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Synthesis of uracil-coumarin conjugates as potential inhibitors of virus replication

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Contents

Experimental

All reagents were obtained at the highest grade available from Sigma or Acros Organics and were used without further purification unless otherwise noted. Anhydrous DMF and isopropyl alcohol were purchased from Sigma-Aldrich Co. Anhydrous acetone, 1,2-dichloroethane (DCE) and EtOAc were purified by distillation over P_2O_5. TLC was performed on Merck TLC Silica gel 60 F_{254} plates using the specified solvents and visualization with a VL-6.LC UV lamp (Vilber, France). Silica gel 60–200 μm 60Å (Acros Organics, Belgium) was used for column chromatography. Yields are referred to ^{1}H and ^{13}C NMR spectroscopically homogeneous materials. Melting points were determined using glass capillaries on a Mel-Temp 3.0 apparatus (Laboratory Devices Inc., USA). NMR spectra were obtained using a Bruker Avance 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) and a Bruker Avance 600 (600 MHz for ^{1}H and 150 MHz for ^{13}C) spectrometers in DMSO-d_6 or $CDCl_3$ with tetramethylsilane as an internal standard. High resolution mass spectra were measured on a Bruker micrOTOF II instrument using electrospray ionization (HRESIMS) in positive ion mode with interface capillary voltage –4500 V in an *m*/*z* range 50–3000 Da, external or internal calibration was performed with ESI Tuning MixTM (Agilent Technologies). A syringe injection of MeCN solutions was used with flow rate 3 μl min^{-1}. Dry N_2 was used as a carrier gas, the interface temperature was 180 °C.

General procedure for the synthesis of 1-[5-(3-bromophenoxy)pentyl]uracil **1b** *and 1-[5-(2-bromophenoxy)pentyl]uracil* **1c**. A mixture of uracil (1.0 g, 8.92 mmol) and NH_4Cl (0.15 g, 2.80 mmol) was boiled in hexamethyldisilazane (20 ml) for 12 h with protection from air moisture until a clear solution was formed. Excess of hexamethyldisilazane was removed *in vacuo*, then an equimolar amount of 1-bromo-3-[(5-bromopentyl)oxy]benzene or 1-bromo-2-[(5-bromopentyl)oxy]benzene was added to the residue. The reaction mixture was heated at 160–170 °C for 1 h with protection from air moisture and left overnight at room temperature. Then ethyl acetate (40 ml) and isopropanol (10 ml) were added to the reaction mixture, the mixture was stirred for 30 min at room temperature, filtered, and the filtrate was evaporated to dryness *in vacuo*. The residue was purified by chromatography on a silica gel column with chloroform–methanol (10 : 1). The fractions containing the product were combined, evaporated *in vacuo* and crystallized from isopropyl alcohol–DMF (1 : 1).

1-[5-(3-Bromophenoxy)pentyl]uracil **1b**. Yield 82%, mp 124.5–126 ºC, R_f 0.42 (ethyl acetate). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 1.38 (2H, quin, *J* 7.6 Hz, CH_2), 1.62 (2H, quin, *J* 7.5 Hz, CH_2), 1.71 (2H, quin, *J* 7.5 Hz, CH_2), 3.66 (2H, t, *J* 7.2 Hz, NCH_2), 3.97 (2H, t, *J* 6.5 Hz, OCH_2), 5.53 (1H, dd, *J* 7.8 and 2.2 Hz, H^5-Ura), 6.93 (1H, dd, *J* 8.3 and 2.2 Hz, H-6'), 7.06–7.14 (2H, m, H-2', H-4'), 7.22 (1H, t, *J* 8.2 Hz, H-5'), 7.65 (1H, d, *J* 7.8 Hz, H^6-Ura), 11.22 (1H, s, NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 22.6, 28.4, 40.5, 47.6, 67.9, 101.1, 114.3, 117.5, 122.4, 123.6, 131.5, 146.0, 151.3, 160.0, 164.1.

1-[5-(2-Bromophenoxy)pentyl]uracil **1c**. Yield 70%, mp 149–150.5 ºC, R_f 0.38 (ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.41 (2H, quin, *J* 7.6 Hz, CH_2), 1.64 (2H, quin, *J* 7.4 Hz, CH_2), 1.75 (2H, quin, *J* 7.3 Hz, CH_2), 3.67 (2H, t, *J* 7.2 Hz, NCH_2), 4.02 (2H, t, *J* 6.2 Hz, OCH_2), 5.54 (1H, dd, *J* 7.8 and 2.0 Hz, H^5-Ura), 6.86 (1H, t, *J* 6.8 Hz, H-4'), 7.07 (1H, d, *J* 8.2 Hz, H-6'), 7.31 (1H, t, *J* 7.0 Hz, H-5'), 7.54 (1H, dd, *J* 7.9 and 1.4 Hz, H-

3'), 7.65 (1H, d, *J* 7.8 Hz, H^6-Ura), 11.23 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 25.7, 31.48, 31.50, 50.7, 71.6, 104.2, 114.4, 117.1, 125.2, 132.3, 136.3, 149.1, 154.3, 158.1, 167.1.

1-{2-[2-(4-Bromophenoxy)ethoxy]ethyl}uracil **1d**. A mixture of uracil (2.1 g, 18.75 mmol) and K_2CO_3 (0.7 g, 5.065 mmol) in DMF (50 ml) was stirred at 80 °C for 1 h, then 1-bromo-4-[2-(2-bromoethoxy)ethoxy]benzene (1.5 g, 4.630 mmol) was added, and the resulting mixture was stirred at 80 °C for 2 days. Then the reaction mixture was evaporated *in vacuo*, the solid residue was treated with hot chloroform–isopropanol (1 : 1) (4 × 25 ml) and the resulting extracts were evaporated *in vacuo*. The residue was purified by chromatography on a silica gel column with chloroform–methanol (10 : 1). The fractions containing the product were combined, evaporated *in vacuo*, and crystallized from isopropanol–DMF (4 : 1). The product was filtered off to afford small white crystals. Yield 0.92 g, 56%, mp 116.5–117.5 °C, R_f 0.36 (ethyl acetate). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 3.64 (2H, t, *J* 5.2 Hz, CH_2), 3.72 (2H, t, *J* 4.4 Hz, CH_2), 3.84 (2H, t, *J* 5.1 Hz, CH_2), 4.05 (2H, t, *J* 4.3 Hz, CH_2), 5.49 (1H, d, *J* 7.9 Hz, H^5-Ura), 6.89 (2H, d, *J* 9.0 Hz, H-3', H-5'), 7.42 (2H, d, *J* 9.0 Hz, H-2', H-6'), 7.55 (1H, d, *J* 7.8 Hz, H^6-Ura), 11.25 (1H, s, NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 50.4, 70.7, 71.3, 72.0, 103.7, 115.4, 120.1, 135.5, 149.7, 154.3, 161.1, 167.1.

7-(2-Bromoethoxy)-3,4-dimethyl-2H-chromen-2-one **2f**. A mixture of 7-hydroxy-3,4-dimethyl-2*H*-chromen-2-one (3.0 g, 15.77 mmol), K_2CO_3 (3.2 g, 23.15 mmol) and 1,2-dibromoethane (6.0 ml, 69.63 mmol) in acetone (150 ml) was boiled with stirring for 4 days. Then the reaction mixture was cooled to room temperature, filtered, and the filtrate was evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel with ethyl acetate. The eluate was evaporated *in vacuo* to dryness and crystallized from ethyl acetate–hexane (1 : 1) to afford small white crystals. Yield 3.4 g, 72.5%, mp 143.5–145 °C, R_f 0.60 (ethyl acetate-hexane, 1 : 1). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 2.03 (3H, s, Me), 2.31 (3H, s, Me), 3.80 (2H, t, *J* 5.1 Hz, $BrCH_2$), 4.39 (2H, t, *J* 5.2 Hz, OCH_2), 6.92 (2H, m, H^6-chromene, H^8-chromene), 7.64 (1H, d, *J* 9.6 Hz, H^5-chromene). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 12.8, 14.8, 31.0, 68.2, 101.1, 112.2, 113.9, 118.1, 126.1, 146.6, 152.9, 159.8, 161.1.

General procedure for the synthesis of uracil–coumarin conjugates **3a–i**. A mixture of 1-substituted uracil **1a**–**d** (2.26 mmol) and K_2CO_3 (0.4 g, 2.89 mmol) was stirred in DMF (15 ml) at 80 °C for 1 h, then the corresponding bromide **2a–f** (2.30 mmol) was added, and the resulting mixture was stirred at 80 °C for 18 h. Then the reaction mixture was evaporated *in vacuo*, the residue was treated with cold water (80 ml), the precipitate was filtered off, dried in air at room temperature and purified by flash chromatography on silica gel with ethyl acetate. Eluate was evaporated to dryness *in vacuo* and the residue was crystallized from ethyl acetate–hexane (2 : 1).

1-[5-(4-Bromophenoxy)pentyl]-3-{2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]ethyl}uracil **3a**. Yield 78%, mp 181.5–183 °C, R_f 0.46 (1,2-dichloroethane–ethyl acetate, 1 : 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.39 (2H, quin, *J* 7.0 Hz, CH_2), 1.64 (2H, quin, *J* 7.3 Hz, CH_2), 1.72 (2H, quin, *J* 7.1 Hz, CH_2), 2.37 (3H, s, Me), 3.74 (2H, t, *J* 7.2 Hz, N^1CH_2), 3.92 (2H, t, *J* 6.5 Hz, OCH_2), 4.21–4.26 (4H, m, $N^3CH_2CH_2$), 5.69 (1H, d, *J* 7.9 Hz, H^5-Ura), 6.17 (1H, s, H^3-chromene), 6.85 (2H, d, *J* 8.9 Hz, H-3', H-5'), 6.89 (1H, dd, *J* 8.8 and 2.6 Hz, H^6-chromene), 6.94 (1H, d, *J* 2.3 Hz, H^8-chromene), 7.38 (2H, d, *J* 8.9 Hz, H-2', H-6'), 7.62 (1H, d, *J* 8.7 Hz, H^5-chromene), 7.69 (1H, d, *J* 7.8 Hz, H^6-Ura). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 18.0, 22.2, 27.9, 28.0, 48.5, 64.5, 67.4, 78.5, 78.9, 79.2,

100.0, 101.1, 111.2, 112.3, 113.2, 116.6, 126.3, 131.9, 144.3, 151.0, 153.1, 154.6, 157.8, 160.0, 161.1, 162.3. HRMS (ESI), *m*/*z*: 555.1125 $[M+H]^+$ (calc. for $C_{27}H_{28}BrN_2O_6$, *m*/*z*: 555.1121), *m*/*z*: 577.0938 $[M+Na]^+$ (calc. for $C_{27}H_{27}BrN_2O_6Na$, *m*/*z*: 577.0945).

1-[5-(4-Bromophenoxy)pentyl]-3-{3-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]propyl}uracil **3b**. Yield 85%, mp 135–136 °C, R_f 0.44 (1,2-dichloroethane–ethyl acetate, 1 : 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.35 (2H, quin, *J* 7.0 Hz, CH_2), 1.58 (2H, quin, *J* 7.3 Hz, CH_2), 1.66 (2H, quin, *J* 7.5 Hz, CH_2), 2.01 (2H, quin, *J* 6.2 Hz, CH_2), 2.36 (3H, s, Me), 3.69 (2H, t, *J* 7.1 Hz, N^1CH_2), 3.89 (2H, t, *J* 6.4 Hz, OCH_2), 3.99 (2H, t, *J* 6.7 Hz, N^3CH_2), 4.09 (2H, t, *J* 5.9 Hz, OCH_2), 5.67 (1H, d, *J* 7.8 Hz, H^5-Ura), 6.16 (1H, s, H^3-chromene), 6.83–6.87 (4H, m, H-3', H-5', H^6-chromene, H^8-chromene), 7.39 (2H, d, *J* 8.9 Hz, H-2', H-6'), 7.62 (1H, d, *J* 8.5 Hz, H^5-chromene), 7.69 (1H, d, *J* 7.8 Hz, H^6-Ura). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 18.0, 22.2, 26.7, 27.97, 28.03, 37.9, 48.4, 66.6, 67.4, 100.0, 101.0, 111.0, 111.7, 112.2, 113.0, 116.6, 126.3, 132.0, 144.0, 151.0, 153.2, 154.6, 157.8, 160.0, 161.6, 162.4. HRMS (ESI), *m*/*z*: 569.1275 $[M+H]^+$ (calc. for $C_{28}H_{30}BrN_2O_6$, *m*/*z*: 569.1275), *m*/*z*: 591.1096 $[M+Na]^+$ (calc. for $C_{28}H_{29}BrN_2O_6Na$, *m*/*z*: 591.1101).

1-[5-(4-Bromophenoxy)pentyl]-3-{4-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]butyl}uracil **3c**. Yield 82%, mp 126.5–128 °C, R_f 0.46 (1,2-dichloroethane–ethyl acetate, 1 : 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.37 (2H, quin, *J* 7.0 Hz, CH_2), 1.60–1.72 (8H, m, CH_2 × 4), 2.36 (3H, s, Me), 3.72 (2H, t, *J* 6.9 Hz, N^1CH_2), 3.85 (2H, t, *J* 6.5 Hz, N^3CH_2), 3.91 (2H, t, *J* 6.3 Hz, OCH_2), 4.06 (2H, t, *J* 5.6 Hz, OCH_2), 5.67 (1H, d, *J* 7.8 Hz, H^5-Ura), 6.16 (1H, s, H^3-chromene), 6.85 (2H, d, *J* 8.9 Hz, H-3', H-5'), 6.88–6.91 (2H, m, H^6-chromene, H^8-chromene), 7.38 (2H, d, *J* 8.9 Hz, H-2', H-6'), 7.61 (1H, d, *J* 9.4 Hz, H^5-chromene), 7.68 (1H, d, *J* 7.9 Hz, H^6-Ura). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 18.0, 22.2, 23.8, 25.9, 27.97, 28.03, 48.4, 67.4, 67.8, 100.0, 101.1, 111.0, 111.7, 112.3, 113.0, 116.6, 126.3, 132.0, 144.0, 151.0, 153.2, 154.7, 157.8, 160.0, 161.6, 162.3. HRMS (ESI), *m*/*z*: 583.1436 $[M+H]^+$ (calc. for $C_{29}H_{32}BrN_2O_6$, *m*/*z*: 583.1438), *m*/*z*: 605.1256 $[M+Na]^+$ (calc. for $C_{29}H_{31}BrN_2O_6Na$, *m*/*z*: 605.1258).

1-[5-(4-Bromophenoxy)pentyl]-3-{5-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]pentyl}uracil **3d**. Yield 86%, mp 135–136.5 °C, R_f 0.47 (1,2-dichloroethane–ethyl acetate, 1 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45–1.53 (4H, m, CH_2 × 2), 1.65–1.87 (8H, m, CH_2 × 4), 2.36 (3H, s, Me), 3.74 (2H, t, *J* 7.3 Hz, N^1CH_2), 3.90 (2H, t, *J* 6.0 Hz, N^3CH_2), 3.94 (2H, t, *J* 7.5 Hz, OCH_2), 3.99 (2H, t, *J* 6.6 Hz, OCH_2), 5.69 (1H, d, *J* 7.8 Hz, H^5-Ura), 6.08 (1H, d, *J* 0.9 Hz, H^3-chromene), 6.72 (2H, d, *J* 9.0 Hz, H-3', H-5'), 6.76 (1H, d, *J* 2.5 Hz, H^8-chromene), 6.81 (1H, dd, *J* 8.9 and 2.5 Hz, H^6-chromene), 7.09 (1H, d, *J* 7.8 Hz, H^5-chromene), 7.32 (2H, d, *J* 8.8 Hz, H-2', H-6'), 7.44 (1H, d, *J* 7.8 Hz, H^6-Ura). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.7, 23.1, 23.4, 27.3, 28.67, 28.74, 28.8, 41.0, 49,7, 67.7, 68.4, 101.5, 101.7, 111.9, 112.7, 112.9, 113.5, 116.3, 125.5, 132.3, 142.2, 151.5, 152.6, 155.4, 158.1, 161.4, 162.2, 163.1. HRMS (ESI), *m*/*z*: 597.1583 $[M+H]^+$ (calc. for $C_{30}H_{34}BrN_2O_6$, *m*/*z*: 597.1595), *m*/*z*: 619.1407 $[M+Na]^+$ (calc. for $C_{30}H_{33}BrN_2O_6Na$, *m*/*z*: 619.1414).

1-[5-(4-Bromophenoxy)pentyl]-3-{6-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]hexyl}uracil **3e**. Yield 80%, mp 105–107 °C, R_f 0.52 (1,2-dichloroethane–ethyl acetate, 1 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40 (2H, quin, *J* 7.0 Hz, CH_2), 1.47–1.54 (4H, m, CH_2 × 2), 1.65 (2H, quin, *J* 7.5 Hz, CH_2), 1.72–1.83 (6H, m, CH_2 × 3), 2.36 (3H, s, Me), 3.74 (2H, t, *J* 7.3 Hz, N^1CH_2), 3.90 (2H, t, *J* 6.3 Hz, N^3CH_2), 3.92 (2H, t, *J* 7.7 Hz, OCH_2), 3.98 (2H, t, *J*

6.6 Hz, OCH_2), 5.69 (1H, d, *J* 7.8 Hz, H^5-Ura), 6.09 (1H, d, *J* 1.0 Hz, H^3-chromene), 6.72 (2H, d, *J* 8.8 Hz, H-3', H-5'), 6.76 (1H, d, *J* 2.5 Hz, H^8-chromene), 6.82 (1H, dd, *J* 8.7 and 2.5 Hz, H^6-chromene), 7.08 (1H, d, *J* 7.9 Hz, H^6-chromene), 7.32 (2H, d, *J* 9.0 Hz, H-2', H-6'), 7.45 (1H, d, *J* 7.8 Hz, H^6-Ura). ^{13}C NMR (150 MHz, $CDCl_3$) *δ*: 18.7, 23.1, 25.7, 26.7, 27.5, 28.75, 28.82, 28.9, 41.2, 49,7, 67.7, 68.5, 101.5, 101.8, 111.9, 112.7, 112.9, 113.5, 116.3, 125.5, 132.3, 142.1, 151.5, 152.6, 155.4, 158.1, 161.4, 162.3, 163.1. HRMS (ESI), *m*/*z*: 611.1750 $[M+H]^+$ (calc. for $C_{31}H_{36}BrN_2O_6$, *m*/*z*: 611.1751), *m*/*z*: 633.1572 $[M+Na]^+$ (calc. for $C_{31}H_{35}BrN_2O_6Na$, *m*/*z*: 633.1571).

1-[5-(3-Bromophenoxy)pentyl]-3-{2-[(3,4-dimethyl-2-oxo-2H-chromen-7-yl)oxy]ethyl}uracil **3f**. Yield 78%, mp 103.5–105.5 °C, R_f 0.58 (1,2-dichloroethane–ethyl acetate, 1 : 1). ^{1}H NMR (600 MHz, DMSO-d_6) *δ*: 1.35 (2H, quin, *J* 6.5 Hz, CH_2), 1.61 (2H, quin, *J* 6.9 Hz, CH_2), 1.68 (2H, quin, *J* 7.4 Hz, CH_2), 2.03 (3H, s, Me), 2.30 (3H, s, Me), 3.71 (2H, t, *J* 7.0 Hz, N^1CH_2), 3.92 (2H, t, *J* 6.3 Hz, OCH_2), 4.18–4.22 (4H, m, $N^3CH_2CH_2$), 5.68 (1H, d, *J* 7.9 Hz, H^5-Ura), 6.84–6.89 (3H, m, H-2', H-4', H-6'), 7.06 (2H, m, H^6-chromene, H^8-chromene), 7.18 (1H, t, *J* 8.4 Hz, H-5'), 7.60 (1H, d, *J* 8.9 Hz, H^5-chromene), 7.69 (1H, d, *J* 7.8 Hz, H^6-Ura). ^{13}C NMR (150 MHz, DMSO-d_6) *δ*: 12.8, 14.8, 22.2, 27.9, 28.0, 38.9, 48.5, 64.5, 67.6, 100.0, 100.9, 112.2, 113.8, 113.9, 117.2, 118.0, 122.0, 123.2, 126.1, 131.1, 144.4, 146.6, 151.1, 152.9, 159.6, 160.1, 161.1, 162.4. HRMS (ESI), *m*/*z*: 569.1277 $[M+H]^+$ (calc. for $C_{28}H_{30}BrN_2O_6$, *m*/*z*: 569.1282), *m*/*z*: 591.1098 $[M+Na]^+$ (calc. for $C_{28}H_{29}BrN_2O_6Na$, *m*/*z*: 591.1101).

1-[5-(2-Bromophenoxy)pentyl]-3-{2-[(3,4-dimethyl-2-oxo-2H-chromen-7-yl)oxy]ethyl}uracil **3g**. Yield 74%, mp 72–74 °C, R_f 0.59 (1,2-dichloroethane–ethyl acetate, 1 : 1). ^{1}H NMR (600 MHz, DMSO-d_6) *δ*: 1.41 quin (2H, *J* 7.4 Hz, CH_2), 1.64 quin (2H, *J* 7.4 Hz, CH_2), 1.72 quin (2H, *J* 7.5 Hz, CH_2), 2.02 (3H, s, Me), 2.28 (3H, s, Me), 3.72 (2H, t, *J* 7.1 Hz, N^1CH_2), 3.98 (2H, t, *J* 6.3 Hz, OCH_2), 4.18–4.21 (4H, m, $N^3CH_2CH_2$), 5.68 (1H, d, *J* 7.8 Hz, H^5-Ura), 6.81–6.88 (3H, m, H-4', H-6'), 6.88 (2H, d, *J* 2.4 Hz, H^8-chromene), 7.03 (2H, dd, *J* 8.3 and 0.9 Hz, H^6-chromene, H^8-chromene), 7.27 (1H, dt, *J* 8.7 and 1.4 Hz, H-5'), 7.50 (1H, dd, *J* 7.8 and 1.4 Hz, H-3'), 7.58 (1H, d, *J* 8.9 Hz, H^5-chromene), 7.69 (1H, d, *J* 7.9 Hz, H^6-Ura). ^{13}C NMR (150 MHz, DMSO-d_6) *δ*: 12.8, 14.8, 22.3, 27.9, 28.1, 38.9, 48.5, 64.5, 68.2, 100.0, 100.9, 111.1, 112.2, 113.69, 113.73, 117.9, 121.8, 126.0, 128.9, 132.8, 144.4, 146.6, 151.1, 152.9, 154.7, 160.1, 161.1, 162.4. HRMS (ESI), *m*/*z*: 569.1275 $[M+H]^+$ (calc. for $C_{28}H_{30}BrN_2O_6$, *m*/*z*: 569.1282), *m*/*z*: 591.1096 $[M+Na]^+$ (calc. for $C_{28}H_{29}BrN_2O_6Na$, *m*/*z*: 591.1101).

1-[5-(4-Bromophenoxy)pentyl]-3-{2-[(3,4-dimethyl-2-oxo-2H-chromen-7-yl)oxy]ethyl}uracil **3h**. Yield 77%, mp 174–176 °C, R_f 0.26 (1,2-dichloroethane–ethyl acetate, 1 : 1). ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 1.39 (2H, quin, *J* 7.7 Hz, CH_2), 1.64 (2H, quin, *J* 7.4 Hz, CH_2), 1.71 (2H, quin, *J* 7.3 Hz, CH_2), 2.04 (3H, s, Me), 2.30 (3H, s, Me), 3.74 (2H, t, *J* 7.1 Hz, N^1CH_2), 3.91 (2H, t, *J* 6.5 Hz, OCH_2), 4.21–4.24 (4H, m, $N^3CH_2CH_2$), 5.71 (1H, d, *J* 7.9 Hz, H^5-Ura), 6.86–6.91 (4H, m, H-3', H-5', H^6-chromene, H^8-chromene), 7.23–7.26 (2H, m, H-2', H-6'), 7.60 (1H, d, *J* 8.8 Hz, H^5-chromene), 7.71 (1H, d, *J* 7.8 Hz, H^6-Ura). ^{13}C NMR (100 MHz, DMSO-d_6) *δ*: 12.8, 14.8, 22.3, 28.0, 28.2, 38.9, 45.0, 48.5, 64.4, 67.0, 100.0, 100.9, 112.2, 113.7, 114.3, 117.9, 120.3, 126.0, 129.4, 144.4, 146.6, 151.0, 152.9, 158.6, 160.1, 161.1,162.4. HRMS (ESI), *m*/*z*: 569.1275 $[M+H]^+$ (calc. for $C_{28}H_{30}BrN_2O_6$, *m*/*z*: 569.1282), *m*/*z*: 591.1097 $[M+Na]^+$ (calc. for $C_{28}H_{29}BrN_2O_6Na$, *m*/*z*: 591.1101).

1-{2-[2-(4-Bromophenoxy)ethoxy]ethyl}-3-{2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]ethyl}uracil **3i**. Yield 81%, mp 102–103.5 ºC, R_f 0.50 (ethyl acetate). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 2.37 (3H, s, Me), 3.69 (2H, t, J 7.2 Hz, CH_2), 3.74 (2H, t, J 6.1 Hz, N^1CH_2), 3.93 (2H, t, J 5.2 Hz, CH_2), 4.04 (2H, t, J 5.7 Hz, CH_2), 4.20–4.24 (4H, m, $N^3CH_2CH_2$), 5.68 (1H, d, J 7.8 Hz, H^5-Ura), 6.18 (1H, d, J 1.1 Hz, H^3-chromene), 6.85–6.92 (3H, m, H-3', H-5', H^6-chromene), 6.95 (1H, d, J 2.4 Hz, H^8-chromene), 7.40 (2H, d, J 9.0 Hz, H-2', H-6'), 7.61 (1H, d, J 8.7 Hz, H^6-chromene), 7.64 (1H, d, J 7.8 Hz, H^6-Ura). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 18.5, 48.7, 65.0, 67.8, 68.3, 69.3, 100.1, 101.7, 111.7, 112.5, 112.8, 113.8, 117.2, 126.9, 132.5, 145.5, 151.6, 153.7, 155.1, 158.2, 160.5, 161.6, 162.8. HRMS (ESI), *m*/*z*: 557.0911 $[M+H]^+$ (calc. for $C_{26}H_{26}BrN_2O_7$, *m*/*z*: 557.0918), *m*/*z*: 579.0733 $[M+Na]^+$ (calc. for $C_{26}H_{25}BrN_2O_7Na$, *m*/*z*: 579.0737).

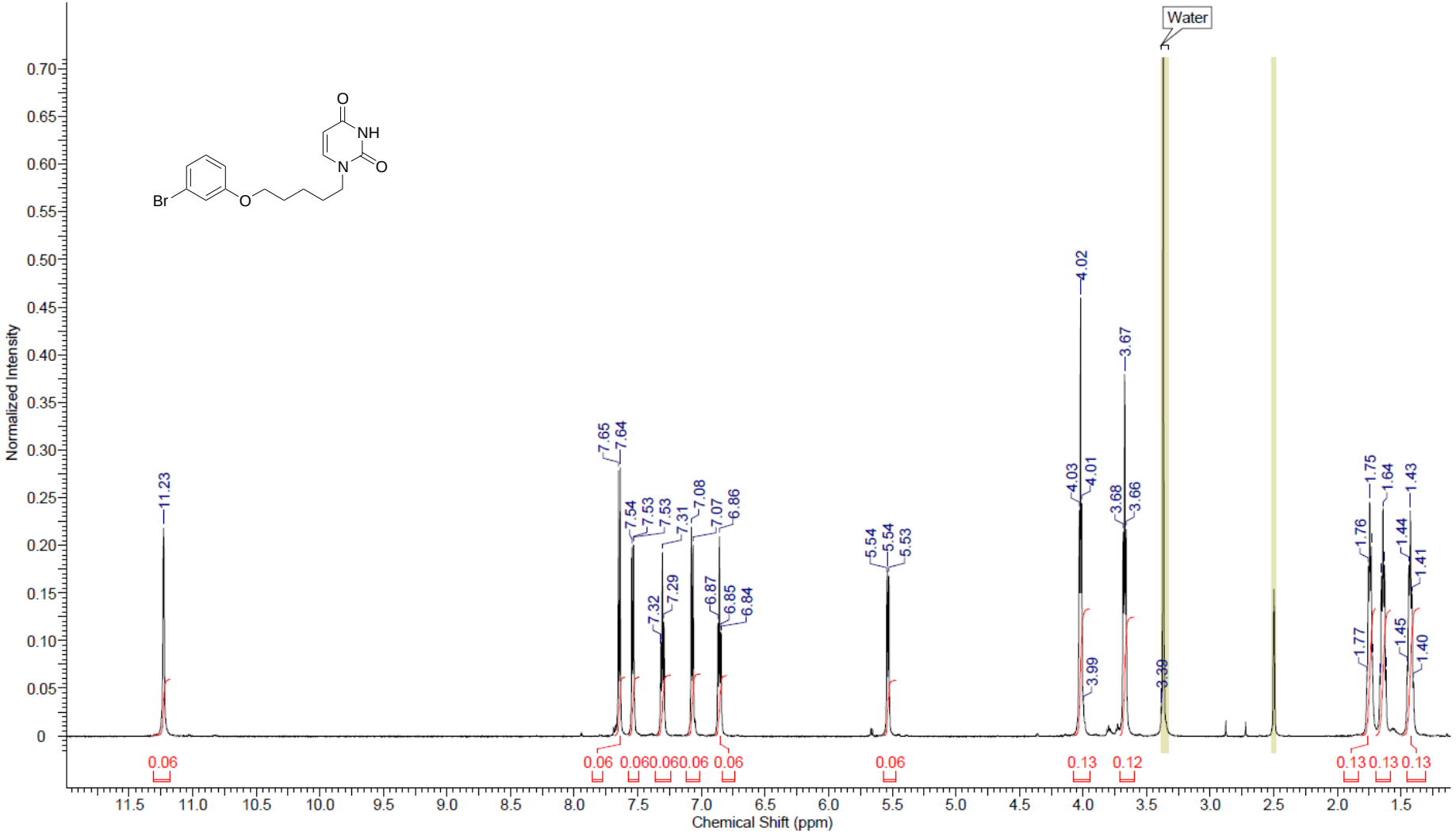

Figure S1 ^{1}H NMR spectrum of compound **1b** in DMSO-d_6 at 600 MHz.

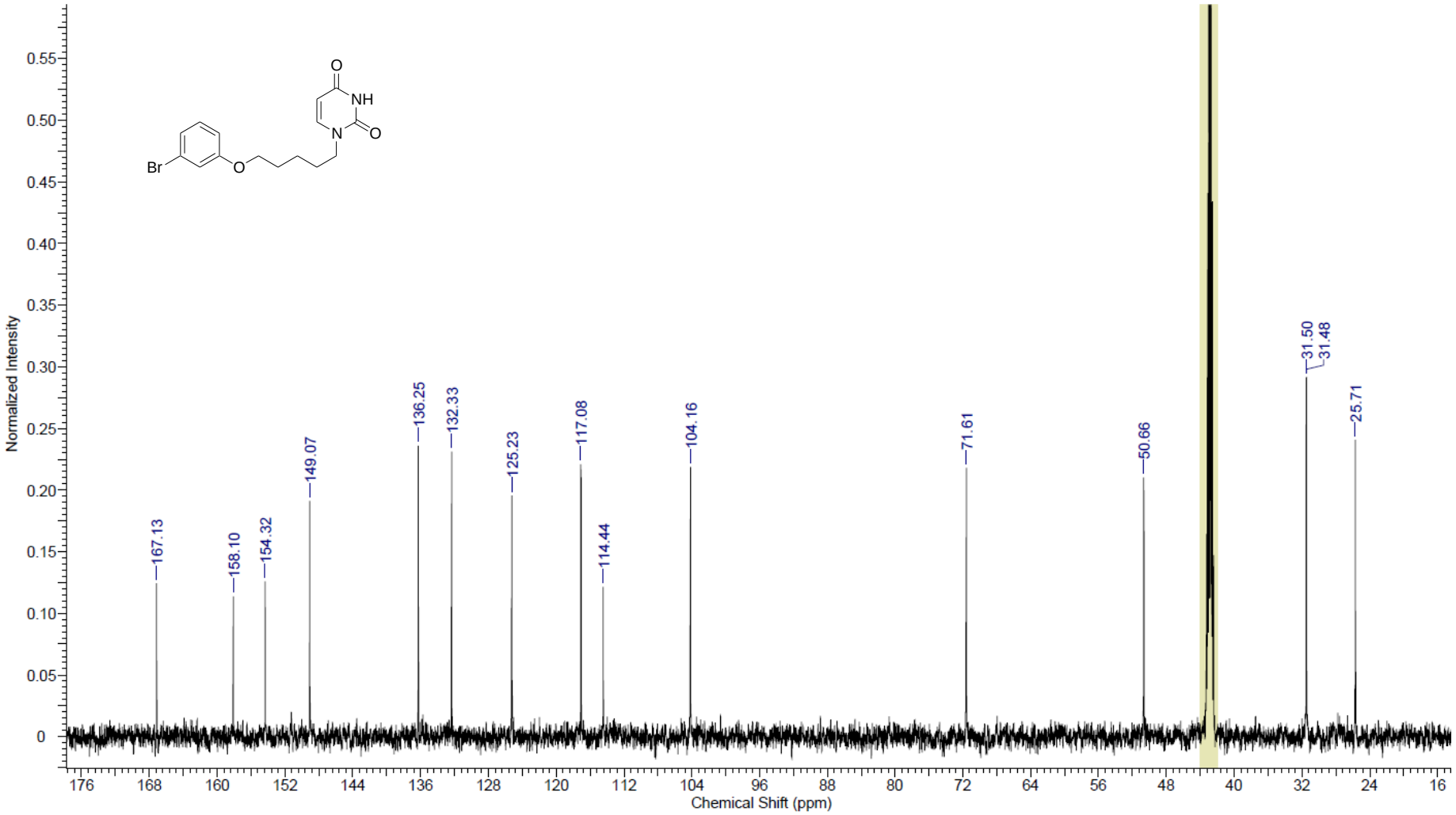

Figure S2 ^{13}C NMR spectrum of compound **1b** in DMSO-d_6 at 150 MHz.

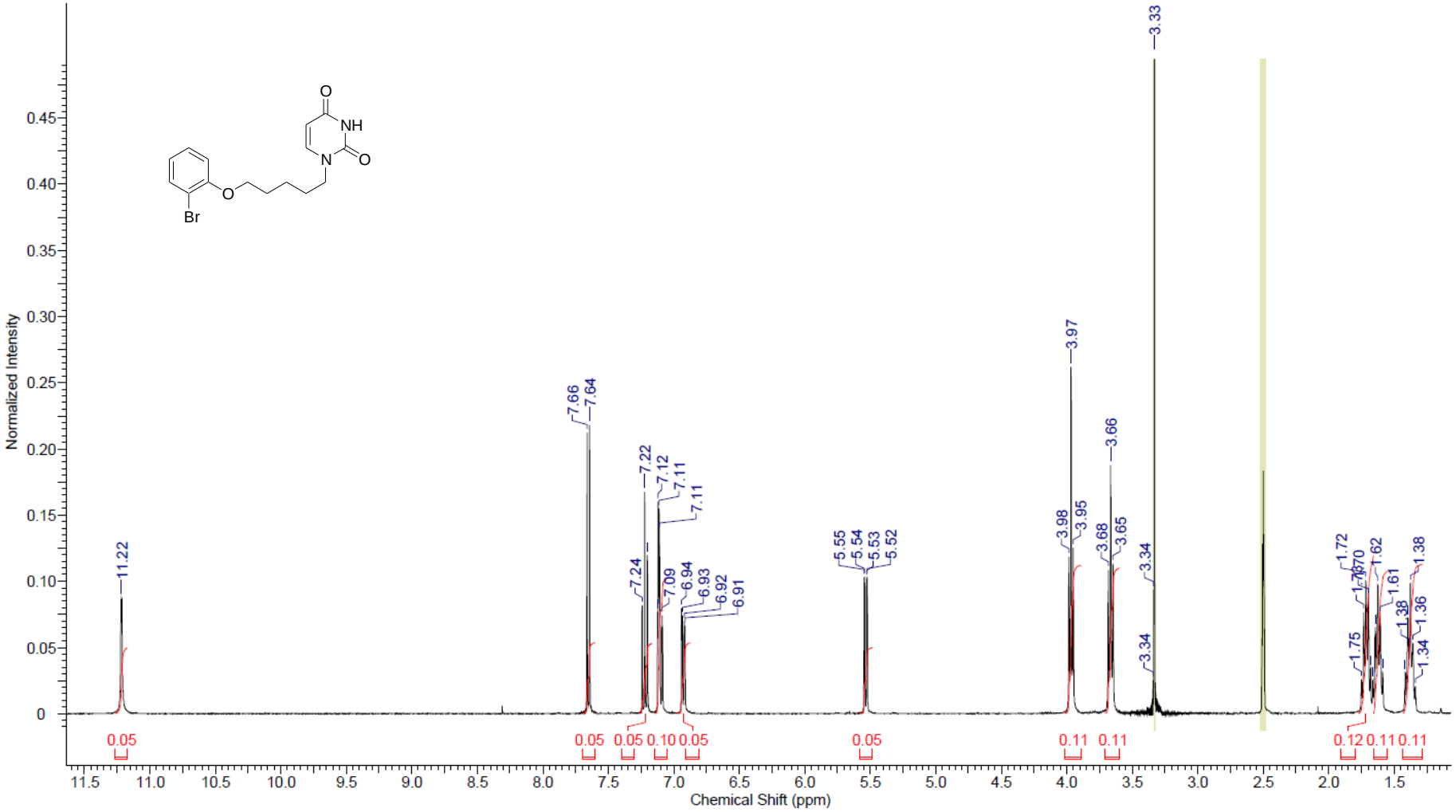

Figure S3 ^{1}H NMR spectrum of compound **1c** in DMSO-d_6 at 400 MHz.

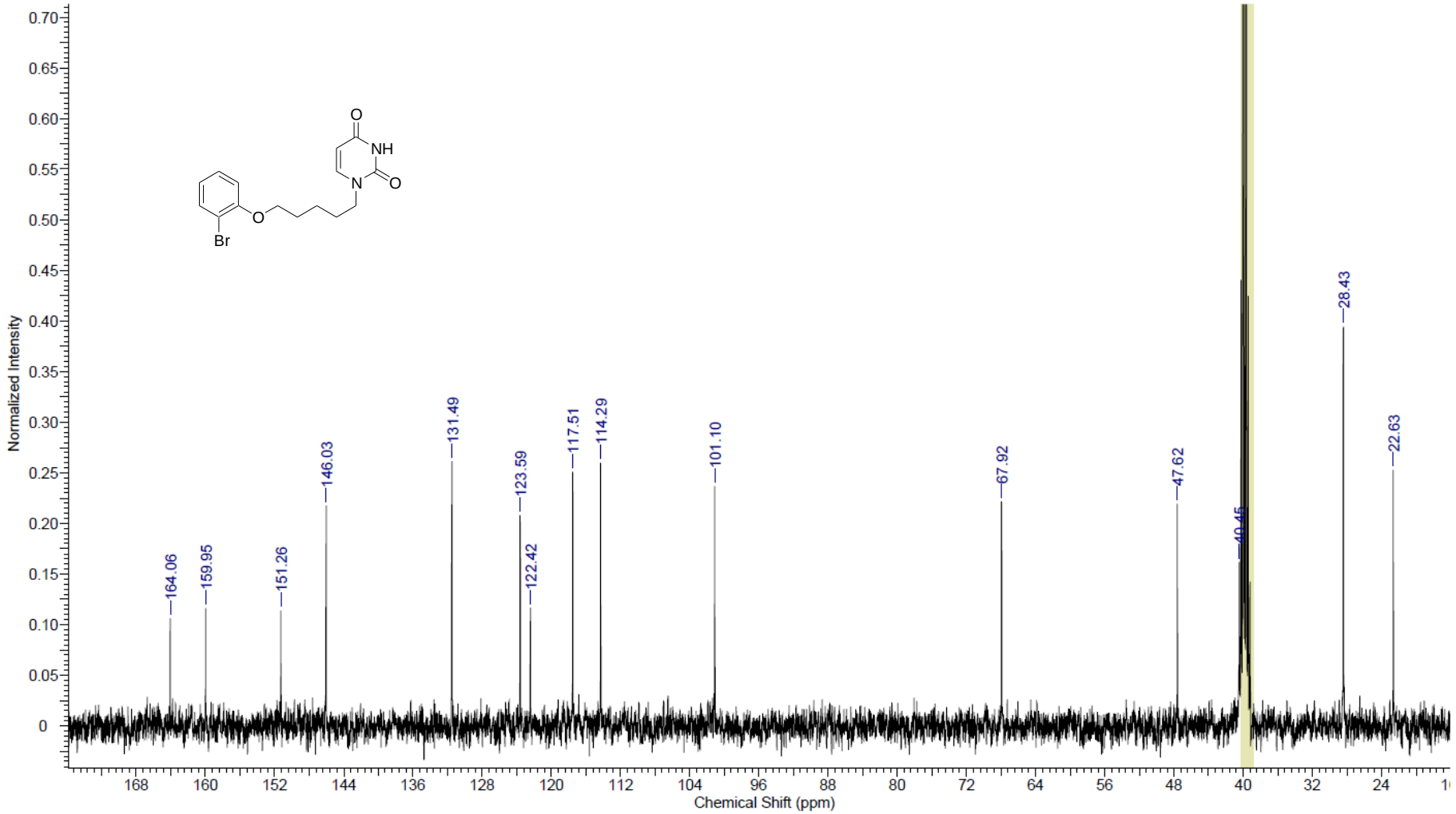

Figure S4 ^{13}C NMR spectrum of compound **1c** in DMSO-d_6 at 100 MHz.

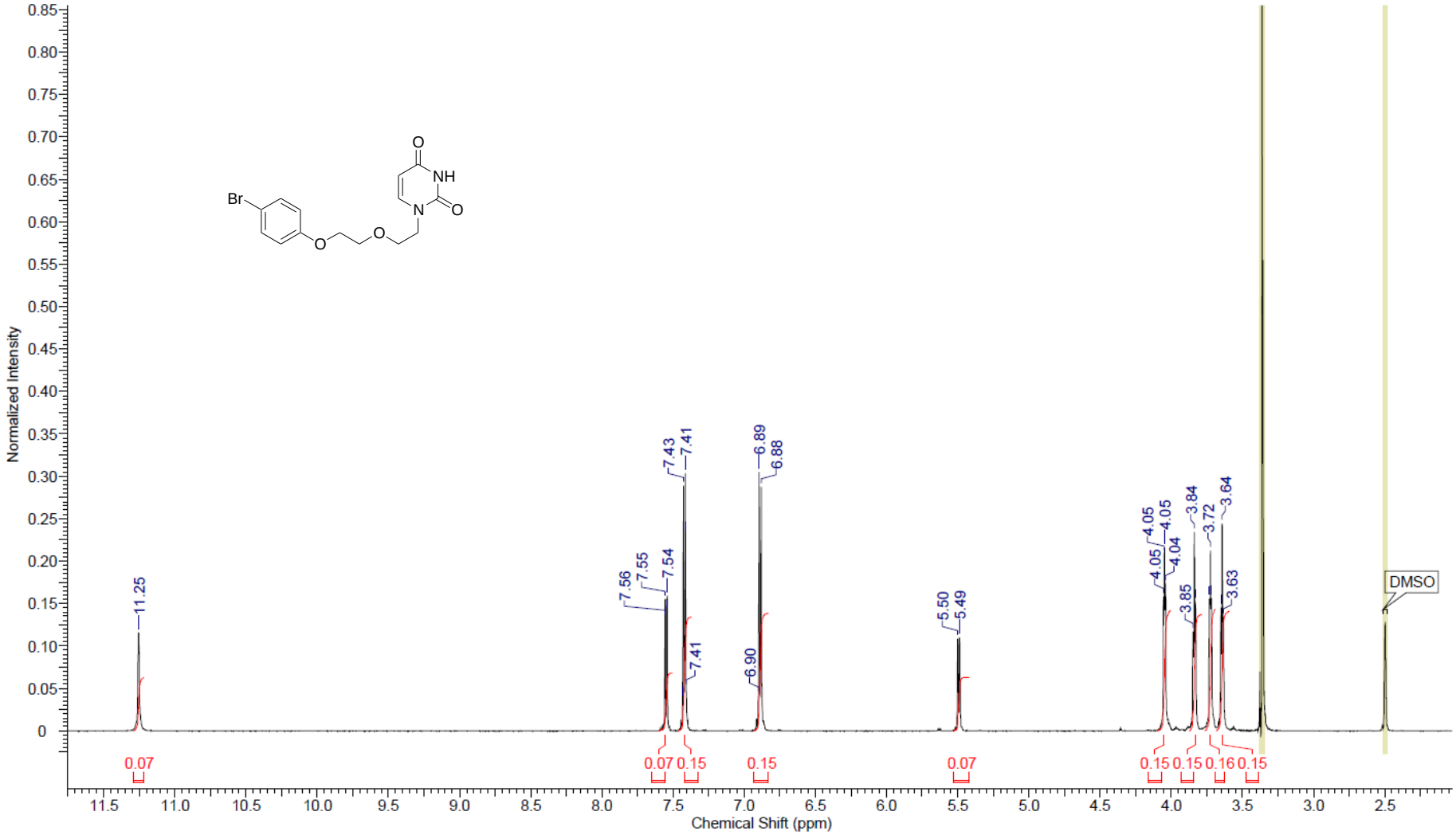

Figure S5 ^{1}H NMR spectrum of compound **1d** in DMSO-d_6 at 600 MHz.

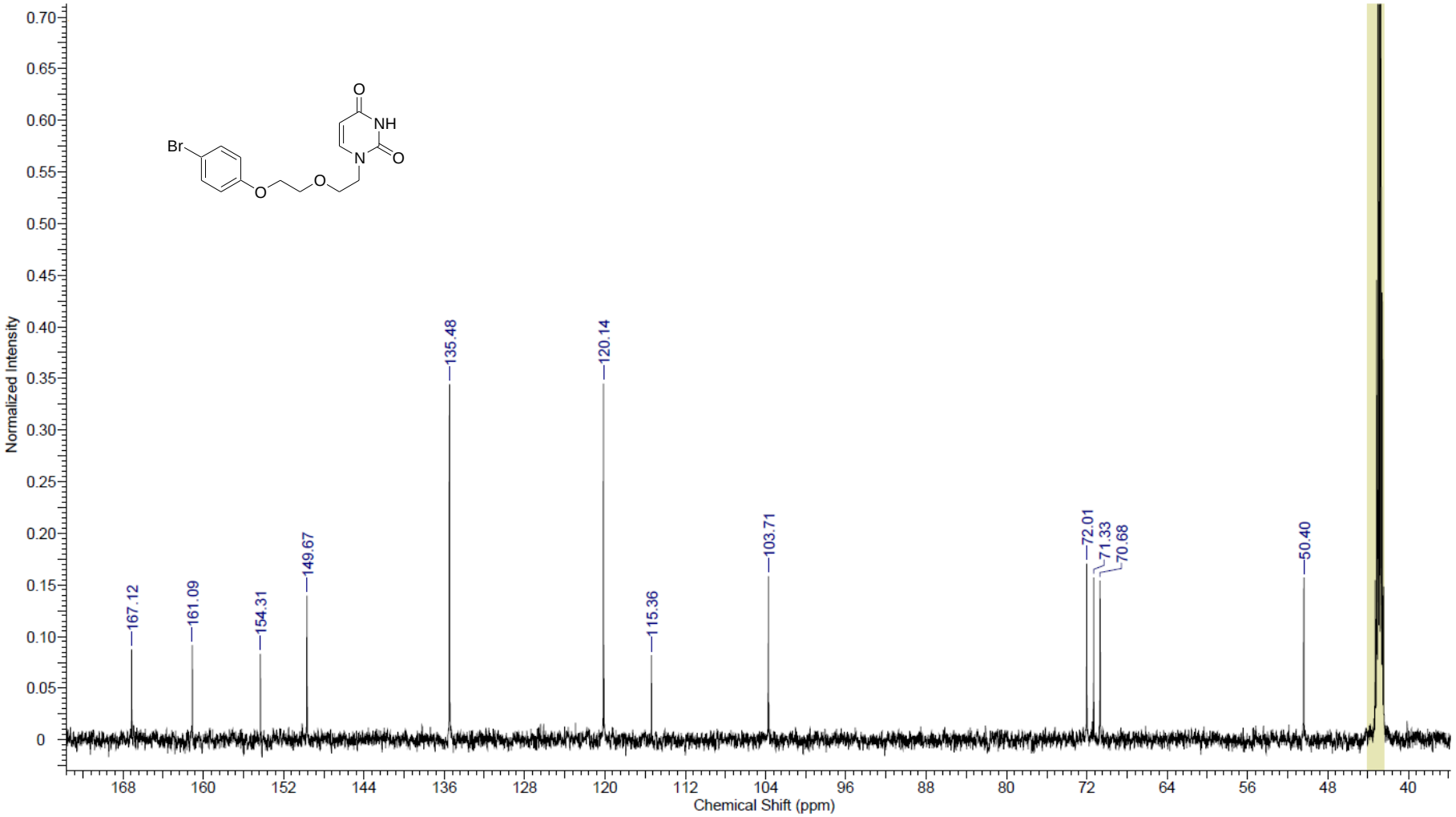

Figure S6 ^{13}C NMR spectrum of compound **1d** in DMSO-d_6 at 150 MHz.

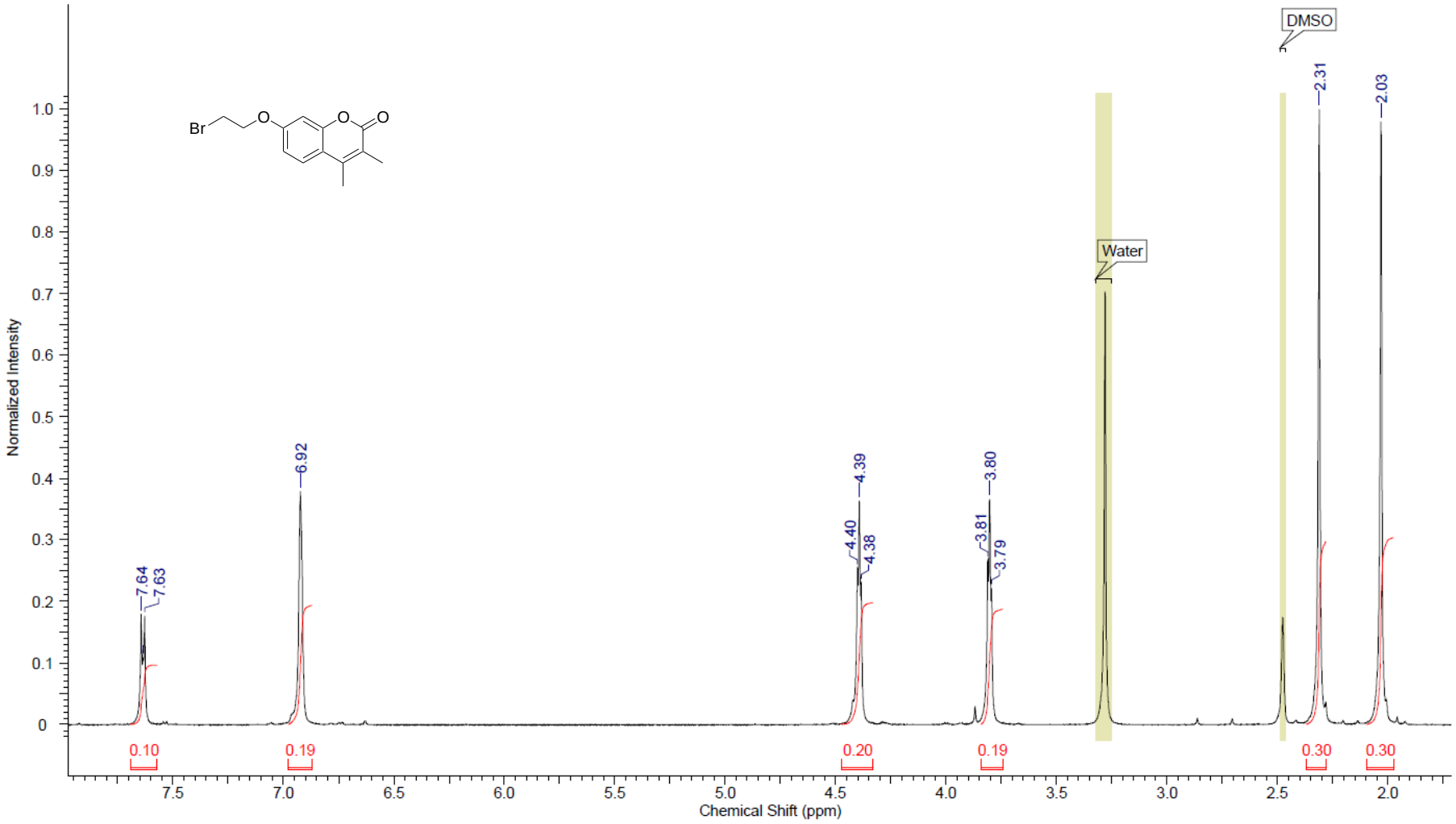

Figure S7 ^{1}H NMR spectrum of compound **2f** in DMSO-d_6 at 600 MHz.

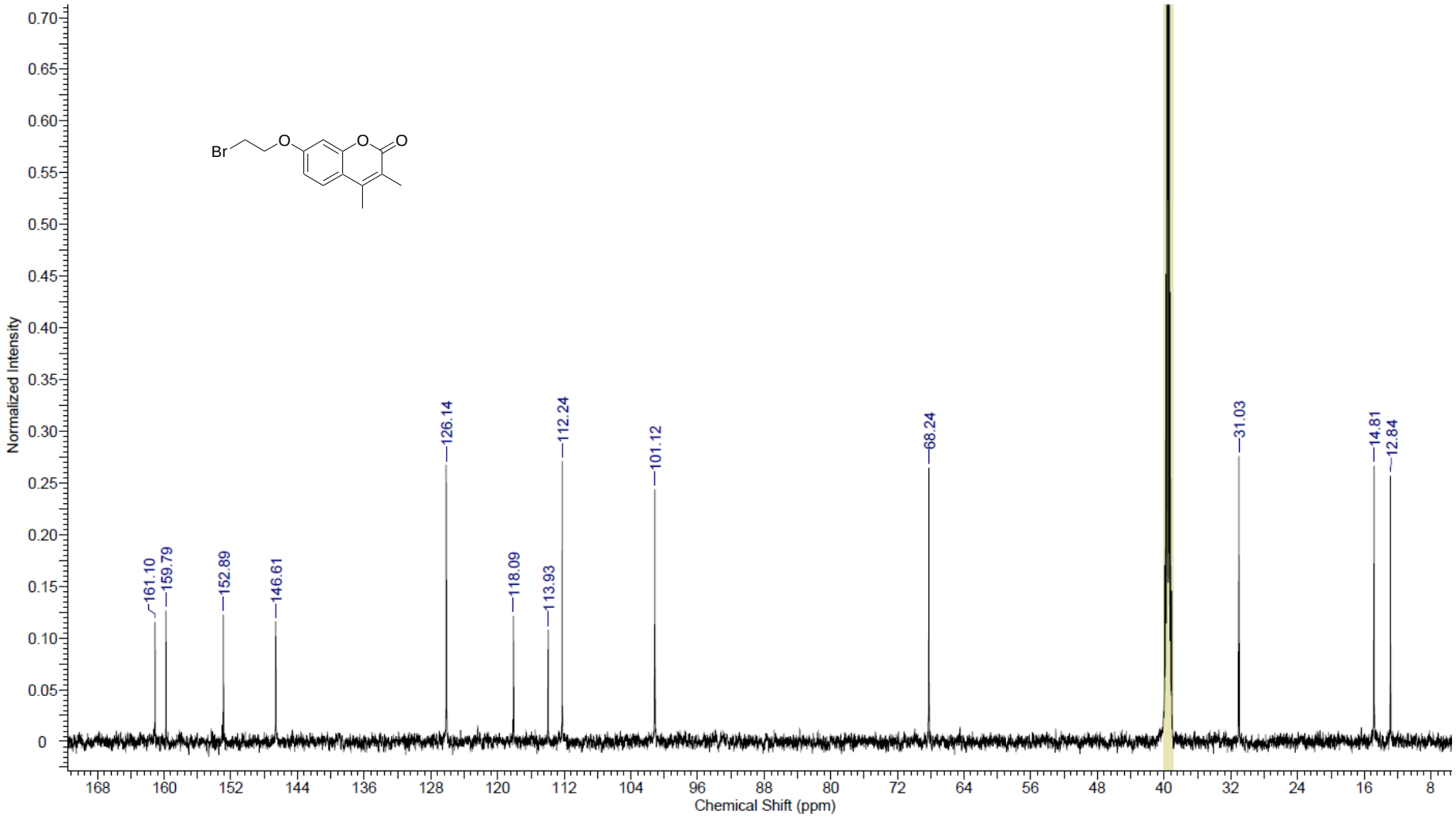

Figure S8 ^{13}C NMR spectrum of compound **2f** in DMSO-d_6 at 150 MHz.

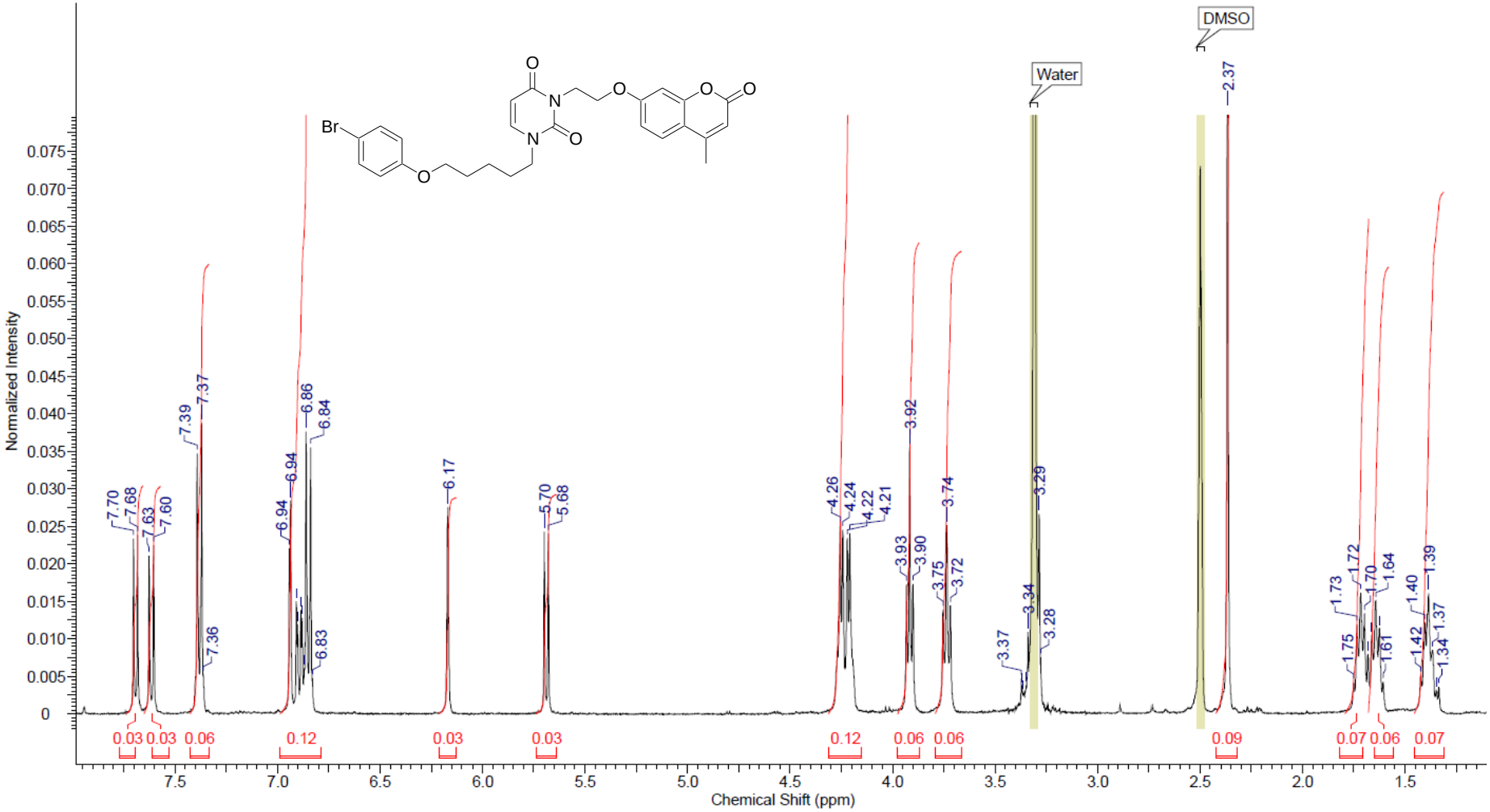

Figure S9 ^{1}H NMR spectrum of compound **3a** in DMSO-d_6 at 400 MHz.

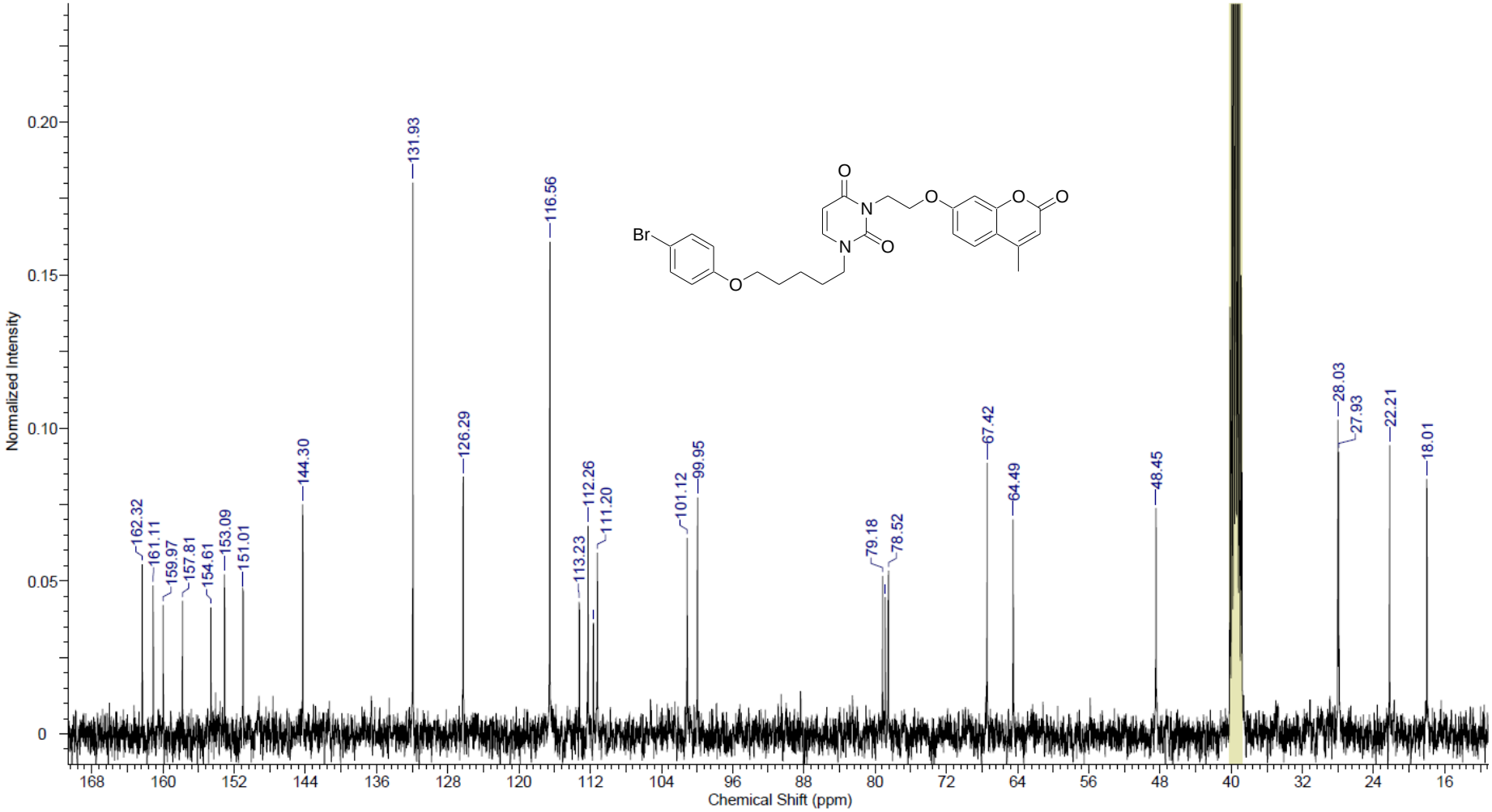

Figure S10 ^{13}C NMR spectrum of compound **3a** in DMSO-d_6 at 100 MHz.

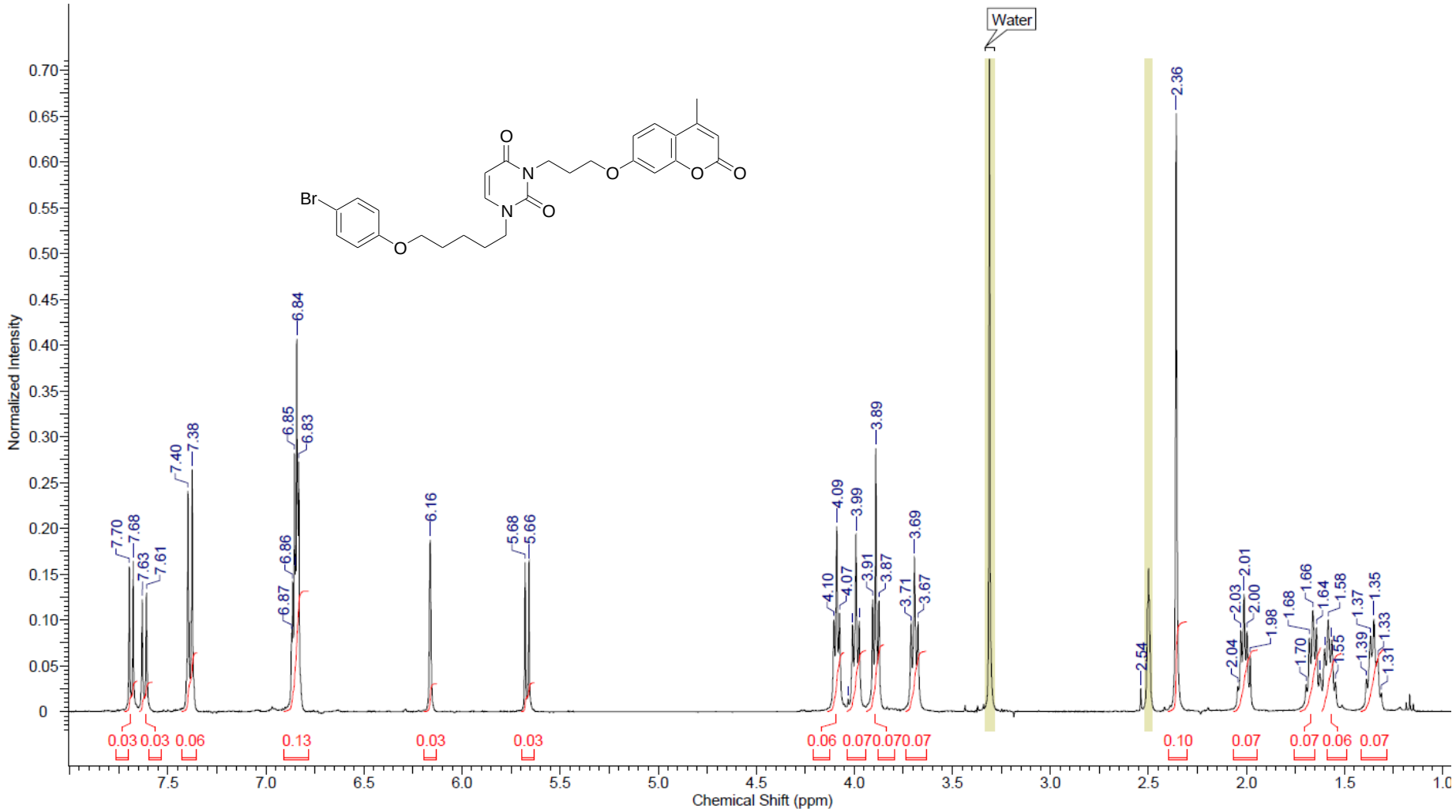

Figure S11 ^{1}H NMR spectrum of compound **3b** in DMSO-d_6 at 400 MHz.

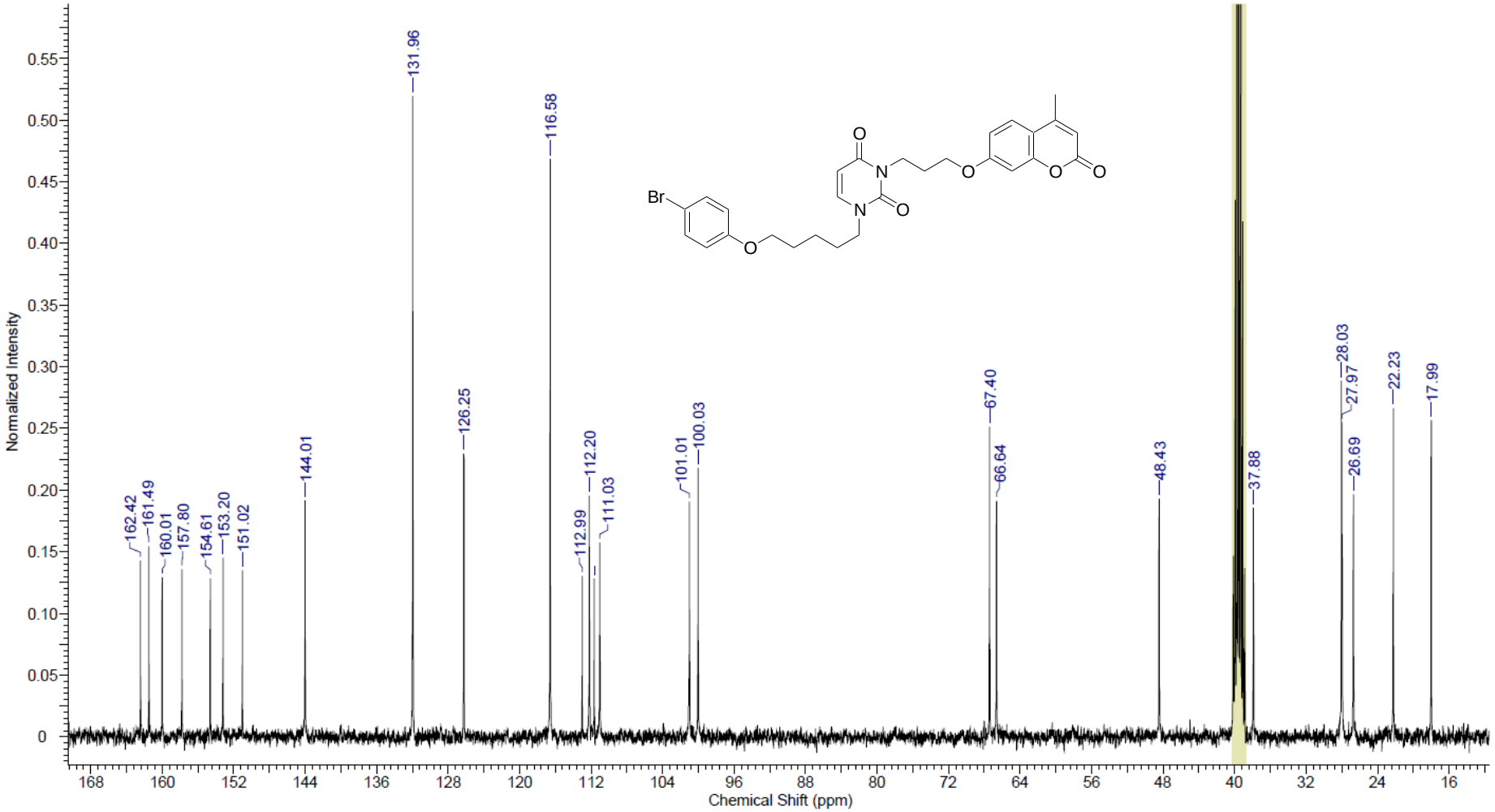

Figure S12 ^{13}C NMR spectrum of compound **3b** in DMSO-d_6 at 100 MHz.

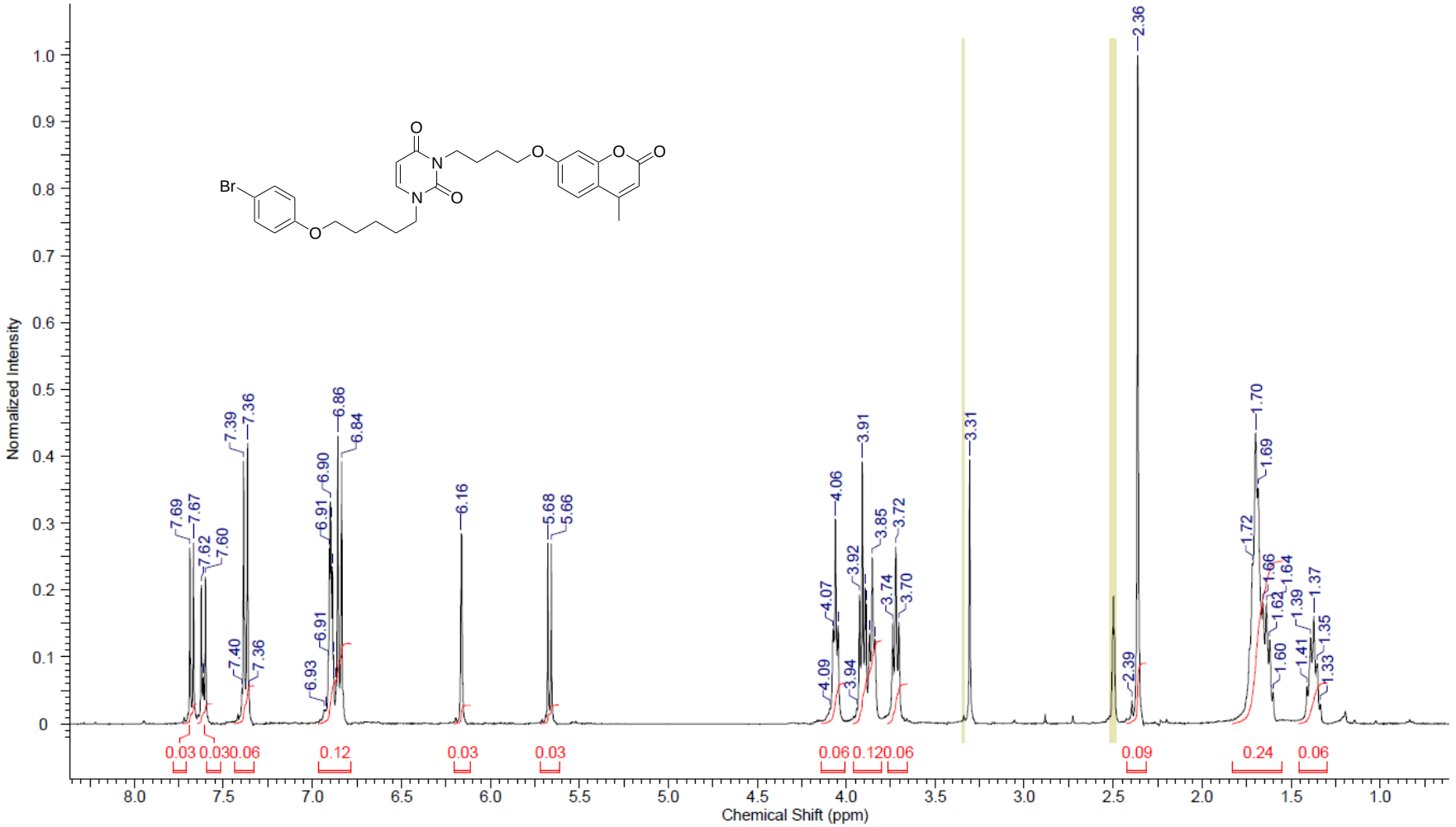

Figure S13 ^{1}H NMR spectrum of compound **3c** in DMSO-d_6 at 400 MHz.

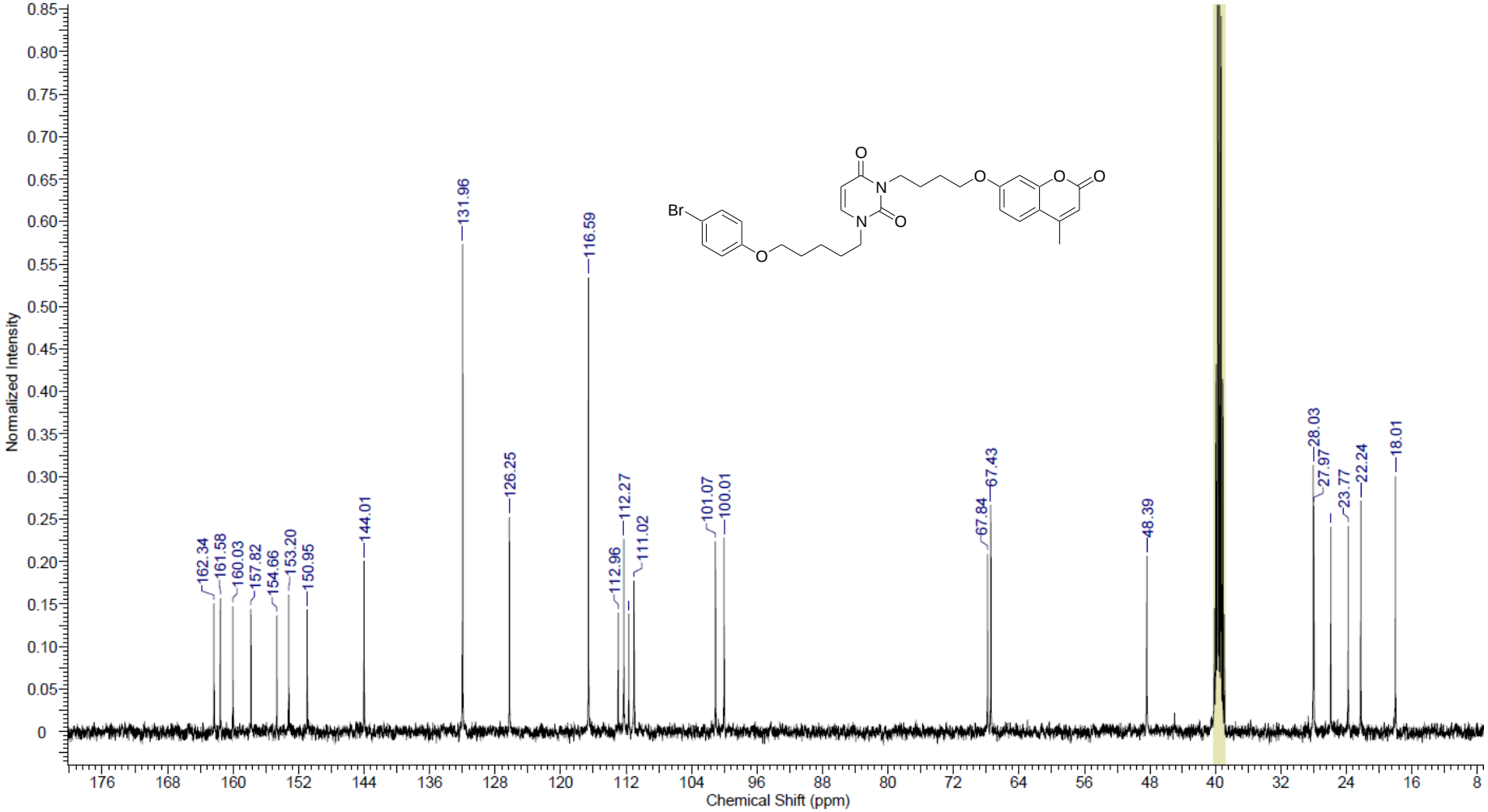

Figure S14 ^{13}C NMR spectrum of compound **3c** in DMSO-d_6 at 100 MHz.

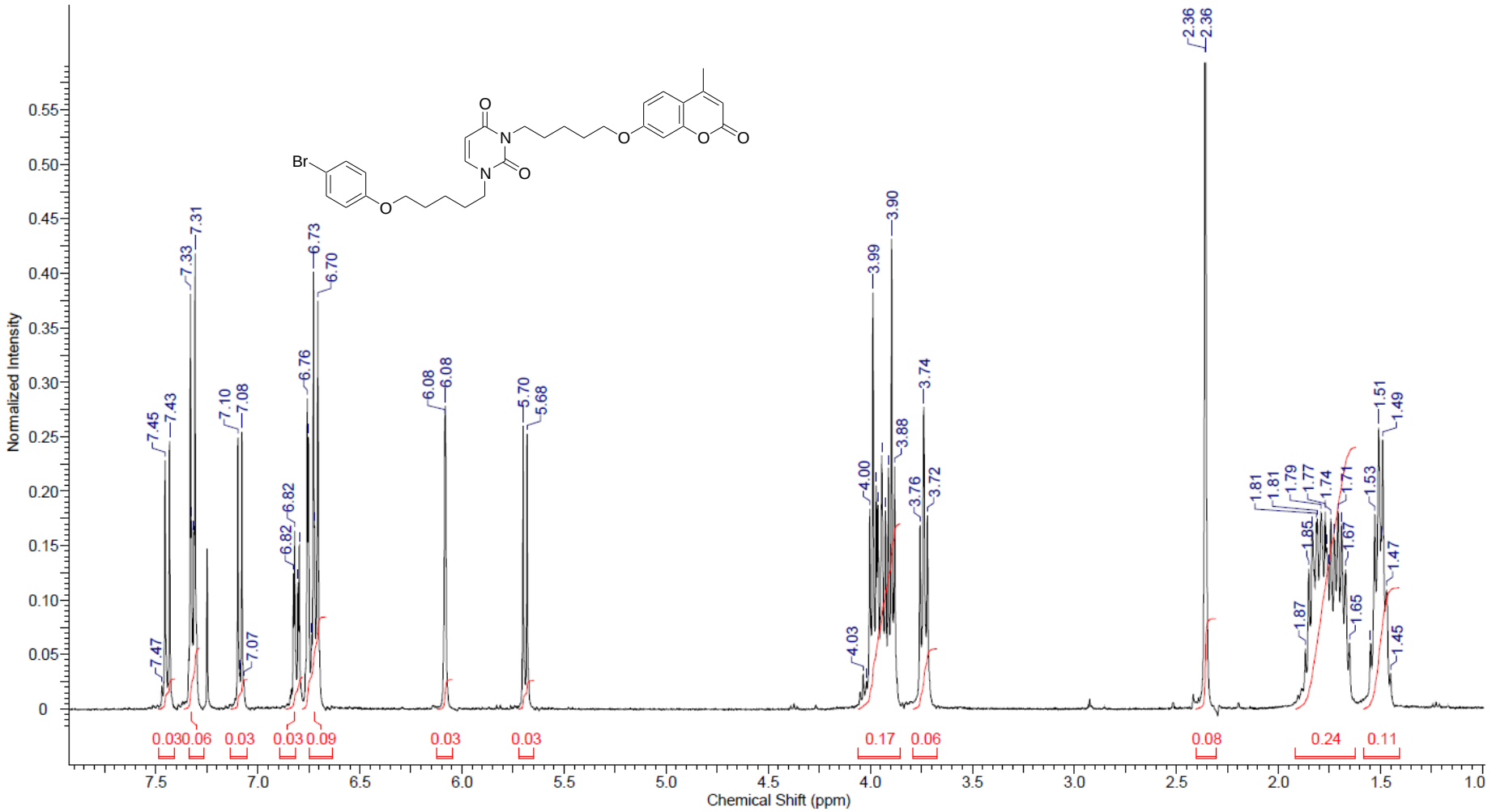

Figure S15 ^{1}H NMR spectrum of compound **3d** in $CDCl_3$ at 400 MHz.

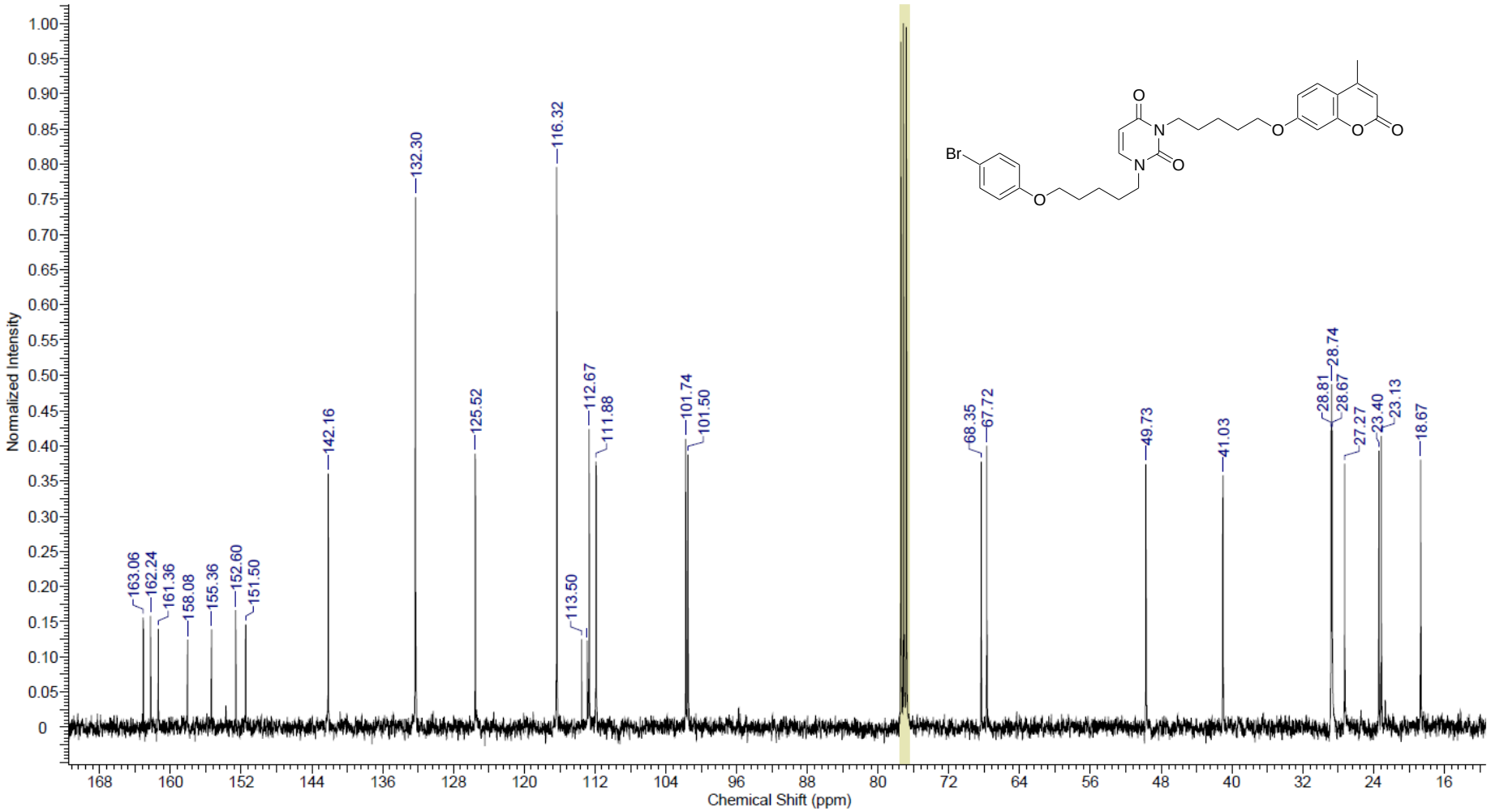

Figure S16 ^{13}C NMR spectrum of compound **3d** in $CDCl_3$ at 100 MHz.

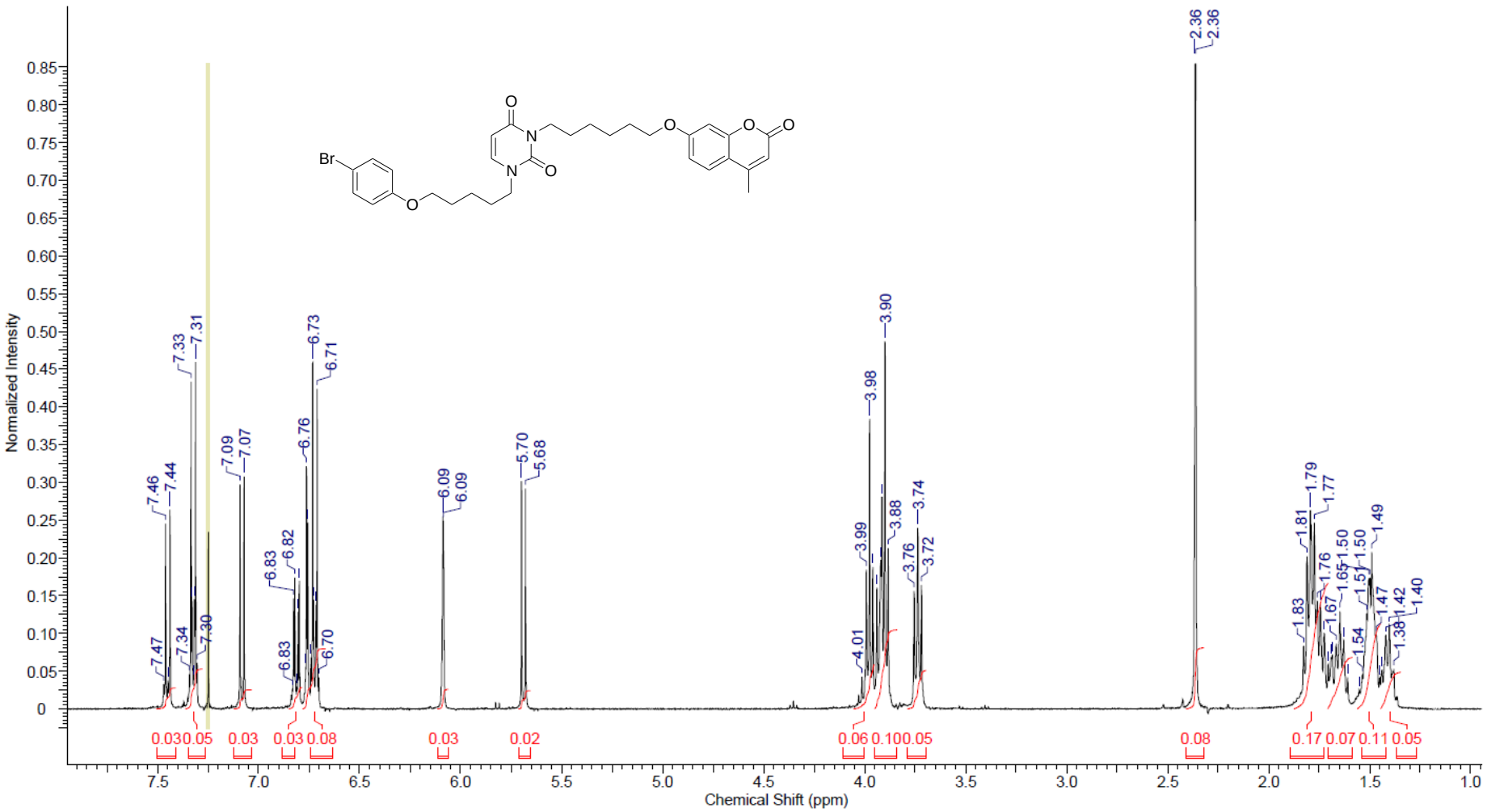

Figure S17 ^{1}H NMR spectrum of compound **3e** in $CDCl_3$ at 400 MHz.

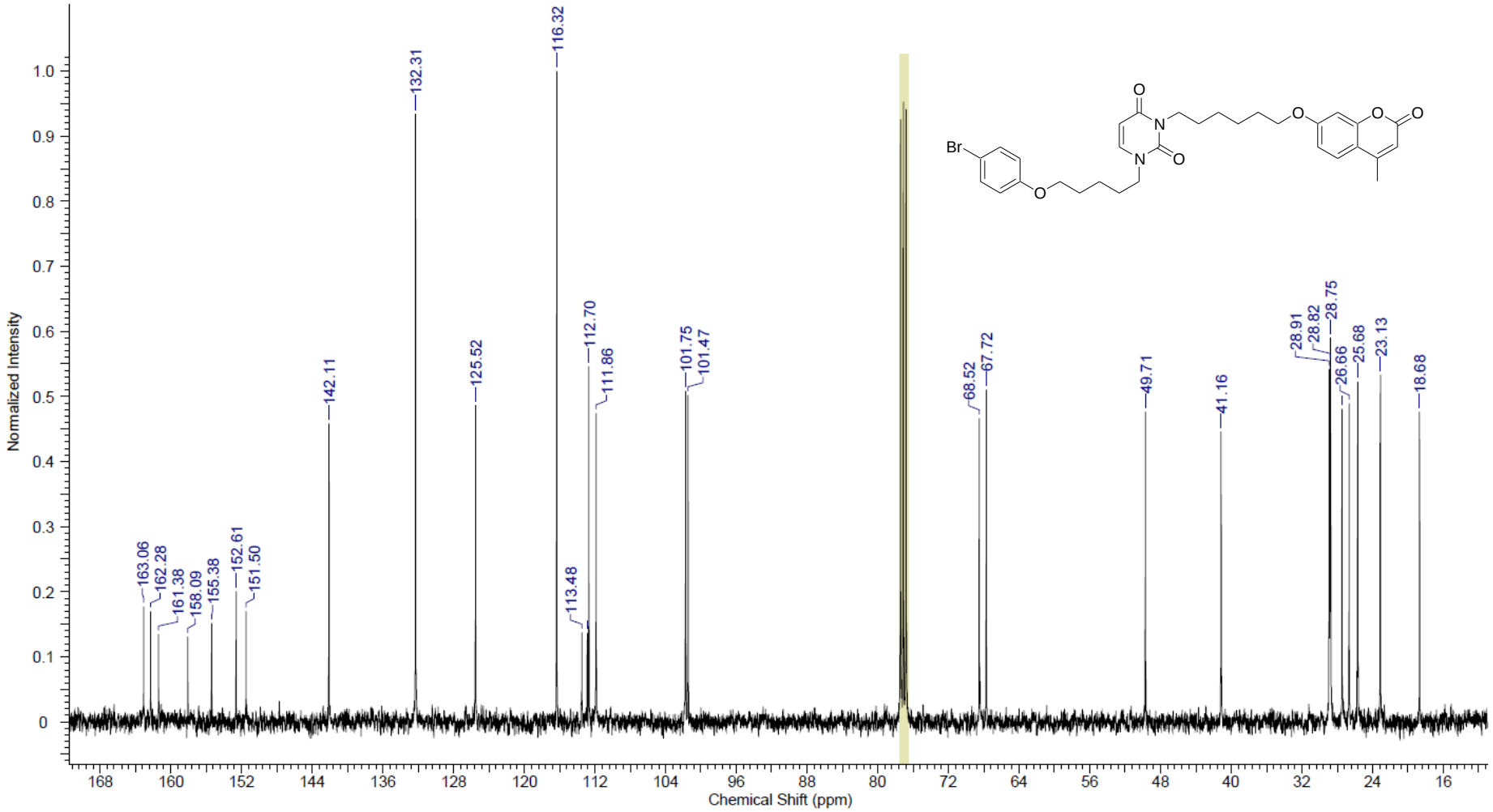

Figure S18 ^{13}C NMR spectrum of compound **3e** in $CDCl_3$ at 100 MHz.

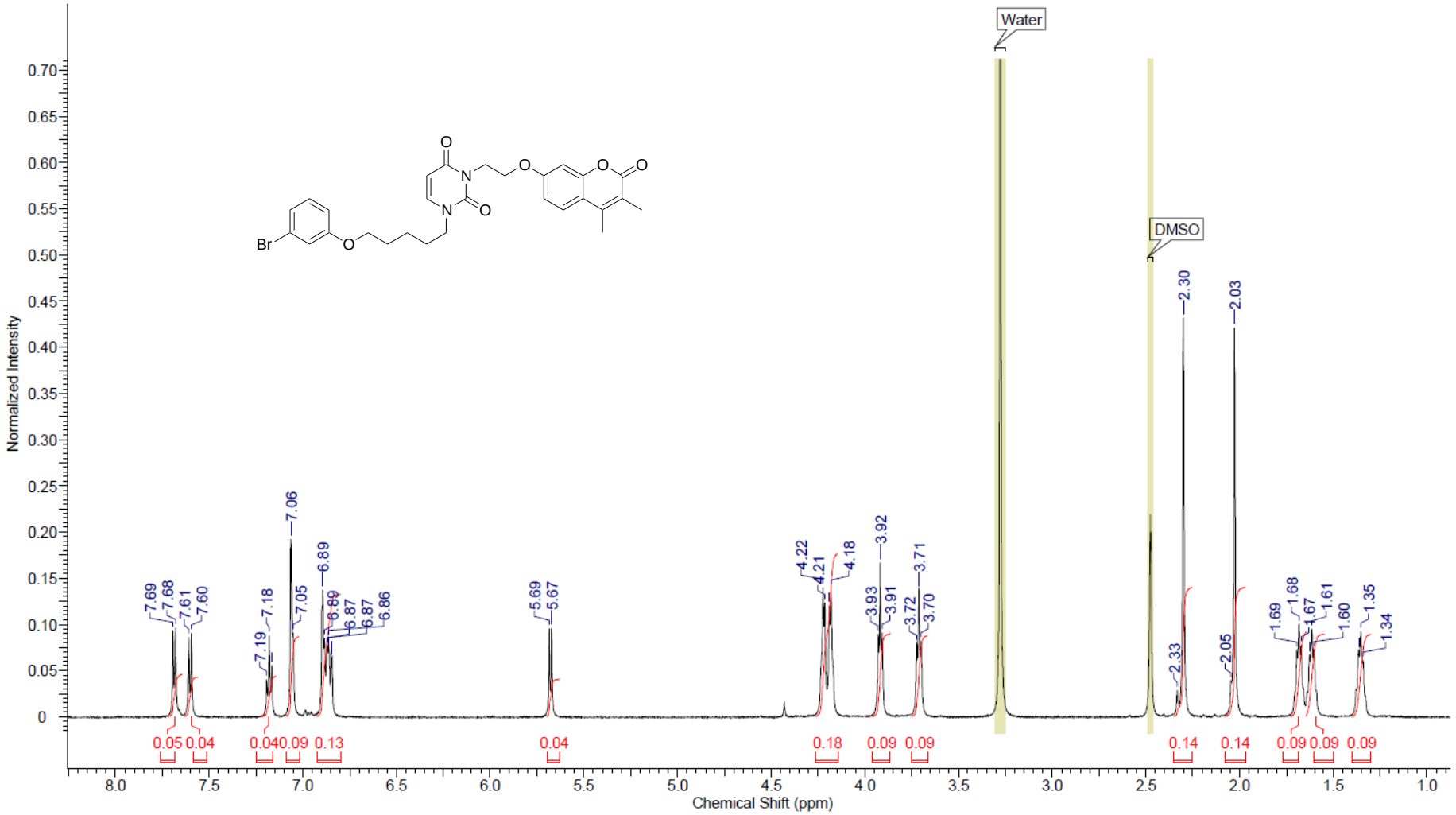

Figure S19 ^{1}H NMR spectrum of compound **3f** in DMSO-d_6 at 600 MHz.

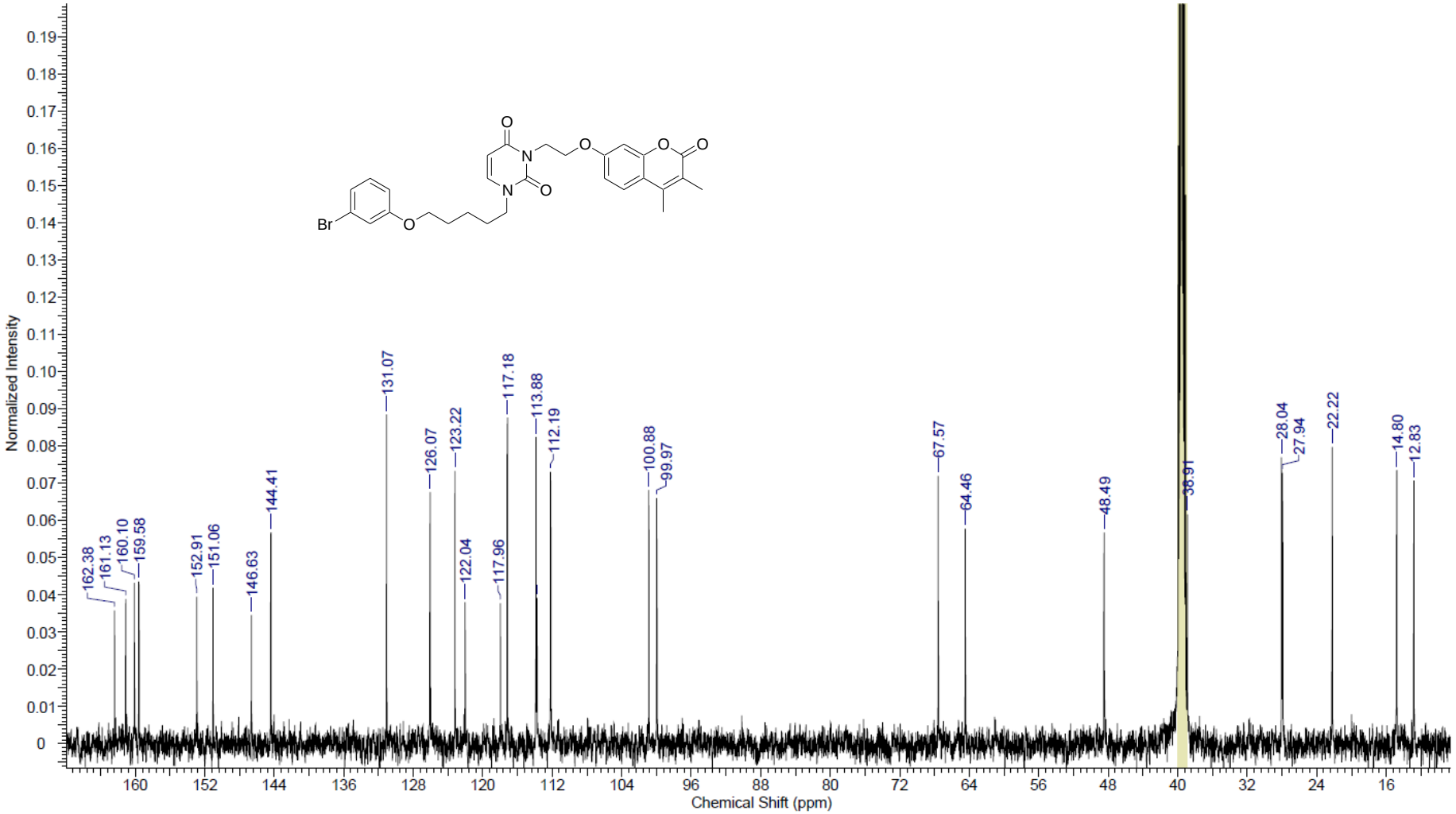

Figure S20 ^{13}C NMR spectrum of compound **3f** in DMSO-d_6 at 150 MHz.

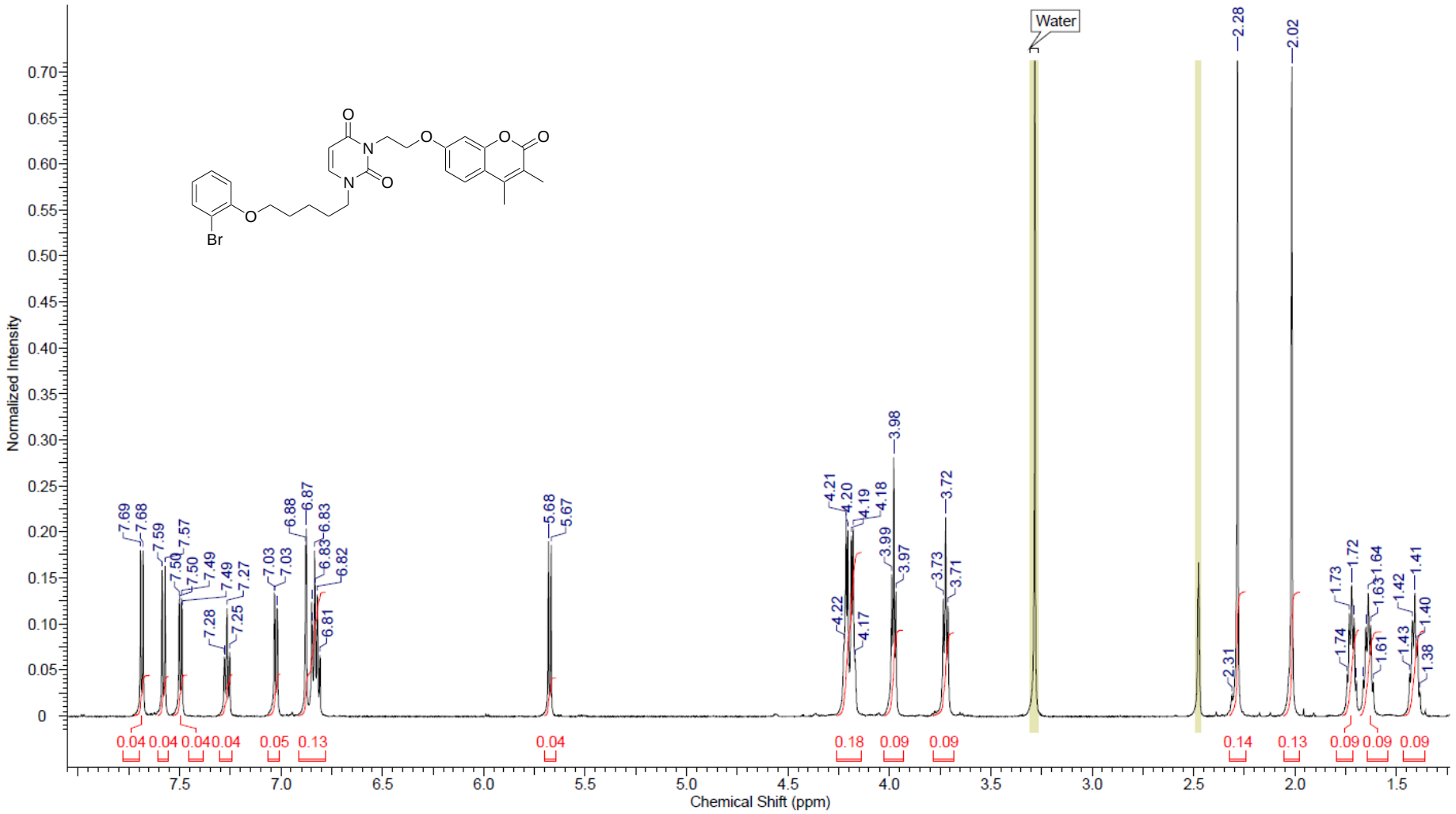

Figure S21 ^{1}H NMR spectrum of compound **3g** in DMSO-d_6 at 600 MHz.

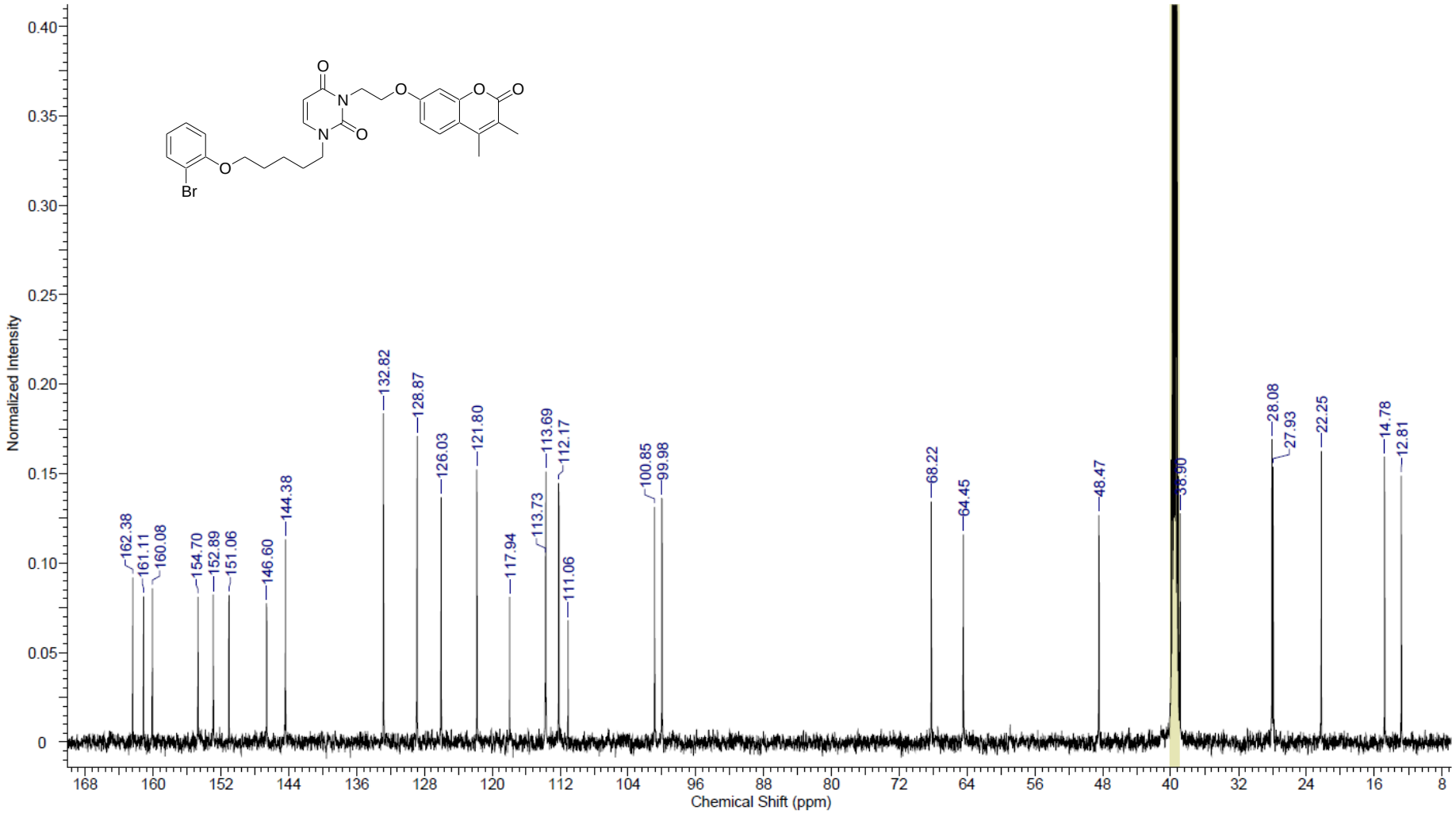

Figure S22 ^{13}C NMR spectrum of compound **3g** in DMSO-d_6 at 150 MHz.

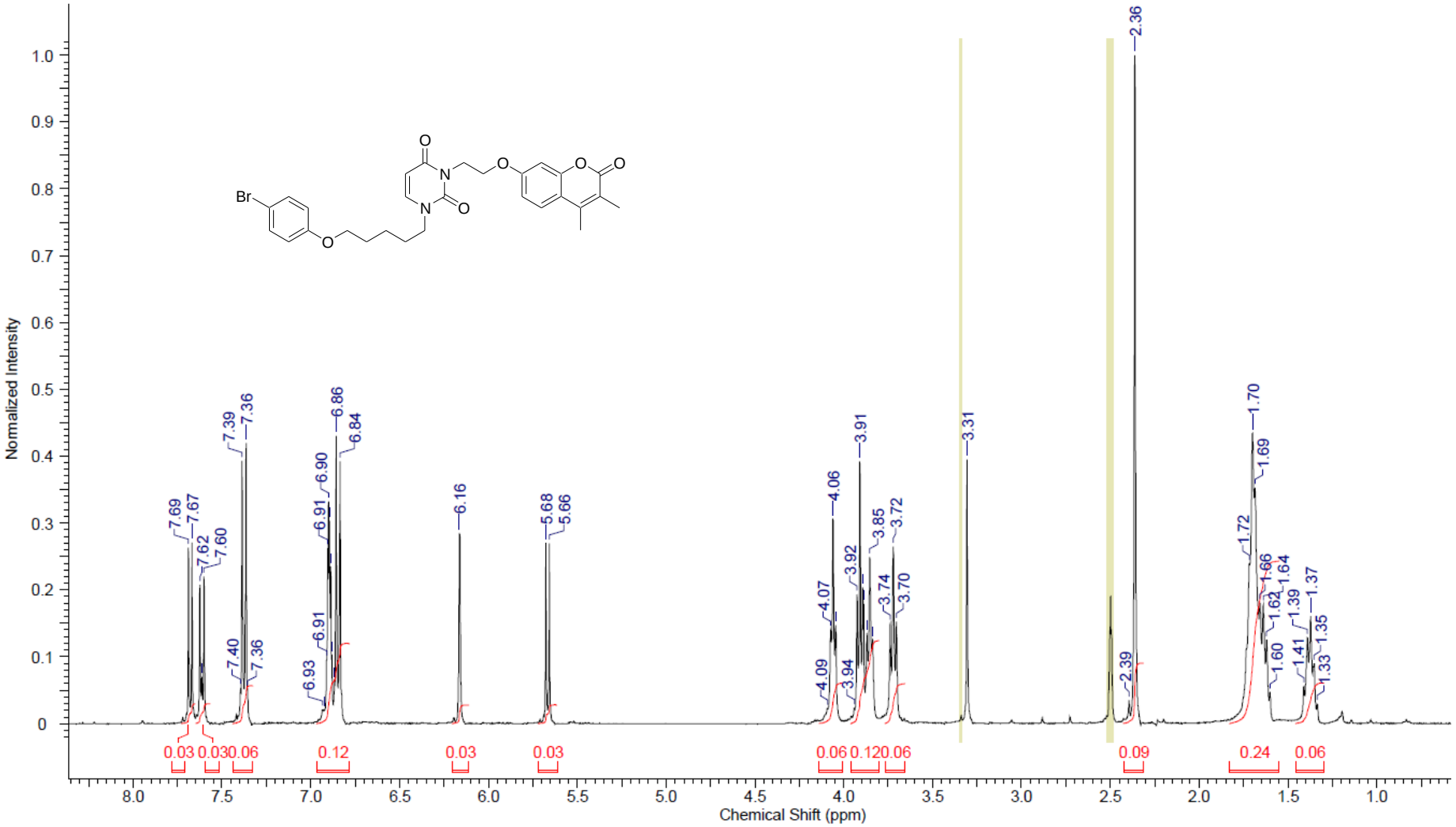

Figure S23 ^{1}H NMR spectrum of compound **3h** in DMSO-d_6 at 400 MHz.

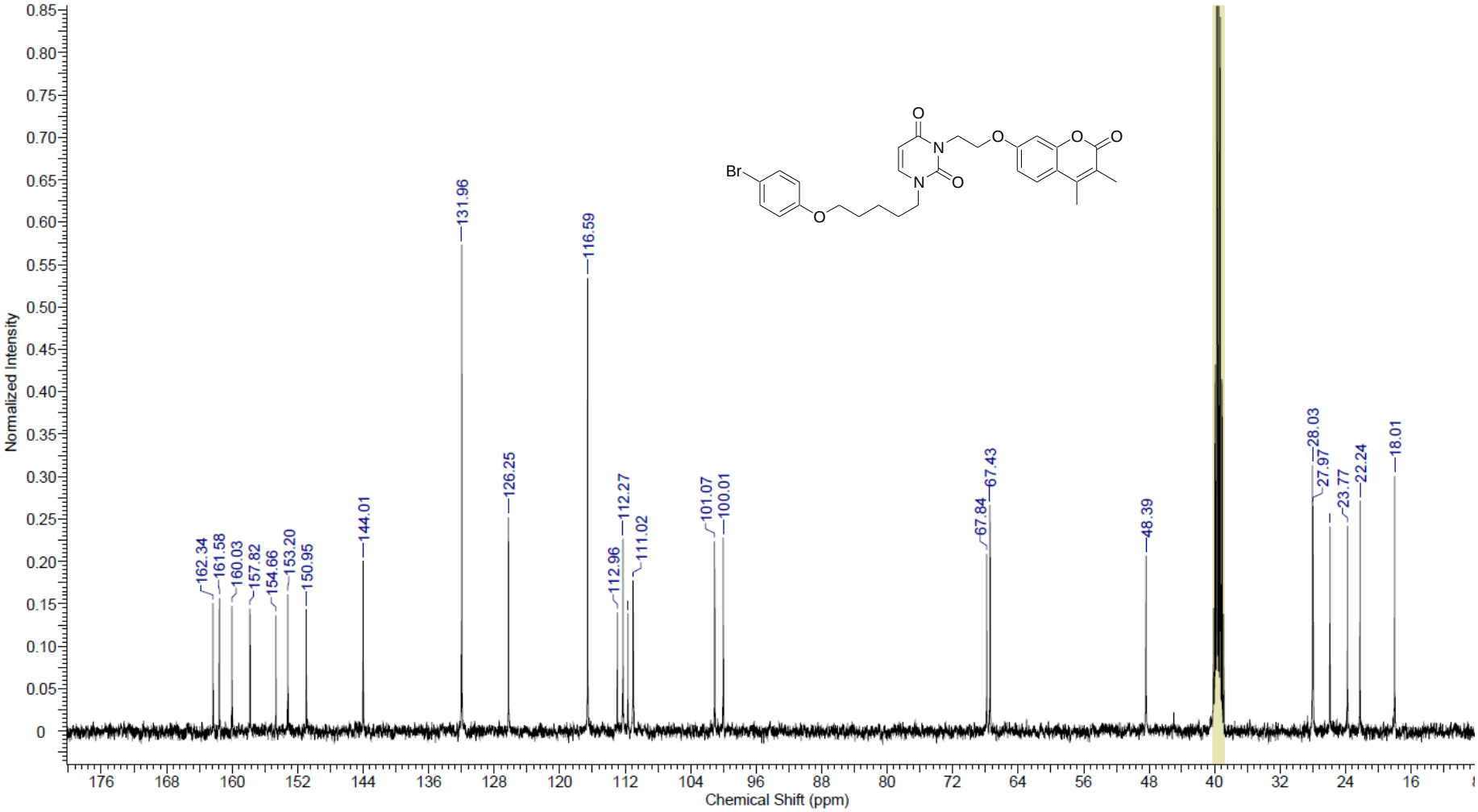

Figure S24 ^{13}C NMR spectrum of compound **3h** in DMSO-d_6 at 100 MHz.

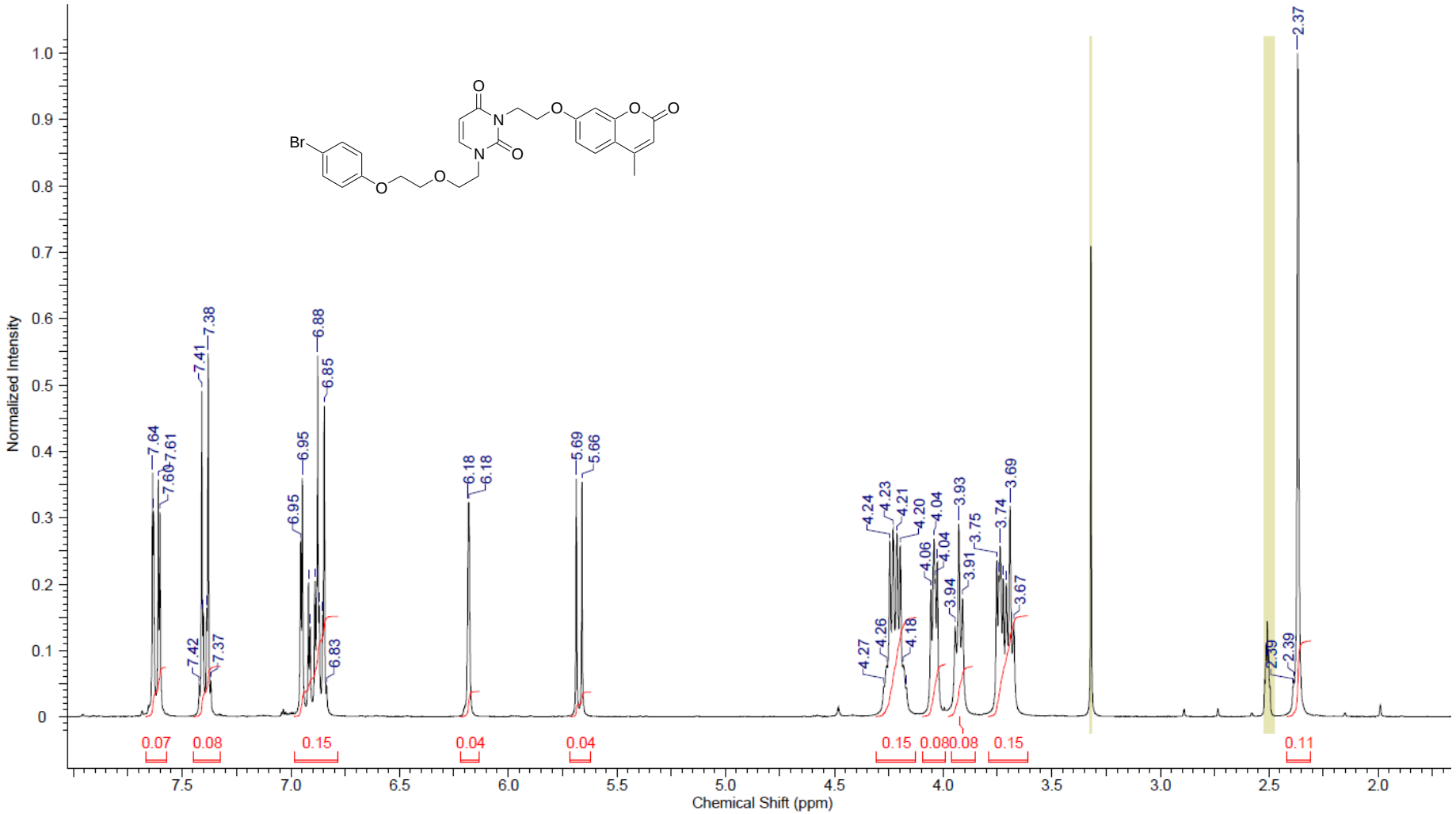

Figure S25 ^{1}H NMR spectrum of compound **3i** in DMSO-d_6 at 400 MHz.

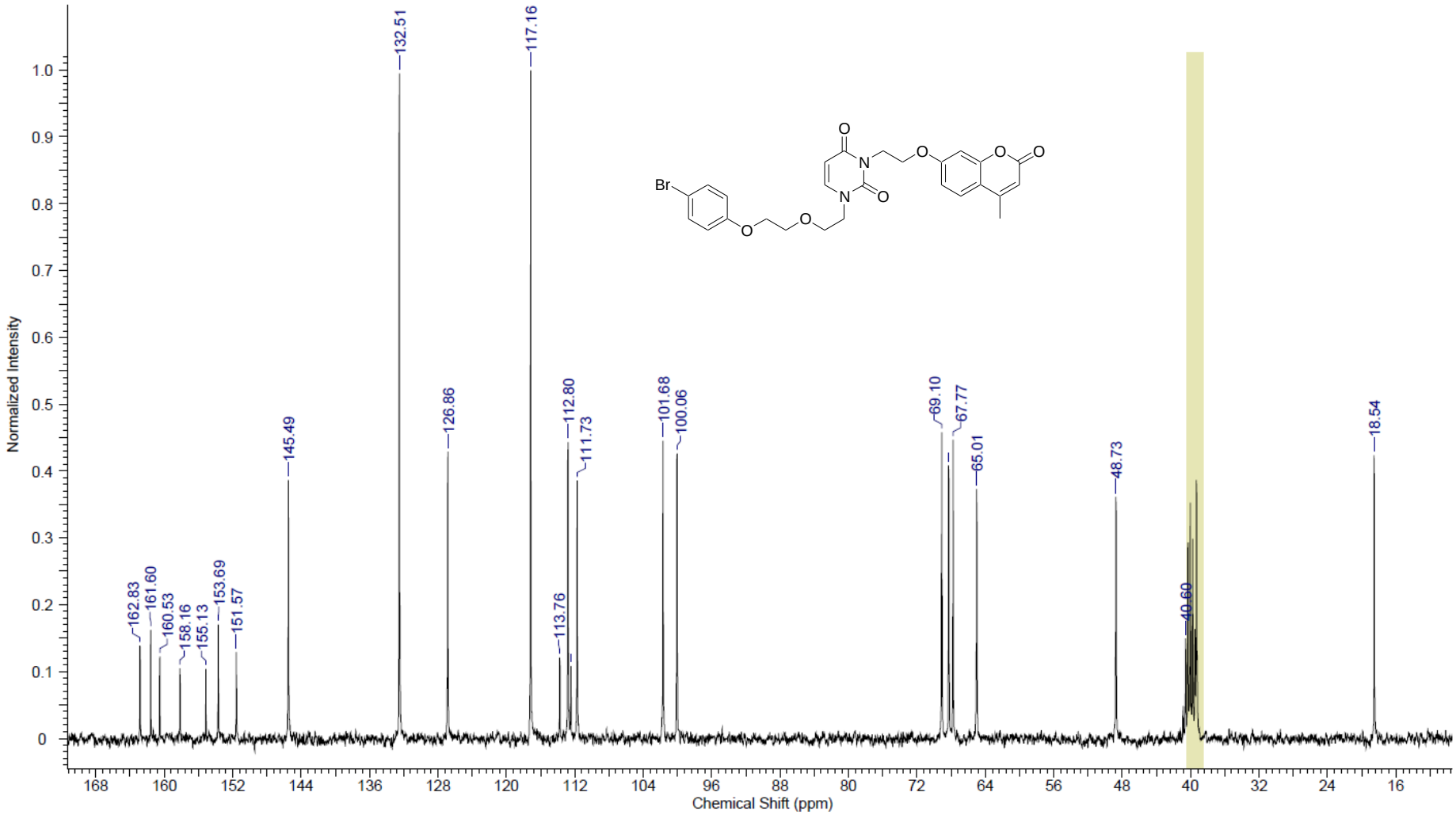

Figure S26 ^{13}C NMR spectrum of compound **3i** in DMSO-d_6 at 100 MHz.