Supplementary Material (ESI) for Chemical Communications

Encapsulated Binding Sites – Synthetically Simple Receptors for the Binding and Transport of HCl

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SUPPLEMENTARY INFORMATION

Contents

1. Synthesis and Characterisation

(3,4-Bis-benzyloxy-phenyl)-acetic acid, an important building block in the synthesis of receptor 1 was synthesised according to literature methods.[1] Receptors **3**,[2] **7**,[3] and **8**[4] were also synthesised according to literature methods.

General synthesis method 1: To a solution of tris-(2-aminoethyl)-amine (1.02 mL, 6.9 mmol) in EtOAc, the appropriate acid anhydride (26.7 mmol) and pyridine (1.66 mL, 20.1 mmol) were added. The reaction was left to stir overnight and the solvent was removed under vacuum.

General synthesis method 2: To a solution of tris-(2-aminoethyl)-amine (1.02 mL, 6.9 mmol) and Et_3N (3.5 mL) in 100 ml of CH_2Cl_2 at 10°C was added the appropriate acid chloride (24 mmol) with stirring. The reaction was left to stir overnight and then poured into 200 mL of water. The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The organic layers were dried with $MgSO_4$, filtered and the solvent removed under vacuum.

Receptor 1. (3,4-Bis-benzyloxy-phenyl)-acetic acid (1.30 g, 3.7 mmol) was dissolved in CH_2Cl_2 (~30 mL). DCC (1.55 g, 7.5 mmol) and HOBt (1.01 g, 7.5 mmol) were added to the acid as a mixture of solids. The mixture was left to cool to 0°C for 10 min in an ice bath with a N_2 balloon. In a separate beaker, tris-(2-aminoethyl)-amine (0.19 mL, 1.25 mmol) and Et_3N (0.52 ml, 3.7 mmol) were dissolved in CH_2Cl_2 (~30 mL). This was added to the acid mixture and stirred for 3 d. The reaction mixture was filtered. The filtrate was evaporated to dryness under vacuum. The product was purified by column chromatography with a starting eluent of 99:1 CH_2Cl_2:MeOH, gradient elution was employed until a solvent ratio of 92:8 was reached. A small amount of Et_3N was added to the eluent. The product was obtained as a white solid in a 56% yield. m.p. 142°C. R_f 0.61 (9:1 CH_2Cl_2:MeOH). ^{1}H NMR ($CDCl_3$): δ 7.48-7.35 (12H, m, Ar *H*), 7.34-7.27 (18H, m, Ar *H*), 6.90 (3H, d, J = 1.8 Hz, Ar *H*), 6.83 (3H, d, J = 7.9 Hz, Ar *H*), 6.74 (3H, dd, J = 6.4, 1.8 Hz, Ar *H*), 6.32 (3H, t, J = 5.5 Hz, N*H*), 5.07 (6H, s, CH_2-O), 5.06 (6H, s, CH_2-O), 3.41 (6H, s, CH_2-C=O), 3.08 (6H, q, J = 4.9 Hz, N*H*-CH_2), 2.37 (6H, t, J = 5.5 Hz, CH_2). ^{13}C NMR

($CDCl_3$): δ 171.9 (*C*=O), 149.2 (Ar *C*-O), 148.3 (Ar *C*-O), 137.4 (Ar *C*-CH_2), 137.3 (Ar *C*-CH_2), 128.6 (Ar *C*), 128.5 (Ar *C*), 127.9 (Ar *C*), 127.5 (Ar *C*), 127.4 (Ar *C*), 122.4 (Ar *C*), 116.1 (Ar *C*), 115.4 (Ar *C*), 71.4 (*C*H_2-O), 71.2 (*C*H_2-O), 54.9 (*C*H_2-N), 43.1 (*C*H_2-C=O), 38.1 (NH-*C*H_2). ν_{max} (solid): 3287*m* (N-H), 3063*w* (Ar C-H), 3032*w* (Ar C-H), 2932*w* (C-H), 2862*w* (C-H), 1639*s* (C=O), 1589*m*, 1543*m*, 1508*s*, 1454*m*, 1427*m*, 1381*m*, 1339*m*, 1258*s*, 1223*s*, 1157*m*, 1134*s*, 1080*w*, 1007*s*. ESIMS *m/z*: 1159 ($[M+Na]^+$, 100%). HRESIMS: Calculated for $C_{72}H_{73}N_4O_9$, 1137.5372; found, 1137.5329.

Receptor 2. 3,4-Dimethoxyphenyl acetic acid (1.00 g, 5.1 mmol) was dissolved in CH_2Cl_2 (~30 mL). DCC (2.10 g, 10.2 mmol) and HOBt (1.38 g, 10.2 mmol) were added to the acid as a mixture of solids. The mixture was left to cool to 0°C for 10 min in an ice bath with a N_2 balloon. In a separate beaker, tris-(2-aminoethyl)-amine (0.25 mL, 1.7 mmol) and Et_3N (0.71 ml, 5.1 mmol) were dissolved in CH_2Cl_2 (~30 mL). This was added to the acid mixture and stirred for 3 d. The reaction mixture was filtered. The filtrate was evaporated to dryness under vacuum. The product was purified by column chromatography (CH_2Cl_2:MeOH 98:2). A small amount of Et_3N was added to the eluent. The product was obtained as a white solid in a 42% yield. m.p. 123°C. R_f 0.53 (CH_2Cl_2:MeOH 9:1). ^{1}H NMR (DMSO-d_6): δ 7.86 (3H, t, J = 5.5 Hz, N*H*), 6.85-6.79 (6H, m, Ar *H*), 6.74 (3H, dd, J = 8.2, 1.2 Hz, Ar *H*), 3.69 (9H, s, OCH_3), 3.68 (9H, s, OCH_3), 3.30 (6H, s, CH_2-C=O), 3.04 (6H, q, J = 6.1 Hz, NHCH_2), 2.45 (6H, t, J = 6.7 Hz, CH_2N). ^{13}C NMR ($CDCl_3$): δ 171.9 (*C*=O), 148.9 (Ar *C*-O), 148.0 (Ar *C*-O), 127.8 (Ar *C*), 121.3 (Ar *C*), 112.4 (Ar *C*), 111.3 (Ar *C*), 55.81 (O-*C*H_3), 55.78 (O-*C*H_3), 54.6 (*C*H_2-N), 42.9 (*C*H_2C=O), 37.9 (NH-*C*H_2). ν_{max} (solid): 3283*s* (N-H), 2936*m* (C-H), 2835*m* (C-H), 1639*s* (C=O), 1593*m*, 1543*m*, 1512*s*, 1450*m*, 1420*m*, 1342*m*, 1261*s*, 1231*s*, 1138*s*, 1026*s*. ESIMS *m/z*: 703 ($[M+Na]^+$, 100%). HRCIMS: Calculated for $C_{36}H_{49}N_4O_9$, 681.3500; found, 681.3509.

Receptor 4. Using general synthesis method 1 and propionic anhydride (3.44 mL) and purifying the product by washing with diethyl ether gave receptor **4** as a cream solid in a 21% yield. m.p. 80°C. ^{1}H NMR ($CDCl_3$): δ 6.50 (3H, bt, N*H*), 3.28 (6H, bq, NHCH_2), 2.54 (6H, bt, CH_2N), 2.24 (6H, q, J = 7.6 Hz, CH_2CO), 1.15 (9H, t, J = 7.3 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 174.8 (*C*=O), 54.6 (*C*H_2N), 37.8 (NH*C*H_2), 29.6

(CO*C*H_2), 10.1 (*C*H_3). ν_{max} (solid): 3294*m* (N-H), 2970*m* (C-H), 2936*m* (C-H), 2878*w* (C-H), 1643*s* (C=O), 1543*s*, 1454*m*, 1361*m*, 1319*w*, 1258*w*, 1234*m*, 1165*m*, 1049*m*, 999*m*. ESIMS *m/z*: 315 ($[M+H]^+$, 100%). HRESIMS: Calculated for $C_{15}H_{31}N_4O_3$, 315.2391; found, 315.2396.

Receptor 5. Using general synthesis method 1 and butyric anhydride (4.3 mL) and purifying the product by washing with diethyl ether gave receptor **5** as a white solid in a 34% yield. m.p. 96°C. ^{1}H NMR ($CDCl_3$): δ 6.60 (3H, bt, N*H*), 3.28 (6H, bq, NHC*H*$_2$), 2.53 (6H, bt, C*H*$_2$N), 2.19 (6H, t, J = 7.3 Hz, C*H*$_2$CO), 1.67 (6H, sex, J = 7.6 Hz, CH_3C*H*$_2$), 0.94 (9H, t, J = 7.6 Hz, C*H*$_3$). ^{13}C NMR ($CDCl_3$): δ 174.0 (*C*=O), 54.6 (*C*H_2N), 38.6 (NH*C*H_2), 37.7 (CO*C*H_2), 19.3 (*C*H_2), 14.0 (*C*H_3). ν_{max} (solid): 3294*m* (N-H), 2958*m* (C-H), 2932*m* (C-H), 2873*w* (C-H), 1649*s* (C=O), 1543*s*, 1423*m*, 1366*m*, 1319*m*, 1288*m*, 1250*m*, 1211*m*, 1165*m*, 1072*w*, 1034*w*, 995*w*. ESIMS *m/z*: 357 ($[M+H]^+$, 100%). HRESIMS: Calculated for $C_{18}H_{37}N_4O_3$, 357.2860; found, 357.2860.

Receptor 6. Using general synthesis method 2 and valeroyl chloride (2.8 mL) and purifying the product by recrystallisation from ethyl acetate gave receptor **6** as a white solid in a 27% yield. m.p. 99°C. ^{1}H NMR ($CDCl_3$): δ 6.57 (3H, bt, N*H*), 3.28 (6H, bq, NHC*H*$_2$), 2.53 (6H, bt, C*H*$_2$N), 2.21 (6H, t, J = 7.6 Hz, C*H*$_2$CO), 1.61 (6H, quin, J = 7.6 Hz, C*H*$_2$), 1.34 (6H, sex, J = 7.6 Hz, CH_3C*H*$_2$), 0.91 (9H, t, J = 7.3 Hz, C*H*$_3$). ^{13}C NMR ($CDCl_3$): δ 174.1 (*C*=O), 54.6 (*C*H_2N), 37.6 (NH*C*H_2), 36.3 (CO*C*H_2), 28.0 (*C*H_2), 22.6 (*C*H_2), 13.9 (*C*H_3). ν_{max} (solid): 3294*m* (N-H), 2955*m* (C-H), 2932*m* (C-H), 2866*m* (C-H), 2828*w* (C-H), 1639*s* (C=O), 1543*s*, 1454*m*, 1423*m*, 1381*m*, 1354*m*, 1319*w*, 1258*m*, 1231*m*, 1204*w*, 1165*m*, 1072*m*, 999*m*. ESIMS *m/z*: 399 ($[M+H]^+$, 100%). HRESIMS: Calculated for $C_{21}H_{43}N_4O_3$, 399.3330; found, 399.3324.

2a Job Plot Data

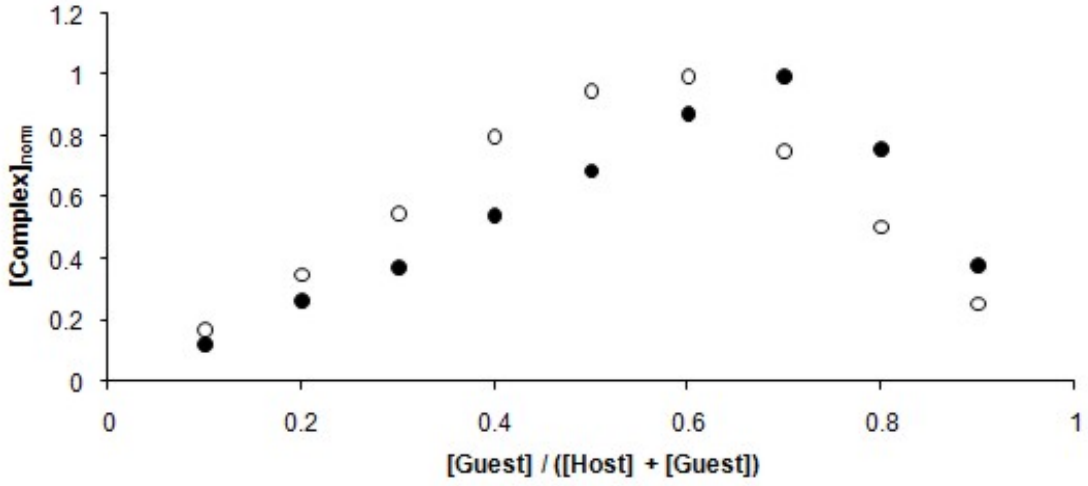
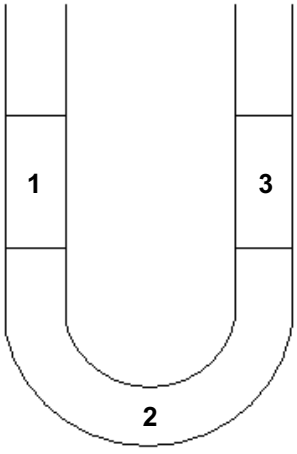


Figure S1. Job plot analysis for compound **2** on the addition of HCl (2.0 mM in diethyl ether) (black circles) or HBF_4 (54% wt. sol. in diethyl ether) (white circles) in CD_3CN:DMSO-d_6 (9:1), demonstrating different stoichiometries for the interaction of this receptor with the different acids.

2b U-Tube Method



All U-tube experiments were run in the same glassware with three separate solutions; 15.5 mL of 0.01 M transporter in dichloromethane (solution **2**), 6 mL of HCl (pH 0.9) (solution **1**) in deionised water and 6 mL of deionised water (solution **3**). The

organic phase was stirred using a custom made magnetic stirrer bar at a setting of 3.5 using a 728 Metrohm stirrer. The pH of the neutral phase was monitored using a 702 SM Titrino Metrohm potentiometer with a combined glass electrode taking readings every 10 minutes for 240 minutes, after an initial lag-time of 1 minute.

3. References

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