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(54) Title: HETEROARYL-SUBSTITUTED BICYCLIC SMAC MIMETICS AND THE USES THEREOF

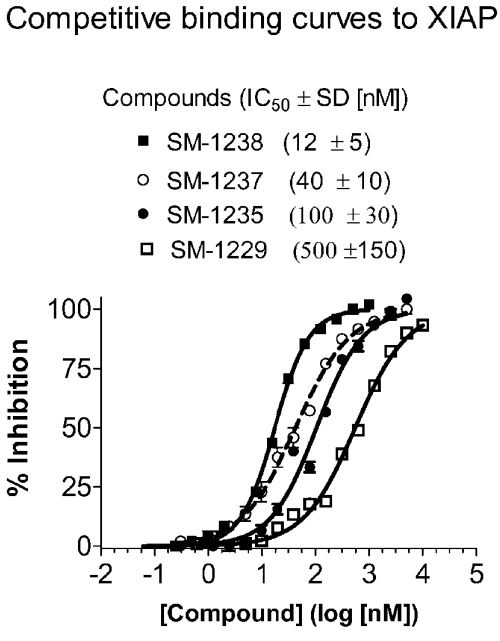

Fig. 1

(57) Abstract: The invention relates to heteroaryl-substituted bicyclic mimetics of Smac which function as inhibitors of Inhibitor of Apoptosis Proteins. The invention also relates to the use of these mimetics for inducing apoptotic cell death and for sensitizing cells to inducers of apoptosis.

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HETEROARYL-SUBSTITUTED BICYCLIC SMAC MIMETICS AND THE USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to pending U.S. Provisional Patent Application No. 61/044,330 filed April 11, 2008, and pending U.S. Provisional Patent Application No. 61/106,887 filed October 20, 2008, both of which are herein incorporated by reference in their entireties..

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with government support under R01CA109025 awarded by the National Institutes of Health. The government has certain rights in the invention.

Field of the Invention

[0003] This invention is in the field of medicinal chemistry. In particular, the invention relates to heteroaryl-substituted bicyclic Smac mimetics of the N-terminal sequence of Smac which function as inhibitors of Inhibitor of Apoptosis Proteins. The invention also relates to the use of these mimetics for inducing or sensitizing cells to the induction of apoptotic cell death.

Related Art

[0004] The aggressive cancer cell phenotype is the result of a variety of genetic and epigenetic alterations leading to deregulation of intracellular signaling pathways (Ponder, *Nature 411*:336 (2001)). The commonality for all cancer cells, however, is their failure to execute an apoptotic program, and lack of appropriate apoptosis due to defects in the normal apoptosis machinery is a hallmark of cancer (Lowe *et al., Carcinogenesis 21*:485 (2000)). Most current cancer therapies, including chemotherapeutic agents, radiation, and immunotherapy, work by indirectly inducing apoptosis in cancer cells. The inability of cancer cells to execute an apoptotic program due to defects in the normal apoptotic machinery is thus often associated with an increase in resistance to chemotherapy,

radiation, or immunotherapy-induced apoptosis. Primary or acquired resistance of human cancer of different origins to current treatment protocols due to apoptosis defects is a major problem in current cancer therapy (Lowe *et al., Carcinogenesis 21*:485 (2000); Nicholson, *Nature 407*:810 (2000)). Accordingly, current and future efforts towards designing and developing new molecular target-specific anticancer therapies to improve survival and quality of life of cancer patients must include strategies that specifically target cancer cell resistance to apoptosis. In this regard, targeting crucial negative regulators that play a central role in directly inhibiting apoptosis in cancer cells represents a highly promising therapeutic strategy for new anticancer drug design.

[0005] Two classes of central negative regulators of apoptosis have been identified. The first class of regulators is the Bcl-2 family of proteins, as exemplified by two potent anti-apoptotic molecules, Bcl-2 and Bcl-XL proteins (Adams *et al., Science 281*:1322 (1998); Reed, *Adv. Pharmacol. 41*:501 (1997); Reed *et al., J. Cell. Biochem. 60*:23 (1996)). Therapeutic strategies for targeting Bcl-2 and Bcl-XL in cancer to restore cancer cell sensitivity and overcome resistance of cancer cells to apoptosis have been extensively reviewed (Adams *et al., Science 281*:1322 (1998); Reed, *Adv. Pharmacol. 41*:501 (1997); Reed *et al., J. Cell. Biochem. 60*:23 (1996)). Several laboratories are interested in designing small molecule inhibitors of Bcl-2 and Bcl-XL.

[0006] The second class of central negative regulators of apoptosis is the inhibitor of apoptosis proteins (IAPs) (Deveraux *et al., Genes Dev. 13*:239 (1999); Salvesen *et al., Nat. Rev. Mol. Cell. Biol. 3*:401 (2002)). This class includes proteins such as XIAP, cIAP-1, cIAP-2, ML-IAP, HIAP, KIAP, TSIAP, NAIP, survivin, livin, ILP-2, apollon, and BRUCE. IAP proteins potently suppress apoptosis induced by a large variety of apoptotic stimuli, including chemotherapeutic agents, radiation, and immunotherapy in cancer cells.

[0007] X-linked IAP (XIAP) is the most potent inhibitor in suppressing apoptosis among all of the IAP members (Holcik *et al., Apoptosis 6*:253 (2001); LaCasse *et al., Oncogene 17*:3247 (1998); Takahashi *et al., J. Biol. Chem. 273*:7787 (1998); Deveraux *et al., Nature 388*:300 (1997); Sun *et al., Nature 401*:818 (1999); Deveraux *et al., EMBO J. 18*:5242 (1999); Asselin *et al., Cancer Res. 61*:1862 (2001)). XIAP plays a key role in the negative regulation of apoptosis in both the death receptor-mediated and the mitochondria-mediated pathways. XIAP functions as a potent endogenous apoptosis

inhibitor by directly binding and potently inhibiting three members of the caspase family of enzymes, caspase-3, -7, and -9 (Takahashi *et al., J. Biol. Chem. 273*:7787 (1998); Deveraux *et al., Nature 388*:300 (1997); Sun *et al., Nature 401*:818 (1999); Deveraux *et al., EMBO J. 18*:5242 (1999); Asselin *et al., Cancer Res. 61*:1862 (2001); Riedl *et al., Cell 104*:791 (2001); Chai *et al., Cell 104*:769 (2001); Huang *et al., Cell 104*:781 (2001)). XIAP contains three baculovirus inhibitor of apoptosis repeat (BIR) domains as well as a C-terminal RING finger. The third BIR domain (BIR3) selectively targets caspase-9, the initiator caspase in the mitochondrial pathway, whereas the linker region between BIR1 and BIR2 inhibits both caspase-3 and caspase-7 (Salvesen *et al., Nat. Rev. Mol. Cell. Biol. 3*:401 (2002)). While binding to XIAP prevents the activation of all three caspases, it is apparent that the interaction with caspase-9 is the most critical for its inhibition of apoptosis (Ekert *et al., J. Cell Biol. 152*:483 (2001); Srinivasula *et al., Nature 410*:112 (2001)). Because XIAP blocks apoptosis at the down-stream effector phase, a point where multiple signaling pathways converge, strategies targeting XIAP may prove to be especially effective to overcome resistance of cancer cells to apoptosis (Fulda *et al., Nature Med. 8*:808 (2002); Arnt *et al., J. Biol. Chem. 277*:44236 (2002)).

[0008] Although the precise role of XIAP in each type of cancer is far from completely understood, evidence is mounting to indicate that XIAP is widely overexpressed in many types of cancer and may play an important role in the resistance of cancer cells to a variety of current therapeutic agents (Holcik *et al., Apoptosis 6*:253 (2001); LaCasse *et al., Oncogene 17*:3247 (1998)).

[0009] XIAP protein was found to be expressed in most of the NCI 60 human cancer cell lines (Tamm *et al., Clin. Cancer Res. 6*:1796 (2000)). Analysis of tumor samples in 78 previously untreated patients showed that those with lower levels of XIAP had significantly longer survival (Tamm *et al., Clin. Cancer Res. 6*:1796 (2000)). XIAP was found to be expressed in human malignant glioma (Wagenknecht *et al., Cell Death Differ. 6*:370 (1999); Fulda *et al., Nature Med. 8*:808 (2002)). XIAP was found to be expressed in human prostate cancer cells and blocks Apo2 ligand/tumor necrosis factor-related apoptosis inducing ligand-mediated apoptosis of prostate cancer cells in the presence of mitochondrial activation (McEleny *et al., Prostate 51*:133 (2002); Ng *et al., Mol. Cancer Ther. 1*:1051 (2002)). XIAP is overexpressed in non-small cell lung cancer (NSCLC) in patients and has been implicated in pathogenesis of NSCLC (Hofmann *et al., J. Cancer*

Res. Clin. Oncol. 128:554 (2002)). Expression of XIAP and lack of down-regulation of XIAP upon treatment with cisplatin have been implicated in cisplatin resistance of human ovarian cancer (Li *et al., Endocrinology 142*:370 (2001); Cheng *et al., Drug Resist. Update 5*:131 (2002)). Taken together, these data suggest that XIAP may play an important role in resistance of several human cancers to current therapeutic agents.

[0010] Integrity of the blood vessel wall is essential for vascular homeostasis and organ function. A dynamic balance between endothelial cell survival and apoptosis contributes to this integrity during vascular development and pathological angiogenesis. It has been shown that cIAP-1 is essential for maintaining endothelial cell survival and blood vessel homeostasis during vascular development (Santoro *et al., Nature Genetics 39*:1397 (2007). As such, cIAP-1 may play an important role in the control of angiogenesis and blood vessel homeostasis during embryogenesis, regeneration and tumorigenesis.

[0011] Apoptosis is not a single process, rather, it is involved with a number of different, sometimes interconnected, signaling pathways leading to cell degradation. The pathways involved in a particular form of apoptosis depend on many factors, such as the insult or insults that initiate the process. Other factors include the activation or overactivation of specific receptors, such as the activation of "death" receptors by tumor necrosis factor alpha (TNFα), tumor necrosis factor-related apoptosis-inducing ligand (TRAIL or Apo2L), or FAS ligand. Another determining factor is the type of cell which is involved, since different signaling pathways are shown for so called type I and type II cells after Fas or TNFα receptor activation.

[0012] TRAIL (Apo2L) has been shown to be a selective and potent inducer of apoptosis in cancer cells (but not normal cells) upon binding to either of two pro-apoptotic TRAIL receptors, TRAIL-R1 (or DR4) (Pan *et al., Science 276*:111 (1997)) or TRAIL-R2 (KILLER, or DR5) (Wu *et al., Nat. Genet. 17*:141-143 (1997); Pan *et al., Science 277*:815 (1997); Walczak *et al., EMBO J. 16*:5386 (1997)). Activation of the pro-apoptotic death receptors by TRAIL induces the formation of death inducing signaling complex (DISC), which consists of receptor FADD as an adaptor (Kischkel *et al., Immunity 12*:611 (2000); Kuang *et al., J. Biol. Chem. 275*:25065 (2000)), and caspase-8 as an initiator caspase. Once DISC is formed, caspase-8 is auto-processed and activated by induced proximity (Medema *et al., EMBO J. 16*:2794 (1997); Muzio *et al., J. Biol. Chem. 273*:2926 (1998)).

[0013] TRAIL has generated significant interest as a potential cancer therapeutic (French *et al., Nat. Med. 5*:146 (1999)) because of its selective targeting of cancer cells, whereas most normal cells appear to be resistant to TRAIL (Ashkenazi *et al., Science 281*:1305 (1998); Walczak *et al., Nat. Med. 5*:157 (1999)). Systemic administration of TRAIL has proven to be safe and effective at killing breast or colon xenografted tumors and prolonging survival in mice (Walczak *et al., Nat. Med.5*:157 (1999)). Although TRAIL can specifically kill many types of cancer cells, many others display TRAIL-resistance (Kim *et al., Clin. Cancer Res. 6*:335 (2000); Zhang *et al., Cancer Res. 59*:2747 (1999)). In addition, cancer cells have been killed by application of antibodies (monoclonal or polyclonal) that specifically recognize either TRAIL-R1 or TRAIL-R2.

[0014] Numerous mechanisms have been identified as potential factors responsible for TRAIL-resistance. Such mechanisms exist at a number of levels, including at the receptor level, mitochondria level, post-mitochondria level, and at the DISC level. For example, loss of caspase-8 expression (Teitz *et al., Nat. Med. 6*:529 (2000); Griffith *et al., J. Immunol. 161*:2833 (1998)), or high expression of the cellular FLICE inhibitor protein (cFLIP) (Kim *et al., Clin. Cancer Res. 6*:335 (2000); Zhang *et al.*, *Cancer Res. 59*:2747 1999; Kataoka *et al., J. Immunol. 161*:3936 (1998)) make cancer cells resistant to TRAIL. Yeh *et al.* have shown that cFLIP-deficient embryonic mouse fibroblasts are particularly sensitive to receptor-mediated apoptosis (Yeh *et al., Immunity 12*:533 (2000)). Several splice variants of cFLIP are known, including a short splice variant, cFLIP-S, and a longer splice variant, cFLIP-L. It has been shown that cFLIP-deficient embryonic mouse fibroblasts become resistant to TRAIL-induced apoptosis as a result of retroviral-mediated transduction of cFLIP-S (Bin *et al., FEBS Lett. 510*:37 (2002)).

[0015] Although TRAIL represents a potentially promising candidate for tumor-selective death receptor activation (i.e., it induces apoptosis preferentially in tumor cells but not in normal tissues), many cancer cells are resistant to apoptosis-inducing drugs, as discussed above. As a result, treatment with such drugs often requires co-treatment with irradiation and/or cytotoxic chemicals to achieve a therapeutic effect. However, both radiation and chemotherapy have significant side effects, and are generally avoided if possible.

[0016] Thus, a need exists for an agent that can selectively and efficiently sensitize tumor cells to selective, apoptosis-inducing drugs such as TRAIL or TRAIL receptor antibodies, without also sensitizing surrounding normal cells. Such an agent would also be useful for

reducing or preventing the drug resistance commonly associated with the use of receptor-mediated apoptotic cancer drugs, thus improving their effectiveness and eliminating the need for combination therapies.

[0017] Recently, Smac/DIABLO (second mitochondria-derived activator of caspases) was identified as a protein released from mitochondria into the cytosol in response to apoptotic stimuli (Budihardjo *et al., Annu. Rev. Cell Dev. Biol. 15*:269 (1999); Du *et al., Cell 102*:33 (2000)). Smac is synthesized with an N-terminal mitochondrial targeting sequence that is proteolytically removed during maturation to the mature polypeptide. Smac was shown to directly interact with XIAP and other IAPs and to disrupt their binding to caspases and facilitate caspase activation. Smac is a potent endogenous inhibitor of XIAP.

[0018] High resolution, experimental three-dimensional (3D) structures of the BIR3 domain of XIAP in complex with Smac protein and peptide have recently been determined (Sun *et al., J. Biol. Chem. 275*:36152 (2000); Wu *et al., Nature 408*:1008 (2000)) (Figure 1). The N-terminal tetrapeptide of Smac (Ala-Val-Pro-Ile, or AVPI (SEQ ID NO:1)) recognizes a surface groove on the BIR3 domain of XIAP through several hydrogen-bonding interactions and van der Waals contacts. The interaction between BIR3 and caspase-9 has also been shown to involve four residues (Ala-Thr-Pro-Phe, or ATPF (SEQ ID NO:2)) on the amino terminus of the small subunit of caspase-9 to the same surface groove on the BIR3 domain. Several recent studies have convincingly demonstrated that Smac promotes the catalytic activity of caspase-9 by competing with caspase-9 for the same binding groove on the surface of the BIR3 domain (Ekert *et al., J. Cell Biol. 152*:483 (2001); Srinivasula *et al., Nature 410*:112 (2001)).

[0019] Unlike most protein-protein interactions, the Smac-XIAP interaction is mediated by only four amino acid residues on the Smac protein and a well-defined surface groove on the BIR3 domain of XIAP. The K_d value of Smac peptide AVPI (SEQ ID NO:1) to XIAP BIR3 (K_d = 0.4 μM) is essentially the same as the mature Smac protein (K_d = 0.42 μM). This well-defined interaction site is ideal for the design of non-peptide, drug-like small molecules that mimic the binding of Smac to XIAP.

[0020] A cell permeable Smac peptide, which consists of the first four amino acid residues (AVPI (SEQ ID NO:1)) of the N-terminus of Smac tethered to a carrier peptide to facilitate intracellular delivery, was recently shown to sensitize various tumor cells *in*

vitro and malignant glioma cells *in vivo* to apoptosis induced by death receptor ligation or cytotoxic drugs (Fulda *et al., Nature Med. 8*:808 (2002)). Importantly, this Smac peptide strongly enhanced the anti-tumor activity of Apo2L/TRAIL in an intracranial malignant glioma xenograft model *in vivo*. Complete eradication of established tumors and survival of mice was only achieved upon combined treatment with Smac peptides and Apo2L/TRAIL. Of significance, Smac peptide does not have detectable toxicity to normal brain tissue.

[0021] A second recent independent study also showed that peptides consisting of the first four to eight amino acid residues of the N-terminus of Smac tethered to a different carrier peptide enhanced the induction of apoptosis and the long term anti-proliferative effects of diverse chemotherapeutic drugs, including paclitaxel, etoposide, SN-38, and doxorubicin in MCF-7 and other human breast cancer cell lines (Arnt *et al., J. Biol. Chem. 277*:44236 (2002). This study conclusively showed that XIAP and cIAP-1 are the primary molecular targets for these peptides in cells.

[0022] A third study showed that a Smac peptide of the first seven N-terminal residues tethered to polyarginine restored the apoptosome activity and reversed the apoptosis resistance in non-small cell lung cancer H460 cells (Yang *et al., Cancer Res. 63*:831 (2003)). XIAP was shown to be responsible for the defect in apoptosome activity and suppression of caspase activity in H460 cells. When used in combination with chemotherapy, the cell-permeable Smac peptide regressed tumor growth *in vivo* with little murine toxicity. Taken together, these recent independent studies strongly suggest that a potent, stable, cell-permeable Smac mimetic may have great therapeutic potential for the treatment of human breast cancer and other types of cancer.

[0023] Peptide-based inhibitors are useful tools to elucidate the anti-apoptotic function of IAPs and the role of IAPs in response of cancer cells to chemotherapeutic agents. But peptide-based inhibitors in general have intrinsic limitations as potentially useful therapeutic agents. These limitations include their poor cell-permeability and poor *in vivo* stability. Indeed, in these three published studies using Smac-based peptide inhibitors, the peptides had to be fused to carrier peptides to make them relatively cell-permeable.

[0024] To overcome the intrinsic limitations of peptide-based inhibitors, the present invention provides conformationally constrained Smac mimetics having heteroaromatic substitution on the bicyclic scaffold.

SUMMARY OF THE INVENTION

[0025] It is generally accepted that the inability of cancer cells or their supporting cells to undergo apoptosis in response to genetic lesions or exposure to inducers of apoptosis (such as anticancer agents and radiation) is a major factor in the onset and progression of cancer. The induction of apoptosis in cancer cells or their supporting cells (e.g., neovascular cells in the tumor vasculature) is thought to be a universal mechanism of action for virtually all of the effective cancer therapeutic drugs or radiation therapies on the market or in practice today. One reason for the inability of a cell to undergo apoptosis is increased expression and accumulation of IAPs.

[0026] The present invention contemplates that exposure of animals suffering from cancer or other hyperproliferative disorders or diseases associated with dysregulation of apoptosis to therapeutically effective amounts of drug(s) (e.g., small molecules) that inhibit the function(s) of IAPs will kill the diseased cells or supporting cells outright (those cells whose continued survival is dependent on the overactivity or overexpression of IAPs) and/or render such cells as a population more susceptible to the cell death-inducing activity of cancer therapeutic drugs or radiation therapies. The present invention contemplates that inhibitors of IAPs satisfy an unmet need for the treatment of multiple cancer types, either when administered as monotherapy to induce apoptosis in cancer cells dependent on IAP function, or when administered in a temporal relationship with other cell death-inducing cancer therapeutic drugs or radiation therapies so as to render a greater proportion of the cancer cells or supportive cells susceptible to executing the apoptosis program compared to the corresponding proportion of cells in an animal treated only with the cancer therapeutic drug or radiation therapy alone.

[0027] The present invention also contemplates that treatment of animals suffering from endothelial cell-associated diseases (e.g., tumor angiogenesis, retinopathies and atherosclerosis) with therapeutically effective amounts of drug(s) (e.g., small molecules) that inhibit the function(s) of IAPs (e.g., cIAP-1) may prevent or inhibit angiogenesis and disrupt blood vessel homeostasis during vascular development in pathological conditions. Particular disorders that may be treated with the compounds of the invention include macular degeneration, rheumatoid arthritis, psoriasis, diabetic retinopathy, retinopathy of

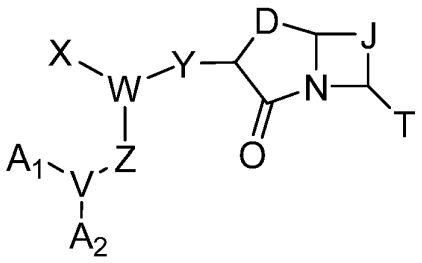
prematurity, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, Osler-Webber Syndrome, myocardial angiogenesis, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma, wound granulation, intestinal adhesions, atherosclerosis, scleroderma and hypertrophic scars.

[0028] Applicants have found that certain Smac mimetics having heteroaryl substitution on the bicyclic scaffold display unexpected *in vitro* potency in cancer cell lines. Thus, the compounds of the invention are expected to be useful for the treatment of a wide variety of diseases responsive to the induction of apoptotic cell death.

[0029] In certain embodiments of the invention, combination treatment of animals with a therapeutically effective amount of a compound of the present invention and a course of an anticancer agent or radiation is expected to produce a greater tumor response and clinical benefit in such animals compared to those treated with the compound or anticancer drugs/radiation alone. Put another way, because it is believed the compounds of the present invention lower the apoptotic threshold of all cells that express IAPs, the proportion of cells that successfully execute the apoptosis program in response to the apoptosis inducing activity of anticancer drugs/radiation is increased. Alternatively, the compounds of the present invention are expected to allow administration of a lower, and therefore less toxic and more tolerable, dose of an anticancer agent and/or radiation to produce the same tumor response/clinical benefit as the conventional dose of the anticancer agent/radiation alone. Since the doses for all approved anticancer drugs and radiation treatments are known, the present invention contemplates the various combinations of them with the compounds of the present invention. Also, since the compounds of the present invention act at least in part by inhibiting IAPs, the exposure of cancer cells and supporting cells to therapeutically effective amounts of the compounds can be temporally linked to coincide with the attempts of cells to execute the apoptosis program in response to the anticancer agent or radiation therapy. Thus, in some embodiments, administering the compositions of the present invention in connection with certain temporal relationships, is expected to provide especially efficacious therapeutic practices.

[0030] The present invention relates to Smac mimetics that are useful for inhibiting the activity of IAP proteins and *inter alia* increasing the sensitivity of cells to inducers of

apoptosis. In one particular embodiment, the Smac mimetics are compounds of Formula I:



I

wherein:

A_1 and A_2 are independently selected from the group consisting of hydrogen and optionally substituted alkyl, wherein A_2 is absent when V is O;

V is selected from the group consisting of N, CH and O;

W is selected from the group consisting of CH and N;

X is selected from the group consisting of hydrogen, optionally substituted alkyl and aralkyl;

Y is selected from the group consisting of $CON(R^1)$, $N(R^1)CO$, C(O)O, OC(O), $(CH_2)_{1-3}$, wherein one or more CH_2 groups can be replaced by O, S, or NR^1, optionally substituted aryl and optionally substituted heteroaryl;

Z is $(CR^{2a}R^{2b})_r$;

D is $(CR^{3a}R^{3b})_n$-U-$(CR^{4a}R^{4b})_m$;

U is selected from the group consisting of $CR^{5a}R^{5b}$ and NR^6;

J is $(CR^{7a}R^{7b})_p$-L-$(CR^{8a}R^{8b})_q$;

T is optionally substituted heteroaryl;

n, m, p and q are independently selected from the group consisting of 0-5;

r is 0-3;

R^1 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

each R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^{7a}, R^{7b}, R^{8a}, R^{8b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally

substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

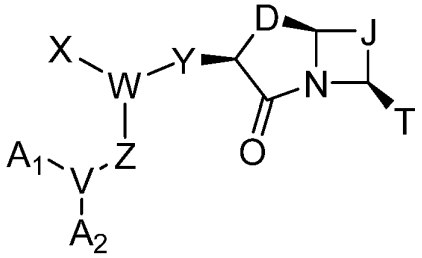
R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

L is selected from the group consisting of O, S, NR^1, $NCOR^9$, $CR^{7a}R^{7b}$, C=O, C=S and $C=NR^1$; and

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

or pharmaceutically acceptable salt or prodrug thereof.

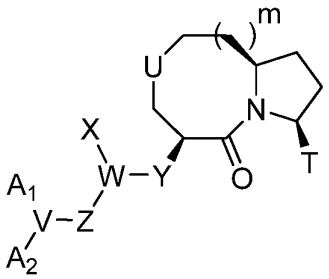
[0031] In another particular embodiment, Smac mimetics are compounds of Formula II:



II

wherein A_1, A_2, V, Z, W, X, Y, D, J and T have the meanings as described above for Formula I; or a pharmaceutically acceptable salt or prodrug thereof.

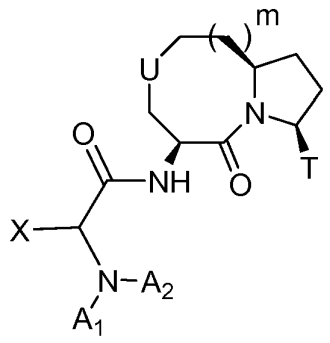
[0032] In another particular embodiment, Smac mimetics are compounds of Formula III:



III

wherein A_1, A_2, V, Z, W, X, Y, U, and T have the meanings as described above for Formula I, and m is 1 or 2; or a pharmaceutically acceptable salt or prodrug thereof.

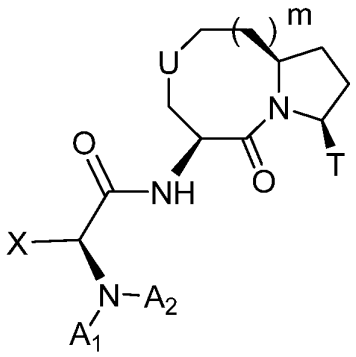
[0033] In another particular embodiment, Smac mimetics are compounds of Formula IV:



IV

wherein A_1, A_2, X, U, and T have the meanings as described above for Formula I, and m is 1 or 2; or a pharmaceutically acceptable salt or prodrug thereof.

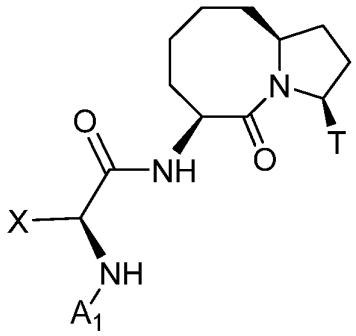
[0034] In another particular embodiment, Smac mimetics are compounds of Formula V:



V

wherein A_1, A_2, X, U and T have the meanings as described above for Formula I, and m is 1 or 2; or a pharmaceutically acceptable salt or prodrug thereof.

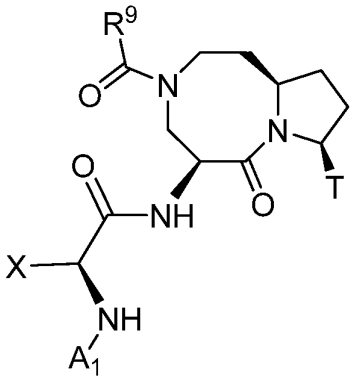
[0035] In another particular embodiment, Smac mimetics are compounds of Formula VI:



VI

wherein A_1 and X are optionally substituted alkyl and T is optionally substituted heteroaryl; or a pharmaceutically acceptable salt or prodrug thereof.

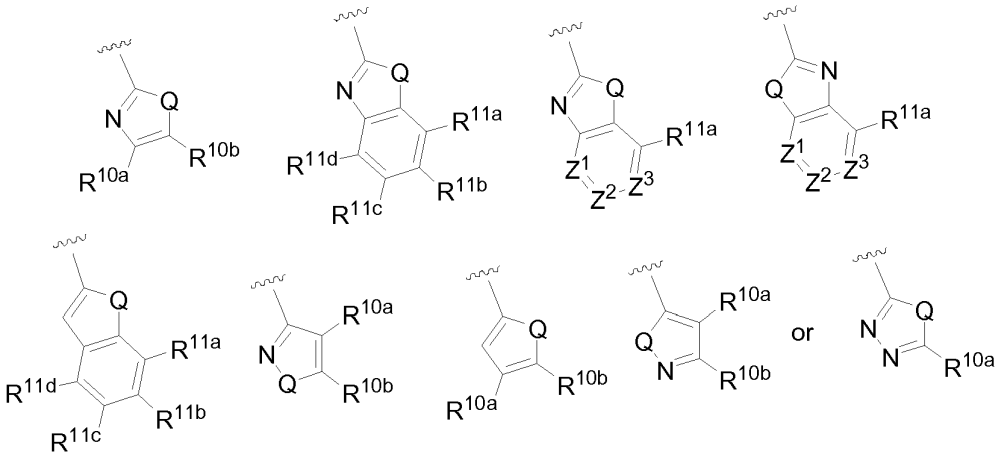
[0036] In another particular embodiment, Smac mimetics are compounds of Formula VII:



VII

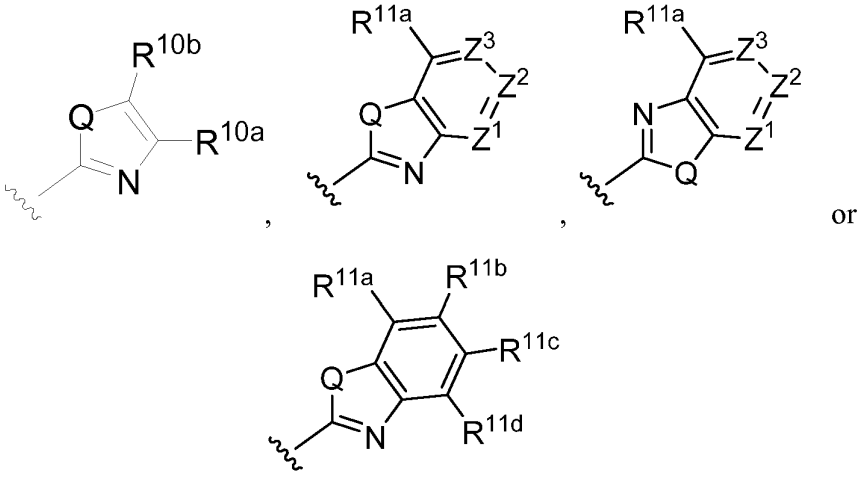
wherein A_1 and X are optionally substituted alkyl, R^9 is optionally substituted alkyl or aralkyl, and T is optionally substituted heteroaryl; or a pharmaceutically acceptable salt or prodrug thereof.

[0037] In another particular embodiment, Smac mimetics are compounds of Formulae I-VII wherein T is



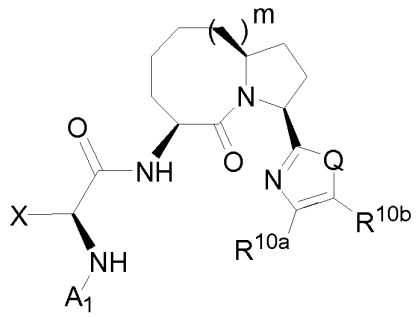
wherein Q is O, S or NR^{12}, R^{12} is hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclo, R^{10a}, R^{10b}, R^{11a}, R^{11b}, R^{11c} and R^{11d} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido, Z^1, Z^2, and Z^3 are independently CR^{11e} or N, wherein at least one of Z^1, Z^2, and Z^3 is CR^{11e} and at least one of Z^1, Z^2, and Z^3 is N, and R^{11e} is selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido; or a pharmaceutically acceptable salt or prodrug thereof.

[0038] In another particular embodiment, Smac mimetics are compounds of Formulae I-VII wherein T is



wherein Q, Z^1, Z^2, Z^3, R^{10a}, R^{10b}, R^{11a}, R^{11b}, R^{11c} and R^{11d} have the meanings described above; or pharmaceutically acceptable salt or prodrug thereof.

[0039] In another particular embodiment, Smac mimetics are compounds of Formula VIII:

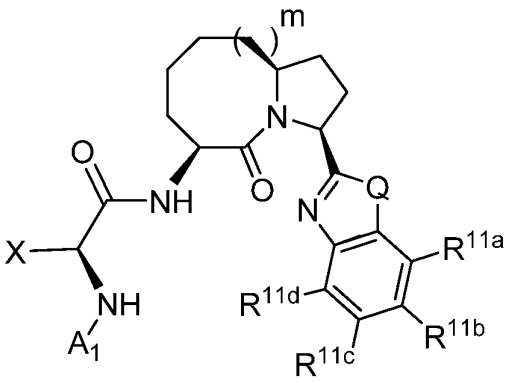


VIII

wherein A_1 and X are optionally substituted alkyl, m is 1 or 2 , Q is O, S or NR^{12}, R^{12} is hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclo, and R^{10a} and R^{10b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy,

arylalkyloxy, alkylthio, carboxamido and sulfonamido; or a pharmaceutically acceptable salt or prodrug thereof.

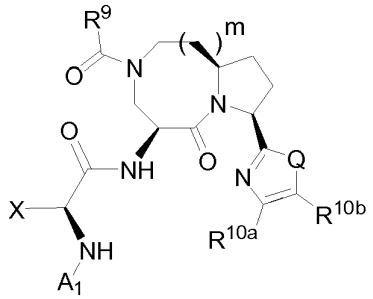
[0040] In another particular embodiment, Smac mimetics are compounds of Formula IX:



IX

wherein A_1 and X are optionally substituted alkyl, m is 1 or 2, Q is O, S or NR^{12}, R^{12} is hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclo, and R^{11a}, R^{11b}, R^{11c} and R^{11d} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido; or a pharmaceutically acceptable salt or prodrug thereof.

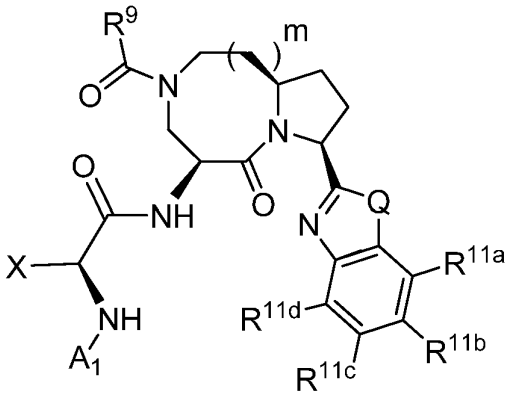
[0041] In another particular embodiment, Smac mimetics are compounds of Formula X:



X

wherein A_1 and X are optionally substituted alkyl, R^9 is optionally substituted alkyl or aralkyl, m is 1 or 2, Q is O, S or NR^{12}, R^{12} is hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclo, and R^{10a} and R^{10b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido; or a pharmaceutically acceptable salt or prodrug thereof.

[0042] In another particular embodiment, Smac mimetics are compounds of Formula XI:



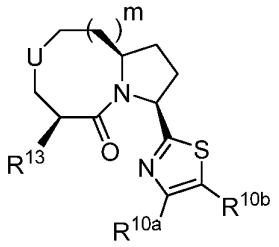
XI

wherein A_1 and X are optionally substituted alkyl, R^9 is optionally substituted alkyl or aralkyl, m is 1 or 2, Q is O, S or NR^{12}, R^{12} is hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclo, and R^{11a}, R^{11b}, R^{11c} and R^{11d} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido; or a pharmaceutically acceptable salt or prodrug thereof.

[0043] The invention relates to compounds represented by Formulae I-XIa which are inhibitors of IAP proteins. The invention relates to the use of the compounds of the invention to induce apoptosis in cells and inhibit angiogenesis. The invention also relates to the use of the compounds of the invention for sensitizing cells to inducers of apoptosis. The compounds are useful for the treatment, amelioration, or prevention of disorders responsive to induction of apoptotic cell death, e.g., disorders characterized by dysregulation of apoptosis, including hyperproliferative diseases such as cancer. In certain embodiments, the compounds can be used to treat, ameliorate, or prevent cancer that is characterized by resistance to cancer therapies (e.g., those which are chemoresistant, radiation resistant, hormone resistant, and the like). In other embodiments, the compounds can be used to treat hyperproliferative diseases characterized by overexpression of IAPs. In other embodiments, the compounds can be used as a method of preventing or inhibiting angiogenesis in animals in need thereof. The present invention provides pharmaceutical compositions comprising compounds of Formulae I-XIa in a therapeutically effective amount to induce apoptosis in cells or to sensitize cells to inducers of apoptosis.

[0044] The invention further provides kits comprising a compound of Formula I and instructions for administering the compound to an animal. The kits may optionally contain other therapeutic agents, e.g., anticancer agents or apoptosis-modulating agents.

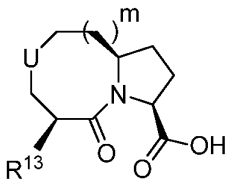
[0045] The present invention also provides a process for preparing a compound of Formula XII



XII

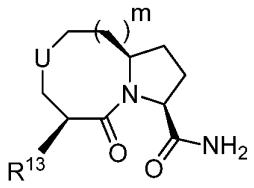
comprising:

a) condensing a compound of Formula XIII



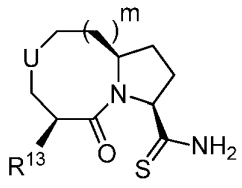
XIII

with ammonia to give a compound of Formula XIV



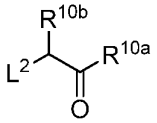
XIV

b) converting a compound of Formula XIV to a compound of Formula XV



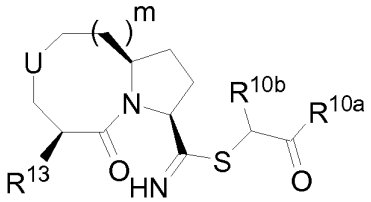
XV

c) condensing a compound of Formula XV with a compound of Formula XVI



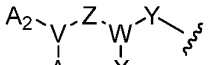
XVI

wherein L^2 is a leaving group, to give a compound of Formula XVII,



XVII

and b) cyclizing a compound of Formula XVII, to give a compound of Formula XII, wherein:

R^{13} is selected from the group consisting of $N(H)P^1$ and  ;

P^1 is an amine protecting group;

A_1 and A_2 are independently selected from the group consisting of hydrogen and optionally substituted alkyl, wherein A_2 is absent when V is O;

V is selected from the group consisting of N, CH and O;

W is selected from the group consisting of CH and N;

X is selected from the group consisting of hydrogen, optionally substituted alkyl and aralkyl;

Y is selected from the group consisting of $CON(R^1)$, $N(R^1)CO$, C(O)O, OC(O), $(CH_2)_{1-3}$, wherein one or more CH_2 groups can be replaced by O, S, or NR^1, optionally substituted aryl and optionally substituted heteroaryl;

Z is $(CR^{2a}R^{2b})_r$;

U is selected from the group consisting of $CR^{5a}R^{5b}$ and NR^6;

m is 1 or 2;

r is 0-3;

R^1 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

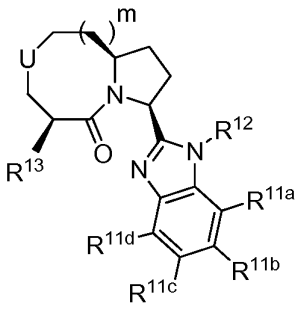
each R^{2a}, R^{2b}, R^{5a} and R^{5b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo; and

[0046] R^{10a} and R^{10b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo.

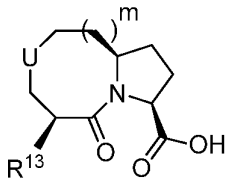
[0047] The present invention also provides a process for preparing a compound of Formula XVIII



XVIII

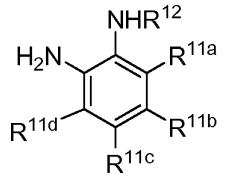
comprising:

a) condensing a compound of Formula XIII



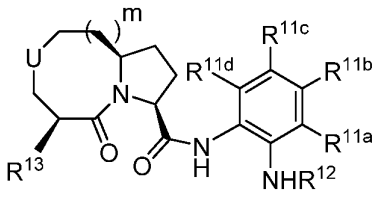
XIII

with a compound of Formula XIX



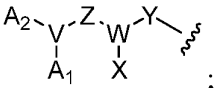
XIX

to give a compound of Formula XX



XX

and b) cyclizing a compound of Formula XX, to give a compound of Formula XVIII, wherein:

R^{13} is selected from the group consisting of $N(H)P^1$ and  ;

P^1 is an amine protecting group;

A_1 and A_2 are independently selected from the group consisting of hydrogen and optionally substituted alkyl, wherein A_2 is absent when V is O;

V is selected from the group consisting of N, CH and O;

W is selected from the group consisting of CH and N;

X is selected from the group consisting of hydrogen, optionally substituted alkyl and aralkyl;

Y is selected from the group consisting of $CON(R^1)$, $N(R^1)CO$, C(O)O, OC(O), $(CH_2)_{1-3}$, wherein one or more CH_2 groups can be replaced by O, S, or NR^1, optionally substituted aryl and optionally substituted heteroaryl;

Z is $(CR^{2a}R^{2b})_r$;

U is selected from the group consisting of $CR^{5a}R^{5b}$ and NR^6;

m is 1 or 2;

r is 0-3;

R^1 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

each R^{2a}, R^{2b}, R^{5a} and R^{5b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

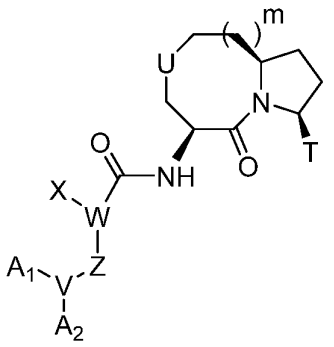
R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

R^{11a}, R^{11b}, R^{11c} and R^{11d} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido, and

R^{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo.

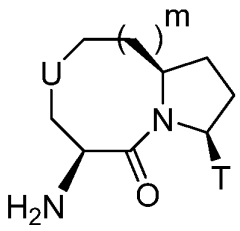
[0048] The present also provides a process for preparing a compound of Formula XXI



XXI

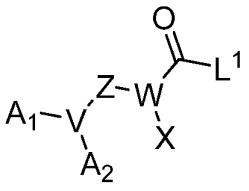
comprising:

condensing a compound of Formula XXIII



XXIII

with a compound of Formula XXIV



XXIV

wherein L^1 is a leaving group, to give a compound of Formula XXI,

wherein:

A_1 and A_2 are independently selected from the group consisting of hydrogen and optionally substituted alkyl, wherein A_2 is absent when V is O;

V is selected from the group consisting of N, CH and O;

W is selected from the group consisting of CH and N;

X is selected from the group consisting of hydrogen, optionally substituted alkyl and aralkyl;

Z is $(CR^{2a}R^{2b})_r$;

U is selected from the group consisting of $CR^{5a}R^{5b}$ and NR^6;

m is 1 or 2;

r is 0-3;

each R^{2a}, R^{2b}, R^{5a} and R^{5b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo; and

T is optionally substituted heteroaryl.

BRIEF DESCRIPTION OF DRAWINGS

[0049] **Fig. 1** is a graph illustrating competitive binding curves of Smac mimetics to the XIAP BIR3 domain.

[0050] **Fig. 2** is a graph illustrating competitive binding curves of Smac mimetics to the cIAP1 domain.

[0051] **Fig. 3** is a bar graph showing the induction of cell death by SM-1238 in the human breast cancer MDA-MB-231 and human ovarian cancer SK-OV-3 cell lines.

DETAILED DESCRIPTION OF THE INVENTION

[0052] The present invention relates to conformationally constrained compounds represented by Formulae I-XIa, which are mimetics of Smac and function as inhibitors of IAPs. Smac mimetics of Formula I-XIa display potent *in vitro* inhibitory activity in cancer cell lines. The invention relates to methods of sensitizing cells to inducers of apoptosis and to methods of inducing apoptosis in cells, comprising contacting the cells with a compound of Formulae I-XIa alone or in combination with an inducer of apoptosis. The invention further relates to methods of treating, ameliorating, or preventing disorders in an animal that are responsive to induction of apoptosis comprising administering to the animal a compound of Formulae I-XIa and an inducer of apoptosis. Such disorders include those characterized by a dysregulation of apoptosis and those characterized by overexpression of IAPs. The invention further relates methods of preventing or inhibiting angiogenesis in an animal in need thereof comprising administering to an animal a compound of Formulae I-XIa.

[0053] The term "IAP proteins," as used herein, refers to any known member of the Inhibitor of Apoptosis Protein family, including, but not limited to, XIAP, cIAP-1,

cIAP-2, ML-IAP, HIAP, TSIAP, KIAP, NAIP, survivin, livin, ILP-2, apollon, and BRUCE.

[0054] The term "overexpression of IAPs," as used herein, refers to an elevated level (e.g., aberrant level) of mRNAs encoding for an IAP protein(s), and/or to elevated levels of IAP protein(s) in cells as compared to similar corresponding non-pathological cells expressing basal levels of mRNAs encoding IAP proteins or having basal levels of IAP proteins. Methods for detecting the levels of mRNAs encoding IAP proteins or levels of IAP proteins in a cell include, but are not limited to, Western blotting using IAP protein antibodies, immunohistochemical methods, and methods of nucleic acid amplification or direct RNA detection. As important as the absolute level of IAP proteins in cells is to determining that they overexpress IAP proteins, so also is the relative level of IAP proteins to other pro-apoptotic signaling molecules (e.g., pro-apoptotic Bcl-2 family proteins) within such cells. When the balance of these two are such that, were it not for the levels of the IAP proteins, the pro-apoptotic signaling molecules would be sufficient to cause the cells to execute the apoptosis program and die, said cells would be dependent on the IAP proteins for their survival. In such cells, exposure to an inhibiting effective amount of an IAP protein inhibitor will be sufficient to cause the cells to execute the apoptosis program and die. Thus, the term "overexpression of an IAP protein" also refers to cells that, due to the relative levels of pro-apoptotic signals and anti-apoptotic signals, undergo apoptosis in response to inhibiting effective amounts of compounds that inhibit the function of IAP proteins.

[0055] The terms "anticancer agent" and "anticancer drug," as used herein, refer to any therapeutic agents (e.g., chemotherapeutic compounds and/or molecular therapeutic compounds), radiation therapies, or surgical interventions, used in the treatment of hyperproliferative diseases such as cancer (e.g., in mammals).

[0056] The term "prodrug," as used herein, refers to a pharmacologically inactive derivative of a parent "drug" molecule that requires biotransformation (e.g., either spontaneous or enzymatic) within the target physiological system to release, or to convert (e.g., enzymatically, physiologically, mechanically, electromagnetically) the prodrug into the active drug. Prodrugs are designed to overcome problems associated with stability, toxicity, lack of specificity, or limited bioavailability. Exemplary prodrugs comprise an active drug molecule itself and a chemical masking group (e.g., a group that reversibly

suppresses the activity of the drug). Some preferred prodrugs are variations or derivatives of compounds that have groups cleavable under metabolic conditions. Exemplary prodrugs become pharmaceutically active *in vivo* or *in vitro* when they undergo solvolysis under physiological conditions or undergo enzymatic degradation or other biochemical transformation (e.g., phosphorylation, hydrogenation, dehydrogenation, glycosylation). Prodrugs often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism. (See e.g., Bundgard, Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam (1985); and Silverman, The Organic Chemistry of Drug Design and Drug Action, pp. 352-401, Academic Press, San Diego, CA (1992)). Common prodrugs include acid derivatives such as esters prepared by reaction of parent acids with a suitable alcohol (e.g., a lower alkanol), amides prepared by reaction of the parent acid compound with an amine, or basic groups reacted to form an acylated base derivative (e.g., a lower alkylamide).

[0057] The term "pharmaceutically acceptable salt," as used herein, refers to any salt (e.g., obtained by reaction with an acid or a base) of a compound of the present invention that is physiologically tolerated in the target animal (e.g., a mammal). Salts of the compounds of the present invention may be derived from inorganic or organic acids and bases. Examples of acids include, but are not limited to, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, sulfonic, naphthalene-2-sulfonic, benzenesulfonic acid, and the like. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

[0058] Examples of bases include, but are not limited to, alkali metal (e.g., sodium) hydroxides, alkaline earth metal (e.g., magnesium) hydroxides, ammonia, and compounds of formula NW_4^+, wherein W is C_{1-4} alkyl, and the like.

[0059] Examples of salts include, but are not limited to: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, flucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, chloride, bromide, iodide, 2-hydroxyethanesulfonate, lactate, maleate, mesylate,

methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, undecanoate, and the like. Other examples of salts include anions of the compounds of the present invention compounded with a suitable cation such as Na^+, NH_4^+, and NW_4^+ (wherein W is a C_{1-4} alkyl group), and the like. For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

[0060] The term "therapeutically effective amount," as used herein, refers to that amount of the therapeutic agent sufficient to result in amelioration of one or more symptoms of a disorder, or prevent advancement of a disorder, or cause regression of the disorder. For example, with respect to the treatment of cancer, a therapeutically effective amount preferably refers to the amount of a therapeutic agent that decreases the rate of tumor growth, decreases tumor mass, decreases the number of metastases, increases time to tumor progression, or increases survival time by at least 5%, preferably at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

[0061] The terms "sensitize" and "sensitizing," as used herein, refer to making, through the administration of a first agent (e.g., a compound of Formula I), an animal or a cell within an animal more susceptible, or more responsive, to the biological effects (e.g., promotion or retardation of an aspect of cellular function including, but not limited to, cell division, cell growth, proliferation, invasion, angiogenesis, or apoptosis) of a second agent. The sensitizing effect of a first agent on a target cell can be measured as the difference in the intended biological effect (e.g., promotion or retardation of an aspect of cellular function including, but not limited to, cell growth, proliferation, invasion, angiogenesis, or apoptosis) observed upon the administration of a second agent with and without administration of the first agent. The response of the sensitized cell can be increased by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 150%, at least 200%,

at least 350%, at least 300%, at least 350%, at least 400%, at least 450%, or at least 500% over the response in the absence of the first agent.

[0062] The term "dysregulation of apoptosis," as used herein, refers to any aberration in the ability of (e.g., predisposition) a cell to undergo cell death via apoptosis. Dysregulation of apoptosis is associated with or induced by a variety of conditions, including for example, autoimmune disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis, graft-versus-host disease, myasthenia gravis, or Sjögren's syndrome), chronic inflammatory conditions (e.g., psoriasis, asthma or Crohn's disease), hyperproliferative disorders (e.g., tumors, B cell lymphomas, or T cell lymphomas), viral infections (e.g., herpes, papilloma, or HIV), and other conditions such as osteoarthritis and atherosclerosis. It should be noted that when the dysregulation is induced by or associated with a viral infection, the viral infection may or may not be detectable at the time dysregulation occurs or is observed. That is, viral-induced dysregulation can occur even after the disappearance of symptoms of viral infection.

[0063] The term "angiogenesis," as used herein means the generation of new blood vessels into a tissue or organ. The term "antiangiogenesis," as used herein, refers to prevention or reduction of the growth of new blood vessels. Examples of diseases or disorders associated with angiogenesis that may be treated with the compounds of the invention include macular degeneration, rheumatoid arthritis, psoriasis, diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, Osler-Webber Syndrome, myocardial angiogenesis, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma, wound granulation, intestinal adhesions, atherosclerosis, scleroderma and hypertrophic scars.

[0064] The term “hyperproliferative disease,” as used herein, refers to any condition in which a localized population of proliferating cells in an animal is not governed by the usual limitations of normal growth. Examples of hyperproliferative disorders include, but are not restricted to cancers (e.g., tumors, neoplasms, lymphomas and the like) or autoimmune disorders. A neoplasm is said to be benign if it does not undergo invasion or metastasis and malignant if it does either of these. A “metastatic” cell means that the cell can invade and destroy neighboring body structures. Hyperplasia is a form of cell proliferation involving an increase in cell number in a tissue or organ without significant alteration in structure or function. Metaplasia is a form of controlled cell growth in which

one type of fully differentiated cell substitutes for another type of differentiated cell. In another embodiment, the hyperproliferative disease is rheumatoid arthritis, inflammatory bowel disease, osteoarthritis, leiomyomas, adenomas, lipomas, hemangiomas, fibromas, vascular occlusion, restenosis, atherosclerosis, pre-neoplastic lesions (such as adenomatous hyperplasia and prostatic intraepithelial neoplasia), carcinoma in situ, oral hairy leukoplakia, or psoriasis.

[0065] The pathological growth of activated lymphoid cells often results in an autoimmune disorder or a chronic inflammatory condition. As used herein, the term "autoimmune disorder" refers to any condition in which an organism produces antibodies or immune cells which recognize the organism's own molecules, cells or tissues. Non-limiting examples of autoimmune disorders include autoimmune hemolytic anemia, autoimmune hepatitis, Berger's disease or IgA nephropathy, celiac sprue, chronic fatigue syndrome, Crohn's disease, dermatomyositis, fibromyalgia, graft versus host disease, Grave's disease, Hashimoto's thyroiditis, idiopathic thrombocytopenia purpura, lichen planus, multiple sclerosis, myasthenia gravis, psoriasis, rheumatic fever, rheumatic arthritis, scleroderma, Sjögren's syndrome, systemic lupus erythematosus, type 1 diabetes, ulcerative colitis, vitiligo, and the like.

[0066] The term "neoplastic disease," as used herein, refers to any abnormal growth of cells being either benign (non-cancerous) or malignant (cancerous).

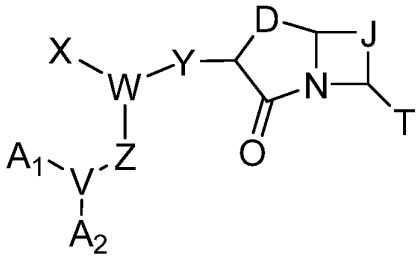
[0067] The term "anti-neoplastic agent," as used herein, refers to any compound that retards the proliferation, growth, or spread of a targeted (e.g., malignant) neoplasm.

[0068] The terms "prevent," "preventing," and "prevention," as used herein, refer to a decrease in the occurrence of pathological cells (e.g., hyperproliferative or neoplastic cells) in an animal. The prevention may be complete, e.g., the total absence of pathological cells in a subject. The prevention may also be partial, such that the occurrence of pathological cells in a subject is less than that which would have occurred without the present invention.

[0069] The term "apoptosis-modulating agents," as used herein, refers to agents which are involved in modulating (e.g., inhibiting, decreasing, increasing, promoting) apoptosis. In one embodiment, the apoptosis-modulating agent is an inducer of apoptosis. The term "inducer of apoptosis," as used herein, refers to an agent that induces apoptosis in cells (e.g., cancer cells), rendering those cells more susceptible to executing the apoptosis

program. In one embodiment, an agent that induces apoptosis is an anticancer agent. Examples of apoptosis-modulating agents include proteins which comprise a death domain such as, but not limited to, Fas/CD95, TRAMP, TNF RI, DR1, DR2, DR3, DR4, DR5, DR6, FADD, and RIP. Other examples of apoptotic-modulating agents include, but are not limited to, TNFα, Fas ligand, antibodies to Fas/CD95 and other TNF family receptors, TRAIL (also known as Apo2 Ligand or Apo2L/TRAIL), agonists (*e.g.*, monoclonal or polyclonal agonistic antibodies) of TRAIL-R1 or TRAIL-R2, Bcl-2, p53, BAX, BAD, Akt, CAD, PI3 kinase, PP1, and caspase proteins. Modulating agents broadly include agonists and antagonists of TNF family receptors and TNF family ligands. Apoptosis-modulating agents may be soluble or membrane bound (e.g. ligand or receptor). Preferred apoptosis-modulating agents are inducers of apoptosis, such as TNF or a TNF-related ligand, particularly a TRAMP ligand, a Fas/CD95 ligand, a TNFR-1 ligand, or TRAIL

[0070] The inhibitors of IAPs of the present invention are Smac mimetics having the general Formula I:



I

wherein:

A_1 and A_2 are independently selected from the group consisting of hydrogen and optionally substituted alkyl, wherein A_2 is absent when V is O;

V is selected from the group consisting of N, CH and O;

W is selected from the group consisting of CH and N;

X is selected from the group consisting of hydrogen, optionally substituted alkyl and aralkyl;

Y is selected from the group consisting of $CON(R^1)$, $N(R^1)CO$, C(O)O, OC(O), $(CH_2)_{1-3}$, wherein one or more CH_2 groups can be replaced by O, S, or NR^1, optionally substituted aryl and optionally substituted heteroaryl;

Z is $(CR^{2a}R^{2b})_r$;

D is $(CR^{3a}R^{3b})_n$-U-$(CR^{4a}R^{4b})_m$;

U is selected from the group consisting of $CR^{5a}R^{5b}$ and NR^6;

J is $(CR^{7a}R^{7b})_p$-L-$(CR^{8a}R^{8b})_q$;

T is optionally substituted heteroaryl;

n, m, p and q are independently selected from the group consisting of 0-5;

r is 0-3;

R^1 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

each R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^{7a}, R^{7b}, R^{8a} and R^{8b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

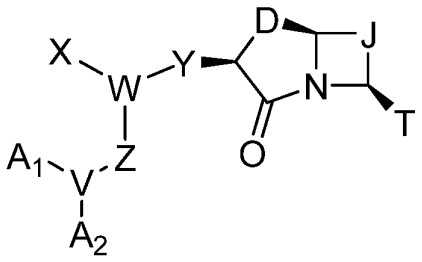
L is selected from the group consisting of O, S, NR^1, $NCOR^9$, $CR^{7a}R^{7b}$, C=O, C=S and $C=NR^1$; and

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

or pharmaceutically acceptable salt or prodrug thereof.

[0071] In another embodiment, Smac mimetics are compounds of Formula I wherein n is 1, m is 1 or 2, p is 0, L is CH_2 and q is 1. In another embodiment, Smac mimetics are compounds of Formula I wherein R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{8a} and R^{8b} are hydrogen. In another embodiment, Smac mimetics are compounds of Formula I wherein Y is CON(H), W is CH, r is 0 and V is N. In another embodiment, Smac mimetics are compounds of Formula I wherein Y is CON(H), W is CH, r is 1, V is N, R^{2a} is optionally substituted alkyl, R^{2b} is hydrogen and X is hydrogen.

[0072] In another particular embodiment, Smac mimetics are compounds of Formula II:

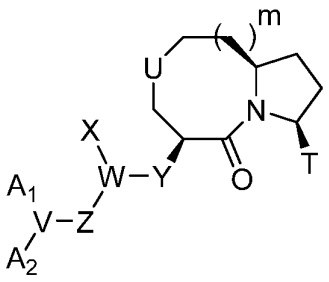


II

wherein A_1, A_2, V, Z, W, X, Y, D, J and T having the meanings as described above for Formula I; or a pharmaceutically acceptable salt or prodrug thereof.

[0073] In one embodiment, Smac mimetics are compounds of Formula II wherein n is 1, m is 1 or 2, p is 0, L is CH_2 and q is 1. In another embodiment, Smac mimetics are compounds of Formula II wherein R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{8a} and R^{8b} are hydrogen. In another embodiment, Smac mimetics are compounds of Formula II wherein Y is CON(H), W is CH, r is 0 and V is N. In another embodiment, Smac mimetics are compounds of Formula II wherein Y is CON(H), W is CH, r is 1, V is N, R^{2a} is optionally substituted alkyl, R^{2b} is hydrogen and X is hydrogen.

[0074] In another particular embodiment, Smac mimetics are compounds of Formula III:

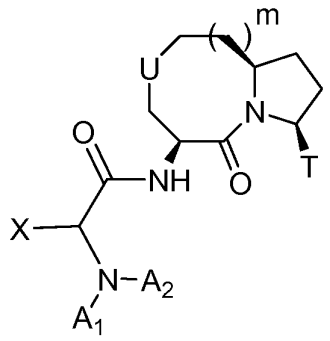


III

wherein A_1, A_2, V, Z, W, X, Y, U, and T have the meanings as described above for Formula I, and m is 1 or 2; or a pharmaceutically acceptable salt or prodrug thereof.

[0075] In another embodiment, Smac mimetics are compounds of Formula III wherein Y is CON(H), W is CH, r is 1, V is N, R^{2a} is optionally substituted alkyl, R^{2b} is hydrogen and X is hydrogen. In one embodiment, m is 1. In another embodiment, m is 2.

[0076] In another particular embodiment, Smac mimetics are compounds of Formula IV:

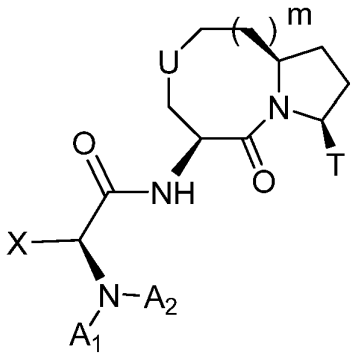


IV

wherein A_1, A_2, X, U, and T have the meanings as described above for Formula I, and m is 1 or 2; or a pharmaceutically acceptable salt or prodrug thereof.

[0077] In another embodiment, Smac mimetics are compounds of Formula IV wherein m is 1. In another embodiment, m is 2.

[0078] In another particular embodiment, Smac mimetics are compounds of Formula V:

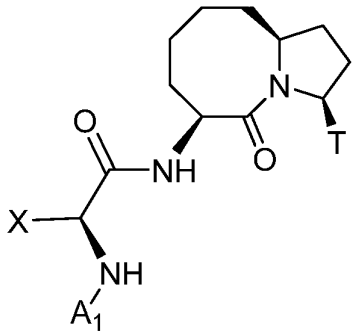


V

wherein A_1, A_2, X, U and T have the meanings as described above for Formula I, and m is 1 or 2; or a pharmaceutically acceptable salt or prodrug thereof.

[0079] In another embodiment, Smac mimetics are compounds of Formula V wherein A_1 is optionally substituted alkyl and A_2 is hydrogen. In another embodiment, X is optionally substituted alkyl. In another embodiment, U is CH_2. In another embodiment, U is NR^6. In another embodiment, R^6 is COR^9. In another embodiment, R^9 is optionally substituted alkyl or aralkyl. In another embodiment, R^9 is $-CH_2CH(CH_3)_2$. In another embodiment, m is 2. In another embodiment, m is 1.

[0080] In another particular embodiment, Smac mimetics are compounds of Formula VI:

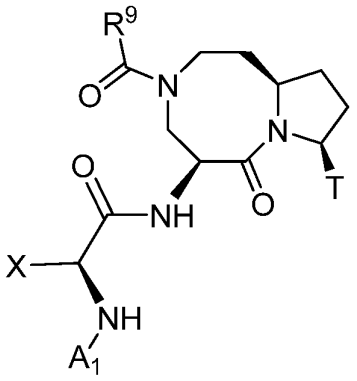


VI

wherein A_1 and X are optionally substituted alkyl and T is optionally substituted heteroaryl; or a pharmaceutically acceptable salt or prodrug thereof.

[0081] In one embodiment, A_1 and X are independently optionally substituted C_1-C_4 alkyl. In another embodiment, A_1 and X are independently C_1-C_4 alkyl. In another embodiment, A_1 and X are independently selected from the group consisting of methyl and ethyl. In one embodiment, A_1 and X are methyl. In one embodiment, A_1 is hydroxyalkyl and X is optionally substituted alkyl. In another embodiment, A_1 is $HOCH_2CH_2$-.

[0082] In another particular embodiment, Smac mimetics are compounds of Formula VII:



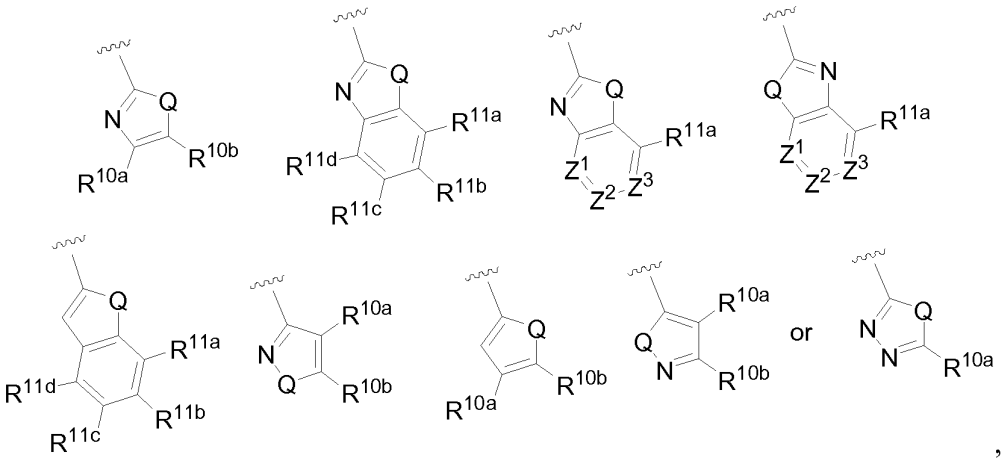
VII

wherein A_1 and X are optionally substituted alkyl, R^9 is optionally substituted alkyl or aralkyl, and T is optionally substituted heteroaryl; or a pharmaceutically acceptable salt or prodrug thereof.

[0083] In one embodiment, A_1 and X are independently optionally substituted C_1-C_4 alkyl. In another embodiment, A_1 and X are independently C_1-C_4 alkyl. In another

embodiment, A_1 and X are independently selected from the group consisting of methyl and ethyl. In one embodiment, A_1 and X are methyl. In another embodiment, A_1 is hydroxyalkyl and X is optionally substituted alkyl. In another embodiment, A_1 is $HOCH_2CH_2$-.

[0084] In another particular embodiment, Smac mimetics are compounds of Formulae I-VII wherein T is



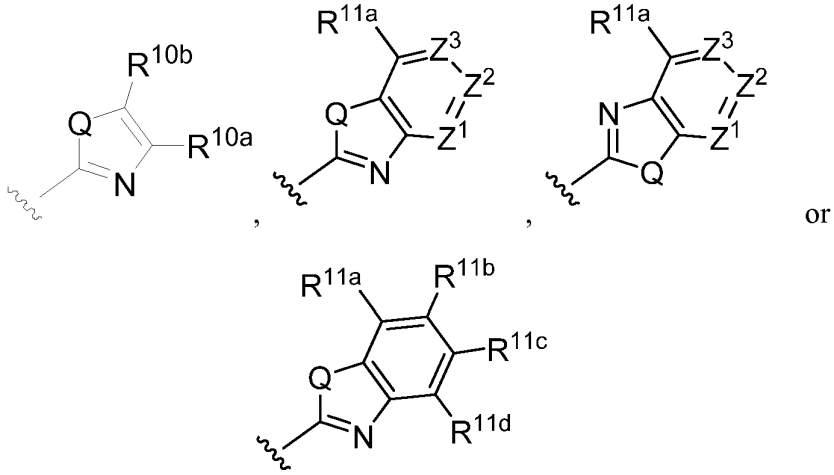
,

wherein Q is O, S or NR^{12}, R^{12} is hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclo, R^{10a}, R^{10b}, R^{11a}, R^{11b}, R^{11c} and R^{11d} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido, Z^1, Z^2, and Z^3 are independently CR^{11e} or N, wherein at least one of Z^1, Z^2, and Z^3 is CR^{11e} and at least one of Z^1, Z^2, and Z^3 is N, and R^{11e} is selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy,

aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido; or a pharmaceutically acceptable salt or prodrug thereof.

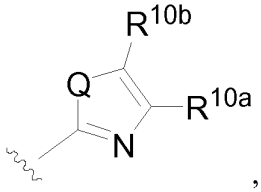
[0085] In one embodiment, at least one of R^{10a}, R^{10b}, R^{11a}, R^{11b}, R^{11c} and R^{11d} is optionally substituted phenyl, aralkyl, or optionally substituted alkyl. In one embodiment, R^{12} is hydrogen or optionally substituted alkyl. In one embodiment, R^{12} is hydrogen. In one embodiment, R^{10a} is optionally substituted phenyl. In one embodiment, R^{11a} is optionally substituted phenyl.

[0086] In another particular embodiment, Smac mimetics are compounds of Formulae I-VII wherein T is



wherein Q, Z^1, Z^2, Z^3, R^{10a}, R^{10b}, R^{11a}, R^{11b}, R^{11c} and R^{11d} have the meanings described above; or a pharmaceutically acceptable salt or prodrug thereof.

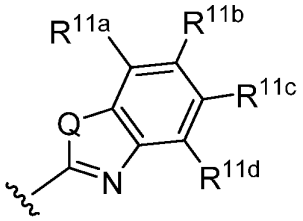
[0087] In another particular embodiment, Smac mimetics are compounds of Formulae I-VII wherein T is



wherein Q, R^{10a} and R^{10b} have the meanings described above; or a pharmaceutically acceptable salt or prodrug thereof.

[0088] In one embodiment, R^{10a} is optionally substituted aryl, aralkyl, or optionally substituted alkyl. In one embodiment, R^{10b} is hydrogen. In another embodiment, R^{10a} is optionally substituted aryl and R^{10b} is hydrogen. In one embodiment, Q is S. In one embodiment, Q is O. In one embodiment, Q is NR^{12}. In one embodiment, R^{12} is hydrogen or optionally substituted alkyl. In another embodiment R^{12} is hydrogen.

[0089] In another particular embodiment, Smac mimetics are compounds of Formulae I-VII wherein T is

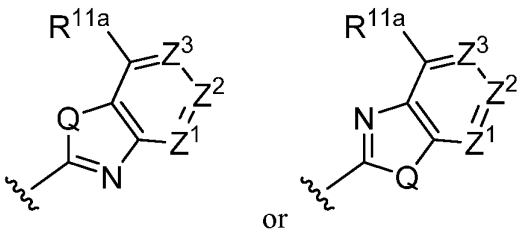


,

wherein Q, R^{11a}, R^{11b}, R^{11c} and R^{11d} have the meanings described above; or a pharmaceutically acceptable salt or prodrug thereof.

[0090] In one embodiment, R^{11a} is optionally substituted aryl, aralkyl, or optionally substituted alkyl. In one embodiment, R^{11b}, R^{11c} and R^{11d} are hydrogen. In another embodiment, R^{11a} is optionally substituted aryl and R^{11b}, R^{11c} and R^{11d} are hydrogen. In another embodiment, R^{11d} is optionally substituted aryl and R^{11a}, R^{11b}, and R^{11c} are hydrogen. In one embodiment, Q is S. In one embodiment, Q is O. In one embodiment, Q is NR^{12}. In one embodiment, R^{12} is hydrogen or optionally substituted alkyl. In another embodiment, R^{12} is hydrogen.

[0091] In another particulular embodiment, Smac mimetics are compounds of Formulae I-VII wherein T is

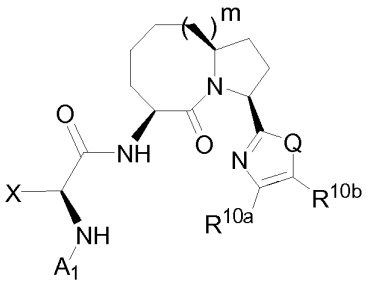


or

wherein Q, Z^1, Z^2, Z^3, and R^{11a} have the meanings described above; or a pharmaceutically acceptable salt or prodrug thereof.

[0092] In one embodiment, R^{11a} is optionally subsituted aryl, aralkyl, or optionally substituted alkyl and at least one of Z^1, Z^2, and Z^3 is N. In one embodiment, R^{11a} is optionally subsituted aryl. In one embodiment, Z^1 is N and Z^2 and Z^3 are CH. In one embodiment, Z^2 is N and Z^1 and Z^3 are CH. In one embodiment, Z^3 is N and Z^1 and Z^2 are CH. In one embodiment, Z^1 and Z^3 are N and Z^2 is CH. In one embodiment, Q is S. In one embodiment, Q is O. In one embodiment, Q is NR^{12}. In one embodiment, R^{12} is hydrogen or optionally substituted alkyl. In another embodiment, R^{12} is hydrogen.

[0093] In another particular embodiment, Smac mimetics are compounds of Formula VIII:

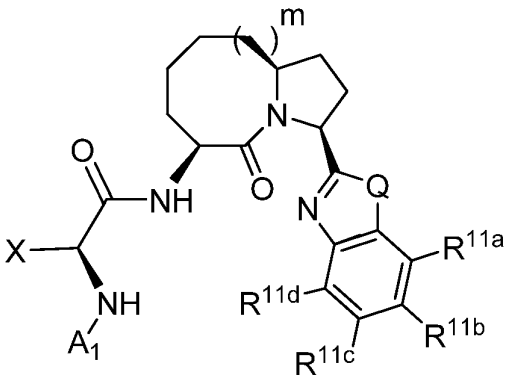


VIII

wherein A_1 and X are optionally substituted alkyl, m is 1 or 2 , Q is O, S or NR^{12}, R^{12} is hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclo, and R^{10a} and R^{10b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido; or a pharmaceutically acceptable salt or prodrug thereof.

[0094] In one embodiment, m is 2. In another embodiment, m is 1. In one embodiment, R^{10a} is optionally substituted aryl. In another embodiment, R^{10b} is hydrogen. In another embodiment, R^{10a} is optionally substituted aryl and R^{10b} is hydrogen. In one embodiment, R^9 is hydrogen or optionally substituted alkyl. In one embodiment, Q is S.

[0095] In another particular embodiment, Smac mimetics are compounds of Formula IX:

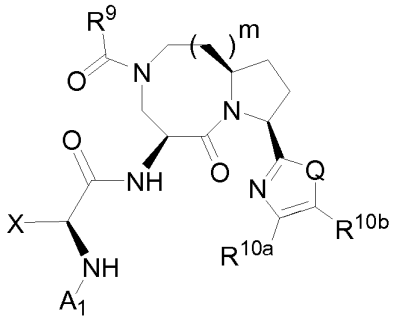


IX

wherein A_1 and X are optionally substituted alkyl, m is 1 or 2, Q is O, S or NR^{12}, R^{12} is hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclo, and R^{11a}, R^{11b}, R^{11c} and R^{11d} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido; or a pharmaceutically acceptable salt or prodrug thereof.

[0096] In one embodiment, m is 2. In another embodiment, m is 1. In one embodiment, R^{11a} is optionally substituted aryl, aralkyl, or optionally substituted alkyl. In one embodiment, R^{11b}, R^{11c} and R^{11d} are hydrogen. In another embodiment, R^{11a} is optionally substituted aryl and R^{11b}, R^{11c} and R^{11d} are hydrogen. In another embodiment, R^{11d} is optionally substituted aryl and R^{11a}, R^{11b}, and R^{11c} are hydrogen. In one embodiment, Q is NR^{12}. In one embodiment, R^{12} is hydrogen or optionally substituted alkyl. In another embodiment, R^{12} is hydrogen. In one embodiment, Q is S. In one embodiment, Q is O.

[0097] In another particular embodiment, Smac mimetics are compounds of Formula X:

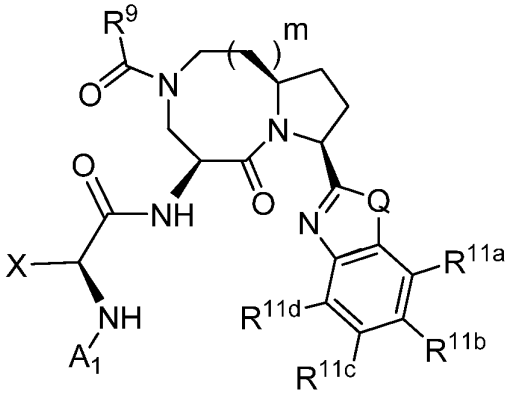


X

wherein A_1 and X are optionally substituted alkyl, R^9 is optionally substituted alkyl or aralkyl,, m is 1 or 2, Q is O, S or NR^{12}, R^{12} is hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclo, and R^{10a} and R^{10b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido; or a pharmaceutically acceptable salt or prodrug thereof.

[0098] In one embodiment, m is 2. In another embodiment, m is 1. In one embodiment, R^{10a} is optionally substituted aryl. In one embodiment, R^{10b} is hydrogen. In another embodiment, R^{10a} is optionally substituted aryl and R^{10b} is hydrogen. In one embodiment, R^{12} is hydrogen or optionally substituted alkyl. In one embodiment, R^9 is $-CH_2CH(CH_3)_2$. In one embodiment, Q is S.

[0099] In another particular embodiment, Smac mimetics are compounds of Formula XI:



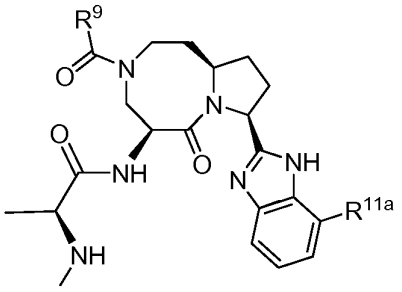
XI

wherein A_1 and X are optionally substituted alkyl, R^9 is optionally substituted alkyl or aralkyl, m is 1 or 2, Q is O, S or NR^{12}, R^{12} is hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclo, and R^{11a}, R^{11b}, R^{11c} and R^{11d} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido; or a pharmaceutically acceptable salt or prodrug thereof.

[00100] In one embodiment, m is 2. In another embodiment, m is 1. In one embodiment, R^{11a} is optionally substituted aryl, aralkyl, or optionally substituted alkyl. In one embodiment, R^{11b}, R^{11c} and R^{11d} are hydrogen. In another embodiment, R^{11a} is optionally substituted aryl and R^{11b}, R^{11c} and R^{11d} are hydrogen. In another embodiment, R^{11d} is optionally substituted aryl and R^{11a}, R^{11b}, and R^{11c} are hydrogen. In one embodiment, Q is NR^{12}. In one embodiment, R^{12} is hydrogen or optionally substituted alkyl. In another embodiment, R^{12} is hydrogen. In one embodiment, Q is S. In one embodiment, Q is O. In one embodiment, R^9 is $-CH_2CH(CH_3)_2$.

[00101] In another particular embodiment, Smac mimetics are compounds of Formula X wherein A_1 and X are methyl, m is 1, R^9 is optionally substituted alkyl or aralkyl, R^{10a} is optionally substituted aryl, R^{10b} is hydrogen, and Q is S.

[00102] In another particular embodiment, Smac mimetics are compounds of Formula XIa:



XIa

wherein R^9 is optionally substituted alkyl or aralkyl and R^{11a} is optionally substituted aryl.

[00103] The term "alkyl" as used herein by itself or part of another group refers to a straight-chain or branched saturated aliphatic hydrocarbon having from one to eighteen carbons or the number of carbons designated (e.g., C_1-C_{18} means 1 to 18 carbons). In one embodiment, the alkyl is a C_1-C_8 alkyl. In another embodiment, the alkyl is a C_1-C_6 alkyl. In another embodiment, the alkyl is a C_1-C_4 alkyl. Exemplary alkyl groups include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, *n*-hexyl, isohexyl, *n*-heptyl, 4,4-dimethylpentyl, *n*-octyl, 2,2,4-trimethylpentyl, nonyl, decyl and the like.

[00104] The term "optionally substituted alkyl" as used herein by itself or part of another group means that the alkyl as defined above is either unsubstituted or substituted with one, two or three substituents independently selected from hydroxy (i.e., -OH), nitro (i.e., $-NO_2$), cyano (i.e., -CN), optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido or sulfonamido. In one embodiment, the optionally substituted alkyl is substituted with two substituents. In another embodiment, the optionally substituted alkyl is substituted with one substituents. In another embodiment, the substituents are selected from hydroxyl (i.e., a hydroxyalkyl) or amino (i.e., an aminoalkyl). Exemplary optionally substituted alkyl groups include $-CH_2OCH_3$, $-CH_2CH_2NH_2$, $-CH_2CH_2CN$, $-CH_2SO_2CH_3$, hydroxymethyl, hydroxyethyl, hydroxypropyl and the like.

[00105] The term "alkylenyl" as used herein by itself or part of another group refers to a divalent alkyl radical containing one, two, three or four joined methylene groups. Exemplary alkylenyl groups include $-(CH_2)-$, $-(CH_2)_2-$, $-(CH_2)_3-$ and $-(CH_2)_4-$.

[00106] The term "haloalkyl" as used herein by itself or part of another group refers to an alkyl as defined above having one to six halo substituents. In one embodiment, the haloalkyl has one, two or three halo substituents. Exemplary haloalkyl groups include trifluoromethyl, $-CH_2CH_2F$ and the like.

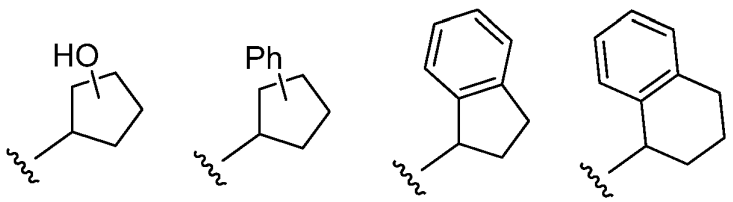
[00107] The term "hydroxyalkyl" as used herein by itself or part of another group refers to an alkyl as defined above having one, two or three hydroxy substituents. In one embodiment, the hydroxyalkyl has one hydroxy substituent. Exemplary hydroxyalkyl groups include hydroxymethyl, hydroxyethyl, hydroxypropyl and the like.

[00108] The term "aralkyl" as used herein by itself or part of another group refers to an optionally substituted alkyl as defined above having one, two or three optionally

substituted aryl substituents. In one embodiment, the aralkyl has two optionally substituted aryl substituents. In another embodiment, the aralkyl has one optionally substituted aryl substituent. In another embodiment, the aralkyl is an aryl(C_1-C_4 alkyl). In another embodiment, the aryl(C_1-C_4 alkyl) has two optionally substituted aryl substituents. In another embodiment, the aryl(C_1-C_4 alkyl) has one optionally substituted aryl substituent. Exemplary aralkyl groups include, for example, benzyl, phenylethyl, (4-fluorophenyl)ethyl, phenylpropyl, diphenylmethyl (i.e., Ph_2CH-), diphenylethyl (Ph_2CHCH_2-) and the like.

[00109] The term "cycloalkyl" as used herein by itself or part of another group refers to saturated and partially unsaturated (containing one or two double bonds) cyclic hydrocarbon groups containing one to three rings having from three to twelve carbon atoms (i.e., C_3-C_{12} cycloalkyl) or the number of carbons designated. In one embodiment, the cycloalkyl has one ring. In another embodiment, the cycloalkyl is a C_3-C_7 cycloalkyl. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, decalin, adamantyl and the like.

[00110] The term “optionally substituted cycloalkyl” as used herein by itself or part of another group means the cycloalkyl as defined above is either unsubstituted or substituted with one, two or three substituents independently selected from halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido or sulfonamido. The term "optionally substituted cycloalkyl" also means the cycloalkyl as defined above may be fused to an optionally substituted aryl. Exemplary optionally substituted cycloalkyl groups include



and the like.

[00111] The term "alkenyl" as used herein by itself or part of another group refers to an alkyl group as defined above containing one, two or three carbon-to-carbon double bonds. In one embodiment, the alkenyl has one carbon-to-carbon double bond. Exemplary alkenyl groups include $-CH=CH_2$, $-CH_2CH=CH_2$, $-CH_2CH_2CH=CH_2$, $-CH_2CH_2CH=CHCH_3$ and the like.

[00112] The term "optionally substituted alkenyl" as used herein by itself or part of another group means the alkenyl as defined above is either unsubstituted or substituted with one, two or three substituents independently selected from halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido or sulfonamido. Exemplary optionally substituted alkenyl groups include $-CH=CHPh$, $-CH_2CH=CHPh$ and the like.

[00113] The term "cycloalkenyl" as used herein by itself or part of another group refers to a cycloalkyl group as defined above containing one, two or three carbon-to-carbon double bonds. In one embodiment, the cycloalkenyl has one carbon-to-carbon double bond. Exemplary cycloalkenyl groups include cyclopentene, cyclohexene and the like.

[00114] The term "optionally substituted cycloalkenyl" as used herein by itself or part of another group means the cycloalkenyl as defined above is either unsubstituted or substituted with one, two or three substituents independently selected from halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido or sulfonamido.

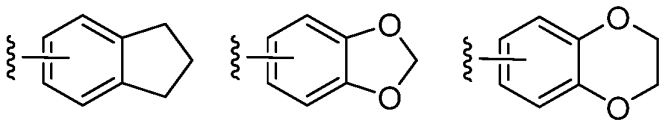
[00115] The term "alkynyl" as used herein by itself or part of another group refers to an alkyl group as defined above containing one to three carbon-to-carbon triple bonds. In one embodiment, the alkynyl has one carbon-to-carbon triple bond. Exemplary alkynyl groups include $-C\equiv CH$, $-C\equiv CCH_3$, $-CH_2C\equiv CH$, $-CH_2CH_2C\equiv CH$ and $-CH_2CH_2C\equiv CCH_3$.

[00116] The term "optionally substituted alkynyl" as used herein by itself or part of another group means the alkynyl as defined above is either unsubstituted or substituted

with one, two or three substituents independently selected from halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido or sulfonamido. Exemplary optionally substituted alkenyl groups include -C≡CPh, -CH_2C≡CPh and the like.

[00117] The term "aryl" as used herein by itself or part of another group refers to monocyclic and bicyclic aromatic ring systems having from six to fourteen carbon atoms (i.e., C_6-C_{14} aryl) such as phenyl (abbreviated as Ph), 1-naphthyl and 2-naphthyl and the like.

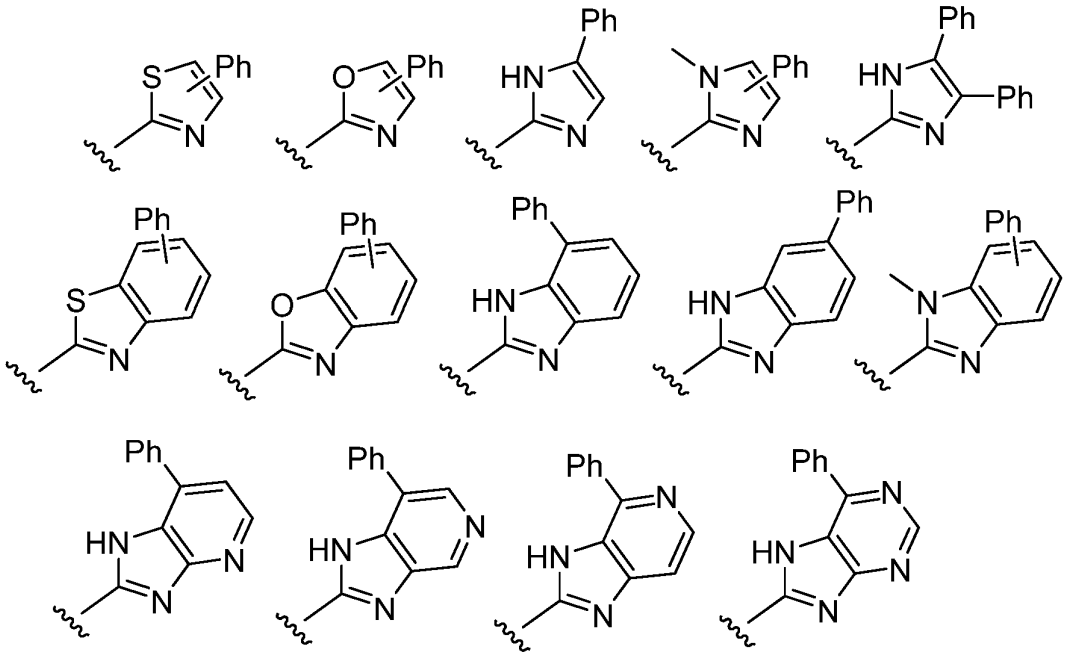
[00118] The term “optionally substituted aryl” as used herein by itself or part of another group means the aryl as defined above is either unsubstituted or substituted with one to five substituents independently selected from halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido or sulfonamido. In one embodiment, the optionally substituted aryl is an optionally substituted phenyl. In one embodiment, the optionally substituted phenyl has four substituents. In another embodiment, the optionally substituted phenyl has three substituents. In another embodiment, the optionally substituted phenyl has two substituents. In another embodiment, the optionally substituted phenyl has one substituent. Exemplary substituted aryl groups include 2-methylphenyl, 2-methoxyphenyl, 2-fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 3-methylphenyl, 3-methoxyphenyl, 3-fluorophenyl, 3-chlorophenyl, 4-methylphenyl, 4-ethylphenyl, 4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 2,6-di-fluorophenyl, 2,6-di-chlorophenyl, 2-methyl, 3-methoxyphenyl, 2-ethyl, 3-methoxyphenyl, 3,4-di-methoxyphenyl, 3,5-di-fluorophenyl 3,5-di-methylphenyl and 3,5-dimethoxy, 4-methylphenyl and the like. The term optionally substituted aryl is meant to include groups having fused optionally substituted cycloalkyl and fused optionally substituted heterocyclo rings. Examples include



and the like.

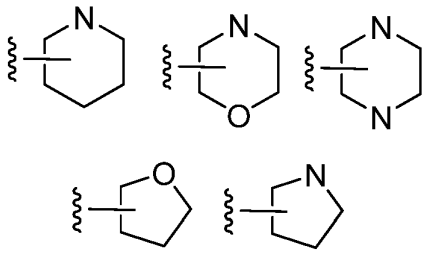
[00119] The term "heteroaryl" as used herein by itself or part of another group refers to monocyclic and bicyclic aromatic ring systems having from five to fourteen carbon atoms (i.e., C_5-C_{14} heteroaryl) and one, two, three or four heteroatoms independently selected from the group consisting of oxygen, nitrogen and sulfur. In one embodiment, the heteroaryl has three heteroatoms. In one embodiment, the heteroaryl has two heteroatoms. In one embodiment, the heteroaryl has one heteroatom. Exemplary heteroaryl groups include 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, purinyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 2-benzthiazolyl, 4-benzthiazolyl, 5-benzthiazolyl, 5-indolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 2-quinolyl 3-quinolyl, 6-quinolyl and the like. The term heteroaryl is meant to include possible N-oxides. Exemplary N-oxides include pyridyl N-oxide and the like.

[00120] The term "optionally substituted heteroaryl" as used herein by itself or part of another group means the heteroaryl as defined above is either unsubstituted or substituted with one to four substituents, typically one or two substituents, independently selected from halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido or sulfonamido. In one embodiment, the optionally substituted heteroaryl has one substituent. In another embodiment, the substituent is an optionally substituted aryl, aralkyl, or optionally substituted alkyl. In another embodiment, the substituent is an optionally substituted phenyl. Any available carbon or nitrogen atom my be substituted. Exemplary optionally substituted heteroaryl groups include



and the like.

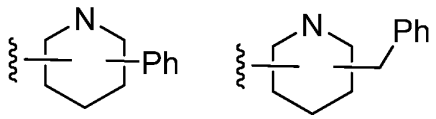
[00121] The term "heterocyclo" as used herein by itself or part of another group refers to saturated and partially unsaturated (containing one or two double bonds) cyclic groups containing one to three rings having from two to twelve carbon atoms (i.e., C_2-C_{12} heterocyclo) and one or two oxygen, sulfur or nitrogen atoms. The heterocyclo can be optionally linked to the rest of the molecule through a carbon or nitrogen atom. Exemplary heterocyclo groups include



and the like.

[00122] The term "optionally substituted heterocyclo" as used herein by itself or part of another group means the heterocyclo as defined above is either unsubstituted or substituted with one to four substituents independently selected from halo, nitro, cyano,

hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, $-COR^c$, $-SO_2R^d$, $-N(R^e)COR^f$, $-N(R^e)SO_2R^g$ or $-N(R^e)C=N(R^h)$-amino. Substitution may occur on any available carbon or nitrogen atom. Exemplary substituted heterocyclo groups include



and the like. An optionally substituted heterocyclo may be fused to an aryl group to provide an optionally substituted aryl as described above.

[00123] The term "alkoxy" as used herein by itself or part of another group refers to a haloalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl or optionally substituted alkynyl attached to a terminal oxygen atom. Exemplary alkoxy groups include methoxy, *tert*-butoxy, $-OCH_2CH=CH_2$ and the like.

[00124] The term "aryloxy" as used herein by itself or part of another group refers to an optionally substituted aryl attached to a terminal oxygen atom. Exemplary aryloxy groups include phenoxy and the like.

[00125] The term "aralkyloxy" as used herein by itself or part of another group refers to an aralkyl attached to a terminal oxygen atom. Exemplary aralkyloxy groups include benzyloxy and the like.

[00126] The term "alkylthio" as used herein by itself or part of another group refers to a haloalkyl, aralkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl or optionally substituted alkynyl attached to a terminal sulfur atom. Exemplary alkyl groups include $-SCH_3$ and the like.

[00127] The term "halo" or "halogen" as used herein by itself or part of another group refers to fluoro, chloro, bromo or iodo. In one embodiment, the halo is fluoro or chloro.

[00128] The term "amino" as used herein by itself or part of another group refers to a radical of formula $-NR^aR^b$ wherein R^a and R^b are independently hydrogen, haloalkyl, aralkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclo, optionally substituted aryl or optionally substituted heteroaryl; or

R^a and R^b taken together with the nitrogen atom to which they are attached form a four to seven membered optionally substituted heterocyclo. Exemplary amino groups include -NH_2, -N(H)CH_3, -N(CH_3)$_2$, N(H)CH_2CH_3, N(CH_2CH_3), -N(H)CH_2Ph and the like.

[00129] The term "carboxamido" as used herein by itself or part of another group refers to a radical of formula –CO-amino. Exemplary carboxamido groups include -$CONH_2$, -CON(H)CH_3, -CON(H)Ph, -CON(H)CH_2CH_2Ph, -CON(CH_3)$_2$, CON(H)$CHPh_2$ and the like.

[00130] The term "sulfonamido" as used herein by itself or part of another group refers to a radical of formula -SO_2-amino. Exemplary sulfonamido groups include -SO_2NH_2, -SO_2N(H)CH_3, -SO_2N(H)Ph and the like.

[00131] The term "about," as used herein, includes the recited number ± 10%. Thus, "about 10" means 9 to 11.

[00132] The term "leaving group" as used herein refers to an atom or group that becomes detached from an atom or group in what is considered to be the residual or main part of the substrate in a specified reaction. In amide coupling reactions, exemplary leaving groups (i.e., leaving groups designated L^1) include -F, -Cl, -Br, -OH, -OC_6F_5, -O(CO)alkyl and the like. In one embodiment, the leaving group, L^1, is -Cl. In another embodiment, the leaving group, L^1, is an activated form of -OH (e.g., OBt, O-acylisourea). An activating agent (e.g., dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBop)) may be employed to active a carboxylic acid (i.e, the leaving group is -OH) toward amide formation. Such activating agents are well known to those of skill in the art of organic synthesis. Other additives, such as N-hydroxybenzotriazole (HOBt) or N-hydroxysuccinimide (HOSu), may also be added to optimize reaction parameters (e.g., rate, yield, purity, racemization). In nucleophilic displacement reactions (e.g., S_N2 reactions), exemplary leaving groups (i.e., leaving groups designated L^2) include -Cl, -Br, -I, -OSO_2Me (mesylate), -OSO_2CF_3 (triflate), -$OSO_2C_6H_5$ (besylate), -$OSO_2CH_3C_6H_4$ (tosylate) and the like. In one embodiment, the leaving group, L^2, is -Cl or -Br. In another embodiment, the leaving group, L^2, is -Br.

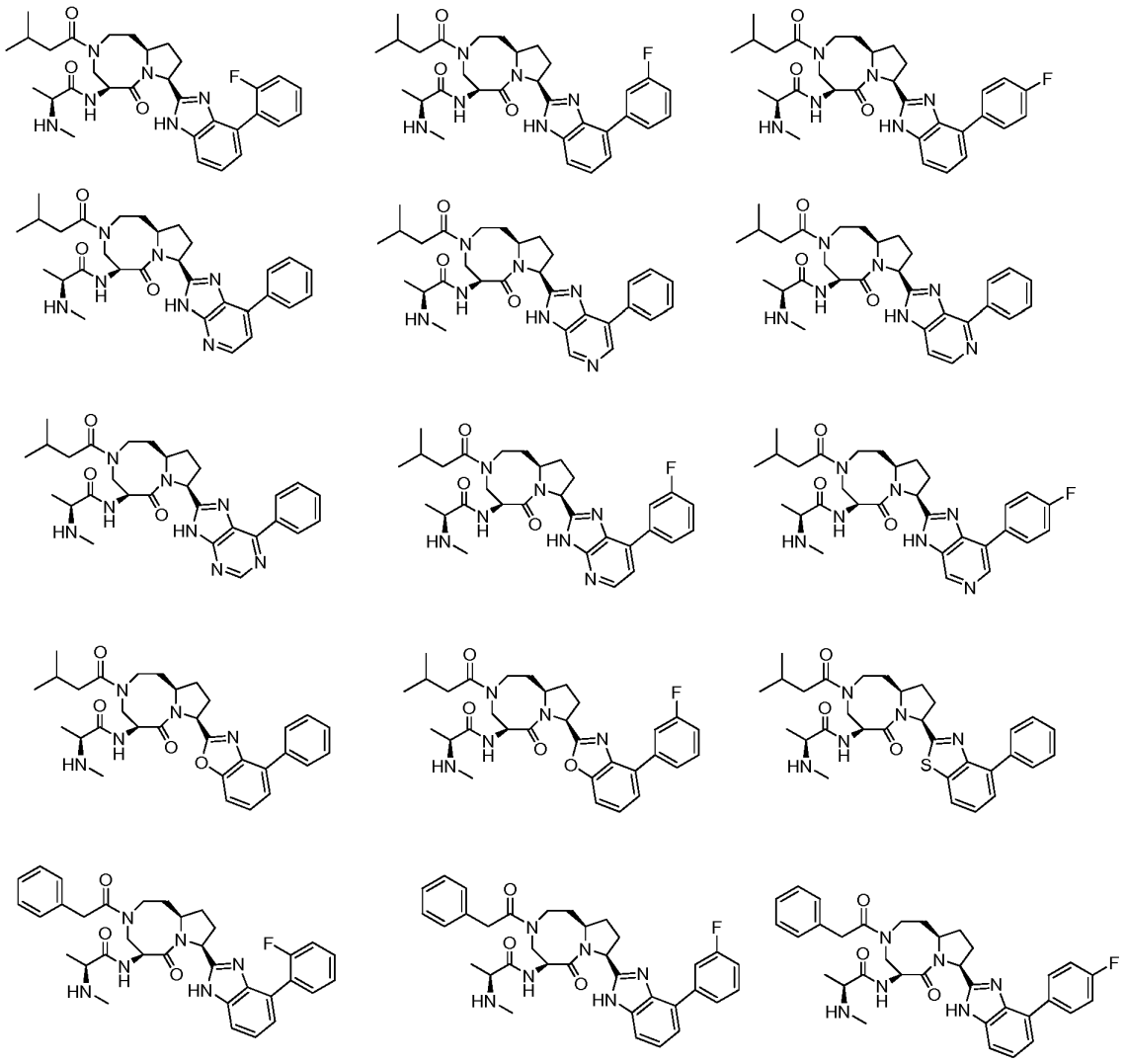
[00133] The term "amine protecting group" as used herein refers to group that blocks (i.e., protects) the amine functionality while reactions are carried out on other functional

groups or parts of the molecule. Those skilled in the art will be familiar with the selection, attachment, and cleavage of amine protecting groups and will appreciate that many different protective groups are known in the art, the suitability of one protective group or another being dependent on the particular the synthetic scheme planned. Treatises on the subject are available for consultation, such as Greene and Wuts, "Protective Groups in Organic Synthesis," 3rd Ed., pp. 17-245 (J. Wiley & Sons, 1999), the disclosure of which is incorporated by reference. Suitable amine protecting groups include the carbobenzyloxy (Cbz), *tert*-butyloxycarbonyl (BOC), 9-fluorenylmethyloxycarbonyl (FMOC) and benzyl (Bn) group.

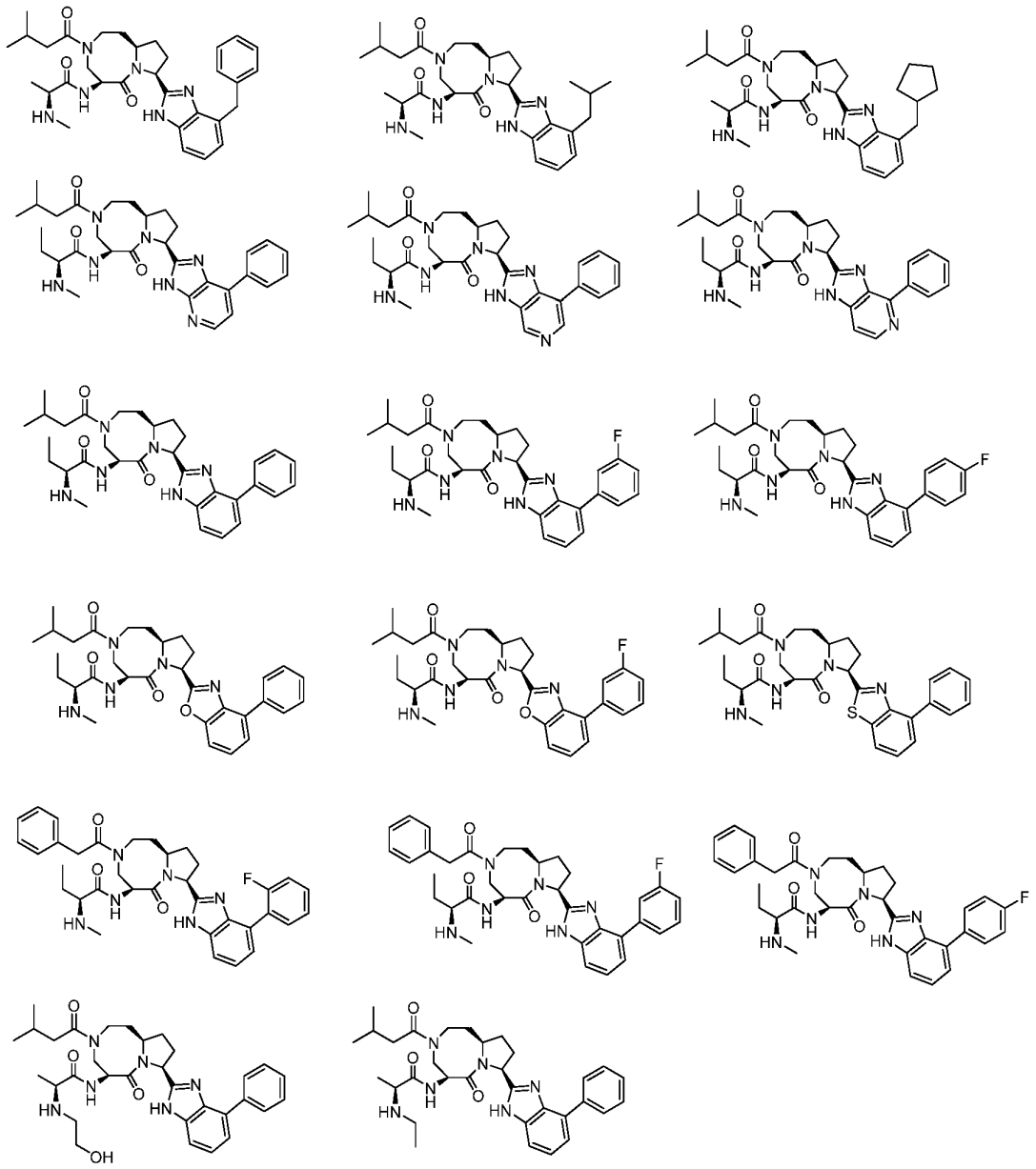
[00134] Throughout the specification, groups an optional substituents thereof are chosen to provide stable moieties and compounds.

[00135] Certain of the compounds of the present invention may exist as stereoisomers including optical isomers. The invention includes all stereoisomers, both as pure individual stereoisomer preparations and enriched preparations of each, and both the racemic mixtures of such stereoisomers as well as the individual enantiomers that may be separated according to methods that are well known to those of skill in the art.

[00136] In certain embodiments of the invention, the compound of Formula I is:



[00137] In other embodiments of the invention, the compound of Formula I is:



[00138] In particular embodiments of the invention the compound of Formula I is selected from the group consisting of:

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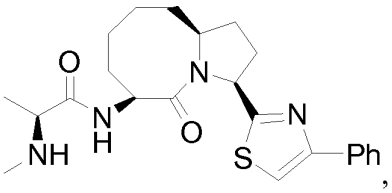

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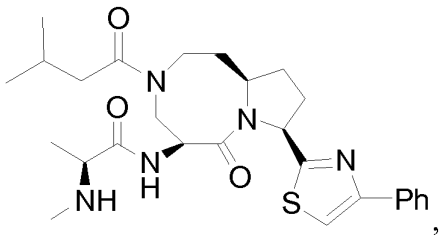
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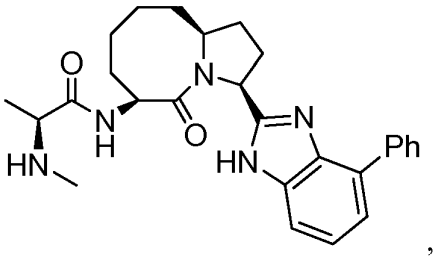
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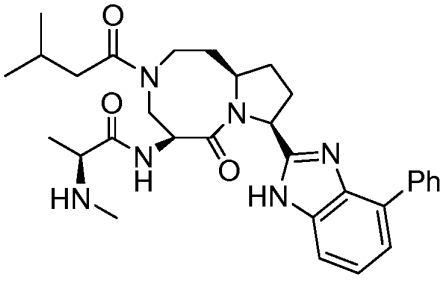
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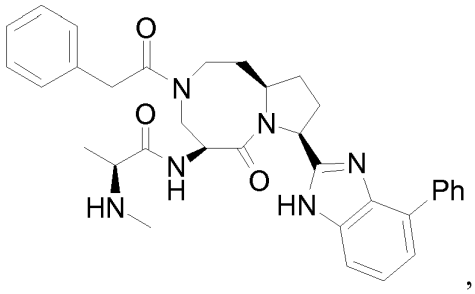
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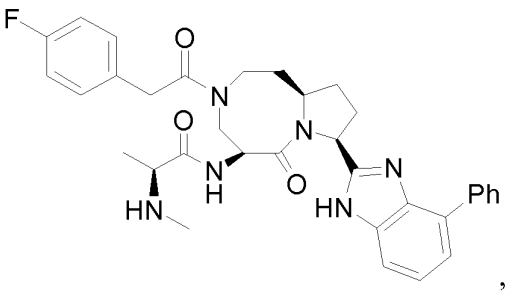
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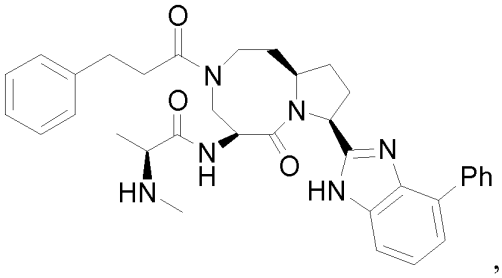
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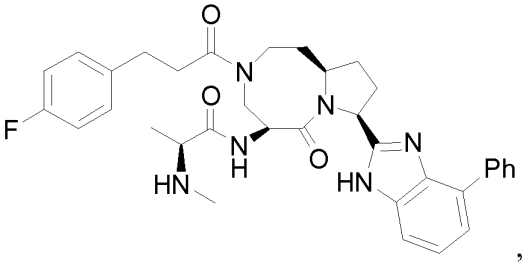
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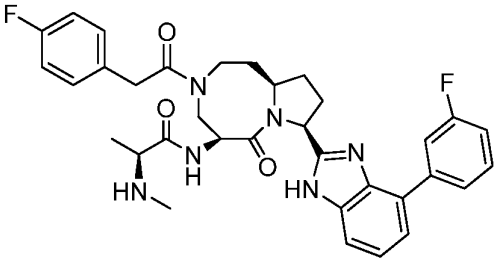
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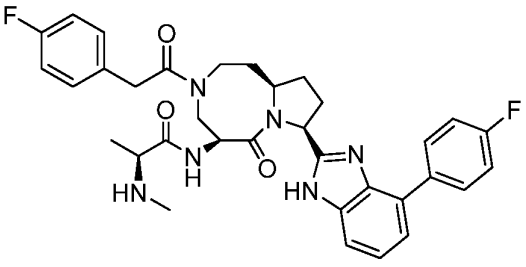
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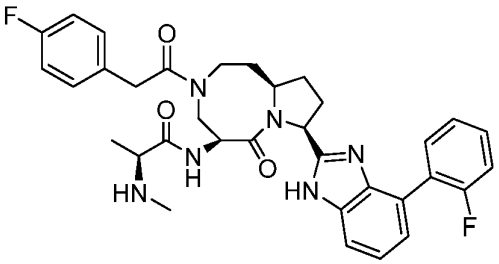
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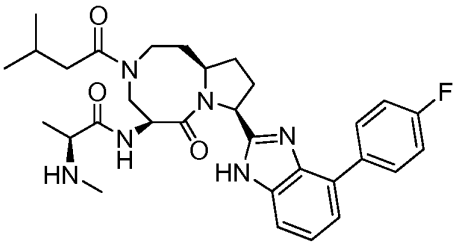
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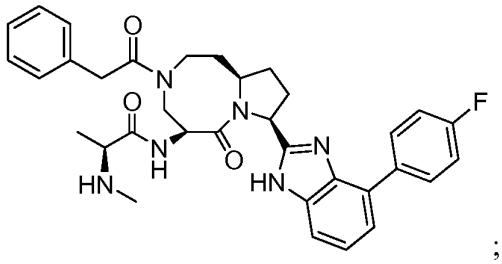

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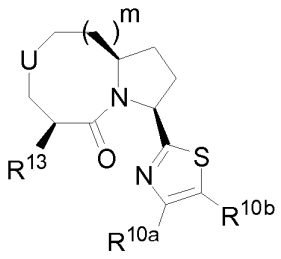
or a pharmaceutically acceptable salt or prodrug thereof.

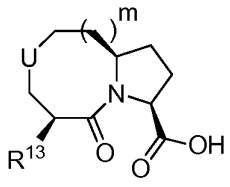
[00139] The present invention also pertains to a process for the preparation of a compound of Formula XII



XII

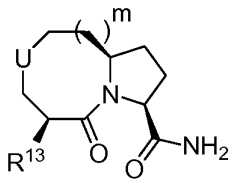
comprising:

a) condensing a compound of Formula XIII



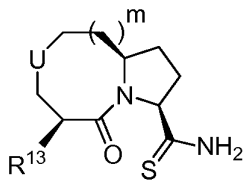
XIII

with ammonia to give a compound of Formula XIV



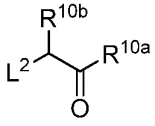
XIV

b) converting a compound of Formula XIV to a compound of Formula XV



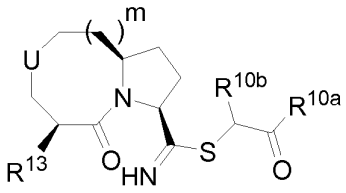
XV

c) condensing a compound of Formula XV with a compound of Formula XVI



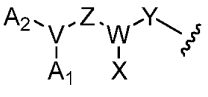
XVI

wherein L^2 is a leaving group, to give a compound of Formula XVII,



XVII

and b) cyclizing a compound of Formula XVII, to give a compound of Formula XII, wherein:

R^{13} is selected from the group consisting of $N(H)P^1$ and  ;

P^1 is an amine protecting group;

A_1 and A_2 are independently selected from the group consisting of hydrogen and optionally substituted alkyl, wherein A_2 is absent when V is O;

V is selected from the group consisting of N, CH and O;

W is selected from the group consisting of CH and N;

X is selected from the group consisting of hydrogen, optionally substituted alkyl and aralkyl;

Y is selected from the group consisting of $CON(R^1)$, $N(R^1)CO$, C(O)O, OC(O), $(CH_2)_{1-3}$, wherein one or more CH_2 groups can be replaced by O, S, or NR^1, optionally substituted aryl and optionally substituted heteroaryl;

Z is $(CR^{2a}R^{2b})_r$;

U is selected from the group consisting of $CR^{5a}R^{5b}$ and NR^6;

m is 1 or 2;

r is 0-3;

R^1 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

each R^{2a}, R^{2b}, R^{5a} and R^{5b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

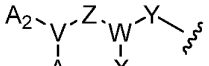
R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo; and

R^{10a} and R^{10b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo.

[00140] In one embodiment, R^{13} is $-N(H)P^1$. In one embodiment, P^1 is selected from the group consisting of carbobenzyloxy, *tert*-butyloxycarbonyl and benzyl. In one embodiment, P^1 is selected from the group consisting of carbobenzyloxy and *tert*-butyloxycarbonyl. In one embodiment, P^1 is carbobenzyloxy. In one embodiment, P^1 is *tert*-butyloxycarbonyl. In one embodiment, U is CH_2. In one embodiment, U is $NCOR^9$.

In another embodiment, R^9 is optionally substituted alkyl. In one embodiment, m is 2. In one embodiment, m is 1.

[00141] In one embodiment, L^2 is selected from the group consisting of Cl, -Br, -I, $-OSO_2Me$, $-OSO_2CF_3$, $-OSO_2C_6H_5$ and $-OSO_2CH_3C_6H_4$. In another embodiment, L^2 is selected from the group consisting of -Cl and -Br. In another embodiment, L^2 is Br. In one embodiment, R^{10a} is optionally substituted phenyl. In one embodiment, R^{10b} is hydrogen.

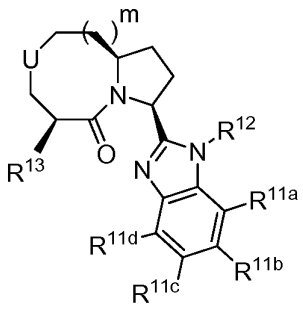
[00142] In one embodiment, R^{13} is  . In one embodiment, Y is CON(H), W is CH, r is 0 and V is N. In one embodiment, U is CH_2. In one embodiment, U is $NCOR^9$. In another embodiment, R^9 is optionally substituted alkyl. In one embodiment, m is 2. In one embodiment, m is 1.

[00143] In one embodiment, ammonia is condensed with a compound of Formula XIII in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and N-hydroxybenzotriazole in an inert organic solvent (e.g., acetonitrile, tetrahydrofuran, dimethylformamide, etc.) at a temperature of about -20°C to about 25°C. In one embodiment, a compound of XIV is converted to a compound of Formula XV using P_4S_{10} in an inert organic solvent (e.g., dichloromethane, etc.) at a temperature of about -20°C to about 45°C. In one embodiment, the condensation of a compound of Formula XV with a compound of Formula XVI is carried out in an inert organic solvent (e.g., acetonitrile, tetrahydrofuran, dimethylformamide, etc.) at a temperature of about 0°C to about 50°C. In one embodiment, a compound of Formula XVII is cyclized in methanol, ethanol, propanol, isopropanol, or butanol. In one embodiment, the cyclization of a compound of Formula XVII is carried out at a temperature of about 25°C to about 100°C, in one embodiment, above 30°C. In one embodiment, the cyclization of a compound of Formula XVIII is carried out in refluxing solvent. In one embodiment, the cyclization of a compound of Formula XVIII is carried out in refluxing ethanol.

[00144] The progress of any of the above reactions can be monitored by analytical methods known in the art such as TLC, LC, LC/MS, HPLC, NMR, etc. A compound of Formula XII, as well as any synthetic intermediates (i.e., a compound of Formula XIV, XV or XVII), can be isolated and purified by any means known in the art such normal- and reverse-phase column chromatography (e.g., column chromatography on silica gel or

reverse-phase HPLC), crystallization, extraction, etc. The product thus isolated can be subjected to further purification (e.g., recrystallization) until the desired level of purity is achieved. In one embodiment, a compound of Formula XII has a purity of 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more.

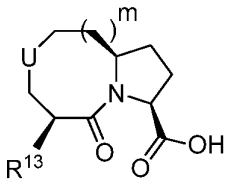
[00145] In another embodiment, the invention pertains to a process for the preparation of a compound of Formula XVIII



XVIII

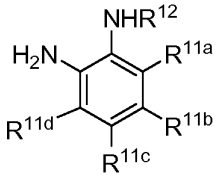
comprising:

a) condensing a compound of Formula XIII



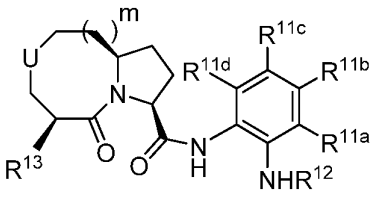
XIII

with a compound of Formula XIX



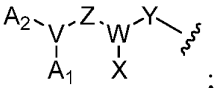
XIX

to give a compound of Formula XX



XX

and b) cyclizing a compound of Formula XX, to give a compound of Formula XVIII, wherein:

R^{13} is selected from the group consisting of $N(H)P^1$ and  ;

P^1 is an amine protecting group;

A_1 and A_2 are independently selected from the group consisting of hydrogen and optionally substituted alkyl, wherein A_2 is absent when V is O;

V is selected from the group consisting of N, CH and O;

W is selected from the group consisting of CH and N;

X is selected from the group consisting of hydrogen, optionally substituted alkyl and aralkyl;

Y is selected from the group consisting of $CON(R^1)$, $N(R^1)CO$, C(O)O, OC(O), $(CH_2)_{1-3}$, wherein one or more CH_2 groups can be replaced by O, S, or NR^1, optionally substituted aryl and optionally substituted heteroaryl;

Z is $(CR^{2a}R^{2b})_r$;

U is selected from the group consisting of $CR^{5a}R^{5b}$ and NR^6;

m is 1 or 2;

r is 0-3;

R^1 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

each R^{2a}, R^{2b}, R^{5a} and R^{5b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

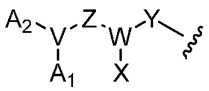
R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

R^{11a}, R^{11b}, R^{11c} and R^{11d} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido, and

R^{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo.

[00146] In one embodiment, R^{11a} is optionally substituted phenyl. In one embodiment, R^{11b}, R^{11c} and R^{11d} are hydrogen. In one embodiment, R^{11a} is optionally substituted phenyl, and R^{11b}, R^{11c} and R^{11d} are hydrogen. In one embodiment, m is 2. In one embodiment, m is 1. In one embodiment, U is CH_2. In one embodiment, U is $NCOR^9$. In another embodiment, R^9 is optionally substituted alkyl. In one embodiment, R^{12} is hydrogen.

[00147] In one embodiment, R^{13} is $-N(H)P^1$. In one embodiment, P^1 is selected from the group consisting of carbobenzyloxy, *tert*-butyloxycarbonyl and benzyl. In one embodiment, P^1 is selected from the group consisting of carbobenzyloxy and *tert*-butyloxycarbonyl. In one embodiment, P^1 is carbobenzyloxy. In one embodiment, P^1 is *tert*-butyloxycarbonyl. In one embodiment, U is CH_2. In one embodiment, U is $NCOR^9$. In another embodiment, R^9 is optionally substituted alkyl. In one embodiment, m is 2. In one embodiment, m is 1.

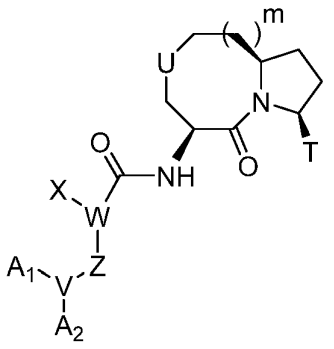
[00148] In one embodiment, R^{13} is  . In one embodiment, Y is CON(H), W is CH, r is 0 and V is N. In one embodiment, U is CH_2. In one embodiment, U is

$NCOR^9$. In another embodiment, R^9 is optionally substituted alkyl. In one embodiment, m is 2. In one embodiment, m is 1.

[00149] In one embodiment, a compound of Formula XIII is condensed with a compound of Formula XIX in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and N-hydroxybenzotriazole in an inert organic solvent (e.g., acetonitrile, tetrahydrofuran, dimethylformamide, etc.) at a temperature of about -20°C to about 25°C. In one embodiment, a compound of Formula XX is cyclized in acetic acid at a temperature of about 25°C to about 118°C. In another embodiment, a compound of Formula XX is cyclized in refluxing acetic acid.

[00150] The progress of any of the above reactions can be monitored by analytical methods known in the art such as TLC, LC, LC/MS, HPLC, NMR, etc. A compound of Formula XVIII, as well as any synthetic intermediate(s) (i.e., a compound of XIX), can be isolated and purified by any means known in the art such normal- and reverse-phase column chromatography (e.g., column chromatography on silica gel or reverse-phase HPLC), crystallization, extraction, etc. The product thus isolated can be subjected to further purification (e.g., recrystallization) until the desired level of purity is achieved. In one embodiment, a compound of Formula XVIII has a purity of 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more.

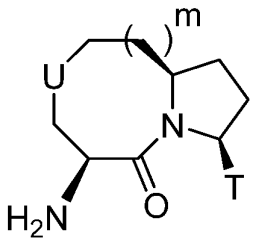
[00151] The present invention also pertains to a process for preparing a compound of Formula XXI



XXI

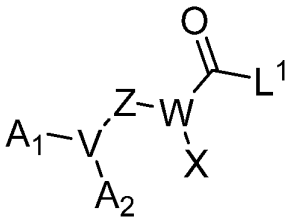
comprising:

condensing a compound of Formula XXIII



XXIII

with a compound of Formula XXIV



XXIV

wherein L^1 is a leaving group, to give a compound of Formula XXI,

wherein:

A_1 and A_2 are independently selected from the group consisting of hydrogen and optionally substituted alkyl, wherein A_2 is absent when V is O;

V is selected from the group consisting of N, CH and O;

W is selected from the group consisting of CH and N;

X is selected from the group consisting of hydrogen, optionally substituted alkyl and aralkyl;

Z is $(CR^{2a}R^{2b})_r$;

U is selected from the group consisting of $CR^{5a}R^{5b}$ and NR^6;

m is 1 or 2;

r is 0-3;

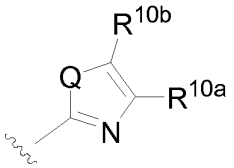
each R^{2a}, R^{2b}, R^{5a} and R^{5b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

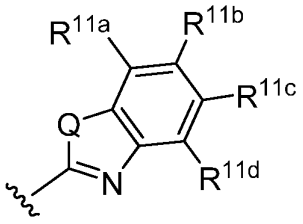
R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo; and

T is optionally substituted heteroaryl.

[00152] In one embodiment, W is CH and V is N. In one embodiment, T is selected from the group consisting of



and



,

wherein:

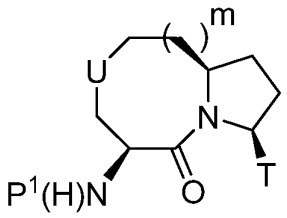
Q is selected from the group consisting of O, S and NR^{12};

R^{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo; and

R^{10a}, R^{10b}, R^{11a}, R^{11b}, R^{11c} and R^{11d} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido. In one embodiment, U is CH_2. In one embodiment, U is $NCOR^9$. In one embodiment, R^9 is optionally substituted alkyl. In one embodiment, m is 2. In one embodiment, m is 1.

[00153] In one embodiment, L^1 is selected from the group consisting of -Cl and -OH. In one embodiment, L^1 is -OH and the reaction is carried out in the presence of an activating agent.

[00154] In one embodiment, a compound of Formula XXIII is prepared by removing P^1 from a compound of Formula XXII



XXII

wherein P^1 is a leaving group. In one embodiment, P^1 is carbobenzyloxy, *tert*-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl or benzyl. In one embodiment, P^1 is carbobenzyloxy or *tert*-butyloxycarbonyl. In one embodiment, P^1 is carbobenzyloxy. In one embodiment, P^1 is or *tert*-butyloxycarbonyl.

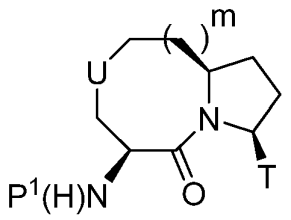
[00155] In one embodiment, the condensation reaction is conducted in an inert organic solvent such as acetonitrile, benzene, chloroform, 1,2-dichloroethane, 1,2,-dimethoxyethane, dimethylformamide, dimethylsulfoxide, dioxane, dichloromethane, N-methyl-2-pyrrolidinone or tetrahydrofuran. In another embodiment, the condensation reaction is carried out in tetrahydrofuran. In another embodiment, the condensation reaction is carried out in dichloromethane. In one embodiment, the condensation reaction is carried out at about -20°C to about 35°C. In another embodiment, the condensation reaction is carried out at about 25°C. In one embodiment, the condensation reaction is complete in about 1 hour to about 48 hours. In another embodiment, the condensation reaction is complete in about 12 hours.

[00156] In one embodiment, L^1 is Cl, -OH or -OBt. In one embodiment, L^1 is -OH or -OBt. In another embodiment, the condensation reaction is carried out in the presence of an activating agent. In another embodiment, the activating agent is dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide or benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate. In another embodiment, the activating agent is 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. In another embodiment, the condensation reaction is carried out in the presence of an

activating agent and an additive that optimize reaction parameters such as purity and yield. In another embodiment, the additive is N-hydroxybenzotriazole.

[00157] The progress of the condensation reaction between a compound of Formula XXIII and Formula XXIV can be monitored by analytical methods known in the art such as TLC, LC, LC/MS, HPLC, NMR, etc. A compound of Formula XXI can be isolated and purified by any means known in the art such normal- and reverse-phase column chromatography (e.g., column chromatography on silica gel or reverse-phase HPLC), crystallization, extraction, etc. The product thus isolated can be subjected to further purification (e.g., recrystallization) until the desired level of purity is achieved. In one embodiment, a compound of Formula XXI has a purity of 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more.

[00158] In another embodiment, the invention pertains to a compound having Formula XXII:



XXII

wherein:

T is optionally substituted heteroaryl;

m is 1 or 2;

U is CH_2 or NR^6

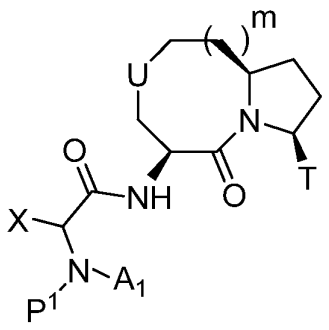
R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo; and

P^1 is an amine protecting group.

[00159] In one embodiment, P^1 is selected from the group consisting of t-butoxycarbonyl and benzyloxycarbonyl.

[00160] In another embodiment, the invention pertains to a compound having Formula XXV:



XXV

wherein:

T is optionally substituted heteroaryl;

m is 1 or 2;

U is CH_2 or NR^6

R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

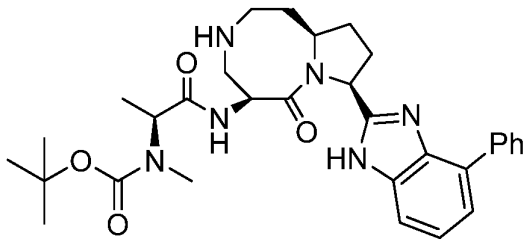
X is selected from the group consisting of hydrogen, optionally substituted alkyl, and aralkyl;

A_1 is selected from the group consisting of hydrogen an optionally substituted alkyl; and

P^1 is an amine protecting group.

[00161] In one embodiment, P^1 is selected from the group consisting of t-butoxycarbonyl and benzyloxycarbonyl.

[00162] In one embodiment the compound of Formula XXV is:



[00163] The compounds of this invention may be prepared using methods known to those of skill in the art. Specifically, compounds of the invention can be prepared as illustrated by the exemplary reactions in the Examples.

[00164] An important aspect of the present invention is that compounds of Formulae I-XIa induce apoptosis and also potentiate the induction of apoptosis in response to apoptosis induction signals. Therefore, it is contemplated that these compounds will sensitize cells to inducers of apoptosis, including cells that are resistant to such inducers. The IAP inhibitors of the present invention can be used to induce apoptosis in any disorder that can be treated, ameliorated, or prevented by the induction of apoptosis. Thus, the present invention provides compositions and methods for targeting animals characterized as overexpressing an IAP protein. In some of the embodiments, the cells (e.g., cancer cells) will show elevated expression levels of IAP proteins as compared to non-pathological samples (e.g., non-cancerous cells). In other embodiments, the cells operationally will manifest elevated expression levels of IAP proteins by virtue of executing the apoptosis program and dying in response to an inhibiting effective amount of a compound of Formulae I-XIa, said response occurring, at least in part, due to the dependence in such cells on IAP protein function for their survival.

[00165] In another embodiment, the invention pertains to modulating an apoptosis-associated state which is associated with one or more apoptosis-modulating agents. Examples of apoptosis-modulating agents include, but are not limited to, Fas/CD95, TRAMP, TNF RI, DR1, DR2, DR3, DR4, DR5, DR6, FADD, RIP, TNFα, Fas ligand, TRAIL, antibodies to TRAIL-R1 or TRAIL-R2, Bcl-2, p53, BAX, BAD, Akt, CAD, PI3 kinase, PP1, and caspase proteins. Other agents involved in the initiation, decision and degradation phase of apoptosis are also included. Examples of apoptosis-modulating agents include agents, the activity, presence, or change in concentration of which, can modulate apoptosis in a subject. Preferred apoptosis-modulating agents are inducers of

apoptosis, such as TNF or a TNF-related ligand, particularly a TRAMP ligand, a Fas/CD95 ligand, a TNFR-1 ligand, or TRAIL.

[00166] In some embodiments, the compositions and methods of the present invention are used to treat diseased cells, tissues, organs, or pathological conditions and/or disease states in an animal (e.g., a mammalian subject including, but not limited to, humans and veterinary animals). In this regard, various diseases and pathologies are amenable to treatment or prophylaxis using the present methods and compositions. A non-limiting exemplary list of these diseases and conditions includes, but is not limited to, breast cancer, prostate cancer, lymphoma, skin cancer, pancreatic cancer, colon cancer, melanoma, malignant melanoma, ovarian cancer, brain cancer, primary brain carcinoma, head–neck cancer, glioma, glioblastoma, liver cancer, bladder cancer, non-small cell lung cancer, head or neck carcinoma, breast carcinoma, ovarian carcinoma, lung carcinoma, small-cell lung carcinoma, Wilms' tumor, cervical carcinoma, testicular carcinoma, bladder carcinoma, pancreatic carcinoma, stomach carcinoma, colon carcinoma, prostatic carcinoma, genitourinary carcinoma, thyroid carcinoma, esophageal carcinoma, myeloma, multiple myeloma, adrenal carcinoma, renal cell carcinoma, endometrial carcinoma, adrenal cortex carcinoma, malignant pancreatic insulinoma, malignant carcinoid carcinoma, choriocarcinoma, mycosis fungoides, malignant hypercalcemia, cervical hyperplasia, leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic granulocytic leukemia, acute granulocytic leukemia, hairy cell leukemia, neuroblastoma, rhabdomyosarcoma, Kaposi's sarcoma, polycythemia vera, essential thrombocytosis, Hodgkin's disease, non-Hodgkin's lymphoma, soft-tissue sarcoma, osteogenic sarcoma, primary macroglobulinemia, and retinoblastoma, and the like, T and B cell mediated autoimmune diseases; inflammatory diseases; infections (e.g., as antiulcerous agents, e.g., in the context of H. pylori infection); hyperproliferative diseases; AIDS; degenerative conditions; vascular diseases (e.g., primary varicosis), and the like. The compounds of the present invention may also be useful in the treatment of diseases in which there is a defect in the programmed cell-death or the apoptotic machinery e.g., multiple sclerosis, asthma, artherosclerosis and the like. In some embodiments, the cancer cells being treated are metastatic. In other embodiments, the cancer cells being treated are resistant to anticancer agents.

[00167] In some embodiments, infections suitable for treatment with the compositions and methods of the present invention include, but are not limited to, infections caused by viruses, bacteria, fungi, mycoplasma, prions, and the like.

[00168] Some embodiments of the present invention provide methods for administering an effective amount of a compound of Formulae I-XIa and at least one additional therapeutic agent (including, but not limited to, chemotherapeutic antineoplastics, apoptosis-modulating agents, antimicrobials, antivirals, antifungals, and anti-inflammatory agents) and/or therapeutic technique (e.g., surgical intervention, and/or radiotherapies).

[00169] A number of suitable anticancer agents are contemplated for use in the methods of the present invention. Indeed, the present invention contemplates, but is not limited to, administration of numerous anticancer agents such as: agents that induce apoptosis; polynucleotides (e.g., anti-sense, ribozymes, siRNA); polypeptides (e.g., enzymes and antibodies); biological mimetics (e.g., gossypol or BH3 mimetics); agents that bind (e.g., oligomerize or complex) with a Bcl-2 family protein such as Bax; alkaloids; alkylating agents; antitumor antibiotics; antimetabolites; hormones; platinum compounds; monoclonal or polyclonal antibodies (e.g., antibodies conjugated with anticancer drugs, toxins, defensins), toxins; radionuclides; biological response modifiers (e.g., interferons (e.g., IFN-α) and interleukins (e.g., IL-2)); adoptive immunotherapy agents; hematopoietic growth factors; agents that induce tumor cell differentiation (e.g., all-trans-retinoic acid); gene therapy reagents (e.g., antisense therapy reagents and nucleotides); tumor vaccines; angiogenesis inhibitors; proteosome inhibitors: NF-KB modulators; anti-CDK compounds; HDAC inhibitors; and the like. Numerous other examples of chemotherapeutic compounds and anticancer therapies suitable for co-administration with the disclosed compounds are known to those skilled in the art.

[00170] In certain embodiments, anticancer agents comprise agents that induce or stimulate apoptosis. Agents that induce apoptosis include, but are not limited to, radiation (e.g., X-rays, gamma rays, UV); tumor necrosis factor (TNF)-related factors (e.g., TNF family receptor proteins, TNF family ligands, TRAIL, antibodies to TRAIL-R1 or TRAIL-R2); kinase inhibitors (e.g., epidermal growth factor receptor (EGFR) kinase inhibitor, vascular growth factor receptor (VGFR) kinase inhibitor, fibroblast growth factor receptor (FGFR) kinase inhibitor, platelet-derived growth factor receptor (PDGFR) kinase inhibitor, and Bcr-Abl kinase inhibitors (such as GLEEVEC)); antisense

molecules; antibodies (e.g., HERCEPTIN, RITUXAN, ZEVALIN, and AVASTIN); anti-estrogens (e.g., raloxifene and tamoxifen); anti-androgens (e.g., flutamide, bicalutamide, finasteride, aminoglutethamide, ketoconazole, and corticosteroids); cyclooxygenase 2 (COX-2) inhibitors (e.g., celecoxib, meloxicam, NS-398, and non-steroidal anti-inflammatory drugs (NSAIDs)); anti-inflammatory drugs (e.g., butazolidin, DECADRON, DELTASONE, dexamethasone, dexamethasone intensol, DEXONE, HEXADROL, hydroxychloroquine, METICORTEN, ORADEXON, ORASONE, oxyphenbutazone, PEDIAPRED, phenylbutazone, PLAQUENIL, prednisolone, prednisone, PRELONE, and TANDEARIL); and cancer chemotherapeutic drugs (e.g., irinotecan (CAMPTOSAR), CPT-11, fludarabine (FLUDARA), dacarbazine (DTIC), dexamethasone, mitoxantrone, MYLOTARG, VP-16, cisplatin, carboplatin, oxaliplatin, 5-FU, doxorubicin, gemcitabine, bortezomib, gefitinib, bevacizumab, TAXOTERE or TAXOL); cellular signaling molecules; ceramides and cytokines; staurosporine, and the like.

[00171] In still other embodiments, the compositions and methods of the present invention provide a compound of Formulae I-XIa and at least one anti-hyperproliferative or antineoplastic agent selected from alkylating agents, antimetabolites, and natural products (e.g., herbs and other plant and/or animal derived compounds).

[00172] Alkylating agents suitable for use in the present compositions and methods include, but are not limited to: 1) nitrogen mustards (e.g., mechlorethamine, cyclophosphamide, ifosfamide, melphalan (L-sarcolysin); and chlorambucil); 2) ethylenimines and methylmelamines (e.g., hexamethylmelamine and thiotepa); 3) alkyl sulfonates (e.g., busulfan); 4) nitrosoureas (e.g., carmustine (BCNU); lomustine (CCNU); semustine (methyl-CCNU); and streptozocin (streptozotocin)); and 5) triazenes (e.g., dacarbazine (DTIC; dimethyltriazenoimid-azolecarboxamide).

[00173] In some embodiments, antimetabolites suitable for use in the present compositions and methods include, but are not limited to: 1) folic acid analogs (e.g., methotrexate (amethopterin)); 2) pyrimidine analogs (e.g., fluorouracil (5-fluorouracil; 5-FU), floxuridine (fluorode-oxyuridine; FudR), and cytarabine (cytosine arabinoside)); and 3) purine analogs (e.g., mercaptopurine (6-mercaptopurine; 6-MP), thioguanine (6-thioguanine; TG), and pentostatin (2'-deoxycoformycin)).

[00174] In still further embodiments, chemotherapeutic agents suitable for use in the compositions and methods of the present invention include, but are not limited to: 1) vinca alkaloids (e.g., vinblastine (VLB), vincristine); 2) epipodophyllotoxins (e.g., etoposide and teniposide); 3) antibiotics (e.g., dactinomycin (actinomycin D), daunorubicin (daunomycin; rubidomycin), doxorubicin, bleomycin, plicamycin (mithramycin), and mitomycin (mitomycin C)); 4) enzymes (e.g., L-asparaginase); 5) biological response modifiers (e.g., interferon-alfa); 6) platinum coordinating complexes (e.g., cisplatin (cis-DDP) and carboplatin); 7) anthracenediones (e.g., mitoxantrone); 8) substituted ureas (e.g., hydroxyurea); 9) methylhydrazine derivatives (e.g., procarbazine (N-methylhydrazine; MIH)); 10) adrenocortical suppressants (e.g., mitotane (o,p'–DDD) and aminoglutethimide); 11) adrenocorticosteroids (e.g., prednisone); 12) progestins (e.g., hydroxyprogesterone caproate, medroxyprogesterone acetate, and megestrol acetate); 13) estrogens (e.g., diethylstilbestrol and ethinyl estradiol); 14) antiestrogens (e.g., tamoxifen); 15) androgens (e.g., testosterone propionate and fluoxymesterone); 16) antiandrogens (e.g., flutamide): and 17) gonadotropin-releasing hormone analogs (e.g., leuprolide).

[00175] Any oncolytic agent that is routinely used in a cancer therapy context finds use in the compositions and methods of the present invention. For example, the U.S. Food and Drug Administration maintains a formulary of oncolytic agents approved for use in the United States. International counterpart agencies to the U.S.F.D.A. maintain similar formularies. Table 1 provides a list of exemplary antineoplastic agents approved for use in the U.S. Those skilled in the art will appreciate that the "product labels" required on all U.S. approved chemotherapeutics describe approved indications, dosing information, toxicity data, and the like, for the exemplary agents.

Table 1

Aldesleukin (des-alanyl-1, serine-125 human interleukin-2)	Proleukin	Chiron Corp., Emeryville, CA
Alemtuzumab (IgG1κ anti CD52 antibody)	Campath	Millennium and ILEX Partners, LP, Cambridge, MA
Alitretinoin (9-cis-retinoic acid)	Panretin	Ligand Pharmaceuticals, Inc., San Diego CA

Allopurinol (1,5-dihydro-4 H -pyrazolo[3,4-d]pyrimidin-4-one monosodium salt)	Zyloprim	GlaxoSmithKline, Research Triangle Park, NC
Altretamine (N,N,N',N',N",N",- hexamethyl-1,3,5-triazine-2, 4, 6-triamine)	Hexalen	US Bioscience, West Conshohocken, PA
Amifostine (ethanethiol, 2-[(3-aminopropyl)amino]-, dihydrogen phosphate (ester))	Ethyol	US Bioscience
Anastrozole (1,3-Benzenediacetonitrile, a, a, a', a'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl))	Arimidex	AstraZeneca Pharmaceuticals, LP, Wilmington, DE
Arsenic trioxide	Trisenox	Cell Therapeutic, Inc., Seattle, WA
Asparaginase (L-asparagine amidohydrolase, type EC-2)	Elspar	Merck & Co., Inc., Whitehouse Station, NJ
BCG Live (lyophilized preparation of an attenuated strain of *Mycobacterium bovis* (*Bacillus Calmette-Gukin* [BCG], substrain Montreal)	TICE BCG	Organon Teknika, Corp., Durham, NC
bexarotene capsules (4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-napthalenyl) ethenyl] benzoic acid)	Targretin	Ligand Pharmaceuticals
bexarotene gel	Targretin	Ligand Pharmaceuticals
Bleomycin (cytotoxic glycopeptide antibiotics produced by *Streptomyces verticillus*; bleomycin A_2 and bleomycin B_2)	Blenoxane	Bristol-Myers Squibb Co., NY, NY
Capecitabine (5'-deoxy-5-fluoro-N-[(pentyloxy)carbonyl]-cytidine)	Xeloda	Roche
Carboplatin (platinum, diammine [1,1-cyclobutanedicarboxylato(2-)-0, 0']-,(SP-4-2))	Paraplatin	Bristol-Myers Squibb
Carmustine (1,3-bis(2-chloroethyl)-1-nitrosourea)	BCNU, BiCNU	Bristol-Myers Squibb
Carmustine with Polifeprosan 20 Implant	Gliadel Wafer	Guilford Pharmaceuticals, Inc., Baltimore, MD

Celecoxib (as 4-[5-(4-methylphenyl)-3- (trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide)	Celebrex	Searle Pharmaceuticals, England
Chlorambucil (4-[bis(2chlorethyl)amino]benzenebutanoic acid)	Leukeran	GlaxoSmithKline
Cisplatin ($PtCl_2H_6N_2$)	Platinol	Bristol-Myers Squibb
Cladribine (2-chloro-2'-deoxy-b-D-adenosine)	Leustatin, 2-CdA	R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ
Cyclophosphamide (2-[bis(2-chloroethyl)amino] tetrahydro-2H-13,2-oxazaphosphorine 2-oxide monohydrate)	Cytoxan, Neosar	Bristol-Myers Squibb
Cytarabine (1-b-D-Arabinofuranosylcytosine, $C_9H_{13}N_3O_5$)	Cytosar-U	Pharmacia & Upjohn Company
cytarabine liposomal	DepoCyt	Skye Pharmaceuticals, Inc., San Diego, CA
Dacarbazine (5-(3,3-dimethyl-l-triazeno)-imidazole-4-carboxamide (DTIC))	DTIC-Dome	Bayer AG, Leverkusen, Germany
Dactinomycin, actinomycin D (actinomycin produced by *Streptomyces parvullus,* $C_{62}H_{86}N_{12}O_{16}$)	Cosmegen	Merck
Darbepoetin alfa (recombinant peptide)	Aranesp	Amgen, Inc., Thousand Oaks, CA
daunorubicin liposomal ((8S-cis)-8-acetyl-10-[(3-amino-2,3,6-trideoxy-á-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride)	DanuoXome	Nexstar Pharmaceuticals, Inc., Boulder, CO
Daunorubicin HCl, daunomycin ((1 *S* ,3 *S*)-3-Acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1-naphthacenyl 3-amino-2,3,6-trideoxy-(alpha)-L- *lyxo* -hexopyranoside hydrochloride)	Cerubidine	Wyeth Ayerst, Madison, NJ
Denileukin diftitox (recombinant peptide)	Ontak	Seragen, Inc., Hopkinton, MA

Dexrazoxane ((S)-4,4'-(1-methyl-1,2-ethanediyl)bis-2,6-piperazinedione)	Zinecard	Pharmacia & Upjohn Company
Docetaxel ((2R,3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5b-20-epoxy-12a,4,7b,10b,13a-hexahydroxytax- 11-en-9-one 4-acetate 2-benzoate, trihydrate)	Taxotere	Aventis Pharmaceuticals, Inc., Bridgewater, NJ
Doxorubicin HCl (8S,10S)-10-[(3-amino-2,3,6-trideoxy-a-L-lyxo-hexopyranosyl)oxy] -8-glycolyl-7,8,9,10-tetrahydro-6,8,11- trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride)	Adriamycin, Rubex	Pharmacia & Upjohn Company
doxorubicin	Adriamycin PFS Intravenous injection	Pharmacia & Upjohn Company
doxorubicin liposomal	Doxil	Sequus Pharmaceuticals, Inc., Menlo park, CA
dromostanolone propionate (17b-Hydroxy-2a-methyl-5a-androstan-3-one propionate)	Dromostanolone	Eli Lilly & Company, Indianapolis, IN
dromostanolone propionate	Masterone injection	Syntex, Corp., Palo Alto, CA
Elliott's B Solution	Elliott's B Solution	Orphan Medical, Inc
Epirubicin ((8S-cis)-10-[(3-amino-2,3,6-trideoxy-a-L-arabino-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8- (hydroxyacetyl)-1-methoxy-5,12-naphthacenedione hydrochloride)	Ellence	Pharmacia & Upjohn Company
Epoetin alfa (recombinant peptide)	Epogen	Amgen, Inc
Estramustine (estra-1,3,5(10)-triene-3,17-diol(17(beta))-, 3-[bis(2-chloroethyl)carbamate] 17-(dihydrogen phosphate), disodium salt, monohydrate, or estradiol 3-[bis(2-chloroethyl)carbamate] 17-(dihydrogen phosphate), disodium salt, monohydrate)	Emcyt	Pharmacia & Upjohn Company

Etoposide phosphate (4'-Demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-(beta)-D-glucopyranoside], 4'-(dihydrogen phosphate))	Etopophos	Bristol-Myers Squibb
etoposide, VP-16 (4'-demethylepipodophyllotoxin 9-[4,6-0-(R)-ethylidene-(beta)-D-glucopyranoside])	Vepesid	Bristol-Myers Squibb
Exemestane (6-methylenandrosta-1,4-diene-3, 17-dione)	Aromasin	Pharmacia & Upjohn Company
Filgrastim (r-metHuG-CSF)	Neupogen	Amgen, Inc
floxuridine (intraarterial) (2'-deoxy-5-fluorouridine)	FUDR	Roche
Fludarabine (fluorinated nucleotide analog of the antiviral agent vidarabine, 9-b -D-arabinofuranosyladenine (ara-A))	Fludara	Berlex Laboratories, Inc., Cedar Knolls, NJ
Fluorouracil, 5-FU (5-fluoro-2,4(1H,3H)-pyrimidinedione)	Adrucil	ICN Pharmaceuticals, Inc., Humacao, Puerto Rico
Fulvestrant (7-alpha-[9-(4,4,5,5,5-penta fluoropentylsulphinyl) nonyl]estra-1,3,5-(10)- triene-3,17-beta-diol)	Faslodex	IPR Pharmaceuticals, Guayama, Puerto Rico
Gemcitabine (2'-deoxy-2', 2'-difluorocytidine monohydrochloride (b-isomer))	Gemzar	Eli Lilly
Gemtuzumab Ozogamicin (anti-CD33 hP67.6)	Mylotarg	Wyeth Ayerst
Goserelin acetate (acetate salt of [D-Ser(But)^{6},Azgly^{10}]LHRH; pyro-Glu-His-Trp-Ser-Tyr-D-Ser(But)-Leu-Arg-Pro-Azgly-NH2 acetate [$C_{59}H_{84}N_{18}O_{14}$ •$(C_2H_4O_2)_x$	Zoladex Implant	AstraZeneca Pharmaceuticals
Hydroxyurea	Hydrea	Bristol-Myers Squibb
Ibritumomab Tiuxetan (immunoconjugate resulting from a thiourea covalent bond between the monoclonal antibody Ibritumomab and the linker-chelator tiuxetan [N-[2-bis(carboxymethyl)amino]-3-(p-isothiocyanatophenyl)-propyl]-[N-[2-bis(carboxymethyl)amino]-2-(methyl) -ethyl]glycine)	Zevalin	Biogen IDEC, Inc., Cambridge MA

Idarubicin (5, 12-Naphthacenedione, 9-acetyl-7-[(3-amino-2,3,6-trideoxy-(alpha)-L- lyxo -hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxyhydrochloride, (7S- cis))	Idamycin	Pharmacia & Upjohn Company
Ifosfamide (3-(2-chloroethyl)-2-[(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide)	IFEX	Bristol-Myers Squibb
Imatinib Mesilate (4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate)	Gleevec	Novartis AG, Basel, Switzerland
Interferon alfa-2a (recombinant peptide)	Roferon-A	Hoffmann-La Roche, Inc., Nutley, NJ
Interferon alfa-2b (recombinant peptide)	Intron A (Lyophilized Betaseron)	Schering AG, Berlin, Germany
Irinotecan HCl ((4S)-4,11-diethyl-4-hydroxy-9-[(4- piperi-dinopiperidino)carbonyloxy]-1H-pyrano[3', 4': 6,7] indolizino[1,2-b] quinoline-3,14(4H, 12H) dione hydrochloride trihydrate)	Camptosar	Pharmacia & Upjohn Company
Lenalidomide 3-(4-amino-1-oxo 1,3-dihydro-2H-isoindol-2-yl) piperidine-2,6-dione	Revlimid	Celgene
Letrozole (4,4'-(1H-1,2,4 -Triazol-1-ylmethylene) dibenzonitrile)	Femara	Novartis
Leucovorin (L-Glutamic acid, N[4[[(2amino-5-formyl1,4,5,6,7,8 -hexahydro4oxo6-pteridinyl)methyl]amino]benzoyl], calcium salt (1:1))	Wellcovorin, Leucovorin	Immunex, Corp., Seattle, WA
Levamisole HCl ((-)-(S)-2,3,5, 6-tetrahydro-6-phenylimidazo [2,1-b] thiazole monohydrochloride $C_{11}H_{12}N_2S{\cdot}HCl$)	Ergamisol	Janssen Research Foundation, Titusville, NJ
Lomustine (1-(2-chloro-ethyl)-3-cyclohexyl-1-nitrosourea)	CeeNU	Bristol-Myers Squibb

Meclorethamine, nitrogen mustard (2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride)	Mustargen	Merck
Megestrol acetate 17α(acetyloxy)- 6- methylpregna- 4,6- diene- 3,20- dione	Megace	Bristol-Myers Squibb
Melphalan, L-PAM (4-[bis(2-chloroethyl) amino]-L-phenylalanine)	Alkeran	GlaxoSmithKline
Mercaptopurine, 6-MP (1,7-dihydro-6 H -purine-6-thione monohydrate)	Purinethol	GlaxoSmithKline
Mesna (sodium 2-mercaptoethane sulfonate)	Mesnex	Asta Medica
Methotrexate (N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid)	Methotrexate	Lederle Laboratories
Methoxsalen (9-methoxy-7H-furo[3,2-g][1]-benzopyran-7-one)	Uvadex	Therakos, Inc., Way Exton, Pa
Mitomycin C	Mutamycin	Bristol-Myers Squibb
mitomycin C	Mitozytrex	SuperGen, Inc., Dublin, CA
Mitotane (1,1-dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl) ethane)	Lysodren	Bristol-Myers Squibb
Mitoxantrone (1,4-dihydroxy-5,8-bis[[2- [(2-hydroxyethyl)amino]ethyl]amino]-9,10-anthracenedione dihydrochloride)	Novantrone	Immunex Corporation
Nandrolone phenpropionate	Durabolin-50	Organon, Inc., West Orange, NJ
Nofetumomab	Verluma	Boehringer Ingelheim Pharma KG, Germany
Oprelvekin (IL-11)	Neumega	Genetics Institute, Inc., Alexandria, VA
Oxaliplatin (cis-[(1R,2R)-1,2-cyclohexanediamine-N,N'] [oxalato(2-)-O,O'] platinum)	Eloxatin	Sanofi Synthelabo, Inc., NY, NY

Paclitaxel (5ß, 20-Epoxy-1,2a, 4,7ß, 10ß, 13a-hexahydroxytax-11-en-9-one 4,10-diacetate 2- benzoate 13-ester with (2R, 3 S)- N-benzoyl-3-phenylisoserine)	TAXOL	Bristol-Myers Squibb
Pamidronate (phosphonic acid (3-amino-1-hydroxypropylidene) bis-, disodium salt, pentahydrate, (APD))	Aredia	Novartis
Pegademase ((monomethoxypolyethylene glycol succinimidyl) 11 - 17 -adenosine deaminase)	Adagen (Pegademase Bovine)	Enzon Pharmaceuticals, Inc., Bridgewater, NJ
Pegaspargase (monomethoxypolyethylene glycol succinimidyl L-asparaginase)	Oncaspar	Enzon
Pegfilgrastim (covalent conjugate of recombinant methionyl human G-CSF (Filgrastim) and monomethoxypolyethylene glycol)	Neulasta	Amgen, Inc
Pentostatin	Nipent	Parke-Davis Pharmaceutical Co., Rockville, MD
Pipobroman	Vercyte	Abbott Laboratories, Abbott Park, IL
Plicamycin, Mithramycin (antibiotic produced by *Streptomyces plicatus*)	Mithracin	Pfizer, Inc., NY, NY
Porfimer sodium	Photofrin	QLT Phototherapeutics, Inc., Vancouver, Canada
Procarbazine (N-isopropyl-µ-(2-methylhydrazino)-p-toluamide monohydrochloride)	Matulane	Sigma Tau Pharmaceuticals, Inc., Gaithersburg, MD
Quinacrine (6-chloro-9-(1 –methyl-4-diethyl-amine) butylamino-2-methoxyacridine)	Atabrine	Abbott Labs
Rasburicase (recombinant peptide)	Elitek	Sanofi-Synthelabo, Inc.,
Rituximab (recombinant anti-CD20 antibody)	Rituxan	Genentech, Inc., South San Francisco, CA
Sargramostim (recombinant peptide)	Prokine	Immunex Corp

Streptozocin (streptozocin 2 –deoxy - 2 - [[(methylnitrosoamino)carbonyl]amino] - a(and b) - D - glucopyranose and 220 mg citric acid anhydrous)	Zanosar	Pharmacia & Upjohn Company
Talc ($Mg_3Si_4O_{10}$ $(OH)_2$)	Sclerosol	Bryan, Corp., Woburn, MA
Tamoxifen ((Z)2-[4-(1,2-diphenyl-1-butenyl) phenoxy]-N, N-dimethylethanamine 2-hydroxy-1,2,3-propanetricarboxylate (1:1))	Nolvadex	AstraZeneca Pharmaceuticals
Temozolomide (3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-as-tetrazine-8-carboxamide)	Temodar	Schering
teniposide, VM-26 (4'-demethylepipodophyllotoxin 9-[4,6-0-(R)-2-thenylidene-(beta)-D-glucopyranoside])	Vumon	Bristol-Myers Squibb
Testolactone (13-hydroxy-3-oxo-13,17-secoandrosta-1,4-dien-17-oic acid [dgr]-lactone)	Teslac	Bristol-Myers Squibb
Thioguanine, 6-TG (2-amino-1,7-dihydro-6 H - purine-6-thione)	Thioguanine	GlaxoSmithKline
Thiotepa (Aziridine, 1,1',1"-phosphinothioylidynetris-, or Tris (1-aziridinyl) phosphine sulfide)	Thioplex	Immunex Corporation
Topotecan HCl ((S)-10-[(dimethylamino) methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3', 4': 6,7] indolizino [1,2-b] quinoline-3,14-(4H,12H)-dione monohydrochloride)	Hycamtin	GlaxoSmithKline
Toremifene (2-(p-[(Z)-4-chloro-1,2-diphenyl-1-butenyl]-phenoxy)-N,N-dimethylethylamine citrate (1:1))	Fareston	Roberts Pharmaceutical Corp., Eatontown, NJ
Tositumomab, I 131 Tositumomab (recombinant murine immunotherapeutic monoclonal IgG_{2a} lambda anti-CD20 antibody (I 131 is a radioimmunotherapeutic antibody))	Bexxar	Corixa Corp., Seattle, WA
Trastuzumab (recombinant monoclonal IgG_1 kappa anti-HER2 antibody)	Herceptin	Genentech, Inc

Tretinoin, ATRA (all-trans retinoic acid)	Vesanoid	Roche
Uracil Mustard	Uracil Mustard Capsules	Roberts Labs
Valrubicin, N-trifluoroacetyladriamycin-14-valerate ((2S-cis)-2- [1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7 methoxy-6,11-dioxo-[[4 2,3,6-trideoxy-3-[(trifluoroacetyl)-amino-α-L-*lyxo*-hexopyranosyl]oxyl]-2-naphthacenyl]-2-oxoethyl pentanoate)	Valstar	Anthra --> Medeva
Vinblastine, Leurocristine ($C_{46}H_{56}N_4O_{10}$•H_2SO_4)	Velban	Eli Lilly
Vincristine ($C_{46}H_{56}N_4O_{10}$•H_2SO_4)	Oncovin	Eli Lilly
Vinorelbine (3' ,4'-didehydro-4'-deoxy-C'-norvincaleukoblastine [R-(R*,R*)-2,3-dihydroxybutanedioate (1:2)(salt)])	Navelbine	GlaxoSmithKline
Zoledronate, Zoledronic acid ((1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate)	Zometa	Novartis

[00176] Anticancer agents further include compounds which have been identified to have anticancer activity but are not currently approved by the U.S. Food and Drug Administration or other counterpart agencies or are undergoing evaluation for new uses. Examples include, but are not limited to, 3-AP, 12-O-tetradecanoylphorbol-13-acetate, 17AAG, 852A, ABI-007, ABR-217620, ABT-751, ADI-PEG 20, AE-941, AG-013736, AGRO100, alanosine, AMG 706, antibody G250, antineoplastons, AP23573, apaziquone, APC8015, atiprimod, ATN-161, atrasenten, azacitidine, BB-10901, BCX-1777, bevacizumab, BG00001, bicalutamide, BMS 247550, bortezomib, bryostatin-1, buserelin, calcitriol, CCI-779, CDB-2914, cefixime, cetuximab, CG0070, cilengitide, clofarabine, combretastatin A4 phosphate, CP-675,206, CP-724,714, CpG 7909, curcumin, decitabine, DENSPM, doxercalciferol, E7070, E7389, ecteinascidin 743, efaproxiral, eflornithine, EKB-569, enzastaurin, erlotinib, exisulind, fenretinide, flavopiridol, fludarabine, flutamide, fotemustine, FR901228, G17DT, galiximab, gefitinib, genistein, glufosfamide, GTI-2040, histrelin, HKI-272, homoharringtonine, HSPPC-96, hu14.18-interleukin-2

fusion protein, HuMax-CD4, iloprost, imiquimod, infliximab, interleukin-12, IPI-504, irofulven, ixabepilone, lapatinib, lestaurtinib, leuprolide, LMB-9 immunotoxin, lonafarnib, luniliximab, mafosfamide, MB07133, MDX-010, MLN2704, monoclonal antibody 3F8, monoclonal antibody J591, motexafin, MS-275, MVA-MUC1-IL2, nilutamide, nitrocamptothecin, nolatrexed dihydrochloride, nolvadex, NS-9, O6-benzylguanine, oblimersen sodium, ONYX-015, oregovomab, OSI-774, panitumumab, paraplatin, PD-0325901, pemetrexed, PHY906, pioglitazone, pirfenidone, pixantrone, PS-341, PSC 833, PXD101, pyrazoloacridine, R115777, RAD001, ranpirnase, rebeccamycin analogue, rhuAngiostatin protein, rhuMab 2C4, rosiglitazone, rubitecan, S-1, S-8184, satraplatin, SB-, 15992, SGN-0010, SGN-40, sorafenib, SR31747A, ST1571, SU011248, suberoylanilide hydroxamic acid, suramin, talabostat, talampanel, tariquidar, temsirolimus, TGFa-PE38 immunotoxin, thalidomide, thymalfasin, tipifarnib, tirapazamine, TLK286, trabectedin, trimetrexate glucuronate, TroVax, UCN-1, valproic acid, vinflunine, VNP40101M, volociximab, vorinostat, VX-680, ZD1839, ZD6474, zileuton, and zosuquidar trihydrochloride.

[00177] In one embodiment, the anticancer agent is selected from the group consisting of taxotere, gemcitabine, lapatinib (Tykerb®) and etoposide.

[00178] For a more detailed description of anticancer agents and other therapeutic agents, those skilled in the art are referred to any number of instructive manuals including, but not limited to, the Physician's Desk Reference and to Goodman and Gilman's "Pharmaceutical Basis of Therapeutics" tenth edition, Eds. Hardman et al., 2002.

[00179] The present invention provides methods for administering a compound of Formulae I-XIa with radiation therapy. The invention is not limited by the types, amounts, or delivery and administration systems used to deliver the therapeutic dose of radiation to an animal. For example, the animal may receive photon radiotherapy, particle beam radiation therapy, other types of radiotherapies, and combinations thereof. In some embodiments, the radiation is delivered to the animal using a linear accelerator. In still other embodiments, the radiation is delivered using a gamma knife.

[00180] The source of radiation can be external or internal to the animal. External radiation therapy is most common and involves directing a beam of high-energy radiation to a tumor site through the skin using, for instance, a linear accelerator. While the beam of radiation is localized to the tumor site, it is nearly impossible to avoid exposure of

normal, healthy tissue. However, external radiation is usually well tolerated by animals. Internal radiation therapy involves implanting a radiation-emitting source, such as beads, wires, pellets, capsules, particles, and the like, inside the body at or near the tumor site including the use of delivery systems that specifically target cancer cells (e.g., using particles attached to cancer cell binding ligands). Such implants can be removed following treatment, or left in the body inactive. Types of internal radiation therapy include, but are not limited to, brachytherapy, interstitial irradiation, intracavity irradiation, radioimmunotherapy, and the like.

[00181] The animal may optionally receive radiosensitizers (e.g., metronidazole, misonidazole, intra-arterial Budr, intravenous iododeoxyuridine (IudR), nitroimidazole, 5-substituted-4-nitroimidazoles, 2H-isoindolediones, [[(2-bromoethyl)-amino]methyl]-nitro-1H-imidazole-1-ethanol, nitroaniline derivatives, DNA-affinic hypoxia selective cytotoxins, halogenated DNA ligand, 1,2,4 benzotriazine oxides, 2-nitroimidazole derivatives, fluorine-containing nitroazole derivatives, benzamide, nicotinamide, acridine-intercalator, 5-thiotretrazole derivative, 3-nitro-1,2,4-triazole, 4,5-dinitroimidazole derivative, hydroxylated texaphrins, cisplatin, mitomycin, tiripazamine, nitrosourea, mercaptopurine, methotrexate, fluorouracil, bleomycin, vincristine, carboplatin, epirubicin, doxorubicin, cyclophosphamide, vindesine, etoposide, paclitaxel, heat (hyperthermia), and the like), radioprotectors (e.g., cysteamine, aminoalkyl dihydrogen phosphorothioates, amifostine (WR 2721), IL-1, IL-6, and the like). Radiosensitizers enhance the killing of tumor cells. Radioprotectors protect healthy tissue from the harmful effects of radiation.

[00182] Any type of radiation can be administered to an animal, so long as the dose of radiation is tolerated by the patient without unacceptable negative side-effects. Suitable types of radiotherapy include, for example, ionizing (electromagnetic) radiotherapy (e.g., X-rays or gamma rays) or particle beam radiation therapy (e.g., high linear energy radiation). Ionizing radiation is defined as radiation comprising particles or photons that have sufficient energy to produce ionization, i.e., gain or loss of electrons (as described in, for example, U.S. 5,770,581 incorporated herein by reference in its entirety). The effects of radiation can be at least partially controlled by the clinician. The dose of radiation is preferably fractionated for maximal target cell exposure and reduced toxicity.

[00183] The total dose of radiation administered to an animal preferably is about .01 Gray (Gy) to about 100 Gy. More preferably, about 10 Gy to about 65 Gy (e.g., about 15 Gy, 20 Gy, 25 Gy, 30 Gy, 35 Gy, 40 Gy, 45 Gy, 50 Gy, 55 Gy, or 60 Gy) are administered over the course of treatment. While in some embodiments a complete dose of radiation can be administered over the course of one day, the total dose is ideally fractionated and administered over several days. Desirably, radiotherapy is administered over the course of at least about 3 days, e.g., at least 5, 7, 10, 14, 17, 21, 25, 28, 32, 35, 38, 42, 46, 52, or 56 days (about 1-8 weeks). Accordingly, a daily dose of radiation will comprise approximately 1-5 Gy (e.g., about 1 Gy, 1.5 Gy, 1.8 Gy, 2 Gy, 2.5 Gy, 2.8 Gy, 3 Gy, 3.2 Gy, 3.5 Gy, 3.8 Gy, 4 Gy, 4.2 Gy, or 4.5 Gy), preferably 1-2 Gy (e.g., 1.5-2 Gy). The daily dose of radiation should be sufficient to induce destruction of the targeted cells. If stretched over a period, radiation preferably is not administered every day, thereby allowing the animal to rest and the effects of the therapy to be realized. For example, radiation desirably is administered on 5 consecutive days, and not administered on 2 days, for each week of treatment, thereby allowing 2 days of rest per week. However, radiation can be administered 1 day/week, 2 days/week, 3 days/week, 4 days/week, 5 days/week, 6 days/week, or all 7 days/week, depending on the animal's responsiveness and any potential side effects. Radiation therapy can be initiated at any time in the therapeutic period. Preferably, radiation is initiated in week 1 or week 2, and is administered for the remaining duration of the therapeutic period. For example, radiation is administered in weeks 1-6 or in weeks 2-6 of a therapeutic period comprising 6 weeks for treating, for instance, a solid tumor. Alternatively, radiation is administered in weeks 1-5 or weeks 2-5 of a therapeutic period comprising 5 weeks. These exemplary radiotherapy administration schedules are not intended, however, to limit the present invention.

[00184] Antimicrobial therapeutic agents may also be used as therapeutic agents in the present invention. Any agent that can kill, inhibit, or otherwise attenuate the function of microbial organisms may be used, as well as any agent contemplated to have such activities. Antimicrobial agents include, but are not limited to, natural and synthetic antibiotics, antibodies, inhibitory proteins (e.g., defensins), antisense nucleic acids, membrane disruptive agents and the like, used alone or in combination. Indeed, any type of antibiotic may be used including, but not limited to, antibacterial agents, antiviral agents, antifungal agents, and the like.

[00185] In some embodiments of the present invention, a compound of Formulae I-XIa and one or more therapeutic agents or anticancer agents are administered to an animal under one or more of the following conditions: at different periodicities, at different durations, at different concentrations, by different administration routes, in a single composition, in separate compositions, etc. In some embodiments, the compound is administered prior to the therapeutic or anticancer agent, e.g., 0.5, 1, 2, 3, 4, 5, 10, 12, or 18 hours, 1, 2, 3, 4, 5, or 6 days, 1, 2, 3, or 4 weeks prior to the administration of the therapeutic or anticancer agent. In some embodiments, the compound is administered after the therapeutic or anticancer agent, e.g., 0.5, 1, 2, 3, 4, 5, 10, 12, or 18 hours, 1, 2, 3, 4, 5, or 6 days, 1, 2, 3, or 4 weeks after the administration of the anticancer agent. In some embodiments, the compound and the therapeutic or anticancer agent are administered concurrently but on different schedules, e.g., the compound is administered daily while the therapeutic or anticancer agent is administered once a week, once every two weeks, once every three weeks, or once every four weeks. In other embodiments, the compound is administered once a week while the therapeutic or anticancer agent is administered daily, once a week, once every two weeks, once every three weeks, or once every four weeks.

[00186] Compositions within the scope of this invention include all compositions wherein the compounds of the present invention are contained in an amount which is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typically, the compounds may be administered to mammals, e.g. humans, orally at a dose of 0.0025 to 50 mg/kg, or an equivalent amount of the pharmaceutically acceptable salt thereof, per day of the body weight of the mammal being treated for disorders responsive to induction of apoptosis. For example, about 0.01 to about 25 mg/kg is orally administered to treat, ameliorate, or prevent such disorders. For intramuscular injection, the dose is generally about one-half of the oral dose. For example, a suitable intramuscular dose would be about 0.0025 to about 25 mg/kg, e.g., from about 0.01 to about 5 mg/kg.

[00187] The unit oral dose may comprise from about 0.01 to about 1000 mg, e.g., about 0.1 to about 100 mg of the compound. The unit dose may be administered one or more times daily as one or more tablets or capsules each containing from about 0.1 to about 10, conveniently about 0.25 to 50 mg of the compound or its solvates.

[00188] In a topical formulation, the compound may be present at a concentration of about 0.01 to 100 mg per gram of carrier. In one embodiment, the compound is present at a concentration of about 0.07-1.0 mg/ml, e.g., about 0.1-0.5 mg/ml, e.g., about 0.4 mg/ml.

[00189] In addition to administering the compound as a raw chemical, the compounds of the invention may be administered as part of a pharmaceutical preparation containing suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the compounds into preparations which can be used pharmaceutically. Preferably, the preparations, particularly those preparations which can be administered orally or topically and which can be used for the preferred type of administration, such as tablets, dragees, slow release lozenges and capsules, mouth rinses and mouth washes, gels, liquid suspensions, hair rinses, hair gels, shampoos and also preparations which can be administered rectally, such as suppositories, as well as suitable solutions for administration by intravenous infusion, injection, topically or orally, contain from about 0.01 to 99 percent, e.g., from about 0.25 to 75 percent of active compound(s), together with the excipient.

[00190] The pharmaceutical compositions of the invention may be administered to any animal which may experience the beneficial effects of the compounds of the invention. Foremost among such animals are mammals, e.g., humans, although the invention is not intended to be so limited. Other animals include veterinary animals (cows, sheep, pigs, horses, dogs, cats and the like).

[00191] The compounds and pharmaceutical compositions thereof may be administered by any means that achieve their intended purpose. For example, administration may be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, buccal, intrathecal, intracranial, intranasal or topical routes. Alternatively, or concurrently, administration may be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

[00192] The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of

granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

[00193] Suitable excipients are, in particular, fillers such as saccharides, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

[00194] Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

[00195] Possible pharmaceutical preparations which can be used rectally include, for example, suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use

gelatin rectal capsules which consist of a combination of the active compounds with a base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

[00196] Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

[00197] The topical compositions of this invention are formulated preferably as oils, creams, lotions, ointments and the like by choice of appropriate carriers. Suitable carriers include vegetable or mineral oils, white petrolatum (white soft paraffin), branched chain fats or oils, animal fats and high molecular weight alcohol (greater than C12). The preferred carriers are those in which the active ingredient is soluble. Emulsifiers, stabilizers, humectants and antioxidants may also be included as well as agents imparting color or fragrance, if desired. Additionally, transdermal penetration enhancers can be employed in these topical formulations. Examples of such enhancers can be found in U.S. Pat. Nos. 3,989,816 and 4,444,762.

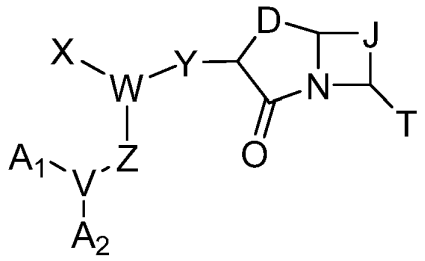
[00198] Creams are preferably formulated from a mixture of mineral oil, self-emulsifying beeswax and water in which mixture the active ingredient, dissolved in a small amount of an oil such as almond oil, is admixed. A typical example of such a cream is one which includes about 40 parts water, about 20 parts beeswax, about 40 parts mineral oil and about 1 part almond oil.

[00199] Ointments may be formulated by mixing a solution of the active ingredient in a vegetable oil such as almond oil with warm soft paraffin and allowing the mixture to cool. A typical example of such an ointment is one which includes about 30% almond oil and about 70% white soft paraffin by weight.

[00200] Lotions may be conveniently prepared by dissolving the active ingredient, in a suitable high molecular weight alcohol such as propylene glycol or polyethylene glycol.

[00201] In certain aspects, the present invention is drawn to the following particular embodiments:

[00202] I. A compound having Formula I:



I

wherein:

A_1 and A_2 are independently selected from the group consisting of hydrogen and optionally substituted alkyl, wherein A2 is absent when V is O;

V is selected from the group consisting of N, CH and O;

W is selected from the group consisting of CH and N;

X is selected from the group consisting of hydrogen, optionally substituted alkyl and aralkyl;

Y is selected from the group consisting of $CON(R^1)$, $N(R^1)CO$, C(O)O, OC(O), $(CH_2)_{1-3}$, wherein one or more CH_2 groups can be replaced by O, S, or NR^1, optionally substituted aryl and optionally substituted heteroaryl;

Z is $(CR^{2a}R^{2b})$;

D is $(CR^{3a}R3b)_n$-U-$(CR^{4a}R^{4b})_m$;

U is selected from the group consisting of $CR^{5a}R^{5b}$ and NR^6;

J is $(CR^{7a}R^{7b})_p$-L-$(CR^{8a}R^{8b})_q$;

T is optionally substituted heteroaryl;

n, m, p and q are independently selected from the group consisting of 0-5;

r is 0-3;

R1 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

each R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^{7a}, R^{7b}, R^{8a}, R^{8b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl,

optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

L is selected from the group consisting of O, S, NR^1, $NCOR^9$, $CR^{7a}R^{7b}$, C=O, C=S and $C=NR^1$; and

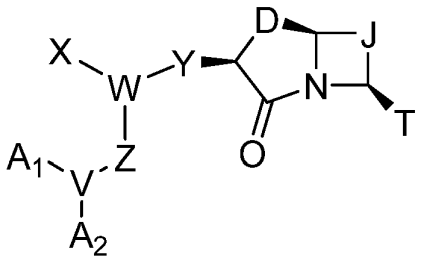
R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

or pharmaceutically acceptable salt or prodrug thereof.

[00203] II. The compound of I, wherein n is 1, m is 1 or 2, p is 0, L is $CR^{7a}R^{7b}$, q is 1, and R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{8a}, R^{8b} are hydrogen.

[00204] III. The compound of II, wherein Y is CON(H), W is CH, r is 0 and V is N.

[00205] IV. The compound of I having formula II:

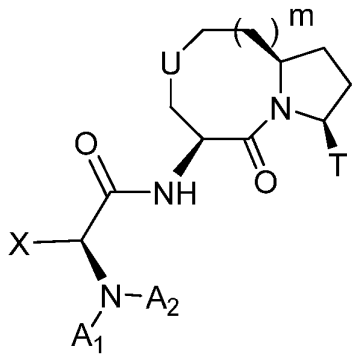


II

[00206] V. The compound of IV, wherein n is 1, m is 1 or 2, p is 0, L is CH2, q is 1, and R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{8a}, R^{8b} are hydrogen.

[00207] VI. The compound of V, Y is CON(H), W is CH, r is 0 and V is N.

[00208] VII. The compound of VI having Formula V:



V

[00209] VIII. The compound of VII, wherein A1 is optionally substituted alkyl and A_2 is hydrogen.

[00210] IX. The compound of VII, wherein X is optionally substituted alkyl.

[00211] X. The compound of VII, wherein U is CH_2.

[00212] XI. The compound of VII, wherein U is NR^6.

[00213] XII. The compound of XI, wherein R^6 is COR^9.

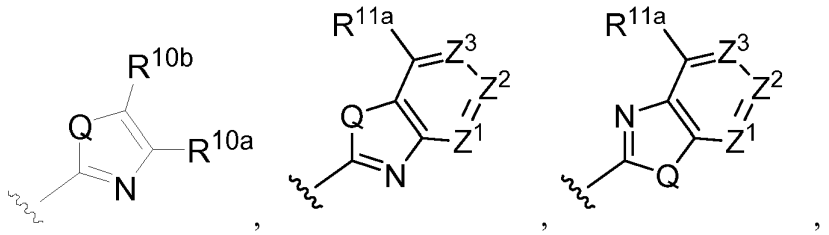
[00214] XIII. The compound of XII, wherein R^9 is selected from the group consisting of optionally substituted alkyl and aralkyl.

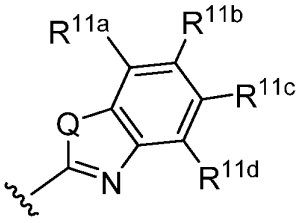
[00215] XIV. The compound of VII, wherein m is 2.

[00216] XV. The compound of VII, wherein m is 1.

[00217] XVI. The compound of VII, wherein A1 is optionally substituted alkyl, A_2 is hydrogen, X is optionally substituted alkyl, U is NR^6, R^6 is COR^9, R^9 is selected from the group consisting of optionally substituted alkyl and aralkyl, and m is 1.

[00218] XVII. The compound of I-XV, wherein T is selected from the group consisting of



and 

,

wherein:

Q is selected from the group consisting of O, S and NR^{12};

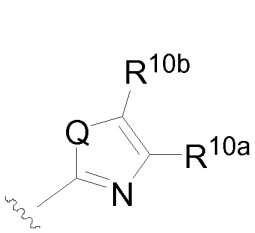
R^{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

R^{10a}, R^{10b}, R^{11a}, R^{11b}, R^{11c} and R^{11d} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido;

Z^1, Z^2, and Z^3 are independently selected from the group consisting of CR^{11e} and N, wherein at least one of Z^1, Z^2, and Z^3 is CR^{11e}, and at least one of Z^1, Z^2, and Z^3 is N; and

R^{11e} is selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido.

[00219] XVIII. The compound of XVI, wherein T is selected from the group consisting of



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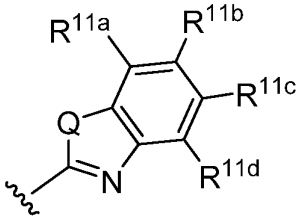


,

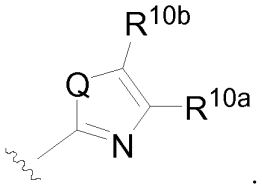
wherein:

Q is selected from the group consisting of O, S and NR^{12};

R^{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo; and

R^{10a}, R^{10b}, R^{11a}, R^{11b}, R^{11c} and R^{11d} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido.

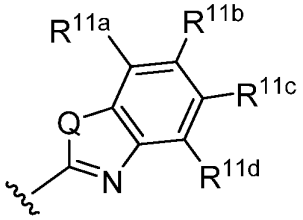
[00220] XIX. The compound of XVIII wherein T is



.

[00221] XX. The compound of XIX, wherein R^{10a} is optionally substituted aryl and R10b is hydrogen.

[00222] XXI. The compound of XVIII, wherein T is

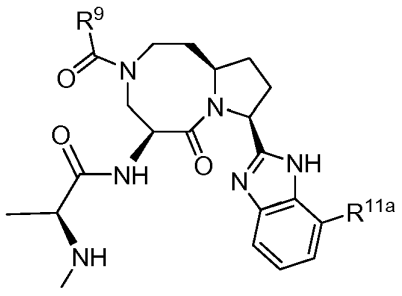


.

[00223] XXII. The compound of XXI, wherein R^{11a} is selected from the group consisting of optionally substituted aryl, aralkyl, and optionally substituted alkyl; and R^{11b}, R^{11c} and R^{11d} are each hydrogen.

[00224] XXIII. The compound of XXI, wherein R^{11d} is selected from the group consisting of optionally substituted aryl, aralkyl, and optionally substituted alkyl; R^{11a}, R^{11b} and R^{11c} are each hydrogen.

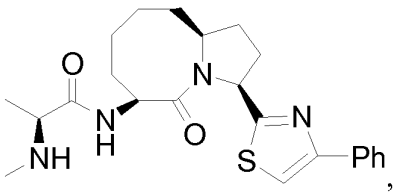
[00225] XXIV. The compound of XXII having Formula XIa:



XIa

wherein R^9 is optionally substituted alkyl or aralkyl, and R^{11a} is optionally substituted aryl.

[00226] XXV. The compound of I, selected from the group consisting of:



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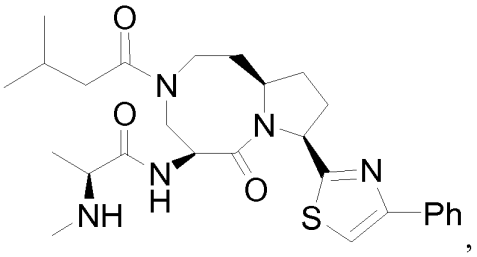
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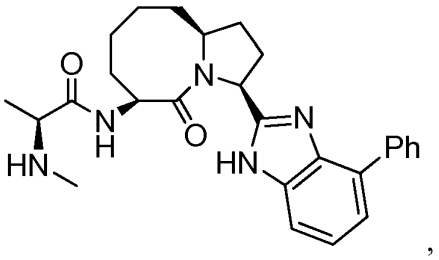
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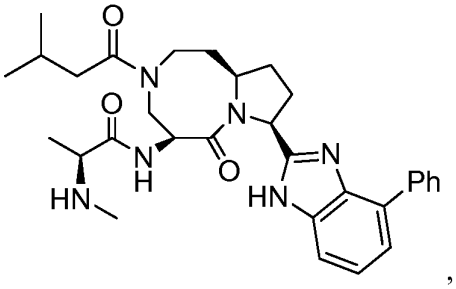
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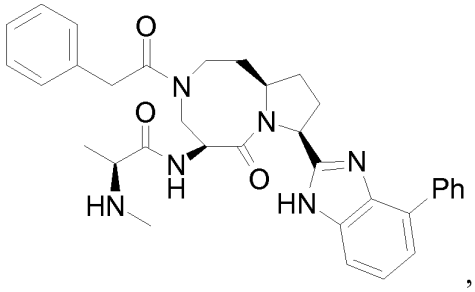
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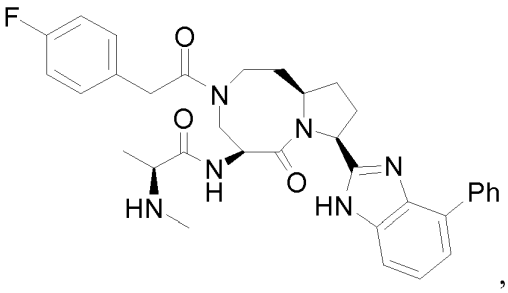
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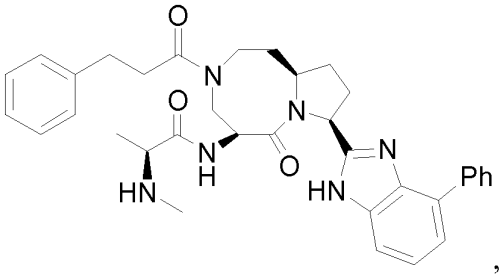
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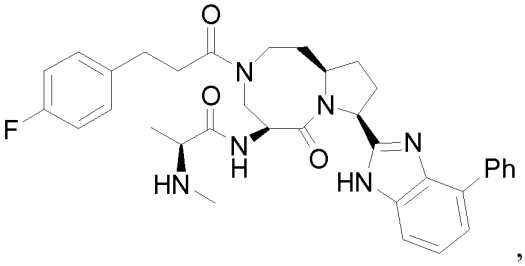
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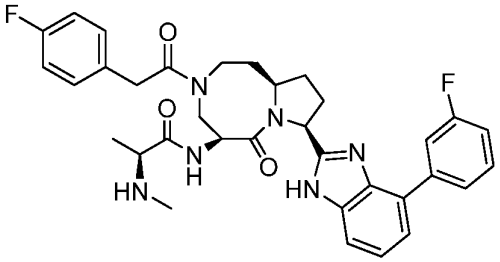
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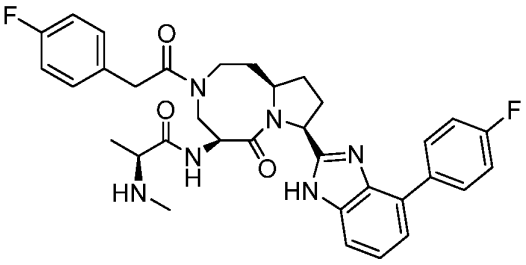
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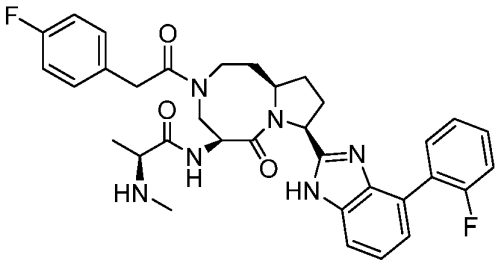
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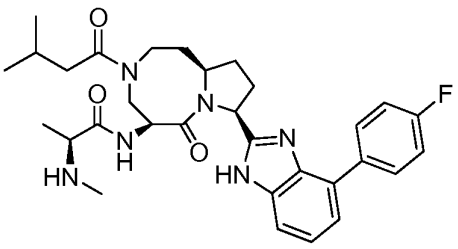
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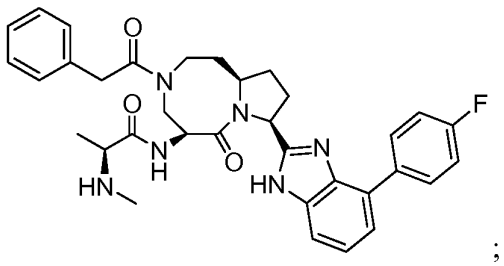


;

or a pharmaceutically acceptable salt or prodrug thereof.

[00227] XXVI. A pharmaceutical composition comprising the compound of any one of I-XXV and a pharmaceutically acceptable carrier.

[00228] XXVII. A method of inducing apoptosis in a cell comprising contacting the cell with the compound of any one of I-XXV.

[00229] XXVIII. A method of rendering a cell sensitive to an inducer of apoptosis comprising contacting the cell with the compound of any one of I-XXV.

[00230] XXIX. The method of XXVIII, further comprising contacting the cell with an inducer of apoptosis.

[00231] XXX. The method of XXIX, wherein said inducer of apoptosis is a chemotherapeutic agent.

[00232] XXXI. The method of XXIX, wherein said inducer of apoptosis is radiation.

[00233] XXXII. The method of XXIX, wherein said inducer of apoptosis is a tumor necrosis factor (TNF), a TNF-related ligand, or an agonist of TRAIL-R1 or TRAIL-R2.

[00234] XXXIII. The method of XXXII, wherein said TNF-related ligand is selected from the group consisting of a TRAMP ligand, a Fas/CD95 ligand, a TNFR-1 ligand, and TRAIL.

[00235] XXXIV. The method of XXXIII, wherein said TNF-related ligand is TRAIL.

[00236] XXXV. The method of XXXIV, wherein said agonist of TRIAL-R1 or TRAIL-R2 is an antibody.

[00237] XXXVI. A method of treating, ameliorating, or preventing a disorder responsive to the induction of apoptosis in an animal, comprising administering to said animal a therapeutically effective amount of the compound of any one of I-XXV.

[00238] XXXVII. The method of XXXVI, further comprising administering an inducer of apoptosis.

[00239] XXXVIII. The method of XXXVII, wherein said inducer of apoptosis is a chemotherapeutic agent.

[00240] XXXIX. The method of XXXVIII, wherein said inducer of apoptosis is radiation.

[00241] XL. The method of XXXVII, wherein said inducer of apoptosis is a TNF, a TNF-related ligand, or an agonist of TRAIL-R1 or TRAIL-R2.

[00242] XLI. The method of XL, wherein said TNF-related ligand is selected from the group consisting of a TRAMP ligand, a Fas/CD95 ligand, a TNFR-1 ligand, and TRAIL.

[00243] XLII. The method of XLI, wherein said TNF-related ligand is TRAIL.

[00244] XLIII. The method of XLII, wherein said agonist of TRAIL-R1 or TRAIL-R2 is an antibody.

[00245] XLIV. The method of XXXVI, wherein said disorder responsive to the induction of apoptosis is a hyperproliferative disease.

[00246] XLV. The method of XLIV, wherein said hyperproliferative disease is cancer.

[00247] XLVI. The method of XXXVI, wherein said compound of I-XXV is administered prior to said inducer of apoptosis.

[00248] XLVII.The method of XXXVI, wherein said compound of I-XXV is administered after said inducer of apoptosis.

[00249] XLVIII. The method of XXXVI, wherein said compound of I-XXV is administered concurrently with said inducer of apoptosis.

[00250] XLIX. A method of treating, ameliorating, or preventing a hyperproliferative disease in an animal, comprising administering to said animal a therapeutically effective amount of the compound of any one of I-XXV.

[00251] L. The method of XLIX, further comprising administering an anticancer agent.

[00252] LI. The method of L, wherein said anticancer agent is an inducer of apoptosis.

[00253] LII. The method of LI, wherein said inducer of apoptosis is a chemotherapeutic agent.

[00254] LIII. The method of LII, wherein said inducer of apoptosis is radiation.

[00255] LIV. The method of LI, wherein said inducer of apoptosis is a TNF, a TNF-related ligand, or an agonist of TRAIL-R1 or TRAIL-R2.

[00256] LV. The method of LIV, wherein said TNF-related ligand is selected from the group consisting of a TRAMP ligand, a Fas/CD95 ligand, a TNFR-1 ligand, and TRAIL.

[00257] LVI. The method of LIV, wherein said TNF-related ligand is TRAIL.

[00258] LVII. The method of LIV, wherein said agonist of TRAIL-R1 or TRAIL-R2 is an antibody.

[00259] LVIII. The method of XLIX, wherein said hyperproliferative disease is cancer.

[00260] LIX. The method of L, wherein said compound of I-XXV is administered prior to said anticancer agent.

[00261] LX. The method of L, wherein said compound of I-XXV is administered after said anticancer agent.

[00262] LXI. The method of L, wherein said compound of I-XXV is administered concurrently with said anticancer agent.

[00263] LXII. The method of L, wherein said anticancer agent is selected from the group consisting of taxotere, lapatinib and gemcitabine.

[00264] LXIII. A method of preventing or inhibiting angiogenesis in an animal in need thereof, comprising administering to said animal a therapeutically effective amount of the compound of any one of I-XXV.

[00265] LXIV. The method of LXIII wherein said animal has a disease or disorder selected from the group consisting of macular degeneration, rheumatoid arthritis, psoriasis, diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, Osler-Webber Syndrome, myocardial angiogenesis, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma, wound granulation, intestinal adhesions, atherosclerosis, scleroderma and hypertrophic scars.

[00266] LXV. A kit comprising the compound of any one of I-XXV and instructions for administering said compound to an animal.

[00267] LXVI. The kit of LXV, further comprising an anticancer agent.

[00268] LXVII. The kit of LXVI, wherein said anticancer agent is an inducer of apoptosis.

[00269] LXVIII. The kit of LXVII wherein said inducer of apoptosis is a chemotherapeutic agent.

[00270] LXIX. The kit of LXVII, wherein said inducer of apoptosis is a TNF, a TNF-related ligand, or an agonist of TRAIL-R1 or TRAIL-R2.

[00271] LXX. The kit of LXIX, wherein the TNF-related ligand is selected from the group consisting of a TRAMP ligand, a Fas/CD95 ligand, a TNFR-1 ligand, and TRAIL.

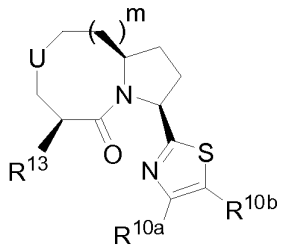
[00272] LXXI. The kit of LXX, wherein said TNF-related ligand is TRAIL.

[00273] LXXII.The kit of LXIX, wherein said agonist of TRAIL-R1 or TRAIL-R2 is an antibody.

[00274] LXXIII. The kit of LXV, wherein said instructions are for administering said compound to an animal having a hyperproliferative disease.

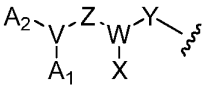
[00275] LXXIV. The kit of LXXIII, wherein said hyperproliferative disease is cancer.

[00276] LXXV. A process for preparing a compound of Formula XII



XII

wherein

R^{13} is selected from the group consisting of N(H)P1 and 

;

P^1 is an amine protecting group;

A_1 and A_2 are independently selected from the group consisting of hydrogen and optionally substituted alkyl, wherein A_2 is absent when V is O;

V is selected from the group consisting of N, CH and O;

W is selected from the group consisting of CH and N;

X is selected from the group consisting of hydrogen, optionally substituted alkyl and aralkyl;

Y is selected from the group consisting of $CON(R^1)$, $N(R^1)CO$, C(O)O, OC(O), $(CH_2)_{1-3}$, wherein one or more CH_2 groups can be replaced by O, S, or NR^1, optionally substituted aryl and optionally substituted heteroaryl;

Z is $(CR^{2a}R^{2b})_r$;

U is selected from the group consisting of $CR^{5a}R^{5b}$ and NR^6;

m is 1 or 2;

r is 0-3;

R^1 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

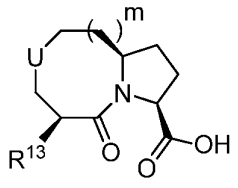
each R^{2a}, R^{2b}, R^{5a} and R^{5b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo; and

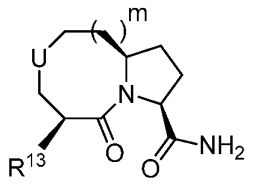
R^{10a} and R^{10b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo, comprising:

a) condensing a compound of Formula XIII



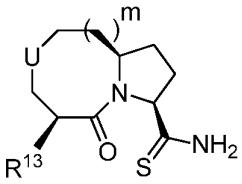
XIII

with ammonia to give a compound of Formula XIV



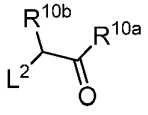
XIV,

b) converting a compound of Formula XIV to a compound of Formula XV



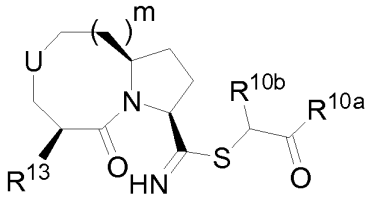
XV,

c) condensing a compound of Formula XV with a compound of Formula XVI,



XVI

wherein L2 is a leaving group, to give a compound of Formula XVII,



XVII

and b) cyclizing a compound of Formula XVII, to give a compound of Formula XII.

[00277] LXXVI. The process of LXXV, wherein L^2 is selected from the group consisting of Cl and Br.

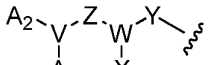
[00278] LXXVII. The process of LXXVI, wherein L^2 is Br.

[00279] LXXVIII. The process of LXXVI, wherein R^{10a} is optionally substituted aryl.

[00280] LXXIX. The process of LXXV, wherein m is 1.

[00281] LXXX. The process of LXXV, wherein R^{13} is -N(H)P^1.

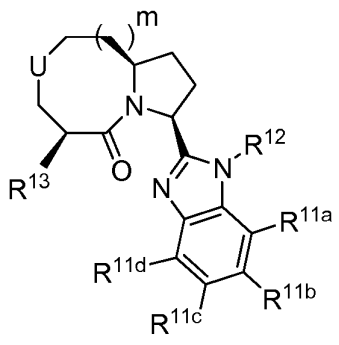
[00282] LXXXI. The process of LXXX, wherein P^1 is selected from the group consisting of t-butoxycarbonyl and benzyloxycarbonyl.

[00283] LXXXII. The process of LXXV, wherein $R1^3$ is  .

[00284] LXXXIII. The process of LXXXII, wherein Y is CON(H), W is CH, r is 0 and V is N.

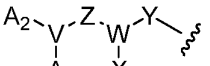
[00285] LXXXIV. The process of LXXV, wherein U is NR^6 and R^6 is COR^9.

[00286] LXXXV. A process for the preparing a compound of Formula XVIII



XVIII

wherein

R^{13} is selected from the group consisting of $N(H)P^1$ and  ;

P^1 is an amine protecting group;

A_1 and A_2 are independently selected from the group consisting of hydrogen and optionally substituted alkyl, wherein A_2 is absent when V is O;

V is selected from the group consisting of N, CH and O;

W is selected from the group consisting of CH and N;

X is selected from the group consisting of hydrogen, optionally substituted alkyl and aralkyl;

Y is selected from the group consisting of $CON(R^1)$, $N(R^1)CO$, C(O)O, OC(O), $(CH_2)_{1-3}$, wherein one or more CH_2 groups can be replaced by O, S, or NR^1, optionally substituted aryl and optionally substituted heteroaryl;

Z is $(CR^{2a}R^{2b})_r$;

U is selected from the group consisting of $CR^{5a}R^{5b}$ and NR^6;

m is 1 or 2;

r is 0-3;

R^1 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

each R^{2a}, R^{2b}, R^{5a} and R^{5b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

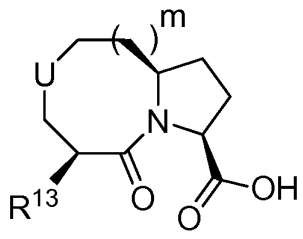
R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

R^{11a}, R^{11b}, R^{11c} and R^{11d} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido, and

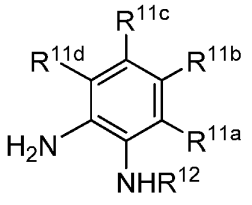
R^{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo, comprising:

a) condensing a compound of Formula XIII



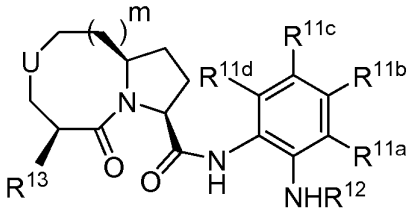
XIII

with a compound of Formula XIX



XIX

to give a compound of Formula XX



XX,

and b) cyclizing a compound of Formula XX, to give a compound of Formula XVIII.

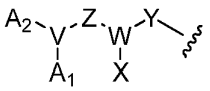
[00287] LXXXVI. The process of LXXXV, wherein R^{12} is hydrogen.

[00288] LXXXVII. The process of LXXXV, wherein R^{11a} is optionally substituted phenyl.

[00289] LXXXVIII. The process of LXXXV, wherein m is 1.

[00290] LXXXIX. The process of LXXXV, wherein R^{13} is $-N(H)P^1$.

[00291] XC. The process of LXXXIX, wherein P^1 is selected from the group consisting of t-butoxycarbonyl and benzyloxycarbonyl.

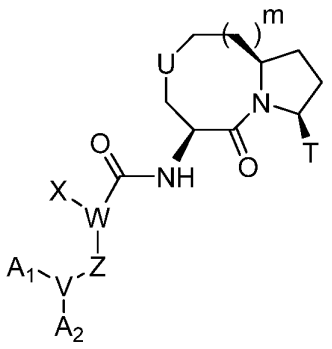
[00292] XCI. The process of LXXXV, wherein R^{13} is 

.

[00293] XCII. The process of XCI, wherein Y is CON(H), W is CH, r is 0 and V is N.

[00294] XCIII. The process of LXXXV, wherein U is NR^6 and R^6 is COR^9.

[00295] XCIV. A process for preparing a compound of Formula XXI



XXI

wherein:

A_1 and A_2 are independently selected from the group consisting of hydrogen and optionally substituted alkyl, wherein A_2 is absent when V is O;

V is selected from the group consisting of N, CH and O;

W is selected from the group consisting of CH and N;

X is selected from the group consisting of hydrogen, optionally substituted alkyl and aralkyl;

Z is $(CR^{2a}R^{2b})_r$;

U is selected from the group consisting of $CR^{5a}R^{5b}$ and NR^6;

m is 1 or 2;

r is 0-3;

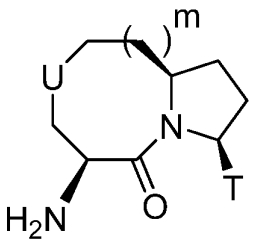
each R^{2a}, R^{2b}, R^{5a} and R^{5b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo; and

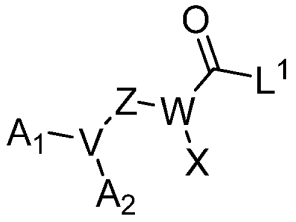
T is optionally substituted heteroaryl, comprising:

reacting a compound of Formula XXIII



XXIII

with a compound of Formula XXIV

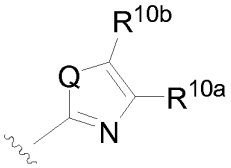


XXIV

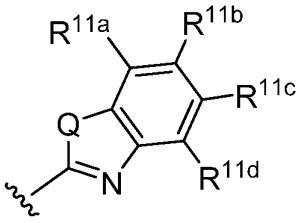
wherein L^1 is a leaving group, to give a compound of Formula XXI.

XCV. The process of XCIV, wherein W is CH and V is N.

XCVI. The process of XCIV wherein T is selected from the group consisting of



and



,

wherein:

Q is selected from the group consisting of O, S and NR^{12};

R^{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo; and

R^{10a}, R^{10b}, R^{11a}, R^{11b}, R^{11c} and R^{11d} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido.

[00296] XCVII. The process of XCIV, wherein U is CH_2.

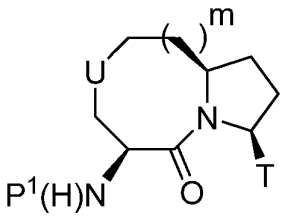
[00297] XCVIII. The process of XCIV, wherein U is $NCOR^9$.

[00298] XCIX. The process of XCVIII, wherein R^9 is optionally substituted alkyl.

[00299] C. The process of XCIV, wherein L^1 is selected from the group consisting of -Cl and -OH.

[00300] CI. The process of C, wherein L^1 is -OH and the condensation is carried out in the presence of an activating agent.

[00301] CII. The process of XCIV, wherein said compound of Formula XXIII is prepared by removing P^1 from a compound of Formula XXII

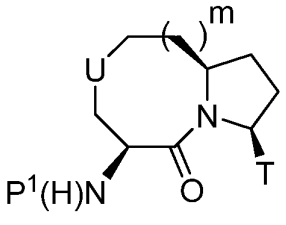


XXII

wherein P^1 is an amine protecting group.

[00302] CIII. The process of CII, wherein P^1 is selected from the group consisting of t-butoxycarbonyl and benzyloxycarbonyl.

[00303] CIV. A compound having Formula XXII:



XXII

wherein:

T is optionally substituted heteroaryl;

m is 1 or 2;

U is CH_2 or NR^6

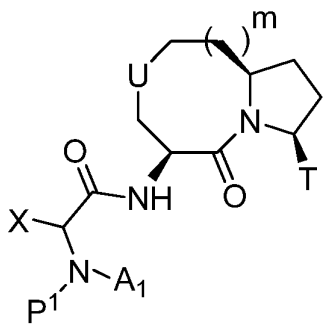
R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo; and

P^1 is an amine protecting group.

[00304] CV. The compound of CIV, wherein P^1 is selected from the group consisting of t-butoxycarbonyl and benzyloxycarbonyl.

[00305] CVI. A compound having Formula XXV



XXV

wherein:

T is optionally substituted heteroaryl;

m is 1 or 2;

U is CH_2 or NR^6

R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally

substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

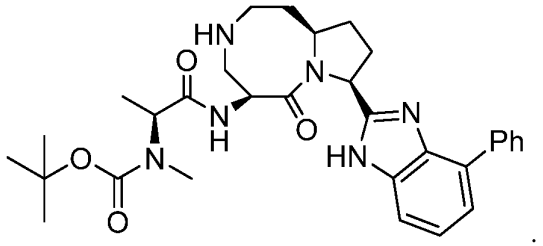
X is selected from the group consisting of hydrogen, optionally substituted alkyl, and aralkyl;

A_1 is selected from the group consisting of hydrogen an optionally substituted alkyl; and

P^1 is an amine protecting group.

[00306] CVII. The compound of CVI, wherein P^1 is selected from the group consisting of t-butoxycarbonyl and benzyloxycarbonyl.

[00307] CVIII. The compound of CVII having the structure:



[00308] The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered in clinical therapy and which are obvious to those skilled in the art are within the spirit and scope of the invention.

EXAMPLE 1

Synthesis of Covalently Constrained Smac Mimetics

[00309] General Methods: NMR spectra were acquired at a proton frequency of 300 MHz. ^1H chemical shifts are reported with Me_4Si (0.00 ppm), $CHCl_3$ (7.26 ppm), CD_2HOD (3.31 ppm), or DHO (4.79 ppm) as internal standards. ^{13}C chemical shifts are reported with $CDCl_3$ (77.00 ppm), CD_3OD (49.00 ppm), or 1,4-dioxane (67.16 ppm) as internal standards. Optical rotations were measured at room temperature. Compounds of the invention may be purified by reverse phase HPLC (0.1% TFA in water and 0.1% TFA in acetonitrile as the eluent) and isolated as the TFA salt.

General procedure A (condensation between carboxylic acid and amine):

[00310] To a solution of the two substrates in CH_2Cl_2 (20 mg/mL for the minor substrate) was added EDC (1.1 eq per amino group), HOBt (1.1 eq per amino group) and N,N-diisopropylethyl amine (4 eq per amino group) at 0 °C with stirring. The mixture was stirred at room temperature for eight hours and then concentrated. The residue was purified by chromatography to give the product.

General procedure B (deprotection of Boc):

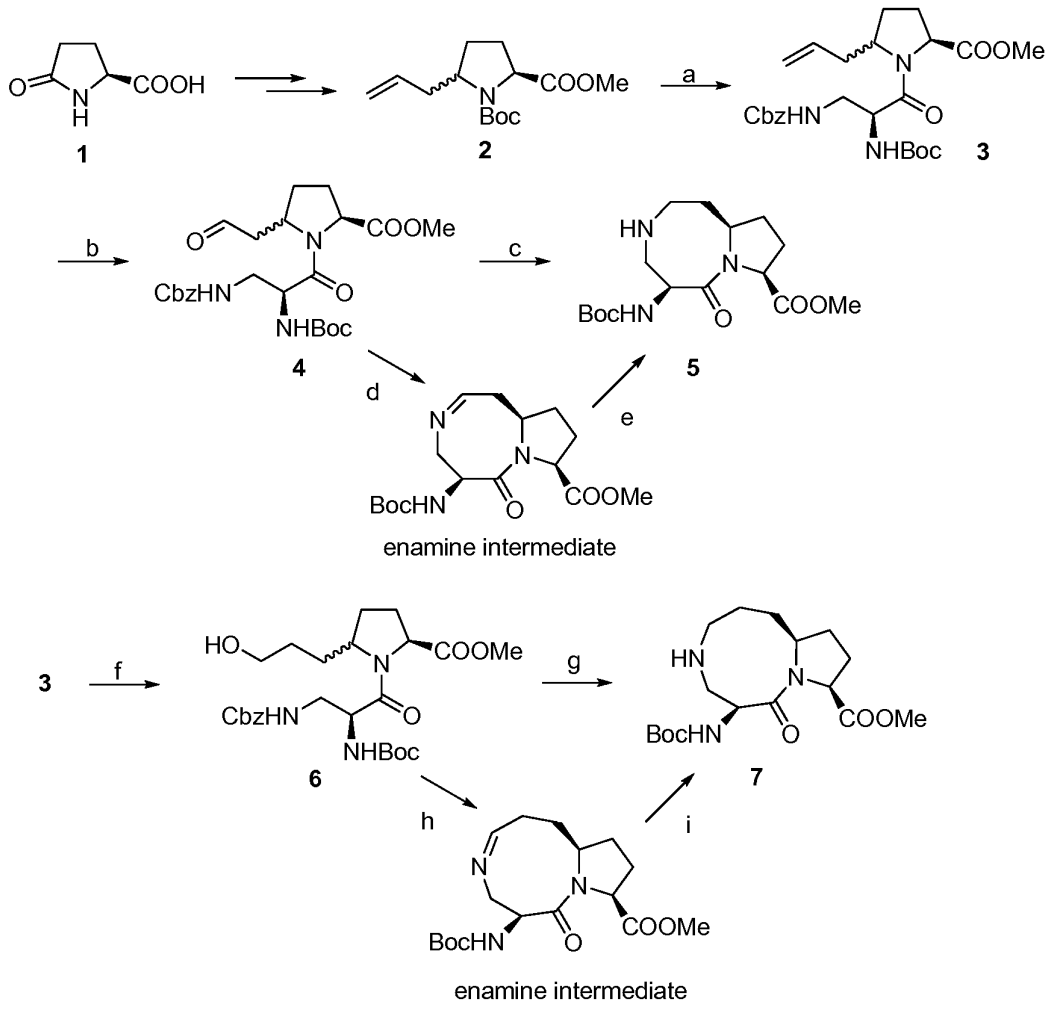
[00311] To a solution of the substrate in methanol (20 mg/mL) was added a solution of HCl in 1,4-dioxane (4 M, 10-20 eq per Boc). The solution was stirred at room temperature overnight and then condensed to give the product.

EXAMPLE 2

Synthesis of Smac Mimetic Intermediates

[00312] Intermediates in the synthetic pathway for conformationally constrained Smac mimetics may be synthesized using methodology described in Schemes 1-7.

Scheme 1



Reagents and conditions: (a) i. 4 N HCl in 1,4-dioxane, methanol; ii. Boc-Dap(Z)-OH, EDC, HOBt, *N,N*-diisopropylethylamine, CH_2Cl_2, 52% over two steps; (b) O_3, then PPh_3, CH_2Cl_2, 90%; (c) H_2, 10% Pd-C, *i*-PrOH, 41%; (d) H_2, 10% Pd-C, *i*-PrOH; (e) $NaBH(OAc)_3$, THF; (f) 9-BBN (2 eq), THF, reflux, 12h, then 3 N NaOH (2 eq), 35% H_2O_2 (2.5 eq), 0 °C - rt, 85%; (f) i. Dess-Martin periodinane, CH_2Cl_2; ii. H_2, 10% Pd-C, *i*-PrOH, 50% over two steps; (h) H_2, 10% Pd-C, *i*-PrOH; (i) $NaBH(OAc)_3$, THF.

[00313] The synthesis of intermediates **5** and **7** is shown in Scheme 1. Compound **2** may be prepared in five steps from pyroglutamic acid **1** according to reported methods (see: (1) Zhang, J.; Xiong, C.; Wang, W.; Ying, J.; Hruby, V., J. *Org. Lett.*, **2002**, *4* (23), 4029-4032, (2) Polyak, F. and Lubell, W. D. *J. Org, Chem.* **1998**, *63*, 5937-5949, and (3) *Tetrahedron Letters* **2005**, *46*, 945-947.) as a mixture of two diastereoisomers with the *R* form isomer as the major product (ratio is about 4:1). Removal of the Boc group in **2**

followed by condensation with *N*-α-(*tert*-butoxylcarbonyl)-*N*-β-(benzoxylcarbonyl)-*L*-diamino-propionic acid (Boc-Dap(Z)-OH) gave amide **3**. Ozone oxidation of the C-C double bond in **3** yielded aldehyde **4**. Cleavage of the Cbz group in **4**, intramolecular condensation of the resulting amine with the aldehyde group and subsequent reduction of the enamine were realized in one pot to give compound **5** under prolonged reaction times. Alternatively, deprotection of the CBz group of **4**, intramolecular cyclization, isolation of the enamine intermediate and reduction provides **5**. In this transformation only compound **5** was obtained and there was no detectable formation of its isomer, suggesting that the amino aldehyde from the minor isomer does not cyclize under these conditions.

[00314] To a solution of compound **2** (540 mg, 2 mmol) in 20 mL of methanol was added 4 mL of a solution of 4 N HCl in 1,4-dioxane. The solution was stirred at room temperature overnight and then concentrated to give an ammonium salt. To a mixture of this salt in 15 mL of dichloromethane were added 1.17 g (2.4 eq) of Boc-Dap(Z)-OH·DCHA, 460 mg (2.4 mmol) of EDC, 320 mg (2.4 mmol) of HOBt, and 3 mL of *N,N*-diisopropylethyl amine. The mixture was stirred at room temperature overnight and then condensed. The residue was purified by chromatography to afford compound **3** (YP-348) (580 mg, 59%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS) (major isomer) δ 7.34-7.28 (m, 5H), 5.80-5.77 (m, 1H), 5.59 (m, 1H), 5.36-5.33 (d, J = 10.0 Hz, 2H), 5.19-5.01 (m, 4H), 4.67-4.62 (m, 1H), 4.47-4.44 (m, 1H), 3.76-3.74 (s, 1H), 3.74-3.71 (s, 2H), 2.32-2.30 (m, 1H), 2.16-2.12 (m, 1H), 1.99-1.95 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 170.5, 156.5, 155.2, 136.4, 134.6, 133.8, 128.3, 127.9, 118.5, 117.1, 80.0, 66.6, 59.7, 58.2, 52.6, 43.4, 29.2, 28.1, 26.6.

[00315] O_3 was bubbled through a solution of compound **3** (490 mg, 1 mmol) in 20 mL of CH_2Cl_2 at -78 °C until the color turned to pale blue. O_3 was bubbled for 15 min more before air was bubbled to get rid of excessive O_3. After adding 3 mL of Et_3N, the mixture was warmed to room temperature and stirred for 1h. The solvent was evaporated and the residue was purified by chromatography to give aldehyde **4** (YP-367) (340 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS) (major isomer) δ 9.78-9.67 (m, 1H), 7.53-7.32 (m, 5H), 5.44 (s, 1/2 H), 5.32 (s, 1/2 H), 5.15-5.06 (m, 2H), 4.64 (m, 1H), 4.40-4.39 (m, 1H), 3.78-3.76 (s, 3/2 H), 3.76-3.74 (s, 3/2H), 3.48-3.42 (m, 3H), 2.78-2.52 (m, 1H), 2.40-2.20 (m, 1H), 2.16 (m, 2H), 2.06-1.89 (m, 1H), 1.44-1.43 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

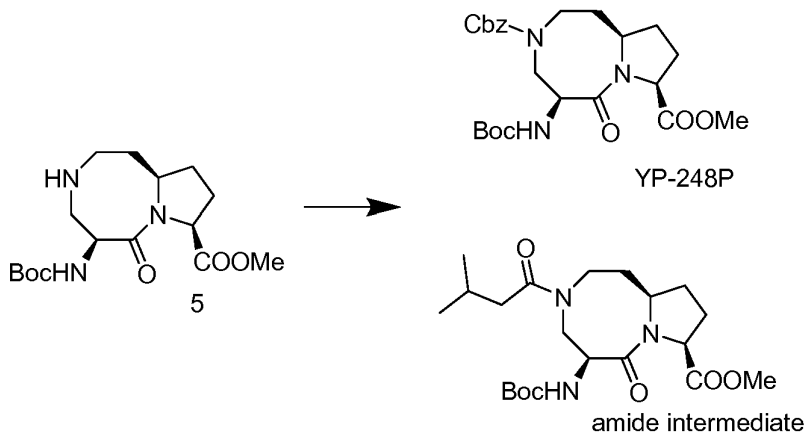
200.3, 199.5, 172.6, 172.2, 170.3, 156.5, 136.4, 128.4, 128.0, 66.7, 59.7, 59.1, 54.3, 52.4, 52.3, 48.4, 43.3, 29.6, 28.2, 21.0.

[00316] To a solution of compound **4** (290 mg, 0.6 mmol) in 20 mL of isopropanol was added 0.2 g of 10% Pd/C. The mixture was stirred at room temperature under H_2 overnight, filtered through celite and concentrated. The residue was dissolved in dry THF. To this solution was added $NaBH(OAc)_3$ (380 mg, 1.8 mmol). The mixture was stirred at room temperature overnight, diluted with CH_2Cl_2, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography to give compound **5** (72 mg, 35%). $[\alpha]^{20}_D$ – 30.2 (c = 1.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 5.45 (brd, *J* = 8.0 Hz, 1H), 4.67 (m, 1H), 4.52 (t, *J* = 9.0 Hz, 1H), 4.23 (m, 1H), 3.74 (s, 3H), 3.20 (m, 2H), 2.94 (m, 1H), 2.74 (dd, J = 13.6, 10.9 Hz, 1), 2.35 (m, 1H), 2.14 (m, 1H), 1.99 (m, 1H), 1.86-1.74 (m, 3H), 1.66 (m, 1H), 1.43 (brs, 9H); 13C NMR (75 MHz, CDCl3, TMS) δ 173.42, 170.60, 155.16, 79.68, 59.46, 58.39, 54.92, 52.44, 46.72, 37.45, 32.15, 29.64, 28.29, 26.98.

[00317] Hydroboration of the C-C double bond in **3** with 9-BBN followed by alkaline oxidation of the resulted borane afforded alcohol **6**. Oxidation of **6** with Dess-Martin periodinane furnished a mixture of two aldehydes, which was cyclized in the same procedure as that for compound **5** to give compound **7**. Similar to **5**, during this transformation only one isomer was obtained.

[00318] Analytical data for compound **7**: $[\alpha]^{20}_D$ – 23.2 (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 5.23 (brd, J = 8.0 Hz, 1H), 4.79 (m, 1H), 4.65 (dd, J = 9.7, 8.2 Hz), 4.22 (m, 1H), 3.74 (s, 3H), 3.02-2.80 (m, 4H), 2.38-1.70 (m, 9H), 1.43 (brs, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 173.38, 171.59, 155.09, 79.68, 62.03, 59.82, 53.72, 53.15, 52.48, 50.09, 34.66, 34.55, 29.47, 28.31, 27.33.

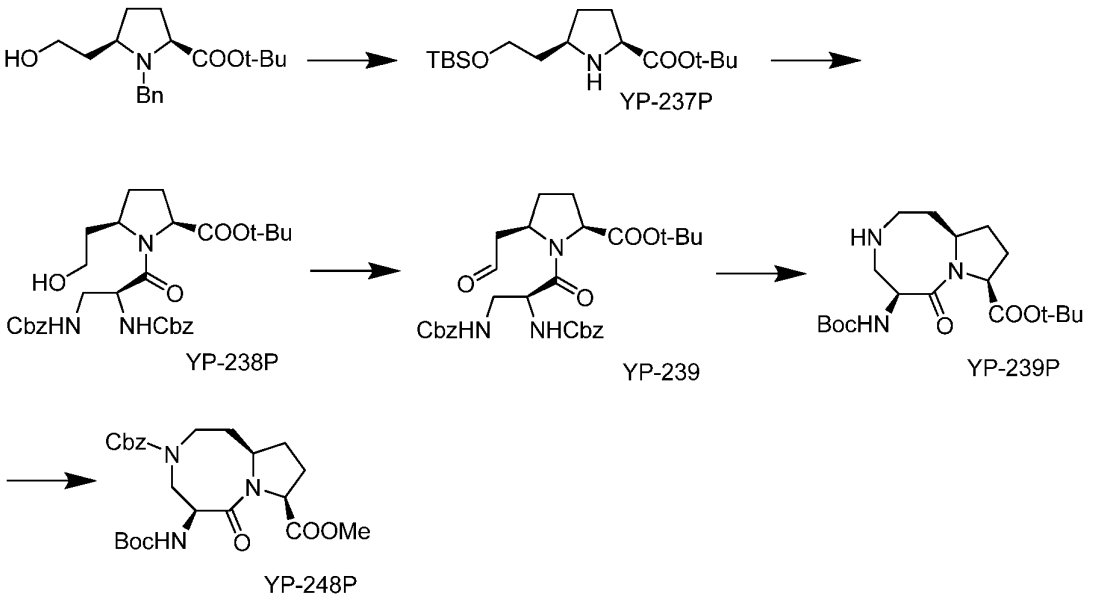
Scheme 2



[00319] Analytical data for **YP-248P:** ^{1}H NMR shows that this compound has two rotamers with a ratio of 2:1. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 7.47-7.44 (m, 1H), 7.38-7.32 (m, 4H), 5.65-5.62 (d, *J* = 8 Hz, 1H), 5.31-5.16 (m, 2H), 4.64-4.60 (m, 1H), 4.51-4.46 (t, *J* = 8 Hz, 1H), 4.24-4.23 (m, 1H), 4.23-4.21 (m, 1H), 3.75 (s, 1H), 3.73 (s, 2H), 3.66-3.63 (m, 1H), 3.63-3.61 (m, 1H), 3.61-3.31 (m, 1H), 2.36-2.34 (m, 1H), 2.11-1.76 (m, 6H), 1.44-1.45 (s, 9H).

[00320] Analytical data for amide intermediate: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 5.79 (brd, J = 7.0 Hz, 1H), 4.50-4.35 (m, 2H), 4.05 (m, 1H), 3.98-3.85 (m, 2H), 3.70 (s, 3H), 3.32-3.04 (m, 2H), 2.54 (m, 1H), 2.40-2.26 (m, 2H), 2.25-1.60 (m, 6H), 1.39 (s, 9H), 0.98-0.89 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.12, 172.52, 168.85, 154.69, 79.80, 59.51, 56.11, 54.38, 53.51, 52.23, 46.18, 42.02, 32.51, 31.12, 28.12, 26.54, 25.81, 22.69, 22.40.

Scheme 3



[00321] Analytical data for **YP-237P:** [α] $^{20}_{D}$ -21.5° (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 3.71 (t, *J* = 6.5 Hz, 3H), 3.60 (dd, *J* = 9.0, 5.4 Hz, 1H), 3.11 (m, 1H), 2.05 (m, 1H), 1.95-1.63 (m, 3H), 1.46 (s, 9H), 1.25 (m, 1H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 80.8, 61.5, 60.6, 57.5, 38.8, 31.8, 30.4, 28.0, 25.9, 18.2, -5.4; HRMS: calcd. m/z for $[M+H]^+$ 330.2464; found 330.2466.

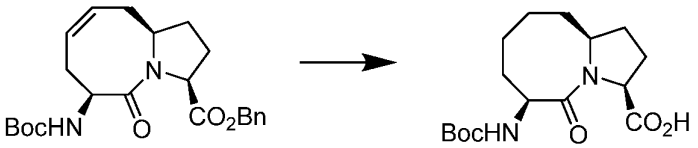
[00322] Analytical data for **YP-238P:** [α] $^{20}_{D}$ -90.0° (c = 1.67, $CHCl_3$); ^{1}H NMR shows this compound has two rotamers with a ratio of 1:1. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 7.28 (m, 5H), 5.59 (m,1H), 5.35 (m, 1H), 5.20-5.05 (m, 2H), 4.85 (m, ½ H), 4.65 (m, ½ H), 4.46 (m, 1H), 4.35 (m, 1H), 3.80 (m, ½ H), 3.70-3.50 (m, 2H), 3.40 (m, 1H), 3.25 (m, ½ H), 2.32 (m, 1H), 2.20-1.50 (m, 4H), 1.46 (s, 4.5H), 1.44 (s, 4.5H), 1.43 (s, 4.5H), 1.41 (s, 4.5H); HRMS: calcd m/z 558.2791 for $[M+Na]^+$; found 558.2794.

[00323] Analytical data for **YP-239:** [α] $^{20}_{D}$ -51.6° (c = 1.67, $CHCl_3$); ^{1}H NMR shows that this compound has two rotamers with a ratio of 2:1. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 9.76 (s, 2/3 H), 9.71 (s, 1/3 H), 7.40-7.28 (m, 5H), 5.72-5.30 (m, 2H), 5.20-4.95 (m, 2H), 4.90-4.25 (m, 3H), 3.52-3.05 (m, 3H), 2.90-1.60 (m, 4H), 1.50-1.35 (m, 18H); HRMS: calcd m/z 556.2635 for $[M+Na]^+$; found 556.2629.

[00324] Analytical data for **YP-239P:** [α] $^{20}_{D}$ -8.4° (c = 0.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 5.49 (brd, *J* = 8.1 Hz, 1H), 4.70 (m, 1H), 4.41 (t, *J* = 9.3 Hz, 1H), 4.30

(m, 1H), 3.25-3.18 (m, 2H), 2.89 (m, 1H), 2.75 (dd, J = 13.5, 11.1 Hz, 1H), 2.34 (m, 1H), 2.18-1.60 (m, 6H), 1.49 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 170.4, 155.2, 81.7, 79.5, 60.6, 58.5, 54.9, 52.3, 46.9, 37.5, 32.1, 28.3, 28.0, 27.0; HRMS: calcd m/z 406.2318 for $[M+Na]^+$; found 406.2317.

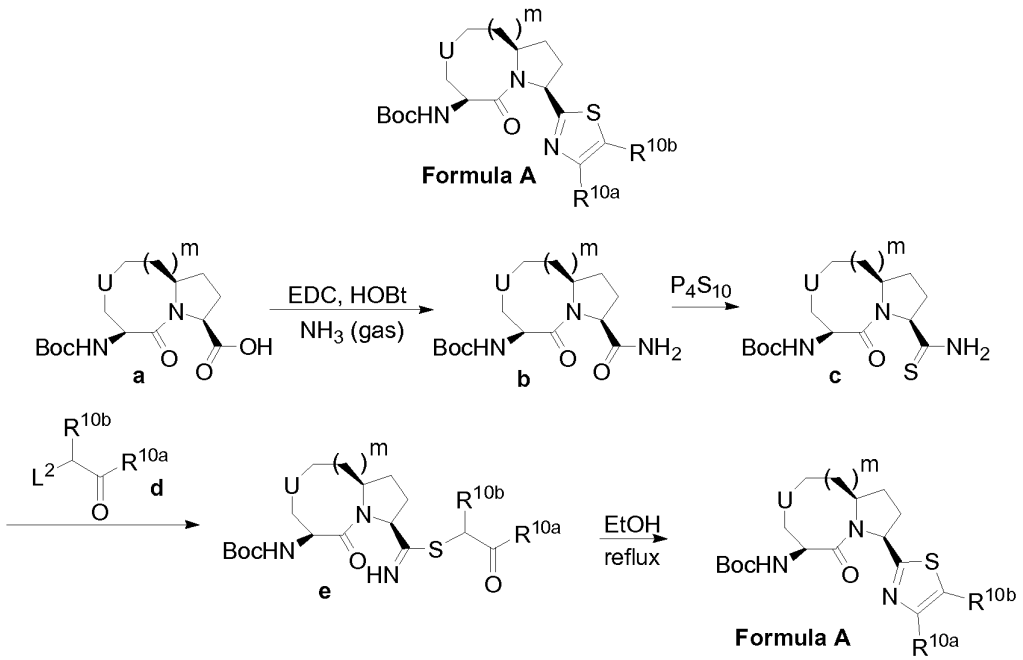
Scheme 4



6 7

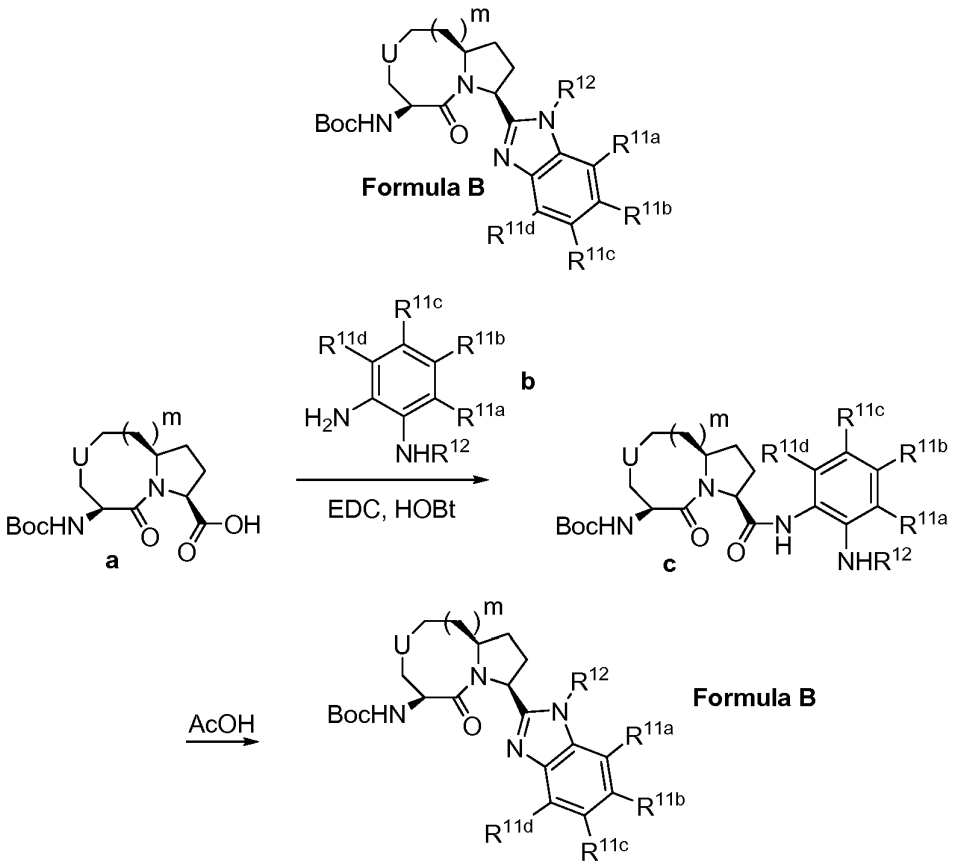
[00325] Compound **6** can be prepared according to methods reported in the literature (Duggan *et al., Org. Biomol. Chem. 3:*2287 (2005)) (Scheme 4). Reduction of the alkene and hydrolysis of the benzyl ester gave acid **7**.

Scheme 5



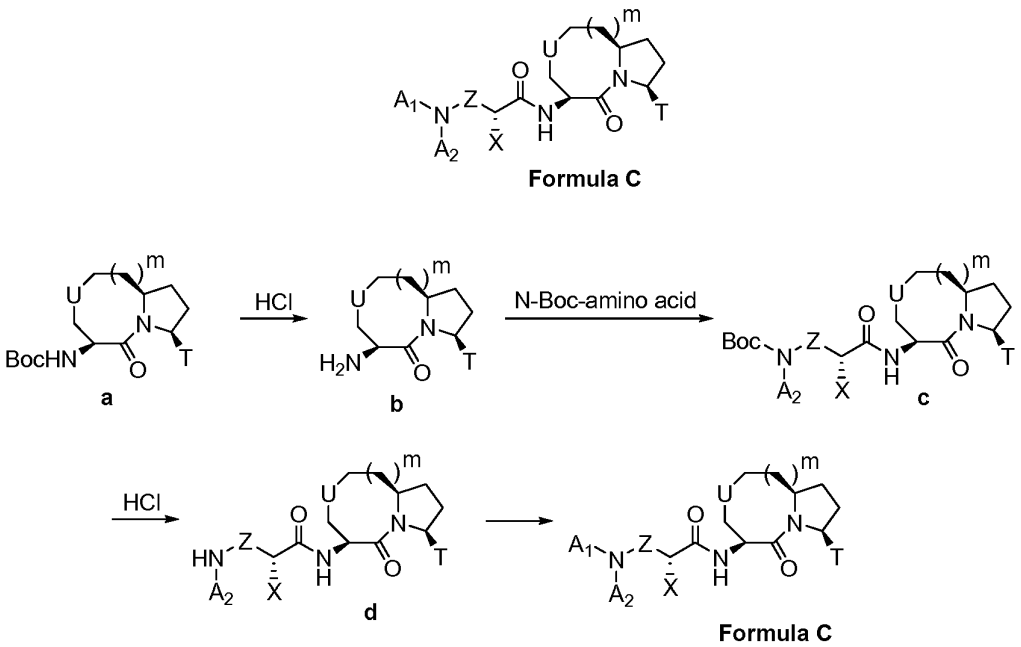
[00326] A compound represented by formula A, wherein m is 1-2, R^{10a} and R^{10b} are independently hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclo, and U has the meaning as described above for Formula I, may be prepared by the method shown in Scheme 5. Briefly, condensation of acid **a** with ammonia gives primary amide **b**. Selective transformation of the primary amide to thioamide **c** can be realized by reaction of **b** with P_4S_{10} in CH_2Cl_2 at room temperature. Reaction of **c** with **d**, wherein L^2 is a leaving group, furnishes **e**. L^2 is a leaving group. In one embodiment, **d** is an α-bromoketone. Cyclization of **e** by refluxing in ethanol provides thiozole of Formula A.

Scheme 6



[00327] A compound represented by Formula B, wherein m is 1-2, R^{11a}, R^{11b}, R^{11c} and R^{11d} are independently hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido, R^{12} is hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, and U has the meaning as described above for Formula I, may be prepared as described in Scheme 6. Briefly, condensation of acid **a** with a substituted diaminobenzene **b** gives amide **c**. Cyclization of **c** by refluxing in AcOH provided compound of Formula B.

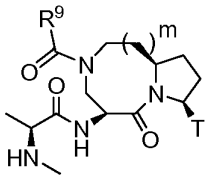
Scheme 7



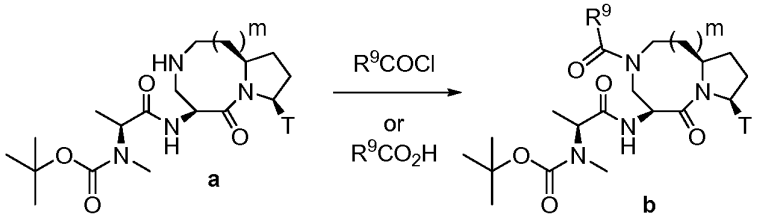
[00328] A compound represented by Formula C wherein m is 1 or 2, and A_1, A_2, Z, X, T and U have the meanings as described above for Formula I, may be prepared as shown in Scheme 7. Briefly, removal of the Boc protecting group in **a** provides amine **b**. Condensation of **b** with corresponding Boc-protected amino acid gives amide **c**. Removal

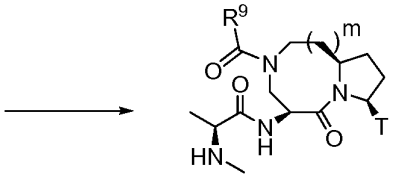
of the Boc protecting group in **c** affords **d**. Introduction of the A_1 group by substitution of **d** with an alkyl halide or reductive amination of **d** with the corresponding aldehyde provides Smac mimetic represented by Formula C.

Scheme 8



Formula D

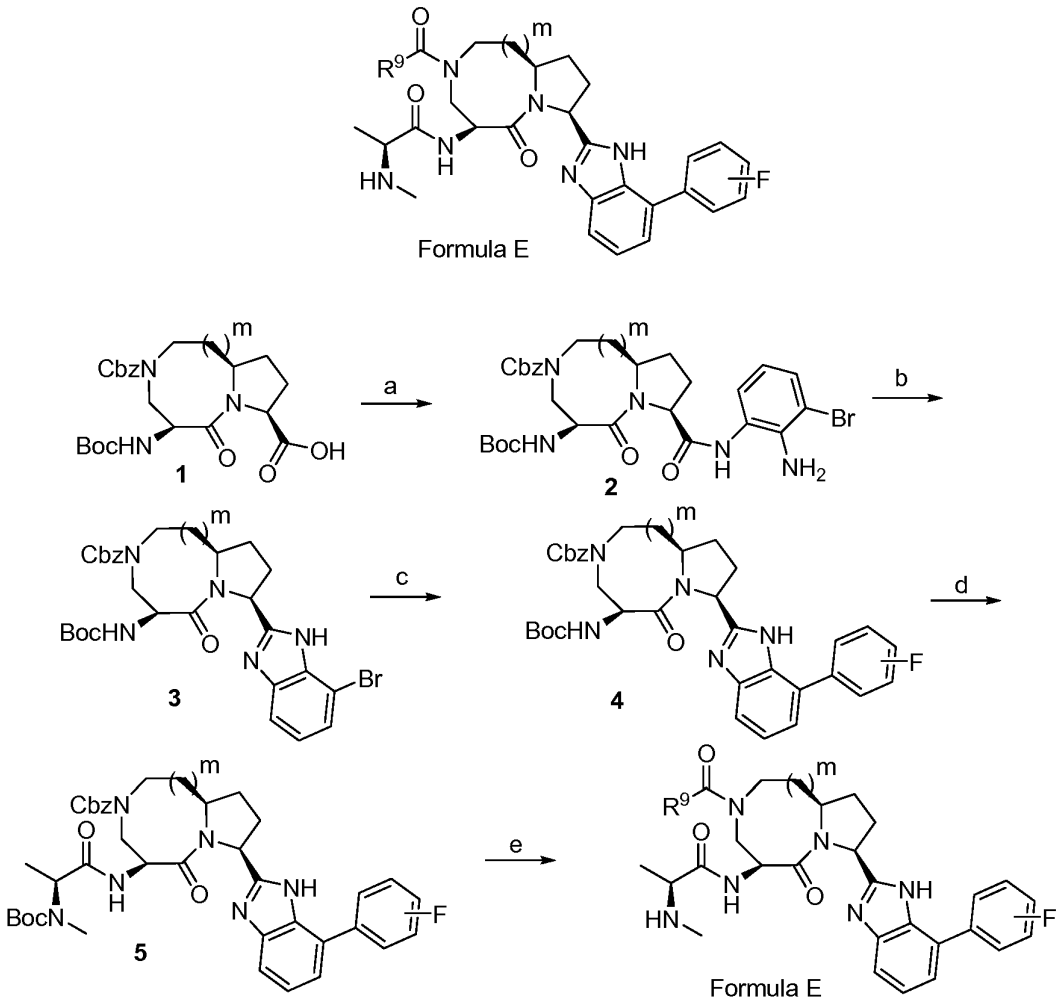




Formula D

[00329] A compound represented by Formula D wherein m is 1 or 2, and T and R^9 have the meanings as described above for Formula I, may be prepared as described in Scheme 8. Briefly, reaction of amine **a** with carboxylic acid R^9CO_2H or carboxylic acid chloride R^9COCl gives amide **b**. Removal of the Boc protecting group of **b** gives a compound represented by Formula D.

Scheme 9

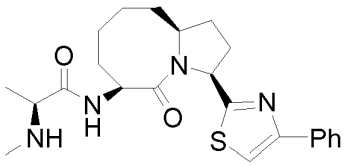


Reagents and conditions: (a) 3-bromo-1,2-diamine, EDC, HOBt, N,N-diisopropylethylamine, CH_2Cl_2; (b) HOAc, 70 °C, 10 h; (c) arylboronic acid, dba Pd, tri-tert-butylphosphine, K_2CO_3, methylene glycol dimethyl ether, refulx, overnight; (d) i. 4 N HCl in 1,4-dioxane, methanol; ii. L-N-Boc-N-methyl-alanine, EDC, HOBt, N,N-diisopropylethylamine, CH_2Cl_2; (e) i. H_2, 10% Pd-C, methanol; ii. R^9CO_2H , EDC, HOBt, N,N-diisopropylethylamine, CH_2Cl_2; iii. 4 N HCl in 1,4-dioxane, methanol.

[00330] A compound represented by Formula E wherein m is 1 or 2, and R^9 has the meaning as described for Formula I, may be prepared as described in Scheme 9. Briefly, reaction of acid **1** with 3-bromo-1,2-diamine gives amide **2**. Cyclization of **2** in acetic acid gives benzimidazole **3**. Suzuki compling with an arylboronic acid (e.g., 2-, 3-, or 4-fluorophenyl boronic acid) gives **4**. Boc deprotection of **4** and reaction with L-N-Boc-N-methylalanine gives **5**. Cbz deprotection, coupling with R^9CO_2H, and Boc deprotection gives a compound represented by Formula E.

EXAMPLE 3

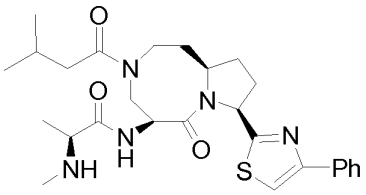
SM-1229



[00331] Analytical data for **SM-1229**: ^{1}H NMR (300 MHz, D_2O) δ 7.65-7.50 (m, 2H), 7.21 (s, 1H), 7.18-6.96 (m, 3H), 5.20 (t, J = 6.86 Hz, 1H), 4.70 (m, 1H), 4.20 (m, 1H), 3.89 (m, 1H), 2.65 (s, 3H), 2.20-1.70 (m, 4H), 1.70-1.20 (m, 11H); ^{13}C NMR (75 MHz, D_2O) δ 173.18, 172.38, 169.49, 153.65, 133.89, 129.09, 128.52, 126.44, 114.79, 60.55, 60.26, 57.20, 50.95, 37.08, 33.03, 32.44, 31.37, 31.15, 25.28, 22.63, 15.72.

EXAMPLE 4

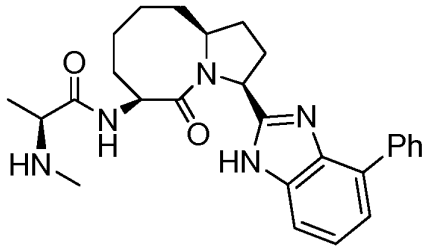
SM-1235



[00332] Analytical data for **SM-1235** (major conformer): ^{1}H NMR (300 MHz, D_2O) δ 7.72-7.65 (m, 2H), 7.48 (s, 1H), 7.40-7.20 (m, 3H), 5.21 (m, 1H), 5.02 (m, 1H), 4.32 (m, 1H), 3.98-3.20 (m, 5H), 2.55 (s, 3H), 2.35-1.70 (m, 9H), 1.42 (d, J = 7.2 Hz, 3H), 0.80-0.62 (m, 6H); ^{13}C NMR (75 MHz, D_2O) δ 175.84, 173.60, 169.91, 154.59, 133.96, 129.42, 126.69, 114.57, 71.08, 61.57, 59.80, 57.28, 51.35, 46.62, 42.82, 34.30, 31.62, 22.25, 22.09, 15.61.

EXAMPLE 5

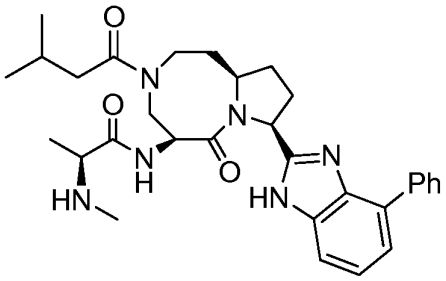
SM-1237



[00333] Analytical data for **SM-1237**: ^{1}H NMR (300 MHz, D_2O) δ 7.45 (d, J = 7.5 Hz, 1H), 7.36-7.20 (m, 6H), 71.5 (d, J = 7.5 Hz, 1H), 5.13 (m, 1H), 4.72 (m, 1H), 4.33 (m, 1H), 3.80 (m, 1H), 2.51 (s, 3H), 2.45-2.10 (m, 3H), 1.92-1.37 (m, 8H), 1.36 (d, J = 7.2 Hz, 3H), 1.15 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 173.85, 169.76, 153.02, 135.56, 131.66, 129.48, 129.18, 128.72, 128.50, 128.26, 127.10, 113.10, 60.97, 57.15, 55.36, 51.23, 36.59, 32.72, 32.34, 31.31, 29.58, 24.86, 22.80, 15.55.

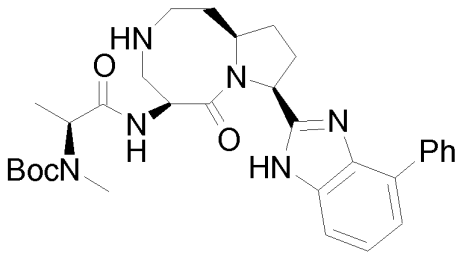
EXAMPLE 6

SM-1238



[00334] Analytical data for **SM-1238** (major conformer): ^{1}H NMR (300 MHz, D_2O) δ 7.70 (m, 1H), 7.60-7.40 (m, 7H), 5.40 (m, 1H), 5.15 (m, 1H), 4.55 (m, 1H), 4.03-3.86 (m, 2H), 3.62-3.55 (m, 2H), 3.20 (m, 1H), 2.62 (s, 3H), 2.60-2.20 (m, 4H), 2.15-1.70 (m, 3H), 1.50 (d, J = 7.2 Hz, 3H), 1.42 (m, 1H), 0.96 (m, 1H), 0.55 (d, J = 7.2 Hz, 3H), 0.36 (d, J = 7.2 Hz, 3H).

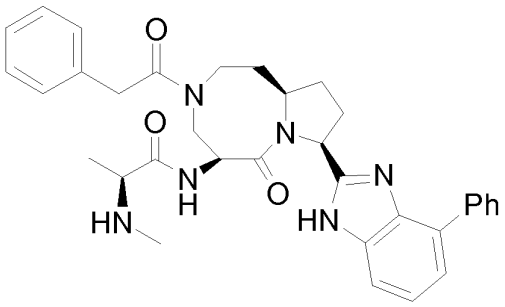
EXAMPLE 7



[00335] Analytical data for the compound of Example 7: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 7.70-7.35 (m, 6H), 7.32-7.15 (m, 2H), 6.88 (brs, 1H), 5.55 (m, 1H), 5.20 (m, 1H), 4.65 (brm, 1H), 4.42 (m, 1H), 4.15 (m, 1H), 3.25-3.08 (m, 2H), 2.85 (m, 1H), 2.75 (s, 3H), 2.70 (m, 1H), 2.52 (m, 1H), 2.35-1.75 (m, 5H), 1.45 (brs, 9H), 1.35 (d, J = 7.0 Hz, 3H); ESI MS (m/z) 561.3 $(M+H)^+$.

EXAMPLE 8

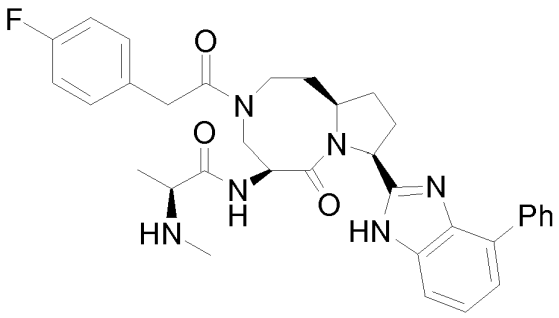
SM-1257



[00336] Analytical data for **SM-1257** (major conformer): ^{1}H NMR (300 MHz, D_2O) δ 7.70-7.49 (m, 8H), 7.15-7.02 (m, 3H), 6.72-6.62 (m, 2H), 5.47 (m, 1H), 5.15 (m, 1H), 4.75 (m, 1H), 4.59 (m, 1H), 4.10-3.85 (m, 2H), 3.72-3.62 (m, 2H), 3.43 (m, 1H), 2.88 (m, 1H), 2.70 (s, 3H), 2.68-2.25 (m, 4H), 2.20-1.82 (m, 3H), 1.55 (d, J = 7.0 Hz, 3H); ESI MS (m/z) 579.3 $(M+H)^+$.

EXAMPLE 9

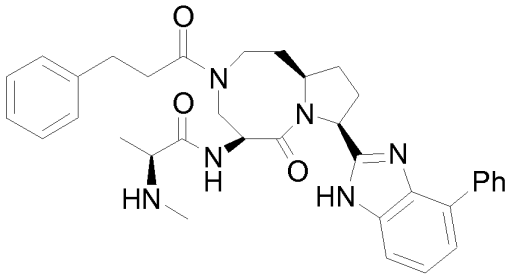
SM-1268



[00337] Analytical data for **SM-1268** (major conformer): ^{1}H NMR (300 MHz, D_2O) δ 7.69-7.42 (m, 8H), 6.70-6.52 (m, 4H), 5.48 (m, 1H), 5.20 (m, 1H), 4.75 (m, 1H), 4.62 (m, 1H), 4.09-3.92 (m, 2H), 3.75-3.62 (m, 2H), 3.42 (m, 1H), 2.85 (m, 1H), 2.70 (s, 3H), 2.68-2.25 (m, 4H), 2.18-1.83 (m, 3H); ESI MS (m/z) 597.3 $(M+H)^+$.

EXAMPLE 10

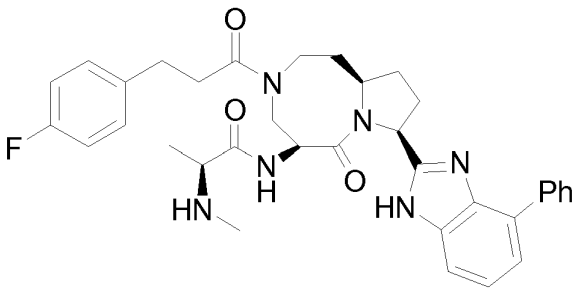
SM-1270



[00338] Analytical data for **SM-1270** (major conformer): ^{1}H NMR (300 MHz, D_2O) δ 7.82 (m, 1H), 7.70-6.97 (m, 7H), 7.20-7.09 (m, 3H), 6.73-6.65 (m, 2H), 5.49 (m, 1H), 5.23 (m, 1H), 4.75 (m, 1H), 4.53 (m, 1H), 4.10-3.95 (m, 2H), 3.68-3.58 (m, 2H), 3.32 (m, 1H), 2.72 (s, 3H), 2.72-2.55 (m, 2H), 2.52-1.95 (m, 6H), 1.80-1.62 (m, 2H), 1.55 (d, J = 7.0 Hz, 3H); ESI MS (m/z) 593.3 $(M+H)^+$.

EXAMPLE 11

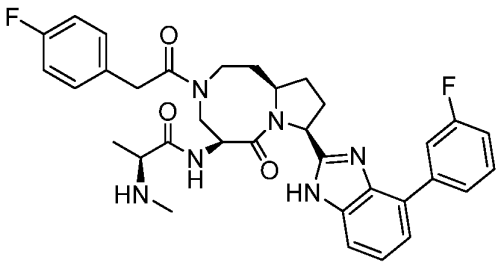
SM-1271



[00339] Analytical data for **SM-1271** (major conformer): ^{1}H NMR (300 MHz, D_2O) δ 7.64 (m, 1H), 7.45-7.20 (m, 6H), 7.05 (m, 1H), 6.65-6.50 (m, 2H), 6.50-6.39 (m, 2H), 5.42 (m, 1H), 5.20 (m, 1H), 4.85 (m, 1H), 4.55 (m, 1H), 4.10-3.90 (m, 2H), 3.65-3.45 (m, 2H), 3.25 (m, 1H), 2.68 (s, 3H), 2.65-2.02 (m, 7H), 1.95-1.70 (m, 1H), 1.55 (d, J = 7.0 Hz, 3H), 1.54 (m, 1H); ESI MS (m/z) 611.3 $(M+H)^+$.

EXAMPLE 12

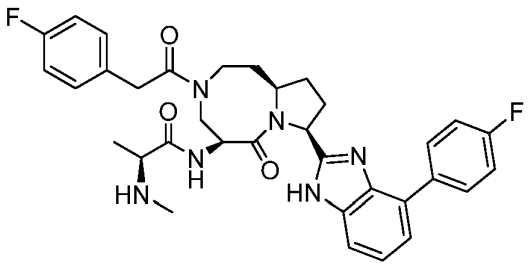
SM-1306



[00340] Analytical data for **SM-1306** : ^{1}H NMR (300 MHz, D_2O) δ 7.70-7.50 (m, 4H), 7.40-7.20 (m, 3H), 6.82-6.58 (m, 4H), 5.47 (m, 1H), 5.18 (m, 1H), 4.75-4.50 (m, 2H), 4.05-3.88 (m, 2H), 3.75-3.65 (m, 2H), 3.50-3.30 (m, 2H), 2.90 (m, 1H), 2.65 (m, 3H), 2.62-1.90 (m, 6H), 1.55 (d, J = 7.0 Hz, 3H); ESI MS (m/z) 615.3 $(M+H)^+$.

EXAMPLE 13

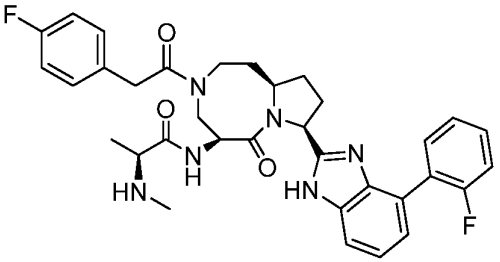
SM-1307



[00341] Analytical data for **SM-1307**: ^{1}H NMR (300 MHz, D_2O) δ 7.40 (m, 1H), 7.25-7.15 (m, 3H), 7.05-5.85 (m, 3H), 6.60-6.35 (m, 4H), 5.38 (m, 1H), 5.15 (m, 1H), 4.75 (m, 1H), 4.50 (m, 1H), 4.05-3.80 (m, 2H), 3.70-3.50 (m, 2H), 3.50-3.20 (m, 2H), 2.70 (m, 1H), 2.63 (s, 3H), 2.60-1.70 (m, 6H), 1.55 (d, J = 7.0 Hz, 3H); ESI MS (m/z) 615.3 $(M+H)^+$.

EXAMPLE 14

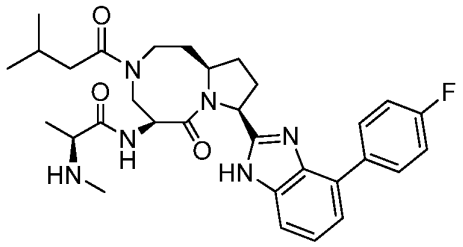
SM-1308



[00342] Analytical data for **SM-1308**: ^{1}H NMR (300 MHz, D_2O) δ 7.38 (m, 1H), 7.30-7.10 (m, 2H), 7.05-6.85 (m, 4H), 6.60-6.35 (m, 4H), 5.35 (m, 1H), 5.15 (m, 1H), 4.75 (m, 1H), 4.42 (m, 1H), 3.95 (m, 1H), 3.75 (m, 1H), 3.60-3.02 (m, 4H), 2.75-2.60 (m, 4), 2.58-1.60 (m, 6H), 4.05-3.80 (m, 2H), 3.70-3.50 (m, 2H), 3.50-3.20 (m, 2H), 2.70 (m, 1H), 2.63 (s, 3H), 2.60-1.70 (m, 6H), 1.55 (d, J = 7.0 Hz, 3H); ESI MS (m/z) 615.3 $(M+H)^+$.

EXAMPLE 15

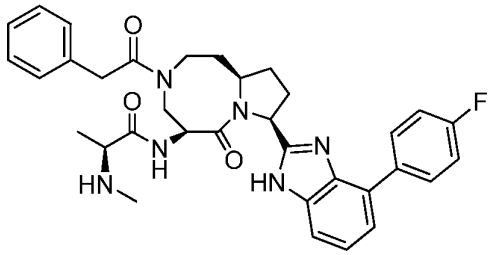
SM-1316



[00343] Analytical data for **SM-1316** : ^{1}H NMR (300 MHz, D_2O) δ 7.70 (m, 1H), 7.55-7.45 (m, 2H), 7.40 (m, 1H), 7.25-7.15 (m, 2H), 5.45 (m, 1H), 5.20 (m, 1H), 4.75 (m, 1H), 4.55 (m, 1H), 4.03-3.90 (m, 2H), 3.70-3.50 (m, 2H), 3.25 (m, 1H), 2.70 (s, 3H), 2.60-1.60 (m, 7H), 1.55 (d, J = 7.0 Hz, 3H); 1.50 (m, 1H), 1.02 (m, 1H), 0.55 (d, J = 7.2 Hz, 3H), 0.30 (d, J = 7.2 Hz, 3H); ESI MS (m/z) 563.3 $(M+H)^+$.

EXAMPLE 16

SM-1317



[00344] Analytical data for **SM-1317** : ^{1}H NMR (300 MHz, D_2O) δ 7.55 (m, 1H), 7.50-7.30 (m, 3H), 7.22 (m, 1H), 7.18-7.05 (m, 2H), 6.98-6.90 (m, 3H), 6.85-6.50 (m, 2H), 5.38 (m, 1H), 5.10 (m, 1H), 4.80 (m, 1H), 4.50 (m, 1H), 4.02-3.80 (m, 2H), 3.75-3.50 (m, 2H), 3.45-3.20 (m, 2H), 2.78 (m, 1H), 2.68 (s, 3H), 2.58-1.75 (m, 6H), 1.55 (d, J = 7.0 Hz, 3H); ESI MS (m/z) 597.3 $(M+H)^+$.

EXAMPLE 17

Binding of Inhibitors to XIAP

[00345] A sensitive and quantitative *in vitro* binding assay using the fluorescence polarization (FP) based method was used to determine the binding affinity of Smac mimetics to XIAP protein (Nikolovska-Coleska *et al.*, *Anal. Biochem. 332*:261-73 (2004)). For this assay, 5-carboxyfluorescein (5-Fam) was coupled to the lysine side chain of the mutated Smac peptide, AbuRPF-K-(5-Fam)-NH_2 (termed SM5F). Another fluorescently tagged Smac mimetic (termed SM-F1) with higher affinities than SM5F was also used.

[00346] For determination of the Kd values, fluorescence polarization values were measured using the Ultra plate reader (Tecan U.S., Research Triangle Park, NC) in Microfluor 2 96-well, black, round-bottom plates (Thermo Scientific). As one example for the SM-F1 tracer, to each well, SM-F1 (2nM, 1nM, and 1nM for experiments with XIAP-BIR3, cIAP1-BIR3, and cIAP2-BIR3, respectively) and different concentrations of proteins were added to a final volume of 125 μl in the assay buffer (100mM potassium phosphate, pH 7.5, 100 μg/ml bovine γ-globulin, 0.02% sodium azide, Invitrogen, with 4% DMSO). Plates were mixed and incubated at room temperature for 3 hours with gentle shaking to assure equilibrium. The polarization values in millipolarization units (mP) were measured at an excitation wavelength of 485 nm and an emission wavelength of 530 nm. Equilibrium dissociation constants (K_d) were then calculated by fitting the sigmoidal dose-dependent FP increases as a function of protein concentrations using Graphpad Prism 5.0 software (Graphpad Software, San Diego, CA).

[00347] The Kd values of SM5F to recombinant XIAP BIR3, cIAP-1 BIR3, cIAP-2 BIR3 were determined to be 17.9 nM (Nikolovska-Coleska *et al.*, *Anal. Biochem. 332*:261-73 (2004)). The K_d values of SM-F1 to recombinant XAIP-BIR3 protein was determined to be 4.7 nM.

[00348] In competitive binding experiments using SM5F as the tracer to XIAP BIR3 protein, the tested compound was incubated with XIAP BIR3 protein (30 nM) and SM5F (5 nM) in the assay buffer (100 mM potassium phosphate, pH 7.5; 100 μg/ml bovine gamma globulin; 0.02 % sodium azide, Invitrogen). Dose-dependent competitive binding FP experiments were carried out with serial dilutions of tested compounds. For each

assay, the bound peptide control containing recombinant XIAP BIR3 protein and SM5F (equivalent to 0% inhibition) and free peptide control containing only free SM5F (equivalent to 100% inhibition) will be included. The polarization values were measured after 3 hrs of incubation when the binding reached equilibrium using an ULTRA READER (Tecan U.S. Inc., Research Triangle Park, NC). IC_{50} values, the inhibitor concentration at which 50% of bound peptide is displaced, will be determined from a plot using nonlinear least-squares analysis. Curve fitting will be performed using GRAPHPAD PRISM software (GraphPad Software, Inc., San Diego, CA).

[00349] In competitive binding experiments using SM-F1 as the tracer to XIAP BIR3 protein, the tested compound was incubated with XIAP BIR3 protein (10 nM) and SM-1F (2 nM) in the assay buffer (100 mM potassium phosphate, pH 7.5; 100 μg/ml bovine gamma globulin; 0.02 % sodium azide, Invitrogen). Dose-dependent competitive binding FP experiments were carried out with serial dilutions of tested compounds. For each assay, the bound peptide control containing recombinant XIAP BIR3 protein and SM-1F (equivalent to 0% inhibition) and free peptide control containing only free SM-1F (equivalent to 100% inhibition) will be included. The polarization values were measured after 3 hrs of incubation when the binding reached equilibrium using an ULTRA READER (Tecan U.S. Inc., Research Triangle Park, NC). IC_{50} values, the inhibitor concentration at which 50% of bound peptide is displaced, will be determined from a plot using nonlinear least-squares analysis. Curve fitting will be performed using GRAPHPAD PRISM software (GraphPad Software, Inc., San Diego, CA).

[00350] Negative controls containing protein/tracer complex only (equivalent to 0% inhibition), and positive controls containing only free tracers (equivalent to 100% inhibition), were included in each assay plate. FP values were measured as described above. IC_{50} values were determined by nonlinear regression fitting of the competition curves. The K_i values of competitive inhibitors were calculated using the equation described before (Nikolovska-Coleska *et al.*, *Anal. Biochem. 332*:261-73 (2004)), based upon the measured IC_{50} values, the K_d values of the tracer to different proteins, and the concentrations of the proteins and tracers in the competitive assays. K_i values were also calculated using a commonly used equation known in the literature (Huang, X. *J. Biomol. Screen. 8*:34–38 (2003)).

[00351] When tested in the binding assay, Smac mimetics of the present invention exhibited strong binding affinity to XIAP BIR3 protein as illustrated in Table 2 using either SM5F or SM-F1 as the tracer and Fig. 1 using the SM5F as the tracer. These data indicate that these Smac mimetics bind to XIAP with high affinities.

Table 2

Compounds	XIAP BIR3 IC_{50} (nM)
SM-1238	<200
SM-1237	<200
SM-1235	<200
SM-1299	<5000
SM-1257	<500
SM-1268	<500
SM-1270	<500
SM-1271	<500
SM-1306	<5000
SM-1307	<500
SM-1308	<500
SM-1316	<500
SM-1317	<500

EXAMPLE 18

Binding of Inhibitors to Other IAP Proteins

[00352] In order to test the binding ability of conformationally constrained Smac mimetics to other IAP proteins (cIAP1 and cIAP2) binding assay conditions were developed. The recombinant cIAP1 BIR3 domain (residues 253-363), cIAP2 BIR3 domain (residues 238-349), fused to a His-tag, were used in the binding assays. Competitive binding assays for other IAP proteins are performed similarly as that described for XIAP BIR3. The Kd values of SM5F to recombinant cIAP-1 BIR3 and cIAP-2 BIR3 were determined to be 4.1 nM (Peng et al. *J. Med. Chem.51*: 8158–8162 (2008)) and 6.6 nM (Peng et al. *J. Med. Chem.51*: 8158–8162 (2008)), respectively. The K_d values of SM-F1 to recombinant cIAP-BIR3, and cIAP2-BIRs proteins were determined to be 1.1 nM and 2.3 nM, respectively.

[00353] In competitive binding experiments using SM5F as the tracer to cIAP-1 BIR3 protein, the tested compound was incubated with cIAP-1 BIR3 protein (10 nM) and

SM5F (2 nM) in the assay buffer. In competitive binding experiments using SM5F as the tracer to cIAP-2 BIR3 protein, the tested compound was incubated with cIAP-2 BIR3 protein (25 nM) and SM5F (2 nM) in the assay buffer. All other procedures for cIAP-1 BIR3 and cIAP-2 BIR3 proteins were the same as those used for XIAP BIR3 protein competitive assays.

[00354] In competitive binding experiments using SM-F1 as the tracer to cIAP-1 BIR3 protein, the tested compound was incubated with cIAP-1 BIR3 protein (3 nM) and SM-F1 (1 nM) in the assay buffer. In competitive binding experiments using SM-F1 as the tracer to cIAP-2 BIR3 protein, the tested compound was incubated with cIAP-2 BIR3 protein (5 nM) and SM-F1 (1 nM) in the assay buffer.

[00355] As illustrated in Fig. 2 using SM5F as the tracer, Smac mimetics of the present invention exhibited strong binding affinity to cIAP1 BIR3 protein. Table 3 shows binding affinities of compounds of the invention to cIAP1 and cIAP2 proteins using either SM5F or SM-F1 as the tracer. These data suggest that compounds of the invention will act as potent inhibitors of cIAP1 and cIAP2 activity.

Table 3

Compounds	**cIAP1 BIR3 IC_{50} (nM)**	**cIAP2 BIR3 IC_{50} (nM)**
SM-1238	<100	<100
SM-1237	<100	<100
SM-1235	<1000	<1000
SM-1229	<2000	<2000
SM-1257	<100	<100
SM-1268	<100	<100
SM-1270	<100	<100
SM-1271	<100	<100
SM-1306	<100	<100
SM-1307	<100	<100
SM-1308	<100	<100
SM-1316	<100	<100
SM-1317	<100	<100

EXAMPLE 19

Cell Growth Inhibition by Conformationally Constrained Smac Mimetics

[00356] The effect of the compounds of the present invention on the growth of various cancer cell lines was tested. Cells were seeded in 96-well flat bottom cell culture plates at a density of 3000 cells/well with a tested compound and incubated at 37°C in an atmosphere of 95% air and 5% CO_2 for 4 days. The rate of cell growth inhibition after treatment with different concentrations of the compound was determined using a WST-8 kit (2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2, 4 disulfophenyl)-2H-tetrazolium monosodium salt; Dojindo Molecular Technologies, Inc., Gaithersburg, Maryland). WST-8 was added at a final concentration of 10% to each well, and then the plates were incubated at 37°C for 2-3 hrs. The absorbance of the samples was measured at 450 nm using a ULTRA Tecan Reader (Molecular Device). The concentration of the tested compound that inhibited cell growth by 50% (IC_{50}) was calculated by comparing absorbance in untreated cells and the cells treated with the tested compound.

[00357] When tested against the MDA-MB-231 human breast cancer cell line and SK-OV-3 ovarian cancer cell line, compounds of the present invention exhibited strong inhibitory activity as shown in Table 4, suggesting that the compounds are inhibitors of cancer cell growth.

Table 4

Name	MDA-MB-231 IC_{50} (μM)	SK-OV-3 IC_{50} (μM)
SM-1235	<3	<3
SM-1237	<3	<3
SM-1238	<3	<3
SM-1229	<100	<100
SM-1257	<3	<3
SM-1268	<3	<3
SM-1270	<3	<3
SM-1271	<3	<3
SM-1306	<3	<3
SM-1307	<3	<3
SM-1308	<3	<3
SM-1316	<3	<3
SM-1317	<3	<3

EXAMPLE 20

Induction of Cell Death

[00358] The ability of SM-1238 to induce cell death was tested in the breast cancer MDA-MB-231 and ovarian cancer SK-OV-3 cell lines (Fig. 3). Cells were treated with SM-1238 for 48 hours and cell viability was determined using the trypan blue exclusion assay. SM-1238 induced cell death in both cell lines in a concentration-dependant fashion.

EXAMPLE 21

Pharmacokinetics in Rats Following Oral Administration

[00359] Following oral administration of SM-1238 (Example 6) to male Sprague-Dawley rats at a dose of 25 mg/kg, the mean ± SD values for C_{max}, T_{max}, AUC(0-∞), and half-life

(T½) were 831 ± 135 ug/L, 2.0 ± 1.7 hrs, 7099 ± 931 μg/L*hr, and 3.7 ± 2.0 hr, respectively (n = 3.)

[00360] Following oral administration of SM-1268 (Example 9) to male Sprague-Dawley rats at a dose of 25 mg/kg, the mean ± SD values for C_{max}, T_{max}, AUC(0-∞), and half-life (T½) were 612 ± 16 ug/L, 2.0 ± 0.0 hrs, 6489 ± 965 μg/L*hr, and 4.2 ± 1.0 hr, respectively (n = 3)

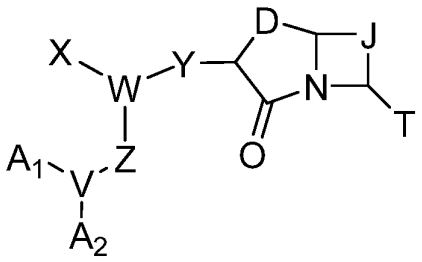
[00361] Following oral administration of SM-1316 (Example 15) to male Sprague-Dawley rats at a dose of 25 mg/kg, the mean ± SD values of C_{max}, T_{max}, AUC(0-∞), and half-life (T½) were 1528 ± 275 ug/L, 2.0 ± 0.0 hrs, 14304 ± 1968 μg/L*hr, and 6.7 ± 1.2 hr, respectively (n = 3).

[00362] These experiments show that the compounds of the invention are orally bioavailable.

[00363] Having now fully described the invention, it will be understood by those of skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the invention or any embodiment thereof. All patents, patent applications and publications cited herein are fully incorporated by reference herein in their entirety.

WHAT IS CLAIMED IS:

1. A compound having Formula I:



I

wherein:

A_1 and A_2 are independently selected from the group consisting of hydrogen and optionally substituted alkyl, wherein A_2 is absent when V is O;

V is selected from the group consisting of N, CH and O;

W is selected from the group consisting of CH and N;

X is selected from the group consisting of hydrogen, optionally substituted alkyl and aralkyl;

Y is selected from the group consisting of $CON(R^1)$, $N(R^1)CO$, C(O)O, OC(O), $(CH_2)_{1-3}$, wherein one or more CH_2 groups can be replaced by O, S, or NR^1, optionally substituted aryl and optionally substituted heteroaryl;

Z is $(CR^{2a}R^{2b})_r$;

D is $(CR^{3a}R^{3b})_n$-U-$(CR^{4a}R^{4b})_m$;

U is selected from the group consisting of $CR^{5a}R^{5b}$ and NR^6;

J is $(CR^{7a}R^{7b})_p$-L-$(CR^{8a}R^{8b})_q$;

T is optionally substituted heteroaryl;

n, m, p and q are independently selected from the group consisting of 0-5;

r is 0-3;

R^1 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

each R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^{7a}, R^{7b}, R^{8a}, R^{8b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted

cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

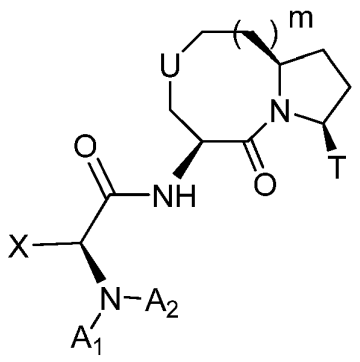
R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

L is selected from the group consisting of O, S, NR^1, $NCOR^9$, $CR^{7a}R^{7b}$, C=O, C=S and $C=NR^1$; and

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

or pharmaceutically acceptable salt or prodrug thereof.

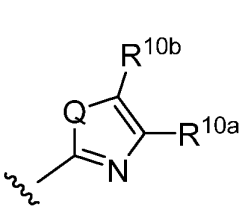
2. The compound of claim 1 having Formula V:



V.

3. The compound of claim 2, wherein A_1 is optionally substituted alkyl, A_2 is hydrogen, X is optionally substituted alkyl, U is NR^6, R^6 is COR^9, R^9 is optionally substituted alkyl and m is 1.

4. The compound of claim 1, wherein T is selected from the group consisting of



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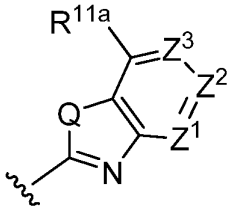

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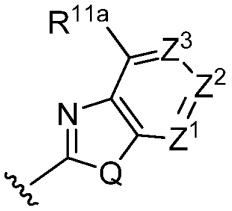

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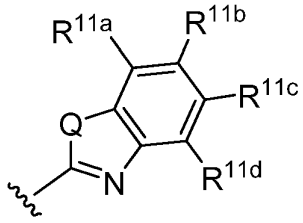

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wherein:

Q is selected from the group consisting of O, S and NR^{12};

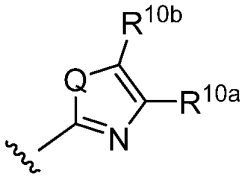
R^{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

R^{10a}, R^{10b}, R^{11a}, R^{11b}, R^{11c} and R^{11d} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido;

Z^1, Z^2, and Z^3 are independently selected from the group consisting of CR^{11e} and N, wherein at least one of Z^1, Z^2, and Z^3 is CR^{11e}, and at least one of Z^1, Z^2, and Z^3 is N; and

R^{11e} is selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido.

5. The compound of claim 4, wherein T is selected from the group consisting of



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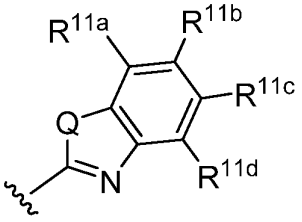

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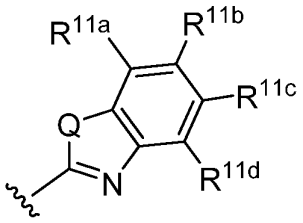
6. The compound of claim 5, wherein:

T is



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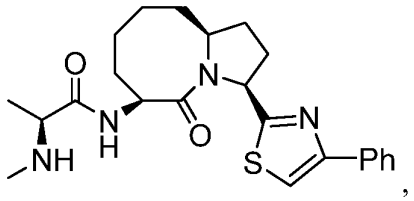
R^{11a} is selected from the group consisting of optionally substituted aryl, aralkyl, and optionally substituted alkyl; and

R^{11b}, R^{11c} and R^{11d} are each hydrogen.

7. The compound of claim 1, selected from the group consisting of:



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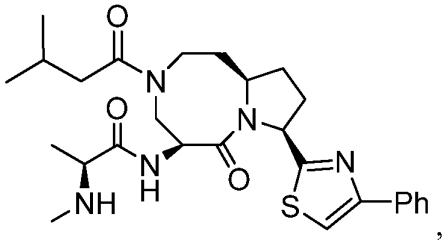

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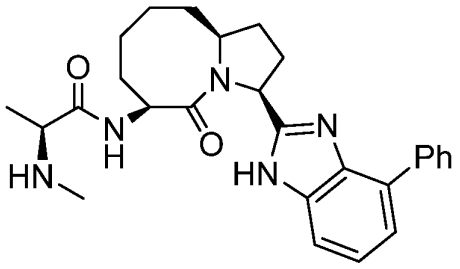
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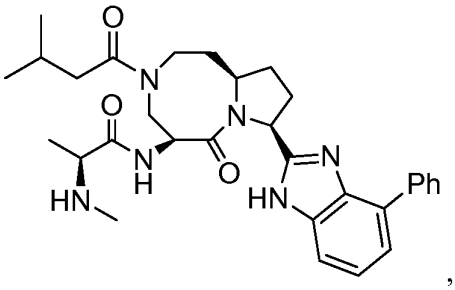
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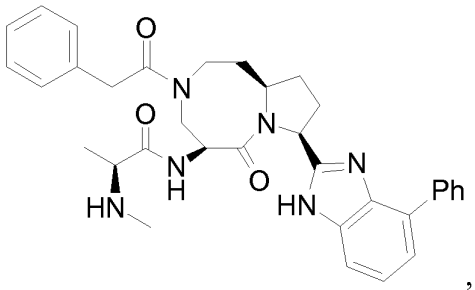
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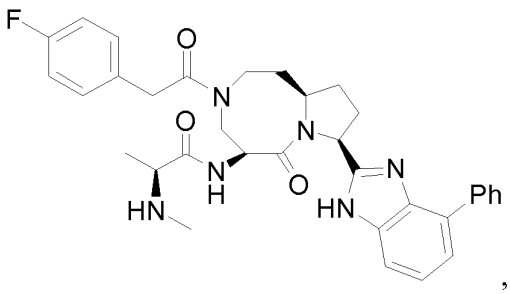
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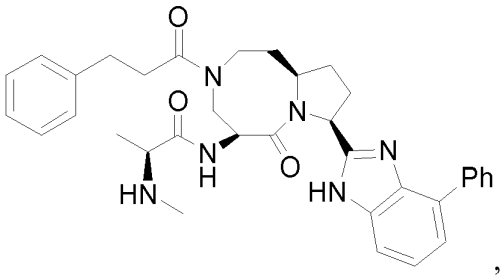
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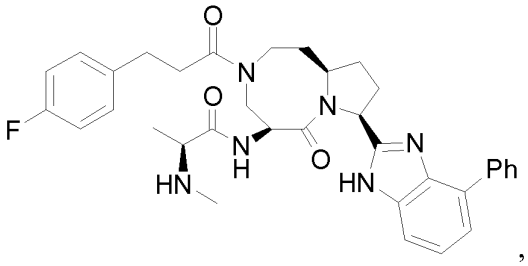

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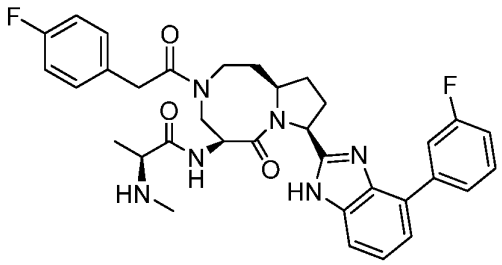
or a pharmaceutically acceptable salt or prodrug thereof.

8. The compound of claim 1, selected from the group consisting of:



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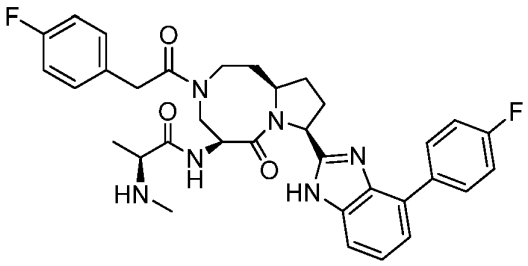

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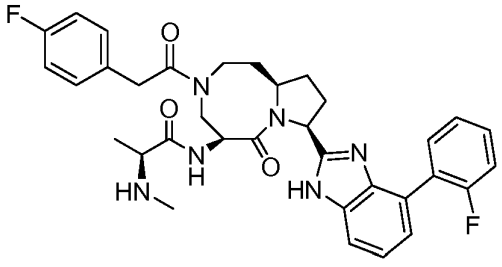

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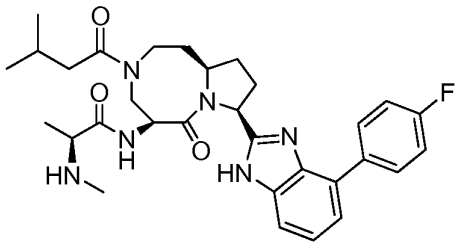
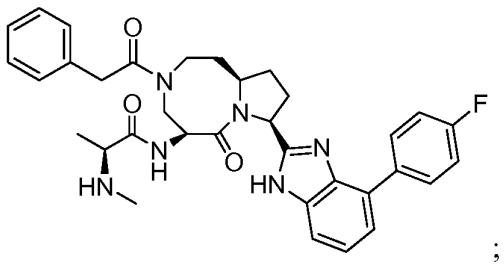


, and



;

or a pharmaceutically acceptable salt or prodrug thereof.

9. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

10. Use of a compound of claim 1 for the manufacture of a medicament for treating, ameliorating, or preventing a disorder responsive to the induction of apoptosis in an animal.

11. The use of claim 10, further comprising administering an inducer of apoptosis.

12. The use of claim 10 wherein said disorder responsive to the induction of apoptosis is a cancer.

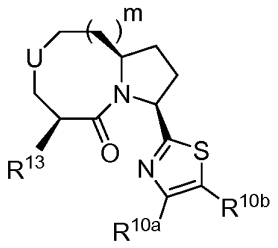
13. The use of claim 12, further comprising administering an anticancer agent.

14. A kit comprising the compound of claim 1 and instructions for administering said compound to an animal.

15. The kit of claim 14, further comprising an anticancer agent.

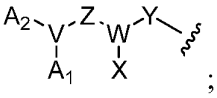
16. The kit of claim 14, wherein said instructions are for administering said compound to an animal having cancer.

17. A process for preparing a compound of Formula XII



XII

wherein

R^{13} is selected from the group consisting of $N(H)P^1$ and  ;

P^1 is an amine protecting group;

A_1 and A_2 are independently selected from the group consisting of hydrogen and optionally substituted alkyl, wherein A_2 is absent when V is O;

V is selected from the group consisting of N, CH and O;

W is selected from the group consisting of CH and N;

X is selected from the group consisting of hydrogen, optionally substituted alkyl and aralkyl;

Y is selected from the group consisting of $CON(R^1)$, $N(R^1)CO$, C(O)O, OC(O), $(CH_2)_{1-3}$, wherein one or more CH_2 groups can be replaced by O, S, or NR^1, optionally substituted aryl and optionally substituted heteroaryl;

Z is $(CR^{2a}R^{2b})_r$;

U is selected from the group consisting of $CR^{5a}R^{5b}$ and NR^6;

m is 1 or 2;

r is 0-3;

R^1 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

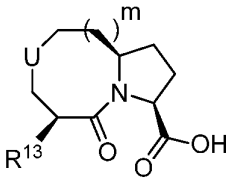
each R^{2a}, R^{2b}, R^{5a} and R^{5b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo; and

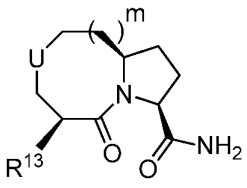
R^{10a} and R^{10b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo, comprising:

a) condensing a compound of Formula XIII



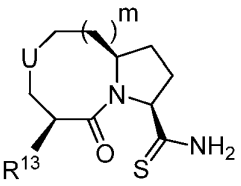
XIII

with ammonia to give a compound of Formula XIV



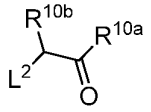
XIV,

b) converting a compound of Formula XIV to a compound of Formula XV



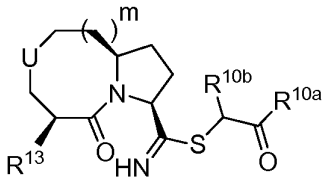
XV,

c) condensing a compound of Formula XV with a compound of Formula XVI,



XVI

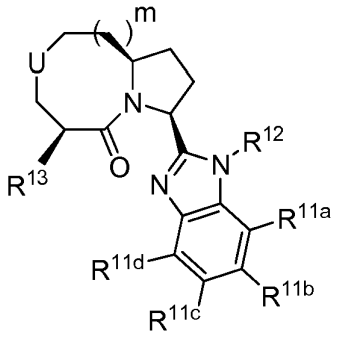
wherein L^2 is a leaving group, to give a compound of Formula XVII,



XVII

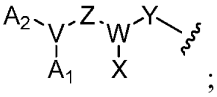
and b) cyclizing a compound of Formula XVII, to give a compound of Formula XII.

18. A process for the preparing a compound of Formula XVIII



XVIII

wherein

R^{13} is selected from the group consisting of $N(H)P^1$ and  ;

P^1 is an amine protecting group;

A_1 and A_2 are independently selected from the group consisting of hydrogen and optionally substituted alkyl, wherein A_2 is absent when V is O;

V is selected from the group consisting of N, CH and O;

W is selected from the group consisting of CH and N;

X is selected from the group consisting of hydrogen, optionally substituted alkyl and aralkyl;

Y is selected from the group consisting of $CON(R^1)$, $N(R^1)CO$, C(O)O, OC(O), $(CH_2)_{1-3}$, wherein one or more CH_2 groups can be replaced by O, S, or NR^1, optionally substituted aryl and optionally substituted heteroaryl;

Z is $(CR^{2a}R^{2b})_r$;

U is selected from the group consisting of $CR^{5a}R^{5b}$ and NR^6;

m is 1 or 2;

r is 0-3;

R^1 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

each R^{2a}, R^{2b}, R^{5a} and R^{5b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

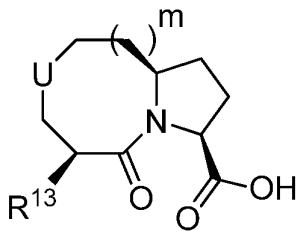
R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

R^{11a}, R^{11b}, R^{11c} and R^{11d} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, haloalkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, halo, nitro, cyano, hydroxy, amino, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido and sulfonamido, and

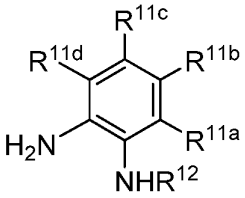
R^{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo, comprising:

a) condensing a compound of Formula XIII



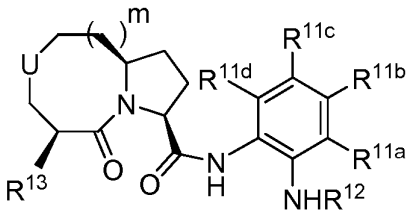
XIII

with a compound of Formula XIX



XIX

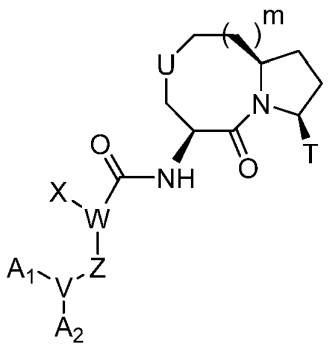
to give a compound of Formula XX



XX,

and b) cyclizing a compound of Formula XX, to give a compound of Formula XVIII.

19. A process for preparing a compound of Formula XXI



XXI

wherein:

A_1 and A_2 are independently selected from the group consisting of hydrogen and optionally substituted alkyl, wherein A_2 is absent when V is O;

V is selected from the group consisting of N, CH and O;

W is selected from the group consisting of CH and N;

X is selected from the group consisting of hydrogen, optionally substituted alkyl and aralkyl;

Z is $(CR^{2a}R^{2b})_r$;

U is selected from the group consisting of $CR^{5a}R^{5b}$ and NR^6;

m is 1 or 2;

r is 0-3;

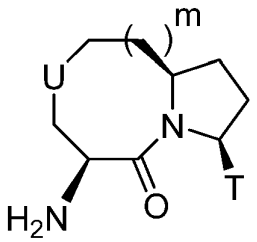
each R^{2a}, R^{2b}, R^{5a} and R^{5b} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo; and

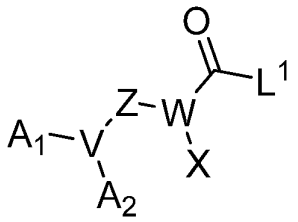
T is optionally substituted heteroaryl, comprising:

reacting a compound of Formula XXIII



XXIII

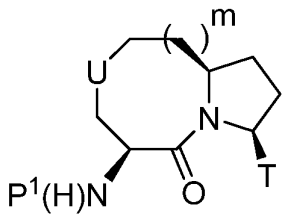
with a compound of Formula XXIV



XXIV

wherein L^1 is a leaving group, to give a compound of Formula XXI.

20. A compound having Formula XXII:



XXII

wherein:

T is optionally substituted heteroaryl;

m is 1 or 2;

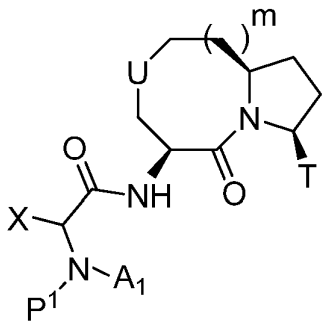
U is CH_2 or NR^6

R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo; and

P^1 is an amine protecting group.

21. A compound having Formula XXV



XXV

wherein:

T is optionally substituted heteroaryl;

m is 1 or 2;

U is CH_2 or NR^6

R^6 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo and COR^9;

R^9 is selected from the group consisting of hydrogen, optionally substituted alkyl, aralkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclo;

X is selected from the group consisting of hydrogen, optionally substituted alkyl, and aralkyl;

A_1 is selected from the group consisting of hydrogen an optionally substituted alkyl; and

P^1 is an amine protecting group

Fig. 1

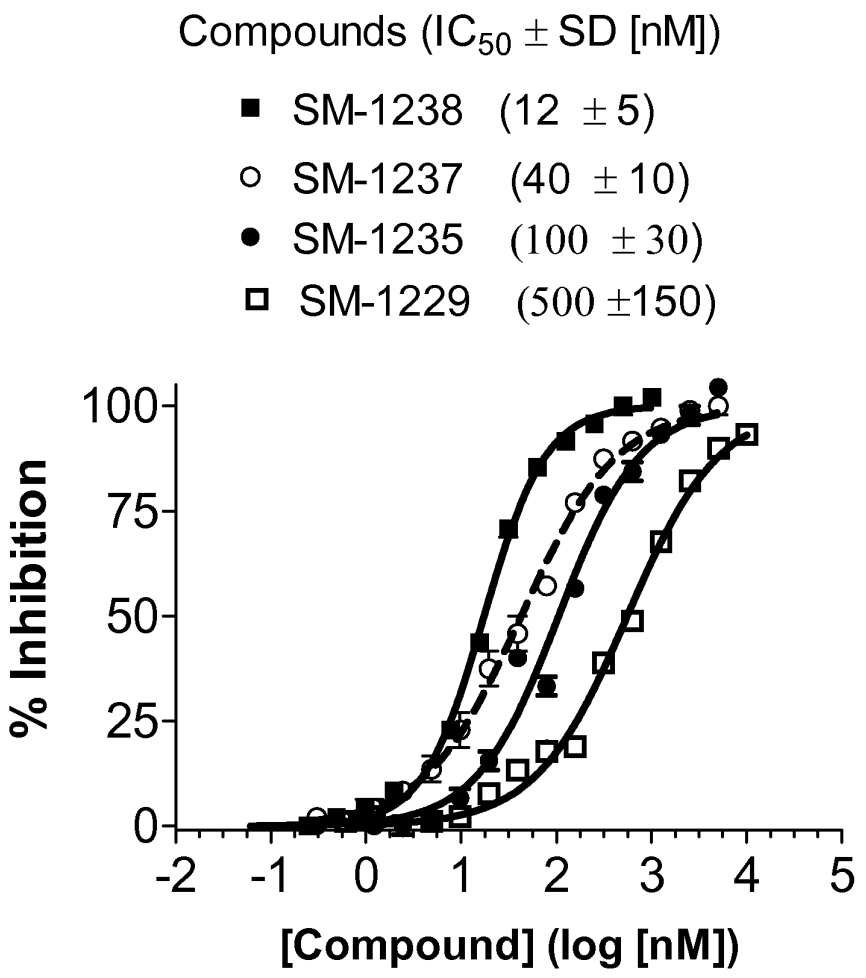

Competitive binding curves to XIAP BIR3
Compounds ($IC_{50} \pm SD$ [nM])
SM-1238 (12 ±5)
SM-1237 (40 ±10)
SM-1235 (100 ±30)
SM-1229 (500 ±150)
% Inhibition
100
75
50
25
0
-2
-1
0
1
2
3
4
5
[Compound] (log [nM])

Fig. 2

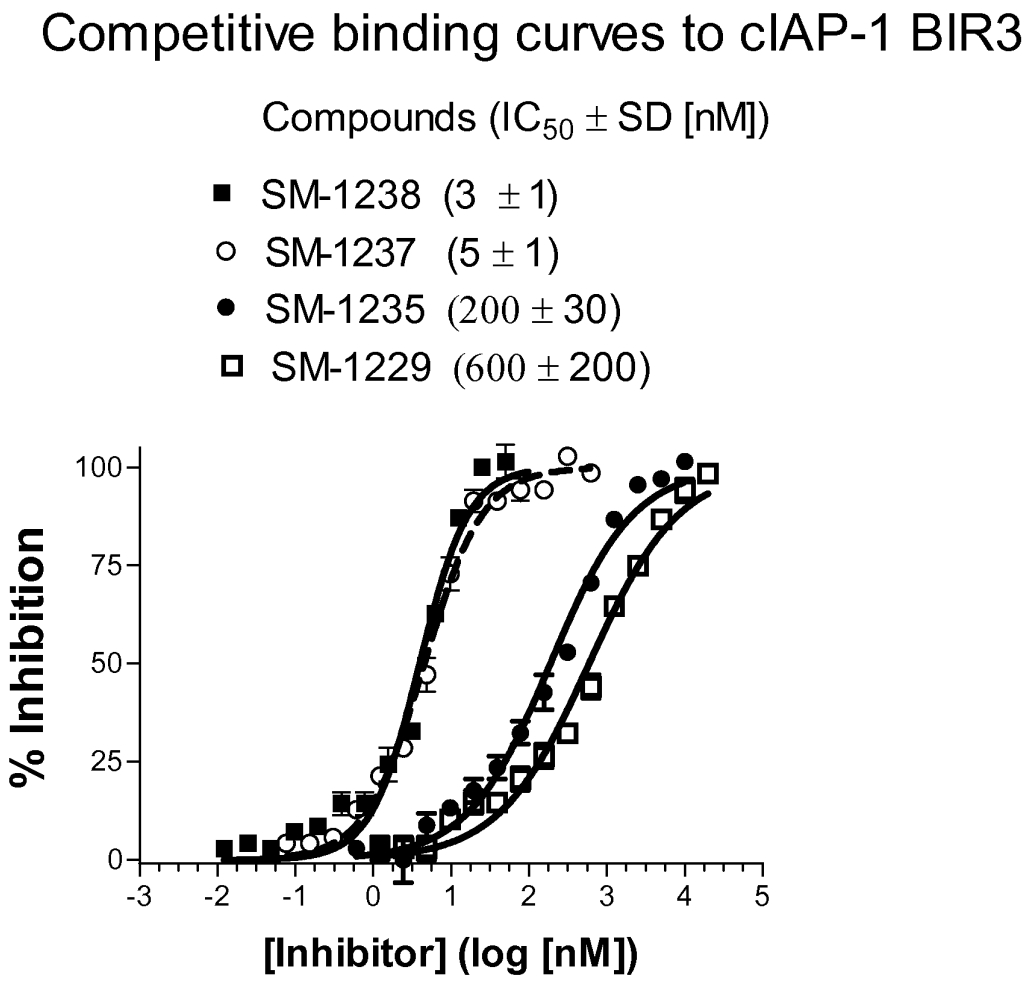
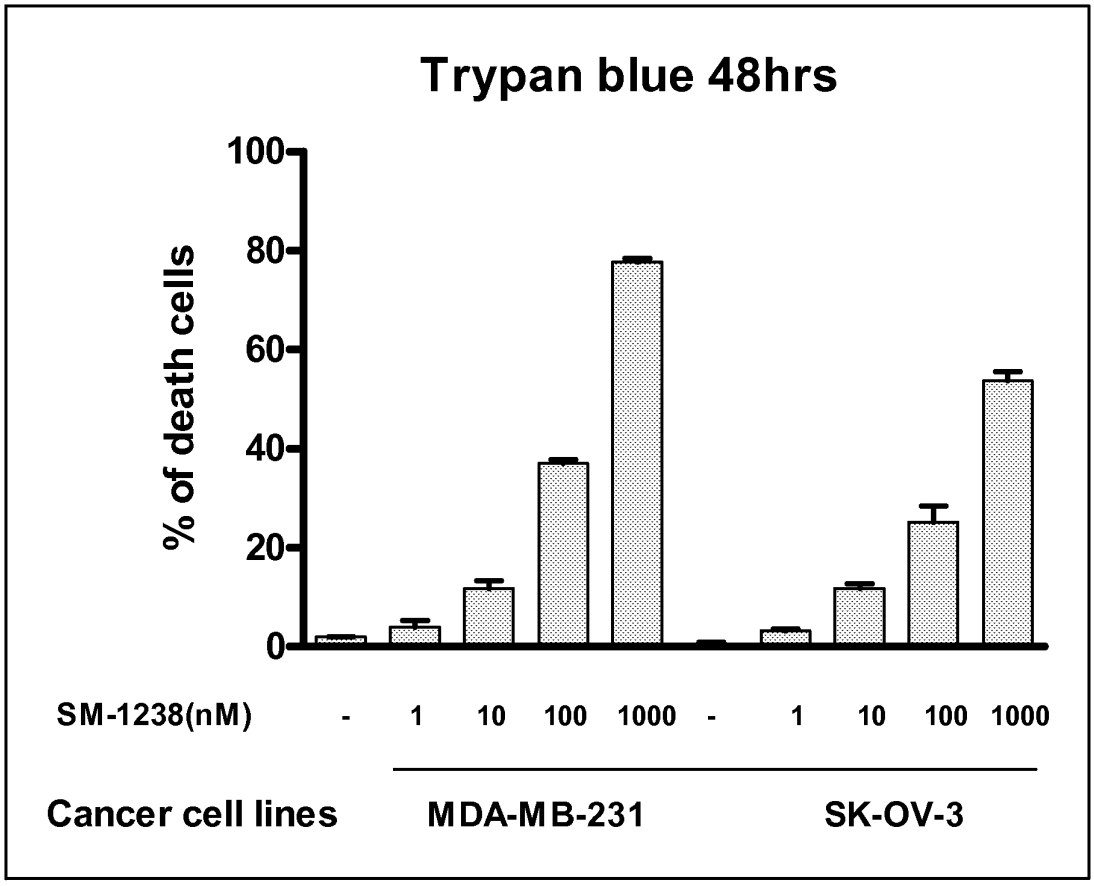

Competitive binding curves to cIAP-1 BIR3
Compounds ($IC_{50} \pm SD$ [nM])
SM-1238 (3 ± 1)
SM-1237 (5 ± 1)
SM-1235 (200 ± 30)
SM-1229 (600 ± 200)
% Inhibition
100
75
50
25
0
-3
-2
-1
0
1
2
3
4
5
[Inhibitor] (log [nM])

Fig. 3


Trypan blue 48hrs
% of death cells
100
80
60
40
20
0
SM-1238(nM)
-
1
10
100
1000
-
1
10
100
1000
Cancer cell lines
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SK-OV-3

SEQUENCE LISTING

<110> Wang, Shaomeng
Sun, Haiying
Nikolovska-Coleska, Zaneta

<120> Heteroaryl-Substituted Bicyclic Smac Mimetics and the Uses Thereof

<130> UM-30445/WO-1/ORD

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