

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 December 2009 (03.12.2009)

PCT

(10) International Publication Number
WO 2009/143630 A1

(51) International Patent Classification:

C07D 211/46 (2006.01) *C07D 223/08* (2006.01)
A23L 1/30 (2006.01) *C07H 15/12* (2006.01)
C07D 207/12 (2006.01)

(21) International Application Number:

PCT/CA2009/000757

(22) International Filing Date:

29 May 2009 (29.05.2009)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/057,539	30 May 2008 (30.05.2008)	US
61/057,521	30 May 2008 (30.05.2008)	US
61/057,509	30 May 2008 (30.05.2008)	US
61/057,489	30 May 2008 (30.05.2008)	US
61/057,469	30 May 2008 (30.05.2008)	US
61/059,938	9 June 2008 (09.06.2008)	US
12/229,979	28 August 2008 (28.08.2008)	US
12/229,955	28 August 2008 (28.08.2008)	US

(71) Applicant (for all designated States except US):
NORTHERN INNOVATIONS AND FORMULATIONS CORP. [CA/CA]; 381 North Service Road West, Oakville, Ontario L6M 0H4 (CA).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **HEUER, Marvin A.** [US/CA]; 381 North Service Road West, Oakville, Ontario L6M 0H4 (CA). **MOLINO, Michele** [CA/CA]; 381 North Service Road West, Oakville, Ontario L6M 0H4 (CA). **MACDOUGALL, Joseph** [CA/CA]; 381 North Service Road West, Oakville, Ontario L6M 0H4 (CA).

(74) Agent: **TORYS LLP**; 79 Wellington Street West, Suite 3000, Box 270, TD Centre, Toronto, Ontario M5K 1N2 (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, 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, 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, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report (Art. 21(3))

(54) Title: CREATINE SUGAR AMIDES AND SALTS THEREOF

(57) Abstract: Compounds produced by combining imino sugars and creatine and salts thereof are herein disclosed. The compounds being in the form of creatine imino sugar amides and the salts being combinations of various creatine imino sugar amides with an inorganic or organic acid. The resulting creatine imino sugar amides have enhanced stability in solution as compared to related esters and the resulting salts are particularly well suited for oral and parenteral use. In addition, specific benefits are conferred by the imino sugar in addition to, and separate from, the creatine substituent. Methods of preparation and use of these compounds are also disclosed.



WO 2009/143630 A1

CREATINE SUGAR AMIDES AND SALTS THEREOF

Related Applications

[0001] The present application is related to and claims benefit of priority to U.S. Provisional Application Number: 61/059,938 entitled "Salts of Creatine Imino Sugar Amides" filed June 9, 2008, the disclosure of which is hereby fully incorporated by reference; and 61/057,539, U.S. Provisional Application Number: 61/057,521, U.S. Provisional Application Number: 61/057,509, U.S. Provisional Application Number: 61/057,489, and U.S. Provisional Application Number: 61/057,469, all of which were filed May 30, 2008; and U.S. Application Number: 12/229,979, and U.S. Application Number 12/229,955 both of which were filed August 28, 2008, the disclosures of which are all hereby fully incorporated by reference.

Field of the Invention

[0002] The present invention relates to structures and methods for producing creatine imino sugar amides and salts thereof. Specifically, the present invention relates to compounds comprising an imino sugar bound to creatine, via an amide linkage, and formed salts thereof that are particularly well suited for oral and parenteral use.

Background of the Invention

[0003] Creatine is a naturally occurring amino acid that is derived from the amino acids; glycine, arginine and methionine. Although it is ingested from meats and fish, the human body also synthesizes its own creatine. About 65% of creatine is stored in the musculature of mammals in the form of phosphocreatine (creatine bound to a phosphate molecule), and utilized mostly as a source of energy for muscle. Oral supplementation of creatine has been shown to increase creatine concentration in muscle, and also enables an increase in the resynthesis of phosphocreatine, resulting in a rapid replenishment of ATP within the first two minutes of the start of exercise.

[0004] The beneficial effects of creatine supplementation with regard to skeletal muscle are apparently not restricted to the role of creatine in energy metabolism. Creatine supplementation in combination with strength training results in specific, measurable physiological changes in skeletal muscle compared to strength training alone. For example, creatine supplementation amplifies the strength training-induced increase of human skeletal satellite cells as well as the number of myonuclei in human skeletal muscle fibers. Satellite cells, stem cells of adult muscle, are normally in a quiescent state and become activated to

fulfill roles of routine maintenance, repair and hypertrophy. Postnatal muscle growth involves both myofiber hypertrophy and increased numbers of myonuclei – the source of which are satellite cells.

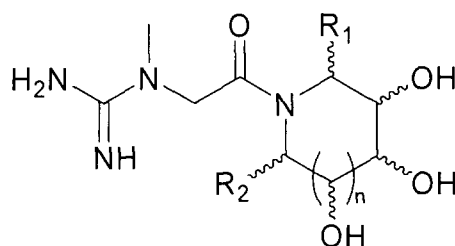
[0005] Imino sugars constitute a major class of naturally occurring molecules that have important and diverse biological functions. Imino sugars may be pentose, hexose or heptose sugars where at least one oxygen-containing group is replaced by a nitrogen-containing group. These imino sugars are useful in pharmacology, since they have been found to play major roles in the selective inhibition of various enzymatic functions.

[0006] Many have attempted to address issues such as stability, solubility, and bioavailability of creatine and imino sugars, independently, through the use of salts, esters, and amides. However, compounds of an imino sugar and a creatine bound via an amide bond are not known. It is commonly understood that hydrolysis of amides is more difficult to accomplish than the hydrolysis of esters. Therefore, an amide of creatine and an imino sugar would be more stable in solution than the related ester.

Summary of the Invention

[0007] In the present invention, compounds and methods of production are disclosed, wherein the compounds comprise an imino sugar bound to creatine, via an amide linkage, and having a structure corresponding to Formula 1:

Formula 1



where R₁ = H, OH, or CH₂OH;

R₂ = H, OH, CH₃ or CH₂OH; and

n = 0, 1 or 2.

[0008] An additional aspect of the present invention discloses a method for producing the compound corresponding to Formula 1.

[0009] In a further aspect of the present invention, the compound corresponding to Formula 1 may be combined with one or more pharmaceutically acceptable carriers to form a nutritional composition, which can be orally administered to a subject.

[0010] In an additional aspect of the present invention, creatine imino sugar amide salts, methods for their production, and solid compositions comprising said creatine imino sugar amide salts, are disclosed. Specifically, the creatine imino sugar amide salts comprise an acceptable inorganic or organic acid and a creatine imino sugar amide.

5 [0011] An additional aspect of the present invention discloses a method for producing creatine imino sugar amide salts.

[0012] In a further aspect of the present invention, the creatine imino sugar amide salts may be combined with one or more pharmaceutically acceptable carriers to form a nutritional composition, which can be administered to a subject.

10 Detailed Description of the Invention

[0013] In the following description, for the purposes of explanation, numerous specific details are set forth in order to provide a thorough understanding of the present invention. It will be apparent, however, to one skilled in the art that the present invention may be practiced without these specific details.

15 [0014] The present invention relates to compounds of creatine imino sugar amides, salts thereof, and their routes of syntheses. Specific benefits are conferred by the creatine portion of the compound in addition to, and separate from, the imino sugar substituent. Additionally, the present invention provides for combinations of creatine imino sugar amides and inorganic or organic acid, which are free of physiologically unsafe additives. Furthermore, the present
20 invention is particularly well suited for use in tablets, capsules, powders, granules, powdered beverage mixes and other forms known in the art of dietary supplements.

[0015] As used herein, 'creatine' refers to the chemical N-methyl-N-guanyl Glycine, (CAS Registry No. 57-00-1), also known as, (alpha-methyl guanido) acetic acid, N-(aminoiminomethyl)-N-glycine, Methylglycocyanine, Methylguanidoacetic Acid, or N-Methyl-N-guanylglycine. Additionally, as used herein, 'creatine' also includes derivatives of
25 creatine such as esters and salts, as well as other derivatives, including derivatives having pharmacoproperties upon metabolism to an active form.

[0016] As used herein, 'deoxynojirimycin' refers to the chemical (2*R*,3*R*,4*R*,5*S*)-2-(hydroxymethyl)-3,4,5-piperideinetriol, (CAS Registry No. 19130-96-2), also known as D-5-amino-1,5-dideoxyglucopyranose, 1,5-dideoxy-1,5-imino-D-glucitol, (2*R*,3*R*,4*R*,5*S*)-2-hydroxymethyl-3,4,5-trihydroxypiperidine, or moranoline. Additionally, as used herein,
30 'deoxynojirimycin' also includes derivatives of deoxynojirimycin such as esters and salts.

[0017] As used herein, 'deoxygalactonojirimycin' refers to the chemical 2-(hydroxymethyl)piperidine-3,4,5-triol, (CAS Registry No. 75172-81-5), also known as 1,5-dideoxy-1,5-imino-D-galactitol, or galactostatin. Additionally, as used here, 'deoxygalactonojirimycin' also includes derivatives of deoxygalactonojirimycin such as esters and salts.

[0018] As used herein, 'deoxymannojirimycin' refers to the chemical (2R,3R,4R,5R)-2-(hydroxymethyl)piperidine-3,4,5-triol, (CAS Registry No. 73465-43-7), also known as 1,5-dideoxy-1,5-imino-D-mannitol. Additionally, as used here, 'deoxymannojirimycin' also includes derivatives of deoxymannojirimycin such as esters and salts.

[0019] As used herein, 'homomannojirimycin' refers to the chemical (2R,3R,5R,6R)-2,6-bis(hydroxymethyl)piperidine-3,4,5-triol, (CAS Registry No. 127995-29-3). Additionally, as used here, 'homomannojirimycin' also includes derivatives of homomannojirimycin such as esters and salts.

[0020] As used herein, 'homonojirimycin' refers to the chemical (2R,3R,5S,6R)-2,6-bis(hydroxymethyl)piperidine-3,4,5-triol, (CAS Registry No. 119557-99-2). Additionally, as used here, 'homonojirimycin' also includes derivatives of homonojirimycin such as esters and salts.

[0021] As used herein, the term 'subject' refers to mammals and non-mammals. Mammals refers to any member of the mammalia class including, but not limited to, humans; non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, and swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice, and guinea pigs; and the like. Examples of non-mammals include, but are not limited to, birds, and the like.

[0022] As used herein, 'citric acid' refers to the chemical 2-hydroxy-1,2,3-propanetricarboxylic acid, (CAS Registry No. 77-92-9), also known as, β -hydroxytricarboxylic acid. Additionally, as used herein, 'citric acid' also includes derivatives of citrate such as esters, amides, and salts, as well as other derivatives, including derivatives having pharmacoproperties upon metabolism to an active form.

[0023] As used herein, 'maleic acid' refers to the chemical (Z)-butenedioic acid, (CAS registry No. 110-16-7), also known as toxilic acid, *cis*-1,2-ethylenedicarboxylic acid. Additionally, as used herein, 'maleic acid' also includes derivatives of maleic acid such as esters, amides, and salts, as well as other derivatives, including derivatives having pharmacoproperties upon metabolism to an active form.

[0024] As used herein, 'malic acid' refers to the chemical 1-Hydroxy-1,2-ethanedicarboxylic acid, (CAS Registry No. 6915-15-17), also known as, hydroxybutanedioic acid, hydroxysuccinic acid, malate, or 2-hydroxybutanedioate. Additionally, as used herein, 'malic acid' also includes derivatives of malate such as esters, amides, and salts, as well as other derivatives, including derivatives having pharmacoproperties upon metabolism to an active form.

[0025] As used herein, 'fumaric acid' refers to the chemical (*E*)-2-butenedioic acid, (CAS Registry No. 110-17-8), also known as, *trans*-1,2-ethylenedicarboxylic acid, allomaleic acid, and boletic acid. Additionally, as used herein, 'fumaric acid' also includes derivatives of fumarate such as esters, amides, and salts, as well as other derivatives, including derivatives having pharmacoproperties upon metabolism to an active form.

[0026] As used herein, the term 'organic acid' refers to organic compounds which contain carboxylic acids (-C(O)OH). Typical examples of organic acids include, but are not limited to; malic acid, fumaric acid, citric acid, orotic acid, lactic acid, pyruvic acid, and tartaric acid.

[0027] As used here, the term 'acceptable oral dosage form' would be known by one of skill in the art to include, for example, powder beverage mixes, liquid beverages, ready-to-eat bars, capsules, liquid capsules, tablets, capleta, dietary gels, soft-gel™ caplets, and gel-caps.

[0028] As used here, the term 'parenteral' refers to methods of administration of nutrients to that region outside of the digestive tract. Examples of parenteral routes of administration include, but are not limited to, subcutaneous, intramuscular or intravenous injection, and nasopharyngeal, mucosal or transdermal absorption.

[0029] As used herein, the term 'pharmaceutically-acceptable salt' refers to acid-addition salts of creatine imino sugar amides with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric, maleic, malic, or fumaric acid.

[0030] The term 'pharmaceutically acceptable carrier' is art-recognized and refers to a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting any subject composition or component thereof. Each carrier must be 'acceptable' in the sense of being compatible with the subject composition and its components and not injurious to the individual to which it is administered. Some examples of materials which may serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter; (9) oils, such as

peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; and (15) other
5 non-toxic compatible substances employed in pharmaceutical formulations, and combinations thereof.

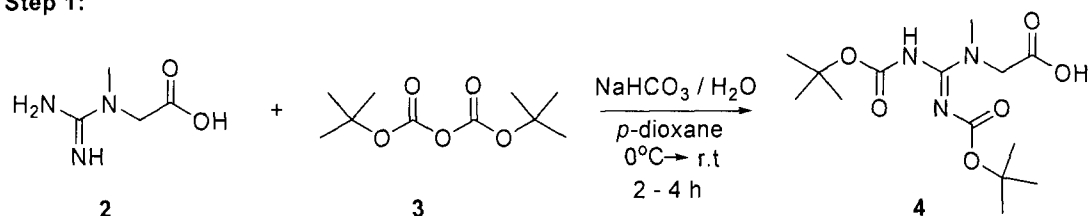
[0031] As used herein, the term 'nutritional composition' includes dietary supplements, diet supplements, nutritional supplements, supplemental compositions and supplemental dietary compositions or those similarly envisioned and termed compositions not belonging to the
10 conventional definition of pharmaceutical interventions as is known in the art. Furthermore, 'nutritional compositions' as disclosed herein belong to category of compositions having at least one physiological function when administered to a subject by conventional routes of administration.

[0032] Alternatively, formulations and nutritional compositions belonging to the present
15 invention may be considered to be nutraceuticals. As used herein, the term 'nutraceutical' is recognized and used in the art to describe a specific chemical compound or combination of compounds found in, organic matter for example, which may prevent, ameliorate or otherwise confer benefits against an undesirable condition. As is known in the art, the term 'nutraceutical' is used to refer any substance that is a food, a part of food, or an extract of
20 food which is suitable for consumption by an individual and providing physiological benefit which may be medical or health-related. Furthermore, the term has been used to refer to a product isolated, extracted or purified from foods or naturally-derived material suitable for consumption by an individual and usually sold in medicinal forms, such as caplets, tablets, capsules, soft-gelTM caplets, gel-caps and the like, not associated with food.

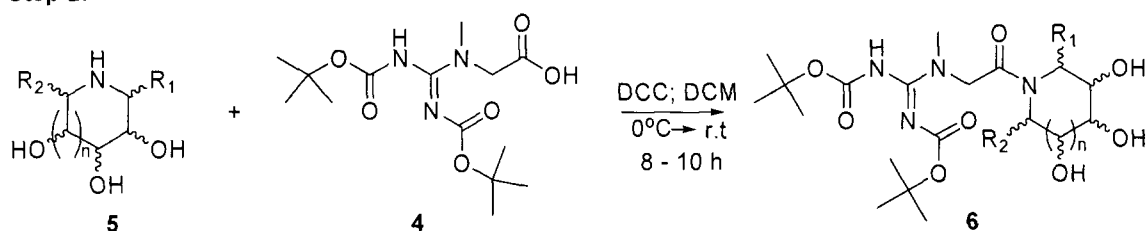
[0033] According to the present invention, the compounds disclosed herein comprise imino
25 sugars bound to creatine. Furthermore, the imino sugars and creatine are bound by an amide linkage and have a structure according to Formula 1. The aforementioned compounds can be prepared, for example, according to the reaction as set forth for the purposes of the description in Scheme 1 below:

Scheme 1

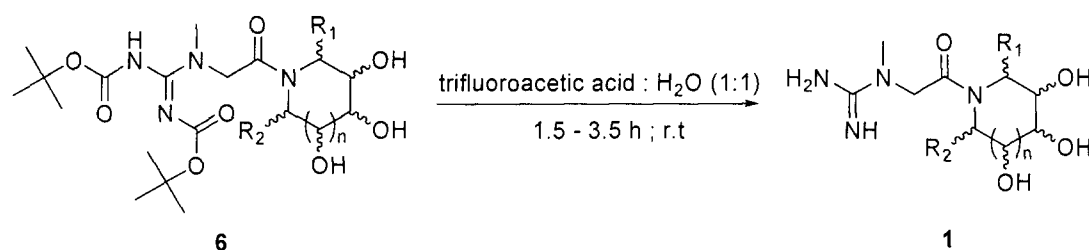
Step 1:



Step 2:



Step 3:



$R_1 = \text{H, OH or CH}_2\text{OH};$
 $R_2 = \text{H, OH, CH}_3 \text{ or CH}_2\text{OH};$
 and $n = 0, 1 \text{ or } 2$

[0034] As an example in Scheme 1, Step 1, creatine (2) is dissolved in water and an excess of sodium bicarbonate (NaHCO_3) is added with stirring and then cooled in an ice-water bath.

- 5 The resultant solution is cooled in an ice-water bath and di-*tert*-butyl carbonate (3), also known as boc anhydride, is added as a solution in *p*-dioxane (also cooled). The mixture is then stirred at about 0°C for about one hour and allowed to warm to room temperature ($\sim 23^\circ\text{C}$) for between 2-4 hours. Water is added to the mixture and the aqueous layer is extracted twice with ethyl acetate. The resultant organic layer is then back extracted twice
- 10 with a saturated sodium bicarbonate solution. The combined aqueous layers are acidified to a pH of 1 with 10% HCl and then extracted three times with ethyl acetate. The organic layers are combined, dried over sodium sulfate, filtered and concentrated *in vacuo*. The resultant protected creatine (4) would be of sufficient purity to be used in subsequent steps. It should be noted at this step that any amino protecting group, as would be known to one of skill in the
- 15 art, could be used in place of boc anhydride. Examples of amino protecting groups include, but are not limited to: 9-fluorenylmethyl carbamate, di-*tert*-butyl carbonate, benzyl

carbamate, acetamide, trifluoroacetamide, phthalimide, benzylamine, benzylideneamine, *p*-toluenesulfonamide, most preferably, di-*tert*-butyl carbonate.

[0035] Step 2 describes the combining of an imino sugar (5) and the protected creatine (4).

The two substrates, 5 and 4, are stirred in DCM and submersed in an ice-water bath to bring to the temperature of the reaction to about 0°C. After cooling, a solution of dicyclohexylcarbodiimine (DCC) and DCM is added to the mixture of 5 and 4 with vigorous stirring; the DCC acts to activate the carboxylic acid of the protected creatine *in situ*.

Following the addition of the DCC the reaction is allowed to warm to room temperature (~23°C) with constant agitation. Stirring is maintained overnight (between about 8 and about 10 hours). The mixture is then filtered through Celite® in order to remove any by-products and unreacted materials. The filtrate is then concentrated under reduced pressure and purified by flash chromatography through a silica gel packed column to yield the bis-boc-protected creatine imino sugar amide (6).

[0036] In the preferred embodiment of the present invention, deoxynojirimycin is the imino sugar used. However any imino sugar, as is known by one of skill in the art, may be utilized to synthesize a creatine imino sugar amide according to the method disclosed herein.

[0037] Step 3 describes the removal of the two boc protecting groups from the guanidine group of 6, via acidification. The bis-boc-protected creatine imino sugar amide (6) is dissolved in a trifluoroacetic acid:H₂O (1:1) mixture. The reaction is stirred at room temperature for between about 1.5 and about 3.5 hours. After the reaction is complete the mixture is concentrated under reduced pressure and then purified by flash chromatography through a silica gel packed column to yield the target amide, creatine imino sugar amide (1).

[0038] According to an additional embodiment, the creatine imino sugar amide of the present invention may be formulated into nutritional compositions that may be consumed in any form. For instance, the dosage form of the nutritional compositions may be provided as, e.g. a powder beverage mix, a liquid beverage, a ready-to-eat bar or drink product, a capsule, a liquid capsule, a tablet, a caplet, or as a dietary gel. The preferred dosage forms of the present invention are provided as a powder beverage mix.

[0039] Furthermore, the dosage form of the nutritional composition may be provided in accordance with customary processing techniques for herbal and nutritional compositions in any of the forms mentioned above. Additionally, the nutritional composition, comprising the creatine imino sugar amide may contain any appropriate number and type of pharmaceutically acceptable carriers, as is well known in the art.

[0040] Compounds of an imino sugar and a creatine bound via an amide bond offer increased resistance to the cyclization of creatine while in solution. It is commonly understood that hydrolysis of amides is more difficult to accomplish than the hydrolysis of esters. While amides of creatine and an imino sugar would be more stable in solution than related esters, the salts of these amides of creatine and an imino sugar would offer the further advantage of enhanced nutritional and/or therapeutical efficacy due to increased solubility.

[0041] According an aspect of the present invention, creatine imino sugar amides combined with an inorganic or organic acid to form a creatine imino sugar amide salts are disclosed. The creatine imino sugar amide salts can be prepared according to the details set forth in the description below.

[0042] In one step of the process, a creatine imino sugar amide is dissolved in an excess of hot lower alcohol. The lower alcohol is considered to be hot, as would be known by one of ordinary skill in the art. Preferably the lower alcohol is considered to be hot when heated to a temperature about 5°C below the boiling point of the corresponding lower alcohol.

[0043] In various embodiments of the present invention, the creatine imino sugar amide may be selected, for example, from the group including of 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl) guanidine, also known as creatine deoxyojirimycin amide; 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine, also known as creatine deoxygalactonojirimycin amide; 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine, also known as creatine deoxymannojoirimycin amide; 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine, also known as creatine homomannojoirimycin amide; and 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl) piperidin-1-yl)ethyl)guanidine, also known as creatine homonojoirimycin amide. However, it should be noted that a creatine imino sugar amine may be made with any imino sugar as would be known by one of skill in the art, and would be acceptable for use in the present invention.

[0044] Additionally, in various embodiments of the present invention, the lower alcohol preferably is selected from the group consisting of methanol, ethanol, propanol, and isopropanol. These lower alcohols may be used singly or in admixture containing two or more alcohols.

[0045] In another step of the process, the inorganic or organic acid is dissolved in an excess of hot lower alcohol. The lower alcohol is considered to be hot, as would be known by one

of ordinary skill in the art. Preferably the lower alcohol is considered to be hot when heated to a temperature about 5°C below the boiling point of the corresponding lower alcohol.

[0046] In various embodiments of the present invention, the inorganic or organic acid preferably is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, trifluoroacetic acid, citric acid, maleic acid, malic acid and fumaric acid.

[0047] The order in which the creatine imino sugar amide and the inorganic or organic acid are dissolved is not critical. Both solutions prepared above are then mixed together and heated to about the boiling point of the corresponding lower alcohol. If there are solids still present after heating, the combined solution is filtered while hot to remove any unreacted starting materials. The combined solution is then allowed to cool to room temperature, covered and refrigerated or cooled until crystallization occurs, preferably for between about 24 to about 48 hours. The resultant solid is filtered under vacuum and washed with ice cold lower alcohol, yielding the creatine imino sugar amide salt.

[0048] In larger scale preparations of the present invention, diethyl ether can be added until the cloud point, as would be known to one of skill in the art, is reached after the mixture is cooled to room temperature, after which the solution is refrigerated or cooled to allow crystallization to complete. This will facilitate greater precipitation of the product thus yielding more of the creatine imino sugar amide salt, which would be desired in industrial settings.

[0049] Creatine imino sugar amide salts are used advantageously alone or with additional active ingredients, such as, trace elements, vitamins, mineral substances, or other amino acids as well as, optionally, excipients usually used for the preparation of the respective forms of administration. The forms of administration include, particularly, all varieties of tablets, both those that are swallowed without being chewed, and tablets to be chewed or dissolved in the mouth of an individual, as well as those that are dissolved in a liquid before being ingested by an individual. The tablet forms include uncoated tablets, one-layer or multilayer or encased forms or effervescent tablets. Further preferred forms of administration are capsules of hard and soft gelatin, the latter being particularly suitable to include a liquid core. Additionally, creatine imino sugar amide salts can be used advantageously for the preparation of solutions and suspensions and as a powder, either effervescent or granulated.

[0050] Creatine imino sugar amide salts of the present invention may, for example include:

1. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hydrochloride;

2. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hydrobromide;
3. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine sulfate;
- 5 4. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemisulfate;
5. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine 2,2,2-trifluoroacetate;
6. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxy-methyl)piperidin-10 1-yl)ethyl)guanidine-2-hydroxypropane-1,2,3-tricarboxylate;
7. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxy-methyl)piperidin-1-yl)ethyl)guanidine-hemi(2-hydroxypropane-1,2,3-tricarboxylate);
8. tris(1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxy-methyl)piperidin-1-yl)ethyl)guanidine)-2-hydroxypropane-1,2,3-tricarboxylate;
- 15 9. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine maleate;
10. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemimalate;
11. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-20 1-yl)ethyl)guanidine malate;
12. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemimalate;
13. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine fumarate;
- 25 14. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemifumarate;
15. 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hydrochloride;
16. 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxy-methyl)piperidin-1-yl)ethyl)guanidine hydrobromide;
- 30 17. 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxy-methyl)piperidin-1-yl)ethyl)guanidine sulfate;
18. 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemisulfate;

19. 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine 2,2,2-trifluoroacetate;
20. 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxy-methyl)piperidin-1-yl)ethyl)guanidine-2-hydroxypropane-1,2,3-tricarboxylate;
- 5 21. 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxy-methyl)piperidin-1-yl)ethyl)guanidine-hemi(2-hydroxypropane-1,2,3-tricarboxylate);
22. tris(1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxy-methyl)piperidin-1-yl)ethyl)guanidine)-2-hydroxypropane-1,2,3-tricarboxylate;
23. 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine maleate;
- 10 24. 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemimaleate;
25. 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine malate;
- 15 26. 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemimalate;
27. 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine fumarate;
28. 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemifumarate;
- 20 29. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hydrochloride;
30. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hydrobromide;
- 25 31. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine sulfate;
32. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemisulfate;
33. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine 2,2,2-trifluoroacetate;
- 30 34. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxy-methyl)piperidin-1-yl)ethyl)guanidine-2-hydroxypropane-1,2,3-tricarboxylate;
35. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxy-methyl)piperidin-1-yl)ethyl)guanidine-hemi(2-hydroxypropane-1,2,3-tricarboxylate);

36. tris(1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine)-2-hydroxypropane-1,2,3-tricarboxylate;
37. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine maleate;
- 5 38. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemimaleate;
39. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine malate;
40. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemimalate;
- 10 41. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine fumarate;
42. 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemifumarate;
- 15 43. 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hydrochloride;
44. 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hydrobromide;
45. 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine sulfate;
- 20 46. 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemisulfate;
47. 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine 2,2,2-trifluoroacetate;
- 25 48. 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine-2-hydroxypropane-1,2,3-tricarboxylate;
49. 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine-hemi(2-hydroxypropane-1,2,3-tricarboxylate);
- 30 50. tris(1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine)-2-hydroxypropane-1,2,3-tricarboxylate;

51. 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine maleate;
52. 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemimaleate;
- 5 53. 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine malate;
54. 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemimalate;
55. 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine fumarate;
- 10 56. 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemifumarate;
57. 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hydrochloride;
- 15 58. 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hydrobromide;
59. 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine sulfate;
60. 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemisulfate;
- 20 61. 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine 2,2,2-trifluoroacetate;
62. 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine 2-hydroxypropane-1,2,3-tricarboxylate;
- 25 63. 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemi(2-hydroxypropane-1,2,3-tricarboxylate);
64. tris(1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine) 2-hydroxypropane-1,2,3-tricarboxylate;
- 30 65. 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine maleate;

66. 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemimalate;
67. 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine malate;
- 5 68. 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemimalate;
69. 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine fumarate; and
70. 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine hemifumarate.
- 10

[0051] The non-limiting examples given above provide examples of creatine imino sugar amides salts which are within the present invention. One of skill in the art may readily envision various other salts within the scope of the present invention, considering the examples with reference to the specification herein provided.

15 **[0052]** The following non-limiting example illustrates feasible synthesis of various creatine imino sugar amides and salts thereof. One of skill in the art may readily envision various other combinations within the scope of the present invention, considering the example with reference to the specification herein provided.

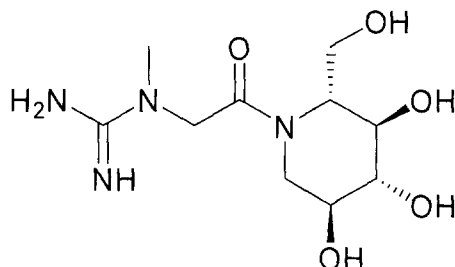
20 **[0053]** Also provided below is a method for producing creatine imino sugar amide salts of the present invention. Provided with the present specification, those of skill in the art will readily appreciate that certain modifications and variations may be made in the process of "scaling-up" the reaction to manufacture larger batches of creatine imino sugar amide salts which may be required or useful for commercial uses and supply requirements. Other methods of synthesis may also be apparent to those of skill in the art.

25 **[0054]** Furthermore, it would be known by one of skill in the art that varying the stoichiometric ratios of the various creatine imino sugar amides to the inorganic or organic acids will result in various salts. For example using equimolar ratios of creatine deoxynojirimycin amide and malic acid will lead to creatine deoxynojirimycin amide malate, whereas using 2 molar equivalents of creatine deoxynojirimycin amide for every 1 molar
30 equivalent of malic acid will lead to creatine deoxynojirimycin amide hemimalate.

Examples

Example 1

1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine



5

[0055] In a round bottomed flask, equipped with a magnetic stirrer, 7.87 g (0.060mol) of creatine is dissolved in 200 mL of water and 10.08 g (0.120mol) of sodium bicarbonate is added with stirring. The solution is then cooled to about about 0°C in an ice-water bath. To the cooled solution is added a cooled solution of 31.10 ml (0.150mol) of di-tert-butyl dicarbonate dissolved in 150 mL of *p*-dioxane. The mixture is then stirred at about 0°C in an ice-water bath for an hour, after which the ice bath is removed and the solution is allowed to warm to room temperature (~23°C). After stirring at room temperature for an additional 2 hours, the mixture is diluted with 150 mL of water and transferred to a 1-L separatory funnel, where the aqueous layer is extracted sequentially with one 300 mL and one 150 mL portions of ethyl acetate. The resultant organic layer is then back extracted sequentially one 150 mL and one 75 mL portions of saturated sodium bicarbonate solution. The combined aqueous portions are then slowly acidified to a pH of 1, in a 1-L separatory funnel, with 10% HCl, and then extracted with three 100 mL ethyl acetate portions. The organic layers are then combined, dried over sodium sulphate, filtered and then concentrated under reduced pressure.

20 The resultant 2-(2,3-bis(tert-butoxycarbonyl)-1-methylguanidino)acetic acid would be sufficiently pure to use in subsequent steps.

[0056] A dry, 2-necked round bottomed flask, equipped with a magnetic stirrer and a dropping funnel containing a solution of 10.83 g (0.0525mol) of *N,N'*-dicyclohexylcarbodiimide (DCC) dissolved in 125 mL of DCM, is charged with 16.57g (0.050mol) of 2-(2,3-bis(tert-butoxycarbonyl)-1-methylguanidino)acetic acid, 8.97 g (0.055mol) of deoxynojirimycin, and 100mL of DCM (all of which is under an argon atmosphere). The resultant mixture is stirred in an ice-water bath to cool the solution to a temperature of about 0°C. Following cooling, the solution of DCC from the dropping funnel

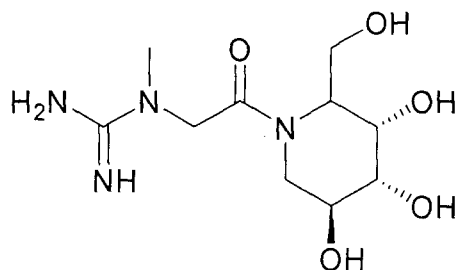
25

is added and the reaction is allowed to warm to room temperature and then to stir overnight. The mixture is then filtered through a Celite[®] plug and the filtrate is purified by flash chromatography (ethyl acetate/hexanes; 1/3) to yield the bis-boc protected creatine deoxynojirimycin amide, tert-butyl (tert-butoxycarbonylamino)(methyl(2-oxo-2-
 5 ((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)amino)methylene-carbamate.

[0057] In a dry, round bottomed flask, equipped with a magnetic stirrer, 19.06 g (0.040mol) of tert-butyl (tert-butoxycarbonylamino)(methyl(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)amino) methylenecarbamate is dissolved in 250 mL of a
 10 trifluoroacetic acid:H₂O (1:1) mixture. The resultant mixture is stirred for 1.5 hours at room temperature, after which it is concentrated under reduced pressure and then purified by flash chromatography (ethyl acetate/hexanes; 1/5) to yield the creatine deoxynojirimycin amide, 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine.

15 Example 2

1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine



[0058] In a round bottomed flask, equipped with a magnetic stirrer, 6.50 g (0.050mol) of
 20 creatine is dissolved in 175 mL of water and 8.40 g (0.10mol) of sodium bicarbonate is added with stirring. The solution is then cooled to about 0°C in an ice-water bath. To the cooled solution is added a cooled solution of 28.72 ml (0.10mol) of di-tert-butyl dicarbonate dissolved in 125 mL of *p*-dioxane. The mixture is then stirred at 0°C in an ice-water bath for
 25 an hour, after which the ice-water bath is removed and the solution is allowed to warm to room temperature (~23°C). After stirring at room temperature for an additional 2 hours, the mixture is diluted with 150 mL of water and transferred to a 1-L separatory funnel, where the aqueous layer is extracted sequentially with one 300 mL and one 150 mL portions of ethyl acetate. The resultant organic layer is then back extracted sequentially one 150 mL and one 75 mL portions of saturated sodium bicarbonate solution. The combined aqueous portions

are then slowly acidified to a pH of 1, in a 1-L separatory funnel, with 10% HCl, and then extracted with three 100 mL ethyl acetate portions. The organic layers are then combined, dried over sodium sulphate, filtered and then concentrated under reduced pressure. The resultant 2-(2,3-bis(tert-butoxycarbonyl)-1-methylguanidino)acetic acid would be sufficiently pure to use in subsequent steps.

[0059] A dry, 2-necked round bottomed flask, equipped with a magnetic stirrer and a dropping funnel containing a solution of 8.66 g (0.042mol) of *N,N'*-dicyclohexylcarbodiimide (DCC) dissolved in 100 mL of DCM, is charged with 13.25 g (0.040mol) of 2-(2,3-bis(tert-butoxycarbonyl)-1-methylguanidino)acetic acid, 7.18 g (0.044mol) of

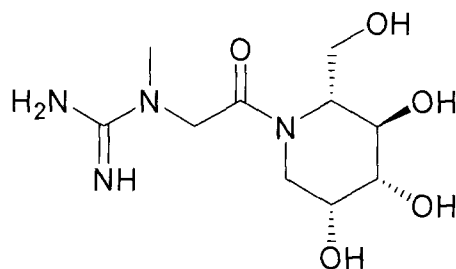
deoxygalactonojirimycin, and 75 mL of DCM (all of which is under an argon atmosphere).

The resultant mixture is stirred in an ice-water bath to cool the solution to a temperature of about 0°C. Following cooling, the solution of DCC from the dropping funnel is added and the reaction is allowed to warm to room temperature and then to stir overnight. The mixture is then filtered through a Celite® plug and the filtrate is purified by flash chromatography (ethyl acetate/hexanes; 1/3) to yield the bis-boc protected creatine deoxygalactonojirimycin amide, tert-butyl(tert-butoxycarbonylamino)(methyl(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)amino) methylenecarbamate.

[0060] In a dry, round bottomed flask, equipped with a magnetic stirrer, 23.81 g (0.050mol) of tert-butyl(tert-butoxycarbonylamino)(methyl(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)amino) methylenecarbamate is dissolved in 275 mL of a trifluoroacetic acid:H₂O (1:1) mixture. The resultant mixture is stirred for 2 hours at room temperature, after which it is concentrated under reduced pressure and then purified by flash chromatography (ethyl acetate/hexanes; 2/3) to yield the creatine deoxygalactonojirimycin amide, 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine.

Example 3

1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine



[0061] In a round bottomed flask, equipped with a magnetic stirrer, 9.17 g (0.070mol) of creatine is dissolved in 300 mL of water and 11.76 g (0.140mol) of sodium bicarbonate is added with stirring. The solution is then cooled to about 0°C in an ice-water bath. To the cooled solution is added a cooled solution of 40.20 ml (0.175mol) of di-tert-butyl dicarbonate dissolved in 175 mL of *p*-dioxane. The mixture is then stirred at about 0°C in an ice-water bath for an hour, after which the ice-water bath is removed and the solution is allowed to warm to room temperature (~23°C). After stirring at room temperature for an additional 3 hours, the mixture is diluted with 250 mL of water and transferred to a 2-L separatory funnel, where the aqueous layer is extracted sequentially with one 300 mL and one 150 mL portions of ethyl acetate. The resultant organic layer is then back extracted sequentially one 150 mL and one 75 mL portions of saturated sodium bicarbonate solution. The combined aqueous portions are then slowly acidified to a pH of 1, in a 2-L separatory funnel, with 10% HCl, and then extracted with three 100 mL ethyl acetate portions. The organic layers are then combined, dried over sodium sulphate, filtered and then concentrated under reduced pressure. The resultant 2-(2,3-bis(tert-butoxycarbonyl)-1-methyl-guanidino)acetic acid would be sufficiently pure to use in subsequent steps.

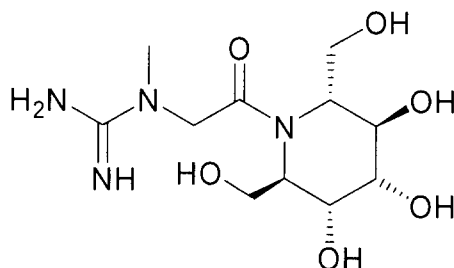
[0062] A dry, 2-necked round bottomed flask, equipped with a magnetic stirrer and a dropping funnel containing a solution of 13.00 g (0.063mol) of *N,N'*-dicyclohexylcarbodiimide (DCC) dissolved in 150 mL of DCM, is charged with 19.88 g (0.060mol) of 2-(2,3-bis(tert-butoxycarbonyl)-1-methylguanidino)acetic acid, 10.77 g (0.066mol) of deoxymannojirimycin, and 150mL of DCM (all of which is under an argon atmosphere). The resultant mixture is stirred in an ice-water bath to cool the solution to a temperature of about 0°C. Following cooling, the solution of DCC from the dropping funnel is added and the reaction is allowed to warm to room temperature and then to stir overnight. The mixture is then filtered through a Celite® plug and the filtrate is purified by flash chromatography (ethyl acetate/hexanes; 1/3) to yield the bis-boc protected creatine deoxymannojirimycin amide, tert-butyl (tert-butoxycarbonylamino)(methyl(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)amino)methylenecarbamate.

[0063] In a dry, round bottomed flask, equipped with a magnetic stirrer, 30.96 g (0.065mol) of tert-butyl (tert-butoxycarbonylamino)(methyl(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)amino)methylenecarbamate is dissolved in 325 mL of a trifluoroacetic acid:H₂O (1:1) mixture. The resultant mixture is stirred for 3 hours at room temperature, after which it is concentrated under reduced pressure and then purified by flash

chromatography (ethyl acetate/hexanes; 1/5) to yield the creatine deoxymannojirimycin amide, 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine.

Example 4

5 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine



[0064] In a round bottomed flask, equipped with a magnetic stirrer, 3.93 g (0.030mol) of creatine is dissolved in 150 mL of water and 5.04 g (0.060mol) of sodium bicarbonate is added with stirring. The solution is then cooled to about 0°C in an ice-water bath. To the cooled solution is added a cooled solution of 17.24 mL (0.075mol) of di-tert-butyl dicarbonate dissolved in 100 mL of *p*-dioxane. The mixture is then stirred at about 0°C in an ice-water bath for an hour, after which the ice-water bath is removed and the solution is allowed to warm to room temperature (~23°C). After stirring at room temperature for an additional hour, the mixture is diluted with 125 mL of water and transferred to a 1-L separatory funnel, where the aqueous layer is extracted sequentially with one 200 mL and one 75 mL portions of ethyl acetate. The resultant organic layer is then back extracted sequentially one 100 mL and one 50 mL portions of saturated sodium bicarbonate solution. The combined aqueous portions are then slowly acidified to a pH of 1, in a 1-L separatory funnel, with 10% HCl, and then extracted with three 75 mL ethyl acetate portions. The organic layers are then combined, dried over sodium sulphate, filtered and then concentrated under reduced pressure. The resultant 2-(2,3-bis(tert-butoxycarbonyl)-1-methyl-guanidino)acetic acid would be sufficiently pure to use in subsequent steps.

[0065] A dry, 2-necked round bottomed flask, equipped with a magnetic stirrer and a dropping funnel containing a solution of 6.50 g (0.0315mol) of *N,N'*-dicyclohexylcarbodiimide (DCC) dissolved in 80 mL of DCM, is charged with 9.94 g (0.030mol) of 2-(2,3-bis(tert-butoxycarbonyl)-1-methylguanidino)acetic acid, 6.38 g (0.033mol) of homomannojirimycin, and 100mL of DCM (all of which is under an argon atmosphere). The resultant mixture is stirred in an ice-water bath to cool the solution to a

temperature of about 0°C. Following cooling, the solution of DCC from the dropping funnel is added and the reaction is allowed to warm to room temperature and then to stir overnight.

The mixture is then filtered through a Celite® plug and the filtrate is purified by flash chromatography (ethyl acetate/hexanes; 1/3) to yield the bis-boc protected creatine

5 homomannojirimycin amide, tert-butyl (tert-butoxycarbonylamino)(methyl(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)amino)methylene-carbamate.

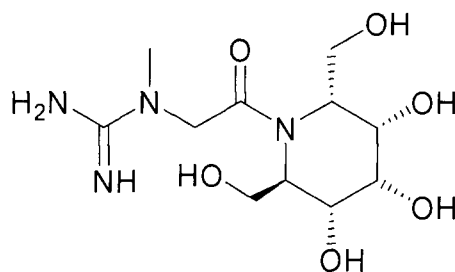
[0066] In a dry, round bottomed flask, equipped with a magnetic stirrer, 10.12 g (0.020mol) of tert-butyl(tert-butoxycarbonylamino)(methyl(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl) amino)methylenecarbamate is dissolved in 150

10 mL of a trifluoroacetic acid:H₂O (1:1) mixture. The resultant mixture is stirred for 2 hours at room temperature, after which it is concentrated under reduced pressure and then purified by flash chromatography (ethyl acetate/hexanes; 1/5) to yield the creatine homomannojirimycin

15 amide, 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine.

Example 5

1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine



20 [0067] In a round bottomed flask, equipped with a magnetic stirrer, 7.87 g (0.060mol) of creatine is dissolved in 200 mL of water and 10.08 g (0.120mol) of sodium bicarbonate is added with stirring. The solution is then cooled to about 0°C in an ice-water bath. To the cooled solution is added a cooled solution of 31.10 ml (0.150mol) of di-tert-butyl dicarbonate dissolved in 150 mL of *p*-dioxane. The mixture is then stirred at about 0°C in an ice-water

25 bath for an hour, after which the ice-water bath is removed and the solution is allowed to warm to room temperature (~23°C). After stirring at room temperature for an additional 2 hours, the mixture is diluted with 150 mL of water and transferred to a 1-L separatory funnel, where the aqueous layer is extracted sequentially with one 300 mL and one 150 mL portions of ethyl acetate. The resultant organic layer is then back extracted sequentially one 150 mL

and one 75 mL portions of saturated sodium bicarbonate solution. The combined aqueous portions are then slowly acidified to a pH of 1, in a 1-L separatory funnel, with 10% HCl, and then extracted with three 100 mL ethyl acetate portions. The organic layers are then combined, dried over sodium sulphate, filtered and then concentrated under reduced pressure.

5 The resultant 2-(2,3-bis(tert-butoxycarbonyl)-1-methyl-guanidino)acetic acid would be sufficiently pure to use in subsequent steps.

[0068] A dry, 2-necked round bottomed flask, equipped with a magnetic stirrer and a dropping funnel containing a solution of 10.83 g (0.0525mol) of *N,N'*-dicyclohexylcarbodiimide (DCC) dissolved in 60 mL of DCM, is charged with 16.57 g
10 (0.050mol) of 2-(2,3-bis(tert-butoxycarbonyl)-1-methylguanidino)acetic acid, 10.62 g (0.055mol) of homonojirimycin, and 100mL of DCM (all of which is under an argon atmosphere). The resultant mixture is stirred in an ice-water bath to cool the solution to a temperature of about 0°C. Following cooling, the solution of DCC from the dropping funnel is added and the reaction is allowed to warm to room temperature and then to stir overnight.
15 The mixture is then filtered through a Celite[®] plug and the filtrate is purified by flash chromatography (ethyl acetate/hexanes; 1/3) to yield the bis-boc protected creatine homonojirimycin amide, tert-butyl(tert-butoxycarbonylamino)(methyl(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)amino)methylene-carbamate.

20 [0069] In a dry, round bottomed flask, equipped with a magnetic stirrer, 20.62 g (0.040mol) of tert-butyl (tert-butoxycarbonylamino)(methyl(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl) amino)methylenecarbamate is dissolved in 250 mL of a trifluoroacetic acid:H₂O (1:1) mixture. The resultant mixture is stirred for 2 hours at room temperature, after which it is concentrated under reduced pressure
25 and then purified by flash chromatography (ethyl acetate/hexanes; 1/5) to yield the creatine homonojirimycin amide, 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine.

Example 5

[0070] 552.58 g (2 mol) of creatine deoxynojirimycin amide is dissolved into 400mL of hot
30 ethanol, solution 1. Concurrently, 134.09 g (1 mol) of malic acid is dissolved in 200mL of hot ethanol, solution 2. Solution 2 is added to solution 1 with stirring and the resultant combined solution is heated to the boiling point. If there are solids still present the combined solution is filtered at this temperature to remove unreacted starting materials. The combined solution is then allowed to cool to room temperature and then covered and refrigerated to

allow crystallization to complete; about 24 hours. The resultant crystals are filtered under vacuum and washed with ice cold ethanol, yielding the creatine deoxynojirimycin amide hemimalate.

Example 6

5 [0071] 552.58 g (2 mol) of creatine deoxygalactonojirimycin amide is dissolved into 400mL of hot propanol, solution 1. Concurrently, 116.07 g (1 mol) of fumaric acid is dissolved in 200mL of hot propanol, solution 2. Solution 2 is added to solution 1 with stirring and the resultant combined solution is heated to the boiling point. If there are solids still present the combined solution is filtered at this temperature to remove unreacted starting materials. The
10 combined solution is then allowed to cool to room temperature and refrigerated to allow crystallization to complete; about 24 hours. The resultant crystals are filtered under vacuum and washed with ice cold ethanol, yielding the creatine deoxygalactonojirimycin amide hemifumarate.

Example 7

15 [0072] 828.27 g (3 mol) of creatine deoxymannojirimycin amide is dissolved into 600mL of hot isopropanol, solution 1. Concurrently, 192.12 g (1 mol) of citric acid is dissolved in 300mL of hot isopropanol, solution 2. Solution 2 is added to solution 1 with stirring and the resultant combined solution is heated to the boiling point. If there are solids still present the combined solution is filtered at this temperature to remove unreacted starting materials. The
20 combined solution is then allowed to cool to room temperature and refrigerated to allow crystallization to complete; about 24 hours. The resultant crystals are filtered under vacuum and washed with ice cold ethanol, yielding the tris(creatine deoxymannojirimycin amide) citrate.

Extensions and Alternatives

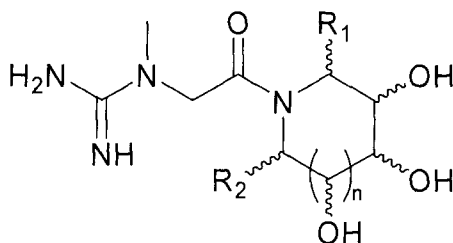
25 [0073] In the foregoing specification, the invention has been described with respect to specific embodiments thereof; however, it will be evident to one skilled in the art that various modifications and changes may be made thereto without departing from the scope of the invention.

[0074] All publications which are cited herein are hereby specifically incorporated by
30 reference into the disclosure for the teachings for which they are cited.

Claims

What is claimed:

1. A compound having the structure:



where $R_1 = \text{H, OH, or CH}_2\text{OH}$;

$R_2 = \text{H, OH, CH}_3 \text{ or CH}_2\text{OH}$; and

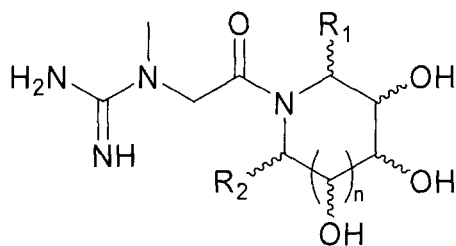
$n = 0, 1 \text{ or } 2..$

2. A nutritional composition comprising at least one pharmaceutically acceptable carrier or diluent and the compound of claim 1.
3. The nutritional composition of claim 2, wherein the composition is provided to a subject in an acceptable oral dosage form.
4. The nutritional composition of claim 3, wherein the subject is a mammal.
5. The nutritional composition of claim 3, wherein the acceptable oral dosage form is selected from the group consisting of a powder beverage mix, a liquid beverage, a ready-to-eat bar, a capsule, a liquid capsule, a tablet, a caplet, a dietary gel, a soft-gelTM caplet, and a gel-cap.
6. A compound selected from the group consisting of: 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine; 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine; 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine; 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine; and 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine.
7. A method for producing a creatine imino sugar amide comprising at least the steps of:
 - reacting creatine with an amino protecting group to form a protected creatine;
 - concentrating said protected creatine;
 - reacting an activated protected creatine with an imino sugar to form a protected creatine imino sugar amide;
 - isolating and purifying said protected creatine imino sugar amide;

removing the protecting groups from said protected creatine imino sugar amide; and

concentrating and purifying the deprotected creatine imino sugar amide.

8. The method of claim 7 wherein the formation of protected creatine occurs at temperatures between about 0°C and about 23°C.
9. The method of claim 7 wherein the protected creatine is concentrated under reduced pressure.
10. The method of claim 7 wherein the protected creatine is activated *in situ* by *N,N'*-dicyclohexylcarbodiimide.
11. The method of claim 7 where in the activated protected creatine is reacted with the imino sugar at temperatures between about 0°C and about 23°C.
12. The method of claim 7 wherein the imino sugar is selected from the group consisting of deoxynojirimycin, deoxygalactonojirimycin, deoxymannojirimycin, homomannojirimycin and homonojirimycin.
13. The method of claim 7 wherein the protected creatine imino sugar amide is isolated by filtration and then concentrated under reduced pressure.
14. The method of claim 7, wherein the amino protecting group is 9-fluorenylmethyl carbamate, di-*tert*-butyl carbonate, benzyl carbamate, acetamide, trifluoroacetamide, phthalimide, benzylamine, benzylideneamine or *p*-toluenesulfonamide.
15. The method of claim 14, wherein the amino protecting group is di-*tert*-butyl carbonate.
16. The method of claim 7 wherein the protected creatine imino sugar amide is purified by flash chromatography using a silica gel packed column.
17. The method of claim 7 wherein the protecting groups are removed from the protected creatine imino sugar amide by acidification with trifluoroacetic acid.
18. The method of claim 7 wherein the deprotected creatine imino sugar amide is concentrated under reduced pressure.
19. The method of claim 7 wherein the deprotected creatine imino sugar amide is purified by flash chromatography using a silica gel packed column.
20. The method of claim 7 wherein the deprotected creatine imino sugar amide has the structure of:



where $R_1 = \text{H, OH, or CH}_2\text{OH}$;

$R_2 = \text{H, OH, CH}_3 \text{ or CH}_2\text{OH}$; and

$n = 0, 1 \text{ or } 2$

21. The method of claim 7 wherein the deprotected creatine imino sugar amide is selected from the group consisting of: 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine; 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine; 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine; 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine; and 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine.
22. A composition comprising at least one salt of a creatine imino sugar amide.
23. The composition of claim 22, wherein the salt is an acid-addition salt of a creatine imino sugar amide with an inorganic or organic acid is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, trifluoroacetic acid, citric acid, maleic acid, malic acid and fumaric acid.
24. The composition of claim 22, wherein the creatine imino sugar amide is selected from the group consisting of 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine, 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine, 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine, 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine, and 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine.
25. The composition of claim 22, wherein the salt is a mono- creatine imino sugar amide salt.

26. The composition of claim 22, wherein the salt is a di-creatine imino sugar amide salt.
27. The composition of claim 22, wherein the salt is a tri-creatine imino sugar amide salt.
28. The composition of claim 22, further comprising at least one pharmaceutically acceptable carrier or diluent.
29. The composition of claim 28, wherein the composition is provided to a subject in an acceptable oral dosage form.
30. The composition of claim 28, wherein the composition is administered to a subject parenterally.
31. The composition of claim 29, wherein the acceptable oral dosage form is selected from the group consisting of a powder beverage mix, a liquid beverage, a ready-to-eat bar, a capsule, a liquid capsule, a tablet, a caplet, a dietary gel, a soft-gel™ caplet, and a gel-cap.
32. A method for producing salts of creatine imino sugar amides, comprising at least the steps of:
 - a) dissolving a creatine imino sugar amide in hot lower alcohol;
 - b) dissolving an acid in hot lower alcohol;
 - c) combining the resultant solutions of a) and b);
 - d) cooling the resultant combined solution of c) until crystallization occurs;
and
 - e) isolating the resulting creatine imino sugar amide salt.
33. The method of claim 32 wherein the lower alcohol is selected from the group consisting of methanol, ethanol, propanol, butanol, and isopropanol.
34. The method of claim 32 wherein the creatine imino sugar amide and the acid are present in a 1:1 ratio.
35. The method of claim 32 wherein the creatine imino sugar amide and the acid are present in a 2:1 ratio.
36. The method of claim 32 wherein the creatine imino sugar amide and the acid are present in a 3:1 ratio.
37. The method of claim 32 wherein the creatine imino sugar amide is selected from the group consisting of 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine, 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine, 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine, 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-

bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine, and 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine.

38. The method of claim 32 wherein the acid is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, trifluoroacetic acid, citric acid, maleic acid, malic acid and fumaric acid.
39. The method of claim 32 wherein the creatine imino sugar amide salt is isolated by vacuum filtration followed by washing of the filtrate with cold lower alcohol.
40. A method for supplementing a diet comprising administering to a subject a composition comprising at least one salt of a creatine imino sugar amide.
41. The method according to claim 40 wherein the salt is an acid-addition salt of a creatine imino sugar amide with an inorganic or organic acid is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, trifluoroacetic acid, citric acid, maleic acid, malic acid and fumaric acid.
42. The method according to claim 40 wherein the creatine imino sugar amide is selected from the group consisting of 1-methyl-1-(2-oxo-2-((2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine, 1-methyl-1-(2-oxo-2-((3S,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine, 1-methyl-1-(2-oxo-2-((2R,3R,4R,5R)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidin-1-yl)ethyl)guanidine, 1-methyl-1-(2-oxo-2-((2R,3R,5R,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine, and 1-methyl-1-(2-oxo-2-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-2,6-bis(hydroxymethyl)piperidin-1-yl)ethyl)guanidine.
43. The method according to claim 40 wherein the salt is a mono- creatine imino sugar amide salt.
44. The method according to claim 40 wherein the salt is a di-creatine imino sugar amide salt.
45. The method according to claim 40 wherein the salt is a tri-creatine imino sugar amide salt.
46. The method according to claim 40 wherein the composition is administered to a subject in an acceptable oral dosage form.
47. The method according to claim 46 wherein the acceptable oral dosage form is selected from the group consisting of a powder beverage mix, a liquid beverage, a

ready-to-eat bar, a capsule, a liquid capsule, a tablet, a caplet, a dietary gel, a soft-gel™ caplet, and a gel-cap.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2009/000757

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC: <i>C07D 211/46</i> (2006.01), <i>A23L 1/30</i> (2006.01), <i>C07D 207/12</i> (2006.01), <i>C07D 223/08</i> (2006.01), <i>C07H 15/12</i> (2006.01) According to International Patent Classification (IPC) or to both national classification and IPC</p>											
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) IPC: <i>C07D 211/46</i> (2006.01), <i>A23L 1/30</i> (2006.01), <i>C07D 207/12</i> (2006.01), <i>C07D 223/08</i> (2006.01), <i>C07H 15/12</i> (2006.01)</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p> <p>Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used) STN (CAPLUS), Canadian Patent Database, Delphion, Scopus and PubMed (keywords creatine, guanidine and nojirimycin)</p>											
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1" style="width:100%; border-collapse: collapse;"> <thead> <tr> <th style="width:10%;">Category*</th> <th style="width:60%;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="width:30%;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td align="center">A</td> <td>CA 2260790C (MACROZYME DNM B.V.) 22 January 1998 (22-01-1998) *see entire document*</td> <td align="center">1-47</td> </tr> <tr> <td align="center">A</td> <td>Cipolla et al. Synthesis and biological evaluation of a small library of nojirimycin-derived bicyclic iminosugars. Carbohydrate Research, 342, 2007, 1813-1830 *see entire document*</td> <td align="center">1-47</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	A	CA 2260790C (MACROZYME DNM B.V.) 22 January 1998 (22-01-1998) *see entire document*	1-47	A	Cipolla et al. Synthesis and biological evaluation of a small library of nojirimycin-derived bicyclic iminosugars. Carbohydrate Research, 342, 2007, 1813-1830 *see entire document*	1-47
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.									
A	CA 2260790C (MACROZYME DNM B.V.) 22 January 1998 (22-01-1998) *see entire document*	1-47									
A	Cipolla et al. Synthesis and biological evaluation of a small library of nojirimycin-derived bicyclic iminosugars. Carbohydrate Research, 342, 2007, 1813-1830 *see entire document*	1-47									
<p><input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.</p> <table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="width:50%; vertical-align: top;"> <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </td> <td style="width:50%; vertical-align: top;"> <p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p> </td> </tr> </table>			<p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>							
<p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>										
<p>Date of the actual completion of the international search</p> <p>12 August 2009 (12-08-2009)</p>		<p>Date of mailing of the international search report</p> <p>24 August 2009 (24-08-2009)</p>									
<p>Name and mailing address of the ISA/CA 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</p>		<p>Authorized officer</p> <p>Ayub Reayi 819- 934-0481</p>									

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. Claim Nos. : 40-47

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

Claims 40-47 are directed to a method for treatment of the human or animal body by surgery or therapy, are not required to be searched nor is a written opinion required by the Authority. Regardless, this Authority has established a written opinion based on the alleged effect or purpose/use of the product defined in claim 1.

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 :

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. 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. :

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

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

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2009/000757

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CA 2260790C	22-01-1998	AT 322900T	15-04-2006
		AU 732552B2	26-04-2001
		AU 3464797A1	09-02-1998
		DE 69735669D1	24-05-2006
		DE 69735669T2	29-03-2007
		EP 0912179A1	06-05-1999
		EP 0912179B1	12-04-2006
		IL 128036A1	31-08-2005
		JP 2000516577T	12-12-2000
		US 6177447B1	23-01-2001
		WO 9802161A1	22-01-1998