(12) STANDARD PATENT (11) Application No. **AU 2017318087 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Amino mercaptan compound and preparation method therefor and use thereof in protection against radiation

(51) International Patent Classification(s)
C07C 319/06 (2006.01) ***C07C 319/12*** (2006.01)
A61K 31/16 (2006.01) ***C07C 321/04*** (2006.01)
A61P 35/00 (2006.01)

(21) Application No: **2017318087** (22) Date of Filing: **2017.09.01**

(87) WIPO No: **WO18/041245**

(30) Priority Data

(31) Number	(32) Date	(33) Country
201610802313.8	**2016.09.05**	**CN**

(43) Publication Date: **2018.03.08**
(44) Accepted Journal Date: **2020.12.10**

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(56) Related Art
CAS RN 1779600-46-2, STN Entry Date 14 June 2015
JP H04321674 A
CN 1679488 A
ATKINSON, et al: Journal of Medicinal Chemistry, Potential Antiradiation Drugs. I. Amide, Hydroxamic Acid, and Hydrazine Derivatives of Mercapto Acids. Amino Thioacids, 1965, pp. 29-32.

(12) 按照专利合作条约所公布的国际申请

(19) 世界知识产权组织
国 际 局

(43) 国际公布日
2018 年 3 月 8 日 (08.03.2018)

WIPO | PCT

(10) 国际公布号
WO 2018/041245 A1

(51) 国际专利分类号:
C07C 319/06 (2006.01) *A61K 31/16* (2006.01)
C07C 321/04 (2006.01) *A61P 35/00* (2006.01)
C07C 319/12 (2006.01)

(21) 国际申请号: PCT/CN2017/100158

(22) 国际申请日: 2017 年 9 月 1 日 (01.09.2017)

(25) 申请语言: 中文

(26) 公布语言: 中文

(30) 优先权:
201610802313.8 2016年9月5日 (05.09.2016) CN

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(81) 指定国 (除另有指明, 要求每一种可提供的国家保护): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW。

WO 2018/041245 A1

(54) **Title:** AMINO MERCAPTAN COMPOUND AND PREPARATION METHOD THEREFOR AND USE THEREOF IN PROTECTION AGAINST RADIATION

(54) 发明名称: 胺基硫醇类化合物及其制备方法和其在辐射防护中的应用

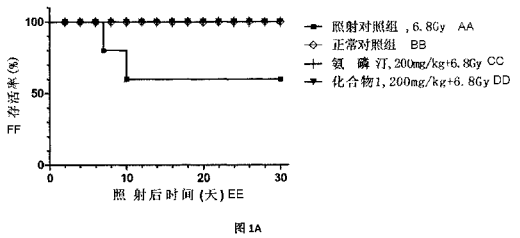


图 1A

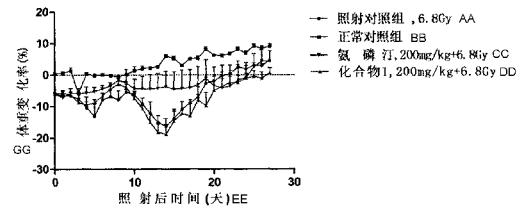
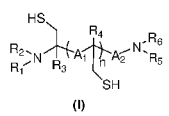


图 1B



(I)

AA RADIATION GROUP, 6.8 GY
BB NORMAL CONTROL GROUP
CC AMIFOSTINE, 200 MG/KG + 6.8 GY
DD COMPOUND 1, 200 MG/KG + 6.8 GY
EE TIME AFTER RADIATION (DAY)
FF SURVIVAL RATE (%)
GG BODY WEIGHT CHANGE RATE (%)

(57) **Abstract:** Disclosed are an amino mercaptan compound and a preparation method therefor and the use thereof in protection against radiation. The compound has the structure of formula I, wherein A_1 is selected from $-C(O)NR^8-$, $-S(O)_2-NR^8-$, $-S(O)NR^8-$ and $-R^7-NR^8-$; A_2 is selected from carbonyl, sulfonyl, sulfinyl, substituted or unsubstituted C_{1-6}alkyl; R^1, R^2, R^5 and R^6 can be the same or different, and are selected from hydrogen, substituted or unsubstituted C_1-C_5alkyl or heteroalkyl; n is an integer from 0 to 20,000; R^3 and R^4 are independently selected from hydrogen, X, substituted or unsubstituted C_{1-6}alkyl; X is selected from F, Cl, Br and I; R^7 is selected from substituted or unsubstituted C_1-C_6alkyl; and R^8 is selected from hydrogen, substituted or unsubstituted C_1-C_6alkyl. The compound has the effect of decreasing the biological damage induced by ionizing radiation, and at the same time also has the effect of prolonging the lifetime and survival rate of an animal exposed to radiation, and has significant alleviating effects on the side effects of radiotherapy. In addition, the compound has a comparatively low toxicity. The present invention opens up a new approach for preventing, treating and curing ionizing radiation damage.

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(84) 指定国(除另有指明，要求每一种可提供的地区保护)：ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), 欧亚 (AM, AZ, BY, KG, KZ, RU, TJ, TM), 欧洲 (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG)。

本国际公布:

— 包括国际检索报告(条约第21条(3))。

(57) 摘要：本发明公开了胺基硫醇类化合物及其制备方法和其在辐射防护中的应用，所述的化合物具有式I的结构，其中，A_1选自：-C(O)NR^8-、-$S(O)_2$-NR^8-、-S(O)NR^8-和-R^7-NR^8-；A_2选自：羰基、磺酰基、亚硫酰基、取代或未取代的C_{1-6}烷基；R^1、R^2、R^5、R^6可相同或不同，选自：氢、取代或未取代的C_1-C_5烷基或杂烷基；n为0-20000的整数，R^3、R^4独立地选自：氢、X、取代或未取代的C_{1-6}烷基；X选自：F、Cl、Br和I；R^7选自：取代或未取代的C_1-C_6烷基，R^8选自：氢、取代或未取代的C_1-C_6烷基。所述化合物具有降低电离辐射引起的生物损伤的作用，同时还具有延长被辐射的动物生存期和存活率的作用，对放疗副作用具有明显的缓解作用，且该化合物毒性较低，本发明开辟了电离辐射损伤防护与救治的新途径。

AMINO MERCAPTAN COMPOUND AND PREPARATION METHOD THEREFOR AND USE THEREOF IN PROTECTION AGAINST RADIATION

Technical Field

The present invention relates to the field of medicine, in particular to the protection against ionizing radiation damage, in particular to a new class of compounds having the effect of radiation protection. The present invention also relates to a method for preparing the compound. The present invention also relates to the use of the compound in the prevention and treatment of damages and diseases caused by ionizing radiation.

Background Art

With the vigorous development of the global nuclear cause, the nuclear technology has been widely used in various fields such as nuclear power plants, aerospace, national defense and biomedicine, and the chance of human exposure to ionizing radiation and thus causing damage has increased. In the meantime, with the nuclear war and hidden nuclear terror incident worries brought about by the world's tense nuclear security situation, the protection and treatment of body damage caused by ionizing radiation (referred to as radiation damage) is receiving more and more attention.

On the other hand, the incidence of malignant tumors and the number of patients has been increasing in recent years. Radiation therapy plays an indispensable role as one of the main treatments. However, high-dose radiation exposure inevitably leads to acute radiation damage to normal tissues and organs surrounding the tumor and even to the whole body. The side effects of radiation damage seriously restrict the wide application of radiotherapy in tumor therapy, and also significantly affect the efficacy and quality of life of cancer patients after radiotherapy.

At present, there are mainly related drugs for radiation damage treatment: sulfur compounds, hormones, cytokines and Chinese herbal medicines, which have their own inherent defects. For example, sulfur compounds are generally associated with greater side effects, such as amifostine, a representative of such compounds, is currently recognized as the best protective compound and is the first selective broad-spectrum cytoprotective agent approved by the international regulatory agencies, but the extremely short half-life (7 min) and high price (the domestic medical market price is 400-500 yuan per dose) limit its application. The prevention and treatment of radiation damage by hormone drugs are mainly for the nucleated cells, hematopoietic stem cells and progenitor cells in bone marrow, and the effects of such drugs on the sexual and reproductive systems limit their widespread use. Cytokine drugs such as interleukins and colony stimulating factor drugs can alleviate and treat radiation-induced bone marrow hematopoietic system damage, but their radiation protection effect is closely related to the time of administration (in the medical practice for prevention and treatment, such drugs require a high level of medical testing and attention), with obvious inflammatory effect, and it is expensive and difficult to store at room temperature. The anti-radiation components of Chinese herbal medicines mainly comprise phenols, polysaccharides and natural flavones, which have the characteristics of unclear active ingredients and low toxicity, and after years of research, there are no similar drugs on the market or to be marketed.

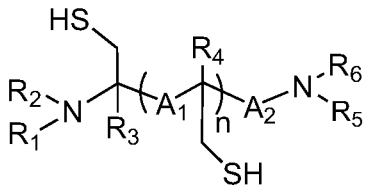
Summary of the Invention

One purpose of the present invention is to provide a new class of compounds with radiation protection. It has the effects of prolonging the survival period and reducing the death rate of animals after sublethal dose irradiation. It can be used alone as a radiation damage protection and treatment drug, or in combination with radiotherapy, which can alleviate and prevent the adverse reactions caused by radiotherapy.

Another purpose of the present invention is to provide a method for preparing the compound.

The further purpose of the present invention is to provide the use of the compound in the preparation of drugs for the prevention and/or treatment of damages and diseases related to ionizing radiation.

According to an aspect of the present invention, a compound having the following chemical structural formula is provided:



(I)

wherein A_1 is selected from: $-C(O)NR^8-$, $-S(O)_2-NR^8-$, $-S(O)NR^8-$, and $-R^7-NR^8-$;

A_2 is selected from: carbonyl, sulfonyl, sulfinyl, substituted or unsubstituted C_{1-6} alkyl;

R^1, R^2, R^5, and R^6 may be the same or different and are selected from: hydrogen, substituted or unsubstituted C_1-C_5 alkyl or heteroalkyl;

n is an integer from 0 to 20,000;

R^3 and R^4 are independently selected from: hydrogen, X, substituted or unsubstituted C_{1-6} alkyl;

X is selected from: F, Cl, Br and I;

R^7 is selected from: substituted or unsubstituted C_1-C_6 alkyl; R^8 is selected from: hydrogen, substituted or unsubstituted C_1-C_6 alkyl;

and stereoisomers thereof or pharmaceutically acceptable salts, prodrugs and solvates thereof.

Preferably, the above compound of formula I does not comprise (R)-2-amino-N-((R)-1-amino-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropionamide.

Preferably, A_1 is selected from: $-C(O)NR^8-$, and $-R^7-NR^8-$; more preferably, A_1 is selected from: $-C(O)NR^8-$, and $-CH_2-NR^8-$;

preferably, A_2 is selected from: carbonyl, sulfonyl, sulfinyl, and substituted or unsubstituted C_{1-3} alkyl; more preferably, A_2 is selected from: carbonyl, sulfonyl, sulfinyl, and methylene; further preferably, A_2 is selected from: carbonyl, and methylene;

preferably, R^1, R^2, R^5, and R^6 may be the same or different and are selected from: hydrogen, C_{1-3} alkyl, and hydroxy or amino substituted C_1-C_3 alkyl or heteroalkyl; more preferably, R^1, R^2, R^5, and R^6 may be the same or different and are selected from: hydrogen, methyl, and ethyl; more preferably, one of $R^1$and R^2 is hydrogen, and the other is C_1-C_3 alkyl (e.g., methyl, ethyl or propyl), as well as one of R^5 and R^6 is hydrogen, and the other is C_1-C_3 alkyl (e.g., methyl, ethyl or propyl); even more preferably, one of $R^1$and R^2 is hydrogen, and the other is methyl, as well as one of R^5 and R^6 is hydrogen, and the other is methyl; or alternatively, $R^1$and R^2 are methyl or ethyl, as well as R^5 and R^6 are methyl or ethyl;

preferably, n is an integer from 0 to 2,000; more preferably, n is an integer from 1 to 200; further preferably, n is an integer from 1 to 200; still further preferably, n is an integer from 1 to 50; more preferably an integer from 1 to 10 (including 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10);

preferably, R^3 and R^4 are independently selected from: hydrogen, X, substituted or unsubstituted C_{1-3} alkyl; more preferably, R^3 and R^4 are independently selected from: hydrogen, X, and methyl;

preferably, X is selected from F and Cl; more preferably, X is F;

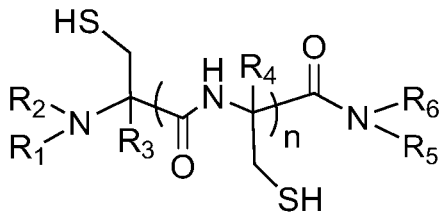
preferably, R^7 is selected from: substituted or unsubstituted C_1-C_3 alkyl; more preferably, R^7 is methylene;

preferably, R^8 is selected from: hydrogen, substituted or unsubstituted C_1-C_3 alkyl; more preferably, R^8 is selected from: hydrogen, methyl, and ethyl; further preferably, R^8 is hydrogen;

in the compound, the chiral carbon directly attached to R^3 and R^4 is in the R configuration or the S configuration. Preferably, the chiral carbon directly attached to R^3 and R^4 is in the R configuration.

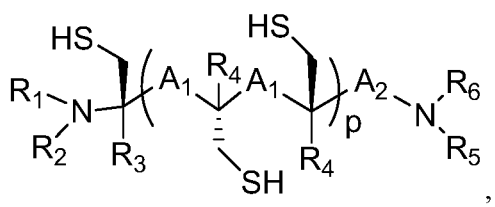
More preferably, the chiral carbon directly attached to R^3 and R^4 is in the R configuration; one of R^1 and R^2 is hydrogen, and the other is methyl, as well as one of R^5 and R^6 is hydrogen, and the other is methyl.

In a preferred embodiment of the present invention, the compound has the following general formula:

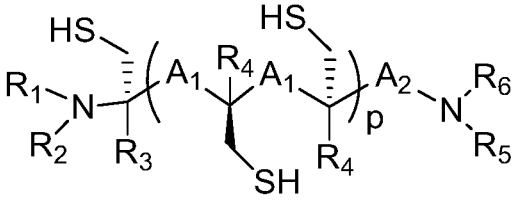


(II).

In another preferred embodiment of the present invention, the compound has the following general formulas:



(III)

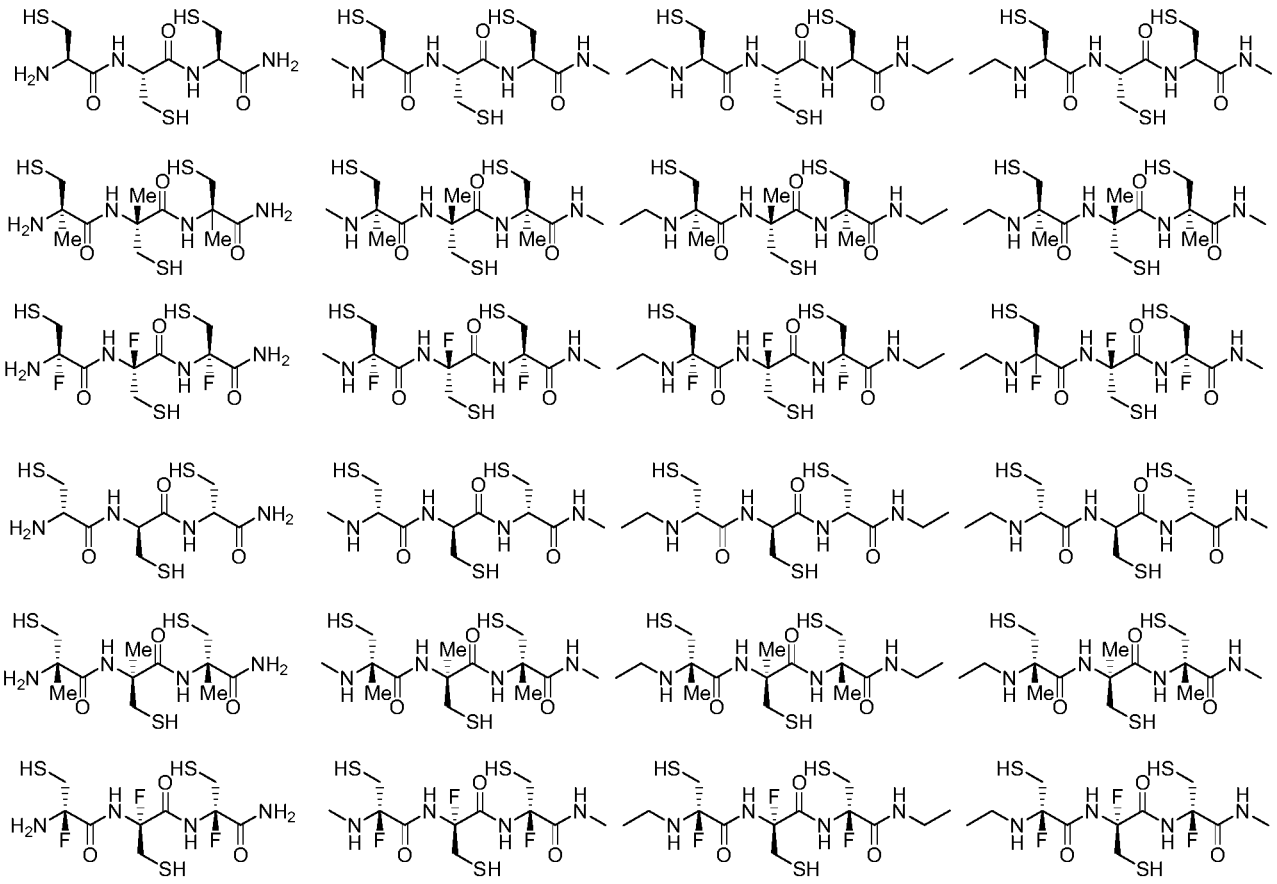


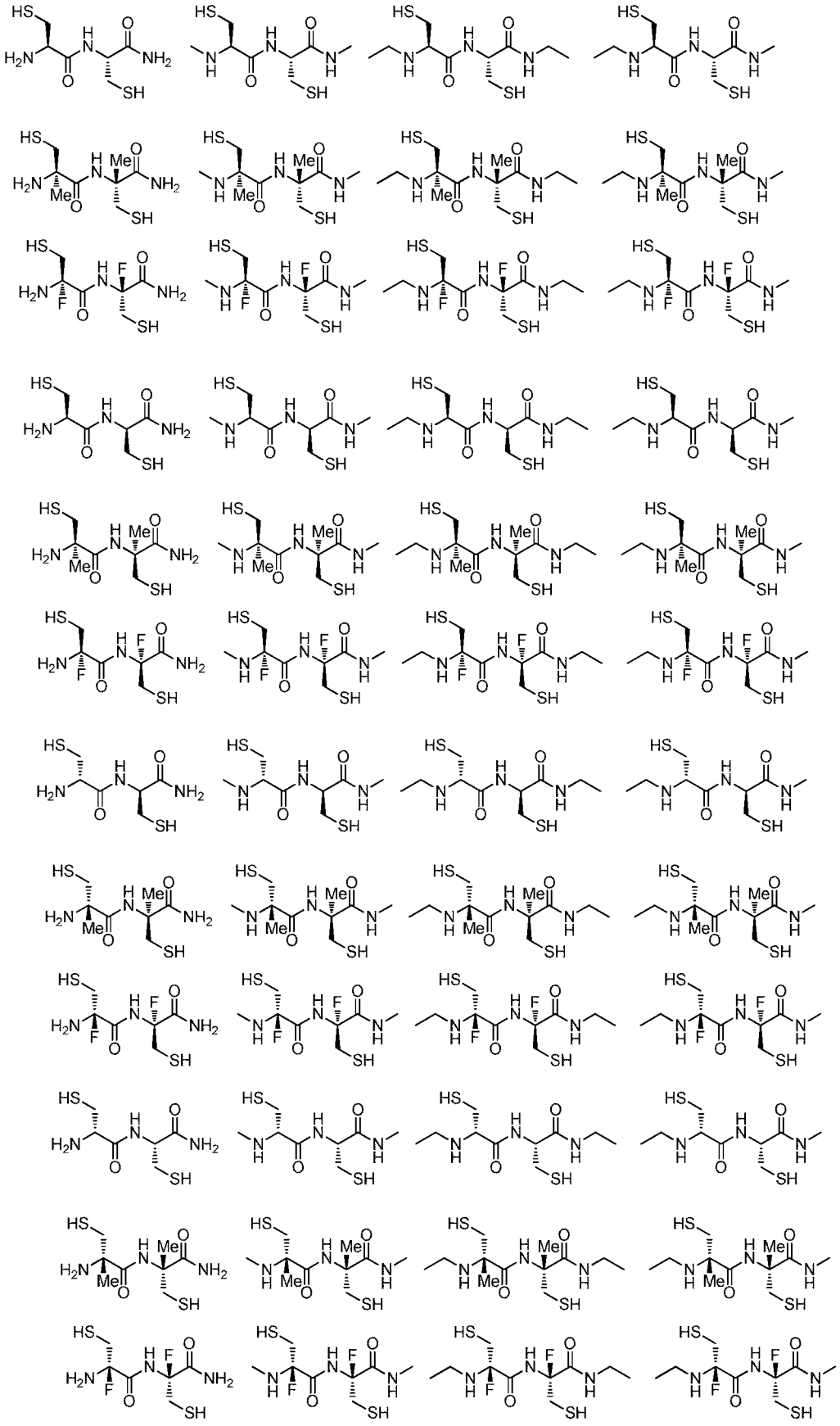
(IV)

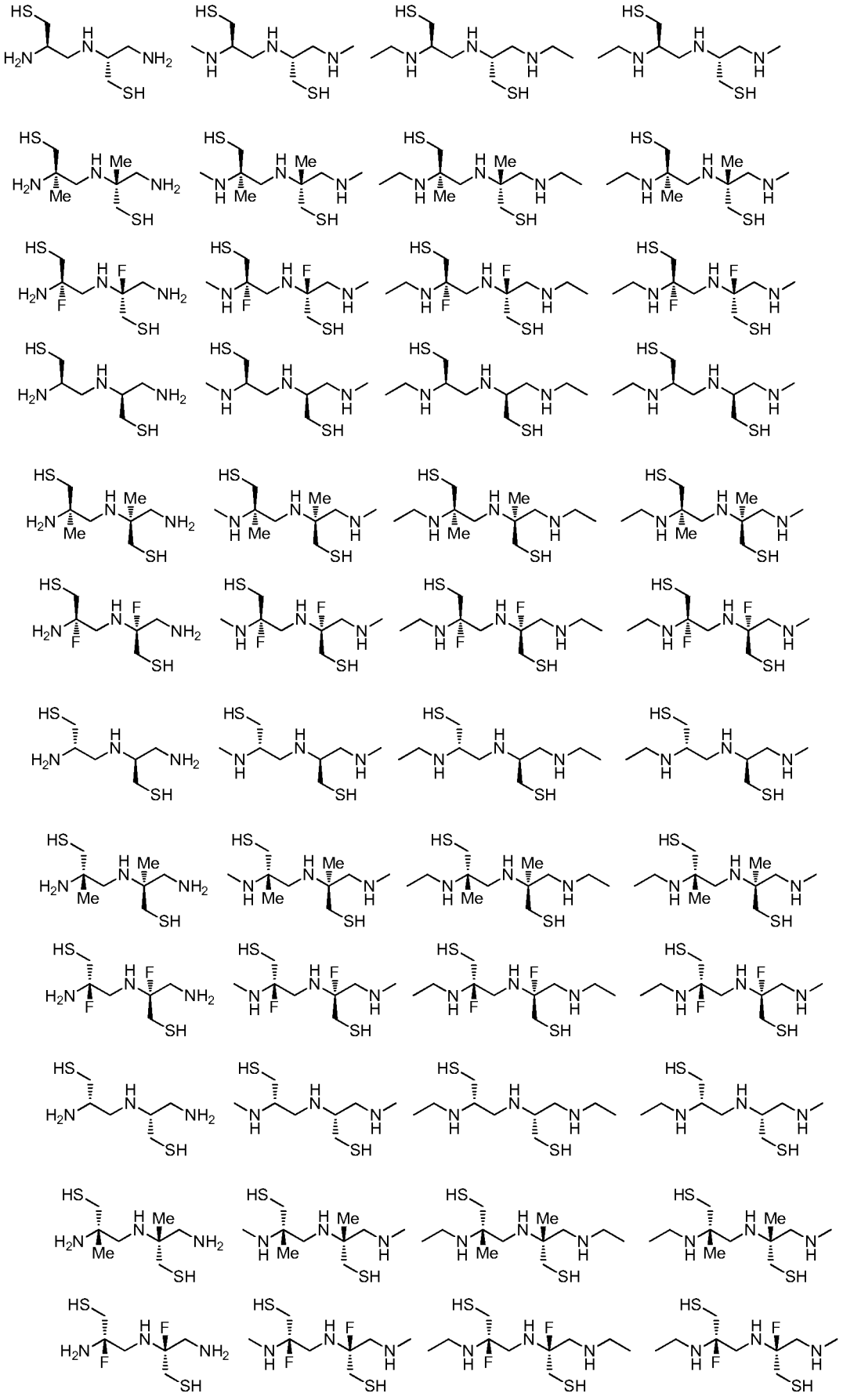
wherein p is an integer of from 1 to 10,000, preferably an integer of from 1 to 1,000, more preferably an integer of from 1 to 100, further preferably an integer of from 1 to 10; more preferably an integer of from 1 to 5 (including 1, 2, 3, 4 and 5);

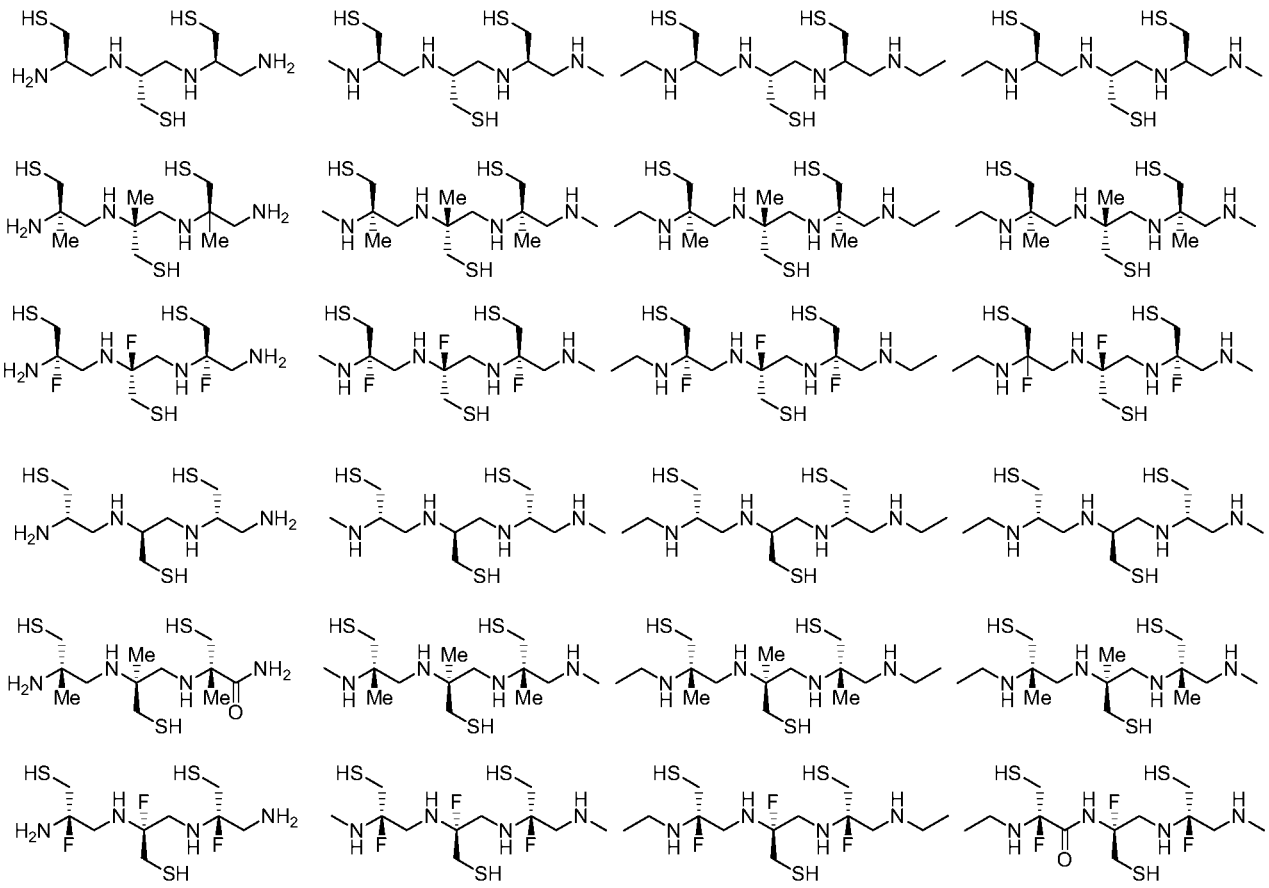
in a preferred embodiment of the present invention, the R^1, R^2, R^5, R^6, and R^8 are all hydrogen;

In another preferred embodiment of the present invention, R^1 and R^5 are hydrogen, and R^2 and R^6 are selected from: methyl and ethyl; in a preferred embodiment of the present invention, the above compounds may preferably be the following compounds, but are not limited to the following compounds:

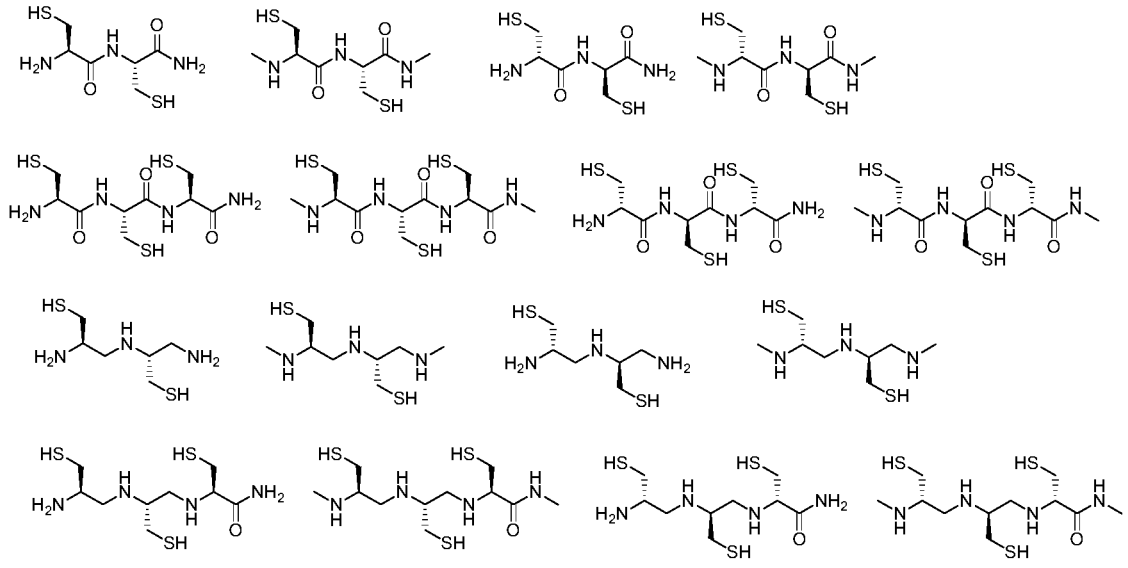






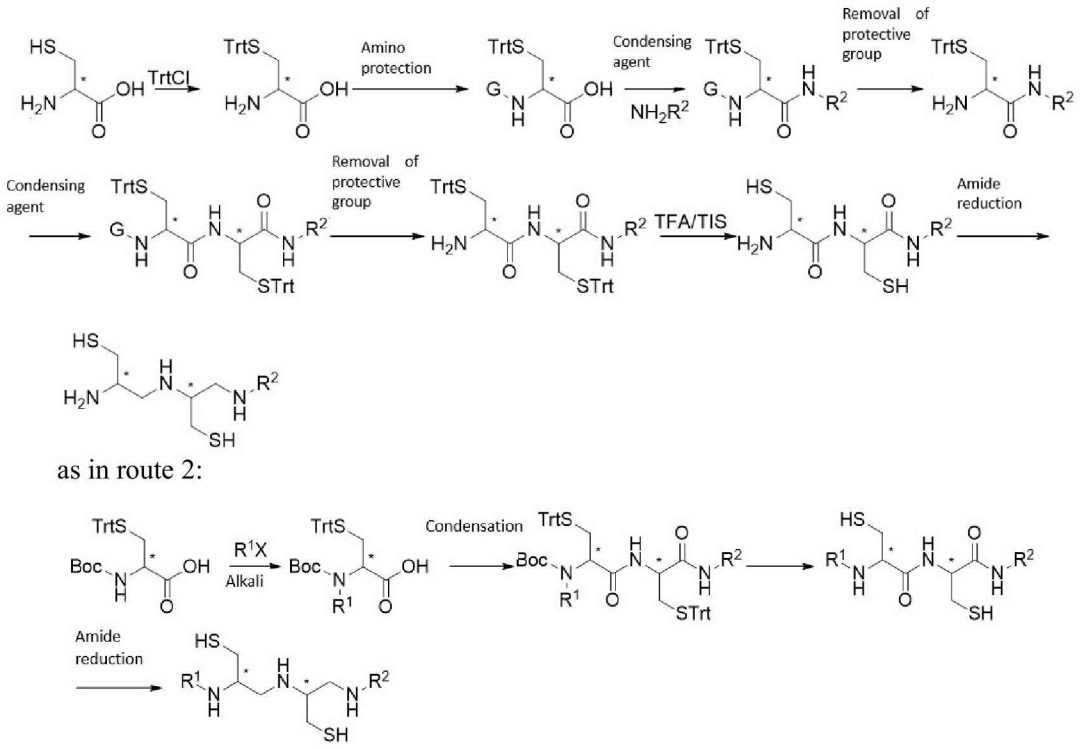


In a preferred embodiment of the present invention, the above compounds may preferably be the following compounds, but are not limited to the following compounds:



According to another aspect of the present invention, the method for preparing the compound of the present invention is provided:

preferably, as in route 1:



as in route 2:

wherein R^1 and R^2 may be the same or different and are selected from: hydrogen, substituted or unsubstituted C_1-C_5 alkyl or heteroalkyl;

preferably, the amino-protecting group G is selected from: tert-butyloxycarbonyl, fluorenylmethoxycarbonyl (Fmoc), benzyloxycarbonyl, benzyl, and the like;

X is a halogen;

preferably, the condensing agent is selected from: Carbonyldiimidazole (CDI), 1-hydroxybenzotriazole (HOBT), 2-(7-oxidized benzotriazole)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), N, N'-dicyclohexylcarbodiimide (DCC), BOP, PyBOP, HBTU, TBTU, EDCI, etc.;

the corresponding amino-protecting group may be removed by an acid method such as formic acid, hydrochloric acid and trifluoroacetic acid or an alkali method such as piperidine, aqueous ammonia and triethylamine, or the corresponding amino-protecting group may also be removed by hydrogenation; and

amide can be reduced to amine by borane, $NaBH_4$, $NaBH_4$-Lewis acid, lithium aluminum hydride and other methods.

According to a further aspect of the present invention, a pharmaceutical composition comprising the compound of the present invention and a derivative thereof are provided;

preferably, the above pharmaceutical composition further comprises one or more pharmaceutically acceptable vehicles, carriers, adjuvants, auxiliaries or diluents;

preferably, the dosage forms of the pharmaceutical composition comprise but are not limited to: injections, emulsions, microemulsions, submicro-emulsions, nanoparticles, tablets, capsules, pills, inhalants, lozenges, gels, powder, suppositories, suspensions, creams, jellies, sprays, etc.;

preferably, the pharmaceutical composition can be administered by means of, but not limited to: subcutaneous injection, intramuscular injection, intravenous injection, oral administration, rectal administration, vaginal administration, nasal administration, transdermal administration, subconjunctival administration, intraocular administration, eyelid administration, retrobulbar administration, retinal administration, choroidal

administration, intrathecal injection, and the like.

According to a further aspect of the present invention, the use of the compound of the present invention (e.g., a compound of formula I) and the pharmaceutical composition thereof in the preparation of drugs and/or cosmetics for the treatment and/or prevention of radiation damage and chemotherapy damage is provided.

The radiation comprises ionizing radiation, non-ionizing radiation or a combination of various types of radiation;

the ionizing radiation includes but is not limited to: alpha rays, beta rays, gamma rays, X rays, and neutron radiation;

the radiation damage comprises direct damage and indirect damage caused by radiation; preferably, the radiation damage comprises radiation-induced reduction of peripheral blood leukocytes, platelets and erythrocytes in mammals;

the chemotherapeutic drugs refer to the anti-tumor drugs that act on DNA, RNA, and tubulin, and that are vital to the survival of cells;

preferably, the use comprises the use of the above compound and the pharmaceutical composition thereof in the preparation of drugs and/or cosmetics for the treatment and/or prevention of sunburn damage; more preferably, the use comprises the use of the above compound and the pharmaceutical composition thereof in the preparation of cosmetics for the treatment and/or prevention of sunburn damage.

The compound of the present invention or a pharmaceutical composition thereof can be used alone as a radiation damage protection and treatment drug, or can be used in combination with a known radioprotectant, or can be combined with radiation therapy or chemotherapy to treat tumors, thereby reducing the adverse reactions of radiotherapy to surrounding tissues and organs and even the whole body, and alleviating and preventing the adverse reactions caused by radiotherapy.

The present invention also provides the use of the above compound or the pharmaceutical composition thereof in the preparation of anti-tumor drugs.

The present invention provides a novel stable compound which has the effects of reducing biological damage caused by ionizing radiation, extending the survival period and survival rate of the radiated animals, and significantly alleviating the side effects of radiotherapy, and has a low toxicity. The present invention opens up a new way for protection and treatment of ionizing radiation damage, wherein the radiation damage comprises direct damage and indirect damage caused by radiation; including radiation-induced reduction of peripheral blood leukocytes, platelets and erythrocytes in mammals. The chemotherapeutic drugs refer to the anti-tumor drugs that act on DNA, RNA, and tubulin, and that are vital to the survival of cells. The compounds provided by the present invention and derivatives thereof can also be used in combination with known radioprotectants.

Brief Description of the Drawings

Figures 1A and 1B show the effect of compound 1 on the mice irradiated with 6.8Gy γ rays, wherein Figure 1A shows the effect of compound 1 on 30-day survival rate of mice irradiated with 6.8Gy γ rays, Figure 1B shows the effect of compound 1 on the body weight of mice irradiated with 6.8Gy γ rays.

Figures 2A-2J show the effect of compound 1 on organs and white blood cells in mice 30 days after irradiation with 6.8Gy γ rays, wherein Figure 2A shows the effect of compound 1 on heart in mice 30 days after irradiation with 6.8Gy γ rays, Figure 2B shows the effect of compound 1 on liver in mice 30 days after

irradiation with 6.8Gy γ rays, Figure 2C shows the effect of compound 1 on spleen in mice 30 days after irradiation with 6.8Gy γ rays, Figure 2D shows the effect of compound 1 on lung in mice 30 days after irradiation with 6.8Gy γ rays, Figure 2E shows the effect of compound 1 on kidney in mice 30 days after irradiation with 6.8Gy γ rays, Figure 2F shows the effect of compound 1 on thymus in mice 30 days after irradiation with 6.8Gy γ rays, Figure 2G shows the effect of compound 1 on testis in mice 30 days after irradiation with 6.8Gy γ rays, Figure 2H shows the effect of compound 1 on splenic nodules in mice 30 days after irradiation with 6.8Gy γ rays, Figure 2I shows the effect of compound 1 on unilateral femoral bone marrow leukocytes in mice 30 days after irradiation with 6.8Gy γ rays, Figure 2J shows the effect of compound 1 on white blood cells in blood of mice 30 days after irradiation with 6.8Gy γ rays.

Figures 3A and B show the effect of compounds 1-4 on the survival rate and body weight of mice 30 days after irradiation with 7.2Gy γ rays, wherein Figure 3A shows the effect of compounds 1-4 on survival rate of mice 30 days after irradiation with 7.2Gy γ rays, Figure 3B shows the effect of compounds 1-4 on the body weight of mice irradiated with 7.2Gy γ rays.

Figures 4A-4J show the effect of compounds 1-4 on organs and white blood cells in mice 30 days after irradiation with 7.2Gy γ rays, wherein Figure 4A shows the effect of compounds 1-4 on heart in mice 30 days after irradiation with 7.2Gy γ rays, Figure 4B shows the effect of compounds 1-4 on liver in mice 30 days after irradiation with 7.2Gy γ rays, Figure 4C shows the effect of compounds 1-4 on spleen in mice 30 days after irradiation with 7.2Gy γ rays, Figure 4D shows the effect of compounds 1-4 on lung in mice 30 days after irradiation with 7.2Gy γ rays, Figure 4E shows the effect of compounds 1-4 on kidney in mice 30 days after irradiation with 7.2Gy γ rays, Figure 4F shows the effect of compounds 1-4 on thymus in mice 30 days after irradiation with 7.2Gy γ rays, Figure 4G shows the effect of compounds 1-4 on testis in mice 30 days after irradiation with 7.2Gy γ rays, Figure 4H shows the effect of compounds 1-4 on splenic nodules in mice 30 days after irradiation with 7.2Gy γ rays, Figure 4I shows the effect of compounds 1-4 on unilateral femoral bone marrow leukocytes in mice 30 days after irradiation with 7.2Gy γ rays, Figure 4J shows the effect of compounds 1-4 on white blood cells in blood of mice 30 days after irradiation with 7.2Gy γ rays.

Figures 5A and 5B show the effect of compound 1 on survival rate and body weight of mice 30 days after irradiation with 7.5Gy γ rays, wherein Figure 5A shows the effect of compound 1 on survival rate of mice 30 days after irradiation with 7.5Gy γ rays, Figure 5B shows the effect of compound 1 on the body weight of mice irradiated with 7.5Gy γ rays.

Figures 6A-6J show the effect of amifostine on organs and white blood cells in mice 30 days after irradiation with 7.5Gy γ rays, wherein Figure 6A shows the effect of amifostine on heart in mice 30 days after irradiation with 7.5Gy γ rays, Figure 6B shows the effect of amifostine on liver in mice 30 days after irradiation with 7.5Gy γ rays, Figure 6C shows the effect of amifostine on spleen in mice 30 days after irradiation with 7.5Gy γ rays, Figure 6D shows the effect of amifostine on lung in mice 30 days after irradiation with 7.5Gy γ rays, Figure 6E shows the effect of amifostine on kidney in mice 30 days after irradiation with 7.5Gy γ rays, Figure 6F shows the effect of amifostine on thymus in mice 30 days after irradiation with 7.5Gy γ rays, Figure 6G shows the effect of amifostine on testis in mice 30 days after irradiation with 7.5Gy γ rays, Figure 6H shows the effect of amifostine on splenic nodules in mice 30 days after irradiation with 7.5Gy γ rays, Figure 6I shows the effect of amifostine on unilateral femoral bone marrow leukocytes in mice 30 days after irradiation with 7.5Gy γ rays, Figure 6J shows the effect of amifostine on white blood cells in blood of mice 30 days after

irradiation with 7.5Gy γ rays.

Figures 7A-7F show the effects of irradiation on peripheral blood, wherein Figure 7A shows the peripheral white blood cell (WBC) count, Figure 7B shows the peripheral red blood cell (RBC) count, Figure 7C shows the peripheral hemoglobin (HGB) concentration, Figure 7D shows the peripheral platelet (PLT) count, Figure 7E shows the peripheral blood lymphocyte ratio (LY%), Figure 7F shows the peripheral blood neutrophil ratio (NE%).

Figures 8A-8E show the effect of irradiation on bone marrow cells, wherein Figure 8A shows the number of leukocytes in bone marrow, Figure 8B shows the ratio of hematopoietic stem cell (LSK) in bone marrow cells, Figure 8C shows the ratio of hematopoietic progenitor cells (HPC) in bone marrow cells, Figure 8D shows the ratio of CD34-LSK in bone marrow cells, Figure 8E shows the ratio of CD34+LSK in bone marrow cells.

Figures 9A and 9B show the effect of irradiation on the levels of reactive oxygen species (ROS) in LSK cells and the levels of ROS in HPC cells, wherein Figure 9A shows the levels of reactive oxygen species (ROS) in LSK cells, Figure 9B shows the levels of ROS in HPC cells.

Figure 10 shows the 30-day survival rate of Example 4 and amifostine in mice exposed to local abdominal radiation of 18Gy.

Figure 11 shows the protective effect of Example 4 on the intestinal tract.

Figure 12 shows the effect of Example 4 and amifostine on radiation pneumonia.

Figure 13 shows the effect of stereoisomerism of the compound on the survival rate.

Detailed Description of Embodiments

According to the present invention, the term "radiation damage" in the present invention refers to the injury caused by various rays in the electromagnetic spectrum, such as microwave, infrared ray, visible light, ultraviolet ray, X ray, beta ray and gamma ray. Neutron or proton beam irradiation can also cause such damage.

The term "pharmaceutically acceptable salt" refers to any salt (generally referred to as non-toxic) that is physiologically compatible when used in an appropriate manner for treatment, use, or especially in humans and/or mammals. Unless otherwise stated, salts of acidic groups which may be present in the compounds of the present invention (for example, but not limited to, potassium salts, sodium salts, magnesium salts, calcium salts, etc.) or salts of basic groups (for example, but not limited to, sulfates, hydrochlorides, phosphates, nitrates, carbonates, etc.).

The term "solvate" refers to a complex compound of molecules of solute or ions in a solution, formed by attracting neighboring solvent molecules through intermolecular forces such as coulomb force, van der Waals force, charge transfer force, and hydrogen bond. In one embodiment, the solvent is water, that is, the compound of the invention forms a hydrate.

Depending on the substituent, the compound in formula (I) may be in the form of optically active isomers or mixtures of isomers of different compositions, and the mixtures may be separated by conventional means if appropriate. The present invention provides pure isomers and mixtures of isomers, methods for preparation and uses, and compositions comprising them. For the sake of simplicity, it is referred to below as a compound of formula (I), which refers to both pure optical isomers and, where appropriate, mixtures of different proportions of isomers.

A person skilled in the art will have a better understanding of the above and other purposes,

advantages and characteristics of the present invention according to the following and the detailed description of the specific embodiments of the present invention in conjunction with the accompanying drawings. A person skilled in the art will have a better understanding of the above and other purposes, advantages and characteristics of the present invention according to the following and the detailed description of the specific embodiments of the present invention in conjunction with the accompanying drawings.

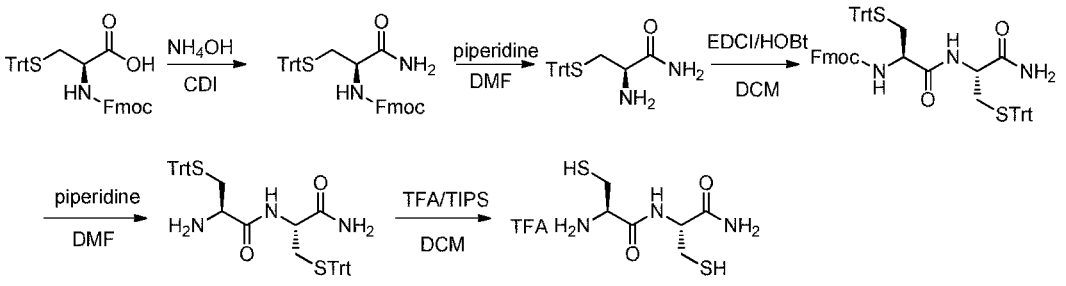
Synthesis

Suitable solvents commonly used in organic reactions can be used in the following various steps of the preparation method of the present invention, such as, but not limited to, aliphatic and aromatic, optionally hydrocarbon or halogenated hydrocarbons (e.g., pentane, hexane, heptane, cyclohexane, petroleum ether, gasoline, volatile oil, benzene, toluene, xylene, dichloromethane, dichloroethane, chloroform, carbon tetrachloride, chlorobenzene and o-dichlorobenzene); aliphatic and aromatic, optional alcohols (e.g., methanol, ethanol, propanol, isopropanol, tertiary butanol, ethylene glycol, etc.), ethers (e.g., diethyl ether and dibutyl ether, ethylene glycol dimethyl ether and diglyme, tetrahydrofuran and dioxane, etc.), esters (e.g., methyl acetate or ethyl acetate, etc.), nitriles (e.g., acetonitrile or propionitrile, etc.), ketone (e.g., acetone, methyl ethyl ketone, etc.), amides (e.g., dimethylformamide, dimethylacetamide, N-methylpyrrolidone, etc.); as well as dimethyl sulfoxide, tetramethylene sulfone and hexamethylphosphoric triamide and N,N-dimethyl propylene urea (DMPU), etc.

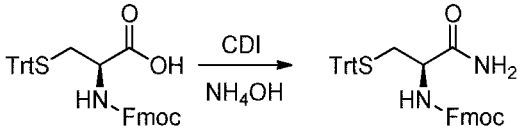
Synthesis Examples:

The present invention may be further explained by the following examples which do not imply any limitation to the present invention.

Example 1: Synthesis of (R)-2-amino-N-((R)-1-amino-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropanamide trifluoroacetate:



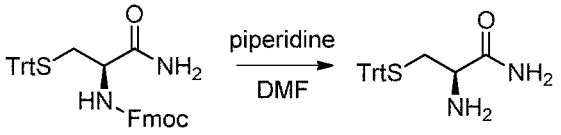
Step 1: Synthesis of (9H-fluoren-9-yl) methyl (R)-(1-amino-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



The compound (R)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tritylthio) propionic acid (10 g, 17.07 mmol) was dissolved in tetrahydrofuran (50ml). N,N'-carbonyldiimidazole (5.59g, 34.48mmol) was added at 0-5°C. After stirring for 2 hours under nitrogen protection, aqueous ammonia (5ml, 68.28mmol) was added, and reacted at 0-5°C for 30 minutes. After the reaction was completed as detected by TLC, 2 M hydrochloric acid (60ml) was added for quenching. The reaction mixture was extracted with ethyl acetate, the organic phase was washed with a saturated saline, then dried with sodium sulfate, and concentrated to obtain a crude product. After adding anhydrous methanol (20ml) and stirring at room temperature overnight, white solids were precipitated,

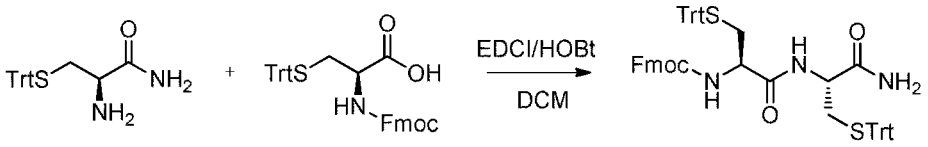
and filtered to obtain the product in the filter cake. The methanol phasewas concentrated and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the target product as a white solid (9.3g, yield: 93.19%). ^{1}H NMR (400MHz, DMSO-d6) δ 7.89(d, 2H), 7.74(d, 2H), 7.58(d, 1H), 7.3(m, 18H), 7.11(s, 1H), 4.24(m, 3H), 4.01(m, 1H), 2.39(m, 2H).

Step 2: Synthesis of (R)-2-amino-3-(tritylthio) propionamide:



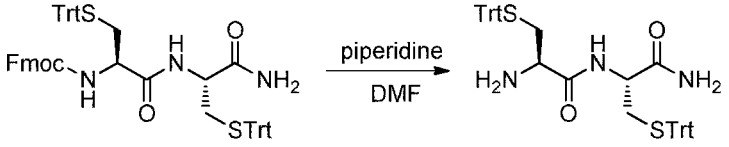
The compound (9H-fluoren-9-yl) methyl (R)-(1-amino-1-oxo-3-(tritylthio)propan-2-yl) carbamate (4g, 6.84mmol) was dissolved in N,N-dimethylformamide (20ml). Piperidine (0.14ml, 1.368mmol) was added and reacted at room temperature for 4 hours. After the reaction was completed as detected by TLC, the reaction mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane = 1%-5%) to obtain the target product as a yellow oil (2.3g, yield: 92%). ^{1}H NMR (400MHz, DMSO-d6) δ 7.29(m, 17H), 3.08(d, 1H), 2.33(d, 1H), 2.18(s, 1H), 1.85(s, 2H).

Step 3: Synthesis of (9H-fluoren-9-yl) methyl ((R)-1-(((R)-1-amino-1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



The compound (R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tritylthio) propanoic acid (1.29g, 2.21mmol) was dissolved in dichloromethane (15ml). 1-hydroxybenzotriazole (448mg, 3.315mmol) and EDCI (635mg, 3.315mmol) were added, and stirred at room temperature for 5min. (9H-fluoren-9-yl) methyl (R)-(1-amino-1-oxo-3-(tritylthio)propan-2-yl) carbamate (960mg, 2.65mmol) was added and reacted at room temperature for 30 minutes. After the reaction was completed as detected by TLC, the mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (2.05g, yield: 99.76%). ^{1}H NMR (400MHz, DMSO-d6) δ 7.89(m, 3H), 7.7(m, 3H), 7.4(m, 2H), 7.24(m, 34H), 4.21(m, 4H), 4.10(m, 1H), 2.33(m, 4H).

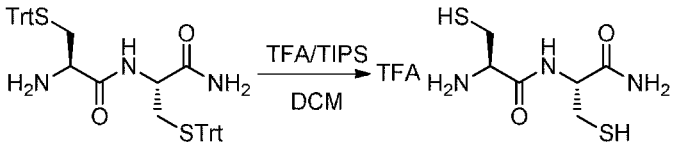
Step 4: Synthesis of (R)-2-amino-N-((R)-1-amino-1-oxo-3-(tritylthio) propan-2-yl)-3-(tritylthio) propionamide:



The compound (9H-fluoren-9-yl) methyl ((R)-1-(((R)-1-amino-1-oxo-3-(tritylthio)propan-2-yl) amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate (2.05g, 2.2mmol) was dissolved in N,N-dimethylformamide (20ml). Piperidine (0.04ml, 0.44mmol) was added and stirred at room temperature for 4 hours. After the reaction was completed as detected by TLC detection, the reaction mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, concentrated, and separated

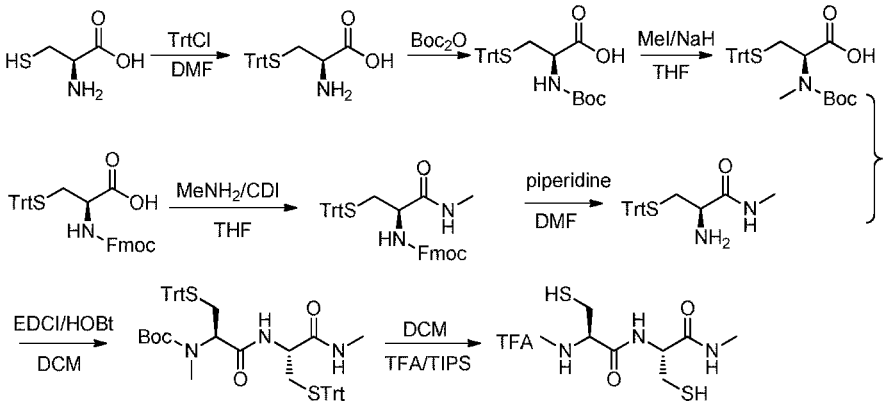
by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (600mg, yield: 38.54%). ^{1}H NMR (400MHz, DMSO-d6) δ 8.1(s,1H), 7.37-7.14(m, 32H), 4.23(m, 1H), 3.17(m,1H), 2.39(dd, 1H), 2.33(d, 2H), 2.19(m, 1H).

Step 5: Synthesis of (R)-2-amino-N-((R)-1-amino-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropanamide trifluoroacetate:

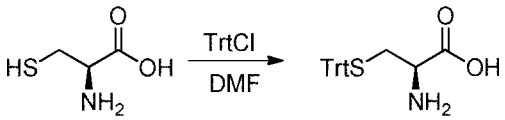


The compound (R)-2-amino-N-((R)-1-amino-1-oxo-3-(tritylthio)propan-2-yl)-3-(tritylthio) propionamide (150mg, 0.21mmol) was dissolved in dichloromethane (5ml). Triisopropylsilane (0.11ml, 0.525mmol) and trifluoroacetic acid (1ml) were added at 0°C under a nitrogen atmosphere and stirred in an ice bath for 2 hours. After the reaction was completed as detected by TLC, the mixture was concentrated, diethyl ether was added, and stirred in the ice bath. White solids were precipitated, filtered and dried to obtain the product (60mg, yield: 84.7%). ^{1}H NMR (400MHz, DMSO-d6) δ 8.72(d, 1H), 8.23(s, 3H), 7.56(s, 1H), 7.32(s, 1H), 4.43(m, 1H), 4.09(m, 1H), 2.99(d, 2H), 2.89(m, 1H), 2.74(m, 1H); HESI:224.05 [M +H]+.

Example 2: Synthesis of (R)-3-mercapto-N-((R)-3-mercapto-1-(methylamino)-1-oxopropan-2-yl)-2-(methylamino) propionamide trifluoroacetate:

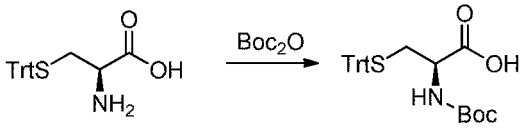


Step 1: Synthesis of S-trityl-L-cysteine:



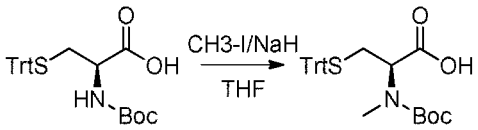
The compound L-cysteine hydrochloride (10g, 63.45mmol) was dissolved in N,N-dimethylformamide (120ml). Triphenylchloromethane (19.46g, 69.795mmol) was added, heated to 60-65°C, and reacted for 8h. After the reaction was completed as detected by TLC, the reaction was cooled to room temperature, and 10% sodium acetate solution (300ml) was added. White solids were then precipitated and filtered. Filter residue was washed with pure water (300ml), then washed with acetone (200ml), and dried to obtain the product as a white solid (17.56g, yield: 76.15%).^{1}H NMR (400MHz, DMSO-d6) δ 7.28(m, 18H), 2.92(dd, 1H), 2.59(dd, 1H), 2.41(dd, 1H).

Step 2: Synthesis of N-(tert-butoxycarbonyl)-S-trityl-L-cysteine:



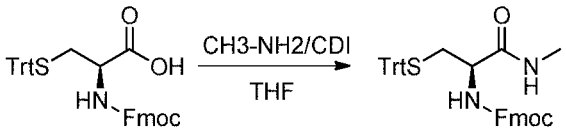
The compound S-trityl-L-cysteine (5g, 13.76mmol) was dissolved in a mixture of dioxane (40ml), water (20ml) and 1M sodium hydroxide solution (14ml), and stirred in an ice bath. Boc-anhydride (3.5ml, 15.14mmol) was added, then reacted until the mixture was naturally warmed to room temperature, and stirred for 8 hours. After the reaction was completed as detected by TLC, the reaction mixture was concentrated to 20-25ml. Ethyl acetate was added, and the sodium bisulfate solution was added dropwise under the ice bath while stirring. After pH was adjusted to 2-3, ethyl acetate was used for extraction. The organic layer was washed with a saturated saline, then dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (5.5g, yield :86.21%). ^{1}H NMR (400MHz, DMSO-d6) δ 7.26(m, 16H), 3.78(d, 1H), 2.51(m, 1H), 2.36(dd, 1H), 1.4(d, 9H).

Step 3: Synthesis of N-(tert-butoxycarbonyl)-N-methyl-S-trityl-L-cysteine:



The compound N-(tert-butoxycarbonyl)-S-trityl-L-cysteine (2.1g, 4.53mmol) was dissolved in anhydrous tetrahydrofuran (6ml). Sodium hydride (436mg, 10.9mmol) was dissolved in anhydrous tetrahydrofuran (14ml). The solution of amino acid in tetrahydrofuran was added dropwise to the solution of sodium hydride in tetrahydrofuran in an ice bath. Then, methyl iodide (0.93ml, 14.95mmol) was slowly added dropwise and stirred overnight. After the reaction was completed as detected by TLC, phosphate buffer at pH=7 was added for quenching. pH was adjusted to 6-7 with a saturated ammonium chloride solution, and was extracted with ethyl acetate. The organic layer was washed with a saturated saline, then dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (1.3g, yield: 60.19%). ^{1}H NMR (400MHz, DMSO-d6) δ 7.3(m, 15H), 3.75(s, 1H), 2.8(s, 1H), 2.66(d, 4H), 1.4(d, 9H).

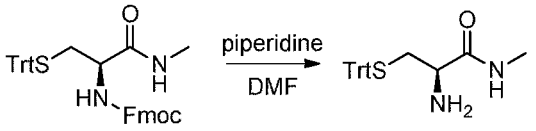
Step 4: Synthesis of (9H-fluoren-9-yl) methyl (R)-(1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



The compound (R)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tritylthio) propionic acid (10g, 17.07mmol) was dissolved in tetrahydrofuran (50ml). N,N'-carbonyldiimidazole (5.59g, 34.48mmol) was added at 0-5°C. After stirring for 2 hours under nitrogen atmosphere, methylamine (3.03ml, 68.28mmol) was added, and reacted at 0-5°C for 2 hours. After the reactants were consumed, 2M hydrochloric acid (60ml) was added for quenching, and the reaction mixture was extracted with dichloromethane. The organic layer was washed with a saturated saline, then dried with sodium sulfate and concentrated to obtain a crude product. Methanol (20ml) was added and stirred overnight at room temperature. White solids were precipitated, and filtered to obtain the product in filter residue. The methanol phase was concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain a white solid (9.44g, yield: 92.37%). ^{1}H NMR (400MHz, DMSO)

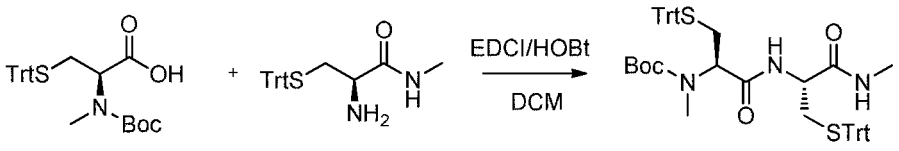
δ 7.89(d, 2H), 7.81(d, 1H), 7.74(d, 2H), 7.66(d, 1H), 7.41(t, 2H), 7.29(m, 17H), 4.31(d, 1H), 4.22(t, 2H), 4.00(d, 1H), 2.53(d, 3H), 2.39(d, 2H).

Step 5: Synthesis of (R)-2-amino-N-methyl-3-(tritylthio) propionamide



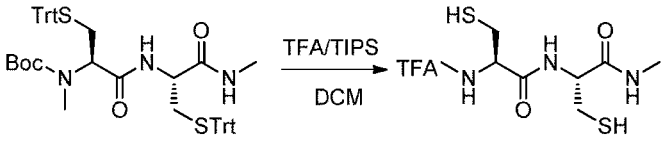
The compound (9H-fluoren-9-yl) methyl (R)-(1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate (2g, 3.34mmol) was dissolved in N,N-dimethylformamide (20ml). Piperidine (0.07ml, 0.668mmol) was added and reacted at room temperature for 4 hours. After the reaction was completed as detected by TLC, the reaction mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a yellowish white solid (879mg, yield: 69.76%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.77(d, 1H), 7.29(m, 15H), 3.08(m, 1H), 2.55(d. 3H), 2.37(dd, 1H), 2.19(dd, 1H), 1.80(s, 2H).

Step 6: Synthesis of tert-butyl methyl ((R)-1-(((R)-1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



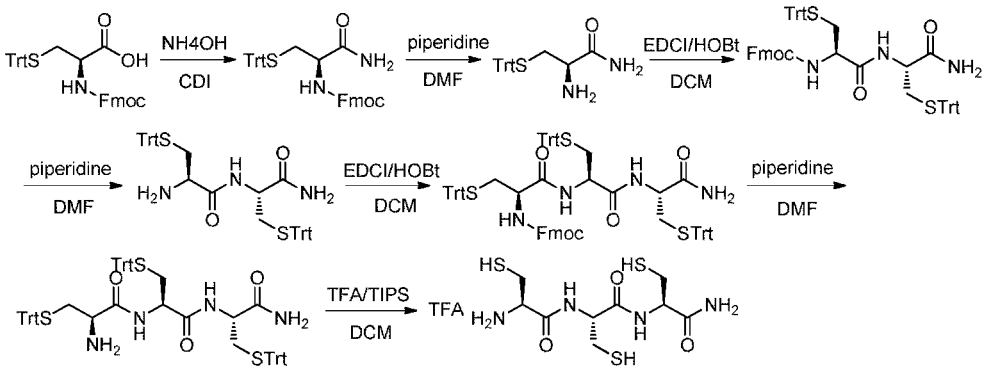
The compound N-(tert-butoxycarbonyl)-N-methyl-S-trityl-L-cysteine (150g, 0.314mmol) was dissolved in dichloromethane (5ml). 1-hydroxybenzotriazole (63.7mg, 0.471mmol) and EDCI (90.3mg, 0.471mmol) were added, and stirred at room temperature for 5min. (R)-2-amino-N-methyl-3-(tritylthio) propanamide (141.9mg, 0.377mmol) was added and stirred at room temperature for 30 minutes. After the reaction was completed as detected by TLC, the mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, then concentrated and purified with TLC (dichloromethane : methanol: 15 : 1) to obtain the product as a white solid (260mg, yield: 99.2%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.39(m, 12H), 7.22(m, 20H), 4.1(d, 1H), 3.95(s, 1H), 2.61(dd, 10H), 1.39(s, 9H).

Step 7: Synthesis of (R)-3-mercapto-N-((R)-3-mercapto-1-(methylamino)-1-oxopropan-2-yl)-2-(methylamino) propionamide trifluoroacetate:

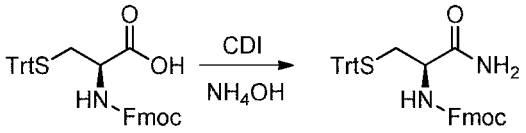


The compound tert-butyl methyl ((R)-1-(((R)-1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate (1.1g, 1.32mmol) was dissolved in dichloromethane : trifluoroacetic acid : triisopropylsilane (50 : 47 : 3 by volume) (25ml), stirred at room temperature for 5min. After the reaction was completed as detected by TLC, the mixture was concentrated, diethyl ether was added, and stirred in an ice bath. White solids were precipitated, filtered and dried to obtain the product (400mg, yield: 86.9%). ^{1}H NMR (400MHz,MeOD) δ 4.5(m, 1H), 4.07(t, 1H), 3.18-2.96(m, 3H), 2.82(m, 1H), 2.78(s, 3H), 2.74(s, 3H); HESI:252.08$[M+H]^+$.

Example 3: Synthesis of (R)-2-amino-N-((R)-1-(((R)-1-amino-3-mercapto-1-oxopropan-2-yl)amino)-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropanamide trifluoroacetate:

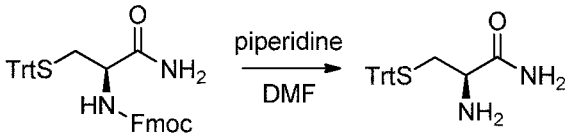


Step 1: Synthesis of (9H-fluoren-9-yl) methyl (R)-(1-amino-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



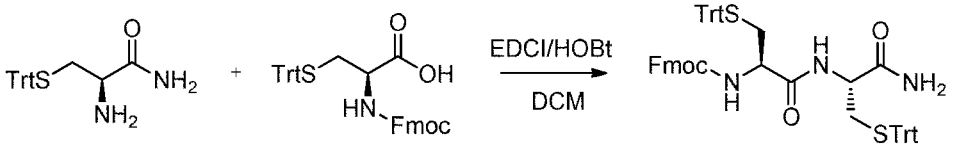
The compound (R)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tritylthio) propionic acid (10g, 17.07mmol) was dissolved in tetrahydrofuran (50ml). N,N'-carbonyldiimidazole (5.59g, 34.48mmol) was added at 0-5°C. After stirring for 2 hours under nitrogen atmosphere, aqueous ammonia (5ml, 68.28mmol) was added, and reacted at 0-5°C for 30 minutes. After the reactants were consumed, 2M hydrochloric acid (60ml) was added for quenching. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with a saturated saline, then dried with sodium sulfate, evaporated under reduced pressure to remove the solvent, thereby obtaining a crude product. After adding anhydrous methanol (20ml) and stirring at room temperature overnight, white solids were precipitated, and filtered to obtain a product in the filter residue. The methanol phase was concentrated and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain a white solid (a total of 9.3g products, yield: 93.19%). ^{1}H NMR (400MHz, DMSO-d6) δ 7.89(d, 2H), 7.74(d, 2H), 7.58(d, 1H), 7.3(m, 18H), 7.11(s, 1H), 4.24(m, 3H), 4.01(m, 1H), 2.39(m, 2H).

Step 2: Synthesis of (R)-2-amino-3-(tritylthio) propionamide:



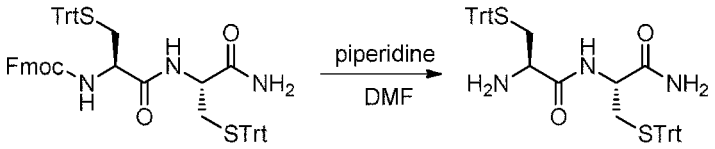
The compound (9H-fluoren-9-yl) methyl (R)-(1-amino-1-oxo-3-(tritylthio)propan-2-yl) carbamate (4g, 6.84mmol) was dissolved in N,N-dimethylformamide (20ml). Piperidine (0.14ml, 1.368mmol) was added and reacted at room temperature for 4 hours. After the reaction was completed as detected by TLC, the reaction mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, then concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a yellow oil (2.3g, yield: 92%).^{1}H NMR (400MHz, DMSO-d6) δ 7.29(m, 17H), 3.08(d, 1H), 2.33(d, 1H), 2.18(s, 1H), 1.85(s, 2H).

Step 3: Synthesis of (9H-fluoren-9-yl) methyl ((R)-1-(((R)-1-amino-1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



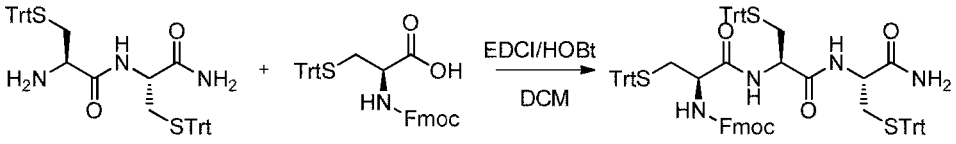
The compound (R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tritylthio) propanoic acid (1.29g, 2.21mmol) was dissolved in dichloromethane (15ml). 1-hydroxybenzotriazole (448mg, 3.315mmol) and EDCI (635mg, 3.315mmol) were added, and stirred at room temperature for 5min. (9H-fluoren-9-yl) methyl (R)-(1-amino-1-oxo-3-(tritylthio)propan-2-yl) carbamate (960mg, 2.65mmol) was added and reacted at room temperature for 30 minutes. After the reaction was completed as detected by TLC, the mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, then concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (2.05g, yield: 99.76%).^{1}H NMR (400MHz, DMSO-d6) δ 7.89(m, 3H), 7.7(m, 3H), 7.4(m, 2H), 7.24(m, 34H), 4.21(m, 4H), 4.10(m, 1H), 2.33(m, 4H).

Step 4: Synthesis of (R)-2-amino-N-((R)-1-amino-1-oxo-3-(tritylthio) propan-2-yl)-3-(tritylthio) propionamide:



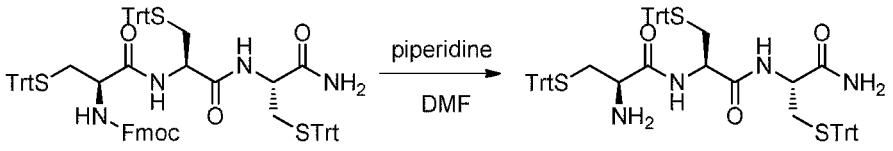
The compound (9H-fluoren-9-yl) methyl ((R)-1-(((R)-1-amino-1-oxo-3-(tritylthio)propan-2-yl) amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate (2.05g, 2.2mmol) was dissolved in N,N-dimethylformamide (20ml). Piperidine (0.04ml, 0.44mmol) was added and stirred at room temperature for 4 hours. After the reaction was completed as detected by TLC detection, the reaction mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, then concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain a white solid (600mg, yield: 38.54%).^{1}H NMR (400MHz, DMSO-d6) δ 8.1(s,1H), 7.37-7.14(m, 32H), 4.23(m, 1H), 3.17(m,1H), 2.39(dd, 1H), 2.33(d, 2H), 2.19(m, 1H).

Step 5: Synthesis of (9H-fluoren-9-yl) methyl ((4R,7R,10R)-4-carbamoyl-6,9-dioxo 1,1,1,13,13,13-hexaphenyl-7-((tritylthio)methyl) -2,12-dithia-5,8-diazatridec-10-yl) carbamate:



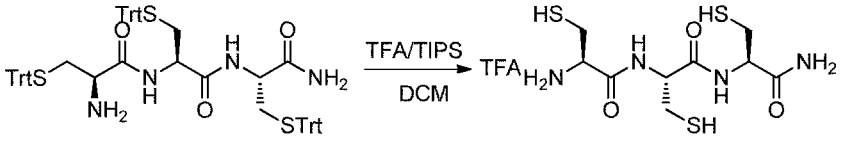
The compound (R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tritylthio) propanoic acid (688.21mg, 1.175mmol) was dissolved in dichloromethane (5ml). 1-hydroxybenzotriazole (237.95mg, 1.76mmol) and EDCI (337.39mg, 1.76mmol) were added, and stirred at room temperature for 5min. (R)-2-amino-N-((R)-1-amino-1-oxo-3-(tritylthio)propan-2-yl)-3-(tritylthio) propanamide (1g, 1.41mmol) was added and reacted at room temperature for 30 minutes. After the reaction was completed as detected by TLC, the mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, then concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (1.4g, yield: 93.33%). ^{1}H NMR (400MHz, DMSO) δ 8.03(s, 3H), 7.87(d, 2H), 7.55(d, 2H), 7.38-7.26(m, 49H), 4.81-4.70(m, 5H), 4.46(m,1H), 3.28-2.81(m, 6H).

Step 6: Synthesis of (R)-2-amino-N-((R)-1-(((R)-1-amino-1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl)-3-(tritylthio) propionamide:



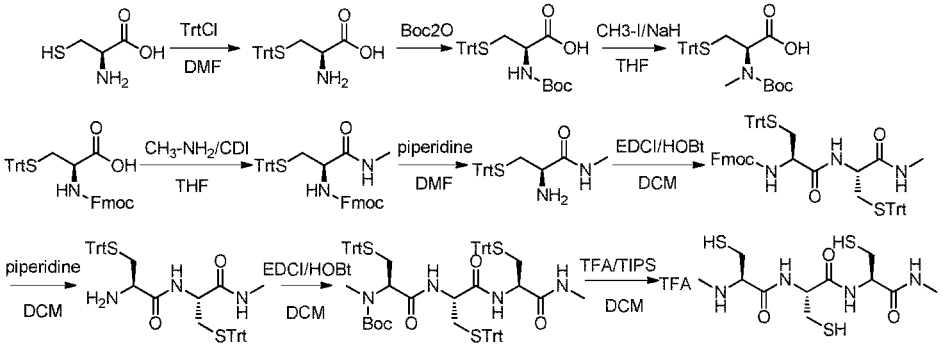
The compound (9H-fluoren-9-yl) methyl ((4R,7R,10R)-4-carbamoyl-6,9-dioxo 1,1,1,13,13,13-hexaphenyl-7-((tritylthio)methyl) -2,12-dithia-5,8-diazatridec-10-yl) carbamate (1.4g, 1.1mmol) was dissolved in N,N-dimethylformamide (10ml). Piperidine (0.02ml, 0.22mmol) was added and stirred at room temperature for 4 hours. After the reaction was completed as detected by TLC, the reaction mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, then concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain a white solid (748mg, yield: 64.48%). ^{1}H NMR (400MHz, DMSO) δ 8.03(s, 2H), 7.33-7.16(m, 45H), 4.81(m, 2H), 3.84(m, 1H), 3.26-2.78(m, 6H).

Step 7: Synthesis of (R)-2-amino-N-((R)-1-(((R)-1-amino-3-mercapto-1-oxopropan-2-yl)amino)-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropanamide trifluoroacetate:

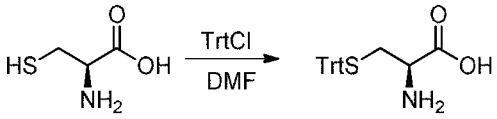


The compound (R)-2-amino-N-((R)-1-(((R)-1-amino-1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl)-3-(tritylthio) propionamide (1.2g, 1.1mmol) was dissolved in dichloromethane (10ml). Triisopropylsilane (0.56ml, 2.75mmol) and trifluoroacetic acid (2ml) were added at 0°C under a nitrogen atmosphere and stirred in an ice bath for 2 hours. After the reaction was completed as detected by TLC, the mixture was concentrated, diethyl ether was added, and stirred in the ice bath. White solids were precipitated, filtered and dried to obtain the product (62mg, yield: 17.27%). ^{1}H NMR (400MHz, DMSO-d6) δ 8.49-8.14(m, 2H), 7.50-7.16(m, 3H), 4.63-4.05(m, 3H), 2.85-2.63(m, 5H), 2.32-2.23(m, 1H).HESI:327.06[M +H]$^+$.

Example 4: Synthesis of (R)-3-mercapto-N-((R)-3-mercapto-1-(((R)-3-mercapto-1-(methylamino)-1-oxopropan-2-yl)amino)-1-oxopropan -2-yl)-2-(methylamino) propanamide trifluoroacetate:

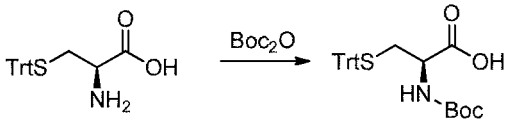


Step 1: Synthesis of S-trityl-L-cysteine:



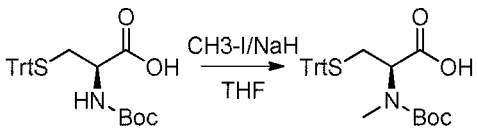
The compound L-cysteine hydrochloride (10g, 63.45mmol) was dissolved in N,N-dimethylformamide (120ml). Triphenylchloromethane (19.46g, 69.795mmol) was added, heated to 60-65°C, and reacted for 8h. After the reaction was completed as detected by TLC, the reaction was cooled to room temperature, and 10% sodium acetate solution (300ml) was added. White solids were then precipitated and filtered. Filter residue was washed with pure water (300ml), then washed with acetone (200ml), and dried to obtain the product as a white solid (17.56g, yield: 76.15%).^{1}H NMR (400MHz, DMSO) δ 7.28(m, 18H), 2.92(dd, 1H), 2.59(dd, 1H), 2.41(dd, 1H).

Step 2: Synthesis of N-(tert-butoxycarbonyl)-S-trityl-L-cysteine:



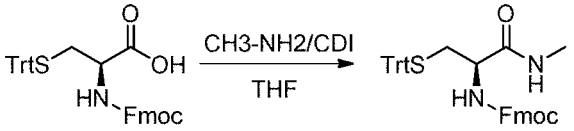
The compound S-trityl-L-cysteine (5g, 13.76mmol) was dissolved in a mixture of dioxane (40ml), water (20ml) and 1M sodium hydroxide solution (14ml), and stirred in an ice bath. Boc-anhydride (3.5ml, 15.14mmol) was added, then reacted until the mixture was naturally warmed to room temperature, and stirred for 8 hours. After the reaction was completed as detected by TLC, the reaction mixture was concentrated to 20-25ml. Ethyl acetate was added, and the sodium bisulfate solution was added dropwise under the ice bath while stirring. After pH was adjusted to 2-3, ethyl acetate was used for extraction. The organic layer was washed with a saturated saline, then dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (5.5g, yield :86.21%).^{1}H NMR (400MHz, DMSO-d6) δ 7.26(m, 16H), 3.78(m, 1H), 2.51(m, 1H), 2.36(dd, 1H), 1.4(s, 9H).

Step 3: Synthesis of N-(tert-butoxycarbonyl)-N-methyl-S-trityl-L-cysteine:



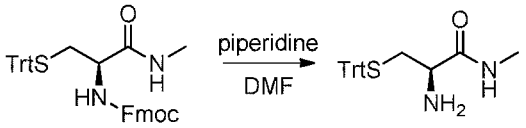
The compound N-(tert-butoxycarbonyl)-S-trityl-L-cysteine (2.1g, 4.53mmol) was dissolved in anhydrous tetrahydrofuran (6ml). Sodium hydride (436mg, 10.9mmol) was dissolved in anhydrous tetrahydrofuran (14ml). The solution of amino acid in tetrahydrofuran was added dropwise to the solution of sodium hydride in tetrahydrofuran in an ice bath. Then, methyl iodide (0.93ml, 14.95mmol) was slowly added dropwise and stirred overnight. After the reaction was completed as detected by TLC, phosphate buffer at pH of 7 was added for quenching. pH was adjusted to 6-7 with a saturated ammonium chloride solution, and was extracted with ethyl acetate. The organic layer was washed with a saturated saline, then dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (1.3g, yield: 60.19%).^{1}H NMR (400MHz, DMSO-d6) δ 7.3(m, 15H), 3.75(s, 1H), 2.8(s, 1H), 2.66(d, 4H), 1.4(d, 9H).

Step 4: Synthesis of (9H-fluoren-9-yl) methyl (R)-(1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



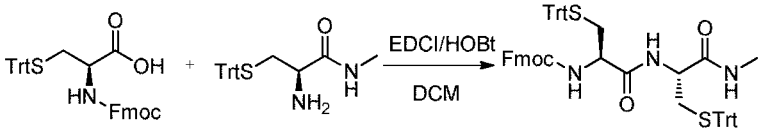
The compound (R)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tritylthio) propionic acid (10g, 17.07mmol) was dissolved in tetrahydrofuran (50ml). N,N'-carbonyldiimidazole (5.59g, 34.48mmol) was added at 0-5°C. After stirring for 2 hours under nitrogen atmosphere, methylamine (3.03ml, 68.28mmol) was added, and reacted at 0-5°C for 2 hours. After the reactants were consumed, 2M hydrochloric acid (60ml) was added for quenching, and the reaction mixture was extracted with dichloromethane. The organic layer was washed with a saturated saline, then dried with sodium sulfate and then concentrated to obtain a crude product. Methanol (20ml) was added and stirred overnight at room temperature. White solids were precipitated, and filtered to obtain the product in filter residue. The methanol phase was concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain a white solid (9.44g, yield: 92.37%).^{1}H NMR (400MHz, DMSO-d6) δ 7.89(d, 2H), 7.81(d, 1H), 7.74(d, 2H), 7.66(d, 1H), 7.41(t, 2H), 7.29(m, 17H), 4.31(d, 1H), 4.22(t, 2H), 4.00(d, 1H), 2.53(d, 3H), 2.39(d, 2H).

Step 5: Synthesis of (R)-2-amino-N-methyl-3-(tritylthio) propionamide:



The compound (9H-fluoren-9-yl) methyl (R)-(1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate (2g, 3.34mmol) was dissolved in N,N-dimethylformamide (20ml). Piperidine (0.07ml, 0.668mmol) was added and reacted at room temperature for 4 hours. After the reaction was completed as detected by TLC, the reaction mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a yellowish white solid (879mg, yield: 69.76%). ^{1}H NMR (400MHz, DMSO-d6) δ 7.77(d, 1H), 7.29(m, 15H), 3.08(m, 1H), 2.55(d, 3H), 2.37(m, 1H), 2.19(m, 1H), 1.80(s, 2H).

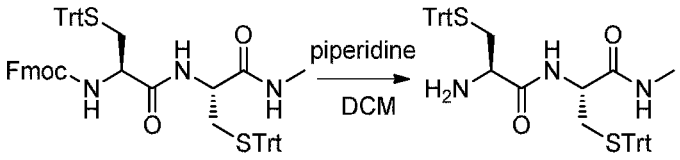
Step 6: Synthesis of (9H-fluoren-9-yl) methyl ((R)-1-(((R)-1-(methylamino) -1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



The compound (R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tritylthio) propanoic acid (100mg, 0.17mmol) was dissolved in dichloromethane (5ml). 1-hydroxybenzotriazole (34.5mg, 0.255 mmol) and EDCI (48.9mg, 0.255mmol) were added, and stirred at room temperature for 5min. (R)-2-amino-N-methyl-3-(tritylthio) propanamide (76.8mg, 0.204mmol) was added and reacted at room temperature for 30 minutes. After the reaction was completed as detected by TLC, the mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, then concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (160mg, yield: 99.68%).^{1}H NMR (400MHz, DMSO-d6) δ 7.89(d, 2H), 7.71(m, 4H), 7.40(m, 2H), 7.38-7.25(m, 30H), 4.25(m, 4H), 4.01(m, 1H), 2.50-2.33(m, 7H).

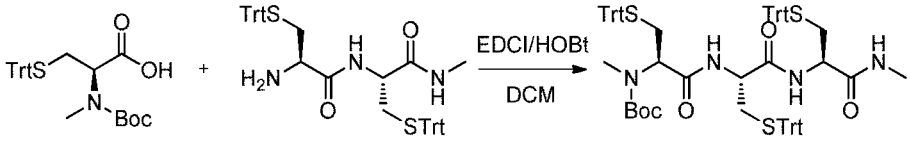
Step 7: Synthesis of (R)-2-amino-N-((R)-1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl)-3-(tritylthio)

propionamide:



The compound (9H-fluoren-9-yl) methyl ((R)-1-(((R)-1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl) amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate (3.6g, 3.8mmol) was dissolved in N,N-dimethylformamide (15ml). Piperidine (0.07ml, 0.76mmol) was added and reacted at room temperature for 4 hours. After the reaction was completed as detected by TLC detection, the reaction mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, then concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (1.3g, yield: 47.44%).^{1}H NMR (400MHz, DMSO-d6) δ 8.12(s, 1H), 7.83(d, 1H), 7.27(m, 30H), 4.25(s, 1H), 3.29(m, 2H), 3.20(s, 1H), 2.65-2.23(m, 5H).

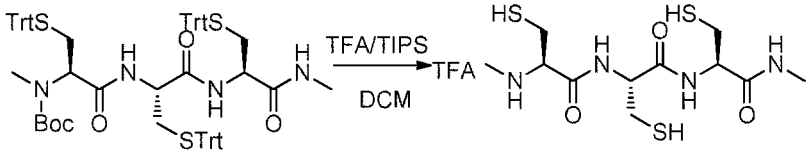
Step 8: Synthesis of tert-butyl methyl((4R,7R,10R)-3,6,9-trioxo-13,13,13-triphenyl-4,7-bis((tritylthio)methyl)-12-thia-2,5,8-triazatridec-10-yl) carbamate:



The compound N-(tert-butoxycarbonyl)-N-methyl-S-trityl-L-cysteine (509mg, 1.07mmol) was dissolved in dichloromethane (10ml). 1-hydroxybenzotriazole (218mg, 1.61mmol) and EDCI (309mg, 1.61mmol) were added, and stirred at room temperature for 5min.

(R)-2-amino-N-((R)-1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl)-3-(tritylthio) propanamide (924mg, 1.28mmol) was added and reacted at room temperature for 30 minutes. After the reaction was completed as detected by TLC, the mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (985mg, yield: 77.93%).^{1}H NMR (400MHz, DMSO-d6) δ 8.11(d, 1H), 7.73(d, 2H), 7.32-7.21(m, 45H), 4.25(m, 3H), 2.62(m, 1H), 2.49(m, 6H) 2.47-2.23(m, 5H), 1.35-1.21(d, 9H).

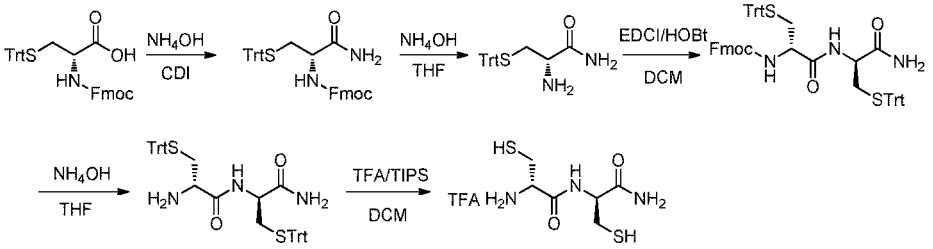
Step 9: Synthesis of (R)-3-mercapto-N-((R)-3-mercapto-1-(((R)-3-mercapto-1-(methylamino)-1-oxopropan-2-yl)amino)-1-oxopropan -2-yl)-2-(methylamino) propanamide trifluoroacetate:



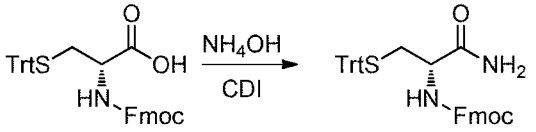
The compound tert-butyl methyl((4R,7R,10R)-3,6,9-trioxo-13,13,13-triphenyl-4,7-bis((tritylthio)methyl)-12-thia-2,5,8-triazatridec-10-yl) carbamate (1.5g, 1.27mmol) was dissolved in dichloromethane : trifluoroacetic acid : triisopropylsilane (50 : 47 : 3 by volume) (40ml), stirred at room temperature for 5min. After the reaction was completed as detected by TLC,

the mixture was concentrated, diethyl ether was added, and stirred in an ice bath. White solids were precipitated, filtered and dried to obtain the product (446mg, yield: 77.77%). ^{1}HNMR(400MHz, MeOD)δ 4.54(m, 1H), 4.42(m, 1H), 4.05(t, J=5.2Hz, 1H), 3.13(m, 1H),2.99(m, 2H), 2.85(m, 2H), 2.79(m, 1H), 2.73(s, 3H), 2.70(s, 3H).MS: $C_{11}H_{22}N_4O_3S_3$, the calculated value is 354.51, and the measured value is 355.1, $[M+H]^+$.

Example 5: Synthesis of (S)-2-amino-N-((S)-1-amino-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropanamide trifluoroacetate:

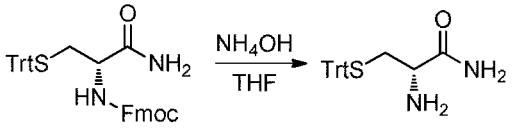


Step 1: Synthesis of (9H-fluoren-9-yl) methyl (S)-(1-amino-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



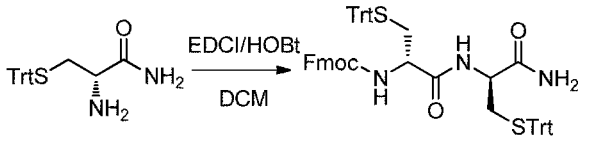
CDI (1.64g, 10.1mmol) was dissolved in a double-neck flask of DCM (50ml) and stirred at room temperature for 2h under N_2 protective conditions. The compound N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-trityl-D-cysteine (2.93g, 5mmol) was added to a reaction flask and stirred for 15min. After the completion of the reaction, a saturated saline was added for washing (20ml×3). Anhydrous Na_2SO_4 was used to dry the organic phase, and the reaction liquid was concentrated by distillation under reduced pressure. After adding anhydrous methanol (50ml) and stirring for about 1h, the product was precipitated and filtered, and the filter cake was repeatedly washed twice to obtain the white crystalline powder (2.2g, yield: 75.30%). ^{1}H NMR(400MHz, $CDCl_3$) δ 7.73(m, 2H), 7.54 (d,J=7.6 Hz, 2H), 7.37(m, 8H), 5.69(s, 1H), 5.25(s, 1H), 4.93(d, J=5.6 Hz 1H), 4.43 (m, 2H), 4.17(t, J=6.4 Hz, 1H), 3.80(s, 1H)2.64(m, 2H).

Step 2: Synthesis of (S)-2-amino-3-(tritylthio) propionamide:



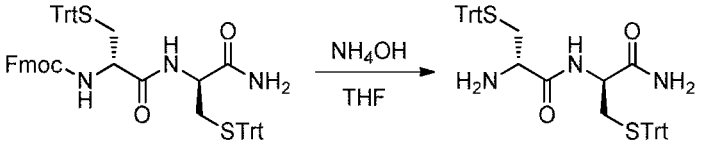
The compound (9H-fluoren-9-yl) methyl (S)-(1-amino-1-oxo-3-(tritylthio)propan-2-yl) carbamate (2.2g, 3.76mmol) was dissolved in a single-neck flask of THF (50ml), NH_4OH (25%, 11.6ml) was added, and stirred at room temperature overnight. After completion of the reaction, the mixture was washed with a saturated saline (30×3ml) and extracted with EA (30ml). The organic phases were combined and dried with anhydrous Na_2SO_4. After concentrating by distillation under reduced pressure, the crude product was separated and purified by silica gel column to obtain a colorless oily product (1.20g, yield: 88.24%). ^{1}H NMR(400MHz, $CDCl_3$) δ 7.44(m, 6H), 7.24(m, 9H), 6.80(s, 1H), 5.46(s, 1H), 2.98(m, 1H), 2.70(m, 1H), 2.55(m, 1H).

Step 3: Synthesis of (9H-fluoren-9-yl) methyl ((S)-1-(((S)-1-amino-1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



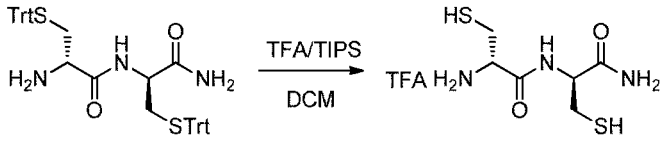
The compound N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-trityl-D-cysteine (10.33g, 17.64mmol) was dissolved in a single-neck flask of DCM (200ml), EDCI (5.10g, 26.46mmol) and HOBT (3.58g, 26.46mmol) were added, the compound (S)-2-amino-3-(tritylthio)propanamide (7.0g, 19.40mmol) was added, and stirred at room temperature for 20min. After completion of the reaction, the mixture was washed with a saturated saline (100×3ml) and extracted with DCM (20ml). The organic phase was dried with anhydrous Na_2SO_4. After concentrating by distillation under reduced pressure, the crude product was purified by silica gel column chromatography to obtain a colorless oily product (15.0g, yield: 91.46%). ^{1}H NMR(400MHz, $CDCl_3$) δ 7.88(m, 3H), 7.70(m, 3H), 7.40(m, 2H), 7.24(m, 30H), 4.25(m, 3H), 2.35(m, 3H).

Step 4: Synthesis of (S)-2-amino-N-((S)-1-amino-1-oxo-3-(tritylthio)propan-2-yl)-3-(tritylthio) propionamide:



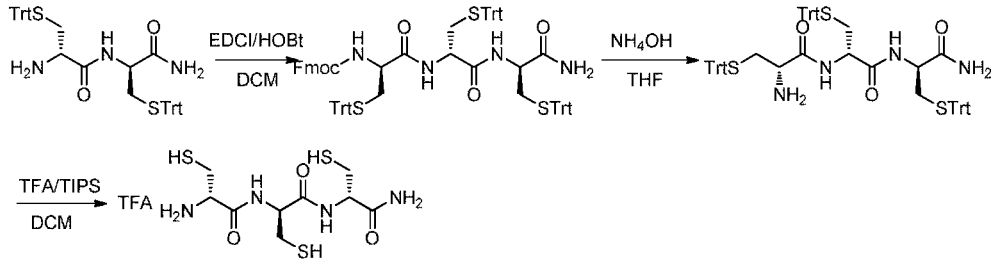
The compound (9H-fluoren-9-yl) methyl ((S)-1-(((S)-1-amino-1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate (3.5g, 3.76mmol) was dissolved in a single-neck flask of THF (30ml), NH_4OH (25%, 11.60ml) was added, and stirred at room temperature overnight. After completion of the reaction, the mixture was washed with a saturated saline (30×3ml) and extracted with EA (30ml). The organic phases were combined and dried with anhydrous Na_2SO_4. After concentrating by distillation under reduced pressure, the crude product was separated and purified by silica gel column to obtain a colorless oily product (1.64g, yield: 61.65%).^{1}H NMR(400MHz, $CDCl_3$) δ 7.90(m, 12H), 7.23(m, 18H), 6.07(s, 1H), 5.15(s, 1H), 3.92(m, 1H), 2.66(m, 2H), 2.94(m, 2H).

Step 5: Synthesis of (S)-2-amino-N-((S)-1-amino-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropanamide trifluoroacetate:

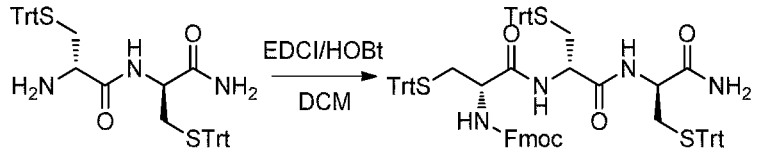


The compound (S)-2-amino-N-((S)-1-amino-1-oxo-3-(tritylthio)propan-2-yl)-3-(tritylthio) propionamide (2.8g, 3.96mmol) was dissolved in a single-neck flask of DCM (30ml), TFA (18g, 158.4mmol) and triethyl silicane (2.76g, 23.8mmol) were added, and stirred at room temperature for about 30min. After the completion of reaction, white solids appeared in the reaction liquid concentrated by distillation under reduced pressure, and anhydrous diethyl ether (50ml×3) was added for stirring and washing, and then filtered to obtain a white-like solid (710mg, yield: 80%). ^{1}HNMR(400MHz, MeOD) δ 4.50(m, 1H), 4.10(t, J=5.6Hz, 1H), 3.28(m, 2H), 2.85(m, 2H).MS: $C_6H_{13}N_3O_2S_2$, the calculated value was 223.04, and the measured value was 244.1, $[M+H]^+$.

Example 6: Synthesis of (S)-2-amino-N-((S)-1-(((S)-1-amino-3-mercapto-1-oxopropan-2-yl)amino)-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropionamide:

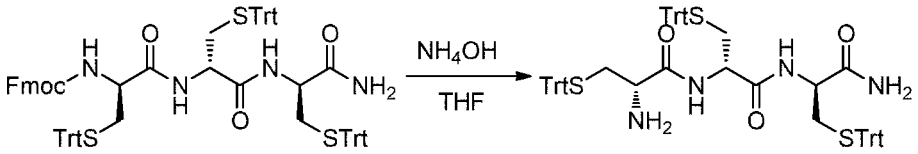


Step 1: Synthesis of (9H-fluoren-9-yl) methyl ((4S,7S,10S)-4-carbamoyl-6,9-dioxo -1,1,1,13,13,13-hexaphenyl-7-((tritylthio)methyl) -2,12-dithia-5,8-diazatridec-10-yl) carbamate:



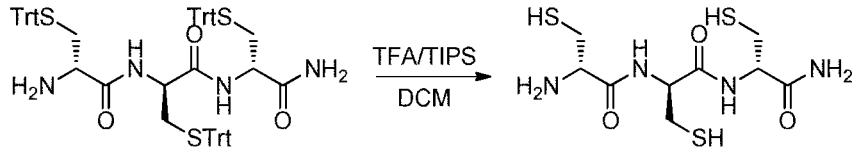
The compound N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-trityl-D-cysteine (1.24g, 2.12mmol) was dissolved in a single-neck flask of DCM (50ml), EDCI (609.6mg, 3.18mmol) and HOBT (429.94mg, 3.18mmol) were added, the compound (S)-2-amino-N-((S)-1-amino-1-oxo-3-(tritylthio)propan-2-yl)-3-(tritylthio) propanamide (1.65g, 2.33mmol) was added, and stirred at room temperature for 20min. DCM (20ml) was added for extraction and saturated saline (20ml×3) for washing. The organic phase was dried with anhydrous Na_2SO_4 and then concentrated. The crude product was purified by silica gel column chromatography to obtain a colorless oily product (2.57g, yield: 92.5%). ^{1}H NMR(400MHz, $CDCl_3$) δ 7.78(t, J=8.6Hz, 2H), 7.48(m, 2H), 7.37(m, 20H), 7.16(m, 29H), 6.52(d, J=8Hz, 1H), 6.36(s, 1H), 6.22(d, J=5.6Hz, 1H), 4.98(s, 1H), 4.82(d, J=5.2Hz,1H), 4.43(m, 1H), 4.22(m, 1H), 4.10(m, 2H), 3.91(m, 2H), 3.52(m, 1H), 2.61(m, 5H).

Step 2: Synthesis of (S)-2-amino-N-((S)-1-(((S)-1-amino-1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl)-3-(tritylthio) propionamide:



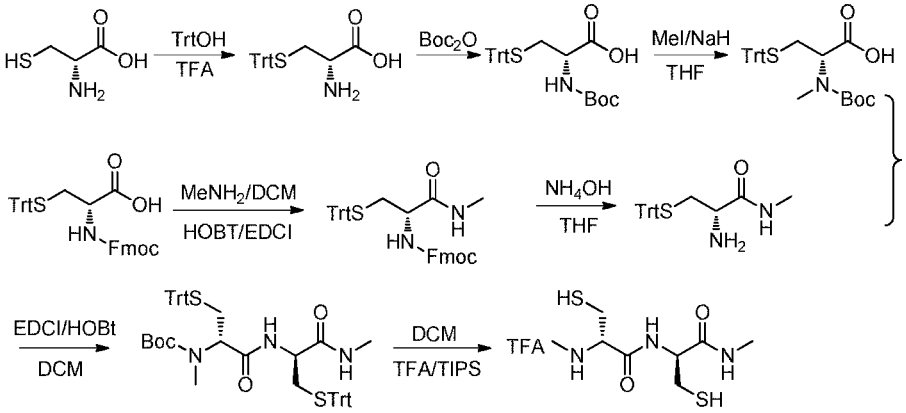
The compound (9H-fluoren-9-yl) methyl ((4S,7S,10S)-4-carbamoyl-6,9-dioxo -1,1,1,13,13,13-hexaphenyl-7-((tritylthio)methyl) -2,12-dithia-5,8-diazatridec-10-yl) carbamate (1.0g, 0.78mmol) was dissolved in a single-neck flask of THF (20ml), NH_4OH (25%, 2.40ml) was added, and stirred at room temperature overnight. After completion of the reaction, the mixture was washed with a saturated saline (10×3ml) and extracted with EA (20ml). The organic phases were combined and dried with anhydrous Na_2SO_4. After concentrating by distillation under reduced pressure, the crude product was separated and purified by silica gel column to obtain a colorless oily product (583.37mg, yield: 71.0%).^{1}H NMR(400MHz, $CDCl_3$) δ 7.22(m, 45H)6.52(d, J=8Hz, 1H), 6.36(s, 1H), 6.22(d, J=5.6Hz, 1H), 4.99(s, 1H), 4.82(d, J=5.2Hz, 1H), 4.22(m, 1H), 3.90(m, 2H), 3.52(m, 1H), 2.60(m, 5H).

Step 3: Synthesis of (S)-2-amino-N-((S)-1-(((S)-1-amino-3-mercapto-1-oxopropan-2-yl)amino)-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropionamide:

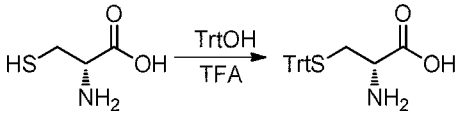


The compound (S)-2-amino-N-((S)-1-(((S)-1-amino-1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl)-3-(tritylthio) propionamide (1.20g, 1.14mmol) was dissolved in a single-neck flask of DCM (30ml), TFA (5.20g, 45.56mmol) and triethyl silicane (795.36mg, 6.84mmol) were added, and stirred at room temperature for about 30min. After the completion of reaction, white solids appeared in the reaction liquid concentrated by distillation under reduced pressure, and anhydrous diethyl ether (50ml) was added for stirring and washing, and then filtered and repeatedly washed with anhydrous diethyl ether 3 times to obtain the white-like solids (192.78mg, yield: 51.80%). ^{1}HNMR (400MHz, MeOD) δ 4.54 (m, 1H), 4.42 (m, 1H), 4.05 (t, J=5.2Hz, 1H), 3.13 (m, 1H), 2.99 (m, 2H), 2.85 (m, 2H), 2.79 (m, 1H). MS: $C_9H_{18}N_4O_3S_3$, the calculated value was 326.05, and the measured value was 327.1, $[M+H]^+$.

Example 7: Synthesis of (S)-3-mercapto-N-((S)-3-mercapto-1-(methylamino)-1-oxopropan-2-yl)-2-(methylamino) propionamide:

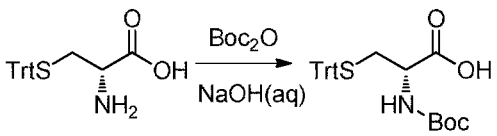


Step 1: Synthesis of S-trityl-D-cysteine:



The compound D-cysteine (242.30mg, 2.0mmol) was added to a single-neck flask, TFA (4ml) was added, and stirred at room temperature. Triphenylmethanol (520.68mg, 2.0mmol) was added, stirred at room temperature for 2h, then cooled to 0°C. Anhydrous diethyl ether (30ml) was added, and a 4 N aqueous NaOH solution was added dropwise with stirring to a pH of about 4-5. A 10% saturated aqueous solution of sodium acetate was added to a pH of about 5-6 and filtered. The filter cake was washed with anhydrous diethyl ether (30ml×2) to obtain a white powdery product (566.4mg, yield: 77.90%). ^{1}H NMR(400MHz, DMSO-d6) δ 4.45(m, 1H), 7.21(m, 3H), 2.90(m, 1H), 2.52(m, 1H), 2.26 (t, J= 10.8 Hz, 1H), 1.82(s, 1H).

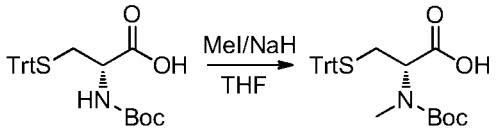
Step 2: Synthesis of N-(tert-butoxycarbonyl)-S-trityl-D-cysteine:



The compound S-trityl-D-cysteine (3.63g, 10mmol) was added to a single-neck flask with 2N NaOH (aq)

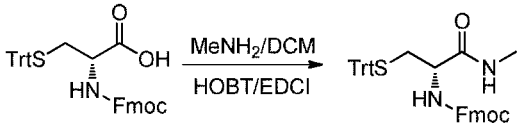
(70ml), Boc_2O (3.43g, 15.7mmol) was added, and stirred at room temperature overnight. The reaction liquid was acidified with HCl (aq) to a pH value of about 2, extracted with DCM (20ml×3), and washed with a saturated saline (20ml×3). The organic phases were combined, dried with anhydrous Na_2SO_4, concentrated by distillation under reduced pressure and purified by flash column chromatography to obtain a colorless oily product (4.10g, yield: 88.40%). ^1H NMR(400MHz, $CDCl_3$) δ 7.39 (m, 6H), 7.25(m, 9H), 4.9(d, J= 7.6 Hz, 1H), 4.10(m, 1H),2.65(d, J= 4.4 Hz, 2H), 1.42(s, 9H).

Step 3: Synthesis of N-(tert-butoxycarbonyl)-N-methyl-S-trityl-D-cysteine:



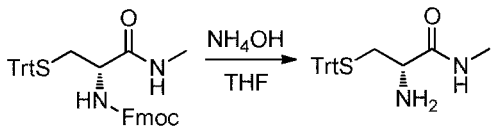
Under the condition of N_2 protection, NaH (60%, 1.035g, 25.88mmol) was dissolved in a three-neck flask of anhydrous THF (20ml), and the solution (20ml) of the compound N-(tert-butoxycarbonyl)-S-trityl-D-cysteine (4.0g, 8.63mmol) in anhydrous THF was added dropwise at 0°C. After stirring for 5min, iodomethane (9.8g, 69.03mmol) was added dropwise, and stirred at 0°C for 1h and then stirred at room temperature overnight. After completion of the reaction, a phosphate buffer solution (50ml) with pH=7 was added for quenching reaction, and EA (20ml) was added for extraction. The mixture was washed with a saturated saline (20ml×3). The organic phases were combined and dried with anhydrous Na_2SO_4. The crude product was separated and purified by silica gel column chromatography to obtain a colorless oily product (3.52g, yield: 85.44%). ^{1}HNMR (400MHz, $CDCl_3$) δ 7.41 (m, 6H), 7.25 (m, 9H), 3.85 (m, 0.5H), 2.63 (m, 0.5H), 2.79 (m, 1H), 2.65 (d, J= 14 Hz, 4H), 1.34 (d, J=10Hz, 9H).

Step 4: Synthesis of (9H-fluoren-9-yl) methyl (S)-(1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate



The compound N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-trityl-D-cysteine (11.75g, 20mmol) was dissolved in a single-neck flask of DCM (200ml), and EDCI (5.75g, 30mmol) and HOBT (4.05g, 30mmol) were added. The THF solution of methylamine (2.0mol/L, 15ml) was added dropwise, stirred at room temperature for 20min, extracted with DCM (50ml), washed with a saturated saline (100×3ml), and dried with anhydrous Na_2SO_4. After concentrating by distillation under reduced pressure, anhydrous methanol (200ml) was added and stirred at room temperature for about 1h, and filtered to obtain white solids, which were washed repeatedly three times with anhydrous methanol to obtain a white solid (10.84g, yield: 90.64%). ^1H NMR(400MHz, $CDCl_3$) δ 7.73(t, J=6.6Hz, 2H), 7.54(d, J=6.8Hz, 2H),7.36(m, 8H), 7.23(m, 11H), 5.73(s, 1H), 4.94(d, J=6.8Hz, 1H), 4.39(d, J=6.4Hz, 2H), 4.16(t, J=6.6 Hz, 1H), 3.78(m, 1H), 2.69(d, J=4.4Hz, 3H), 2.62(m, 2H).

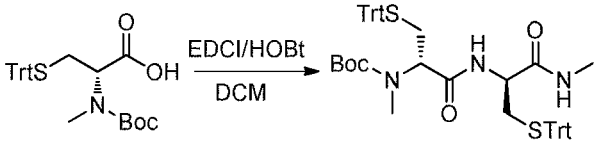
Step 5: Synthesis of (S)-2-amino-N-methyl-3-(tritylthio) propionamide:



The compound (9H-fluoren-9-yl) methyl (S)-(1-(methylamino) -1-oxo-3-(tritylthio)propan-2-yl) carbamate (10.84g, 18.10mmol) was dissolved in a single-neck flask of THF (100ml), NH_4OH (25%, 28ml) was added, and

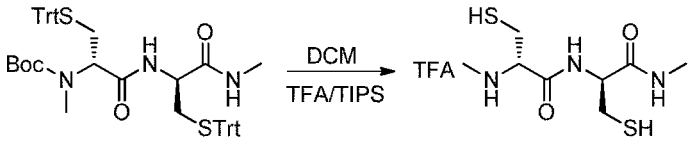
stirred at room temperature overnight.After completion of the reaction, the mixture was washed with a saturated saline (30×3ml) and extracted with EA (30ml). The organic phases were combined and dried with anhydrous Na_2SO_4. After concentrating by distillation under reduced pressure, PE(100ml) was added and stirred at room temperature for about 1h, and filtered to obtain white-like crystals, which were washed repeatedly 3 times with PE to obtain a white solid (6.8g, yield: 99.7%). ^1H NMR(400MHz, $CDCl_3$) δ 7.42(m, 6H), 7.23(m, 9H), 6.96(s, 1H), 3.00(m, 1H), 2.74(m, 1H), 2.70(d, J=4.8Hz, 3H), 2.50(m, 1H).

Step 6: Synthesis of tert-butyl methyl ((S)-1-(((S)-1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



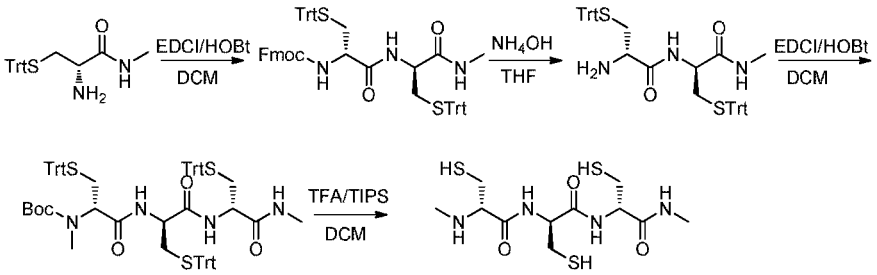
The compound N-(tert-butoxycarbonyl)-N-methyl-S-trityl-D-cysteine (3.52g, 7.37mmol) was dissolved in a single-neck flask of DCM (80ml), EDCI (2.12g, 11.1mmol) and HOBT (1.49g, 11.1mmol) were added, and the compound (S)-2-amino-N-methyl-3-(tritylthio) propanamide (3.05g, 8.1mmol) was added and stirred at room temperature for 20min. After completion of the reaction, the mixture was washed with a saturated saline (30ml×3) and extracted with DCM (30ml). The organic phase was dried with anhydrous Na_2SO_4. After concentrating by distillation under reduced pressure, the crude product was purified by silica gel column chromatography to obtain a colorless oily product (5.58g, yield: 90.58%). ^{1}HNMR (400MHz, $CDCl_3$) δ 7.32 (m, 30H), 6.30 (s, 1H), 6.16 (s, 1H), 3.94 (m, 2H), 2.70 (m, 1H), 2.63 (s, 3H), 2.57 (s, 3H), 2.50 (m, 2H), 2.39 (m, 1H),1.38 (s, 9H).

Step 7: Synthesis of (S)-3-mercapto-N-((S)-3-mercapto-1-(methylamino)-1-oxopropan-2-yl)-2-(methylamino) propionamide:

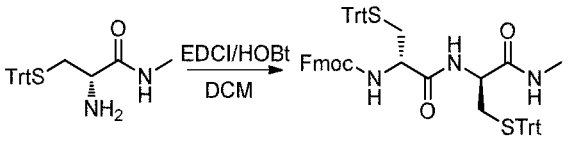


The compound tert-butyl methyl ((S)-1-(((S)-1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate (745.7mg, 0.89mmol) was dissolved in a single-neck flask of DCM (10ml), TFA (5.10g, 44.6mmol) and triethyl silicane (622.33mg, 5.352mmol) were added, and stirred at room temperature for about 30min. After the completion of reaction, white solids appeared in the reaction liquid concentrated by distillation under reduced pressure, and anhydrous diethyl ether (20ml) was added for stirring and washing, and then filtered and repeatedly washed 3 times to obtain a white powdery solid (215.70mg, yield: 96.21%). ^{1}HNMR (400MHz, MeOD) δ 4.45 (m, 1H), 4.05 (t, J=5.4Hz, 1H), 3.29 (m, 2H), 3.10 (m, 2H), 2.73 (s, 3H), 2.70 (s, 3H). MS: $C_8H_{17}N_3O_2S_2$, the calculated value was 251.08, and the measured value was 252.1, $[M+H]^+$.

Example 8: Synthesis of (S)-3-mercapto-N-((S)-3-mercapto-1-(((S)-3-mercapto-1-(methylamino)-1-oxopropan-2-yl)amino)-1-oxopropan-2-yl)-2-(methylamino) propanamide:

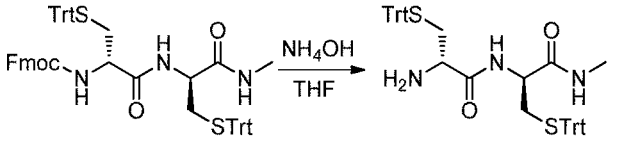


Step 1: Synthesis of (9H-fluoren-9-yl) methyl ((S)-1-(((S)-1-(methylamino) -1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



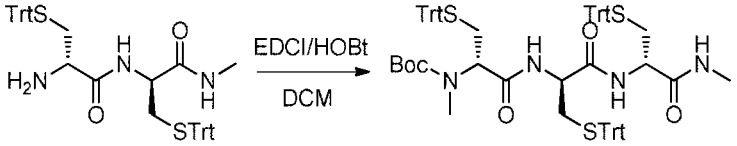
The compound N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-trityl-D-cysteine (5.63g, 9.6mmol) was dissolved in a single-neck flask of DCM (150ml), EDCI (2.76g, 14.4mmol) and HOBT (1.95g, 14.4mmol) were added, and the compound (S)-2-amino-N-methyl-3-(tritylthio)propanamide (3.80mg, 10.1mmol) was added, and stirred at room temperature for 20min. After the completion of the reaction, a saturated saline was added for washing (30ml×3) and extracted with DCM (30ml). Anhydrous Na_2SO_4 was used to dry organic phase, and the reaction liquid was concentrated by distillation under reduced pressure to form solid. PE (50ml×2) was added and stirred at room temperature for 20mim for filtration. The filter cake was stirred by adding anhydrous methanol (50ml×3) at room temperature for 20min and filtered to obtain white crystalline powder (8.42g, yield :92.8%) which was directly used for the next step.

Step 2: Synthesis of (S)-2-amino-N-((S)-1-(methylamino) -1-oxo-3-(tritylthio)propan-2-yl)-3-(tritylthio) propionamide:



The compound (9H-fluoren-9-yl) methyl ((S)-1-(((S)-1-(methylamino) -1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate (8.42g, 8.92mmol) was dissolved in a single-neck flask of THF (100ml), NH_4OH (25%, 27.5ml) was added, and stirred at room temperature overnight.After completion of the reaction, the mixture was washed with a saturated saline (30×3ml) and extracted with EA (30ml). The organic phases were combined and dried with anhydrous Na_2SO_4. After concentrating by distillation under reduced pressure, PE (50ml×2) was added and stirred at room temperature for about 1h. After filtration, white solids (5.95g, yield: 92.4%) were obtained and directly used for the next step.

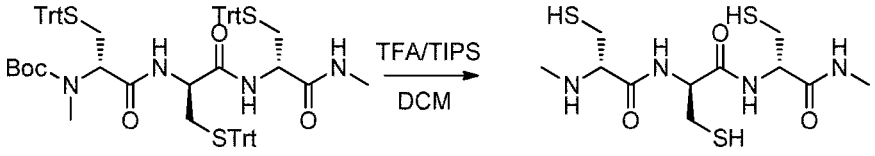
Step 3: Synthesis of tert-butyl methyl((4S,7S,10S)-3,6,9-trioxo-13,13,13-triphenyl-4,7-bis((tritylthio)methyl)-12-thia-2,5,8-triazatridec-10-yl) carbamate:



The compound N-(tert-butoxycarbonyl)-N-methyl-S-trityl-D-cysteine (1.97g, 4.12mmol) was dissolved in a

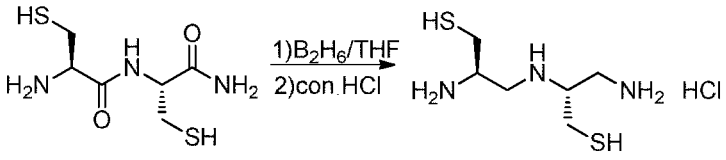
single-neck flask of DCM (100ml), EDCI (1.19g, 6.19mmol) and HOBT (836.9mg, 6.19mmol) were added, and the compound (S)-2-amino-N-((S)-1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl)-3-(tritylthio)propionamide (3.28g, 4.54mmol) was added and stirred at room temperature for 20min. After completion of the reaction, the mixture was washed with a saturated saline (30ml×3) and extracted with DCM (20ml). The organic phase was dried with anhydrous Na_2SO_4. After concentrating by distillation under reduced pressure, the crude product was purified by silica gel column chromatography to obtain a white-like oily product (2.12g, yield: 43.2%). ^1H NMR(400MHz, $CDCl_3$) δ 7.28(m, 45H), 6.64(s, 1H), 5.75(s, 1H), 4.18 (s,2H), 3.80(m, 1H), 3.20(m, 1H), 2.79(m, 1H), 2.65(m, 1H), 2.63(m, 4H), 2.52(m, 1H), 2.36(m, 4H), 2.24(m, 1H), 1.37(s, 9H).

Step 4: Synthesis of (S)-3-mercapto-N-((S)-3-mercapto-1-(((S)-3-mercapto-1-(methylamino)-1-oxopropan-2-yl)amino)-1-oxopropan-2-yl)-2-(methylamino) propanamide:



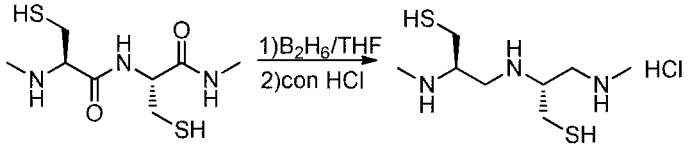
The compound methyl((4S,7S,10S)-3,6,9-trioxo-13,13,13-triphenyl-4,7-bis((tritylthio)methyl)-12-thia-2,5,8-triazatridec-10-yl) carbamate (1.0g, 0.85mmol) was dissolved in a single-neck flask of DCM (40ml), TFA (3.86g, 33.85mmol) and triethylsilane (593mg, 5.1mmol) were added, and stirred at room temperature for about 30min. After the completion of reaction, white solids appeared in the reaction liquid concentrated by distillation under reduced pressure, and anhydrous diethyl ether (50ml×3) was added for stirring and washing, and then filtered to obtain a white solid powder (290mg, yield: 96.67%).^{1}HNMR(400MHz, MeOD)δ 4.54(m, 1H), 4.42(m, 1H), 4.05(t, J=5.2Hz, 1H), 3.13(m, 1H),2.99(m, 2H), 2.85(m, 2H), 2.79(m, 1H), 2.73(s, 3H), 2.70(s, 3H).MS: $C_{11}H_{22}N_4O_3S_3$, the calculated value was 354.09, and the measured value was 355.1, $[M+H]^+$.

Example 9: Synthesis of (R)-2-amino-3-(((R)-1-amino-3-mercaptopropan-2-yl)amino)propane-1-thiol hydrochloride:



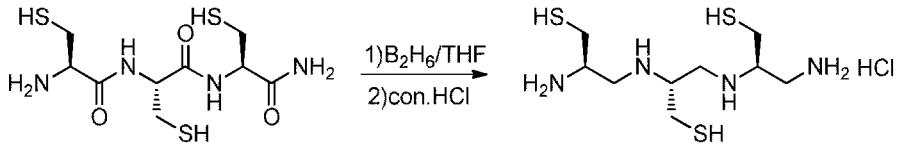
The compound (R)-2-amino-N-((R)-1-amino-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropanamide (0.5g, 2.24mmol) (prepared in Example 1) was added to a reaction flask, anhydrous THF (20ml) was added, and cooled with an ice-salt bath. A borane tetrahydrofuran solution (1M, 13.44ml, 13.44mmol) was added dropwise under a nitrogen atmosphere. After the dropwise addition was completed, the mixture was stirred at room temperature for 1 hour and heated to reflux for 18 hours. After the reaction was completed as detected by TLC, the mixture was cooled to 0°C, and methanol (1ml) was added for quenching the reaction. After stirring for 30 minutes, concentrated hydrochloric acid (12N, 0.95ml, 11.42mmol) was added and heated to 80°C for 1 hour. After the reaction was completed, the mixture was cooled to room temperature and concentrated. Diethyl ether (5ml) was added to the solids obtained and stirred for 1h, filtered, washed with diethyl ether, and dried to obtain the hydrochlorinated target compound as a white solid (360mg, yield: 52.6%). ^1H NMR (400MHz, D_2O) δ 3.18(m, 2H), 2.91-2.52(m, 8H).MS (ES+) m/z 196.35 $[M+H]^+$.

Example 10: Synthesis of (R)-2-(((R)-3-mercapto-2-(methylamino)propyl)amino)-3-(methylamino)propane-1-thiol hydrochloride:



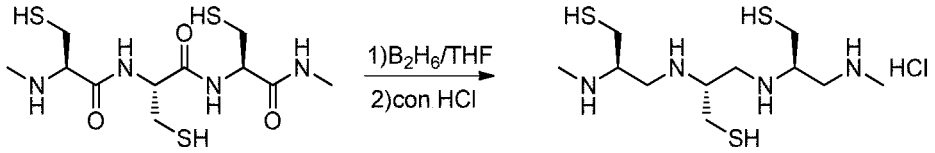
The compound (R)-3-mercapto-N-((R)-3-mercapto-1-(methylamino)-1-oxopropan-2-yl)-2-(methylamino) propanamide (2.0g, 7.96mmol) (prepared in Example 2) was added to a reaction flask, anhydrous THF (50 ml) was added, and cooled with an ice-salt bath. A borane tetrahydrofuran solution (1M, 47.76ml, 47.76mmol) was added dropwise under a nitrogen atmosphere. After the dropwise addition was completed, the mixture was stirred at room temperature for 1 hour and heated to reflux for 18 hours. After the reaction was completed as detected by TLC, the mixture was cooled to 0°C, and methanol (1ml) was added for quenching the reaction. After stirring for 30 minutes, concentrated hydrochloric acid (12N, 3.38ml, 40.60mmol) was added and heated to 80°C for 1 hour. After the reaction was completed, the mixture was cooled to room temperature and concentrated. Diethyl ether (5ml) was added to the solids obtained and stirred for 1h, filtered, washed with diethyl ether, and dried to obtain the hydrochlorinated target compound as a white solid (2.2g, yield: 84.39%).^{1}H NMR (400MHz, D_2O) δ 3.28(s, 6H), 3.17(m, 2H), 2.77-2.75(m, 4H), 2.52-2.50(m, 4H).MS (ES+) m/z 224.40 $[M+H]^+$.

Example 11: Synthesis of (R)-2-amino-3-(((R)-1-(((R)-1-amino-3-mercaptopropan-2-yl)amino)-3-mercaptopropan-2-yl)amino)propane-1-thiol hydrochloride:



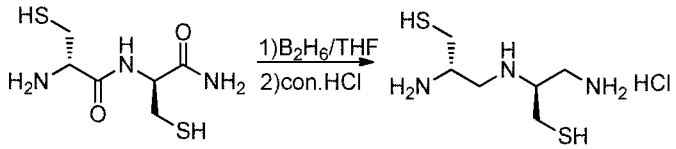
The compound (R)-2-amino-N-((R)-1-((R)-1-amino-3-mercapto-1-oxopropan-2-ylamino)-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropionamide (2.5g, 7.66mmol) (prepared in Example 3) was added to a reaction flask, anhydrous THF (50 ml) was added, and cooled with an ice-salt bath. A borane tetrahydrofuran solution (1M, 68.94ml, 68.94 mmol) was added dropwise under a nitrogen atmosphere. After the dropwise addition was completed, the mixture was stirred at room temperature for 1 hour and heated to reflux for 18 hours. After the reaction was completed as detected by TLC, the mixture was cooled to 0°C, and methanol (3ml) was added for quenching the reaction. After stirring for 30 minutes, concentrated hydrochloric acid (12N, 4.7 ml, 57.45mmol) was added and heated to 80°C for 1 hour. After the reaction was completed, the mixture was cooled to room temperature and concentrated. Diethyl ether (5ml) was added to the solids obtained and stirred for 1h, filtered, washed with diethyl ether, and dried to obtain the hydrochlorinated target compound as a white solid (2.42 g, yield: 73.44%).^{1}H NMR (400MHz, D_2O) δ 3.17(m, 3H), 2.92-2.52(m, 12H).MS (ES+) m/z 285.51 $[M+H]^+$.

Example 12: Synthesis of (R)-2-((R)-3-mercapto-2-((R)-3-mercapto-2-(methylamino)propylamine)propylamino)-3-(methylamino)propane-1-thiol hydrochloride:



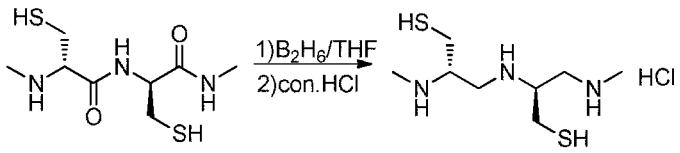
The compound (R)-3-mercapto-N-((R)-3-mercapto-1-((R)-3-mercapto-1-(methylamino)-1-oxopropan-2-ylamino)-1-oxopropan-2-yl)-2-(methylamino) propanamide (1.5g, 4.59mmol) (prepared in Example 4) was added to a reaction flask, anhydrous THF (20 ml) was added, and cooled with an ice-salt bath. A borane tetrahydrofuran solution (1M, 41.31 ml, 41.31 mmol) was added dropwise under a nitrogen atmosphere. After the dropwise addition was completed, the mixture was stirred at room temperature for 1 hour and heated to reflux for 18 hours. After the reaction was completed as detected by TLC, the mixture was cooled to 0°C, and methanol (1ml) was added for quenching the reaction. After stirring for 30 minutes, concentrated hydrochloric acid (12N, 1.9 ml, 22.8 mmol) was added and heated to 80°C for 1 hour. After the reaction was completed, the mixture was cooled to room temperature and concentrated. Diethyl ether (5ml) was added to the solids obtained and stirred for 1h, filtered, washed with diethyl ether, and dried to obtain the hydrochlorinated target compound as a white solid (2.1g, yield: 69.65%).^{1}H NMR (400MHz, D_2O) δ 3.26(s, 6H), 3.17(m, 3H), 2.77-2.75(m, 6H), 2.52-2.50(m, 6H).MS (ES+) m/z 327.55 $[M+H]^+$.

Example 13: Synthesis of (S)-2-amino-3-(((S)-1-amino-3-mercaptopropan-2-yl)amino)propane-1-thiol hydrochloride:



The compound (S)-2-amino-N-((S)-1-amino-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropanamide (1.0g, 4.48mmol) (prepared in Example 5) was added to a reaction flask, anhydrous THF (20ml) was added, and cooled with an ice-salt bath. A borane tetrahydrofuran solution (1M, 26.88ml, 26.88mmol) was added dropwise under a nitrogen atmosphere. After the dropwise addition was completed, the mixture was stirred at room temperature for 1 hour and heated to reflux for 18 hours. After the reaction was completed as detected by TLC, the mixture was cooled to 0°C, and methanol (1ml) was added for quenching the reaction. After stirring for 30 minutes, concentrated hydrochloric acid (12N, 1.90ml, 22.84mmol) was added and heated to 80°C for 1 hour. After the reaction was completed, the mixture was cooled to room temperature and concentrated. Diethyl ether (10ml) was added to the solids obtained and stirred for 1h, filtered, washed with diethyl ether, and dried to obtain the hydrochlorinated target compound as a white solid (780mg, yield: 57.16%).^{1}H NMR (400MHz, D_2O) δ 3.18(m, 2H), 2.91-2.52(m, 8H).MS (ES+) m/z 196.35 $[M+H]^+$.

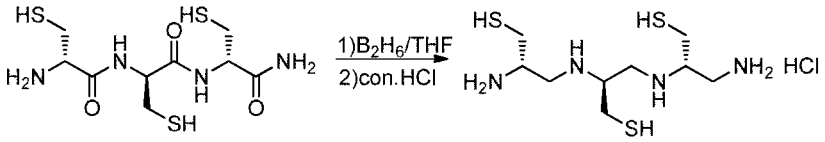
Example 14: Synthesis of (S)-2-(((S)-3-mercapto-2-(methylamino)propyl)amino)-3-(methylamino)propane-1-thiol hydrochloride



The compound (S)-3-mercapto-N-((S)-3-mercapto-1-(methylamino)-1-oxopropan-2-yl)-2-(methylamino) propanamide (1.0g, 3.98mmol) (prepared in Example 7) was added to a reaction flask, anhydrous THF (25ml)

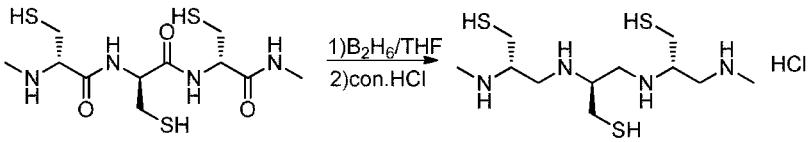
was added, and cooled with an ice-salt bath. A borane tetrahydrofuran solution (1M, 23.88ml, 23.88mmol) was added dropwise under a nitrogen atmosphere. After the dropwise addition was completed, the mixture was stirred at room temperature for 1 hour and heated to reflux for 18 hours. After the reaction was completed as detected by TLC, the mixture was cooled to 0°C, and methanol (1ml) was added for quenching the reaction. After stirring for 30 minutes, concentrated hydrochloric acid (12N, 1.69ml, 20.30mmol) was added and heated to 80°C for 1 hour. After the reaction was completed, the mixture was cooled to room temperature and concentrated. Diethyl ether (5ml) was added to the solids obtained and stirred for 1h, filtered, washed with diethyl ether, and dried to obtain the hydrochlorinated target compound as a white solid (683mg, yield: 56.26%).^{1}H NMR (400MHz, D_2O) δ 3.28(s, 6H), 3.17(m, 2H), 2.77-2.75(m, 4H), 2.52-2.50(m, 4H).MS (ES+) m/z 224.40 $[M+H]^+$.

Example 15: Synthesis of (S)-2-amino-3-(((S)-1-(((R)-1-amino-3-mercaptopropan-2-yl)amino)-3-mercaptopropan-2-yl)amino)propane-1-thiol hydrochloride



The compound (S)-2-amino-N-((S)-1-((R)-1-amino-3-mercapto-1-oxopropan-2-ylamino)-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropionamide (1.0g, 3.06mmol) (prepared in Example 6) was added to a reaction flask, anhydrous THF (10ml) was added, and cooled with an ice-salt bath. A borane tetrahydrofuran solution (1M, 18.36ml, 18.36mmol) was added dropwise under a nitrogen atmosphere. After the dropwise addition was completed, the mixture was stirred at room temperature for 1 hour and heated to reflux for 18 hours. After the reaction was completed as detected by TLC, the mixture was cooled to 0°C, and methanol (3ml) was added for quenching the reaction. After stirring for 30 minutes, concentrated hydrochloric acid (12N, 1.3ml, 15.61mmol) was added and heated to 80°C for 1 hour. After the reaction was completed, the mixture was cooled to room temperature and concentrated. Diethyl ether (5ml) was added to the solids obtained and stirred for 1h, filtered, washed with diethyl ether, and dried to obtain the hydrochlorinated target compound as a white solid (760mg, yield: 63.11%).^{1}H NMR (400MHz, D_2O) δ 3.17(m, 3H), 2.92-2.52(m, 12H).MS (ES+) m/z 285.51 $[M+H]^+$.

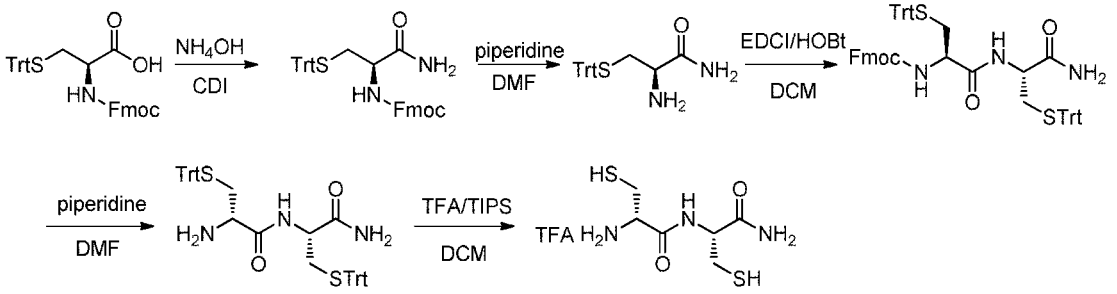
Example 16: Synthesis of (S)-2-((S)-3-mercapto-2-((S)-3-mercapto-2-(methylamino)propylamine)propylamino)-3-(methylamino)propane-1-thiol hydrochloride:



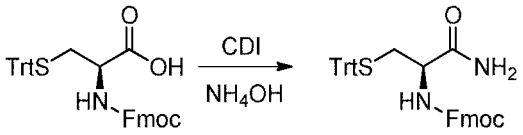
The compound (S)-3-mercapto-N-((S)-3-mercapto-1-((S)-3-mercapto-1-(methylamino)-1-oxopropan-2-ylamino)-1-oxopropan-2-yl)-2-(methylamino) propanamide (1.0g, 2.82mmol) (prepared in Example 8) was added to a reaction flask, anhydrous THF (10ml) was added, and cooled with an ice-salt bath. A borane tetrahydrofuran solution (1M, 16.92ml, 16.92mmol) was added dropwise under a nitrogen atmosphere. After the dropwise addition was completed, the mixture was stirred at room temperature for 1 hour and heated to reflux for 18 hours. After the

reaction was completed as detected by TLC, the mixture was cooled to 0°C, and methanol (1ml) was added for quenching the reaction. After stirring for 30 minutes, concentrated hydrochloric acid (12N, 1.20ml, 14.38mmol) was added and heated to 80°C for 1 hour. After the reaction was completed, the mixture was cooled to room temperature and concentrated. Diethyl ether (5ml) was added to the solids obtained and stirred for 1h, filtered, washed with diethyl ether, and dried to obtain the hydrochlorinated target compound as a white solid (756mg, yield: 68.05%).^{1}H NMR (400MHz, D_2O) δ 3.26(s, 6H), 3.17(m, 3H), 2.77-2.75(m, 6H), 2.52-2.50(m, 6H).MS (ES+) m/z 327.55 $[M+H]^+$.

Example 17: Synthesis of (S)-2-amino-N-((R)-1-amino-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropanamide trifluoroacetate

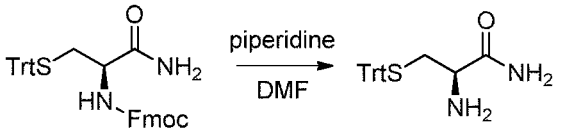


Step 1: Synthesis of (9H-fluoren-9-yl) methyl (R)-(1-amino-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



The compound (R)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tritylthio) propionic acid (10 g, 17.07 mmol) was dissolved in tetrahydrofuran (50ml). N,N'-carbonyldiimidazole (5.59g, 34.48mmol) was added at 0-5°C. After stirring for 2 hours under nitrogen protection, aqueous ammonia (5ml, 68.28mmol) was added, and reacted at 0-5°C for 30 minutes. After the reaction was completed as detected by TLC, 2 M hydrochloric acid (60ml) was added for quenching. The reaction mixture was extracted with ethyl acetate, the organic phase was washed with a saturated saline, then dried with sodium sulfate, and concentrated to obtain a crude product. After adding anhydrous methanol (20ml) and stirring at room temperature overnight, white solids were precipitated, and filtered to obtain the product in the filter cake. The methanol phasewas concentrated and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the target product as a white solid (9.3g, yield: 93.19%). ^{1}H NMR (400MHz, DMSO-d6) δ 7.89(d, 2H), 7.74(d, 2H), 7.58(d, 1H), 7.3(m, 18H), 7.11(s, 1H), 4.24(m, 3H), 4.01(m, 1H), 2.39(m, 2H).

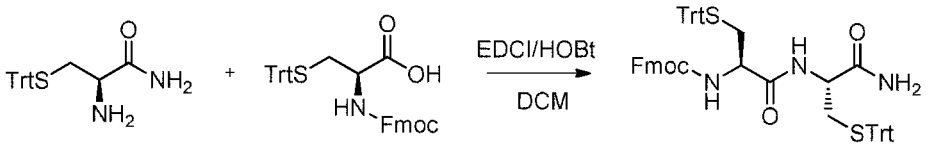
Step 2: Synthesis of (R)-2-amino-3-(tritylthio) propionamide:



The compound (9H-fluoren-9-yl) methyl (R)-(1-amino-1-oxo-3-(tritylthio)propan-2-yl) carbamate (4g, 6.84mmol) was dissolved in N,N-dimethylformamide (20ml). Piperidine (0.14ml, 1.368mmol) was added and reacted at room temperature for 4 hours. After the reaction was completed as detected by TLC, the reaction mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane =

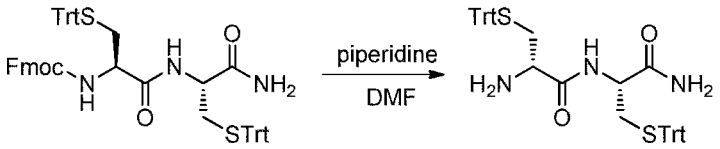
1%-5%) to obtain the target product as a yellow oil (2.3g, yield: 92%). ^{1}H NMR (400MHz, DMSO-d6) δ 7.29(m, 17H), 3.08(d, 1H), 2.33(d, 1H), 2.18(s, 1H), 1.85(s, 2H).

Step 3: Synthesis of (9H-fluoren-9-yl) methyl ((R)-1-(((R)-1-amino-1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



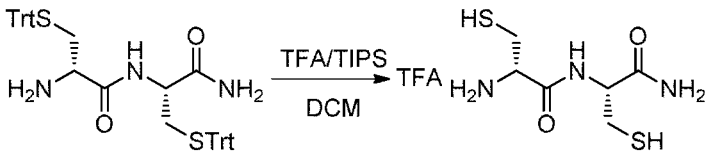
The compound (R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tritylthio) propanoic acid (1.29g, 2.21mmol) was dissolved in dichloromethane (15ml). 1-hydroxybenzotriazole (448mg, 3.315mmol) and EDCI (635mg, 3.315mmol) were added, and stirred at room temperature for 5min. (9H-fluoren-9-yl) methyl (R)-(1-amino-1-oxo-3-(tritylthio)propan-2-yl) carbamate (960mg, 2.65mmol) was added and reacted at room temperature for 30 minutes. After the reaction was completed as detected by TLC, the mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (2.05g, yield: 99.76%). ^{1}H NMR (400MHz, DMSO-d6) δ 7.89(m, 3H), 7.7(m, 3H), 7.4(m, 2H), 7.24(m, 34H), 4.21(m, 4H), 4.10(m, 1H), 2.33(m, 4H).

Step 4: Synthesis of (S)-2-amino-N-((R)-1-amino-1-oxo-3-(tritylthio) propan-2-yl)-3-(tritylthio) propionamide:



The compound (9H-fluoren-9-yl) methyl ((R)-1-(((R)-1-amino-1-oxo-3-(tritylthio)propan-2-yl) amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate (2.05g, 2.2mmol) was dissolved in N,N-dimethylformamide (20ml). Piperidine (0.04ml, 0.44mmol) was added and stirred at room temperature for 4 hours. After the reaction was completed as detected by TLC detection, the reaction mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (460mg, yield: 29.54%).^{1}H NMR (400MHz, DMSO-d6) δ 8.1(s,1H), 7.37-7.14(m, 32H), 4.23(m, 1H), 3.17(m,1H), 2.39(dd, 1H), 2.33(d, 2H), 2.19(m, 1H).

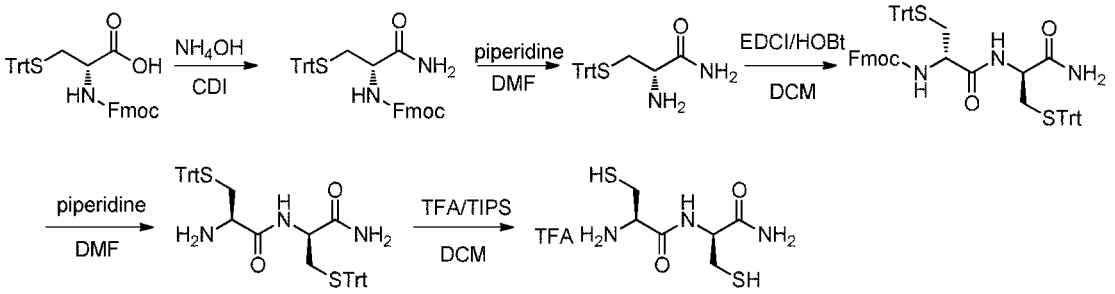
Step 5: Synthesis of (S)-2-amino-N-((R)-1-amino-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropanamide trifluoroacetate:



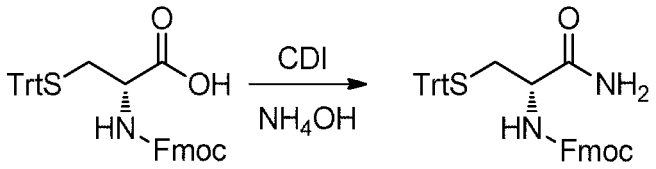
The compound (S)-2-amino-N-((R)-1-amino-1-oxo-3-(tritylthio)propan-2-yl)-3-(tritylthio) propionamide (200mg, 0.28mmol) was dissolved in dichloromethane (5ml). Triisopropylsilane (0.14ml, 0.7mmol) and trifluoroacetic acid (1ml) were added at 0°C under a nitrogen atmosphere and stirred in an ice bath for 2 hours. After the reaction was completed as detected by TLC, the mixture was concentrated, diethyl ether was added, and

stirred in the ice bath. White solids were precipitated, filtered and dried to obtain the product (79mg, yield: 88.08%).^{1}H NMR (400MHz, DMSO-d6) δ 8.72(d, 1H), 8.23(s, 3H), 7.56(s, 1H), 7.32(s, 1H), 4.43(m, 1H), 4.09(m, 1H), 2.99(d, 2H), 2.89(m, 1H), 2.74(m, 1H); HESI:224.05 [M +H]+.

Example 18: Synthesis of (R)-2-amino-N-((S)-1-amino-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropanamide trifluoroacetate

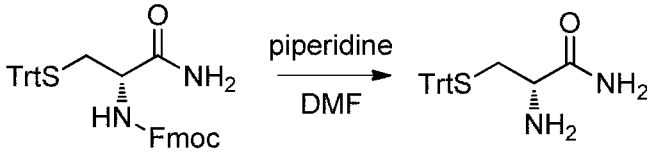


Step 1: Synthesis of (9H-fluoren-9-yl) methyl (S)-(1-amino-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



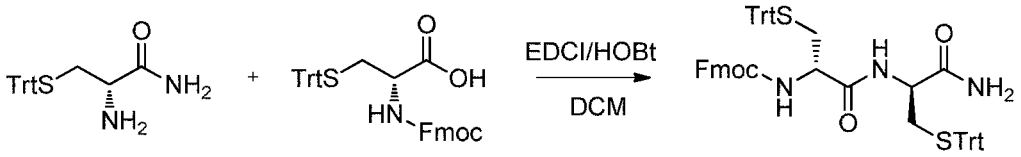
The compound (S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tritylthio) propionic acid (10 g, 17.07 mmol) was dissolved in tetrahydrofuran (50ml). N,N'-carbonyldiimidazole (5.59g, 34.48mmol) was added at 0-5°C. After stirring for 2 hours under nitrogen protection, aqueous ammonia (5ml, 68.28mmol) was added, and reacted at 0-5°C for 30 minutes. After the reaction was completed as detected by TLC, 2 M hydrochloric acid (60ml) was added for quenching. The reaction mixture was extracted with ethyl acetate, the organic phase was washed with a saturated saline, then dried with sodium sulfate, and concentrated to obtain a crude product. After adding anhydrous methanol (20ml) and stirring at room temperature overnight, white solids were precipitated, and filtered to obtain the product in the filter cake. The methanol phasewas concentrated and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the target product as a white solid (8.93g, yield: 89.48%).^{1}H NMR (400MHz, DMSO-d6) δ 7.89(d, 2H), 7.74(d, 2H), 7.58(d, 1H), 7.3(m, 18H), 7.11(s, 1H), 4.24(m, 3H), 4.01(m, 1H), 2.39(m, 2H).

Step 2: Synthesis of (S)-2-amino-3-(tritylthio) propionamide:



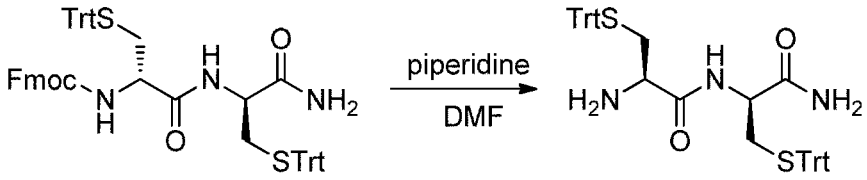
The compound (9H-fluoren-9-yl) methyl (S)-(1-amino-1-oxo-3-(tritylthio)propan-2-yl) carbamate (5.98g, 10.23mmol) was dissolved in N,N-dimethylformamide (20ml). Piperidine (0.2ml, 2.046mmol) was added and reacted at room temperature for 4 hours. After the reaction was completed as detected by TLC, the reaction mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane = 1%-5%) to obtain the target product as a yellow oil (2.68g, yield: 72.24%).^{1}H NMR (400MHz, DMSO-d6) δ 7.29(m, 17H), 3.08(d, 1H), 2.33(d, 1H), 2.18(s, 1H), 1.85(s, 2H).

Step 3: Synthesis of (9H-fluoren-9-yl) methyl ((S)-1-(((S)-1-amino-1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



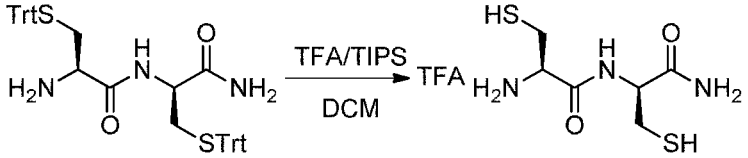
The compound (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tritylthio) propanoic acid (3.61g, 6.16mmol) was dissolved in dichloromethane (25ml). 1-hydroxybenzotriazole (1.25mg, 9.24 mmol) and EDCI (1.77mg, 9.24mmol) were added, and stirred at room temperature for 5min. (9H-fluoren-9-yl) methyl (S)-(1-amino-1-oxo-3-(tritylthio)propan-2-yl) carbamate (2.68mg, 7.39mmol) was added and reacted at room temperature for 30 minutes. After the reaction was completed as detected by TLC, the mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (5.56g, yield: 97.03%).^{1}H NMR (400MHz, DMSO-d6) δ 7.89(m, 3H), 7.7(m, 3H), 7.4(m, 2H), 7.24(m, 34H), 4.21(m, 4H), 4.10(m, 1H), 2.33(m, 4H).

Step 4: Synthesis of (R)-2-amino-N-((S)-1-amino-1-oxo-3-(tritylthio) propan-2-yl)-3-(tritylthio) propionamide:



The compound (9H-fluoren-9-yl) methyl ((S)-1-(((S)-1-amino-1-oxo-3-(tritylthio)propan-2-yl) amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate (5.56g, 5.98mmol) was dissolved in N,N-dimethylformamide (25ml). Piperidine (0.12ml, 1.196mmol) was added and stirred at room temperature for 4 hours. After the reaction was completed as detected by TLC detection, the reaction mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (1.27g, yield: 30%).^{1}H NMR (400MHz, DMSO-d6) δ 8.1(s,1H), 7.37-7.14(m, 32H), 4.23(m, 1H), 3.17(m,1H), 2.39(dd, 1H), 2.33(d, 2H), 2.19(m, 1H).

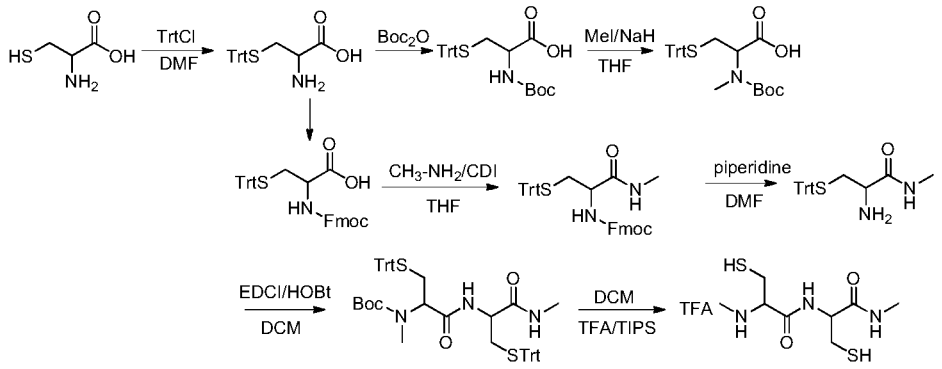
Step 5: Synthesis of (R)-2-amino-N-((S)-1-amino-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropanamide trifluoroacetate:



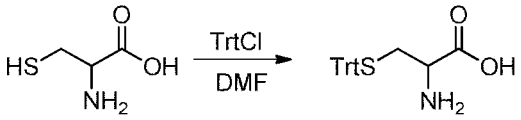
The compound (R)-2-amino-N-((S)-1-amino-1-oxo-3-(tritylthio)propan-2-yl)-3-(tritylthio) propionamide (40mg, 0.057mmol) was dissolved in dichloromethane (5ml). Triisopropylsilane (0.03ml, 0.1425mmol) and trifluoroacetic acid (1ml) were added at 0°C under a nitrogen atmosphere and stirred in an ice bath for 2 hours. After the reaction was completed as detected by TLC, the mixture was concentrated, diethyl ether was added, and stirred in the ice bath. White solids were precipitated, filtered and dried to obtain the product (16mg, yield:

83.2%).[1]H NMR (400MHz, DMSO-d6) δ 8.72(d, 1H), 8.23(s, 3H), 7.56(s, 1H), 7.32(s, 1H), 4.43(m, 1H), 4.09(m, 1H), 2.99(d, 2H), 2.89(m, 1H), 2.74(m, 1H); HESI:224.05 [M +H]+.

Example 19: Synthesis of 3-mercapto-N-(3-mercapto-1-(methylamino)-1-oxopropan-2-yl)-2-(methylamino) propionamide trifluoroacetate

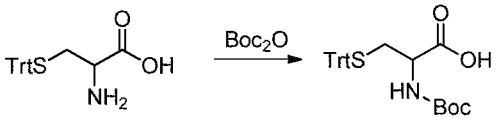


Step 1: Synthesis of S-trityl-DL-cysteine:



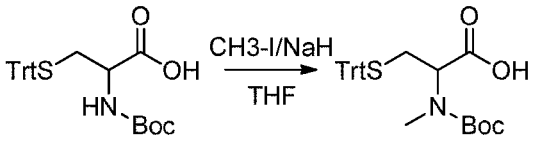
The compound DL-cysteine hydrochloride (10g, 63.45mmol) was dissolved in N,N-dimethylformamide (120ml). Triphenylchloromethane (19.46g, 69.795mmol) was added, heated to 60-65°C, and reacted for 8h. After the reaction was completed as detected by TLC, the reaction was cooled to room temperature, and 10% sodium acetate solution (300ml) was added. White solids were then precipitated and filtered. Filter residue was washed with pure water (300ml), then washed with acetone (200ml), and dried to obtain the product as a white solid (17.54g, yield: 76.06%). [1]H NMR (400MHz, DMSO-d6) δ 7.27(m, 18H), 2.92(dd, 1H), 2.59(dd, 1H), 2.41(dd, 1H).

Step 2: Synthesis of N-(tert-butoxycarbonyl)-S-trityl-DL-cysteine:



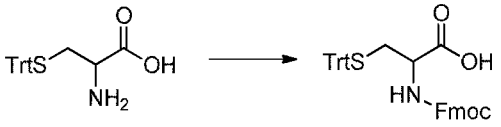
The compound S-trityl-DL-cysteine (5g, 13.76mmol) was dissolved in a mixture of dioxane (40ml), water (20ml) and 1M sodium hydroxide solution (14ml), and stirred in an ice bath. Boc-anhydride (3.5ml, 15.14mmol) was added, then reacted until the mixture was naturally warmed to room temperature, and stirred for 8 hours. After the reaction was completed as detected by TLC, the reaction mixture was concentrated to 20-25ml. Ethyl acetate was added, and the sodium bisulfate solution was added dropwise under the ice bath while stirring. After pH was adjusted to 2-3, ethyl acetate was used for extraction. The organic layer was washed with a saturated saline, then dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (4.72g, yield :73.98%).[1]H NMR (400MHz, DMSO-d6) δ 7.26(m, 16H), 3.77(d, 1H), 2.51(m, 1H), 2.36(dd, 1H), 1.4(d, 9H).

Step 3: Synthesis of N-(tert-butoxycarbonyl)-N-methyl-S-trityl-DL-cysteine:



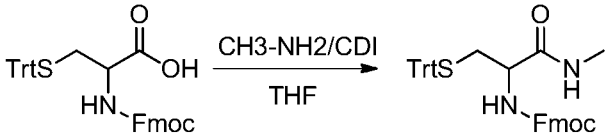
The compound N-(tert-butoxycarbonyl)-S-trityl-DL-cysteine (1g, 2.16mmol) was dissolved in anhydrous tetrahydrofuran (6ml). Sodium hydride (259.2mg, 6.48mmol) was dissolved in anhydrous tetrahydrofuran (10ml). The solution of amino acid in tetrahydrofuran was added dropwise to the solution of sodium hydride in tetrahydrofuran in an ice bath. Then, methyl iodide (1.08ml, 17.28mmol) was slowly added dropwise and stirred overnight. After the reaction was completed as detected by TLC, phosphate buffer at pH=7 was added for quenching. pH was adjusted to 6-7 with a saturated ammonium chloride solution, and was extracted with ethyl acetate. The organic layer was washed with a saturated saline, then dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (462mg, yield: 44.85%).^{1}H NMR (400MHz, DMSO-d6) δ 7.3(m, 15H), 3.75(s, 1H), 2.7(s, 1H), 2.66(d, 4H), 1.4(d, 9H).

Step 4: Synthesis of (RS)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tritylthio) propionic acid:



The compound S-trityl-DL-cysteine (5g, 13.76mmol) was dissolved in tetrahydrofuran (30ml) and water (30ml), sodium hydrogen carbonate (2.31g, 27.52mmol) was added with stirring, and 9-fluorenyl methyl-N-succinimidyl carbonate (4.39g, 13mmol) was stirred at room temperature for 3.5 hours. After the reactants were consumed, the reaction mixture was extracted with dichloromethane. The organic layer was washed with a saturated saline, then dried with sodium sulfate, concentrated and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain a white solid (6.61g, yield: 82.02%). ^{1}H NMR (300 MHz, DMSO) δ 7.89 (d, J = 7.5 Hz, 2H), 7.73 (d, J = 7.5 Hz, 2H), 7.52 – 7.14 (m, 19H), 4.38 – 4.09 (m, 3H), 3.84 (dd, J = 8.6, 5.1 Hz, 1H), 2.67 – 2.56 (m, 1H), 2.41 (dd, J = 12.3, 4.6 Hz, 1H).

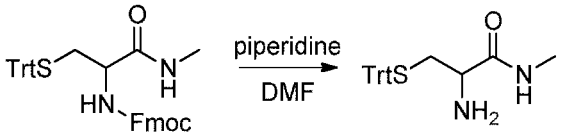
Step 5: Synthesis of (9H-fluoren-9-yl) methyl (RS)-(1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



The compound (RS)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tritylthio) propionic acid (6.6g, 11.27mmol) was dissolved in tetrahydrofuran (25ml). N,N'-carbonyldiimidazole (3.7g, 22.77mmol) was added at 0-5°C. After stirring for 2 hours under nitrogen atmosphere, methylamine (2ml, 45.08mmol) was added, and reacted at 0-5°C for 2 hours. After the reactants were consumed, 2M hydrochloric acid (30ml) was added for quenching, and the reaction mixture was extracted with dichloromethane. The organic layer was washed with a saturated saline, then dried with sodium sulfate and concentrated to obtain a crude product. Methanol (20ml) was added and stirred overnight at room temperature. White solids were precipitated, and filtered to obtain the product in filter residue. The methanol phase was concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain a white solid (6.5g, yield: 96.32%).^{1}H NMR (400MHz, DMSO)

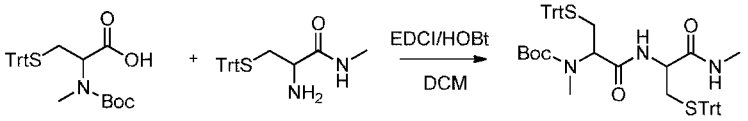
δ 7.89(d, 2H), 7.81(d, 1H), 7.74(d, 2H), 7.66(d, 1H), 7.41(t, 2H), 7.29(m, 17H), 4.31(d, 1H), 4.22(t, 2H), 4.00(d, 1H), 2.53(d, 3H), 2.39(d, 2H).

Step 6: Synthesis of (RS)-2-amino-N-methyl-3-(tritylthio) propionamide



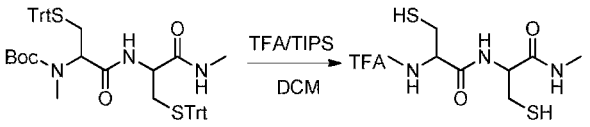
The compound (9H-fluoren-9-yl) methyl (RS)-(1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate (1g, 1.67mmol) was dissolved in N,N-dimethylformamide (20ml). Piperidine (0.03ml, 0.334 mmol) was added and reacted at room temperature for 4 hours. After the reaction was completed as detected by TLC, the reaction mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a yellowish white solid (540mg, yield: 85.88%).^{1}H NMR (400MHz, $CDCl_3$) δ 7.77(d, 1H), 7.29(m, 15H), 3.08(m, 1H), 2.55(d. 3H), 2.37(dd, 1H), 2.19(dd, 1H), 1.80(s, 2H).

Step 7: Synthesis of tert-butyl methyl ((RS)-1-(((RS)-1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



The compound N-(tert-butoxycarbonyl)-N-methyl-S-trityl-DL-cysteine (500g, 1.328mmol) was dissolved in dichloromethane (5ml). 1-hydroxybenzotriazole (269.32mg, 1.992mmol) and EDCI (381.87mg, 1.992mmol) were added, and stirred at room temperature for 5min. (RS)-2-amino-N-methyl-3-(tritylthio) propanamide (634mg, 1.328mmol) was added and stirred at room temperature for 30 minutes. After the reaction was completed as detected by TLC, the mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, then concentrated and purified with TLC (dichloromethane : methanol: 15 : 1) to obtain the product as a white solid (940mg, yield: 84.66%).^{1}H NMR (400MHz, $CDCl_3$) δ 7.39(m, 12H), 7.22(m, 20H), 4.1(d, 1H), 3.95(s, 1H), 2.61(dd, 10H), 1.39(s, 9H).

Step 8: Synthesis of (RS)-3-mercapto-N-((RS)-3-mercapto-1-(methylamino)-1-oxopropan-2-yl)-2-(methylamino) propionamide trifluoroacetate:

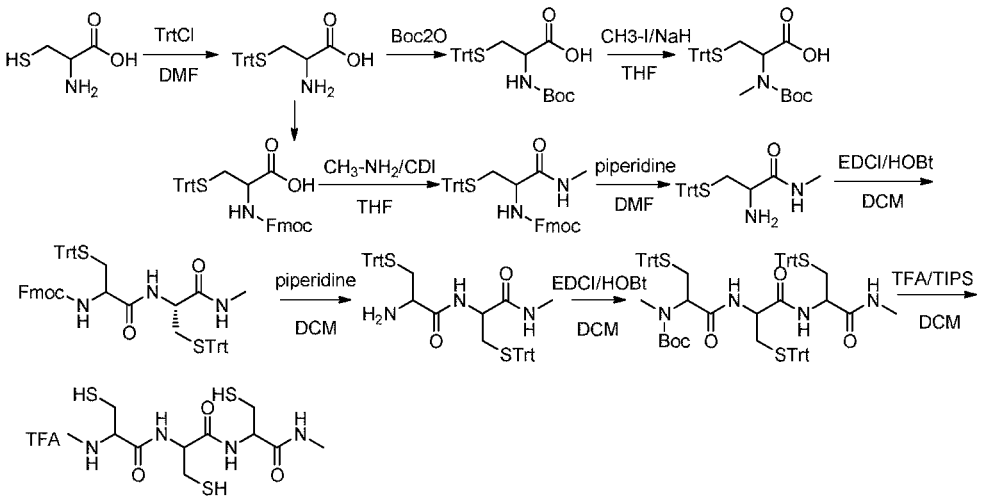


The compound tert-butyl methyl ((RS)-1-(((RS)-1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate (200mg, 0.239mmol) was dissolved in dichloromethane : trifluoroacetic acid : triisopropylsilane (50 : 47 : 3 by volume) (5ml), stirred at room temperature for 5min. After the reaction was completed as detected by TLC, the mixture was concentrated, diethyl ether was added, and stirred in an ice bath. White solids were precipitated, filtered and dried to obtain the product (70mg, yield: 84.07%).^{1}H NMR (400 MHz, DMSO) δ 8.89 (d, J = 8.1 Hz, 2H), 8.12 (d, J = 4.3 Hz, 1H), 4.48 – 4.34 (m, 1H), 4.04 (s, 1H), 3.10 (dt, J = 12.5, 6.2 Hz, 1H),

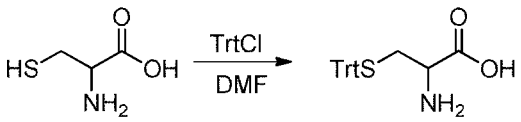
3.04 – 2.93 (m, 1H), 2.91–2.81 (m, 1H), 2.78–2.65 (m, 1H), 2.62 (d, J = 4.6 Hz, 3H), 2.56 (s, 3H), 2.37 (t, J = 13.7 Hz, 1H), 1.29 (d, J = 7.0 Hz, 1H).

Example 20: Synthesis of

2-amino-N-(1-((1-amino-3-mercapto-1-oxopropan-2-yl)amino)-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropyl amide trifluoroacetate

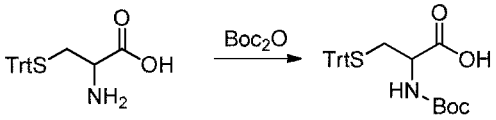


Step 1: Synthesis of S-trityl-DL-cysteine:



The compound DL-cysteine hydrochloride (10g, 63.45mmol) was dissolved in N,N-dimethylformamide (120ml). Triphenylchloromethane (19.46g, 69.795mmol) was added, heated to 60-65°C, and reacted for 8h. After the reaction was completed as detected by TLC, the reaction was cooled to room temperature, and 10% sodium acetate solution (300ml) was added. White solids were then precipitated and filtered. Filter residue was washed with pure water (300ml), then washed with acetone (200ml), and dried to obtain the product as a white solid (17.54g, yield: 76.06%). ^{1}H NMR (400MHz, DMSO-d6) δ 7.28(m, 18H), 2.92(dd, 1H), 2.59(dd, 1H), 2.41(dd, 1H).

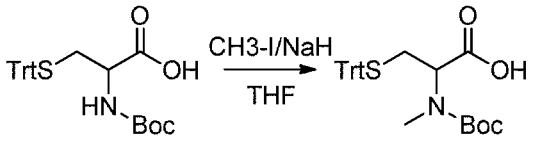
Step 2: Synthesis of N-(tert-butoxycarbonyl)-S-trityl-DL-cysteine:



The compound S-trityl-DL-cysteine (5g, 13.76mmol) was dissolved in a mixture of dioxane (40ml), water (20ml) and 1M sodium hydroxide solution (14ml), and stirred in an ice bath. Boc-anhydride (3.5ml, 15.14mmol) was added, then reacted until the mixture was naturally warmed to room temperature, and stirred for 8 hours. After the reaction was completed as detected by TLC, the reaction mixture was concentrated to 20-25ml. Ethyl acetate was added, and the sodium bisulfate solution was added dropwise under the ice bath while stirring. After pH was adjusted to 2-3, ethyl acetate was used for extraction. The organic layer was washed with a saturated saline, then dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (4.72g, yield :73.98%).^{1}H NMR (400MHz,

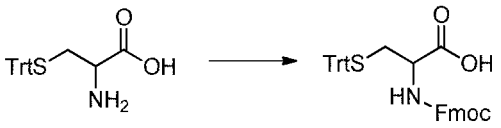
DMSO-d6) δ 7.26(m, 16H), 3.78(d, 1H), 2.51(m, 1H), 2.36(dd, 1H), 1.4(d, 9H).

Step 3: Synthesis of N-(tert-butoxycarbonyl)-N-methyl-S-trityl-DL-cysteine:



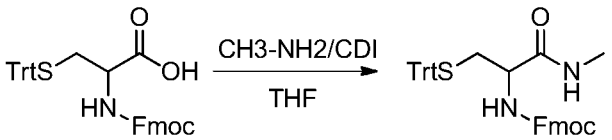
The compound N-(tert-butoxycarbonyl)-S-trityl-DL-cysteine (1g, 2.16mmol) was dissolved in anhydrous tetrahydrofuran (6ml). Sodium hydride (259.2mg, 6.48mmol) was dissolved in anhydrous tetrahydrofuran (10ml). The solution of amino acid in tetrahydrofuran was added dropwise to the solution of sodium hydride in tetrahydrofuran in an ice bath. Then, methyl iodide (1.08ml, 17.28mmol) was slowly added dropwise and stirred overnight. After the reaction was completed as detected by TLC, phosphate buffer at pH=7 was added for quenching. pH was adjusted to 6-7 with a saturated ammonium chloride solution, and was extracted with ethyl acetate. The organic layer was washed with a saturated saline, then dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (462mg, yield: 44.85%).^{1}H NMR (400MHz, DMSO-d6) δ 7.3(m, 15H), 3.75(s, 1H), 2.8(s, 1H), 2.66(d, 4H), 1.4(d, 9H).

Step 4: Synthesis of (RS)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tritylthio) propionic acid:



The compound S-trityl-DL-cysteine (5g, 13.76mmol) was dissolved in tetrahydrofuran (30ml) and water (30ml), sodium hydrogen carbonate (2.31g, 27.52mmol) was added with stirring, and 9-fluorenyl methyl-N-succinimidyl carbonate (4.39g, 13mmol) was stirred at room temperature for 3.5 hours. After the reactants were consumed, the reaction mixture was extracted with dichloromethane. The organic layer was washed with a saturated saline, then dried with sodium sulfate, concentrated and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain a white solid (6.61g, yield: 82.02%). ^{1}H NMR (300 MHz, DMSO) δ 7.89 (d, J = 7.5 Hz, 2H), 7.73 (d, J = 7.5 Hz, 2H), 7.52 – 7.14 (m, 19H), 4.38 – 4.09 (m, 3H), 3.84 (dd, J = 8.6, 5.1 Hz, 1H), 2.67 – 2.56 (m, 1H), 2.41 (dd, J = 12.3, 4.6 Hz, 1H).

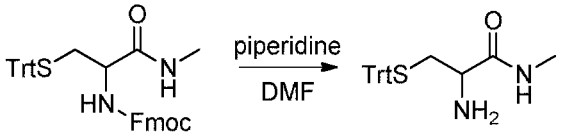
Step 5: Synthesis of (9H-fluoren-9-yl) methyl (RS)-(1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



The compound (RS)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tritylthio) propionic acid (6.6g, 11.27mmol) was dissolved in tetrahydrofuran (25ml). N,N'-carbonyldiimidazole (3.7g, 22.77mmol) was added at 0-5°C. After stirring for 2 hours under nitrogen atmosphere, methylamine (2ml, 45.08mmol) was added, and reacted at 0-5°C for 2 hours. After the reactants were consumed, 2M hydrochloric acid (30ml) was added for quenching, and the reaction mixture was extracted with dichloromethane. The organic layer was washed with a saturated saline, then dried with sodium sulfate and concentrated to obtain a crude product. Methanol (20ml) was added and stirred overnight at room temperature. White solids were precipitated, and filtered to obtain the

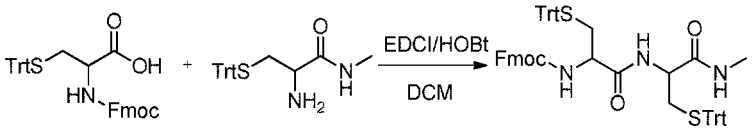
product in filter residue. The methanol phase was concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain a white solid (6.5g, yield: 96.32%).^{1}H NMR (400MHz, DMSO) δ 7.89(d, 2H), 7.81(d, 1H), 7.74(d, 2H), 7.66(d, 1H), 7.41(t, 2H), 7.29(m, 17H), 4.31(d, 1H), 4.22(t, 2H), 4.00(d, 1H), 2.53(d, 3H), 2.39(d, 2H).

Step 6: Synthesis of (RS)-2-amino-N-methyl-3-(tritylthio) propionamide



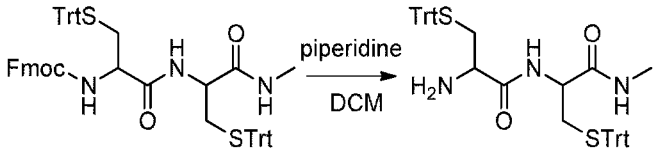
The compound (9H-fluoren-9-yl) methyl (RS)-(1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate (1g, 1.67mmol) was dissolved in N,N-dimethylformamide (20ml). Piperidine (0.03ml, 0.334 mmol) was added and reacted at room temperature for 4 hours. After the reaction was completed as detected by TLC, the reaction mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a yellowish white solid (540mg, yield: 85.88%).^{1}H NMR (400MHz, $CDCl_3$) δ 7.77(d, 1H), 7.29(m, 15H), 3.08(m, 1H), 2.55(d. 3H), 2.37(dd, 1H), 2.19(dd, 1H), 1.80(s, 2H).

Step 7: Synthesis of (9H-fluoren-9-yl) methyl ((RS)-1-(((RS)-1-(methylamino) -1-oxo-3-(tritylthio)propan-2-yl)amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate:



The compound (RS)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tritylthio) propanoic acid (1g, 1.71mmol) was dissolved in dichloromethane (15ml). 1-hydroxybenzotriazole (347mg, 2.565 mmol) and EDCI (492mg, 2.565mmol) were added, and stirred at room temperature for 5min. (R)-2-amino-N-methyl-3-(tritylthio) propanamide (644mg, 1.71mmol) was added and reacted at room temperature for 30 minutes. After the reaction was completed as detected by TLC, the mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, then concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (1.06g, yield: 65.63%).^{1}H NMR (400MHz, DMSO-d6) δ 7.89(d, 2H), 7.71(m, 4H), 7.40(m, 2H), 7.38-7.25(m, 30H), 4.25(m, 4H), 4.01(m, 1H), 2.50-2.33(m, 7H).

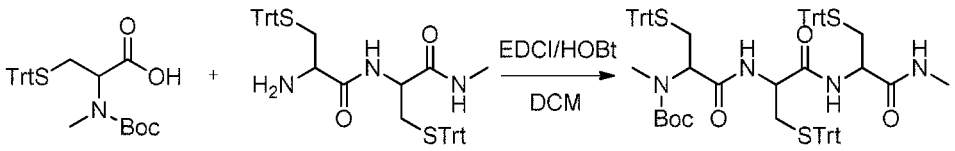
Step 8: Synthesis of (RS)-2-amino-N-((RS)-1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl)-3-(tritylthio) propionamide:



The compound (9H-fluoren-9-yl) methyl ((RS)-1-(((RS)-1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl) amino)-1-oxo-3-(tritylthio)propan-2-yl) carbamate (1.06g, 1.12mmol) was dissolved in N,N-dimethylformamide (10ml). Piperidine (0.02ml, 0.224mmol) was added and reacted at room temperature for 4 hours. After the reaction was completed as detected by TLC detection, the reaction mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, then concentrated, and

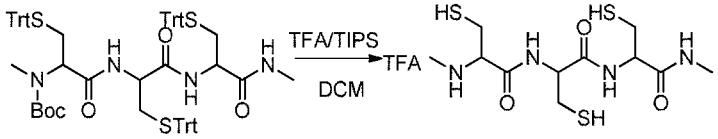
separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (790mg, yield: 97.7%).^{1}H NMR (400MHz, DMSO-d6) δ 8.12(s, 1H), 7.83(d, 1H), 7.27(m, 30H), 4.25(s, 1H), 3.29(m, 2H), 3.20(s, 1H), 2.65-2.23(m, 5H).

Step 9: Synthesis of tert-butyl methyl((4RS,7RS,10RS)-3,6,9-trioxo-13,13,13-triphenyl-4,7-bis((tritylthio)methyl)-12-thia-2,5,8-triazatridec-10-yl) carbamate:



The compound N-(tert-butoxycarbonyl)-N-methyl-S-trityl-DL-cysteine (505mg, 1.06mmol) was dissolved in dichloromethane (10ml). 1-hydroxybenzotriazole (215mg, 1.59mmol) and EDCI (304.8mg, 1.59mmol) were added, and stirred at room temperature for 5min. (RS)-2-amino-N-((RS)-1-(methylamino)-1-oxo-3-(tritylthio)propan-2-yl)-3-(tritylthio) propanamide (765.3mg, 1.06mmol) was added and reacted at room temperature for 30 minutes. After the reaction was completed as detected by TLC, the mixture was washed with a saturated saline and extracted with dichloromethane. The organic phase was dried with sodium sulfate, concentrated, and separated by column chromatography (methanol : dichloromethane: 1%-5%) to obtain the product as a white solid (1.1g, yield: 88%).^{1}H NMR (400MHz, DMSO-d6) δ 8.11(d, 1H), 7.73(d, 2H), 7.32-7.21(m, 45H), 4.25(m, 3H), 2.62(m, 1H), 2.49(m, 6H) 2.47-2.23(m, 5H), 1.35-1.21(d, 9H).

Step 10: Synthesis of (RS)-3-mercapto-N-((RS)-3-mercapto-1-(((RS)-3-mercapto-1-(methylamino)-1-oxopropan-2-yl)amino)-1-oxopropan-2-yl)-2-(methylamino) propanamide trifluoroacetate:



The compound tert-butyl methyl((4RS,7RS,10RS)-3,6,9-trioxo-13,13,13-triphenyl-4,7-bis((tritylthio)methyl)-12-thia-2,5,8-triazatridec-10-yl) carbamate (400mg, 0.339mmol) was dissolved in dichloromethane : trifluoroacetic acid : triisopropylsilane (50 : 47 : 3 by volume) (10ml), stirred at room temperature for 5min. After the reaction was completed as detected by TLC, the mixture was concentrated, diethyl ether was added, and stirred in an ice bath. White solids were precipitated, filtered and dried to obtain the product (131mg, yield: 85.4%).^{1}H NMR (400 MHz, DMSO) δ 8.92 (dd, J = 14.8, 9.8 Hz, 3H), 8.58 – 8.33 (m, 1H), 7.97 (dd, J = 22.8, 4.4 Hz, 1H), 4.64 – 4.50 (m, 1H), 4.34 (td, J = 13.4, 7.9 Hz, 1H), 4.05 (d, J = 5.4 Hz, 1H), 3.17 – 2.66 (m, 7H), 2.60 (d, J = 3.9 Hz, 3H), 2.56 (d, J = 5.7 Hz, 3H), 2.36 – 2.27 (m, 1H).

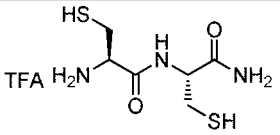
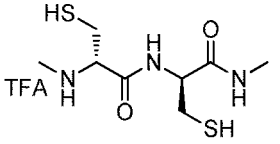
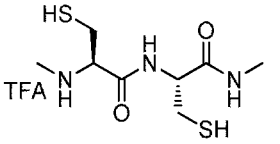
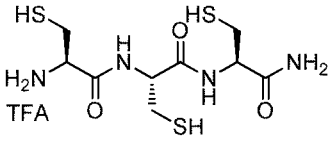
Examples of biological activity:

Example A: The protective effects of compounds 1, 2, 3 and 4 on survival rate, white blood cells and organs of mice 30 days after irradiation.

Material: The gamma ray irradiation device is a ^{137}Cs irradiator, with a dose rate of 0.7Gy/min. C57BL/6

mice, male, weighing 21-22 g, purchased from Beijing HFK Bioscience Co. Ltd., certificate number SCXK (Beijing) 2014-0004, grouped as: no irradiation group, irradiation and blank solvent group, irradiation and administration group, with 5 mice in each group. The structures of compounds 1, 2, 3 and 4 (prepared from Examples 1, 7, 2 and 3, respectively) are shown in Table 1.

Table 1 Nomenclature and structural formula of compounds 1-4

Compound No.	Compound name	Structural formula
Compound 1 (Example 1)	(R)-2-amino-N-((R)-1-amino-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropanamide trifluoroacetate	
Compound 2 (Example 7)	(S)-3-mercapto-N-((S)-3-mercapto-1-(methylamino)-1-oxopropan-2-yl)-2-(methylamino) propionamide trifluoroacetate	
Compound 3 (Example 2)	(R)-3-mercapto-N-((R)-3-mercapto-1-(methylamino)-1-oxopropan-2-yl)-2-(methylamino) propionamide trifluoroacetate	
Compound 4 (Example 3)	(R)-2-amino-N-((R)-1-(((R)-1-amino-3-mercapto-1-oxopropan-2-yl)amino)-3-mercapto-1-oxopropan-2-yl)-3-mercaptopropanamide trifluoroacetate	

Method: Irradiation and drug treatment: ^{137}Cs γ-ray irradiation was carried out on the whole body at an irradiation dose rate of 0.7Gy/min, and the absorbed dose of mice was 6.8Gy, 7.2Gy and 7.5Gy, respectively; aminofostine, compound 1, compound 2, compound 3, and compound 4 were dissolved in normal saline, shaken evenly when administering them (200mg/kg BW), and injected intraperitoneally 30min before irradiation. The 30-day survival of the mice in each group was observed, the survival rates were calculated, the body weights were followed, and the organs and white blood cells of mice in each group were compared after 30 days.

Results: At the same administration dose of the four compounds (200mg/kg, one dose at 24 hours before irradiation and one dose at 30 minutes before irradiation), one-time whole body irradiation with 6.8Gy, 7.2Gy and 7.5Gy ^{137}Cs gamma rays was performed, respectively, compared with the radiation and blank solvent group. The 30-day survival rate of mice was 100% when compound 1 was used in the cases of irradiations of 6.8Gy and 7.2Gy, respectively. The survival rate and body weight of mice in each group with different irradiation doses are shown in Figures 1, 3 and 5. The effects of normal control group and compound 1, compound 2, compound 3 and compound 4 on organs and leukocytes in mice 30 days after irradiation with 7.2Gy are shown in Figure 4. The effects of normal control group and compound 1 on organs and leukocytes in mice 30 days after irradiation with 6.8Gy and 7.5Gy, respectively, are shown in Figures 2 and 6.

Example B: This example studies the effects of different compounds (i.e., Example 17, Example 2, Example 3, Example 18, Example 8, Example 1, Example 4) on the survival rate of mice without radiation dose, respectively.

Laboratory animals: C57 male mice, 8-10 weeks old, 20-22g, were divided into 4 groups, 5 or 10 or 15 or 20 or 25 mice in each group. Irradiation conditions: 137Cs-γ rays, the dose rate was 0.7Gy/min, and the absorbed

doses of mice were 6.8Gy, 7.2Gy and 7.5Gy, respectively, one-time whole body irradiation (if not specified, the irradiation rays were all 137Cs-γ rays)

Administration and grouping:

In normal control group, intraperitoneal injection of normal saline was performed.

In irradiation control group, intraperitoneal injection of normal saline was performed 30min before the irradiation.

In amifostine + 6.8Gy (or 7.2Gy or 7.5Gy) group, intraperitoneal injection of amifostine (dissolved in normal saline, at a dosage of 200mpk) was performed 30min before the irradiation.

In Example 17 + 6.8Gy (or 7.2Gy or 7.5Gy) group, Example 17 (dissolved in normal saline, at a dosage of 200mpk) was intraperitoneally injected 30min before the irradiation.

Observation index: The death and weight of the mice were recorded, and the survival rate was calculated on the 30th day. The surviving mice were sacrificed, dissected, and each organ index (the weight of each organ as a percentage of the body weight of the mouse) was calculated.

Experimental results:

Group	6.8Gy (Survival number / Test number Survival rate)	7.2Gy (Survival number / Test number Survival rate)	7.5Gy (Survival number / Test number Survival rate)
Irradiation control group	3/5 60%	1/10 10%	0/5 0%
Amifostine, 200mpk, IP	5/5 100%	9/10 90%	5/5 100%
Example 17, 200mpk, IP	5/5 100%	9/10 90%	0/5 0%

The experimental operation was the same as the above, for the effects of different dosages on the survival rate of mice, except that the intraperitoneal injection of Example 17 was performed 90min before the irradiation.

Group	7.5Gy (Survival number / Test number Survival rate)
7.5Gy irradiation group	0/5 0%
Amifostine, 200mpk, IP	4/5 80%
Example 17, 400mpk, IP	0/5 0% (intraperitoneal injection 90min before irradiation)
Example 17, 800mpk, IP	0/5 0% intraperitoneal injection 90min before irradiation

The irradiation was invalid 90 minutes after administration.

Note: In the toxicity test of Example 17, muscle tremors and other toxic reactions were observed after intraperitoneal injection of 400mpk and 800mpk, followed by irradiation 90min after administration.

Example 2, Example 3, Example 18, Example 8, Example 1 and Example 4 were tested at different absorbed doses using the above similar conditions or operations. The experimental results are as follows:

Group	7.2Gy (Survival number / Test number Survival rate)
7.2Gy irradiation group	1/15 6.67%
Amifostine, 200mpk, IP	12/15 80%
Example 2, 200mpk, IP	10/15 66.67%

Group	7.2Gy (Survival number / Test number Survival rate)
7.2Gy irradiation group	1/15 6.67%
Amifostine, 200mpk, IP	12/15 80%
Example 3, 200mpk, IP	10/15 66.67%

Group	7.2Gy (Survival number / Test number Survival rate)
7.2Gy irradiation group	0/5 0%
Amifostine, 200mpk, IP	4/5 80%
Example 18, 200mpk, IP	4/5 80%

5

Group	7.2Gy (Survival number / Test number Survival rate)
7.2Gy irradiation group	0/5 0%
Amifostine, 200mpk, IP	4/5 80%
Example 8, 200mpk, IP	1/5 20%

Group	7.2Gy (Survival number / Test number Survival rate)
7.2Gy irradiation group	0/10 0%
Amifostine, 200mpk, IP	7/10 70%
Example 1, 200mpk, IP	6/10 60%

Group	7.2Gy (Survival number / Test number Survival

	rate)
Irradiation control group	4/25 16%
Amifostine, 200mpk, IP	20/25 80%
Example 4, 200mpk, IP	20/25 80%

Group	7.5Gy (Survival number / Test number Survival rate)
7.5Gy irradiation group	0/10 0%
Amifostine, 200mpk, IP	1/10 10%
Example 4, 800mpk, IP	7/10 70%

Group	7.5Gy (Survival number / Test number Survival rate)
7.5Gy irradiation group	2/10 20%
Amifostine, 365mpk, IP	10/10 100%
Example 4, 517mpk, IP	9/10 90%

Group	10Gy (Survival number / Test number Survival rate)
10Gy irradiation group	0/20 0%
Amifostine, 517mpk, IP	15/20 75%
Example 4, 365mpk, IP	15/20 75%

Group	12.5Gy (Survival number / Test number Survival rate)
12.5Gy irradiation group	0/10 0%
Amifostine, 517mpk, IP	5/10 50%
Example 4, 365mpk, IP	4/10 40%

The above results indicated that the mice using compounds of Example 17, Example 2, Example 3, Example 18, Example 8, Example 1, and Example 4 had survival rates comparable to those using amifostine when the absorbed dose was 6.8Gy and 7.2Gy, among which the mice using the compound of Example 4 had a survival rate equivalent to those using amifostine when the absorbed dose was even higher, such as as high as 12.5Gy.

Example C: Acute toxicity test:

Laboratory animals: C57 male mice, 8-10 weeks old, 20-22g, 5 or 10 mice in each group.

Administration and grouping: Each group was intraperitoneally injected with one corresponding dose of amifostine.

Each group was intraperitoneally injected with one corresponding dose of Example 17 (IP).

The 30-day survival rate of mice in each group was recorded. The results are shown in the table:

Dosage (mpk)	400mpk (Survival number / Test number)	600mpk (Survival number / Test number)	800mpk (Survival number / Test number)	900mpk (Survival number / Test number)	1000mpk (Survival number / Test number)	1100mpk (Survival number / Test number)	1200mpk (Survival number / Test number)	1600mpk (Survival number / Test number)	3200mpk (Survival number / Test number)
Amifostine (IP)	5/5	5/5	3/5	NA	NA	NA	NA	0/5	NA
Example 17 (IP)	5/5	NA	5/5	NA	NA	NA	NA	4/5	NA
Example 4 (IP)	10/10	5/5	10/10	10/10	6/6 10/10	8/10	6/10	3/10	NA

Acute toxicity tests indicated that the compound of the present invention, especially Example 4, was as safe as or even better than amifostine at high doses, in which the compound of Example 4 even had a 100% survival rate at a dose of 1000mpk.

Example D: Protective effect of the compounds in the present invention on the hematopoietic system:

Laboratory animals: C57 male mice, 8-10 weeks old, 20-22g, 5 mice in each group.

Administration and grouping: In normal control group, intraperitoneal injection of normal saline was performed, without irradiation.

In administration control group, intraperitoneal injection of Example 4 (800mpk) was performed, without irradiation.

In irradiation control group, intraperitoneal injection of normal saline was performed 30min before the irradiation at 4Gy.

In irradiation administration group, intraperitoneal injection of Example 4 (800mpk) was performed 30min before the irradiation at 4Gy.

The mice were sacrificed on the 15th day after the irradiation, followed by blood collection. Femoral bone marrow cells, spleen and thymus were weighed, and cells were extracted for detecting the peripheral white blood cell (WBC) count, peripheral red blood cell (RBC) count, peripheral hemoglobin (HGB) concentration, peripheral platelet (PLT) count, peripheral blood lymphocyte ratio (LY%), and peripheral blood neutrophil ratio (NE%). The results are shown in Figure 7. The results showed that the number of WBC and RBC in the peripheral blood of mice was reduced by irradiation, and the number of these cells was increased by administration of Example 4 with significant difference; irradiation reduced LY% and increased NE% in peripheral blood of mice, and administration of Example 4 alleviated this abnormal differentiation with significant difference.

In addition, the number of leukocytes in bone marrow, ratio of hematopoietic stem cell (LSK) in bone

marrow cells, ratio of hematopoietic progenitor cells (HPC) in bone marrow cells, ratio of CD34-LSK in bone marrow cells, and ratio of CD34+LSK in bone marrow cells were detected. The results are shown in Figure 8. The results showed that the number of WBC, LSK% and HPC% in the bone marrow of mice was decreased by irradiation, and the number of these cells was increased by administration of Example 4 with significant difference; irradiation increased CD34-LSK% and decreased CD34+LSK% in the bone marrow of mice, and administration of Example 4 alleviated this abnormal differentiation with significant difference.

The effects of irradiation on LSK intracellular reactive oxygen species (ROS) level and HPC intracellular ROS level were also detected. The results are shown in Figure 9. The results showed that irradiation increased the ROS levels in LSK and HPC cells in the bone marrow of mice, and administration of Example 4 reduced the ROS levels with significant difference.

Example E: Protective effect of the compounds of the present invention on the intestinal tract

Example E1: Survival rate of radiation intestinal damage

Laboratory animals: C57 male mice, 8-10 weeks old, 20-22g, 5 mice in each group.

Administration and grouping: In irradiation control group, intraperitoneal injection of normal saline was performed 30min before the irradiation, with local abdominal irradiation at 18Gy.

In amifostine group, intraperitoneal injection was performed 30min before the local abdominal irradiation at 18Gy, wherein amifostine was dissolved in normal saline, 200mpk.

In Example 4 group, intraperitoneal injection was performed 30min before the local abdominal irradiation at 18Gy, wherein Example 4 was dissolved in normal saline, 800mpk.

The 30-day survival rate of mice in each group was recorded. The results are shown in Figure 10.

Example E2: HE staining on the 5^{th} day after local intestinal irradiation

Laboratory animals: C57 male mice, 8-10 weeks old, 20-22g, 3 mice in each group

Administration and grouping: In normal control group, intraperitoneal injection of normal saline was performed, with false irradiation.

In irradiation control group, intraperitoneal injection of normal saline was performed 30min before the irradiation, with local abdominal irradiation at 16Gy

In amifostine group, intraperitoneal injection was performed 30min before the local abdominal irradiation at 16Gy, wherein amifostine was dissolved in normal saline, 365mpk.

In Example 4 group, intraperitoneal injection was performed 30min before the local abdominal irradiation at 16Gy, wherein Example 4 was dissolved in normal saline, 517mpk.

The mice were sacrificed on the 5^{th} day after the irradiation, and the small intestine was taken and sectioned for HE staining. The results are shown in Figure 11, and Figure 11 shows that the normal unirradiated intestinal villi had clear and dense structures; the structure of villi in the small intestine changed after irradiation; the intestinal villi in the Example 4 irradiation group and the amifostine irradiation group showed slight changes compared with the irradiation group.

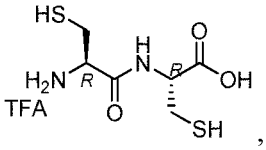
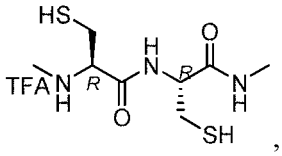
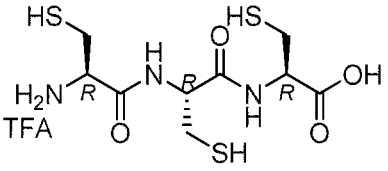
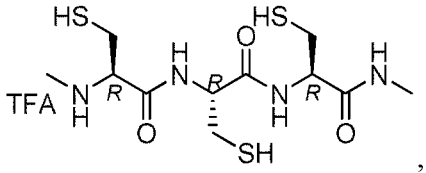
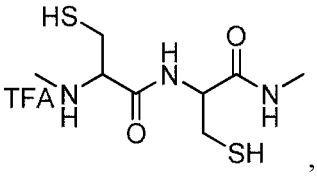
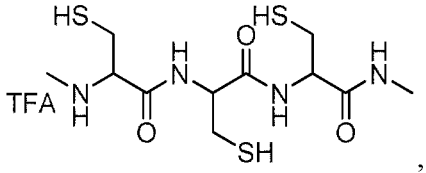
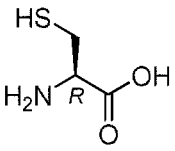
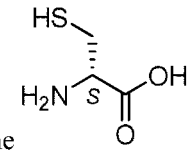
Example F: Effect of Example 4 on radiation pneumonia:

Laboratory animals: C57 male mice, 8-10 weeks old, 20-22g, 3 mice in each group

Administration and grouping: Mice were intraperitoneally injected with normal saline, Example 4 (400mpk), and amifostine (200mpk) respectively 30min before irradiation, and the right lungs were irradiated at 17Gy by X rays. The right lungs were taken on the 60^{th} day for HE staining (n=3):

Two months after irradiation of the unilateral lung, the most important lung manifestation was radiation pneumonia. The lung tissues in mice of the control group showed obvious vacuolar structure, and no alveolar wall thickening was observed. The alveolar structure of mice in the 17Gy group was changed, which was manifested as a large area of inflammatory infiltration of the lung (the blue dots were inflammatory cells), and the alveoli were filled with inflammatory cells. Both amifostine and Example 4 could partially relieve inflammatory cell infiltration and reduce the incidence of radiation pneumonia. The results are shown in Figure 12.

Example G: This example investigated the effect of stereoisomerism on survival rate

In this Example, the effects of compounds such as Example 1  , Example 2  , Example 3  , Example 4  , Example 19  , Example 20  , as well as L-cysteine  and D-cysteine  on the survival rate of mice under irradiation were further studied.

Laboratory animals: C57 male mice, 19-21g, purchased from Beijing HFK Bioscience Co. Ltd., license number SCXK (Beijing), 9 mice in each group.

Administration and grouping: In 7.5Gy irradiation control group, intraperitoneal injection of normal saline was performed 30min before the irradiation.

The other administration groups were treated by intraperitoneal injection of normal saline solutions of the corresponding drugs, 200mg/kg, 30min before the irradiation.

The experimental results are shown in the table below and Figure 13:

	7.5Gy (Survival number / Test number)		7.5Gy (Survival number / Test number)		7.5Gy (Survival number / Test number)
Irradiation control group	0/9 (9 deaths)				
L-Cys	1/9				

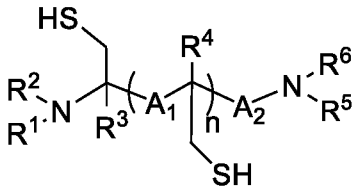
	(8 deaths)				
D-Cys	0/9 (9 deaths)				
Example 4	5/9 (4 deaths)	Example 20	1/9 (8 deaths)	Example 3	2/9 (7 deaths)
Example 2	4/9 (5 deaths)	Example 19	2/9 (7 deaths)	Example 1	1/9 (8 deaths)

The survival rate in the case of Example 4 was approximately 56%, significantly higher than that of cysteine trimer of Example 3 (approximately 22%) and the racemate of Example 20; the survival rate in the case of Example 2 was approximately 44%, significantly higher than that of cysteine dimer of Example 1 (approximately 11%) and the racemate of Example 19. It indicates that N-methylation of cysteine polymer can significantly improve the survival rate of irradiated mice and further enhance the irradiation protection ability of the compounds.

At this point, a person skilled in the art should realize that although the present invention has illustrated and described several exemplary embodiments of the present invention in detail, many other variations or modifications conforming to the principle of the present invention can be directly determined or deduced according to the disclosed contents of the present invention without departing from the spirit and scope of the present invention. Therefore, the scope of the present invention shall be understood and deemed to cover all such other variations or modifications.

What is claimed is:

1. A compound of formula (I):



(I)

wherein

A_1 is selected from: $-C(O)NR^8-$, $-S(O)_2-NR^8-$, $-S(O)NR^8-$, and $-R^7-NR^8-$;

A_2 is selected from: carbonyl, sulfonyl, sulfinyl, and unsubstituted C_{1-6} alkylene;

R^1 is selected from: hydrogen, unsubstituted C_1-C_5 alkyl or unsubstituted heteroalkyl;

R^2 is selected from: unsubstituted C_1-C_5 alkyl or unsubstituted heteroalkyl;

R^5 is selected from: hydrogen, unsubstituted C_1-C_5 alkyl or unsubstituted heteroalkyl;

R^6 is selected from: unsubstituted C_1-C_5 alkyl or unsubstituted heteroalkyl;

n is an integer of 1 or 2;

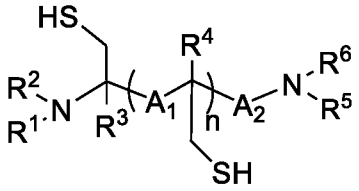
R^3 and R^4 are independently selected from: hydrogen, X, and unsubstituted C_{1-6} alkyl;

X is selected from: F, Cl, Br and I; and

R^7 is selected from: unsubstituted C_1-C_6 alkylene; R^8 is selected from: hydrogen, and unsubstituted C_1-C_6 alkyl;

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

2. A compound of formula (I):



(I)

wherein

A_1 is selected from: $-C(O)NR^8-$, $-S(O)_2-NR^8-$, $-S(O)NR^8-$, and $-R^7-NR^8-$;

A_2 is selected from: carbonyl, sulfonyl, sulfinyl, and unsubstituted C_{1-3} alkylene;

R^1 is selected from: hydrogen, C_{1-3} alkyl, and hydroxy- or amino-substituted C_1-C_3 alkyl or unsubstituted heteroalkyl;

R^2 is selected from: C_{1-3} alkyl, and hydroxy- or amino-substituted C_1-C_3 alkyl or unsubstituted heteroalkyl;

R^5 is selected from: hydrogen, C_{1-3} alkyl, and hydroxy- or amino-substituted C_1-C_3 alkyl or unsubstituted heteroalkyl;

R^6 is selected from: hydrogen, C_{1-3} alkyl, and hydroxy- or amino-substituted C_1-C_3 alkyl or unsubstituted heteroalkyl;

n is an integer of 1 or 2;

R^3 and R^4 are independently selected from: hydrogen, X, and unsubstituted C_{1-3} alkyl;

X is selected from: F and Cl;

R^7 is selected from: unsubstituted C_1-C_3 alkylene; and

R^8 is selected from: hydrogen, and unsubstituted C_1-C_3 alkyl;

wherein the chiral carbon directly attached to R^3 and R^4 is in R configuration or S configuration.

3. The compound of claim 1 or 2, wherein A_2 is selected from: carbonyl, sulfonyl, sulfinyl, and methylene;

R^1 is selected from: hydrogen, methyl, and ethyl;

R^2 is selected from: methyl, and ethyl;

R^5 is selected from: hydrogen, methyl, and ethyl;

R^6 is selected from: methyl, and ethyl;

n is an integer of 1 or 2;

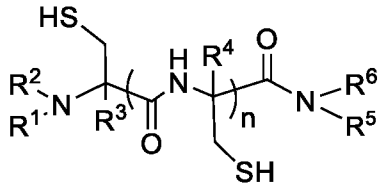
R^3 and R^4 are independently selected from: hydrogen, X, and methyl;

X is F;

R^7 is methylene; and

R^8 is selected from: hydrogen, methyl, and ethyl.

4. The compound of claim 1 or 2, wherein the compound has the following general formula:



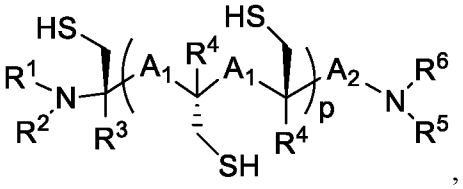
(II)

wherein the varaibles R^1, R^2, R^3, R^4, R^5, R^6 and n are defined as in claim 1.

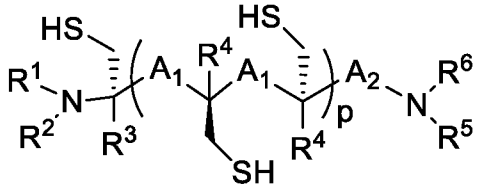
5. The compound of claim 1 or 2, wherein n an interger of is 1.

6. The compound of claim 1 or 2, wherein n an interger of is 2.

7. The compound of claim 1 or 2, wherein the compound has the following general formulas:



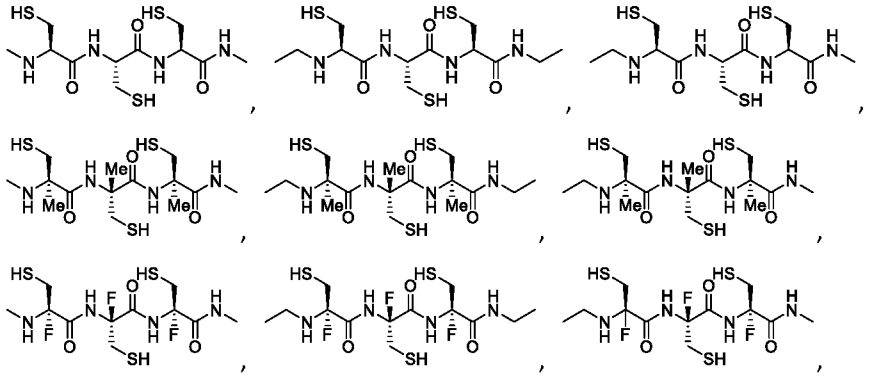
, or

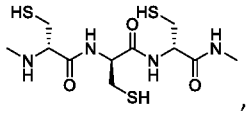


(III) (IV)

wherein p is an integer of 1.

8. The compound of claim 1, wherein the compound is selected from:

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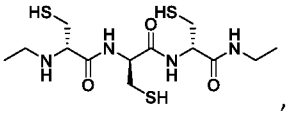
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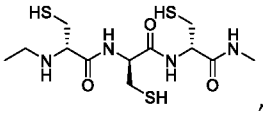
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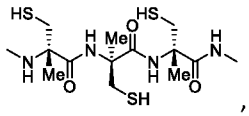
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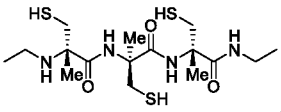
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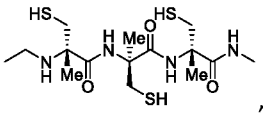
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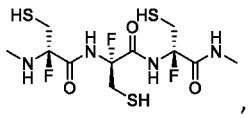
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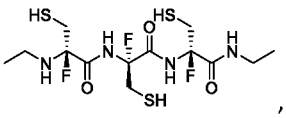
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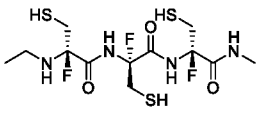
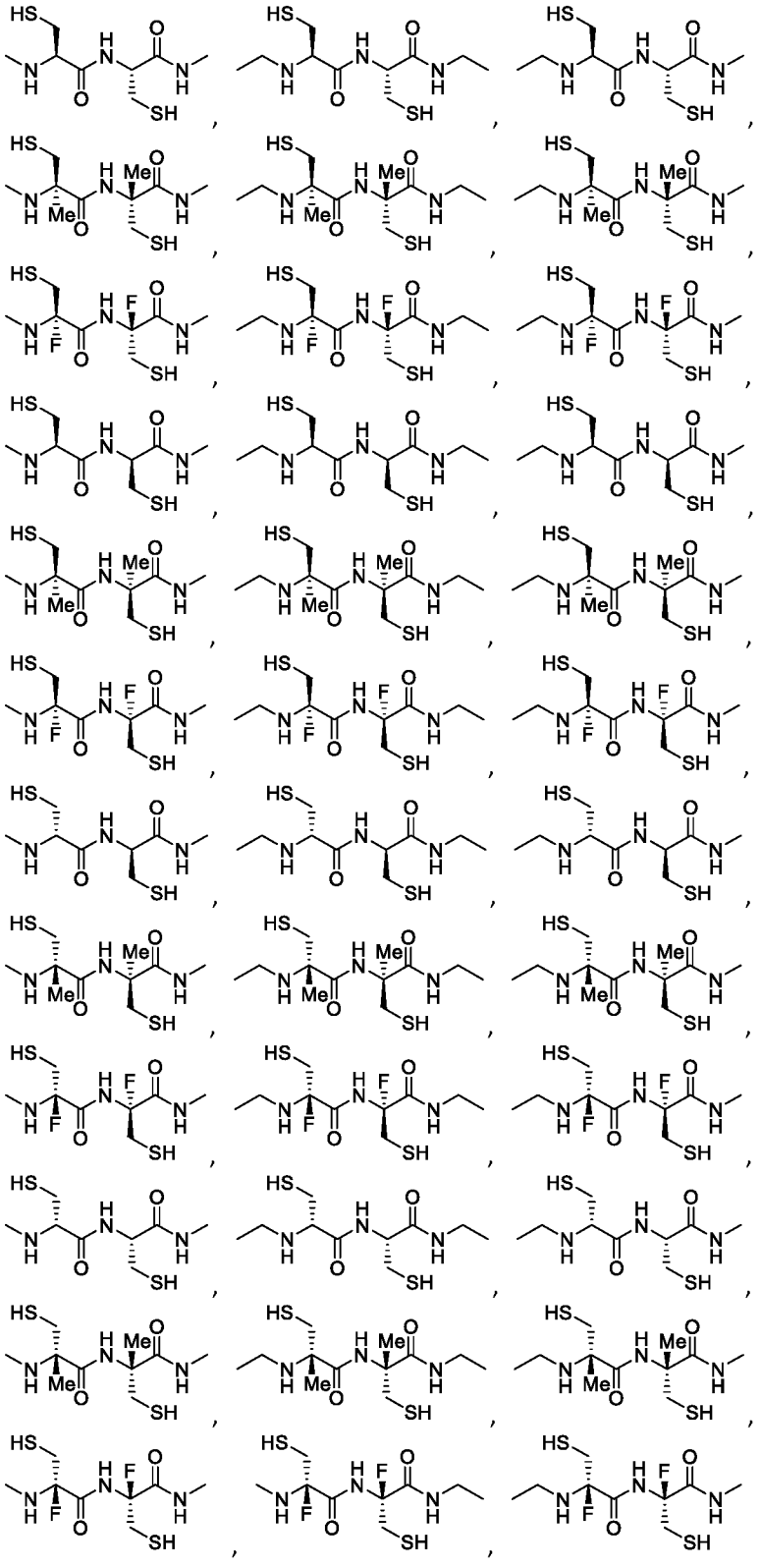
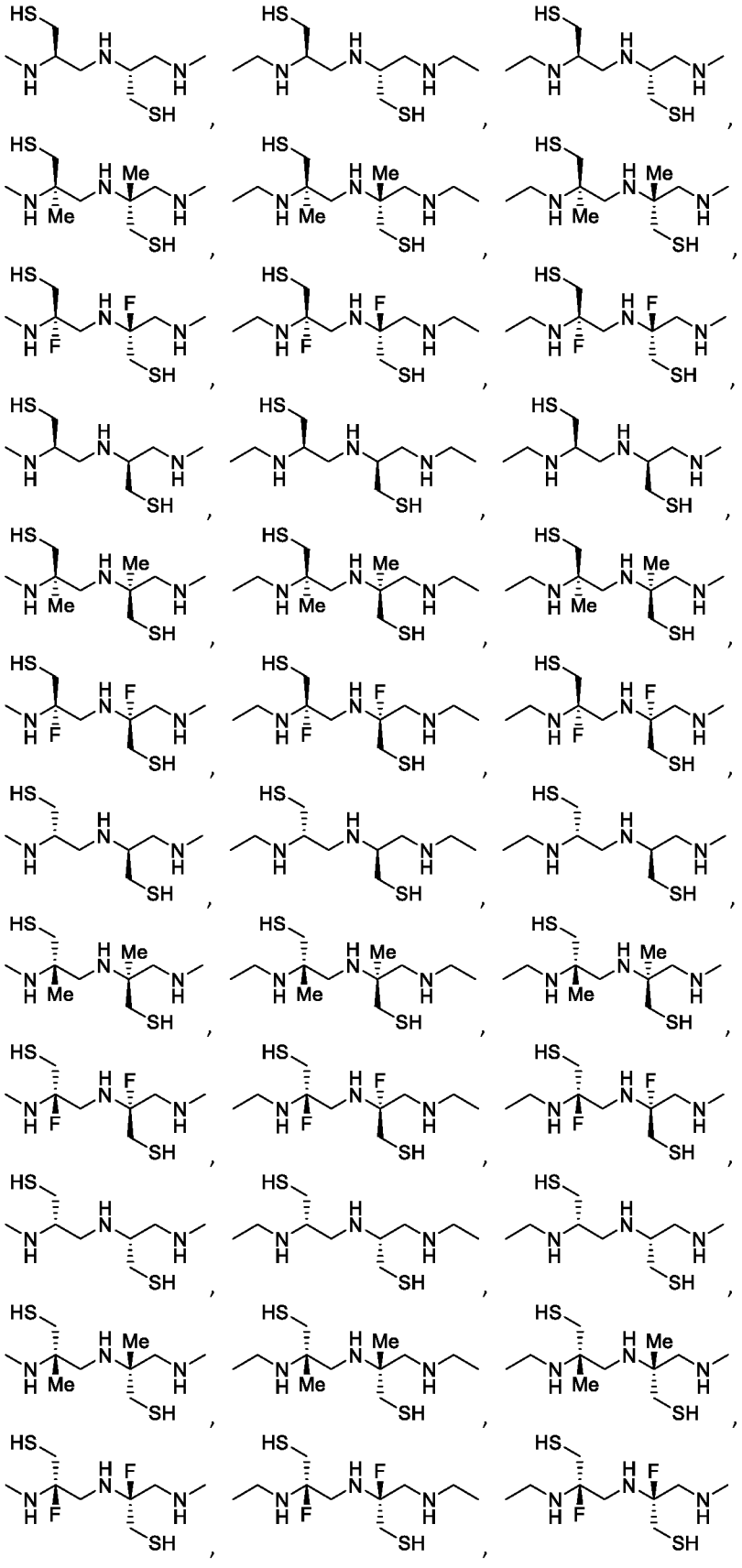
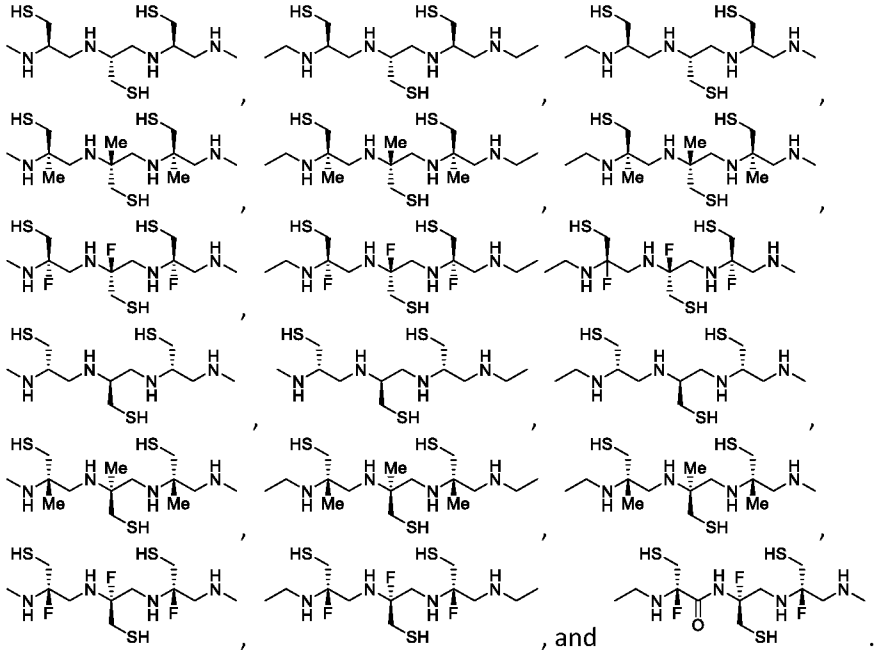
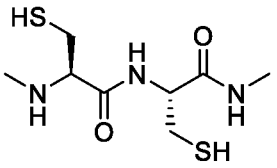


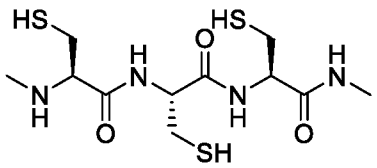






, and .

9. The compound of claim 1, wherein the compound is  .

10. The compound of claim 1, wherein the compound is  .

11. A pharmaceutical composition comprising the compound of any one of claims 1-10 and one or more pharmaceutically acceptable vehicles, carriers, adjuvants, auxiliaries or diluents.

12. The pharmaceutical composition of claim 11, wherein the pharmaceutical composition is in a dosage form selected from an injection, an emulsion, a microemulsion, a sub-microemulsion, a nanoparticle, a tablet, a capsule, a pill, an inhalant, a lozenge, a gel, a powder, a suppository, a suspension, a cream, a jelly, or a spray.

13. The use of the compound of any one of claims 1-10 or the pharmaceutical composition of any one of claims 11-12 in the preparation of drugs or cosmetics for the treatment or prevention of radiation damage or chemotherapy damage.

14. The use of claim 13, wherein the radiation comprises ionizing radiation, non-ionizing radiation or a combination of various types of radiation;

the ionizing radiation comprises alpha rays, beta rays, gamma rays, X rays, or neutron radiation;

the radiation damage comprises direct damage or indirect damage caused by radiation; and

the chemotherapy damage results from anti-tumor drugs acting on DNA, RNA or tubulin.

15. The use of claim 13, wherein the use is the use of the compound of any one of claims 1-10 or the pharmaceutical composition of any one of claims 11-12 in the preparation of drugs and cosmetics for the treatment or prevention of sunburn damage.

16. The use of the compound of any one of claims 1-10 or the pharmaceutical composition of any one of

claims 11-12 in the preparation of a medicament for treating tumor related to radiation damage.

17. The use of claim 13, wherein the pharmaceutical composition further comprises a radioprotective agent.

18. A method of treating or preventing radiation damage or chemotherapy damage including the step of administering a therapeutically effective amount of the compound of any one of claims 1-10 or the pharmaceutical composition of any one of claims 11-12.

19. A method of treating or preventing sunburn damage including the step of administering a therapeutically effective amount of the compound of any one of claims 1-10 or the pharmaceutical composition of any one of claims 11-12.

20. A method of treating a tumor related to radiation damage including the step of administering a therapeutically effective amount of the compound of any one of claims 1-10 or the pharmaceutical composition of any one of claims 11-12.

Figure 1A

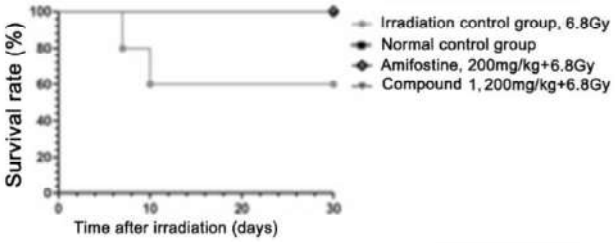


Figure 1B

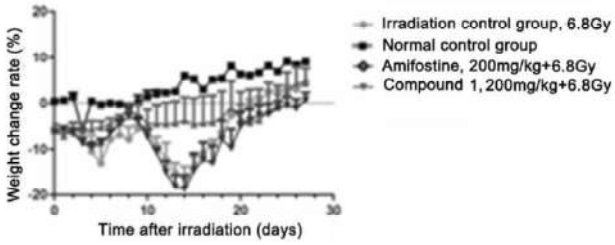


Figure 2A

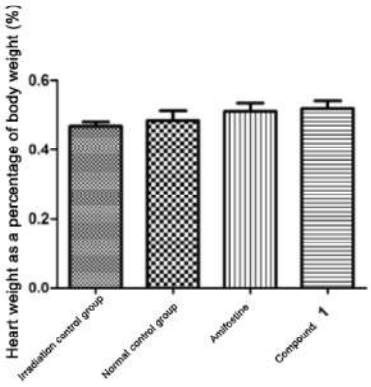


Figure 2B

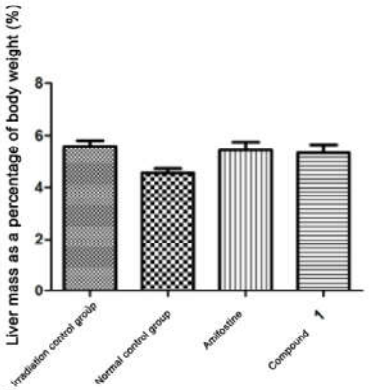


Figure 2C

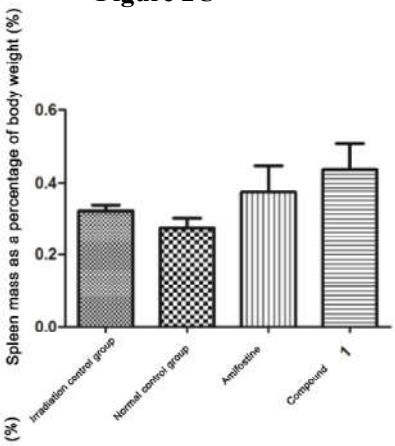


Figure 2D

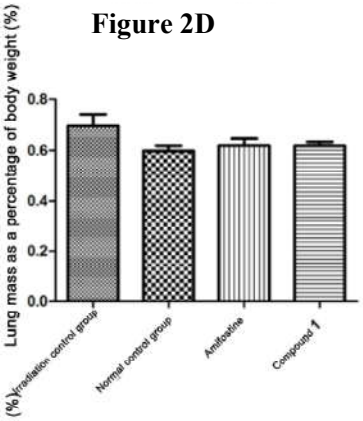


Figure 2E

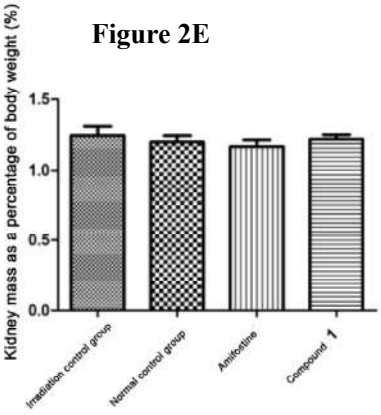


Figure 2F

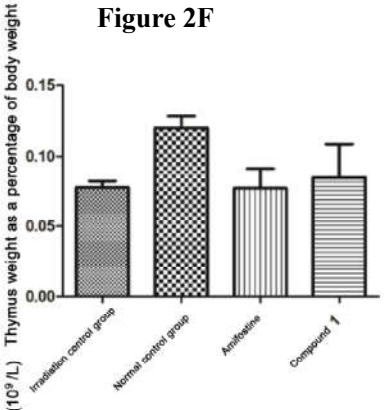


Figure 2G

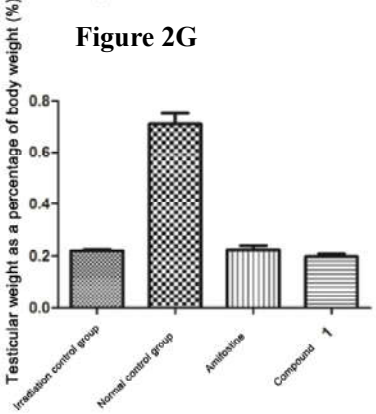


Figure 2H

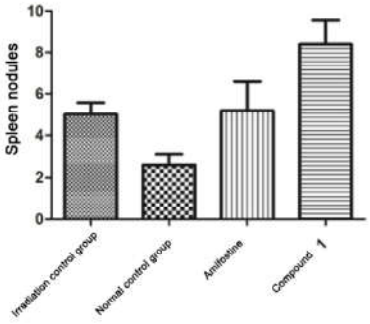


Figure 2I

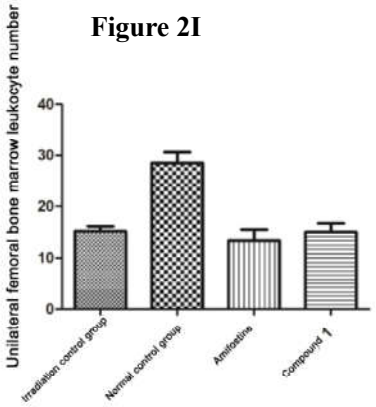


Figure 2J

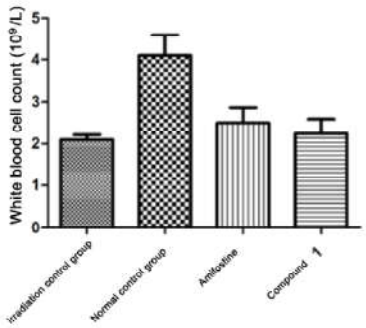


Figure 3A

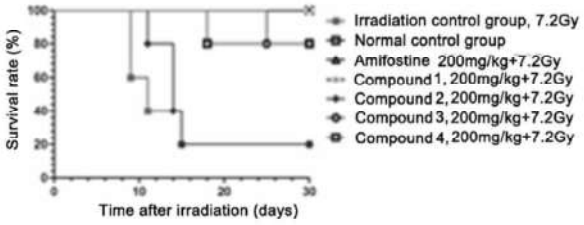


Figure 3B

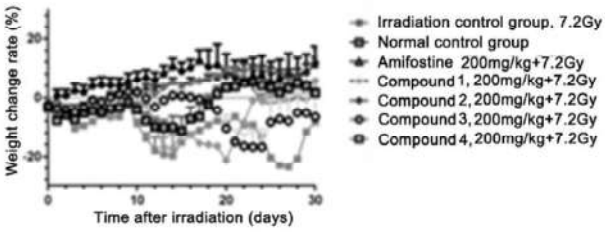


Figure 4A

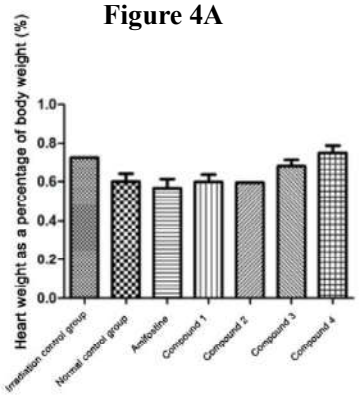


Figure 4B

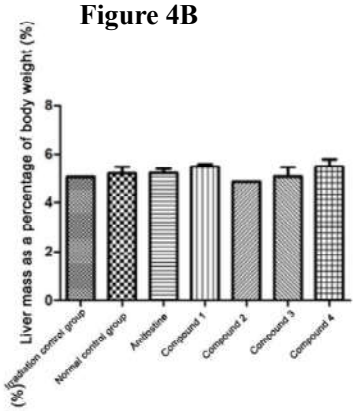


Figure 4C

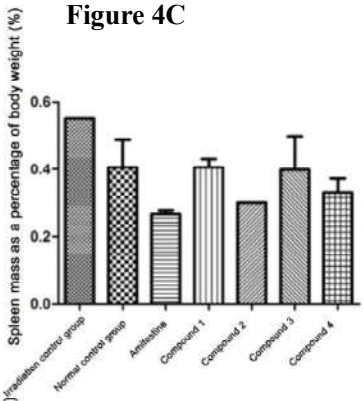


Figure 4D

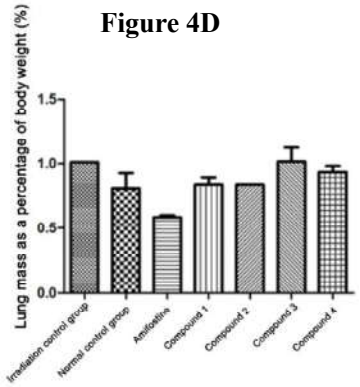


Figure 4E

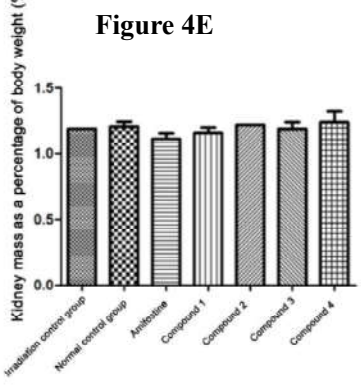


Figure 4F

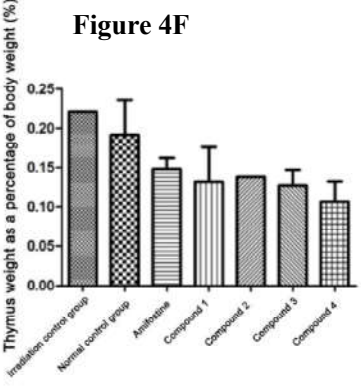


Figure 4G

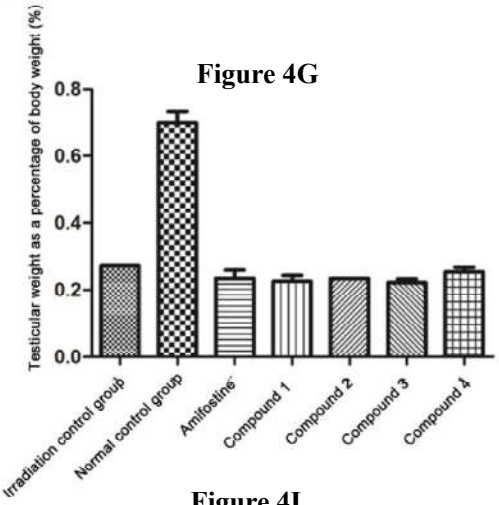


Figure 4H

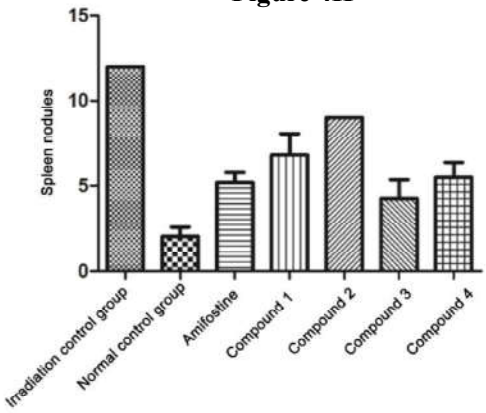


Figure 4I

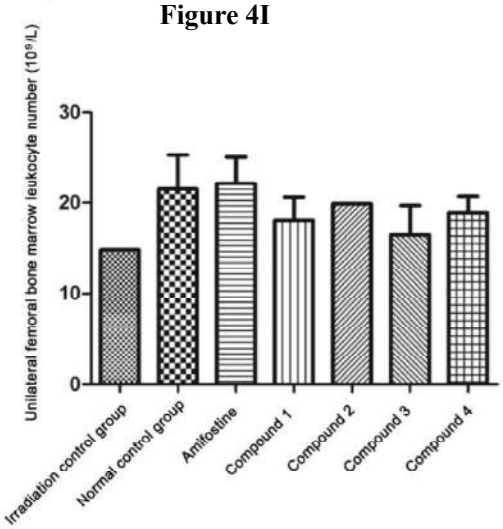


Figure 4J

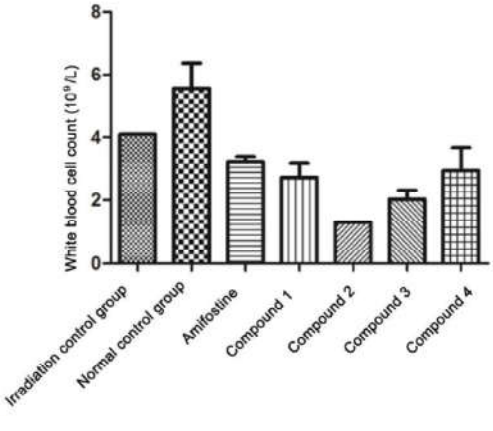


Figure 5A

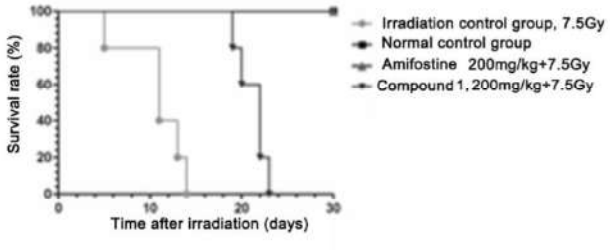


Figure 5B

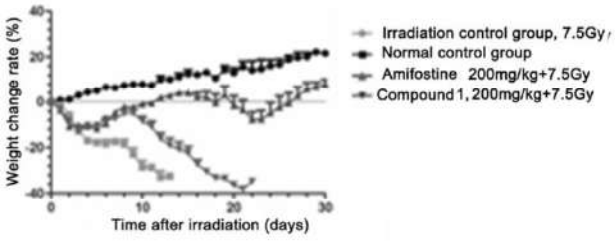


Figure 6A

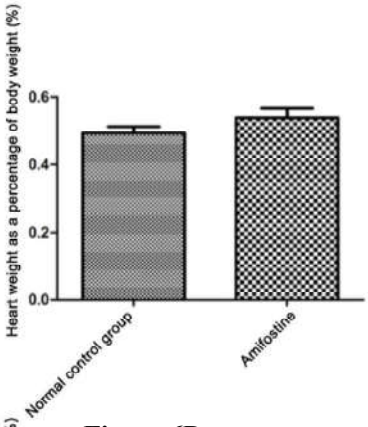


Figure 6B

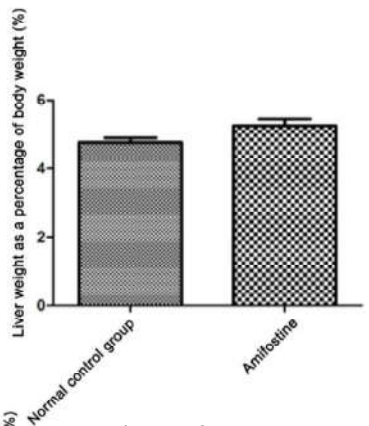


Figure 6C

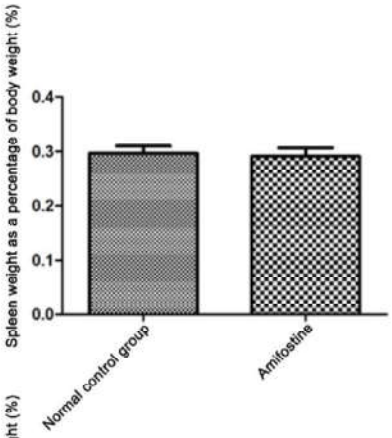


Figure 6D

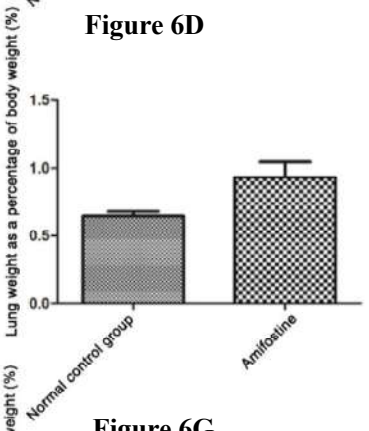


Figure 6E

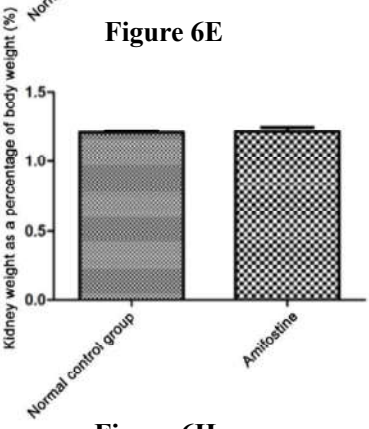


Figure 6F

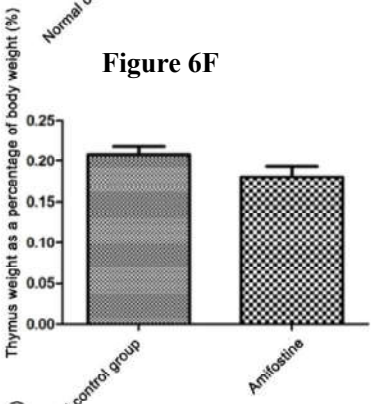


Figure 6G

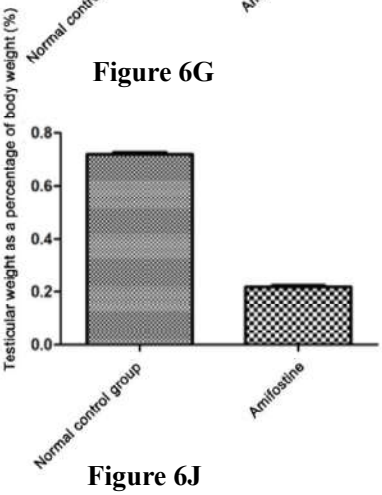


Figure 6H

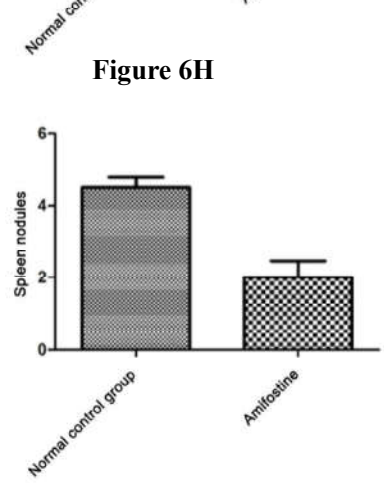


Figure 6I

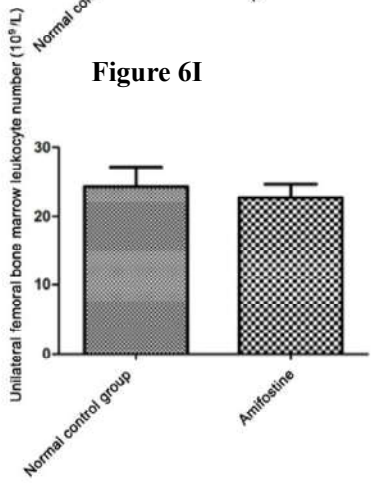


Figure 6J

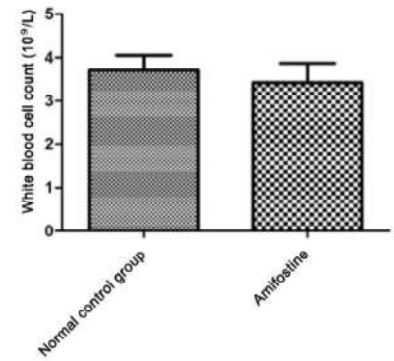


Figure 7A

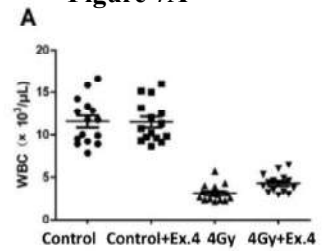


Figure 7B

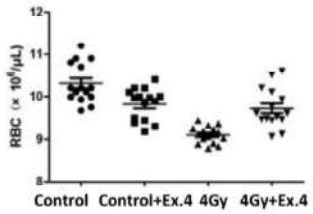


Figure 7C

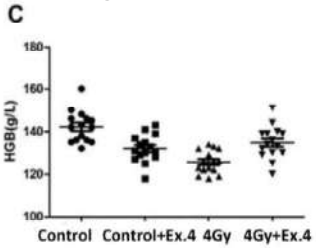


Figure 7D

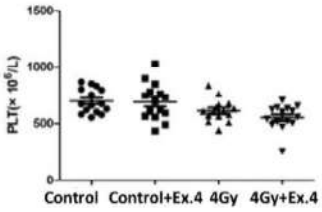


Figure 7E

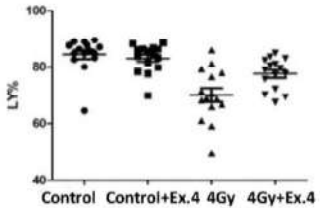


Figure 7F

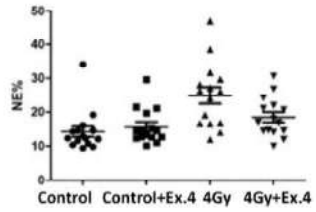


Figure 8A

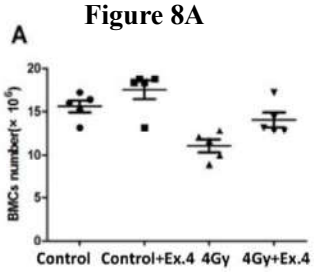


Figure 8B

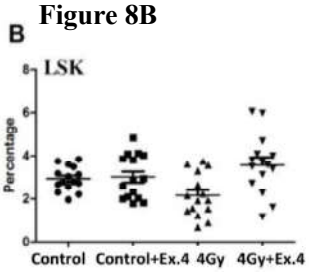


Figure 8C

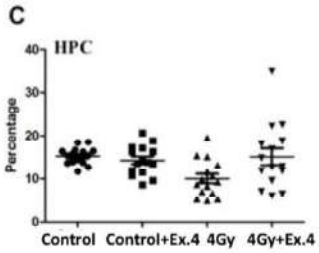


Figure 8D

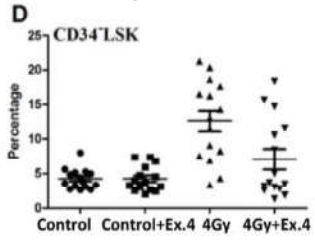


Figure 8E

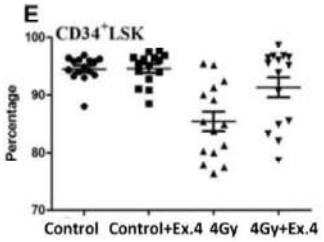


Figure 9A

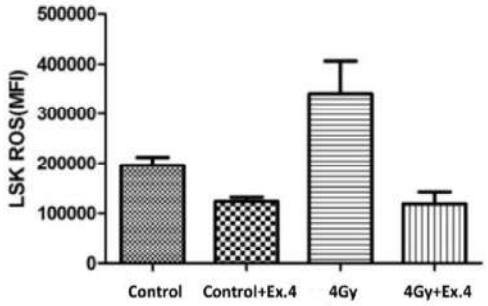


Figure 9B

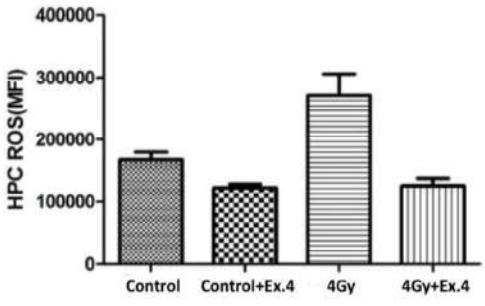


Figure 10

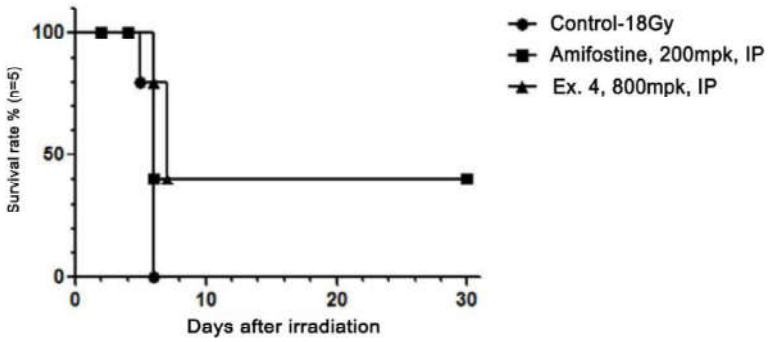


Figure 11

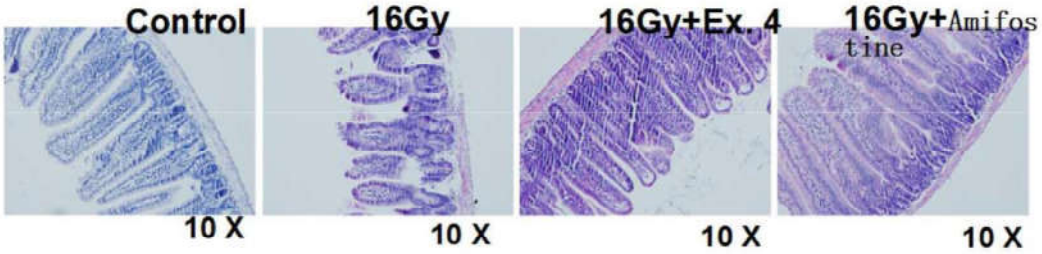


Figure 12

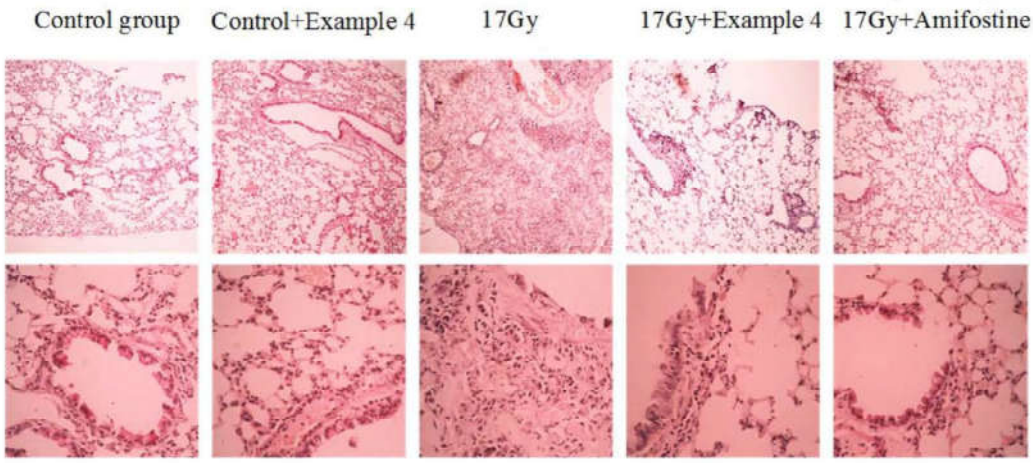


Figure 13