



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/IT98/00144 (22) International Filing Date: 29 May 1998 (29.05.98) (30) Priority Data: RM97A000322 30 May 1997 (30.05.97) IT (71) Applicant (for all designated States except US): SIGMA-TAU HEALTHSCIENCE S.P.A. [IT/IT]; Via Treviso, 4, I-00040 Pomezia (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): SANTANIELLO, Mosé [IT/IT]; Via dei Giardini, 15, I-00048 Nettuno (IT). SCAFETTA, Nazareno [IT/IT]; Via Siena, 10, I-00040 Pavona di Albano (IT). TINTI, Maria, Ornella [IT/IT]; Via Ernesto Basile, 81, I-00182 Roma (IT). (74) Agents: CAVATTONI, Fabio et al.; Viale dei Parioli, 160, I-00197 Roma (IT).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: WATER-SOLUBLE SALTS OF DODECANDIOIC ACID AND PHARMACEUTICAL AND NUTRITIONAL COMPOSITIONS CONTAINING SAME (57) Abstract Water-soluble dodecandioates wherein the cationic moiety is selected from the group comprising the cations of basic aminoacids (e.g. lysine) and choline and orally or parenterally administrable compositions containing same, are disclosed.		

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**"Water-soluble salts of dodecandioic acid and pharmaceutical
and nutritional compositions containing same"**

The present invention relates to water-soluble salts of dodecandioic acid and compositions with therapeutic or nutritional
5 activity containing such salts.

Dodecandioic acid, $\text{HOOC}(\text{CH}_3)_{10}\text{COOH}$, and its derivatives such as amides with amino acids, triglycerides and their pharmacologically acceptable salts have recently aroused substantial interest in the nutritional field.

10 EP 0569393 B1 discloses the use of linear C6-C12 dicarboxylic acids, including dodecandioic acid, and their esters, amides and triglycerides in enteral and parenteral nutrition in which the use of such dicarboxylic acids with an even number of carbon atoms as an alternative energy substrate proves particularly useful
15 in those conditions wherein the utilisation of glucose and/or free fatty acids is prevented.

Since these linear acids with an even number of carbon atoms are symmetrical, they can be β -oxidised starting from the α or ω -carboxyl group supplying acetyl CoA and succinic acid as the end
20 product. The increased availability of succinic acid stimulates the metabolism of other substrates via the Krebs cycle. In addition, succinic acid is a gluconeogenic precursor, with the result that the administration of such acids is believed to increase the

accumulation of glycogen in those clinical conditions that give rise to a decrease in glycogen owing to inadequate glycogen-synthase activity (as occurs in diabetes mellitus) and to reduce the catabolic breakdown of amino acids in conditions of increased glycogenolysis
5 (as occurs in conditions of sepsis, trauma or major abdominal surgery).

Dodecandioic acid has also recently been proposed for cosmetic use, particularly for the production of creams for the treatment of wrinkles, for the regeneration of the skin and to combat
10 the damage of ageing and exposure to the sun's rays.

All the above-mentioned applications are facilitated when derivatives of dodecandioic acid are available which are water-soluble, since dodecandioic acid is known to be practically insoluble in water (0.05 g in 1 liter of H₂O at 23°C; Ber. 23, 2347 [1890]).
15 Water-soluble derivatives of dodecandioic acid could, on the other hand, be easily administered and promptly used as an energy substrate.

Water-soluble salts of dodecandioic acid are already known.

Such salts are, however, dodecandioates of alkaline metals, particularly sodium. The administration of substantial amounts of
20 these salts, particularly by parenteral nutrition, may alter the electrolyte balance in subjects who are already severely debilitated by the disease or surgical intervention that makes parenteral

nutrition necessary and may prove damaging in general in anyone obliged to go on a low-sodium diet.

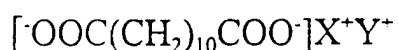
One object of the present invention is to provide water-soluble salts of dodecandioic acid which do not present the aforesaid
5 drawbacks.

A further object of the present invention is to provide water-soluble salts of dodecandioic acid, whose cationic moiety, unlike the above-mentioned known salts, presents an intrinsic therapeutic or nutritional value.

10 It should, therefore, be clearly understood that the usefulness of the salts of the present invention does not consist merely in their water-solubility but also in the fact that such salts present as a whole an increased therapeutic and/or nutritional value as compared to the known dodecandioates, this latter value therefore
15 not being exclusively brought about by the anionic moiety of the salt.

In accordance with the present invention, the aforesaid objects are achieved by the dodecandioic acid salts of general formula (I):

20



(I)

wherein:

if X^+ is the same as Y^+ , it is selected from the group comprising the cations of basic amino acids and choline; or

if X^+ is other than Y^+ , they are selected from:

- 5 (a) the cations of basic aminoacids and choline; and
- (b) the cations of alkaline, alkaline-earth metals and ammonium, provided that if either of X^+ or Y^+ is a (b) cation, the other is an (a) cation.

The cations of the basic aminoacids are the cations of lysine,
10 arginine, hystidine and ornithine, while the cations of the alkaline and alkaline-earth metals are selected from the groups comprising Na^+ , K^+ , Mg^{+2} and Ca^{+2} .

The compositions of the present invention comprise a salt of formula (I) as active ingredient, optionally in combination with one
15 or more further active ingredients and, optionally, a pharmacologically acceptable excipient.

The aforesaid compositions comprise the enterally or parenterally administrable compositions. These generally occur as aqueous solutions generally containing 0.1-1.0 moles/liter of salt of
20 formula (I) or a molar equivalent amount of a pharmacologically acceptable salts thereof.

In the compositions which comprise a further active ingredient, preferably this is L-carnitine or an alkanoyl L-carnitine

wherein the alkanoyl group has 2-6 carbon atoms or a pharmacologically acceptable salt thereof.

What is meant by pharmacologically acceptable salt of L-carnitine or alkanoyl L-carnitine is any salt of these with an acid
5 that does not give rise to unwanted toxic or side effect. These acids are well known to pharmacologists and to experts in pharmacy.

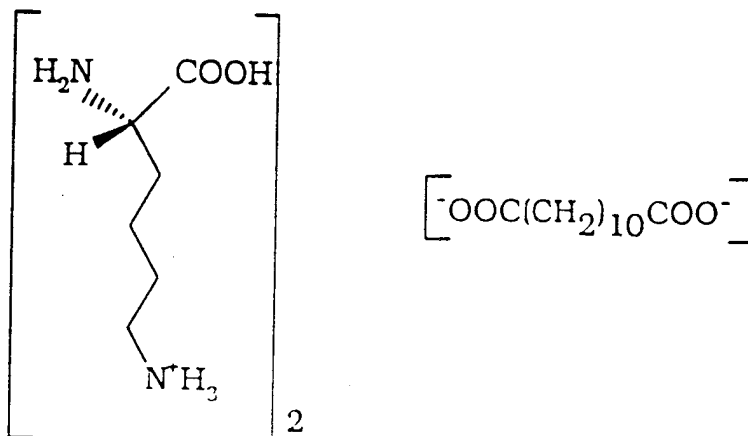
Non-limiting examples of such salts are: chloride; bromide; iodide; aspartate; acid aspartate; citrate; acid citrate; tartrate; phosphate; acid phosphate; fumarate; acid fumarate;
10 glycerophosphate; glucose phosphate; lactate; maleate; acid maleate; orotate; oxalate; acid oxalate; sulphate; acid sulphate; trichloroacetate; trifluoroacetate and methanesulphonate.

A list of FDA-approved pharmacologically acceptable salts is disclosed in Int. J. Pharm. 33, (1986), 201-217; this latter
15 publication is incorporated herein by reference.

The following non-limiting examples show the preparation of some dodecandioic salts according to the invention.

EXAMPLE 1**Preparation of L-lysine dodecandioate (ST 1284)**

5



L-lysine (14.6 g; 0.1 moles) was dissolved in 250 mL of H₂O.

10 Dodecandioic acid (11.5 g; 0.05 moles) was added to the resulting solution portionwise.

The resulting mixture was kept under stirring at room temperature till dissolution.

15 The opalescent solution thus obtained was filtered and the filtrate concentrated under vacuum to dryness at 40°C.

The residue was taken up with acetone and the resulting mixture was kept under stirring at room temperature overnight.

The mixture was then filtered and the filter cake dried under vacuum at 40°C.

20 25 grams of a solid, non-hygroscopic, water-soluble compound were thus obtained.

pH= 7.1 (c = 1% H₂O)

Thermal analysis: DSC = 196.8°C

NMR D₂O 3.6 (2H,t,2 $\underline{\text{CH}}\text{NH}_2$); 2.9(4H,2 $\underline{\text{CH}_2}\text{N}^+\text{H}_3$);
 2.0(4H,t,2 $\underline{\text{CH}_2}\text{COOH}$); 1.7(2H,m, $\underline{\text{CH}_2}\text{CH}_2\text{COOH}$);
 1.5(2H,m, $\text{CH}_2\underline{\text{CH}_2}\text{COOH}$); 1.4-1.3(6H,m,2-(CH₂)₃N⁺H₃;
 1.1(14H,m,(CH₂)₇)

5 Elementary analysis for C₂₄H₅₂N₄O₆

	C%	H%	N%
Cal. (+ 1.9% H ₂ O)	57.63	10.64	11.14
Found	55.30	10.43	10.59

HPLC analysis was conducted using two different chromatographic

10 columns.

Column Speherisorb-SCX (5 μm) 250 X 4 mm

Temperature = 25°C

Eluant CH₃CN/KH₂PO₄ 0.1 M 50/50

pH = 3.2 con H₃PO₄

15 Lysine R_t = 18,65

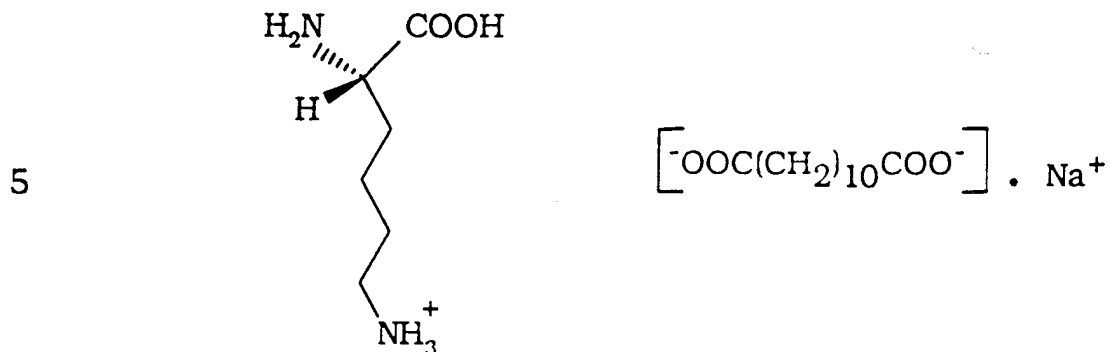
Column Symmetry - C18 (5 μm) 3.9 X 300 mm

Temperature = 30°C

Eluant CH₃CN/KH₂PO₄ 0.1 M 70/30

Dodecandioic acid R_t = 13.45

20

EXAMPLE 2**Preparation of L-lysine dodecandioate, sodium salt (ST 1309)**

Dodecandioic acid (23 g; 0.01 moles), L-lysine (1.46 g; 0.01 moles) and NaHCO_3 (0.84 g; 0.01 moles) were suspended in 50 mL of H_2O . The resulting mixture was kept under stirring till complete dissolution. The resulting solution was brought to dryness under vacuum.

The raw residue was taken up with acetone under stirring and the mixture thus obtained was filtered.

15 4 g of a solid, non hygroscopic, water-soluble compound were obtained.

pH = 7.5 (c = 1% in H_2O)

Thermal analysis

The compound decomposes at about 200°C without melting.

20 Elementary analysis for $\text{C}_{18}\text{H}_{35}\text{N}_2\text{O}_6\text{Na}$

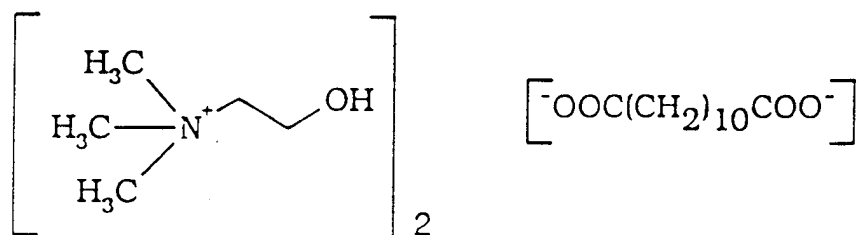
	C	H	N
Calc.	54.25	8.85	7.03
Found	53.63	9.49	7.25

NMR and HPLC as in Example 1, but in this case the molar ratio L-lysine/dodecandioic acid was 1:1.

EXAMPLE 3

Preparation of choline dodecandioate (ST 1313)

5



10

Choline chloride (1.4 g; 0.01 moles) was dissolved in water. The resulting solution was eluted on IRA-402 (HCO_3) resin. To the aqueous solution thus obtained dodecandioic acid (1.15 g; 0.005 moles) was added. The mixture was kept under stirring till complete dissolution (about 12 hours).

15

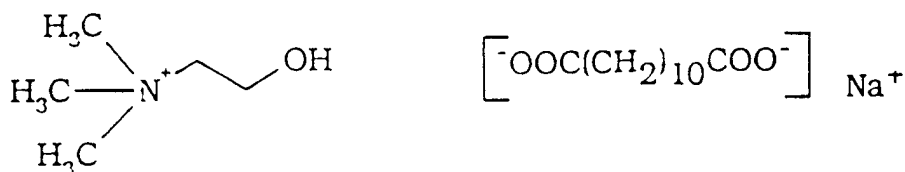
The resulting solution was concentrated under vacuum at 40°C .

2.1 g of a hygroscopic, oily compound were obtained.

EXAMPLE 4

Preparation of choline dodecandioate, sodium salt (ST 1314)

20



Dodecandioic acid (2.3 g; 0.01 moles) was suspended in 50 mL of water. To the resulting suspension, first sodium bicarbonate (0.84 g; 0.01 moles) and then a 50% aqueous solution of choline (2.42 g; 0.01 moles) were added under stirring.

5 The mixture thus obtained was kept under stirring for 2 hours till complete dissolution, the resulting solution was concentrated under vacuum at 40°C and the residue dried under vacuum with an oil pump.

4.9 g of a hygroscopic compound were obtained.

10 It is apparent that in the salts of formula (I) also the cationic moiety consisting of basic aminoacids and/or choline markedly contributes to the therapeutic/nutritional value of the salts.

Amino acids are the constituent building blocks of proteins which are metabolised in the body to produce energy.

15 The carbon skeletons of amino acids can be incorporated in fatty acids and in carbohydrates.

Lysine is one of the least abundant essential amino acids in nature. It is not synthesised in the human body and its supply occurs exclusively through the diet.

20 In mammals, the catabolism of lysine leads to the formation of acetyl coenzyme A.

Lysine is utilised as a food supplement because it favours the growth and synthesis of tissues (Feldberg Hetzel, Food Technol. 12, 496 [1958]).

Moreover, the therapeutic use of this amino acid has been
5 proposed for the treatment and prevention of herpetic lesions (McCune et al. [1984]; Simon Van Melle and Ramelet [1985]).

Choline is a quaternary amine extensively present in food.

It is a precursor of the synthesis of the neurotransmitter acetylcholine, is a source of labile methyl groups and is a precursor
10 of membrane phospholipids.

Choline is an essential nutrient for man. It has been demonstrated, in fact, that human cells in culture need choline for growth (Eagle H.: J. Exp. Med., 102: 595-600, 1955). Under-nourished subjects present a reduced concentration of plasma
15 choline (Chawla R.K., Wolf D.C., Kutner M.H., Bonkovsky H.L.: Gastroenterology, 97: 1514-1520, 1989). Patients receiving parenteral nutrition with solutions containing low concentrations of choline develop liver dysfunctions similar to those noted in animals put on a diet deficient in choline (Sheard N.F., Tayek J.A., Bistrian B.R. et
20 al.: Am. J. Clin. Nutr., 43: 219-224, 1986).

A choline-deficient diet may also give rise to kidney abnormalities and to abnormal fertility, growth and haematopoiesis, as well as to hypertension.

Choline and phosphatidyl choline are so extensively present in food that a deficiency syndrome has been recently identified only in a hospitalized population unable to feed on normal food.

Liver abnormalities (fatty infiltrations in the liver and liver-cell
5 damage) associated with total parenteral nutrition (TPN) have been reported by many clinical groups (Poley J.R.: In: Lebenthal E. Ed., Textbook of Gastroenterology and Nutrition in Infancy, New York, Raven Press, 1981, pp. 743-763).

TPN often has to be discontinued due to the severity of the
10 associated liver diseases.

It has been found that subjects receiving TPN have a much lower plasma choline concentration than is found in normally fed subjects (Sheard N.F., Tayek J.A., Bistrian B.R. et al.: Am. J. Clin. Nutr., 43: 219-224, 1986).

15 It has been calculated that patients fed via TPN need from 1000 to 1700 μmol of choline-containing phospholipids during the first week of TPN.

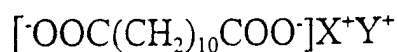
After administration of choline given in the form of lecithin during TPN, it has been observed that normal plasma levels of
20 choline are restored and that the incidence of liver dysfunctions and hepatic steatosis decreases (Buchman A.L., Dubin M., Jenden D. et al.: Gastroenterology, 102: 1363-1370, 1992).

It is clear that the salts formula (I), particularly when utilised in TPN, afford considerable benefits of both a therapeutic and nutritional nature.

CLAIMS

1. A salt of dodecandioic acid of general formula (I)

5



(I)

wherein:

10

if X^+ is the same as Y^+ , it is selected from the group comprising

the cations of basic aminoacids and choline; or

if X^+ is other than Y^+ , they are selected from:

(a) the cations of basic aminoacids and choline; and

(b) the cations of alkaline, alkaline-earth metals and

15

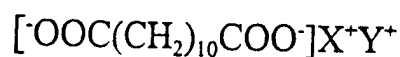
ammonium, provided that if either of X^+ or Y^+ is a (b)

cation, the other is an (a) cation.

2. The salt of claim 1, wherein the cations of the basic aminoacids are the cations of lysine, arginine, histidine and ornithine.

3. The salt of claims 1 or 2, wherein the cations of alkaline and
- 20 alkaline-earth metals are selected from the group comprising Na^+ , K^+ , Mg^{+2} and Ca^{+2} .

4. A composition comprising a salt of general formula (I)



(I)

5

wherein:

if X^+ is the same as Y^+ , it is selected from the group comprising the cations of basic aminoacids and choline; or

10 if X^+ is other than Y^+ , they are selected from:

(a) the cations of basic aminoacids and choline; and

(b) the cations of alkaline, alkaline-earth metals and ammonium, provided that if either of X^+ or Y^+ is a (b) cation, the other is an (a) cation,

15 and a pharmacologically acceptable excipient.

5. The composition of claim 4, wherein in the salt of formula (I) the cations of the basic aminoacids are the cations of lysine, arginine, histidine and ornithine.

6. The composition of claims 4 or 5, wherein in the salt of formula
20 (I) the cations of the alkaline and alkaline-earth metals are Na^+ , K^+ , Mg^{+2} and Ca^{+2} .

7. The composition of anyone of claims 4-6, suitable to be enterally or parenterally administered.

8. The composition of claim 7 in the form of an aqueous solution, comprising 0.1-1 moles/liter of salt of formula (I).
9. The composition of anyone of claims 4-8, comprising a further active ingredient.
- 5 10. The composition of claim 9 wherein the further active ingredient is selected from the group comprising L-carnitine and an alkanoyl L-carnitine wherein the alkanoyl group has 2-6 carbon atoms and the pharmacologically acceptable salts thereof.
- 10 11. The composition of claim 10, comprising 0.1-0.5 moles/liter of L-carnitine or alkanoyl L-carnitine or a molar equivalent amount of a pharmacologically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IT 98/00144

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C55/21 C07C229/26 C07C279/14 C07D233/64 A61K31/195
C07D233/54

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)

IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92 12960 A (PINAROO LTD ;CASTAGNETO MARCO (IT)) 6 August 1992 see the whole document & EP 0 569 393 A cited in the application ---	1,7-11
A	FR 2 235 938 A (ARIES ROBERT) 31 January 1975 see claim 1 ---	1
A	EP 0 000 158 A (BASF AG) 10 January 1979 see claim 1 ---	1
A	GB 2 048 262 A (LUBRIZOL CORP) 10 December 1980 see claim 1; example 9 ---	1
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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17 August 1998

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/IT 98/00144

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Section Ch, Derwent Publications Ltd., London, GB: Class E12, AN 73-81227U XP002074206 & JP 48 043 487 B (TOA GOSEI CHEM IND LTD) see abstract ---	1
A	PHILIP L. GOULD: "Salt selection for basic drugs" INTERNATIONAL JOURNAL OF PHARMACEUTICS, vol. 33, no. 1-3, 1986, pages 201-217, XP002074725 cited in the application see page 211 - page 216 -----	2,3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IT 98/00144

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