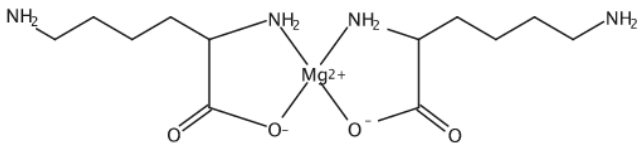
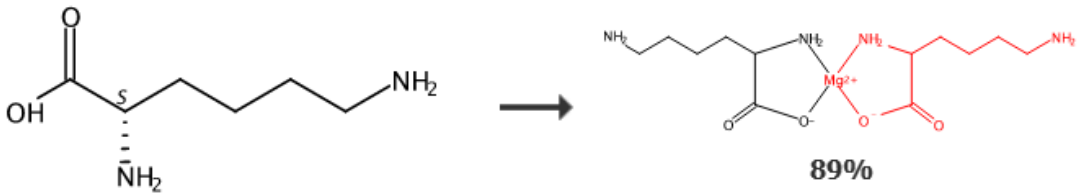
Mg-lysinate

CAS: 151753-50-3 Magnesium lysinate **(2 procedures, 1 supplier)**

(Supplier: DSK Biopharma United States, 95-98%, 1 and 5 g amounts, http://www.dskbiopharma.com/, Phone: 919-455-6252 (mobile), Fax: 800-980-2260, Order Number: DSA0005177, Last Updated: 23 Feb 2015)





PROCEDURE:[1] $Mg(OH)_2$, EtOH, 6h, rt to reflux.

ABSTRACT: The present invention provides preparation of $[M(L)_2]AE$ (HL = (I)) and related compounds for treatment of disorders (R = independently a branched or unbranched carbon chain of from 1 to 20 carbons having at least one basic function; X = independently H and -CO-Z, where Z is a peptide moiety incorporating from 1 to 5 amino acids, or a pharmaceutically acceptable salt thereof; M is a divalent metal cation selected from **magnesium (Mg^{2+})**, calcium (Ca^{2+}), and zinc (Zn^{2+}); A and E are each a molecule having at least one acidic function, either A or E, but not both, may be absent, and when both A and E are present

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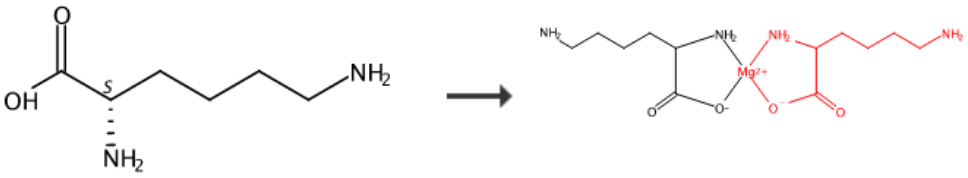
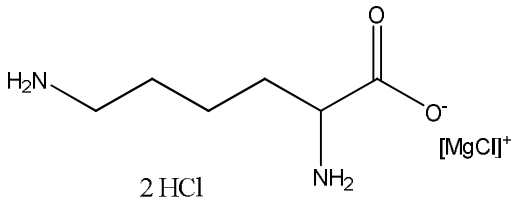


[1] **Preparation of mineral calcium, magnesium and zinc amino-acid complexes for treatment of disorders,** Sciavolino, Frank C. and Mathias, Gary, **PCT Int. Appl.**, 2015195491, 23 Dec **2015**. (patent in EN language)

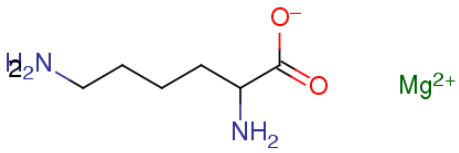
PROCEDURE:[2] $MgCl_2$, H_2O, rt, 3 h, pH 7.5.



PROCEDURE:[3] Evaporation an aq solution containing equimolar amounts of L-lysine-2HCl and CaCl2 to dryness at 90 ° gives 99 % [H3NCH2(CH2)3CH(NH3)CO2Ca]3+.3 Cl- which is fed to Ca-deficient calves. **Analogously prepared is Mg L-lysinate trichloride** and a mixed preparation containing both Ca and Mg.

RXN: 15570003

magnesium lysinate (bioactivity, no synthesis)



RXN: 29485312

magnesium bis-lysinate monohydrate (1 synthesis, spectra, phys-chem data)

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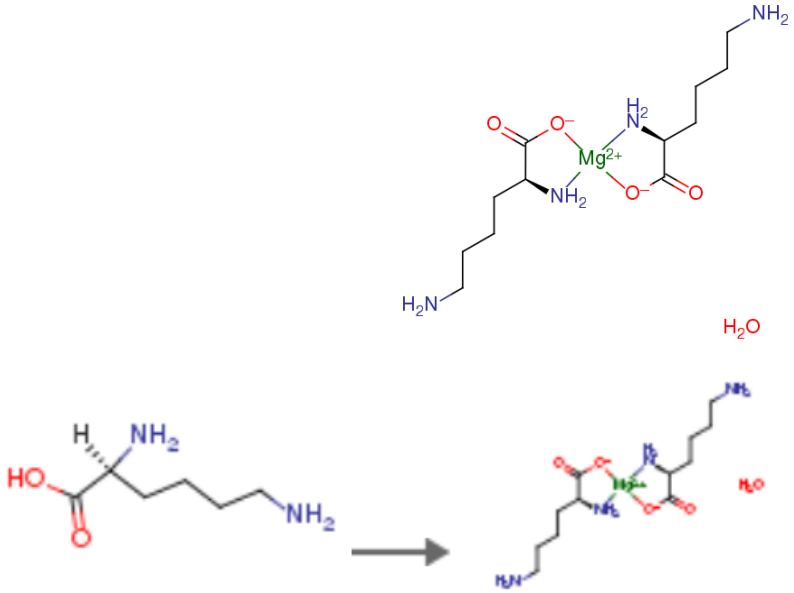
[2] **Process for preparation of ε-*N*-lauroyl lysine,** Pang, Baohua; Ye, Aiying; Wei, Pinghe; Ding, Jingmin; Wang, Ping, Faming Zhuanli Shenqing, 102617390, 01 Aug **2012**. (patent in Chinese language)

[3] **Drugs containing L-lysine-bound calcium and magnesium** Struhar, Milan; Dvorakova, Edita; Mandak, Milan; Kral, Lukas Czech. (**1985**), **CS 225920 B1** 19840319.

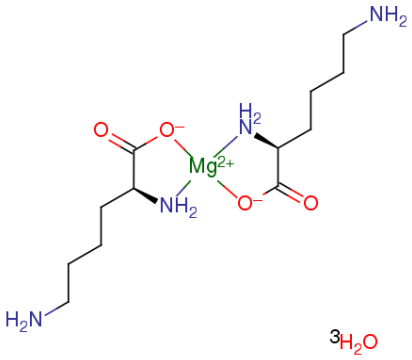


PROCEDURE:[4] 89%, magnesium hydroxide; water in ethanol, 6 h, inert atmosphere, reflux.

A stirred mixture of magnesium hydroxide (1.75 g, 30 mmol) and L-lysine (8.77 g, 60 mmol) in reagent ethanol (30 mL) under nitrogen was heated to reflux for 6 h and cooled to room temperature. The thick suspension was filtered (slow) and rinsed with ethanol, collected, and dried in vacuo to afford 9.86 g (89percent) of subject compound as a white solid. ^{1}H NMR (D_4-AcOH): δ 4.00 (t, 2H, J=6 Hz); 3.06 (t, 4H, J=7.5 Hz); 1.90-2.05 (m, 4H); 1.71-1.78 (m, 4H); 1.52-1.63 (m, 4H). Elemental Analysis Calcd: C, 39.09; H, 8.75; N, 15.20. Found: C, 39.42; H, 8.47; N, 14.96. EA hits for trihydrate $C_{12}H_{26}MgN_4O_4.3H_2O$.

RXN: 29485313

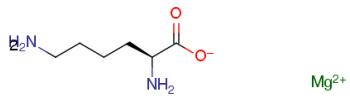
magnesium bis(lysinate) trihydrate (no synthesis)



[4] **Mineral Amino-Acid Complexes of Fatty Acids,** Thetis Pharmaceuticals LLC; Sciavolino, Frank C.; Mathias, Gary Patent: US2015/366980 A1, 2015; Paragraph 0109-0110.

RXN: 29669225

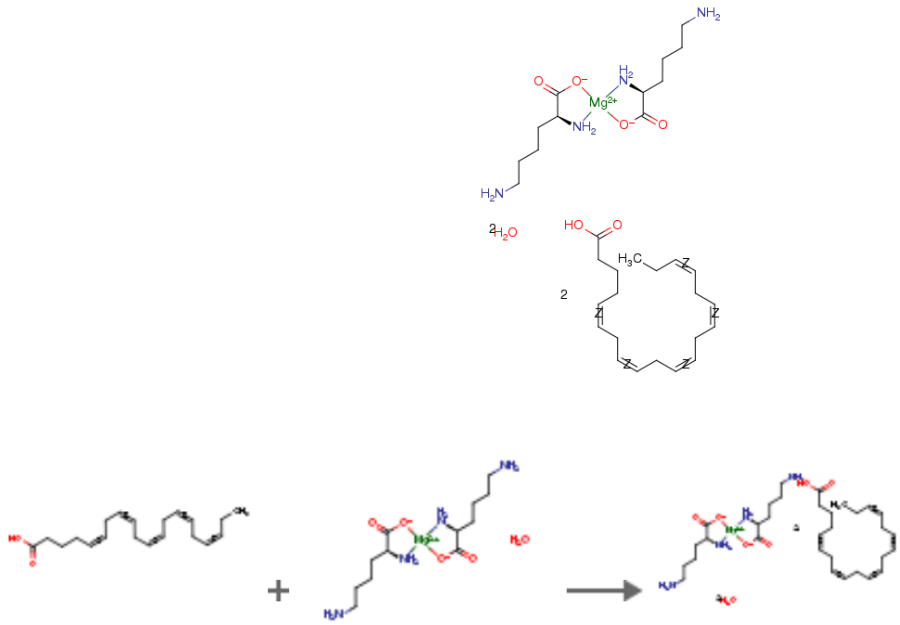
magnesium lysinate (0 synthesis)



Other known Mg-lysinates

RXN: 29485317

magnesium bis-lysinate bis-EPA dehydrate (1 synthesis)



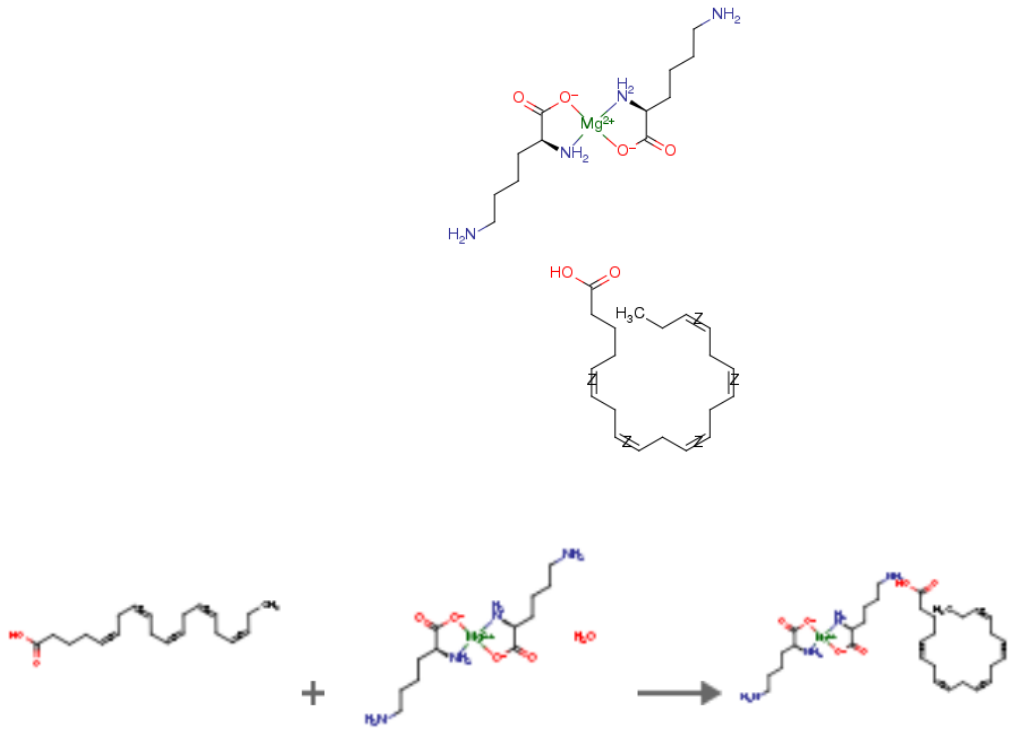
PROCEDURE:[5] 100 %, Tocopherol in methanol; ethyl acetate, T=50°C; 0.333333 h; Inert atmosphere.

A warmed (50° C.) stirred suspension of magnesium bis-lysinate monohydrate (1.844 g, 5.0 mmol) in methanol (10 mL) under nitrogen was treated with a solution of EPA (3.63 g, 12 mmol) in methanol (10 mL) containing alpha-D-tocopherol (100 mg) dissolved in ethyl acetate (0.5 mL), stirred for 20 min, then the mixture was concentrated in vacuo and suspended in acetonitrile (50 mL). The suspension was stirred for 3 h, filtered, washed with acetonitrile, collected and dried in vacuo to afford 4.78 g (100percent) of magnesium lysinate his EPA as a white solid. NMR (d4-AcOH): δ 5.27-5.44 (m, 20H) 4.00 (t, 2H, J=6 Hz) 3.06 (t, 4H, J=7.5 Hz) 2.80-2.89 (m, 16H) 2.36 (t, 4H, J=7.5 Hz) 2.05-2.16 (m, 8H) 1.91-2.00 (m, 4H) 1.65-1.78 (m, 8H) 1.54-1.63 (m, 4H) 0.95 (t, 6H, J=7.5 Hz). Elemental Analysis from previous batch: Calcd: C, 65.36; H, 9.49; N, 5.86. Found: C, 65.12; H, 9.49; N. Passes as a dihydrate.

[5] **Mineral Amino-Acid Complexes of Fatty Acids**, Thetis Pharmaceuticals LLC; Sciavolino, Frank C.; Mathias, Gary, Patent: US2015/366980 A1, 2015; Paragraph 0111.

RXN: 29485318 (2 synthesis)

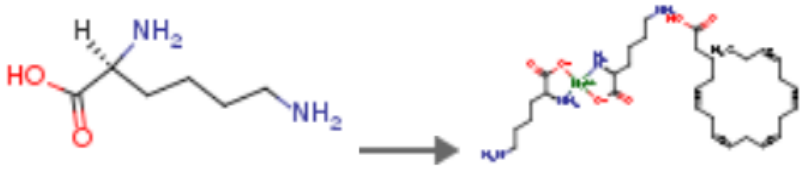
magnesium bis-lysinate mono-EPA



PROCEDURE:[6] 100 %, tocopherol in methanol; ethyl acetate, T=50°C; 0.333333 h; Inert atmosphere.

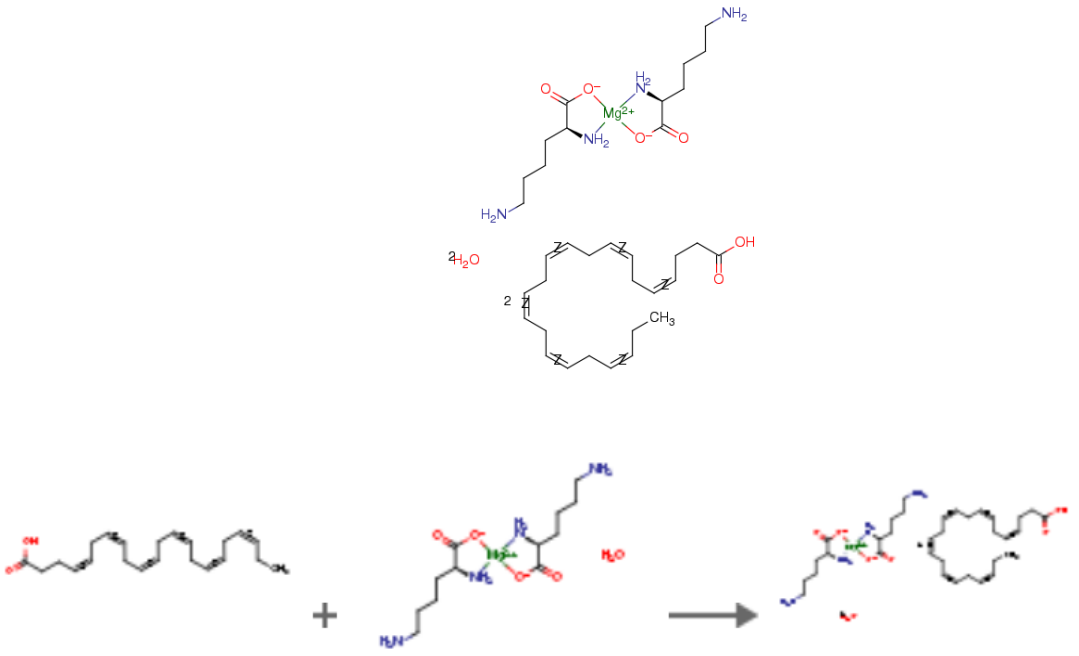
A warmed (50° C.) stirred suspension of magnesium bis-lysinate monohydrate (1.00 g, 3.0 mmol) in methanol (5 mL) under nitrogen was treated with a solution of EPA (0.94 g, 3.1 mmol) in methanol (10 mL) containing alpha-D-tocopherol (100 mg) dissolved in ethyl acetate (0.5 mL), and stirred for 20 min, then most of the methanol was removed in vacuo and replaced with acetonitrile (20 mL). The mixture was stirred for 3 h, filtered, washed with acetonitrile, collected and dried in vacuo to afford 1.855 g (100percent) of subject material as a pale beige solid. MP 152-154° C. 1H NMR (d4-AcOH): δ 5.25-5.45 (m, 10H); 3.99 (t, 2H, J=6 Hz); 3.06 (t, 4H, J=7.5 Hz); 2.75-2.90 (m, 8H); 2.36 (t, 2H, J=7.5 Hz); 2.05-2.20 (m, 4H); 1.90-2.05 (m, 4H); 1.65-1.80 (m, 6H); 1.50-1.65 (m, 4H); 0.95 (t, 3H, J=7.5 Hz). 13C NMR (d4-AcOH): δ 179.27, 173.97, 131.60, 128.71, 128.24, 127.99, 127.97, 127.88, 127.68, 126.93, 54.35, 39.40, 32.90, 29.53, 26.21, 26.14, 25.23, 25.21, 25.12, 24.30, 21.41, 20.16, 13.50.

[6] **Mineral Amino-Acid Complexes of Fatty Acids,** Thetis Pharmaceuticals LLC; Sciavolino, Frank C.; Mathias, Gary, Patent: US2015/366980 A1, 2015; Paragraph 0112-0113.



PROCEDURE:[7] 1/ magnesium hydroxide; water / ethanol / 6 h / Inert atmosphere / Reflux 2: Tocopherol / methanol; ethyl acetate / 0.33 h / 50 °C / Inert atmosphere.

RXN: 29485319 (1 synthesis)
magnesium bis-lysinate bis-DHA dehydrate



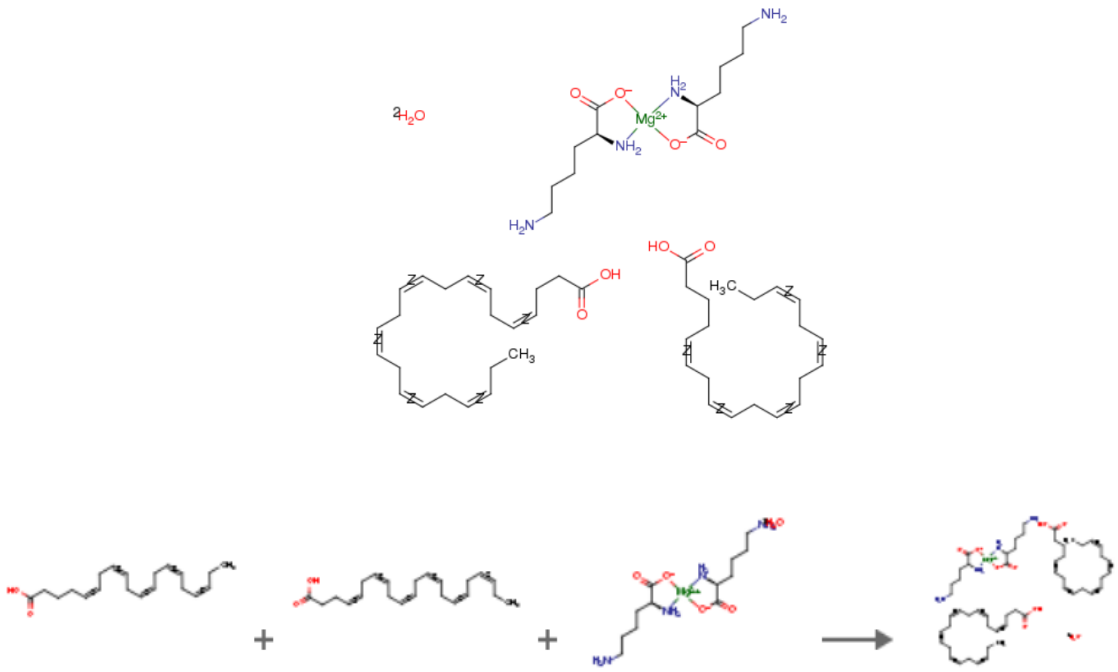
PROCEDURE:[8] 96 %, tocopherol in methanol; ethyl acetate, T=50°C; 0.333333 h; Inert atmosphere.

[7] **Mineral Amino-Acid Complexes of Fatty Acids**, Thetis Pharmaceuticals LLC; Sciavolino, Frank C.; Mathias, Gary, Patent: US2015/366980 A1, 2015.

A warmed (50° C.) stirred suspension of magnesium bis-lysinate monohydrate (1.663 g, 5.0 mmol) in methanol (10 mL) under nitrogen was treated with a solution of DHA (3.53 g, 10.75 mmol) in methanol (10 mL) which had been combined with alpha-D-tocopherol (60 mg) in ethyl acetate (0.5 mL), and stirred for 20 min, then most of the methanol was removed in vacuo and replaced with acetonitrile (30 mL). The mixture was stirred for 3 h, filtered, washed with acetonitrile, collected and dried in vacuo to afford 4.85 g (96percent) of subject material as a very pale beige solid. Calcd for $C_{56}H_{90}MgN_4O_8.2H_2O$: C, 66.75; H, 9.40; N, 5.56. Found: C, 67.05; H, 9.49; N, 5.30. MP 147-150° C. ^{1}H NMR (d4-AcOH): δ 5.25-5.45 (m, 24H); 4.01 (t, 2H, J=6 Hz); 3.07 (t, 4H, J=7.5 Hz); 2.75-2.95 (m, 20H); 2.35-2.45 (m, 8H); 2.05-2.15 (m, 4H); 1.90-2.05 (m, 4H); 1.70-1.80 (m, 4H); 1.50-1.65 (m, 4H); 0.95 (t, 6H, J=7.5 Hz). ^{13}C NMR (d4-AcOH): δ 178.76; 173.91, 131.59, 129.15, 128.24, 127.97, 127.95, 127.89, 127.86, 127.68, 127.62, 126.93, 54.33, 39.40, 33.46, 29.46, 26.16, 25.24, 25.23, 25.22, 25.18, 25.11, 22.21, 21.34, 20.16, 13.48.

RXN: 29485320 (1 synthesis)

magnesium Bis-Lysinate Mono-EPA Mono-DHA dehydrate



PROCEDURE:[9] 100 %, tocopherol in methanol; ethyl acetate, T=50°C; 0.333333 h; Inert atmosphere.

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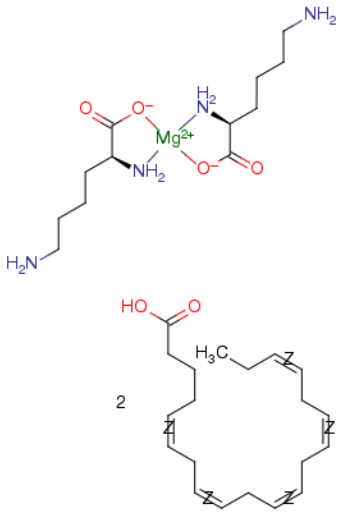
[8] **Mineral Amino-Acid Complexes of Fatty Acids**, Thetis Pharmaceuticals LLC; Sciavolino, Frank C.; Mathias, Gary Patent: US2015/366980 A1, 2015. Paragraph 0114-0115.

[9] **Mineral Amino-Acid Complexes of Fatty Acids**, Thetis Pharmaceuticals LLC; Sciavolino, Frank C.; Mathias, Gary, Patent: US2015/366980 A1, 2015; Paragraph 0116-0117.

A warmed (50° C.) stirred suspension of magnesium bis-lysinate trihydrate (1.844 g, 5.0 mmol) in methanol (25 mL) under nitrogen was treated with a solution of EPA (1.66 g, 5.5 mmol) and DHA (1.81, 5.5 mmol) in methanol (25 mL) which had been combined with alpha-D-tocopherol (100 mg) in ethyl acetate (1 mL), and stirred for 20 min, then the mixture was concentrated in vacuo and suspended in acetonitrile (75 mL). The mixture was stirred for 3 h, filtered, washed with acetonitrile, collected and dried in vacuo to afford 4.93 g (100percent) of subject material as a pale beige solid. MP 153-155° C. 1H NMR (d4-AcOH): δ 5.25-5.45 (m, 22H); 4.00 (t, 2H, J=6 Hz); 3.07 (t, 4H, J=7.5 Hz); 2.80-2.90 (m, 18H); 2.40 (m, 4H); 2.37 (t, 2H, J=7.5 Hz); 2.10-2.17 (m, 2H); 2.08 (t, 4H, J=7.5 Hz); 1.92-2.02 (m, 4H); 1.72-1.80 (m, 4H); 1.65-1.70 (m, 2H); 1.52-1.62 (m, 4H); 0.96 (t, 6H, J=7.5 Hz). 13C NMR (d4-AcOH): δ 179.31, 178.75, 173.94, 131.59, 129.15, 128.71, 128.69, 128.24, 127.97, 127.95, 127.89, 127.87, 127.68, 127.63, 126.92, 54.33, 39.39, 33.47, 32.88, 29.48, 26.18, 26.13, 25.24, 25.22, 25.18, 25.11, 24.28, 22.22, 22.05, 21.36, 20.16, 13.49. LCMS (m-1): lysine (145.9, 100percent); EPA (301.8, 100percent); DHA (327.8, 100percent).

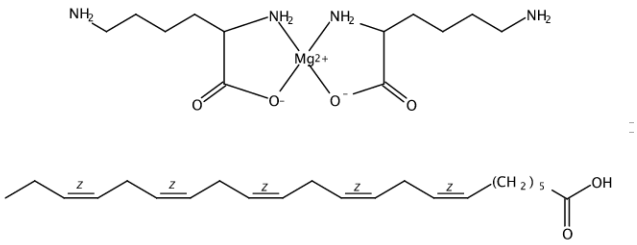
RXN: 29485323 (0 synthesis)

magnesium Bis-Lysinate Mono-EPA Mono-DHA dehydrate

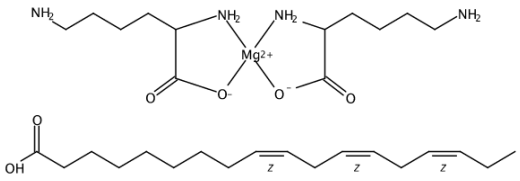


CAS: 1841444-59-4

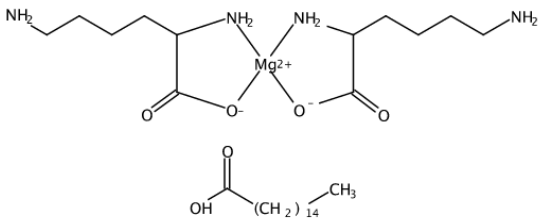
Magnesium, L-lysinato / docosapentaenoate (2:1). Literature (synthesis).[1]



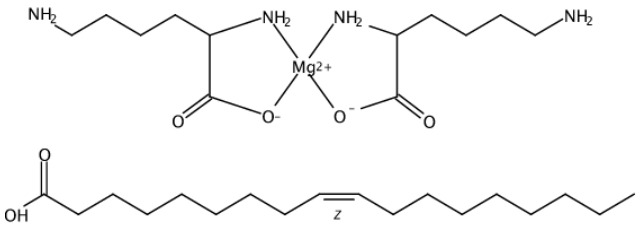
CAS: 1841444-58-3 octadecatrienoate. Literature (synthesis).[1]



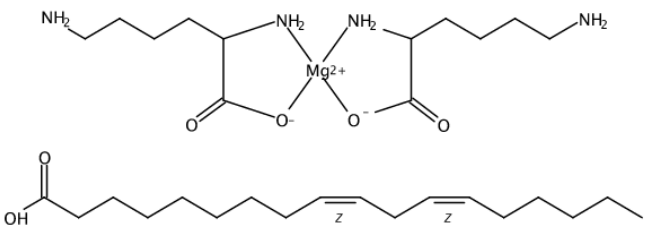
CAS: 1841444-57-2 hexadecanoate Literature (synthesis). Literature (synthesis).[1]



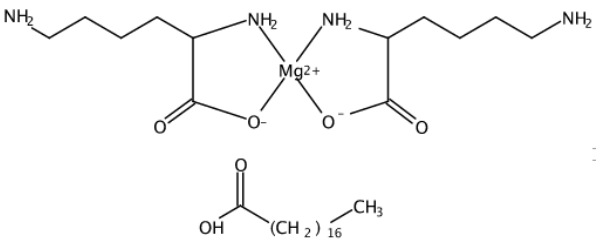
CAS: 1841444-56-1 octadecenoate. Literature (synthesis).[1]



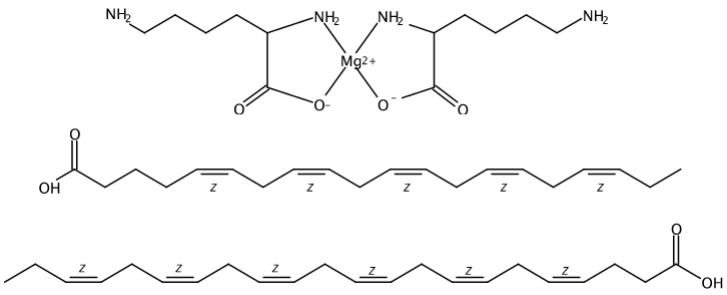
CAS: 1841444-55-0 octadecadienoate. Literature (synthesis).[1]



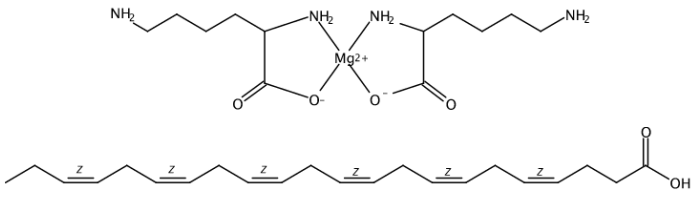
CAS: 1841444-54-9 octadecanoate. Literature (synthesis).[1]



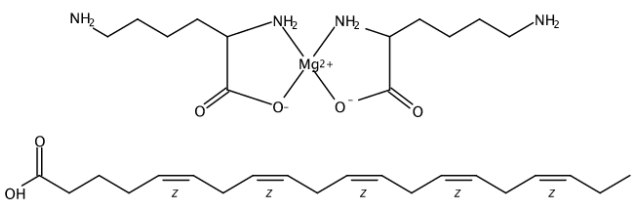
CAS: 1841444-53-8 docosahexaenoate, eicosapentaenoate. Literature (synthesis).[1]



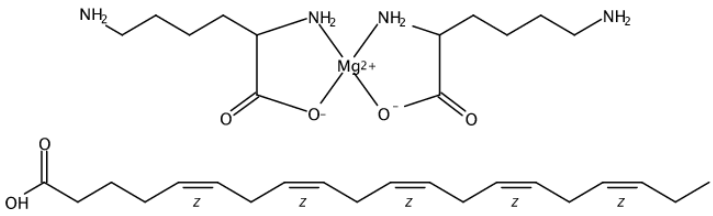
CAS: 1841444-52-7 docosahexaenoate. Literature (synthesis). Literature (synthesis).[1]



CAS: 1841444-51-6 eicosapentaenoate. Literature (synthesis).[1]

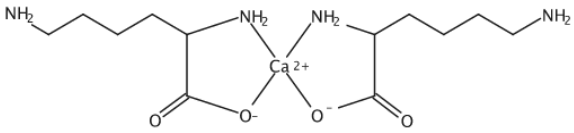


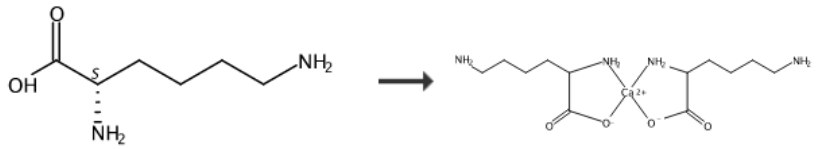
CAS: 1841444-50-5 eicosapentaenoate. Literature (synthesis).[1]



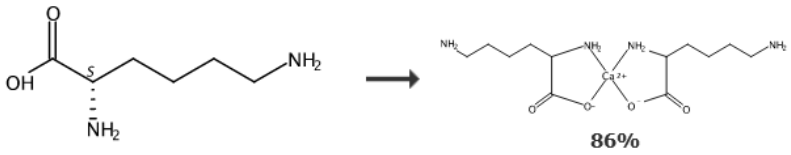
Other relative compounds and procedures

CAS: 763079-48-7 *CALCIUM ANALOG (3 synthesis)*

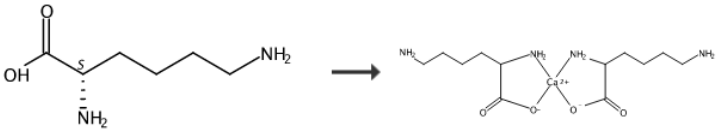




PROCEDURE:[10] $CaCl_2$, NaOH, HCl, H_2O, 30-40 min, 60-70°C, pH 8-9.



PROCEDURE:[1] $Ca(OH)_2$, H_2O, 3 h, rt.



PROCEDURE:[2] $CaCl_2$, H_2O, rt; 3 h, rt, pH 8.

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[10] **Preparation of calcium lysine chelate** Sang, Yaxin; Wang, Xianghong; Hou, Baoyan; Liu, Weihua; Yu, Wenlong; Liu, Xiaoyu, Faming Zhuanli Shenqing, 106631848, 10 May **2017**. (Chinese language)