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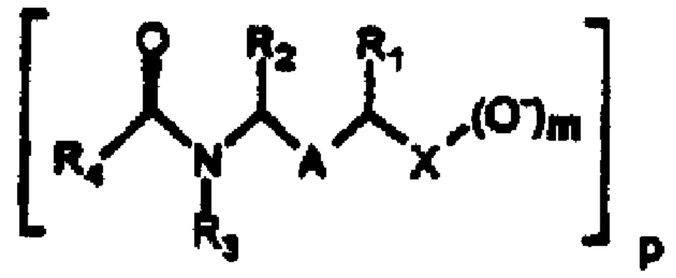
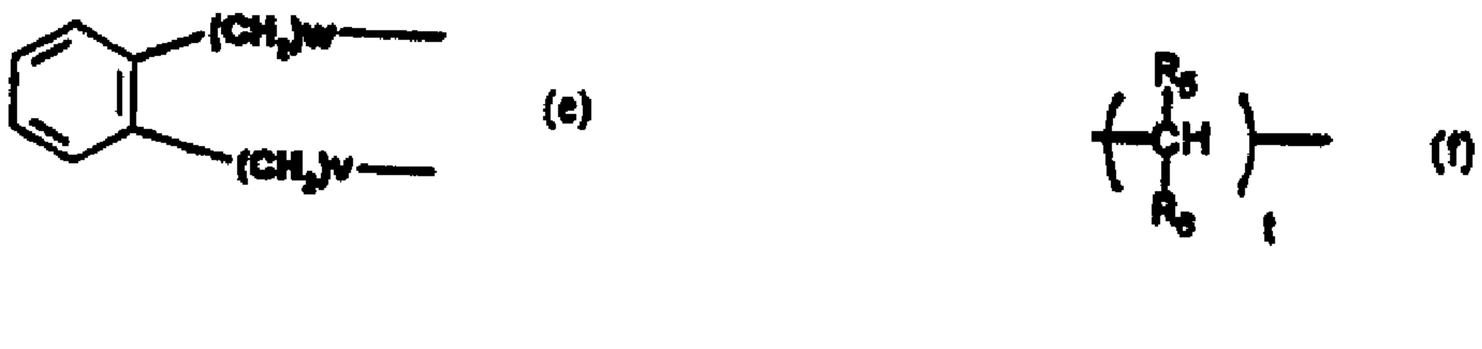
(54) Titre : NOUVEAUX DERIVES D'ACIDES AMINOALKANE SULFONIQUES, PHOSPHONIQUES ET PHOSPHINIQUES, LEUR PREPARATION ET LEUR UTILISATION COMME MEDICAMENTS

(54) Title: NOVEL AMINOALKANESULPHONIC, -PHOSPHONIC AND -PHOSPHINIC ACID DERIVATIVES, THEIR PREPARATION AND THEIR USE AS MEDICAMENTS



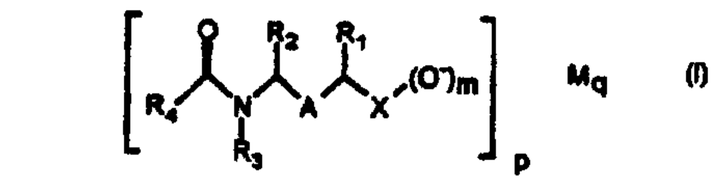
(I)

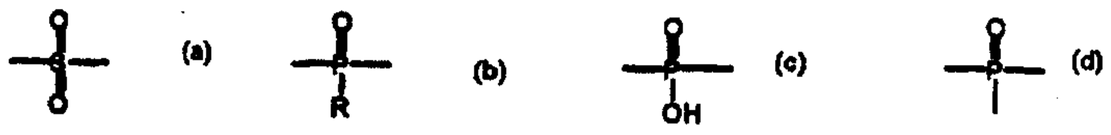


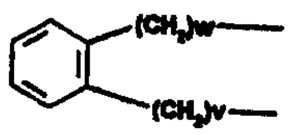
(57) Abrégé/Abstract:
The invention relates to new derivatives of sulfonic, phosphonic or phosphinic aminoalkane acids, corresponding to formula (I), where X is selected from among (a), (b), (c) and (d), where R is a C_1-C_7 alkyl radical, R_1, R_2 and R_3 are selected from hydrogen and a C_1-C_7 alkyl radical, and A is a group of formula (e) where v and w are 0, 1, 2 or a group of formula (f) where R_5 and R_6 are selected independently of each other from hydrogen, a C_1-C_7 alkyl radical, an aryl radical having between 6 and 14 carbon atoms and a heteroaryl radical; t is 1-3; R_4 is selected from hydrogen, a C_1-C_7 alkyl radical, a CF_3 radical, an aryl radical having between 6 and 14 carbon atoms and a heteroaryl radical; M is a monovalent metal (Na, K, Li) or divalent metal (Ca, Mg, Sr, Zn); m is 1 or 2; p is 1-2 and q is 1-2; and where p and q are such that the electrical neutrality of the salt is ensured. The above components can be used for the treatment of alcohol dependence.

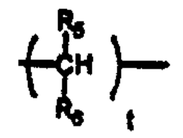
(57) Abstract

The invention relates to new derivatives of sulfonic, phosphonic or phosphinic aminoalkane acids, corresponding to formula (I), where X is selected from among (a), (b), (c) and (d), where R is a C_1–C_7 alkyl radical, R_1, R_2 and R_3 are selected from hydrogen and a C_1–C_7 alkyl radical, and A is a group of formula (e) where v and w are 0, 1, 2 or a group of formula (f) where R_5 and R_6 are selected independently of each other from hydrogen, a C_1–C_7 alkyl radical, an aryl radical having between 6 and 14 carbon atoms and a heteroaryl radical; t is 1–3; R_4 is selected from hydrogen, a C_1–C_7 alkyl radical, a CF_3 radical, an aryl radical having between 6 and 14 carbon atoms and a heteroaryl radical; M is a monovalent metal (Na, K, Li) or divalent metal (Ca, Mg, Sr, Zn); m is 1 or 2; p is 1–2 and q is 1–2; and where p and q are such that the electrical neutrality of the salt is ensured. The above components can be used for the treatment of alcohol dependence.





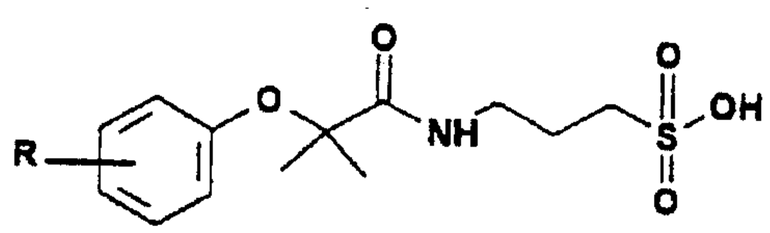




"Novel aminoalkanesulphonic, -phosphonic and -phosphinic acid derivatives, their preparation and their use as medicaments"

The present invention relates to sulphonic, phosphonic and phosphinic acid derivatives intended for the treatment of dependency on alcohol and on other substances.

Japanese Patent JP 7612093 discloses compounds of formula:

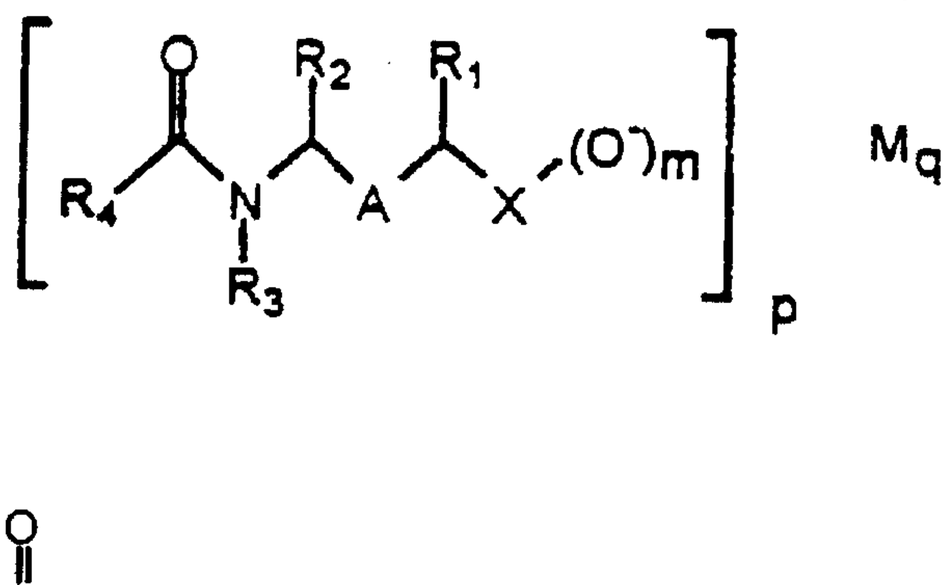


as hypocholesterolaemics

Japanese Patent JP 63201643 discloses the use of potassium 4-palmitylsulphonate as adjuvant in photographic substrates.

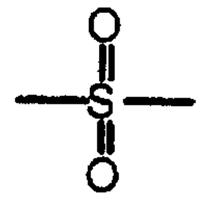
FR-A-2,457,281 has disclosed acetylhomotaurine salts as membrane stabilizers. The calcium salt of acethylhomotaurine is used in the treatment of alcoholism (under the name of acamprosate).

A subject-matter of the present invention is novel sulphonic, phosphonic and phosphinic acid derivatives represented by the formula (I):



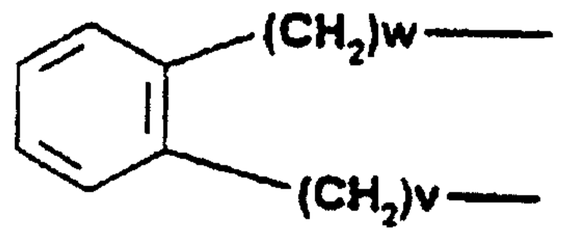
in which

X is



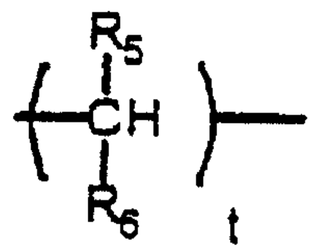
R_1, R_2 and R_3 are selected from hydrogen and a C_1-C_7 alkyl radical,

A is a group of formula



with v and w = 0, 1 or 2

or a group of formula



R_5 and R_6 being selected, independently of one another, from hydrogen, a C_1-C_7 alkyl radical, an aryl radical having from 6 to 14 carbon atoms and a heteroaryl radical selected from furyl, thienyl and thiazolyl, it being possible for the aryl and heteroaryl radicals to carry 1 to 3 substituents selected from a C_1-C_7 alkyl group, a halogen or a trifluoromethyl group, and t = 1-3,

R_4 is selected from hydrogen, a C_1-C_7 alkyl radical, a CF_3 radical, an aryl radical having from 6 to 14 carbon atoms and a heteroaryl radical selected from furyl, thienyl and thiazolyl, it being possible for the aryl and heteroaryl radicals to carry 1 to 3 substituents selected from a C_1-C_7 alkyl group, a halogen or a trifluoromethyl group,

M is a monovalent metal (Na, K, Li) or a divalent metal (Ca, Mg, Sr, Zn),

m = 1 or 2,

p = 1-2 and q = 1-2, p and q being such that the electrical neutrality of the salt is ensured,

R_4 not being a methyl radical when R_1, R_2 and R_3 are hydrogen.

The compounds of the invention can comprise chiral centres. The optical isomers, the racemates, the enantiomers and the diastereoisomers form part of the invention.

The Applicant company has shown that this family of products make it possible to decrease the consumption of alcohol in rats exhibiting alcohol

dependency. Their therapeutic applications relate, inter alia, to the field of dependency on alcohol and on other substances capable of leading to habituation, such as, for example, opiates, nicotine derivatives, caffeine derivatives, amphetamines, cannabinoids or tranquillizers.

The present invention also applies to pharmaceutical compositions comprising, as active principle, one of the compounds of formula (I), optionally in combination with one or more pharmaceutically acceptable excipients or vehicles.

Mention may be made, among the compositions according to the invention, by way of example and without implied limitation, of tablets, capsules, including hard gelatin capsules, or solutions to be taken orally.

The compounds of the invention can be administered at doses of between 0.01 g and 1 g from one to three times daily.

Mention may be made, among the preferred compounds of the formula 1, of, for example:

calcium 3-(2-(methyl)propanoylamino)propanesulphonate

magnesium 3-(2-(methyl)propanoylamino)propanesulphonate

calcium 3-(butanoylamino)propanesulphonate

magnesium 3-(butanoylamino)propanesulphonate

calcium 3-(pentanoylamino)propanesulphonate

calcium 3-(benzoylamino)propanesulphonate

magnesium 3-(benzoylamino)propanesulphonate

zinc 3-(2-(methyl)propanoylamino)propanesulphonate

strontium 3-(2-(methyl)propanoylamino)propanesulphonate

calcium 3-(3-(methyl)butanoylamino)propanesulphonate

magnesium 3-(3-(methyl)butanoylamino)propanesulphonate

calcium 3-(2-2-(dimethyl)propanoylamino)propane-sulphonate

magnesium 3-(2-2-(dimethyl)propanoylamino)propane-sulphonate

calcium 3-(acetylamino)-2-methylpropanesulphonate

calcium 3-(acetylamino)-3-methylpropanesulphonate

magnesium 3-(acetylamino)-3-methylpropanesulphonate
calcium 3-(acetylamino)-1-methylpropanesulphonate
calcium 3-(acetylamino)-2-phenylpropanesulphonate
calcium 2-(2-acetylaminomethyl)phenylmethanesulphonate
calcium N-methyl-3-(acetylamino)propanesulphonate
calcium 3-(acetylamino)-2-2-dimethylpropanesulphonate
calcium 3-(trifluoromethylcarbonyl)propanesulphonate

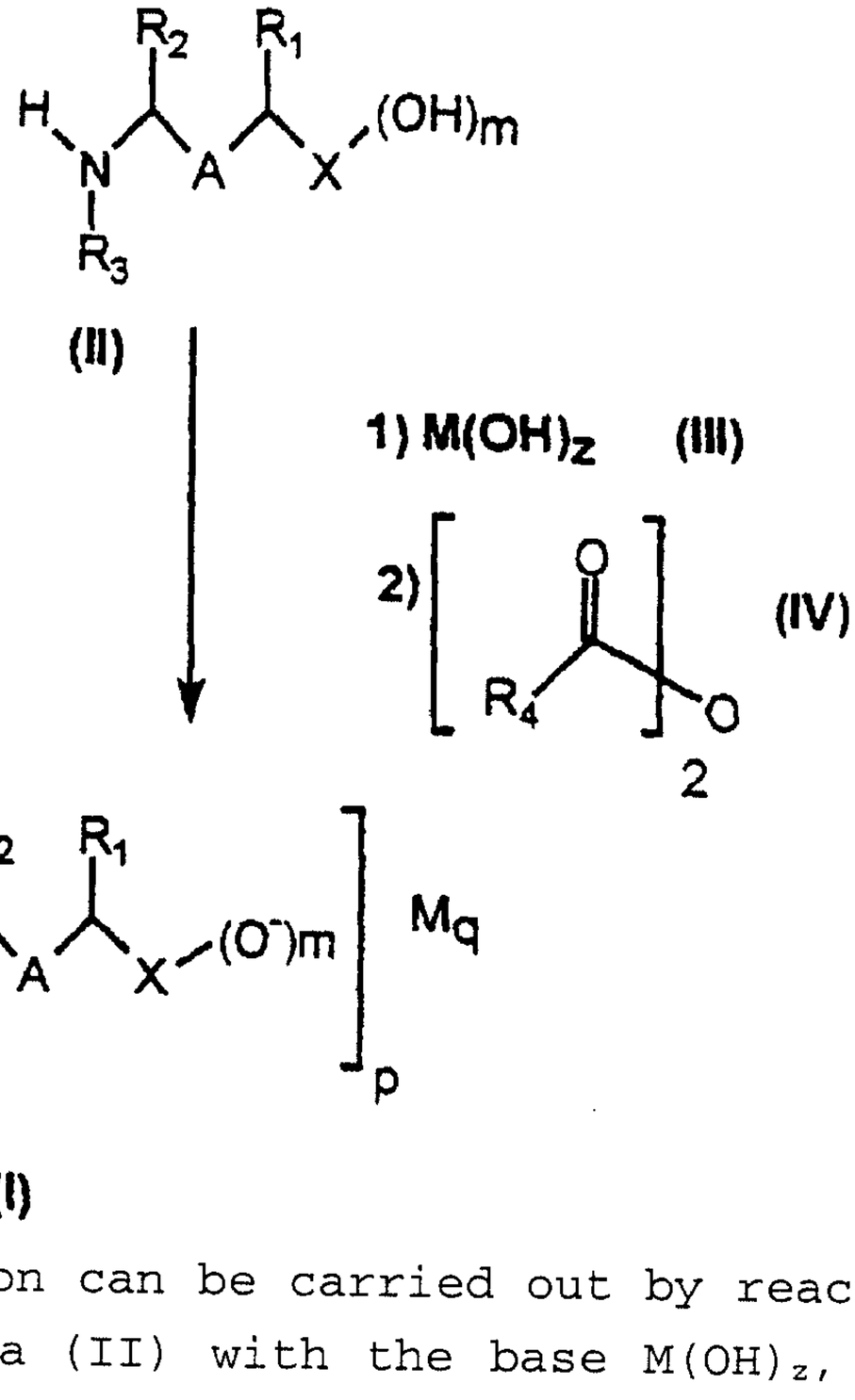
Preference is very particularly given to the compounds of formula I in which R_4 is a C_2-C_7 alkyl radical and in particular a branched radical.

The following compounds also form part of the invention:

3-((2-methyl)propanoylamino)propanesulphonic acid
3-(butanoylamino)propanesulphonic acid
3-(pentanoylamino)propanesulphonic acid
3-(benzoylamino)propanesulphonic acid
3-(acetylamino)propanephosphonic acid
N-methyl-3-(acetylamino)propanesulphonic acid
3-((3-methyl)butanoylamino)propanesulphonic acid
3-((2-2-dimethyl)propanoylamino)propanesulphonic acid
3-(acetylamino)-2-methylpropanesulphonic acid
3-(acetylamino)-3-methylpropanesulphonic acid
3-(acetylamino)-1-methylpropanesulphonic acid
3-(acetylamino)-2-phenylpropanesulphonic acid
2-(2-acetylaminomethyl)phenylmethanesulphonic acid
3-(acetylamino)-2-2-dimethylpropanesulphonic acid
3-(trifluoromethylcarbonoyl)propanesulphonic acid

The invention is also targeted at a process for the preparation of the compounds of the invention. The latter is summarized in Scheme 1.

Scheme 1:



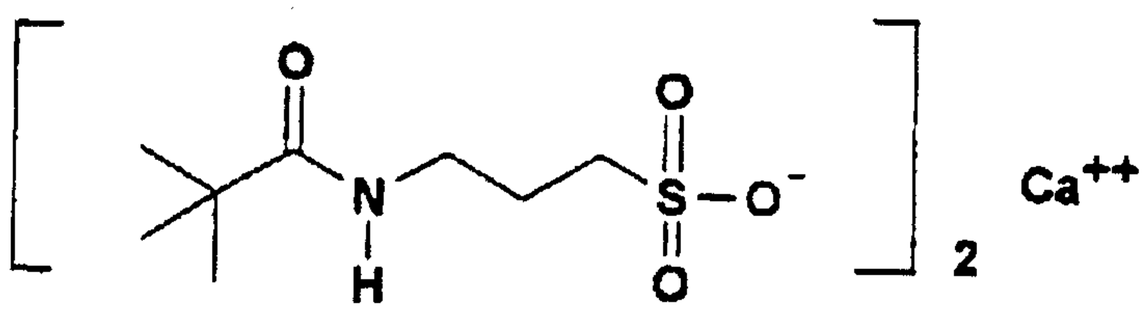
The reaction can be carried out by reacting the compound of formula (II) with the base $M(OH)_z$, where z is the valency of M, and then, while maintaining at a temperature of between 15°C and 20°C, the anhydride of formula (IV) is added. Reaction is allowed to take place overnight and, after treatment, the compound of formula (I) is obtained.

The list of the following examples illustrating the invention is not limiting. In the proton nuclear magnetic resonance (^{1}H NMR) data, the following abbreviations were employed:

- ppm for parts per million
- s for singlet
- d for doublet
- t for triplet
- q for quartet
- m for complex unresolved peak
- j for the couplings, expressed in Hertz
- dd for double doublet

Example 1

calcium 3-(2-2-(dimethyl)propanoylamino)propane-sulphonate



$C_{16}H_{32}CaN_2O_8S_2$ W = 484.65

8.1 g (0.11 mol) of $Ca(OH)_2$ are added to a solution of 22.3 g (0.1 mol) of aminopropanesulphonic acid in a sufficient amount of distilled water. A white suspension is obtained, which suspension is kept stirred for 15 minutes.

The suspension is cooled to 15°C and 35.2 g (0.2 mol) of (2-2-dimethyl)propanoic anhydride are added dropwise while maintaining the temperature between 15°C and 20°C. The mixture is subsequently brought to room temperature overnight with stirring. The solution obtained is subsequently evaporated under vacuum and the residue is taken up with q.s. of distilled water to dissolve it. 17.6 g (0.1 mol) of (2-2-dimethyl)propanoic anhydride are again added between 15°C and 20°C and then the reaction mixture is again left overnight with stirring at room temperature. The mixture is evaporated to dryness under vacuum. The residue is taken up in 300 ml of absolute ethanol comprising 1.5 ml of concentrated hydrochloric acid. The precipitate obtained is filtered off and dried. It is subsequently taken up in the amount of distilled water necessary to dissolve it. After washing with ether, acetone is slowly added to the aqueous phase until a persistent cloudiness is obtained. Stirring is continued until precipitation is complete, and the product is filtered off and dried.

Weight obtained: 4.5 g (Yd: 37%)

MP_G: 300°C

$IR_{\gamma C=O}$: 1623 cm^{-1}

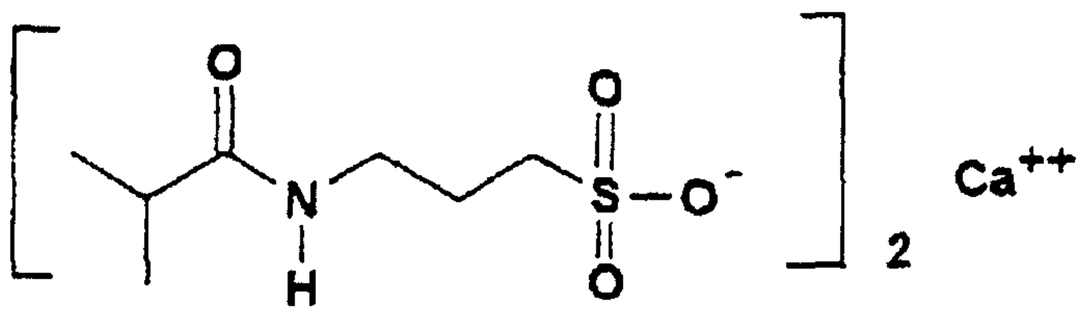
^{1}H NMR (D_2O) δ in ppm: 0.83 (s, $3CH_3$), 1.59 (m, CH_2), 2.56 (m, CH_2), 2.97 (m, CH_2).

Analysis by weight: ($C_{16}H_{32}CaN_2O_8S_3 \cdot 0.25H_2O$)

	C %	H %	Ca %	N %	S %
Calculated	39.65	6.66	8.27	5.78	13.23
Found	38.72	6.61	8.49	5.87	13.33

Example 2

calcium 3-(2-(methyl)propanoylamino)propanesulphonate



$C_{14}H_{28}CaN_2O_8S_2$ MW = 456.60

MP_G > 360°C

$IR_{\gamma C=O}$: 1644 cm^{-1}

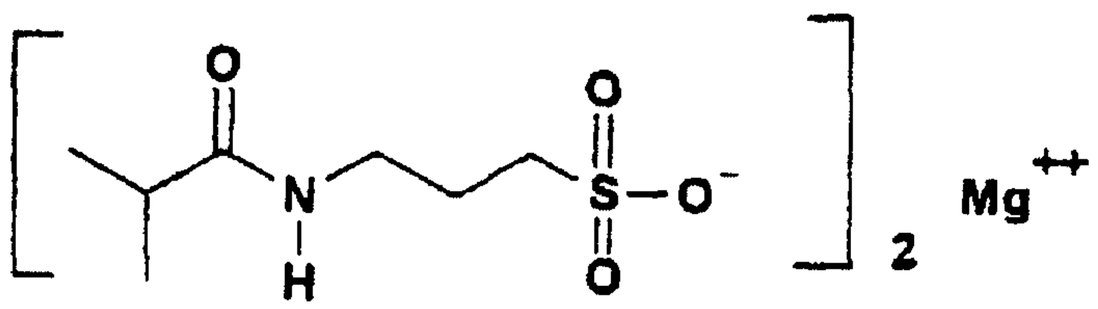
^{1}H NMR (D_2O) δ in ppm: 1.1 (d, $2CH_3$), 1.93 (m, CH_2), 2.48 (m, CH_2), 2.90 (m, CH_2), 3.29 (t, CH_2)

Analysis by weight:

	C %	H %	Ca %	N %	S %
Calculated	36.83	6.18	8.78	6.14	14.04
Found	36.96	6.27	8.70	6.27	14.25

Example 3

magnesium 3-(2-(methyl)propanoylamino)propanesulphonate



$C_{14}H_{28}MgN_2O_8S_2$ MW = 440.83

MP_G: 270-273°C

$IR_{\gamma C=O}$: 1644 cm^{-1}

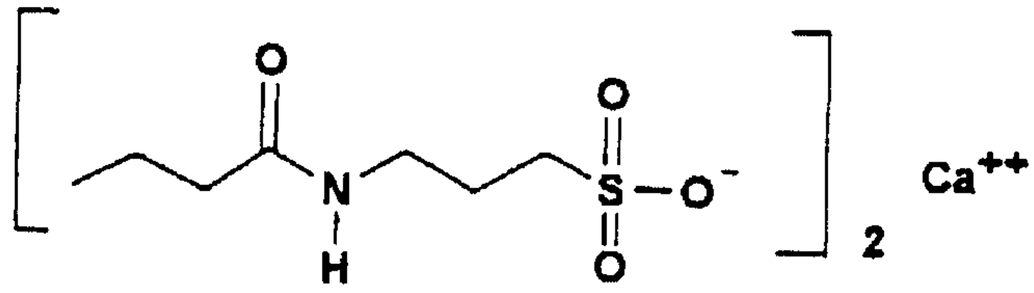
^{1}H NMR (D_2O) δ in ppm: 0.95 (d, $2CH_3$), 1.78 (m, CH_2), 2.34 (m, CH_2), 2.76 (m, CH_2), 3.14 (t, CH_2)

Analysis by weight:

	C %	H %	Mg %	N %	S %
Calculated	36.65	6.59	5.30	6.11	13.97
Found	36.56	6.60	5.52	6.15	13.57

Example 4

calcium 3-(butanoylamino)propanesulphonate



$C_{14}H_{28}CaN_2O_8S_2$ MW = 456.60

MP_G > 360°C

$IR_{\gamma C=O}$: 1633 cm^{-1}

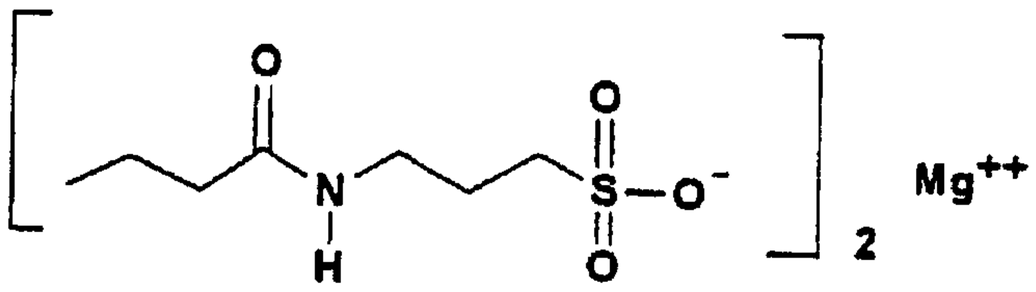
^1H NMR (D_2O) δ in ppm: 0.81 (t, CH_3), 1.49 (m, CH_2), 1.84 (m, CH_2), 2.12 (t, CH_2), 2.83 (m, CH_2), 3.21 (t, CH_2)

Analysis by weight:

	C %	H %	Ca %	N %	S %
Calculated	36.83	6.18	8.78	6.14	14.04
Found	36.84	6.23	8.79	6.30	14.29

Example 5

magnesium 3-(butanoylamino)propanesulphonate



$C_{14}H_{28}MgN_2O_8S_2$ MW = 440.83

MP_G: 325°C

$IR_{\gamma C=O}$: 1635 cm^{-1}

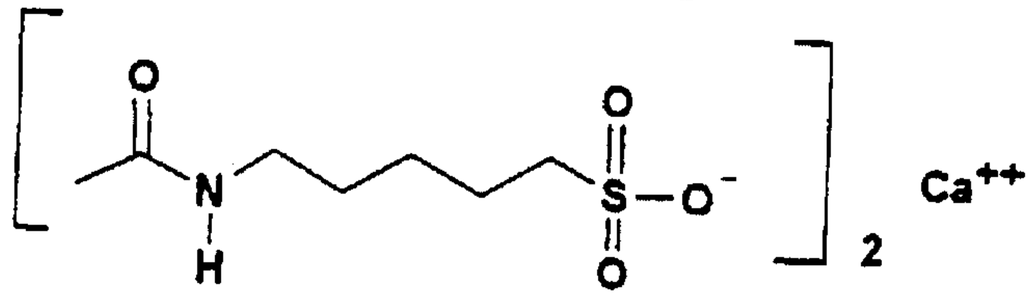
^1H NMR (D_2O) δ in ppm: 0.94 (t, CH_3), 1.64 (m, CH_2), 1.98 (m, CH_2), 2.26 (t, CH_2), 2.97 (m, CH_2), 3.35 (t, CH_2)

Analysis by weight: ($C_{14}H_{28}MgN_2O_8S_2 \cdot 2H_2O$)

	C %	H %	Mg %	N %	S %
Calculated	35.26	6.76	5.10	5.38	13.45
Found	35.11	6.62	5.35	5.90	13.10

Example 6

calcium 5-(acetylamino)pentanesulphonate



$C_{14}H_{28}CaN_2O_8S_2$ MW = 456.60

MP_G: 325-330°C

$IR_{\gamma C=O}$: 1637 cm^{-1}

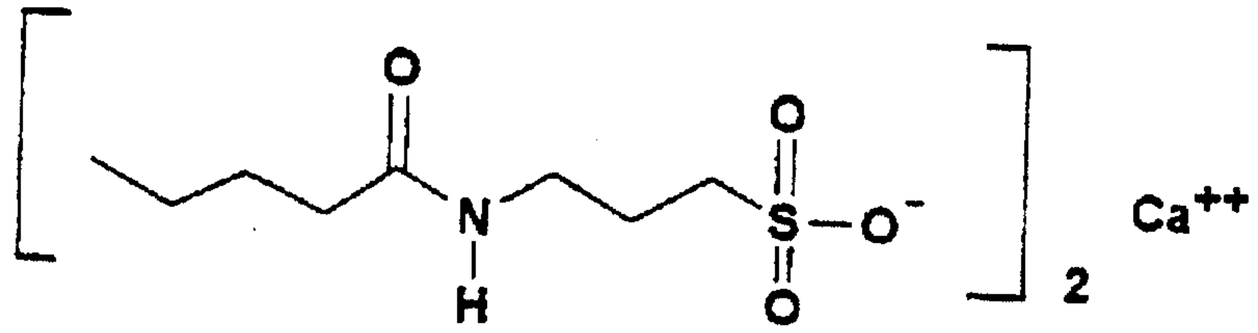
^1H NMR (D_2O) δ in ppm: 1.38-1.58 (m, $2CH_2$), 1.74 (m, CH_2), 1.97 (s, CH_2), 2.93 (t, CH_2), 3.17 (t, CH_2)

Analysis by weight:

	C %	H %	Ca %	N %	S %
Calculated	36.83	6.18	8.78	6.14	14.04
Found	36.53	6.25	8.44	6.29	13.95

Example 7

calcium 3-(pentanoylamino)propanesulphonate



$C_{16}H_{32}CaN_2O_8S_2$ MW = 484.65

MP_G > 360°C

$IR_{\gamma C=O}$: 1633 cm^{-1}

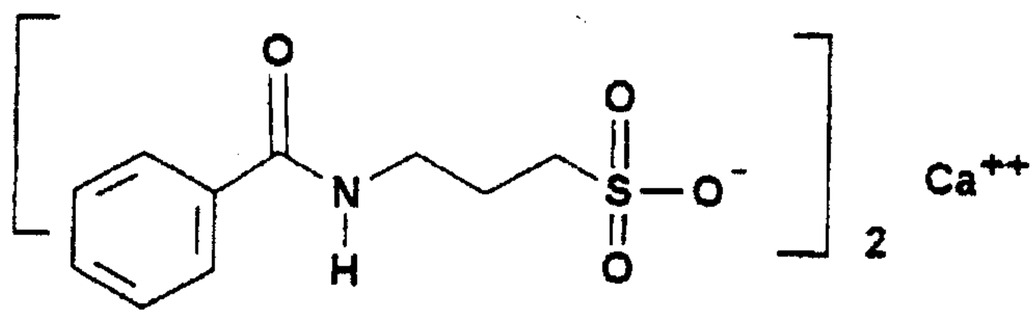
^1H NMR (D_2O) δ in ppm: 0.99 (t, CH_3), 1.4 (m, CH_2), 1.67 (m, CH_2), 2.04 (m, CH_2), 2.35 (t, CH_2), 3.03 (m, CH_2), 3.41 (t, CH_2)

Analysis by weight:

	C %	H %	Ca %	N %	S %
Calculated	39.65	6.66	8.27	5.78	13.23
Found	39.75	6.75	8.33	5.54	13.23

Example 8

calcium 3-(benzoylamino)propanesulphonate



$C_{20}H_{24}CaN_2O_8S_2$ MW = 524.63

MP_G > 360°C

$IR_{\gamma C=O}$: 1637 cm^{-1}

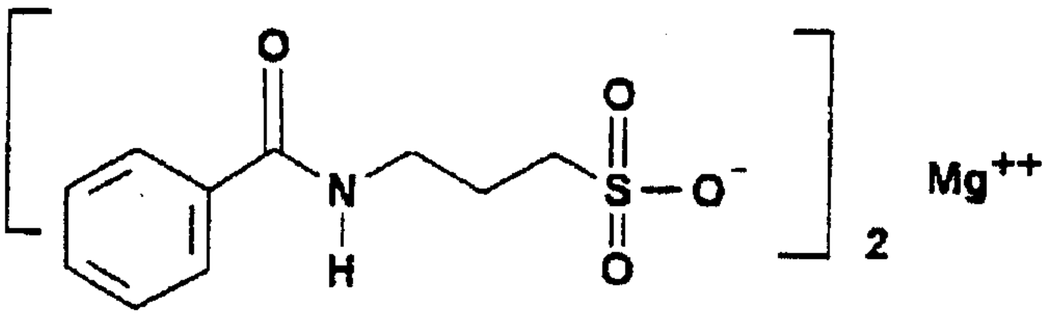
^1H NMR (D_2O) δ in ppm: 1.78 (m, CH_2), 2.72 (m, CH_2), 3.21 (t, CH_2), 7.2-7.45 (m, 5AR)

Analysis by weight: ($C_{20}H_{24}CaN_2O_8S_2 \cdot 1H_2O$)

	C %	H %	Ca %	N %	S %
Calculated	44.27	4.83	7.39	5.16	11.82
Found	43.98	4.75	7.23	5.11	11.42

Example 9

magnesium 3-(benzoylamino)propanesulphonate



$C_{20}H_{24}MgN_2O_8S_2$ MW = 508.86

MP_G: 350°C

$IR_{\gamma C=O}$: 1640 cm^{-1}

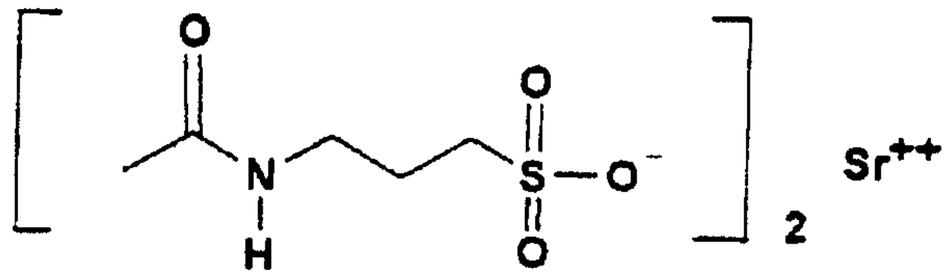
^1H NMR (D_2O) δ in ppm: 1.9 (m, CH_2), 2.83 (m, CH_2), 3.33 (t, CH_2), 7.32-7.68 (m, 5AR)

Analysis by weight: ($C_{20}H_{24}MgN_2O_8S_2 \cdot 2H_2O$

	C %	H %	Mg %	N %	S %
Calculated	44.08	5.18	4.46	5.14	11.77
Found	44.49	5.18	4.48	5.16	11.42

Example 10

strontium 3-(acetylamino)propanesulphonate



$C_{10}H_{20}N_2O_8S_2Sr$ MW = 448.03

MP_G: 305-308°C

$IR_{\gamma C=O}$: 1632 cm^{-1}

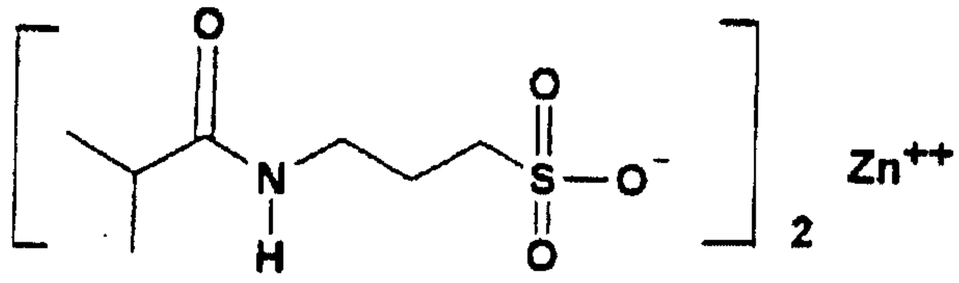
^1H NMR (D_2O) δ in ppm: 1.6 (m, CH_2), 1.66 (s, CH_3), 2.61 (m, CH_2), 2.97 (t, CH_2)

Analysis by weight:

	C %	H %	N %	S %	Sr %
Calculated	26.81	4.50	6.25	14.31	19.56
Found	20.77	4.57	6.16	13.77	19.53

Example 11

zinc 3-(2-(methyl)propanylamino)propanesulphonate



$C_{14}H_{28}N_2O_8S_2Zn$ MW = 481.89

MP_G: 114°C

$IR_{\gamma C=O}$: 1637 cm^{-1}

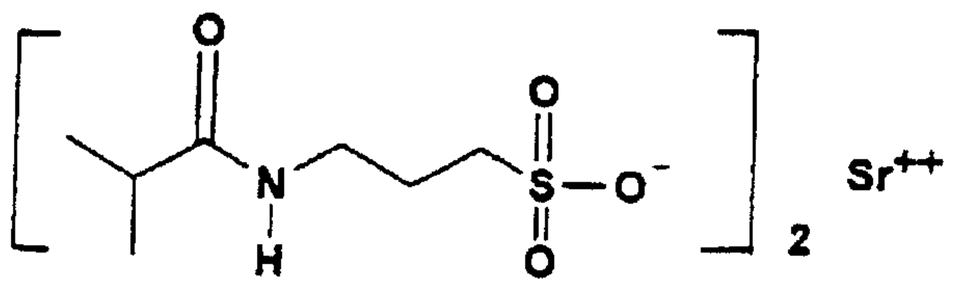
^1H NMR (D_2O) δ in ppm: 0.77 (d, CH_3), 1.6 (m, CH_2), 2.17 (m, CH), 2.58 (m, CH_2), 2.97 (t, CH_2)

Analysis by weight: ($C_{14}H_{28}N_2O_8S_2Zn \cdot 2H_2O$)

	C %	H %	N %	S %	Zn %
Calculated	32.46	6.27	5.41	12.38	12.62
Found	32.46	6.27	5.30	12.38	12.44

Example 12

strontium 3-(2-(methyl)propanoylamino)propanesulphonate



$C_{14}H_{28}N_2O_8S_2Sr$ MW = 504.14

MP_G: 345-350°C

$IR_{\gamma C=O}$: 1642 cm^{-1}

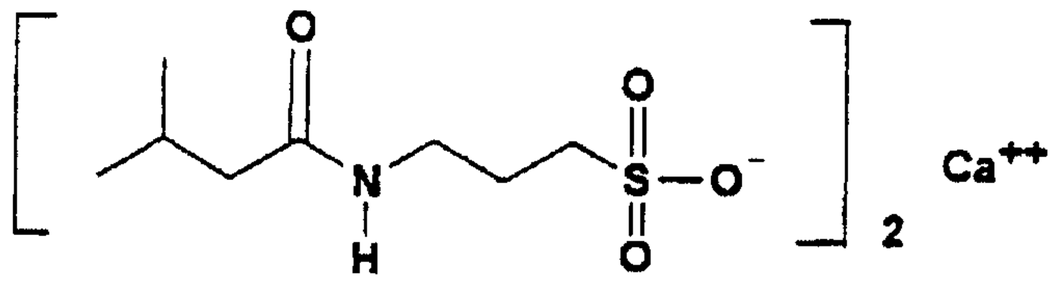
^1H NMR (D_2O) δ in ppm: 1 (d, CH_3), 1.83 (m, CH_2), 2.39 (m, CH), 2.8 (m, CH_2), 3.19 (t, CH_2)

Analysis by weight:

	C %	H %	N %	S %	Sr %
Calculated	33.36	5.60	5.56	12.72	17.38
Found	33.12	5.62	5.24	12.24	17.85

Example 13

calcium 3-(3-(methyl)butanoylamino)propanesulphonate



$C_{16}H_{32}CaN_2O_8S_2$ MW = 484.65

MP_G > 350°C

$IR_{\gamma C=O}$: 1633 cm^{-1}

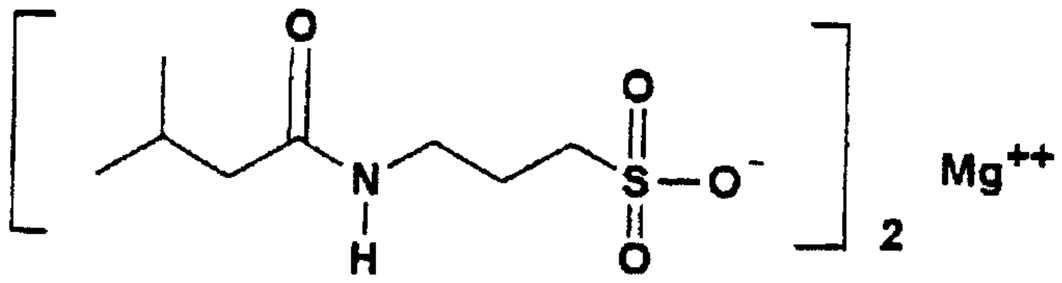
^1H NMR (D_2O) δ in ppm: 0.91 (d, $2CH_3$), 1.89-2.12 (m, $2CH_2$ + CH), 2.92 (m, CH_2), 3.3 (t, CH_2)

Analysis by weight:

	C %	H %	Ca %	N %	S %
Calculated	39.65	6.66	8.27	5.78	13.23
Found	39.07	6.41	8.37	5.83	13.08

Example 14

magnesium 3-(3-(methyl)butanoylamino)propanesulphonate



$C_{16}H_{32}MgN_2O_8S_2$ MW = 468.88

MP_G: 280-287°C

$IR_{\gamma C=O}$: 1644 cm^{-1}

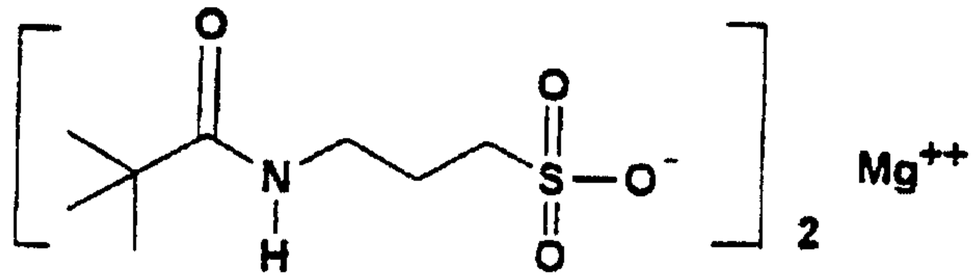
^1H NMR (D_2O) δ in ppm: 0.66 (d, $2CH_3$), 1.63-1.87 (m, $2CH_2$ + CH), 2.67 (m, CH_2), 3.05 (t, CH_2)

Analysis by weight: ($C_{16}H_{32}MgN_2O_8S_2 \cdot 2H_2O$)

	C %	H %	Mg %	N %	S %
Calculated	38.05	7.18	4.81	5.55	12.70
Found	38.40	7.10	5.53	5.67	13.13

Example 15

magnesium 3-(2,2-(dimethyl)propanoylamino)propane-sulphonate



$C_{16}H_{32}MgN_2O_8S_2$ MW = 468.88

MP_G: 200-250°C

$IR_{\gamma C=O}$: 1630 cm^{-1}

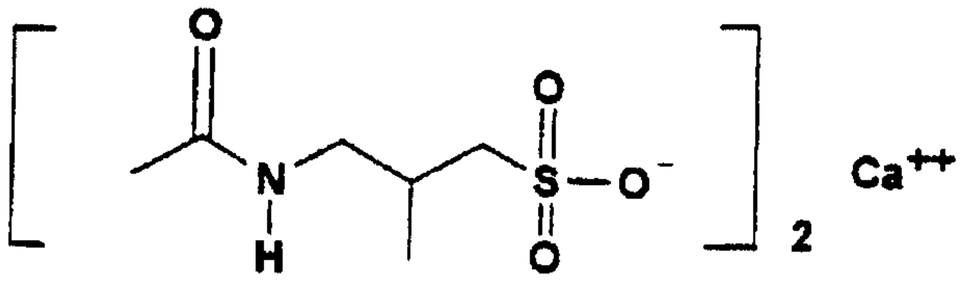
^1H NMR (D_2O) δ in ppm: 1.28 (s, $3CH_3$), 2.04 (m, CH_2), 3.02 (m, CH_2), 3.42 (t, CH_2)

Analysis by weight: ($C_{16}H_{32}MgN_2O_8S_2 \cdot 5H_2O$)

	C %	H %	Mg %	N %	S %
Calculated	34.42	7.57	4.35	5.04	11.49
Found	33.94	7.48	4.35	5.38	11.68

Example 16

calcium 3-(acetylamino)-2-methylpropanesulphonate



$C_{12}H_{24}CaN_2O_8S_2$ MW = 428.54

MP_G: 270°C

$IR_{\gamma C=O}$: 1638 cm^{-1}

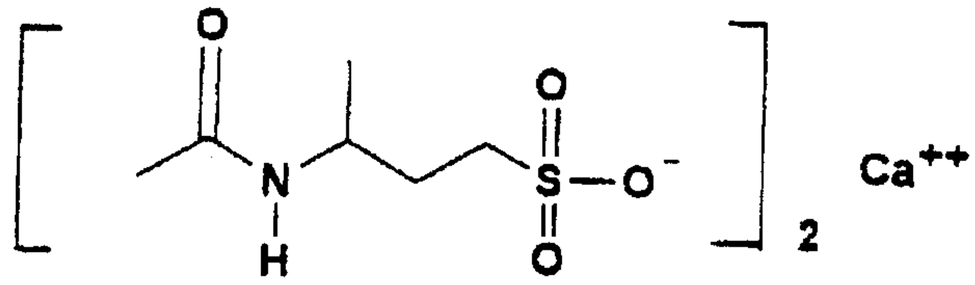
^1H NMR (D_2O) δ in ppm: 1.15 (d, CH_3), 2.07 (s, CH_3), 2.25 (m, CH), 2.83 (m, CH), 3.02 (m, CH), 3.24 (n, CH_2)

Analysis by weight: ($C_{12}H_{24}CaN_2O_8S_2 \cdot 0.5H_2O$)

	C %	H %	Ca %	N %	S %
Calculated	33.63	5.65	9.35	6.54	14.96
Found	32.41	5.74	9.28	6.27	14.47

Example 17

calcium 3-(acetylamino)-3-methylpropanesulphonate



$C_{12}H_{24}CaN_2O_8S_2$ MW = 428.54

MP_G: 275-285°C

$IR_{\gamma C=O}$: 1364 cm^{-1}

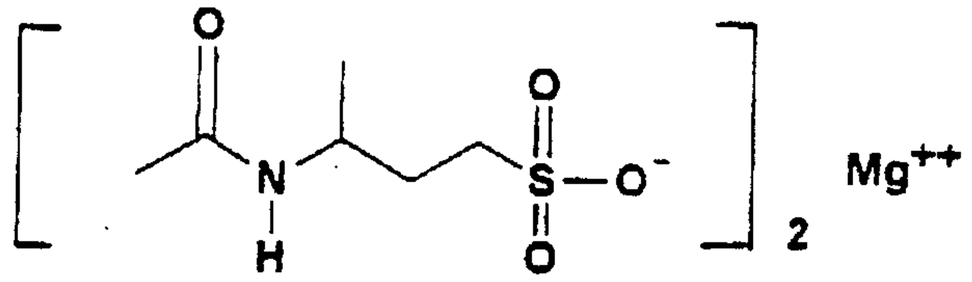
^1H NMR (D_2O) δ in ppm: 1.15 (d, CH_3), 1.85 (m, CH_2), 1.98 (s, CH_2), 2.91 (t, CH_2), 3.94 (m, CH)

Analysis by weight: ($C_{12}H_{24}CaN_2O_8S_2 \cdot 0.5H_2O$)

	C %	H %	Ca %	N %	S %
Calculated	32.96	5.76	9.17	6.41	14.66
Found	32.61	5.79	8.95	6.34	14.29

Example 18

magnesium 3-(acetylamino)-3-methylpropanesiphonate

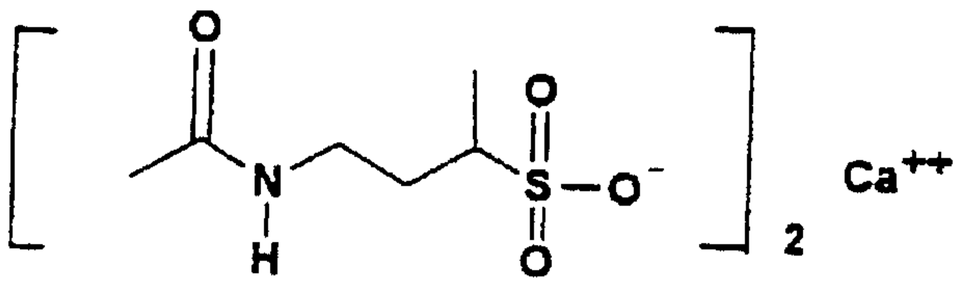


$C_{12}H_{24}CaN_2O_8S_2$ MW = 428.54

^1H NMR (D_2O) δ in ppm: 1.1 (d, CH_3), 1.78 (m, CH_2), 1.9 (s, CH_3), 2.84 (t, CH_2), 3.85 (m, CH)

Example 19

calcium 3-(acetylamino)-1-methylpropanesulphonate



$C_{12}H_{24}CaN_2O_8S_2$ MW = 428.54

MP_G > 360°C

$IR_{\gamma C=O}$: 1670 cm^{-1}

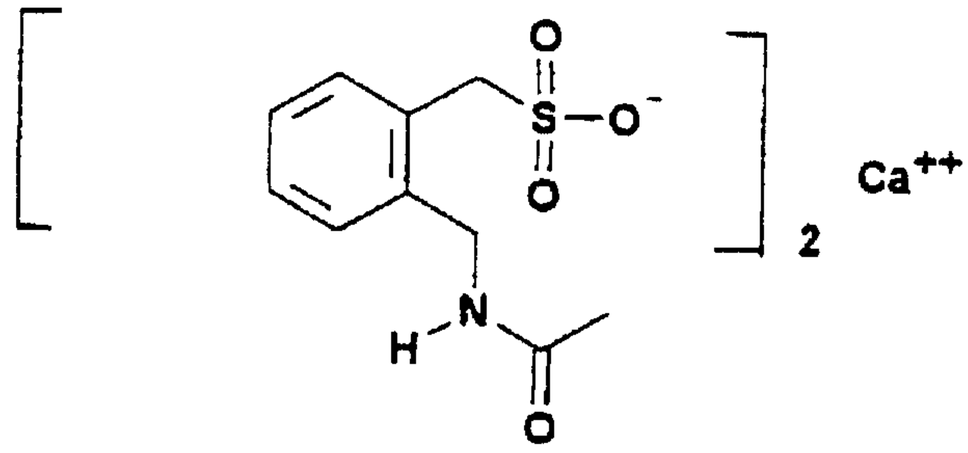
^1H NMR (D_2O) δ in ppm: 1.44 (d, CH_3), 1.77 (m, CH), 2.11 (s, CH_3), 2.33 (m, CH), 3.03 (m, CH), 3.45 (m, CH_2)

Analysis by weight:

	C %	H %	Ca %	N %	S %
Calculated	33.63	5.65	9.35	6.54	14.96
Found	33.34	5.67	9.35	6.50	15.06

Example 20

calcium 2-(2-acetylaminomethyl)phenylmethanesulphonate



$C_{20}H_{24}CaN_2O_8S_2$ MW = 524.63

MP_G: 260-265°C

$IR_{\gamma C=O}$: 1640 cm^{-1}

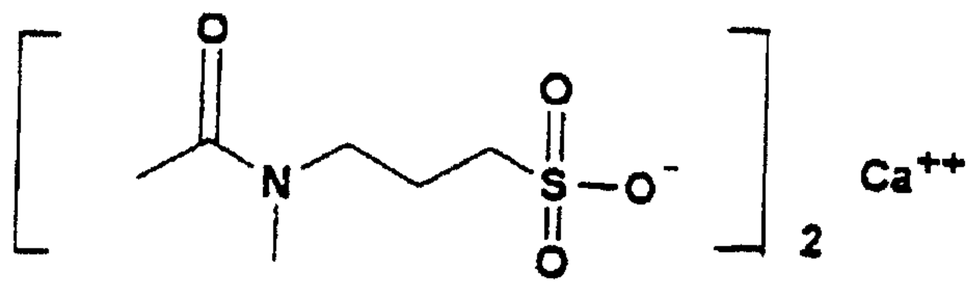
^1H NMR (D_2O) δ in ppm: 2 (s, CH_3), 4.26 (m, CH_2), 7.3-7.4 (m, 4AR)

Analysis by weight: ($C_{20}H_{24}CaN_2O_8S_2 \cdot 1H_2O$)

	C %	H %	Ca %	N %	S %
Calculated	44.26	4.83	7.38	5.16	11.81
Found	44.45	4.80	7.63	5.23	11.25

Example 21

calcium N-methyl-3-(acetylamino)propanesulphonate



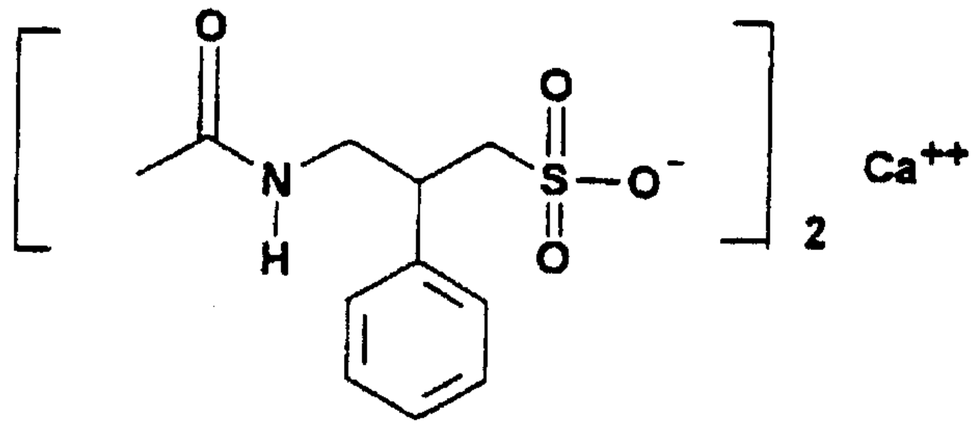
$C_{12}H_{24}CaN_2O_8S_2$ MW = 428.54

$IR_{\gamma C=O}$: 1611 cm^{-1}

^1H NMR (D_2O) δ in ppm: 2 (m, CH_2), 2.1 (s, CH_3), 2.9 (m, CH_2), 3.06 (s, CH_3), 3.48 (n, CH_2)

Example 23

calcium 3-(acetylamino)-2-phenylpropanesulphonate



$C_{22}H_{28}CaN_2O_8S_2$ MW = 552.69

MP_G: 240-250°C

$IR_{\gamma C=O}$: 1636 cm^{-1}

^1H NMR (D_2O) δ in ppm: 1.88 (s, CH_3), 3.28-3.48 (m, $2CH_2$), 3.59-3.66 (m, CH), 7.33-7.46 (m, 5Ar)

Analysis by weight: ($C_{22}H_{28}CaN_2O_8S_2 \cdot 1H_2O$)

	C %	H %	Ca %	N %	S %
Calculated	46.33	5.30	7.02	4.91	11.24
Found	46.66	5.04	7.23	4.96	10.36

The results of a pharmacological study on the compounds of the invention will be given below.

Consumption of alcohol in dependent rats:

Rats of the Long-Evans strain, weighing 200 g at the beginning of the test, are isolated in individual cages. In order to establish alcohol dependency, they are given, as the only drink, a 10% (V/V) solution of alcohol in water for 3 weeks. They are allowed to feed ad libitum.

At the end of this period of 3 weeks, the animal is offered the choice between water and aqueous/alcoholic solution for 2 weeks. Only the rats consuming more than 3 g/kg of alcohol per day are retained for the continuation of the tests.

On conclusion of this period, the product to be studied is administered intraperitoneally at a dose of 100 mg/kg/d for two weeks to batches of 5 to 8 rats. A control batch receives physiological water intraperitoneally. All the rats have a free choice between water and the aqueous/alcoholic solution, and feeding is ad libitum.

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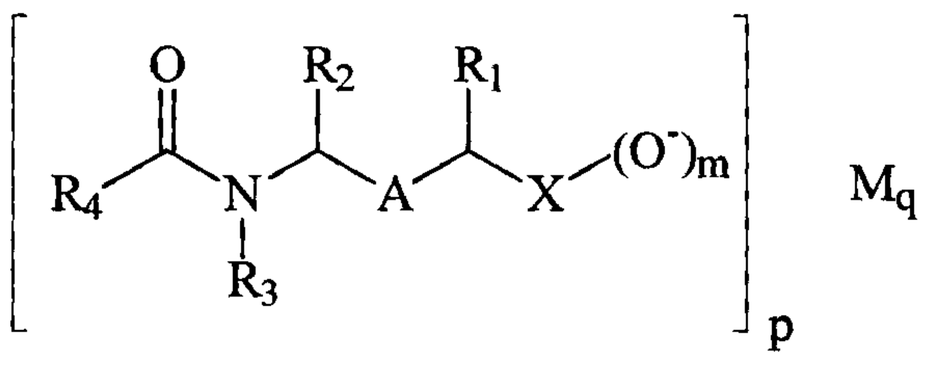
CLAIMS:

1. A compound of general formula (I):



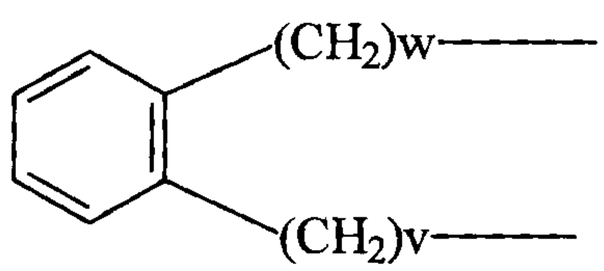
(I)

wherein:

X is ;

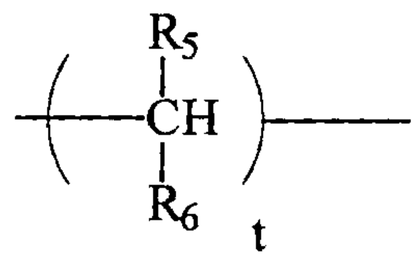
R_1, R_2 and R_3 are selected from the group consisting of H and a C_1-C_7 alkyl radical;

A is a group of general formula:



wherein v and w are 0, 1 or 2, or

a group of general formula:



wherein R_5 and R_6 are selected, independently of one another, from the group consisting of a C_1-C_7 alkyl radical, an aryl radical having from 6 to 14 carbon atoms and a heteroaryl radical selected from the group consisting

of furyl, thienyl and thiazolyl, wherein the aryl and heteroaryl radicals are optionally substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_7 alkyl group, a halogen atom and a trifluoromethyl group, and t is 1-3;

R_4 is selected from the group consisting of H, a C_1-C_7 alkyl radical, a CF_3 radical, an aryl radical having from 6 to 14 carbon atoms and a heteroaryl radical selected from the group consisting of furyl, thienyl and thiazolyl, wherein the aryl and heteroaryl radicals are optionally substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_7 alkyl group, a halogen atom and a trifluoromethyl group;

M is a monovalent metal or a divalent metal;

m is 1 or 2; and

p is 1-2 and q is 1-2, wherein p and q are such that an electrically neutral salt is ensured;

with the proviso that R_4 is not a methyl radical when R_1, R_2 and R_3 are H.

2. A compound as defined in claim 1, wherein M is Na, K, Li, Ca, Mg, Sr or Zn.

3. A compound as defined in claim 1, selected from the group consisting of:

calcium 3-(2-(methyl)propanoylamino)propanesulphonate,

magnesium 3-(2-(methyl)propanoylamino)propanesulphonate,

calcium 3-(butanoylamino)propanesulphonate,

magnesium 3-(butanoylamino)propanesulphonate,

calcium 3-(pentanoylamino)propanesulphonate,

calcium 3-(benzoylamino)propanesulphonate,

magnesium 3-(benzoylamino)propanesulphonate,

zinc 3-(2-(methyl)propanoylamino)propanesulphonate,

strontium 3-(2-(methyl)propanoylamino)propanesulphonate,

calcium 3-(3-(methyl)butanoylamino)propanesulphonate,

magnesium 3-(3-(methyl)butanoylamino)propanesulphonate,

calcium 3-(2-2-(dimethyl)propanoylamino)propanesulphonate,

magnesium 3-(2-2-(dimethyl)propanoylamino)propanesulphonate,

calcium 3-(acetylamino)-2-methylpropanesulphonate,

calcium 3-(acetylamino)-3-methylpropanesulphonate,

magnesium 3-(acetylamino)-3-methylpropanesulphonate,

calcium 3-(acetylamino)-1-methylpropanesulphonate,

calcium 3-(acetylamino)-2-phenylpropanesulphonate,

calcium 2-(2-acetylaminomethyl)phenylmethanesulphonate,

calcium N-methyl-3-(acetylamino)propanesulphonate,

calcium 3-(acetylamino)-2-2-dimethylpropanesulphonate, and

calcium 3-(trifluoromethylcarbonoyl)propanesulphonate.

4. A process for the preparation of a compound of the general formula I as defined in claim 1, which consists in reacting a compound of general formula II:

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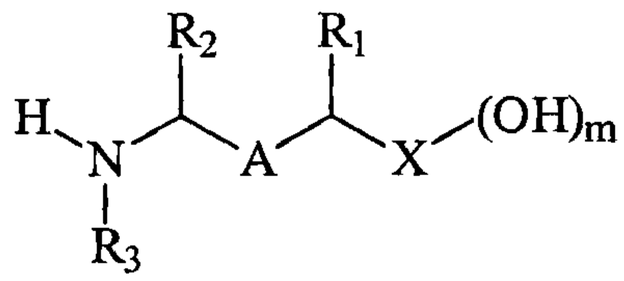
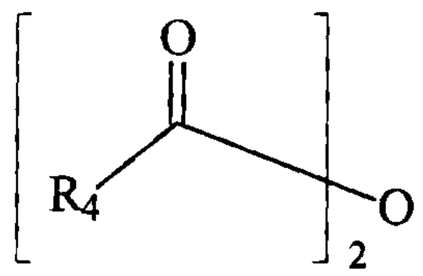


(II)

wherein R_1, R_2, R_3, X and m are as defined in claim 1, with a compound of general formula III:

$$M(OH)_z \qquad \text{(III)}$$

wherein z has the valency of the metal M as defined in claim 1, and then with a compound of general formula IV:



(IV)

wherein R_4 is as defined in claim 1.

5. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 3, and a pharmaceutically acceptable carrier.

FETHERSTONHAUGH & CO.
OTTAWA, CANADA
PATENT AGENTS

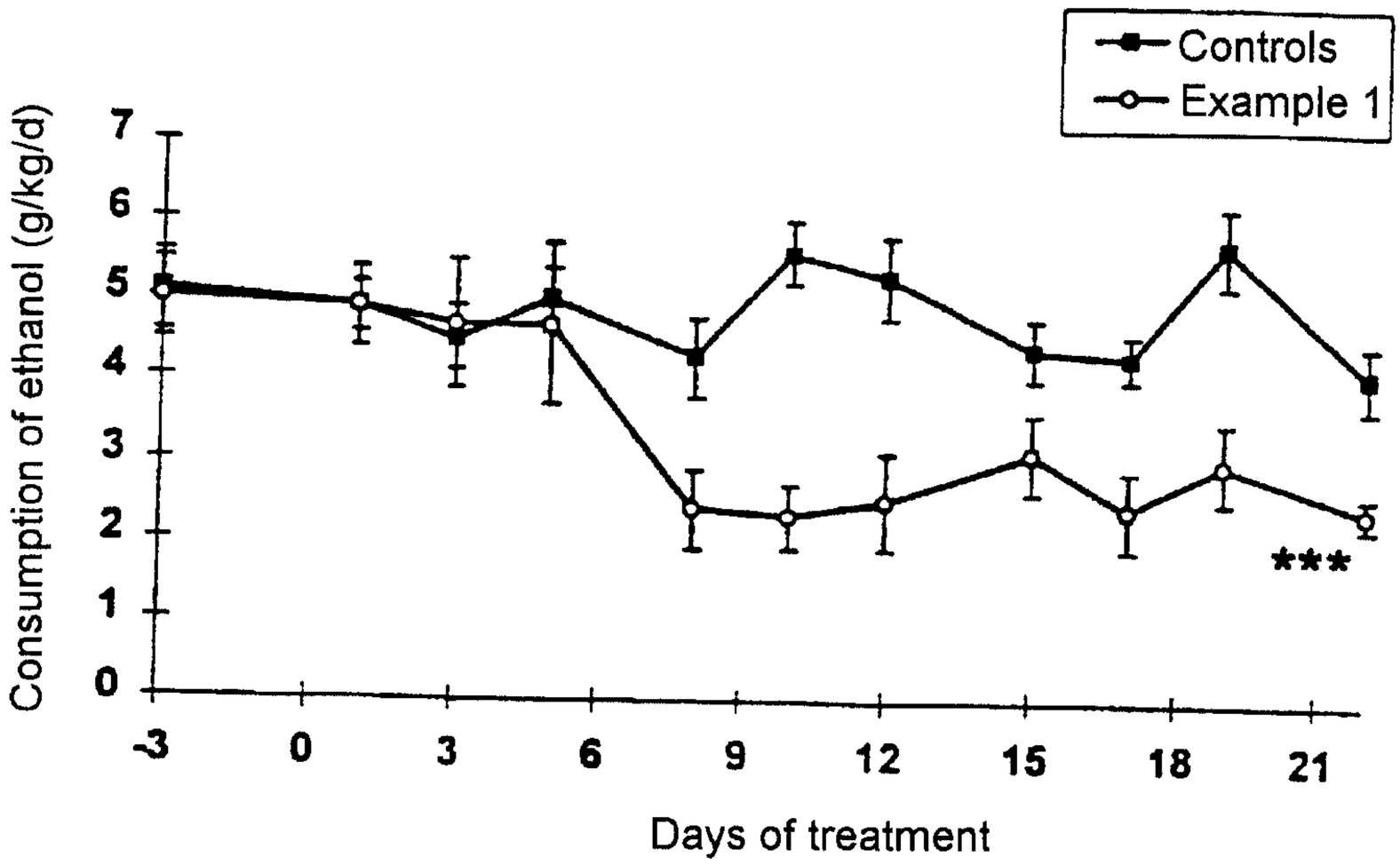
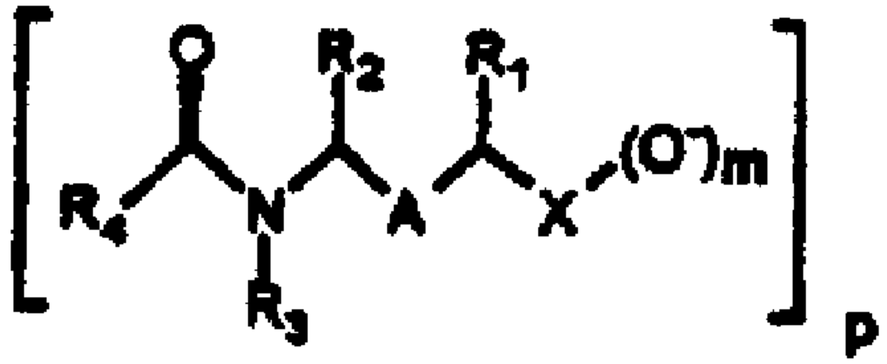

Controls
Example 1
Consumption of ethanol (g/kg/d)
0
1
2
3
4
5
6
7
-3
0
3
6
9
12
15
18
21
***
Days of treatment

FIGURE 1



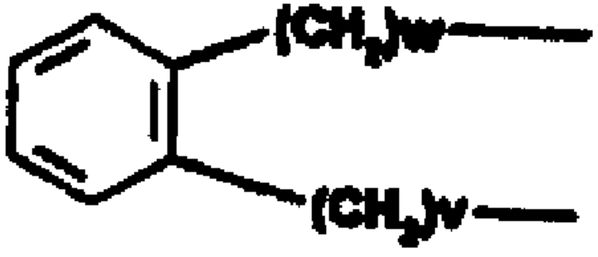
(I)

(a)

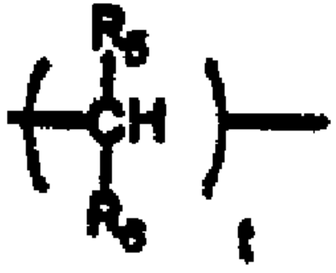
(b)

(c)

(d)



(e)



(f)