Supporting Information:

Synthesis of novel derivatives of 1,4,7-triazacyclononane.

Andrew Warden,[a] Bim Graham,[a] Milton T W Hearn [b] and Leone Spiccia[a*]

[a] *School of Chemistry, P.O. Box 23, Monash University, Victoria, 3800, Australia*

[b] *Department of Biochemistry and Molecular Biology, P.O. Box 130, Monash University, Victoria, 3800, Australia.*

Experimental Details

Reagents Reagents obtained from commercial suppliers were of reagent grade quality or better, and were used without further purification. Organic solvents were dried over 4Å molecular sieves or were used as received. High purity nitrogen gas was used directly from the reticulated system. Water was distilled prior to use.

Instrumentation *^{1}H and broad band decoupled ^{13}C NMR spectra* were recorded on a Varian Mercury AM300Hz spectrometer. The chemical shifts, δ, are reported in ppm (parts per million) using the high frequency positive convention, relative to an internal standard of tetramethylsilane (TMS) for non-aqueous solvents and sodium (2,2,3,3-d4-3-(trimethylsilyl))propionate (TMSP-D) or acetone for D_2O. The abbreviations for the peak multiplicities are as follows: **s** (singlet), **d** (doublet), **dd** (doublet of doublets), **t** (triplet), **q** (quartet), **m** (multiplet) and **br** (broad). *Infrared Spectra* were recorded as KBr pellets or as neat liquids using a Perkin-Elmer 1600 series Fourier-transform Infrared (FTIR) spectrometer at a resolution of 4.0 or 8.0 cm^{-1}. Signal intensities are abbreviated: s (strong), m (medium), w (weak) and br (broad). Microanalyses were performed by the Campbell Microanalytical Laboratory, Department of Chemistry, University of Otago, New Zealand. Mass spectra were

---

[*] Corresponding author: *School of Chemistry, P.O. Box 23, Monash University, Victoria, 3800, Australia*
Email: leone.spiccia@sci.monash.edu.au; *Phone: +61 3 9905 4526; Fax: +61 3 9905 4597*

obtained using a Micromass Platform Quadrupole Mass Spectrometer fitted with an electrospray source or a Bruker BioApex 47e Fourier Transform Mass Spectrometer with a 4.7 Tesla superconducting magnet and an Analytica electrospray source.

1-propylamino-4-acetato-1,4,7-triazacyclononane (1)

1,4,7-triazatricyclo[5.2.1.0^{4,10}]decane (tacn orthoamide, 4) The synthesis of **4** was adapted from a published method.[1] Tacn.3HCl (20.0 g, 83.9 mmol) was dissolved in 120 ml of water and sodium hydroxide pellets (13.0 g) were slowly added with stirring. Dissolution of the pellets gave a light purple solution, whose volume was reduced under vacuum to give a white suspension. The remaining water was removed by azeotropic distillation with toluene (200 ml) using a Dean-stark apparatus. The toluene fraction was collected by filtration. Further toluene (100 ml) was added to the white precipitate and azeotropic distillation repeated. Dimethylformamide dimethylacetal (10.6 g, 83.6 mmol) was added to the combined toluene fractions. The solution was then heated, with stirring, at 90°C for 4 hours. Removal of the toluene under vacuum gave a yellow oil, which was distilled in *vacuo* (64°C, 0.8 Torr) to give **4** as a clear colourless oil. Yield: 9.00 g, 64.7 mmol (77 %).

^{1}H NMR ($CDCl_3$): δ 2.97 (12H, m, tacn C$\underline{H_2}$'s), 4.85 (1H, s, cap C$\underline{H}$). **^{13}C NMR ($CDCl_3$):** δ 52.17 (tacn $\underline{C}H_2$'s), 104.48 (cap $\underline{C}$H). **IR spectrum (neat, cm^{-1}):** 3371br, 2934s, 1673m, 1493s, 1458s, 1356m, 1334s, 1298s, 1270s, 1234s, 1196s, 1151s, 1101s, 1058s, 1027s, 930s, 902m.

1-(N-(3-propyl)phthalimido)-1,4,7-triazacyclononane orthoamidinium bromide (5)

A solution of N-(3-bromopropyl)phthalimide (7.70 g, 28.7 mmol) in acetonitrile (40ml) was added to a solution of **4** (4.00 g, 28.7 mmol) in acetonitrile (30 ml). The mixture was stirred at room temperature for three days. The white precipitate of **5** that formed was collected by vacuum filtration, washed with acetonitrile (2 x 50ml), diethyl ether (2 x 50ml) and then dried in the oven at 90 °C for 25 minutes. Yield: 8.35 g, 21.5 mmol (71 %).

^{1}H NMR (D_2O): δ 2.29 (2H, m, $NCH_2\underline{CH_2}CH_2$phth), 3.26 (4H, m, $NC\underline{H_2}$), 3.62 (8H, m, $NC\underline{H_2}$), 3.79 (4H, m, $NC\underline{H_2}$), 5.59 (1H, s, cap C$\underline{H}$), 7.89 (4H, m, Ar $\underline{H}$). **^{13}C NMR (D_2O):** δ 26.47 ($NCH_2\underline{C}H_2CH_2$phth), 37.58 ($NCH_2CH_2\underline{C}H_2$phth), 53.85, 56.16, 60.11, 60.62 ($N\underline{C}H_2$), 126.24 (cap $\underline{C}$H), 133.50 (Ar $\underline{C}$H), 133.92 (Ar quaternary $\underline{C}$), 137.54 (Ar $\underline{C}$H), 172.99 (phth$\underline{C}$=O), 173.01 (phth$\underline{C}$=O). **IR spectrum (KBr, cm^{-1}):** 3407m, 3942m, 1770m, 1713s, 1464m, 1442m, 1407m, 1379m, 1287m, 1217m, 1178m, 1088m, 1047m, 992m, 892w, 849w, 805w, 729w, 668w.

1-formyl-4-(N-(3-propyl)phthalimido)--1,4,7-triazacyclononane (6)

The amidinium salt, **5**, (8.30 g, 20.4 mmol) was dissolved in water (100 ml) and heated at reflux for 4 hours. Most of the water was removed under vacuum and the remainder via azeotropic distillation with toluene (200 ml). The toluene was removed under vacuum to give **6** as a viscous, yellow oil. Yield: 7.00 g, 20.4 mmol (97 %).

^{1}H NMR ($CDCl_3$): δ 1.94 (2H, m, $NCH_2\underline{CH_2}CH_2$phth, two resonance forms), 2.64-3.94 (16H, m, $NC\underline{H_2}$, from two resonance forms), 7.72 and 7.84 (4H, dd, phth C$\underline{H}$, from two resonance forms), 8.22 and 8.41 (1H, s, NC$\underline{H}$O, from two resonance forms). **^{13}C NMR ($CDCl_3$):** δ 26.37 and 26.63 ($NCH_2\underline{C}H_2CH_2$phth, from two resonance forms) 35.90 and 36.10 ($NCH_2CH_2\underline{C}H_2$phth), 44.21, 44.26, 44.61, 44.63, 45.46, 45.61, 47.00, 50.71, 51.69, 52.19, 53.05, 54.67, 54.90, 55.24 ($N\underline{C}H_2CH_2CH_2$phth and tacn ring $\underline{C}H_2$'s, from two resonance forms), 123.34 (phth $\underline{C}$H), 131.77 and 131.86 (phth quaternary $\underline{C}$), 134.07 and 134.10 (phth $\underline{C}$H), 164.86 (N$\underline{C}$HO, assuming one co-incidence), 168.35 and 168.38 (phth $\underline{C}$=O, from two

---

[1] a) Atkins, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6365. b) Weisman, G. R.; Johnson, V.; Fiala, R. E. *Tetrahedron Letts* **1980**, *21*, 3635.

resonance forms). **IR spectrum (KBr, cm^{-1}):** 3459br, 2941m, 1769m, 1709s, 1667s, 1560m, 1436m, 1398s, 1372s, 1218w, 1187m, 1088w, 1037m, 981w, 890w, 751m, 721m, 663w.

1-ethylacetato-4-formyl-7-(N-(3-propyl)phthalimido)-1,4,7-triazacyclononane (7)

Compound **6** (6.99 g, 19.7 mmol) was dispersed in acetonitrile (50 ml), anhydrous sodium carbonate (15 g) was added and the suspension was warmed to 50 ^{o}C. A solution of ethyl bromoacetate (3.19 g, 19.1 mmol) in acetonitrile (200 ml) was added and the mixture heated at reflux for 3 days. After cooling to room temperature, the sodium carbonate and bromide salts were removed by filtration to give a yellow solution. The solvent was removed under vacuum to give a honey-coloured oil. This was dissolved in water (50 ml), decolourised with activated carbon, extracted into chloroform (4 x 50 ml), dried over magnesium sulfate and reduced in volume to give **7** as a viscous orange oil. Yield: 7.70 g, 18.6 mmol (94 %).

^{1}H NMR ($CDCl_3$): δ 1.30 (3H, t, $OCH_2\underline{CH_3}$), 1.81 (2H, quintet, $NCH_2\underline{CH_2}CH_2N$, from two resonance forms), 2.45 – 3.62 (18H, m, $NC\underline{H_2}CH_2C\underline{H_2}N$, tacn $C\underline{H_2}$'s $C\underline{H_2}COO$), 4.12 and 4.13 (2H, q, $OC\underline{H_2}CH_3$, from two resonance forms) 7.67 and 7.78 (4H, m, Ar$\underline{H}$, from two resonance forms), 8.07 and 8.11 (1H, s, NC$\underline{H}$O, from two resonance forms). **^{13}C NMR ($CDCl_3$):** δ 14.28 ($\underline{C}H_3$, assuming one co-incidence), 26.95 and 27.22 ($CH_2\underline{C}H_2CH_2$, from two resonance forms), 36.13 and 36.25 (phthN$\underline{C}H_2CH_2$, from two resonance forms), 46.91, 47.12, 48.76, 50.05, 50.23, 50.82, 53.48, 53.74, 53.89, 54.82, 55.10, 55.57, 55.67 (tacn N$\underline{C}H_2$'s, N$\underline{C}H_2CH_2CH_2$Nphth, from two resonance forms assuming one co-incidence), 57.85 and 57.96 (N$\underline{C}H_2$COO, from two resonance forms), 60.24 and 60.28 (COO$\underline{C}H_2CH_3$, from two resonance forms), 122.94 and 123.00 (2 x Ar $\underline{C}$H, from two resonance forms), 131.76 and 131.84 (2 x Ar quaternary $\underline{C}$, from two resonance forms), 133.74 and 133.81 (2 x Ar CH), 163.48 and 163.52 (NCHO, from two resonance forms), 168.01 and 168.04 (2 x phth$\underline{C}$O, from two resonance forms), 171.50 and 171.69 ($CH_2\underline{C}OO$, from two resonance forms). **IR**

spectrum (KBr, ν, cm^{-1}): 3459br, 2941m, 1769m, 1730s, 1709s, 1667s, 1560m, 1436m, 1399s, 1372s, 1218w, 1188m, 1089w, 1038m, 981w, 890w, 751m, 721s, 664w.

1-acetato-4-propylamino-1,4,7-triazacyclononane trihydrobromide dihydrate (1)

Compound **7** (7.65 g, 18.5 mmol) was dissolved in hydrochloric acid (5M, 170 ml) and the solution was heated at 93°C for 20 hours. The resulting solution was placed in a refrigerator overnight and then filtered to remove the phthalic acid precipitate. The filtrate was reduced *in vacuo* to give a viscous light orange oil. This was dissolved in hydrobromic acid (48%, 20 ml) and glacial acetic acid (20 ml) was added. Diethyl ether was then added until two phases were just discernible and the mixture stored in a refrigerator overnight. The white, hygroscopic powder that precipitated was collected by filtration under a nitrogen blanket, washed with a small amount of diethyl ether and then dried in a stream of nitrogen overnight. Yield: 6.03 g, 11.5 mmol (62 %).

Microanalysis: Found: C 25.3; H 5.8; N 10.8 %. Calc. for $C_{11}H_{31}N_4O_4Br_3$ {**1**.3HBr.2H$_2$O} C 25.3; H 5.9; N 10.7 %. **^{1}H NMR (D$_2$O):** δ 2.28 (2H, m, $+H_3NCH_2C\underline{H_2}CH_2$), 2.82-3.72 (16H, m, tacn CH$_2$'s, $+H_3NC\underline{H_2}CH_2C\underline{H_2}NH$), 3.62 (2H, s, $C\underline{H_2}COOH$). **^{13}C NMR** (D$_2$O): 22.32 ($+H_3NCH_2\underline{C}H_2CH_2$), 36.76 ($+H_3N\underline{C}H_2CH_2CH_2$), 43.77, 48.27, 49.06, 51.32, 51.89, 55.16 and 55.37 (tacn ring $\underline{C}H_2$'s, $+H_3NCH_2CH_2\underline{C}H_2N$), 55.68 ($\underline{C}H_2COOH$) and 175.60 ($\underline{C}OOH$). **Mass spectrum m/z (+ve ion):** 245 (corresponds to 1.H$^+$).

1-acetato-4-benzyl-1,4,7-triazacyclononane (2)

1-benzyl-4-formyl-1,4,7-triazacyclononane (8)

Addition of benzyl bromide (1.72 g, 10.1 mmol) to a solution of **4** (1.40 g, 10.1 mmol) in tetrahydrofuran (35 ml) produced a white precipitate almost immediately. Stirring was continued for another 30 minutes after which the product was collected and washed with absolute ethanol (2 x 10 ml) and ether (3 x 10 ml). The solid was then dissolved in water (50 ml) and heated at reflux for 4 hours. The solution pH was adjusted to ~12, the product extracted into chloroform (4 x 50 ml), the extracts dried over magnesium sulfate and the solvent removed under reduced pressure to give **8** as a viscous orange oil. Yield 2.30 g, 9.32 mmol, 92 %.

^{1}H NMR ($CDCl_3$): δ 2.22-2.30 (N$\underline{H}$, br), 2.53-3.44 (12H, m, tacn NC$\underline{H}_2$, from two resonance forms), 3.67 and 3.69 (2H, s, C$\underline{H}_2$Ph from two resonance forms), 7.21-7.36 (5H, m, aromatic C$\underline{H}$, from two resonance forms), 7.97 and 8.12 (1H, s, NC$\underline{H}$O, from two resonance forms). **^{13}C NMR ($CDCl_3$):** δ 46.55, 46.72, 47.13, 47.92, 48.76, 50.12, 52.06, 52.13, 52.87, 55.45, 57.00 (6 ring $\underline{C}H_2$, from two resonance forms), 62.11 and 62.22 (Ph$\underline{C}H_2$, from two resonance forms), 126.81 and 127.03 (aromatic $\underline{C}$H, from two resonance forms), 128.05 and 128.18 (aromatic $\underline{C}$H, from two resonance forms), 128.71 and 128.76 (aromatic $\underline{C}$H, from two resonance forms), 139.19 and 139.28 (Aromatic quaternary $\underline{C}$), 163.43 and 163.61 (N$\underline{C}$HO). **IR spectrum (neat, cm^{-1}):** 3367br, 3084w, 3060w, 3029w, 2921s, 2865s, 1668s, 1493m, 1451s, 1419s, 1400s, 1354s, 1279m, 1214m, 1185m, 1148m, 1096m, 1078m, 1028m, 987m, 910w, 872w, 812w, 731m, 700m, 636w.

1-benzyl-4-ethylacetato-7-formyl-1,4,7-triazacyclononane (9)

Compound **8** (0.85g, 3.4 mmol) was dissolved in acetonitrile (30 ml), sodium carbonate (3 g) and ethyl bromoacetate (0.57 g, 3.4 mmol) were added. The mixture was stirred at reflux for 3 days. The solution was filtered and the solvent removed under reduced pressure. The crude product (an orange oil) was dissolved in water (50 ml) and the pH adjusted to ~ 12 using sodium hydroxide (5M) and the product was then extracted into chloroform (5 x 50 ml). The collected extracts were dried over magnesium sulfate and the solvent removed under reduced pressure to give a viscous, yellow/orange oil. Yield 0.88 g, 2.6 mmol, 77 %.

^{1}H NMR ($CDCl_3$): δ 1.26 and 1.27 (3H, t, $OCH_2C\underline{H}_3$, from two resonance forms), 2.48 – 3.68 (12H, m, tacn C$\underline{H}_2$'s, from two resonance forms), 3.18 and 3.39 (2H, s, C$\underline{H}_2$Ph, from two resonance forms), 3.67 and 3.68 (2H, s, NC$\underline{H_2}$COOEt, from two resonance forms), 7.30 (3H, s, Ar C$\underline{H}$), 7.32 (2H, s, Ar C$\underline{H}$), 8.05 and 8.06 (1H, s, NC$\underline{H}$O, from two resonance forms). **^{13}C NMR ($CDCl_3$):** δ 14.23 ($OCH_2\underline{C}H_3$), 46.93, 47.29, 50.17, 50.38, 50.51, 52.63, 53.46, 53.95, 54.52, 54.66, 55.06, 57.67, 58.27, 58.43 (N$\underline{C}H_2$, from two resonance forms), 60.19 and 60.56 ($O\underline{C}H_2CH_3$, from two resonance forms), 61.88 and 62.41 (Ph$\underline{C}H_2$, from two resonance forms), 126.70 and 126.78 (Ar $\underline{C}$H, from two resonance forms), 127.98 and 128.05 (Ar $\underline{C}$H, from two resonance forms), 128.50 and 128.69 (Ar $\underline{C}$H, from two resonance forms), 139.47 (Ar quaternary $\underline{C}$, from two resonance forms assuming one co-incidence), 163.42 (N$\underline{C}$HO, from two resonance forms assuming one co-incidence), 171.42 and 171.67 ($\underline{C}$OO, from two resonance forms). **IR spectrum (KBr, cm^{-1}):** 3447br, 3061w, 3027w, 2978m, 2927m, 2850m, 1739s, 1668s, 1494m, 1451s, 1418m, 1370m, 1301m, 1190s, 1152s, 1123m, 1065m, 1028m, 984m, 911w, 879w, 732m, 700m, 636w.

1-acetato-4-benzyl-1,4,7-triazacyclononane (2)

Compound **9** (0.78 g 2.3 mmol) was dissolved in 5M HCl (25 ml) and the solution refluxed overnight. Removal of the solvent gave a light purple colored oil, which was dissolved in 50 ml of water and decolourised by heating with finely divided charcoal. The solution was filtered and reduced to dryness. The residue was dissolved glacial acetic acid (30 ml) and HBr gas was bubbled through the solution until a white precipitate formed. This was collected by filtration and dried under nitrogen. The product was isolated as a trihydrobromide dihydrate salt. Yield: 0.43 g, 0.73 mmol (32 %). **Microanalysis:** Found: C 31.2; H 5.5; N 7.3; Br 41.1 %. Calc. for $C_{15}H_{34}N_3O_6Br_3$ {**2**.3HBr.4H_2O} C 30.8; H 5.9; N 7.2; Br 41.1 %. **^{1}H NMR (D_2O):** δ 3.16-3.60 (12H, m, tacn NC$\underline{H_2}$'s), 3.84 (2H, s, C$\underline{H_2}$Ph), 4.59 (2H, s, NC$\underline{H_2}$COOH), 7.56-7.65 (5H, m, Ar$\underline{H}$). **^{13}C NMR (D_2O):** δ 41.42, 43.91, 47.82, 48.95, 50.97, 55.59 (tacn $\underline{C}H_2$'s), 61.81 (N$\underline{C}H_2$Ph), 62.17 (N$\underline{CH_2}$COOH), 128.53 (aromatic quaternary $\underline{C}$), 129.52, 129.83, 130.61, 131.24, 131.58 (aromatic $\underline{C}$H's), 176.00 ($\underline{C}$OOH). Mass spectrum m/z (+ve ion): 278 (corresponds to $2.H^+$).

1-benzyl-4-propylamino-1,4,7-triazacyclononane (3)

1-benzyl-4-formyl-7-propylphthalimido-1,4,7-triazacyclononane (10)

Compound **8** (0.84 g, 3.40 mmol) was dissolved in acetonitrile (30 ml) and sodium carbonate (2 g) was added. Whilst the suspension was being stirred, N-(3-bromopropyl)phthalimide (0.92 g, 3.4 mmol) was added and the resulting mixture heated at reflux with stirring for 3 days. The solution was then filtered and the solvent removed under reduced pressure to give a slightly opaque orange oil. This was dissolved in water (50 ml), adjusted to pH ~ 11 and extracted into chloroform (5 x 30 ml). The extracted fractions were combined and dried over magnesium sulfate. Following filtration, the solvent was removed under reduced pressure to give an orange oil. Yield 1.12 g, 2.57 mmol, 75 %.

^{1}H NMR ($CDCl_3$): δ 1.79 (2H, quintet, $NCH_2\underline{CH_2}CH_2$phth), 2.44-3.78 (16H, m, $N\underline{CH_2}CH_2\underline{CH_2}$phth and 6 tacn $\underline{CH_2}$'s, two resonance forms), 3.65 and 3.93 (2H, s, $\underline{CH_2}$Ph, two resonance forms), 7.31 (5H, m, aromatic C$\underline{H}$ benzyl), 7.73 and 7.85 (4H, m, aromatic C$\underline{H}$ phthalimide, two resonance forms), 8.05 and 8.11 (1H, s, NC$\underline{H}$O, two resonance forms).

^{13}CNMR ($CDCl_3$): δ 43.22, 44.83, 44.96, 45.21, 45.27, 47.07, 49.69, 51.10, 52.33, 52.91, 53.10, ($N\underline{C}H_2CH_2\underline{C}H_2$phth and tacn $\underline{C}H_2$'s, two resonance forms), 61.63 and 61.97 ($Ph\underline{C}H_2$, two resonance forms), 127.63, 127.81, 128.54, 129.23, 129.82 (aromatic $\underline{C}$H's), 137.06 (aromatic quaternary $\underline{C}$), 164.28 and 164.64 ($\underline{C}$HO, two resonance forms). **IR spectrum (neat, ν, cm^{-1}):** 3462br, 3026w, 2927m, 1770m, 1711s, 1667s, 1494w, 1438w, 1396s, 1368m, 1223w, 1188w, 1124w, 1035w, 889w, 753w, 722m, 700w, 667w, 632w.

1-benzyl-4-propylamino-1,4,7-triazacyclononane (3)

The orange oil, **10**, (1.10 g, 2.52 mmol) was dissolved in a 5M solution of hydrochloric acid (20 ml) and the solution was heated at reflux for 4 hours. The solution was then placed in a refrigerator overnight, to precipitate the phthalic acid side product. This was removed by filtration and the pH of the filtrate was then adjusted to 12 with 5M sodium hydroxide. The product was extracted into chloroform (5 x 30 ml) and the combined extracts dried over magnesium sulfate. Following filtration, the solvent was removed under reduced pressure to give the product as viscous orange oil. Yield: 0.46 g, 1.67 mmol (66 %). **Microanalysis:** Found: C 57.7; H 9.2; N 15.9 %. Calc. for $C_{16}H_{34}N_4O_3$ {**1**.1/2$CHCl_3$.1/2H_2O} C 57.4; H 8.6; N 16.2 %. **^{1}H NMR ($CDCl_3$):** δ 1.55 (2H, quintet, $NCH_2C\underline{H_2}CH_2$), 2.42-2.82 (16H, m, propylamino and tacn $C\underline{H_2}$'s), 3.73 (2H, s, $C\underline{H_2}Ph$), 7.32 (3H, m, aromatic $C\underline{H}$), 7.33 (2H, m, aromatic $C\underline{H}$). **^{13}C NMR (D_2O):** δ 31.63 ($CH_2\underline{C}H_2CH_2$), 40.19 ($\underline{C}H_2NH_2$), 46.26, 51.13, 51.43, 52.66, 55.19 (tacn $\underline{C}H_2$'s assuming two co-incidences), 61.75 (Ph-$\underline{C}H_2$), 126.67, 127.91, 128.51, 128.72 (Aromatic $\underline{C}H$), 139.51 (Aromatic quaternary $\underline{C}$). **IR spectrum (neat, ν, cm^{-1}):** 3292br, 3066w, 3030w, 2920m, 1656s, 1585m, 1449m, 1399m, 1311w, 1122w, 751m, 699m, 636w. **Mass spectrum m/z (+ve ion):** 277 (corresponds to **3**.H^+)