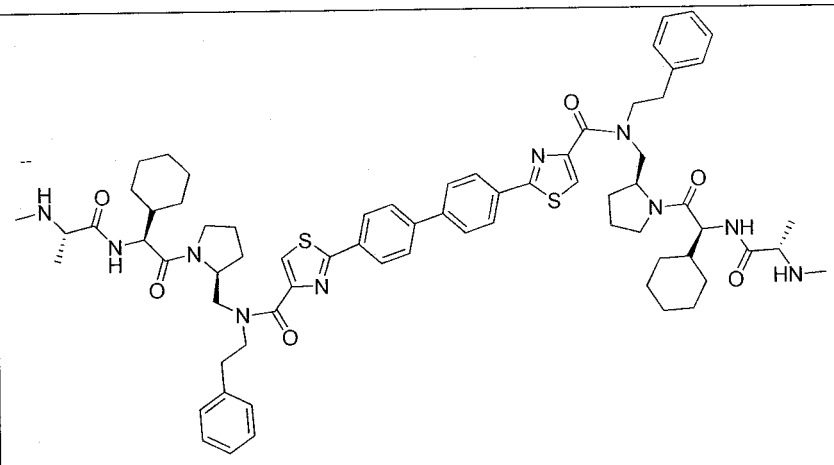
33		M+1=1205.7
34		M+1=1153.6
35		M+1=1229.5

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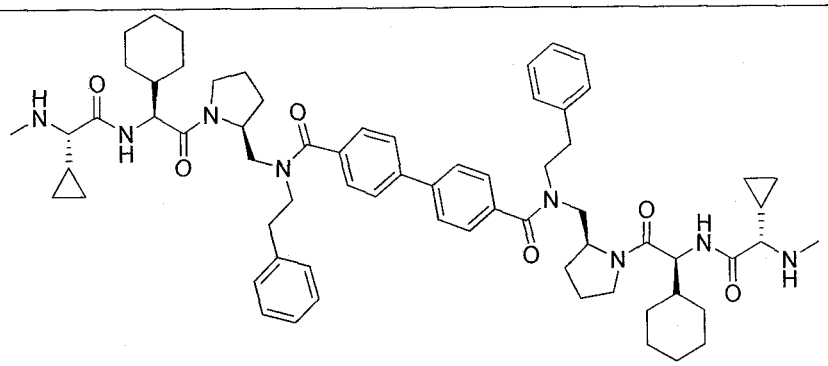
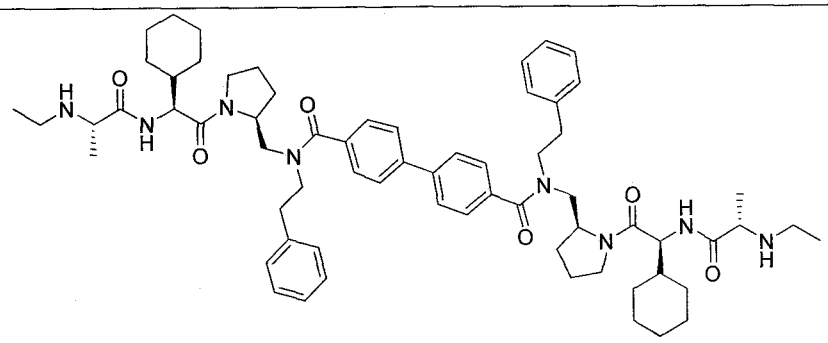
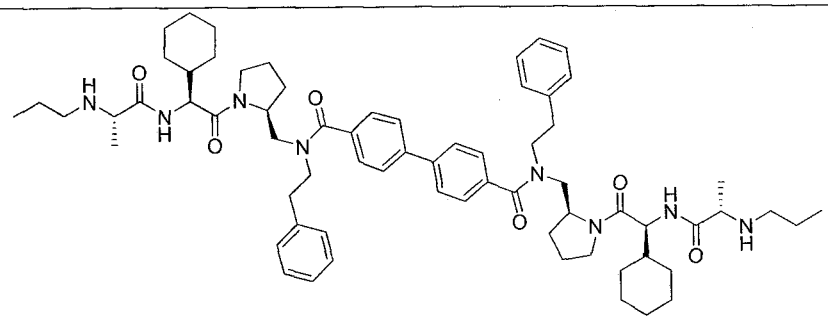
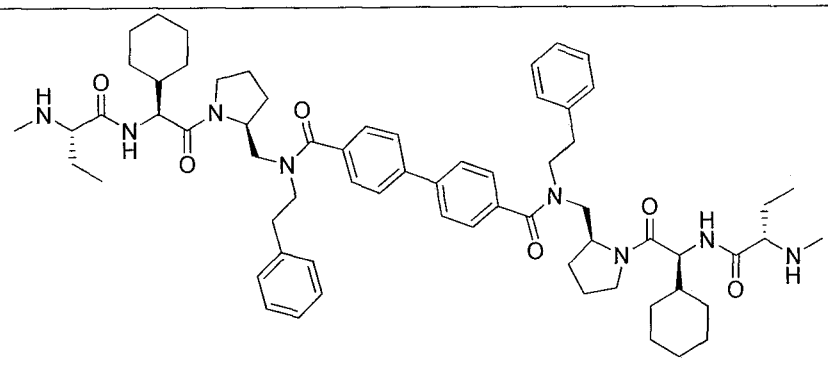
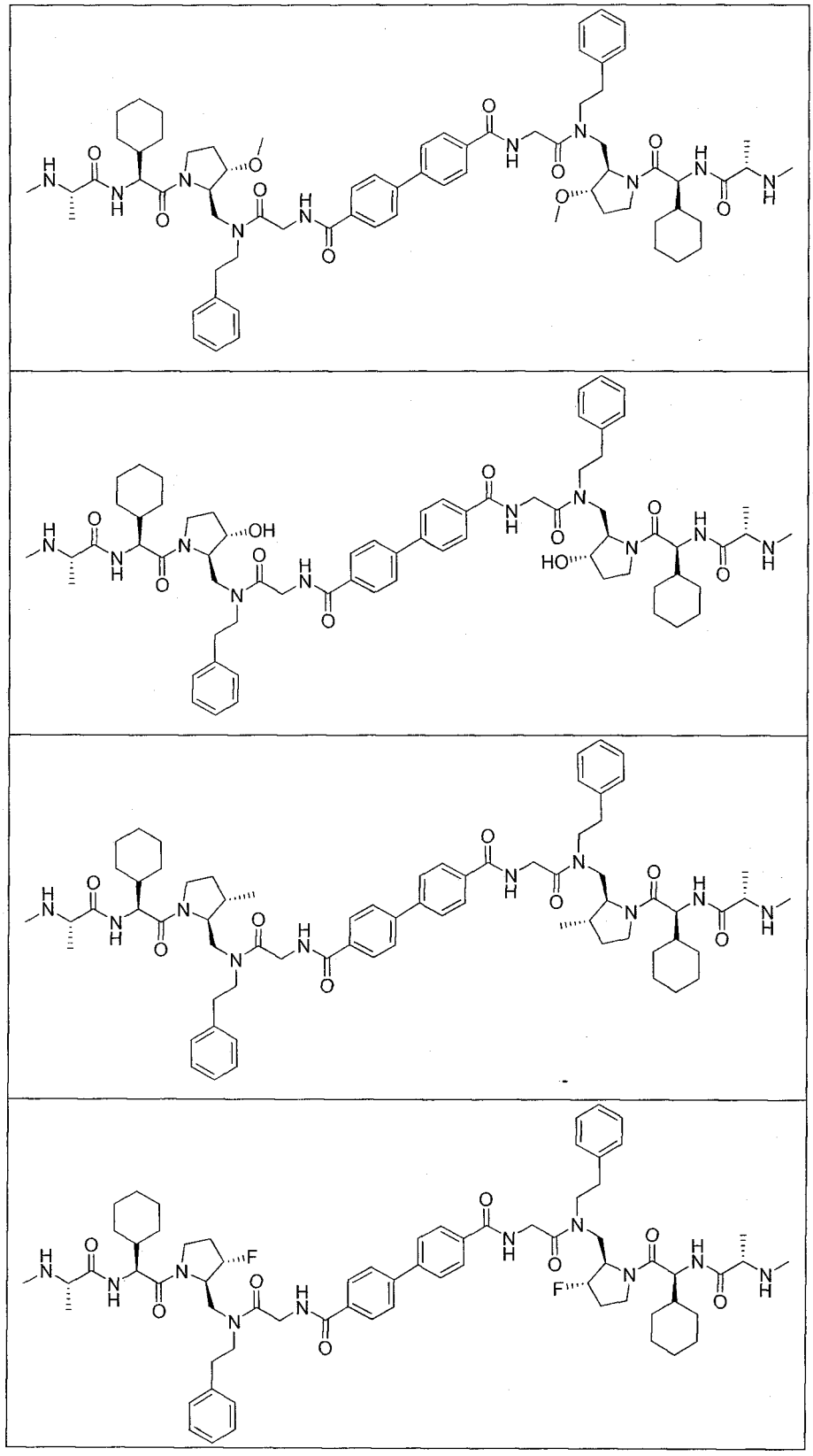
36		M+1=1115.6
37		M+1=1091.7
38		M+1=1119.7
39		M+1=1091.6

[0248] Other compounds of the instant invention include those of Table 1.1, below:

Table 1.1



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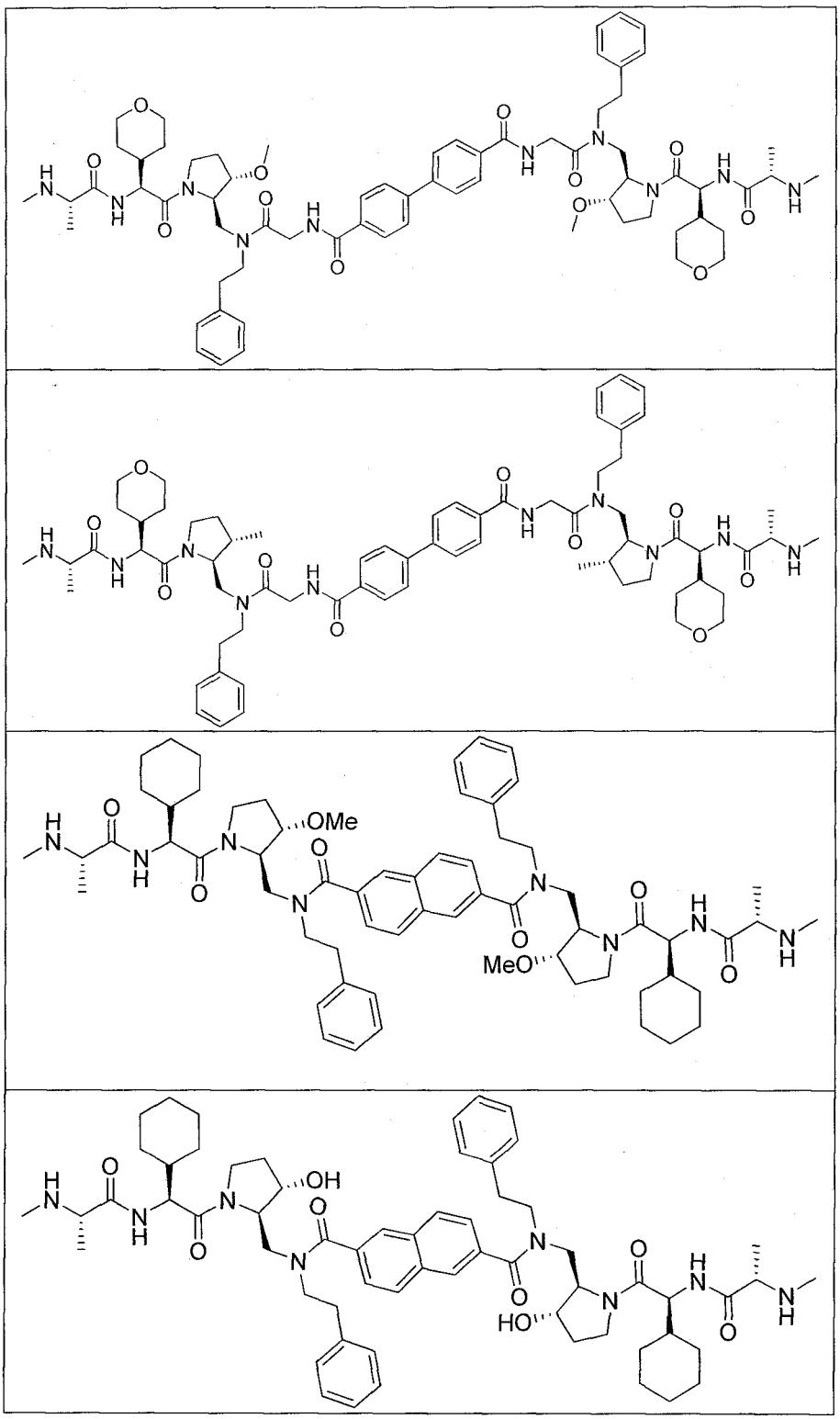
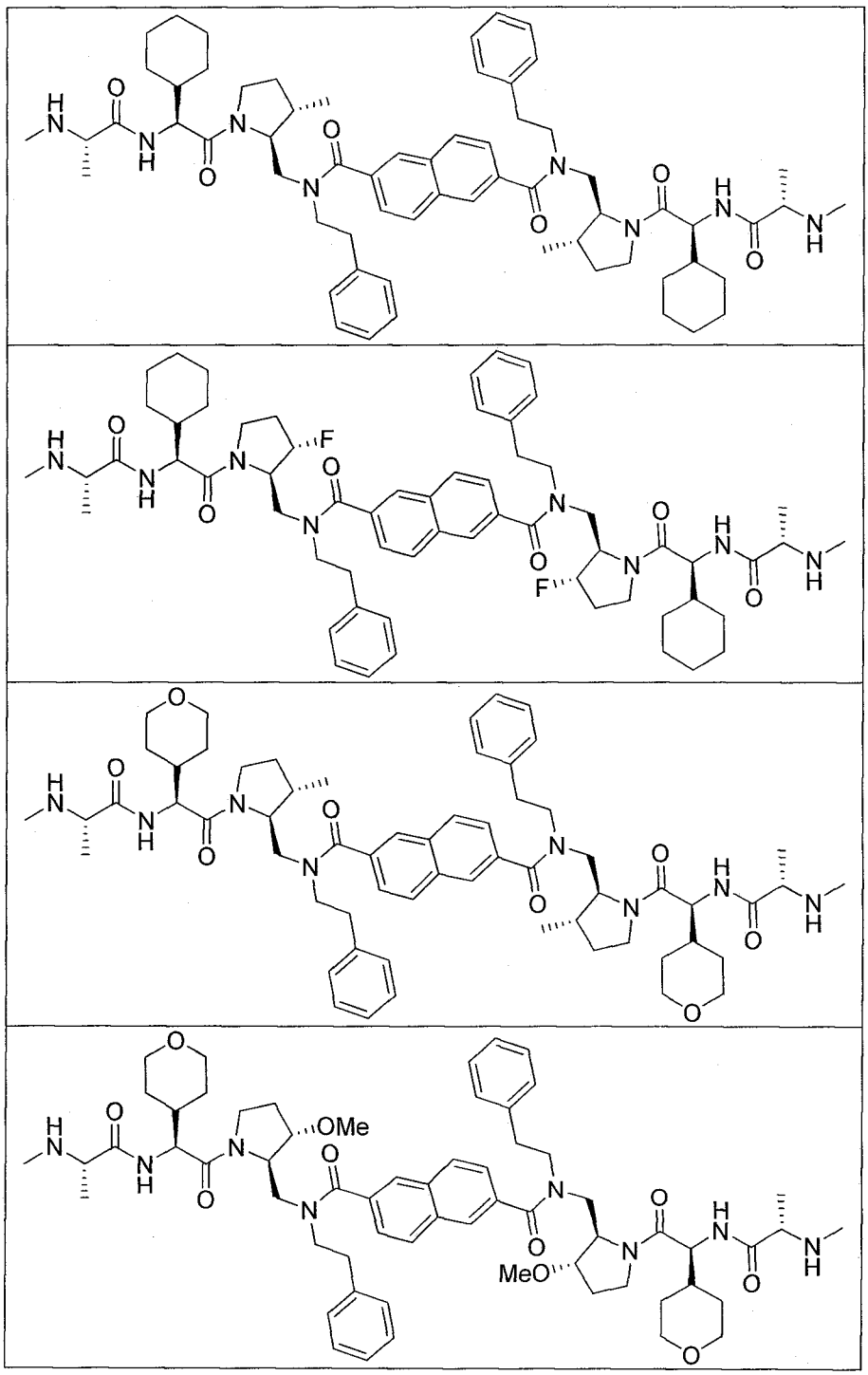
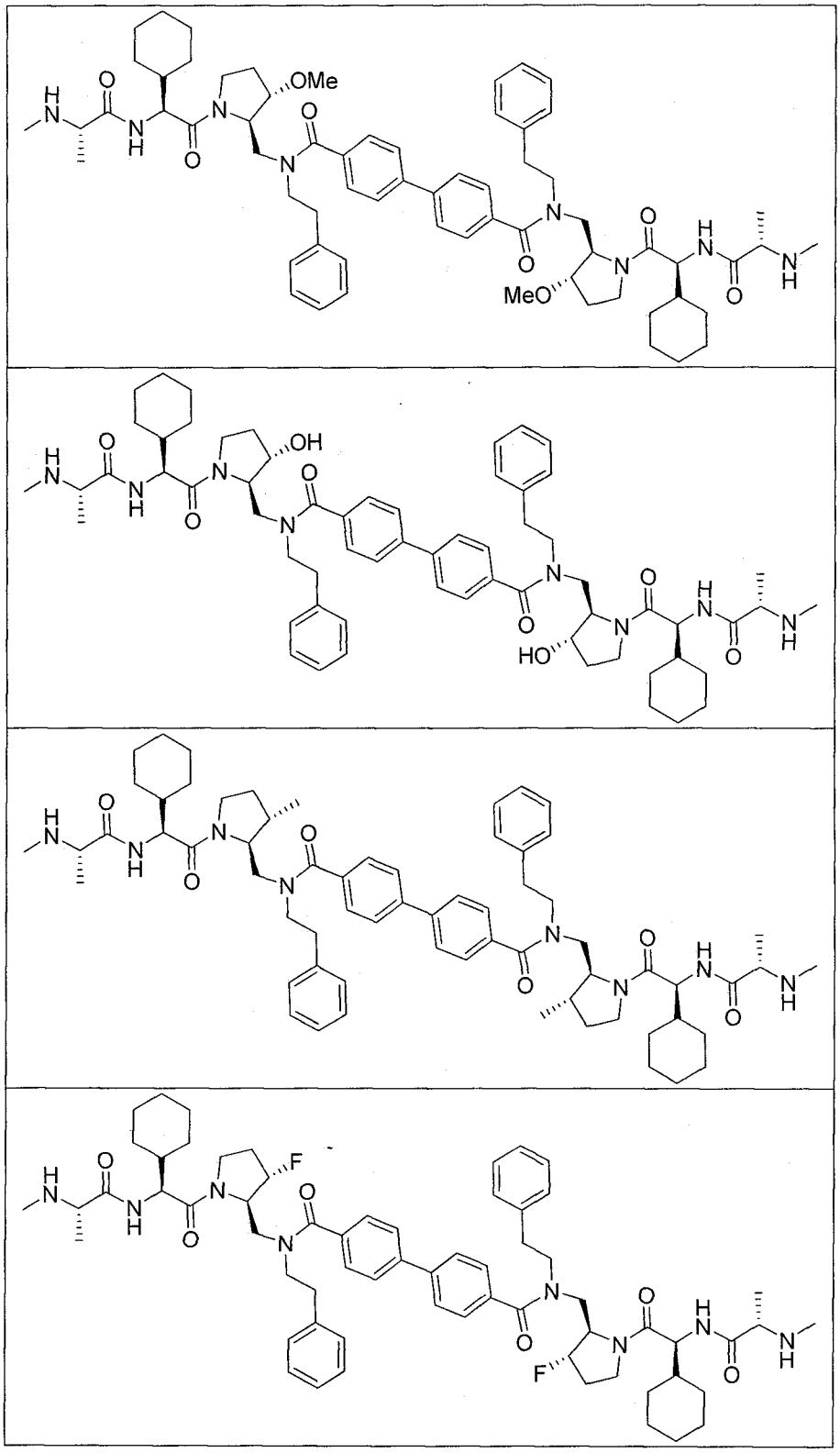
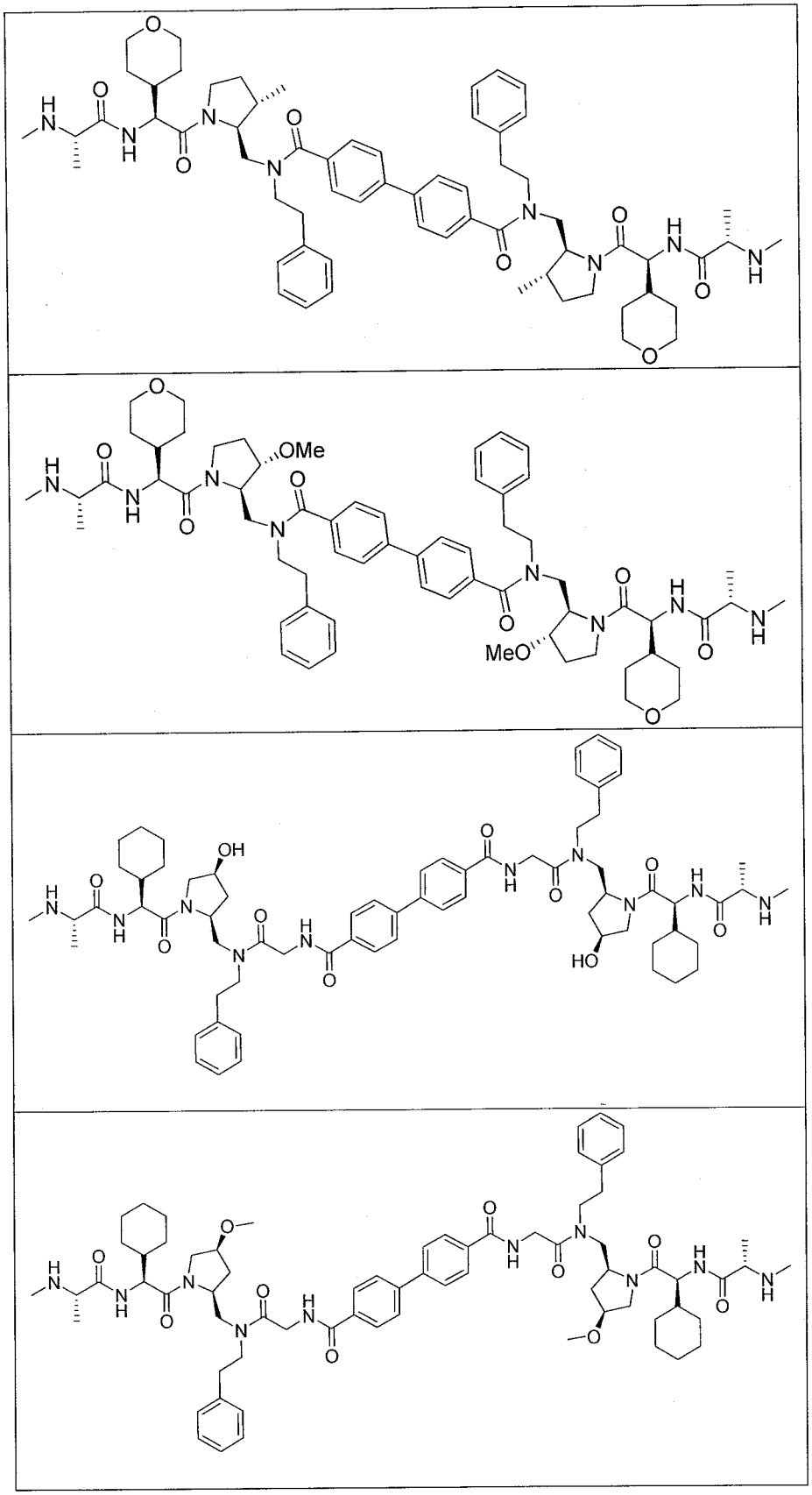
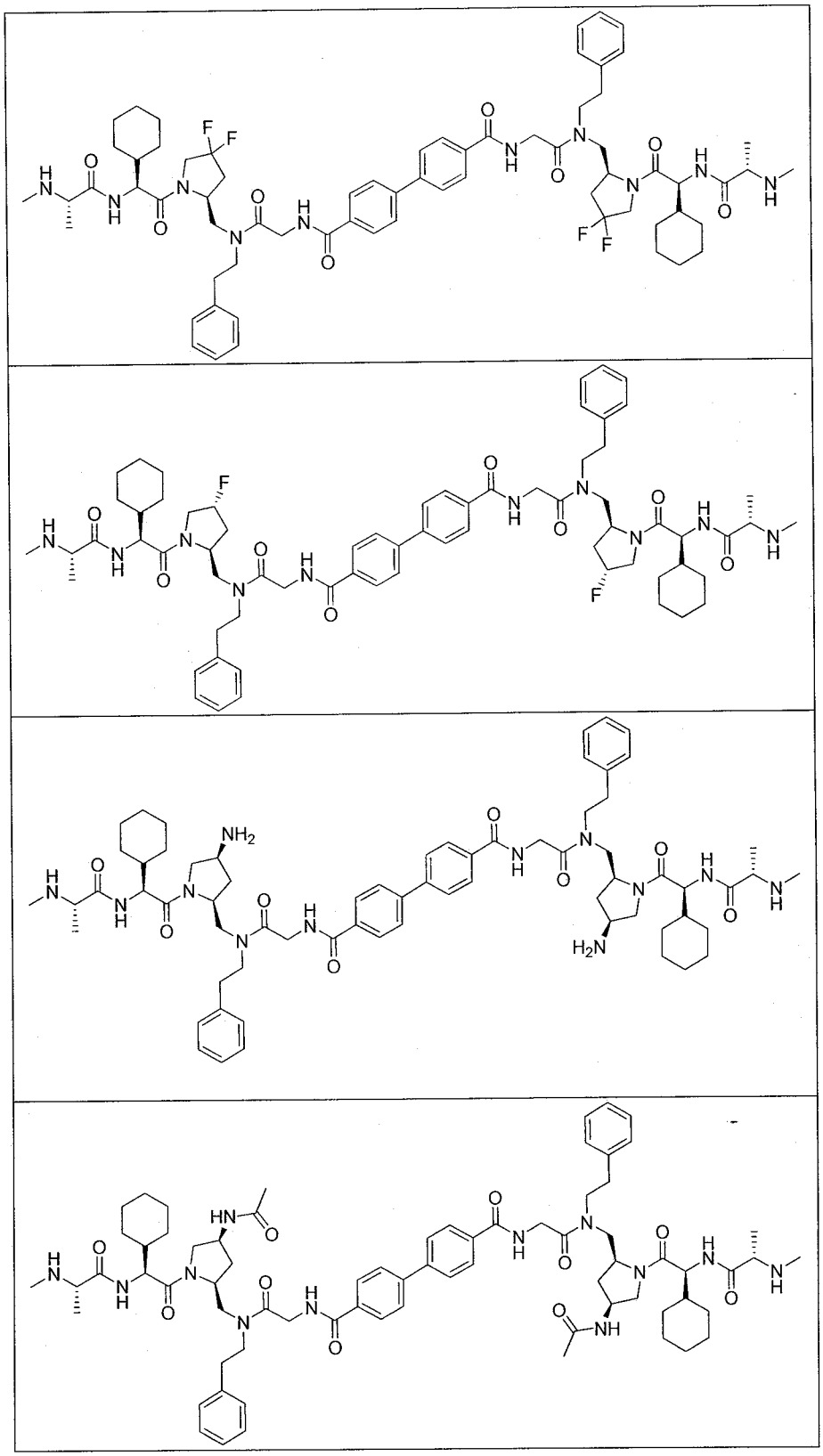
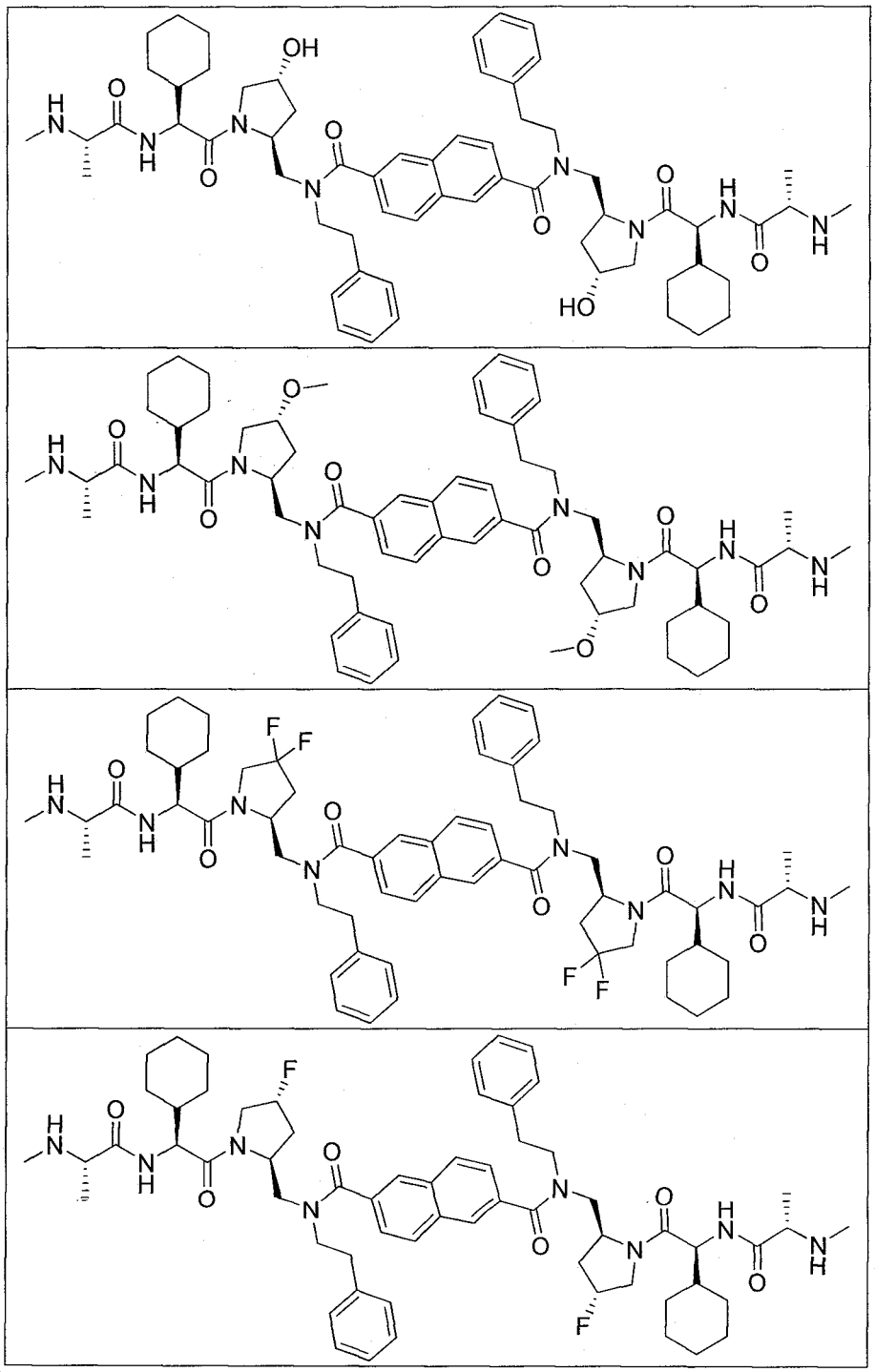


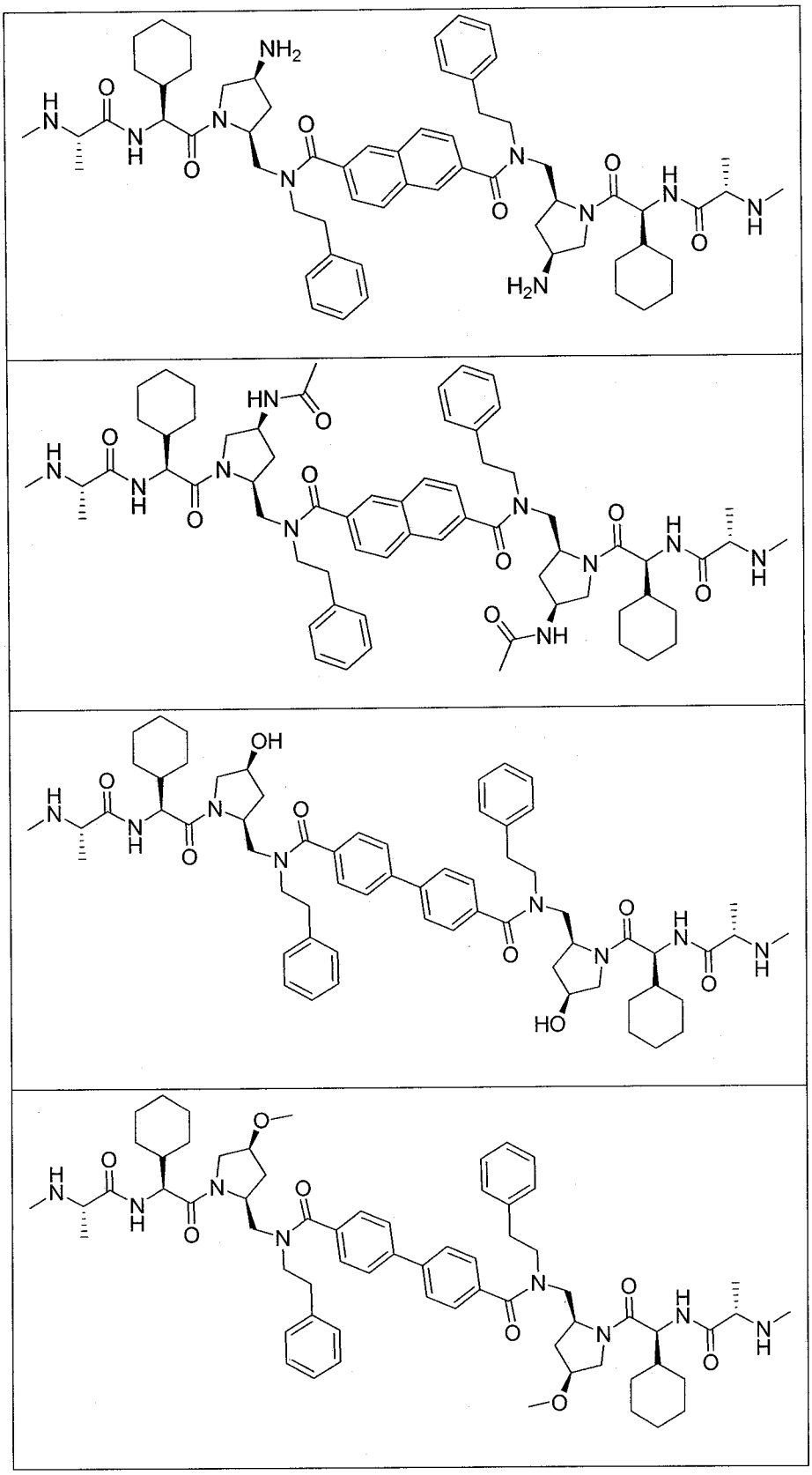


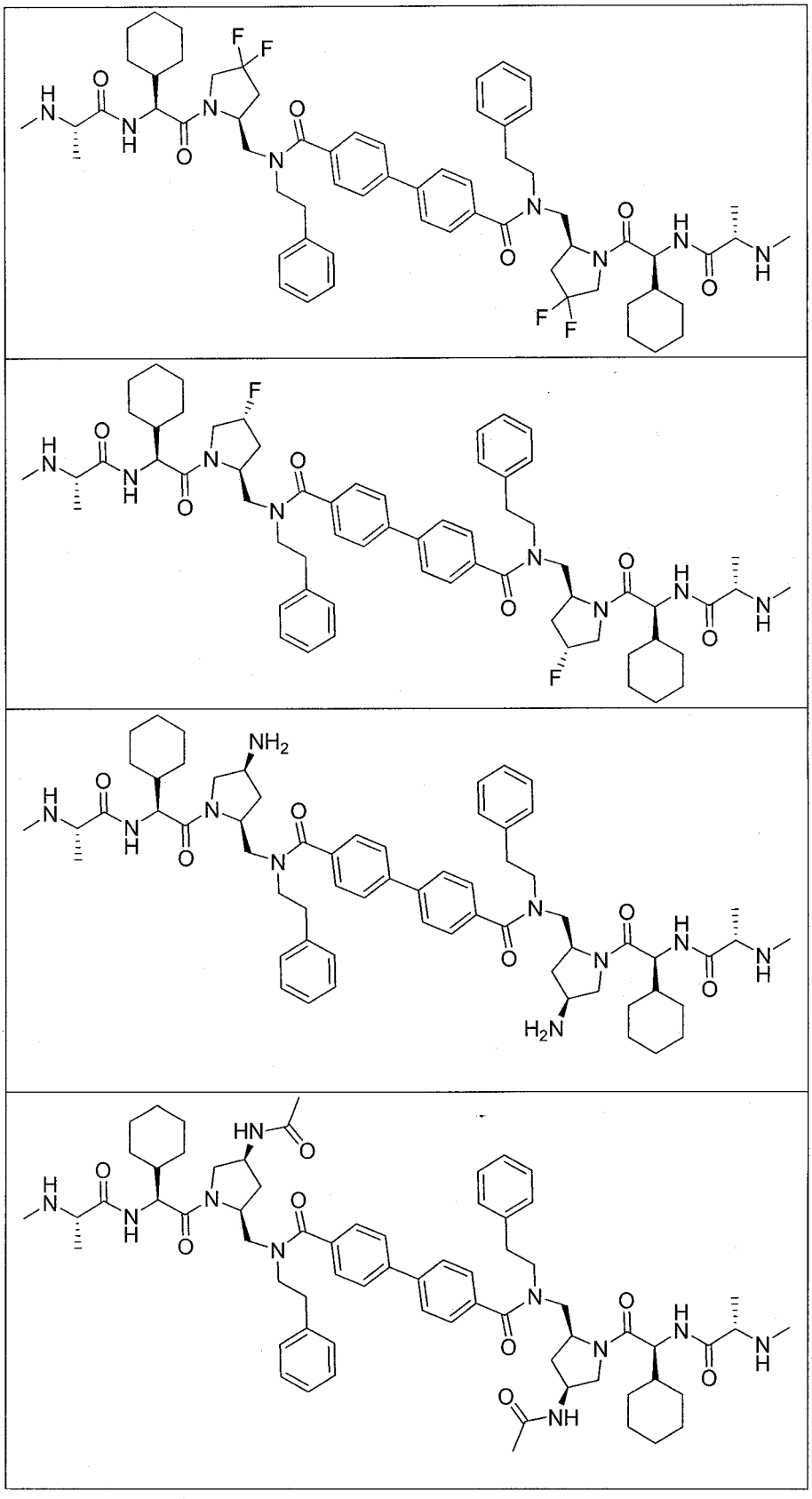

OMe
MeO
OH
HO
F
F

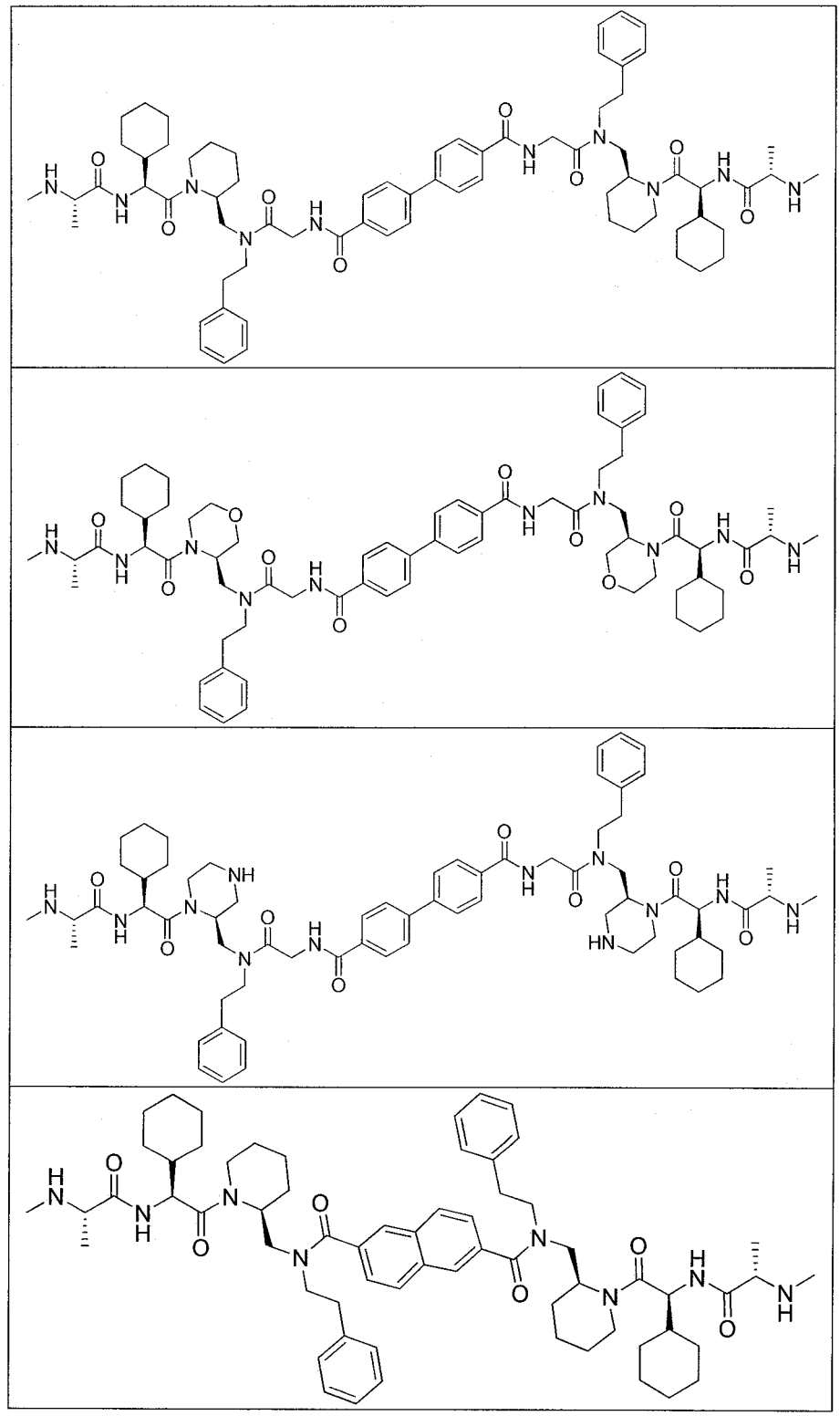


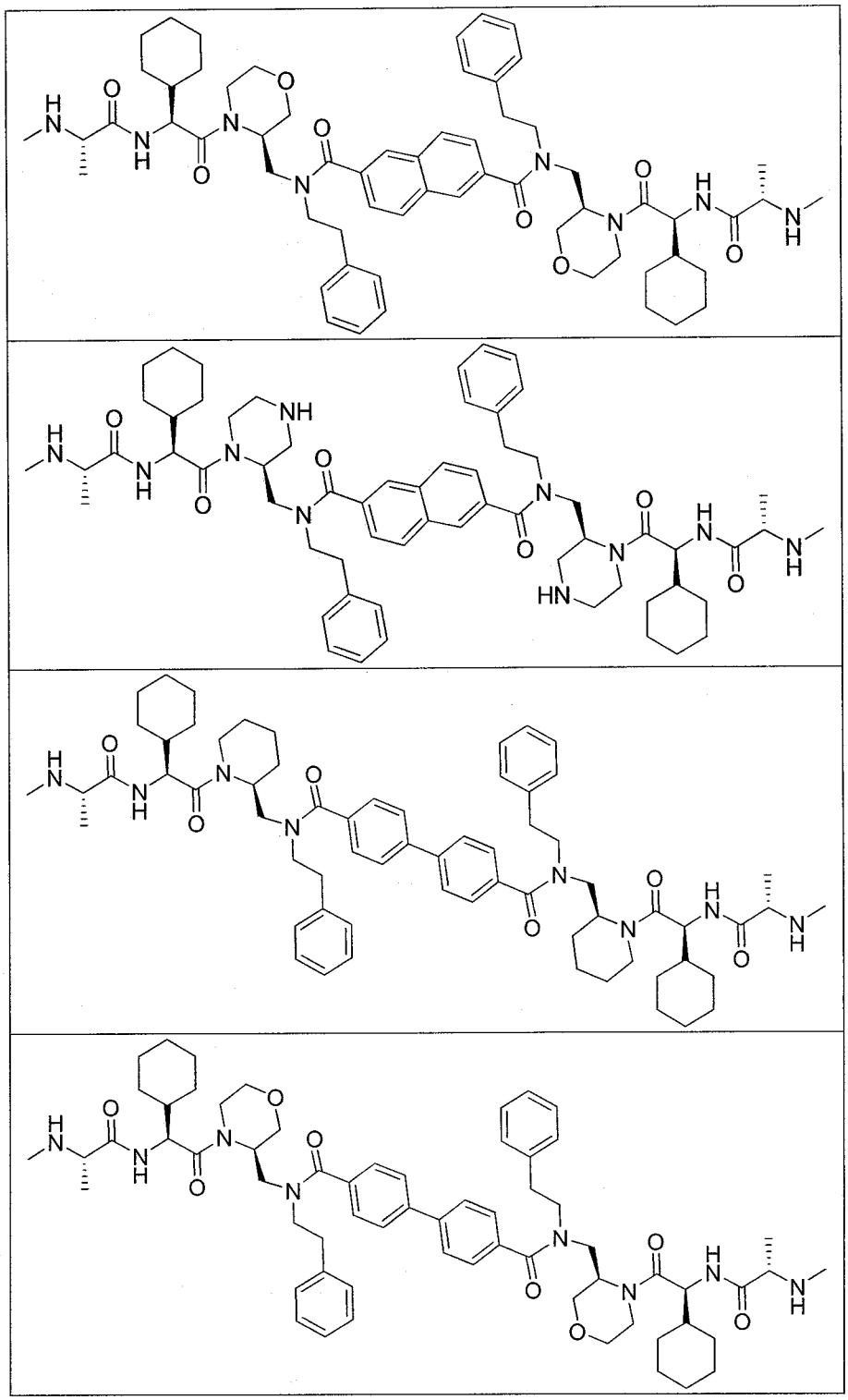


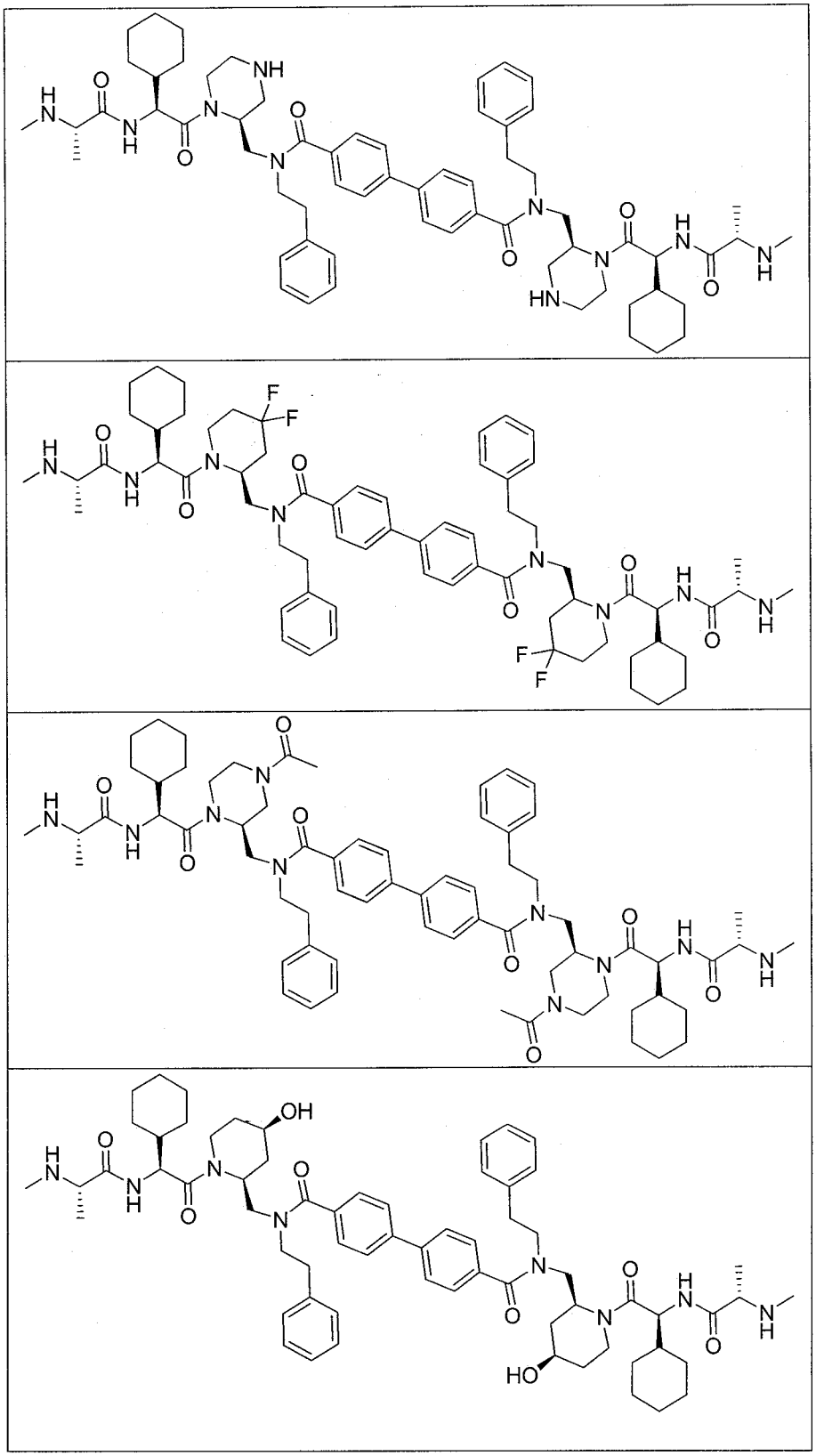


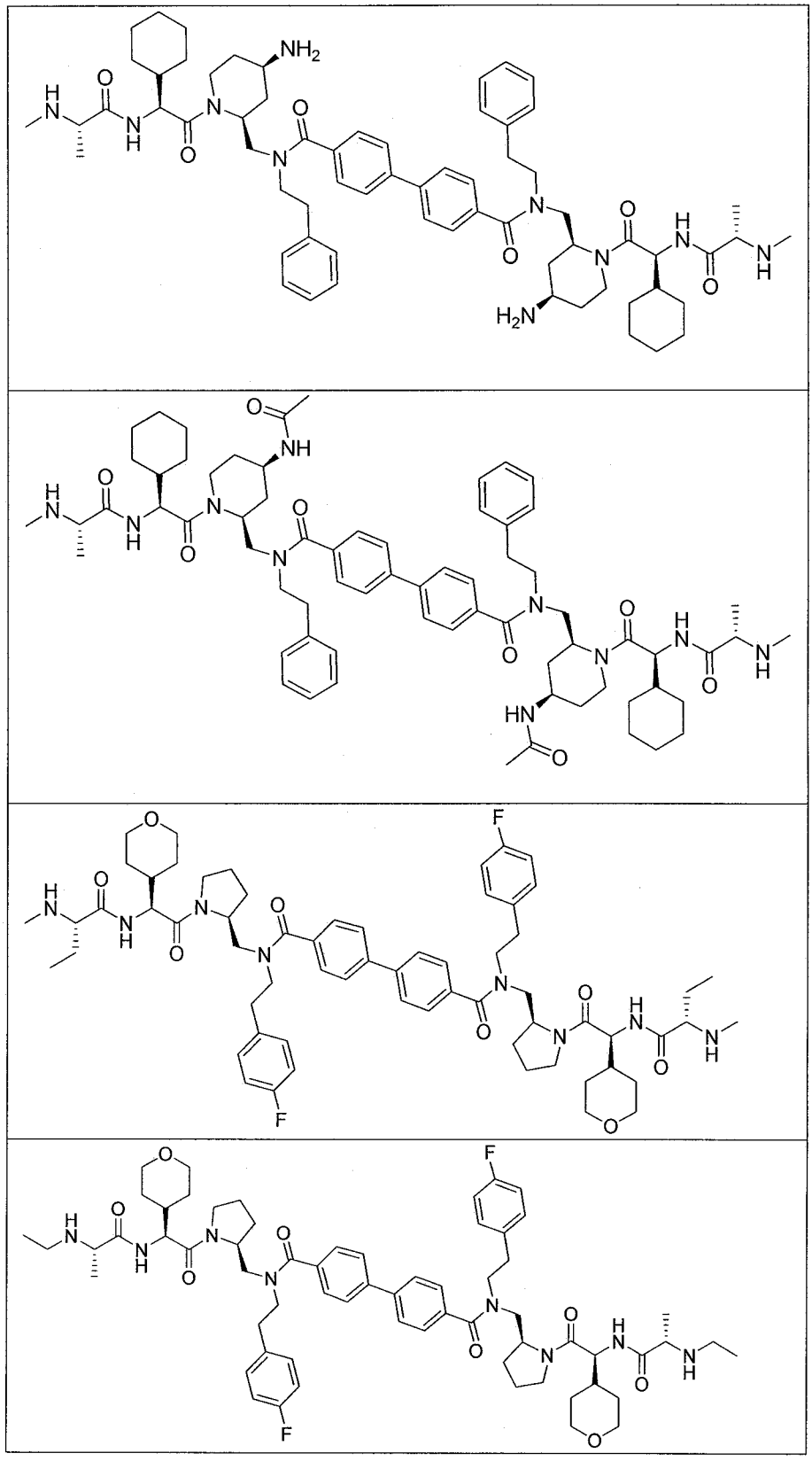


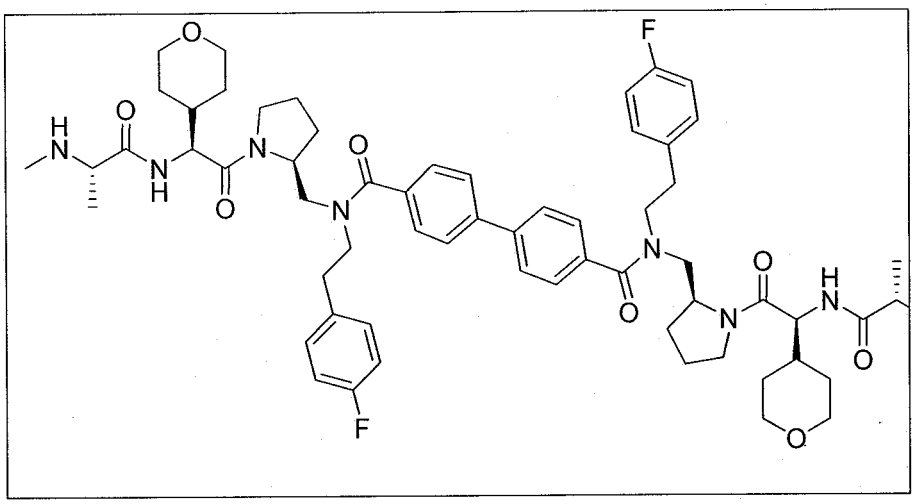












Assays

Molecular constructs for expression

[0249] GST-XIAP BIR3RING: XIAP coding sequence amino acids 246-497 cloned into PGEX2T1 via BamH1 and AVA I. The plasmid was transformed into E. coli DH5α for use in protein expression and purification.

[0250] GST-HIAP2 (cIAP-1) BIR 3: HIAP2 coding sequence from amino acids 251-363 cloned into PGex4T3 via BamH1 and XhoI. The plasmid was transformed into E. coli DH5α for use in protein expression and purification.

[0251] GST-HIAP1(cIAP-2) BIR 3: HIAP1 coding sequence from amino acids 236-349, cloned into PGex4T3 via BamH1 and XhoI. The plasmid was transformed into E. coli DH5α for use in protein expression and purification.

[0252] GST- linker BIR 2 BIR3Ring: XIAP coding sequence from amino acids 93-497 cloned into PGex4T1 via BamH1 and XhoI. Amino acids 93-497 were amplified from full length XIAP in pGex4t3, using the primers: TTAATAGGATCCATCAACGGCTTTTATC and GCTGCATGTGTGTCAGAGG, using standard PCR conditions. The PCR fragment was TA cloned into pCR-2.1 (invitrogen). Linker BIR 2 BIR 3Ring was subcloned into pGex4T1 by BamHI/XhoI digestion. The plasmid was transformed into E. coli DH5α for use in protein expression and purification.

[0253] Full-length human XIAP, AEG plasmid number 23. XIAP coding sequence amino acids 1-497 cloned into GST fusion vector, PGEX4T1 via BamH1 and Xho I restriction sites. The plasmid was transformed into E. coli DH5α for use in protein purification.

[0254] GST-XIAP linker BIR 2: XIAP linker BIR 2 coding sequence from amino acids 93-497 cloned into pGex4T3 via BamHI and XhoI. The plasmid was transformed into E. coli DH5α for use in protein expression and purification.

Expression and purification of recombinant proteins

A. Expression of Recombinant Proteins

[0255] Glutathione S-transferase (GST) tagged proteins were expressed in *Escherichia coli* strains DH5-alpha. For expression of full length XIAP, individual or combinations of XIAP-BIR domains, cIAP-1, cIAP-2 and Livin transformed bacteria were cultured overnight at 37 °C in Luria Broth (LB) medium supplemented with 50 ug/ml of ampicillin. The overnight culture was then diluted 25 fold into fresh LB ampicillin supplemented media and bacteria were grown up to A_{600} = 0.6 then induced with 1 mM isopropyl-D-1-thiogalactopyranoside for 3 hours. Upon induction, cells were centrifuged at 5000 RPM for 10 minutes and the media was removed. Each pellet obtained from a 1 liter culture received 10 ml of lysis buffer (50 mM Tris-HCl, 200 mM NaCl, 1 mM DTT, 1 mM PMSF, 2 mg/ml of lysosyme, 100 □g/ml)), was incubated at 4 °C with gentle shaking. After 20 minutes of incubation, the cell suspension was placed at -80 °C overnight or until needed.

B. Purification of recombinant proteins

[0256] For purification of recombinant proteins, the IPTG-induced cell lysate was thawed vortexed and then disrupted by flash freezing in liquid nitrogen two times with vortexing after each thaw. The cells were disrupted further by passing the extract four times through a Bio-Neb Cell disruptor device (Glas-col) set at 100 psi with Nitrogen gas. The extract was clarified by centrifugation at 4 °C at 15000 RPM in a SS-34 Beckman rotor for 30 minutes. The resulting supernatant was then mixed with 2 ml of glutathione-Sepharose beads (Pharmacia) per 500 ml cell culture (per 1000ml culture for full length XIAP) for 1 hour at 4 °C. Afterwards, the beads were washed 3 times with 1X Tris-Buffered Saline (TBS) to remove unbound proteins. The retained proteins were eluted with 2 washes of 2 ml of 50 mM TRIS pH 8.0 containing 10 mM reduced glutathione. The eluted proteins were pooled and precipitated with 604 g/liter of ammonium sulfate and the resulting pellet re-suspended into an appropriate buffer. As judged

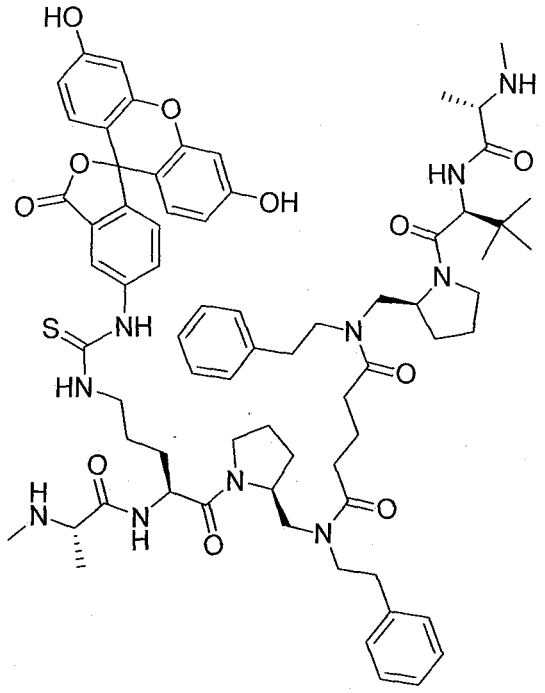
by SDS-PAGE the purified proteins were >90% pure. The protein concentration of purified proteins was determined from the Bradford method.

[0257] His-tag proteins were expressed in the E. Coli strain in E. coli AD494 cells using a pet28ACPP32 construct. The soluble protein fraction was prepared as described above. For protein purification, the supernatant was purified by affinity chromatography using chelating-Sepharose (Pharmacia) charged with $NiSO_4$ according to the manufacturer's instructions. Purity of the eluted protein was >90% pure as determined by SDS-PAGE. The protein concentration of purified proteins was determined from the Bradford assay.

Synthesis of fluorescent probe P1

[0258] A fluorescent peptide probe, Fmoc-Ala-Val-Pro-Phe-Tyr(t-Bu)-Leu-Pro-Gly(t-Bu)-Gly-OH was prepared using standard Fmoc chemistry on 2-chlorotrityl chloride resin (see Int. J. Pept. Prot. Res. 38:555-561, 1991). Cleavage from the resin was performed using 20% acetic acid in dichloromethane (DCM), which left the side chain still blocked. The C-terminal protected carboxylic acid was coupled to 4'-(aminomethy)fluorescein (Molecular Probes, A-1351; Eugene, Oreg.) using excess diisopropylcarbodiimide (DIC) in dimethylformamide (DMF) at room temperature and was purified by silica gel chromatography (10% methanol in DCM). The N-terminal Fmoc protecting group was removed using piperidine (20%) in DMF, and purified by silica gel chromatography (20% methanol in DCM, 0.5% HOAc). Finally, the t-butyl side chain protective groups were removed using 95% trifluoroacetic acid containing 2.5% water and 2.5% triisopropyl silane, to provide probe P1 (>95% pure, HPLC).

Probe P2



[0259] Probe P2 was prepared using methods as described in WO 2007/131,366.

Binding assay

Fluorescence polarization-based competition assay

[0260] For all assays, the fluorescence and fluorescence-polarization was evaluated using a Tecan Polarion instrument with the excitation filter set at 485 nm and the emission filter set at 535 nm. For each assay, the concentration of the target protein was first established by titration of the selected protein in order to produce a linear dose-response signal when incubated alone in the presence of the fluorescent probe P1 or P2. Upon establishing these conditions, the compounds potency (IC_{50}) and selectivity, was assessed in the presence of a fix defined-amount of target protein and fluorescent probe and a 10 point serial dilution of the selected compounds. For each IC_{50} curve, the assays were run as followed: 25 uL/well of diluted compound in 50 mM MES buffer pH 6.5 was added into a black 96 well plate then 25 ul/well of bovine serum albumin (BSA) at 0.5 mg/ml in 50 mM MES pH 6.5. Auto-fluorescence for each compound was first assessed by performing a reading of the compound/BSA solution alone. Then 25 uL of the fluorescein probe (P1 or P2) diluted into 50 mM MES containing 0.05 mg/ml BSA were added and a reading to detect quenching of fluorescein signal done. Finally 25 uL/well of the target or control protein (GST- BIRs) diluted at the appropriate concentration in

50 mM MES containing 0.05 mg/ml BSA were added and the fluorescence polarization evaluated.

Determination of IC_{50} and Inhibitory constants

[0261] For each assay the relative polarization-fluorescence units were plotted against the final concentrations of compound and the IC_{50} calculated using the Grad pad prism software and/or Cambridge soft. The ki value were derived from the calculated IC_{50} value as described above and according to the equation described in Nikolovska-Coleska, Z. (2004) Anal Biochem 332, 261-273.

Fluorescence polarization competition assay

[0262] The k_i of various compounds in the BIR2-BIR3-ring FP assay, using probe P2, was determined as described above. The majority of compounds displayed a k_i of less than 10 uM.

Cell Culture and Cell Death Assays

SKOV3:

[0263] Ovarian adenocarcinoma SKOV3 cells were cultured as monolayers in McCoy's 5a medium (HyClone) supplemented with 2.2 g/L sodium bicarbonate (Gibco), 10% FBS (HyClone) and 1% penicillin/streptomycin (HyClone). Cells were seeded in 96 well plates at 5000 cells/well. After 24 hours in culture, cells were treated with compound. Cells were incubated in the presence of compound for 72 hours. Metabolic viability of remaining cells was assessed by MTT (thiazolyl blue tetrazolium bromide, Sigma) assay. The results are presented in Table 7.

HCT116 + ETR1:

[0264] Colorectal carcinoma HCT116 cells were cultured as monolayers in 96 well plates at a density of 2000 cells per well in McCoy's 5a medium (HyClone) supplemented with 2.2 g/L sodium bicarbonate (Gibco), 10% FBS (HyClone) and 1% penecillin/streptomycin (HyClone). 24 hours later, triplicate wells were treated with HGS ETR1 (40ng/ml) in combination with compound. Cells were incubated in the presence of compound and HGS agonistic Trail receptor antibody, ETR1 (Mapatumamab, 40ng/ml) for 72 hours. Metabolic viability of remaining cells was assessed by MTT (thiazolyl blue tetrazolium bromide, Sigma) assay. The results are presented in Table 7.

Synoviocytes:

[0265] Rheumatoid arthritis human fibroblast-like synoviocytes (HFLS-RA, Cell Applications Inc.) were seeded in 96-well plates at 3000 cells per well in complete synoviocyte growth medium (Cell Applications Inc.) one day prior to treatment. Triplicate wells were treated for 72 hours compound in combination with 300ng/ml anti-human CD95 (Fas) antibody (clone CH-11, Beckman Coulter/Immunotech). Cell survival was measured by Cell Titer-Glo Luminescent Assay (Promega). The results are presented in Table 7.

Determination of EC_{50} Values

[0266] EC_{50} values (50% cell survival in the presence of compound as compared to untreated controls) were calculated from survival curves using BioAssay software (CambridgeSoft, HCT116 and SKOV3 SAR) and GraphPad Prism (Graph Pad Software Inc., Synoviocyte SAR).

TABLE 7

Compound	EC_{50} SKOV3 (nM)	EC_{50} HCT116 + ETR1 (nM)	EC_{50} synoviocytes +FAS (nM)
1	a	a	-
2	a	a	a
3	a	a	-
4	a	a	-
5	a	a	-
6	a	a	a
7	a	a	-
8	a	a	a
9	a	a	-
10	-	a	-
11	-	a	a
12	-	a	-
13	-	b	-
14	-	b	-
15	-	a	-
16	a	a	-
17	a	a	a
18	-	a	a
19	-	a	a
20	-	a	b
21	-	a	a
22	-	a	a
23	-	a	a
24	-	a	-
25	-	a	-
26	-	a	-

Compound	EC_{50} SKOV3 (nM)	EC_{50} HCT116 + ETR1 (nM)	EC_{50} synoviocytes +FAS (nM)
27	-	a	-
28	-	a	-
29	-	a	-
30	-	a	-
31	-	a	-
32	-	a	-
33	-	a	-
34	-	a	-
35	-	a	-
36	-	a	-
37	-	a	-
38	-	a	-
39	-	a	-

a = EC_{50} less than 100 nM
b = EC_{50} greater than 100 nM

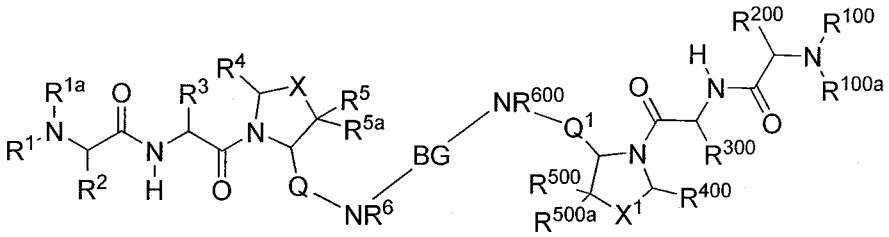
Other Embodiments

[0267] From the foregoing description, it will be apparent to one of ordinary skill in the art that variations and modifications may be made to the invention described herein to adapt it to various usages and conditions. Such embodiments are also within the scope of the present invention.

[0268] All publications mentioned in this specification are hereby incorporated by reference.

CLAIMS

1. A compound of Formula 1.1A:



1.1A

or a salt thereof,

wherein X is C_1-C_3 alkylene or heteroalkylene optionally substituted with one or more R^{11} substituents; or X is –C(O)-;

Q and Q^1 are independently

–CH_2–,

–CH_2CH_2–,

–CH(C_1–C_6 alkyl)–,

–CH(C_3–C_7 cycloalkyl)–,

–C_3–C_7 cycloalkyl–,

–CH(C_1–C_6 alkyl–C_3–C_7 cycloalkyl)–; or

–C(O) –

BG is

–L–;

–Y^1-L-Y^{100}–;

–L^1-Z-L^{100}–; or

–Y^1-L^1-Z-L^{100}-Y^{100}–.

wherein Y^1 and Y^{100} are equal or Y^1 and Y^{100} are different, L^1 and L^{100} are equal or L^1 and L^{100} are different;

Y is O, NR^8, or S;

Y^1 and Y^{100} are independently

–C(O) –,

$–S(O)_2–$,

$–C(O)N(R^8)$ –,or

–C(O)O–,

L, L^1 and L^{100} are :

$–C_1$-C_{12} alkyl–,

$–C_2$-C_{12} alkenyl–,

$–C_2–C_{12}$ alkynyl–,

$–C_3$-C_7 cycloalkyl–,

$–C_3$-C_7 cycloalkenyl–,

–aryl–,

–biphenyl–,

–heteroaryl–,

–biheteroaryl–,

–heterocyclyl–,

$–C_1$-C_6 alkyl–(C_2-C_6 alkenyl)– C_1-C_6 alkyl–,

$–C_1$-C_6 alkyl–($C_2–C_4$ alkynyl)–C_1-C_6 alkyl–,

$–C_1$-C_6 alkyl–(C_3-C_7 cycloalkyl)–C_1-C_6 alkyl–,

$–C_1$-C_6 alkyl–aryl–C_1-C_6 alkyl–,

$–C_1$-C_6 alkyl–biphenyl–C_1-C_6 alkyl–,

$–C_1$-C_6 alkyl–heteroaryl–C_1-C_6 alkyl–,

$–C_1$-C_6 alkyl–biheteroaryl–C_1-C_6 alkyl–,

$–C_1$-C_6 alkyl heterocycyl–C_1-C_6 alkyl–,

$–C_1$-C_6 alkyl-Y-C_1-C_6 alkyl–; or

$–C_1$-C_6 alkyl–Z– C_1-C_6 alkyl–.

wherein the alkyl, alkenyl, alkynyl, cycloalkyenyl and cycloalkyl are optionally substituted with one or more R^7 substituents; and the aryl, heteroaryl, biphenyl and heterocyclyl are optionally substituted with one or more R^{11} substituents;

Z is :

–C(O)–,

Client Ref. No. 229-PCT

$-S(O)_2-$,
$-N(R^8)C(O)-$,
$-C(O)N(R^8)-$,
$-OC(O)N(R^8)-$,
$-S(O)_2N(R^8)-$,
$-N(R^8)CON(R^8)-$,
$-N(R^8)-C_1-C_{12}$-alkyl-$N(R^8)-$,
$-N(R^8)-C_3-C_{12}$-cycloalkyl-$N(R^8)-$,
$-N(R^8)-C(O)C(O)-N(R^8)-$,
$-N(R^8)-C(O)-C_1-C_{12}$-alkyl-$C(O)-N(R^8)-$,
$-N(R^8)-C(O)-C_3-C_{12}$-cycloalkyl-$C(O)-N(R^8)-$
$-N(R^8)-C(O)$-aryl-$C(O)-N(R^8)-$,
$-N(R^8)-C(O)$-aryl-O-aryl-$C(O)-N(R^8)-$,
$-N(R^8)-C(O)$-heteroaryl-$C(O)-N(R^8)-$,
$-N(R^8)-C(O)$-biheteroaryl-$C(O)-N(R^8)-$,
$-N(R^8)-C(O)$-biphenyl-$C(O)-N(R^8)-$,
$-N(R^8)-S(O)_2-C_1-C_{12}$-alkyl-$S(O)_2-N(R^8)-$,
$-N(R^8)-S(O)_2$-aryl-$S(O)_2-N(R^8)-$,
$-N(R^8)-S(O)_2$-heteroaryl-$S(O)_2-N(R^8)-$,
$-N(R^8)-S(O)_2$-biheteroaryl-$S(O)_2-N(R^8)-$,
$-N(R^8)-S(O)_2$-biphenyl-$S(O)_2-N(R^8)-$,
$-N(R^8)-C_1-C_{12}$-alkyl-$N(R^8)-$,
$-N(R^8)$-aryl-$N(R^8)-$,
$-N(R^8)$-heteroaryl-$N(R^8)-$,
$-N(R^8)$-biheteroaryl-$N(R^8)-$, or
$-N(R^8)$-biphenyl-$N(R^8)-$;

wherein the alkyl and cycloalkyl are optionally substituted with one or more R^7 substituents, and the aryl, heteroaryl and heterocyclyl are optionally substituted with one or more R^{11} substituents;

R^1 ,R^{100} , R^{1a} and R^{100a} are independently

H, or

C_1-C_6 alkyl optionally substituted with one or more R^7 substituents;

R^2 and R^{200} are independently

H,

C_1–C_6 alkyl optionally substituted with one or more R^7 substituents, or

C_3-C_7 cycloalkyl optionally substituted with one or more R^7 substituents;

R^3 and R^{300} are independently

cycloalkyl,

cycloalkenyl,

aryl,

biphenyl,

heteroaryl,

heterocyclyl, or

heterobicyclyl,

wherein the cycloalkyl and cycloalkenyl are optionally substituted with one or more R^7 substituents; and the aryl, heteroaryl, heterocyclyl, and heterobicyclyl are optionally substituted with one or more R^{11} substituents.

R^4, R^{400}, R^5, R^{5a}, R^{500} and R^{500a} are each independently :

H

halogen,

NO_2,

-CN,

haloalkyl,

C_1–C_6 alkyl,

C_2-C_6 alkenyl,

C_2-C_4 alkynyl,

C_3–C_7 cycloalkyl,

C_3-C_7 cycloalkenyl,

aryl,

biphenyl,

heteroaryl,

heterocyclyl,
heterobicyclyl,
$-OR^8$,
$-S(O)_m R^8$,
$-NR^9R^{10}$,
$-NR^9S(O)_2R^{12}$,
$-C(O)O_nR^8$,
$-CONR^9R^{10}$,
$-S(O)_2NR^9R^{10}$,
$-OC(O)R^8$,
$-OC(O)Y-R^{12}$,
$-SC(O)R^8$, or
$-NC(Y)\ R^9R^{10}$,

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl are optionally substituted with one or more R^7 substitutents; the aryl, heteroaryl, heterocyclyl, and heterobicyclyl are optionally substituted with one or more R^{11} substituents; R^5 and R^{5a} may together be a carbonyl oxygen atom; and R^{500} and R^{500a} may together be a carbonyl oxygen atom;

R^6 and R^{600} are each independently
H,
haloalkyl,
C_1–C_6 alkyl,
C_2-C_6 alkenyl,
C_2-C_4 alkynyl,
C_3–C_7 cycloalkyl,
C_3-C_7 cycloalkenyl,
aryl,
biphenyl,
heteroaryl,
heterocyclyl,
heterobicyclyl,
$-C(O)(O)_n-R^{12}$,
$-C(=Y)NR^9R^{10}$, or

$-S(O)_2-R^{12}$,

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl are optionally substituted with one or more R^7 substitutents; and the aryl, heteroaryl, heterocyclyl, and heterobicyclyl are optionally substituted with one or more R^{11} substituents;

R^7 is

halogen,
NO_2,
CN,
haloalkyl,
C_1–C_6 alkyl,
C_2-C_6 alkenyl,
C_2-C_4 alkynyl,
C_3–C_7 cycloalkyl,
C_3-C_7 cycloalkenyl,
aryl,
biphenyl,
heteroaryl,
heterocyclyl,
heterobicyclyl,
$-OR^8$,
$-S(O)_m R^8$,
$-NR^9R^{10}$,
$-NR^9S(O)_2R^{12}$,
$-C(O)O_nR^8$,
$-CONR^9R^{10}$,
$-S(O)_2NR^9R^{10}$,
$-OC(O)R^8$,
$-OC(O)Y-R^{12}$,
$-SC(O)R^8$, or
$-NC(Y)\ R^9R^{10}$.

wherein the aryl, heteroaryl, heterocyclyl, and heterobicyclyl are optionally substituted with one or more R^{11} substituents;

R^8 is

H,
haloalkyl,
C_1–C_6 alkyl,
C_2-C_6 alkenyl,
C_2-C_4 alkynyl,
C_3–C_7 cycloalkyl,
C_3-C_7 cycloalkenyl,
aryl,
biphenyl,
heteroaryl,
heterocyclyl,
heterobicyclyl,
$-C(Y)NR^9R^{10}$,
$-C_1$-C_6 alkyl-C_2-C_4 alkenyl, or
$-C_1$-C_6 alkyl-C_2-C_4 alkynyl,

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl are optionally substituted with one or more R^7 substituents; and the aryl, heteroaryl, heterocyclyl, and heterobicyclyl are optionally substituted with one or more R^{11} substituents;

R^9 and R^{10} are each independently

H,
haloalkyl,
C_1–C_6 alkyl,
C_2-C_6 alkenyl,
C_2-C_4 alkynyl,
C_3–C_7 cycloalkyl,
C_3-C_7 cycloalkenyl,
aryl,
biphenyl,
heteroaryl,
heterocyclyl,

heterobicyclyl,
$-C(O)R^{12}$,
$-C(O)YR^{12}$, or
$-S(O)_2R^{12}$.

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl are optionally substituted with one or more R^7 substituents; and the aryl, heteroaryl, heterocyclyl, and heterobicyclyl are optionally substituted with one or more R^{11} substituents;

or R^9 and R^{10} together with the nitrogen atom to which they are bonded form a five, six or seven membered heterocyclic ring optionally substituted with one or more R^7 substituents;

R^{11} is

halogen,
$-NO_2$,
-CN,
$-B(OR^{13})(OR^{14})$,
C_1-C_6 alkyl,
C_2-C_6 alkenyl,
C_2-C_4 alkynyl,
C_3-C_7 cycloalkyl,
C_3-C_7 cycloalkenyl,
haloalkyl,
$-OR^8$,
$-NR^9R^{10}$,
$-SR^8$,
$-C(O)O_nR^8$,
$-S(O)_mR^8$,
$-CONR^9R^{10}$,
$-S(O)_2NR^9R^{10}$,
aryl,
biphenyl,
heteroaryl,
heterocyclyl, or

heterobicyclyl.

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl are optionally substituted with one or more R^7 substituents;

R^{12} is

haloalkyl,

C_1–C_6 alkyl,

C_2-C_6 alkenyl,

C_2-C_4 alkynyl,

C_3–C_7 cycloalkyl,

C_3-C_7 cycloalkenyl,

aryl,

biphenyl,

heteroaryl,

heterocyclyl, or

heterobicyclyl.

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl are optionally substituted with one or more R^7 substituents; and the aryl, heteroaryl, heterocyclyl, and heterobicyclyl are optionally substituted with one or more R^{11} substituents;

and R^{13} and R^{14} are each independently

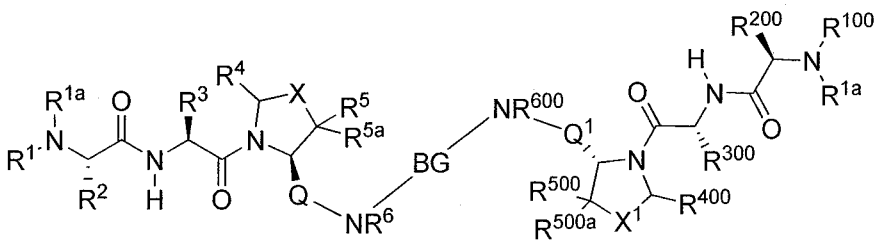
H, or

C_1-C_6 alkyl,

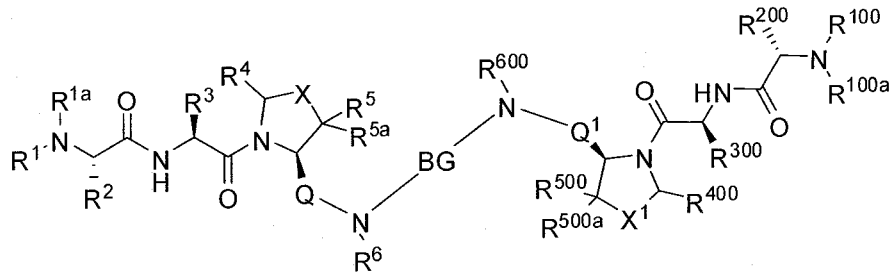
or R^{13} and R^{14} are combined to form a ring system.

2. The compound according to claim 1, wherein Q and Q^1 are both $–CH_2-$ or –C(O)-.

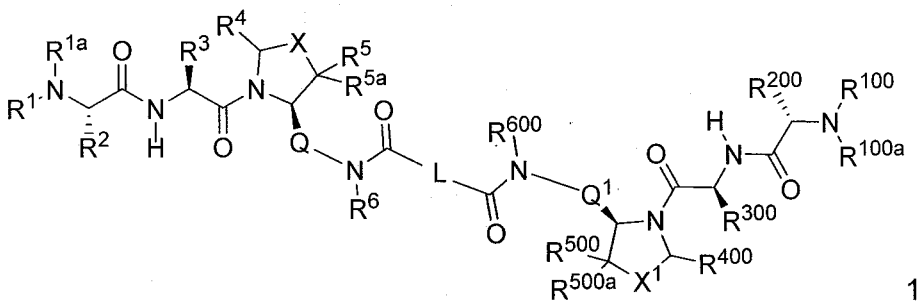
3. The compound according to claim 1, of any one of Formulas 1.1A2 or 1A3-1A8:



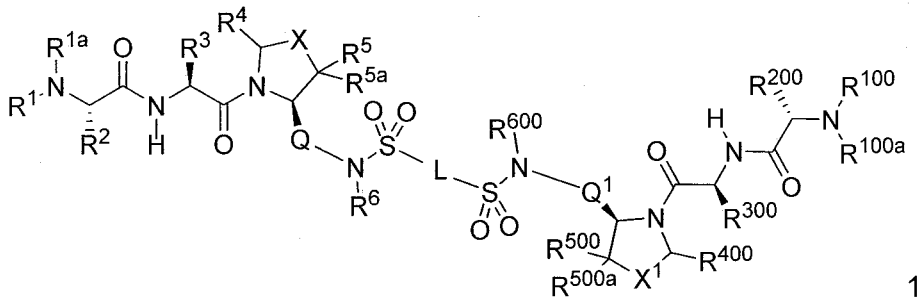
1.1A2



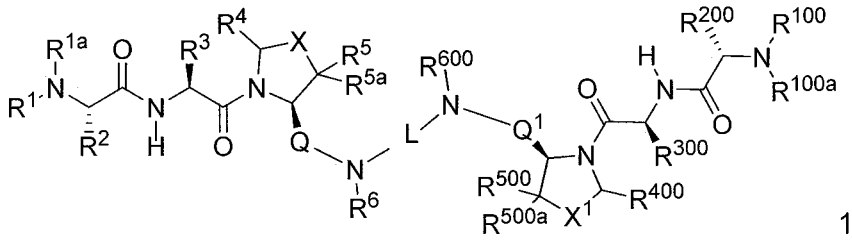
1A3



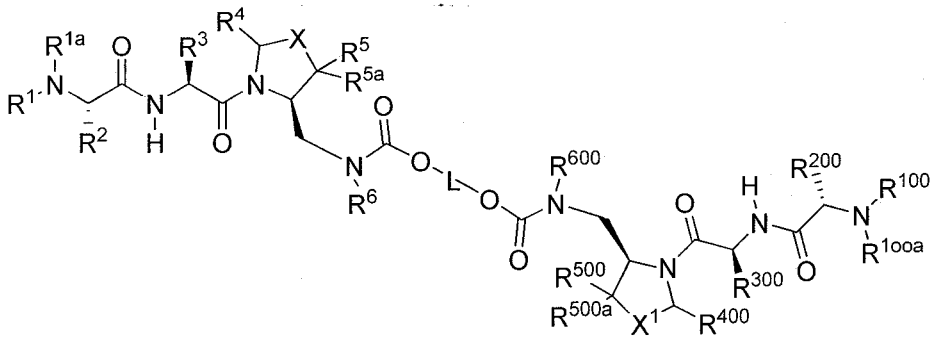
1A4



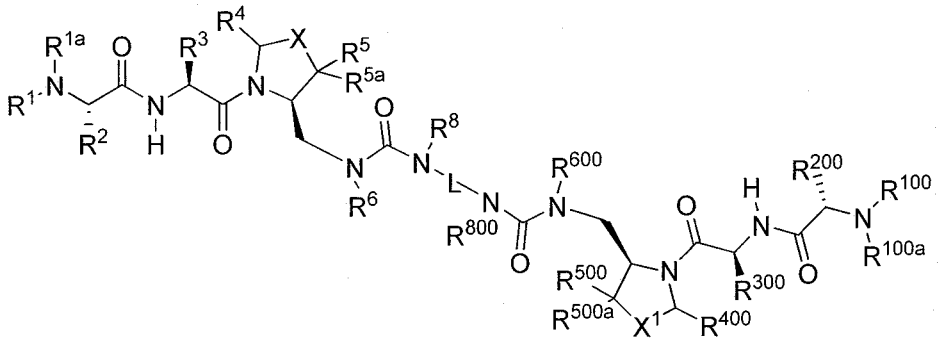
1A5



1A6



1A7



1A8.

4. The compound according to any of claims 1-3, wherein X is

$-CH_2-$

-CH(OH)-

$-CH(OCH_3)-$

$-CF_2-$

-CHF-

$-CHNH_2-$

$-CH(NHC(O)CH_3)-$

$-CH_2CH_2-$

$-CH_2O-$

$-CH_2NH-$

$-CH_2CF_2-$

$-CH_2N(C(O)CH_3)-$

$-CH_2CH(OH)-$

$-CH_2CH(NH_2)-$, or

$-CH_2CH(NHC(O)CH_3)-$.

5. The compound according to any of claims 1-4, wherein L, L^1 and L^{100} are $-C_1$-C_6 alkyl–Z– C_1-C_6 alkyl–, wherein the alkyl is optionally substituted with one or more R^7 substituents.

6. The compound according to any of claims 1-4, wherein L, L^1, and L^{100} are –biheteroaryl– or $-C_1$-C_6 alkyl–biheteroaryl–C_1-C_6 alkyl–,

7. The compound according to any of claims 1-3, wherein Z is –N(R8)-C(O)-biheteroaryl-C(O)-N(R8)– or –N(R8)-S(O)2-biheteroaryl-S(O)2-N(R8)–.

8. The compound according to any of claims 1-7, wherein R^1, R^{1a}, R^{100} and R^{100} are independently selected from H or CH_3.

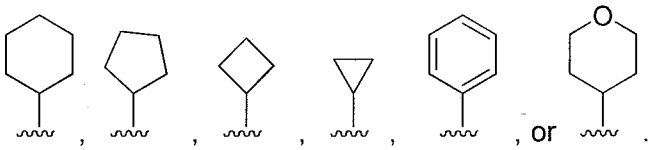
9. The compound according to any of claims 1-8, wherein both R^2 and R^{200} display (S)-stereochemistry.

10. The compound according to any of claims 1-9, wherein R^3 and R^{300} are independently selected from

a) cycloalkyl,
b) cycloalkenyl,
c) aryl,
d) heteroaryl,
e) heterocyclyl, or
f) heterobicyclyl;

wherein the cycloalkyl and cycloalkenyl are optionally substituted with one or more R^7 substituents; and the aryl, heteroaryl, heterocyclyl and heterobicyclyl are optionally substituted with one or more R^{11} substituents.

11. The compound according to claim 10, wherein R^3 and R^{300} are



12. The compound according to any of claims 1-11, wherein R^6 and R^{600} are each independently

a) H,
b) haloalkyl,
c) C_1–C_6 alkyl,
d) C_2-C_6 alkenyl,
e) C_2-C_4 alkynyl,

f) C_3–C_7 cycloalkyl,

g) C_3-C_7 cycloalkenyl,

h) aryl,

i) heteroaryl,

j) heterocyclyl,

k) heterobicyclyl,

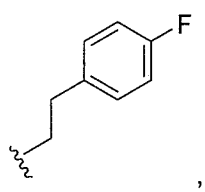
l) $-C(O)(O)_n-R^{12}$,

m) $-C(=Y)NR^9R^{10}$, or

n) $-S(O)_2-R^{12}$,

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl are optionally substituted with one or more R^7 substitutents; and wherein the aryl, heteroaryl, heterocyclyl, and heterobicyclyl are optionally substituted with one or more R^{11} substituents;

13. The compound according to claim 12, wherein R^6 and R^{600} are:



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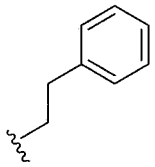
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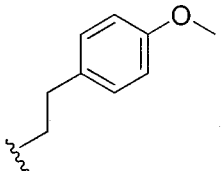
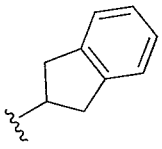


, or

.

14. The compound according to any of claims 1-13, wherein R^7 is

a) C_3–C_7 cycloalkyl,

b) aryl,

c) heteroaryl, or

d) $NHC(O)OCH_2$phenyl,

wherein the aryl and the heteroaryl are optionally substituted with one or more R^{11} substituents.

15. The compound according to any of claims 1-14, wherein R^8 is

a) H,

b) haloalkyl,

c) C_1–C_6 alkyl,

d) C_3–C_7 cycloalkyl,

e) aryl,

f) heteroaryl,

g) heterocyclyl, or

h) heterobicyclyl,

wherein the alkyl and cycloalkyl, are optionally substituted with one or more R^7 substituents; and wherein the aryl, heteroaryl, heterocyclyl, and heterobicyclyl are optionally substituted with one or more R^{11} substituents.

16. The compound according to any of claims 1-15, wherein R^{11} is

a) halogen,

b) CF_3,

c) OH,

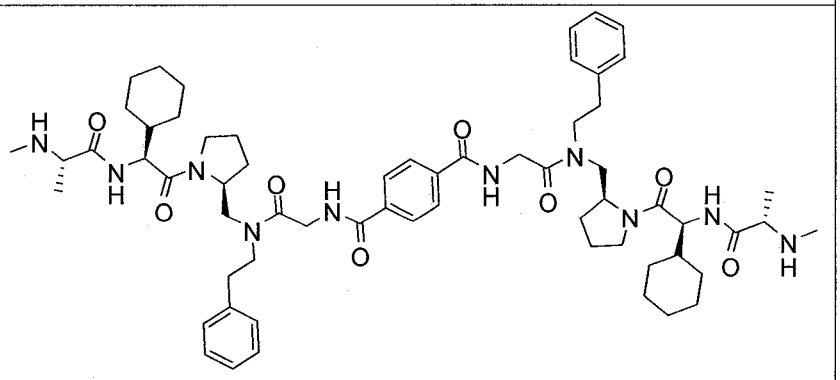
d) OMe,

e) aryl, or

f) heteroaryl.

17. The compound according to claim 16, wherein R^{11} is F, Cl, Br, OH, OMe, CF_3, phenyl and tetrazole.

18. A compound according to claim 1, wherein the compound is:

Cmpd #	Structure
1	

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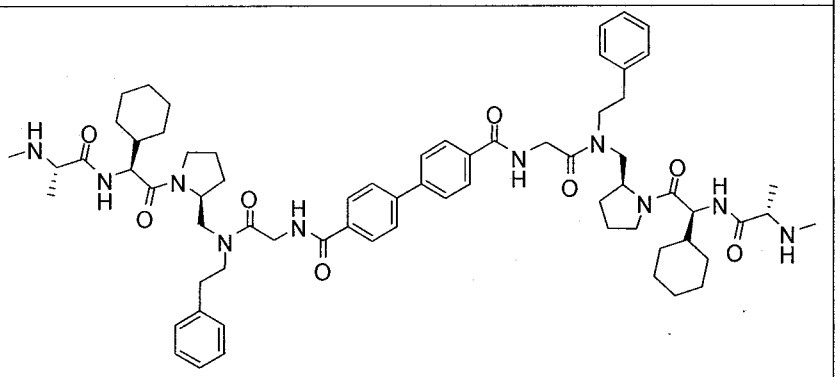
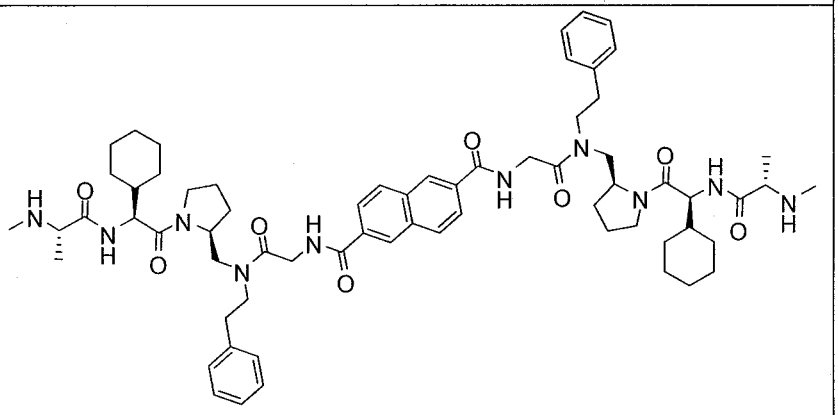
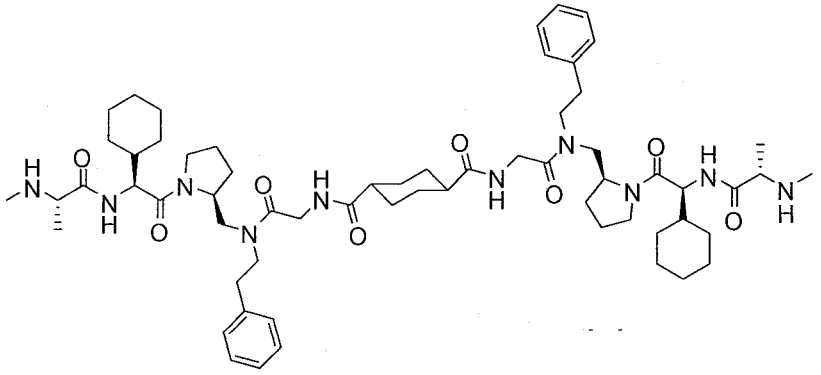
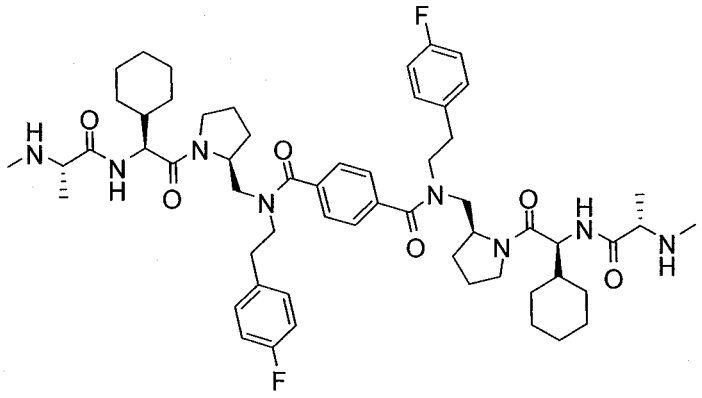
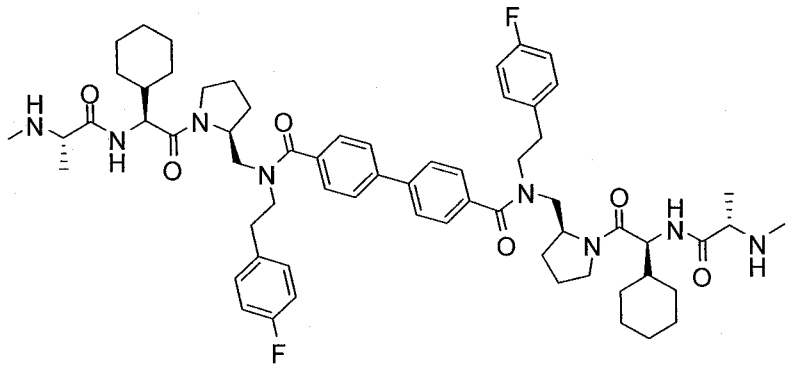
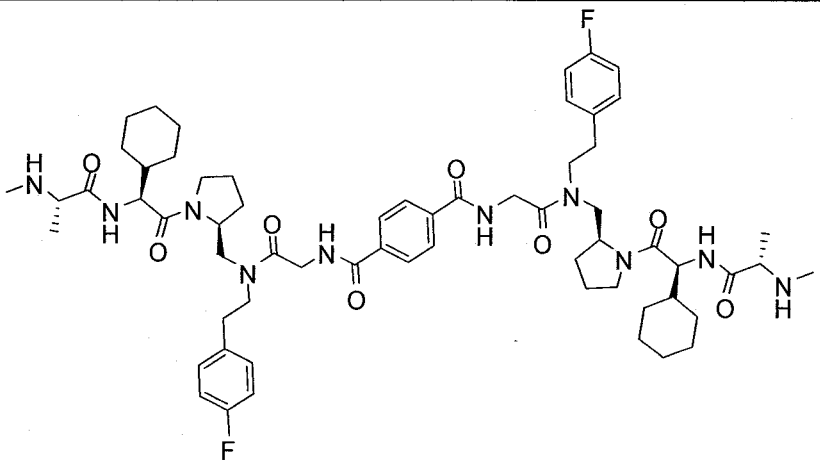
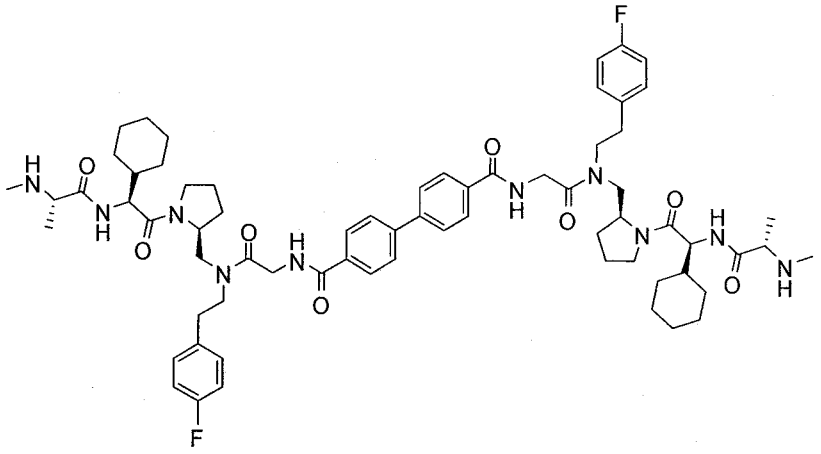
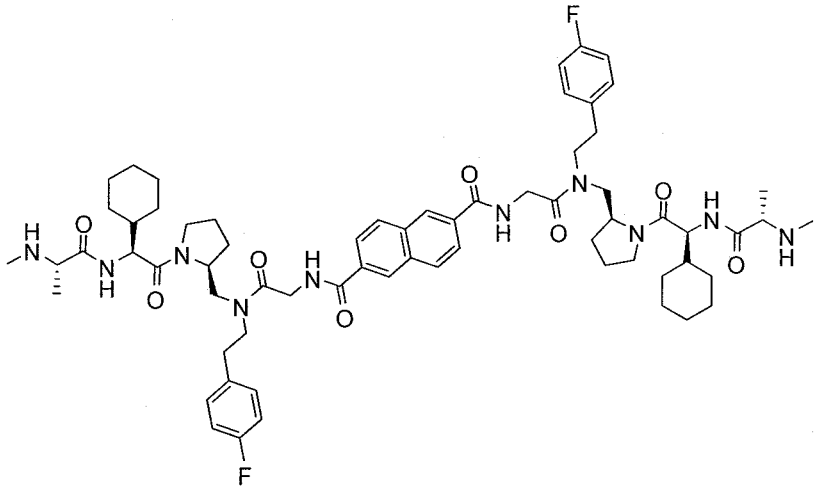
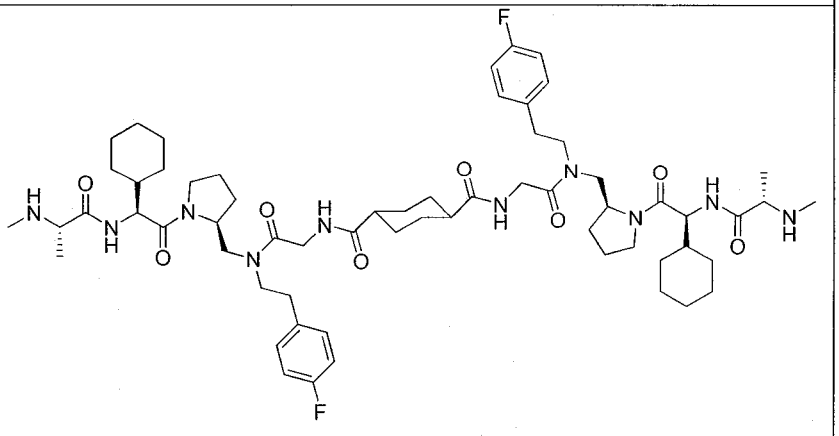
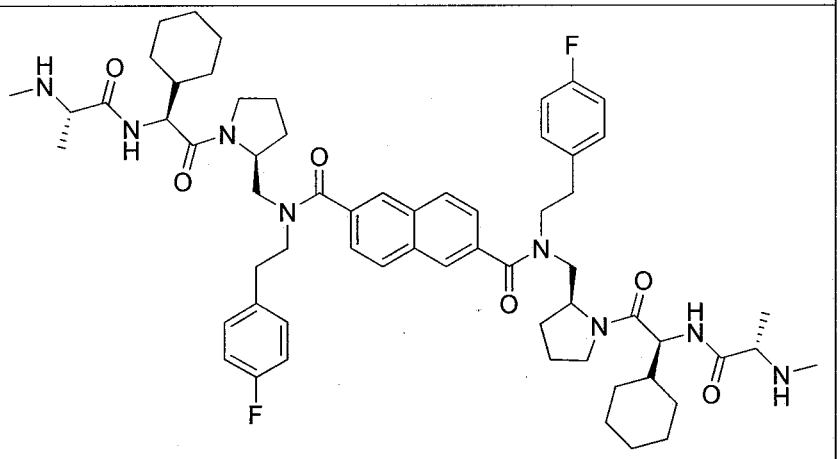
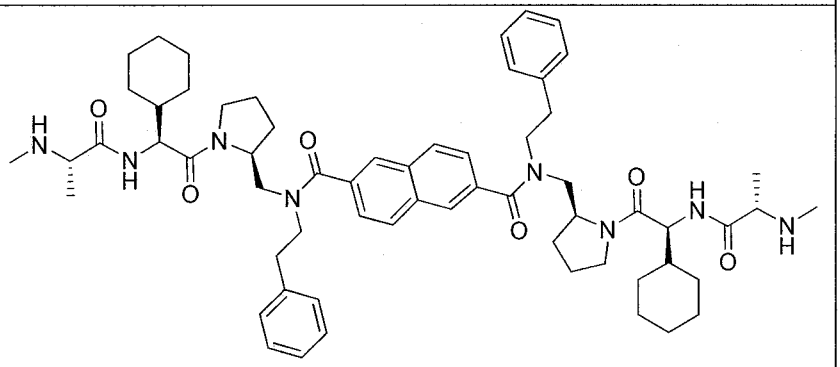
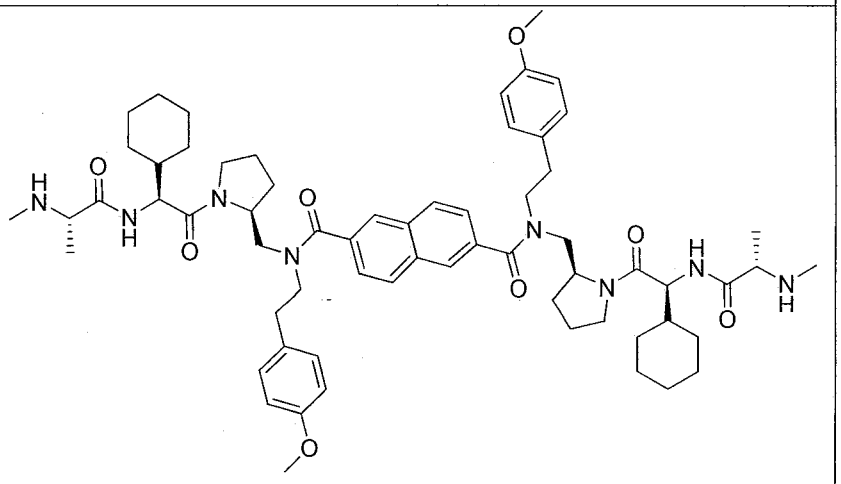
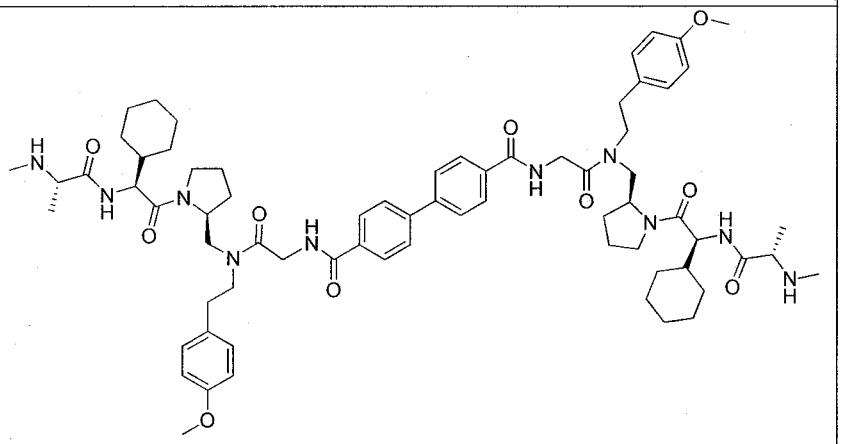
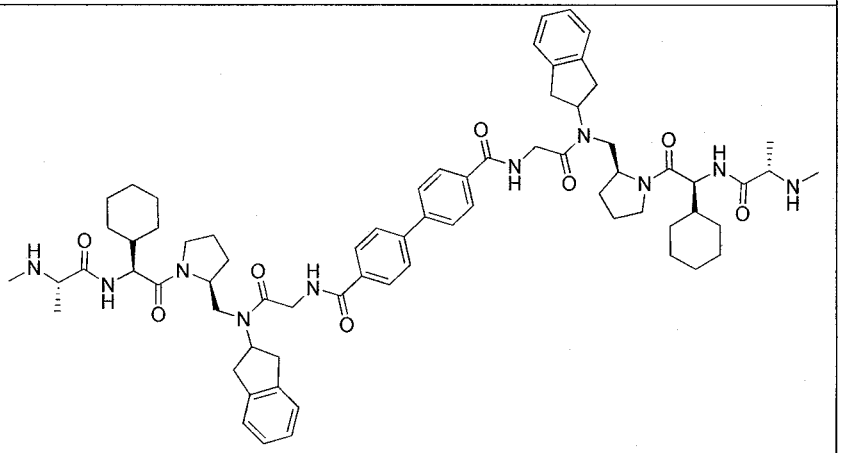
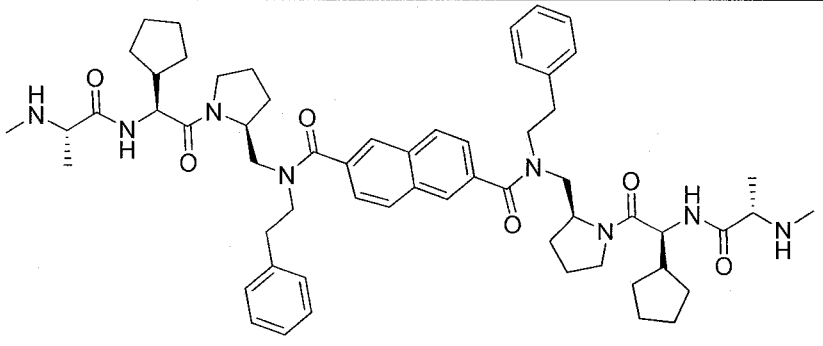
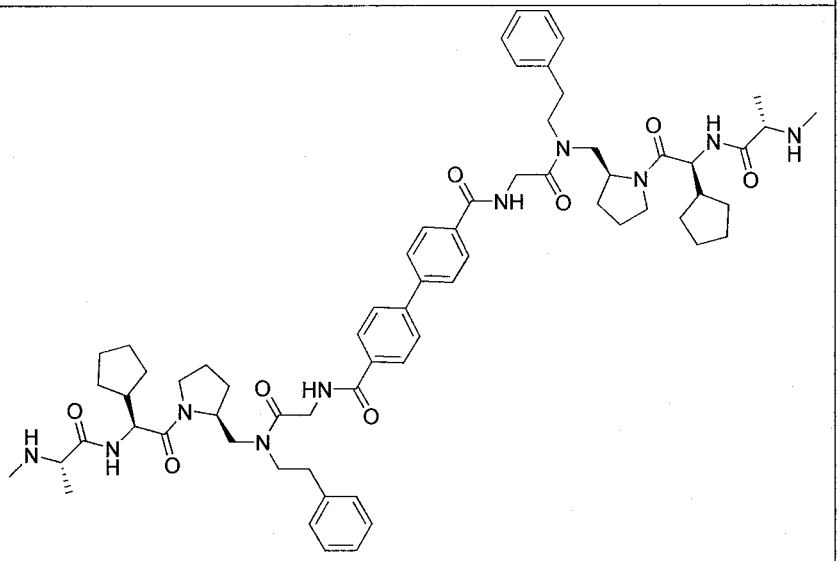
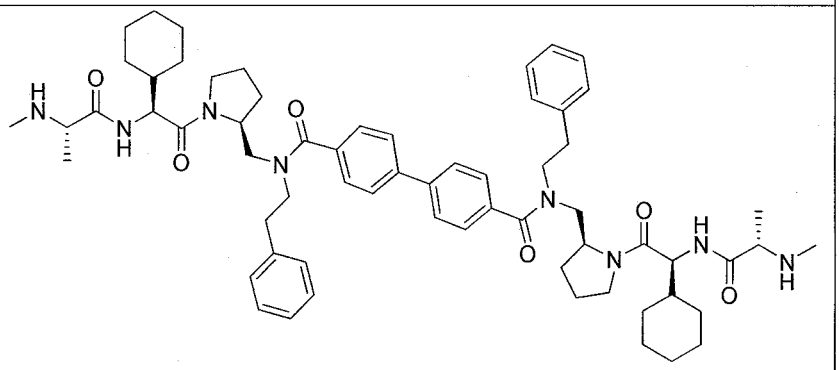
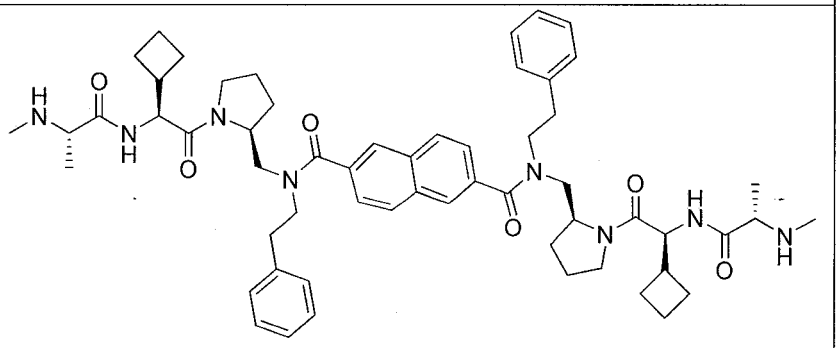
Cmpd #	Structure
2	 ;
3	 ;
4	 ;

Cmpd #	Structure
5	 ;
6	 ;
7	 ;

Cmpd #	Structure
8	 ;
9	 ;
10	 ;

Cmpd #	Structure
11	
12	
13	

Cmpd #	Structure
14	 ;
15	 ;
16	 ;

Cmpd #	Structure
17	
18	
19	

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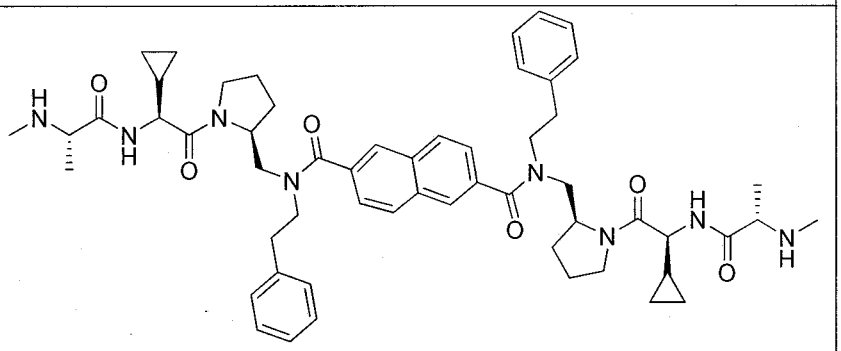
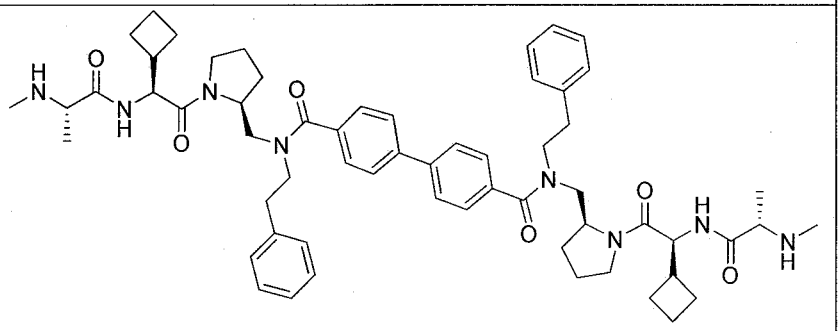
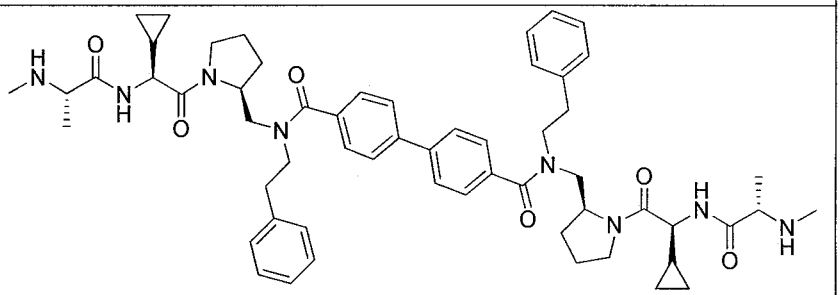
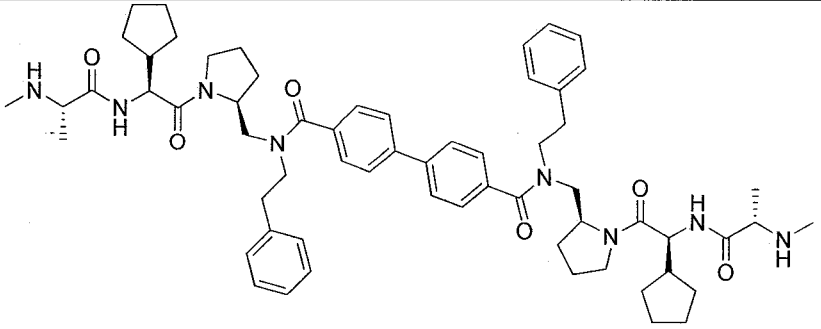
20	 ;
21	 ;
22	 ;
23	 ;

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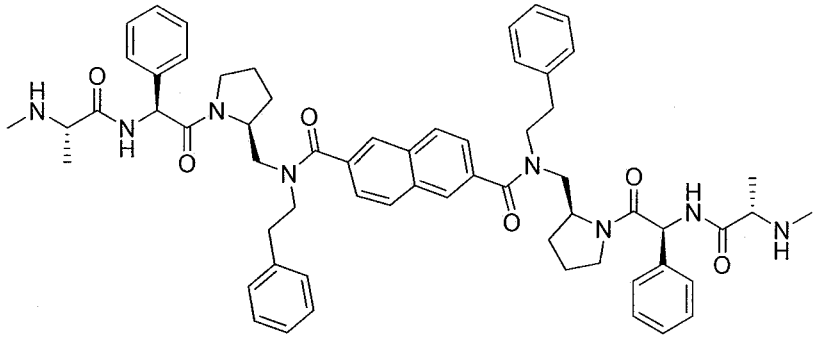
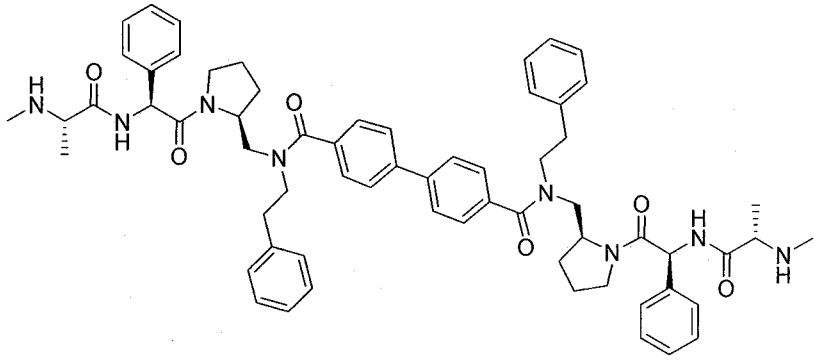
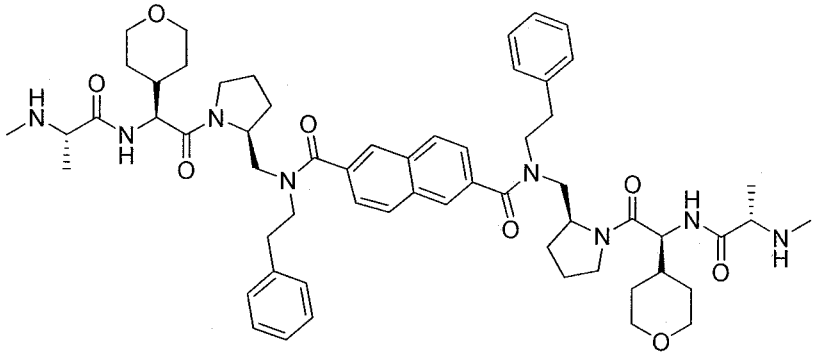
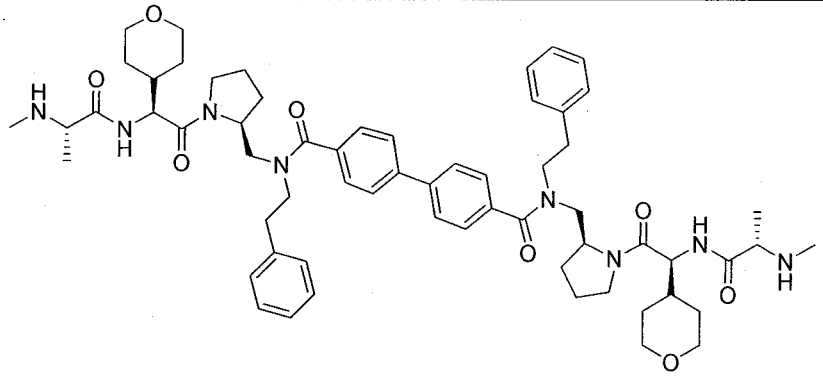
24	
25	
26	
27	

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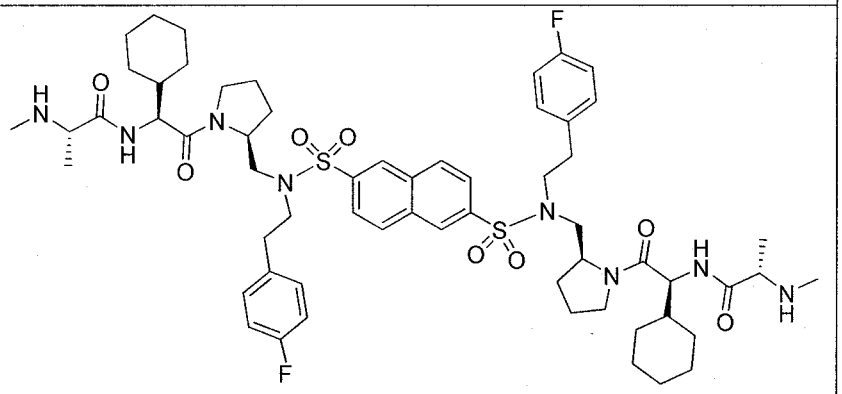
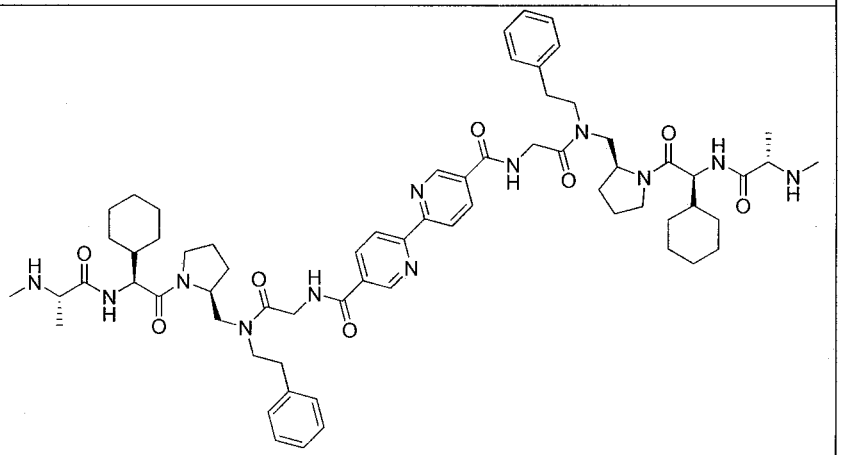
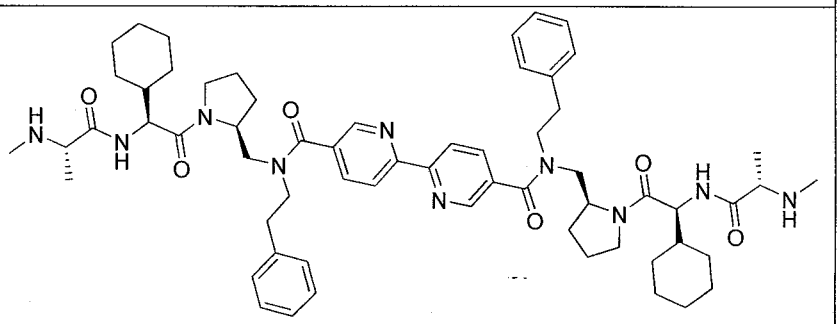
28	
29	
30	

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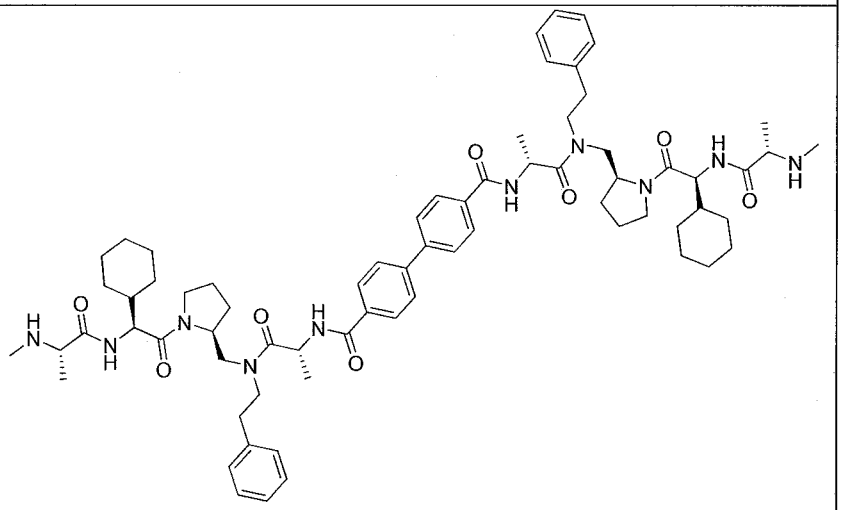
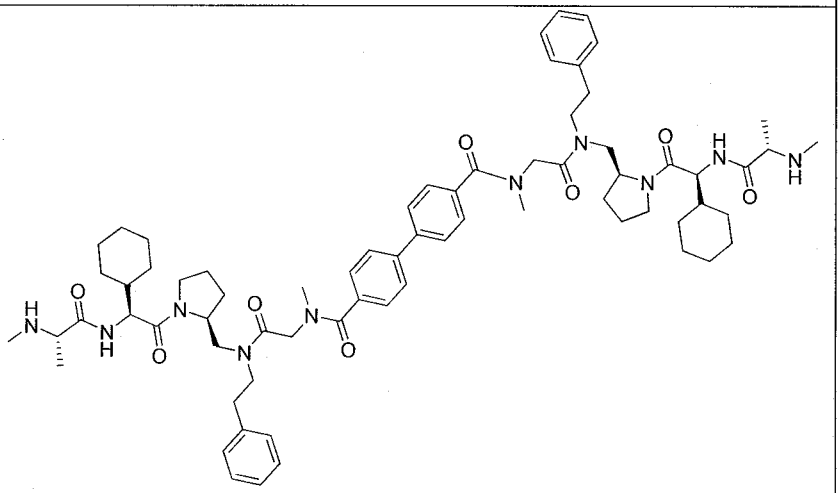
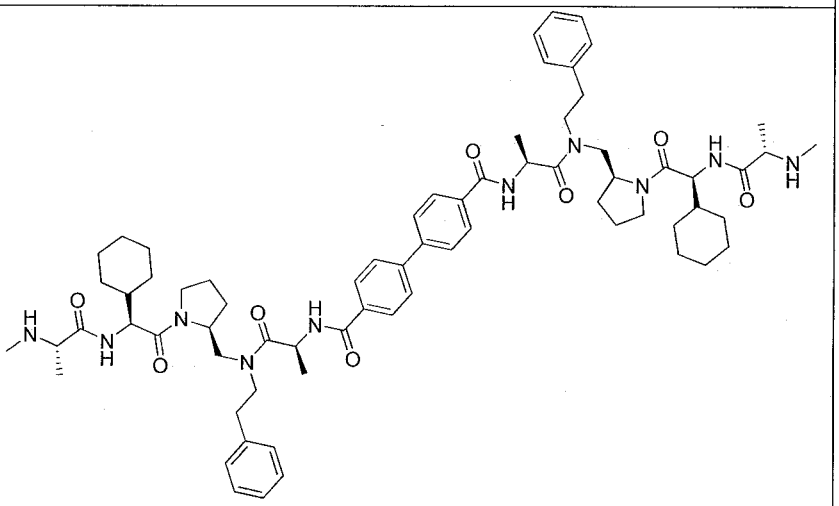
31	 ;
32	 ;
33	 ;

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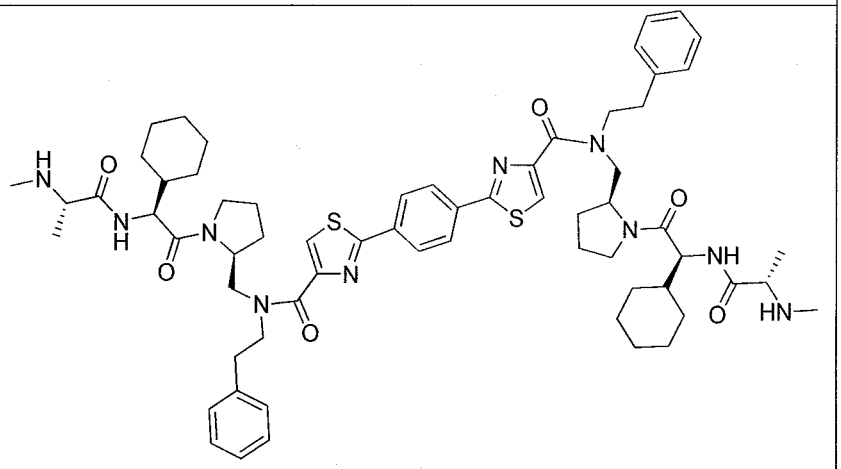
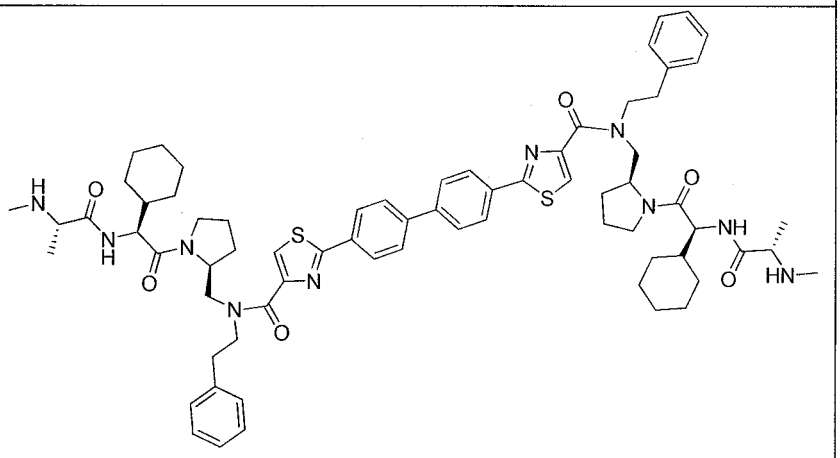
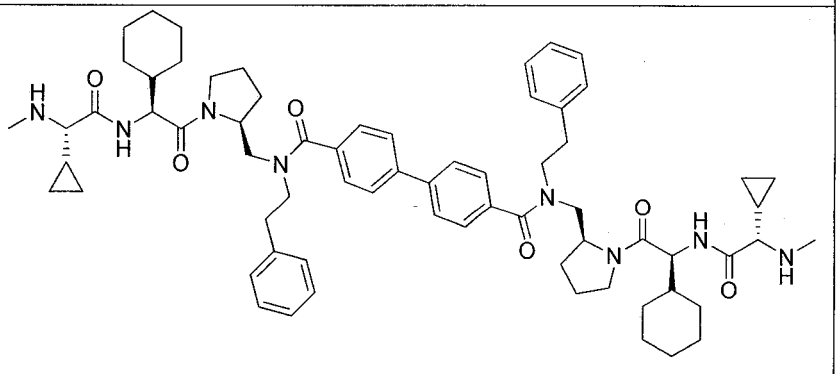
34	
35	
36	

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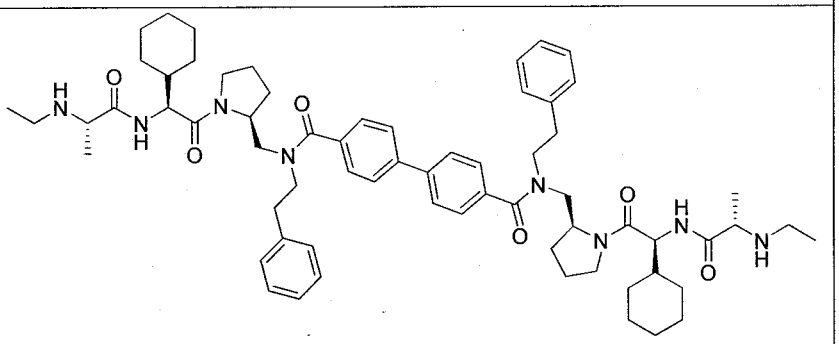
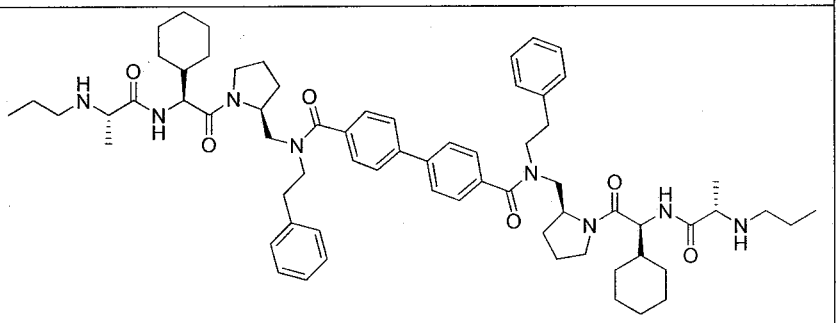
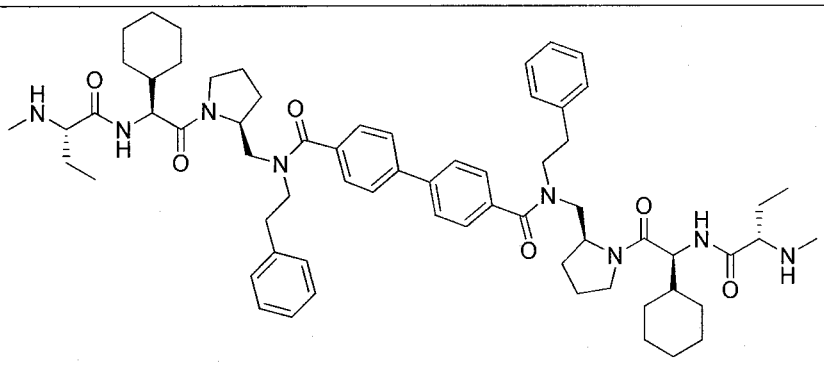
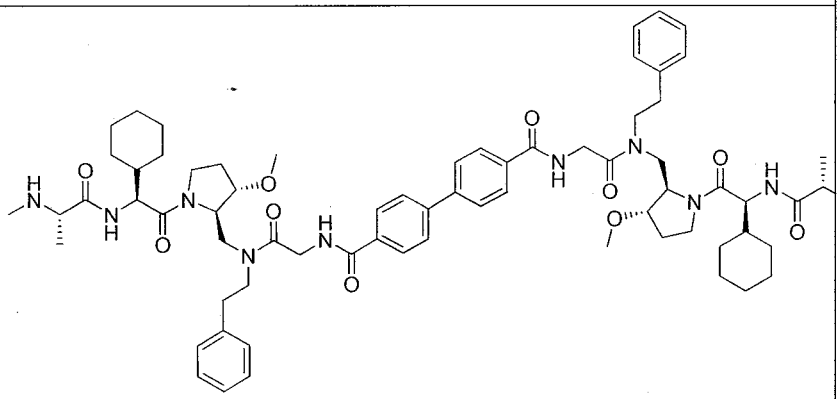
37	 ;
38	 ;
39	 ;
40	 ;

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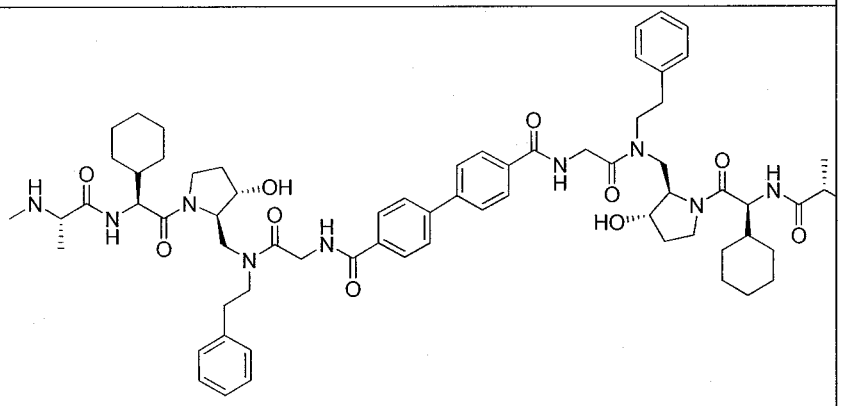
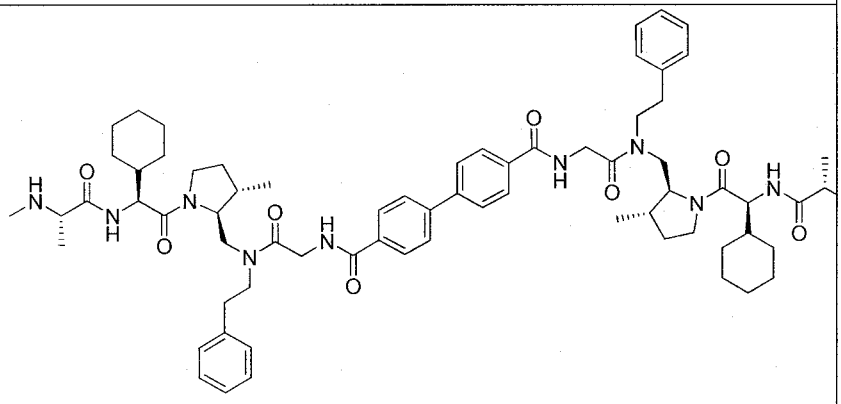
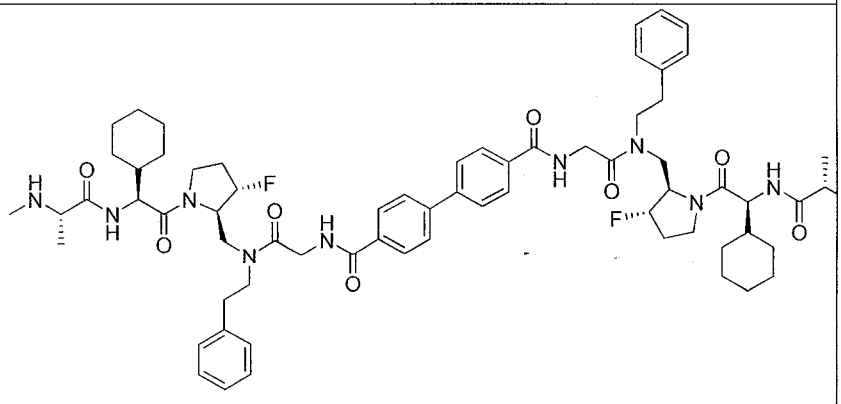
41	 ;
42	 ;
43	 ;

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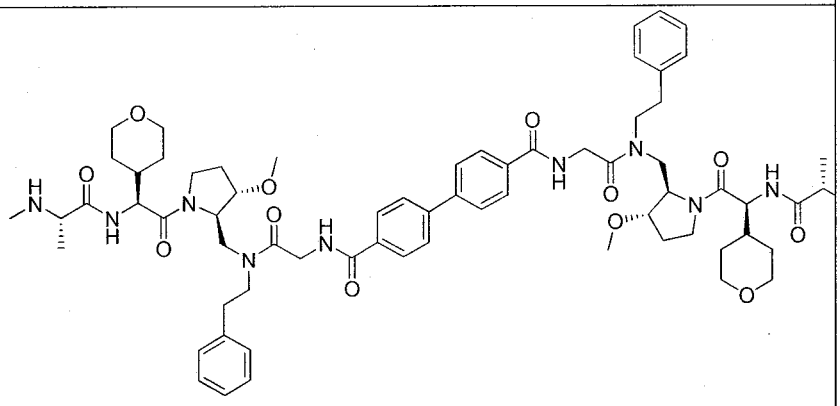
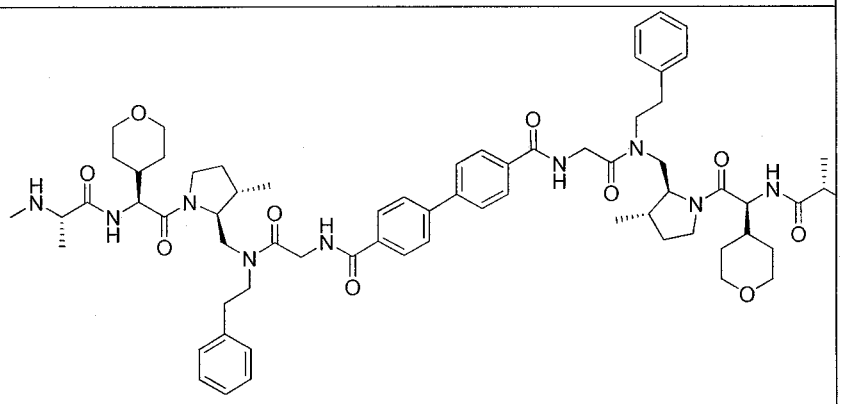
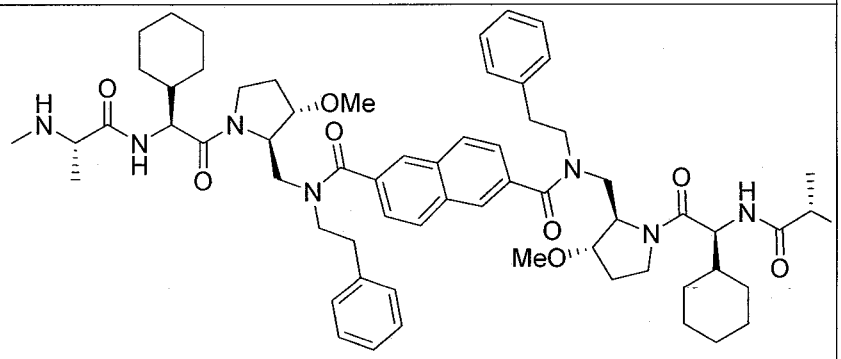
44	 ;
45	 ;
46	 ;

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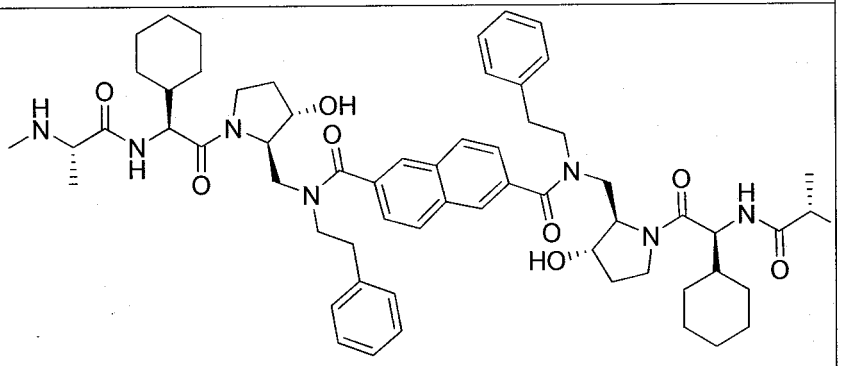
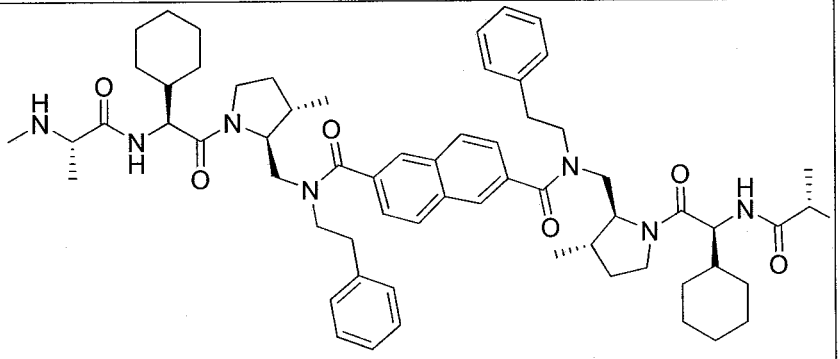
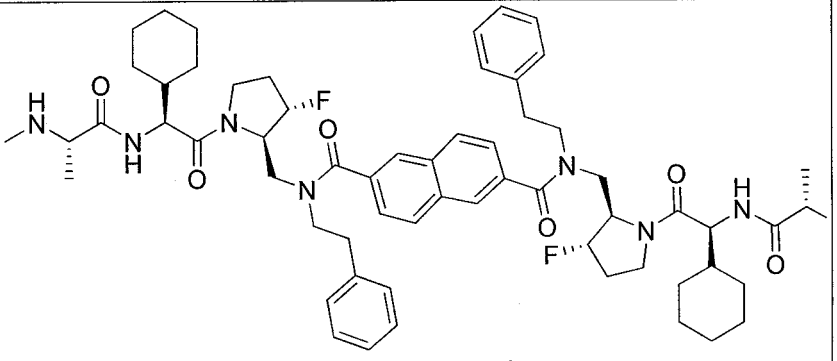
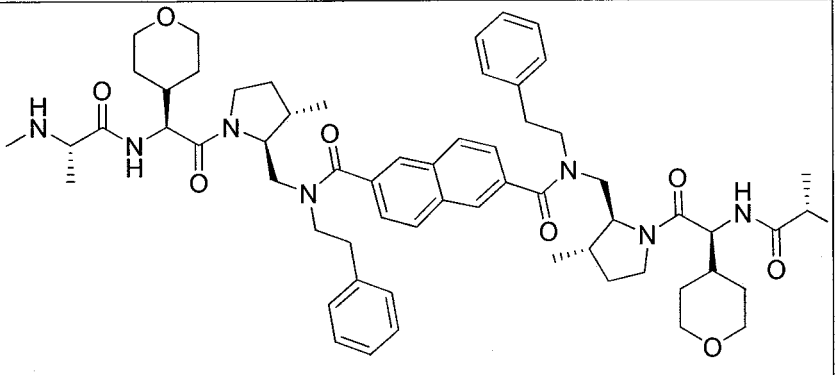
47	 ;
48	 ;
49	 ;
50	 ;

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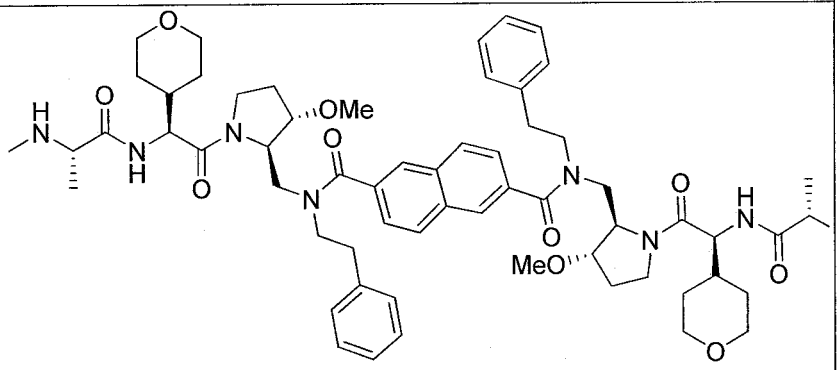
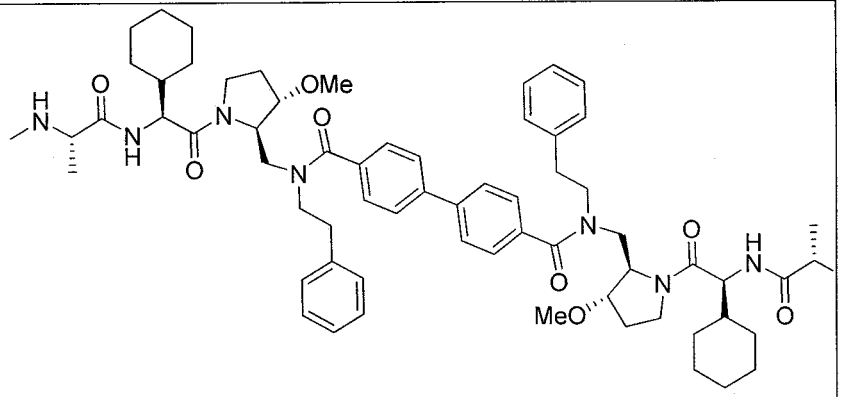
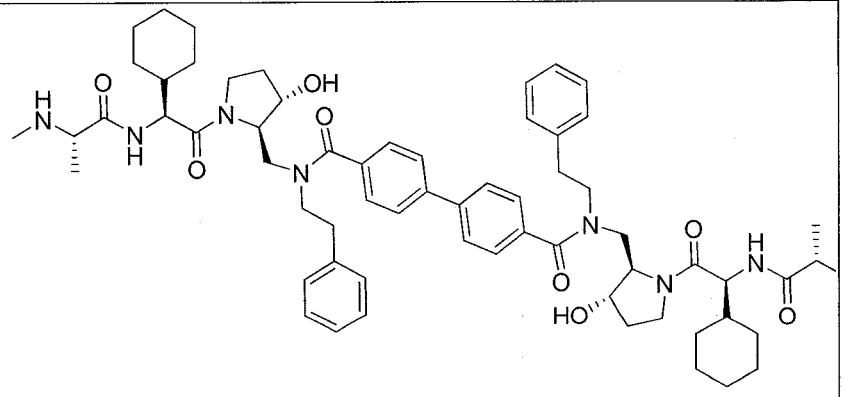
51	
52	
53	

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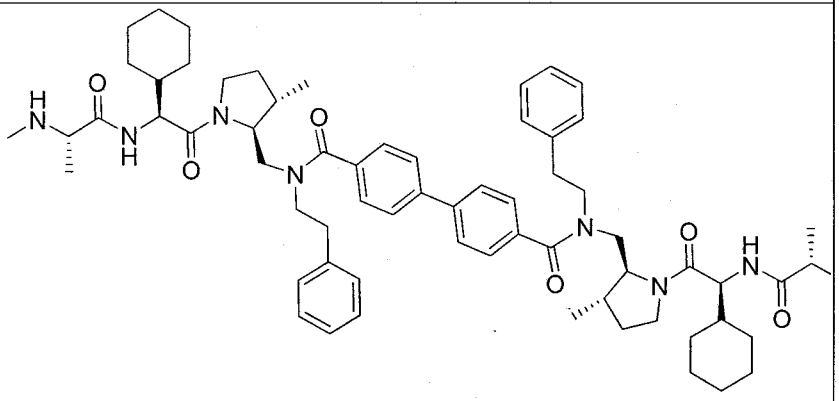
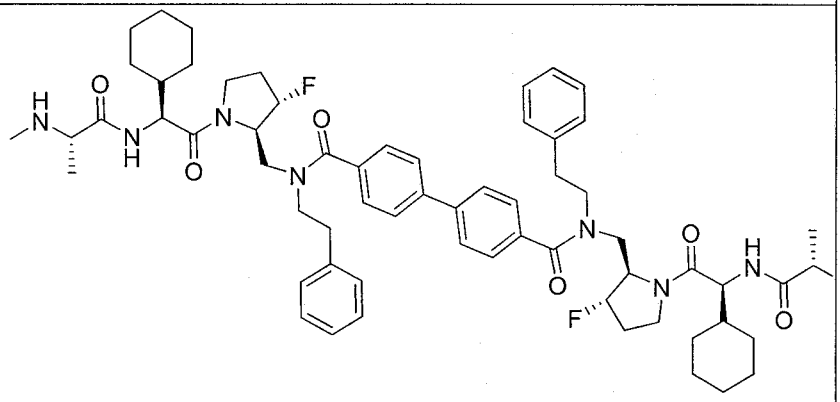
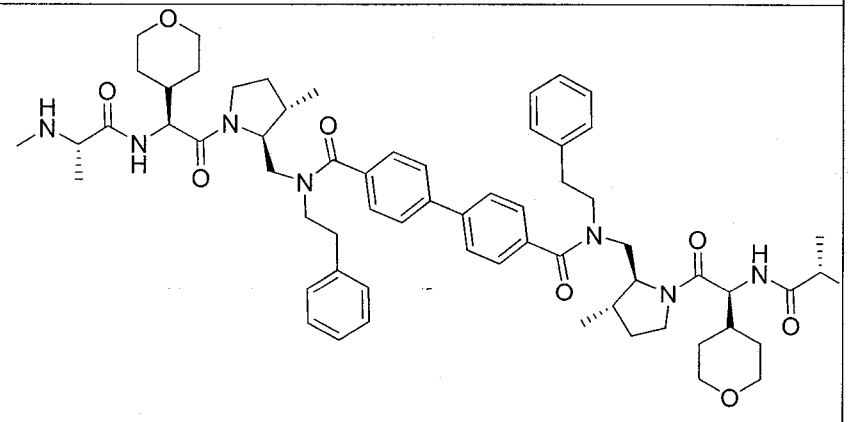
54	
55	
56	

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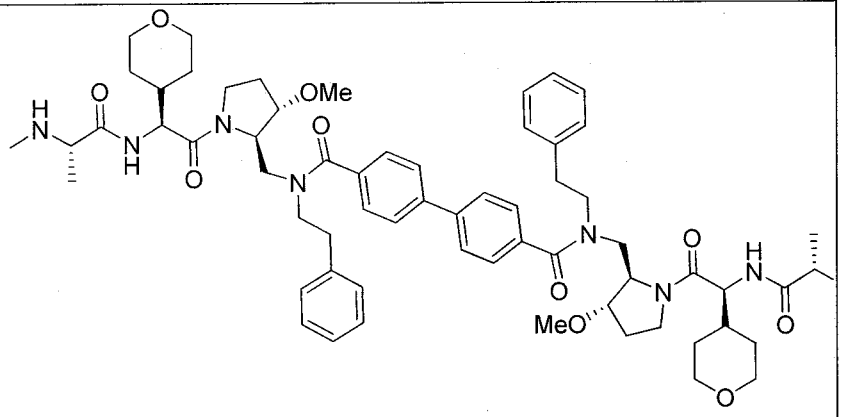
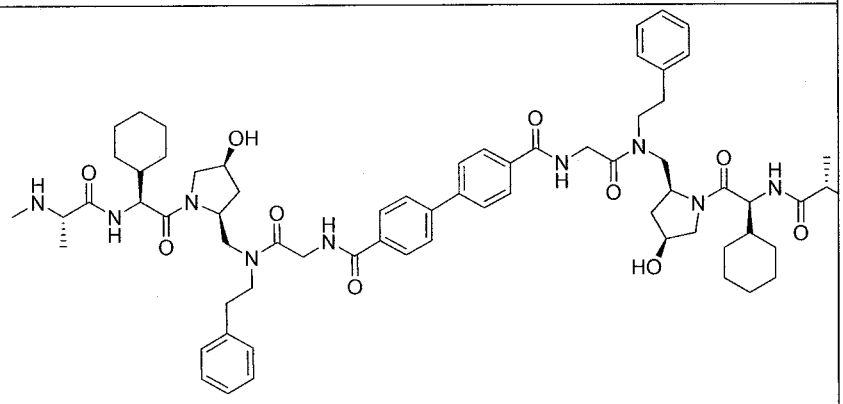
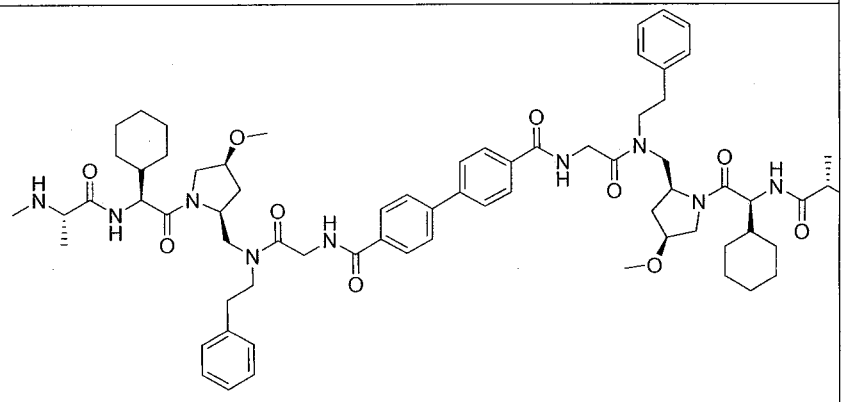
57	
58	
59	

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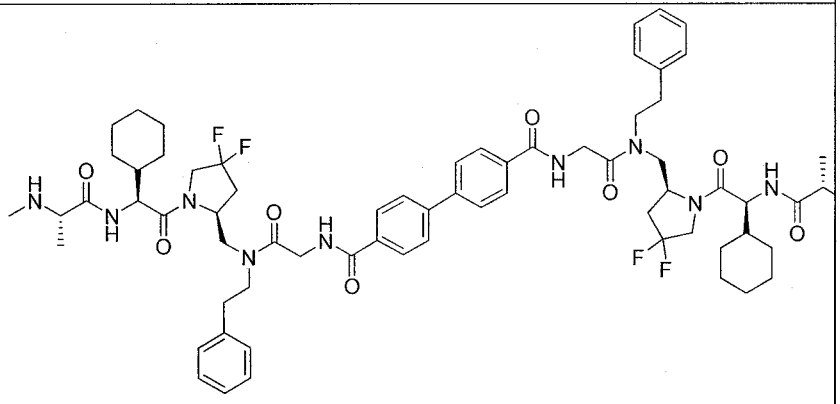
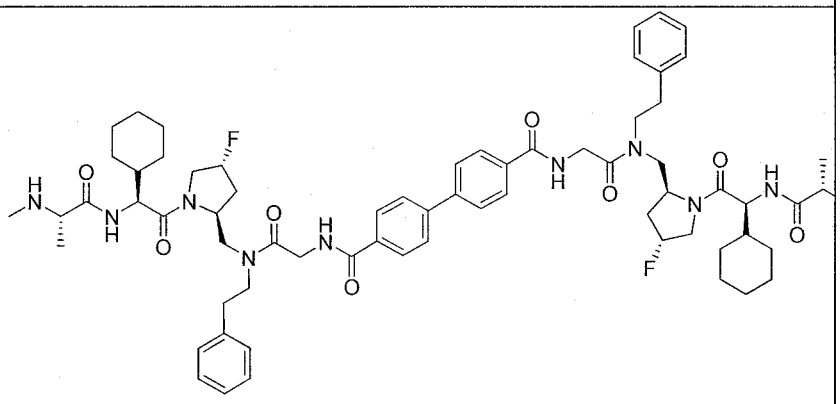
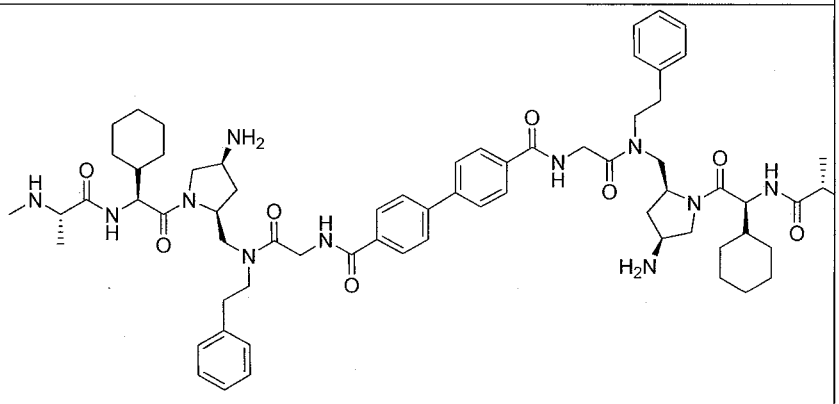
60	 ;
61	 ;
62	 ;

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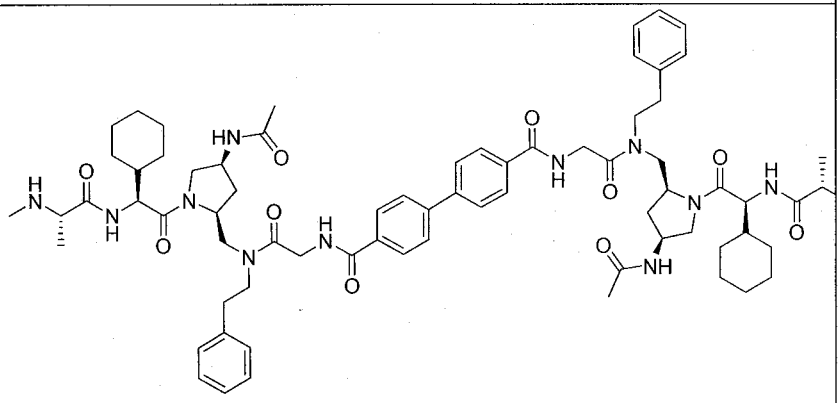
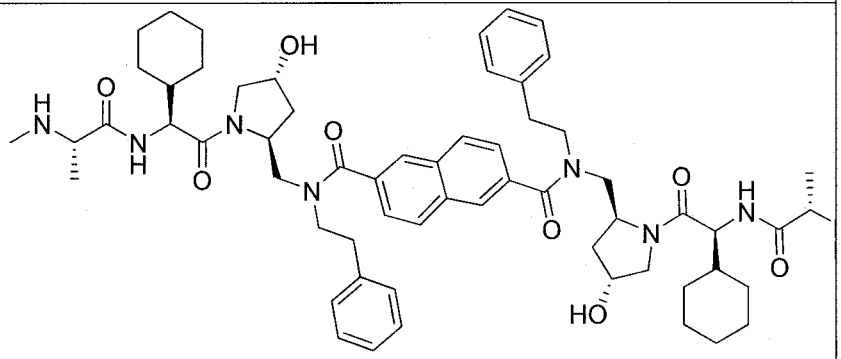
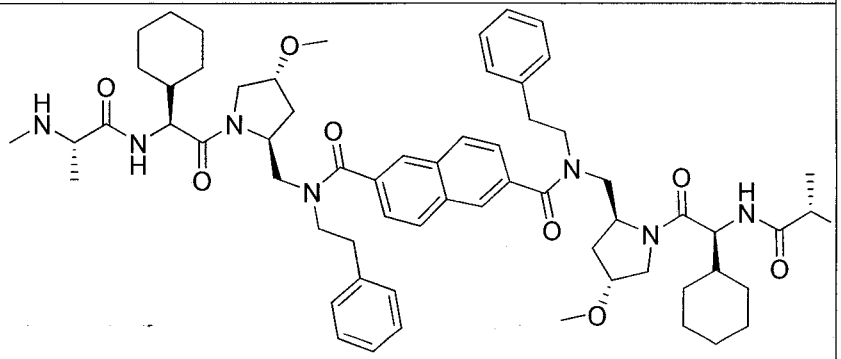
63	 ;
64	 ;
65	 ;

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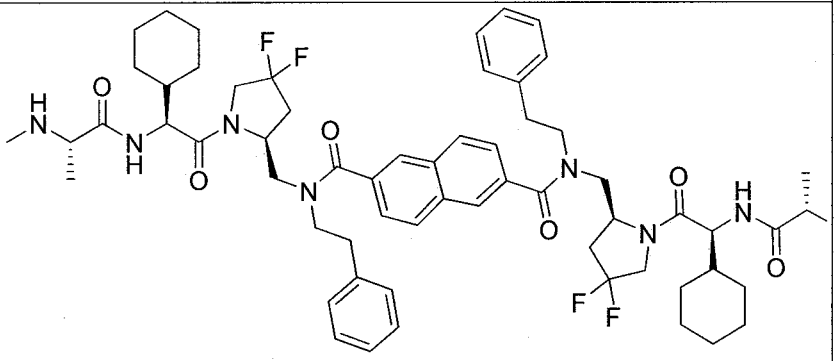
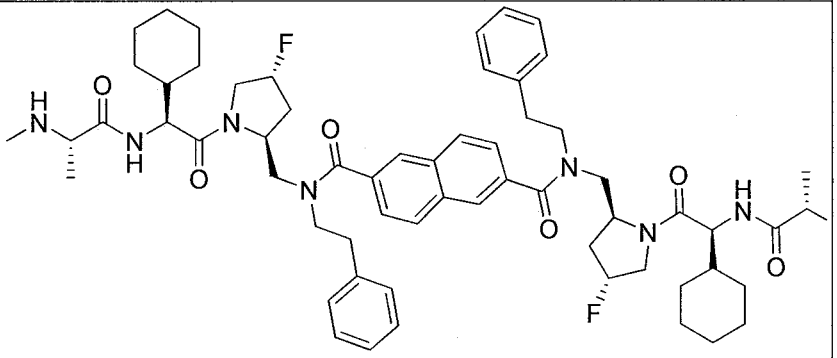
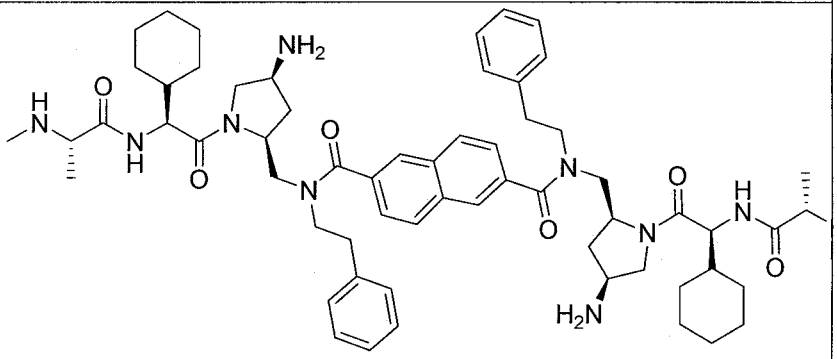
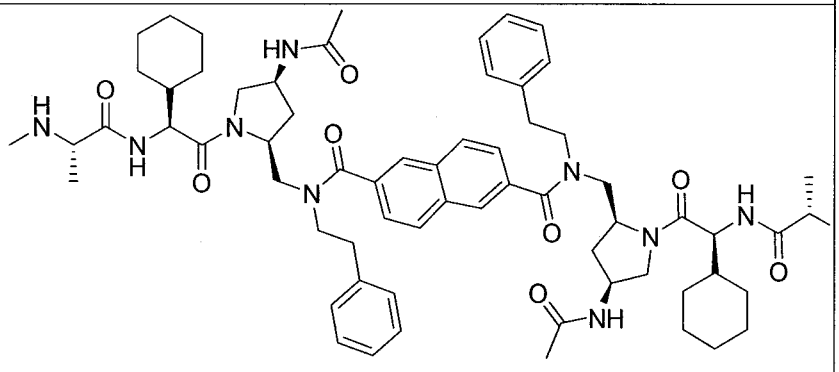
66	 ;
67	 ;
68	 ;
69	 ;

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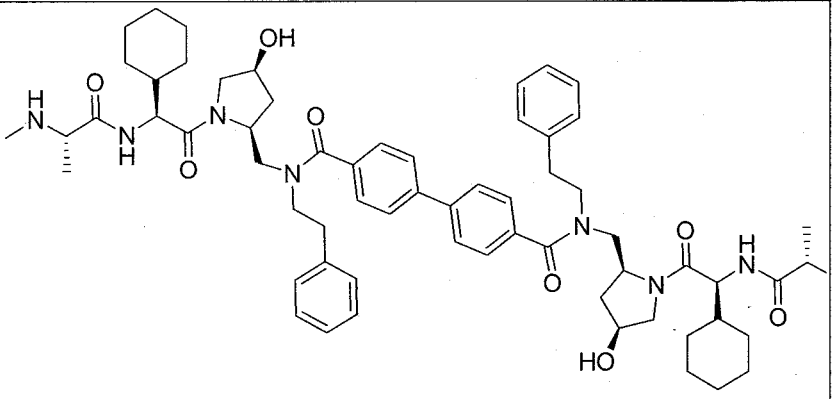
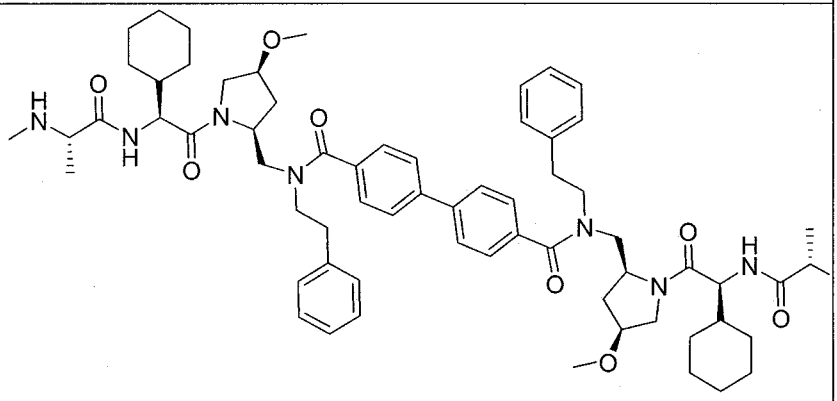
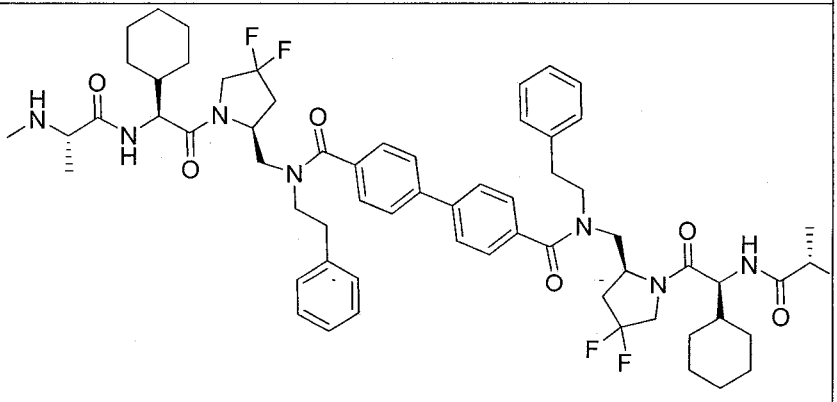
70	
71	
72	

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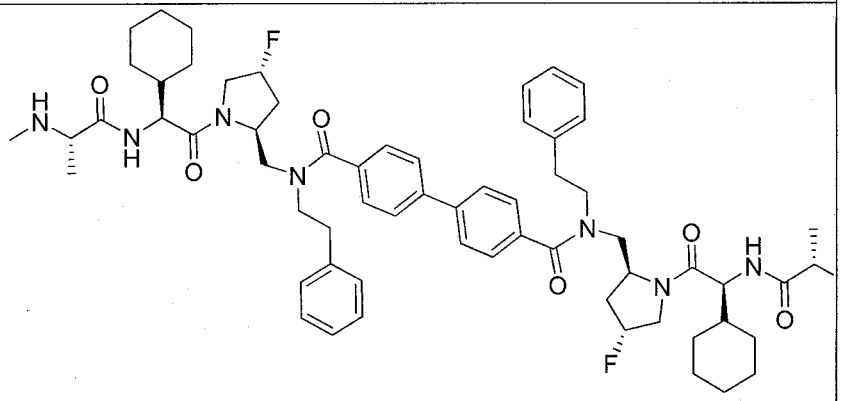
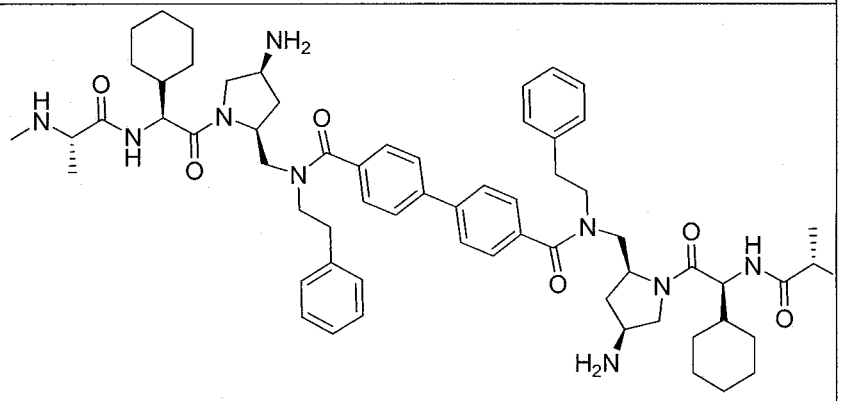
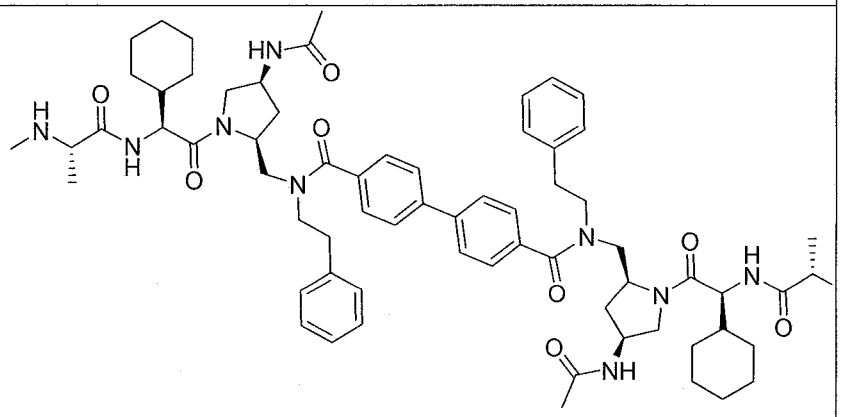
73	
74	
75	

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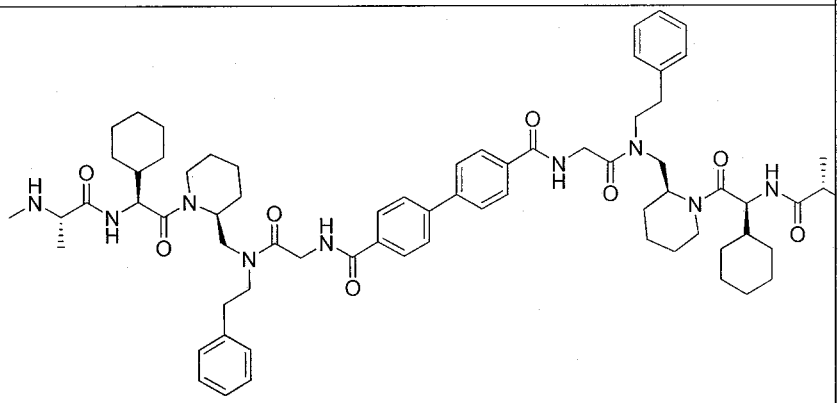
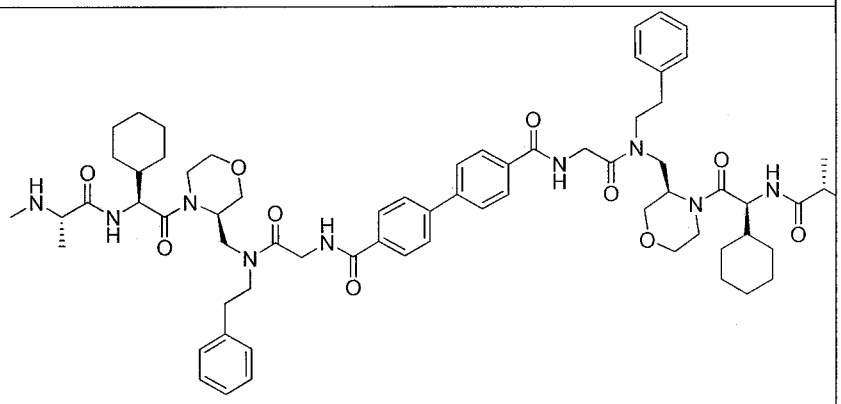
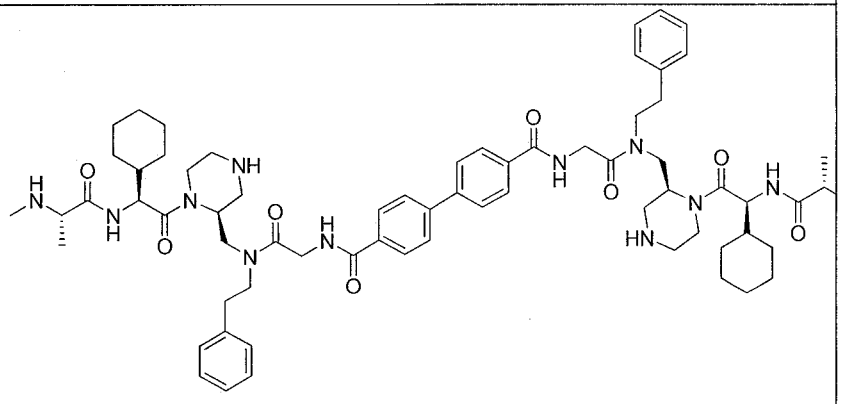
76	 ;
77	 ;
78	 ;

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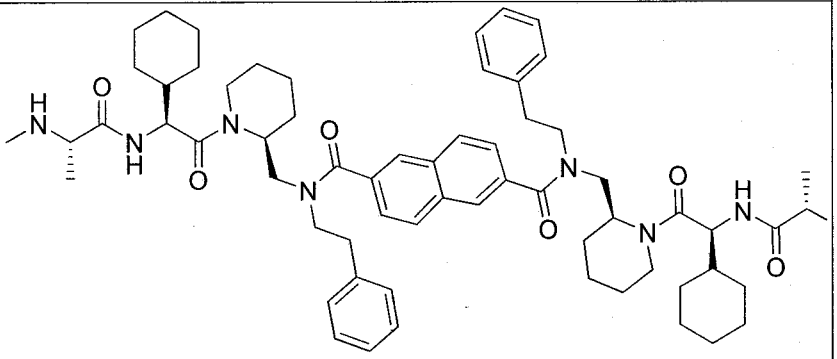
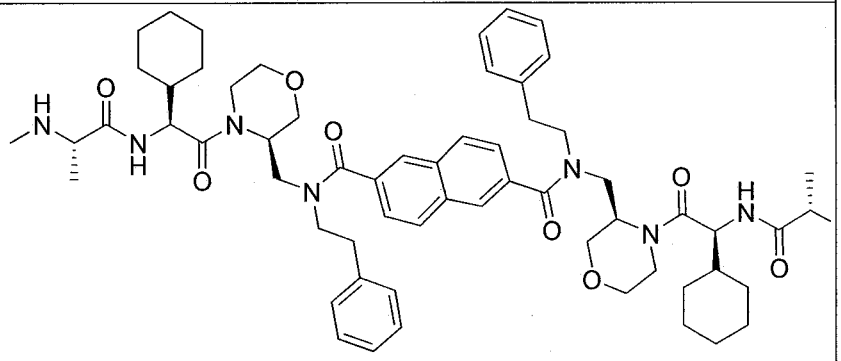
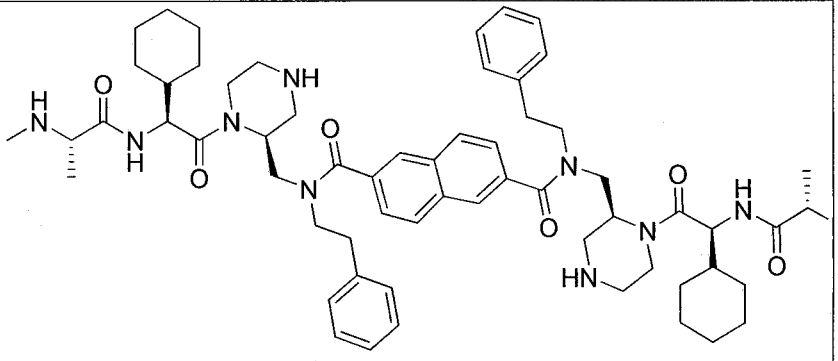
79	 ;
80	 ;
81	 ;

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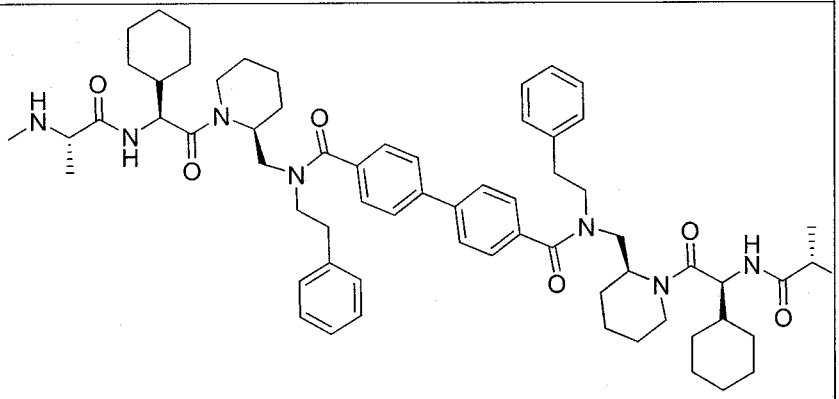
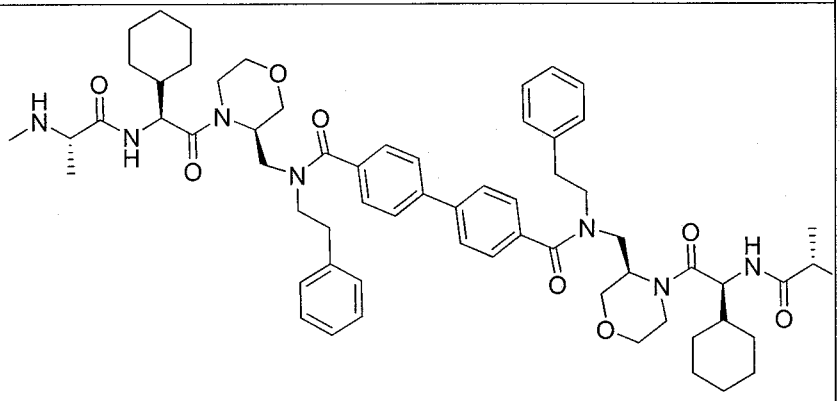
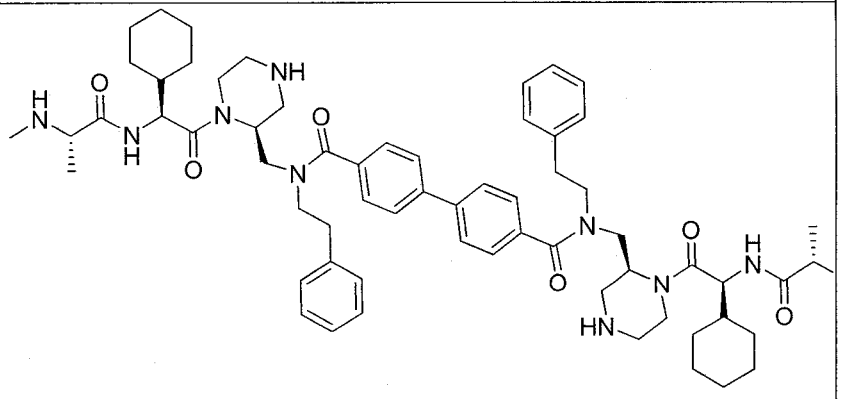
82	 ;
83	 ;
84	 ;

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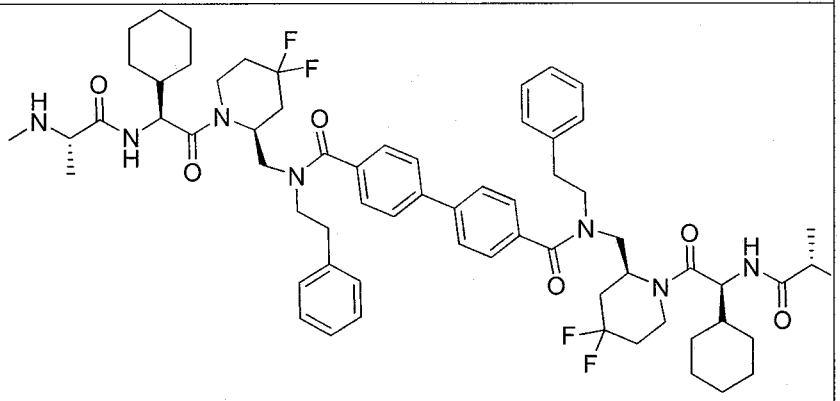
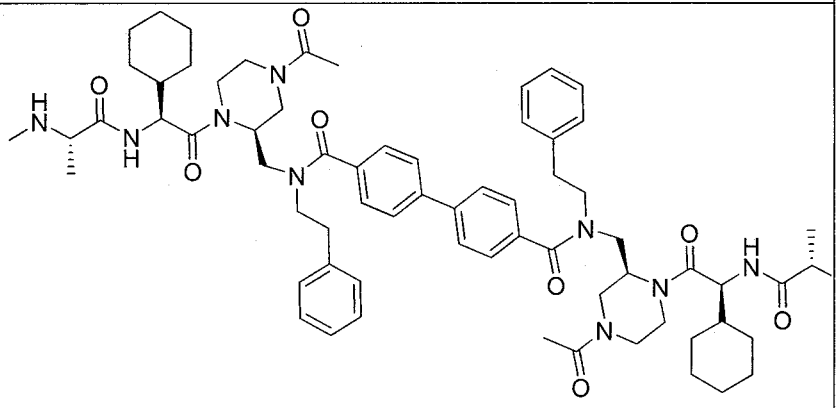
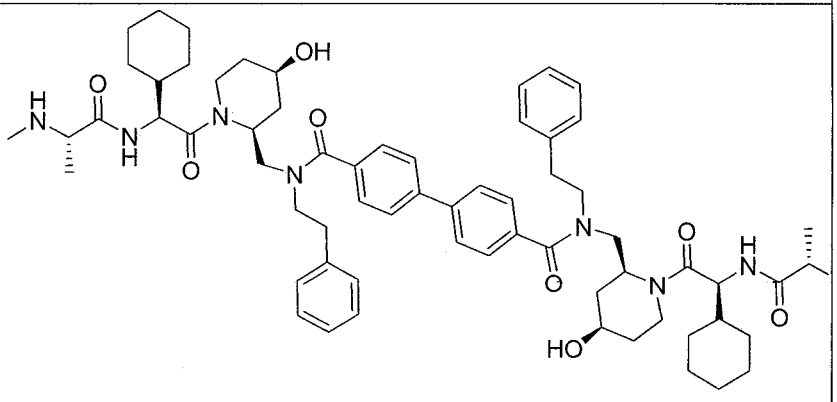
85	 ;
86	 ;
87	 ;

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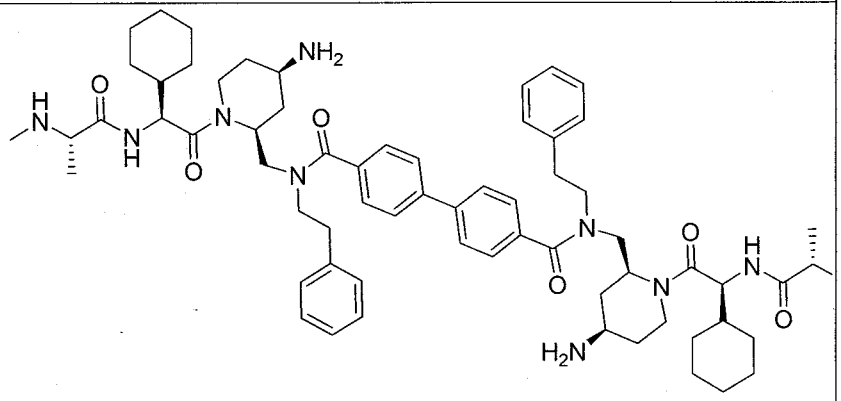
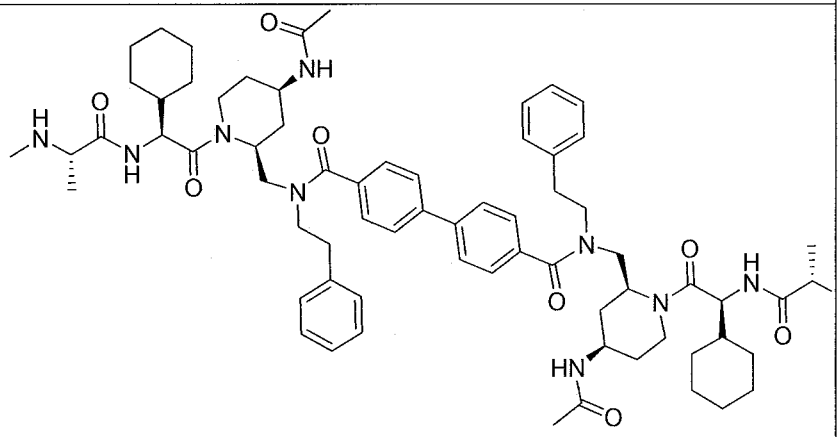
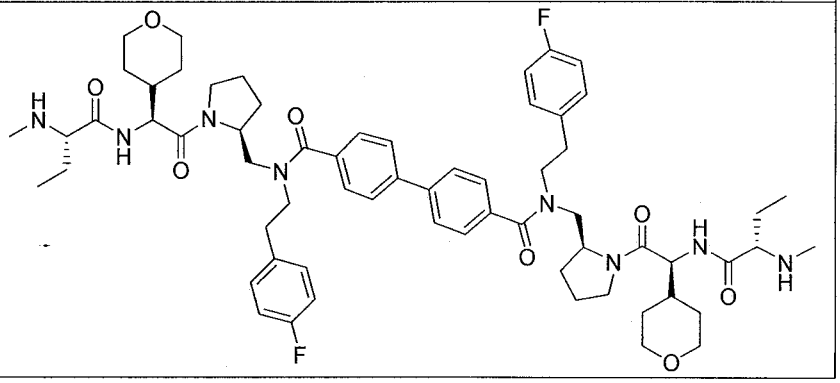
88	
89	
90	

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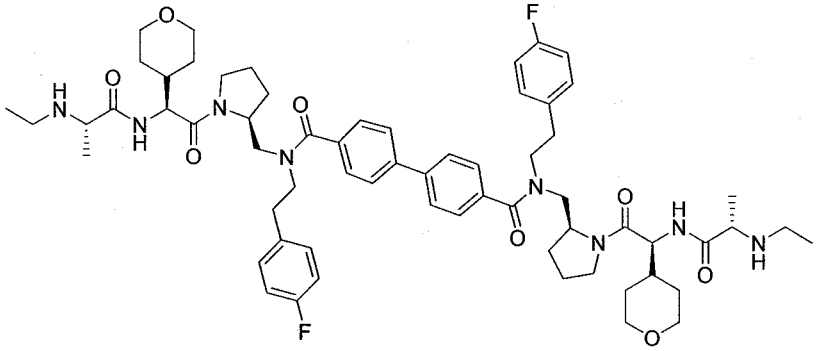
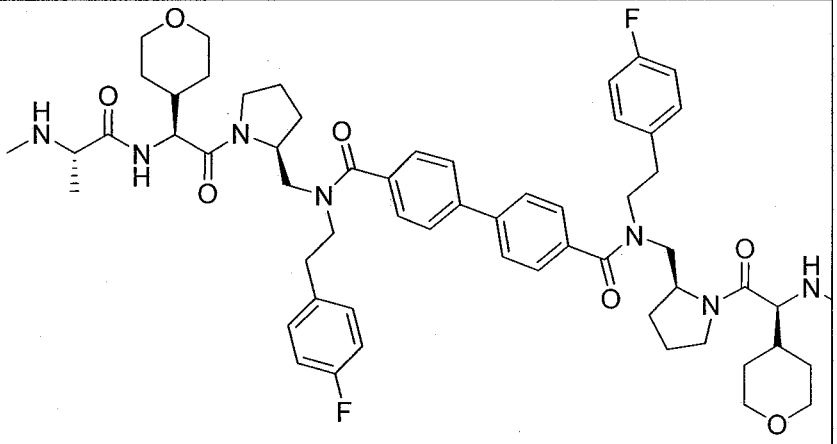
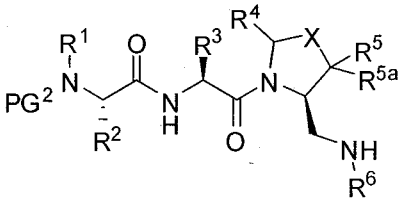
91	
92	

19. A compound having the formula:



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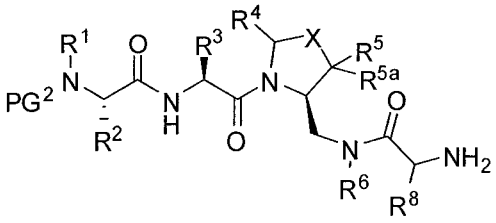

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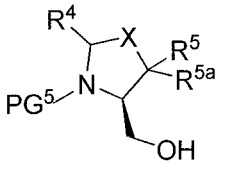

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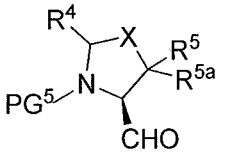

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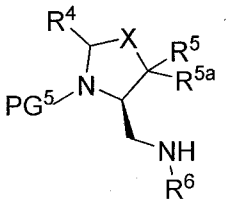

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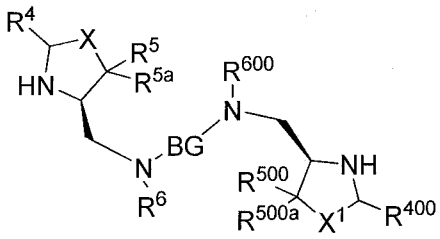

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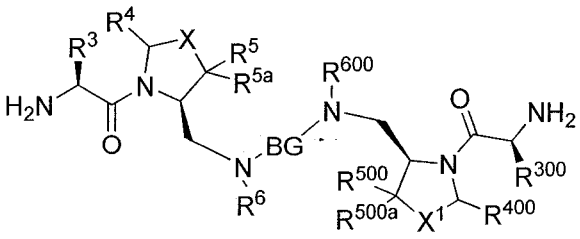

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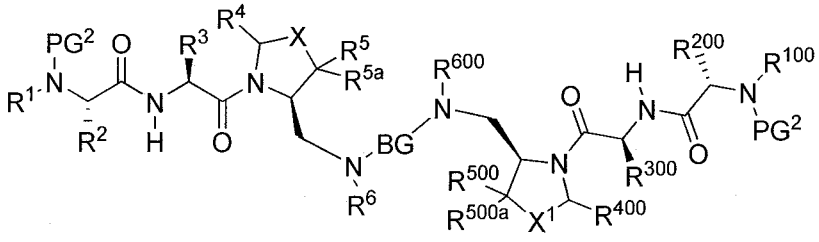


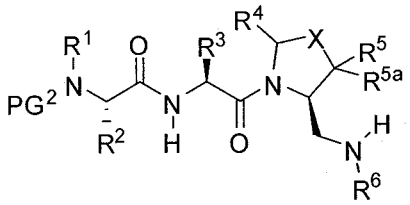
or

165

wherein R^1, R^2, R^3, R^4, R^{400}, R^5, R^{500}, R^{5a}, R^{500a}, R^6, R^{600}, R^8, BG, and X are as defined in claim 1, and PG^2 and PG^5 are each a suitable protecting group.

20. A process for producing a compound according to claim 1, the process comprising:

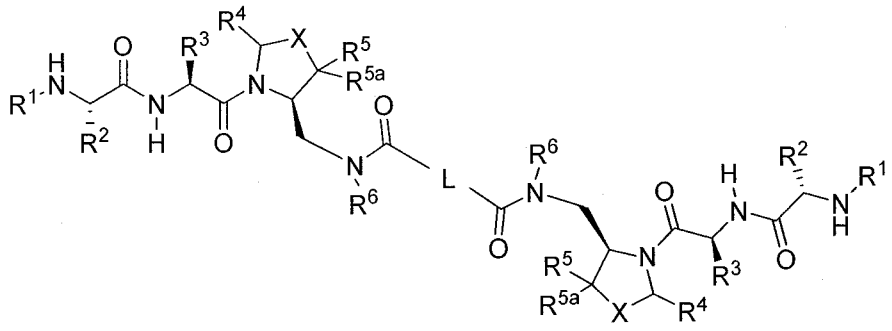
a) combining two compounds of Formula 6:



6

and LG-C(O)-L-C(O)-LG in a solvent with a base; and

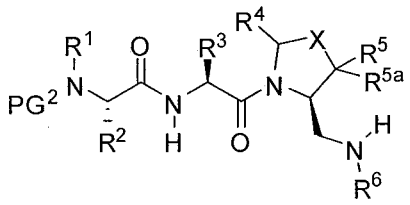
b) deprotecting PG^2 to provide a compound of Formula 8:



8

or

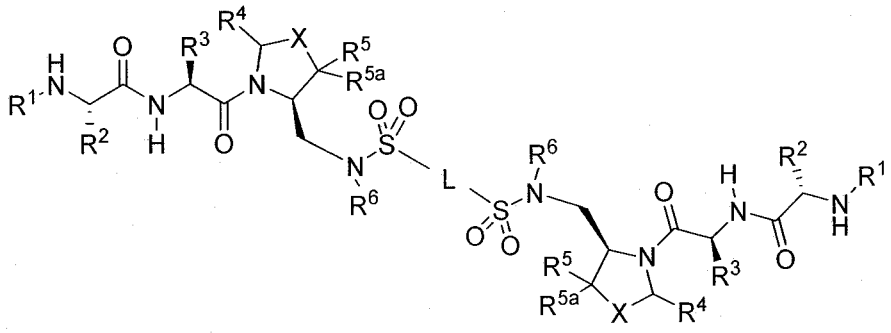
a) combining two compounds of Formula 6:



6

and LG-$S(O)_2$-L-$S(O)_2$-LG in a solvent with a base; and

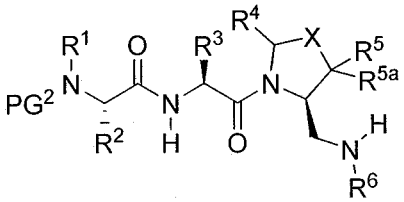
b) deprotecting PG^2 to provide a compound of Formula 9:



9

or

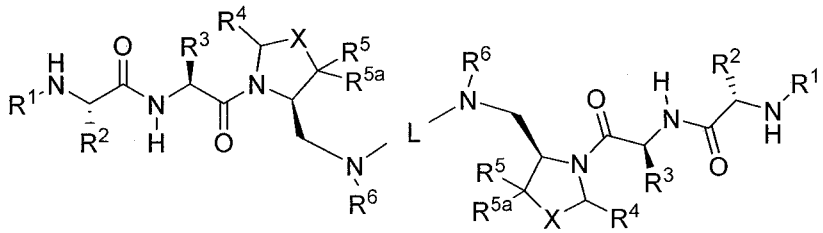
a) combining two compounds of Formula 6:



6

and LG-L-LG in a solvent with a base; and

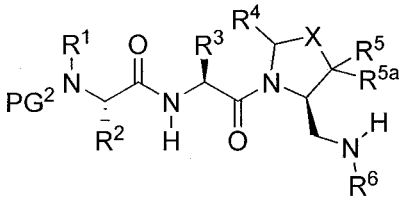
b) deprotecting PG^2 to provide a compound of Formula 10:



10

or

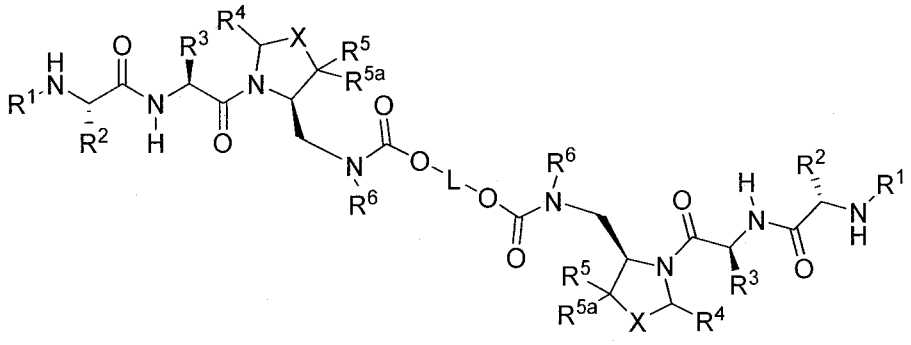
a) combining two compounds of Formula 6:



6

and LG-C(O)O-L-OC(O)-LG in a solvent with a base; and

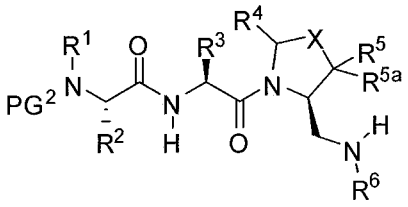
b) deprotecting PG^2 to provide a compound of Formula 11:



11

or

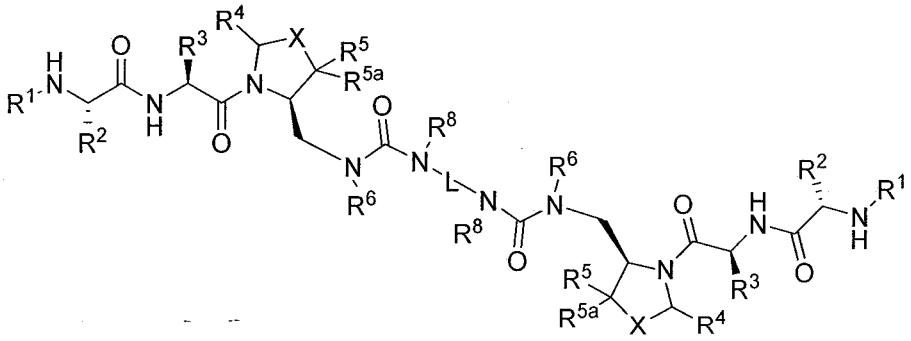
a) combining two compounds of Formula 6:



6

and LG-C(O)N(R^8)-L-(R^8)NC(O)-LG in a solvent with a base; and

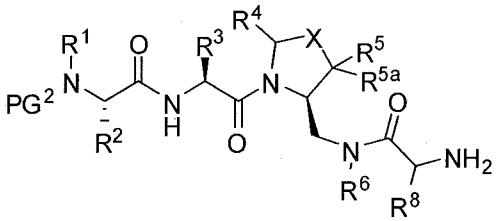
b) deprotecting PG^2 to provide a compound of Formula 12:



12

or

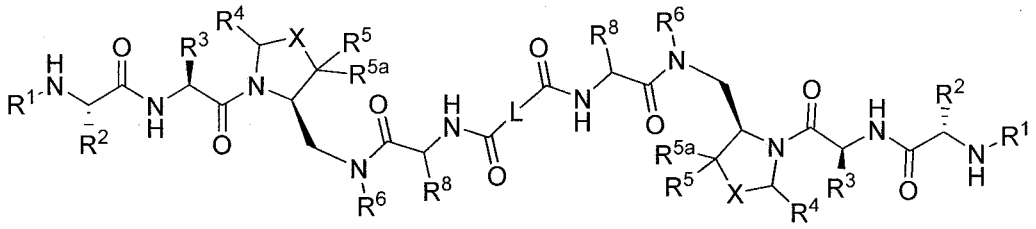
a) combining two compounds of Formula 7:



7

and LG-C(O)-L-C(O)-LG in a solvent with a base; and

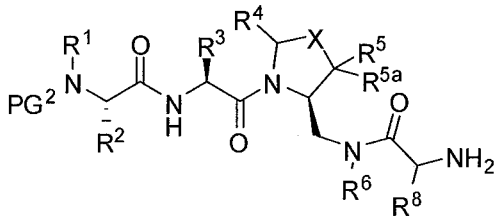
b) deprotecting PG^2 to provide a compound of Formula 13:



13

or

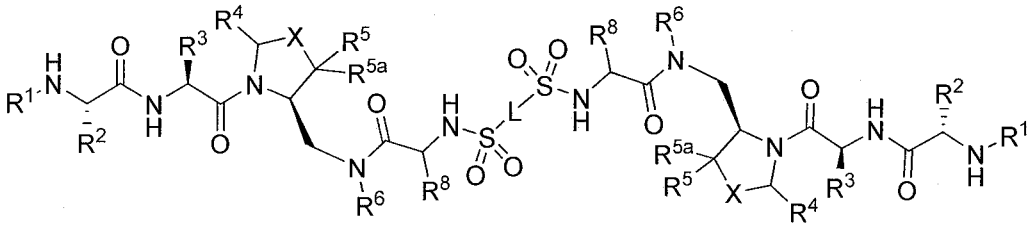
a) combining two compounds of Formula 7:



7

and LG-$S(O)_2$-L-$S(O)_2$-LG in a solvent with a base; and

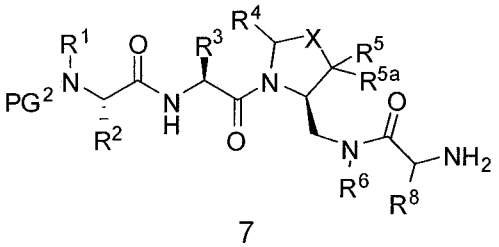
b) deprotecting PG^2 to provide a compound of Formula 14:



14

or

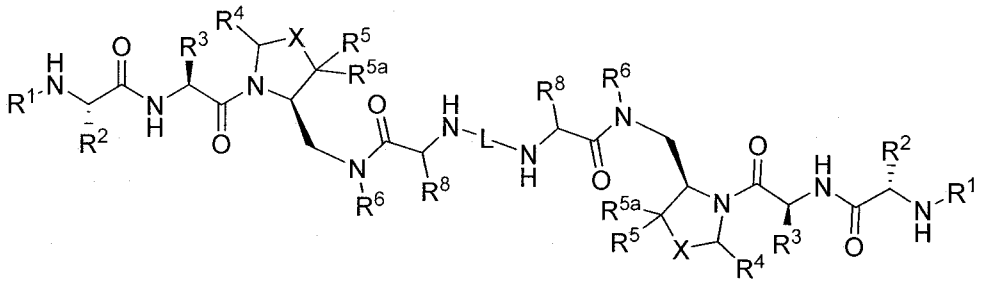
a) combining two compounds of Formula 7:



7

and LG-L-LG in a solvent with a base; and

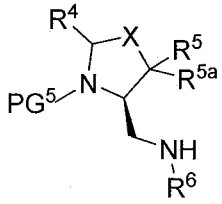
b) deprotecting PG^2 to provide a compound of Formula 15:



15

or

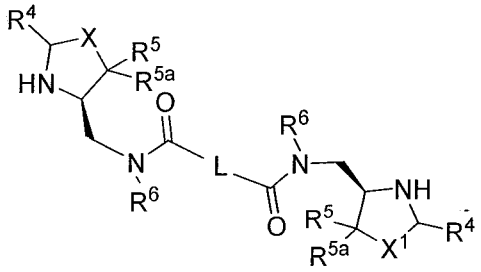
a) combining two compounds of Formula 18:



18

and LG-C(O)-L-C(O)-LG in a solvent with a base; and

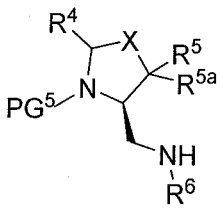
b) deprotecting PG^5 to provide a compound of Formula 20:



20

or

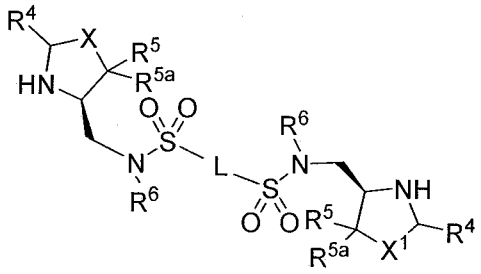
a) combining two compounds of Formula 18:



170

and LG-$S(O)_2$-L-$S(O)_2$-LG in a solvent with a base; and

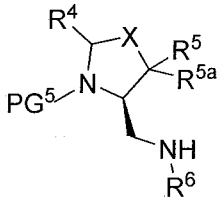
b) deprotecting PG^5 to provide a compound of Formula 21:



21

or

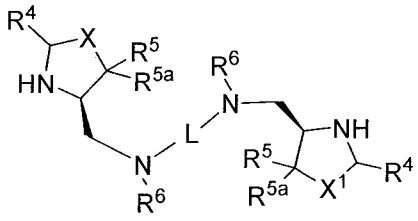
a) combining two compounds of Formula 18:



18

and LG-L-LG in a solvent with a base; and

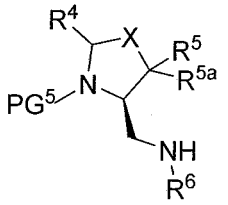
b) deprotecting PG^5 to provide a compound of Formula 22:



22

or

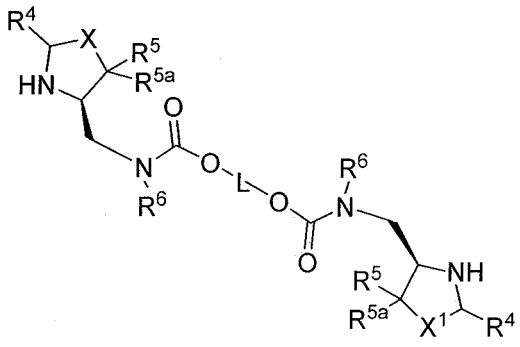
a) combining two compounds of Formula 18:



18

and LG-C(O)O-L-OC(O)-LG in a solvent with a base; and

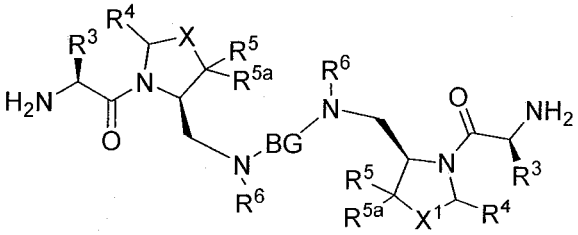
b) deprotecting PG^5 to provide a compound of Formula 23:



23

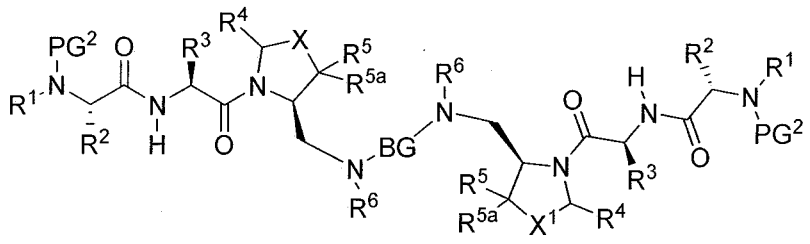
or

a) combining a compound of Formula 24:



24

and $PG^2(R^1)NCH(R^2)CO_2H$ with the appropriate amino acid coupling agent(s) in a solvent with a base; to provide a compound of Formula 25:



25

wherein PG^2 and PG^5 are suitable protecting groups.

21. A method for preparing a pharmaceutically acceptable salt of a compound of claim 1, comprising treating a compound of claim 1 with a pharmaceutically acceptable acid, so as to form a pharmaceutically acceptable salt of a compound of claim 1.

22. A pharmaceutical composition comprising a compound according to any of claims 1-18, and a pharmaceutically acceptable carrier, diluent or excipient.

23. The pharmaceutical composition of claim 22 further comprising one or more death receptor agonists.

24. The pharmaceutical composition of claim 23, wherein the pharmaceutical composition comprises TRAIL or an anti-TRAIL receptor antibody.

25. The pharmaceutical composition of any of claims 22-24 further comprising a therapeutic agent that increases the response of one or more death receptor agonists.

26. The pharmaceutical composition of any of claims 22-25 further comprising a chemotherapeutic agent.

27. Use of a pharmaceutical composition of any of claims 22-26 to treat a proliferative disease or a disease state characterized by insufficient apoptosis.

28. The use of claim 27, wherein the proliferative disease or disease state characterized by insufficient apoptosis is cancer or rheumatoid arthritis.

29. A method of preparing a pharmaceutical composition of any of claims 22-26, the method comprising combining a compound of any of claims 1-18 with a pharmaceutically acceptable carrier, diluent or excipient.

30. A method of treating a proliferative disease or a disease state characterized by insufficient apoptosis, the method comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition of any of claims 22-26, so as to treat the proliferative disease or disease state characterized by insufficient apoptosis.

31. The method of claim 30, wherein the proliferative disease or disease state characterized by insufficient apoptosis is cancer.

32. The method of claim 30 or 31, wherein the pharmaceutical composition is administered in combination, simultaneously or sequentially, with:
a) an estrogen receptor modulator,
b) an androgen receptor modulator,
c) retinoid receptor modulator,
d) a cytotoxic agent,
e) an antiproliferative agent,
f) a prenyl-protein transferase inhibitor,
g) an HMG-CoA reductase inhibitor,
h) an HIV protease inhibitor,
i) a reverse transcriptase inhibitor,
k) an angiogenesis inhibitor,
l) a PPAR-γ agonist,
m) a PPAR-δ agonist,
n) an inhibitor of inherent multidrug resistance,
o) an anti-emetic agent,
p) an agent useful in the treatment of anemia,
q) agents useful in the treatment of neutropenia,
r) an immunologic-enhancing drug,
s) a proteasome inhibitor,

t) an HDAC inhibitor,
u) an inhibitor of the chymotrypsin-like activity in the proteasome,
v) E3 ligase inhibitors,
w) a modulator of the immune system, or
z) radiation therapy,
so as to treat the cancer.

33. The method of claim 30 or 31, further comprising administering to the subject a therapeutically effective amount of a chemotherapeutic agent prior to, simultaneously with or after administration of the pharmaceutical composition.

34. The method of claim 30, wherein the proliferative disease or disease state characterized by insufficient apoptosis is rheumatoid arthritis.

35. The method of claim 30 or 34, wherein the pharmaceutical composition is administered in combination, simultaneously or sequentially, with a non-steroidal anti-inflammatory drug (NSAID), analgesic, corticosteroid, or antirheumatic.

36. The method of claim 30 or 34, wherein the pharmaceutical composition is administered in combination, simultaneously or sequentially, with a tumor necrosis factor inhibitor, a T-cell costimulatory blocking agent, a B cell depleting agent, an Interleukin-1 (IL-1) receptor antagonist, a p38 inhibitor, a JAK inhibitor, an anti-CD20 MAb, or an anti-IL/ILR agent.

37. The method of claim 30 or 34, wherein the pharmaceutical composition is administered in combination, simultaneously or sequentially, with tocilizumab, hydroxychloroquine, sulfasalazine, leflunomide, etanercept, adalimumab, and infliximab, rituximab, anakinra, intramuscular gold, azathioprine, cyclophosphamide, cyclosporine A, methotrexate, alemtuzumab, anti-RANKL MAb (denosumab), anti-Blys MAb, belimumab, certolizumab pegol, toclizumab, IL-4, IL-13, or IL-23.

38. The method of any of claims 30-37, further comprising administering to the subject a therapeutically effective amount of a death receptor agonist prior to, simultaneously with, or

after administration of the pharmaceutical composition, wherein the death receptor agonist is TRAIL or an anti-TRAIL receptor antibody.

39. A probe comprising a compound of any of claims 1-18 labeled with a detectable label or an affinity tag.

40. A method of identifying a compound that binds to an IAP BIR domain, the assay comprising:

a) contacting an IAP BIR domain with a probe of claim 39 to form a probe:BIR domain complex, the probe being displaceable by a test compound;

b) measuring a signal from the probe so as to establish a reference level;

c) incubating the probe:BIR domain complex with the test compound;

d) measuring the signal from the probe; and

e) comparing the signal from step d) with the reference level,

wherein a modulation of the signal indicates that the test compound binds to the BIR domain.

41. A method of detecting loss of function or suppression of IAPs in vivo, the method comprising:

a) administering to a subject a pharmaceutical composition of any of claims 22-26;

b) isolating a tissue sample from the subject; and

c) detecting a loss of function or suppression of IAPs from the sample.

42. A method of modulating IAP function, the method comprising contacting a cell with a compound according to any of claims 1-18 so as to prevent binding of a BIR binding protein to an IAP BIR domain, thereby modulating the IAP function.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2009/000893

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***C07K 5/062*** (2006.01), ***A61K 38/04*** (2006.01), ***A61P 35/00*** (2006.01), ***C07K 5/00*** (2006.01), ***C07K 5/06*** (2006.01), ***C12Q 1/00*** (2006.01), ***G01N 33/53*** (2006.01), ***C07K 14/81*** (2006.01), ***C12N 9/64*** (2006.01), ***C12N 9/99*** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: ***C07K 5/062*** (2006.01), ***A61K 38/04*** (2006.01), ***A61P 35/00*** (2006.01), ***C07K 5/00*** (2006.01), ***C07K 5/06*** (2006.01), ***C12Q 1/00*** (2006.01), ***G01N 33/53*** (2006.01), ***C07K 14/81*** (2006.01), ***C12N 9/64*** (2006.01), ***C12N 9/99*** (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

Canadian Patent Database, NCBI (searched "IAP" and "BIR"), STN (Registry and CAPlus databases; structure search of claimed compounds)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/131366 A1 (LAURENT, A. et al.) 22 November 2007 *entire document*	1-42
X	WO 2006/122408 A1 (LAURENT, A. et al.) 23 November 2006 *especially compounds 175-178 on pages 153-154*	1-42

[ ] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 August 2009 (28-08-2009)	17 September 2009 (17-09-2009)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
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Facsimile No.: 001-819-953-2476

Authorized officer

Neena Kushwaha 819- 934-7928

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2009/000893

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [X] Claim Nos. : 30-38 and 42

because they relate to subject matter not required to be searched by this Authority, namely :

Claims 30-38 and 42 are directed to a method for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search under Rule 39.1(iv). However, this Authority has carried out an examination based on the alleged effect or purpose/use of the product defined in said claims.

2. [ ] Claim Nos. :

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. [ ] Claim Nos. :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

The claims are directed to a plurality of inventive concepts as follows:

Group A - Claims 1-18 and 21-42 (fully) and claim 20 (partially) are featuring a compound of Formula 1.1A.
Group B - Claim 19 (fully) and claim 20 (partially) are featuring intermediate compounds of Formulae 6, 7, 16, 17, 18, 19, 24 and 25 (structures defined in claim 19).

(**Continued on extra sheet**)

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2009/000893

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO 2007/131366 A1	22-11-2007	AU 2007250443A1	22-11-2007
		CA 2652455A1	22-11-2007
		EP 2024362A1	18-02-2009
		KR 20090010242A	29-01-2009
		MX 2008014502A	27-11-2008
		NO 20084581A	12-12-2008
		US 2009192140A1	30-07-2009
WO 2006/122408 A1	23-11-2006	CA 2607940A1	23-11-2006
		EP 1883627A1	06-02-2008
		JP 2008545629T	18-12-2008
		US 2006264379A1	23-11-2006
		WO 2006122408A9	25-01-2007

INTERNATIONAL SEARCH REPORT

International application No.
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Continued from **Box No. III**:

The claims must be limited to one inventive concept as set out in Rule 13 of the PCT.

An *a posteriori* analysis has concluded that the prior art documents D1 (WO2007/131366) and D2 (WO2006/122408) independently disclose essentially the same compounds as those of Formula 1.1A, as defined in instant claim 1, with the exception of the substituents represented by R3 and R300. In instant claim 1, substituents R3 and R300 represent, inter alia, cycloalkyl groups, whereas in each of D1 and D2, R3 and R300 represent C1-C6 alkyl groups. Since the present application does not disclose any particular special advantage or surprising effect afforded by the presence of a cycloalkyl group (versus an alkyl group) at positions R3 and R300 in the compound of Formula 1.1A, substitution of a cycloalkyl group for an alkyl group at said positions cannot be considered an inventive step. Therefore the compound of Formula 1.1A as defined in instant claim 1, and its intermediates as defined in instant claim 19, are not considered to be linked by a single inventive concept.