Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.
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Supplementary Information

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1. Experimental

1.1. General Experimental

All anhydrous solvents and reagents were obtained from commercial suppliers (Aldrich, Alfa Aesar, Fluorochem) and used without further purification.

Reactions were performed in oven-dried, round-bottom flasks fitted with rubber septa under an atmosphere of argon unless otherwise stated. Analytical thin layer chromatography (TLC) was performed on pre-coated aluminium sheets of silica (60 F_{254}, Merck) and visualised by short-wave UV light.

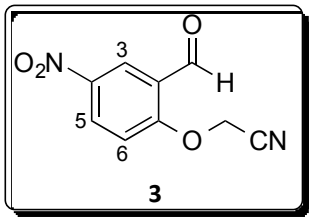
^{1}H NMR spectra were recorded at 500 MHz on a Bruker Avance-500 using an internal deuterium lock. Chemical shifts were measured in parts per million (ppm) relative to tetramethylsilane (δ = 0) using the following internal references for residual protons in the solvent : $CDCl_3$ (δ 7.26) and $(CD_3)_2SO$ (δ 2.50). Data is presented as follows: chemical shift, multiplicity, coupling constant (*J*) in Hz, integration and assignment.

^{13}C NMR specta were recorded at 126 MHz on a Bruker Avance-500 using an internal deuterium lock. Chemical shifts were measured in parts per million (ppm) relative to tetramethylsilane (δ = 0) using the following internal references for residual protons in the solvent: $CDCl_3$ (δ 77.0) and $(CD_3)_2SO$ (δ 39.5). Data is presented as follows: chemical shift and assignment.

HRMS analysis was performed on an Agilent 1200 series HPLC and diode array detector coupled to a 6520 Quadrupole-Time of flight mass spectrometer with dual multimode APCI/ESI source. Analytical separation was carried out at 30 °C in a Merck Purospher STAR column (RP-18e, 30 x 4 mm) using a flow rate of 1.5 mL/min in a 4 min gradient elution with detection at 254 nm. The mobile phase was a mixture of methanol (solvent A) and water (solvent B) both containing formic acid at 0.1%. Gradient elution was as follows: 1:9 (A/B) to 9:1 (A/B) over 2.5 min, 9:1 A/B for 1 min, and then reversion back to 1:9 (A/B) over 0.3 min, finally 1:9 (A/B) for 0.2 min. The following reference masses were used for HRMS analysis: caffeine $[M+H]^+$ 195.087652; (hexakis(1H,1H,3H-tetrafluoropentoxy)phosphazene $[M+H]^+$ 922.009798 and hexakis(2,2-difluoroethoxy)phosphazene $[M+H]^+$ 622.02896 or reserpine $[M+H]^+$ 609.280657.

1.2. Experimental Procedures

Synthesis of 2-(2-formyl-4-nitrophenoxy)acetonitrile (3)[1]

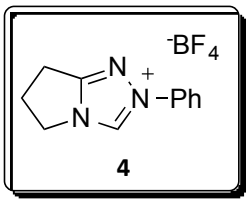


3

To a solution of 2-hydroxy-5-nitrobenzaldehyde (0.50 g, 3.0 mmol) in DMF (2.5 mL) was added K_2CO_3 (0.60 g, 4.4 mmol). The resulting suspension was stirred for 15 min before the addition of bromoacetonitrile (0.40 mL, 5.8 mmol). The reaction was allowed to stir at room temperature for a period of 18 h. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was separated, dried over magnesium sulphate, and concentrated under vacuum. The crude material was purified by column chromatography (50% ethyl acetate in cyclohexane) to afford **3** (0.50 mg, 82%) as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.46 (s, 1H, **H**C=O), 8.79 (d, *J* = 2.9 Hz, 1H, **H^3**), 8.55 (dd, *J* = 9.1, 2.9 Hz, 1H, **H^5**), 7.25 (d, *J* = 9.1 Hz, 1H, **H^6**), 5.08 (s, 2H, OC**H$_2$**CN); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.1 (C_q), 161.5 (C_q) 130.6 (CH), 125.6 (CH), 125.3 (C_q), 113.2 (C_q), 112.8 (CH), 54.0 (CH_2). N.B. Mass Spec. data could not be obtained. N.B. One C_q could not be resolved.

Synthesis of 2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoroborate (4)[2]



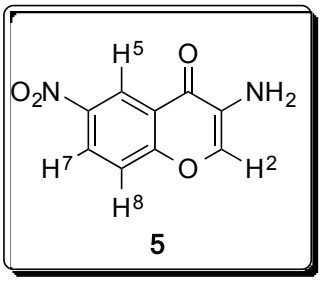
4

Trimethyloxonium tetrafluoroborate (0.96 g, 6.4 mmol) was added in one portion to a solution of pyrrolidin-2-one (0.50 g, 6.0 mmol) in DCM (20 mL). The reaction was allowed to stir at room temperature for 24 h. Phenylhydrazine (0.63 g, 5.8 mmol) was added and stirring was continued at room temperature for a further 48 h. The reaction mixture was then concentrated under vacuum and re-dissolved in a mixture

of methanol (2.0 mL) and triethyl orthoformate (8.0 ml). The solution was heated to reflux overnight and then allowed to cool to room temperature. The resulting precipitate was collected by filtration and washed with methanol to afford **4** (1.1 g, 70%) as a pale tan solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.70 (s, 1H, NC**H**NPh), 7.90 – 7.84 (m, 2H, ArC**H**), 7.72 – 7.66 (m, 2H, ArC**H**), 7.66 – 7.60 (m, 1H, ArC**H**), 4.66 – 4.13 (m, 2H, NC**H$_2$**), 3.23 – 3.12 (m, 2H, C**H$_2$**), 2.89 – 2.61 (m, 2H, C**H$_2$**); ^{13}C NMR (126 MHz, d_6 DMSO) δ 163.5 (C_q), 138.8 (CH), 136.1 (C_q), 130.9 (CH), 130.7 (CH), 121.1 (CH), 47.4 (CH_2), 27.1 (CH_2), 21.7 (CH_2). NB. Mass spec. data could not be obtained.

Synthesis of 3-amino-6-nitro-4*H*-chromen-4-one (5)[1]

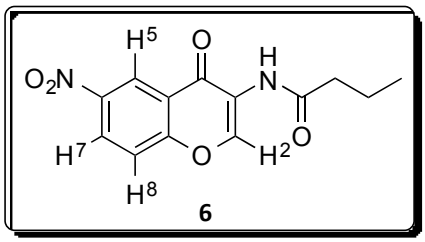


5

Compound **3** (0.47 g, 2.3 mmol) was dissolved in DCM (20 mL) before addition of catalyst **4**[2] (62 mg, 0.20 mmol) and DBU (30 µL, 0.20 mmol). The resulting solution was allowed to stir at room temperature for 16 h. The reaction was then concentrated under vacuum. The crude material was purified by column chromatography (40-60% ethyl acetate in cyclohexane) to afford **5** (0.27 g, 57%) as an orange solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.82 (d, *J* = 2.9 Hz, 1H, **H^5**), 8.46 (dd, *J* = 9.3, 2.9 Hz, 1H, **H^7**), 8.06 (s, 1H, **H^2**), 7.84 (d, *J* = 9.3 Hz, 1H, **H^8**), 4.85 (s, 2H, N**H$_2$**); ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.8 (C_q), 158.4 (C_q), 143.8 (C_q), 137.3 (CH), 133.7 (C_q), 127.0 (CH), 121.9 (CH), 121.3 (C_q), 121.1 (CH); HRMS (ESI) $[M+H]^+$ 207.0403, $C_9H_6N_2O_4$ $[M+H]^+$ requires 207.0406.

Synthesis of *N*-(6-nitro-4-oxo-4*H*-chromen-3-yl)butyramide (6)

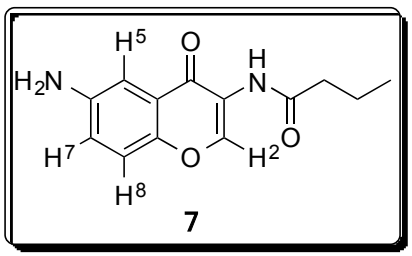


6

Compound **5** (0.17 g, 0.83 mmol) and DIPEA (0.22 mL, 1.2 mmol) were dissolved in THF (10 mL) and cooled to 0 °C before the addition of butyryl chloride (0.10 mL, 0.90 mmol). The reaction was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was then diluted with ethyl acetate and washed with sat. $NaHCO_3$ (aq.) and brine. The organic layer was separated, dried over sodium sulphate and concentrated under vacuum. The crude material was purified by column chromatography (50% ethyl acetate in cyclohexane) to afford **6** (0.18 g, 80%) as an orange solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (s, 1H, **H^2**), 9.17 (d, *J* = 2.7 Hz, 1H, **H^5**), 8.54 (dd, *J* = 9.2, 2.7 Hz, 1H, **H^7**), 8.01 (s, 1H, N**H**), 7.69 (d, *J* = 9.2 Hz, 1H, **H^8**), 2.56 – 2.41 (m, 2H, C**H$_2$**CH_2CH_3), 1.88 – 1.72 (m, 2H, CH_2C**H$_2$**CH_3), 1.04 (t, *J* = 7.4 Hz, 3H, CH_2CH_2C**H$_3$**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9 (C_q), 170.9 (C_q), 158.2 (C_q), 145.0 (CH), 128.0 (CH), 125.1 (C_q) 122.8 (CH), 121.7 (C_q), 120.3 (CH), 39.0 (CH_2), 18.8 (CH_2), 13.6 (CH_3); HRMS (ESI) $[M+H]^+$ 277.0818 $C_{13}H_{12}N_2O_3$ $[M+H]^+$ requires 277.0819; N.B. One C_q not resolved

Synthesis of *N*-(6-amino-4-oxo-4*H*-chromen-3-yl)butyramide (7)



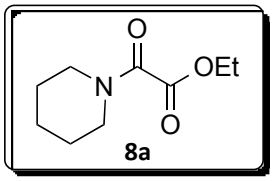
7

Compound **6** (0.18 g, 0.70 mmol), iron powder (0.26 g, 4.6 mmol) and ammonium chloride (0.25 g, 4.6 mmol) were heated to reflux in a mixture of ethanol and water

(3:1) (20 mL) for 16 h. The reaction mixture was diluted with ethyl acetate and filtered through celite and then washed with sat. $NaHCO_3$ (aq.) and brine. The organic layer was separated, dried over sodium sulphate and concentrated under vacuum. The crude material was purified by column chromatography (35-60% ethyl acetate in DCM) to afford **7** (0.12 g, 76%) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (s, 1H, **H^2**), 8.05 (s, 1H, N**H**), 7.41 (d, *J* = 2.9 Hz, 1H, **H^5**), 7.37 (d, *J* = 9.0 Hz, 1H, **H^8**), 7.08 (dd, *J* = 9.0, 2.9 Hz, 1H, **H^7**), 3.89 (s, 2H, N**H$_2$**), 2.61 – 2.27 (m, 2H, C**H$_2$**CH_2CH_3), 1.85 – 1.70 (m, 2H, CH_2C**H$_2$**CH_3), 1.03 (t, *J* = 7.4 Hz, 3H, CH_2CH_2C**H$_3$**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6 (C_q), 171.5 (C_q), 149.7 (C_q), 144.8 (CH), 143.5 (C_q), 123.7 (C_q), 122.9 (CH), 122.6 (C_q), 119.5 (CH), 107.2 (CH), 39.1 (CH_2), 18.9 (CH_2), 13.7 (CH_3); HRMS (ESI) $[M+H]^+$ 247.1077, $C_{13}H_{14}N_2O_3$ $[M+H]^+$ requires 247.1077.

Synthesis of ethyl 2-oxo-2-(piperidin-1-yl)acetate (8a)

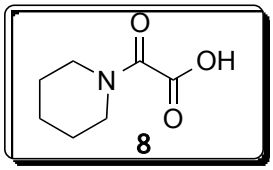


8a

Piperidine (1.2 mL, 11.7 mmol) and DIPEA (3.1 mL, 17.6 mmol) were dissolved in DCM (15 mL) and cooled to 0 °C before the addition of ethyl 2-chloro-2-oxoacetate (1.6 mL, 14.1 mmol). The reaction was allowed to warm to room temperature and stirred for 2 h. The reaction was then diluted with DCM and washed with sat. $NaHCO_3$ (aq.) and brine. The organic layer was separated, dried over sodium sulphate and concentrated under vacuum. The crude material was purified by column chromatography (10-50% ethyl acetate in cyclohexane) to afford compound **8a** (1.9 g, 85 %) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (q, *J* = 7.2 Hz, 2H, OC**H$_2$**CH_3), 3.60 – 3.54 (m, 2H, NC**H$_2$**), 3.37 – 3.32 (m, 2H, NC**H$_2$**), 1.67-1.73 (m, 2H, CH_2C**H$_2$**CH_2), 1.59-1.66 (m, 4H, C**H$_2$**CH_2C**H$_2$**), 1.37 (t, *J* = 7.2 Hz, 3H, OCH_2C**H$_3$**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2 (C_q), 160.2 (C_q), 61.8 (CH_2), 47.2 (CH_2), 42.17 (CH_2), 26.1 (CH_2), 25.1 (CH_2), 24.3 (CH_2), 14.0 (CH_3); HRMS (ESI) $[M+Na]^+$ 208.0942, $C_9H_{15}NO_3$ $[M+Na]^+$ requires 208.0944.

Synthesis of 2-oxo-2-(piperidin-1-yl)acetic acid (8)

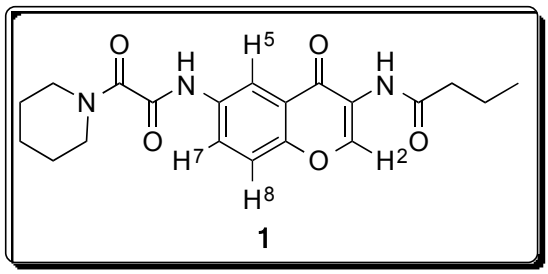


8

Sodium hydroxide 0.45 M (16.0 mL, 11.0 mmol) was cooled to 0 °C before the addition of compound **8a** (1.9 g, 10.0 mmol) in THF (40 mL). The reaction was allowed to stir overnight. The reaction mixture was acidified to pH 1 with 1 M HCl (aq.) and extracted with ethyl acetate (x 3). The combined organic extracts were dried over sodium sulphate and concentrated to afford compound **8** (1.5 g, 96 %) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13-4.08 (m, 2H, NC**H$_2$**), 3.69-3.64 (m, 2H, NC**H$_2$**), 1.81 – 1.42 (m, 6H, CH_2C**H$_2$**C**H$_2$**C**H$_2$**CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.4 (C_q), 159.4 (C_q), 47.9 (CH_2), 45.2 (CH_2), 26.6 (CH_2), 25.6 (CH_2), 24.1 (CH_2); HRMS (ESI) $[M+H]^+$ 158.0812, $C_7H_{11}NO_3$ $[M+H]^+$ requires 158.0812.

Synthesis of *N*-(4-oxo-6-(2-oxo-2-(piperidin-1-yl)acetamido)-4*H*-chromen-3-yl)butyramide (1)

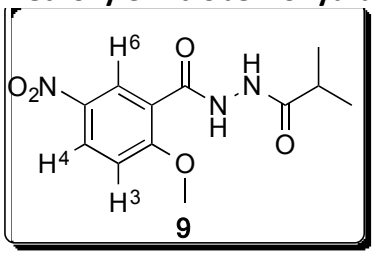


1

Compound **8** (30 mg, 0.20 mmol) and DIPEA (80 µL, 0.50 mmol) were dissolved in DMF (1.5 mL) before the addition of HATU (94 mg, 0.30 mmol) and **7** (42 mg, 0.20 mmol). After a period of 16 h the reaction mixture was diluted with ethyl acetate and washed with sat. $NaHCO_3$ (aq.) and brine. The organic layer was separated, dried over sodium sulphate and concentrated under vacuum. The crude material was purified by column chromatography (50-80% ethyl acetate in cyclohexane) to afford **1** (48 mg, 65%) as a cream solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H, N**H**), 9.50 (s, 1H, **H^{2}**), 8.51 (s, 1H, N**H**), 8.46 (d, *J* = 2.6 Hz, 1H, **H^{5}**), 8.28 (dd, *J* = 9.2, 2.6 Hz, 1H, **H^{7}**), 7.55 (d, *J* = 9.2 Hz, 1H, **H^{8}**), 4.13 - 4.08 (m, 2H, NC**H$_2$**), 3.74 - 3.53 (m, 2H, NC**H$_2$**), 2.50 (t, *J* = 7.5 Hz, 2H, C**H$_2$**CH_2CH_3), 1.82 – 1.75 (m, 2H, CH_2C**H$_2$**CH_3), 1.74 – 1.69 (m, 6H, CH_2C**H$_2$**C**H$_2$**C**H$_2$**CH_2), 1.02 (t, *J* = 7.4 Hz, 3H, CH_2CH_2C**H$_3$**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2 (C_q), 171.6 (C_q), 160.3 (C_q), 159.3 (C_q), 152.6 (C_q), 145.5 (CH), 134.4 (C_q), 126.6 (CH), 124.5 (C_q), 122.2 (C_q), 119.3 (CH), 115.7 (CH), 47.7 (CH_2), 45.0 (CH_2), 38.8 (CH_2), 26.8 (CH_2), 25.8 (CH_2), 24.4 (CH_2), 18.9 (CH_2), 13.7 (CH_3); HRMS (ESI) $[M+H]^+$ 386.1714, $C_{20}H_{23}N_3O_5$ $[M+H]^+$ requires 386.1710.

Synthesis of *N*-isobutyryl-2-methoxy-5-nitrobenzohydrazide (9)[3]



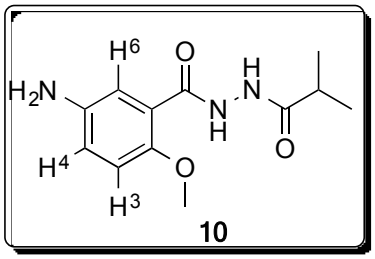
9

Thionyl chloride (1.2 mL), 2-methoxy-5-nitrobenzoic acid (0.20 g, 1.0 mmol) and DMF (10 µL) were heated to reflux for 2 h. The reaction mixture was concentrated to give a yellow solid. The crude acid chloride was dissolved in DCM (10 mL) and cooled to 0 °C before the addition of isobutyryl hydrazine (0.11 g, 1.1 mmol) and triethylamine (0.17 mL, 1.2 mmol) in DCM (10 mL). The reaction was allowed to warm to room temperature and stir for 2 h. The reaction mixture was then poured into sat. $NaHCO_3$ (aq.), the organic layer was separated and the aqueous extracted with DCM (x 3). The combined organic extracts were dried over sodium sulphate and concentrated under vacuum. The crude material was purified by column chromatography (50-100% ethyl acetate in DCM) to isolate compound **9** (0.26 g, 90% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.82 (d, *J* = 7.3 Hz, 1H, N**H**), 9.85 (d, *J* = 7.4 Hz, 1H, N**H**), 9.07 (d, *J* = 2.9 Hz, 1H, **H^{6}**), 8.39 (dd, *J* = 9.1, 3.0 Hz, 1H, **H^{4}**), 7.15 (d, *J* = 9.2 Hz, 1H, **H^{3}**), 4.19 (s, 3H, OC**H$_3$**), 2.72 (hept., *J* = 6.9 Hz, 1H, C**H**), 1.28 (d, *J* = 6.9 Hz, 6H, 2 x C**H$_3$**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5 (C_q), 161.5 (C_q), 157.4 (C_q), 142.0 (C_q), 128.7

(CH), 128.0 (CH), 119.8 (C_q), 112.0 (CH), 57.4 (CH_3), 33.4 (CH), 19.3 (2 x CH_3); HRMS (ESI) $[M+H]^+$ 282.1079, $C_{12}H_{15}N_3O_5$ $[M+H]^+$ requires 282.1084.

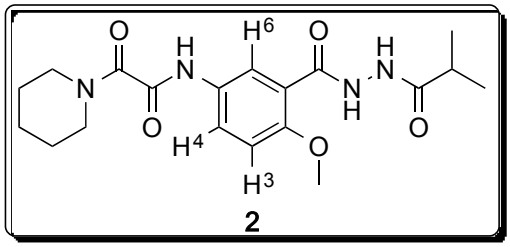
Synthesis of 5-amino-*N*-isobutyryl-2-methoxybenzohydrazide (10)[3]



Compound **10** (0.10 g, 0.40 mmol) was dissolved in THF (10 mL) and the reaction flask was purged by vacuum/argon cycles (x 3) before the addition of palladium 10% on carbon (10 mg). The reaction vessel was placed under an atmosphere of hydrogen (40 psi) and stirred for 2 h at room temperature. The reaction mixture was filtered through celite and concentrated under vacuum. The crude material was purified by column chromatography (0-10% EtOH in DCM) to isolate compound **10** (85 mg, 95 % yield) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.94 (d, *J* = 7.4 Hz, 1H, N**H**), 9.54 (d, *J* = 7.5 Hz, 1H, N**H**), 7.51 (dd, *J* = 2.4, 1.0 Hz, 1H, **H^4**), 6.83 (m, 2H, **H^3**+**H^6**), 3.96 (s, 3H, OC**H$_3$**), 2.59 (hept., *J* = 6.9 Hz, 1H, C**H**), 1.23 (d, *J* = 6.9 Hz, 6H, 2xC**H$_3$**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1 (C_q), 160.2 (C_q), 150.8 (C_q), 140.4 (C_q), 120.1 (CH), 119.1 (C_q), 117.9 (CH), 112.8 (CH), 56.5 (CH_3), 33.4 (CH), 19.4 (2 x CH_3); HRMS (ESI) $[M+H]^+$ 252.1341, $C_{12}H_{17}N_3O_3$ $[M+H]^+$ requires 252.1343.

Synthesis of *N*-(3-(2-isobutyrylhydrazinecarbonyl)-4-methoxyphenyl)-2-oxo-2-(piperidin-1-yl)acetamide (2)

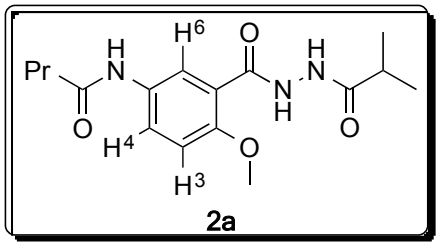


Compound **8** (0.2 g, 1.2 mmol), thionyl chloride (4.5 ml) and DMF (10 µL) were heated to reflux for 2 h. The reaction mixture was concentrated to give a yellow

solid. The crude acid chloride was dissolved in DCM (5.0 mL) and cooled to 0 °C before compound **10** (0.24 mg, 1.0 mmol) and triethylamine (0.16 mL, 1.2 mmol) in DCM (5.0 mL) were added. The reaction was allowed to warm to room temperature and stir for 1 h before it was poured into sat. $NaHCO_3$ (aq.). The organic layer was separated and the aqueous layer was extracted with DCM (x 3). The combined organic extracts were dried over sodium sulphate and concentrated under vacuum. The crude material was purified by column chromatography (50-100% ethyl acetate in DCM) to afford compound **2** (0.36 g, 97 % yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.34 (d, *J* = 8.4 Hz, 1H, N**H**), 11.07 (d, *J* = 8.3 Hz, 1H, N**H**), 10.71 (s, 1H, N**H**), 8.41 (d, *J* = 2.8 Hz, 1H, **H^6**), 8.37 (dd, *J* = 8.9, 2.7 Hz, 1H, **H^4**), 7.01 (d, *J* = 9.0 Hz, 1H, **H^3**), 4.05 (s, 3H, OC**H$_3$**) 3.84 (t, *J* = 4.9 Hz, 2H, NC**H$_2$**), 3.63 (t, *J* = 5.3 Hz, 2H, NC**H$_2$**), 2.84 (hept., *J* = 6.8 Hz, 1H, C**H**), 1.72-1.62 (m, 6H, C**H$_2$**C**H$_2$**C**H$_2$**), 1.22 (d, *J* = 6.9 Hz, 6H, 2 x C**H$_3$**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0 (C_q), 162.5 (C_q), 160.2 (C_q), 158.0 (C_q), 154.3 (C_q), 131.6 (C_q), 125.9 (CH), 124.4 (CH), 118.9 (C_q), 111.7 (CH), 56.6 (CH_3), 47.8 (CH_2), 44.2 (CH_2), 32.6 (CH), 26.6 (CH_2), 25.7 (CH_2), 24.4 (CH_2), 19.6 (2 x CH_3); HRMS (ESI) $[M+H]^+$ 391.1964, $C_{19}H_{26}N_4O_5$ $[M+H]^+$ requires 391.1976.

Synthesis of *N*-(3-(2-isobutyrylhydrazine-1-carbonyl)-methoxyphenyl)butyramide (2a)

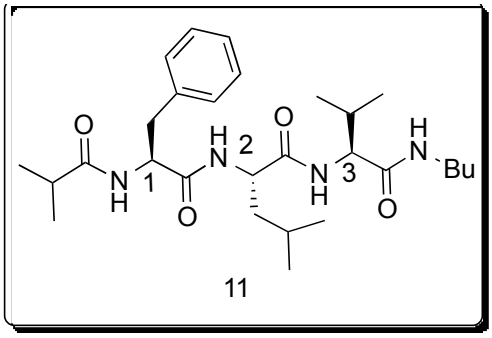


Compound **10** (0.5 g, 2.0 mmol) and pyridine (0.24 mL, 3.0 mmol) were dissolved in DCM (10 mL) and cooled to 0 °C before the addition of butyric anhydride (0.36 mL, 2.2 mmol). The reaction was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was then diluted with DCM and washed with sat. $NaHCO_3$ (aq.) and brine. The organic layer was separated, dried over sodium sulphate and concentrated under vacuum. The crude material was purified by column chromatography (0-10% EtOH in DCM) to afford **2a** (0.53 g, 83 % yield) as a white

solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.41 (s, 1H, N**H**), 9.45 (s, 1H, N**H**), 8.09 (dd, *J* = 9.0, 2.8 Hz, 1H, **H^{4}**), 7.83 (d, *J* = 2.8 Hz, 1H, **H^{6}**), 6.89 (d, *J* = 9.0 Hz, 1H, **H^{3}**), 3.97 (s, 3H, O**CH_3**), 2.63 (app. quint., *J* = 6.9 Hz, 1H, C**H**), 2.10 (s, 2H, **CH_2**), 1.60 (q, *J* = 8.2, 7.3 Hz, 2H, **CH_2**), 1.21 (d, *J* = 6.9 Hz, 6H, 2 x **CH_3**), 0.78 (s, 3H, **CH_3**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.5 (C_q), 172.7 (C_q), 160.5 (C_q), 153.6 (C_q), 132.5 (C_q), 126.1 (CH), 123.4 (CH), 118.5 (C_q), 111.8 (CH), 56.5 (CH_3), 38.9 (CH_2), 33.2 (CH), 19.4 (2 x CH_3), 18.9 (CH_2), 13.6 (CH_3); HRMS (ESI) $[M+H]^+$ 322.1757, $C_{16}H_{23}N_3O_4$ $[M+H]^+$ requires 391.1761.

Synthesis of (*S*)-*N*-((*S*)-1-(butylamino)-3-methyl-1-oxobutan-2-yl)-2-((*S*)-2-isobutyramido-3-phenylpropanamido)-4-methylpentanamide (11)[4]



11

Compound **11** was synthesized *via* solid phase peptide synthesis using an Activotec P14 peptide synthesizer. Fmoc-Pal-Am Resin (2.5 g, 0.53 mmol/g) was shaken with DMF (2 x 25 ml) for 5 mins. The resin was then shaken with a 20% piperidine solution in NMP (3 x 25 ml) for 12 minutes. The resin was then washed (2 x DMF, 2 x DCM, 2 x MeOH, 2 x DCM and MeOH alternately and then diethyl ether).

- To the resin was added DCM (25 mL), collidine (1.0 mL, 8.0 mmol) and 2-nitrobenzene-1-sulfonyl chloride (0.88 g, 4.0 mmol). The resulting suspension was agitated for 3 h. The resin was drained and washed as described above.
- To the resin was added DMF (25 mL), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) (0.80 mL, 5.3 mmol) and 1-iodobutane (1.5 mL, 13.3 mmol) . The resulting suspension agitated for a period of 8 h after which the resin was drained and washed as before.
- To the resin was added DMF (25 mL), DBU (1.0 ml, 6.6 mmol) and

mercaptoethanol (0.90 mL, 13.3 mmol). The resin was agitated for 3 h and then drained. The process was repeated and then resin was washed as before.

- Fmoc-Val-OH (4.5 g, 13.3 mmol) was dissolved in a 10% solution of DIPEA in DMF (25 mL) before the addition of HATU (4.5 g, 12.0 mmol). The reaction mixture was allowed to stir for 15 mins after which time it was added to the resin and agitated for 2 h. The process was repeated and the resin was washed as before.
- The resin was then shaken with a 20% piperidine solution in NMP (3 x 25 ml) for 12 minutes. The resin was then washed (2 x DMF, 2 x DCM, 2 x MeOH, 2 x DCM and MeOH alternately and then diethyl ether).
- Fmoc-Leu-OH (2.1 g, 5.3 mmol) was dissolved in a 10% solution of DIPEA in DMF (25 mL) before the addition of HATU (1.8 g, 4.8 mmol). The reaction mixture was allowed to stir for 15 mins after which time it was added to the resin and agitated for 2 h. The process was repeated and the resin was washed as before.
- The resin was then shaken with a 20% piperdine solution in NMP (3 x 25 ml) for 12 minutes. The resin was then washed (2 x DMF, 2 x DCM, 2 x MeOH, 2 x DCM and MeOH alternately and then diethyl ether).
- Fmoc-Phe-OH (1.9 g, 5.3 mmol) was dissolved in a 10% solution of DIPEA in DMF (25 mL) before the addition of HATU (1.8 g, 4.8 mmol). The reaction mixture was allowed to stir for 15 min after which time it was added to the resin and agitated for 2 h. The process was repeated and the resin was washed as before.
- The resin was then shaken with a 20% piperdine solution in NMP (3 x 25 ml) for 12 minutes. The resin was then washed (2 x DMF, 2 x DCM, 2 x MeOH, 2 x DCM and MeOH alternately and then diethyl ether).
- To the resin was added a 10% solution of DIPEA in DMF (25 mL) and isobutyryl chloride (0.60 ml, 5.3 mmol). The suspension was agitated for 2 h before the resin was drained and washed as before.
- The resin was suspended in a 1:1 mixture of TFA and DCM (20 mL) for 1 h

without agitation. The resin was removed by filtration and the filtrate was concentrated under vacuum. The crude material was purified by HPLC to afford **11** (0.17 g, 31 %) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H, N**H**), 7.62 (s, 2H, 2 x N**H**), 7.24 – 7.02 (m, 6H, ArC**H**, N**H**), 5.19 (app. q, *J* = 7.0 Hz, 1H, **H^{1}**), 4.82 (app. q, *J* = 7.8 Hz, 1H, **H^{2}**), 4.50 (app. t, *J* = 8.9 Hz, 1H, **H^{3}**), 3.34 – 3.26 (m, 1H, NC**H**), 3.20 – 3.12 (m, 1H, NC**H**), 3.07 – 2.98 (m, 2H, PhC**H$_2$**), 2.48 (h, *J* = 6.8 Hz, 1H, **H**C$(CH_3)_2$), 2.13 – 2.05 (m, 1H, **H**C$(CH_3)_2$), 1.70 – 1.54 (m, 3H, C**H$_2$**CH$(CH_3)_2$, CH_2C**H**$(CH_3)_2$), 1.54 – 1.46 (m, 2H, CH_3CH_2C**H$_2$**CH_2NH), 1.34 (app. h, *J* = 7.3 Hz, 2H, CH_3C**H$_2$**CH_2CH_2NH), 1.06 (d, J = 7.0 Hz, 3H, C**H$_3$**), 1.04 (d, *J* = 7.1 Hz, 3H, C**H$_3$**), 0.97 (d, *J* = 6.7 Hz, 3H, C**H$_3$**), 0.94 (d, *J* = 6.8 Hz, 3H, C**H$_3$**), 0.91 (t, *J* = 7.4 Hz, 3H, C**H$_3$**$CH_2CH_2CH_2$NH), 0.87 (t, *J* = 6.3 Hz, 6H, 2 x C**H$_3$**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8 (C_q), 172.0 (C_q), 171.1 (C_q), 136.6 (C_q), 129.5 (ArCH), 128.1 (ArCH), 126.6 (ArCH), 58.8 (CH), 53.2 (CH), 51.6 (CH), 42.5 (CH_2), 39.1 (CH_2), 38.9 (CH_2), 34.9 (CH), 31.5 (CH_2), 31.0 (CH), 29.7 (CH), 24.8 (CH_3), 22.6 (CH_3), 20.11 (CH_2) , 19.7 (CH_3), 19.2 (CH_3), 19.1 (CH_3), 18.6 (CH_3), 13.7 (CH_3); HRMS (ESI) $[M+H]^+$ 503.3577, $C_{28}H_{46}N_4O_4$ $[M+H]^+$ requires 503.3592.

2. ^{1}H NMR Titration Data

2.1. Compound 1 Homodimer VT ^{1}H NMR Titration

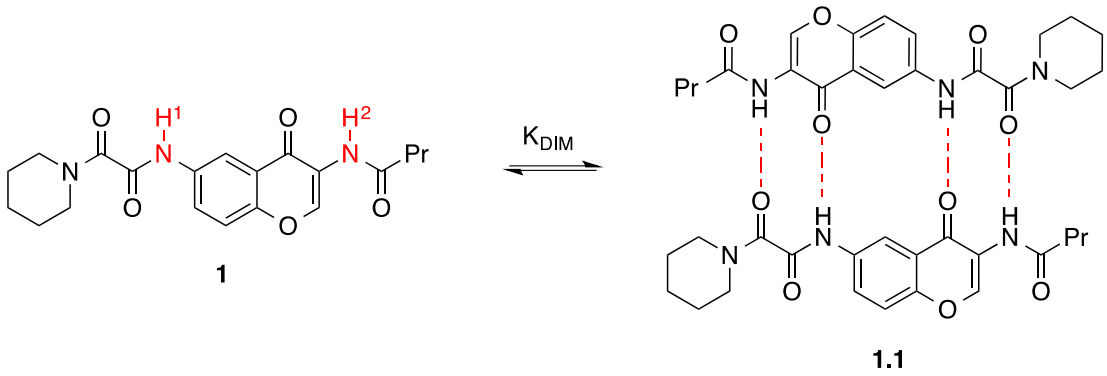
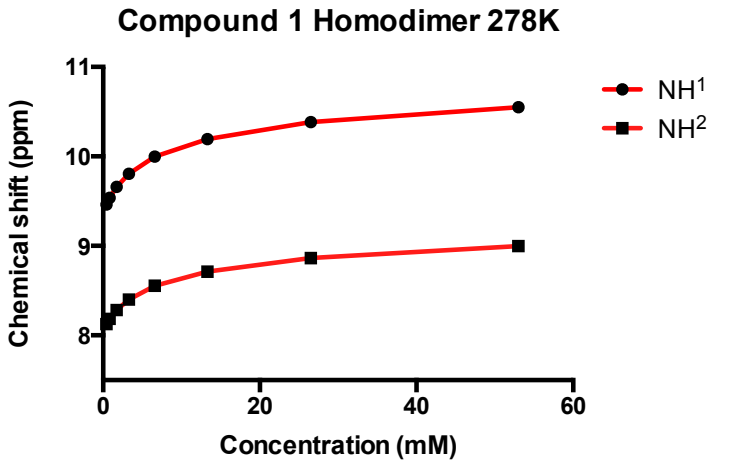


Figure 1: *Homodimerisation of compound **1**. Resonances (NH^1 and NH^2) used to determine K_{DIM} are highlighted in red.*

2.1.1. Compound 1 Homodimer ^{1}H NMR Titration Experiment 1

Table 1: *^{1}H NMR titration of compound 1 at 278 K*

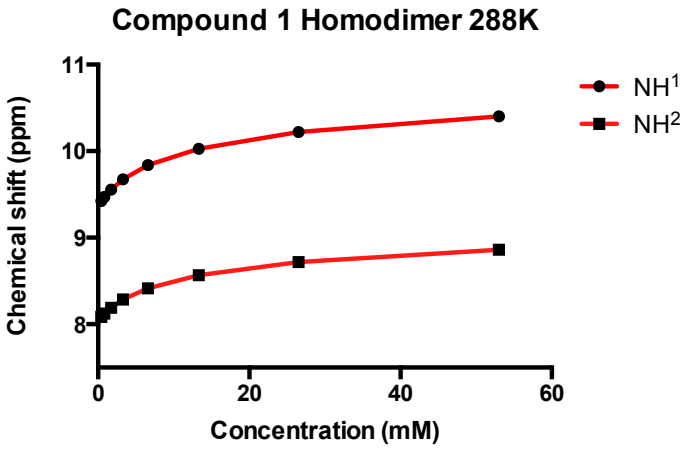
[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)
53.0	10.5505	8.9984
26.5	10.3825	8.8643
13.3	10.1934	8.7124
6.6	9.9977	8.5552
3.3	9.8063	8.4009
1.7	9.6605	8.2840
0.8	9.5363	8.1837
0.4	9.4622	8.1245



K_{DIM}= 68 M^{-1} **sigma= 3.1**

Table 2: *^{1}H NMR titration of compound 1 at 288 K*

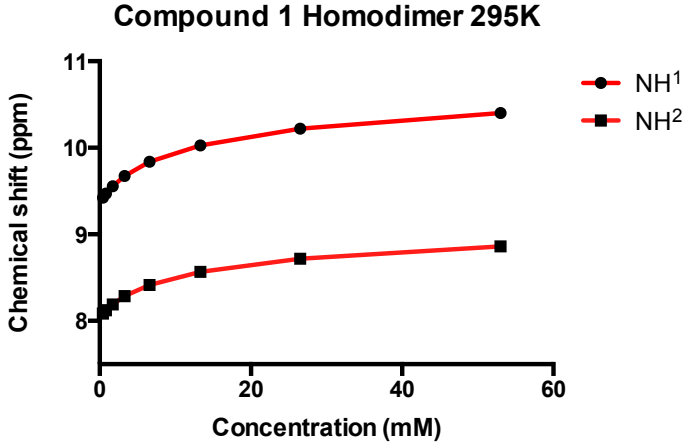
[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)
53.0	10.4004	8.8607
26.5	10.2200	8.7183
13.3	10.0273	8.5654
6.6	9.8382	8.4147
3.3	9.6755	8.2853
1.7	9.5556	8.1899
0.8	9.4702	8.1220
0.4	9.4224	8.0837



K_{DIM}= 42 M^{-1} **sigma= 1.5**

Table 3: *^{1}H NMR titration of compound 1 at 295 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)
53.0	10.2977	8.7681
26.5	10.1116	8.6221
13.3	9.9219	8.4724
6.6	9.7446	8.3323
3.3	9.6041	8.2218
1.7	9.5046	8.1433
0.8	9.4393	8.0915
0.4	9.4023	-*

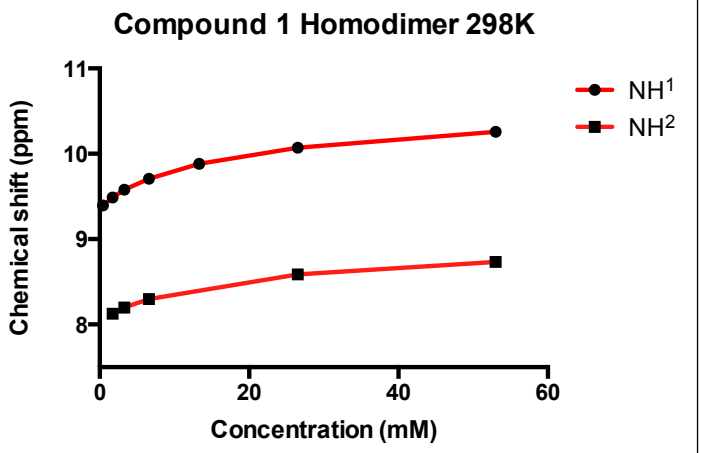


K_{DIM}= 30 M^{-1} **sigma= 1.6**

*Obscured by another proton signal

Table 4: *^{1}H NMR titration of compound 1 at 298 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)
53.0	10.2589	8.7332
26.5	10.0699	8.5852
13.3	9.8821	-*
6.6	9.7066	8.2990
3.3	9.5782	8.1985
1.7	9.4863	8.1263
0.8	-*	-*
0.4	9.3958	-*

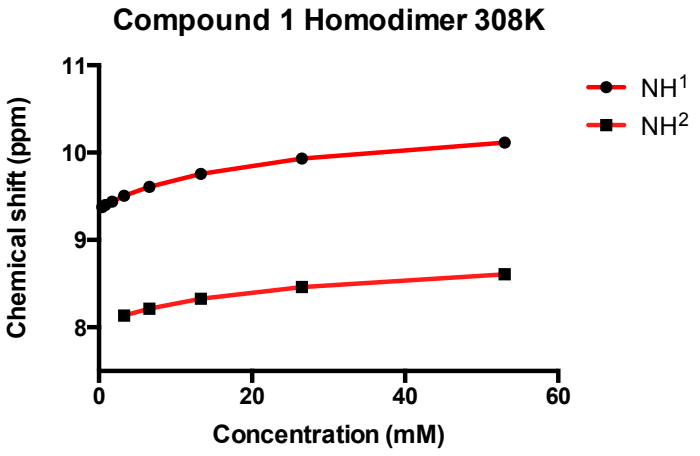


K_{DIM}= 26 M^{-1} **sigma= 2.2**

* Obscured by another proton signal

Table 5: *^{1}H NMR titration of compound 1 at 308 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)
53.0	10.1159	8.6061
26.5	9.9297	8.4624
13.3	9.7562	8.3277
6.6	9.6084	8.2126
3.3	9.5065	8.1338
1.7	9.4387	-*
0.8	9.3994	-*
0.4	9.3773	-*



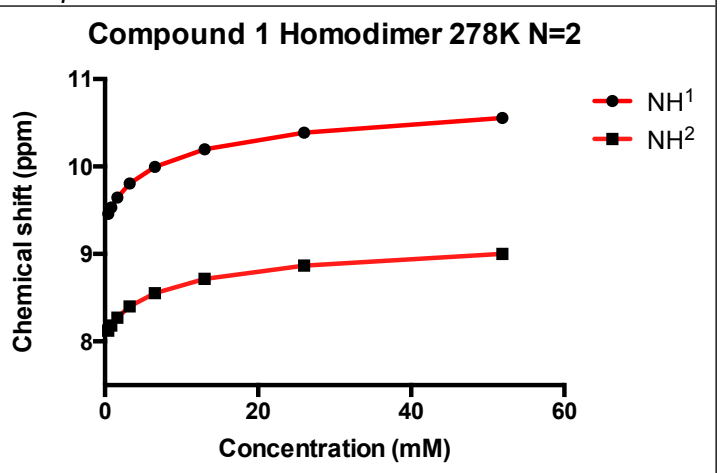
K_{DIM}= 17 M^{-1} **sigma= 1.4**

*Obscured by another proton signal

2.1.2. Compound 1 Homodimer ^{1}H NMR Titration Experiment 2

Table 6: *^{1}H NMR titration of compound 1 at 278 K*

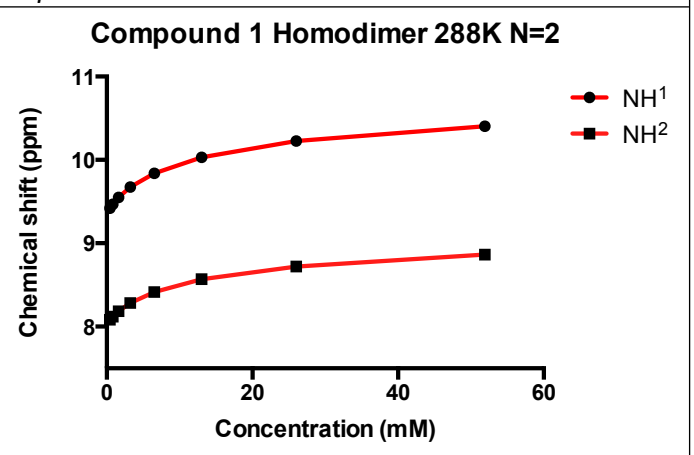
[1] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)
51.9	10.5544	9.0007
26.0	10.3862	8.8667
13.0	10.1956	8.7139
6.5	9.9942	8.5520
3.2	9.8055	8.4000
1.6	9.6456	8.2714
0.8	9.5321	8.1801
0.4	9.4599	8.1223



K_{DIM} = 74 M^{-1} sigma= 6.9

Table 7: *^{1}H NMR titration of compound 1 at 288 K*

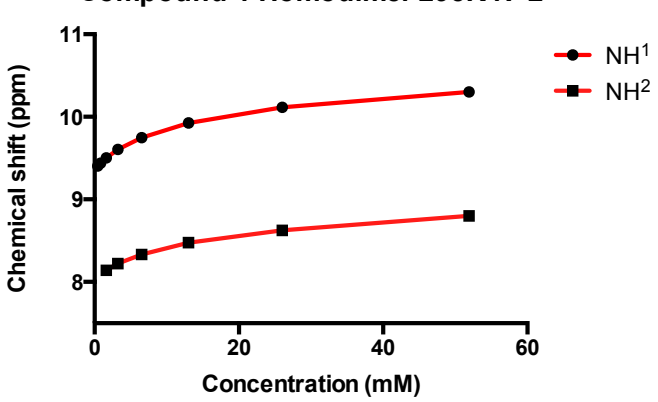
[1] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)
51.9	10.4034	8.8622
26.0	10.2246	8.7215
13.0	10.0302	8.5675
6.5	9.8384	8.4148
3.2	9.6746	8.2842
1.6	9.5495	8.1848
0.8	9.4681	8.1202
0.4	9.4197	8.0816



K_{DIM}= 41 M^{-1} sigma= 5.7

Table 8: *^{1}H NMR titration of compound 1 at 295 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)
51.9	10.3008	8.7995
26.0	10.1161	8.6252
13.0	9.9246	8.4744
6.5	9.7463	8.3337
3.2	9.6041	8.2216
1.6	9.5018	8.1409
0.8	9.4383	-*
0.4	9.4021	-*

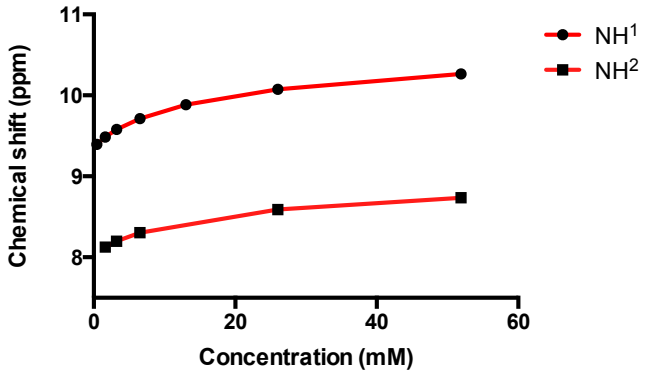


K_{DIM}= 30 M^{-1} **sigma= 6.6**

*Obscured by another proton signal

Table 9: *^{1}H NMR titration of compound 1 at 298 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)
51.9	10.2621	8.7348
26.0	10.0746	8.5884
13.0	9.8847	-*
6.5	9.7128	8.3043
3.2	9.5780	8.1983
1.6	9.4845	8.1251
0.8	-*	-*
0.4	9.3948	-*

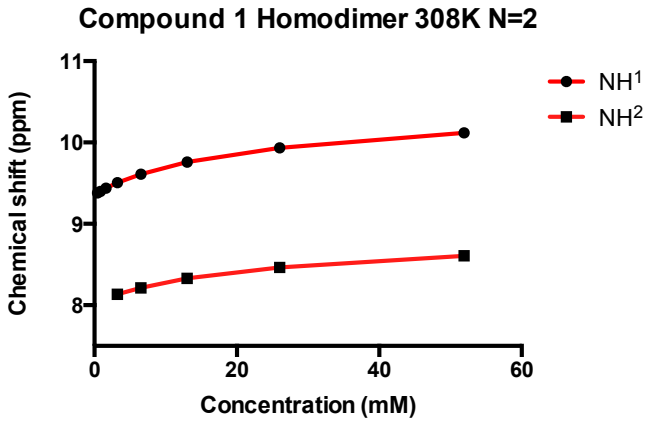


K_{DIM}= 27 M^{-1} **sigma= 1.7**

*Obscured by another proton signal

Table 10: *^{1}H NMR titration of compound 1 at 308 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)
51.9	10.1185	8.6073
26.0	9.9332	8.4645
13.0	9.7576	8.3285
6.5	9.6105	8.2143
3.2	9.5060	8.1333
1.6	9.4372	-*
0.8	9.3981	-*
0.4	9.3791	-*



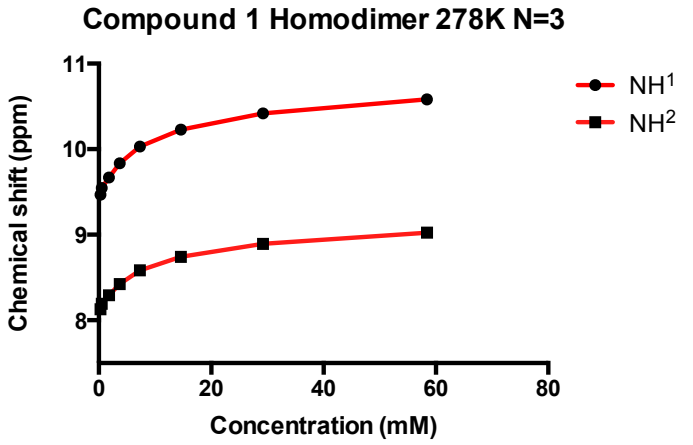
K_{DIM}= 18 M^{-1} **sigma= 1.2**

*Obscured by another proton signal

2.1.3. Compound 1 Homodimer ^{1}H NMR Titration Experiment 3

Table 11: *^{1}H NMR titration of compound 1 at 278 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)
58.4	10.5825	9.0239
29.2	10.4181	8.8931
14.6	10.2295	8.7421
7.3	10.0303	8.5824
3.7	9.8350	8.4243
1.8	9.6685	8.2913
0.5*	9.5470	8.1937
0.3	9.4667	8.1295

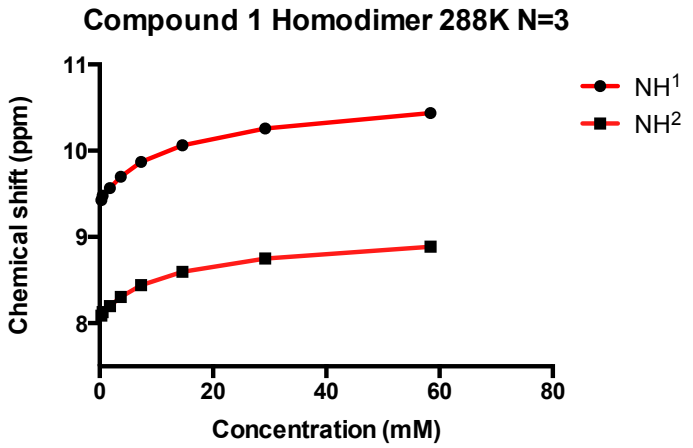


K_{DIM}= 61 M^{-1} **sigma= 3.7**

*Outlier excluded from K_{DIM} determination

Table 12: *^{1}H NMR titration of compound 1 at 288 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)
58.4	10.4353	8.8880
29.2	10.2587	8.7493
14.6	10.0629	8.5941
7.3	9.8693	8.4399
3.7	9.6982	8.3039
1.8	9.5658	8.1986
0.5*	9.4778	8.1287
0.3	9.4264	8.0882

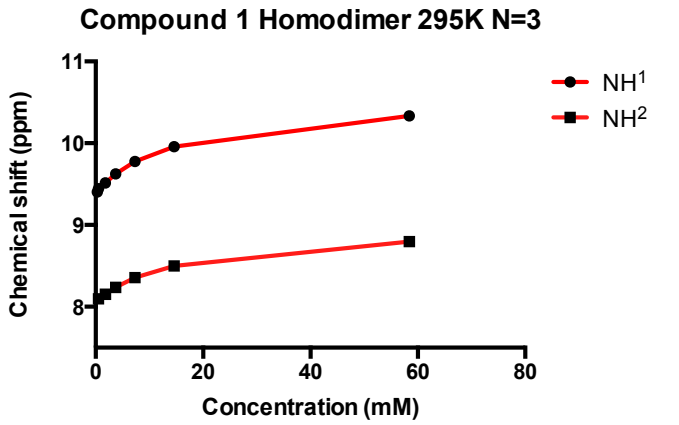


K_{DIM}= 39 M^{-1} **sigma= 3.5**

*Outlier excluded from K_{DIM} determination

Table 13: *^{1}H NMR titration of compound 1 at 295 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)
58.4	10.3332	8.7954
14.6	9.9567	8.5003
7.3	9.7754	8.3574
3.7	9.6240	8.2378
1.8	9.5142	8.1512
0.5**	9.4452	8.0967
0.3	9.4045	-*



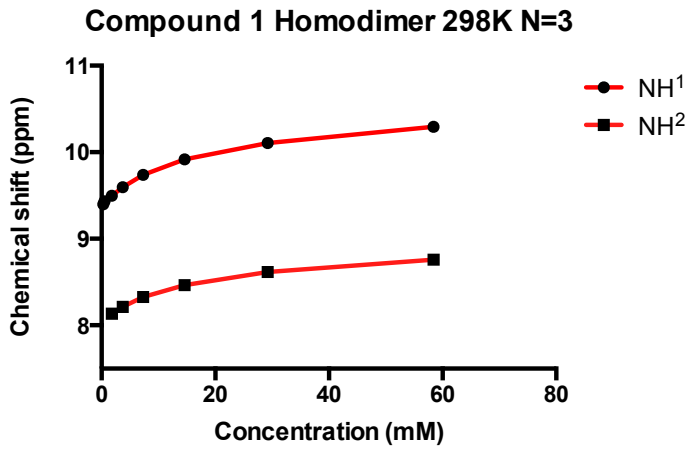
K_{DIM}= 29 M^{-1} **sigma= 2.8**

*Obscured by another proton signal

**Outlier excluded from K_{DIM} determination

Table 14: *^{1}H NMR titration of compound 1 at 298 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)
58.4	10.2934	8.7595
29.2	10.1073	8.6145
14.6	9.9155	8.4641
7.3	9.7393	8.3256
3.7	9.5961	8.2128
1.8	9.4955	8.1338
0.5	9.4329	-*
0.3	9.3967	-*

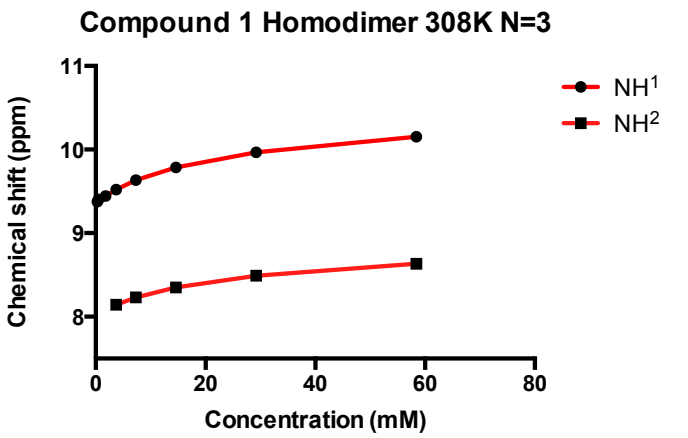


K_{DIM}= 25 M^{-1} **sigma= 6.7**

*Obscured by another proton signal

Table 15: *^{1}H NMR titration of compound 1 at 308 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)
58.4	10.1517	8.6331
29.2	9.9650	8.4894
14.6	9.7851	8.3500
7.3	9.6326	8.2317
3.7	9.5192	8.1437
1.8	9.4449	-*
0.5	9.4020	-*
0.3	9.3777	-*



K_{DIM}= 17 M^{-1} **sigma= 5.0**

*Obscured by another proton signal

2.2.4. Compound 1 Homodimer VT ^{1}H NMR Summary and Van't Hoff Plots

Table 16*: Summary of Compound 1 Homodimer Experiment 1 and Van't Hoff Plot*

Temp (K)	K_{DIM} (M^{-1})	1/T	ln(K_{DIM})
278	73	0.003597122	4.290459441
288	45	0.003472222	3.80666249
295	30	0.003389831	3.401197382
298	26	0.003355705	3.258096538
308	18	0.003246753	2.890371758

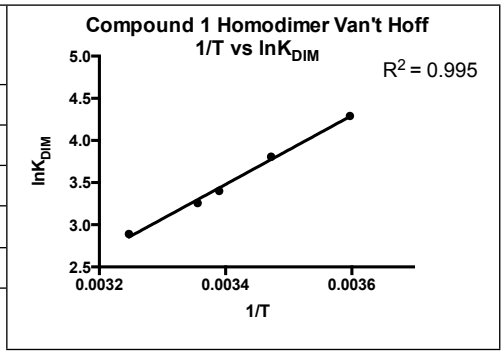


Table 17*: Summary of Compound 1 Homodimer Experiment 2 and Van't Hoff Plot*

Temp (K)	K_{DIM} (M^{-1})	1/T	ln(K_{DIM})
278	74	0.003597122	4.304065093
288	41	0.003472222	3.713572067
295	30	0.003389831	3.401197382
298	27	0.003355705	3.295836866
308	18	0.003246753	2.890371758

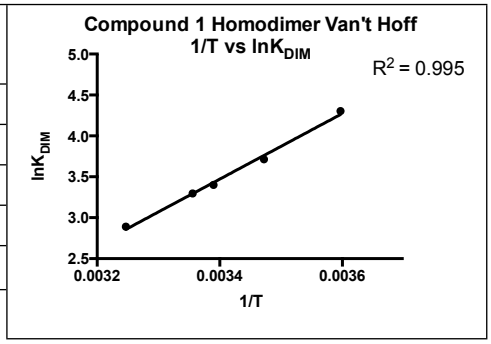


Table 18*: Summary of Compound 1 Homodimer Experiment 3 and Van't Hoff Plot*

Temp (K)	K_{DIM} (M^{-1})	1/T	ln(K_{DIM})
278	61	0.003597122	4.110873864
288	39	0.003472222	3.663561646
295	29	0.003389831	3.36729583
298	25	0.003355705	3.218875825
308	17	0.003246753	2.833213344

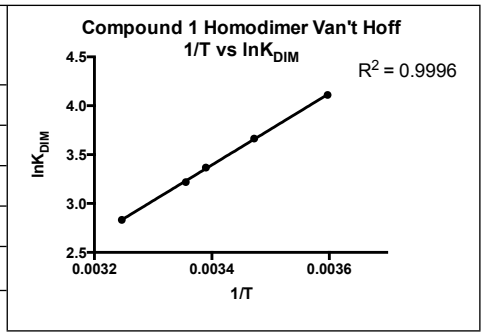


Table 19: *Summary of thermodynamic parameters for compound 1 homodimer*

Expt	ΔH (kcal mol^{-1})	$-T\Delta S^{295\ K}$ (kcal mol^{-1})	ΔG (kcal mol^{-1})
1	-8.1	6.1	-2.0
2	-7.9	6.0	-1.9
3	-7.3	5.3	-2.0
Average	**-7.8**	**5.8**	**-2.0**

2.2. Tripeptide 11 Homodimer ^{1}H NMR Titration

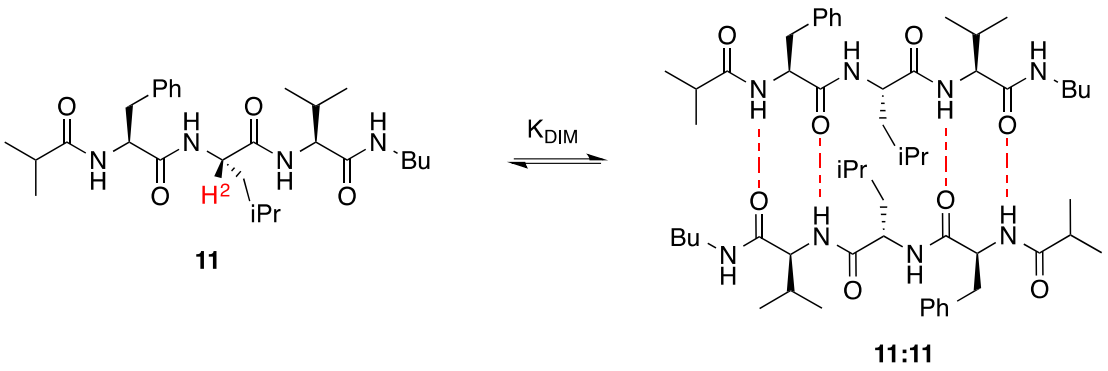


Figure 2: *Homodimerisation of **11**. Resonance (H^2) used to determine K_{DIM} is highlighted in red*

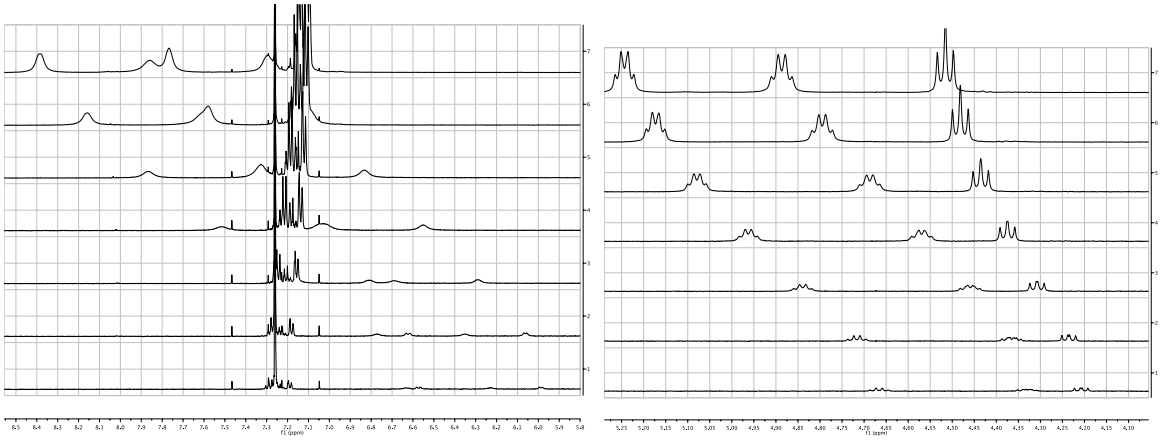
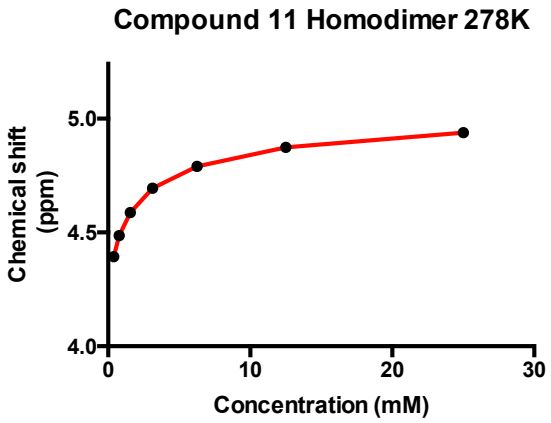


Figure 3: *Comparison between NH shifts (left) and αCH shifts (right) of compound 11. NH signals broaden into the baseline at lower concentrations making it difficult to accurately measure chemical shift. αCH signals are relatively sharp compared to NH signals and therefore were used to determine binding constants*

2.2.1 Compound 11 Homodimer ^{1}H NMR Titration Experiment 1

Table 20: *^{1}H NMR titration of compound 11 at 278 K*

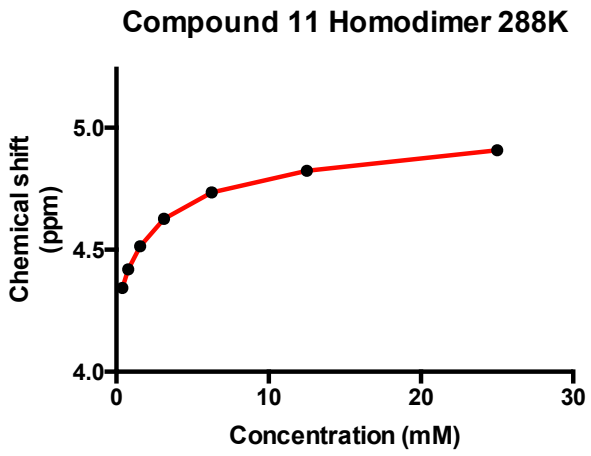
[11] (mM)	δ H^2 (ppm)
25.0	4.9379
12.5	4.8733
6.3	4.7905
3.1	4.6945
1.6	4.5865
0.8	4.4861
0.4	4.3930



K_{DIM}= 360 M^{-1} **sigma = 1.5**

Table 21: *^{1}H NMR titration of compound 11 at 288 K*

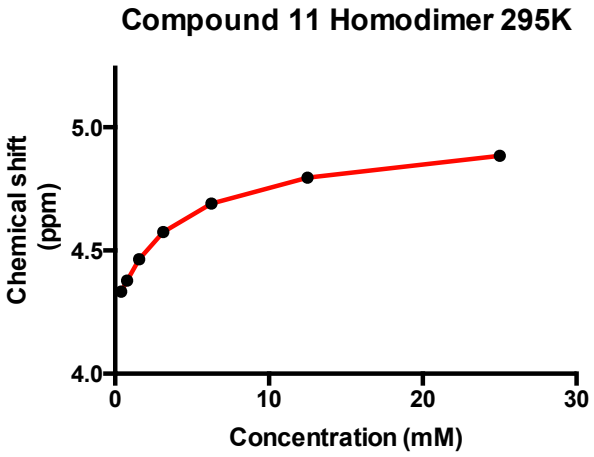
[11] (mM)	δ H^2 (ppm)
25.0	4.9082
12.5	4.8230
6.3	4.7349
3.1	4.6262
1.6	4.5141
0.8	4.4190
0.4	4.3437



K_{DIM} = 214 M^{-1} **sigma= 3.0**

Table 22: *^{1}H NMR titration of compound 11 at 295 K*

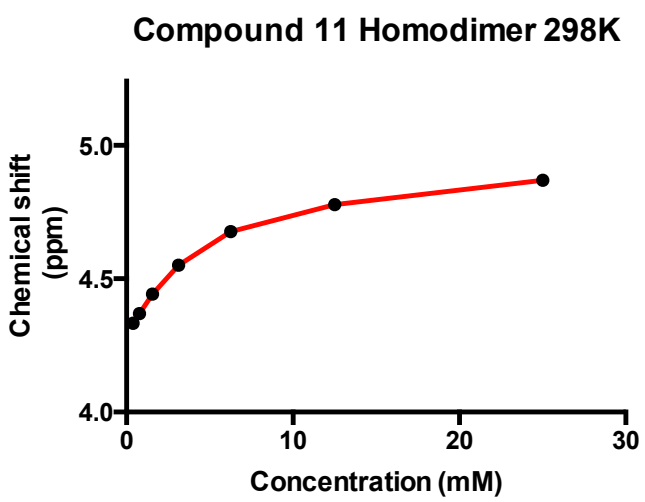
[11] (mM)	δ H² (ppm)
25.0	4.8837
12.5	4.7956
6.3	4.6898
3.1	4.5742
1.6	4.4639
0.8	4.3779
0.4	4.3327



K_{DIM} = 126 M^{-1} sigma= 6.2

Table 23: *^{1}H NMR titration of compound 11 at 298 K*

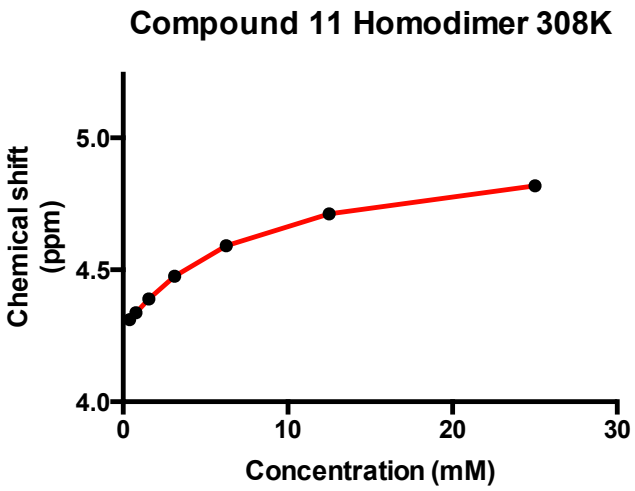
[11] (mM)	δ H² (ppm)
25.0	4.8693
12.5	4.7777
6.3	4.6761
3.1	4.5502
1.6	4.4426
0.8	4.3691
0.4	4.3323



K_{DIM}= 103 M^{-1} sigma= 9.8

Table 24: *^{1}H NMR titration of compound 11 at 308 K*

[11] (mM)	δ H^2 (ppm)
25.0	4.8184
12.5	4.7124
6.3	4.5916
3.1	4.4754
1.6	4.3886
0.8	4.3367
0.4	4.3114

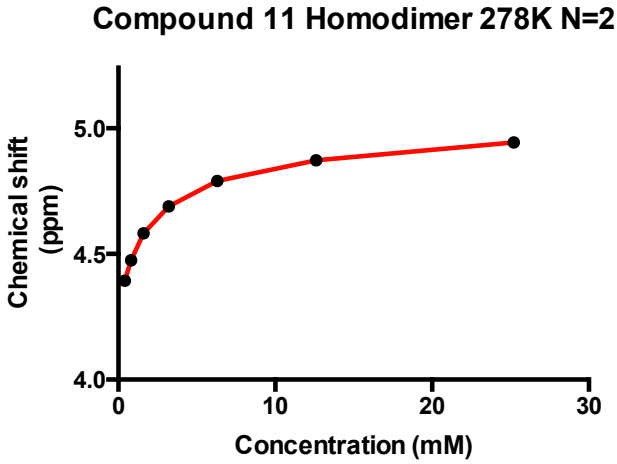


K_{DIM}= 54 M^{-1} **sigma= 7.2**

2.2.2. Compound 11 Homodimer ^{1}H NMR Titration Experiment 2

Table 25: *^{1}H NMR titration of compound 11 at 278 K*

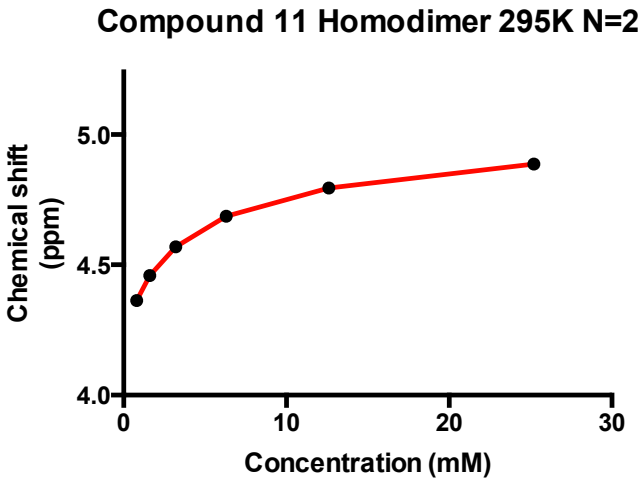
[11] (mM)	δ H^2 (ppm)
25.2	4.9435
12.6	4.8725
6.3	4.7902
3.2	4.6889
1.6	4.5814
0.8	4.4740
0.4	4.3933



K_{DIM} = 301 M^{-1} sigma= 1.8

Table 26: *^{1}H NMR titration of compound 11 at 295 K*

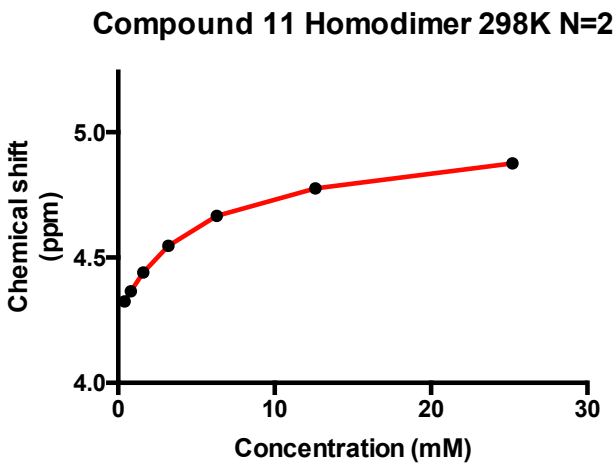
[11] (mM)	δ H^2 (ppm)
25.2	4.8868
12.6	4.7948
6.3	4.6870
3.2	4.5693
1.6	4.4584
0.8	4.3635
0.4	4.3329



K_{DIM}= 156 M^{-1} sigma= 1.5

Table 27: *^{1}H NMR titration of compound 11 at 298 K*

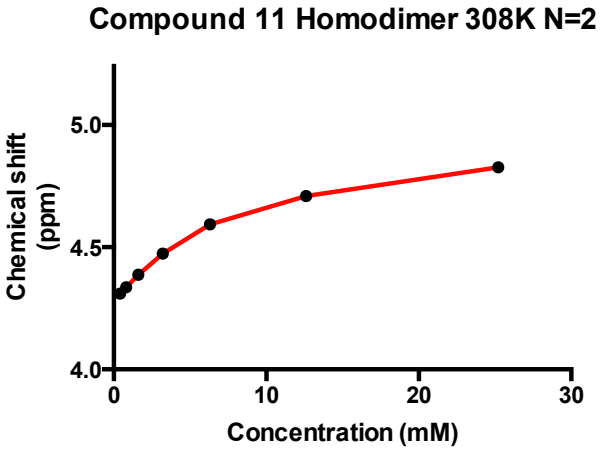
[11] (mM)	δ H^2 (ppm)
25.2	4.8751
12.6	4.7751
6.3	4.6662
3.2	4.5466
1.6	4.4403
0.8	4.3647
0.4	4.3243



K_{DIM}= 95 M^{-1} sigma= 6.2

Table 28: *^{1}H NMR titration of compound 11 at 308 K*

[11] (mM)	δ H^2 (ppm)
25.2	4.8269
12.6	4.7089
6.3	4.5930
3.2	4.4735
1.6	4.3869
0.8	4.3363
0.4	4.3100

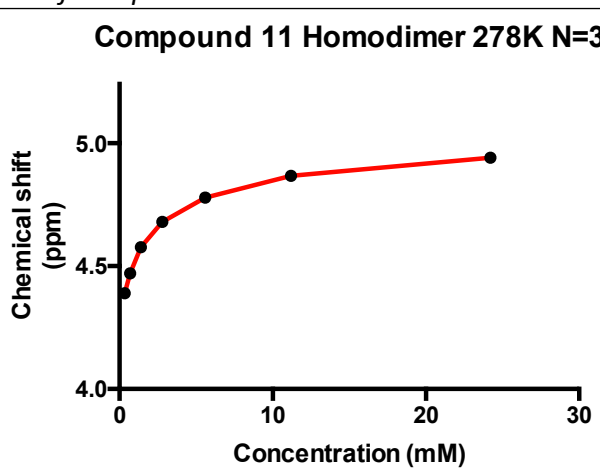


K_{DIM} = 50 M^{-1} sigma= 6.9

2.2.3. Compound 11 Homodimer ^{1}H NMR Titration Experiment 3

Table 29: *^{1}H NMR titration of compound 11 at 278 K*

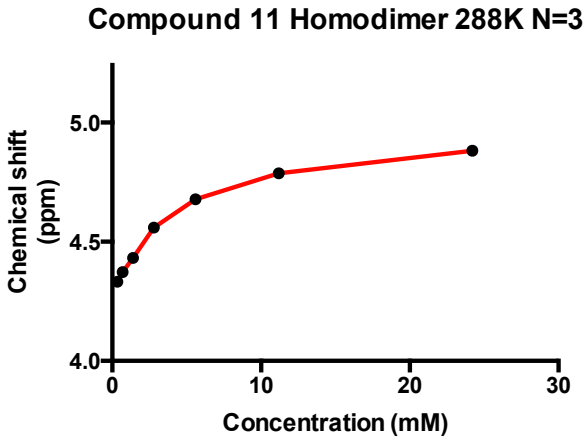
[11] (mM)	δ H^2 (ppm)
24.2	4.9408
11.2	4.8677
5.6	4.7789
2.8	4.6794
1.4	4.5767
0.7	4.4702
0.4	4.3894



K_{DIM}= 335 M^{-1} sigma=2.3

Table 30: *^{1}H NMR titration of compound 11 at 288 K*

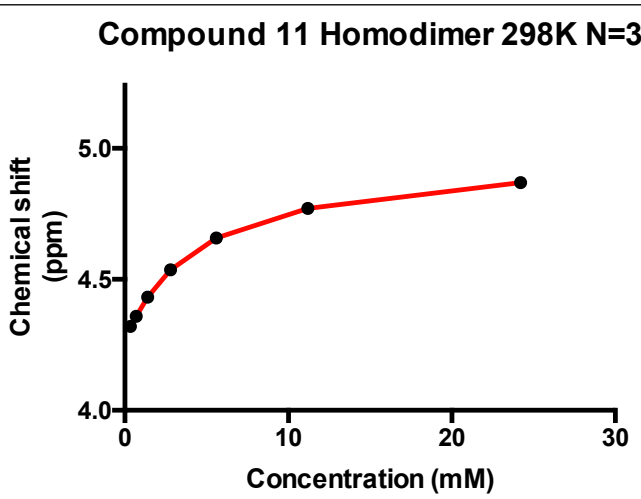
[11] (mM)	δ H^2 (ppm)
24.2	4.8815
11.2	4.7867
5.6	4.6781
2.8	4.5588
1.4	4.4314
0.7	4.3723
0.4	4.3317



K_{DIM} = 118 M^{-1} sigma= 14.4

Table 31: *^{1}H NMR titration of compound 11 at 298 K*

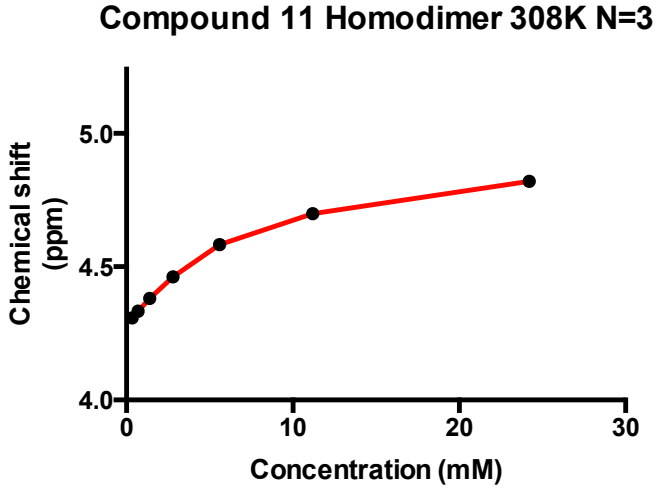
[11] (mM)	δ H^2 (ppm)
24.2	4.8692
11.2	4.7705
5.6	4.6573
2.8	4.5364
1.4	4.4322
0.7	4.3593
0.4	4.3208



K_{DIM}= 109 M^{-1} sigma= 8.1

Table 32: *^{1}H NMR titration of compound 11 at 308 K*

[11] (mM)	δ H^2 (ppm)
24.2	4.8202
11.2	4.6984
5.6	4.5830
2.8	4.4624
1.4	4.3804
0.7	4.3328
0.4	4.3075



K_{DIM} = 57 M^{-1} sigma = 8.0

2.2.4. Compound 11 Homodimer VT ^{1}H NMR Summary and Van't Hoff Plots

Table 33*: Summary of compound 11 Homodimer Experiment 1 and Van't Hoff Plot*

Temp (K)	K_{DIM} (M^{-1})	1/T	ln(K_{DIM})
308	54	0.003246753	3.988984047
298	110	0.003355705	4.700480366
295	126	0.003389831	4.836281907
288	214	0.003472222	5.365976015
278	360	0.003597122	5.886104031

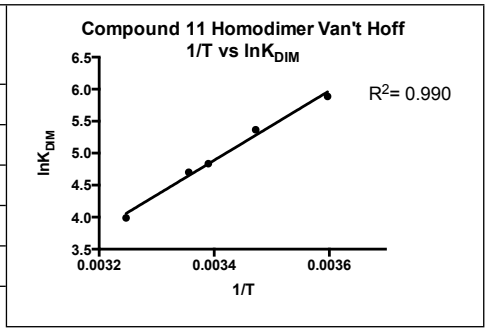


Table 34*: Summary of compound 11 Homodimer Experiment 2 and Van't Hoff Plot*

Temp (K)	K_{DIM} (M^{-1})	1/T	ln(K_{DIM})
308	57	0.003246753	4.043051268
298	109	0.003355705	4.691347882
295	118	0.003389831	4.770684624
278	335	0.003597122	5.814130532

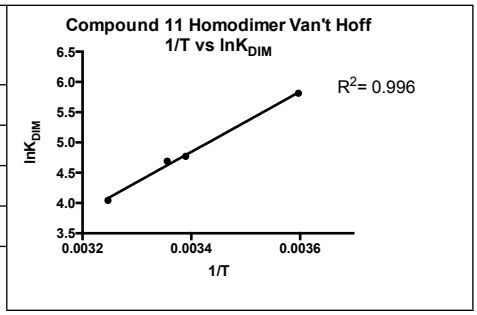


Table 35*: Summary of compound 11 Homodimer Experiment 3 and Van't Hoff Plot*

Temp (K)	K_{DIM} (M^{-1})	1/T	ln(K_{DIM})
308	50	0.003246753	3.912023005
298	95	0.003355705	4.553876892
295	156	0.003389831	5.049856007
278	301	0.003597122	5.707110265

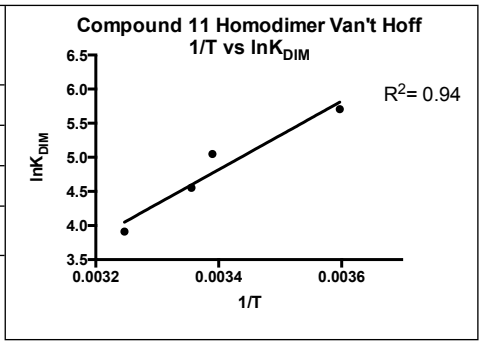


Table 36: *Summary of thermodynamic parameters for compound 11 homodimer*

Expt	ΔH (kcal mol^{-1})	$-T\Delta S^{295\ K}$ (kcal mol^{-1})	ΔG (kcal mol^{-1})
1	-10.8	7.9	-2.9
2	-10.0	7.2	-2.8
3	-9.9	7.1	-2.8
Average	**-10.2**	**7.4**	**-2.8**

2.3. Compound 2 Homodimer VT ^{1}H NMR Titration

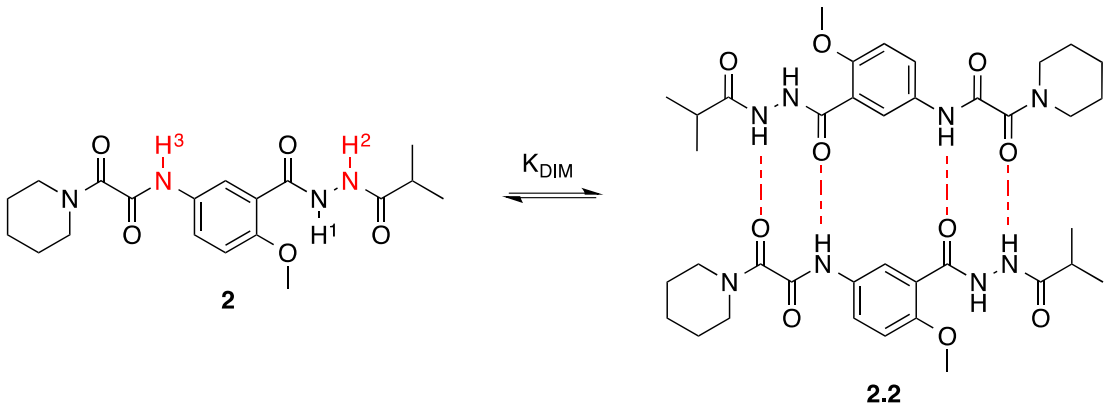


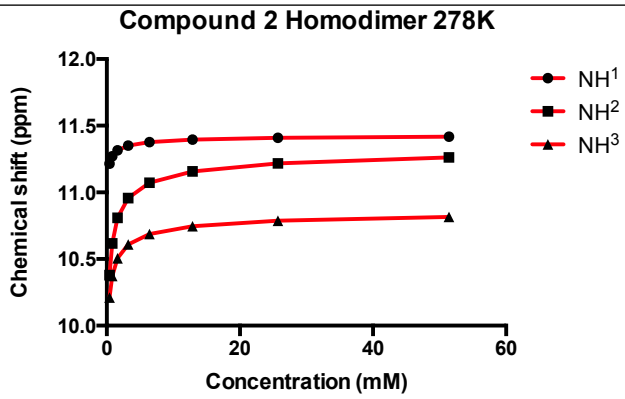
Figure 4: *Homodimerisation of HAO. Resonances used to calculate K_{DIM} are highlighted in red.*

N.B. K_{DIM} was calculated using NH^2 and NH^3. The shifts of NH^1 are included for completeness.

2.3.1. Compound 2 Homodimer ^{1}H NMR Titration Experiment 1

Table 37: *^{1}H NMR titration of 2 at 278 K*

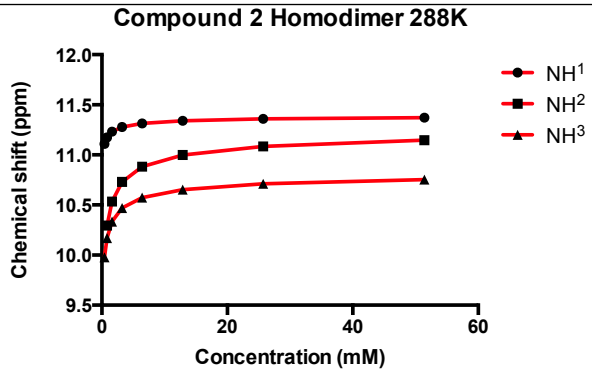
[2] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)
51.4	11.4178	11.2621	10.8163
25.7	11.4094	11.2182	10.7872
12.9	11.3964	11.1572	10.7457
6.4	11.3771	11.0726	10.6876
3.2	11.3507	10.9579	10.6093
1.6	11.3160	10.8086	10.5055
0.8	11.2709	10.6180	10.3733
0.4	11.2163	10.3790	10.2100



K_{DIM}= 4747 M^{-1} **sigma= 0.8**

Table 38: *^{1}H NMR titration of 2 at 288 K*

[2] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)
51.4	11.3713	11.1460	10.7535
25.7	11.3594	11.0851	10.7122
12.9	11.3405	10.9994	10.6540
6.4	11.3135	10.8831	10.5742
3.2	11.2780	10.7310	10.4699
1.6	11.2315	10.5340	10.3346
0.8	11.1741	10.2938	10.1696
0.4	11.1086	-*	9.9778

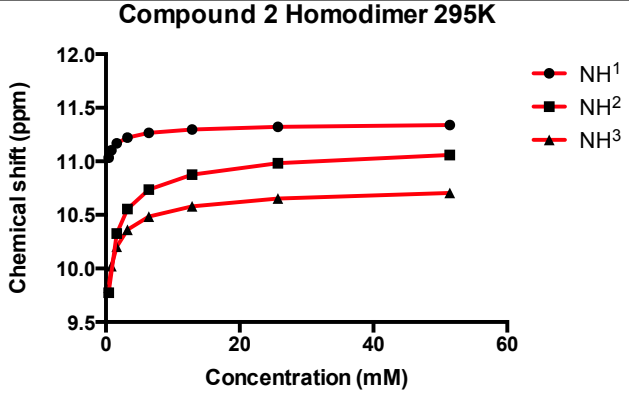


K_{DIM}=2352 M^{-1} **sigma= 0.6**

***Obscured by another proton signal**

Table 39: *^{1}H NMR titration of 2 at 295 K*

[2] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)
51.4	11.3377	11.0589	10.7046
25.7	11.3223	10.9828	10.6531
12.9	11.2978	10.8756	10.5801
6.4	11.2652	10.7356	10.4841
3.2	11.2226	10.5555	10.3606
1.6	11.1678	10.3256	10.2035
0.8	11.1029	-*	10.0209
0.4	11.0338	9.7735	9.8217

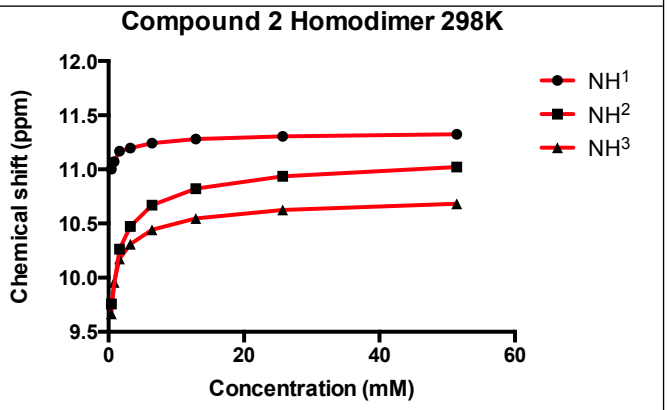


K_{DIM}= 1360 M^{-1} **sigma= 1.4**

***Obscured by another proton signal**

Table 40: *^{1}H NMR titration of 2 at 298 K*

[2] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)
51.4	11.3230	11.0216	10.6830
25.7	11.3054	10.9370	10.6259
12.9	11.2792	10.8217	10.5475
6.4	11.2433	10.6697	10.4433
3.2	11.1964	10.4738	10.3092
1.6	11.1683	10.2641	10.1745
0.8**	11.0725	-*	9.9582
0.4**	11.0025	9.7570	9.6655



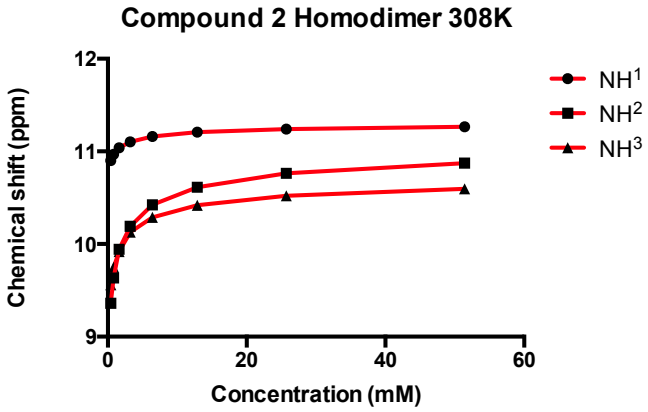
K_{DIM}= 577 M^{-1} **sigma= 4.6**

*** Obscured by another proton signal**

****Outlier excluded from K_{DIM} determination**

Table 41: *^{1}H NMR titration of 2 at 308 K*

[2] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)
51.4	11.2662	10.8737	10.5953
25.7	11.2422	10.7626	10.5203
12.9	11.2078	10.6146	10.4197
6.4	11.1620	10.4244	10.2895
3.2	11.1049	10.1903	10.1294
1.6	11.0387	9.9437	9.9191
0.8	10.9681	9.6337	9.7483
0.4	10.9020	9.3610	9.5624

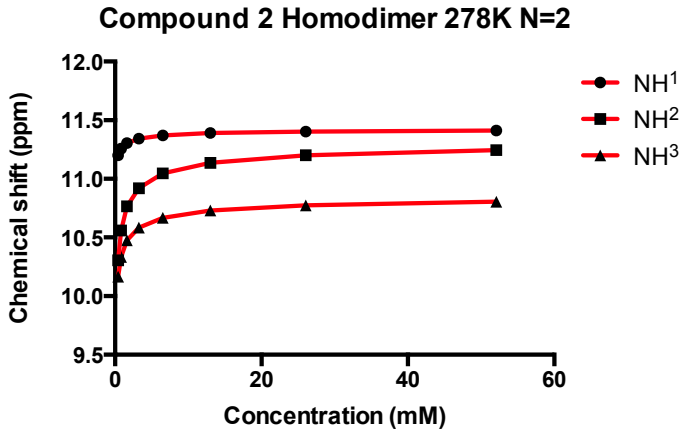


K_{DIM}= 571 M^{-1} **sigma= 0.6**

2.3.2. Compound 2 Homodimer ^{1}H NMR Titration Experiment 2

Table 42: *^{1}H NMR titration of 2 at 278 K*

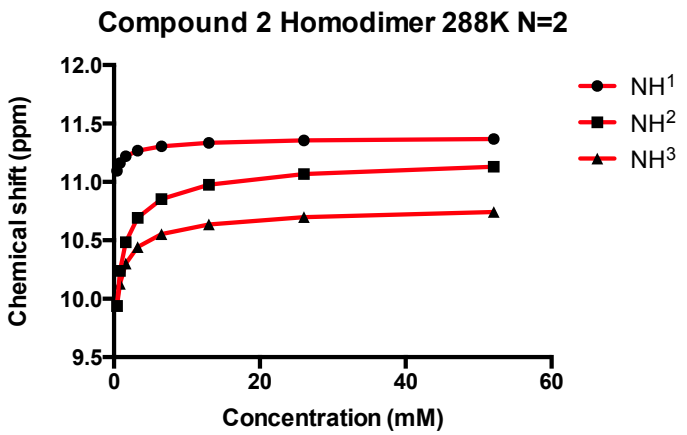
[2] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)
52.1	11.4121	11.2452	10.8046
26.1	11.4039	11.2003	10.7743
13.0	11.3902	11.1365	10.7304
6.5	11.3698	11.0464	10.6686
3.3	11.3420	10.9203	10.5852
1.6	11.3055	10.7661	10.4761
0.8	11.2578	10.5585	10.3345
0.4	11.2006	10.305	10.1648



K_{DIM} = 4928 M^{-1} **sigma= 1.9**

Table 43: *^{1}H NMR titration of 2 at 288 K*

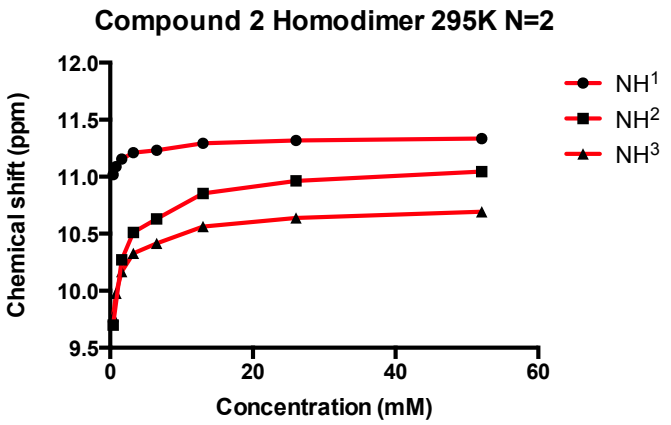
[2] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)
52.1	11.3671	11.1300	10.7419
26.1	11.3550	11.0668	10.6991
13.0	11.3340	10.9757	10.6364
6.5	11.3059	10.8535	10.5530
3.3	11.2683	10.6931	10.4426
1.6	11.2203	10.4852	10.3020
0.8	11.1608	10.2394	10.1289
0.4	11.0945	9.9384	9.9384



K_{DIM} = 2262 M^{-1} **sigma= 3.3**

Table 44: *^{1}H NMR titration of 2 at 295 K*

[2] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)
52.1	11.3341	11.0446	10.6934
26.1	11.3175	10.9638	10.6389
13.0	11.2922	10.8523	10.5628
6.5	11.2333	10.6310	10.4159
3.3	11.2113	10.5106	10.3291
1.6	11.1547	10.2709	10.1667
0.8	11.0880	-*	9.9777
0.4	11.0174	9.699	9.7735



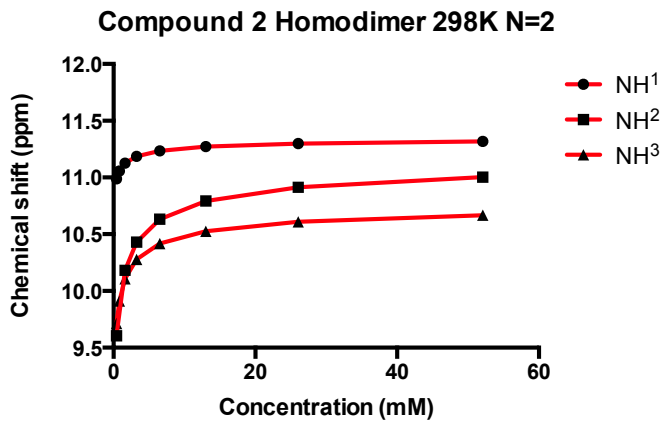
K_{DIM} = 1271 M^{-1} **sigma= 1.4**

N.B. Based on NH^3 only

*Obscured by another proton signal

Table 45: *^{1}H NMR titration of 2 at 298 K*

[2] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)
52.1	11.3175	11.0021	10.6684
26.1	11.2995	10.9140	10.6093
13.0	11.2717	10.7929	10.5265
6.5	11.2339	10.6332	10.4174
3.3	11.1855	10.4296	10.2780
1.6	11.1259	10.182	10.1082
0.8	11.0577	-*	9.9120
0.4	10.9879	9.6042	9.7140

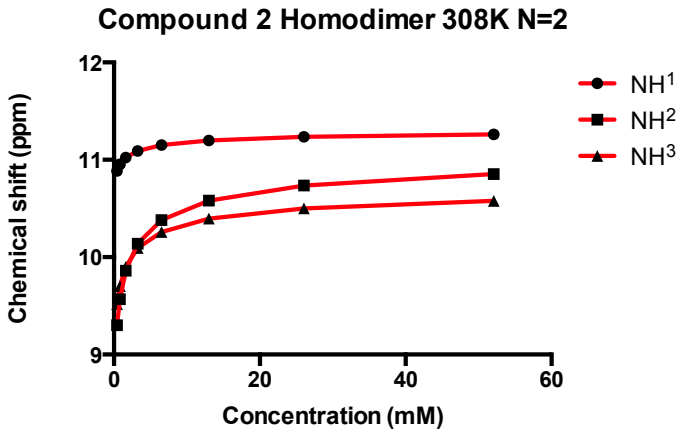


K_{DIM} = 1009 M^{-1} **sigma= 0.9**

*Obscured by another proton signal

Table 46: *^{1}H NMR titration of 2 at 308 K*

[2] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)
52.1	11.2611	10.8531	10.5799
26.1	11.2356	10.7363	10.5012
13.0	11.1992	10.5810	10.3954
6.5	11.1505	10.3800	10.2582
3.3	11.0918	10.1382	10.0929
1.6	11.0235	9.8602	9.9022
0.8	10.9531	9.5699	9.7030
0.4	10.8861	9.301	9.5194

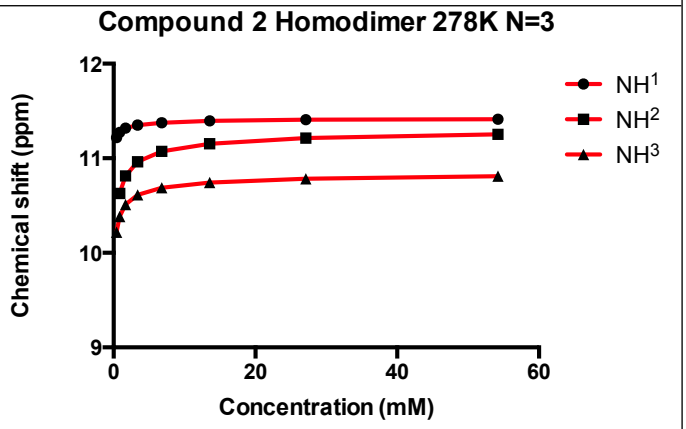


K_{DIM} = 502 M^{-1} sigma= 1.0

2.3.3. Compound 2 Homodimer ^{1}H NMR Titration Experiment 3

Table 47: *^{1}H NMR titration of 2 at 278 K*

[2] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)
54.2	11.4141	11.2535	10.8103
27.1	11.4077	11.2146	10.7847
13.6	11.3951	11.1539	10.7440
6.8	11.3772	11.0729	10.6890
3.4	11.3520	10.9635	10.6132
1.7	11.3178	10.8147	10.5117
0.9	11.2747	10.6290	10.3839
0.4	11.2194	-*	10.2199

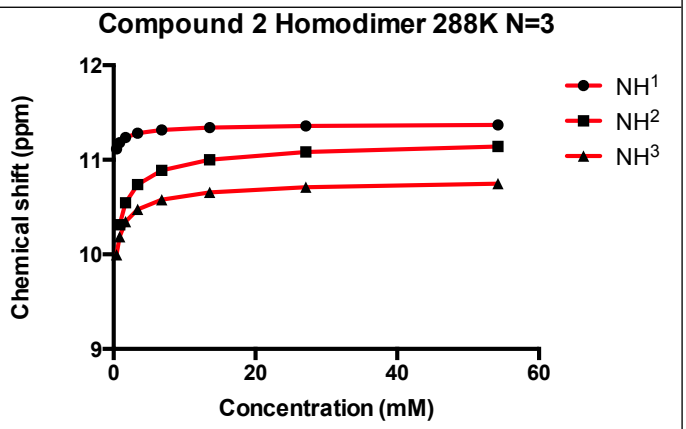


K_{DIM} = 5430 M^{-1} **sigma= 1.4**

*Broadened signal

Table 48: *^{1}H NMR titration of 2 at 288 K*

[2] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)
54.2	11.3694	11.1407	10.7491
27.1	11.3597	11.0849	10.7124
13.6	11.3416	11.0007	10.6555
6.8	11.3161	10.8882	10.5789
3.4	11.2812	10.7384	10.4766
1.7	11.2362	10.547	10.3450
0.9	11.1813	10.3145	10.1856
0.4	11.1158	-*	9.9954

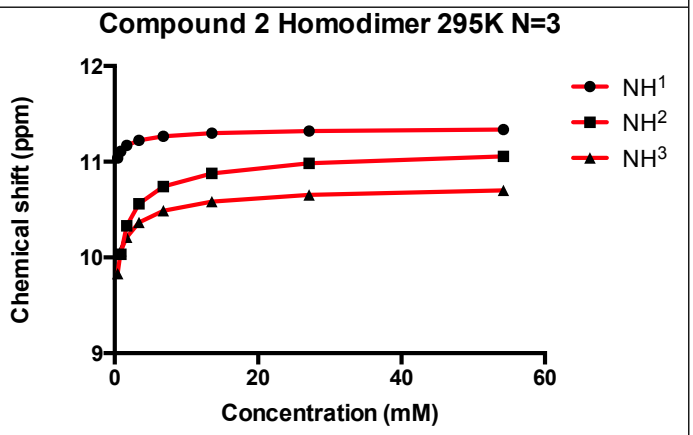


K_{DIM} = 2318 M^{-1} **sigma= 1.7**

*Obscured by another proton signal

Table 49: *^{1}H NMR titration of 2 at 295 K*

[2] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)
54.2	11.3366	11.0570	10.7018
27.1	11.3221	10.9845	10.6536
13.6	11.2995	10.8797	10.5831
6.8	11.2671	10.7410	10.4887
3.4	11.2248	10.5612	10.3660
1.7	11.1705	10.3311	10.2119
0.9*	11.1087	10.0339	10.0709
0.4	11.0376	9.7825	9.8307



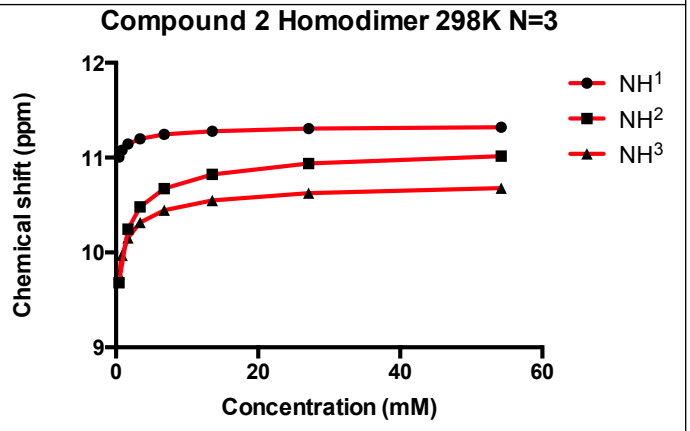
K_{DIM} = 1403 M^{-1} **sigma= 1.6**

NB K_{DIM} based on NH^3 only

***Outlier excluded from K_{DIM} determination**

Table 50: *^{1}H NMR titration of 2 at 298 K*

[2] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)
54.2	11.3213	11.0169	10.6787
27.1	11.3055	10.9380	10.6264
13.6	11.2800	10.8235	10.5490
6.8	11.2451	10.6740	10.4473
3.4	11.1992	10.4820	10.3163
1.7	11.1429	10.2461	10.1550
0.9	11.0784	-*	9.9716
0.4	11.0070	9.6810	9.7684

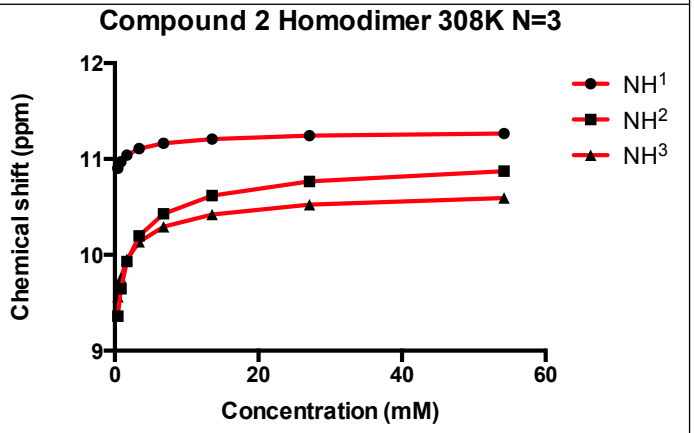


K_{DIM} = 1099 M^{-1} **sigma= 1.6**

*Obscured by another proton signal

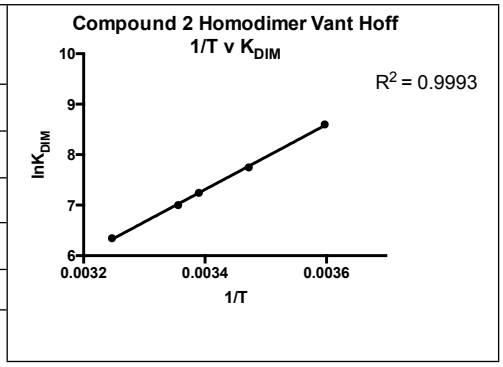
Table 51: *^{1}H NMR titration of 2 at 308 K*

[2] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)
54.2	11.2664	10.8735	10.5939
27.1	11.2437	10.7672	10.5230
13.6	11.2093	10.6183	10.4223
6.8	11.1639	10.4294	10.2939
3.4	11.1078	10.1978	10.1361
1.7	11.0423	9.9305	9.9530
0.9	10.9723	9.6451	9.7583
0.4	10.9025	9.361	9.5647



K_{DIM} = 570 M^{-1} **sigma= 1.7**

Temp (K)	K_{DIM} (M^{-1})	1/T	lnK
308	570	0.003246753	6.345636361
298	1099	0.003355705	7.002155954
295	1403	0.003389831	7.24636808
288	2318	0.003472222	7.748460024
278	5430	0.003597122	8.599694413



2.3.4. Compound 2 Homodimer VT ^{1}H NMR Summary and Van't Hoff Plots

Table 52*: Summary of compound 2 Homodimer Experiment 1 and Van't Hoff Plot*

Temp (K)	K_{DIM} (M^{-1})	1/T	lnK
308	571	0.003246753	6.34738921
295	1360	0.003389831	7.215239979
288	2352	0.003472222	7.763021309
278	4747	0.003597122	8.465268119

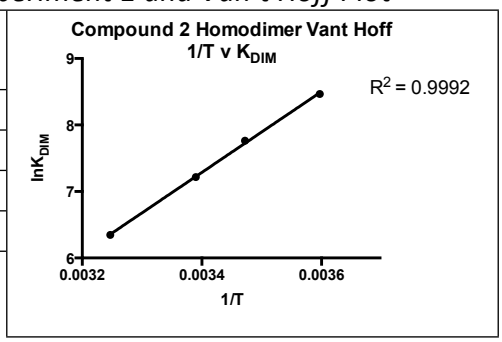


Table 53*: Summary of compound 2 Homodimer Experiment 2 and Van't Hoff Plot*

Temp (K)	K_{DIM} (M^{-1})	1/T	lnK
308	502	0.003246753	6.21860012
298	1009	0.003355705	6.91671502
295	1271	0.003389831	7.147559271
288	2262	0.003472222	7.724004657
278	4928	0.003597122	8.502688505

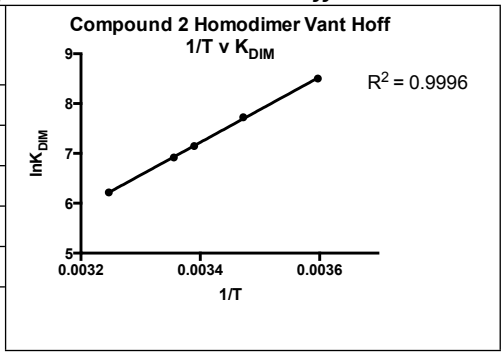


Table 54*: Summary of compound 2 Homodimer Experiment 3 and Van't Hoff Plot*

Table 55: *Summary of thermodynamic parameters for compound 2 homodimer*

Expt	ΔH (kcal mol^{-1})	$-T\Delta S^{295\ K}$ (kcal mol^{-1})	ΔG (kcal mol^{-1})
N1	- 12.1	7.8	- 4.3
N2	- 13.0	8.4	- 4.6
N3	- 12.8	8.5	- 4.3
Average	**- 12.6**	**8.4**	**- 4.4**

2.4. 11:1 Heterodimer VT ^{1}H NMR Titration Experiment

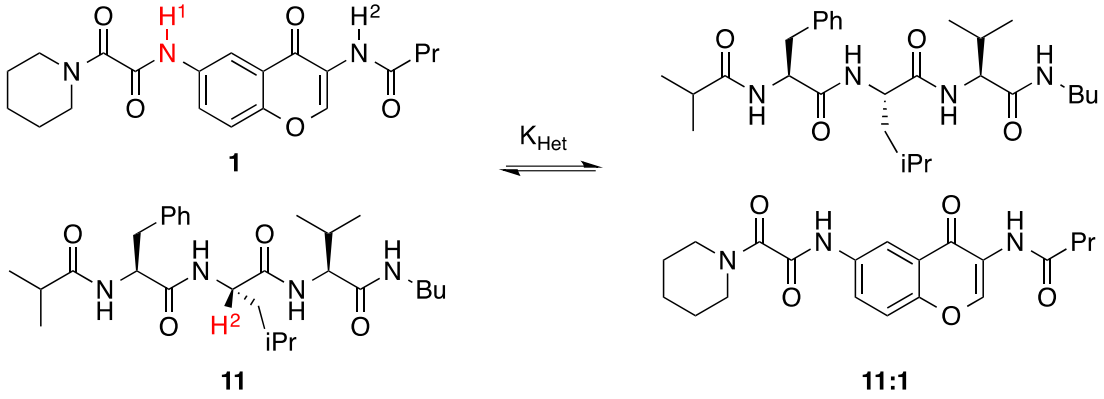


Figure 5: *Heterodimerisation of 1 and 11. Resonances used to determine binding constants are highlighted in red.*

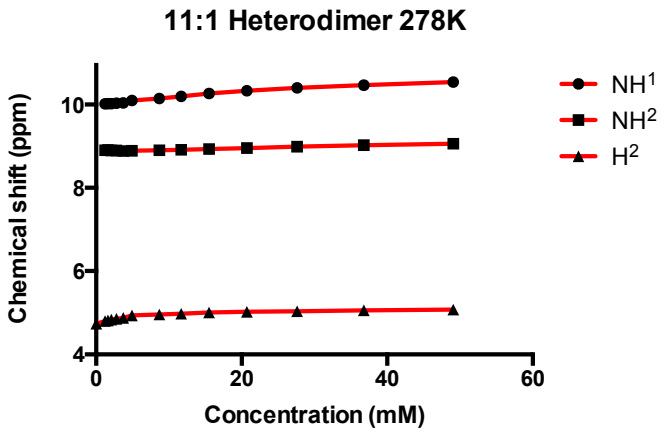
N.B. K_{Het} was calculated using NH^1 and H^2. The shift of NH^2 is included for completeness

2.4.1 11:1 Heterodimer ^{1}H NMR Titration Experiment 1

Peptide concentration: 4 mM

Table 56: 11:1 Heterodimer *^{1}H NMR titration at 278 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ H^2 (ppm)
49.1	10.5411	9.0581	5.0745
36.8	10.4644	9.0234	5.0581
27.6	10.4024	8.9899	5.0347
20.7	10.3342	8.9575	5.0240
15.5	10.2651	8.9323	5.0043
11.7	10.1969	8.9150	4.9798
8.7	10.1427	8.9013	4.9571
4.9*	10.0997	8.8941	4.9347
3.7	10.0422	8.8867	4.8776
2.8	10.0322	8.8973	4.8540
2.1	10.0212	8.8943	4.8345
1.6	10.0233	8.9067	4.8153
1.2	10.0189	8.9034	4.8037
0	-	-	4.7381

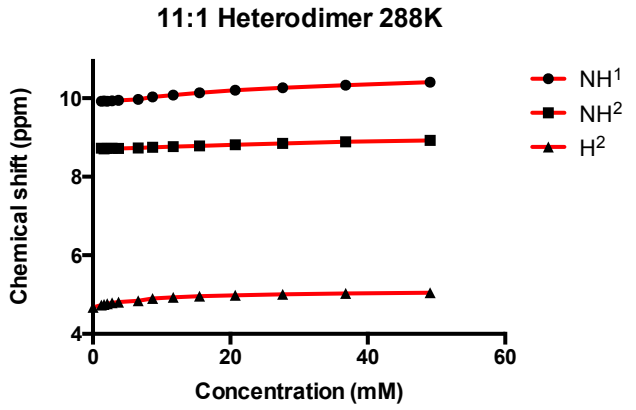


K_{Het}= 904 M^{-1} **sigma= 8.4**

*Outlier not included in K_{Het} determination

Table 57: 11:1 Heterodimer ^{1}H *NMR titration at 288 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ H^2 (ppm)
49.1	10.4097	8.9277	5.0460
36.8	10.3329	8.8893	5.0293
27.6	10.2707	8.8522	5.0064
20.7	10.2046	8.8172	4.9835
15.5	10.1397	8.7878	4.9581
11.7	10.0794	8.7668	4.9278
8.7	10.0328	8.7500	4.8987
6.6*	9.9692	8.7356	4.8405
3.7*	9.9457	8.7226	4.8100
2.8	9.9376	8.7288	4.7889
2.1	9.9256	8.7218	4.7656
1.6	9.9272	8.7116	4.7498
1.2	9.9209	8.7257	4.7341
0	-	-	4.6723

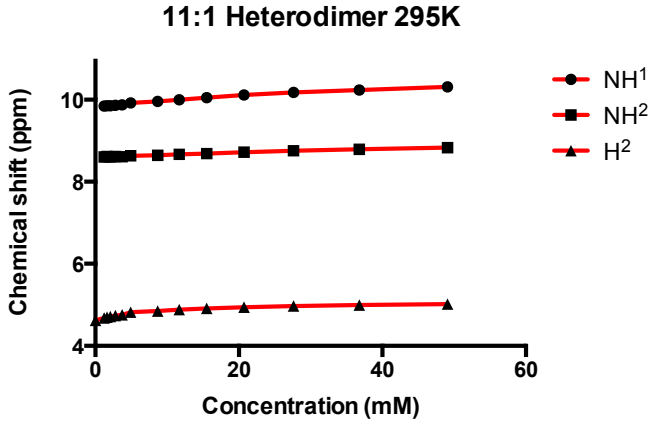


K_{Het}= 512 M^{-1} **sigma= 7.0**

*Outlier not included in K_{Het} determination

Table 58: 11:1 Heterodimer ^{1}H *NMR titration at 295 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ H^2 (ppm)
49.1*	10.3148	8.8347	5.0179
36.8	10.2394	8.7947	4.9958
27.6	10.1793	8.7575	4.9719
20.7	10.1147	8.7202	4.9438
15.5	10.0539	8.6896	4.9150
11.7	9.9993	8.6671	4.8819
8.7	9.9570	8.6484	4.8504
4.9*	9.9229	8.6336	4.8185
3.7	9.8764	8.6130	4.7582
2.8	9.8679	8.6159	4.7364
2.1	9.8551	8.6067	4.7137
1.6	9.8560	8.6144	4.6989
1.2	9.8491	8.6080	4.6798
0	-	-	4.6241

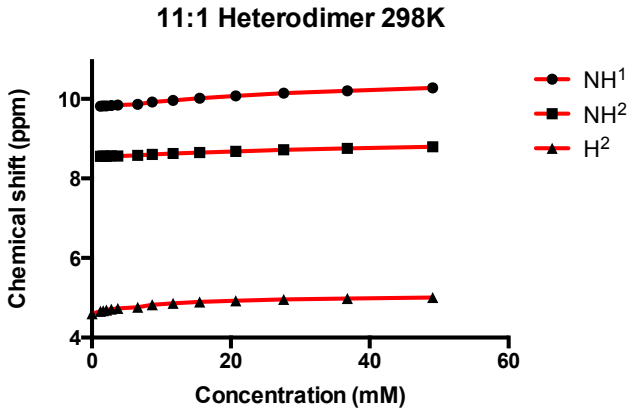


K_{Het}= 332 M^{-1} **sigma= 7.3**

*Outlier not included in K_{Het} determination

Table 59: 11:1 Heterodimer *^{1}H NMR titration at 298 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ H^2 (ppm)
49.1	10.2791	8.7998	5.0061
36.8	10.2022	8.7570	4.9811
27.6	10.1457	8.7221	4.9570
20.7	10.0778	8.6804	4.9251
15.5	10.0187	8.6494	4.8945
11.7	9.9661	8.6260	4.8597
8.7	9.9248	8.6059	4.8268
6.6*	9.8677	8.5821	4.7634
3.7	9.8460	8.5673	4.7337
2.8	9.8371	8.5684	4.7123
2.1	9.8237	8.5581	4.6893
1.6	9.8240	8.5644	4.6747
1.2	9.8168	8.5580	4.6598
0	-	-	4.6007

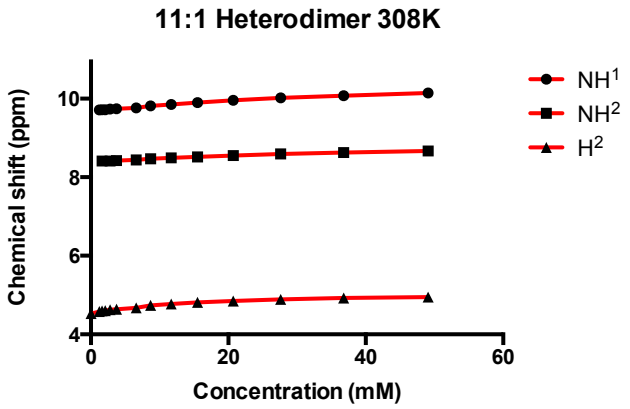


K_{Het}= 272 M^{-1} **sigma= 6.8**

*Outlier excluded from K_{Het} determination

Table 60: 11:1 Heterodimer *^{1}H NMR titration at 308 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ H^2 (ppm)
49.1	10.1454	8.6701	4.9459
36.8	10.0737	8.6282	4.9218
27.6	10.0200	8.5926	4.8901
20.7	9.9568	8.5507	4.8492
15.5	9.9027	8.5182	4.8137
11.7	9.8555	8.4922	4.7753
8.7	9.8191	8.4706	4.7407
6.6**	9.7659	8.4395	4.6756
3.7	9.7440	8.4217	4.6379
2.8	9.7346	8.4129	4.6262
2.1	9.7203	-*	4.6048
1.6	9.7192	8.4104	4.5954
1.2	9.7126	-*	4.5801
0	-	-	4.5264



K_{Het}= 141 M^{-1} **sigma= 5.6**

*Obscured by another signal

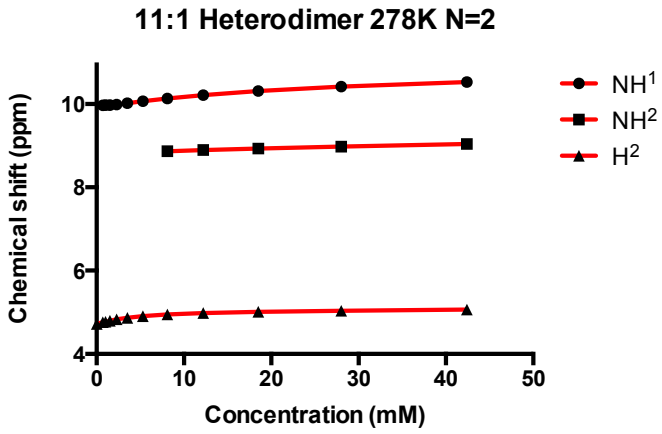
**Outlier excluded from K_{Het} determination

2.4.2. 11:1 Heterodimer ^{1}H NMR Titration Experiment 2

Peptide concentration: 4.3 mM

Table 61: 11:1 Heterodimer *^{1}H NMR titration at 278 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ H^2 (ppm)
42.4	10.5293	9.0430	5.0649
28.0	10.4168	8.9813	5.0377
18.5	10.3134	8.9344	5.0118
12.2	10.2139	8.8966	4.9801
8.1	10.1323	8.8663	4.9491
5.3	10.0673	-*	4.9057
3.5	10.0200	-*	4.8672
2.3	9.9901	-*	4.8290
1.5	9.9778	-*	4.7984
1.0	9.9747	-*	4.7739
0.7	9.9689	-*	4.7586
0		-	4.7215

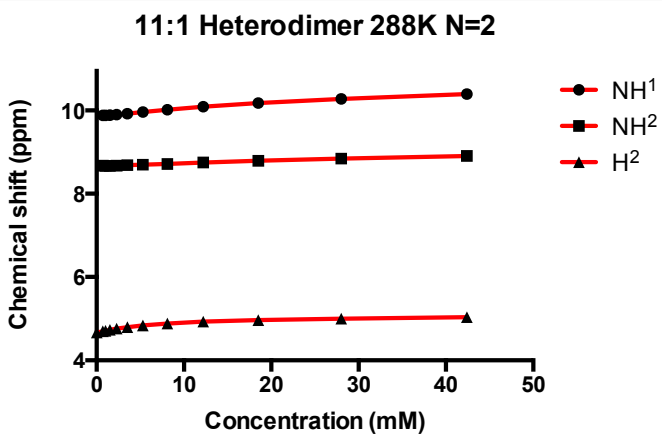


K_{Het}= 838 M^{-1} **sigma= 9.8**

*Broadened signal

Table 62: 11:1 Heterodimer *^{1}H NMR titration at 288 K*

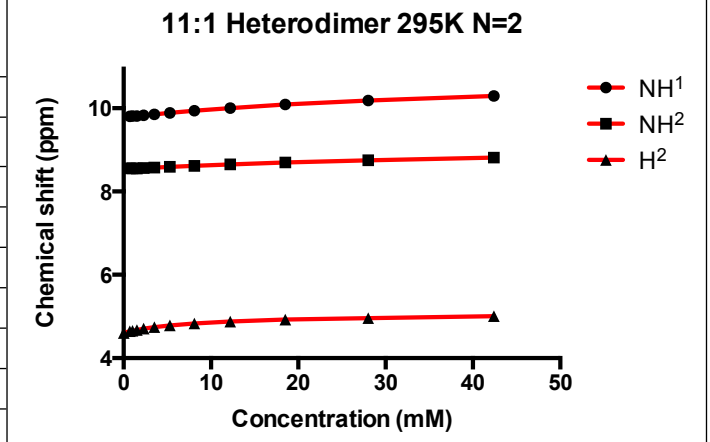
[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ H^2 (ppm)
42.4	10.3939	8.9099	5.0342
28.0	10.2815	8.8443	5.0009
18.5	10.1814	8.7916	4.9671
12.2	10.0918	8.7504	4.9278
8.1	10.0177	8.7166	4.8838
5.3	9.9619	8.6962	4.8397
3.5	9.9253	8.6843	4.7977
2.3	9.9021	8.6759	4.7606
1.5	9.8875	8.6694	4.7306
1.0	9.8835	8.6722	4.7095
0.7	9.8824	8.6748	4.6950
0	-	-	4.6673



K_{Het}= 501 M^{-1} sigma= 5.6

Table 63: 11:1 Heterodimer *^{1}H NMR titration at 295 K*

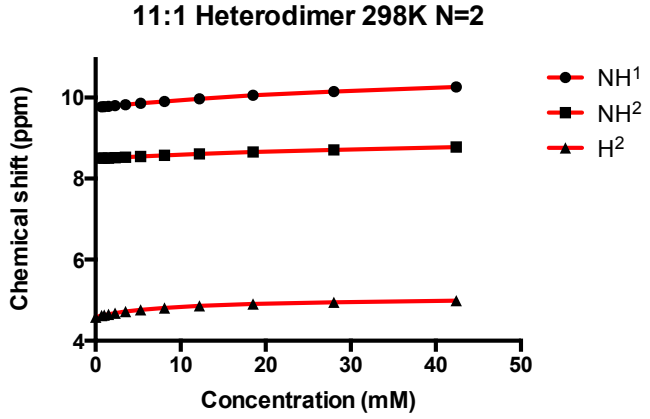
[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ H^2 (ppm)
42.4	10.2978	8.8164	5.0035
28.0	10.1872	8.7492	4.9621
18.5	10.0921	8.6961	4.9257
12.2	10.0075	8.6519	4.8806
8.1	9.9395	8.6161	4.8329
5.3	9.8881	8.5919	4.7857
3.5	9.8531	8.5746	4.7422
2.3	9.8309	8.5642	4.7059
1.5	9.8154	8.5550	4.6765
1.0	9.8124	8.5577	4.6579
0.7	9.8076	8.5560	4.6426
0	-	-	4.6014



K_{Het}= 323 M^{-1} **sigma= 9.1**

Table 64: 11:1 Heterodimer *^{1}H NMR titration at 298 K*

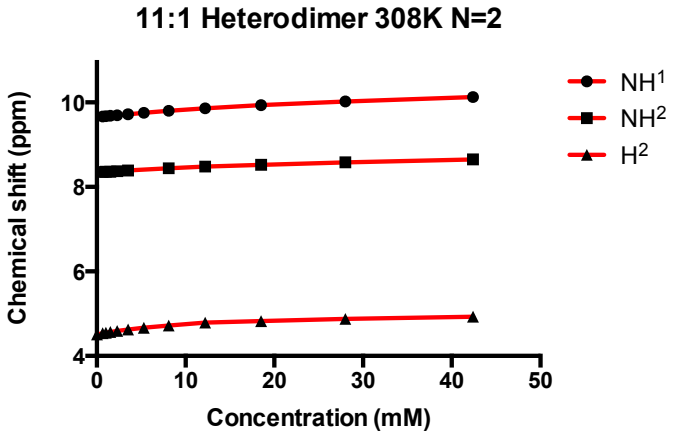
[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ H^2 (ppm)
42.4	10.2612	8.7810	4.9914
28.0	10.1492	8.7109	4.9479
18.5	10.0550	8.6562	4.9053
12.2	9.9720	8.6105	4.8580
8.1	9.9064	8.5742	4.8083
5.3	9.8575	8.5493	4.7610
3.5	9.8228	8.5303	4.7178
2.3	9.8005	8.5182	4.6815
1.5	9.7845	8.5078	4.6521
1.0	9.7799	8.5084	4.6335
0.7	9.7746	8.5059	4.6184
0	-	-	4.5787



K_{Het}= 257 M^{-1} **sigma= 7.2**

Table 65: 11:1 Heterodimer *^{1}H NMR titration at 308 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ H^2 (ppm)
42.4	10.1283	8.6530	4.9288
28.0	10.0210	8.5826	4.8752
18.5	9.9328	8.5264	4.8262
12.2	9.8598	8.4815	4.7908
8.1	9.7996	8.4420	4.7197
5.3	9.7541	-*	4.6703
3.5	9.7205	8.3894	4.6272
2.3	9.6988	8.3742	4.5944
1.5	9.6818	8.3611	4.5708
1.0	9.6755	8.3584	4.5517
0.7	9.6695	8.3542	4.5392
0	-	-	4.5129



K_{Het}= 157 M^{-1} **sigma= 6.7**

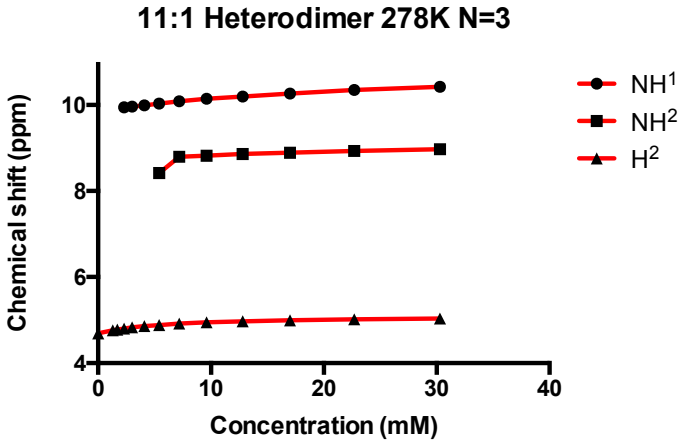
*Obscured by another proton signal

2.4.3. 11:1 Heterodimer ^{1}H NMR Titration Experiment 3

Peptide concentration: 3.3 mM

Table 66: 11:1 Heterodimer *^{1}H NMR titration at 278 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ H^2 (ppm)
30.3	10.4276	8.9756	5.0376
22.7	10.3525	8.9317	5.0169
17.0	10.2685	8.8932	4.9956
12.8	10.1976	8.8615	4.9703
9.6	10.1474	8.8223	4.9458
7.2	10.0888	8.7983	4.9170
5.4	10.0366	8.4192	4.8864
4.1	9.9959	-*	4.8606
3.0	9.9663	-*	4.8301
2.3	9.9487	-*	4.8044
1.7	-*	-*	4.7806
1.3	-*	-*	4.7612
0	-	-	4.6908

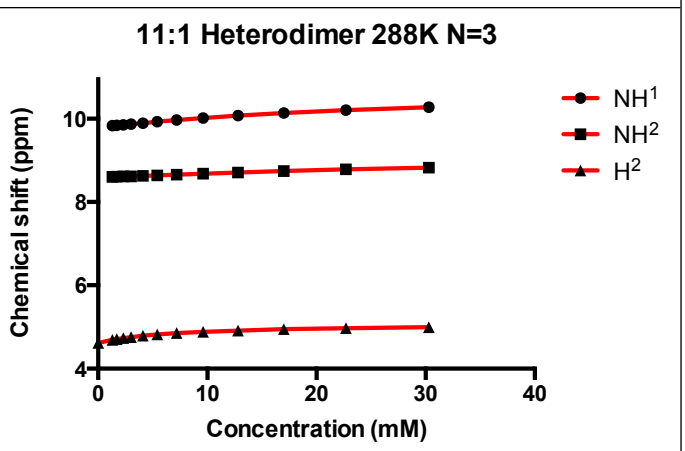


K_{Het} = 779 M^{-1} **sigma=7.6**

*Broadened signal

Table 67: 11:1 Heterodimer *^{1}H NMR titration at 288 K*

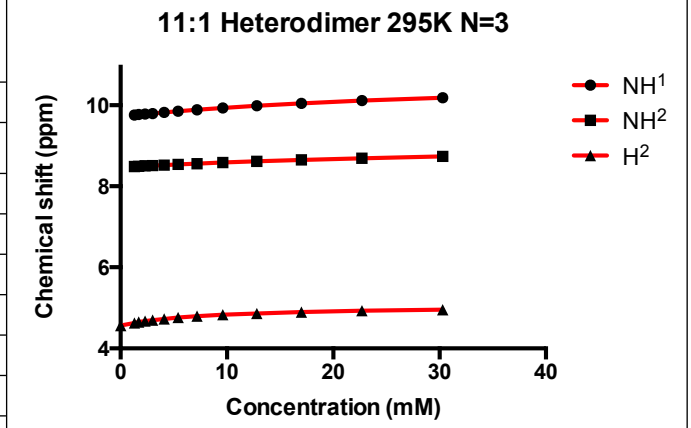
[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ H^2 (ppm)
30.3	10.2793	8.8281	4.9952
22.7	10.2100	8.7867	4.9713
17.0	10.1383	8.7475	4.9477
12.8	10.0735	8.7132	4.9128
9.6	10.0179	8.6835	4.8825
7.2	9.9683	8.6602	4.8536
5.4	9.9271	8.6426	4.8189
4.1	9.8958	8.6308	4.7877
3.0	9.8711	8.6194	4.7572
2.3	9.8559	8.6163	4.7311
1.7	9.8438	8.6113	4.7090
1.3	9.8355	8.6083	4.6887
0	-	-	4.6169



K_{Het}= 471 M^{-1} **sigma= 6.6**

Table 68: 11.1 Heterodimer *^{1}H NMR titration at 295 K*

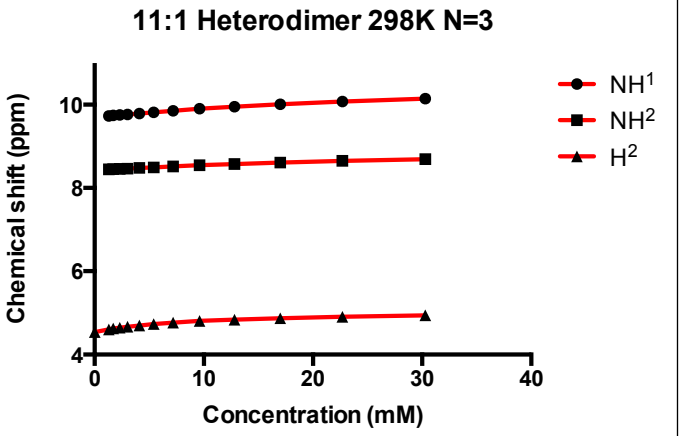
[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ H^2 (ppm)
30.3	10.1863	8.7372	4.9564
22.7	10.1175	8.6925	4.9295
17.0	10.0482	8.6517	4.8980
12.8	9.9866	8.6157	4.8625
9.6	9.9382	8.5887	4.8329
7.2	9.8890	8.5596	4.7937
5.4	9.8513	8.5400	4.7593
4.1	9.8221	8.5249	4.7264
3.0	9.7980	8.5104	4.6957
2.3	9.7830	8.5042	4.6715
1.7	9.7700	8.4962	4.6494
1.3	9.7604	8.4903	4.6299
0	-	-	4.5626



K_{Het}= 294 M^{-1} **sigma= 6.1**

Table 69: 11:1 Heterodimer *^{1}H NMR titration at 298 K*

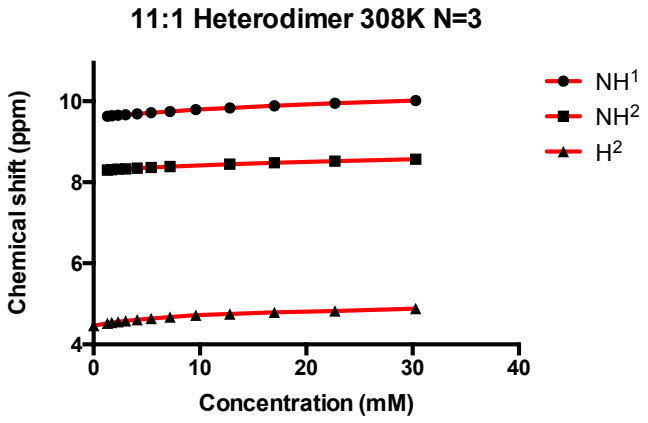
[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ H^2 (ppm)
30.3	10.1447	8.6952	4.9440
22.7	10.0767	8.6513	4.9078
17.0	10.0093	8.6105	4.8710
12.8	9.9508	8.5755	4.8387
9.6	9.9045	8.5489	4.8086
7.2	9.8557	8.5180	4.7661
5.4	9.8190	8.4973	4.7317
4.1	9.7906	8.4811	4.6993
3.0	9.7678	8.4670	4.6700
2.3	9.7529	8.4600	4.6453
1.7	9.7407	8.4521	4.6248
1.3	9.7306	8.4458	4.6061
0	-	-	4.5418



K_{Het}= 225 M^{-1} **sigma= 5.5**

Table 70: 11:1 Heterodimer *^{1}H NMR titration at 308 K*

[1] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ H^2 (ppm)
30.3	10.0174	8.5704	4.8861
22.7	9.9517	8.5250	4.8282
17.0	9.8903	8.4847	4.7893
12.8	9.8353	8.4477	4.7478
9.6	9.7974	-*	4.7182
7.2	9.7508	8.3899	4.6729
5.4	9.7180	8.3687	4.6380
4.1	9.6915	8.3493	4.6069
3.0	9.6690	8.3323	4.5786
2.3	9.6551	8.3237	4.5580
1.7	9.6410	8.3123	4.5383
1.3	9.6303	8.3039	4.5222
0	-	-	4.4657



K_{Het}= 115 M^{-1} **sigma= 5.6**

*Obscured by another proton signal

2.4.4. 11:1 Heterodimer VT ^{1}H NMR Summary and Van't Hoff Plots

Table 71*: Summary of 11:1 Heterodimer Experiment 1 and Van't Hoff Plot*

Temp (K)	K_{Het} (M^{-1})	1/T	lnK_{Het}
308	142	0.003246753	4.955827058
298	272	0.003355705	5.605802066
295	332	0.003389831	5.805134969
288	512	0.003472222	6.238324625
278	904	0.003597122	6.80682936

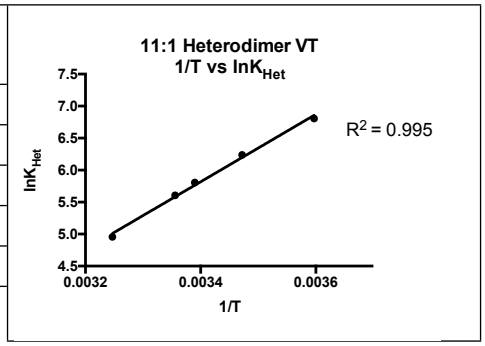


Table 72*: Summary of 11:1 Heterodimer Experiment 2 and Van't Hoff Plot*

Temp (K)	K_{Het} (M^{-1})	1/T	lnK_{Het}
308	157	0.003246753	5.056245805
298	257	0.003355705	5.549076085
295	323	0.003389831	5.777652323
288	501	0.003472222	6.216606101
278	838	0.003597122	6.7310181

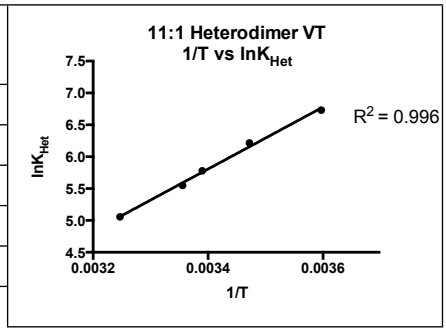


Table 73*: Summary of 11:1 Heterodimer Experiment 3 and Van't Hoff Plot*

Temp (K)	K_{Het} (M^{-1})	1/T	lnK_{Het}
308	115	0.003246753	4.744932128
298	225	0.003355705	5.416100402
295	294	0.003389831	5.683579767
288	471	0.003472222	6.154858094
278	779	0.003597122	6.658011046

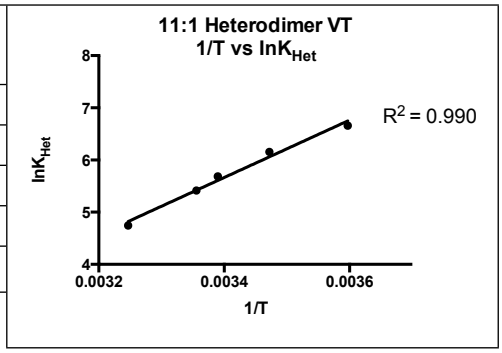


Table 74: *Summary of thermodynamic parameters for 11:1 heterodimer*

Expt	ΔH (kcal mol^{-1})	$-T\Delta S^{295\ K}$ (kcal mol^{-1})	ΔG (kcal mol^{-1})
N1	- 10.9	7.6	- 3.3
N2	- 9.7	6.3	- 3.1
N3	- 10.5	7.1	- 3.4
Average	**- 10.4**	**7.0**	**- 3.3**

2.5. 11:2 Heterodimer VT ^{1}H NMR Titration Experiment

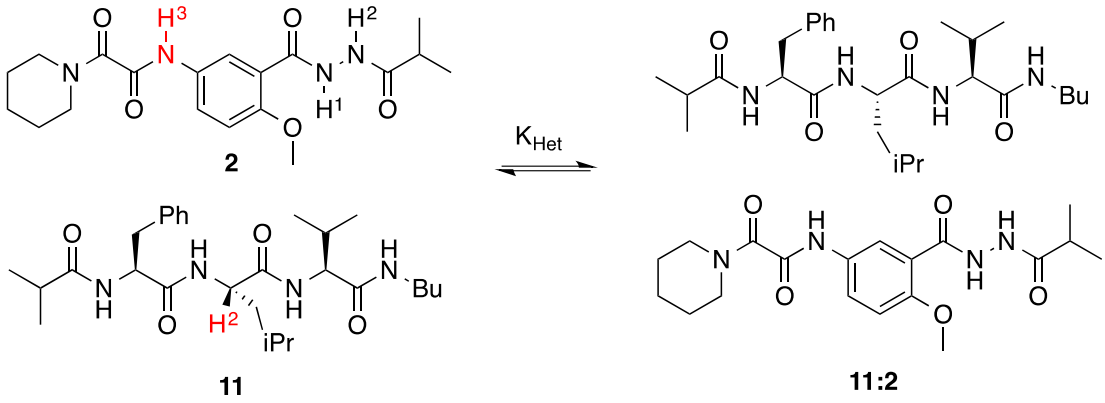


Figure 6: *Heterodimerisation of 2 and 11. Resonances used to determine binding constants are highlighted in red.*

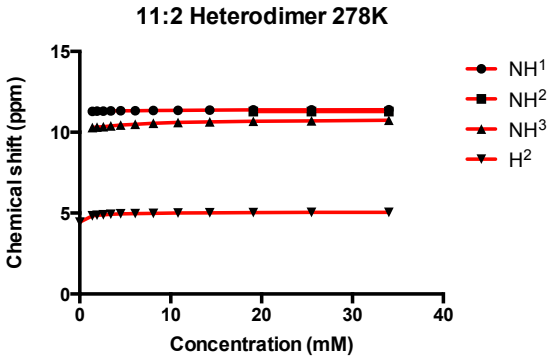
N.B. K_{Het} was calculated on using NH^3 and H^2. Shifts NH^1 and NH^2 are included for completeness

2.5.1. 11:2 Heterodimer ^{1}H NMR Titration Experiment 1

Peptide concentration: 3.1 mM

Table 75: 11:2 Heterodimer *^{1}H NMR titration at 278 K*

[2] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)	δ H^2 (ppm)
34.0	11.3932	11.2824	10.7386	5.0457
25.5	11.3870	11.2795	10.7124	5.0387
19.1	11.3783	11.2777	10.6782	5.0298
14.3	11.3705	-*	10.6443	5.0200
10.8	11.3605	-*	10.6006	5.0075
8.1	11.3493	-*	10.5508	4.9874
6.1	11.3372	-*	10.4955	4.9725
4.5	11.3259	-*	10.4395	4.9524
3.4	11.3153	-*	10.3878	4.9266
2.6	11.3076	-*	10.3444	4.8988
1.9	11.3011	-*	10.3155	4.8644
1.4	11.2955	-*	10.2884	4.8307
0	-	-	-	4.4425

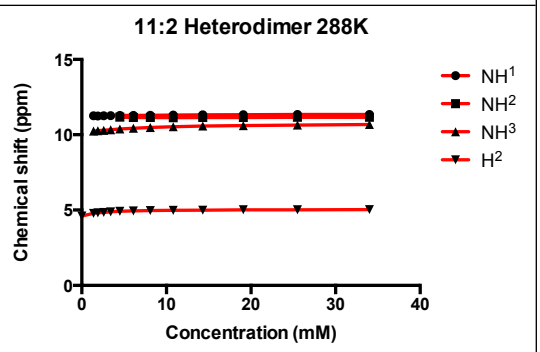


K_{DIM}= 13,433 M^{-1} **sigma= 6.8**

*Broadened signal

Table 76: 11:2 Heterodimer *^{1}H NMR titration at 288 K*

[2] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)	δ H^{2} (ppm)
34.0	11.3480	11.1624	10.6768	5.0344
25.5	11.3398	11.1521	10.6471	5.0238
19.1	11.3308	11.1468	10.6117	5.0126
14.3	11.3212	11.1388	10.5754	4.9985
10.8	11.3096	11.1359	10.5307	4.9817
8.1	11.2987	11.1382	10.4837	4.9678
6.1	11.2865	11.1486	10.4321	4.9397
4.5	11.2756	11.1699	10.3816	4.9144
3.4	11.2659	-*	10.3371	4.8851
2.6	11.2501	-*	10.2983	4.8479
1.9	11.2441	-*	10.2690	4.8130
1.4	11.2534	-*	10.2485	4.7780
0	-	-*	-	4.6061

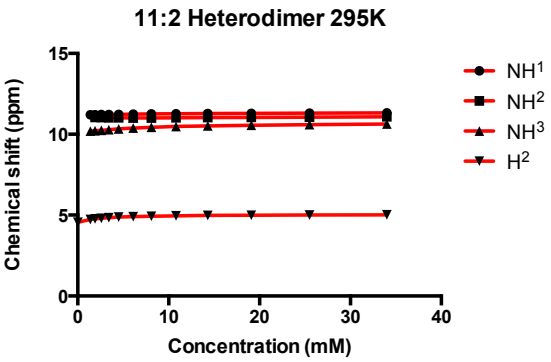


K_{DIM}= 5530 M^{-1} **sigma=6.8**

*Broadened signal

Table 77: 11:2 Heterodimer *^{1}H NMR titration at 295 K*

[2] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)	δ H^{2} (ppm)
34.0	11.3163	11.0776	10.6315	5.0225
25.5	11.3051	11.0557	10.5961	5.0086
19.1	11.2947	11.0388	10.5580	4.9935
14.3	11.2837	11.0262	10.5195	4.9771
10.8	11.2718	11.0153	10.4756	4.9573
8.1	11.2590	11.0073	10.4265	4.9370
6.1	11.2462	11.0068	10.3763	4.9078
4.5	11.2342	11.0128	10.3280	4.8803
3.4	11.2247	11.0240	10.2865	4.8431
2.6	11.2156	11.0342	10.2494	4.8056
1.9	11.2088	11.0460	10.2207	4.7686
1.4	11.2042	-*	10.1996	4.7322
0	-	-	-	4.5531

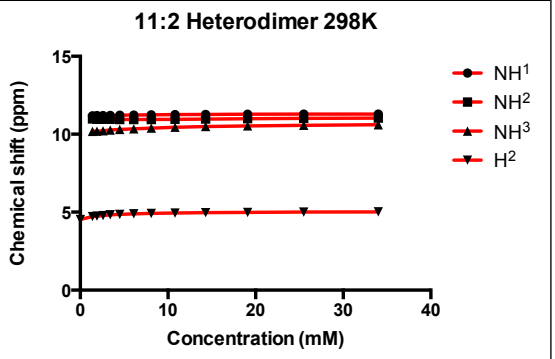


K_{DIM}= 3182 M^{-1} **sigma= 10.3**

*Broadened signal

Table 78: 11:2 Heterodimer *^{1}H NMR titration at 298 K*

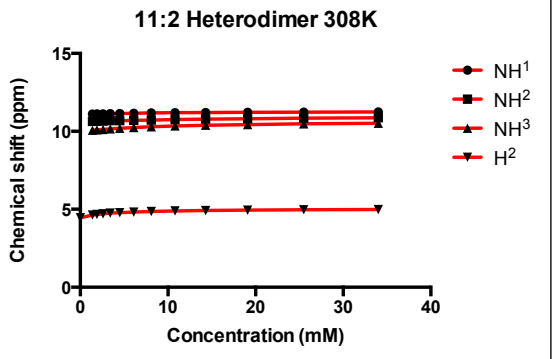
[2] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)	δ H^2 (ppm)
34.0	11.2993	11.0313	10.6061	5.0148
25.5	11.2904	11.0131	10.5737	5.0016
19.1	11.2790	10.9953	10.5344	4.9847
14.3	11.2673	10.9739	10.4931	4.9669
10.8	11.2542	10.9606	10.4477	4.9439
8.1	11.2407	10.9464	10.3991	4.9226
6.1	11.2277	10.9428	10.3497	4.8890
4.5	11.2154	10.9434	10.3018	4.8584
3.4	11.2063	10.9536	10.2626	4.8255
2.6	11.1963	10.9530	10.2245	4.7867
1.9	11.1892	10.9606	10.1959	4.7494
1.4	11.1847	10.9802	10.1751	4.7178
0	-	-	-	4.5326



K_{DIM}= 2095 M^{-1} **sigma= 13.3**

Table 79: 11:2 Heterodimer *^{1}H NMR titration at 308 K*

[2] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)	δ H^2 (ppm)
34.0	11.2425	10.8723	10.5181	4.9845
25.5	11.2305	10.8416	10.4798	4.9652
19.1	11.2171	10.8094	10.4356	4.9431
14.3	11.2046	10.7834	10.3942	4.9197
10.8	11.1894	10.7509	10.3449	4.8910
8.1	11.1754	10.7235	10.2959	4.8594
6.1	11.1606	10.7014	10.2458	4.8246
4.5	11.1470	10.6834	10.1990	4.7854
3.4	11.1368	10.6752	10.1608	4.7522
2.6	11.1243	10.6502	10.1200	4.7080
1.9	11.1154	10.6386	10.0893	4.6705
1.4	11.1087	10.6361	10.0648	4.6362
0	-	-	-	4.4581



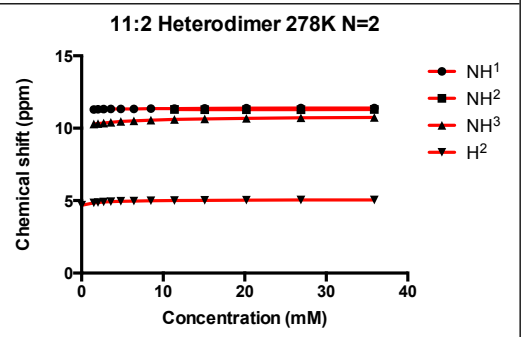
K_{DIM}= 1178 M^{-1} **sigma=6.9**

2.5.2. 11:2 Heterodimer ^{1}H NMR Titration Experiment 2

Peptide concentration: 3.1 mM

Table 80: 11:2 Heterodimer *^{1}H NMR titration at 278 K*

[2] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)	δ H^{2} (ppm)
35.9	11.3964	11.2951	10.7453	5.0465
26.9	11.3881	11.2854	10.7166	5.0386
20.2	11.3807	11.2817	10.6863	5.0312
15.1	11.3721	11.2837	10.6492	5.0207
11.4	11.3612	11.2936	10.6031	5.0087
8.5	11.3517	-*	10.5603	4.9938
6.4	11.3345	-*	10.5124	4.9739
4.8	11.3305	-*	10.4680	4.9580
3.6	11.3255	-*	10.4121	4.9323
2.7	11.3170	-*	10.3535	4.9040
2.0	11.3106	-*	10.3194	4.8718
1.5	11.2973	-*	10.2963	4.8413
0	-	-*	-	4.6830

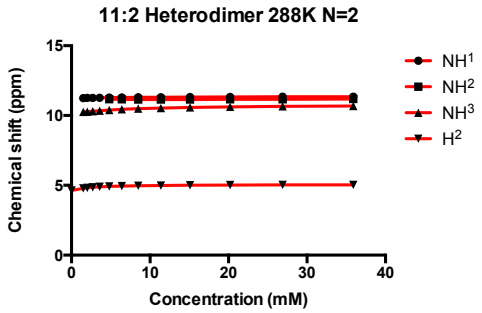


K_{DIM}= 9, 679 M^{-1} **sigma= 4.5**

*Broadened signal

Table 81: 11:2 Heterodimer *^{1}H NMR titration at 288 K*

[2] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)	δ H^{2} (ppm)
35.9	11.3490	11.1750	10.6814	5.0343
26.9	11.3415	11.1566	10.6521	5.0251
20.2	11.3335	11.1549	10.6204	5.0153
15.1	11.3229	11.1436	10.5812	5.0008
11.4	11.3109	11.1412	10.5355	4.9835
8.5	11.3002	11.1406	10.4923	4.9657
6.4	11.2879	11.1523	10.4392	4.9434
4.8	11.2777	11.1687	10.3920	4.9178
3.6	11.2684	-*	10.3442	4.8914
2.7**	11.2594	-*	10.3075	4.8562
2.0**	11.2517	-*	10.2724	4.8192
1.5**	11.2465	-*	10.2528	4.7862
0	-	-	-	4.6363



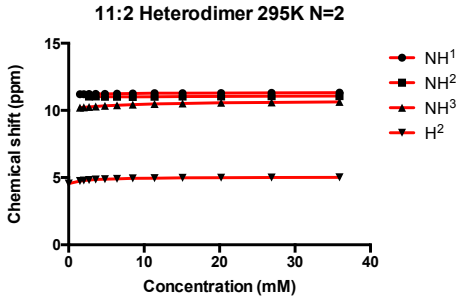
K_{DIM}= 5346 M^{-1} **sigma= 3.6**

*Obscured by another proton signal

**Outlier not included in K_{Het} determination

Table 82: 11:2 Heterodimer *^{1}H NMR titration at 295 K*

[2] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)	δ H^2 (ppm)
35.9	11.3139	11.0727	10.6310	5.0211
26.9	11.3056	11.0582	10.5996	5.0095
20.2	11.2970	11.0455	10.5665	4.9972
15.1	11.2849	11.0303	10.5246	4.9790
11.4	11.2772	11.0201	10.4787	4.9593
8.5	11.2606	11.0105	10.4347	4.9380
6.4	11.2484	11.0136	10.3843	4.9100
4.8	11.2370	11.0175	10.3383	4.8835
3.6	11.2280	11.0388	10.2954	4.8530
2.7	11.2182	11.0342	10.2588	4.8166
2.0	11.2123	-*	10.2278	4.7778
1.5	11.2076	-*	10.2079	4.7421
0	-	-	-	4.5564

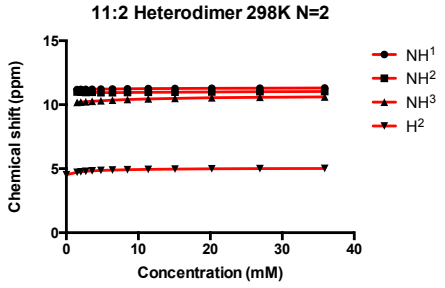


K_{DIM}= 3351 M^{-1} sigma= 12.4

*Broadened signal

Table 83: 11:2 Heterodimer *^{1}H NMR titration at 298 K*

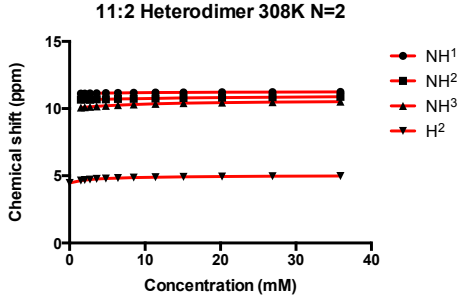
[2] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)	δ H^2 (ppm)
35.9	11.3002	11.0343	10.6105	5.0156
26.9	11.2901	11.0151	10.5764	5.0017
20.2	11.2805	10.9979	10.5414	4.9878
15.1	11.2689	10.9801	10.4999	4.9688
11.4	11.2557	10.9695	10.4532	4.9480
8.5	11.2435	10.9525	10.4087	4.9242
6.4	11.2297	10.9482	10.3572	4.8962
4.8	11.2182	10.9481	10.3119	4.8666
3.6	11.2092	10.9662	10.2707	4.8351
2.7	11.1992	10.9552	10.2339	4.7953
2.0	11.1927	10.9860	10.2034	4.7597
1.5	11.1872	10.9932	10.1821	4.7222
0	-	-	-	4.5300



K_{DIM}= 2218 M^{-1} sigma= 14.0

Table 84: 11:2 Heterodimer *^{1}H NMR titration at 308 K*

[2] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)	δ H^2 (ppm)
35.9	11.2428	10.8763	10.5224	4.9856
26.9	11.2323	10.8488	10.4857	4.9680
20.2	11.2208	10.8206	10.4466	4.9487
15.1	11.2065	10.7890	10.4009	4.9238
11.4	11.1918	10.7617	10.3520	4.8966
8.5	11.1776	10.7321	10.3052	4.8658
6.4	11.1636	10.7126	10.2551	4.8323
4.8	11.1506	10.6935	10.2098	4.7964
3.6	11.1415	10.6967	10.1724	4.7659
2.7	11.1282	10.6614	10.1312	4.7206
2.0	11.1225	10.6809	10.1042	4.6844
1.5	11.1142	10.6663	10.0776	4.6468
0	-	-	-	4.4740



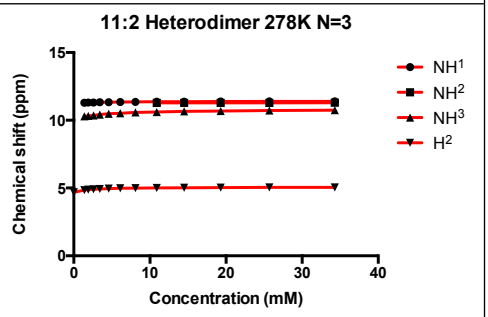
K_{DIM}= 1205 M^{-1} **sigma= 7.9**

2.5.3. 11:2 Heterodimer ^{1}H NMR Titration Experiment 3

Peptide concentration: 3.2 mM

Table 85: 11:2 Heterodimer *^{1}H NMR titration at 278 K*

[2] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)	δ H^2 (ppm)
34.3	11.3982	11.2954	10.7459	5.0475
25.7	11.3904	11.2873	10.7184	5.0407
19.3	11.3813	11.2821	10.6851	5.0314
14.5	11.3730	11.2811	10.6516	5.0211
10.9	11.3632	11.2869	10.6056	5.0055
8.1	11.3557	-*	10.5779	4.9919
6.1	11.3448	-*	10.5237	4.9782
4.6	11.3319	-*	10.4781	4.9575
3.4	11.3265	-*	10.4155	4.9356
2.6**	11.3102	-*	10.3624	4.9062
1.9**	11.3044	-***	10.3233	4.8759
1.4**	11.2979	-***	10.2948	4.8406
0	-	-	-	4.6766



K_{DIM}= 11,876 M^{-1} **sigma= 8.23**

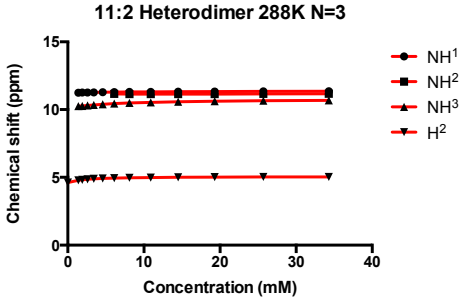
*Obscured by another proton signal

** Outlier not included in K_{Het} determination

***Broadened signal

Table 86: 11:2 Heterodimer *^{1}H NMR titration at 288 K*

[2] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)	δ H^2 (ppm)
34.3	11.3506	11.1715	10.6815	5.0357
25.7	11.3421	11.1574	10.6519	5.0255
19.3	11.3334	11.1499	10.6180	5.0141
14.5	11.3239	11.1403	10.5829	5.0010
10.9	11.3112	11.1427	10.5331	4.9846
8.1	11.3012	11.1424	10.4903	4.9685
6.1	11.2897	11.1515	10.4418	4.9443
4.6	11.2782	-*	10.3895	4.9163
3.4	11.2687	-*	10.3464	4.8893
2.6	11.2599	-**	10.3040	4.8565
1.9	11.2528	-**	10.2742	4.8206
1.4	11.2469	-**	10.2511	4.7836
0	-	-	-	4.6197



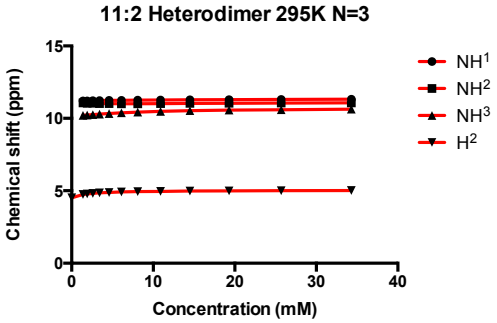
K_{DIM}= 5675 M^{-1} **sigma= 13.5**

*Broadened signal

**Obscured by another proton signal

Table 87: 11:2 Heterodimer *^{1}H NMR titration at 295 K*

[2] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)	δ H^2 (ppm)
34.3	11.3153	11.0736	10.6307	5.0224
25.7	11.3061	11.0553	10.5991	5.0101
19.3	11.2964	11.0429	10.5632	4.9959
14.5	11.2857	11.0321	10.5258	4.9790
10.9	11.2724	11.0220	10.4762	4.9598
8.1	11.2615	11.0124	10.4332	4.9390
6.1	11.2491	11.0099	10.3854	4.9149
4.6	11.2375	11.0165	10.3372	4.8827
3.4	11.2271	11.0224	10.2948	4.8503
2.6	11.2185	11.0412	10.2562	4.8133
1.9*	11.2114	11.0487	10.2273	4.7775
1.4*	11.2065	11.0712	10.2046	4.7393
0	-	-	-	4.5186

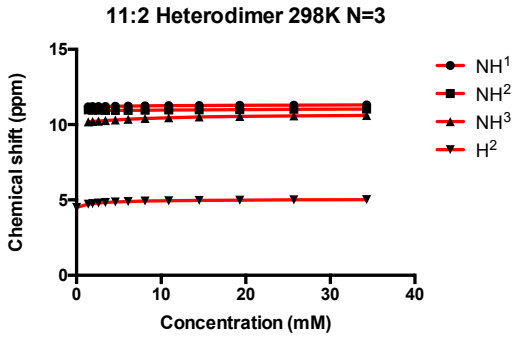


K_{DIM}= 4170 M^{-1} **sigma= 9.6**

*Outlier not included in K_{Het} determination

Table 88: 11:2 Heterodimer *^{1}H NMR titration at 298 K*

[2] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)	δ H^2 (ppm)
34.3	11.3003	11.0332	10.6086	5.0156
25.7	11.2913	11.0148	10.5762	5.0027
19.3	11.2799	10.9943	10.5380	4.9866
14.5	11.2696	10.9759	10.5007	4.9689
10.9	11.2557	10.9668	10.4504	4.9395
8.1	11.2433	10.9529	10.4062	4.9253
6.1	11.2302	10.9449	10.3580	4.8979
4.6	11.2185	10.9462	10.3106	4.8677
3.4	11.2077	10.9467	10.2688	4.8301
2.6*	11.1989	10.9587	10.2309	4.7930
1.9*	11.1913	10.9613	10.2016	4.7556
1.4*	11.1869	10.9799	10.1794	4.7183
0	-	-	-	4.5004

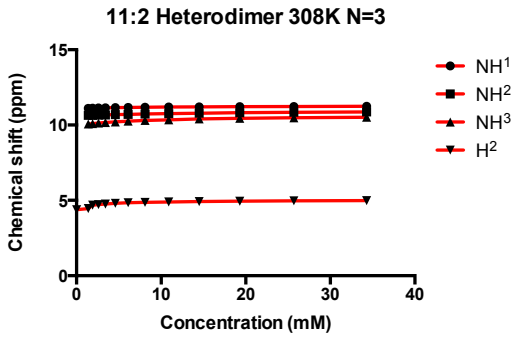


K_{DIM}= 2552 M^{-1} **sigma= 7.9**

*Outlier not included in K_{Het} determination

Table 89: 11:2 Heterodimer *^{1}H NMR titration at 308 K*

[2] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)	δ H^2 (ppm)
34.3	11.2433	10.8741	10.5204	4.9856
25.7	11.2330	10.8465	10.4846	4.9686
19.3	11.2198	10.8154	10.4424	4.9463
14.5	11.2069	10.7840	10.4007	4.9220
10.9	11.1912	10.7580	10.3483	4.8949
8.1	11.1777	10.7314	10.3024	4.8716
6.1	11.1639	10.7067	10.2550	4.8377
4.6	11.1503	10.6883	10.2077	4.8013
3.4	11.1385	10.6708	10.1663	4.7582
2.6	11.1279	10.6618	10.1284	4.7173
1.9*	11.1186	10.6461	10.0969	4.6802
1.4*	11.1117	10.6449	10.0714	4.4623
0	-	-	-	4.3857



K_{DIM}= 1818 M^{-1} **sigma= 10.0**

*Outlier not included in K_{Het} determination

2.5.4. 11:2 Heterodimer VT ^{1}H NMR Summary and Van't Hoff Plots

Table 90*: Summary of 11:2 Heterodimer Experiment 1 and Van't Hoff Plot*

Temp (K)	K_{Het} (M^{-1})	1/T	lnK
278	13,433	0.003597122	9.505469645
288	5530	0.003472222	8.617943095
295	3182	0.003389831	8.065265209
298	2095	0.003355705	7.647308832
308	1178	0.003246753	7.071573364

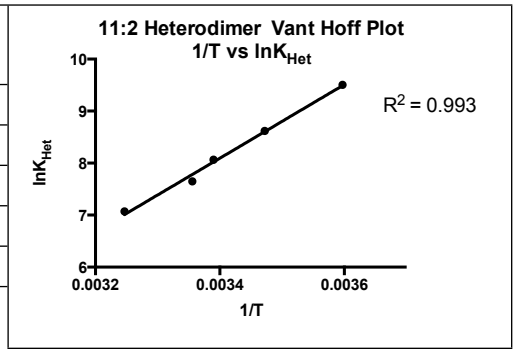


Table 91*: Summary of 11:2 Heterodimer Experiment 2 and Van't Hoff Plot*

Temp (K)	K_{Het} (M^{-1})	1/T	lnK
278	9,679	0.003597122	9.177713869
288	5,346	0.003472222	8.584103897
295	3351	0.003389831	8.117014088
298	2218	0.003355705	7.704361168
308	1205	0.003246753	7.094234846

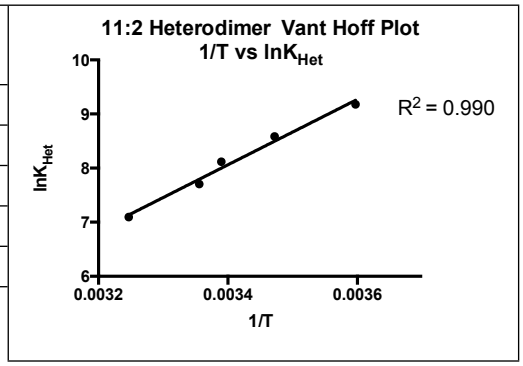


Table 92*: Summary of 11:2 Heterodimer Experiment 3 and Van't Hoff Plot*

Temp (K)	K_{Het} (M^{-1})	1/T	lnK
278	11,876	0.003597122	9.382274836
288	5,675	0.003472222	8.643825842
295	4170	0.003389831	8.335671315
298	2552	0.003355705	7.844632644
308	1818	0.003246753	7.505492275

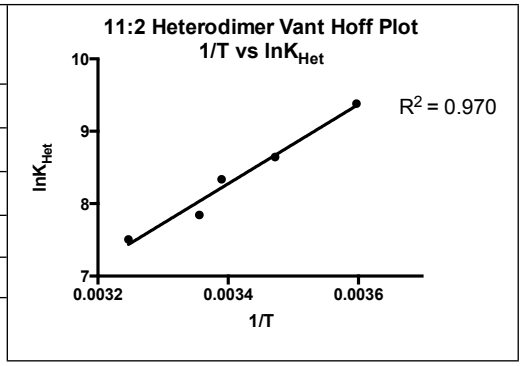


Table 93: *Summary of thermodynamic parameters for 11:2 heterodimer*

Expt	ΔH (kcal mol^{-1})	$-T\Delta S^{295\ K}$ (kcal mol^{-1})	ΔG (kcal mol^{-1})
N1	-14.0	9.3	- 4.7
N2	-12.0	7.3	- 4.7
N3	-11.6	6.1	- 5.5
Average	**-12.5**	**7.6**	**- 5.0**

2.6. 11:2a Heterodimer VT ^{1}H NMR Titration Experiment

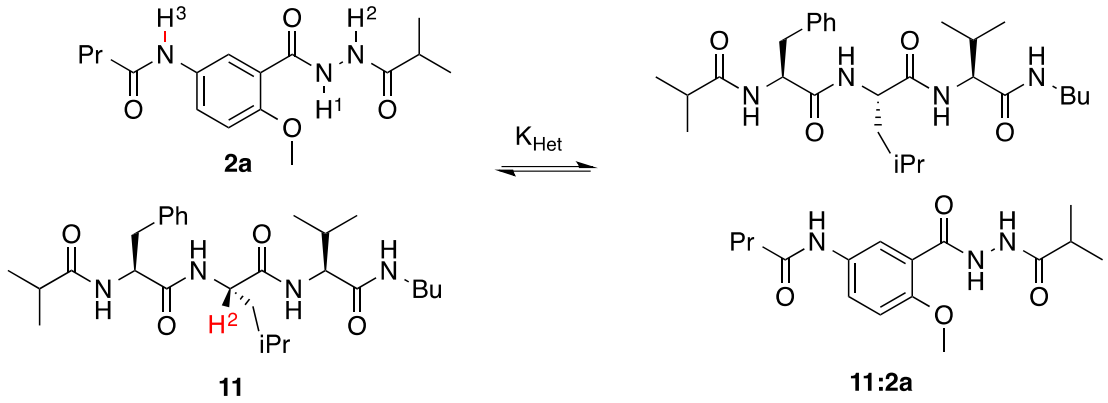


Figure 7: *Heterodimerisation of 2a and 11. Resonances used to determine binding constants are highlighted in red.*

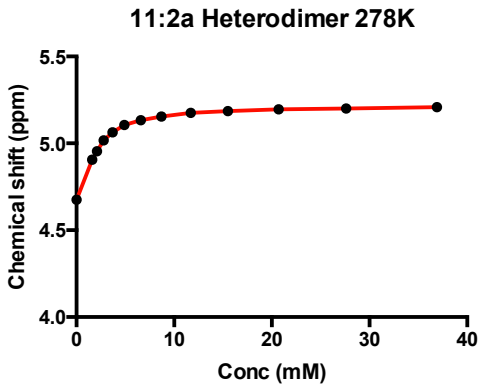
N.B. K_{Het} was calculated on using H^2 only. Shifts of NH signals in **2a** were broad and therefore not included in K_{Het} calculation.

2.6.1. 11:2a Heterodimer ^{1}H NMR Titration Experiment 1

Peptide concentration: 3.1 mM

Table 94: 11:2a Heterodimer *^{1}H NMR titration at 278 K*

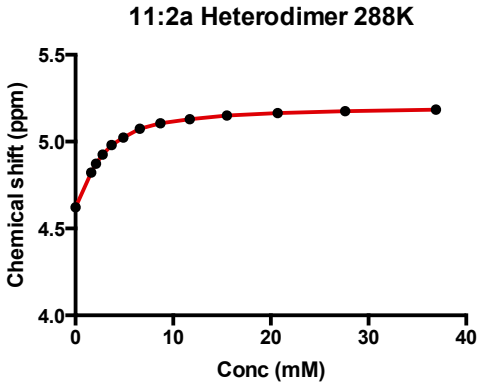
[2a] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)	δ H^2 (ppm)
36.9	-	-	-	5.2081
27.6	-	-	-	5.2011
20.7	-	-	-	5.1957
15.5	-	-	-	5.1860
11.7	-	-	-	5.1758
8.7	-	-	-	5.1540
6.6	-	-	-	5.1336
4.9	-	-	-	5.1053
3.7	-	-	-	5.0630
2.8	-	-	-	5.0170
2.1	-	-	-	4.9541
1.6	-	-	-	4.9054
0	-	-	-	4.6751



K$_{Het}$ = 5923 M^{-1} **sigma= 22.09**

Table 95: 11:2a Heterodimer *^{1}H NMR titration at 288 K*

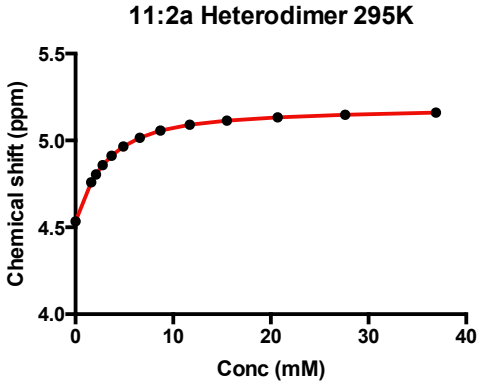
[2a] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)	δ H^{2} (ppm)
36.9	-	-	-	5.1845
27.6	-	-	-	5.1750
20.7	-	-	-	5.1638
15.5	-	-	-	5.1502
11.7	-	-	-	5.1294
8.7	-	-	-	5.1060
6.6	-	-	-	5.0740
4.9	-	-	-	5.0236
3.7	-	-	-	4.9808
2.8	-	-	-	4.9262
2.1	-	-	-	4.8732
1.6	-	-	-	4.8221
0	-	-	-	4.6221



K_{Het} = 2357 M^{-1} **sigma= 16.5**

Table 96: 11:2a Heterodimer *^{1}H NMR titration at 295 K*

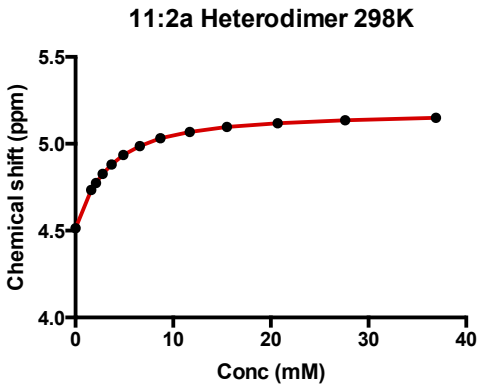
[2a] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)	δ H^{2} (ppm)
36.9	-	-	-	5.1609
27.6	-	-	-	5.1479
20.7	-	-	-	5.1335
15.5	-	-	-	5.1141
11.7	-	-	-	5.0901
8.7	-	-	-	5.0570
6.6	-	-	-	5.0160
4.9	-	-	-	4.9654
3.7	-	-	-	4.9115
2.8	-	-	-	4.8575
2.1	-	-	-	4.8050
1.6	-	-	-	4.7594
0	-	-	-	4.5339



K_{Het} = 1504 M^{-1} **sigma= 19.0**

Table 97: 11:2a Heterodimer *^{1}H NMR titration at 298 K*

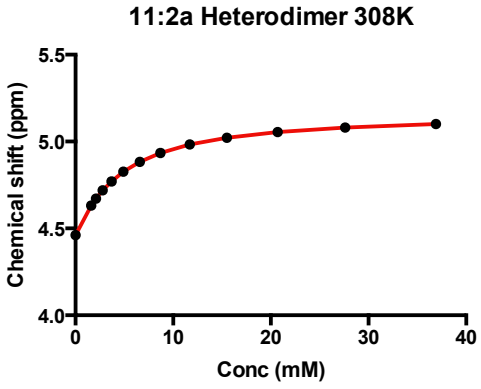
[2a] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)	δ H^{2} (ppm)
36.9	-	-	-	5.1493
27.6	-	-	-	5.1362
20.7	-	-	-	5.1186
15.5	-	-	-	5.0966
11.7	-	-	-	5.0684
8.7	-	-	-	5.0317
6.6	-	-	-	4.9870
4.9	-	-	-	4.9358
3.7	-	-	-	4.8804
2.8	-	-	-	4.8269
2.1	-	-	-	4.7747
1.6	-	-	-	4.7340
0	-	-	-	4.5138



K_{Het} = 1099 M^{-1} **sigma= 16.9**

Table 98: 11:2a Heterodimer *^{1}H NMR titration at 308 K*

[2a] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)	δ H^{2} (ppm)
36.9	-	-	-	5.1004
27.6	-	-	-	5.0808
20.7	-	-	-	5.0549
15.5	-	-	-	5.0223
11.7	-	-	-	4.9831
8.7	-	-	-	4.9344
6.6	-	-	-	4.8831
4.9	-	-	-	4.8267
3.7	-	-	-	4.7706
2.8	-	-	-	4.7191
2.1	-	-	-	4.6724
1.6	-	-	-	4.6317
0	-	-	-	4.4614



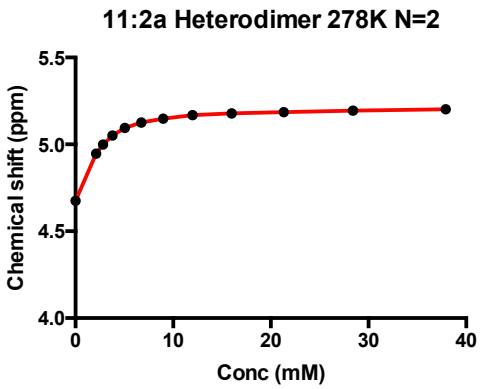
K_{Het} = 537 M^{-1} **sigma= 10.1**

2.6.2. 11:2a Heterodimer ^{1}H NMR Titration Experiment 2

Peptide concentration: 3.1 mM

Table 99: 11:2a Heterodimer *^{1}H NMR titration at 278 K N=2*

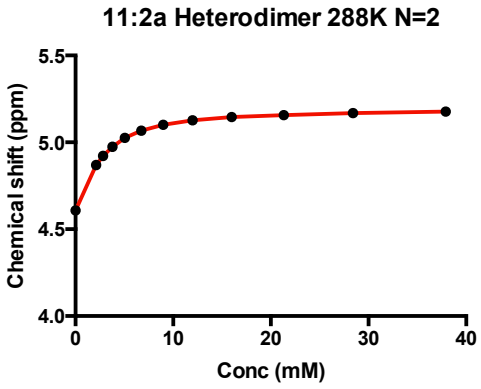
[2a] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)	δ H^{2} (ppm)
37.9	-	-	-	5.2013
28.4	-	-	-	5.1948
21.3	-	-	-	5.1856
16.0	-	-	-	5.1779
12.0	-	-	-	5.1679
9.0	-	-	-	5.1483
6.7	-	-	-	5.1253
5.1	-	-	-	5.0938
3.8	-	-	-	5.0507
2.8	-	-	-	4.9994
2.1	-	-	-	4.9474
0	-	-	-	4.6754



K_{Het} = 4735 M^{-1} **sigma= 18.0**

Table 100: 11:2a Heterodimer *^{1}H NMR titration at 288 K N=2*

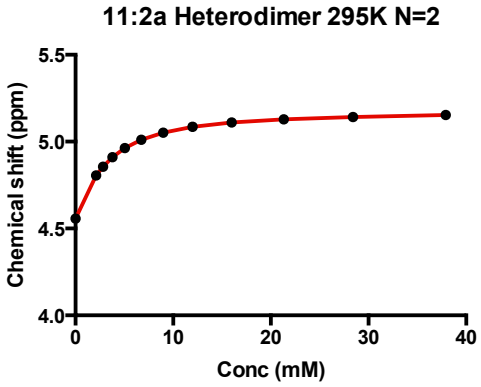
[2a] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)	δ H^{2} (ppm)
37.9	-	-	-	5.1768
28.4	-	-	-	5.1677
21.3	-	-	-	5.1571
16.0	-	-	-	5.1453
12.0	-	-	-	5.1265
9.0	-	-	-	5.1012
6.7	-	-	-	5.0672
5.1	-	-	-	5.0255
3.8	-	-	-	4.9740
2.8	-	-	-	4.9222
2.1	-	-	-	4.8690
0	-	-	-	4.6082



K_{Het} = 2329 M^{-1} **sigma= 16.1**

Table 101: 11:2a Heterodimer *^{1}H NMR titration at 295 K N=2*

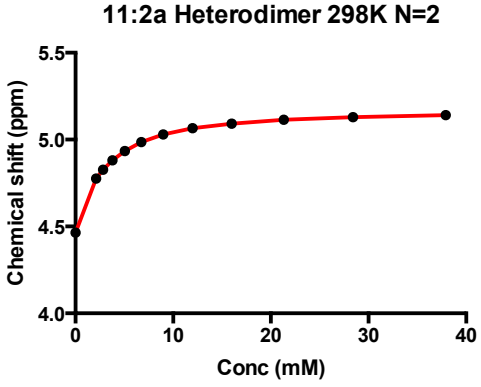
[2a] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)	δ H^{2} (ppm)
37.9	-	-	-	5.1534
28.4	-	-	-	5.1425
21.3	-	-	-	5.1277
16.0	-	-	-	5.1100
12.0	-	-	-	5.0858
9.0	-	-	-	5.0521
6.7	-	-	-	5.0103
5.1	-	-	-	4.9636
3.8	-	-	-	4.9101
2.8	-	-	-	4.8558
2.1	-	-	-	4.8054
0	-	-	-	4.5564



K_{Het} = 1361 M^{-1} **sigma= 14.7**

Table 102: 11:2a Heterodimer *^{1}H NMR titration at 298 K N=2*

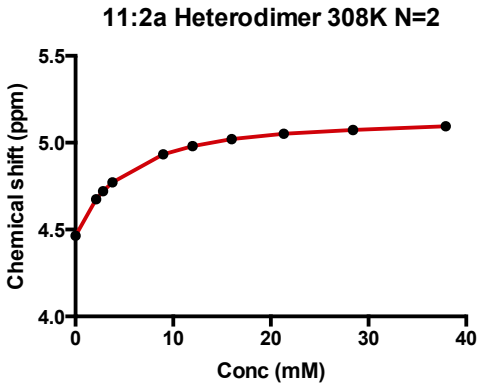
[2a] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)	δ H^{2} (ppm)
37.9	-	-	-	5.1412
28.4	-	-	-	5.1296
21.3	-	-	-	5.1139
16.0	-	-	-	5.0919
12.0	-	-	-	5.0653
9.0	-	-	-	5.0291
6.7	-	-	-	4.9852
5.1	-	-	-	4.9350
3.8	-	-	-	4.8803
2.8	-	-	-	4.8273
2.1	-	-	-	4.7750
0	-	-	-	4.4646



K_{Het} = 1240 M^{-1} **sigma= 20.3**

Table 103: 11:2a Heterodimer *^{1}H NMR titration at 308 K N=2*

[2a] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)	δ H^{2} (ppm)
37.9	-	-	-	5.0949
28.4	-	-	-	5.0737
21.3	-	-	-	5.0516
16.0	-	-	-	5.0208
12.0	-	-	-	4.9812
9.0	-	-	-	4.9333
6.7	-	-	-	-*
5.1	-	-	-	-*
3.8	-	-	-	4.7716
2.8	-	-	-	4.7205
2.1	-	-	-	4.6742
0	-	-	-	4.4646



K_{Het} = 565 M^{-1} **sigma= 11.0**

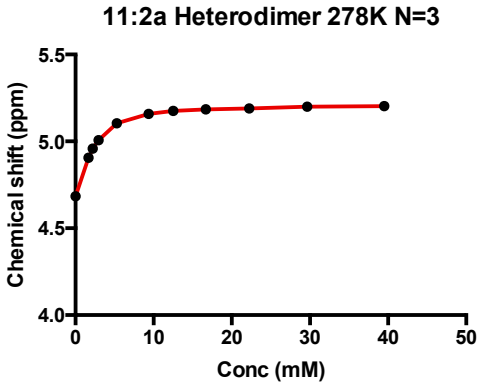
***Broadened signal**

2.6.3. 11:2a Heterodimer ^{1}H NMR Titration Experiment 3

Peptide concentration: 3.3 mM

Table 104: 11:2a Heterodimer *^{1}H NMR titration at 278 K N=3*

[2a] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)	δ H^{2} (ppm)
39.52	-	-	-	5.2035
29.64	-	-	-	5.1996
22.23	-	-	-	5.1894
16.67	-	-	-	5.1846
12.50	-	-	-	5.1754
9.37	-	-	-	5.1579
7.03	-	-	-	-*
5.28	-	-	-	5.1044
3.96	-	-	-	-*
2.96	-	-	-	5.0071
2.2	-	-	-	4.9586
1.67	-	-	-	4.9062
0	-	-	-	4.6840

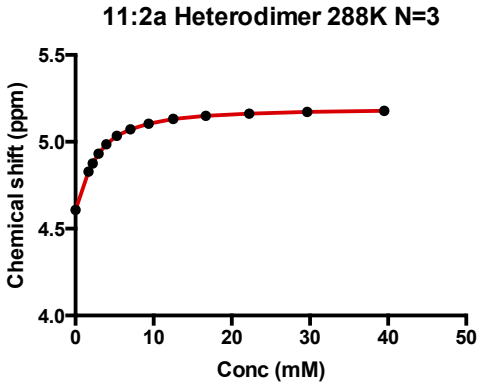


K_{Het} = 5721 M^{-1} **sigma=21.6**

*Broadened signal

Table 105: 11:2a Heterodimer *^{1}H NMR titration at 288 K N=3*

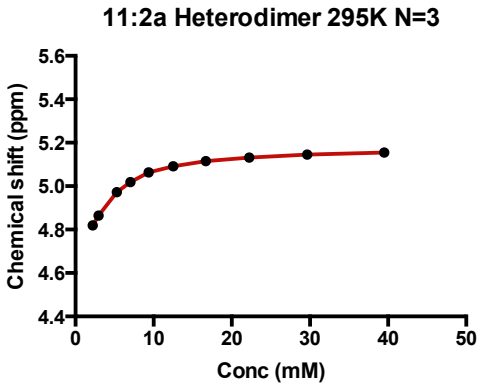
[2a] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)	δ H^{2} (ppm)
39.52	-	-	-	5.1780
29.64	-	-	-	5.1716
22.23	-	-	-	5.1619
16.67	-	-	-	5.1495
12.50	-	-	-	5.1322
9.37	-	-	-	5.1046
7.03	-	-	-	5.0723
5.28	-	-	-	5.0349
3.96	-	-	-	4.9855
2.96	-	-	-	4.9317
2.2	-	-	-	4.8759
1.67	-	-	-	4.8277
0	-	-	-	4.6086



K_{Het} = 2693 M^{-1} **sigma=21.0**

Table 106: 11:2a Heterodimer *^{1}H NMR titration at 295 K N=3*

[2a] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)	δ H^{2} (ppm)
39.52	-	-	-	5.1546
29.64	-	-	-	5.1451
22.23	-	-	-	5.1317
16.67	-	-	-	5.1155
12.50	-	-	-	5.0913
9.37	-	-	-	5.0637
7.03	-	-	-	5.0186
5.28	-	-	-	4.9727
3.96	-	-	-	-*
2.96	-	-	-	4.8642
2.2	-	-	-	4.8193
1.67	-	-	-	-*
0				-*

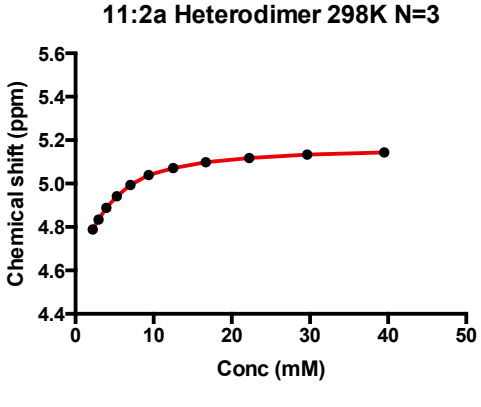


K_{Het} = 1055 M^{-1} **sigma= 1.9**

*Broadened signal

Table 107: 11:2a Heterodimer *^{1}H NMR titration at 298 K N=3*

[2a] (mM)	δ NH^{1} (ppm)	δ NH^{2} (ppm)	δ NH^{3} (ppm)	δ H^{2} (ppm)
39.52	-	-	-	5.1438
29.64	-	-	-	5.1334
22.23	-	-	-	5.1176
16.67	-	-	-	5.0984
12.50	-	-	-	5.0718
9.37	-	-	-	5.0397
7.03	-	-	-	4.9930
5.28	-	-	-	4.9416
3.96	-	-	-	4.8886
2.96	-	-	-	4.8348
2.2	-	-	-	4.7885
1.67	-	-	-	-*
0				-*

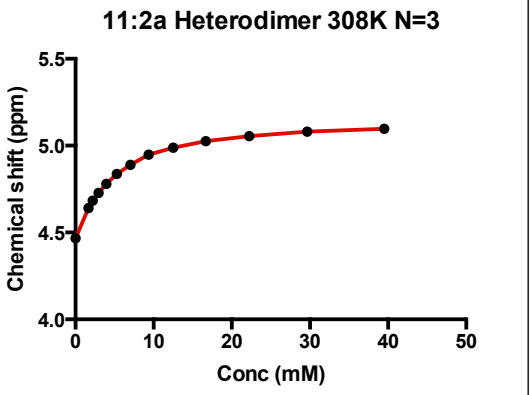


K_{Het} = 863 M^{-1} **sigma= 1.57**

*Broadened signal

Table 108: 11:2a Heterodimer *^{1}H NMR titration at 308 K N=3*

[2a] (mM)	δ NH^1 (ppm)	δ NH^2 (ppm)	δ NH^3 (ppm)	δ H^2 (ppm)
39.52	-	-	-	5.0966
29.64	-	-	-	5.0807
22.23	-	-	-	5.0548
16.67	-	-	-	5.0261
12.50	-	-	-	4.9880
9.37	-	-	-	4.9482
7.03	-	-	-	4.8893
5.28	-	-	-	4.8372
3.96	-	-	-	4.7793
2.96	-	-	-	4.7282
2.2	-	-	-	4.6837
1.67	-	-	-	4.6404
0				4.4666



K_{Het} = 574 M^{-1} **sigma= 11.7**

2.6.4. 11:2a Heterodimer VT ^{1}H NMR Summary and Van't Hoff Plots

Table 109*: Summary of 11:2a Heterodimer Experiment 1 and Van't Hoff Plot*

Temp (K)	K_{Het} (M^{-1})	1/T	lnK
278	5,923	0.003597122	8.686598356
288	2357	0.003472222	7.765144903
295	1504	0.003389831	7.315883505
298	1099	0.003355705	7.002155954
308	537	0.003246753	6.285998095

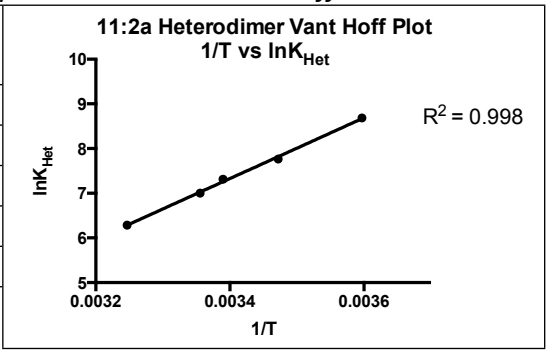


Table 110*: Summary of 11:2a Heterodimer Experiment 2 and Van't Hoff Plot*

Temp (K)	K_{Het} (M^{-1})	1/T	lnK
278	4,735	0.003597122	8.462737006
288	2329	0.003472222	7.75319427
295	1361	0.003389831	7.215975003
298	1240	0.003355705	7.122866659
308	565	0.003246753	6.336825731

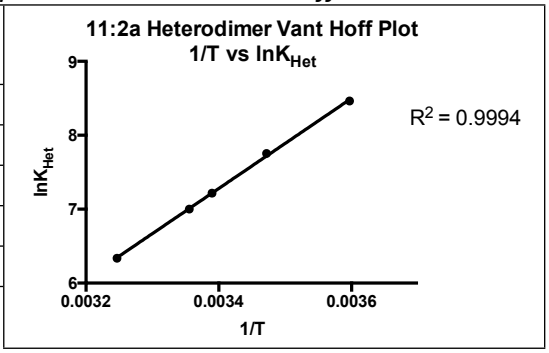


Table 111*: Summary of 11:2a Heterodimer Experiment 3 and Van't Hoff Plot*

Temp (K)	K_{Het} (M^{-1})	1/T	lnK
278	5,721	0.003597122	8.651898894
288	2693	0.003472222	7.898411093
295	1055	0.003389831	6.961296046
298	863	0.003355705	6.760414691
308	574	0.003246753	6.352629396

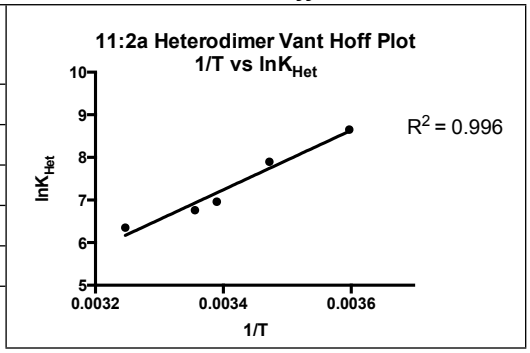
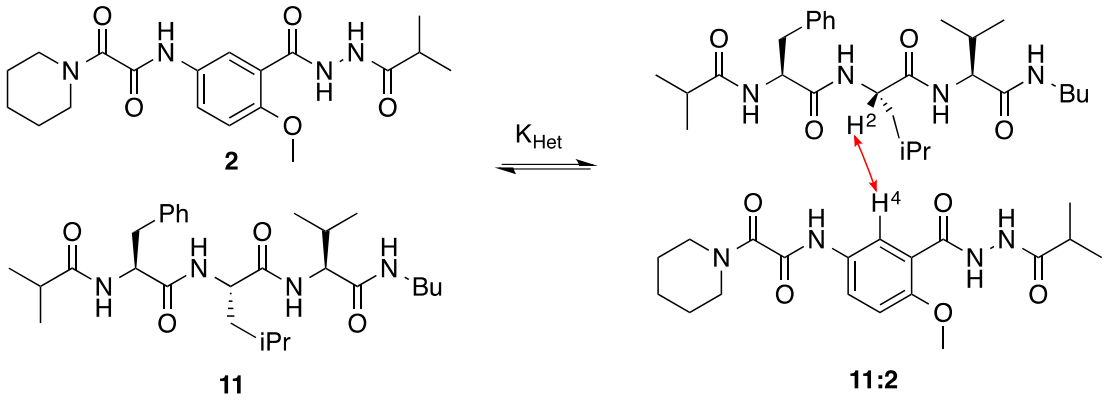
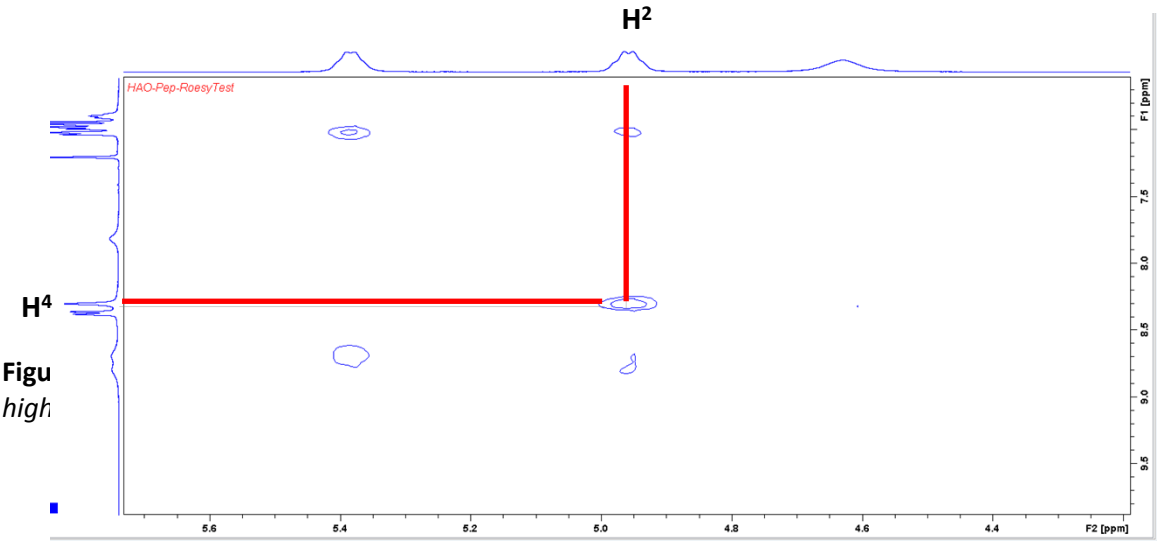


Table 112: *Summary of thermodynamic parameters for 11:2 heterodimer*

Expt	ΔH (kcal mol^{-1})	$-T\Delta S^{295\ K}$ (kcal mol^{-1})	ΔG (kcal mol^{-1})
N1	-13.5	9.3	- 4.2
N2	-11.9	7.7	- 4.2
N3	-13.9	9.7	- 4.2
Average	**-13.1**	**8.9**	**- 4.2**

2.7. ROESY Study of 2:11 Heterodimer





Figu
high

References

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(2) J. E. Thomson, C. D. Campbell, C. Concellon, N. Duguet, K. Rix, A. M. Z. Slawin, and A. D. Smith, *J. Org. Chem.*, 2008, **73,** 2784.

(3) J. S. Nowick, M.D. Chung, K. Maitra, S. Mairita, K. D. Stigers and Y. Sun, *J. Am. Chem. Soc.*, 2000, **122**, 7654.

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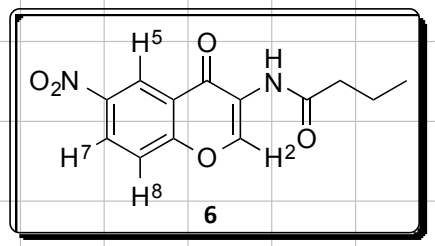
^{1}H and 13C NMR Spectra

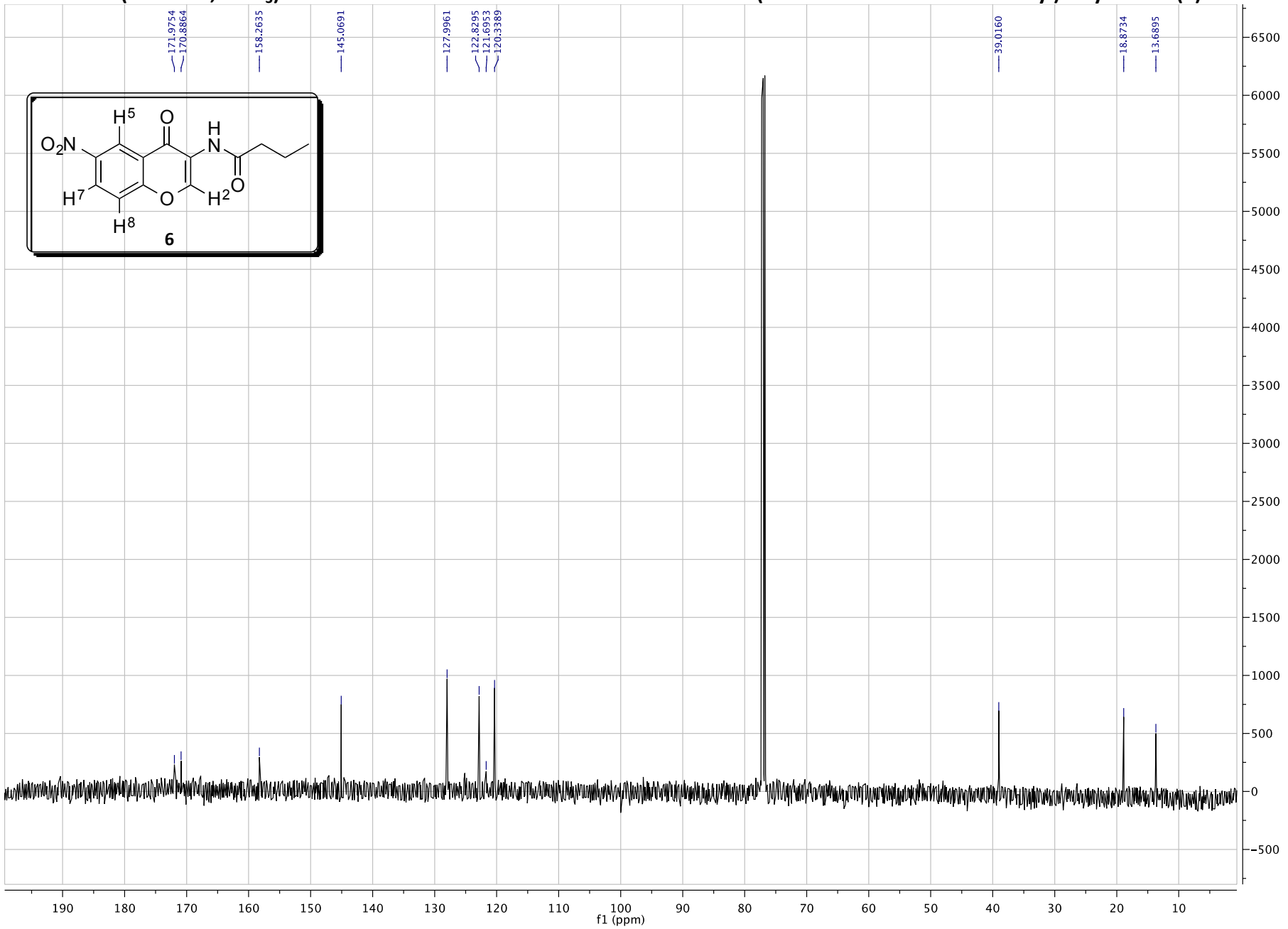
^{1}H NMR (500 MHz, $CDCl_3$)

***N*-(6-nitro-4-oxo-4*H*-chromen-3-yl)butyramide (6)**



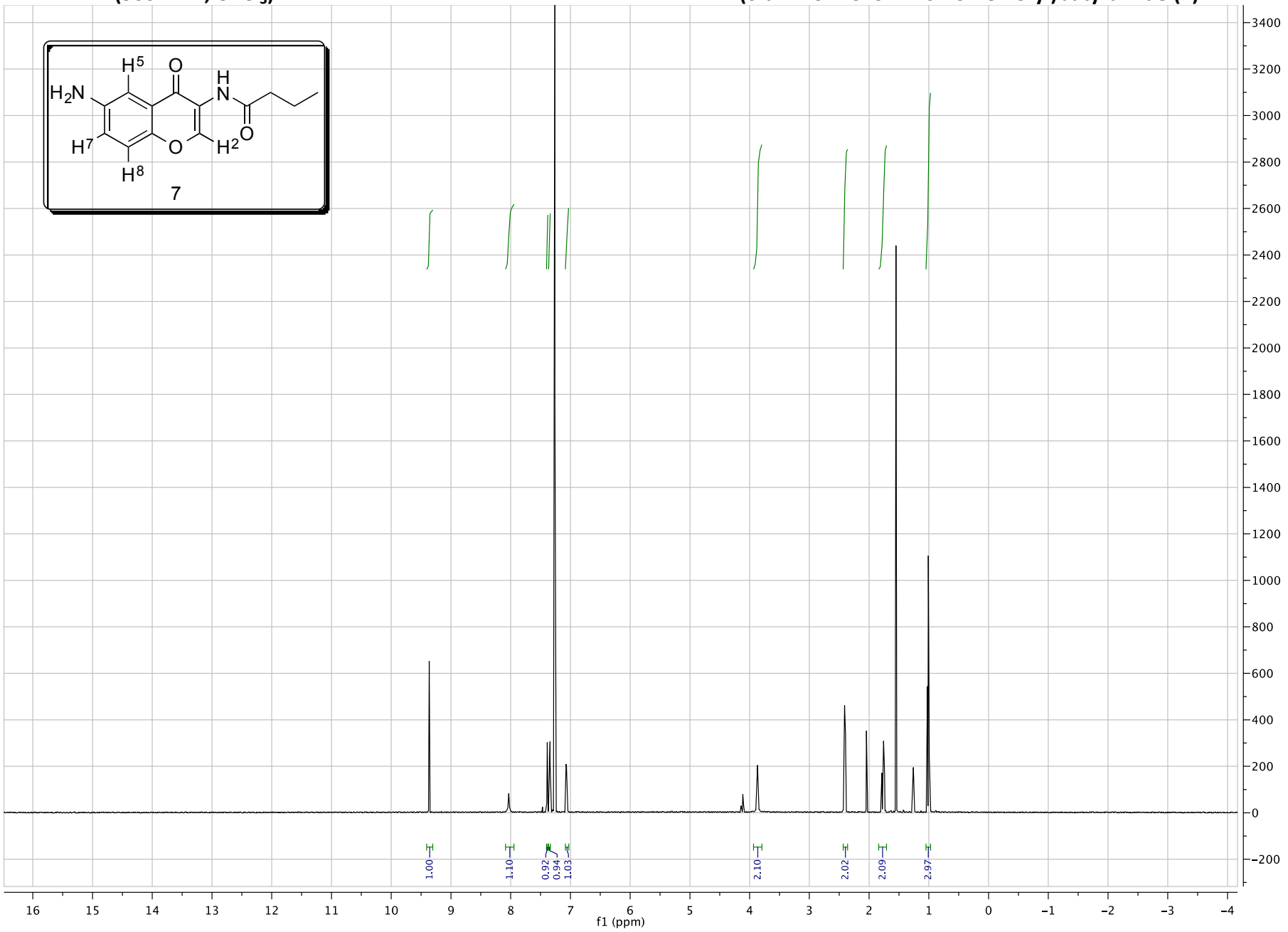
6

^{13}C NMR (126 MHz, $CDCl_3$) ***N*-(6-nitro-4-oxo-4*H*-chromen-3-yl)butyramide (6)**



^{1}H NMR (500 MHz, $CDCl_3$)

***N*-(6-amino-4-oxo-4*H*-chromen-3-yl)butyramide (7)**

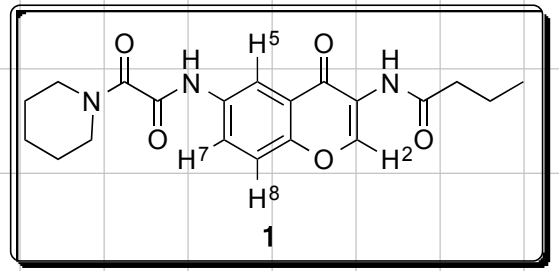


^{13}C NMR (126 MHz, $CDCl_3$)

***N*-(6-amino-4-oxo-4*H*-chromen-3-yl)butyramide (7)**

^{1}H NMR (500 MHz, $CDCl_3$)

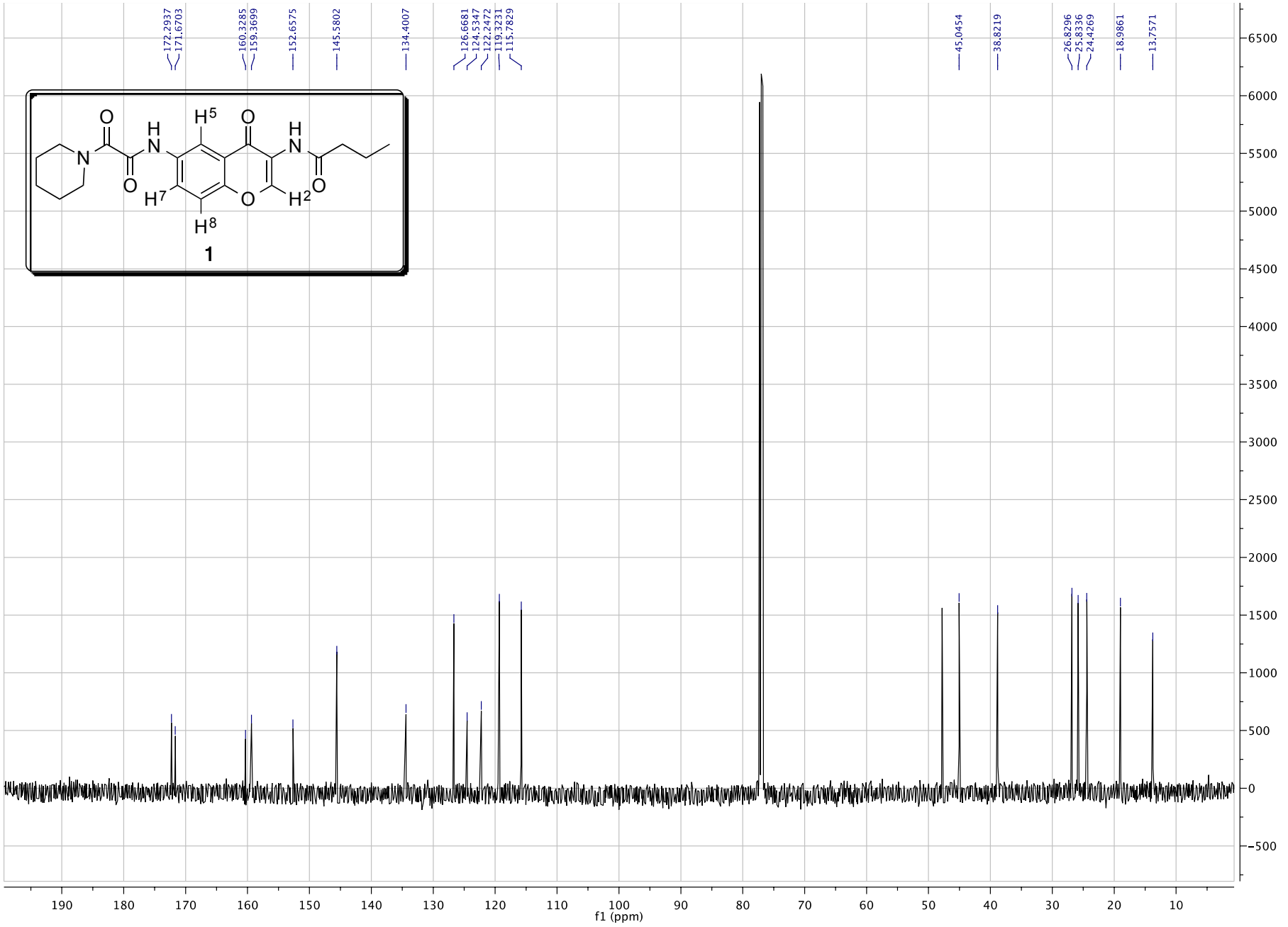
***N*-(4-oxo-6-(2-oxo-2-(piperidin-1-yl)acetamido)-4*H*-chromen-3-yl)butyramide (1)**



1

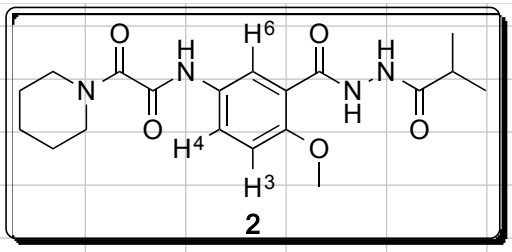
^{13}C NMR (126 MHz, $CDCl_3$)

***N*-(4-oxo-6-(2-oxo-2-(piperidin-1-yl)acetamido)-4*H*-chromen-3-yl)butyramide (1)**



^{1}H NMR (500 MHz, $CDCl_3$)

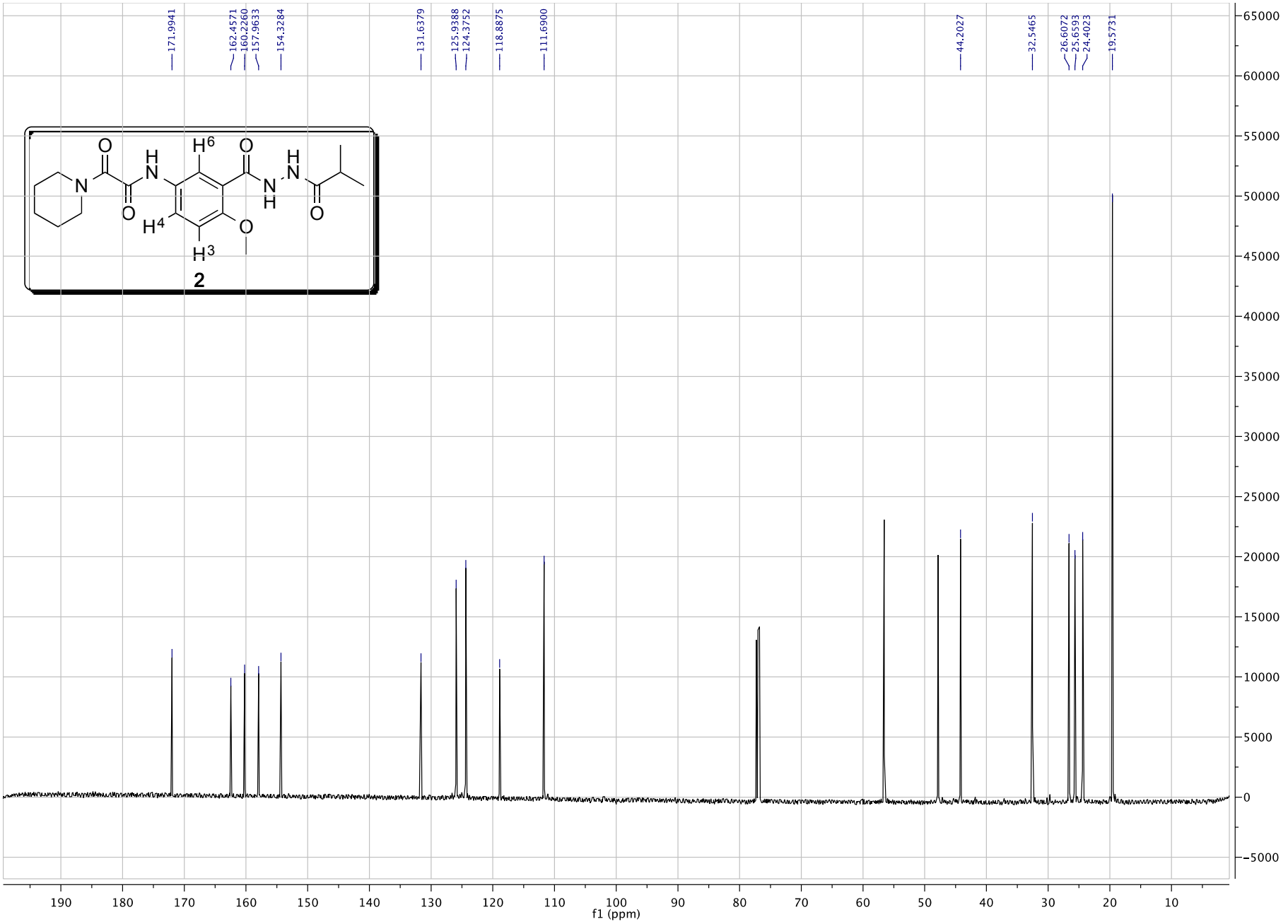
***N*-(3-(2-isobutyrylhydrazinecarbonyl)-4-methoxyphenyl)-2-oxo-2-(piperidin-1-yl)acetamide (2)**



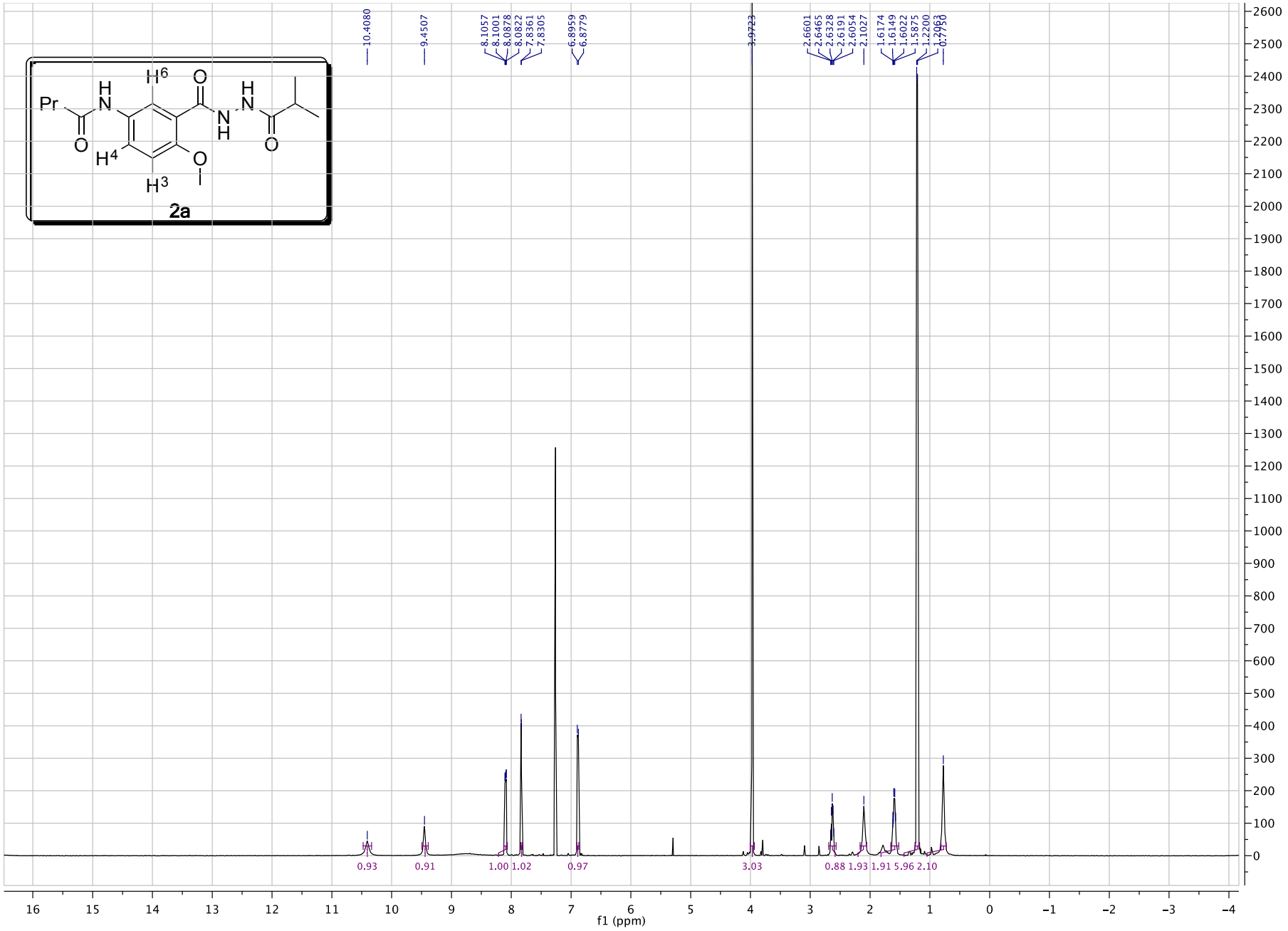
2

^{13}C NMR (126 MHz, $CDCl_3$)

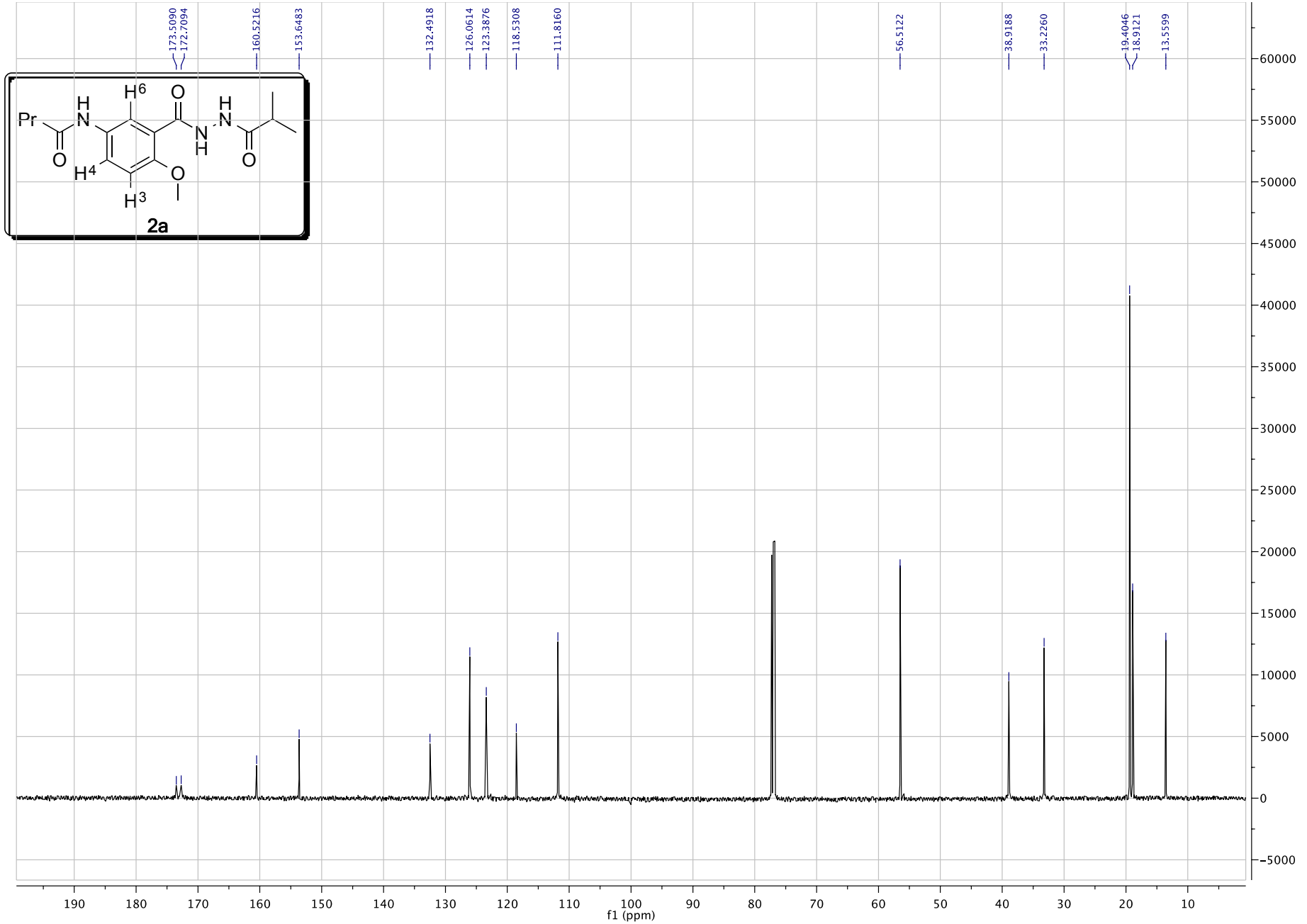
***N*-(3-(2-isobutyrylhydrazinecarbonyl)-4-methoxyphenyl)-2-oxo-2-(piperidin-1-yl)acetamide (2)**



^{1}H NMR (500 MHz, $CDCl_3$) ***N*-(3-(2-isobutyrylhydrazine-1-carbonyl)-methoxyphenyl)butyramide (2a)**

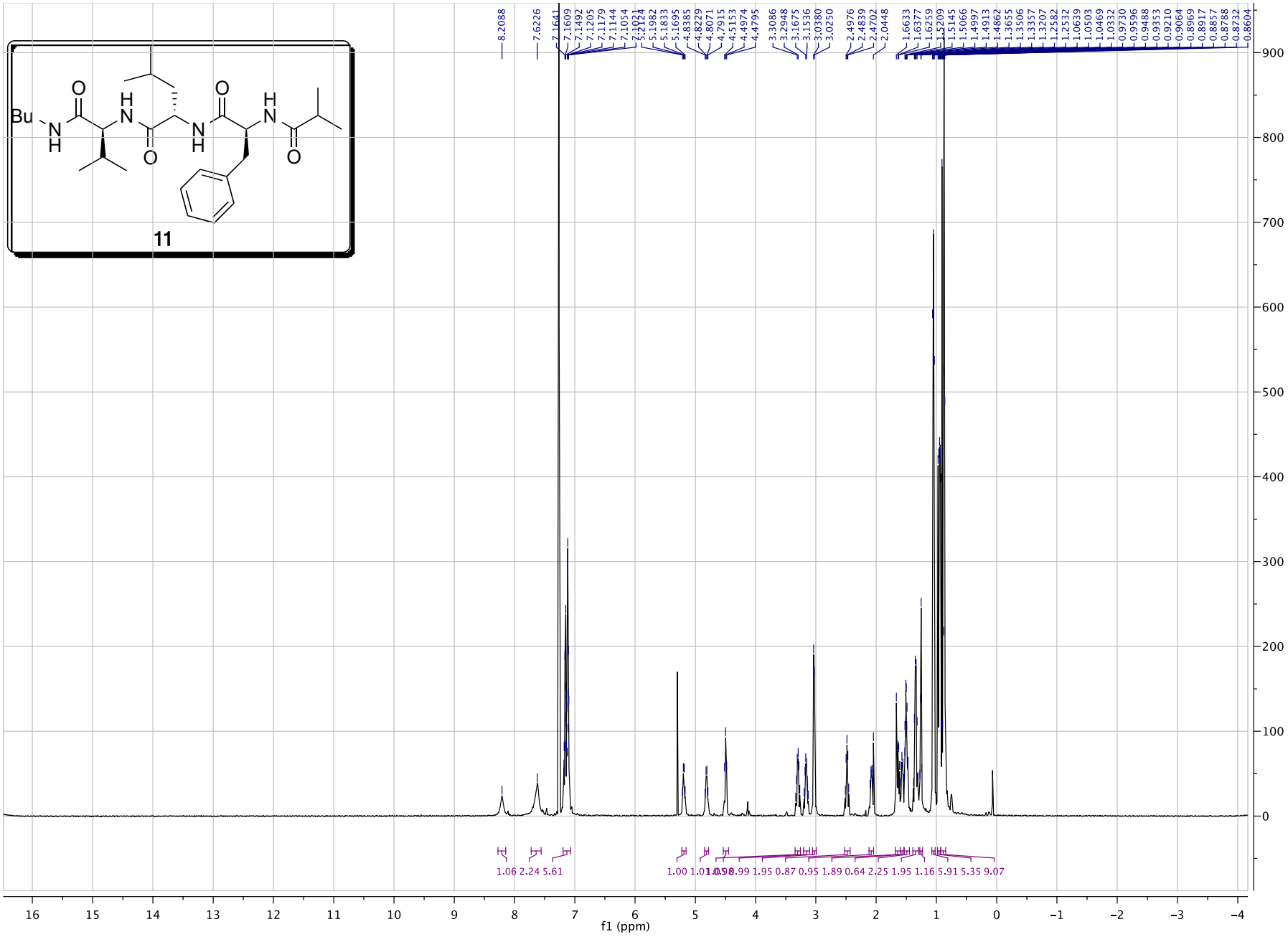


^{13}C NMR (126 MHz, $CDCl_3$) ***N*-(3-(2-isobutyrylhydrazine-1-carbonyl)-methoxyphenyl)butyramide (2a)**



^{1}H NMR (500 MHz, $CDCl_3$)

(*S*)-*N*-((*S*)-1-(butylamino)-3-methyl-1-oxobutan-2-yl)-2-((*S*)-2-isobutyramido-3-phenylpropanamido)-4-methylpentanamide



^{13}C NMR (126 MHz, $CDCl_3$)

(*S*)-*N*-((*S*)-1-(butylamino)-3-methyl-1-oxobutan-2-yl)-2-((*S*)-2-isobutyramido-3-phenylpropanamido)-4-methylpentanamide