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

Supplementary Information

A green and convergent approach to the preparation of NS5A inhibitors by CH activation

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Contents

1. General Information

All reactions were conducted under an atmosphere of nitrogen unless otherwise stated. Anhydrous solvents were used as purchased or were purified under nitrogen as follows using activated molecular sieves.

Thin layer chromatography was performed on glass plates pre-coated with Merck silica gel 60 F_{254}. Visualisation was achieved with U.V. fluorescence (254 nm) or by staining with a phosphomolybdic acid dip or a potassium permanganate dip. Flash column chromatography was carried out using pre-packed columns filled with Aldrich silica gel (40-63 µm) on an ISCO Combiflash Rf, or a Biotage Isolera Prime.

Proton nuclear magnetic resonance spectra were recorded at 500 MHz on a Varian 500 spectrometer (at 30 °C), using residual isotopic solvent ($CHCl_3$, δ_H = 7.27 ppm, DMSO δ_H = 2.50 ppm, 3.33 ppm (H_2O), MeOH δ_H = 3.31 ppm, 4.87 ppm (H_2O)) as an internal reference. Chemical shifts are quoted in parts per million (ppm). Coupling constants (*J*) are recorded in Hertz (Hz).

Carbon nuclear magnetic resonance spectra were recorded at 125 MHz on a Varian 500 spectrometer and are proton decoupled, using residual isotopic solvent ($CHCl_3$, δ_C = 77.00 ppm, DMSO δ_C = 39.52 ppm, MeOH δ_C = 49.00 ppm) as an internal reference. Carbon spectra assignments are supported by DEPT editing and chemical shifts (δ_C) are quoted in ppm.

Infrared spectra were recorded on a Perkin Elmer FT-IR One spectrometer as either an evaporated film or liquid film on sodium chloride plates. Absorption maxima are reported in wave numbers (cm^{-1}). Only significant absorptions are presented in the data, with key stretches identified in brackets.

LCMS data was recorded on a Waters 2695 HPLC using a Waters 2487 UV detector and a Thermo LCQ ESI-MS. Samples were eluted through a Phenomenex Lunar 3µ C18 50 mm × 4.6 mm column, using acetonitrile and water (3 : 7 to 7 : 3) acidified by 0.01% formic acid

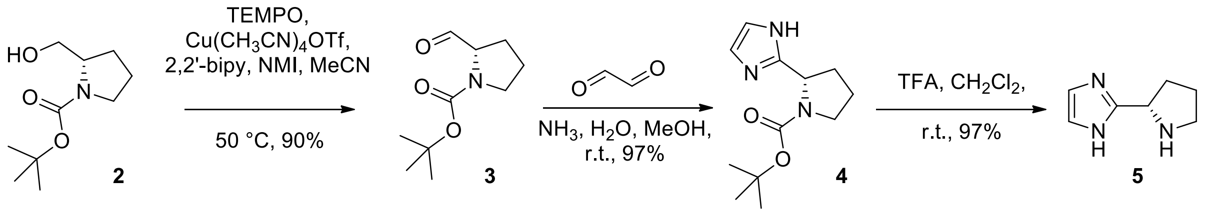
HPLC data and purification was performed on an Agilent 1100 series HPLC spectrometer, using a Phenominex Luna 10 µ C18 150 mm × 15 mm column, eluted using acetonitrile and water (3 : 7 to 7 : 3)

High resolution mass spectrometry data (ESI) was recorded on Bruker Daltonics Apex III ESI-MS, with an Apollo ESI using a methanol spray. Only molecular ions, fractions from molecular ions and other major peaks are reported as mass/charge (*m/z*) ratios.

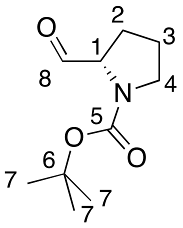
Microwave reactions were performed using a Biotage Initiator 8+ microwave reactor.

2. Synthesis of Imidazole reagents for C-H Activation

Synthesis of pyrrole 4



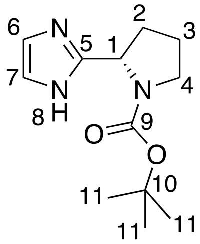
(*S*)-*tert*-Butyl 2-formylpyrrolidine-1-carboxylate (3)[1]



To a stirred solution of *tert*-butyl (2*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (**1**, 6.06 g, 30.11 mmol) in acetonitrile (100 mL) at was added (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO, 235.2 mg, 1.51 mmol), 2,2'-Bipyridyl (235.1 mg, 1.51 mmol), and tetrakisacetonitrile copper(I) triflate (567.2 mg, 1.51 mmol). 1-Methylimidazole (0.24 mL, 3.01 mmol) was then added to the solution, and stirred for 36 hours in an open flask, replacing solvent as it evaporated. The solution was then diluted with water (150 mL) and extracted with diethyl ether (3 x 150 mL). The combined organic phase was washed with brine (2 x 100 mL) and dried over MgSO$_4$, before being concentrated to dryness under reduced pressure. The crude material was then passed through a silica plug (approx. 30 g silica), eluted with a 1:1 mixture of petrol ether/diethyl ether, and concentrated under reduced pressure to give the product as a light orange oil (5.40 g, 90 %).

^{1}H NMR (500 MHz, CDCl$_3$) 9.53 (0.4H, s, 8-C*H*O), 9.44 (0.6H, s, 8-C*H*O), 4.17 (0.4H, t, *J* 5.6, 1- C*H*), 4.03 (0.6H, t, *J* 5.6, 1- C*H*), 3.63-3.37 (2H, m, 4-C*H*$_2$), 2.15-1.73 (4H, m, 2-C*H*$_2$, 3-C*H*$_2$), 1.49-1.36 (9H, m, 7-C(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, CDCl$_3$) 200.5 (8-*C*HO), 200.3 (8-*C*HO), 154.9 (5-*C*O), 153.9 (5-*C*O), 80.5 (7-*C*(CH$_3$)$_3$), 80.1 (7-*C*(CH$_3$)$_3$), 65.0 (1-*C*H), 64.8 (1-*C*H), 46.8 (4-*C*H$_2$), 46.7 (4-*C*H$_2$), 28.2 (C(*C*H$_3$)$_3$), 27.9 (2-*C*H$_2$), 26.7 (2-*C*H$_2$), 24.6 (4-*C*H$_2$), 23.9 (4-*C*H$_2$); **IR** (neat, ν_{max}, cm^{-1}) 2976 (m), 2880 (w), 1735 (m), (1687 (s), 1390 (s), 1256 (m), 1160 (s), 1119 (m), 911 (w), 858 (w), 772 (m); **[α]$_D$** -94.5 (*c* 0.6 in CHCl$_3$, T 24.2 °C).

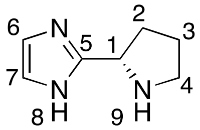
(*S*)-*tert*-Butyl 2-(1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (4)[2]



To a solution of (*S*)-*tert*-butyl 2-formylpyrrolidine-1-carboxylate (16.7 g, 84.2 mmol) in methanol (150 mL) and glyoxal solution (40 % in water, 35.6 mL, 353.0 mmol) at 0 °C was added dropwise ammonia solution (35 % in water, 31 mL, 555.0 mmol). The solution was allowed to warm to room temperature and stirred for 15 hours. The solution was concentrated under reduced pressure, and the resultant residue was extracted with EtOAc (2 × 150 mL). Any precipitate was removed by filtration, and the organic phase was washed with concentrated aqueous NaHCO$_3$ solution (2 × 100 mL), and brine (2 × 100 mL). The solution was then concentrated under reduced pressure to give imidazole **3** as a brown solid (19.4 g, 97%).

^{1}H NMR (500 MHz, CDCl$_3$) 6.95 (2H, s, 7,8-C*H*), 4.94 (1H, dd, *J* 7.6 Hz, 2.6 Hz, 1-C*H*), 3.43 - 3.34 (1H, m, 3-C*H$_2$*), 2.95 - 2.88 (1H, m, 2-C*H$_A$*), 2.17 - 2.08 (2H, m, 2-C*H$_B$*, 4-C*H$_A$*), 1.95 (1H, tt, *J* 8.9 Hz, 4.2 Hz, 4-C*H$_B$*), 1.48 (9H, s, 10-C(C*H$_3$*)$_3$); ^{13}C NMR (126 MHz, CDCl$_3$) 156.4 (8-*C*O), 148.9 (5- N*C*NH), 80.2 (9-*C*(CH$_3$)$_3$), 53.9 (1-*C*H), 47.2 (3-*C*H$_2$), 28.5 (10-C(*C*H$_3$)$_3$), 28.1 (2-*C*H$_2$), 24.8 (4-*C*H$_2$); **IR** (neat, ν_{max}, cm^{-1}) 2977 (w), 2877 (w), 1687 (s), 1390 (s), 1161 (s), 1101 (s), 966 (w), 890 (m), 760 (m), 694 (w); **HRMS (ESI):** calcd. for $C_{12}H_{20}N_3O_2$ [M+H]$^+$ 238.1550, found 238.1551; **[α]$_D$** -159.4 (*c* 1.4 in CHCl$_3$, T 24.6 °C);

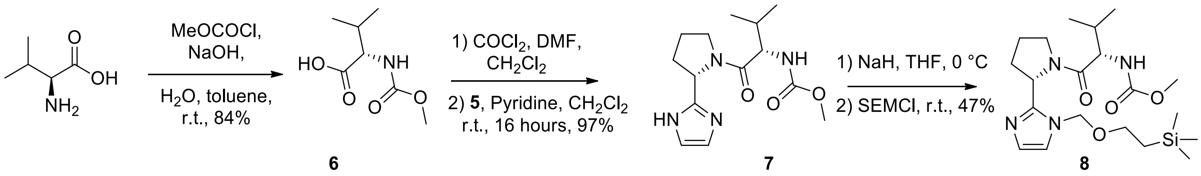
(*S*)-2-(Pyrrolidin-2-yl)-1*H*-imidazole (5)[2]



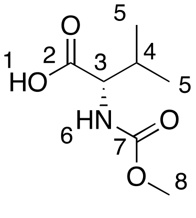
To a solution of (*S*)-*tert*-butyl 2-(1H-imidazol-2-yl)pyrrolidine-1-carboxylate (10.0 g, 42.14 mmol) in dichloromethane (200 mL) at 0 °C, was added dropwise trifluoroacetic acid (24 mL, 316.0 mmol). The solution was allowed to warm to room temperature, and stirred for a further 16 hours, before being concentrated under reduced pressure. The crude material was then purified by adsorption onto an ion exchange column (SCX-2, 2 × 50 g silica), followed by elution by ammonia in methanol (2.0 M), and concentration under reduced pressure to give amine **4** as a brown oil (5.6 g, 97%).

^{1}H NMR (500 MHz, $CDCl_3$) 7.44 (1H, s, 9-N*H*), 6.89 (2H, s, 6,7-C*H*), 4.25 (1H, t, *J* 7.4 Hz, 1-C*H*), 3.02-2.95 (1H, m, 4-CH_A), 2.93-2.86 (1H, m, 4-CH_B), 2.17-2.06 (1H, m, 2-CH_A), 2.03-1.94 (1H, m, 2-CH_B), 1.86-1.69 (2H, m, 3-CH_2); **^{13}C NMR** (126 MHz, $CDCl_3$) 150.1 (5-*C*), 121.7 (6,7-*C*H), 56.1 (1-*C*H), 46.5 (4-*C*H_2), 32.0 (2-*C*H_2), 25.5 (3-*C*H_2); **IR** (neat, ν_{max}, cm^{-1}) 2971 (bm), 1648 (m), 1531 (m), 1408 (s), 1342 (m), 1065 (m), 748 (s); **HRMS (ESI):** calcd. for $C_7H_{12}N_3$ $[M+H]^+$ 138.1026, found 138.1026.

Synthesis of C-H activation reagent 8



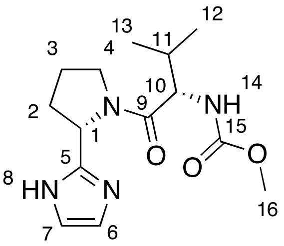
(*S*)-2-(Methoxycarbonylamino)-3-methylbutanoic acid (6)[2]



To a stirred solution of L-valine (20.0 g, 171 mmol) in water (150 mL) and toluene (150 mL) was added NaOH (13.7 g, 341 mmol). The solution was cooled to 0 °C, and methyl chloroformate (14.5 mL, 188 mmol) was added dropwise over 10 minutes. The solution was allowed to warm to room temperature and stirred for 16 hours. The solution was diluted with EtOAc (200 mL) to dissolve any precipitate, and the organic phase was separated. The aqueous phase was acidified with aqueous HCl (1 M, 100 mL), and extracted with EtOAc (2 × 200 mL). The combined organic phases were concentrated under reduced pressure, and the resultant white paste dissolved in warm water (500 mL). The solution was freeze dried, and the resulting white powder dried under reduced pressure at 70 °C for 16 hours to give the product as a white powder (25.7 g, 84 %).

^{1}H NMR (500 MHz, DMSO-*d*$_6$) 12.54 (1H, bs, 1-COO*H*), 7.27 (1H, d *J* 8.4, 6-N*H*), 3.84 (1H, dd, *J* 8.5, 5.9, 3-C*H*), 3.53 (3H, s, 8-C*H*$_3$), 2.08 – 1.96 (1H, m, 4-C*H*), 0.97 – 0.77 (6H, m, 5-CH(C*H*$_3$)$_2$); **^{13}C NMR** (126 MHz, DMSO-*d*$_6$) 173.7 (2-*C*O), 157.4 (7-*C*O), 60.0 (3-*C*H), 51.8 (8-*C*H$_3$), 30.00 (4-*C*H), 19.61 (5-CH(*C*H$_3$)$_2$), 18.45 (5-CH(*C*H$_3$)$_2$); **IR** (neat, ν_{max}, cm^{-1}) 3397 (m), 2965 (m), 1732 (s), 1664 (s), 1551 (s), 1395 (m), 1306 (s), 1255 (s), 1179 (s), 1104 (s), 1019 (s), 892 (s), 778 (s), 735 (m); **HRMS (ESI):** calcd. for $C_7H_{13}NNaO_4$ $[M+Na]^+$ 198.0737, found 198.0738.

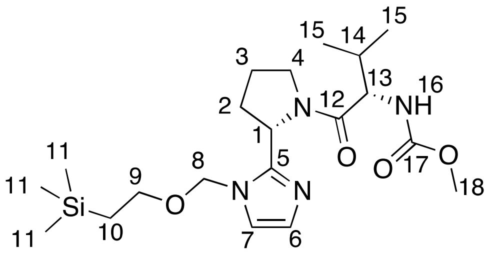
Methyl (*S*)-1-((*S*)-2-(1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (7)



To a solution of (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid 1.25 g, 6.98 mmol) in dichloromethane (20 mL) and a drop of dimethylformamide at 0 °C was added dropwise oxalyl chloride (0.67 mL, 7.0 mmol). The solution was allowed to warm to room temperature, and stir for 3 hours. This solution was then added dropwise to a solution of (*S*)-2-(pyrrolidin-2-yl)-1*H*-imidazole (870 mg, 6.35 mmol) and pyridine (1.9 mL, 19 mmol) in dichloromethane (30 mL) at 0 °C. The solution was allowed to warm to room temperature and stir for 16 hours. The solution was then neutralized by the slow addition of NH_3 (2 M) in isopropanol (20 mL) dropwise. The resultant precipitate was removed by vacuum filtration, and the filtrate was concentrated under reduced pressure to give a brown solid. This was then lyophilized from ice to remove residual water and pyridine, and to give the product as a brown glass foam (1.82 g, 97 %).

^{1}H NMR (500 MHz, $CDCl_3$) 11.50 (1H, s, 8-N*H*), 7.21 (1H, d, *J* 8.4 Hz, 14-N*H*), 6.92 (1H, s, 6-C*H*), 6.72 (1H, s, 7-C*H*), 5.05 (1H, dd, *J* 7.7, 3.5, 1-C*H*), 4.04-3.98 (1H, m, 10-C*H*), 3.80-3.64 (2H, m, 4-C*H*$_2$), 3.53 (3H, s, 60-C*H*$_3$), 2.19-1.80 (5H, m, 2-C*H*$_2$, 3-C*H*$_2$, 11-C*H*), 0.90-0.75 (6H, m, 12-C*H*$_3$, 13-C*H*$_3$); **^{13}C NMR** (500 MHz, $CDCl_3$) 170.8 (9-*C*O), 157.2 (15-*C*O), 148.9 (5-*C*H), 127.3 (6-*C*H), 115.9 (7-*C*H), 58.4 (10-*C*H), 54.4 (1-*C*H), 51.9 (16-*C*H$_3$), 47.2 (4-*C*H$_2$), 30.9 (3-*C*H$_2$), 30.2 (11-*C*H), 24.7 (2.*C*H$_2$), 19.4 (12-*C*H$_3$, 13-*C*H$_3$), 18.9 (12-*C*H$_3$, 13-*C*H$_3$); **IR** (neat, ν_{max}, cm^{-1}) 3151 (bw), 2970 (w), 1703 (m), 1632 (m), 1520 (m), 1446 (m), 1362 (m), 1520 (m), 1446 (m), 1362 (m), 1261 (m), 1183 (m), 1099 (m), 835 (s), 741 (s); **HRMS (ESI):** calcd. for $C_{14}H_{23}N_4O_3$ $[M+H]^+$ 295.1765, found 295.1761.

Methyl (*S*)-3-methyl-1-oxo-1-((*S*)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)butan-2-ylcarbamate (8)

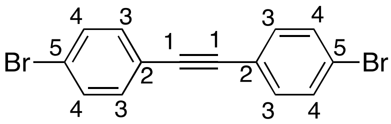


To a stirred suspension of NaH (305 mg, 7.63 mmol) in dry THF (100 mL) at 0 °C, was added dropwise a solution of methyl (*S*)-1-((*S*)-2-(1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (**6**, 1.35 g, 4.54 mmol) in dry THF (20 mL), and allowed to stir for one hour. To this solution was added dropwise 2-(trimethylsilyl)ethoxymethyl chloride (1.35 mL, 7.63 mmol) in dry THF (5 mL), before warming to room temperature and stirring for 16 hours. The reaction was quenched with deionized water (100 mL), and extracted with EtOAc (2 × 100 mL). The combined organic phase was washed with water (100 mL) and brine (2 × 100 mL), before being dried over $MgSO_4$ and concentrated under reduced pressure to give an orange oil (2.03 g). The crude material was purified by flash chromatography (25 g silica, EtOAc : petroleum ether, 30 % to 100 %), to give protected imidazole **8** (0.91 g, 47 %) as a pale brown oil.

^{1}H NMR (500 MHz, DMSO-d_6) 7.17 (1H, s, 16-N*H*), 7.10 (1H, d, *J* 1.3 Hz, 7-C*H*), 6.77 (1H, d, *J* 1.2 Hz, 6-C*H*), 5.71 (1H, d, *J* 10.9 Hz, 8-CH_A), 5.24 (1H, d, *J* 10.9 Hz, 8-CH_B), 5.11 (1H, dd, *J* 8.2 Hz, 3.8 Hz, 1-C*H*), 3.99 (1H, t, *J* 8.4, 13-C*H*), 3.88 - 3.80 (1H, m, 4-CH_A), 3.69 (1H, m, 4-CH_B), 3.56 - 3.45 (5H, m, 9-CH_2, 18-CH_3), 2.37 - 2.27 (1H, m, 3-CH_A), 2.14 - 2.05 (1H, m, 2-CH_A), 1.98 - 1.88 (2H, m, 2-CH_A, 3-CH_B), 1.84 - 1.73 (1H, m, 14-C*H*), 0.92 - 0.69 (9H, m, 10-CH_2, 15-CH_3), -0.04 (9H, s, 11-CH_3); **^{13}C NMR** (126 MHz, DMSO d_6) 170.4 (12-*C*O), 157.2 (17-*C*O), 149.3 (5-*C*), 127.0 (6-*C*H), 120.3 (7-*C*H), 74.6 (8-*C*H_2), 65.4 (9-*C*H_2), 58.3 (13-*C*H), 51.9 (1-*C*H), 51.8 (18-*C*H_3), 47.2 (4-*C*H_2), 31.5 (2-*C*H_2), 30.3 (14-*C*H), 24.9 (3-*C*H_2), 19.1 (15-*C*H_3), 17.7 (10-*C*H_2), -0.9 (11-*C*H_3); **IR** (neat, ν_{max}, cm^{-1}) 3261 (w), 2955 (w), 1716 (s), 1619 (s), 1522 (m), 1444 (m), 1248 (m), 1091 (s), 1033 (m), 834 (s), 725 (m); **HRMS (ESI):** calcd. for $C_{20}H_{36}N_4NaO_4$ $[M+H]^+$ 447.2398, found 447.2395; **$[\alpha]_D$** 32.1 (c 0.6 in $CHCl_3$, T 20.5 °C).

3. Synthesis of Dibromide Cores

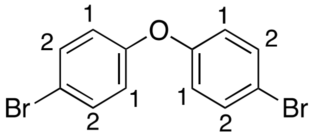
1,2-*bis*(4-Bromophenyl)ethyne[3]



To a solution of 1-bromo-4-iodo benzene (1.0 g, 3.5 mmol), $Pd(PPh_3)Cl_2$ (74 mg, 0.21 mmol), and CuI (67.2 mg) in benzene under N_2 gas, was added dropwise DBU (3.2 mL, 21 mmol), trimethylsilyl acetylene (0.25 mL, 1.8 mmol), and H_2O (25 µL, 1.41 mmol). The solution was stirred at room temperature for 20 hours, before being diluted with water (75 mL), and diethyl ether (75 mL). The phases were separated, and the organic phase was washed with aqueous HCl (1 M, 3 × 50 mL), before being dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by flash chromatography (10 g silica, petroleum ether, 100%), to give the product as a pale yellow solid (0.26 g, 44%).

^{1}H NMR (500 MHz, $CDCl_3$) 7.50 (4H, d, *J* 8.4 Hz, 4-C*H*), 7.39 (4H, d, *J* 8.4 Hz, 3-C*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) 133.0 (3-CH), 131.7 (4-*C*H), 122.8 (2-*C*), 121.9 (5-*C*), 89.4 (1-*C*);

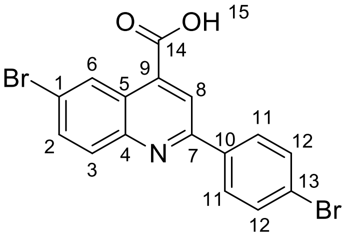
4,4'-Oxybis(bromobenzene)[4]



To a solution of diphenyl ether (0.50 mL, 3.2 mmol), and $NaBrO_3$ (158 mg, 1.05 mmol) in dichloromethane (2.5 mL) and water (2.5 mL), was added dropwise bromine (0.20 ml, 3.5 mmol). The solution was then stirred at room temperature for 2 hours, until no starting material was visible by TLC. The solution was diluted with dichloromethane (10 mL) and water (10 mL), and 1 M aqueous sodium thiosulfate solution was added until the solution had turned colourless. The organic phase was washed with water (2 × 10 mL) and brine (2 × 10 mL), before being dried over $MgSO_4$, and concentrated under reduced pressure to the product as an off-white solid (792 mg 77%).

^{1}H NMR (500 MHz, $CDCl_3$) 7.46 (4H, d, *J* 8.8 Hz, 3-C*H*), 6.89 (4H, d, *J* 8.9 Hz, 2-C*H*), **^{13}C NMR** (126 MHz, $CDCl_3$) 156.0 (1-*C*O), 132.8 (3-*C*H), 120.6 (2-*C*H), 116.2 (4-*C*Br)

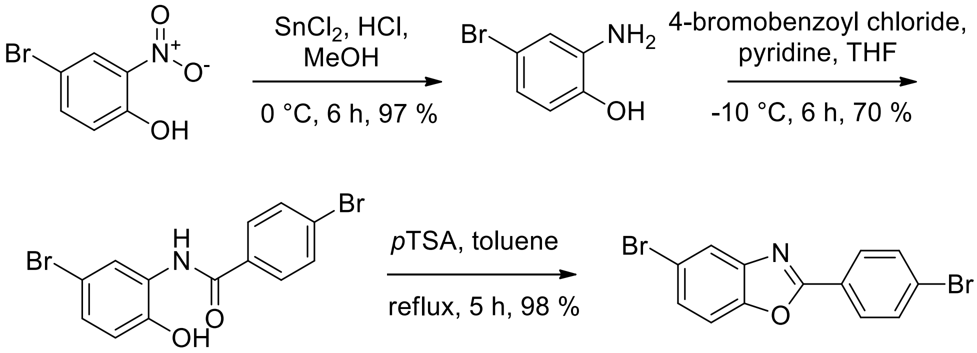
7-Bromo-3-(4-bromophenyl)quinoline-4-carboxylic acid



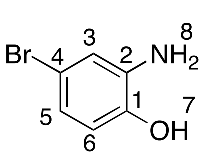
A solution of 5-bromoisatin (2.00 g, 8.85 mmol), 1-(4-bromophenyl)ethanone (1.76 g, 8.85 mmol) and potassium hydroxide (1.48 g, 26.6 mmol) in ethanol (100 mL) was heated at 60 °C for 15 hours. The solution was then concentrated under reduced pressure to give a red residue, which was redissolved in water (200 mL) and petroleum ether (150 mL). The precipitate was removed by filtration, and the filtrate separated. The aqueous phase was acidified with 1 M HCl, to give an orange precipitate. This precipitate was then triturated in a mixture of hot ethanol (90 mL) and water (10 mL) to give the product as a pale brown solid (621 mg, 17 %).

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 9.05 (1H, s, 8-C*H*), 8.42 (1H, s, 6-C*H*), 8.18 (2H, d, *J* 8.1 Hz, 11-C*H*), 8.01 (1H, d, *J* 8.9 Hz, 3-C*H*), 7.89 (1H, d, *J* 8.9 Hz, 2-C*H*), 7.73 (2H, d, *J* 8.1 Hz, 12-C*H*); **^{13}C NMR** (126 MHz, DMSO-*d*$_6$) δ 155.6 (14-*C*OOH), 147.4 (7-*C*), 137.6 (4-*C*), 133.3 (2-*C*H), 132.4 (12-*C*H), 132.0 (3-*C*H), 129.6 (11-*C*H), 129.0 (8-*C*H), 125.9 (1-*C*Br), 124.2 (13-*C*Br), 120.9 (5-*C*), 119.7 (6-*C*H).

Synthesis of Benzoxazole dibromide Reagent



2-Amino-4-bromophenol[5]

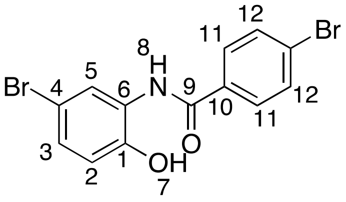


A suspension of tin (II) chloride (5.9 g, 23 mmol) in concentrated aqueous HCl (37 %, 11 mL) and MeOH (20 mL) was cooled to 0 °C. 4-bromo-2-nitrophenol (1.0 g, 4.6 mmol) was then added to the solution in one portion, and allowed to stir for 6 hours, whereby the solution had gone colourless. The solution was then diluted with ethyl acetate (60 mL), and neutralized with saturated aqueous $NaHCO_3$ solution.

The white precipitate was then removed by filtration, and washed with ethyl acetate (120 mL). The filtrate was separated, and the aqueous phase extracted with ethyl acetate (3 × 50 mL). The combined organic phase was dried over $MgSO_4$, and concentrated under reduced pressure, to give the product as a light brown solid (836 mg, 97%).

^{1}H NMR (500 MHz, $CDCl_3$) 9.21 (1H, s, 7-O*H*), 6.71 (1H, d, *J* 2.5 Hz, 3-C*H*), 6.55 (1H, d, *J* 8.3 Hz, 6-C*H*), 6.48 (1H, dd, *J* 8.3 Hz, 2.4 Hz, 5-C*H*), 4.76 (2H, s, 8-N*H₂*); **^{13}C NMR** (126 MHz, $CDCl_3$) 143.7 (1-*C*OH), 139.3 (2-*C*NH_2), 118.5 (5-*C*H), 116.4 (3-*C*H), 116.1 (6-*C*H), 111.1 (4-*C*Br).

4-Bromo-*N*-(5-bromo-2-hydroxyphenyl)benzamide

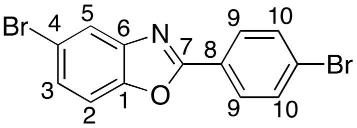


A solution of 4-bromobenzoic acid (1.0 g, 5 mmol), and 3 drops of dimethylformamide in sulfuryl chloride (7 mL) was refluxed at 80 °C for 3 hours. The solution was then concentrated under reduced pressure to yield a yellow, crystalline solid (1.03 g).

To a stirred solution of 2-amino-4-bromophenol (**21**, 568 mg, 3.02 mmol) and pyridine (0.8 mL, 10 mmol) in dry THF (20 mL) at −10 °C, was added dropwise a solution of the yellow solid (676 mg, 3.3 mmol) in dry THF (6 mL). The solution was allowed to stir at −10 °C for 6 hours, before being quenched with concentrated aqueous $NaHCO_3$ solution (30 mL), and diluted with ethyl acetate (40 mL). The aqueous phase was extracted with ethyl acetate (30 mL), and the combined organic phases were washed with HCl (1 M, 50 mL), and brine (50 mL), before being concentrated under reduced pressure to give a brown solid. This crude material was dissolved in a solution of NaOH (150 mg, 3.8 mmol) in water (10 mL) and THF (20 mL), and allowed to stir at room temperature for 20 hours. The resulting solution was diluted with ethyl acetate (100 mL), and the organic phase was washed with HCl (1 M, 2 × 150 mL), saturated aqueous $NaHCO_3$ solution (2 × 150 mL), and brine (2 × 100 mL). The solution was then dried over $MgSO_4$ and concentrated under reduced pressure, to give the product as a light brown, crystalline solid (787 mg, 70 %).

^{1}H NMR (500 MHz, DMSO-*d*$_6$) 10.11 (1H, s, 8-N*H*), 9.57 (1H, s, 7-O*H*), 8.00 - 7.81 (3H, m, 6-C*H*, 11-C*H*), 7.74 (2H, d, *J* 8.5 Hz, 12-C*H*), 7.19 (1H, dd, *J* 8.6 Hz, 2.5 Hz, 3-C*H*), 6.88 (1H, d, *J* 8.6 Hz, 2-C*H*); **^{13}C NMR** (126 MHz, DMSO-*d*$_6$) 164.9 (9-*C*O), 149.3 (1-*C*OH), 133.7 (3-*C*H), 132.0 (12-*C*H), 130.2 (11-*C*H), 128.8 (10-*C*), 128.3 (13-*C*Br), 127.7 (5-*C*H), 126.9 (6-*C*NH), 126.0 (2-*C*H), 109.9 (4-*C*Br); **IR** (neat, ν_{max}, cm^{-1}) 3182 (bm), 1631 (s), 1587 (s), 1519 (s), 1481 (s), 1409 (s), 1320 (s), 1283 (s), 1104 (s), 1068 (s), 1009 (s), 930 (m), 870 (s), 844 (s), 812 (s), 752 (m), 723 (m), 688 (m); **HRMS (ESI):** calcd. for $C_{13}H_{10}Br_2N_1O_2$ [M+H]$^+$ 369.9073, found 369.9073

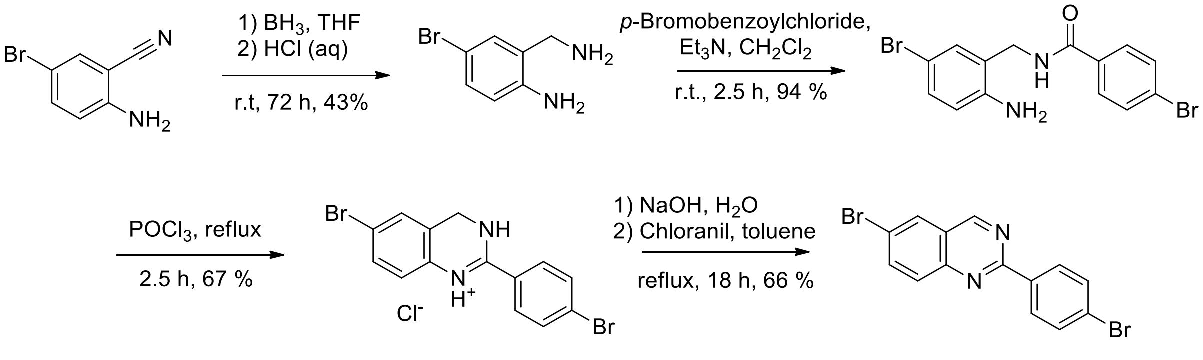
5-Bromo-2-(4-bromophenyl)benzo[*d*]oxazole



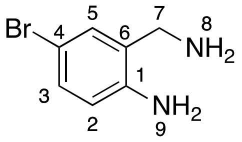
To a solution of *p*-toluenesulfonic acid monohydrate (80 mg, 0.42 mmol) in toluene (5 mL) was added 4-bromo-*N*-(5-bromo-2-hydroxyphenyl)benzamide (**22**, 50 mg, 0.13 mmol), and heated at 110 °C for 5 hours. The resulting solution was diluted with water (15 mL) and ethyl acetate (15 mL). The aqueous phase was extracted with ethyl acetate (15 mL), before the combined organic phase was washed with $NaHCO_3$ solution (2 × 20 mL) and brine (2 × 20 mL). The solution was then dried over $MgSO_4$, and concentrated under reduced pressure to give the product as a light brown solid (45 mg, 98%).

^{1}H NMR (500 MHz, $CDCl_3$) 8.11 (2H, d, *J* 8.6 Hz, 10-*C*H), 7.91 (1H, d, *J* 1.9 Hz, 5-*C*H), 7.69 (2H, d, *J* 8.6 Hz, 9-*C*H), 7.54 - 7.42 (2H, m, 2-*C*H, 3-*C*H); **^{13}C NMR** (126 MHz, $CDCl_3$) 163.2 (7-*C*), 149.8 (6-*C*), 143.6 (1-*C*), 132.3 (10-*C*H), 129.1 (9-*C*H), 128.4 (3-*C*H), 126.7 (8-*C*), 125.6 (11-*C*Br), 123.1 (5-*C*H), 117.5 (4-*C*Br), 111.8 (2-*C*H); **IR** (neat, ν_{max}, cm^{-1}) 3084 (w), 2919 (w), 1587 (m), 1546 (m), 1474 (s), 1446 (s), 1423 (m), 1397 (s), 1260 (s), 1069 (s), 1008 (s), 891 (m), 830 (s), 797 (s), 750 (m), 726 (s), 679 (m); **HRMS (ESI):** calcd. for $C_{13}H_8Br_2NO$ [M+H]$^+$ 351.8967, found 351.8967.

Quinazoline Aryl-Dibromide Synthesis



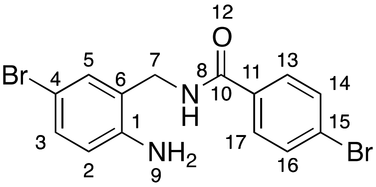
2-(Aminomethyl)-4-bromoaniline (20)



To a solution of 2-amino-5-bromobenzonitrile (2.00 g, 10.2 mmol) in dry THF (20 mL) at 0 °C was added dropwise a solution of borane in THF (1 M, 12.5 mL, 12.5 mmol). The solution was then allowed to warm to room temperature, and stir for a further 72 hours. The solution was quenched dropwise with ethanol (10 mL), before hydrochloric acid (4 M, 10 mL) was added, and the solution was allowed to stir for a further 16 hours. The solution was then concentrated under reduced pressure, and *tert*-butyl acetate (20 mL) was added, before basifying the aqueous phase with sodium hydroxide pellets. The organic phase was then separated and washed with water (2 × 15 mL), before being dried over magnesium sulfate, and concentrated under reduced pressure to give a light brown solid. This crude material was then purified by column chromatography (25 g silica, MeOH:CH_2Cl_2, 0% to 15%) to give the product as a white, crystalline solid (874 mg, 43 %).

^{1}**H NMR** (500 MHz, DMSO-d_6) 7.18 (1H, d, *J* 2.4 Hz, 5-C*H*), 7.04 (1H, dd, *J* 8.5 Hz, 2.5 Hz, 3-C*H*), 6.54 (1H, d, *J* 8.4 Hz, 2-C*H*), 5.21 (2H, s, 9-N*H$_2$*), 3.56 (2H, s, 7-C*H$_2$*), 1.75 (2H, bs, 8-N*H$_2$*); ^{13}**C NMR** (126 MHz, DMSO-d_6) 146.3 (1-*C*NH$_2$), 130.4 (5-*C*H), 129.7 (3-*C*H), 117.7 (6-*C*H), 116.7 (2-*C*H), 107.0 (4-*C*Br), 43.0 (7-*C*H$_2$);

N-(2-Amino-5-bromobenzyl)-4-bromobenzamide

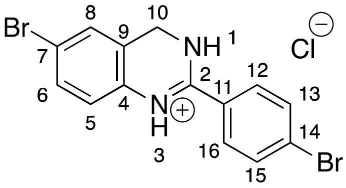


4-Bromobenzoic acid (1.0 g, 5 mmol) was suspended in thionyl chloride (5 mL), and a drop of DMF was added. The solution was heated to reflux, and stirred for 2 hours, until no more effervescence was observed. The solution was then cooled to room temperature and concentrated under reduced pressure to give an orange, crystalline solid (1.1 g).

To a stirred solution of 2-(aminomethyl)-4-bromoaniline (**20**, 730 mg, 3.63 mmol) and triethylamine (0.70 mL, 5.4 mmol) in dichloromethane (10 mL) at 0 °C was added dropwise a solution of the previously formed orange solid (800 mg, 3.64 mmol) in dichloromethane (5 mL). The solution was allowed to warm to room temperature and stir for a further 2.5 hours. The reaction was quenched with water (15 mL), causing precipitation of a white solid upon formation of an emulsion. The white solid was redissolved using ethyl acetate (100 mL), the phases separated, and the organic phase washed with potassium carbonate solution (conc., 2 × 50 mL) and water (2 × 50 mL). The solution was then dried over magnesium sulphate, and concentrated under reduced pressure to yield amide **21** as an oil, which later solidified to an off-white solid (1.31 g, 94 %)

^{1}H NMR (500 MHz, DMSO-*d*$_6$) 9.01 (1H, s, 8-N*H*), 7.82 (2H, d, *J* 8.4 Hz, 13-C*H*, 17-C*H*), 7.69 (2H, d, *J* 8.4 Hz, 14-C*H*, 16-C*H*), 7.14 – 7.07 (2H, m, 3-C*H*, 5-C*H*), 6.59 (1H, d, *J* 8.4 Hz, 3-CH), 5.31 (2H, s, 9-N*H*$_2$), 4.29 (2H, d, *J* 6.0 Hz, 7-C*H*$_2$); **^{13}C NMR** (126 MHz, DMSO-*d*$_6$) 166.0 (10-*C*O), 146.0 (1-*C*NH$_2$), 133.5 (11-*C*), 131.9 (14-*C*H, 16-*C*H), 131.6 (5-*C*H), 130.7 (3-*C*H), 129.8 (13-*C*H, 17-*C*H), 125.6 (15-*C*Br), 124.7 (6-*C*), 117.0 (2-*C*H), 106.7 (4-*C*Br).

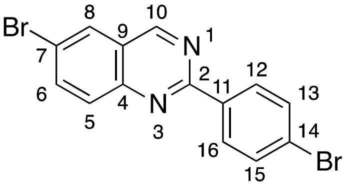
6-Bromo-2-(4-bromophenyl)-3,4-dihydroquinazolin-1-ium chloride



A solution of *N*-(2-amino-5-bromobenzyl)-4-bromobenzamide in phosphoryl chloride (7 mL) was refluxed for 2.5 hours. The solution was then concentrated under reduced pressure, and the residue was neutralized by washing with concentrated aqueous sodium bicarbonate (30 mL). The solid material was extracted with ethyl acetate (50 mL), and the precipitate was removed by vacuum filtration. The filtrate was dried over magnesium sulfate, before being concentrated under reduced pressure to give the product as an off-white, crystalline solid (767 mg, 67 %).

^{1}H NMR (500 MHz, DMSO-*d*$_6$) 12.64 (1H, s, 1-N*H*), 11.10 (1H, s, 3-N*H*), 7.98 – 7.83 (4H, m, 12-C*H*, 13-C*H*, 15-C*H*, 16-C*H*), 7.58 – 7.48 (2H, m, 6-C*H*, 8-C*H*), 7.40 (1H, d, *J* 8.5 Hz, 5-C*H*), 4.85 (2H, s, 10-C*H*$_2$); **^{13}C NMR** (126 MHz, DMSO-*d*$_6$) 157.5 (2-*C*), 132.4 (13-*C*H, 15-*C*H), 132.0 (4-*C*), 131.9 (6-*C*H), 131.3 (12-*C*H, 16-*C*H), 129.8 (8-*C*H), 128.5 (11-*C*), 126.3 (9-*C*), 121.0 (14-*C*Br), 119.8 (5-*C*H), 119.2 (7-*C*Br), 42.1 (10-*C*H$_2$); **HRMS (ESI):** calcd. for $C_{14}H_{10}Br_2N_4$ [M+H]$^+$ 364.9283, found 364.9283.

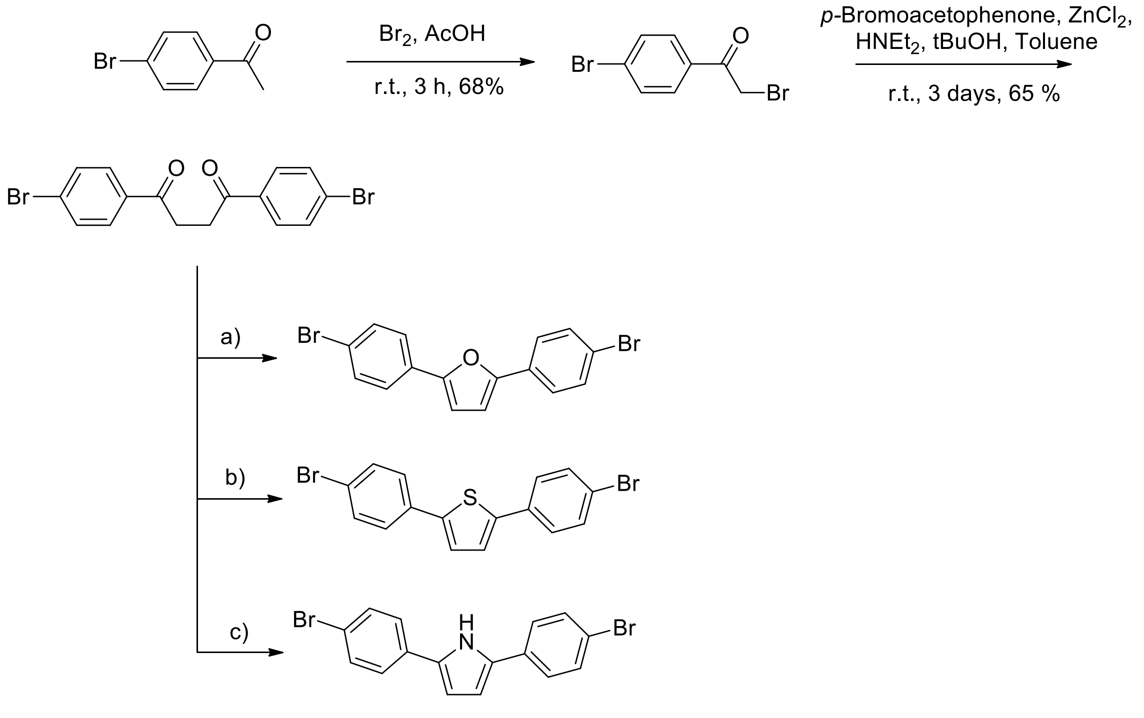
6-Bromo-2-(4-bromophenyl)quinazoline



6-Bromo-2-(4-bromophenyl)-3,4-dihydroquinazolin-1-ium chloride (**22,** 569 mg, 1.42 mmol) was stirred in an emulsion of aqueous sodium hydroxide (30 mL) and dichloromethane (30 mL) at room temperature for 2 hours. The resulting solution was extracted with ethyl acetate (2 × 75 mL), and dried over magnesium sulfate, before being concentrated under reduced pressure. This residue was taken up in toluene (10 mL), and chloranil (350 mg, 1.42 mmol) was added. The solution was for 18 hours, then concentrated under reduced pressure. The solid residue was taken up in dichloromethane (250 mL), and the remaining precipitate removed by vacuum filtration. The filtrate was washed with aqueous sodium hydroxide solution (3 M, 100 mL) and water (2 × 100 mL), and dried over magnesium sulfate, before being concentrated under reduced pressure to give quinazoline **23** as an off-white solid (341 mg, 66 %)

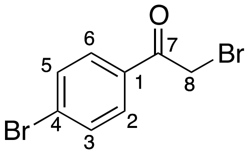
^{1}H NMR (500 MHz, $CDCl_3$) 9.39 (1H, s, 10-C*H*), 8.50 (2H, d, *J* 8.6 Hz, 12-C*H*, 16-C*H*), 8.10 (1H, d, *J* 2.0 Hz, 8-C*H*), 8.02 − 7.93 (2H, m, 5-C*H*, 6-C*H*), 7.67 (2H, d, *J* 8.5 Hz, 13-CH, 15-CH); **^{13}C NMR** (126 MHz, $CDCl_3$) 160.4 (2-*C*), 159.4 (10-*C*H), 149.4 (4-*C*), 137.8 (1-*C*H), 136.5 (9-*C*H), 131.9 (13-C*H*, 15-C*H*), 130.4 (5-*C*H), 130.2 (12-*C*H, 16-*C*H), 129.2 (8-*C*H), 125.8 (11-*C*), 124.5 (14-*C*Br), 121.0 (7-*C*Br).

Furan, Thiophene and Pyrrole Syntheses



a) HCl (g), MeOH, CH_2Cl_2, 0 °C, r.t., 3 h, 74%; b) Lawesson's reagent, toluene, reflux, 3 h, 75 %; c)NH_4OAc, AcOH, reflux, 21 h, 62%

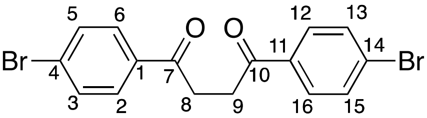
2-Bromo-1-(4-bromophenyl)ethanone[6]



To a stirred solution of 4-bromoacetophenone (6.00 g, 30.3 mmol) in acetic acid (45 mL) was added dropwise bromine (1.55 mL, 30.3 mmol). The solution was allowed to stir at room temperature for a further three hours, until a colour change from dark brown to yellow had occurred. The solution was then diluted with ethyl acetate (100 mL), and washed with sodium thiosulfate solution (2 M, 2 × 50 mL), sodium bicarbonate solution (saturated, 2 × 50 mL), and water (2 × 50 mL). The solution was then dried over magnesium sulfate and concentrated under reduced pressure to give a white solid. The crude material was then recrystallised from a 10 : 1 mixture of petrol ether and ethyl acetate to give the product as a white, crystalline solid (5.75 g, 68 % yield).

^{1}H NMR (500 MHz, $CDCl_3$) 7.85 (2H, d, *J* 8.6 Hz, 2-C*H*, 6-C*H*), 7.65 (2H, d, *J* 8.6 Hz, 3-C*H*, 5-C*H*), 4.40 (2H, s, 8-C*H₂*); **^{13}C NMR** (126 MHz, $CDCl_3$) 190.4 (7-*C*O), 132.7 (1-*C*), 132.2 (3-*C*H, 5-*C*H), 130.4 (2-*C*H, 6-*C*H), 129.3 (4-*C*Br), 30.3 (8-*C*H_2).

1,4-*bis*(4-Bromophenyl)butane-1,4-dione[7]

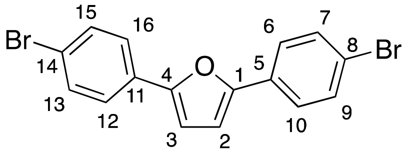


Zinc (II) chloride (3.91 g, 28.7 mmol) was dried by melting at 350 °C for 25 minutes, until gas evolution had ceased. After cooling to room temperature, the solidified material was then stirred in a solution of toluene (13.5 mL), diethylamine (2.2 mL, 22 mmol) and *tert*-butanol (2.1 mL, 22 mmol) for 2.5 hours, until all solid material had dissolved. To this solution was added 4-bromoacetophenone (4.26 g, 21.5 mmol), followed by 2-bromo-1-(4-bromophenyl)ethanone (**24**, 4.00 g, 14.3 mmol), and the reaction vessel was sealed under an inert atmosphere and stirred for a further 3 hours. The solution was then allowed to stand for 3 days, causing a precipitate to form. The reaction mixture was then quenched with sulfuric acid (5 % in water, 20 mL), and the precipitate collected by vacuum filtration. The precipitate was washed with toluene (20 mL), water (20 mL) and methanol (20 mL) to give the product as a crystalline, white solid (3.67 g, 65 %).

^{1}H NMR (500 MHz, $CDCl_3$) 7.90 (4H, d, *J* 8.5 Hz, 2-C*H*, 6-C*H*, 12-C*H*, 16-C*H*), 7.63 (4H, d, *J* 8.5 Hz, 3-C*H*, 5-C*H*, 12-C*H*, 16-C*H*), 3.41 (4H, s, 8-C*H₂*, 9-C*H₂*); **^{13}C NMR** (126 MHz, $CDCl_3$) 197.5 (7-*C*O, 10-*C*O), 135.4

(1-*C*, 11-*C*), 131.9 (3-*C*H, 5-*C*H, 12-*C*H, 16-*C*H), 129.6 (2-*C*H, 6-*C*H, 12-*C*H, 16-*C*H), 128.4 (4-*C*Br, 14-*C*Br), 32.4 (8-*C*H_2, 9-*C*H_2).

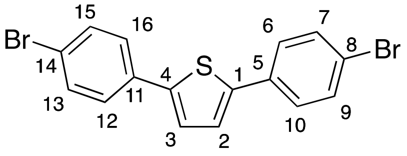
2,5-*bis*(4-Bromophenyl)furan[8]



A stirred solution of 1,4-*bis*(4-bromophenyl)butane-1,4-dione (**25**, 250 mg, 0.635 mmol) in methanol (3.0 mL) and dichloromethane (7.0 mL) at 0 °C was saturated with HCl gas, produced from the reaction of concentrated sulfuric acid with sodium chloride. The solution was allowed to warm to room temperature and stirred for a further 3 hours. The solution was then concentrated under reduced pressure give a brown solid, which was washed with concentrated aqueous potassium carbonate solution (30 mL). The remaining crude material was then recrystallised from a mixture of chloroform and diethyl ether (3 : 7) to give 2,5-*bis*(4-bromophenyl)furan (**26**) as a white, crystalline solid (177 mg, 74%).

^{1}H NMR (500 MHz, DMSO-*d*$_6$) 7.77 (4H, d, *J* 8.6 Hz, 6-C*H*, 10-C*H*, 13-C*H*, 15-C*H*), 7.63 (4H, d, *J* 8.5 Hz, 7-C*H*, 9-C*H*, 13-C*H*, 15-C*H*), 7.14 (2H, s, 2-C*H*, 3-C*H*); **^{13}C NMR** (126 MHz, DMSO-*d*$_6$) 152.4 (1-*C*H, 4-*C*H), 132.3 (7-*C*H, 9-*C*H, 13-*C*H, 15-*C*H), 129.6 (5-*C*, 11-*C*), 125.9 (6-*C*H, 10-*C*H, 12-*C*H, 16-*C*H), 121.1 (8-*C*Br, 14-*C*Br), 109.6 (2-*C*H, 3-*C*H).

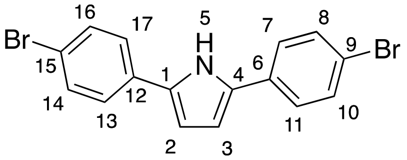
2,5-*bis*(4-Bromophenyl)thiophene[9]



A stirred solution of 1,4-*bis*(4-bromophenyl)butane-1,4-dione (**25**, 250 mg, 0.64 mmol) and Lawesson's reagent (308 mg, 0.76 mmol) in toluene (5.0 mL) was allowed to reflux for 3 hours. The solution was then allowed to cool to room temperature, before adding diethyl ether (10.0 mL) and further cooling the solution to −78 °C . After 10 minutes, the resulting precipitate was collected by vacuum filtration, and washed with chilled (−78 °C) diethyl ether (10 mL), to give 2,5-*bis*(4-bromophenyl)thiophene (**27**) as a white, crystalline solid (188 mg, 75 %).

^{1}H NMR (500 MHz, $CDCl_3$) 7.55 - 7.46 (8H, m, 6-C*H*, 7-C*H*, 9-C*H*, 10-C*H*, 12-C*H*, 13-C*H*, 15-C*H*, 16-C*H*), 7.27 (2H, s, 2-C*H*, 3-C*H*); **^{13}C NMR** (126 MHz, $CDCl_3$) 142.7 (1-*C*, 4-*C*), 133.1 (5-*C*, 11-*C*), 132.0 (7-*C*H, 9-*C*H, 13-*C*H, 15-*C*H), 127.1 (6-*C*H, 10-*C*H, 12-*C*H, 16-*C*H), 124.5 (2-*C*H, 3-*C*H), 121.5 (8-*C*Br, 14-*C*Br).

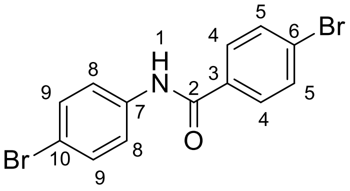
2,5-*bis*(4-Bromophenyl)-1*H*-pyrrole[10]



A stirred solution of 1,4-*bis*(4-bromophenyl)butane-1,4-dione (**25**, 500 mg, 1.28 mmol) and ammonium acetate (346 mg, 4.48 mmol) in acetic acid (10 mL) was allowed to reflux for 21 hours. The solution was then allowed to cool to room temperature, and concentrated under reduced pressure. The resulting brown solid was washed with concentrated aqueous potassium carbonate (30 mL), before being recrystallised from acetic acid to give the product as a white, crystalline solid (301 mg, 62 %).

^{1}H NMR (500 MHz, DMSO-*d*$_6$) 11.34 (1H, s, 5-N*H*), 7.72 (4H, d, *J* 8.1 Hz, 7-C*H*, 11-C*H*, 13-C*H*, 17-C*H*), 7.55 (4H, d, *J* 8.1 Hz, 8-C*H*, 10-C*H*, 14-C*H*, 16-C*H*), 6.65 (2H, s, 2-C*H*, 3-C*H*); **^{13}C NMR** (126 MHz, DMSO-*d*$_6$) 132.8 (1-*C*, 4-*C*), 132.0 (6-*C*, 12-*C*), 131.9 (8-*C*H, 10-*C*H, 14-*C*H, 16-*C*H), 126.4 (7-*C*H, 11-*C*H, 14-*C*H, 16-*C*H), 119.0 (9-*C*Br, 15-*C*Br), 109.0 (2-*C*H, 3-*C*H).

4-Bromo-*N*-(4-bromophenyl)benzamide[11]



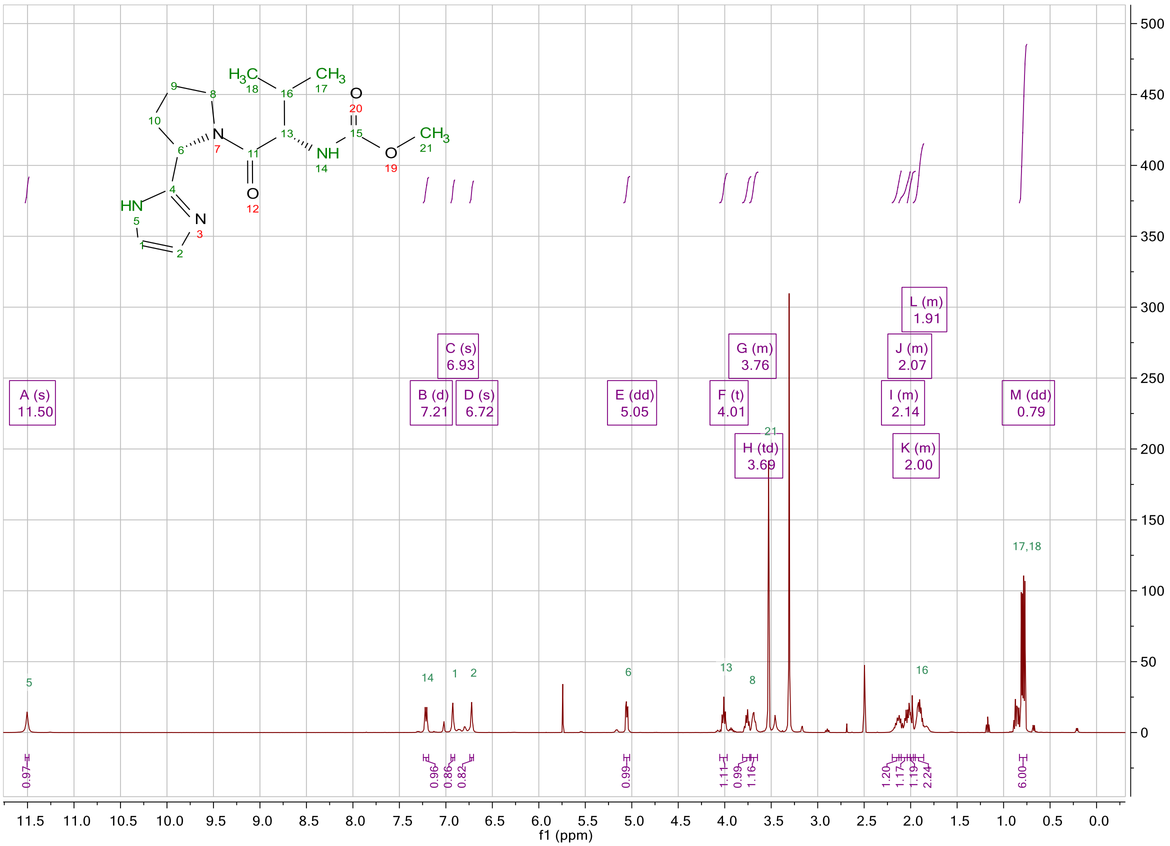
A suspension of 4-bromobenzoic acid (1.00 g, 4.97 mmol) in thionyl chloride (5.0 mL, 69 mmol) with a drop of DMF was heated to reflux under stirring. The solution was allowed to reflux for 2 hours, then concentrated under reduced pressure, to give a light orange oil, which solidified upon cooling to a crystalline solid (1.09 g)

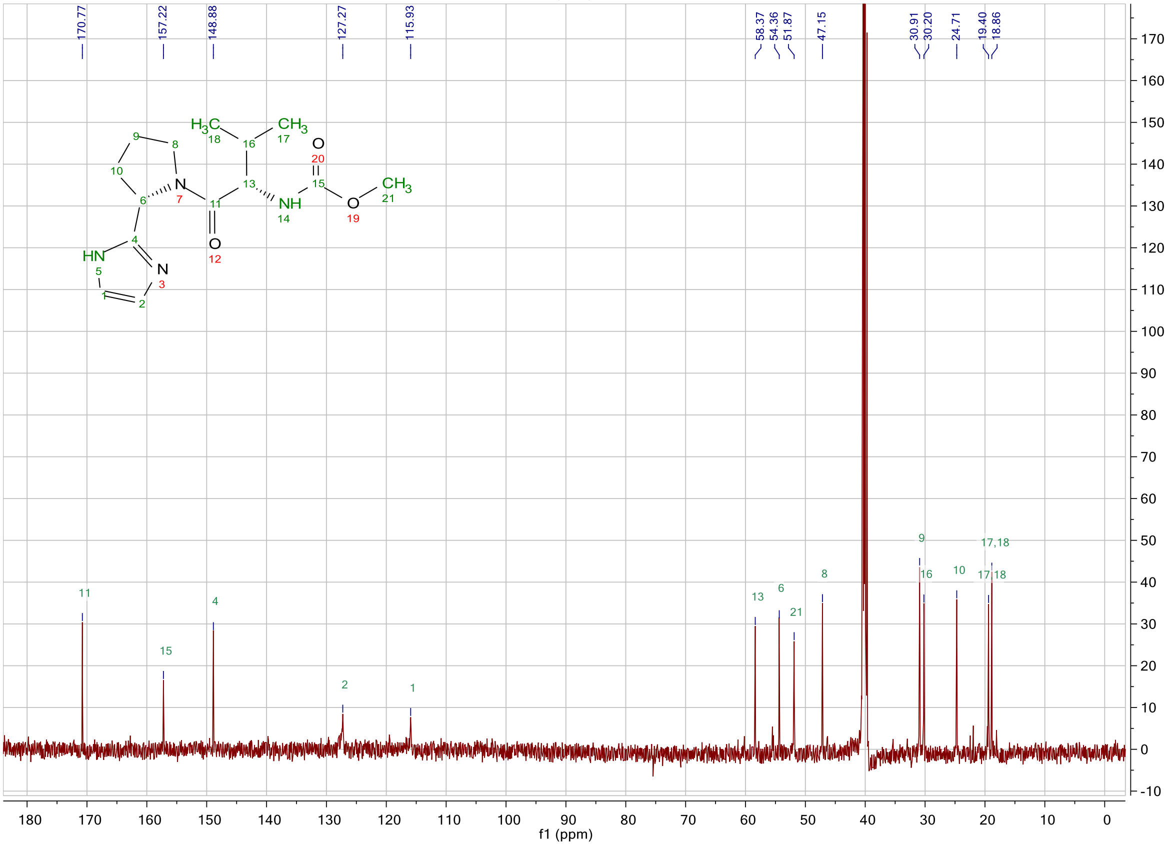
To a stirred solution of 4-bromoaniline (777 mg, 4.52 mmol) and triethylamine (1.9 mL, 13.6 mmol) in dichloromethane (30 mL) at 0 °C was added dropwise a solution of the crystalline solid produced in the first part of the experiment in dichloromethane (10 mL). After addition, the solution was allowed to warm to room temperature, and allowed to stir for a further 3 hours. The solution was then cooled to −78 °C, and the resulting white precipitate was collected by vacuum filtration, and washed with cold dichloromethane (2 x 20 mL) to give the product as a fine, white, crystalline powder (872 mg, 54 %)

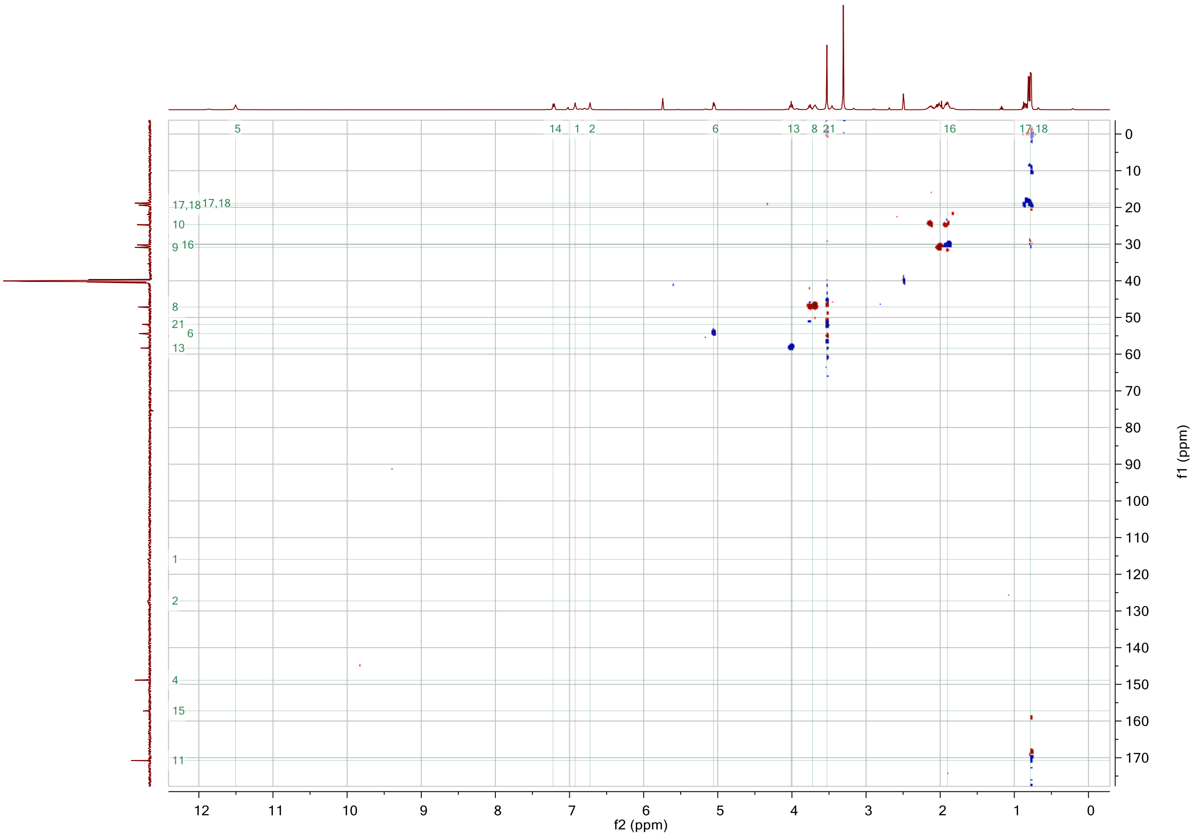
^{1}H NMR (500 MHz, DMSO-d_6) ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.40 (1H, s, 1-N*H*), 7.90 (2H, d, *J* 7.9 Hz, 4-C*H*), 7.75 (4H, d, *J* 8.3 Hz, 5-C*H*, 8-C*H*), 7.53 (2H, d, *J* 8.4 Hz, 9-C*H*). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 165.1 (2-*C*O), 138.8 (7-*C*), 134.2 (3-*C*), 131.9 (*9*-CH), 131.9 (5-*C*H), 130.3 (4-*C*H), 125.9 (6-*C*Br), 122.8 (8-*C*H), 116.0 (10-*C*Br).

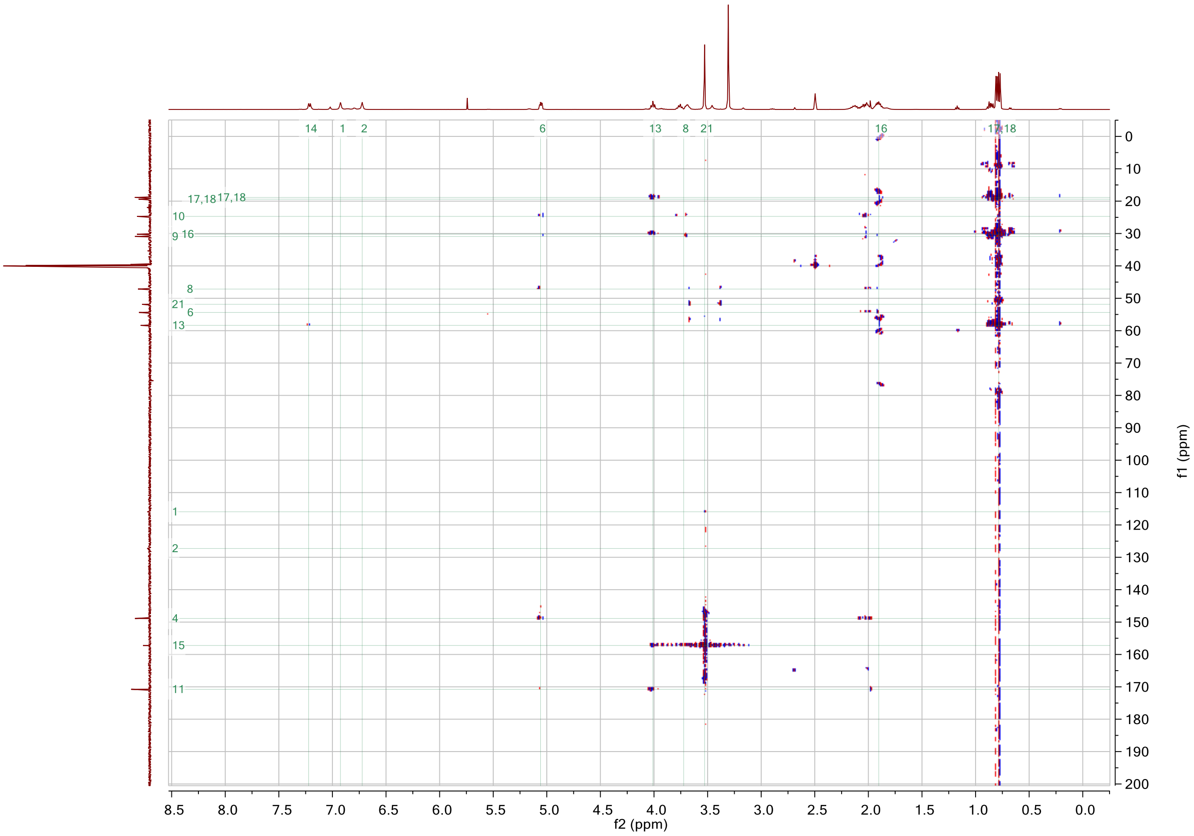
4. NMR Spectra

Methyl (S)-1-((S)-2-(1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (7)

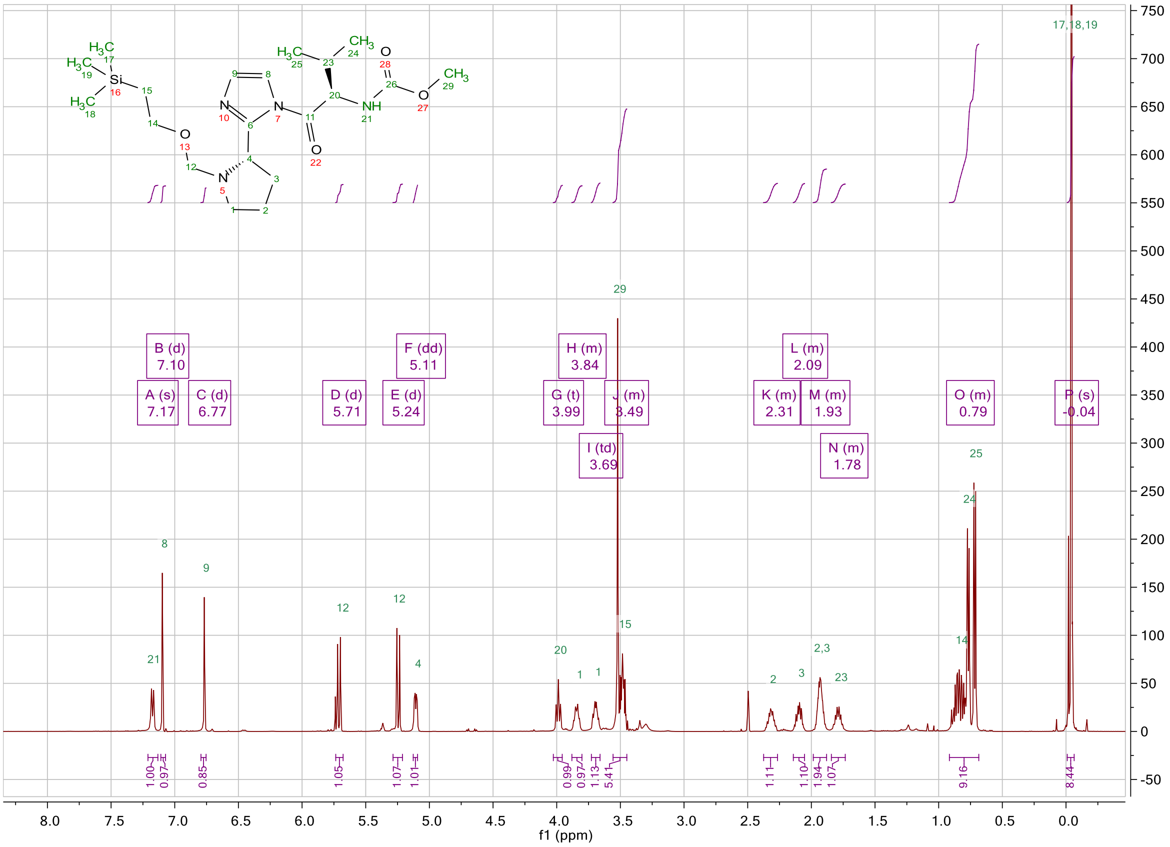


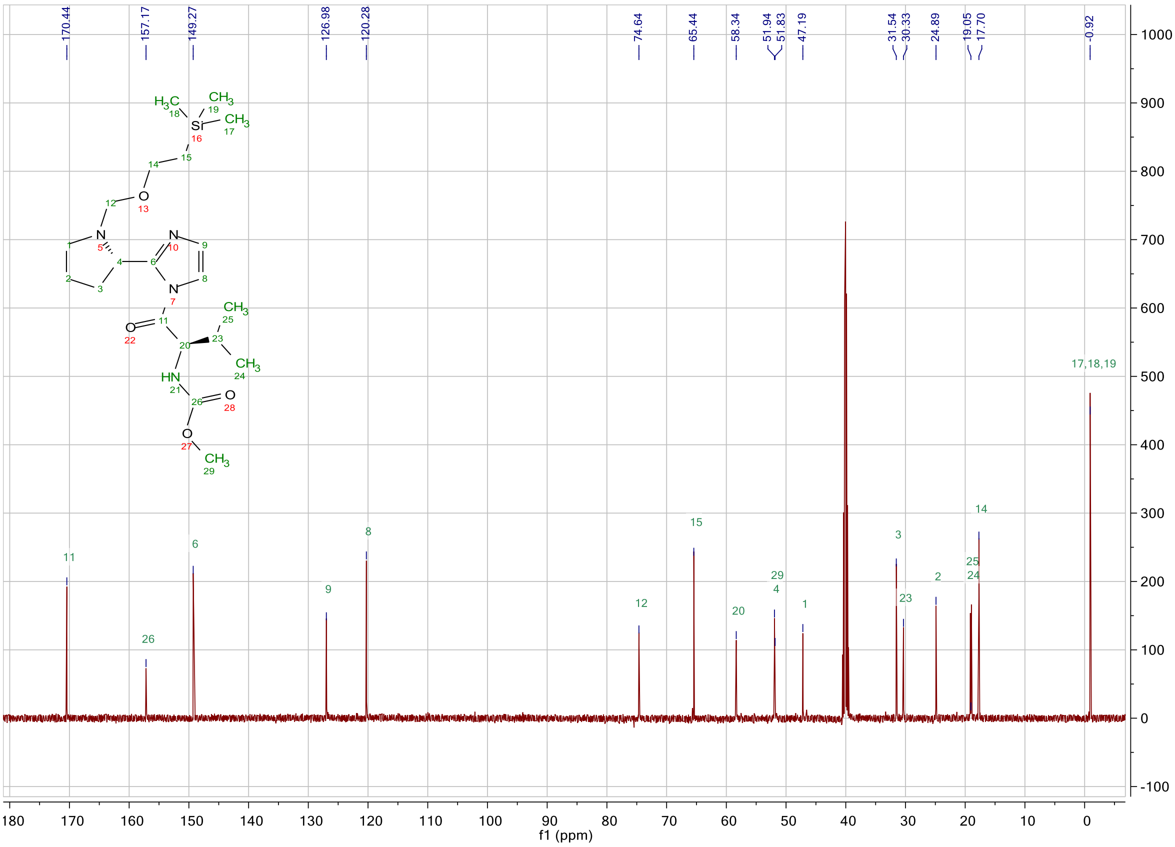


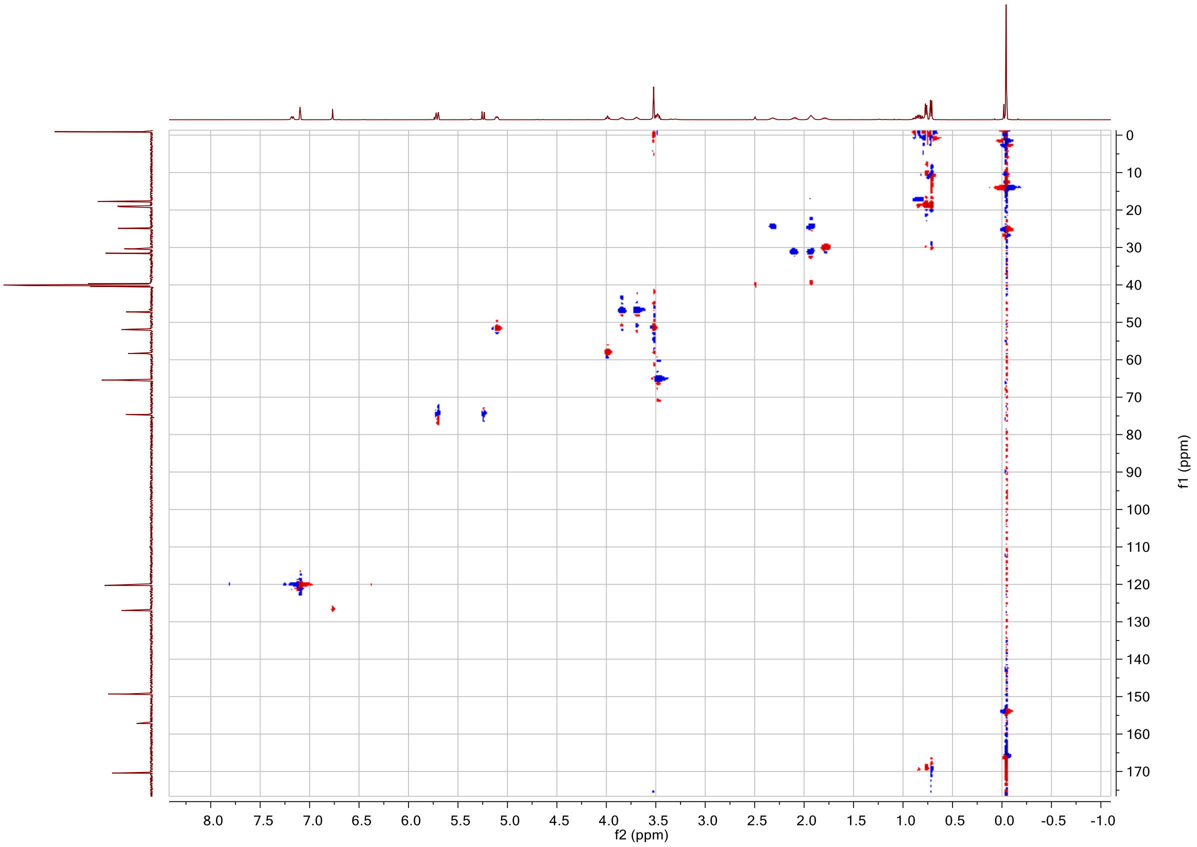

5
14
1
2
6
13
8
21
16
17,18
17,18
17,18
10
9
16
8
21
6
13
1
2
4
15
11
f2 (ppm)
f1 (ppm)


14
1
2
6
13
8
21
16
17,18
17,18
17,18
10
9
16
8
21
6
13
1
2
4
15
11
f2 (ppm)
f1 (ppm)

Methyl (*S*)-3-methyl-1-oxo-1-((*S*)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)butan-2-ylcarbamate (8)



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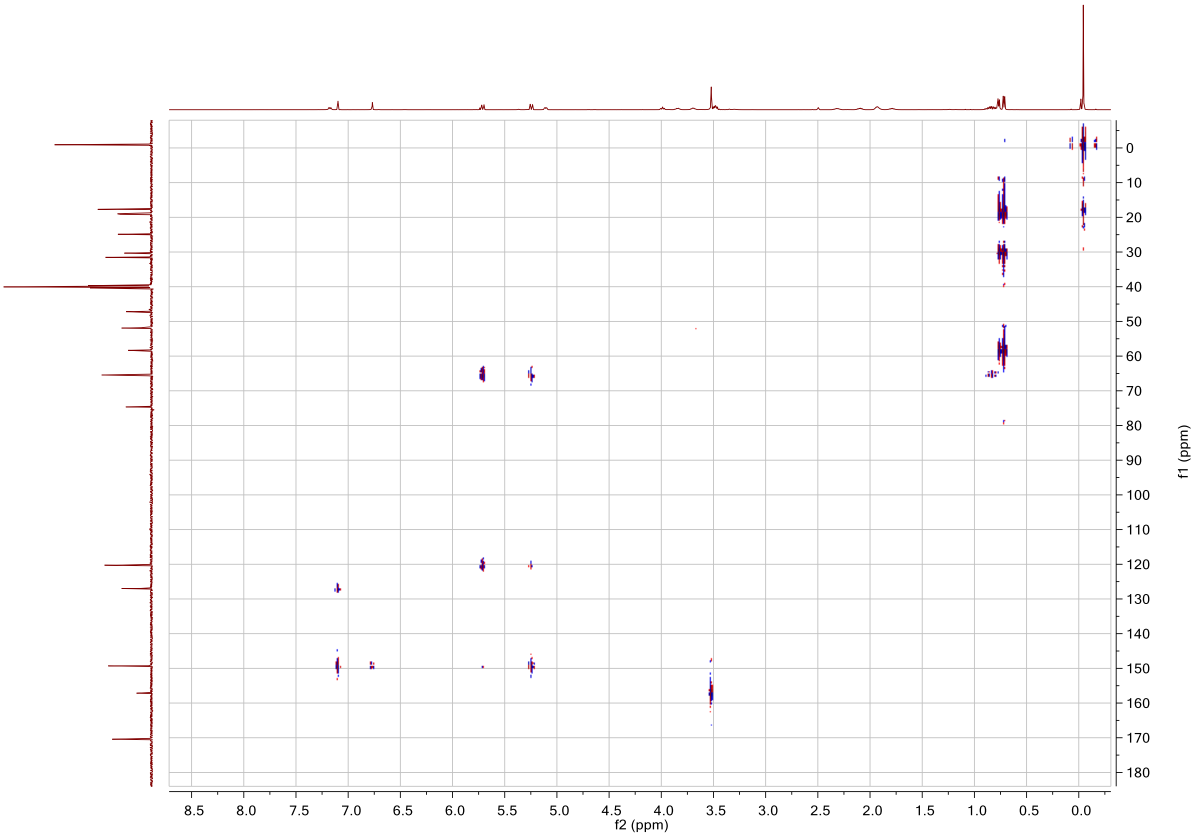
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f2 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)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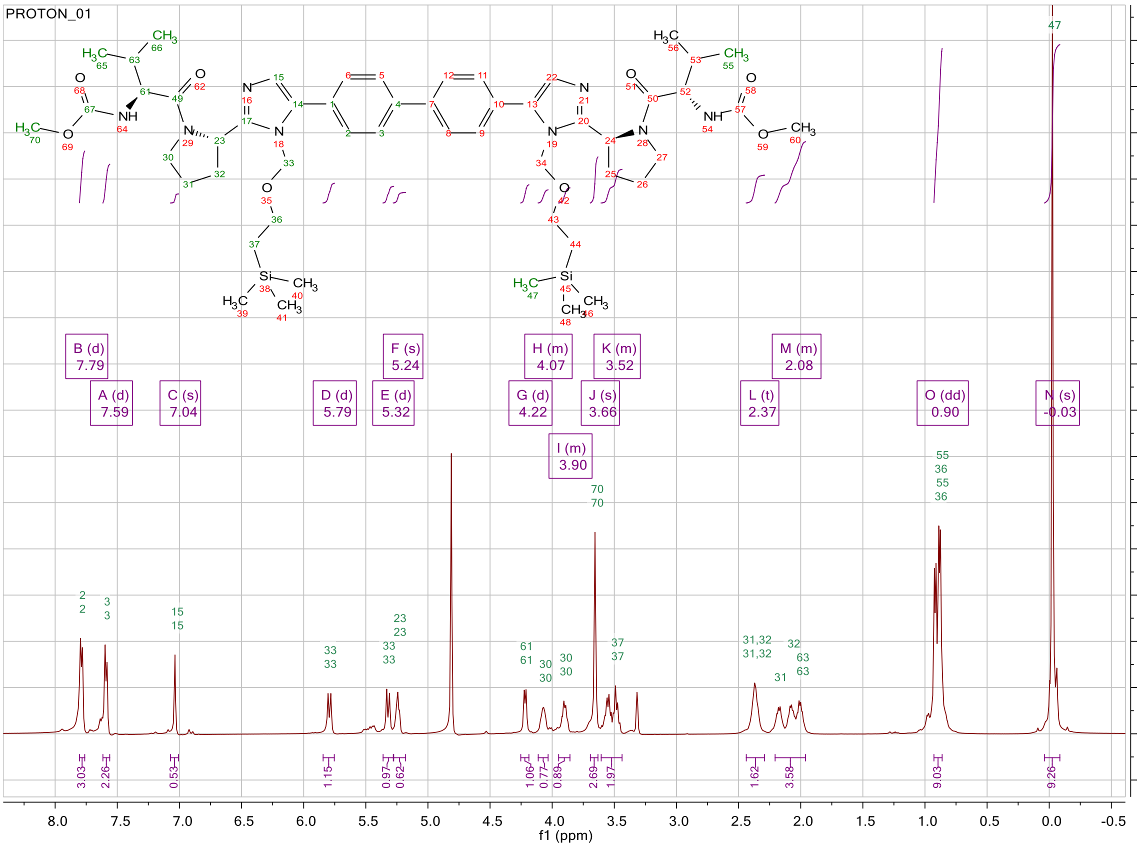
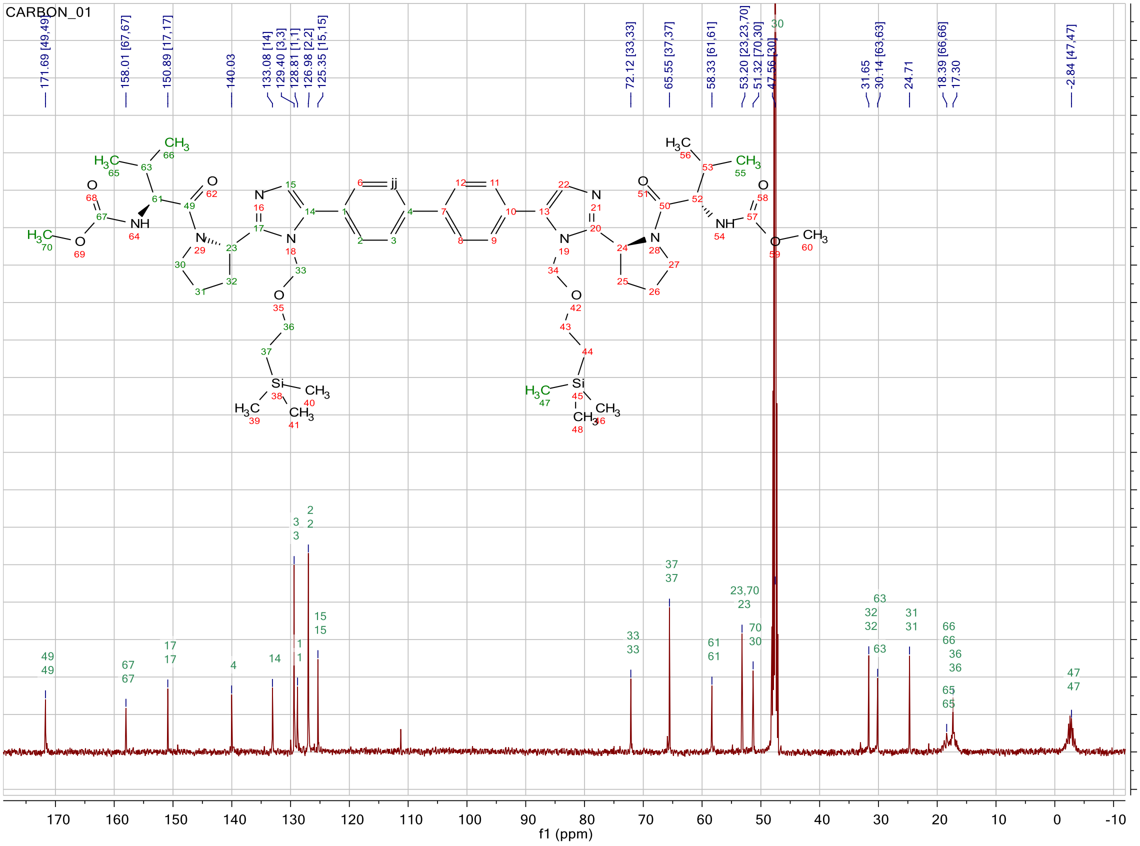
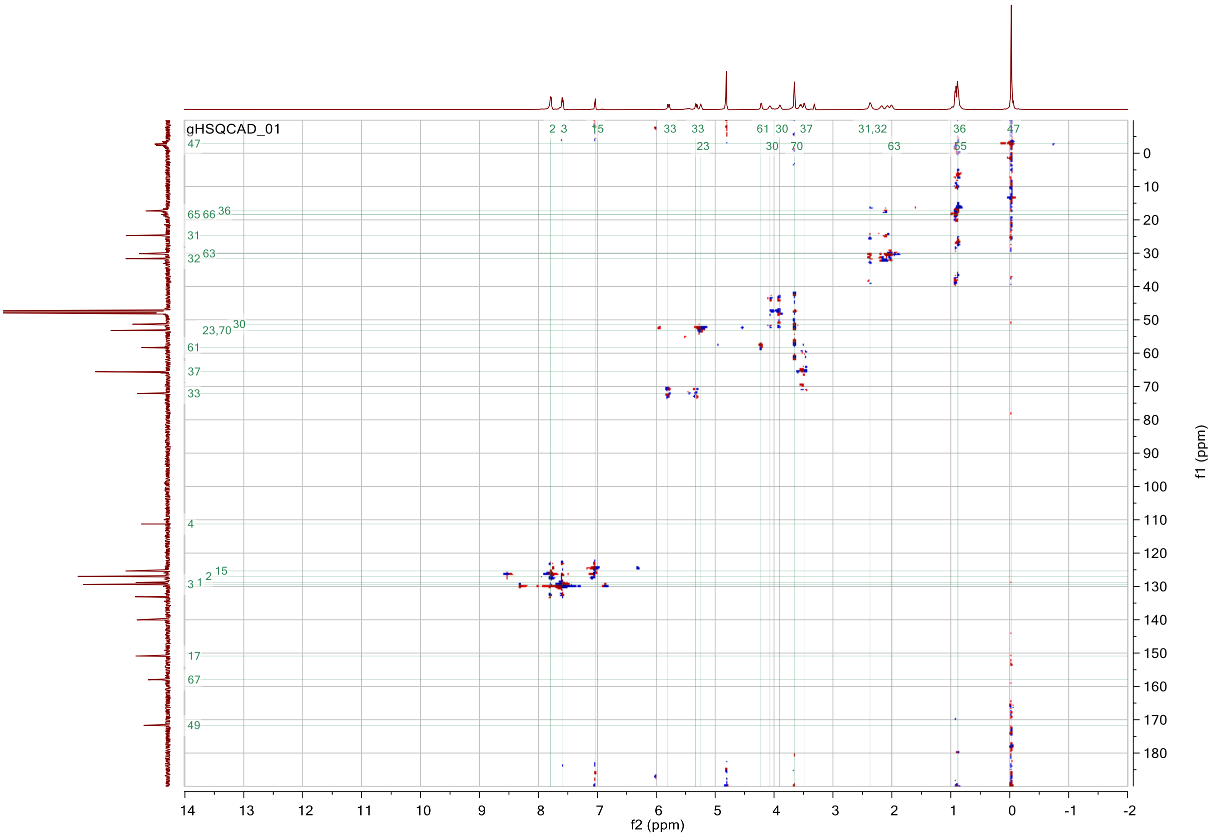
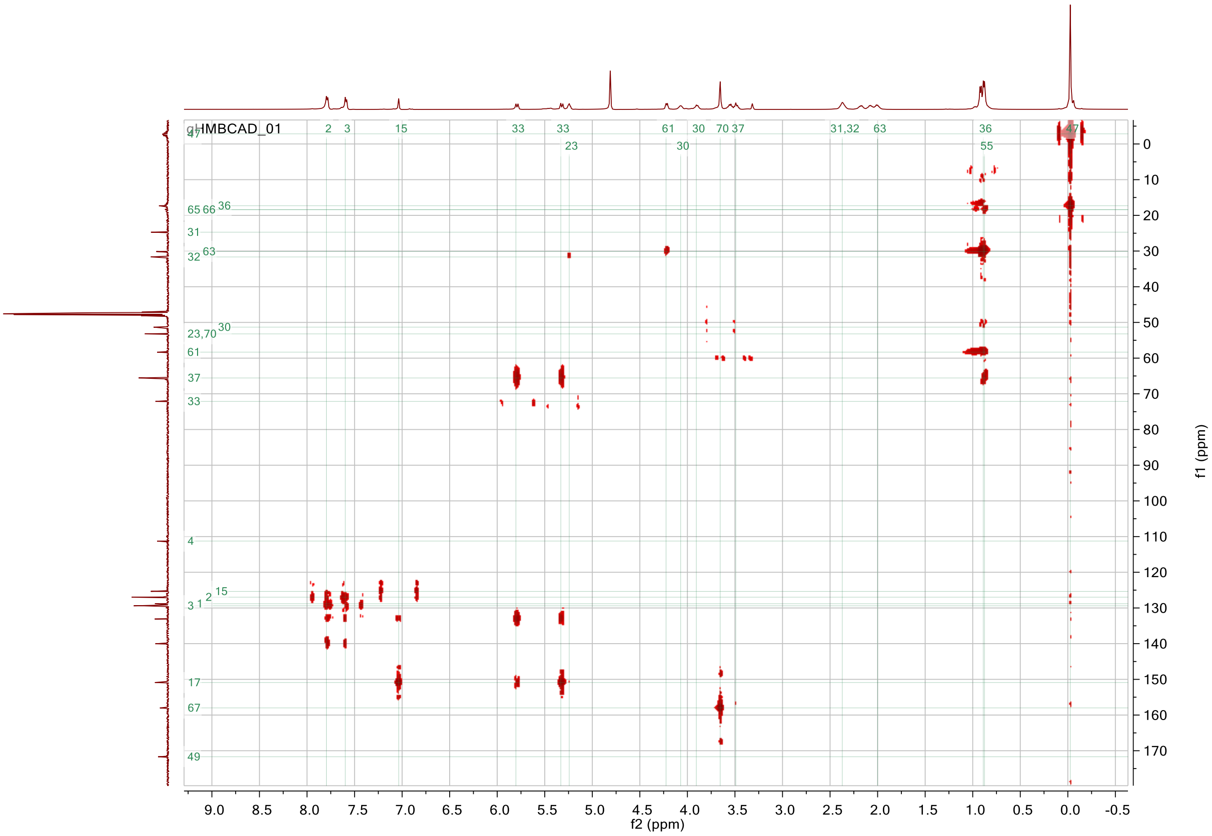
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-(biphenyl-4,4'-diyl)bis(1-((2-(trimethylsilyl) ethoxy)methyl)-1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate (10)

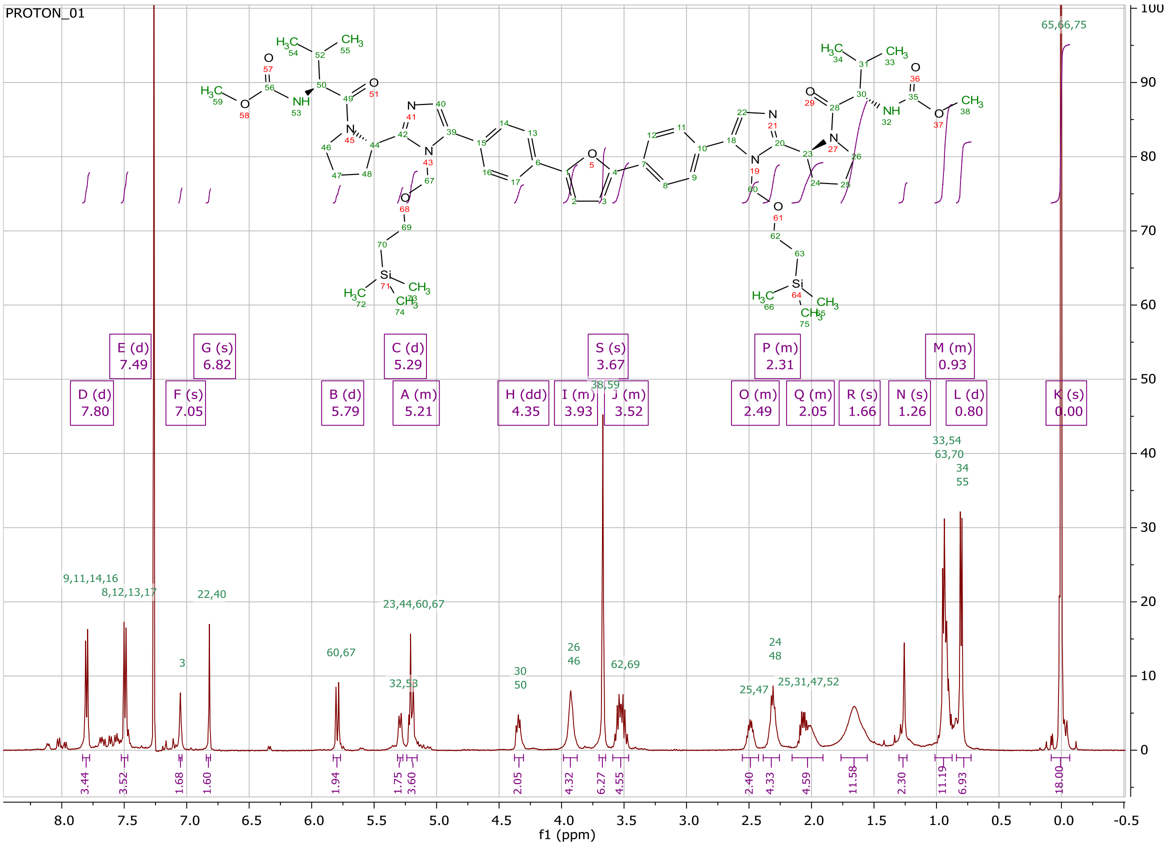


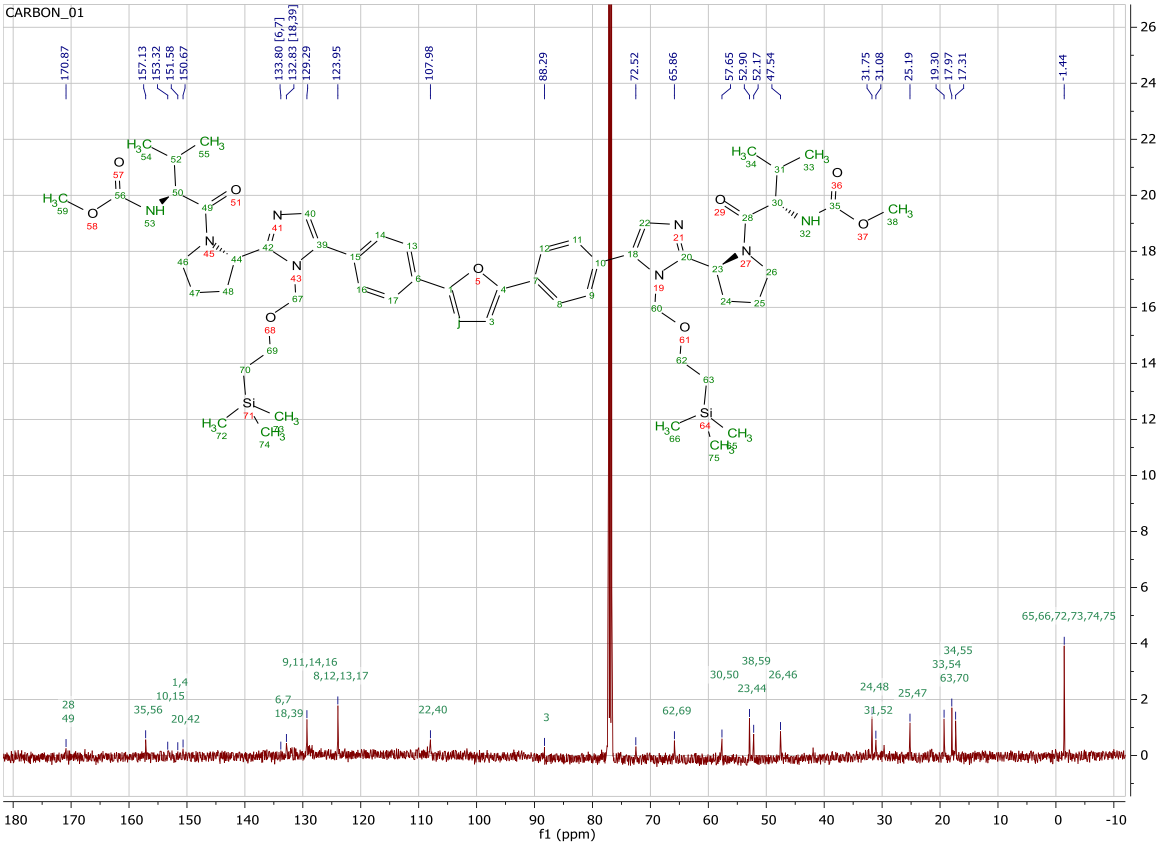


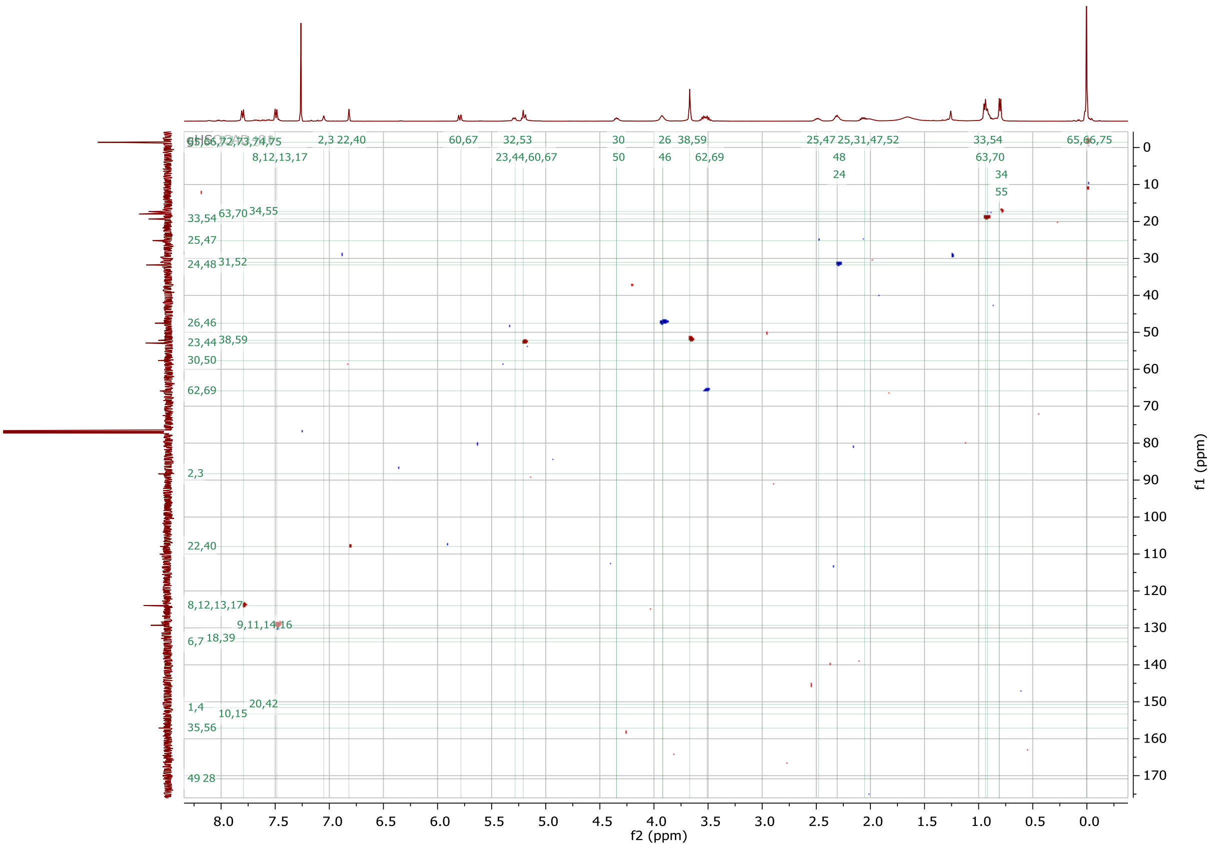

gHSQCAD_01
2 3 15 33 33 23 61 30 30 70 37 31,32 63 36 65 47
47
65 66 36
31
32 63
23,70 30
61
37
33
4
3 1 2 15
17
67
49
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f2 (ppm)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
f1 (ppm)

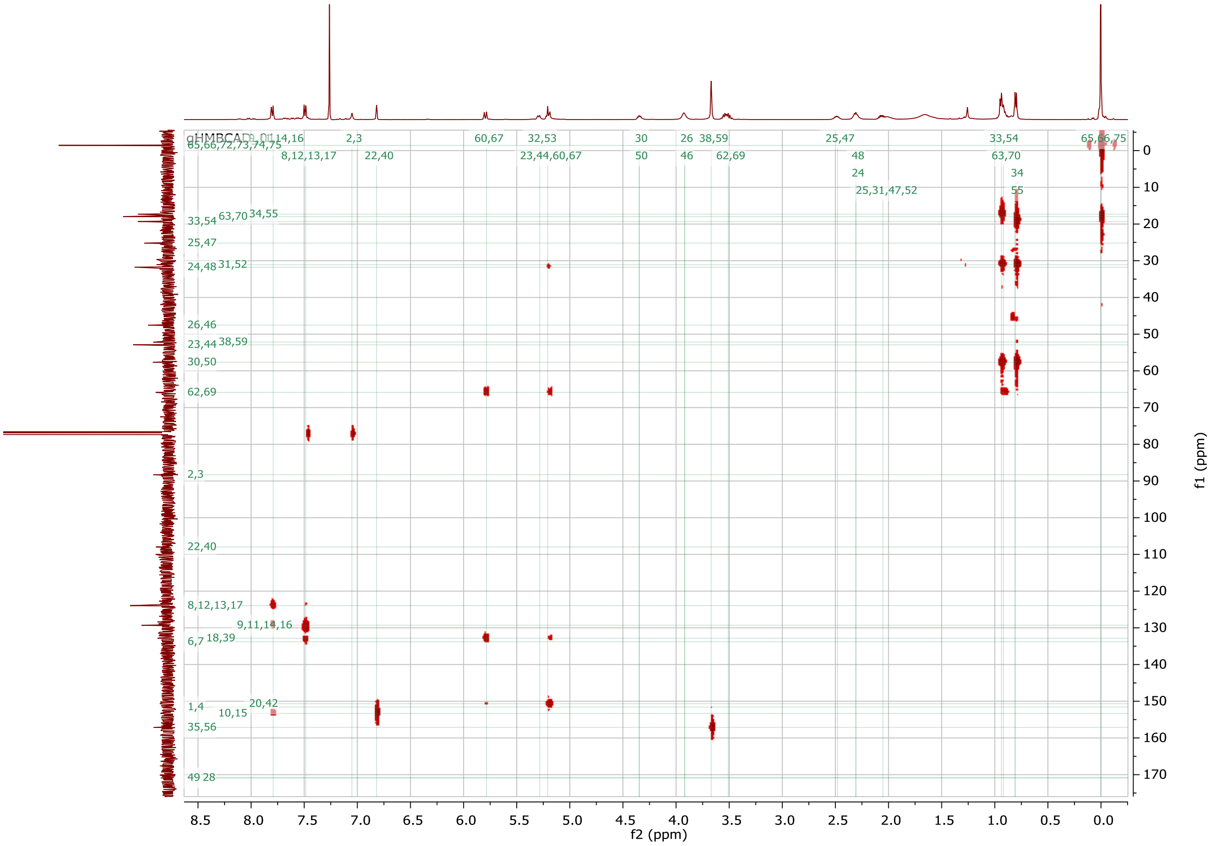

gHMBCAD_01
2 3 15 33 33 23 61 30 30 70 37 31,32 63 36 55 47
47
65 66 36
31
32 63
23,70 30
61
37
33
4
3 1 2 15
17
67
49
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f2 (ppm)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170
f1 (ppm)

Dimethyl ((2S,2'S)-((2S,2'S)-2,2'-(5,5'-(furan-2,5-diylbis(4,1-phenylene))bis(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (12)

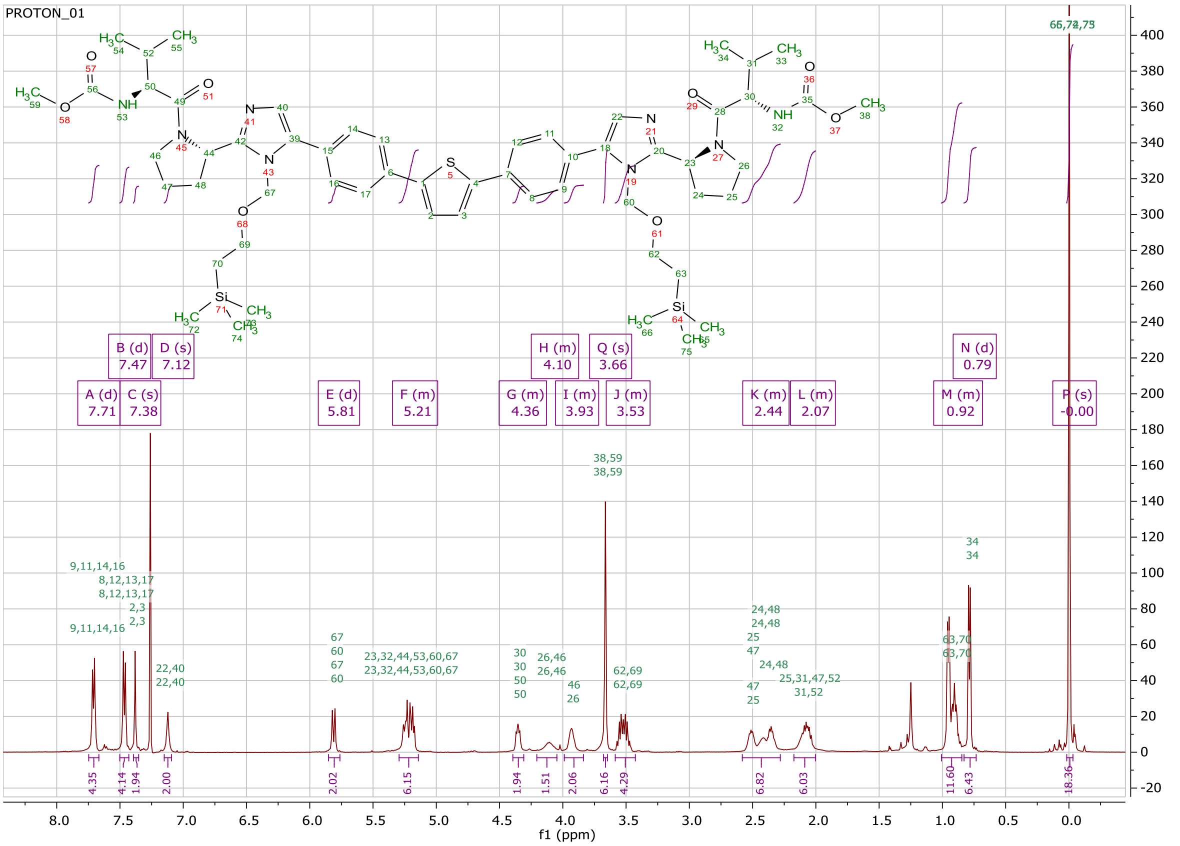


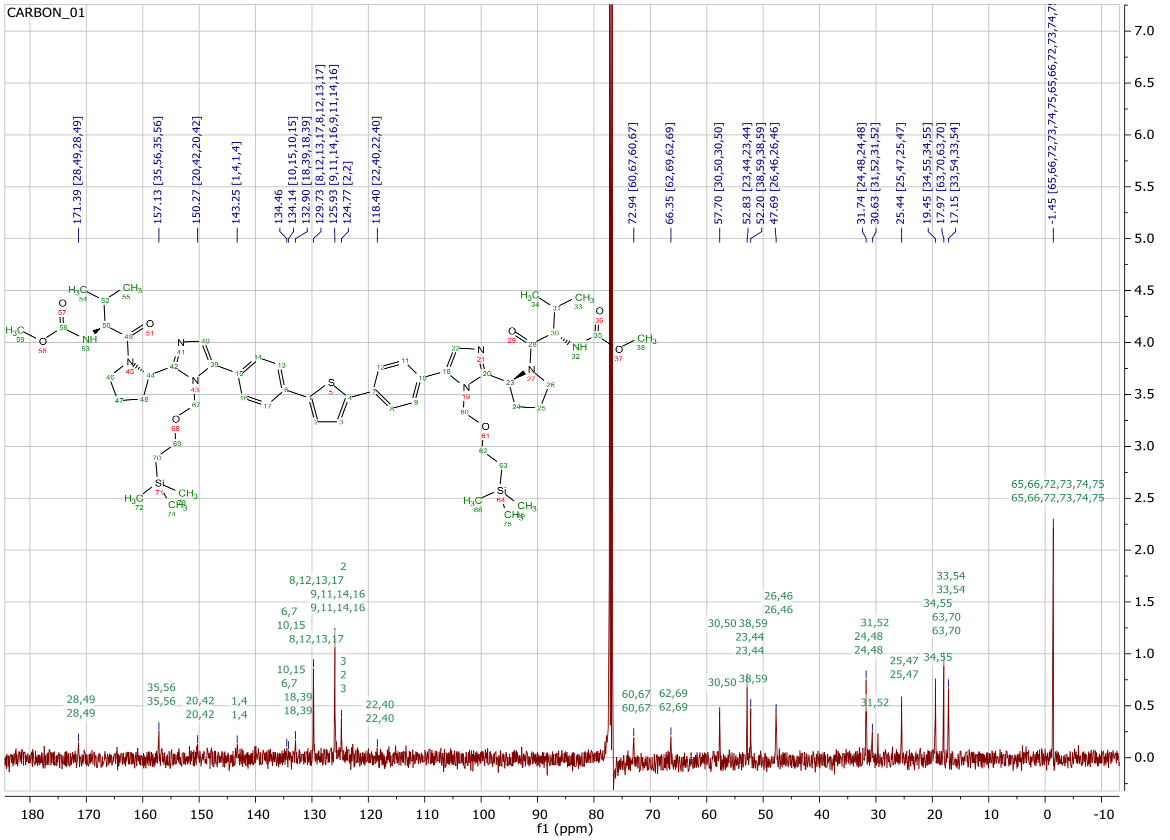


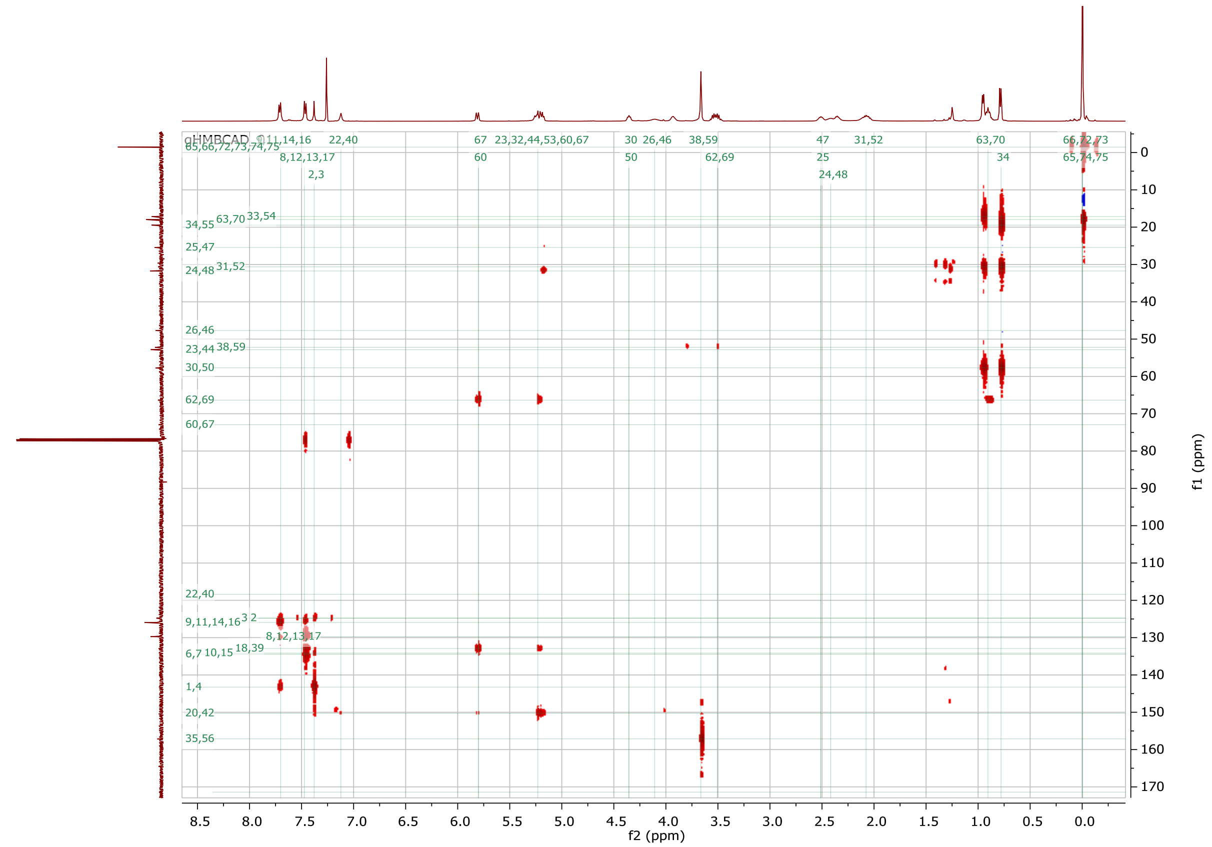

gHSQCAD
65,66,72,73,74,75
8,12,13,17
2,3 22,40
60,67
32,53
23,44,60,67
30
50
26 38,59
46 62,69
25,47 25,31,47,52
48
24
33,54
63,70
34
55
65,66,75
33,54 63,70 34,55
25,47
24,48 31,52
26,46
23,44 38,59
30,50
62,69
2,3
22,40
8,12,13,17
9,11,14,16
6,7 18,39
1,4
10,15
20,42
35,56
49 28
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f2 (ppm)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170
f1 (ppm)

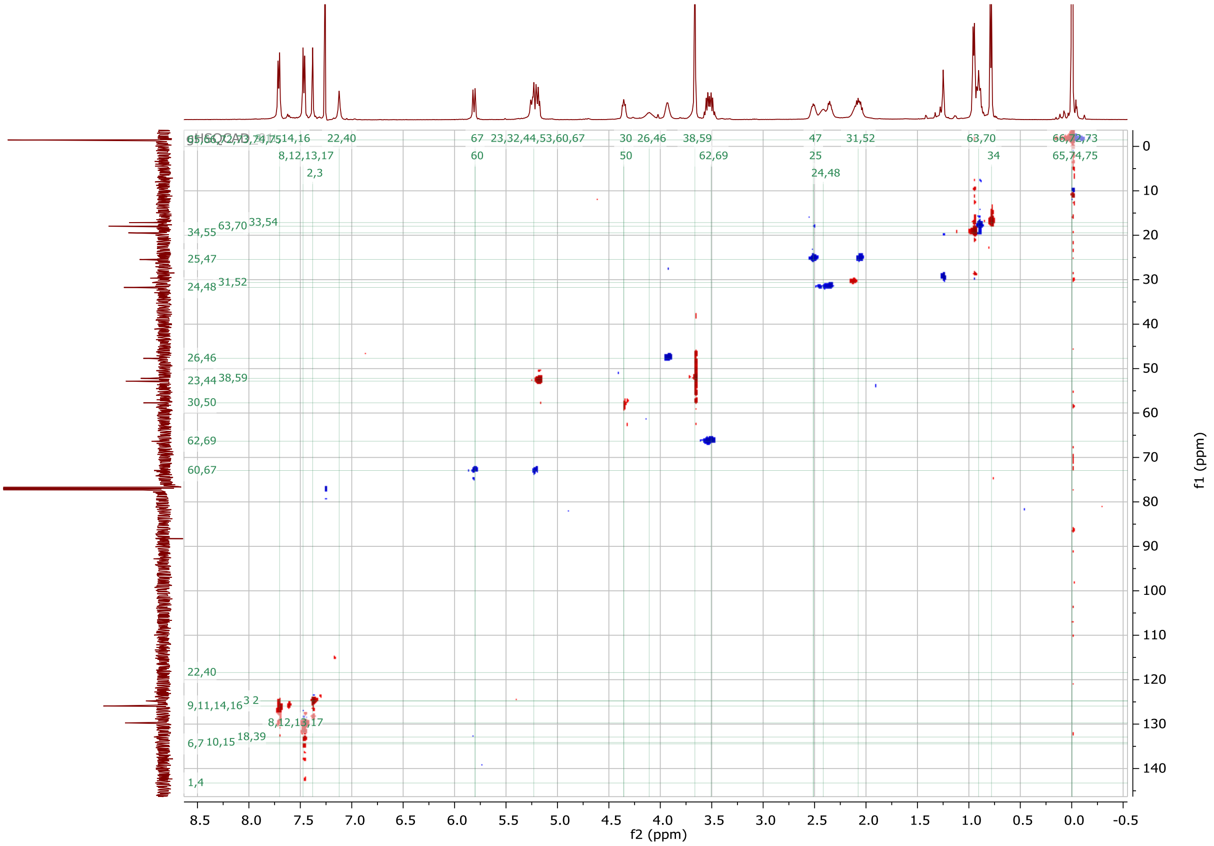

gHMBCAD
65,66,72,73,74,75
9,11,14,16
8,12,13,17
2,3
22,40
60,67
32,53
23,44,60,67
30
50
26 38,59
46 62,69
25,47
48
24
25,31,47,52
33,54
63,70
34
55
65,66,75
33,54 63,70 34,55
25,47
24,48 31,52
26,46
23,44 38,59
30,50
62,69
2,3
22,40
8,12,13,17
9,11,14,16
6,7 18,39
1,4
10,15
20,42
35,56
49 28
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f2 (ppm)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170
f1 (ppm)

Dimethyl ((2S,2'S)-((2S,2'S)-2,2'-(5,5'-(thiophene-2,5-diylbis(4,1-phenylene))bis(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (13)

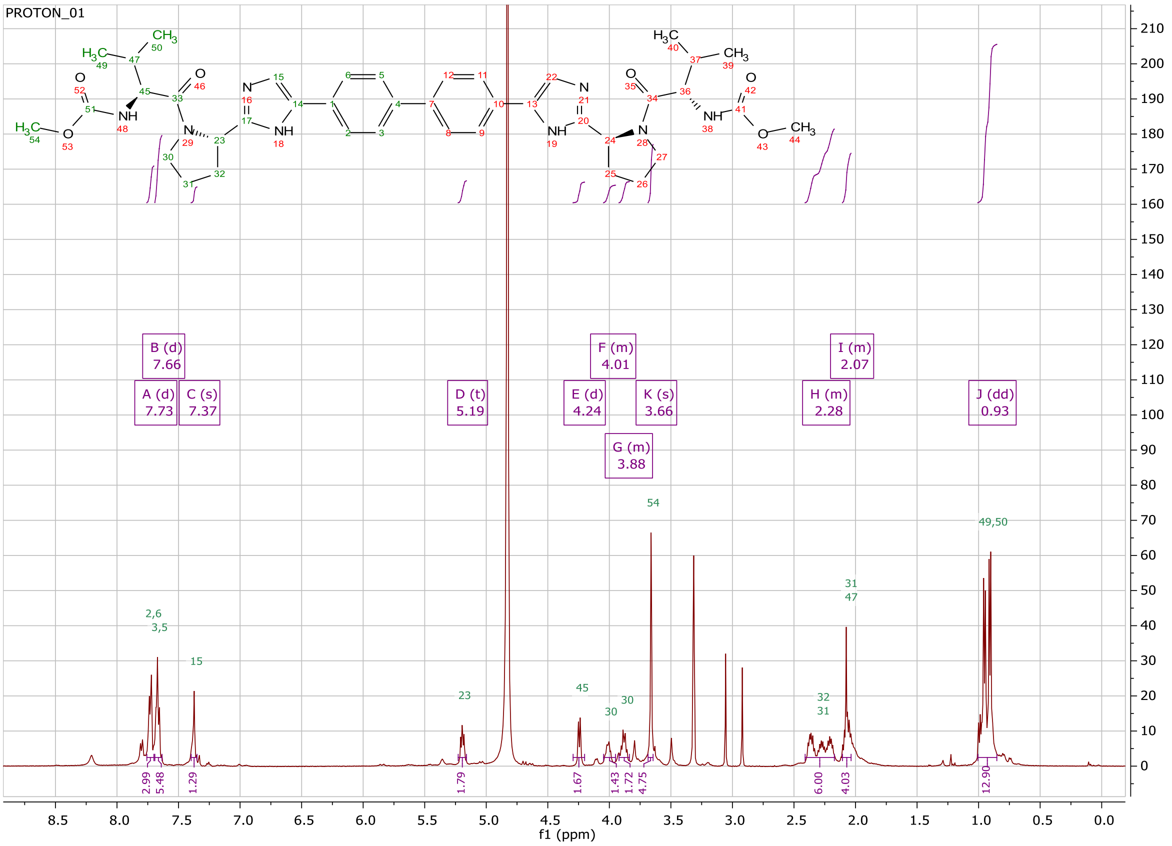


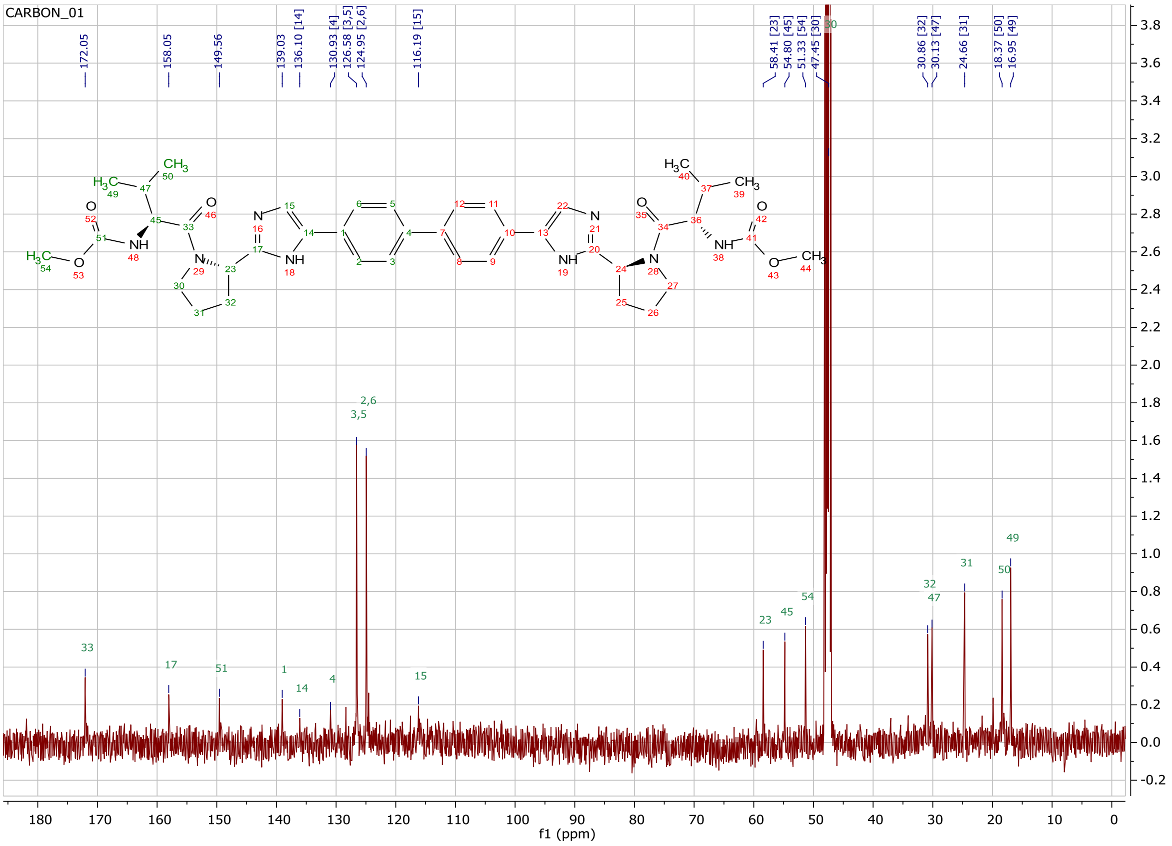


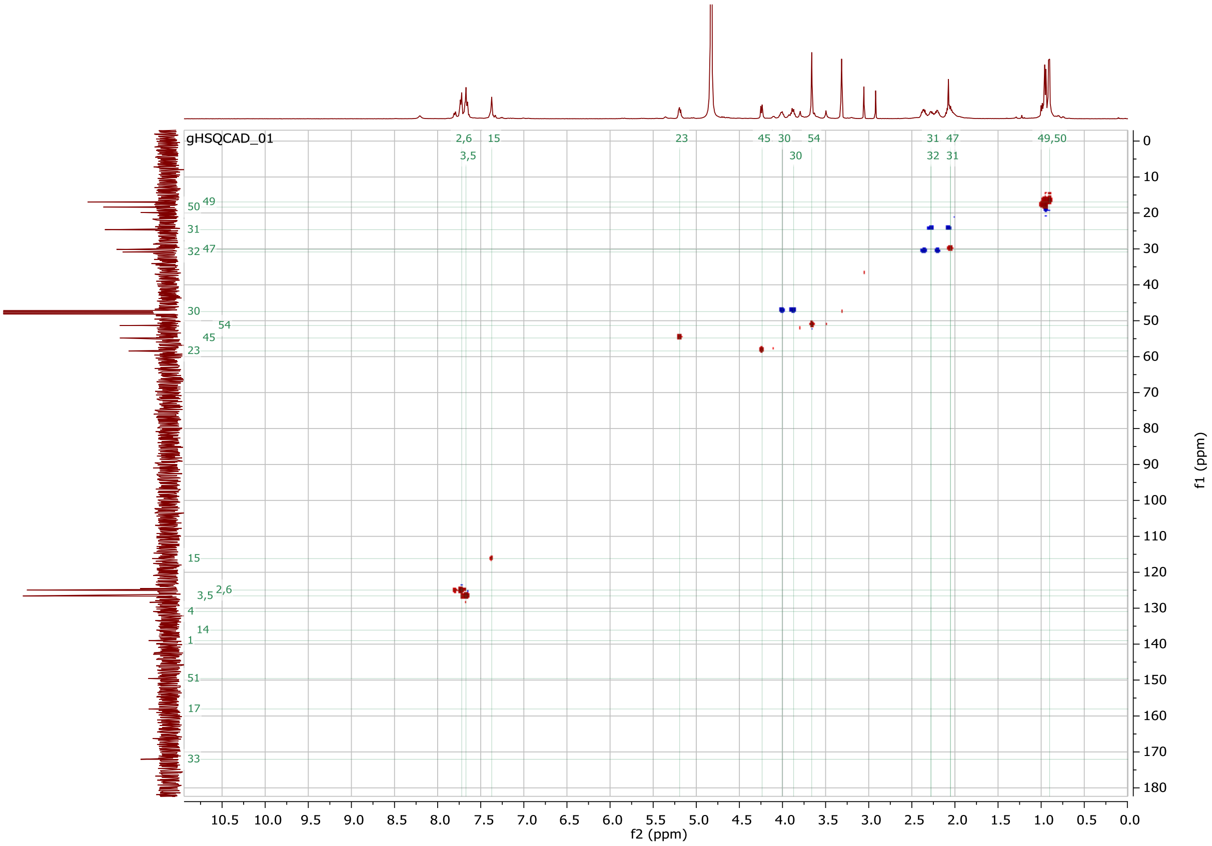

gHMBCAD
65,66,72,73,74,75
11,14,16
22,40
8,12,13,17
2,3
67
23,32,44,53,60,67
60
30
26,46
50
38,59
62,69
47
31,52
25
24,48
63,70
34
66,72,73
65,74,75
34,55
63,70
33,54
25,47
24,48
31,52
26,46
23,44
38,59
30,50
62,69
60,67
22,40
9,11,14,16
3
2
8,12,13,17
6,7
10,15
18,39
1,4
20,42
35,56
f2 (ppm)
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170


gHSQCAD
65,66,72,73,74,75
11,14,16
22,40
8,12,13,17
2,3
67
23,32,44,53,60,67
60
30
26,46
50
38,59
62,69
47
31,52
25
24,48
63,70
34
66,72,73
65,74,75
34,55
63,70
33,54
25,47
24,48
31,52
26,46
23,44
38,59
30,50
62,69
60,67
22,40
9,11,14,16
3
2
8,12,13,17
6,7
10,15
18,39
1,4
f2 (ppm)
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140

Dimethyl ((2S,2'S)-((2S,2'S)-2,2'-(5,5'-([1,1'-biphenyl]-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (1)






gHSQCAD_01
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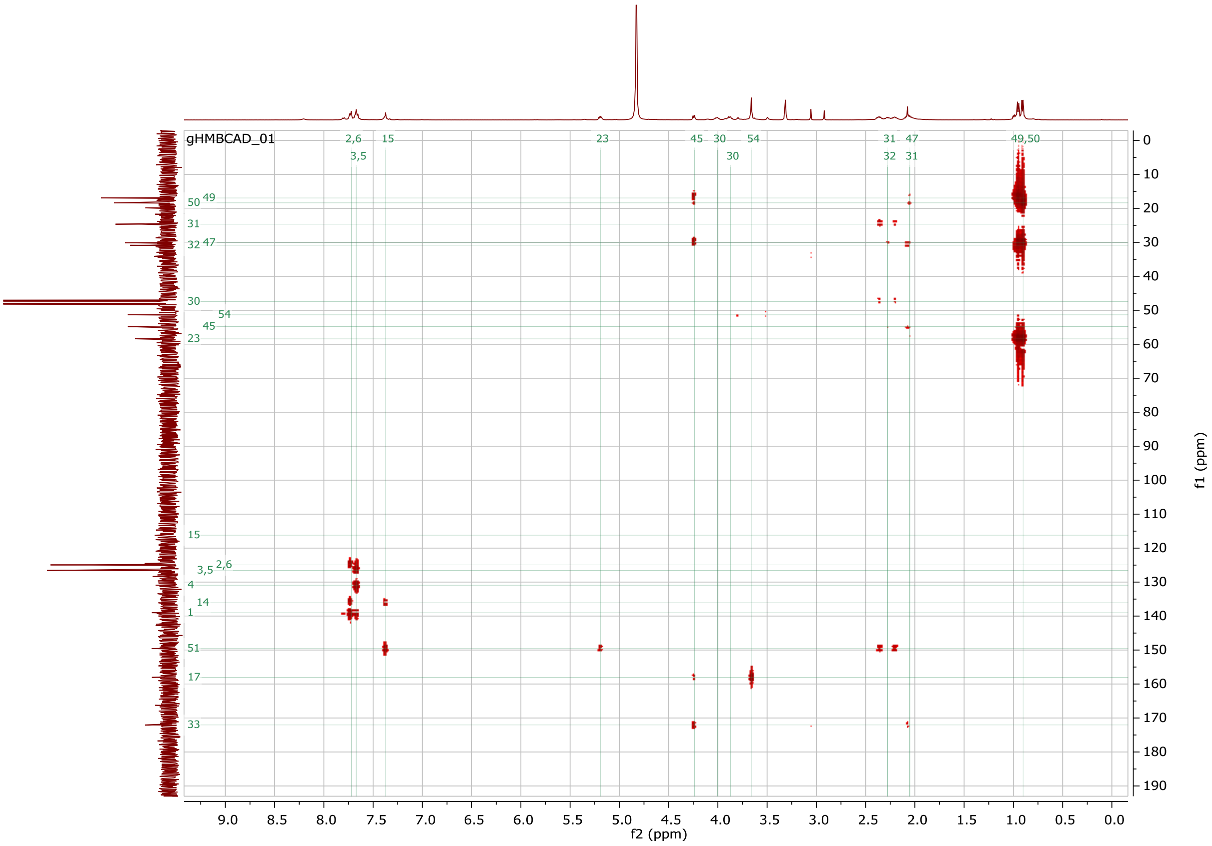
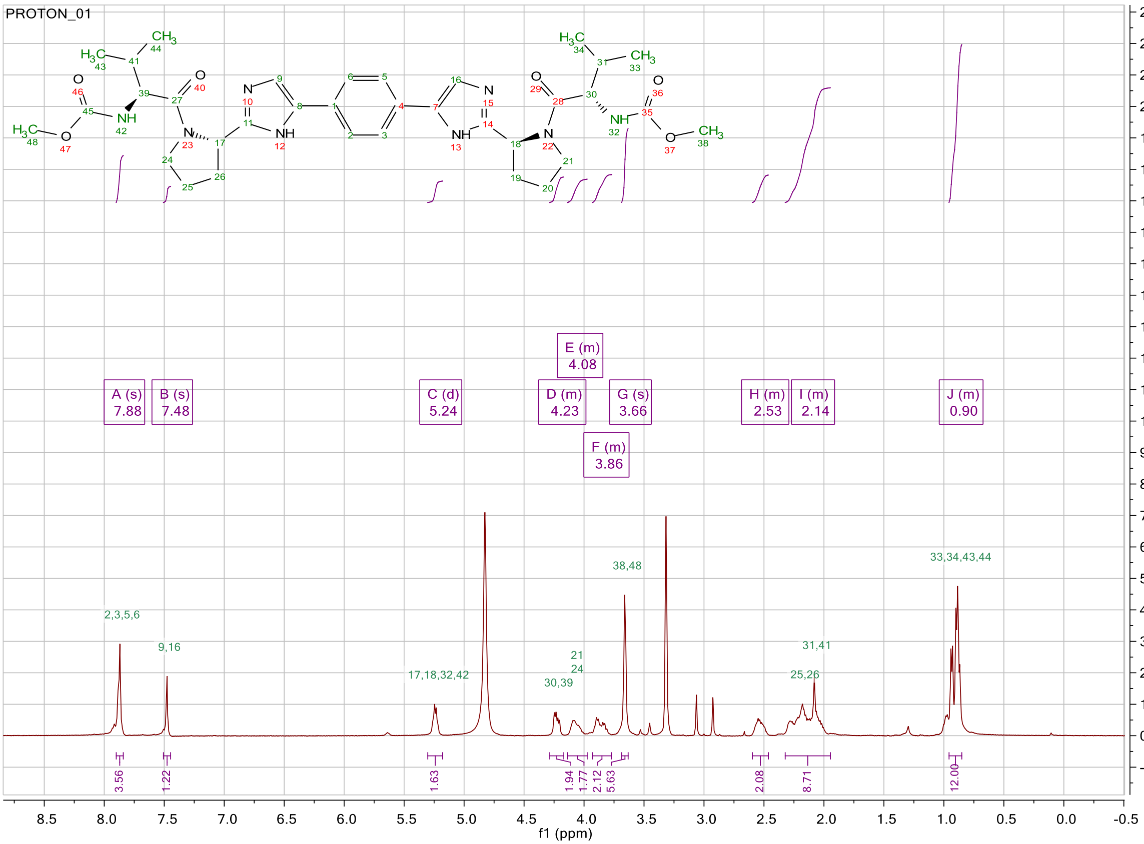
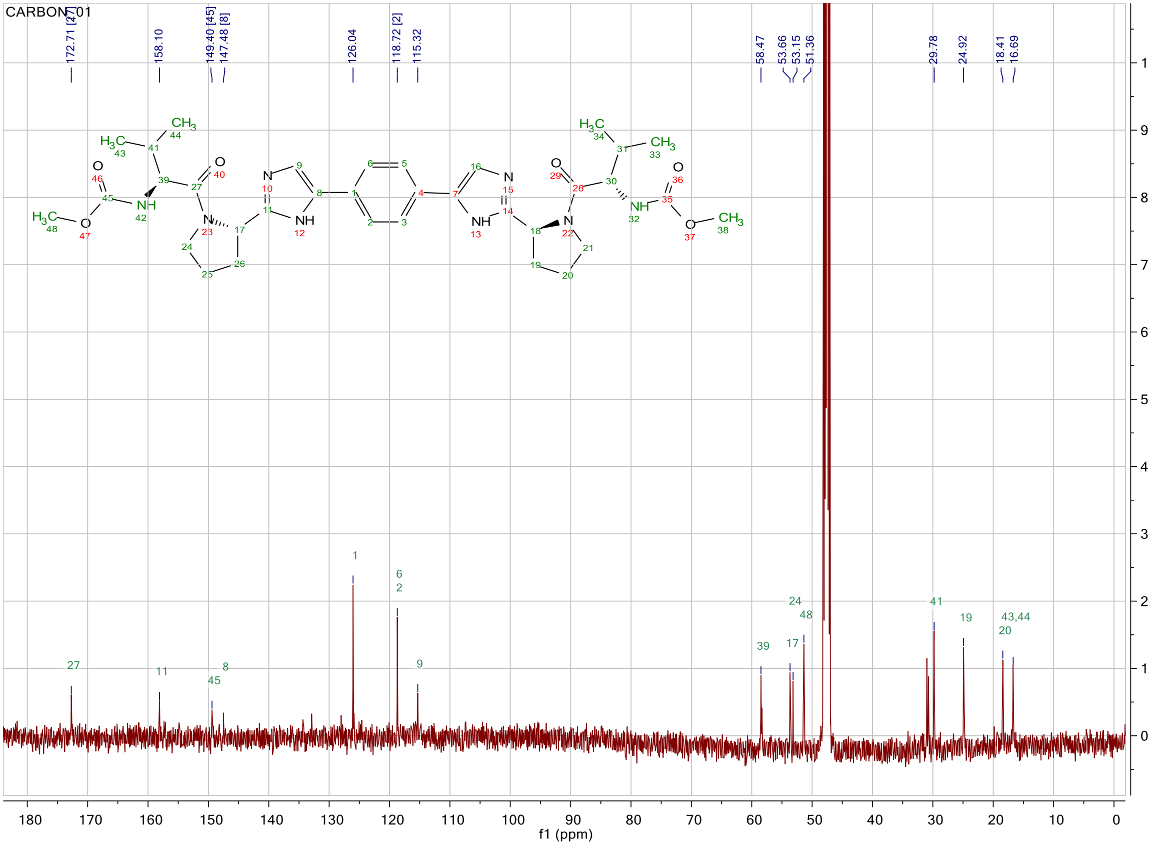
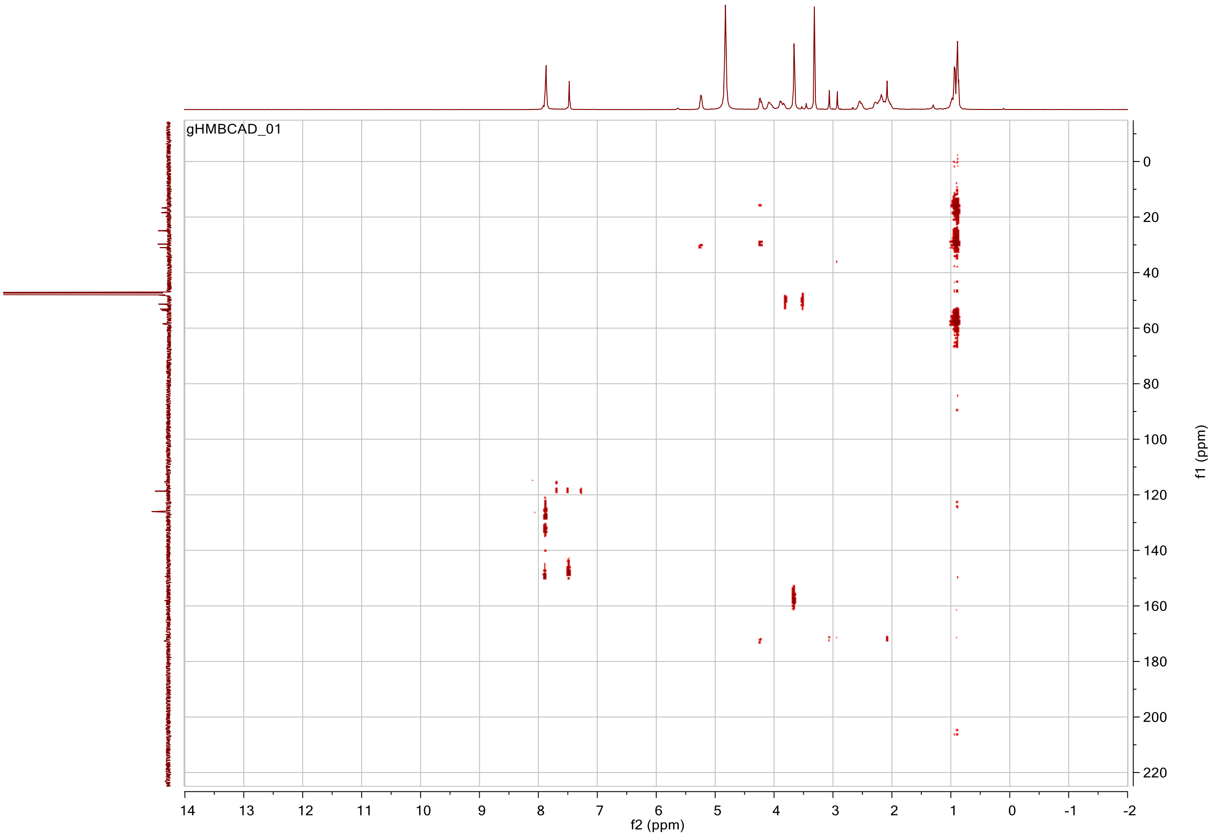
3,5
15
23
45
30
30
54
31
32
47
31
49,50
50
49
31
32
47
30
54
45
23
15
3,5
2,6
4
14
1
51
17
33
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f2 (ppm)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


gHMBCAD_01
2,6
3,5
15
23
45
30
30
54
31
32
47
31
49,50
50
49
31
32
47
30
54
45
23
15
3,5
2,6
4
14
1
51
17
33
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f2 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

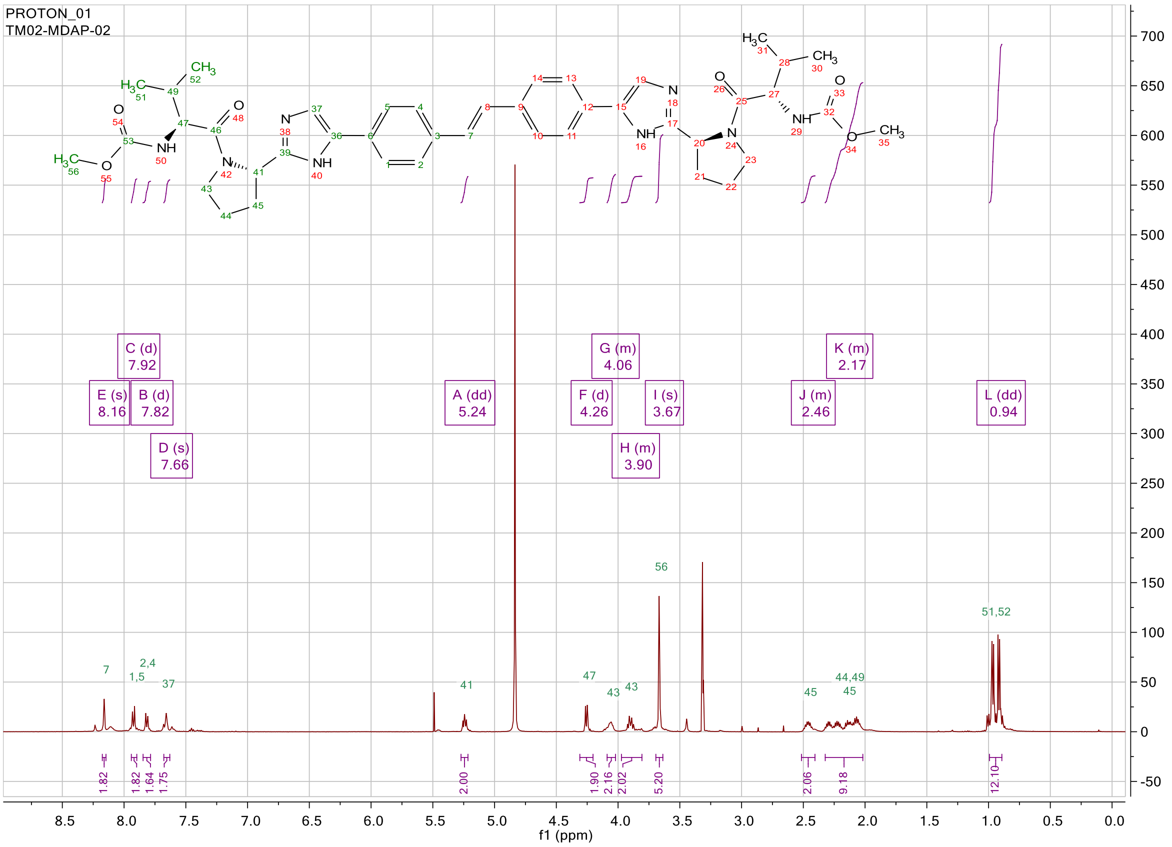
Dimethyl ((2S,2'S)-((2S,2'S)-2,2'-(5,5'-(1,4-phenylene)bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (14)

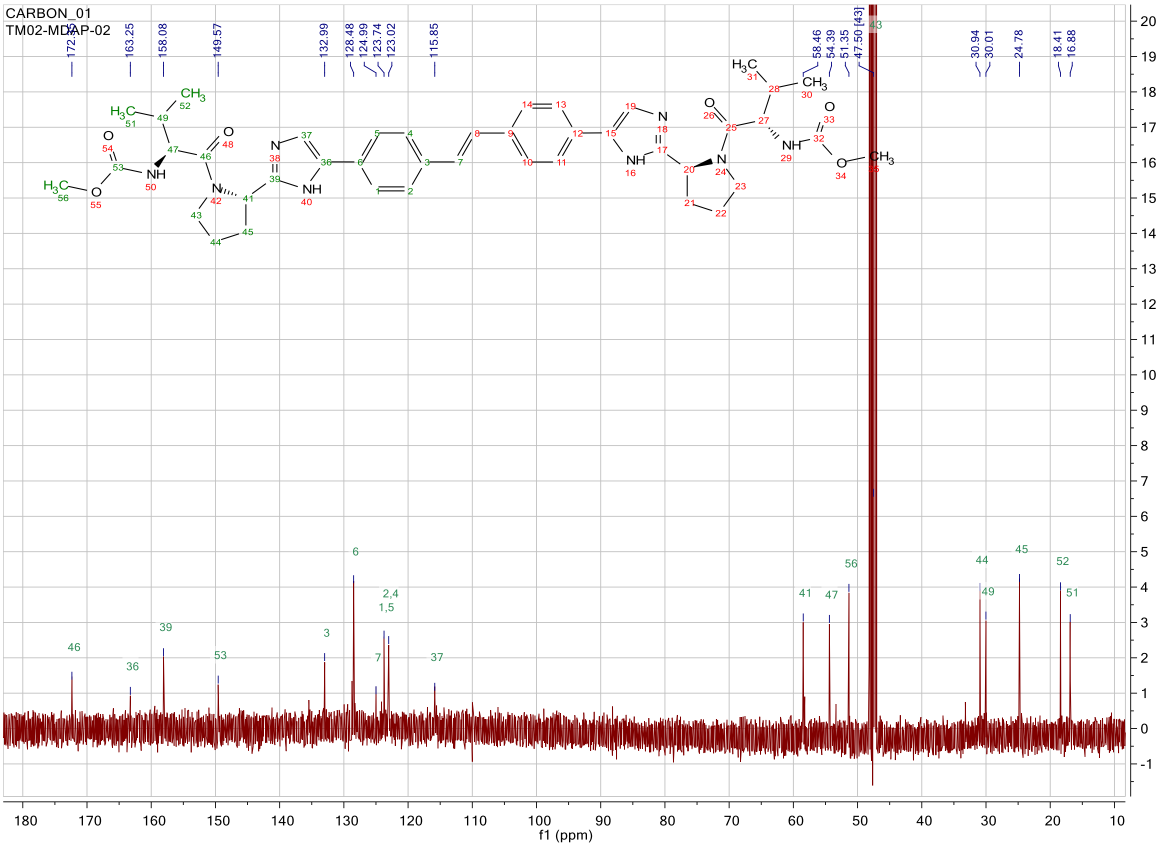


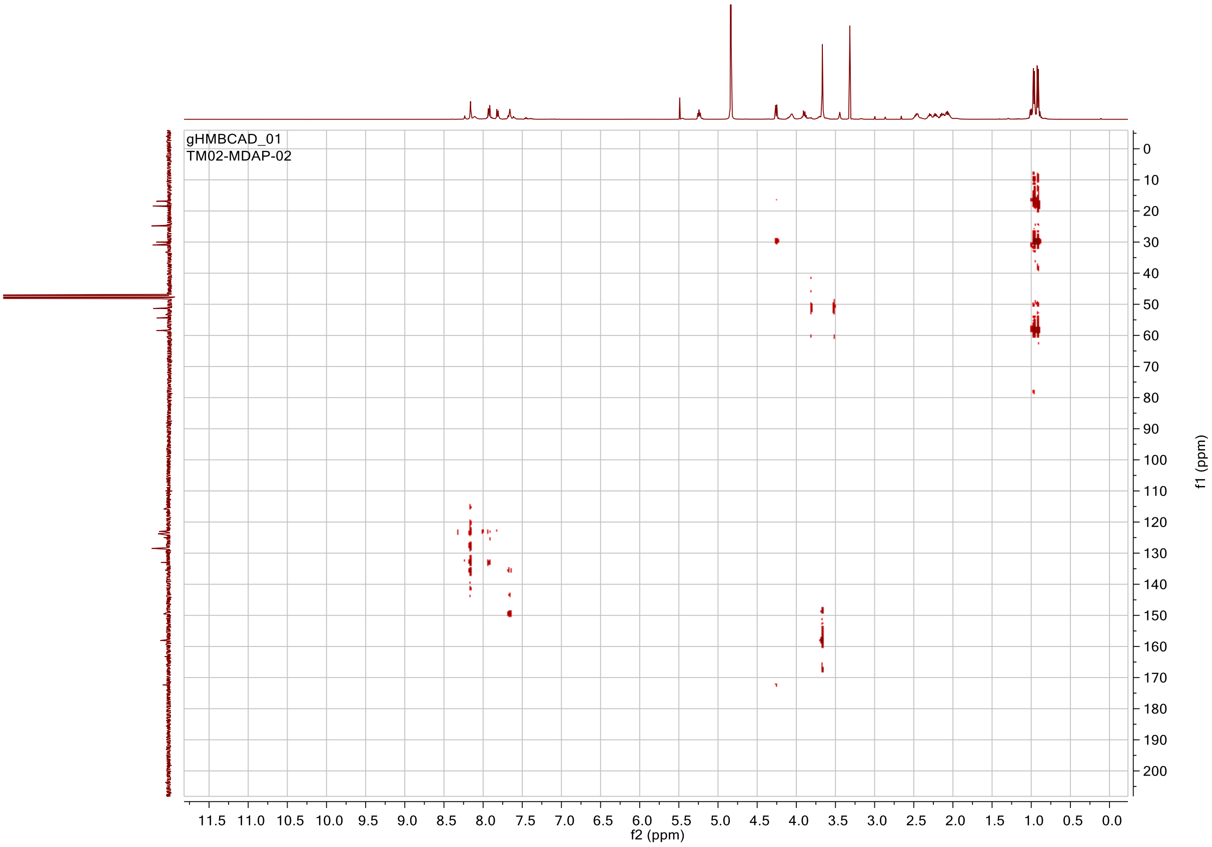



gHMBCAD_01
f2 (ppm)
f1 (ppm)
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
0
20
40
60
80
100
120
140
160
180
200
220

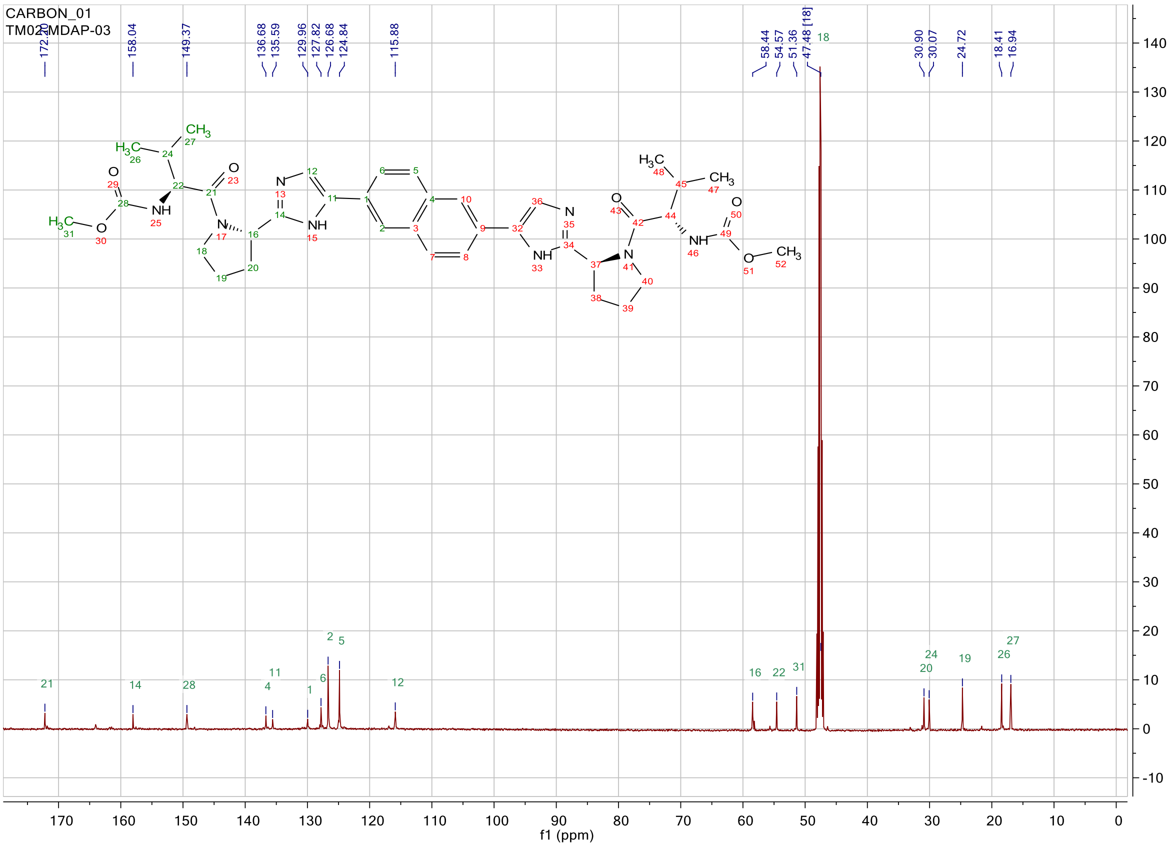
Dimethyl ((2S,2'S)-((2S,2'S)-2,2'-(5,5'-((E)-ethene-1,2-diylbis(4,1-phenylene))bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (15)

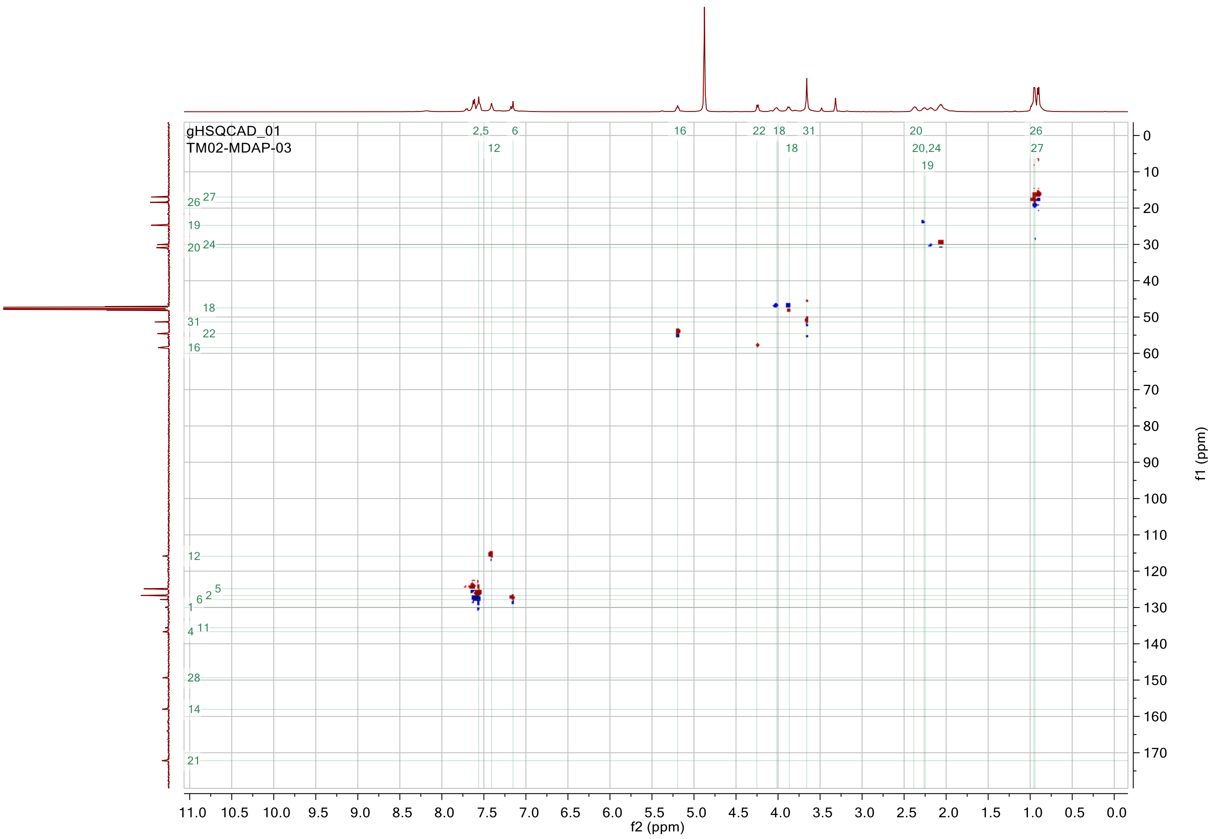





gHMBCAD_01
TM02-MDAP-02
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

Dimethyl ((2S,2'S)-((2S,2'S)-2,2'-(5,5'-(naphthalene-2,6-diyl)bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (16)




gHSQCAD_01
TM02-MDAP-03
2,5
6
12
16
22
18
31
18
20
20,24
19
26
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26 27
19
20 24
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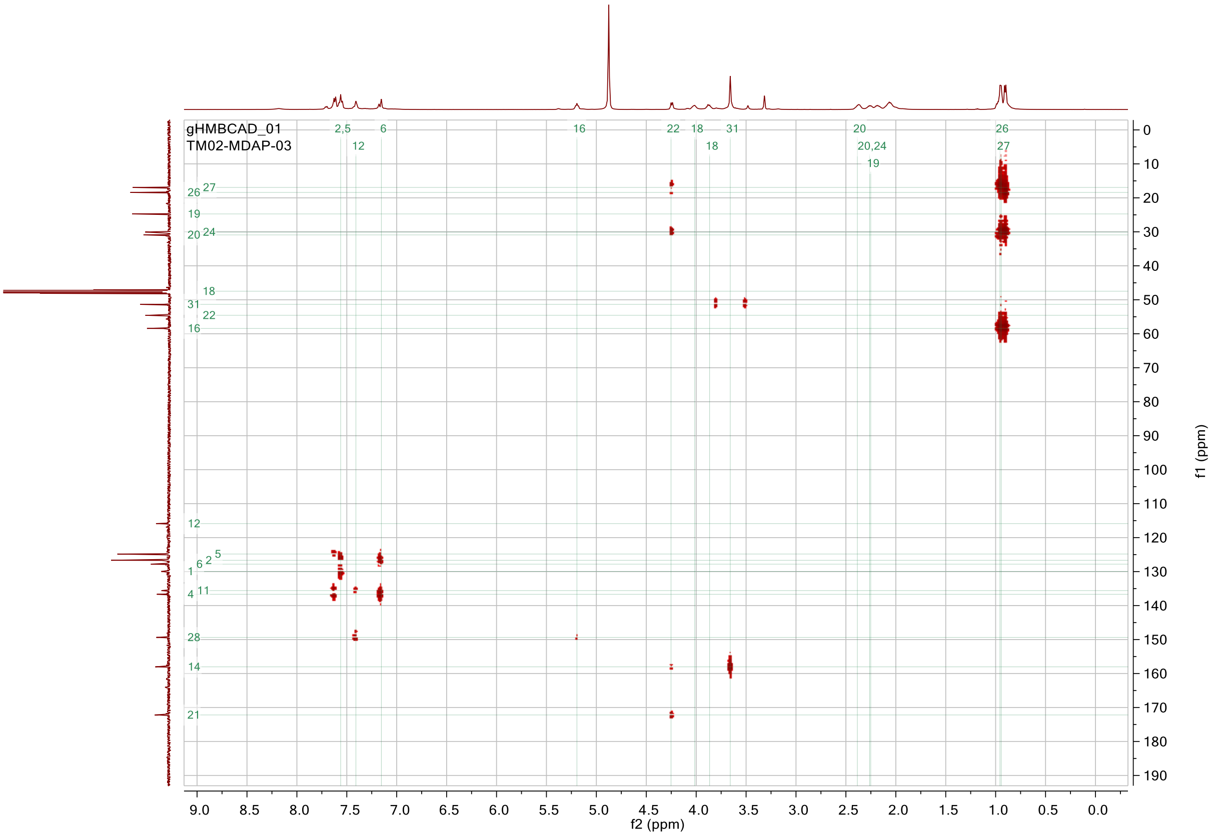
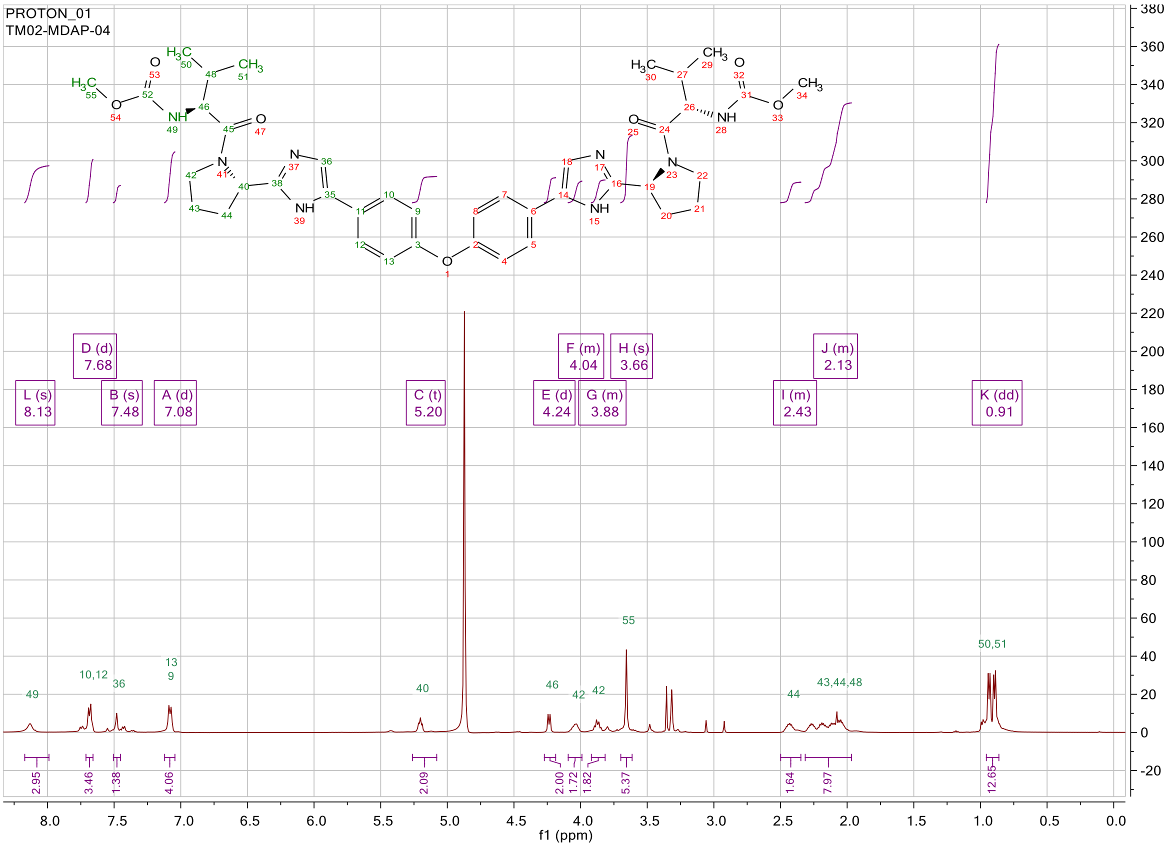
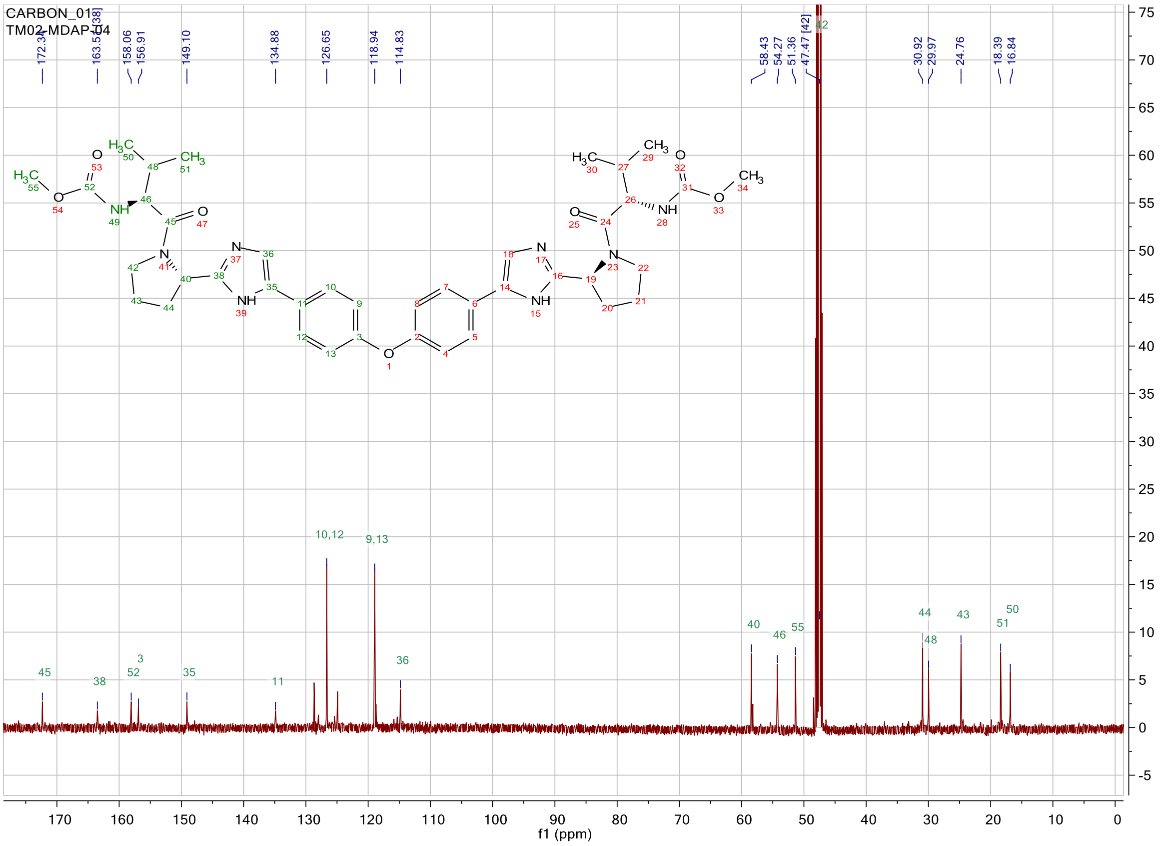
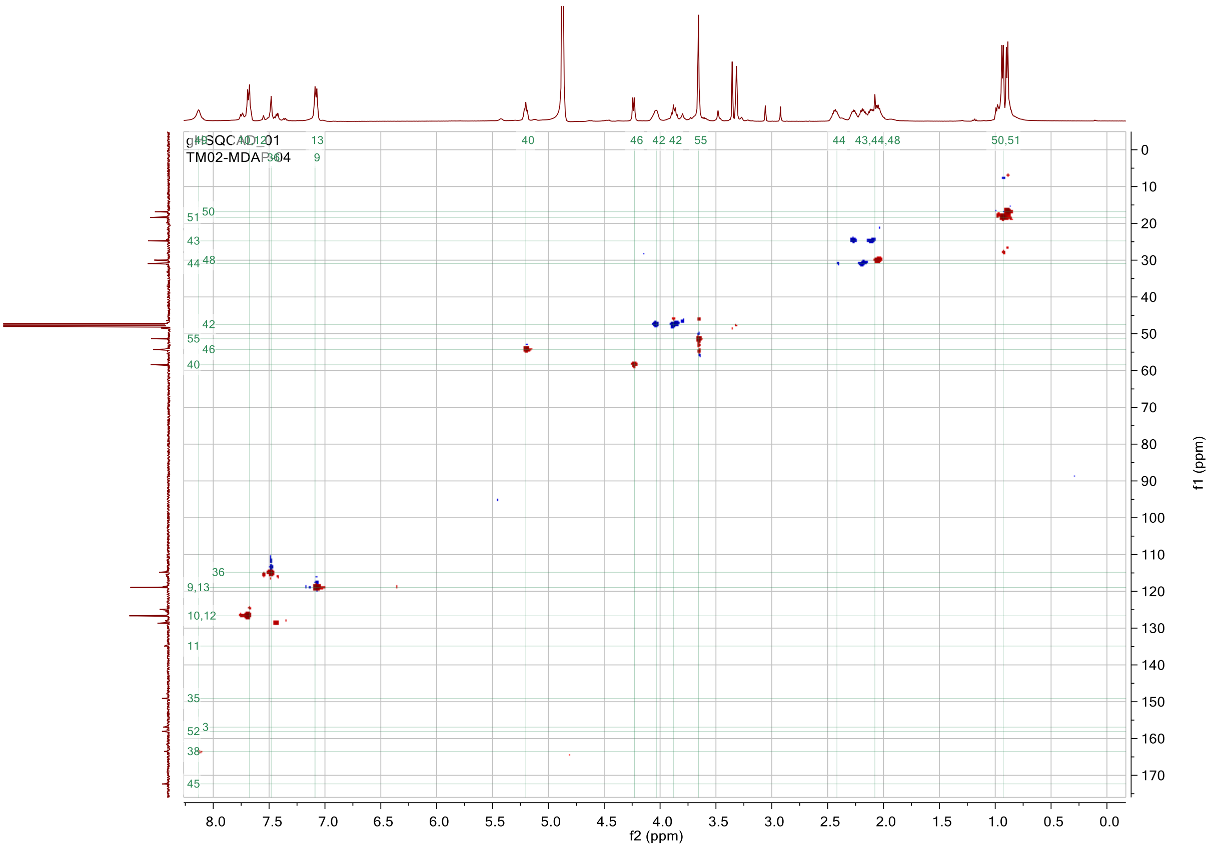
31
22
16
12
6 2 5
1
4 11
28
14
21
f2 (ppm)
f1 (ppm)

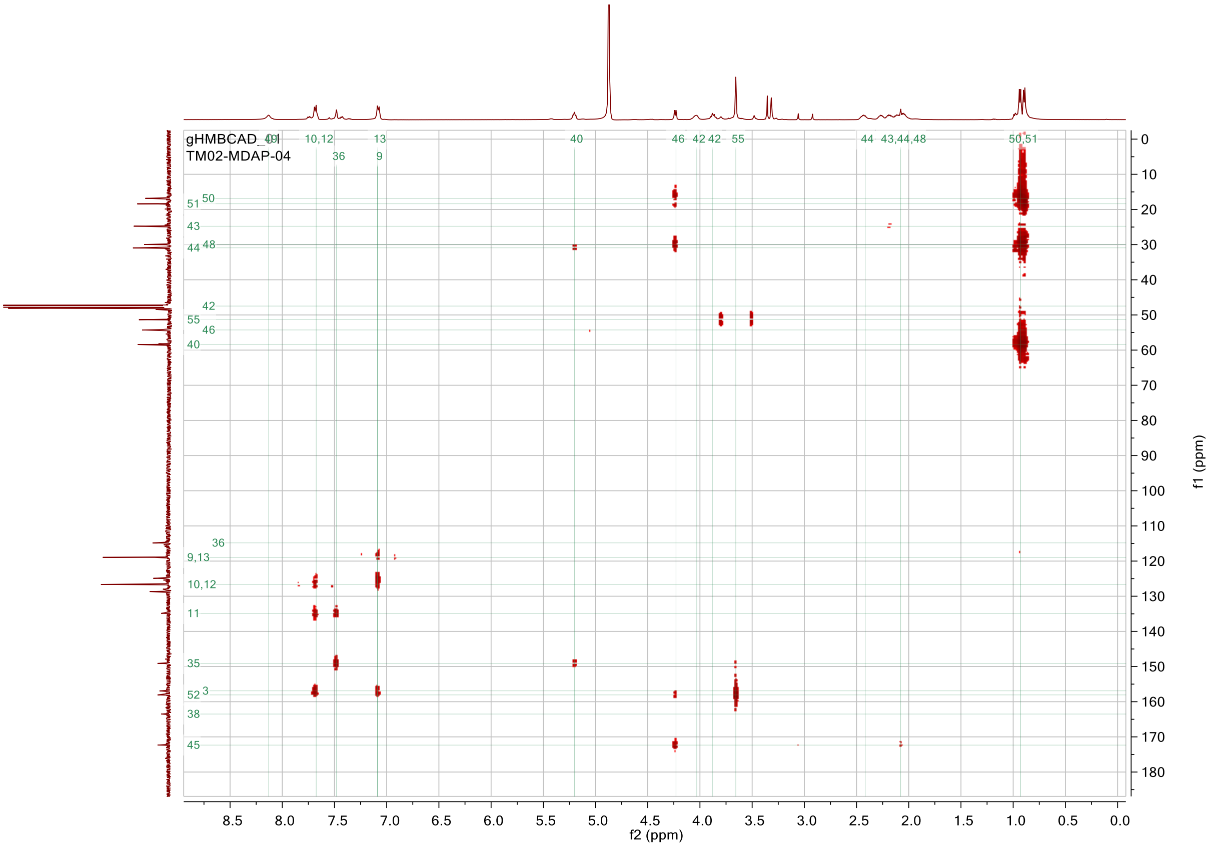

gHMBCAD_01
TM02-MDAP-03
2,5
6
12
16
22
18
31
18
20
20,24
19
26
27
26 27
19
20 24
18
31
22
16
12
6 2 5
1
4 11
28
14
21
f2 (ppm)
f1 (ppm)

Dimethyl ((2S,2'S)-((2S,2'S)-2,2'-(5,5'-(oxybis(4,1-phenylene))bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate (17)

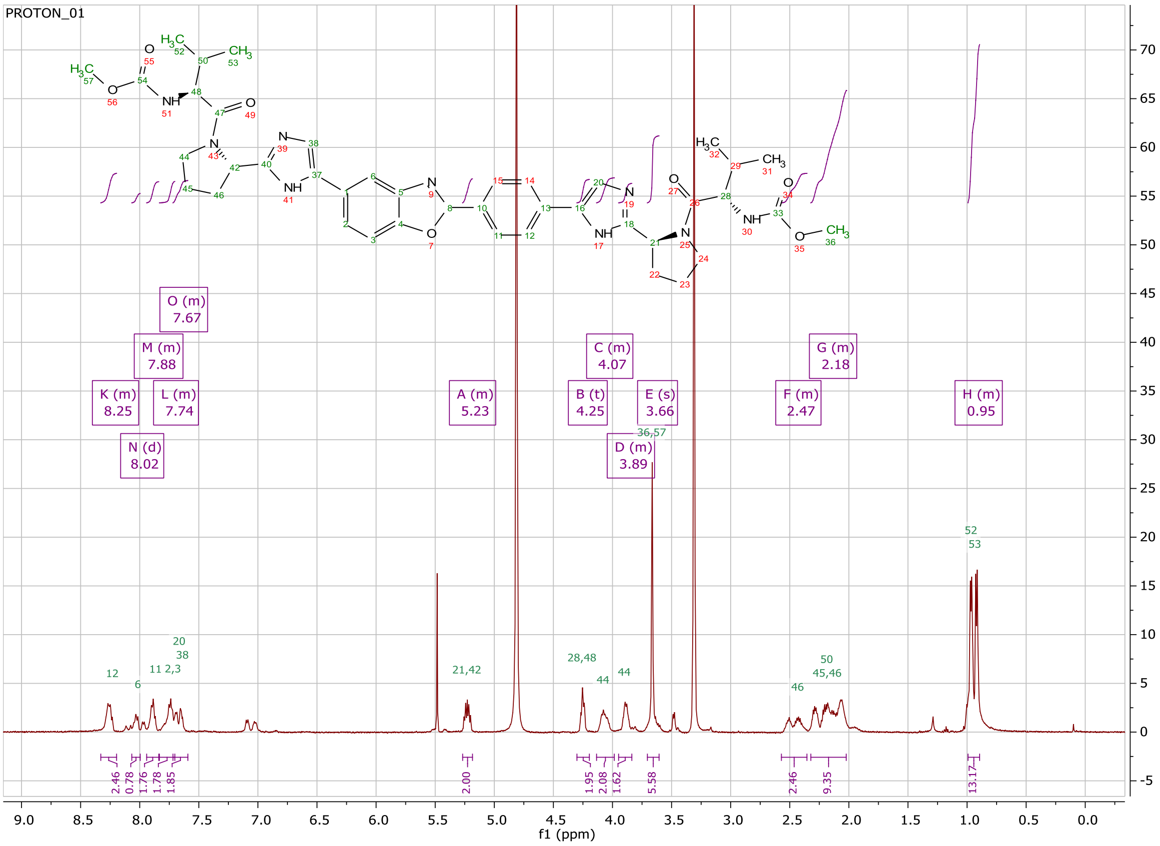


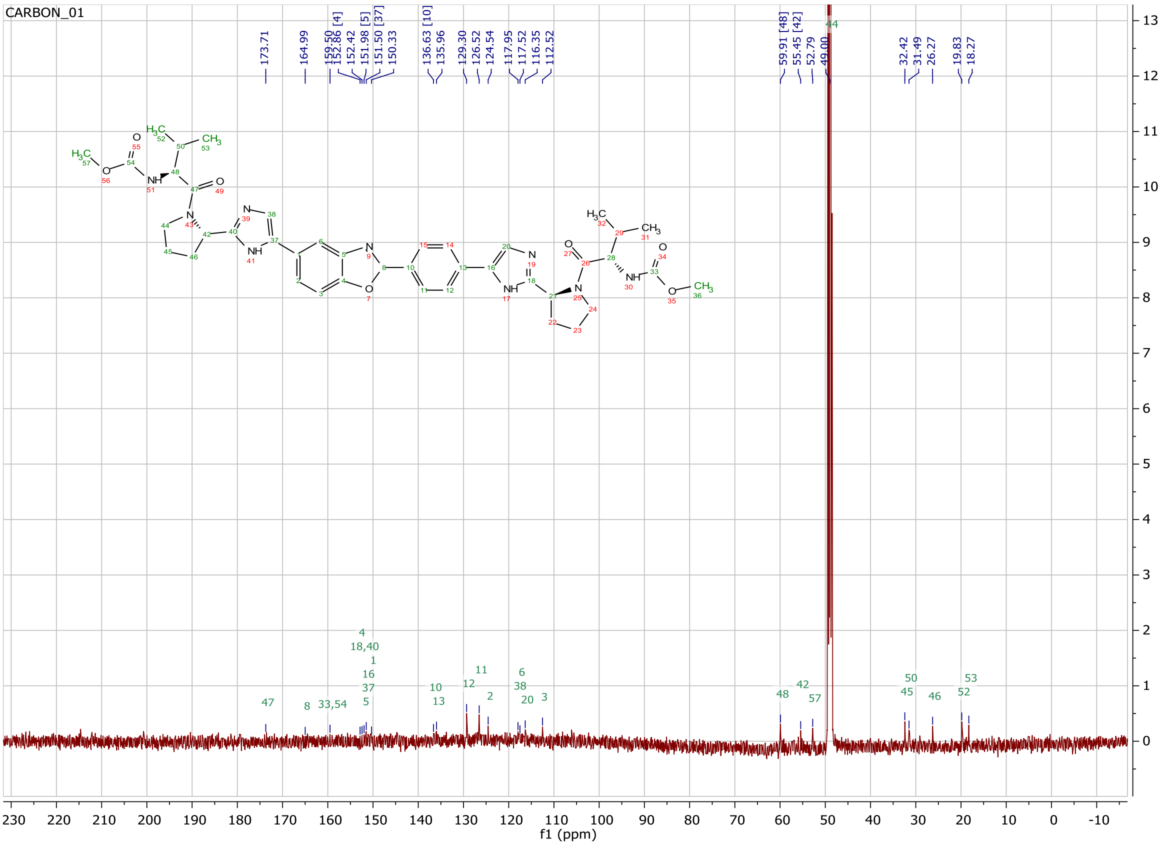


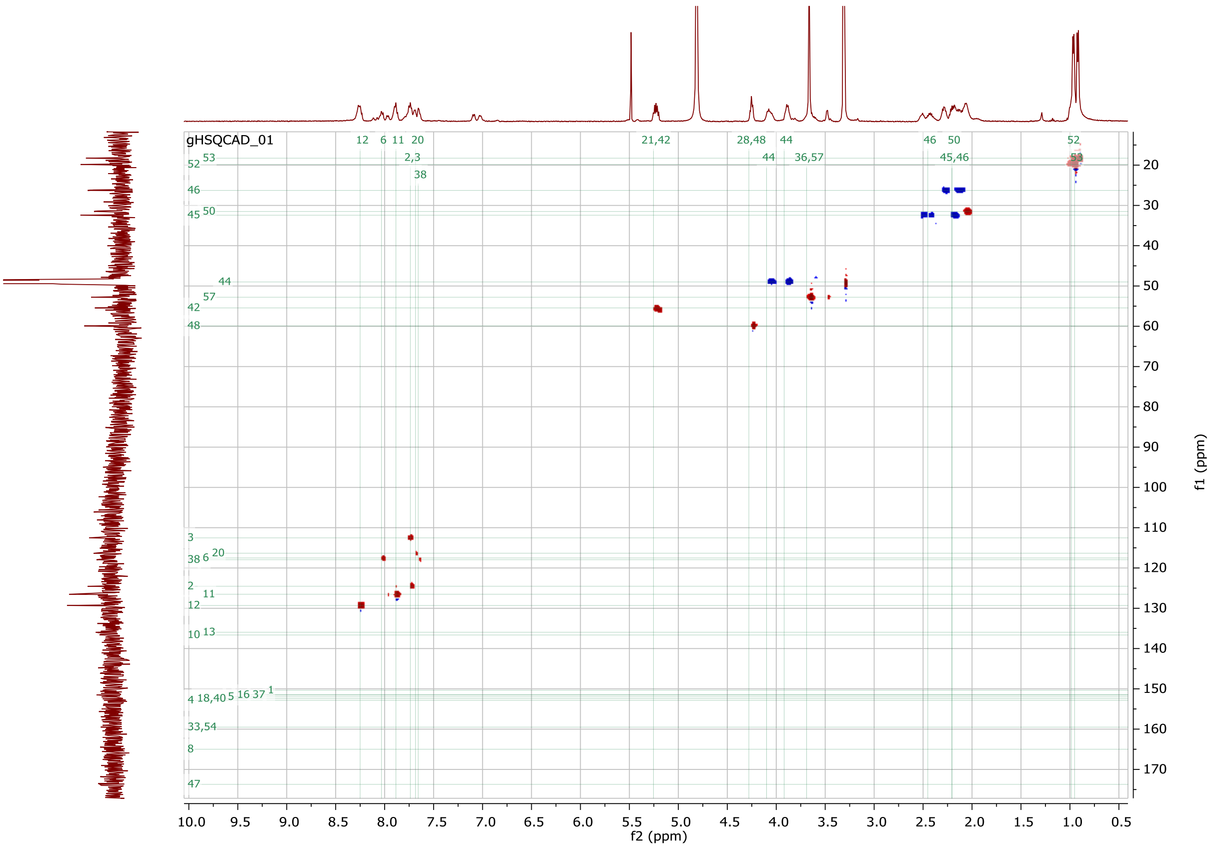

gHSQCAD_01
TM02-MDAP-04
13
9
40
46
42
42
55
44
43,44,48
50,51
51
50
43
44
48
42
55
46
40
36
9,13
10,12
11
35
52
3
38
45
f2 (ppm)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

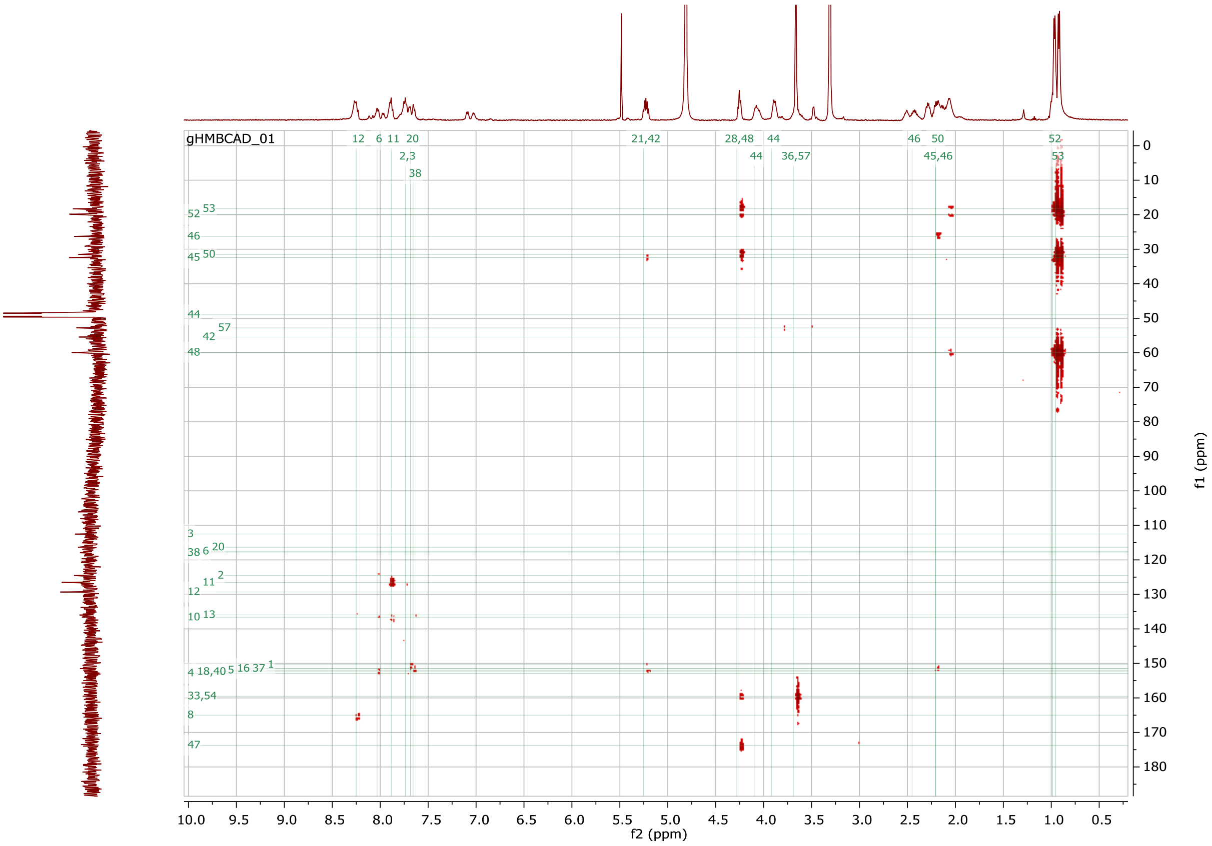

gHMBCAD_01
TM02-MDAP-04
10,12
36
13
9
40
46
42
42
55
44
43,44,48
50,51
51
50
43
44
48
42
55
46
40
36
9,13
10,12
11
35
52
3
38
45
f2 (ppm)
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

Methyl *N*-[(2S)-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-[(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl]pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,3-benzoxazol-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate (18)

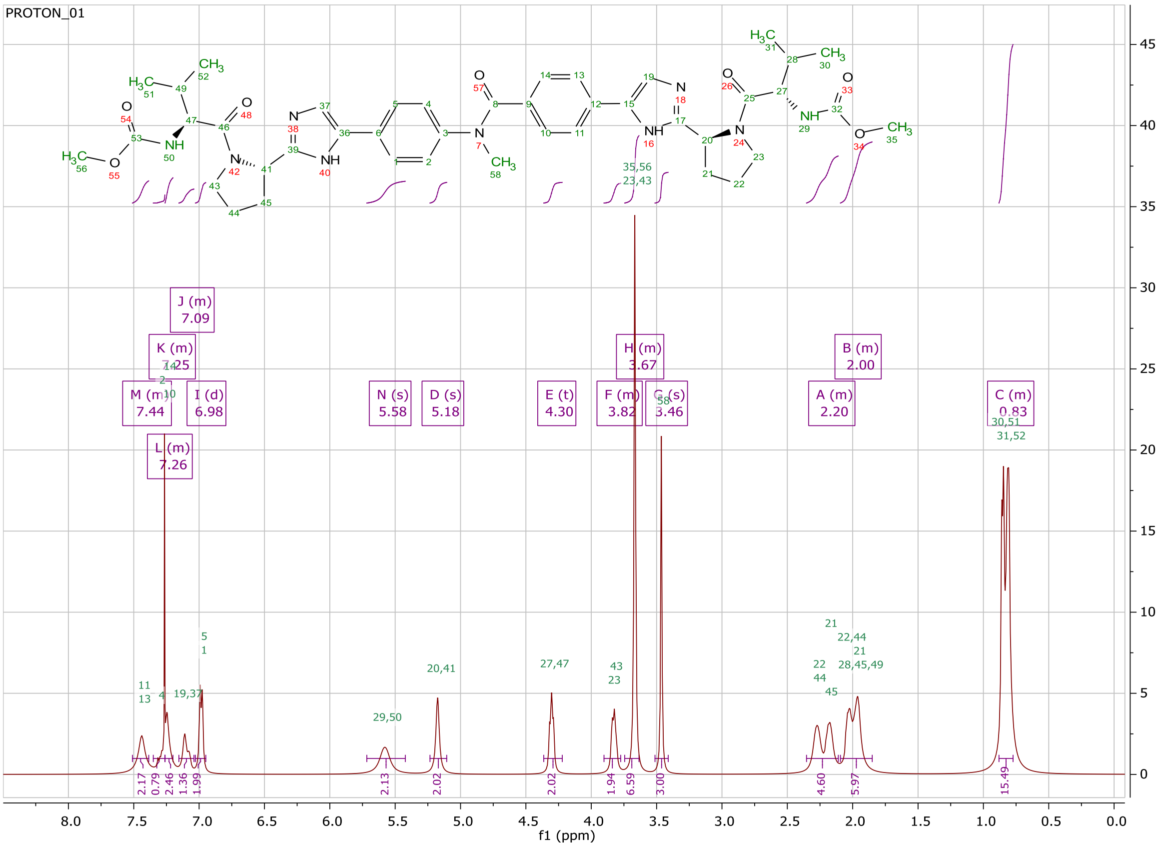


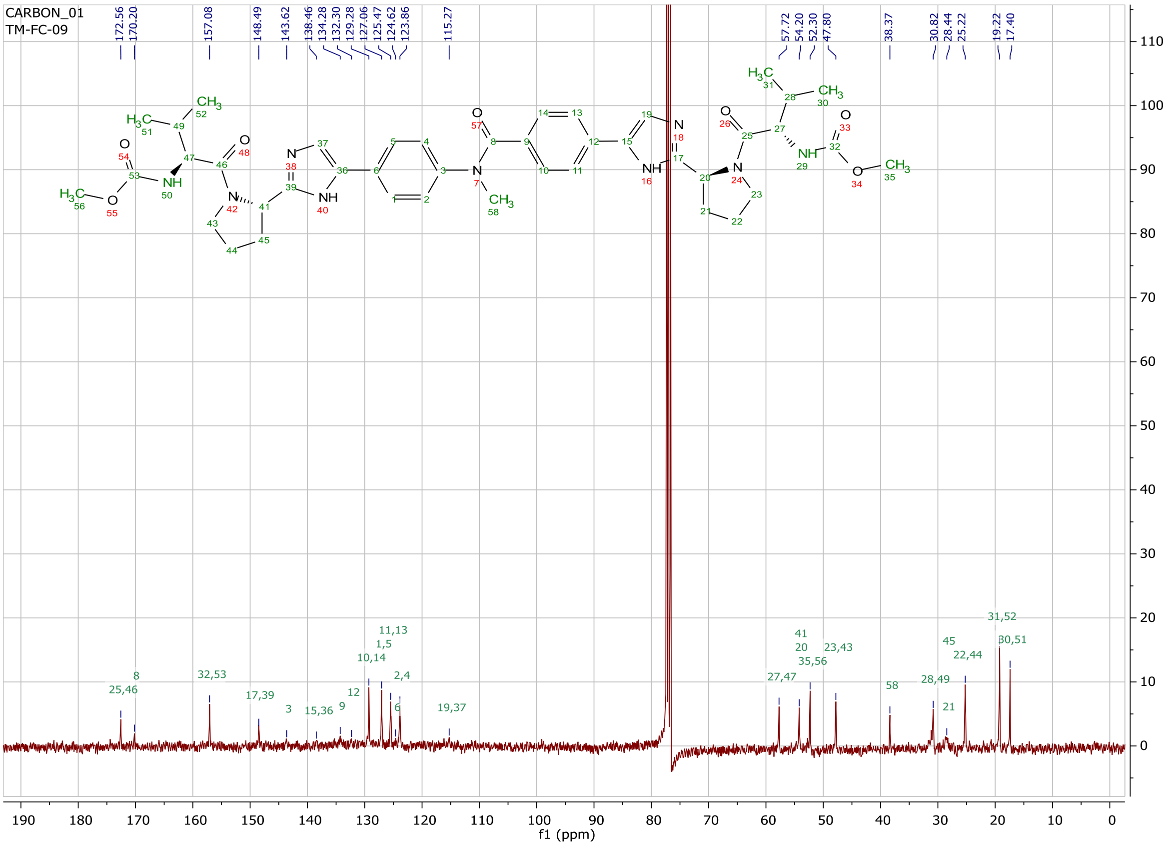


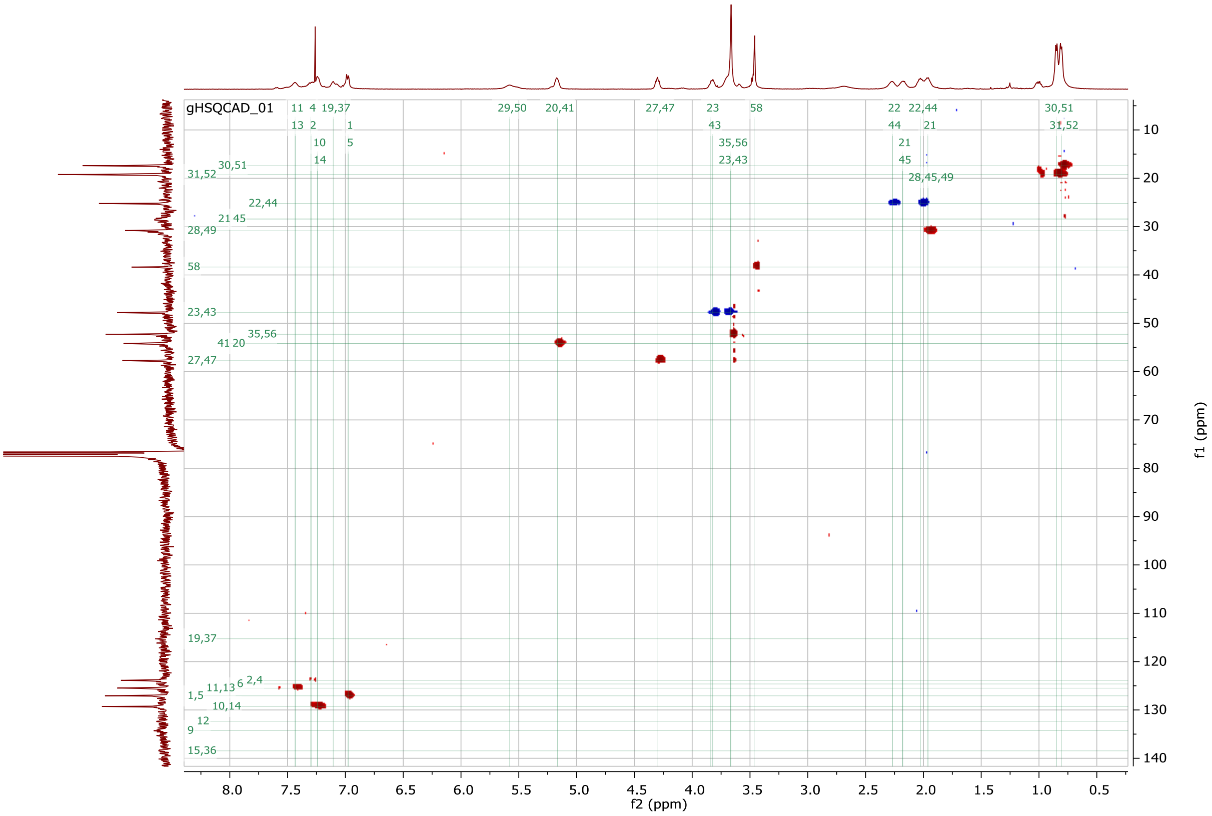

gHSQCAD_01
12 6 11 20
2,3
38
21,42
28,48 44
44 36,57
46 50
45,46
52
53
52 53
46
45 50
44
57
42
48
3
38 6 20
2
11
12
10 13
4 18,40 5 16 37 1
33,54
8
47
f2 (ppm)
f1 (ppm)

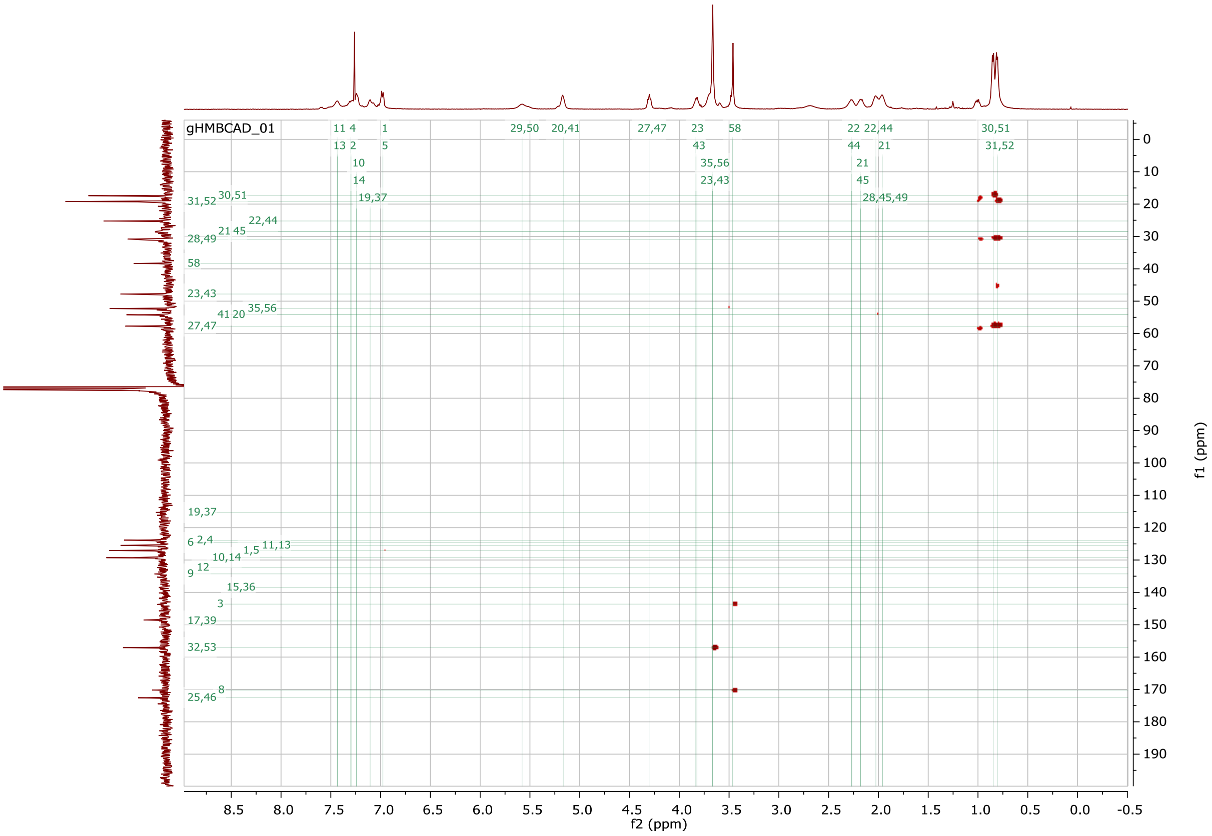

gHMBCAD_01
12 6 11 20
2,3
38
21,42
28,48 44
44 36,57
46 50
45,46
52
53
52 53
46
45 50
44
42 57
48
3
38 6 20
11 2
12
10 13
4 18,40 5 16 37 1
33,54
8
47
f2 (ppm)
f1 (ppm)

Methyl *N*-[(2S)-1-[(2S)-2-(5-{4-[(4-{2-[(2S)-1-[(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl]pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)(methyl)carbamoyl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate (19)






gHSQCAD_01
11 4 19,37
13 2 1
10 5
14
29,50 20,41 27,47 23 58
43
35,56
23,43
22 22,44 30,51
44 21 31,52
21
45
28,45,49
31,52 30,51
22,44
21 45
28,49
58
23,43
35,56
41 20
27,47
19,37
6 2,4
11,13
1,5
10,14
12
9
15,36
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f2 (ppm)
10 20 30 40 50 60 70 80 90 100 110 120 130 140
f1 (ppm)


gHMBCAD_01
11 4 1
13 2 5
10
14
19,37
29,50 20,41 27,47 23 58
43
35,56
23,43
22 22,44
44 21
21
45
28,45,49
30,51
31,52
31,52 30,51
22,44
21 45
28,49
58
23,43
35,56
41 20
27,47
19,37
6 2,4
1,5 11,13
10,14
9 12
15,36
3
17,39
32,53
25,46 8
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f2 (ppm)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190
f1 (ppm)

5. References

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