(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 February 2014 (27.02.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/031487 A1

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61P 35/00* (2006.01)
A61K 31/395 (2006.01)

(21) International Application Number:
PCT/US2013/055384

(22) International Filing Date:
16 August 2013 (16.08.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/692,429 23 August 2012 (23.08.2012) US

(71) Applicant: **THE REGENTIS OF THE UNIVERSITY OF MICHIGAN** [US/US]; Office of Technology Transfer, 1600 Huron Parkway, 2nd Floor, Ann Arbor, MI 48109-2590 (US).

(72) Inventors: **WANG, Shaomeng**; 9343 Yorkshire Dr., Saline, MI 48176 (US). **SHENG, Rong**; 1976 Traver Road. Apt. 203, Ann Arbor, MI 48105 (US). **SUN, Haiying**; 1246 North Bay Drive, Ann Arbor, MI 48103 (US). **LIU, Liu**; 2358 Spring Ridge Ct, Ann Arbor, MI 48103 (US). **LU, Jianfeng**; 2600 Arrowwood Tri, Ann Arbor, MI 48109 (US). **MCEACHERN, Donna**; 2208 Glencoe Hills Dr. Apt 2, Ann Arbor, MI 48108 (US).

(74) Agent: **NAPOLI, James, J.**; Marshall, Gerstein & Borun LLP, 233 S. Wacker Drive, 6300 Wills Tower, Chicago, IL 60606-6357 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) Title: BIVALENT INHIBITORS OF IAP PROTEINS AND THERAPEUTIC METHODS USING THE SAME

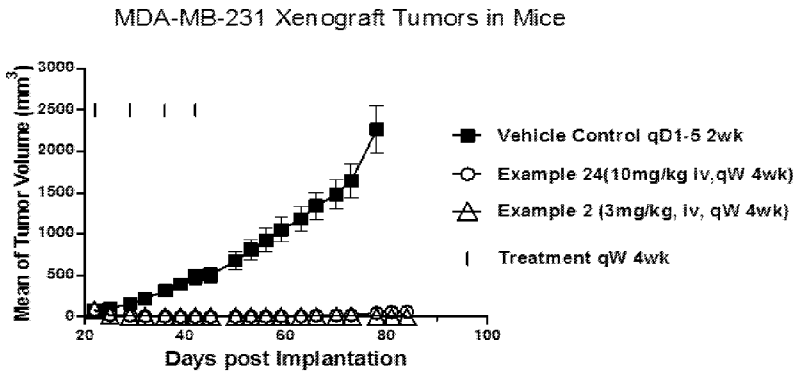


Figure 1

(57) Abstract: Inhibitors of IAP proteins and compositions containing the same are disclosed. Methods of using the IAP protein inhibitors in the treatment of diseases and conditions wherein inhibition of IAP proteins provides a benefit, like cancers, also are disclosed.

WO 2014/031487 A1

BIVALENT INHIBITORS OF IAP PROTEINS AND THERAPEUTIC METHODS USING THE SAME

GOVERNMENT FUNDING

[0001] This invention was made with government support under Grant Nos. CA127551 and CA109025 awarded by National Institutes of Health. The government has certain rights in the invention.

FIELD OF THE INVENTION

[0002] The present invention relates to bivalent inhibitors of Inhibitors of Apoptosis Proteins (IAPs) and to therapeutic methods of treating conditions and diseases wherein inhibition of IAP proteins provides a benefit. The present inhibitors bind to IAP proteins, including cIAP1, cIAP2, and XIAP, with very high affinities to induce apoptosis in human cancer cell lines to enhance the antitumor activity of other anticancer drugs.

BACKGROUND OF THE INVENTION

[0003] Apoptosis, or programmed cell death, is a cell process critical for homeostasis, normal development, host defense, and suppression of oncogenesis. Faulty regulation of apoptosis has been implicated in many human diseases,[(1)] including cancer,[(1),(3)] and it is now recognized that resistance to apoptosis is a hallmark of cancer.[(4)] As a consequence, targeting of key apoptosis regulators has emerged as an attractive strategy for the development of new approaches to human cancer treatment. [(1)]

[0004] Most current cancer therapies, including chemotherapeutic agents, radiation, and immunotherapy, indirectly induce 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. Such primary or acquired resistance of human cancers to current therapies due to apoptosis defects is a major problem in current cancer therapy.

[0005] In order to improve survival and quality of life of cancer patients, current and future efforts in the design and development of new molecular target-specific anticancer therapies includes strategies that specifically target cancer cell resistance to apoptosis. In this regard, targeting 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.

[0006] One class of central negative regulators of apoptosis is the Inhibitors of Apoptosis Proteins (IAPs). This class includes proteins such as XIAP, cIAP1, cIAP2, ML-IAP, HIAP, KIAP, TSIAP, NAIP, survivin, livin, ILP-2, apollon, and BRUCE. IAP proteins potently suppress cancer cell apoptosis induced by a large variety of apoptotic stimuli, including chemotherapeutic agents, radiation, and immunotherapy.

[0007] Although their roles are not limited to regulation of apoptosis,[(7),(8)] IAP proteins are a class of key apoptosis regulators, and are characterized by the presence of one or more BIR (Baculoviral IAP Repeat) domains.[(5)-(6)] Among the IAPs, cellular IAP1 (cIAP1) and cIAP2 play a key role in the regulation of death-receptor mediated apoptosis, whereas X-linked IAP (XIAP) inhibits both death-receptor mediated and mitochondria mediated apoptosis by binding to and inhibiting caspase-3/7 and caspase-9, three cysteine proteases critical for execution of apoptosis.[(5)] These IAP proteins are highly overexpressed both in cancer cell lines and in human tumor tissues and have low expression in normal cells and tissues.[(9)] Extensive studies have demonstrated that overexpression of IAP proteins make cancer cells resistant to apoptosis induction by a variety of anticancer drugs.[(10)-(12)] A detailed discussion of IAP proteins and their role is cancer and apoptosis is set forth in U.S. Patent No. 7,960,372, incorporated herein by reference. Hence, targeting one or more of these IAP proteins is a promising therapeutic strategy for the treatment of human cancer.[(10)-(12)]

[0008] Studies have shown that peptide-based inhibitors are useful tools to elucidate the anti-apoptotic function of IAPs and the role of IAPs in the response of cancer cells to chemotherapeutic agents. However, peptide-based inhibitors have intrinsic limitations as useful therapeutic agents, including a poor cell permeability and poor *in vivo* stability. In published studies using Smac-based peptide inhibitors, the peptides had to be fused to carrier peptides to make them relatively cell-permeable.

[0009] Small molecule inhibitors of IAP proteins also are known. For example, U.S. Patent Publication Application No. 2005/0197403 and U.S. Patent No. 7,960,372 disclose dimeric Smac mimetic compounds, each incorporated herein by reference in its entirety.

[0010] Despite the discovery of small molecule inhibitors of IAP proteins, the design of potent, non-peptide inhibitors of IAP proteins remains a significant challenge in modern drug discovery. Accordingly, a need still exists in the art for IAP inhibitors having physical and pharmacological properties that permit use of the inhibitors in therapeutic applications. The

present invention provides compounds designed to bind to IAP proteins and inhibit IAP protein activity.

SUMMARY OF THE INVENTION

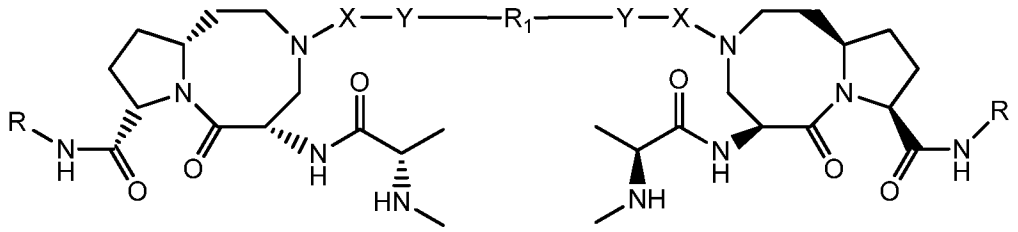
[0011] It is generally accepted that the inability of cancer cells or their supporting cells to undergo apoptosis in response to genetic lesions or exposure to inducers of apoptosis (such as chemotherapeutic agents and radiation) is a major factor in the onset and progression of cancer. The induction of apoptosis in cancer cells or their supporting cells (e.g., neovascular cells in the tumor vasculature) is considered a universal mechanism of action for virtually all the effective cancer therapeutic drug and radiation therapies in practice today. One reason for the inability of a cell to undergo apoptosis is an increased expression and accumulation of IAPs.

[0012] The present invention therefore is directed to inhibitors of IAP proteins, to compositions comprising the inhibitors, and to methods of using the inhibitors in a therapeutic treatment of conditions and diseases wherein inhibition of IAP protein activity provides a benefit. The present compounds are potent inhibitors of IAP protein activation, and induce apoptosis of cancer cells.

BRIEF DESCRIPTION OF THE DRAWING

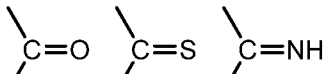
[0013] Figure 1 is a plot of Mean Tumor Volume (mm^3) vs. Days Past Implantation showing the antitumor activity of Examples 2 and 24 in the MDA-MB-231 xenograft model in nude mice.

[0014] More particularly, the present invention is directed to compounds having a structural formula (I):



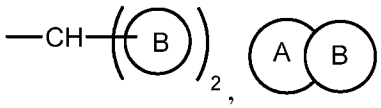
(I)

,

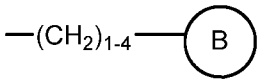
[0015] wherein X is selected from the group consisting of 

, and $-SO_2-$;

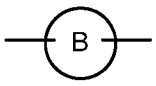
[0016] Y is selected from the group consisting of –NH-, -O-,–S-, and null;

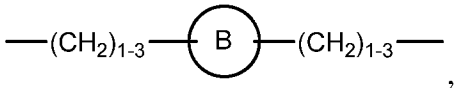
[0017] R is selected from the group consisting of 

, wherein ring A is a C_{4-8} aliphatic ring, 

, and 

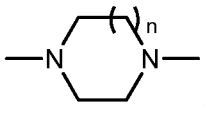
, wherein the B ring is aryl or nitrogen atom-containing heteroaryl and the B rings are optionally substituted; and

[0018] R_1 is selected from the group consisting of $-(CH_2)_{4-10}-$, 

, 

, 

,

, wherein Z is O, S, or NH, and 

, wherein n is 0, 1, or 2, and wherein the B ring is aryl or nitrogen atom-containing heteroaryl and the 

rings are optionally substituted;

[0019] or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof.

[0020] In one embodiment, the present invention provides compounds that inhibit the activity of IAP proteins and increase the sensitivity of cells to inducers of apoptosis, such as an chemotherapeutic agents and radiation therapy.

[0021] In other embodiments, the present compounds are used in methods to induce apoptosis in cells and to sensitize cells to inducers of apoptosis.

[0022] In still another embodiment, the present invention provides a method of treating a condition or disease by administering a therapeutically effective amount of a compound of structural formula (I) to an individual in need thereof. The disease or condition of interest is treatable by inhibition of IAP proteins, for example, a cancer. The present compounds therefore are useful for the treatment and amelioration 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 and ameliorate a cancer that is characterized by resistance to cancer therapies (e.g., are chemoresistant, radiation resistant, hormone resistant, and the like). In other embodiments, the present compounds can be used to treat hyperproliferative diseases characterized by overexpression of IAPs.

[0023] Another embodiment of the present invention is to provide a composition comprising (a) an IAP inhibitor of structural formula (I) and (b) an excipient and/or pharmaceutically acceptable carrier useful in treating diseases or conditions wherein inhibition of IAP proteins provides a benefit.

[0024] Another embodiment of the present invention is to utilize a composition comprising a compound of structural formula (I) and a second therapeutically active agent in a method of treating an individual for a disease or condition wherein inhibition of IAP proteins provides a benefit.

[0025] In a further embodiment, the invention provides for use of a composition comprising a IAP protein inhibitor of structural formula (I) and an optional second therapeutic agent for the manufacture of a medicament for treating a disease or condition of interest, e.g., a cancer.

[0026] Still another embodiment of the present invention is to provide a kit for human pharmaceutical use comprising (a) a container, (b1) a packaged composition comprising an IAP protein inhibitor of structural formula (I), and, optionally, (b2) a packaged composition comprising a second therapeutic agent useful in the treatment of a disease or condition of interest, and (c) a package insert containing directions for use of the composition or compositions, administered simultaneously or sequentially, in the treatment of the disease or condition.

[0027] An IAP protein inhibitor of structural formula (I) and the second therapeutic agent can be administered together as a single-unit dose or separately as multi-unit doses, wherein the IAP inhibitor of structural formula (I) is administered before the second therapeutic agent or vice versa. It is envisioned that one or more dose of an IAP inhibitor of structural formula (I) and/or one or more dose of a second therapeutic agent can be administered.

[0028] In one embodiment, an IAP protein inhibitor of structural formula (I) and a second therapeutic agent are administered simultaneously. In related embodiments, the IAP protein inhibitor of structural formula (I) and second therapeutic agent are administered from a single composition or from separate compositions. In a further embodiment, the IAP protein inhibitor of structural formula (I) and second therapeutic agent are administered sequentially. An IAP protein inhibitor of structural formula (I), as used in the present invention, can be administered in an amount of about 0.005 to about 500 milligrams per dose, about 0.05 to about 250 milligrams per dose, or about 0.5 to about 100 milligrams per dose.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0029] The present invention is described in connection with preferred embodiments. However, it should be appreciated that the invention is not limited to the disclosed embodiments. It is understood that, given the description of the embodiments of the invention herein, various modifications can be made by a person skilled in the art. Such modifications are encompassed by the claims below.

[0030] Smac/DIABLO (second mitochondria-derived activator of caspases or direct IAP binding protein with low pI) is a protein released from mitochondria in response to apoptotic stimuli and functions as an endogenous inhibitor of cIAP1, cIAP2 and XIAP.[(14),(15)] The interaction between Smac and IAPs is mediated by the N-terminal AVPI tetrapeptide motif in Smac and one or more BIR domains in these IAP proteins.[(16),(17)] Smac is a homodimer which binds to both the BIR2 and BIR3 domains in XIAP and antagonizes the inhibition of XIAP to caspase-3/-7 and caspase-9.[(18)] In comparison, Smac binds to only the BIR3 domain in cIAP1 and cIAP2[(19)] and induces rapid proteins degradation in cells.[(20)] Through two distinct mechanisms, Smac is a very efficient antagonist of these three IAP proteins.

[0031] The crystal and NMR structures of XIAP BIR3 complexed with Smac protein or Smac peptide show that the AVPI tetrapeptide motif in Smac binds to a well-defined surface groove in XIAP and this interaction represents an attractive site for the design of small-molecule XIAP inhibitors.[(16)-(18)] By use of AVPI tetrapeptide as the lead structure,

several classes of small-molecule Smac mimetics have been designed as antagonists of XIAP and cIAP1/2.[21)-(38)] Two different types of Smac mimetics have been designed.[21)-(23)] The first type, designed to mimic a single AVPI binding motif, is called monovalent Smac mimetics.[21)-(23)] The second type, the bivalent Smac mimetics, consists of two AVPI mimetics, tethered through a linker, to mimic the dimeric form of Smac proteins.[21)-(23)]

[0032] One advantage of monovalent Smac mimetics as potential drugs is an oral bioavailability, but a drawback is a modest potency in antagonizing full-length XIAP in functional assays. A major advantage of bivalent Smac mimetics is that they are much more potent antagonists of XIAP than monovalent Smac mimetics by concurrently targeting both BIR2 and BIR3 domains in XIAP.[30)] Bivalent Smac mimetics typically are 2-3 orders of magnitude more potent than their monovalent Smac mimetic counterparts in induction of apoptosis in cancer cells.[21)] Currently, three monovalent and two bivalent Smac mimetics have advanced into clinical trials for the treatment of human cancer.[21)]

[0033] Because bivalent Smac mimetics are significantly more potent than monovalent Smac mimetics in targeting XIAP and cIAP1/2, in induction of apoptosis of cancer cells *in vitro* and *in vivo*, and in inhibition of tumor growth, the present bivalent compounds have been designed for use in cancer treatment and the treatment of other diseases and conditions mediated by IAP protein activity.

[0034] The term "IAP proteins," as used herein, refers to any known member of the Inhibitors 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.

[0035] 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.

[0036] The term "a disease or condition wherein inhibition of an IAP protein provides a benefit" pertains to a condition in which an IAP protein, and/or an action of an IAP protein, is important or necessary, e.g., for the onset, progress, expression of that disease or condition, or a disease or a condition which is known to be treated by an IAP protein inhibitor. An example of such a condition includes, but is not limited to, a cancer. One of ordinary skill in the art is readily able to determine whether a compound treats a disease or condition mediated by an IAP protein for any particular cell type, for example, by assays which conveniently can be used to assess the activity of particular compounds.

[0037] The term "second therapeutic agent" refers to a therapeutic agent different from an IAP inhibitor of structural formula (I) and that is known to treat the disease or condition of interest. For example when a cancer is the disease or condition of interest, the second therapeutic agent can be a known chemotherapeutic drug, like taxol, or radiation, for example.

[0038] The term "disease" or "condition" denotes disturbances and/or anomalies that as a rule are regarded as being pathological conditions or functions, and that can manifest themselves in the form of particular signs, symptoms, and/or malfunctions. As demonstrated below, a compound of structural formula (I) is a potent inhibitor of IAP proteins and can be used in treating diseases and conditions wherein inhibition an IAP protein provides a benefit.

[0039] As used herein, the terms "treat," "treating," "treatment," and the like refer to eliminating, reducing, or ameliorating a disease or condition, and/or symptoms associated therewith. Although not precluded, treating a disease or condition does not require that the disease, condition, or symptoms associated therewith be completely eliminated. As used herein, the terms "treat," "treating," "treatment," and the like may include "prophylactic treatment," which refers to reducing the probability of redeveloping a disease or condition, or of a recurrence of a previously-controlled disease or condition, in a subject who does not

have, but is at risk of or is susceptible to, redeveloping a disease or condition or a recurrence of the disease or condition. The term "treat" and synonyms contemplate administering a therapeutically effective amount of a compound of the invention to an individual in need of such treatment.

[0040] Within the meaning of the invention, "treatment" also includes relapse prophylaxis or phase prophylaxis, as well as the treatment of acute or chronic signs, symptoms and/or malfunctions. The treatment can be orientated symptomatically, for example, to suppress symptoms. It can be effected over a short period, be oriented over a medium term, or can be a long-term treatment, for example within the context of a maintenance therapy.

[0041] The terms "sensitize" and "sensitizing," as used herein, refer to making, through the administration of a first agent (e.g., a compound of structural 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.

[0042] 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 tumors, neoplasms, lymphomas and the like. 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.

[0043] 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. Nonlimiting 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.

[0044] The term "neoplastic disease," as used herein, refers to any abnormal growth of cells being either benign (non-cancerous) or malignant (cancerous).

[0045] 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.

[0046] The term "apoptosis-modulating agents," as used herein, refers to agents which are involved in modulating (e.g., inhibiting, decreasing, increasing, promoting) apoptosis. 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.

[0047] 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.

[0048] The term "therapeutically effective amount" or "effective dose" as used herein refers to an amount of the active ingredient(s) that is(are) sufficient, when administered by a method of the invention, to efficaciously deliver the active ingredient(s) for the treatment of condition or disease of interest to an individual in need thereof. In the case of a cancer or other proliferation disorder, the therapeutically effective amount of the agent may reduce (i.e., retard to some extent and preferably stop) unwanted cellular proliferation; reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., retard to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., retard to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; reduce IAP protein signaling in the target cells increase survival time; and/or relieve, to some extent, one or more of the symptoms associated with the cancer 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 100%. To the extent the administered compound or composition prevents growth and/or kills existing cancer cells, it may be cytostatic and/or cytotoxic.

[0049] The term "container" means any receptacle and closure therefor suitable for storing, shipping, dispensing, and/or handling a pharmaceutical product.

[0050] The term "insert" means information accompanying a pharmaceutical product that provides a description of how to administer the product, along with the safety and efficacy data required to allow the physician, pharmacist, and patient to make an informed decision regarding use of the product. The package insert generally is regarded as the "label" for a pharmaceutical product.

[0051] "Concurrent administration," "administered in combination," "simultaneous administration," and similar phrases mean that two or more agents are administered concurrently to the subject being treated. By "concurrently," it is meant that each agent is administered either simultaneously or sequentially in any order at different points in time. However, if not administered simultaneously, it is meant that they are administered to an individual in a sequence and sufficiently close in time so as to provide the desired therapeutic effect and can act in concert. For example, an IAP protein inhibitor of structural formula (I) can be administered at the same time or sequentially in any order at different points in time as a second therapeutic agent. A present IAP protein inhibitor and the second therapeutic agent can be administered separately, in any appropriate form and by any suitable route. When a present IAP protein inhibitor and the second therapeutic agent are not administered concurrently, it is understood that they can be administered in any order to a subject in need thereof. For example, a present IAP protein inhibitor can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapeutic agent treatment modality (e.g., radiotherapy), to an individual in need thereof. In various embodiments, an IAP protein inhibitor of structural formula (I) and the second therapeutic agent are administered 1 minute apart, 10 minutes apart, 30 minutes apart, less than 1 hour apart, 1 hour apart, 1 hour to 2 hours apart, 2 hours to 3 hours apart, 3 hours to 4 hours apart, 4 hours to 5 hours apart, 5 hours to 6 hours apart, 6 hours to 7 hours apart, 7 hours to 8 hours apart, 8 hours to 9 hours apart, 9 hours to 10 hours apart, 10 hours to 11 hours apart, 11 hours to 12 hours apart, no more than 24 hours apart or no more than 48 hours apart. In one embodiment, the components of the combination therapies are administered at 1 minute to 24 hours apart.

[0052] The use of the terms "a", "an", "the", and similar referents in the context of describing the invention (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated. Recitation of ranges of values herein merely are intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The use

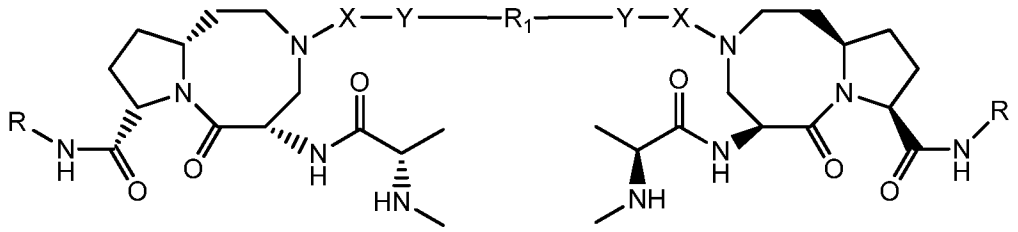
of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended to better illustrate the invention and is not a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0053] The present invention is directed to compounds of structural formula (I), which are mimetics of Smac and function as inhibitors of IAPs proteins. The present compounds sensitize cells to inducers of apoptosis and, in some instances, themselves induce apoptosis by inhibiting IAPs proteins. Therefore, 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 structural formula (I) alone or in combination with an inducer of apoptosis. The invention further relates to methods of treating or ameliorating disorders in an animal that are responsive to induction of apoptosis comprising administering to the animal a compound of structural formula (I) and an inducer of apoptosis. Such disorders include those characterized by a dysregulation of apoptosis and those characterized by overexpression of IAP proteins.

[0054] The present invention is directed to potent inhibitors of IAP proteins. The present IAP protein inhibitors are nonpeptidic, bivalent Smac mimetics that bind to XIAP, cIAP1, and cIAP2 with low to sub-nanomolar affinities and are highly effective in antagonizing XIAP in cell-free functional assays. The present compounds efficiently induce the degradation of cIAP1 and cIAP2 in cancer cells at low concentrations, activate caspase-3 and -8, and cleave PARP. The present compounds have a low IC_{50} in inhibition of cell growth in both MDA-MB-231and SK-OV-3 cell lines.

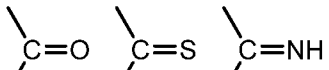
[0055] The IAP protein inhibitors of the present invention therefore are useful in the treatment of unwanted proliferating cells, including cancers and precancers, in subjects in need of such treatment. Also provided are methods of treating a subject having unwanted proliferating cells comprising administering a therapeutically effective amount of a present compound to a subject in need of such treatment. Also provided are methods of preventing the proliferation of unwanted proliferating cells, such as cancers and precancers, in a subject comprising the step of administering a therapeutically effective amount of a compound of structural formula (I) to a subject at risk of developing a condition characterized by unwanted proliferating cells. In some embodiments, the compounds of structural formula (I) reduced the proliferation of unwanted cells by inducing apotosis in those cells.

[0056] The present invention is directed to IAP protein inhibitors having a structural formula (I):



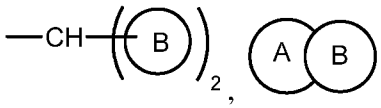
(I)

,

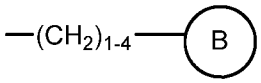
[0057] wherein X is selected from the group consisting of 

, and $-SO_2-$;

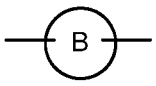
[0058] Y is selected from the group consisting of –NH-, -O-,–S-, and null;

[0059] R is selected from the group consisting of 

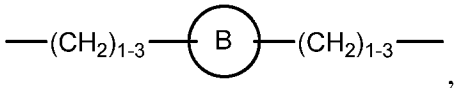
, wherein ring A is a C_{4-8} aliphatic ring, 

, and 

, wherein the B ring is aryl or nitrogen atom-containing heteroaryl and the B rings are optionally substituted; and

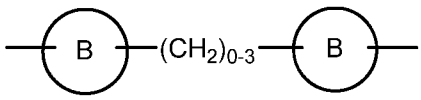
[0060] R_1 is selected from the group consisting of $-(CH_2)_{4-10}-$, 

,



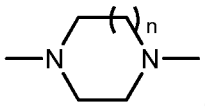
, 

,



,

, wherein Z is O, S, or NH, and



, wherein n is 0, 1, or 2, and wherein the B ring is aryl or nitrogen atom-containing heteroaryl and the 

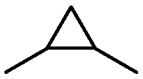
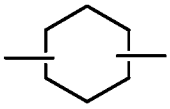
rings are optionally substituted;

[0061] or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof.

[0062] As used herein, the term "C_{4-8} aliphatic ring" refers to cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl, either unsubstituted or substituted with 1 to 3

groups, for example, C_{1-4}alkyl, halo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, nitro, cyano, alkylamino, or amino groups.

[0063] As used herein, the term "alkyl" refers to straight chained and branched saturated C_{1-10} hydrocarbon groups, nonlimiting examples of which include methyl, ethyl, and straight chain and branched propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, and decyl groups. The term C_n means the alkyl group has "n" carbon atoms.

[0064] The term "C_{3-6}cycloalkylene" refers to a disubstituted cycloalkane having 3 to 6 carbon atoms, for example  ,  ,  , and  . The "C_{3-6}cycloalkylene" can be unsubstituted, or substituted with 1 to 3 groups, for example, C_{1-4}alkyl, halo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, nitro, cyano, alkylamino, or amino groups.

[0065] The term "alkenyl" is defined identically as "alkyl," except for containing a carbon-carbon double bond, e.g., ethenyl, propenyl, and butenyl.

[0066] As used herein, the term "halo" is defined as fluoro, chloro, bromo, and iodo.

[0067] The term "hydroxy" is defined as —OH.

[0068] The term "alkoxy" is defined as —OR, wherein R is alkyl.

[0069] The term "amino" is defined as —NH_2, and the term "alkylamino" is defined as -NR_2, wherein at least one R is alkyl and the second R is alkyl or hydrogen.

[0070] The term "nitro" is defined as —NO_2.

[0071] The term "cyano" is defined as —CN.

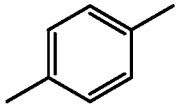
[0072] The term "trifluoromethyl" is defined as —CF_3.

[0073] The term "trifluoromethoxy" is defined as —OCF_3.

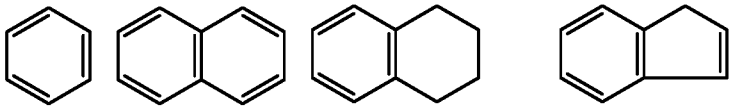
[0074] As used herein, the term "aryl" refers to a monocyclic or polycyclic aromatic group, preferably a monocyclic or bicyclic aromatic group, e.g., phenyl or naphthyl. Unless otherwise indicated, an aryl group can be unsubstituted or substituted with one or more, and in particular one to four, groups independently selected from, for example, halo, alkyl, alkenyl, -OCF_3, -NO_2, -CN, -NC, -OH, alkoxy, amino, alkylamino, -CO_2H, -CO_2alkyl, alkynyl, cycloalkyl, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, silyl,

alkylthio, sulfonyl, sulfonamide, aldehyde, heterocycloalkyl, trifluoromethyl, aryl, and heteroaryl.

[0075] As used herein, the term "heteroaryl" refers to a monocyclic or bicyclic ring system containing one or two aromatic rings and containing at least one and up to four nitrogen atoms in an aromatic ring. Unless otherwise indicated, a heteroaryl group can be unsubstituted or substituted with one or more, and in particular one to four, substituents selected from, for example, halo, alkyl, alkenyl, —OCF_3, —NO_2, —CN, —NC, —OH, alkoxy, amino, alkylamino, —CO_2H, —CO_2alkyl, alkynyl, cycloalkyl, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, silyl, alkylthio, sulfonyl, sulfonamide, aldehyde, heterocycloalkyl, trifluoromethyl, aryl, and heteroaryl.

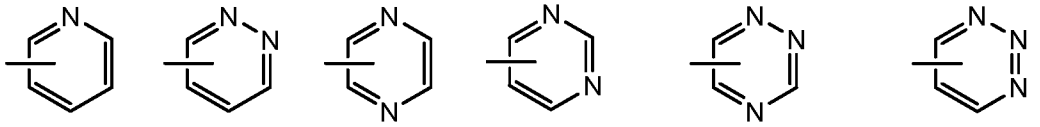
[0076] The term "arylene" refers to a bidentate aryl group that bonds to two other groups and serves to connect these groups, e.g.,  . The term "heteroarylene" is similarly defined.

[0077] Nonlimiting examples of aryl groups are

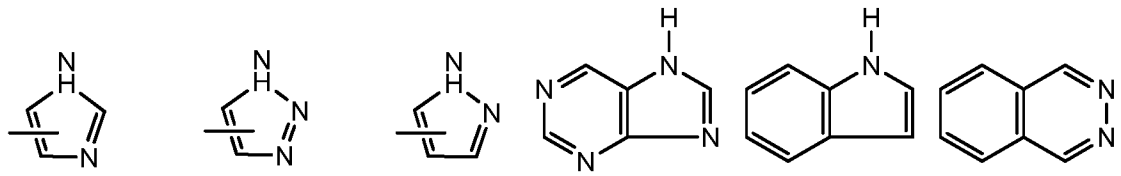


phenyl, naphthalene, tetralin, and indene.

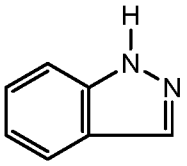
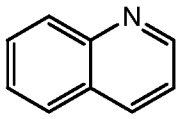
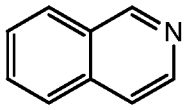
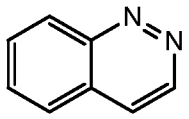
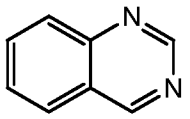
[0078] Nonlimiting examples of heteroaryl groups are

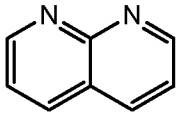
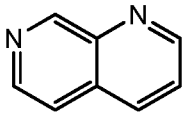
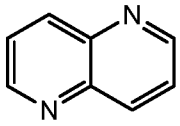
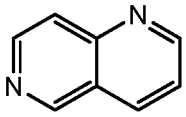


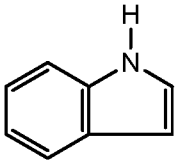
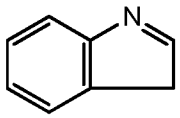
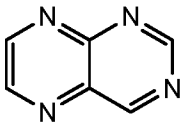
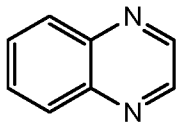
pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, 1, 2, 4-triazinyl, 1, 2, 3-triazinyl,



imidazolyl, 1, 2, 3,-triazolyl, pyrazolyl, purinyl, indolinyl, phthalzinyl,


indazolyl,

quinolinyl,

isoquinolinyl,

cinnolinyl,

quinazolinyl,

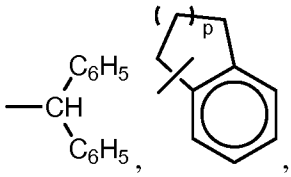

naphthyridinyl,

pyrido[3,4-b]-pyridinyl,

pyrido[3,2-b]-pyridinyl,

pyrido[4,3-b]-pyridinyl,

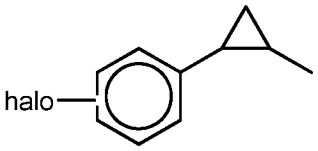

indolyl,

3H-indolyl (indolenine),

pteridinyl, and

quinoxalinyl.

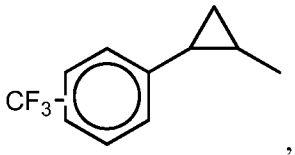
[0079] The compounds of structural formula (I) inhibit IAP proteins and are useful in the treatment of a variety of diseases and conditions. In particular, the compounds of structural formula (I) are used in methods of treating a disease or condition wherein inhibition of an IAP protein provides a benefit, for example, cancers, autoimmune disorders, and chronic inflammatory conditions. The method comprises administering a therapeutically effective amount of a compound of structural formula (I) to an individual in need thereof. The present methods also encompass administering a second therapeutic agent to the individual in addition to the compound of structural formula (I). The second therapeutic agent is selected from drugs known as useful in treating the disease or condition afflicting the individual in need thereof, e.g., a chemotherapeutic agent and/or radiation known as useful in treating a particular cancer.

[0080] In some preferred embodiments, the B ring is phenyl, naphthyl, pyridinyl, pyridazinyl, pyrazinyl, or pyrimidinyl.

[0081] In some preferred embodiments, R includes, but is not limited to:



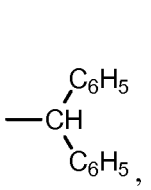
, wherein p is 0 to 4,


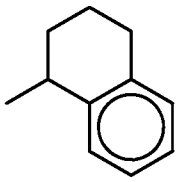
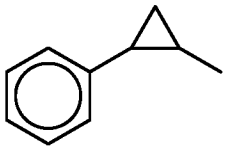
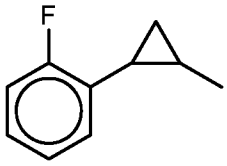
,


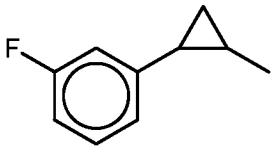
,

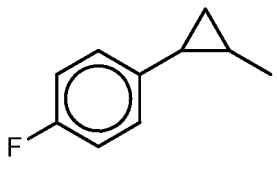

, wherein q is 0 to 2, and $-(CH_2)_{2\text{-}4}\text{-}C_6H_5$.

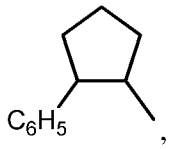
[0082] Specific R groups include, but are not limited to:

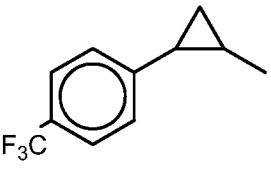


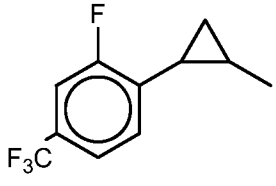
,

,

,


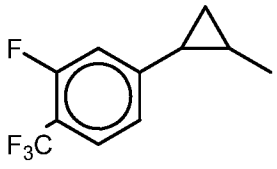
,


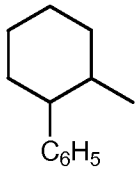
,


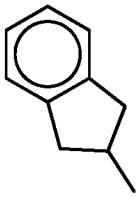
,


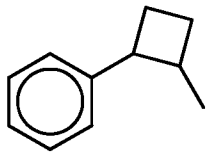
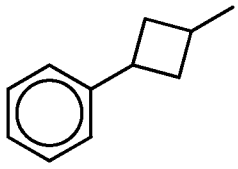
,


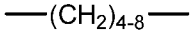
,


,


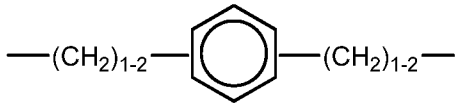
,


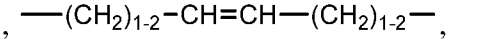
,

,

,

, and

.

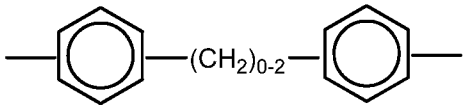
[0083] In some preferred embodiments R_1 is, but not limited to, 

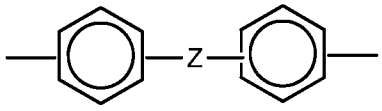
,

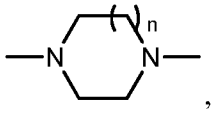
,


,


,

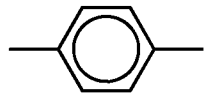
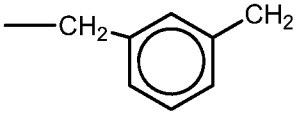
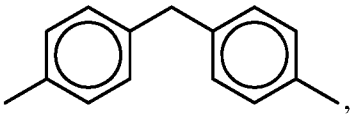
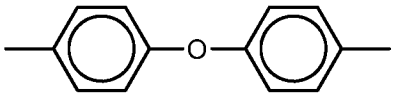
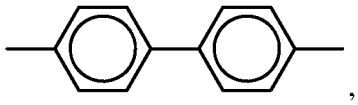
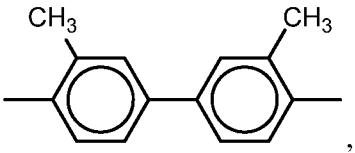
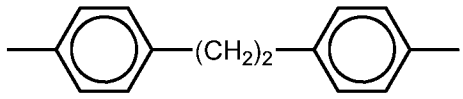
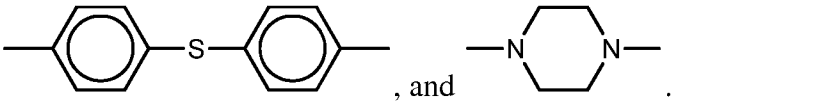


,


, and


,

wherein n is 0 or 1.

[0084] Specific R_1 groups include, but are not limited to, —$(CH_2)_4$—, —$(CH_2)_6$—, —$(CH_2)_8$—,  ,  , —$(CH_2)_2$—CH=CH—$(CH)_{1-2}$—,  ,  ,  ,  ,  ,  , , and .

[0085] In some preferred embodiments, X is  and Y is –NH-.

[0086] In other preferred embodiments, X is SO_2 and Y is null.

[0087] In another preferred embodiment, X is  and Y is null.

[0088] In still another preferred embodiment, X is  and Y is –NH-.

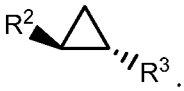
[0089] In still yet another preferred embodiment, X and X' are  and Y is –O-.

[0090] Additionally, salts, hydrates, solvates, and prodrugs of the present compounds also are included in the present invention and can be used in the methods disclosed herein. The present invention further includes all possible stereoisomers and geometric isomers of the compounds of structural formula (I). The present invention includes both racemic compounds and optically active isomers. When a compound of structural formula (I) is desired as a single enantiomer, it can be obtained either by resolution of the final product or by stereospecific synthesis from either isomerically pure starting material or use of a chiral auxiliary reagent, for example, see Z. Ma et al., *Tetrahedron: Asymmetry, 8(6)*, pages 883-888 (1997). Resolution of the final product, an intermediate, or a starting material can be achieved by any suitable method known in the art. Additionally, in situations where

tautomers of the compounds of structural formula (I) are possible, the present invention is intended to include all tautomeric forms of the compounds.

[0091] Compounds of the invention can exist as salts. Pharmaceutically acceptable salts of the compounds of the invention often are preferred in the methods of the invention. 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. The term "pharmaceutically acceptable salts" also refers to zwitterionic forms of the compounds of structural formula (I). Salts of compounds of formula (I) can be prepared during the final isolation and purification of the compounds or separately by reacting the compound with an acid having a suitable cation. The pharmaceutically acceptable salts of compounds of structural formula (I) can be acid addition salts formed with pharmaceutically acceptable acids. Examples of acids which can be employed to form pharmaceutically acceptable salts include inorganic acids such as nitric, boric, hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Nonlimiting examples of salts of compounds of the invention include, but are not limited to, the hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, 2-hydroxyethansulfonate, phosphate, hydrogen phosphate, acetate, adipate, alginate, aspartate, benzoate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerolphsphate, hemisulfate, heptanoate, hexanoate, formate, succinate, fumarate, maleate, ascorbate, isethionate, salicylate, methanesulfonate, mesitylenesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, paratoluenesulfonate, undecanoate, lactate, citrate, tartrate, gluconate, methanesulfonate, ethanedisulfonate, benzene sulphonate, and p-toluenesulfonate salts. 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. In addition, available amino groups present in the compounds of the invention can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides.

[0092] Compounds of structural formula (I) can contain one or more asymmetric center, and therefore can exist as stereoisomers. The present invention includes both mixtures and individual stereoisomers. In particular, the compounds of structural formula (I) include both the individual *cis*- and *trans*- isomers, and mixtures of the *cis*- and *trans*- isomers, e.g.,

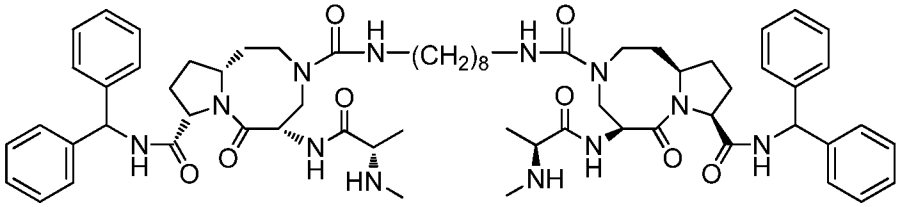
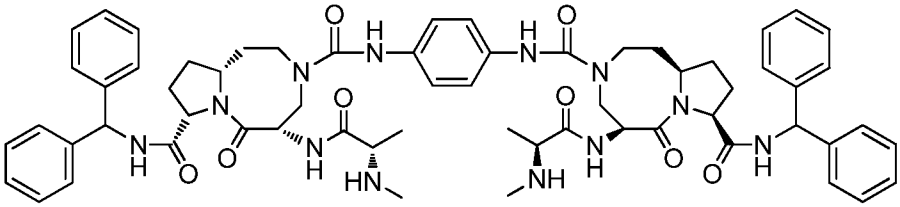
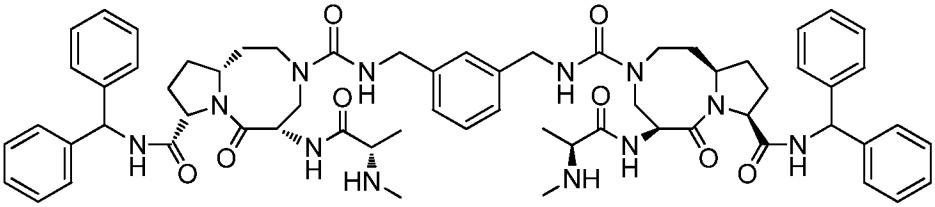
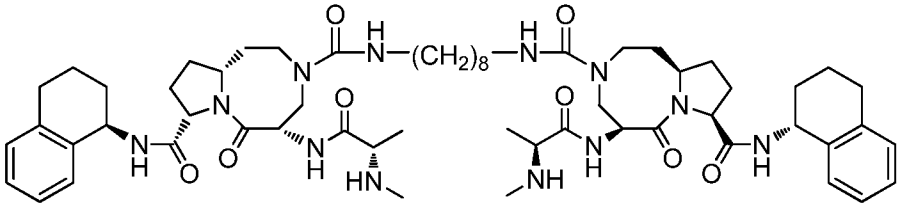
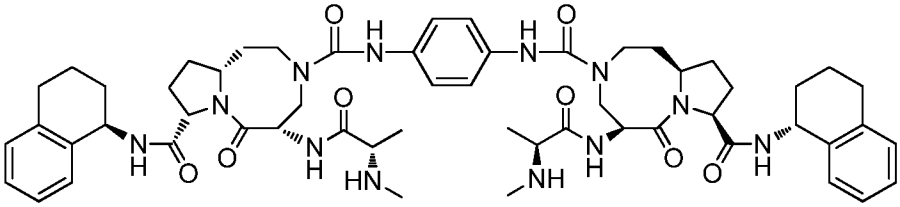
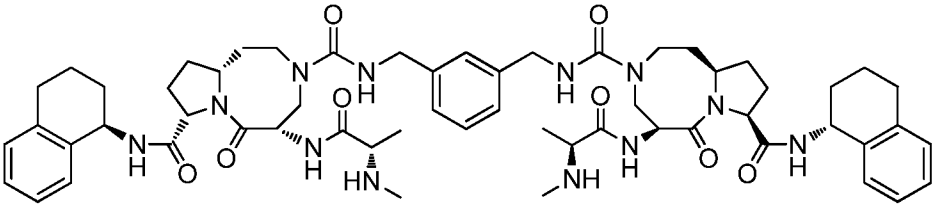
and


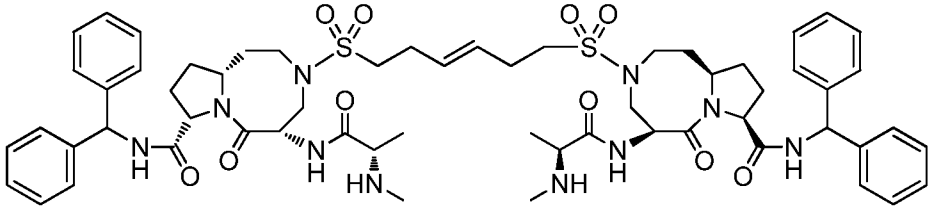
.

[0093] 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.

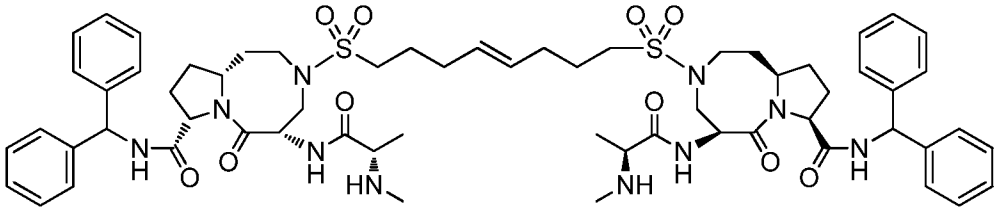
[0094] Prodrugs often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism. (See e.g., Bundgard, "Design of Prodrugs", pp. 7-9, 21-24, Elsevier, Amsterdam (1985); and Silverman, "The Organic Chemistry of Drug Design and Drug Action", pp. 352-401, Academic Press, San Diego, CA (1992)). 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). 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).

[0095] Specific compounds of the present invention include, but are not limited to, compounds having the structure set forth below.

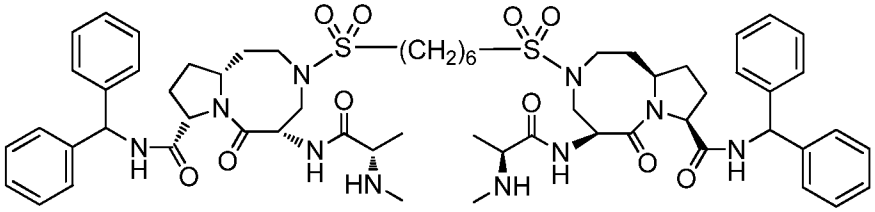
Structures
 Example 1
 Example 2
 Example 3
 Example 4
 Example 5
 Example 6



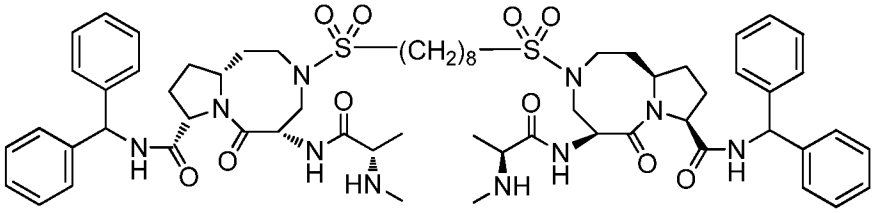
Example 7



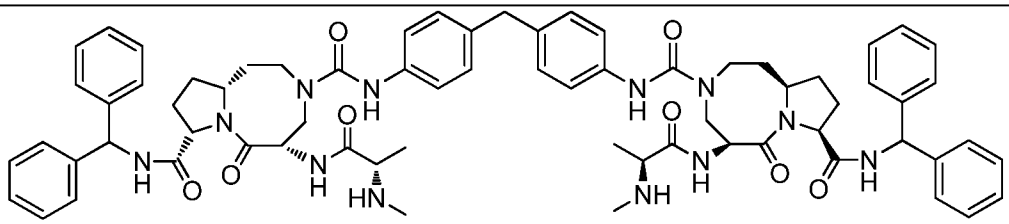
Example 8



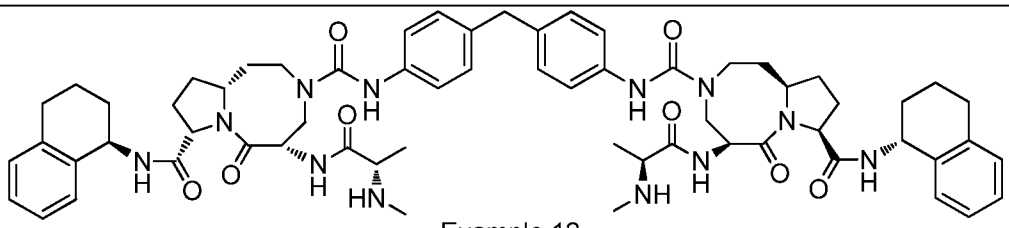
Example 9



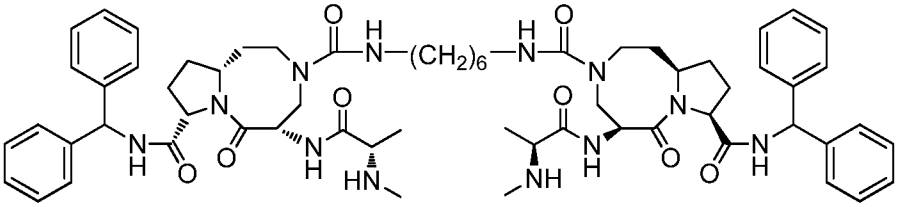
Example 10



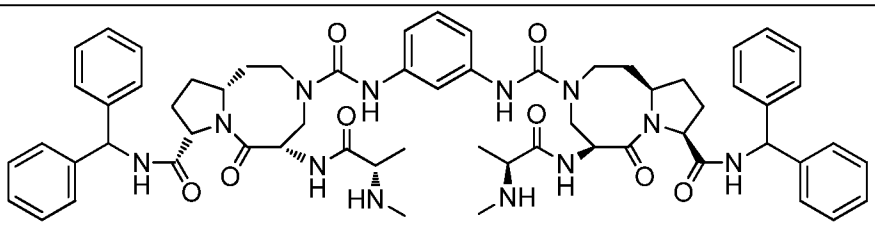
Example 11



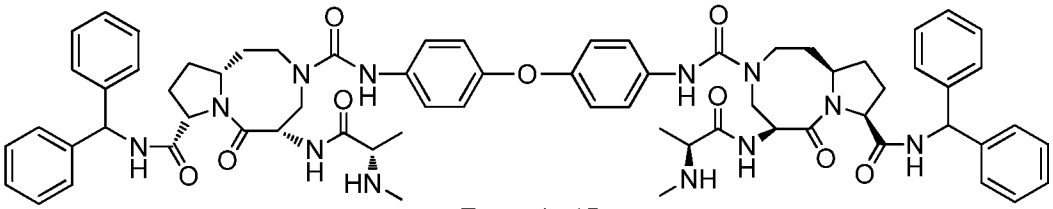
Example 12



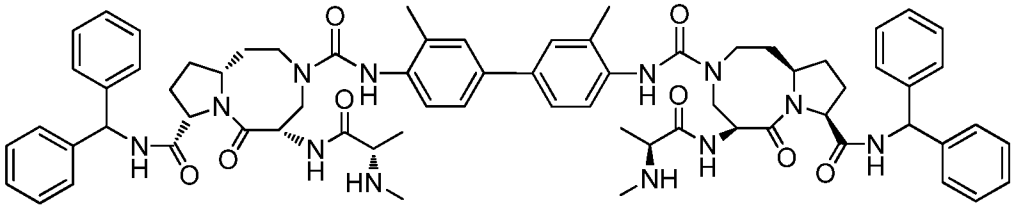
Example 13



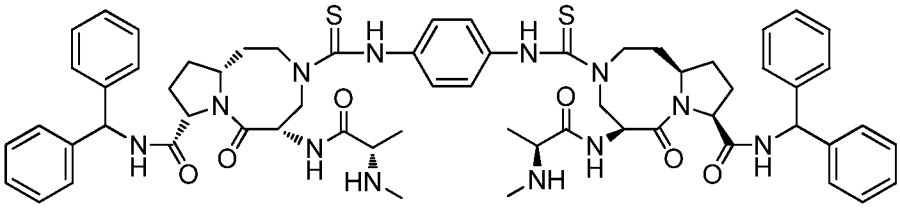
Example 14



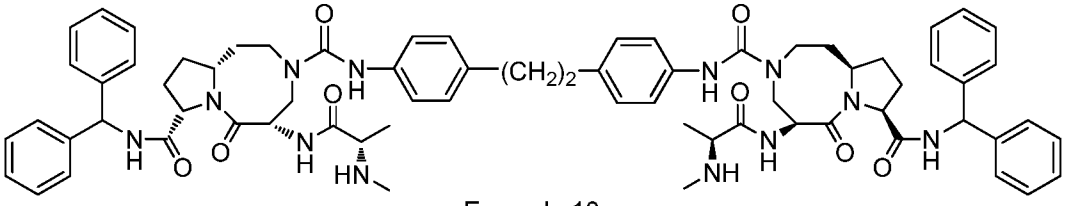
Example 15



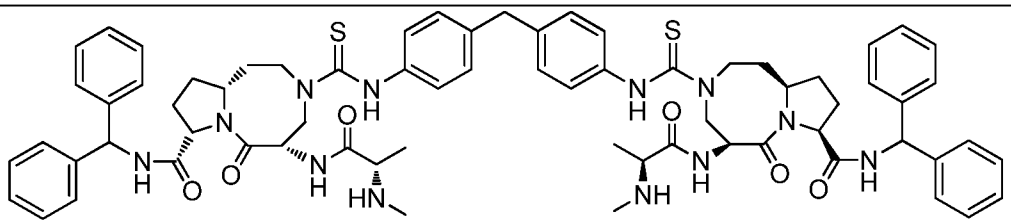
Example 16



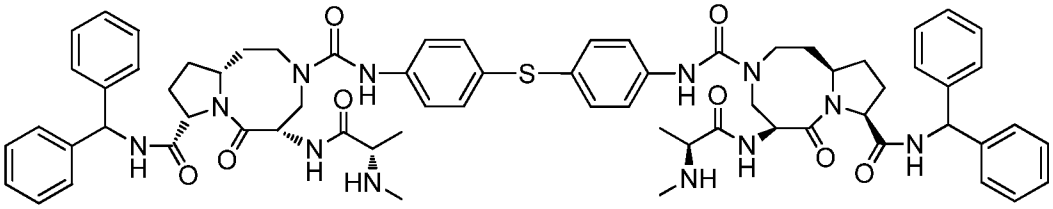
Example 17



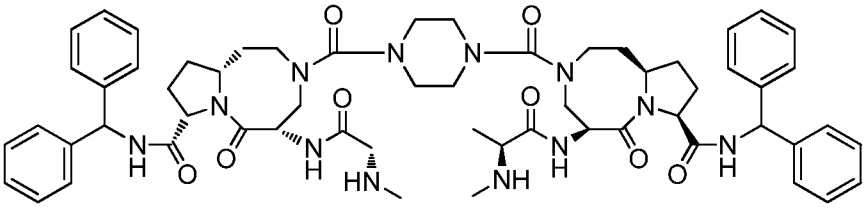
Example 18



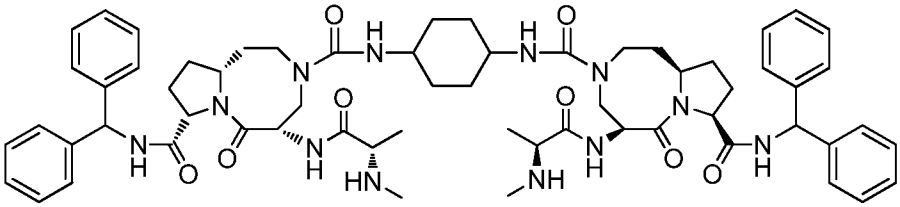
Example 19



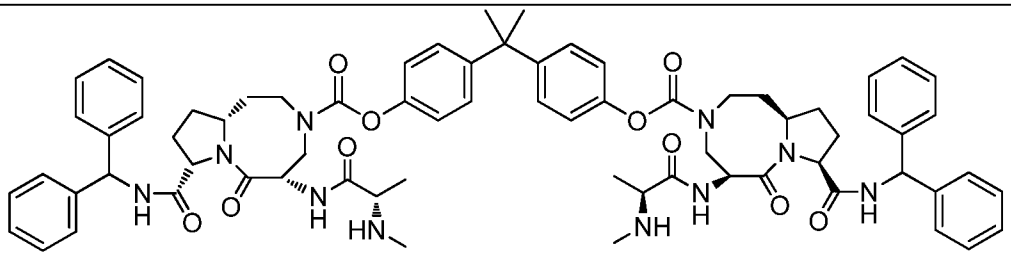
Example 20



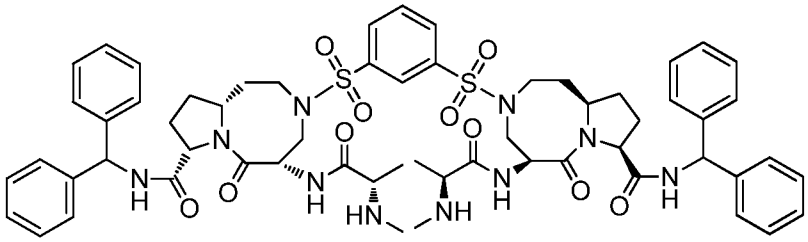
Example 21



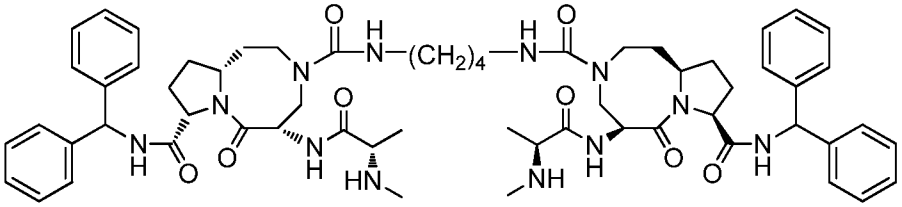
Example 22



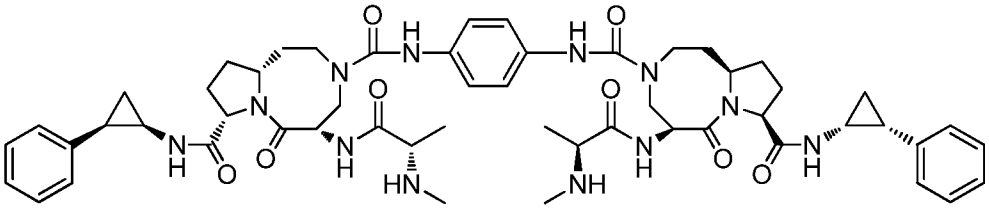
Example 23



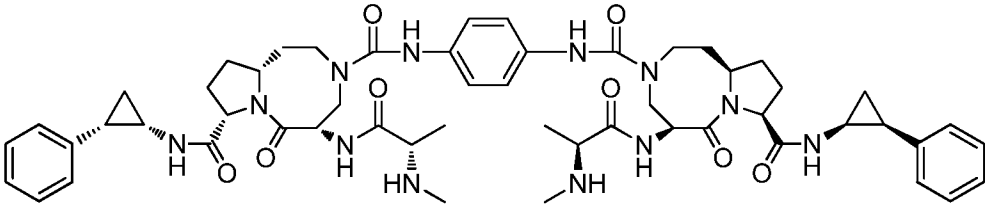
Example 24



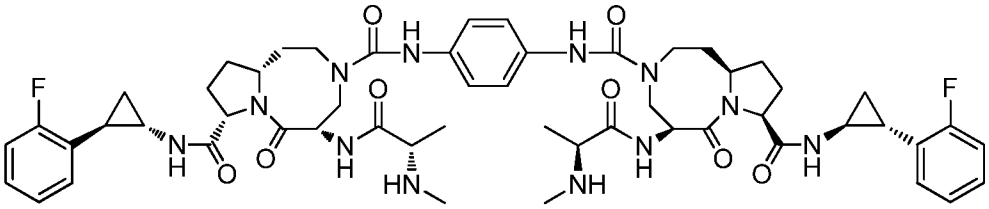
Example 25



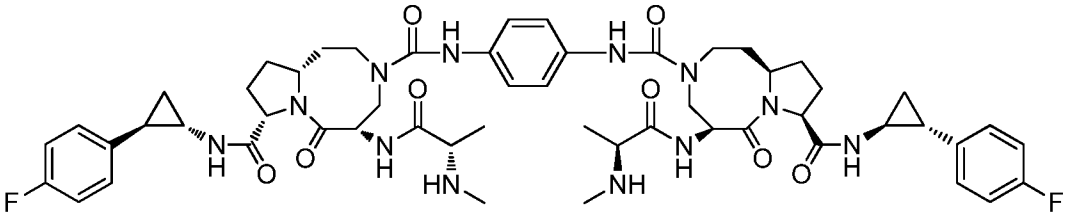
Example 26



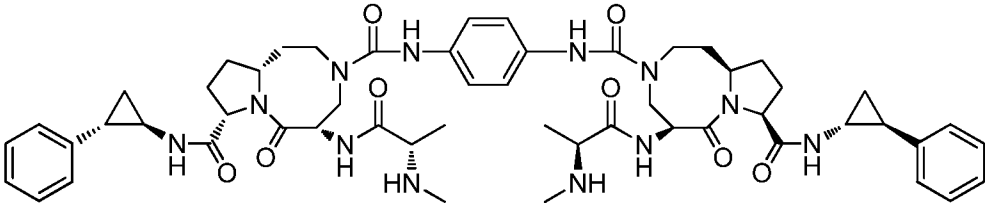
Example 27



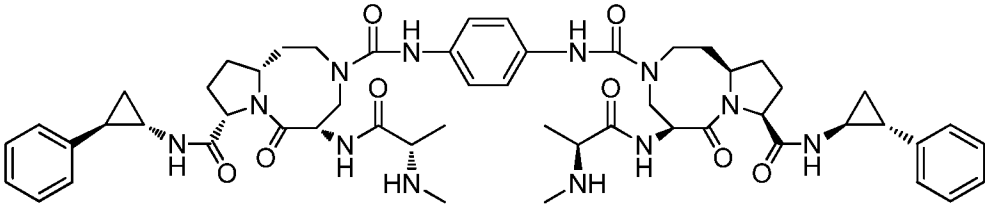
Example 28



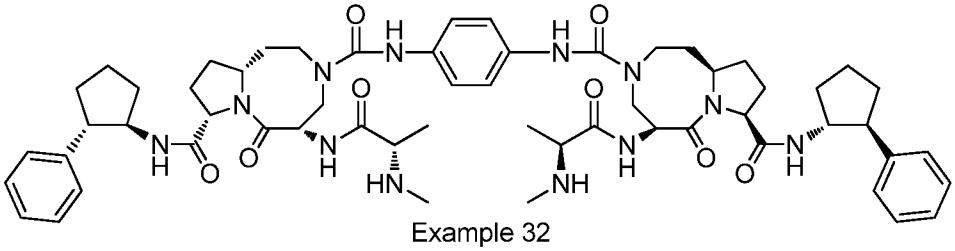
Example 29



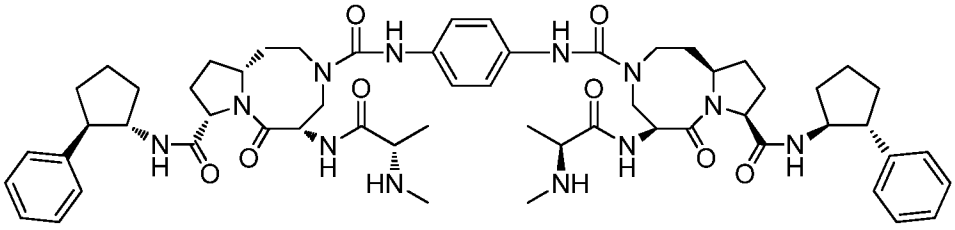
Example 30



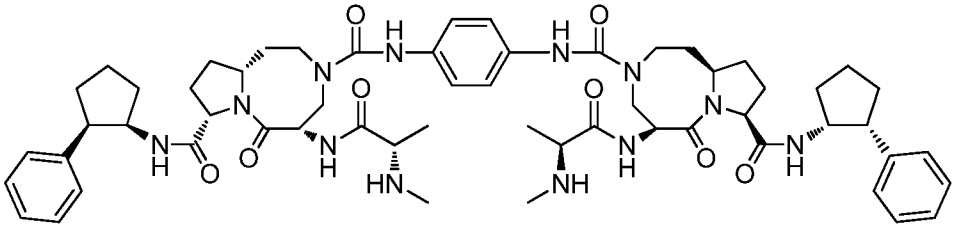
Example 31



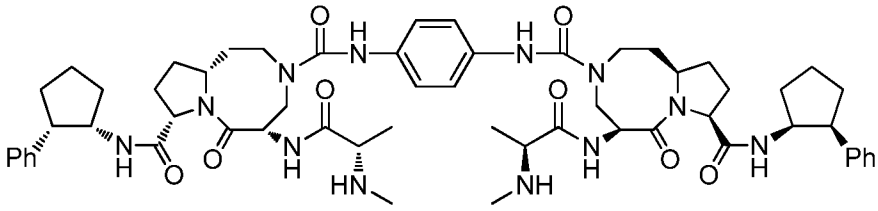
Example 32



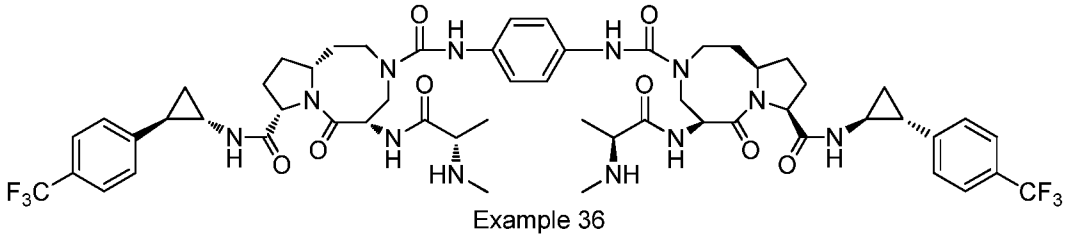
Example 33



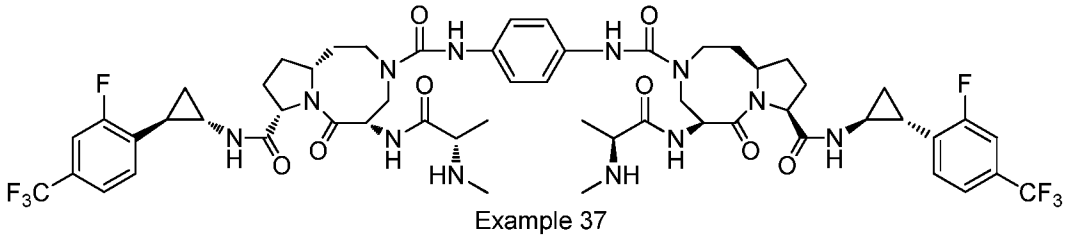
Example 34



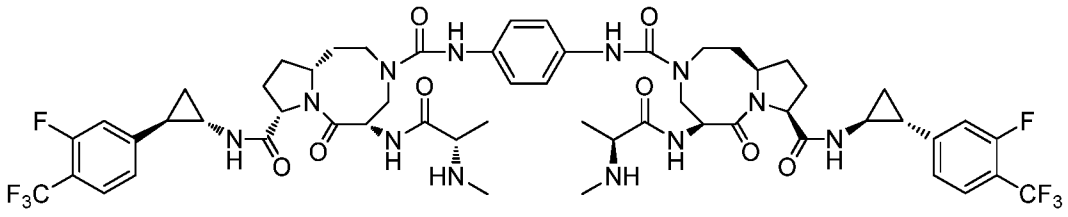
Example 35



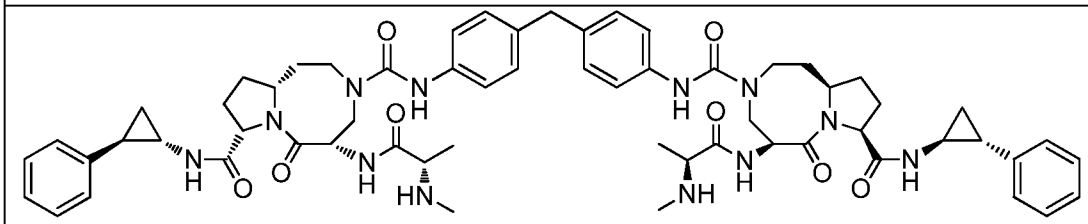
Example 36



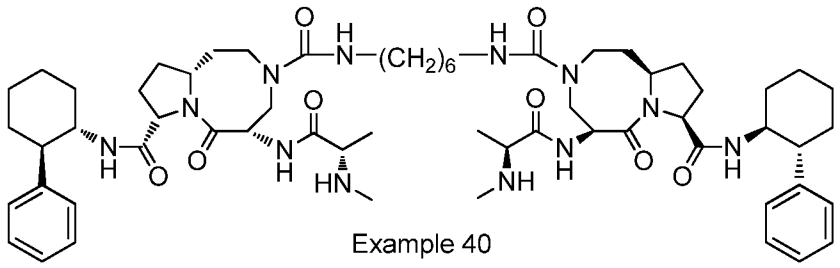
Example 37



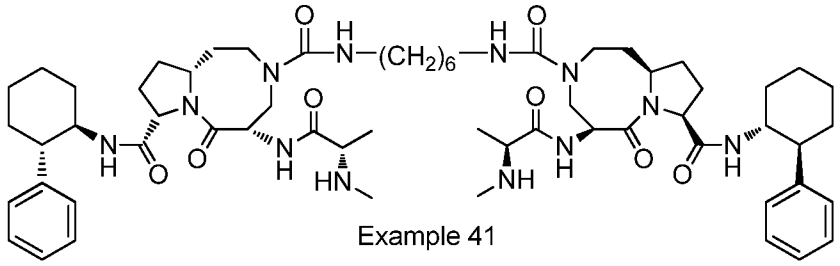
Example 38



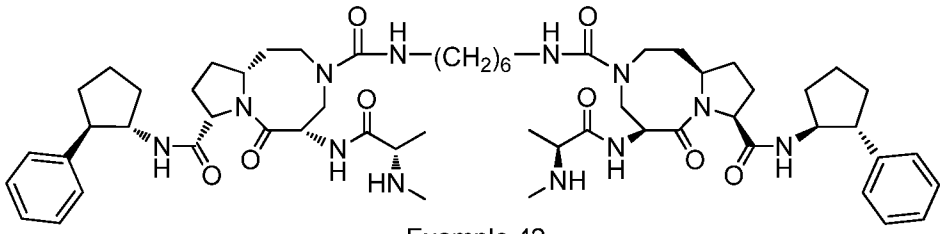
Example 39



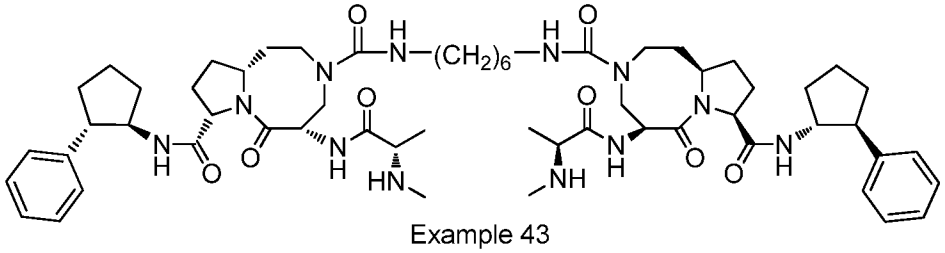
Example 40



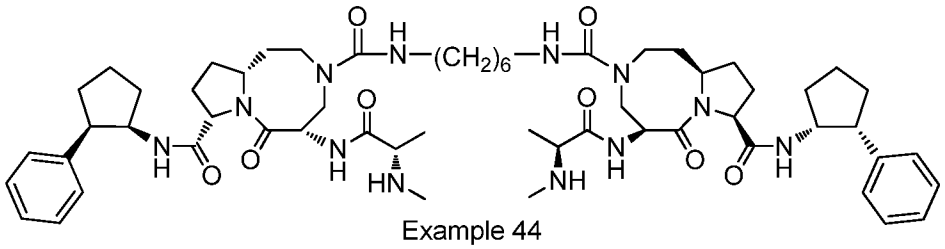
Example 41



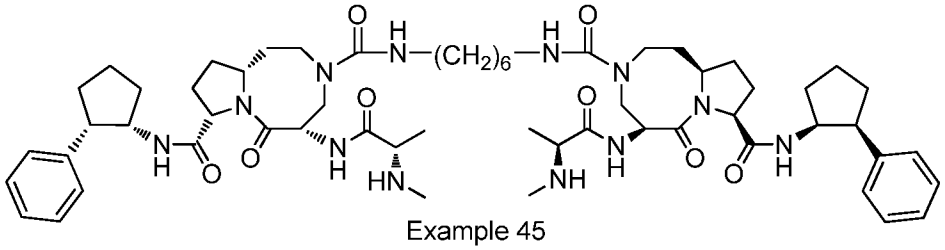
Example 42



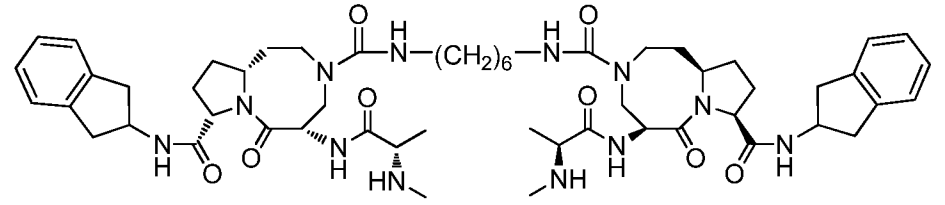
Example 43



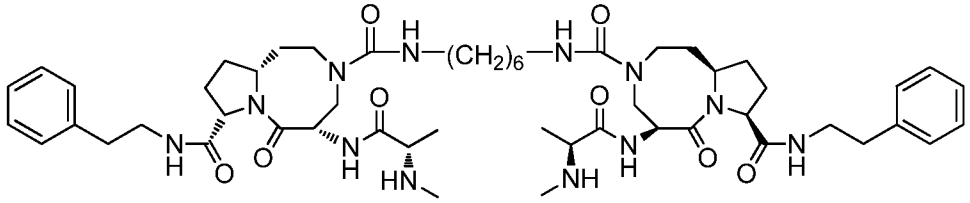
Example 44



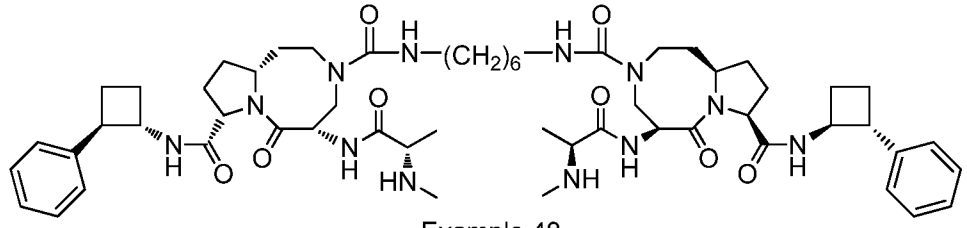
Example 45



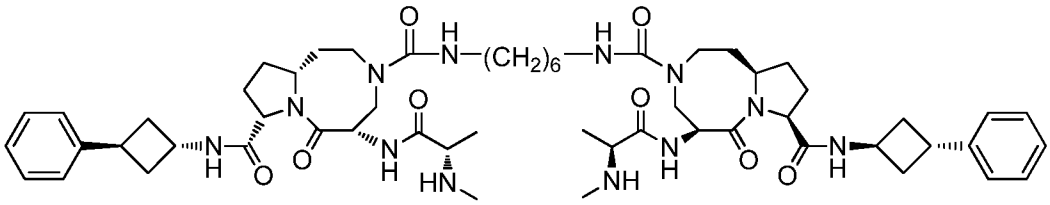
Example 46



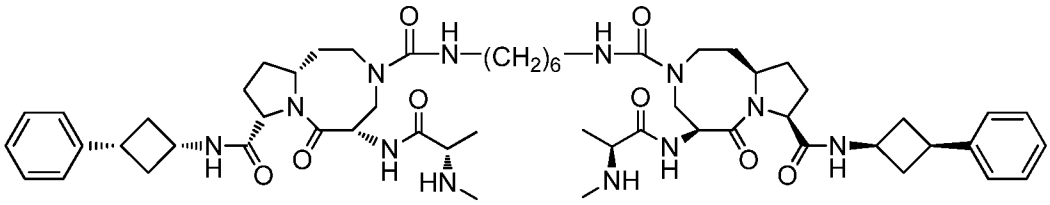
Example 47



Example 48



Example 49



Example 50

[0096] The present invention provides IAP protein inhibitors, as exemplified by compounds of structural formula (I), for the treatment of a variety of diseases and conditions wherein inhibition of IAP proteins has a beneficial effect. In one embodiment, the present invention relates to a method of treating an individual suffering from a disease or condition wherein inhibition of IAP proteins provides a benefit comprising administering a therapeutically effective amount of a compound of structural formula (I) to an individual in need thereof.

[0097] The present IAP protein inhibitors satisfy a 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 anticancer therapies so as to render a greater proportion of the cancer 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.

[0098] The term "anticancer therapy" as used herein, refers to therapeutic agents (e.g., chemotherapeutic compounds and/or molecular therapeutic compounds), radiation therapies, and surgical interventions used in the treatment of hyperproliferative diseases, such as a cancer in mammals.

[0099] The method of the present invention can be accomplished by administering a compound of structural formula (I) as the neat compound or as a pharmaceutical composition. Administration of a pharmaceutical composition, or neat compound of structural formula (I), can be performed during or after the onset of the disease or condition of interest. Typically,

the pharmaceutical compositions are sterile, and contain no toxic, carcinogenic, or mutagenic compounds that would cause an adverse reaction when administered. Further provided are kits comprising a compound of structural formula (I) and, optionally, a second therapeutic agent useful in the treatment of diseases and conditions wherein inhibition of an IAP protein provides a benefit, packaged separately or together, and an insert having instructions for using these active agents.

[0100] In many embodiments, a compound of structural formula (I) is administered in conjunction with a second therapeutic agent useful in the treatment of a disease or condition wherein inhibition of an IAP protein provides a benefit. The second therapeutic agent is different from the compound of structural formula (I). A compound of structural formula (I) and the second therapeutic agent can be administered simultaneously or sequentially to achieve the desired effect. In addition, the compound of structural formula (I) and second therapeutic agent can be administered from a single composition or two separate compositions.

[0101] The second therapeutic agent is administered in an amount to provide its desired therapeutic effect. The effective dosage range for each second therapeutic agent is known in the art, and the second therapeutic agent is administered to an individual in need thereof within such established ranges.

[0102] In certain embodiments, a combination treatment comprising administering a therapeutically effective amount of a compound of structural formula (I) and a second therapeutic agent produces a greater tumor response and greater clinical benefit compared to treatment with a compound of structural formula (I) or second therapeutic agent alone.

[0103] The compounds of structural formula (I) also can be used to achieve administration of a lower, and therefore less toxic and more tolerable, dose of a second therapeutic agent to produce the same tumor response/clinical benefit as the conventional dose of a second therapeutic agent. Also, because the compounds of the present invention act at least in part by inhibiting IAP proteins, the exposure of cancer and supporting cells to therapeutically effective amounts of the present IAP protein inhibitors can be temporally linked to coincide with the attempts of cells to execute the apoptosis program in response to a second therapeutic agent. Thus, in some embodiments, administering compound of the present invention in connection with a second therapeutic agent in certain temporal relationships provides especially efficacious therapeutic results.

[0104] A compound of structural formula (I) and the second therapeutic agent therefore can be administered together as a single-unit dose or separately as multi-unit doses, wherein the compound of structural formula (I) is administered before the second therapeutic agent or *vice versa*. One or more dose of the compound of structural formula (I) and/or one or more dose of the second therapeutic agent can be administered. The compounds of structural formula (I) therefore can be used in conjunction with one or more second therapeutic agents, for example, but not limited to, anticancer agents.

[0105] The diseases and conditions that can be treated in accordance to the invention include, for example, cancers. A variety of cancers can be treated including, but not limited to: carcinomas, including bladder (including accelerated and metastic bladder cancer), breast, colon (including colorectal cancer), kidney, liver, lung (including small and non-small cell lung cancer and lung adenocarcinoma), ovary, prostate, testes, genitourinary tract, lymphatic system, rectum, larynx, pancreas (including exocrine pancreatic carcinoma), esophagus, stomach, gall bladder, cervix, thyroid, renal, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, histiocytic lymphoma, and Burketts lymphoma, hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome, myeloid leukemia, and promyelocytic leukemia; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas; tumors of mesenchymal origin, including fibrosarcoma, rhabdomyoscarcoma, and osteosarcoma; and other tumors, including melanoma, xenoderma pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer, teratocarcinoma, renal cell carcinoma (RCC), pancreatic cancer, myeloma, myeloid and lymphoblastic leukemia, neuroblastoma, and glioblastoma.

[0106] Additional forms of cancer treatable by the IAP protein inhibitors of the present invention include, for example, adult and pediatric oncology, growth of solid tumors/malignancies, myxoid and round cell carcinoma, locally advanced tumors, metastatic cancer, human soft tissue sarcomas, including Ewing's sarcoma, cancer metastases, including lymphatic metastases, squamous cell carcinoma, particularly of the head and neck, esophageal squamous cell carcinoma, oral carcinoma, blood cell malignancies, including multiple myeloma, leukemias, including acute lymphocytic leukemia, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, and hairy cell

leukemia, effusion lymphomas (body cavity based lymphomas), thymic lymphoma lung cancer (including small cell carcinoma, cutaneous T cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cancer of the adrenal cortex, ACTH-producing tumors, nonsmall cell cancers, breast cancer, including small cell carcinoma and ductal carcinoma), gastrointestinal cancers (including stomach cancer, colon cancer, colorectal cancer, and polyps associated with colorectal neoplasia), pancreatic cancer, liver cancer, urological cancers (including bladder cancer, such as primary superficial bladder tumors, invasive transitional cell carcinoma of the bladder, and muscle-invasive bladder cancer), prostate cancer, malignancies of the female genital tract (including ovarian carcinoma, primary peritoneal epithelial neoplasms, cervical carcinoma, uterine endometrial cancers, vaginal cancer, cancer of the vulva, uterine cancer and solid tumors in the ovarian follicle), malignancies of the male genital tract (including testicular cancer and penile cancer), kidney cancer (including renal cell carcinoma, brain cancer (including intrinsic brain tumors, neuroblastoma, astrocytic brain tumors, gliomas, and metastatic tumor cell invasion in the central nervous system), bone cancers (including osteomas and osteosarcomas), skin cancers (including malignant melanoma, tumor progression of human skin keratinocytes, and squamous cell cancer), thyroid cancer, retinoblastoma, neuroblastoma, peritoneal effusion, malignant pleural effusion, mesothelioma, Wilms's tumors, gall bladder cancer, trophoblastic neoplasms, hemangiopericytoma, and Kaposi's sarcoma.

[0107] Another embodiment of the present invention is to induce apoptosis and potentiate the induction of apoptosis in response to apoptosis induction signals by use of an IAP protein inhibition of structural formula (I). The present IAP protein inhibitors also sensitize cells to inducers of apoptosis, including cells that are resistant to such inducers. The IAP protein 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) show elevated expression levels of IAP proteins as compared to non-pathological samples (e.g., non-cancerous cells). In other embodiments, the cells operationally manifest elevated expression levels of IAP proteins by virtue of executing the apoptosis program and dying in response to a therapeutically effective amount of a compound of structural formula (I), said response occurring, at least in part, due to the dependence in such cells on IAP protein function for their survival.

[0108] 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.

[0109] These therapies can be used in a variety of settings for the treatment of various cancers. In a specific embodiment, the individual in need of treatment has previously undergone treatment for cancer. Such previous treatments include, but are not limited to, prior chemotherapy, radiotherapy, surgery, or immunotherapy, such as cancer vaccines.

[0110] In one embodiment, the present invention provides a method of treating a cancer comprising: (a) administering to an individual in need thereof a therapeutically effective amount of an IAP protein inhibitor of structural formula (I); and (b) administering to the individual a therapeutically effective amount of one or more of radiotherapy, chemotherapy, and immunotherapy. The amounts administered are each effective to treat cancer. In another embodiment, the amounts are together effective to treat the cancer.

[0111] In another embodiment, the invention provides a method for treating a cancer, said method comprising administering to a subject in need thereof a pharmaceutical composition comprising an IAP protein inhibitor of structural formula (I).

[0112] In another embodiment, the present IAP protein inhibitors are used in methods of treating T and B cell mediated autoimmune diseases; inflammatory diseases; infections; hyperproliferative diseases; AIDS; degenerative conditions; vascular diseases; and the like. 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.

[0113] The present compounds and methods also are useful in the treatment of 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.

[0114] Additional diseases and conditions, including cancers, that can be treated by administration of a present IAP protein inhibitor are disclosed in U.S. Patent No. 7,960,372; incorporated herein by reference in its entirety.

[0115] In the present method, a therapeutically effective amount of one or more compound (I), typically formulated in accordance with pharmaceutical practice, is administered to a human being in need thereof. Whether such a treatment is indicated depends on the individual case and is subject to medical assessment (diagnosis) that takes into consideration signs, symptoms, and/or malfunctions that are present, the risks of developing particular signs, symptoms and/or malfunctions, and other factors.

[0116] A compound of structural formula (I) can be administered by any suitable route, for example by oral, buccal, inhalation, sublingual, rectal, vaginal, intracisternal or intrathecal through lumbar puncture, transurethral, nasal, percutaneous, i.e., transdermal, or parenteral (including intravenous, intramuscular, subcutaneous, intracoronary, intradermal, intramammary, intraperitoneal, intraarticular, intrathecal, retrobulbar, intrapulmonary injection and/or surgical implantation at a particular site) administration. Parenteral administration can be accomplished using a needle and syringe or using a high pressure technique.

[0117] Pharmaceutical compositions include those wherein a compound of structural formula (I) is administered in an effective amount to achieve its intended purpose. The exact formulation, route of administration, and dosage is determined by an individual physician in view of the diagnosed condition or disease. Dosage amount and interval can be adjusted individually to provide levels of a compound of structural formula (I) that is sufficient to maintain therapeutic effects.

[0118] Toxicity and therapeutic efficacy of the compounds of structural formula (I) can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the maximum tolerated dose (MTD) of a compound, which defines as the highest dose that causes no toxicity in animals. The dose ratio between the maximum tolerated dose and therapeutic effects (e.g. inhibiting of tumor growth) is the therapeutic index. The dosage can vary within this range depending upon the dosage form employed, and the route of administration utilized. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0119] A therapeutically effective amount of a compound of structural formula (I) required for use in therapy varies with the nature of the condition being treated, the length of time that activity is desired, and the age and the condition of the patient, and ultimately is determined by the attendant physician. Dosage amounts and intervals can be adjusted individually to provide plasma levels of the IAP protein inhibitor that are sufficient to maintain the desired therapeutic effects. The desired dose conveniently can be administered in a single dose, or as multiple doses administered at appropriate intervals, for example as one, two, three, four or more subdoses per day. Multiple doses often are desired, or required. For example, a present IAP protein inhibitor can be administered at a frequency of: four doses delivered as one dose per day at four-day intervals (q4d x 4); four doses delivered as one dose per day at three-day intervals (q3d x 4); one dose delivered per day at five-day intervals (qd x 5); one dose per week for three weeks (qwk3); five daily doses, with two days rest, and another five daily doses (5/2/5); or, any dose regimen determined to be appropriate for the circumstance.

[0120] A compound of structural formula (I) used in a method of the present invention can be administered in an amount of about 0.005 to about 500 milligrams per dose, about 0.05 to about 250 milligrams per dose, or about 0.5 to about 100 milligrams per dose. For example, a compound of structural formula (I) can be administered, per dose, in an amount of about 0.005, 0.05, 0.5, 5, 10, 20, 30, 40, 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 milligrams, including all doses between 0.005 and 500 milligrams.

[0121] The dosage of a composition containing an IAP protein inhibitor of structural formula (I), or a composition containing the same, can be from about 1 ng/kg to about 200 mg/kg, about 1 μg/kg to about 100 mg/kg, or about 1 mg/kg to about 50 mg/kg. The dosage of a composition can be at any dosage including, but not limited to, about 1 μg/kg. The dosage of a composition may be at any dosage including, but not limited to, about 1 μg/kg,

10 μg/kg, 25 μg/kg, 50 μg/kg, 75 μg/kg, 100 μg/kg, 125 μg/kg, 150 μg/kg, 175 μg/kg, 200 μg/kg, 225 μg/kg, 250 μg/kg, 275 μg/kg, 300 μg/kg, 325 μg/kg, 350 μg/kg, 375 μg/kg, 400 μg/kg, 425 μg/kg, 450 μg/kg, 475 μg/kg, 500 μg/kg, 525 μg/kg, 550 μg/kg, 575 μg/kg, 600 μg/kg, 625 μg/kg, 650 μg/kg, 675 μg/kg, 700 μg/kg, 725 μg/kg, 750 μg/kg, 775 μg/kg, 800 μg/kg, 825 μg/kg, 850 μg/kg, 875 μg/kg, 900 μg/kg, 925 μg/kg, 950 μg/kg, 975 μg/kg, 1 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 60 mg/kg, 70 mg/kg, 80 mg/kg, 90 mg/kg, 100 mg/kg, 125 mg/kg, 150 mg/kg, 175 mg/kg, or 200 mg/kg. The above dosages are exemplary of the average case, but there can be individual instances in which higher or lower dosages are merited, and such are within the scope of this invention. In practice, the physician determines the actual dosing regimen that is most suitable for an individual patient, which can vary with the age, weight, and response of the particular patient.

[0122] In the treatment of a cancer, a compound of structural formula (I) can be administered with a chemotherapeutic agent and/or an immunotherapeutic agent and/or radiation or in conjunction with another therapeutic technique, such as a surgery. As used herein, the term chemotherapeutic includes an anticancer agent, an anti-neoplastic agent, an apoptosis-modulating agent.

[0123] Embodiments of the present invention employ electromagnetic radiation of: gamma-radiation (10^{-20} to 10^{-13} m), X-ray radiation (10^{-12} to 10^{-9} m), ultraviolet light (10 nm to 400 nm), visible light (400 nm to 700 nm), infrared radiation (700 nm to 1 mm), and microwave radiation (1 mm to 30 cm).

[0124] Many cancer treatment protocols currently employ radiosensitizers activated by electromagnetic radiation, e.g., X-rays. Examples of X-ray-activated radiosensitizers include, but are not limited to, metronidazole, misonidazole, desmethylmisonidazole, pimonidazole, etanidazole, nimorazole, mitomycin C, RSU 1069, SR 4233, EO9, RB 6145, nicotinamide, 5-bromodeoxyuridine (BUdR), 5-iododeoxyuridine (IUdR), bromodeoxycytidine, fluorodeoxyuridine (FUdR), hydroxyurea, cis-platin, and therapeutically effective analogs and derivatives of the same.

[0125] Photodynamic therapy (PDT) of cancers employs visible light as the radiation activator of the sensitizing agent. Examples of photodynamic radiosensitizers include the following, but are not limited to: hematoporphyrin derivatives, PHOTOFRIN®, benzoporphyrin derivatives, NPe6, tin etioporphyrin (SnET2), pheoborbide-a,

bacteriochlorophyll-a, naphthalocyanines, phthalocyanines, zinc phthalocyanine, and therapeutically effective analogs and derivatives of the same.

[0126] Radiosensitizers can be administered in conjunction with a therapeutically effective amount of one or more compounds in addition to a present IAP protein inhibitor, such compounds including, but not limited to, compounds that promote the incorporation of radiosensitizers to the target cells, compounds that control the flow of therapeutics, nutrients, and/or oxygen to the target cells, chemotherapeutic agents that act on the tumor with or without additional radiation, or other therapeutically effective compounds for treating cancer or other disease. Examples of additional therapeutic agents that can be used in conjunction with radiosensitizers include, but are not limited to, 5-fluorouracil (5-FU), leucovorin, oxygen, carbogen, red cell transfusions, perfluorocarbons (e.g., FLUOSOLW®-DA), 2,3-DPG, BW12C, calcium channel blockers, pentoxifylline, antiangiogenesis compounds, hydralazine, and L-BSO.

[0127] The chemotherapeutic agent can be any pharmacological agent or compound that induces apoptosis. The pharmacological agent or compound can be, for example, a small organic molecule, peptide, polypeptide, nucleic acid, or antibody. Chemotherapeutic agents that can be used include, but are not limited to, alkylating agents, antimetabolites, hormones and antagonists thereof, natural products and their derivatives, radioisotopes, antibodies, as well as natural products, and combinations thereof. For example, an IAP protein inhibitor of the present invention can be administered with antibiotics, such as doxorubicin and other anthracycline analogs, nitrogen mustards, such as cyclophosphamide, pyrimidine analogs such as 5-fluorouracil, cis-platin, hydroxyurea, taxol and its natural and synthetic derivatives, and the like. As another example, in the case of mixed tumors, such as adenocarcinoma of the breast, where the tumors include gonadotropin-dependent and gonadotropin-independent cells, the compound can be administered in conjunction with leuprolide or goserelin (synthetic peptide analogs of LH-RH). Other antineoplastic protocols include the use of an inhibitor compound with another treatment modality, e.g., surgery or radiation, also referred to herein as "adjunct anti-neoplastic modalities." Additional chemotherapeutic agents useful in the invention include hormones and antagonists thereof, radioisotopes, antibodies, natural products, and combinations thereof.

[0128] Examples of chemotherapeutic agents useful in a method of the present invention are listed in the following table.

TABLE 1

Alkylating agents

Nitrogen mustards
mechlorethamine
cyclophosphamide
ifosfamide
melphalan
chlorambucil
uracil mustard
temozolomide

Nitrosoureas
carmustine (BCNU)
lomustine (CCNU)
semustine (methyl-CCNU)
chlormethine
streptozocin

Ethylenimine/Methyl-melamine
triethylenemelamine (TEM)
triethylene thiophosphoramide (thiotepa)
hexamethylmelamine (HMM, altretamine)

Alkyl sulfonates
busulfan
pipobroman

Triazines
dacarbazine (DTIC)

Antimetabolites

Folic Acid analogs
methotrexate
trimetrexate
pemetrexed (Multi-targeted antifolate)

Pyrimidine analogs
5-fluorouracil
fluorodeoxyuridine
gemcitabine
cytosine arabinoside (AraC, cytarabine)
5-azacytidine
2,2´- difluorodeoxy-cytidine
floxuridine
pentostatine

Purine analogs
6-mercaptopurine
6-thioguanine

Natural products

Antimitotic drugs

Taxanes
paclitaxel
Vinca alkaloids
vinblastine (VLB)
vincristine
vinorelbine
vindesine
Taxotere® (docetaxel)
estramustine
estramustine phosphate

Epipodophylotoxins
etoposide
teniposide

Antibiotics
actimomycin D
daunomycin (rubidomycin)
doxorubicin (adriamycin)
mitoxantroneidarubicin
bleomycin
splicamycin (mithramycin)
mitromycin-C
dactinomycin
aphidicolin
epirubicin
idarubicin
daunorubicin
mithramycin
deoxy co-formycin

Enzymes
L-asparaginase
L-arginase

Radiosensitizers

metronidazole
misonidazole
desmethylmisonidazole
pimonidazole
etanidazole
nimorazole
RSU 1069
EO9
RB 6145

Nonsteroidal antiandrogens
SR4233
flutamide

azathioprine
2'-deoxycoformycin
(pentostatin)
erythrohydroxynonyl-adenine (EHNA)
fludarabine phosphate
2-chlorodeoxyadenosine
(cladribine, 2-CdA)

Type I Topoisomerase Inhibitors
camptothecin
topotecan
irinotecan

Biological response modifiers
G-CSF
GM-CSF

Differentiation Agents
retinoic acid derivatives

Hormones and antagonists
Adrenocorticosteroids/ antagonists
prednisone and equivalents
dexamethasone
ainoglutethimide

Progestins
hydroxyprogesterone caproate
medroxyprogesterone acetate
megestrol acetate

Estrogens
diethylstilbestrol
ethynyl estradiol/ equivalents

Antiestrogen
tamoxifen

Androgens
testosterone propionate
fluoxymesterone/equivalents

Antiandrogens
flutamide
gonadotropin-releasing
hormone analogs
leuprolide

nicotinamide
5-bromodeozyuridine
5-iododeoxyuridine
bromodeoxycytidine

Miscellaneous agents
Platinium coordination complexes
cisplatin
carboplatin
oxaliplatin
anthracenedione
mitoxantrone

Substituted urea
hydroxyurea

Methylhydrazine derivatives
N-methylhydrazine (MIH)
procarbazine

Adrenocortical suppressant
mitotane (*o,p´*- DDD)
ainoglutethimide

Cytokines
interferon (α, β, γ)
interleukin-2

Photosensitizers
hematoporphyrin derivatives
PHOTOFRIN®
benzoporphyrin derivatives
Npe6
tin etioporphyrin (SnET2)
pheoboride-a
bacteriochlorophyll-a
naphthalocyanines
phthalocyanines
zinc phthalocyanines

Radiation
X-ray
ultraviolet light
gamma radiation
visible light
infrared radiation
microwave radiation

[0129] Microtubule affecting agents interfere with cellular mitosis and are well known in the art for their cytotoxic activity. Microtubule affecting agents useful in the invention include, but are not limited to, allocolchicine (NSC 406042), halichondrin B (NSC 609395),

colchicines (NSC 757), colchicines derivatives (e.g., NSC 33410), dolastatin 10 (NSC 376128), maytansine (NSC 153858), rhizoxin (NSC 332598), paclitaxel (NSC 125973), TAXOL® derivatives (e.g., NSC 608832), thiocolchicine NSC 361792), trityl cysteine (NSC 83265), vinblastine sulfate (NSC 49842), vincristine sulfate (NSC 67574), natural and synthetic epothilones including but not limited to epothilone A, eopthilone B, and discodermolide (see Service, (1996) Science, 274:2009) estramustine, nocodazole, MAP4, and the like. Examples of such agents are also described in Bulinski (1997) *J. Cell Sci.* 110:3055 3064; Panda (1997) *Proc. Natl. Acad. Sci. USA* 94:10560-10564; Muhlradt (1997) *Cancer Res.* 57:3344-3346; Nicolaou (1997) *Nature* 397:268-272; Vasquez (1997) *Mol. Biol. Cell.* 8:973-985; and Panda (1996) *J. Biol. Chem.* 271:29807-29812.

[0130] Cytostatic agents that may be used include, but are not limited to, hormones and steroids (including synthetic analogs): 17-α-ethinylestadiol, diethylstilbestrol, testosterone, prednisone, fluoxymesterone, dromostanolone propionate, testolactone, megestrolacetate, methylprednisolone, methyl-testosterone, prednisolone, triamcinolone, hlorotrianisene, hydroxyprogesterone, aminogluthimide, estramustine, medroxyprogesteroneacetate, leuprolide, flutamide, toremifene, zoladex.

[0131] Other cytostatic agents are antiangiogenics, such as matrix metalloproteinase inhibitors, and other VEGF inhibitors, such as anti-VEGF antibodies and small molecules such as ZD6474 and SU668. Anti-Her2 antibodies also may be utilized. An EGFR inhibitor is EKB-569 (an irreversible inhibitor). Also included are antibody C225 immunospecific for the EGFR and Src inhibitors.

[0132] Also suitable for use as a cytostatic agent is CASODEX® (bicalutamide, Astra Zeneca) which renders androgen-dependent carcinomas non-proliferative. Yet another example of a cytostatic agent is the antiestrogen TAMOXIFEN® which inhibits the proliferation or growth of estrogen dependent breast cancer. Inhibitors of the transduction of cellular proliferative signals are cytostatic agents. Representative examples include epidermal growth factor inhibitors, Her-2 inhibitors, MEK-1 kinase inhibitors, MAPK kinase inhibitors, PI3 inhibitors, Src kinase inhibitors, and PDGF inhibitors.

[0133] Antimicrobial therapeutic agents may also be used as second 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.

[0134] Additional second therapeutic agents that can be administered with an IAP protein inhibitor of the present invention are disclosed in U.S. Patent No. 7,960,372, incorporated herein by reference in its entirety.

[0135] The compounds of the present invention typically are administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. Pharmaceutical compositions for use in accordance with the present invention are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries that facilitate processing of compounds of structural formula (I).

[0136] These pharmaceutical compositions can be manufactured, for example, by conventional mixing, dissolving, granulating, dragee-making, emulsifying, encapsulating, entrapping, or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen. When a therapeutically effective amount of the compound of structural formula (I) is administered orally, the composition typically is in the form of a tablet, capsule, powder, solution, or elixir. When administered in tablet form, the composition additionally can contain a solid carrier, such as a gelatin or an adjuvant. The tablet, capsule, and powder contain about 0.01% to about 95%, and preferably from about 1% to about 50%, of a compound of structural formula (I). When administered in liquid form, a liquid carrier, such as water, petroleum, or oils of animal or plant origin, can be added. The liquid form of the composition can further contain physiological saline solution, dextrose or other saccharide solutions, or glycols. When administered in liquid form, the composition contains about 0.1% to about 90%, and preferably about 1% to about 50%, by weight, of a compound of structural formula (I).

[0137] When a therapeutically effective amount of a compound of structural formula (I) is administered by intravenous, cutaneous, or subcutaneous injection, the composition is in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like,

is within the skill in the art. A preferred composition for intravenous, cutaneous, or subcutaneous injection typically contains, an isotonic vehicle.

[0138] Compounds of structural formula (I) can be readily combined with pharmaceutically acceptable carriers well-known in the art. Such carriers enable the active agents to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by adding the compound of structural formula (I) to a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers and cellulose preparations. If desired, disintegrating agents can be added.

[0139] A compound of structural formula (I) can be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, e.g., in ampules or in multidose containers, with an added preservative. The compositions can take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing, and/or dispersing agents.

[0140] Pharmaceutical compositions for parenteral administration include aqueous solutions of the active agent in water-soluble form. Additionally, suspensions of a compound of structural formula (I) can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils or synthetic fatty acid esters. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension. Optionally, the suspension also can contain suitable stabilizers or agents that increase the solubility of the compounds and allow for the preparation of highly concentrated solutions. Alternatively, a present composition can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0141] A compound of structural formula (I) also can be formulated in rectal compositions, such as suppositories or retention enemas, e.g., containing conventional suppository bases. In addition to the formulations described previously, the compound of structural formula (I) also can be formulated as a depot preparation. Such long-acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of structural formula (I) can be formulated with

suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins.

[0142] In particular, the compounds of structural formula (I) can be administered orally, buccally, or sublingually in the form of tablets containing excipients, such as starch or lactose, or in capsules or ovules, either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. Such liquid preparations can be prepared with pharmaceutically acceptable additives, such as suspending agents. The compounds of structural formula (I) also can be injected parenterally, for example, intravenously, intramuscularly, subcutaneously, or intracoronarily. For parenteral administration, the IAP protein inhibitors are best used in the form of a sterile aqueous solution which can contain other substances, for example, salts or monosaccharides, such as mannitol or glucose, to make the solution isotonic with blood.

[0143] As an additional embodiment, the present invention includes kits which comprise one or more compounds or compositions packaged in a manner that facilitates their use to practice methods of the invention. In one simple embodiment, the kit includes a compound or composition described herein as useful for practice of a method (e.g., a composition comprising a compound of structural formula (I) and an optional second therapeutic agent), packaged in a container, such as a sealed bottle or vessel, with a label affixed to the container or included in the kit that describes use of the compound or composition to practice the method of the invention. Preferably, the compound or composition is packaged in a unit dosage form. The kit further can include a device suitable for administering the composition according to the intended route of administration.

[0144] Prior IAP protein inhibitors possessed properties that hindered their development as therapeutic agents. In accordance with an important feature of the present invention, compounds of structural formula (I) were synthesized and evaluated as inhibitors of IAP proteins. For example, compounds of the present invention typically have a bonding affinity (IC_{50}) to IAP proteins of less than 100 nM, less than 50 nM, less than 25 nM, and less than 10 nM.

SYNTHESIS OF COMPOUNDS

[0145] Compounds of the present invention and were prepared as follows. The following synthetic schemes are representative of the reactions used to synthesize compounds of

structural formula (I). Modifications and alternate schemes to prepare IAP protein inhibitors of the invention are readily within the capabilities of persons skilled in the art.

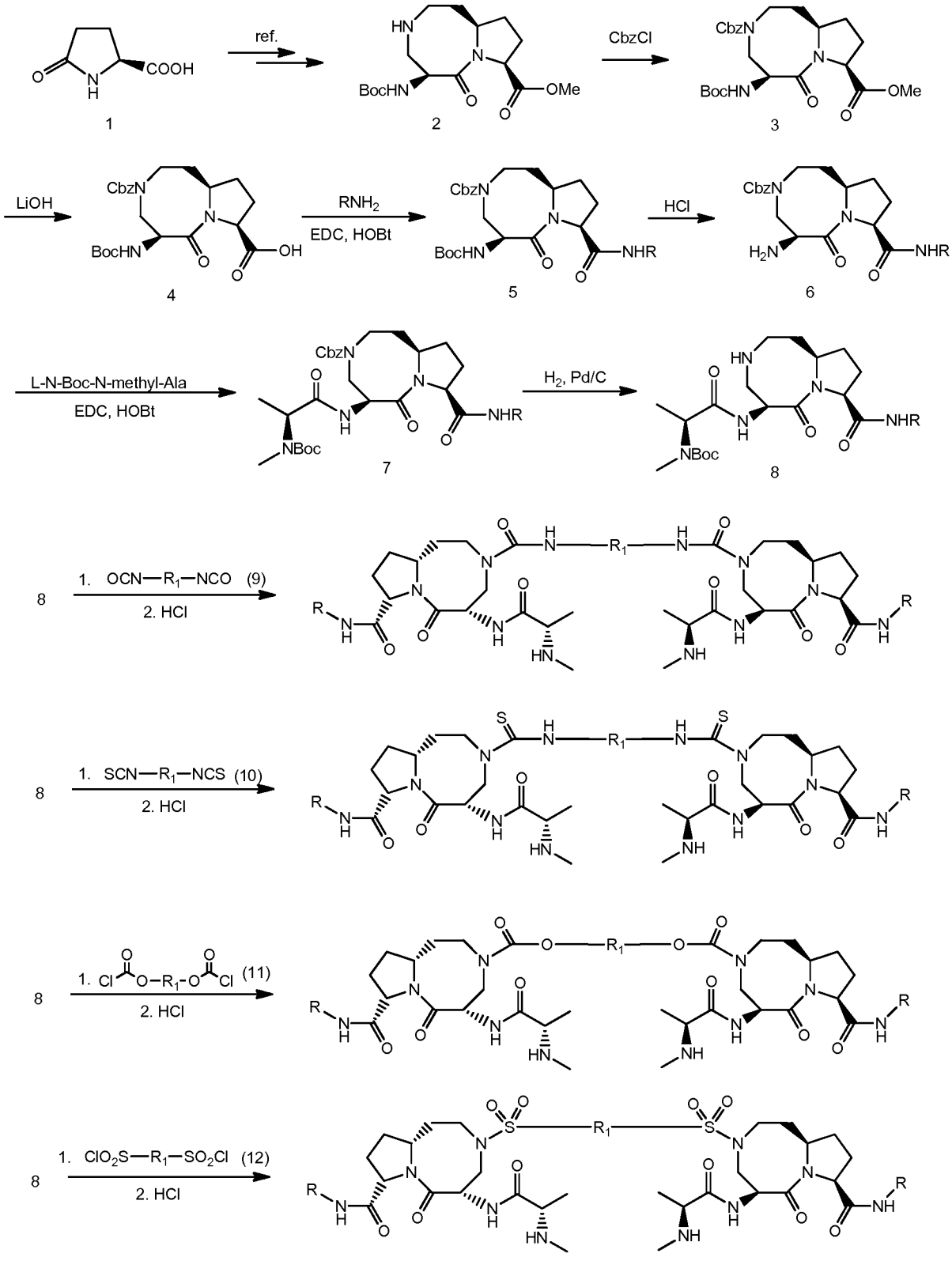
[0146] Solvents and reagents were obtained commercially and used without further purification. Chemical shifts (δ) of NMR spectra are reported as δ values (ppm) downfield relative to an internal standard, with multiplicities reported in the usual manner.

[0147] Unless otherwise stated all temperatures are in degrees Celsius.

[0148] In the synthetic methods, the examples, and throughout the specification, the abbreviations have the following meanings:

MS	mass spectrometry
CbzCl	benzyl chloroformate
LiOH	lithium hydroxide
HCl	hydrochloric acid
CD_3OD	deuterated methanol
NMR	nuclear magnetic resonance spectrometry
Hz	Hertz
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
HOBt	1-hydroxybenzotriazole
Pd/C	palladium on carbon

Synthetic Scheme 1

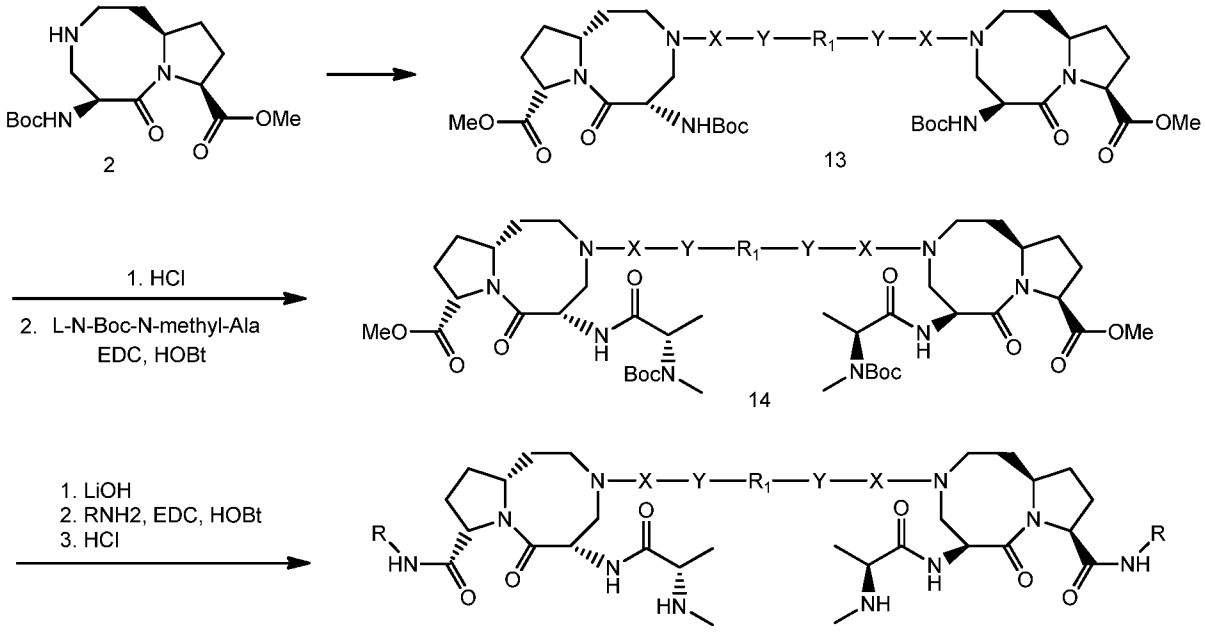


[0149] Each compound of structural formula (I), except those having a cyclopropyl ring in R, are synthesized according to the method shown in the above Synthetic Scheme 1. Compound 2 was synthesized according to the method disclosed in Q. Cai et al., J. Med.

Chem., 2011, 2714-26. Protection of the amino group in compound 2 with Cbz gave a carbamate 3. Hydrolysis of the methyl ester in carbamate 3 yielded acid 4. Condensation of acid 4 with a series of amines respectively afforded amides 5. Removal of the Boc protecting group in amide 5 yielded amine 6. Condensation of amine 6 with L-N-Boc-N-methyl-alanine provided amides 7. Cleavage of the Cbz protecting group in amide 7 afforded amines 8.

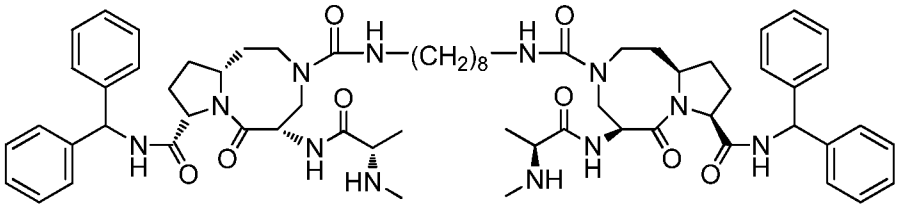
[0150] Condensation of amine 8 with a series of diisocyanates (9), and the subsequent removal of the Boc protecting groups yielded bis-urea containing Smac mimetics. Condensation of amine 8 with a series of diisothiocyanates (10) and the subsequent removal of the Boc protecting groups yielded bis-thiourea containing Smac mimetics. Condensation of amine 8 with a series of dicarbonochloridate (12) and the subsequent removal of the Boc protecting groups yielded bis-carbamate contained Smac mimetics. Condensation of amine 8 with a series of disulfonyl chlorides and the subsequent removal of the Boc protecting groups yielded bis-sulfonamides containing Smac mimetics.

Synthetic Scheme 2



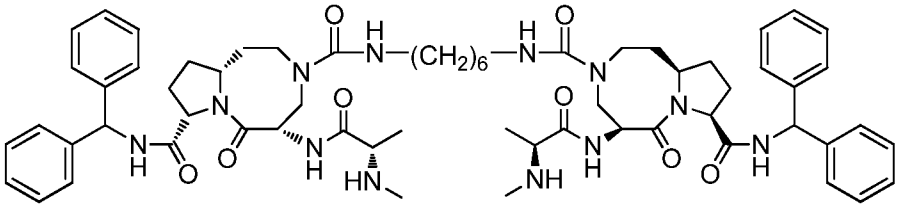
[0151] Compounds of general structural formula (I) having a cyclopropyl ring in R, the synthesis is shown in above Synthetic Scheme 2. Condensation of compound 2 with diisocyanates, diisothiocyanates, dicarbonochloridate, or disulfonyl chlorides respectively gave intermediates 13. Removal of the Boc protecting groups in compound 13, and the subsequent condensation with L-N-Boc-N-methyl-Ala yielded amides 14. Hydrolysis of the methyl esters in amide 14 furnished a series of acids. Condensation of the acids with a series

of amine and the subsequent deprotection of the Boc protecting groups provided final compounds.



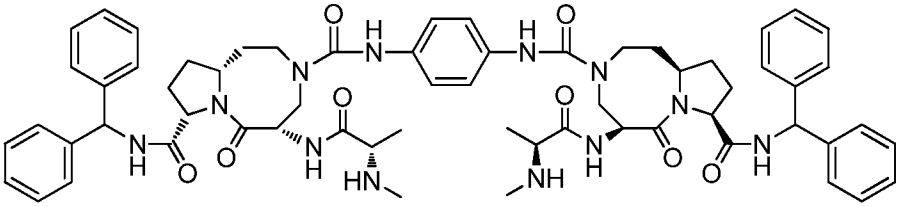
Example 1

[0152] ^{1}H NMR (300 MHz, CD_3OD): δ 7.37-7.24 (m, 20H), 6.16 (s, 2H), 4.72-4.60 (m, 4H), 4.10 (m, 2H), 4.00-3.85 (m, 6H), 3.25-3.04 (m, 8H), 2.69 (s, 6H), 2.34 (m, 2H), 2.14-2.03 (m, 6H), 1.77-1.48 (m, 8H), 1.54 (d, *J*=6.9 Hz, 6H), 1.35 (m, 8H); ESI MS: *m/z* 1151.8 $(M+H)^+$.



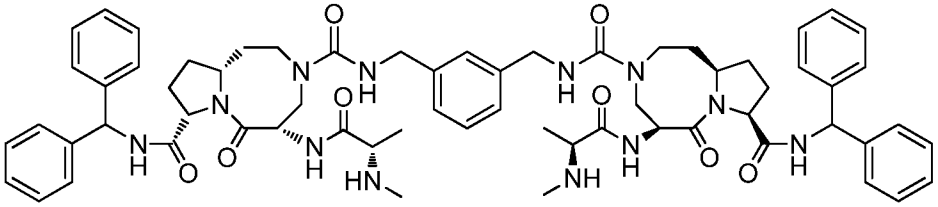
Example 13

[0153] ^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.23 (m, 20H), 6.15 (s, 2H), 4.70-4.60 (m, 4H), 4.10 (m, 2H), 3.97-3.80 (m, 6H), 3.25-3.03 (m, 8H), 2.69 (s, 6H), 2.34 (m, 2H), 2.10-2.03 (m, 6H), 1.78-1.57 (m, 8H), 1.52 (d, *J*=7.2 Hz, 6H), 1.39 (m, 4H); ESI MS: *m/z* 1123.6 $(M+H)^+$.



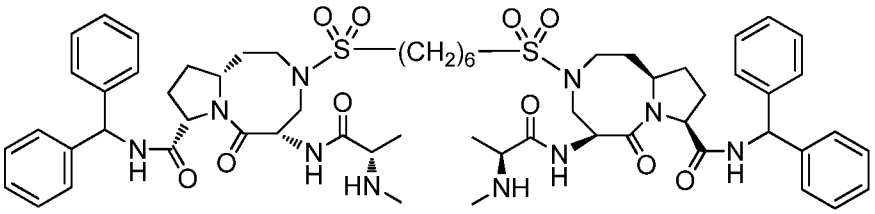
Example 2

[0154] ^{1}H NMR (300 MHz, CD_3OD): δ 7.53 (s, 4H), 7.37 (m, 20H), 6.18 (s, 2H), 4.84 (m, 2H), 4.67 (t, *J*= 8.4 Hz, 2H), 4.27 (m, 2H), 4.09-3.80 (m, 6H), 3.30-3.05 (m, 4H), 2.71 (s, 6H), 2.37 (m, 2H), 2.35-1.80 (m, 4H), 1.70-1.55 (m, 6H), 1.45 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1115.9 $(M+H)^+$.



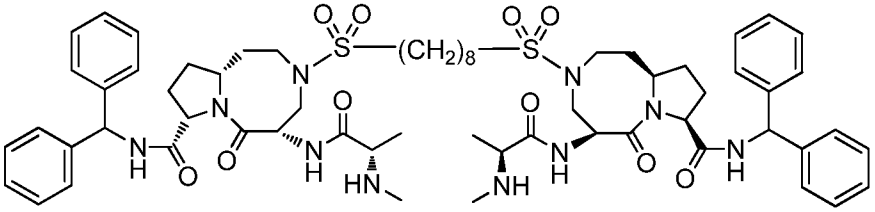
Example 3

[0155] ^{1}H NMR (300 MHz, CD_3OD): δ 7.36-7.15 (m, 24H), 6.15 (s, 2H), 4.84 (m, 2H), 4.63 (m, 4H), 4.32-4.14 (m, 4H), 3.99-3.81 (m, 6H), 3.16-3.06 (m, 4H), 2.63 (s, 6H), 2.34 (m, 2H), 2.18-2.85 (m, 6H), 1.85-1.60 (m, 4H), 1.50(d, *J*=7.2 Hz, 6H); ESI MS: *m/z* 1143.67 $(M+H)^+$.



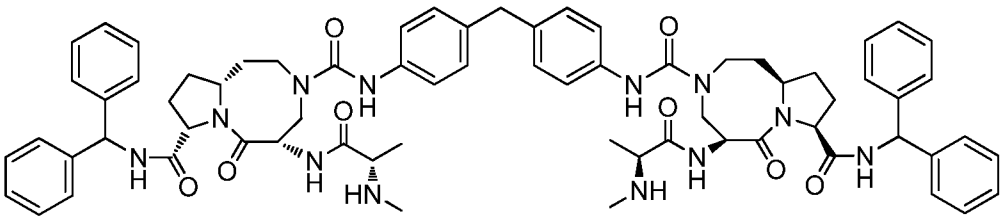
Example 9

[0156] ^{1}H NMR (300 MHz, CD_3OD): δ 7.36 (m, 20H), 6.14 (s, 2H), 4.82 (m, 2H), 4.60 (t, *J*= 8.4 Hz, 2H), 4.44 (m, 2H), 3.92-3.80 (m, 4H), 3.70 (m, 2H), 3.42 (m, 2H), 3.16-3.03 (m, 6H), 2.66 (s, 6H), 2.36 (m, 2H), 2.16 (m, 2H), 2.00 (m, 4H), 1.73 (m, 8H), 1.52-1.43 (m, 10H); ESI MS: m/z 1165.4 $(M+H)^+$.



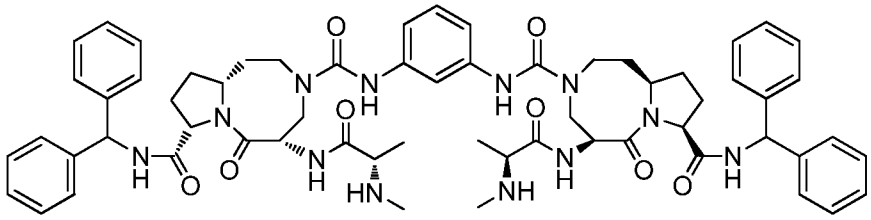
Example 10

[0157] ^{1}H NMR (300 MHz, CD_3OD): δ 7.36-7.22 (m, 20H), 6.14 (s, 2H), 4.82 (m, 2H), 4.60 (t, *J*= 8.4 Hz, 2H), 4.44 (m, 2H), 3.91-3.85 (m, 4H), 3.65 (m, 2H), 3.48 (m, 2H), 3.15-3.03 (m, 6H), 2.66 (s, 6H), 2.32 (m, 2H), 2.14 (m, 2H), 2.00 (m, 4H), 1.85-1.70 (m, 8H), 1.52 (d, J=8.7 Hz, 6H), 1.42-1.33 (m, 6H); ESI MS: m/z 1193.7 $(M+H)^+$.



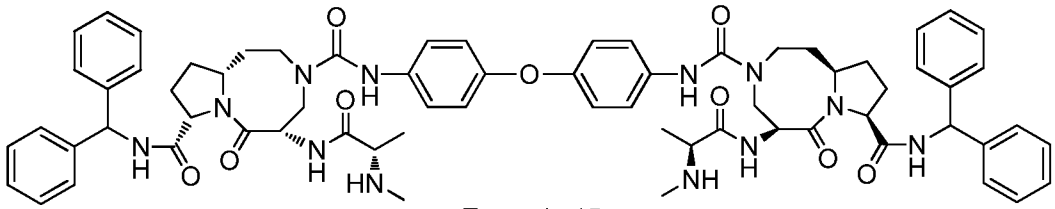
Example 11

[0158] ^{1}H NMR (300 MHz, CD_3OD): δ 7.48 (d, *J*=8.1 Hz, 4H), 7.33 (m, 20H), 7.11 (d, *J*=8.1 Hz, 4H), 6.17 (s, 2H), 4.82 (m, 2H), 4.63 (m, 2H), 4.25 (m, 2H), 4.08-4.03 (m, 6H), 3.88 (s, 2H), 3.30-3.20 (m, 4H), 2.70 (s, 6H), 2.34 (m, 2H), 2.20-1.80 (m, 6H), 1.75-1.60 (m, 4H), 1.55 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1206.4 $(M+H)^+$.



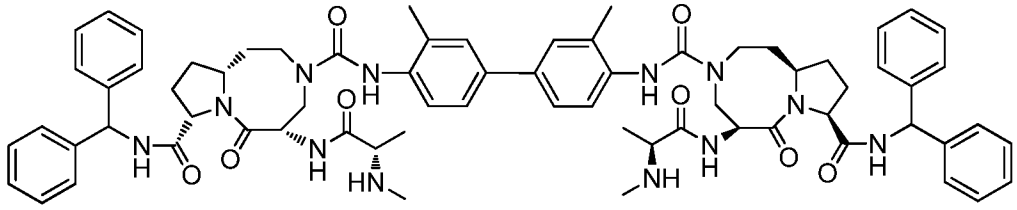
Example 14

[0159] ^{1}H NMR (300 MHz, CD_3OD): δ 8.14 (m, 1H), 7.34-7.18 (m, 23H), 6.17 (s, 2H), 4.84 (m, 2H), 4.67 (t, *J*=8.4 Hz, 2H), 4.22 (m, 2H), 4.07 (m, 6H), 3.24 (m, 4H), 2.73 (s, 6H), 2.34 (m, 2H), 2.14-2.04 (m, 6H), 1.77-1.66 (m, 4H), 1.57 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1115.9 $(M+H)^+$.



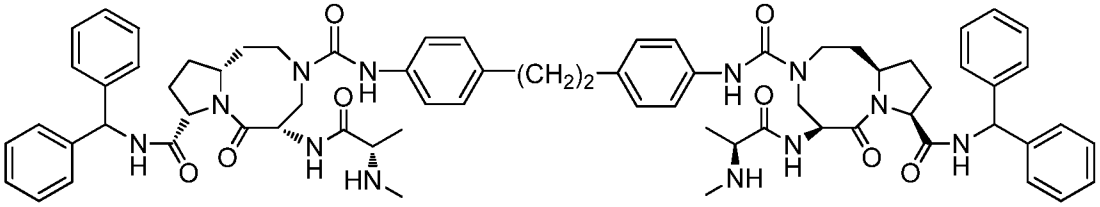
Example 15

[0160] ^{1}H NMR (300 MHz, CD_3OD): δ 7.55 (d, *J*=9.0 Hz, 4H), 7.36-7.24 (m, 20H), 6.91(d, *J*=9.0Hz, 4H), 6.17 (m, 2H), 4.84 (m, 2H), 4.64 (t, *J*=8.1Hz, 2H), 4.23 (m, 2H), 4.09 (m, 6H), 3.21 (m, 4H), 2.71 (s, 6H), 2.34 (m, 2H), 2.14-2.02 (m, 6H), 1.80-1.73 (m, 4H), 1.56 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1207.3 $(M+H)^+$.



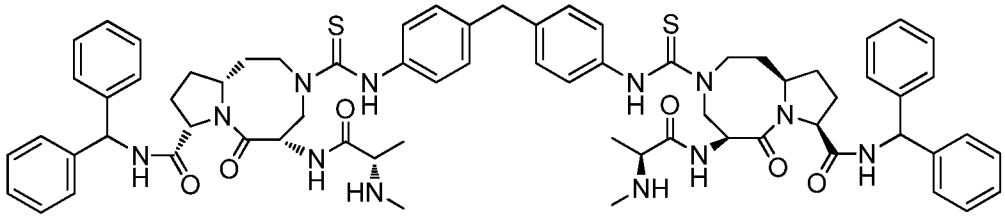
Example 16

[0161] ^{1}H NMR (300 MHz, CD_3OD): δ 7.46-7.25 (m, 26H), 6.17 (s, 2H), 4.84 (m, 2H), 4.65 (m, 2H), 4.32 (m, 2H), 4.19-4.02 (m, 6H), 3.22 (m, 4H), 2.66 (s, 6H), 2.37 (s, 6H), 2.24-2.02 (m, 8H), 1.83-1.70 (m, 4H), 1.53 (d, *J*=6.6 Hz, 6H); ESI MS: *m/z* 1220.2 $(M+H)^+$.



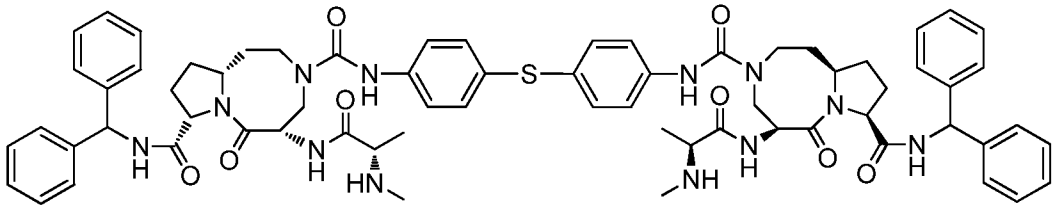
Example 18

[0162] ^{1}H NMR (300 MHz, CD_3OD): δ 7.47 (d, *J*=8.4 Hz, 4H), 7.36 (m, 20H), 7.06 (d, *J*=8.4 Hz, 4H), 6.16 (s, 2H), 4.94 (m, 2H), 4.67 (t, *J*=8.4 Hz, 2H), 4.25 (m, 2H), 4.09-4.04 (m, 6H), 3.17-3.28 (m, 4H), 2.84 (s, 4H), 2.66 (s, 6H), 2.37 (m, 2H), 2.15-2.02 (m, 6H), 1.79-1.67 (m, 4H), 1.56 (d, *J*=6.6 Hz, 6H); ESI MS: *m/z* 1220.25 $(M+H)^+$.



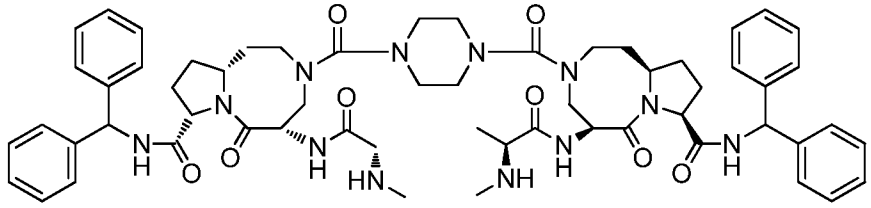
Example 19

[0163] ^{1}H NMR (300 MHz, CD_3OD): δ 7.83 (d, *J*=8.4 Hz, 4H), 7.63 (d, *J*=8.4 Hz, 4H), 7.36-7.16 (m, 20H), 6.17 (s, 2H), 5.01 (m, 2H), 4.67 (m, 2H), 4.17 (m, 2H), 4.00-3.94 (m, 4H), 3.73 (s, 4H), 3.59-3.40 (m, 4H), 2.64 (s, 6H), 2.55-2.37 (m, 4H), 2.06 (m, 4H), 1.80-1.67 (m, 4H), 1.53 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1237.6 $(M+H)^+$.



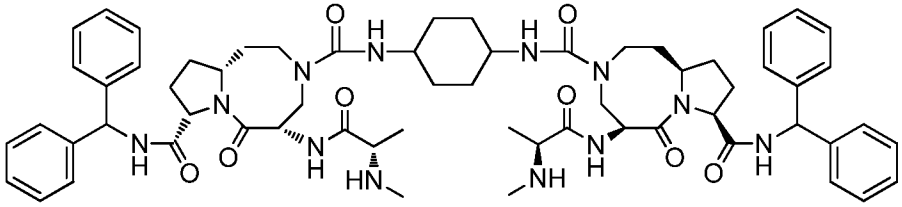
Example 20

[0164] ^{1}H NMR (300 MHz, CD_3OD): δ 7.60 (d, *J*=8.4 Hz, 4H), 7.36-7.21 (m, 24H), 6.17 (s, 2H), 4.82 (m, 2H), 4.64 (t, *J*=8.1Hz, 2H), 4.21 (m, 2H), 4.08-4.02 (m, 6H), 3.24 (m, 4H), 2.70 (s, 6H), 2.24 (m, 2H), 2.14-2.03 (m, 6H), 1.78-1.71 (m, 4H), 1.56 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1223.3 $(M+H)^+$.



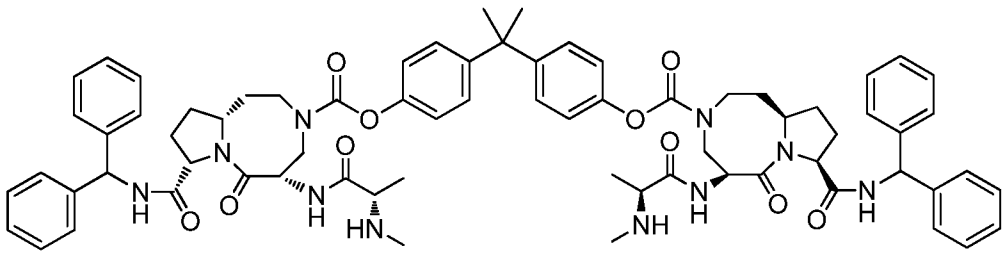
Example 21

[0165] ^{1}H NMR (300 MHz, CD_3OD): δ 7.33-7.21 (m, 20H), 6.12 (s, 2H), 5.11 (m, 2H), 4.84 (m, 2H), 4.56 (t, *J*=8.4Hz, 2H), 4.25 (m, 2H), 3.93 (m, 2H), 3.66-3.53 (m, 6H), 3.22-3.15 (m, 8H), 2.67 (s, 6H), 2.34 (m, 2H), 2.15-1.96 (m, 4H), 1.83-1.77 (m, 6H), 1.54 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1093.7 $(M+H)^+$.



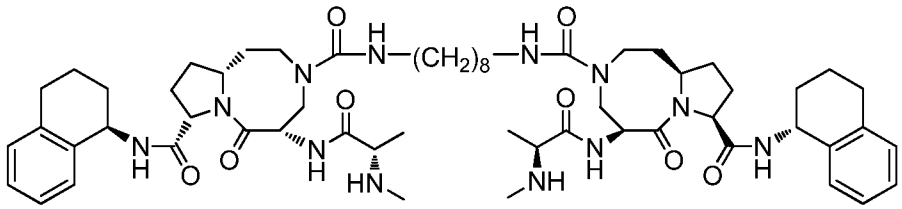
Example 22

[0166] ^{1}H NMR (300 MHz, CD_3OD): δ 7.34-7.23 (m, 20H), 6.14 (s, 2H), 4.92 (m, 2H), 4.70 (m, 4H), 4.08-3.86 (m, 8H), 3.59 (m, 2H), 3.16-3.05 (m, 4H), 2.70 (s, 6H), 2.36 (m, 2H), 2.10-1.92 (m, 10H), 1.79-1.71 (m, 4H), 1.60-1.40 (m, 8H), 1.40-1.25 (m, 2H); ESI MS: *m/z* 1121.7 $(M+H)^+$.



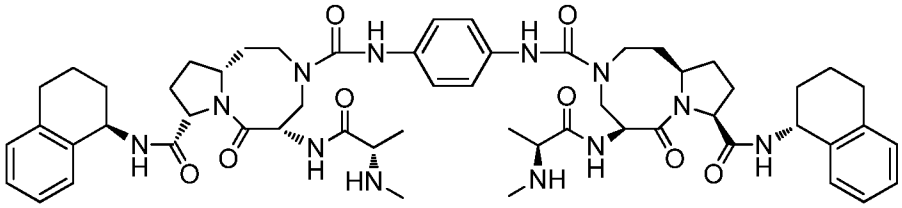
Example 23

[0167] ^{1}H NMR (300 MHz, CD_3OD): δ 7.27-7.02 (m, 28H), 6.12 (m, 2H), 5.07-4.97 (m, 2H), 4.60 (m, 2H), 4.39 (m, 2H), 3.89-3.85 (m, 4H), 3.73-3.54 (m, 6H), 2.66 (s, 6H), 2.31 (m, 2H), 2.11-1.81 (m, 10H),1.65 (m, 6H) 1.56 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1236.2 $(M+H)^+$.



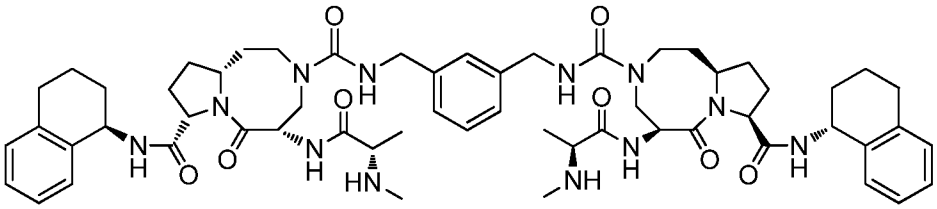
Example 4

[0168] ^{1}H NMR (300 MHz, CD_3OD): δ 7.40 (m, 2H), 7.14-7.06 (m, 6H), 5.06 (m, 2H), 4.84 (m, 2H), 4.72 (m, 2H), 4.50 (t, *J*= 8.4 Hz, 2H), 4.12 (m, 2H), 4.02-3.93 (m, 6H), 3.27-3.10 (m, 6H), 2.80 (m, 4H), 2.67 (s, 6H), 2.34 (m, 2H), 2.14-1.90 (m, 10H), 1.81-1.72 (m, 8H), 1.58 (m, 4H), 1.53 (d, *J*= 6.9 Hz, m, 6H), 1.35 (m, 8H); ESI MS: *m/z* 1151.8 $(M+H)^+$.



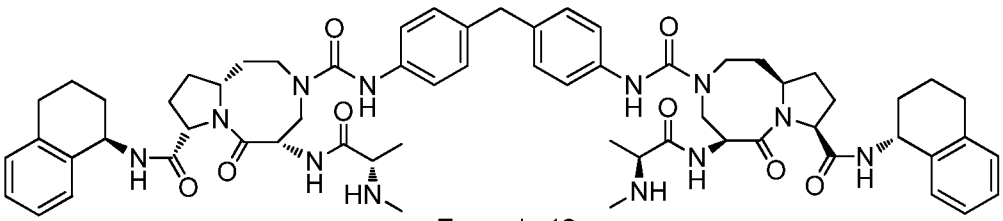
Example 5

[0169] ^{1}H NMR (300 MHz, CD_3OD): δ 7.55 (s, 4H),7.43 (m, 2H), 7.17-7.07 (m, 6H), 5.09 (m, 2H), 4.83 (m, 2H), 4.52 (t, *J*= 8.4 Hz, 2H), 4.25 (m, 2H), 4.16-4.05 (m, 6H), 3.39-3.34 (m, 4H), 2.81 (m, 4H), 2.73 (s, 6H), 2.32 (m, 4H), 2.05-1.93 (m, 8H), 1.82-1.74 (m, 8H), 1.57 (d, *J*= 6.9 Hz, m, 6H); ESI MS: *m/z* 1044.0 $(M+H)^+$.



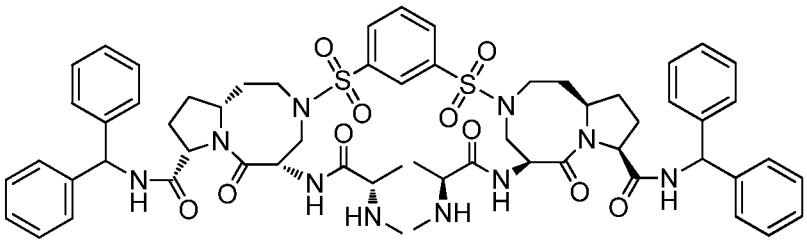
Example 6

[0170] ^{1}H NMR (300 MHz, CD_3OD): δ 7.38-7.09 (m, 12H), 5.03 (m, 2H), 4.85 (m, 2H), 4.78 (m, 2H), 4.60 (m, 2H), 4.55 (t, *J*= 8.4 Hz, 2H), 4.35-4.17 (m, 4H), 4.05-3.92 (m, 6H), 3.61 (m, 2H), 2.80 (m, 4H), 2.66 (s, 6H), 2.31 (m, 2H), 2.15-1.91 (m, 10H), 1.78-1.72 (m, 8H), 1.51 (d, *J*= 6.9 Hz, m, 6H); ESI MS: *m/z* 1071.63 $(M+H)^+$.



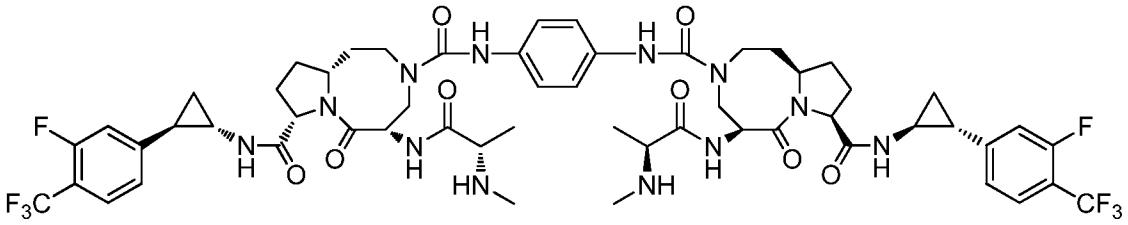
Example 12

[0171] ^{1}H NMR (300 MHz, CD_3OD): δ 7.51 (d, *J* = 8.4 Hz, 4H), 7.43 (m, 2H), 7.14-7.07 (m, 10H), 5.08 (m, 2H), 4.82 (m, 2H), 4.51 (t, *J* = 8.4 Hz, 2H), 4.28 (m, 2H), 4.15-4.04 (m, 6H), 3.89 (s, 2H), 3.38-3.33 (m, 4H), 2.87 (m, 4H), 2.71 (s, 6H), 2.31 (m, 2H), 2.10-1.73 (m, 18H), 1.56 (d, *J* = 6.9 Hz, m, 6H); ESI MS: *m/z* 1134.1 $(M+H)^+$.



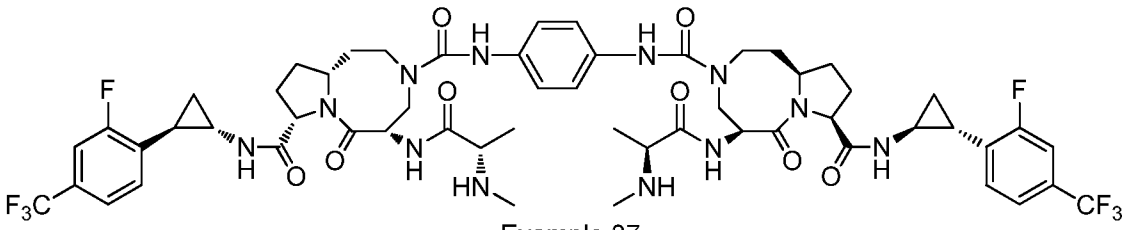
Example 24

[0172] ^{1}H NMR (300 MHz, CD_3OD): δ 8.21 (m, 3H), 7.85 (m, 1H), 7.34-7.18 (m, 20H), 6.10 (s, 2H), 4.85 (m, 2H), 4.58 (t, *J*=8.4 Hz, 2H), 4.31 (m, 2H), 3.93 (m, 4H), 3.73 (m, 2H), 3.21 (m, 2H), 2.96 (m, 2H), 2.67 (s, 6H), 2.33 (m, 2H), 2.06-1.93 (m, 6H), 1.84-1.76 (m, 4H), 1.51 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1157.6 $(M+H)^+$.



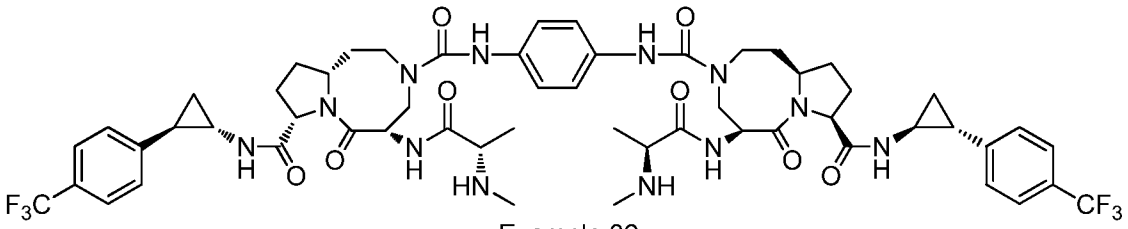
Example 38

[0173] ^{1}H NMR (300 MHz, D_2O): δ 7.50-6.70 (m, 10H), 4.90 (m, 2H), 4.70 (m, 2H), 4.45-4.10 (m, 4H), 3.95-3.40 (m, 10H), 2.60 (m, 2H), 2.55 (s, 6H), 2.30-1.60 (m, 12 H), 1.45 (brd, J = 7.0 Hz, 6H), 1.40-1.05 (m, 4H); ESI MS: *m/z* 1187.3 $(M+H)^+$.



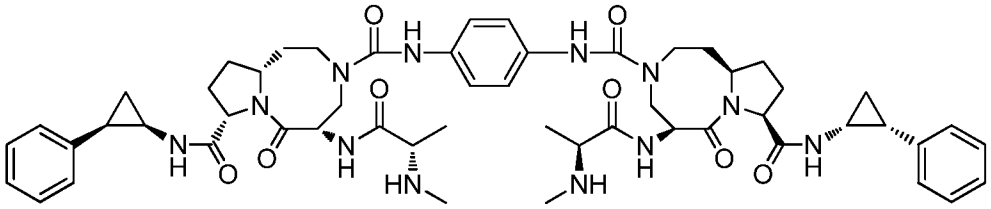
Example 37

[0174] ^{1}H NMR (300 MHz, D_2O): δ 7.50-6.70 (m, 10H), 4.92 (m, 2H), 4.80 (m, 2H), 4.45-4.20 (m, 4H), 3.95 (m, 2H), 3.80-3.40 (m, 8H), 2.60 (m, 2H), 2.55 (s, 6H), 2.30-1.60 (m, 12 H), 1.45 (brd, *J* = 7.0 Hz, 6H), 1.40-1.05 (m, 4H); ESI MS: *m/z* 1187.3 $(M+H)^+$.



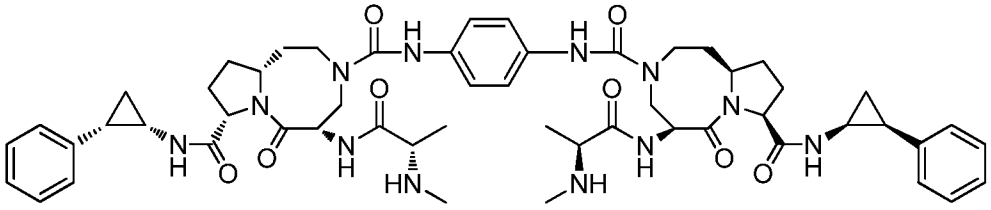
Example 36

[0175] ^{1}H NMR (300 MHz, D_2O): δ 7.65-7.45 (m, 4H), 7.35-6.90 (m, 8H), 5.05 (m, 2H), 4.80 (m, 2H), 4.50-4.30 (m, 4H), 4.05 (m, 2H), 3.90-3.40 (m, 8H), 2.60 (m, 2H), 2.50 (s, 6H), 2.40-1.60 (m, 12 H), 1.45 (brd, *J* = 7.0 Hz, 6H), 1.40-1.05 (m, 4H); ESI MS: *m/z* 1151.2 $(M+H)^+$.



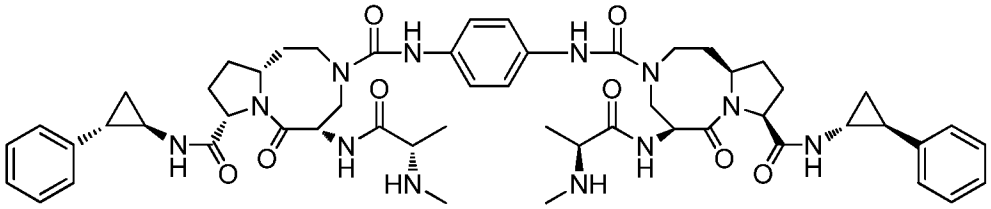
Example 26

[0176] ^{1}H NMR (300 MHz, D_2O): δ 7.35-7.05 (m, 14H), 4.75 (m, 2H), 4.20-3.90 (m, 4H), 3.90-3.65 (m, 6H), 3.35-3.10 (m, 4H), 2.90 (m, 2H), 2.60 (s, 6H), 2.30 (m, 2H), 2.05-1.55 (m, 8H), 1.45 (brd, J = 7.2 Hz, 6H), 1.40-1.05 (m, 6H), 0.80 (m, 2H); ESI MS: *m/z* 1015.5 $(M+H)^+$.



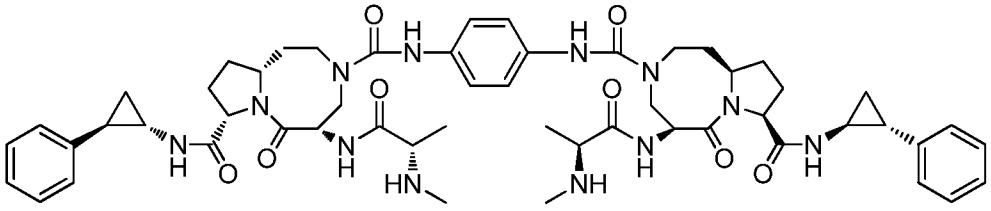
Example 27

[0177] ^{1}H NMR (300 MHz, D_2O): δ 7.35-7.05 (m, 14H), 4.75 (m, 2H), 4.30-3.95 (m, 4H), 3.95-3.65 (m, 6H), 3.40-3.10 (m, 4H), 2.90 (m, 2H), 2.60 (s, 6H), 2.25 (m, 2H), 2.05-1.55 (m, 8H), 1.45 (brd, J = 7.2 Hz, 6H), 1.40-1.05 (m, 6H), 0.80 (m, 2H); ESI MS: *m/z* 1015.5 $(M+H)^+$.



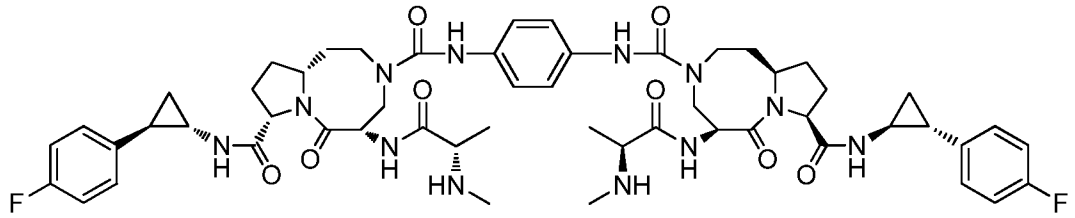
Example 30

[0178] ^{1}H NMR (300 MHz, CD_3OD): δ 7.60 (s, 4H), 7.30-7.10 (m, 10H), 4.80 (m, 2H), 4.45 (m, 2H), 4.25 (m, 2H), 4.20-4.02 (m, 6H), 3.50-3.30 (m, 4H), 2.95 (m, 2H), 2.70 (s, 6H), 2.40-2.05 (m, 10H), 1.90-1.70 (m, 4H), 1.55 (d, J = 7.2 Hz, 6H), 1.30-1.10 (m, 4H); ESI MS: *m/z* 1015.5 $(M+H)^+$.



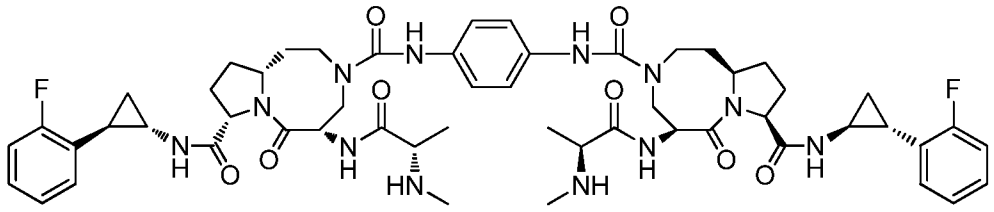
Example 31

[0179] ^{1}H NMR (300 MHz, CD_3OD) : δ 7.60 (s, 4H), 7.30-7.10 (m, 10H), 4.80 (m, 2H), 4.45 (m, 2H), 4.30 (m, 2H), 4.20-4.02 (m, 6H), 3.50-3.30 (m, 4H), 2.90 (m, 2H), 2.70 (s, 6H), 2.35-2.05 (m, 10H), 1.90-1.70 (m, 4H), 1.55 (d, J = 7.2 Hz, 6H), 1.30-1.10 (m, 4H); ESI MS: *m/z* 1015.5 $(M+H)^+$.



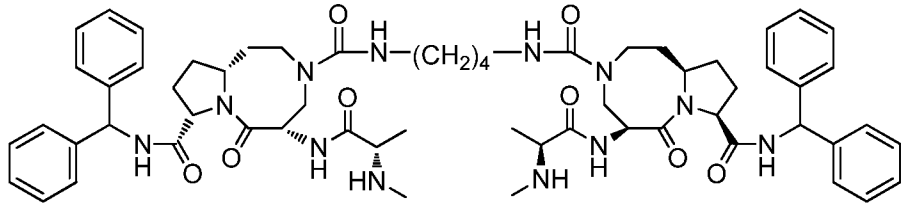
Example 29

[0180] ^{1}H NMR (300 MHz, D_2O): δ 7.30-6.90 (m, 12H), 4.90 (m, 2H), 4.70 (m, 2H), 4.40-4.20 (m, 4H), 3.95 (m, 2H), 3.90-3.30 (m, 8H), 2.65 (m, 2H), 2.60 (s, 6H), 2.30-1.75 (m, 12H), 2.50 (d, J = 7.0 Hz, 6H), 1.20 (m, 4H); ESI MS: *m/z* 1051.2 $(M+H)^+$.



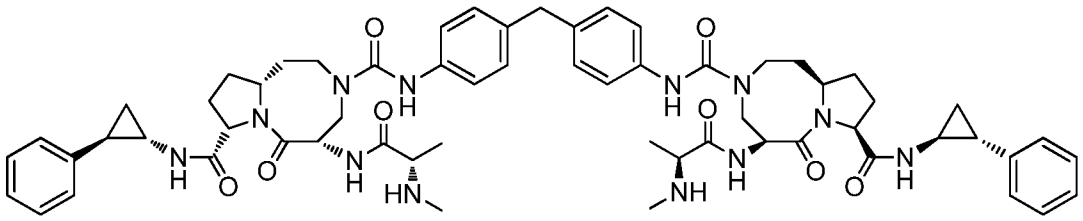
Example 28

[0181] ^{1}H NMR (300 MHz, CD_3OD) : δ 7.30-6.80 (m, 12H), 4.85 (m, 2H), 4.70 (m, 2H), 4.30-4.20 (m, 4H), 4.05-3.60 (m, 6H), 3.50-3.30 (m, 4H), 2.65 (m, 2H), 2.55 (s, 6H), 2.30-1.70 (m, 12H), 2.50 (d, J = 7.0 Hz, 6H), 1.20 (m, 4H); ESI MS: *m/z* 1051.2 $(M+H)^+$.



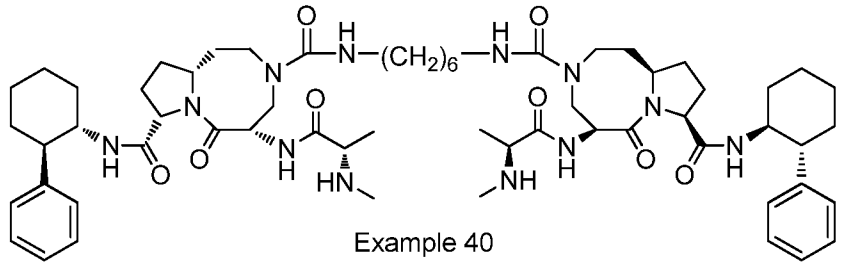
Example 25

[0182] ^{1}H NMR (300 MHz, D_2O) : δ 7.40-7.20 (m, 10H), 5.99 (s, 2H), 4.75 (m, 2H), 4.45 (m, 2H), 4.10 (m, 2H), 3.95 (m, 2H), 3.80 (m, 2H), 3.65 (m, 2H), 3.25-3.05 (m, 8H), 2.62 (m, 6H), 2.30 (m, 2H), 2.20-1.70 (m, 12H), 1.45 (m, 2H), 1.40 (d, J = 7.2 Hz, 6H); ESI MS: *m/z* 1095.4 $(M+H)^+$.



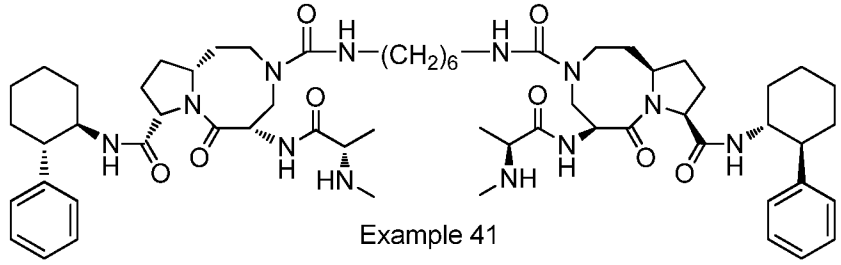
Example 39

[0183] ^{1}H NMR (300 MHz, CD_3OD): δ 7.48-7.08 (m, 18H), 4.92 (m, 2H), 4.42 (m, 2H), 4.21-4.03 (m, 8H), 3.87 (m, 2H), 3.36-3.20 (m, 4H), 2.85 (m, 2H), 2.70 (s, 6H), 2.30-2.02 (m, 10H), 1.76 (m, 4H), 1.56 (d, J = 6.9Hz, 6H), 1.23 (m, 4H); ESI MS: m/z 1105.4 $(M+H)^+$.



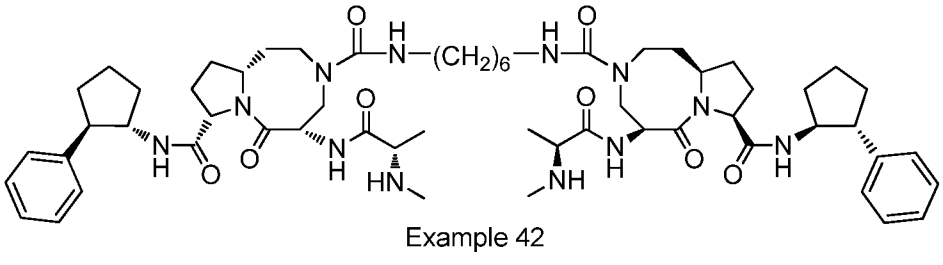
Example 40

[0184] ^{1}H NMR (300 MHz, CD_3OD) δ 7.35-7.15 (m, 10H), 4.84 (m, 2H), 4.40-3.90 (m, 8H), 3.75-3.50 (m, 6H), 3.40-3.20 (m, 8H), 2.71 (s, 6H), 2.65 (m, 2H), 1.90-1.43 (m, 42H); ESI MS: m/z 1107.9 $(M+H)^+$.



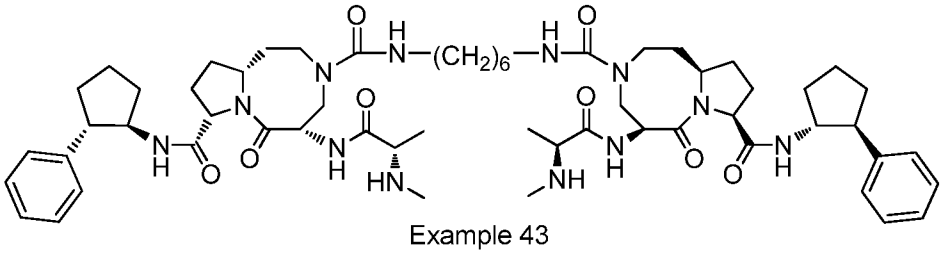
Example 41

[0185] ^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.20 (m, 10H), 4.84 (m, 2H), 4.61 (d, J = 9.0Hz, 2H), 4.20 (t, J = 9.0Hz, 2H), 3.97-3.81(m, 10H), 3.30-2.95 (m, 6H), 2.68 (s, 6H), 2.51 (m, 2H), 2.01-1.31 (m, 42H); ESI MS: m/z 1107.6 $(M+H)^+$.



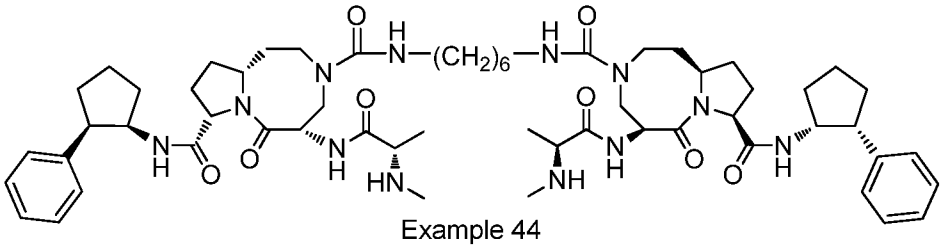
Example 42

[0186] ^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.10 (m, 10H), 4.84 (m, 2H), 4.66 (m, 2H), 4.43 (m, 2H), 4.22 (m, 2H), 4.04-3.72 (m, 8H), 3.10-2.85 (m, 6H), 2.68 (s, 6H), 2.24-1.37 (m, 40H); ESI MS: m/z 1079.5$(M+H)^+$.



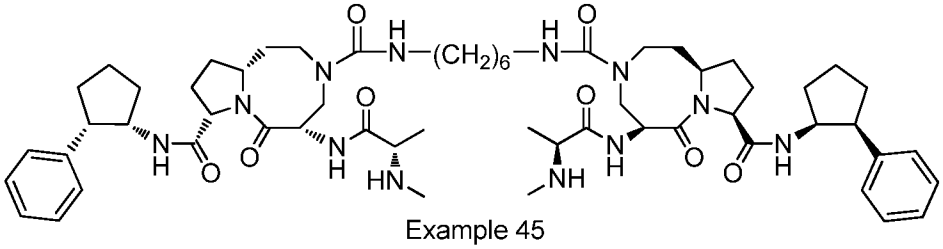
Example 43

[0187] ^{1}H NMR (300 MHz, CD_3CD): δ 7.35-7.15 (m, 10H), 4.81 (m, 2H), 4.65 (m, 2H), 4.35 (m, 2H), 4.22 (m, 2H), 3.98-3.80 (m, 8H), 3.25-2.87 (m, 6H), 2.68 (s, 6H), 2.20-1.33 (m, 40H); ESI MS: *m/z* 1079.9 $(M+H)^+$.



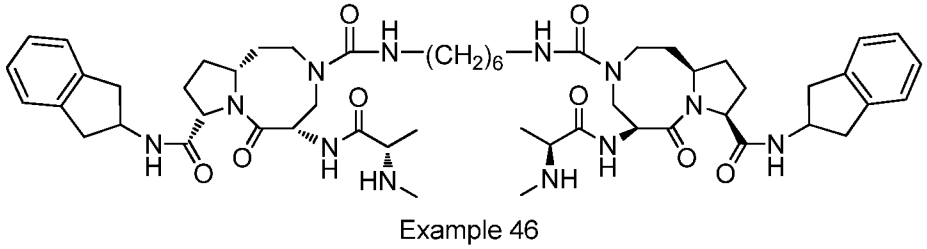
Example 44

[0188] ^{1}H NMR (300 MHz, CD_3OD): δ 7.30-7.10 (m, 10H), 4.84 (m, 2H), 4.61 (m, 4H), 4.24 (t, J = 9.0Hz, 2H), 3.97-3.81(m, 8H), 3.41-3.02 (m, 6H), 2.64 (s, 6H), 2.17-1.37 (m, 40H); ESI MS: *m/z* 1079.3 $(M+H)^+$.



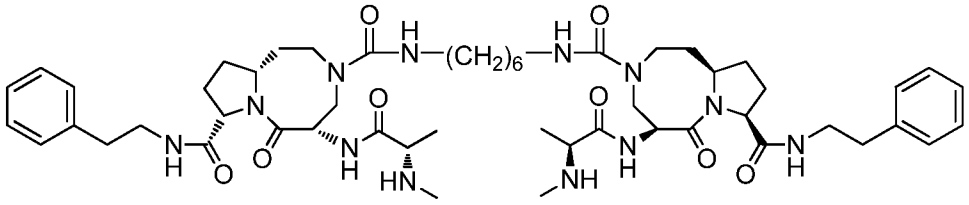
Example 45

[0189] ^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.10 (m, 10H), 4.84 (m, 2H), 4.67-4.24 (m, 6H), 3.97-3.81(m, 8H), 3.41-3.02 (m, 6H), 2.68 (s, 6H), 2.17-1.37 (m, 40H); ESI MS: *m/z* 1079.5 $(M+H)^+$.



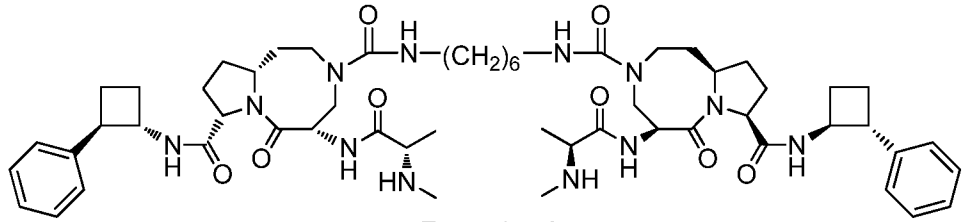
Example 46

[0190] ^{1}H NMR (300 MHz, CD_3OD): δ 7.19-7.11 (m, 8H), 4.84 (m, 2H), 4.70 (m, 2H), 4.57 (m, 2H), 4.42 (m, 2H), 4.10 (m, 2H), 4.00 (m, 6H), 3.22-3.06 (m, 6H), 2.92-2.75 (m, 4H), 2.66 (s, 6H), 2.26-1.37 (m, 30H); ESI MS: *m/z* 1023.7 $(M+H)^+$.



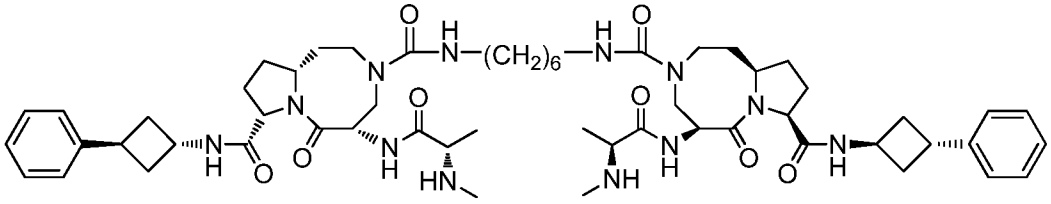
Example 47

[0191] ^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.15 (m, 10H), 4.84 (m, 2H), 4.71 (m, 2H), 4.41 (m, 2H), 4.11 (m, 2H), 3.98-3.88 (m, 6H), 3.48-3.08 (m, 10H), 2.82 (m, 4H), 2.69 (s, 6H), 2.22-1.39 (m, 26H); ESI MS: *m/z* 999.7 $(M+H)^+$.



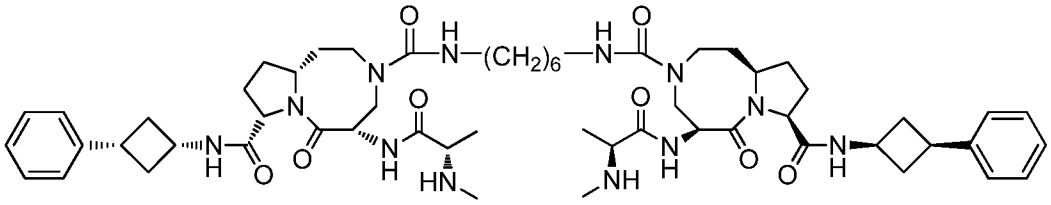
Example 48

[0192] ^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.15 (m, 10H), 4.84 (m, 2H), 4.69 (m, 2H), 4.50-4.30 (m, 4H), 4.11-3.86 (m, 8H), 3.48 (m, 2H), 3.25-3.06 (m, 6H), 2.68 (s, 6H), 2.31-1.28 (m, 34H); ESI MS: *m/z* 1051.4 $(M+H)^+$.



Example 49

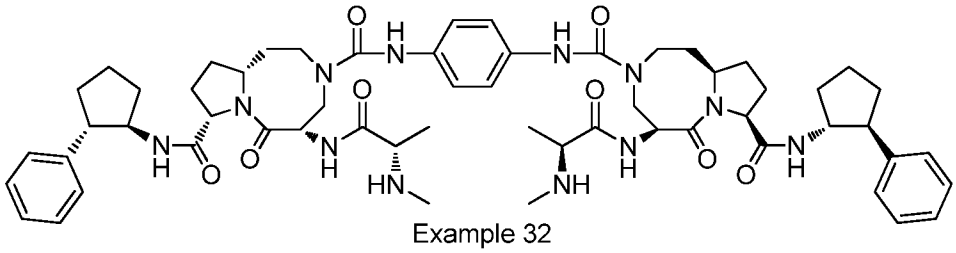
[0193] ^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.10 (m, 10H), 4.82 (m, 2H), 4.70 (d, *J* = 8.4Hz, 2H), 4.43-4.34 (m, 4H), 4.12 (m, 2H), 4.01-3.90 (m, 6H), 3.65 (m, 2H), 3.25-3.06 (m, 6H), 2.67 (s, 6H), 2.52- 2.34 (m, 10H), 2.10 (m, 6H), 1.80-1.39 (18H); ESI MS: *m/z* 1051.9 $(M+H)^+$.



Example 50

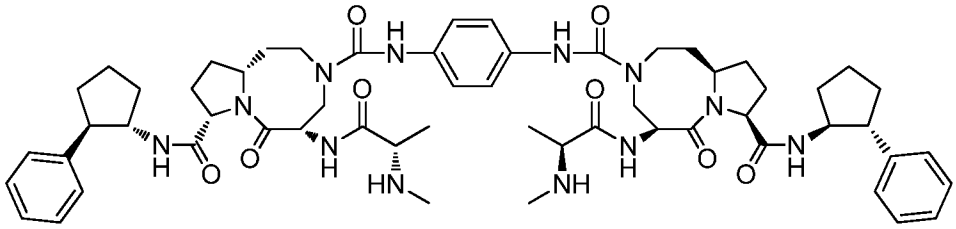
[0194] ^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.15 (m, 10H), 4.82 (m, 2H), 4.70 (d, *J* = 9.0Hz, 2H), 4.43- 4.28 (m, 4H), 4.12 (m, 2H), 4.01-3.90 (m, 6H), 3.25-3.06 (m, 6H), 2.77 (m,

2H), 2.70 (s, 6H), 2.51 (m, 2H), 2.30 (m, 2H), 2.20-1.90 (m, 10H), 1.90-1.45 (m, 16H), 1.45-1.35 (m, 4H); ESI MS: *m/z* 1051.7$(M+H)^+$.



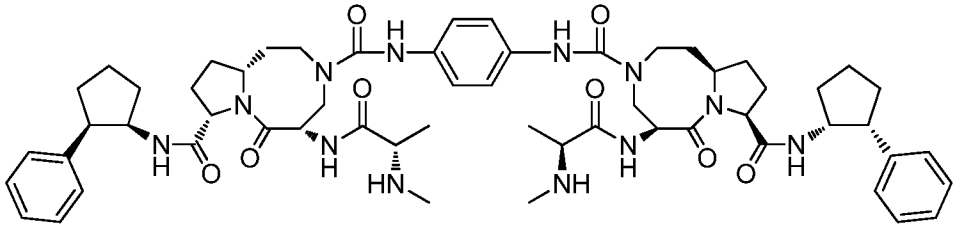
Example 32

[0195] ^{1}H NMR (300 MHz, D_2O): δ 7.35-7.10 (m, 14H), 4.80 (m, 2H), 4.40-4.25 (m, 4H), 4.20 (m, 2H), 4.15-4.05 (m, 4H), 3.90 (m, 2H), 3.40-3.30 (m, 4H), 2.90 (m, 2H), 2.70 (s, 6H), 2.30-1.90 (m, 10H), 1.90-1.55 (m, 14H), 1.55 (d, J = 7.2 Hz, 6H); ESI MS: *m/z* 1071.5 $(M+H)^+$.



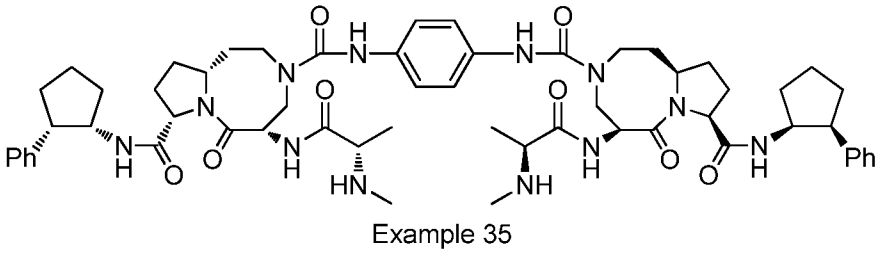
Example 33

[0196] ^{1}H NMR (300 MHz, D_2O): δ 7.35-7.10 (m, 14H), 4.75 (m, 2H), 4.40-4.25 (m, 4H), 4.20 (m, 2H), 4.15-4.05 (m, 4H), 3.90 (m, 2H), 3.40-3.30 (m, 4H), 2.90 (m, 2H), 2.70 (s, 6H), 2.30-1.90 (m, 10H), 1.90-1.35 (m, 20H); ESI MS: *m/z* 1071.7 $(M+H)^+$.



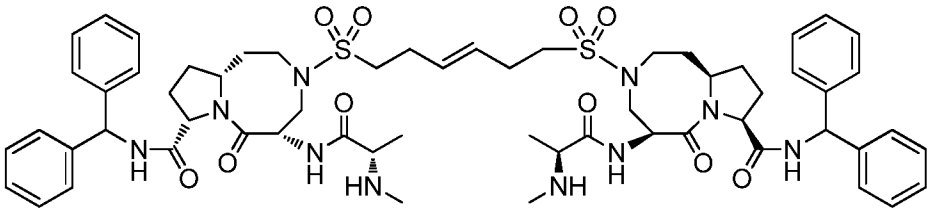
Example 34

[0197] ^{1}H NMR (300 MHz, D_2O): δ 7.35-7.10 (m, 14H), 4.80 (m, 2H), 4.40 (m, 2H), 4.25-4.05 (m, 4H), 4.05-3.85 (m, 4H), 3.80 (m, 2H), 3.30-3.15 (m, 6H), 2.70 (s, 6H), 2.30-1.60 (m, 24H), 1.55 (d, J = 7.2 Hz, 6H); ESI MS: *m/z* 1071.7 $(M+H)^+$.



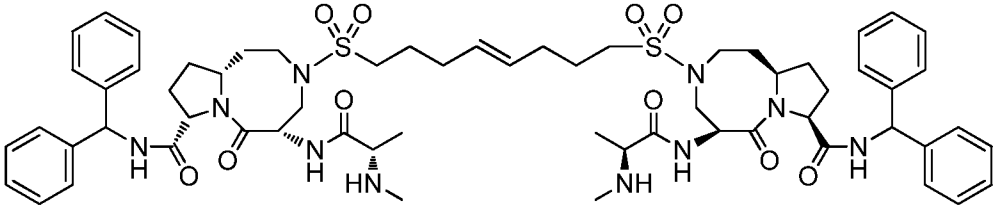
Example 35

[0198] ^{1}H NMR (300 MHz, D_2O): δ 7.35-7.10 (m, 14H), 4.80 (m, 2H), 4.45 (m, 2H), 4.20-3.90 (m, 6H), 3.80 (m, 2H), 3.30-3.20 (m, 6H), 2.70 (s, 6H), 2.30-1.60 (m, 24H), 1.55 (d, J = 7.2 Hz, 6H); ESI MS: *m/z* 1071.7 $(M+H)^+$.



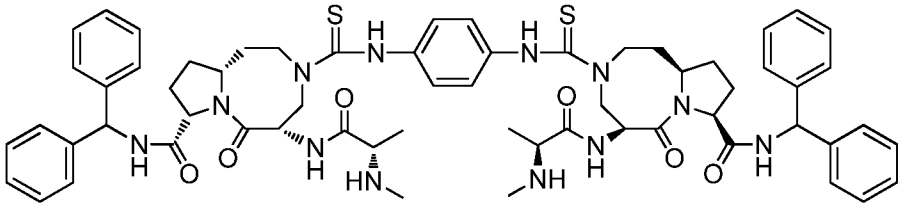
Example 7

[0199] ^{1}H NMR (300 MHz, CD_3OD): δ 7.40-7.20 (m, 20H), 6.15 (m, 2H), 5.60 (m, 2H), 4.85 (m, 2H), 4.55 (m, 2H), 4.40 (m, 2H), 3.95-3.80 (m, 4H), 3.65 (m, 2H), 3.35-2.05 (m, 6H), 2.65 (s, 6H), 2.45-1.70 (m, 16H), 1.55 (d, J = 7.2 Hz, 6H); ESI MS: *m/z* 1162.5 $(M+H)^+$.



Example 8

[0200] ^{1}H NMR (300 MHz, CD_3OD): δ 7.40-7.20 (m, 20H), 6.15 (m, 2H), 5.45 (m, 2H), 4.82 (m, 2H), 4.55 (m, 2H), 4.40 (m, 2H), 3.95-3.72 (m, 4H), 3.65 (m, 2H), 3.35-2.95 (m, 6H), 2.65 (s, 6H), 2.45-1.70 (m, 20H), 1.55 (d, J = 7.2 Hz, 6H); ESI MS: *m/z* 1190.6 $(M+H)^+$.



Example 17

[0201] ESI MS: *m/z* 1147.6 $(M+H)^+$.

Binding Affinities to XIAP linker-BIR2-BIR3, cIAP1-BIR3, and cIAP-2 BIR2

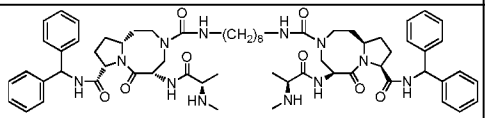
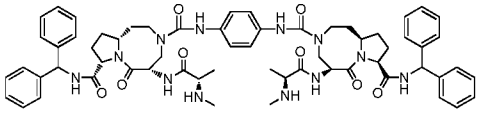
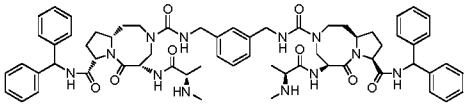
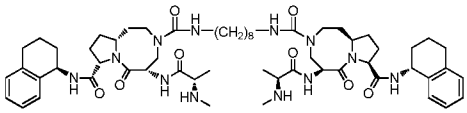
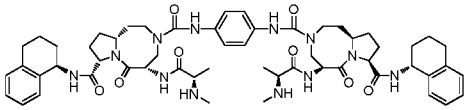
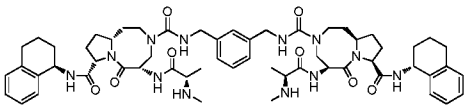
[0202] Binding affinities of the present compounds to XIAP linker-BIR2-BIR3 (residues 120-356), cIAP1-BIR3 (residues 253-363), and cIAP-2 BIR3 (residues 238-349) proteins were determined by fluorescence polarization (FP) based competitive assays. For cIAP-1 BIR3 and cIAP-2 BIR3 assays, a fluorescently labeled Smac mimetic (Smac-2F) was used as the fluorescent probe. The K_d values of Smac-2F to cIAP-1 BIR3 and cIAP-2 BIR3 were determined by monitoring the total fluorescence polarization of mixtures composed with the

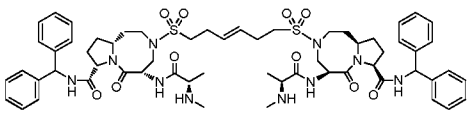
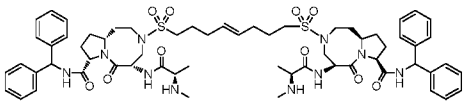
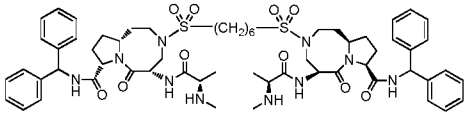
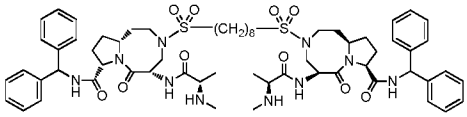
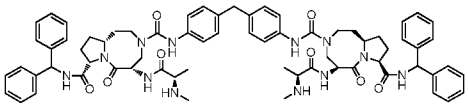
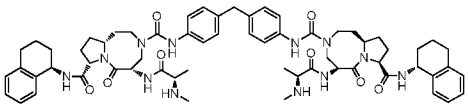
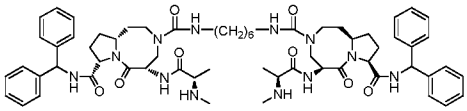
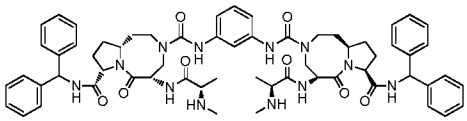
fluorescent probe at a fixed concentration and proteins with increasing concentrations up to full saturation. Fluorescence polarization values were measured using the Infinite M-1000 plate reader (Tecan U.S., Research Triangle Park, NC) in Microfluor 2 96-well, black, round-bottom plates (Thermo Scientific). To each well, 1nM of SMAC-2F and increasing concentrations of protein 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 incubated at room temperature for 1-2 hours and mixed 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).

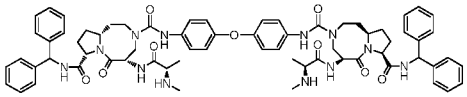
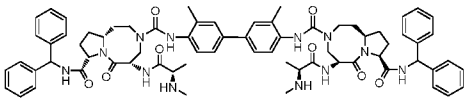
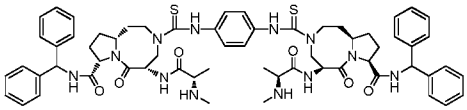
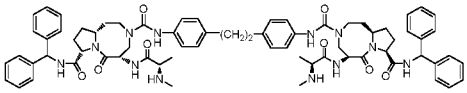
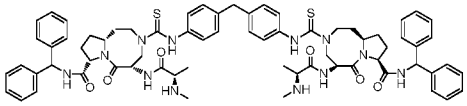
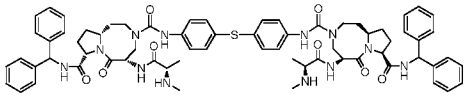
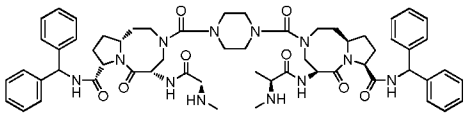
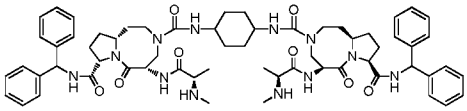
[0203] The K_i values of compounds were determined through a compound dose-dependent competitive binding experiment in which serial dilutions of compounds competed against fixed concentration of the fluorescent probe for binding to a fixed concentration of the protein (typically 2 to 3 times the K_d values determined above). Mixtures of 5 μl of the tested compounds in DMSO and 120 μl of preincubated protein/tracer complex in the assay buffer (100mM potassium phosphate, pH 7.5, 100 μg/ml bovine γ-globulin, 0.02% sodium azide, Invitrogen) were added into assay plates and incubated at room temperature for 2 hours with gentle shaking. Final concentrations of proteins and probes were 3nM and 1nM, 5nM and 1nM for assays for cIAP-1 BIR3 and cIAP-2 BIR3, respectively. Negative controls containing protein/probe complex only (equivalent to 0% inhibition), and positive controls containing only free probes (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 derived equation described previously, based upon the measured IC_{50} values, the K_d values of the probe to different proteins, and the concentrations of the proteins and probes in the competitive assays.

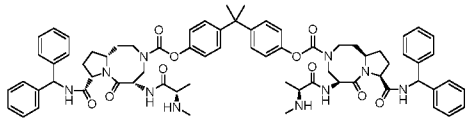
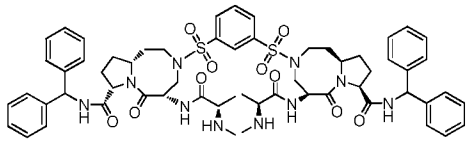
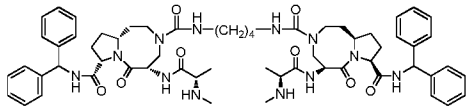
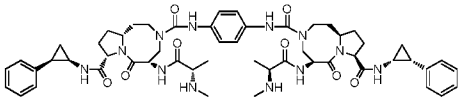
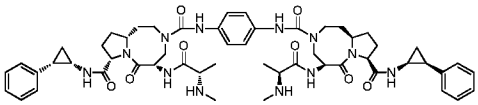
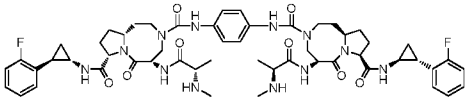
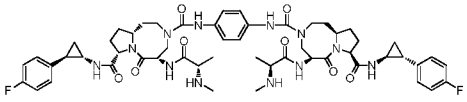
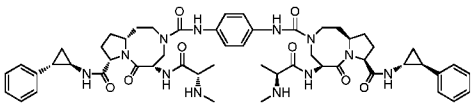
[0204] The FP-based assay for XIAP linker-BIR2-BIR3 protein was performed with the same procedures. In this assay, a bivalent fluorescently tagged peptidic Smac mimetic (Smac-1F) was used as the fluorescent probe whose K_d value to XIAP linker-BIR2-BIR3 was determined similarly through the saturation experiments. 0.01% of Triton X-100 was added in the assay buffer to achieve stable fluorescence and polarization value of the dimeric

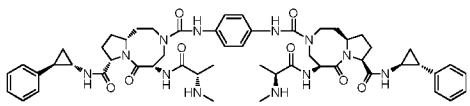
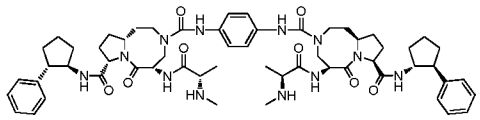
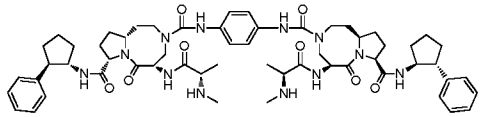
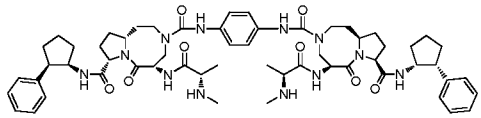
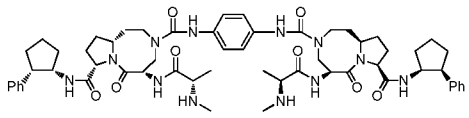
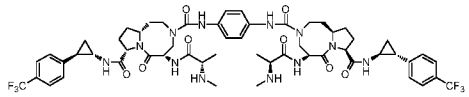
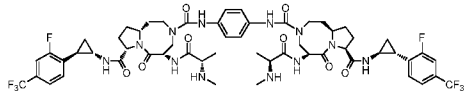
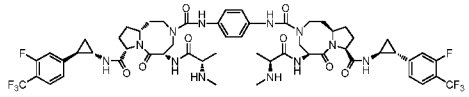
fluorescent probe. Final protein and probe concentrations utilized in the competitive assay were 3nM and 1nM, respectively.

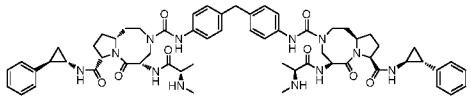
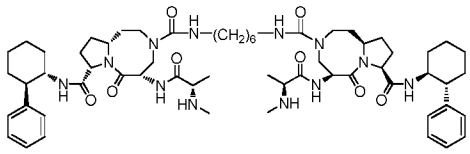
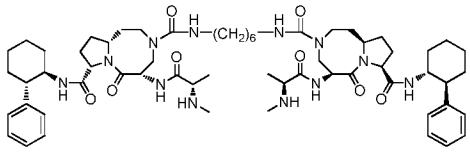
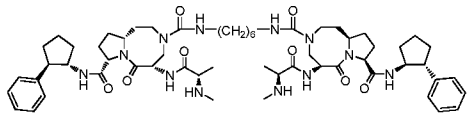
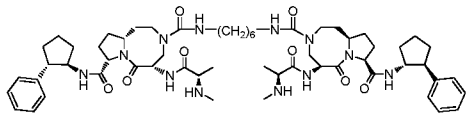
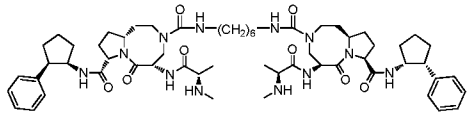
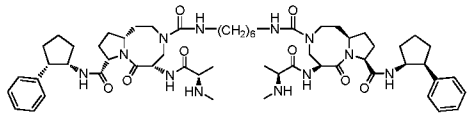
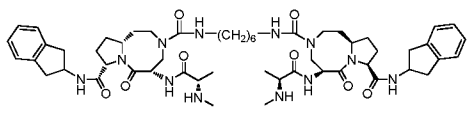
Example	Structures	Binding Affinities IC50 (nM)		
		XIAP Protein	cIAP1 Protein	cIAP2 Protein
1		<10	<300	<300
2		<10	<100	<100
3		<10	<100	<100
4		<10	<100	<100
5		<10	<100	<100
6		<10	<100	<100

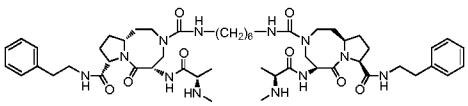
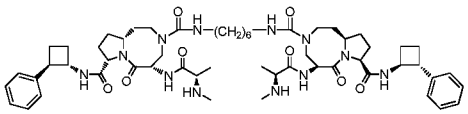
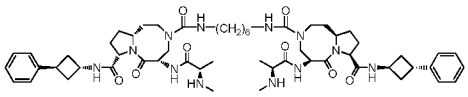
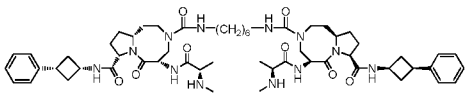
7		<10	<300	<300
8		<10	<100	<100
9		<10	<100	<100
10		<10	<100	<100
11		<10	<100	<100
12		<10	<100	<100
13		<30	<300	<300
14		<30	<300	<300

15		<30	<300	<300
16		<100	<300	<300
17		<30	<300	<300
18		<30	<300	<300
19		<30	<300	<300
20		<30	<100	<300
21		<30	<300	<300
22		<30	<300	<300

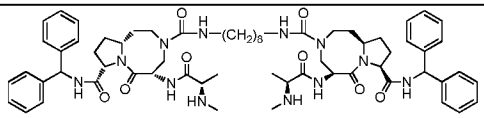
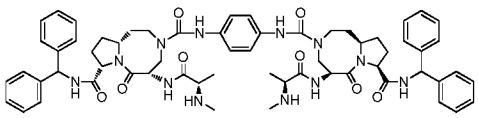
23		<30	<300	<300
24		<30	<300	<300
25		<30	<300	<300
26		<1000	<1000	<1000
27		<1000	<1000	<1000
28		<1000	<1000	<1000
29		<1000	<1000	<1000
30		<3000	<3000	<3000

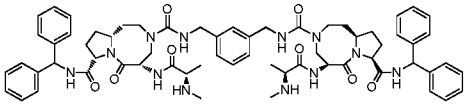
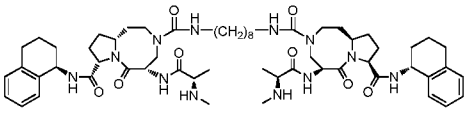
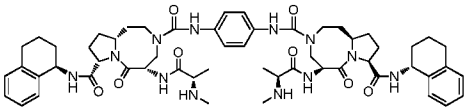
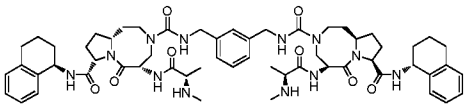
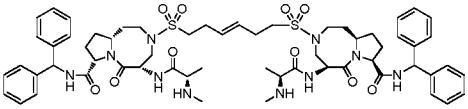
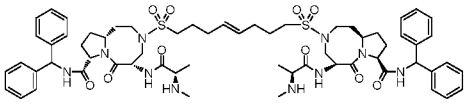
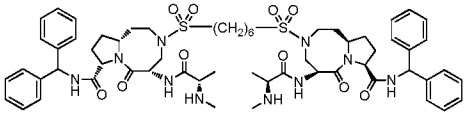
31		<1000	<1000	<1000
32		<3000	<3000	<3000
33		<3000	<3000	<3000
34		<1000	<1000	<1000
35		<1000	<1000	<1000
36		<3000	<3000	<3000
37		<3000	<3000	<3000
38		<3000	<3000	<3000

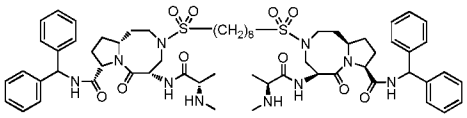
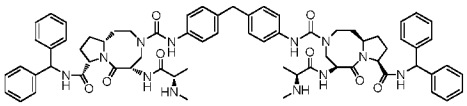
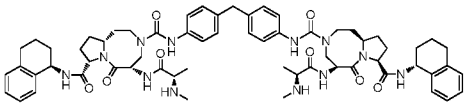
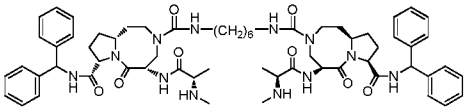
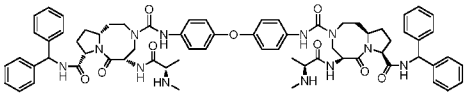
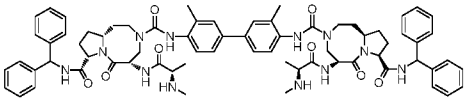
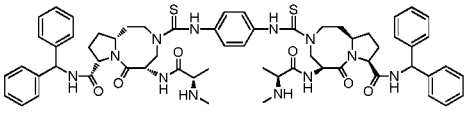
39		<1000	<3000	<3000
40		<3000	<3000	<3000
41		<5000	<5000	<5000
42		<1000	<1000	<3000
43		<3000	<3000	<3000
44		<1000	<1000	<3000
45		<1000	<3000	<3000
46		<1000	<10000	<5000

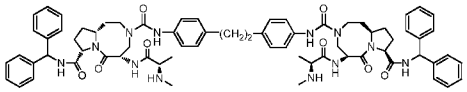
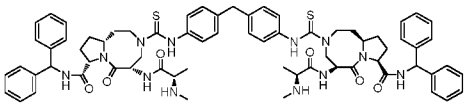
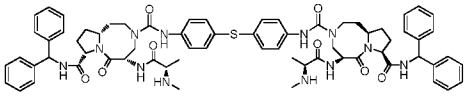
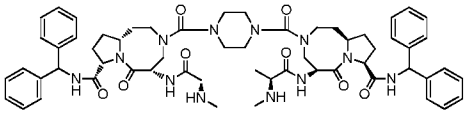
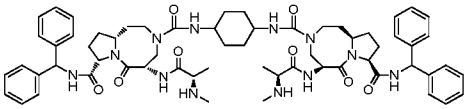
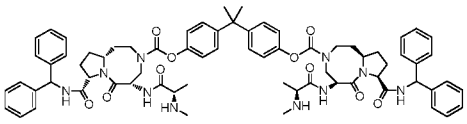
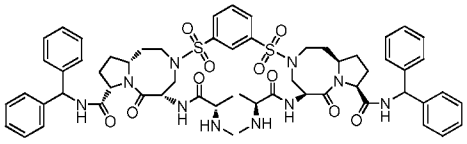
47		<1000	<1000	<5000
48		<1000	<1000	<1000
49		<1000	<1000	<5000
50		<1000	<1000	<1000

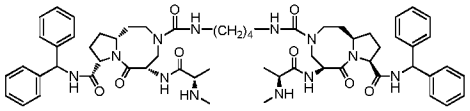
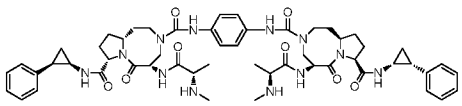
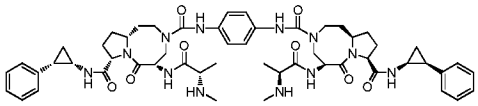
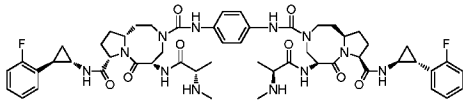
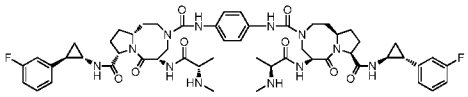
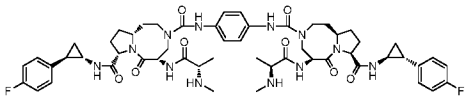
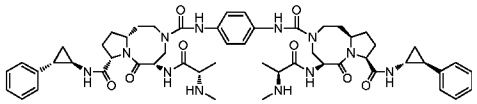
Inhibition of Cell Growth in MDA-MB-231
Breast Cancer and SK-OV-3 Ovarian Cancer Cell Line

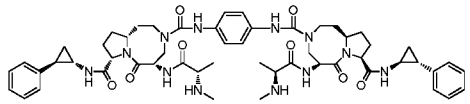
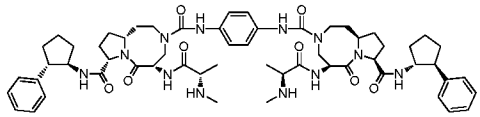
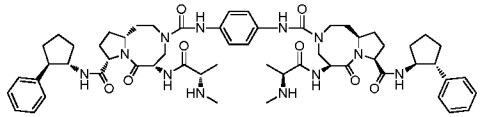
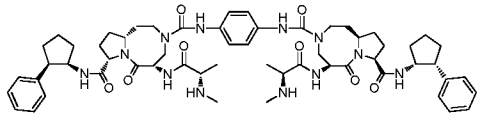
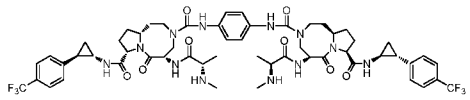
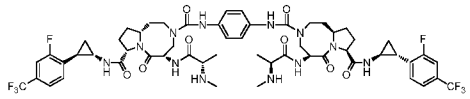
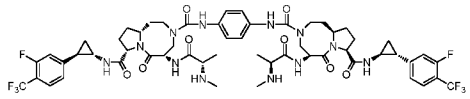
Example	Structures	Cell growth Inhibition (IC_{50}, nM)	
		MDA-MB-231 Cancer Cell Line	SK-OV-3 Cancer Cell Line
1		<100	<100
2		<100	<100

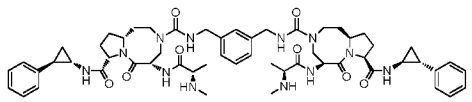
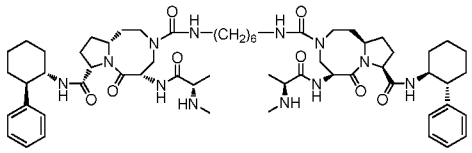
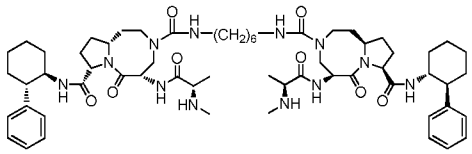
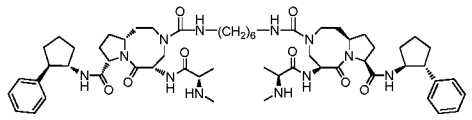
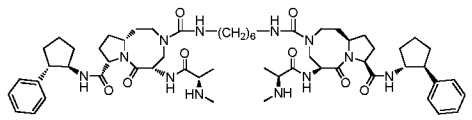
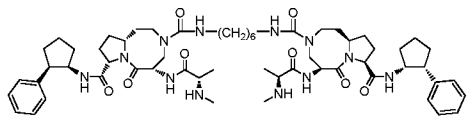
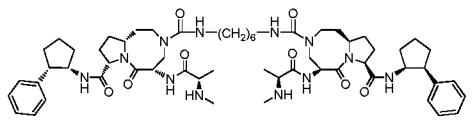
3		<100	<100
4		<100	<100
5		<100	<100
6		<100	<100
7		<1000	<1000
8		<1000	<1000
9		<1000	<1000

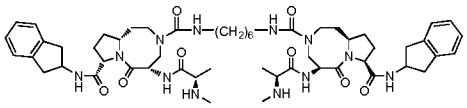
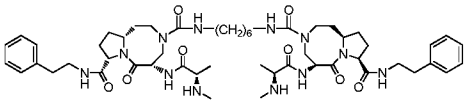
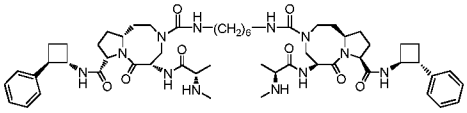
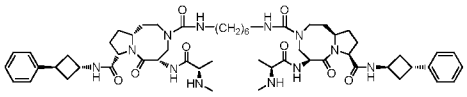
10		<1000	<1000
11		<100	<100
12		<100	<100
13		<100	<100
14		<1000	<1000
15		<1000	<1000
16		<100	Not tested

17		<100	Not tested
18		<100	Not tested
19		<1000	<1000
20		<10,000	<10,000
21		<1000	<1000
22		<100	<1000
23		<100	<100

24		<100	<100
25		<1000	<1000
26		<1000	<1000
27		<5000	<5000
28		Not tested	Not tested
29		<5000	<5000
30		<10,000	<10,000

31		<1000	<1000
32		<1000	<1000
33		<1000	<1000
34		<100	<100
35		<10,000	<10,000
36		<10,000	<10,000
37		<10,000	<10,000

38		<10,000	<10,000
39		>1000	>1000
40		>10,000	>10,000
41		>1000	>1000
42		>1000	>1000
43		>1000	>1000
44		>1000	>1000

45		>1000	>1000
46		>1000	>1000
47		>1000	>1000
48		>10,000	>10,000

[0205] Figure 1 shows the antitumor activity of Example 2 and Example 24 in the MDA-MB-231 xenograft model in nude mice. Treatments started when the tumors reached an average volume of 80 mm^3. Example 24 was given intravenously, weekly dose for 4 weeks (qwkx4, iv) at 10 mg/kg. Example 2 was given weekly dose for 4 weeks (qwkx4, iv) at 3 mg/kg. Control treatment was given vehicle control. Each group has 8-10 mice and each mouse has one tumor. Tumor regression was achieved for Examples 2 and 24.

REFERENCES

(1) D.W. Nicholson, *Nature* 2000, *407*, 810-816.

(2) B.A. *Ponder*, *Nature* 2001, *411*, 336-341.

(3) S.W. *Lowe* et al., *Carcinogenesis* 2000, *21*, 485-495.

(4) D. *Hanahan* et al., *Cell* 2000, *100*, 57-70.

(5) G. S. *Salvesen* et al., *Nat. Rev. Mol. Cell. Biol.* 2002, *3*, 401-410.

(6) Q. L. *Deveraux* et al., *Genes Dev.* 1999, *13*, 239-252.

(7) S.M. Srinivasula et al., *Mol. Cell* 2008, *30*, 123-135.

(8) M. Gyrd-Hansen et al., *Nat Rev Cancer*, 2010, *10*, 561-574.

(9) I. Tamm et al., *Clin Cancer Res.* 2000, *6*, 1796-1803.

(10) D. Vucic et al., *Clin Cancer Res.* 2007, *13*, 5995-6000.

(11) A. M. Hunter et al., *Apoptosis* 2007, *12*, 1543-1568.

(12) E. C. LaCasse et al., *Oncogene* 2008, *27*, 6252-6275.

(13) S. Fulda, *Expert Rev Anticancer Ther.* 2007, *7*, 1255–64.

(14) C. Du et al., *Cell* 2000, *102*, 33–42.

(15) A. M. Verhagen et al., *Cell* 2000, *102*, 43–53.

(16) G. Wu et al., *Nature* 2000, *408*, 1008–1012.

(17) Z. Liu et al., *Nature* 2000, *408*, 1004–1008.

(18) E. N. Shiozaki et al., *Trends Biochem. Sci.* 2004, *29*, 486-494.

(19) T. Samuel et al., *J. Biol. Chem.* 2006, 281, 1080-1090.

(20) Q. Yang et al., *J Biol Chem.* 2004, 279, 16963-16970.

(21) S. Wang, *Curr Top Microbiol Immunol.* 2011, *348*, 89-113.

(22) H. Sun et al., *Acc Chem Res.* 2008, *41*, 1264-1277.

(23) R. Mannhold et al., *Drug Discov Today.* 2010, 15, 210-219.

(24) L. Li et al., *Science* 2004, *305*, 1471-1474.

(25) T.K. Oost et al., *J. Med. Chem.* 2004, *47*, 4417–4426.

(26) H. Sun et al., *J. Am. Chem. Soc.* 2004, *126*, 16686-16697.

(27) H. Sun et al., *J. Med. Chem.* 2004, *47*, 4147-4150.

(28) H. Sun et al., *J. Med. Chem.* 2006, *49*, 7916-7920.

(29) K. Zobel et al., *ACS Chem. Biol.* 2006, *1*, 525–33.

(30) H. Sun et al., *J. Am. Chem. Soc.*, 2007, *129*, 15279–15294.

(31) J. Lu et al., *Cancer Res.* 2008, 68, 9384-9393.

(32) H. Sun et al., *J. Med. Chem.*, 2008, *51*, 7169–7180.

(33) Y. Peng et al., *J. Med. Chem.*, 2008, *51*, 8158–8162.

(34) B. Zhang et al., *J. Med. Chem.*, 2008, *51*, 7352–7355.

(35) W. Sun et al., *J. Med. Chem.*, 2009, *52*, 593–596.

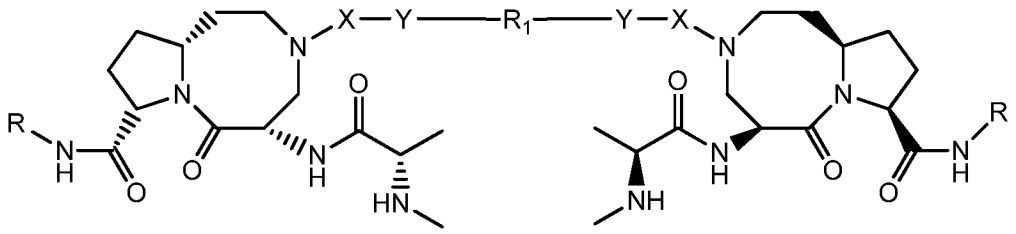
(36) H. Sun et al., *J. Med. Chem.*, 2010, *53* 6361–6367.

(37) Q. Cai et al., *J Med Chem.* 2011, 54, 2714-2726.

(38) H. Sun et al., *J Med Chem.* 2011, *54*, 3306-3318.

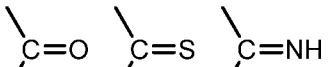
CLAIMS

1. A compound having a structure



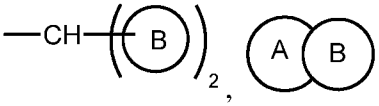
(I)

,

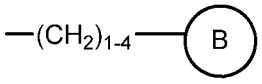
wherein X is selected from the group consisting of 

, and $-SO_2-$;

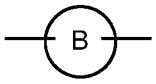
Y is selected from the group consisting of –NH-, -O-,–S-, and null;

R is selected from the group consisting of 

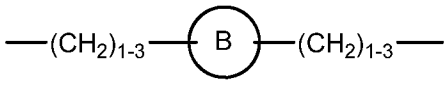
, wherein ring A is a C_{4-8} aliphatic ring, 

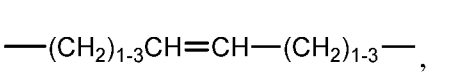
, and 

, wherein the B ring is aryl or nitrogen atom-containing heteroaryl and the B rings are optionally substituted; and

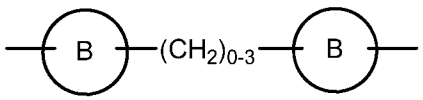
R_1 is selected from the group consisting of $–(CH_2)_{4-10}-$, 

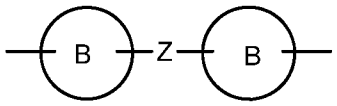
,



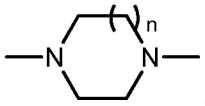
, 

,



, 

, wherein Z is O, S, or NH, and

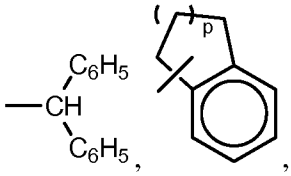
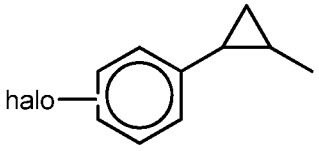
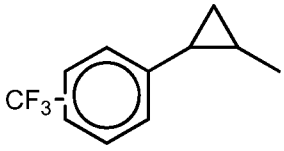
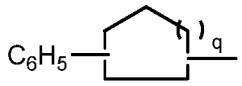


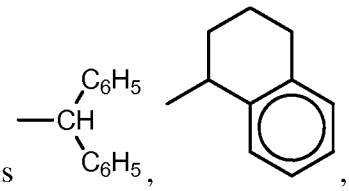
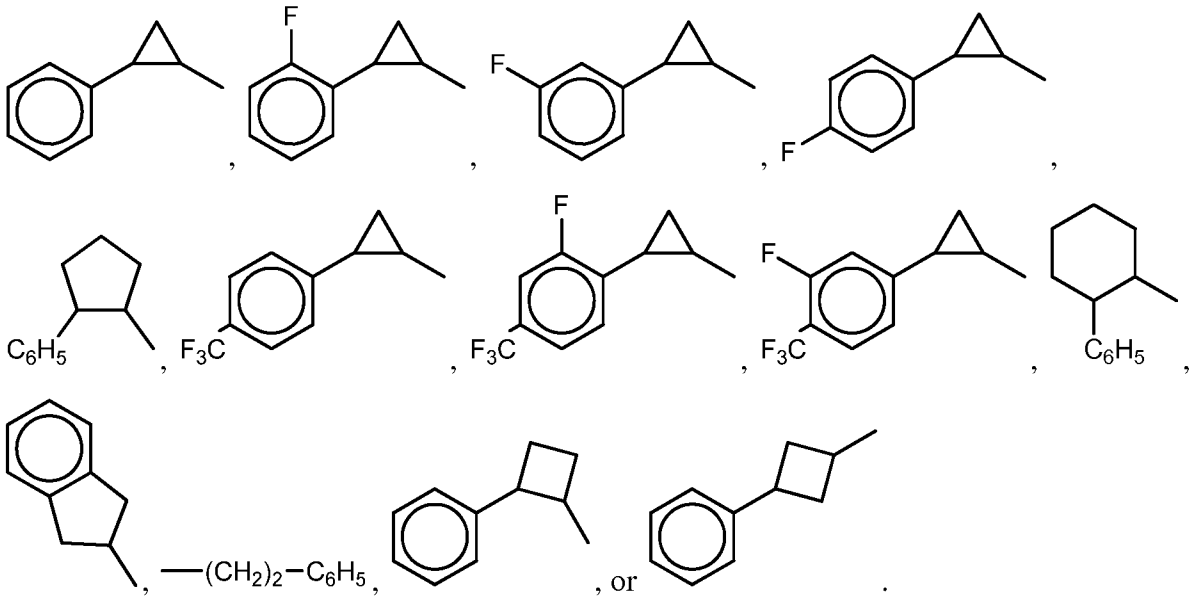
, wherein n is 0, 1, or 2, and wherein the B ring is aryl or nitrogen atom-containing heteroaryl and the 

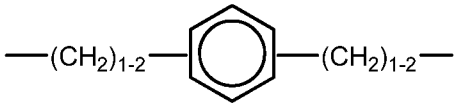
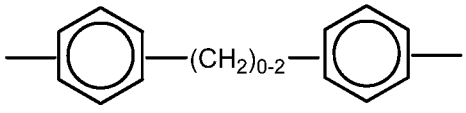
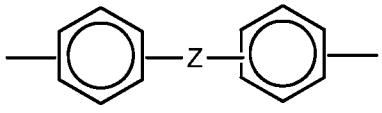
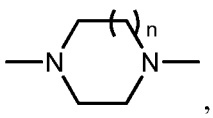
rings are optionally substituted;

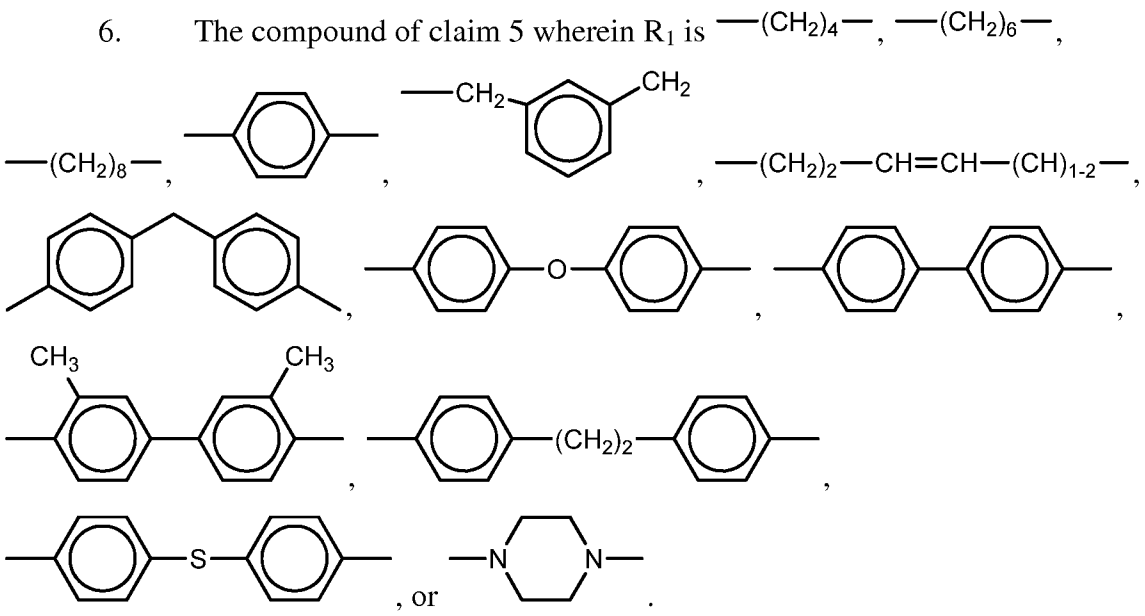
or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof.

2. The compound of claim 1 wherein the B ring is phenyl, naphthyl, pyridinyl, pyridazinyl, pyrazinyl, or pyrimidinyl.

3. The compound of claim 1 wherein R is  , wherein p is 0 to 4,  ,  ,  , wherein q is 0 to 2, or $-(CH_2)_{2-4}-C_6H_5$.

4. The compound of claim 3 wherein R is  ,  .

5. The compound of claim 1 wherein R_1 is $-(CH_2)_{4-8}-$, $-(CH_2)_{4-8}-$,  , $-(CH_2)_{1-2}-CH=CH-(CH_2)_{1-2}-$,  ,  ,  , wherein n is 0 or 1.

6. The compound of claim 5 wherein R_1 is 

7. The compound of claim 1 wherein X is  and Y is –NH-.

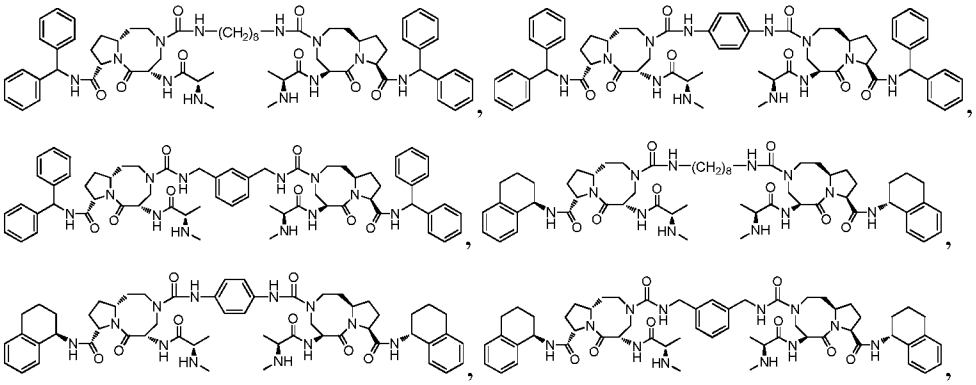
8. The compound of claim 1 wherein X is SO_2 and Y is null.

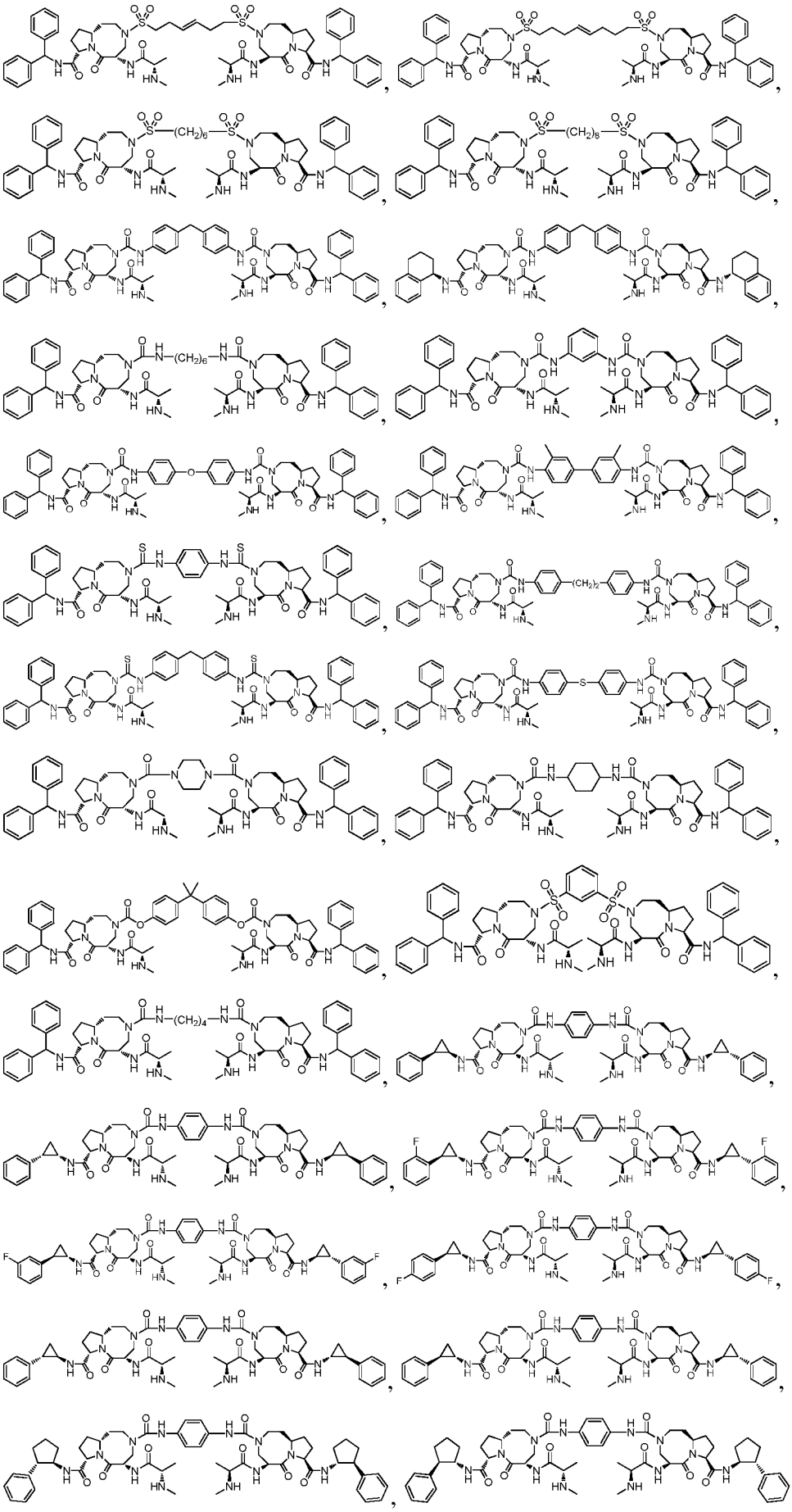
9. The compound of claim 1 wherein X is  and Y is null.

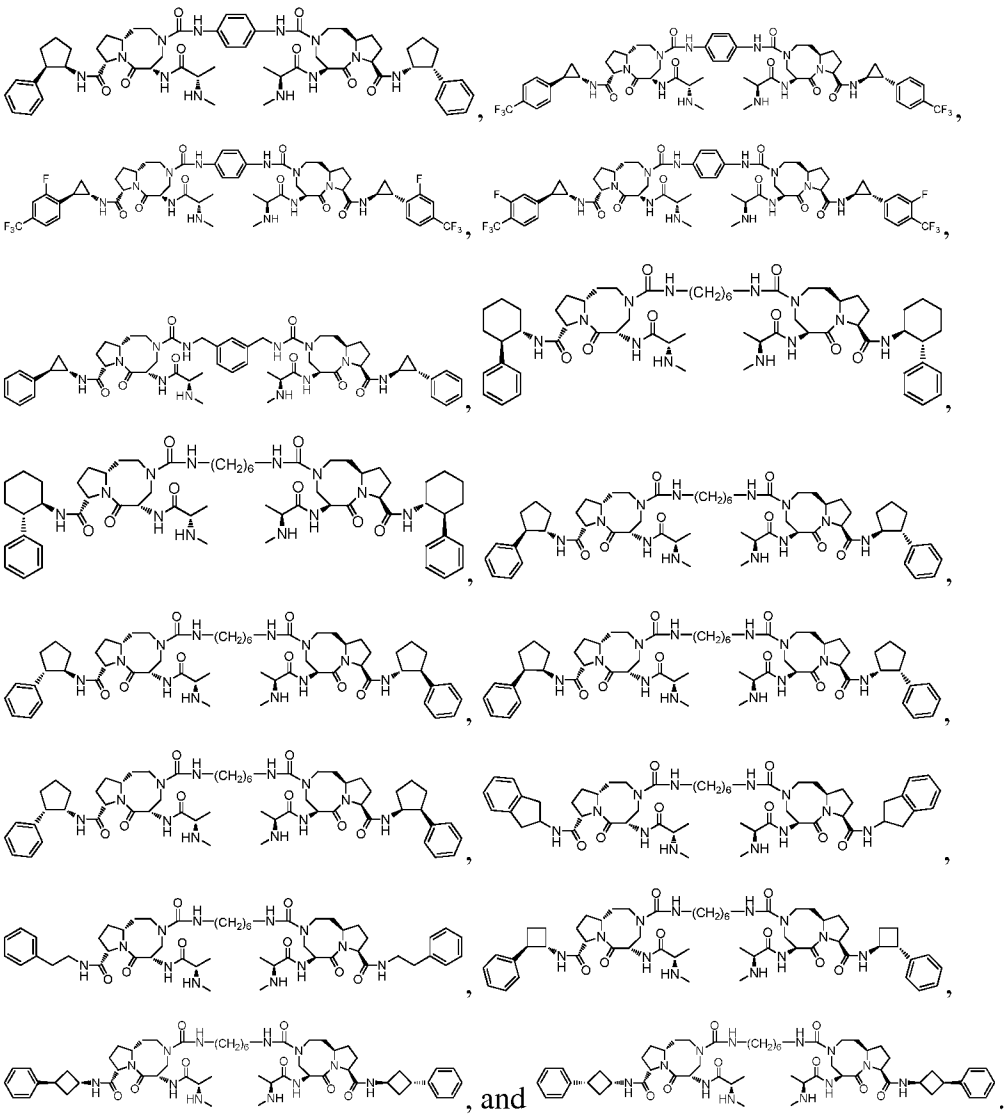
10. The compound of claim 1 wherein X is  and Y is –NH-.

11. The compound of claim 1 wherein X and X' are  and Y is –O-.

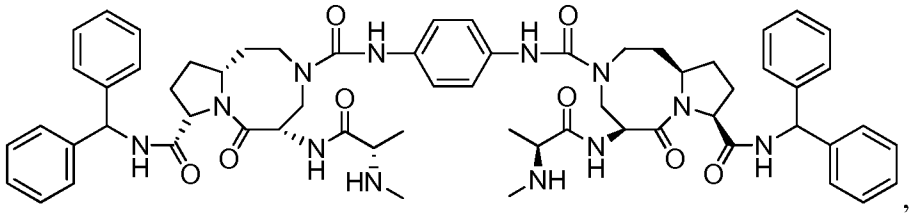
12. The compound of claim 1 selected from the group consisting of

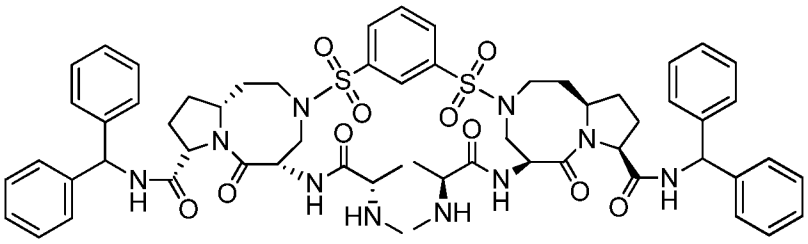




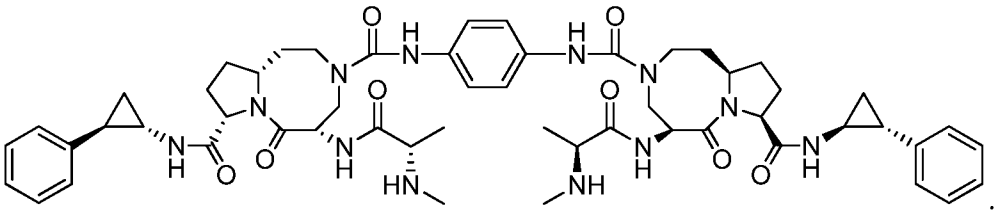


13. A compound selected from the group consisting of





, and



.

14. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier or vehicle.

15. A composition comprising (a) compound of claim 1, (b) a second therapeutic agent useful in the treatment of a disease or condition wherein inhibition of an IAP protein provides a benefit, and (c) an optional excipient and/or pharmaceutically acceptable carrier.

16. The composition of claim 15 wherein the second therapeutic agent comprises a chemotherapeutic agent useful in the treatment of cancer.

17. A method of treating a disease or condition wherein inhibition of an IAP protein provides a benefit comprising administering a therapeutically effective amount of a compound of claim 1 to an individual in need thereof.

18. The method of claim 17 further comprising administering a therapeutically effective amount of a second therapeutic agent useful in the treatment of the disease or condition.

19. The method of claim 18 wherein the compound of claim 1 and the second therapeutic agent are administered simultaneously.

20. The method of claim 18 wherein the compound of claim 1 and the second therapeutic agent are administered separately.

21. The method of claim 17 wherein the disease or condition is a cancer.

22. The method of claim 18 wherein the disease is a cancer and the second therapeutic agent is one or more of a chemotherapeutic agent and radiation.

23. The method of claim 18 wherein the disease is a cancer and the second therapeutic agent is selected from the agents disclosed in paragraph [0107] and paragraphs [0126] through [0131].

24. The method of claim 18 wherein the second therapeutic agent comprises radiation, and the radiation optionally is administered in conjunction with radiosensitizers and/or therapeutic agents disclosed in paragraphs [0123] through [0125] herein.

25. The method of claim 21 wherein the cancer is selected from a cancer disclosed in paragraphs [0104] through [0105] herein.

26. The method of claim 18 wherein the compound of claim 1 and the second therapeutic agent are administered from a single composition.

27. The method of claim 18 wherein the compound of claim 1 and the second therapeutic agent are administered from separate compositions.

28. The method of claim 18 wherein the compound of claim 1 is administered prior to the second therapeutic agent.

29. The method of claim 18 wherein the compound of claim 1 is administered after the second therapeutic agent.

30. The method of claim 17 wherein the disease or condition is selected from the group consisting of T and B cell mediated autoimmune diseases; inflammatory diseases; infections; hyperproliferative diseases; AIDS; degenerative conditions; vascular diseases; and the like. 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.

31. The method of claim 30 wherein the disease or condition is selected from the group consisting of 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.

32. The method of claim 30 further comprising administering a therapeutically effective amount of a second therapeutic agent useful in the treatment of the disease or condition.

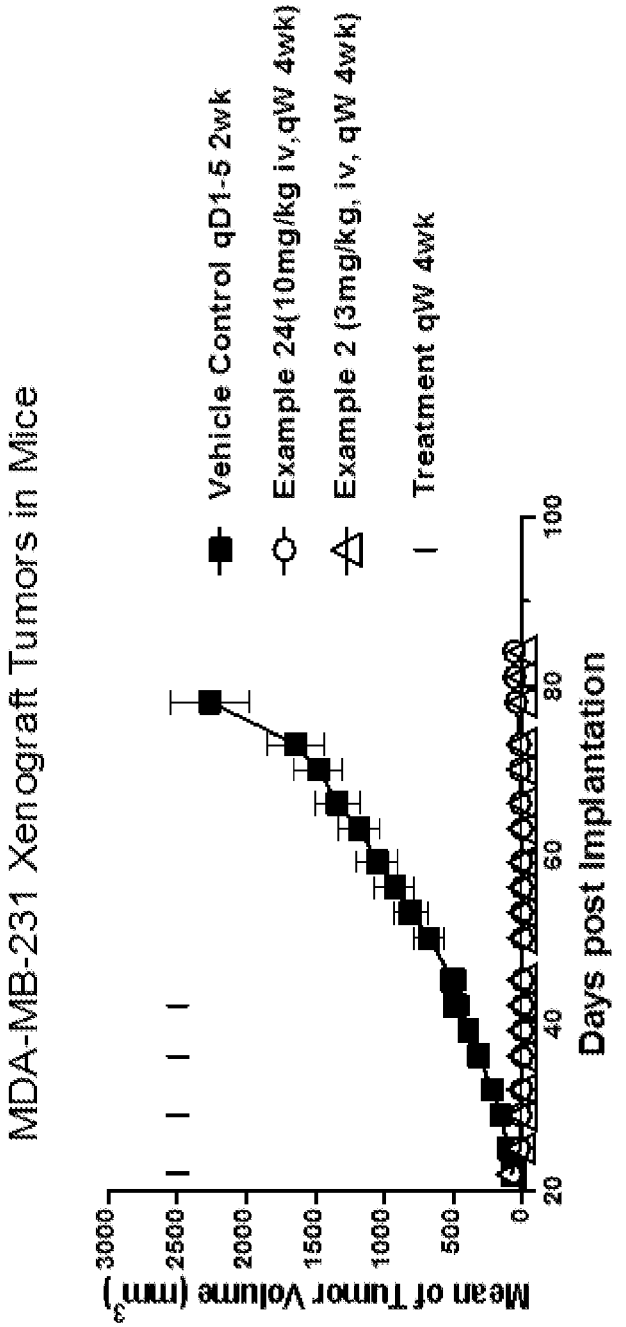

MDA-MB-231 Xenograft Tumors in Mice
Vehicle Control qD1-5 2wk
Example 24(10mg/kg iv,qW 4wk)
Example 2 (3mg/kg, iv, qW 4wk)
Treatment qW 4wk
Mean of Tumor Volume (mm3)
3000
2500
2000
1500
1000
500
0
20
40
60
80
100
Days post implantation

Figure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/055384

A. CLASSIFICATION OF SUBJECT MATTER

C07D 487/04(2006.01)i, A61K 31/395(2006.01)i, A61P 35/00(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC C07D 487/04; A61K 31/43; A61K 31/429; A61K 31/395; A61P 35/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal), PubMed, NCBI, Esp@snet, PAJ, USPTO, Google

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007-130626 A2 (THE REGENTS OF THE UNIVERSITY OF MICHIGAN, et al.) 15 November 2007 See the abstract, paragraph [0025]-[0026], [0097], claims 12, 18, 37.	1-6,9,14-16
A		7-8,10-13
X	YUEFENG PENG, et al., Bivalent Smac Mimetics with a Diazabicyclic Core as Highly Potent Antagonists of XIAP and cIAP1/2 and Novel Anticancer Agents. Journal of Medicinal Chemistry. 12 January 2012, 55(1), pp.106-114 See the abstract, Figure 2.	1-6,9
A		7-8,10-16

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

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 November 2013 (28.11.2013)	**28 November 2013 (28.11.2013)**

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea
Facsimile No. +82-42-472-7140

Authorized officer
KIM, Bum Soo
Telephone No. +82-42-481-5412

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/055384

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

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

1. ☒ Claims Nos.: 17-32
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 17-32 pertain to methods for treatment of the human body by surgery or therapy, as well as diagnostic methods, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

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

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

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

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

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

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

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

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2013/055384

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007-130626 A2	15/11/2007	AU 2007-248473 A1	15/11/2007
		AU 2007-248473 B2	27/01/2011
		BR PI0711326A2	30/08/2011
		CA 2651206 A1	15/11/2007
		CN101484151 A	15/07/2009
		CN101484151 B	21/11/2012
		EA017279B1	30/11/2012
		EA200802285A1	28/08/2009
		EP 2019671 A2	04/02/2009
		EP 2019671 A4	02/06/2010
		IL195075D0	03/08/2009
		JP 05-230610B2	10/07/2013
		JP 2009-536204 T	08/10/2009
		JP 2009-536204A	08/10/2009
		KR 10-1071516 B1	10/10/2011
		KR20090009307A	22/01/2009
		MX2008014140 A	19/01/2009
		NO20085074A	04/02/2009
		NZ572531A	30/09/2011
		US 2008-0089896 A1	17/04/2008
		US 2009-0123480 A1	14/05/2009
		US 7960372 B2	14/06/2011
		US 8202902 B2	19/06/2012
		WO 2007-130626 A3	17/01/2008

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 February 2014 (27.02.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/031487 A8

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61P 35/00* (2006.01)
A61K 31/395 (2006.01)

(21) International Application Number:
PCT/US2013/055384

(22) International Filing Date:
16 August 2013 (16.08.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/692,429 23 August 2012 (23.08.2012) US

(71) Applicant: **THE REGENTS OF THE UNIVERSITY OF MICHIGAN** [US/US]; Office of Technology Transfer, 1600 Huron Parkway, 2nd Floor, Ann Arbor, MI 48109-2590 (US).

(72) Inventors: **WANG, Shaomeng**; 9343 Yorkshire Dr., Saline, MI 48176 (US). **SHENG, Rong**; 1976 Traver Road. Apt. 203, Ann Arbor, MI 48105 (US). **SUN, Haiying**; 1246 North Bay Drive, Ann Arbor, MI 48103 (US). **LIU, Liu**; 2358 Spring Ridge Ct, Ann Arbor, MI 48103 (US). **LU, Jianfeng**; 2600 Arrowwood Tri, Ann Arbor, MI 48109 (US). **MCEACHERN, Donna**; 2208 Glencoe Hills Dr. Apt 2, Ann Arbor, MI 48108 (US).

(74) Agent: **NAPOLI, James, J.**; Marshall, Gerstein & Borun LLP, 233 S. Wacker Drive, 6300 Wills Tower, Chicago, IL 60606-6357 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(48) Date of publication of this corrected version:
30 May 2014

(15) Information about Correction:
see Notice of 30 May 2014

(54) Title: BIVALENT INHIBITORS OF IAP PROTEINS AND THERAPEUTIC METHODS USING THE SAME

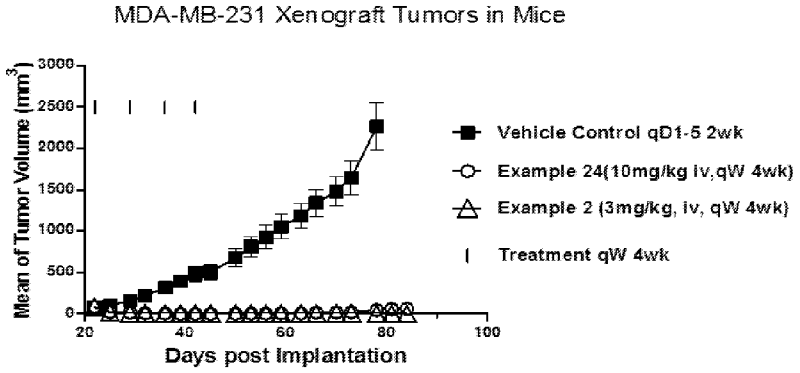


Figure 1

(57) Abstract: Inhibitors of IAP proteins and compositions containing the same are disclosed. Methods of using the IAP protein inhibitors in the treatment of diseases and conditions wherein inhibition of IAP proteins provides a benefit, like cancers, also are disclosed.

WO 2014/031487 A8

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 104718209 A
(43)申请公布日 2015.06.17

(21)申请号 201380055219.5
(22)申请日 2013.08.16
(30)优先权数据
61/692429 2012.08.23 US
(85)PCT国际申请进入国家阶段日
2015.04.22
(86)PCT国际申请的申请数据
PCT/US2013/055384 2013.08.16
(87)PCT国际申请的公布数据
WO2014/031487 EN 2014.02.27
(71)申请人 密执安大学评议会
地址 美国密执安州
(72)发明人 S.王 R.盛 H.孙 L.刘 J.卢 D.麦凯克恩
(74)专利代理机构 中国专利代理(香港)有限公司 72001
代理人 刘健 彭昶
(51)Int.Cl.
C07D 487/04(2006.01)
A61K 31/395(2006.01)
A61P 35/00(2006.01)

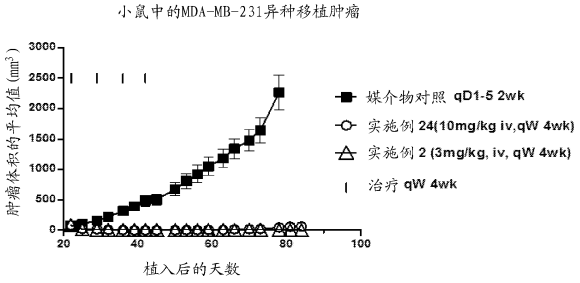
权利要求书7页 说明书64页 附图1页

(54)发明名称

IAP蛋白的二价抑制剂和使用其的治疗方法

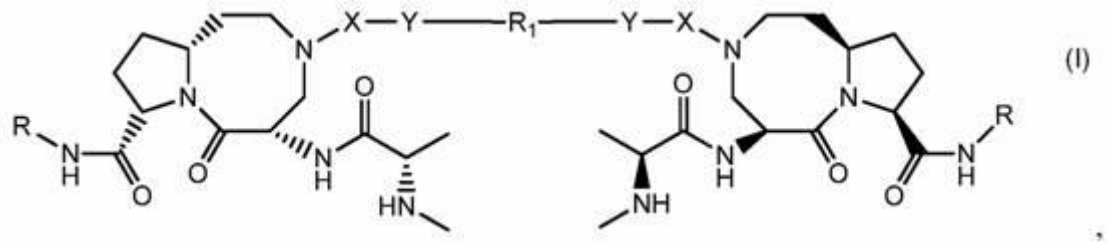
(57)摘要

公开了IAP蛋白的抑制剂和含有其的组合物。还公开了使用IAP蛋白抑制剂治疗其中IAP蛋白的抑制提供益处的疾病和病症如癌症的方法。

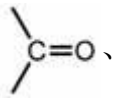
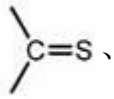
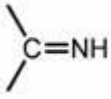


CN 104718209 A

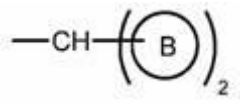
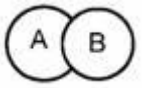
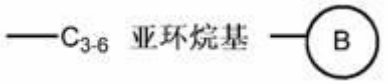
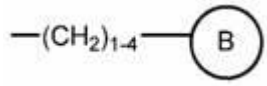
1.具有以下结构的化合物

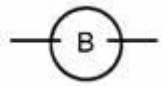
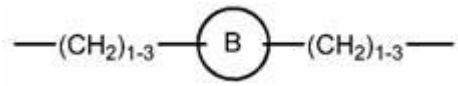


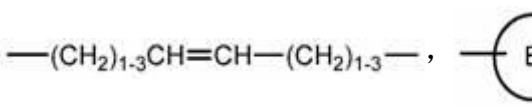
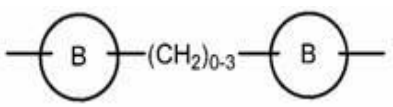
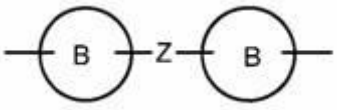
(I)

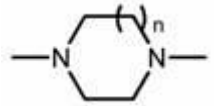
其中 X 选自  、  、  和 $-SO_2-$；

Y 选自 -NH-、-O-、-S-、和不存在；

R 选自  ，  ，其中环 A 是 C_{4-8} 脂族环，  ，和  ，其中 B 环是芳基或含氮原子的杂芳基，且 B 环是任选取代的；且

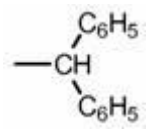
R_1选自 $-(CH_2)_{4-10}-$，  ，  ，

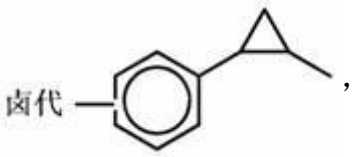
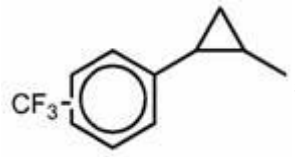
 ，  ，  ，

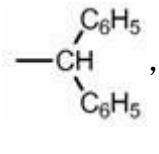
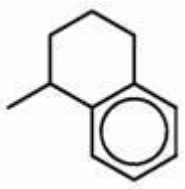
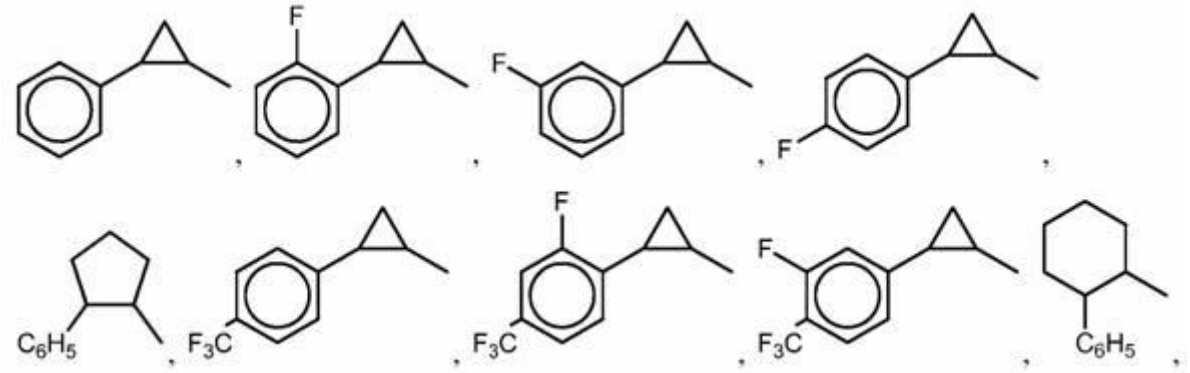
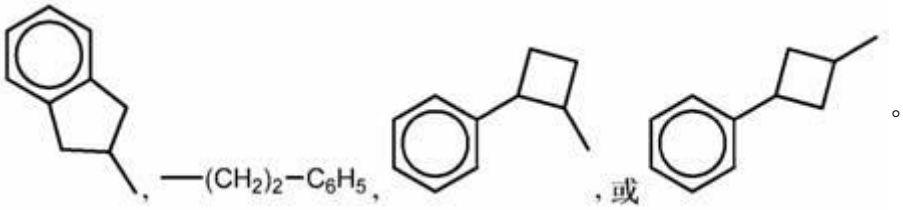
其中 Z 是 O、S 或 NH，和  ，其中 n 是 0、1 或 2，且其中 B 环是芳基或含氮原子的杂芳基，且  环是任选取代的；

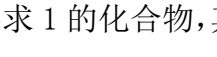
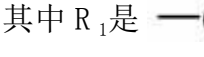
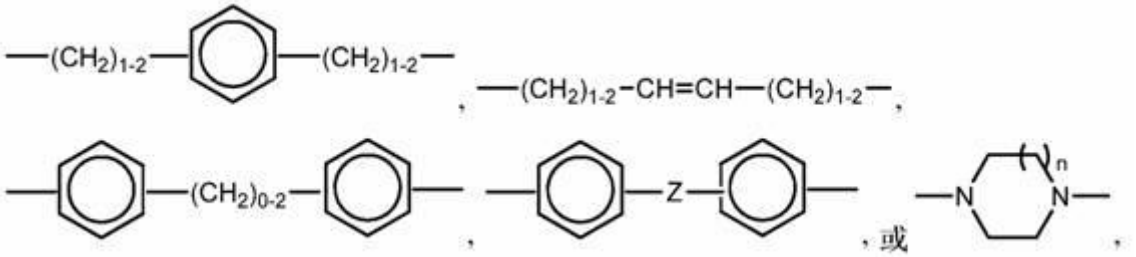
或其药学上可接受的盐、水合物、溶剂化物或前药。

2.权利要求 1 的化合物，其中 B 环是苯基、萘基、吡啶基、哒嗪基、吡嗪基或嘧啶基。

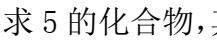
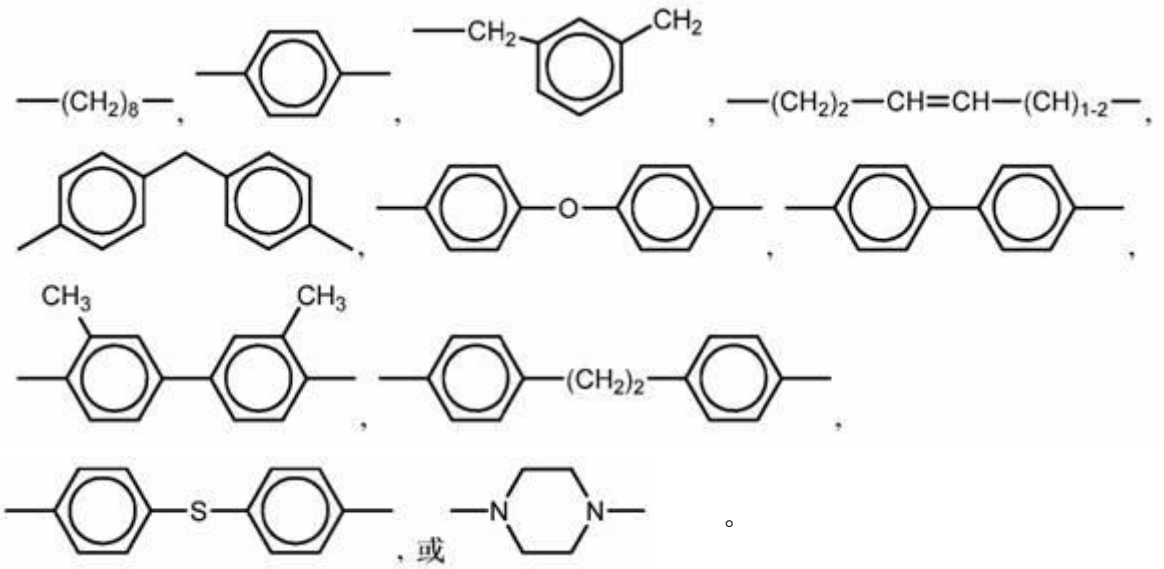
3.权利要求 1 的化合物，其中 R 是  ，  ，其中 p 是 0 至 4，

 ，  ，  ，其中 q 是 0 至 2，或 $-(CH_2)_{2-4}-C_6H_5$。

4. 权利要求 3 的化合物，其中 R 是  ，  ，  ，  。

5. 权利要求 1 的化合物，其中 R_1 是  ，  ， 

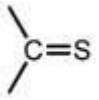
其中 n 是 0 或 1。

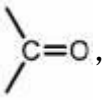
6. 权利要求 5 的化合物，其中 R_1 是  ，  ，  。

7. 权利要求 1 的化合物，其中 X 是  ，且 Y 是 －NH－。

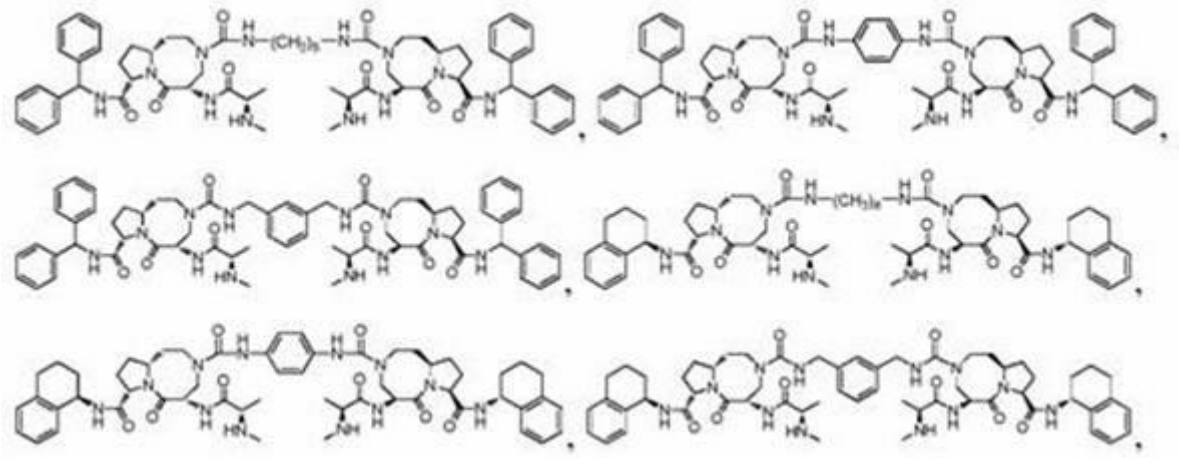
8. 权利要求 1 的化合物，其中 X 是 SO_2，且 Y 不存在。

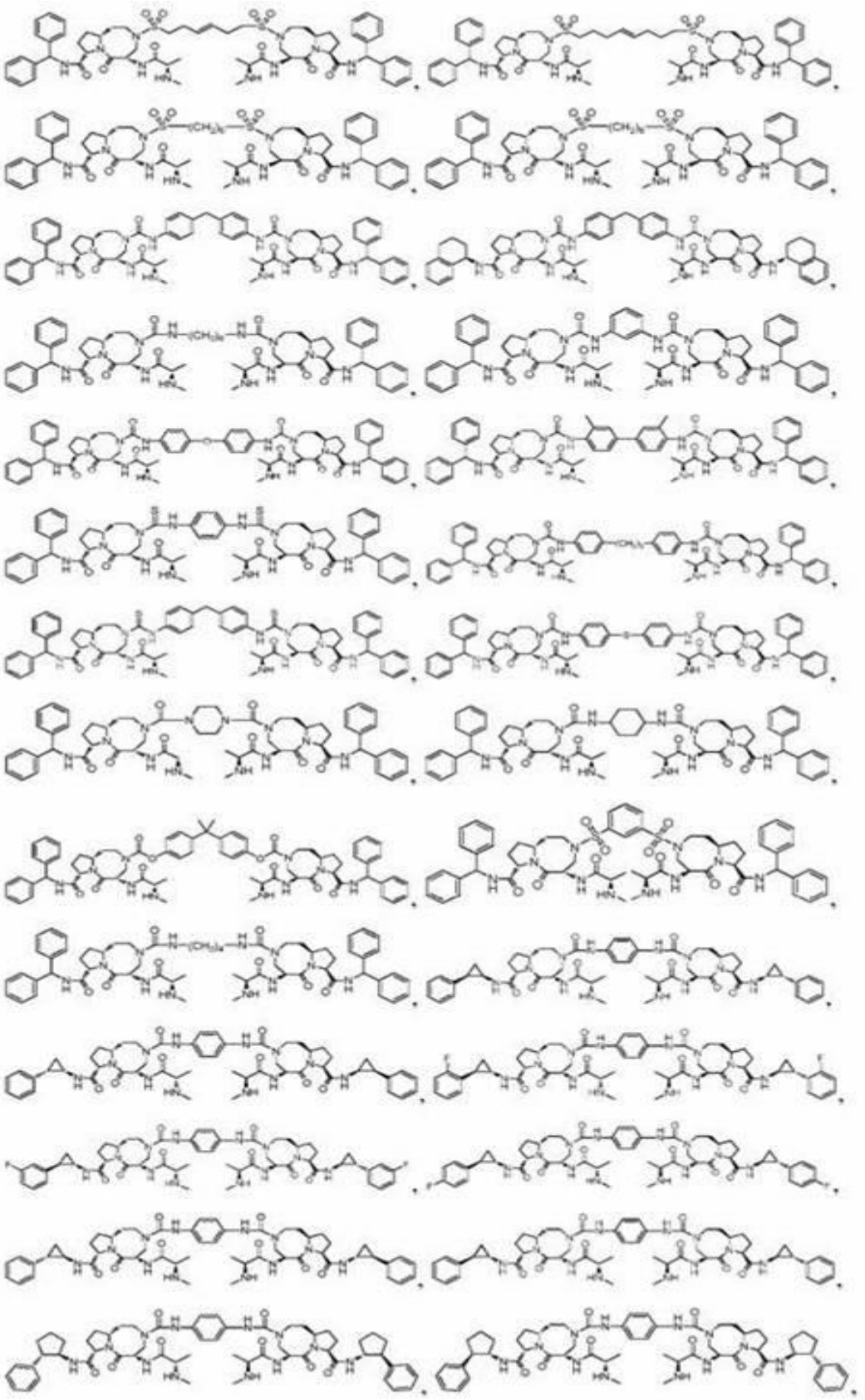
9. 权利要求 1 的化合物，其中 X 是  ，且 Y 不存在。

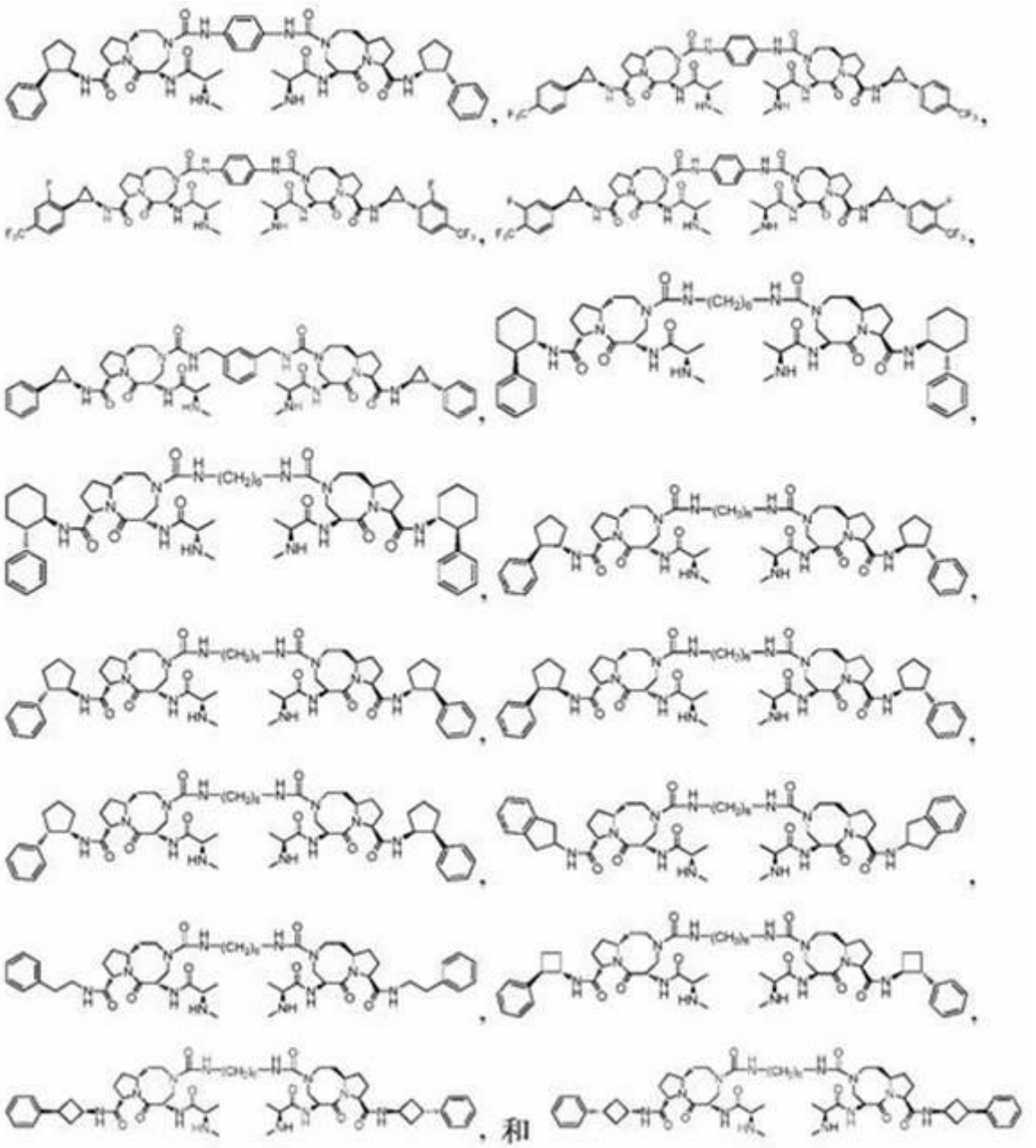
10. 权利要求 1 的化合物，其中 X 是  ，且 Y 是 －NH－。

11. 权利要求 1 的化合物，其中 X 和 X’ 是  ，且 Y 是 －O－。

12. 权利要求 1 的化合物，其选自

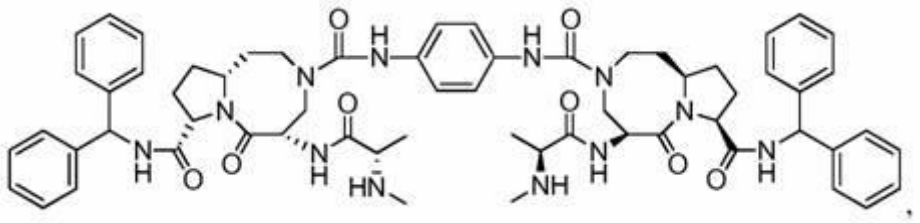


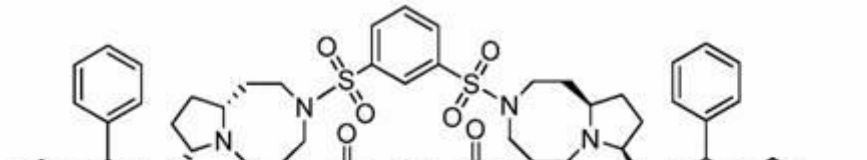




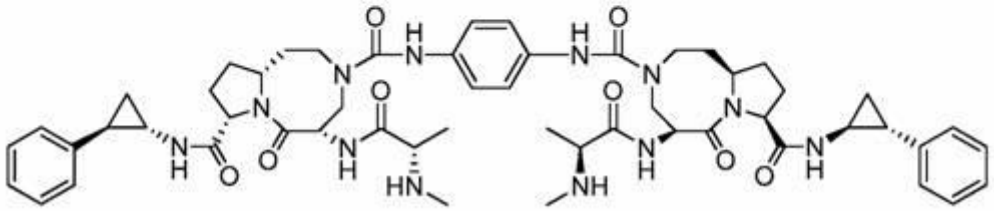
。

13.选自以下的化合物：





，和



。

14. 药物组合物，其包含权利要求 1 的化合物和药学上可接受的载体或媒介物。

15. 组合物，其包含 (a) 权利要求 1 的化合物，(b) 可用于治疗其中 IAP 蛋白的抑制提供益处的疾病或病症的第二治疗剂，和 (c) 任选的赋形剂和 / 或药学上可接受的载体。

16. 权利要求 15 的组合物，其中所述第二治疗剂包含可用于治疗癌症的化疗剂。

17. 治疗其中 IAP 蛋白的抑制提供益处的疾病或病症的方法，其包括向有需要的个体施用治疗有效量的权利要求 1 的化合物。

18. 权利要求 17 的方法，其进一步包括施用治疗有效量的可用于治疗所述疾病或病症的第二治疗剂。

19. 权利要求 18 的方法，其中同时施用权利要求 1 的化合物和所述第二治疗剂。

20. 权利要求 18 的方法，其中分开施用权利要求 1 的化合物和所述第二治疗剂。

21. 权利要求 17 的方法，其中所述疾病或病症是癌症。

22. 权利要求 18 的方法，其中所述疾病是癌症，且所述第二治疗剂是化疗剂和放射中的一种或多种。

23. 权利要求 18 的方法，其中所述疾病是癌症，且所述第二治疗剂选自第 [0097] 段和第 [0116] 至 [0122] 段公开的药剂。

24. 权利要求 18 的方法，其中所述第二治疗剂包括放射，且所述放射任选与放射增敏剂和 / 或本文中第 [0113] 至 [0115] 段中公开的治疗剂结合施用。

25. 权利要求 21 的方法，其中所述癌症选自本文中第 [0094] 至 [0095] 段中公开的癌症。

26. 权利要求 18 的方法，其中从单一组合物施用权利要求 1 的化合物和所述第二治疗剂。

27. 权利要求 18 的方法，其中从分开组合物施用权利要求 1 的化合物和所述第二治疗剂。

28. 权利要求 18 的方法，其中在所述第二治疗剂之前施用权利要求 1 的化合物。

29. 权利要求 18 的方法，其中在所述第二治疗剂之后施用权利要求 1 的化合物。

30. 权利要求 17 的方法，其中所述疾病或病症选自 :T 和 B 细胞介导的自身免疫性疾病 ;炎性疾病 ;感染 ;过度增殖性疾病 ;AIDS ;退化性病症 ;血管疾病 ;等，在一些实施方案

中，适用于用本发明的组合物和方法治疗的感染包括，但不限于，由病毒、细菌、真菌、支原体、朊病毒等引起的感染。

31. 权利要求 30 的方法，其中所述疾病或病症选自 ：自身免疫性溶血性贫血、自身免疫性肝炎、贝格尔病或 IgA 肾病、口炎性腹泻、慢性疲乏综合征、克罗恩病、皮肌炎、纤维肌痛、移植物抗宿主病、格雷夫斯病、桥本甲状腺炎、特发性血小板减少性紫癜、扁平苔癣、多发性硬化、重症肌无力、银屑病、风湿热、风湿性关节炎、硬皮病、斯耶格伦综合征、系统性红斑狼疮、1 型糖尿病、溃疡性结肠炎、白癜风等。

32. 权利要求 30 的方法，其进一步包括施用治疗有效量的可用于治疗所述疾病或病症的第二治疗剂。

IAP 蛋白的二价抑制剂和使用其的治疗方法

[0001] 政府资助

本发明是在美国国立卫生研究院授予的批准号 CA127551 和 CA109025 下在政府支持下做出的。美国政府在本发明中具有某些权利。

发明领域

[0002] 本发明涉及细胞凋亡蛋白抑制剂 (IAPs) 的二价抑制剂，并且涉及治疗其中 IAP 蛋白的抑制提供益处的病症和疾病的治疗方法。本抑制剂以非常高的亲和力结合 IAP 蛋白 (包括 cIAP1、cIAP2 和 XIAP) 以诱导人癌细胞系中的细胞凋亡，以增强其他抗癌药物的抗肿瘤活性。

[0003] 发明背景

细胞凋亡或程序性细胞死亡是对于体内平衡、正常发育、宿主防御和肿瘤发生的抑制关键的细胞过程。细胞凋亡的错误调控已经牵涉于多种人疾病 [1]，包括癌症 [1],[3]，并且现在认识到，对细胞凋亡的抵抗是癌症的标志 [4]。作为结果，关键细胞凋亡调节剂的靶向已经成为用于开发人癌症治疗的新方法的一个有吸引力的策略 [1]。

[0004] 大部分目前的癌症疗法，包括化疗剂、放射和免疫疗法，间接诱导癌细胞中的细胞凋亡。因此，癌细胞由于正常细胞凋亡机制中的缺陷而无法执行细胞凋亡程序通常与对化疗、放射或免疫疗法诱导的细胞凋亡的抵抗增加相关。人癌症由于细胞凋亡缺陷而对目前疗法的此类原发性或获得性抗性是目前癌症疗法中的主要问题。

[0005] 为了改善癌症患者的存活和生活质量，目前和未来在设计和开发新分子靶 - 特异性抗癌疗法的努力包括特异性地靶向对细胞凋亡抵抗的癌细胞的策略。在这方面，靶向在直接抑制癌细胞中的细胞凋亡方面起重要作用的负调节物代表了用于新抗癌药设计的非常有前途的治疗策略。

[0006] 一类细胞凋亡的中心负调节剂是细胞凋亡蛋白 (IAP) 的抑制剂。这一类别包括蛋白例如 XIAP、cIAP1、cIAP2、ML-IAP、HIAP、KIAP、TSIAP、NAIP、生存素、livin、ILP-2、apollon 和 BRUCE。IAP 蛋白有效抑制相当多种细胞凋亡刺激 (包括化疗剂、放射和免疫疗法) 诱导的癌细胞细胞凋亡。

[0007] 尽管它们的作用不限于细胞凋亡的调节 [7],[8]，IAP 蛋白是一类关键细胞凋亡调节剂，并且特征在于一个或多个 BIR(杆状病毒 IAP 重复) 结构域的存在 [5]-[6]。在 IAP 间，细胞 IAP1 (cIAP1) 和 cIAP2 在死亡受体介导的细胞凋亡的调节中发挥关键作用，而 X 连锁的 IAP(XIAP) 通过结合和抑制胱天蛋白酶 -3/7 和胱天蛋白酶 -9(对于执行细胞凋亡关键的三种半胱氨酸蛋白酶) 抑制死亡受体介导的和线粒体介导的细胞凋亡 [5]。这些 IAP 蛋白在癌细胞系和人肿瘤组织中都高度过表达，并且在正常细胞和组织中具有低表达 [9]。广泛的研究已经表明，IAP 蛋白的过表达使癌细胞抵抗多种抗癌药物的细胞凋亡诱导 [10]-[12]。IAP 蛋白和它们的作用的详细讨论是癌症，并且细胞凋亡记载于美国专利号 7,960,372，其通过引用并入本文。因此，靶向这些 IAP 蛋白中的一种或多种是用于治疗人癌症的有希望的治疗策略 [10]-[12]。

[0008] 研究已经显示，基于肽的抑制剂是阐明 IAP 的抗细胞凋亡功能和 IAP 在癌细胞对化疗剂的响应方面的作用的有用工具。然而，基于肽的抑制剂作为有用的治疗剂具有内在局限性，包括细胞渗透性差和体内稳定性差。在公布的使用基于 Smac 的肽抑制剂的研究中，所述肽必须与载体肽融合以使其具有相对的细胞渗透性。

[0009] IAP 蛋白的小分子抑制剂也是已知的。例如，美国专利公开申请号 2005/0197403 和美国专利号 7,960,372 公开了二聚的 Smac 模拟物化合物，各自以其整体通过引用并入本文。

[0010] 尽管发现 IAP 蛋白的小分子抑制剂，但 IAP 蛋白的有效的非肽抑制剂的设计仍然是现代药物发现中的重大挑战。因此，在本领域中仍然存在对于具有允许抑制剂在治疗应用中使用的物理和药学特性的 IAP 抑制剂的需要。本发明提供了设计以结合至 IAP 蛋白并且抑制 IAP 蛋白活性的化合物。

[0011] 发明概述

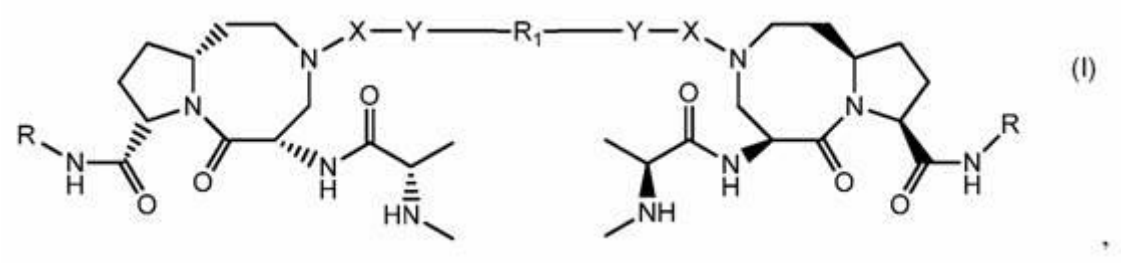
普遍接受的是，癌细胞或其支持细胞不能响应于遗传损害或对细胞凋亡诱导物（例如化疗剂和放射）的暴露而经历细胞凋亡是癌症发作和进展的主要因素。认为诱导癌细胞或其支持细胞（例如肿瘤脉管系统中的新血管细胞）中的细胞凋亡是实际上当今实践中的所有有效癌症治疗药和放射疗法的普遍作用机制。细胞不能经历细胞凋亡的一个原因是 IAP 的表达和积累的增加。

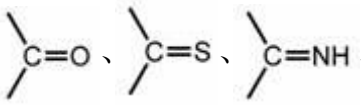
[0012] 因此，本发明涉及 IAP 蛋白的抑制剂，涉及包含所述抑制剂的组合物，并且涉及在其中 IAP 蛋白活性的抑制提供益处的病症和疾病的治疗性处理中使用所述抑制剂的方法。本发明的化合物是 IAP 蛋白活化的有效抑制剂，并且诱导癌细胞的细胞凋亡。

[0013] 附图简述

图 1 是平均肿瘤体积 (mm^3) vs. 植入后天数的图，其显示裸鼠中的 MDA-MB-231 异种移植模型中实施例 2 和 24 的抗肿瘤活性。

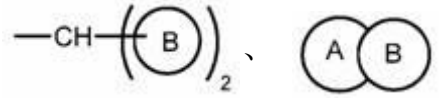
[0014] 更具体地，本发明涉及结构式 (I) 的化合物：



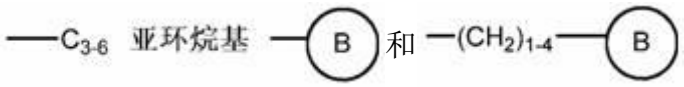
其中 X 选自 

；

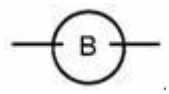
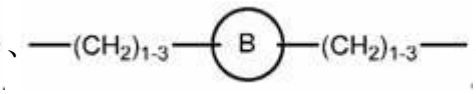
Y 选自 -NH-、-O-、-S- 和不存在；

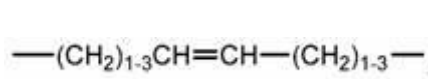
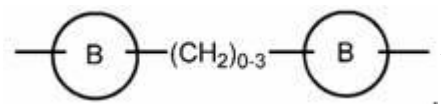
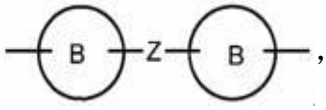
R 选自 

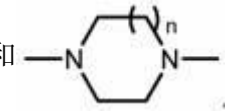
、

，其中环 A 是 C_{4-8}脂族环、 

，其中 B 环是芳基或含氮原子的杂芳基，且 B 环是任选取代的；且

R_1选自 $-(CH_2)_{4\text{-}10}-$、  、  、

 、  、  ，

其中 Z 是 O、S 或 NH 和  ，其中 n 是 0、1 或 2，且其中 B 环是芳基或含氮原子的杂芳基，且  环是任选取代的；

或其药学上可接受的盐、水合物、溶剂化物或前药。

[0015] 在一个实施方案中，本发明提供了抑制 IAP 蛋白的活性且增加细胞对细胞凋亡的诱导物（例如化疗剂和放射治疗）的敏感性的化合物。

[0016] 在其他实施方案中，本发明化合物用于诱导细胞的细胞凋亡且使细胞对细胞凋亡诱导物敏感的方法中。

[0017] 在再另一个实施方案中，本发明提供了通过将治疗有效量的结构式 (I) 的化合物施用于有需要的个体而治疗病症或疾病的方法。感兴趣的疾病或病症例如癌症通过 IAP 蛋白的抑制是可治疗的。因此，本发明化合物可用于治疗和改善对细胞凋亡性细胞死亡的诱导响应的疾病，例如特征在于细胞凋亡的失调的疾病，包括过度增殖性疾病，诸如癌症。在某些实施方案中，化合物可以用于治疗和改善特征在于对癌症疗法的耐受性（例如为化学耐受性、放射耐受性、激素耐受性等）的癌症。在其他实施方案中，本发明化合物可以用于治疗特征在于 IAP 的过表达的过度增殖性疾病。

[0018] 本发明的另一个实施方案是提供组合物，所述组合物包含 (a) 结构式 (I) 的 IAP 抑制剂和 (b) 赋形剂和 / 或药学上可接受的载体，其可用于治疗其中 IAP 蛋白的抑制提供益处的疾病或病症。

[0019] 本发明的另一个实施方案是在治疗个体的其中 IAP 蛋白的抑制提供益处的疾病或病症的方法中利用组合物，所述组合物包含结构式 (I) 的化合物和第二治疗活性剂。

[0020] 在一个进一步实施方案中，本发明提供了包含结构式 (I) 的 IAP 蛋白抑制剂和任选的第二治疗剂的组合物用于制备治疗感兴趣的疾病或病症（例如，癌症）的药物的用途。

[0021] 本发明的再另一个实施方案是提供用于人类药物用途的药剂盒，所述药剂盒包含 (a) 容器，(b1) 包装的组合物，其包含结构式 (I) 的 IAP 蛋白抑制剂，和任选地 (b2) 包装的组合物，其包含可用于治疗感兴趣的疾病或病症的第二治疗剂，和 (c) 包装插页，其含有用于在疾病或病症的治疗中使用所述组合物或组合物（同时或相继施用）的说明。

[0022] 结构式 (I) 的 IAP 蛋白抑制剂和第二治疗剂可以一起作为单一的单位剂量或分开作为多单位剂量施用，其中结构式 (I) 的 IAP 抑制剂在第二治疗剂之前施用，或反之亦然。设想可以施用一个或多个剂量的结构式 (I) 的 IAP 抑制剂和 / 或一个或多个剂量的第二治疗剂。

[0023] 在一个实施方案中，结构式 (I) 的 IAP 蛋白抑制剂和第二治疗剂同时施用。在相关实施方案中，结构式 (I) 的 IAP 蛋白抑制剂和第二治疗剂从单一组合物或从分开的组合物施用。在一个进一步实施方案中，结构式 (I) 的 IAP 蛋白抑制剂和第二治疗剂相继施用。

如在本发明中使用的结构式(I)的IAP蛋白抑制剂可以每个剂量约0.005至约500毫克的量、每个剂量约0.05至约250毫克的量、或每个剂量约0.5至约100毫克的量而施用。

[0024] 优选实施方案的详述

结合优选的实施方案来说明本发明。然而,应当理解的是,本发明不限于公开的实施方案。应当理解的是,考虑到在此的本发明的实施方案的说明,本领域技术人员可以作出各种修改。此类修改被以下权利要求涵盖。

[0025] Smac/DIABLO(胱天蛋白酶的第二线粒体衍生的活化剂或具有低PI的直接IAP结合蛋白)是响应于细胞凋亡刺激从线粒体释放的蛋白,并且充当cIAP1、cIAP2和XIAP的内源抑制剂[14],[15]。Smac和IAP之间的相互作用通过Smac中的N末端AVPI四肽基序和这些IAP蛋白中的一个或多个BIR结构域介导[16],[17]。Smac是同型二聚体,其结合XIAP中的BIR2和BIR3结构域两者,并且拮抗XIAP对胱天蛋白酶-3/-7和胱天蛋白酶-9的抑制[18]。相比之下,Smac仅结合cIAP1和cIAP2中的BIR3结构域[19],并且诱导细胞中的快速蛋白降解[20]。通过两种不同的机制,Smac是这三种IAP蛋白的非常有效的拮抗剂。

[0026] 与Smac蛋白或Smac肽复合的XIAP BIR3的晶体和NMR结构显示Smac中的AVPI四肽基序结合XIAP中的充分定义的表面凹槽,并且这种相互作用代表用于设计小分子XIAP抑制剂的有吸引力的位点[16]-[18]。通过使用AVPI四肽作为前导结构,已经设计几类小分子Smac模拟物作为XIAP和cIAP1/2的拮抗剂[21]-[38]。已经设计了两种不同类型的Smac模拟物[21]-[23]。被设计成模拟单一AVPI结合基序的第一种类型被称为单价Smac模拟物[21]-[23]。第二种类型,二价Smac模拟物,由通过接头拴系的两个AVPI模拟物组成,以模拟Smac蛋白的二聚体形式[21]-[23]。

[0027] 单价Smac模拟物作为潜在药物的一个优点是口服生物利用度,但缺点是在功能测定中拮抗全长XIAP的温和效力。二价Smac模拟物的主要优点是,它们通过同时靶向XIAP中的BIR2和BIR3结构域两者而是比单价Smac模拟物有效得多的XIAP拮抗剂[30]。二价Smac模拟物在诱导癌细胞的细胞凋亡方面的功效通常比它们的单价Smac模拟物对应物高2-3个数量级[21]。当前,三种单价和两种二价Smac模拟物已进入临床试验,用于治疗人癌症[21]。

[0028] 因为二价Smac模拟物在靶向XIAP和cIAP1/2、诱导癌细胞在体外和体内的细胞凋亡和抑制肿瘤生长的方面比单价Smac模拟物显著更有效的,所以已经设计本二价化合物用于癌症治疗和治疗通过IAP蛋白活性介导的其他疾病和病症。

[0029] 本文使用的术语“IAP蛋白”是指细胞凋亡蛋白家族抑制剂中的任何已知成员,包括,但不限于XIAP、cIAP-1、cIAP-2、ML-IAP、HIAP、TSIAP、KIAP、NAIP、生存素、livin、ILP-2、apollon和BRUCE。

[0030] 本文使用的术语“IAP过表达”是指细胞中与表达编码IAP蛋白的mRNA基础水平或具有IAP蛋白基础水平的类似相应非病态细胞相比,编码IAP蛋白的mRNA水平升高(例如异常水平)和/或IAP蛋白的水平升高。用于检测细胞中编码IAP蛋白的mRNA水平或IAP蛋白水平的方法包括,但不限于使用IAP蛋白抗体的蛋白印迹、免疫组织化学法和核酸扩增或直接RNA检测法。与细胞中IAP蛋白的绝对水平同样重要的是测定它们过表达IAP蛋白,所以还有此类细胞内IAP蛋白与其他促细胞凋亡信号传导分子(例如促细胞凋亡Bcl-2族蛋白)相比的相对水平。当这两者的平衡使得,如果其不是用于IAP蛋白水平,

促细胞凋亡信号传导分子将足以引起细胞执行细胞凋亡程序并且死亡时，所述细胞将依赖于 IAP 蛋白而存活。在此类细胞中，暴露于抑制有效量的 IAP 蛋白抑制剂将足以引起细胞执行细胞凋亡程序并且死亡。因此，术语“IAP 蛋白的过表达”还指由于促细胞凋亡信号和抗-细胞凋亡信号的相对水平而导致细胞响应于抑制 IAP 蛋白功能的抑制有效量的化合物而经受细胞凋亡。

[0031] 术语“其中 IAP 蛋白的抑制提供益处的疾病或病症”涉及其中 IAP 蛋白、和 / 或 IAP 蛋白的作用例如对于该疾病或病症的发作、进展、表现重要或必需的病症，或者已知通过 IAP 蛋白抑制剂治疗的疾病或病症。此类病症的实例包括但不限于癌症。本领域普通技术人员能够易于例如通过可以便利地用来评价特定化合物的活性的测定而确定化合物是否治疗针对任何特定细胞类型的由 IAP 蛋白介导的疾病或病症。

[0032] 术语“第二治疗剂”是指不同于结构式 (I) 的 IAP 抑制剂的且已知治疗感兴趣的疾病或病症的治疗剂。例如，当癌症是感兴趣的疾病或病症时，第二治疗剂可以是例如已知的化疗药（像紫杉酚）或放射。

[0033] 术语“疾病”或“病症”表示紊乱和 / 或异常，所述紊乱和 / 或异常通常被认为是病理状态或功能，并且可以将它们自己表现为特定体征、症状、和 / 或功能障碍的形式。如以下所证明，结构式 (I) 的化合物是 IAP 蛋白的有效抑制剂，并且可以用于治疗其中 IAP 蛋白的抑制提供益处的疾病和病症。

[0034] 如本文使用的术语“治疗”（“treat”）、“治疗”（“treating”）、“治疗”（“treatment”）等是指消除、减少、或改善疾病或病症、和 / 或与其相关的症状。虽然未排除，但治疗疾病或病症不要求将该疾病、病症或与其相关的症状完全消除。如本文使用的术语“治疗”（“treat”）、“治疗”（“treating”）、“治疗”（“treatment”）等可以包括“预防性治疗”，“预防性治疗”是指在不具有疾病或病症、但处于重新发展疾病或病症或复发该疾病或病症的风险中或者易于重新发展疾病或病症或复发该疾病或病症的受试者中，降低疾病或病症的重新发展或者先前控制的疾病或病症的复发的可能性。术语“治疗”和同义词考虑将治疗有效量的本发明的化合物施用于需要此类治疗的个体。

[0035] 在本发明的意义内，“治疗”还包括复发预防或阶段预防，以及急性或慢性体征、症状和 / 或功能障碍的治疗。治疗可以根据症状定向，例如，以抑制症状。它可以经过短的时期实现，经中等时期定向，或例如在维持疗法的背景下可以是长期治疗。

[0036] 如本文使用的术语“致敏 (sensitize)”和“致敏 (sensitizing)”是指通过施用第一治疗剂（例如结构式 I 的化合物）使动物或动物内的细胞对第二活性剂的生物作用（例如促进或阻滞细胞功能的方面，包括，但不限于细胞分裂、细胞生长、增殖、侵袭、血管发生或细胞凋亡）更敏感或更响应。可以将第一试剂对靶细胞的致敏效应作为在与和不与第一试剂的施用一起施用第二试剂后观察到的指定生物作用（例如促进或阻滞细胞功能的方面，包括，但不限于细胞生长、增殖、侵袭、血管发生或细胞凋亡）的差异来测量。致敏细胞的响应可以比在没有第一试剂存在下的响应增加至少 10％，至少 20％，至少 30％，至少 40％，至少 50％，至少 60％，至少 70％，至少 80％，至少 90％，至少 100％，至少 150％，至少 200％，至少 350％，至少 300％，至少 350％，至少 400％，至少 450％或至少 500％。

[0037] 如本文使用的术语“过度增殖性疾病”是指动物中的增殖细胞的局限化群体不受通常的正常生长限制的任何病症。过度增殖性疾病的实例包括但不限于肿瘤、赘生物、淋巴

瘤等。如果赘生物未经历侵袭或转移，那么认为赘生物为良性的；如果这两种情况中发生一种，那么认为是恶性的。“转移”细胞意指细胞可以侵入和破坏附近的身体结构。增生是细胞增殖的一种形式，其涉及组织或器官中的细胞数量增加，而结构或功能没有显著改变。组织变形是受控细胞生长的一种形式，其中一种类型的完全分化细胞取代另一种类型的分化细胞。

[0038] 活化淋巴样细胞的病理性生长通常导致自身免疫性疾病或慢性炎症疾病。如本文使用的术语“自身免疫性疾病”是指其中生物体产生识别生物体自身分子、细胞或组织的抗体或免疫细胞的任何疾病。自身免疫性疾病的非限制性实例包括自身免疫性溶血性贫血、自身免疫性肝炎、贝格尔病或 IgA 肾病、口炎性腹泻、慢性疲乏综合征、克罗恩病、皮肌炎、纤维肌痛、移植物抗宿主病、格雷夫斯病、桥本甲状腺炎、特发性血小板减少性紫癜、扁平苔癣、多发性硬化、重症肌无力、银屑病、风湿热、风湿性关节炎、硬皮病、斯耶格伦综合征、系统性红斑狼疮、1 型糖尿病、溃疡性结肠炎、白癜风等。

[0039] 如本文使用的术语“肿瘤性疾病”是指为良性（非癌性）或恶性（癌性）的任何异常细胞生长。

[0040] 如本文使用的术语“抗肿瘤剂”是指阻滞被靶向的（例如恶性）赘生物增殖、生长或扩散的任何化合物。

[0041] 如本文使用的术语“细胞凋亡调节剂”是指参与细胞凋亡的调节（例如，抑制、减少、增加、促进）的试剂。细胞凋亡调节剂的实例包括包含死亡结构域的蛋白，例如但不限于 Fas/CD95、TRAMP、TNF RI、DR1、DR2、DR3、DR4、DR5、DR6、FADD 和 RIP。细胞凋亡调节剂的其他实例包括但不限于，TNFα、Fas 配体、针对 Fas/CD95 和其他 TNF 家族受体的抗体、TRAIL（亦称为 Apo2 配体或 Apo2L/TRAIL）、TRAIL-R1 或 TRAIL-R2 的激动剂（例如，单克隆或多克隆激动抗体）、Bcl-2、p53、BAX、BAD、Akt、CAD、PI3 激酶、PP1 和胱天蛋白酶蛋白。调节剂广泛地包括 TNF 家族受体和 TNF 家族配体的激动剂和拮抗剂。细胞凋亡调节剂可以是可溶性的或膜结合的（例如配体或受体）。优选的细胞凋亡调节剂是细胞凋亡诱导物，例如 TNF 或 TNF 相关的配体，尤其是 TRAMP 配体、Fas/CD95 配体、TNFR-1 配体或 TRAIL。

[0042] 如本文使用的术语“细胞凋亡的失调”是指细胞通过细胞凋亡经历细胞死亡（例如倾向性）的能力的任何异常。细胞凋亡的失调与各种状况相关或由它们诱导，所述状况包括：例如自身免疫性疾病（例如系统性红斑狼疮、类风湿性关节炎、移植物抗宿主病、重症肌无力或斯耶格伦综合征）、慢性炎症状况（例如银屑病、哮喘或克罗恩病）、过度增殖性疾病（例如肿瘤、B 细胞淋巴瘤或 T 细胞淋巴瘤）、病毒感染（例如疱疹、乳头瘤或 HIV）和其他状况，例如骨关节炎和动脉粥样硬化。应注意，当所述失调由病毒感染诱导或与之相关时，在发生或观察到失调时可检测到病毒感染，或可检测不到病毒感染。即病毒－诱导的失调甚至可在病毒感染症状消失后发生。

[0043] 如本文使用的术语“治疗有效量”或“有效剂量”是指当通过本发明的方法施用时足以将用于治疗感兴趣的病症或疾病的一种或多种活性成分有效地递送至有需要的个体的一种或多种活性成分的量。在癌症或其他增殖失调的情况下，治疗有效量的药剂可以减少（即，在一定程度上延迟并且优选终止）不需要的细胞增殖；减少癌细胞的数目；减小肿瘤大小；抑制（即，在一定程度上延迟并且优选终止）癌细胞浸润入外周器官；抑制（即，在一定程度上延迟并且优选终止）肿瘤转移；在一定程度上抑制肿瘤生长；减少 IAP 蛋白在

靶细胞中的信号传导增加存活时间；和 / 或在一定程度上使一种或多种与癌症相关的症状减轻至少 5%、优选至少 10%、至少 15%、至少 20%、至少 25%、至少 30%、至少 35%、至少 40%、至少 45%、至少 50%、至少 55%、至少 60%、至少 65%、至少 70%、至少 75%、至少 80%、至少 85%、至少 90%、至少 95%、或 100%。在施用的化合物或组合物防止存在的癌细胞的生长和 / 或杀死存在的癌细胞的程度上，它可以是细胞抑制性的和 / 或细胞毒性的。

[0044] 术语“容器”（“container”）意指任何适用于储存、装运、分配、和 / 或操作药物产品的容器和其封盖。

[0045] 术语“插页”意指伴随药物产品的信息，该信息提供如何施用该产品的说明，连同允许医师、药剂师、和患者做出关于该产品的使用方面的知情决定所需要的安全性和有效性数据。包装插页通常被认为是用于药物产品的“标记”。

[0046] “同步施用”、“联合施用”、“同时施用”和类似短语意指同时将两种或更多种药剂施用于所治疗的受试者。“同时地”意指同时地或在不同的时间点以任何顺序相继施用每种药剂。然而，如果不是同时施用，则意指它们是按顺序并且在时间上足够接近地施用于个体，以便提供所希望的治疗效果并且可以协同地起作用。例如，可以与第二治疗剂在相同的时间或在不同的时间点以任何顺序相继施用结构式 (I) 的 IAP 蛋白抑制剂。可以任何适当形式并且通过任何适合的途径分开施用本发明的 IAP 蛋白抑制剂和第二治疗剂。当本发明的 IAP 蛋白抑制剂和第二治疗剂不是同时施用时，应当理解的是，它们可以任何顺序施用于有需要的受试者。例如，本发明的 IAP 蛋白抑制剂可以在第二治疗剂治疗方式（例如，放射疗法）的施用之前（例如，之前 5 分钟、15 分钟、30 分钟、45 分钟、1 小时、2 小时、4 小时、6 小时、12 小时、24 小时、48 小时、72 小时、96 小时、1 周、2 周、3 周、4 周、5 周、6 周、8 周、或 12 周）、与第二治疗剂治疗方式的施用伴随性地、或在第二治疗剂治疗方式的施用之后（例如，之后 5 分钟、15 分钟、30 分钟、45 分钟、1 小时、2 小时、4 小时、6 小时、12 小时、24 小时、48 小时、72 小时、96 小时、1 周、2 周、3 周、4 周、5 周、6 周、8 周、或 12 周）施用于有需要的个体。在各个实施方案中，结构式 (I) 的 IAP 蛋白抑制剂和第二治疗剂间隔 1 分钟、间隔 10 分钟、间隔 30 分钟、间隔小于 1 小时、间隔 1 小时、间隔 1 小时至 2 小时、间隔 2 小时至 3 小时、间隔 3 小时至 4 小时、间隔 4 小时至 5 小时、间隔 5 小时至 6 小时、间隔 6 小时至 7 小时、间隔 7 小时至 8 小时、间隔 8 小时至 9 小时、间隔 9 小时至 10 小时、间隔 10 小时至 11 小时、间隔 11 小时至 12 小时、间隔不多于 24 小时或间隔不多于 48 小时施用。在一个实施方案中，联合治疗的组分间隔 1 分钟至 24 小时施用。

[0047] 在描述本发明的背景下（尤其是在权利要求的背景下），术语“一种 / 一个”(“a”、“an”)、“该”（“the”）和类似的指示词的使用应当理解为覆盖单数和复数两者，除非另有说明。除非在此另有说明，在此的值的范围的陈述仅仅旨在充当单个引用落入范围内的每个单独值的快捷方法，并且每个单独值并入本说明书中，如同将其在此单独列举。在此提供的任何和所有的实例或示例性语言（诸如，“例如”）的使用旨在更好地说明本发明，而不是对本发明的范围的限制，除非另外要求保护。在说明书中没有任何语言应被理解为指示任何未要求保护的对本发明的实践必不可少的要素。

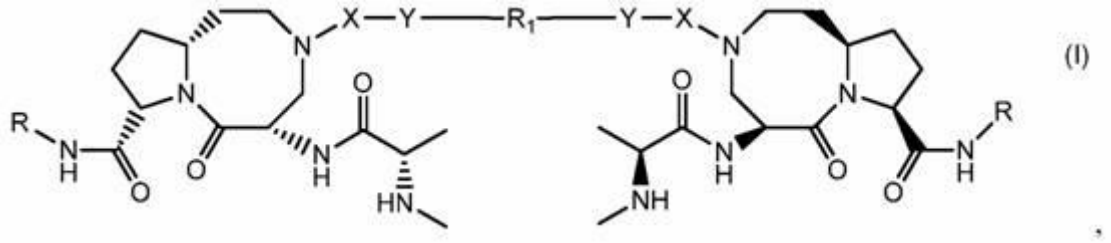
[0048] 本发明涉及结构式 (I) 的化合物，其是 Smac 的模拟物，并且作为 IAP 蛋白抑制剂发挥作用。本发明化合物使细胞对细胞凋亡诱导物敏感，并且在某些情况下，其自身通过抑制 IAP 蛋白诱导细胞凋亡。因此，本发明涉及使细胞对细胞凋亡诱导物敏感的方法和诱导

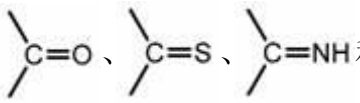
细胞中细胞凋亡的方法，其包括使所述细胞与单独或与细胞凋亡诱导物组合的结构式 I 的化合物接触。本发明进一步涉及治疗或改善动物中响应于细胞凋亡的诱导的疾病的方法，其包括向所述动物施用结构式 I 的化合物和细胞凋亡诱导物。此类疾病包括特征在于细胞凋亡的失调的疾病和特征在于 IAP 蛋白的过表达的疾病。

[0049] 本发明涉及 IAP 蛋白的有效抑制剂。本 IAP 蛋白抑制剂是以低至亚纳摩尔亲和力结合 XIAP、cIAP1 和 cIAP2 的非肽类二价 Smac 模拟物，并且在无细胞功能测定中高效拮抗 XIAP。本发明化合物在低浓度有效诱导癌细胞中 cIAP1 和 cIAP2 的降解，活化胱天蛋白酶 -3 和 -8，并裂解 PARP。本发明化合物在抑制 MDA-MB-231 和 SK-OV-3 细胞系两者中的细胞生长中具有低 IC_{50}。

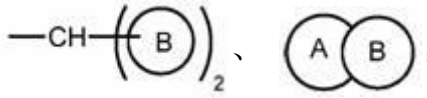
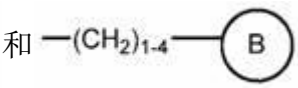
[0050] 因此本发明的 IAP 蛋白抑制剂可用于治疗需要此类治疗的受试者中的不需要的增殖细胞（包括癌症和癌前期）。还提供了治疗具有不需要的增殖细胞的受试者的方法，该方法包括将治疗有效量的本发明的化合物施用于需要此类治疗的受试者。还提供了预防受试者中不需要的增殖细胞的增殖（例如癌症和癌前期）的方法，该方法包括将治疗有效量的结构式 (I) 的化合物施用于处于发展特征在于不需要的增殖细胞的病症的风险中的受试者的步骤。在一些实施例中，结构式 (I) 的化合物通过诱导那些细胞中的凋亡而减少不需要的细胞的增殖。

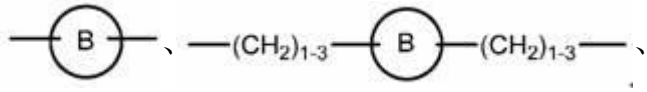
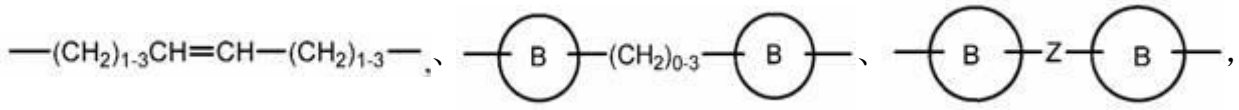
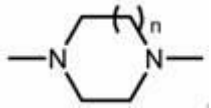
[0051] 本发明涉及具有结构式 (I) 的 IAP 蛋白抑制剂：



其中 X 选自  ；

Y 选自 -NH-、-O-、-S- 和不存在；

R 选自  ，其中环 A 是 C_{4-8} 脂族环、C_{3-6} 亚环烷基  和  ，其中 B 环是芳基或含氮原子的杂芳基，且 B 环是任选取代的；且

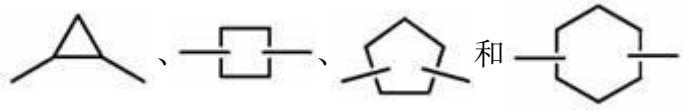
R_1 选自 $-(CH_2)_{4-10}-$、  、  ，其中 Z 是 O、S 或 NH 和  ，其中 n 是 0、1 或 2，且其中 B 环是芳基或含氮原子的

杂芳基，且  环是任选取代的；

或其药学上可接受的盐、水合物、溶剂化物、或前药。

[0052] 如本文使用的术语“C_{4-8}脂族环”是指未取代或被 1 至 3 个基团（例如，C_{1-4}烷基、卤素、三氟甲基、三氟甲氧基、羟基、烷氧基、硝基、氰基、烷基氨基或氨基）取代的环丁基、环戊基、环己基、环庚基和环辛基。

[0053] 如本文使用的术语“烷基”是指直链和支链饱和的 C_{1-10}烃基，其非限制性实例包括甲基、乙基和直链和支链的丙基、丁基、戊基、己基、庚基、辛基、壬基和癸基。术语 C_n意指烷基具有“n”个碳原子。

[0054] 术语“C_{3-6}亚环烷基”是指具有 3 至 6 个碳原子的二取代的环烷烃，例如，  。“C_{3-6}亚环烷基”可以是未取代的，或被 1 至 3 个基团取代的，所述基团例如，C_{1-4}烷基、卤素、三氟甲基、三氟甲氧基、羟基、烷氧基、硝基、氰基、烷基氨基或氨基。

[0055] 术语“烯基”与“烷基”相同定义，除了含有碳 - 碳双键，例如乙烯基、丙烯基、和丁烯基。

[0056] 如本文使用的术语“卤素 (halo)”被定义为氟、氯、溴、和碘。

[0057] 术语“羟基”被定义为 -OH。

[0058] 术语“烷氧基”被定义为 -OR，其中 R 是烷基。

[0059] 术语“氨基”被定义为 $-NH_2$，并且术语“烷基氨基”被定义为 $-NR_2$，其中至少一个 R 是烷基并且第二个 R 是烷基或氢。

[0060] 术语“硝基”被定义为 $-NO_2$。

[0061] 术语“氰基”被定义为 -CN。

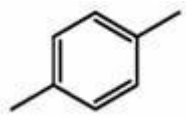
[0062] 术语“三氟甲基”被定义为 $-CF_3$。

[0063] 术语“三氟甲氧基”被定义为 $-OCF_3$。

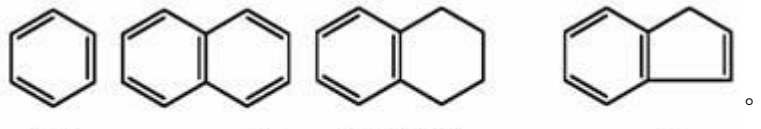
[0064] 如本文使用的术语“芳基”是指单环或多环的芳香基团，优选是单环或二环的芳香基团，例如苯基或萘基。除非另有说明，芳基基团可以是未被取代的或被一个或多个并且特别是一个至四个独立选自以下的基团取代：例如，卤素、烷基、烯基、$-OCF_3$、$-NO_2$、-CN、-NC、-OH、烷氧基、氨基、烷基氨基、$-CO_2H$、$-CO_2$烷基、炔基、环烷基、硝基、巯基、亚氨基、酰胺基、膦酸酯、亚膦酸酯、甲硅烷基、烷硫基、磺酰基、磺酰胺、醛、杂环烷基、三氟甲基、芳基和杂芳基。

[0065] 如本文使用的术语“杂芳基”是指含有一个或两个芳香环并且在一个芳香环中含有至少一个且至多四个氮原子的单环或二环的环系统。除非另有说明，杂芳基基团可以是未被取代的或被一个或多个并且特别是一个至四个选自以下的取代基取代：例如，卤素、烷基、烯基、$-OCF_3$、$-NO_2$、-CN、-NC、-OH、烷氧基、氨基、烷基氨基、$-CO_2H$、$-CO_2$烷基、炔基、环烷基、硝基、巯基、亚氨基、酰胺基、膦酸酯、亚膦酸酯、甲硅烷基、烷硫基、磺酰基、磺酰胺、醛、杂环烷基、三氟甲基、芳基和杂芳基。

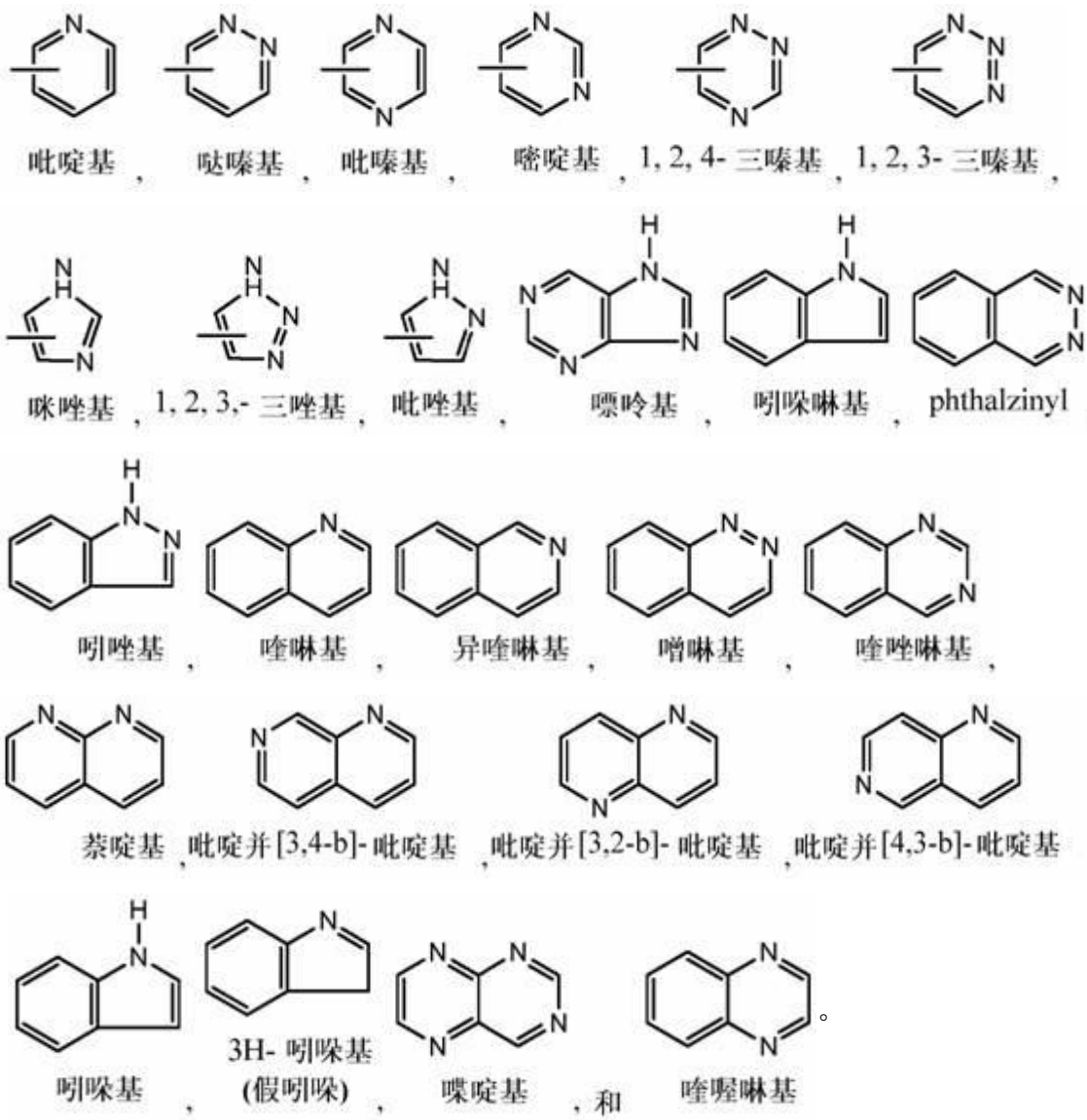
[0066] 术语“亚芳基”是指键合至两个其他基团并用于连接这些基团的二齿芳基，例如，

 。类似地定义术语“亚杂芳基”。

[0067] 芳基的非限制性实例是


苯基，萘，四氢化萘，和茚。

[0068] 杂芳基的非限制性实例是


吡啶基，哒嗪基，吡嗪基，嘧啶基，1,2,4-三嗪基，1,2,3-三嗪基，

咪唑基，1,2,3,-三唑基，吡唑基，嘌呤基，吲哚啉基，phthalzinyl，

吲唑基，喹啉基，异喹啉基，噌啉基，喹唑啉基，

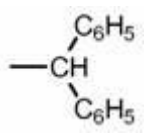
萘啶基，吡啶并[3,4-b]-吡啶基，吡啶并[3,2-b]-吡啶基，吡啶并[4,3-b]-吡啶基，

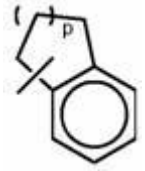
吲哚基，3H-吲哚基(假吲哚)，喋啶基，和喹喔啉基。

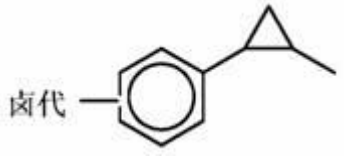
[0069] 结构式(I)的化合物抑制IAP蛋白，并且可用于治疗各种疾病和病症。具体而言，结构式(I)的化合物用于治疗其中IAP蛋白的抑制提供益处的疾病或病症(例如，癌症、自身免疫性疾病和慢性炎性病症)的方法中。该方法包括将治疗有效量的结构式(I)的化合物施用于有需要的个体。除了结构式(I)的化合物之外，本发明的方法还涵盖将第二治疗剂施用于个体。该第二治疗剂选自已知可用于治疗折磨有需要的个体的疾病或病症的药物，例如已知可用于治疗特定癌症的化疗剂和/或放射。

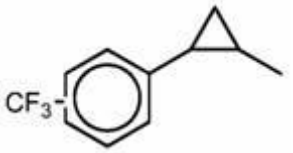
[0070] 在一些优选的实施方案中，B 环是苯基、萘基、吡啶基、哒嗪基、吡嗪基或嘧啶基。

[0071] 在一些优选的实施方案中，R 包括，但不限于：



， 

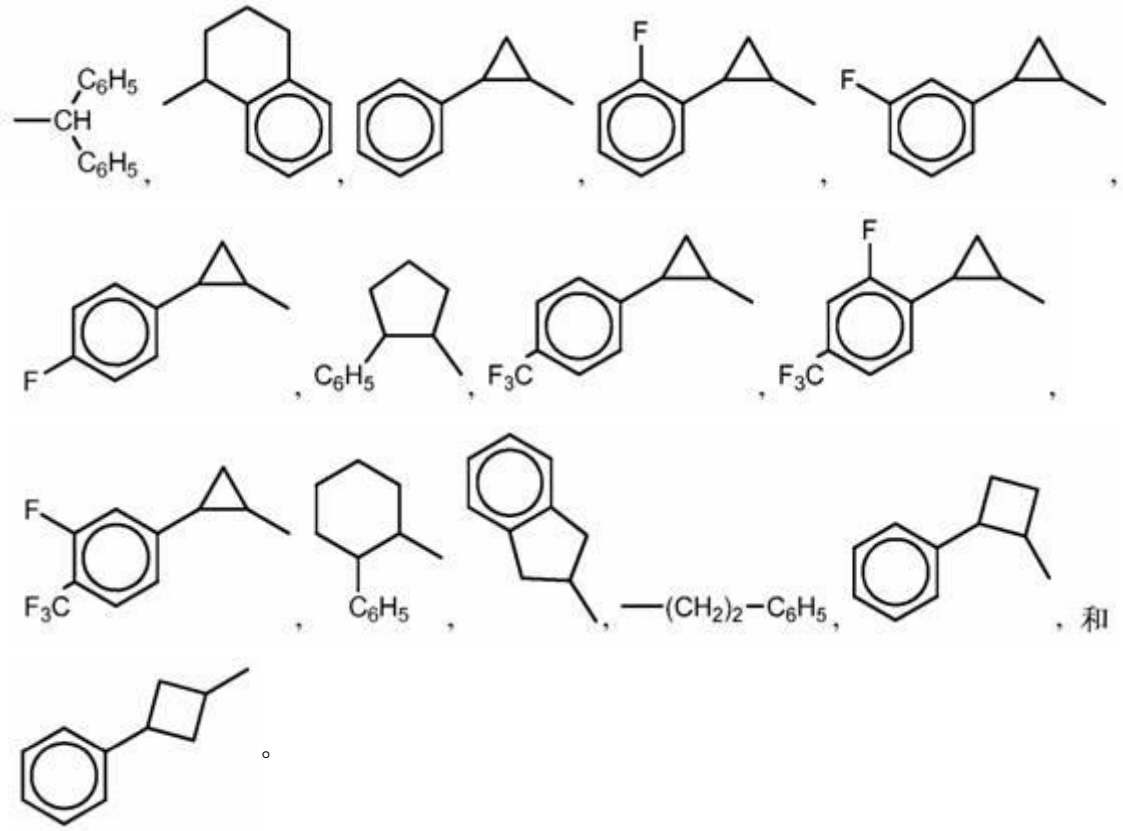
，其中 p 是 0 至 4， 

， 

， 

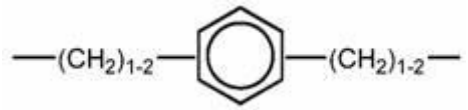
，其中 q 是 0 至 2，和 $-(CH_2)_{2-4}-C_6H_5$。

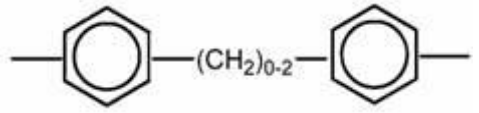
[0072] 具体 R 基团包括，但不限于：

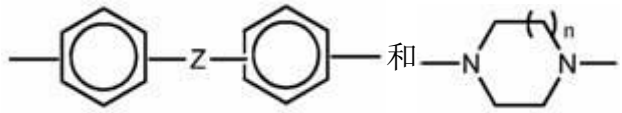


和

。

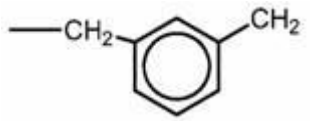
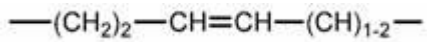
[0073] 在一些优选的实施方案中，R_1是，但不限于 $—(CH_2)_{4-8}—$，$—(CH_2)_{4-8}—$， 

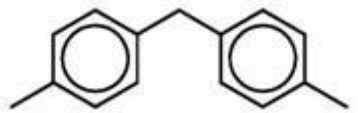
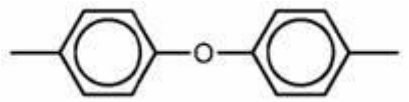
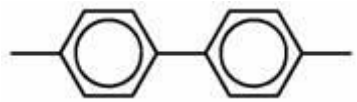
，$—(CH_2)_{1-2}-CH=CH—(CH_2)_{1-2}—$， 

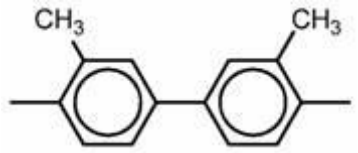
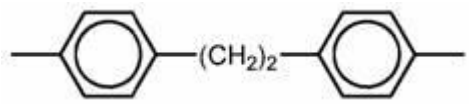
， 

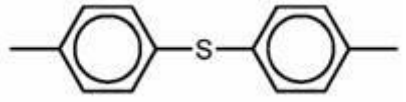
，其中 n 是 0 或 1。

[0074] 具体 R_1基团包括但不限于，$—(CH_2)_4—$，$—(CH_2)_6—$，$—(CH_2)_8—$

，  ，  ，  ，

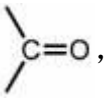
 ，  ， 

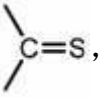
，  ， 

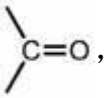
，  ，和  。

[0075] 在一些优选的实施方案中，X 是  ，且 Y 是 -NH-。

[0076] 在其他优选的实施方案中，X 是 SO_2，且 Y 不存在。

[0077] 在另一个优选的实施方案中，X 是  ，且 Y 不存在。

[0078] 在又一个优选的实施方案中，X 是  ，且 Y 是 -NH-。

[0079] 在又一个优选的实施方案中，X 和 X' 是  ，且 Y 是 -O-。

[0080] 另外，本发明化合物的盐、水合物、溶剂化物和前药也被包含在本发明中，并且可以用于在此公开的方法中。本发明进一步包括结构式 (I) 的化合物的所有可能的立体异构体和几何异构体。本发明包括外消旋化合物和旋光异构体两者。当希望结构式 (I) 的化合物为单一的对映异构体时，它可以通过最终产物的拆分或通过从同分异构纯的起始材料或使用手性助剂进行的立体定向合成而获得，例如，参见 Z. Ma 等人，*Tetrahedron: Asymmetry, 8(6)*, pages 883-888 (1997)。最终产物、中间体或起始材料的拆分可以通过任何本领域中已知的适合的方法实现。另外，在结构式 (I) 的化合物的互变异构体是可能的情况下，本发明旨在包括所述化合物的所有互变异构形式。

[0081] 本发明的化合物可以作为盐存在。本发明的化合物的药学上可接受的盐常常在本发明的方法中是优选的。如本文使用的术语“药学上可接受的盐”是指在目标动物（例如，哺乳动物）中生理上耐受的本发明的化合物的任何盐（例如，通过与酸或碱反应获得）。本发明的化合物的盐可衍生自无机或有机酸和碱。术语“药学上可接受的盐”也是指结构式 (I) 的化合物的两性离子形式。式 (I) 的化合物的盐可以在化合物的最终分离和纯化过程中制备，或者分开地通过使化合物与具有适合阳离子的酸发生反应而制备。结构式 (I) 的化合物的药学上可接受的盐可以是与药学上可接受的酸形成的酸加成盐。可以采用以形成药学上可接受的盐的酸的实例包括无机酸（例如硝酸、硼酸、盐酸、氢溴酸、硫酸、和磷酸）和有机酸（例如草酸、马来酸、琥珀酸、和柠檬酸）。本发明的化合物的盐的非限制性实例包

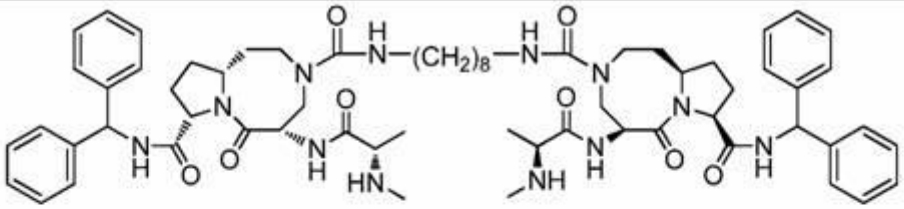
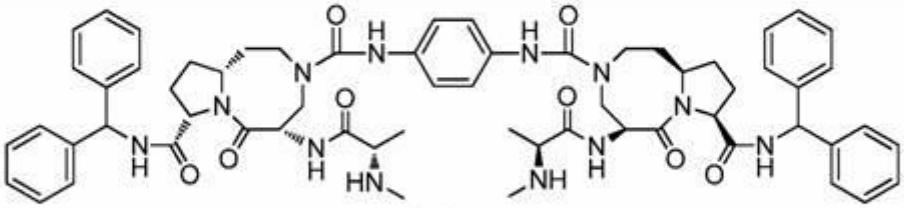
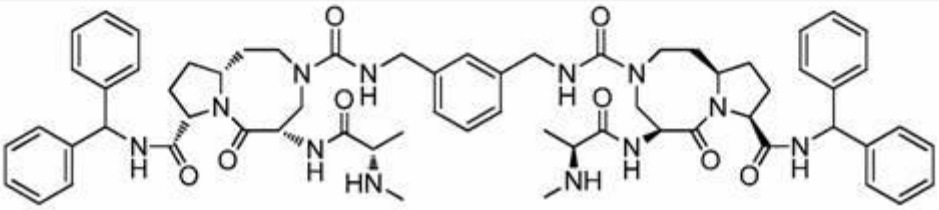
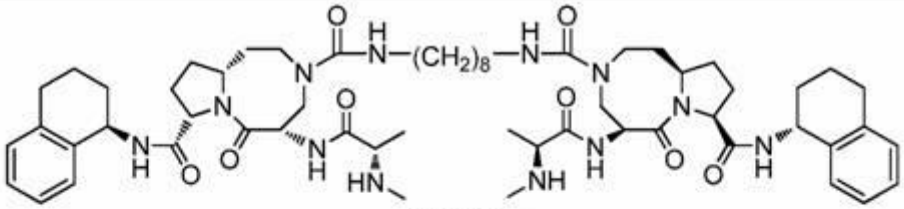
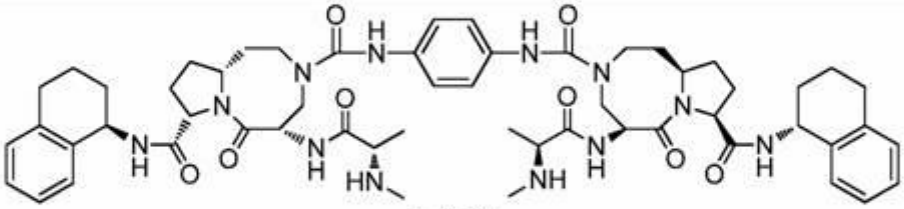
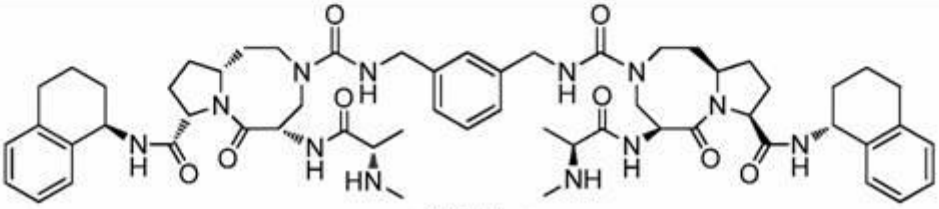
括但不限于盐酸盐、氢溴酸盐、氢碘酸盐、硫酸盐、硫酸氢盐、2- 羟乙磺酸盐、磷酸盐、磷酸氢盐、乙酸盐、己二酸盐、藻酸盐、天冬氨酸盐、苯甲酸盐、硫酸氢盐、丁酸盐、樟脑酸盐、樟脑磺酸盐、二葡萄糖酸盐、甘油磷酸盐、半硫酸盐、庚酸盐、己酸盐、甲酸盐、琥珀酸盐、富马酸盐、马来酸盐、抗坏血酸盐、羟乙基磺酸盐、水杨酸盐、甲磺酸盐、均三甲苯磺酸盐、萘磺酸盐、烟酸盐、2- 萘磺酸盐、草酸盐、双羟萘酸盐、果胶盐、过硫酸盐、3- 苯丙酸盐、苦味酸盐、新戊酸盐、丙酸盐、三氯乙酸盐、三氟乙酸盐、磷酸盐、谷氨酸盐、碳酸氢盐、对甲苯磺酸盐、十一酸盐、乳酸盐、柠檬酸盐、酒石酸盐、葡萄糖酸盐、甲磺酸盐、乙二磺酸盐、苯磺酸盐、和对甲苯磺酸盐。碱的实例包括，但不限于碱金属（例如钠）氢氧化物、碱土金属（例如镁）氢氧化物、氨和式 NW_4^+ 的化合物，其中 W 为 C_{1-4} 烷基，等。另外，可以使存在于本发明的化合物中的可用的氨基基团与甲基、乙基、丙基、和丁基的氯化物、溴化物和碘化物；二甲基、二乙基、二丁基、和二戊基的硫酸盐；癸基、十二基、肉豆寇基、和甾基 (steryl) 的氯化物、溴化物和碘化物；以及苄基和苯乙基的溴化物发生季铵化。

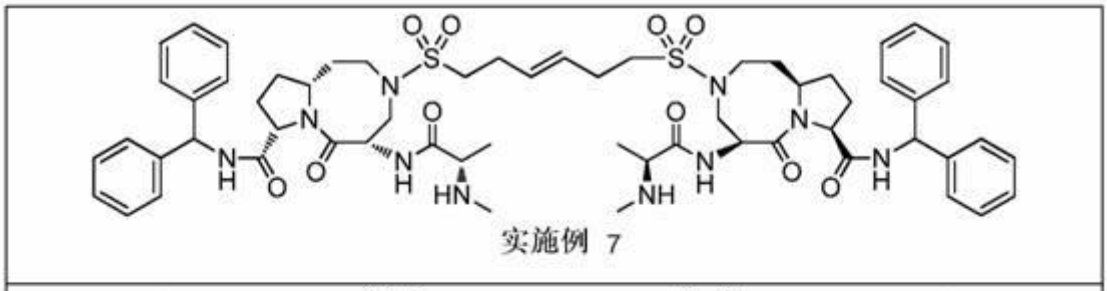
[0082] 结构式 (I) 的化合物可以含有一个或多个不对称中心，因此可以作为立体异构体存在。本发明包括混合物和个别立体异构体两者。具体而言，结构式 (I) 的化合物包括个别顺式和反式异构体以及顺式和反式异构体的混合物，例如，  和  。

[0083] 如本文使用的术语“前药”是指需要在目标生理系统内发生生物转化（例如自发或酶促）以将前药释放或转化（例如通过酶促、生理、机械、电磁方式）成活性药物的母体“药物”分子的药学上无活性的衍生物。设计前药以克服与稳定性、毒性、缺乏特异性或有限的生物利用度相关的问题。

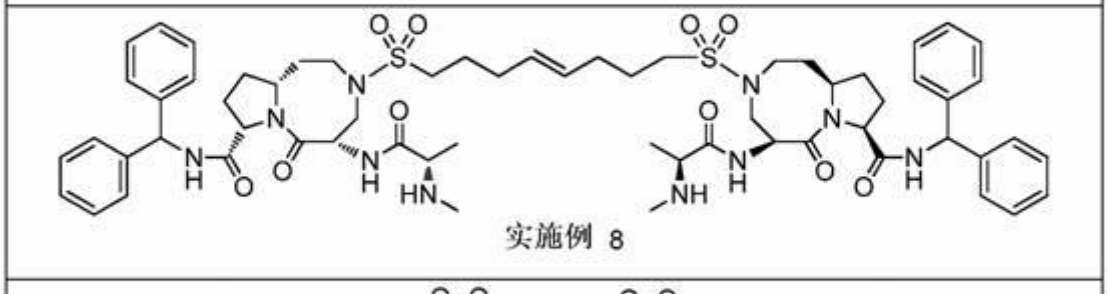
[0084] 前药通常提供在哺乳动物体内溶解度、组织相容性或延缓释放的优点（参见例如 Bundgard, "Design of Prodrugs", pp. 7-9, 21-24, Elsevier, Amsterdam (1985); 和 Silverman, "The Organic Chemistry of Drug Design and Drug Action", pp. 352-401, Academic Press, San Diego, CA (1992))。示例性前药包含活性药物分子自身和化学掩蔽基团（例如可逆地抑制所述药物活性的基团）。一些优选的前药是具有在代谢条件下可裂解的基团的化合物的变型或衍生物。示例性前药当它们在生理条件下经历溶剂解或进行酶促降解或其他生物化学转化（例如磷酸化、氢化、脱氢、糖基化）时在体内或体外变成具有药学活性。常用的前药包括酸衍生物，例如通过使母体酸与合适的醇（例如低级链烷醇）反应制备的酯类，通过使母体酸化合物与胺反应制备的酰胺类，或反应以形成酰化的碱衍生物的碱性基团（例如低级烷基酰胺）。

[0085] 本发明的具体化合物包括但不限于具有下文列出的结构的化合物。

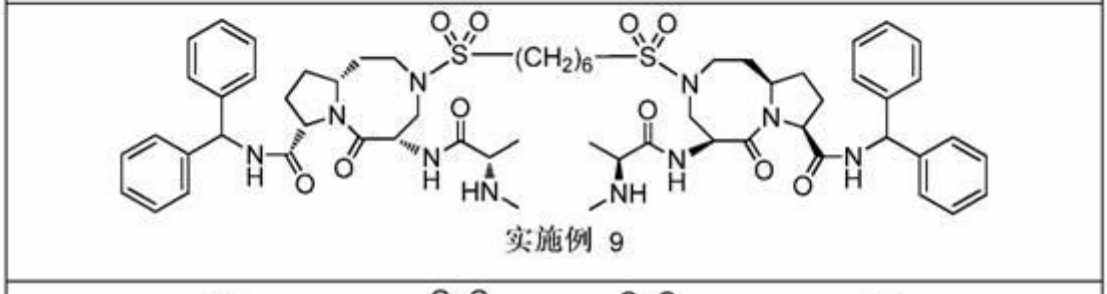
结构
 实施例 1
 实施例 2
 实施例 3
 实施例 4
 实施例 5
 实施例 6



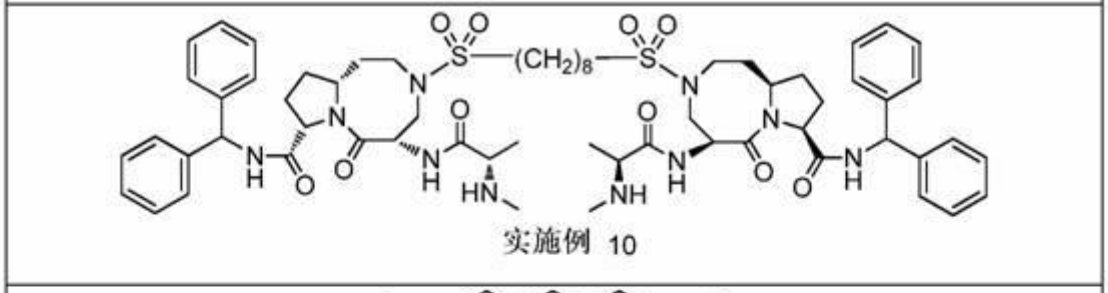
实施例 7



实施例 8



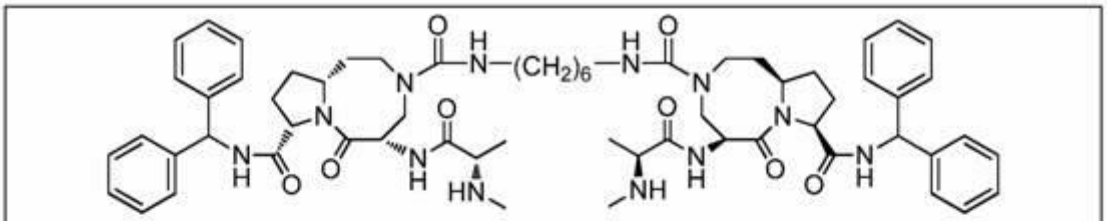
实施例 9



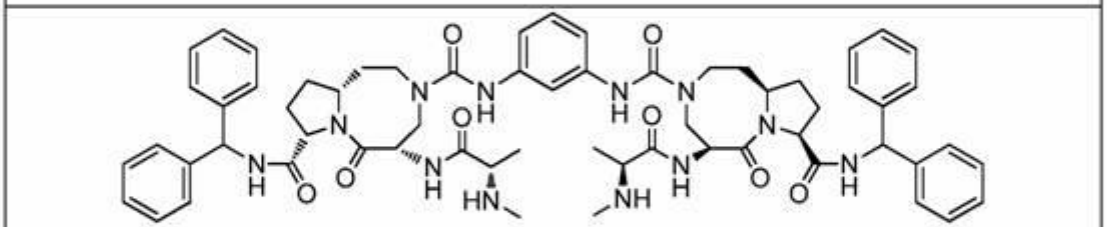
实施例 10

实施例 11

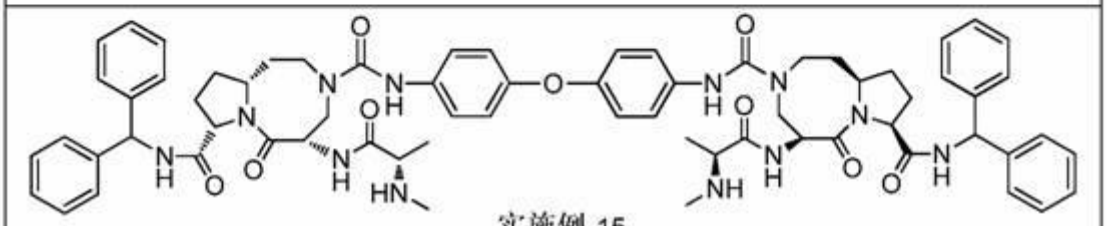
实施例 12



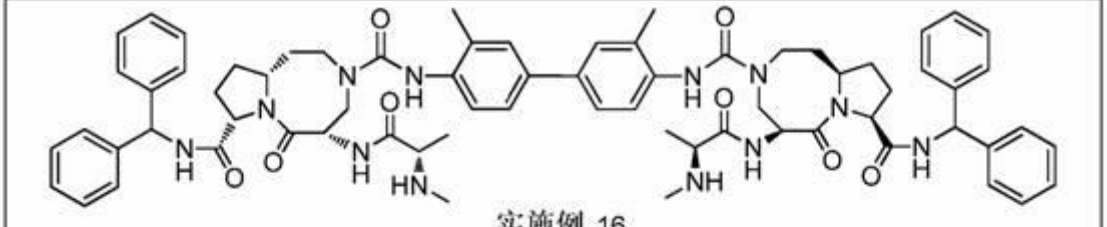
实施例 13



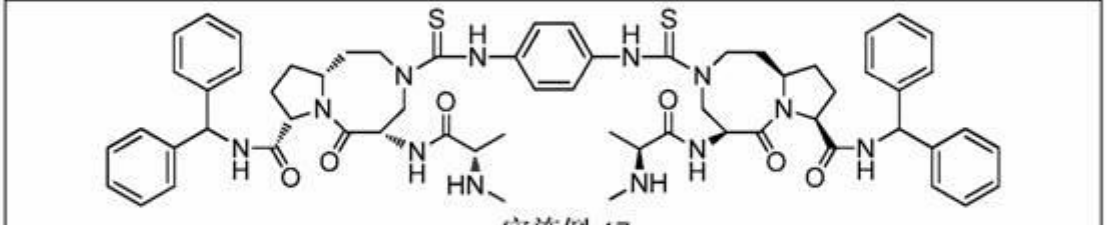
实施例 14



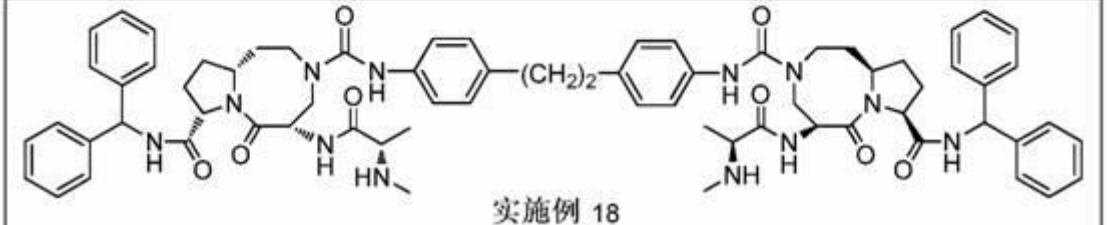
实施例 15



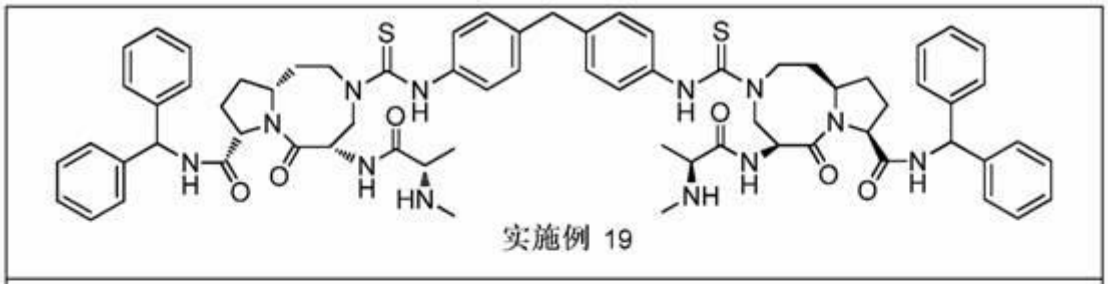
实施例 16



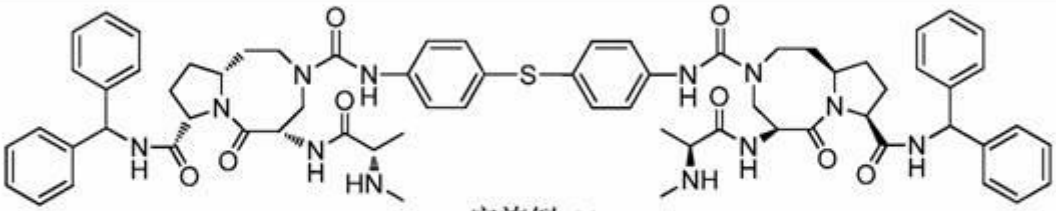
实施例 17



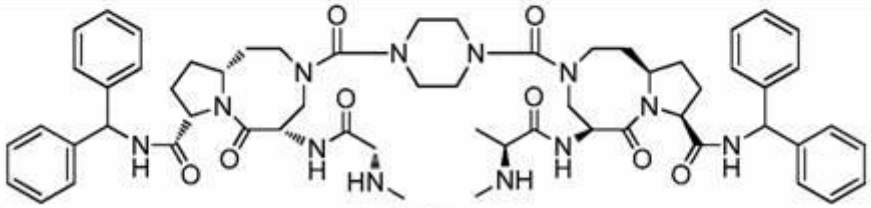
实施例 18



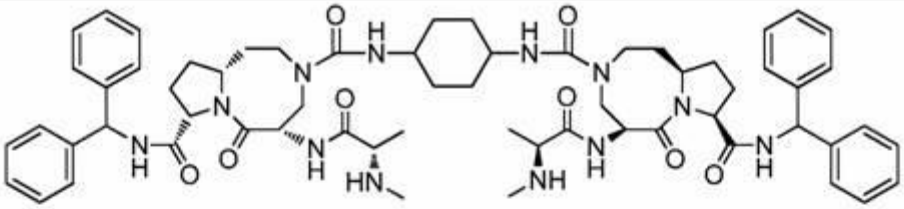
实施例 19



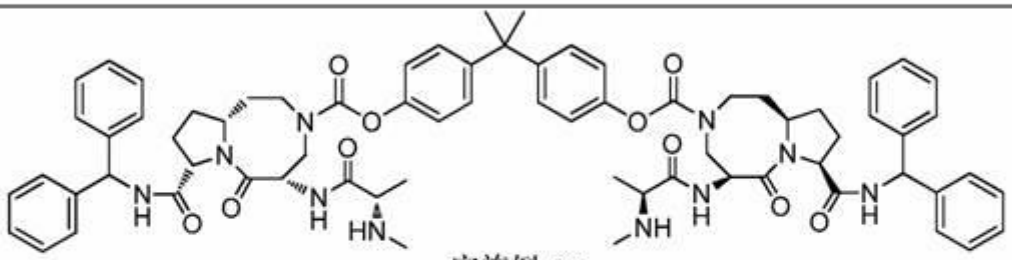
实施例 20



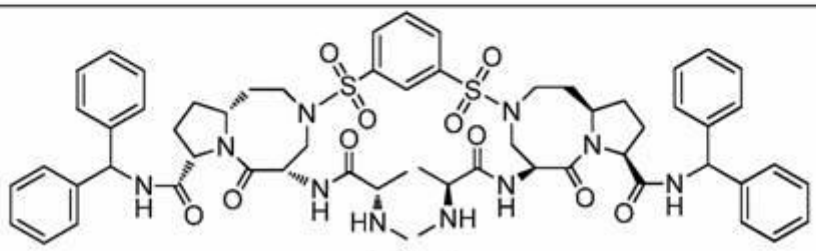
实施例 21



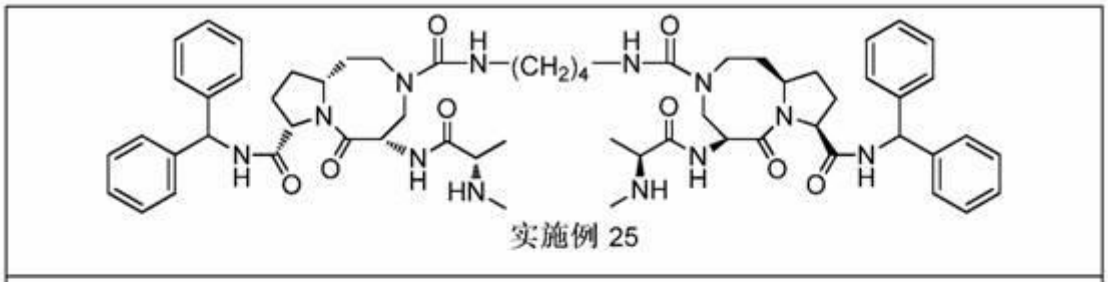
实施例 22



实施例 23

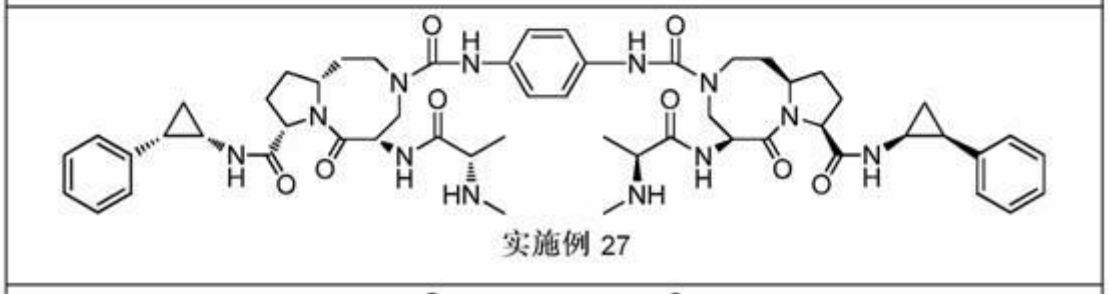


实施例 24

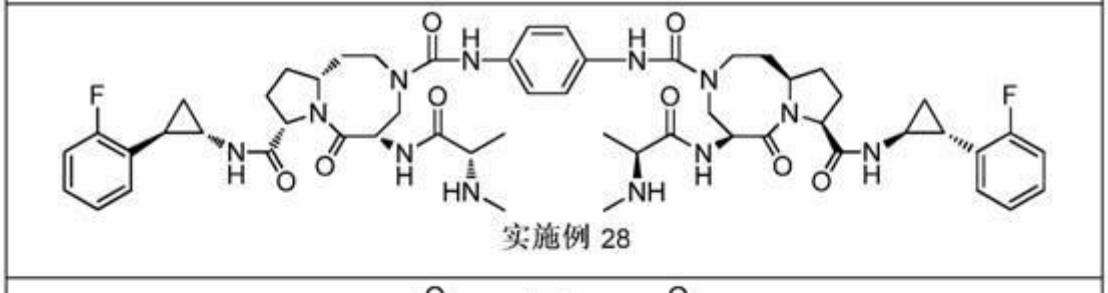


实施例 25

实施例 26



实施例 27

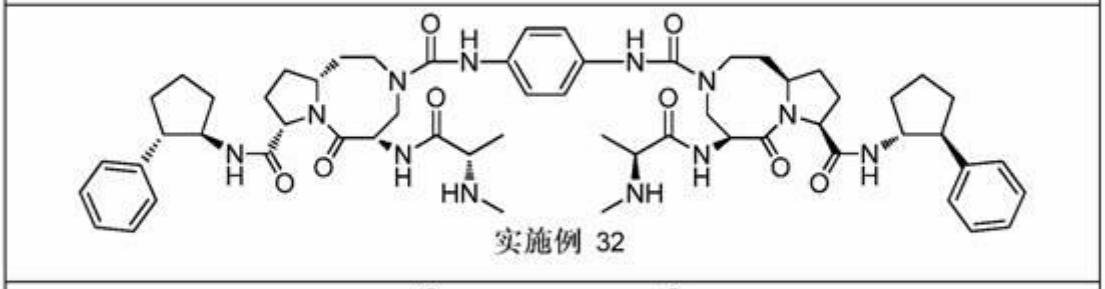


实施例 28

实施例 29

实施例 30

实施例 31

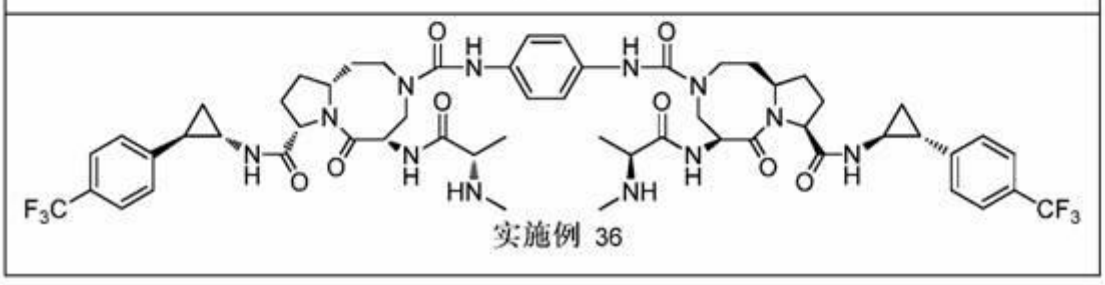


实施例 32

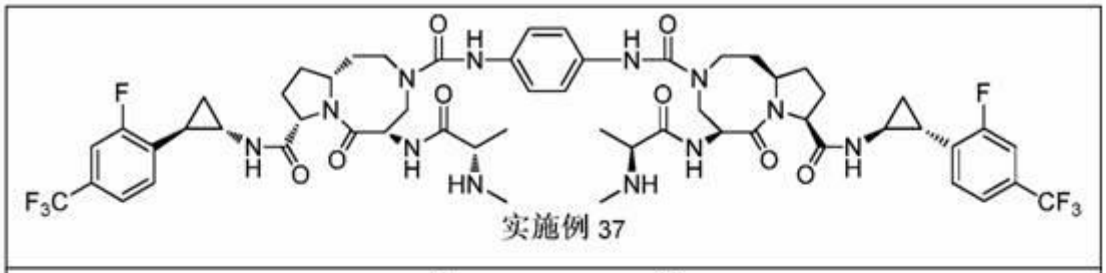
实施例 33

实施例 34

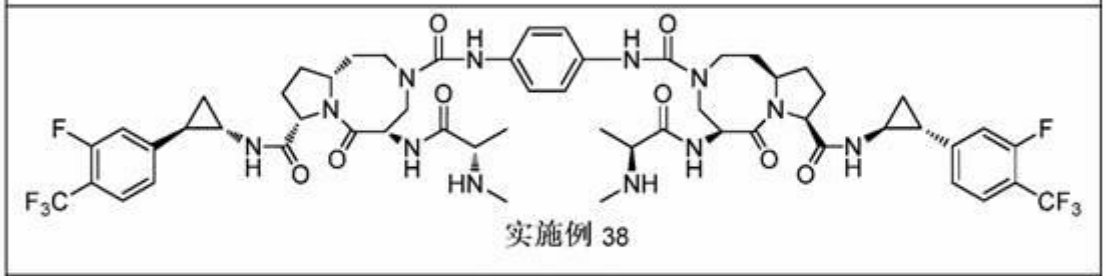
实施例 35



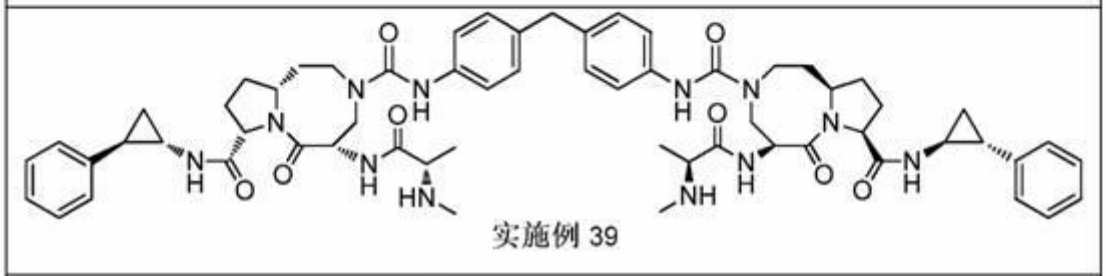
实施例 36



实施例 37



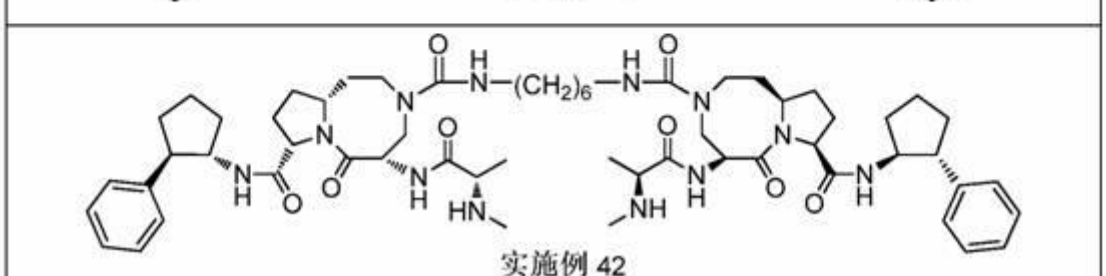
实施例 38



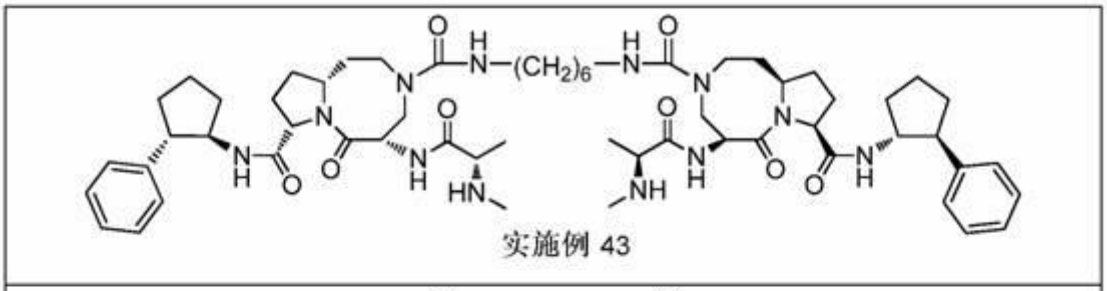
实施例 39

实施例 40

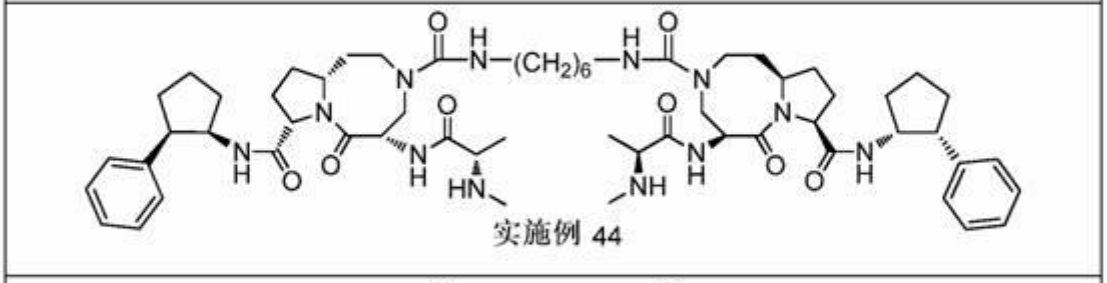
实施例 41



实施例 42

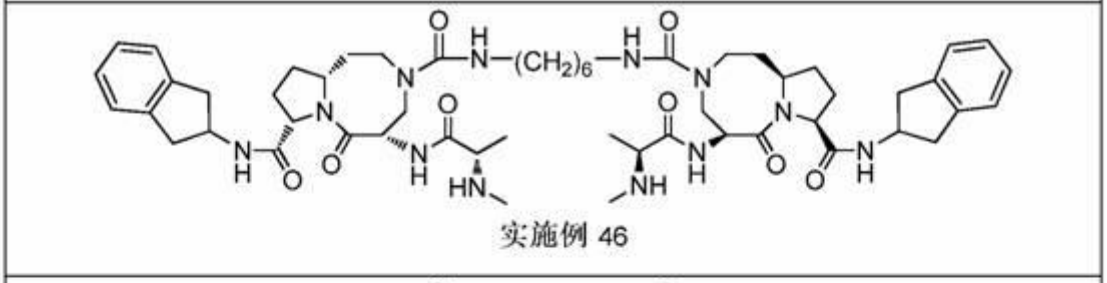


实施例 43

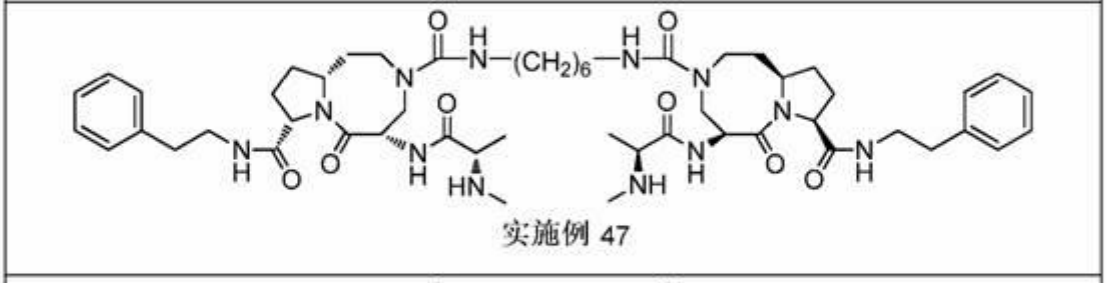


实施例 44

实施例 45

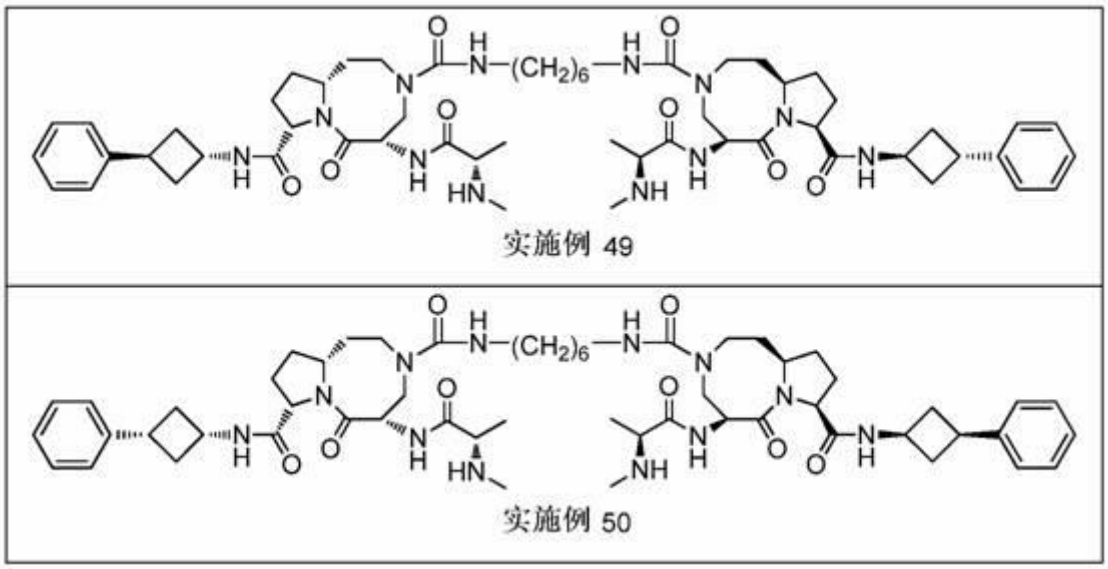


实施例 46



实施例 47

实施例 48



[0086] 本发明提供了如由结构式 (I) 的化合物所例举的 IAP 蛋白抑制剂，其用于治疗其中 IAP 蛋白的抑制具有有益效果的多种疾病和病症。在一个实施方案中，本发明涉及治疗患有其中 IAP 蛋白的抑制提供益处的疾病或病症的个体的方法，该方法包括将治疗有效量的结构式 (I) 的化合物施用于有需要的个体。

[0087] 本 IAP 蛋白抑制剂满足了对治疗多种癌症类型的需求，无论是当作为单一疗法施用以在依赖于 IAP 功能的癌细胞中诱导细胞凋亡时，还是当与其他抗癌治疗以时间关系施用，以使得与仅单独使用癌症治疗药或放疗治疗的动物中相应比例的细胞相比，更大比例的癌细胞易于执行细胞凋亡程序。

[0088] 如本文使用的术语“抗癌治疗”是指用于治疗过度增殖性疾病，例如哺乳动物中的癌症的治疗剂 (例如化疗化合物和 / 或分子治疗化合物)、放疗和手术干预。

[0089] 本发明的方法可以通过将结构式 (I) 的化合物作为纯净的化合物或作为药物组合物施用来完成。药物组合物或结构式 (I) 的纯净的化合物的施用可以在感兴趣的疾病或病症期间或发作之后进行。通常，药物组合物是灭菌的，并且不含有当施用时会引起不良反应的有毒的、致癌的或致突变的化合物。进一步提供了药剂盒，所述药剂盒包含 :结构式 (I) 的化合物和任选地可用于治疗其中 IAP 蛋白的抑制提供益处的疾病和病症的第二治疗剂 (两者分开或一起包装)、以及具有用于使用这些活性剂的说明的插页。

[0090] 在许多实施方案中，结构式 (I) 的化合物连同可用于治疗其中 IAP 蛋白的抑制提供益处的疾病或病症的第二治疗剂施用。该第二治疗剂不同于结构式 (I) 的化合物。结构式 (I) 的化合物和第二治疗剂可以同时或相继施用以实现所希望的效果。另外，结构式 (I) 的化合物和第二治疗剂可以从单一组合物或两种分开的组合物施用。

[0091] 第二治疗剂以提供其所希望的治疗效果的量而施用。对于各第二治疗剂的有效剂量范围在本领域中是已知的，并且第二治疗剂在该确立范围之内施用于有需要的个体。

[0092] 在某些实施方案中，与用单独的结构式 (I) 的化合物或第二治疗剂的治疗相比，包括施用治疗有效量的结构式 (I) 的化合物和第二治疗剂的组合治疗产生更大肿瘤应答和更大临床益处。

[0093] 结构式 (I) 的化合物也可以用于实现施用更低、因此毒性更小且更可耐受的剂量的第二治疗剂，以产生与常规剂量的第二治疗剂相同的肿瘤应答 / 临床益处。此外，因为本

发明的化合物至少部分通过抑制 IAP 蛋白起作用，所以使癌细胞和支持细胞暴露于治疗有效量的本 IAP 蛋白抑制剂可以在时间上联系以便与使细胞响应于第二治疗剂而执行细胞凋亡程序的尝试一致。因此，在一些实施方案中，以某些时间关系施用本发明的化合物连同第二治疗剂尤其提供了有效的治疗结果。

[0094] 因此，结构式 (I) 的化合物和第二治疗剂可以一起作为单一的单位剂量或分开地作为多单位剂量施用，其中结构式 (I) 的化合物在第二治疗剂之前施用，或反之亦然。可以施用一个或多个剂量的结构式 (I) 的化合物和 / 或一个或多个剂量的第二治疗剂。因此，结构式 (I) 的化合物因此可以与一种或多种第二治疗剂 (例如但不限于抗癌剂) 联合使用。

[0095] 可以根据本发明治疗的疾病或病症包括例如癌症。可以治疗多种癌症，包括但不限于 :癌，包括膀胱癌 (包括加速性和转移性膀胱癌)、乳癌、结肠癌 (包括结肠直肠癌)、肾癌、肝癌、肺癌 (包括小细胞肺癌和非小细胞肺癌以及肺腺癌)、卵巢癌、前列腺癌、睾丸癌、泌尿生殖道癌、淋巴系统癌、直肠癌、喉癌、胰腺癌 (包括外分泌源性胰腺癌)、食道癌、胃癌、胆囊癌、宫颈癌、甲状腺癌、肾脏癌、和皮肤癌 (包括鳞状细胞癌) ;淋巴系的造血肿瘤，包括白血病、急性淋巴细胞白血病、急性成淋巴细胞白血病、B 细胞淋巴瘤、T 细胞淋巴瘤、霍奇金淋巴瘤、非霍奇金淋巴瘤、毛细胞淋巴瘤、组织细胞性淋巴瘤、和伯基特淋巴瘤 ;骨髓系的造血肿瘤，包括急性和慢性骨髓性白血病、骨髓增生异常综合征、髓细胞性白血病、和早幼粒细胞白血病 ;中枢和周围神经系统的肿瘤，包括星形细胞瘤、成神经细胞瘤、神经胶质瘤、和神经鞘瘤 ;间充质起源的肿瘤，包括纤维肉瘤、横纹肌肉瘤、和骨肉瘤 ;以及其他肿瘤，包括黑色素瘤、着色性干皮病 (xenoderma pigmentosum)、角化棘皮瘤 (keratoactanthoma)、精原细胞瘤、甲状腺滤泡癌、畸胎癌、肾细胞癌 (RCC)、胰腺癌、骨髓瘤、髓细胞性和成淋巴细胞性白血病、成神经细胞瘤、和胶质母细胞瘤。

[0096] 由本发明的 IAP 蛋白抑制剂可治疗的癌症的另外形式包括例如，成人和儿科肿瘤、实体瘤 / 恶性肿瘤的生长、粘液细胞和圆细胞癌、局部晚期肿瘤、转移癌、人软组织肉瘤 (包括尤因肉瘤)、癌转移 (包括淋巴转移)、鳞状细胞癌 (特别是头和颈部的)、食管鳞状细胞癌、口腔癌、血细胞恶性肿瘤 (包括多发性骨髓瘤、白血病 (包括急性淋巴细胞白血病、急性非淋巴细胞白血病、慢性淋巴细胞白血病、慢性髓细胞性白血病、和毛细胞白血病))、渗出性淋巴瘤 (基于体腔的淋巴瘤)、胸腺淋巴瘤肺癌 (包括小细胞癌)、皮肤 T 细胞淋巴瘤、霍奇金淋巴瘤、非霍奇金淋巴瘤、肾上腺皮质癌、产 ACTH 的肿瘤、非小细胞癌、乳癌 (包括小细胞癌和导管癌)、胃肠癌 (包括胃癌、结肠癌、结肠直肠癌、和与结肠直肠瘤形成相关的息肉)、胰腺癌、肝癌、泌尿系统癌 (包括膀胱癌，例如原发性浅表膀胱肿瘤、浸润性膀胱移行细胞癌、和肌层浸润性膀胱癌)、前列腺癌、女性生殖道的恶性肿瘤 (包括卵巢癌、原发性腹膜上皮瘤、宫颈癌、子宫内膜癌、阴道癌、外阴癌、子宫癌和卵泡中的实体瘤)、男性生殖道恶性肿瘤 (包括睾丸癌和阴茎癌)、肾癌 (包括肾细胞癌，脑癌 (包括内在脑肿瘤 (intrinsic brain tumor)、成神经细胞瘤、星形细胞性脑肿瘤、神经胶质瘤、和中枢神经系统中的转移性肿瘤细胞浸润)、骨癌 (包括骨瘤和骨肉瘤)、皮肤癌 (包括恶性黑色素瘤、人皮肤角质形成细胞的肿瘤进展、和鳞状细胞癌)、甲状腺癌、视网膜母细胞瘤、成神经细胞瘤、腹腔积液、恶性胸腔积液、间皮瘤、维尔姆斯瘤、胆囊癌、滋养细胞肿瘤、血管外皮细胞瘤、和卡波西肉瘤。

[0097] 本发明的另一个实施方案是通过使用结构式 (I) 的 IAP 蛋白抑制剂诱导细胞凋亡

并且增强响应于细胞凋亡诱导信号的细胞凋亡的诱导。本 IAP 蛋白抑制剂还使细胞对细胞凋亡诱导物敏感，包括对此类诱导物抵抗的细胞。本发明的 IAP 蛋白抑制剂可以用于诱导可以通过诱导细胞凋亡进行治疗、改善或预防的任何疾病中的细胞凋亡。因此，本发明提供了用于靶向特征为过表达 IAP 蛋白的动物的组合物和方法。在一些实施方案中，所述细胞（例如癌细胞）与非病理性样品（例如非癌细胞）相比显示 IAP 蛋白的表达水平升高。在其他实施方案中，所述细胞凭借响应于治疗有效量的结构式 (I) 的化合物执行细胞凋亡程序和死亡而可操作地表现出 IAP 蛋白的表达水平升高，所述响应至少部分由于此类细胞中其存活对 IAP 蛋白功能的依赖性而导致。

[0098] 在另一个实施方案中，本发明涉及调节细胞凋亡相关的状态，该状态与一种或多种细胞凋亡调节剂有关。细胞凋亡调节剂的实例包括但不限于 Fas/CD95、TRAMP、TNF RI、DR1、DR2、DR3、DR4、DR5、DR6、FADD、RIP、TNF α 、Fas 配体、TRAIL、TRAIL-RI 或 TRAIL-R2 的抗体、Bcl-2、p53、BAX、BAD、Akt、CAD、PI3 激酶、PP1 和胱天蛋白酶蛋白。还包括参与细胞凋亡的引发、决定和退化阶段的其他试剂。细胞凋亡调节剂的实例包括其活性、存在或浓度改变可以调节受试者的细胞凋亡的试剂。优选的细胞凋亡调节剂是细胞凋亡诱导物，例如 TNF 或 TNF 相关的配体，尤其是 TRAMP 配体、Fas/CD95 配体、TNFR-1 配体或 TRAIL。

[0099] 这些治疗可以用于多种设置中用于治疗各种癌症。在一个具体实施方案中，需要治疗的个体先前已经经历针对癌症的治疗。此类先前治疗包括，但不限于，先前化疗、放疗、手术或免疫治疗，例如癌症疫苗。

[0100] 在一个实施方案中，本发明提供了治疗癌症的方法，其包括 :(a) 向有需要的个体施用治疗有效量的结构式 (I) 的 IAP 蛋白抑制剂 ;和 (b) 向个体施用治疗有效量的放疗、化疗和免疫治疗中的一种或多种。施用的量各自对于治疗癌症是有效的。在另一个实施方案中，所述量一起对于治疗癌症是有效的。

[0101] 在另一个实施方案中，本发明提供了治疗癌症的方法，所述方法包括向有需要的个体施用包含结构式 (I) 的 IAP 蛋白抑制剂的药物组合物。

[0102] 在另一个实施方案中，本 IAP 蛋白抑制剂用于治疗以下疾病的方法中 :T 和 B 细胞介导的自身免疫性疾病 ;炎性疾病 ;感染 ;过度增殖性疾病 ;AIDS ;退化性病症 ;血管疾病 ;等。在一些实施方案中，适合于用本发明组合物和方法治疗的感染包括，但不限于由病毒、细菌、真菌、支原体、肮病毒等导致的感染。

[0103] 本发明化合物和方法也可用于治疗自身免疫性疾病或慢性炎性病症。如本文使用的术语“自身免疫性疾病”是指其中生物体产生识别生物体自身分子、细胞或组织的抗体或免疫细胞的任何病症。自身免疫性疾病的非限制性实例包括自身免疫性溶血性贫血、自身免疫性肝炎、贝格尔病或 IgA 肾病、口炎性腹泻、慢性疲乏综合征、克罗恩病、皮肌炎、纤维肌痛、移植物抗宿主病、格雷夫斯病、桥本甲状腺炎、特发性血小板减少性紫癜、扁平苔癣、多发性硬化、重症肌无力、银屑病、风湿热、风湿性关节炎、硬皮病、斯耶格伦综合征、系统性红斑狼疮、1 型糖尿病、溃疡性结肠炎、白癜风等。

[0104] 可以通过施用本发明的 IAP 蛋白抑制剂而治疗的包括癌症的另外的疾病和病症公开于美国专利 7,960,372 中 ;以其整体通过引用并入本文。

[0105] 在本发明的方法中，将通常根据制药实践配制的治疗有效量的一种或多种化合物 (I) 施用于有需要的人。是否指示此类治疗取决于个体病例并且经受考虑以下的医学评价

（诊断）：存在的体征、症状、和／或功能障碍，发展特定的体征、症状和／或功能障碍的风险，以及其他因素。

[0106] 结构式（I）的化合物可以通过任何适合的途径施用，例如通过口腔、颊、吸入、舌下、直肠、阴道、通过腰椎穿刺经脑池内或硬膜内、经尿道、鼻、经皮（即，透皮）、或肠胃外（包括静脉内、肌肉内、皮下、冠状动脉内、真皮内、乳房内、腹膜内、关节内、鞘内、眼球后、肺内注射和／或在特定部位的外科植入）施用。可以使用针和注射器或使用高压技术来完成肠胃外施用。

[0107] 药物组合物包括其中结构式（I）的化合物以实现其预期目的的有效量施用的那些。精确制剂、施用途径和剂量由个体医师鉴于诊断的病症或疾病而确定。剂量数量和时间间隔可以单独地进行调整，从而提供足以维持治疗效果的结构式（I）的化合物的水平。

[0108] 结构式（I）的化合物的毒性和治疗效力可以通过在细胞培养物或实验动物中的例如用于确定化合物的最大耐受剂量（MTD）（定义为在动物中不引起任何毒性的最高剂量）的标准药学程序来确定。在最大耐受剂量和治疗效果（例如，肿瘤生长的抑制）之间的剂量比是治疗指数。该剂量可以取决于所采用的剂型以及利用的施用途径而在该范围内变化。治疗有效量的确定，尤其是鉴于本文提供的详细公开，完全在本领域技术人员的能力之内。

[0109] 用于在治疗中使用所需要的结构式（I）的化合物的治疗有效量随着所治疗的病症的性质、所希望的活性的时间长度、和患者的年龄和病症而变化，并且最终由监护医师确定。剂量数量和时间间隔可以单独地进行调整，从而提供足以维持所希望的治疗效果的IAP蛋白抑制剂的血浆水平。所希望的剂量可以方便地以单一剂量施用或作为多剂量以适当的时间间隔施用，例如为每天一、二、三、四或更多个亚剂量。多剂量经常是所希望的或需要的。例如，本发明的IAP蛋白抑制剂可以以下频率施用：四个剂量，递送为每天一个剂量，以四天时间间隔（q4d × 4）；四个剂量，递送为每天一个剂量，以三天时间间隔（q3d × 4）；每天递送一个剂量，以五天时间间隔（qd × 5）；每周一个剂量，持续三周（qwk3）；五个日剂量，两天休息，以及另外的五个日剂量（5/2/5）；或被确定为针对情况适当的任何剂量方案。

[0110] 在本发明的方法中使用的结构式（I）的化合物可以每个剂量约0.005至约500毫克的量、每个剂量约0.05至约250毫克的量、或每个剂量约0.5至约100毫克的量施用。例如，结构式（I）的化合物可以每个剂量约0.005、0.05、0.5、5、10、20、30、40、50、100、150、200、250、300、350、400、450、或500毫克的量（包括在0.005毫克和500毫克之间的所有剂量）施用。

[0111] 含有结构式（I）的IAP蛋白抑制剂的组合物或者含有其的组合物的剂量可以是约1 ng/kg至约200 mg/kg、约1 μg/kg至约100 mg/kg、或约1 mg/kg至约50 mg/kg。组合物的剂量可以是任何剂量，包括但不限于约1 μg/kg。组合物的剂量可以是任何剂量，包括但不限于：约1 μg/kg、10 μg/kg、25 μg/kg、50 μg/kg、75 μg/kg、100 μg/kg、125 μg/kg、150 μg/kg、175 μg/kg、200 μg/kg、225 μg/kg、250 μg/kg、275 μg/kg、300 μg/kg、325 μg/kg、350 μg/kg、375 μg/kg、400 μg/kg、425 μg/kg、450 μg/kg、475 μg/kg、500 μg/kg、525 μg/kg、550 μg/kg、575 μg/kg、600 μg/kg、625 μg/kg、650 μg/kg、675 μg/kg、700 μg/kg、725 μg/kg、750 μg/kg、775 μg/kg、800 μg/kg、825 μg/

kg、850 μg/kg、875 μg/kg、900 μg/kg、925 μg/kg、950 μg/kg、975 μg/kg、1 mg/kg、5 mg/kg、10 mg/kg、15 mg/kg、20 mg/kg、25 mg/kg、30 mg/kg、35 mg/kg、40 mg/kg、45 mg/kg、50 mg/kg、60 mg/kg、70 mg/kg、80 mg/kg、90 mg/kg、100 mg/kg、125 mg/kg、150 mg/kg、175 mg/kg、或 200 mg/kg。以上剂量是平均情况的示例，但可以存在其中较高或较低的剂量是理所当然的的个别情况，并且这是在本发明的范围之内。在实践中，医师确定最适合于个体患者的实际给药方案，其可以随具体患者的年龄、重量、和响应而变化。

[0112] 在癌症的治疗中，结构式 (I) 的化合物可以与化疗剂和 / 或免疫治疗剂和 / 或放射或结合另一种治疗技术例如手术一起施用。如本文使用的术语化疗剂包括抗癌剂、抗肿瘤剂、细胞凋亡调节剂。

[0113] 本发明的实施方案采用以下的电磁放射：γ - 放射 (10^{-20}至 10^{-13} m)、X- 射线放射 (10^{-12}至 10^{-9} m)、紫外光 (10 nm 至 400 nm)、可见光 (400 nm 至 700 nm)、红外放射 (700 nm 至 1 mm)、以及微波放射 (1 mm 至 30 cm)。

[0114] 许多癌症治疗方案当前采用由电磁放射 (例如，X- 射线) 激活的放射增敏剂。X- 射线激活的放射增敏剂的实例包括但不限于甲硝唑、醚醇硝唑、去甲基醚醇硝唑、哌莫硝唑、依他硝唑、尼莫唑、丝裂霉素 C、RSU 1069、SR 4233、EO9、RB 6145、烟酰胺、5- 溴脱氧尿苷 (BUdR)、5- 碘脱氧尿苷 (IUdR)、溴脱氧胞苷、氟脱氧尿苷 (FUdR)、羟基脲、顺铂、及其治疗有效的类似物和衍生物。

[0115] 癌症的光动力疗法 (PDT) 采用可见光作为敏化剂的放射激活剂。光动力放射增敏剂的实例包括以下，但不限于：血卟啉衍生物、PHOTOFRIN®、苯并卟啉衍生物、NPe6、初卟啉锡 (SnET2)、脱镁叶绿酸 -a (pheoborbide-a)、细菌叶绿素 -a、萘酞菁、酞菁、酞菁锌、及其治疗有效的类似物和衍生物。

[0116] 放射增敏剂除了联合本发明的 IAP 蛋白抑制剂之外还可以联合治疗有效量的一种或多种化合物而施用，此类化合物包括但不限于：促进放射增敏剂掺入靶细胞的化合物，控制治疗剂、营养素、和 / 或氧向靶细胞流动的化合物，在有或没有另外的放射下作用于肿瘤的化疗剂，或者其他用于治疗癌症或其他疾病的治疗有效的化合物。可以与放射增敏剂联合使用的另外的治疗剂的实例包括但不限于 5- 氟尿嘧啶 (5-FU)、甲酰四氢叶酸、氧、卡波金 (carbogen)、红细胞输血、全氟化碳 (例如 FLUOSOLW®-DA)、2,3-DPG、BW12C、钙通道阻滞剂、己酮可可碱、抗血管生成化合物、肼屈嗪、和 L-BSO。

[0117] 化疗剂可以是诱导细胞凋亡的任何药理活性剂或化合物。药理活性剂或化合物可以是例如小有机分子、肽、多肽、核酸、或抗体。可以使用的化疗剂包括但不限于烷化剂、抗代谢药、激素和其拮抗剂 (天然产物和它们的衍生物)、放射性同位素、抗体、以及天然产物、以及它们的组合。例如，本发明的 IAP 蛋白抑制剂可以与抗生素 (例如多柔比星和其他蒽环类抗生素类似物)、氮芥类 (例如环磷酰胺)、嘧啶类似物 (例如 5- 氟尿嘧啶)、顺铂、羟基脲、紫杉酚和其天然及合成衍生物等一起施用。作为另一个实例，在混合肿瘤的情况下，例如乳腺腺癌，在肿瘤包括依赖于促性腺激素和不依赖于促性腺激素的细胞的情况下，该化合物可以联合亮丙瑞林或戈舍瑞林 (LH-RH 的合成肽类似物) 而施用。其他抗肿瘤方案包括使用抑制剂化合物与另一治疗方式 (例如，外科手术或放射)，后者在此还被称为“辅助抗肿瘤方式”。在本发明中有用的另外的化疗剂包括激素和其拮抗剂、放射性同位素、抗体、天然产物、以及其组合。

[0118] 在本发明的方法中有用的化疗剂的实例列于下表中。

[0119] 表 1

烷化剂	天然产物
氮芥类	抗有丝分裂药
双氯乙基甲胺(mechlorethamine)	
环磷酰胺	紫杉烷类
异环磷酰胺	紫杉醇
美法仑	长春花碱(Vinca alkaloid)
苯丁酸氮芥	长春碱(vinblastine，VLB)
尿嘧啶氮芥	长春新碱(vincristine)
替莫唑胺	长春瑞滨
	长春地辛
亚硝基脲类	Taxotere®(多西他赛)
卡莫司汀(BCNU)	雌莫司汀
洛莫司汀(CCNU)	磷酸雌莫司汀
司莫司汀(甲基-CCNU)	
盐酸氮芥(chlormethine)	表鬼臼毒素类
链佐星	依托泊苷
	替尼泊苷
乙烯亚胺/甲基-三聚氰胺	
曲他胺(TEM)	抗生素类
三亚乙基硫代磷酰胺(triethylene thiophosphoramide)(噻替派)	放线菌素D(actimomycin D)
	道诺霉素(红比霉素)
六甲三聚氰胺	多柔比星(阿霉素)
(HMM，六甲蜜胺(altretamine))	米托蒽醌伊达比星
	博来霉素
烷基磺酸盐类	splicamycin(光辉霉素)
白消安	光辉霉素-C
哌泊溴烷	更生霉素
	阿非迪霉素
三嗪类	表柔比星
达卡巴嗪(DTIC)	伊达比星
	柔红霉素
抗代谢物类	光辉霉素
叶酸类似物	脱氧助间型霉素
氨甲蝶呤	
三甲曲沙	酶类
培美曲塞	L-天门冬酰胺酶
(多靶向抗叶酸剂)	L-精氨酸酶
嘧啶类似物	放射增敏剂
5-氟尿嘧啶	甲硝唑
氟脱氧尿苷	米索硝唑
吉西他滨	去甲基米索硝唑

胞嘧啶阿拉伯糖苷
(AraC，阿糖胞苷)
5-氮杂胞苷
2,2′-二氟脱氧-胞苷
氮尿苷
喷司他丁(pentostatine)

嘌呤类似物
6-巯基嘌呤
6-硫代鸟嘌呤
硫唑嘌呤
2'-脱氧助间型霉素
(喷司他丁(pentostatin))
赤羟基壬基-腺嘌呤(EHNA)
磷酸氟达拉滨
2-氯脱氧腺苷
(克拉屈滨，2-CdA)

I型拓扑异构酶抑制剂
喜树碱
托泊替康
伊立替康

生物反应调节剂
G-CSF
GM-CSF

分化剂
视黄酸衍生物

激素类和拮抗剂类
肾上腺皮质类固醇类/拮抗剂
强的松和等效物
地塞米松
氨鲁米特(ainoglutethimide)

孕激素类
己酸羟孕酮
醋酸甲羟孕酮
醋酸甲地孕酮(megestrol acetate)

雌激素类
己烯雌酚
炔雌醇/等效物

哌莫硝唑
依他硝唑
尼莫唑
RSU 1069
EO9
RB 6145

非甾体抗雄激素药
SR4233
氟他胺
烟酰胺
5-溴脱氧尿苷
5-碘脱氧尿苷
溴脱氧胞苷

其他药剂
铂配位复合物
顺铂
卡铂
奥沙利铂
蒽二酮
米托蒽醌

取代的脲
羟基脲

甲基肼衍生物
N-甲基肼(MIH)
丙卡巴肼

肾上腺皮质抑制剂
米托坦(*o,p'*-DDD)
氨鲁米特(ainoglutethimide)

细胞因子类
干扰素(α, β, γ)
白介素-2

光敏剂
血卟啉衍生物
PHOTOFRIN®
苯并卟啉衍生物
Npe6
初卟啉锡(SnET2)
脱镁叶绿酸-a (pheoboride-a)
细菌叶绿素-a

抗雌激素药	萘酞菁
他莫昔芬	酞菁
	酞菁锌
雄激素类	
丙酸睾酮	放射
氟羟甲睾酮/等效物	X-射线
	紫外光
抗雄激素药	γ放射
氟他胺	可见光
促性腺激素释放药	红外放射
激素类似物	微波放射
亮丙瑞林	

[0120] 影响微管的药剂干扰细胞有丝分裂，并且关于它们的细胞毒活性在本领域中是众所周知的。在本发明中有用的影响微管的药剂包括但不限于：别秋水仙碱 (NSC 406042)、软海绵素 B(NSC 609395)、秋水仙碱 (NSC 757)、秋水仙碱衍生物 (例如 NSC 33410)、多拉司他汀 10(NSC 376128)、美登素 (NSC 153858)、根霉素 (NSC 332598)、紫杉醇 (NSC 125973)、紫杉酚 ®(TAXOL®) 衍生物 (例如，NSC 608832)、硫代秋水仙碱 (NSC 361792)、三苯甲基半胱氨酸 (NSC 83265)、硫酸长春碱 (NSC 49842)、硫酸长春新碱 (NSC 67574)、天然的和合成的埃坡霉素 (包括但不限于埃坡霉素 A、埃坡霉素 B、和替斯利得 (discodermolide)(参见 Service, (1996) Science, 274:2009) 雌莫司汀、诺考达唑、MAP4，等。此类药剂的实例还描述于 Bulinski (1997) *J. Cell Sci.* 110:3055 3064; Panda (1997) *Proc. Natl. Acad. Sci. USA* 94:10560-10564; Muhlradt (1997) *Cancer Res.* 57:3344-3346; Nicolaou (1997) *Nature* 397:268-272; Vasquez (1997) *Mol. Biol. Cell.* 8:973-985; 和 Panda (1996) *J. Biol. Chem.* 271:29807-29812。

[0121] 可以使用的细胞生长抑制剂包括但不限于以下激素和类固醇 (包括合成类似物)：17-α- 炔雌醇 (17-α-ethinylestadiol)、己烯雌酚、睾酮、强的松、氟甲睾酮、丙酸屈他雄酮、睾内酯、醋酸甲地孕酮、甲泼尼龙、甲基睾酮、泼尼松龙、曲安西龙、氯烯雌醚 (hlorotrianisene)、羟孕酮、氨鲁米特 (aminogluthimide)、雌莫司汀、醋酸甲羟孕酮、亮丙瑞林、氟他胺、托瑞米芬、诺雷德。

[0122] 其他细胞生长抑制剂是抗血管生成剂，例如基质金属蛋白酶抑制剂、和其他 VEGF 抑制剂 (例如抗 VEGF 抗体以及例如 ZD6474 和 SU668 的小分子)。还可以利用抗 Her2 抗体。EGFR 抑制剂是 EKB-569(不可逆抑制剂)。还包括的是对于 EGFR 具有免疫特异性的抗体 C225 和 Src 抑制剂。

[0123] 还适合作为细胞生长抑制剂使用的是 CASODEX®(比卡鲁胺，Astra Zeneca)，它致使雄激素依赖性癌变为非增殖性的。细胞生长抑制剂的又另一个实例是抗雌激素药他莫昔芬 ®(TAMOXIFEN®)，其抑制雌激素依赖性乳腺癌的增殖或生长。细胞增殖信号的转导的抑制剂是细胞生长抑制剂。代表性实例包括表皮生长因子抑制剂、Her-2 抑制剂、MEK-1 激酶抑制剂、MAPK 激酶抑制剂、PI3 抑制剂、Src 激酶抑制剂、和 PDGF 抑制剂。

[0124] 抗微生物治疗剂也可以用作本发明中的第二治疗剂。可以使用可以杀伤、抑制或者减弱微生物功能的任何药剂以及考虑具有此类活性的任何药剂。抗微生物剂包括，但不

限于天然和合成的抗生素、抗体、抑制蛋白（例如防御素）、反义核酸、膜破裂剂等，其可以单独使用或组合使用。实际上，可以使用任何类型的抗生素，包括，但不限于抗细菌剂、抗病毒剂、抗真菌剂等。

[0125] 可以与本发明的 IAP 蛋白抑制剂施用的另外的第二治疗剂公开于美国专利号 7,960,372 中，以其整体通过引用并入本文。

[0126] 本发明的化合物通常与药物载体混合施用，所述药物载体是关于预期施用途径和标准制药实践而选择的。使用一种或多种生理上可接受的载体（包含促进结构式 (I) 的化合物的加工的赋形剂和助剂）以常规方式配制用于根据本发明使用的药物组合物。

[0127] 可以例如通过常规的混合、溶解、制粒、制糖衣 (dragee-making)、乳化、包封 (encapsulating)、包埋 (entrapping)、或冻干过程来制备这些药物组合物。适当的制剂取决于所选择的施用途径。当治疗有效量的结构式 (I) 的化合物经口施用时，该组合物通常呈片剂、胶囊、散剂、溶液、或酏剂的形式。当以片剂形式施用时，该组合物可以另外地含有固体载体，例如明胶或佐剂。片剂、胶囊、和散剂含有约 0.01% 至约 95%、并且优选约 1% 至约 50% 的结构式 (I) 的化合物。当以液体形式施用时，可以添加液体载体（例如水、石油、或者动物或植物来源的油）。组合物的液体形式可以进一步含有生理盐水溶液、葡萄糖或其他糖类溶液、或二醇类。当以液体形式施用时，该组合物含有以重量计约 0.1% 至约 90%、并且优选约 1% 至约 50% 的结构式 (I) 的化合物。

[0128] 当治疗有效量的结构式 (I) 的化合物通过静脉内、皮肤、或皮下注射施用时，该组合物呈无热原、肠胃外可接受的水溶液的形式。此类肠胃外可接受的溶液的制备（充分考虑到 pH、等渗性、稳定性，等等）是在本领域技术之内。用于静脉内、皮肤、或皮下注射的优选组合物通常含有等渗的媒介物。

[0129] 结构式 (I) 的化合物可以容易地与本领域中众所周知的药学上可接受的载体组合。此类载体使得活性剂能够被配制为用于由待治疗的患者口服摄取的片剂、丸剂、锭剂、胶囊、液体、凝胶、糖浆、浆料、悬浮剂等。用于口服使用的药物制剂可以通过以下获得：将结构式 (I) 的化合物添加至固体赋形剂、任选地将所得混合物进行研磨、并且如果需要的话在添加适合的助剂之后将颗粒混合物进行加工以获得片剂或糖锭剂芯。适合的赋形剂包括例如填充剂和纤维素制剂。如果需要的话，可以添加崩解剂。

[0130] 结构式 (I) 的化合物可以被配制为用于通过注射（例如通过单次快速注射或连续输注）而肠胃外施用。用于注射的制剂可以单位剂型（例如在安瓿瓶中或在多剂量容器中）与添加的防腐剂一起呈现。组合物可以采取例如在油性或水性媒介物中的悬浮剂、溶液、或乳液的形式，并且可以含有配方剂，例如助悬剂、稳定剂、和 / 或分散剂。

[0131] 用于肠胃外施用的药物组合物包括水溶性形式的活性剂的水溶液。另外，结构式 (I) 的化合物的悬浮剂可以制备为适当的油性注射悬浮剂。适合的亲脂性溶剂或媒介物包括脂肪油或合成脂肪酸酯。水性注射悬浮剂可以含有增加悬浮剂粘度的物质。任选地，悬浮剂还可以含有增加化合物溶解度并且允许高度浓缩溶液的制备的适合的稳定剂或试剂。或者，本发明的组合物可以呈散剂形式，该散剂形式用于在使用前与适合的媒介物（例如灭菌无热原的水）构造。

[0132] 结构式 (I) 的化合物还可以配制为直肠组合物，如，例如含有常规的栓剂基质的栓剂或保留灌肠剂。除了先前描述的制剂外，结构式 (I) 的化合物还可以配制为长效制剂

(depot preparation)。此类长效制剂可以通过植入（例如，皮下或肌内）或者通过肌内注射来施用。因此，例如，结构式 (I) 的化合物可以用适合的聚合物材料或疏水材料（例如，作为在可接受的油中的乳液）或离子交换树脂进行配制。

[0133] 具体而言，结构式 (I) 的化合物可以经口、颊、或舌下以含有赋形剂（例如淀粉或乳糖）的片剂的形式、或以单独或与赋形剂混合的胶囊或胚珠制剂 (ovules)、或者以含有调味剂或着色剂的酏剂或悬浮剂的形式施用。可以用药学上可接受的添加剂（例如助悬剂）制备此类液体制剂。还可以肠胃外注射结构式 (I) 的化合物，例如静脉内、肌内、皮下、或冠状动脉内。对于肠胃外施用，IAP 蛋白抑制剂最好以无菌水溶液的形式使用，该无菌水溶液可以含有其他物质（例如盐或单糖（例如甘露醇或葡萄糖）），从而使得溶液与血液等渗。

[0134] 作为另外的实施方案，本发明包括药剂盒，所述药剂盒包含以促进它们实践本发明的方法的用途的方式包装的一种或多种化合物或组合物。在一个简单的实施方案中，该药剂盒包括对于实践方法有用的本文所述的化合物或组合物（例如，包含结构式 (I) 的化合物和任选的第二治疗剂的组合物），其包装在容器中（例如密封的瓶子或容器），具有附着至容器或包括在药剂盒中的标签，该标签描述该化合物或组合物实践本发明的方法的用途。优选地，该化合物或组合物被包装为单位剂型。该药剂盒可以进一步包括适用于根据预期的施用途径施用该组合物的装置。

[0135] 先前的 IAP 蛋白抑制剂具有妨碍它们发展为治疗剂的特性。根据本发明的重要特征，结构式 (I) 的化合物被合成并且作为 IAP 蛋白的抑制剂而进行评估。例如，本发明的化合物通常具有对 IAP 蛋白的小于 100 nM、小于 50 nM、小于 25 nM、和小于 10 nM 的结合亲和力 (IC_{50})。

[0136] 化合物的合成

本发明的化合物如下制备。以下合成方案代表用来合成结构式 (I) 的化合物的反应。制备本发明的 IAP 蛋白的修改和替代方案容易地在本领域技术人员的能力之内。

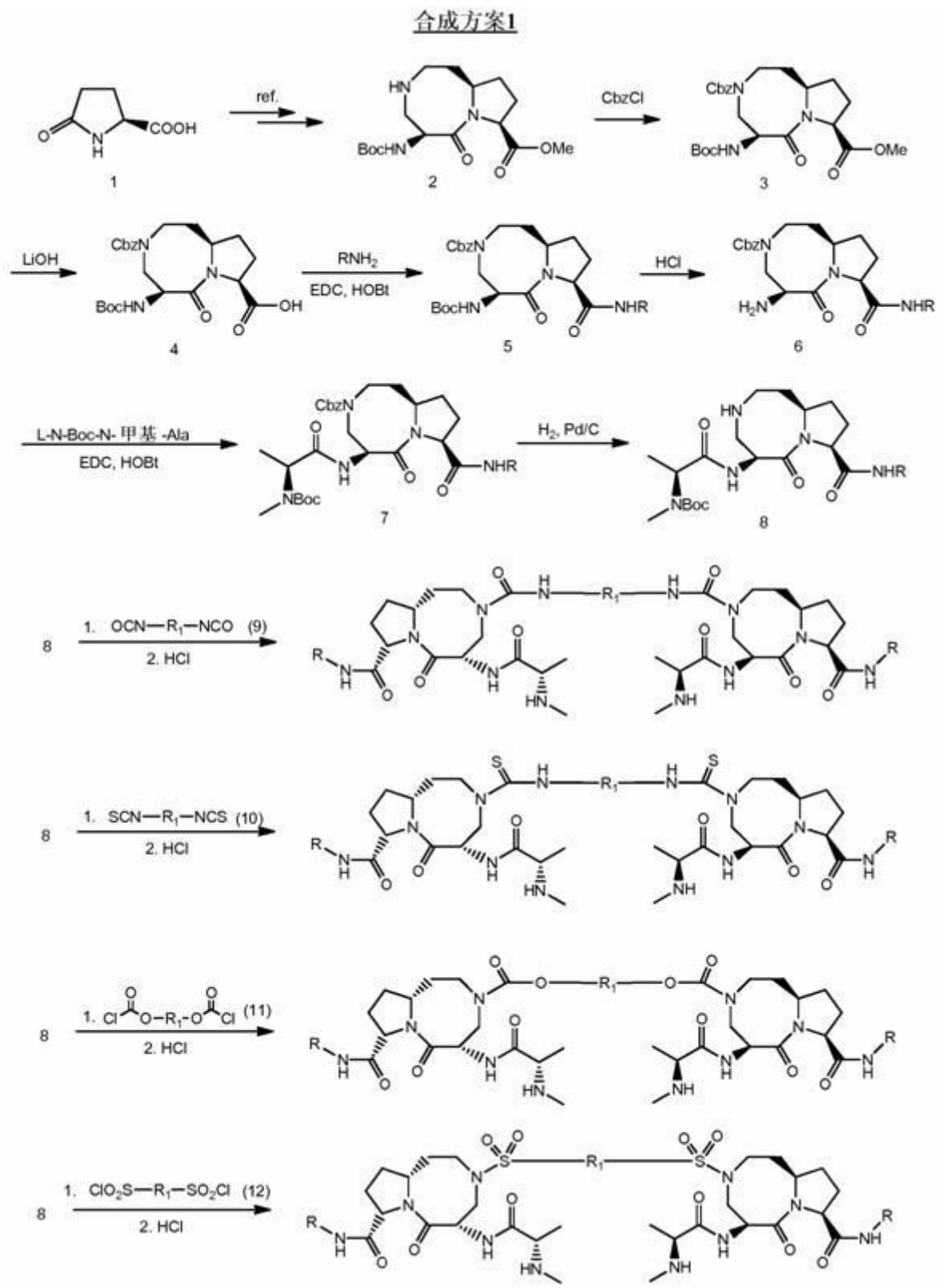
[0137] 溶剂和试剂是从商业上获得的并且没有进一步纯化即使用。NMR 谱的化学位移（δ）被报道为相对于内标的 δ 值 (ppm) 低场 (downfield)，其中多重性以通常方式报道。

[0138] 除非另有说明，所有温度以摄氏度计。

[0139] 在合成方法、实施例中和说明书通篇，缩写具有以下含义：

MS	质谱法
CbzCl	氯甲酸苄酯
LiOH	氢氧化锂
HCl	盐酸
CD_3OD	氘代甲醇
NMR	核磁共振波谱法
Hz	赫兹
EDC	1- 乙基 -3-(3- 二甲基氨基丙基）碳二亚胺盐酸盐
HOBt	1- 羟基苯并三唑
Pd/C	钯碳

合成方案1

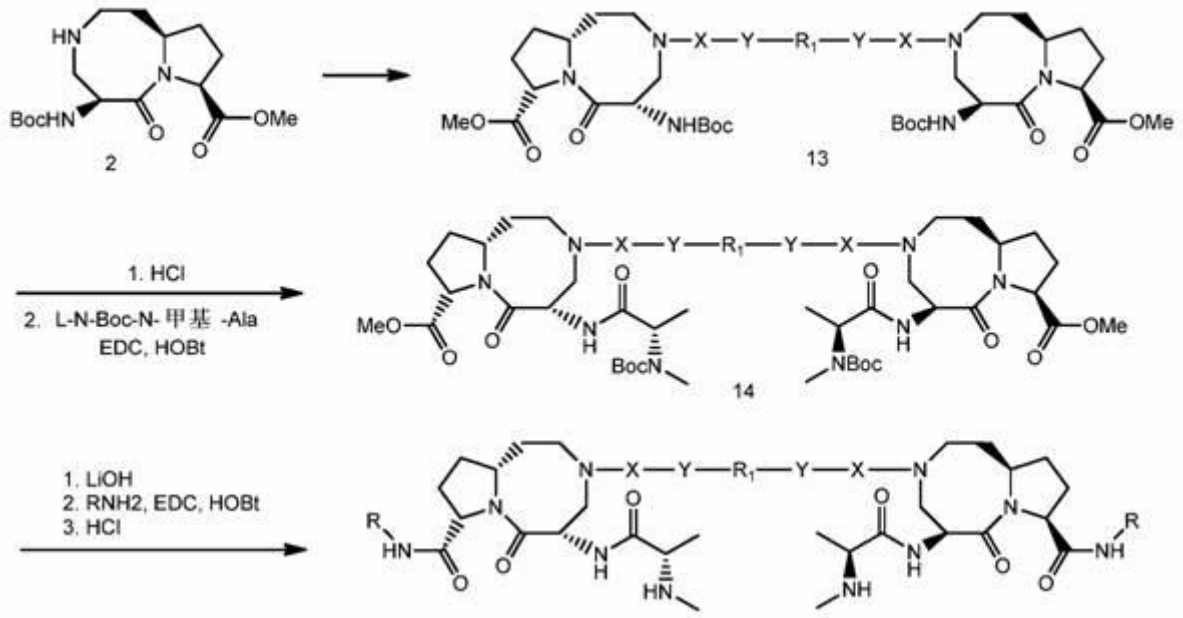


[0140] 根据上述合成方案 1 中显示的方法合成结构式 (I) 的每种化合物,除了在 R 中具有环丙基环的那些。根据 Q. Cai 等人, J. Med. Chem., 2011, 2714-26 中公开的方法合成化合物 2。用 Cbz 保护化合物 2 中的氨基得到氨基甲酸酯 3。氨基甲酸酯 3 中的甲基酯的水解产生酸 4。酸 4 与一系列胺的缩合分别得到酰胺 5。酰胺 5 中 Boc 保护基团的去除得到胺 6。胺 6 与 L-N-Boc-N- 甲基 - 丙氨酸的缩合提供酰胺 7。酰胺 7 中 Cbz 保护基团的

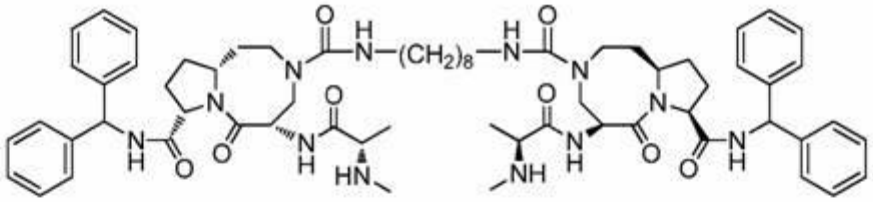
裂解得到胺 8。

[0141] 胺 8 与一系列二异氰酸酯 (9) 的缩合，以及随后除去 Boc 保护基团，得到含有 Smac 模拟物的双脲。胺 8 与一系列二异硫氰酸酯 (10) 的缩合，以及随后除去 Boc 保护基团，得到含有 Smac 模拟物的双 - 硫脲。胺 8 与一系列二氯甲酸酯 (dicarbonochloridate) (12) 的缩合，以及随后除去 Boc 保护基团，得到含有 Smac 模拟物的双 - 氨基甲酸酯。胺 8 与一系列二磺酰氯的缩合，以及随后除去 Boc 保护基团，得到含有 Smac 模拟物的双 - 磺酰胺。

合成方案2

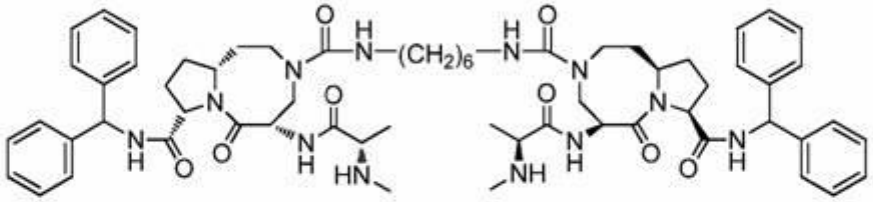


[0142] 在 R 中具有环丙基环的通用结构式 (I) 的化合物，合成显示于上述合成方案 2 中。化合物 2 与二异氰酸酯、二异硫氰酸酯、二氯甲酸酯 (dicarbonochloridate) 或二磺酰氯的缩合分别得到中间体 13。去除化合物 13 中的 Boc 保护基团，以及随后与 L-N-Boc-N- 甲基 -Ala 的缩合，得到酰胺 14。酰胺 14 中甲基酯的水解得到一系列酸。所述酸与一系列胺的缩合和随后 Boc 保护基团的脱保护提供了最终化合物。



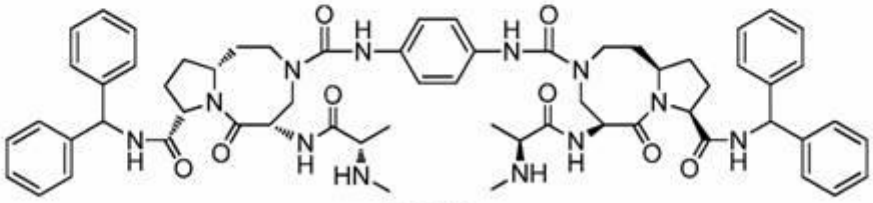
实施例 1

^{1}H NMR (300 MHz, CD_3OD): δ 7.37-7.24 (m, 20H), 6.16 (s, 2H), 4.72-4.60 (m, 4H), 4.10 (m, 2H), 4.00-3.85 (m, 6H), 3.25-3.04 (m, 8H), 2.69 (s, 6H), 2.34 (m, 2H), 2.14-2.03 (m, 6H), 1.77-1.48 (m, 8H), 1.54 (d, *J*=6.9 Hz, 6H), 1.35 (m, 8H); ESI MS: *m/z* 1151.8 $(M+H)^+$.



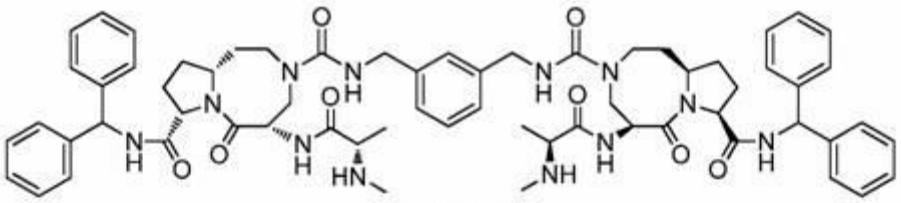
实施例 13

^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.23 (m, 20H), 6.15 (s, 2H), 4.70-4.60 (m, 4H), 4.10 (m, 2H), 3.97-3.80 (m, 6H), 3.25-3.03 (m, 8H), 2.69 (s, 6H), 2.34 (m, 2H), 2.10-2.03 (m, 6H), 1.78-1.57 (m, 8H), 1.52 (d, *J*=7.2 Hz, 6H), 1.39 (m, 4H); ESI MS: *m/z* 1123.6 $(M+H)^+$.



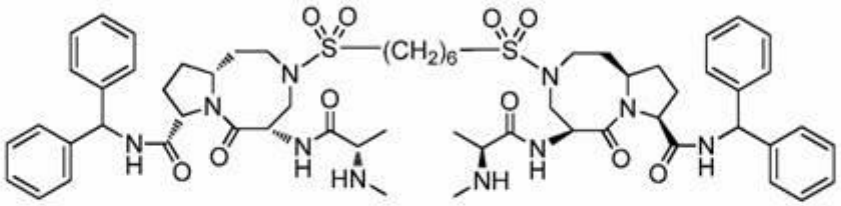
实施例 2

^{1}H NMR (300 MHz, CD_3OD): δ 7.53 (s, 4H), 7.37 (m, 20H), 6.18 (s, 2H), 4.84 (m, 2H), 4.67 (t, *J*= 8.4 Hz, 2H), 4.27 (m, 2H), 4.09-3.80 (m, 6H), 3.30-3.05 (m, 4H), 2.71 (s, 6H), 2.37 (m, 2H), 2.35-1.80 (m, 4H), 1.70-1.55 (m, 6H), 1.45 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1115.9 $(M+H)^+$.



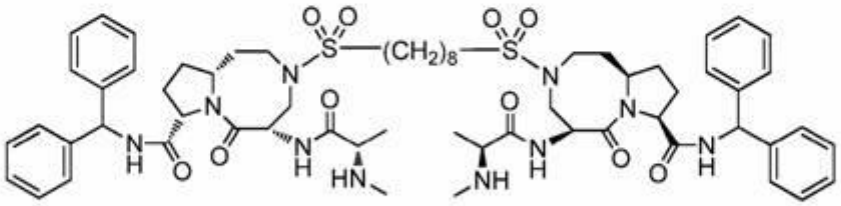
实施例 3

^{1}H NMR (300 MHz, CD_3OD): δ 7.36-7.15 (m, 24H), 6.15 (s, 2H), 4.84 (m, 2H), 4.63 (m, 4H), 4.32-4.14 (m, 4H), 3.99-3.81 (m, 6H), 3.16-3.06 (m, 4H), 2.63 (s, 6H), 2.34 (m, 2H), 2.18-2.85 (m, 6H), 1.85-1.60 (m, 4H), 1.50(d, *J*=7.2 Hz, 6H); ESI MS: *m/z* 1143.67 $(M+H)^+$.



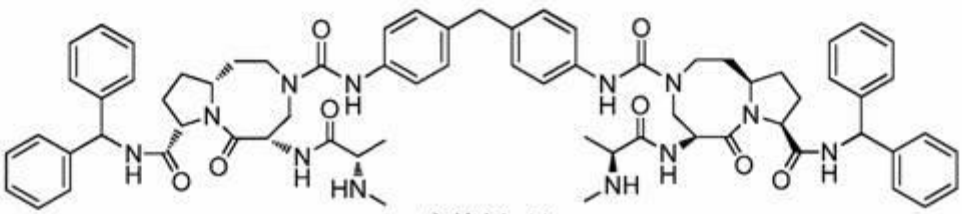
实施例 9

^{1}H NMR (300 MHz, CD_3OD): δ 7.36 (m, 20H), 6.14 (s, 2H), 4.82 (m, 2H), 4.60 (t, *J*= 8.4 Hz, 2H), 4.44 (m, 2H), 3.92-3.80 (m, 4H), 3.70 (m, 2H), 3.42 (m, 2H), 3.16-3.03 (m, 6H), 2.66 (s, 6H), 2.36 (m, 2H), 2.16 (m, 2H), 2.00 (m, 4H), 1.73 (m, 8H), 1.52-1.43 (m, 10H); ESI MS: m/z 1165.4 $(M+H)^+$.



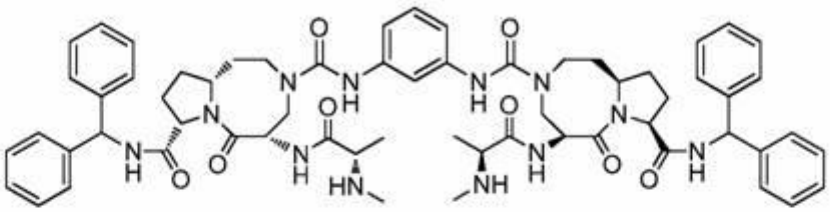
实施例 10

^{1}H NMR (300 MHz, CD_3OD): δ 7.36-7.22 (m, 20H), 6.14 (s, 2H), 4.82 (m, 2H), 4.60 (t, *J*= 8.4 Hz, 2H), 4.44 (m, 2H), 3.91-3.85 (m, 4H), 3.65 (m, 2H), 3.48 (m, 2H), 3.15-3.03 (m, 6H), 2.66 (s, 6H), 2.32 (m, 2H), 2.14 (m, 2H), 2.00 (m, 4H), 1.85-1.70 (m, 8H), 1.52 (d, J=8.7 Hz, 6H), 1.42-1.33 (m, 6H); ESI MS: m/z 1193.7 $(M+H)^+$.



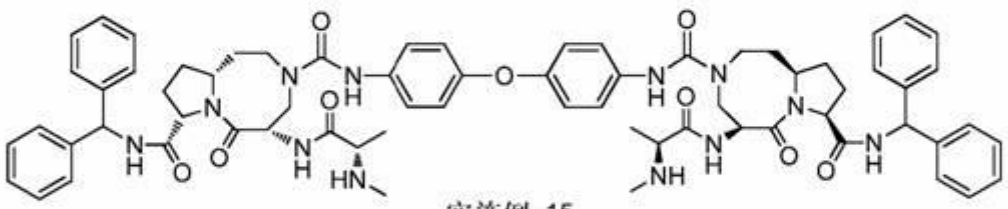
实施例 11

^{1}H NMR (300 MHz, CD_3OD): δ 7.48 (d, *J*=8.1 Hz, 4H), 7.33 (m, 20H), 7.11 (d, *J*=8.1 Hz, 4H), 6.17 (s, 2H), 4.82 (m, 2H), 4.63 (m, 2H), 4.25 (m, 2H), 4.08-4.03 (m, 6H), 3.88 (s, 2H), 3.30-3.20 (m, 4H), 2.70 (s, 6H), 2.34 (m, 2H), 2.20-1.80 (m, 6H), 1.75-1.60 (m, 4H), 1.55 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1206.4 $(M+H)^+$.



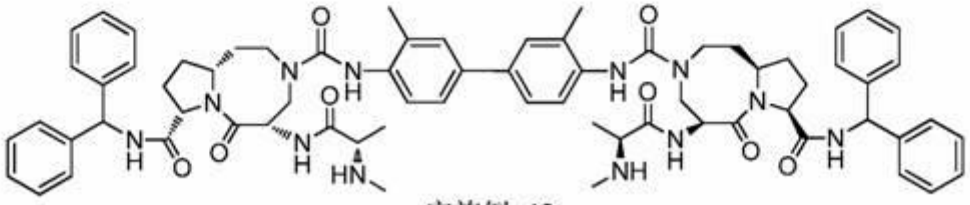
实施例 14

^{1}H NMR (300 MHz, CD_3OD): δ 8.14 (m, 1H), 7.34-7.18 (m, 23H), 6.17 (s, 2H), 4.84 (m, 2H), 4.67 (t, *J*=8.4 Hz, 2H), 4.22 (m, 2H), 4.07 (m, 6H), 3.24 (m, 4H), 2.73 (s, 6H), 2.34 (m, 2H), 2.14-2.04 (m, 6H), 1.77-1.66 (m, 4H), 1.57 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1115.9 $(M+H)^+$.



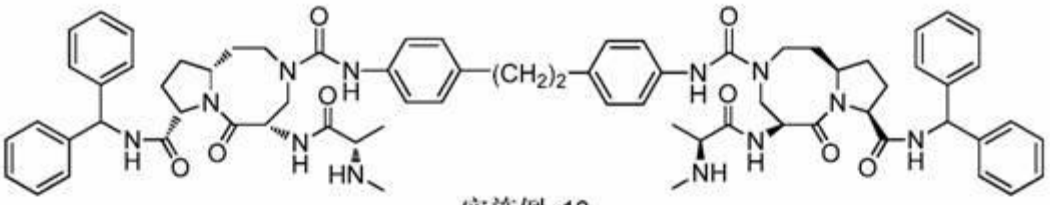
实施例 15

^{1}H NMR (300 MHz, CD_3OD): δ 7.55 (d, *J*=9.0 Hz, 4H), 7.36-7.24 (m, 20H), 6.91(d, *J*=9.0Hz, 4H), 6.17 (m, 2H), 4.84 (m, 2H), 4.64 (t, *J*=8.1Hz, 2H), 4.23 (m, 2H), 4.09 (m, 6H), 3.21 (m, 4H), 2.71 (s, 6H), 2.34 (m, 2H), 2.14-2.02 (m, 6H), 1.80-1.73 (m, 4H), 1.56 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1207.3 $(M+H)^+$.



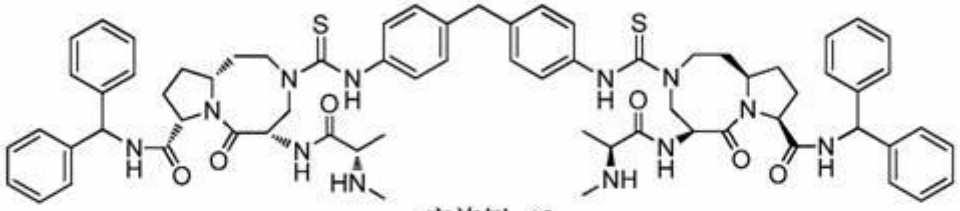
实施例 16

^{1}H NMR (300 MHz, CD_3OD): δ 7.46-7.25 (m, 26H), 6.17 (s, 2H), 4.84 (m, 2H), 4.65 (m, 2H), 4.32 (m, 2H), 4.19-4.02 (m, 6H), 3.22 (m, 4H), 2.66 (s, 6H), 2.37 (s, 6H), 2.24-2.02 (m, 8H), 1.83-1.70 (m, 4H), 1.53 (d, *J*=6.6 Hz, 6H); ESI MS: *m/z* 1220.2 $(M+H)^+$.



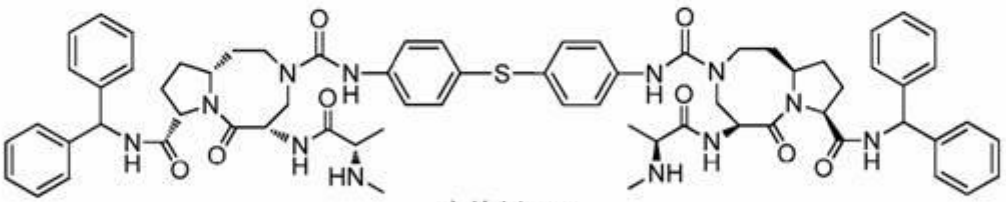
实施例 18

^{1}H NMR (300 MHz, CD_3OD): δ 7.47 (d, *J*=8.4 Hz, 4H), 7.36 (m, 20H), 7.06 (d, *J*=8.4 Hz, 4H), 6.16 (s, 2H), 4.94 (m, 2H), 4.67 (t, *J*=8.4 Hz, 2H), 4.25 (m, 2H), 4.09-4.04 (m, 6H), 3.17-3.28 (m, 4H), 2.84 (s, 4H), 2.66 (s, 6H), 2.37 (m, 2H), 2.15-2.02 (m, 6H), 1.79-1.67 (m, 4H), 1.56 (d, *J*=6.6 Hz, 6H); ESI MS: *m/z* 1220.25 $(M+H)^+$.



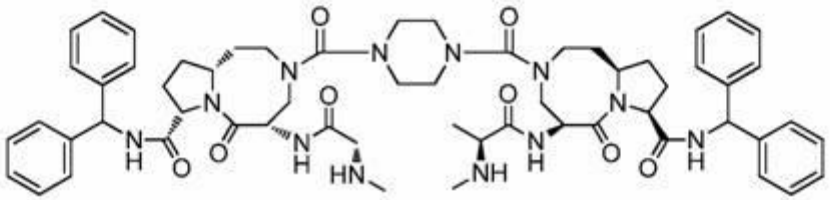
实施例 19

^{1}H NMR (300 MHz, CD_3OD): δ 7.83 (d, *J*=8.4 Hz, 4H), 7.63 (d, *J*=8.4 Hz, 4H), 7.36-7.16 (m, 20H), 6.17 (s, 2H), 5.01 (m, 2H), 4.67 (m, 2H), 4.17 (m, 2H), 4.00-3.94 (m, 4H), 3.73 (s, 4H), 3.59-3.40 (m, 4H), 2.64 (s, 6H), 2.55-2.37 (m, 4H), 2.06 (m, 4H), 1.80-1.67 (m, 4H), 1.53 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1237.6 $(M+H)^+$.



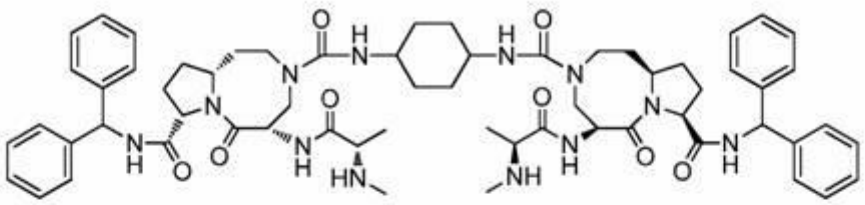
实施例 20

^{1}H NMR (300 MHz, CD_3OD): δ 7.60 (d, *J*=8.4 Hz, 4H), 7.36-7.21 (m, 24H), 6.17 (s, 2H), 4.82 (m, 2H), 4.64 (t, *J*=8.1Hz, 2H), 4.21 (m, 2H), 4.08-4.02 (m, 6H), 3.24 (m, 4H), 2.70 (s, 6H), 2.24 (m, 2H), 2.14-2.03 (m, 6H), 1.78-1.71 (m, 4H), 1.56 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1223.3 $(M+H)^+$.



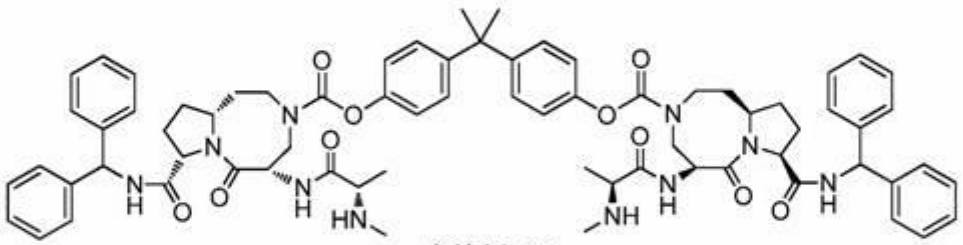
实施例 21

^{1}H NMR (300 MHz, CD_3OD): δ 7.33-7.21 (m, 20H), 6.12 (s, 2H), 5.11 (m, 2H), 4.84 (m, 2H), 4.56 (t, *J*=8.4Hz, 2H), 4.25 (m, 2H), 3.93 (m, 2H), 3.66-3.53 (m, 6H), 3.22-3.15 (m, 8H), 2.67 (s, 6H), 2.34 (m, 2H), 2.15-1.96 (m, 4H), 1.83-1.77 (m, 6H), 1.54 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1093.7 $(M+H)^+$.



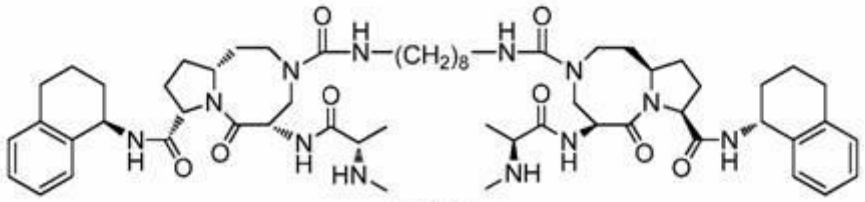
实施例 22

^{1}H NMR (300 MHz, CD_3OD): δ 7.34-7.23 (m, 20H), 6.14 (s, 2H), 4.92 (m, 2H), 4.70 (m, 4H), 4.08-3.86 (m, 8H), 3.59 (m, 2H), 3.16-3.05 (m, 4H), 2.70 (s, 6H), 2.36 (m, 2H), 2.10-1.92 (m, 10H), 1.79-1.71 (m, 4H), 1.60-1.40 (m, 8H), 1.40-1.25 (m, 2H); ESI MS: *m/z* 1121.7 $(M+H)^+$.



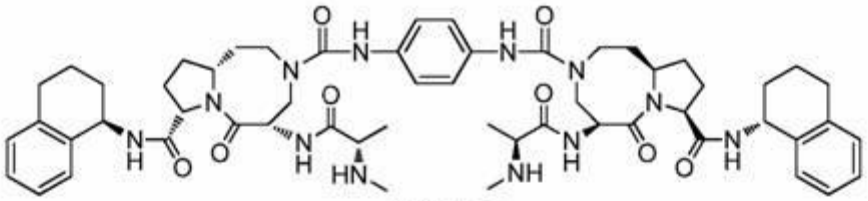
实施例 23

^{1}H NMR (300 MHz, CD_3OD): δ 7.27-7.02 (m, 28H), 6.12 (m, 2H), 5.07-4.97 (m, 2H), 4.60 (m, 2H), 4.39 (m, 2H), 3.89-3.85 (m, 4H), 3.73-3.54 (m, 6H), 2.66 (s, 6H), 2.31 (m, 2H), 2.11-1.81 (m, 10H),1.65 (m, 6H) 1.56 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1236.2 $(M+H)^+$.



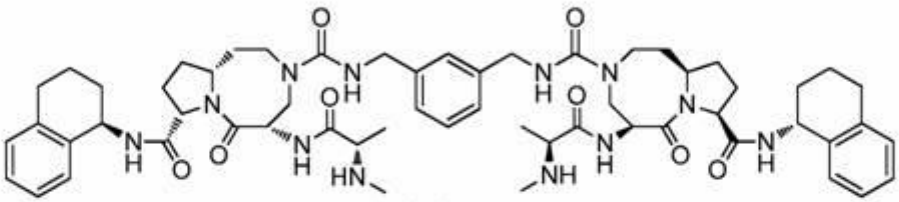
实施例 4

^{1}H NMR (300 MHz, CD_3OD): δ 7.40 (m, 2H), 7.14-7.06 (m, 6H), 5.06 (m, 2H), 4.84 (m, 2H), 4.72 (m, 2H), 4.50 (t, *J*= 8.4 Hz, 2H), 4.12 (m, 2H), 4.02-3.93 (m, 6H), 3.27-3.10 (m, 6H), 2.80 (m, 4H), 2.67 (s, 6H), 2.34 (m, 2H), 2.14-1.90 (m, 10H), 1.81-1.72 (m, 8H), 1.58 (m, 4H), 1.53 (d, *J*= 6.9 Hz, m, 6H), 1.35 (m, 8H); ESI MS: *m/z* 1151.8 $(M+H)^+$.



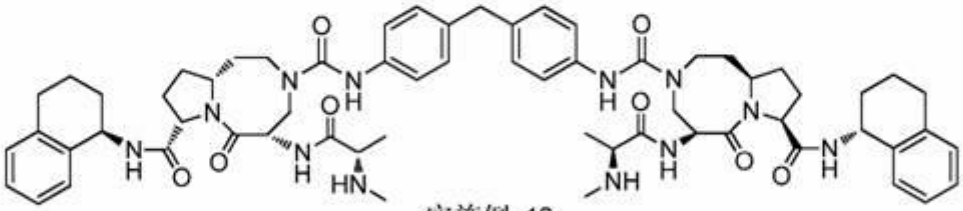
实施例 5

^{1}H NMR (300 MHz, CD_3OD): δ 7.55 (s, 4H),7.43 (m, 2H), 7.17-7.07 (m, 6H), 5.09 (m, 2H), 4.83 (m, 2H), 4.52 (t, *J*= 8.4 Hz, 2H), 4.25 (m, 2H), 4.16-4.05 (m, 6H), 3.39-3.34 (m, 4H), 2.81 (m, 4H), 2.73 (s, 6H), 2.32 (m, 4H), 2.05-1.93 (m, 8H), 1.82-1.74 (m, 8H), 1.57 (d, *J*= 6.9 Hz, m, 6H); ESI MS: *m/z* 1044.0 $(M+H)^+$.



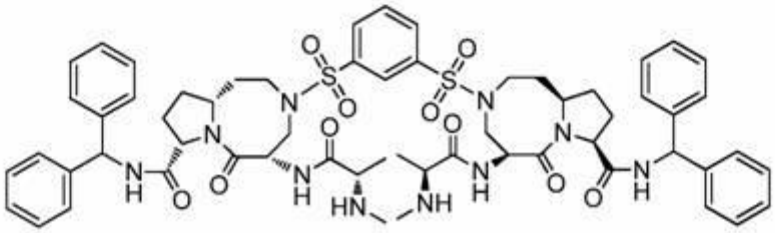
实施例 6

^{1}H NMR (300 MHz, CD_3OD): δ 7.38-7.09 (m, 12H), 5.03 (m, 2H), 4.85 (m, 2H), 4.78 (m, 2H), 4.60 (m, 2H), 4.55 (t, *J*= 8.4 Hz, 2H), 4.35-4.17 (m, 4H), 4.05-3.92 (m, 6H), 3.61 (m, 2H), 2.80 (m, 4H), 2.66 (s, 6H), 2.31 (m, 2H), 2.15-1.91 (m, 10H), 1.78-1.72 (m, 8H), 1.51 (d, *J*= 6.9 Hz, m, 6H); ESI MS: *m/z* 1071.63 $(M+H)^+$.



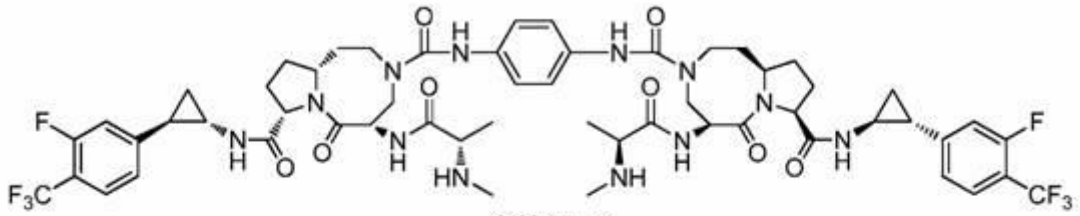
实施例 12

^{1}H NMR (300 MHz, CD_3OD): δ 7.51 (d, *J* = 8.4 Hz, 4H), 7.43 (m, 2H), 7.14-7.07 (m, 10H), 5.08 (m, 2H), 4.82 (m, 2H), 4.51 (t, *J* = 8.4 Hz, 2H), 4.28 (m, 2H), 4.15-4.04 (m, 6H), 3.89 (s, 2H), 3.38-3.33 (m, 4H), 2.87 (m, 4H), 2.71 (s, 6H), 2.31 (m, 2H), 2.10-1.73 (m, 18H), 1.56 (d, *J* = 6.9 Hz, m, 6H); ESI MS: *m/z* 1134.1 $(M+H)^+$.



实施例 24

^{1}H NMR (300 MHz, CD_3OD): δ 8.21 (m, 3H), 7.85 (m, 1H), 7.34-7.18 (m, 20H), 6.10 (s, 2H), 4.85 (m, 2H), 4.58 (t, *J*=8.4 Hz, 2H), 4.31 (m, 2H), 3.93 (m, 4H), 3.73 (m, 2H), 3.21 (m, 2H), 2.96 (m, 2H), 2.67 (s, 6H), 2.33 (m, 2H), 2.06-1.93 (m, 6H), 1.84-1.76 (m, 4H), 1.51 (d, *J*=6.9 Hz, 6H); ESI MS: *m/z* 1157.6 $(M+H)^+$.



实施例 38

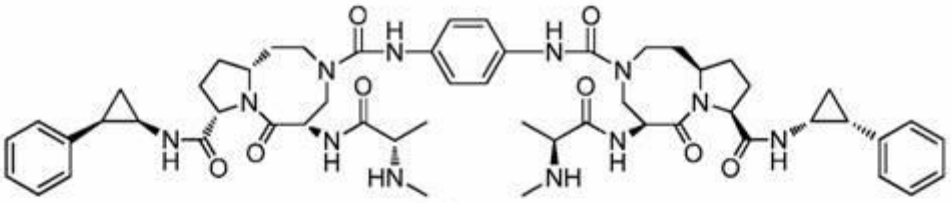
^{1}H NMR (300 MHz, D_2O): δ 7.50-6.70 (m, 10H), 4.90 (m, 2H), 4.70 (m, 2H), 4.45-4.10 (m, 4H), 3.95-3.40 (m, 10H), 2.60 (m, 2H), 2.55 (s, 6H), 2.30-1.60 (m, 12 H), 1.45 (brd, J = 7.0 Hz, 6H), 1.40-1.05 (m, 4H); ESI MS: *m/z* 1187.3 $(M+H)^+$.

实施例 37

^{1}H NMR (300 MHz, D_2O): δ 7.50-6.70 (m, 10H), 4.92 (m, 2H), 4.80 (m, 2H), 4.45-4.20 (m, 4H), 3.95 (m, 2H), 3.80-3.40 (m, 8H), 2.60 (m, 2H), 2.55 (s, 6H), 2.30-1.60 (m, 12 H), 1.45 (brd, *J* = 7.0 Hz, 6H), 1.40-1.05 (m, 4H); ESI MS: *m/z* 1187.3 $(M+H)^+$.

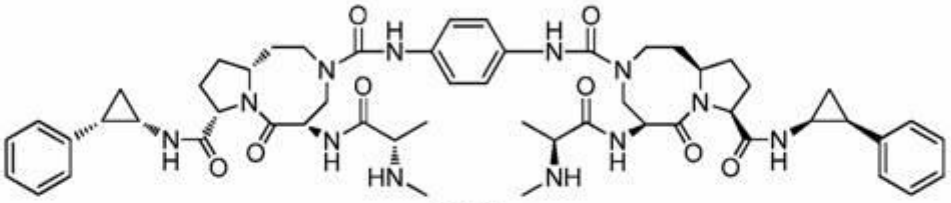
实施例 36

^{1}H NMR (300 MHz, D_2O): δ 7.65-7.45 (m, 4H), 7.35-6.90 (m, 8H), 5.05 (m, 2H), 4.80 (m, 2H), 4.50-4.30 (m, 4H), 4.05 (m, 2H), 3.90-3.40 (m, 8H), 2.60 (m, 2H), 2.50 (s, 6H), 2.40-1.60 (m, 12 H), 1.45 (brd, *J* = 7.0 Hz, 6H), 1.40-1.05 (m, 4H); ESI MS: *m/z* 1151.2 $(M+H)^+$.



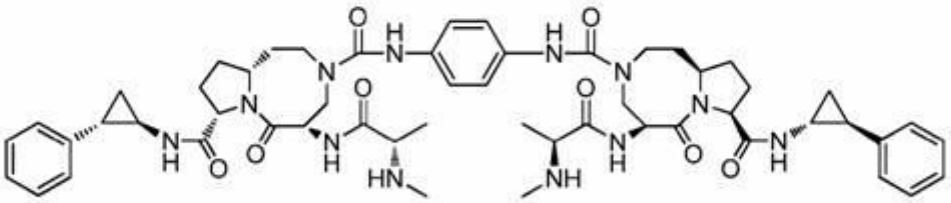
实施例 26

^{1}H NMR (300 MHz, D_2O): δ 7.35-7.05 (m, 14H), 4.75 (m, 2H), 4.20-3.90 (m, 4H), 3.90-3.65 (m, 6H), 3.35-3.10 (m, 4H), 2.90 (m, 2H), 2.60 (s, 6H), 2.30 (m, 2H), 2.05-1.55 (m, 8H), 1.45 (brd, J = 7.2 Hz, 6H), 1.40-1.05 (m, 6H), 0.80 (m, 2H); ESI MS: *m/z* 1015.5 $(M+H)^+$.



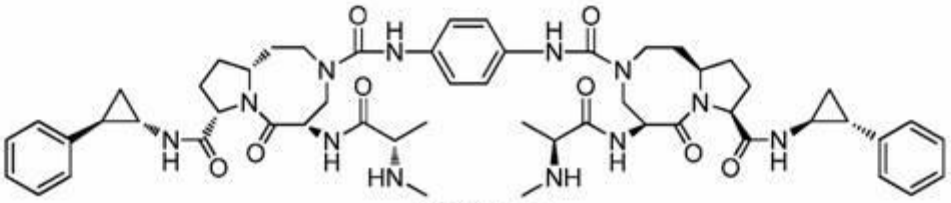
实施例 27

^{1}H NMR (300 MHz, D_2O): δ 7.35-7.05 (m, 14H), 4.75 (m, 2H), 4.30-3.95 (m, 4H), 3.95-3.65 (m, 6H), 3.40-3.10 (m, 4H), 2.90 (m, 2H), 2.60 (s, 6H), 2.25 (m, 2H), 2.05-1.55 (m, 8H), 1.45 (brd, J = 7.2 Hz, 6H), 1.40-1.05 (m, 6H), 0.80 (m, 2H); ESI MS: *m/z* 1015.5 $(M+H)^+$.



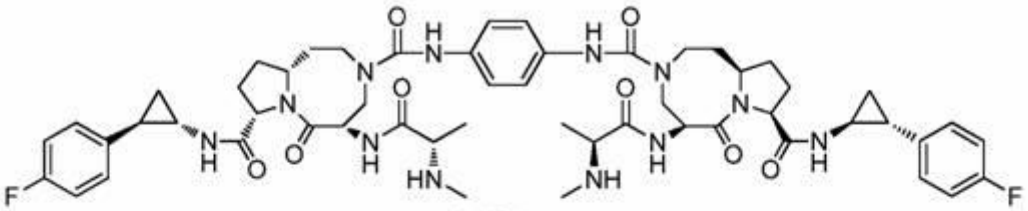
实施例 30

^{1}H NMR (300 MHz, CD_3OD): δ 7.60 (s, 4H), 7.30-7.10 (m, 10H), 4.80 (m, 2H), 4.45 (m, 2H), 4.25 (m, 2H), 4.20-4.02 (m, 6H), 3.50-3.30 (m, 4H), 2.95 (m, 2H), 2.70 (s, 6H), 2.40-2.05 (m, 10H), 1.90-1.70 (m, 4H), 1.55 (d, J = 7.2 Hz, 6H), 1.30-1.10 (m, 4H); ESI MS: *m/z* 1015.5 $(M+H)^+$.



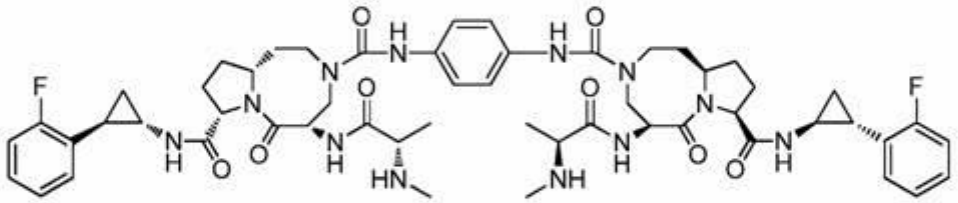
实施例 31

^{1}H NMR (300 MHz, CD_3OD) : δ 7.60 (s, 4H), 7.30-7.10 (m, 10H), 4.80 (m, 2H), 4.45 (m, 2H), 4.30 (m, 2H), 4.20-4.02 (m, 6H), 3.50-3.30 (m, 4H), 2.90 (m, 2H), 2.70 (s, 6H), 2.35-2.05 (m, 10H), 1.90-1.70 (m, 4H), 1.55 (d, J = 7.2 Hz, 6H), 1.30-1.10 (m, 4H); ESI MS: *m/z* 1015.5 $(M+H)^+$.



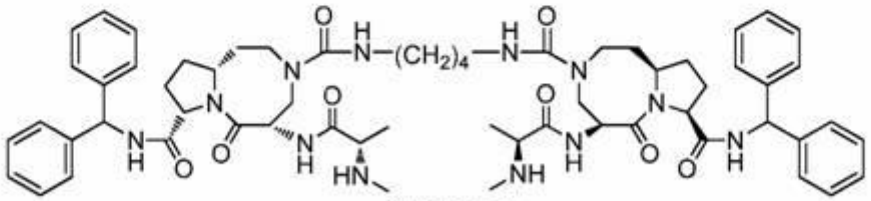
实施例 29

^{1}H NMR (300 MHz, D_2O): δ 7.30-6.90 (m, 12H), 4.90 (m, 2H), 4.70 (m, 2H), 4.40-4.20 (m, 4H), 3.95 (m, 2H), 3.90-3.30 (m, 8H), 2.65 (m, 2H), 2.60 (s, 6H), 2.30-1.75 (m, 12H), 2.50 (d, J = 7.0 Hz, 6H), 1.20 (m, 4H); ESI MS: *m/z* 1051.2 $(M+H)^+$.



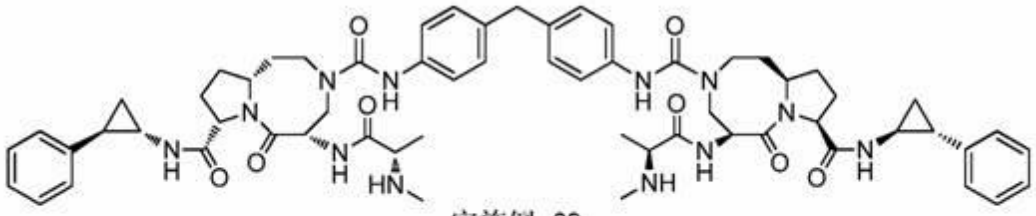
实施例 28

^{1}H NMR (300 MHz, CD_3OD) : δ 7.30-6.80 (m, 12H), 4.85 (m, 2H), 4.70 (m, 2H), 4.30-4.20 (m, 4H), 4.05-3.60 (m, 6H), 3.50-3.30 (m, 4H), 2.65 (m, 2H), 2.55 (s, 6H), 2.30-1.70 (m, 12H), 2.50 (d, J = 7.0 Hz, 6H), 1.20 (m, 4H); ESI MS: *m/z* 1051.2 $(M+H)^+$.



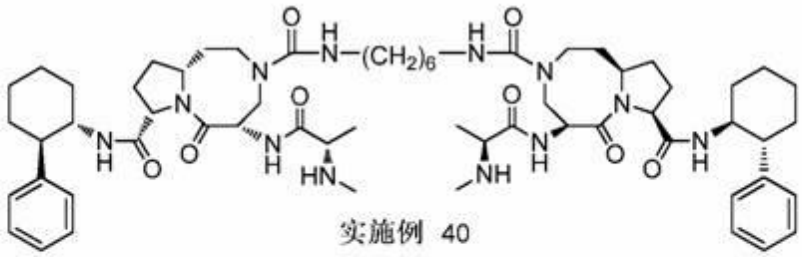
实施例 25

^{1}H NMR (300 MHz, D_2O) : δ 7.40-7.20 (m, 10H), 5.99 (s, 2H), 4.75 (m, 2H), 4.45 (m, 2H), 4.10 (m, 2H), 3.95 (m, 2H), 3.80 (m, 2H), 3.65 (m, 2H), 3.25-3.05 (m, 8H), 2.62 (m, 6H), 2.30 (m, 2H), 2.20-1.70 (m, 12H), 1.45 (m, 2H), 1.40 (d, J = 7.2 Hz, 6H); ESI MS: *m/z* 1095.4 $(M+H)^+$.



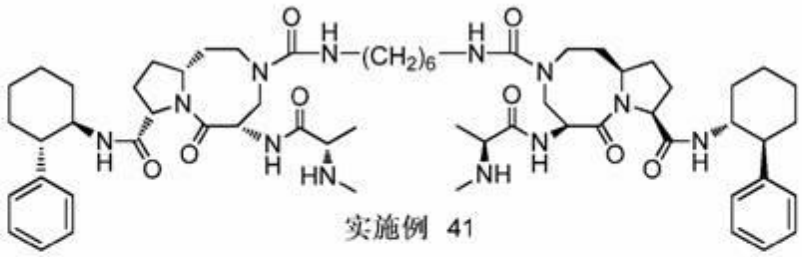
实施例 39

^{1}H NMR (300 MHz, CD_3OD): δ 7.48-7.08 (m, 18H), 4.92 (m, 2H), 4.42 (m, 2H), 4.21-4.03 (m, 8H), 3.87 (m, 2H), 3.36-3.20 (m, 4H), 2.85 (m, 2H), 2.70 (s, 6H), 2.30-2.02 (m, 10H), 1.76 (m, 4H), 1.56 (d, J = 6.9Hz, 6H), 1.23 (m, 4H); ESI MS: m/z 1105.4 $(M+H)^+$.



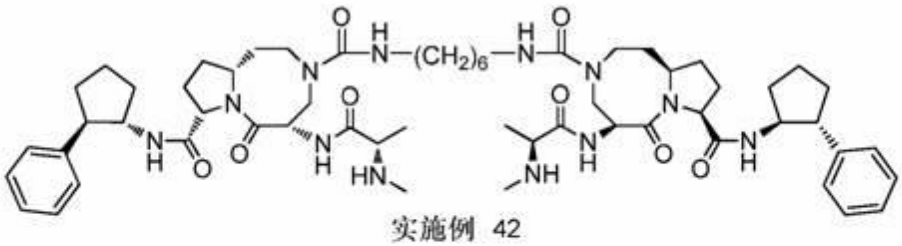
实施例 40

^{1}H NMR (300 MHz, CD_3OD) δ 7.35-7.15 (m, 10H), 4.84 (m, 2H), 4.40-3.90 (m, 8H), 3.75-3.50 (m, 6H), 3.40-3.20 (m, 8H), 2.71 (s, 6H), 2.65 (m, 2H), 1.90-1.43 (m, 42H); ESI MS: m/z 1107.9 $(M+H)^+$.



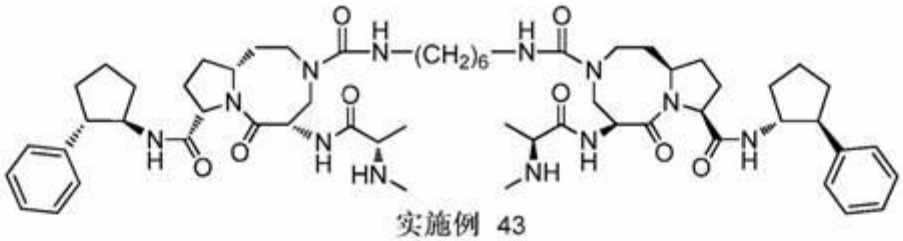
实施例 41

^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.20 (m, 10H), 4.84 (m, 2H), 4.61 (d, J = 9.0Hz, 2H), 4.20 (t, J = 9.0Hz, 2H), 3.97-3.81(m, 10H), 3.30-2.95 (m, 6H), 2.68 (s, 6H), 2.51 (m, 2H), 2.01-1.31 (m, 42H); ESI MS: m/z 1107.6 $(M+H)^+$.



实施例 42

^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.10 (m, 10H), 4.84 (m, 2H), 4.66 (m, 2H), 4.43 (m, 2H), 4.22 (m, 2H), 4.04-3.72 (m, 8H), 3.10-2.85 (m, 6H), 2.68 (s, 6H), 2.24-1.37 (m, 40H); ESI MS: m/z 1079.5$(M+H)^+$.



实施例 43

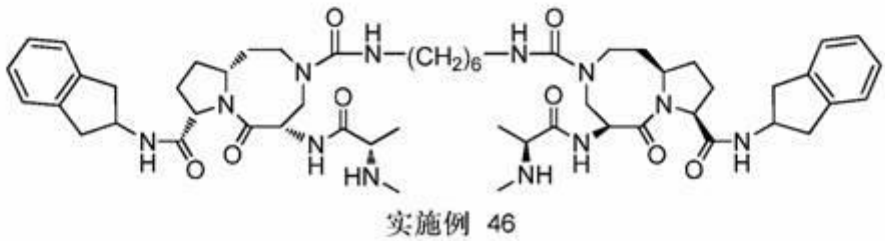
^{1}H NMR (300 MHz, CD_3CD): δ 7.35-7.15 (m, 10H), 4.81 (m, 2H), 4.65 (m, 2H), 4.35 (m, 2H), 4.22 (m, 2H), 3.98-3.80 (m, 8H), 3.25-2.87 (m, 6H), 2.68 (s, 6H), 2.20-1.33 (m, 40H); ESI MS: *m/z* 1079.9 $(M+H)^+$.

实施例 44

^{1}H NMR (300 MHz, CD_3OD): δ 7.30-7.10 (m, 10H), 4.84 (m, 2H), 4.61 (m, 4H), 4.24 (t, J = 9.0Hz, 2H), 3.97-3.81(m, 8H), 3.41-3.02 (m, 6H), 2.64 (s, 6H), 2.17-1.37 (m, 40H); ESI MS: *m/z* 1079.3 $(M+H)^+$.

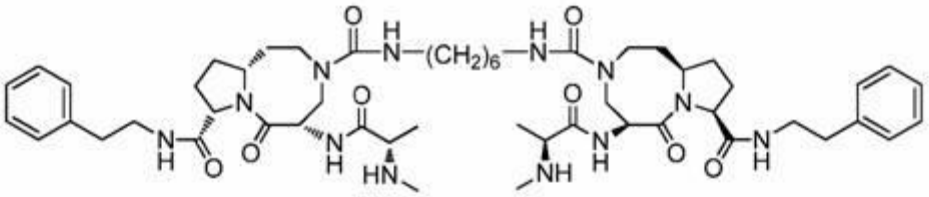
实施例 45

^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.10 (m, 10H), 4.84 (m, 2H), 4.67-4.24 (m, 6H), 3.97-3.81(m, 8H), 3.41-3.02 (m, 6H), 2.68 (s, 6H), 2.17-1.37 (m, 40H); ESI MS: *m/z* 1079.5 $(M+H)^+$.



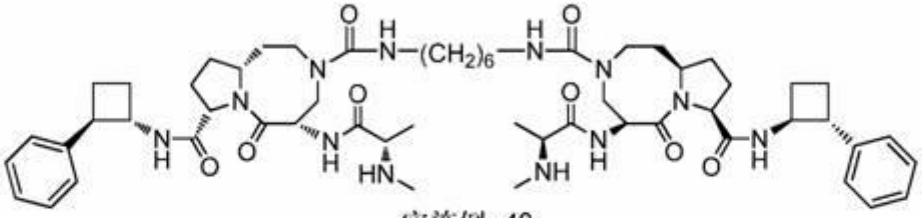
实施例 46

^{1}H NMR (300 MHz, CD_3OD): δ 7.19-7.11 (m, 8H), 4.84 (m, 2H), 4.70 (m, 2H), 4.57 (m, 2H), 4.42 (m, 2H), 4.10 (m, 2H), 4.00 (m, 6H), 3.22-3.06 (m, 6H), 2.92-2.75 (m, 4H), 2.66 (s, 6H), 2.26-1.37 (m, 30H); ESI MS: *m/z* 1023.7 $(M+H)^+$.



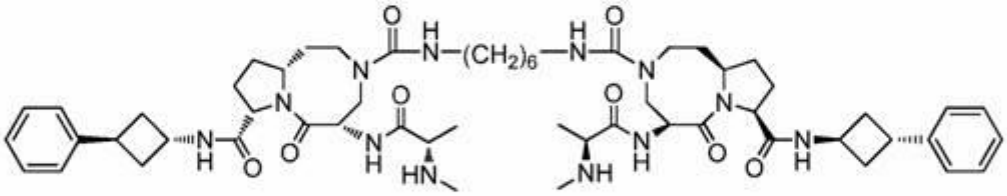
实施例 47

^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.15 (m, 10H), 4.84 (m, 2H), 4.71 (m, 2H), 4.41 (m, 2H), 4.11 (m, 2H), 3.98-3.88 (m, 6H), 3.48-3.08 (m, 10H), 2.82 (m, 4H), 2.69 (s, 6H), 2.22-1.39 (m, 26H); ESI MS: *m/z* 999.7 $(M+H)^+$.



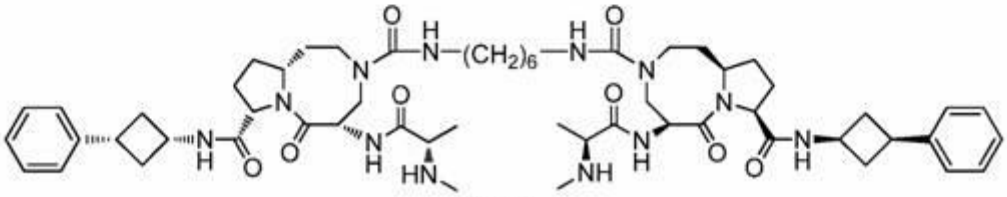
实施例 48

^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.15 (m, 10H), 4.84 (m, 2H), 4.69 (m, 2H), 4.50-4.30 (m, 4H), 4.11-3.86 (m, 8H), 3.48 (m, 2H), 3.25-3.06 (m, 6H), 2.68 (s, 6H), 2.31-1.28 (m, 34H); ESI MS: *m/z* 1051.4 $(M+H)^+$.



实施例 49

^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.10 (m, 10H), 4.82 (m, 2H), 4.70 (d, *J* = 8.4Hz, 2H), 4.43-4.34 (m, 4H), 4.12 (m, 2H), 4.01-3.90 (m, 6H), 3.65 (m, 2H), 3.25-3.06 (m, 6H), 2.67 (s, 6H), 2.52- 2.34 (m, 10H), 2.10 (m, 6H), 1.80-1.39 (18H); ESI MS: *m/z* 1051.9 $(M+H)^+$.



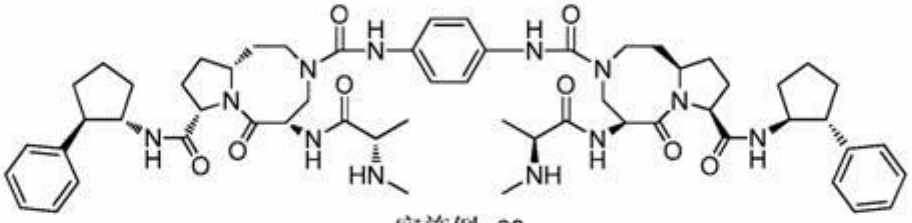
实施例 50

^{1}H NMR (300 MHz, CD_3OD): δ 7.35-7.15 (m, 10H), 4.82 (m, 2H), 4.70 (d, *J* = 9.0Hz, 2H), 4.43- 4.28 (m, 4H), 4.12 (m, 2H), 4.01-3.90 (m, 6H), 3.25-3.06 (m, 6H), 2.77 (m,

2H), 2.70 (s, 6H), 2.51 (m, 2H), 2.30 (m, 2H), 2.20-1.90 (m, 10H), 1.90-1.45 (m, 16H), 1.45-1.35 (m, 4H); ESI MS: *m/z* 1051.7$(M+H)^+$.

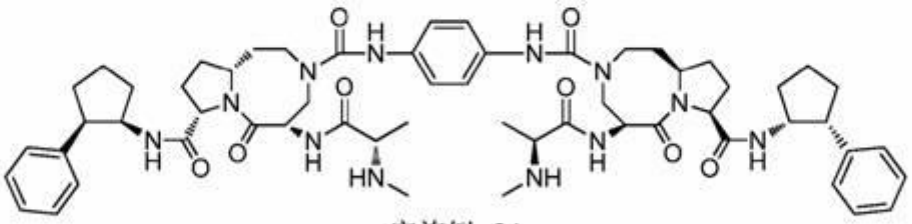
实施例 32

^{1}H NMR (300 MHz, D_2O): δ 7.35-7.10 (m, 14H), 4.80 (m, 2H), 4.40-4.25 (m, 4H), 4.20 (m, 2H), 4.15-4.05 (m, 4H), 3.90 (m, 2H), 3.40-3.30 (m, 4H), 2.90 (m, 2H), 2.70 (s, 6H), 2.30-1.90 (m, 10H), 1.90-1.55 (m, 14H), 1.55 (d, J = 7.2 Hz, 6H); ESI MS: *m/z* 1071.5 $(M+H)^+$.



实施例 33

^{1}H NMR (300 MHz, D_2O): δ 7.35-7.10 (m, 14H), 4.75 (m, 2H), 4.40-4.25 (m, 4H), 4.20 (m, 2H), 4.15-4.05 (m, 4H), 3.90 (m, 2H), 3.40-3.30 (m, 4H), 2.90 (m, 2H), 2.70 (s, 6H), 2.30-1.90 (m, 10H), 1.90-1.35 (m, 20H); ESI MS: *m/z* 1071.7 $(M+H)^+$.

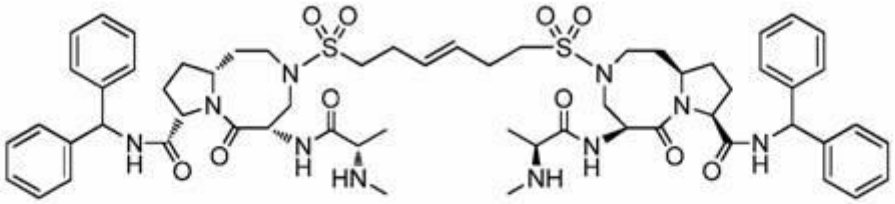


实施例 34

^{1}H NMR (300 MHz, D_2O): δ 7.35-7.10 (m, 14H), 4.80 (m, 2H), 4.40 (m, 2H), 4.25-4.05 (m, 4H), 4.05-3.85 (m, 4H), 3.80 (m, 2H), 3.30-3.15 (m, 6H), 2.70 (s, 6H), 2.30-1.60 (m, 24H), 1.55 (d, J = 7.2 Hz, 6H); ESI MS: *m/z* 1071.7 $(M+H)^+$.

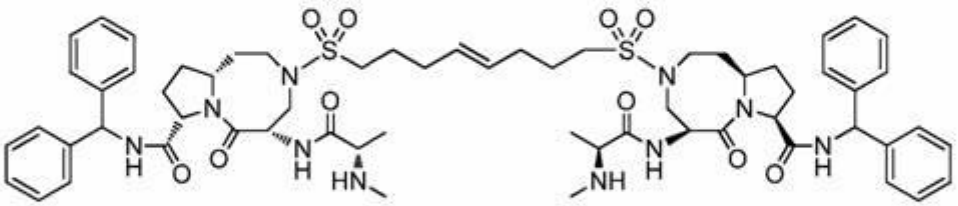
实施例 35

^{1}H NMR (300 MHz, D_2O): δ 7.35-7.10 (m, 14H), 4.80 (m, 2H), 4.45 (m, 2H), 4.20-3.90 (m, 6H), 3.80 (m, 2H), 3.30-3.20 (m, 6H), 2.70 (s, 6H), 2.30-1.60 (m, 24H), 1.55 (d, J = 7.2 Hz, 6H); ESI MS: *m/z* 1071.7 $(M+H)^+$.



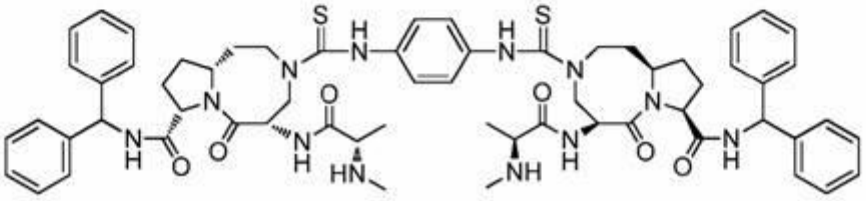
实施例 7

^{1}H NMR (300 MHz, CD_3OD): δ 7.40-7.20 (m, 20H), 6.15 (m, 2H), 5.60 (m, 2H), 4.85 (m, 2H), 4.55 (m, 2H), 4.40 (m, 2H), 3.95-3.80 (m, 4H), 3.65 (m, 2H), 3.35-2.05 (m, 6H), 2.65 (s, 6H), 2.45-1.70 (m, 16H), 1.55 (d, J = 7.2 Hz, 6H); ESI MS: *m/z* 1162.5 $(M+H)^+$.



实施例 8

^{1}H NMR (300 MHz, CD_3OD): δ 7.40-7.20 (m, 20H), 6.15 (m, 2H), 5.45 (m, 2H), 4.82 (m, 2H), 4.55 (m, 2H), 4.40 (m, 2H), 3.95-3.72 (m, 4H), 3.65 (m, 2H), 3.35-2.95 (m, 6H), 2.65 (s, 6H), 2.45-1.70 (m, 20H), 1.55 (d, J = 7.2 Hz, 6H); ESI MS: *m/z* 1190.6 $(M+H)^+$.



实施例 17

ESI MS: *m/z* 1147.6 $(M+H)^+$.

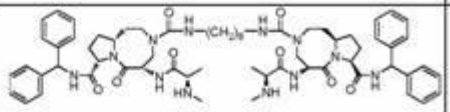
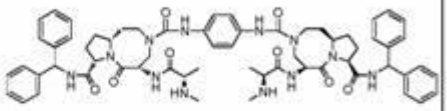
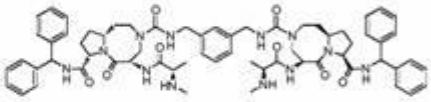
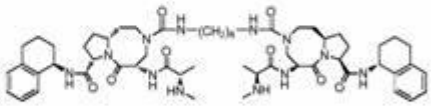
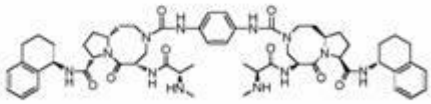
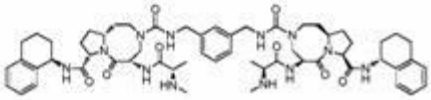
[0143] 与 XIAP接头 -BIR2-BIR3、cIAP1-BIR3和 cIAP-2 BIR2的结合亲和力

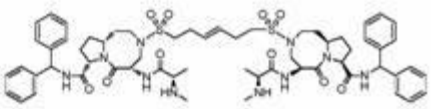
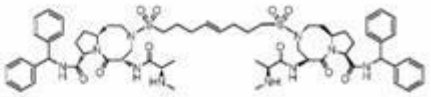
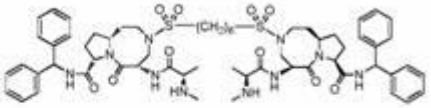
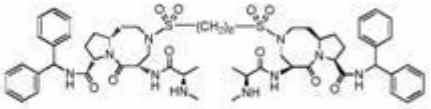
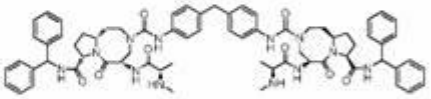
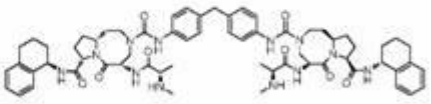
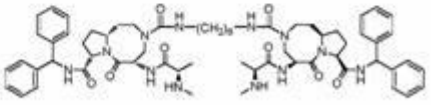
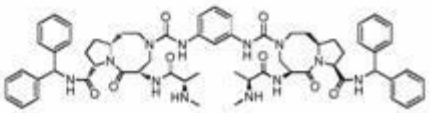
本发明化合物与 XIAP 接头 -BIR2-BIR3 （残基 120-356）、cIAP1-BIR3 （残基 253-363）和 cIAP-2 BIR3 （残基 238-349）蛋白的结合亲和力通过基于荧光偏振 (FP) 的竞争性测定法进行测定。对于 cIAP-1 BIR3 和 cIAP-2 BIR3 测定法，荧光标记的 Smac 模拟物 (Smac-2F) 用作荧光探针。Smac-2F 与 cIAP-1 BIR3 和 cIAP-2 BIR3 的 K_d 值通过监测用固定浓度的荧光探针和高达完全饱和的渐增浓度的蛋白构成的混合物的总的荧光偏振来测定。使用 Infinite M-1000 酶标仪 (Tecan U.S., Research Triangle Park, NC) 在 Microfluor 2 96-孔黑色圆底板 (Thermo Scientific) 中测量荧光偏振值。向每个孔中添加 1nM SMAC-2F 和渐增浓度的蛋白至测定缓冲液 (100mM 磷酸钾， pH 7.5， 100 μg/ml 牛 γ 球蛋白，0.02% 叠氮化钠， Invitrogen， 含有 4% DMSO) 中的 125 μl 最终体积。将板在室温下孵

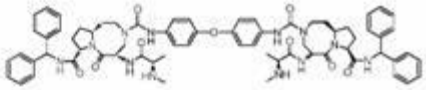
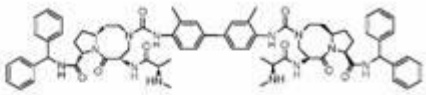
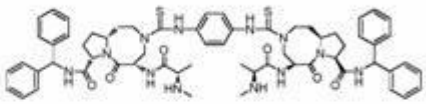
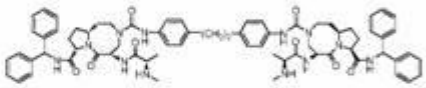
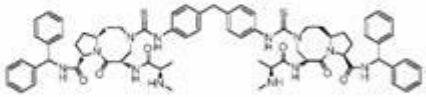
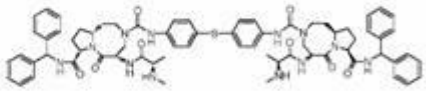
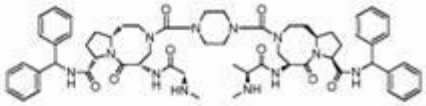
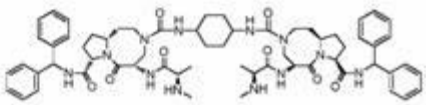
育 1-2 小时，并且伴随轻轻振摇混合以确保平衡。在 485 nm 的激发波长以及 530 nm 的发射波长，以毫偏振单位 (millipolarization unit)(mP) 测量偏振值。然后使用 Graphpad Prism 5.0 软件 (Graphpad Software, San Diego, CA) 通过拟合 S 形剂量依赖性 FP 增加作为蛋白浓度的函数来计算平衡解离常数 (K_d)。

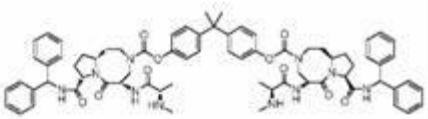
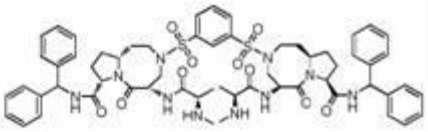
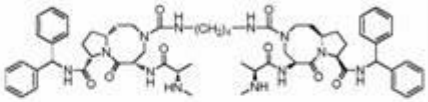
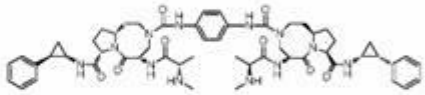
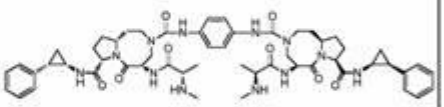
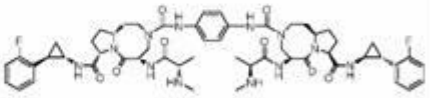
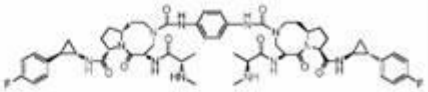
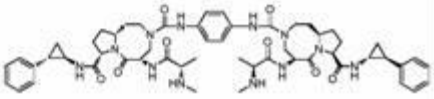
[0144] 化合物的 K_I 值通过化合物剂量依赖性的竞争性结合实验来测定，其中化合物的系列稀释液与固定浓度的荧光探针竞争结合固定浓度的蛋白（通常为上述测定的 K_d 值的 2 至 3 倍）。将 5 μl 的在 DMSO 中的测试化合物与 120 μl 在测定缓冲液 (100mM 磷酸钾，pH 7.5, 100 μg/ml 牛 γ 球蛋白，0.02% 叠氮化钠，Invitrogen) 中的预孵育蛋白 / 示踪剂复合物的混合物添加至测定板，并且在室温下伴随轻轻振摇孵育 2 小时。蛋白和探针的终浓度对于 cIAP-1 BIR3 和 cIAP-2 BIR3 测定分别为 3nM 和 1nM、5nM 和 1nM。仅含有蛋白 / 探针复合物的阴性对照（相当于 0% 抑制）、和仅含有游离探针的阳性对照（相当于 100% 抑制）包含在每个测定板中。如上所述测量 FP 值。通过竞争曲线的非线性回归拟合测定 IC_{50} 值。竞争性抑制剂的 Ki 值使用先前描述的推导方程，基于所测量的 IC_{50} 值、探针与不同蛋白的 K_d 值和竞争性测定中蛋白和探针的浓度来计算。

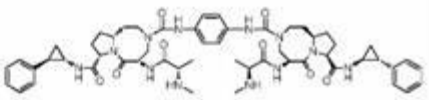
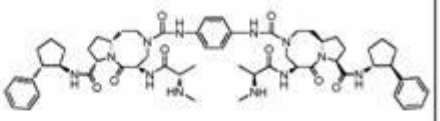
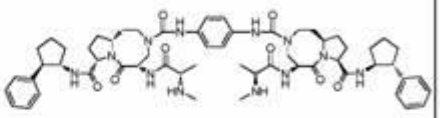
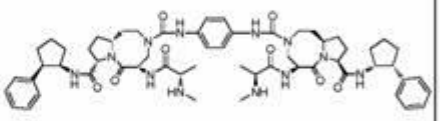
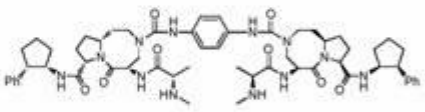
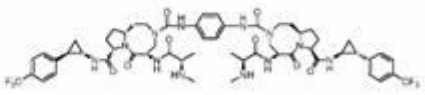
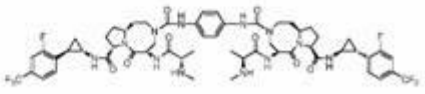
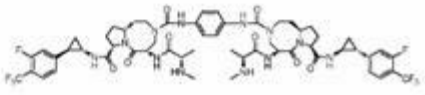
[0145] 对于 XIAP 接头 -BIR2-BIR3 蛋白的基于 FP 的测定使用相同程序进行。在该测定中，二价荧光标签的肽类 Smac 模拟物 (Smac-1F) 用作荧光探针，其与 XIAP 接头 -BIR2-BIR3 的 K_d 值通过饱和实验类似地测定。将 0.01% Triton X-100 添加至测定缓冲液中以实现二聚体荧光探针的稳定的荧光和偏振值。竞争性测定中利用的最终蛋白和探针浓度分别为 3nM 和 1nM。

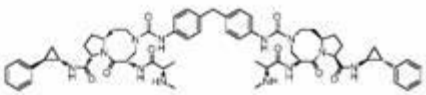
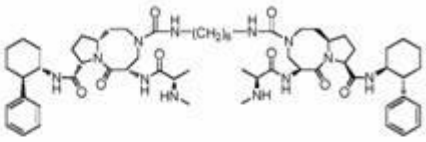
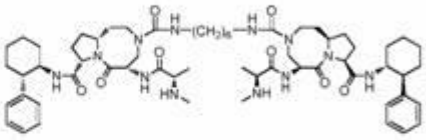
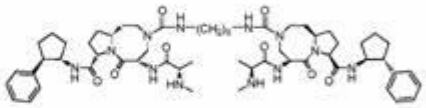
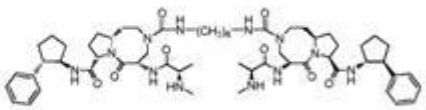
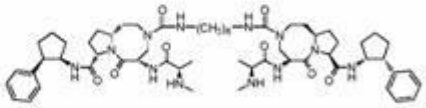
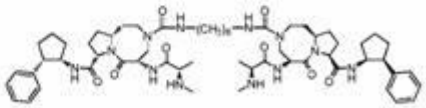
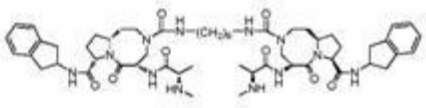
实施例	结构	结合亲和力 IC50 (nM)		
		XIAP 蛋白	cIAP1 蛋白	cIAP2 蛋白
1		<10	<300	<300
2		<10	<100	<100
3		<10	<100	<100
4		<10	<100	<100
5		<10	<100	<100
6		<10	<100	<100

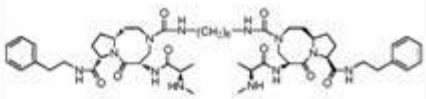
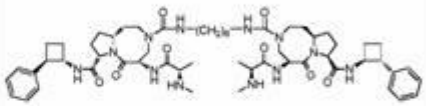
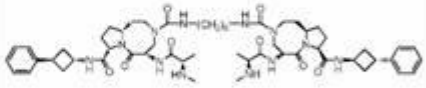
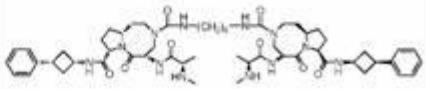
7		<10	<300	<300
8		<10	<100	<100
9		<10	<100	<100
10		<10	<100	<100
11		<10	<100	<100
12		<10	<100	<100
13		<30	<300	<300
14		<30	<300	<300

15		<30	<300	<300
16		<100	<300	<300
17		<30	<300	<300
18		<30	<300	<300
19		<30	<300	<300
20		<30	<100	<300
21		<30	<300	<300
22		<30	<300	<300

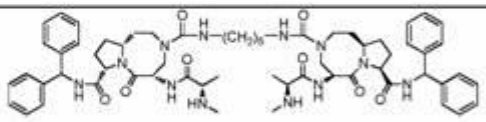
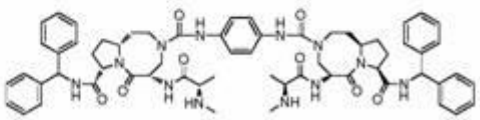
23		<30	<300	<300
24		<30	<300	<300
25		<30	<300	<300
26		<1000	<1000	<1000
27		<1000	<1000	<1000
28		<1000	<1000	<1000
29		<1000	<1000	<1000
30		<3000	<3000	<3000

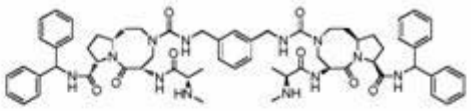
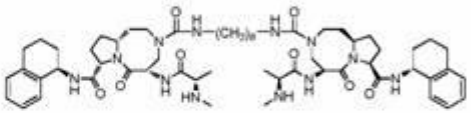
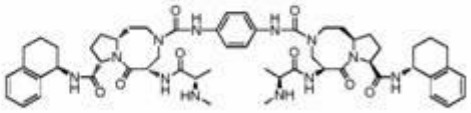
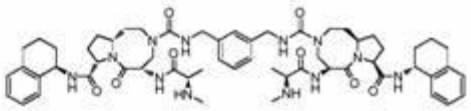
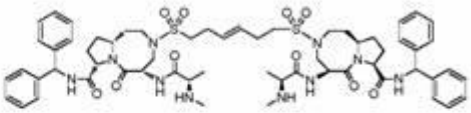
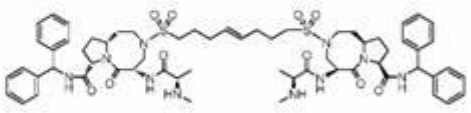
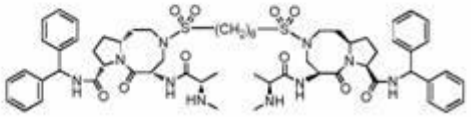
31		<1000	<1000	<1000
32		<3000	<3000	<3000
33		<3000	<3000	<3000
34		<1000	<1000	<1000
35		<1000	<1000	<1000
36		<3000	<3000	<3000
37		<3000	<3000	<3000
38		<3000	<3000	<3000

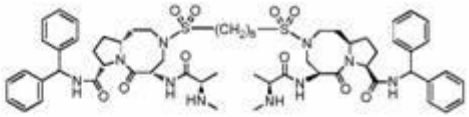
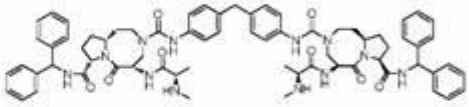
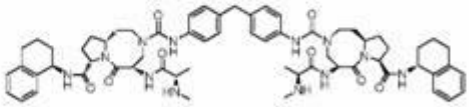
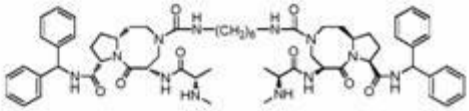
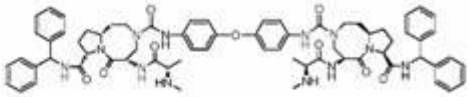
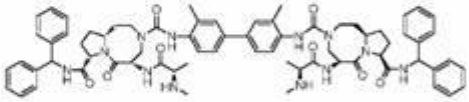
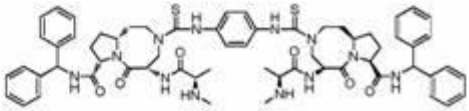
39		<1000	<3000	<3000
40		<3000	<3000	<3000
41		<5000	<5000	<5000
42		<1000	<1000	<3000
43		<3000	<3000	<3000
44		<1000	<1000	<3000
45		<1000	<3000	<3000
46		<1000	<10000	<5000

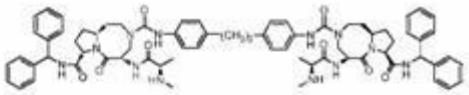
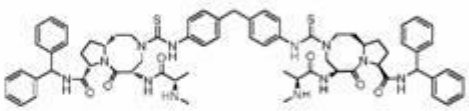
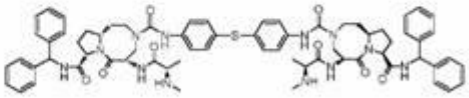
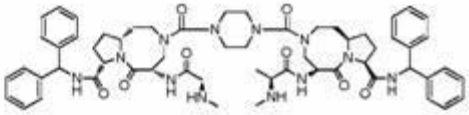
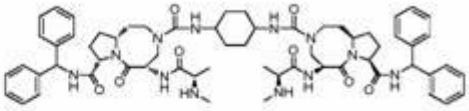
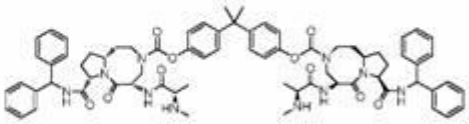
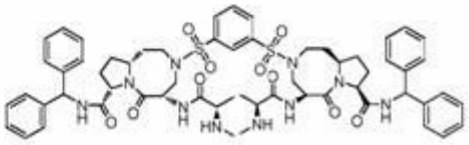
47		<1000	<1000	<5000
48		<1000	<1000	<1000
49		<1000	<1000	<5000
50		<1000	<1000	<1000

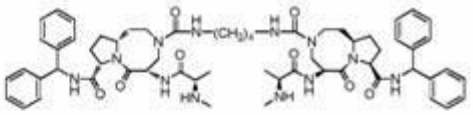
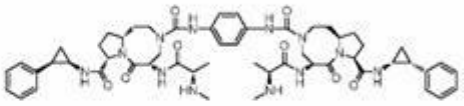
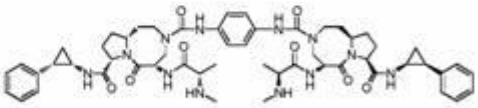
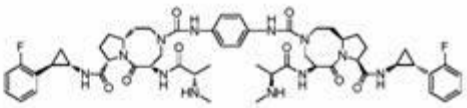
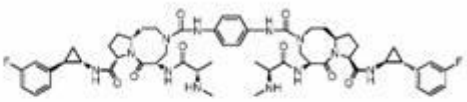
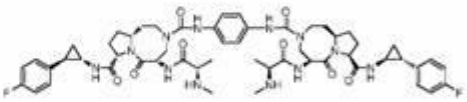
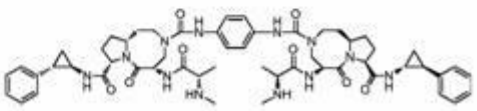
[0146] MDA-MB-231乳腺癌和 SK-OV-3卵巢癌细胞系中细胞生长的抑制

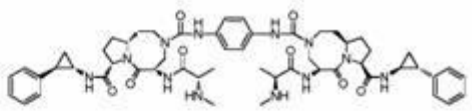
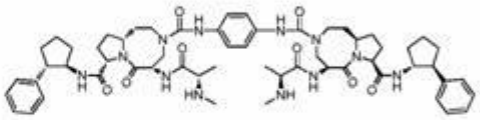
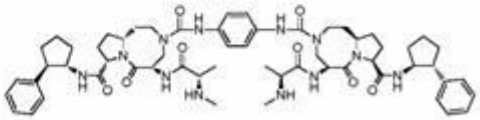
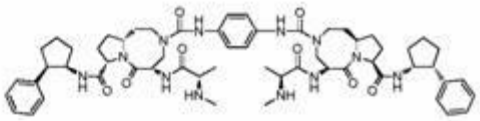
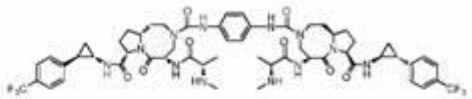
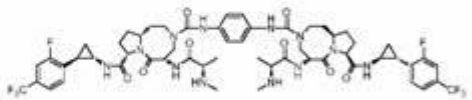
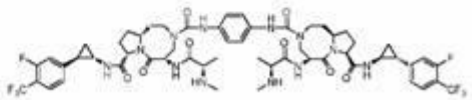
实施例	结构	细胞生长抑制 (IC_{50}, nM)	
		MDA-MB-231 癌细胞系	SK-OV-3 癌细胞系
1		<100	<100
2		<100	<100

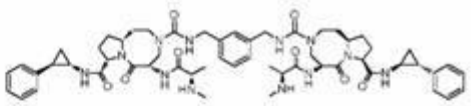
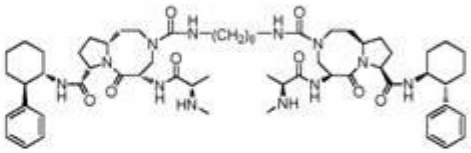
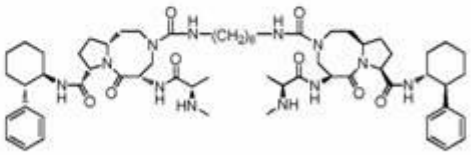
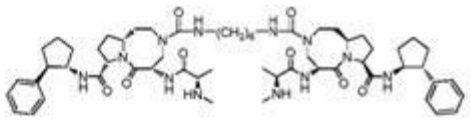
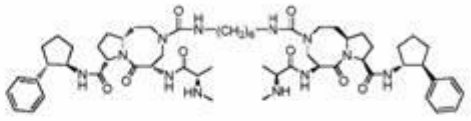
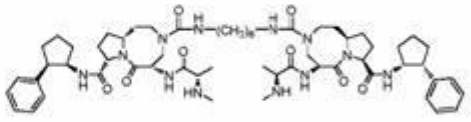
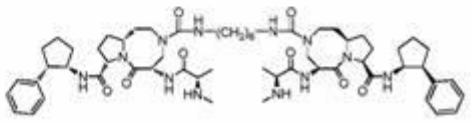
3		<100	<100
4		<100	<100
5		<100	<100
6		<100	<100
7		<1000	<1000
8		<1000	<1000
9		<1000	<1000

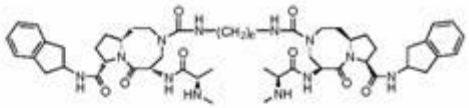
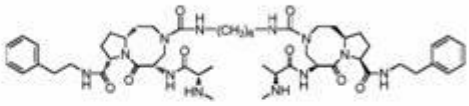
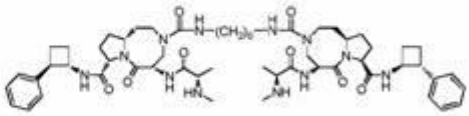
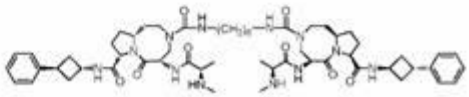
10		<1000	<1000
11		<100	<100
12		<100	<100
13		<100	<100
14		<1000	<1000
15		<1000	<1000
16		<100	未测试

17		<100	未测试
18		<100	未测试
19		<1000	<1000
20		<10,000	<10,000
21		<1000	<1000
22		<100	<1000
23		<100	<100

24		<100	<100
25		<1000	<1000
26		<1000	<1000
27		<5000	<5000
28		未测试	未测试
29		<5000	<5000
30		<10,000	<10,000

31		<1000	<1000
32		<1000	<1000
33		<1000	<1000
34		<100	<100
35		<10,000	<10,000
36		<10,000	<10,000
37		<10,000	<10,000

38		<10,000	<10,000
39		>1000	>1000
40		>10,000	>10,000
41		>1000	>1000
42		>1000	>1000
43		>1000	>1000
44		>1000	>1000

45		>1000	>1000
46		>1000	>1000
47		>1000	>1000
48		>10,000	>10,000

[0147] 图 1 显示裸鼠中的 MDA-MB-231 异种移植模型中实施例 2 和实施例 24 的抗肿瘤活性。当肿瘤达到 80 mm^3的平均体积时开始治疗。以 10 mg/kg 的每周剂量静脉内给予实施例 24,持续 4 周 (qwkx4, iv)。以 3 mg/kg 的每周剂量给予实施例 2,持续 4 周 (qwkx4, iv)。对照治疗给予媒介物对照。每组具有 8-10 只小鼠,每只小鼠具有一个肿瘤。对于实施例 2 和 24 实现了肿瘤消退。

参考文献

(1) D.W. Nicholson, *Nature* 2000, *407*, 810-816.

(2) B.A. *Ponder*, *Nature* 2001, *411*, 336-341.

(3) S.W. *Lowe* et al., *Carcinogenesis* 2000, *21*, 485-495.

(4) D. *Hanahan* et al., *Cell* 2000, *100*, 57-70.

(5) G. S. *Salvesen* et al., *Nat. Rev. Mol. Cell. Biol.* 2002, *3*, 401-410.

(6) Q. L. *Deveraux* et al., *Genes Dev.* 1999, *13*, 239-252.

(7) S.M. Srinivasula et al., *Mol. Cell* 2008, *30*, 123-135.

(8) M. Gyrd-Hansen et al., *Nat Rev Cancer*, 2010, *10*, 561-574.

(9) I. Tamm et al., *Clin Cancer Res.* 2000, *6*, 1796-1803.

(10) D. Vucic et al., *Clin Cancer Res.* 2007, *13*, 5995-6000.

(11) A. M. Hunter et al., *Apoptosis* 2007, *12*, 1543-1568.

(12) E. C. LaCasse et al., *Oncogene* 2008, *27*, 6252-6275.

(13) S. Fulda, *Expert Rev Anticancer Ther.* 2007, *7*, 1255–64.

(14) C. Du et al., *Cell* 2000, *102*, 33–42.

(15) A. M. Verhagen et al., *Cell* 2000, *102*, 43–53.

(16) G. Wu et al., *Nature* 2000, *408*, 1008–1012.

(17) Z. Liu et al., *Nature* 2000, *408*, 1004–1008.

(18) E. N. Shiozaki et al., *Trends Biochem. Sci.* 2004, *29*, 486-494.

(19) T. Samuel et al., *J. Biol. Chem.* 2006, 281, 1080-1090.

(20) Q. Yang et al., *J Biol Chem.* 2004, 279, 16963-16970.

(21) S. Wang, *Curr Top Microbiol Immunol.* 2011, *348*, 89-113.

(22) H. Sun et al., *Acc Chem Res.* 2008, *41*, 1264-1277.

(23) R. Mannhold et al., *Drug Discov Today.* 2010, 15, 210-219.

(24) L. Li et al., *Science* 2004, *305*, 1471-1474.

(25) T.K. Oost et al., *J. Med. Chem.* 2004, *47*, 4417–4426.

(26) H. Sun et al., *J. Am. Chem. Soc*. 2004, *126*, 16686-16697.

(27) H. Sun et al., *J. Med. Chem.* 2004, *47*, 4147-4150.

(28) H. Sun et al., *J. Med. Chem.* 2006, *49*, 7916-7920.

(29) K. Zobel et al., *ACS Chem. Biol.* 2006, *1*, 525–33.

(30) H. Sun et al., *J. Am. Chem. Soc.*, 2007, *129*, 15279–15294.

(31) J. Lu et al., *Cancer Res.* 2008, 68, 9384-9393.

(32) H. Sun et al., *J. Med. Chem.*, 2008, *51*, 7169–7180.

(33) Y. Peng et al., *J. Med. Chem.*, 2008, *51*, 8158–8162.

(34) B. Zhang et al., *J. Med. Chem.*, 2008, *51*, 7352–7355.

(35) W. Sun et al., *J. Med. Chem.*, 2009, *52*, 593–596.

(36) H. Sun et al., *J. Med. Chem.*, 2010, *53* 6361–6367.

(37) Q. Cai et al., *J Med Chem.* 2011, 54, 2714-2726.

(38) H. Sun et al., *J Med Chem.* 2011, *54*, 3306-3318.

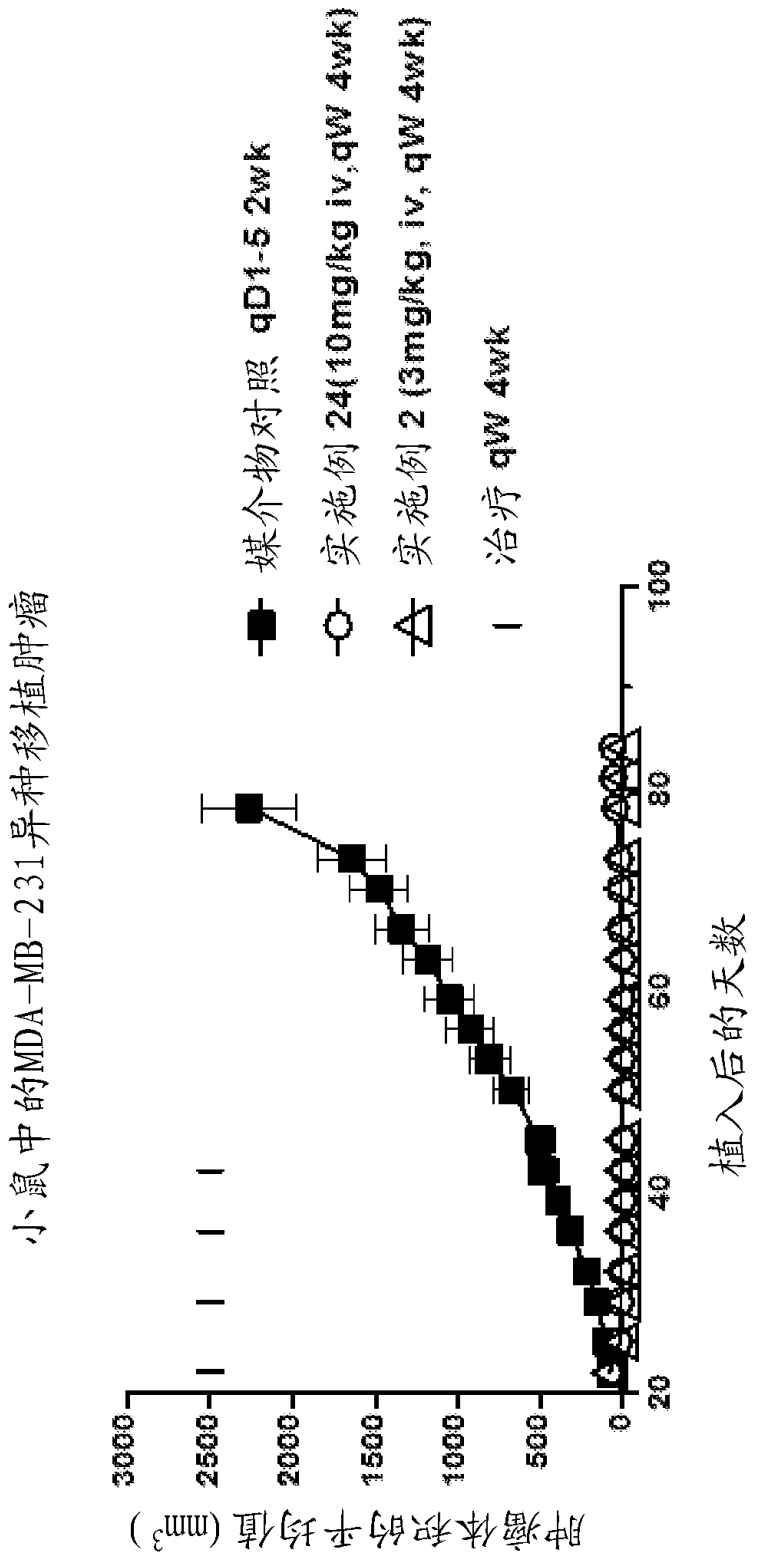

小鼠中的MDA-MB-231异种移植肿瘤
媒介物对照 qD1-5 2wk
实施例 24(10mg/kg iv,qW 4wk)
实施例 2 (3mg/kg, iv, qW 4wk)
治疗 qW 4wk
肿瘤体积的平均值 (mm³)
植入后的天数
3000
2500
2000
1500
1000
500
0
20
40
60
80
100

图 1