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New acetamide derivatives containing (ω-*p*-bromophenoxyalkyl)uracil moiety and their anticytomegalovirus activity

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Experimental

All reagents were obtained at the highest grade available from Sigma and 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 and EtOAc were obtained by distillation over P_2O_5. TLC was performed on Merck TLC Silica gel 60 F_{254} plates eluting with the specified solvents and samples were made visual with a VL-6.LC UV lamp (Vilber). Acros Organics (Belgium) silica gel (Kieselgur 60–200 μm, 60A) was used for column chromatography. Yields refer to spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials. Melting points were determined in glass capillaries on a Mel-Temp 3.0 (Laboratory Devices Inc., USA). NMR spectra were obtained using Bruker Avance 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) and 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.

The starting chloroacetanilides were prepared according to the previously described methods: 2-chloro-*N*-(4-phenoxyphenyl)acetamide **1a** [S1], 2-chloro-*N*-[4-(4-methylphenoxy)phenyl]acetamide **1b** [S2], 2-chloro-N-[4-(4-chlorophenoxy)phenyl]acetamide **1c** [S3]. 1-Bromo-10-(4-bromophenoxy)decane and 1-bromo-12-(4-bromophenoxy)dodecane were obtained as described [S4].

2-Chloro-*N*-[4-(3,4-dimethylphenoxy)phenyl]acetamide 1d. Chloroacetyl chloride (0.8 ml, 10.06 mmol) was added dropwise to a stirred mixture of 4-(3,4-dimethylphenoxy)aniline (1.95 g, 9.14 mmol) and K_2CO_3 (1.8 g, 13.02 mmol) in anhydrous 1,2-dichloroethane (50 ml) at 0 °C. The mixture was stirred for 2 h at the same temperature and allowed to reach the room one. The inorganic material was filtered off and washed with 1,2-dichloroethane (25 ml). The filtrate was evaporated under reduced pressure, and the residue was recrystallized from hexane-ethyl acetate (3:2). Yield 75%, mp 145-146 °C, R_f 0.72 (ethyl acetate-hexane, 1:1). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 2.17 (6H, s, CH_3 × 2), 4.23 (2H, s, CH_2CO), 6.69 (1H, dd, *J* 8.3 and 2.7 Hz, H-6'), 6.79 (1H, d, *J* 2.5 Hz, H-2'), 6.92–6.96 (2H, m, H-3, H-5), 7.10 (1H, d, *J* 8.1 Hz, H-5'), 7.55–7.59 (2H, m, H-2, H-6,), 10.30 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 18.9, 19.8, 43.8, 116.0, 119.1, 119.9, 121.4, 131.0, 131.4, 134.1, 138.3, 153.4, 155.1, 164.7.

2-Chloro-*N*-[4-(3,4-dichlorophenoxy)phenyl]acetamide (1e). Yield 78%, mp 137-138 °C, R_f 0.43 (hexane-ethyl acetate, 2 : 1). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 4.25 (2H, s, CH_2CO), 6.95 (1H, dd, *J* 8.9 and 2.8 Hz, H-6'), 7.06–7.10 (2H, m, H-3, H-5), 7.21 (1H, d, *J* 2.9 Hz, H-2'), 7.58 (1H, d, *J* 8.8 Hz, H-5'), 7.63–7.67 (2H, m, *J* 8.9 Hz, H-2, H-6), 10.39 (1H, s, CO-NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 43.8, 118.3, 119.9, 120.4, 121.5, 125.2, 131.8, 132.3, 135.5, 151.4, 157.3, 164.9.

General procedure for the synthesis of 1-[10-(4-bromophenoxy)decyl]- (2b) and 1-[12-(4-bromophenoxy)dodecyl]uracil (2c). An equimolar mixture of 1-bromo-10-(4-bromophenoxy)decane or 1-bromo-12-(4-bromophenoxy)dodecane (13.51 mmol) and 2,4-bis(trimethylsilyloxy)pyrimidine (3.43 g, 13.38 mmol) was heated at 160-170 °C for 1 h. The resulting amber-colored viscous liquid was dissolved in ethyl acetate (50 ml) and treated with Pr^{i}OH (10 ml). The precipitate formed was filtered off and purified by flash chromatography, eluting the column with 1:5 ethyl acetate/1,2-dichloroethane mixture. The relevant fractions were combined, evaporated under reduced pressure and recrystallized from ethyl acetate-hexane (2:1).

1-[10-(4-Bromophenoxy)decyl]uracil (2b). Yield 82%; mp 84-86 °C; R_f 0.50 (ethyl acetate). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.24-1.28 (10H, m, CH_2 × 5), 1.36 (2H, qu, J = 7.7 Hz, CH_2), 1.54 (2H, q, J = 6.9 Hz, CH_2), 1.67 (2H, q, J = 7.5 Hz, CH_2), 3.62 (2H, t, J = 7.3 Hz, CH_2), 3.91 (2H, t, J = 6.5 Hz, CH_2), 5.53 (1H, dd, J = 7.8 and 2.3 Hz, H-5), 6.88 (2H, d, J = 9.0 Hz, H-3', H-5'), 7.41 (2H, d, J = 9.1 Hz, H-2', H-6'), 7.63 (1H, d, J = 7.8 Hz, H-6), 11.21 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 28.8, 29.2, 31.8, 31.9, 32.0, 32.1, 32.2, 32.3, 50.8, 71.1, 104.1, 115.1, 120.1, 135.4, 149.1, 154.3, 161.3, 167.1.

1-[12-(4-Bromophenoxy)dodecyl]uracil (2c). Yield 80%; mp 95-96.5 °C; R_f 0.54 (ethyl acetate). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.21-1.27 (14H, m, CH_2 × 7), 1.37 (2H, qu, J = 7.6 Hz, CH_2), 1.54 (2H, qu, J = 6.8 Hz, CH_2), 1.67 (2H, qu, J = 7.0 Hz, CH_2), 3.62 (2H, t, J = 7.3 Hz, CH_2), 3.92 (2H, t, J = 6.6 Hz, CH_2), 5.52 (1H, dd, J = 7.9 and 2.2 Hz, H-5), 6.88 (2H, d, J = 9.0 Hz, H-3', H-5'), 7.41 (2H, d, J = 9.0 Hz, H-2', H-6'), 7.63 (1H, d, J = 7.8 Hz, H-6), 11.21 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 28.6, 29.2, 31.8, 31.9, 32.0, 32.1, 32.3, 50.8, 71.7, 104.1, 115.1, 120.1, 135.4, 149.1, 154.3, 161.3, 167.1.

General procedure for the synthesis of 2-[3-[ω-(4-bromophenoxy)alkyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]-*N*-(4-phenoxyphenyl)acetamides 3a-g. A solution of 1-substituted uracil **2a-c** (1.42 mmol) and K_2CO_3 (0.29 g, 2.10 mmol) in DMF (10 ml) was stirred at 80 °C for 1 h, then the mixture was cooled to room temperature and the corresponding chloroacetamide **1a-e** was added, and this was stirred at the same temperature for 24 h. The mixture was evaporated *in vacuo*, the residue was treated with water (60 ml) and extracted with 1,2-dichloroethane (5×20 ml). The extracts were combined, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The precipitate was purified by flash chromatography, eluting the column with 1:3 ethyl acetate/1,2-dichloroethane mixture. The relevant fractions were combined, evaporated under reduced pressure and recrystallized from ethyl acetate-hexane (1:1).

2-[3-[8-(4-Bromophenoxy)octyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]-*N*-[4-(4-methylphenoxy)phenyl]acetamide 3a. Yield 78%, mp 139.5-140.5 °C, R_f 0.55 (ethyl acetate-1,2-dichloroethane, 1:1). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.27-1.37 (8H, m, CH_2 × 4), 1.59 (2H, quin, *J* 6.3 Hz, CH_2), 1.67 (2H, quin, *J* 6.9 Hz, CH_2), 2.26 (3H, s, CH_3), 3.72 (2H, t, *J* 7.1 Hz, CH_2), 3.91 (2H, t, *J* 6.1 Hz, CH_2), 4.59 (2H, s, CH_2), 5.74 (1H, d, *J* 7.9 Hz, uracil-H$^{(5)}$), 6.86 (2H, d, *J* 8.3 Hz, H-3, H-5), 6.87 (2H, d, *J* 7.9 Hz, H-3', H-5'), 6.93 (2H, d, *J* 8.8 Hz, H-3", H-5"), 7.15 (2H, d, *J* 8.6 Hz, H-2", H-6"), 7.41 (2H, d, *J* 8.0 Hz, H-3, H-5), 7.54 (2H, d, *J* 8.8 Hz, H-2', H-6'), 7.76 (1H, d, *J* 7.8 Hz, uracil-H$^{(6)}$), 10.24 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 20.5, 25.7, 26.0, 28.7, 28.8, 28.9, 43.4, 48.9, 68.0, 100.2, 112.0, 117.0, 118.5, 119.2, 120.9, 130.6, 132.4, 132.5, 134.7, 144.9, 151.3, 152.8, 155.2, 158.3, 162.6, 165.4. HRMS: m/z[M + Na]+ calcd for $C_{33}H_{36}BrN_3O_5$: 656.1731, found: 656.1730.

2-[3-[8-(4-Bromophenoxy)octyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]-*N*-[4-(4-chlorophenoxy)phenyl]acetamide 3b. Yield 77%, mp 90-91.5 °C, R_f 0.54 (ethyl acetate-1,2-dichloroethane, 1:1). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.27-1.37 (8H, m, CH_2 × 4), 1.57 (2H, quin, *J* 6.3 Hz, CH_2), 1.67 (2H, quin, *J* 6.8 Hz, CH_2), 3.72 (2H, t, *J* 7.1 Hz, CH_2), 3.91 (2H, t, *J* 6.4 Hz, CH_2), 4.60 (2H, s, CH_2), 5.75 (1H, d, *J* 7.8 Hz, uracil-H$^{(5)}$), 6.87 (d, 2H, J 8.8, H-3, H-5), 6.97 (d, 2H, J 9.0, H-3', H-5'), 7.01 (d, 2H, J 8.6, H-3", H-5"), 7.39 (2H, d, *J* 8.1 Hz, H-2", H-6"), 7.41 (2H, d, *J* 8.6 Hz, H-3, H-5), 7.58 (2H, d, *J* 8.8 Hz, H-2', H-6'), 7.76 (1H, d, *J* 7.8 Hz, uracil-H$^{(6)}$), 10.29 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 25.7, 26.0, 28.7, 28.8, 28.9, 43.4, 48.9, 68.0, 100.2, 112.0, 117.0, 119.8, 120.0, 121.0, 127.0, 130.1, 132.4, 135.4, 144.9, 151.3, 151.7, 156.7, 158.3, 162.6, 165.5. HRMS: m/z[M + Na]+ calcd for $C_{32}H_{33}BrClN_3O_5$: 676.1184, found: 676.1181.

2-[3-[10-(4-Bromophenoxy)decyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]-*N*-(4-phenoxyphenyl)acetamide 3c. Yield 81%, mp 116-117 °C, R_f 0.58 (ethyl acetate-1,2-dichloroethane, 1:1). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.24-1.27 (14H, m, CH_2 × 7), 1.36 (2H, quin, *J* 7.0 Hz, CH_2), 1.58 (2H, quin, *J* 6.3 Hz, CH_2), 1.66 (2H, quin, *J* 7.6 Hz, CH_2), 3.71 (2H, t, *J* 7.2 Hz, CH_2), 3.91 (2H, t, *J* 6.5 Hz, CH_2), 4.59 (2H, s, CH_2), 5.74 (1H, d, *J* 7.9 Hz, uracil-H$^{(5)}$), 6.87 (2H, d, *J* 8.9 Hz, H-3, H-5), 6.95 (2H, d, *J* 8.5 Hz, H-3', H-5'), 6.98 (2H, d, *J* 8.9 Hz, H-2", H-6"), 7.09 (1H, t, *J* 7.3 Hz, H-4"), 7.35 (2H, t, *J* 8.0 Hz, H-3", H-5"), 7.41 (2H, d, *J* 8.8 Hz, H-3, H-5), 7.57 (2H, d, *J* 8.9 Hz, H-2', H-6'), 7.76 (1H, d, *J* 7.9

Hz, uracil-H$^{(6)}$), 10.27 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 28.8, 29.1, 31.9, 32.1, 32.2, 46.5, 52.0, 71.1, 103.3, 115.0, 120.1, 121.3, 122.9, 124.0, 126.4, 126.8, 133.3, 135.4, 138.1, 147.9, 154.4, 155.1, 160.7, 161.3, 165.6, 168.5. HRMS: m/z[M + Na]+ calcd for $C_{34}H_{38}BrN_3O_5$: 670.1887, found: 670.1880.

2-[3-[12-(4-Bromophenoxy)dodecyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]-*N*-(4-phenoxyphenyl)acetamide 3d. Yield 80%, mp 115-116 °C, R_f 0.61 (ethyl acetate-1,2-dichloroethane, 1:1). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.22-1.25 (18H, m, CH_2 × 9), 1.36 (2H, quin, *J* 7.8 Hz, CH_2), 1.58 (2H, quin, *J* 6.8 Hz, CH_2), 1.66 (2H, quin, *J* 7.1 Hz, CH_2), 3.71 (2H, t, *J* 6.8 Hz, CH_2), 3.91 (2H, t, *J* 6.4 Hz, CH_2), 4.59 (2H, s, CH_2), 5.74 (1H, d, *J* 7.8 Hz, uracil-H$^{(5)}$), 6.88 (2H, d, *J* 9.0 Hz, H-3, H-5), 6.95 (2H, d, *J* 8.6 Hz, H-3', H-5'), 6.98 (2H, d, *J* 9.3 Hz, H-2", H-6"), 7.09 (1H, dt, *J* 7.6 and 1.1 Hz, H-4"), 7.35 (2H, t, *J* 7.6 Hz, H-3", H-5"), 7.41 (2H, d, *J* 8.8 Hz, H-3, H-5), 7.57 (2H, d, *J* 8.9 Hz, H-2', H-6'), 7.76 (1H, d, *J* 7.8 Hz, uracil-H$^{(6)}$), 10.26 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 25.8, 26.0, 28.7, 28.85, 28.92, 29.1, 29.2, 29.3, 43.4, 48.9, 68.0, 100.2, 112.0, 117.0, 118.2, 119.8, 120.9, 123.3, 130.3, 132.4, 135.0, 144.9, 151.3, 152.1, 157.6, 158.3, 162.6, 165.4. HRMS: m/z[M + Na]+ calcd for $C_{36}H_{42}BrN_3O_5$: 698.2200, found: 698.2201.

2-[3-[12-(4-Bromophenoxy)dodecyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]-*N*-[4-(4-chloro-phenoxy)phenyl]acetamide (3e). Yield 72%, mp 122.5-124 °C, R_f 0.61 (ethyl acetate-1,2-dichloroethane, 1:1). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.24 (18H, m, CH_2 × 9), 1.34-1.36 (2H, m, CH_2), 1.58 (2H, m, CH_2), 1.67 (2H, quin, *J* 6.8 Hz, CH_2), 3.72 (2H, t, *J* 7.3 Hz, CH_2), 3.91 (2H, t, *J* 6.5 Hz, CH_2), 4.61 (2H, s, CH_2), 5.75 (1H, d, *J* 7.9 Hz, uracil-H$^{(5)}$), 6.88 (2H, d, *J* 9.1 Hz, H-3, H-5), 6.98 (2H, d, *J* 9.1 Hz, H-3', H-5'), 7.01 (2H, d, *J* 9.7 Hz, H-3", H-5"),7.38 (2H, d, *J* 7.6 Hz, H-2", H-6"), 7.41 (2H, d, *J* 7.9 Hz, H-3, H-5), 7.60 (2H, d, *J* 9.0 Hz, H-2', H-6'), 7.76 (1H, d, *J* 7.9 Hz, uracil-H$^{(6)}$), 10.29 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 25.9, 26.2, 28.8, 29.0, 29.1, 29.2, 29.4, 40.6, 40.8, 43.6, 49.1, 68.2, 100.4, 112.1, 117.1, 119.9, 120.1, 121.1, 127.2, 130.2, 132.5, 135.6, 145.0, 151.5, 151.8, 156.8, 158.4, 162.7, 165.6. HRMS: m/z[M + Na]+ calcd for $C_{36}H_{41}BrClN_3O_5$: 732.1810, found: 73.1799.

2-[3-[12-(4-Bromophenoxy)dodecyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]-*N*-[4-(3,4-dichlorophenoxy)phenyl]acetamide (3f). Yield 80%, mp 121-122 °C, R_f 0.62 (ethyl acetate-1,2-dichloroethane, 1:1). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.23 (18H, m, CH_2 × 9), 1.33-1.35 (2H, m, CH_2), 1.58 (2H, m, CH_2), 1.66 (2H, quin, *J* 6.7 Hz, CH_2), 3.72 (2H, t, *J* 7.4 Hz, CH_2), 3.91 (2H, t, *J* 6.4 Hz, CH_2), 4.62 (2H, s, CH_2), 5.75 (1H, d, *J* 7.9 Hz, uracil-H$^{(5)}$), 6.87 (2H, d, *J* 9.1 Hz, H-3, H-5), 6.95 (1H, dd, *J* 8.9 and 2.9 Hz, H-6"), 7.06 (2H, d, *J* 9.0 Hz, H-3', H-5'), 7.20 (1H, d, *J* 2.9 Hz, H-2"), 7.40 (2H, d, *J* 9.1 Hz, H-3, H-5), 7.58 (1H, d, *J* 8.8 Hz, H-5"), 7.62 (2H, d, *J* 9.0 Hz, H-2', H-6'), 7.76 (1H, d, *J* 7.9 Hz, uracil-H$^{(6)}$), 10.33 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 25.9, 26.2, 28.8, 29.0, 29.1, 29.2, 29.4, 43.6, 49.1, 68.2, 100.4, 112.1, 117.1, 118.4, 119.9, 120.6, 121.2, 125.3, 131.9, 132.5, 136.1, 145.0, 151.1, 151.5, 157.6, 158.4, 162.7, 165.7. HRMS: m/z[M + Na]+ calcd for $C_{38}H_{46}BrN_3O_5$: 726.2513, found: 726.2512.

2-[3-[12-(4-Bromophenoxy)dodecyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]-*N*-[4-(3,4-dimethylphenoxy)phenyl]acetamide (3g). Yield 73%, mp 89-90.5 °C, R_f 0.60 (ethyl acetate-1,2-dichloroethane, 1:1). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.23 (18H, m, CH_2 × 9), 1.32-1.37 (2H, m, CH_2), 1.58 (2H, quin, *J* 6.3 Hz, CH_2), 1.67 (2H, quin, *J* 7.7 Hz, CH_2), 2.17 (6H, s, CH_3 × 2), 3.72 (2H, t, *J* 7.2 Hz, CH_2), 3.91 (2H, t, *J* 6.5 Hz, CH_2), 4.61 (2H, s, CH_2), 5.75 (1H, d, *J* 7.9 Hz, uracil-H$^{(5)}$), 6.69 (1H, dd, *J* 8.3 and 2.7 Hz, H-6"), 6.78 (1H, d, *J* 2.5 Hz, H-2"), 6.87 (2H, d, *J* 9.1 Hz, H-3, H-5), 6.93 (2H, d, *J* 9.0 Hz, H-3', H-5'), 7.10 (1H, d, *J* 8.3 Hz, H-5"), 7.41 (2H, d, *J* 8.9 Hz, H-3, H-5), 7.55 (2H, d, *J* 9.0 Hz, H-2', H-6'), 7.75 (1H, d, *J* 7.9 Hz, uracil-H$^{(6)}$), 10.24 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 19.0, 19.9, 25.9, 26.2, 28.9, 29.0, 29.1, 29.2, 29.4, 43.6, 49.1, 68.2, 100.4, 112.1, 116.0, 117.1, 119.3, 119.9, 121.0, 131.0, 131.4, 132.5, 134.7, 138.4, 144.9, 151.5, 153.0, 155.4, 158.4, 162.7, 165.5. HRMS: m/z[M + Na]+ calcd for $C_{36}H_{42}BrCl_2N_3O_5$: 766.1421, found: 766.1413.

Antiviral assays

Compounds were evaluated against the following viruses: human cytomegalovirus (HCMV, strains AD-169 and Davis) and varicella zoster virus (VZV, strains OKA and YS). The antiviral assays were

based on inhibition of virus-induced cytopathicity or plaque formation in human embryonic lung (HEL) fibroblasts. Confluent cell cultures in microtiter 96-well plates were inoculated with 100 $CCID_{50}$ of virus (1 $CCID_{50}$ being the virus dose to infect 50% of the cell cultures) or 10 or 100 plaque forming units (PFU) (for VZV and HCMV) in the presence of varying concentrations of the test compounds. Viral cytopathicity or plaque formation was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds. Antiviral activity was expressed as the EC_{50} or compound concentration required to reduce virus-induced cytopathogenicity or viral plaque formation by 50%.

Cytostatic Activity Assays

All assays were performed in 96-well microtiter plates. To each well were added $(5-7.5) \times 10^4$ tumor cells and a given amount of the test compound. The cells were allowed to proliferate for 48 h (murine leukemia L1210 cells) or 72 h (human lymphocytic CEM and human cervix carcinoma HeLa cells) at 37 °C in a humidified CO_2-controlled atmosphere. At the end of the incubation period, the cells were counted in a Coulter counter. The IC_{50} (50% inhibitory concentration) was defined as the concentration of the compound that inhibited cell proliferation by 50%.

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List of spectra images

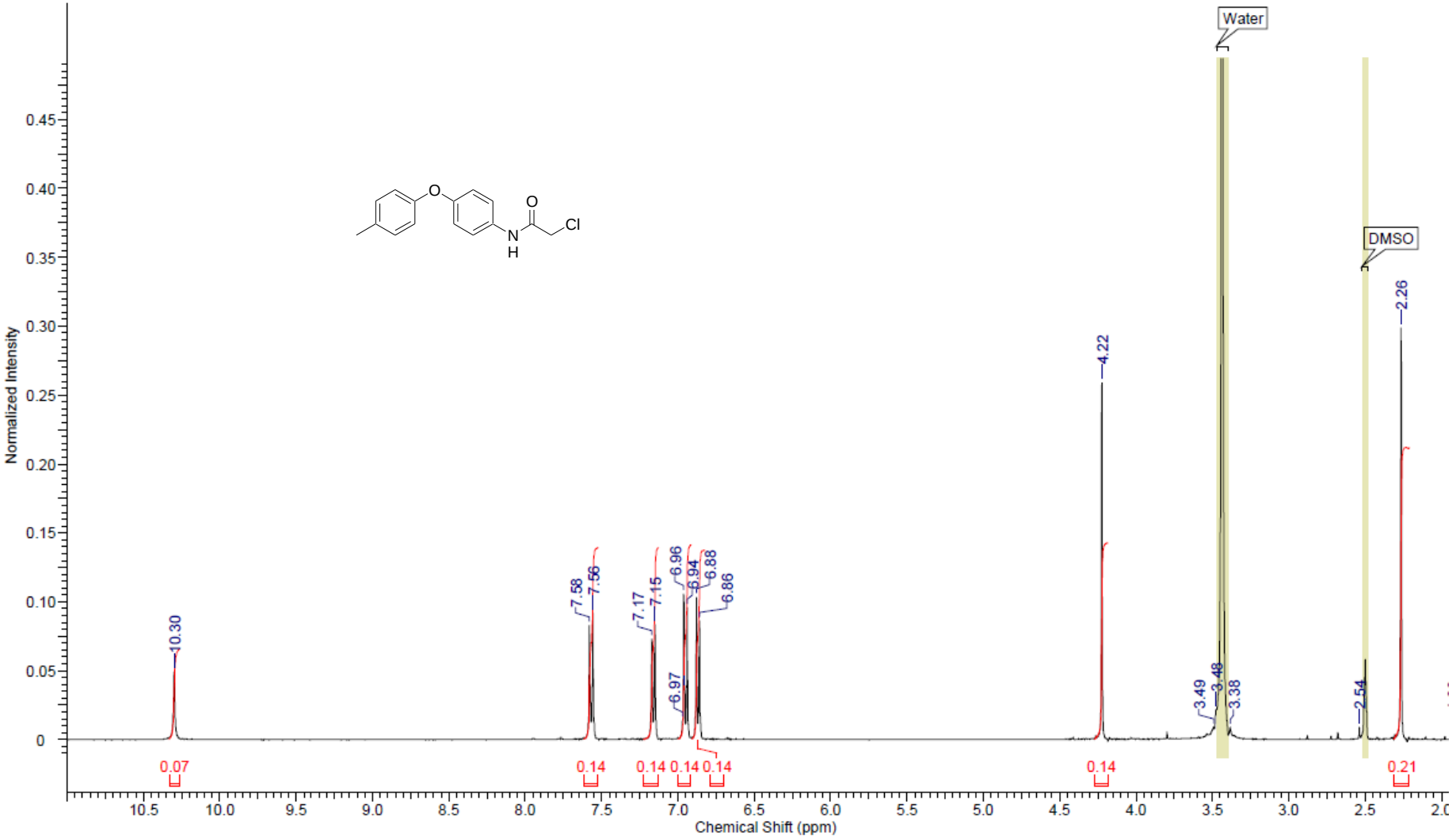

Figure S1 ^{1}H NMR spectrum of compound **1b** in DMSO-d_6 at 300 MHz.

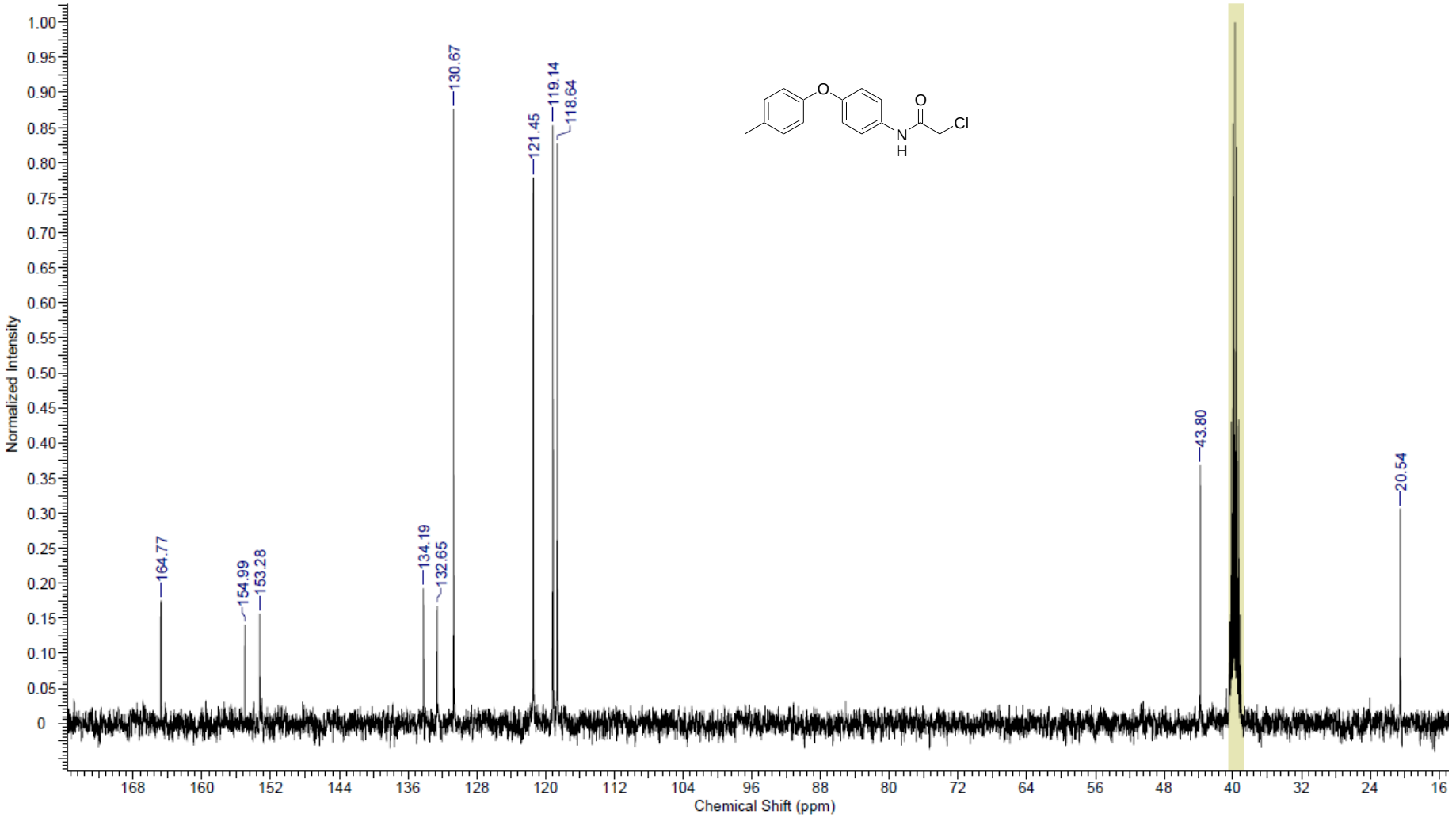

Figure S2 ^{13}C NMR spectrum of compound **1b** in DMSO-d_6 at 75 MHz.

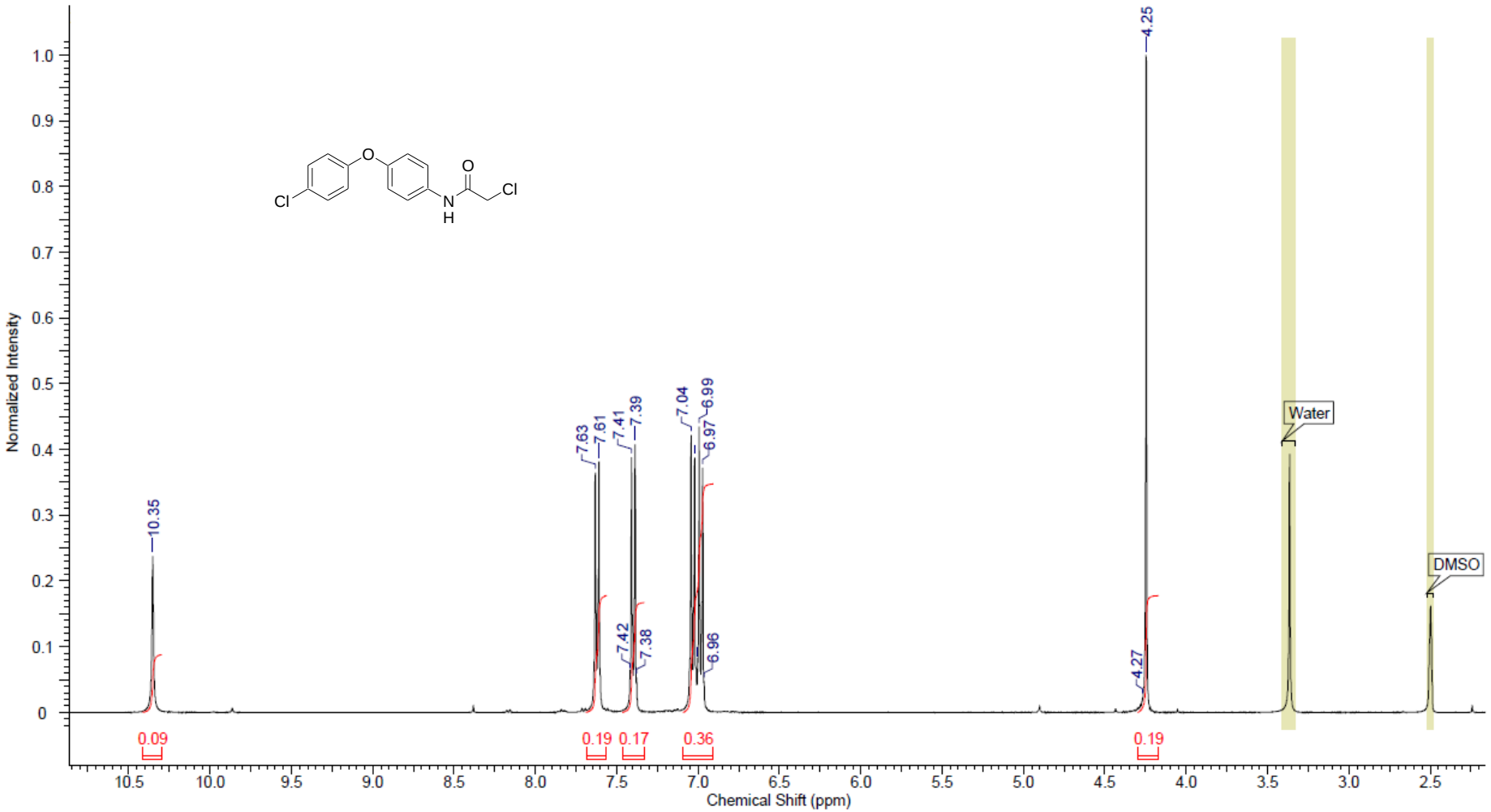

Figure S3 ^{1}H NMR spectrum of compound **1c** in DMSO-d_6 at 400 MHz.

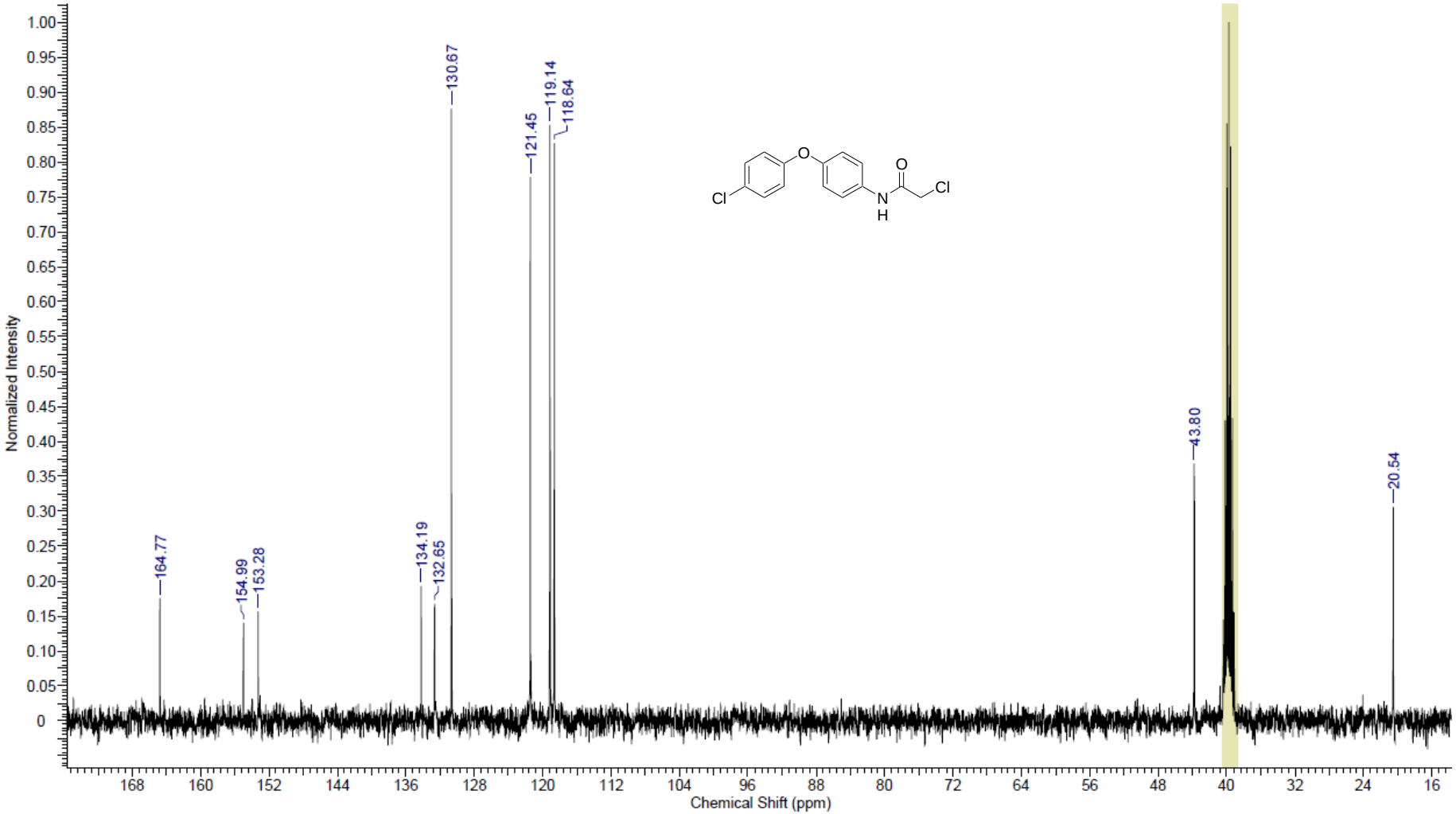

Figure S4 ^{13}C NMR spectrum of compound **1c** in DMSO-d_6 at 100 MHz.

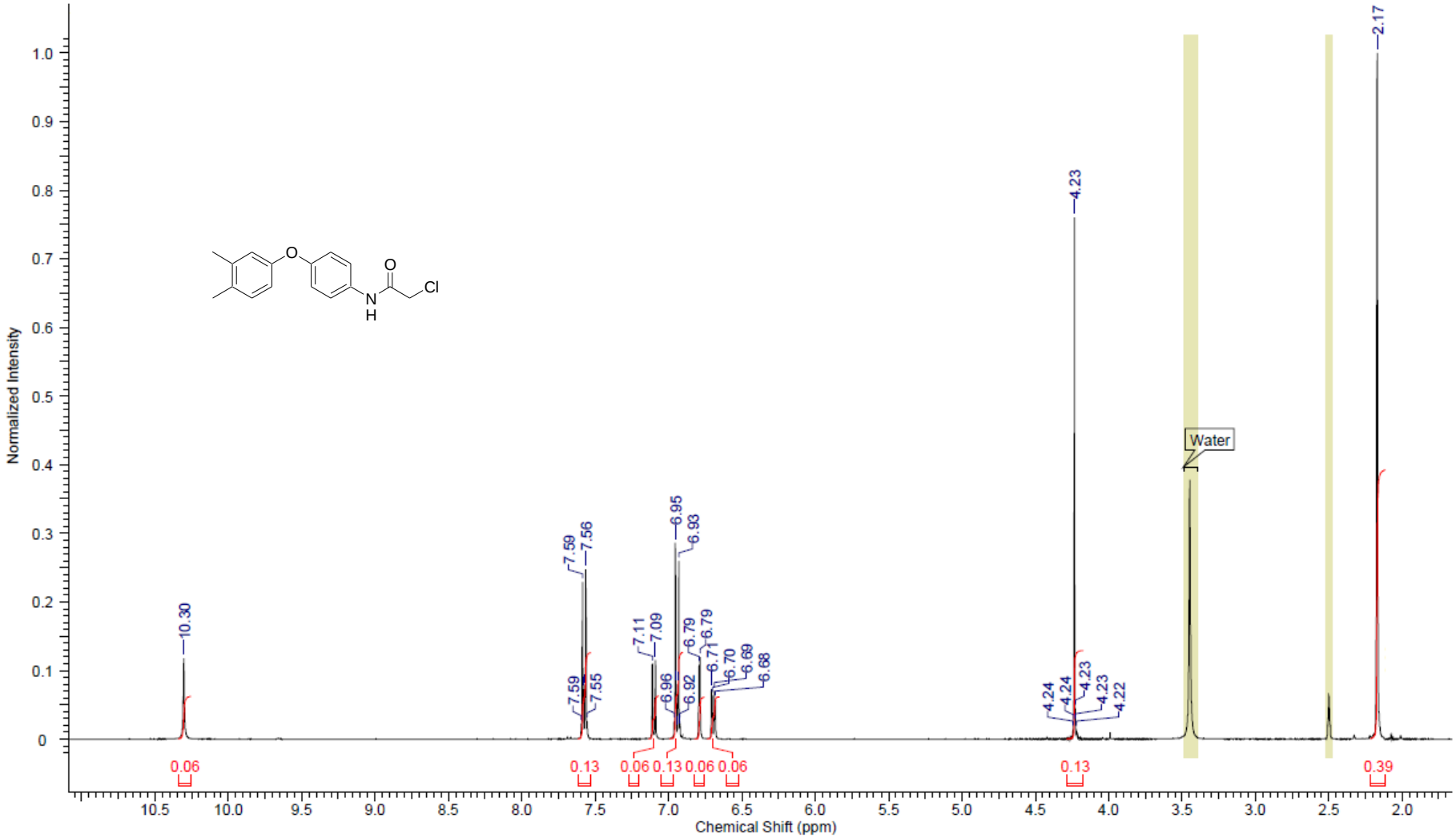

Figure S5 ^{1}H NMR spectrum of compound **1d** in DMSO-d_6 at 400 MHz.

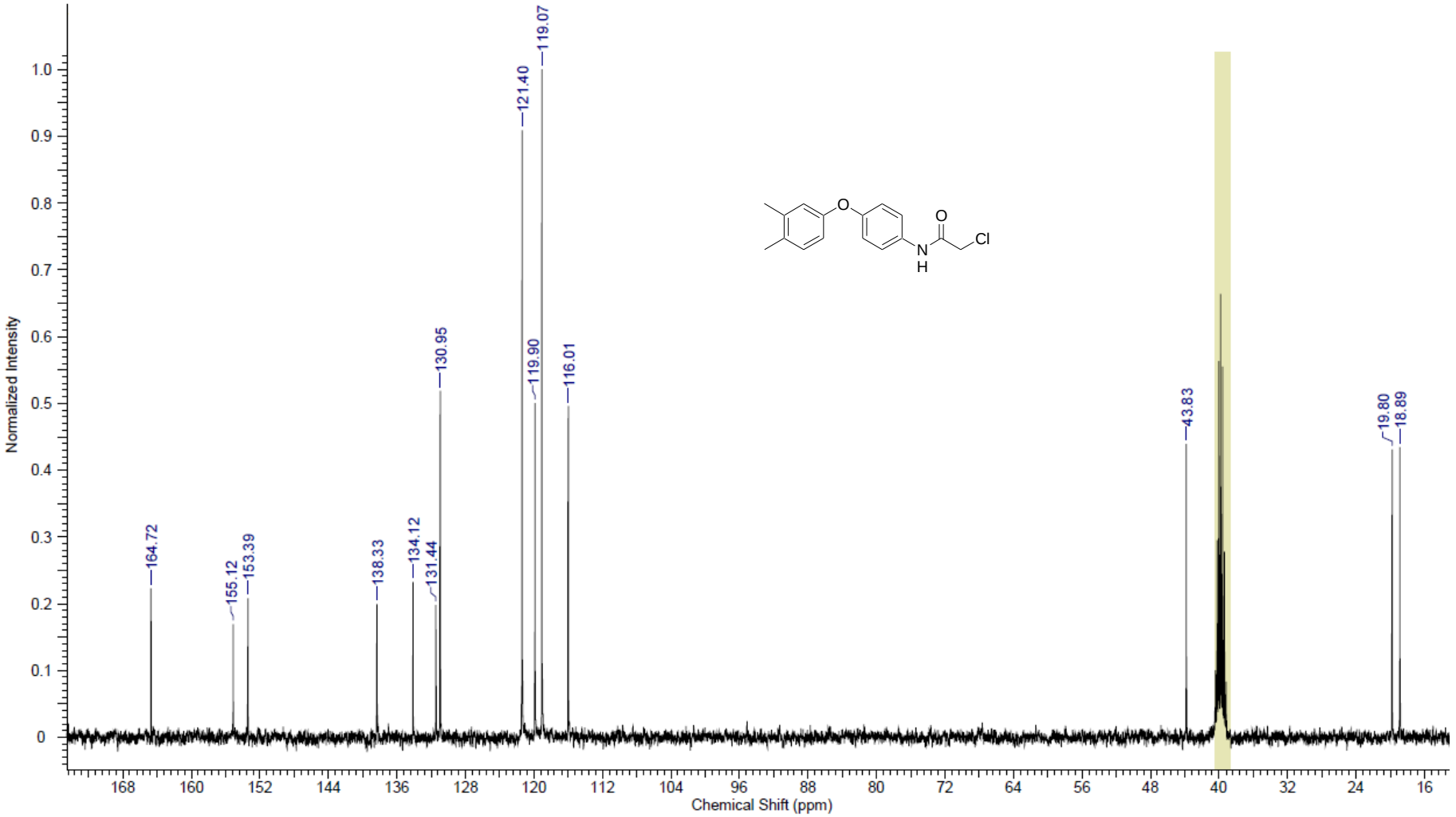

Figure S6 ^{13}C NMR spectrum of compound **1d** in DMSO-d_6 at 100 MHz.

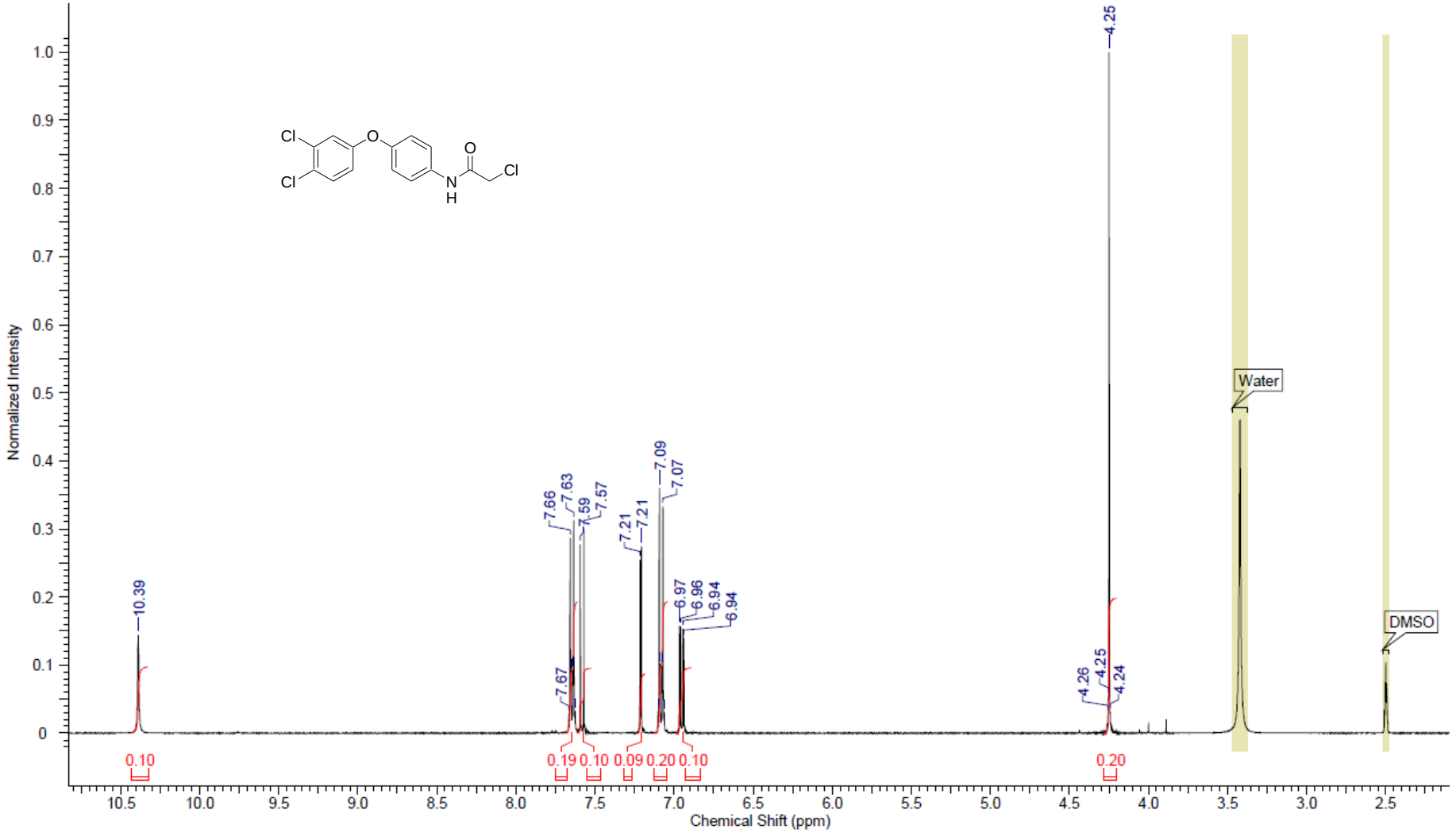

Figure S7 ^{1}H NMR spectrum of compound **1e** in DMSO-d_6 at 400 MHz.

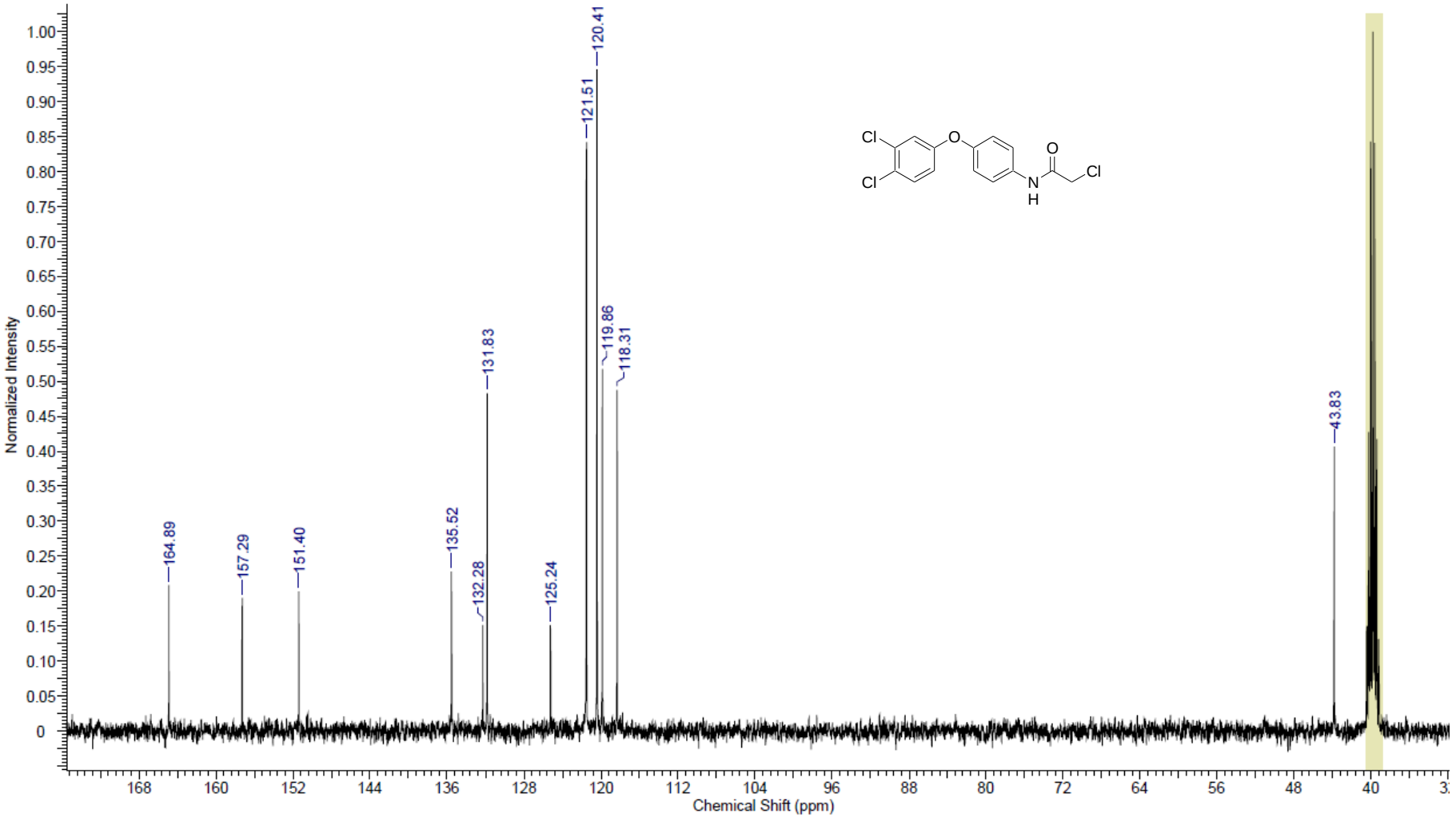

Figure S8 ^{13}C NMR spectrum of compound **1e** in DMSO-d_6 at 100 MHz.

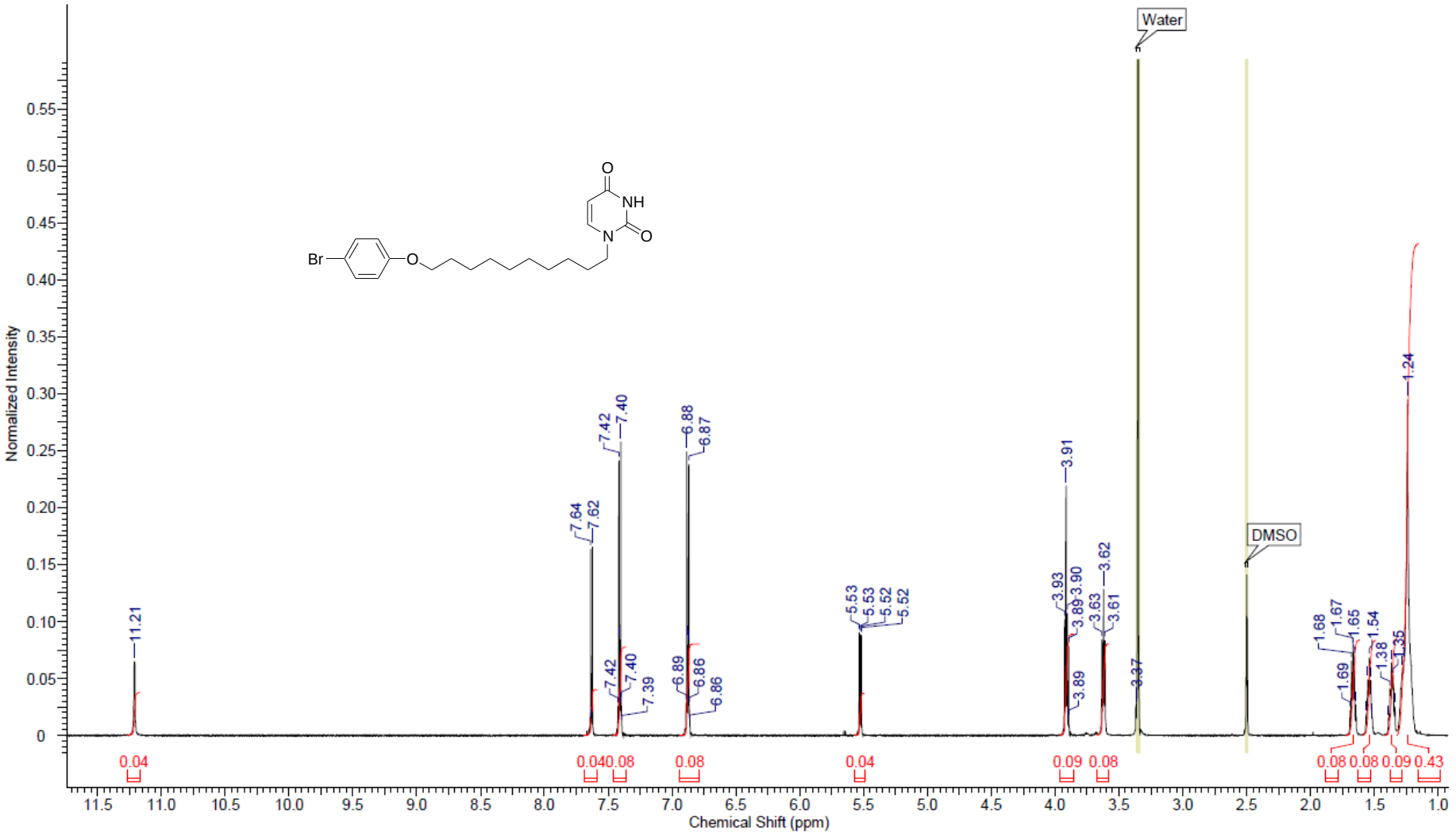

Figure S9 ^{1}H NMR spectrum of compound **2b** in DMSO-d_6 at 400 MHz.

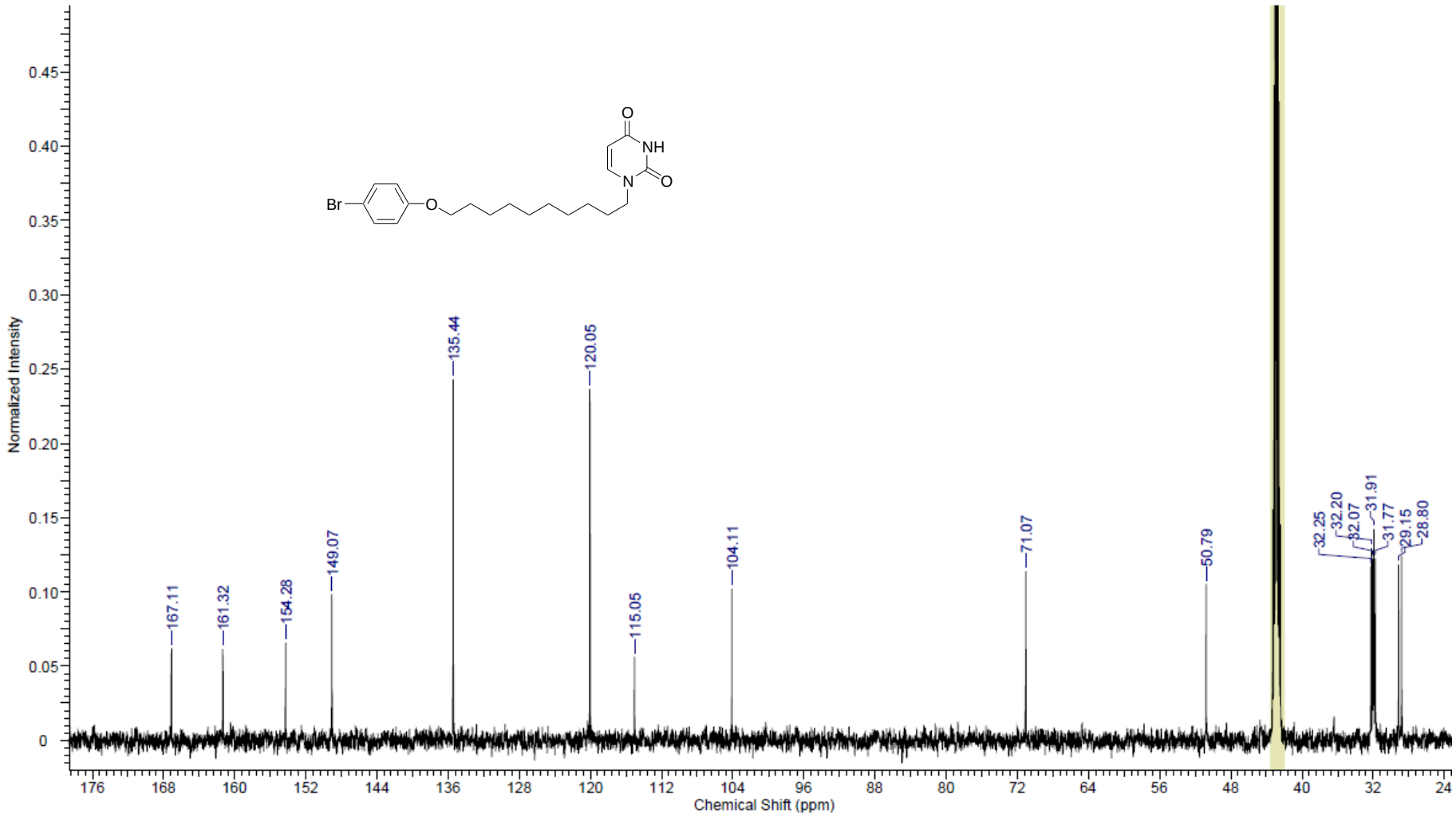

Figure S10. ^{13}C NMR spectrum of compound **2b** in DMSO-d_6 at 100 MHz.

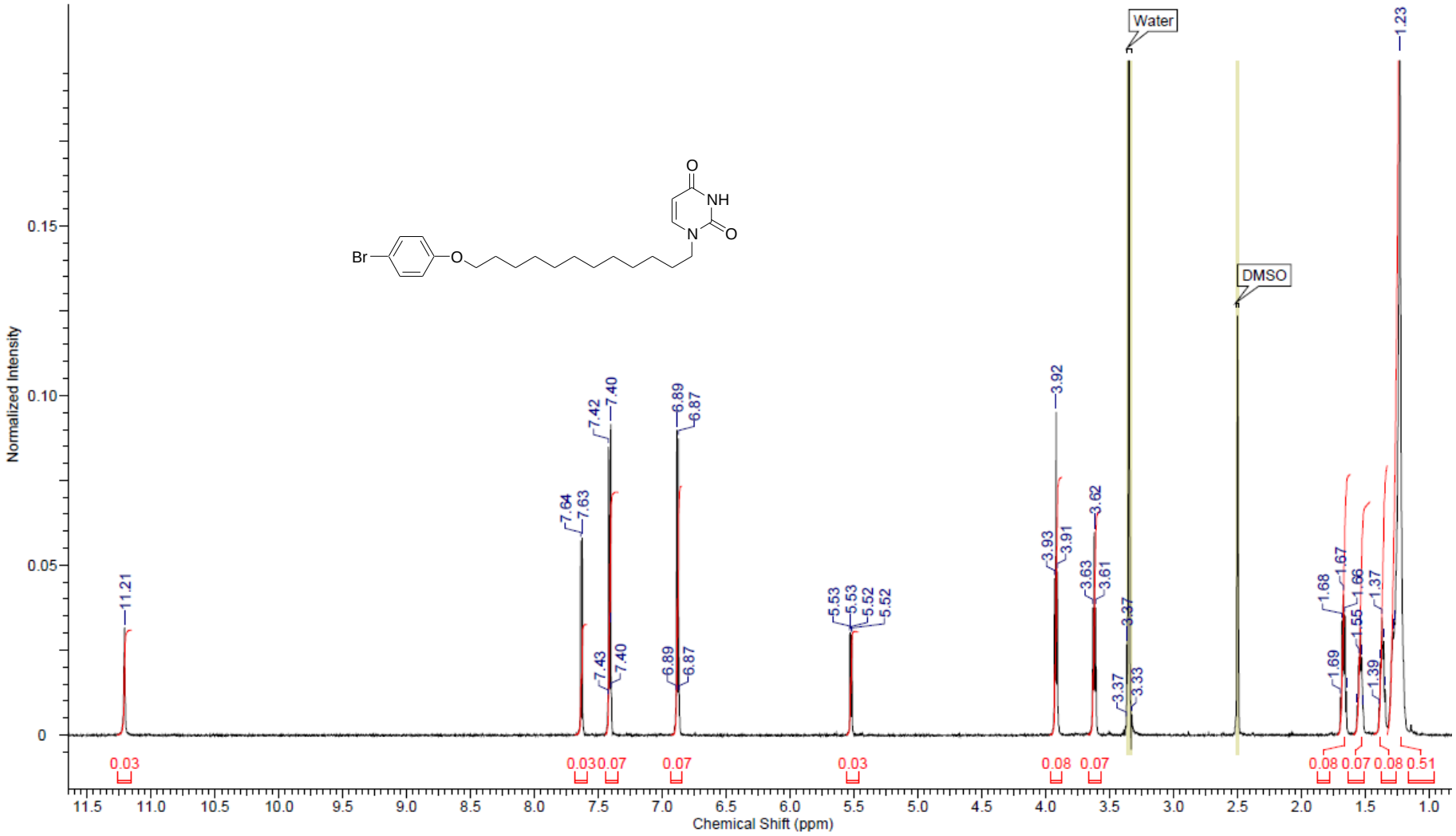

Figure S11 ^{1}H NMR spectrum of compound **2c** in DMSO-d_6 at 400 MHz.

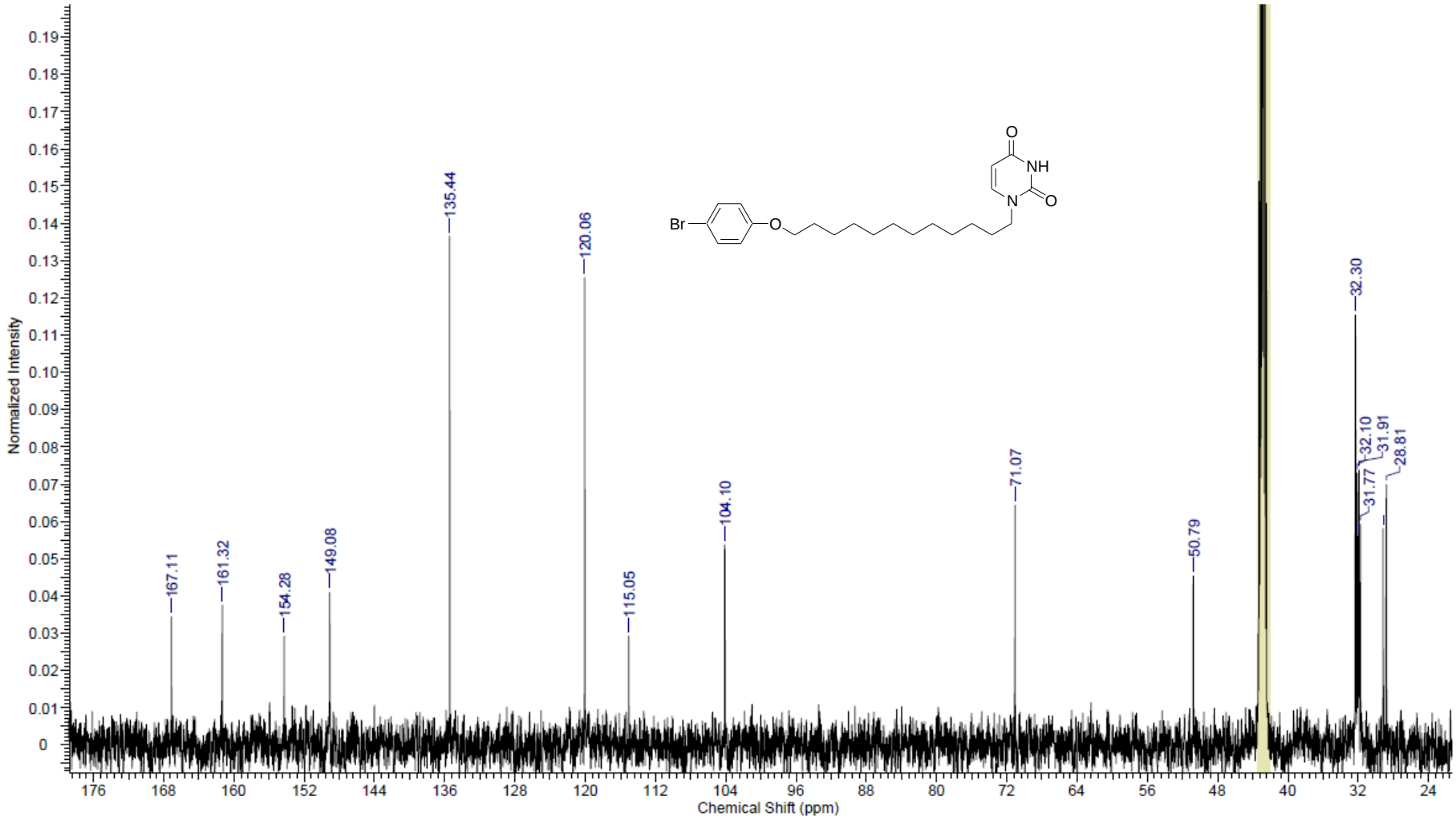

Figure S12 ^{13}C NMR spectrum of compound **2c** in DMSO-d_6 at 100 MHz.

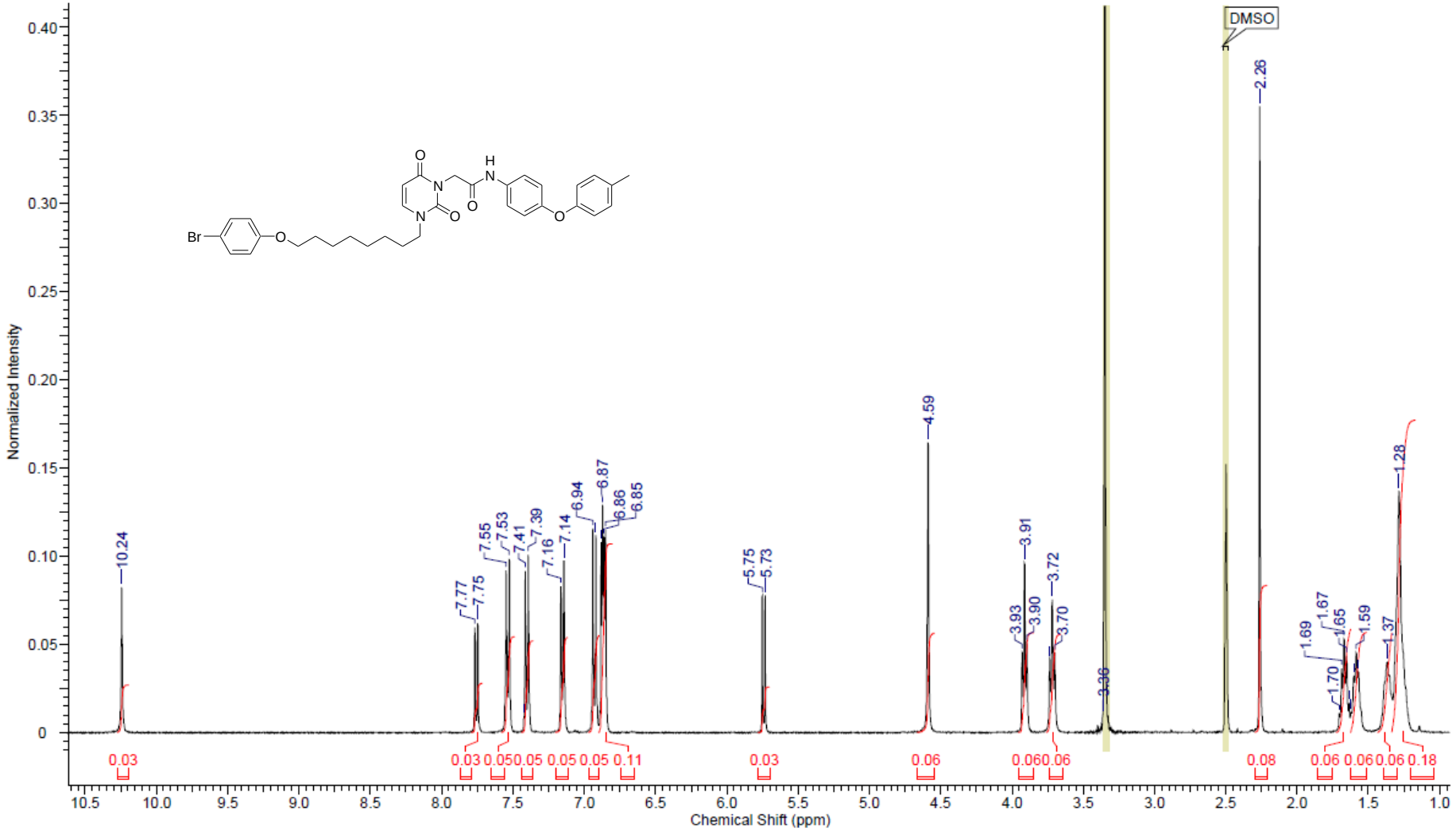

Figure S13. ^{1}H NMR spectrum of compound **3a** in DMSO-d_6 at 400 MHz.

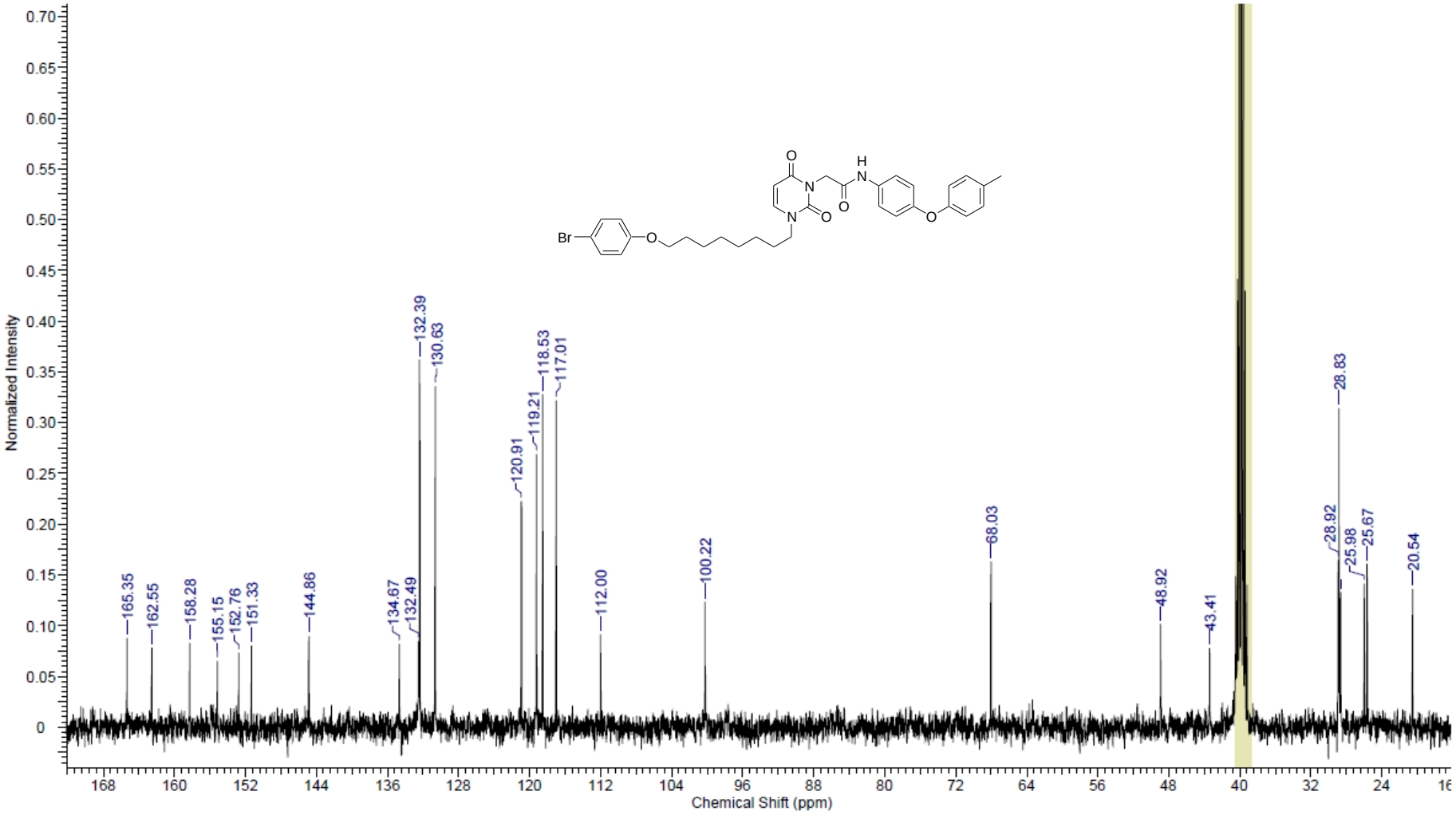

Figure S14 ^{13}C NMR spectrum of compound **3a** in DMSO-d_6 at 100 MHz.

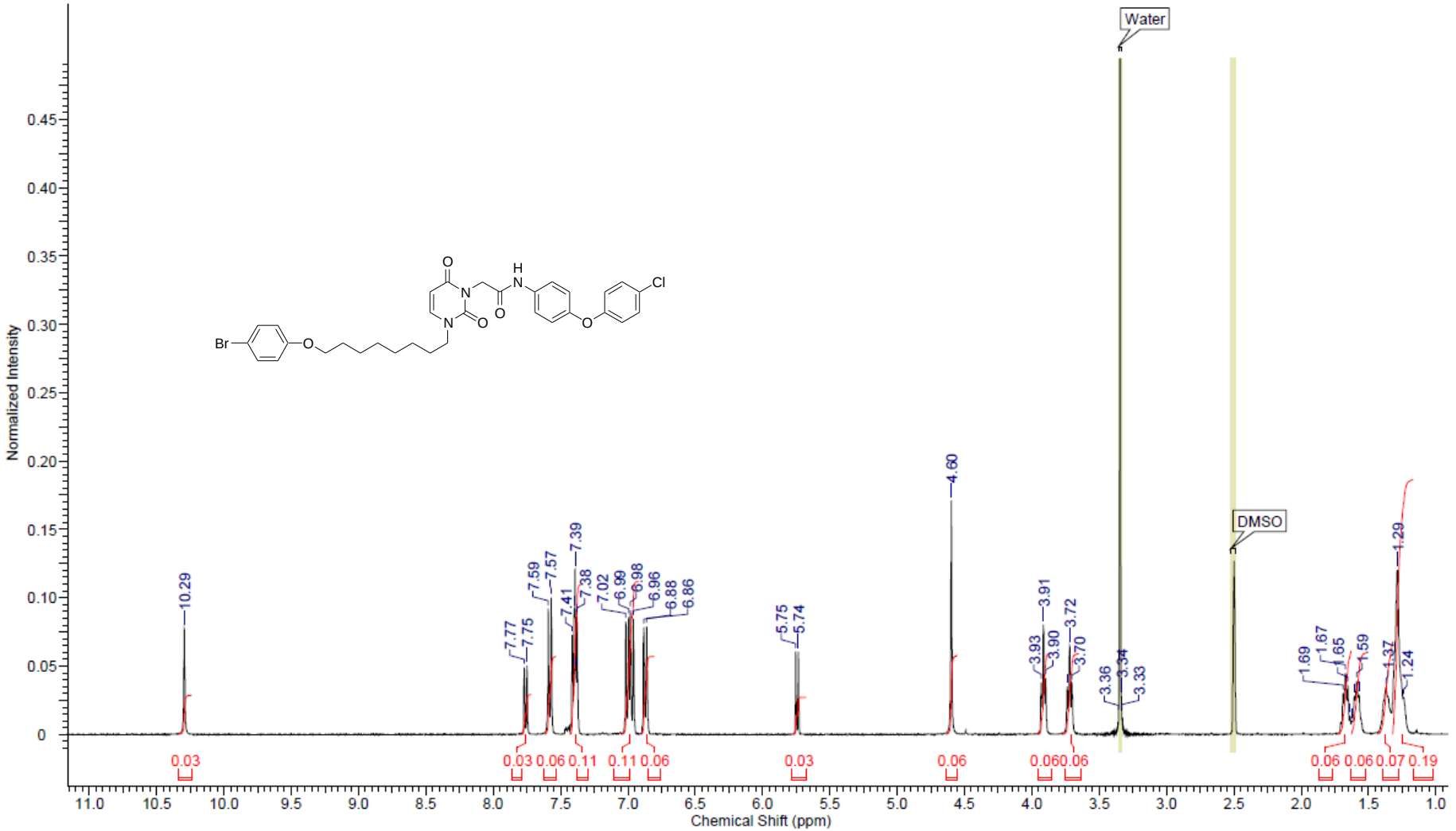

Figure S15 ^{1}H NMR spectrum of compound **3b** in DMSO-d_6 at 400 MHz.

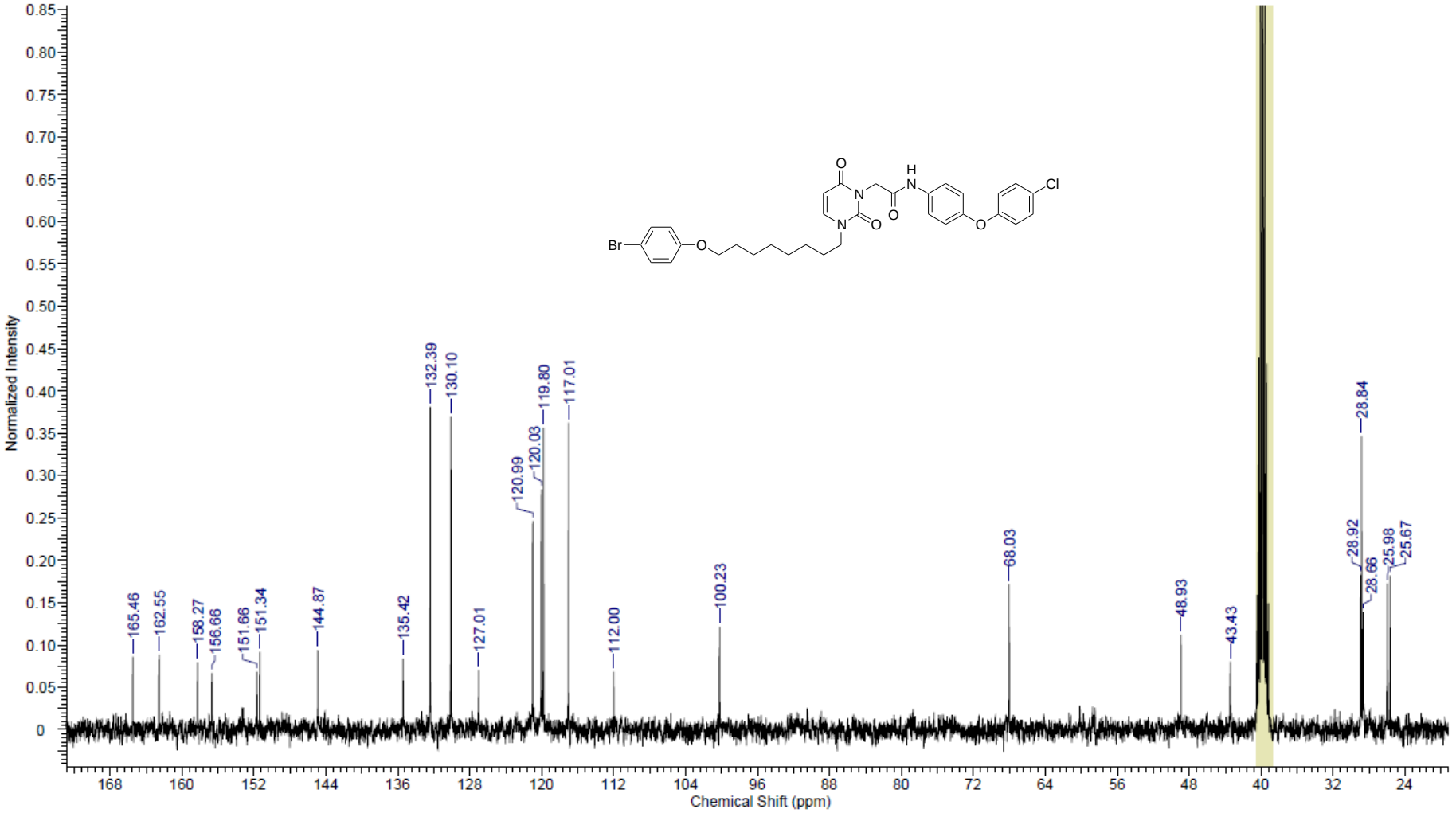

Figure S16 ^{13}C NMR spectrum of compound **3b** in DMSO-d_6 at 100 MHz.

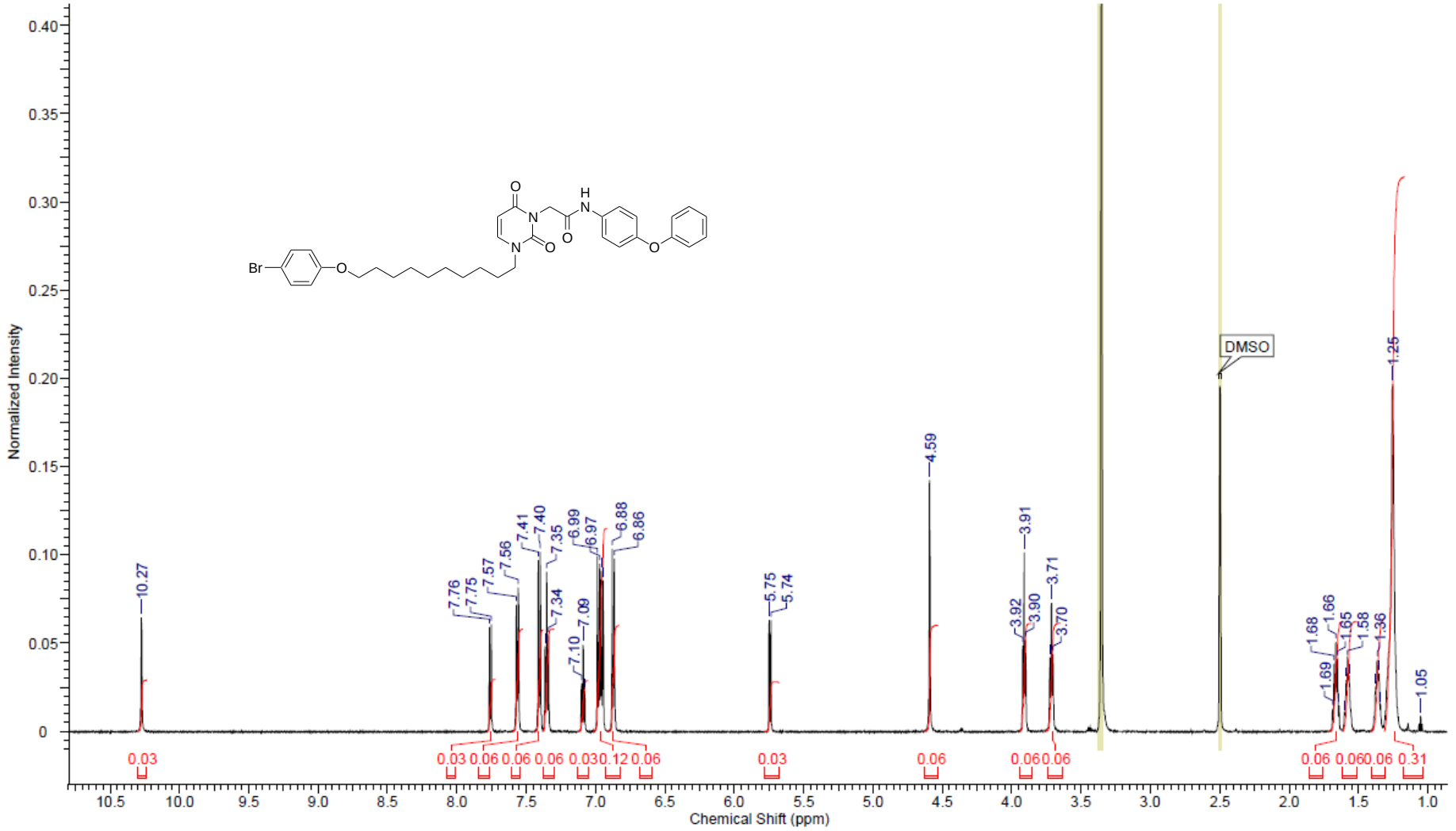

Figure S17 ^{1}H NMR spectrum of compound **3c** in DMSO-d_6 at 400 MHz.

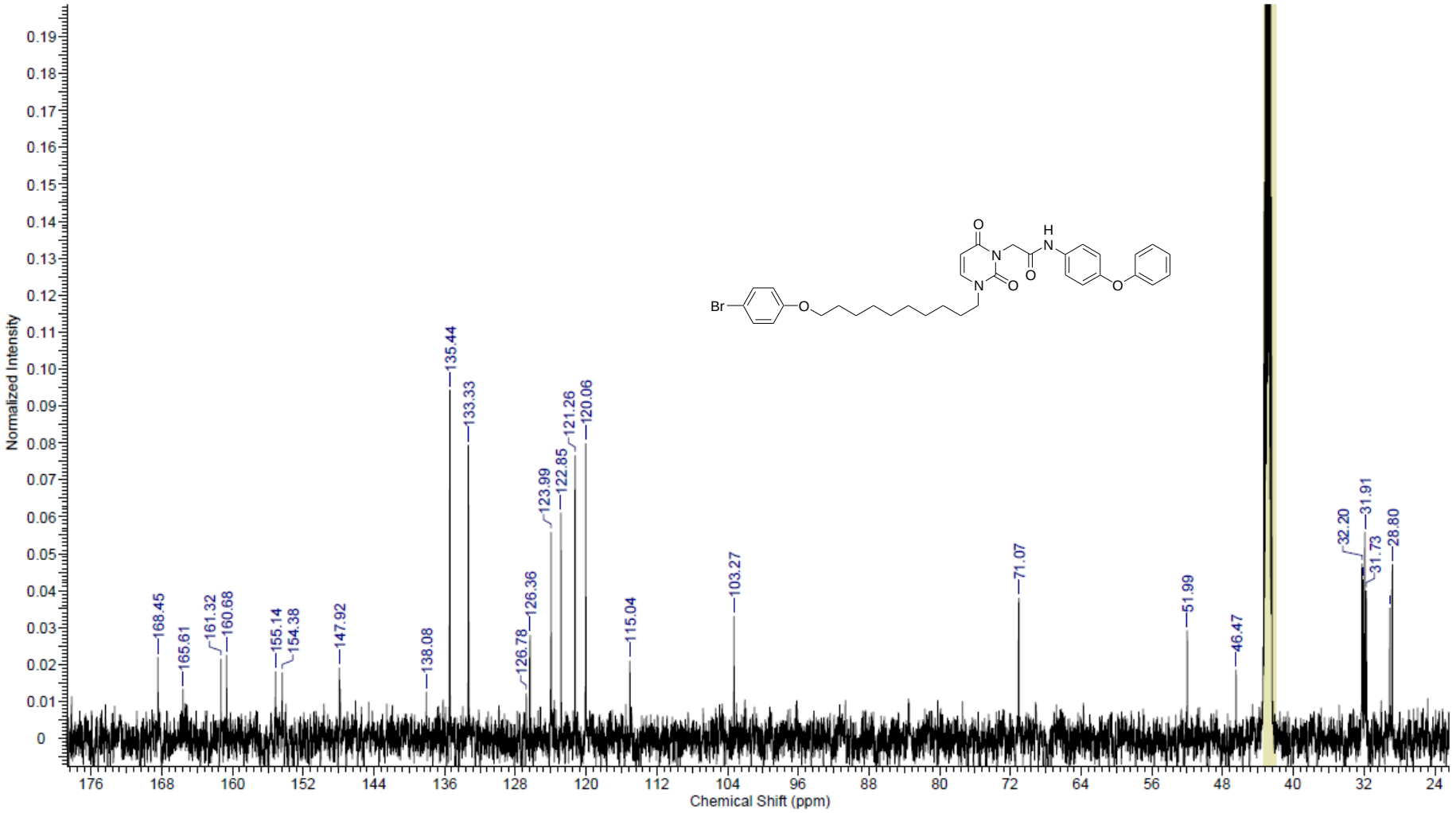

Figure S18 ^{13}C NMR spectrum of compound **3c** in DMSO-d_6 at 100 MHz.

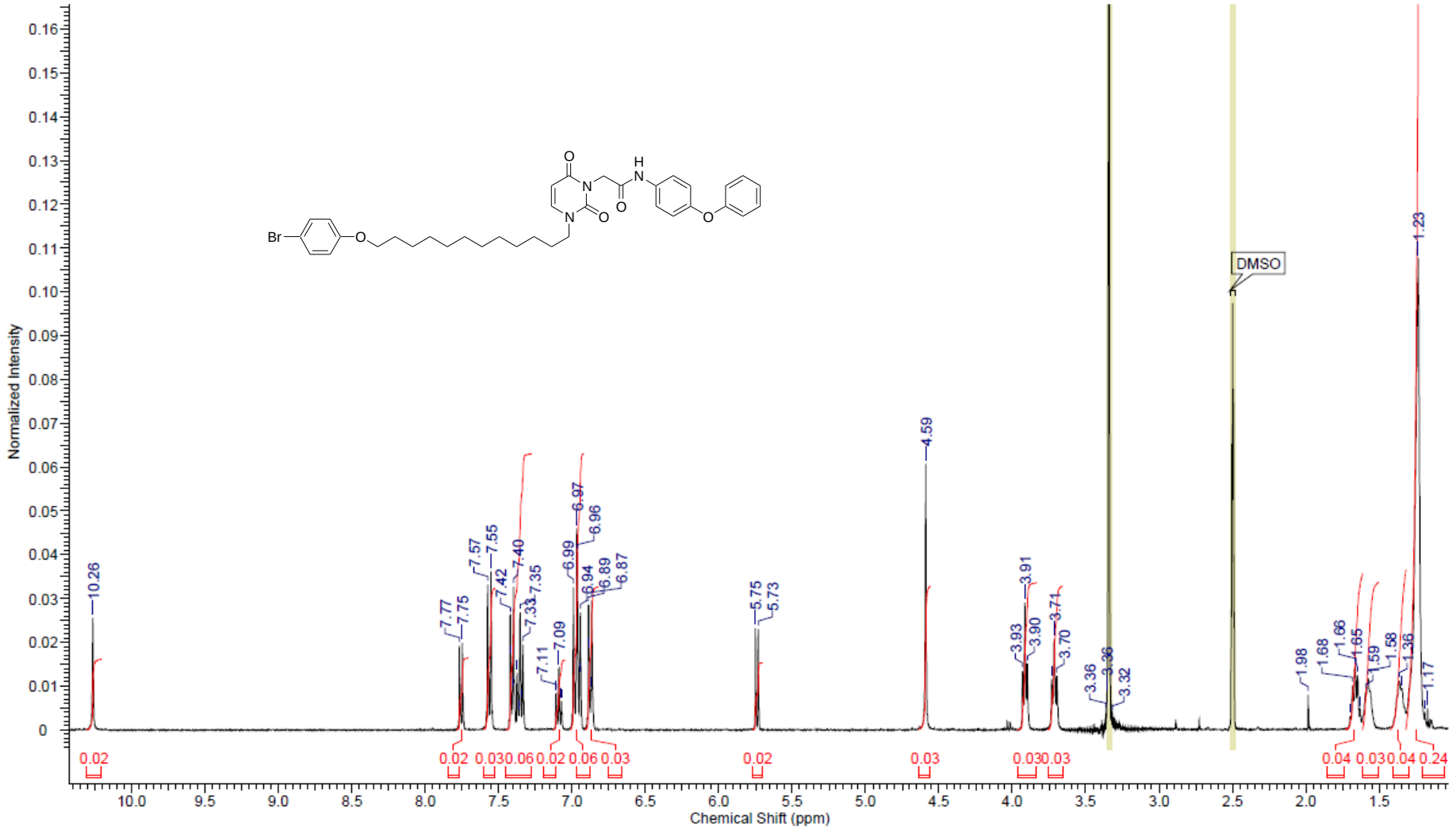

Figure S19 ^{1}H NMR spectrum of compound **3d** in DMSO-d_6 at 400 MHz.

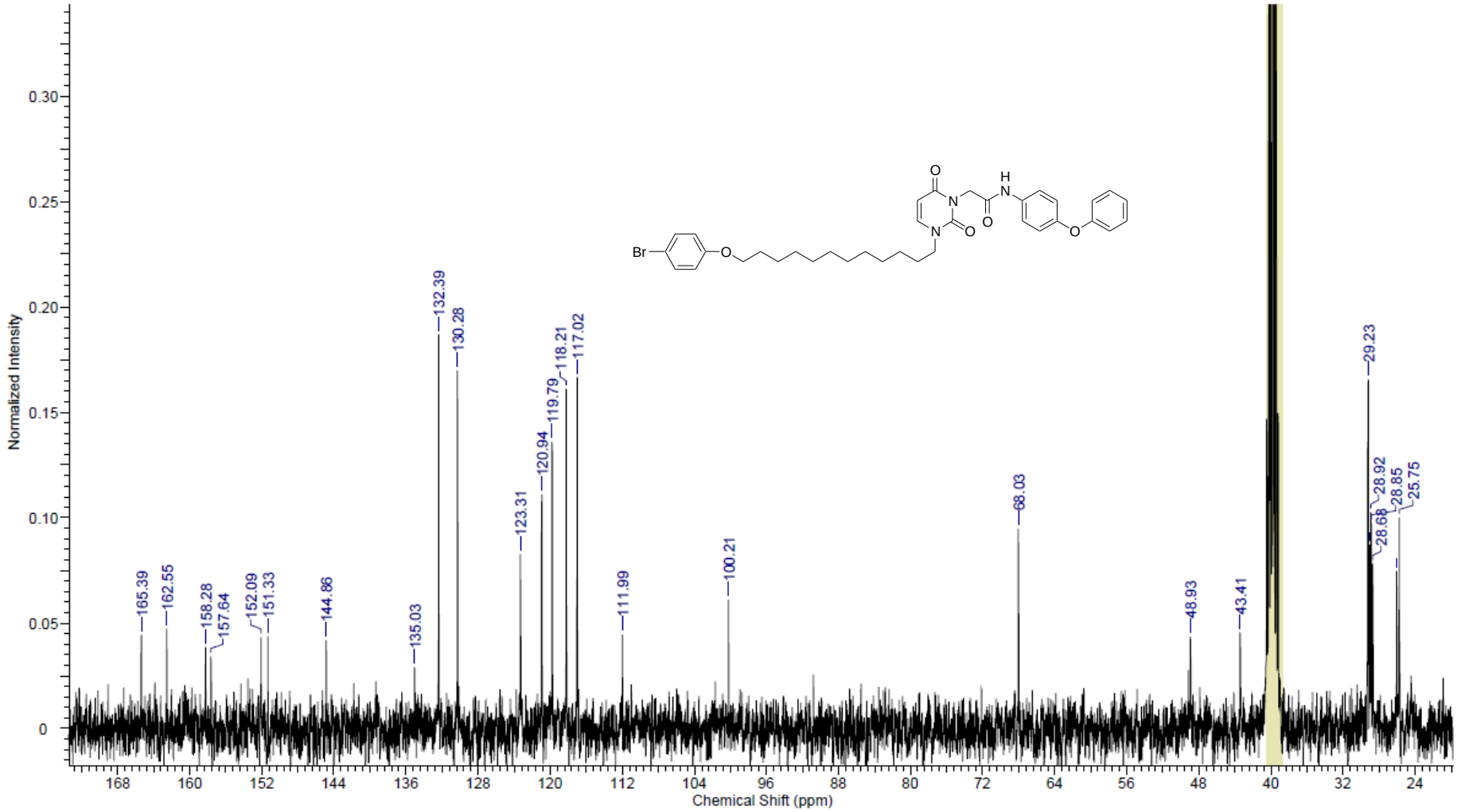

Figure S20 ^{13}C NMR spectrum of compound **3d** in DMSO-d_6 at 100 MHz.

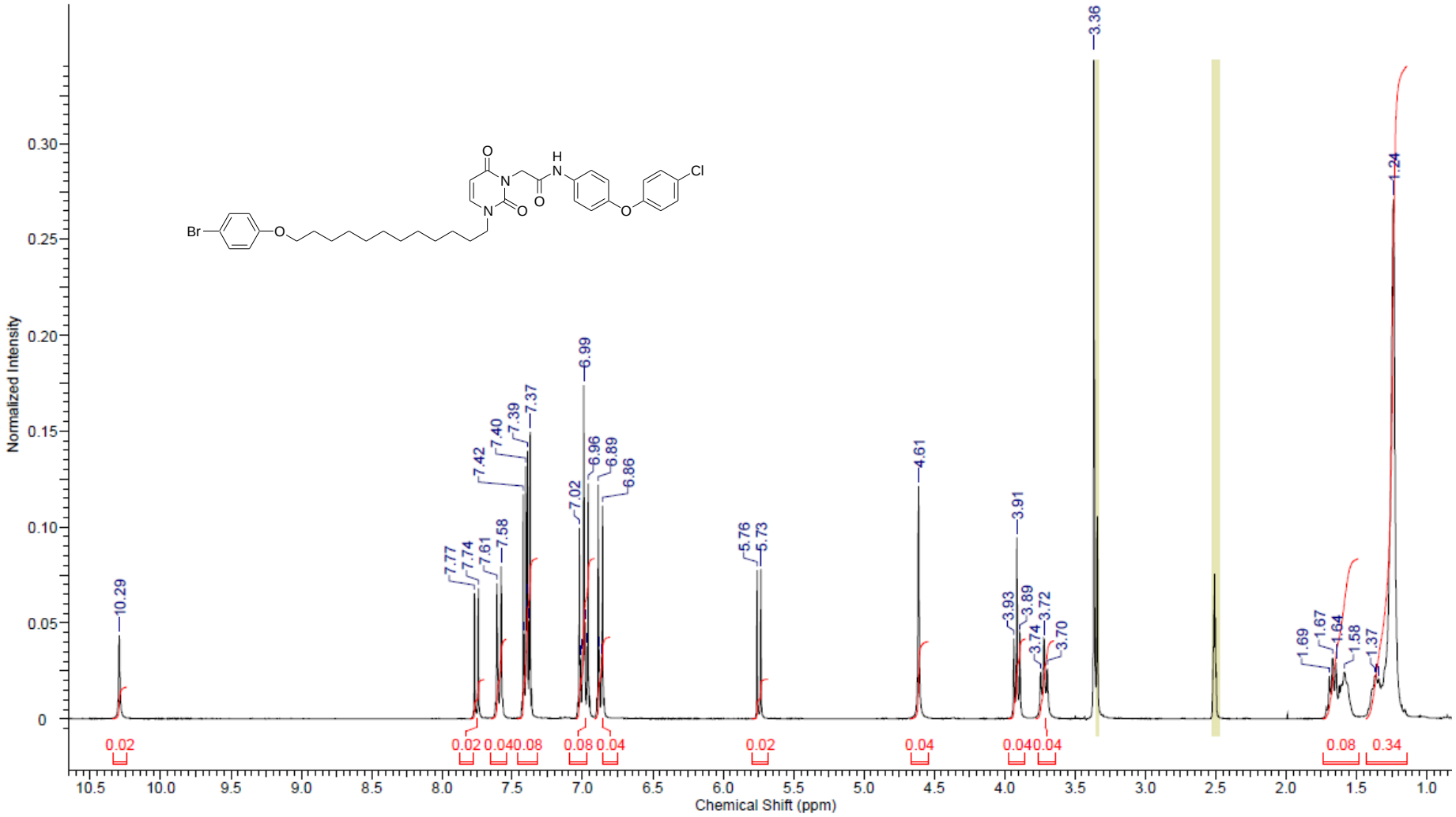

Figure S21 ^{1}H NMR spectrum of compound **3e** in DMSO-d_6 at 400 MHz.

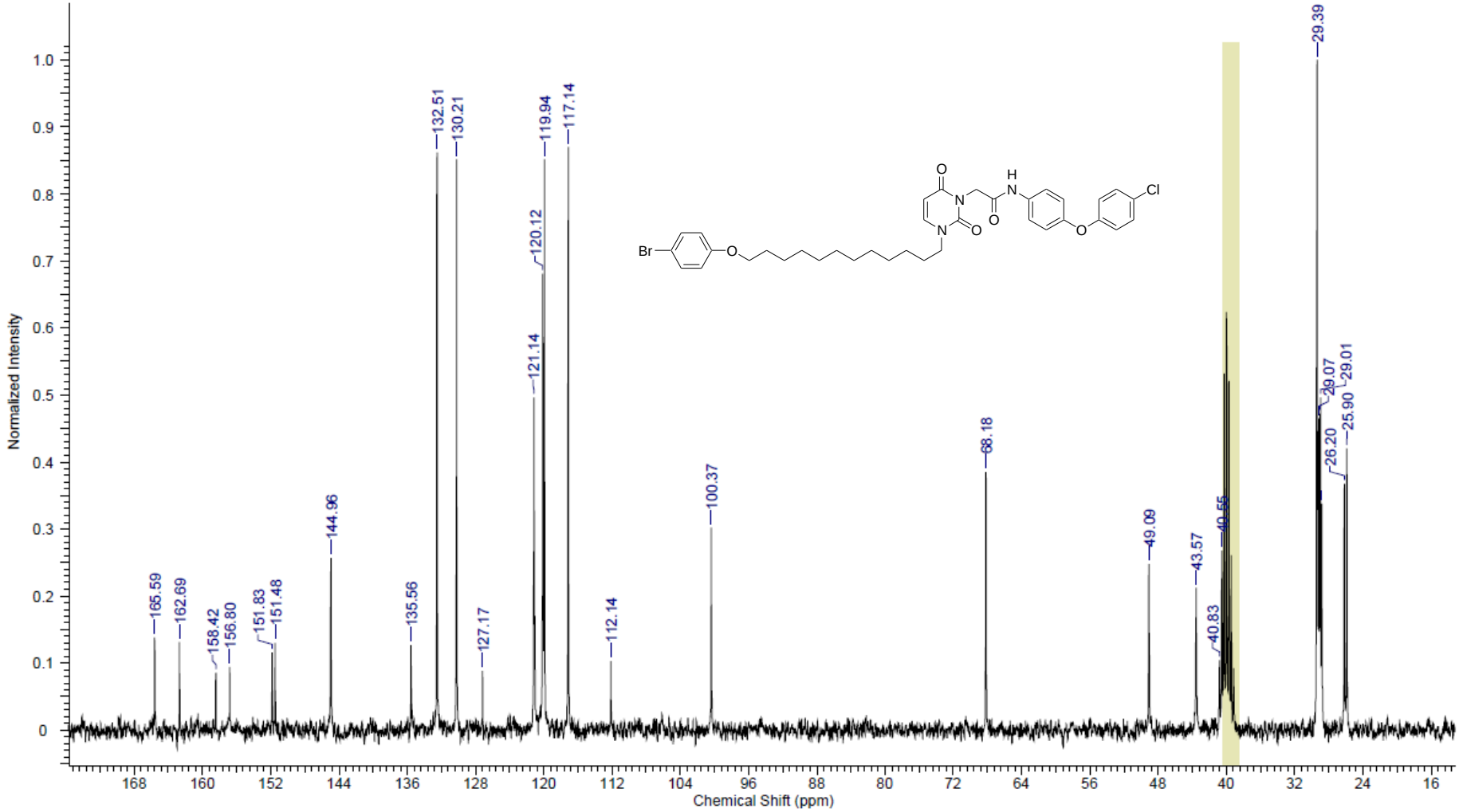

Figure S22 ^{13}C NMR spectrum of compound **3e** in DMSO-d_6 at 100 MHz.

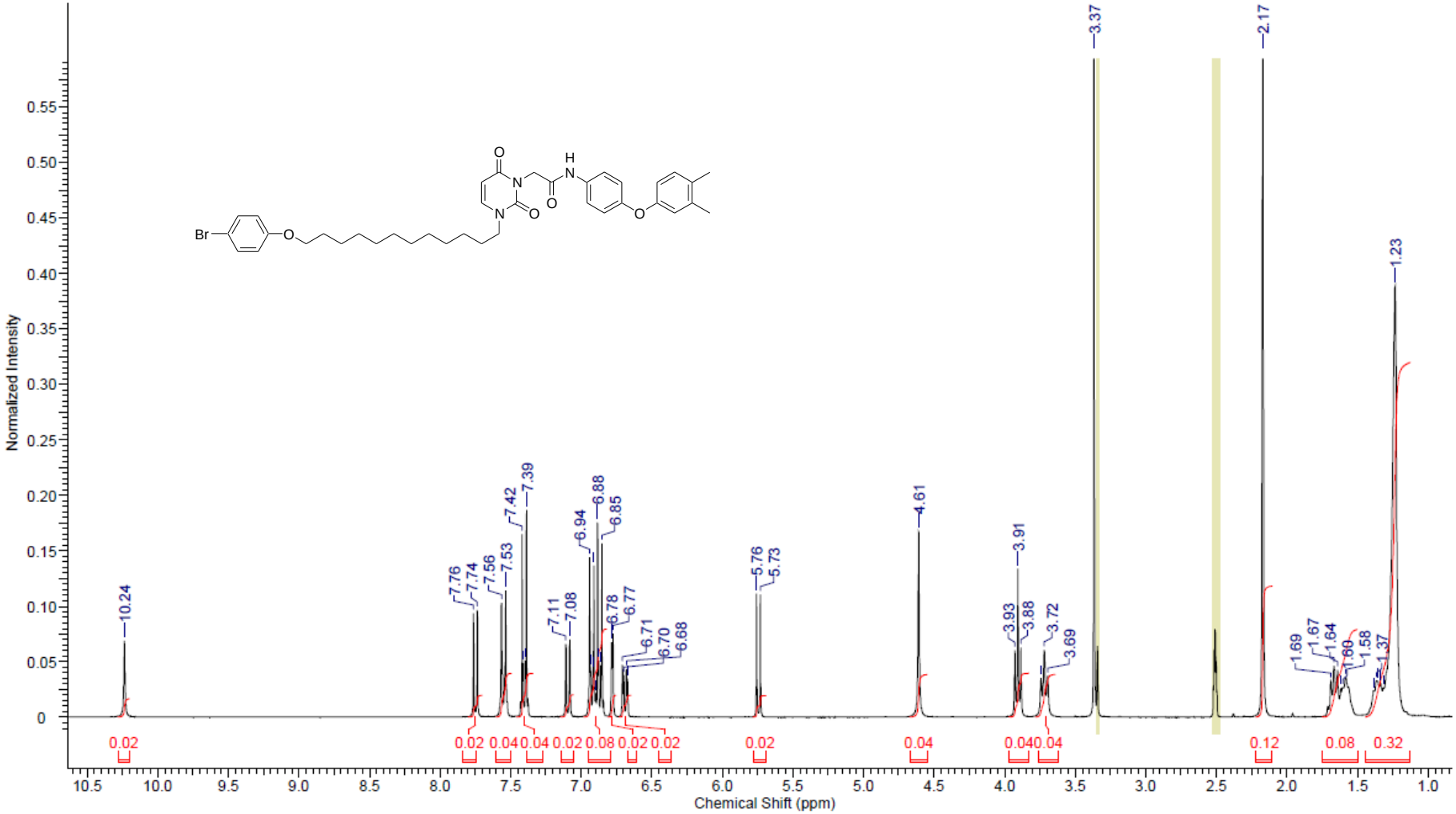

Figure S23 ^{1}H NMR spectrum of compound **3f** in DMSO-d_6 at 400 MHz.

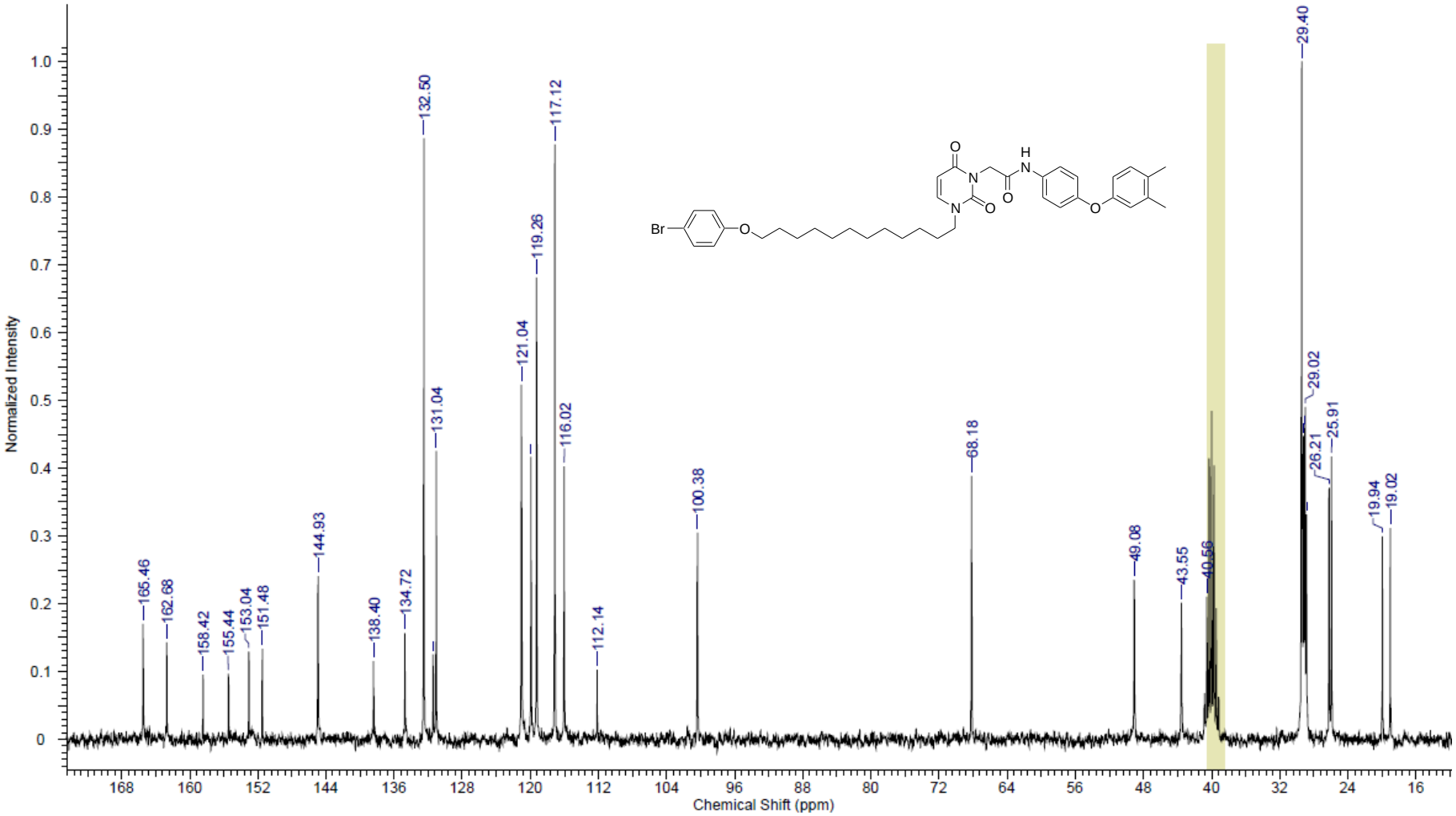

Figure S24 ^{13}C NMR spectrum of compound **3f** in DMSO-d_6 at 100 MHz.

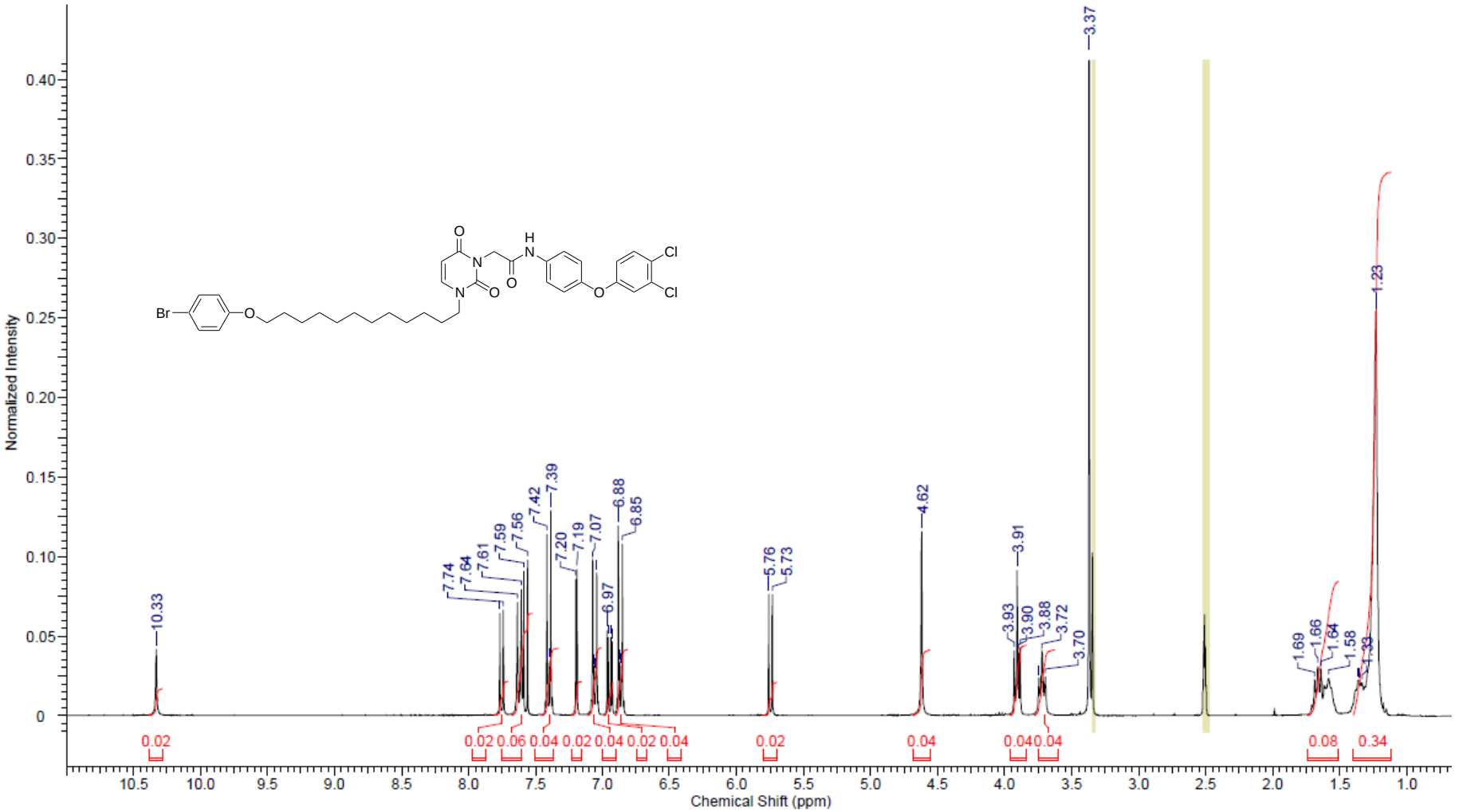

Figure S25 ^{1}H NMR spectrum of compound **3g** in DMSO-d_6 at 400 MHz.

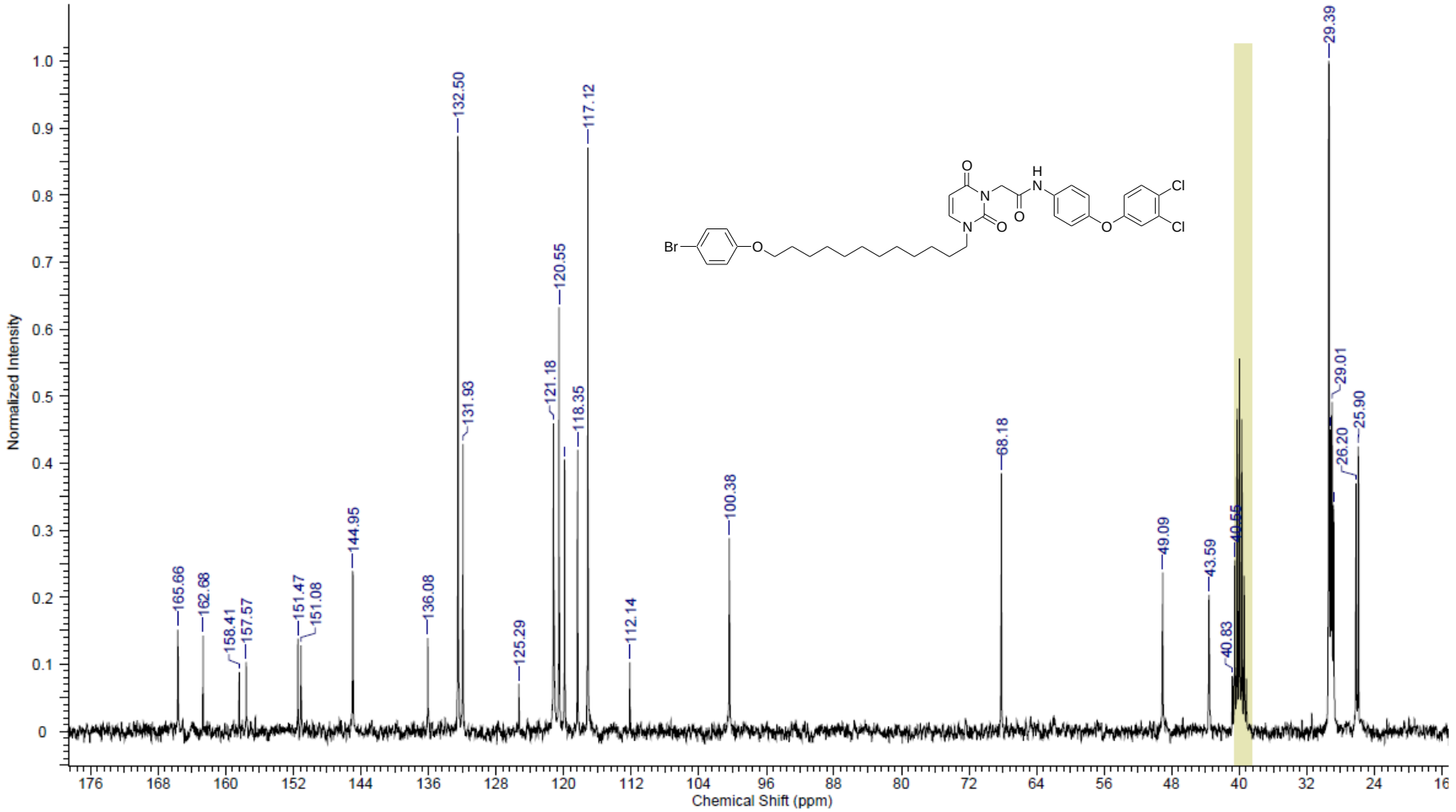

Figure S26 ^{13}C NMR spectrum of compound **3g** in DMSO-d_6 at 100 MHz.