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, CDCl3) $\delta_H$ 1.46(m, 2H, cyclohexyl), 1.58(m, 4H, cyclohexyl), 1.84(t, 4H, $J = 6.46$Hz, cyclohexyl), 8.1(s, 2H, OH), $^{13}$CNMR (100MHz, CDCl3), $\delta_C$ 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% H₂O₂ 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 with diluted NaHSO₄, dried over MgSO₄ and solvent evaporated under reduced pressure. Products were determined by NMR spectroscopy, isolated by column chromatography (SiO₂, CH₂Cl₂: Hexane = 9:1) to give the tetraoxane in 38%. Mpt. 78-80°C  
\[ V_{max} (\text{CHCl}_3)/\text{cm}^{-1} 1719.8, 2856.2, 2942.3, 3012.7 \]
\[ ^1\text{HNMR} (400MHz, \text{CDCl}_3) \delta ^H, 1.5(m, 6H, cyclohexyl), 1.80(s, 4H, cyclohexyl), 2.15(t, 2H, J = 7.42Hz, CH₂), 2.30(t, 2H, J = 7.08Hz, CH₂), 2.5(m, 4H, CH₂), ^{13}\text{CNMR} (100MHz, \text{CDCl}_3) \delta ^C 14.0, 23.07, 25.84, 31.98, 37.25, 106.60, 108.56, 210.77, \text{MS (ES+)} [M + Na]^+ (100), 265.0, [M + Na + CH₃OH]^+ (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%.

$V_{\text{max}}$ (CHCl$_3$/cm$^{-1}$) 14445.3, 2856.2, 2934.5, 3012.7, 3443.2 $^1$HNMR (400MHz, CDCl$_3$) $\delta$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$_3$), $\delta$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 (Cl+) calculated for 284.18616 C$_{15}$H$_{26}$O$_4$N 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.

$V_{\text{max}}$ (CHCl$_3$/cm$^{-1}$) 14445.5, 2859.1, 2931.2, 3011.3 $^1$HNMR (400MHz, CDCl$_3$) $\delta$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$_3$), $\delta$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 (Cl+) calculated for 314.19675 C$_{16}$H$_{28}$O$_5$N found, 314.19687.
Preparation of \((7,8,15,16\text{-Tetraoxa-dispiro}[5.2.5.2]\text{hexadec-3-yl})\text{-acetic acid ethyl ester 17}\)

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 NaHCO₃, dried in MgSO₄ and the solvent evaporated under reduced pressure. Purification of the crude by column chromatography gave the diaspirotetraoxane in 35%. Mpt. 48-50°C \(V_{\text{max}}\) (CHCl₃)/cm'1 1444.4, 1724.8, 2859.1, 2931.2, 3019.3 \(^{1}\)HNMR (400MHz, CDCl₃) \(\delta\)H 1.25(t, 3H, \(J = 7.15\)Hz, CH₃), 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, \(J = 7.15\)Hz, CH₂), \(^{13}\)CNMR (100MHz, CDCl₃), \(\delta\)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 C₁₅H₂₄O₆Na 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°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 Na₂SO₄ and evaporated to dryness. Purification by column chromatography gave the pure acid 18 in 85%.

\[ V_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1} \] 951.4, 1067.6, 1406.2, 1436.5, 1557.8, 1694.3, 2854.1, 2935.0, 3005.7, 3379.9

\[ ^1\text{HNMR}(400\text{MHz, CDCl}_3) \delta_H \] 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)

\[ ^{13}\text{CNMR}(100\text{MHz, CDCl}_3) \delta_C \] 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 C₁₃H₁₉O₆ 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**

![Cyclopropylamide](image)

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°C. (0.033g, 0.04ml, 0.58mmol) of cyclopropylamine was added,
and after 30 minutes of stirring the reaction mixture was warmed to room temperature. After 90 minutes, it was diluted with water and extracted with dichloromethane. The organic extract was washed with brine, dried over anhydrous Na$_2$SO$_4$. The crude product was purified by flash chromatography to give the pure amide in 76% $V_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 1444.8, 1548.6, 1636.7, 2859.1, 2931.2, 3011.3, 3235.5 Mpt. 170-172$^\circ$C $^1$HNMR (400MHz, CDCl$_3$) $\delta$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$_3$), $\delta$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$_5$NNa found, 334.1616.

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

![Structure](image)

This product was prepared in 48% according to the general procedure for amide coupling reactions. $V_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 1444.6, 1653.3, 2934.5, 2965.8, 3003.3, 3404.1 $^1$HNMR (400MHz, CDCl$_3$) $\delta$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$_2$N), 3.38(q,
2H, J = 4.93Hz, NHCH2), 6.92(s, 1H, NH) 13CNMR (100MHz, CDCl3), δC 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 C19H35O5N2Na found, 371.2539 and for 393.93 C19H34O5N2Na 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.

\[ V_{\text{max}} \text{(CHCl}_3\text{)/cm}^{-1} 1444.6, 1648.8, 2859.1, 2931.2, 3011.3, 3315.6 \] 1HNMR (400MHz, CDCl3) δH 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, NCH2/CH2N), 3.28(q, 2H, J = 5.72Hz, NHCH2), 3.71(q, 4H, J = 4.45Hz, CH2O), 6.08(s, 1H, NH) 13CNMR (100MHz, CDCl3), δC 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 C19H32O6N2Na 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.

$V_{\text{max}}$ (CHCl₃)/cm$^{-1}$ 1444.5, 1632.7, 2859.1, 2939.2, 3003.3 Mpt. 154-156°C $^1$H NMR (400MHz, CDCl₃) $\delta$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, NCH₂), 3.61(bs, 2H, NCH₂), 3.67(t, 4H, J = 4.77Hz, CH₂O) $^{13}$C NMR (100MHz, CDCl₃), $\delta$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$_6$NNa 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%. $V_{\text{max}}$ (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 $^1$H NMR (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), $^{13}$C NMR (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 (Cl) [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**

![Chemical Structure](image)

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 3 hours. The solvent was removed under vacuum and product purified by flash chromatography to give 25 in 90%. $V_{\text{max}}$ (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, $^1$H NMR (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, cyclohexyl), 2.2(d, 2H, J = 6.99Hz, CH$_2$CO), 3.93(s, 4H, OCH$_2$), 4.13(q, 2H, J = 7.15Hz, CH$_2$), 5.7(s, 1H, CH), $^{13}$C NMR (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 (Cl) [M + H]$^+$ (100), 229
[M + NH₄]⁺ (30), 246, HRMS calculated for 229.1440 C₁₂H₁₉O₄ 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**

![Chemical structure](image)

To a solution of the ketal 25 (1g, 4.4mmol) in dry THF (20ml) was treated with H₂O₂ (30% aq, 20ml) and tungstic acid (2.2g, 8.8mmol) and stirred for 48hrs at 0°C. The reaction mixture was extracted with dichloromethane, washed with brine and dried with MgSO₄. Purification by column chromatography gave the product in 73%. ¹HNMR (400MHz, CDCl₃) δH, 1.26(t, 3H, J = 7.15Hz, CH₃), 1.62(m, 2H, cyclohexyl),1.78(m, 4H, cyclohexyl), 1.92(m, 2H, cyclohexyl), 2.22(d, 2H, J = 13.51Hz, CH₂CO), 2.4(m, 1H, CH), 4.14(q, 2H, J = 7.15Hz, OCH₂), 8.55(bs, 2H, OH), ¹³CNMR (100MHz, CDCl₃), δC 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**

![Chemical structure](image)
A stirred solution of cyclohexanone 5 (1.7g, 7.26mmol) in ethyl acetate was added 54% ethereal solution of HBF₄ (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%. $\nu_{\text{max}}$ (CHCl₃)/cm⁻¹ 1444.8, 1731.6, 2853.8, 2926.4, 3014.3 $^1$HNMR (400MHz, CDCl₃) δH, 1.25(t, 4H, J = 7.15Hz, CH₃), 1.4-1.84(m, 14H, cyclohexyl), 1.9(m, 2H, CH₂), 2.14-2.50(m, 4H, cyclohexyl), 3.09(bs, 1H, CH), 4.13(q, 2H, J = 4.45Hz, CH₂) $^{13}$CNMR (100MHz, CDCl₃), δC 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 C₁₂H₂₀O₆Na found, 337.1615.

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

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This product was prepared in 33% according to the general procedure for preparing 1,2,4,5-tetraoxane esters. $\nu_{\text{max}}$ (CHCl₃)/cm⁻¹ 1450.0, 1723.0, 2849.8, 2936.8, 3020.4, 3435.3 $^1$HNMR (400MHz, CDCl₃) δH, 1.25(t, 3H, J = 7.21Hz, CH₃), 1.26-1.40(m, 16H, CH₂), 1.40-1.49(m, 4H, CH₂), 1.50-1.62(m, 4H, CH₂), 1.64-1.81(m, 6H, CH₂), 1.85-1.99(m, 1H, CH), 1.23(d, 2H, J = 4.56Hz, CH₂CO), 4.13(q, 2H, J = 7.21Hz, OCH₂) $^{13}$CNMR (100MHz, CDCl₃), δC 14.67, 22.65, 22.97, 24.62,
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 $V_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 1446.8, 1718.5, 2858.9, 2922.3, 3003.8 \[^1\text{HNMR} (400\text{MHz, CDCl}_3) \delta_H, 1.25(t, 3H, J = 7.31\text{Hz, 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$_2$CO), 4.13(q, 2H, J = 7.21Hz, CH$_2$)\[^{13}\text{CNMR} (100\text{MHz, CDCl}_3), \delta_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 \text{MS (ES+), } [M + Na]^+ (100), 389.1 [2M + Na]^+ 755.2 \text{HRMS calculated for 389.1940 C}_{20}\text{H}_{30}\text{O}_6\text{Na 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°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 Na₂SO₄ and evaporated to dryness. Purification by column chromatography gave the pure acid 27b in 75%. Melting point 124-126°C ¹H NMR (400MHz, CDCl₃) δH, 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, CH₂CO), 2.12-2.39(m, 2H, cyclohexyl) ¹³C NMR (100MHz, CDCl₃), δC 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

![Chemical structure of 28b](image)

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

Melting point 166-168°C νmax (CHCl₃)/cm⁻¹ 1692.8, 2851.1, 2931.2, 3019.3, 3355.7 ¹H NMR (400MHz, CDCl₃) δH, 1.22-1.45(m, 22H, CH₂), 1.51-1.64(m, 4H, CH₂), 1.65-1.77(m, 4H, CH₂),
1.90-1.90 (m, 1H, CH), 2.28 (d, 2H, J = 7.03 Hz, CH₂CO), $^{13}$CNMR (100 MHz, CDCl₃), $\delta$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°C $V_{max}$ (CHCl₃)/cm⁻¹ 991.8, 1057.5, 1446.7, 1694.3, 2844.0, 2924.8, 3005.7 3355.7 $^1$HNMR (400 MHz, CDCl₃) $\delta$H, 1.22-1.46 (m, 2H, CH₂), 1.50-1.90 (m, 12H, CH₂), 1.01-2.05 (m, 4H, CH₂), 2.06-2.15 (m, 5H, CH), 2.29 (d, 2H, J = 6.83 Hz, CH₂CO), $^{13}$CNMR (100 MHz, CDCl₃), $\delta$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 C₁₈H₂₅O₆ 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 60 minutes at 0°C. (0.06g, 0.06ml, 0.70mmol) of morpholine was added, and after 30 minutes of stirring the reaction mixture was warmed to room temperature. After 90 minutes, it was diluted with water and extracted with dichloromethane. The organic extract was washed with brine, dried over anhydrous Na₂SO₄. The crude product was purified by flash chromatography to give the pure amide in 84%. Melting point. 126-128°C  

**Vmax (CHCl₃)/cm⁻¹** 1444.5, 1632.7, 2851.1, 2931.2, 3011.3  
**¹HNMR (400MHz, CDCl₃)** δ_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, CH₂/cyclohexyl), 3.45(t, 2H, J = 4.76Hz, NCH₂), 3.59-3.67(m, 6H, CH₂O).  
**¹³CNMR (100MHz, CDCl₃)** 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 C₁₈H₂₉NO₆Na found, 378.1886.

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

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

Melting point 148-150°C $V_{\text{max}}$ (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$_2$CO), 1.96-2.08(m, 2H, cyclohexyl), 2.71(m, 1H, CH-cyclopropyl), 5.7(bs, 1H, NH) $^{13}$CNMR (100MHz, CDCl$_3$) $\delta_C$ 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$_5$NNa 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°C $V_{\text{max}}$ (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/CH₂), 2.16(d, 2H, J = 6.99Hz, CH₂CO), 2.23-2.32(m, 2H, cyclohexyl), 2.68-2.79(m, 2H, CH₂N), 2.86(t, 4H, J = 6.04Hz, NCH₂), 3.49(q, 2H, J = 5.88Hz, NHCH₂), 6.98(bs, 1H, NH). ¹³CNMR (100MHz, CDCl₃), 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 C₂₀H₃₅O₅ found, 383.2553 and 405.2365 C₂₀H₃₄N₂O₅Na, 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**

![Chemical Structure]

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

Melting point 68-78°C  ν_max (CHCl₃)/cm⁻¹ 1444.4, 1508.6, 1648.8, 2856.2, 2934.5, 3012.7, 3325.8 ¹HNM R (400MHz, CDCl₃) δ_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, CH₂CO), 2.30(m, 2H, cyclohexyl), 2.53(m, 2H, NCH₂), 2.66(m, 4H, CH₂N), 3.45(q, 2H, J = 5.73Hz, NHCH₂), 6.84(bs, 1H, NH). ¹³CNMR (100MHz, CDCl₃), 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 C₂₁H₃₇N₂O₅ found, 397.2704, and for 419.2522 C₂₁H₃₆N₂O₅Na found 419.2518.

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

![Chemical structure of 27f](image)

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

\(V_{\text{max}}\) (CHCl₃)/cm⁻¹ 1444.4, 1508.6, 1656.8, 2811.1, 2851.1, 2931.2, 3307.6 \(^1\)HNMR (400MHz, CDCl₃) \(\delta\) 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, CH₂CO), 2.13-2.37(m, 2H, cyclohexyl), 2.41-2.51(m, 6H, CH₂N/NCH₂), 3.36(q, 2H, J = 5.88Hz, NHCH₂), 3.7(m, 4H, CH₂O), 5.98(bs, 1H, NH) \(^{13}\)CNMR (100MHz, CDCl₃), \(\delta\) 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 C₂₀H₃₄O₅N₂Na 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.

$V_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$: 1444.5, 1508.6, 1652.8, 2859.1, 2939.2, 3011.4, 3323.6

$^1$HNMR (400MHz, CDCl$_3$) $\delta$, 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$_2$CO), 2.14-2.35(m, 2H, cyclohexyl), 2.57(m, 6H, CH$_2$N/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$_3$), $\delta$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$_2$O$_5$ found, 385.2695.

Preparation of $N$-Cyclopropyl-2-(7,8,21,22-tetraoxa-dispiro[5.2.11.2]docos-3-yl)-acetamide 28c
This product was prepared in 88% according to the general procedure for the amide coupling reactions.

Mpt. 136-138°C  $V_{\text{max}}$ (CHCl₃)/cm⁻¹ 1523.8, 1637.0, 2849.8, 2931.3, 3003.8, 3311.7 $^1$HNMR (400MHz, CDCl₃) δH 0.46(m, 2H, cyclopropyl), 0.77(m, 2H, cyclopropyl), 1.14-1.47(m, 22H, CH₂), 1.50-1.84(m, 8H, CH₂),1.94(m, 1H, CH), 2.02(d, 2H, J = 7.02Hz, CH₂CO), 2.70(m, 1H, CH), 5.6(bs, 1H, NH), $^{13}$CNMR (100MHz, CDCl₃), δC 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 C₂₃H₃₉O₅Na 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 $V_{\text{max}}$ (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$_2$CO), 2.81-3.18 (m, 6H, NCH$_2$/CH$_2$N), 3.51(q, 2H, J = 5.70Hz, NHCH$_2$), 7.1(bs, 1H, NH) $^{13}$CNMR (100MHz, CDCl$_3$), $\delta$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$_5$N$_2$ 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 $V_{\text{max}}$ (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$_2$CO), 2.49-2.62(m, 6H, CH$_2$N/NCH$_2$), 3.41(q, 2H, J = 5.88Hz, NHCH$_2$), 6.20(bs, 1H, NH) $^{13}$CNMR (100MHz, CDCl$_3$), $\delta$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 503.3461C$_{27}$H$_{48}$ON$_2$Na found, 503.3449.
Preparation of \( N\)-(2-Morpholin-4-yl-ethyl)-2-(7,8,21,22-tetraoxa-dispiro[5.2.11.2]docos-3-yl)acetamide 28f

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

Mpt. 78-80°C \( V_{\text{max}} \) (CHCl₃)/cm⁻¹ 1533.1, 1643.0, 2806.2, 2850.2, 2920.5, 3315.9 ¹HNMR (400MHz, CDCl₃) δH, 1.10-1.49(m, 22H, CH₂), 1.50-1.80(m, 8H, CH₂), 1.86(m, 1H, CH), 2.11(d, 2H, J = 7.03Hz, CH₂CO), 2.42-2.51(m, 6H, NCH₂CH₂N), 3.37(q, 2H, J = 5.88Hz, NHCH₂), 3.72(t, 4H, J = 4.55Hz, CH₂O), 6.0(bs, 1H, NH) ¹³CNMR (100MHz, CDCl₃), δC 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 C₂₆H₄₇O₆N₂ 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  ν_max (CHCl₃)/cm⁻¹ 1446.6, 1660.8, 2812.3, 2931.2, 3003.8, 3251.6 ¹HNMR (400MHz, CDCl₃) δ_H, 1.15(t, 6H, J = 7.21Hz, CH₃), 1.23-1.49(m, 22H, CH₂), 1.50-1.79(m, 8H, CH₂), 1.85(m, 1H, CH), 2.12(d, 2H, J = 7.02Hz, CH₂CO), 2.73(q, 6H, J = 7.02Hz, NCH₂/CH₂N), 3.42(q, 2H, J = 5.89Hz, NCH₂), 6.30(bs, 1H, NH) ¹³CNMR (100MHz, CDCl₃), 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 C₂₆H₄₉O₅N₂ 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.
reactions.

Mpt. 118-120°C $V_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 1437.7, 1632.5, 2858.9, 2931.3, 3003.7
$^1$HNMR (400MHz, CDCl$_3$) $\delta_H$, 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$_3$), $\delta_C$
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$_6$Na found, 462.2834.

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

![Chemical Structure](attachment:image)

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

Mpt. 140-142°C $V_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 1496.6, 1664.2, 2858.9, 2922.3, 3012.8, 3320.8
$^1$HNMR (400MHz, CDCl$_3$) $\delta_H$, 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$_2$CO), 1.83-2.05(m, 7H, CH/CH$_2$), 2.70(m, 1H, CH-cyclopropyl), 5.5(bs, 1H, NH), $^{13}$CNMR (100MHz, CDCl$_3$), $\delta_C$ 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$_5$NNa 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°C  \(V_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 1446.7, 1559.9, 1641.1, 2859.1, 2931.2, 2937.7, 3260.8

\(^1\)HNMR (400MHz, CDCl\(_3\))  \(\delta_H\) 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, \(J = 7.02\)Hz, CH\(_2\)CO), 2.50-2.67(m, 6H, NCH\(_2\)/CH\(_2\)N), 3.31(q, 4H, \(J = 5.50\)Hz, CH\(_2\)), 6.55(bs, 1H, NH), \(^{13}\)CNMR (100MHz, CDCl\(_3\)),  \(\delta_C\) 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\(_5\)N\(_2\)Na 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 $V_{\text{max}}$ (CHCl$_3$/cm$^{-1}$) 1446.7, 1541.3, 1650.3, 2794.9, 2846.8, 2919.4, 3324.1
$^1$HNMR (400MHz, CDCl$_3$) $\delta_{\text{H}}$ ) 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, $J = 6.83$Hz, CH$_2$CO), 3.10(t, 6H, $J = 5.50$Hz, CH$_2$N/NCH$_2$), 3.68(q, 2H, $J = 5.31$Hz, NHCH$_2$), 8.15(bs, 1H, NH), $^{13}$CNMR (100MHz, CDCl$_3$), $\delta_{C}$ 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$_5$N$_2$Na 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.

$V_{\text{max}}$ (neat)/cm$^{-1}$ 1446.2, 1539.6, 1648.6, 2858.9, 2913.2, 2926.4, 3331.1
$^1$HNMR (400MHz, CDCl$_3$) $\delta_{\text{H}}$ 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, $J = 7.02$Hz, CH$_2$CO), 3.28(q, 2H, $J = 5.51$Hz, CH$_2$N/NCH$_2$), 3.67-3.73(m, 4H, CH$_2$O), 6.0(bs, 1H, NH)
$^{13}$CNMR (100MHz, CDCl$_3$), $\delta_{C}$ 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 C₂₄H₃₈O₆N₂Na 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.

$V_{\text{max}}$ (neat)/cm⁻¹ 1446.7, 1524.1, 1660.6, 2812.3, 2928.4, 2957.5, 3341.5 ¹HNMR (400MHz, CDCl₃) δH, 1.18(t, 6H, J = 7.21Hz, CH₃), 1.22-1.40(m, 2H, CH₂), 1.50-1.78(m, 14H, CH₂), 1.80-1.88(m, 2H, CH₂), 1.90-2.04(m, 5H, CH), 2.15(d, 2H, J = 7.02Hz, CH₂CO), 2.76-2.85(m, 6H, NCH₂/CH₂N), 3.45(m, 2H, NCH₂), 7.18(bs, 1H, NH) ¹³CNMR (100MHz, CDCl₃), δC 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 C₂₄H₄₁O₅N₂ 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°C $V_{\text{max}}$ (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$_2$CO), 3.46(t, 2H, J = 4.56Hz, NCH$_2$), 3.60-3.69(m, 6H, NCH$_2$/CH$_2$O) $^{13}$CNMR (100MHz, CDCl$_3$), $\delta_c$: 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$_6$NNa 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.

$V_{\text{max}}$ (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$_3$) $\delta_H$ 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$_3$), $\delta_C$ 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$_3$) $\delta_H$ 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$_3$), $\delta_C$ 19.22, 22.99, 25.00, 25.64, 25.81, 29.38,
Preparation of \( \text{N-Cyclopropyl-3-[12-(2-cyclopropylcarbamoyl-ethyl)-9,12-dimethyl-7,8,10,11,13,14-hexaoxa-spiro[5.8]tetradec-9-yl]-propionamide 32} \)

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

\[
V_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} \quad 911.0, 956.5, 1017.1, 1269.8, 1365.8, 1451.7, 1557.8, 1638.7, 2945.1, 2985.5, 3066.3, 3308.9
\]

\( ^1\text{HNMRI} (400\text{MHz, } \text{CDCl}_3) \quad \delta_{\text{H}} \quad 0.51(\text{m, 4H, cyclopropyl}), 0.73(\text{m, 4H, cyclopropyl}), 1.36(\text{s, 6H, CH}_3), 1.38\text{-}1.61(\text{m, 6H, cyclohexyl}), 1.68\text{-}1.85(\text{m, 4H, cyclohexyl}), 1.92\text{-}2.06(\text{m, 2H, CH}_2), 2.07\text{-}2.19(\text{m, 2H, CH}_2), 2.20\text{-}2.39(\text{m, 4H, CH}_2), 2.48\text{-}2.55(\text{m, 2H, CH}), 5.20(\text{bs, 2H, NH}) \)

\( ^{13}\text{CNRMI} (100\text{MHz, } \text{CDCl}_3), \delta_{\text{C}} \quad 6.82, 7.50, 8.54, 14.53, 19.15, 19.20, 21.35, 22.95, 23.02, 23.05, 25.78, 30.14, 30.34, 30.67, 30.81, 30.86, 31.35, 31.50, 60.71, 108.31, 109.06, 174.23 \)

\( \text{MS (ES+)} [\text{M + Na}]^+ (100), 479.3, \text{HRMS m/z calculated for 479.2369 C}_{22}\text{H}_{36}\text{O}_8\text{N}_2\text{Na found, 479.2353}. \)
Preparation of 3-N-(2-morpholin-4-yl-ethyl)-propionamide 33

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{H} \\
\end{align*}
\]

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

Melting point 136-138°C \( V_{\text{max}} \) (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 \( ^1\text{HNMR} \) (400MHz, CDCl\(_3\)) \( \delta_H \) 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\(_2\)N), 3.36(q, 4H, J = 6.08Hz, NCH\(_2\)), 3.71(t, 8H, J = 3.42Hz, CH\(_2\)O), 6.10(bs, 2H, NH) \( ^{13}\text{CNMR} \) (100MHz, CDCl\(_3\)), \( \delta_C \) 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+) \([\text{M + Na}^+]\) (100), 625.4, HRMS m/z calculated for 625.3425 C\(_{28}\)H\(_{50}\)O\(_{10}\)N\(_4\)Na 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.

$V_{\text{max}}$ (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$_3$) $\delta_H$ 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$_3$), $\delta_C$ 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$_2$O$_{10}$ Na found, 539.2570.

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

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

$V_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 1449.8, 1737.5, 2864.9, 2939.6, 3003.4 $^1$HNMR (400MHz, CDCl$_3$) $\delta_H$ 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$_3$), $\delta_C$ 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°C $V_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 1448.5, 1536.6, 1648.8, 2859.1, 2947.2, 3003.3, 3235.5 $^1$HNMR (400MHz, CDCl$_3$) $\delta_H$ 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$_3$), $\delta_C$ 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$_2$NaO$_{10}$ 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.

$V_{\text{max}}$ (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$_2$O), 6.13(bs, 1H, CH) $^{13}$CNMR (100MHz, CDCl$_3$), $\delta_C$ 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$_2$O$_6$ 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.
$V_{\text{max}}$ (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) $^1$CNMR (100MHz, CDCl$_3$), $\delta$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$_2$O$_5$ 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°C $V_{\text{max}}$ (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$_2$O) $^1$CNMR (100MHz, CDCl$_3$), $\delta$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.