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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 April 2010 (22.04.2010)

PCT

(10) International Publication Number
WO 2010/043029 A1

(51) International Patent Classification:
A61K 31/7004 (2006.01) *A61P 35/00* (2006.01)
A61K 45/00 (2006.01)

(21) International Application Number:
PCT/CA2009/001440

(22) International Filing Date:
8 October 2009 (08.10.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/105,665 15 October 2008 (15.10.2008) US

(72) Inventors; and
(71) Applicants : **WANG, Xingnong** [CA/CA]; 1071 Ruthina Avenue, North Vancouver, British Columbia V7R 2E7 (CA). **WEI, Youcheng** [CA/CA]; 1071 Ruthina Avenue, North Vancouver, British Columbia V7R 2E7 (CA).

(74) Agent: **TAYLOR, Euan, R.**; Davis LLP, 2800 Park Place, 666 Burrard Street, Vancouver, British Columbia V6C 2Z7 (CA).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (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, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

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

WO 2010/043029 A1

(54) **Title**: USE OF TETROSE TO INHIBIT CANCER AND TO INCREASE CELL VIABILITY

(57) **Abstract**: There are disclosed methods for inhibiting the growth of cancer cells comprising directly or indirectly exposing the cancer cells to a pharmaceutically effective concentration of tetrose. There are also disclosed methods for treating a mitochondrial disorder in a subject having such disorder, the method comprising directly or indirectly administering to the subject an effective dose of tetrose. There are also disclosed compositions for use in the methods.

USE OF TETROSE TO INHIBIT CANCER AND TO INCREASE CELL VIABILITY

FIELD

The subject application relates to therapeutic uses of tetroses and compositions comprising tetroses.

BACKGROUND

US Patent No. 7465734 Shephard, issued December 16, 2008 discloses the use of oxetanes as a constituent group of a prodrug.

US Patent No. 6642205 Klyosov, issued November 4, 2003 discloses the use of tetroses as spacers in therapeutic compounds

PCT Patent Application WO04050100 Berrada, filed December 3, 2003, discloses the use of combination of a chitosan and a salt of erythrulose or threose to treat a tumor.

US Patent Application No. 9/830,912 Jariwalla, Filed Apr 30, 2001 discloses the use of threonate either alone or in combination with ascorbate, to promote apoptosis.

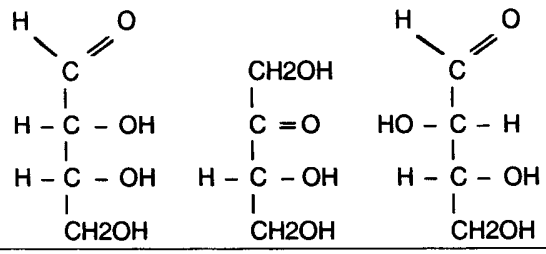
PCT Patent Application WO07074344 Knox, Filed December 29, 2006, discloses the use of erythrose, erythrulose, and 3-hydroxy-2-butanone to assist processing of a prodrug.

SUMMARY OF THE INVENTION

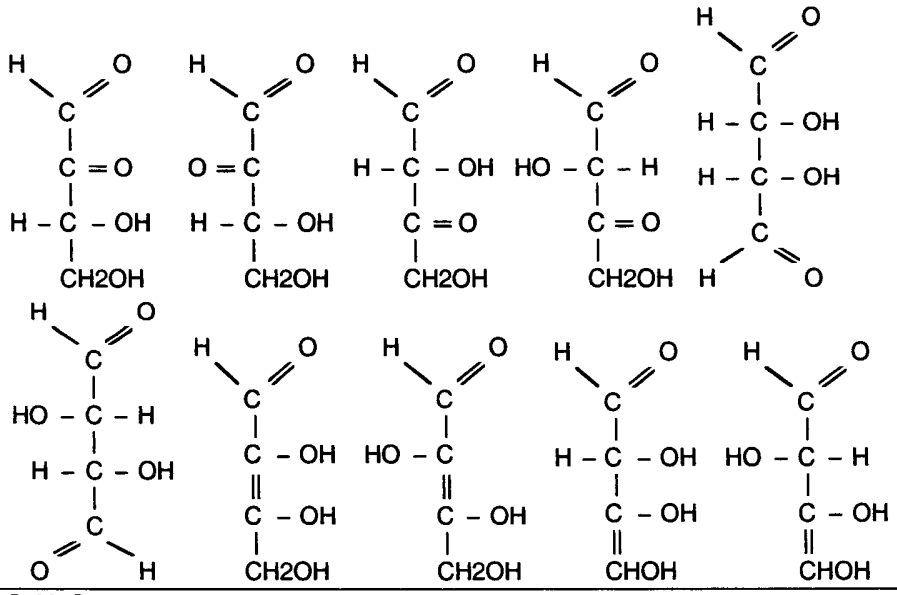
In a first embodiment, there is disclosed a method for inhibiting the growth of a cancer cell. The method may comprise directly or indirectly exposing the cancer cell to a pharmaceutically effective concentration of tetrose.

In alternative embodiments, the tetrose may have a structural formula selected from the group consisting of:

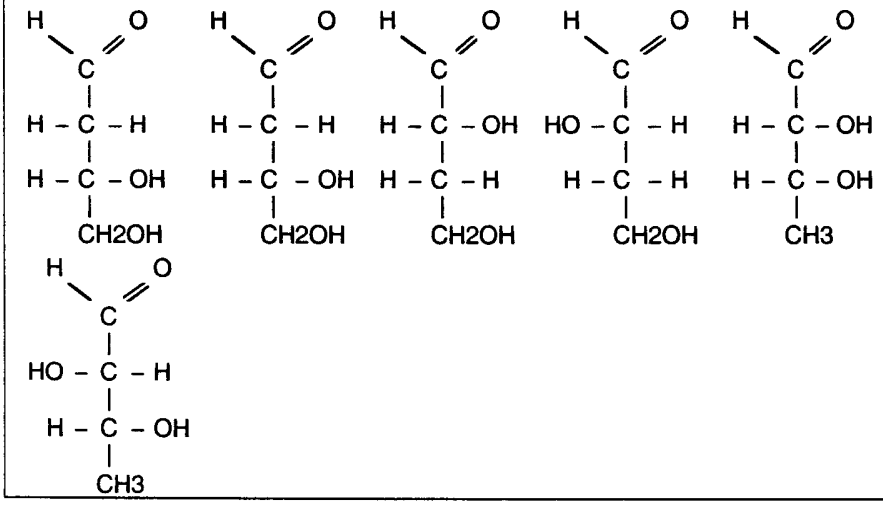
$C_4H_8O_4$



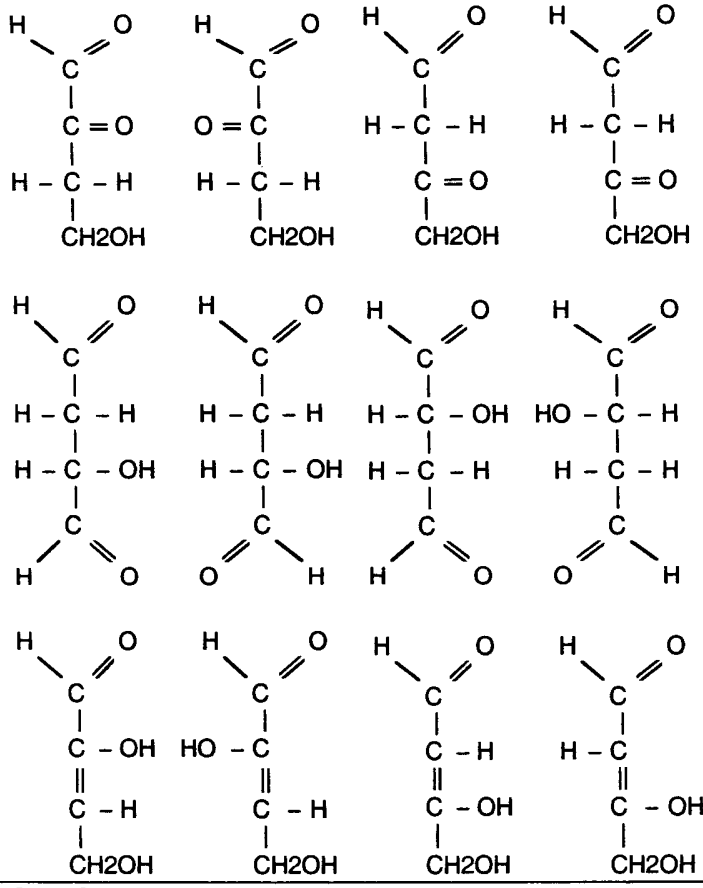
$C_4H_6O_4$



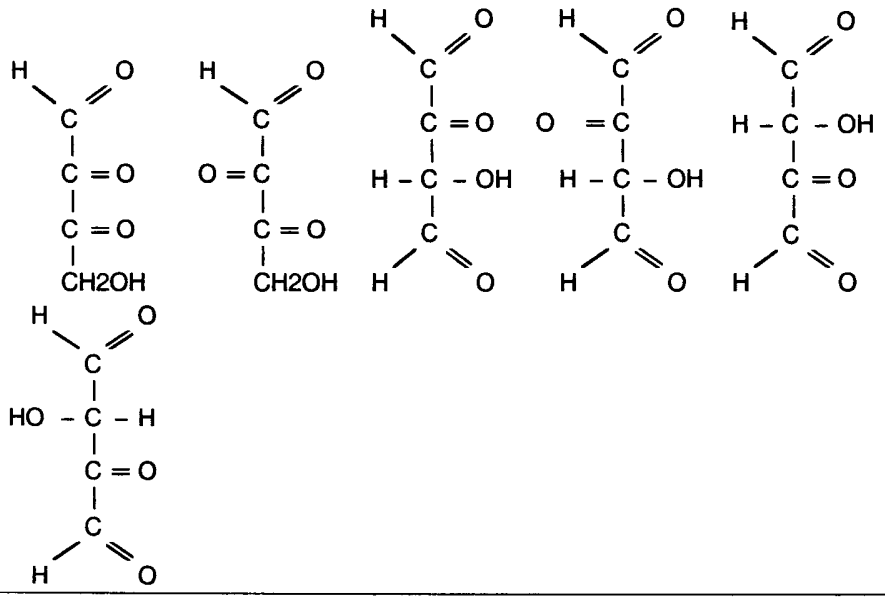
$C_4H_8O_3$



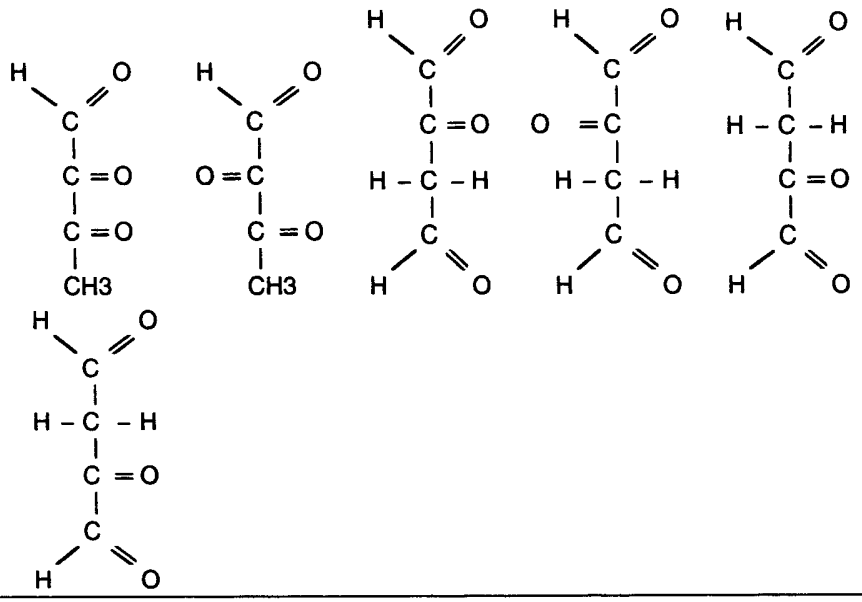
$C_4H_6O_3$



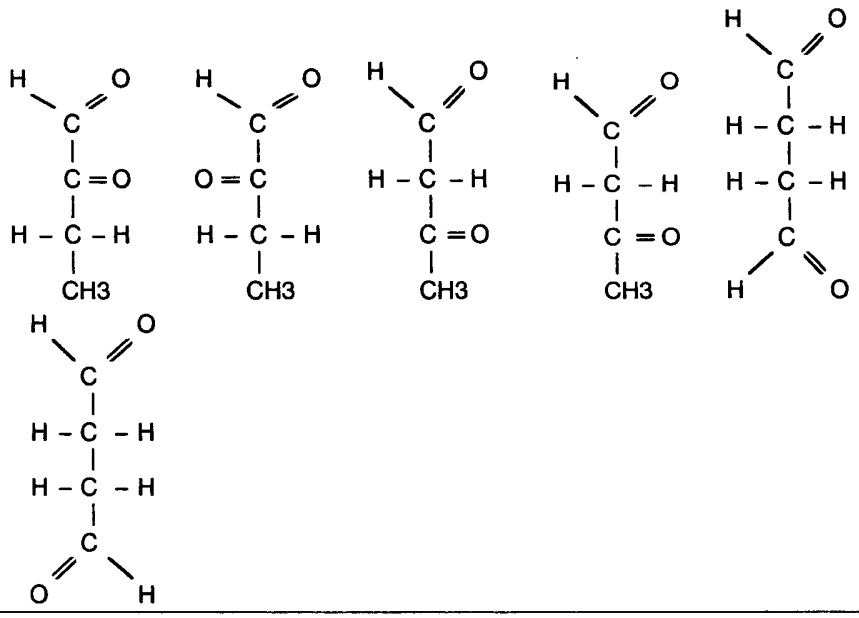
$C_4H_4O_4$

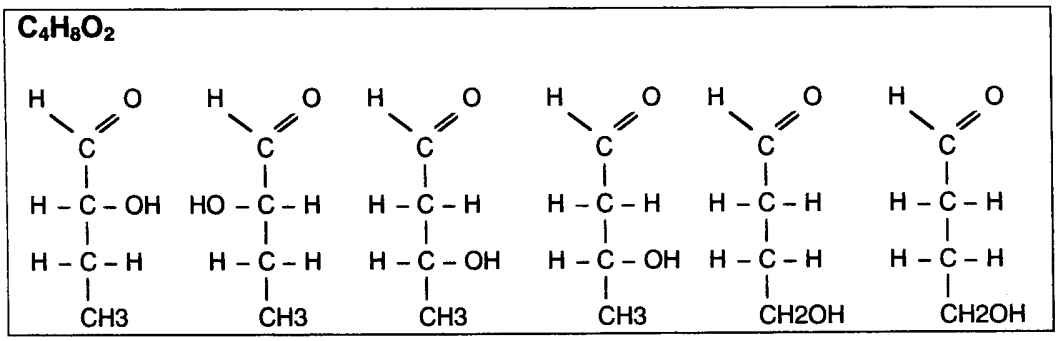


$C_4H_4O_3$



$C_4H_6O_2$





and any pharmaceutically effective derivatives thereof.

In alternative embodiments, the derivative may be a conjugated, substituted, ionised, salt, isomeric, acid, base, aldehyde, ketone, alcohol, amine, amide, thiol, ring or linear form.

In alternative embodiments the tetrose may be selected from the group consisting of erythrose, threose and erythrulose.

In alternative embodiments, the indirect exposing may comprise exposing the cancer cell to a prodrug metabolisable to release tetrose.

In alternative embodiments the cancer cell may be exposed to a concentration of greater than about 100 mg/litre of tetrose and exposed to a glucose concentration of greater than about 500 mg/litre before or simultaneous with the exposure to tetrose.

In alternative embodiments, the cancer may be selected from the group consisting of carcinoma, sarcoma, adenoma, leukemia, lymphomas and myeloma.

In alternative embodiments, the exposure may occur in combination with exposing the cell to a modulator of carbonic anhydrase activity.

In alternative embodiments, the modulator may comprise a Zinc salt.

In alternative embodiments, there is disclosed a method for improving the viability of a cell, the method may comprise directly or indirectly exposing the cell to a therapeutically effective amount of tetrose.

In alternative embodiments, the derivative may be a conjugated, substituted, ionised, salt, isomeric, acid, base, aldehyde, ketone, alcohol, amine, amide, thiol, ring or linear form.

In alternative embodiments, the exposure may occur in combination with exposing the cell to a modulator of carbonic anhydrase activity. The cell may be under conditions of limited energy supply and may have a mitochondrial disorder.

In alternative embodiments, the tetrose may be selected from the group consisting of erythrose, threose and erythrulose.

In alternative embodiments, indirect exposing may comprise exposing the cell to a prodrug metabolisable to release tetrose.

In alternative embodiments, the methods of embodiments may comprise exposing the cells to a concentration of between about 1 mg/litre and about 200 mg/litre of the tetrose to increase the viability of cell.

In alternative embodiments, the mitochondrial disorder may be associated with a disorder selected from the group consisting of neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, cardiovascular disease, stroke, obesity, diabetes, multiple sclerosis, systemic lupus erythematosis, rheumatoid arthritis, schizophrenia, bipolar disorder, depression, ataxia, autism, epilepsy, migraine, Batten disease, Lactic acidemia, Leber's disease, mitochondrial cardiomyopathy and myopathy, paraplegin, NASH, and Wilson's disease.

In alternative embodiments, there is disclosed a method of treating a mitochondrial disorder in a subject having such disorder, the method may

comprise directly or indirectly administering to the subject a pharmaceutically effective dose of tetrose.

In a further embodiment there is disclosed a composition which may comprise a direct or indirect source of tetrose in an amount effective to inhibit the growth of a cancer cell; and a pharmaceutically acceptable carrier or diluent.

In a further embodiment there is disclosed a composition which may comprise a direct or indirect source of tetrose in an amount effective to increase the viability of a cell having a mitochondrial disorder; and a pharmaceutically acceptable carrier or diluent

In a further embodiment there is disclosed the use of an effective dose of a direct or indirect source of tetrose to achieve an effect selected from the group consisting of: inhibiting the growth of a cancer cell; increasing the viability of a cell under low energy conditions; and increasing the viability of a cell having a mitochondrial disorder.

In a further embodiment there is disclosed the use of a prodrug to manufacture a dietary supplement.

In a further embodiment there is disclosed a composition which may comprise a prodrug metabolisable to yield a pharmaceutically effective amount of tetrose.

In a further embodiment there is disclosed the use of tetrose to manufacture a medicament for: inhibiting the growth of a cancer cell; or improving the viability of a cell exhibiting a mitochondrial disorder.

Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

In this disclosure the term "in combination with" means that the elements or procedures to be combined may be mixed, or may be used simultaneously, or sequentially, or in any other way temporally, spatially or otherwise combined.

In this disclosure an "effective amount" of a compound means a therapeutically effective amount, a prophylactically effective amount, or a nutritionally effective amount as the case may be or as the context requires. In embodiments a therapeutic, nutritional or prophylactic result may comprise stopping or slowing or preventing the progress of a disease; and may include inhibiting growth of or division of cancer cells, or increasing tumor apoptosis, or causing the shrinking, or disappearance of a tumour. Those skilled in the art will recognise that what constitutes an "effective amount" of a compound may very according to a variety of factors including but not limited to the nature and extent of progression of a disease state, and the age, sex, and weight of the subject. In embodiments "effective amounts" may be comprised in one or more dosages of the same or different types or quantities, spread over a desired time period, and may be adjusted as necessary in ways readily apparent to one skilled in the art. It will be understood that those skilled in the art will avoid dosages and combinations that would cause unacceptable deleterious effects on the subject.

In this disclosure a "cell" or "tissue" may be isolated, may be comprised in group of cells, may be in culture, or may be comprised in a living subject and may be a mammalian cell and may be a human cell.

In this disclosure "cancer" "means and includes any malignancy, or malignant cell division or malignant tumour, or any condition comprising uncontrolled or inappropriate cell proliferation and includes without limitation any disease characterized by uncontrolled or inappropriate cell proliferation. In embodiments cancers cells may exhibit mitochondrial disorders, deficiencies or dysfunctions. In embodiments cancer may include but is not limited to carcinomas, sarcomas,

adenoma, leukemias, lymphomas and myelomas. In particular embodiments a cancer may include carcinoma, adenocarcinoma, adenoma, sarcoma, lymphoma, and leukemia. In particular embodiments a cancer may be or may include Bladder Cancer, Breast Cancer, Colon and Rectal Cancer, Endometrial Cancer, Kidney (Renal Cell) Cancer, Leukemia, Lung Cancer, Melanoma, Skin Cancer (Nonmelanoma), Non-Hodgkin Lymphoma, Pancreatic Cancer, Prostate Cancer, Thyroid Cancer, Stomach Cancer, Liver Cancer, Ovarian Cancer. In particular embodiments cancer may be Adrenal Cancer, Anal cancer, Aplastic Anemia, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Cancer, Breast Cancer, Bronchus and Lung Cancer, Central Nervous System Cancer, Cervical Cancer, Colon and Rectum Cancer, Connective Tissue Cancer, Cranial Nerves Cancer, Digestive organs Cancer, Endometrial Cancer, Endocrine Cancer, Esophageal Cancer, Ewing's Family of Tumors, Gallbladder Cancer, Gastrointestinal Carcinoid Tumors, Gastrointestinal Stromal Tumors, Gestational Trophoblastic Disease, Head and Neck Cancer, Hodgkin Lymphoma Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal and Hypopharyngeal Cancer, Larynx Cancer, Leukaemia Cancer, Leukaemia - Lymphoid Cancer, Leukaemia - Myeloid Cancer, Leukaemia of Unspecified Cell Type Cancer, Lip Cancer, Liver Cancer, Lung Carcinoid Tumors, Lymphoid, Haematopoietic and Related Tissues Cancer, Lymphoma Cancer, Malignant Immunoproliferative Cancer, Malignant Neoplasm Cancer, Malignant Neoplasm of Genital Organs Cancer, Malignant Neoplasm of Urinary Tract Cancer, Meninges Cancer, Mesothelioma Cancer, Multiple myeloma Cancer, Myelodysplastic Syndrome, Nasal Cavity and Middle Ear Cancer, Nasopharyngeal Cancer, Nasopharynx Cancer, Neuroblastoma, Non-Hodgkin's Lymphoma Cancer, Non-Hodgkin's lymphoma, Other and Unspecified Cancer, Neuroblasma, Oral Cavity and Oropharyngeal Cancer, Osteosarcoma, Oropharynx Cancer, Ovarian Cancer, Pancreas Cancer, Parathyroid Cancer, Penis Cancer, Peripheral and Cutaneous T-cell Lymphomas Cancer, Peripheral Nerves Cancer, Peritoneum Cancer, Pharyngeal Cancer, Pituitary Tumor, Postcricoid Region Cancer, Prostate cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Glands Cancer, Sarcoma, Soft Tissue Cancer, Melanoma Skin Cancer, Nonmelanoma Skin Cancer, Sinus Cancer, Small

Intestine Cancer, Small Intestine Cancer, Stomach Cancer, Testicular Cancer, Thymoma and Thymic Carcinoma, Thyroid Cancer, Tongue Cancer, Tonsil Cancer, Trachea Cancer, Cancer NOS, Urinary Organs Cancer, Urethral cancer, Uterine Cancer, Uterine Sacrcoma, Vaginal Cancer, Vulvar Cancer, Cancer of Unknown Primary, Waldenström macroglobulinemia, and Wilms Tumour. In particular embodiment the cancer may be Bladder, Brain, Breast, cervical, Colorectal, uterine, Esophagus, Hodgkin lymphoma, Kidney, Larynx, Leukaemia, Lip, Lung, Multiple myeloma, Non-Hodgkin lymphoma, Oral cavity, Ovary, Pancreas, Prostate, Skin, Stomach, Testicular, or Thyroid cancer. In particular embodiment the cancer may be Stomach Cancer, Lung and Bronchus Cancer, Liver Cancer, Esophageal Cancer, Breast Cancer, Colon and Rectal Cancer, Prostate Cancer, Cervical Cancer, Uterine Cancer, Oral Cancer, Sarcoma, Bladder Cancer, Melanoma, Ovarian Cancer, Endometrial Cancer, Pancreas Cancer, Kidney (Renal Cell) Cancer, Lymphoma, or Leukemia. In particular embodiments the cancer may be ductal carcinoma, glioblastoma, epithelioid carcinoma, adenocarcinoma, carcinoma, or erythroleukemia,

In this disclosure the term "nutritional supplement" means a preparation intended to provide supplementary nutrients that are not present in sufficient quantity or desired quantity in a subject's diet.

In this disclosure the terms "directly exposing", "directly administering" and the like, a cell or tissue to tetrose, means that the cell or tissue is exposed to a composition or medium, which may without limitation be a fluid, comprising free tetrose.

In this disclosure the terms "indirectly exposing", "indirectly administering" or the like of a cell or tissue to tetrose means that the cell or tissue is exposed to a prodrug or other composition that is metabolisable to release a pharmaceutically effective amount of free tetrose.

In this disclosure the term "modulator" means a chemical whose presence modifies the behaviour of an enzyme, which may be a carbonic anhydrase

enzyme. In embodiments a modulator may be or may comprise Zinc, or a zinc salt, or a carbonic anhydrase inhibitor.

In this disclosure the term "prodrug" means an inactive form of tetrose, that is or may be converted into an active form of tetrose by normal metabolic processes. Without limitations, an active form of tetrose may be or may comprise a free tetrose monosaccharide. It will be understood that an "inactive form" of tetrose means a form of tetrose that is not directly metabolically available to a cell and in embodiments inactive tetrose may be or may include tetrose that is conjugated, modified, derivatised, complexed, isomerised or in any other form, which can be converted to an active form of tetrose by a cell. In particular embodiments a prodrug may be or may comprise any metabolisable disaccharide or polysaccharide form of tetrose that is metabolised to release active tetrose. A wide range of alternative prodrug forms of tetrose will be readily recognised, selected among, synthesised and used by those skilled in the art. In particular embodiments a prodrug may be or may comprise heptose, sedoheptulose, mannoheptulose, ascorbate, or Vitamin C and in embodiments may be used to treat non-cancerous conditions. In embodiments the prodrug may be or may comprise heptose, may comprise a monosaccharide having the molecular formula $C_7H_{14}O_7$ and may be or may comprise sedoheptulose, mannoheptulose. In particular embodiments any one or more compounds in the foregoing definition may be excluded. In particular embodiments, which may be embodiments for the treatment of cancer, such excluded compounds may be or may comprise mannoheptulose, Vitamin C and ascorbate.

In this disclosure a "limiting supply" or "limited availability" and similar terms, of a sugar or other chemical or substrate or of energy supply, means circumstances wherein the supply of a suitable metabolisable chemical has the effect of limiting the growth or viability of the cell or the normal chemical and physical processes of the cell or wherein the cell is unable to utilise available substrates effectively to maintain a suitable energy supply. Similarly "glucose deficiency" means that a cell has a low internal glucose concentration that may arise from causes including low glucose supply or deficient ability to absorb glucose or metabolise other chemicals

to liberate intracellular glucose. Similarly "energy deficiency" and similar terms mean that the cell is unable to maintain a suitable energy supply because of glucose deficiency or because of an inability to properly or efficiently use glucose or ketone bodies, or pyruvate or their metabolites to generate energy, as the case may be.

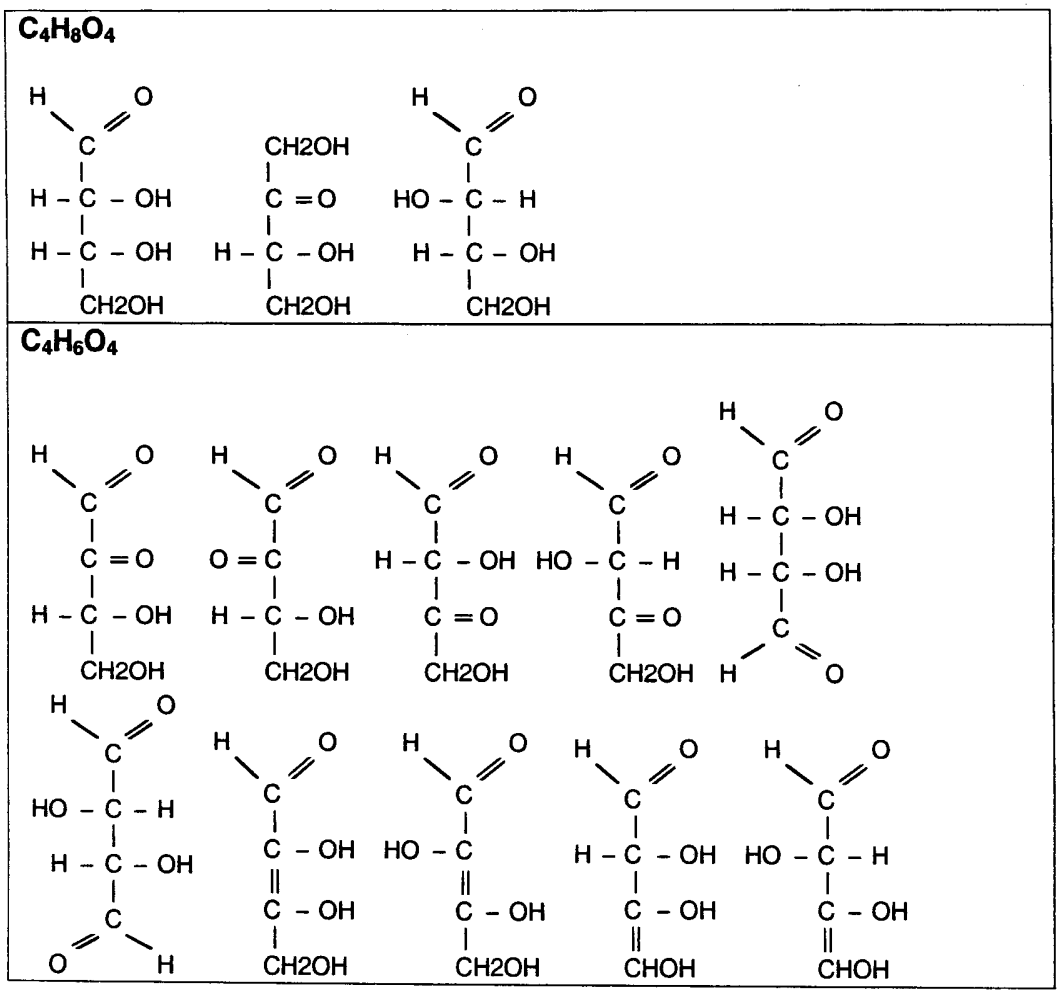
In this disclosure the term "mitochondrial disorder" means any condition or disorder which is partly or wholly, directly or indirectly caused by mitochondrial deficiency or dysfunction and in alternative embodiments may include but is not limited to cancer, aging and neurodegenerative disease. In embodiments mitochondrial disorders may be characterised by inability of cells to properly or efficiently use glucose or ketone bodies, or pyruvate or their metabolites to generate energy. Without limitation such diseases may include but are not limited to Alzheimer's disease, Parkinson's disease, Huntington's disease, cardiovascular disease, stroke, obesity, diabetes, multiple sclerosis, systemic lupus erythematosis, rheumatoid arthritis, schizophrenia, bipolar disorder, depression, ataxia, autism, epilepsy, migraine, Batten disease, Lactic academia, Leber's disease, mitochondrial cardiomyopathy and myopathy, paraplegin, Nonalcoholic steatohepatitis (NASH), and Wilson's disease.

In this disclosure the term "inhibit" where used with reference to cancer cells or the growth or development thereof, means and includes any effects that result in or comprise slowing or preventing growth or cell division of the cells, killing the cells, disabling the cells, and in any way reducing the viability, rate of division or longevity of the cells.

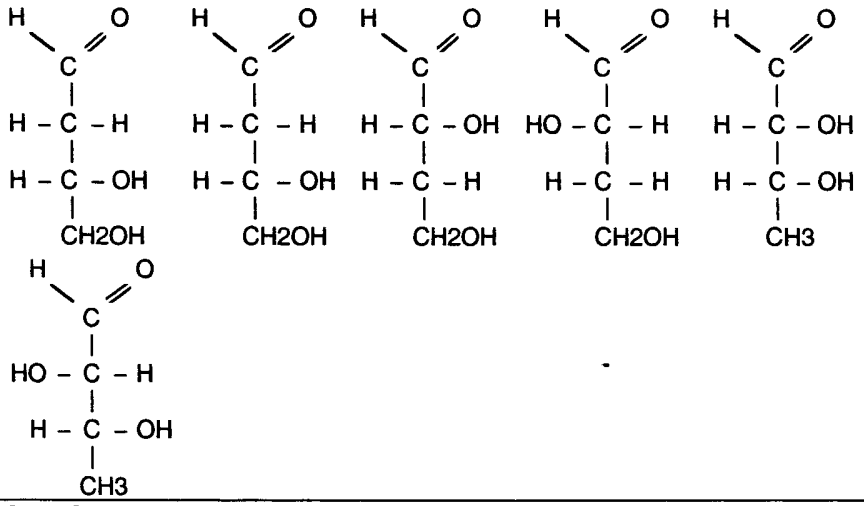
In this disclosure the term "tetrose" means without limitation, pharmaceutically effective monoshaccharides with the molecular formula $C_4H_8O_4$ or that are otherwise represented by any of the structural formulae set out in Table A and without limitation may include any pharmaceutically effective derivatives of any of the foregoing including without limitation any conjugated forms, substituted forms, ionised forms, salts and isomers including D and L stereoisomers, and any acid, base, aldehyde, ketone, alcohol, amine, amide, thiol, ring and linear forms of any

of the foregoing. In particular embodiments "tetrose" may be or may include erythrulose, erythrose, threose, deoxy-tetrose, dehydro-tetrose, and deoxy-dehydro-tetrose and any D and L isomers thereof. In embodiments, tetrose may be or comprise erythrose, erythrulose or threose, and in selected embodiments may be or may comprise D-erythrose, L-erythrose, D-threose, L-threose, D-erythrulose or L-erythrulose. In particular embodiments tetroses may be pure or may be substantially pure or may comprise mixtures of one or more tetroses. Tetroses, derivatives thereof, and prodrugs comprising the foregoing, can be prepared by conventional methods well known to those skilled in the art, who will readily identify, select and utilise suitable tetroses for particular purposes.

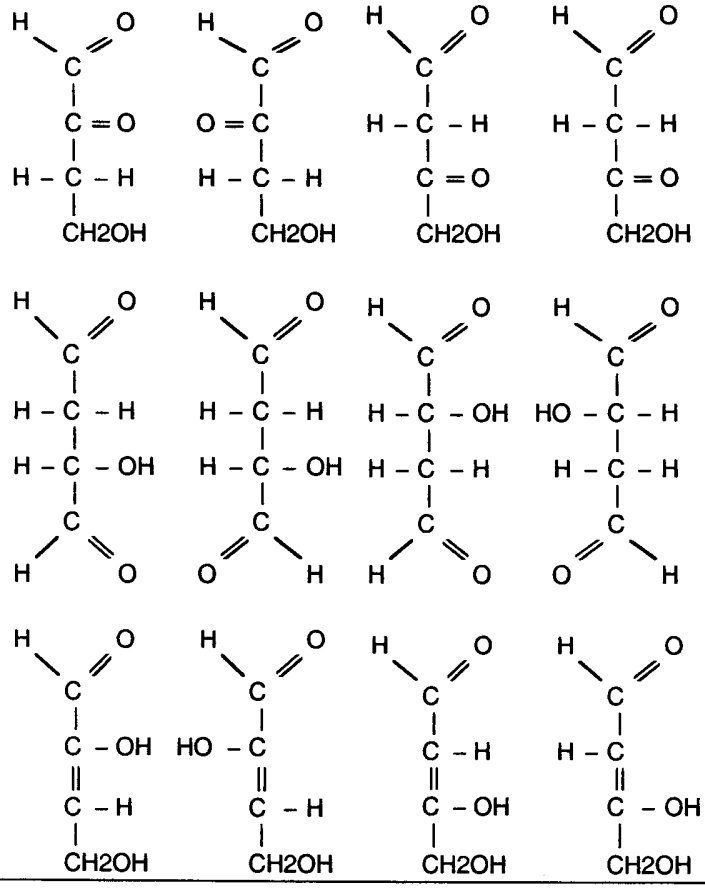
Table A: Illustrative non-limiting examples of tetroses:

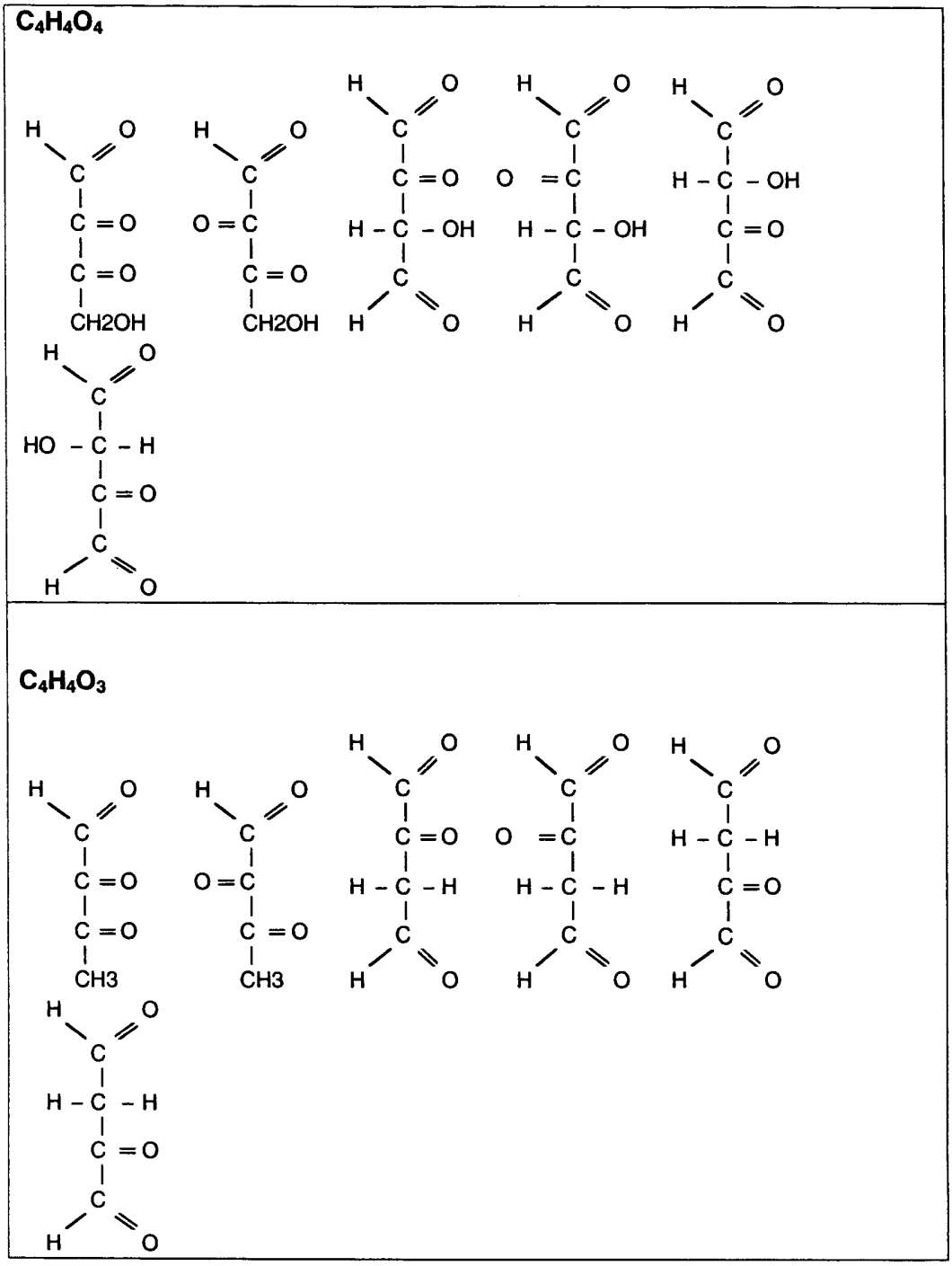


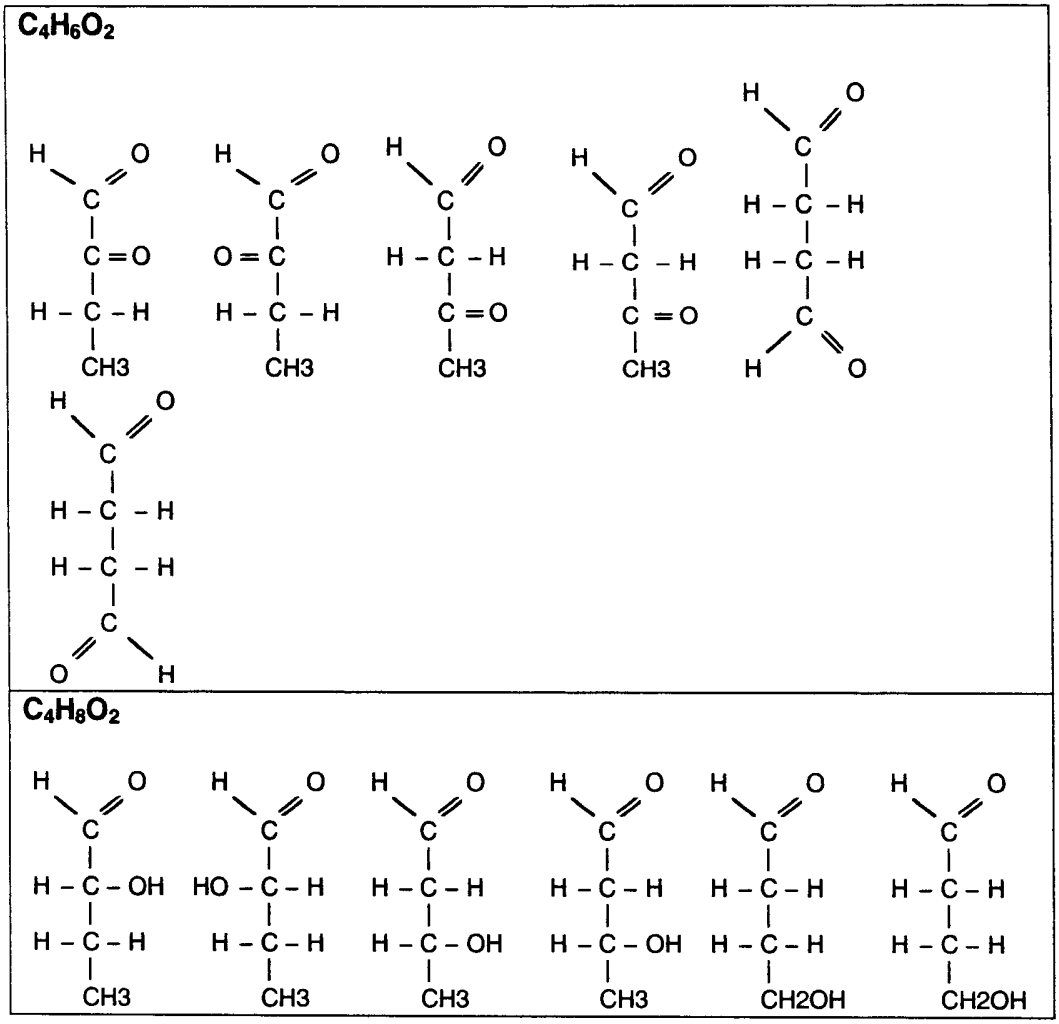
$C_4H_8O_3$



$C_4H_6O_3$




C4H4O4
CH2OH
CH2OH
HO - C - H
C4H4O3
CH3
CH3
H - C - H



For greater certainty and without limitation, in particular embodiments any one or more compounds in the definition of tetrose may be excluded and in particular embodiments such excluded tetroses may be or may comprise one or more of threonate, erythrose-4-phosphate, acetoacetate, sodium butyrate, succinic acid, and D-beta-hydroxybutyrate.

It will be understood that the tetrose used in particular embodiments may be used in combination with suitable pharmaceutically acceptable carriers or excipients and may be used in any suitable dosage forms. Those skilled in the art will readily identify, select from, and use the foregoing to suit the circumstances in question.

Where the cell to be treated is comprised in the body of a subject the methods disclosed may be implemented and the compositions disclosed may be delivered to the cell in any conventional ways including without limitation the delivery of the tetrose or prodrug, orally, parentally, enterally, intramuscularly, subcutaneously, intravenously, or by inhalation and may be delivered in combination with suitable carriers or excipients, in suitable dosage forms including without limitation tablets, capsules, subdermal pumps or other routes useful to achieve an effect. Alternative delivery methods may include osmotic pumps, implantable infusion systems, intravenous drug delivery systems, and refillable implantable drug delivery systems. Delivery by inhalation may comprise delivery using nebulizers, metered dose inhalers, powder inhalers, all of which are familiar to those skilled in the art. Suitable methods, compositions and routes of delivery will be readily recognised and implemented by those skilled in the art.

Embodiments:

First embodiment: In a first embodiment there is disclosed a method for inhibiting the growth of cancer cells comprising directly or indirectly exposing said cancer cells to a pharmaceutically effective concentration of tetrose. In embodiments the tetrose may be or may comprise erythrose, erythrulose or threose, and in selected embodiments may be or may comprise D-erythrose, L-erythrose, D-threose, L-threose, D-erythrulose, L-erythrulose, and in particular examples the tetrose may be D-erythrose, D-threose, or L-erythrulose In alternative embodiments there is disclosed the use of tetrose to inhibit the growth of cancer cells.

In embodiments cells may be exposed to the tetrose at a concentration of from at least about 100mg/litre up to about 1000 mg/litre or more. In alternative embodiments the cells may be exposed to the tetrose at a concentration of at least about 100 mg/litre, or at least about 200 mg/litre, at least about 300 mg/litre, at least about 400 mg/litre, at least about 500 mg/litre, at least about 600 mg/litre, at least about 700 mg/litre, at least about 800 mg/litre, at least about 900 mg/litre, at least about 1000 mg/litre or more. In embodiments the tetrose may be applied to cells under conditions where the cells are simultaneously exposed to glucose at

a concentration of greater than about 600 mg/litre, greater than about 700mg/litre, greater than about 800mg/litre, greater than about 900mg/litre, or greater than about 1000mg/litre. In one alternative embodiment the tetrose may be D-erythrose, which may be used at a concentration of between about 200mg/litre and about 1000mg/litre or between about 500 mg/litre and about 1000mg/litre. In embodiments the D-erythrose or other tetrose may be used at concentrations above 1000mg/litre.

It will be understood that the specific dosage desirable or suitable will vary depending on a variety of factors including but not limited to the disease to be treated, weight, sex, metabolism of the subject and the specific tetrose or composition being applied. Where the tetrose is D-erythrose and is applied at a concentration of between about 200 mg/litre and about 1000mg/litre, then in some cases an accompanying glucose concentration of greater than about 500 mg/litre, 600mg/litre, 700 mg/litre, 800mg/litre, 900mg/litre or greater than about 1000 mg/litre may be required in order to obtain a desired effect on cell growth. In particular embodiments lower glucose levels or more severely limited availability of glucose or energy supply may require increased levels of tetrose to inhibit the growth of cancer cells.

In particular embodiments an effective dose of a selected tetrose may comprise up to about 0.1 gram of tetrose per kg body weight of a subject or may comprise up to about 0.5g/kg body weight of the subject, up to about 1g/kg body weight of the subject or up to about 2g/kg; or up to about 3g/kg, or up to about 4g/kg, or up to about 5g/kg, or up to about 10g/kg body weight of the subject, or more. In embodiments an effective dose of a selected tetrose may comprise up to about 0.5g, 1.0g, 1.5g or up to about 2.0g of tetrose per kg body weight of a subject. In alternative embodiments the tetrose or combination thereof may be administered in a solution of up to about 1% or up to about 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 35%, 40%, 45%, 50% or greater than about 50% concentration by weight. In embodiments the tetrose or combination thereof may be administered in a solution containing up to about 16% to 40%

tetrose. In alternative embodiments the compositions may be administered to a subject continuously, once a day, twice a day, three times a day, four times a day, at least about once an hour, or more or less frequently. In embodiments the tetrose may be administered to a subject twice a day or three times a day. In embodiments the tetrose may be administered at least about 1, 2, 3, 4, 5, 6 or more times a day, or at least 1,2,3,4,5,6 or more times a week, and may be administered alone or in combination with other active or inactive agents. In embodiments the tetrose may be administered to a subject for 1, 2, 3, 4, 5, 6 or more days continuously.

In alternative embodiments of the first embodiment, the tetrose may be selected from the group consisting of erythrose, threose and erythrulose and isomers thereof. In further alternative embodiments of the first embodiment indirect exposing may comprise administering a prodrug. In alternative embodiments the cancer cells may be exposed to a concentration of greater than about 100mg/litre, 200mg/litre, 300 mg/litre, 400mg/litre, 500mg/litre, 600mg/litre, 700mg/litre, 800mg/litre, 900mg/litre or more than about 1000 mg/litre of tetrose, or may be exposed to a glucose concentration of greater than about 500 mg/litre before or simultaneous with said exposure to tetrose.

Second embodiment: In a second embodiment there is disclosed a method for improving the viability of a cell, the method comprising directly or indirectly exposing said cell to a therapeutically effective amount of tetrose. There is also disclosed the use of tetrose for improving the viability of a cell. In embodiments the cell may be unable to use glucose to maintain cell viability, or may be subject to conditions of low energy supply or glucose or energy deficiency or may have a mitochondrial disorder. In further embodiments there is disclosed a method of treating a mitochondrial disorder or compensating the energy deficiency in a cell comprising directly or indirectly supplementing the nutrient supply to said cell with an effective dose of tetrose.

Tetrose may be an effective energy source for mammalian cells under conditions wherein the cells are unable to use glucose to maintain cellular functions. Suitable

conditions for the use of tetrose as an energy source for cells may include conditions wherein the cells are unable to use glucose efficiently, such as mitochondrial deficiency/dysfunction, infection with virus or bacteria, or other medical conditions resulting in low cellular energy generation or abnormal cellular energy generation, including without limitation extreme high anaerobic glycolysis. In particular embodiments the tetrose may be or may comprise erythrose, erythrulose or threose, and in selected embodiments may be or may comprise D-erythrose, L-erythrose, D-threose, L-threose, D-erythrulose, L-erythrulose, and in particular examples the tetrose may be D-erythrose or L-erythrulose. In particular embodiments the tetrose may be D-erythrose and may be applied to the cells at a concentration of about 1-200 mg/litre and may be applied at concentrations of up to about 20 mg/litre, up to about 40 mg/litre, up to about 60 mg/litre, up to about 80 mg/litre, up to about 100 mg/litre, up to about 200 mg/litre, up to about 300 mg/litre, up to about 400 mg/litre, up to about 600 mg/litre, up to about 800 mg/litre, up to about 1000mg/litre or more than about 1000mg/litre. In alternative embodiments the cells may be exposed to tetrose at any concentration and in any form sufficient to adjust the ATP or pH homeostasis of the targeted cells to support cellular function, which concentrations and forms will be readily determined by those skilled in the art using known procedures.

In embodiments improving the viability of cells may comprise improving mitochondrial function in the cells, which may be achieved by exposing the cells to tetrose in combination with other pharmaceutically active compounds that will be readily identified, selected from and utilised by those skilled in the art. In particular embodiments tetrose may be delivered or used in combination with one or more compounds that may include but are not limited to DCA (dichloroacetate), ginkgo biloba extract, hydroxytyrosol, and resveratrol.

In alternative embodiments of the second embodiment the cell may be exposed to conditions of energy limitation. In alternative embodiments of the second embodiment the cell may have a mitochondrial disorder. In alternative embodiments tetrose may be selected from the group consisting of erythrose, threose and erythrulose. In alternative embodiments of the second embodiment

the method may comprise exposing said cells to a concentration of between about 1 mg/litre and about 1000 mg/litre of tetrose. In embodiments the method may comprise exposing the cells to a concentration of between about 1 mg/litre and about 200 mg/litre of tetrose.

In alternative embodiments of the second embodiment the mitochondrial disorder may be associated with a disorder selected from the group consisting of neurodegenerative disease Alzheimer's disease, Parkinson's disease, Huntington's disease, cardiovascular disease, stroke, obesity, diabetes, multiple sclerosis, systemic lupus erythematosis, rheumatoid arthritis, schizophrenia, bipolar disorder, depression, ataxia, autism, epilepsy, migraine, Batten disease, Lactic acidemia, Leber's disease, mitochondrial cardiomyopathy and myopathy, paraplegin, NASH, and Wilson's disease.

In a further alternative embodiment of the second embodiment there is disclosed a method of treating a mitochondrial disorder in a subject having such disorder, the method comprising directly or indirectly administering to the subject an effective dose of tetrose. In a further embodiment there is disclosed the use of tetrose to treat a mitochondrial disorder, or to treat other medical conditions which may include without limitation conditions of energy deficiency.

Third embodiment:

In a third embodiment there are disclosed compositions comprising a pharmaceutically acceptable carrier or diluent and a direct or indirect sources of tetrose in amounts effective to inhibit the growth of a cancer cell or to increase the viability of a cell under conditions of low energy supply; or to increase the viability of a cell having a mitochondrial disorder.

In alternative embodiments there is disclosed a composition comprising: a direct or indirect source of tetrose in an amount effective to inhibit the growth of cancer cells; and a pharmaceutically acceptable carrier or diluent. In alternative embodiments the compositions disclosed may comprise a direct or indirect source

of tetrose in an amount effective to increase the viability of a cell having a mitochondrial disorder; and a pharmaceutically acceptable excipient.

Fourth embodiment:

In any embodiment there are disclosed compositions comprising a prodrug metabolisable to yield a pharmaceutically effective amount of tetrose. In alternative embodiments there are disclosed compositions comprising a prodrug metabolisable to yield a pharmaceutically effective amount of tetrose and in alternative embodiments there is disclosed the use of the prodrug to manufacture a dietary supplement, to inhibit the growth of cancer cells; to increase the viability of cells under low energy conditions; and to increase the viability of cells having a mitochondrial disorder.

In alternative embodiments there is disclosed the use of an effective dose of a prodrug metabolisable to yield tetrose to achieve an effect selected from the list consisting of: inhibiting the growth of cancer cells; increasing the viability of cells under low energy conditions; and increasing the viability of cells having a mitochondrial disorder. In alternative embodiments there is disclosed the use of a tetrose containing prodrug to manufacture a dietary supplement. In embodiments the prodrug may be or may comprise heptose, may comprise a monosaccharide having the molecular formula $C_7H_{14}O_7$ and may comprise sedoheptulose, mannoheptulose, vitamin C or ascorbate.

Fifth embodiment:

In an embodiment there are disclosed methods of increasing the viability of a cell under limited energy supply and methods of inhibiting the growth of a cancer cell. The methods may comprise directly or indirectly exposing the cell to tetrose in the presence of compounds known to enhance intracellular carbonic anhydrase activity or otherwise modulate cellular or extracellular enzymes. In embodiments the compound may be or may comprise a pharmaceutically acceptable zinc salt which may be zinc Chloride, zinc sulfate, zinc acetate, zinc monomethionine, zinc gluconate, a zinc salt of an amino acid, such as: zinc glutamate, zinc aspartate, a

zinc salt of an organic acid, such as zinc oxaloacetate, zinc malate, zinc fumarate, zinc succinate, a zinc salt of a monosaccharide acid, zinc ascorbate, or in any other form readily taken up by a cell, all of which will be readily identified, understood, selected from and utilised by those skilled in the art. In embodiments cells may be exposed to the zinc at a concentration of from at least about 5μM, 10μM, 15μM, 20μM, 25μM, 30μM, 35μM, or more up to about 40μM or more. Suitable concentrations will be readily identified, selected from and utilised by those skilled in the art.

Sixth Embodiment:

In an embodiment there are disclosed methods of increasing the viability of a cell under limited energy supply and methods of inhibiting the growth of a cancer cell. The methods may comprise directly or indirectly exposing the cell to tetrose in the presence of compounds known to inhibit extracellular carbonic anhydrase activity. In embodiments the compound may be or may comprise quaternary ammonium sulfanilamide, or may comprise other suitable carbonic anhydrase inhibitors, all of which will be readily identified, selected from and used by those skilled in the art. In embodiments the carbonic anhydrase inhibitor may be a compound to which the cell membrane is partially or wholly impermeable. Where the compound is ammonium sulfanilamide it may be provided to a subject in amounts of from 125mg to 1000mg one to four times a day.

Seventh Embodiment:

In an embodiment there are disclosed methods of increasing the viability of a cell under limited energy supply. The methods may comprise directly or indirectly exposing the cell to tetrose in the presence of a compound or composition known to enhance mitochondrial function. In particular embodiments these may be or may comprise without limitation dichloroacetate, ginkgo biloba extract, hydroxytyrosol, reservatrol, ascorbic acid, ascorbate. A wide range of suitable compounds and preparations will be readily recognised, selected from and used by those skilled in the art.

EXAMPLES

The following examples are presented for the purpose of illustrating embodiments and are not limiting.

Methods

Cell Culture: Cell lines are cultured in cell culture incubator in media of DMEM or RMPI1640 with different concentrations of glucose, D-erythrose, L-erythrulose, D-threose, $ZnCl_2$ and 10% FBS.

Trypan-Blue assay: Cell number and viability was determined using a standard Trypan-Blue assay counted on a hemocytometer.

MTT assay: It measures the special activity of mitochondria to cleave the tetrazolium ring of the soluble dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide ("MTT") to differentiate live cells from dead cells. Media for adherent cells is washed before MTT assay. The MTT assay is based on the production of a dark blue formazan product by active dehydrogenase in the mitochondria of live cells. The numbers of live cells (cell proliferation), or the mitochondria activity of live cells, can be measured by absorbance of visible light by the formazan at 595 nm.

Example 1: D-Erythrose inhibits cancer cell growth.

Example 1.1: MCF-7 (Human breast adenocarcinoma cell line) was cultivated with different concentrations of D-erythrose in 1g/L glucose DMEM media for 24 hours. Live and dead cells were counted with Trypan-Blue assay (Table 1.1).

Table 1.1: Live and dead cell percentage with different D-erythrose concentration

D-erythrose (mg/L)	10		50		100		200		300		400	
	live	dead	live	dead	live	dead	live	dead	live	dead	live	dead
MCF-7	98.1	1.9	99.4	0.6	99.4	0.6	100.0	0.0	100.0	0.0	55.4	44.6

Example 1.2: Mouse Lung Carcinoma (LL2) was cultivated with different concentrations of D-erythrose and glucose for 48 hours in DMEM media. Live cell percentage was counted with Trypan-Blue assay (Table 1.2a), 0 mg/L D-erythrose was control at 100%. Lower concentration had no effect in cell death; cell proliferation was inhibited with increasing concentration of D-erythrose. Cell proliferation based on mitochondria activity was measured by MTT assay (Table 1.2b). Cell proliferation decreased with increasing D-erythrose.

Table 1.2a: Live cell comparison of LL2 with different D-erythrose and glucose concentration for 48 hr

D-erythrose(mg/L)	0	10	25	50	75	100	150	250	500
Media\	Live Cell Comparison								
1g/L glucose	100%	100%	100%	100%	100%	100%	95%	85%	30%
2g/L glucose	100%	100%	100%	100%	100%	100%	95%	85%	30%
4g/L glucose	100%	100%	100%	100%	100%	100%	95%	85%	30%

Table 1.2b: Cell proliferation of LL2 with different D-erythrose and glucose concentration for 48 hr

D-erythrose (mg/L)	0	10	25	50	75	100	150	250	500
1g/L glucose	1.51 (±0.16)	1.77 (±0.13)	1.83 (±0.02)	1.80 (±0.28)	1.87 (±0.16)	1.76 (±0.41)	1.77 (±0.19)	1.61 (±0.15)	1.13 (±0.31)
2g/L glucose	1.58 (±0.58)	1.50 (±0.09)	1.48 (±0.13)	1.62 (±0.33)	1.33 (±0.37)	1.62 (±0.36)	1.56 (±0.39)	1.36 (±0.38)	0.74 (±0.25)
4g/L glucose	1.59 (±0.18)	1.49 (±0.07)	1.52 (±0.03)	1.48 (±0.06)	1.42 (±0.12)	1.43 (±0.22)	1.49 (±0.08)	1.51 (±0.13)	0.97 (±0.09)

Example 1.3: Human colorectal cancer cell line (SW480) was cultivated with different concentrations of D-erythrose in 1g/L glucose DMEM media for 48 hours and mouse colon cancer cell line (CT26) was cultivated with different concentrations of D-erythrose in 1g/L glucose RPMI1640 media for 48 hours. Cell proliferation based on mitochondria activity was measured by MTT assay (Table 1.3).

Table 1.3: Cell proliferation of SW480 and CT26 with D-erythrose in 1g/L glucose media for 48 hr

D-erythrose (mg/L)	0	10	25	50	75	100	150	250	500
SW480 in DMEM	0.65 (±0.02)	0.68 (±0.05)	0.67 (±0.07)	0.7 (±0.07)	0.71 (±0.08)	0.66 (±0.03)	0.68 (±0.03)	0.54 (±0.07)	0.15 (±0.00)
CT26 in RPMI 1640	0.6 (±0.01)	0.58 (±0.03)	0.53 (±0.14)	0.56 (±0.01)	0.57 (±0.02)	0.55 (±0.04)	0.49 (±0.05)	0.41 (±0.00)	0.13 (±0.03)

Example 1.4: Mouse colon cancer cell line (CT26) was cultivated with different concentrations of D-erythrose in 1g/L glucose DMEM media for 24 or 48 hours. Cell proliferation based on mitochondria activity was measured by MTT assay (Table 1.4).

Table 1.4: Cell proliferation of CT26 with D-erythrose in 1g/L DMEM media for 24 or 48 hr

D-erythrose (mg/L)	0	25	50	75	100	150	250	500
24hr	0.76 (±0.02)	0.78 (±0.02)	0.76 (±0.04)	0.73 (±0.02)	0.77 (±0.02)	0.68 (±0.03)		0.11 (±0.01)
48hr	0.8 (±0.00)	0.71 (±0.11)	0.64 (±0.04)	0.68 (±0.04)	0.66 (±0.05)	0.59 (±0.02)	0.54 (±0.00)	0.16 (±0.02)

Example 1.5: With different concentrations of glucose and D-erythrose in DMEM tissue culture media, three cells lines in vitro were tested: U87MG, BT474 and Panc-1. After 96 hours incubation, no massive adhering cell population could be observed for all cancer cell lines under microscopy. Cell viability was determined with Trypan-Blue assay (Table 1.5).

Table 1.5: Viability after culture with different concentration of glucose and D-erythrose

Cancer Cell Line	Growth condition	Cell/Well at the start of culture	Cell/Well at the end of culture	Viability (%)	Live cell number change (%)
Panc-1	4.5 g/L glucose	100,000	780,000	92	617.6
	1.0 g/L glucose + 3.5 g/L D-erythrose	100,000	45,000	33.3	-85.02
	4.5 g/L D-erythrose	100,000	20,000	66.7	-86.66
U87mg	4.5 g/L glucose	70,000	435,000	100	521.43
	1.0 g/L glucose + 3.5 g/L D-erythrose	70,000	0	0	-100
	4.5 g/L D-erythrose	70,000	0	0	-100
BT474	4.5 g/L glucose	80,000	85,000	100	6.25
	1.0 g/L glucose + 3.5 g/L D-erythrose	80,000	0	0	-100
	4.5 g/L D-erythrose	80,000	0	0	-100

Example 2: Zinc enhance D-Erythrose's ability of inhibiting cancer cell growth

MCF-7 (Human breast adenocarcinoma cell line) was cultivated with different concentrations of $ZnCl_2$ in 1g/L glucose and 400 mg/L D-erythrose DMEM media for 24 hours (Table 2.1). HEL (Human Erythroleukemia) was cultivated with different concentrations of $ZnCl_2$ and D-erythrose in 1g/L glucose DMEM media for 24 hours, live cell comparison with 0μM added $ZnCl_2$ as 100% (Table 2.2). Live and dead cells were counted with Trypan-Blue assay.

Table 2.1: Live and dead cell percentage of MCF-7 with different concentration of $ZnCl_2$

Added $ZnCl_2$ (μM)	0		3		5		10		20		40	
	live	dead	live	dead	live	dead	live	dead	live	dead	live	dead
MCF-7	55.4	44.6	56.8	43.2	28.0	72.0	19.6	80.4	24.7	75.3	5.2	94.8

Table 2.2: Live cell comparison of HEL with different concentration of $ZnCl_2$ and D-erythrose

D-erythrose (mg/L) \ Added $ZnCl_2$ (μM)	0	3	5	10	20	40
400	100%	75%	81%	82%	52%	48%
300	100%	89%	96%	99%	78%	75%

Example 3: D-Erythrose enhance cell viability.

Mouse Lung Carcinoma (LL2) and mouse colon cancer cell line (CT26) were cultivated with different concentrations of D-erythrose in low glucose (0.5g/L) DMEM media for 48 hours. Live cell percentage of LL2 was counted with Trypan-Blue assay (Table 3.1), 0 mg/L D-erythrose was control as 100%; data of treatment was comparable result of same glucose concentration. Cell proliferation based on mitochondria activity was measured by MTT assay (Table 3.2). In low glucose (0.5 g/L) media, D-erythrose increased cell viability.

Table 3.1: Live cell comparison of LL2 for 48 hr with D-erythrose in 0.5g/L glucose DMEM

D-erythrose(mg/L)	0	10	25	50	75	100	150	250	500
LL2	100%	120%	120%	120%	120%	120%	120%	120%	120%

Table 3.2: Cell proliferation of LL2 and CT26 for 48 hr with D-erythrose in 0.5g/L glucose DMEM

D-erythrose (mg/L)	0	10	25	50	100	150	250	500
LL2	0.27 (±0.03)	0.35 (±0.06)	0.36 (±0.01)	0.37 (±0.01)	0.43 (±0.01)	0.42 (±0.02)	0.52 (±0.03)	0.4 (±0.03)
CT26	0.12 (±0.02)	0.17 (±0.03)	0.17 (±0.03)	0.17 (±0.10)	0.15 (±0.01)	0.16 (±0.03)	0.2 (±0.02)	0.15 (±0.00)

Example 4: Zinc enhance D-Erythrose's ability of increasing cell viability

MCF-7 (Human breast adenocarcinoma cell line) was cultivated with different concentrations of D-erythrose and $ZnCl_2$ in 1g/L glucose DMEM media for 24 hours. Live cell percentage was counted with Trypan-Blue assay (Table 4.1 and Table 4.2). Zinc enhances D-erythrose's ability of increasing cell viability.

Table 4.1: Live cell percentage of MCF-7 with different concentration of D-erythrose and $ZnCl_2$ compare to 0mg/L D-erythrose

D-erythrose (mg/L) \ Added $ZnCl_2$ (μM)	5	10	20	40
100	106%	128%	137%	110%
50	116%	139%	131%	121%
10	131%	142%	107%	131%
0	100%	100%	100%	100%

Table 4.2: Live cell percentage of MCF-7 with different concentration of D-erythrose and $ZnCl_2$ compare to 0 or 1 μM Added ZnCl2

D-erythrose (mg/L) \ Added $ZnCl_2$ (μM)	0 or 1	5	10	20	40
100	100%	117%	124%	141%	115%
50	100%	111%	117%	117%	110%
10	100%	126%	119%		119%

Example 5: L-Erythrulose inhibits cancer cell growth.

Mouse Lung Carcinoma (LL2) was cultivated with different concentrations of D-erythrulose for 24 hours in 1g/L glucose DMEM media. Cell proliferation based on mitochondria activity was measured by MTT assay (Table 5). L-erythrulose has anti-cancer effect.

Table 5: Cell proliferation of LL2 for 24 hr with L-erythrulose in 1g/L glucose DMEM

L-erythrulose (mg/L)	0	1000	2000	5000	10000
LL2	0.83±0.01	0.64±0.02	0.54±0.02	0.53±0.04	0.34±0.05

Example 6: L-Erythrulose enhance cell viability

Mouse Lung Carcinoma (LL2) was cultivated with different concentrations of D-erythrulose in low glucose (0.5g/L) DMEM media for 24 hr. Cell proliferation based on mitochondria activity was measured by MTT assay (Table 6).

Table 6: Cell proliferation of LL2 for 24 hr with L-erythrulose in 0.5g/L glucose DMEM

L-erythrulose & Glucose (mg/L)	0 & 500	1000 & 500	2000 & 500	5000 & 500	0 & 1000
LL2	0.56±0.03	0.82±0.03	0.86±0.17	0.82±0.18	0.73±0.04

Example 7: D-threose inhibit cancer cell growth.

Mouse Lung Carcinoma (LL2) was cultivated with different concentrations of D-threose for 48 hours in 1g/L glucose DMEM media. Live cell percentage was counted with Trypan-Blue assay (Table 7.1), 0 mg/L D-threose was control as 100%. Cell proliferation based on mitochondria activity was measured by MTT assay (Table 7.2). Cell proliferation decreased with increasing D-threose in 1g/L glucose DMEM media.

Table 7.1: Live cell comparison of LL2 for 48 hr with different D-threose concentration in 1g/L glucose

D-threose concentration (mg/L)	0	100	150	200	250	300	350	400	450	500
LL2	100%	100%	100%	95%	95%	90%	90%	85%	80%	75%

Table 7.2: Cell proliferation of LL2 for 48 hr with different D-threose concentration in 1g/L glucose

D-threose concentration (mg/L)	0	500	1000	1500	2000	2500	3000
LL2	1.52 (±0.04)	1.04 (±0.07)	0.47 (±0.06)	0.45 (±0.02)	0.45 (±0.01)	0.34 (±0.03)	0.28 (±0.02)

Example 8: D-Erythrose inhibit tumour growth in mice.

Mice with tumours grown from CT26 cell line under mice's skin were treated with an injection of 8mg D-erythrose beside the tumour per mouse daily. Comparing to control (treated with PBS), tumour growth rate was decreased by 19.46% in two days by the treatment of D-erythrose. There was no significant difference (<1%) in weight changes between the treatment group and the control group.

Another two groups of mice with tumour were treated with 1) an injection of 20mg D-erythrose beside the tumour per mouse daily; 2) two injections of 20mg D-erythrose beside the tumour per mouse daily.

Tumour growth rate reduced 90% for group 1. (Table 8). For group 2, the average tumour size shrank about 50% of the original size on day 4 (six mice in the group, except of an extreme one, the average tumour size for other 5 mice shrank 95%.)

Table 8: Tumour size (mm^3) and tumour growth rate with once a day or twice a day 20 mg D-erythrose injection.

	Day 1	Day 4	Change %
Control	7.38±3.45	47.92±10.74	549.66%
Once daily	7.94±1.71	12.31±16.80	55.01%
Twice daily	9.48±3.11	4.26±9.44	-55.04%

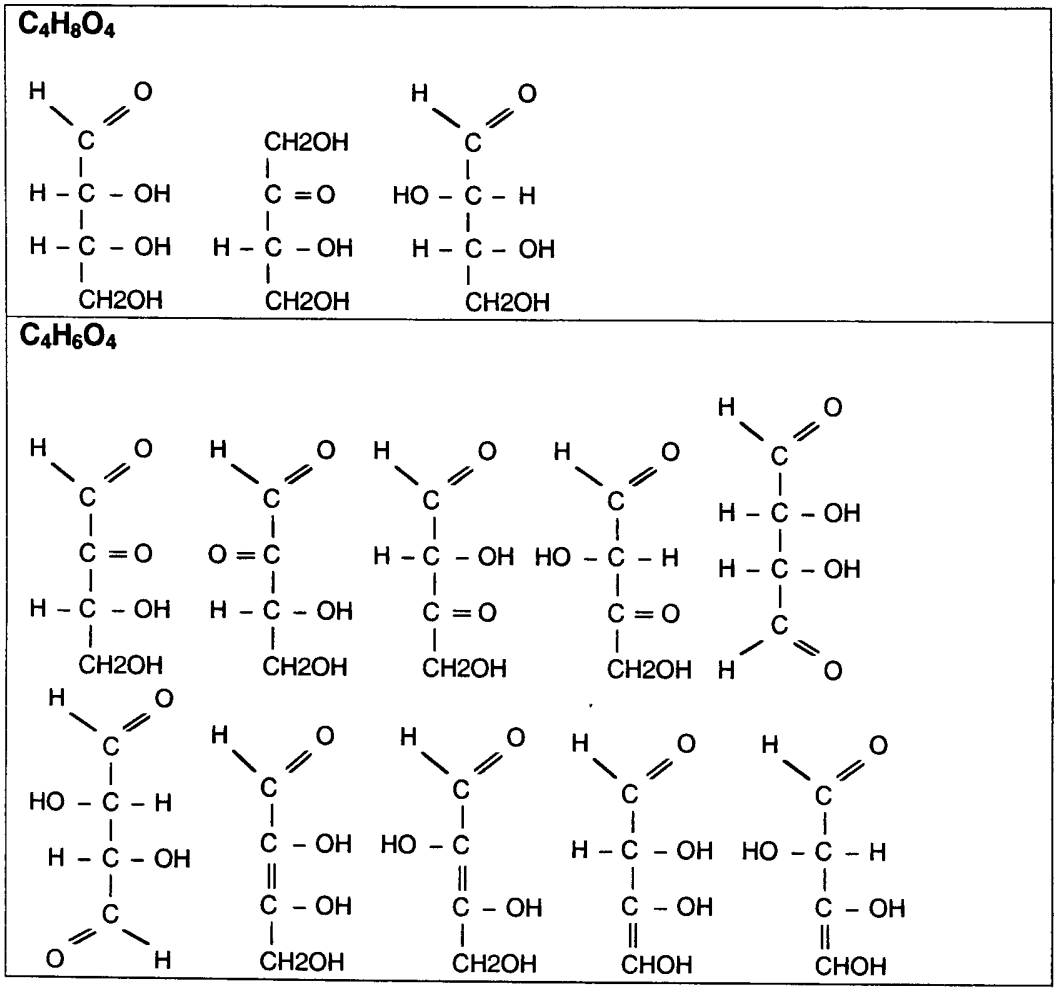
Examples and embodiments not limiting:

The embodiments and examples presented herein are illustrative of the general nature of the subject matter claimed and are not limiting. It will be understood by those skilled in the art how these embodiments can be readily modified and/or adapted and/or combined for various applications and in various ways without departing from the spirit and scope of the subject matter disclosed claimed. The claims hereof are to be understood to include without limitation all alternative embodiments and equivalents of the subject matter hereof. Phrases, words and terms employed herein are illustrative and are not limiting. Where permissible by law, all references cited herein are incorporated by reference in their entirety. It will be appreciated that any aspects of the different embodiments disclosed herein may be combined in a range of possible alternative embodiments, and alternative combinations of features, all of which varied combinations of features are to be understood to form a part of the subject matter claimed.

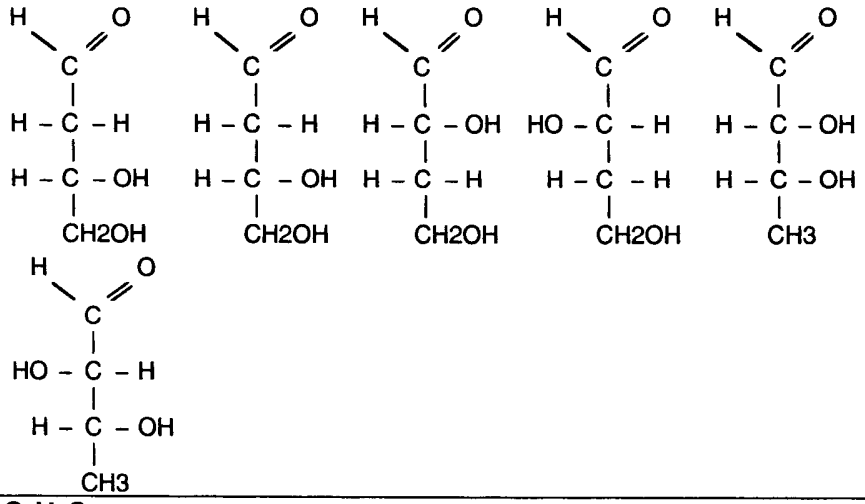
THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A method for inhibiting the growth of a cancer cell comprising directly or indirectly exposing said cancer cell to a pharmaceutically effective concentration of tetrose.

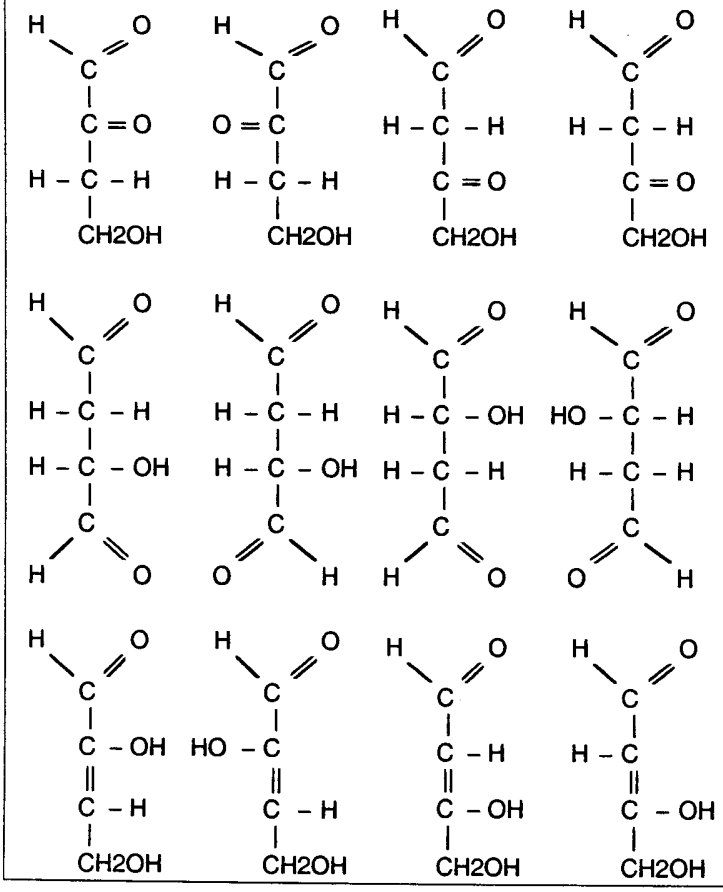
2. The method according to claim 1 wherein the tetrose has a structural formula selected from the group consisting of:

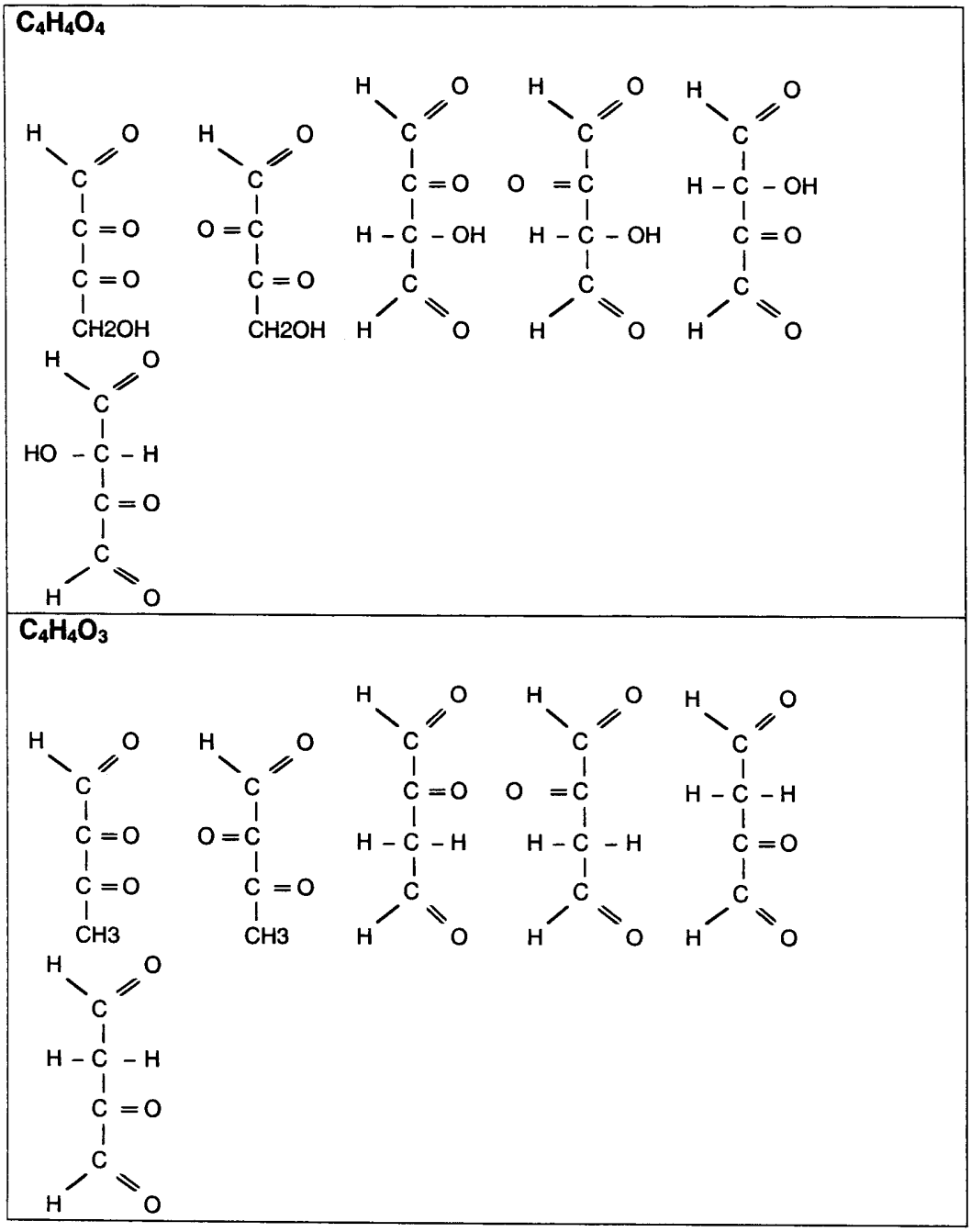


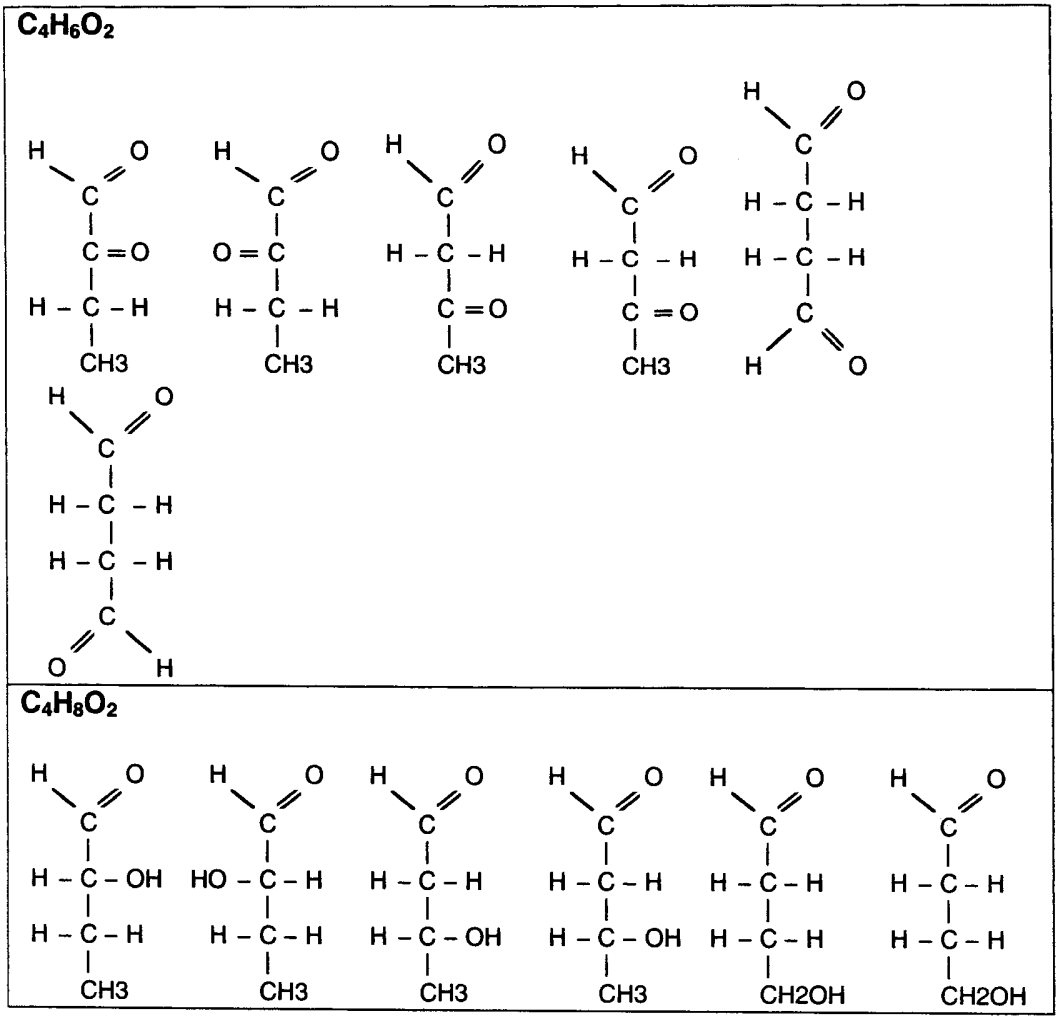
$C_4H_8O_3$



$C_4H_6O_3$




C4H4O4
CH2OH
CH2OH
HO - C - H
C4H4O3
CH3
CH3



and any pharmaceutically effective derivatives thereof.

3. The method according to claim 2 wherein the derivative is a conjugated, substituted, ionised, salt, isomeric, acid, base, aldehyde, ketone, alcohol, amine, amide, thiol, ring or linear form.

4. The method according to claim 1 wherein the tetrose is selected from the group consisting of erythrose, threose and erythrulose.

5. The method according to claim 1 wherein said indirect exposing comprises exposing said cancer cell to a prodrug metabolisable to release tetrose.

6. The method according to claim 1 wherein said cancer cell is exposed to a concentration of greater than about 100 mg/litre of tetrose.

7. The method according to claim 1 wherein said cancer cell is exposed to a glucose concentration of greater than about 500 mg/litre before or simultaneous with said exposure to tetrose.

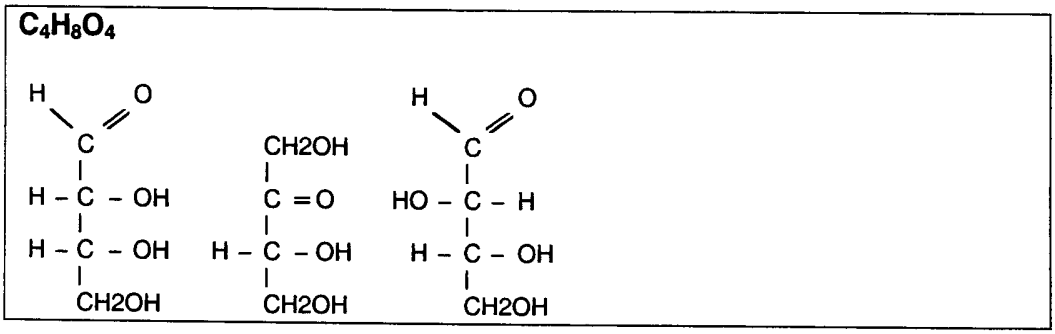
8. The method according to claim 1 wherein said cancer is selected from the group consisting of carcinoma, sarcoma, adenoma, leukemia, lymphomas and myeloma

9. The method according to claim 1 wherein said exposure occurs in combination with exposing said cell to a modulator of carbonic anhydrase activity.

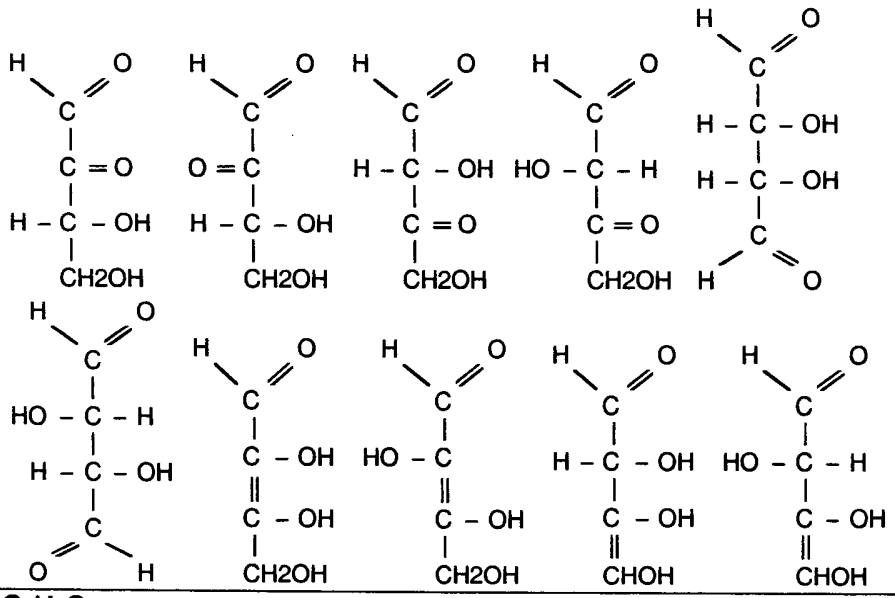
10. The method according to claim 9 wherein said modulator comprises a Zinc salt.

11. A method for improving the viability of a cell, said method comprising directly or indirectly exposing said cell to a therapeutically effective amount of tetrose.

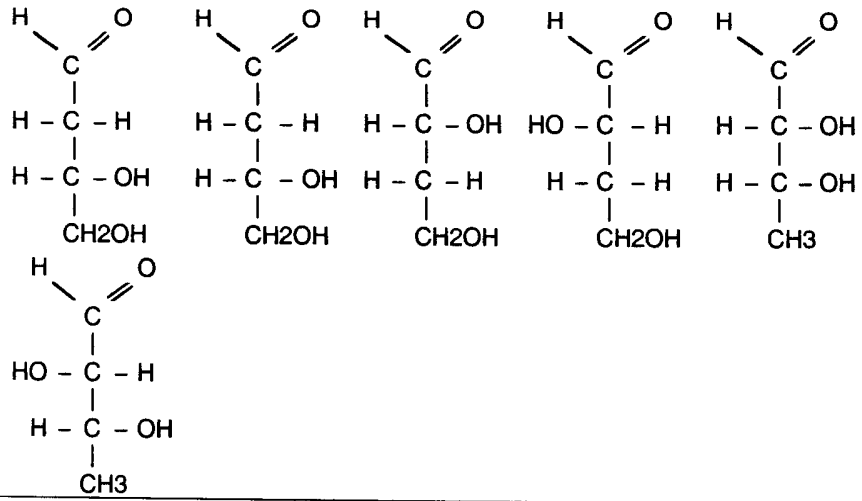
12. The method according to claim 11 wherein the tetrose has a structural formula selected from the group consisting of:



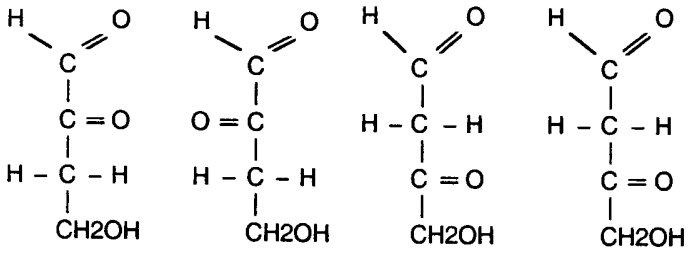
$C_4H_6O_4$

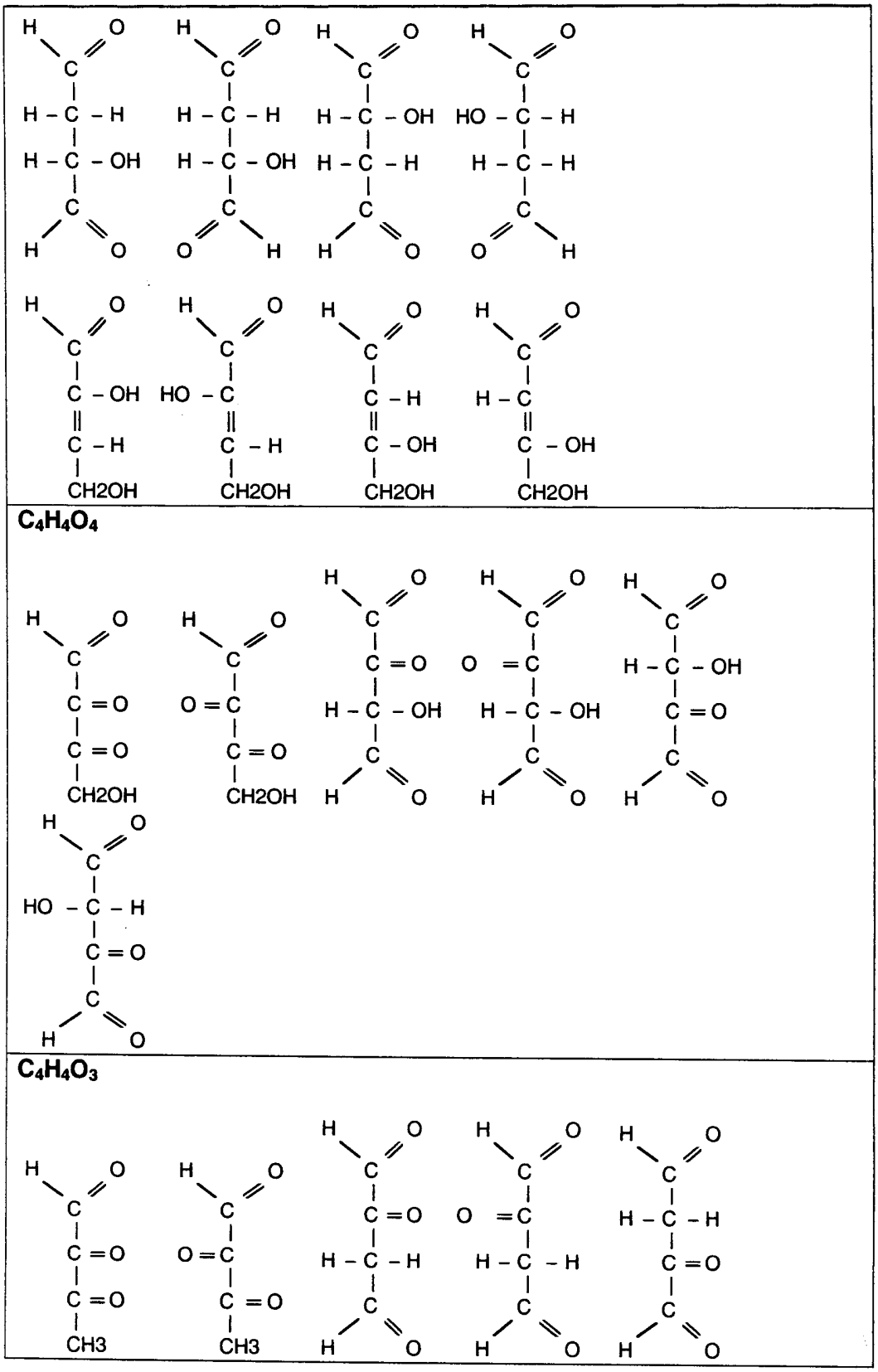


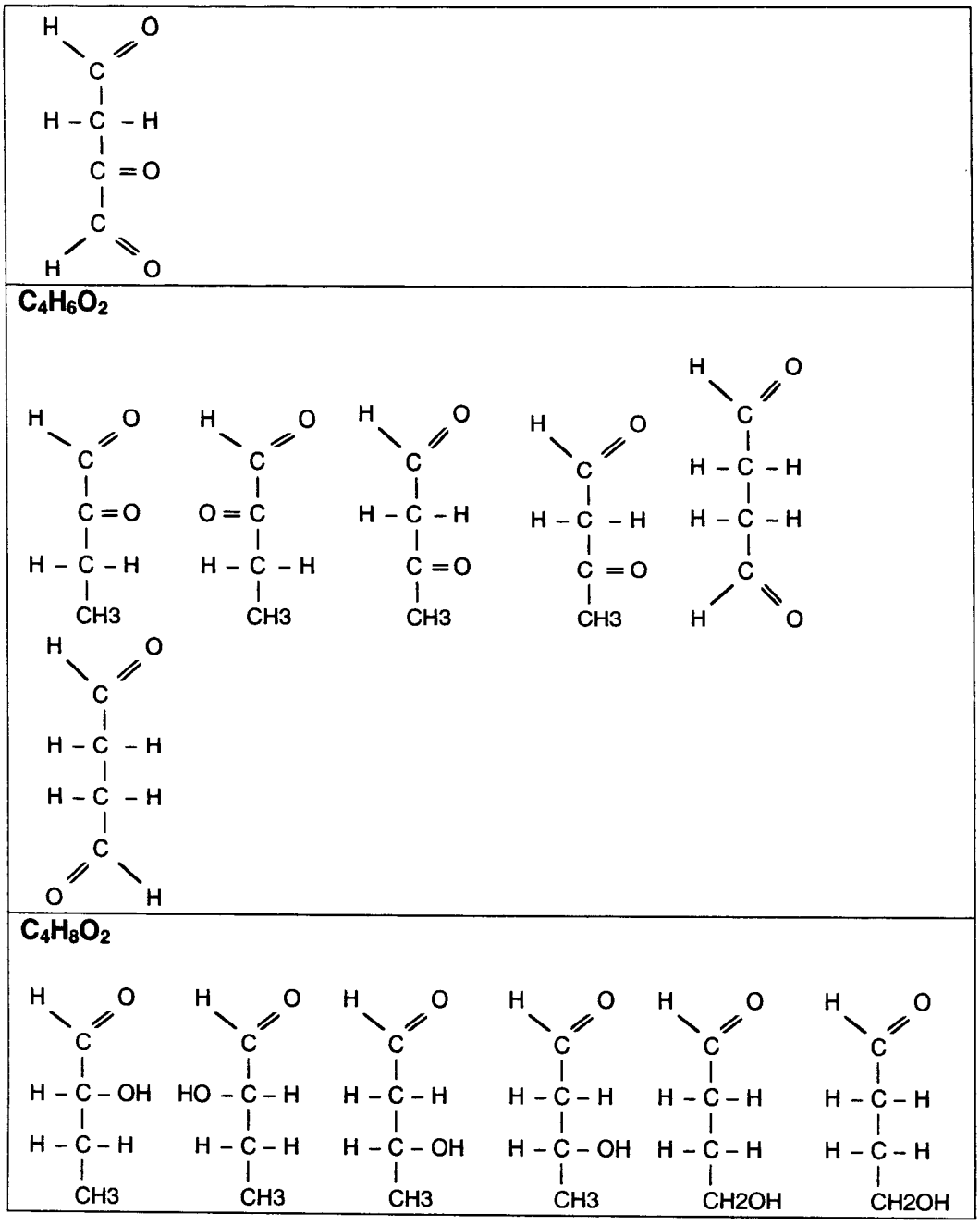
$C_4H_8O_3$



$C_4H_6O_3$




C4H4O4
C4H4O3



and any pharmaceutically effective derivatives thereof.

13. The method according to claim 12 wherein the derivative is a conjugated, substituted, ionised, salt, isomeric, acid, base, aldehyde, ketone, alcohol, amine, amide, thiol, ring or linear form.

14. The method according to claim 11 wherein said exposure occurs in combination with exposing said cell to a modulator of carbonic anhydrase activity.

15. The method according to claim 11 wherein said cell is under conditions of limited energy supply.

16. The method according to claim 11 wherein said cell has a mitochondrial disorder.

17. The method according to claim 11 wherein the tetrose is selected from the group consisting of erythrose, threose and erythrulose.

18. The method according to claim 11 wherein said indirect exposing comprises exposing said cell to a prodrug metabolisable to release tetrose.

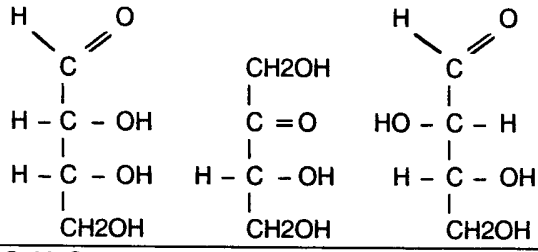
19. The method according to claim 11 comprising exposing said cells to a concentration of between about 1 mg/litre and about 200 mg/litre of said tetrose.

20. The method according to claim 16 wherein said mitochondrial disorder is associated with a disorder selected from the group consisting of neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, cardiovascular disease, stroke, obesity, diabetes, multiple sclerosis, systemic lupus erythematosis, rheumatoid arthritis, schizophrenia, bipolar disorder, depression, ataxia, autism, epilepsy, migraine, Batten disease, Lactic acidemia, Leber's disease, mitochondrial cardiomyopathy and myopathy, paraplegin, NASH, and Wilson's disease.

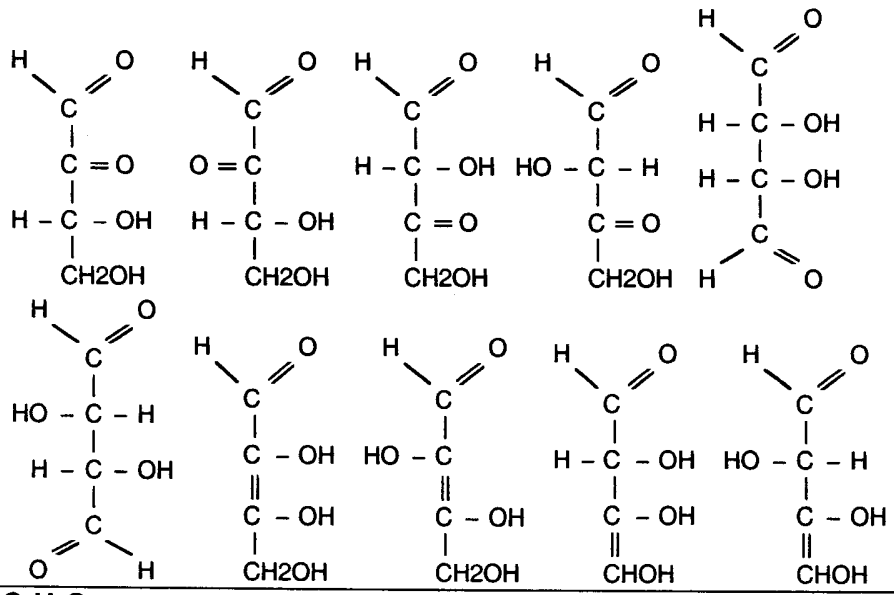
21. A method of treating a mitochondrial disorder in a subject having such disorder, said method comprising directly or indirectly administering to the subject a pharmaceutically effective dose of tetrose.

22. The method according to claim 21 wherein the tetrose has a structural formula selected from the group consisting of:

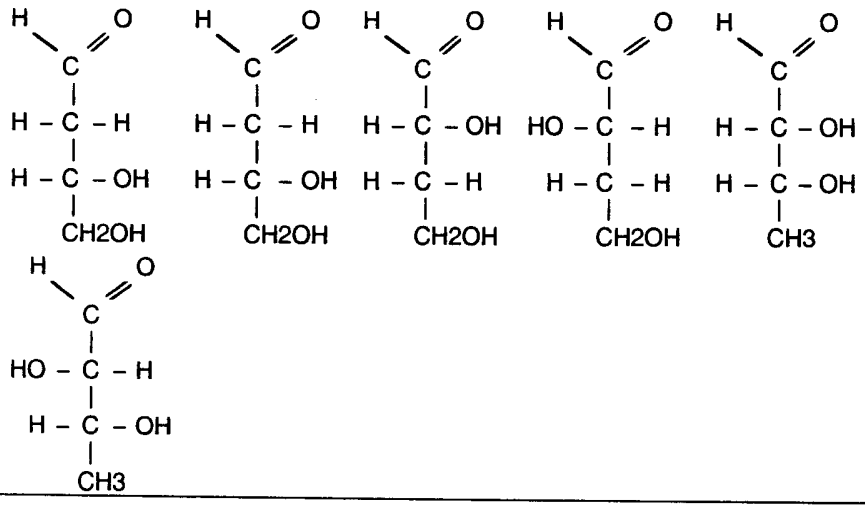
$C_4H_8O_4$



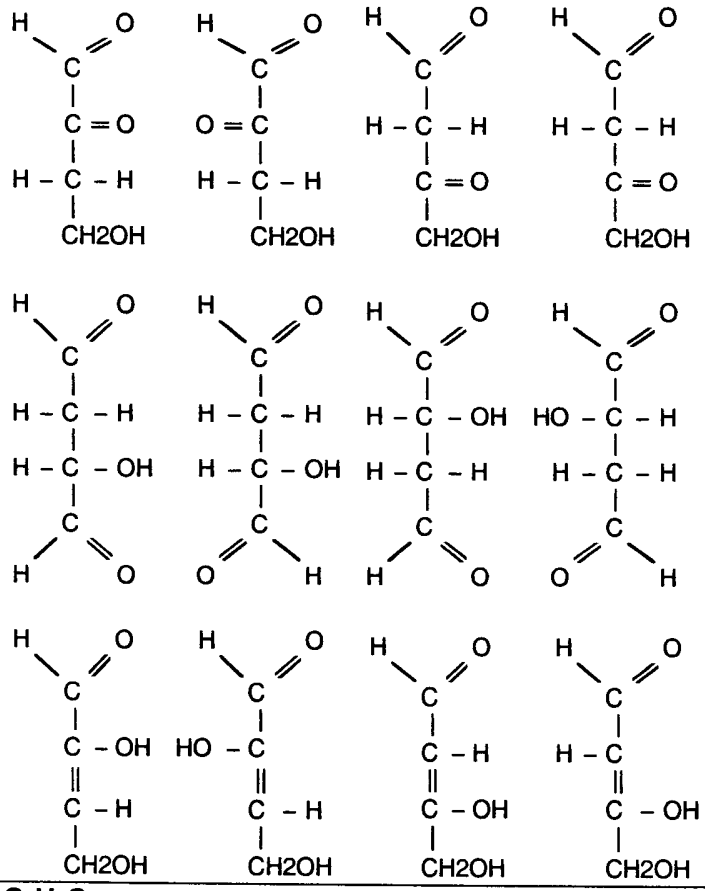
$C_4H_6O_4$



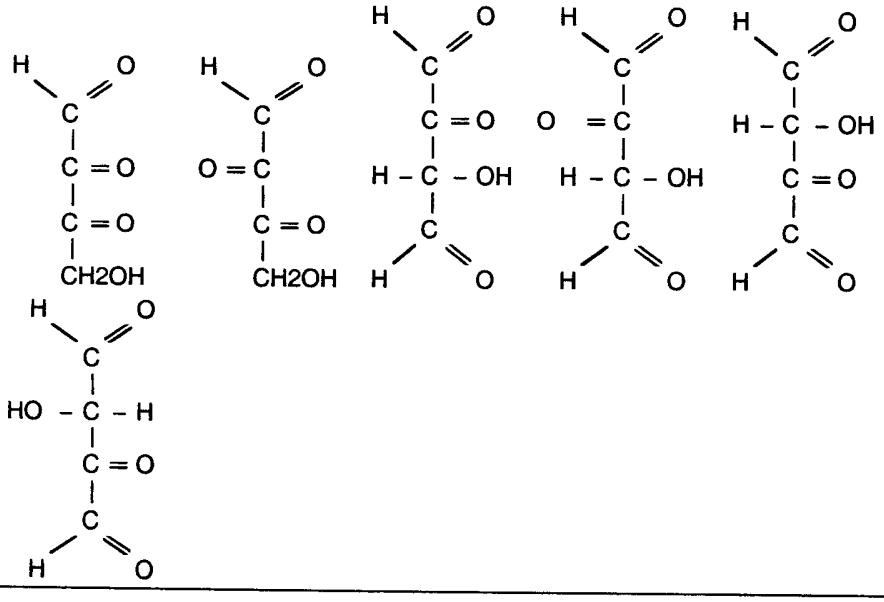
$C_4H_8O_3$

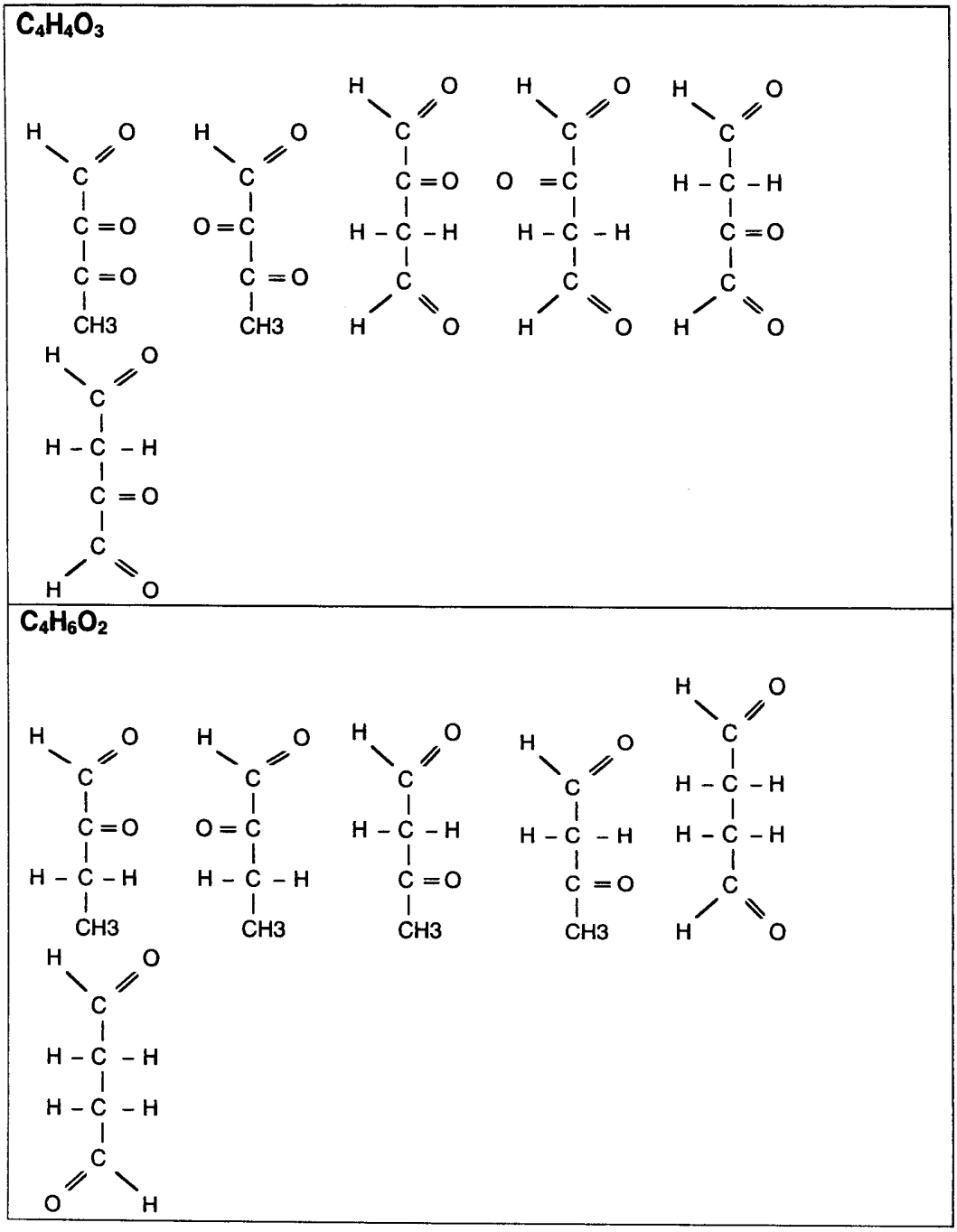


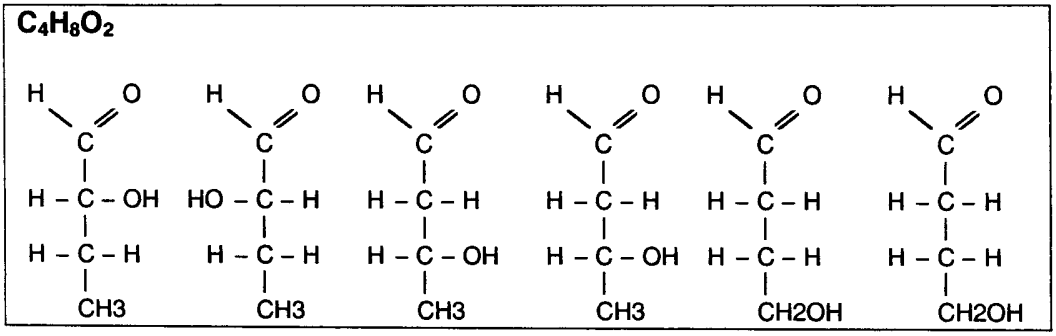
$C_4H_6O_3$



$C_4H_4O_4$




C4H4O3
C4H6O2



and any pharmaceutically effective derivatives thereof.

23. The method according to claim 22 wherein the derivative is a conjugated, substituted, ionised, salt, isomeric, acid, base, aldehyde, ketone, alcohol, amine, amide, thiol, ring or linear form.

24. The method according to claim 21 wherein the tetrose is selected from the group consisting of erythrose, threose and erythrulose.

25. The method according to claim 21 wherein said exposure occurs in combination with exposing said cell to a modulator of carbonic anhydrase activity.

26. A composition comprising:

a direct or indirect source of tetrose in an amount effective to inhibit the growth of a cancer cell; and

a pharmaceutically acceptable carrier or diluent.

27. A composition comprising:

a direct or indirect source of tetrose in an amount effective to increase the viability of a cell having a mitochondrial disorder; and

a pharmaceutically acceptable carrier or diluent

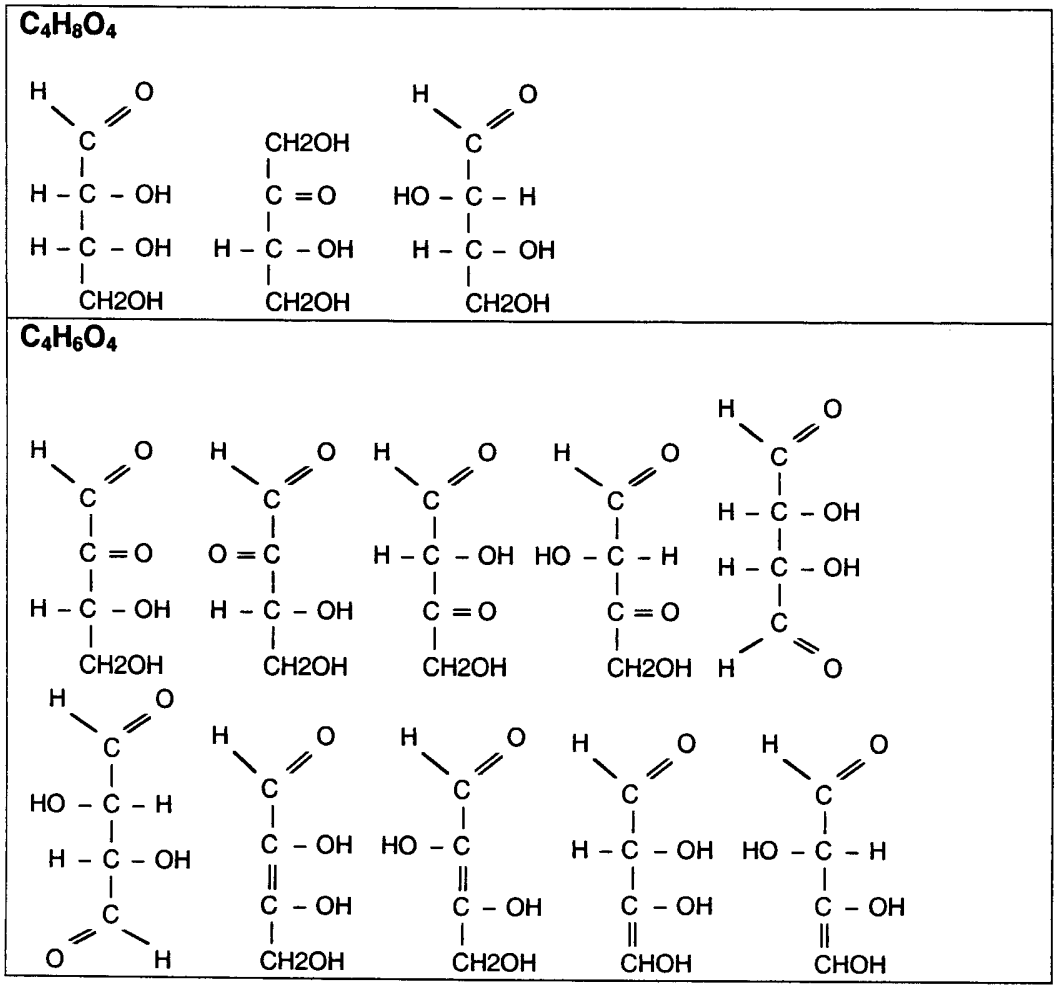
28. The use of an effective dose of a direct or indirect source of tetrose to achieve an effect selected from the group consisting of:

inhibiting the growth of a cancer cell;

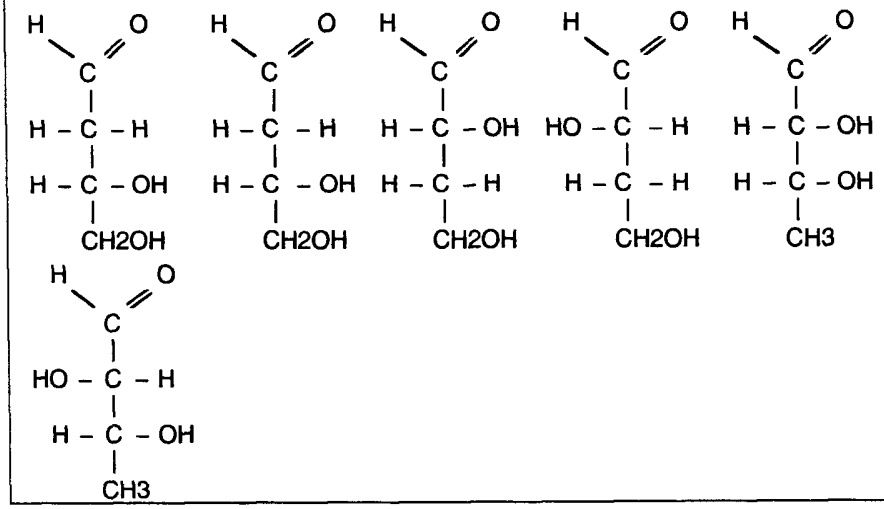
increasing the viability of a cell under low energy conditions; and

increasing the viability of a cell having a mitochondrial disorder.

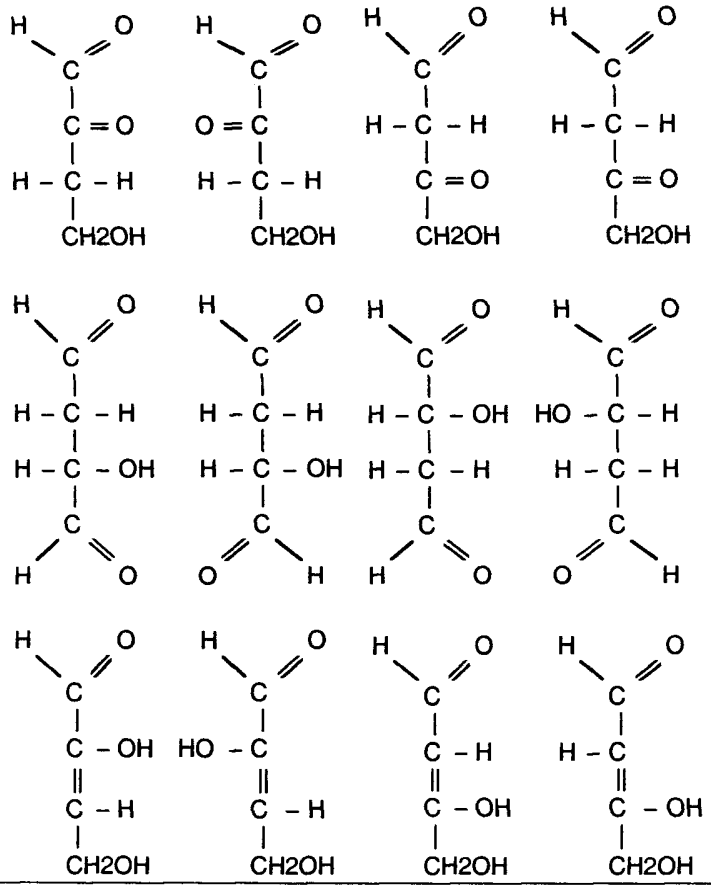
29. The use according to claim 28 wherein the tetrose has a structural formula selected from the group consisting of:

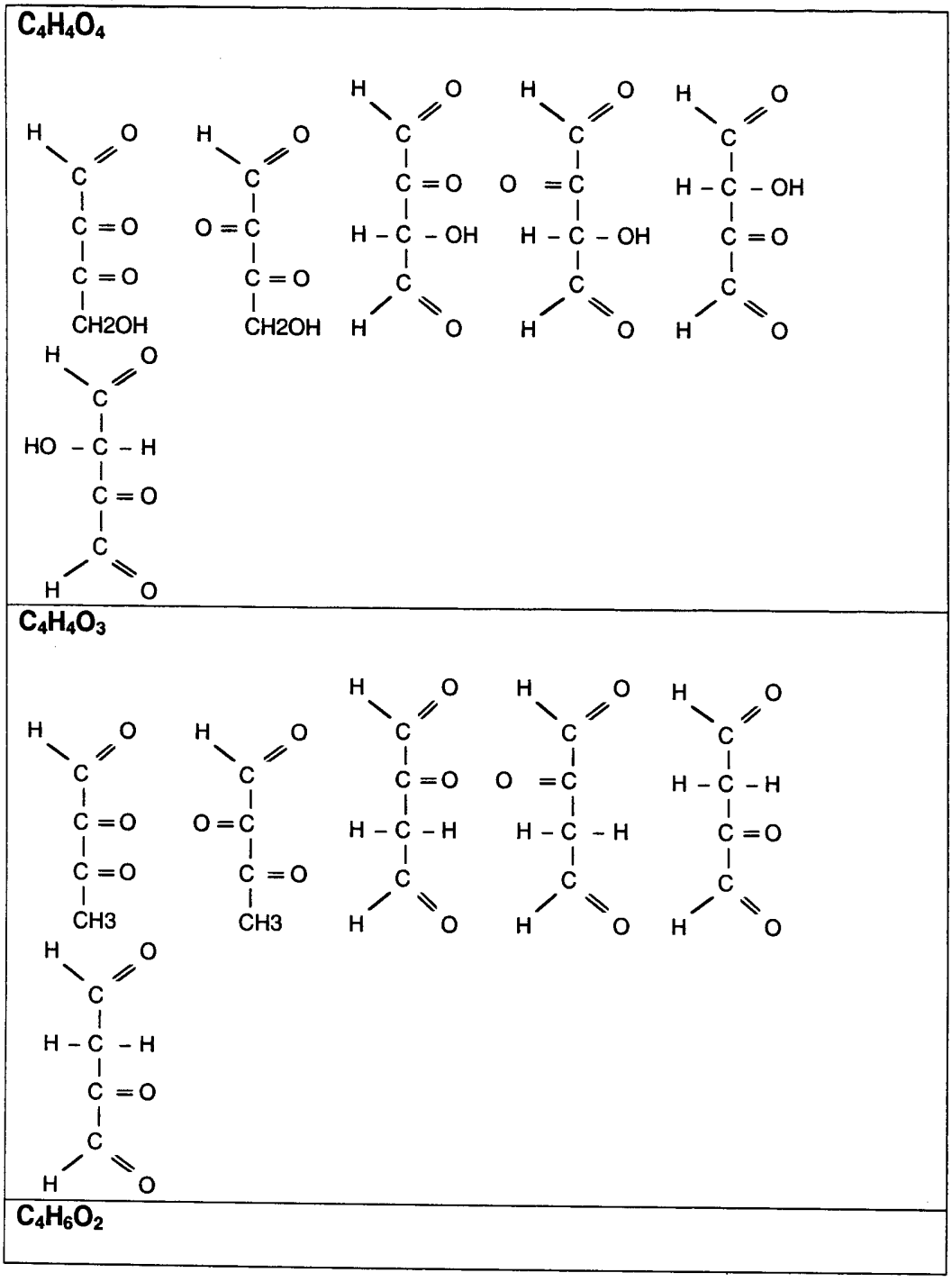


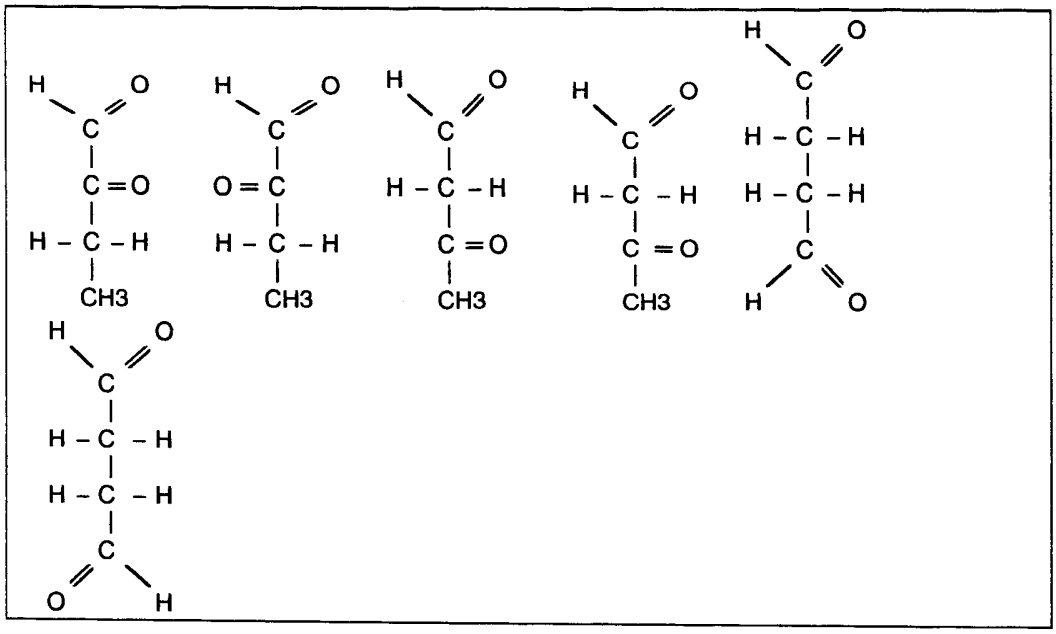
$C_4H_8O_3$

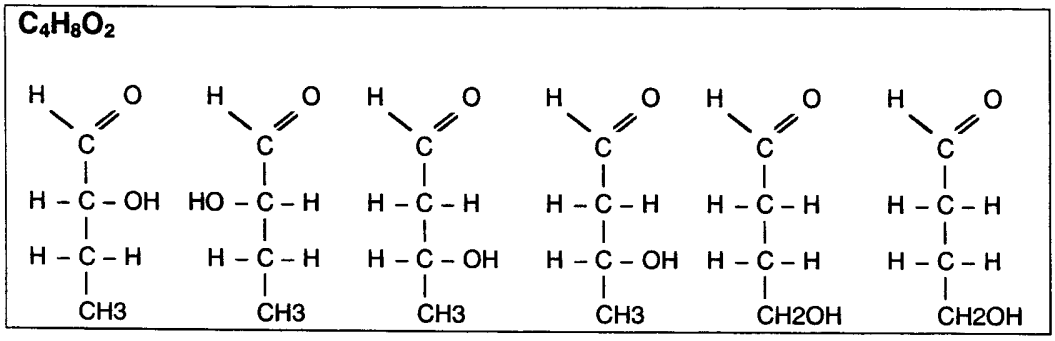


$C_4H_6O_3$




C4H4O4
C4H4O3
C4H6O2





and any pharmaceutically effective derivatives thereof.

30. The method according to claim 28 wherein the derivative is a conjugated, substituted, ionised, salt, isomeric, acid, base, aldehyde, ketone, alcohol, amine, amide, thiol, ring or linear form.

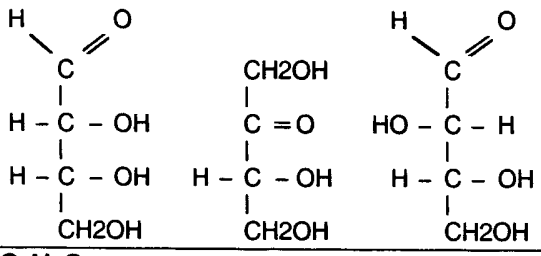
31. The method according to claim 28 wherein the tetrose is selected from the group consisting of erythrose, threose and erythrulose.

32. The use of tetrose or a prodrug of tetrose to manufacture a dietary supplement.

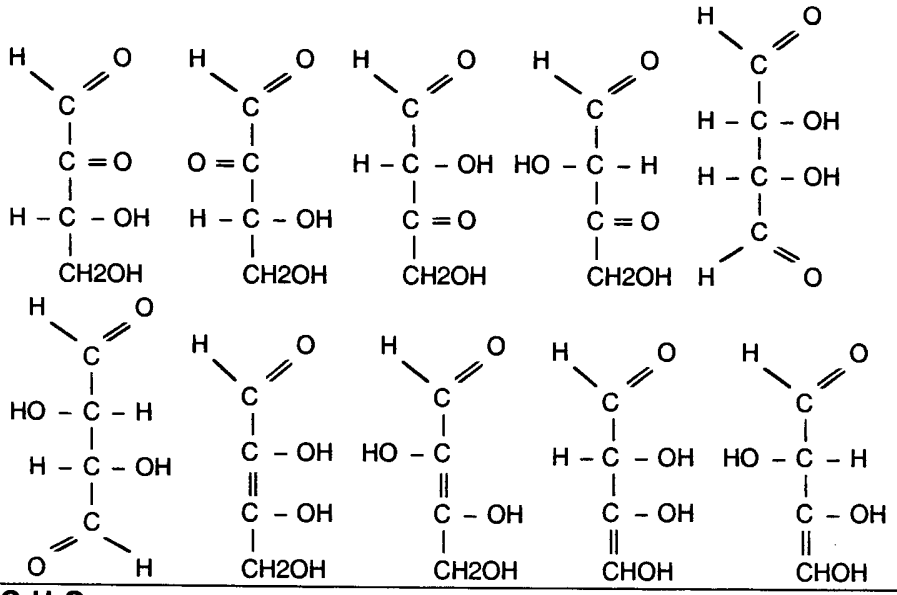
33. A composition comprising a prodrug metabolisable to yield a pharmaceutically effective amount of tetrose to:
inhibit the growth of a cancer cell;
increase the viability of a cell under low energy conditions; and
increase the viability of a cell having a mitochondrial disorder.

34. The composition according to claim 33 wherein the tetrose has a structural formula selected from the group consisting of:

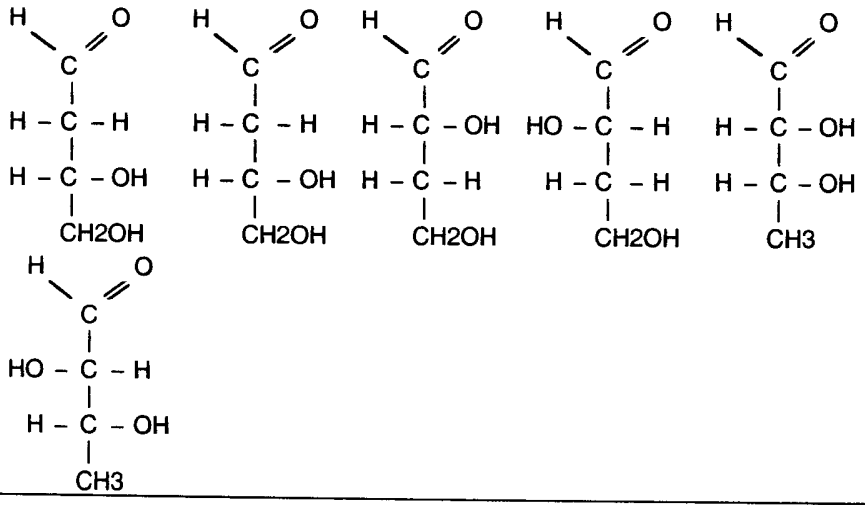
$C_4H_8O_4$



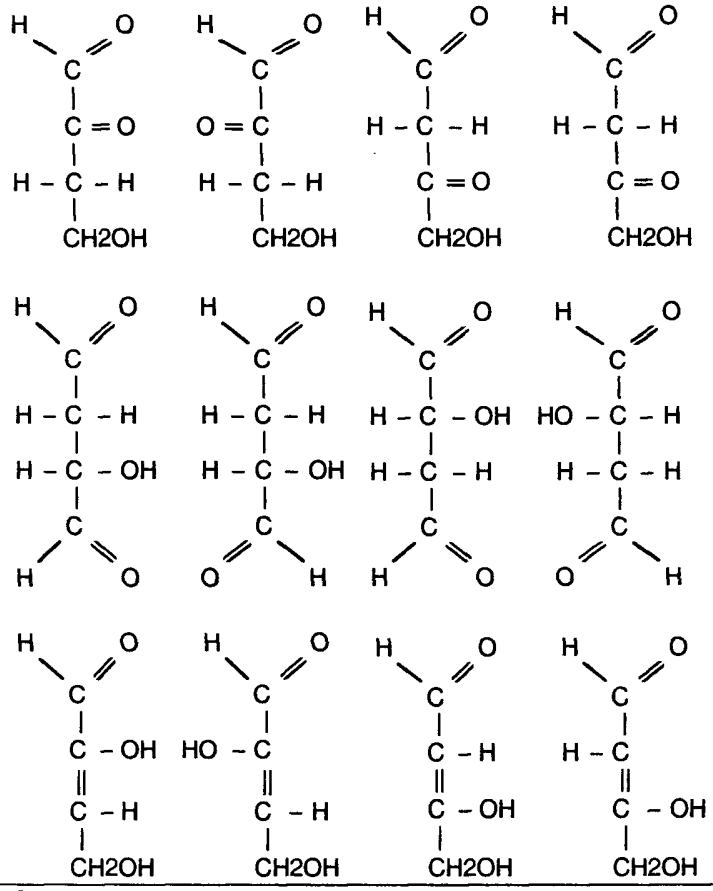
$C_4H_6O_4$



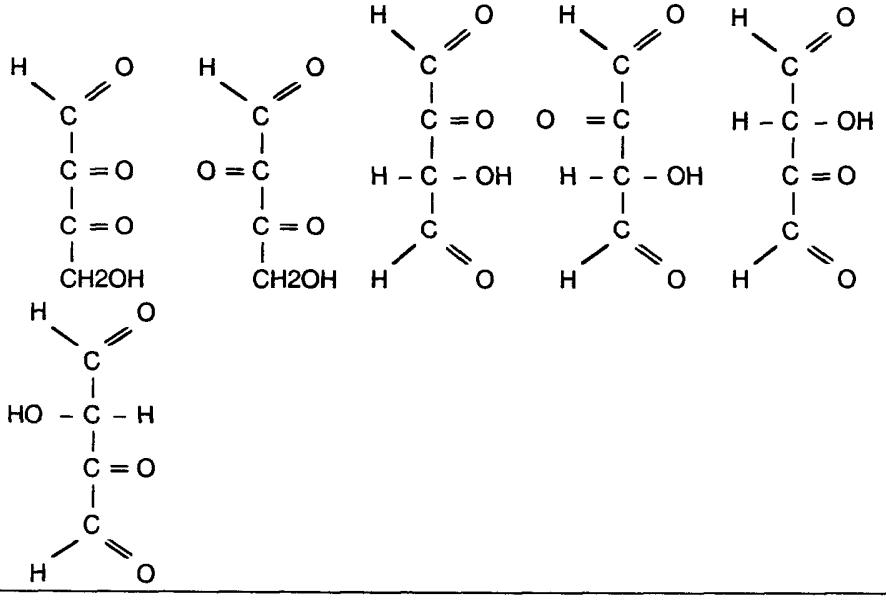
$C_4H_8O_3$

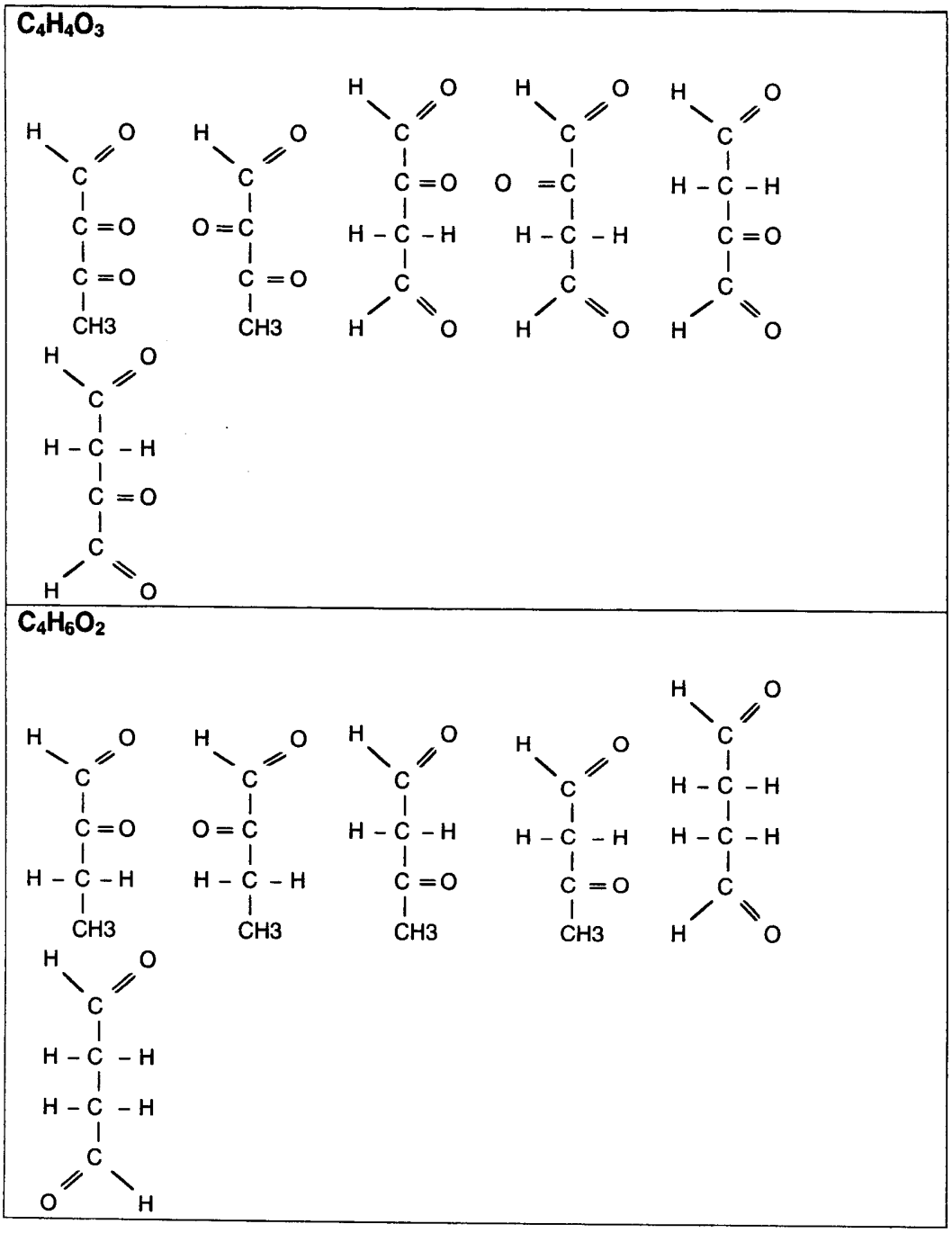


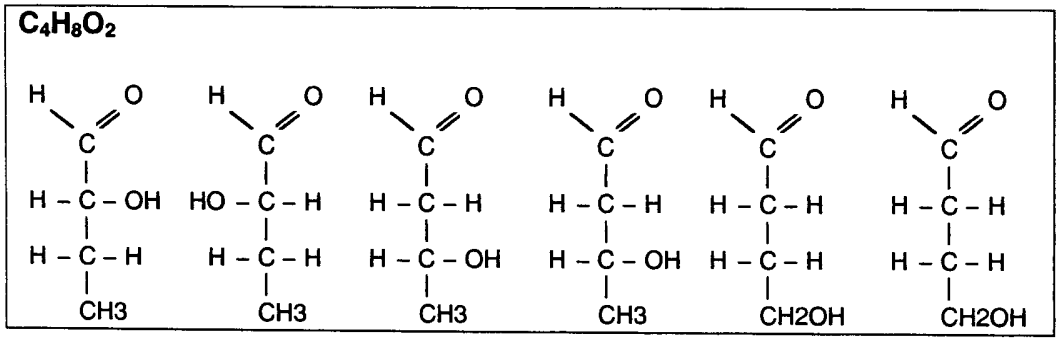
$C_4H_6O_3$



$C_4H_4O_4$




C4H4O3
C4H6O2



and any pharmaceutically effective derivatives thereof.

35. The composition according to claim 33 wherein the derivative is a conjugated, substituted, ionised, salt, isomeric, acid, base, aldehyde, ketone, alcohol, amine, amide, thiol, ring or linear form.

36. The use of tetrose to manufacture a medicament for:

a) inhibiting the growth of a cancer cell; or

b) improving the viability of a cell exhibiting a mitochondrial disorder.

37. The use according to any one of claims 32, 33 and 36 wherein the tetrose is selected from the group consisting of erythrose, threose and erythrulose.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2009/001440

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***A61K 31/7004*** (2006.01), ***A61K 45/00*** (2006.01), ***A61P 35/00*** (2006.01).
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 31/7004 (2006.01), ***A61K 45/00*** (2006.01), ***A61P 35/00*** (2006.01).

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
A61K 31/70 (2006.01).

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Canadian Patent Database; EPOQUE; Delphion, PubMed; Google: tetrose, erythrose/erythronate, threose/threonate, erythrulose | cancer, tumo?r, neoplas*, anti?neoplas*, carcinoma, sarcoma, adenoma, leukemia, lymphoma?, myeloma.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO01/15692 A1 08 March 2001 JARIWALLA *Methods and compositions for selecting cancer chemotherapy.* D1: see pages 13, 14 - 17, 21 - 23, and table 1.	26, 28 - 29, 33 - 37
X	TALUKDER *et al.*, October 2002, Clin. Cancer. Res., **8** (10): pp. 3285 - 3289. *Antihuman epidermal growth factor receptor 2 antibody herceptin inhibits autocrine motility factor (AMF) expression and potentiates antitumor effects of AMF inhibitors.* [ISSN:1078-0432] http://clincancerres.aacrjournals.org/content/8/10/3285.full.pdf+html D2: See abstract; page 3288.	26, 28 - 29, 33 - 37
X	FAY *et al.*, November 1994, Gen. Pharmac., **25** (7), pp. 1465-1469. *Effect of aldonic acids on the uptake of ascorbic acid by 3T3 mouse fibroblasts and human T lymphoma cells.* [doi:10.1016/0306-3623(94)90175-9] [ISSN: 0306-3623] D3: See page1468.	26, 28 - 29, 33 - 37

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 January 2010 (28-01-2010)	1 February 2010 (01-02-2010)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	C. Bourque (819) 934-3596

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2009/001440

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

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

1. [X] Claim Nos. : 1 - 10, 30 - 31

because they relate to subject matter not required to be searched by this Authority, namely :

Claims 1 - 25, and 30 - 31 are directed to methods for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. However, this Authority has carried out a search based on the alleged effects or purposes/uses of the compositions defined in claims 1 - 10.

2. [ ] Claim Nos. :

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

3. [ ] Claim Nos. :

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

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

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

The claims are directed to a plurality of alleged inventive.
See extra sheet for claim groups and explanation.

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

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

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

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. : 1 - 10, 26, 28 - 31 & 33 - 37

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/074344 A1 05-July-2007 KNOX *Use of alpha-hydroxy carbonyl compounds as reducing agents.* D4: See abstract, claims 42 - 47.	26, 28 - 29, 33 - 37

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO 0115692A1	08-03-2001	AT 401071T	15-08-2008
		AU 783283B2	13-10-2005
		AU 5785399A	26-03-2001
		CA 2348565A1	08-03-2001
		CN 1165301C	08-09-2004
		CN 1329489A	02-01-2002
		DE 69939123D1	28-08-2008
		DK 1124550T3	17-11-2008
		EP 1124550A1	22-08-2001
		EP 1124550A4	21-08-2002
		EP 1124550B1	16-07-2008
		EP 1124550B9	05-11-2008
		ES 2310941T3	16-01-2009
		JP 2003508437T	04-03-2003
		NO 326995B1	30-03-2009
		NO 20012027A	20-06-2001
		NO 20012027D0	25-04-2001
		NZ 511396A	29-08-2003
		PT 1124550E	29-08-2008
		TW 245643B	21-12-2005
		US 2004092549A1	13-05-2004
		WO 0115692A8	11-10-2001
WO 2007074344A1	05-07-2007	AU 2006329678A1	05-07-2007
		CA 2635388A1	05-07-2007
		CN 101389320A	18-03-2009
		EP 1951213A1	06-08-2008
		GB 0526552D0	08-02-2006
		JP 2009522244T	11-06-2009
		KR 20080091354A	10-10-2008
		MX 2008008616A	27-11-2008
		NO 20082852A	29-09-2008
		WO 2007074344A8	27-12-2007

Continuation of BOX III: Observations Where Unity of Invention is Lacking

The claims are directed to a plurality of alleged inventive concepts as follows:

Group A - Claims 1 - 10, 26, 28 - 31 (in part), and 33 - 37 (in part) are directed to the use of a tetrose (*i.e.* a 4 carbon sugar), derivatives thereof, or compositions thereof for the treatment of cancer or inhibiting cancer cell growth.

Group B - Claims 11 - 14 (in part), 15, 17 - 19 (in part), 28 - 31 (in part), 33 - 35 (in part), and 37 (in part) are directed to the use of a tetrose, derivatives thereof, or compositions thereof for enhancing/increasing cell viability under conditions of limited energy supply.

Group C - Claims 11 - 14 (in part), 16, 17 - 19 (in part), 20 - 25, 27, 28 - 31(in part), and 33 - 37 (in part) are directed to the use of a tetrose, derivatives thereof, or compositions thereof for enhancing cell viability wherein the cell has a mitochondrial disorder, or for treating mitochondrial disorders including neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, cardiovascular disease, stroke, obesity, diabetes, multiple sclerosis, systematic lupus erythematosis, rheumatoid arthritis, schizophrenia, bipolar disorder, depression, ataxia, autism, epilepsy, migraine, Batten disease, Lactic acidemia, Leber's disease, mitochondrial cardiomyopathy and myopathy, paraplegin, NASH, and Wilson's disease.

Group D - Claim 32 and 37 (in part) are directed to a dietary composition comprising a tetrose or prodrug thereof for no particular therapeutic use.

The claims must be limited to one inventive concept as set out in Rule 13 of the PCT.

The documents referred to on page 1 of present description indicate that tetroses are well known compounds. Thus tetroses cannot be considered as a technical feature which links all claims by a single general inventive concept. Furthermore, there is no single general inventive technical feature linking the treatment of cancer or inhibiting cancer cell growth (Group A) with the treatment of any of the above defined mitochondrial disorders (Group C). Nor is there a single general inventive technical feature linking the treatment of cancer or inhibiting cancer cell growth (Group A) with enhancing\increasing cell viability under conditions of limited energy supply (Group B).