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Design and Synthesis of Orally Active Dispiro 1, 2, 4, 5-Tetraoxanes; Synthetic Antimalarials with Superior Activity to Artemisinin

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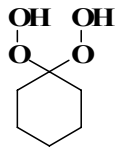
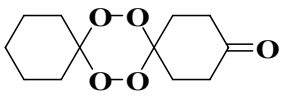
General procedure for the preparation of bishydroperoxides.

Preparation of **Cyclohexane-1,1-diyl bis-hydro peroxide 5a**



A stirred solution of cyclohexanone **5** (5.889g, 60mmol) in formic acid (40ml) was added 30% aqueous hydrogen peroxide (20ml) and the mixture was stirred at room temperature for 4 minutes. The mixture was then poured into ice-cold water and the organic products were extracted by diethyl ether (300ml). After conventional workup, the residue was separated by column chromatography on silica gel to give the bishydroperoxide in 76%. ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.46(m, 2H, cyclohexyl), 1.58(m, 4H, cyclohexyl), 1.84(t, 4H, J = 6.46Hz, cyclohexyl), 8.1(s, 2H, OH), ^{13}CNMR (100MHz, $CDCl_3$), δ_C 22.81, 25.61, 25.69, 29.91, 111.20.

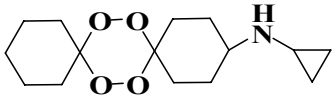
Preparation of 7,8,15,16-Tetraoxa-dispiro[5.2.5.2]hexadecan-3-one 7a



A solution of (0.12g, 2mmol) of cyclohexanone **5**, (0.05g, 4mmol) of 30% H_2O_2 and (0.0005g, 0.002mmol) of methyltrioxorhenium (MTO) in 4ml of 2,2,2-trifluoroethanol (TFE) was stirred for 2 hours at room temperature. Into the solution, (0.4485g, 4mmol) of 1,4-cyclohexanedione **6** was added, followed by the addition of (0.095g, 2mmol) of 54%ethereal solution of tetrafluoroboric acid. The reaction mixture was left under stirring for an additional hour. Dichloromethane was added and the organic phases washed wish diluted $NaHSO_4$, dried over $MgSO_4$ and solvent evaporated under reduced pressure. Products were determined by NMR spectroscopy, isolated by column chromatography (SiO_2, CH_2Cl_2: Hexane = 9:1) to give the tetraoxane in 38%. Mpt. 78-80^oC V_{max} ($CHCl_3$)/cm^{-1}1719.8, 2856.2, 2942.3, 3012.7 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.5(m, 6H, cyclohexyl), 1.80(s, 4H, cyclohexyl), 2.15(t, 2H, J = 7.42Hz, CH_2), 2.30(t, 2H, J= 7.08Hz, CH_2), 2.5(m, 4H, CH_2), ^{13}CNMR (100MHz, $CDCl_3$), δ_C 14.0, 23.07, 25.84, 31.98, 37.25, 106.60, 108.56, 210.77, MS (ES+) $[M + Na]^+$ (100), 265.0, $[M + Na + CH_3OH]^+$ (60) 297.1.

General procedure for reductive amination of tetraoxane ketones.

Preparation of **Cyclopropyl-(7,8,15,16-tetraoxa-dispiro[5.2.5.2]hexadec-3-yl)-amine 9**

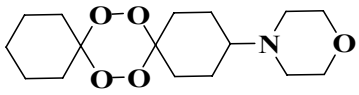


The 7,8,15,16-Tetraoxa-dispiro[5.2.5.2]hexadecan-3-one **7a** (0.2g, 0.8mmol) and morpholine (0.35g, 0.4ml, 6.06mmol) were mixed in dichloromethane (30ml) before addition of

sodiumtriacetoxyborohydride (1.2g, 6.06mmol). The reaction was stirred at room temperature for 18hrs and then washed with distilled water. The organic layer was dried and evaporated under vacuum to dryness. Purification by chromatography afforded the product in 55%.

V_{max} ($CHCl_3$)/cm^{-1} 14445.3, 2856.2, 2934.5, 3012.7, 3443.2 ^{1}HNMR (400MHz, $CDCl_3$) δ_H ^{13}CNMR 0.36(m, 2H, cyclopropyl), 0.47(m, 2H, cyclopropyl), 1.37-1.37(m, 4H, cyclohexyl), 1.52-1.66(m, 6H, cyclohexyl), 1.84-1.99(m, 4H, cyclohexyl), 2.14(m, 1H, CH), 2.18-2.49(m, 4H, cyclohexyl), 2.75(m, 1H, CH), 5.7(bs, 1H, NH) (100MHz, $CDCl_3$), δ_C 8.54, 22.38, 24.19, 25.76, 27.76, 28.64, 28.82, 30.09, 30.52, 32.47, 32.95, 34.99, 56.00, 108.18, 109.62 MS (ES+) $[M + H]^+$ (100),283.8 HRMS (CI+) calculated for 284.18616 $C_{15}H_{26}O_4N$ found 284.18622.

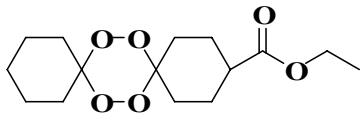
Preparation of **4-(7,8,15,16-Tetraoxa-dispiro[5.2.5.2]hexadec-3-yl)-morpholine 14**



This product was prepared in 56% according to the general procedure for reductive amination of tetraoxane ketones.

V_{max} ($CHCl_3$)/cm^{-1}1444.5, 2859.1, 2931.2, 3011.3 ^{1}HNMR (400MHz, $CDCl_3$) δ_H 1.4-1.5(m, 4H, cyclohexyl), 1.6(bs, 6H, cyclohexyl), 1.7-1.9(m, 6H, cyclohexyl), 2.15-2.3(m, 2H, cyclohexyl), 2.35(m, 1H, CH), 2.55(t, 4H, J = 4.61Hz, NCH_2), 3.7(t, 4H, J = 4.61Hz, NCH_2) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 22.39, 24.20, 25.31, 25.76, 30.06, 30.63, 32.76, 33.38, 34.95, 35.00, 50.14, 50.41, 62.50, 67.74, 107.99, 108.72. MS (ES+) $[M + H]^+$ (100) 314.2 $[M – H + Na]^+$ (50) 336.1, HRMS (CI+) calculated for 314.19675 $C_{16}H_{28}O_5N$ found, 314.19687.

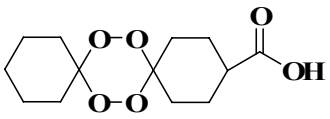
Preparation of **(7,8,15,16-Tetraoxa-dispiro[5.2.5.2]hexadec-3-yl)-acetic acid ethyl ester 17**



To a stirred solution of **5a** (1g, 6.8mmol) in 10ml ethyl acetate was added ethyl-oxocyclohexanecarboxylate (0.60g, 3.53mmol). 54% ethereal solution of tetrafluoroboric acid (0.6g, 6.8mmol) was added and the reaction mixture stirred for an hour. The mixture was washed with $NaHCO_3$, dried in $MgSO_4$ and the solvent evaporated under reduced pressure. Purification of the crude by column chromatography gave the diaspirotetraoxane in 35%. Mpt. 48-50^oC V_{max} ($CHCl_3$)/cm^-1 1444.4, 1724.8, 2859.1, 2931.2, 3019.3 ^{1}HNMR (400MHz, $CDCl_3$) δ_H 1.25(t, 3H, J = 7.15Hz, CH_3), 1.40-1.70(m, 18H, cyclohexyl), 1.71-2.04(m, 6H, cyclohexyl), 2.28(bs, 2H, cyclohexyl), 2.4(m, 2H, cyclohexyl), 2.89(bs, 1H, CH), 4.14(q, 2H, J = 7.15Hz, CH_2), ^{13}CNMR (100MHz, $CDCl_3$), δ_C 14.58, 22.30, 24.23, 25.03, 25.73, 28.49, 29.91, 30.73, 32.12, 42.00, 60.78, 107.68, 108.76, 174.95 MS (ES+) $[M + Na]^+$ (100), 323.1 HRMS calculated 321.1471 $C_{15}H_{24}O_6Na$ found, 323.1456.

General procedure for the preparation of carboxylic acids.

Preparation of 7,8,15,16-Tetraoxa-dispiro[5.2.5.2]hexadecane-3-carboxylic acid 18



The ethyl ester **17** (1.82g, 6.2mmol) was hydrolyzed in 60ml methanol at 70^{o}C with KOH (1.8g, 31.65mmol) and 6ml water. After one hour heating, the reaction mixture was cooled and diluted with 90ml dichloromethane and 30ml water. The aqueous layer was acidified with concentrated HCl (6ml). The aqueous layer was further extracted with DCM. The combined organic layers were washed with water, brine, dried over Na_2SO_4 and evaporated to dryness. Purification by column chromatography gave the pure acid **18** in 85%.

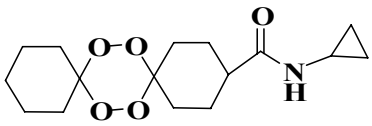
V_{max} ($CHCl_3$)/cm^{-1} 951.4, 1067.6, 1406.2, 1436.5, 1557.8, 1694.3, 2854.1, 2935.0, 3005.7, 3379.9

^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.47(m, 4H, cyclohexyl), 1.59(bs, 6H, cyclohexyl), 1.74-1.88(m, 4H, cyclohexyl), 1.89-2.1(m, 2H, cyclohexyl), 2.14-2.39(bs, 2H, cyclohexyl), 2.46(m, 1H, CH)

^{13}CNMR (100MHz, $CDCl_3$), δ_C 22.41, 24.74, 25.75, 28.39, 30.08, 32.11, 41.61, 107.55, 108.83, 180.97 MS (ES+), $[M - H]^+$ (100), 271.1, $[2M - H]^+$, 543.2 HRMS calculated for 271.1182 $C_{13}H_{19}O_6$ found, 271.1109.

General procedure for amide coupling reaction.

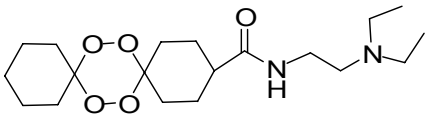
Preparation of 7,8,15,16-Tetraoxa-dispiro[5.2.5.2]hexadecane-3-carboxylic acid cyclopropylamide 19



A solution of the acid **18** (0.08g, 0.29mmol) in dry dichloromethane (15ml), with added triethylamine (0.03g, 0.005ml, 0.29mmol) and ethylchloroformate (0.004g, 0.03ml, 0.38mmol) was stirred for 60 minutes at 0^{o}C. (0.033g, 0.04ml, 0.58mmol) of cyclopropylamine was added,

and after 30minutes of stirring the reaction mixture was warmed to room temperature. After 90minutes, it was diluted with water and extracted with dichloromethane. The organic extract was washed with brine, dried over anhydrous Na_2SO_4. The crude product was purified by flash chromatography to give the pure amide in76% V_{max} ($CHCl_3$)/cm^{-1} 1444.8, 1548.6, 1636.7, 2859.1, 2931.2, 3011.3, 3235.5 Mpt. 170-172^oC ^{1}HNMR (400MHz, $CDCl_3$) δ_H 0.45(m, 2H, cyclopropyl), 0.77(m, 2H, cyclopropyl), 1.47(m, 4H, cyclohexyl), 1.58(bs, 6H, cyclohexyl), 1.65-1.79(m, 2H, cyclohexyl), 1.85(m, 4H, cyclohexyl), 1.19-2.40(m, 2H, cyclohexyl), 2.15(m, 1H, cyclohexyl), 2.70(m, 1H, cyclopropyl)5.56(s, 1H, NH) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 7.07, 22.41, 22.98, 25.75, 44.19, 107.61, 108.82, 176.08. MS (ES+) $[M + Na]^+$ (100), 334.2 HRMS calculated for 334.1630 $C_{16}H_{25}O_5NNa$ found, 334.1616.

Preparation of **7,8,15,16-Tetraoxa-dispiro[5.2.5.2]hexadecane-3-carboxylic acid (2-diethylamino-ethyl)-amide 20**

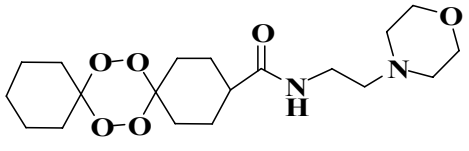


This product was prepared in 48% according to the general procedure for amide coupling reactions.

V_{max} ($CHCl_3$)/cm^{-1} 1444.6, 1653.3, 2934.5, 2965.8, 3003.3, 3404.1 ^{1}HNMR (400MHz, $CDCl_3$) δ_H 1.05(t, 3H, J = 7.15Hz, CH3), 1.12(t, 3H, J = 7.16Hz, CH3), 1.24(t, 4H, J = 7.15Hz, cyclohexyl), 1.47(bs, 2H, cyclohexyl), 1.58(bs, 6H, cyclohexyl), 1.75(m, 4H, cyclohexyl), 1.87(m, 2H, cyclohexyl), 2.15-2.38(m, 1H, CH), 2.6(m, 4H, NCH_2), 2.71(m, 2H, CH_2N), 3.38(q,

2H, J = 4.93Hz, $NHCH_2$), 6.92(s, 1H, NH) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 11.06, 11.24, 22.35, 25.70, 36.52, 38.62, 43.99, 47.26, 47.41, 52.05, 52.32, 107.65, 108.65, 175.12 MS (ES+) $[M + Na]^+$ (48.93), 373.2 and $[M + H]^+$ (100) 371.2 HRMS calculated for 371.2546 $C_{19}H_{35}O_5N_2Na$ found, 371.2539 and for 393.93 $C_{19}H_{34}O_5N_2Na$ found 393.2356.

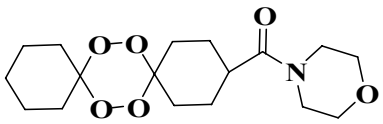
Preparation of **7,8,15,16-Tetraoxa-dispiro[5.2.5.2]hexadecane-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide 21**



This product was prepared in 78% according to the general procedure of amide coupling reactions.

V_{max} ($CHCl_3$)/cm^{-1} 1444.6, 1648.8, 2859.1, 2931.2, 3011.3, 3315.6 ^{1}HNMR (400MHz, $CDCl_3$) δ_H 1.25(t, 4H, J = 7.17Hz, cyclohexyl), 1.37-1.52(m, 2H, cyclohexyl), 1.58(bs, 6H, cyclohexyl), 1.71-1.93(m, 6H, cyclohexyl), 2.26(m, 1H ,CH), 2.46(m, 6H, NCH_2/CH_2N), 3.28(q, 2H, J = 5.72Hz, $NHCH_2$), 3.71(q, 4H, J = 4.45Hz, CH_2O), 6.08(s, 1H, NH) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 22.33, 25.00, 25.15, 30.37, 35.12, 36.86, 43.49, 52.98, 53.02, 57.15, 66.56, 106.91, 108.07, 174.00 MS (ES+) $[M + Na]^+$ (100), 407.2 HRMS calculated for 407.2158 $C_{19}H_{32}O_6N_2Na$ found, 407.2141.

Preparation of **Morpholin-4-yl-(7,8,15,16-tetraoxa-dispiro[5.2.5.2]hexadec-3-yl)-methanone 22**

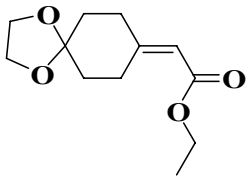


This product was prepared in 80% according to the general procedure for amide coupling reactions.

V_{max} ($CHCl_3$)/cm^{-1} 1444.5, 1632.7, 2859.1, 2939.2, 3003.3 Mpt. 154-156^oC ^{1}HNMR (400MHz, $CDCl_3$) δ_H 1.48(m, 4H, cyclohexyl), 1.60(bs, 6H, cyclohexyl), 1.72(m, 4H, cyclohexyl), 1.81-1.93(m, 1H, CH), 3.49(bs, 2H, NCH_2), 3.61(bs, 2H, NCH_2), 3.67(t, 4H, J = 4.77Hz, CH_2O) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 22.36, 25.76, 30.06, 30.98, 39.23, 42.45, 46.42, 67.30, 107.55, 108.76, 173.57 MS (ES+) $[M + Na]^+$ (100), 364.1 and [2M +Na] (50) 705.3 HRMS calculated for 364.1736 $C_{17}H_{27}O_6NNa$ found, 364.1721.

General procedure for the Wittig reaction.

Preparation of (1,4-Dioxa-spiro[4.5]dec-8-ylidene)-acetic acid ethyl ester 24

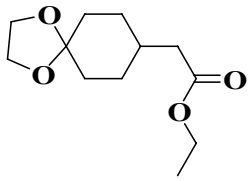


A solution of 1,4-cyclohexanedionemonoethylketal **23** (6g, 40mmol) and ethyl-(triphenylphosphoranylidene)acetate (15g, 44mmol) in dry benzene (80ml) were refluxed under argon for 24hours. The solvent was removed under vacuum and product purified by flash

chromatography to give the product in 90%. V_{max} (neat)/cm^{-1} 926.3, 1104.9, 1169.1, 1237.8, 1269.8, 1301.9, 1352.3, 1430.2, 1650.1, 1709.6, 2876.1, 2949.4 ^{1}HNMR (400MHz, $CDCl_3$) δ_H, 1.28(t, 3H, J = 7.15Hz, CH_3), 1.77(m, 4H, cyclohexyl), 2.38(t, 2H, J = 6.68Hz, CH_2), 3.0(t, 2H, J = 7.47Hz, CH_2), 3.98(s, 4H, OCH_2), 4.15(q, 2H, J = 7.15Hz, CH_2), 5.7(s, 1H, CH), ^{13}CNMR (100MHz, $CDCl_3$), δ_C 14.31, 26.09, 34.61, 35.01, 35.81, 59.63, 64.47, 108.06, 114.37, 160.14, 166.56. MS (CI) $[M + H]^+$ (100), 227 $[M + NH_4]^+$ (95), 244, HRMS calculated for 227.1283 $C_{12}H_{19}O_4$ found, 227.1280.

General procedure for hydrogenation reaction.

Preparation of (1,4-Dioxa-spiro[4.5]dec-8-yl)-acetic acid ethyl ester 25

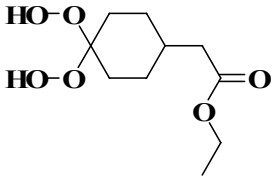


A suspension of the **24** (3.14g, 13.7mmol) in ethyl acetate (80ml) and Pd-C (10%w/w, 1.97g) was stirred in a hydrogen atmosphere for 3hours. The solvent was removed under vacuum and product purified by flash chromatography to give **25** in 90%. V_{max} (neat)/cm^{-1} 926.3, 1031.6, 1104.9, 1169.9, 1237.8, 1288.2, 1375.2, 1443.9, 1728.0, 2876.1, 2931.0, ^{1}HNMR (400MHz, $CDCl_3$) δ_H, 1.25(t, 3H, J = 7.15Hz, CH_3), 1.33(m, 2H, cyclohexyl), 1.56(m, 2H, cyclohexyl), 1.74(d, 4H, J = 6.99Hz, cycloheyxl), 2.2(d, 2H, J = 6.99Hz, CH_2CO), 3.93(s, 4H, OCH_2), 4.13(q, 2H, J = 7.15Hz, CH_2), 5.7(s, 1H, CH), ^{13}CNMR (100MHz, $CDCl_3$), δ_C 14.29, 30.02, 30.16, 33.34, 33.50, 34.16, 34.48, 41.01, 60.35, 64.25, 108.62, 172.87. MS (CI) $[M + H]^+$ (100), 229

$[M + NH_4]^+$ (30), 246, HRMS calculated for 229.1440 $C_{12}H_{19}O_4$ found, 229.1440.

General procedure for the preparation of bishydroperoxide via tungstic acid.

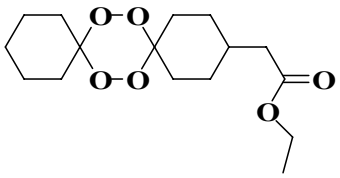
Preparation of (4,4-Bis-hydroperoxy-cyclohexyl)-acetic acid ethyl ester 26



To a solution of the ketal **25** (1g, 4.4mmol) in dry THF (20ml) was treated with H_2O_2 (30% aq, 20ml) and tungstic acid (2.2g, 8.8mmol) and stirred for 48hrs at 0^oC. The reaction mixture was extracted with dichloromethane, washed with brine and dried with $MgSO_4$. Purification by column chromatography gave the product in 73%. ^{1}HNMR (400MHz, $CDCl_3$) δ_H, 1.26(t, 3H, J = 7.15Hz, CH_3), 1.62(m, 2H, cyclohexyl),1.78(m, 4H, cyclohexyl), 1.92(m, 2H, cyclohexyl), 2.22(d, 2H, J = 13.51Hz, CH_2CO), 2.4(m, 1H, CH), 4.14(q, 2H, J = 7.15Hz, OCH_2), 8.55(bs, 2H, OH), ^{13}CNMR (100MHz, $CDCl_3$), δ_C 14.20, 24.78, 28.19, 41.76, 60.67, 109.58.

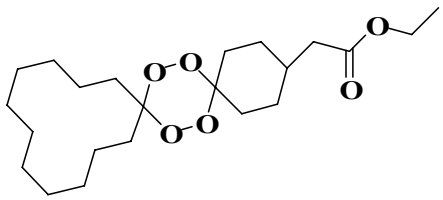
General procedure for the preparation of the 1,2,4,5-tetraoxane esters.

Preparation of (7,8,15,16-Tetraoxa-dispiro[5.2.5.2]hexadec-3-yl)acetic acid ethyl Ester 27a



A stirred solution of cyclohexanone **5** (1.7g, 7.26mmol) in ethyl acetate was added 54% ethereal solution of HBF_4 (1.25g, 14.2mmol) to ethyl 2-(4,4-dihydroperoxycyclohexyl)acetate **26** and stirred for 3hrs at room temperature. Purification by column chromatography gave the product in 50%. V_{max} ($CHCl_3$)/cm^{-1} 1444.8, 1731.6, 2853.8, 2926.4, 3014.3 ^{1}HNMR (400MHz, $CDCl_3$) δ_H, 1.25(t, 4H, J = 7.15Hz, CH_3), 1.4-1.84(m, 14H, cyclohexyl), 1.9(m, 2H, CH_2), 2.14-2.50(m, 4H, cyclohexyl), 3.09(bs, 1H, CH), 4.13(q, 2H, J = 4.45Hz, CH_2) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 14.65, 22.57, 25.75, 28.75, 29.10, 31.46, 34.07, 41.12, 60.79, 108.15, 108.70, 173.07 MS (ES+) $[M + Na]^+$ (100), 337.2 $[2M + Na]^+$, 651.4 HRMS calculated for 337.1627 $C_{12}H_{20}O_6Na$ found, 337.1615.

Preparation of **(7,8,21,22-Tetraoxa-dispiro[5.2.11.2]docos-3-yl)-acetic acid ethyl ester 28a**

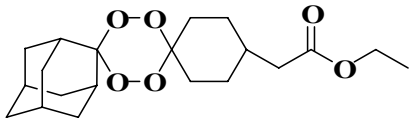


This product was prepared in 33% according to the general procedure for preparing 1,2,4,5-tetraoxane esters.

V_{max} ($CHCl_3$)/cm^{-1} 1450.0, 1723.0, 2849.8, 2936.8, 3020.4, 3435.3 ^{1}HNMR (400MHz, $CDCl_3$) δ_H, 1.25(t, 3H, J = 7.21Hz, CH_3), 1.26-1.40(m, 16H, CH_2), 1.40-1.49(m, 4H, CH_2), 1.50-1.62(m, 4H, CH_2), 1.64-1.81(m, 6H, CH_2), 1.83-1.99(m, 1H, CH), 1.23(d, 2H, J = 4.56Hz, CH_2CO), 4.13(q, 2H, J = 7.21Hz, OCH_2) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 14.67, 22.65, 22.97, 24.62,

24.99, 25.15, 25.77, 26.29, 26.39, 27.82, 34.10, 40.79, 41.15, 60.71, 107.94, 112.81, 173.11 MS (ES+), m/z 398.53 $[M + Na]^+$ (100), 421.1HRMS calculated for421.2566 $C_{22}H_{38}O_6Na$ found, 421.2581.

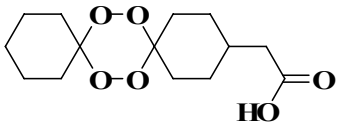
Preparation of **adamantyl tetraoxane ethylester 29a**



This product was prepared in 50% according to the general procedure for preparing 1,2,4,5-tetraoxane esters. Melting point 60-62°C V_{max} $(CHCl_3)/cm^{-1}$ 1446.8, 1718.5, 2858.9, 2922.3, 3003.8 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.25(t, 3H, J = 7.31Hz, CH_3), 1.28-1.37(m, 2H, CH_2), 1.48-1.79(m, 10H, CH_2), 1.87(bs, 2H, CH_2), 1.91-2.20(m, 9H, CH_2/CH), 2.23(d, 2H, J = 6.83Hz, CH_2CO), 4.13(q, 2H, J = 7.21Hz, CH_2)^{13}CNMR (100MHz, $CDCl_3$), δ_C 14.62, 27.48, 27.87, 34.10, 36.72, 37.37, 39.65, 41.12, 47.38, 60.62, 107.99, 110.78, 173.00 MS (ES+), $[M + Na]^+$ (100), 389.1 $[2M + Na]^+$ 755.2 HRMS calculated for 389.1940 $C_{20}H_{30}O_6Na$ found, 389.1954.

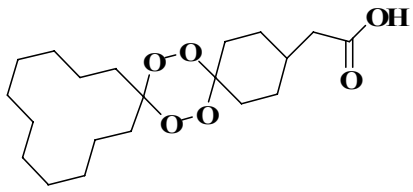
General procedure for the preparation of the carboxylic acids.

Preparation of 7,8,15,16-Tetraoxa-dispiro[5.2.5.2]hexadec-3-yl)acetic acid 27b



The ethyl ester **27a** (1.82g, 5.8mmol) was hydrolyzed in 60ml methanol at 70^{o}C with KOH (1.8g, 31.65mmol) and 6ml water. After one hour heating, the reaction mixture was cooled and diluted with 90ml dichloromethane and 30ml water. The aqueous layer was acidified with concentrated HCl (6ml). The aqueous layer was further extracted with DCM. The combined organic layers were washed with water, brine, dried over Na_2SO_4 and evaporated to dryness. Purification by column chromatography gave the pure acid **27b** in 75%. Melting point 124-126^{o}C ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.2-1.37(m, 4H, cyclohexyl), 1.46(m, 2H, cyclohexyl), 1.57(bs, 6H, cyclohexyl), 1.75(m, 4H, cyclohexyl), 1.88(m, 1H, CH), 2.27(d, 2H, J = 6.3Hz, CH_2CO), 2.12-2.39(m, 2H, cyclohexyl) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 23.12, 25.76, 25.80, 25.92, 28.97, 30.02, 30.24, 30.95, 32.28, 33.86, 40.63, 107.51, 108.04, 178.42 MS (ES+), $[M - H]^+$ (100), 285.1, $[2M - H]^+$, 571.1.

Preparation of **(7,8,21,22-Tetraoxa-dispiro[5.2.11.2]docos-3-yl)-acetic acid 28b**

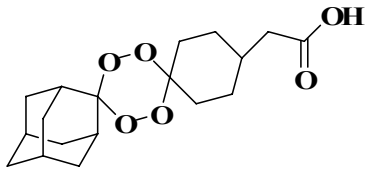


This product was prepared in 66% according to the general procedure for preparing of carboxylic acids.

Melting point 166-168^{o}C V_{max} ($CHCl_3$)/cm^{-1} 1692.8, 2851.1, 2931.2, 3019.3, 3355.7 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.22-1.45(m, 22H, CH_2), 1.51-1.64(m, 4H, CH_2), 1.65-1.77(m, 4H, CH_2),

1.90-1.90(m, 1H, CH), 2.28(d, 2H, J = 7.03Hz, CH_2CO), ^{13}CNMR (100MHz, $CDCl_3$), δ_C 19.77, 22.41, 22.98, 24.70, 25.06, 25.20, 26.37, 29.77, 40.81, 107.30, 118.89, 177.48.

Preparation of **adamantyl tetraoxane carboxylic acid 29b**

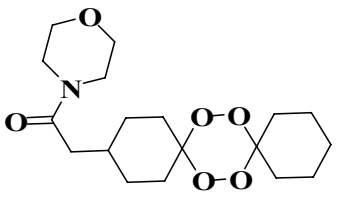


This product was prepared in 66% according to the general procedure for preparing carboxylic acids.

Melting point 119-121^{o}C V_{max} ($CHCl_3$)/cm^{-1} 991.8, 1057.5, 1446.7, 1694.3, 2844.0, 2924.8, 3005.7 3355.7 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.22-1.46(m, 2H, CH_2), 1.50-1.90(m, 12H, CH_2), 1.01-2.05(m, 4H, CH_2), 2.06-2.15(m, 5H, CH), 2.29(d, 2H, J = 6.83Hz, CH_2CO), ^{13}CNMR (100MHz, $CDCl_3$), δ_C 27.47, 27.84, 33.52, 33.86, 36.69, 37.35, 39.65, 40.75, 47.34, 108.89, 110.79, 178.23. MS (ES+), $[M - H]^+$ (100), 337.2 HRMS calculated for 337.1651 $C_{18}H_{25}O_6$ found, 337.1663.

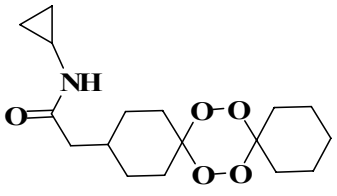
General procedure for amide coupling reactions.

Preparation of 1-Morpholin-4-yl-2-(7,8,15,16-tetraoxa-dispiro[5.2.5.2]hexadec-3-yl)-Ethanone 27h



A solution of 7,8,15,16-Tetraoxa-dispiro[5.2.5.2]hexadec-3-yl)acetic acid **27b** (0.1g, 0.35mmol) in dry dichloromethane (18ml), with added triethylamine (0.04g, 0.005ml, 0.35mmol) and ethylchloroformate (0,005g, 0.04ml, 0.46mmol) was stirred for 60minutes at 0^{o}C. (0.06g, 0.06ml, 0.70mmol) of morpholine was added, and after 30minutes of stirring the reaction mixture was warmed to room temperature. After 90minutes, it was diluted with water and extracted with dichloromethane. The organic extract was washed with brine, dried over anhydrous Na_2SO_4. The crude product was purified by flash chromatography to give the pure amide in 84%. Melting point. 126-128^{o}C V_{max} ($CHCl_3$)/cm^{-1} 1444.5, 1632.7, 2851.1, 2931.2, 3011.3 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.19-1.35(m, 4H, cyclohexyl), 1.46(bs, 2H, cyclohexyl), 1.57(bs, 6H, cyclohexyl), 1.77(m, 4H, cyclohexyl), 1.98(m, 1H, CH) 2.16-2.35(m, 4H, CH_2/cyclohexyl), 3.45(t, 2H, J = 4.76Hz, NCH_2), 3.59-3.67(m, 6H, CH_2O). ^{13}CNMR (100MHz, $CDCl_3$), δ_C 25.76, 34.20, 39.22, 67.35, 108.21, 108.69, 170.9 MS (ES+), $[M + Na]^+$ (100) 378.2, $[2M + Na]^+$ 733.4 HRMS calculated for 378.1893 $C_{18}H_{29}NO_6$ Na found, 378.1886.

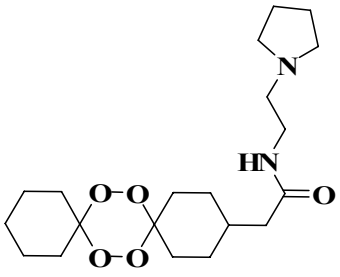
Preparation of *N*-Cyclopropyl-2-(7,8,15,16-tetraoxa-dispiro[5.2.5.2]hexadec-3-yl)-acetamide 27c



This product was prepared in 84% according to the general procedure for the amide coupling reactions.

Melting point 148-150^{o}C V_{max} ($CHCl_3$)/cm^{-1} 1444.6, 1535.6, 1636.7, 2851.1, 2939.2, 3019.3, 3299.6 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 0.47(m, 2H, cyclopropyl), 0.77(m, 2H, cyclopropyl), 1.25(m, 4H, cyclohexyl), 1.46(m, 2H, cyclohexyl), 1.57(bs, 6H, cyclohexyl), 1.72(m, 4H, cyclohexyl), 1.94(m, 1H, CH), 2.02(d, 2H, J = 5.04Hz, CH_2CO), 1.96-2.08(m, 2H, cyclohexyl), 2.71(m, 1H, CH-cyclopropyl), 5.7(bs, 1H, NH) ^{13}CNMR (100MHz, $CDCl_3$) δ_C 7.03, 22.99, 25.75, 34.43, 43.49, 108.20, 108.67, 173.54 MS (ES+), [M + Na] $^{+}$ (100) 348.2, [2M + Na]+ 673.3 HRMS calculated for 348.1787 $C_{17}H_{27}O_5NNa$ found, 348.1791.

Preparation of *N*-(2-Pyrrolidin-1-yl-ethyl)-2-(7,8,15,16-tetraoxa-dispiro[5.2.5.2]-hexadec-3-yl)-acetamide 27d

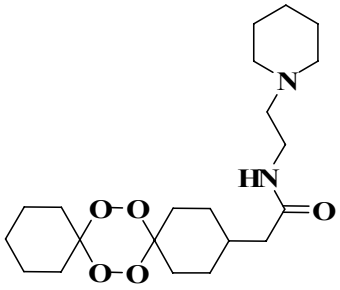


This product was prepared in 78% according to the general procedure for the amide coupling reactions.

Melting point 110-112^{o}C V_{max} ($CHCl_3$)/cm^{-1} 1444.6, 1512.6, 1652.8, 2859.2, 2931.2, 3011.3, 3315.6 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.2-1.34(m, 4H, cyclohexyl), 1.47(m, 2H, cyclohexyl),

1.57(bs, 6H, cyclohexyl), 1.73(m, 4H, cyclohexyl), 1.83-2.1(m, 5H, CH/CH_2), 2.16(d, 2H, J = 6.99Hz, CH_2CO), 2.23-2.32(m, 2H,cyclohexyl), 2.68-2.79(m, 2H, CH_2N), 2.86(t, 4H, J = 6.04Hz, NCH_2), 3.49(q, 2H, J = 5.88Hz, $NHCH_2$), 6.98(bs, 1H, NH). ^{13}CNMR (100MHz, $CDCl_3$), δ_C 15.01, 23.77, 23.82, 25.75, 34.42, 37.26, 43.33, 54.42, 55.57, 108.23, 108.61, 172.79 MS (ES+), m/z 382.49 $[M + H]^+$ (74.77) 383.1, $[M + Na]^+$ (100) 405.1 HRMS calculated for 383.2546 $C_{20}H_{35}O_5$ found, 383.2553 and 405.2365 $C_{20}H_{34}N_2O_5Na$, found, 405.2364.

Preparation of *N*-(2-Piperidin-1-yl-ethyl)-2-(7,8,15,16-tetraoxa-dispiro[5.2.5.2]-hexadec-3-yl)-acetamide 27e

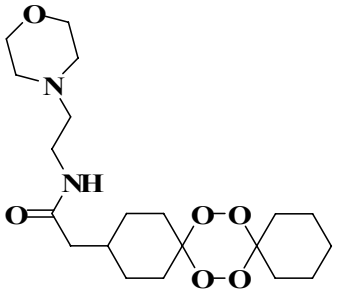


This product was prepared in 81% according to the general procedure for the amide coupling reactions.

Melting point 68-78°C V_{max} ($CHCl_3$)/cm^{-1} 1444.4, 1508.6, 1648.8, 2856.2, 2934.5, 3012.7, 3325.8 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.25(t, 4H, J = 7.16Hz, cyclohexyl), 1.47(m, 4H, cyclohexyl/piperidyl), 1.57(bs, 6H, cyclohexyl), 1.65(m, 4H, cyclohexyl), 1.74(m, 4H, piperidyl), 1.94(m, 1H, CH), 2.15(d, 2H, J = 7.0Hz, CH_2CO), 2.30(m, 2H, cyclohexyl), 2.53(m, 2H, NCH_2), 2.66(m, 4H, CH_2N), 3.45(q, 2H, J = 5.73Hz, $NHCH_2$), 6.94(bs, 1H, NH). ^{13}CNMR (100MHz, $CDCl_3$), δ_C 20.08, 21.53, 21.99, 22.75, 23.41, 32.11, 33.24, 35.34, 41.07, 52.26,

52.39, 55.38, 55.77, 58.78, 105.89, 106.27, 170.30 MS (ES+), $[M + H]^+$ (66.29) 397.1, $[M + Na]^+$ (100) 419.1 HRMS calculated for 397.2702 $C_{21}H_{37}N_20_5$ found, 397.2704, and for 419.2522 $C_{21}H_{36}N_20_5Na$ found 419.2518.

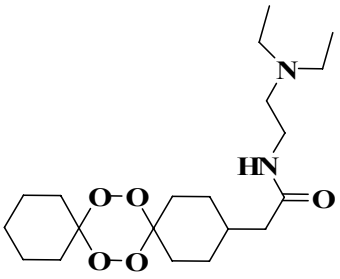
Preparation of *N*-(2-Morpholin-4-yl-ethyl)-2-(7,8,15,16-tetraoxa-dispiro[5.2.5.2]-hexadec-3-yl)-acetamide 27f



This product was prepared in 76% according to the general procedure for the amide coupling reactions.

V_{max} $(CHCl_3)/cm^{-1}$ 1444.4, 1508.6, 1656.8, 2811.1, 2851.1, 2931.2, 3307.6 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.25(m, 4H, cyclohexyl), 1.47(m, 2H, cyclohexyl), 1.58(m, 6H, cyclohexyl), 1.70-1.78(m, 4H, cyclohexyl), 1.94(m, 1H, CH), 2.1(d, 2H, J = 7.15Hz, CH_2CO), 2.13-2.37(m, 2H, cyclohexyl), 2.41-2.51(m, 6H, CH_2N/NCH_2), 3.36(q, 2H, J = 5.88Hz, $NHCH_2$), 3.7(m, 4H, CH_2O), 5.98(bs, 1H, NH) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 15.03, 25.74, 34.44, 35.92, 43.66, 53.75, 57.52, 67.25, 67.29, 108.20, 108.68, 172.16 MS (ES+), $[M + Na]^+$ (100) 421.1, HRMS calculated for 421.2315 $C_{20}H_{34}O_6N_2Na$ found, 421.2323.

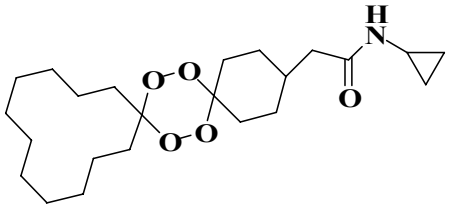
Preparation of *N*-(2-Diethylamino-ethyl)-2-(7,8,15,16-tetraoxa-dispiro[5.2.5.2]-hexadec-3-yl)-acetamide 27g



This product was prepared in 58% according to the general procedure for the amide coupling reactions.

V_{max} ($CHCl_3$)/cm^{-1} 1444.5, 1508.6, 1652.8, 2859.1, 2939.2, 3011.4, 3323.6 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.02(t, 3H, J = 7.15Hz, CH_3), 1.05(t, 3H, J = 7.15Hz, CH_3), 1.25(m, 4H, cyclohexyl), 1.46(m, 2H, cyclohexyl), 1.59(bs, 6H, cyclohexyl), 1.74(m, 4H, cyclohexyl), 1.94(m, 1H, CH), 2.1(d, 2H, J = 7.16Hz, CH_2CO), 2.14-2.35(m, 2H, cyclohexyl), 2.57(m, 6H, CH_2N/NCH_2), 3.23(q, 1H, J = 5.88Hz, $NHCH_2$), 3.33(q, 1H, J = 6.2Hz, $NHCH_2$), 6.30(bs, 1H, NH) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 11.76, 11.98, 15.02, 25.73, 34.43, 36.95, 43.60, 47.19, 51.99, 52.33, 108.21, 108.60, 172.25 MS (ES+), $[M + H]^+$ (100) 385.2, HRMS calculated for 385.2702 $C_{20}H_{37}N_2O_5$ found, 385.2695.

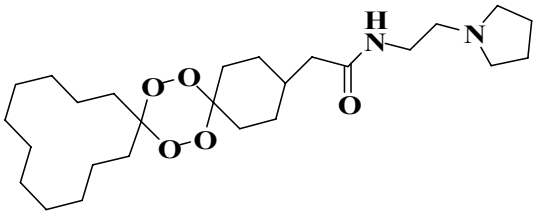
Preparation of ***N*-Cyclopropyl-2-(7,8,21,22-tetraoxa-dispiro[5.2.11.2]docos-3-yl)-acet-amide 28c**



This product was prepared in 88% according to the general procedure for the amide coupling reactions.

Mpt. 136-138°C V_{max} ($CHCl_3$)/cm^{-1} 1523.8, 1637.0, 2849.8, 2931.3, 3003.8, 3311.7 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 0.46(m, 2H, cyclopropyl), 0.77(m, 2H, cyclopropyl), 1.14-1.47(m, 22H, CH_2), 1.50-1.84(m, 8H, CH_2),1.94(m, 1H, CH), 2.02(d, 2H, J = 7.02Hz, CH_2CO), 2.70(m, 1H, CH), 5.6(bs, 1H, NH), ^{13}CNMR (100MHz, $CDCl_3$), δ_C 7.04, 8.88, 22.43, 22.72, 23.00, 26.33, 26.39, 28.74, 29.56, 34.46, 43.51, 107.99, 112.77, 173.54 MS (ES+), $[M + Na]^+$ (100), 432.2 $[2M + Na]^+$, 841.4 HRMS calculated for 432.2726 $C_{23}H_{39}O_5Na$ found, 432.2723.

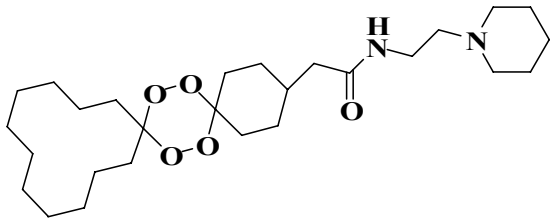
Preparation of ***N*-(2-Pyrrolidin-1-yl-ethyl)-2-(7,8,21,22-tetraoxa-dispiro[5.2.11.2]do-cos-3-yl)-acetamide 29d**



This product was prepared in 81% according to the general procedure for the amide coupling reactions.

Mpt. 108-110°C V_{max} ($CHCl_3$)/cm^{-1} 1548.6, 1628.7, 2859.1, , 2931.5, 3003.7, 3327.1 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.10-1.49(m, 22H, CH_2), 1.50-1.83(m, 8H, CH_2),1.94-2.00(m, 5H, CH), 2.16(d, 2H, J = 7.03Hz, CH_2CO), 2.81-3.18 (m, 6H, NCH_2/CH_2N), 3.51(q, 2H, J = 5.70Hz, $NHCH_2$), 7.1(bs, 1H, NH) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 18.60, 19.74, 22.34, 22.70, 23.77, 26.30, 26.37, 28.58, 29.40, 31.54, 34.41, 37.14, 43.28, 54.42, 55.48, 107.97, 112.67, 172.88 MS (ES+), $[M + H]^+$ (100), 467.3 HRMS calculated for 467.3485 $C_{26}H_{47}O_5N_2$ found, 467.3487.

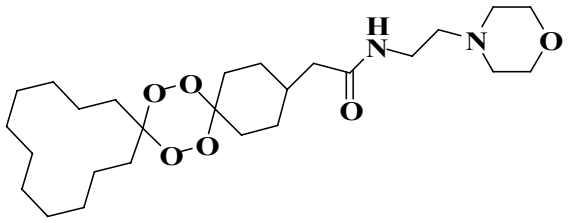
Preparation of ***N*-(2-Piperidin-1-yl-ethyl)-2-(7,8,21,22-tetraoxadispiro[5.2.11.2]-docos-3-yl)-acetamide 28e**



This product was prepared in 82% according to the general procedure for the amide coupling reactions.

Mpt. 96-98°C V_{max} ($CHCl_3$)/cm^{-1} 1505.7, 1650.6, 2849.0, 2931.3, 3019.3, 3320.8 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.18-1.64(m, 30H, CH_2), 1.65-1.79(m, 6H, CH_2), 1.89-1.86-1.90(m,1H, CH)1.13(d, 2H, J = 7.02Hz, CH_2CO), 2.49-2.62(m, 6H, CH_2N/NCH_2), 3.41(q, 2H, J = 5.88Hz, $NHCH_2$), 6.20(bs, 1H, NH) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 22.72, 24.17, 25.51, 26.39, 34.50, 35.81, 43.55, 54.65, 57.69, 108.03, 112.73, 172.47 MS (ES+), $[M + Na]^+$ (100), 5.5.2 $[M + H]^+$, 481.2 HRMS calculated for 503.3461$C_{27}H_{48}ON_2Na$ found, 503.3449.

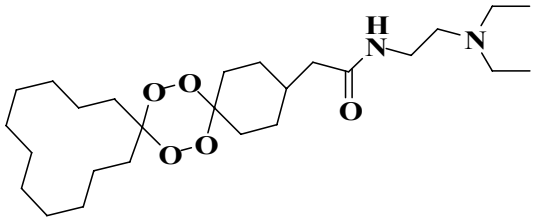
Preparation of ***N*-(2-Morpholin-4-yl-ethyl)-2-(7,8,21,22-tetraoxa-dispiro[5.2.11.2]do-cos-3-yl)-acetamide 28f**



This product was prepared in 78% according to the general procedure for the amide coupling reactions.

Mpt. 78-80^{o}C V_{max} ($CHCl_3$)/cm^{-1} 1533.1, 1643.0, 2806.2, 2850.2, 2920.5, 3315.9 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.10-1.49(m, 22H, CH_2), 1.50-1.80(m, 8H, CH_2),1.86(m, 1H, CH), 2.11(d, 2H, J = 7.03Hz, CH_2CO), 2.42-2.51(m, 6H, NCH_2/CH_2N), 3.37(q, 2H, J = 5.88Hz, $NHCH_2$), 3.72(t, 4H, J = 4.55Hz, CH_2O), 6.0(bs, 1H, NH) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 19.67, 19.73, 19.81, 22.33, 2251, 22.59, 26.28, 26.35, 26.54, 26.59, 26.98, 27.06, 28.77, 29.21, 29.49, 29.80, 31.86, 34.70, 35.87, 44.01, 53.72, 57.50, 67.26, 107.47, 112.14, 172.55 MS (ES+), $[M + H]^+$ (100), 483.3 $[M + Na]^+$, 505.2 HRMS calculated for 483.3434 $C_{26}H_{47}O_6N_2$ found, 483.3424.

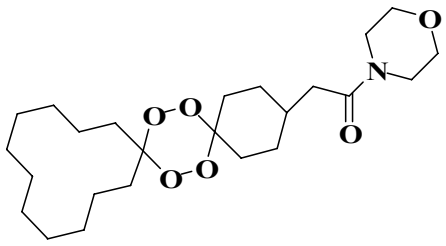
Preparation of ***N*-(2-Diethylamino-ethyl)-2-(7,8,21,22-tetraoxa-dispiro[5.2.11.2]-docos-3-yl)-acetamide 28g**



This product was prepared in 74% according to the general procedure for the amide coupling reactions.

Mpt. 64-66°C V_{max} ($CHCl_3$)/cm^{-1} 1446.6, 1660.8, 2812.3, 2931.2, 3003.8, 3251.6 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.15(t, 6H, J = 7.21Hz, CH_3), 1.23-1.49(m, 22H, CH_2), 1.50-1.79(m, 8H, CH_2), 1.85(m, 1H, CH), 2.12(d, 2H, J = 7.02Hz, CH_2CO), 2.73(q, 6H, J = 7.02Hz, NCH_2/CH_2N), 3.42(q, 2H, J = 5.89Hz, NCH_2), 6.30(bs, 1H, NH) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 10.97, 19.70, 19.76, 19.79, 22.40, 22.59, 22.67, 26.33, 26.38, 26.56, 26.62, 27.04, 27.11, 28.77, 29.21, 29.47, 31.86, 34.61, 36.44, 43.80, 47.51, 51.08, 52.38, 107.49, 112.11, 172.90 MS (ES+), $[M + H]^+$ (100), 469.3 $[M + Na]^+$, 491.3 HRMS calculated for 469.3641 $C_{26}H_{49}O_5N_2$ found, 469.3659.

Preparation of **1-Morpholin-4-yl-2-(7,8,21,22-tetraoxa-dispiro[5.2.11.2]docos-3-yl)-ethanone 28h**

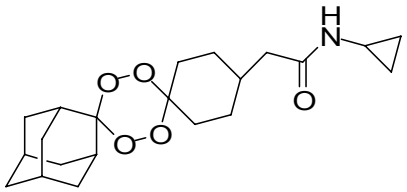


This product was prepared in 90% according to the general procedure for the amide coupling

reactions.

Mpt. 118-120°C V_{max} ($CHCl_3$)/cm^{-1} 1437.7, 1632.5, 2858.9, 2931.3, 3003.7 ^{1}HNMR (400MHz, $CDCl_3$) δ_H, 1.15-1.49(m, 22H, CH_2), 1.50-1.84(m, 8H, CH_2),1.98(m, 1H, CH), 2.23(bs, 2H, CH_2), 3.45(m, 2H, morpholine), 3.65(m, 6H, morpholine), ^{13}CNMR (100MHz, $CDCl_3$), δ_C 22.25, 22.72, 26.33, 26.39, 29.52, 31.61, 34.23, 39.23, 42.37, 46.60, 67.06, 67.37, 107.99, 112.79, 170.92 MS (ES+), $[M + Na]^+$ (100), 462.2 $[2M + Na]^+$, 901.4 HRMS calculated for 462.2832 $C_{24}H_{41}O_6Na$ found, 462.2834.

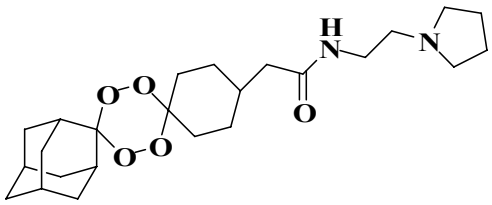
Preparation of adamantyl- ***N*-Cyclopropyl tetraoxane acetamide 29c**



This product was prepared in 83% according to the general procedure for the amide coupling reactions.

Mpt. 140-142°C V_{max} ($CHCl_3$)/cm^{-1} 1496.6, 1664.2, 2858.9, 2922.3, 3012.8, 3320.8 ^{1}HNMR (400MHz, $CDCl_3$) δ_H, 0.48(m, 2H, cyclopropyl), 0.78(m, 2H, cyclopropyl), 1.14-1.38(m, 2H, CH_2), 1.40-1.80(m, 14H, CH_2),1.88(bs, 2H, CH_2CO), 1.83-2.05(m, 7H, CH/CH_2), 2.70(m, 1H, CH-cyclopropyl), 5.5(bs, 1H, NH), ^{13}CNMR (100MHz, $CDCl_3$), δ_C 7.05, 8.89, 23.00, 27.47, 27.49, 33.54, 33.56, 34.46, 37.37, 39.48, 43.52, 108.09, 110.80, 173.53 MS (ES+), $[M + Na]^+$ (100), 400.2 $[2M + Na]^+$, 777.4 HRMS calculated for 400.21 $C_{21}H_{31}O_5NNa$ found, 400.2083.

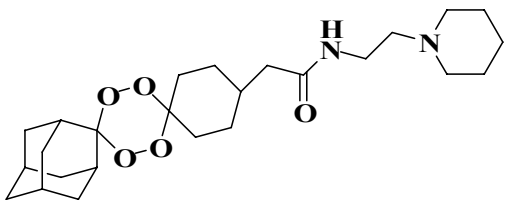
Preparation of ***N*-(2-Pyrrolidin-1-yl-ethyl)-[adamantyl] acetamide 29d**



This product was prepared in 80% according to the general procedure for the amide coupling reactions.

Mpt. 142-144^{o}C V_{max} ($CHCl_3$)/cm^{-1} 1446.7, 1559.9, 1641.1, 2859.1, 2931.2, 2937.7, 3260.8 ^{1}HNMR (400MHz, $CDCl_3$) δ_H 1.19-1.35(m, 2H, CH_2), 1.50-1.83(m, 14H, CH_2), 1.83-1.89(m, 4H, CH_2), 1.90-2.04(m, 5H, CH), 2.12(d, 2H, J = 7.02Hz, CH_2CO), 2.50-2.67(m, 6H, NCH_2/CH_2N), 3.31(q, 4H, J = 5.50Hz, CH_2), 6.55(bs, 1H, NH), ^{13}CNMR (100MHz, $CDCl_3$), δ_C 23.81, 23.83, 27.47, 27.85, 28.61, 33.52, 33.53, 34.45, 36.69, 37.35, 37.95, 39.64, 39.80, 43.51, 47.36, 50.89, 54.29, 55.33, 55.57, 61.06, 108.12, 110.74, 172.53 MS (ES+), $[M + Na]^+$ (100), 457.2 $[2M + Na]^+$, 891.3 HRMS calculated for 457.2678 $C_{24}H_{38}O_5N_2Na$ found, 457.2680.

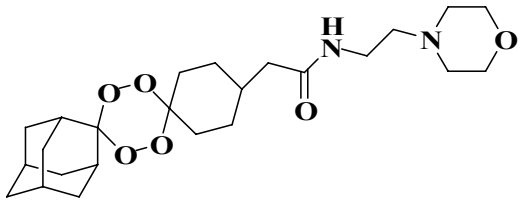
Preparation of ***N*-(2-Piperidin-1-yl-ethyl)-[adamantyl]acetamide 29e**



This product was prepared in 78% according to the general procedure for the amide coupling reactions.

Mpt. 119-121°C V_{max} ($CHCl_3$)/cm^{-1} 1446.7, 1541.3, 1650.3, 2794.9, 2846.8, 2919.4, 3324.1 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$) 1.22-1.41(m, 2H, CH_2), 1.45-1.79(m, 16H, CH_2), 1.86(bs, 2H, CH_2), 1.89-2.17(m, 9H, CH/CH_2), 2.24(d, 2H, J = 6.83Hz, CH_2CO), 3.10(t, 6H, J = 5.50Hz, CH_2N/NCH_2), 3.68(q, 2H, J = 5.31Hz, $NHCH_2$), 8.15(bs, 1H, NH), ^{13}CNMR (100MHz, $CDCl_3$), δ_C 22.44, 22.94, 27.50, 33.55, 34.16, 34.48, 37.40, 43.05, 54.64, 58.15, 108.10, 110.70, 173.46 MS (ES+), $[M + Na]^+$ (100), 471.2 HRMS calculated for 471.2835 $C_{25}H_{40}O_5N_2Na$ found, 471.2854.

Preparation of ***N*-(2-Morpholin-4-yl-ethyl)-adamantyl acetamide 29f**

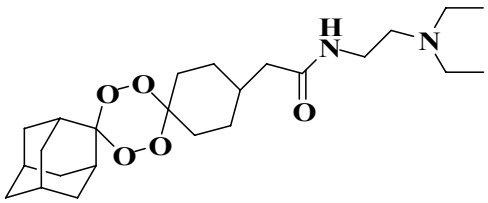


This product was prepared in 77% according to the general procedure for the amide coupling reactions.

V_{max} (neat)/cm^{-1} 1446.2, 1539.6, 1648.6, 2858.9, 2913.2, 2926.4, 3331.1 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.42-1.79(m, 14H, CH_2), 1.80, 1.99(m, 2H, CH_2), 1.99-2.20(m, 5H, CH), 2.30-2.07(m, 2H, CH_2), 2.09(d, 2H, J = 7.02Hz, CH_2CO), 3.28(q, 2H, J = 5.51Hz, CH_2N/NCH_2), 3.67-3.73(m, 4H, CH_2O), 6.0(bs, 1H, NH) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 27.45, 27.47, 33.53, 33.55, 34.46, 35.94, 37.35, 43.68, 53.74, 67.28, 108.08, 110.80, 172.23 MS (ES+), $[M + Na]^+$

(100), 473.2 $[M + H/K]^+$, 451.2/489.2 HRMS calculated for 473.2628 $C_{24}H_{38}O_6N_2Na$ found, 473.2649.

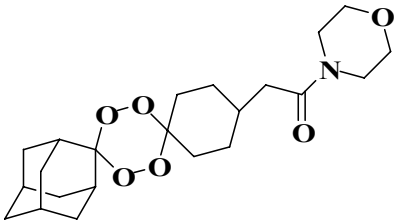
Preparation of ***N*-(2-Diethylamino-ethyl)-[adamantly]acetamide 29g**



This product was prepared in 66% according to the general procedure for the amide coupling reactions.

V_{max} (neat)/cm^{-1} 1446.7, 1524.1, 1660.6, 2812.3, 2928.4, 2957.5, 3341.5 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.18(t, 6H, J = 7.21Hz, CH_3), 1.22-1.40(m, 2H, CH_2), 1.50-1.78(m, 14H, CH_2), 1.80-1.88(m, 2H, CH_2), 1.90-2.04(m, 5H, CH), 2.15(d, 2H, J = 7.02Hz, CH_2CO), 2.76-2.85(m, 6H, NCH_2/CH_2N), 3.45(m, 2H, NCH_2), 7.18(bs, 1H, NH) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 10.68, 27.47, 33.53, 34.43, 37.36, 43.39, 47.56, 50.99,52.39, 52.51, 108.10, 110.10, 172.86 MS (ES+), $[M + H]^+$ (100), 437.2 $[M + Na]^+$, 459.2 HRMS calculated for 437.3015 $C_{24}H_{41}O_5N_2$ found, 437.3035.

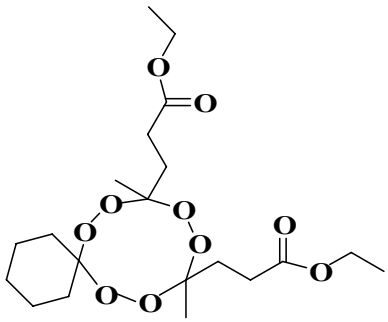
Preparation of **adamantly-1-Morpholin-4-yl tetraoxane acetamide 29h**



This product was prepared in 81% according to the general procedure for the amide coupling reactions.

Mpt. 139-140^{o}C V_{max} ($CHCl_3$)/cm^{-1} 1442.3, 1632.5, 2858.9, 2913.2, 3003.8 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.11-1.38(m, 2H, CH_2), 1.50-1.82(m, 12H, CH_2), 1.85(bs, 2H, CH_2), 1.90-2.18(m, 5H, CH), 2.30(d, 2H, J = 7.02Hz, CH_2CO), 3.46(t, 2H, J = 4.56Hz, NCH_2), 3.60-3.69(m, 6H, NCH_2/CH_2O) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 26.52, 27.47, 27.49, 28.94, 30.69, 33.54, 33.56, 33.82, 34.25, 35.20, 37.37, 39.21, 42.37, 46.60, 67.07, 67.37, 108.10, 110.81, 170.92 MS (ES+), $[M + Na]^+$ (100), 430.2 $[2M + Na]^+$, 837.4 HRMS calculated for 430.2206 $C_{22}H_{33}O_6NNa$ found, 430.2213.

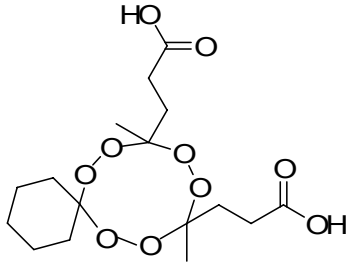
Preparation of 3-[12-(2-Ethoxycarbonyl-ethyl)-9,12-dimethyl-7,8,10,11,13,14-hexaoxa-spiro[5.8]tetradec-9-yl]-propionic acid ethyl ester 31



This product was prepared in 68% according to the general procedure for preparation of 1,2,4,5-tetraoxane esters.

V_{max} (neat)/cm^{-1} 947.3, 1023.1, 1058.4, 1114.0, 1371.8, 1447.6, 1730.6, 2866.0, 2936.8, 2977 ^{1}HNMR (400MHz, $CDCl_3$) δ_H 1.27(t, 6H, J = 7.15Hz, CH_3), 1.38(t, 6H, J = 5.25Hz, CH_3), 1.41-1.63(m, 6H, cyclohexyl), 1.64-1.90(m, 4H, cyclohexyl), 1.94-2.07(m, 2H, CH_2), 2.10-2.24(m, 2H, CH_2) 2.35-2.51(m, 4H, CH_2), 4.14(q, 4H, OCH_2) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 14.56, 19.15, 22.94, 22.97, 23.00, 23.02, 25.81, 29.62, 29.85, 29.88, 29.90, 30.03, 30.60, 30.77, 30.84, 31.01, 108.33, 108.79, 173.30 MS (ES+) $[M + Na]^+$ (100), 457.1, HRMS calculated for 457.2050 $C_{20}H_{34}O_{10}Na$ found, 457.1992.

Preparation of **3-[12-(2-Carboxy-ethyl)-9,12-dimethyl-7,8,10,11,13,14-hexaoxa-spiro-[5.8]tetradec-9-yl]-propionic acid 31a**

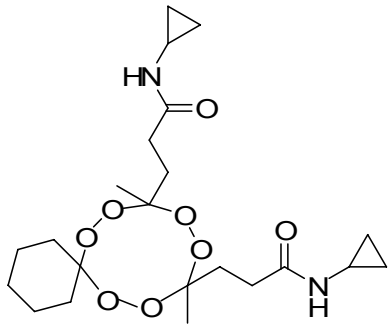


This product was prepared in 88% according to the general procedure for preparation of carboxylic acids.

^{1}HNMR (400MHz, $CDCl_3$) δ_H 1.37-1.43(m, 6H, CH_3), 1.48-1.62(m, 6H, cyclohexyl), 1.70-1.90(m, 4H, cyclohexyl), 1.95-2.12(m, 2H, CH_2), 2.13-2.26(m, 2H, CH_2), 2.41-2.64(m, 4H, CH_2), 8.90(bs, 2H, OH) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 19.22, 22.99, 25.00, 25.64, 25.81, 29.38,

29.49, 29.65, 29.88, 29.99, 30.56, 30.84, 32.50, 34.36, 108.46, 108.71, 179.39. MS (ES+) [M - H] $^{+}$ (100), 377.2, HRMS calculated for 377.1448 $C_{16}H_{25}O_{10}$ found, 377.1377.

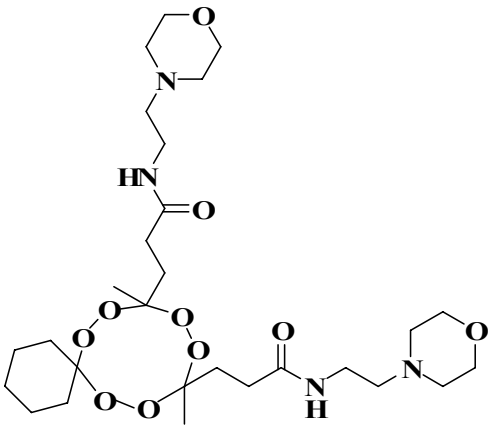
Preparation of *N*-Cyclopropyl-3-[12-(2-cyclopropylcarbamoyl-ethyl)-9,12-dimethyl-7,8,10,11,13,14-hexaoxa-spiro[5.8]tetradec-9-yl]-propionamide 32



This product was prepared in 70% according to the general procedure for amide coupling reactions.

V_{max} ($CHCl_3$)/cm^{-1} 911.0, 956.5, 1017.1, 1269.8, 1365.8, 1451.7, 1557.8, 1638.7, 2945.1, 2985.5, 3066.3, 3308.9 ^{1}HNMR (400MHz, $CDCl_3$) δ_H 0.51(m, 4H, cyclopropyl), 0.73(m, 4H, cyclopropyl), 1.36(s, 6H, CH_3), 1.38-1.61(m, 6H, cyclohexyl), 1.68-1.85(m, 4H, cyclohexyl), 1.92-2.06(m, 2H, CH_2),2.07-2.19(m, 2H, CH_2), 2.20-2.39(m, 4H, CH_2), 2.48-2.55(m, 2H, CH), 5.20(bs, 2H, NH) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 6.82, 7.50, 8.54, 14.53, 19.15, 19.20, 21.35, 22.95, 23.02, 23.05, 25.78, 30.14, 30.34, 30.67, 30.81, 30.86, 31.35, 31.50, 60.71, 108.31, 109.06, 174.23 MS (ES+) [M + Na] $^{+}$ (100), 479.3, HRMS m/z calculated for 479.2369 $C_{22}H_{36}O_8N_2Na$ found, 479.2353.

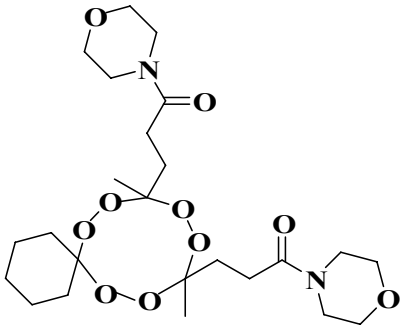
Preparation of 3-*N*-(2-morpholin-4-yl-ethyl)-propionamide 33



This product was prepared in 74% according to the general procedure for amide coupling reactions.

Melting point 136-138°C V_{max} (neat)/cm^{-1} 856.5, 1037.3, 1118.2, 1254.6, 1456.8, 1542.7, 1694.3, 2803.6, 2844.0, 2945.1, 3308.9 ^{1}HNMR (400MHz, $CDCl_3$) δ_H 1.36-1.64(m, 12H, CH_3/cyclohexyl), 1.66-1.89(m, 4H, cyclohexyl), 1.97-2.09(m, 2H, CH_2), 2.10-2.23(m, 2H, CH_2), 2.24-2.42(m, 4H, CH_2), 2.43-2.53(m, 12H, NCH_2/CH_2N), 3.36(q, 4H, J = 6.08Hz, NCH_2), 3.71(t, 8H, J = 3.42Hz, CH_2O), 6.10(bs, 2H, NH) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 23.13, 25.82, 30.41, 30.46, 30.67, 30.73, 30.76, 30.86, 30.90, 31.07, 36.11, 36.15, 53.78, 57.55, 67.28, 108.36, 109.04, 172.53 MS (ES+) $[M + Na]^+$ (100), 625.4, HRMS m/z calculated for 625.3425 $C_{28}H_{50}O_{10}N_4Na$ found, 625.3409.

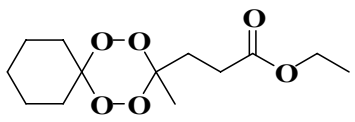
Preparation of 3-[9,12-Dimethyl-12-(3-morpholin-4-yl-3-oxo-propyl)-7,8,10,11,13,14-hexaoxa-spiro[5.8]tetradec-9-yl]-1-morpholin-4-yl-propan-1-one 34



This product was prepared in 78% according to the general procedure for amide coupling reactions.

V_{max} ($CHCl_3$)/cm^{-1} 986.8, 1113.1, 1239.5, 1274.8, 1426.4, 1648.8, 1694.4, 2854.1, 2924.8, 2965.3, ^{1}HNMR (400MHz, $CDCl_3$) δ_H, 1.37-1.64(m, 12H, CH_3/cyclohexyl), 1.65-1.89(m, 4H, cyclohexyl), 1.90-2.07(m, 2H, CH_2), 2.07-2.23(m, 2H, CH_2), 2.30-2.45(m, 2H, CH_2), 2.45-2.61(m, 2H, CH_2), 2.92(bs, 2H, NH), 3.43-3.75(m, 16H, morpholine) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 19.15, 19.26, 22.92, 22.98, 23.06, 25.73, 28.25, 28.37, 30.09, 30.20, 30.28, 30.63, 30.84, 30.98, 42.37, 46.26, 66.97, 67.21, 67.79, 108.33, 108.95, 171.29 MS (ES+), $[M + Na]^+$ (100) 539.3, HRMS calculated for 539.2581 $C_{24}H_{40}N_2O_{10}Na$ found, 539.2570.

Preparation of **3-(3-Methyl-1,2,4,5-tetraoxa-spiro[5.5]undec-3-yl)-propionic acid ethyl ester 35**

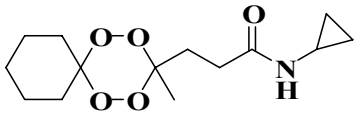


This product was prepared in 18% according to the general procedure for preparation of 1,2,4,5-

tetraoxane esters.

V_{max} ($CHCl_3$)/cm^{-1} 1449.8, 1737.5, 2864.9, 2939.6, 3003.4 ^{1}HNMR (400MHz, $CDCl_3$) δ_H, 1.26(t, 3H, J = 7.21Hz, CH_3), 1.41-1.50(m, 3H, CH_3), 1.51-1.90(m, 4H, CH_2), 2.40-2.65(m, 4H, CH_2), 4.15q, 2H, J = 7.21Hz, CH_2) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 14.54, 20.24, 22.41, 25.71, 30.19, 60.91, 108.42, 108.86, 173.19 MS (ES+), $[M + Na]^+$ (100) 297.1, HRMS calculated for 297.1314 $C_{13}H_{22}NaO_6$ found, 297.1328.

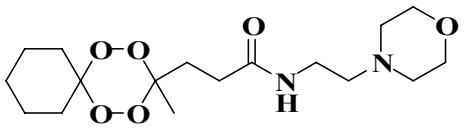
Preparation of ***N*-Cyclopropyl-3-(3-methyl-1,2,4,5-tetraoxa-spiro[5.5]undec-3-yl)-propionamide 37**



This product was prepared in 77% according to the general procedure for amide coupling reactions.

Mpt. 88-90^{o}C V_{max} ($CHCl_3$)/cm^{-1} 1448.5, 1536.6, 1648.8, 2859.1, 2947.2, 3003.3, 3235.5 ^{1}HNMR (400MHz, $CDCl_3$) δ_H, 0.46-0.52(m, 2H, cyclopropyl), 0.73-0.79(m, 2H, cyclopropyl), 1.16-1.35(m, 2H, CH_2), 1.42-1.50(bs, 3H, CH_3), 1.51-1.80(m, 8H, CH_2), 1.81-2.30(m, 4H, CH_2), 2.67-2.74(m, 1H, cyclopropyl), 5.8(bs, 1H, NH) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 6.52, 8.23, 19.96, 21.97, 22.66, 23.77, 25.31, 29.66, 108.05, 108.87, 173.09 MS (ES+), $[M + Na]^+$ (100) 308.1,[2M + Na]+ 593.2 HRMS calculated for 593.3050 $C_{28}H_{46}N_2NaO_{10}$ found, 593.3046.

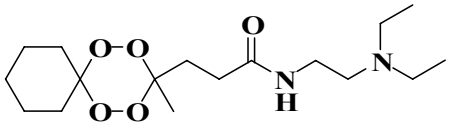
Preparation of **3-(3-Methyl-1,2,4,5-tetraoxa-spiro[5.5]undec-3-yl)-*N*-(2-morpholin-4-yl-ethyl)-propionamide 38**



This product was prepared according to the 70% according to the general procedure for amide coupling reactions.

V_{max} (neat)/cm^{-1} 1454.8, 1641.5, 2812.7, 2856.0, 2935.2, 3324.0 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.47(bs, 3H, CH_3), 1.58(bs, 8H, cyclohexyl), 1.68-1.89(m, 2H, cyclohexyl), 2.42-2.51(m, 10H, CH_2), 3.36(q, 2H, J = 5.69Hz, $NHCH_2$), 3.70(q, 4H, J = 4.75Hz, CH_2O), 6.13(bs, 1H, CH) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 14.86, 19.97, 22.06, 25.34, 25.90, 28.32, 29.68, 30.47, 31.64, 35.80, 37.26, 53.41, 53.81, 108.05, 108.89, 156.69, 171.88, MS (ES+), $[M + Na]^+$ (100) 381.0 HRMS calculated for 381.2002 $C_{17}H_{30}N_2NaO_6$ found, 381.1990.

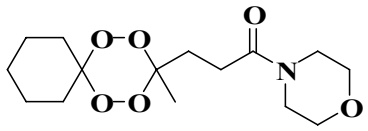
Preparation of ***N*-(2-Diethylamino-ethyl)-3-(3-methyl-1,2,4,5-tetraoxa-spiro[5.5]undec -3-yl) –propionamide 39**



This product was prepared in 78% according to the general procedure for amide coupling reactions.

V_{max} (neat)/cm^{-1} 1448.2, 1539.6, 1653.8, 28.64.9, 2926.4, 2957.5, 3320.8 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.03(t, 6H, J = 7.41Hz, CH_3), 1.07(t, 3H, J = 7.02Hz, CH_3), 1.47(bs, 2H, cyclohexyl), 1.58(bs, 6H, cyclohexyl), 1.64-1.90(m, 2H, cyclohexyl), 2.52-2.65(m, 10H, CH_2), 3.5(q, 2H, J = 5.89Hz, $NHCH_2$), 6.5(bs, 1H, NH) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 11.28, 11.57, 14.70, 19.98, 22.09, 25.38, 29.69, 31.31, 36.73, 38.47, 46.93, 51.71, 52.06, 108.06, 108.93, 172.00 MS (ES+), $[M + Na]^+$ (100) 367.1,[2M + Na]+ 711.1 HRMS calculated for 367.2209 $C_{17}H_{32}N_2NaO_5$ found, 367.2198.

Preparation of **3-(3-Methyl-1,2,4,5-tetraoxa-spiro[5.5]undec-3-yl)-1-morpholin-4-yl-propan-1-one 40**



This product was prepared in 75% according to the general procedure for amide coupling reactions.

Mpt. 94-96^{o}C V_{max} ($CHCl_3$)/cm^{-1} 1442.3, 1641.5, 2849.8, 2931.3, 2994.7 ^{1}HNMR (400MHz, $CDCl_3$) $\delta_{H,}$ 1.30(bs, 3H, CH_3), 1.47(bs, 2H, cyclohexyl), 1.58(bs, 6H, cyclohexyl), 1.71-1.86(m, 2H, cyclohexyl), 2.26(bs, 1H, CH_2), 2.29-2.49(m, 2H, CH_2), 2.60(bs, 1H, CH_2), 3.50(bs, 2H, NCH_2), 3.62(bs, 2H, NCH_2), 3.67(bs, 4H, CH_2O) ^{13}CNMR (100MHz, $CDCl_3$), δ_C 20.34, 22.42, 25.70, 25.86, 28.59, 29.96, 32.11, 42.42, 46.35, 66.66, 66.90, 108.09, 108.92, 170.69 MS (ES+), $[M + Na]^+$ (100) 338.0,[2M + Na]+ 653.0 HRMS calculated for 338.1580 $C_{15}H_{25}NNaO_6$ found, 338.1594.