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(54) Benævnelse: **SMÅ KIMERISKE MOLEKYLER TIL REKRUTTERING AF ANTISTOFFER TIL CANCERCELLER**

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DESCRIPTION

Field of the Invention

[0001] The present invention relates to chemical compounds which are used to recruit antibodies to cancer cells, in particular, prostate cancer cells or metastasized prostate cancer cells. The compounds according to the present invention comprise an antibody binding terminus (ABT) moiety covalently bonded to a cell binding terminus(CBT) through a linker and optionally and preferably, a connector molecule. In addition, given that the protein target is found on the neovasculature of most non-prostatic cancer cells, the compounds in the present invention also serves as an antiangiogenic therapy for other cancer types.

Background of the Invention

[0002] It has been predicted that one out of every six American men will develop prostate cancer in their lifetime. See, American Cancer Society, Cancer Facts and Figures 2008. Atlanta: American Cancer Society; 2008 . Despite recent advances in both prostate cancer detection and treatment, it remains one of the leading causes of cancer-related death among the American male population.

[0003] Anti-DNP antibodies are readily present in high concentrations of the human bloodstream. See Ortega, E.; Kostovetzky, M.; Larralde, C. Mol. Immun. 1984, 21, 883. A number of cancer-related, antibody directing small molecules having been synthesized. See, Lu, et al., Adv. Drug Deliv. Rev. 2004, 56, 1161 ; Lu, et al., Mol. Pharmaceut. 2007, 4, 695; Carlson, et al., ACS Chem. Bio. 2007, 2, 119; and Popkov, M.; Gonzalez, B.; Sinha, S. C.; Barbas, C. F., III. Proc. Nat. Acad. Sci., 2009, 1.

[0004] The present invention is directed to the design and synthesis of a new small-molecule capable of redirecting endogenous anti-dinitrophenyl (DNP) antibodies selectively to prostate cancer cells, and inducing antibody-directed, cell-mediated cytotoxicity.

[0005] When prostate cancer is diagnosed prior to metastasis, the patient has a greater then 99% chance of survival. The most successful means for treating prostate cancer at this stage is a radical prostatectoiny. Unfortunately, this surgery carries with it the risk of severing nerves and blood vessels associated with sexual organs and the bladder, and can potentially result in impotency or incontinency. Radiation therapy is yet another commonly used procedure that carries the risk of impotency. Half the patients who undergo radiation therapy for prostate cancer become impotent within 2 years of treatment. In addition to the adverse affects associated with these procedures, they are significantly less effective in patients whose cancer has already delocalized or metastasized on diagnosis. In these cases, patients generally undergo even more invasive procedures such as hormonal therapy or chemotherapy. Unfortunately, most patients eventually stop responding to hormonal therapy and the most successful chemotherapeutic, Taxotere, only prolongs the life of advanced prostate cancer patients by 2.5 months on average.

[0006] As another alternative therapeutic, monoclonal antibody (mAb)-based immunotherapy has proven clinically beneficial for cancer patients while allowing them to maintain a good quality of life. These antibodies can either regulate proliferation of cancer cells through the manipulation of signal transduction, or promote cytotoxicity. Two examples of FDA-approved mAb-based anticancer drugs are Herceptin and Rituxan (Rituximab), which are currently being used for the treatment of breast cancer and non-Hodgkin's lymphoma, respectively. While there are no mAb-based therapeutics currently available for prostate cancer patients, advanced clinical studies on mAb-based immunotherapy has shown promise for the treatment of prostate cancer including advanced prostate cancer. Despite the major advantages of mAb-based immunotherapy, there are significant pitfalls which may limit its potential. In general, mAb-based therapeutics are highly costly ($70,000 for full course of treatment of Herceptin), lack oral bioavailability, and can lead to severe and often fatal side-effects. For example, Herceptin is associated with heart problems and cannot be administered to approximately 10% of cancer patients because of heart-related complications. Rituxan can cause several side-effects which include renal failure, infections and immune and pulmonary toxicity.

[0007] Although still in its infancy, the concept of using small molecules to template the human immune response has shown realistic potential. Recent reports have surfaced in which small molecules have been used to direct antibodies to cancerous cells such as breast carcinoma cells, melanoma cells, and nasopharyngeal epidermal carcinoma cells. Animal studies have demonstrated that these molecules can promote tumor rejection and antitumor immunity in mice. Because this process allows for the direction of endogenous antibodies selectively to the cell of interest, it has the potential to harness the power of mAb-based therapeutics while limiting the costs and side effects associated with administering exogenous antibodies. By developing similar methods which recruit anti-DNP antibodies to prostate cancer cells, the proposed research will help broaden this field while creating a new therapy for all forms of prostate cancer.

[0008] HAGINS D. M. ET AL: "A comparison of the amino terminal amino-acids sequences of early and late pools of anti-DNP and anti-DNP-p-aminobenzoylglutamate antibody light chains", IMMUNOLOGY, vol. 34, no. 5, 1978, pages 853-862, is a reference which discloses N-terminal amino acid sequences of early and late pools of anti-DNP and related compounds. It discloses a process for preparing an antigen comprising preparation of DNP-ABG by reacting N-(p-aminobenzoyl)-L-glutamic acid with excess of 1-fluoro-2,4-dinitrobenzene. The DNP-ABG obtained was subsequentially conjugated to BGG and to to HAS.

[0009] WO2007002222 discloses antibody-drag conjugates (ADCs) which comprise an antibody or antigen-binding fragment thereof which binds to prostate-specific membrane antigen (PSMA) and is conjugated to monomethylauristatin norephedrine or monomethylauristatin phenylalanine.

[0010] US2004029778 discloses peptide prodrugs which contain cleavage sites specifically cleaved by prostate specific membrane antigen (PSMA). These prodrugs are useful for substantially inhibiting the non-specific toxicity of a variety of therapeutic drugs. Upon cleavage of the prodrug by PSMA, the therapeutic drug are activated and exert their toxicity. Sesquiterpene-gamma-lactones form part of the prodrugs, and are designed to be linked to carrier moieties such as said peptides. Methods for treating cell proliferative disorders are also disclosed in US2004029778.

[0011] NICULESCU-DUVAZ D ET AL: "Long functionalized poly(ethylene glycol)s of defined molecular weight: Synthesis and application in solid-phase synthesis of conjugates", BIOCONJUGATE CHEMISTRY 200804 US LNKD- DOI:10.1021/BC060242+, vol. 19, no. 4, April 2008 (2008-04), pages 973-981, discloses that (poly)ethylene oxide groups can function as linkers in bifunctional molecules and the applicability of these linkers to solid-phase synthesis of conjugates.

[0012] SIBRIAN-VAZQUEZ MARTHA ET AL: "Synthesis and properties of cell-targeted Zn(II)-phthalocyanine-peptide conjugates", BIOCONJUGATE CHEMISTRY, vol. 18, no. 2, March 2007 (2007-03), pages 410-420, XP002633589, ISSN: 1043-1802 discloses a number of Zn-phthalocyanine-peptide conjugates comprising a PEG linker.

[0013] WO2009026177 discloses prostate specific membrane antigen (PSMA) binding conjugates that are useful for delivering therapeutic, diagnostic and imaging agents. It describes pharmaceutical composition containing them and methods of using the conjugates and compositions. It describes processes for manufacture of the conjugates too.

Brief Description of the Figures

[0014]

Figure 1 shows scheme 1, which is a schematic depiction of small-molecule templated immunotherapy.

Figure 2(A) shows computational modeling of cell-binding terminus in the binding pocket of PSMA. Figure 2(B) shows a model of PSMA-small molecule-Anti-DNP antibody ternary complex.

Figure 3 shows a prostate cancer antibody-recruiting molecule of the present invention, PC-ARM (**3**).

Figure 4 shows the synthesis of the prostate cancer antibody-recruiting molecule of Figure 3. The azide-functionalized cell-binding terminus was synthesized in 3 steps by coupling Cbz-protected lysine and *t*-butyl protected glutamic acid with triphosgetie, followed by Cbz deprotection and azide formation (scheme 2). Heterobifunctional PEG 10 was synthesized in a five step process from octaethylene glycol (scheme 2). These intermediates were coupled via microwave assisted, copper-catalyzed Huisgen cyloaddition, and deprotected using microwave assisted TFA deprotection (scheme 3) afforded the prostate cancer antibody-recruiting molecule of the present invention PC-ARM (**3**).

Figure 5 shows in (A) a representative flow cytometry histogram illustrating small-molecule **3**-dependant anti-DNP antibody binding to PSMA-expressing LNCaP cells. LNCaP cells were preincubated with **3** (50 nM), and subsequently incubated with Alexa Fluor 488-conjugated anti-DNP antibodies. (B) Representative flow cytometry histogram illustrating no small-molecule **3** dependant anti-DNP antibody binding to PSMA-negative DU-145 cells. DU-145 cells were preincubated with **3** (50 nM), and subsequently incubated with Alexa Fluor 488-conjugated anti-DNP antibodies.

Figure 6 shows the change in % cell killing induced by PC-ARM (**3**) (shown in the figure as P-ARM8). In short, LNCaP cells and PBMCs were incubated in the presence of anti-DNP antibody IgGI, IgG3 and a sample of normal human IgG known to have anti-DNP antibodies for 24 hours at 37°C. The change in % cell-killing reflects the increase associated with addition of 50 nM P-ARM8 (**3**). The data was run in dodecaplets, and is reported as the average ± SEM. In addition, each experiment was run in parallel with

50 nM P-ARM8 alone to screen for inherent small-molecule induced cell-killing.

Figure 7 shows exemplary compounds according to the present disclosure.

Figure 8 shows additional exemplary compounds according to the present disclosure.

Figure 9 shows divergent synthetic scheme 1a.

Figure 10 shows Scheme 2a- synthesis toward propargyl intermediates used in synthesizing compounds according to the invention.

Figure 11 shows Scheme 3a which is directed to the synthesis of intermediate 15, and proposed access to azide intermediate 16 to be used in click chemistry.

Figure 12 shows scheme 4a which describes a synthetic approach to bis di-DNP lysine 21.

Figure 13 shows scheme 5a which describes a synthetic approach to the trisazidylated analog which can be used to condense with the bis-diDNP lysine 21 to produce compound 3 of Figure 8 or similar compounds.

Objects of the Invention

[0015] It is an object of the invention to provide chimeric compounds as defined in the claims which can be used to treat virtually any cancer, especially including prostate cancer and metastatic prostate cancer.

[0016] It is an additional object of the invention to provide chimeric compounds as defined in the claims which can be used to provide pharmaceutical compositions, including pharmaceutical compositions which include additional bioactive agents or agents which assist in the treatment of cancer, especially prostate cancer, including metastatic prostate cancer.

[0017] It is still another object of the invention to provide compounds for treating cancer, including prostate cancer, including metastatic prostate cancer as defined in the claims.

[0018] Yet a further object of the disclosure is to provide compounds for inhibiting metastatis of cancer, especially including metastatic prostate cancer.

[0019] These and/or other objects of the invention may be readily gleaned from a review of the invention as described herein.

Brief Description of the Invention

[0020] It is an aspect of the invention to provide chimeric antibody recruiting molecules as defined in the claims which bind to prostate specific membrane antigen (PMSA) and attract antibodies such that the chimeric molecules will assist in immunotherapy of a patient with virtually any cancer, especially including prostate cancer, and further including metastatic prostate cancer.

[0021] In this first aspect of the invention, chimeric antibody recruiting molecules are as defined in claim 1.

[0022] In an additional aspect of the invention, a pharmaceutical composition comprises an effective amount of a chimeric compound as described above, optionally and preferably in combination with a pharmaceutically acceptable carrier, additive or excipient. In alternative aspects, pharmaceutical combination compositions comprise an effective amount of a chimeric compound as described herein, in combination with at least one additional agent which is used to treat cancer, including prostate cancer, especially including metastatic prostate cancer or a secondary condition or effect of cancer, especially prostate cancer (e.g., bone pain, hyperplasia, osteoporosis, etc. as otherwise described herein).

[0023] A further aspect of the invention, relates to compounds according to the present invention for treating cancer in a patient, especially prostate cancer in male patients in need thereof. The method of treating cancer comprises administering to a patient in need an effective amount of a chimeric compound as otherwise described herein in combination with a pharmaceutically acceptable carrier, additive or excipient, optionally in further combination with at least one additional agent which is effective in treating cancer, especially including prostate cancer, metastatic cancer or one or more of its secondary conditions or effects.

[0024] The present disclosure also relates to compounds for inhibiting prostate cancer to reduce or inhibit the spread or metastasis of the cancer into other tissues of the patients' body, especially including bones, the lymph (lymph nodes) system, bladder, vas deferens, kidneys, liver, lungs and brain, among others.

[0025] The present disclosure also relates to instances in which destruction of non-cancerous cells which possess PSMA can be of therapeutic use, especially in cancer therapy. For example, given that PSMA is found on the neovasculare of many non-prostatic cancer cells, but not on normal vasculature, the invention could be used for antiangiogenic therapy for other forms of cancer by targeting the neovasculature of those cancers.

Detailed Description of the Invention

[0026] The following terms are used to describe the present invention. In instances where a term is not specifically defined herein, that term is given an art-recognized meaning by those of ordinary skill applying that term in context to its use in describing the present invention.

[0027] The term "compound", as used herein, unless otherwise indicated, refers to any specific chemical compound disclosed herein and includes tautomers, regioisomers, geometric isomers, and where applicable, optical isomers (enantiomers) thereof, as well as pharmaceutically acceptable salts and derivatives (including prodrug forms) thereof. Within its use in context, the term compound generally refers to a single compound, but also may include other compounds such as stereoisomers, regioisomers and/or optical isomers (including racemic mixtures) as well as specific enantiomers or enantiomerically enriched mixtures of disclosed compounds. The term also refers, in context to prodrug forms of compounds which have been modified to facilitate the administration and delivery of compounds to a site of activity. It is noted that in describing the present compounds, numerous substituents, linkers and connector molecules and variables associated with same, among others, are described. It is understood by those of ordinary skill that molecules which are described herein are stable compounds as generally described hereunder.

[0028] The term "patient" or "subject" is used throughout the specification within context to describe an animal, generally a mammal and preferably a human, to whom treatment, including prophylactic treatment (prophylaxis), with the compositions according to the present invention is provided. For treatment of those infections, conditions or disease states which are specific for a specific animal such as a human patient or a patient of a particular gender, such as a human male patient, the term patient refers to that specific animal. Compounds according to the present invention are useful for the treatment of cancer, especially including prostate cancer and in particular, metastatic prostate cancer.

[0029] The term "effective" is used herein, unless otherwise indicated, to describe an amount of a compound or composition which, in context, is used to produce or effect an intended result, whether that result relates to the inhibition of the effects of a toxicant on a subject or the treatment of a subject for secondary conditions, disease states or manifestations of exposure to toxicants as otherwise described herein. This term subsumes all other effective amount or effective concentration terms (including the term "therapeutically effective") which are otherwise described in the present application.

[0030] The terms "treat", "treating", and "treatment", etc., as used herein, refer to any action providing a benefit to a patient at risk for prostate cancer or metastasis of prostate cancer, including improvement in the condition through lessening or suppression of at least one symptom, inhibition of cancer growth, reduction in cancer cells or tissue, prevention or delay in progression of metastasis of the cancer, prevention or delay in the onset of disease states or conditions which occur secondary to cancer or remission or cure of the cancer, among others. Treatment, as used herein, encompasses both prophylactic and therapeutic treatment. The term "prophylactic" when used, means to reduce the likelihood of an occurrence or the severity of an occurrence within the context of the treatment of cancer, including cancer metastasis as otherwise described hereinabove.

[0031] The term "neoplasia" or "cancer" is used throughout the specification to refer to the pathological process that results in the formation and growth of a cancerous or malignant neoplasm, i.e., abnormal tissue that grows by cellular proliferation, often more rapidly than normal and continues to grow after the stimuli that initiated the new growth cease. Malignant neoplasms show partial or complete lack of structural organization and functional coordination with the normal tissue and most invade surrounding tissues, metastasize to several sites, and are likely to recur after attempted removal and to cause the death of the patient unless adequately treated. As used herein, the term neoplasia is used to describe all cancerous disease states and embraces or encompasses the pathological process associated with malignant hematogenous, ascitic and solid tumors. Representative cancers include, for example, prostate cancer, metastatic prostate cancer, stomach, colon, rectal, liver, pancreatic, lung, breast, cervix uteri, corpus uteri, ovary, testis, bladder, renal, brain/CNS, head and neck, throat, Hodgkin's disease, non-Hodgkin's

lymphoma, multiple myeloma, leukemia, melanoma, non-melanoma skin cancer, acute lymphocytic leukemia, acute myelogenous leukemia, Ewing's sarcoma, small cell lung cancer, choriocarcinoma, rhabdomyosarcoma, Wilms' tumor, neuroblastoma, hairy cell leukemia, mouth/pharynx, oesophagus, larynx, kidney cancer and lymphoma, among others, which may be treated by one or more compounds according to the present invention. Because of the activity of the present compounds as anti-angiogenic compounds, the present invention has general applicability treating virtually any cancer in any tissue, thus the compounds, compositions and methods of the present invention are generally applicable to the treatment of cancer. Given that the protein target is found on the neovasculature of most non-prostatic cancer cells, the compounds in the present invention may also serve as an antiangiogenic therapy for other cancer types.

[0032] In certain particular aspects of the present invention, the cancer which is treated is prostate cancer or metastatic prostate cancer. Separately, metastatic prostate cancer may be found in virtually all tissues of a cancer patient in late stages of the disease, typically metastatic prostate cancer is found in seminal vesicles, lymph system/nodes (lymphoma), in bones, in bladder tissue, in kidney tissue, liver tissue and in virtually any tissue, including brain (brain cancer/tumor). Thus, the present invention is generally applicable and may be used to treat any cancer in any tissue, regardless of etiology.

[0033] The term "prostate cancer" is used to describe a disease in which cancer develops in the prostate, a gland in the male reproductive system. It occurs when cells of the prostate mutate and begin to multiply uncontrollably. These cells may metastasize (metastatic prostate cancer) from the prostate to virtually any other part of the body, particularly the bones and lymph nodes, but the kidney, bladder and even the brain, among other tissues. Prostate cancer may cause pain, difficulty in urinating, problems during sexual intercourse, erectile dysfunction. Other symptoms can potentially develop during later stages of the disease.

[0034] Rates of detection of prostate cancers vary widely across the world, with South and East Asia detecting less frequently than in Europe, and especially the United States. Prostate cancer develops most frequently in men over the age of fifty and is one of the most prevalent types of cancer in men. However, many men who develop prostate cancer never have symptoms, undergo no therapy, and eventually die of other causes. This is because cancer of the prostate is, in most cases, slow-growing, and because most of those affected are over the age of 60. Hence, they often die of causes unrelated to the prostate cancer. Many factors, including genetics and diet, have been implicated in the development of prostate cancer. The presence of prostate cancer may be indicated by symptoms, physical examination, prostate specific antigen (PSA), or biopsy. There is concern about the accuracy of the PSA test and its usefulness in screening. Suspected prostate cancer is typically confirmed by taking a biopsy of the prostate and examining it under a microscope. Further tests, such as CT scans and bone scans, may be performed to determine whether prostate cancer has spread.

[0035] Treatment options for prostate cancer with intent to cure are primarily surgery and radiation therapy. Other treatments such as hormonal therapy, chemotherapy, proton therapy, cryosurgery, high intensity focused ultrasound (HIFU) also exist depending on the clinical scenario and desired outcome.

[0036] The age and underlying health of the man, the extent of metastasis, appearance under the microscope, and response of the cancer to initial treatment are important in determining the outcome of the disease. The decision whether or not to treat localized prostate cancer (a tumor that is contained within the prostate) with curative intent is a patient trade-off between the expected beneficial and harmful effects in terms of patient survival and quality of life.

[0037] An important part of evaluating prostate cancer is determining the stage, or how far the cancer has spread. Knowing the stage helps define prognosis and is useful when selecting therapies. The most common system is the four-stage TNM system (abbreviated from Tumor/Nodes/Metastases). Its components include the size of the tumor, the number of involved lymph nodes, and the presence of any other metastases.

[0038] The most important distinction made by any staging system is whether or not the cancer is still confined to the prostate or is metastatic. In the TNM system, clinical T1 and T2 cancers are found only in the prostate, while T3 and T4 cancers have spread elsewhere and metastasized into other tissue. Several tests can be used to look for evidence of spread. These include computed tomography to evaluate spread within the pelvis, bone scans to look for spread to the bones, and endorectal coil magnetic resonance imaging to closely evaluate the prostatic capsule and the seminal vesicles. Bone scans often reveal osteoblastic appearance due to *increased* bone density in the areas of bone metastasis - opposite to what is found in many other cancers that metastasize. Computed tomography (CT) and magnetic resonance imaging (MRI) currently do not add any significant information in the assessment of possible lymph node metastases in patients with prostate cancer according to a meta-analysis.

[0039] Prostate cancer is relatively easy to treat if found early. After a prostate biopsy, a pathologist looks at the samples under a microscope. If cancer is present, the pathologist reports the grade of the tumor. The grade tells how much the tumor tissue differs from normal prostate tissue and suggests how fast the tumor is likely to grow. The Gleason system is used to grade

prostate tumors from 2 to 10, where a Gleason score of 10 indicates the most abnormalities. The pathologist assigns a number from 1 to 5 for the most common pattern observed under the microscope, then does the same for the second most common pattern. The sum of these two numbers is the Gleason score. The Whitmore-Jewett stage is another method sometimes used. Proper grading of the tumor is critical, since the grade of the tumor is one of the major factors used to determine the treatment recommendation.

[0040] Early prostate cancer usually causes no symptoms. Often it is diagnosed during the workup for an elevated PSA noticed during a routine checkup. Sometimes, however, prostate cancer does cause symptoms, often similar to those of diseases such as benign prostatic hypertrophy. These include frequent urination, increased urination at night, difficulty starting and maintaining a steady stream of urine, blood in the urine, and painful urination. Prostate cancer is associated with urinary dysfunction as the prostate gland surrounds the prostatic urethra. Changes within the gland therefore directly affect urinary function. Because the vas deferens deposits seminal fluid into the prostatic urethra, and secretions from the prostate gland itself are included in semen content, prostate cancer may also cause problems with sexual function and performance, such as difficulty achieving erection or painful ejaculation.

[0041] Advanced prostate cancer can spread to other parts of the body and this may cause additional symptoms. The most common symptom is bone pain, often in the vertebrae (bones of the spine), pelvis or ribs. Spread of cancer into other bones such as the femur is usually to the proximal part of the bone. Prostate cancer in the spine can also compress the spinal cord, causing leg weakness and urinary and fecal incontinence.

[0042] The specific causes of prostate cancer remain unknown. A man's risk of developing prostate cancer is related to his age, genetics, race, diet, lifestyle, medications, and other factors. The primary risk factor is age. Prostate cancer is uncommon in men less than 45, but becomes more common with advancing age. The average age at the time of diagnosis is 70. However, many men never know they have prostate cancer.

[0043] A man's genetic background contributes to his risk of developing prostate cancer. This is suggested by an increased incidence of prostate cancer found in certain racial groups, in identical twins of men with prostate cancer, and in men with certain genes. Men who have a brother or father with prostate cancer have twice the usual risk of developing prostate cancer. Studies of twins in Scandinavia suggest that forty percent of prostate cancer risk can be explained by inherited factors. However, no single gene is responsible for prostate cancer; many different genes have been implicated. Two genes (*BRCA1* and *BRCA2*) that are important risk factors for ovarian cancer and breast cancer in women have also been implicated in prostate cancer.

[0044] Dietary amounts of certain foods, vitamins, and minerals can contribute to prostate cancer risk. Dietary factors that may increase prostate cancer risk include low intake of vitamin E, the mineral selenium, green tea and vitamin D. A large study has implicated dairy, specifically low-fat milk and other dairy products to which vitamin A palmitate has been added. This form of synthetic vitamin A has been linked to prostate cancer because it reacts with zinc and protein to form an unabsorbable complex. Prostate cancer has also been linked to the inclusion of bovine somatotropin hormone in certain dairy products.

[0045] There are also some links between prostate cancer and medications, medical procedures, and medical conditions. Daily use of anti-inflammatory medicines such as aspirin, ibuprofen, or naproxen may decrease prostate cancer risk. Use of the cholesterol-lowering drugs known as the statins may also decrease prostate cancer risk. Infection or inflammation of the prostate (prostatitis) may increase the chance for prostate cancer, and infection with the sexually transmitted infections chlamydia, gonorrhea, or syphilis seems to increase risk. Obesity and elevated blood levels of testosterone may increase the risk for prostate cancer.

[0046] Prostate cancer is classified as an adenocarcinoma, or glandular cancer, that begins when normal semen-secreting prostate gland cells mutate into cancer cells. The region of prostate gland where the adenocarcinoma is most common is the peripheral zone. Initially, small clumps of cancer cells remain confined to otherwise normal prostate glands, a condition known as carcinoma *in situ* or prostatic intraepithelial neoplasia (PIN). Although there is no proof that PIN is a cancer precursor, it is closely associated with cancer. Over time these cancer cells begin to multiply and spread to the surrounding prostate tissue (the stroma) forming a tumor. Eventually, the tumor may grow large enough to invade nearby organs such as the seminal vesicles or the rectum, or the tumor cells may develop the ability to travel in the bloodstream and lymphatic system. Prostate cancer is considered a malignant tumor because it is a mass of cells which can invade other parts of the body. This invasion of other organs is called metastasis. Prostate cancer most commonly metastasizes to the bones, lymph nodes, rectum, and bladder.

[0047] In prostate cancer, the regular glands of the normal prostate are replaced by irregular glands and clumps of cells. When a man has symptoms of prostate cancer, or a screening test indicates an increased risk for cancer, more invasive evaluation is

offered. The only test which can fully confirm the diagnosis of prostate cancer is a biopsy, the removal of small pieces of the prostate for microscopic examination. However, prior to a biopsy, several other tools may be used to gather more information about the prostate and the urinary tract. Cystoscopy shows the urinary tract from inside the bladder, using a thin, flexible camera tube inserted down the urethra. Transrectal ultrasonography creates a picture of the prostate using sound waves from a probe in the rectum.

[0048] After biopsy, the tissue samples are then examined under a microscope to determine whether cancer cells are present, and to evaluate the microscopic features (or Gleason score) of any cancer found. In addition, tissue samples may be stained for the presence of PSA and other tumor markers in order to determine the origin of maligant cells that have metastasized. A number of other potential approaches for diagnosis of prostate cancer are ongoing such as early prostate cancer antigen-2 (EPCA-2), and prostasome analysis.

[0049] In addition to therapy using the compounds according to the present invention, therapy (including prophylactic therapy) for prostate cancer supports roles in reducing prostate cancer for dietary selenium, vitamin E, lycopene, soy foods, vitamin D, green tea, omega-3 fatty acids and phytoestrogens. The selective estrogen receptor modulator drug toremifene has shown promise in early trials. Two medications which block the conversion of testosterone to dihydrotestosterone (and reduce the tendency toward cell growth), finasteride and dutasteride, are shown to be useful. The phytochemicals indole-3-carbinol and diindolylmethane, found in cruciferous vegetables (califlower and broccholi), have favorable antiandrogenic and immune modulating properties. Prostate cancer risk is decreased in a vegetarian diet.

[0050] Treatment for prostate cancer may involve active surveillance, surgery (prostatecomy or orchiectomy), radiation therapy including brachytherapy (prostate brachytherapy) and external beam radiation as well as hormonal therapy. There are several forms of hormonal therapy which include the following, each of which may be combined with compounds according to the present invention.

- Antiandrogens such as flutamide, bicalutamide, nilutamide, and cyproterone acetate which directly block the actions of testosterone and DHT within prostate cancer cells.
- Medications such as ketoconazole and aminoglutethimide which block the production of adrenal androgens such as DHEA. These medications are generally used only in combination with other methods that can block the 95% of androgens made by the testicles. These combined methods are called total androgen blockade (TAB), which can also be achieved using antiandrogens.
- GnRH modulators, including agonists and antagonists. GnRH antagonists suppress the production of LH directly, while GnRH agonists suppress LH through the process of downregulation after an initial stimulation effect. Abarelix is an example of a GnRH antagonist, while the GnRH agonists include leuprolide, goserelin, triptorelin, and buserelin.
- The use of abiraterone acetate can be used to reduce PSA levels and tumor sizes in aggressive end-stage prostate cancer for as high as 70% of patients. Sorafenib may also be used to treat metastatic prostate cancer.

[0051] Each teatment described above has disadvantages which limit its use in certain circumstances. GnRH agonists eventually cause the same side effects as orchiectomy but may cause worse symptoms at the beginning of treatment. When GnRH agonists are first used, testosterone surges can lead to increased bone pain from metastatic cancer, so antiandrogens or abarelix are often added to blunt these side effects. Estrogens are not commonly used because they increase the risk for cardiovascular disease and blood clots. The antiandrogens do not generally cause impotence and usually cause less loss of bone and muscle mass. Ketoconazole can cause liver damage with prolonged use, and aminoglutethimide can cause skin rashes.

[0052] Palliative care for advanced stage prostate cancer focuses on extending life and relieving the symptoms of metastatic disease. As noted above, abiraterone acetate shows some promise in treating advance stage prostate cancer as does sorafenib. Chemotherapy may be offered to slow disease progression and postpone symptoms. The most commonly used regimen combines the chemotherapeutic drug docetaxel with a corticosteroid such as prednisone. Bisphosphonates such as zoledronic acid have been shown to delay skeletal complications such as fractures or the need for radiation therapy in patients with hormone-refractory metastatic prostate cancer. Alpharadin may be used to target bone metastasis. The phase II testing shows prolonged patient survival times, reduced pain and improved quality of life.

[0053] Bone pain due to metastatic disease is treated with opioid pain relievers such as morphine and oxycodone. External beam radiation therapy directed at bone metastases may provide pain relief. Injections of certain radioisotopes, such as strontium-89, phosphorus-32, or samarium-153, also target bone metastases and may help relieve pain.

[0054] As an alternative to active surveillance or definitive treatments, alternative therapies may also be used for the management of prostate cancer. PSA has been shown to be lowered in men with apparent localized prostate cancer using a vegan diet (fish allowed), regular exercise, and stress reduction. Many other single agents have been shown to reduce PSA, slow PSA doubling times, or have similar effects on secondary markers in men with localized cancer.in short term trials, such as pomegranate juice or genistein, an isoflavone found in various legumes.

[0055] Manifestations or secondary conditions or effects of metastatic and advanced prostate cancer may include anemia, bone marrow suppression, weight loss, pathologic fractures, spinal cord compression, pain, hematuria, ureteral and/or bladder outlet obstruction, urinary retention, chronic renal failure, urinary incontinence, and symptoms related to bony or soft-tissue metastases, among others.

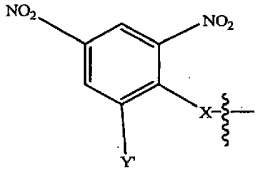
[0056] Additional prostate drugs which can be used in combination with the chimeric antibody recruiting compounds according to the present invention include, for example, the enlarged prostate drugs/agents, as well as eulexin, flutamide, goserelin, leuprolide, lupron, nilandron, nilutamide, zoladex and mixtures thereof. Enlarged prostate drugs/agents as above, include for example, ambenyl, ambophen, amgenal, atrosept, bromanyl, bromodiphenhydramine-codeine, bromotuss-codeine, cardura, chlorpheniramine-hydrocodone, ciclopirox, clotrimazole-betamethasone, dolsed, dutasteride, finasteride, flomax, gecil, hexalol, lamisil, lanased, loprox, lotrisone, methenamine, methen-bella-meth Bl-phen sal, meth-hyos-atrp-M blue-BA-phsal, MHP-A, mybanil, prosed/DS, Ro-Sed, S-T Forte, tamsulosin, terbinafine, trac, tussionex, ty-methate, uramine, uratin, uretron, uridon, uro-ves, urstat, usept and mixtures thereof.

[0057] The term "tumor" is used to describe a malignant or benign growth or tumefacent.

[0058] The term "antibody binding terminal moiety", "antibody binding terminus" or "antibody binding moiety" is use to described that portion of a chimeric compound according to the present invention which comprises at least one small molecule or hapten. The term "hapten" is used to describe a small-molecular-weight inorganic or organic molecule that alone is not antigenic but which when linked to another molecule, such as a carrier protein (albumin, etc.) or in the case of the present invention, a cell binding terminal moiety of the present compounds is antigenic; and an antibody raised against the hapten (generally, the hapten bonded or complexed to the carrier) will react with the hapten alone.

[0059] It is preferred that the antibody binding terminal comprise a hapten which is reactive (binds to) an endogenous antibody that pre-exists in the patient prior to initiating therapy with the compounds of the present invention and does not have to be separately raised as part of a treatment regimen. Thus, haptens which comprise a di-or trinitro phenyl group as depicted below.

[0060] The di- or trinitro phenyl hapten (ABT) moiety for use in the present invention may be represented by the following formula:



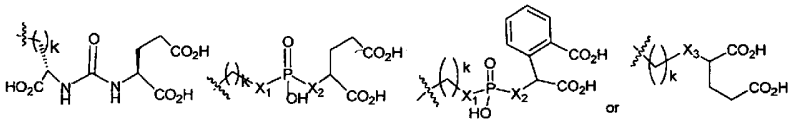
Where Y' is H or NO_2;

X is O, CH_2, NR^1, S(O), $S(O)_2$, -$S(O)_2O$; -$OS(O)_2$, or $OS(O)_2O$;

R^1 is H, a C_1-C_3 alkyl group, or a -C(O)(C_1-C_3) group;

[0061] The term "cell binding terminal moiety" , "cell binding terminus" or "cell binding moiety" is use to described that portion of a chimeric compound according to the present invention which comprises at least one small molecule or moiety which can bind specifically to prostate specific membrane antigen (PSMA).

[0062] CBT groups for use in the present invention are set forth below:



Where X_1 and X_2 are each independently CH_2, O, NH or S;

X_3 is O, CH_2, NR^1, S(O), $S(O)_2$, -$S(O)_2O$, -$OS(O)_2$, or $OS(O)_2O$;

R^1 is a C_1-C_3 alkyl group, or a -C(O)(C_1-C_3) group;

k is an integer from 0 to 20, 8 to 12, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4, 5 or 6; or a salt thereof.

[0063] The term "linker" refers to a chemical entity connecting an antibody binding terminus (ABT) moiety to a cell binding terminus (CBT) moiety, optionally through a connector moiety through covalent bonds. The linker between the two active portions of the molecule, that is the antibody binding terminus (ABT) and the cell binding terminus (CBT) ranges from about 5Å to about 50A or more in length, about 6Å to about 45Å in length, about 7Å to about 40Å in length, about 8Å to about 35Å in length, about 9Å to about 30Å in length, about 10Å to about 25Å in length, about 7Å to about 20 Å in length, about 5Å to about 16Å in length, about 5Å to about 15Å in length, about 6Å to about 14Å in length, about 10Å to about 20Å in length, about 11Å to about 25Å in length, etc. Linkers which are based upon ethylene glycol units and are between 8 and 12 glycol units in length may be preferred. By having a linker with a length as otherwise disclosed herein, the ABT moiety and the CBT moiety may be situated to advantageously take advantage of the biological activity of compounds according to the present invention which bind to prostate specific membrane antigen (PSMA) and attractive endogenous antibodies to the cell to which the compounds are bound, resulting in the selective and targeted cell death of those cells, in whatever tissues they may reside, which have PSMA. The selection of a linker component is based on its documented properties of biocompatibility, solubility in aqueous and organic media, and low immunogenicity/antigenicity. Although numerous linkers may be used as otherwise described herein, a linker based upon polyethyleneglycol (PEG) linkages, polypropylene glycol linkages, or polyethyleneglycol-co-polypropylene oligomers (up to about 100 units, about 1 to 100, about 1 to 75, about 1 to 60, about 1 to 50, about 1 to 35, about 1 to 25 , about 1 to 20, about 1 to 15, 1 to 10, about 8 to 12, about 1 to 8, etc.) may be favored as a linker because of the chemical and biological characteristics of these molecules. The use of polyethylene (PEG) linkages is preferred.

[0064] Preferred linkers include those according to the chemical structures:

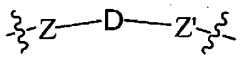


Or a polypropylene glycol or polypropylene-co-polyethylene glycol linker having between 1 and 100 glycol units;

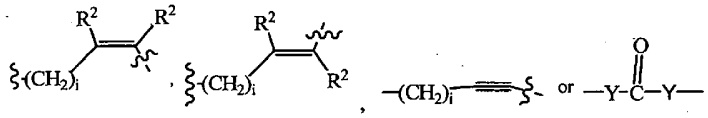
Where R_a is H, C_1-C_3 alkyl or alkanol or forms a cyclic ring with R^3 (proline) and R^3 is a side chain derived of an amino acid preferably selected from the group consisting of alanine (methyl), arginine (propyleneguanidine), asparagine (methylenecarboxyamide), aspartic acid (ethanoic acid), cysteine (thiol, reduced or oxidized di-thiol), glutamine (ethylcarboxyamide), glutamic acid (propanoic acid), glycine (H), histidine (methyleneimidazole), isoleucine (1-methylpropane), leucine (2-methylpropane), lysine (butyleneamine), methionine (ethylmethylthioether), phenylalanine (benzyl), proline (R^3 forms a cyclic ring with R_a and the adjacent nitrogen group to form a pyrrolidine group), serine (methanol), threonine (ethanol, 1-hydroxyethane), tryptophan (methyleneindole), tyrosine (methylene phenol) or valine (isopropyl);

m is an integer from 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5; or

[0065] A linker according to the chemical formula:



[0066] Where Z and Z' are each independently a bond, -$(CH_2)_i$-O, -$(CH_2)_i$-S, -$(CH_2)_i$-N-R,



wherein said -$(CH_2)_i$ group, if present in Z or Z', is bonded to a connector, ABT or CBT;

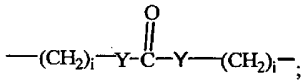
Each R is H, or a C_1-C_3 alkyl or alkanol group;

Each R^2 is independently H or a C_1-C_3 alkyl group;

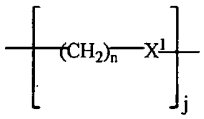
Each Y is independently a bond, O, S or N-R;

Each i is independently 1 to 100, 1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5;

D is



$-(CH_2)_{m'}-$;



or

a bond, with the proviso that Z, Z' and D are not each simultaneously bonds;

j is 1 to 100, 1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5;

m' is 1 to 100, 1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, to 8,1 to 6, 1, 2, 3, 4 or 5;

n is 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5;

X^1 is O, S or N-R; and

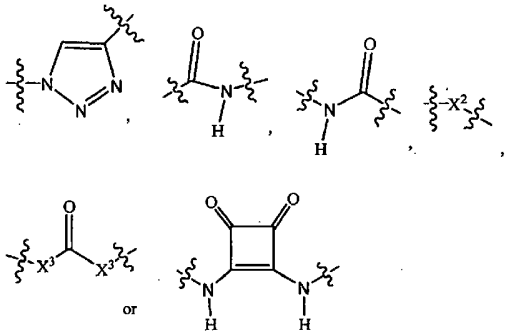
R is as described above, or a pharmaceutical salt thereof.

[0067] The term "connector", symbolized by [CON], is used to describe a chemical moiety which is included in chimeric compounds according to the present invention which forms from the reaction product of an activated ABT-linker with a CBT moiety (which also is preferably activated) or an ABT moiety with an activated linker-CBT as otherwise described herein. The connector group is the resulting moiety which forms from the facile condensation of two separate chemical fragments which contain reactive groups which can provide connector groups as otherwise described to produce chimeric compounds according to the present invention. It is noted that a connector may be distinguishable from a linker in that the connector is the result of a specific chemistry which is used provide chimeric compounds according to the present invention wherein the reaction product of these groups results in an identifiable connector group which is distinguishable from the linker group as otherwise described herein. It is noted that there may be some overlap between the description of the connector group and the linker group, especially with respect to more common connector groups such as amide groups, oxygen (ether), sulfur (thioether) or amine linkages, urea or carbonate -OC(O)O- groups as otherwise described herein. It is further noted that a connector (or linker) may be connected to ABT, a linker or CBT at positions which are represented as being linked to another group using the using the symbol



Where two or more such groups are present in a linker or connector, any of an ABT, a linker or a CBT may be bonded to such a group.

[0068] Common connector groups which are used in the present invention include the following chemical groups:



Where X^2 is O, S, NR^4, S(O), $S(O)_2$, $-S(O)_2O$, $-OS(O)_2$, or $OS(O)_2O$;

X^3 is O, S, NR^4; and

R^4 is H, a C_1-C_3 alkyl or alkanol group, or a $-C(O)(C_1$-$C_3)$ group.

[0069] The term "pharmaceutically acceptable salt" or "salt" is used throughout the specification to describe a salt form of one or more of the compositions herein which are presented to increase the solubility of the compound in saline for parenteral delivery or in the gastric juices of the patient's gastrointestinal tract in order to promote dissolution and the bioavailability of the compounds. Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids. Suitable salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium, magnesium and ammonium salts, among numerous other acids well known in the pharmaceutical art. Sodium and potassium salts may be preferred as neutralization salts of carboxylic acids and free acid phosphate containing compositions according to the present invention. The term "salt" shall mean any salt consistent with the use of the compounds according to the present invention. In the case where the compounds are used in pharmaceutical indications, including the treatment of prostate cancer, including metastatic prostate cancer, the term "salt" shall mean a pharmaceutically acceptable salt, consistent with the use of the

compounds as pharmaceutical agents.

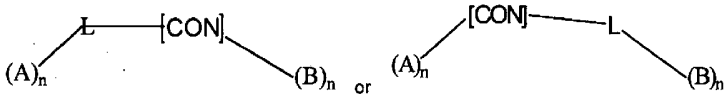
[0070] The term "coadministration" shall mean that at least two compounds or compositions are administered to the patient at the same time, such that effective amounts or concentrations of each of the two or more compounds may be found in the patient at a given point in time. Although compounds according to the present invention may be co-administered to a patient at the same time, the term embraces both administration of two or more agents at the same time or at different times, provided that effective concentrations of all coadministered compounds or compositions are found in the subject at a given time. Chimeric antibody-recruiting compounds according to the present invention may be administered with one or more additional anti-cancer agents or other agents which are used to treat or ameliorate the symptoms of cancer, especially prostate cancer, including metastatic prostate cancer. Exemplary anticancer agents which may be coadministered in combination with one or more chimeric compounds according to the present invention include, for example, antimetabolites, inhibitors of topoisomerase I and II, alkylating agents and microtubule inhibitors (e.g., taxol). Specific anticancer compounds for use in the present invention include, for example, Aldesleukin; Alemtuzumab; alitretinoin; allopurinol; altretamine; amifostine; anastrozole; arsenic trioxide; Asparaginase; BCG Live; bexarotene capsules; bexarotene gel; bleomycin; busulfan intravenous; busulfan oral; calusterone; capecitabine; carboplatin; carmustine; carmustine with Polifeprosan 20 Implant; celecoxib; chlorambucil; cisplatin; cladribine; cyclophosphamide; cytarabine; cytarabine liposomal; dacarbazine; dactinomycin; actinomycin D; Darbepoetin alfa; daunorubicin liposomal; daunorubicin, daunomycin; Denileukin diftitox, dexrazoxane; docetaxel; doxorubicin; doxorubicin liposomal; Dromostanolone propionate; Elliott's B Solution; epirubicin; Epoetin alfa estramustine; etoposide phosphate; etoposide (VP-16); exemestane; Filgrastim; floxuridine (intraarterial); fludarabine; fluorouracil (5-FU); fulvestrant; gemtuzumab ozogamicin; goserelin acetate; hydroxyurea; Ibritumomab Tiuxetan; idarubicin; ifosfamide; imatinib mesylate; Interferon alfa-2a; Interferon alfa-2b; irinotecan; letrozole; leucovorin; levamisole; lomustine (CCNU); meclorethamine (nitrogen mustard); megestrol acetate; melphalan (L-PAM); mercaptopurine (6-MP); mesna; methotrexate; methoxsalen; mitomycin C; mitotane; mitoxantrone; nandrolone phenpropionate; Nofetumomab; LOddC; Oprelvekin; oxaliplatin; paclitaxel; pamidronate; pegademase; Pegaspargase; Pegfilgrastim; pentostatin; pipobroman; plicamycin; mithramycin; porfimer sodium; procarbazine; quinacrine; Rasburicase; Rituximab; Sargramostim; streptozocin; talbuvidine (LDT); talc; tamoxifen; temozolomide; teniposide (VM-26); testolactone; thioguanine (6-TG); thiotepa; topotecan; toremifene; Tositumomab; Trastuzumab; tretinoin (ATRA); Uracil Mustard; valrubicin; valtorcitabine (monoval LDC); vinblastine; vinorelbine; zoledronate; and mixtures thereof, among others.

[0071] In addition to anticancer agents, a number of other agents may be coadministered with chimeric compounds according to the present invention in the treatment of cancer, especially prostate cancer, including metastatic prostate cancer. These include active agents, minerals, vitamins and nutritional supplements which have shown some efficacy in inhibiting prostate cancer tissue or its growth or are otherwise useful in the treatment of prostate cancer. For example, one or more of dietary selenium, vitamin E, lycopene, soy foods, vitamin D, green tea, lycopene, omega-3 fatty acids and phytoestrogens, including beta-sitosterol, may be utilized in combination with the present compounds to treat prostate cancer.

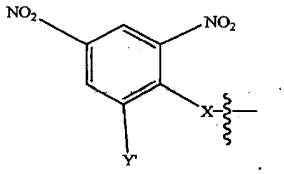
[0072] In addition, active agents, other than traditional anticancer agents have shown some utility in treating prostate cancer. The selective estrogen receptor modulator drug toremifene may be used in combination with the present compounds to treat cancer, especially prostate cancer, including metastatic prostate cancer. In addition, two medications which block the conversion of testosterone to dihydrotestosterone, finasteride and dutasteride, are also useful in the treatment of prostate cancer when coadministered with compounds according to the present invention. The phytochemicals indole-3-carbinol and diindolylmethane, may also be coadministered with the present compounds for their effects in treating prostate cancer. Additional agents which may be combined with compounds according to the present invention include antiandrogens, for example, flutamide, bicalutamide, nilutamide, and cyproterone acetate as well as agents which reduce the production of adrenal androgens (e.g. DHEA), such as ketoconazole and aminoglutethimide. Other active agents which may be combined with compounds according to the present invention include, for example, GnRH modulators, including agonists and antagonists. GnRH antagonists suppress the production of LH directly, while GnRH agonists suppress LH through the process of downregulation after an initial stimulation effect. Abarelix is an example of a GnRH antagonist, while the GnRH agonists include leuprolide, goserelin, triptorelin, and buserelin, among others. These agents may be combined with compounds according to the present invention in effective amounts. In addition, abiraterone acetate may also be combined with one or more compounds according to the present invention in the treatment of prostate cancer, especially including metastatic prostate cancer.

[0073] Other agents which may be combined with one or more compounds according to the present invention,include the bisphosphonates such as zoledronic acid, which have been shown to delay skeletal complications such as fractures which occur with patients having metastatic prostate cancer. Alpharadin, another agent, may be combined with compounds according to the present invention to target bone metastasis. In addition, bone pain due to metastatic prostate cancer may be treated with opioid pain relievers such as morphine and oxycodone, among others, which may be combined with compounds according to the present invention.

[0074] The present invention relates to compounds according to the general chemical structure:



[0075] Wherein A is an antibody binding moiety according to the chemical formula:



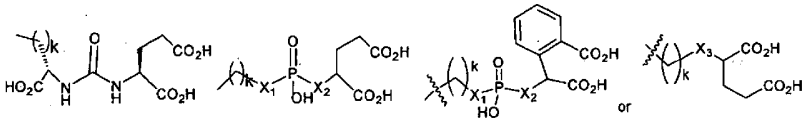
Where Y' is H or NO_2;

X is O, CH_2, NR^1, S(O), $S(O)_2$, -$S(O)_2O$, -$OS(O)_2$, or $OS(O)_2O$;

R^1 is H, a C_1-C_3 alkyl group, or a -C(O)(C_1-C_3) group;

R^1 is H or C_1-C_3 alkyl;

B is a cell binding moiety according to the chemical formula:



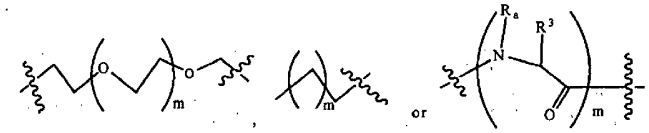
Where X_1 and X_2 are each independently CH_2, O, NH or S;

X_3 is O, CH_2, NR^1, S(O), $S(O)_2$, -$S(O)_2O$, -$OS(O)_2$, or $OS(O)_2O$;

R^1 is H, a C_1-C_3 alkyl group, or a -C(O)(C_1-C_3) group;

k is an integer from 0 to 20, 8 to 12, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4, 5 or 6;

L is a linker according to the chemical formula:

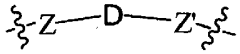


[0076] Or a polypropylene glycol or polypropylene-co-polyethylene glycol linker having between 1 and 100 glycol units (1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 52 and 50, 3 and 45);

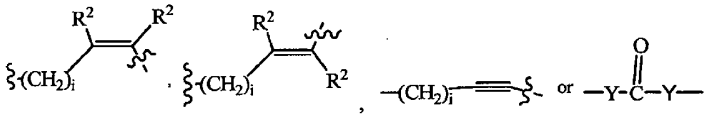
Where R_a is H, C_1-C_3 alkyl or alkanol or forms a cyclic ring with R^3 (proline) and R^3 is a side chain derived of an amino acid preferably selected from the group consisting of alanine (methyl), arginine (propyleneguanidine), asparagine (methylenecarboxyamide), aspartic acid (ethanoic acid), cysteine (thiol, reduced or oxidized di-thiol), glutamine (ethylcarboxyamide), glutamic acid (propanoic acid), glycine (H), histidine (methyleneimidazole), isoleucine (1-methylpropane), leucine (2-methylpropane), lysine (butyleneamine), methionine (ethylmethylthioether), phenylalanine (benzyl), proline (R^3 forms a cyclic ring with R_a and the adjacent nitrogen group to form a pyrrolidine group), serine (methanol), threonine (ethanol, 1-hydroxyethane), tryptophan (methyleneindole), tyrosine (methylene phenol) or valine (isopropyl);

m is an integer from 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5; or

L is a linker according to the chemical formula:



Where Z and Z' are each independently a bond, -$(CH_2)_i$-O, -$(CH_2)_i$-S, -$(CH_2)_i$-N-R,



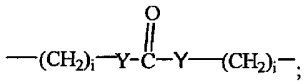
wherein said -$(CH_2)_i$ group, if present in Z or Z', is bonded to[CON] if present, ABT or CBT;

Each R is independently H, or a C_1-C_3 alkyl or alkanol group;

Each R^2 is independently H or a C_1-C_3 alkyl group;

Each Y is independently a bond, O, S or N-R;

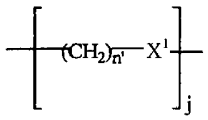
Each i is independently 0 to 100, 1 to 100, 1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5;
D is



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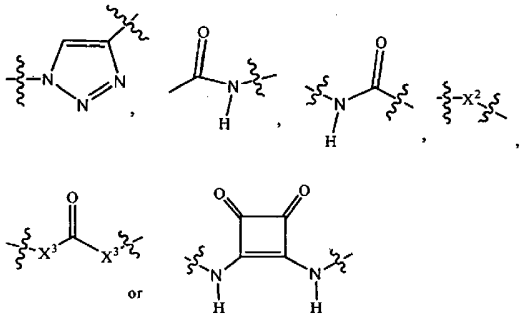


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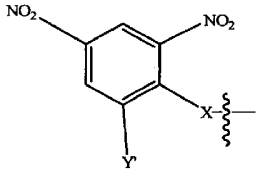
or a bond,
with the proviso that Z, Z' and D are not each simultaneously bonds;
j is 1 to 100, 1 to 75, 1 to 60, 1 to 55, 1 to S0, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5;
m' is 1 to 100, 1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1, 2, 3, 4 or 5;
Each n in a molecule is an integer from 1 to 15;
n' is 1 to 100, 1 to 75, 1 to 60, 1 to 55, 1 to 50, 1 to 45, 1 to 40, 2 to 35, 3 to 30, 1 to 15, 1 to 10, to 8, 1 to 6, 1, 2, 3, 4 or 5; and
X^1 is O, S or N-R,
R is independently H, or a C_1-C_3 alkyl or alkanol group; and

[0077] The connector moiety [CON] is a bond or a moiety according to the chemical structure:



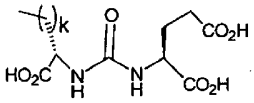
Where X^2 is O, S, NR^4, S(O), $S(O)_2$, -$S(O)_2O$, -$OS(O)_2$, or $OS(O)_2O$;
X^3 is NR^4, O or S; and
R^4 is H, a C_1-C_3 alkyl or alkanol group, or a -C(O)(C_1-C_3) group; or
a pharmaceutically acceptable salt, solvate or polymorph thereof.

[0078] In preferred aspects of the disclosure, the antibody binding terminus (ABT) is



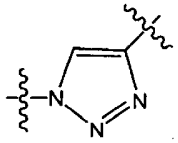
or '
Y' is NO_2;

[0079] In preferred aspects of the disclosure, CBT is



[0080] Where k is an integer from 0 to 20, 1 to 20, more preferably 8 to 12.

[0081] In other preferred aspects the connector moiety [CON} is a

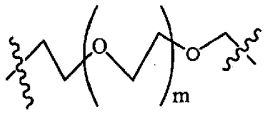


group which can be covalently bonded at



with a ABT group, a CBT group or alternatively, a linker group toprovide compounds as otherwise described herein.

[0082] In still other preferred aspects the linker group is a oligo or polyethyleneglycol moiety of the structure:



[0083] Where m is from 1 to 100 or as otherwise described herein, preferably about 8 to 12. Noted there is that polypropylene glycol or polyethylene glycol-co-polypropylenen glycol linkers may be substituted for PEG groups in the present compounds.

[0084] A number of preferred compounds, **20**,**21**, and **22** are set forth in attached Figure 7.

[0085] Pharmaceutical compositions comprising combinations of an effective amount of at least one chimeric antibody-recruiting compound according to the present invention, and one or more of the compounds otherwise described herein, all in effective amounts, in combination with a pharmaceutically effective amount of a carrier, additive or excipient, represents a further aspect of the present invention.

[0086] The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers and may also be administered in controlled-release formulations. Pharmaceutically acceptable carriers that may be used in these pharmaceutical compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as prolamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0087] The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously.

[0088] Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally-acceptable diluent or solvent, for example as a solution in 1, 3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as Ph. Helv or similar alcohol.

[0089] The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening,

flavoring or coloring agents may also be added.

[0090] Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[0091] The pharmaceutical compositions of this invention may also be administered topically, especially to treat skin cancers, psoriasis or other diseases which occur in or on the skin. Suitable topical formulations are readily prepared for each of these areas or organs. Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-acceptable transdermal patches may also be used.

[0092] For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water.

[0093] Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0094] For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with our without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

[0095] The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[0096] The amount of compound in a pharmaceutical composition of the instant invention that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host and disease treated, the particular mode of administration. Preferably, the compositions should be formulated to contain between about 0.05 milligram to about 750 milligrams or more, more preferably about 1 milligram to about 600 milligrams, and even more preferably about 10 milligrams to about 500 milligrams of active ingredient, alone or in combination with at least one additional non-antibody attracting compound which may be used to treat cancer, prostate cancer or metastatic prostate cancer or a secondary effect or condition thereof.

[0097] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease or condition being treated.

[0098] A patient or subject (e.g. a male human) suffering from cancer can be treated by administering to the patient (subject) an effective amount of a chimeric antibody recruiting compound according to the present invention including pharmaceutically acceptable salts, solvates or polymorphs, thereof optionally in a pharmaceutically acceptable carrier or diluent, either alone, or in combination with other known anticancer or pharmaceutical agents, preferably agents which can assist in treating prostate cancer, including metastatic prostate cancer or ameliorate the secondary effects and conditions associated with prostate cancer. This treatment can also be administered in conjunction with other conventional cancer therapies, such as radiation treatment or surgery.

[0099] These compounds can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid, cream, gel, or solid form, or by aerosol form.

[0100] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount for the desired indication, without causing serious toxic effects in the patient treated. A preferred dose of the active compound for all of the herein-mentioned conditions is in the range from about 10 ng/kg to 300

mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient/patient per day. A typical topical dosage will range from 0.01-3% wt/wt in a suitable carrier.

[0101] The compound is conveniently administered in any suitable unit dosage form, including but not limited to one containing less than 1mg, 1 mg to 3000 mg, preferably 5 to 500 mg of active ingredient per unit dosage form. An oral dosage of about 25-250 mg is often convenient.

[0102] The active ingredient is preferably administered to achieve peak plasma concentrations of the active compound of about 0.00001-30 mM, preferably about 0.1-30 µM. This may be achieved, for example, by the intravenous injection of a solution or formulation of the active ingredient, optionally in saline, or an aqueous medium or administered as a bolus of the active ingredient. Oral administration is also appropriate to generate effective plasma concentrations of active agent.

[0103] The concentration of active compound in the drug composition will depend on absorption, distribution, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

[0104] Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound or its prodrug derivative can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

[0105] The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a dispersing agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or enteric agents.

[0106] The active compound or pharmaceutically acceptable salt thereof can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

[0107] The active compound or pharmaceutically acceptable salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as other anticancer agents, antibiotics, antifungals, antiinflammatories, or antiviral compounds.

[0108] One or more chimeric antibody-recruiting compound according to the present invention is coadministered with another anticancer agent and/or another bioactive agent, as otherwise described herein.

[0109] Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0110] If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

[0111] In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art.

[0112] Liposomal suspensions may also be pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.
For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound are then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

General Chemical Synthesis

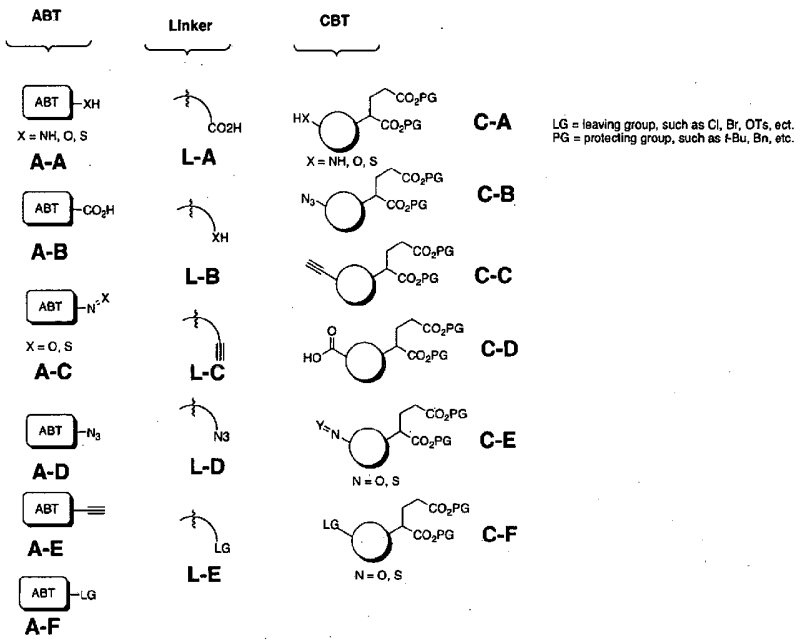
[0113] The chimeric antibody-recruiting compounds according to the present invention may be synthesized readily using standard chemical connectivity between the linker and cell binding terminus (CBT) and the antibody binding terminus (ABT), along with appropriate protecting groups when necessary. The approach uses standard functional group chemistry in order to link a cell binding moiety to an antibody binding moiety through a linker, which, in preferred aspects, provides an optional connector moiety (between the linker and the ABT or the linker and the CBT depending on functional groups, reactions used, etc.) which forms when the CBT is covalently bonded (connected) to the ABT antibody binding through the linker. Noted here is the fact that the connector moiety *per se* is not required and the linker; as otherwise described herein, may be covalently bonded directly to a CBT and/or an ABT without the formation of a specific connector moiety. In the present invention, the connector moiety, which is included in chimeric antibody-recruiting compounds according to the present invention, reflects its formation reflective of favorable synthetic chemistries to provide chimeric compounds as otherwise disclosed herein.

[0114] As depicted in the general scheme below, a carboxylic acid, such L-A, could be coupled to either an amine or an alcohol, such as C-A, to generate esters or amides through standard carbodiimide conditions (DCC, EDC, DIC along with base and catalytic amine (DMAP, imidazole), by conversion to the acid chloride through oxaly chloride or thionyl chloride etc. followed by addition of amine/alcohol.

[0115] Additionally, for example, an amine or an alcohol, such as A-A, can be coupled to an isocyanate or an isothiocyanate, such as C-E, to generate ureas, thioureas, or the corresponding carbonates or thiocarbonates.

[0116] In yet another approach, a triazole may be synthesized through a cycloaddition reaction between an azide, such as C-B, and an alkyne, such as L-C. This can be catalyzed by copper, such as copper sulfate along with ascorbic acid, to facilitate a clean reaction.

[0117] Still, in a further approach, for example, a heterolinker can be made through treating a nucleophile, such as A-A, with the appropriate leaving group, such as L-E. Some leaving groups could be halogens, such as bromine, or sulfonates, such as triflates or tosylates.



Compounds

[0118] Several high affinity ligands have been developed to target PSMA selectively. See, Slusher, et al, Nature Medicine, 1999, 5, 1396. Figure 1 depicts the small molecule templated immunotherapy which is generally understood to represent the principal mechanism of chimeric antibody-recruiting compounds according to the present invention. PC-ARM (**3**, **Figure 3**) was inspired by a urea-based, tetrazole-containing ligand with exceptionally high affinity (**2**, Ki = 0.9 nM) {See, Kozikowski, J. Med. Chem., 2004, 47, 1729] and refined with molecular modeling to accommodate a solvent-exposed appendage (**Figure 2A**). A model of this overall ternary complex (**Figure 2B**) suggested that a sizeable tether length would be required (8-12 polyethylene glycol units).

[0119] The azide-functionalized cell-binding terminus was synthesized in 3 steps by coupling Cbz-protected lysine and t-butyl protected glutamic acid with triphosgene (See, Kozikowski, et al., J. Med. Chem., 2004, 47, 1729) followed by Cbz deprotection and azide formation (**Scheme 2, Figure 4**). Link, et al., J. Am. Chem. Soc., 2004, 126, 10598. Heterobifunctional PEG **10** was synthesized in a five step process from octaethylene glycol (**Scheme 2, Figure 4**). Natarajan, et al., J. Chem. Comm., 2007, 7, 695. These intermediates were coupled via microwave assisted, copper-catalyzed Huisgen cyloaddition, (Bouillon, et al., J. Org. Chem., 2006, 71,4700) and deprotected using microwave assisted TFA deprotection (**Scheme 3, Figure 4**) afforded PC-ARM (**3**). This specific synthesis may be genericized and applied to produce a large number of compounds according to the present invention simply following the experimental section set forth hereinbelow. Inhibition experiments against a human recombinant PSMA (R&D Research) confirmed indirectly that this long-tethered molecule could bind PSMA with high affinity (Ki = 0.9 ± 0.3 nM).

[0120] In order to confirm the antibody-recruiting capability of our small-molecule, live-cell recruitment assays were performed with PSMA-expressing LNCaP cells and Alexafluor488 conjugated anti-DNP antibodies. In the presence of anti-DNP antibodies, only a small shift was observed, likely due to non-specific binding. However, when chimeric molecule **3** was added, an increase in fluorescence was observed, indicating the formation of the desired ternary complex formation (**figure 5A**). In fact, this increase in fluorescence could be observed at concentrations well into the picomolar concentration range, suggesting exceptional activity. An observed decrease in fluorescence with the addition of either 2-phosphonomethyl pentanedioic acid (Slusher, et al., Nature Medicine, 1999, 5, 1396) or di-DNP lysine confirmed that the recruitment was the result of both the cell-binding and antibody-binding termini. In addition, cells expressing no PSMA showed no significant increase in fluorescence (**figure 5B**).

[0121] Further, the ability of our molecules to induce cell killing was tested. While small-molecule (**3**) induced increases in cell-killing were not seen, or were modest, (<20%) using a complement-dependant cytotoxicity assays in the presence of anti-DNP antibodies, significant increases in cell-death was observed in preliminary antibody-dependant cell-mediated cytotoxicity assay. In the presence of a variety anti-DNP antibodies IgG1 and IgG3 along with 50 nM of **3**, the assay suggests that LNCaP cells were killed by peripheral blood mononuclear cells (PBMCs) approximately 40% more then with the anti-DNP antibodies alone (**figure 6**). Moreover, in the presence of a mixture of Human IgG containing various IgG including anti-DNP antibodies, an increase in

cytotoxicity of 70% was observed Background cytotoxicity of approximately 10% was observed in the absence of PBMCs. These results are consistent with reports of naked monoclonal antibodies to PSMA being capable inducing ADCC but not CDC responses.Deo, et al., international patent publication WO2003/064606. Current work is underway to confirm these results, and better understand the mode of action, such as the specific effector cells that mediate the killing.

Alternative Compounds

[0122] Alternatively, in relying on the above described general approach, molecule (**4**) (Figure 9) may be readily synthesized and used as a synthon for the chemical synthesis of dimeric compounds.

[0123] Compound 4 or similar synthetically manageable molecules that have a propargyl tether that can be used for click chemistry (**Scheme 1a, Figure 9**). See, Sharpless and Manetsch, Expel Opinion on Drug Discovery 2006, 1, 525-538. Treating this molecule to azides **5** and **6** with variously lengthened polyethylene glycol units allows rapid entry into a group of chimeric recruiting molecules of different tether lengths. Having the flexibility to alter the chain length is important to assist in identifying an optimal CBT-ABT distance.

[0124] Efforts toward alkyne **4** have provided us with bromide intermediate **12,** which will generate our target through an Arbuzov reaction with known phosphate **13** (**Scheme 2a**, **Figure 10**). See, Jackson, et al., J. Med. Chem.. 2001, 44, 4170-4175. Sonogashira coupling of **7** and **8** provides the carbon framework for the linker, (Liu and Stahl, J. Am. Chem. Soc.; 2007; 129; 6328-6335) and LAH reducing conditions generates **10** in the appropriate *trans*-substituted orientation (Luo, et al., Chem. Comm. 2007, 2136-2138) and deprotects the acyl group. This newly deprotected phenol is selectively deprotonated over the homoallylic alcohol with potassium carbonate and trapped with propargyl bromide to generate **11.** The remaining alcohol can then be converted to an alkyl bromide through the use of phosphorous tribromide.

[0125] The synthesis of the azide coupling partners is also provided. See Scheme 3, Figure 11. The focus was on azide **15** because bis-DNP lysine attached to polyethylene glycol linkers has demonstrated significant affinity toward anti-DNP antibodies. See, Baird, et al. Biochem. 2003, 42, 12739-12748. This particular azide, which possesses 3 polyethylene glycol units, was synthesized in one-pot from commercially available bis(2,4-dinitrophenyl)-lysine and 11-azido-3,6,9-trioxaundecan-1-amine. This was accomplished through a Schotten-Bauman protocol to provide the desired product in an unoptimized yield of 40%. Demko, et al., J. Org. Chem. 2001, 66, 7945-7950. Scheme 3a, Figure 11. Alternatively, mono DNP azide **16** may be readily prepared through nucleophilic aromatic substitution.

Synthesis of Polyvalent Derivatives

[0126] Polyvalent derivatives can be synthesized in a divergent manner from the previously proposed intermediates. Synthetically complementary bis-alkynyl and tris-azidyl compounds are known, and can be used very effectively in this pursuit. Bis-alkynyl **20** can be converted under click conditions with a longer PEG-derived azido-DNP **19**, to generate the desired bis-di DNP analog **21** (Scheme 4a, Figure 12).

[0127] The tris-azidylated analog can be synthesized in a similar manner from a known triazide **23**. See Scheme 5a, Figure 13. See, Kale, et al., Biorg. Med. Chem. Lett. 2007, 17, 2459-2464. This triazide can undergo click chemistry with protected intermediate 22 to provide trimeric 2-PMPA analog **24**. With these synthetic pieces (synthons) in hand, the final molecule can be put together by standard peptide coupling followed by TFA deprotection. The final compound is presented in Figure 8 (compound **3**).

[0128] The experiments conducted and presented here demonstrate that small-molecule antibody-recruiting molecules which bind selectively to prostate-specific membrane antigen can recruit antibodies to PSMA-expressing cells and induce cell killing. This small-molecule mediated response represents a new treatment for cancer.

[0129] The present invention is further described by way of the presentation of the following examples. While these examples are to be taken as exemplary of the present invention, they are not limiting in any way.

EXAMPLES

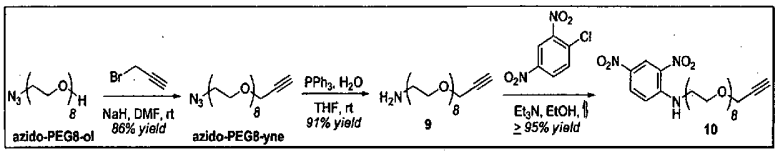
General Information

[0130] Unless otherwise stated, all reactions are carried out in flame-dried glassware under a nitrogen atmosphere. All All reagents were purchased from commercial suppliers and used without further purification except the following: Triethylamine was distilled over calcium hydride; CH_2Cl_2, PhMe, DMF, and THF were purified using a solvent dispensing system; Water was purified using a Milli-Q purification system.

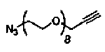
[0131] Infrared (**IR**) spectra bands are characterized as broad (br), strong (s), medium (m) and weak (w). **^{1}H NMR** chemical shifts are reported with the solvent residual peak as the internal standard ($CDCl_3$ δ 7.26 ppm or CD_3OD δ 3.31 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). **^{13}C NMR** chemical shifts are reported in ppm with the solvent as an internal reference ($CDCl_3$ δ 77.2 ppm

Synthesis

[0132]

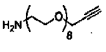


[0133] 1-azido-3,6,9,12,15,18,21,24-octaozaheptacos-26-yne (azido-PEG8-yne): 23-Azido-

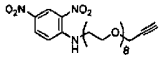


3,6,9,12,15,18,21-heptaozatricosan-1-ol (aziao-PEGB-ol) (1.1g, 3.17 mmol, 1.0 equiv.) was dissolved in N,N'-dimethylformamide (6 mL), and sodium hydride (152 mg, 6.34 mmol, 2.0 equiv.) was added, followed by propargyl bromide (80% in PhMe, 683 µL, 6.34 mmol, 2.0 equiv.). The reaction ran for 4 h at rt, at which time it was found complete by NMR aliquot. The reaction was taken up in CH_2Cl_2 (25 mL) and washed with a saturated aqueous ammonium chloride solution (25 mL). The aqeous solution was back-extracted with dichloromethane (2 x 10 mL), and combined organics were dried over $MgSO_4$ and concentrated to a brown oil. Chromatography (3 cm x 20 cm Silica gel, 3% MeOH/ CH_2Cl_2) yielded **azido-PEG8-yne** (960 mg, 78% yield). **IR (thin film/NaCl)** 2874 (m), 2110 (m), 1160 (s), 1105 (s) cm^{-1}; **^{1}HNMR (400 MHz, $CDCl_3$)** δ 4.20 (d, *J* = 2.4 Hz, 2H), 3.58 (m, 30H), 3.39 (t, *J* = 5.1 Hz, 2H), 2.43 (t, *J* = 2.4 Hz, 1H), 1.82 (s, 1H); **^{13}CNMR (125 MHz, $CDCl_3$)** δ 79.82, 74.72, 70.75, 7022, 68.27, 58.62, 50.84; **HRMS (ES+)** calc'd for **$C_{19}H_{35}N_3O_8$** (M+Na) *m/z* 456.231637. Found 456.23182.

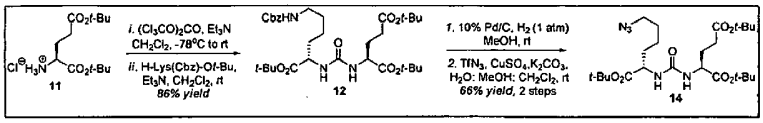
[0134] 3,6,9,12,15,18,21,24-octaozaheptacos-26-yn-1-amine (9): 23-Azido-3,6,9,12,15,18,21-



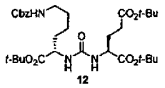
heptaozatricosan-1-ol (azido-PEG8-yne) (960 mg, 2.52 mmol, 1 equiv.), triphenylphosphine (992 mg, 3.78 mmol, 1.5 equiv.), and water (68 µL, 3.78 mmol, 1.5 equiv.) were dissolved in THF (10 mL) and stirred for 12 h. Reaction was concentrated and chromatographed (3 cm x 20 cm Silica, CH_2Cl_2 then ramp to 80:20:1 CH_2Cl_2:MeOH:Et_3N) and concentrated to yield **3,6,9,12,15,18,21,24-octaozaheptacos-26-yn-1-amine (9)** as a clear oil (815 mg, 91% yield). **IR (thin film, NaCl)** 3105 (br), 2914 (m), 1781 (m), 1638 (m), 1169 (s) cm^{-1}. **^{1}H-NMR (500 MHz, $CDCl_3$)** δ 4.17 (d, 2H, *J* = 2.4), 3.66-3.57 (m, 28H), 3.54 (t, 2H, *J* = 5.3 Hz), 2.88 (t, 2H, *J*= 5.0 Hz), 2.41 (t, 1H, *J*= 2.4 Hz), 2.18 (br s, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 79.52, 74.59, 72.54, 70.41, 70.38, 70.38, 70.35, 70.31, 70.20, 70.06, 68.90, 58.20,41.44. **HRMS (ES+)** calc'd for $C_{19}H_{37}NO_8$ (M+H) *m/z* 408.259194. Found 408.25712.



[0135] N-(2,4-dinitrophenyl)-3,6,9,12,15,18,21,24-octaoxaheptacos-26-yn-1-amine (10): 3,6,9,12-tetraoxapentadec-14-yn-1-amine (815 mg, 2.27 mmol, 1 equiv.) was dissolved in EtOH (10 mL), and triethylamine (666 µL, 0.726 mmol, 1.5 equiv.) and 1-chloro-2,4-dinitrobenzene (505 mg, 2.5 mmol, 1.5 equiv.) were added. The reaction flask was fitted with a reflux condenser and the reaction was heated to reflux for 48 h, cooled, and concentrated to a yellow oil. The crude mixture was purified by flash chromatography (3 cm x 20 cm Silica, 3% MeOH:CH_2Cl_2) to yield N-(2,4-dinitrophenyl)-3,6,9,12,15,18,21,24-octaoxaheptacos-26-yn-1-amine **(10)** as a yellow solid (1.15 g, >95% yield). **IR (thin film/NaCl)** 3363 (w), 2871 (s), 1621 (s), 1337 (m), 1103 (s) cm^{-1} ; **^{1}H-NMR (500 MHz, $CDCl_3$)** δ 9.08 (d, 1H, *J* = 2.6 Hz), 8.77 (bs, 1H), 8.21 (dd, 1H, *J* = 2.6, *J*= 9.5 Hz), 6.94 (d, 1H, *J*= 9.5 Hz), 4.16 (6, 2H, *J*= 2.4 Hz), 3.78 (t, 2H, *J*= 5.0 Hz), 3.64 (m, 32H), 3.58 (q, 2H), 2.41 (t, 1H, 2.38 Hz); **^{13}C-NMR (125 MHz, $CDCl_3$)** δ 148.5, 136.1, 130.5, 130.29, 124.3, 114.3, 79.8, 74.6, 70.7, 70.6, 70.5, 69.2, 68.7, 58.5, 43.3; **HRMS (EI)** calc'd for $C_{25}H_{39}N_3O_{12}$ (M^+H) *m/z* 574.260650. Found 574.26106.

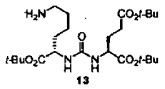


(9S,13S)-tri-tert-butyl 3,11-dioxo-1-phenyl-2-oxa-4,10,12-triazapentadecane-9,13,15-



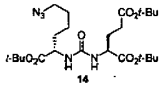
tricarboxylate (12):11(1.0g, 3.38 mmol, 1.0 equiv.) and triethylamine (1.54 mL, 11.09 mmol, 3.28 equiv.) were dissolved in dichloromethane (30 mL) and cooled to -78°C. Triphosgene (341 mg, 1.15 mmol, 0.34 equiv.) in dichloromethane (10 mL) was added dropwise to the reaction mixture. Upon complete addition, the reaction was allowed to warm to room temperature and stirred for 30 minutes. **12** (757 mg, 2.03 mmol, 0.6 equiv) was added, followed by the addition of triethylamine (283 µL, 2.03 mmol, 0.6 equiv.). The reaction was allowed to stir at room temperature overnight for 16 hours. The reaction was then diluted with dichloromethane (50 mL), and washed with water (100 mL x 2). The crude mixture was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography (Silica 1.5:1 hexane: ethyl acetate) yielded **4** (1.09g, 86%) as a colorless oil with the following spectral characteristics: IR (thin film/KBr) 3342 , 2976 , 1731 , 1650 , 1552 , 1454 , 1368 , 1255 , and 1153 cm^{-1} ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J*= 3.75 Hz, 4H), 7.33-7.30 (m, 1H), 5.10 (d, *J*=4.55 Hz, 2H), 5.06-5.01 (m, 2H), 4.99 (s, 1H), 4.34-4.31 (m, 2H), 3.20-3.18 (m, 2H), 2.36-2.23 (m, 2H), 2.10-2.03 (m, 1H), 1.88-1.75 (m, 2H), 1.65-1.57 (m, 1H), 1.57-1.45 (m, 2H), 1.453 (s, 9H), 1.446 (s, 9H), 1.43 (s, 9H), 1.40-1.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ□172.6, 172.5, 172.2, 136.8, 128.6, 128.5, 128.2, 82.2, 82.0, 80.7, 66.7, 53.4, 53.2, 40.7, 32.8, 31.7, 29.4, 28.5, 28.2, 28.1, 22.3; HRMS (EI+) *m/z* 622.3695 [calc'd for $C_{32}H_{51}N_3O_9$ (M+H)+ 622.3698].

[0136] (S)-di-tert-butyl 2-(3-((S)-6-amino-1-tert-butoxy-1-ozohexan-2-



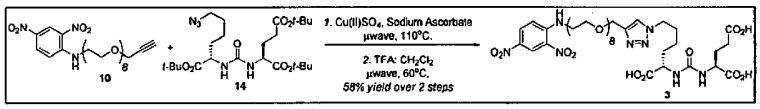
yl)ureido)pentanedioate (12): X (2.35 g, 3.78 mmol, 1.0 equiv.) was dissolved in methanol (37.8 ml) and was added dropwise to a vigorously stirred reaction flask containing dry 10% Pd/C (475 mg). H_2 was bubbled through the solution for 1-2 m, and then ran for 13 h under a balloon of H_2. The reaction was deemed complete by TLC (Rf = 0.48 in 10% MeOH/CH_2Cl_2), plugged through celite, and concentrated to give a viscous oil, which was carried on without further purification.

[0137] (S)-di-tert-butyl 2-(3-((S)-6-azido-1-tert-butogy-1-ogohegan-2-yl)ureido)pentanedioate

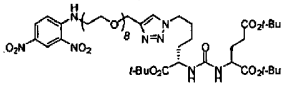


(14): Sodium azide (2.629 g, 40.75 mmol, 10.0 equiv.) was dissolved in water (7.63 mL), and dichloromethane (12.91 mL) was added. The reaction mixture was cooled to 0°C and triflic anhydride (1.36 mL, 8.09 mmol, 2.0 equiv.) was added. The solution was stirred for 3 h at rt, and the organic layer was separated from the aqueous layer. The aqueous layer was extracted with dichloromethane (3 x 4 mL). The organic layers were combined and washed with aqueous $Na_2CO_{3(aq)}$ to give 25 ml of 0.391 M TfN_3. Amine **13** (1.97 g, 4.04 mmol, 1.0 equiv.) was dissolved in water (14.37 mL) and methanol (28.74). To this solution were added $CuSO_4$-$5H_2O$ (10.1 mg, 0.04 mmol, 0.01 equiv.) and K_2CO_3 (837.5 mg, 6.06 mmol, 1.5 equiv.). The TfN_3 solution (25 ml, 8.09 mmol, 2 equiv.) was added rapidly to the stirring solution of **13**, and the reaction stirred for 19 h at rt. The organic layer was seperated from the aqueous layer, and the water / methanol layer was extracted once with dichloromethane. The combined organic layers were dried over MgSO4, concentrated under reduced pressure, and purified by column chromatography to yield **14** as a white solid (1.440 g, 71%). R_f=0.68 in 10% MeOH:CH_2Cl_2. **IR (Thin film / NaCl)** 3335, 2980, 2933 , 2868 , 2097 , 1733 ,

1635 , 1560 , 1368 , 1257 , and 1155 cm^{-1}; **^{1}HNMR (500 MHz, $CDCl_3$)** δ 5.01 (d, *J*= 8.25 Hz, 2H), 4.34 (m, 2H), 3.26 (t, *J*= 7.4 Hz, 2H), 2.35-2.25 (m, 2H), 2.09-2.05 (m, 1H), 1.87-1.76 (m, 2H), 1.66-1.55 (m, 3H), 1.46 (s, 18H), 1.43 (s, 9H), 1.45-1.35 (m, 2H) ppm; **^{13}CNMR (125 MHz, $CDCl_3$)** δ 172.6, 172.4, 172.2, 156.8, 82.3, 82.1, 80.7, 53.4, 53.2, 51.3, 33.0, 31.7, 28.6, 28.5, 28.2, 28.1, 22.4 ppm; HRMS (EI+) *m/z* 514.3225 [calc'd for $C_{24}H_{43}N_5O_7$ (M+H)+ 514.3235].



[0138] (S)-di-tert-butyl 2-(3-((S)-1-tert-butoxy-6-(4-(13-(2,4-dinitrophenylamino)-2,5,8,11-



tetraoxatridecyl)-1H-1,2,3-triazol-1-yl)-1-oxohexan-2-yl)ureido)pentanedioate (3): To a mixture of **10** (76 mg, 0.145 mmol, 1.0 equiv) and **14** (74.4 mg, 0.145 mmol, 1.0 equiv.) in water (1 mL) and *tert*-butanol (1 mL) in a 5 ml µwave reaction tube was added sodium ascorbate (7 mg, 0.036 mmol, 0.25 equiv.) and and aqueous solution of 0.1 M copper (II) sulfate (0.0725 ml, 0.00725 mmol, 0.05 equiv.). The tube was capped, and subjected to microwave radiation for 10 minutes at 110°C. The reaction was then concentrated and redissolved in trifluoroacetic acid (2 mL) and dichloromethane (1 mL) in a 5 ml microwave reaction tube. The tube was capped and subjected to microwave radiation for 2 m at 70°C. The resulting reaction mixture was concentrated under reduced pressure, chromatographed using HPLC, and concentrated to yield **3** (87 mg, 58% yield) as a yellow oil. **IR (thin film/NaCl)** 3359 (w), 2925 (s), 1737 (s), 1622 (m), 1170 (s) cm^{-1}; **^{1}HNMR (100 MHz, MeOD)** δ 9.07 (d, J = 2.7 Hz, 1H), 8.33 (dd, J = 2.7, 9.6 Hz, 1 H), 8.03 (s, 1H), 7.27 (d, J = 9.6 Hz, 1H), 4.66 (s, 2H), 4.45 (t, *J* = 7 Hz, 2H), 4.35-4.28 (m, 2H), 3.83 (t, J = 7 Hz, 2H), 3.73-3.61 (m, 32H), 2.44-2.36 (m, 2H), 2.17-2.08 (m, 1H), 1.99-1.82 (m, 4H), 1.71-1.64 (m, 1H), 1.46-1.38 (m, 2H); **^{13}CNMR (125 MHz, MeOD)** δ 176.4, 176.1, 175.7, 160.0, 149.9, 145.9, 137.0, 131.5, 131.0, 125.2, 124.7, 116.1, 71.6, 71.6, 71.5, 71.5, 70.9, 69.9, 64.8, 53.7, 53.5, 51.2, 44.1, 32.8, 31.1, 30.6, 28.8, 23.4 ppm; **HRMS (ES+)** calc'd for $C_{37}H_{58}N_8O_{19}$ (M+H) *m/z* 919.389098. Found 919.38801.

NAALADase Inhibition Experiments

[0139] A 10 mM stock solution of N-acetyl-aspartyl-glutamate (NAAG) in 40 mM NaOH was diluted to 40 µM in Tris buffer (0.1M Tris-HCl, pH=7.5), and was added to 384 well plate (25 µl per well). For Km measurements and controls, 2x dilution (40 µM - 312 nM) series of NAAG were made and added to separate wells. For IC_{50} measurements, solutions of recruiting molecule **3** in water (2 µL per well, dilution series) were added to wells. For all other wells, 2 µL of water was added. To initiate reactions, rhPSMA (R&D research) diluted in Tris buffer (20 pg/ mL), was added to each well (25 µl per well). For negative controls, Tris buffer was added (25 µl per well). The plate was covered and incubated for 15 minutes, at which time the protein was deactivated by heating the plate to 95°C for 3 minutes. After plate was allowed to cool, glutamic acid release was visualized using an Amplex®-Red glutamic acid/glutamate oxidase assay kit (Invitrogen). Km and IC_{50} values were calculated using graphpad prism software, and Ki was calculated from these values using the Cheng-Prusoff Equation. This process was run in triplicate, and is reported in the manuscript as the average of three runs ± standard deviation.

Flow Cytometry Recruiting Experiments

[0140] Antibody Recruitment Flow Cytometry: LNCaP and DU145 cells were detached, counted, washed, and resuspended with flow cytometry buffer (25 mM Tris-HCl, 150 mM NaCl, 1.5% BSA, 5 mM Glucose, 1.5 mM $MgCl_2$, pH 7.2) to a density of 2 x 10^5 cells mL^{-1} of buffer, and 1 mL was added to each epindorf tube per experiment. Solutions of **3** in water (2 µL, variable concentration per experiment) in flow cytometry buffer were added to the cells, and the cells were incubated at 4°C for 60 minutes. *For cell-binding termini competition experiments, solutions of PMPA in water (2 µL, variable concentrations) were added prior to incubation.* Following incubation, the cells were washed three times with flow cytometry buffer. 20 µL of 1 mg ml^{-1} human IgG in mouse serum were added to each tube and the tubes were incubated for 5 minutes at room temperature to allow blocking of Fc receptors. 200 µL of flow cytometry buffer were added, and to that was added 2 µL of 2 mg ml^{-1} AlexaFluor488 conjugated rabbit anti-dinitrophenyl IgG - fraction KLH. *For antibody-binding terminus competition experiments, a solution of di-DNP Lysine (2 µL of 5mM solution in water) was added prior to incubation.* The tubes were incubated at 4°C for 60 minutes and taken up with

850 µL of flow cytometry buffer. The cells were spun down and washed with flow cytometry buffer (2 x 1 mL). The cells were taken up with 1 mL of Tris buffered saline (25 mM TrisHCl, 150 mM NaCl, pH 7.2) and 2 µL of 500 µg mL^{-1} of propidium iodide was added, and samples were analyzed immediately on FACSCalibur instrument (Becton Dickinson). The data was analyzed using FlowJo (Tree Star Inc.), gating for live cells on FL-3. An experiment omitting **3** was done as a control. The experiment was repeated in triplicate to ensure reproducibility.

[0141] Reference is made to the complete disclosure of all patents, patent applications, and publications, and electronically available material (including, for instance, nucleotide sequence submissions in, e.g., GenBank and RefSeq, and amino acid sequence submissions in, e.g., SwissProt, PIR, PRF, PDB, and translations from annotated coding regions in GenBank and RefSeq) cited. Any inconsistency between the material cited and the material set for in the specification as originally filed shall be resolved in favor of the specification as originally filed. The foregoing detailed description and examples have been given for clarity of understanding only. No unnecessary limitations are to be understood therefrom. The invention is not limited to the exact details shown and described, for variations obvious to one skilled in the art will be included within the invention defined by the following claims.

[0142] All headings are for the convenience of the reader and should not be used to limit the meaning of the text that follows the heading, unless so specified.

REFERENCES CITED IN THE DESCRIPTION

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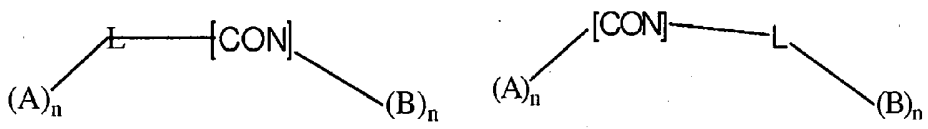
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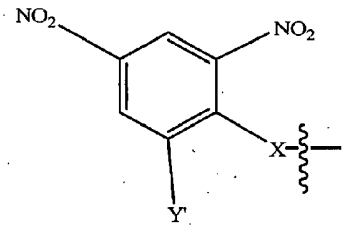
Patentkrav

1. Forbindelse med den kemiske struktur:



hvert n i et molekyle er et heltal fra 1 til 15

Hvor A er en antistofbindingsdel (ABT) med den kemiske struktur:



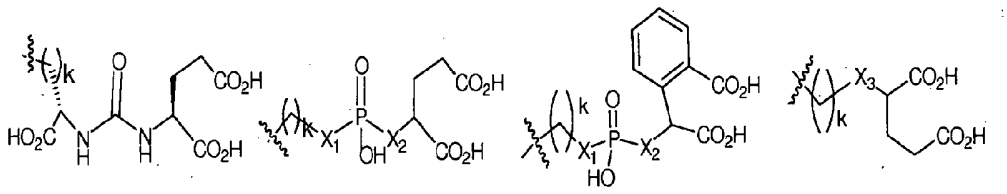
Hvor Y' er H eller NO_2;

X er O, CH_2, NR^1, S(O), $S(O)_2$, $-S(O)_2O$, $-OS(O)_2$, eller $OS(O)_2O$; og

R^1 er H, en C_1-C_3 alkylgruppe, eller en $-C(O)(C_1$-$C_3)$ gruppe;

hvor forbindelsen er **kendetegnet ved at**:

B er en cellebindingsdel (CBT) i stand til at binde til prostataspecifikt membranantigen på celleoverfladen af celler i en patient med den kemiske struktur:;



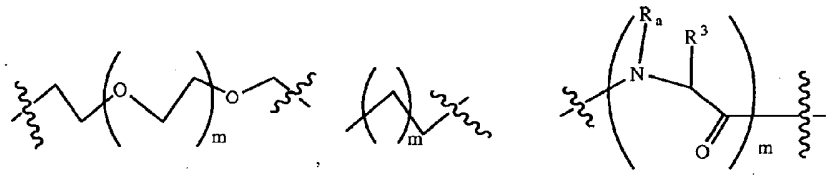
hvor X_1 og X_2 er hver uafhængigt CH_2, O, NH eller S;

X_3 er O, CH_2, NR^1, S(O), $S(O)_2$, $-S(O)_2O$, $-OS(O)_2$, eller $OS(O)_2O$;

R^1 er en C_1-C_3 alkylgruppe, eller en $-C(O)(C_1$-C_3 alkyl) gruppe; og

k er et heltal fra 0 til 20;

L er en linker som linker [CON] med A eller B i et molekyle med den kemiske formel:

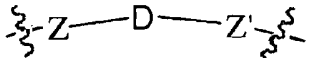


Eller en polypropylenglykol eller polypropylen-co-polyethylenglykollinker med mellem 1 og 100 glykolenheder;

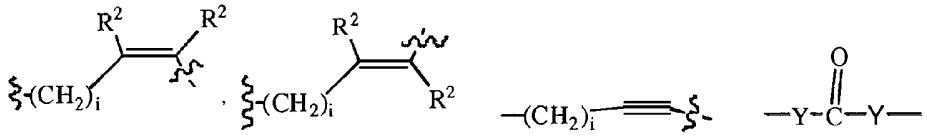
Hvor R_a er H, C_1-C_3 alkyl eller alkanol eller danner en cyklisk ring med R^3 (prolin) og R^3 er en sidekæde afledt fra en aminosyre; og

m er et heltal fra 1 til 45; eller

L er en linker med den kemiske formel:



Hvor Z og Z' er hver uafhængigt en binding, -$(CH_2)_i$-O, -$(CH_2)_i$-S, -$(CH_2)_i$-N-R ,



hvor -$(CH_2)_i$ gruppen, hvis til stede i Z eller Z', er bundet til [CON] ABT eller CBT;

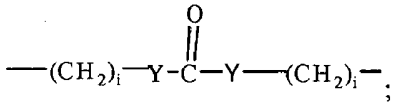
Hvert R er uafhængigt H, eller en C_1-C_3 alkyl- eller alkanolgruppe;

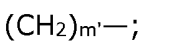
Hvert R^2 er uafhængigt H eller en C_1-C_3 alkylgruppe;

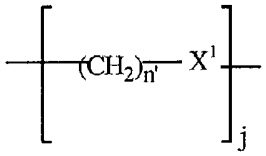
Hvert Y er uafhængigt en binding, O, S eller N-R;

Hvert i er uafhængigt 0 til 100;

D er







eller en binding,

med det forbehold at Z, Z' og D ikke er hver simultane bindinger;

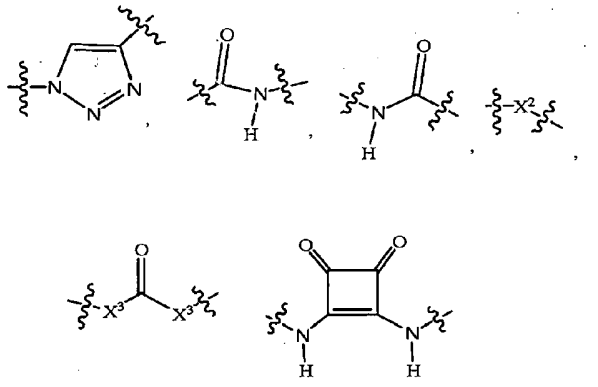
j er 1 til 100;

m' er 1 til 100;

n' er 1 til 100; og

X^1 er O, S eller N-R,

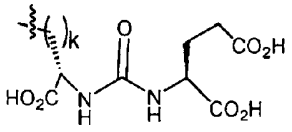
Hvert R er uafhængigt H, eller en C_1-C_3 alkyl- eller alkanolgruppe [CON] er en del med den kemiske struktur:



Hvor X^2 er O, S, NR^4, S(O), $S(O)_2$, $-S(O)_2O$, $-OS(O)_2$, eller $OS(O)_2O$; X^3 er NR^4, O eller S; og

R^4 er H, en C_1-C_3 alkyl- eller alkanolgruppe, eller en $-C(O)(C_1$-$C_3)$ gruppe; eller et farmaceutisk acceptabelt salt, solvat eller polymorf deraf.

2. Forbindelsen ifølge krav 1, hvor cellebindingsdelen (CBT) der er i stand til at binde til prostataspecifikt membranantigen på celleoverfladen af celler i patienten har den kemiske formel:



hvor k er et heltal fra 0 til 20.

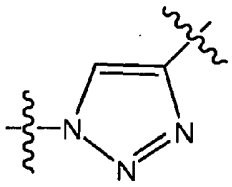
3. Forbindelsen ifølge krav 2, hvor k er fra 1 til 8.

4. Forbindelsen ifølge et hvilket som helst af kravene 1-3, hvor linkeren er gruppe med den kemiske formel:



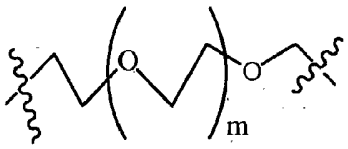
Hvor R_a er H eller danner en cyklisk ring med R^3 og R^3 er en sidekæde afledt fra en aminosyre; og
m er et heltal fra 1 til 15; og
n er 1.

5. Forbindelsen ifølge et hvilket som helst af kravene 1-4, hvor [CON] er en



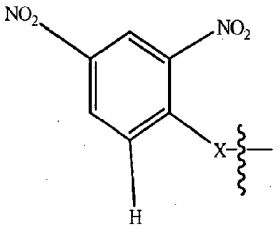
gruppe.

6. Forbindelsen ifølge et hvilket som helst af kravene 1-5, hvor linkeren er en gruppe med formlen:



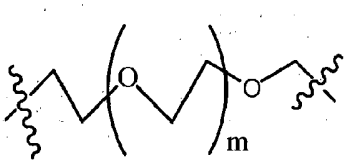
Hvor m er et heltal fra 1 til 10.

7. Forbindelse ifølge et hvilket som helst af kravene 1-5, hvor A er



X er O eller NH;

L er en

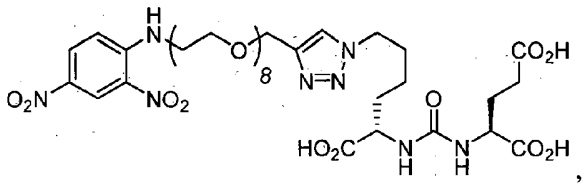


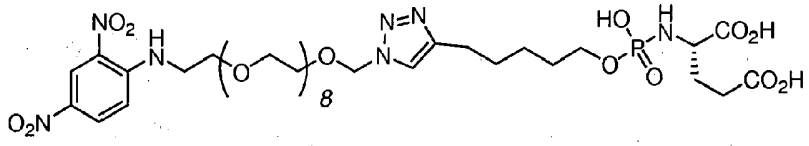
gruppe;

hvor m er et heltal fra 5 til 15; og

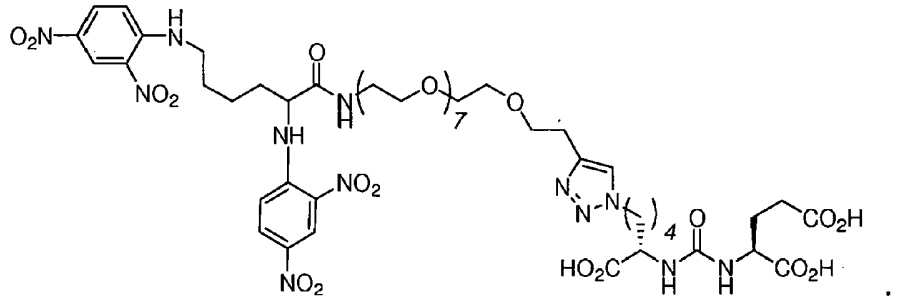
[CON] er bundet til A eller B med linker L.

8. Forbindelse ifølge krav 1 med den kemiske formel:





eller



9. Farmaceutisk sammensætning omfattende en effektiv mængde af en kimerisk forbindelse ifølge et hvilket som helst af kravene 1-8 i kombination med en farmaceutisk acceptabel bærer, additiv eller excipiens.

10. Sammensætningen ifølge krav 9, hvor sammensætningen yderligere omfatter en effektiv mængde af et yderligere anticancermiddel.

11. Sammensætningen ifølge krav 10, hvor det yderligere anticancermiddel er en antimetabolit, en inhibitor af topoisomerase I og II, et alkylerende middel, en mikrotubule inhibitor eller blandinger deraf.

12. Sammensætningen ifølge krav 10, hvor midlet er aldesleukin; aemtuzumab; alitretinoin; allopurinol; altretamin; amifostin; anastrozol; arsenik tlioxid; aparaginase; BCG Live; bexaroten-kapsler; bexaroten-gel; bleomycin; busulfan intravenøs; busulfan oral; calusteron; capecitabin; carboplatin; carmustin; carmustin med poifeprosan 20 iplant; celecoxib; chlorambucil; cisplatin; cladribin; cyclophosphamid; cytarabin; cytarabin liposomal; dacarbazin; dactinomycin; actinomycin D; dabepoetin alfa; daunorubicin liposomal; daunorubicin, daunomycin; dnileukin diftitox, dexrazoxan; docetaxel; doxorubicin; doxorubicin liposomal; domostanolon propionat; Eliotts B opløsning; epirubicin; eoetin alfa estramustin; etoposid phosphat; etoposid (VP-16); exemestan; flgrastim; floxuridin (intraarterial); fludarabin; fluorouracil (5-FU); fulvestrant; gemtuzumab ozogamicin; goserelin acetat; hydroxyurea; Ibritumomab Tiuxetan; idarubicin; ifosfamid; imatinib mesylat; Interferon alfa-2a; Interferon alfa-2b; irinotecan; letrozol; leucovorin; levamisol; lomustin (CCNU); meclorethamin (nitrogensennep); megestrol acetat; melphalan (L-PAM); mercaptopurin (6-MP); mesna; methotrexat; methoxsalen; mitomycin C; mitotan; mitoxantron; nandrolon phenpropionat; nfetumomab; LOddC; orelvekin; oxaliplatin; paclitaxel; pamidronat; pegademas; Pegaspargas; Pegfilgrastim; pentostatin; pipobroman; plicamycin; mithramycin; porfimernatrium; procarbazin; quinacrin; Rasburicase; Rituximab; Sargramostim; streptozocin; talbuvidin (LDT); talkum; tamoxifen; temozolomid; teniposid (VM-26); testolacton; thioguanin (6-TG); thiotepa; topotecan; toremifen; Tositumomab; Trastuzumab; tretinoin (ATRA); Uracil sennep; valrubicin; valtorcitabin (monoval LDC); vinblastin; vinorelbin; zoledronat; og blandinger deraf.

13. Sammensætningen ifølge et hvilket som helst af kravene 9-12 yderligere omfattende mindst en antiandrogen-forbindelse.

14. Sammensætningen ifølge et hvilket som helst af kravene 9-13 yderligere omfattende mindst en GNRh-modulator.

15. Sammensætningen ifølge et hvilket som helst af kravene 9-14 yderligere omfattende mindst et middel valgt fra gruppen bestående af flutamid, bicalutamid, nilutamid, cyproteronacetat, ketoconazol, aminoglutethimid, abarelix, leuprolid, goserelin, triptorelin, buserelin, abirateronacetat, sorafenib og blandinger deraf.

16. Sammensætningen ifølge et hvilket som helst af kravene 9-14 yderligere omfattende mindst et middel valgt fra gruppen bestående af middel mod forstørret prostata, eulexin, flutamid, goserelin, leuprolid, lupron, nilandron, nilutamid, zoladex og blandinger deraf.

17. Sammensætningen ifølge et hvilket som helst af kravene 9-16 i oral eller parenteral doseringsform.

18. Forbindelsen ifølge et hvilket som helst af kravene 1-8 til anvendelse som et medikament.

19. Sammensætningen ifølge et hvilket som helst af kravene 9-12 til anvendelse som et medikament til behandlingen af cancer i en patient.

20. Sammensætningen ifølge et hvilket som helst af kravene 9-16 til anvendelse som et medikament til behandlingen af prostatakræft i en patient med behov derfor.

21. Sammensætningen ifølge krav 20 hvor prostatakræften er metastatisk prostatakræft.

DRAWINGS

FIGURE 1

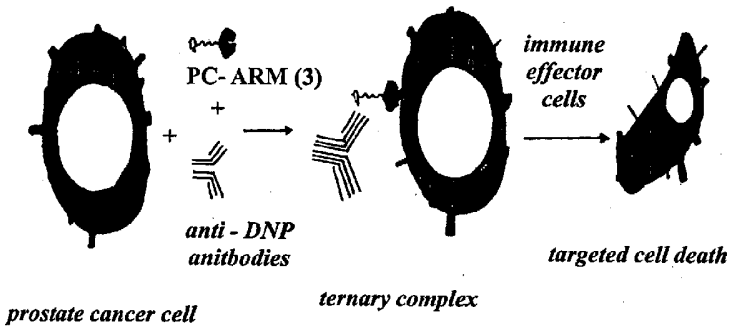


FIGURE 2

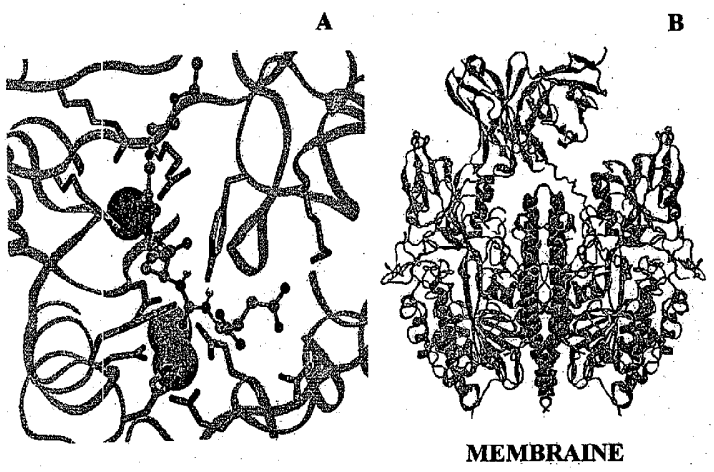


FIGURE 3

PSMA-binding small molecule

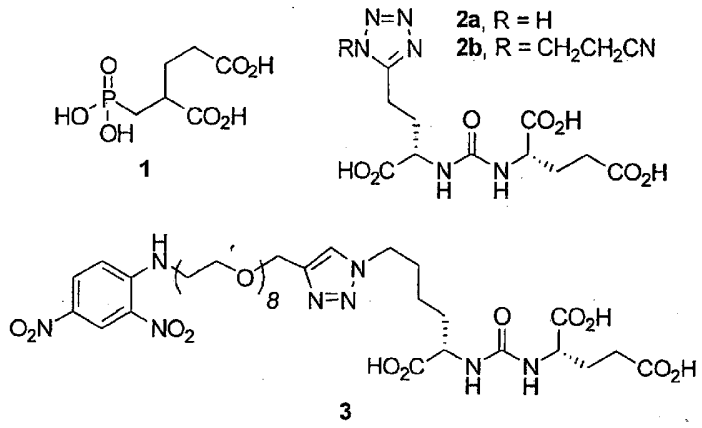
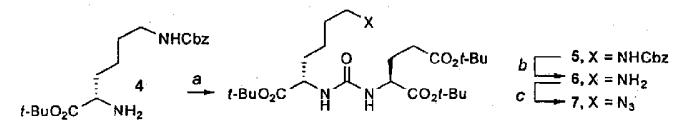
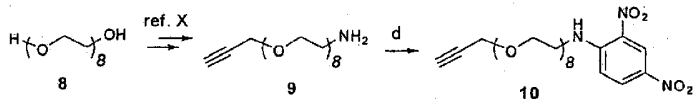


FIGURE 4

Scheme 2

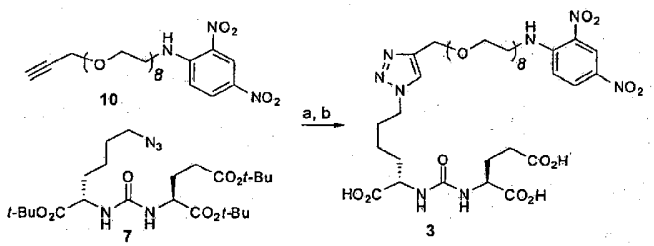


(a) *i*. $(Cl_3CO)_2CO$, Et_3N, CH_2Cl_2, -78°C to rt; H-Lys(Cbz)-O*t*-Bu, Et_3N, CH_2Cl_2, rt, *(86%)*; (b) 10% Pd/C, H_2 (1 atm), MeOH, rt; (c) TfN_3, $CuSO_4$.K_2CO_3, H_2O: MeOH: CH_2Cl_2, rt, *(66%* , 2 steps)



(d)1 chloro 2,4 dinitrobenzene, Et_3N, EtOH, reflux (>98%).

Scheme 3



(a) $Cu(II)SO_3$, Sodium Ascorbate, *t*-BuOH: H_2O (1:1), μwave, 110°C, ;
(b) TFA: CH_2Cl_2 (2:1), μwave, 60°C (*58%* yield following HPLC purification).

FIGURE 5

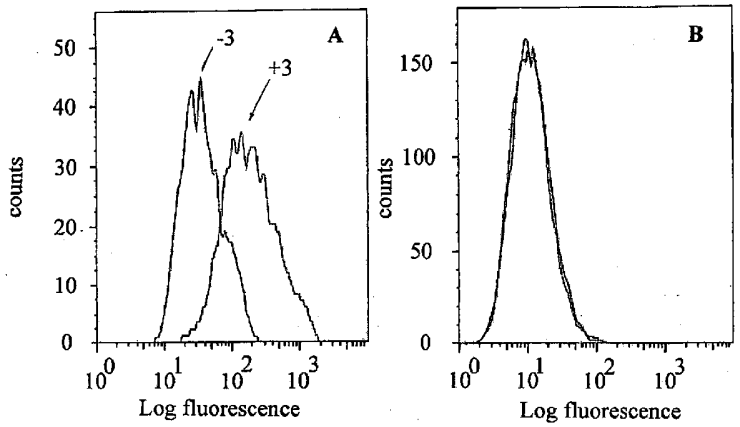

A
-3
+3
counts
50
40
30
20
10
0
10^0 10^1 10^2 10^3
Log fluorescence
B
counts
150
100
50
0
10^0 10^1 10^2 10^3
Log fluorescence

FIGURE 6

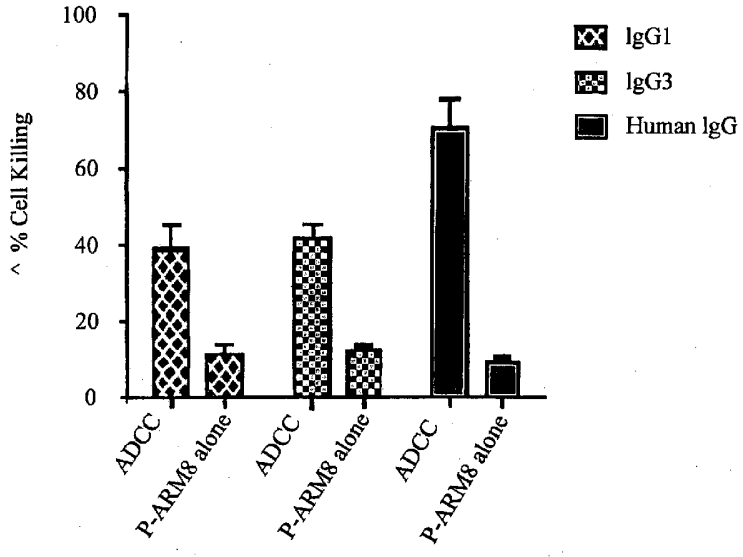

100
80
60
40
20
0
^ % Cell Killing
ADCC
P-ARM8 alone
ADCC
P-ARM8 alone
ADCC
P-ARM8 alone
IgG1
IgG3
Human IgG

FIGURE 7
Exemplary Compounds According to the Invention

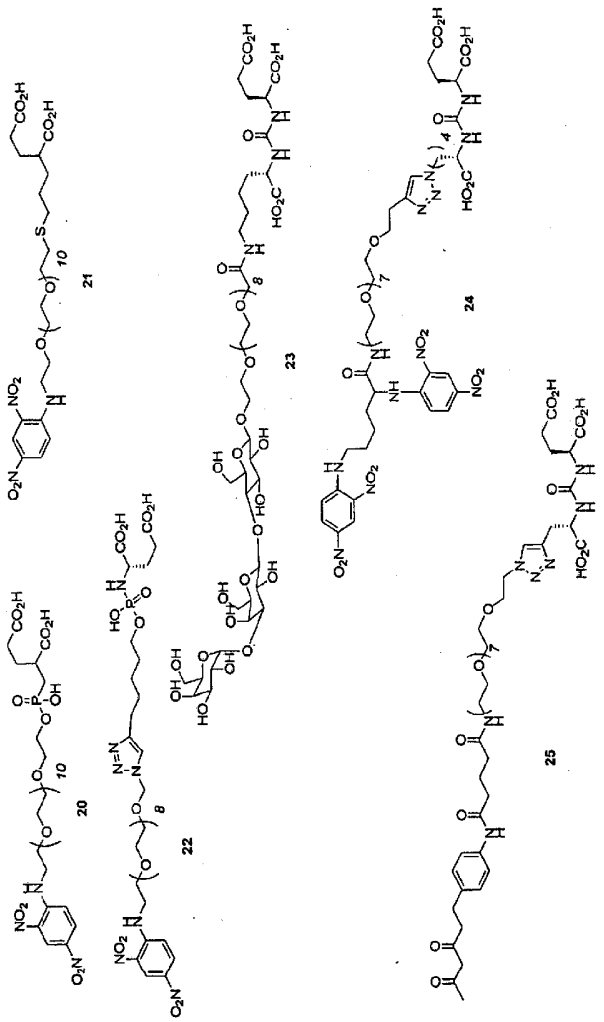


FIGURE 8

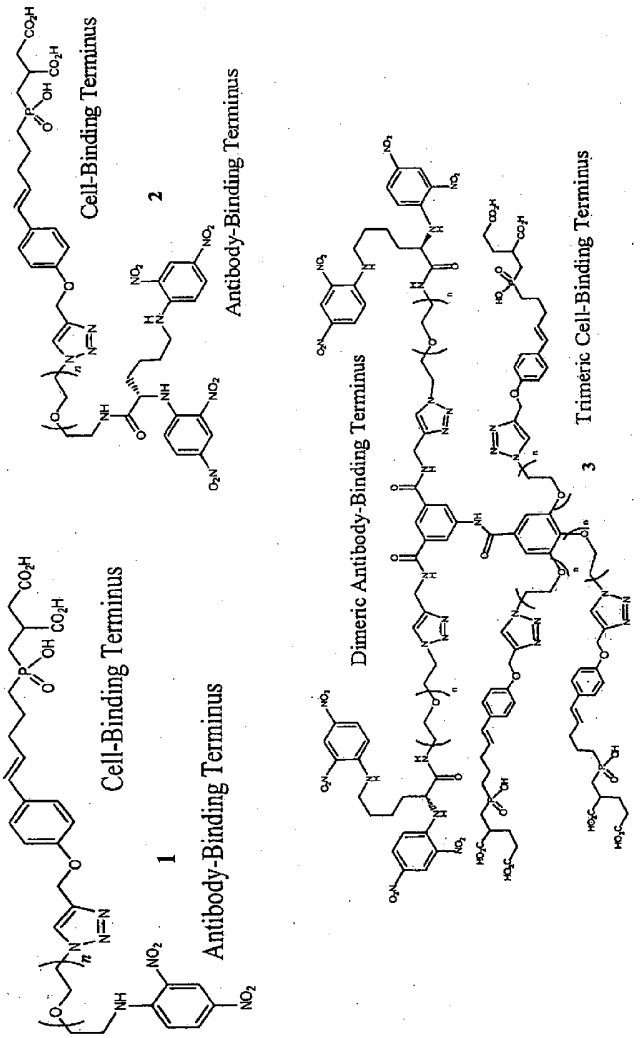

Cell-Binding Terminus
1
Antibody-Binding Terminus
Cell-Binding Terminus
2
Antibody-Binding Terminus
Dimeric Antibody-Binding Terminus
Trimeric Cell-Binding Terminus
3

FIGURE 9
Scheme 1a

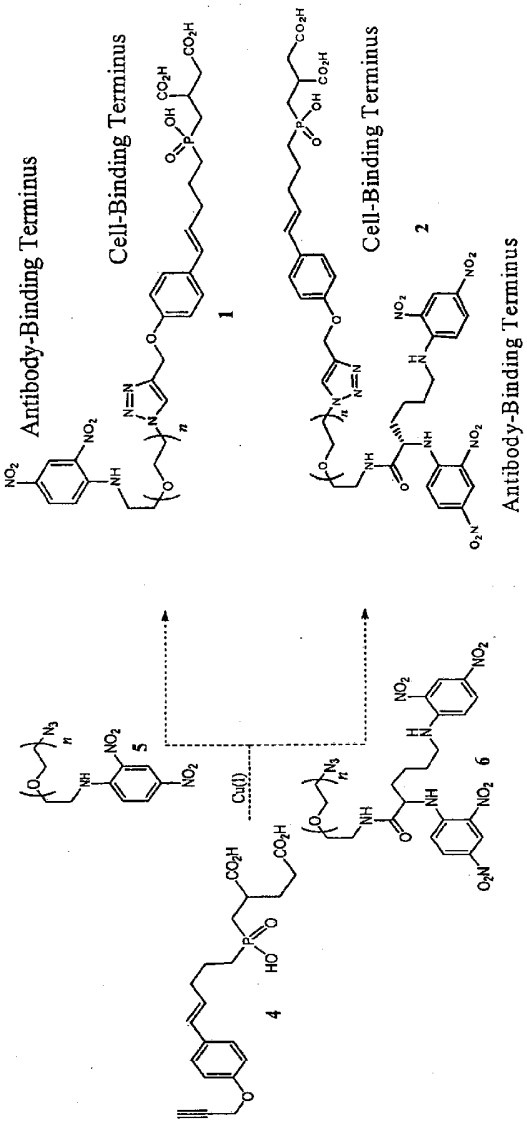


FIGURE 10
Scheme 2a

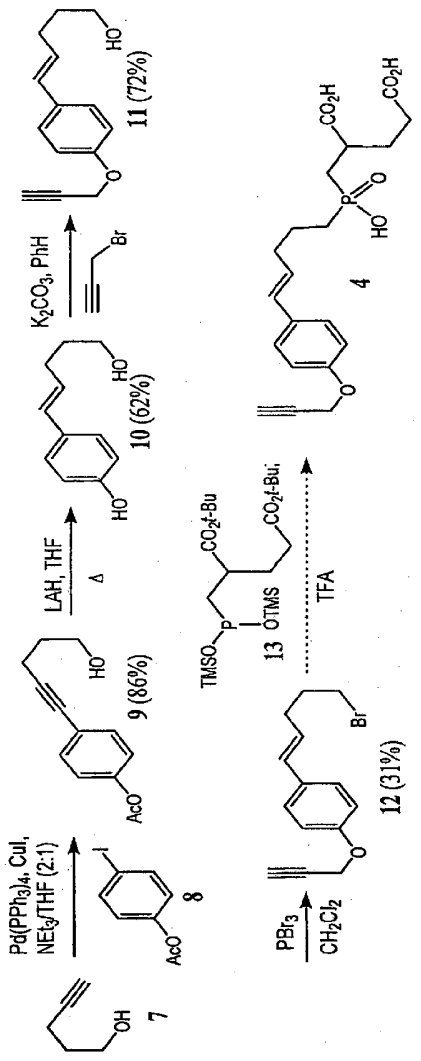


FIGURE 11
Scheme 3a

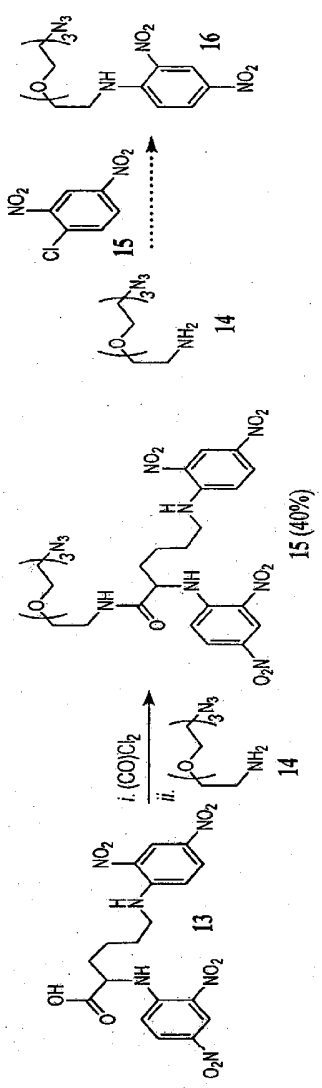


FIGURE 12
Scheme 4a

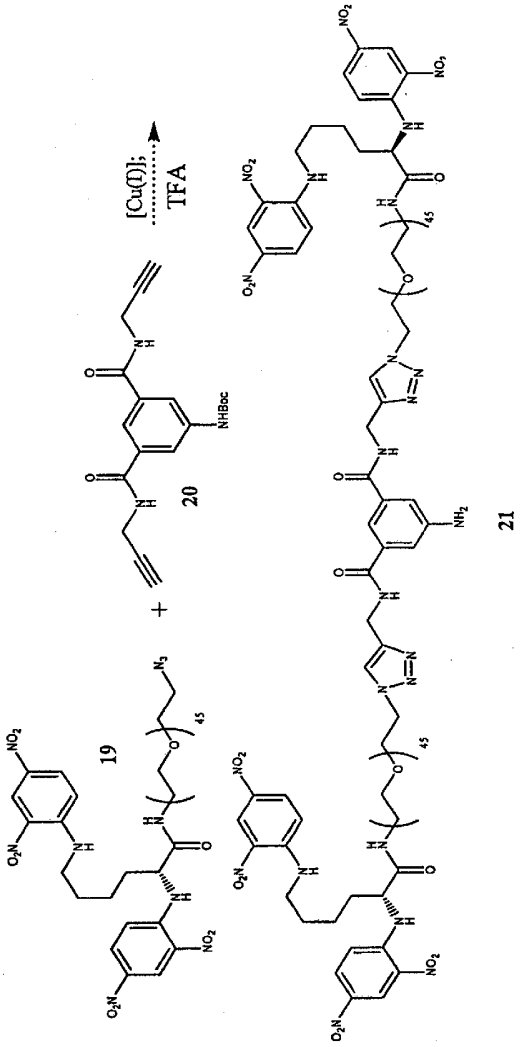


FIGURE 13
Scheme 5a

