Electronic Supplementary Information

Discovery of a small molecule targeting ULK1-modulating cell death of triple negative breast cancer *in vitro* and *in vivo*

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Experimental section

Materials and measurements

^{1}H-NMR spectra were recorded at 400 MHz. The chemical shifts were recorded in ppm relative totetramethylsilane and with the solvent resonance as the internal standard. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration. ^{13}C-NMR data were collected at 100 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the tetramethylsilane with the solvent resonance as internal standard. ESI-HRMS spectra were recorded on a commercial apparatus and methanol was used to dissolve the sample. All chemicals were obtained from commercial sources and used without further purification. Column chromatography was carried out on silica gel (300-400 mesh, Qingdao Marine Chemical Ltd, Qingdao, China). Thin layer chromatography (TLC) was performed on TLC silica gel 60 F254 plates.

General procedure for the synthesis of compounds 2a-d

To a solution of 2',2,4-trichloroacetophenone (5 mmol) in acetonitrile (15 mL) at room temperature was added 1-boc-piperazine or imidazole or benzimidazole or 1*H*-1,2,4-triazole (6 mmol, 1.2 eq), K_2CO_3 (10 mmol, 2 eq) and catalytic amount of potassium iodide. After stirring at 80 ºC for 6-10 h, the mixture was filtered and the solvent was then removed under reduced pressure, and the resulting crude was dissolved in dichloromethane, washed with saturated aqueous sodium bicarbonate and brine. After removing the solvent under reduced pressure,

the crude product was purified by flash chromatography on silica gel, eluting with dichloromethane and methanol (3%-10%), yielding the title compounds **2a-d** (50-80%).

tert-butyl-4-(2-(2,4-dichlorophenyl)-2-oxoethyl)piperazine-1-carboxylate (2a) White needle crystal, yield 75%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.44 (1H, d, *J*=8.3 Hz), 7.43 (1H, d, *J*=2.0 Hz), 7.31 (1H, dd, *J*=8.33, 2.0 Hz), 3.73 (2H, s), 3.43 (4H, t, *J*= 4.9, 4.8 Hz), 2.51 (4H, t, *J*=4.9, 4.8 Hz), 1.45 (9H, s).

1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethan-1-one(2b) Light yellow powder, yield 56%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.58 (2H, d, *J*=8.3 Hz), 7.51 (1H, d, *J*=1.9 Hz), 7.38 (1H, dd, *J*=8.3, 1.9 Hz), 7.13 (1H, s), 6.96 (1H, s), 5.36 (2H, s).

2-(1H-benzo[d]imidazol-1-yl)-1-(2,4-dichlorophenyl)ethan-1-one(2c) Light yellow powder, yield 58%**.** ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.96 (1H, s), 7.84 (1H, m), 7.56 (1H, d, *J*=8.4 Hz), 7.53 (1H, d, *J*=1.8 Hz), 7.36 (1H, dd, *J*=8.4, 1.8 Hz), 7.30 (2H, m), 7.26 (1H, m), 5.55 (2H, s).

1-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethan-1-one(2d) Light yellow powder, yield 60%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 8.27 (1H, s), 7.99 (1H, s), 7.65 (1H, d, *J*=8.4 Hz), 7.51 (1H, d, *J*=1.9 Hz), 7.38 (1H, dd, *J*=8.4, 1.9 Hz), 5.62 (2H, s).

General procedure for the synthesis of compounds 3a-d

To a solution of compounds **2** (2a-d) (5 mmol) in methanol (20 mL) respectively at room temperature was added sodium borohydride (2.5 mmol, 0.5 eq) in small batches. The resulting mixture was stirred about 2 hours at room temperature. After removing the solvent under reduced pressure, the crude product was dissolved in ethyl acetate, washed with water and brine. After removing the solvent under reduced pressure, the crude product was purified by flash chromatography on silica gel, eluting with dichloromethane and methanol, yielding the compounds **3a-d** (90-98%).

tert-butyl-4-(2-(2,4-dichlorophenyl)-2-hydroxyethyl)piperazine-1-carboxylate (3a)

White needle crystal, yield 98%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.60 (1H, d, *J*=8.3 Hz), 7.33 (1H, d, *J*=2.0 Hz), 7.28 (1H, dd, *J*=8.3, 2.0 Hz), 5.10 (1H, dd, *J*=10.3, 2.9 Hz), 3.48 (4H, m), 2.72 (3H, m), 2.42 (2H, m), 2.27 (1H, dd, *J*=12.5, 10.3 Hz), 1.47 (9H, s)

1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethan-1-ol (3b) Light yellow solid, yield 96%. ^{1}H-

NMR (400MHz, $CDCl_3$), δ(ppm): 7.59 (1H, d, *J*=8.3 Hz), 7.40 (1H, d, *J*=2.0 Hz), 7.38 (1H, s), 7.31 (1H, dd, *J*=8.3, 2.0 Hz), 6.91 (1H, s), 6.86 (1H, s), 5.24 (1H, dd, *J*=8.3, 2.1 Hz), 4.22 (1H, dd, *J*=14.1, 2.1 Hz), 3.85 (1H, dd, *J*=14.1, 8.3 Hz).

2-(1H-benzo[d]imidazol-1-yl)-1-(2,4-dichlorophenyl)ethan-1-ol(3c) Light yellow solid, yield 96%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 8.20 (1H, s), 7.63 (2H, m), 7.48 (1H, d, *J*=8.2 Hz), 7.44 (1H, d, *J*=1.9 Hz), 7.30 (1H, dd, *J*=8.2, 1.9 Hz), 7.28 (1H, d, *J*=8.2 Hz), 7.19 (1H, m), 5.47 (1H, dd, *J*=8.6, 2.0 Hz), 4.55 (1H, dd, *J*=14.5, 2.0 Hz), 4.15 (1H, dd, *J*=14.5, 8.6 Hz).

1-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethan-1-ol (3d) Yellow solid, yield 95%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 8.06 (1H, s), 7.96 (1H, s), 7.49 (1H, d, *J*=8.4 Hz), 7.40 (1H, d, *J*=2.0 Hz), 7.29 (1H, dd, *J*=8.4, 2.0 Hz), 5.42 (1H, dd, *J*=7.9, 1.5 Hz), 4.54 (1H, dd, *J*=14.0, 1.5 Hz), 4.20 (1H, dd, *J*=14.0, 7.9 Hz).

General procedure for the synthesis of compounds UA1-01-12

To a solution of compounds **3** (3a-d) (5 mmol) in acetonitrile (15 mL) respectively was added potassium tert-butoxide (6 mmol, 1.2 eq) at 80 ℃ for 30 min and appropriate benzyl halogenated and catalytic amount of potassium iodide and tetrabutylammonium bromide were added. The mixture was allowed to warm up to reflux for 8-16 hours and the solvent was then removed under reduced pressure, and the resulting crude was dissolved in ethyl acetate, washed with saturated aqueous sodium bicarbonate and brine. After removing the solvent under reduced pressure, the crude product was purified by flash chromatography on silica gel, eluting with petroleum ether and ethyl acetate, yielding the compounds **UA1-01-12**.

tert-butyl-4-(2-((4-bromobenzyl)oxy)-2-(2,4-dichlorophenyl)ethyl)piperazine-1-carboxylate (UA1-01) Light yellow solid, yield 65%, ESI-MS *m/z* 456.3 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.48 (1H, d, *J*=8.3 Hz), 7.47 (2H, d, *J*=8.2 Hz), 7.38 (1H, s), 7.30 (1H, d, *J*=8.1 Hz), 7.22 (2H, d, *J*=7.6 Hz), 4.90 (1H, s), 4.47 (1H, d, *J*=11.4 Hz), 4.25 (1H, d, *J*=11.4 Hz), 3.42 (4H, s), 2.70 (1H, s), 2.46 (4H, s), 2.17 (1H, s), 1.46 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 154.9, 137.0, 134.1, 133.7, 131.7, 129.6, 129.4, 128.9, 127.8, 121.9, 79.8, 74.9, 70.3, 63.8, 53.5, 28.6.

tert-butyl-4-(2-((4-chlorobenzyl)oxy)-2-(2,4-dichlorophenyl)ethyl)piperazine-1-

carboxylate (**UA1-02**) Light yellow solid, yield 68%, ESI-MS *m/z* 500.8 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.40 (2H, d, *J*=8.3 Hz), 7.39 (1H, d, *J*=8.3 Hz), 7.29 (1H, d, *J*=1.9 Hz), 7.22 (1H, dd, *J*=8.3, 1.9 Hz), 7.13 (2H, d, *J*=8.3 Hz), 4.90 (1H, dd, *J*=8.5, 2.5 Hz), 4.42 (1H, d, *J*=12.2 Hz), 4.18 (1H, d, *J*=12.2 Hz), 3.33 (4H, m), 2.62 (1H, d, *J*=8.5 Hz), 2.40 (5H, m), 1.38 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 154.8, 136.9, 134.1, 133.6, 131.6, 129.6, 129.4, 128. 8, 127.8, 121.8, 79.8, 74.6, 70.2, 63.6, 53.3, 28.5.

tert-butyl-4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazine-1-carboxylate (**UA1-03**) Light yellow solid, yield 55%, ESI-MS *m/z* 516.5 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.78 (3H, m), 7.74 (1H, s), 7.56 (1H, d, *J*=8.2 Hz), 7.48 (3H, m), 7.37 (1H, d, *J*=1.9 Hz), 7.31 (2H, dd, *J*=8.2, 1.9 Hz), 5.03 (1H, dd, *J*=8.8, 2.8 Hz), 4.71 (1H, d, *J*=12.2 Hz), 4.43 (1H, d, *J*=12.2 Hz), 3.39 (4H, m), 2.72 (1H, d, *J*=8.8 Hz), 2.44 (5H, m), 1.45 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 154.9, 137.3, 135.3, 134.0, 133.8, 133.4, 133.2, 129.4, 129.0, 128.3, 128.0, 127.9, 127.8, 127.0, 126.4, 126.2, 126.1, 79.7, 74.5, 71.2, 63.8, 53.4, 28.6.

1-(2-((4-bromobenzyl)oxy)-2-(2,4-dichlorophenyl)ethyl)-1H-benzo[d]imidazole (**UA1-04**) Light yellow solid, yield 62%, ESI-MS *m/z* 477.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 8.13 (1H, s), 7.86 (1H, d, *J*=8.3 Hz), 7.48 (1H, d, *J*=1.6 Hz), 7.44 (1H, d, *J*=8.5 Hz), 7.36 (1H, m), 7.34 (1H, m), 7.30 (1H, dd, *J*=8.5, 1.6 Hz), 7.28 (1H, m), 7.24 (2H, d, *J*=8.2 Hz), 6.78 (2H, d, *J*=8.2 Hz), 5.05 (1H, dd, *J*=8.6, 2.6 Hz), 4.42 (1H, dd, *J*=14.7, 2.6 Hz), 4.39 (1H, d, *J*=11.8 Hz), 4.24 (1H, dd, *J*=14.7, 8.6 Hz), 4.04 (1H, d, *J*=11.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 144.0, 143.6, 135.4, 135.1, 134.1, 133.8, 133.4, 131.6, 131.5, 129.7, 129.3, 128.5, 128.1, 123.0, 122.2, 122.0, 120.4, 109.6, 75.2, 70.7, 49.4, 29.7.

1-(2-((4-chlorobenzyl)oxy)-2-(2,4-dichlorophenyl)ethyl)-1H-benzo[d]imidazole (**UA1-05**) Light yellow solid, yield 63%, ESI-MS *m/z* 432.7 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 4.07 (1H, d, *J*=11.7 Hz), 4.21 (1H, dd, *J*=14.7, 8.6 Hz), 4.39 (1H, d, *J*=11.7 Hz), 4.41 (1H, dd, *J*=14.7, 2.6 Hz), 5.05 (1H, dd, *J*=8.6, 2.6 Hz), 6.84 (2H, d, *J*=8.2 Hz), 7.09 (2H, d, *J*=8.2 Hz), 7.23 (1H, m), 7.29 (1H, m), 7.30 (1H, dd, *J*=8.3, 2.0 Hz), 7.35 (1H, d, *J*=7.9 Hz), 7.44 (1H, d, *J*=8.3 Hz), 7.47 (1H, d, *J*=2.0 Hz), 7.82 (1H, d, *J*=7.9 Hz), 7.98 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 144.0, 135.2, 135.0, 134.3, 133.9, 133.5, 129.8, 129.1, 128.65, 128.2,123.1, 122.3, 120.4, 109.7, 75.4, 70.8, 49.6.

1-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)-1H-benzo[d]imidazole (**UA1-**

06) Light yellow solid, yield 55%, ESI-MS *m/z* 448.3 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 8.02 (1H, s), 7.82 (1H, d, *J*=7.5 Hz), 7.75 (1H, m), 7.67 (1H, m), 7.62 (1H, d, *J*=8.3 Hz), 7.50 (1H, d, *J*=7.5 Hz), 7.47 (1H, d, *J*=1.9 Hz), 7.45 (1H, d, *J*=6.1 Hz), 7.44 (1H, d, *J*=6.1 Hz), 7.41(1H, s), 7.37 (1H, d, *J*=8.3 Hz), 7.31 (1H, dd, *J*=8.3, 1.9 Hz), 7.25(1H, m), 7.17 (1H, m), 7.03 (1H, d, *J*=8.3 Hz), 5.16 (1H, dd, *J*=8.3, 2.5 Hz), 4.60 (1H, d, *J*=11.7 Hz), 4.44 (1H, dd, *J*=11.7, 2.5 Hz), 4.29 (1H, d, *J*=11.7 Hz), 4.25 (1H, dd, *J*=11.7, 8.3 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 144.1, 143.6, 135.1, 134.5, 134.1, 33.6, 133.1, 133.1, 129.8, 128.8, 128.4, 128.2, 128.0, 127.7, 126.7, 126.2, 126.1, 125.4, 123.0, 122.2, 120.4, 109.8, 75.6, 71.7, 49.6.

1-(2-((4-bromobenzyl)oxy)-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole (**UA1-07**) Light yellow solid, yield 68%, ESI-MS *m/z* 427.1 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.48 (1H, s), 7.45 (2H, d, *J*=8.2 Hz), 7.44 (1H, d, *J*=1.8 Hz), 7.33 (1H, d, *J*=8.4 Hz), 7.29 (1H, dd, *J*=8.4, 1.8 Hz), 7.04 (1H, s), 7.00 (2H, d, *J*=8.2 Hz), 6.90 (1H, s), 4.96 (1H, dd, *J*=7.5, 2.6 Hz), 4.42 (1H, d, *J*=11.7 Hz), 4.19 (1H, dd, *J*=14.1, 2.6 Hz), 4.18 (1H, d, *J*=11.7 Hz), 4.04 (1H, dd, *J*=14.1, 7.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 138.0, 136.0, 135.2, 134.0, 133.49, 131.9, 129.8, 129.5, 129.3, 128.6, 128.2, 122.2,119.9, 77.0, 70.9, 51.5.

1-(2-((4-chlorobenzyl)oxy)-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole (**UA1-08**) Light yellow solid, yield 65%, ESI-MS *m/z* 382.7 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.46(1H, s), 7.43 (1H, d, *J*=1.9 Hz), 7.33 (1H, d, *J*=8.4 Hz), 7.29 (2H, d, *J*=7.5 Hz), 7.28 (1H, dd, *J*=8.4, 1.9 Hz), 7.07 (1H, s), 7.04 (2H, d, *J*=7.2 Hz), 6.89 (1H, s), 4.95 (1H, dd, *J*=7.6, 2.1 Hz), 4.42 (1H, d, *J*=11.6 Hz), 4.19 (1H, d, *J*=11.6 Hz), 4.18 (1H, dd, *J*=14.4, 2.1 Hz), 4.03 (1H, dd, *J*=14.4, 7.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 138.5, 136.0, 135.1, 134.1, 133.5, 131.9, 129.8, 129.5, 128.6, 128.2, 122.2, 119.9, 77.1, 70.9, 51.5.

1-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)-1H-imidazole (**UA1-09**) Light yellow solid, yield 57%, ESI-MS *m/z* 398.3 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.81 (2H, m), 7.79 (1H, s), 7.55 (1H, s), 7.52 (1H, m), 7.49 (2H, m), 7.44 (1H, d, *J*=1.9 Hz), 7.41 (1H, d, *J*=8.3 Hz), 7.31 (1H, dd, *J*=8.3, 1.9 Hz), 7.23 (1H, m), 7.06 (1H, s), 6.93 (1H, s), 5.03 (1H, dd, *J*=7.6, 2.6 Hz), 4.65 (1H, d, *J*=11.8 Hz), 4.39 (1H, d, *J*=11.8 Hz), 4.21 (1H, dd, *J*=14.5, 2.6 Hz), 4.06 (1H, dd, *J*=14.5, 7.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 138.1, 135.1, 134.4, 134.3, 133.6, 133.3, 133.2, 129.8, 129.3, 128.8, 128.6, 128.1, 128.1, 127.9, 126.7, 126.4, 126.3, 125.6, 120.1, 71.8, 51.6.

1-(2-((4-bromobenzyl)oxy)-2-(2,4-dichlorophenyl)ethyl)-1H-1,2,4-triazole (**UA1-10**) Light yellow solid, yield 61%, ESI-MS *m/z* 428.1 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 8.12 (1H, s), 7.93 (1H, s), 7.45 (1H, d, *J*=1.9 Hz), 7.42 (2H, d, *J*=8.2 Hz), 7.41 (1H, d, *J*=8.3 Hz), 7.32 (1H, dd, *J*=8.3, 1.9 Hz), 6.94 (2H, d, *J*=8.2 Hz), 5.14 (1H, dd, *J*=8.5, 2.8 Hz), 4.43 (1H, dd, *J*=14.2, 2.8 Hz), 4.40 (1H, d, *J*=11.7 Hz), 4.24 (1H, dd, *J*=14.2, 8.5 Hz), 4.13 (1H, d, *J*=11.7 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 152.1, 144.4, 135.8, 135.3, 133.9, 133.9, 131.9, 130.0, 129.6, 128.6, 128.1, 122.3, 75.7, 71.0, 54.0.

1-(2-((4-chlorobenzyl)oxy)-2-(2,4-dichlorophenyl)ethyl)-1H-1,2,4-triazole (**UA1-11**) Light yellow solid, yield 63%, ESI-MS *m/z* 383.7 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 8.12 (1H, s), 7.93 (1H, s), 7.45 (1H, d, *J*=1.95 Hz), 7.41 (1H, d, *J*=8.3 Hz), 7.32 (1H, dd, *J*=8.3, 1.9 Hz), 7.27 (2H, d, *J*=8.2 Hz), 7.00 (2H, d, *J*=8.2 Hz), 5.14 (1H, dd, *J*=8.6, 2.9 Hz), 4.43 (1H, dd, *J*=14.2, 2.9 Hz), 4.42 (1H, d, *J*=11.7 Hz), 4.25 (1H, dd, *J*=14.2, 8.6 Hz), 4.15 (1H, d, *J*=11.7 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 152.1, 144.4, 135.3, 135.3, 134.2, 133.9, 133.9, 130.0, 129.3, 128.9, 128.6, 128.1, 75.7, 70.9, 54.0.

1-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)-1H-1,2,4-triazole (**UA1-12**) Light yellow solid, yield 50%, ESI-MS *m/z* 399.3 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 8.17 (1H, s), 7.91 (1H, s), 7.76-7.83 (3H, m), 7.48-7.51 (3H, m), 7.47 (1H, d, *J*=1.5 Hz), 7.45 (1H, d, *J*=1.9 Hz), 7.34 (H, dd, *J*=8.3, 1.9 Hz), 7.16 (1H, dd, *J*=8.4, 1.5 Hz), 5.20 (1H, dd, *J*=8.5, 2.9 Hz), 4.64 (1H, d, *J*=11.6 Hz), 4.46 (1H, dd, *J*=14.2, 2.9 Hz), 4.35 (1H, d, *J*=11.6 Hz), 4.28 (1H, dd, *J*=14.2, 8.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 152.0, 144.4, 135.2, 134.2, 134.1, 134.0, 133.3, 133.3, 130.0, 128.8, 128.6, 128.1, 128.1, 127.9, 127.0, 126.4, 126.4, 125.7, 75.6, 71.8, 54.1.

General procedure for the synthesis of compound 4

To a solution of **UA1-03** (5 mmol) in dichloromethane (15 ml) was added trifluoroacetic (2 ml) and the resulting mixture was stirred about 2 hours at 0 ℃. The crude was washed with saturated aqueous sodium bicarbonate and brine, and then dried over anhydrous sodium sulfate. After removing the solvent under reduced pressure to give the crude product and purified by flash chromatography on silica gel, eluting with dichloromethane and methanol,

yielding the title compound **4** as light yellow oil (yield 89%). ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.82 (3H, m), 7.77 (1H, s), 7.56 (1H, d, *J*=8.4 Hz), 7.47 (3H, m), 7.37 (1H, d, *J*=2.0 Hz), 7.30 (1H, dd, *J*=8.4, 2.0 Hz), 5.05 (1H, dd, *J*=9.0, 2.9 Hz), 4.69 (1H, d, *J*=12.3 Hz), 4.44 (1H, d, *J*=12.3 Hz), 2.87 (4H, m), 2.71 (1H, dd, *J*=9.0, 13.5 Hz), 2.45 (4H, m), 2.43 (1H, dd, *J*=2.9, 13.5 Hz).

General procedure for the synthesis of compounds UA2-01-13

To a solution of compound **4** (5 mmol) and triethylamine (2 eq) in dichloromethane (15 ml) was added, and then a solution of appropriate acyl chloride (1.1 eq) in dichloromethane (5 ml) was added dropwise at room temperature overnight. The mixture was washed with saturated aqueous sodium bicarbonate and brine. After removing the solvent under reduced pressure, the crude product was purified by flash chromatography on silica gel, eluting with petroleum ether and ethyl acetate, yielding the title compounds.

(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)(phenyl)methanone (UA2-01) Light yellow solid, yield 78%. m.p. 96~100 ℃, ESI-MS *m/z* 520.1 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.82 (3H, m), 7.73 (1H, s), 7.56 (1H, d, *J*=8.4 Hz), 7.48 (3H, m), 7.36 (6H, m), 7.32 (1H, dd, *J*=8.4, 2.0 Hz), 5.04 (1H, dd, *J*=8.8, 2.8 Hz), 4.71 (1H, d, *J*=12.2 Hz), 4.41 (1H, d, *J*=12.2 Hz), 3.73 (2H, s), 3.37 (2H, s), 2.75 (1H, dd, *J*=13.6, 8.8 Hz), 2.50 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 170.4, 137.1, 136.0, 135.2, 134.1, 133.8, 133.4, 133.2, 129.7, 129.4, 129.0, 128.6, 128.6, 128.4, 128.0, 127.9, 127.9, 127.2, 127.2, 127.1, 126.4, 126.2, 126.1, 74.6, 71.2, 63.6, 53.5, 46.0, 41.7.

(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)(4-methoxyphenyl)methanone (UA2-02) Light yellow oil, yield 76%, ESI-MS *m/z* 550.1 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.82 (3H, m), 7.74 (1H, s), 7.56 (1H, d, *J*=8.4 Hz), 7.48 (3H, m), 7.33 (3H, m), 6.87 (2H, d, *J*=8.7 Hz), 5.06 (1H, s), 4.76 (1H, d, *J*=12.1 Hz), 4.42 (1H, d, *J*=12.1 Hz), 3.82 (4H, m), 2.76 (1H, s), 2.45 (4H, m), 2.45 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 170.4, 160.9, 137.1, 135.2, 134.2, 133.7, 133.3, 133.2, 129.4, 129.3, 129.3, 129.0, 128.4, 128.0, 127.9, 127.9, 127.9, 127.1, 126.4, 126.2, 126.1, 113.8, 113.8, 74.5, 71.2, 63.5, 55.5, 55.5, 53.6, 46.8, 41.7.

(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)(p-tolyl)methanone (UA2-03) Light yellow solid, yield 76%. m.p. 98~101 ℃, ESI-MS *m/z* 534.1 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.83 (3H, m), 7.73 (1H, s), 7.56 (1H, d, *J*=8.4 Hz), 7.47 (3H, m), 7.39 (1H, d, *J*=1.9 Hz), 7.32 (1H, dd, *J*=8.4, 1.9 Hz), 7.25 (2H, d, *J*=7.9 Hz), 7.17 (2H, d, *J*=7.9 Hz), 5.05 (1H, d, *J*=8.7 Hz), 4.70 (1H, d, *J*=12.1 Hz), 4.42 (1H, d, *J*=12.1 Hz), 3.74 (2H, m), 3.14 (2H, m), 2.75 (1H, dd, *J*=13.0, 8.7 Hz), 2.52 (5H, m), 2.36 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 170.6, 139.9, 137.1, 135.2, 134.1, 133.8, 133.4, 133.2, 133.0, 129.4, 129.2, 129.2, 129.0, 128.4, 128.0, 127.9, 127.9, 127.3, 127.3, 127.1, 126.4, 126.2, 162.1, 74.6, 71.2, 63.6, 53.7, 53.1, 46.8, 41.7, 21.5.

(4-chlorophenyl)(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)methanone (UA2-04) White solid, yield 73%. m.p. 103~105 ℃**,** ESI-MS *m/z* 554.1 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.83 (3H, m), 7.73 (1H, s), 7.56 (1H, d, *J*=8.4 Hz), 7.47 (3H, m), 7.32 (2H, s), 7.37 (1H, d, *J*=2.0 Hz), 7.32 (1H, dd, *J*=8.4, 2.0 Hz), 7.28 (1H, m), 7.23 (1H, m), 5.05 (1H, s), 4.70 (1H, d, *J*=12.1, 3.8 Hz), 4.42 (1H, d, *J*=12.1 Hz), 3.79 (2H, m), 3. 24 (2H, m), 2.76 (1H, dd, *J*=12.8, 8.8 Hz), 2.50 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 166.9, 137.0, 136.0, 135.2, 134.1, 133.8, 133.4, 133.2, 130.5, 130.2, 129.8, 129.4, 129.0, 128.6, 128.4, 128.0, 127.9, 127.9, 127.3, 127.1, 126.4, 126.2, 126.1, 74.6, 71.2, 63.5, 53.7, 53.1, 46.9, 41.8.

(2,4-dichlorophenyl)(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)methanone (UA2-05) White solid, yield 78%. m.p. 93~95 ℃, ESI-MS *m/z* 589.0 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.83 (3H, m), 7.73 (1H, s), 7.55 (1H, d, *J*=8.4 Hz), 7.48 (3H, m), 7.39 (2H, m), 7.32 (1H, dd, *J*=8.4, 1.9 Hz), 7.29 (1H, m), 7.17 (1H, d, *J*=8.2), 5.02 (1H, d, *J*=7.9 Hz), 4.70 (1H, dd, *J*=12.1, 2.9 Hz), 4.39 (1H, d, *J*=12.1 Hz), 3.75 (2H, m), 3. 20 (2H, m), 2.76 (1H, dd, *J*=13.0, 8.8 Hz), 2.45 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 166.0, 135.6, 135.2, 135.2, 134.5, 134.2, 133.8, 133.4, 133.2, 131.5, 129.7, 129.5, 129.0, 128.9, 128.4, 128.0, 127.9, 127.9, 127.8, 127.1, 126.5, 126.3, 126.1, 74.6, 71.2, 63.5, 53.7, 53.0, 46.9, 42.0.

(4-bromophenyl)(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-

1-yl)methanone (UA2-06) Light yellow solid, yield 77%. m.p. 96~100 ℃, ESI-MS *m/z* 599.0 $[M]^+$; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ(ppm): 7.82 (3H, m), 7.73 (1H, s), 7.56 (1H, d, *J*=8.3 Hz), 7.49 (5H, m), 7.39 (1H, d, *J*=1.8 Hz), 7.32 (1H, dd, *J*=8.3, 1.8 Hz), 7.22 (1H, d, *J*=8.4 Hz), 5.05 (1H, s), 4.70 (1H, d, *J*=12.0 Hz), 4.40 (1H, d, *J*=12.0 Hz), 3.73 (2H, s), 3.36 (2H, s), 2.52 (6H, m); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 169.3, 137.0, 135.2, 134.8, 134.2, 133.7, 133.4, 133.2, 131.8, 131.8, 129.5, 129.0, 128.9, 128.9, 128.4, 128.0, 127.9, 127.9, 127.1, 126.5, 126.3, 126.1, 124.1, 74.5, 71.2, 63.5, 53.3, 53.3, 48.0, 41.2.

(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)(4-nitrophenyl)methanone (UA2-07) Light yellow solid, yield 81%. m.p. 117~120 ℃, ESI-MS *m/z* 564.2 $[M]^+$; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ(ppm): 8.23 (2H, d, *J*=8.7 Hz), 7.83 (3H, m), 7.73 (1H, s), 7.56 (1H, d, *J*=8.4 Hz), 7.48 (5H, m), 7.40 (1H, d, *J*=2.0 Hz), 7.33 (1H, dd, *J*=8.4, 2.0 Hz), 5.05 (1H, s), 4.71 (1H, d, *J*=12.1 Hz), 4.39 (1H, d, *J*=12.1 Hz), 3.77 (2H, s), 3.29 (2H, s), 2.60 (6H, m); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 168.0, 148.5, 142.1, 136.9, 135.1, 134.2, 133.7, 133.3, 133.2, 129.5, 129.0, 128.4, 128.2, 128.2, 128.0, 127.9, 127.9, 127.2, 126.5, 126.3, 126.1, 124.0, 124.0, 74.5, 71.2, 63.4, 53.7, 53.1, 47.8, 42.5.

(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)(pyridin-3-yl)methanone (UA2-08) Yellow oil, yield 76%, ESI-MS *m/z* 521.2 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ(ppm): 8.63 (2H, s), 7.82 (3H, s), 7.73 (1H, s), 7.70 (1H, d, *J*=5.4 Hz), 7.56 (1H, m), 7.47 (3H, s), 7.39 (1H, s), 7.33 (2H, s), 5.04 (1H, d, *J*=4.9 Hz), 4.71 (1H, d, *J*=12.1 Hz), 4.41 (1H, d, *J*=12.1 Hz), 3.76 (2H, s), 3.37 (2H, s), 2.58 (6H, m); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 167.7, 150.9, 148.1, 136.9, 135.2, 135.2, 134.2, 133.7, 133.3, 133.2, 131.7, 129.5, 129.0, 128.4, 128.0, 127.9, 127.9, 127.1, 126.5, 126.3, 126.1, 123.6, 74.5, 71.2, 63.4, 53.8, 46.5, 42.4.

(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)(pyridin-4-yl)methanone (UA2-09) White solid, yield75%. m.p. 111~115 ℃**,** ESI-MS *m/z* 521.2 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ(ppm): 8.65 (2H, dd, *J*=4.4, 1.6 Hz), 7.82 (3H, m), 7.73 (1H, s), 7.56 (1H, d, *J*=8.4 Hz), 7.47 (5H, m), 7.39 (1H, d, *J*=2.0 Hz), 7.33 (1H, dd, *J*=8.4, 2.0 Hz), 7.21 (2H, dd, *J*=4.4, 1.6 Hz), 5.04 (1H, d, *J*=8.2 Hz), 4.70 (1H, d, *J*=12.1 Hz), 4.39 (1H, d, *J*=12.1 Hz), 3.76 (2H, s), 3.29 (2H, s), 2.76 (1H, d, *J*=13.6, 8.2 Hz), 2.52 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 167.7, 150.4, 150.4, 143.6, 136.9, 135.1, 134.2, 133.7, 133.4, 133.2, 129.5,

129.0, 128.4, 128.0, 127.9, 127.9, 127.2, 126.5, 126.3, 126.1, 121.3, 121.3, 74.5, 71.2, 63.4, 53.7, 53.1, 47.6, 42.3.

1-(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)-2-(p-tolyl)ethan-1-one (UA2-10) White solid, yield 72%. m.p. 95~110 ℃**,** ESI-MS *m/z* 548.1 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ(ppm): 7.82 (3H, m), 7.72 (1H, s), 7.56 (1H, d, *J*=8.4 Hz), 7.49 (3H, m), 7.37 (1H, d, *J*=2.0 Hz), 7.31 (1H, dd, *J*=8.4, 2.0 Hz), 7.10 (4H, s), 4.99 (1H, s), 4.67 (1H, d, *J*=12.2 Hz), 4.40 (1H, d, *J*=12.2 Hz), 3.64 (4H, s), 3.39 (2H, s), 2.68 (1H, m), 2.44 (4H, s), 2.35 (1H, s), 2.30 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 169.7, 137.1, 136.4, 135.2, 134.1, 133.7, 133.3, 133.2, 132.1, 129.5×2, 129.4, 129.0, 128.6, 128.6, 128.3, 128.0, 127.9, 127.8, 127.0, 126.4, 126.2, 126.1, 74.6, 71.2, 63.5, 53.5, 53.2, 46.2, 41.9, 40.7, 21.2.

1-(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)-2-(4-methoxyphenyl)ethan-1-one (UA2-11) Light yellow oil, yield 69%, ESI-MS *m/z* 564.2 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ(ppm): 7.82 (3H, m), 7.72 (1H, s), 7.51 (1H, d, *J*=8.4 Hz), 7.46 (3H, m), 7.37 (1H, d, *J*=2.0 Hz), 7.31 (1H, dd, *J*=8.4, 2.0 Hz), 7.12 (2H, d, *J*=8.6 Hz), 6.83 (2H, d, *J*=8.6 Hz), 5.01 (1H, d, *J*=8.3 Hz), 4.67 (1H, d, *J*=12.2 Hz), 4.39 (1H, d, *J*=12.2 Hz), 3.77 (3H, s), 3.62 (4H, s), 3.39 (2H, s), 2.70 (1H, d, *J*=13.4, 8.3 Hz), 2.40 (4H, m), 2.25 (1H, m); ^{13}C-NMR(100 MHz, $CDCl_3$), δ(ppm): 169.9, 158.6, 137.1, 135.2, 134.1, 133.7, 133.4, 133.1, 129.8, 129.8, 129.4, 129.0, 128.3, 128.0, 127.9, 127.8, 127.2, 127.0, 126.4, 126.2, 126.1, 114.3, 114.3, 74.6, 71.2, 63.5, 55.4, 53.6, 53.2, 46.2, 42.0, 40.2.

2-(4-chlorophenyl)-1-(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)ethan-1-one (UA2-12) Light yellow oil, yield 73%, ESI-MS *m/z* 567.1 $[M]^+$; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ(ppm): 7.82 (3H, m), 7.73 (1H, s), 7.54 (1H, d, *J*=8.4 Hz), 7.47 (3H, m), 7.38 (1H, d, *J*=2.0 Hz), 7.31 (1H, dd, *J*=8.4, 2.0 Hz), 7.27 (2H, d, *J*=8.4 Hz), 6.83 (2H, d, *J*=8.4 Hz), 5.00 (1H, s), 4.68 (1H, d, *J*=12.2 Hz), 4.40 (1H, d, *J*=12.2 Hz), 3.64 (4H, s), 3.38 (2H, s), 2.71 (1H, m), 2.35 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 169.0, 137.0, 135.2, 134.1, 133.7, 133.7, 133.4, 133.2, 132.8, 130.2, 130.2, 129.4, 129.0, 129.0, 129.0, 128.3, 128.0, 127.9, 127.8, 127.0, 126.4, 126.2, 126.1, 74.6, 71.2, 63.5, 53.5, 53.2, 46.2, 42.0, 40.2.

2-(4-bromophenyl)-1-(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-

ylmethoxy)ethyl)piperazin-1-yl)ethan-1-one (UA2-13) White solid, yield 75%. m.p. 95~98 ℃, ESI-MS *m/z* 613.1 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ(ppm): 7.82 (3H, m), 7.73 (1H, s), 7.54 (1H, d, *J*=8.4 Hz), 7.48 (3H, m), 7.42 (2H, d, *J*=8.3 Hz), 7.38 (1H, d, *J*=2.0 Hz), 7.32 (1H, dd, *J*=8.4, 2.0 Hz), 7.08 (2H, d, *J*=8.3 Hz), 5.00 (1H, dd, *J*=8.8, 2.6 Hz), 4.69 (1H, d, *J*=12.2 Hz), 4.49 (1H, d, *J*=12.2 Hz), 3.62 (4H, s), 3.37 (2H, s), 2.70 (1H, dd, *J*=13.6, 8.8 Hz), 2.40 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 168.9, 137.0, 135.2, 134.2, 134.1, 133.8, 133.4, 133.2, 131.9, 131.9, 130.6, 130.6, 129.4, 129.0, 128.3, 128.0, 127.9, 127.8, 127.0, 126.4, 126.3, 126.1, 120.9, 74.6, 71.2, 63.5, 53.5, 53.2, 46.2, 42.1, 40.3.

General procedure for the synthesis of compound 5

To a solution of compound **4** (5 mmol) and triethylamine (2 eq) in dichloromethane (15 ml) was added, and then a solution of chloroacetyl chloride (1.1 eq) in dichloromethane (5 ml) was added dropwise at room temperature overnight. The mixture was washed with saturated aqueous sodium bicarbonate and brine. After removing the solvent under reduced pressure, the crude product was purified by flash chromatography on silica gel, eluting with petroleum ether and ethyl acetate, yielding the title compound **5**. ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.83 (3H, m), 7.74 (1H, s), 7.56 (1H, d, *J*=8.4 Hz), 7.49 (3H, m), 7.40 (1H, d, *J*=2.0 Hz), 7.33 (1H, dd, *J*=8.4, 2.0 Hz), 5.05 (1H, d, *J*=8.9 Hz), 4.71 (1H, d, *J*=12.1 Hz), 4.41 (1H, d, *J*=12.1 Hz), 4.01 (2H, s), 3.60 (2H, s), 3.46 (2H, s), 2.75 (1H, dd, *J*=13.4, 8.9 Hz), 2.55 (5H, m).

General procedure for the synthesis of compounds UA3-01-07

To a solution of compound **5** (5 mmol) and potassium carbonate (2 eq) in acetonitrile (15 mL) at room temperature was added appropriate amine and catalytic amount of potassium iodide. After stirring at room temperature or 60 ℃ for 10-24 h, the mixture was filtered and the solvent was then removed under reduced pressure, and the resulting crude was dissolved in dichloromethane, washed with saturated aqueous sodium bicarbonate and brine. After removing the solvent under reduced pressure, the crude product was purified by flash chromatography on silica gel, eluting with petroleum ether and ethyl acetate, yielding the title compounds.

2-(dibutylamino)-1-(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)ethan-1-one (UA3-01) Light yellow solid, yield 63%. m.p. 91~92 ℃, ESI-MS *m/z* 585.3 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.85 (3H, m), 7.77 (1H, s), 7.59 (1H, d, *J*=8.3 Hz), 7.50 (3H, m), 7.41 (1H, d, *J*=2.0 Hz), 7.35 (1H, dd, *J*=8.3, 2.0 Hz), 5.06 (1H, dd, J=8.9, 2.8 Hz), 4.73 (1H, d, *J*=12.1 Hz), 4.45 (1H, d, *J*=12.1 Hz), 3.60 (4H, m), 3.26 (2H, s), 2.75 (1H, dd, *J*=13.6, 8.9 Hz), 2.46 (9H, m), 1.43 (4H, m), 0.90 (6H, t, *J*=14.5, 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 168.3, 137.2, 135.3, 134.1, 133.8, 133.4, 133.2, 129.4, 129.0,128.3, 128.0, 127.9, 127.8, 127.0, 126.4, 126.2, 126.1, 74.6, 71.2, 63.7, 59.4, 54.1, 54.1, 53.9, 53.4, 45.6, 41.9, 29.0, 29.0, 20.8, 20.8, 14.2, 14.2.

1-(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)-2-(diisobutylamino)ethan-1-one (UA3-02) Light yellow solid, yield 65%**.** m.p. 90~92 ℃**,** ESI-MS *m/z* 585.3 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.82 (3H, m), 7.74 (1H, s), 7.56 (1H, d, *J*=8.4 Hz), 7.48 (3H, m), 7.39 (1H, d, *J*=1.9 Hz), 7.32 (1H, dd, *J*=8.4, 1.9 Hz), 5.03 (1H, d, *J*=8.6 Hz), 4.71 (1H, d, *J*=12.1 Hz), 4.42 (1H, d, *J*=12.1 Hz), 3.57 (4H, s), 3.17 (2H, s), 2.72 (1H, dd, *J*=13.3, 8.6 Hz), 2.45 (5H, m), 2.15 (4H, d, *J*=6.6), 1.68 (2H, m), 0.86 (12H, s); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 68.2, 137.0, 135.1, 134.0, 133.6, 133.2, 133.0, 129.3, 128.9, 128.2, 127.8, 127.7, 127.7, 126.9, 126.3, 126.1, 125.9, 74.5, 71.1, 64.4, 63.4, 59.9, 54.0, 53.7, 53.2, 45.4, 41.8, 28.6, 27.8, 26.4, 21.1, 20.5, 14.0.

1-(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)-2-(pyrrolidin-1-yl)ethan-1-one (UA3-03) Light yellow solid, yield 64%. m.p. 89~90 ℃, ESI-MS *m/z* 527.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.83 (3H, m), 7.74 (1H, s), 7.56 (1H, d, *J*=8.5 Hz), 7.48 (3H, m), 7.38 (1H, d, *J*=1.8 Hz), 7.32 (1H, dd, *J*=8.5, 1.8 Hz), 5.03 (1H, dd, *J*=8.7, 2.5 Hz), 4.70 (1H, d, *J*=12.1 Hz), 4.42 (1H, d, *J*=12.1 Hz), 3.58 (4H, m), 3.30 (2H, s), 2.73 (1H, dd, *J*=13.5, 8.7 Hz), 2.53 (5H, m), 2.45 (4H, m), 1.78 (4H, s); ^{13}C-NMR(100 MHz, $CDCl_3$), δ(ppm): 168.2, 137.1, 135.3, 134.1, 133.8, 133.4, 133.2, 129.4, 129.0, 128.3, 128.0, 127.9, 127.8, 127.0, 126.4, 126.2, 126.1, 74.6, 71.2, 63.6, 57.4, 53.9, 53.9, 53.9, 55.3, 45.5, 41.9, 24.1, 24.1.

1-(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)-2-(piperidin-1-yl)ethan-1-one (UA3-04) Light yellow oil, yield 64%**,** ESI-MS *m/z* 541.2 $[M+H]^+$;

^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.82 (1H, m), 7.75 (1H, s), 7.56 (1H, d, J=8.4 Hz), 7.48 (3H, m), 7.38 (1H, d, *J*=2.0 Hz), 7.32 (1H, dd, *J*=8.4, 2.0 Hz), 5.04 (1H, dd, *J*=8.8, 2.8 Hz), 4.71 (1H, d, *J*=12.2 Hz), 4.42 (1H, d, *J*=12.2 Hz), 3.57 (4H, m), 3.15 (2H, s), 2.73 (1H, dd, *J*=13.6, 8.8 Hz), 2.48 (9H, m), 1.57 (4H, m), 1.39 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 168.2, 137.1, 135.3, 134.1, 133.8, 133.4, 133.2, 129.4, 129.0, 128.3, 128.0, 127.9, 127.8, 127.0, 126.4, 126.2, 126.0, 74.6, 71.2, 63.7, 54.3, 54.3, 54.3, 54.0, 53.4, 45.7, 42.0, 25.9, 25.9, 23.9.

1-(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)-2-(4-methylpiperazin-1-yl)ethan-1-one (UA3-05) Yellow oil, yield 61%**,** ESI-MS *m/z* 556.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.83 (3H, m), 7.74 (1H, s), 7.56 (1H, d, *J*=8.4 Hz), 7.49 (3H, m), 7.39 (1H, d, *J*=1.8 Hz), 7.32 (1H, dd, *J*=8.4, 1.8 Hz), 5.03 (1H, dd, *J*=8.7, 2.5 Hz), 4.71 (1H, d, *J*=12.2 Hz), 4.42 (1H, d, *J*=12.2 Hz), 3.57 (4H, m), 3.14 (2H, s), 2.74 (1H, dd, *J*=13.6, 8.7 Hz), 2.48 (13H, m), 2.30 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 168.0, 137.1, 135.3, 134.1, 133.8, 133.4, 133.2, 129.4, 129.0, 128.3, 128.0, 127.9, 127.8, 127.0, 126.4, 126.2, 126.1, 74.6, 71.2, 63.7, 61.4, 55.1, 55.0, 54.0, 53.4, 53.1, 53.0, 46.1, 45.7, 42.0.

1-(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)-2-(4-methylpiperazin-1-yl)ethan-1-one (UA3-06) Yellow oil, yield 60%, ESI-MS *m/z* 570.3 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.82 (3H, m), 7.74 (1H, s), 7.56 (1H, d, *J*=8.4 Hz), 7.48 (3H, m), 7.38 (1H, d, *J*=1.6 Hz), 7.32 (1H, d, *J*=8.4 Hz), 5.03 (1H, d, *J*=8.8 Hz), 4.70 (1H, d, *J*=12.2 Hz), 4.40 (1H, d, *J*=12.2 Hz), 3.59 (4H, m), 3.13 (2H, s), 2.73 (1H, dd, *J*=13.6, 8.8 Hz), 2.47 (13H, m), 1.08 (3H, dd, *J*=14.0, 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 168.0, 137.1, 135.3, 134.1, 133.7, 133.4, 133.2, 129.4, 129.0, 128.3, 128.0, 127.9, 127.8, 127.0, 126.4, 126.2, 126.0, 74.6, 71.2, 63.7, 61.4, 54.0, 53.4, 53.2, 53.2, 52.8, 52.8, 52.4, 45.7, 42.0, 12.0.

1-(4-(2-(2,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)ethyl)piperazin-1-yl)-2-morpholinoethan-1-one (UA3-07) Yellow oil, yield 67%, ESI-MS *m/z* 543.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$), δ(ppm): 7.82 (3H, m), 7.74 (1H, s), 7.56 (1H, d, *J*=8.4 Hz), 7.47 (3H, m), 7.38 (1H, d, *J*=2.0 Hz), 7.32 (1H, dd, *J*=8.4, 2.0 Hz), 5.03 (1H, dd, *J*=8.8, 2.9 Hz), 4.71 (1H, d, *J*=12.2 Hz), 4.41 (1H, d, *J*=12.2 Hz), 3.68 (4H, m), 3.56 (4H, m), 3.13 (2H, s), 2.72 (1H, dd, *J*=13.6, 8.8 Hz), 2.47 (9H, m); ^{13}C-NMR (100 MHz, $CDCl_3$), δ(ppm): 167.6, 137.0, 135.2, 134.1, 133.7, 133.3, 133.2, 129.4, 129.0, 128.3, 128.0, 127.9, 127.9, 127.0, 126.4, 126.2, 126.0, 74.5, 71.2, 67.0, 67.0, 63.6, 61.6, 53.9, 53.6, 53.6, 53.4, 46.0, 45.7, 42.0.

Supplementary Results

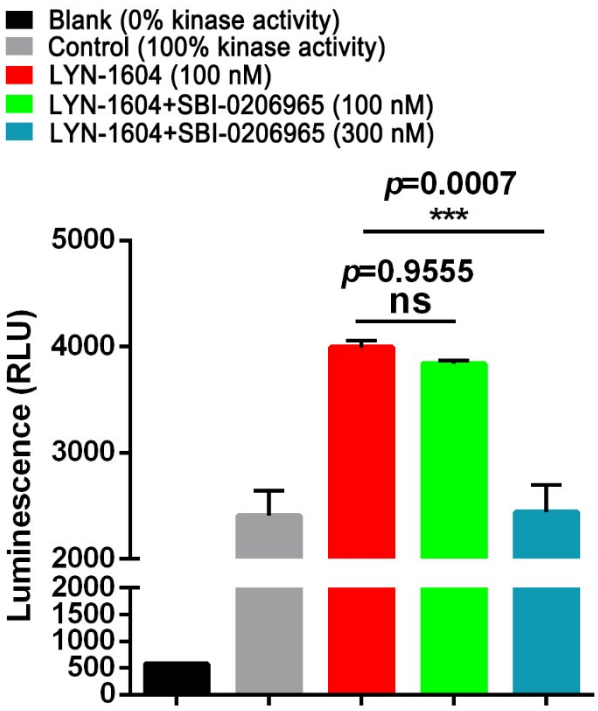


Fig. S1 The ULK1 inhibitor SBI-0206965 inhibits LYN-1604-induced increase of ULK1 kinase activity. ULK1 kinase activity was performed with indicated concentrations of SBI-0206965 in the presence of 100 nM LYN-1604. The luminescence (RLU) of was determined by ADP-Glo ULK1 kinase assay. Blank: no ULK1 kinase (0% kinase activity), Control: containing ULK1 kinase (100% kinase activity). ***p<0.001, *vs.* LYN-1604 group.

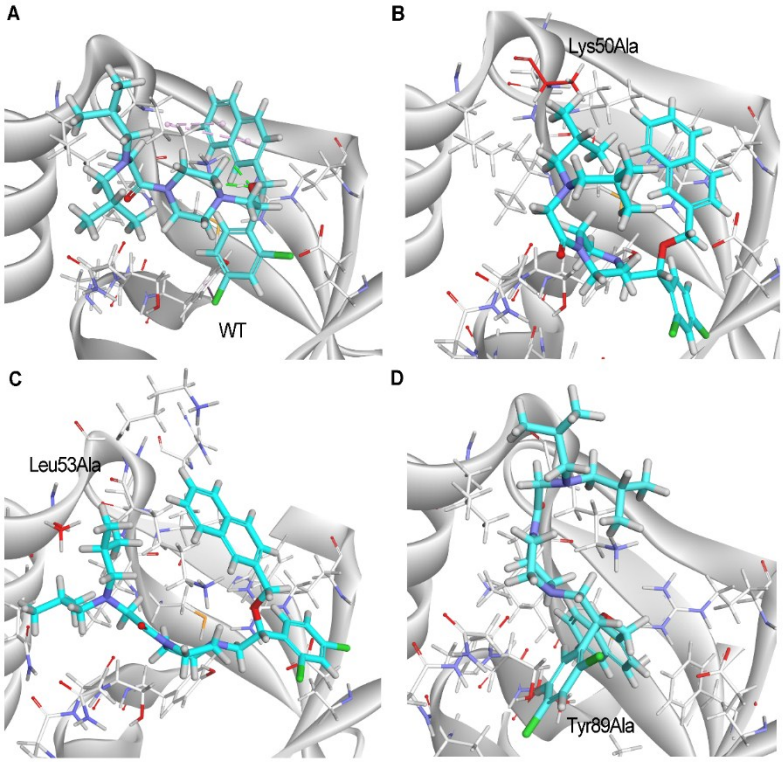


Fig. S2 The binding conformations of LYN-1604 with wild-type and mutant ULK1.

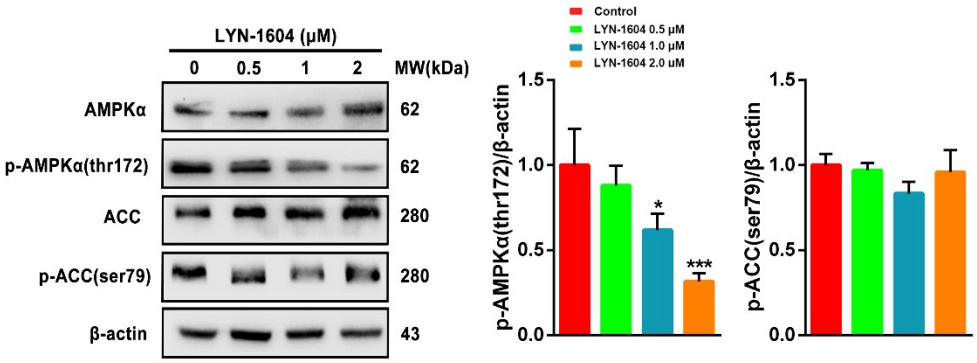


Fig. S3 LYN-1604 decreases the AMPK activity. The MDA-MB-231 cells were treated with LYN-1604 for 24 h, the expression levels of AMPK, p-AMPK (thr172), ACC and p-ACC (ser79) were determined by western blot analysis. β-actin was measured as loading control.

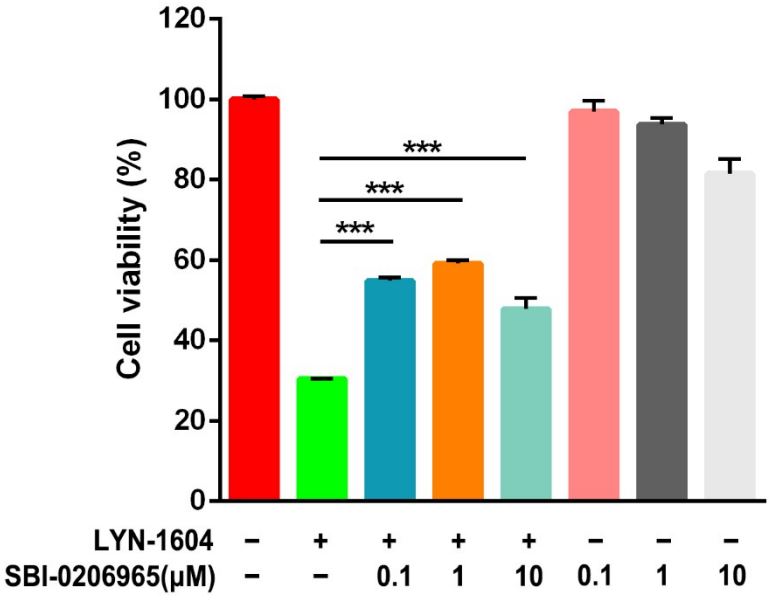


Fig. S4 The ULK1 inhibitor SBI-0206965 restores the decreased cell viability induced by LYN-1604. The MDA-MB-231 cells were co-treated with indicated concentrations of SBI-0206965 in the presence and absence of LYN-1604 for 24 h, then cell viavility was measured by MTT assay. ***p<0.001 *vs.* LYN-1604-treated group.

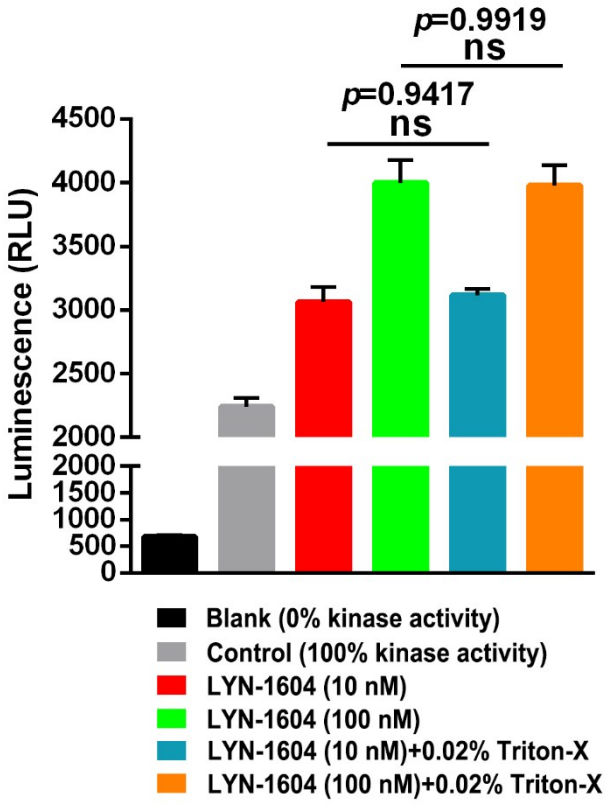


Fig. S5 Triton-X has no effect on LYN-1604-induced increase of ULK1 kinase activity. ULK1 kinase activity was performed with indicated concentrations of LYN-1604 in the presence or absence of 0.02% Triton-X. The luminescence (RLU) of was determined by ADP-Glo ULK1 kinase assay. Blank: no ULK1 kinase (0% kinase activity), Control: containing ULK1 kinase (100% kinase activity).

Figure.S6

Fig. 5F

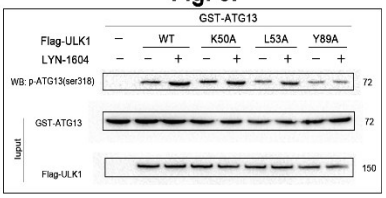


Fig. 6C

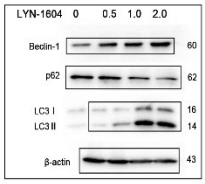


Fig. 6E

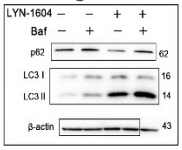


Fig. 7B

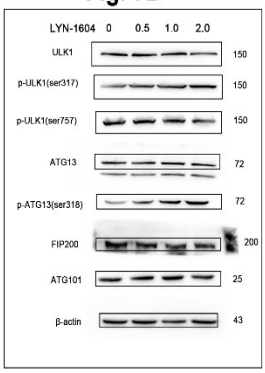


Fig. 7D

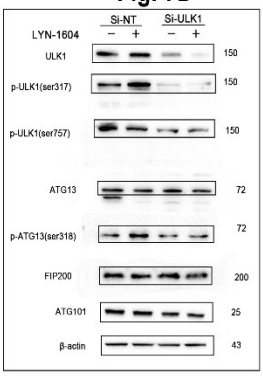


Fig. 7E

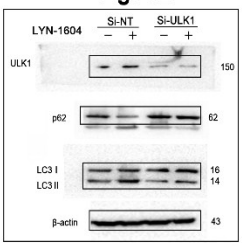


Fig. 7F

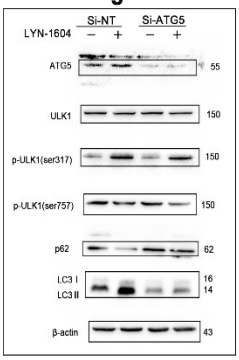


Fig. 9B

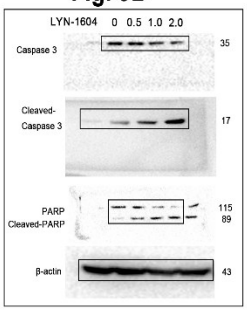


Fig. 9C

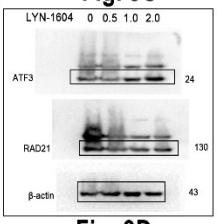


Figure 9F

Fig. 9D

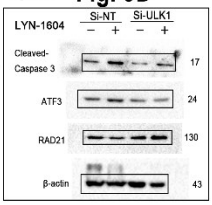


Fig. 10G

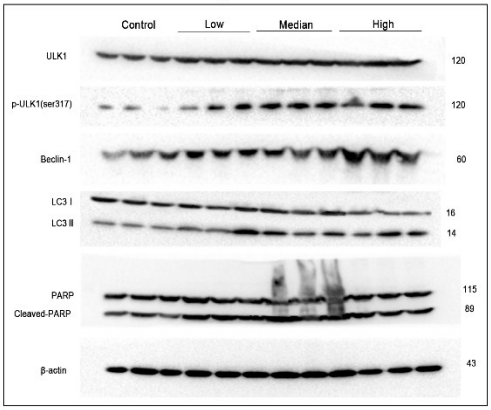


Fig. S3

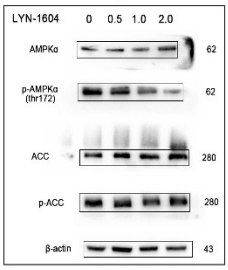
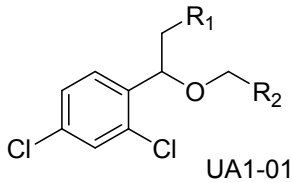
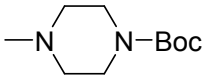
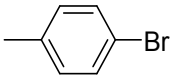
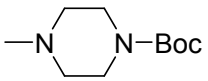
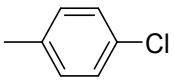
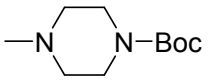
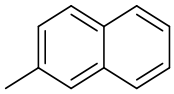
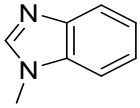
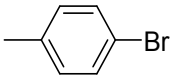
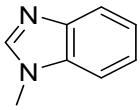
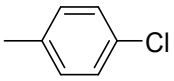
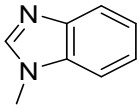
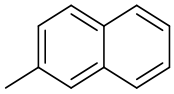
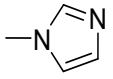
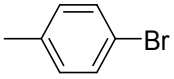
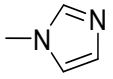
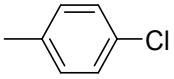
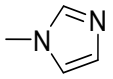
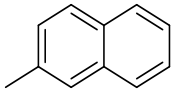
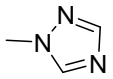
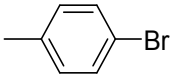
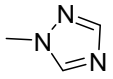
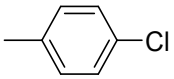
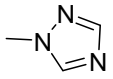
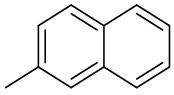


Table S1. Kinase activities of compounds UA1-01-12 against recombinant human ULK1 and relevant anti-proliferative activities in breast cancer cells



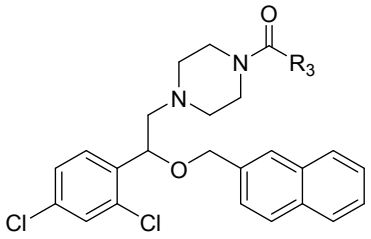
UA1-01-12

Compound	R_1	R_2	Kinase activity% (100 nM)[a]	Anti-proliferative activity (IC_{50}, μM)[b]		
				MCF-7	MDA-MB-231	MDA-MB-468
UA1-01			134.51±6.52	24.14	26.25	22.81
UA1-02			133.36±8.01	26.32	25.40	22.02
UA1-03			153.64±9.77	25.43	20.94	17.64
UA1-04			101.65±1.87	42.91	>50	45.37
UA1-05			104.43±1.91	47.20	>50	48.68
UA1-06			105.80±2.46	37.09	>50	>50
UA1-07			109.96±3.98	>50	49.60	>50
UA1-08			106.08±4.68	>50	41.18	>50
UA1-09			101.87±2.94	48.15	39.75	37.61
UA1-10			110.03±2.53	39.37	35.81	37.99
UA1-11			105.03±3.26	45.62	42.53	40.86
UA1-12			109.99±4.12	41.97	32.98	33.40

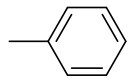
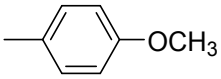
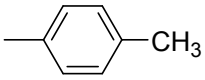
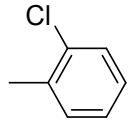
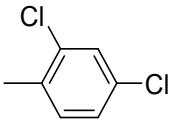
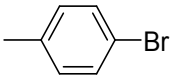
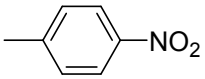
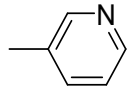
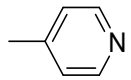
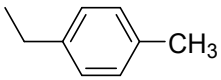
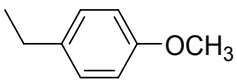
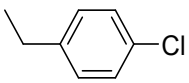
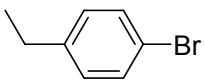
[a] Each compound was tested in triplicate; the data are presented as the mean±SD.

[b] IC_{50} values obtained with cell viability assay for 24 h.

Table S2. Kinase activities of compounds UA2-01-13 against recombinant human ULK1 and relevant anti-proliferative activities in breast cancer cells



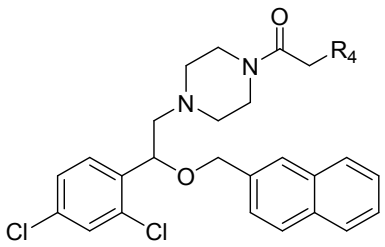
UA2-01~13

Compound	R_3	Kinase activity% (100 nM)[a]	Anti-proliferative activity (IC_{50}, μM)[b]		
			MCF-7	MDA-MB-231	MDA-MB-468
UA2-01		105.62±2.98	>50	>50	>50
UA2-02		113.22±5.33	42.12	40.59	44.73
UA2-03		117.10±4.87	38.41	39.24	43.61
UA2-04		101.82±2.55	>50	47.68	46.91
UA2-05		115.32±6.34	44.48	35.55	38.43
UA2-06		108.86±3.70	>50	45.66	43.50
UA2-07		113.56±4.57	42.76	39.54	38.78
UA2-08		117.40±5.68	29.66	26.51	38.06
UA2-09		112.09±6.89	39.98	37.21	42.44
UA2-10		141.37±3.82	29.32	24.97	25.07
UA2-11		146.17±4.56	23.81	24.48	21.10
UA2-12		160.29±2.87	17.88	15.52	15.04
UA2-13		149.24±4.36	18.62	17.23	19.69

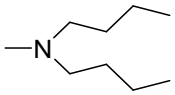
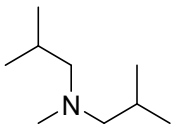
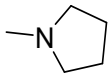
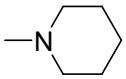
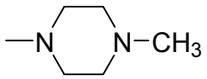
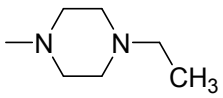
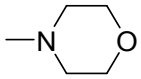
[a] Each compound was tested in triplicate; the data are presented as the mean±SD.

[b] IC_{50} values obtained with cell viability assay for 24 h.

Table S3. Kinase activities of compounds UA3-01-07 against recombinant human ULK1 and relevant anti-proliferative activities in breast cancer cells



UA3-01~07

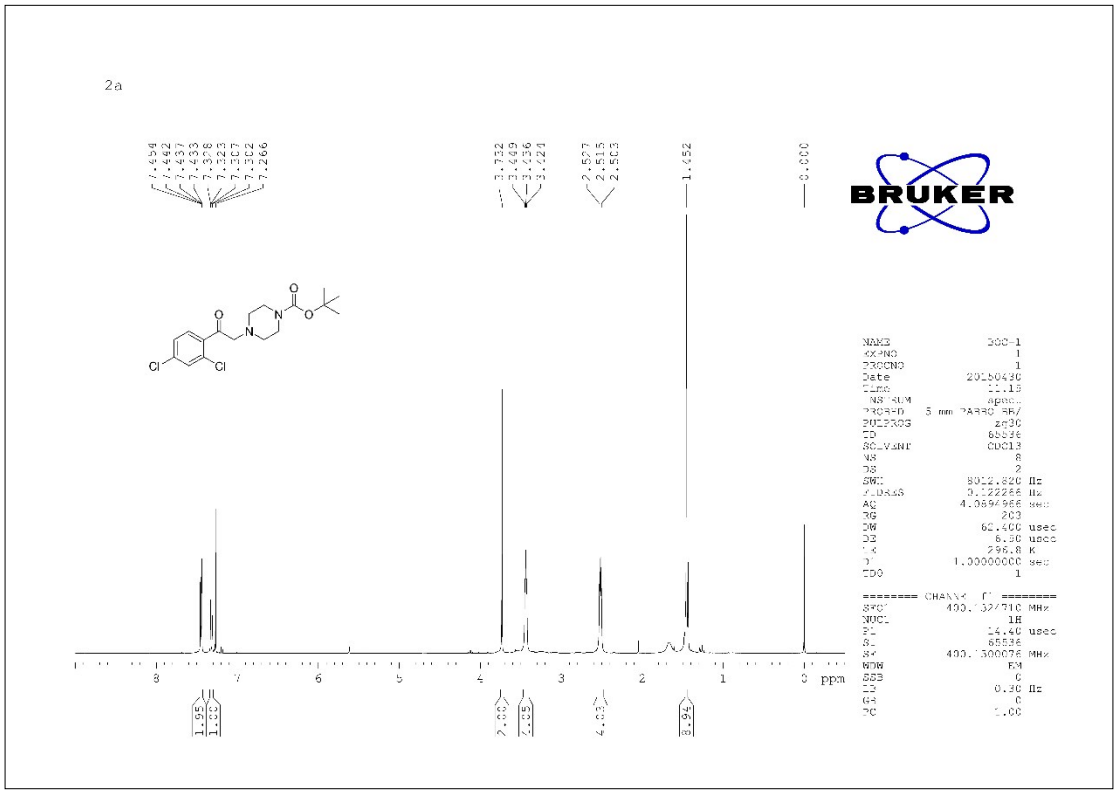
Compound	R_4	Kinase activity% (100 nM) [a]	Anti-proliferative activity (IC_{50}, μM) [b]		
			MCF-7	MDA-MB-231	MDA-MB-468
UA3-01		115.14±4.22	>50	32.86	38.34
UA3-02		195.70±6.93	4.69	1.66	4.68
UA3-03		177.83±4.87	5.39	3.38	5.89
UA3-04		166.51±7.56	17.63	8.08	13.54
UA3-05		162.97±6.44	7.13	4.20	5.81
UA3-06		118.26±3.68	>50	37.56	28.98
UA3-07		107.48±5.60	>50	>50	>50

[a] Each compound was tested in triplicate; the data are presented as the mean±SD.

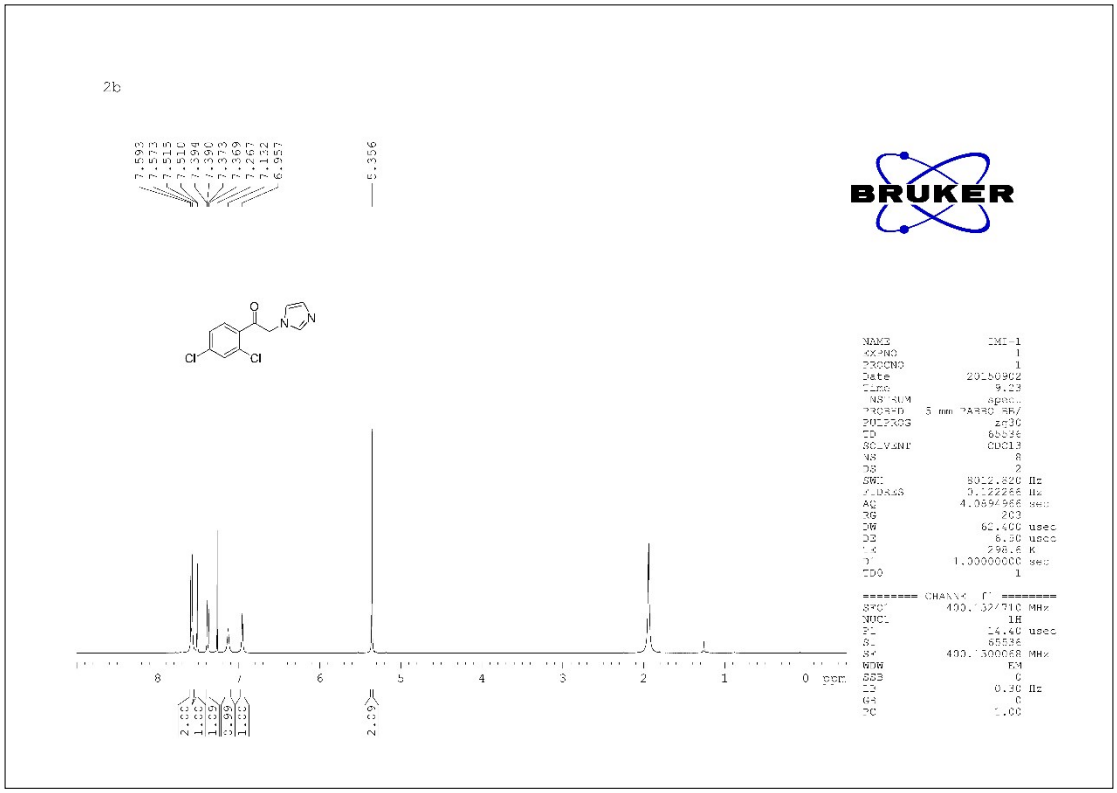
[b] IC_{50} values obtained with cell viability assay for 24 h.

NMR data

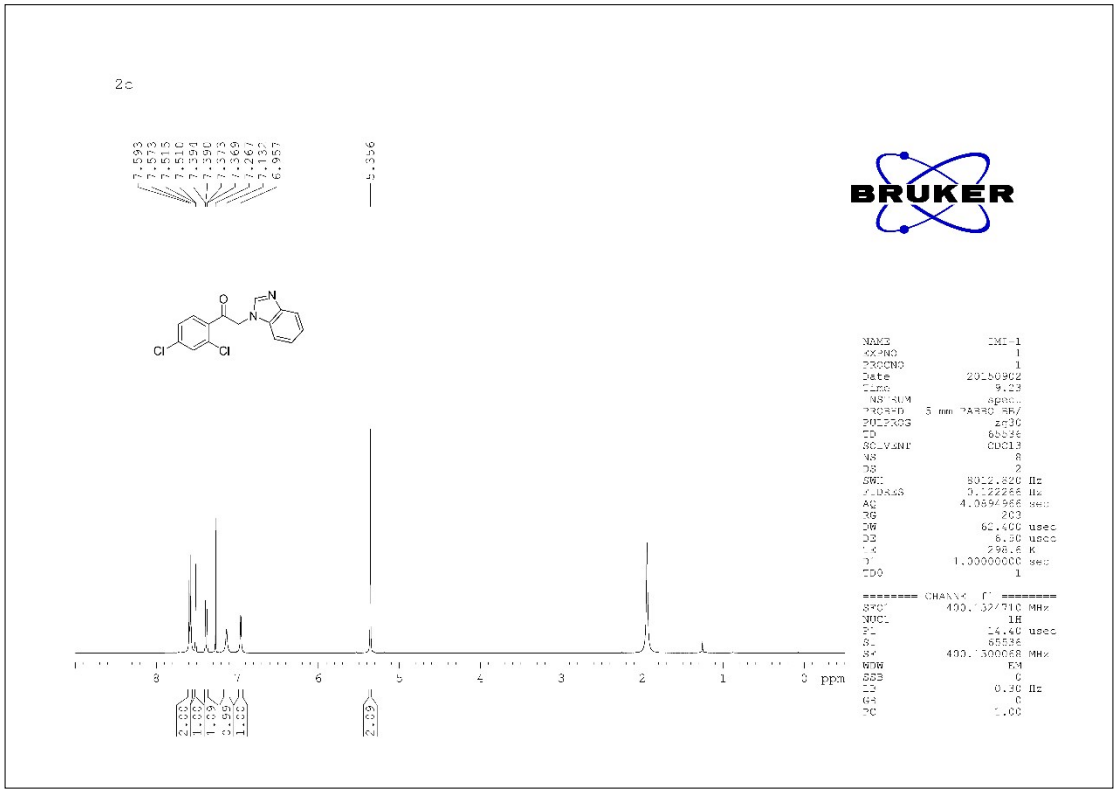
^{1}H-NMR spectrum of **2a**



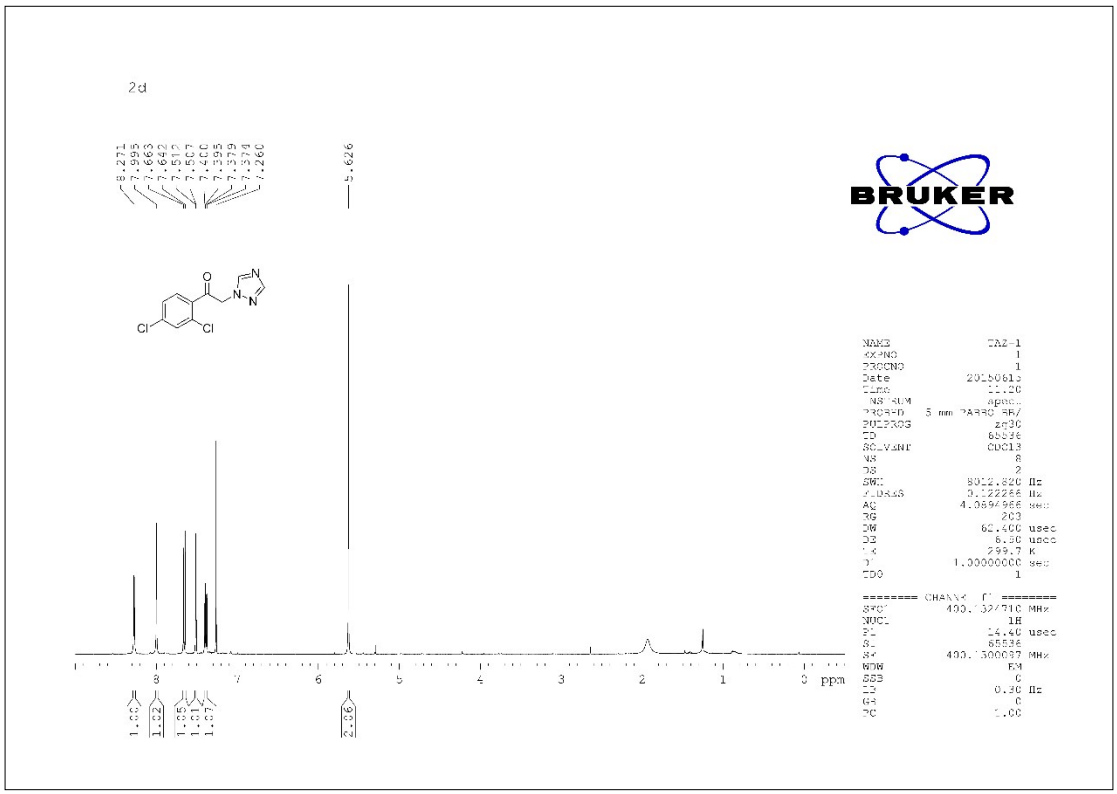
^{1}H-NMR spectrum of **2b**



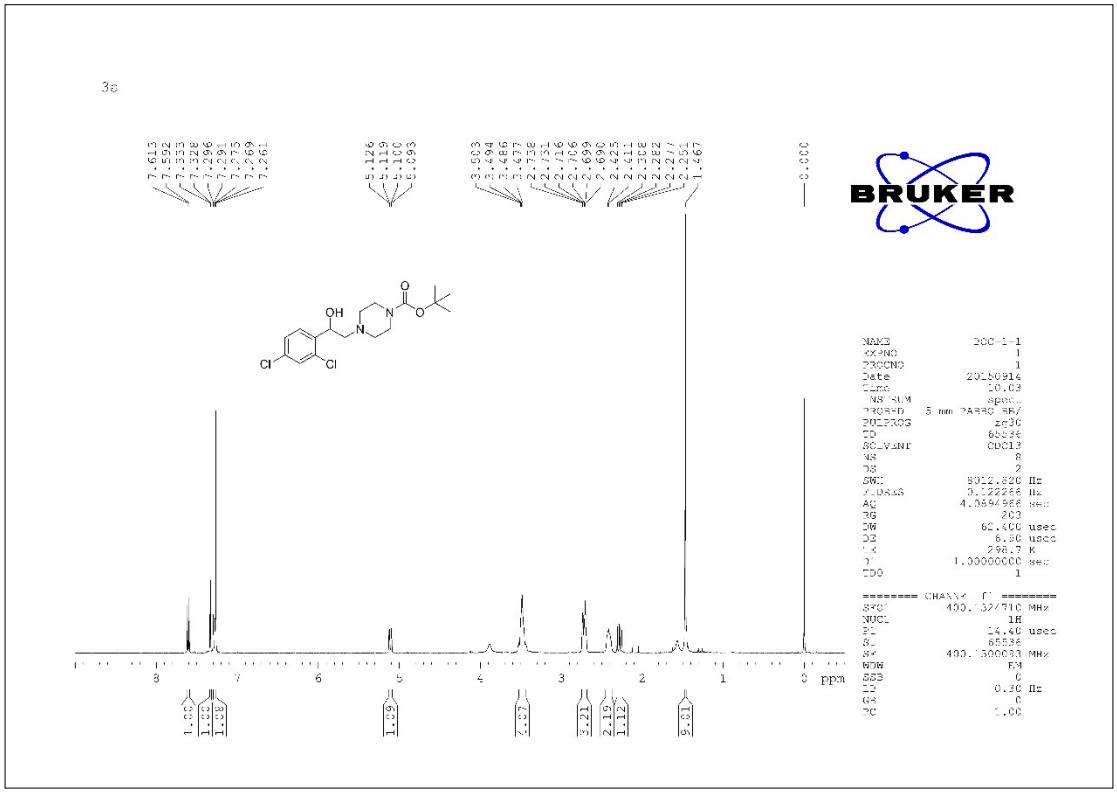
^{1}H-NMR spectrum of **2c**



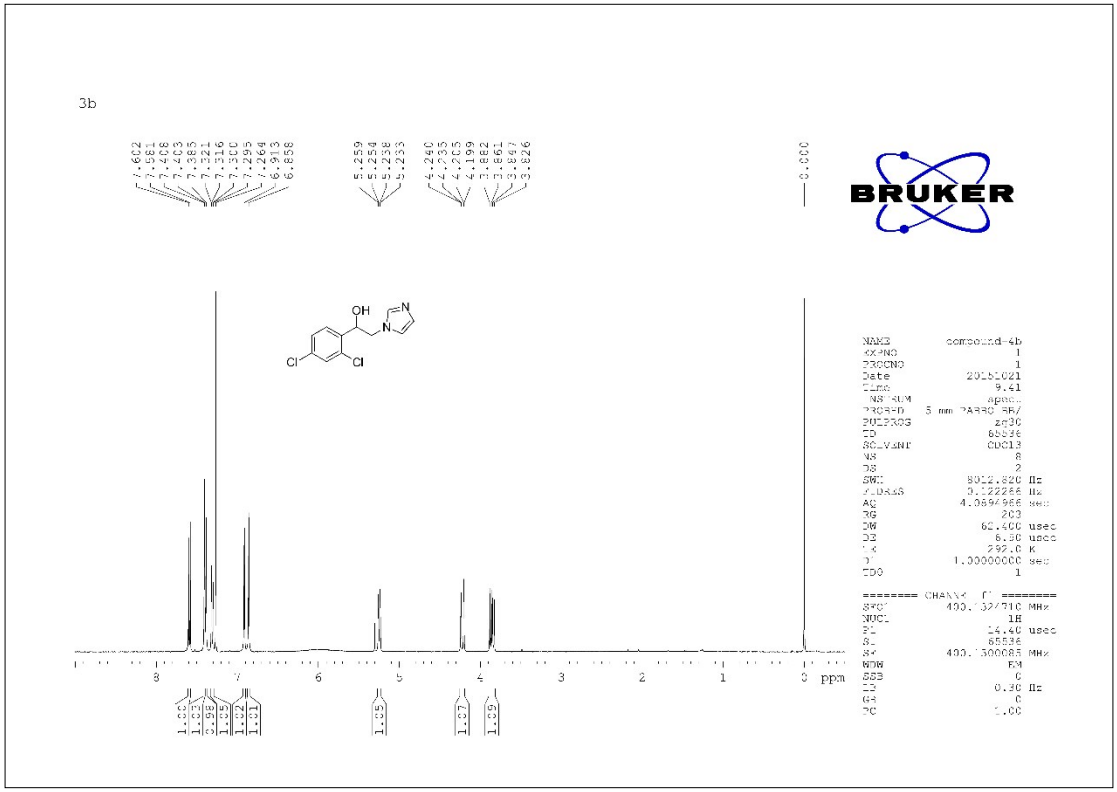
^{1}H-NMR spectrum of **2d**



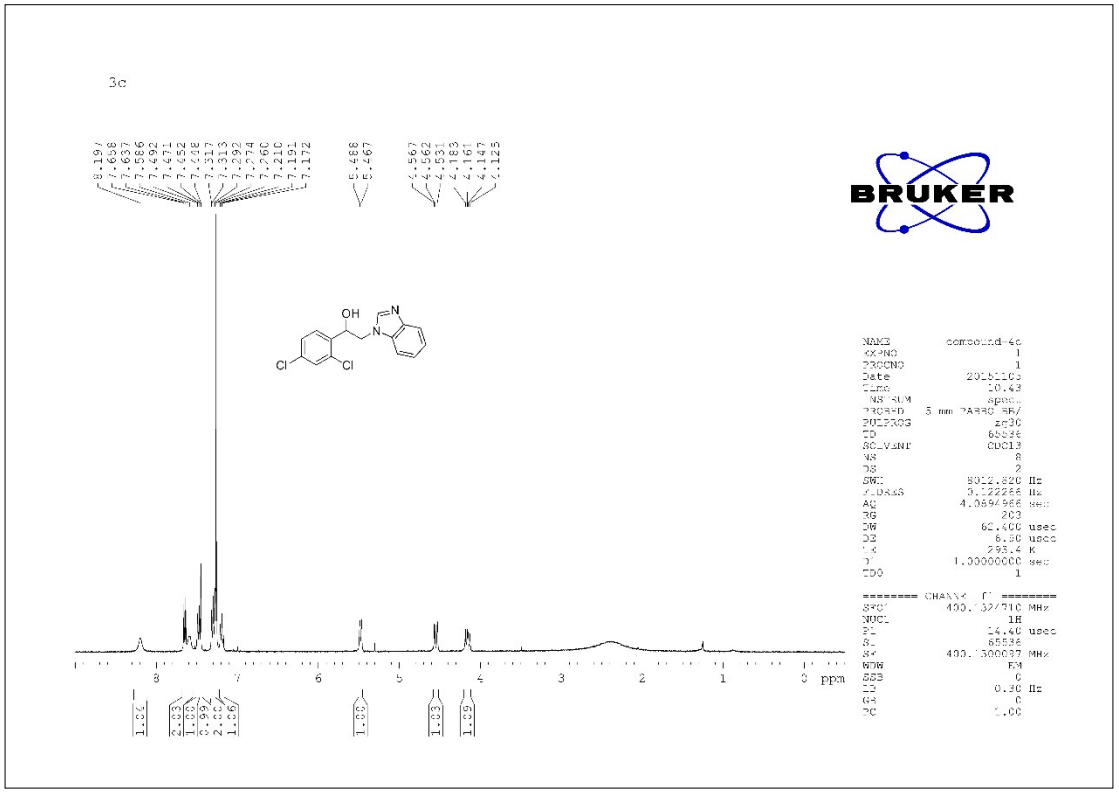
^{1}H-NMR spectrum of **3a**



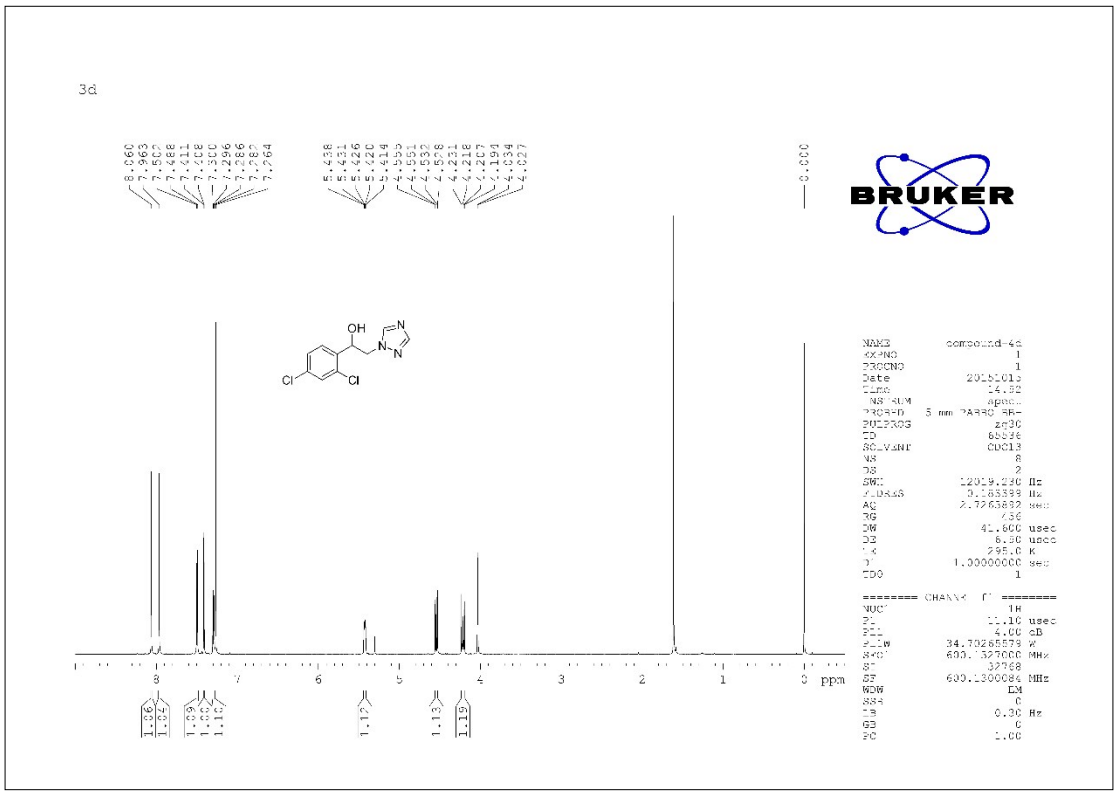
^{1}H-NMR spectrum of **3b**



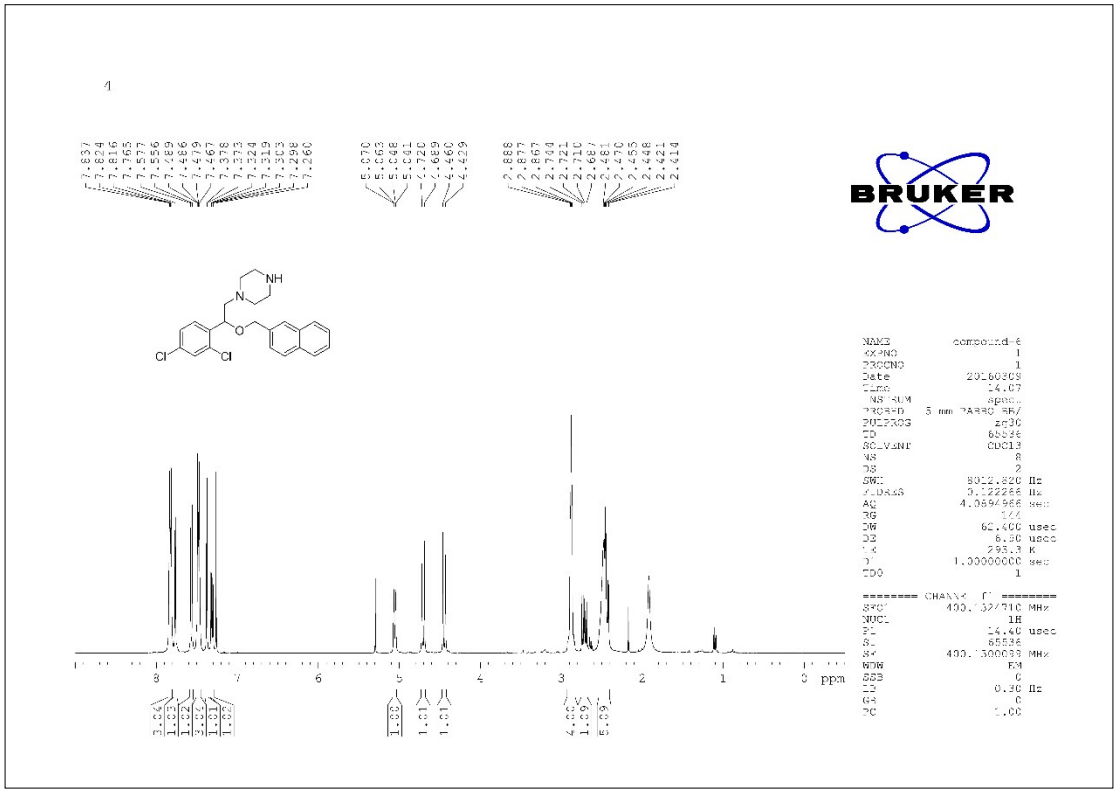
^{1}H-NMR spectrum of **3c**



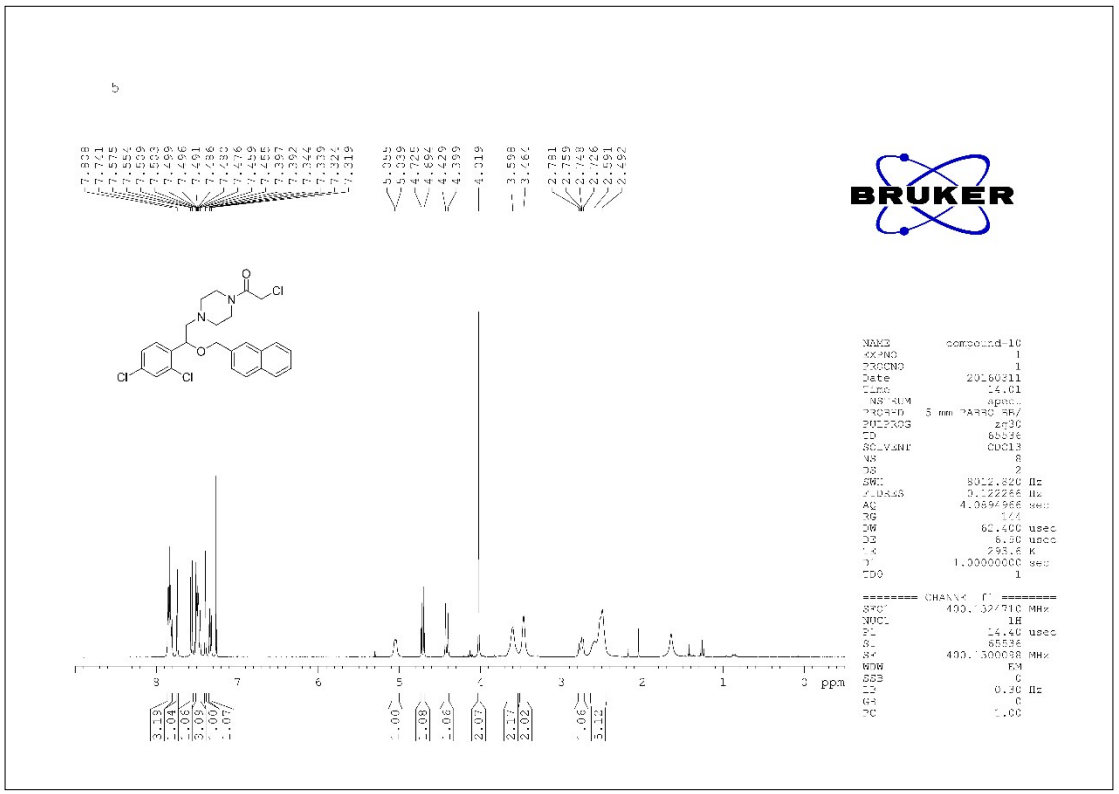
^{1}H-NMR spectrum of **3d**



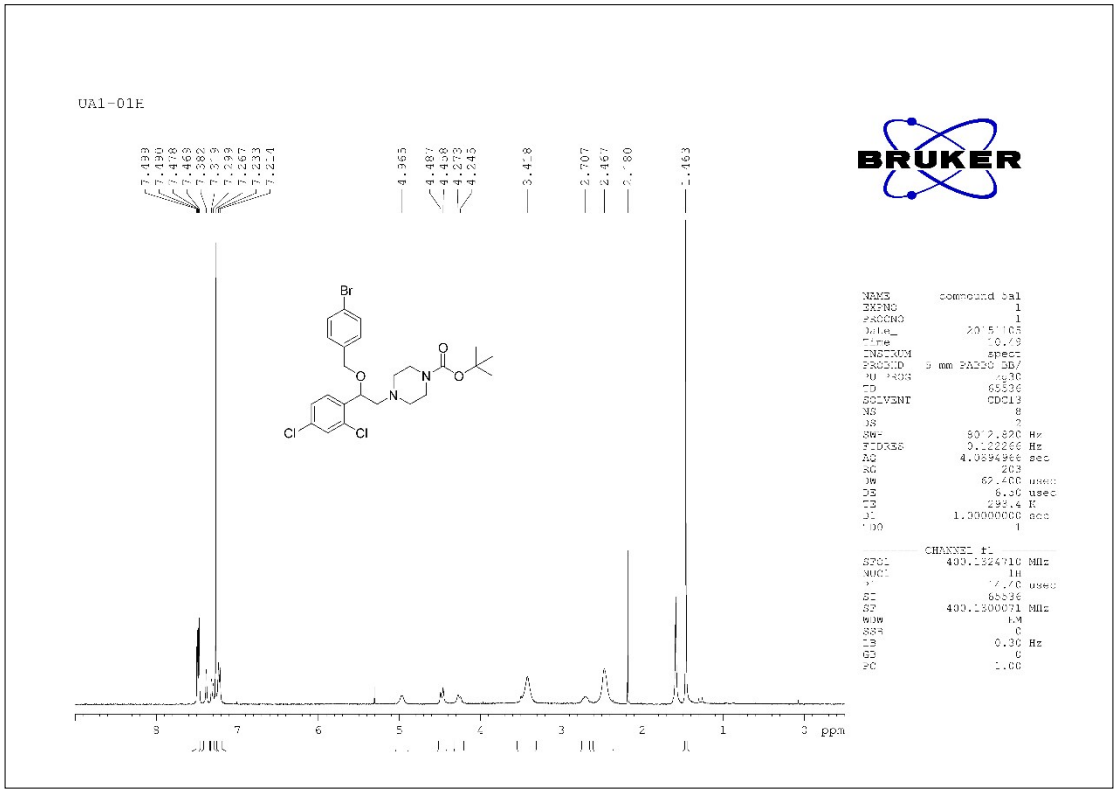
^{1}H-NMR spectrum of **4**



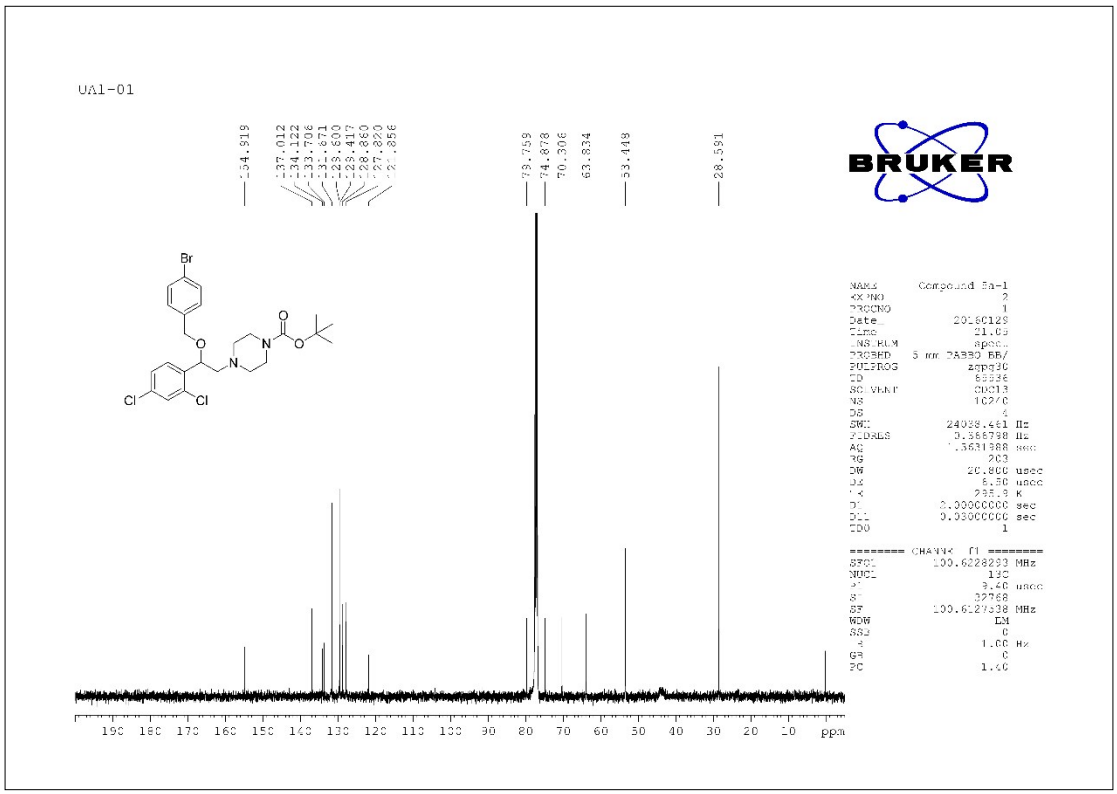
^{1}H-NMR spectrum of **5**



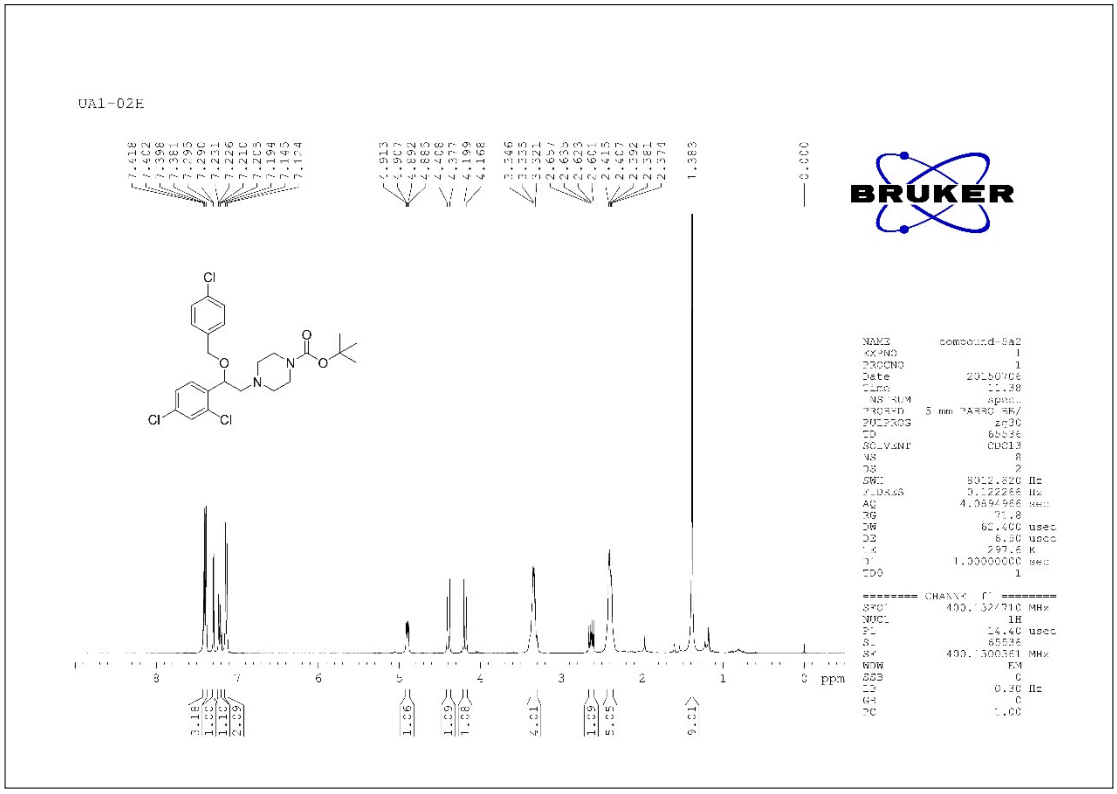
^{1}H-NMR spectrum of **UA1-01**



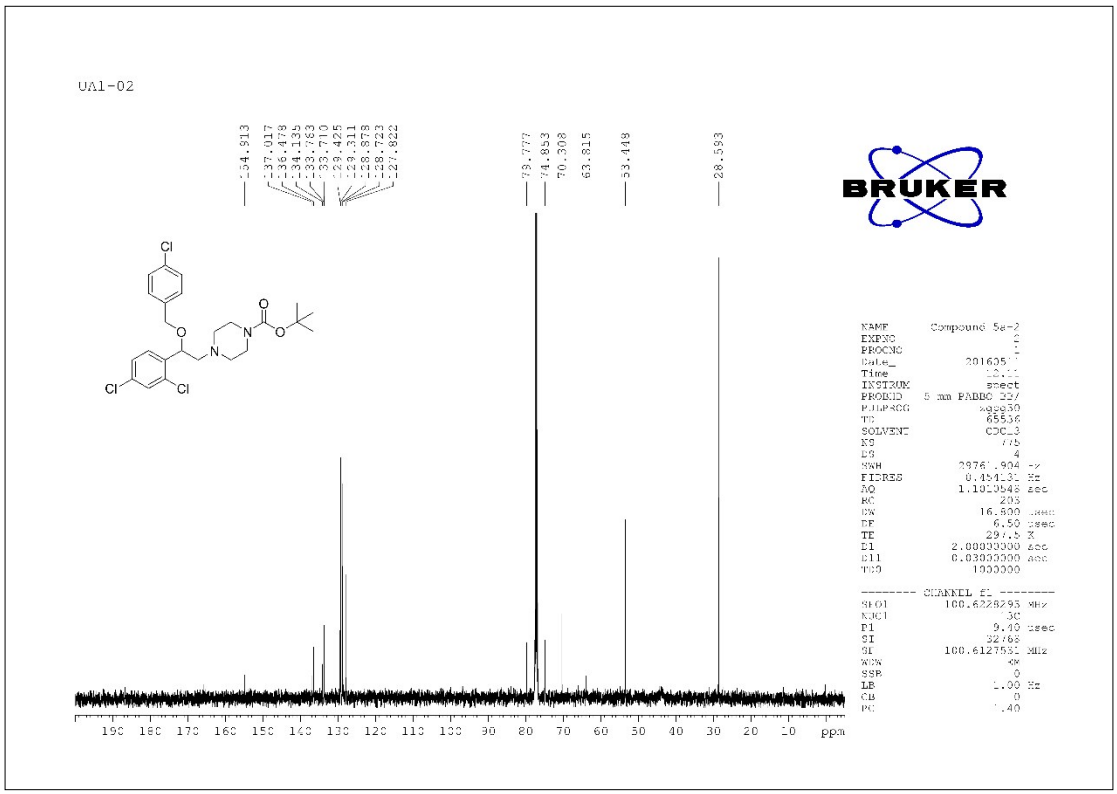
^{13}C-NMR spectrum of **UA1-01**



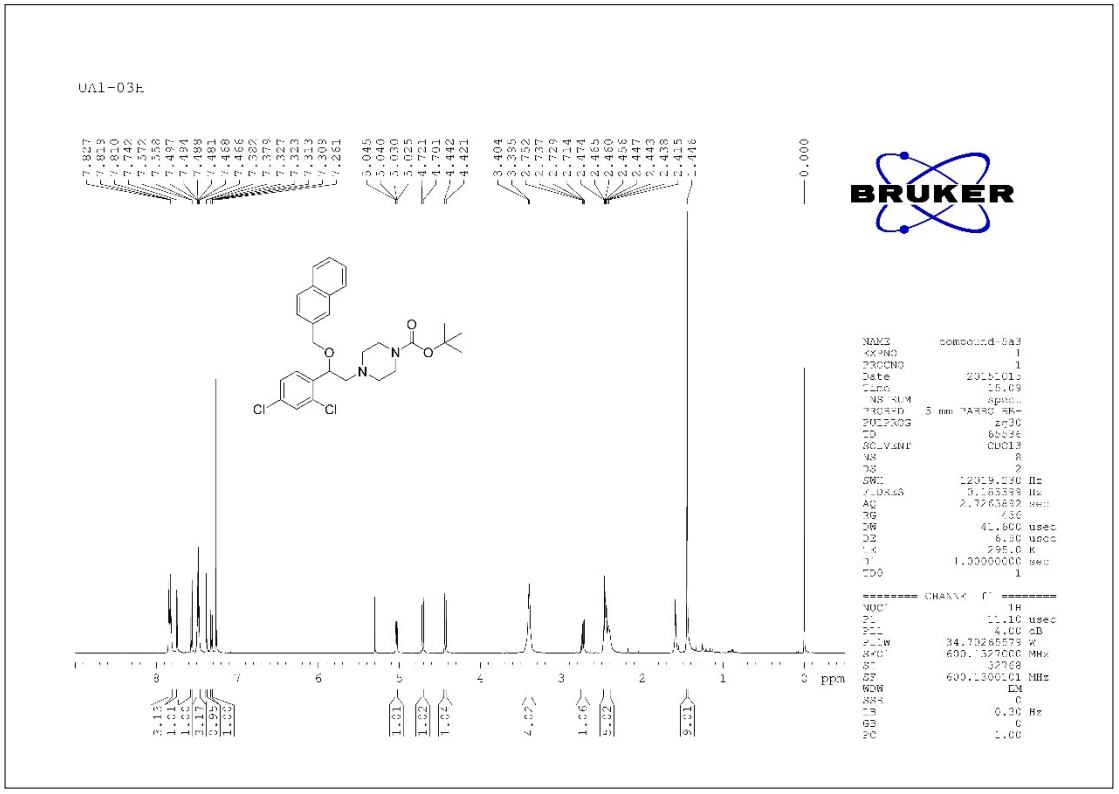
^{1}H-NMR spectrum of **UA1-02**



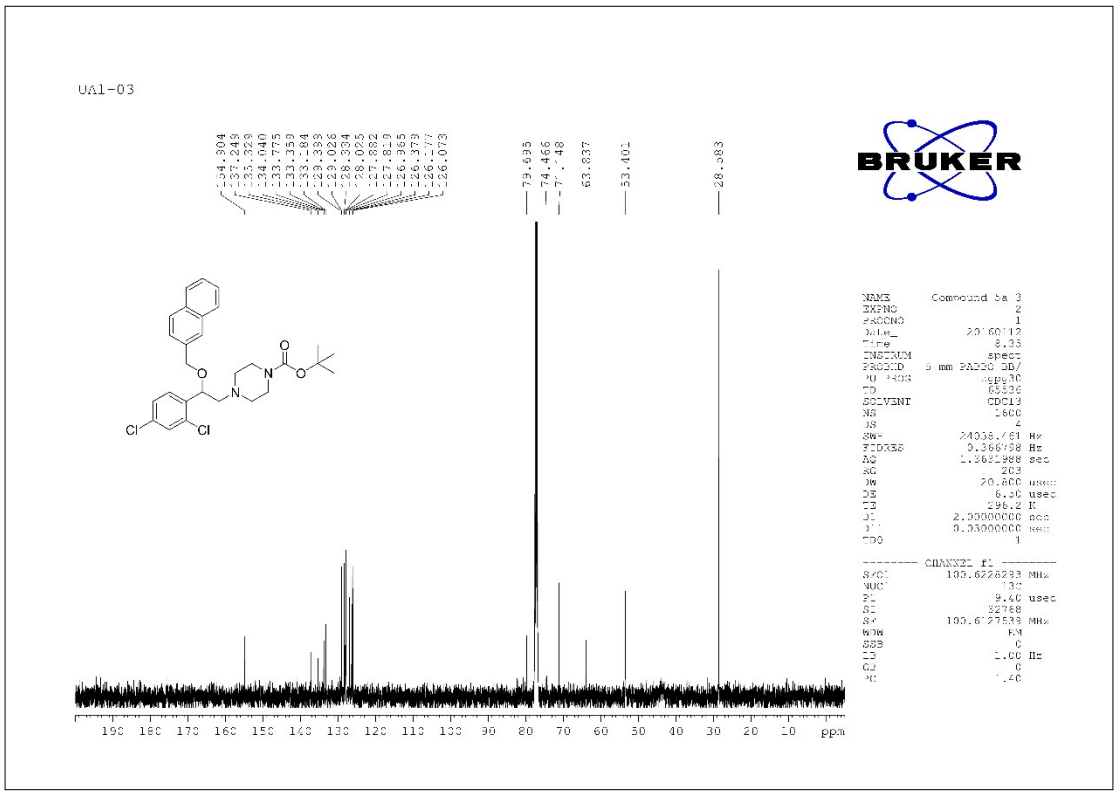
^{13}C-NMR spectrum of **UA1-01**



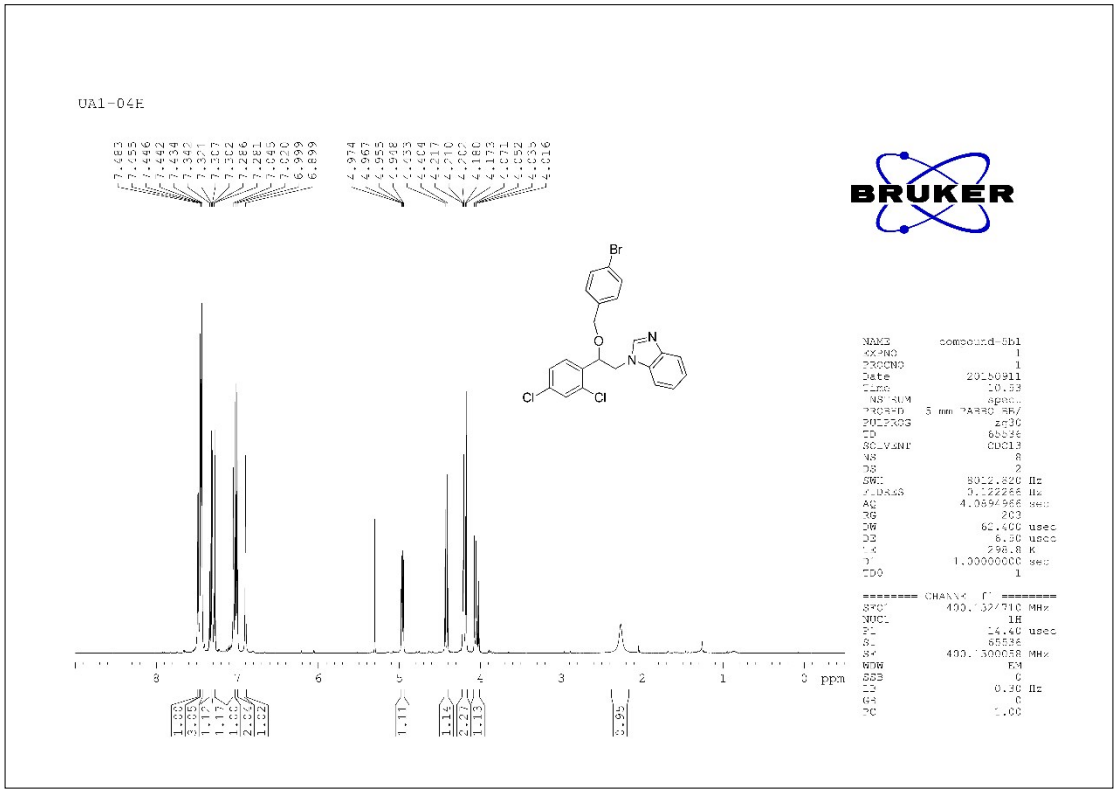
^{1}H-NMR spectrum of **UA1-03**



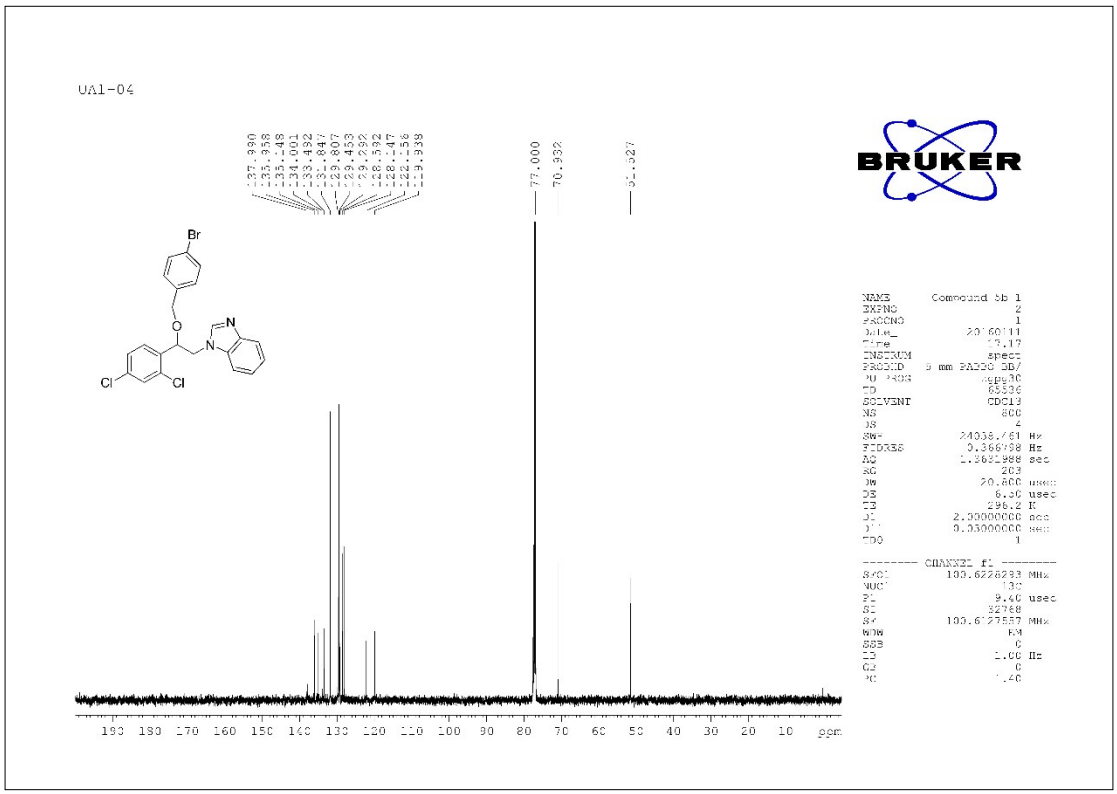
^{13}C-NMR spectrum of **UA1-03**



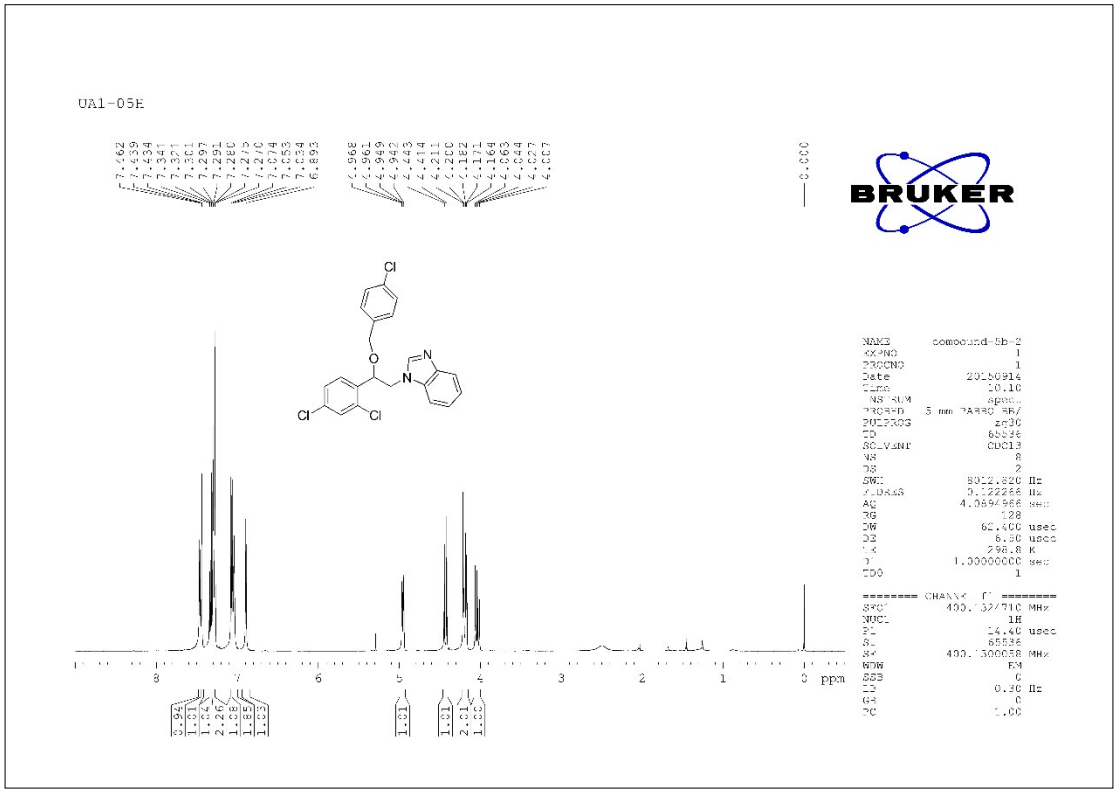
^{1}H-NMR spectrum of **UA1-04**



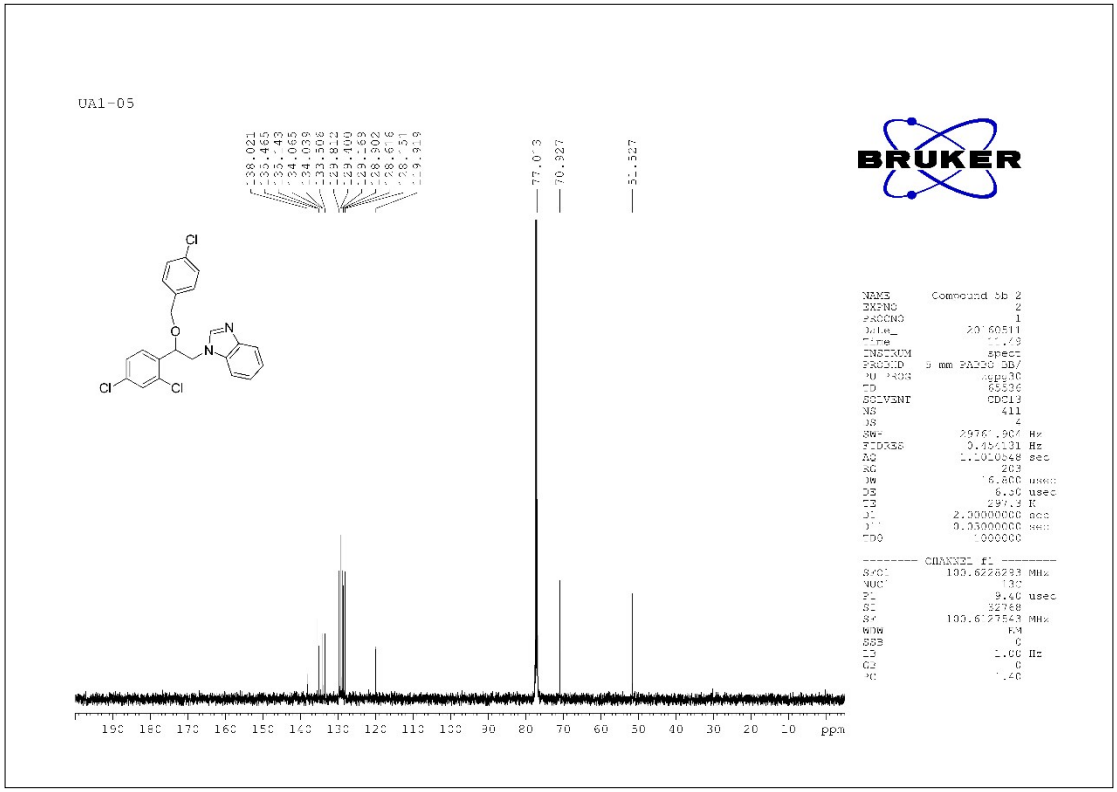
^{13}C-NMR spectrum of **UA1-04**



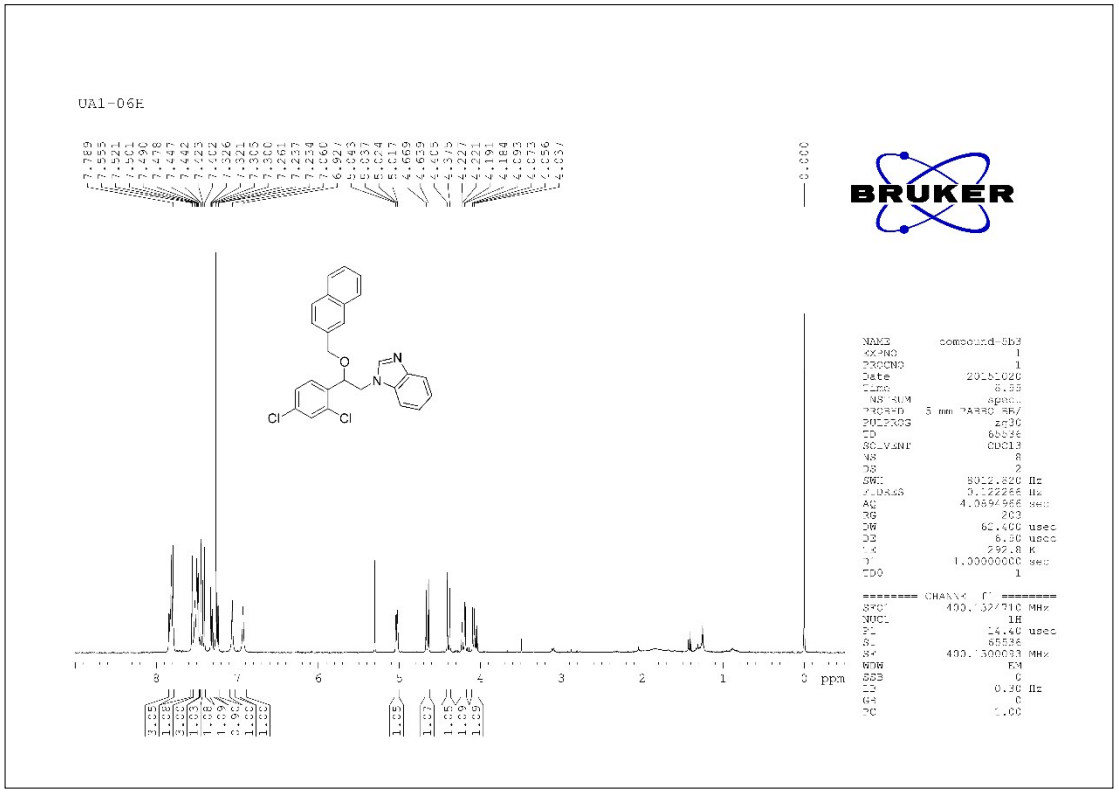
^{1}H-NMR spectrum of **UA1-05**



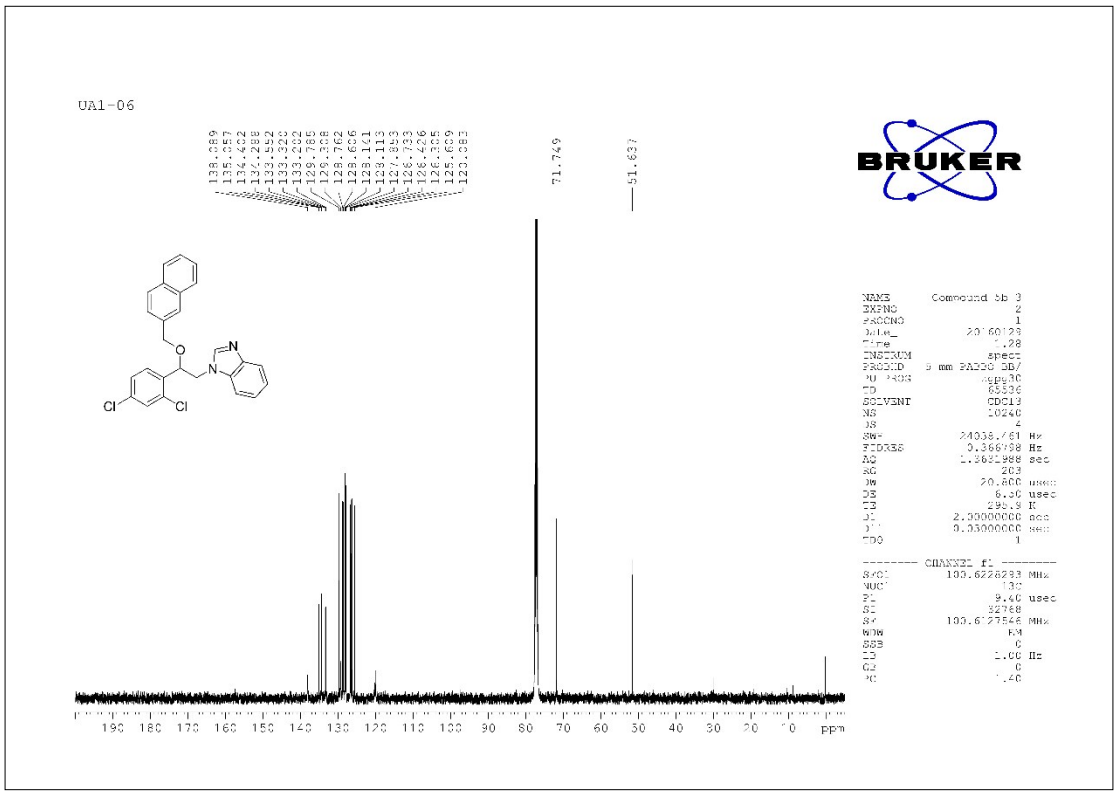
^{13}C-NMR spectrum of **UA1-05**



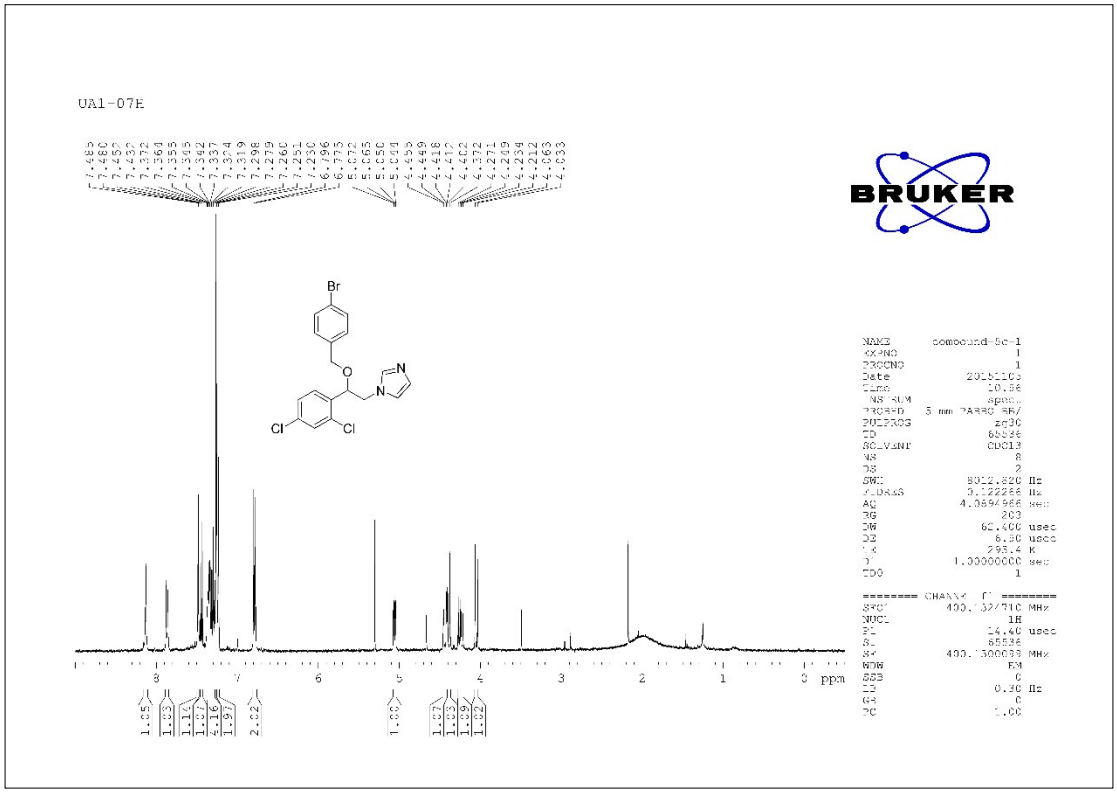
^{1}H-NMR spectrum of **UA1-06**



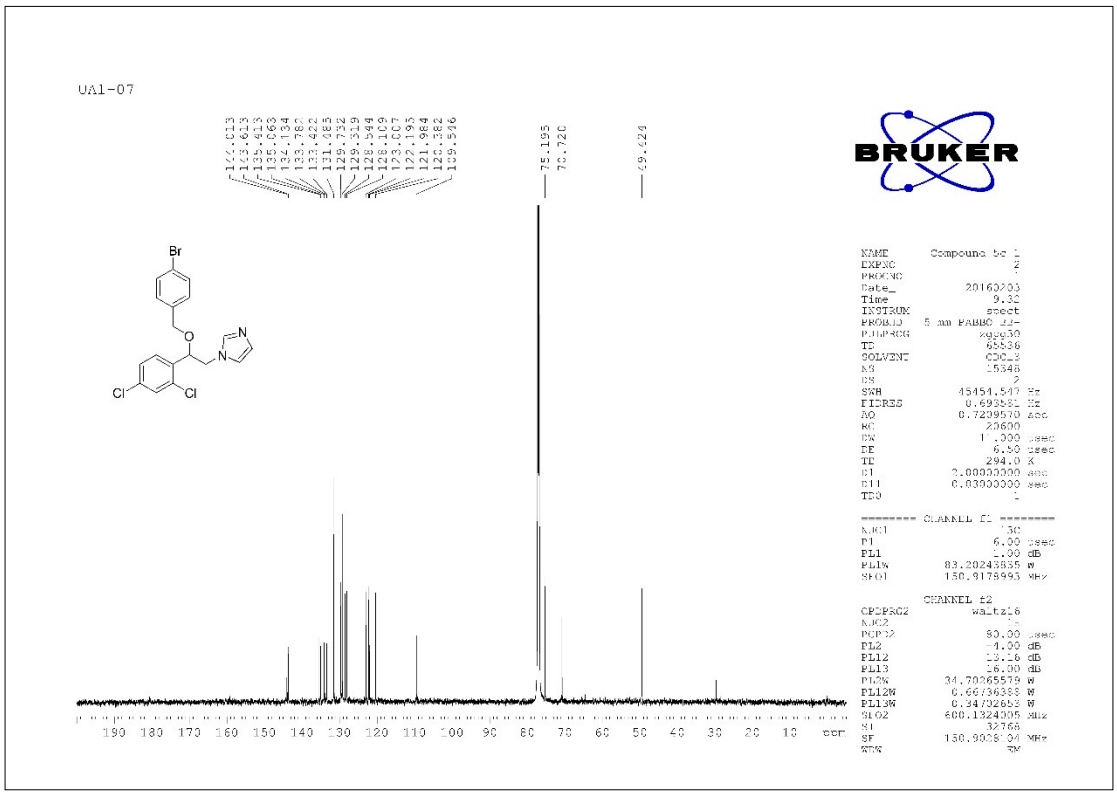
^{13}C-NMR spectrum of **UA1-06**



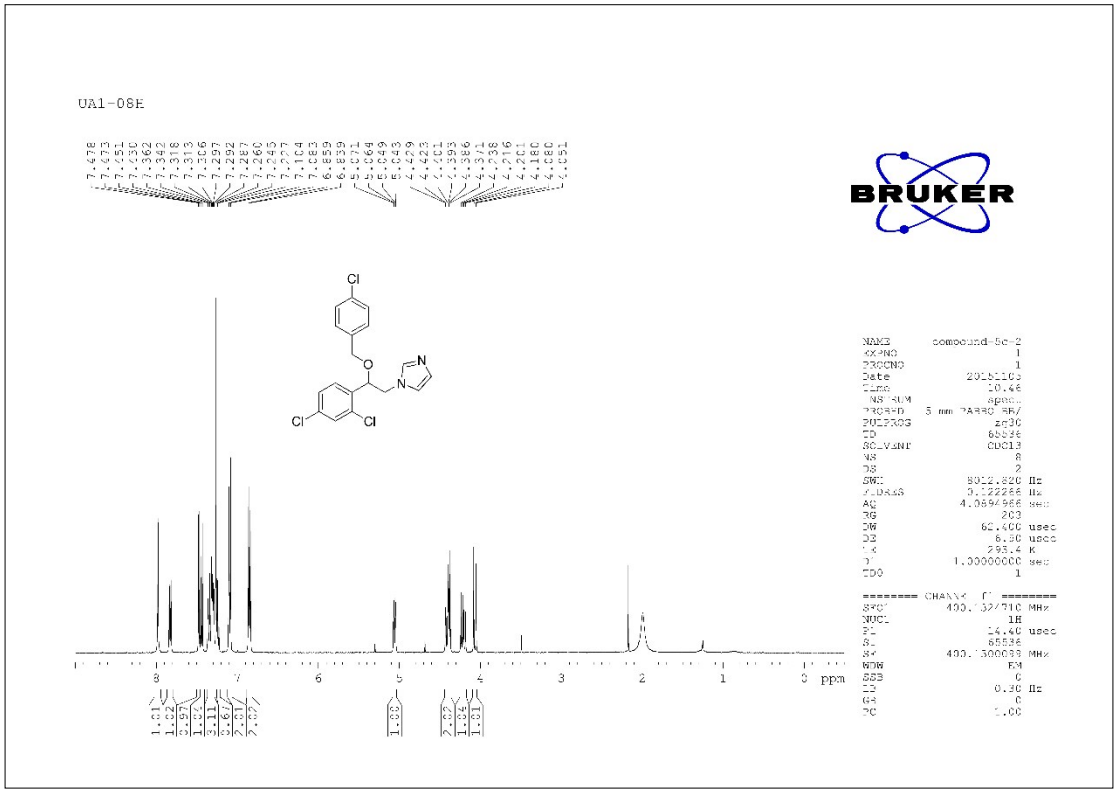
^{1}H-NMR spectrum of **UA1-07**



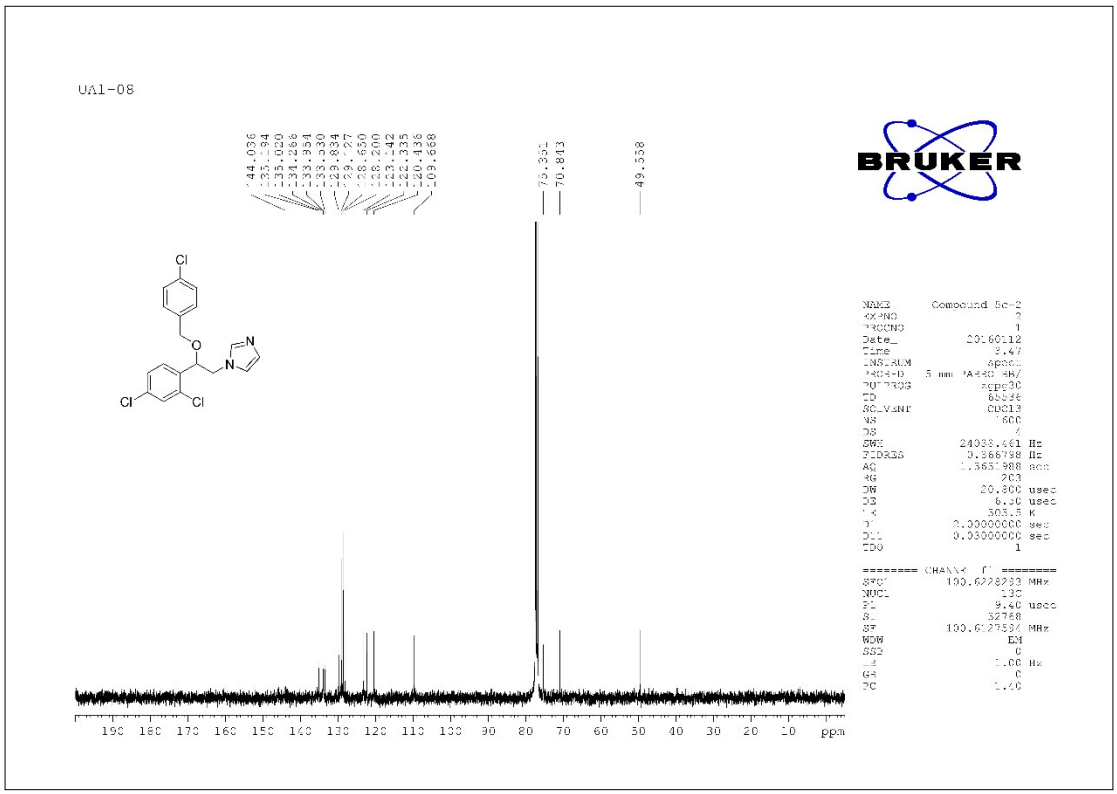
^{13}C-NMR spectrum of **UA1-07**



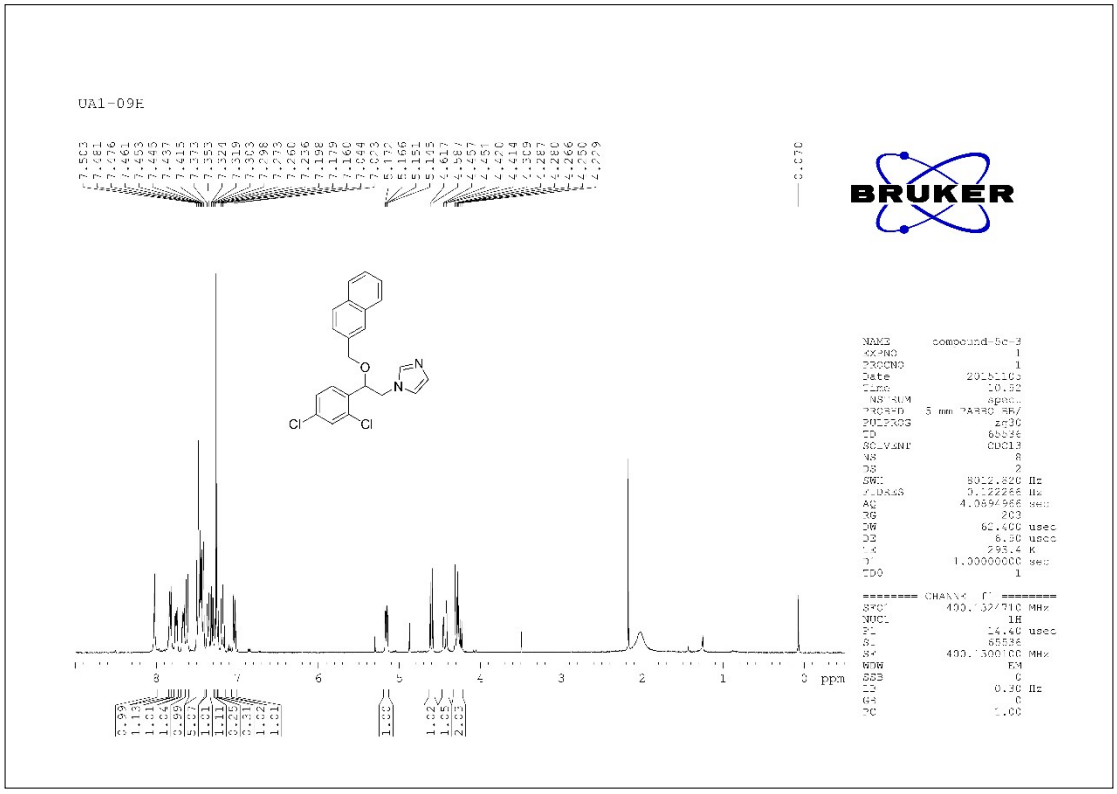
^{1}H-NMR spectrum of **UA1-08**



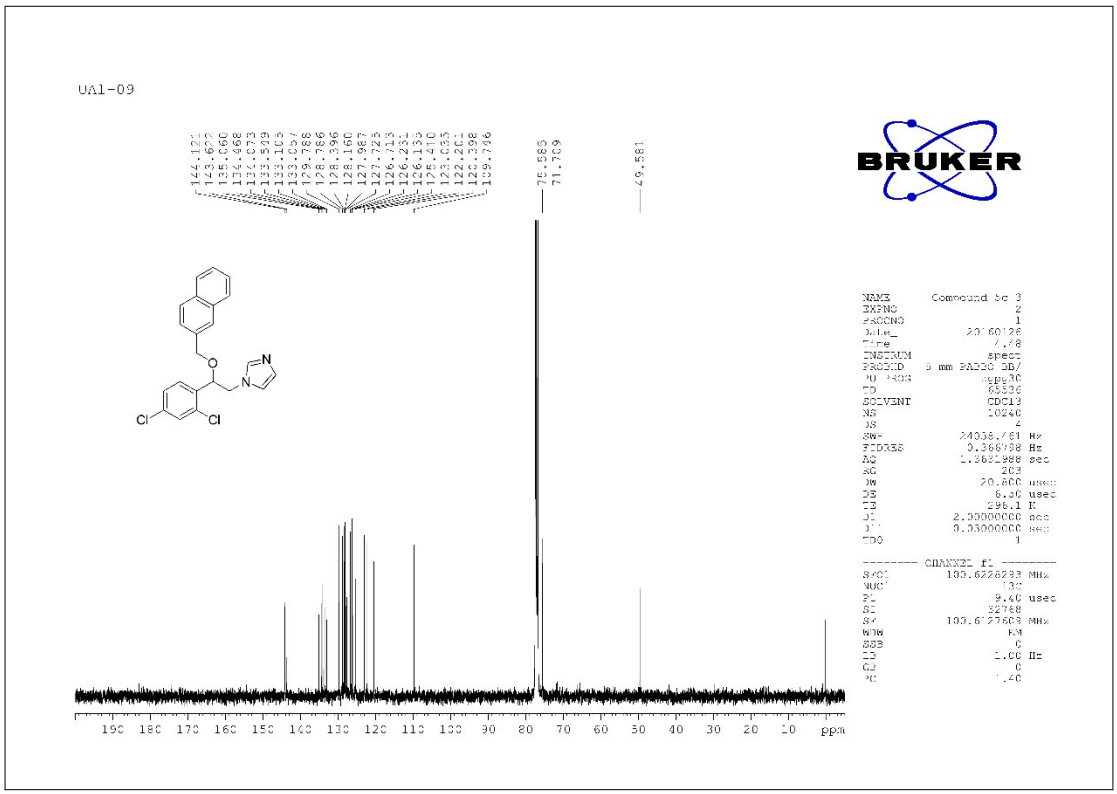
^{13}C-NMR spectrum of **UA1-08**



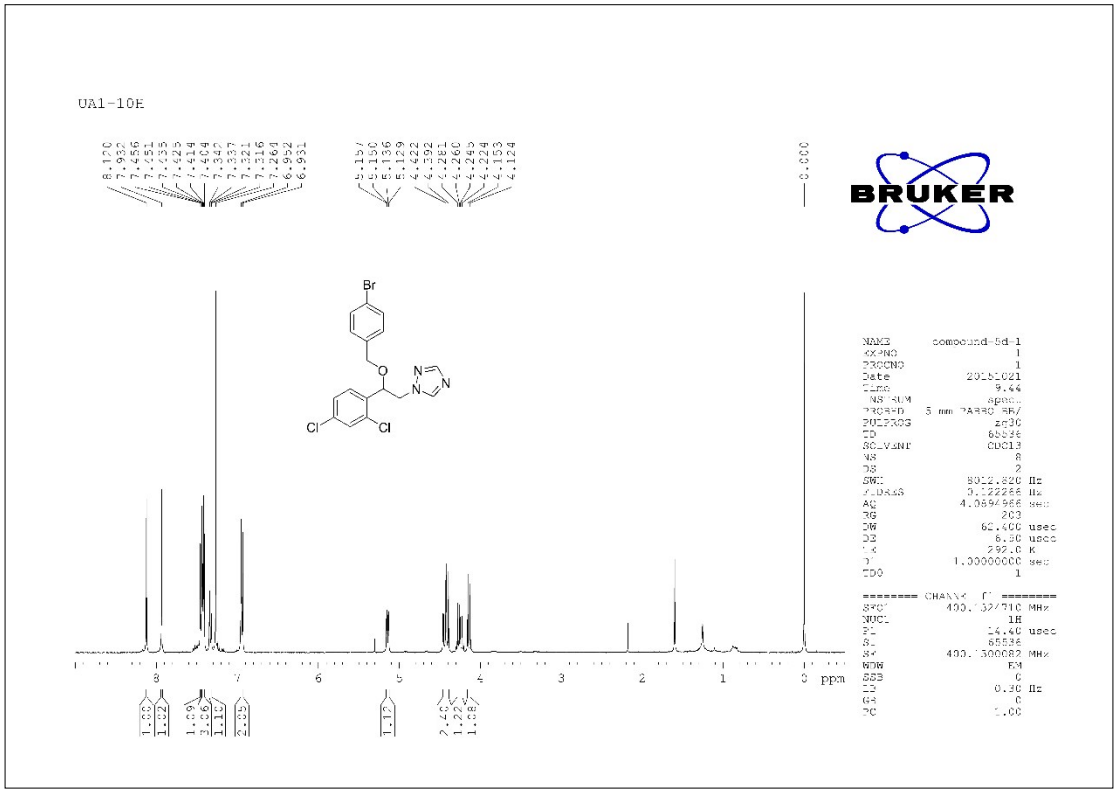
^{1}H-NMR spectrum of **UA1-09**



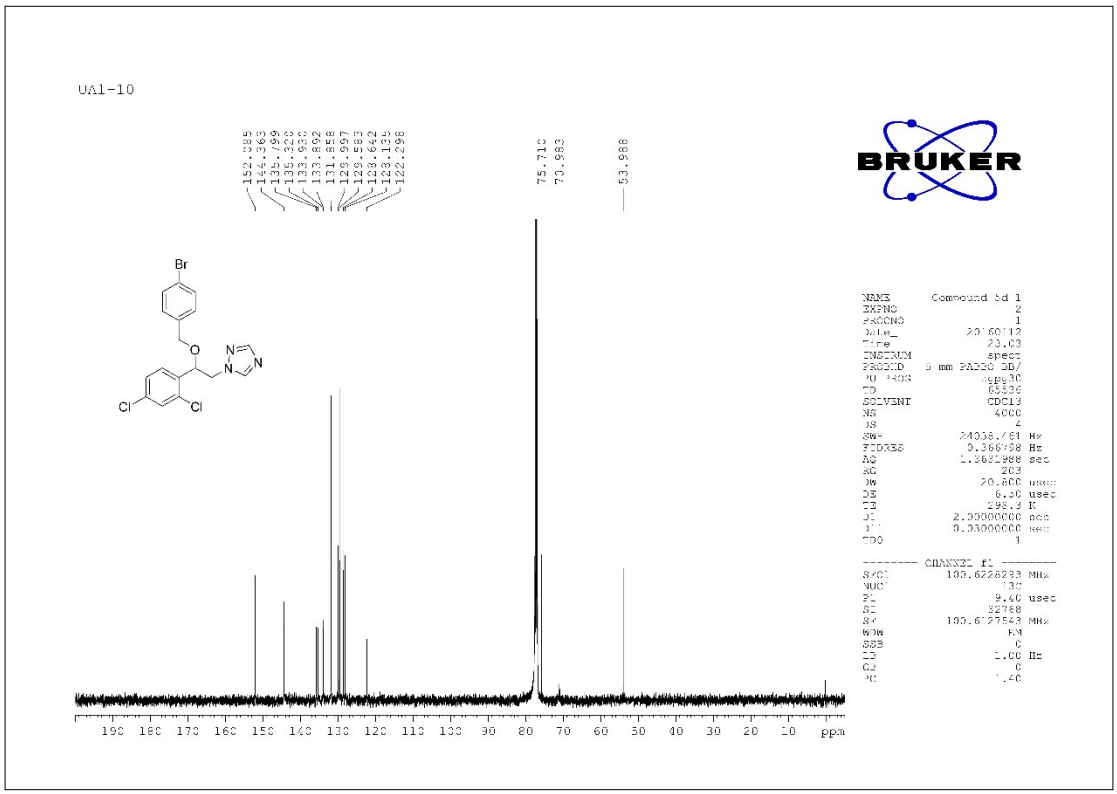
^{13}C-NMR spectrum of **UA1-09**



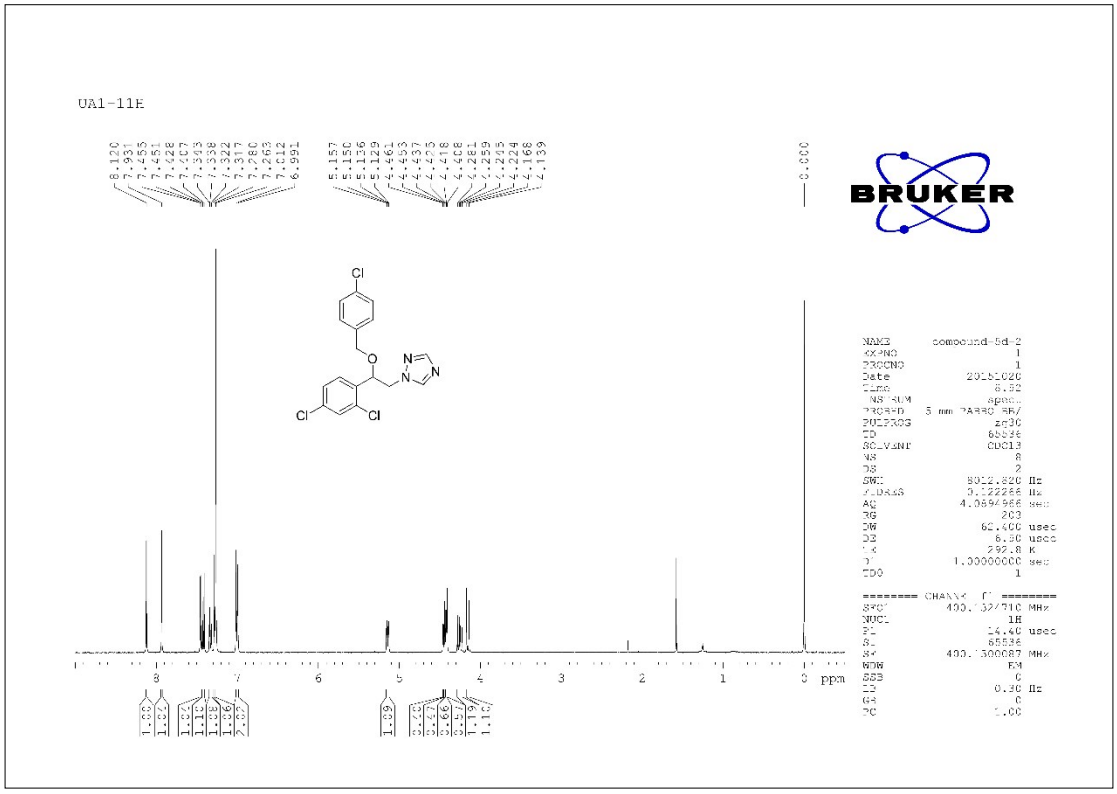
^{1}H-NMR spectrum of **UA1-10**



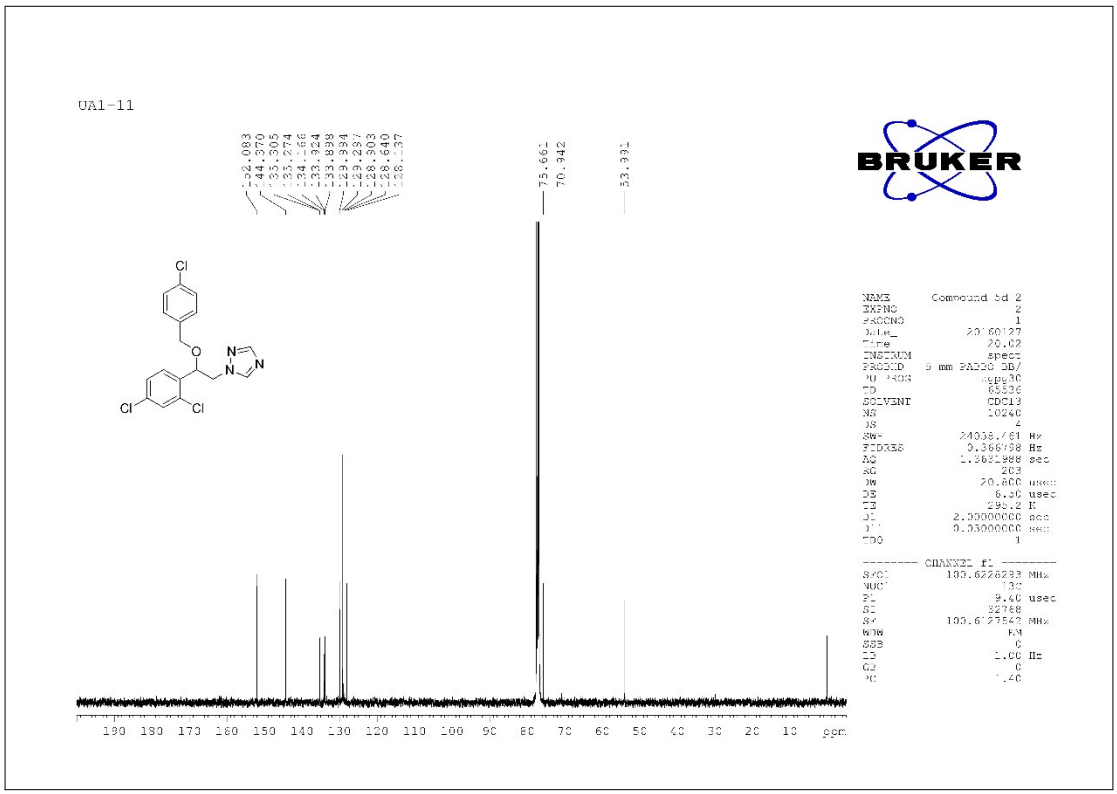
^{13}C-NMR spectrum of **UA1-10**



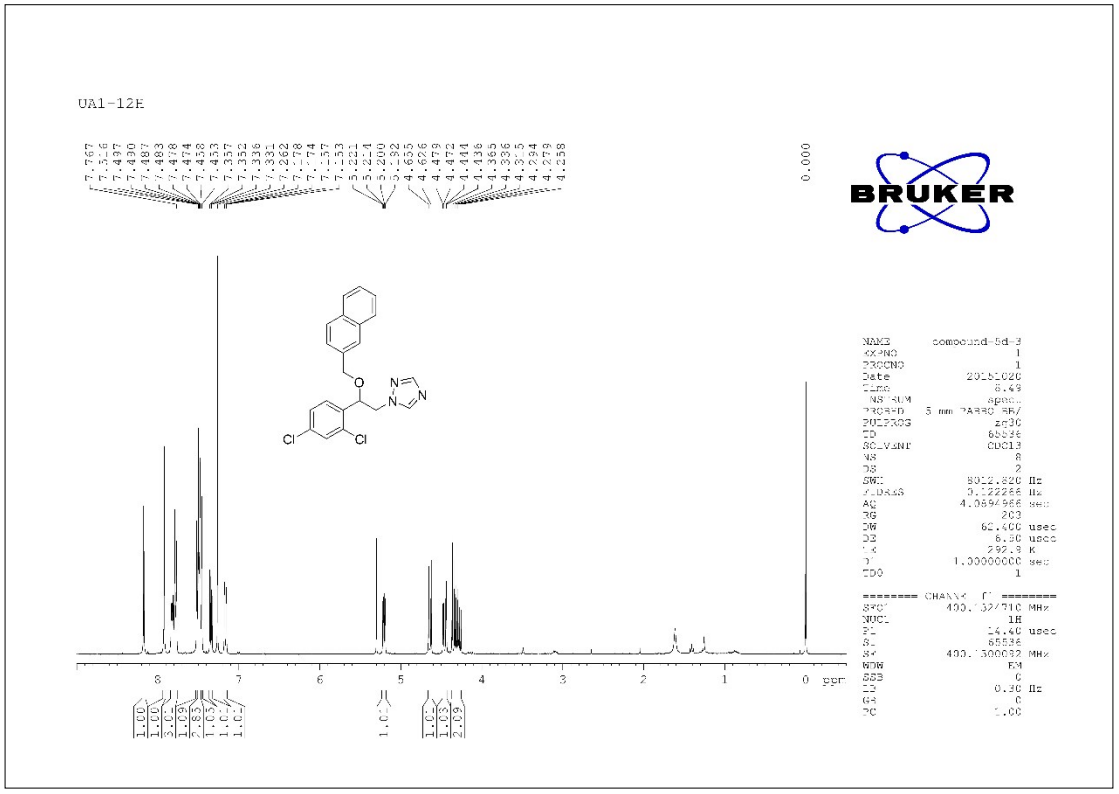
^{1}H-NMR spectrum of **UA1-11**



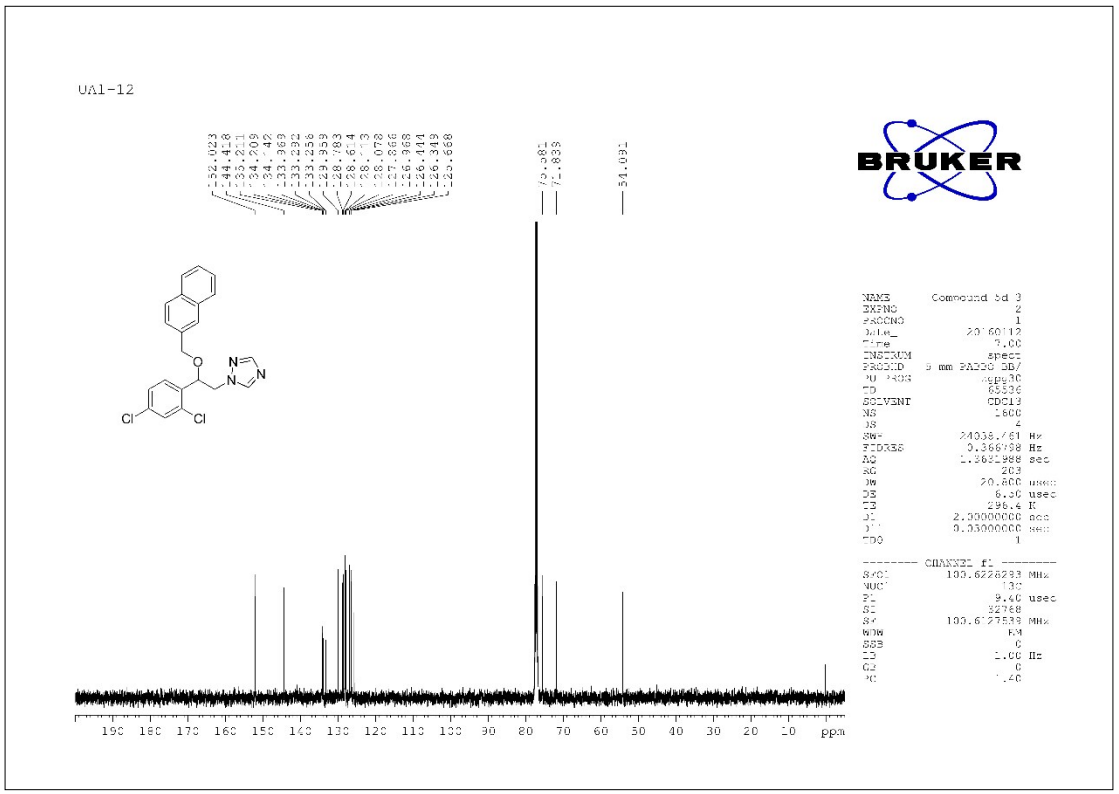
^{13}C-NMR spectrum of **UA1-11**



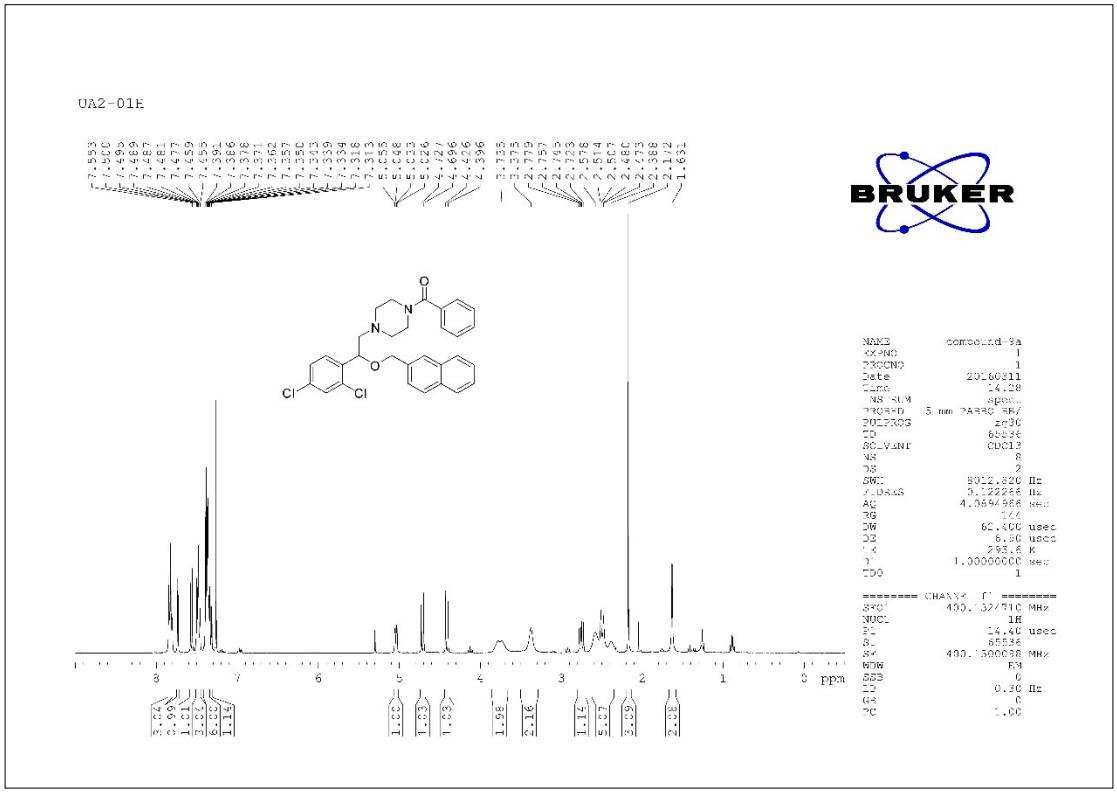
^{1}H-NMR spectrum of **UA1-12**



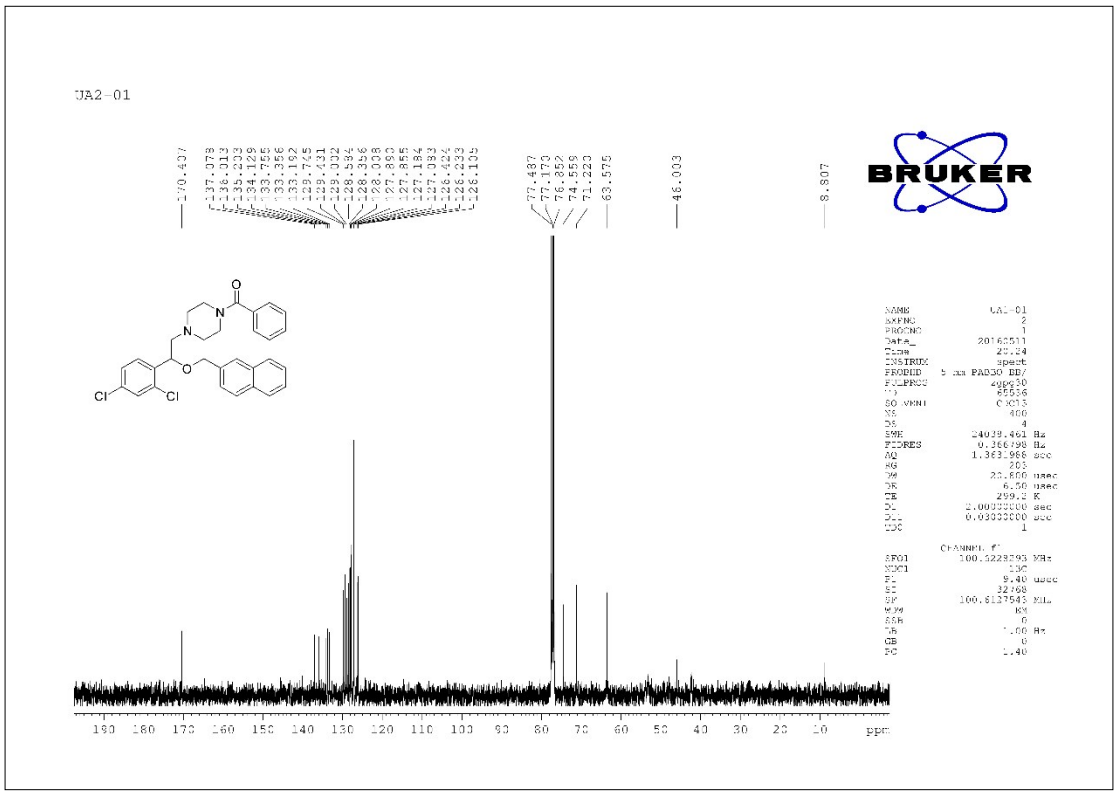
^{13}C-NMR spectrum of **UA1-12**



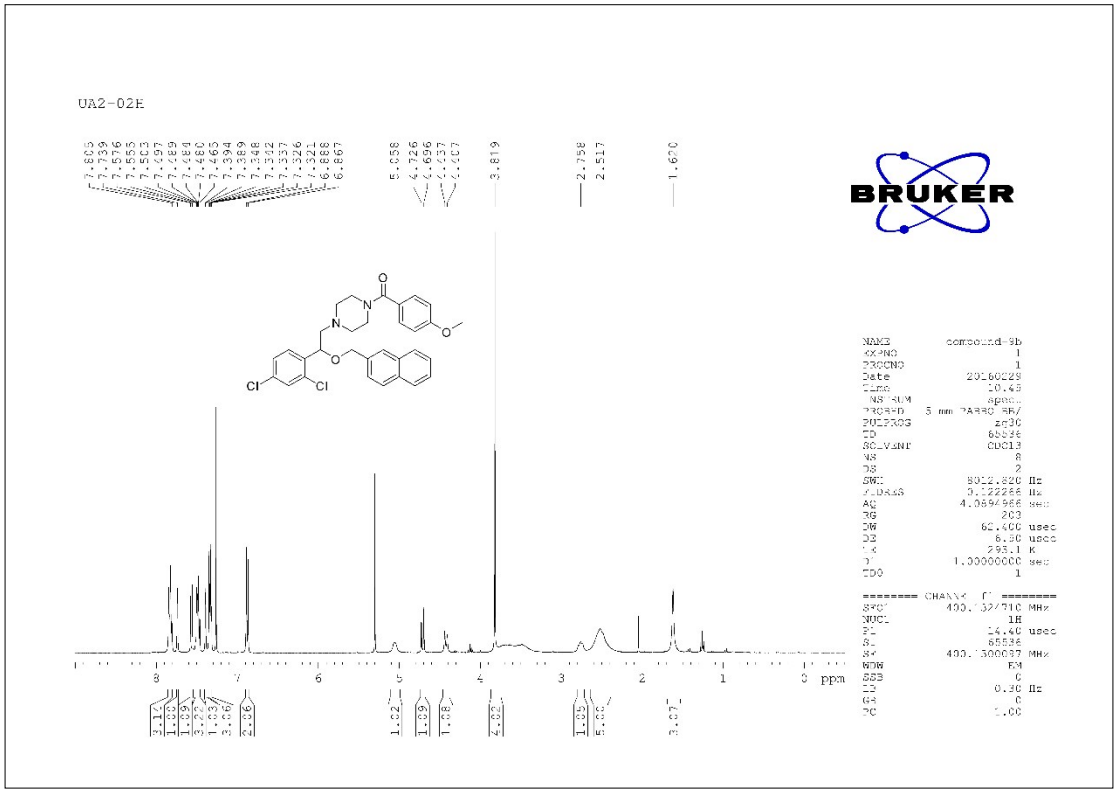
^{1}H-NMR spectrum of **UA2-01**



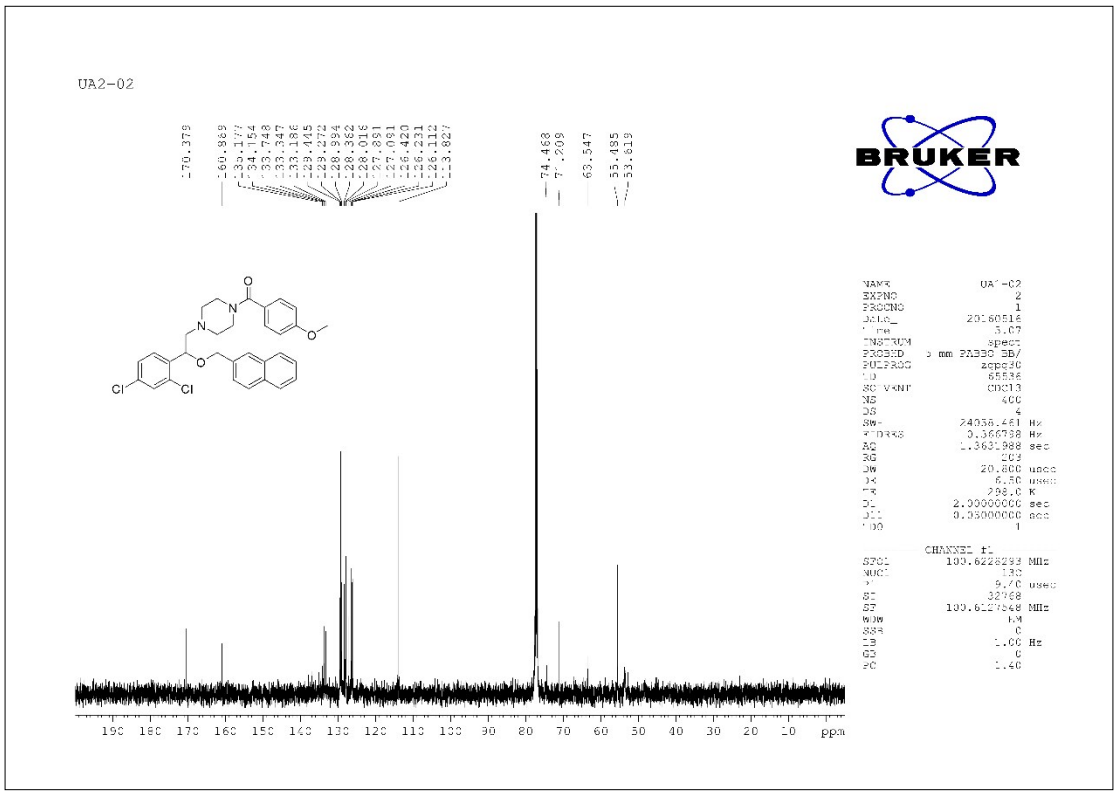
^{13}C-NMR spectrum of **UA2-01**



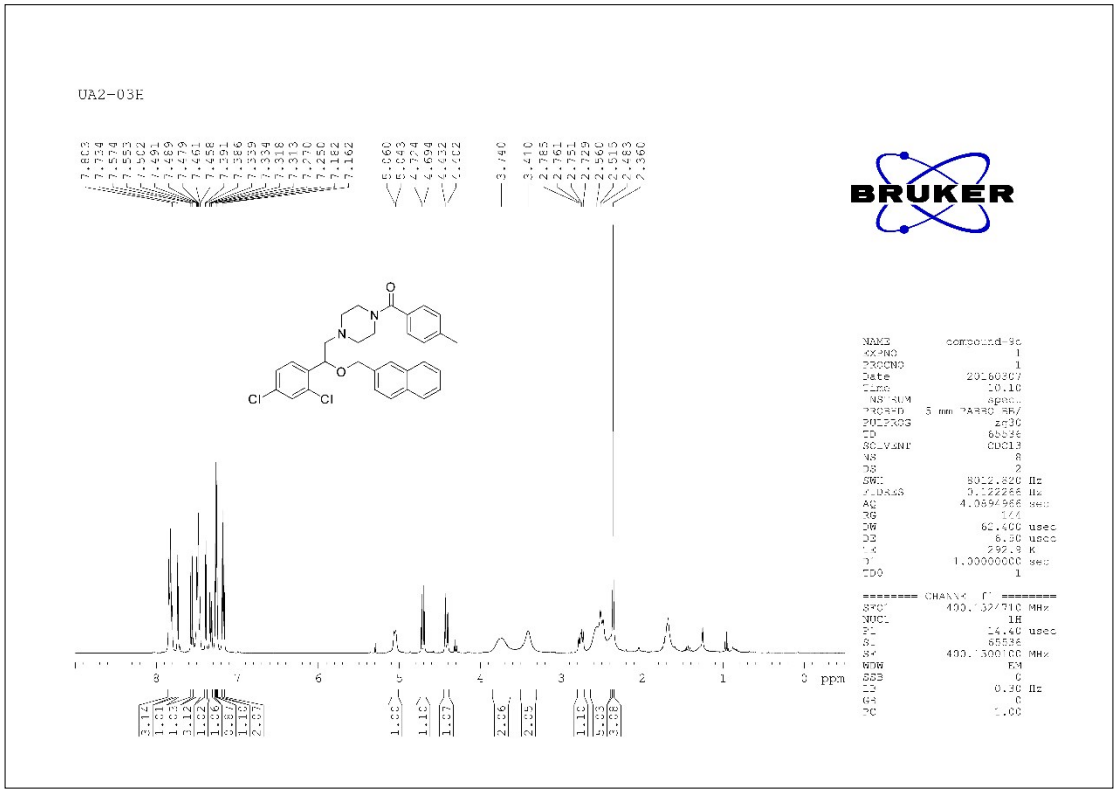
^{1}H-NMR spectrum of **UA2-02**



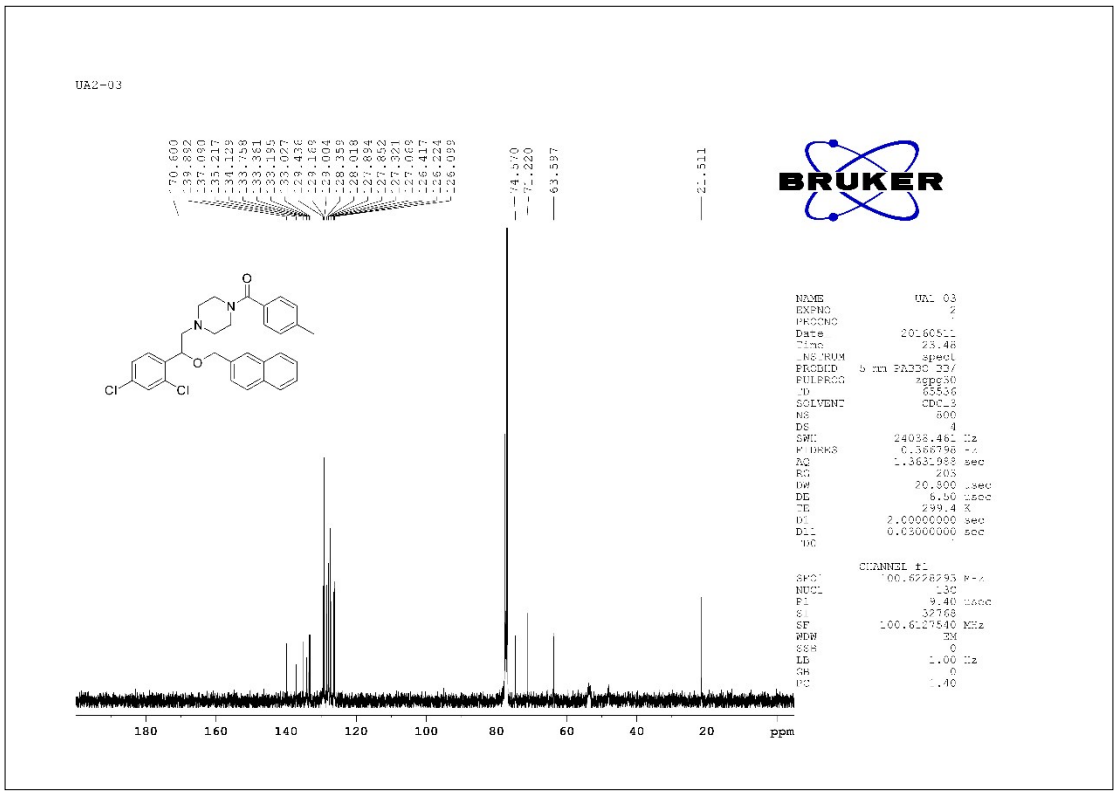
^{13}C-NMR spectrum of **UA2-02**



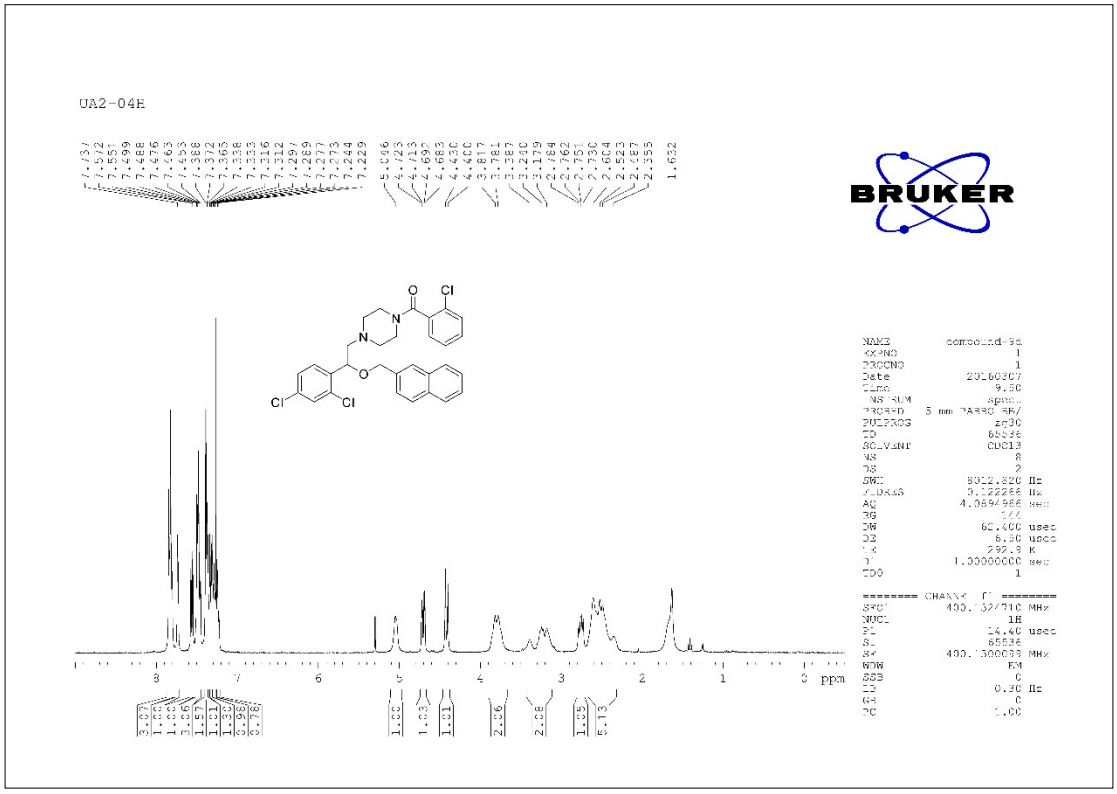
^{1}H-NMR spectrum of **UA2-03**



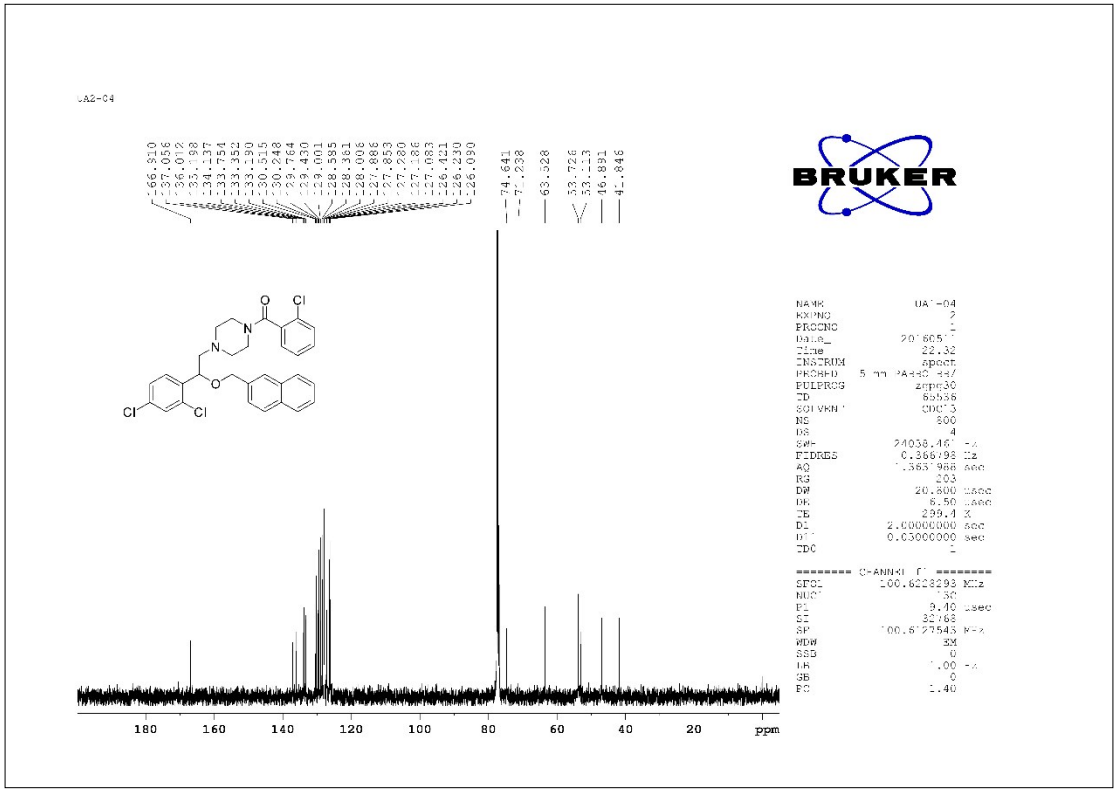
^{13}C-NMR spectrum of **UA2-03**



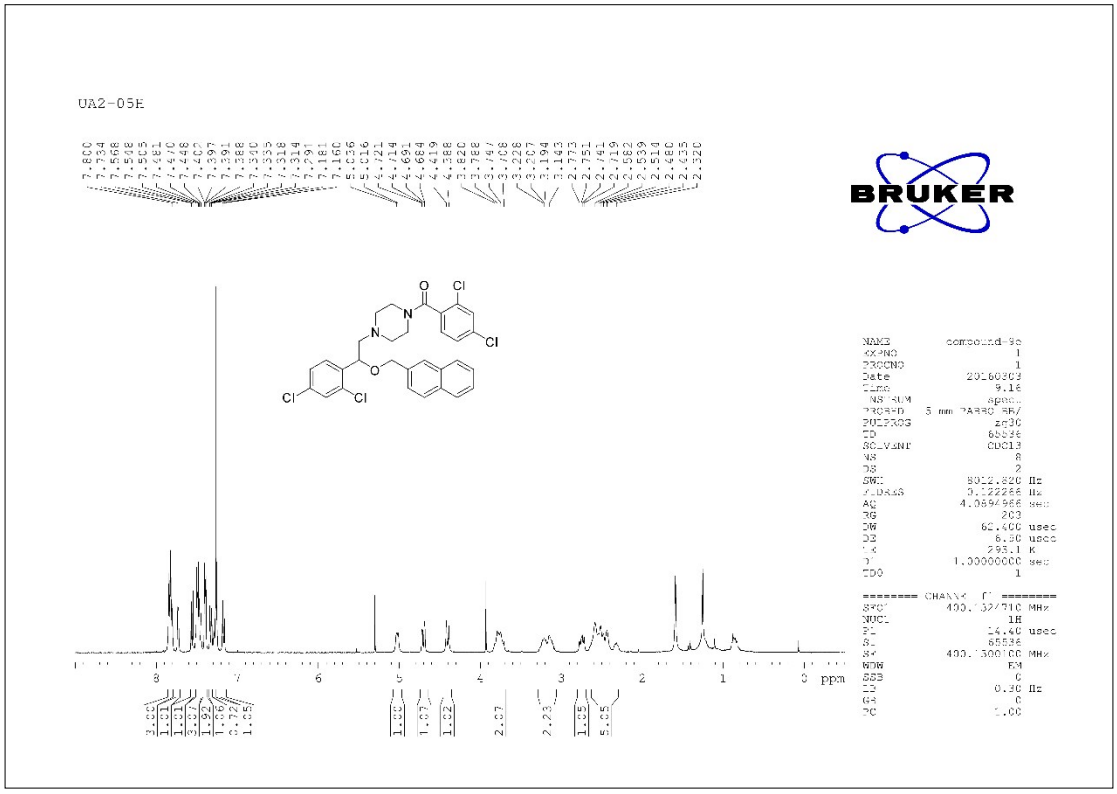
^{1}H-NMR spectrum of **UA2-04**



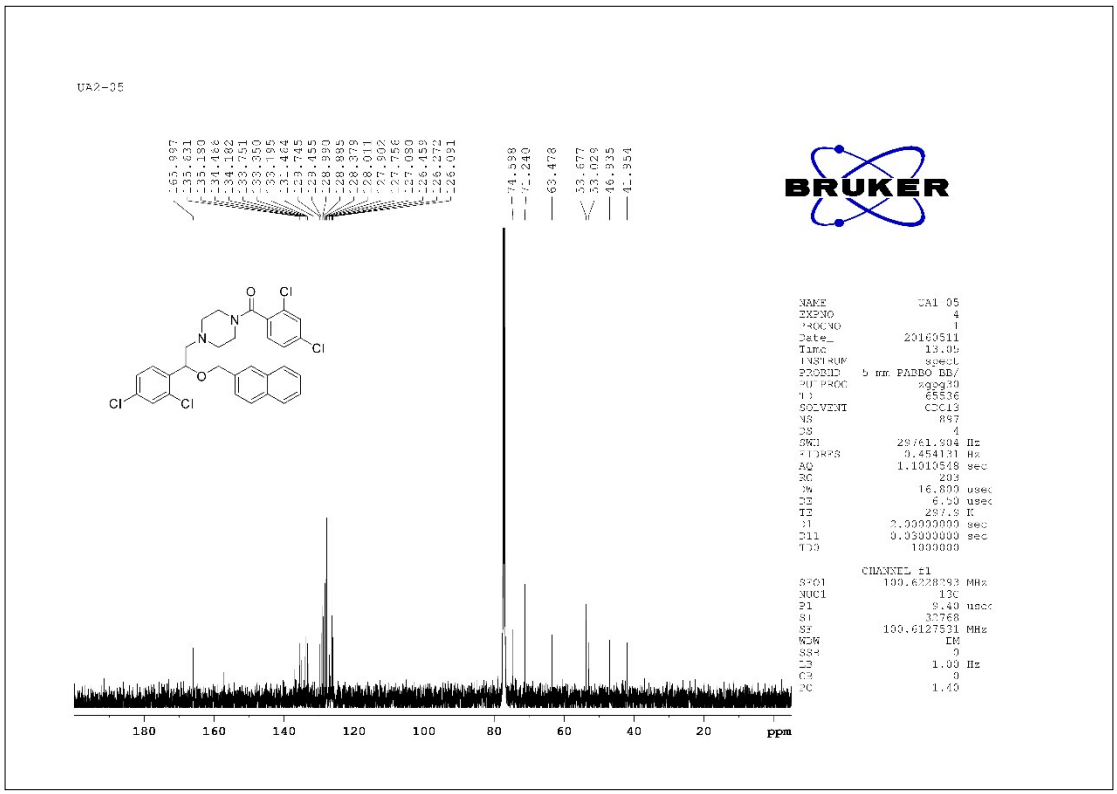
^{13}C-NMR spectrum of **UA2-04**



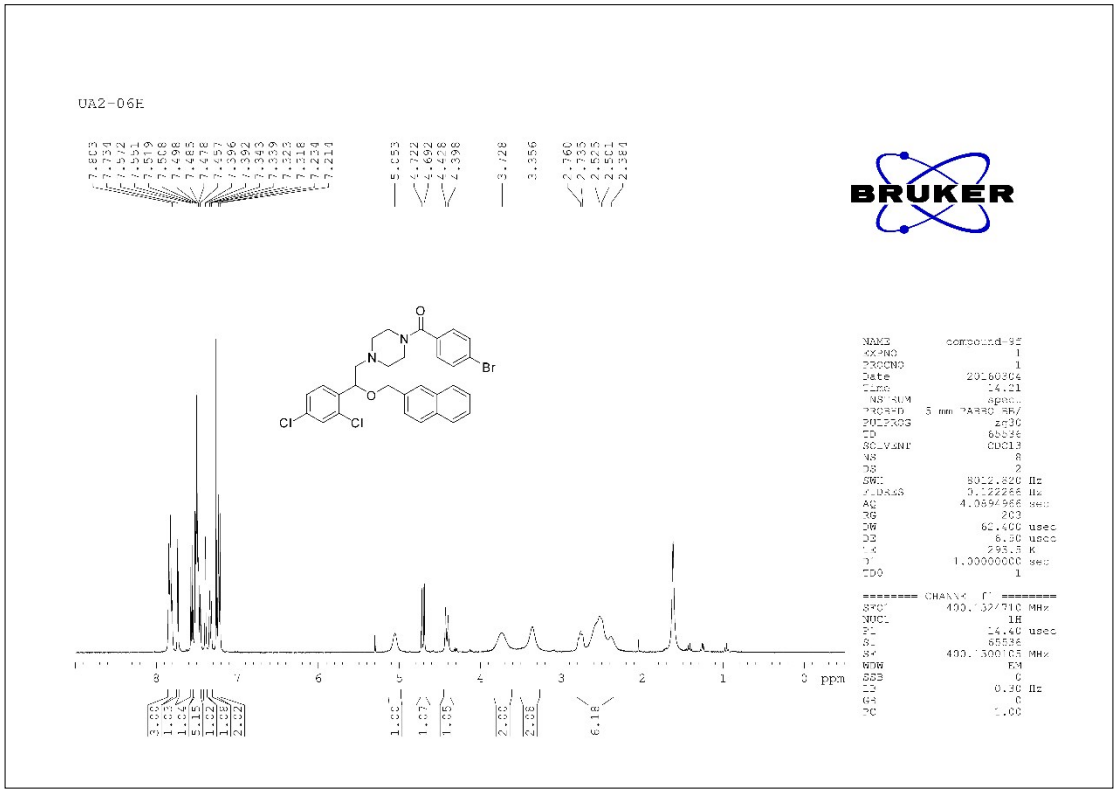
^{1}H-NMR spectrum of **UA2-05**



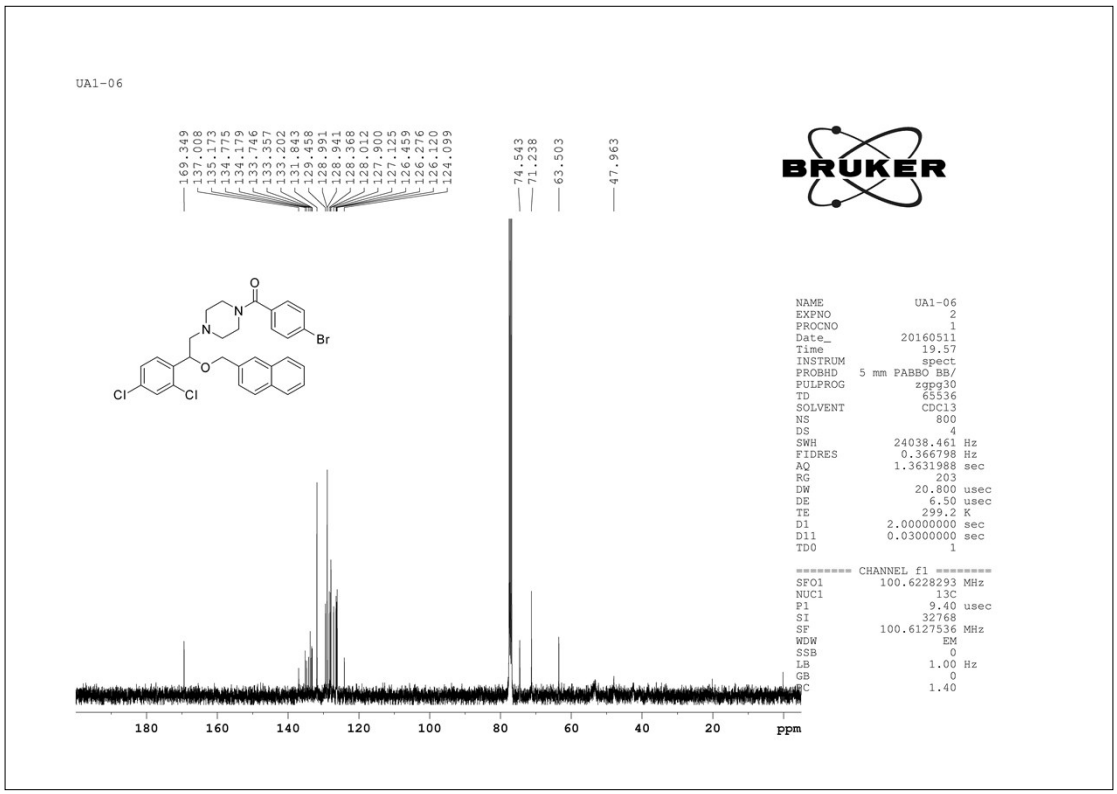
^{13}C-NMR spectrum of **UA2-05**



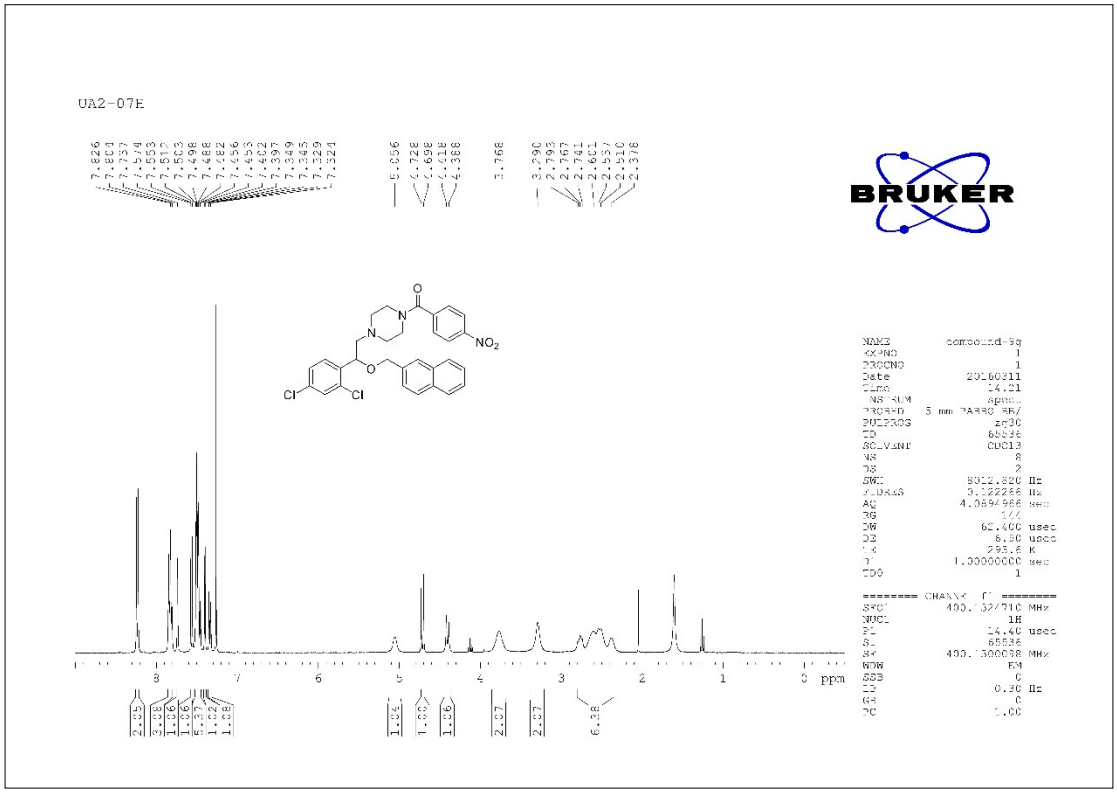
^{1}H-NMR spectrum of **UA2-06**



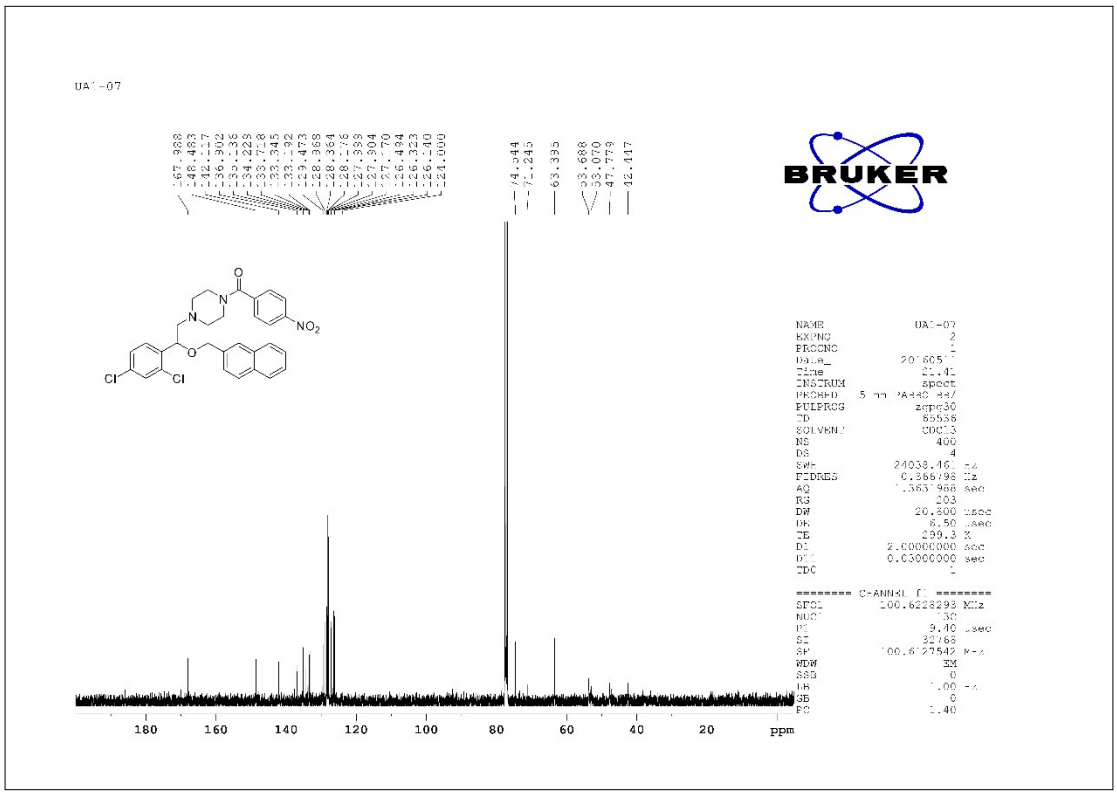
^{13}C-NMR spectrum of **UA2-06**



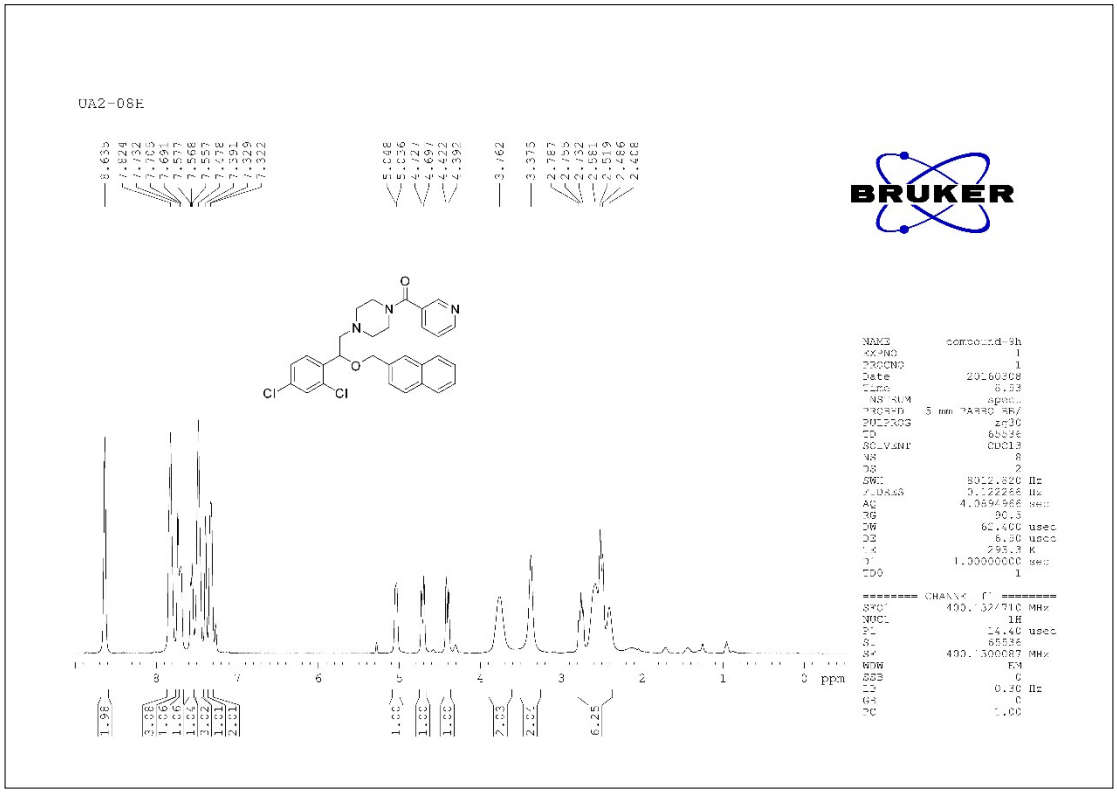
^{1}H-NMR spectrum of **UA2-07**



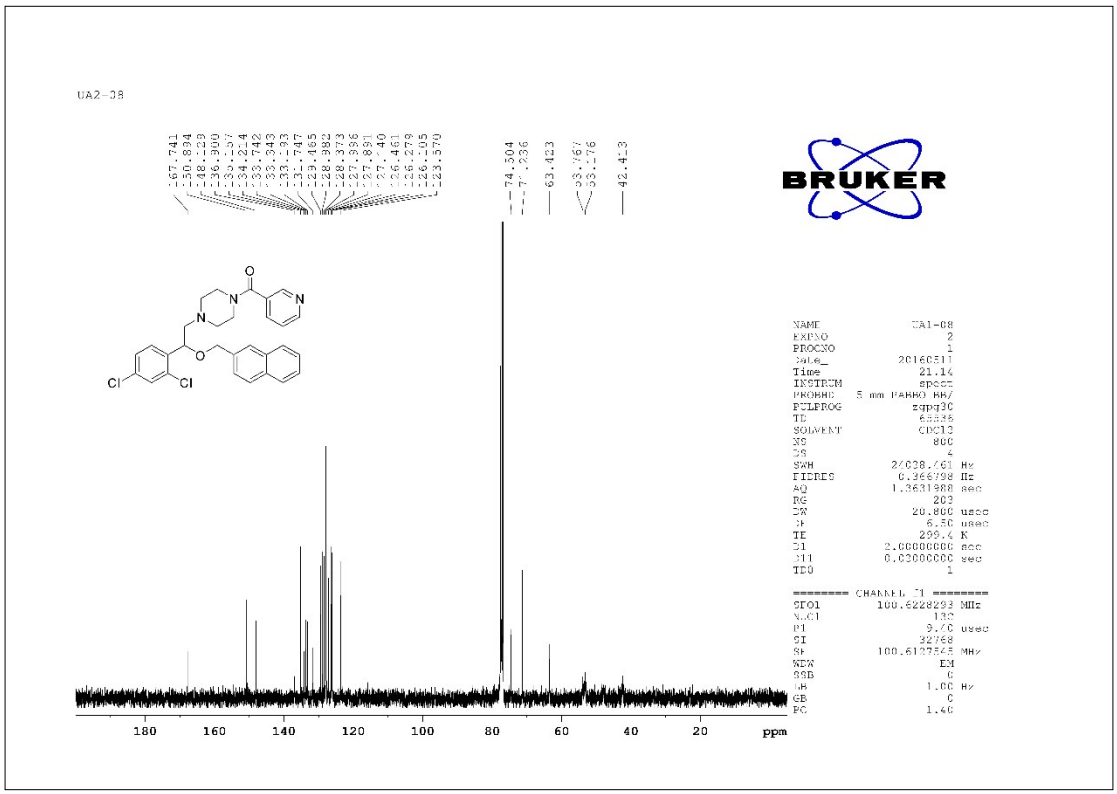
^{13}C-NMR spectrum of **UA2-07**



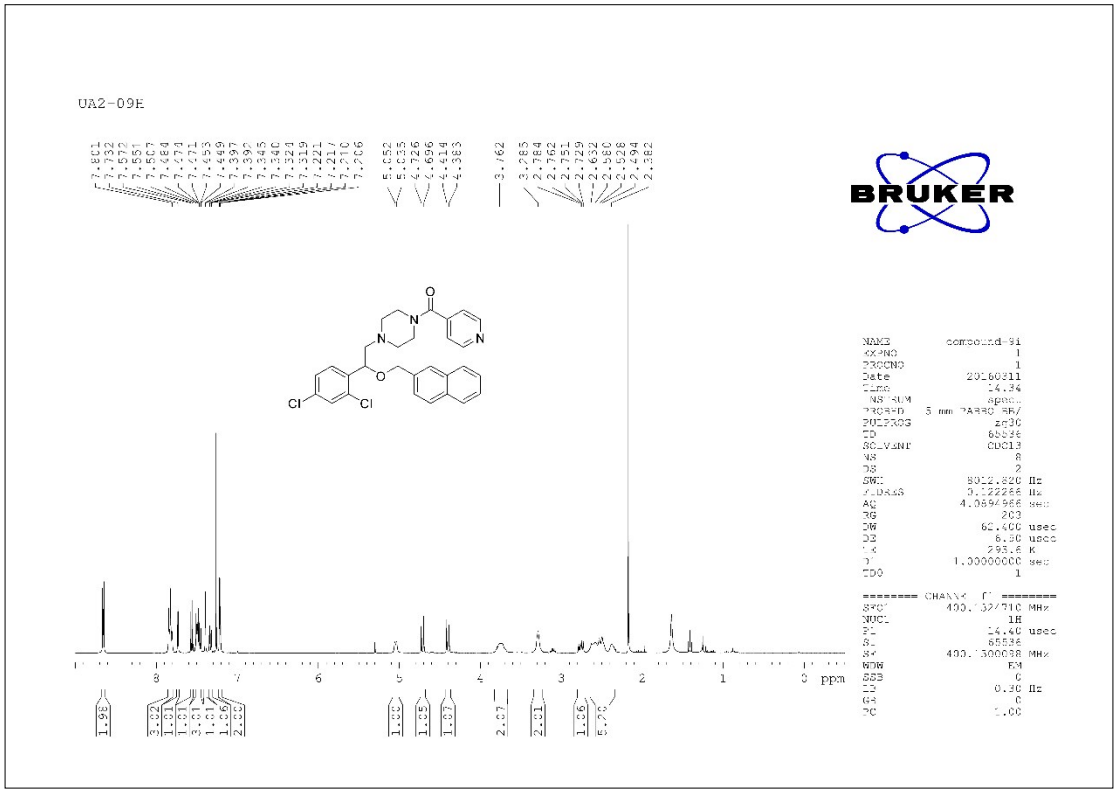
^{1}H-NMR spectrum of **UA2-08**



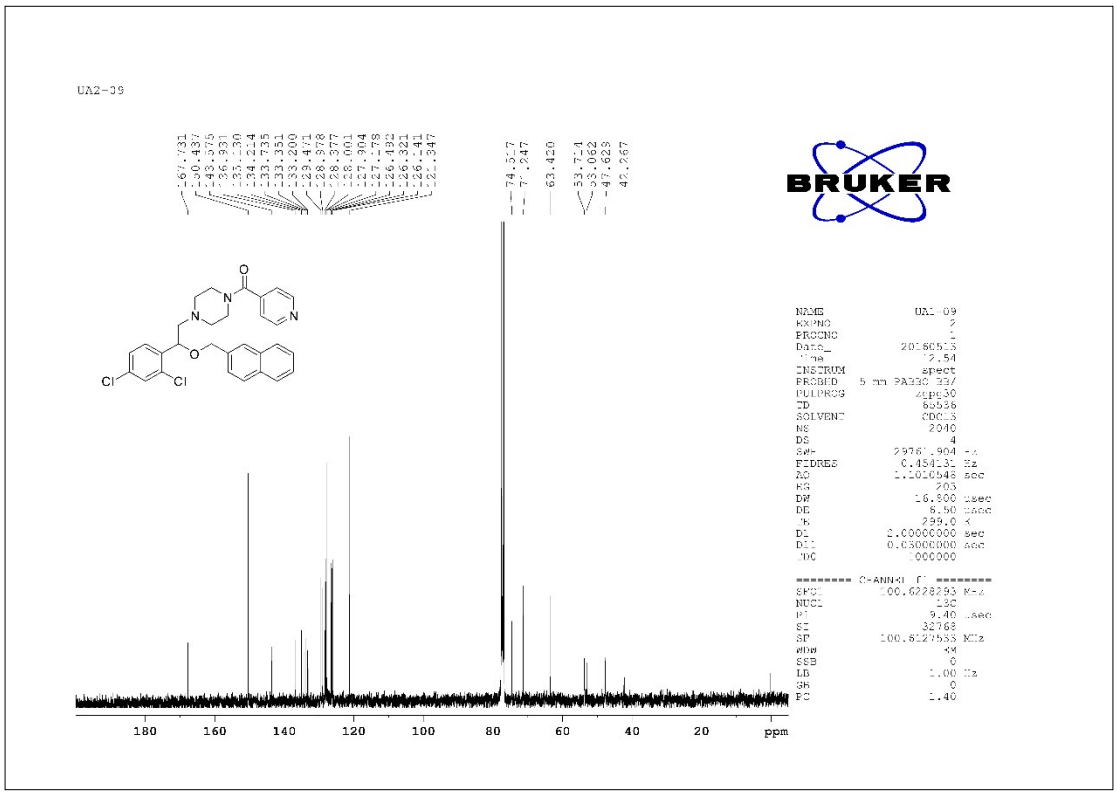
^{13}C-NMR spectrum of **UA2-08**



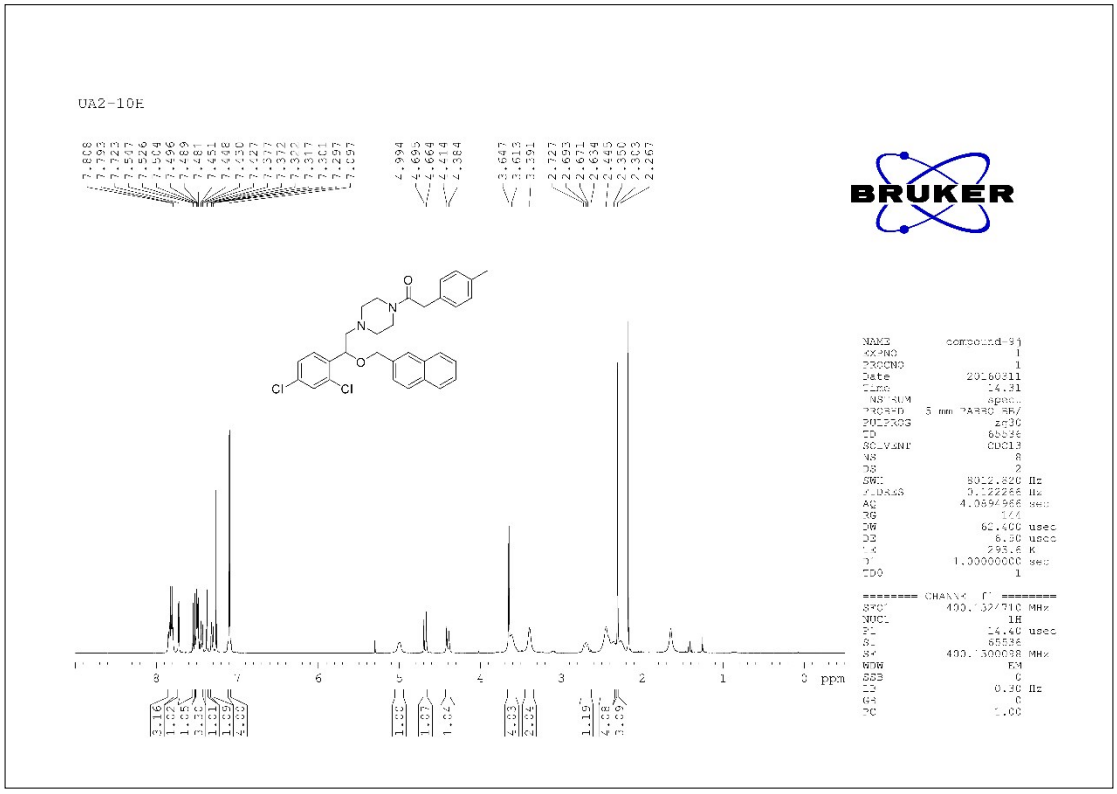
^{1}H-NMR spectrum of **UA2-09**



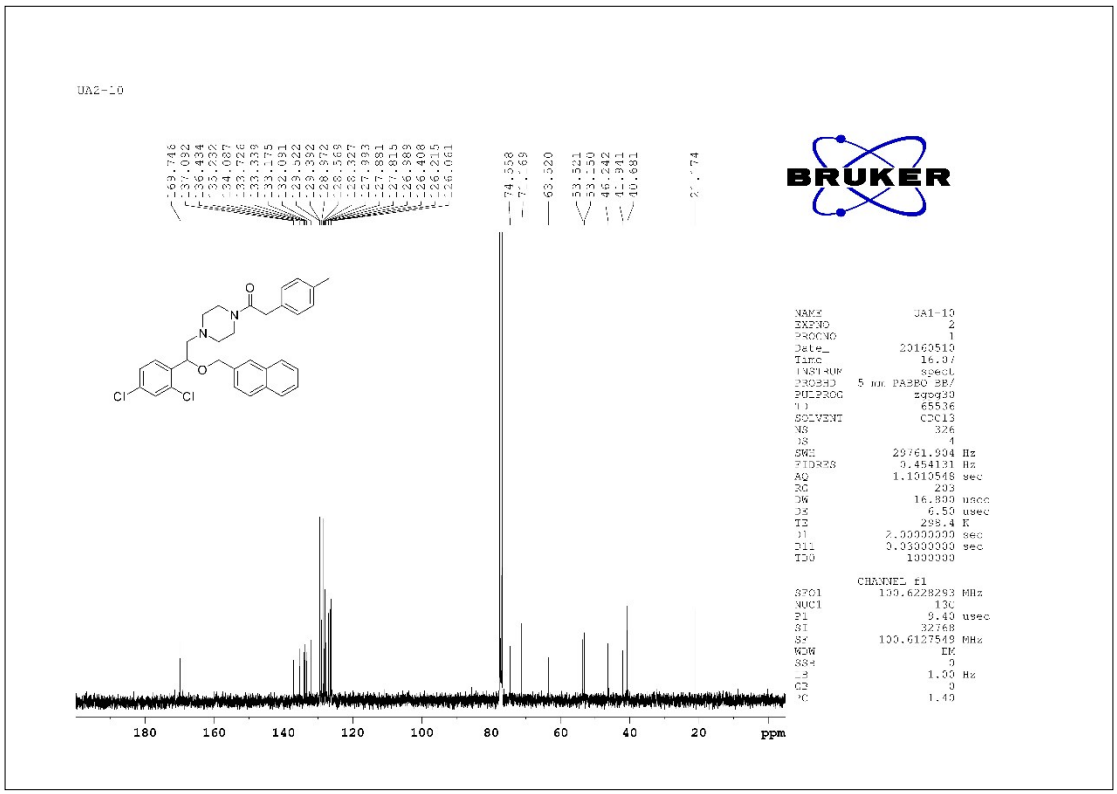
^{13}C-NMR spectrum of **UA2-09**



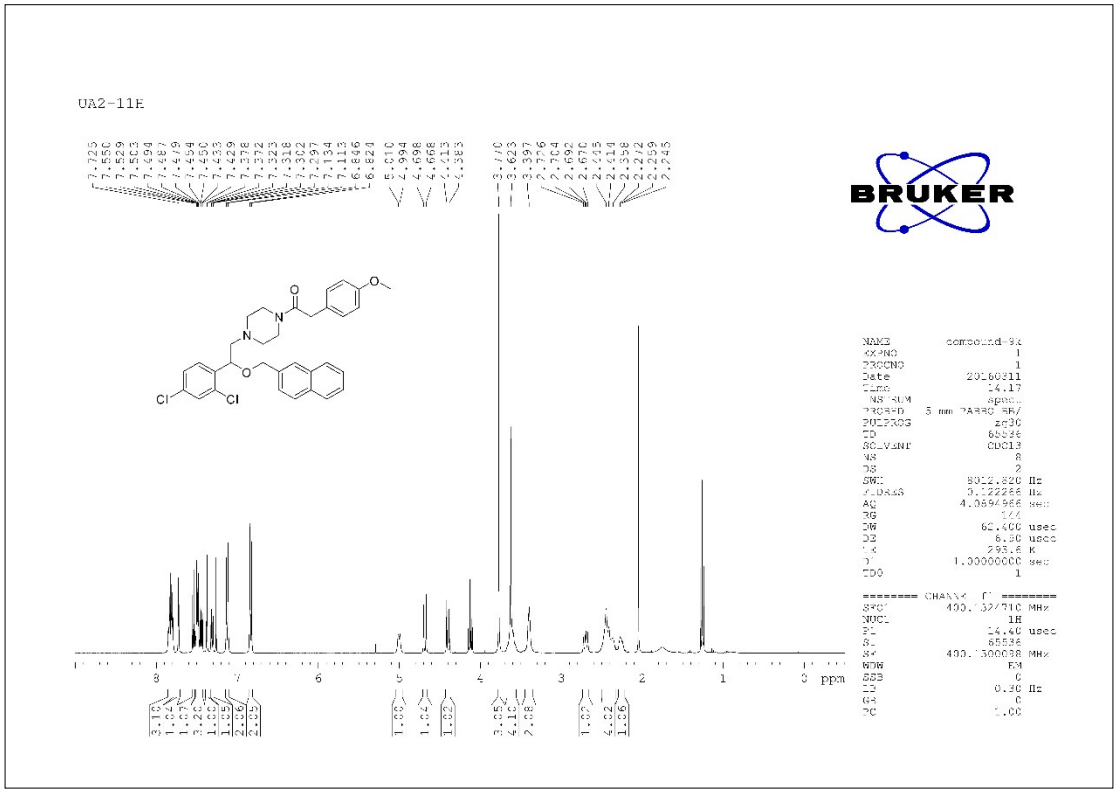
^{1}H-NMR spectrum of **UA2-10**



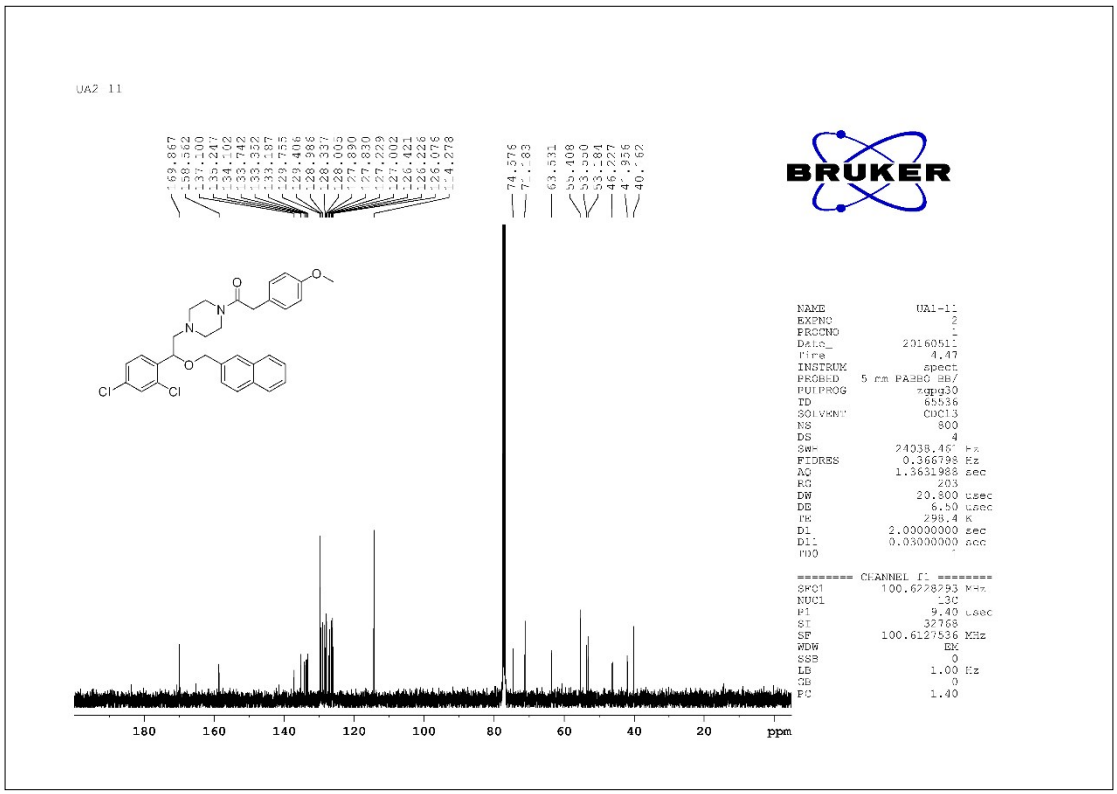
^{13}C-NMR spectrum of **UA2-10**



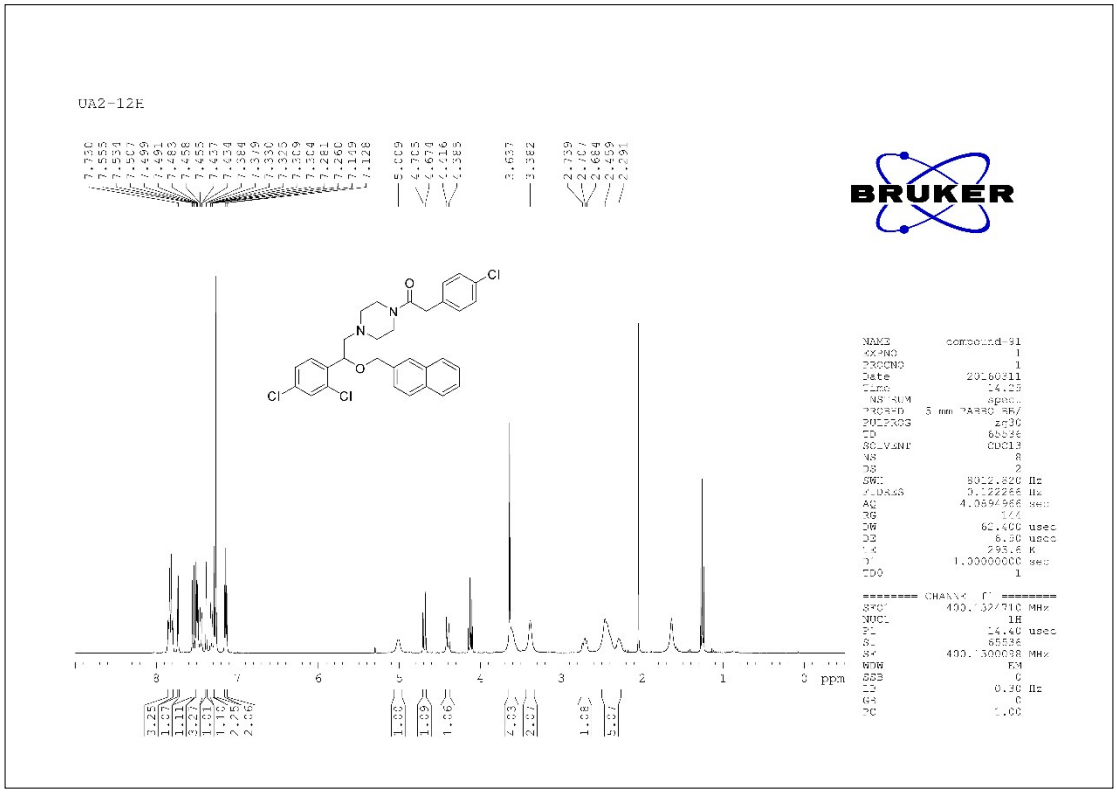
^{1}H-NMR spectrum of **UA2-11**



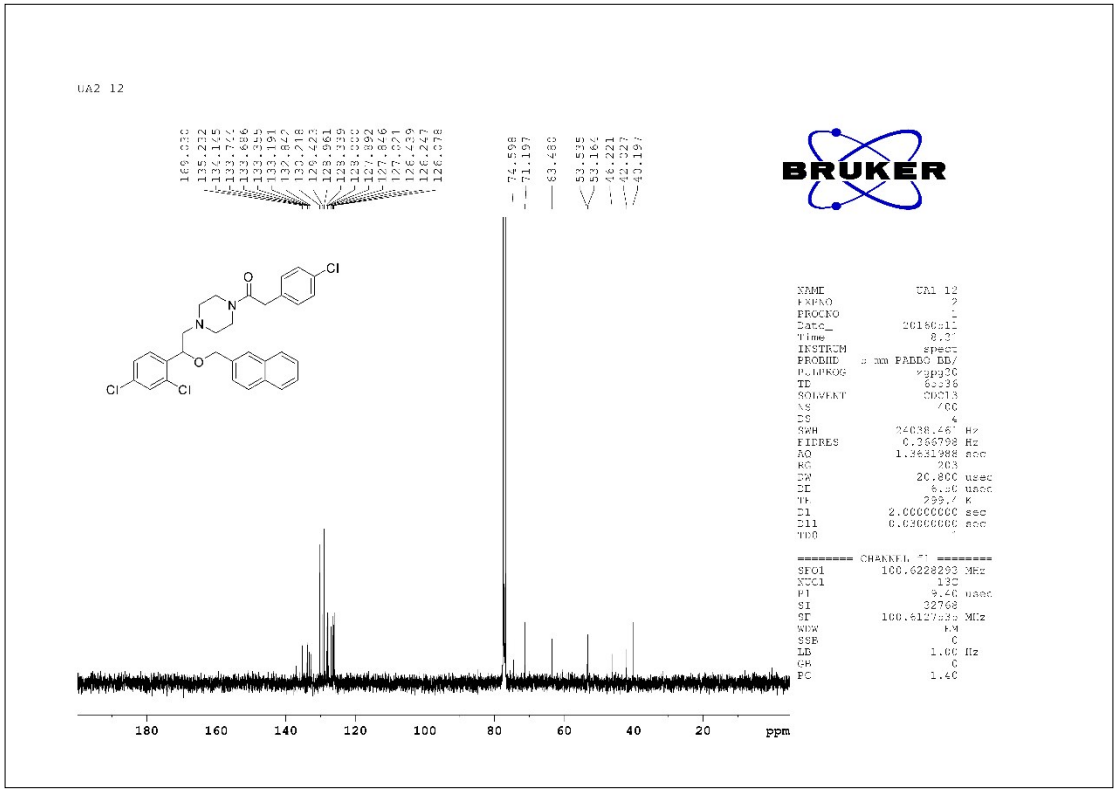
^{13}C-NMR spectrum of **UA2-11**



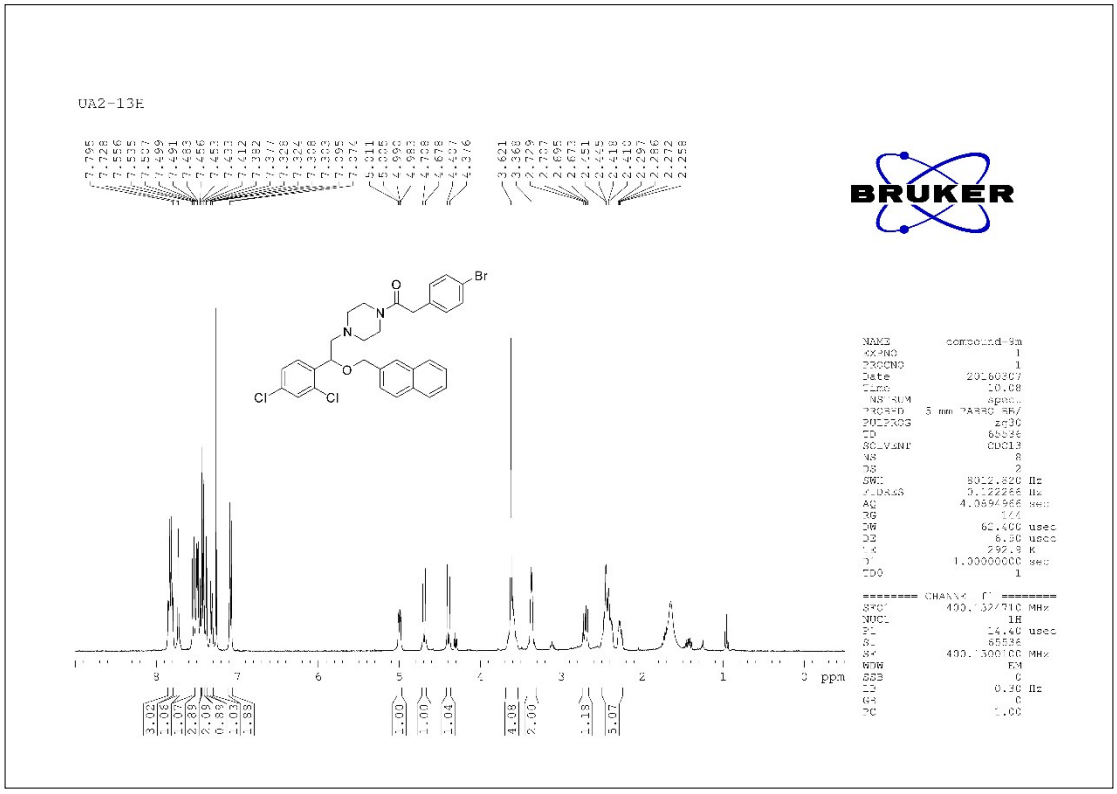
^{1}H-NMR spectrum of **UA2-12**



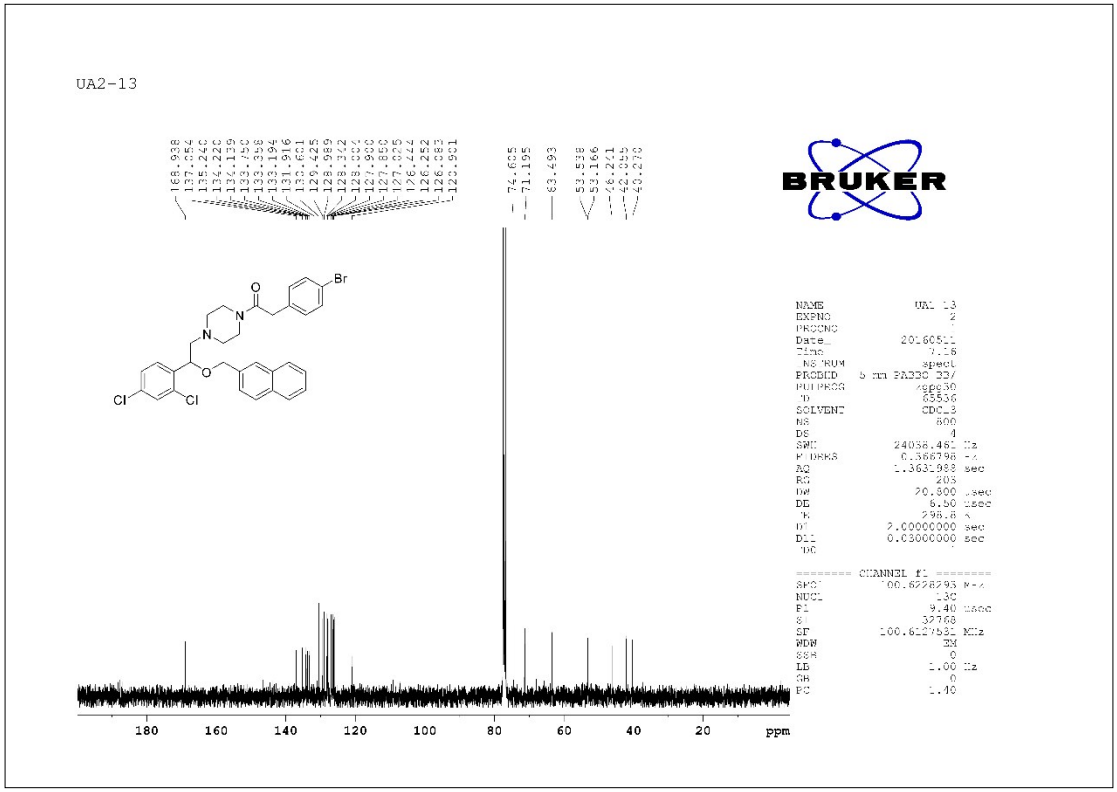
^{13}C-NMR spectrum of **UA2-12**



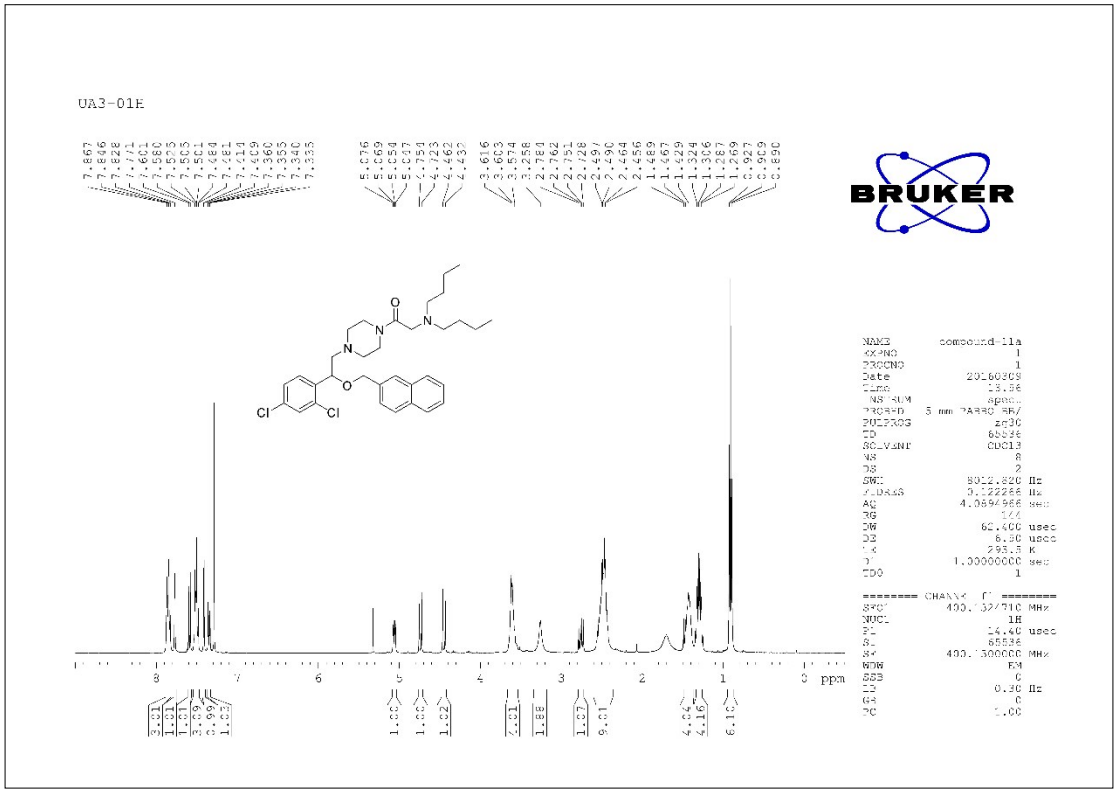
^{1}H-NMR spectrum of **UA2-13**



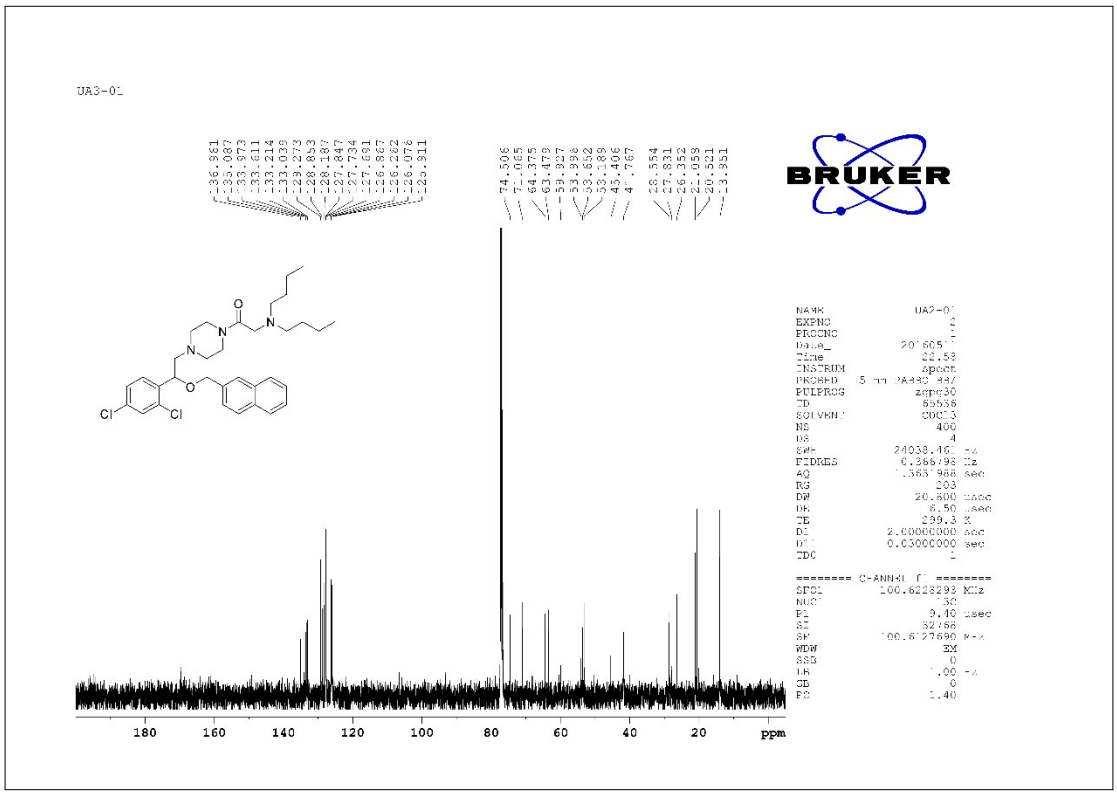
^{13}C-NMR spectrum of **UA2-13**



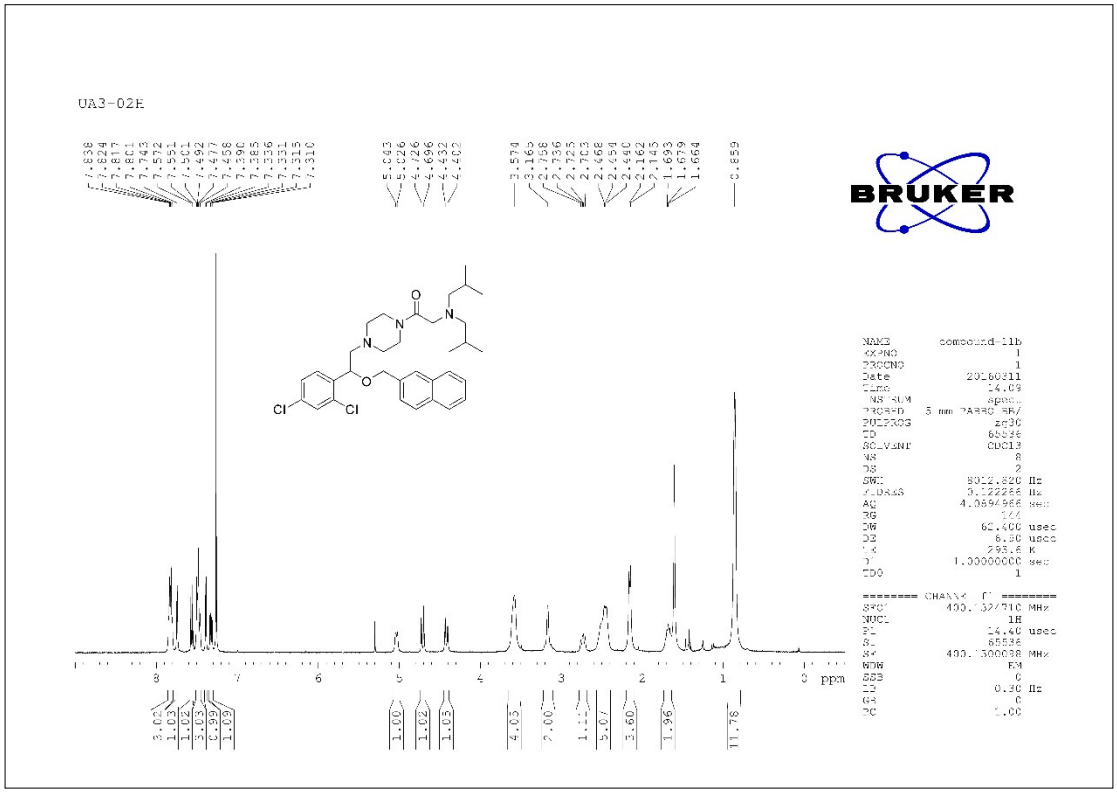
^{1}H-NMR spectrum of **UA3-01**



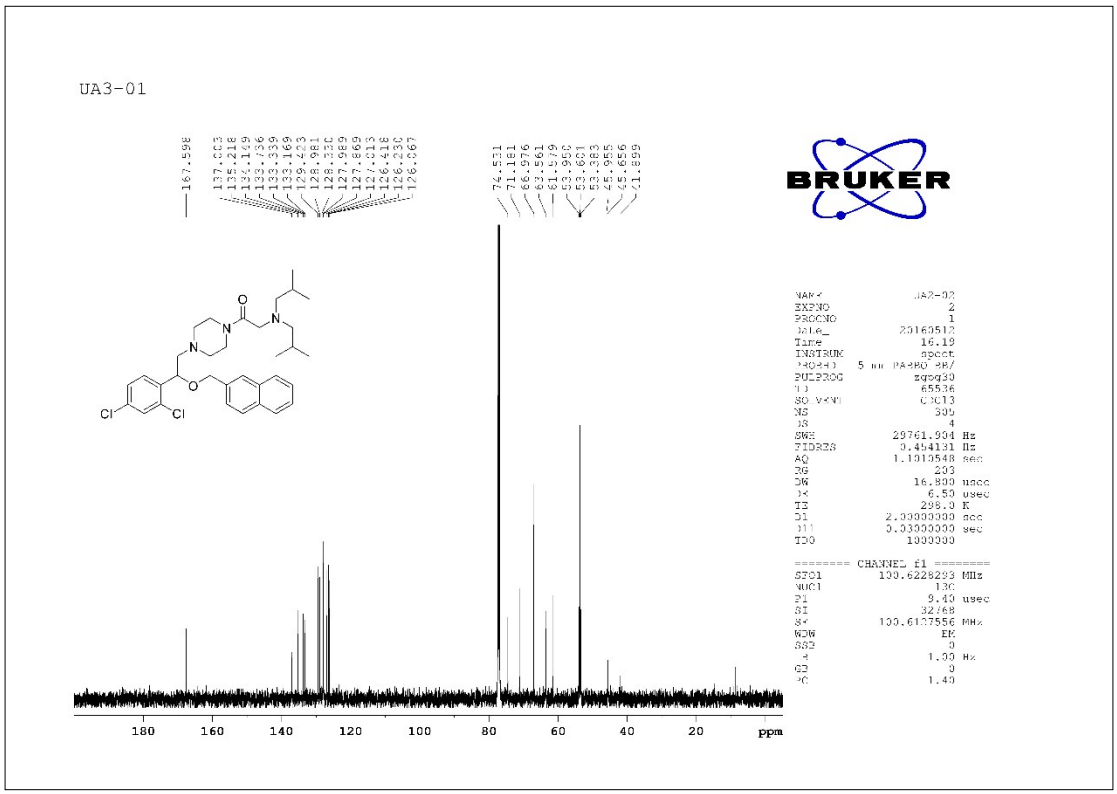
^{13}C-NMR spectrum of **UA3-01**



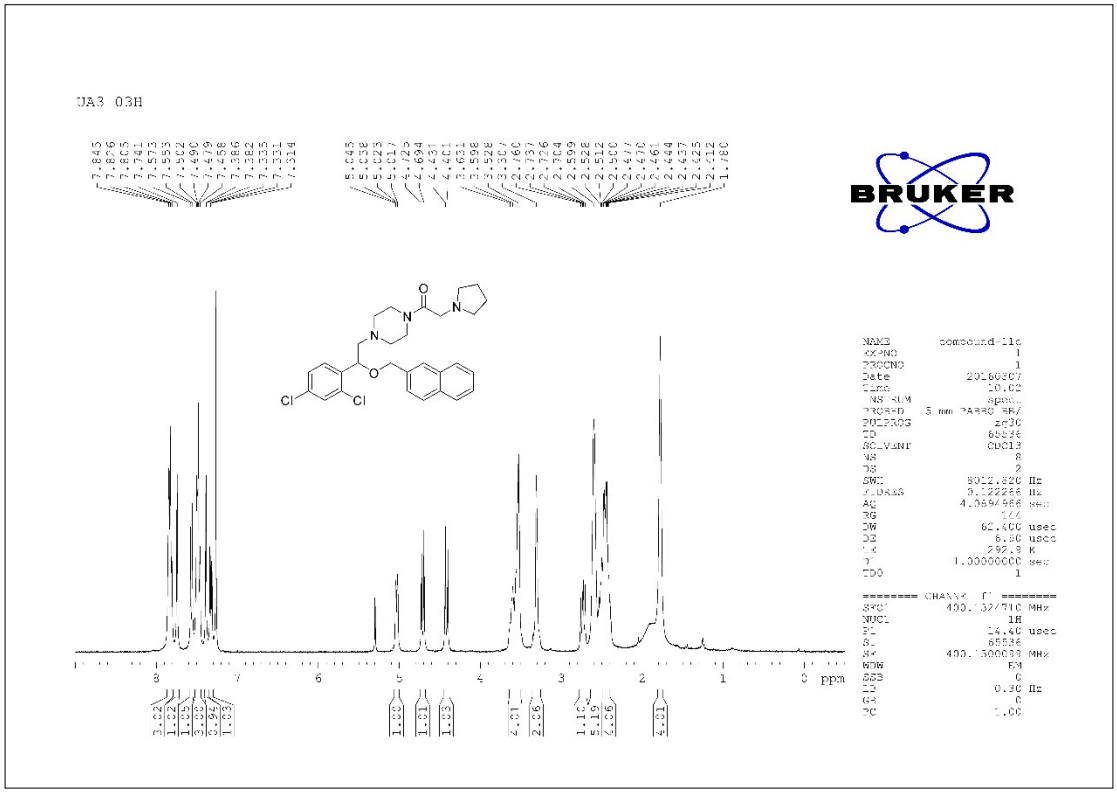
^{1}H-NMR spectrum of **UA3-02**



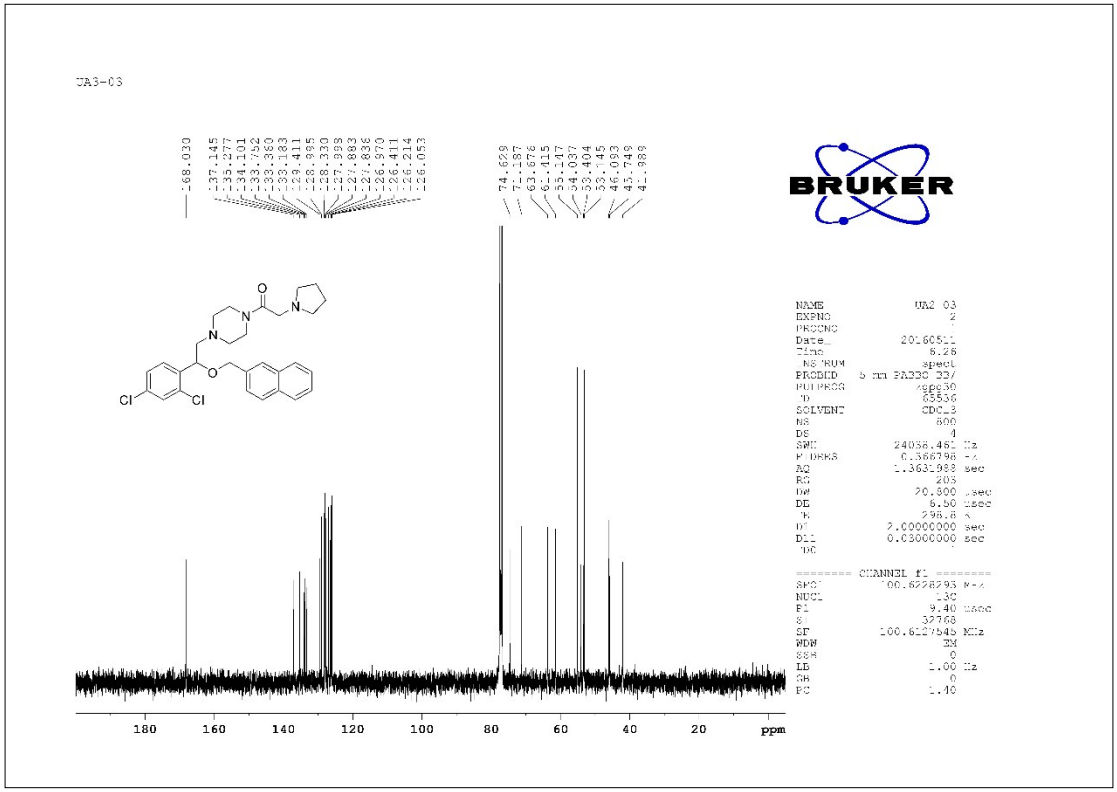
^{13}C-NMR spectrum of **UA3-02**



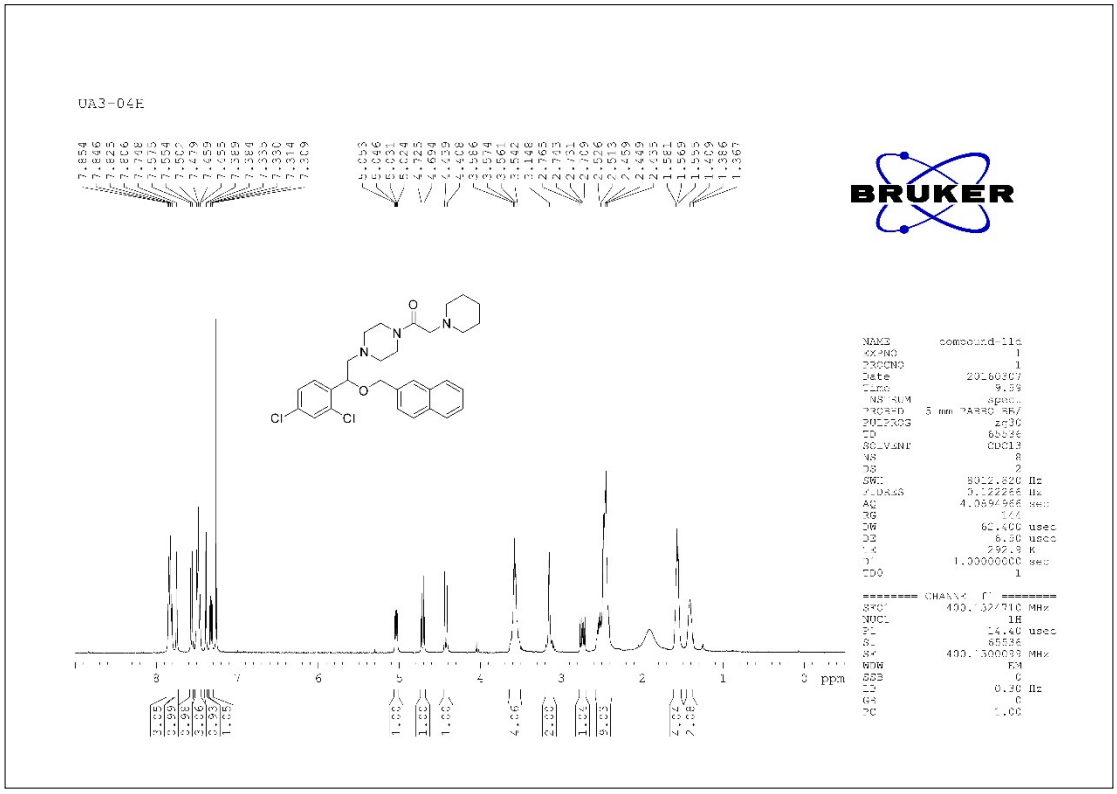
^{1}H-NMR spectrum of **UA3-03**



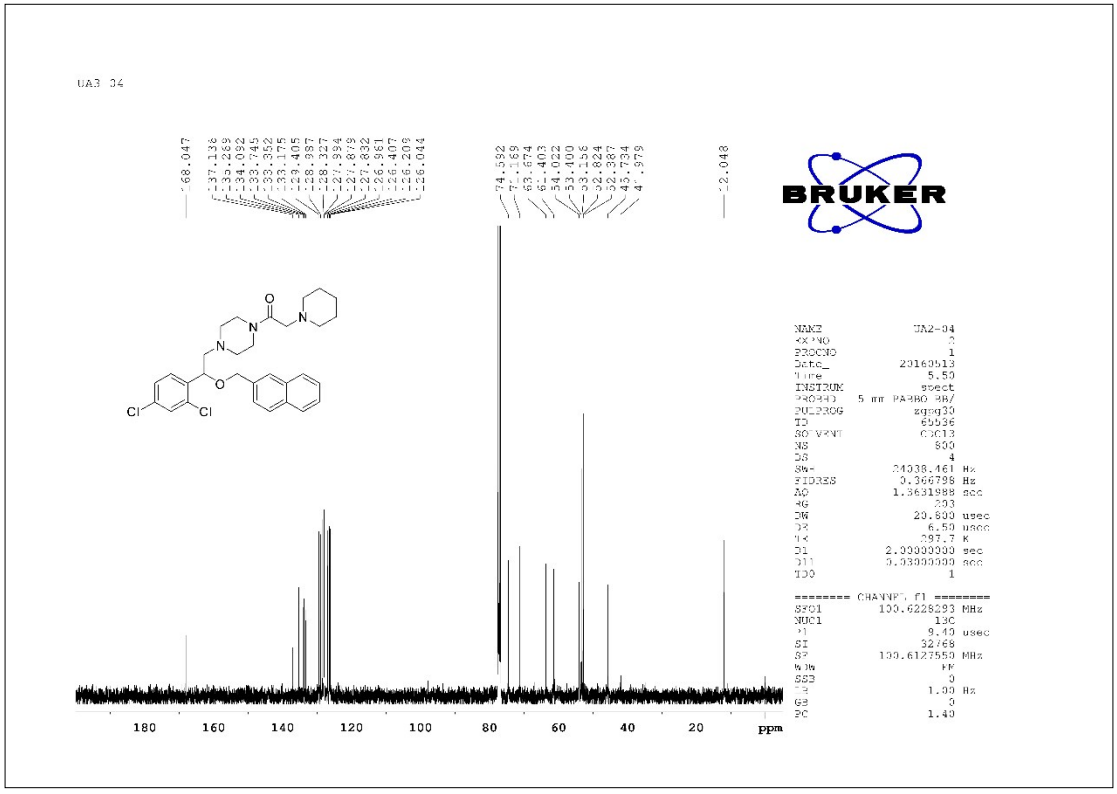
^{13}C-NMR spectrum of **UA3-03**



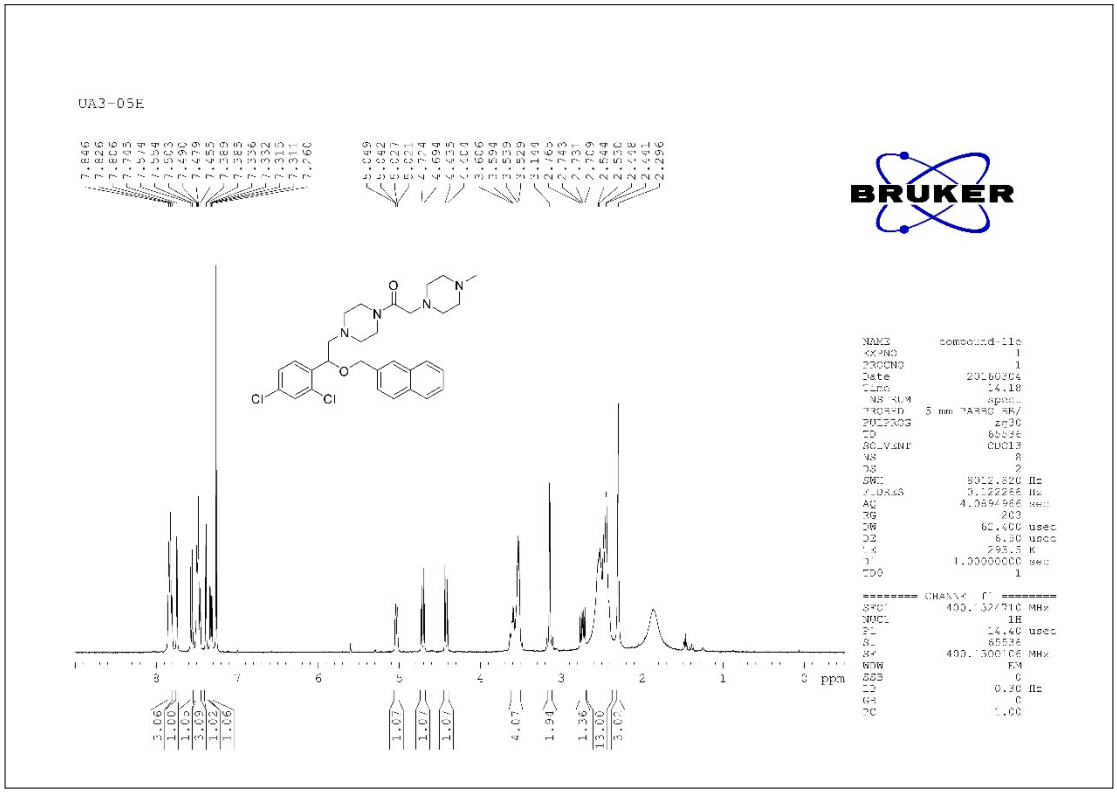
^{1}H-NMR spectrum of **UA3-04**



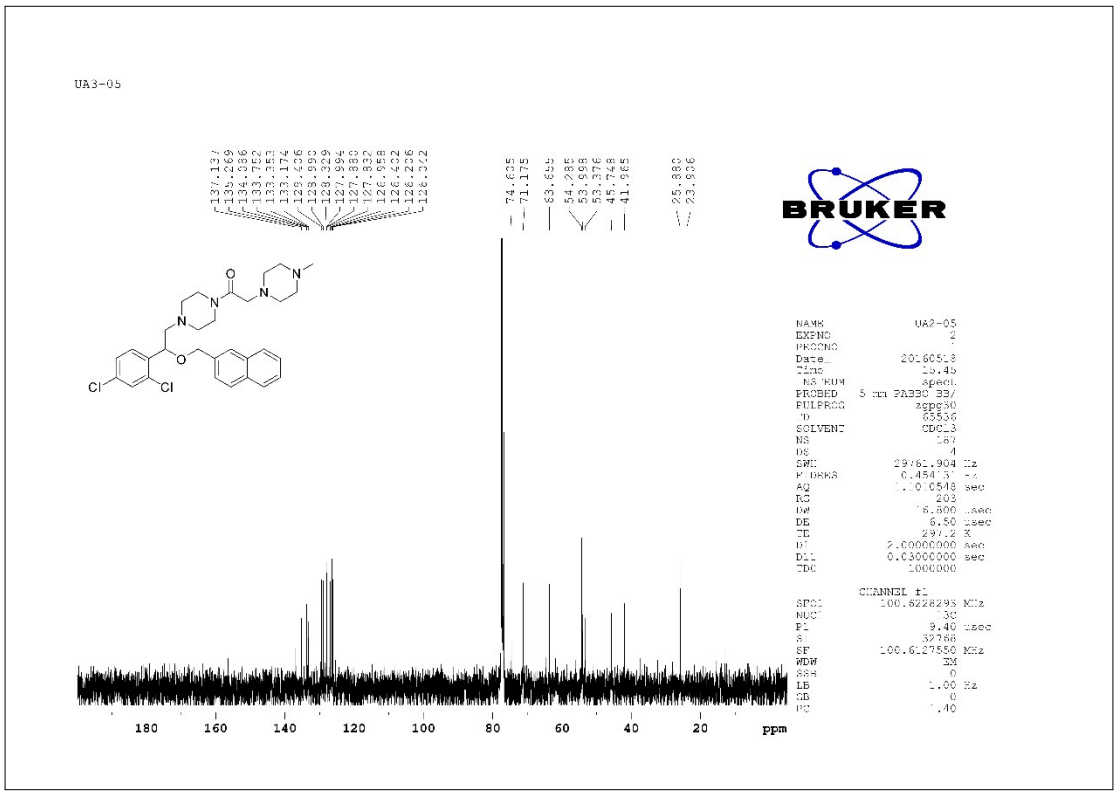
^{13}C-NMR spectrum of **UA3-04**



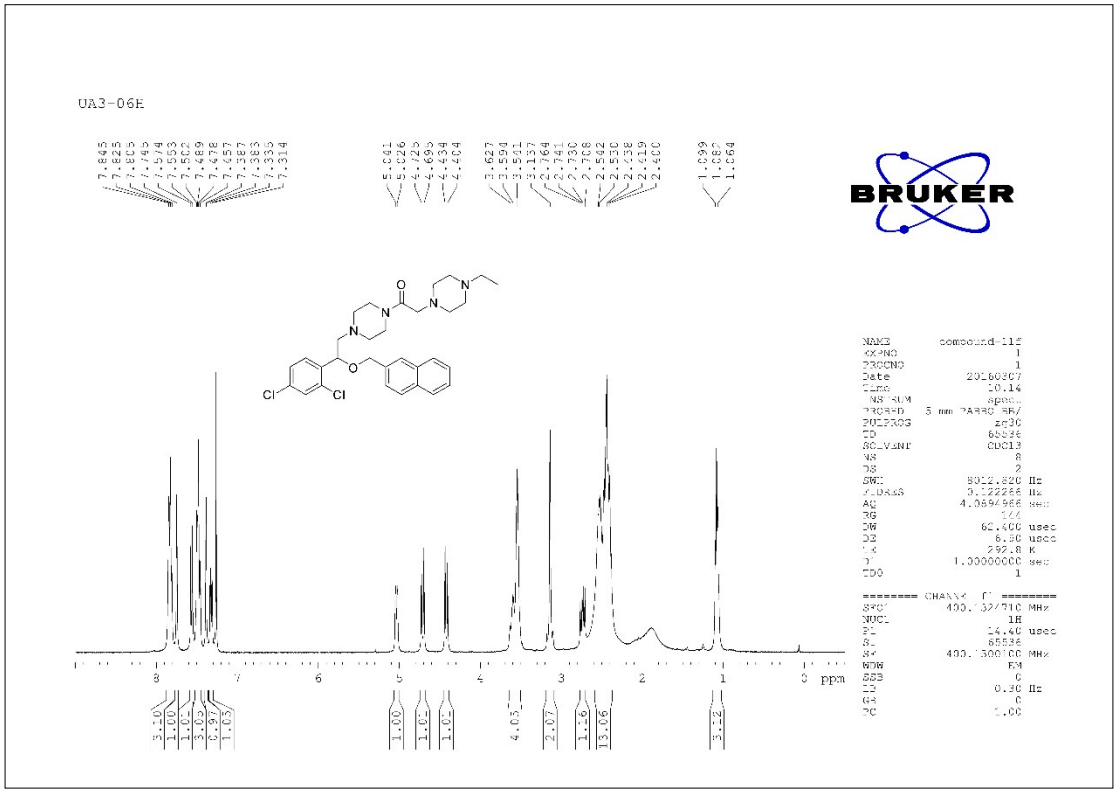
^{1}H-NMR spectrum of **UA3-05**



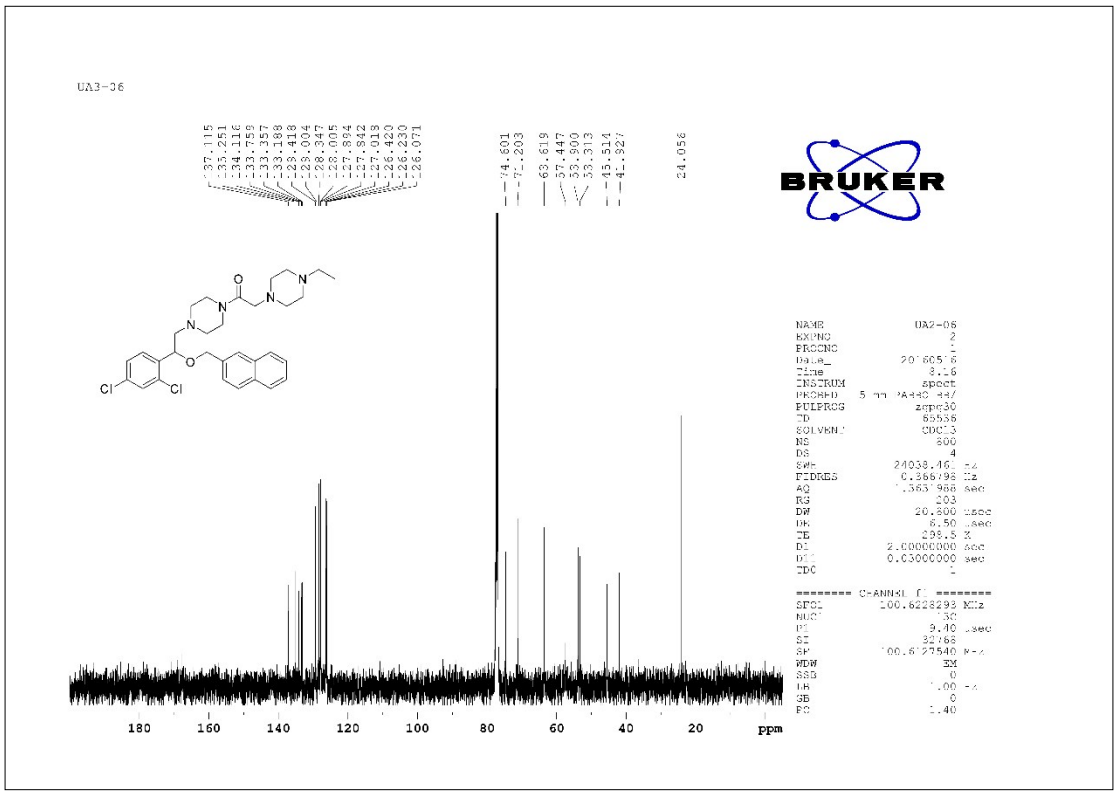
^{13}C-NMR spectrum of **UA3-05**



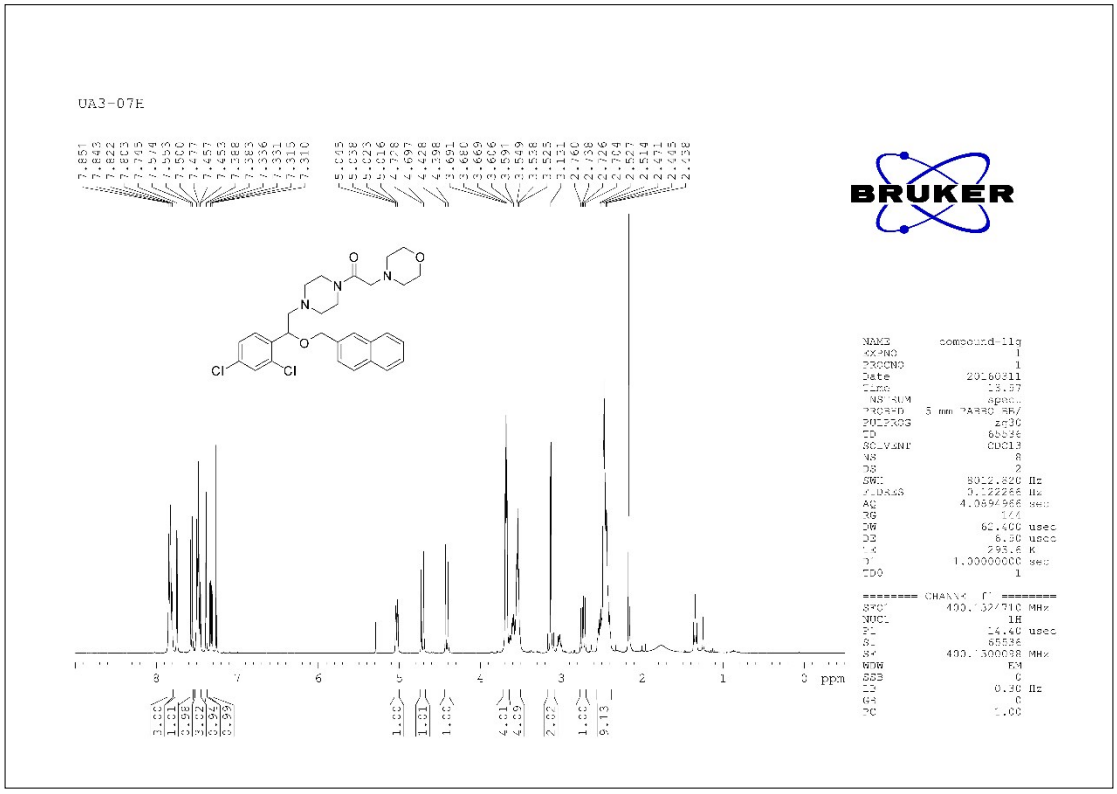
^{1}H-NMR spectrum of **UA3-06**



^{13}C-NMR spectrum of **UA3-06**



^{1}H-NMR spectrum of **UA3-07**



^{13}C-NMR spectrum of **UA3-07**