

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 September 2006 (08.09.2006)

PCT

(10) International Publication Number
WO 2006/092204 A1

(51) International Patent Classification:

C07C 275/16 (2006.01) **A61K 31/17** (2006.01)
C07D 211/90 (2006.01) **A61P 3/10** (2006.01)
C07D 213/82 (2006.01)

(21) International Application Number:

PCT/EP2006/001290

(22) International Filing Date:

13 February 2006 (13.02.2006)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

RM2005A000090 2 March 2005 (02.03.2005) IT

(71) Applicant (for all designated States except US):
SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.P.A. [IT/IT]; 47, Viale Shakespeare, I-00144 Rome (IT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **GIANNESSI, Fabio** [IT/IT]; Via Berlinguer, 7/B, I-00040 Pomezia (IT). **TASSONI, Emanuela** [IT/IT]; Largo Enrico Fermi, 11/F, Ciampino (IT). **TINTI, Maria, Ornella** [IT/IT]; Via Ernesto Basile, 81, I-00128 Rome (IT). **CONTI, Roberto** [IT/IT]; Via Angelo Emo, 15/a, I-00136 Rome (IT). **DELL'UOMO, Natalina** [IT/IT]; Via Berlinguer, 7, I-00040 Pomezia (IT). **BRUNETTI, Tiziana** [IT/IT]; Viale Priamo, 59, I-00040 Pomezia (IT).

(74) Agent: **TAGLIAFICO, Giulia**; Sigma-Tau Industrie Farmaceutiche Riunite S.p.A., Via Pontina, Km. 30,400, I-00040 Pomezia (IT).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, 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, HU, IE, IS, IT, LT, LU, LV, MC, NL, 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))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DERIVATIVES OF AMINOBUTANOIC ACID INHIBITING CPT

(57) Abstract: The invention relates to a new class of compounds with action inhibiting carnitine palmitoyl transferase (CPT), pharmaceutical compounds which contain at least one new compound according to the invention, and their therapeutic use in the treatment of hyperglycaemic conditions such as diabetes and the pathologies associated with it, congestive heart failure and obesity.



WO 2006/092204 A1

DERIVATIVES OF AMINOBUTANOIC ACID INHIBITING CPT

FIELD OF THE INVENTION

The present invention describes a new class of compounds capable of inhibiting carnitine palmitoyl transferase (CPT); the invention also relates to pharmaceutical compositions, which comprise at least one new compound according to the invention, and their therapeutic use in the treatment of hyperglycaemic conditions such as diabetes and the pathologies associated with it, such as for example congestive heart failure and obesity.

BACKGROUND OF THE INVENTION

Known hypoglycaemic treatment is based on the use of drugs with a different mechanism of action (Arch. Intern. Med. 1997, 157, 1802-1817).

The more common treatment is based on insulin or its analogues, which uses the direct hypoglycaemic action of this hormone.

Other compounds act indirectly by stimulating the release of insulin (sulfonyl ureas). Another target of the hypoglycaemic drugs is the reduction of the intestinal absorption of glucose via the inhibition of the intestinal glucosidases, or the reduction of insulin resistance. Hyperglycaemia is also treated with inhibitors of gluconeogenesis such as the biguanides.

Some authors have shown the relationship between gluconeogenesis and the enzyme carnitine palmitoyl transferase.

Carnitine palmitoyl transferase catalyses the formation in the cytoplasm of palmitoyl carnitine (activated fatty acid) from carnitine and palmitoyl coenzyme A. Palmitoyl carnitine is different from palmitic acid in that it easily

crosses the mitochondrial membrane. Palmitoyl coenzyme A reconstitutes itself within the mitochondrial matrix, releasing carnitine. Palmitoyl coenzyme A is oxidised to acetyl-coenzyme A, which activates pyruvic carboxylase, a key enzyme in the gluconeogenic pathway.

5 Some authors report that diabetic patients have high blood levels of fatty acids which are oxidised in the liver producing acetylcoenzyme A, ATP and NADH. The high availability of these substances causes over-regulation of gluconeogenesis, with a subsequent increase in the level of blood glucose. In these situations, the inhibition of CPT would limit the oxidation of the fatty acids
10 and then, consequently, gluconeogenesis and hyperglycaemia. Inhibitors of CPT have been described in J.Med.Chem., 1995, 38(18), p.3448-50, and in the relevant European patent application EP-A-574355 as potential derivatives with hypoglycaemic action.

 The international patent application WO99/59957 in the name of the
15 Applicant describes and claims a class of derivatives of butyric acid which have displayed inhibitory action on CPT. An example of these compounds is R-4-trimethyl ammonium-3-(tetradecyl carbamoyl)-aminobutyrate (ST1326).

 It has recently been demonstrated that the inhibition of CPT-1 in the hypothalamus, produced experimentally by administering
20 intracerebroventricular inhibitors (icv), is capable of significantly and consistently reducing, in terms of extent and duration of the effect, food intake and gluconeogenesis (Nature Medicine, 2003, 9(6), 756-761). This property has also been demonstrated using the compound ST1326.

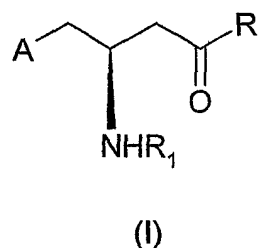
As regards the inhibition of CPT-1 it would therefore be important to be able to synthesize compounds which are able to cross the blood-brain barrier to be able to inhibit the CPT-1 in the hypothalamus and therefore have compounds which are effective in reducing food intake and gluconeogenesis.

- 5 These compounds as drugs would therefore be beneficial in the treatment of obesity and/or diabetes.

DESCRIPTION OF THE INVENTION

The present invention meets this requirement and, in particular, relates to new inhibitors of carnitine palmitoyl transferase with the following formula (I):

10



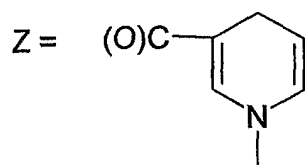
where:

A is selected among $-N(R_2R_3)$, $-N(R_2R_3R_4)^{\oplus}$ and $-C(R_2R_3R_4)$, in which the same

- 15 or different R_2 , R_3 , R_4 are selected among H, alkyl $C_1 - C_2$, phenyl, phenyl-alkyl $C_1 - C_2$;

R is selected among $-OH$, $-O^{\ominus}$, linear or branched alkoxy $C_1 - C_4$, optionally replaced by a carboxy or alkoxycarbonyl group $C_1 - C_4$, or the group Y-Z, in which:

- 20 Y = $-O-(CH_2)_n-O-$, $-O-(CH_2)_n-NH-$, $-S-(CH_2)_n-O-$, $-S-(CH_2)_n-NH-$, where n is selected among 1, 2 and 3, or $-O-(CH_2)_n-NH-$, where n is selected among 0, 1, 2 and 3; and



R_1 is selected among $-\text{COOR}_5$, $-\text{CONHR}_5$, $-\text{SOR}_5$, $-\text{SONHR}_5$, $-\text{SO}_2\text{R}_5$ and $-\text{SO}_2\text{NHR}_5$, in which

R_5 is a saturated or unsaturated, linear or branched alkyl $\text{C}_1 - \text{C}_{20}$, replaced by
 5 aryl $\text{C}_6 - \text{C}_{10}$, aryloxy $\text{C}_6 - \text{C}_{10}$, heteroaryl $\text{C}_4 - \text{C}_{10}$ containing 1 or more atoms
 selected among N, O and S, heteroaryloxy $\text{C}_4 - \text{C}_{10}$ containing 1 or more atoms
 selected among N, O and S, in turn replaced by saturated or unsaturated, linear
 or branched alkyl or alkoxy $\text{C}_1 - \text{C}_{20}$;

on condition that, when A is $-\text{N}(\text{R}_2\text{R}_3\text{R}_4)^{\oplus}$ and R_2 , R_3 and R_4 are the same and
 10 are alkyls, R is different from $-\text{OH}$ or $-\text{O}^{\ominus}$.

As regards other compounds known to be structurally and functionally
 similar, the compounds of the present invention have the advantage of crossing
 the BBB more easily, at the same time maintaining excellent levels of inhibition
 of the activity of CPT. They are therefore able to inhibit the activity of CPT in the
 15 hypothalamus thus presenting the effects in the reduction in food intake, as
 described above.

Preferably R_1 is $-\text{CONHR}_5$ and R_5 is a linear or branched alkyl, saturated
 or unsaturated, containing between 7 and 20 carbon atoms. The preferred R_5
 groups are therefore selected among heptyl, octyl, nonyl, decyl, undecyl,
 20 dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl,
 nonadecyl and eicosyl.

Preferably R_2 or R_3 or both are methyl.

Depending on the meanings of the radicals A, R_1 , R_2 , R_3 , R_4 , R_5 , Y and Z, in the compounds of formula (I), one or more chiral centres (on carbon or nitrogen atoms) may be present. For the purposes of the present invention it is pointed out that each of the products of formula (I) can exist both as a racemic mixture R/S, and in the separate isomeric forms R and S.

The products of formula (I), in which A is $-N(R_2R_3R_4)^{\oplus}$ and R is different from $-OH$ and $-O^{\ominus}$, can exist only as salts with pharmacologically acceptable anions. These anions are here identified by the radical X^- .

The products of formula (I) in which A is $-N(R_2R_3)$ can exist as internal salts, as salts with pharmacologically acceptable acids and also in anionic form without a positive net charge on the nitrogen in group A.

The products of formula (I) in which A does not contain nitrogen can exist in neutral or anionic form.

The present invention covers all these different possibilities of salification for the compounds of formula (I).

Preferred pharmaceutically acceptable salts (I) are acid addition salts formed with pharmaceutically acceptable acids like hydrochloride, hydrobromide, hydroiodide, sulfate or bisulfate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulfonate, benzenesulfonate, and para-toluenesulfonate salts.

Suitable pharmaceutically acceptable base addition salts for the compounds of the present invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Sodium salts are particularly preferred.

The compounds of formula (I) which do not contain positive or negative net charges are expected to be very efficient in crossing the blood-brain barrier.

The following are preferred compounds of formula (I):

- 10 (R)-4-(dimethyl amino)-3-(tetradecyl carbamoyl)- methyl aminobutyrate;
- (R)-4-(dimethyl amino)-3-(tetradecyl carbamoyl)-aminobutyric acid;
- (R)-4-(trimethyl amino)-3-(tetradecyl carbamoyl)-methyl aminobutyrate chloride;
- (R)-4-trimethylammonium-3-(tetradecylcarbamoyl)-amino-butyrate of {2[-(N-methyl-(1,4-dihydro-pyridine)-3-yl)carbonyl]-amino}ethyl iodide; and
- 15 (R)-4-trimethylammonium-3-(tetradecylcarbamoyl)-amino-butyrate of -3-(methoxycarbonyl)-propyl bromide.

The synthesis and the structure of these compounds is reported in detail in the section entitled Examples.

The products of formula (I) can be prepared using reactions known in the state of the art.

Examples of these reactions are reported in WO99/59957, *Eur. J. Org. Chem.* 2003, 4501-4505, *Eur. J. Med. Chem.* 39 (2004), 715-727 and *Helv. Chim. Acta* 1996, 79, 1203-1216.

As an example of this process, Figure 1 shows a synthetic Scheme for compounds of formula (I), in which A is $-N(R_2R_3R_4)^{\oplus}$, R_1 has any of the indicated meanings, R_2 , R_3 and R_4 are methyl and R has any of the indicated meanings. The following steps may be followed in this case.

5 Step a

To compound 1 obtained as described in Eur. J. Org. Chem. 2003, 4501-4505 a solution of dimethylamine in CH_3OH or THF, preferably THF, is added. The reaction mixture is left under magnetic stirring for a time ranging from 4 to 8 hours, preferably 4 hours, at a temperature ranging from 20° C to 40° C
10 preferably 25°C. The residue obtained by evaporation of the solvent is triturated several times with a polar solvent preferably diethyl ether. The ethereal layers are evaporated under vacuum and the residue purified by silica gel chromatography.

Step b

15 The preparation of compound 3, is performed by reacting compound 2 with an inorganic acid in water such as hydrochloric acid or hydrogen bromide preferably HBr/H_2O 48% in presence of an aromatic alcohol preferably phenol for a time ranging from 24 to 48 hours at a temperature ranging from 130 to 140°C.

20 Step c

Preparation of compound 4 is performed by reacting 3 with an alcohol preferably methanol and an acidic chloride such as oxalyl chloride or thionyl

chloride, preferably thionyl chloride at a temperature ranging from 0 to 40°C, for a time ranging from 12 to 24 hours.

Step d

Compound 5 (R = alkoxy) is obtained first by reacting 4 with an
5 appropriate reacting product selected among alkylisocyanate,
alkylchloroformates, alkylsulfonylchloride, preferably
alkylisocyanatealkylisocianate in anhydrous a polar organic solvent such as
CH₃OH or DMF or DMSO, preferably CH₃OH, in presence of an organic base,
preferably triethylamine, in the ratio ranging from 1:2 to 1:5, preferably 1:3, for a
10 time ranging from 24 to 48 hours at a temperature ranging from 20 to 30°C. The
pure product is obtained by silica gel chromatography. Finally, compound 5 (R =
OH) is obtained by acidic hydrolysis performed by inorganic acid, preferably
hydrochloric acid, ranging from 1N to 6N, preferably 2N, at 25° C for a time
ranging from 3 to 7 days.

15 Step h

Compound 4' obtained as described in WO44/59957 (WO99/59957), is
esterified by reacting with anhydrous alcohol such as CH₃OH, CH₃CH₂OH,
isopropanol, preferably CH₃OH and an acidic chloride such as oxalyl chloride or
thionyl chloride, preferably thionyl chloride or by bromoalkylmethoxycarbonile in
20 anhydrous solvent as DMF, CH₃CN, preferably anhydrous DMF..

Pure compounds 5' are obtained by solvent evaporation.

Step e

Compound 6 is obtained by reaction of 4' and hydroxyalkylnicotinamide with condensing agent as DCC or CDI, preferably DCC (ratio 1:1:4-5) in polar aprotic solvent such as CH_2Cl_2 , CHCl_3 or CH_3CN , preferably CH_2Cl_2 , for a time ranging from 24 to 36 hours at a ranging temperature from 20 to 30°C, preferably 25°C.

Step f

Product 7 is obtained by methylation of 6 by methylating agent such as methyl iodide in ratio 1:10-15 in anhydrous polar aprotic solvent such as CH_3CN , Et_2O or DMF, preferably anhydrous CH_3CN at ranging temperature from 20 to 30°C for a ranging time from 24 to 36 hours.

Step g

Product 8 is obtained by 7 by reaction with $\text{Na}_2\text{S}_2\text{O}_4$ (ratio 1:1-2), in presence of an inorganic base preferably NaHCO_3 , using as solvent a mixture of CH_2Cl_2 or CHCl_3 , preferably CH_2Cl_2 in water (9:2). PureFinal pure 8 is obtained by extraction with organic solvent as CH_2Cl_2 or CHCl_3 and evaporation.

The compounds of formula (I) have inhibitory activity on carnitine palmitoyl transferases. This action makes it possible to use them in the treatment and/or in the prevention of obesity, hyperglycaemia, diabetes and associated disorders such as, for example, diabetic retinopathy, diabetic neuropathy and cardiovascular disorders. The compounds of formula (I) are also used in the prevention and treatment of cardiac disorders such as congestive heart failure.

The inhibitory action of the compounds of formula (I) takes place mainly on isoform 1 of carnitine palmitoyl transferase (CPT-1) and, in particular, also in the hypothalamus.

A further object of the present invention are pharmaceutical compounds
5 containing one or more of the products of formula (I) described earlier, in combination with excipients and/or pharmacologically acceptable diluents.

The compounds in question may, together with the compounds of formula (I), contain known active principles.

The pharmaceutical compositions according to the present invention may be
10 adapted for oral, parenteral, rectal and transdermal administration. The oral forms include capsules, tablets, granules, powders, syrups and elixirs. The parenteral forms include solutions or emulsions.

The dosage of the products of the present invention vary depending on the type of product used, the route of administration and the degree of
15 development of the disease to be treated. In general an effective therapeutic effect can be obtained at dosages between 0.1-100 mg/kg.

The invention also includes the use of the products of formula (I) for the preparation of drugs with hypoglycaemic and anti-obesity action.

A further embodiment of the invention is a process for the preparation of
20 pharmaceutical compositions characterised by mixing one or more compounds of formula (I) with suitable excipients, stabilizers and/or pharmaceutically acceptable diluents.

Another object of the present invention is the method of treating a mammal suffering from hyperglycaemia, diabetes, obesity and associated disorders as reported before, comprising administering a therapeutically effective amount of the compound of formula (I).

5 The present invention is now illustrated by the following non-limitative examples.

DESCRIPTION OF THE DRAWINGS

Figure 1 shows a synthetic Scheme for compounds of formula (I), in which A is -
N(R₂R₃R₄)[⊕], R₁ has any of the meanings indicated for formula (I) compounds,
10 R₂, R₃ and R₄ are methyl and R has any of the meanings indicated for formula (I) compounds.

EXAMPLES

PREPARATION OF THE COMPOUNDS OF FORMULA (I)

Example 1

15 **Preparation of methyl (R)-4-(dimethylamino)-3-(tetradecylcarbamoyl)-amino-butyrate (ST 2669)**

Preparation of the intermediate isobutyl (R)-4-Dimethylamino-3-(toluene-4-sulfonyl amino)-butyrate

To 10 g (22.76 mmol) of (R)-4-iodo-3-(toluene-4-sulfonyl amino) butyrate
20 of isobutyl (preparation as described in *Eur. J. Org. Chem.* 2003, 4501-4505)
dimethyl amine (2.0 M in THF) (28.5 ml, 57 mmol) was added. The suspension
thus obtained was left under magnetic agitation for 4 hours. After this time the
solvent was evaporated under vacuum and the residue was triturated several

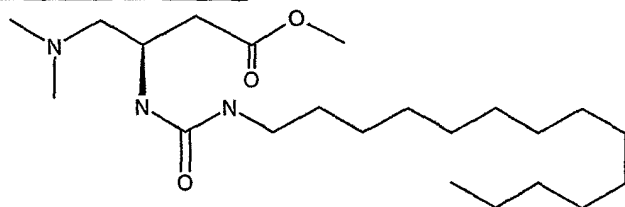
times with ethyl ether. The combined ether phases were evaporated under vacuum and the residue obtained was purified by means of chromatography on a silica gel column using as the eluent $\text{CHCl}_3/\text{MeOH}$ 99.5:0.5 to give 5.84 g of the desired product (72% yield). TLC: silica gel, eluent $\text{CHCl}_3/\text{MeOH}$ 9.6:0.4, $R_f=0.33$; ^1H NMR (300 MHz, MeOH-d_4) δ : 7.84 (d, 2 H, ArH), 7.46 (d, 2 H, ArH), 3.88-3.81 (m, 2H, CH_2), 3.80-3.63 (m, 1H, CH), 2.61-2.44 (m, 5H, CH, CH_3), 2.38-2.25 (m, 2H, CH_2), 2.15 (s, 6H, CH_3), 2.01-1.87 (m, 1H, CH), 1.00 (d, 6H, CH_2); HPLC: SCX column ($5\mu\text{m}$ -4.6 x 250 mm), mobile phase $\text{CH}_3\text{CN}/50\text{ mM NH}_4\text{H}_2\text{PO}_4$ 60/40 v/v, room temperature, flow rate: 0.8 ml/min, detector: UV 205 nm, retention time: 6.73 min.

Preparation of the intermediate methyl (R)-3-amino-4-(dimethylamino)-butyrate dibromohydrate

To the mixture of the above prepared compound (3.0 g, 8.4 mmol) and phenol (2.37 g, 25.2 mmol) HBr 48% in H_2O (45 ml) was added. The obtained solution was brought to 135°C for one night (N.B. the oil bath must already be up to temperature when the flask containing the solution is introduced). After this time the solution was diluted with water and extracted twice with AcOEt and the aqueous phase was evaporated under vacuum. The residue obtained was dissolved in acetonitrile and evaporated under vacuum several times. (R)-3-amino-4-(dimethyl amino) butyric dibromohydrate (2.47 g) was obtained (^1H NMR:(300 MHz, MeOH-d_4) δ : 3.60 (m, 1 H, CH), 2.70-2.42 (m, 4H, 2CH_2), 2.40 (s, 6H, 2CH_3)), which was used as such in the following reaction.

To a solution of the acid prepared as described above (2.47 g, 8 mmol) in anhydrous methanol (7.5 ml), cooled to 0° C, thionyl chloride (2.78 g, 1.7 ml, 24 mmol) was added. The reaction mixture was left under magnetic stirring for ten minutes at 0°C, then, for the same period at room temperature and finally for 12 hours at 40° C. After this time the reaction mixture was dried under vacuum and purified by means of flash chromatography on silica gel using as the eluent a gradient from CHCl₃/MeOH 9:1 to CHCl₃/MeOH 7:3. The intermediate dibromohydrate (1.37 g, 71% yield) was obtained $[\alpha]_D^{20} = -15.1^\circ$ (c = 1.6%, MeOH); ¹H NMR (300 MHz, MeOH-d₄) δ: 3.80 (s, 3H, CH₃), 3.63-3.57 (m, 1H, CH), 2.78-2.35 (m+s, 10H, CH₂, CH₃); A.E. in conformity with C₇H₁₈Br₂N₂O₂.

Preparation of methyl (R)-4-(dimethylamino)-3-(3-tetradecylcarbamoyl)- amino-butyrates (ST2669)

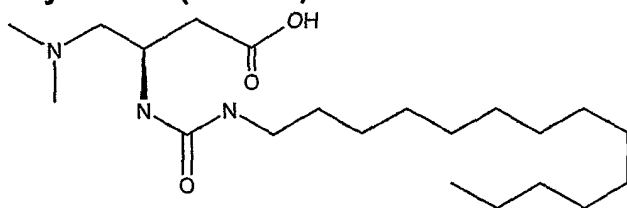


To a solution of methyl (3R)-3-amino-4-(dimethylamino)-butyrate dibromohydrate (1.28 g, 3.97 mmol) in anhydrous methanol (50 ml) triethyl amine (1.20 g, 1.65 ml, 11.91 mmol) was first added, followed by tetradecyl isocyanate (1.42 g, 1.63 ml, 5.95 mmol) at 0° C. The reaction mixture was left under magnetic stirring for 24 hours at room temperature, then the solvent was evaporated under vacuum. The crude product obtained was dissolved in EtOAc and washed with H₂O then with saturated solution of Na₂CO₃. The organic

phase was evaporated under vacuum and the residue is purified by means of flash chromatography on silica gel eluting with $\text{CHCl}_3/\text{MeOH}$ 9.6/0.4. The desired product (1.22 g, 77% yield) was obtained. M.p. 44-45° C; TLC: silica gel, eluent $\text{CHCl}_3/\text{MeOH}$ 8:2, $R_f = 0.32$; $[\alpha]_D^{20} = -28.4^\circ$ (c = 1%, MeOH); ^1H NMR (300 MHz, MeOH-d_4) δ : 4.21-4.10 (m, 1H, CH), 3.65 (s, 3H, CH_3), 3.08 (t, 2H, CH_2), 2.59-2.45 (m, 2H, CH_2), 2.43-2.29 (m, 2H, CH_2), 2.24 (s, 6H, CH_3), 1.45 (m, 2H, CH_2), 1.28 (s, 22H, CH_2), 0.89 (t, 3H, CH_3); HPLC: SCX column (5 μm -4.6 x 250 mm), mobile phase: $\text{CH}_3\text{CN}/50 \text{ mM } \text{NH}_4\text{H}_2\text{PO}_4$ 60/40 v/v, room temperature, flow rate: 0.8 ml/min, detector: UV 205 nm, retention time: 5.69 min; MS (ESI) 400 $[\text{M}+1]^+$, 422 $[\text{M}+\text{Na}]^+$; H_2O ; A.E. in conformity with $\text{C}_{22}\text{H}_{45}\text{N}_3\text{O}_3$.

Example 2

Preparation of (R)-4-(dimethylamino)-3-(tetradecylcarbamoyl)-butyric acid (ST2837)

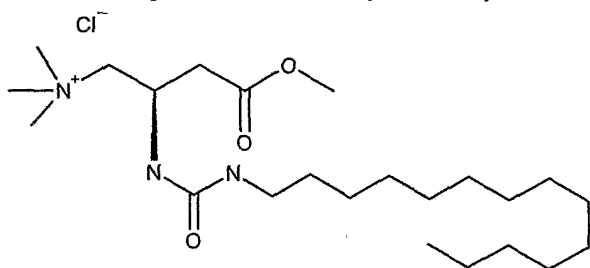


To the product prepared as described in example 1 (ST2669, 0.180 g, 0.45 mmol) an aqueous solution of HCl 6N (3.5 ml) was added. The reaction mixture was left under magnetic stirring at room temperature for one week. After this time the reaction mixture was evaporated under vacuum and the residue was purified by means of flash chromatography on silica gel using as the eluent a gradient from $\text{CHCl}_3/\text{MeOH}$ 8:2 to $\text{CHCl}_3/\text{MeOH}$ 1:1. The desired product (67

mg, 38% yield) was obtained. TLC: silica gel, eluent: CHCl₃/MeOH 7:3, R_f = 0.40; [α]²⁰_D = -8.4° (c = 0.5%, MeOH); ¹H NMR (300 MHz, MeOH-d₄) δ: 4.34-4.26 (m, 1H, CH), 3.30-3.10 (m, 4H, CH₂), 2.90 (s, 6H, CH₃), 2.58 (d, 2H, CH₂), 1.55 (m, 2H, CH₂), 1.40 (s, 22H, CH₂), 1.00 (t, 3H, CH₃); HPLC: SCX
5 column (5 μm - 4.6 x 250 mm), mobile phase: CH₃CN/50 mM NH₄H₂PO₄ 40/60 v/v, pH=3.7 (H₃PO₄), room temperature, flow rate: 0.8 ml/min, detector: UV 205 nm, retention time: 8.09 min; K.F. = 2.3% H₂O; A.E. in conformity with C₂₁H₄₃N₃O₃.

Example 3

10 Preparation of methyl (R)-4-trimethylammonium-3-(tetradecylcarbamoyl)-amino-butyrate chloride (ST2822)



To the solution of (R)-4-trimethylammonium-3-(tetradecylcarbamoyl)-amino-butyrate (ST1326, prepared as described in WO99/59957) (1.20 g, 3.00
15 mmol) in anhydrous MeOH (6 ml) thionyl chloride (1.80 g, 1.10 ml, 15.13 mmol) was added added, at 0°C and drop by drop,, leaving the solution under stirring at 40° C for 72 hours. After drying under vacuum, the reaction mixture was washed with anhydrous ethyl ether. The oil obtained was purified using flash chromatography on silica gel (eluent used MeOH/CHCl₃ 1:1). The product
20 obtained was dissolved in anhydrous dichloromethane and filtered through a

Millex-HV Hydrophilic PVDF 0.45 μm (Millipore) filter. By evaporating the solvent under vacuum the desired product was obtained (164 mg, 12% yield).

TLC: silica gel, eluent (42:7:28:10.5:10.5 $\text{CHCl}_3/\text{isopropanol}/\text{MeOH}/\text{CH}_3\text{COOH}/\text{H}_2\text{O}$), $R_f = 0.83$; $[\alpha]_D^{20} = -8.5^\circ$ ($c = 1\%$,

5 MeOH); ^1H NMR (300 MHz, $\text{MeOH}-d_4$) δ : 4.65 (br s, 1H, CH), 3.70 (s, 3H, CH_3), 3.65-3.40 (m, 2H, CH_2); 3.20 (s, 9H, CH_3), 3.10 (t, 2H, CH_2), 2.70 (m, 2H, CH_2), 1.45-1.40 (m, 2H, CH_2), 1.30 (s, 22H, CH_2), 0.90 (t, 3H, CH_3);
HPLC: SCX column ($5\mu\text{m}$ -4.6 x 250 mm), mobile phase $\text{CH}_3\text{CN}/50\text{ mM}$ $\text{NH}_4\text{H}_2\text{PO}_4$ 40/60 v/v, room temperature, flow rate: 0.8 ml/min, detector: UV
10 205 nm, retention time: 10.94 min; MS (ESI) 355 $[\text{M}-(\text{CH}_3)_3\text{N}]^+$, 414 $[\text{M}]^+$; K.F. = 1.8% H_2O ; A.E. in conformity with $\text{C}_{23}\text{H}_{48}\text{N}_3\text{O}_3\text{Cl}$.

Example 4

**Preparation of (R)-4-trimethylammonium-3-(tetradecylcarbamoyl)-amino-butyr-
ate of {2[-(N-methyl-(1,4-dihydro-pyridine)-3-yl)carbonyl]-amino}ethyl
15 iodide (ST3496)**

Preparation of the intermediate N-(2-hydroxy-ethyl)-nicotinamide

SOCl_2 (455 μl , 6.26 mmol)) was added to a suspension of nicotinic acid (0.385 g, 3.13 mmol) in anhydrous toluene (15 ml) and the reaction mixture was refluxed at 140°C for 4 hours. Then the clear solution was cooled and the
20 solvent was removed under vacuum. The solid residue was washed three times with diethyl ether and fresh anhydrous toluene (15 ml) and ethanolamine (756 μl , 12.52 mmol) were added. The mixture was warmed up to 50°C overnight.

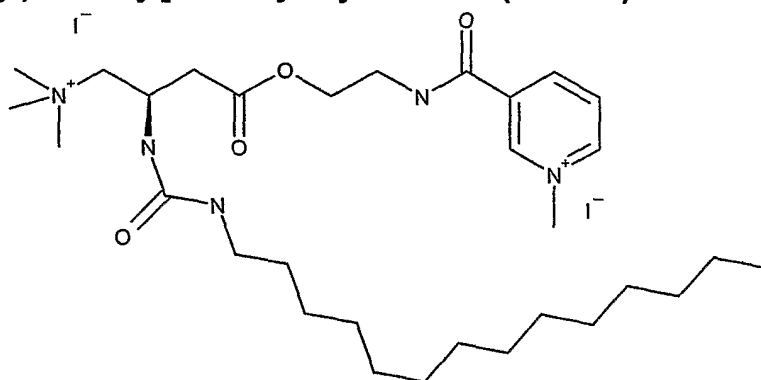
Then the solvent was removed under vacuum and the solid residue was purified by silica gel chromatography using as eluent dichloromethane/methanol 9.2/0.8. The desired product was obtained as a white solid (450 mg, 86% yield). m.p. = 84.5-85.5°C; ¹H NMR (300MHz, DMSO-d₆) δ: 9.00 (s, 1H, NH), 8.68, (m, 2H, Ar), 8.17 (d, 1H, Ar), 7.60 (m, 1H, Ar), 4.74 (m, 1H, OH), 3.51 (m, 2H, CH₂), 3.36 (m, 2H, CH₂).

Preparation of the intermediate (R)-4-trimethylammonium-3-(tetradecylcarbamoyl)-amino-butyrate of {2-[(pyridin-3-yl)carbonyl]-amino}ethyl chloride

To a solution of N-(2-hydroxy-ethyl)-nicotinamide (0.274 g, 1.65 mmol) in anhydrous dichloromethane (16 ml) (R)-4-trimethylammonium-3-(tetradecylcarbamoyl)-amino-butyrate hydrochloride (0.719 g, 1.65 mmol, prepared by adding an equivalent of hydrochloric acid 1N to ST1326 prepared as described in WO99/59957) and dicyclohexylcarbodiimide (DCC) (1.018 g, 5.00 mmol) were added. The reaction mixture was left overnight at room temperature under magnetic stirring. Then the mixture was filtered and the organic layer was concentrated under vacuum. The residue was washed several times with diethyl ether to give, after desiccation under vacuum, the desired product as a white solid (769 mg, 79% yield). TLC: silica gel, eluent CHCl₃/isopropanol/MeOH/CH₃COOH/H₂O 42:7:28:10.5:10.5, R_f = 0.5; ¹H NMR (300MHz, MeOH-d₄) δ: 9.05 (d, 1H, Ar), 8.70 (d, 1H, Ar), 8.30 (dm, 1H, Ar), 7.55 (m, 1H, Ar), 4.70 (brs, 1H, CH), 4.31 (t, 2H, CH₂), 3.70 (t, 2H, CH₂), 3.70-3.50 (m, 2H, CH₂), 3.25 (s, 9H, N(CH₃)₃), 3.04 (t, 2H, CH₂), 2.68 (t, 2H,

CH₂), 2.43 (brm, 2H, CH₂), 2.28 (s, 24H, (CH₂)₁₂), 0.95 (t, 3H, CH₃); MS (ESI) 548 [M]⁺.

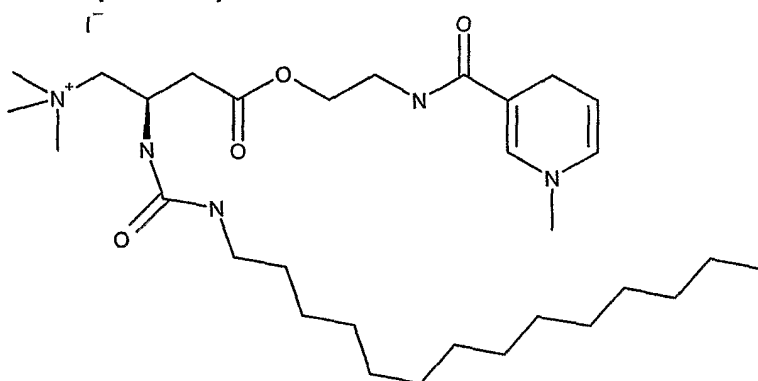
**Preparation of the intermediate (R)-4-trimethylammonium-3-(tetradecylcarbamoyl)-amino-butyr-
5 (tetradecylcarbamoyl)-amino-butyr-ate of {2-(N-methylpyridin-3-yl)carbonyl]-amino}ethyl diiodide (ST3474)**



Methyl iodide (747 μ l, 12.00 mmol) was added to a solution of (R)-4-trimethylammonium-3-(tetradecylcarbamoyl)-amino-butyr-ate of {[(pyridin-3-yl)carbonyl]-amino}ethyl chloride (0.700 g, 1.2 mmol) in anhydrous CH₃CN (40 ml) and the so obtained reaction mixture was left under magnetic stirring at room temperature overnight. Then the solvent was removed under vacuum and the desired product (957 mg, 98% yield) was obtained. M.p.: 179-181°C; TLC: silica gel, eluent CHCl₃/isopropanol/MeOH/CH₃COOH/H₂O 42:7:28:10.5:10.5, R_f: 0.3; [α]_D²⁰ = -0.8° (c = 2%, MeOH); ¹H NMR (300MHz, MeOH-d₄) δ : 9.48 (s, 1H, Ar), 9.00 (dd, 2H, Ar), 8.20 (t, 1H, Ar), 4.75 (brm, 1H, CH), 4.51 (s, 3H, CH₃), 4.32 (t, 2H, CH₂), 3.70 (m, 4H, 2CH₂), 3.25 (s, 9H, N(CH₃)₃), 3.10 (t, 2H, CH₂), 2.75 (dd, 2H, CH₂), 1.42 (brm, 2H, CH₂), 1.30 (s, 22H, (CH₂)₁₁), 0.90 (t, 3H, CH₃); HPLC: Column: Waters Spherisorb S5 SCX(4.6 x 250 mm), mobile

phase: CH₃CN/ NH₄H₂PO₄ 200mM, 60/40 v/v, pH as it is, room temperature,
flow rate: 1.0 ml/min, detector: UV 254 nm, retention time: 20.60 min; MS (ESI)
281 [M]⁺/2; K.F. = 2.70% H₂O; A.E. in conformity with C₃₁H₅₇N₅O₄I₂.

Preparation of (R)-4-trimethylammonium-3-(tetradecylcarbamoyl)-amino-
5 **butyrate of {2[-(N-methyl-(1,4-dihydro-pyridine)-3-yl)carbonyl]-amino}ethyl**
iodide (ST3496)

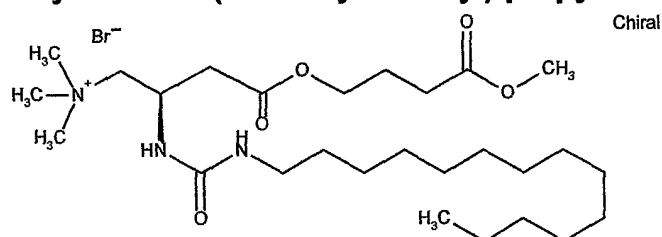


To a solution of (R)-4-trimethylammonium-3-(tetradecylcarbamoyl)-
amino-butyrate of {2[-(N-methylpyridin-3-yl)carbonyl]-amino}ethyl diiodide,
10 prepared as above described (ST3474, 0.100 g, 0.12 mmol) in degased water
(18 ml) chilled to 0°C and under argon atmosphere NaHCO₃ (0.200g, 1.2
mmol), Na₂S₂O₄ (0.046g, 0.26 mmol), both dissolved in 11 ml of a mixture of
water and dichloromethane 9/2 were added. The reaction mixture was left under
magnetic stirring at 0°C for 15 minutes and then for other 30 minutes at room
15 temperature. The organic layer was then separated from water and the aqueous
layer was extracted several times with dichloromethane. The combined organic
layers were dried over Na₂SO₄ then concentrated to give the final product
(0.084 g, 94% yield), which was kept under vacuum to avoid degradation. TLC:
silica gel, eluent CHCl₃/isopropanol/MeOH/CH₃COOH/H₂O 42:7:28:10.5:10.5,

R_f: 0.7; ¹H NMR (300MHz, DMSO-d₆) δ: 7.16 (t, 1H, NH), 6.80 (s, 1H, CH=CH), 6.25 (m, 2H, 2NH), 5.80 (d, 1H, CH=CH), 4.60 (m, 1H, CH=CH), 4.48 (brm, 1H, CH), 4.05 (m, 2H, CH₂), 3.75-3.05 (brm, 4H, 2CH₂), 3.09 (s, 9H, N(CH₃)₃), 2.95 (brs, 4H, 2CH₂), 2.87 (s, 3H, NCH₃), 2.57 (brt, 2H, CH₂), 1.32 (brs, 2H, CH₂),
 5 1.20 (s, 22H, (CH₂)₁₁), 0.82 (t, 3H, CH₃); MS (ESI) 564 [M]⁺; A.E. in conformity with C₃₁H₅₈N₅O₄l.

Example 5

Preparation of (R)-4-trimethylammonium-3-(tetradecylcarbamoyl)-amino-butyrates of -3-(methoxycarbonyl)-propyl bromide (ST3193)



10

Methyl-4-bromo-butyrates was added (0.460 mg 2.54 mmol) to a solution of (R)-4-trimethylammonium-3-(tetradecylcarbamoyl)-amino-butyrates (1.015 g, 2.54 mmol) in 12 ml of anhydrous DMF. The reaction mixture was kept at 50 °C under magnetic stirring overnight. The solvent was then evaporated to give the
 15 desired product as a pale yellow waxy solid (1.108 g, 87% yield).; TLC: silica gel, eluent 42:7:28:10.5:10.5 CHCl₃/isopropanol/MeOH/CH₃COOH/H₂O, R_f = 0.6; [α]_D²⁰ = -7.6° (c = 1%, MeOH); ¹H NMR (300 MHz, MeOH-d₄) δ: 4.67 (brm, 1H, CH), 4.17 (t, 2H, CH₂), 3.70 (s, 3H, CH₃), 3.72-3.46 (m, 2H, CH₂), 3.30 (s, 9H, CH₃), 3.12 (t, 2H, CH₂), 2.68 (m, 2H, CH₂), 2.44 (t, 2H, CH₂), 1.96 (brm, 2H, CH₂), 1.48 (brs, 2H, CH₂), 1.30 (s, 24H, (CH₂)₁₂), 0.91 (t, 3H, CH₃);
 20

HPLC: SCX column (5 μ m-4.6 x 250 mm), mobile phase: CH₃CN/ NH₄H₂PO₄ 50 mM, 40/60 v/v, pH 3.6, room temperature, flow rate: 0.8 ml/min, detector: UV 205 nm, retention time: 10.08 min; MS (ESI) 500 [M]⁺; K.F. = 0.88% H₂O; A.E. in conformity with C₂₇H₅₄N₃O₅Br.

5 **DETERMINATION OF THE PHARMACOLOGICAL ACTIVITY OF THE COMPOUNDS OF FORMULA (I)**

Test 1: Determination of the inhibitory action of CPT

The inhibition of CPT was evaluated on fresh mitochondrial preparations obtained from the liver or heart of Fischer rats, fed normally; the mitochondria
10 taken from the liver or heart are suspended in a 75 mM sucrose buffer, EGTA 1 mM, pH 7.5. 100 μ l of a mitochondrial suspension, containing 50 μ M of [¹⁴C] palmitoyl-CoA (spec.act. 10000 dpm/mole) and 10 mM of L-carnitine, are incubated at 37 °C in the presence of stepped concentrations (0-3 mM) of product under examination.

15 Reaction time: 1 minute.

The IC₅₀ is then determined. The results are reported in Table 1.

Table 1: IC₅₀ of the inhibition curve of CPT1 in rat mitochondria

Substance	IC ₅₀ of CPT1 liver (μ M)	IC ₅₀ of CPT1 heart (μ M)
ST1326	0.36	48.8
ST2837	5.7	70

Test 2: Determination of the production of β -hydroxybutyrate stimulated by
20 oleate

The synthesis of β -hydroxybutyrate is an indication of the activity of CPT. In fact the production of ketone bodies, end-products of mitochondrial beta-oxidation, is linked to the activity of CPT.

Hepatocytes preparations obtained according to the technique described in

5 Venerando R. et al. (1994) Am. J. Physiol. 266: C455-C461] are used.

The hepatocytes are incubated at 37°C in KRB bicarbonate buffer at pH 7.4, glucose 6 mM, 1 % BSA in a O₂/CO₂ 95/5 % atmosphere at the concentration of 2.5 x 10⁶ cells/ml. After a preincubation period of 40 min. with a compound to be assayed at different concentrations, the first series of samples is taken (T_{0 min})

10 and the oleate is added (1 mM final in KRB + BSA 1.4%). After 20 mins the second sample is taken (T_{20 min})

Test 3: β -hydroxy butyrate in the serum of treated rats

Fischer rats, normally fed, are kept in a fasting state for 24 hours and then treated with the compounds to be tested. One hour after the treatment the

15 animals are sacrificed and the serum concentrations of β -hydroxy butyrate are determined.

Other tests

The ability of these compounds to cross the blood-brain barrier in rats or mice after oral or intravenous administration is measured on brain homogenates

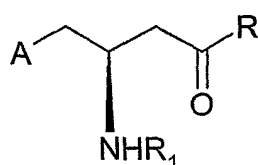
20 using HPLC-MS techniques. From preliminary data the compounds of the invention were shown to be able to efficiently cross the blood-barrier.

Furthermore the evaluation of food intake after oral or intravenous administration is determined in rats with access to food ad libitum or on a time-restricted basis, for acute or fasting administration.

Finally the lowering of glycaemia for oral or intracerebroventricular
5 administration in diabetic mice, for example db/db mice, is measured.

CLAIMS

1. Compound in the racemic form (R,S) or in their R and S enantiomeric forms, and their pharmacologically acceptable salts, having the structure of formula (I):



(I)

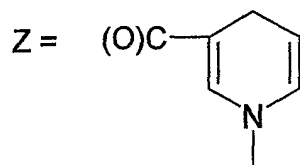
where:

A is selected among $-N(R_2R_3)$, $-N(R_2R_3R_4)^{\oplus}$ and $-C(R_2R_3R_4)$, in which the

10 same or different R_2 , R_3 , R_4 are selected among H, alkyl $C_1 - C_2$, phenyl, phenyl-alkyl $C_1 - C_2$;

R is selected among $-OH$, $-O^{\ominus}$, linear or branched alkoxy $C_1 - C_4$, optionally replaced by a carboxy or alkoxy carbonyl group $C_1 - C_4$, or the group Y-Z, in which:

15 Y = $-O-(CH_2)_n-O-$, $-O-(CH_2)_n-NH-$, $-S-(CH_2)_n-O-$, $-S-(CH_2)_n-NH-$, where n is selected among 1, 2 and 3, or $-O-(CH_2)_n-NH-$, where n is selected among 0, 1, 2 and 3; and



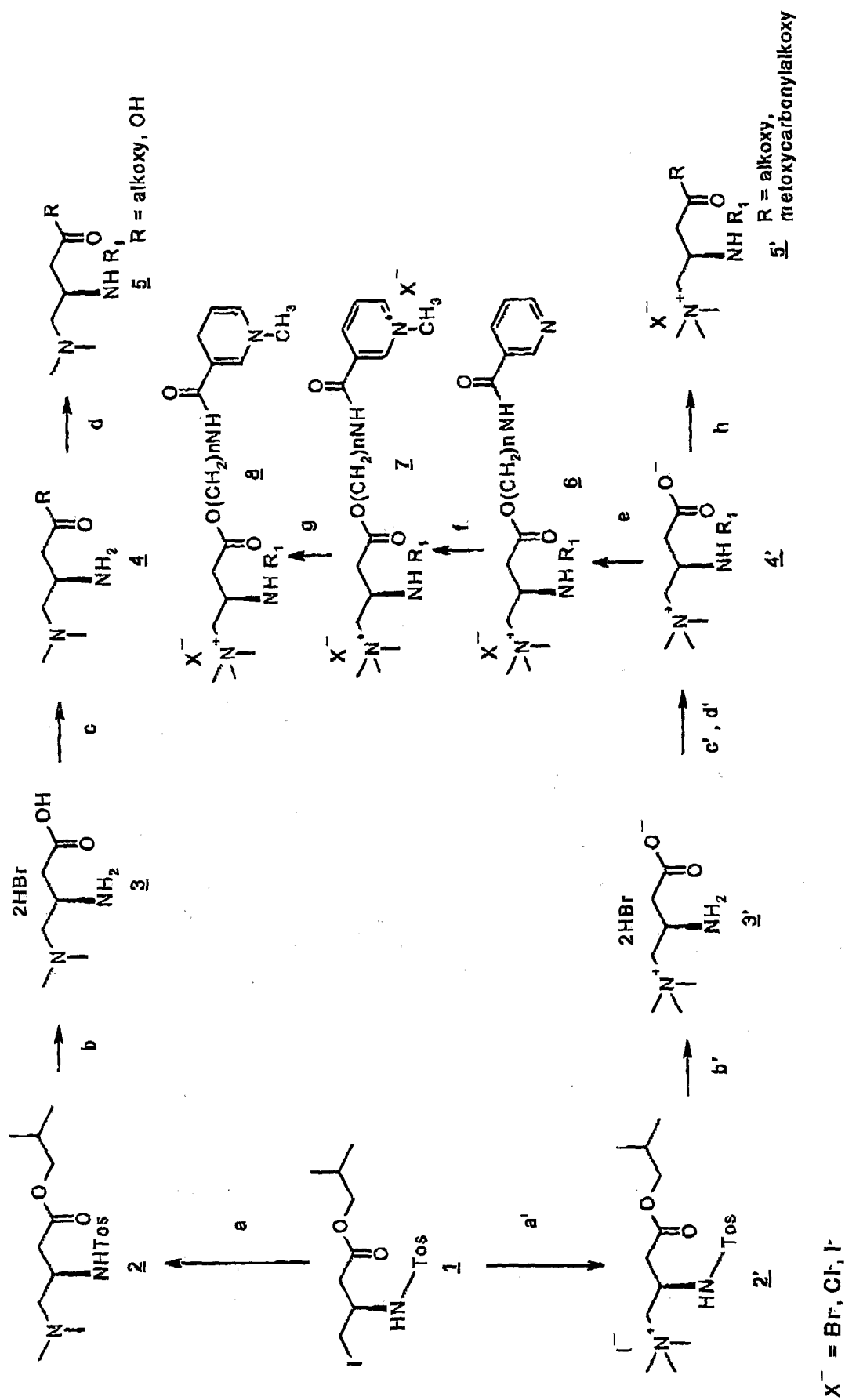
R_1 is selected among $-COOR_5$, $-CONHR_5$, $-SOR_5$, $-SONHR_5$, $-SO_2R_5$ and -

20 SO_2NHR_5 , in which

- R₅ is a saturated or unsaturated, linear or branched alkyl C₁ – C₂₀, replaced by aryl C₆–C₁₀, aryloxy C₆–C₁₀, heteroaryl C₄–C₁₀ containing 1 or more atoms selected among N, O and S, heteroaryloxy C₄–C₁₀ containing 1 or more atoms selected among N, O and S, in turn replaced by saturated or unsaturated, linear or branched alkyl or alkoxy C₁–C₂₀;
- with the proviso that when A is -N(R₂R₃R₄)[⊕] and R₂, R₃ and R₄ are the same and are alkyl, R is different from -OH or -O[⊖].
2. The compound according to Claim 1, where R₂, R₃ and R₄ are methyl.
 3. The compound according to Claim 1, where R₁ is -CONHR₅.
 4. The compound according to Claim 3, where R₅ is a linear or branched, saturated or unsaturated alkyl containing from 7 to 20 carbon atoms.
 5. The compound according to Claims 3 or 4, where R₅ is selected among heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl and eicosyl.
 6. The compound according to claim 1, which is (R)-4-(dimethyl amino)-3-(tetradecyl carbamoyl)-methyl aminobutyrate.
 7. The compound according to claim 1, which is (R)-4-(dimethyl amino)-3-(tetradecyl carbamoyl)-aminobutyric acid.
 8. The compound according to claim 1, which is (R)- 4-(trimethyl amino)-3-(tetradecyl carbamoyl)-methyl aminobutyrate chloride.
 9. The compound according to claim 1, which is (R)-4-trimethylammonium-3-(tetradecylcarbamoyl)-amino-butyrate of {2[-(N-methyl-(1,4-dihydro-pyridine)-3-yl)carbonyl]-amino}ethyl iodide.

10. The compound according to claim 1, which is (R)-4-trimethylammonium-3-(tetradecylcarbamoyl)-amino-butyrates of -3-(methoxycarbonyl)-propyl bromide.
11. Process for the preparation of the compound of any claims from 1 to 10.
- 5 12. The compound according to Claims 1 to 10, for use in therapy.
13. Pharmaceutical composition containing as active ingredient one or more of the compounds according to Claims 1 to 10 in combination with excipients and/or pharmaceutically acceptable diluents.
14. Process for the preparation of the pharmaceutical composition according to claim 13, comprising mixing one or more compounds according to Claims 1 to 10 with excipients, stabilizers and/or pharmaceutically acceptable diluents.
- 10 15. Use of the compound according to Claims 1 to 10 for the preparation of a drug for the treatment of the disorders associated with hyperactivity of carnitine palmitoyl transferase.
- 15 16. The use according to Claim 15, for the prevention and treatment of obesity, hyperglycaemia, diabetes and related disorders, and congestive heart failure.
17. Method of treating a mammal suffering from hyperglycaemia, diabetes, obesity and associated disorders, comprising administering a therapeutically effective amount of one or more compounds according to Claims 1 to 10.
- 20

FIGURE 1



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/001290

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C275/16 C07D211/90 C07D213/82 A61K31/17 A61P3/10

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)

C07C C07D A61K A61P

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)

EP0-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"A practical and stereoconservative synthesis of (R)-3-amino-4-(trimethyl-ammonio)butanoate [(R)-aminocarnitine], and its trimethylphosphonium and simple ammonium analogues starting from D-aspartic acid" EUR. J. ORG. CHEM., vol. 4, 2003, pages 4501-4504, XP002375602 cited in the application Compound 2b (figure 1, page 4501). Compounds 7-8 (scheme 1, page 4502). Paragraph 1, page 4501. ----- -/--	1-17

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

21 April 2006

Date of mailing of the international search report

12/05/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Menchaca, R

International application No
PCT/EP2006/001290

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	P. GMEINER: "GENERAL SYNTHESIS OF ENANTIOMERICALLY PURE BETA-AMINOACIDS" TETRAHEDRON LETTERS, vol. 31, no. 40, 1990, pages 5717-5720, XP002375604 Compound 8 (scheme 4, page 5719).	1,3,4,11
A	-----	13-15,17
X	PHYSIOL. CHEM., vol. 158, 1926, pages 32-41, XP008062603 Lines 13, 23-24 (page 38), lines 12-13 (page 39).	1,3,11
X	-----	
X	WO 99/59957 A (SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.P.A; GIANNESSI, FABIO; MAR) 25 November 1999 (1999-11-25) cited in the application Compounds 1a-b (figure 1). First paragraph (page 1). Examples 1, 6-7. Claims 1-21	1,2, 11-17
X	-----	
X	EP 1 484 313 A (SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.P.A) 8 December 2004 (2004-12-08) Example 14 (pages 17-18). Paragraph [0016], page 3.	1,2, 11-17
X	-----	
X	US 2003/153784 A1 (GIANNESSI FABIO ET AL) 14 August 2003 (2003-08-14) Compounds 6a, 7a (Example 1, page 5). Paragraph [0012] (page 1).	1,2, 11-17
X	-----	
X	CHARLES W JEFFORD ET AL: "The Enantioselective Synthesis of beta-Amino Acids, their alpha-Hydroxy Derivatives and the N-Terminal Components of Bestatin and Microginin" HELVETICA CHIMICA ACTA, VERLAG HELVETICA CHIMICA ACTA. BASEL, CH, vol. 79, 1996, pages 1203-1216, XP002152295 ISSN: 0018-019X cited in the application Compounds 10a-d, 11a-d (scheme 1, page 1204).	1,2,11
A	-----	13-15,17
X	C. W. JEFFORD AND J. WANG: "An enantiospecific synthesis of beta-aminoacids" TETRAHEDRON LETTERS, vol. 34, no. 7, 1993, pages 1111-1114, XP002375603 Compounds 6-10, 12-16 (scheme 1, page 1112).	1,2,11
A	-----	13-15,17

-/-

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/001290

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	"Reversible Carnitine Palmitoyltransferase inhibitors with broad chemical diversity as potential antidiabetic agents" JOURNAL OF MEDICINAL CHEMISTRY, vol. 44, no. 15, 2001, pages 2383-2386, XP002375605 the whole document -----	1,13-15, 17
A	"Discovery of a long-chain carbamoyl aminocarnitine derivative, a reversible carnitine palmitoyltransferase inhibitor with antiketotic and antidiabetic activity" JOURNAL OF MEDICINAL CHEMISTRY, vol. 46, 2003, pages 303-309, XP002375606 the whole document -----	1,11, 13-15,17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/001290

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of 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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims 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. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box 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:

see additional sheet

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 an additional fee, this Authority did not invite payment of any additional fee.
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 claims 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 claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: claims: 1-5 (in part), claim: 7, claims: 11-17 (in part)

Compounds according to formula (I) in claim 1 wherein, R= OH, O-. A process for their preparation, pharmaceutical compositions and therapeutical use thereof.

2. claims: claims: 1-5 (in part), claims: 6, 8-10, claims: 11-17 (in part)

Compounds according to formula (I) in claim 1 wherein, R= linear or branched optionally substituted alkoxy C1-C4. A process for their preparation, pharmaceutical compositions and therapeutical use thereof.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/001290

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9959957	A	25-11-1999	AT 276230 T 15-10-2004
		AU 3847399 A	06-12-1999
		CA 2329930 A1	25-11-1999
		DE 69920208 D1	21-10-2004
		DE 69920208 T2	20-10-2005
		EP 1077925 A1	28-02-2001
		ES 2230854 T3	01-05-2005
		HK 1033573 A1	15-07-2005
		IT MI981075 A1	15-11-1999
		JP 2003513002 T	08-04-2003
		PT 1077925 T	31-12-2004
		US 6369073 B1	09-04-2002
EP 1484313	A	08-12-2004	NONE
US 2003153784	A1	14-08-2003	NONE