Supplementary Material (ESI) for Chemical Communications

Conformer Independent Heterodimerisation of Linear Arrays Using Three Hydrogen Bonds

Electronic Supplementary Material

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General Considerations

All reagents were purchased from Aldrich or Alfa-Aesar and used without further purification unless otherwise stated. Yields are not optimized. Purification by column chromatography was carried out using Merck Kieselgel 60 silica gel. Analytical thin layer chromatography (TLC) was conducted using Merck Kieslegel 0.25mm silica gel pre-coated aluminium plates with fluorescent indicator active at UV_{245}. Where anhydrous solvents were required, THF was freshly distilled from sodium-benzophenone ketyl radical, CH_2Cl_2 freshly distilled from calcium hydride and $CHCl_3$ freshly distilled from calcium chloride under a nitrogen atmosphere. Triethylamine was distilled from calcium hydride under a nitrogen atmosphere and stored, under nitrogen, over potassium hydroxide pellets. Anhydrous DMF was obtained "sure-sealed" from Sigma-Aldrich. NMR spectra were obtained using Bruker AMD300 or Bruker DMX500 spectrometers operating at 500 MHz or 300 MHz for ^1H spectra and 100 MHz or 75 MHz for ^{13}C spectra as stated. NMR solvent was $CDCl_3$ unless otherwise stated. Proton spectra are referenced to residual $CHCl_3$ at 7.26 ppm, and carbon spectra to $CDCl_3$ at 77.4 ppm, unless otherwise stated. The following abbreviations are used: s for singlet, d for doublet, t for triplet, q for quartet, m for multiplet and br for broad. IR spectra were obtained using attenuated total reflectance (ATR) apparatus. Mass spectroscopy and microanalysis were carried out at the University of Leeds.

Synthetic Procedures

***N*-Phenyl-*N'*-(imidazo-2-yl)urea 1a**[1]

To a stirred solution of 2-aminoimidazole sulphate (1.000 g, 3.78 mmol) in water (4.5 mL) was added sodium carbonate (0.402 g, 3.78 mmol). The reaction mixture was allowed to stir for one hour and was then concentrated to leave a brown viscous solid. This was stirred in anhydrous ethanol (25 mL) for one hour and then filtered through a pad of celite, concentrated and dried under vacuum for 2 hours. Under an atmosphere of nitrogen, the resultant crude free amine was stirred in anhydrous THF (50 mL) and triethylamine (1.600 mL, 1.14 g, 11.36 mmol). Phenylisocyanate (0.390 mL, 0.420 g, 3.59 mmol) was then added dropwise in THF (25 mL) over a period of thirty minutes. The solution was allowed to stir overnight and was then concentrated to 5 mL and diluted with dichloromethane (50 mL). The resulting white precipitate was filtered and dried thoroughly to give the product (0.346 g, 50%) as a white solid,

m.p. decomposes >226.0°C (lit. 218-220)[1]; R_f = 0.16 (MeOH/ CH_2Cl_2, 1:20 v/v); υ_{max}/cm^{-1}; 3284 (NH), 1703 (CO), 1577 (CO), 1538 (CO), 1449, 1311, 1200; δ_H (300 MHz, DMSO-d_6); 6.70 (2H, s, imCH), 6.99 (1H, t, *J* = 7.7, ArCH), 7.29 (2H, t, *J* = 7.7, ArCH), 7.48 (2H, d, *J* = 7.7, ArCH), 9.52 (1H, brs, NH), 10.47 (2H, vbrs, NH); δ_C (75 MHz, DMSO-d_6) 114.2, 118.8, 122.6, 129.2, 139.6, 142.6, 152.8; *m/z* (ESI-MS) 203 $[M+H]^+$; Anal. calc'd for $C_{10}H_{10}ON_4$: C, 59.4; H, 4.9; N, 27.7; found: C, 59.2; H, 4.9; N, 27.5.

***N-tert*-Butoxycarbonylguanidine**[2]

The compound was prepared with minor modifications to a previously published procedure.[2] A solution of *tert*-butoxycarbonylanhydride (42.50 g, 210.1 mmol, 1 eq.) in acetone (600 mL) was added in one portion to a stirred solution of guanidine hydrochloride (61.15 g, 639.6 mmol, 3.05 eq.) and NaOH (50.4 g, 1.26 mol, 6 eq.) in H_2O (200 mL) at 0 °C. The reaction mixture was allowed to warm slowly to room temperature and stirred for 16 h. The volatiles were removed under reduced pressure and the remaining aqueous suspension extracted with EtOAc (2 × 200 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Triturating with EtOAc/ hexane (500 mL, 1:2 v/v) provided the title compound (15.35 g, 133.2 mmol, 63%) as a white solid. Refrigeration of the filtrate prompted precipitation of a second crop (10.183 g, 88.4 mol, 42%) also as a white solid. m.p. decomposes > 350 °C; υ_{max}(neat)/cm^{-1} 3402 (NH), 2973 (CH), 1603 (CO), 1535 (CO), 1311, 1253, 1180, 1141, 1068; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (9H, s, 3 x CH_3), 6.15 (3H, vbrs, 3 x NH); δ_C (75 MHz, DMSO-d_6) 28.6, 75.9, 163.1, 163.6; HRMS calc'd for $C_6H_{13}O_2N_3$ (M^+) 159.1008, found 159.1013; Anal. calc'd for $C_6H_{13}O_2N_3$: C, 45.3; H, 8.2; N, 26.3; found: C, 45.2; H, 8.4; N, 26.3.

2-*tert*-Butoxyamido-4-*tert*-butylimidazole

To a stirred solution of *N-tert*-butoxycarbonylguanidine (4.35 g, 37.72 mmol, 3 eq.) and NaI (~100 mg, cat.) in dry DMF (30 mL) at room temperature under N_2 was added 1-bromopinacolone (1.70 mL, 12.57 mmol, 1 eq.) and the reaction stirred for 4 days. The filtrate was collected by filtration, washed with H_2O and vacuum dried over P_2O_5 to provide the title compound (1.27 g, 6.53 mmol, 52%) as a white solid. The filtrate was poured onto H_2O and extracted with EtOAc (3 × 30 mL). The combined organics were washed with H_2O, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the resultant material by column chromatography

(1:1 EtOAc/ CH_2Cl_2 on silica) provided an additional quantity of the title compound (668 mg, 3.43 mmol, 27%), overall yield 79%. m.p. decomposes >167.7 °C; R_f = 0.38 (EtOAc/ CH_2Cl_2, 1:1 v/v); υ_{max}(neat)/cm^{-1} 3434 (NH), 2971 (CH), 1725 (CO), 1641 (CO), 1357, 1258, 1155, 1119; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (9H, s, 3 x CH_3), 1.54 (9H, s, 3 x CH_3), 5.80 (2H, vbrs, NH), 6.48 (1H, s, imCH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.4, 28.7, 29.7, 30.3, 31.9, 84.70, 104.1, 148.8, 150.1, 150.8; ESI-MS *m/z* 240 $[M+H]^+$.

2-Phenylureido-4-*tert*-butylimidazole 1b

Method 1

To a stirred solution of 2-*tert*-Butoxyamido-4-*tert*-butylimidazole (450 mg, 2.32 mmol, 1.05 eq.) in dry CH_2Cl_2 (14 mL) was added trifluoroacetic acid (14 mL) and tri*iso*propylsilane (5 drops, cat.) and the reaction stirred at room temperature for 4 h. The solution was concentrated and the residue dried under vacuum for 1 h. The resulting material was suspended in dry THF (40 mL) and triethylamine (1.55 mL, 11.03 mmol, 5 eq.) under N_2 and the mixture heated to reflux. Phenyl*iso*cyanate (0.24 mL, 2.20 mmol, 1 eq.) in dry THF (18 mL) was added dropwise (syringe pump) over 30 min and the reaction stirred at reflux for 16 h. After cooling to room temperature the volatiles were removed under reduced pressure and the residue partitioned between CH_2Cl_2 and 1M HCl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 20 mL). The combined organics were washed with aq. Sat. $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated. Purification by column chromatography (5% MeOH/ CH_2Cl_2 on silica) provided the title compound (246 mg, 0.95 mmol, 43%) as an off-white solid.

Method 2

To a stirred solution of 2-*tert*-Butoxyamido-4-*tert*-butylimidazole (680 mg, 3.50 mmol, 1.05 eq.) in CH_2Cl_2 (20 mL) was added trifluoroacetic acid (20 mL) and tri*iso*propylsilane (5 drops, cat.) and the reaction stirred at room temperature for 4 h. The solution was concentrated and the residue dried under vacuum for 1 h. The resulting material was dissolved in dry pyridine (50 mL) under N_2 and the mixture heated to 80 °C. Phenyl*iso*cyanate (0.36 mL, 3.33 mmol, 1 eq.) was added dropwise over 10 min and the reaction stirred at 80 °C for 36 h. After cooling to room temperature the reaction was slowly poured onto 1M HCl (80 mL) and the mixture extracted with EtOAc (3 × 50 mL). The combined organics were washed with aq. sat.

$NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated. The resulting material was triturated with CH_2Cl_2 and the precipitate discarded. Purification by column chromatography provided the title compound (227 mg, 0.88 mmol, 26%) as an off-white solid. m.p. decomposes > 147.0°C; R_f = 0.24 (MeOH/ CH_2Cl_2, 1:20 v/v); υ_{max}/cm^{-1}; 3383 (NH), 2955 (CH), 1710 (CO), 1586 (CO), 1560 (CO), 1448, 1309, 1261, 1192; δ_H (500 MHz, $CDCl_3$); 1.25 (9H, s, 3 x CH_3) 6.29 (1H, s, imCH), 7.04 (1H, t, *J* = 7.7 ArCH), 7.26 (2H, dt, *J* = 7.7 ArCH), 7.34 (2H, d, *J* = 7.7 ArCH); δ_C (75 MHz, $CDCl_3$) 30.1 (× 3), 31.0, 120.5 (× 2), 124.0, 129.4 (× 3), 138.6, 144.3, 154.9; HRMS calc'd for $C_{14}H_{19}N_3O$ ($M+H^+$) 259.1553, found 259.1553.

***N*-Phenyl-*N'*-(4-methyl-pyrid-2-yl)urea 2**

To a stirred solution of 4-methyl-2-aminopyridine (1.78 g, 16.46 mmol, 1 eq.) in dry THF (50 mL) at room temperature under N_2 was added phenyl*iso*cyanate (1.79 mL, 16.46 mmol, 1 eq.) and the reaction heated to reflux for 16 h. The mixture was left to cool and the resultant precipitate collected by filtration giving the title compound (1.87 g, 8.21 mmol, 50%) as a white solid. The filtrate was concentrated under reduced pressure and the residue recrystallised from the minimum amount of hot $CHCl_3$ by addition of petroleum ether to provide a second crop of the title compound (1.07 mg, 4.71 mmol, 29%) as a white solid, overall yield 79%. m.p. 181-183 °C; R_f = 0.66 (EtOAc); υ_{max}(neat)/cm^{-1} 3367 (NH), 3029 (NH), 1696 (CO), 1600, 1565, 1483, 1447, 1386, 1300, 1260, 1181; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (3H, s, CH_3), 6.76 (1H, d, *J* = 5.2 Hz, CH), 6.84 (1H, s, CH), 7.09 (1H, t, *J* = 7.4 Hz, CH), 7.36 (2H, t, *J* = 7.8 Hz, 2 × CH), 7.65 (2H, d, *J* = 7.8 Hz, 2 × CH), 8.11 (1H, d, *J* = 5.2 Hz, CH), 9.35 (1H, s, NH), 11.82 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 112.9, 119.1, 120.6 (× 2), 123.6, 129.2 (× 2), 139.1, 145.9, 150.3, 153.6, 154.4; HRMS calc'd for $C_{13}H_{14}N_3O$ ($M + H^+$) 228.1131, found 228.1140; Anal. calc'd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49; found: C, 68.90; H, 5.85; N, 18.60.

Benzamido-5-methyl*iso*cytosine 3

To a stirred mixture of methyl*iso*cytosine (2.10 g, 16.78 mmol, 1 eq.) and 4-*N*,*N*-dimethylaminopyridine (~100 mg, cat.) in dry $CHCl_3$ (80 mL) at room temperature under N_2 was added triethylamine (3.53 ml, 25.17 mmol, 1.5 eq.) and benzoyl chloride (2.14 mL, 18.46 mmol, 1.1 eq.) and the reaction heated to reflux for 16 h. After cooling to room temperature the reaction mixture was washed successively with 1M HCl (40 mL), aqueous saturated $NaHCO_3$ (40 mL) and brine (40 mL). The

organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting off-white solid was recrystallised from methanol and CH_2Cl_2 (1:1 v/v) to provide the title compound (3.25 g, 14.18 mmol, 85%) as a white solid. m.p. 189-192 °C; R_f = 0.33 (EtOAc); υ_{max}(neat)/cm^{-1} 3186 (NH), 1737 (CO), 1640 (CO), 1561 (CO), 1478, 1391, 1271, 1199; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.18 (3H, s, CH_3) 6.01 (1H, s, CH), 7.50 (2H, t, J = 7.7, ArCH), 7.62 (1H, t, J = 7.7, ArCH), 7.92 (2H, d, J = 7.7, ArCH), 11.05 (2H, vbrs, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.9, 108.4, 127.9 (x2), 128.9, 132.3, 133.6, 151.0, 162.3, 169.8; HRMS calc'd for $C_{12}H_{12}N_3O_2$ [M + H^+] 230.0924, found 230.0926; Anal. calc'd for $C_{12}H_{11}N_3O_2$: C, 62.9; H, 4.8; N, 18.3; found: C, 62.7; H, 4.8; N, 18.1

Crystal Structure Determination for 1a

Single crystals were grown by the slow evaporation of a solution of **1a** in methanol. X-ray diffraction data were collected at the University of Leeds.

Crystal data. $C_{10}H_{10}N_4O$, M = 202.22, crystal size 0.36 x 0.19 x 0.05, Monoclinic, a = 11.7156(3), b = 6.0176(2), c = 13.3965(4) Å, β = 92.3690(10)º, U = 943.64(5) Å^3, T = 150(2) K, $P2_1/n$, Z = 4, μ = 0.098 mm^{-1}, λ = 0.71073 Å [Mo-K_α], 12808 reflections measured, 1854 unique (R_{int} = 0.0978), 1533 observed (I>2σ(I)). The final R_1 was 0.0430 (observed reflections 0.0528) and $wR(F^2)$ was 0.1091 (all data 0.1174) for 136 parameters.

Crystal Structure Determination for 3

Single crystals were grown by the slow evaporation of a solution of **3** in methanol and chloroform. X-ray diffraction data were collected at the University of Leeds.

Crystal data. $C_{51}H_{50}Cl_6N_{12}O_8$, M = 1171.73, crystal size 0.26 x 0.23 x 0.22 mm, Triclinic, a = 10.5748(2), b = 11.2109(2), c = 11.8373(3),α = 101.7370(8), β = 100.6000(8), γ = 96.1140(13)°, U = 1335.37(5) Å^3, T = 150(2) K, space group $P\bar{1}$, Z = 2, μ = 0.388 mm^{-1}, λ = 0.71073 Å [Mo-K_α], 25222 reflections measured, 5222 unique (R_{int} = 0.1042), 3827 observed (I>2σ(I)). The final R_1 was 0.0799 (observed reflections 0.1071) and $wR(F^2)$ was 0.2069 (all data 0.2314) for 370 parameters.

NMR Titrations

For NMR titrations anhydrous $CDCl_3$ was purchased from Aldrich. For dilution studies, solutions were made up to concentrations of 100 mM and then the ^{1}H NMR spectrum recorded upon each sequential dilution with $CDCl_3$. For titrations the ^{1}H NMR spectrum was recorded of a solution of host (2mM – 10 mM) in $CDCl_3$ upon

sequential additions of a solution of guest (20-120 mM) containing host (2mM – 10 mM) in $CDCl_3$. The change in chemical shift of key proton resonances was recorded at each dilution/ titration point. The data was subsequently analysed using the HypNMR program using the appropriate model.[3] HypNMR uses data from multiple

resonances for curve fitting – representative data for individual resonances is shown in Fig. S1.

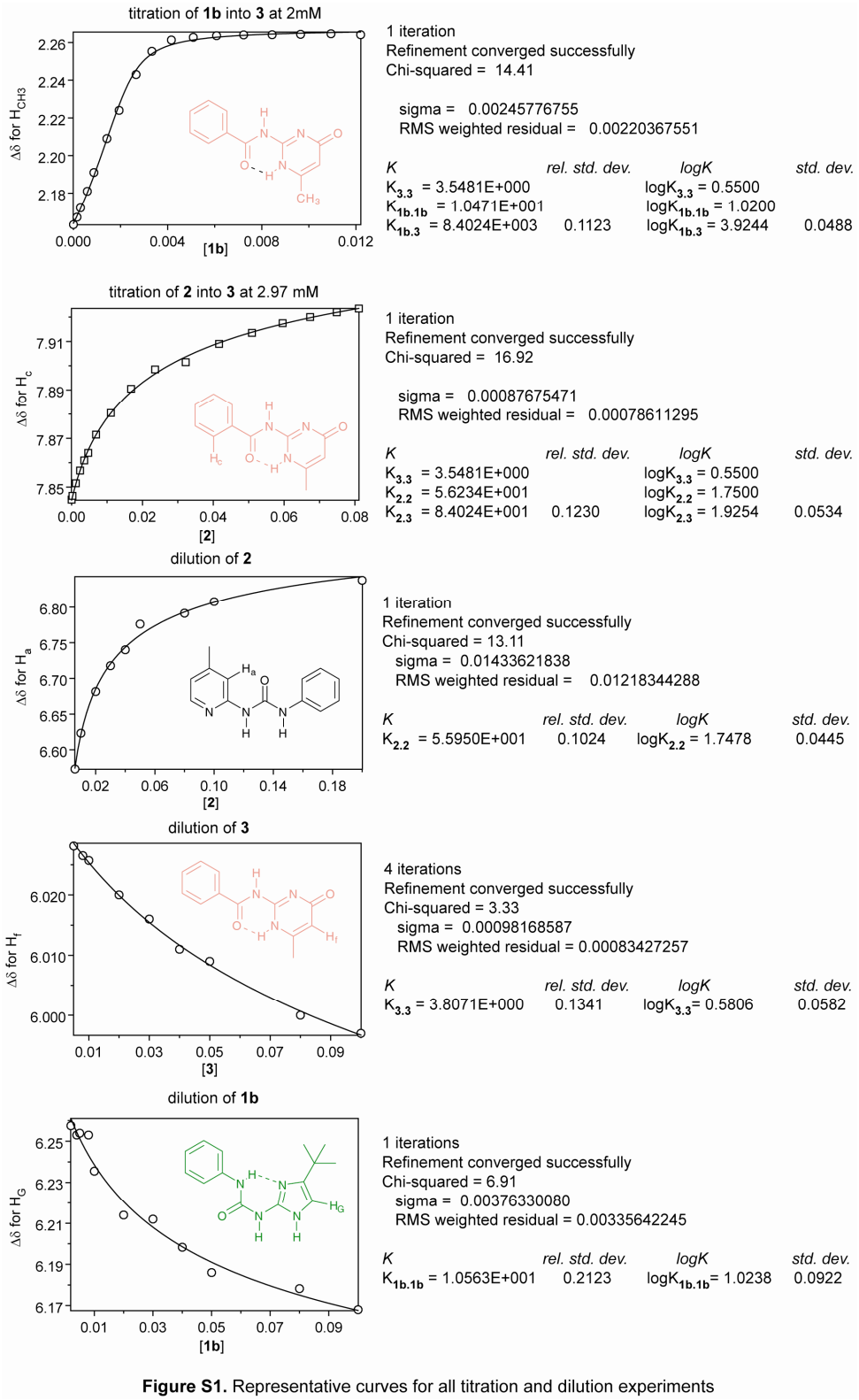

Figure S1. Representative curves for all titration and dilution experiments

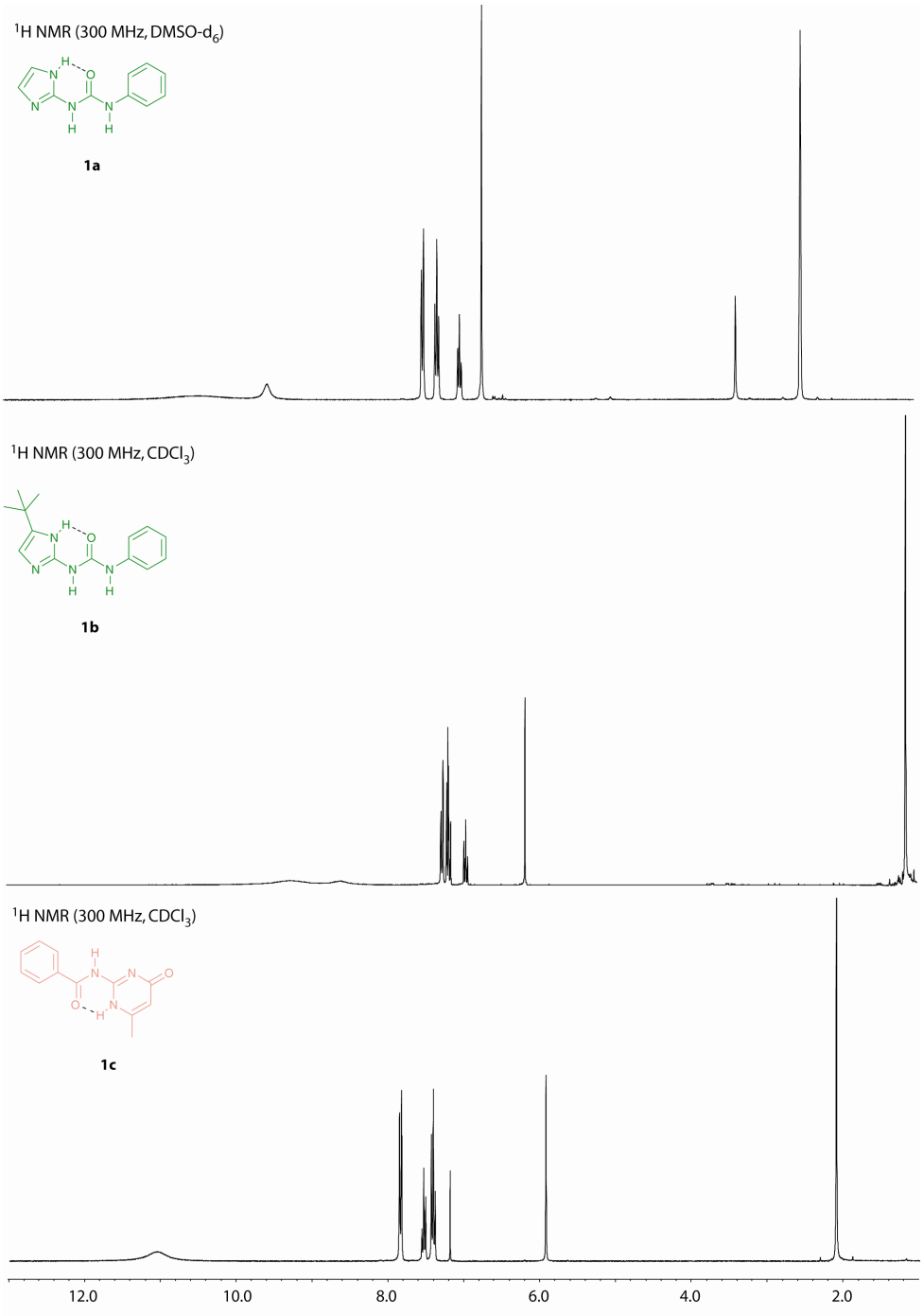

Figure S2. Full ^{1}H NMR spectra for compounds **1a, 1b** and **3**

References

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