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(72) Inventor; and
(71) Applicant: **DEMIR, Caner** [TR/TR]; Kartaltepe Mh. İkiztepe Sk. No:1, İstanbul (TR).

(72) Inventor: **ÜRETMEN, Aybüke**; Atakent Mh. 231. Sk. No:1 K/14, 34307 İstanbul (TR).

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(54) **Title:** CESIUM DICHLOROACETATE COMPOUND TO BE USED IN CANCER TREATMENT

(57) **Abstract:** The invention is about cesium dichloroacetate compound to be used in cancer treatment and its synthesis method. Cesium and dichloroacetate works together to break apoptosis resistance of cancerous cells and make them undergo apoptosis. In the invention's subject compound, cesium dichloroacetate, cesium element anddichloroacetate molecule shows a synergic effect. As a result of metabolic,electrochemical and possible genetic and epigenetic effects caused by the synthesized compound mentioned above, cancerous cells undergo controlled cell death by apoptosis and some of them undergo necrosis.

CESIUM DICHLOROACETATE COMPOUND TO BE USED IN CANCER TREATMENT

The Technical Field

The invention is about a compound and its synthesis method, which is to be used in chemical and pharmaceutical industries.

The invention is especially about cesium dichloroacetate compound and its synthesis method, to be used in cancer treatment.

Background of the invention

Cancer is a large disease group with more than 200 types, effecting any part of the body. Cancer, one of the leading causes of death globally, caused 8,8 million people to lose their lives in 2015 according to World Health Organization (WHO).

Cesium chloride (CsCl) and cesium bicarbonate (CsHCO3) salts of the cesium element (Cs) are used in cancer studies that are done in in vivo and in vitro levels. Cesium is observed to have different reactions in different types of cancer. Known and used salts of cesium in cancer treatment do not have the ability to kill the cancerous cells or tumorous tissue with high effectivity. Cesium initiates programmed cell death in cancerous cells, named as apoptosis. However, most of the cancerous cells are resistant to apoptosis and would not easily undergo apoptosis. Another factor decreasing the effectiveness of the cesium is that entry of cesium inside a cell cannot be done with high effectivity. In addition to these, compounds such as chlorine in cesium salts and bicarbonate are not pestilent on cancerous cells. They only make cesium solutions to have a neutral pH value.

Salts of dichloroacidic acid (2,2 - dichloroacidic acid) such as sodium dichloroacetate and potassium dichloroacetate are utilized for their anti-cancer properties in in vivo and in vitro cancer studies.

In document with the file number US2016339106, a molecular structure, aimed for the production of a metabolic inhibitor that is loaded with cancerous cell activity and anti-tumour immunity is explained. Said structure aims for the mitochondria of the

cancerous cell. The structure consists of a piece like trifenylphosphonium cation and metabolic inhibitors aiming for the mitochondria like dichloroacetic acid, put together with a biologically degradable connecter.

In document with the file number US2016339106, a formulation containing dichloroacetate and arsenic trioxide is explained. This invention also showcases a method for cancer treatment by therapeutically applying a sufficient amount of dichloroacetate and arsenic trioxide.

Dichloroacetate is known to change the energy metabolic pathway in cancerous cells. In the metabolisms of healthy cells, energy production out of glucose is provided by oxidative phosphorylation occurs in the mitochondria, by using oxygen. In the metabolism of cancerous cells, energy production out of glucose is mainly provided by lactic acid fermentation, which does not use oxygen. Dichloroacetate salts lead the increasing lactic acid fermentation pathways in cancerous cells towards oxidative phosphorylation as well. As a result of this, it opens the ways for apoptosis mechanism of the cancer cells. Albeit, dichloroacetate does not poses the power of high fatality in all cancer types.

The application should be done over a certain dose treshold in order for cesium salts and dichloroacetic acid (2,2 - dichloroacetic acid) to have high efficiency upon cancerous cells. This circumstance bring along the risk of harming the healthy cells. On the other hand, when applied in small doses, cesium (Cs) salts and dichloroacetate (DCA) salts may contribute to increase multiplication of cancerous cells.

Subject compound of the invention has high cytotoxic effect on cancerous cells. The cause of this effect is due to the cesium elements and dichloroacetate molecules found together in the compound. In this way, both cesium’s and dichloroacetate’s effect on cancerous cells are brought together and a cytotoxically more effective compound, compared to their salts, are made.

In conclusion, due to inconvenience and inefficacy of current solutions mentioned above, an improvement in the technical field is required.

The Purpose of the Invention

Being influenced by current situations puts the invention together and it aims to solve the inconveniences stated above.

The main purpose of the invention is to break the apoptosis resistance of cancerous cells and make them undergo apoptosis. In subject compound of the invention, cesium and dichloroacetate works together to break apoptosis resistance of cancerous cells and make them undergo apoptosis.

Another purpose of the invention is to acquire cesium dichloroacetate compound used in cancer treatment. In synthesis method of the compound, cesium dichloroacetate is made up of basic cesium hydroxide (CsOH) or cesium bicarbonate ($CsHCO_3$) reacting with acidic dichloroacetic acid ($CHCl_2COOH$). Cesium compounds with basic pH values in aqueous solutions may also be used in the reaction.

To fulfil the purposes stated above, the invention is a drug containing cesium dichloroacetate which is aimed to use for cancer treatment in human and animals, shrinking and terminating in vivo tumors, terminating cell proliferation and division.

The structural and characteristic qualities of the invention and all advantages of it will be understood better with the figures given down below and a detailed explanation referring these figures, because of this, the evaluation must be done regarding these figures and their explanations.

Figures to Help Understand the Invention

Figure 1: FTIR analysis of the synthesized cesium dichloroacetate compound.

Figure 2: FTIR analysis of the cesium hydroxide compound.

Figure 3: FTIR analysis of the dichloroacetic acid compound.

Figure 4: Representation of synthesized cesium dichloroacetate (CsDCA), cesium chloride (CsCl) and sodium dichloroacetate (NaDCA) compounds application over PC3 prostate cancer cell line, measurement times and measurement criteria.

Figure 5-a: The amount of cells, normalized according to the control, after 24 hours, which were treated with cesium chloride (CsCl).

Figure 5-b: The amount of cells, normalized according to the control, after 24 hours, which were treated with sodium dichloroacetate (NaDCA).

Figure 5-c: The amount of cells, normalized according to the control, after 24 hours, which were treated with cesium dichloroacetate (CsDCA).

Figure 6-a: The amount of cells, normalized according to the control, after 48 hours, which were treated with cesium chloride (CsCl).

Figure 6-b: The amount of cells, normalized according to the control, after 48 hours, which were treated with sodium dichloroacetate (NaDCA).

Figure 6-c: The amount of cells, normalized according to the control, after 48 hours, which were treated with cesium dichloroacetate (CsDCA).

Figure 7-a: The amount of cells, normalized according to the control, after 72 hours, which were treated with cesium chloride (CsCl).

Figure 7-b: The amount of cells, normalized according to the control, after 72 hours, which were treated with sodium dichloroacetate (NaDCA).

Figure 7-c: The amount of cells, normalized according to the control, after 72 hours, which were treated with cesium dichloroacetate (CsDCA).

Figure 8: Cl-Caspase-3 amounts of cells that were applied drugs containing synthesized cesium dichloroacetate (CsDCA) compound, cesium chloride (CsCl) and sodium dichloroacetate (NaDCA) compounds at hour 48.

Figure 9: Images of ezrin protein marked by immunohistochemistry method.

A Detailed Explanation Of The Invention

In this detailed explanation, preferred structures of the invention's subject compound cesium dichloroacetate will be explained, solely for a better comprehension of the topic.

The invention's subject compound, cesium dichloroacetate (CsDCA) compound, has high cytotoxic effect on cancerous cells. The reason for this effect is that the compound contains both cesium (Cs) element and dichloroacetate (DCA) molecule. In the invention, basic cesium hydroxide (CsOH) or cesium bicarbonate ($CsHCO_3$) molecule and acidic dichloroacetic acid ($CHCl_2COOH$) molecule are put into reaction and the cesium dichloroacetate (CsDCA) compound is synthesized. In this way, both cesium's and dichloroacetate's effect upon cancerous cells are combined. Aforesaid cesium dichloroacetate compound, when compared to its component's salts, surprisingly showcases a more effective cytotoxic property. Referring to Figure 1, cesium dichloroacetate compound is shown to portray a different bond structure than cesium hydroxide and dichloroacetic acid given in Figure 2 and Figure 3, respectively, and other molecules used in the synthesis.

With the use of cesium element, potassium channels of cancer cells are blocked. In this way, as a result of deterioration in ion flow and cell membrane potential, the cell undergoes apoptosis. Through decreasing glucose entrance inside the cell, feeding of the cancerous cell is restrained. Doing so slows the growth rate of cancer cells down. In this way, it is induced for the cancer cells to undergo apoptosis.

With the use of dichloroacetate molecule, metabolism of the cancerous cell is shifted from lactic acid fermentation into oxidative phosphorylation. The cancerous cell's resistance to apoptosis is lowered and it is facilitated to undergo apoptosis. In this way, the cancerous cell becomes more sensitive to apoptosis. Increased oxygen radicals, increased in accordance to oxidative phosphorylation, cause the cell to enter apoptosis.

In the invention's subject compound, cesium dichloroacetate, cesium element and dichloroacetate molecule shows a synergic effect. By breaking the apoptosis resistance of the cancerous cells, the cancerous cell is led to undergo apoptosis.

Cesium dichloroacetate compound, synthesized to kill cancer cells or tumorous tissue, functions by disrupting the metabolism of cancerous cells. It deranges the intracellular potassium balance by blocking potassium channels from inside or outside of the cell. As a result of this, cell membrane potential is disturbed. Secondary effects develop in accordance with this. Changes occur about the entrance of materials that are carbon sources, like glucose, inside the cell. Flow of ions, between the inside and the outside of the cell, changes. Intracellular ion flow is also affected due to structural deformation of the cell skeleton (cytoskeleton) inside the cell. Thus the intracellular electrical balance changes too. Connection between intracellular skeletal proteins and extracellular matrix is corrupted. Consequently, the migration ability of the cancerous cell is eliminated. In this way, synthesized compound annihilates cancerous cell's ability to metastasize. On the other hand, it increases intracellular reactive oxygen amount by shifting the metabolism of the cell towards aerobic respiration. Hereby, it decreases the apoptosis resistance of cancerous cell by increasing intracellular stress. The amount of lactate and proton produced in the cell decreases due to the shift of metabolism in the cancerous cell. In this way, the acidic environment required for the enzymes, needed for the break down of extracellular matrix, could not be provided and the aggressiveness of the cancerous cell, the tumorous tissue, is decreased. Disrupted membrane potential and ion flow balance, makes it electrochemically harder for the oxygen required for oxidative phosphorylation to enter the cell. The required energy for the cancerous cell to grow, spread and its vital functions cannot be provided due to disruption of oxygen and glucose entry inside the cell.

As a result of metabolic, electrochemical and possible genetic and epigenetic effects caused by the synthesized compound mentioned above, cancerous cells undergo controlled cell death (apoptosis). Necrosis can be observed in a small amount of cells. In an ideal anti cancer drug, controlled cell death by apoptosis in most of the cells in tumorous tissue is requested, in some, death by necrosis is preferred. While the cells die by necrosis, they release molecules that may stimulate immune system, such as protein, fat and glycoprotein. In this way, it is enabled for the immune system to migrate to this area by recognizing the tumorous tissue and the tumorous tissue to be exterminated faster. Simultaneously, most of the tumorous tissue goes into controlled death, by the apoptosis caused by the cesium dichloroacetate (CsDCA) compound.

Referring to Figure 4, synthesized cesium dichloroacetate (CsDCA) compound, cesium chloride (CsCl) and sodium dichloroacetate (NaDCA) compounds are applied on to the cell line of PC3 prostate cancer and the results are evaluated by taking measurements at specific time intervals, according to the control group cells. The purpose of cesium chloride (CsCl) and sodium dichloroacetate (NaDCA) application is to separately specify the effectivity of cesium and dichloroacetate. Since both substances are found in the synthesized cesium dichloroacetate compound, it was aimed to showcase the stronger cytotoxic effect of this synthesis compound, compared to these substances. Application amounts of cesium chloride (CsCl) and sodium dichloroacetate (NaDCA) are determined, through normalization, to be the same amount with cesium (Cs) and dichloroacetate (DCA) in the cesium dichloroacetate (CsDCA).

By applying cesium chloride (CsCl), sodium dichloroacetate (NaDCA) and cesium dichloroacetate (CsDCA) in different doses, on to the cell, cell count was done in every 24th, 48th and 72nd hours, for the cytotoxic effect to be determined.

In Figure 5-a, the amount of cells, after the cesium chloride (CsCl) application, normalized numbers of cells at 24^{th} hour according to control, is shown. In application results, a 20% decrease is observed in cesium chloride (CsCl) applied cells, compared to the cells in control group.

In Figure 5-b, the amount of cells, after the sodium dichloroacetate (NaDCA) application, normalized numbers of cells at 24^{th} hour according to control, is shown. In application results, a 10% decrease is observed in sodium dichloroacetate (NaDCA) applied cells, compared to the cells in control group.

In Figure 5-c, the amount of cells, after the cesium dichloroacetate (CsDCA) application, normalized numbers of cells at 24^{th} hour according to control, is shown. In application results, a 70% decrease is observed in cesium dichloroacetate (CsDCA) applied cells, compared to the cells in control group.

In Figure 6-a, the amount of cells, after the cesium chloride (CsCl) application, normalized numbers of cells at 48^{th} hour according to control, is shown. In application results, a 50% decrease is observed in cesium chloride (CsCl) applied cells, compared to the cells in control group.

In Figure 6-b, the amount of cells, after the sodium dichloroacetate (NaDCA) application, normalized numbers of cells at 48th hour according to control, is shown. In application results, 25% increase is observed in sodium dichloroacetate (NaDCA) applied cells, compared to the cells in control group.

In Figure 6-c, the amount of cells, after the cesium dichloroacetate (CsDCA) application, normalized numbers of cells at 48th hour according to control, is shown. In application results, a 75% decrease is observed in dichloroacetate (CsDCA) applied cells, compared to the cells in control group.

In Figure 7-a, the amount of cells, after the cesium chloride (CsCl) application, normalized numbers of cells at 72th hour according to control, is shown. In application results, a 70% decrease is observed in cesium chloride (CsCl) applied cells, compared to the cells in control group.

In Figure 7-b, the amount of cells, after the sodium dichloroacetate (NaDCA) application, normalized numbers of cells at 72th hour according to control, is shown. In application results, a 40% increase is observed in sodium dichloroacetate (NaDCA) applied cells, compared to the cells in control group.

In Figure 7-c, the amount of cells, after the cesium dichloroacetate (CsDCA) application, normalized numbers of cells at 72th hour according to control, is shown. In application results, an 85% decrease is observed in cesium dichloroacetate (CsDCA) applied cells, compared to the cells in control group.

Active caspase-3 (Cl-Kaspaz-3) amount is checked to determine if cells die by apoptosis to be determined. Referring to Figure 8, Cl-Caspase-3 amounts of cells, in 48th hour, which are applied with drugs containing synthesized cesium dichloroacetate (CsDCA) compound, cesium chloride (CsCl) and sodium dichloroacetate (NaDCA) compounds, is determined by immunohistochemistry method. When the results are evaluated, cesium dichloroacetate (CsDCA) gives the highest apoptotic index value.

For the effects in cellular skeletal structure to be determined, intracellular ezrin protein amount is checked. Referring to Figure 9, ezrin protein amounts, marked with immunohistochemistry method, is shown. When compared to control group, a

decrease in ezrin protein amount is identified in cesium dichloroacetate (CsDCA) applied cells.

Cesium hydroxide is produced through the reaction of pollucite, lime and calcium chloride. Also, it can be synthesized with barium hydroxide and cesium sulphide. Cesium hydroxide used in synthesis reaction is mostly used in parted cesium titanosilicates production, electrical battery production, production of ion exchange materials used in radioactive waste cleaning, as a catalyser in methyl propionate and formaldehyde reaction, as a catalyser in organic synthesis reactions and as additional material in some zeolite types. Cesium hydroxide on its own cannot be used in cancer treatment. Since cesium hydroxide is a strong base, it cannot be administrated to a human being orally or via blood.

The other compound used in the synthesis, dichloroacetic acid, can be chemically produced through methods such as dichlroacetyl chloride hydrolysis, pentachloroethane and sulphuric acid hydrolysis or 1,1- dichloroacetone and nitric acid oxidation. Dichloroacetic acid can be used; in organic synthesis reactions, production of glyoxylic acid, production of sulphonamide, speeding up of iron chelators, fiber production such as polyethylene terephthalate, as medical disinfectant and as chemical burner in living tissues.

Cesium compounds with basic pH value in aqueous solution can be used in he synthesis method. Preferably, cesium compound used in synthesis method is either cesium hydroxide (CsOH) or cesium bicarbonate ($CsHCO_3$). In a preferred application of the invention, cesium hydroxide (CsOH) and dichloroacetic acid (CHCl2COOH) chemicals are used. Synthesis reaction is an acid base reaction. As a result of the synthesis, cesium dichloroacetate and water are released.

Cesium hydroxide is in powder form and it is a hygroscopic substance that absorbs moisture. For this reason, it is in cesium hydroxide hydrate (CsOH.xH2O) form when in powder form. Powder cesium hydroxide may contain water up to 20%, by weight. It can dissolve in water and ethanol. Powder cesium hydroxide should be stored in a dry place. Cesium hydroxide compound can be dried in a vacuumed drying oven, in a temperature range of 30-100°C, before preparation. In the preferred application of the invention, cesium hydroxide hydrate should be dried in a vacuumed drying oven, at 60°C, before preparing the cesium hydroxide compound. In the preferred

application of the invention, aqueous solution containing (w/w) 5-80% of cesium hydroxide can be used directly. The synthesis solution of cesium dichloroacetate contains 50-60% cesium hydroxide and 40-50% dichloroacetic acid respectively by weight. In the preferred application of the invention, the synthesis solution of cesium dichloroacetate contains 53,76% cesium hydroxide and 46,24% dichloroacetic acid.

The synthesis method of the invention's subject compound, cesium dichloroacetate, contains the following steps:

- Preparing the aqueous solution of the cesium compound,
- Mixing the prepared cesium compound solution,
- Adding dichloroacetic acid solution into mixed cesium compound solution,
- Measuring the temperature and pH value by continuing to mix the formed synthesis solution,
- Fixing the pH value of the synthesized solution,
- Bringing cesium dichloroacetate into solid powder form by removing the liquid phase from the synthesis solution,
- Dissolving the powdered product in polar solvent,
- Separating the formed solution into phases,
- Extracting pure cesium dichloroacetate in powder form by removing the solvent from the phase containing cesium dichloroacetate compound.

Cesium hydroxide hydrate powder, containing 1 mole (149,91 gr) of cesium hydroxide, is placed into a vessel. By extracting the weight of the hydrate in added cesium hydroxide hydrate powder, pure deionized water, as much as the weight obtained, is added. Cesium hydroxide powder can also be added into the water. A mixer is used for the cesium hydroxide to homogeneously dissolve. Cesium hydroxide solution is mixed in the range of 100 – 1500 rpm, in the said mixer. In a preferred application of the invention, the rotation speed of the mixer is 400 rpm.

Dichloroacetic acid to be added on top of cesium hydroxide solution is measured to be 1 mole (128,94 gr). The prepared dichloroacetic acid is added to the cesium

hydroxide solution, which is mixed with the use of a dropping funnel or another container. In order to create the synthesis, cesium hydroxide solution can also be added on top of dichloroacetic acid. pH and temperature are measured along the mixing procedure. The pH and temperature of the synthesis solution are expected to become fixated. If the pH value of the synthesis solution is above 7, dichloroacetic acid is added and if the pH value is below 7, 50% cesium hydroxide solution is added. The pH value, regulated while mixing the synthesis solution, is fixed to be in the rage of 6,8 and 7,2. In a preferred application of the invention, pH value is fixed at 7. Change of colour in the synthesis solution can be observed when dichloroacetic acid and cesium hydroxide are mixed. This change is related to pH value. The solution becomes transparent again when pH value comes close to 7.

The liquid phase of the formed synthesis solution is removed in the rotary evaporator under vacuum, in the drying oven and in spray dryer and cesium dichloroacetate is transformed into powder form. Synthesis solution is preferably put in to rotary vacuum evaporator. The liquid phase will be evaporated in pressures lower than 20 millibar, at a temperature range of 20 - 95 ° C and by rotating in the 20 – 300 rpm range. In a preferred application of the invention, the liquid phase is evaporated under a 8 millibar pressure, heated at 40 ° C and by rotating in 100 rpm. The product concentrated in the rotating evaporator is poured into drying vessels and is let to dry in drying ovens with a temperature ranging from 40 to 100°C degrees or a vacuumed oven for 4 to 72 hours. In a preferred application of the invention, the product concentrated in the rotary evaporator is poured into drying vessels and is let to dry in the drying oven with a temperature ranging of 50°C degrees or a vacuumed oven for 24 hours. A spray dryer, after rotary evaporator or on its own can be used to pulverize the solution. The powder extracted after drying processes is dissolved with a needed amount of polar solvent (like water, dimethyl sulfoxide and ethanol) to be dissolved completely. Extracted solution is purified with purification methods such as colon chromatography, precipitation and crystallization. The liquid phase containing purified cesium dichloroacetate is evaporated, to extract pure cesium dichloroacetate, by lyophilisation between the temperature range of (-55°C) – (-85 °C) or drying by vacuumed below 20 millibar or non-vacuumed heating between the temperature range of 40 – 100°C. The liquid phase containing purified cesium dichloroacetate is evaporated, to extract pure cesium dichloroacetate, by lyophilisation at a temperature

of -55°C or drying by vacuumed under 8 millibar or non-vacuumed heating at the temperature of 50°C.

Synthesis Method Sample 1:

299,82 grams of, %50 (w/w) cesium hydroxide solution is weighed. The weighed amount is put into the reactor vessel and start mixing in 400 rpm. In another vessel, 128,94 grams of dichloroacetic acid is weighed. Dichloroacetic acid is placed into the dropping funnel. It is added to the cesium hyroxide solution, mixing at a speed not exceeding 1 minute to be fully added. The pH value is waited to get fixed. If the pH value is above 7, dichloroacetic acid is dropped and if the pH value is below 7, 50% cesium hydroxide solution is dropped to make the pH value 7. The synthesis solution is palced into a rotary evaporator under 8 millibar of pressure, heated at 40°C, at a rotating speed of 100 rpm. Concentrated product is put into drying vessels and is let to dry in vacuumed drying oven at 50°C, for 24 hours. Deionised water, enough to dissolve the powder completely, is added on top of the powder extracted from drying processes. The extracted solution is put into the appropriate chromatography colon and it enables to get rid of impurities such as dichloroacetic acid, cesium hydroxide and etc. The liquid phase containing purified cesium dichloroacetate, is powdered by lyophilisation, at -55°C degrees.

Cesium dichloroacetate compound can be administered to cancer patients via parenteral, orally or dermally. By administrating under the skin with subdermal carrier compounds, such as dimethyl sulfoxide, absorption can be increased.

Cesium dichloroacetate can be used with subdermal and in vivo biocompatible drug release materials and devices. Cesium dichloroacetate compound can be administrated with methods increasing the ability of a drug to reach to cells and to be received by cells such as nanoparticles, nanospheres, controlled drug release systems and targeted drug carrier systems.

CLAIMS

1. It is a drug used for cancer treatment in humans and animals, for shrinking and destruction of body tumors and to prevent cell proliferation and division that contains cesium dichloroacetate.

2. It is a drug appropriate to Claim 1, applied via parenteral, oral or dermal administration.

3. It is a drug appropriate to Claim 1, containing dimethyl sulfoxide or excipients regarded as pharmaceutical.

4. It is a synthesis method for a drug used for cancer treatment in humans and animals, for shrinking and destruction of tumours and to prevent cell proliferation and division, includes below steps;

   a) Preparation of aqueous solution of the cesium compound,

   b) Adding dichloroacetic acid solution into mixed cesium compound solution and making pH value adjustment.

5. It is a synthesis method for a drug appropriate to Claim 3, said cesium compound is cesium hydroxide.

6. It is a synthesis method for a drug appropriate to Claim 3, said cesium compound is cesium bicarbonate.

7. It is a synthesis method for a drug appropriate to Claim 3, characteristically; followed by a temperature and pH value measurement step, after step b.

8. It is a synthesis method for a drug appropriate to Claim 3, characteristically; the pH value of the solution prepared in step b is in the range of 6,8 to 7,2.

9. It is a synthesis method for a drug appropriate to Claim 3, characteristically; as a purification process after step b,

c) Bringing cesium dichloroacetate into solid powder form by removing the liquid phase from the synthesis solution,

d) Powdered cesium dichloroacetate to be dissolved in the polar solvent,

e) Obtaining cesium dichloroacetate in powder form by separating the solution into phases, removing the solvent in the phase containing the cesium dichloroacetate compound,

contains these procedures.

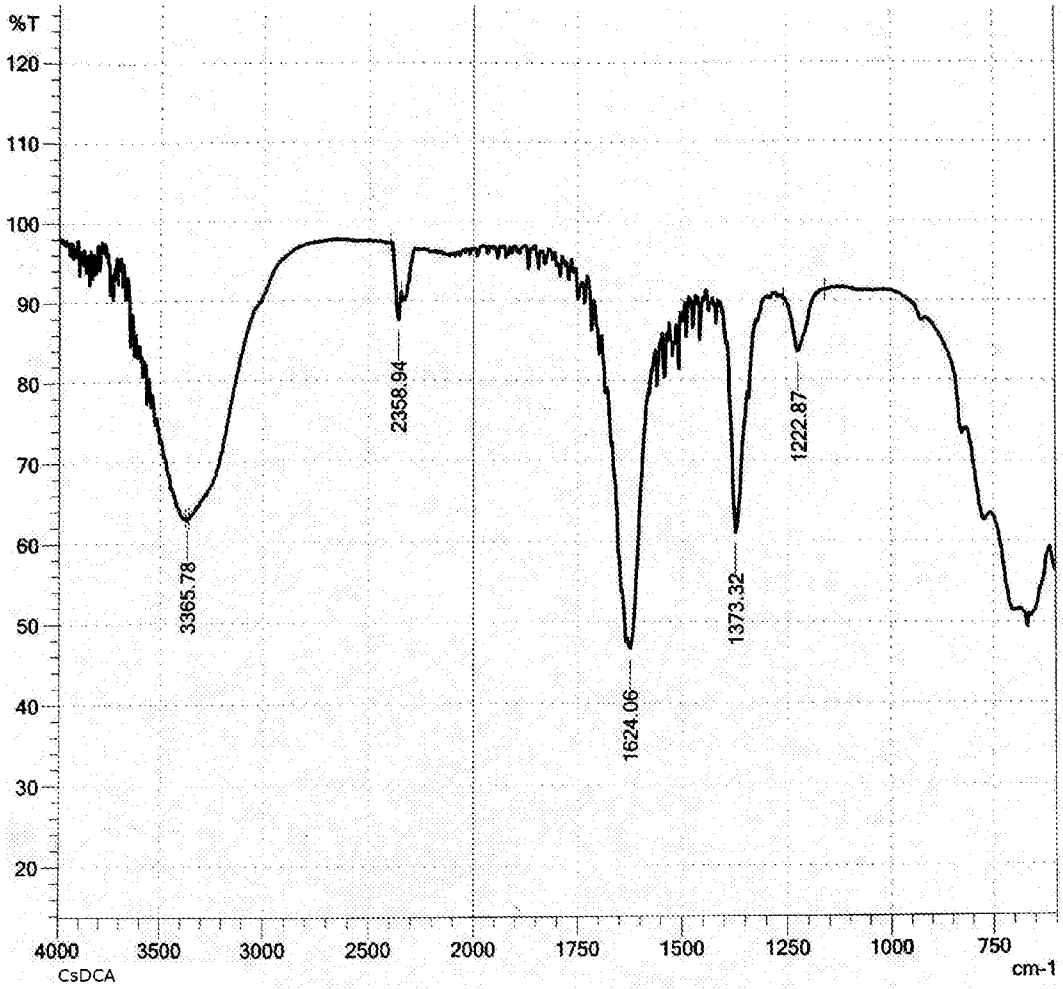

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Figure 1

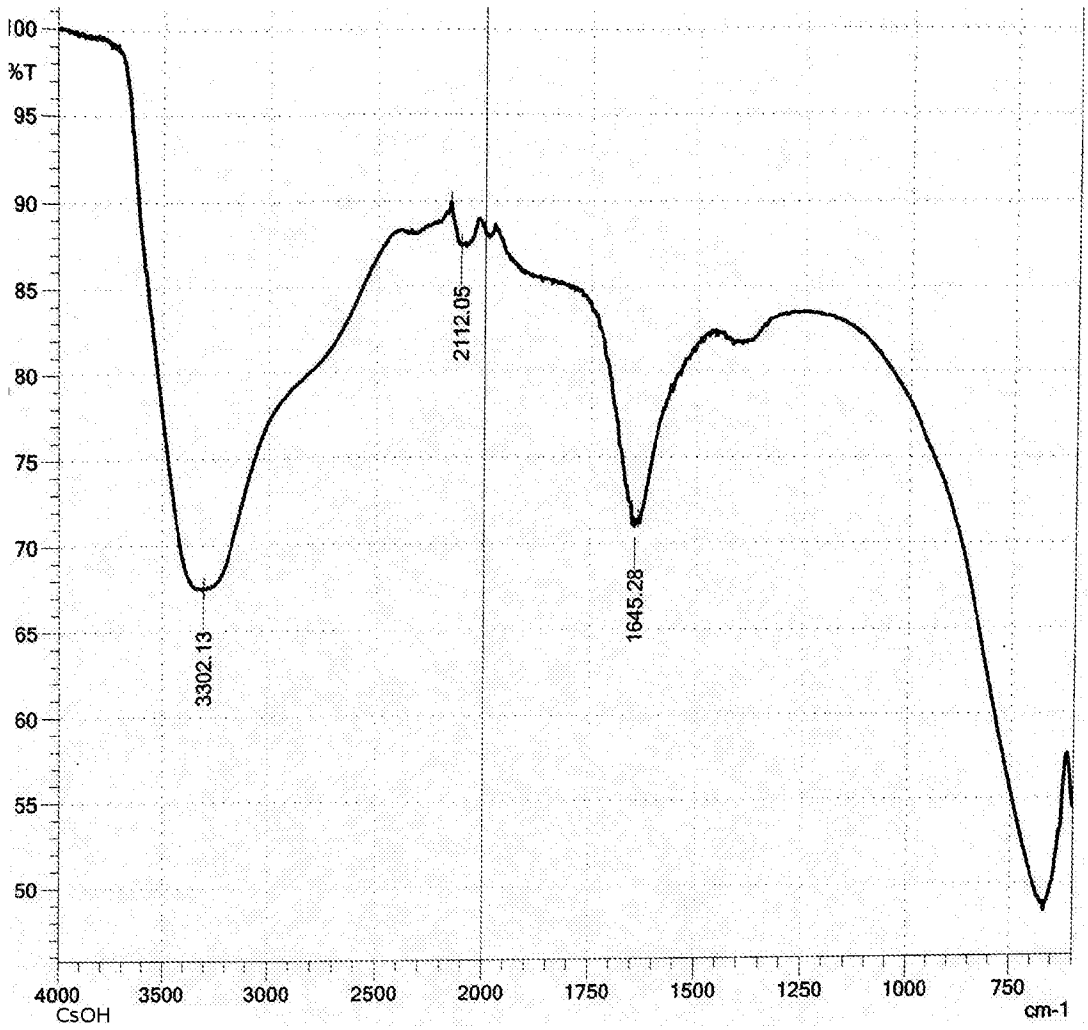

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Figure 2

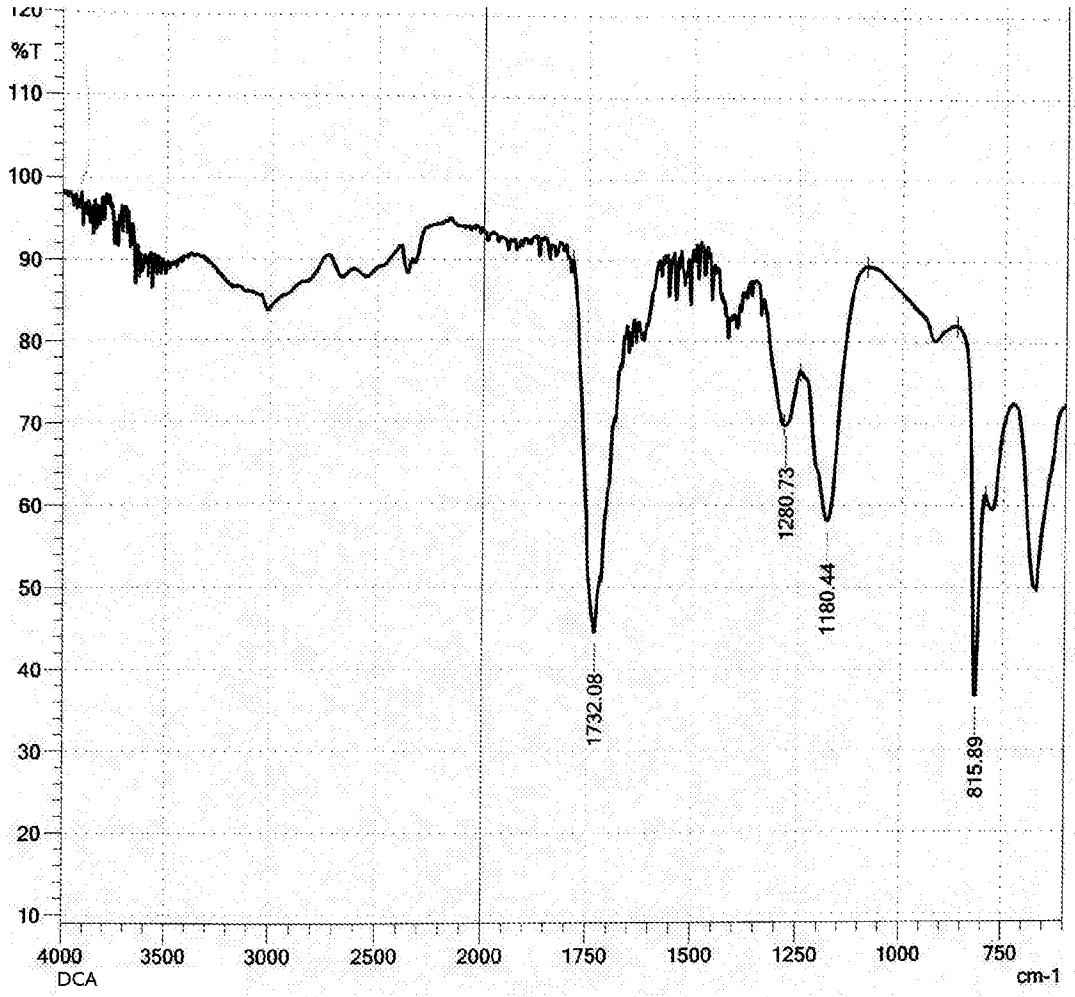

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cm-1
DCA

Figure 3

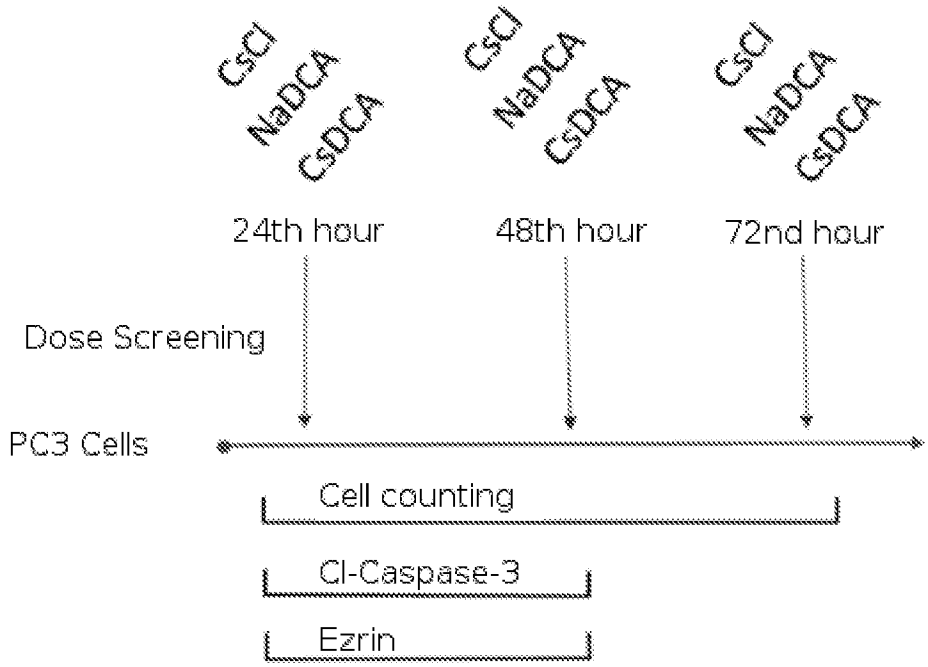


Figure 4

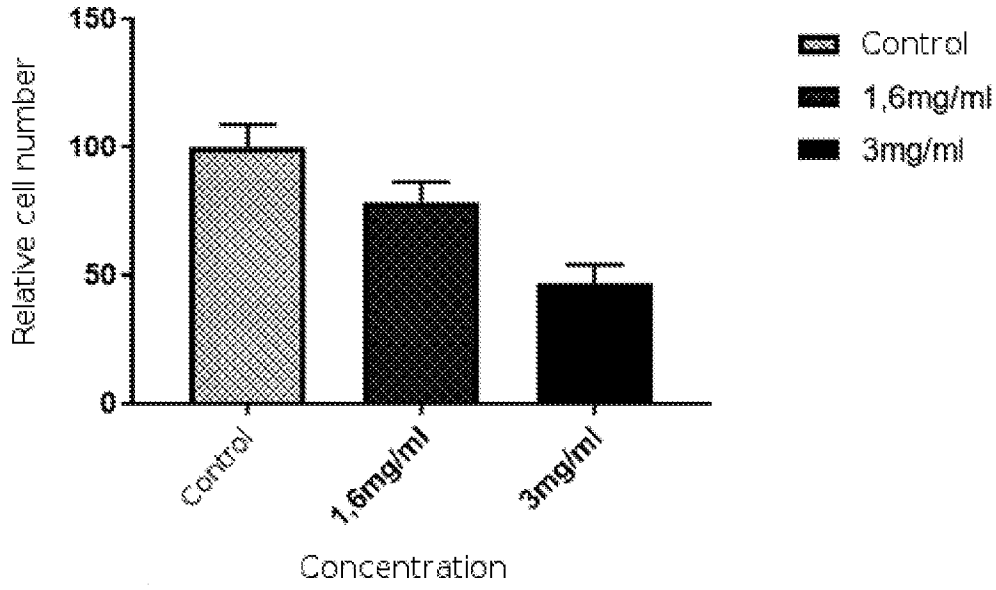


Figure 5-a

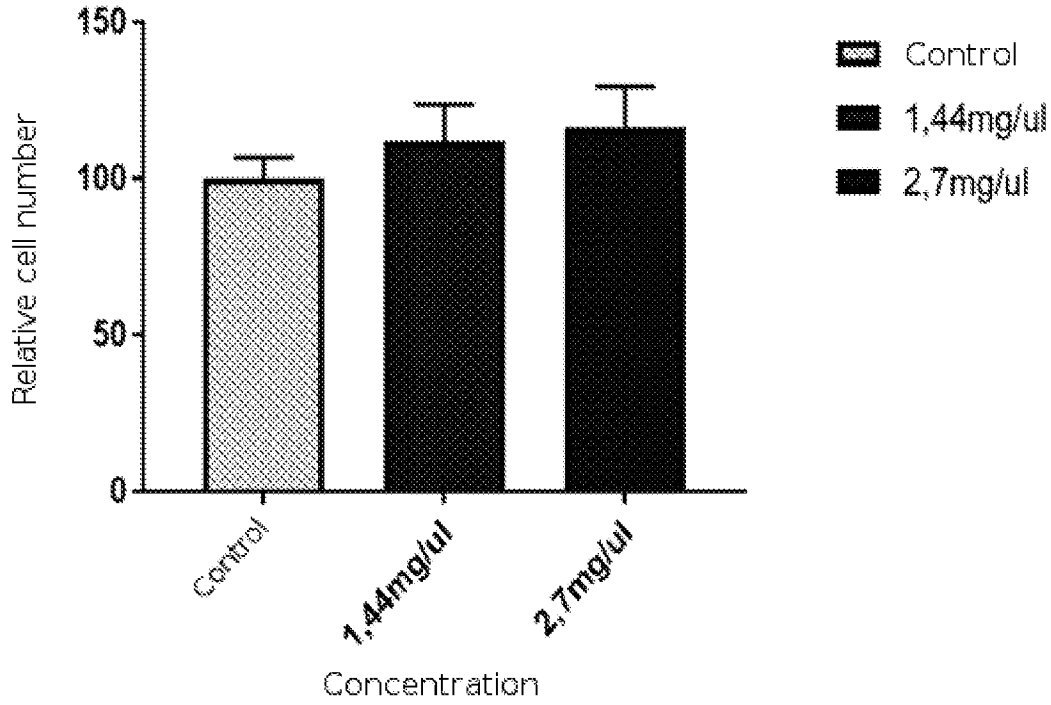


Figure 5-b

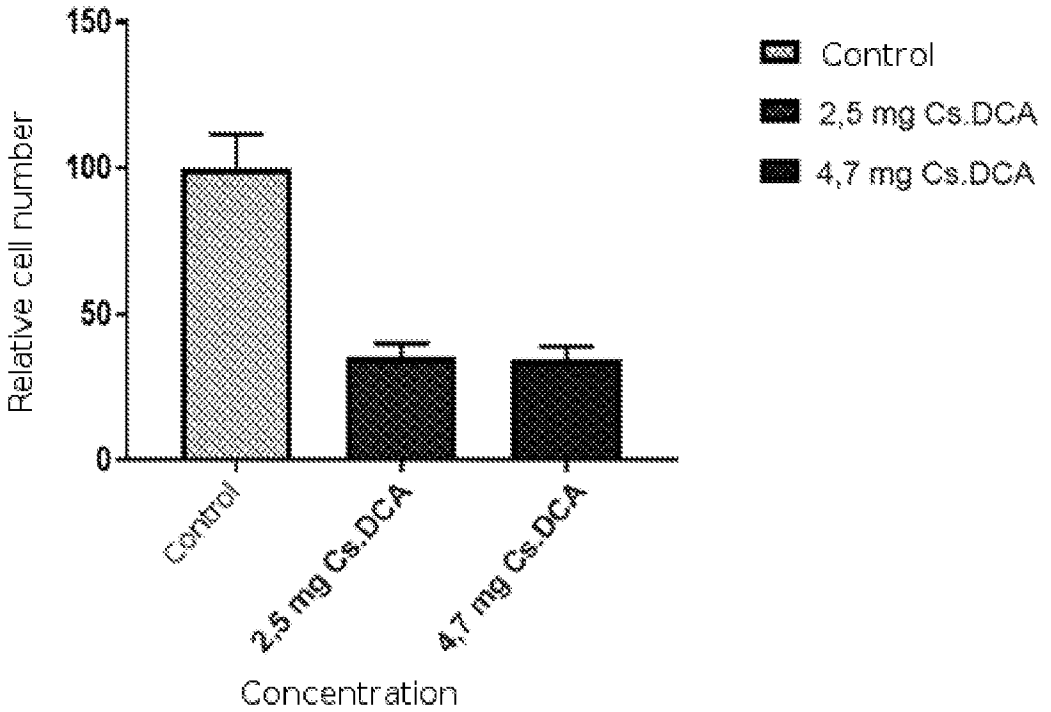


Figure 5-c

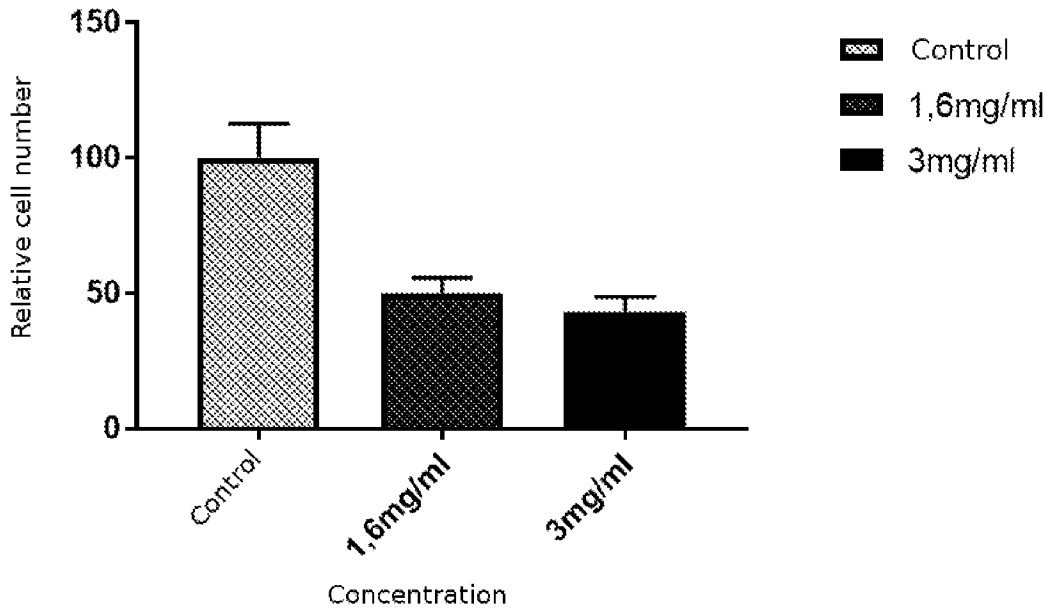


Figure 6-a

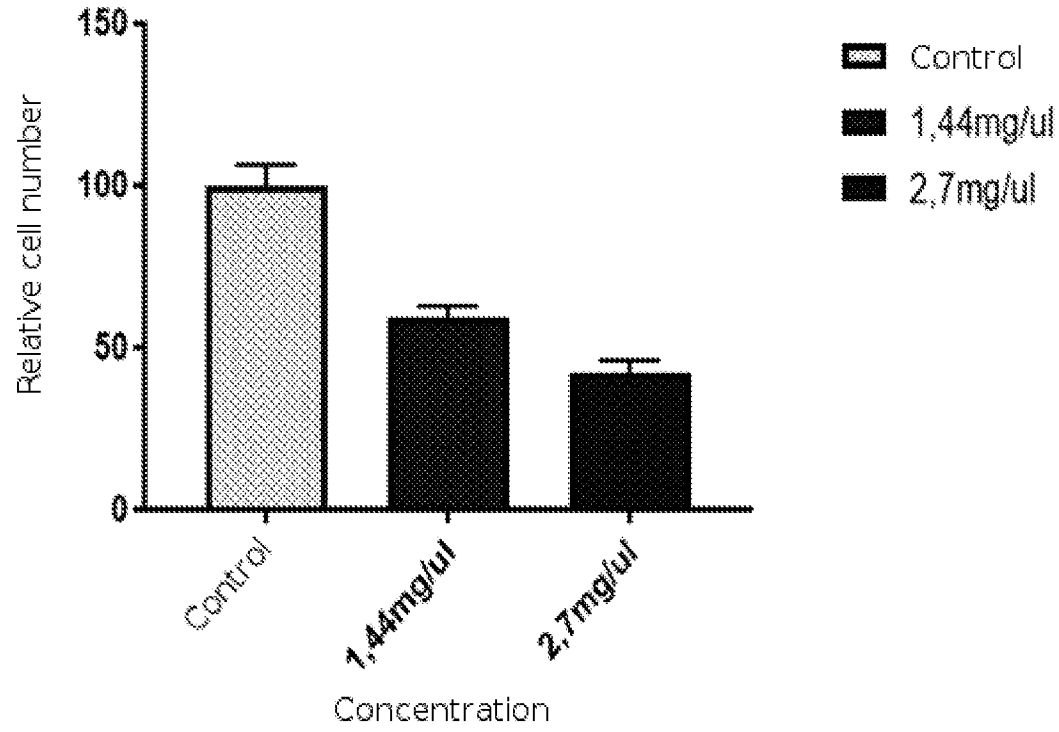


Figure 6-b

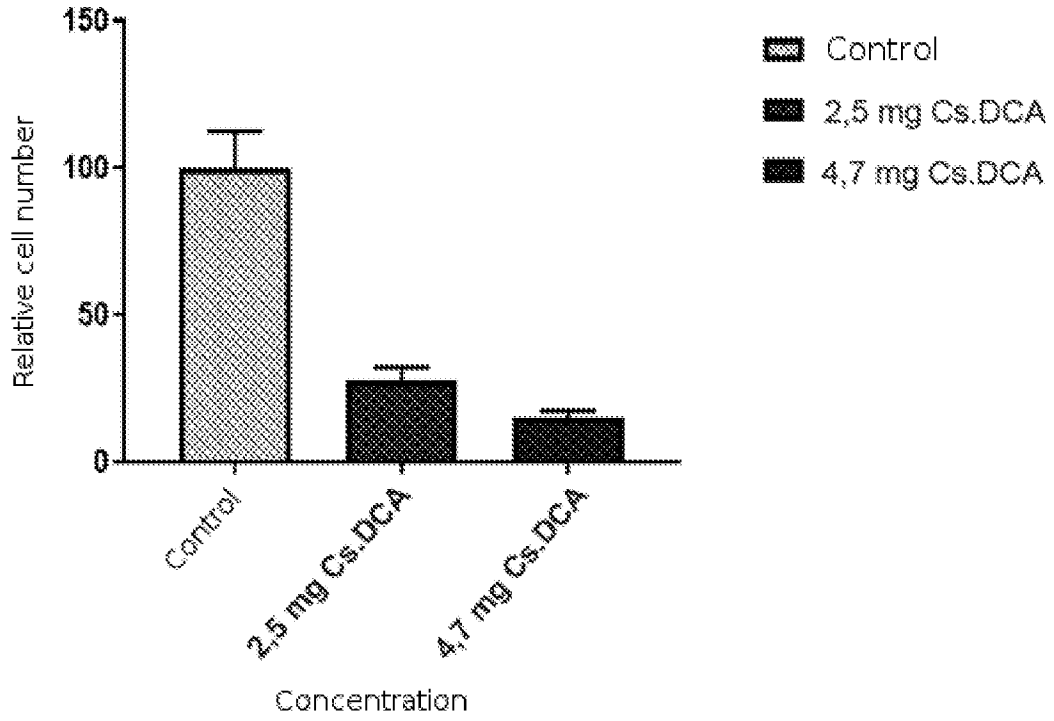


Figure 6-c

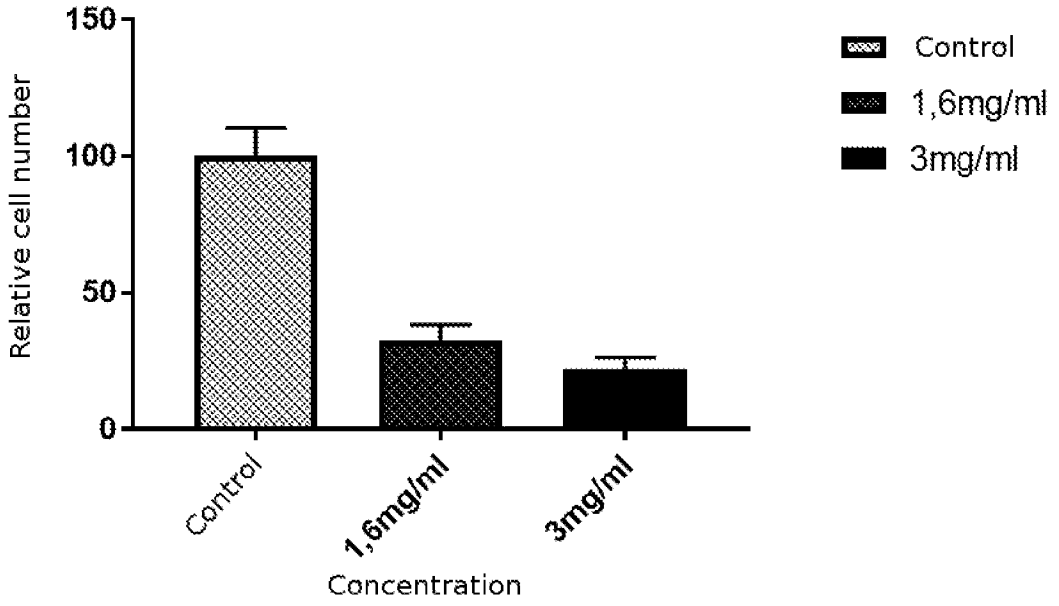


Figure 7-a

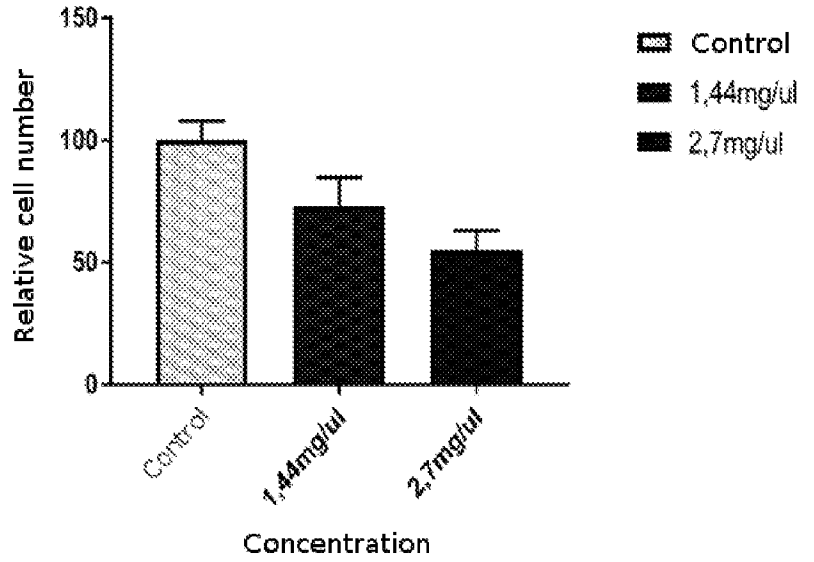


Figure 7-b

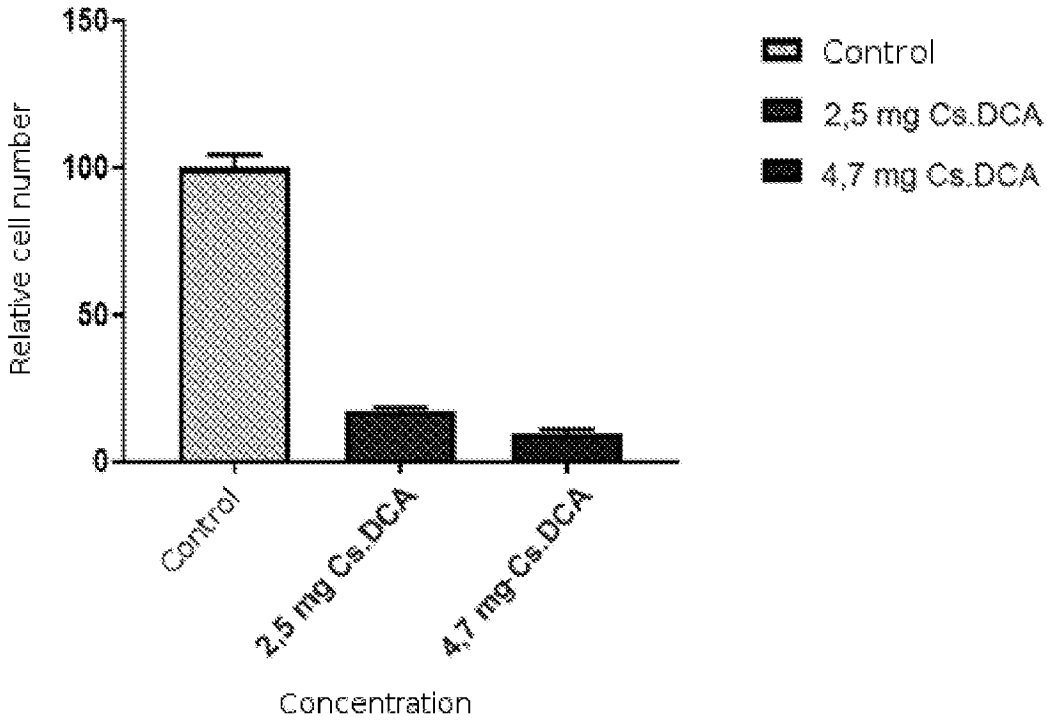


Figure 7-c

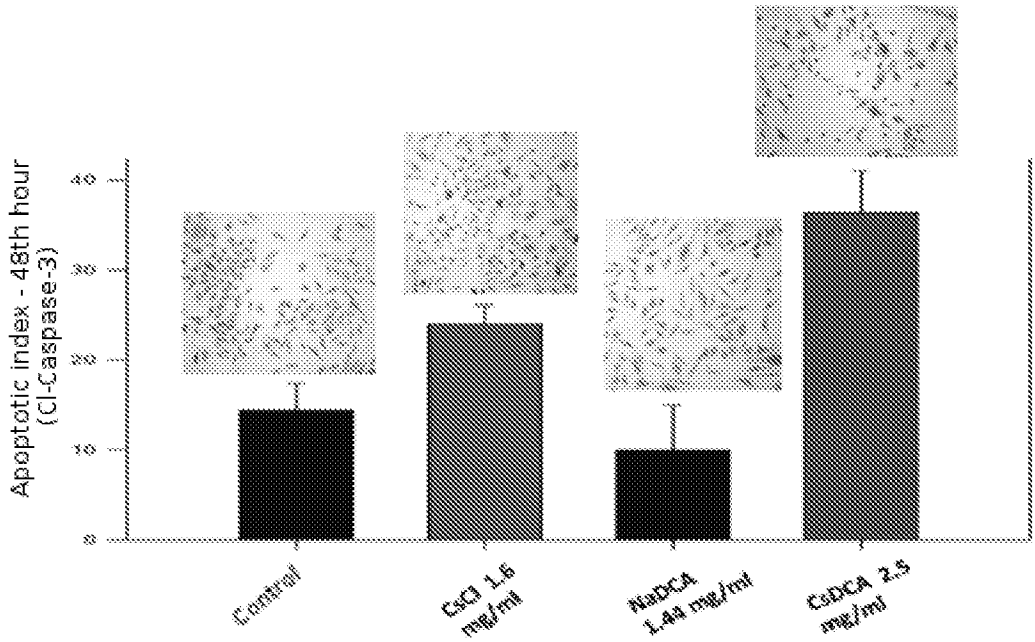


Figure 8

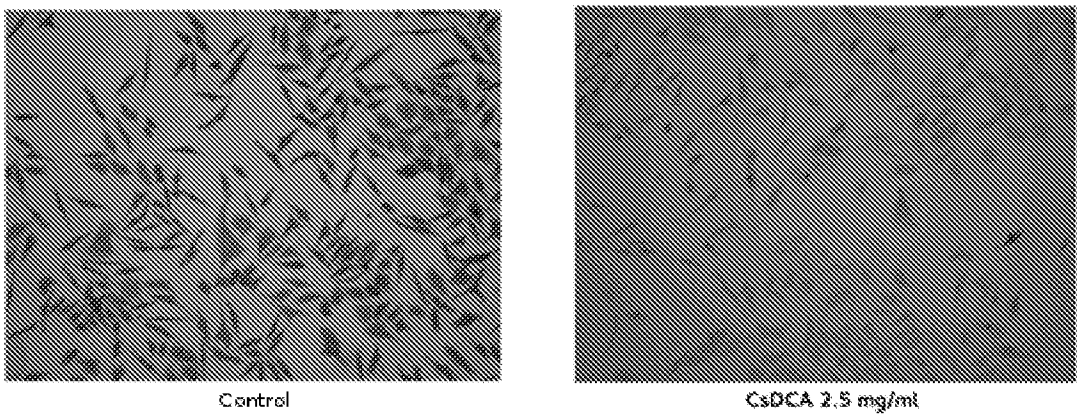


Figure 9