Electronic Supplementary Material (ESI) for RSC Advances

A tetrameric hetero-octanuclear cyclic helicate formed from a bridging ligand with two inequivalent binding sites

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Supporting Information – details of ligand synthesis and ^{1}H NMR spectrum of H_2L

3-(2-pyridyl)pyrazole prepared as published earlier.[S1]

Synthesis of 1

A mixture of 3-(hydroxymethyl)aniline (7.50 g, 60.90 mmol) and di-*tert*-butyl dicarbonate (13.50 g, 61.86 mmol) was stirred in THF (150 cm^3) at 25˚C for 48 h. The resultant brown solution was reduced to dryness before purification of the crude brown oil by silica column. Elution with ethyl acetate/ 40:60 petroleum ether (1:2) followed by sonication for 10 minutes in hexane yielded **1** as a white solid (Yield: 13.01 g, 58.27 mmol, 96 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.48 (1H, s; ArH), 7.32 – 7.23 (2H, m; ArH), 7.08 – 7.06 (1H, m; ArH), 6.52 (1H, bs; NH), 4.69 (2H, d; CH_2), 1.75 (1H, t; OH), 1.54 (9H, s; ^{t}Bu). ESMS: *m/z* 262 $[M + K]^+$, 246 $[M + Na]^+$, 150 $[M - O^tBu]^+$; Found: C, 64.60; H, 7.67; N, 6.17 %. Required for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27 %. Data is in accordance with the literature.[S2]

Synthesis of 2

A solution of **1** (3.22 g, 14.42 mmol) in CH_2Cl_2 (70 cm^3) was maintained at 0˚C with stirring. To this was added PPh_3 (6.10 g, 23.26 mmol) and CBr_4 (7.94 g, 23.94 mmol) sequentially, and the resultant yellow solution was stirred at 0˚C for 1.5 h. The reaction mixture was then diluted with EtOAc and stirred for a further 0.5 h, before washing with brine. The organic layer was extracted with EtOAc, dried over $MgSO_4$ and concentrated before purification by silica column. Elution with ethyl acetate/ 40:60 petroleum ether (1:12) yielded **2** as a white solid (Yield: 2.95 g, 10.31 mmol, 67 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.54 (1H, s; ArH), 7.31 – 7.21 (2H, m; ArH), 7.10 – 7.07 (1H, m; ArH), 6.52 (1H, bs; NH), 4.48 (2H, s; CH_2), 1.75 (1H, t; OH), 1.55 (9H, s; ^{t}Bu). ESMS *m/z* 286 $[M + H]^+$, 288 $[M + H]^+$. Found: C, 50.53; H, 5.42; N, 4.77 %. Required for $C_{12}H_{16}BrNO_2$, 50.37; H, 5.64; N, 4.89 %. Data is in accordance with the literature.[S2]

Synthesis of 3

A mixture of **2** (2.95 g, 10.29 mmol), 3-(2- pyridyl)pyrazole (1.50 g, 10.33 mmol), THF (120 cm^3) and aqueous NaOH (13 M, 7.5 cm^3) was stirred at 75˚C for 24 h. The organic layer was separated, dried over $MgSO_4$ and concentrated before purification by silica column. Elution with EtOAc/ DCM (4:1) yielded **3** as a white solid (Yield: 2.55 g, 71 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.65 (1H, ddd; pyridyl H^6), 7.97 (1H, dt; pyridyl H^3), 7.73 (1H, td; pyridyl H^4), 7.43 (1H, d; pyrazolyl H^5), 7.34 – 7.25 (3H, m; ArH), 7.21 (1H, ddd; pyridyl H^5), 6.94 – 6.92 (2H, m; Ar-H and pyrazolyl H^4), 6.55 (1H, bs; NH), 5.38 (2H, s; CH_2), 1.52 (9H, s; ^{t}Bu). ESMS: *m/z* 373 $[M + Na]^+$, 351 $[M + H]^+$. Found: C, 68.46; H, 6.35; N, 15.78 %. Required for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99 %.

Synthesis of 4

To a solution of **3** (1.51 g, 4.31 mmol) in CH_2Cl_2 (20 cm^3) was added 1,1,1-trifluoroacetic acid (20 cm^3) and the resultant yellow mixture was stirred at 25˚C for 14 h. The solvent was removed *in vacuo* and the clear brown oil was repeatedly washed with CH_2Cl_2/MeOH (1:1) and evaporated to dryness in order to remove all traces of TFA. The cream-coloured solid was washed with aqueous K_2CO_3 and the organic layer extracted with DCM, dried over $MgSO_4$ and evaporated to dryness, yielding **4** as a white solid (Yield: 0.81 g, 75 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.65 (1H, ddd; pyridyl H^6), 7.97 (1H, dt; pyridyl H^3), 7.72 (1H, td; pyridyl H^4), 7.42 (1H, d; pyrazolyl H^5), 7.20 (1H, ddd; pyridyl H^5), 7.14 (1H, t; Ar-H), 6.92 (1H, d; pyrazolyl H^4), 6.68 – 6.61 (2H, m; Ar-H), 6.53 (1H, t; Ar-H), 5.31 (2H, s; CH_2), 3.56 (2H, bs; NH_2). ESMS: *m/z* 251 $[M + H]^+$. Found: C, 70.70; H, 5.46; N, 21.64 %. Required for $C_{15}H_{14}N_4$: C, 71.98; H, 5.64; N, 22.38 %.

Synthesis of 5

2,3-dimethoxybenzoic acid (4.70 g, 25.8 mmol), $SOCl_2$ (7 cm^3, 96.5 mmol) and a drop of DMF were heated to reflux with stirring for 6 h. The condenser was fitted with a $CaCl_2$ drying tube to absorb liberated SO_2 and HCl. The resultant clear yellow solution was diluted with $CHCl_3$ and reduced to dryness three times. Drying under high vacuum yielded **5** as an off white solid, which was used without any further purification, assuming quantitative yield (Yield: 5.10 g, 99 %). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.55 (1H,

dd; Ar-H), 7.20-7.15 (2H, m; Ar-H), 3.94 (3H, s; OMe), 3.92 (3H, s; OMe). EIMS *m/z* 224 $[M + Na]^+$, 165 $[M - Cl^-]^+$. Data is in accordance with the literature.[S3]

Synthesis of 6

A mixture of **4** (0.51 g, 2.0 mmol) and **5** (0.44 g, 2.2 mmol) were stirred in dry CH_2Cl_2 (25 cm^3) under nitrogen flow. To the cloudy solution was added Et_3N (0.55 cm^3, 4.0 mmol), and the resultant clear solution was stirred at room temperature for 1 h. The mixture was then sequentially washed with 1M HCl (50 cm^3) and 1M NaOH (50 cm^3). The organic layer was extracted with DCM, dried over $MgSO_4$ and concentrated before purification by silica column. Elution with EtOAc/CH_2Cl_2 (1:1) yielded **6** as a clear yellow oil (Yield: 0.80 g, 97%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.05 (1H, s; NH), 8.62 (1H, ddd; pyridyl H^6), 7.95 (1H, dt; pyridyl H^3), 7.75 (1H, dd; Ph-H), 7.72 – 7.66 (2H, m; Ph-H and pyridyl H^4), 7.58 (1H, dd; cat-H), 7.46 (1H, d; pyrazolyl H^5), 7.33 (1H, t; cat-H), 7.22 – 7.13 (2H, m; Ph-H and pyridyl H^5), 7.07 (1H, dd; Ph-H), 7.00 (1H, dd; cat-H), 6.92 (1H, d; pyrazolyl H^4), 5.40 (2H, s; CH_2), 3.95 (3H, s; OMe); 3.89 (3H, s; OMe). ESMS: *m/z* 415 $[M + H]^+$. Found: C, 60.67; H, 4.51; N, 11.52 %. Required for $C_{24}H_{22}N_4O_3 \cdot$ DCM: C, 60.13; H, 4.84; N, 11.22 %.

Synthesis of H_2L

BBr_3 (1M solution in CH_2Cl_2, 17 cm^3, 17 mmol) was added dropwise to a solution of **6** (0.80 g, 1.9 mmol) in dry DCM (50 cm^3) maintained at –78°C and then stirred at room temperature overnight. The reaction mixture was quenched with MeOH and the volatiles were removed under reduced pressure. The resultant black residue was suspended in H_2O at 100°C for 2 h and the brown solution was cooled and filtered. The pink precipitate was washed with water and DCM, and the resultant white solid was recrystallized from MeOH, yielding a white solid (Yield: 0.61 g, 83%). ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 11.51 (1H, bs; Ar-OH), 10.39 (1H, s; NH), 8.69 (1H, ddd; pyridyl H^6), 8.41 – 8.25 (2H, m; Ar-H and pyridyl H^3), 8.16 (1H, d; pyrazolyl H^5), 7.78 – 7.68 (2H, m; Ar-H), 7.61 (1H, dd; Ar-H), 7.44 – 7.33 (2H, m; Ar-H and pyridyl H^5), 7.20 (1H, d; pyrazolyl H^4), 7.09 (1H, dt; Ar-H), 6.98 (1H, dd; Ar-H), 6.76 (1H, t; Ar-H), 5.53 (2H, s; CH_2). ESMS: *m/z* 387 $[M + H]^+$. Found: C, 56.50 ; H, 4.04; N, 11.81 %. Required for $C_{22}H_{18}N_4O_3$.HBr: C, 56.54; H, 4.10; N, 11.99 %.

S1. A. J. Amoroso, A. M. C. Thompson, J. C. Jeffery, P. L. Jones, J. A. McCleverty and M. D. Ward, *J. Chem. Soc., Chem. Comm.*, 1994, 2751.

S2. F. J. Brown, P. R. Bernstein, L. A. Cronk, D. L. Dosset, K. C. Hebbel, T. P. Maduskuie, H. S. Shapiro, E. P. Vacek, Y. K. Yee, A. K. Willard, R. D. Krell and D. W. Snyder, *J. Med. Chem.*, 1989, **32**, 807.

S3. M. Meyer, B. Kersting, R. E. Powers and K. N. Raymond, *Inorg. Chem.*, 1997, **36**, 5179.

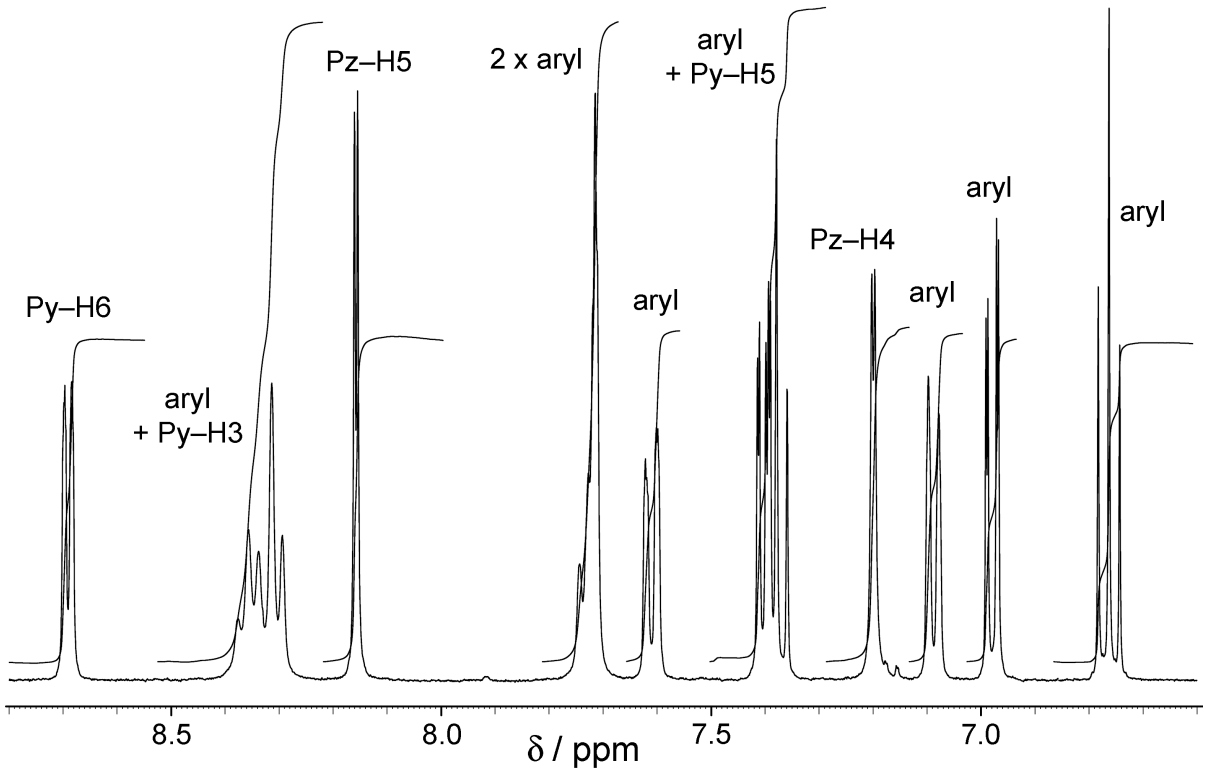

Fig. S1. Part of the ^{1}H NMR spectrum of H_2L in d^6-DMSO (py = pyridyl; pz = pyrazolyl). Not shown are the NH and OH protons at > 10 ppm and the methylene protons at 5.53 ppm.