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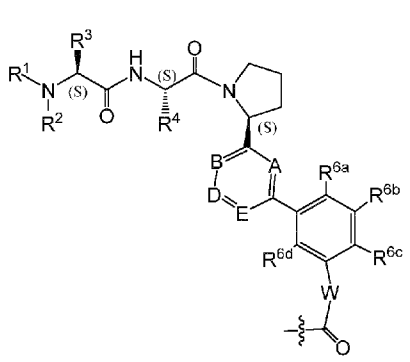
(54) Title: DIMERIC IAP INHIBITORS



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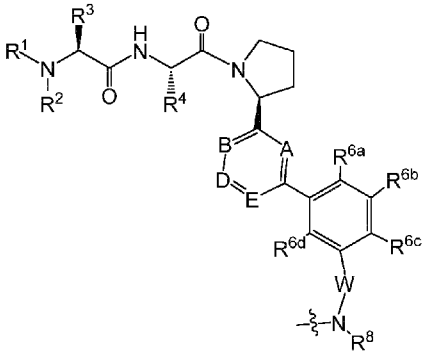

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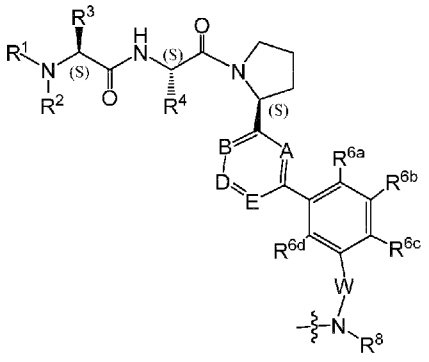

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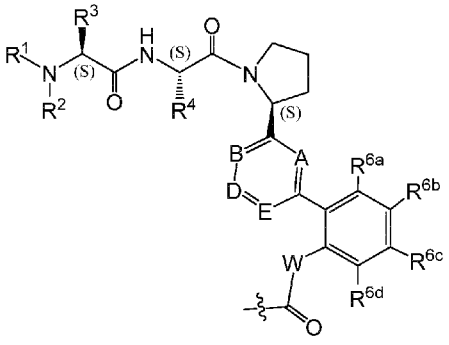

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(57) Abstract: The present invention provides compounds of formula M-L-M' (where M and M' are each independently a monomeric moiety of Formula (I), (II), (III) or (IV) and L is a linker). The dimeric compounds have been found to be effective in promoting apoptosis in rapidly dividing cells.

DIMERIC IAP INHIBITORS

FIELD OF THE INVENTION

The present invention relates to dimeric compounds that act as inhibitors of the Inhibitor of Apoptosis Proteins (IAPs), as well as pharmaceutical compositions thereof, methods of their use, and methods for their manufacture.

BACKGROUND

Programmed cell death plays a critical role in regulating cell number and in eliminating stressed or damaged cells from normal tissues. Indeed, the network of apoptotic signaling mechanisms inherent in most cell types provides a major barrier to the development and progression of human cancer. Since most commonly used radiation and chemo-therapies rely on activation of apoptotic pathways to kill cancer cells, tumor cells which are capable of evading programmed cell death often become resistant to treatment.

Apoptosis signaling networks are classified as extrinsic when mediated by death receptor-ligand interactions or intrinsic when mediated by cellular stress and mitochondrial permeabilization. Both pathways ultimately converge on individual caspases, cysteine-aspartic proteases. Once activated, caspases cleave a number of cell death-related substrates, effecting destruction of the cell.

Tumor cells have devised a number of strategies to circumvent apoptosis. One recently reported molecular mechanism involves the overexpression of members of the IAP (Inhibitor of Apoptosis Protein) family. IAPs sabotage apoptosis by directly interacting with and neutralizing caspases. The prototype IAPs, XIAP and cIAP have three functional domains referred to as BIR 1, 2 & 3 domains. The BIR3 domain interacts directly with caspase 9 and inhibits its ability to bind and cleave its natural substrate, procaspase 3.

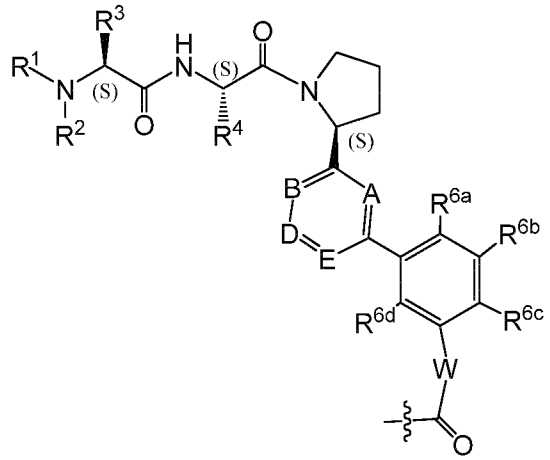
A proapoptotic mitochondrial protein, Smac (also known as DIABLO), can neutralize XIAP and/or cIAP by binding to a peptide binding pocket (Smac binding site) on the surface of BIR3 thereby precluding interaction with caspase 9. Binding of peptides derived from Smac has also been reported to trigger autocatalytic polyubiquitination and subsequent proteosome-mediated degradation of cIAP1. The present invention relates to therapeutic molecules that bind to the Smac binding pocket thereby promoting apoptosis in rapidly dividing cells. Such therapeutic molecules are useful for the treatment of proliferative diseases, including cancer.

SUMMARY

The present invention provides compounds of formula M-L-M' that have been found to be effective in promoting apoptosis in rapidly dividing cells. Advantageously, the compounds of the present invention are selectively more toxic to abnormal cells *e.g.* cells that are proliferating more rapidly than normal cells, particularly in human tumor or cancer cells. Accordingly, the compounds of the present invention are useful in the treatment of diseases and conditions characterized by cell proliferation.

In each of the embodiments below, M and M' are preferably both the same.

In one embodiment of the present invention, a compound of Formula M-L-M', wherein M and M' are each independently a monomeric moiety of Formula (I), (II), (III), or (IV)



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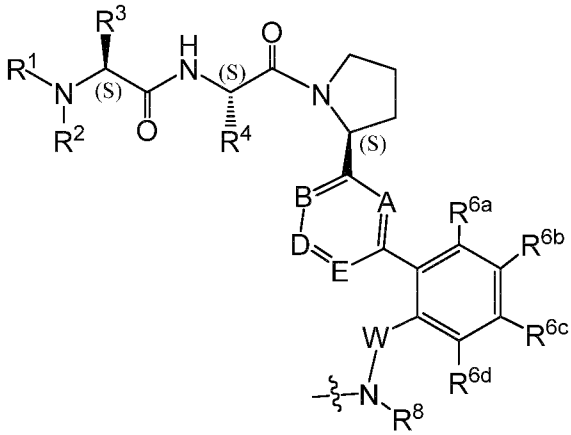

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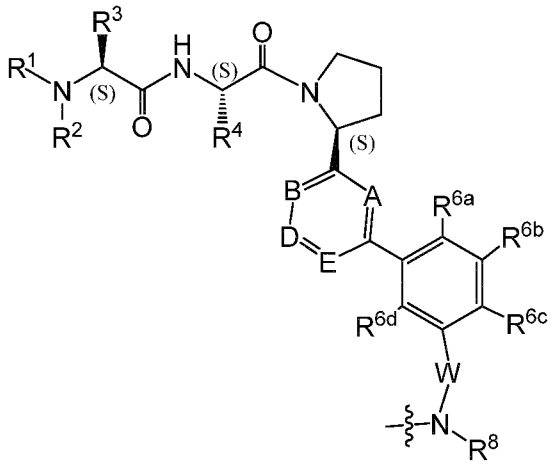

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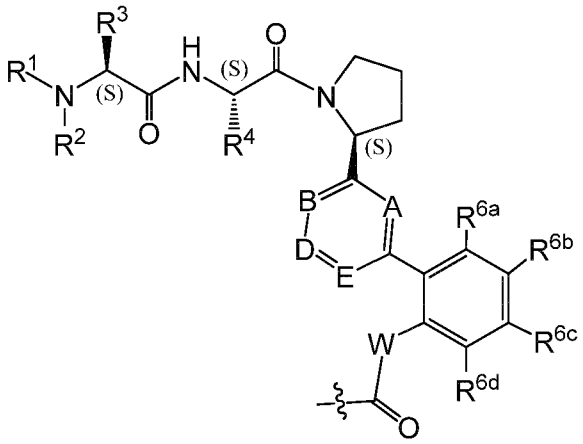


(IV)

wherein,

R^1 is $(C_1\text{-}C_4)$alkyl, deuterated methyl, or hydrogen;

R^2 is $(C_1\text{-}C_4)$alkyl or hydrogen;

R^3 is $(C_1$-$C_4)$alkyl or hydrogen, or

R^1 or R^2 along with the nitrogen to which R^1 or R^2 is attached is taken together with R^3 to form an aziridinyl, azetidinyl, pyrrolidinyl, or piperidinyl;

R^4 is

(i) $(C_1$-$C_{10})$alkyl, $(C_2$-$C_{10})$alkenyl, $(C_2$-$C_{10})$alkynyl, $(C_3$-$C_6)$cycloalkyl, phenyl, a 3- to 7-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, or a 5- to 9-membered heteroaryl containing 1 to 3 heteroatoms each independently selected form O, N or S, or

(ii) R^{4a}-$(C_1$-$C_6)$alkylene, where R^{4a} is $(C_3$-$C_6)$cycloalkyl, phenyl, a 3- to 7-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, or a 5- to 9-membered heteroaryl containing 1 to 3 heteroatoms each independently selected form O, N or S,

where said R^4 and said R^{4a} are optionally substituted with 1 to 3 substituents selected from halo, hydroxyl, -SH, $-CO_2H$, $(C_1$-$C_4)$alkyl, halo-substituted$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkyl-S-, $-SO_2$, $-NH_2$ or $-NO_2$, and where 1 of the ring members of said cycloalkyl and said heterocycle moieties are optionally replaced with oxo or thione;

A, B, and D are CR^5, and E is N,

A, B and E are CR^5 and D is N,

A, D and E are CR^5, and B is N,

B, D and E are CR^5, and A is N,

A and B are both N, and D and E are both CR^5,

A and E are both N, and B and D are both CR^5, or

B and E are both N, and A and D are both CR^5, where R^5 are each independently selected from H, F, $-CH_3$ or $-CF_3$;

R^{6a}, R^{6b}, R^{6c} and R^{6d} are each independently H, $(C_1$-$C_3)$alkyl, Cl, or CN, where at least one of R^{6a}, R^{6b}, R^{6c} and R^{6d} is H or $(C_1$-$C_3)$alkyl;

W is a bond or $(C_1$-$C_4)$alkylene;

when M and M' are a monomeric moiety of Formula (I) or (IV), then L is $-NR^8$-X^1-NR^8-, and

when M and M' are a monomeric moiety of Formula (II) or (III), then L is –C(O)-X^1-C(O)-, where

R^8 is each independently H, $(C_1$-$C_4)$alkyl, or halo-substituted$(C_1$-$C_4)$alkyl, and

X^1 is

(i) a bond,

(ii) $(C_1$-$C_{10})$alkylene, $(C_2$-$C_{10})$alkenylene, $(C_2$-$C_{10})$alkynylene, $((C_1$-$C_{10})$alkylene)-$(O(C_1$-$C_6)$alkylene$)_q$-, or $(C_1$-$C_{10})$alkylene-$NH(C_1$-$C_6)$alkylene, where q is 0, 1 or 2,

(iii) phenylene, napthylene, fluorenylene, 9H-fluoren-9-onylene, 9,10-dihydroanthracenylene, anthracen-9,10-dionylene, a partially or fully saturated (C_3-C_8)cycloalkylene, a 5- to 7-membered heterocyclene containing 1 to 3 heteroatoms each independently selected from O, S, or N, or a 5- to 10-membered heteroarylene containing 1 to 3 heteroatoms each independently selected from O, S or N, where said phenylene is optionally fused to a (C_5-C_6)cycloalkyl,

(iv) (phenylene)-G-(phenylene), where G is a bond, O, S, -NH-, -N=N-, -S=S-, -SO_2-, (C_1-C_6)alkylene, (C_2-C_6)alkenylene, (C_2-C_{10})alkynylene, (C_3-C_6)cycloalkylene, a 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms each independently selected from O, S or N, or a 5- to 6-membered partially or fully saturated heterocyclene containing 1 to 3 heteroatoms each independently selected from O, S or N, and where said phenylene is optionally fused to a phenyl,

(v) ((C_1-C_6)alkylene)$_r$-Z^1-((C_1-C_6)alkylene)$_s$, or ((C_1-C_6)alkenylene)$_r$-Z^1-((C_1-C_6)alkenylene)$_s$, where r and s are each independently 0, 1, or 2; and Z^1 is –O-, –N=N-, (C_3-C_6)cycloalkylene, phenylene, bisphenylene, a 5- to 6-membered partially or fully saturated heterocyclene containing 1 to 3 heteroatoms each independently selected from O, S or N, or a 5- to-6-membered heteroarylene containing 1 to 3 heteroatoms each independently selected from O, S or N, where said heteroarylene and said heterocyclene are optionally fused to a phenyl, phenylene, a 5- to 6-membered partially or fully saturated heterocyclene containing 1 to 3 heteroatoms each independently selected from O, S or N, or a 5- to-6-membered heteroarylene containing 1 to 3 heteroatoms each independently selected from O, S or N, or

(vi) (C_1-C_{20})alkylene or –NH-((C_1-C_{20})alkylene)-NH-, where said alkylene contains 1 to 6 oxygen atoms interspersed within the alkylene chain and optionally 1 to 2 phenylene groups interpersed within the alkylene chain;

or when L is -NR^8-X^1-NR^8-, then X^1 is optionally taken together with one or both R^8 groups along with the nitrogen to which the R^8 group is attached to form a 4- to 14-membered heterocyclene, (4- to 6-membered heterocyclyl)-(C_1-C_6)alkylene-(4- to 6-membered heterocyclyl), or *bis*-(4- to 6-membered heterocyclene, where said heterocyclene and said heterocyclyl moieties optionally contain 1 to 3 additional heteroatoms selected from O, S and N, and X^1 and R^8 are optionally substituted with

oxo or 1 to 3 substituents each independently selected from hydroxyl or $(C_1$-$C_4)$alkyl;

where said group (ii) moieties of X^1 are each independently substituted with one or more fluoro atoms, or 1 to 2 substituents each independently selected from halo, oxo, amino, phenyl, naphthyl, $(C_3$-$C_6)$ cycloalkyl, or 5- to 6-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, where said phenyl, said cycloalkyl, and said heterocycle are optionally substituted with 1 to 3 substituents each independently selected from halo, $(C_1$-$C_4)$alkyl, or trifluoromethyl,

where said group (iii) and (iv) moieties of X^1 are optionally substituted with 1 to 4 substitutents each independently selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo, amino, -OH, benzyl, or a fused 5- to 6-membered cycloalkyl, where said $(C_1$-$C_4)$alkyl, said $(C_1$-$C_4)$alkoxy, and said fused cycloalkyl are optionally substituted with 1 to 3 substituents selected from halo, or $(C_1$-$C_4)$alkyl,

where said group (v) moieties of X^1 are optionally substituted with 1 to 3 substituents each independently selected from halo, hydroxy, oxo, amino, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, or phenyl; or a pharmaceutically acceptable salt thereof.

In one particular embodiment, R^1 is $(C_1$-$C_4)$alkyl or deuterated methyl; R^2 is hydrogen; R^3 is $(C_1$-$C_4)$alkyl; R^4 is

(i) $(C_1$-$C_{10})$alkyl, $(C_3$-$C_6)$cycloalkyl, phenyl, or a 3- to 7-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, or

(ii) R^{4a}-$(C_1$-$C_6)$alkylene, where R^{4a} is $(C_3$-$C_6)$cycloalkyl, or a 3- to 7-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, where said R^4 and said R^{4a} are optionally substituted with 1 to 3 substituents each independently selected from halo or $(C_1$-$C_4)$alkoxy; and

R^{6a}, R^{6b}, R^{6c} and R^{6d} are each independently H, $(C_1$-$C_3)$alkyl or F, where at least one of R^{6a}, R^{6b}, R^{6c} and R^{6d} is H or $(C_1$-$C_3)$alkyl; or a pharmaceutically acceptable salt thereof.

Preferably, R^1 is methyl or deuterated methyl; R^2 is H; R^3 is methyl; R^4 is isopropyl or cyclohexyl; R^{6a}, R^{6b}, and R^{6d} are each H; and R^{6c} is F.

In another particular embodiment, A, B, and D are CR^5, and E is N, where each R^5 is independently selected from H or F; or a pharmaceutically acceptable salt thereof.

In yet another particular embodiment, A, B and E are CR^5 and D is N, where each R^5 is independently selected from H or F; or a pharmaceutically acceptable salt thereof.

In any of the embodiment above, W is preferably a bond or $–CH_2$-.

In one particular embodiment, M and M' are a monomeric moiety of Formula (I) and L is $-NR^8$-X^1-NR^8-; or a pharmaceutically acceptable salt thereof.

Preferably, X^1 is

(i) a bond,

(ii) $(C_1\text{-}C_{10})$alkylene, or $((C_1\text{-}C_{10})\text{alkylene})\text{-}(O(C_1\text{-}C_6)\text{alkylene})_q\text{-}$, where q is 0, 1 or 2,

(iii) phenylene, napthylene, or a fully saturated $(C_3\text{-}C_8)$cycloalkylene,

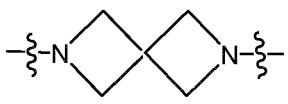
(iv) (phenylene)-G-(phenylene), where G is a bond, O, $-SO_2-$, $(C_1\text{-}C_6)$alkylene, or $(C_2\text{-}C_{10})$alkynylene

(v) $((C_1\text{-}C_6)\text{alkylene})_r\text{-}Z^1\text{-}((C_1\text{-}C_6)\text{alkylene})_s$, where r and s are each independently 0, 1, or 2; and Z^1 is –O-, or

(vi) $(C_1\text{-}C_{20})$alkylene, where said alkylene contains 1 to 6 oxygen atoms interspersed within the alkylene chain;

or when L is $-NR^8\text{-}X^1\text{-}NR^8-$, then X^1 is optionally taken together with one or both R^8 groups along with the nitrogen to which the R^8 group is attached to form a 4- to 14-membered heterocyclene; or a pharmaceutically acceptable salt thereof.

Preferably, L is –NH-NH-, $–NH\text{-}(CH_2)_3\text{-}(O\text{-}CH_2CH_2)_4\text{-}O\text{-}(CH_2)_3\text{-}NH-$, $-NH\text{-}(CH_2)_3\text{-}(O\text{-}CH_2CH_2)_2\text{-}O\text{-}(CH_2)_3\text{-}NH-$, $–NH\text{-}(CH_2)_3\text{-}O\text{-}CH_2CH_2\text{-}O\text{-}(CH_2)_3\text{-}NH-$, $–NH\text{-}(CH_2)_3\text{-}O\text{-}(CH_2)_3\text{-}NH-$, $–NH\text{-}(CH_2)_2\text{-}O\text{-}CH_2CH_2\text{-}O\text{-}(CH_2)_2\text{-}NH-$, $–NH\text{-}(CH_2)_2\text{-}(O\text{-}CH_2CH_2)_2\text{-}O\text{-}(CH_2)_2\text{-}NH-$, $-NH\text{-}((C_1\text{-}C_{12})\text{alkylene})\text{-}NH-$, $-NH\text{-}CH_2\text{-}(\text{phenylene})\text{-}CH_2\text{-}NH-$, $-NH\text{-}CH_2\text{-}(\text{phenylene})\text{-}(\text{phenylene})\text{-}CH_2\text{-}NH-$, -NH-(cyclohexylene)-NH-,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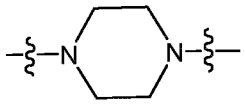

;

or a pharmaceutically acceptable salt thereof.

In another particular embodiment, M and M' are a monomeric moiety of Formula (II) and L is $–C(O)\text{-}X^1\text{-}C(O)-$; or pharmaceutically acceptable salt thereof.

Preferably, X^1 is

(i) a bond,

(ii) $(C_1\text{-}C_{10})$alkylene, or $((C_1\text{-}C_{10})\text{alkylene})\text{-}(O(C_1\text{-}C_6)\text{alkylene})_q\text{-}$, where q is 0, 1 or 2,

(iii) phenylene, napthylene, or a fully saturated $(C_3\text{-}C_8)$cycloalkylene,

(iv) (phenylene)-G-(phenylene), where G is a bond, O, $-SO_2-$, $(C_1\text{-}C_6)$alkylene, or $(C_2\text{-}C_{10})$alkynylene

(v) $((C_1\text{-}C_6)\text{alkylene})_r\text{-}Z^1\text{-}((C_1\text{-}C_6)\text{alkylene})_s$, where r and s are each independently 0, 1, or 2; and Z^1 is –O-, or

(vi) $(C_1\text{-}C_{20})$alkylene, where said alkylene contains 1 to 6 oxygen atoms interspersed within the alkylene chain;

or when L is -NR^8-X^1-NR^8-, then X^1 is optionally taken together with one or both R^8 groups along with the nitrogen to which the R^8 group is attached to form a 4- to 14-membered heterocyclene; or a pharmaceutically acceptable salt thereof.

Preferably, X' is-phenylene-G-phenylene-, where G is a bond-; or a pharmaceutically acceptable salt thereof.

Prepresentative compounds include: 5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-N-(1-(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorophenyl)-1-oxo-6,9,12,15,18-pentaoxa-2-azahenicosan-21-yl)-2-fluorobenzamide;

(S,S,S)-N,N'-(ethane-1,2-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(1,4-phenylenebis(methylene))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(biphenyl-4,4'-diylbis(methylene))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(decane-1,10-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(dodecane-1,12-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(hexane-1,6-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(octane-1,8-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(butane-1,4-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(3,3'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(propane-3,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)-acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-((1S,4S)-cyclohexane-1,4-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(3,3'-(ethane-1,2-diylbis(oxy))bis(propane-3,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(2S,2'S)-N,N'-((1S,1'S)-2,2'-((2S,2'S)-2,2'-(5,5'-(3,3'-(2,6-diazaspiro[3.3]heptane-2,6-diylbis(oxomethylene))bis(4-fluoro-3,1-phenylene))-bis(pyridine-5,3-diyl))bis(pyrrolidine-2,1-diyl))bis(1-cyclohexyl-2-oxoethane-2,1-diyl))bis(2-(methylamino)propanamide);

(2S,2'S)-N,N'-((1S,1'S)-2,2'-((2S,2'S)-2,2'-(5,5'-(3,3'-(hydrazine-1,2-diylbis(oxomethylene))bis(4-fluoro-3,1-phenylene))-bis(pyridine-5,3-diyl))bis(pyrrolidine-2,1-diyl))bis(1-cyclohexyl-2-oxoethane-2,1-diyl))bis(2-(methylamino)propanamide); and

N4,N4'-bis(2-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-5-fluorobenzyl)biphenyl-4,4'-dicarboxamide; or a pharmaceutically acceptable salt thereof.

A preferred compound is 5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-N-(1-(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorophenyl)-1-oxo-6,9,12,15,18-pentaoxa-2-azahenicosan-21-yl)-2-fluorobenzamide; or a pharmaceutically acceptable salt thereof.

Another preferred compound is (S,S,S)-N,N'-(ethane-1,2-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide); or a pharmaceutically acceptable salt thereof.

Yet another preferred compound is (S,S,S)-N,N'-(2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)-pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide); or a pharmaceutically acceptable salt thereof.

Another preferred compound is (S,S,S)-N,N'-(butane-1,4-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide); or a pharmaceutically acceptable salt thereof.

Yet another preferred compound is (S,S,S)-N,N'-(3,3'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(propane-3,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide); or a pharmaceutically acceptable salt thereof.

Another preferred compound is (S,S,S)-N,N'-(3,3'-(ethane-1,2-diylbis(oxy))-bis(propane-3,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide); or a pharmaceutically acceptable salt thereof.

Yet another preferred compound is (2S,2'S)-N,N'-((1S,1'S)-2,2'-((2S,2'S)-2,2'-(5,5'-(3,3'-(hydrazine-1,2-diylbis(oxomethylene))bis(4-fluoro-3,1-phenylene))-bis(pyridine-5,3-diyl))bis(pyrrolidine-2,1-diyl))bis(1-cyclohexyl-2-oxoethane-2,1-diyl))bis(2-(methylamino)propanamide); or a pharmaceutically acceptable salt thereof.

In another aspect of the present invention, a pharmaceutical composition is provided which comprises any one of the compound described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient. The pharmaceutical composition may further comprise at least one additional pharmaceutical agent (described herein below). In particular, the at least one additional pharmaceutical agent is paclitaxel, a PI3K inhibitor, a topoisomerase inhibitor, a Trail antibody, recombinant Trail, or a Trail receptor agonist. More particularly, the at least one additional pharmaceutical agent is paclitaxel.

In yet another aspect of the present invention, a method for treating a disease, disorder, or condition associated with the over expression of an IAP in a subject is provided which comprises the step of administering to a subject in need to such treatment a therapeutically effective amount of any one of the compounds described above, or a pharmaceutically acceptable salt thereof.

In yet another aspect, a method for treating a disease, disorder, or condition mediated by IAPs is provided which comprises the step of administering to a subject in need of such treatment a therapeutically effective amount of any one of the compounds described above, or a pharmaceutically acceptable salt thereof.

In yet another aspect, the use of any one of the compounds described above is provided for inducing or enhancing apoptosis in a tumor or cancer cell.

Any one of the compounds described above may be used in therapy.

Also described is the use of any one of the compounds described above in the manufacture of a medicament for the treatment of a disease, disorder or condition mediated by IAPs.

In another aspect, the use of any one of the compounds described above is provided for the treatment of a disease, disorder or condition associated with the overexpression of one or more IAPs.

In yet another aspect, a method for treating a disease, disorder, or condition mediated by IAPs is provided which comprises the step(s) of administering to a patient in need of such treatment

(i) a compound as defined above, or a pharmaceutically acceptable salt thereof; and

(ii) at least one additional pharmaceutical agent (described herein below).

In particular, the additional pharmaceutical agent is paclitaxel, a PI3K inhibitor, a topoisomerase inhibitor, a Trail antibody, recombinant Trail, or a Trail receptor agonist. More particularly, the additional pharmaceutical agent is paclitaxel.

The compound, or pharmaceutical acceptable salt thereof, and the additional pharmaceutical agent may be administered simultaneously or sequentially.

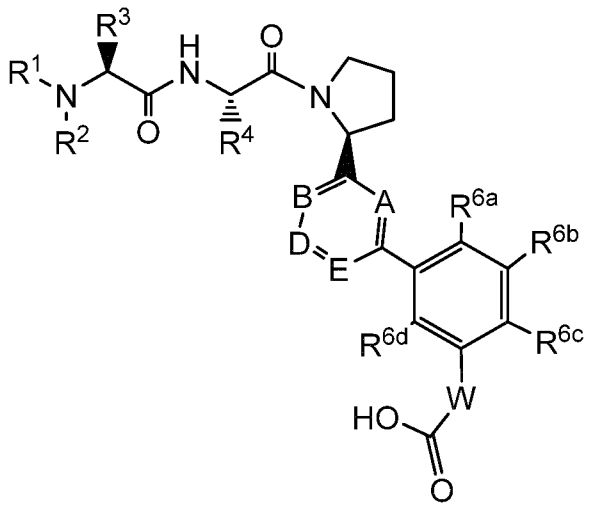
In yet another aspect, a method for treating a disease, disorder, or condition mediated by IAP is provided which comprises the step of administering to a patient in need of such treatment a pharmaceutical composition comprising any one of the compounds described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutical acceptable carrier. The method composition may further comprise at least one additional pharmaceutical agent (described herein below). In particular, the additional pharmaceutical agent is paclitaxel, a PI3K inhibitor, a topoisomerase inhibitor, a Trail antibody, recombinant Trail, or a Trail receptor agonist. More particularly, the additional pharmaceutical agent is paclitaxel.

In yet another aspect, a method for treating a disease, disorder, or condition mediated by IAPs is provided which comprises the step(s) of administering to a patient in need of such treatment

(i) a first composition comprising any one of the compounds described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutical carrier; and

(ii) a second composition comprising at least one additional pharmaceutical agent and a pharmaceutical carrier. In particular, the additional pharmaceutical agent is paclitaxel, a PI3K inhibitor, a topoisomerase inhibitor, a Trail antibody, recombinant Trail, or a Trail receptor agonist. More particularly, the additional pharmaceutical agent is a paclitaxel. The first composition and the second composition may be administered simultaneously or sequentially.

In another aspect of the invention, intermediates are provided such a compound of Formula (I-1c)



(I-1c)

wherein

R^1 is $(C_1$-$C_4)$alkyl or deuterated methyl;

R^2 is hydrogen or an amino-protecting group;

R^3 is $(C_1$-$C_4)$alkyl;

R^4 is

(i) $(C_1$-$C_{10})$alkyl, $(C_3$-$C_6)$cycloalkyl, phenyl, or a 3- to 7-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, or

(ii) R^{4a}-$(C_1$-$C_6)$alkylene, where R^{4a} is $(C_3$-$C_6)$cycloalkyl, or a 3- to 7-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, where said R^4 and said R^{4a} are optionally substituted with 1 to 3 substituents each independently selected from halo or $(C_1$-$C_4)$alkoxy;

A, B, and D are CR^5, and E is N, or A, B and E are CR^5 and D is N, where each R^5 is independently selected from H or F;

W is a bond; and

R^{6a}, R^{6b}, R^{6c} and R^{6d} are each independently H, $(C_1$-$C_3)$alkyl or F, where at least one of R^{6a}, R^{6b}, R^{6c} and R^{6d} is H or $(C_1$-$C_3)$alkyl.

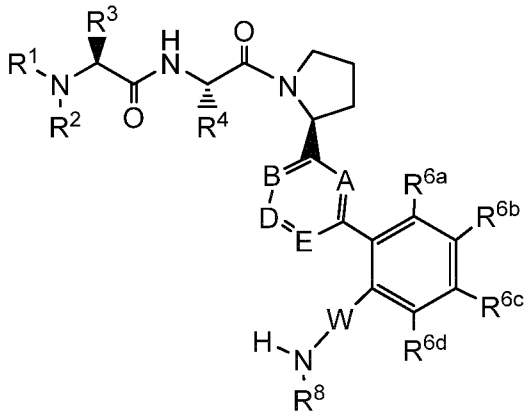
Preferably, R^1 is methyl or deuterated methyl; R^2 is an amino-protecting group; R^3 is methyl; R^4 is isopropyl or cyclohexyl; R^{6a}, R^{6b}, and R^{6d} are each H; and R^{6c} is F.

In one particular embodiment, A, B, and D are CR^5, and E is N, wherein each R^5 is independently selected from H or F.

In another particular embodiment, A, B and E are CR^5 and D is N, where each R^5 is independently selected from H or F.

A preferred intermediate is a compound which is 5-[5-((S)-1-{(S)-2-[(S)-2-(tert-Butoxycarbonyl-methyl-amino)-propionylamino]-2-cyclohexyl-acetyl}-pyrrolidin-2-yl)-pyridin-3-yl]-2-fluoro-benzoic acid.

In another particular embodiment, a compound of Formula (I-2a) is provided



(I-2a)

wherein

R^1 is $(C_1\text{-}C_4)$alkyl or deuterated methyl;

R^2 is H or amino-protecting group;

R^3 is $(C_1\text{-}C_4)$alkyl;

R^4 is

(i) $(C_1\text{-}C_{10})$alkyl, $(C_3\text{-}C_6)$cycloalkyl, phenyl, or a 3- to 7-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, or

(ii) R^{4a}-$(C_1\text{-}C_6)$alkylene, where R^{4a} is $(C_3\text{-}C_6)$cycloalkyl, or a 3- to 7-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, where said R^4 and said R^{4a} are optionally substituted with 1 to 3 substituents each independently selected from halo or $(C_1\text{-}C_4)$alkoxy;

A, B, and D are CR^5, and E is N, or A, B and E are CR^5 and D is N, where each R^5 is independently selected from H or F;

W is a bond;

R^{6a}, R^{6b}, R^{6c} and R^{6d} are each independently H, $(C_1\text{-}C_3)$alkyl or F, where at least one of R^{6a}, R^{6b}, R^{6c} and R^{6d} is H or $(C_1\text{-}C_3)$alkyl; and

R^8 is H.

Preferably, R^1 is methyl or deuterated methyl; R^2 is an amino-protecting group; R^3 is methyl; R^4 is isopropyl or cyclohexyl; R^{6a}, R^{6b}, and R^{6d} are each H; and R^{6c} is F.

In one particular embodiment, A, B, and D are CR^5, and E is N, wherein each R^5 is independently selected from H or F.

In another particular embodiment, A, B and E are CR^5 and D is N, where each R^5 is independently selected from H or F.

A preferred intermediate is a compound which is [(S)-1-((S)-2-{(S)-2-[5-(2-Aminomethyl-4-fluoro-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethylcarbamoyl)-ethyl]-methyl-carbamic acid tert-butyl ester.

Definitions

As used herein, the term “alkyl” refers to a hydrocarbon moiety of the general formula C_nH_{2n+1}. The alkane group may be straight or branched. For example, the term "(C_1-C_{10})alkyl" refers to a monovalent, straight, or branched aliphatic group containing 1 to 10 carbon atoms (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, 3,3-dimethylpropyl, hexyl, 2-methylpentyl, heptyl, and the like). Similarly, the alkyl portion (i.e., alkyl moiety) of an alkoxy have the same definition as above. When indicated as being "optionally substituted", the alkane radical or alkyl moiety may be unsubstituted or substituted with one or more substituents (generally, one to three substituents except in the case of halogen substituents such as perchloro or perfluoroalkyls). “Halo-substituted alkyl” refers to an alkyl group having at least one halogen substitution.

The term “alkenyl” refers to an alkyl moiety containing at least one unsaturation in the alkyl group. The alkenyl group may be straight or branched. For example, vinyl, prop-1-enyl, prop-2-enyl, allenyl, 2-methylprop-2-enyl, 3-methylbut-2-enyl, butadienyl, and the like.

The term “alkynyl” refers to an alkyl moiety containing at least one triple bond. The alkynyl group may be straight of branched. For example, CH_3-C≡C-, H-C≡C-CH_2-, CH_3-C≡C-CH_2-, H-C≡C-CH(CH_3)-, H-C≡C-CH_2CH_2-, H-C≡C-CH(CH_3)CH_2-, H-C≡C-CH_2-C≡C-CH_2-, and the like.

The term “alkylene” or “alkylenyl” refers to an alkyl moiety where the moiety contains two binding sites. The alkylene group may be straight (e.g., -(CH_2)-, -(CH_2)$_2$-, -(CH_2)$_3$-, or branched (e.g., -CH(CH_3)-, -C(CH_3)$_2$-, -CH_2CH(CH_3)-, -CH(CH_3)-CH_2-, -C(CH_3)$_2$-CH_2-, etc.). Suitable alkylene moieties are the same as those described above for alkyl except with two binding sites instead of just one.

The term “alkenylene” or “alkenylenyl” refers to an alkenyl moiety containing two binding sites. For example, -CH_2-CH=CH-CH_2-, -CH=CH-CH=CH-, and the like. Suitable alkenylene moieties are the same as those described above for alkenyl except with two binding sites instead of just one.

The term “alkynylene” or “alkynylenyl” refers to an alkynyl moiety containing two binding sites. For example, -CH_2-C≡C-CH_2-. Suitable alkynylene moieties are the same as those described above for alkynyl except with two binding sites instead of just one.

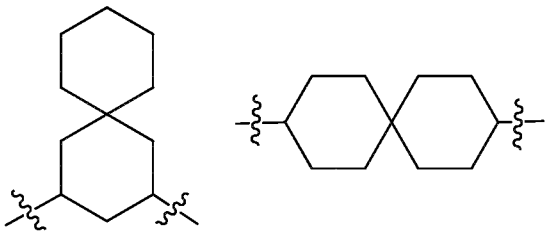
The term “aryl” refers to aromatic moieties having a single (e.g., phenyl) or a fused ring system (e.g., naphthalene, anthracene, phenanthrene, etc.). A typical aryl group is a 6- to 14-membered aromatic carbocyclic ring(s). A fused aromatic ring system may also include a phenyl fused to a partially or fully saturated cycloalkyl. For example,

2,3-dihydroindenyl, 1,2,3,4-tetrahydronaphthalenyl, 1,2-dihydronaphthalenyl, 2,3-dihydronaphthalenyl, 9,10-dihydroanthracenyl, fluorenyl, and the like.

The term "arylene" refers to a carbocyclic aromatic moiety having two binding sites. Suitable arylenes include those groups described above for an aryl moiety except with two binding sites rather than one. For example, 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,3- naphthylene, 1,4- naphthylene, 1,5-naphthylene, 1,6-naphthylene, 1,7-naphthylene, 2,3- naphthylene, 2,4-napthylene, 2,5-naphthylene, 2,6- naphthylene, 2,7-naphthylene, 3,4-naphthylene, 3,5-naphthylene, 3,6-naphthylene, 3,7-naphthylene, etc. The two binding sites on the fused arylene system may be on the same ring or different rings.

The term "partially or fully saturated cycloalkyl" refers to a carbocyclic ring which is fully hydrogenated (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc.) or partially hydrogenated (e.g., cyclopropenyl, cyclobutenyl, cyclopentyl, cyclopenta-1,3-dienyl, cyclohexenyl, cyclohexa-1,3-dienyl, cyclohexa-1,4-dienyl, etc.). The carbocyclic ring may be a single ring (as described above), a bicyclic ring (e.g., octahydropentalenyl, bicyclo[1.1.1]pentanyl, bicyclo[2.1.1]hexanyl, bicyclo[2.1.1]hex-2-enyl, bicyclo[2.2.1]hept-2-enyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[2.2.2]oct-2-enyl, bicyclo[2.2.2]octa-2,5-dienyl, etc.) or a spiral ring (e.g., spiro[2.2]pentanyl, etc.), and the like.

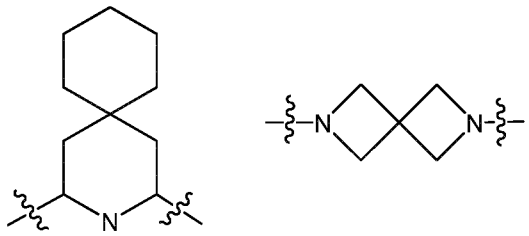
The term "partially or fully saturated cycloalkylene" refers to a carbocyclic ring having either no unsaturation in the ring (fully hydrogenated) or at least one unsaturation (partially hydrogenated) without being aromatic and contains two binding sites. Suitable ring systems include those described above for a partially or fully saturated cycloalkyl except having two bind sites instead of one. For example, 1,2-cyclopropyl, 1,2-cycloprop-1-enyl, 1,2-cyclobutyl, 1,3-cyclobutyl, 1,2-cyclobut-1-enyl, 3,4-cyclobut-1-enyl, 3,5-cyclopent-1-enyl, 1,4-cyclopenta-1,3-dienyl, 1,5-cyclopenta-1,3-dienyl, 1,2-cyclopenta-1,3-dienyl, 1,3-cyclopenta-1,3 -dienyl, etc. The carbocyclic ring may be a single ring, a bicyclic ring, fused ring (e.g., decahydronaphthalene), or a spiral ring where the two binding sites on the bicyclic ring and spiral ring may be on the same ring or different rings. See, e.g., the illustration below.



Same ring Different ring

The term "partially or fully saturated heterocycle" refers to a nonaromatic ring that is either partially or fully hydrogenated and may exist as a single ring, bicyclic ring (including fused rings) or a spiral ring. Unless specified otherwise, the heterocyclic ring is generally a 3- to 14-membered ring containing 1 to 3 heteroatoms (preferably 1 or 2 heteroatoms) independently selected from sulfur, oxygen and/or nitrogen. Partially saturated or fully saturated heterocyclic rings include groups such as epoxy, aziridinyl, azetidinyl, tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, pyrrolidinyl, imidazolidinyl, imidazolinyl, 1H-dihydroimidazolyl, hexahydropyrimidinyl, piperidinyl, piperazinyl, pyrazolidinyl, 2H-pyranyl, 4H-pyranyl, 2H-chromenyl, oxazinyl, morpholino, thiomorpholino, tetrahydrothienyl, tetrahydrothienyl, 1,4,7-triazonane, diazepanyl, 1,1-dioxide, oxazolidinyl, thiazolidinyl, octahydropyrrolo[3,2-b]pyrrolyl, decahydro-2,7-naphthyridinyl, and the like. A partially saturated heterocyclic ring also includes groups wherein the heterocyclic ring is fused to an aryl or heteroaryl ring (e.g., 2,3-dihydrobenzofuranyl, indolinyl (or 2,3-dihydroindolyl), 2,3-dihydrobenzothiophenyl, 2,3-dihydrobenzothiazolyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydropyrido[3,4-b]pyrazinyl, and the like). Examples of spiral rings include 2,6-diazaspiro[3.3]heptanyl, 2,7-diazaspiro[4.4]nonanyl, 3-azaspiro[5.5]undecanyl, 3,9-diazaspiro[5.5]undecanyl, and the like.

The term "partially or fully saturated heterocyclene" refers to a partially or fully saturated heterocyclic ring (as described above) except having two binding sites instead of one. The heterocyclene ring may be a single ring, a bicyclic ring, or a spiral ring where the two binding sites on the bicyclic ring (including fused rings) and spiral ring may be on the same ring or different rings. See, e.g., the illustration below.



Same ring Different ring

The term "heteroaryl" refers to aromatic moieties containing at least one heteratom (e.g., oxygen, sulfur, nitrogen or combinations thereof) within a 5- to 10-membered aromatic ring system (e.g., pyrrolyl, pyridyl, pyrazolyl, indolyl, indazolyl, thienyl, furanyl, benzofuranyl, oxazolyl, imidazolyl, tetrazolyl, triazinyl, pyrimidyl, pyrazinyl, thiazolyl, purinyl, benzimidazolyl, quinolinyl, isoquinolinyl, benzothiophenyl, benzoxazolyl, 1H-benzo[d][1,2,3]triazolyl, and the like.). The heteroaromatic moiety may consist of a single or fused ring system. A typical single heteroaryl ring is a 5- to 6-membered ring containing one to three heteroatoms independently selected from

oxygen, sulfur and nitrogen and a typical fused heteroaryl ring system is a 9- to 10-membered ring system containing one to four heteroatoms independently selected from oxygen, sulfur and nitrogen. The fused heteroaryl ring system may consist of two heteroaryl rings fused together or a hetereoaryl fused to an aryl (e.g., phenyl).

The term "heteroarylene" refers to a heteroaryl having two binding sites instead of one. Suitable heteroarylene groups include those described above for heteroaryl having two binding sites instead of one.

Unless specified otherwise, the term "compounds of the present invention" refers to dimeric Compounds of Formula (M-L-M'), (I-A) and (I-B), and salts thereof, as well as all stereoisomers (including diastereoisomers and enantiomers), rotamers, tautomers and isotopically labeled compounds (including deuterium substitutions), as well as inherently formed moieties (e.g., polymorphs, solvates and/or hydrates). For purposes of this invention, solvates and hydrates are generally considered compositions.

DETAILED DESCRIPTION

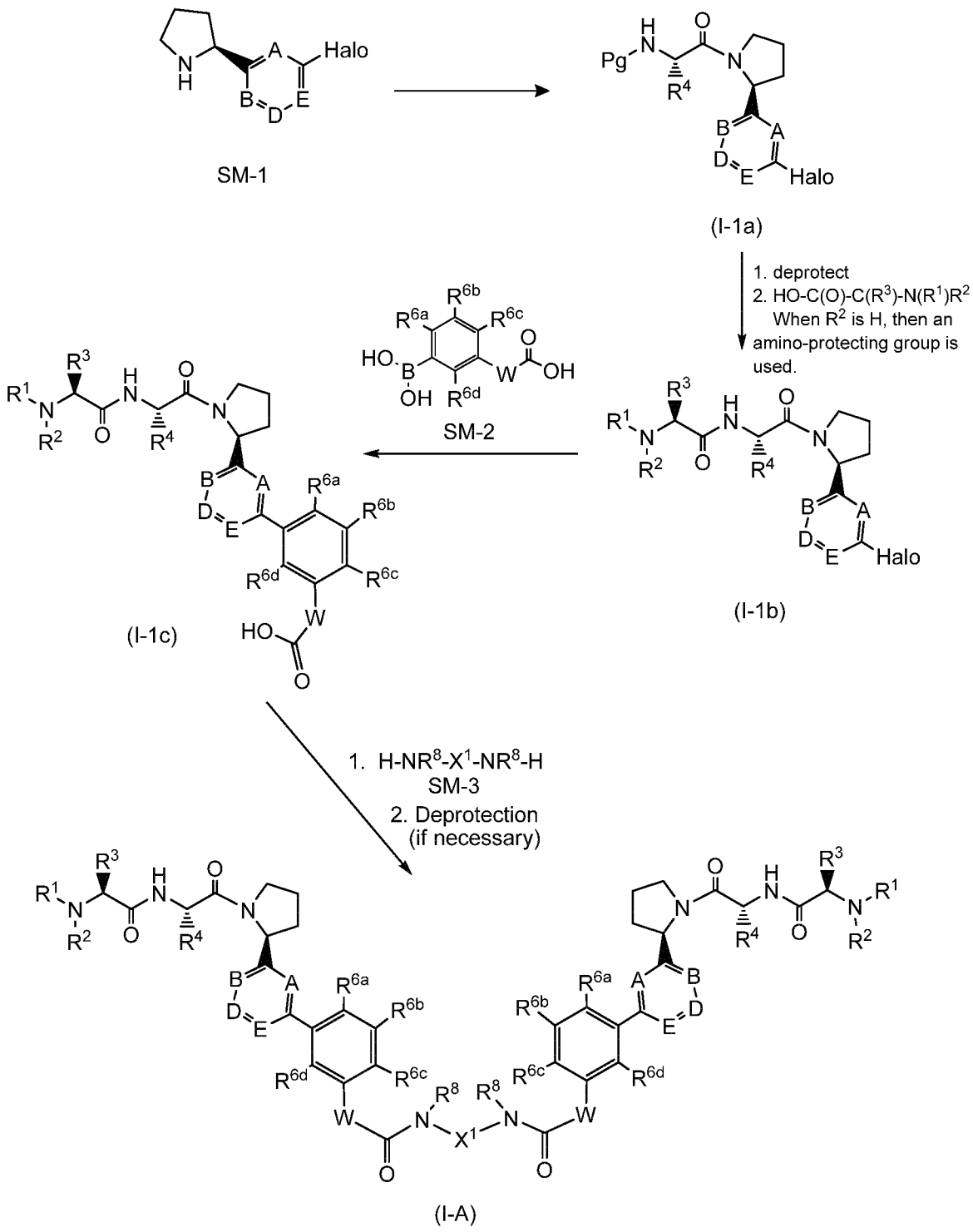
The present invention provides compounds and pharmaceutical formulations thereof that are useful in the treatment of diseases, conditions and/or disorders in which the inhibition of apoptosis contributes to disease pathogenesis.

Compounds of the present invention may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wis.) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, v. 1-19, Wiley, New York (1967-1999 ed.), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

In the preparation of compounds of the present invention, protection of remote functionality (e.g., primary or secondary amino, or carboxyl groups) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups (NH-Pg) include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethyleneoxycarbonyl (Fmoc). Suitable carboxyl protecting groups (C(O)O-Pg) include alkyl esters (e.g., methyl, ethyl or t-butyl), benzyl esters, silyl esters, and the like. The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

Scheme 1 (below) describes a potential route for producing compounds of formula M-L-M', where M and M' are each independently a monomeric unit of Formula (I) and L is $-NR^8-X^1-NR^8-$.



Scheme I

The nitrogen atom of the desired pyrrolidine starting material (SM-1) can first be coupled with the desired amino-protected amino acid derivative (HO-C(O)-C(CR^4)-NH-Pg, such as Boc-L-valine, 2-(Boc-amino)-2-cyclohexylacetic acid, 2-(Boc-amino)-2-morpholinoacetic acid, 2-(Boc-amino)-2-*tert*-butylacetic acid, 2-(Boc-amino)-2-(tetrahydro-2H-pyran-4-yl) acetic acid, 2-(Boc-amino)-2-phenyl acetic acid, 2-(Boc-amino)-2-(4-hydroxycyclohexyl) acetic acid, 2-(Boc-amino)-3-methylpentanoic acid, 2-

(Boc-amino)-3-hydroxy-3-methylbutanoic acid, and 2-(Boc-amino)-2-(4,4-difluorocyclohexyl)acetic acid) using standard peptide coupling conditions. Common activating agents for the coupling reaction include carbodiimides (e.g., dicyclohexylcarbodimide (DCC), 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) and diisopropylcarbodimide (DIC)), triazoles (e.g., 1-hydroxy-benzotriazole (HOBt), 1-hydroxy-7-aza-benzotriazole (HOAt)), (2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (HATU), and O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate (HBTU), triazines (e.g., 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM)). Once the coupling is complete, then the amino acid protecting group can be removed so that a second amino acid (e.g., HO-C(O)-C(R^3)-N(R^1)R^2, when R^2 is H, then an amino-protecting group, such as Boc, is used) can be added using the same or different standard peptide coupling conditions.

Alternatively, the two amino acid derivatives can be coupled prior to condensing onto the pyrrolidine nitrogen of starting material SM-1.

Once the desired amino acid groups are coupled to form Intermediate (I-1b), the desired 3-carboxyphenylboronic or 3-carboxyalkylphenylboronic acid derivative (SM-2) is added to Intermediate I-1b in the presence of a coupling agent (e.g., Bis(triphenylphosphine)palladium dichloride) under an inert atmosphere and elevated temperatures.

Suitable 3-carboxyphenylboronic or 3-carboxyalkylphenylboronic acid derivatives which are available commerically or can be prepared from literature preparations include: 3-carboxy-4-fluorophenylboronic acid, 5-borono-2,3-difluoro-benzoic acid, 3-borono-5-methyl-benzoic acid, 3-borono-2-fluoro-benzoic acid, 3-borono-5-fluoro-4-methyl-benzoic acid, 3-(carboxymethyl)phenylboronic acid, [3-(1-carboxyethyl)phenyl]boronic acid, [3-(1-carboxy-1-methylethyl)phenyl]boronic acid, [3-(2-methylpropionic acid)phenyl]boronic acid, [3-(2-carboxyethyl)phenyl]boronic acid, 3-borono-benzenebutanoic acid, 3-borono-benzenepentanoic acid, 3-borono-2,4,6-trifluoro-benzenepentanoic acid, and the like. Additional useful 3-carboxyphenylboronic acid derivatives can be purchased from Combi-Blocks, Incorporated (San Diego, California, USA), BoroChem SAS (Caen, France) and Boron Molecular (Research Triangle, North Carolina, USA). Those of skill in the art will know how to make modifications to the literature preparations and commercially available materials to make additional derivatives.

Two monomeric units (I-1c) can then be linked using a desired diamino linker (SM-3) to produce the dimeric Compound (I-A) using standard peptide formation procedures well-known to those of skill in the art. When a protecting group is used in the R^2 position, then the amino-protecting group may be removed using conditions

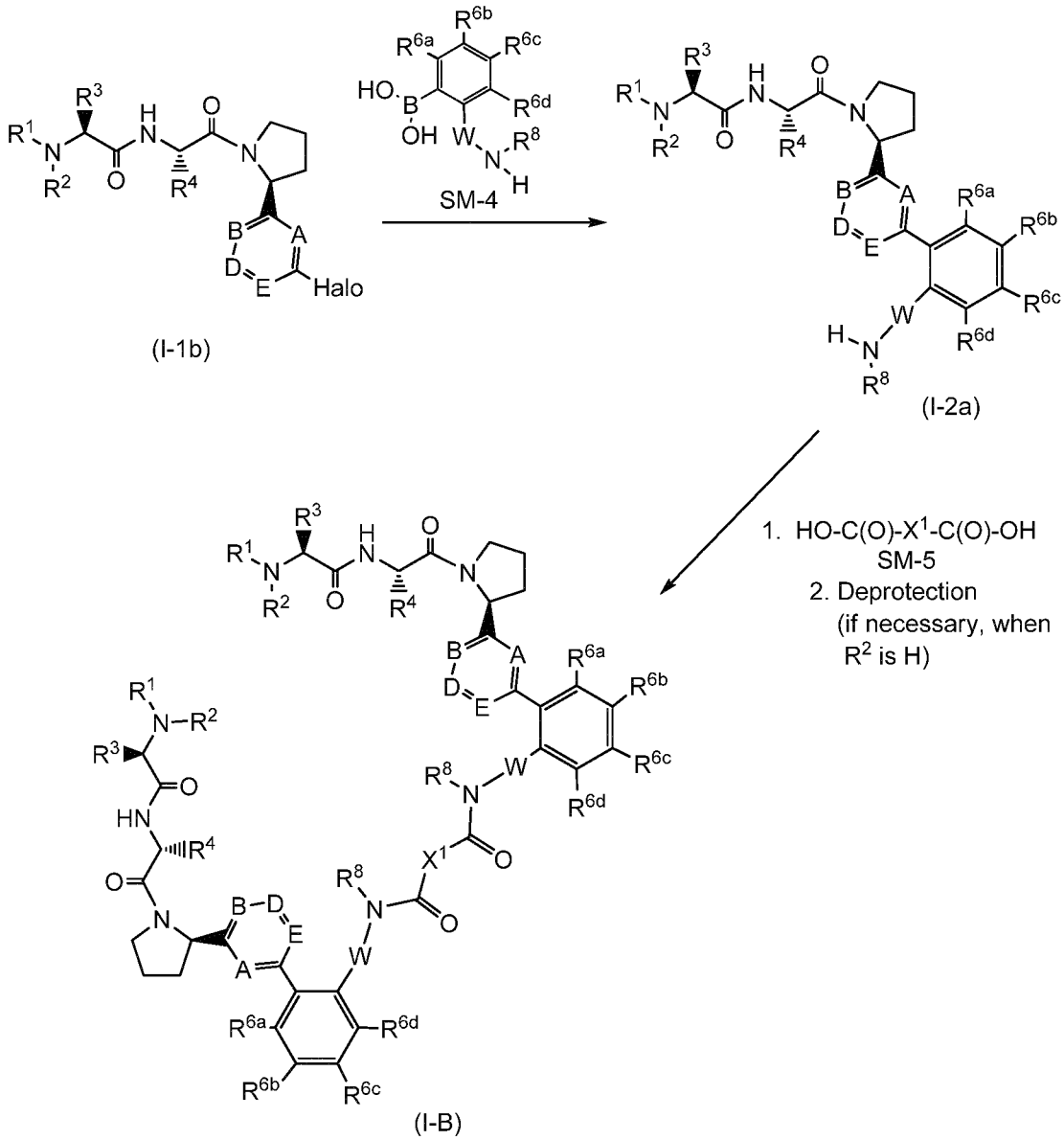
commensurate with the particular amino-protecting group used to provide dimeric Compound (I-A) where R^2 is H in one or both monomeric units.

Suitable diamino linker compounds (H-NR^8-X^1-NR^8-H) which are commercially available or readily prepared from literature preparations include 2,6-diazaspiro[3.3]heptane; 2,2-dimethylpropane-1,3-diamine; 4,7,10,13,16-pentaoxanonadecane-1,19-diamine; 3,3'-oxydipropan-1-amine; 2,2'-(ethane-1,2-diylbis(oxy))diethanamine; 3,3'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))dipropan-1-amine; 2,2'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))diethanamine; 3,3'-(ethane-1,2-diylbis(oxy))dipropan-1-amine; propane-1,3-diamine; butane-1,4-diamine; 4-[2-(4-aminophenyl)ethynyl]aniline; 1,4-bis(3-aminophenyl)butadiyne; 1,4-diamino-2-butyne; hex-3-yne-2,5-diamine; hexa-2,4-diyne-1,6-diamine (see, e.g., Jeon, J. H.; Sayre, L. M., *Biochem. Biophys. Res. Commun.* **2003,** 304(4), 788-794); N^1,N^4-diethylbut-2-yne-1,4-diamine; (*E*)-N^1,N^4-diethylbut-2-ene-1,4-diamine; *cis*-octahydro-pyrrolo[3,4-c]pyridine; 1,1'-ethylenedipiperazine; 1,5-diethyl-3,7-diaza-bicyclo[3.3.1]nonan-9-one; 1-ethyl-5-methyl-3,7-diaza-bicyclo[3.3.1]nonan-9-ol; 1-ethyl-5-methyl-3,7-diaza-bicyclo[3.3.1]nonan-9-one; 4,10-diaza-12-crown-4-ether; 1,5,9-triazacyclododecane; 1,5-dimethyl-3,7-diaza-bicyclo[3.3.1]nonan-9-ol; 4,4-bipiperidine;1,5-dimethyl-3,7-diaza-bicyclo[3.3.1]nonan-9-one; 1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonane; 2,8-diazaspiro[5,5]undecane; decahydro-2,7-naphthyridine; 1,4,7-triazacyclononane; 6,6-dimethyl-1,4-diazepane; (S)-2,7-diazaspiro[4.4]nonane; *cis*-octahydro-pyrrolo[3,4-c]pyridine; 1,5-diazacyclooctane; 6-methyl-[1,4]diazepane; 3,7-diazabicyclo[3.3.0]octane; homopiperazine; 2,6-diazaspiro[3.3]heptane; piperazine; (3aS,7aR)-octahydro-pyrrolo[2,3-c]p; (3aR,7aS)-octahydro-pyrrolo[2,3-c]p; 1-(furan-2-yl)-N-(piperidin-4-ylmethyl)methanamine; 2,2,2-trifluoro-N-(pyrrolidin-3-ylmethyl)ethanamine; N-((morpholin-2-yl)methyl) ethanamine; methyl-morpholin-2-ylmethyl-amine; methyl-piperidin-4-ylmethyl-amine; ethyl-pyrrolidin-3-ylmethyl-amine; methyl-pyrrolidin-3-ylmethyl-amine; N-methyl-3-azetidinemethanamine; and (2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)methanamine. Those of skill in the art will know how to make modifications to the literature preparations or commercial compounds to make additional derivatives.

Dimeric compounds of Formula M-L-M', where M and M' are each independently a monomeric unit of Formula (IV) and L is -NR^8-X^1-NR^8- can be prepared using the process described above in Scheme I by substituting SM-1 with a 2-carboxyphenylboronic or 2-carboxyalkylphenylboronic acid derivative. Suitable 2-carboxyphenylboronic and 2-carboxyalkylphenylboronic acid derivatives include those which are available commerically or can be prepared from literature preparations, such as 2-borono-4-chloro-benzoic acid, 2-borono-5-chloro-benzoic acid, 2-borono-5-fluoro-benzoic acid, 2-borono-benzeneacetic acid, and 2-borono-4-fluoro-benzoic acid. Additional useful 2-

carboxyphenylboronic acid derivatives can be purchased from Combi-Blocks, Incorporated (San Diego, California, USA), BoroChem SAS (Caen, France) and Boron Molecular (Research Triangle, North Carolina, USA). Those of skill in the art will know how to make modifications to the literature preparations and commercially available materials to make additional derivatives.

Scheme 2 (below) describes a potential route for producing dimeric compounds of Formula M-L-M', where M and M' are each independently a monomeric moiety of Formula (II) and L is $-C(O)-X^1-C(O)-$.



Scheme 2

The desired 2-aminophenylboronic or 2-aminoalkylphenylboronic acid derivative (SM-4) is added to Intermediate I-1b (R^2 is replaced with an amino-protecting group when R^2 is H) in the presence of a coupling agent (e.g.,

Bis(triphenylphosphine)palladium dichloride) under an inert atmosphere and elevated temperatures to produce intermediate (I-2a).

Suitable 2-aminophenylboronic acid, or 2-aminoalkylphenylboronic acid derivatives that are available commercially (e.g., American Custom Chemical Corporation, San Diego, CA) or may be prepared using known literature preparations include: 2-aminomethylphenyl boronic acid, 2-aminomethyl-4-fluorophenylboronic acid, 2-aminomethyl-5-fluorophenyl boronic acid, and 2-aminomethyl-6-fluorophenyl boronic acid. Those of skill in the art will know how to make modifications to the literature preparations to make additional derivatives.

Two monomeric units (I-2a), which can be the same or different, can then be linked using a desired dicarboxylic acid linker (SM-5) to produce the dimeric Compound (I-B) using standard peptide formation procedures well-known to those of skill in the art. When a protecting group is used in the R^2 position, then the amino-protecting group may be removed using conditions commensurate with the particular amino-protecting group used to provide dimeric Compound (I-B) where R^2 is H in one or both monomeric units.

Suitable commercially available dicarboxylic acid linker compounds (HO-C(O)-X^1-C(O)-OH) include biphenyl-4,4'-dicarboxylic acid, 2,2'-(ethane-1,2-diylbis(oxy))diacetic acid, 2,2'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))diacetic acid, 4,7,9,12-tetraoxapentadecane-1,15-dioic acid, 2,2'-(2,2'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(2,1-phenylene))bis(oxy)diacetic acid, and 2,2'-(2,2'-(2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy)bis(2,1-phenylene))bis(oxy)diacetic acid.

Alternatively, the dicarboxylic acid compounds can be converted to their acid chloride equivalents by treating with the appropriate reagent (e.g., thionyl chloride, phosphorus trichloride or phosphorus pentachloride). The dicarboxylic acid compounds can also be modified by making the hydroxyl group of the carboxylic acid moieties a leaving group which can subsequently be displaced to create a link to the monomeric units.

Commercially available dicarboxylic acid chloride compounds include oxalyl dichloride, pyridine-2,4-dicarbonyl dichloride, (2E,2'E)-3,3'-(1,4-phenylene)bis-2-propenoyl chloride, malonyl dichloride, pyrazine-2,3-dicarbonyl dichloride, dodecanedioyl dichloride, fumaroyl dichloride, 1-methyl-1H-pyrazole-3,4-dicarbonyl dichloride, cyclohexane-1,4-diylbis(methylene) dicarbonochloridate, succinyl dichloride, thiophene-2,5-dicarbonyl dichloride, (3R,6R)-hexahydrofuro[3,2-b]furan-3,6-diyl dicarbonochloridate, bis(chlorocarbonyl)methylamine, (E)-oct-4-enedioyl dichloride, 2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl) dicarbonochloridate, 2,2-dimethylmalonyl dichloride, cyclohexane-1,4-dicarbonyl dichloride, 2,2,3,3,4,4-hexafluoropentanedioyl dichloride, glutaroyl dichloride, octanedioyl dichloride, biphenyl-2,2'-dicarbonyl dichloride,

2,2'-oxydiacetyl chloride, butane-1,4-diyl dicarbonochloridate, biphenyl-4,4'-dicarbonyl dichloride, cyclobutane-1,2-dicarbonyl dichloride, 2-bromoterephthaloyl dichloride, adipoyl dichloride, (1R,2S,3S,4S)-bicyclo[2.2.1]hept-5-ene-2,3-dicarbonyl dichloride, 4-bromoisophthaloyl dichloride, ethane-1,2-diyl dicarbonochloridate, (1R,3S,4S)-bicyclo[2.2.1]hept-5-ene-2,3-dicarbonyl dichloride, 1-benzyl-1H-pyrazole-3,5-dicarbonyl dichloride, 1H-pyrazole-3,5-dicarbonyl dichloride, 4-methylthiazole-2,5-dicarbonyl dichloride, 4,4'-oxydibenzoyl chloride, 1H-pyrazole-4,5-dicarbonyl dichloride, nonanedioyl dichloride, 2,3-diphenylfumaroyl dichloride, 1H-1,2,3-triazole-4,5-dicarbonyl dichloride, 2,2,3,3-tetrafluorosuccinyl dichloride, (E)-4,4'-(diazene-1,2-diyl)dibenzoyl chloride, 2,2-diethylmalonyl dichloride, 2,2'-oxybis(ethane-2,1-diyl) dicarbonochloridate, 2,2,3,3,4,4,5,5-octafluorohexanedioyl dichloride, 3-methylhexanedioyl dichloride, 4-methoxyisophthaloyl dichloride, 2,3,5,6-tetrachloroterephthaloyl dichloride, 2,2-dimethylpentanedioyl dichloride, (E)-2,2'-(diazene-1,2-diyl)dibutanoyl chloride, (E)-2,2'-(diazene-1,2-diyl)dibenzoyl chloride, heptanedioyl dichloride, decanedioyl dichloride, 4,4'-(propane-2,2-diyl)bis(4,1-phenylene) dicarbonochloridate, isophthaloyl dichloride, 1H-indole-3,5-dicarbonyl dichloride, 4,5-dibromophthaloyl dichloride, terephthaloyl dichloride, hexane-1,6-diyl dicarbonochloridate, 1,1'-binaphthyl-2,2'-dicarbonyl dichloride, phthaloyl dichloride, 2-benzylsuccinyl dichloride, 4,4'-(cyclohexane-1,4-diyl)bis(4,1-phenylene) dicarbonochloridate, pyridine-3,5-dicarbonyl dichloride, naphthalene-2,3-dicarbonyl dichloride, 5-amino-2,4,6-triiodoisophthaloyl dichloride, pyridine-2,6-dicarbonyl dichloride, naphthalene-2,6-dicarbonyl dichloride, pyridine-3,4-dicarbonyl dichloride, and 5-aminoisophthaloyl dichloride.

Dimeric compounds of Formula M-L-M', where M and M' are each independently a monomeric unit of Formula (III) and L is $-C(O)-X^1-C(O)-$ can be prepared using the procedures described above in Scheme II by substituting SM-4 with the desired 3-aminophenylboronic or 3-aminoalkylphenylboronic acid derivatives.

Suitable 3-aminophenylboronic acid, or 3-aminoalkylphenylboronic acid derivatives that are available commercially (e.g., American Custom Chemical Corporation, San Diego, CA) or may be prepared using known literature preparations include: 3-aminophenyl-boronic acid, 3-amino-4,5-difluorophenyl-boronic acid, 5-amino-2,4-difluorophenyl-boronic acid, 3-amino-4-fluorophenyl-boronic acid, 5-amino-2-fluorophenyl-boronic acid, 3-amino-4-chlorophenyl-boronic acid, 3-amino-4-methylphenyl-boronic acid, 5-amino-2,4-dimethylphenyl-boronic acid, 3-amino-4-methylphenyl-boronic acid, 5-aminomethyl-2-fluorophenyl-boronic acid, 3-(aminomethyl)-2-fluorophenyl-boronic acid, and 3-(aminomethyl)phenyl-boronic acid. Those of skill in the art will know how to make modifications to the literature preparations to make additional derivatives.

The dimeric compounds may be isolated and used as the compound *per se* or as its salt. As used herein, the terms "salt" or "salts" refers to an acid addition or base addition salt of a compound of the invention. "Salts" include in particular "pharmaceutical acceptable salts". The term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which typically are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfornate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate and trifluoroacetate salts.

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound, a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I respectively. The invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^{3}H, ^{13}C, and ^{14}C , are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically labeled compounds of this invention can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

Further, substitution with heavier isotopes, particularly deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life, reduced dosage requirements, reduced cyp inhibition (competitive or time dependent) or an improvement in therapeutic index. For example, substitution with deuterium may modulate undesirable side effects of the undeuterated compound, such as competitive cyp inhibition, time dependent cyp inactivation, etc. It is understood that deuterium in this context is regarded as a substituent in compounds of

the present invention (including both the monomeric and linker moieties of the dimer). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

Isotopically-labeled compounds of the present invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

It will be recognized by those skilled in the art that the compounds of the present invention may contain chiral centers and as such may exist in different isomeric forms. As used herein, the term “isomers” refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms. Also as used herein, the term “an optical isomer” or “a stereoisomer” refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound.

“Enantiomers” are a pair of stereoisomers that are non- superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic” mixture. The term is used to designate a racemic mixture where appropriate.

"Diastereoisomers” are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or

(-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-.

Unless specified otherwise, the compounds of the present invention are meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

Compounds of the invention that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of the present invention by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of the present invention with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of the present invention.

Compounds of the present invention have been found to induce or enhance apoptosis and therefore useful in the treatment of cancer. Consequently, a compound of the present invention may be used in the manufacture of a medicament for the treatment of diseases, conditions or disorders associated with the overexpression of an IAP in a subject (or mammal, preferably a human), inducing apoptosis in a tumor or cancer cell, inhibiting the binding of an IAP protein to a caspase protein, or sensitizing a tumor or cancer cell to an apoptotic signal. In the process, a compound of the present invention may also induce the degradation of individual or multiple IAPs in cells (specifically cIAP1, cIAP2 and/or XIAP), and may induce expression of TNFα in some cells.

The compounds of the present invention are typically used as a pharmaceutical composition (e.g., a compound of the present invention and at least one pharmaceutically acceptable carrier). As used herein, the term "pharmaceutically acceptable carrier" includes generally recognized as safe (GRAS) solvents, dispersion media, surfactants, antioxidants, preservatives (*e.g.*, antibacterial agents, antifungal agents), isotonic agents, salts, preservatives, drug stabilizers, buffering agents (e.g., maleic acid, tartaric acid, lactic acid, citric acid, acetic acid, sodium bicarbonate, sodium

phosphate, and the like), and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated. For purposes of this invention, solvates and hydrates are considered pharmaceutical compositions comprising a compound of the present invention and a solvent (i.e., solvate) or water (i.e., hydrate).

The formulations may be prepared using conventional dissolution and mixing procedures. For example, the bulk drug substance (i.e., compound of the present invention or stabilized form of the compound (e.g., complex with a cyclodextrin derivative or other known complexation agent)) is dissolved in a suitable solvent in the presence of one or more of the excipients described above. The compound of the present invention is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to give the patient an elegant and easily handleable product.

The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. Suitable containers are well-known to those skilled in the art and include materials such as bottles (plastic and glass), ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

The pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention is generally formulated for use as a parenteral administration. The pharmaceutical compositions (e.g., intravenous (iv) formulation) can be subjected to conventional pharmaceutical operations such as sterilization and/or can contain conventional inert diluents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers, wetting agents, emulsifers and buffers well known to those of skill in the art.

In certain instances, it may be advantageous to administer the compound of the present invention in combination with at least one additional pharmaceutical (or therapeutic) agent (e.g., an anti-cancer agent or adjunct therapy typically used in chemotherapy). The compound of the present invention may be administered either simultaneously with, or before or after, one or more other therapeutic agent(s). Alternatively, the compound of the present invention may be administered separately, by

the same or different route of administration, or together in the same pharmaceutical composition as the other agent(s).

Suitable additional anti-cancer agents include

(i) Taxane anti-neoplastic agents such as Cabazitaxel (1-hydroxy-7β,10β-dimethoxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl-4-acetate-2-benzoate-13-[(2R,3S)-3-{[(tert-butoxy)carbonyl]amino}-2-hydroxy-3-phenylpropanoate), larotaxel ((2α,3ξ,4α,5β,7α,10β,13α)-4,10-bis(acetyloxy)-13-({(2*R*,3*S*)-3- [(*tert*-butoxycarbonyl) amino]-2-hydroxy-3-phenylpropanoyl}oxy)-1- hydroxy-9-oxo-5,20-epoxy-7,19-cyclotax-11-en-2-yl benzoate) and paclitaxel;

(ii) Vascular Endothelial Growth Factor (VEGF) receptor inhibitors and antibodies such as Bevacizumab (sold under the trademark Avastin® by Genentech/Roche), axitinib, (N-methyl-2-[[3-[(E)-2-pyridin-2-ylethenyl]-1H-indazol-6-yl]sulfanyl]benzamide, also known as AG013736, and described in PCT Publication No. WO 01/002369), Brivanib Alaninate ((S)-((R)-1-(4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yloxy)propan-2-yl)2-aminopropanoate, also known as BMS-582664), motesanib (N-(2,3-dihydro-3,3-dimethyl-1H-indol-6-yl)-2-[(4-pyridinylmethyl)amino]-3-pyridinecarboxamide, and described in PCT Publication No. WO 02/066470), pasireotide (also known as SOM230, and described in PCT Publication No. WO 02/010192), and sorafenib (sold under the tradename Nexavar®);

(iii) Tyrosine kinase inhibitors such as Erlotinib hydrochloride (sold under the trademark Tarceva® by Genentech/Roche), Linifanib (N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea, also known as ABT 869, available from Genentech), sunitinib malate (sold under the tradename Sutent® by Pfizer), bosutinib (4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile, also known as SKI-606, and described in US Patent No. 6,780,996), dasatinib (sold under the tradename Sprycel® by Bristol-Myers Squibb), armala (also known as pazopanib, sold under the tradename Votrient® by GlaxoSmithKline), and imatinib and imatinib mesylate (sold under the tradenames Gilvec® and Gleevec® by Novartis);

(iv) Bcr/Abl kinase inhibitors such as nilotinib hydrochloride (sold under the tradename Tasigna® by Novartis);

(v) DNA Synthesis inhibitors such as Capecitabine (sold under the trademark Xeloda® by Roche), gemcitabine hydrochloride (sold under the trademark Gemzar® by Eli Lilly and Company), and nelarabine ((2R,3S,4R,5R)-2-(2-amino-6-methoxy-purin-9-yl)-5-(hydroxymethyl)oxolane-3,4-diol, sold under the tradenames Arranon® and Atriance® by GlaxoSmithKline);

(vi) Antineoplastic agents such as oxaliplatin (sold under the tradename Eloxatin® ay Sanofi-Aventis and described in US Patent No. 4,169,846);

(vii) Epidermal growth factor receptor (EGFR) inhibitors such as Gefitnib (sold under the tradename Iressa®), N-[4-[(3-Chloro-4-fluorophenyl)amino]-7-[[(3"S")-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4(dimethylamino)-2-butenamide, sold under the tradename Tovok® by Boehringer Ingelheim), cetuximab (sold under the tradename Erbitux® by Bristol-Myers Squibb), and panitumumab (sold under the tradename Vectibix® by Amgen);

(viii) Pro-apoptotic receptor agonists (PARAs) such as Dulanermin (also known as AMG-951, available from Amgen/Genentech);

(ix) PI3K inhibitors such as 4-[2-(1H-Indazol-4-yl)-6-[[4-(methylsulfonyl)piperazin-1-yl]methyl]thieno[3,2-d]pyrimidin-4-yl]morpholine (also known as GDC 0941 and described in PCT Publication Nos. WO 09/036082 and WO 09/055730), and 2-Methyl-2-[4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydroimidazo[4,5-c]quinolin-1-yl]phenyl]propionitrile (also known as BEZ 235 or NVP-BEZ 235, and described in PCT Publication No. WO 06/122806);

(x) BCL-2 inhibitors such as 4-[4-[[2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl]methyl]-1-piperazinyl]-N-[[4-[[(1R)-3-(4-morpholinyl)-1-[(phenylthio)methyl]propyl]amino]-3-[(trifluoromethyl)sulfonyl]phenyl]-sulfonyl]benzamide (also known as ABT-263 and described in PCT Publication No. WO 09/155386);

(xi) Topoisomerase I inhibitors such as Irinotecan (sold under the trademark Camptosar® by Pfizer), topotecan hydrochloride (sold under the tradename Hycamtin® by GlaxoSmithKline);

(xii) Topoisomerase II inhibitors such as etoposide (also known as VP-16 and Etoposide phosphate, sold under the tradenames Toposar®, VePesid® and Etopophos®), and teniposide (also known as VM-26, sold under the tradename Vumon®);

(xiii) CTLA-4 inhibitors such as Tremelimumab (IgG2 monoclonal antibody available from Pfizer, formerly known as ticilimumab, CP-675,206), and ipilimumab (CTLA-4 antibody, also known as MDX-010, CAS No. 477202-00-9);

(xiv) Histone deacetylase inhibitors (HDI) such as Voninostat (sold under the tradename Zolinza® by Merck) and Panobinostat (N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]methyl]phenyl]-(2E)-2-Propenamide described in PCT Publication No. 02/0022577 or US Patent No. 7,067,551);

(xv) Alkylating agents such as Temozolomide (sold under the tradenames Temodar® and Temodal® by Schering-Plough/Merck), dactinomycin (also known as actinomycin-D and sold under the tradename Cosmegen®), melphalan (also known as L-

PAM, L-sarcolysin, and phenylalanine mustard, sold under the tradename Alkeran®), altretamine (also known as hexamethylmelamine (HMM), sold under the tradename Hexalen®), carmustine (sold under the tradename BiCNU®), bendamustine (sold under the tradename Treanda®), busulfan (sold under the tradenames Busulfex® and Myleran®), carboplatin (sold under the tradename Paraplatin®), lomustine (also known as CCNU, sold under the tradename CeeNU®), cisplatin (also known as CDDP, sold under the tradenames Platinol® and Platinol®-AQ), chlorambucil (sold under the tradename Leukeran®), cyclophosphamide (sold under the tradenames Cytoxan® and Neosar®), dacarbazine (also known as DTIC, DIC and imidazole carboxamide, sold under the tradename DTIC-Dome®), altretamine (also known as hexamethylmelamine (HMM) sold under the tradename Hexalen®), ifosfamide (sold under the tradename Ifex®), procarbazine (sold under the tradename Matulane®), mechlorethamine (also known as nitrogen mustard, mustine and mechloroethamine hydrochloride, sold under the tradename Mustargen®), streptozocin (sold under the tradename Zanosar®), and thiotepa (also known as thiophosphoamide, TESPA and TSPA, sold under the tradename Thioplex®;

(xvi) Anti-tumor antibiotics such as doxorubicin (sold under the tradenames Adriamycin® and Rubex®), bleomycin (sold under the tradename lenoxane®), daunorubicin (also known as dauorubicin hydrochloride, daunomycin, and rubidomycin hydrochloride, sold under the tradename Cerubidine®), daunorubicin liposomal (daunorubicin citrate liposome, sold under the tradename DaunoXome®), mitoxantrone (also known as DHAD, sold under the tradename Novantrone®), epirubicin (sold under the tradename Ellence™), idarubicin (sold under the tradenames Idamycin®, Idamycin PFS®), and mitomycin C (sold under the tradename Mutamycin®);

(xvii) Anti-mitotic agents such as Docetaxel (sold under the tradename Taxotere® by Sanofi-Aventis);

(xviii) Proteasome inhibitors such as Bortezomib (sold under the tradename Velcade®);

(xix) Plant Alkaloids such as Paclitaxel protein-bound (sold under the tradename Abraxane®), vinblastine (also known as vinblastine sulfate, vincaleukoblastine and VLB, sold under the tradenames Alkaban-AQ® and Velban®), vincristine (also known as vincristine sulfate, LCR, and VCR, sold under the tradenames Oncovin® and Vincasar Pfs®), vinorelbine (sold under the tradename Navelbine®), and paclitaxel (sold under the tradenames Taxol and Onxal™);

(xx) Glucocorticosteroids such as Hydrocortisone (also known as cortisone, hydrocortisone sodium succinate, hydrocortisone sodium phosphate, and sold under the tradenames Ala-Cort®, Hydrocortisone Phosphate, Solu-Cortef®, Hydrocort Acetate®

and Lanacort®), dexamethazone ((8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*R*,17*R*)-9-fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one), prednisolone (sold under the tradenames Delta-Cortel®, Orapred®, Pediapred® and Prelone®), prednisone (sold under the tradenames Deltasone®, Liquid Red®, Meticorten® and Orasone®), and methylprednisolone (also known as 6-Methylprednisolone, Methylprednisolone Acetate, Methylprednisolone Sodium Succinate, sold under the tradenames Duralone®, Medralone®, Medrol®, M-Prednisol® and Solu-Medrol®);

(xxi) Tumor necrosis factor–related apoptosis-inducing ligand (TRAIL, also referred to as Apo2 Ligand) receptor agonists such as TRAIL antibodies (e.g., Adecatumumab, Belimumab, Cixutumumab, Conatumumab, Figitumumab, Iratumumab, Lexatumumab, Lucatumumab, Mapatumumab, Necitumumab, Ofatumumab, Olaratumab, Panitumumab, Pritumumab, Pritumumab, Robatumumab, Votumumab, Zalutumumab, and TRAIL (referred to as anti-DR-5) antibodies described in US Patent No. 7,229,617 and PCT Publication No. WO2008/066854, incorporated herein by reference), and recombinant TRAIL (e.g., Dulanermin (also known as AMG 951 (rhApo2L/TRAIL)); and

(xxii) Tumor-vascular disrupting agents such as Vadimezan (5,6-dimethyl-9-oxo-9H-Xanthene-4-acetic acid described in US Patent No. 5,281,620).

A preferred anti-cancer agent for use in combination with a compound of the present invention is paclitaxel.

Another preferred anti-cancer agent for use in combination with a compound of the present invention is a PI3K inhibitor (e.g., 2-Methyl-2-[4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydroimidazo[4,5-c]quinolin-1-yl]phenyl]propionitrile).

Another preferred anti-cancer agent for use in combination with a compound of the present invention is a TRAIL (or anti-DR-5) antibody or recombinant TRAIL.

Suitable therapeutic agents for adjunct therapy include steroids, anti-inflammatory agents, anti-histamines, antiemetics, and other agents well-known to those of skill in art for use in improving the quality of care for patients being treated for the diseases, conditions, or disorders described herein.

The compound of the present invention or pharmaceutical composition thereof for use in humans is typically administered intravenously *via* infusion at a therapeutic dose of less than or equal to about 100 mg/kg, 75 mg/kg, 50 mg/kg, 25 mg/kg, 10 mg/kg, 7.5 mg/kg, 5.0 mg/kg, 3.0 mg/kg, 1.0 mg/kg, 0.5 mg/kg, 0.05 mg/kg or 0.01 mg/kg, but preferably not less than about 0.0001 mg/kg. The dosage may depend upon the infusion rate at which the formulation is administered. In general, the therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is

dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, pharmacist, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

The above-cited dosage properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, *e.g.*, mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The compounds of the present invention can be applied *in vitro* in the form of solutions, *e.g.*, aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, *e.g.*, as a suspension or in aqueous solution. The dosage *in vitro* may range between about 10^{-3} molar and 10^{-9} molar concentrations.

In general, a therapeutically effective amount of a compound of the present invention is administered to a patient in need of treatment. The term "a therapeutically effective amount" of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc.

In one non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of a compound of the present invention, when administered to a subject, is effective to (1) at least partially alleviate, inhibit, prevent and/or ameliorate a condition, a disorder or a disease mediated by IAP, or characterized by normal or abnormal activity of such IAP mediation or action; or (2) enhance programmed cancerous cell death (apoptosis). Preferably, when administered to a cancer cell, or a tissue, or a non-cellular biological material, or a medium, the compound of the present invention is effective to at least partially increase or enhance apoptosis. Not to be bound by any particular mechanism, a compound of the present may inhibit the binding of IAP protein to a caspase protein and/or may initiate degradation of XIAP, cIAP1 and/or cIAP2, directly or indirectly.

In one embodiment, a method for inhibiting the binding of an IAP protein to a caspase protein is provided which comprises contacting the IAP protein with a compound of the present invention.

In another embodiment, a method of inducing apoptosis in a tumor or cancer cell is provided which comprises introducing into the cell, a compound of the present invention.

In yet another embodiment, a method of sensitizing a tumor or cancer cell to an apoptotic signal is provided which comprises introducing into the cell a compound of the present invention.

In yet another embodiment, a method for treating a disease, disorder, or condition associated with the over expression of an IAP in a mammal, is provided which comprises administering to the mammal an effective amount of a compound of the present invention.

In yet another embodiment, a method for treating cancer in a mammal is provided which comprises administering to a mammal in need of such treatment an effective amount of a compound of the present invention. A particularly useful method is the treatment of breast cancer.

As used herein, the term “subject” refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (*e.g.*, humans, male or female), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. Preferably, the subject is a human.

As used herein, the term “inhibit”, "inhibition" or “inhibiting” refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term “treat”, “treating" or "treatment" of any disease or disorder, refers (i) to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof); (ii) to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient; or (iii) to preventing or delaying the onset or development or progression of the disease or disorder. In general, the term “treating” or “treatment” describes the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of a compound of the present invention to prevent the onset of the symptoms or complications, alleviating the symptoms or complications, or eliminating the disease, condition or disorder.

As used herein, a subject is “in need of” a treatment if such subject would benefit biologically, medically or in quality of life from such treatment (preferably, a human).

Another aspect of the invention is a product comprising a compound of the present invention and at least one other therapeutic agent (or pharmaceutical agent) as a combined preparation for simultaneous, separate or sequential use in therapy to enhance apoptosis.

In the combination therapies of the invention, the compound of the present invention and the other therapeutic agent may be manufactured and/or formulated by the

same or different manufacturers. Moreover, the compound of the present invention and the other therapeutic (or pharmaceutical agent) may be brought together into a combination therapy: (i) prior to release of the combination product to physicians (*e.g.* in the case of a kit comprising the compound of the invention and the other therapeutic agent); (ii) by the physician themselves (or under the guidance of the physician) shortly before administration; (iii) in the patient themselves, *e.g.* during sequential administration of the compound of the invention and the other therapeutic agent.

Accordingly, the invention provides the use of a compound of the present invention for treating a disease or condition by inhibiting IAPs (or enhancing apoptosis), wherein the medicament is prepared for administration with another therapeutic agent. The invention also provides for the use of another therapeutic agent, wherein the medicament is administered as a combination of a compound of the present invention with the other therapeutic agent.

Embodiments of the present invention are illustrated by the following Examples. It is to be understood, however, that the embodiments of the invention are not limited to the specific details of these Examples, as other variations thereof will be known, or apparent in light of the instant disclosure, to one of ordinary skill in the art.

EXAMPLES

Unless specified otherwise, starting materials are generally available from commercial sources such as Aldrich Chemicals Co. (Milwaukee, Wis.), Lancaster Synthesis, Inc. (Windham, N.H.), Acros Organics (Fairlawn, N.J.), Maybridge Chemical Company, Ltd. (Cornwall, England), Tyger Scientific (Princeton, N.J.), and AstraZeneca Pharmaceuticals (London, England).

The following abbreviations used herein below have the corresponding meanings:

DIEA or DIPEA: *N*,*N*-Diisopropylethylamine (also known as Hunig's base)

DMF: Dimethylformamide

DMTMM: 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methyl morpholinium chloride

EDC: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

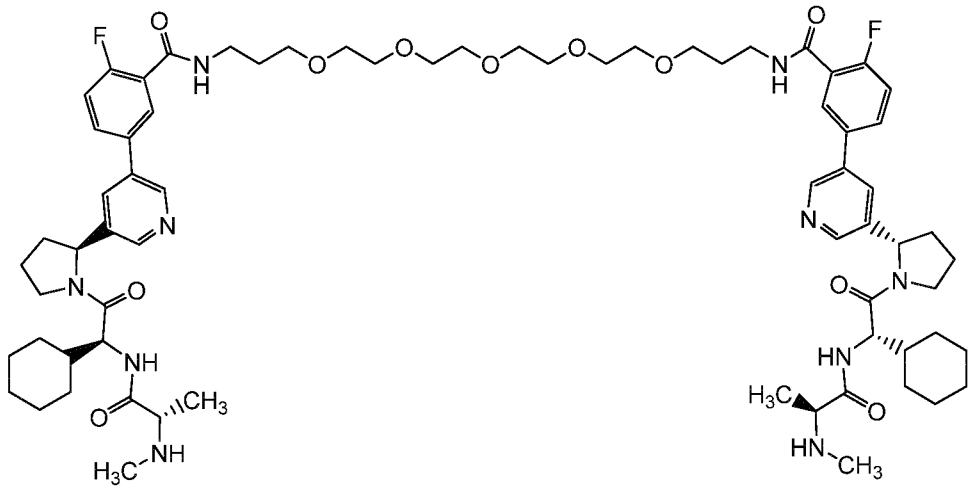
HATU: 2-(1H-7-Azabenzotriazol-1-yl)--1,1,3,3-tetramethyl uronium hexafluorophosphate Methanaminium

TFA: Trifluoroacetic acid

((S)-1-{(S)-2-[(S)-2-(5-Bromo-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxoethylcarbamoyl}-ethyl)-methyl-carbamic acid tert-butyl ester was prepared using the procedures described on page 61 of PCT Patent Application No. WO 2008/045905 A1.

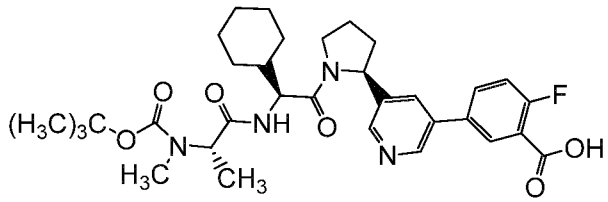
Example 1

Preparation of 5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)-acetyl)pyrrolidin-2-yl)pyridin-3-yl)-N-(1-(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorophenyl)-1-oxo-6,9,12,15,18-pentaoxa-2-azahenicosan-21-yl)-2-fluorobenzamide as the free base (1A), trifluoroacetate salt (1A-1), and citrate salt (1A-2):



(1A)

Preparation of Intermediate 5-[5-((S)-1-{(S)-2-[(S)-2-(tert-Butoxycarbonyl-methyl-amino)-propionylamino]-2-cyclohexyl-acetyl}-pyrrolidin-2-yl)-pyridin-3-yl]-2-fluoro-benzoic acid (I-1A-1a);



(I-1A-1a)

To a mixture of ((S)-1-{(S)-2-[(S)-2-(5-Bromo-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxoethylcarbamoyl}-ethyl)-methyl-carbamic acid tert-butyl ester (2.177 g, 3.95 mmol) and 3-carboxy-4-fluorophenylboronic acid (0.871 g, 4.74 mmol) in toluene (23 mL) and ethanol (7.7 mL) was added an aqueous sodium carbonate solution (1 M, 11.8 mL, 11.8 mmol). Nitrogen was bubbled through the mixture for 15 minutes, then bis(triphenylphosphine)palladium dichloride (0.277 g, 0.395 mmol) was added and the mixture was heated at 80°C for 3 hours. The crude reaction mixture was diluted with water (30 mL) and heptane (30 mL) and filtered through celite. The organic phase from the filtrate was washed with saturated $NaHCO_3$ (10 mL) and water (10 mL) twice. The aqueous washing and the aqueous phase from the original filtrate were combined and were extracted with 1:1 heptane and EtOAc twice and then treated with HCl (12 N) to pH = 3; and were extracted with EtOAc three times. The combined EtOAC layer was

washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the title compound as a yellow solid (2.381g, 99%) used directly without purification in the next step:

^{1}H NMR (400 MHz, CD_3Cl_3 a major component of a rotameric mixture) δ ppm 8.72 - 8.86 (m, 1 H), 8.58 (s, 1 H), 8.25 (dd, *J*=6.76, 2.46 Hz, 1 H), 7.82 (s, 1 H), 7.72 (dt, *J*=6.79, 4.25 Hz, 1 H), 7.15 - 7.26 (m, 1 H), 6.83 (br. s., 1 H), 5.23 - 5.31 (m, 1 H), 4.61 - 4.78 (m, 2 H), 4.04 - 4.18 (m, 1 H), 3.90 (br. s., 1 H), 2.82 (s, 3 H), 2.34 - 2.56 (m, 1 H), 2.12 (br. s., 2 H), 1.90 - 2.01 (m, 1 H), 1.54 - 1.82 (m, 5 H), 1.46 (s, 9 H), 1.35 (d, *J*=7.07 Hz, 3 H), 0.92 - 1.22 (m, 5 H); LCMS calculated for $C_{33}H_{44}FN_4O_6$ 611.3, found 611.5 (ESI *m/e* [M + H^+]); t_R 1.54 minutes (Insertsil C8-3, 3 CM X 3 mm X 3.0 uM column: mobile phase: 5-95% acetonitrile/water with 0.1% formic acid, at 2 mL/minute over 2 minutes).

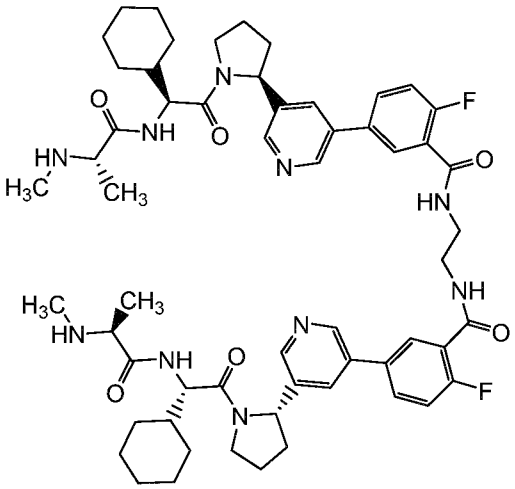
Preparation of Compound 1A:

To 5-[5-((S)-1-{(S)-2-[(S)-2-(tert-Butoxycarbonyl-methyl-amino)-propionylamino]-2-cyclohexyl-acetyl}-pyrrolidin-2-yl)-pyridin-3-yl]-2-fluoro-benzoic acid (I-1A-1a: 300 mg, 0.49 mmol) in anh. DMF (1.5 mL) at 0°C was added EDC hydrogen chloride salt (102 mg, 0.532 mmol). The mixture was stirred at 0°C for 5 minutes and then 3-[2-(2-{2-[2-(3-amino-propoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-propylamine (63 mg, 0.21 mmol) was added. After being stirred at ambient temperature for 3 hours, the reaction mixture was diluted with saturated aqueous sodium carbonate and extracted with EtOAc three times. The organic phase was washed sequentially with saturated aqueous sodium carbonate, 10% citric acid twice, water and brine, then dried over anhydrous sodim sulfate; and concentrated under reduced pressure. To the resulting brown residue was added CH_2Cl_2 (1.5 mL) and TFA (1.5 mL). The reaction mixture was stirred for 1.5 hours and concentrated under reduced pressure to provide the titled compound as a tetra TFA salt (1A-1: 72 mg, 20% for two steps) following preparative HPLC purification (Sunfire: 30 X 100 mm X 5 uM column, 25 - 50% acetonitrile in water with 0.05% of TFA in 10 minute gradient) and lyophilization of the desired fractions. The TFA salt (1A-1) was converted to citric acid salt (1A-2) by the following procedure: the TFA salt (1A-1) mentioned above (43 mg) was dissolved in CH_2Cl_2 (10 mL), and treated with saturated aqueous $NaHCO_3$ (0.3 mL) and dried over anhydrous Na_2SO_4. The result organic solution was washed with water twice (2 mL each), dried over anhydrous Na_2SO_4 and concentrated to give a foaming residue (44 mg) as a free base (1A). To this material dissolved in methanol (0.7 mL) was added citric acid (13 mg, 0.068 mmol) and water (0.7 mL). The clear solution was stirred for 5 minutes and lyophilized to afford the citrate salt (1A-2: 3.3 equivalents) as a white solid (41 mg, 75% conversion):

^{19}F NMR(400 MHz, CD_3OD) δ ppm -115.25; ^{1}H NMR (400 MHz, CD_3OD), δ ppm 8.70 (s, 2 H), 8.47 – 8.44 (m, 2 H), 8.32 – 7.98 (m, 2 H), 7.93 (s, 2 H), 7.86 – 7.80 (m, 2 H), 7.35 (t, J = 9.1 Hz, 2 H), 5.49 – 5.12 (m, 2 H), 4.60 – 4.26 (m, 2 H), 4.15 – 4.09 (m, 2 H), 3.99 – 3.78 (m, 4 H), 3.61 – 3.54 (m, 20 H), 3.50 (t, J = 6.6 Hz, 2 H), 3.31 (m, 2 H), 2.66 (s, 5 H), 2.54 (s, 1 H), 2.49 – 2.40 (m, 2 H), 2.19 – 2.10 (m, 2 H), 2.08 – 2.03 (m, 2 H), 1.79 – 1.87 (m, 6 H), 1.80 – 1.73 (m, 4 H), 1.64 – 1.60 (m, 8 H), 1.47 (d, J = 6.5 Hz, 6 H), 1.34 – 1.28 (m, 2 H), 1.19 – 1.13 (m, 6 H),1.07 – 1.02 (m, 2 H). Citrate signals: 2.70-2.87 (m, 13.2 H); LC-HRMS calculated for $C_{70}H_{99}F_2N_{10}O_{11}$: 1293.7463; found 1293.7457 (ESI m/e [M + H^+]; t_R 3.11 minutes (Insertsil ODS3, 100 X 3 mm C18 column: mobile phase: 5-95% acetonitrile/water with 0.1% formic acid, at 1 mL/minute over 7.75 minutes.). Purity: >98 % by UV 254/214 nm.

Example 2

Preparation of (S,S,S)-N,N'-(ethane-1,2-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide) as the free base (2A), trifluoroacetate salt (2A-1), and citrate salt (2A-2):



(2A)

To 5-[5-((S)-1-{(S)-2-[(S)-2-(tert-Butoxycarbonyl-methyl-amino)-propionylamino]-2-cyclohexyl-acetyl}-pyrrolidin-2-yl)-pyridin-3-yl]-2-fluoro-benzoic acid ((I-1A-1a: 633 mg, 0.1.036 mmol) in anhydrous THF (2 mL) was added DIPEA (0.757 mL, 4.33 mmol) under nitrogen. The reaction flask was kept in an ice bath for a few minutes. Ethane-1,2-diamine (0.031 mL, 0.467 mmol) was added followed by DMTMM (466 mg, 1.685 mmol). After being stirred for 4 hours at ambient temperature, the reaction mixture was diluted with EtOAc, and washed sequentially with 0.5 M citric acid twice, water and brine each, dried over anhydrous sodim sulfate; and concentrated under reduced pressure to provide a white foam. The crude compound was purified *via* Analogix column using heptane: EtOAc (0 to 100%) followed by EtOAc: MeOH (0 to 20%) to yield the boc-protected titled

compound (190 mg, 33% yield, Purity: 98% by UV 254/214 nM). To this product (185 mg, 0.149 mmol) was added CH_2Cl_2 (4.0 mL) and the reaction flask was kept in an ice bath under nitrogen. TFA (0.286 mL, 3.71 mmol) was added. The reaction mixture was stirred at an ambient temperature for 2 hours. It was then concentrated under reduced pressure and dried under high vacuum for 30 minutes to obtain a TFA salt (2A-1). This product was dissolved in a minimal amount of MeOH and passed though two PL-HCO3 MP SPE columns (500 mg in a 6 mL tube) in sequence that were pre-wetted with MeOH. The column was eluted with DCM:MeOH (25:75) by gravity. The washings were combined and concentrated under reduced pressure and dried *in vacuo* to provide the free base (2A: 144 mg, 93% yield, Purity: 99% by UV 254/214 nM). The free base (2A: 190 mg, 0.182 mmol) was dissolved in 8 mL MeOH: 20 mL EtOAc solution. The solution was sonicated for 30 minutes and filtered to remove the cloudiness. To the filtrate was then added freshly prepared citric acid (2.15 eq of 0.07 M, 5.58 mL, 0.391 mmol) in EtOAc solution resulting in formation of a white precipitate. The mixture was stirred for 1 hour and the solid was filtered off. The solid was then washed with 3% MeOH : EtOAc to provide a white powder. The solid residue (116 mg, 0.110 mmol) that was resulted from the sonication above was dissolved in EtOH (9 mL): water (4 mL). To this solution was then added freshly prepared citric acid (2.0 equivalents of 0.07 M, 3.14 mL, 0.220 mmol) in EtOAc solution. The mixture was stirred for 1 hour and concentrated under reduced pressure and combined with the earlier isolated white powder, then dissolved in water and lyophilized to afford the citrate salt (2A-2: 2.1 equivalents) as a white fluffy solid (190 mg, 73% yield).

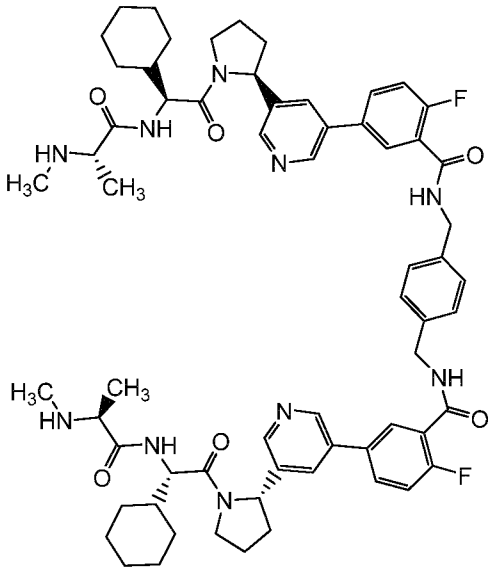
^{19}F NMR(400 MHz, CD_3OD) δ ppm -116.32; 1H NMR (400 MHz, CD_3OD) δ ppm 8.65 - 8.68 (m, 2 H), 8.42 - 8.46 (m, 2 H), 7.98 - 8.31 (m, 2 H), 7.89 - 7.96 (m, 2 H), 7.78 - 7.88 (m, 2 H), 7.33 - 7.39 (m, 2 H), 5.12 (dd, *J*=8.08, 6.06 Hz, 2 H), 4.59 (d, *J*=7.58 Hz, 2 H), 4.05 - 4.28 (m, 2 H), 3.90 – 3.98 (m, 2 H), 3.75 - 3.83 (m, 2 H), 3.63 - 3.71 (m, 5 H), 2.62 (s, 5 H), 2.41 - 2.51 (m, 2 H), 2.10 - 2.18 (m, 2 H), 2.01 - 2.09 (m, 2 H), 1.91 - 2.00 (m, 2 H), 1.71 - 1.81 (m, 4 H), 1.57 - 1.67 (m, 8 H), 1.44 (d, *J*=7.07 Hz, 5 H), 1.29 (d, *J*=7.07 Hz, 1 H), 1.00 - 1.26 (m, 10 H). Citrate signals 2.70 - 2.87 (m, 8 H); LC-HRMS calculated for $C_{58}H_{75}F_2N_{10}O_6$: 1045.5893; found 1045.5880 (ESI *m/e* [M + H^+]); t_R 3.16 minutes (Insertsil ODS3, 100 X 3 mm C18 column: mobile phase: 5-95% acetonitrile/water with 0.1% formic acid, at 1 mL/minute over 7.75 minutes); Purity: >99% by UV 254/214 nM.

Alternatively, the free base was converted to the corresponding citrate using the following procedure. The free base obtained from a TFA salt of a desired dimeric product is dissolved in a 15% MeOH:EtOAc mixture by adding MeOH first to obtain a clear solution followed by EtOAc to obtain a final solution of 0.054 M. To this solution is then

added freshly prepared citric acid (2.0 eq of 0.07 M) in EtOAc solution, resulting in formation of a white precipitate. After being stirred for 1 hour, the resuling white precipitates are filtered off, then dissolved in water and lyophilized to afford the citrate salt (2 equivalents) of the desired dimeric product as a white fluffy solid.

The following compounds below were prepared using procedures analogous to those described above for the preparation of Example (1A), (1A-1), (1A-2), (2A), (2A-1), or (2A-2) using the appropriate starting materials.

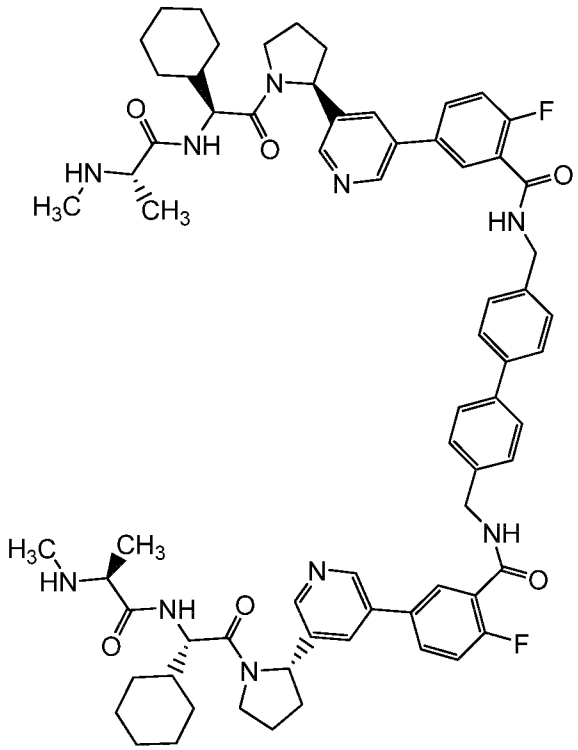
Preparation of (S,S,S)-N,N'-(1,4-phenylenebis(methylene))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide) as the free base (2B) and trifluoroacetate salt (2B-1):



(2B)

The TFA salt (4 equivalents) was prepared as a white solid (38 mg, 16% in two steps). LC-HRMS calculated for $C_{64}H_{79}F_2N_{10}O_6$ 1121.6152; found 1121.6168 (ESI *m/e* [M + H^+]); t_R 3.19 minutes (Insertsil ODS3, 100 X 3 mm C18 column: mobile phase: 5-95% acetonitrile/water with 0.1% formic acid, at 1 mL/minute over 7.75 minutes); purity 100% by UV 254/214 nm.

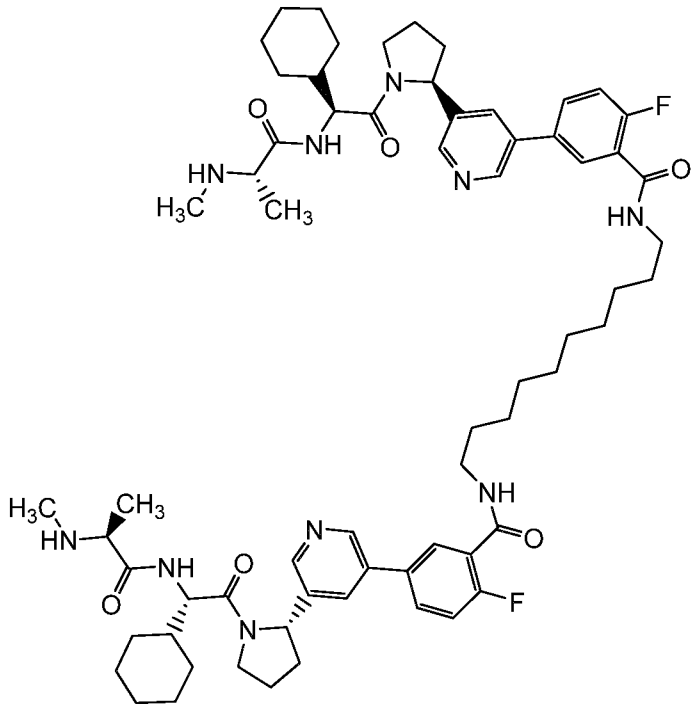
Preparation of (S,S,S)-N,N'-(biphenyl-4,4'-diylbis(methylene))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide) as the free base (2C), trifluoroacetate salt (2C-1), and citrate salt (2C-2):



(2C)

The citrate salt (2.4 equivalents) was prepared as a white solid (51 mg, 16% in three steps). LC-HRMS calculated for $C_{70}H_{83}F_2N_{10}O_6$: 1197.6465; found 1197.6464 (ESI *m/e* [M + H^+]); t_R 3.49 minutes (Insertsil ODS3, 100 X 3 mm C18 column: mobile phase: 5-95% acetonitrile/water with 0.1% formic acid, at 1 mL/minute over 7.75 minutes); purity 100% by UV 254/214 nm.

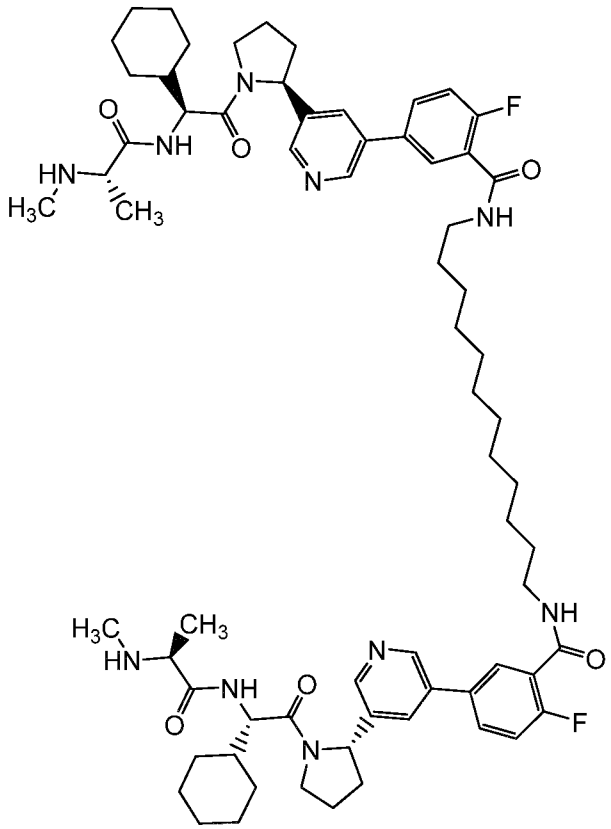
Preparation of (S,S,S)-N,N'-(decane-1,10-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide) as the free base (2D), trifluoroacetate salt (2D-1), and citrate salt (2D-2):



(2D)

The citrate salt (2.2 equivalents) was prepared as a white solid (19 mg, 10% in three steps). LC-HRMS calculated for $C_{66}H_{91}F_2N_{10}O_6$ 1157.7091; found 1157.7115 (ESI *m/e* [M + H^+]); t_R 3.63 minutes (Insertsil ODS3, 100 X 3 mm C18 column: mobile phase: 5-95% acetonitrile/water with 0.1% formic acid, at 1 mL/minute over 7.75 minutes); purity 97% by UV 254/214 nm.

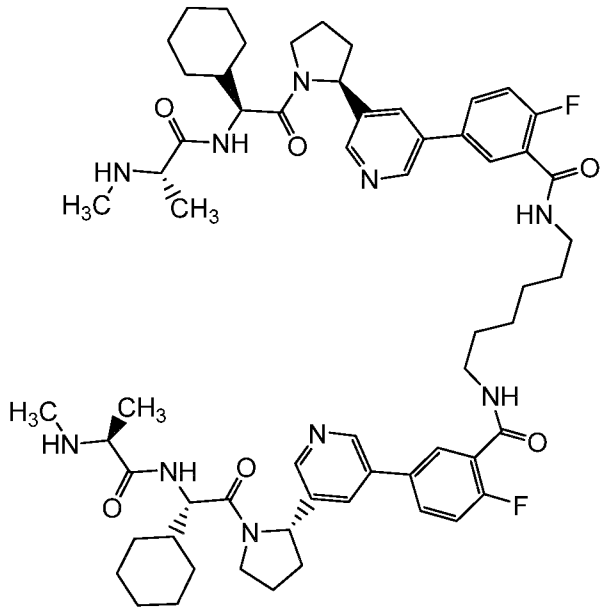
Preparation of (S,S,S)-N,N'-(dodecane-1,12-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide) as the free base (2E), trifluoroacetate salt (2E-1), and citrate salt (2E-2):



(2E)

The citrate salt (2.9 equivalents) was prepared as a white solid (49 mg, 19% in three steps). LC-HRMS calculated for $C_{68}H_{95}F_2N_{10}O_6$ 1185.7404; found 1185.7461 (ESI *m/e* [M + H^+]); t_R 3.82 minutes (Insertsil ODS3, 100 X 3 mm C18 column: mobile phase: 5-95% acetonitrile/water with 0.1% formic acid, at 1 mL/minute over 7.75 minutes); purity 96% by UV 254/214 nm.

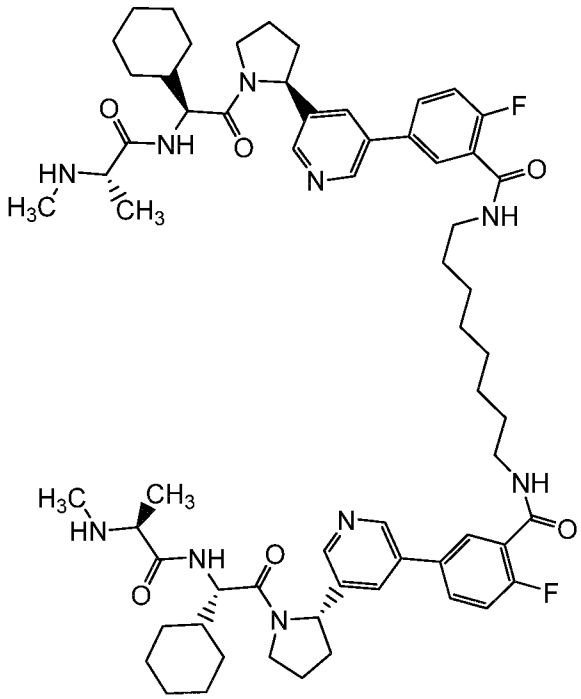
Preparation of (S,S,S)-N,N'-(hexane-1,6-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide) as the free base (2F) and trifluoroacetate salt (2F-1):



(2F)

The TFA salt (4 equivalents) was prepared as a white solid (72 mg, 27% in two steps). LC-HRMS calculated for $C_{62}H_{83}F_2N_{10}O_6$ 1101.6465; found 1101.6511 (ESI *m/e* [M + H^+]); t_R 3.19 minutes (Insertsil ODS3, 100 X 3 mm C18 column: mobile phase: 5-95% acetonitrile/water with 0.1% formic acid, at 1 mL/minute over 7.75 minutes); purity 99% by UV 254/214 nm.

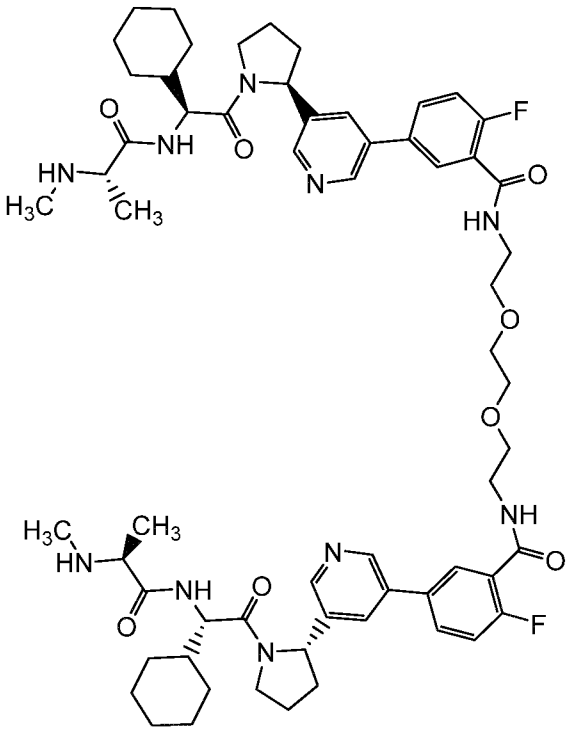
Preparation of (S,S,S)-N,N'-(octane-1,8-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide) as the free base (2G) and trifluoroacetate salt (2G-1):



(2G)

The TFA salt (4 equivalents) was prepared as a white solid (72 mg, 27% in two steps). LC-HRMS calculated for $C_{64}H_{87}F_2N_{10}O_6$ 1129.6778; found 1129.6830 (ESI *m/e* [M + H^+]); t_R 3.19 minutes (Insertsil ODS3, 100 X 3 mm C18 column: mobile phase: 5-95% acetonitrile/water with 0.1% formic acid, at 1 mL/minute over 7.75 minutes); purity 98% by UV 254/214 nm.

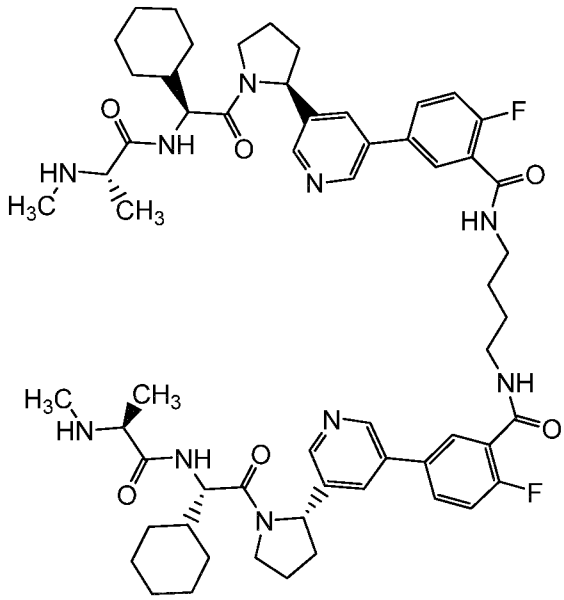
Preparation of (S,S,S)-N,N'-(2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide) as the free base (2H) and trifluoroacetate salt (2H-1):



(2H)

The TFA salt (2.5 equivalents) was prepared as a white solid (5 mg, 2% in two steps). ^{19}F NMR (400 MHz, CD_3OD) δ ppm -116.06; TFA signal: -78.50. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.68 - 8.81 (m, 2 H), 8.45 - 8.61 (m, 2 H), 7.98 - 8.37 (m, 4 H), 7.78 - 7.90 (m, 2 H), 7.27 - 7.41 (m, 2 H), 5.10 - 5.55 (m, 2 H), 4.59 (m, 2 H), 3.52 - 4.30 (m, 18 H), 2.65 (s, 4.6 H), 2.54 (s, 1.4 H), 1.52 - 2.52 (m, 20 H), 1.47 (d, *J*=6.6 Hz, 4.6 H), 1.36 (d, *J*=6.6 Hz, 1.4 H), 1.06 - 1.32 (m, 10 H); LC-HRMS calculated for $C_{62}H_{83}F_2N_{10}O_8$ 1133.6363; found 1133.6339 (ESI *m/e* [M + H^+]); t_R 3.90 minutes (Insertsil ODS3, 100 X 3 mm C18 column: mobile phase: 5-95% acetonitrile/water with 0.1% formic acid, at 1 mL/minute over 7.75 minutes); purity 99% by UV 254/214 nm.

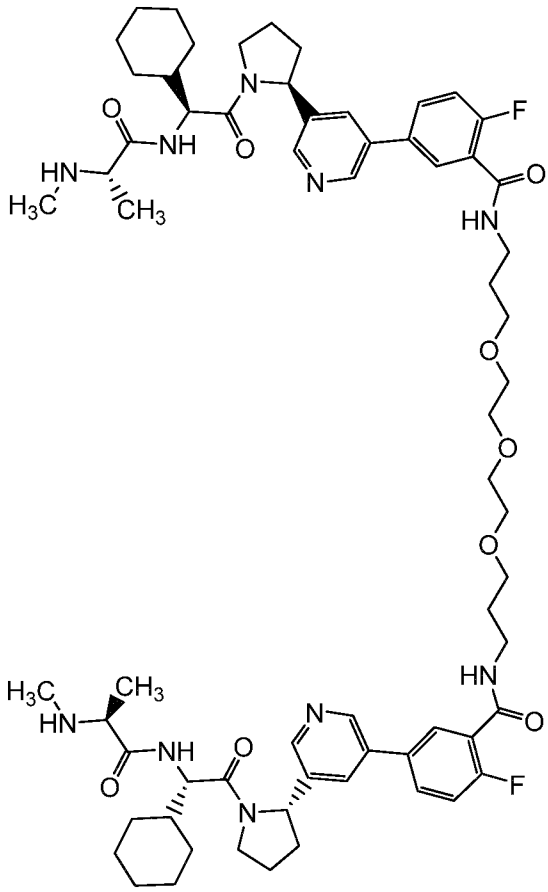
Preparation of (S,S,S)-N,N'-(butane-1,4-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide) as the free base (2I) and trifluoroacetate salt (2I-1):



(2I)

The TFA salt (2 equivalents) was prepared as a white solid (3 mg, 1% in two steps). ^{19}F NMR (400 MHz, CD_3OD) δ ppm -116.50; TFA signal: -78.50. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.26 - 8.81 (m, 5 H), 7.78 - 8.05 (m, 5 H), 7.28 - 7.41 (m, 2 H), 5.07 - 5.52 (m, 2 H), 4.54 - 4.63 (m, 2 H), 3.43 - 4.29 (m, 10 H), 2.66 (s, 4.6 H), 2.54 (s, 1.4 H), 1.51 - 2.52 (m, 24 H), 1.47 (d, *J*=7.1 Hz, 4.6 H) 1.01 - 1.40 (m, 11.4 H);LC-HRMS calculated for $C_{60}H_{79}F_2N_{10}O_6$ 1073.6152; found 1073.6151 (ESI *m/e* [M + H^+]); t_R 2.96 minutes (Insertsil ODS3, 100 X 3 mm C18 column: mobile phase: 5-95% acetonitrile/water with 0.1% formic acid, at 1 mL/minute over 7.75 minutes); purity 99% by UV 254/214 nm.

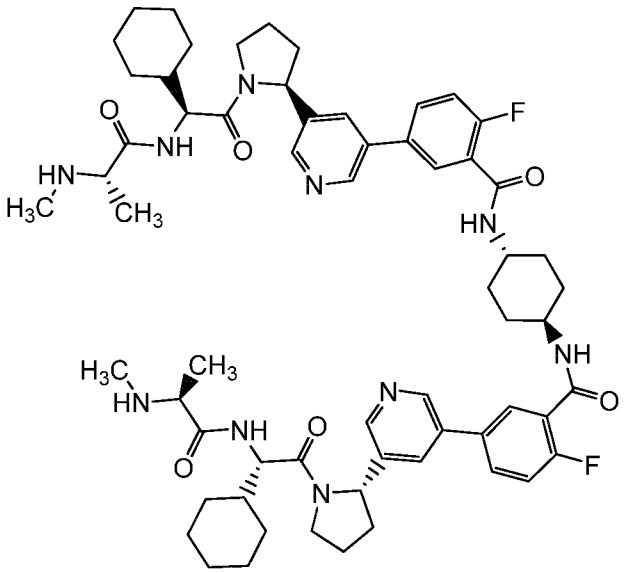
Preparation of (S,S,S)-N,N'-(3,3'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(propane-3,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide) as the free base (2J), trifluoroacetate salt (2J-1), and citrate salt (2J-2):



(2J)

The citrate salt (3 equivalents) was prepared as a white solid (13 mg, 5% in three steps). LC-HRMS calculated for $C_{66}H_{91}F_2N_{10}O_9$ 1205.6939; found 1205.6893 (ESI *m/e* [M + H^+]); t_R 4.22 minutes (Insertsil ODS3, 100 X 3 mm C18 column: mobile phase: 5-95% acetonitrile/water with 0.1% formic acid, at 1 mL/minute over 7.75 minutes); purity 100% by UV 254/214 nm.

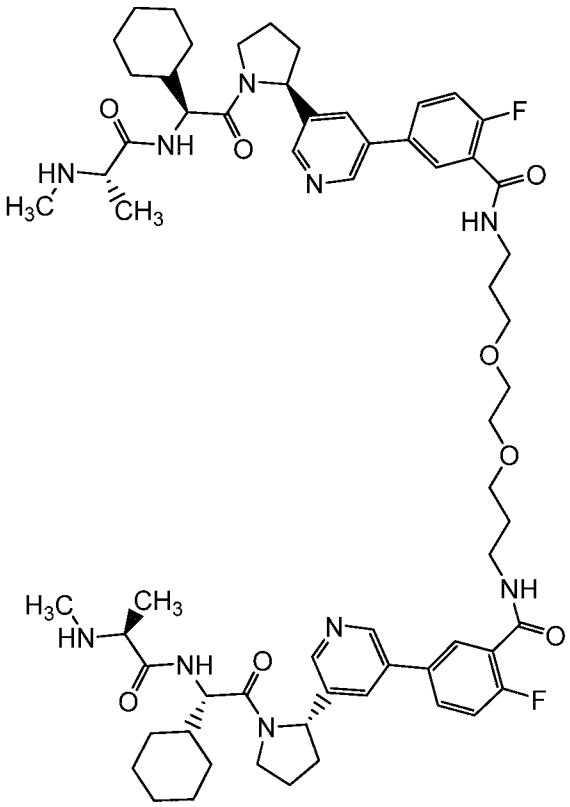
Preparation of (S,S,S)-N,N'-((1S,4S)-cyclohexane-1,4-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide) as the free base (2K) and trifluoroacetate salt (2K-1):



(2K)

The TFA salt (1 equivalent) was prepared as a white solid (9 mg, 4% in two steps). LC-HRMS calculated for $C_{62}H_{81}F_2N_{10}O_6$ 1099.6309; found 1099.6356 (ESI *m/e* [M + H^+]); t_R 3.06 minutes (Insertsil ODS3, 100 X 3 mm C18 column: mobile phase: 5-95% acetonitrile/water with 0.1% formic acid, at 1 mL/minute over 7.75 minutes); purity 100% by UV 254/214 nm.

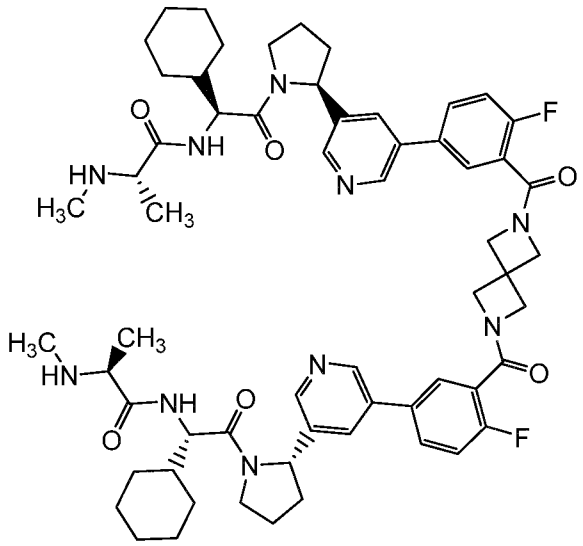
Preparation of (S,S,S)-N,N'-(3,3'-(ethane-1,2-diylbis(oxy))bis(propane-3,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide) as the free base (2L), trifluoroacetate salt (2L-1), and citrate salt (2L-2):



(2L)

The citrate salt (2 equivalents) was prepared as a white solid (29 mg, 8% in three steps). LC-HRMS calculated for $C_{64}H_{87}F_2N_{10}O_8$ 1161.6676; found 1161.6671 (ESI *m/e* [M + H^+]); t_R 4.19 minutes (Insertsil ODS3, 100 X 3 mm C18 column: mobile phase: 5-95% acetonitrile/water with 0.1% formic acid, at 1 mL/minute over 7.75 minutes); purity 100% by UV 254/214 nm.

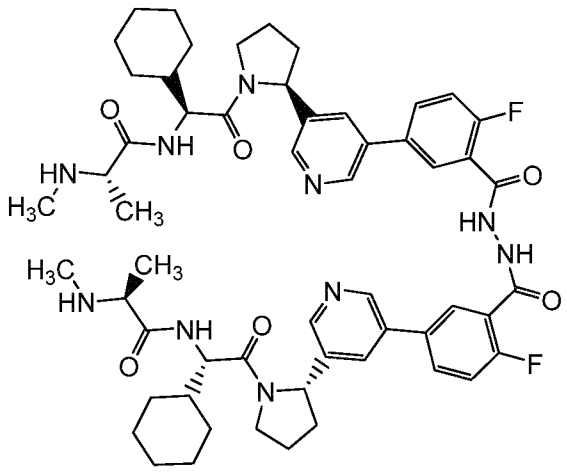
Preparation of (2S,2'S)-N,N'-((1S,1'S)-2,2'-((2S,2'S)-2,2'-(5,5'-(3,3'-(2,6-diazaspiro[3.3]heptane-2,6-diylbis(oxomethylene))bis(4-fluoro-3,1-phenylene))bis(pyridine-5,3-diyl))bis(pyrrolidine-2,1-diyl))bis(1-cyclohexyl-2-oxoethane-2,1-diyl))bis(2-(methylamino)propanamide) as the free base (2M), trifluoroacetate salt (2M-1), and citrate salt (2M-2):



(2M)

The citrate salt (2 equivalents) was prepared as a white solid (44 mg, 26% in three steps). LC-HRMS calculated for $C_{61}H_{77}F_2N_{10}O_6$ 1083.5996; found 1083.5948 (ESI *m/e* [M + H^+]); t_R 3.99 minutes (Insertsil ODS3, 100 X 3 mm C18 column: mobile phase: 5-95% acetonitrile/water with 0.1% formic acid, at 1 mL/minute over 7.75 minutes); purity 100% by UV 254/214 nm.

Preparation of (2S,2'S)-N,N'-((1S,1'S)-2,2'-((2S,2'S)-2,2'-(5,5'-(3,3'-(hydrazine-1,2-diylbis(oxomethylene))bis(4-fluoro-3,1-phenylene))bis(pyridine-5,3-diyl))bis(pyrrolidine-2,1-diyl))bis(1-cyclohexyl-2-oxoethane-2,1-diyl))bis(2-(methylamino)propanamide) as the free base (2N), trifluoroacetate salt (2N-1), and citrate salt (2N-2):



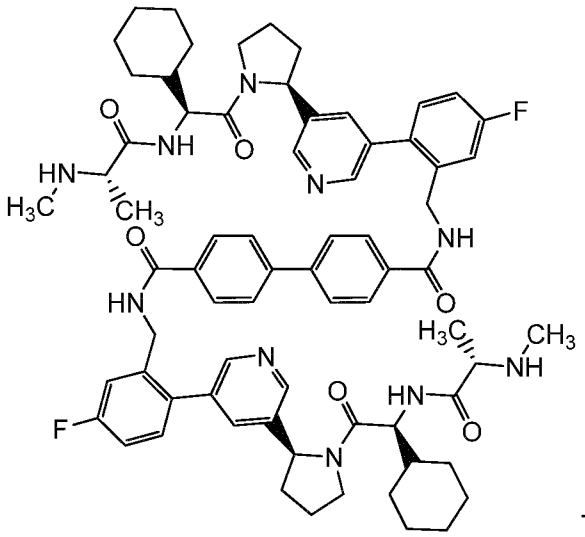
(2N)

The citrate salt (5 equivalents) was prepared as a white solid (13 mg, 3% in three steps). LC-HRMS calculated for $C_{56}H_{71}F_2N_{10}O_6$ 1017.5526; found 1017.5494 (ESI *m/e* [M + H^+]); t_R 6.18 minutes (Insertsil ODS3, 100 X 3 mm C18 column: mobile phase: 5-

95% acetonitrile/water with 0.1% formic acid, at 1 mL/minute over 7.75 minutes); purity 99% by UV 254/214 nm.

Example 3

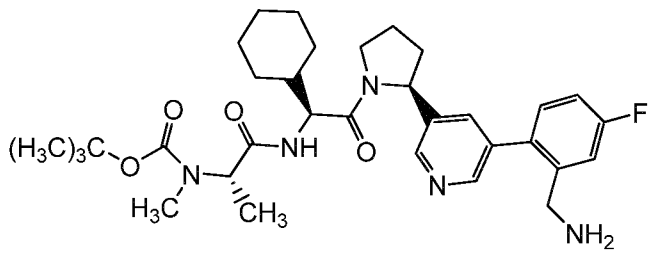
Preparation of N4,N4'-bis(2-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-5-fluorobenzyl)biphenyl-4,4'-dicarboxamide, trifluoroacetate (3A):



TFA salt

(3A)

Preparation of Intermediate [(S)-1-((S)-2-{(S)-2-[5-(2-Aminomethyl-4-fluoro-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethylcarbamoyl)-ethyl]-methyl-carbamic acid tert-butyl ester (I-3A-3a):



(I-3A-3a)

To a mixture of (S)-1-{(S)-2-[(S)-2-(5-Bromo-pyridin-3-yl)-pyrrolidin-1-yl]-1-cyclohexyl-2-oxoethylcarbamoyl}-ethyl)-methyl-carbamic acid tert-butyl ester (0.400 g, 0.725 mmol, and 2-aminomethyl-4-fluorophenylboronic acid (0.148 g, 0.725 mmol) in toluene (10.9 mL) and ethanol (3.6 mL) was added sodium carbonate (0.461, 4.35 mmol). Nitrogen was bubbled through the mixture for 15 minutes, then bis(triphenylphosphine)palladium dichloride (0.102 g, 0.145 mmol) was added and the mixture was heated at 80°C fo 6 hours. After cooling the mixture to ambient temperature, more reagents were added: 2-aminomethyl-4-fluorophenylboronic acid (0.074 g, 0.36 mmol) and bis(triphenylphosphine)palladium dichloride (0.051 g, 0.073

mmol). The mixture was heated at 80°C fo 6 hours. The crude reaction mixture was diluted with water (10 mL) and extracted with EtOAc twice (10 mL each). The organic layer was washed with HCl twice (1N, 15 and 5 mL). All aqueous layers were combined, then treated with saturated aqueous Na_2CO_3 until basic and extracted with EtOAc three times. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford a yellow solid (436 mg). The yellow solid was used directly in the next step without purification. This material contains a des-Br analog of the starting material as a major impurity by LC-HRMS (calculated for $C_{26}H_{41}N_4O_4$ 473.3130, found ESI *m/e* 473.3159 ($M+H^+$); average 22% by UV 254/214 nm; t_R 4.17 minutes) and the titled compound: LC-HRMS calculated for $C_{33}H_{47}FN_5O_4$: 596.3612, found 596.3611 (ESI *m/e* [M + H^+]); t_R 3.72 minutes (Insertsil ODS3, 100 X 3 mm C18 column: mobile phase: 5-95% acetonitrile/water with 0.1% formic acid, at 1 mL/minute over 7.75 minutes). Purity: average 62% by UV 254/214 nM.

Preparation of the title compound (3A):

To biphenyl-4,4'-dicarboxylic acid (30 mg, 0.12 mmol) and [(S)-1-((S)-2-{(S)-2-[5-(2-aminomethyl-4-fluoro-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethylcarbamoyl)-ethyl]-methyl-carbamic acid tert-butyl ester (I-3A-3a: crude 192 mg, 0.322 mmol) in anhydrous DMF (1 mL) at 0°C was added EDC hydrogen chloride salt (52 mg, 0.27 mmol). The mixture was stirred at 0°C for 15 minutes and then ambient temperature for 18 hours. DIEA (64 µL, 0.38 mmol) was added and the reaction mixture was further stirred at ambient temperature for 2 hours. The mixture was diluted with EtOAc and washed with saturated aqueous Na_2CO_3 twice. The organic layer was washed in sequence with 10% citric acid twice, water and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to provide a brown residue. This material was treated with CH_2Cl_2 (1 mL) and TFA (1 mL) and stirred at ambient temperature for 2 hours. The solvent was then removed *in vacuo*. The resulting residue was purified by preparative HPLC (Sunfire: 30 X 100 mm X 5 uM column, 25 - 50% acetonitrile in water with 0.05% of TFA in 10 minute gradient) and lyophilization of the desired fractions to afford a white powder (14 mg, 6.7%) as a tetra TFA salt.

^{19}F NMR (400 MHz, CD_3OD) δ ppm -116.01; TFA signal: -78.50. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.89 - 9.01 (m, 1 H), 8.59 (br. s, 3 H), 7.72 - 8.11 (m, 10 H), 7.09 - 7.45 (m, 6 H), 5.08 - 5.49 (m, 2 H), 4.29 - 4.67 (m, 6 H), 3.65 - 4.15 (m, 6 H), 2.66 (s, 5 H), 2.55 (s, 1 H), 1.51 - 2.49 (m, 20 H), 1.47 (d, *J*=7.0 Hz, 5 H), 1.30 (d, *J*=7.0 Hz, 1 H), 0.96 - 1.25 (m, 10 H); LC-HRMS calculated for $C_{70}H_{83}F_2N_{10}O_6$: 1197.6465; found 1197.6520 (ESI *m/e* [M + H^+]); t_R 3.51 minutes (Insertsil ODS3, 100 X 3 mm C18 column:

mobile phase: 5-95% acetonitrile/water with 0.1% formic acid, at 1 mL/minute over 7.75 minutes); purity >99% by UV 254/214 nm.

PHARMACOLOGICAL DATA

The compounds described herein above were profiled using a cellular assay (using Panc3.27 tumor cells) and a binding assay to determine the competition between the compounds of the present invention and smac7mer peptide for XIAP-BIR3 and cIAP1-BIR3 binding groove occupancy.

Cellular Assay - Treatment of Panc3.27 tumor cells with dimeric IAP antagonists

On day one adherent Panc3.27 cells are plated into two 96-well, clear, flat bottom plates. All wells in row A contain 90uL of media. All wells in rows B-G contain a total volume of 90uL per well and 4000 cells per well for Panc3.27 cell lines. Plates are then incubated overnight for 18 hours at 37°C, 5% CO_2.

On day two cells are treated with the compounds of formula M-L-M'. Treatments are done in triplicate. The compounds are first serially diluted in DMSO and then added to media giving a final concentration of 0.2% DMSO when added to cells. Cells are treated with 10uL of serially diluted compounds of formula M-L-M' at a final concentration of 1000nM, 200nM, 40nM, 8nM, 1.6nM, 0.32nM, 0.06nM, 0.013nM, 0.0026nM, and one untreated well. Plate two is used as a time zero plate.

To measure cell viability 50uL of Cell Titer Glo (CTG) solution is added to row A, media only and B, cells and media. CTG is purchased from Promega Corporation catalog number G7573. The solution is prepared according to manufacturer's instructions. CTG measures the amount of ATP released from viable cells that is proportional to the number of cells in each well. After incubating for ten minutes with CTG plates are measured on a luminescent reader at 700nM wavelength. Read time is approximately one second per well for a 96-well plate.

On day five 50uL of CTG is added to plate one, rows A-G, incubated for 10 minutes at room temperature and read on a luminescent reader. Raw data is adjusted to account for the time zero plate as well as background noise. Triplicate values are averaged and percent control growth is calculated. Percent control growth is calculated using the following logical test: If well read data point (a) is greater than time zero data point (t=0), then 100*[(a) – (t=0)] / [(72hour total growth) – (t=0)], OR 100*[(a) – (t=0)] / [(t=0)]. Data is represented by line graph with the concentration of compound on the x axis and percent control growth on the y axis.

The results are presented in Table 1 below.

Binding Assay

The present method includes utility of a Surface plasmon resonance (SPR)-based biosensor (Biacore™, GE Healthcare, Uppsala, Sweden) to examine competition between the compounds of the present invention and smac7mer peptide for XIAP-BIR3 and cIAP1-BIR3 binding groove occupancy.

Biacore™ utilizes the phenomenon of surface plasmon resonance (SPR) to detect and measure binding interactions. In a typical Biacore experiment, one of the interacting molecules is immobilized on a flexible dextran matrix while the interacting partner is flowed over the derivatized surface. A binding interaction results in an increase in mass on the sensor surface and a corresponding direct change in the refractive index of the medium in the vicinity of the sensor surface. Changes in refractive index or signal are recorded in resonance units (R.U.) Signal changes due to association and dissociation of complexes are monitored in a non-invasive manner, continuously and in real-time, the results of which are reported in the form of a sensorgram.

Solution inhibition assay format:

Biacore™ T100 (GE Healthcare, Uppsala, Sweden) was used to conduct all experiments reported herein. Sensor surface preparation and interaction analyses were performed at 25^{0}C. Buffer and Biacore reagents were purchased from GE Healthcare. Running buffer containing 10mM Hepes, pH7.4, 150mM sodium chloride, 1.25mM Dithiothreitol, 2% Dimethyl sulfoxide and 0.05% polysorbate 20 was utilized throughout all experiments.

Biotinylated smac7mer peptide was diluted to 10nM in running buffer and captured onto a sensor surface pre-derivatized with streptavidin (sensor chip SA) towards peptide surface densities in the range 40 – 100 R.U. Peptide captured surfaces were blocked with 500μM PEO_2-Biotin (Thermo Scientific). A blank flowcell was similarly blocked with PEO_2-biotin and served as a reference flowcell in the competition assay.

Interaction analyses were performed by first equilibrating each compound within a six point seven fold compound dilution series in the range 1μM to 0.06nM with either 100nM XIAP-BIR3 or 6nM cIAP1-BIR3 for at least one hour during instrument start-up procedures. Protein compound mixtures were then injected over reference and smac7mer peptide surfaces in series for 60 seconds at a flow-rate of 60μL/min. Surface regeneration was performed at the end of each analysis cycle by a 30 second injection of 10mM Glycine, pH 2.5, 1M Sodium Chloride, 0.05% polysorbate 20. Additionally, control compound samples and control XIAP-BIR3 or cIAP1-BIR3 samples were prepared and run at regular intervals to monitor surface and assay performance.

Data analyses were carried out using Biacore™ T100 evaluation software v2.0 to validate assay quality. Binding level report points were plotted versus logarithmic

compound concentration values and analyzed in Graphpad prism 5 via non-linear regression using a one-site competition model. EC50 values were generated and used as a measure of inhibitor potency.

The results are presented in Table 1 below.

Table 1

Ex No	Structural Name	XIAP-BIR3 Binding Biacore (Competitive) EC50 [nmol l^{-1}]	CIAP-BIR3 Binding Biacore (Competitive) EC50 [nmol l^{-1}]	PANC proliferation IC50 [nmol l^{-1}]
1A-1	5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-N-(1-(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorophenyl)-1-oxo-6,9,12,15,18-pentaoxa-2-azahenicosan-21-yl)-2-fluorobenzamide, trifluoroacetate	352.5 - 358.8	1.55 - 1.60[1]	0.15 - 2.87
2A-1	(S,S,S)-N,N'-(ethane-1,2-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido) acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide), trifluoroacetate	135.0 - 136.0	1.10 - 1.11	2.11 - 7.69
2B-1	(S,S,S)-N,N'-(1,4-phenylenebis(methylene))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide), trifluoroacetate	346.9 - 353.1	0.77 - 0.79	< 0.0026

Ex No	Structural Name	XIAP-BIR3 Binding Biacore (Competitive) EC50 [nmol l^{-1}]	CIAP-BIR3 Binding Biacore (Competitive) EC50 [nmol l^{-1}]	PANC proliferation IC50 [nmol l^{-1}]
2C-2	(S,S,S)-N,N'-(biphenyl-4,4'-diylbis(methylene))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide), citrate	2330 - 2388[2]	0.98 - 0.99	< 0.0026
2D-1	(S,S,S)-N,N'-(decane-1,10-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido) acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide), trifluoroacetate	1523 - 1922	1.35 - 2.17	<0.0026 - 0.15
2E-1	(S,S,S)-N,N'-(dodecane-1,12-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide), trifluoroacetate	> 1000	5.65 - 6.37	0.07 - 4.93
2F-1	(S,S,S)-N,N'-(hexane-1,6-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido) acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide), trifluoroacetate	305.4 - 306.2	1.34 - 1.36	<0.0026 - 0.01
2G-1	(S,S,S)-N,N'-(octane-1,8-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide), trifluoroacetate	426.4 - 494.8	1.26 - 1.31	<0.0026 - 0.03

Ex No	Structural Name	XIAP-BIR3 Binding Biacore (Competitive) EC50 [nmol l^{-1}]	CIAP-BIR3 Binding Biacore (Competitive) EC50 [nmol l^{-1}]	PANC proliferation IC50 [nmol l^{-1}]
2H-1	(S,S,S)-N,N'-(2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide), trifluoroacetate	243.9 - 251.7	1.84 - 1.89	0.03 - 0.07
2I-1	(S,S,S)-N,N'-(butane-1,4-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido) acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide), trifluoroacetate	317.8 - 325.8	2.79 - 2.80	<0.0026 - 0.4
2J-2	(S,S,S)-N,N'-(3,3'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(propane-3,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide), citrate	156.1 - 156.3	1.39 - 1.40	0.03 - 0.59
2K-1	(S,S,S)-N,N'-((1S,4S)-cyclohexane-1,4-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide), trifluoroacetate	321.3 - 322.4	1.65 - 1.66	< 0.0026

Ex No	Structural Name	XIAP-BIR3 Binding Biacore (Competitive) EC50 [nmol l^{-1}]	CIAP-BIR3 Binding Biacore (Competitive) EC50 [nmol l^{-1}]	PANC proliferation IC50 [nmol l^{-1}]
2L-2	(S,S,S)-N,N'-(3,3'-(ethane-1,2-diylbis(oxy))-bis(propane-3,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide), citrate	479.7 - 488.1	3.35 - 3.38	0.01 - 0.56
2M-2	(2S,2'S)-N,N'-((1S,1'S)-2,2'-((2S,2'S)-2,2'-(5,5'-(3,3'-(2,6-diazaspiro-[3.3]heptane-2,6-diylbis(oxomethylene))bis(4-fluoro-3,1-phenylene))-bis(pyridine-5,3-diyl))bis(pyrrolidine-2,1-diyl))bis(1-cyclohexyl-2-oxoethane-2,1-diyl))bis(2-(methylamino)-propanamide), citrate	175.7 - 176.7	3.74 - 3.75	9.02 - 40.79
2N-2	(2S,2'S)-N,N'-((1S,1'S)-2,2'-((2S,2'S)-2,2'-(5,5'-(3,3'-(hydrazine-1,2-diylbis(oxomethylene))bis(4-fluoro-3,1-phenylene))-bis(pyridine-5,3-diyl))bis(pyrrolidine-2,1-diyl))bis(1-cyclohexyl-2-oxoethane-2,1-diyl))bis(2-(methylamino)propanamide), citrate	75.2 - 75.5	1.27 - 1.36	<0.0026 - 0.02
3A	N4,N4'-bis(2-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-5-fluorobenzyl)biphenyl-4,4'-dicarboxamide, trifluoroacetate	126.0 - 127.4	0.86 - 0.88	<0.0026 - 0.0084

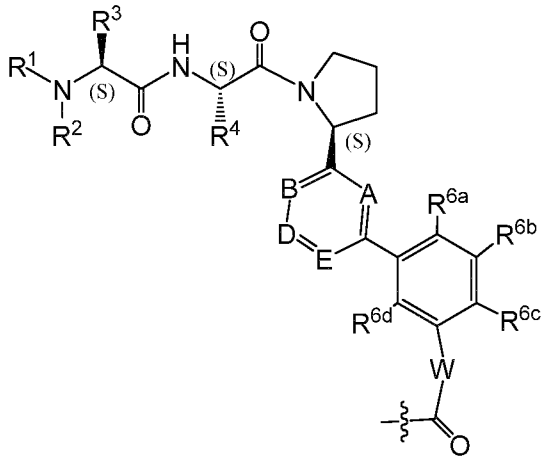
[1] Tested as the citrate salt

[2] Tested as the trifluoroacetate salt

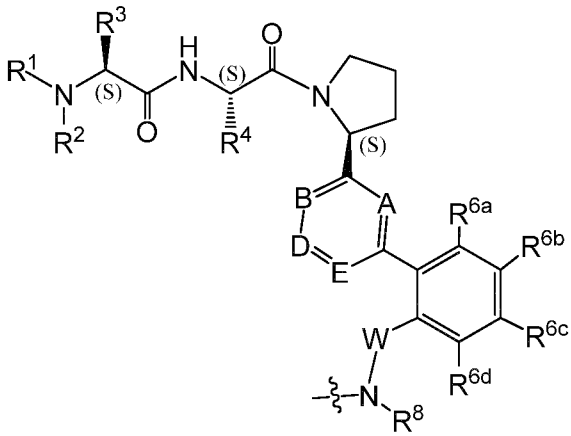
CLAIMS

What is claimed is:

1. A compound of Formula M-L-M', wherein M and M' are each independently a monomeric moiety of Formula (I), (II), (III), or (IV)



(I)



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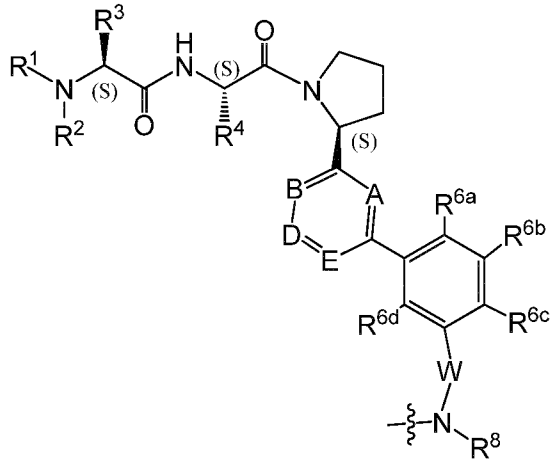
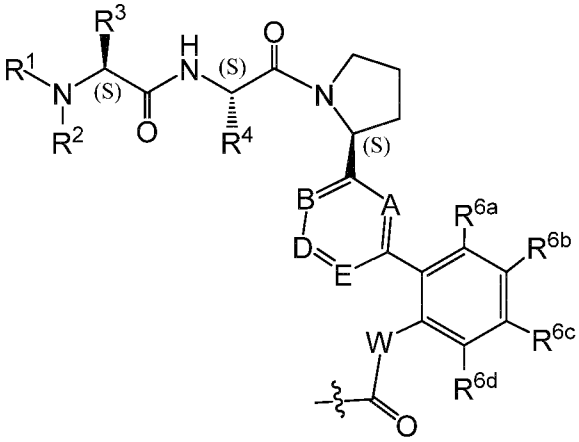


(III)



(IV)

wherein,

R^1 is $(C_1\text{-}C_4)$alkyl, deuterated methyl, or hydrogen;

R^2 is $(C_1\text{-}C_4)$alkyl or hydrogen;

R^3 is $(C_1\text{-}C_4)$alkyl or hydrogen, or

R^1 or R^2 along with the nitrogen to which R^1 or R^2 is attached is taken together with R^3 to form an aziridinyl, azetidinyl, pyrrolidinyl, or piperidinyl;

R^4 is

(i) (C_1-C_{10})alkyl, (C_2-C_{10})alkenyl, (C_2-C_{10})alkynyl, (C_3-C_6)cycloalkyl, phenyl, a 3- to 7-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, or a 5- to 9-membered heteroaryl containing 1 to 3 heteroatoms each independently selected form O, N or S, or

(ii) R^{4a}-(C_1-C_6)alkylene, where R^{4a} is (C_3-C_6)cycloalkyl, phenyl, a 3- to 7-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, or a 5- to 9-membered heteroaryl containing 1 to 3 heteroatoms each independently selected form O, N or S,

where said R^4 and said R^{4a} are optionally substituted with 1 to 3 substituents selected from halo, hydroxyl, -SH, -CO_2H, (C_1-C_4)alkyl, halo-substituted(C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkyl-S-, -SO_2, -NH_2 or -NO_2, and where 1 of the ring members of said cycloalkyl and said heterocycle moieties are optionally replaced with oxo or thione;

A, B, and D are CR^5, and E is N,

A, B and E are CR^5 and D is N,

A, D and E are CR^5, and B is N,

B, D and E are CR^5, and A is N,

A and B are both N, and D and E are both CR^5,

A and E are both N, and B and D are both CR^5, or

B and E are both N, and A and D are both CR^5, where R^5 are each independently selected from H, F, -CH_3 or -CF_3;

R^{6a}, R^{6b}, R^{6c} and R^{6d} are each independently H, (C_1-C_3)alkyl, Cl, or CN, where at least one of R^{6a}, R^{6b}, R^{6c} and R^{6d} is H or (C_1-C_3)alkyl;

W is a bond or (C_1-C_4)alkylene;

when M and M' are a monomeric moiety of Formula (I) or (IV), then L is -NR^8-X^1-NR^8-, and

when M and M' are a monomeric moiety of Formula (II) or (III), then L is –C(O)-X^1-C(O)-, where

R^8 is each independently H, (C_1-C_4)alkyl, or halo-substituted(C_1-C_4)alkyl, and

X^1 is

(i) a bond,

(ii) (C_1-C_{10})alkylene, (C_2-C_{10})alkenylene, (C_2-C_{10})alkynylene, ((C_1-C_{10})alkylene)-(O(C_1-C_6)alkylene)$_q$-, or (C_1-C_{10})alkylene-NH(C_1-C_6)alkylene, where q is 0, 1 or 2,

(iii) phenylene, napthylene, fluorenylene, 9H-fluoren-9-onylene, 9,10-dihydroanthracenylene, anthracen-9,10-dionylene, a partially or fully saturated (C_3-C_8)cycloalkylene, a 5- to 7-membered heterocyclene containing 1 to 3 heteroatoms each independently selected from O, S, or

N, or a 5- to 10-membered heteroarylene containing 1 to 3 heteroatoms each independently selected from O, S or N, where said phenylene is optionally fused to a (C_5-C_6)cycloalkyl,

(iv) (phenylene)-G-(phenylene), where G is a bond, O, S, -NH-, -N=N-, -S=S-, -SO_2-, (C_1-C_6)alkylene, (C_2-C_6)alkenylene, (C_2-C_{10})alkynylene, (C_3-C_6)cycloalkylene, a 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms each independently selected from O, S or N, or a 5- to 6-membered partially or fully saturated heterocyclene containing 1 to 3 heteroatoms each independently selected from O, S or N, and where said phenylene is optionally fused to a phenyl,

(v) ((C_1-C_6)alkylene)$_r$-Z^1-((C_1-C_6)alkylene)$_s$, or ((C_1-C_6)alkenylene)$_r$-Z^1-((C_1-C_6)alkenylene)$_s$, where r and s are each independently 0, 1, or 2; and Z^1 is –O-, –N=N-, (C_3-C_6)cycloalkylene, phenylene, bisphenylene, a 5- to 6-membered partially or fully saturated heterocyclene containing 1 to 3 heteroatoms each independently selected from O, S or N, or a 5- to-6-membered heteroarylene containing 1 to 3 heteroatoms each independently selected from O, S or N, where said heteroarylene and said heterocyclene are optionally fused to a phenyl, phenylene, a 5- to 6-membered partially or fully saturated heterocyclene containing 1 to 3 heteroatoms each independently selected from O, S or N, or a 5- to-6-membered heteroarylene containing 1 to 3 heteroatoms each independently selected from O, S or N, or

(vi) (C_1-C_{20})alkylene or –NH-((C_1-C_{20})alkylene)-NH-, where said alkylene contains 1 to 6 oxygen atoms interspersed within the alkylene chain and optionally 1 to 2 phenylene groups interpersed within the alkylene chain;

or when L is -NR^8-X^1-NR^8-, then X^1 is optionally taken together with one or both R^8 groups along with the nitrogen to which the R^8 group is attached to form a 4- to 14-membered heterocyclene, (4- to 6-membered heterocyclyl)-(C_1-C_6)alkylene-(4- to 6-membered heterocyclyl), or *bis*-(4- to 6-membered heterocyclene, where said heterocyclene and said heterocyclyl moieties optionally contain 1 to 3 additional heteroatoms selected from O, S and N, and X^1 and R^8 are optionally substituted with oxo or 1 to 3 substituents each independently selected from hydroxyl or (C_1-C_4)alkyl;

where said group (ii) moieties of X^1 are each independently substituted with one or more fluoro atoms, or 1 to 2 substituents each independently selected from halo, oxo,

amino, phenyl, naphthyl, (C_3-C_6) cycloalkyl, or 5- to 6-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, where said phenyl, said cycloalkyl, and said heterocycle are optionally substituted with 1 to 3 substituents each independently selected from halo, (C_1-C_4)alkyl, or trifluoromethyl,

where said group (iii) and (iv) moieties of X^1 are optionally substituted with 1 to 4 substitutents each independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo, amino, -OH, benzyl, or a fused 5- to 6-membered cycloalkyl, where said (C_1-C_4)alkyl, said (C_1-C_4)alkoxy, and said fused cycloalkyl are optionally substituted with 1 to 3 substituents selected from halo, or (C_1-C_4)alkyl,

where said group (v) moieties of X^1 are optionally substituted with 1 to 3 substituents each independently selected from halo, hydroxy, oxo, amino, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, or phenyl;

or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1, wherein

R^1 is (C_1-C_4)alkyl or deuterated methyl;

R^2 is hydrogen;

R^3 is (C_1-C_4)alkyl;

R^4 is

(i) (C_1-C_{10})alkyl, (C_3-C_6)cycloalkyl, phenyl, or a 3- to 7-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, or

(ii) R^{4a}-(C_1-C_6)alkylene, where R^{4a} is (C_3-C_6)cycloalkyl, or a 3- to 7-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, where said R^4 and said R^{4a} are optionally substituted with 1 to 3 substituents each independently selected from halo or (C_1-C_4)alkoxy; and

R^{6a}, R^{6b}, R^{6c} and R^{6d} are each independently H, (C_1-C_3)alkyl or F, where at least one of R^{6a}, R^{6b}, R^{6c} and R^{6d} is H or (C_1-C_3)alkyl; and

or a pharmaceutically acceptable salt thereof.

3. The compound of any one of the preceding claims wherein

R^1 is methyl or deuterated methyl;

R^2 is H;

R^3 is methyl;

R^4 is isopropyl or cyclohexyl;

R^{6a}, R^{6b}, and R^{6d} are each H; and

R^{6c} is F;

or a pharmaceutically acceptable salt thereof.

4. The compound of any one of the preceding claims wherein A, B, and D are CR^5, and E is N, where each R^5 is independently selected from H or F; or a pharmaceutically acceptable salt thereof.

5. The compound of any one of the preceding claims wherein A, B and E are CR^5 and D is N, where each R^5 is independently selected from H or F; or a pharmaceutically acceptable salt thereof.

6. The compound of any one of the preceding claims wherein W is a bond or $–CH_2-$; or a pharmaceutically acceptable salt thereof.

7. The compound of any one of the preceding claims, wherein M and M' are a monomeric moiety of Formula (I) and L is $-NR^8-X^1-NR^8-$; or a pharmaceutically acceptable salt thereof.

8. The compound of any one of the preceding claims wherein

X^1 is

(i) a bond,

(ii) (C_1-C_{10})alkylene, or $((C_1-C_{10})$alkylene$)-(O(C_1-C_6)$alkylene$)_q-$, where q is 0, 1 or 2,

(iii) phenylene, napthylene, or a fully saturated (C_3-C_8)cycloalkylene,

(iv) (phenylene)-G-(phenylene), where G is a bond, O, $-SO_2-$, (C_1-C_6)alkylene, or (C_2-C_{10})alkynylene

(v) $((C_1-C_6)$alkylene$)_r-Z^1-((C_1-C_6)$alkylene$)_s$, where r and s are each independently 0, 1, or 2; and Z^1 is –O-, or

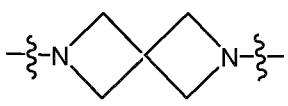
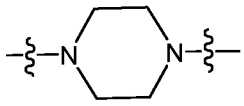
(vi) (C_1-C_{20})alkylene, where said alkylene contains 1 to 6 oxygen atoms interspersed within the alkylene chain;

or when L is $-NR^8-X^1-NR^8-$, then X^1 is optionally taken together with one or both R^8 groups along with the nitrogen to which the R^8 group is attached to form a 4- to 14-membered heterocyclene;

or a pharmaceutically acceptable salt thereof.

9. The compound of Claim 7, wherein L is –NH-NH-, $–NH-(CH_2)_3-(O-CH_2CH_2)_4-O-(CH_2)_3-NH-$, $-NH-(CH_2)_3-(O-CH_2CH_2)_2-O-(CH_2)_3-NH-$, $–NH-(CH_2)_3-O-CH_2CH_2-O-(CH_2)_3-NH-$, $–NH-(CH_2)_3-O-(CH_2)_3-NH-$, $–NH-(CH_2)_2-O-CH_2CH_2-O-(CH_2)_2-NH-$,

–NH-$(CH_2)_2$-(O-$CH_2CH_2)_2$-O-$(CH_2)_2$-NH-, -NH-((C_1-C_{12})alkylene)-NH-, -NH-CH_2-(phenylene)-CH_2-NH-, -NH-CH_2-(phenylene)-(phenylene)-CH_2-NH-, -NH-(cyclohexylene)-NH-,


, or

;

or a pharmaceutically acceptable salt thereof.

10. The compound of Claims 1, 2, 3, 4 or 5, wherein M and M' are a monomeric moiety of Formula (II) and L is –C(O)-X^1-C(O)-;

or pharmaceutically acceptable salt thereof.

11. The compound of Claim 10 wherein

X^1 is

(i) a bond,

(ii) (C_1-C_{10})alkylene, or ((C_1-C_{10})alkylene)-(O(C_1-C_6)alkylene)$_q$-, where q is 0, 1 or 2,

(iii) phenylene, napthylene, or a fully saturated (C_3-C_8)cycloalkylene,

(iv) (phenylene)-G-(phenylene), where G is a bond, O, -SO_2-, (C_1-C_6)alkylene, or (C_2-C_{10})alkynylene

(v) ((C_1-C_6)alkylene)$_r$-Z^1-((C_1-C_6)alkylene)$_s$, where r and s are each independently 0, 1, or 2; and Z^1 is –O-, or

(vi) (C_1-C_{20})alkylene, where said alkylene contains 1 to 6 oxygen atoms interspersed within the alkylene chain;

or when L is -NR^8-X^1-NR^8-, then X^1 is optionally taken together with one or both R^8 groups along with the nitrogen to which the R^8 group is attached to form a 4- to 14-membered heterocyclene; or a pharmaceutically acceptable salt thereof.

12. The compound of Claim 11, wherein X' is-phenylene-G-phenylene-, where G is a bond-; or a pharmaceutically acceptable salt thereof.

13. A compound selected from the group consisting of

5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-N-(1-(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorophenyl)-1-oxo-6,9,12,15,18-pentaoxa-2-azahenicosan-21-yl)-2-fluorobenzamide;

(S,S,S)-N,N'-(ethane-1,2-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(1,4-phenylenebis(methylene))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(biphenyl-4,4'-diylbis(methylene))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(decane-1,10-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(dodecane-1,12-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(hexane-1,6-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(octane-1,8-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(butane-1,4-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(3,3'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(propane-3,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)-acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-((1S,4S)-cyclohexane-1,4-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(S,S,S)-N,N'-(3,3'-(ethane-1,2-diylbis(oxy))bis(propane-3,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide);

(2S,2'S)-N,N'-((1S,1'S)-2,2'-((2S,2'S)-2,2'-(5,5'-(3,3'-(2,6-diazaspiro[3.3]heptane-2,6-diylbis(oxomethylene))bis(4-fluoro-3,1-phenylene))-bis(pyridine-5,3-diyl))bis(pyrrolidine-2,1-diyl))bis(1-cyclohexyl-2-oxoethane-2,1-diyl))bis(2-(methylamino)propanamide);

(2S,2'S)-N,N'-((1S,1'S)-2,2'-((2S,2'S)-2,2'-(5,5'-(3,3'-(hydrazine-1,2-diylbis(oxomethylene))bis(4-fluoro-3,1-phenylene))-bis(pyridine-5,3-diyl))bis(pyrrolidine-2,1-diyl))bis(1-cyclohexyl-2-oxoethane-2,1-diyl))bis(2-(methylamino)propanamide); and

N4,N4'-bis(2-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-5-fluorobenzyl)biphenyl-4,4'-dicarboxamide;

or a pharmaceutically acceptable salt thereof.

14. A compound which is 5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-N-(1-(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorophenyl)-1-oxo-6,9,12,15,18-pentaoxa-2-azahenicosan-21-yl)-2-fluorobenzamide; or a pharmaceutically acceptable salt thereof.

15. A compound which is (S,S,S)-N,N'-(ethane-1,2-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide); or a pharmaceutically acceptable salt thereof.

16. A compound which is (S,S,S)-N,N'-(2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)-pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide); or a pharmaceutically acceptable salt thereof.

17. A compound which is (S,S,S)-N,N'-(butane-1,4-diyl)bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide); or a pharmaceutically acceptable salt thereof.

18. A compound which is (S,S,S)-N,N'-(3,3'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(propane-3,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide); or a pharmaceutically acceptable salt thereof.

19. A compound which is (S,S,S)-N,N'-(3,3'-(ethane-1,2-diylbis(oxy))-bis(propane-3,1-diyl))bis(5-(5-((S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)-propanamido)acetyl)pyrrolidin-2-yl)pyridin-3-yl)-2-fluorobenzamide); or a pharmaceutically acceptable salt thereof.

20. A compound which is (2S,2'S)-N,N'-((1S,1'S)-2,2'-((2S,2'S)-2,2'-(5,5'-(3,3'-(hydrazine-1,2-diylbis(oxomethylene))bis(4-fluoro-3,1-phenylene))-bis(pyridine-5,3-

diyl))bis(pyrrolidine-2,1-diyl))bis(1-cyclohexyl-2-oxoethane-2,1-diyl))bis(2-(methylamino)propanamide); or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising a compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

22. The pharmaceutical composition of Claim 21 further comprising at least one additional pharmaceutical agent.

23. The pharmaceutical composition of Claim 22 wherein said at least one additional pharmaceutical agent is paclitaxel, a PI3K inhibitor, a topoisomerase inhibitor, a Trail antibody, recombinant Trail, or a Trail receptor agonist.

24. The pharmaceutical composition of Claim 22 wherein said at least one additional pharmaceutical agent is paclitaxel.

25. A method for treating a disease, disorder, or condition associated with the overexpression of an IAP in a subject comprising the step of administering to a subject in need to such treatment a therapeutically effective amount of a compound according to Claims 1 through 20, or a pharmaceutically acceptable salt thereof.

26. A method for treating a disease, disorder, or condition mediated by IAPs comprising the step of administering to a subject in need of such treatment a therapeutically effective amount of a compound according to Claims 1 through 20, or a pharmaceutically acceptable salt thereof.

27. The use of a compound as defined in any one of Claims 1 through 20 for inducing or enhancing apoptosis in a tumor or cancer cell.

28. A compound according to any one of claims 1 to 20, for use as a medicament.

29. Use of a compound according to any one of Claim 1 through 20 in the manufacture of a medicament for the treatment of a disease, disorder or condition mediated by IAPs.

30. Use of a compound according to any one of Claims 1 through 20 for the treatment of a disease, disorder or condition associated with the over expression of an IAPs.

31. A method for treating a disease, disorder, or condition mediated by IAPs comprising the steps of administering to a patient in need of such treatment

(i) a compound according to claims 1 to 20, or a pharmaceutically acceptable salt thereof; and

(ii) at least one additional pharmaceutical agent.

32. The method of Claim 31 wherein said additional pharmaceutical agent is paclitaxel, a PI3K inhibitor, a topoisomerase inhibitor, a Trail antibody, recombinant Trail, or a Trail receptor agonist.

33. The method of Claim 31 wherein said additional pharmaceutical agent is paclitaxel.

34. The method of Claim 31, 32 or 33 wherein said compound, or pharmaceutical acceptable salt thereof, and said additional pharmaceutical agent are administered simultaneously.

35. The method of Claim 31, 32 or 33 wherein said compound, or pharmaceutical acceptable salt thereof, and said additional pharmaceutical agent are administered sequentially.

36. A method for treating a disease, disorder, or condition mediated by IAP comprising the step of administering to a patient in need of such treatment a pharmaceutical composition comprising a compound according to Claims 1 through 20, or a pharmaceutically acceptable salt thereof, and a pharmaceutical acceptable carrier.

37. The method of Claim 36 wherein said composition further comprises at least one additional pharmaceutical agent.

38. The method of Claim 37 wherein said additional pharmaceutical agent is paclitaxel, a PI3K inhibitor, a topoisomerase inhibitor, a Trail antibody, recombinant Trail, or a Trail receptor agonist.

39. The method of Claim 37 wherein said additional pharmaceutical agent is paclitaxel.

40. A method for treating a disease, disorder, or condition mediated by IAPs comprising the steps of administering to a patient in need of such treatment

(i) a first composition comprising a compound according to Claims 1 through 20, or a pharmaceutically acceptable salt thereof, and a pharmaceutical carrier; and

(ii) a second composition comprising at least one additional pharmaceutical agent and a pharmaceutical carrier.

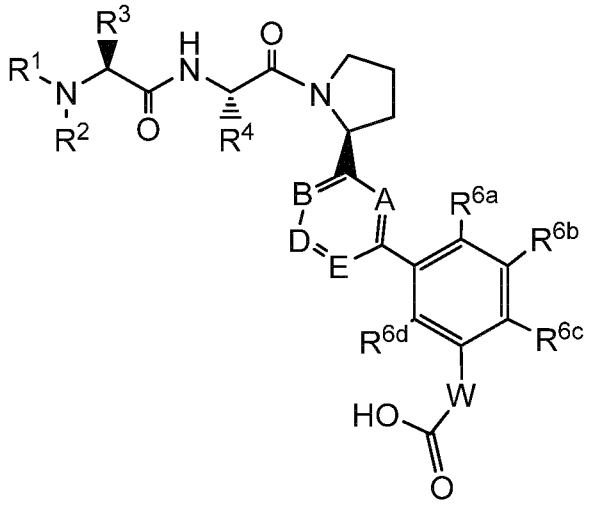
41. The method of Claim 40 wherein said additional pharmaceutical agent is paclitaxel, a PI3K inhibitor, a topoisomerase inhibitor, a Trail antibody, recombinant Trail, or a Trail receptor agonist.

42. The method of Claim 40 wherein said additional pharmaceutical agent is a paclitaxel.

43. The method of Claim 40, 41, or 42 wherein said first composition and said second composition are administered simultaneously.

44. The method of Claim 40, 41, or 42 wherein said first composition and said second composition are administered sequentially.

45. A compound of Formula (I-1c)



(I-1c)

wherein

R^1 is $(C_1$-$C_4)$alkyl or deuterated methyl;

R^2 is hydrogen or an amino-protecting group;

R^3 is $(C_1$-$C_4)$alkyl;

R^4 is

(i) $(C_1$-$C_{10})$alkyl, $(C_3$-$C_6)$cycloalkyl, phenyl, or a 3- to 7-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, or

(ii) R^{4a}-$(C_1$-$C_6)$alkylene, where R^{4a} is $(C_3$-$C_6)$cycloalkyl, or a 3- to 7-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, where said R^4 and said R^{4a} are optionally substituted with 1 to 3 substituents each independently selected from halo or $(C_1$-$C_4)$alkoxy;

A, B, and D are CR^5, and E is N, or A, B and E are CR^5 and D is N, where each R^5 is independently selected from H or F;

W is a bond; and

R^{6a}, R^{6b}, R^{6c} and R^{6d} are each independently H, $(C_1$-$C_3)$alkyl or F, where at least one of R^{6a}, R^{6b}, R^{6c} and R^{6d} is H or $(C_1$-$C_3)$alkyl.

46. The compound of Claim 45 wherein

R^1 is methyl or deuterated methyl;

R^2 is an amino-protecting group;

R^3 is methyl;

R^4 is isopropyl or cyclohexyl;

R^{6a}, R^{6b}, and R^{6d} are each H; and

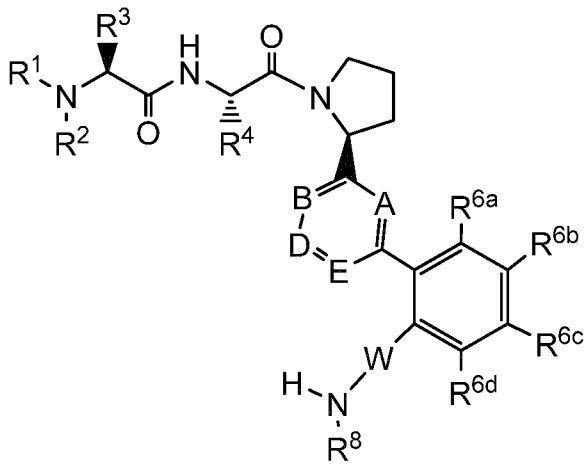
R^{6c} is F.

47. The compound of Claim 45 or 46 wherein A, B, and D are CR^5, and E is N, wherein each R^5 is independently selected from H or F.

48. The compound of Claim 45 or 46 wherein A, B and E are CR^5 and D is N, where each R^5 is independently selected from H or F.

49. A compound which is 5-[5-((S)-1-{(S)-2-[(S)-2-(tert-Butoxycarbonyl-methyl-amino)-propionylamino]-2-cyclohexyl-acetyl}-pyrrolidin-2-yl)-pyridin-3-yl]-2-fluoro-benzoic acid.

50. A compound of Formula (I-2a)



(I-2a)

wherein

R^1 is $(C_1$-$C_4)$alkyl or deuterated methyl;

R^2 is H or amino-protecting group;

R^3 is $(C_1$-$C_4)$alkyl;

R^4 is

(i) $(C_1$-$C_{10})$alkyl, $(C_3$-$C_6)$cycloalkyl, phenyl, or a 3- to 7-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, or

(ii) R^{4a}-$(C_1$-$C_6)$alkylene, where R^{4a} is $(C_3$-$C_6)$cycloalkyl, or a 3- to 7-membered heterocycle containing 1 to 3 heteroatoms each independently selected from O, N or S, where said R^4 and said R^{4a} are optionally substituted with 1 to 3 substituents each independently selected from halo or $(C_1$-$C_4)$alkoxy;

A, B, and D are CR^5, and E is N, or A, B and E are CR^5 and D is N, where each R^5 is independently selected from H or F;

W is a bond;

R^{6a}, R^{6b}, R^{6c} and R^{6d} are each independently H, $(C_1$-$C_3)$alkyl or F, where at least one of R^{6a}, R^{6b}, R^{6c} and R^{6d} is H or $(C_1$-$C_3)$alkyl; and

R^8 is H.

51. The compound of Claim 42 wherein

R^1 is methyl or deuterated methyl;

R^2 is an amino-protecting group;

R^3 is methyl;

R^4 is isopropyl or cyclohexyl;

R^{6a}, R^{6b}, and R^{6d} are each H; and

R^{6c} is F.

52. The compound of Claim 50 or 51 wherein A, B, and D are CR^5, and E is N, wherein each R^5 is independently selected from H or F.

53. The compound of Claim 50 or 51 wherein A, B and E are CR^5 and D is N, where each R^5 is independently selected from H or F.

54. A compound which is [(S)-1-((S)-2-{(S)-2-[5-(2-Aminomethyl-4-fluoro-phenyl)-pyridin-3-yl]-pyrrolidin-1-yl}-1-cyclohexyl-2-oxo-ethylcarbamoyl)-ethyl]-methyl-carbamic acid tert-butyl ester.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/072624

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 A61K31/4439 A61P35/00
ADD.

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)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/045905 A1 (NOVARTIS AG [CH]; CHAREST MARK G [US]; CHEN CHRISTINE HIU-TUNG [US]; C) 17 April 2008 (2008-04-17) cited in the application claims 1, 5 -----	1-54

☐ Further documents are listed in the continuation of Box C.

☒ 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 document 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
24 February 2012	05/03/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bakboord, Joan

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/072624

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008045905 A1	17-04-2008	AU 2007307763 A1	17-04-2008
		CA 2666112 A1	17-04-2008
		CN 101595121 A	02-12-2009
		EP 2102229 A1	23-09-2009
		JP 2010506847 A	04-03-2010
		KR 20090065548 A	22-06-2009
		RU 2009117701 A	20-11-2010
		US 2011015232 A1	20-01-2011
		WO 2008045905 A1	17-04-2008