Supporting Information

Discovery of soluble epoxide hydrolase inhibitors based on the skeleton of piperine: Synthesis, properties, molecular dynamics simulation, and their potentials in acute lung injury

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1. Synthesis

1.1 Synthesis of intermediate 3

To a solution of methyl (*E*)-4-bromobut-2-enoate (0.895 g, 5.00 mmol) in NMP (15 mL) triethyl phosphite (0.95 mL, 5.5 mmol) was added, and then the mixture was heated for 8 h at 130 □. The residueing mixture was poured into 50 ml crushed ice, extracted with dichloromethane (3 × 50 ml). The combined organic layers were washed with saturated aqueous sodium bicarbonate and brine, and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to produce the crude oil and purified by silica gel flash chromatography (dichloromethane/methanol 9:1) as a colorless oil, yield 83%. Methyl (*E*)-4-(diethoxyphosphoryl)but-2-enoate (**3a**): ^{1}H-NMR (400 MHz, $CDCl_3$), δ_H 6.89 (1H, m), 5.97 (1H, ddd, J = 15.5, 5.0, 1.3 Hz), 4.13 (4H, q, J = 6.9 Hz),

3.74 (3H, s), 2.78 (1H, d, J = 7.8 Hz), 2.73 (1H, d, J = 7.8 Hz).

1.2 Synthesis of intermediate 6

To a solution of 3,4-dihydroxybenzaldehyde **4** (1.5 g, 5.0 mmol) in DMF (20 mL), K_2CO_3 (1.38 g, 10.0 mmol) and 1, 2-dibromoethane **5** (1.38 g, 10.0 mmol) were dropwise added. The reaction mixture was allowed to heat at 90 °C for 15 h. The mixture was poured onto crushed ice and extracted with ethyl acetate (3 × 60 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate and brine, and then dried over anhydrous sodium sulfate. After removing the solvent under reduced pressure, and the crude product was purified by silica sel flash chromatography (dichloromethane/methanol 2-3%) as a yellow solid, yield 68%. Benzo[*d*][1,3]dioxole-5-carbaldehyde (**6**): ^{1}H-NMR (400 MHz, $CDCl_3$), δ_H 9.81 (1H, s), 7.41 (1H, dd, J = 8.0, 1.5 Hz), 7.33 (1H, d, J = 1.5 Hz), 6.92 (1H, d, J = 8.0 Hz), 6.07 (2H, s); ^{13}C-NMR (100 MHz, $CDCl_3$), δ_C 190.2, 153.1, 148.7, 131.9, 128.6, 108.3, 106.9, 102.1.

1.3 Synthesis of intermediate 7

To a solution of intermediate **6** (0.75 g, 5.0 mmol) in THF (15 mL), and LiOH (143.7 mg, 6.0 mmol) was added. The reaction mixture was allowed to reflux for 4 h. After removing the solvent under reduced pressure, the mixture was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate and brine, and then dried over anhydrous sodium sulfate. After removing the solvent under reduced pressure, and purified by silica sel flash chromatography (dichloromethane/methanol 2.5%) as a light yellow solid, yield 90%. Methyl (2*E*,4*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)penta-2,4-dienoate (**7**): ^{1}H-NMR (400

MHz, $CDCl_3$), δ_H 7.42 (1H, dd, J = 15.1, 15.2 Hz), 6.99 (1H, d, J = 1.3 Hz), 6.91 (1H, dd, J = 8.1, 1.3 Hz), 6.80 (1H, d, J = 15.4 Hz), 6.78 (1H, d, J = 8.1 Hz), 6.70 (1H, dd, J = 15.4, 15.2 Hz), 5.98 (2H,s), 5.94 (1H, d, J = 15.1 Hz), 3.76 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$), δ_C 167.6, 148.6, 148.3, 144.9, 140.2, 130.5, 130.5, 124.5, 122.9, 119.9, 108.5, 105.8, 101.3, 51.4.

1.4 Synthesis of intermediate 8

The intermediate **7** 1.0 g was solved in 1N NaOH (50% methanol, 20 mL), and the reaction mixture was stirred over night at Room temperature. After removing the most methanol, the aqueous phase was acidified by 1N HCl to pH = 3, and the resulting precipitate was collected by filtration to give the intermediate **8** as a yellow solid, yield 94%. (2*E*,4*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)penta-2,4-dienoic acid (**8**): ^{1}H-NMR (400 MHz, DMSO-d_6), δ_H 12.19 (1H, s), 7.30 (1H, ddd, J = 15.1, 14.5, 6.7 Hz), 7.23 (1H, d, J = 1.3 Hz), 7.00 (1H, dd, J = 8.0, 1.3 Hz), 6.98 (1H, d, J = 2.84 Hz), 6.96 (1H, s), 6.92 (1H, d, J = 8.0 Hz), 6.05 (2H, s), 5.92 (1H, d, J = 15.2 Hz), 1.35 (2H, t, J = 7.1 Hz); ^{13}C-NMR (100 MHz, DMSO-d_6), δ_C 168.1, 148.5, 148.4, 145.1, 140.2, 130.9, 125.3, 123.5, 121.5, 108.9, 106.2, 101.8.

1.5 Synthesis of intermediate 9

To a solution of intermediate **8** (0.5 g, 1.3 mmol), tert-Butyl 1-piperazinecarboxylate (0.24 g, 1.3 mmol) and DIEA (0.33 g，2.6 mmol) in DMF (8 mL), HATU (0.49 g, 1.3 mmol) was added. The mixture was stirred over night at r.t. and the resulting mixture was diluted with water (50 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate and

brine, and then dried over anhydrous sodium sulfate. After removing the solvent under reduced pressure, and purified by silica sel flash chromatography (dichloromethane/methanol 5-8%) as a light yellow solid. Tert-butyl 4-((2*E*,4*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)penta-2,4-dienoyl)piperazine-1-carboxylate (**9**): ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 7.26 (1H, d, *J* = 14.4, 14.8 Hz), 7.18 (1H, d, *J* = 1.3 Hz), 6.99 (1H, dd, *J* = 8.1, 1.6 Hz), 6.93 (1H, d, *J* = 14.5, 15.0 Hz), 6.92 (1H, d, *J* = 8.1 Hz), 6.91 (1H, d, *J* = 14.5, 15.0 Hz), 6.66 (1H, d, *J* = 15.0 Hz), 6.05 (2H, s), 3.54 (4H, brs), 3.33 (4H, brs), 1.41 (9H, s); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 165.0, 154.2, 148.4, 148.3, 142.8, 138.7, 131.2, 125.9, 123.1, 120.6, 109.0, 105.9, 101.7, 79.6, 45.2, 44.0, 43.4, 41.7, 28.5;

1.6 Synthesis of intermediate 10

To a solution of intermediate ***9*** (0.5 g, 1.3 mmol) in CH_2Cl_2 (10 mL), TEA (10 mL) was added. The mixture was stirred for 3 h at r.t. and the solvent was removed under reduced pressure. Water (50 mL) was added and acidified by 1N NaOH to pH = 10, extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate and brine, and then dried over anhydrous sodium sulfate. After removing the solvent under reduced pressure, and purified by silica sel flash chromatography (dichloromethane/methanol 10-15%) as a white solid. (2*E*,4*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)-1-(piperazin-1-yl)penta-2,4-dien-1-one (**10**): ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 7.22 (1H, d, *J* = 14.4, 14.8 Hz), 7.17 (1H, d, *J* = 1.3 Hz), 6.99 (1H, dd, *J* = 8.1, 1.6 Hz), 6.93 (1H, d, *J* = 14.5, 15.0 Hz), 6.92 (1H, d, *J* = 8.1 Hz), 6.91 (1H, d, *J* = 14.5, 15.0 Hz), 6.66 (1H, d, *J* = 15.0 Hz), 6.05 (2H, s), 3.47 (4H, brs),

2.66 (4H, brs); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 164.4, 147.9, 147.7, 141.8, 137.8, 130.8, 125.6, 122.5, 120.5, 108.5, 105.4, 101.3, 46.5, 46.2, 45.5, 42.7.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(p-tolyl)piperazine-1-carboxamide (11a): Light yellow solid, yield 75%, purity, 97%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 8.49 (1H, s), 7.34 (2H, d, J = 8.3 Hz), 7.27 (1H, dd, J = 14.4, 14.5 Hz), 7.18 (1H, d, J = 1.7 Hz), 7.04 (2H, d, J = 8.3 Hz), 6.99 (1H, dd, J = 7.8, 1.7 Hz), 6.97 (1H, dd, J = 14.7, 15.0 Hz), 6.92 (1H, d, J = 7.8 Hz), 6.91 (1H, d, J = 15.0 Hz), 6.71 (1H, d, J = 14.7 Hz), 6.05 (2H, s), 3.60 (4H, br s), 3.47 (4H, br s), 2.22 (3H, s); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 165.1, 155.4, 148.4, 148.3, 142.8, 138.7, 138.2, 131.2, 131.1, 129.2, 129.2, 125.9, 123.1, 120.7, 120.3, 120.3, 109.0, 105.9, 101.7, 45.4, 44.4, 44.0, 41.8, 20.8; HRMS (ESI)$^+$ calculated for $C_{24}H_{25}N_3O_4$, $[M+H]^+$: *m/z* 420.2248, found 420.2253.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(2,4-dimethylphenyl)piperazine-1-carboxamide (11b): Light yellow solid, yield 78%, purity, 99%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 8.05 (1H, s), 7.29-7.25 (1H, m), 7.18 (1H, s), 7.04-7.03 (1H, m), 6.99-6.94 (3H, m), 6.92-6.89(3H, m), 6.68 (1H, d, J = 14.5 Hz), 6.04 (2H, s), 3.59 (4H, s), 3.45 (4H, s) 2.23 (3H, s) 2.10 (3H, s); ^{13}C-NMR (600 MHz, DMSO-d_6), δ_C 164.8, 155.8, 148.2, 148.0, 142.5, 138.4, 135.3, 133.9, 133.4, 130.9, 130.8, 126.5, 126.4, 125.7, 122.8, 120.5, 108.7, 105.7, 101.5, 45.1, 44.3, 43.9, 41.6, 20.6, 18.1; HRMS (ESI)$^+$ calculated for $C_{25}H_{27}N_3O_4$, $[M+H]^+$: *m/z* 434.2074,

found 434.2072.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(4-methoxyphenyl)piperazine-1-carboxamide (11c): Light yellow solid, yield 83%, purity, 97%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 8.44 (1H, s), 7.34 (2H, d, J = 8.0 Hz), 7.29-7.25 (1H, m), 7.18 (1H, s), 6.99-6.97 (2H, m), 6.93-6.90 (2H, m), 6.82 (2H, d, J = 8.0 Hz), 6.72 (1H, d, J = 14.5 Hz), 6.05 (2H, s), 3.70 (3H, s), 3.59 (4H, s), 3.46 (4H, s); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 164.8, 155.4, 154.7, 148.1, 142.5, 138.4, 133.5, 130.9, 125.7, 122.8, 121.8, 120.4, 113.7, 108.7, 105.7, 101.5, 55.3, 45.1, 44.2, 43.7, 41.6; HRMS (ESI) $^{+}$ calculated for $C_{24}H_{25}N_3O_5$, [M+H] $^{+}$: *m/z* 436.1867, found 436.1862.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(3-methoxyphenyl)piperazine-1-carboxamide (11d): Light yellow solid, yield 71%, purity, 97%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 8.57 (1H, s), 7.28-7.24 (1H, m), 7.17 (1H, s), 7.15-7.10 (2H, m), 7.05-7.03 (1H, m), 6.99-6.94 (2H, m), 6.92-6.89(2H, m), 6.72 (1H, d, J = 14.5 Hz), 6.52-6.50 (1H, m), 6.04 (2H, s), 3.69 (3H, s) 3.59 (4H, s), 3.47 (4H, s); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 164.8, 159.6, 154.9, 148.2, 148.0, 142.6, 141.8, 138.4, 130.9, 129.2, 125.7, 122.8, 120.4, 111.9, 108.7, 107.5, 105.7, 105.4.1, 101.5, 55.0, 45.1, 44.2, 43.8, 41.6; HRMS (ESI) $^{+}$ calculated for $C_{24}H_{25}N_3O_5$, [M+H] $^{+}$: *m/z* 436.1867, found 436.1862.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(4-isopropylphenyl)piperazine-1-carboxamide (11e): Light yellow solid, yield 77%, purity, 98%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 8.51 (1H, s), 7.34 (2H, d, J = 8.0 Hz),

7.29-7.25 (1H, m), 7.18 (1H, s), 7.08 (2H, d, J = 8.0 Hz), 6.97 (2H, m), 6.92-6.90 (2H, m), 6.68 (1H, d, J = 14.6 Hz), 6.04 (2H s), 3.59 (4H, s), 3.40 (4H, s) 1.16 (6H, d, J = 7.5 Hz); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 164.8, 155.3, 148.2, 148.0, 142.6, 142.1, 138.4, 138.2, 131.0, 126.2, 125.7, 122.8, 120.4, 120.1, 108.7, 105.7, 101.5, 45.1, 44.2, 43.8, 41.6, 32.9, 24.2; HRMS (ESI)$^+$ calculated for $C_{26}H_{29}N_3O_4$, $[M+H]^+$: *m/z* 448.2231, found 448.2224.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(4-chlorophenyl)piperazine-1-carboxamide (11f): Light yellow solid, yield 78%, purity, 99%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 8.74 (1H, s), 7.51 (2H, d, J = 8.9 Hz), 7.29 (1H, d, J = 8.9 Hz), 7.27 (1H, d, J = 14.5 Hz), 7.18 (1H, d, J = 1.5 Hz), 6.99 (1H, dd, J = 8.0, 1.5 Hz), 6.97 (1H, dd, J = 14.7, 15.0 Hz), 6.92 (1H, d, J = 8.0 Hz), 6.91 (1H, d, J = 15.0 Hz), 6.71 (1H, d, J = 14.5 Hz), 6.05 (2H, s), 3.60 (4H, brs), 3.49 (4H, brs); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 165.1, 155.1, 148.4, 148.3, 142.8, 139.9, 138.7, 131.2, 128.6, 128.6, 125.9, 125.8, 123.1, 121.4, 121.4, 120.6, 109.0, 105.9, 101.7, 45.3, 44.4, 44.1, 41.8; HRMS (ESI)$^+$ calculated for $C_{26}H_{29}N_3O_4$, $[M+H]^+$: *m/z* 440.3407, found 448.3412.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(2-chlorophenyl)piperazine-1-carboxamide (11g): Light yellow solid, yield 68%, purity, 99%; ^{1}H-NMR(600 MHz, DMSO-d_6), δ_H 8.29 (1H, dd, J = 15.1, 15.2 Hz), 7.49 (1H, dd, J = 8.0, 1.5 Hz), 7.45 (1H, dd, J = 8.0, 1.5 Hz), 7.31 - 7.25 (2H, m), 7.18 (1H, d, J = 1.5 Hz), 7.15 (1H, td, J = 7.8, 1.5 Hz), 6.99 (1H, dd, J = 8.0, 1.5 Hz), 6.96 (1H, dd, J = 15.6, 15.4 Hz), 6.93 (1H, s), 6.91 (1H, t, J = 7.4 Hz), 6.71 (1H, d, J = 14.5 Hz), 6.05

(2H, s), 3.62 (4H, m), 3.50 (4H, m); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 165.1, 155.4, 148.4, 148.3, 142.8, 138.7, 137.0, 131.2, 129.7, 128.7, 127.7, 127.5, 126.2, 125.9, 123.1, 120.7, 109.0, 106.0, 101.7, 45.3, 44.5, 44.1, 41.8; HRMS (ESI) $^+$ calculated for $C_{23}H_{22}ClN_3O_4$, [M+H] $^+$: *m/z* 440.3407, found 440.3412.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(3,4-dichlorophenyl)piperazine-1-carboxamide (11h): Light yellow solid, yield 86%, purity, 97%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 8.89 (1H, s), 7.85 (1H, d, J = 2.0 Hz), 7.49 - 7.45 (2H, m), 7.28 (1H, d, J = 14.5 Hz), 7.18 (1H, s), 6.99 (1H, dd, J = 8.0, 1.5 Hz), 6.97 (1H, dd, J = 14.7, 15.0 Hz), 6.93 (1H, d, J = 8.0 Hz), 6.91 (1H, d, J = 15.0 Hz), 6.71 (1H, d, J = 15.0 Hz), 6.05 (2H, s), 3.62 (4H, br s), 3.50 (4H, br s); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 165.1, 156.6, 155.4, 154.9, 148.4, 148.3, 142.8, 138.7, 131.2, 127.9, 127.8, 126.6, 125.9, 125.5, 125.4, 124.4, 124.4, 123.1, 120.7, 116.0, 115.8, 109.0, 105.9, 101.7, 45.3, 44.5, 44.1, 41.8; HRMS (ESI) $^+$ calculated for $C_{23}H_{21}Cl_2N_3O_4$, [M+H] $^+$: *m/z* 475.3469, found 475.3473.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(3,5-dichlorophenyl)piperazine-1-carboxamide (11i): Light yellow solid, yield 71%, purity, 98%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 8.94 (1H, s), 7.61 (2H, d, J = 1.8 Hz), 7.28 (1H, dd, J = 14.5, 14.6 Hz), 7.18 (1H, d, J = 1.8 Hz), 7.12 (1H, d, J = 1.5 Hz), 6.99 (1H, dd, J = 8.0, 1.5 Hz), 6.97 (1H, dd, J = 14.7, 15.0 Hz), 6.93 (1H, d, J = 8.0 Hz), 6.91 (1H, d, J = 15.0 Hz), 6.71 (1H, d, J = 15.0 Hz), 6.05 (2H, s), 3.62 (4H, br s), 3.50 (4H, br s); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 165.1, 154.6, 148.4, 148.3, 143.5, 142.8, 138.7, 134.1, 134.1, 131.2, 125.9, 123.1, 121.1, 120.6, 117.6, 117.6, 109.0, 105.9, 101.7,

45.2, 44.4, 44.0, 41.7; HRMS (ESI) $^{+}$ calculated for $C_{23}H_{21}Cl_2N_3O_4$, [M+H] $^{+}$: *m/z* 475.3469, found 475.3473.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(4-bromophenyl)piperazine-1-carboxamide (11j): Light yellow solid, yield 80%, purity, 98%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 8.73 (1H, s), 7.46-7.45 (2H, m), 7.43-7.39 (2H, m), 7.29-7.25 (1H, m), 6.18-6.17 (1H, m), 6.99-6.94 (2H, m), 6.93-6.90 (2H, m), 6.68 (1H, d, *J* = 14.5 Hz), 6.04 (2H, s), 3.60 (4H, s), 3.48 (4H, s); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 164.8, 154.8, 142.6, 140.1, 138.5, 131.7, 131.3, 130.9, 125.7, 122.8, 121.6, 120.4, 113.5, 108.7, 105.7, 101.5, 45.1, 44.2, 43.8, 41.5; HRMS (ESI) $^{+}$ calculated for $C_{23}H_{22}BrN_3O_4$, [M+H] $^{+}$: *m/z* 484.0866, found 484.0863.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(4-fluorophenyl)piperazine-1-carboxamide (11k): Light yellow solid, yield 74%, purity, 97%; ^{1}H-NMR(600 MHz, DMSO-d_6), δ_H 7.45 (1H, dd, *J* = 14.5, 14.6 Hz), 7.31 (1H, dt, *J* = 11.3, 2.2 Hz), 7.22 (1H, dd, *J* = 14.4, 14.4 Hz), 7.05 (1H, dd, *J* = 8.0, 1.3 Hz), 6.99 (1H, d, *J* = 1.3 Hz), 6.90 (1H, dd, *J* = 8.2, 1.5 Hz), 6.79 (1H, d, *J* = 15.5 Hz), 6.78 (1H, d, *J* = 8.2 Hz), 6.76 - 6.71 (3H, m), 6.38 (1H, d, *J* = 14.6 Hz), 5.97 (2H, s), 3.73 (4H, m), 3.56 (4H, m); ^{13}C-NMR (600 MHz, DMSO-d_6), δ_C 165.9, 163.8, 162.3, 154.5, 148.4, 148.3, 144.0, 140.5, 140.4, 139.6, 130.6, 129.9, 129.9, 124.8, 122.8, 118.4, 115.1, 115.1, 110.0, 109.9, 108.5, 107.4, 107.2, 105.7, 101.3, 45.4, 44.2, 43.4, 41.3; HRMS (ESI) $^{+}$ calculated for $C_{23}H_{22}FN_3O_4$, [M+H] $^{+}$: *m/z* 424.1978, found 424.1983.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(3-fluorophenyl)piperazine-1-carboxamide (11l): Light yellow solid, yield 78%, purity,

99%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 7.43 (1H, dd, J = 14.5, 15.0 Hz), 7.33 - 7.31 (2H, m), 6.99 - 6.96 (3H, m), 6.89 (1H, d, J = 8.0 Hz), 6.97 - 6.70 (4H, m), 6.37 (1H, d, J = 14.6 Hz), 5.97 (2H, s), 4.19 (2H, m), 3.71 (4H, brs), 3.56 (4H, brs); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 165.9, 159.8, 158.3, 155.2, 155.2, 155.1, 148.4, 148.2, 144.1, 139.7, 139.6, 134.7, 134.72, 130.6, 124.7, 124.7, 122.8, 122.4, 122.4, 122.3, 122.3, 122.3, 118.4, 115.6, 115.6, 115.5, 115.4, 115.4, 108.5, 105.7, 101.4, 45.4, 44.1, 43.4, 41.4; HRMS (ESI) $^{+}$ calculated for $C_{23}H_{22}FN_3O_4$, [M+H] $^{+}$: *m/z* 424.1978, found 424.1983.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(2-fluorophenyl)piperazine-1-carboxamide (11m): Light yellow solid, yield 88%, purity, 99%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 8.39 (1H, s), 7.44 (1H, m), 7.27 (1H, dd, J = 14.6, 15.0 Hz), 7.18 (2H, m), 7.11 (2H, m), 6.99 (1H, dd, J = 8.0, 1.5 Hz), 6.97 (1H, dd, J = 14.7, 15.0 Hz), 6.93 (1H, d, J = 8.0 Hz), 6.91 (1H, d, J = 15.0 Hz), 6.71 (1H, d, J = 15.0 Hz), 6.05 (2H, s), 3.61 (4H, br s), 3.48 (4H, br s); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 165.1, 156.7, 155.4, 154.8, 148.4, 148.3, 142.8, 138.7, 131.2, 127.9, 127.9, 126.6, 126.6, 125.9, 125.5, 125.5, 124.5, 124.4, 123.1, 120.7, 116.0, 115.8, 109.0, 105.9, 101.7, 45.3, 44.6, 44.1, 41.8; HRMS (ESI) $^{+}$ calculated for $C_{23}H_{22}FN_3O_4$, [M+H] $^{+}$: *m/z* 424.1978, found 424.1983.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(2,4-difluorophenyl)piperazine-1-carboxamide (11n): Light yellow solid, yield 74%, purity, 96%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 7.96 (1H, m), 7.47 (1H, dd, J = 14.5, 14.6 Hz), 6.99 (1H, d, J = 1.5 Hz), 6.91 (1H, dd, J = 8.0, 1.5 Hz), 6.87 – 6.72 (5H, m), 6.47

(1H, d, J = 2.8 Hz), 6.38 (1H, d, J = 14.6 Hz), 5.98 (2H, s), 3.76 (4H, m), 3.58 (4H, m); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 165.8, 159.0, 158.9, 157.4, 157.3, 154.3, 153.6, 153.5, 152.0, 151.9, 148.4, 148.3, 144.0, 139.6, 130.7, 124.8, 123.3, 123.3, 123.3, 123.2, 123.1, 123.1, 123.1, 123.1, 122.8, 118.5, 111.3, 111.3, 111.2, 111.1, 108.5, 105.7, 103.6, 103.4, 103.4, 103.2, 101.3, 45.2, 44.1, 43.4, 41.3; HRMS (ESI) $^+$ calculated for $C_{23}H_{21}F_2N_3O_4$, [M+H] $^+$: *m/z* 442.1839, found 442.1841.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(4-(trifluoromethyl)phenyl)piperazine-1-carboxamide (11o): Light yellow solid, yield 72%, purity, 97%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 9.0 (1H, s), 7.70 (2H, d, J = 8.0 Hz), 7.58 (2H, s), 7.31-7.27 (1H, m), 7.19 (1H, s), 6.98 (2H, m), 6.93 (2H, m), 6.72 (1H, d, J = 14.5 Hz), 6.06 (2H, s), 3.63 (4H, s), 3.52 (4H, s); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 164.8, 154.7, 148.2, 148.1, 144.5, 142.6, 138.5, 130.8, 125.8, 125.8, 125.6, 123.9, 122.8, 121.9, 121.7, 120.4, 119.1, 108.4, 105.7, 101.5, 45.0, 44.2, 43.9, 41.5; HRMS (ESI) $^+$ calculated for $C_{24}H_{22}F_3N_3O_4$, [M+H] $^+$: *m/z* 474.1635, found 474.1630.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide (11p): Light yellow solid, yield 76%, purity, 97%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 8.94 (1H, s), 7.92 (1H, s), 7.75 (1H, s), 7.47 (1H, m), 7.30-7.26 (2H, m), 7.18 (1H, s), 6.99-6.96 (2H, m), 6.93-6.90 (2H, m), 6.72 (1H, d, J = 14.5 Hz), 6.04 (2H, s), 3.63 (4H, s), 3.51 (4H, s); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 164.8, 154.8, 148.2, 148.1, 142.6, 141.5, 138.5, 130.9, 129.7, 129.4, 129.2, 125.7, 125.4, 123.6, 122.9, 122.8, 120.4, 118.1, 118.1, 115.6, 115.6, 108.7,

105.7, 101.5, 45.0, 44.2, 43.8, 41.5; HRMS (ESI)$^+$ calculated for $C_{24}H_{22}F_3N_3O_4$, [M+H]$^+$: *m/z* 474.1635, found 474.1631.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(2,4-bis(trifluoromethyl)phenyl)piperazine-1-carboxamide (11q): Light yellow solid, yield 83%, purity, 98%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 9.28 (1H, s), 8.22 (2H, s), 7.60 (1H, s), 7.31-7.27 (1H, m), 7.19 (1H, s), 7.00-6.90 (4H, m), 6.72 (1H, d, J = 14.5 Hz,), 6.06 (2H, s), 3.65 (4H, s), 3.54 (4H, s); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 164.8, 154.4, 148.2, 148.1, 142.8, 142.6, 138.5, 130.9, 130.7, 130.5, 125.6, 124.5, 122.8, 122.7, 120.4, 118.9, 108.7, 105.7, 101.5, 44.9, 44.1, 43.8, 41.4; HRMS (ESI)$^+$ calculated for $C_{25}H_{21}F_6N_3O_4$, [M+H]$^+$: *m/z* 542.1509, found 542.1503.

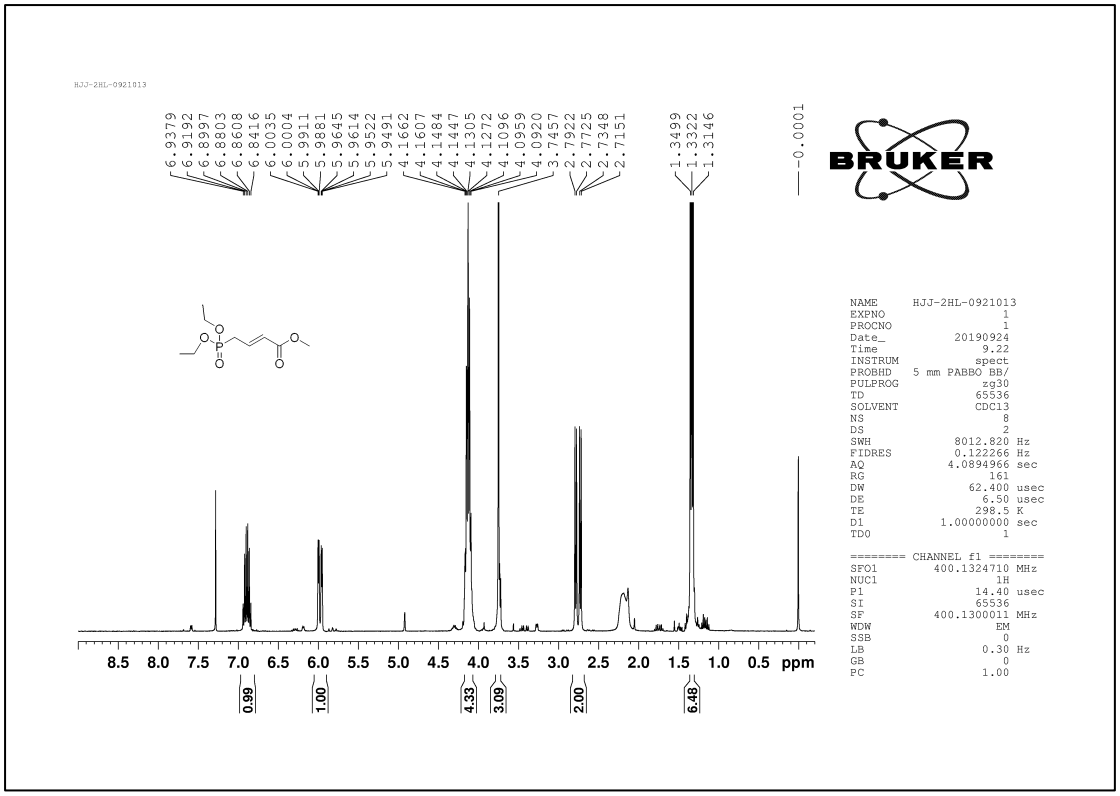
4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(4-cyanophenyl)piperazine-1-carboxamide (11r): Light yellow solid, yield 88%, purity, 98%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 9.09 (1H, s), 7.68-7.67 (4H, m), 7.30-7.26 (1H, m), 7.18 (1H, s), 6.99-6.90 (4H, m), 6.70 (1H, d, J = 14.5 Hz), 6.05 (2H, s), 3.62 (4H, s), 3.51 (4H, s); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 164.8, 154.4, 148.2, 148.1, 145.3, 142.7, 138.5, 133.1, 130.9, 125.7, 122.9, 120.4, 119.6, 119.2, 108.8, 105.3, 103.3, 101.5, 45.0, 44.3, 43.9, 41.5; HRMS (ESI)$^+$ calculated for $C_{24}H_{22}N_4O_4$, [M+H]$^+$: *m/z* 431.1714, found 431.1710.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(3-cyanophenyl)piperazine-1-carboxamide (11s): Light yellow solid, yield 81%, purity, 97%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 8.95 (1H, s), 7.94 (1H, s), 7.75 (1H, s), 7.47 (1H, m), 7.39 (1H, s), 7.30-7.26 (1H, m), 7.18 (1H, s), 6.99-6.95 (2H, m), 6.93-6.90

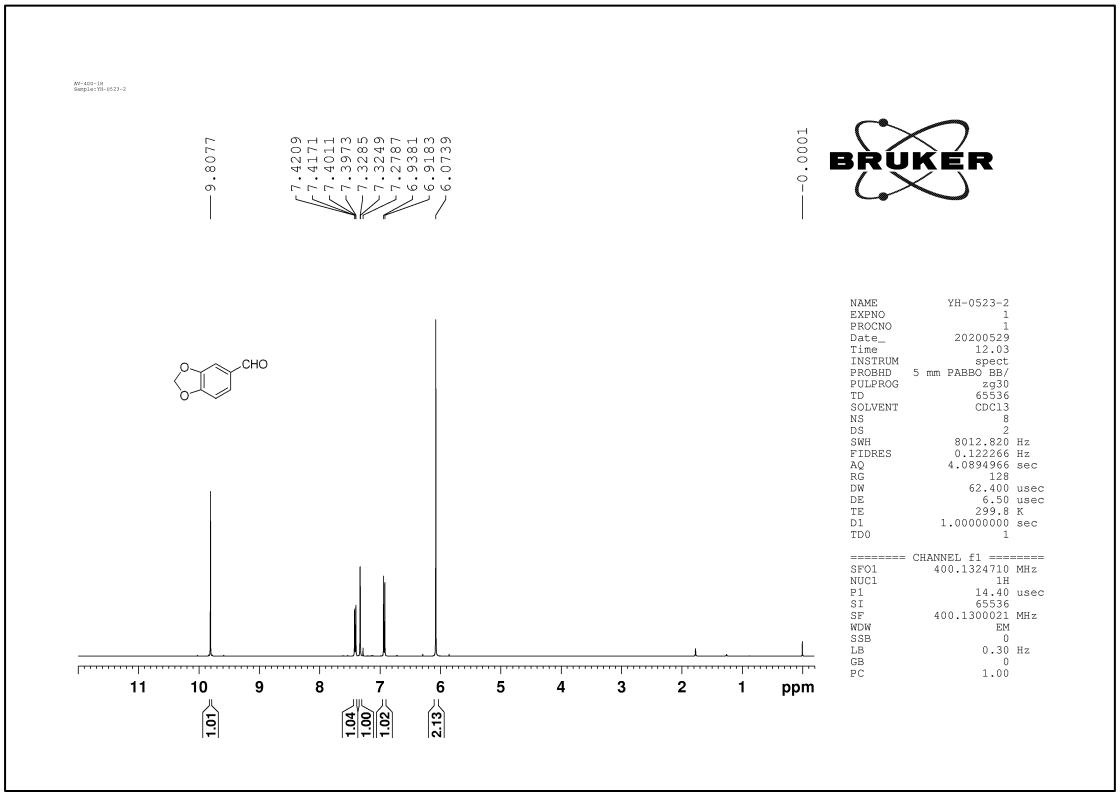
(2H, m), 6.72 (1H, d, J = 14.5 Hz), 6.04 (2H, s), 3.63 (4H, s), 3.51 (4H, s); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 164.8, 154.7, 148.2, 148.1, 142.6, 141.6, 138.5, 130.9, 130.0, 125.7, 125.4, 124.1, 122.8, 122.2, 120.4, 119.2, 111.4, 108.7, 105.7, 101.5, 45.0, 44.2, 43.8, 41.5; HRMS (ESI) $^+$ calculated for $C_{24}H_{22}N_4O_4$, [M+H] $^+$: *m/z* 431.1714, found 431.1710.

4-((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoyl)-N-(naphthalen-1-yl)piperazine-1-carboxamide (11t): Light yellow solid, yield 77%, purity, 99%; ^{1}H-NMR (600 MHz, DMSO-d_6), δ_H 8.68 (1H, s), 7.93-7.88 (2H, m), 7.72 (1H, s), 7.49-7.48 (2H, m), 7.46-7.43 (1H, m), 7.41-7.39 (1H, m), 7.29-7.25 (1H, m), 7.17 (1H, s), 6.98-6.94 (2H, m), 6.92-6.89 (2H, m), 6.72 (1H, d, J = 14.5 Hz), 6.03 (2H, s), 3.65 (4H, s), 3.55 (4H, s); ^{13}C-NMR (150 MHz, DMSO-d_6), δ_C 164.9, 156.3, 148.2, 148.0, 142.6, 138.4, 135.6, 133.9, 130.9, 129.6, 128.1, 125.9, 125.7, 125.7, 125.2, 123.8, 123.1, 122.8, 120.5, 108.8, 105.7, 101.5, 45.2, 44.4, 43.9, 41.7; HRMS (ESI) $^+$ calculated for $C_{27}H_{25}N_3O_4$, [M+H] $^+$: *m/z* 456.1918, found 456.1912.

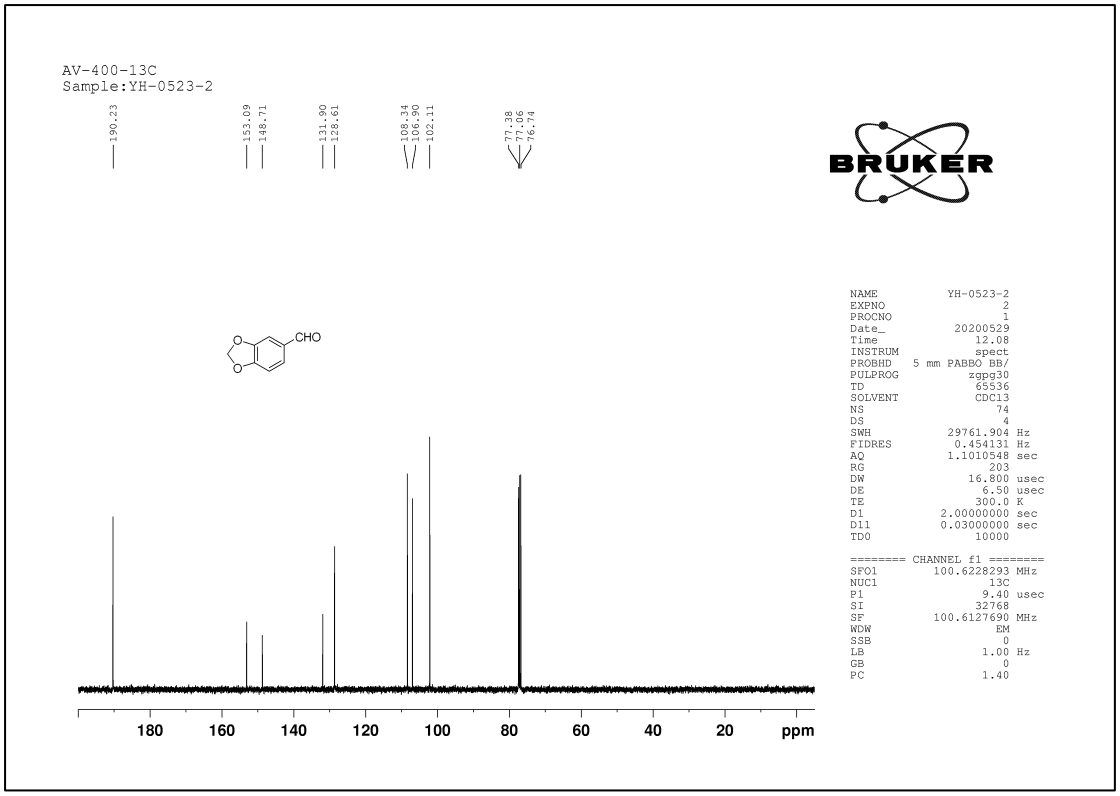
2. ^{1}H and ^{13}C NMR of Compounds



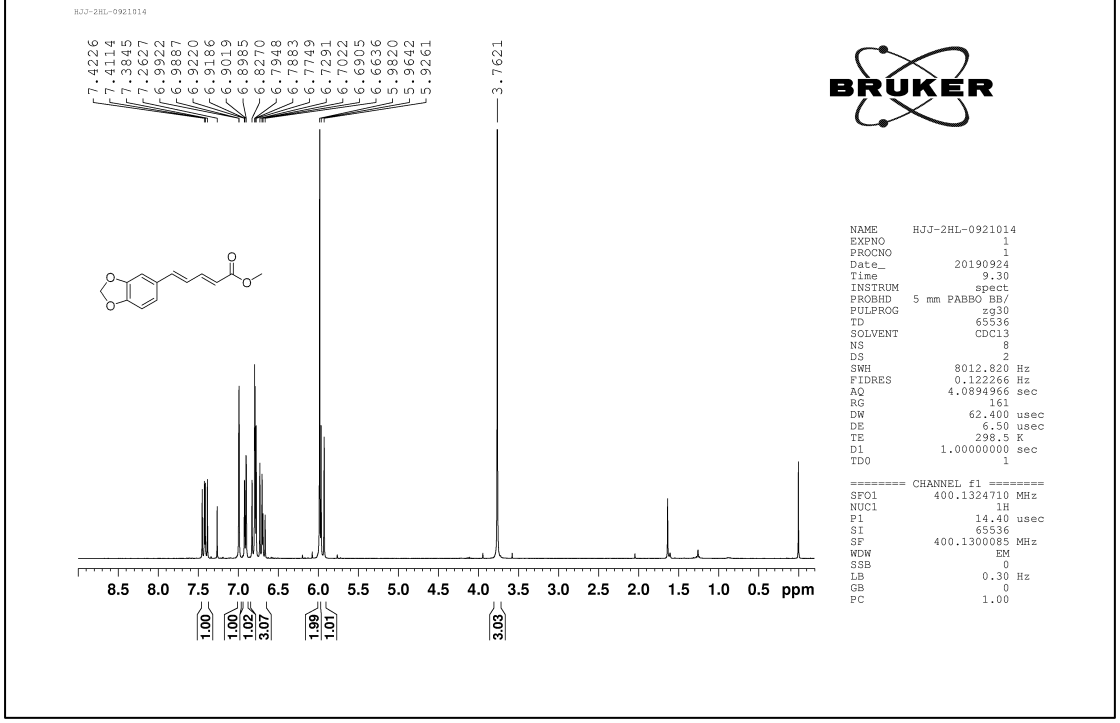
^{1}H-NMR spectrum of compound 3



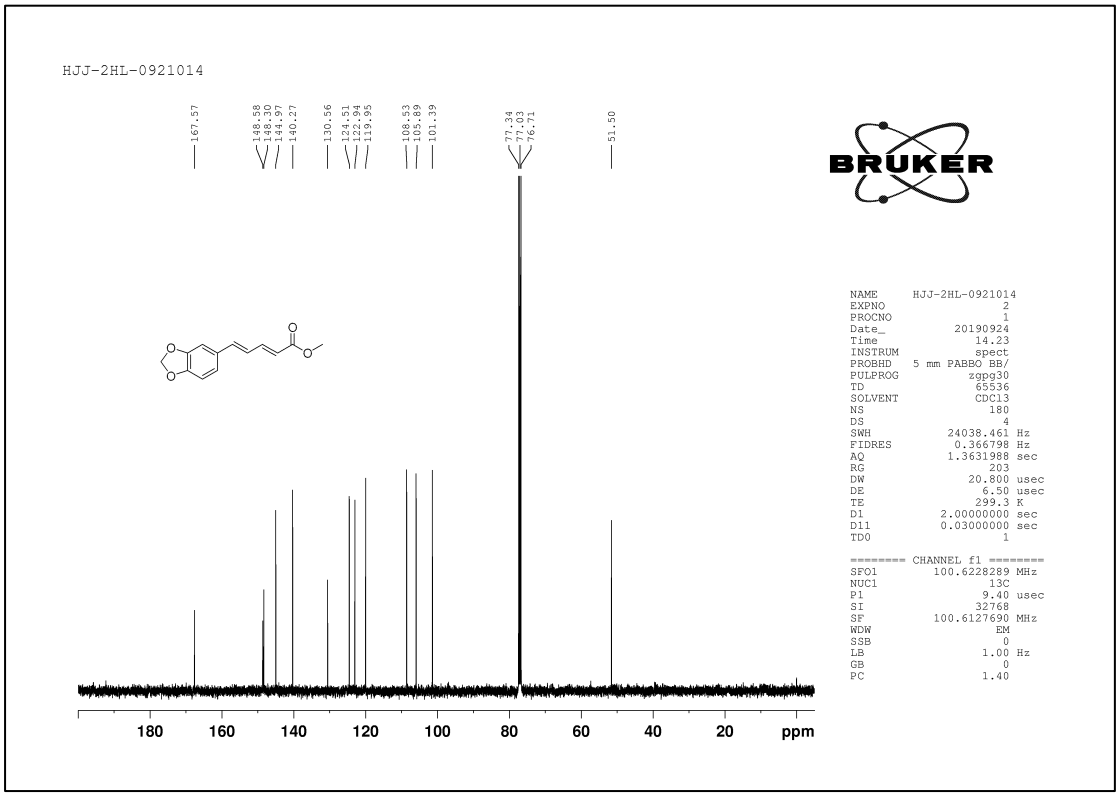
^{1}H-NMR spectrum of compound 6



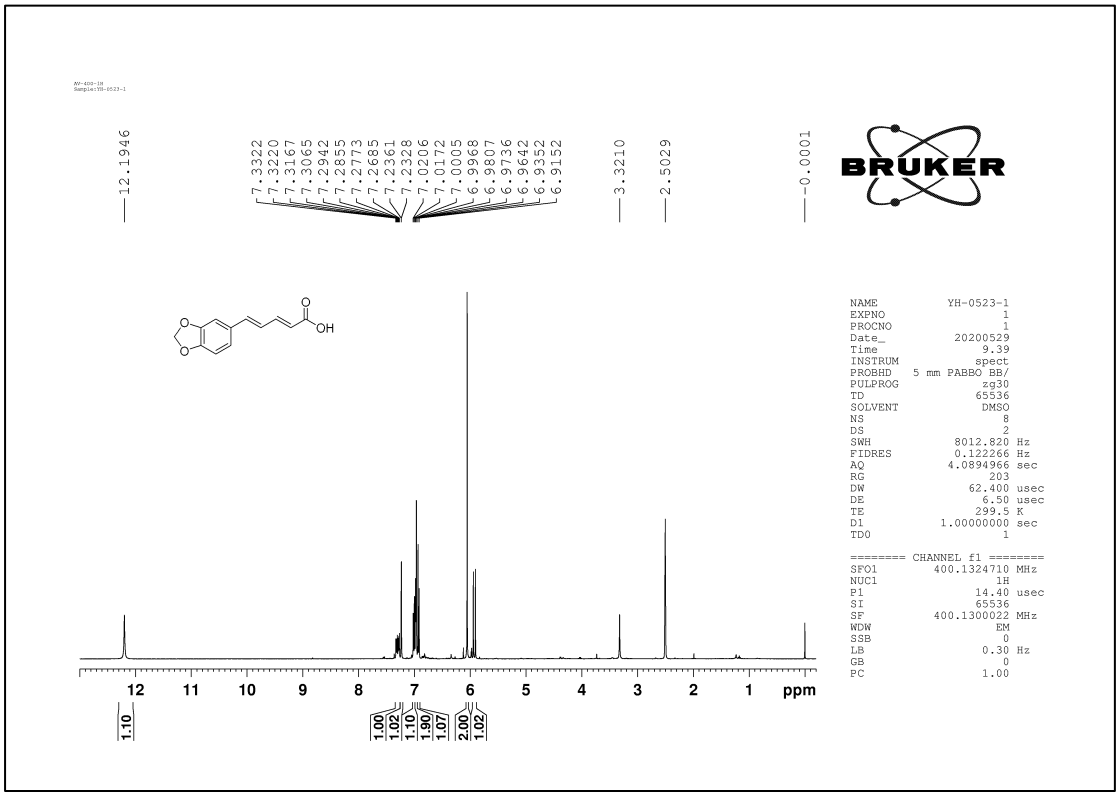
^{13}C-NMR spectrum of compound 6



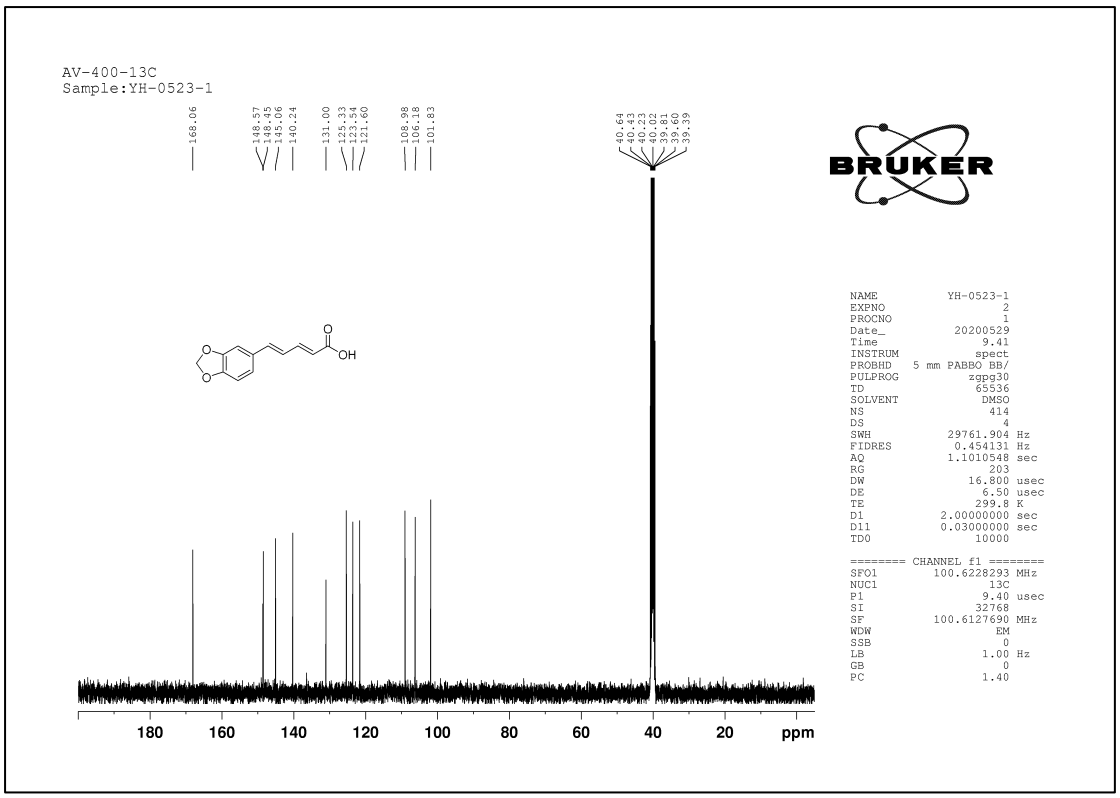
^{1}H-NMR spectrum of compound 7



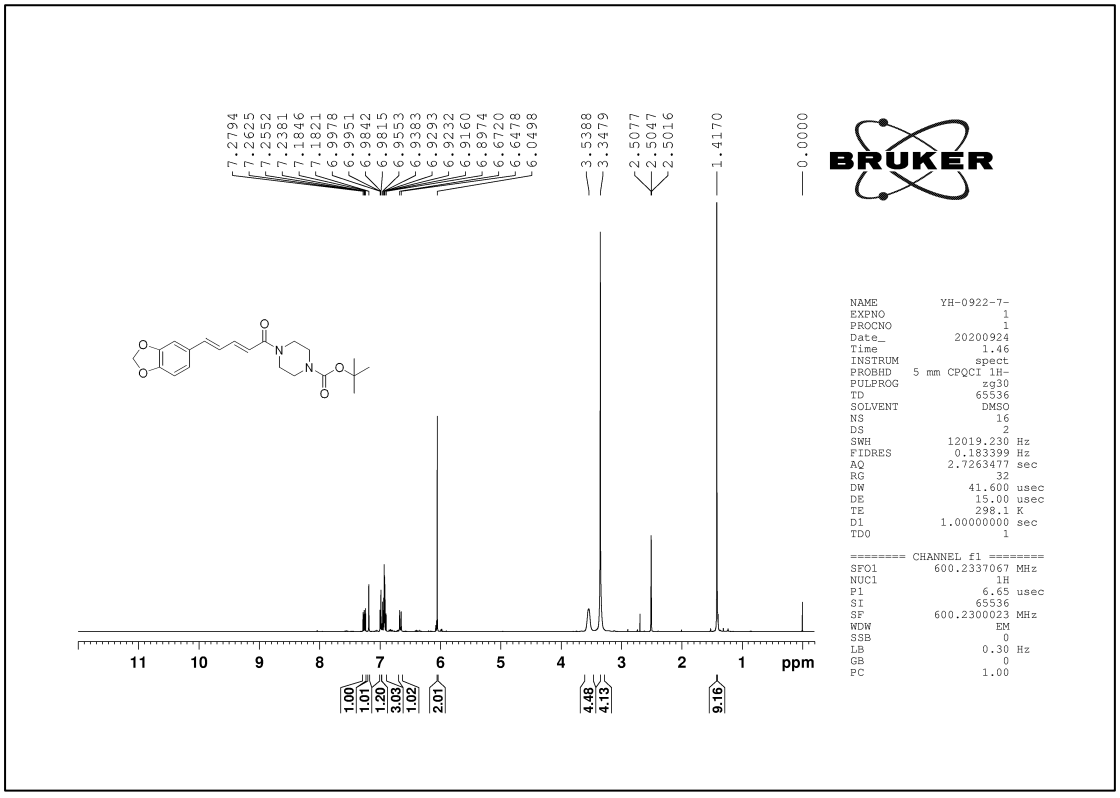
^{13}C-NMR spectrum of compound 7



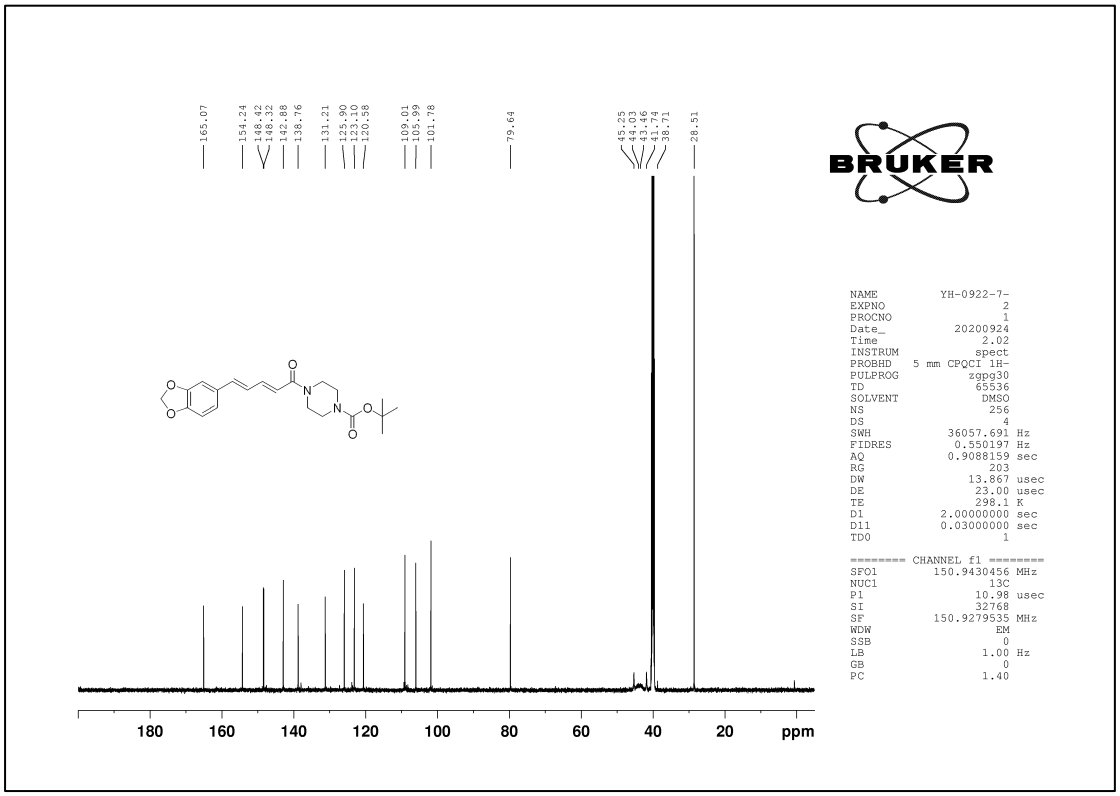
^{1}H-NMR spectrum of compound 8



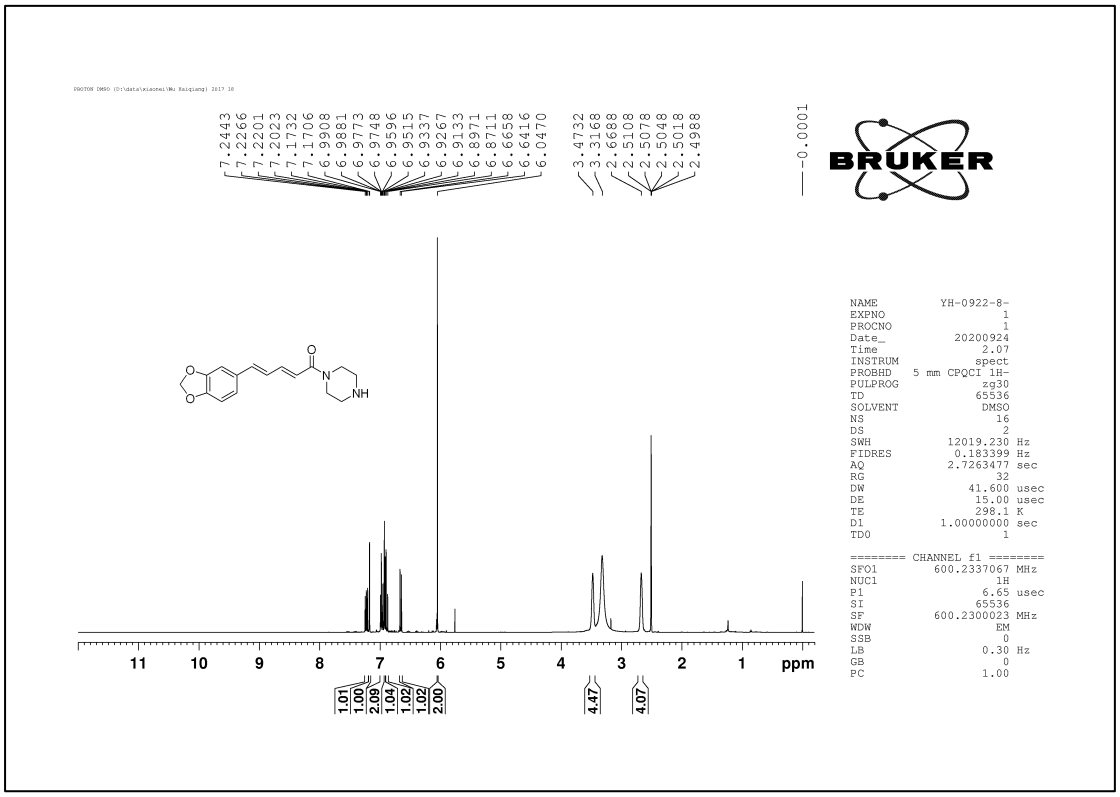
^{13}C-NMR spectrum of compound 8



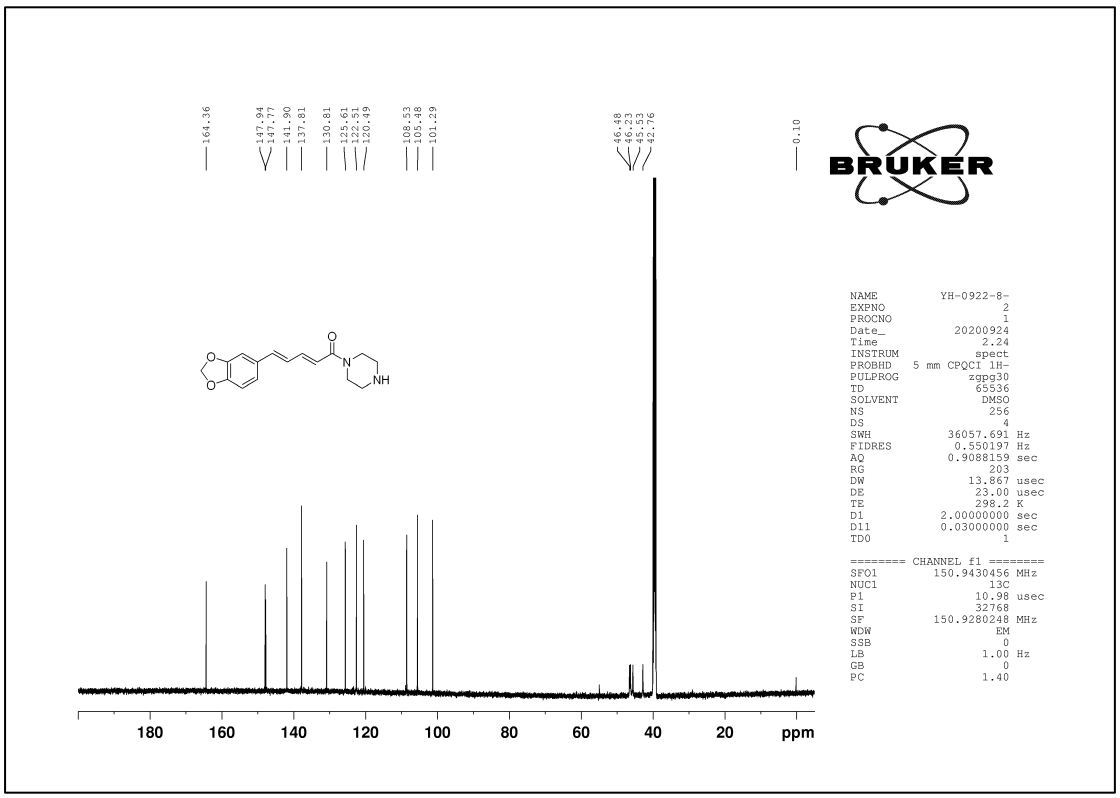
^{1}H-NMR spectrum of compound 9



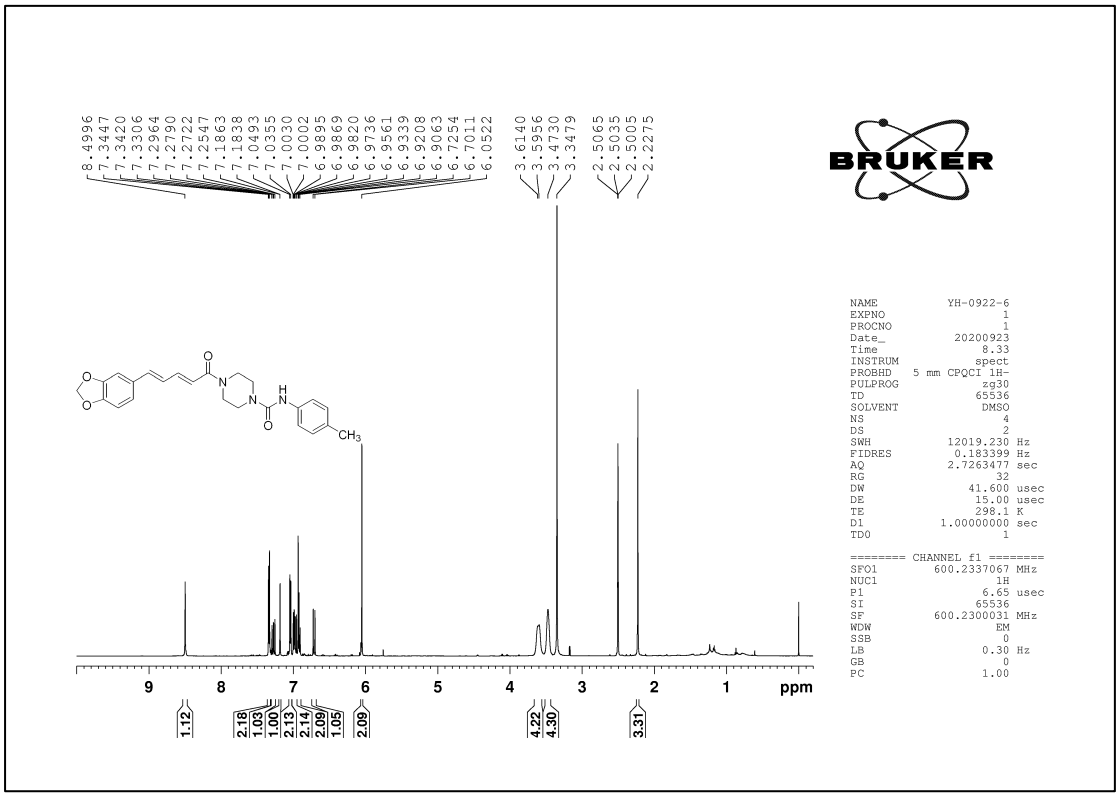
^{13}C-NMR spectrum of compound 9



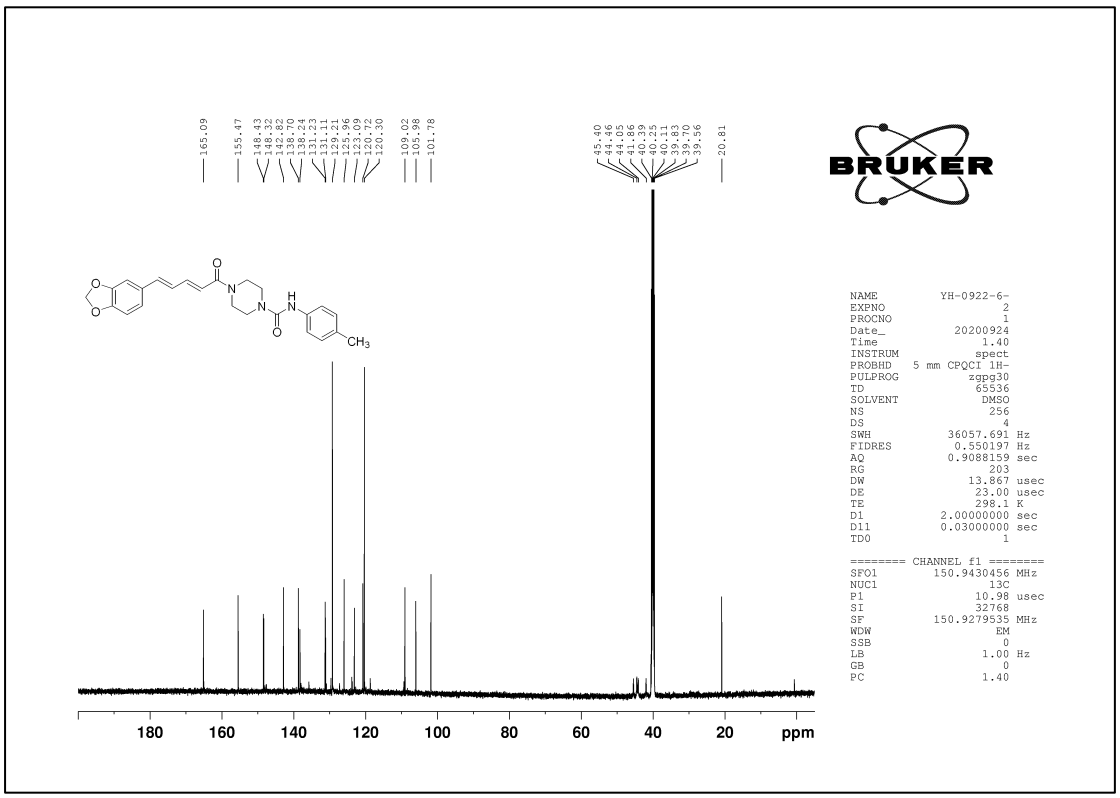
^{1}H-NMR spectrum of compound 10



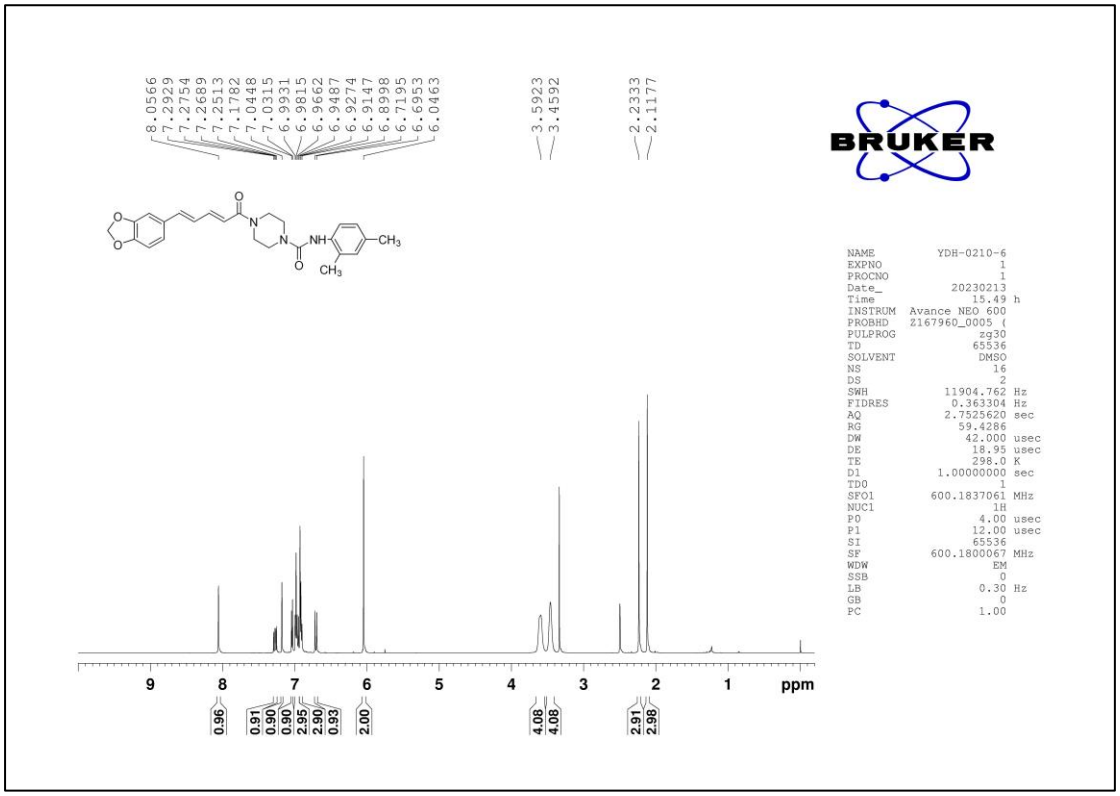
^{13}C-NMR spectrum of compound 10



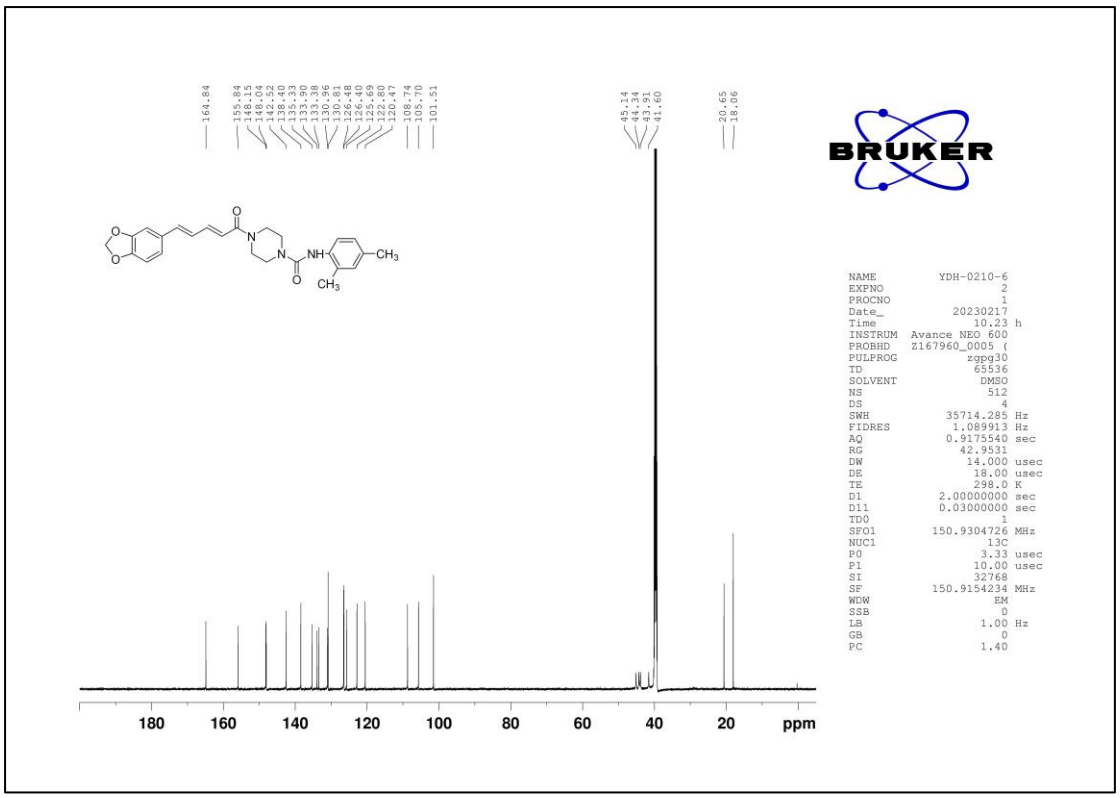
^{1}H-NMR spectrum of compound 11a



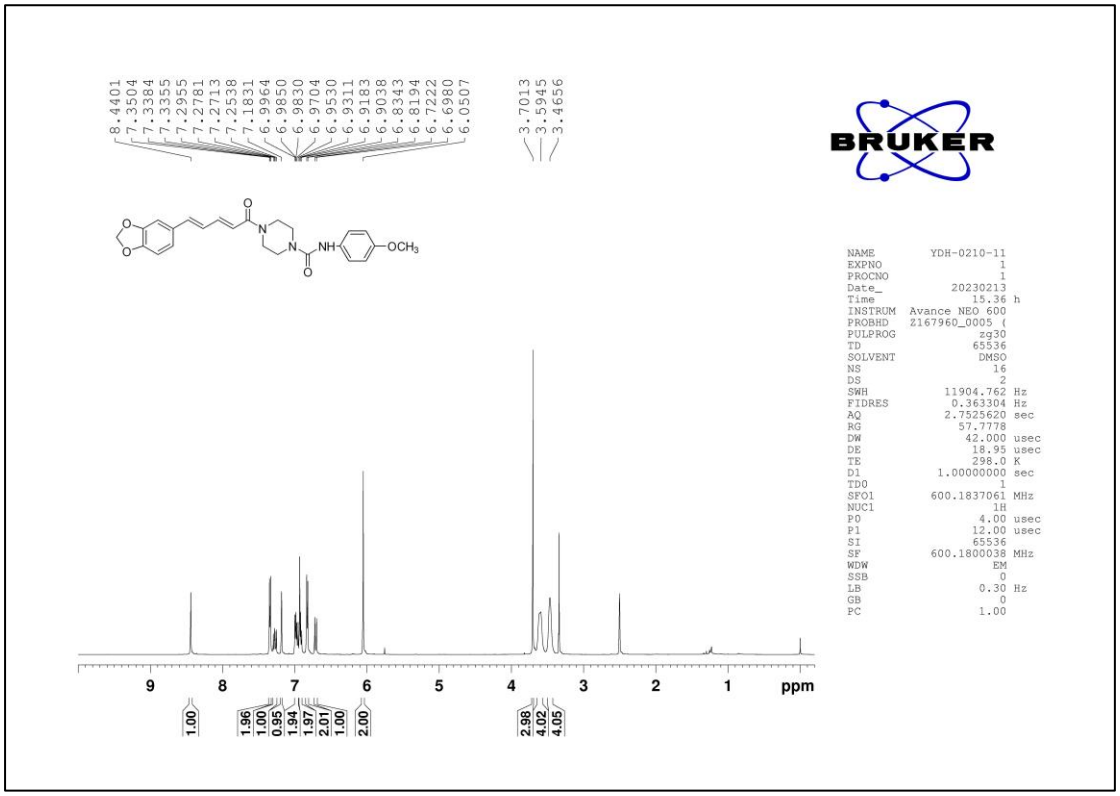
^{13}C-NMR spectrum of compound 11a



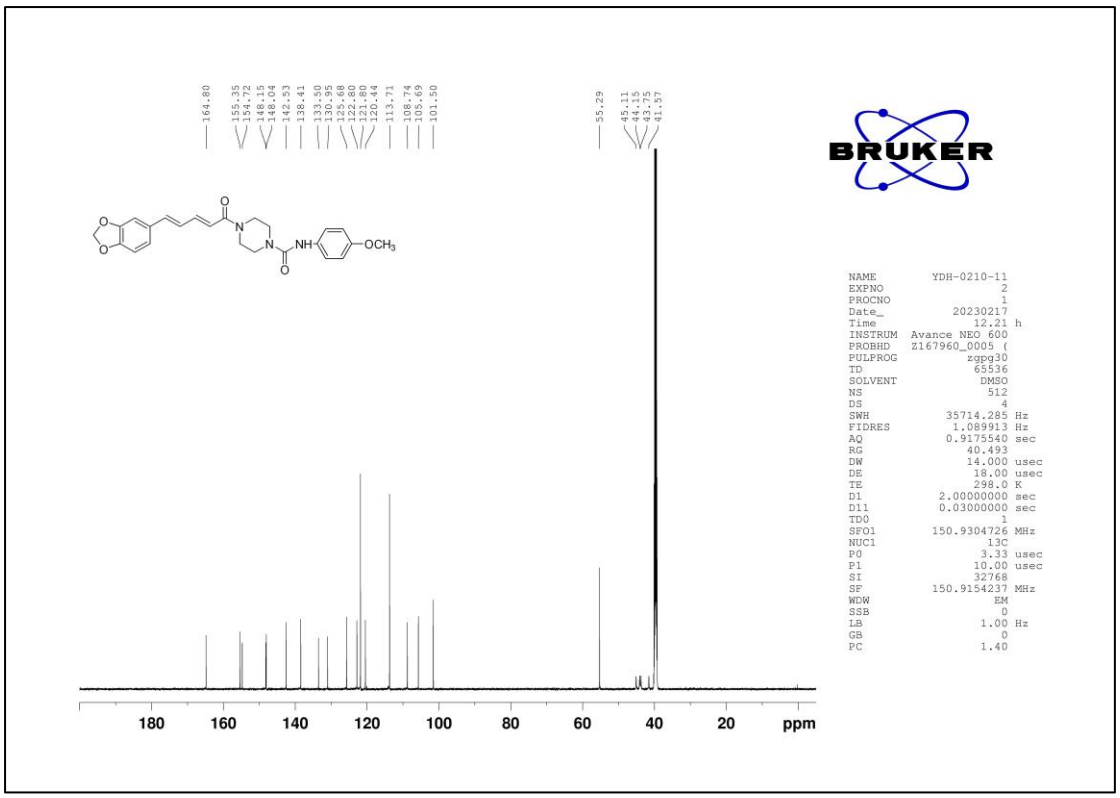
^{1}H-NMR spectrum of compound 11b



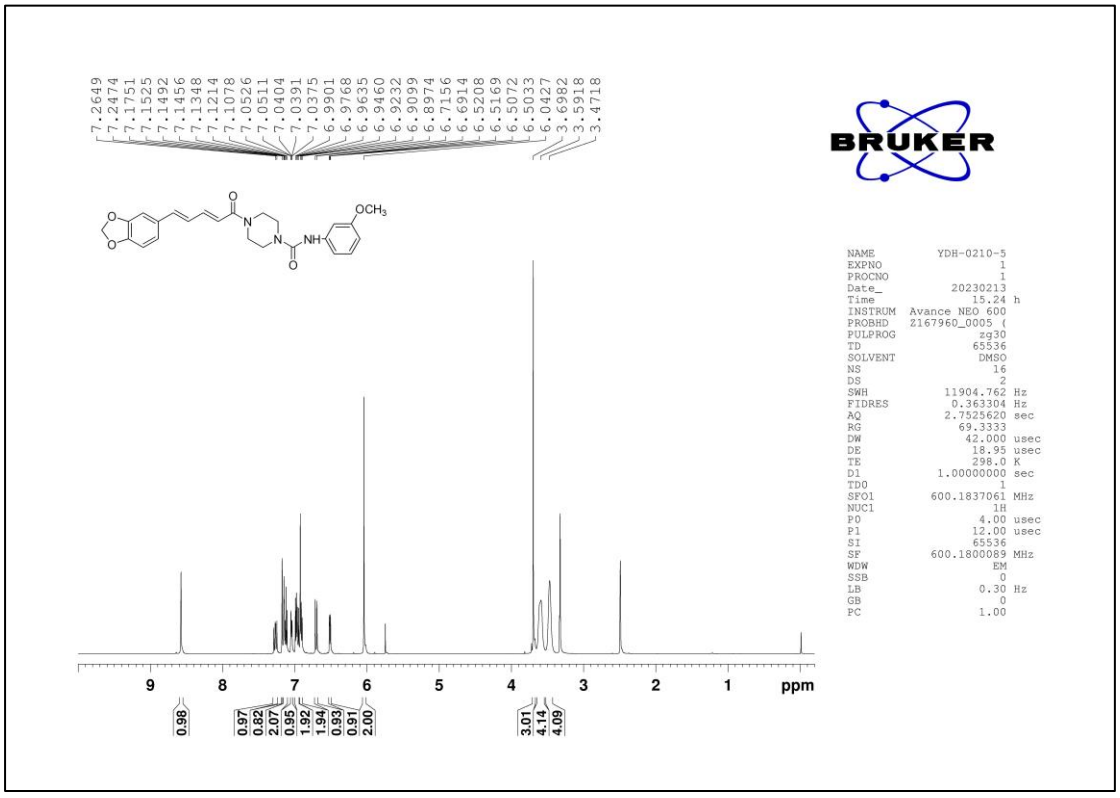
^{13}C-NMR spectrum of compound 11b



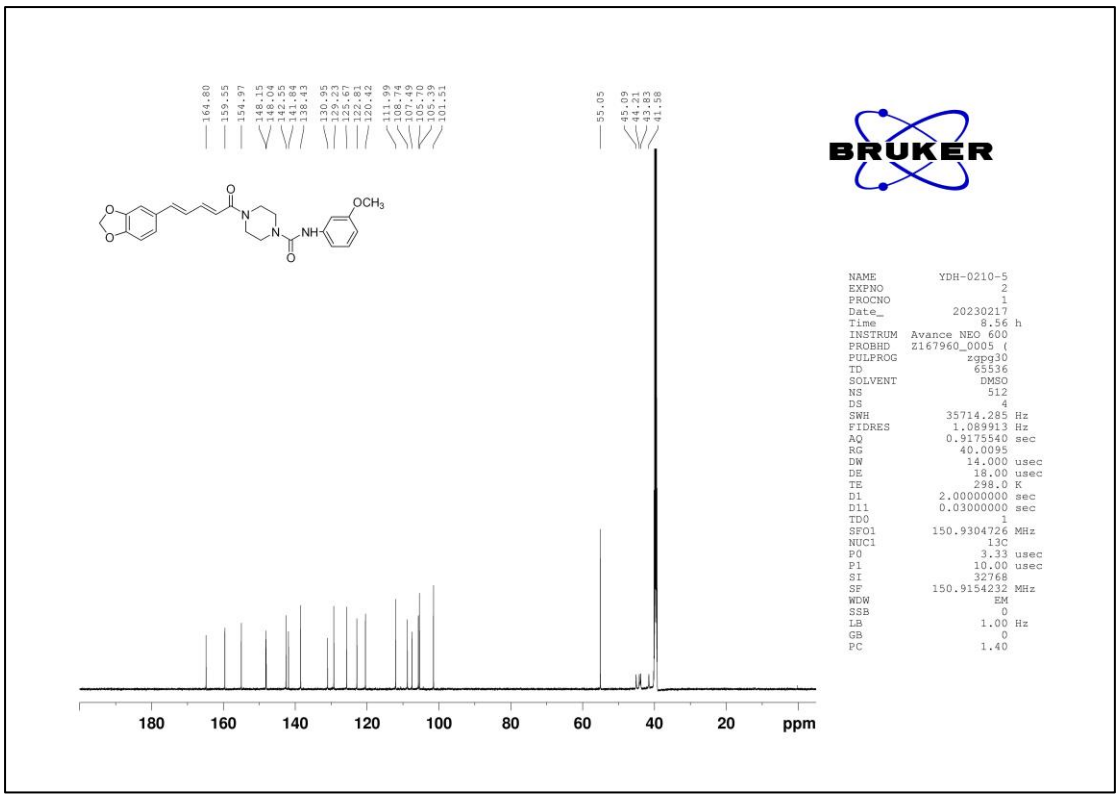
^{1}H-NMR spectrum of compound 11c



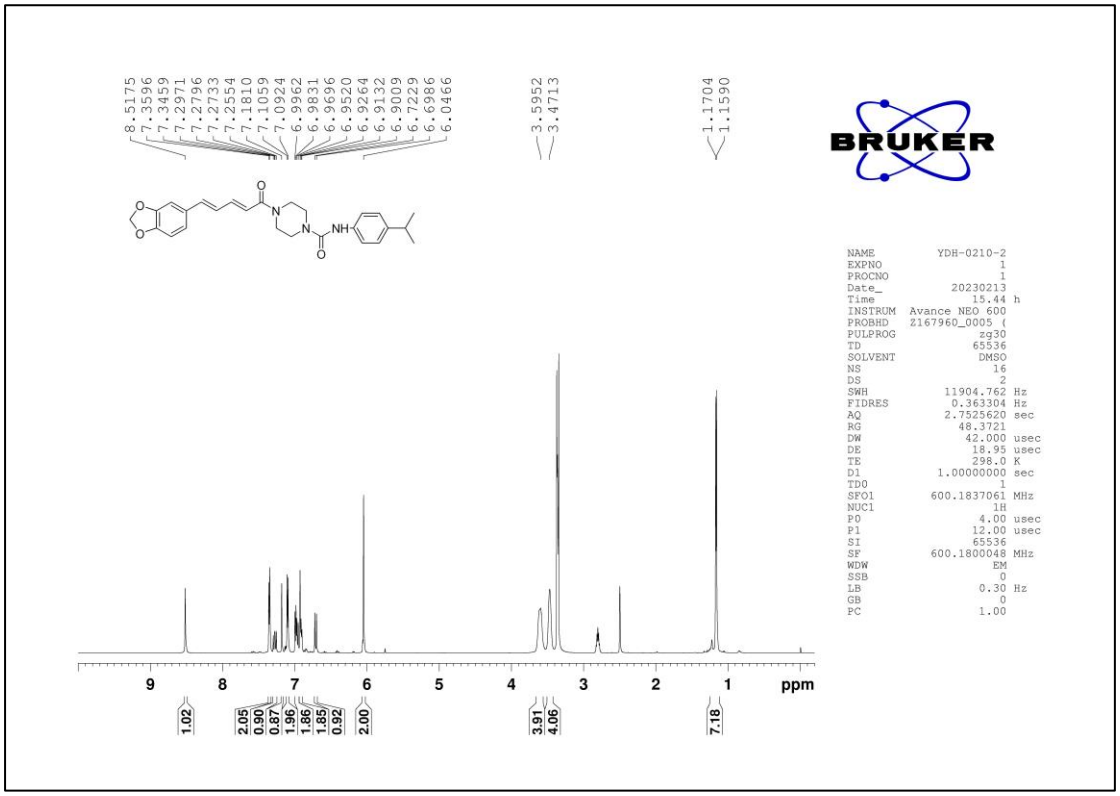
^{13}C-NMR spectrum of compound 11c



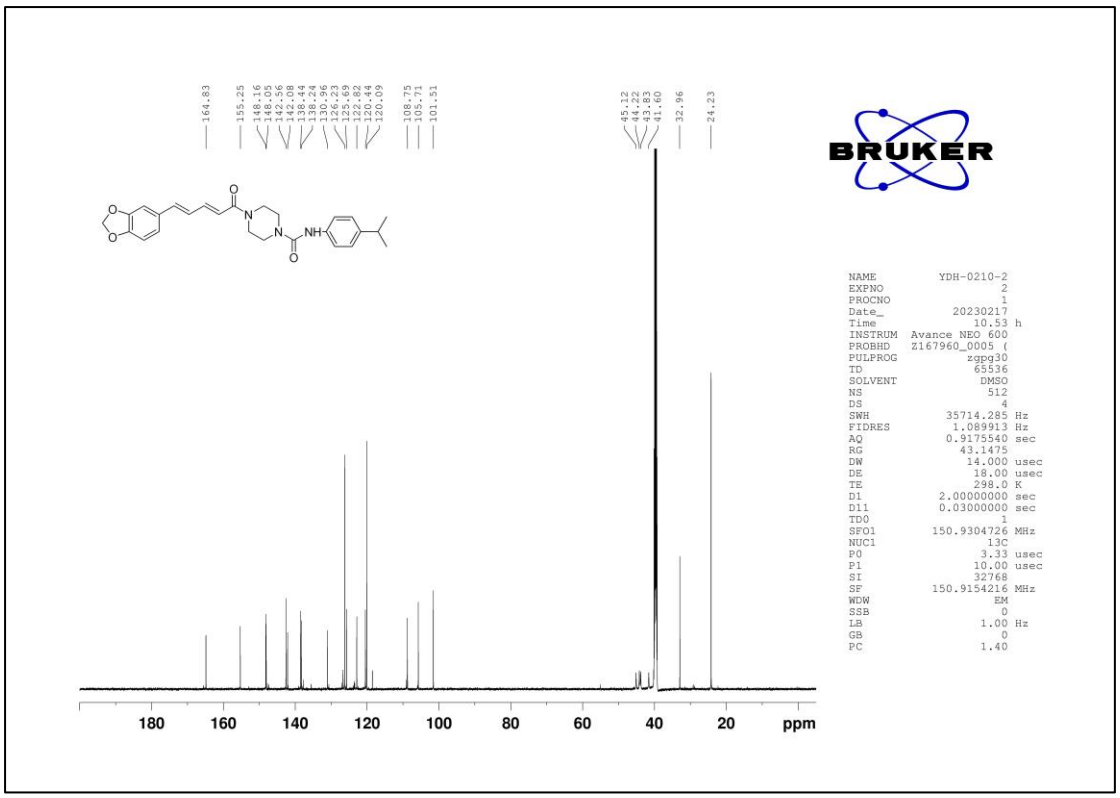
^{1}H-NMR spectrum of compound 11d



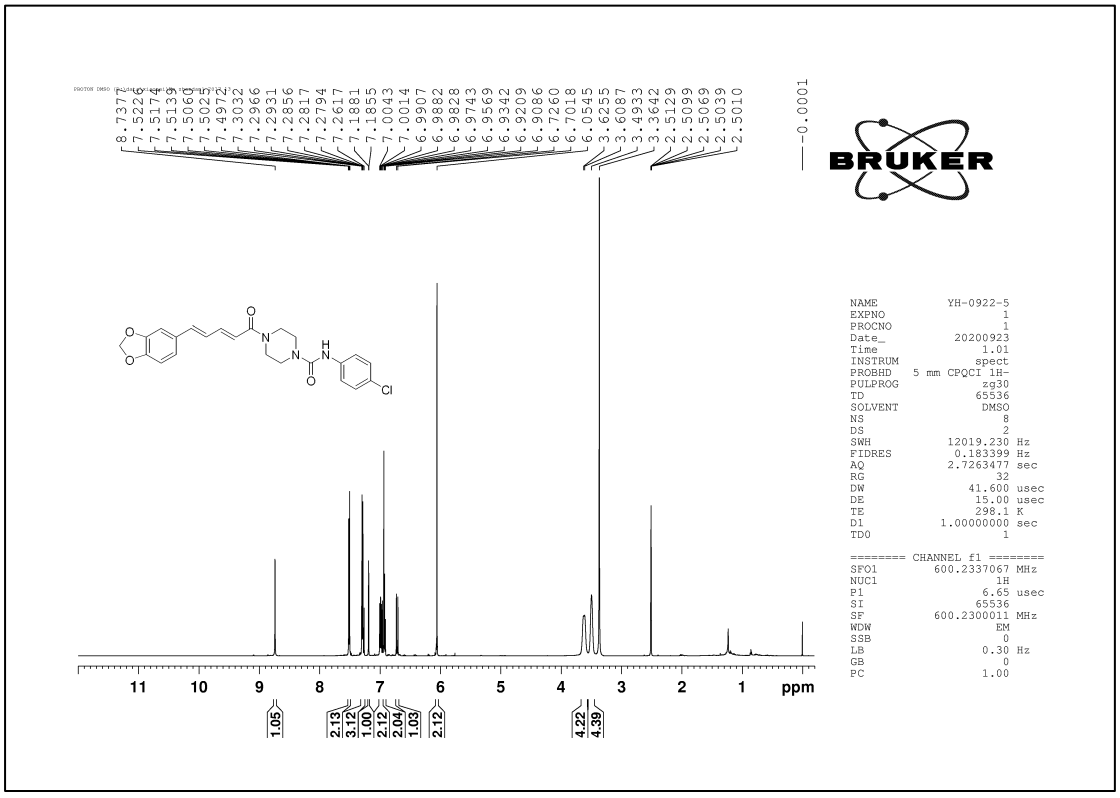
^{13}C-NMR spectrum of compound 11d



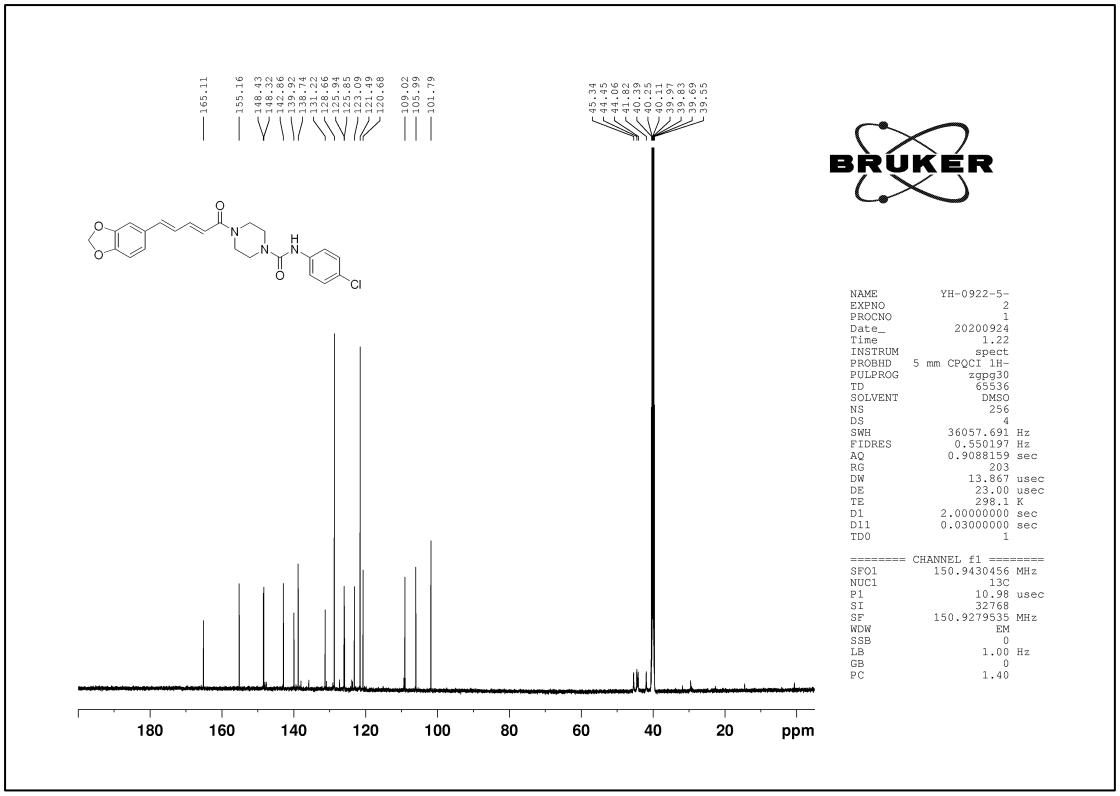
^{1}H-NMR spectrum of compound 11e



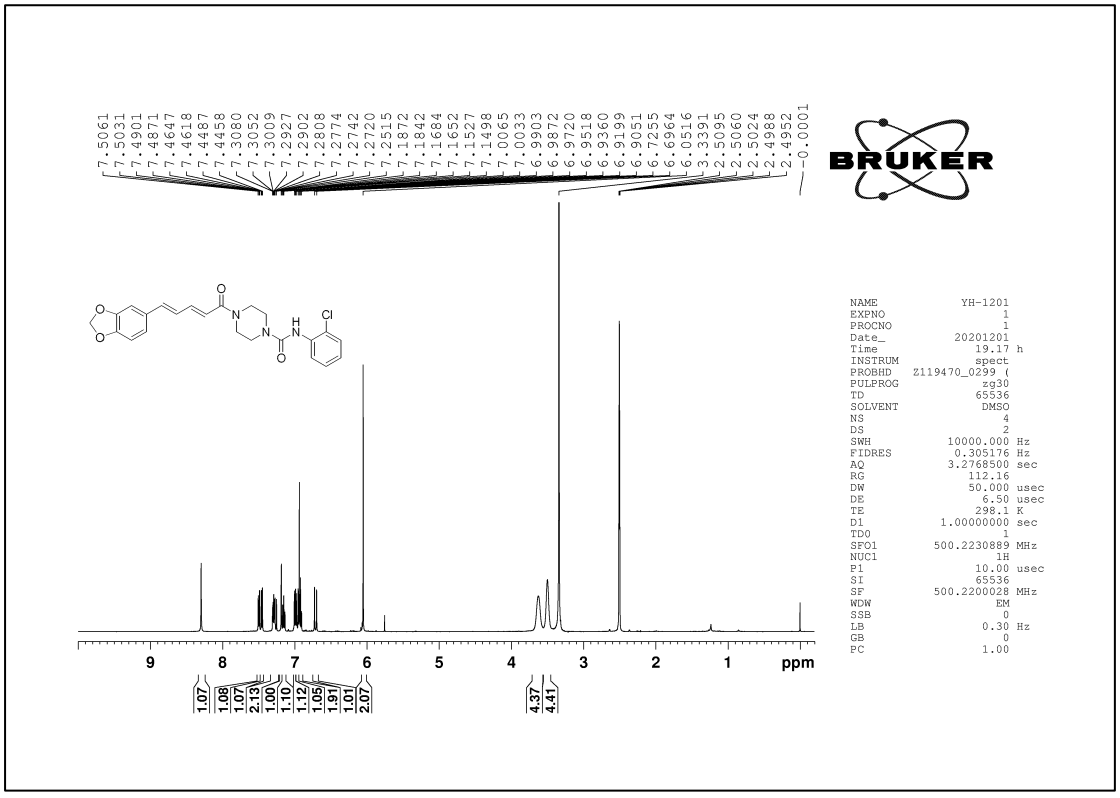
^{13}C-NMR spectrum of compound 11e



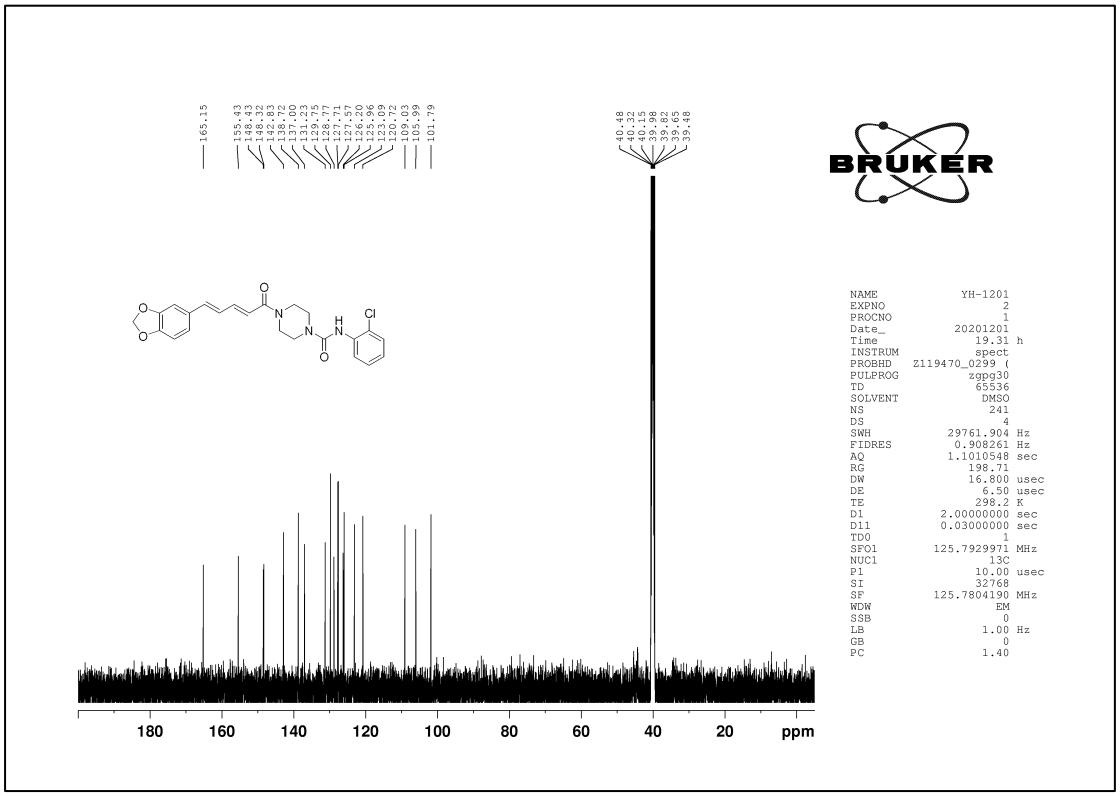
^{1}H-NMR spectrum of compound 11f



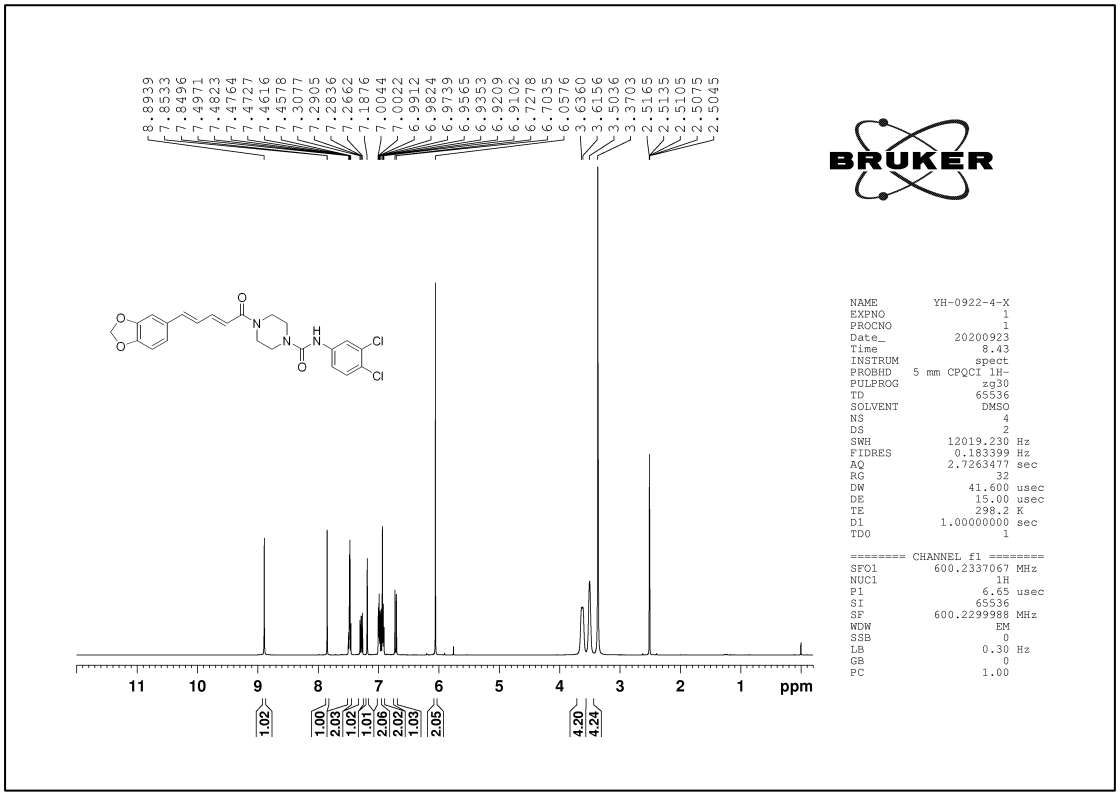
^{13}C-NMR spectrum of compound 11f



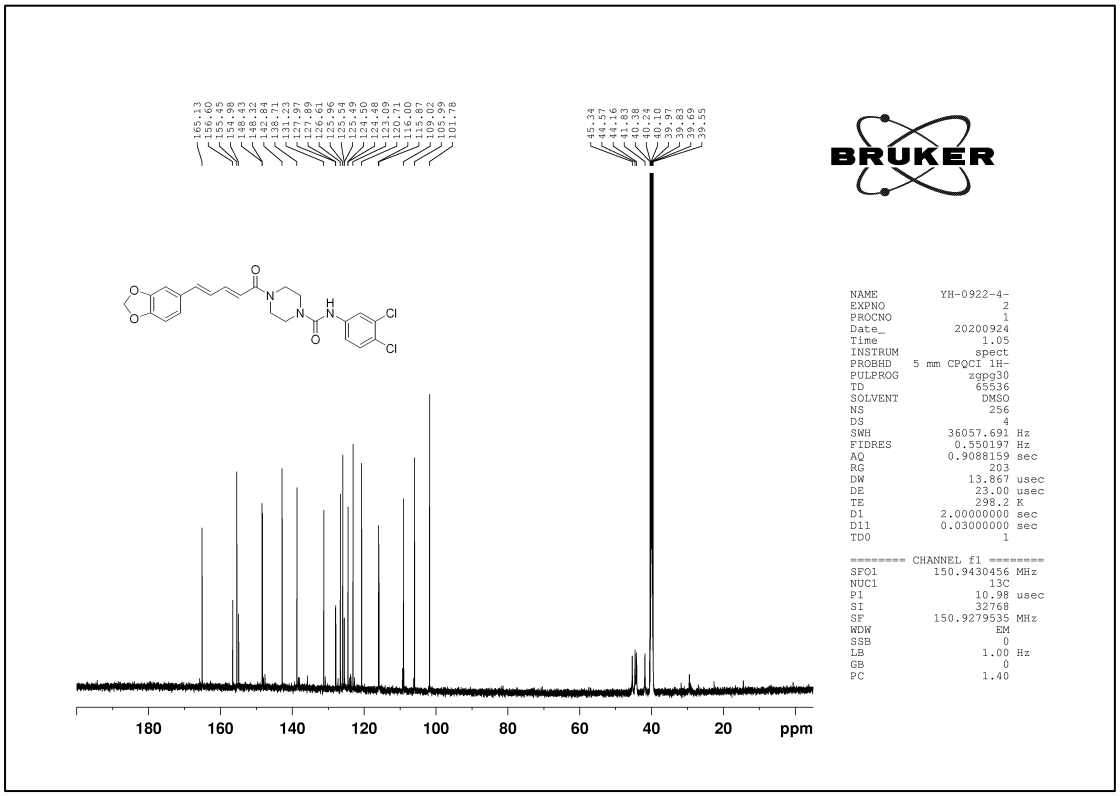
^{1}H-NMR spectrum of compound 11g



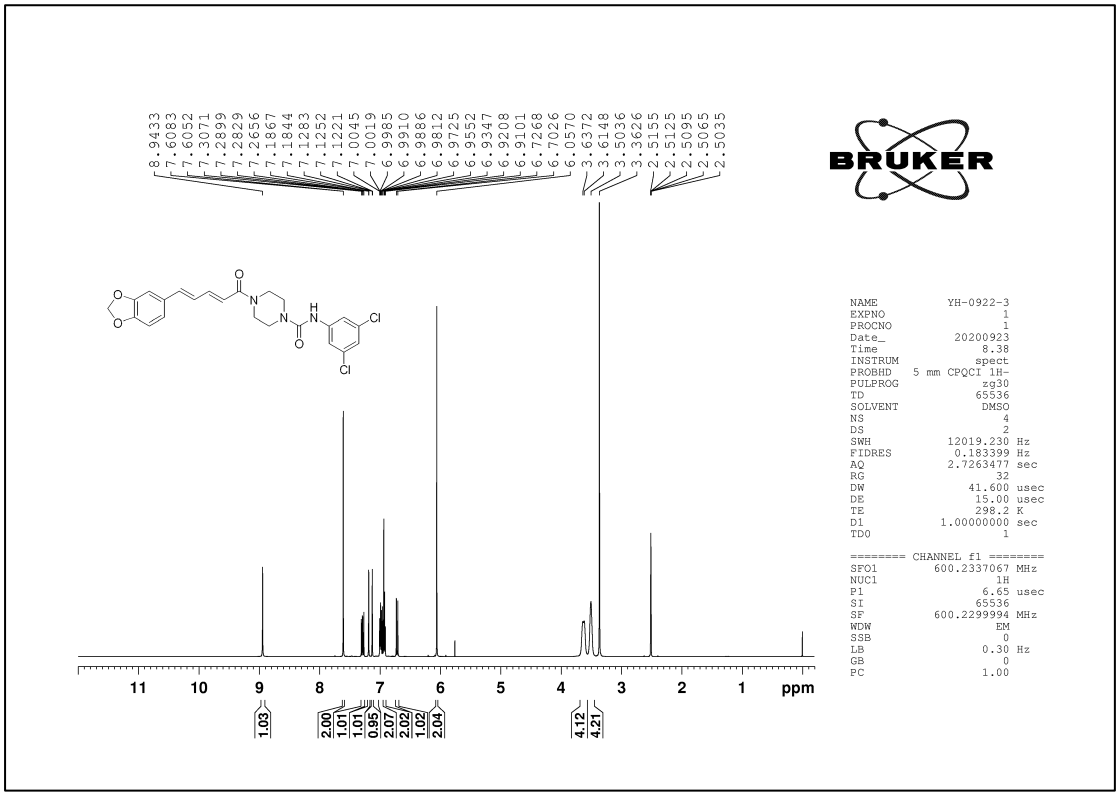
^{13}C-NMR spectrum of compound 11g



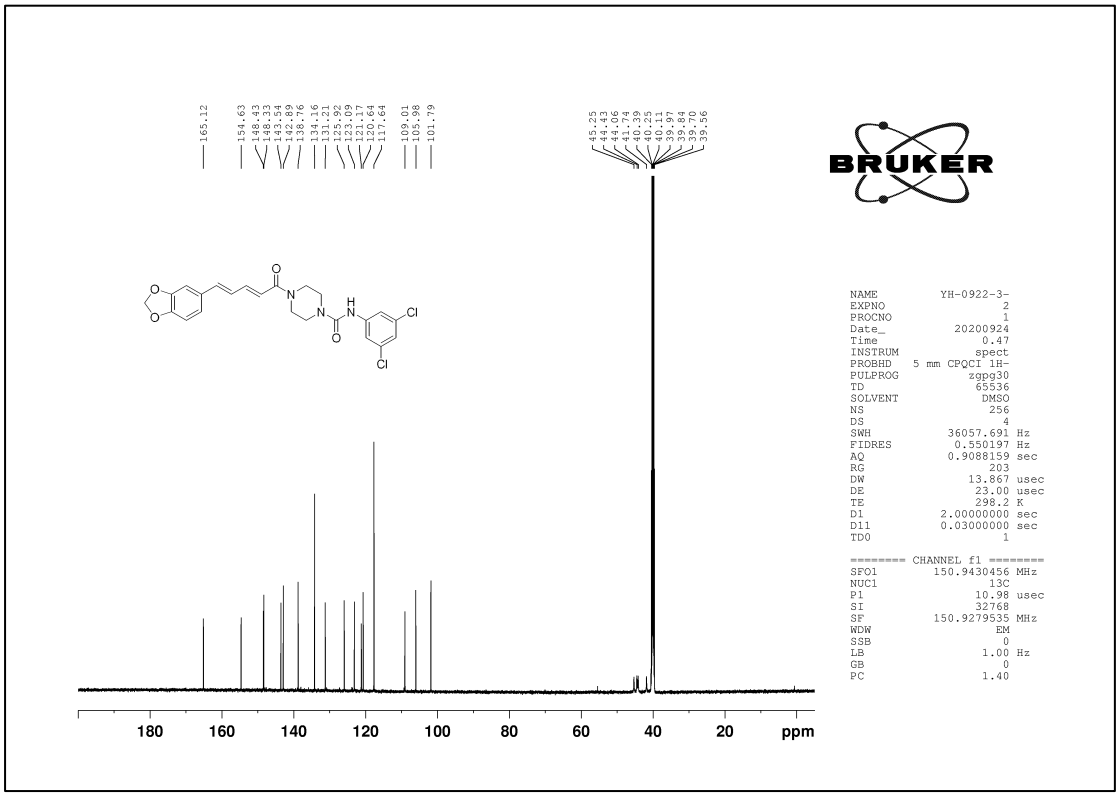
^{1}H-NMR spectrum of compound 11h



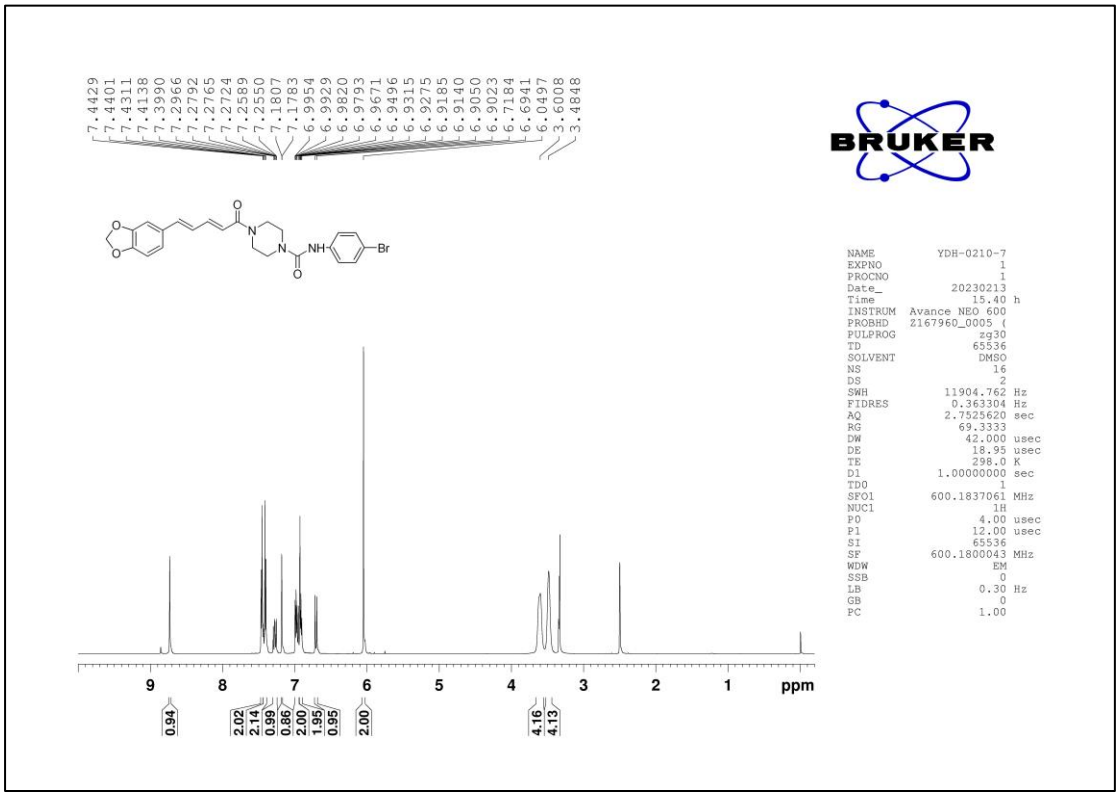
^{13}C-NMR spectrum of compound 11h



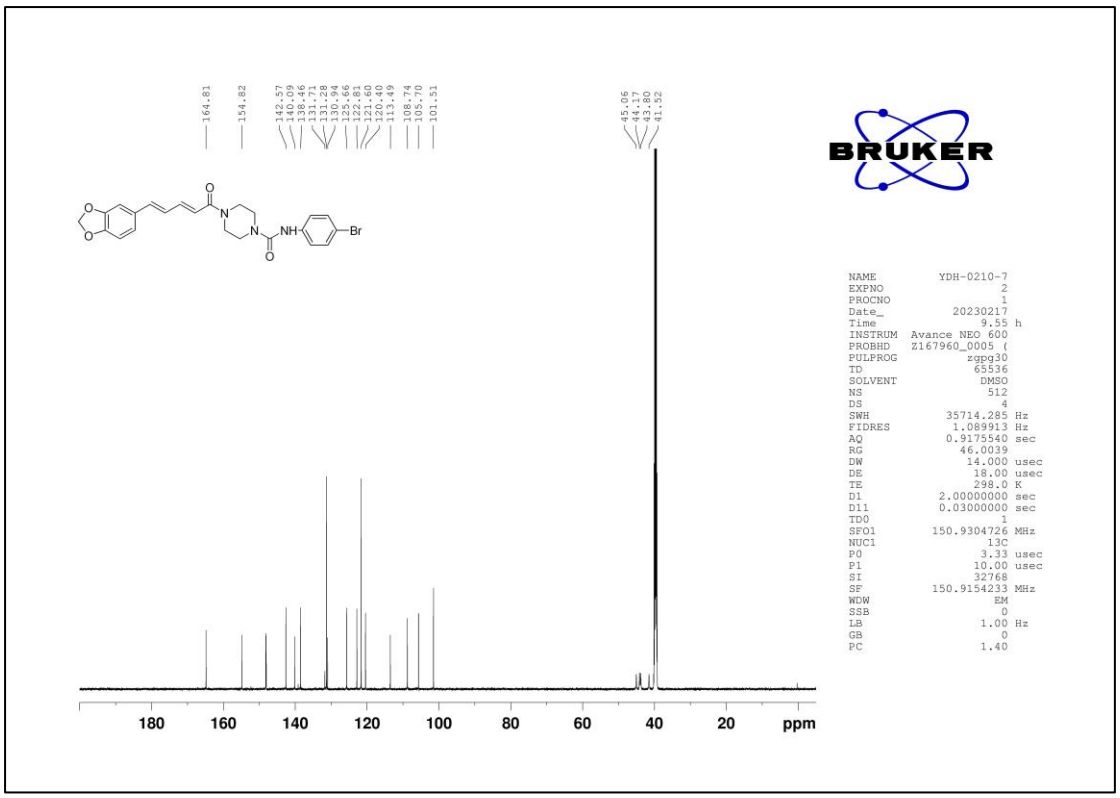
^{1}H-NMR spectrum of compound 11i



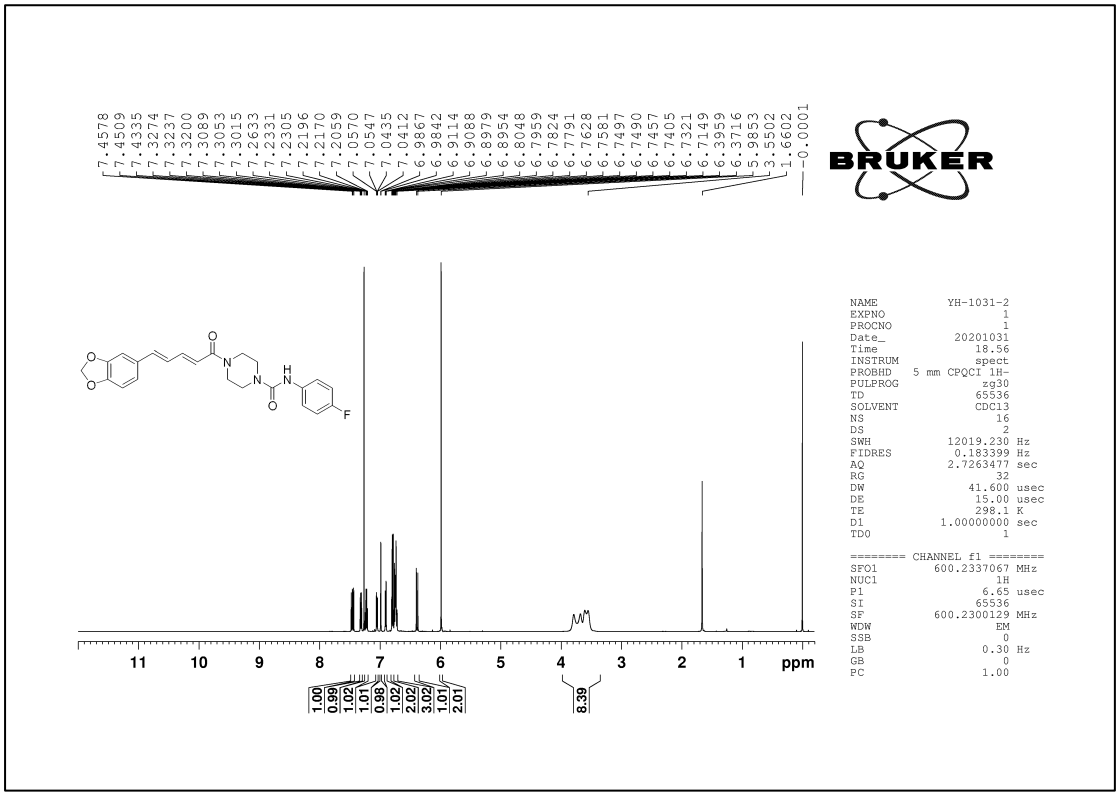
^{13}C-NMR spectrum of compound 11i



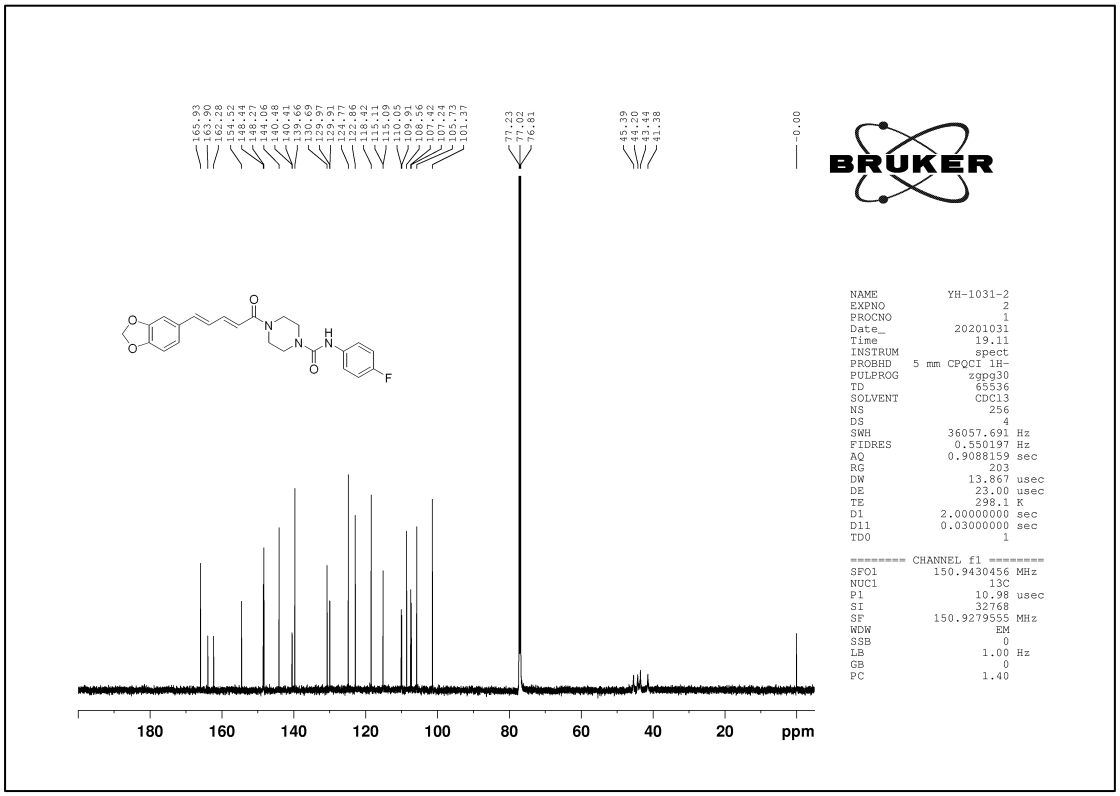
^{1}H-NMR spectrum of compound 11j



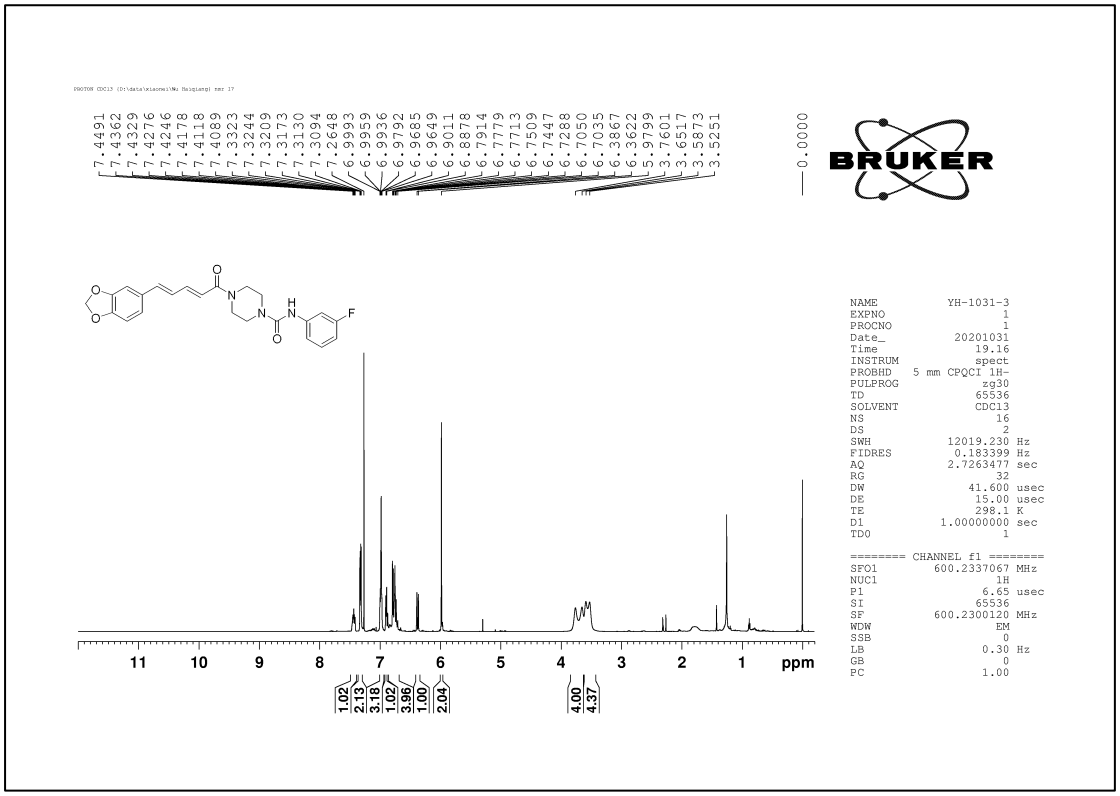
^{13}C-NMR spectrum of compound 11j



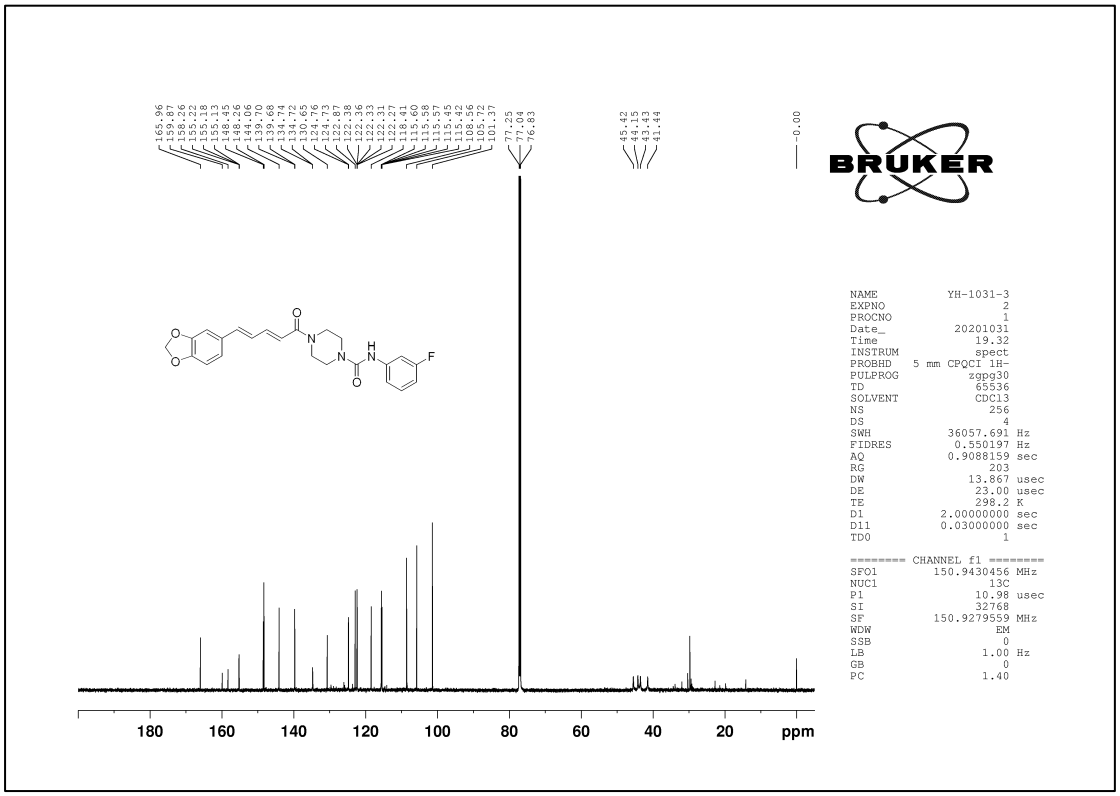
^{1}H-NMR spectrum of compound 11k



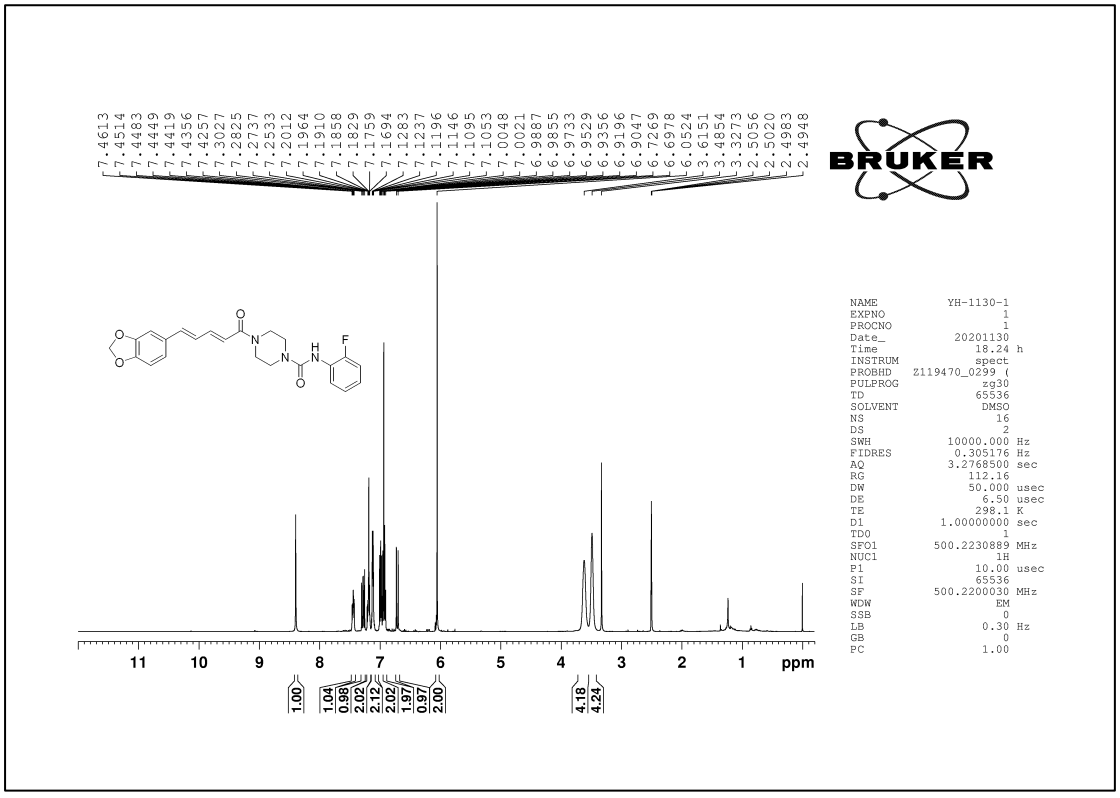
^{13}C-NMR spectrum of compound 11k



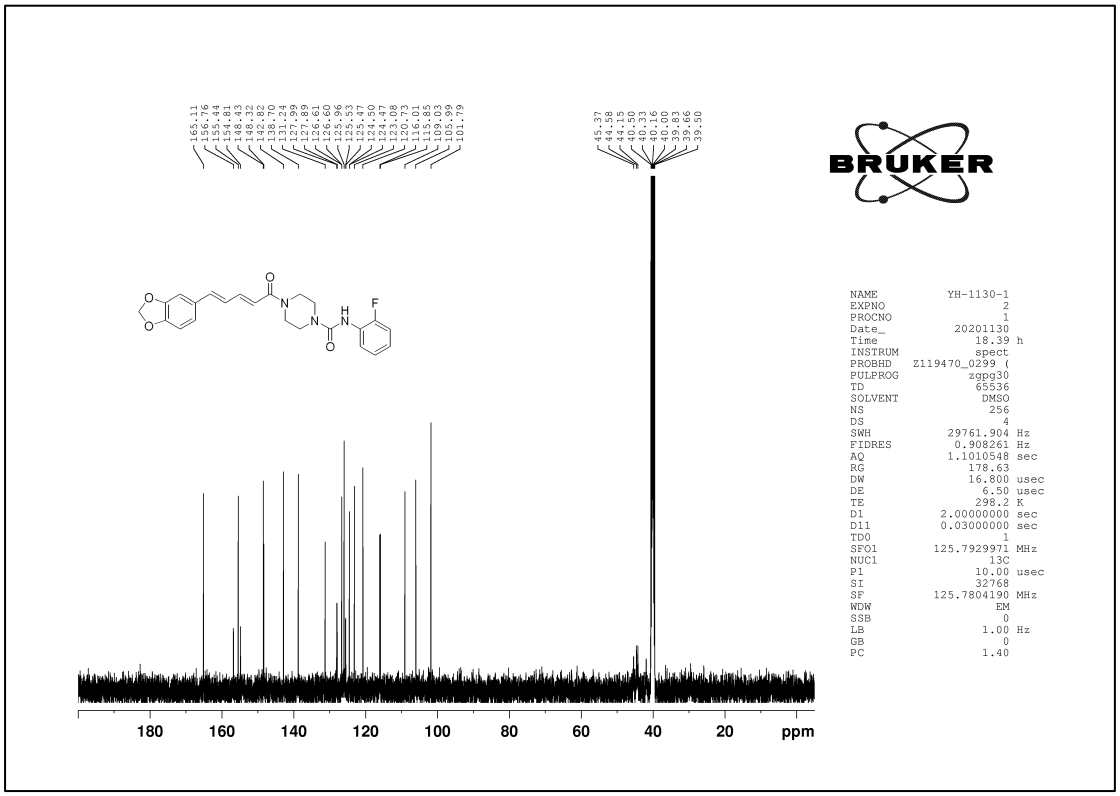
^{1}H-NMR spectrum of compound 11l



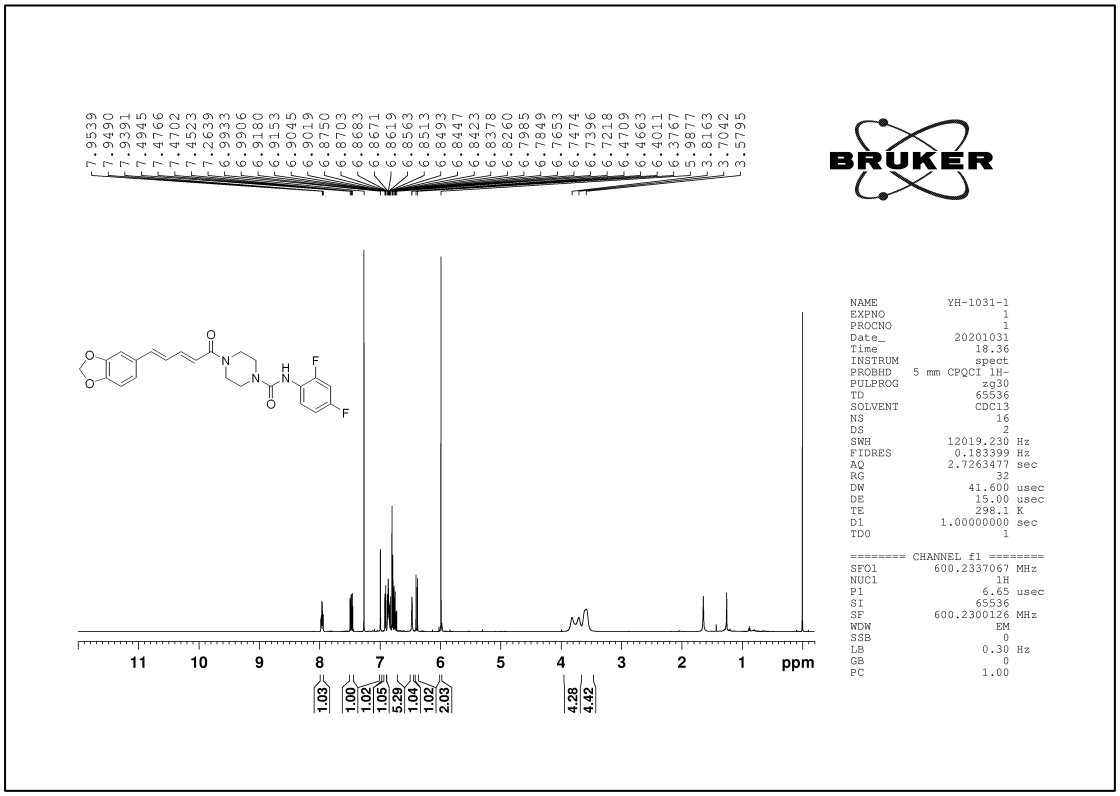
^{13}C-NMR spectrum of compound 11l



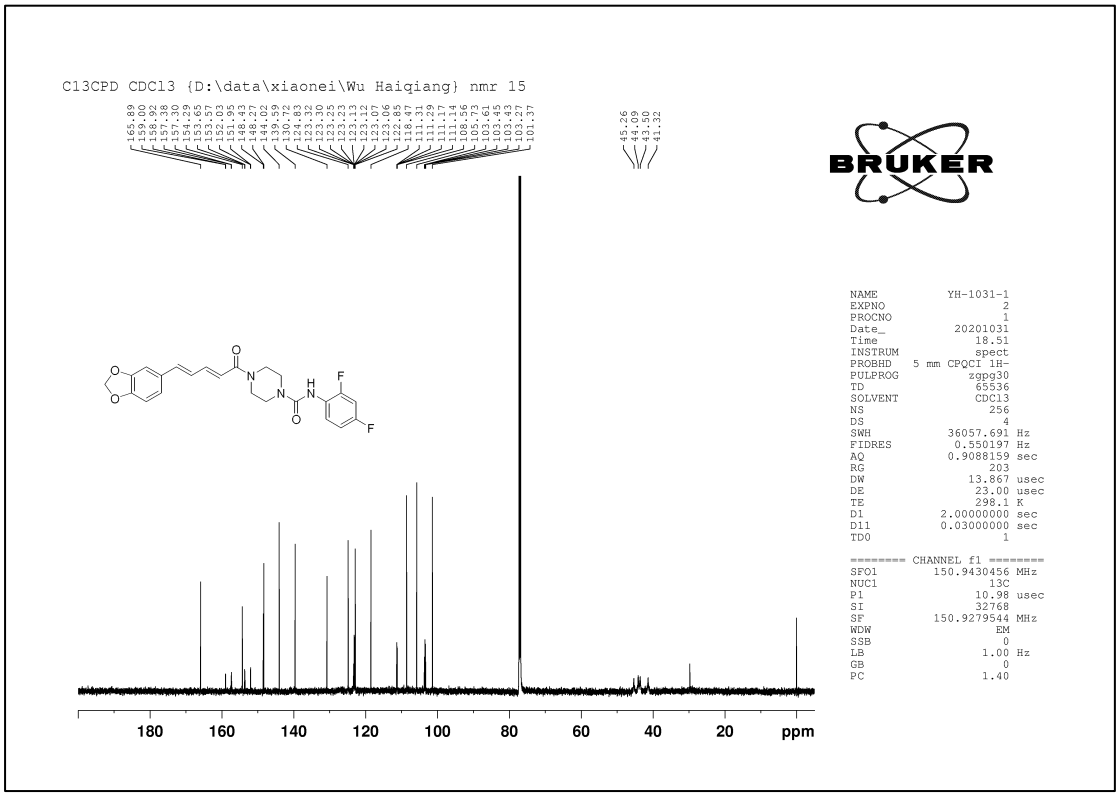
^{1}H-NMR spectrum of compound 11m



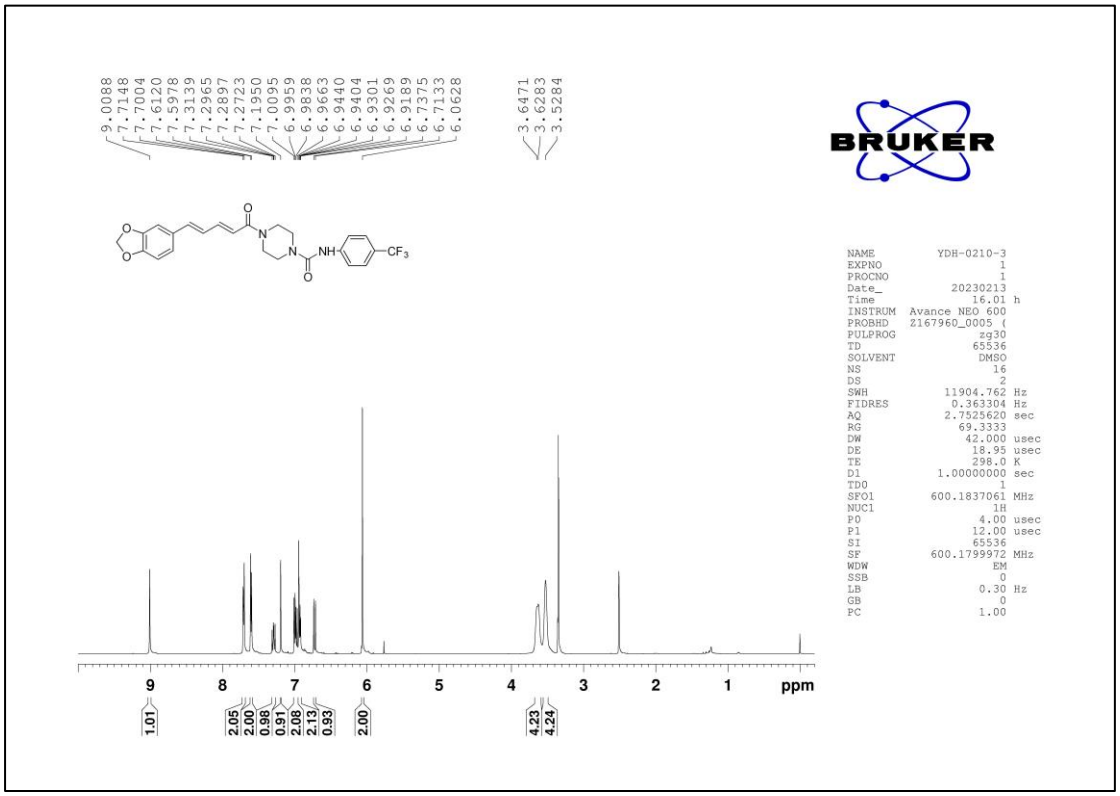
^{13}C-NMR spectrum of compound 11m



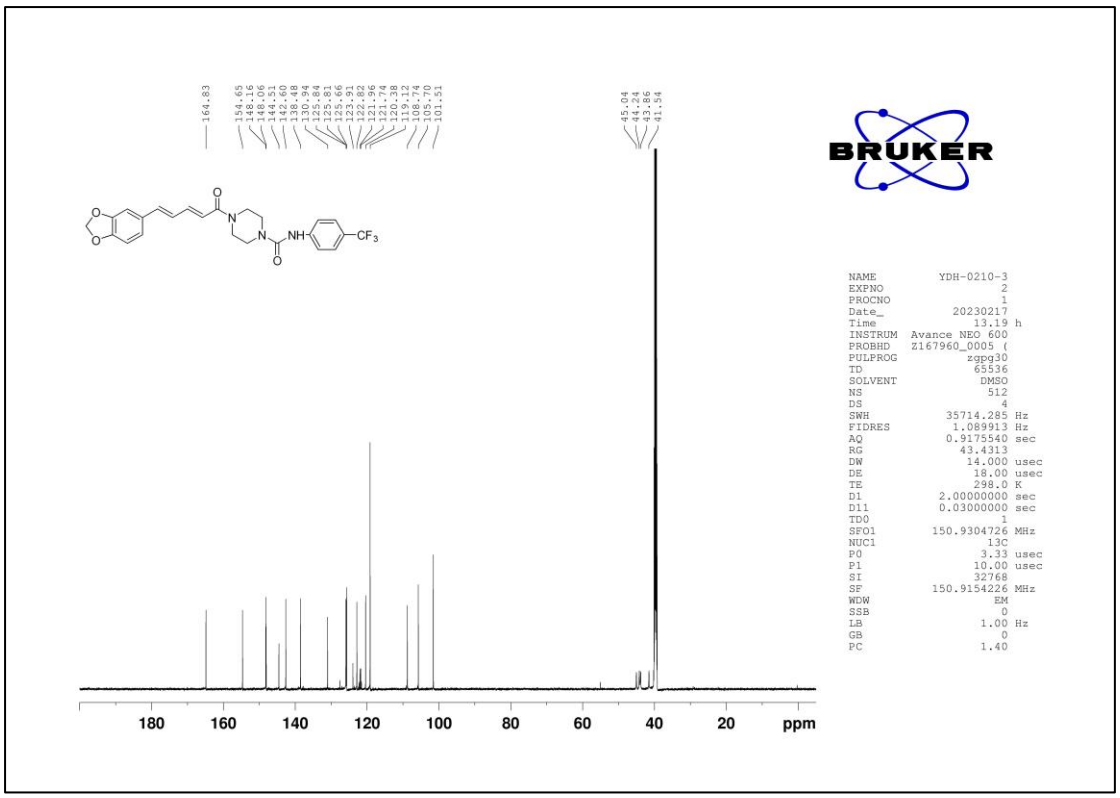
^{1}H-NMR spectrum of compound 11n



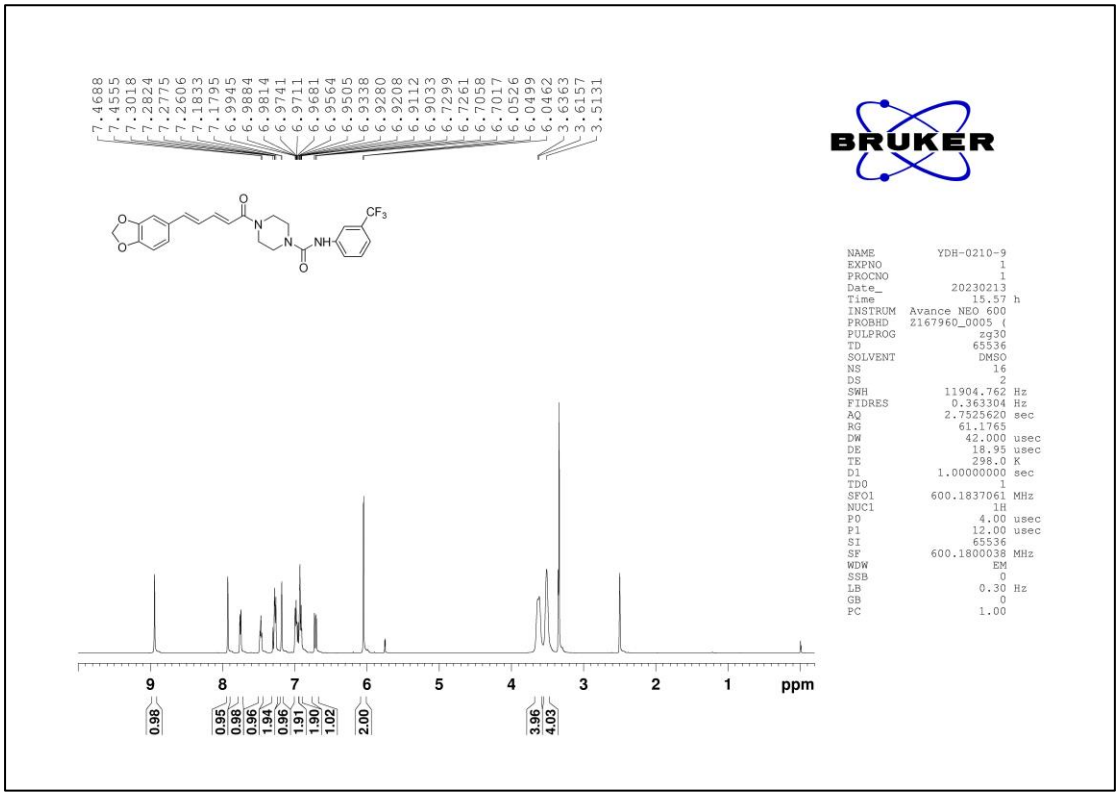
^{13}C-NMR spectrum of compound 11n



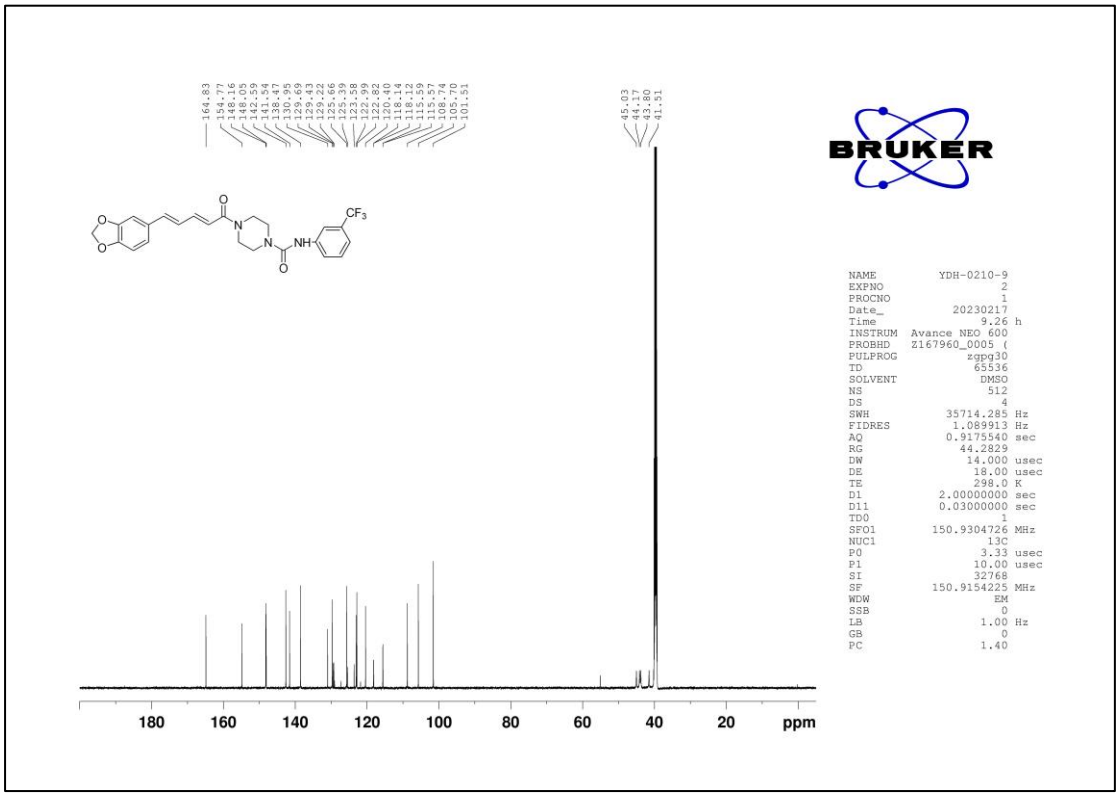
^{1}H-NMR spectrum of compound 11o



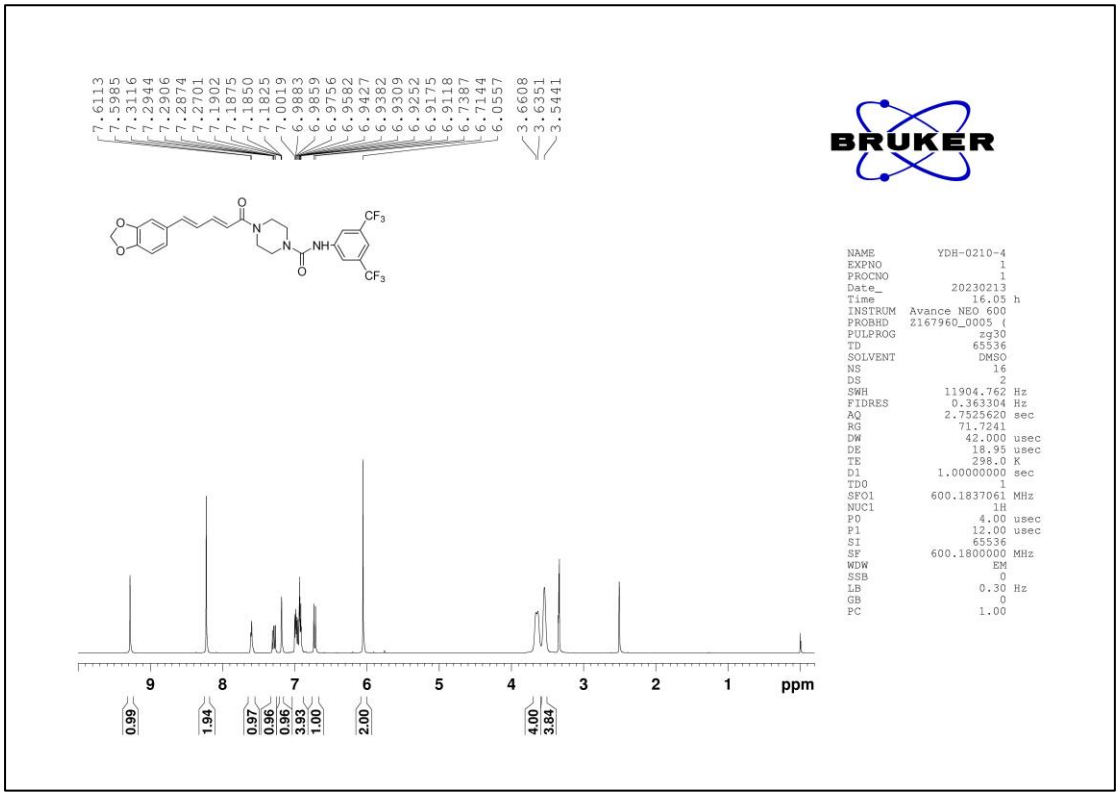
^{13}C-NMR spectrum of compound 11o



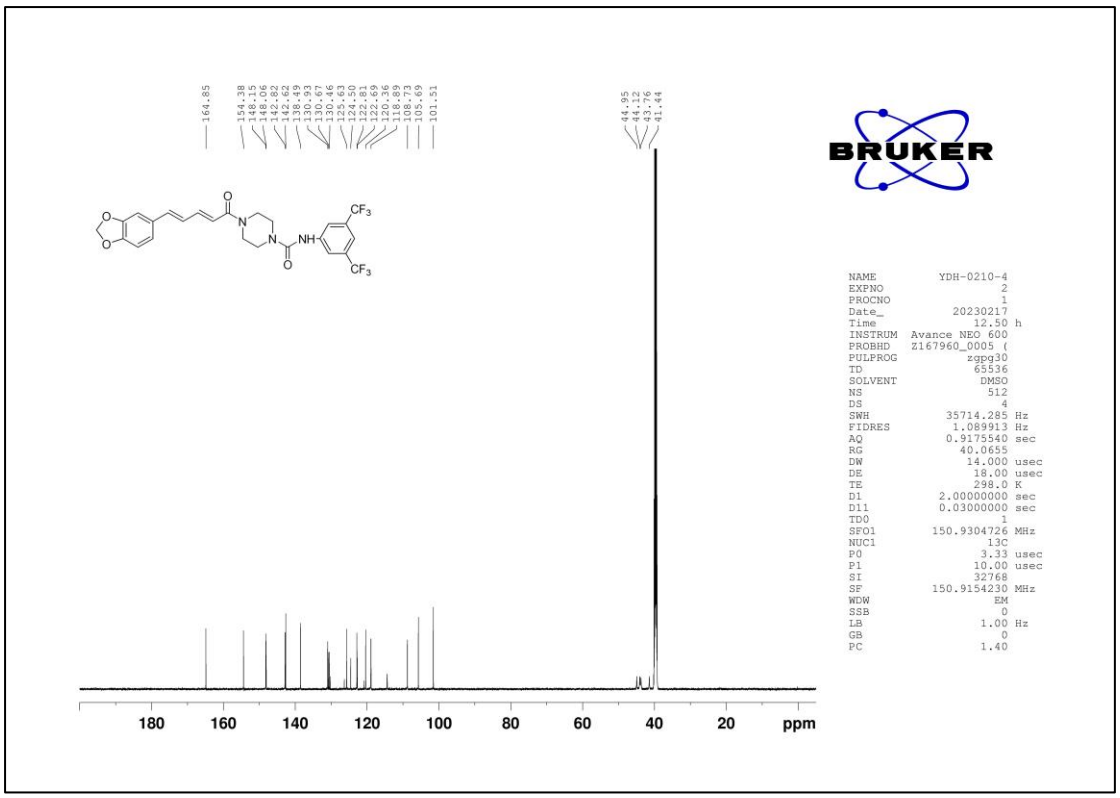
^{1}H-NMR spectrum of compound 11p



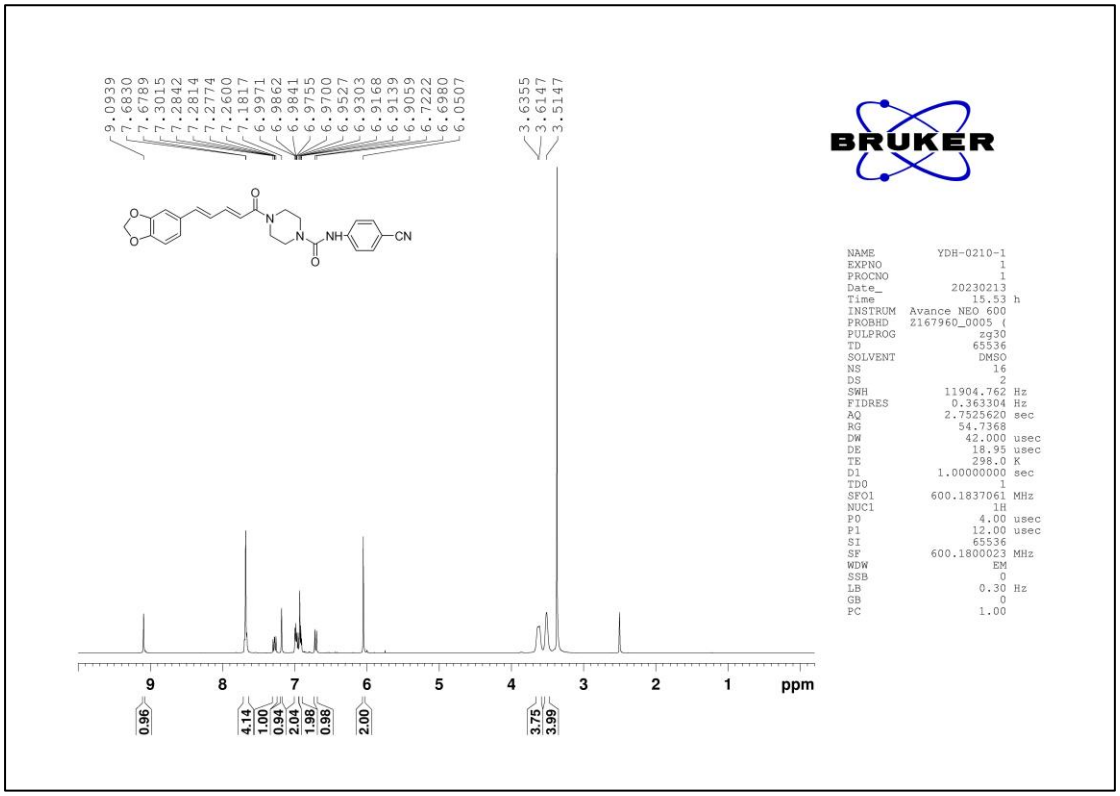
^{13}C-NMR spectrum of compound 11p



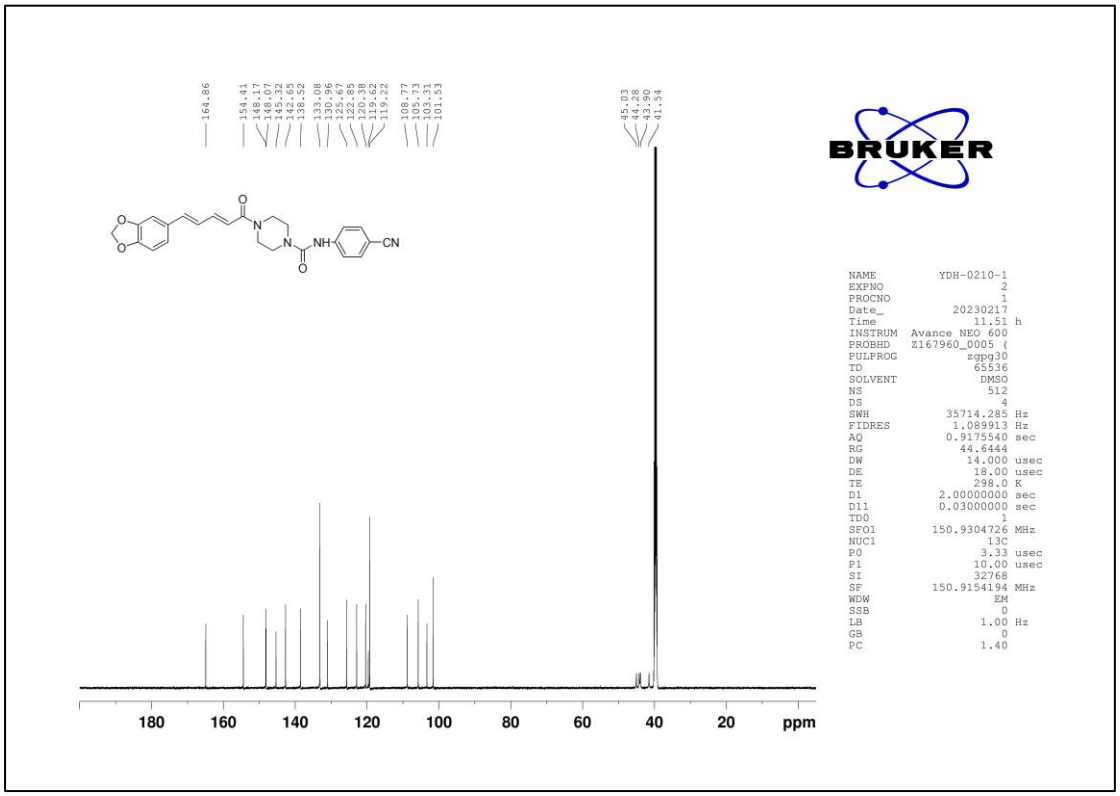
^{1}H-NMR spectrum of compound 11q



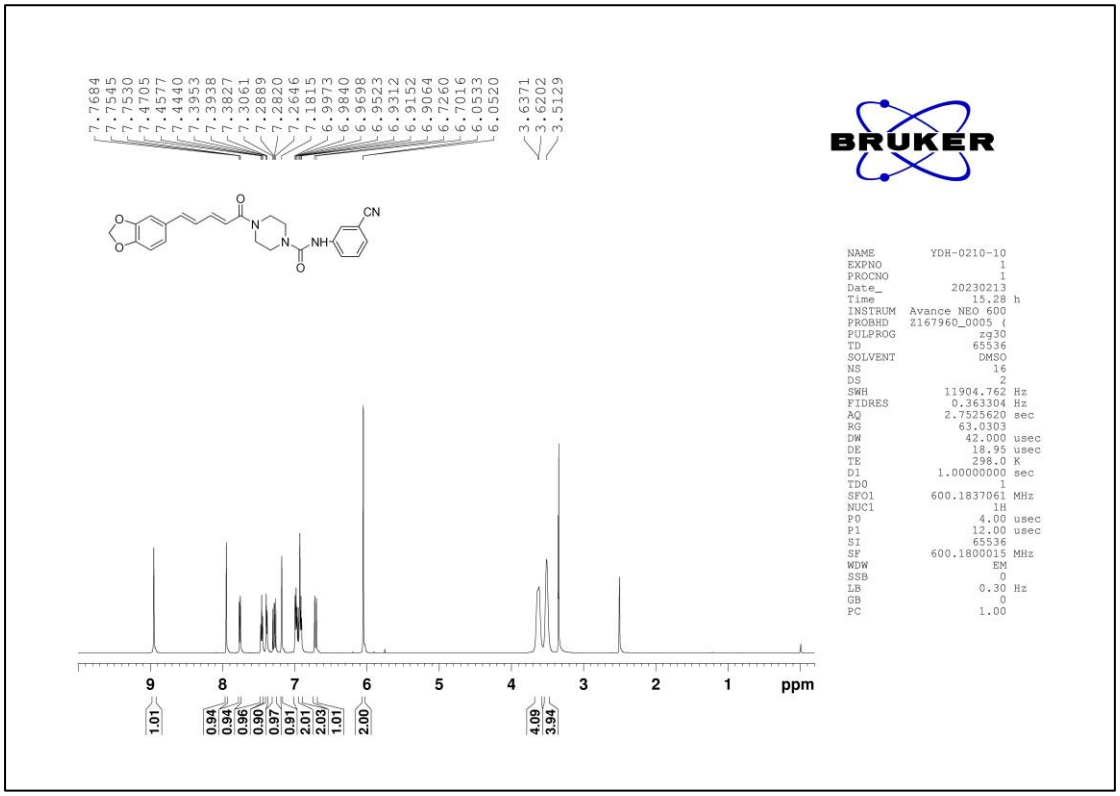
^{13}C-NMR spectrum of compound 11q



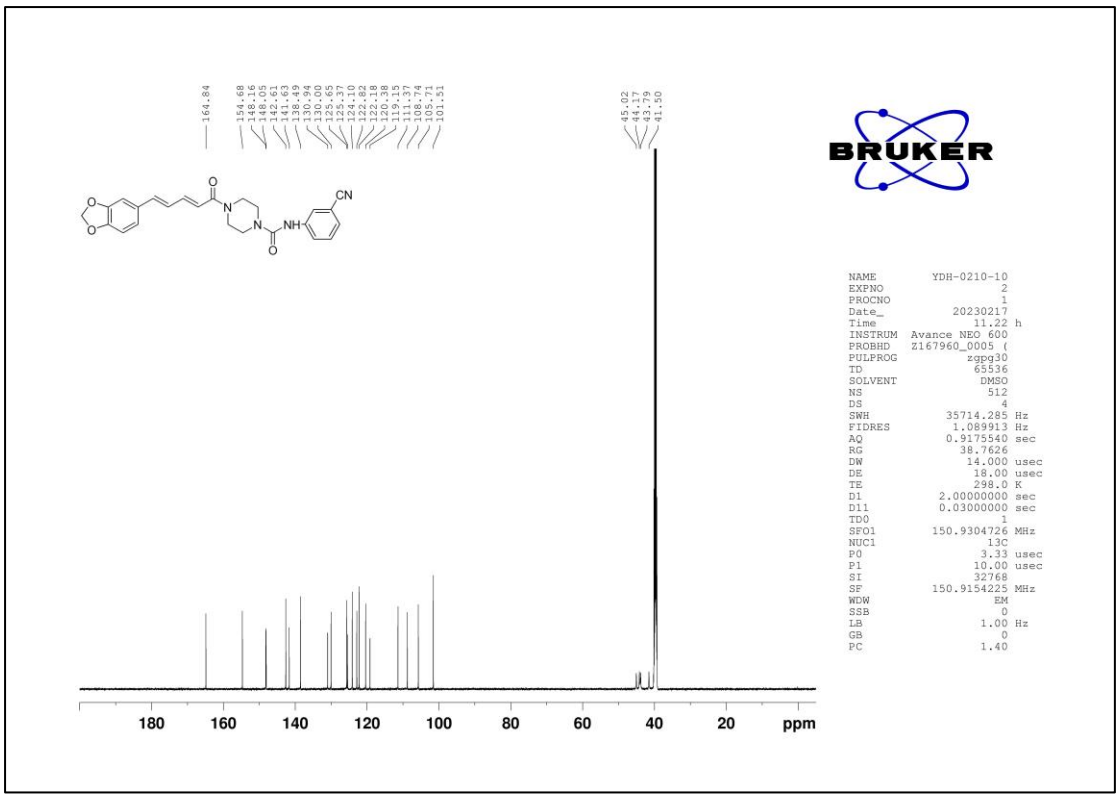
^{1}H-NMR spectrum of compound 11r



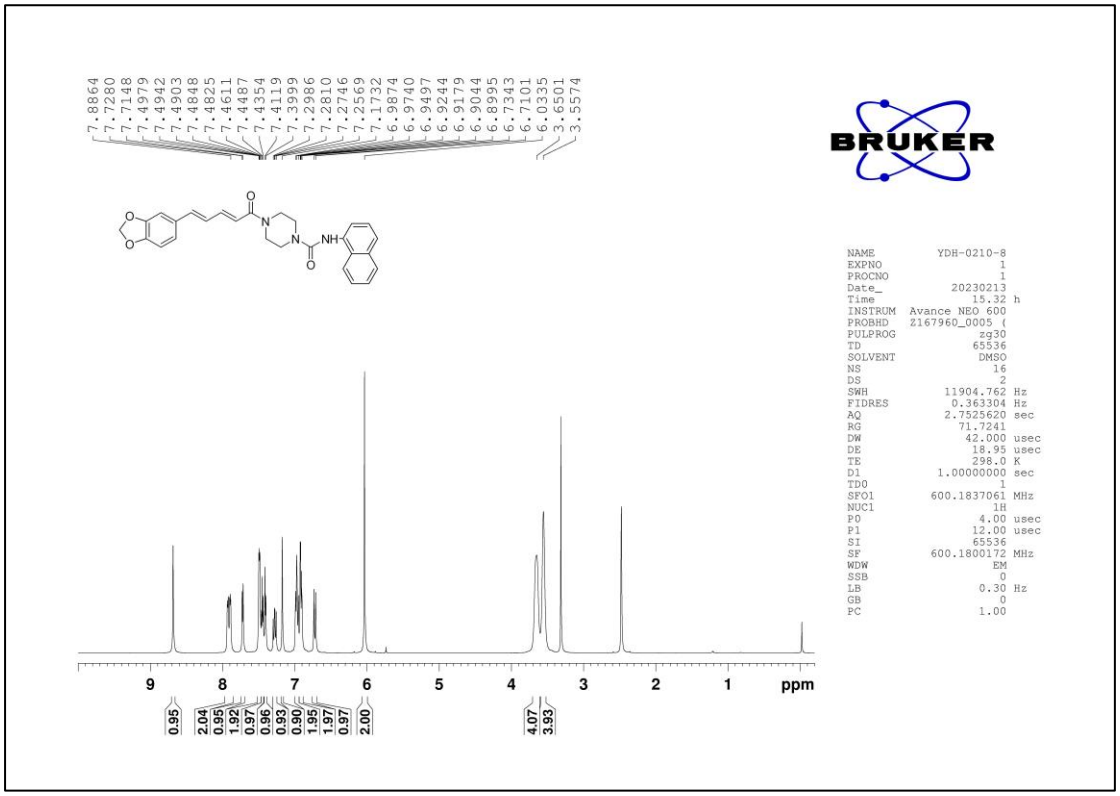
^{13}C-NMR spectrum of compound 11r



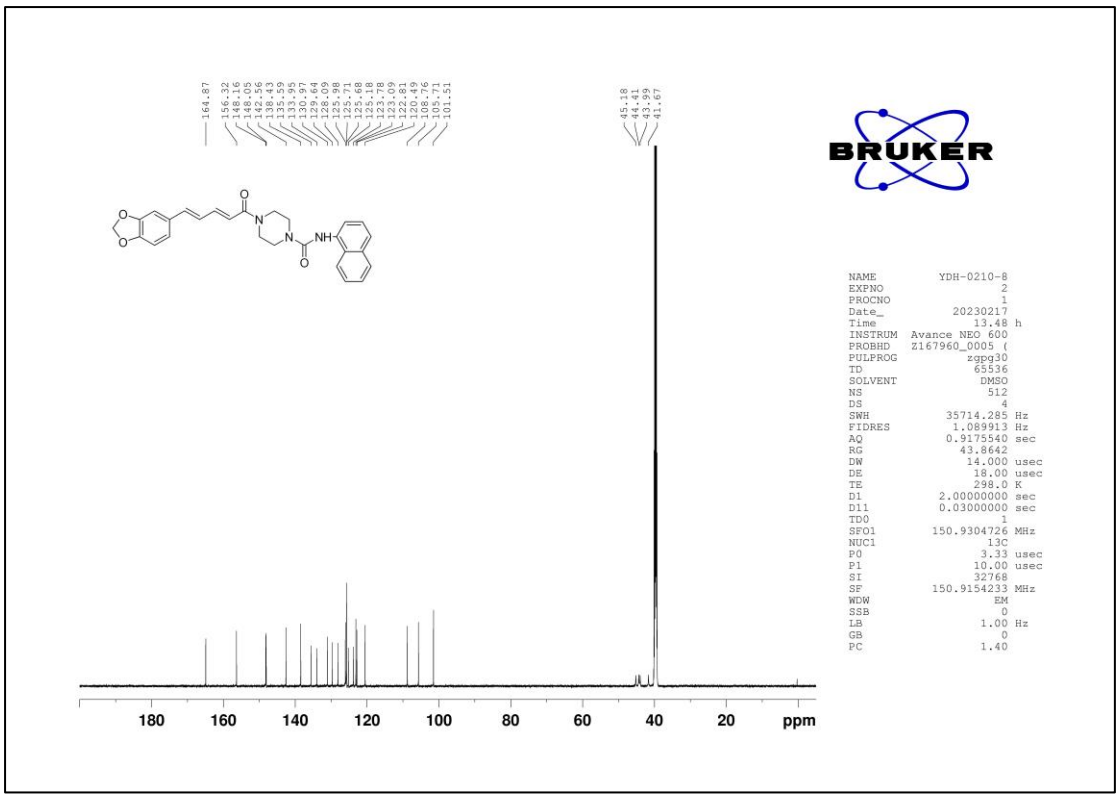
^{1}H-NMR spectrum of compound 11s



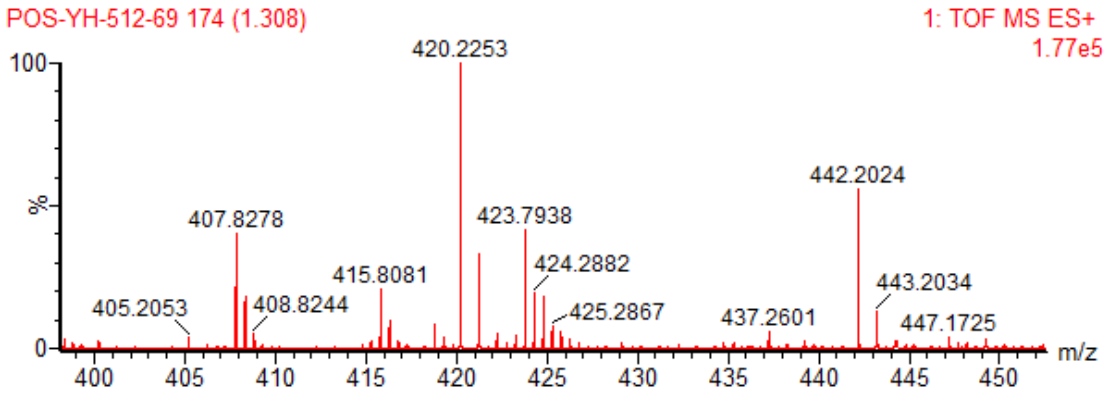
^{13}C-NMR spectrum of compound 11s



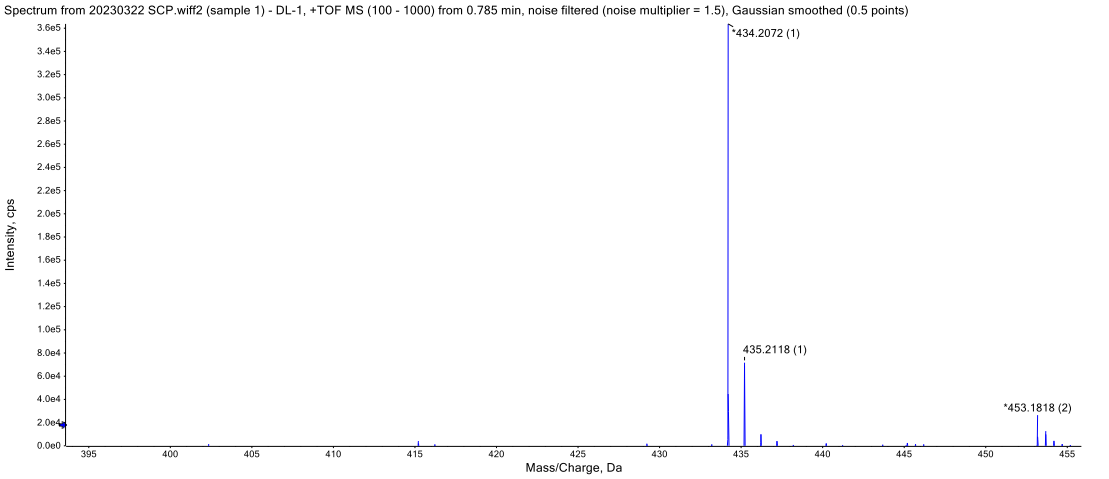
^{1}H-NMR spectrum of compound 11t



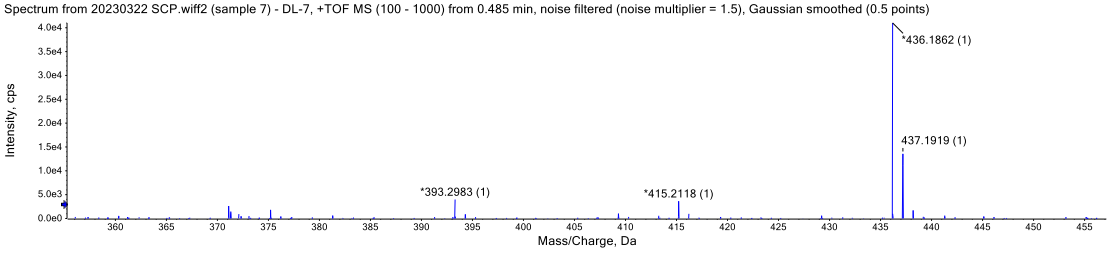
^{13}C-NMR spectrum of compound 11t



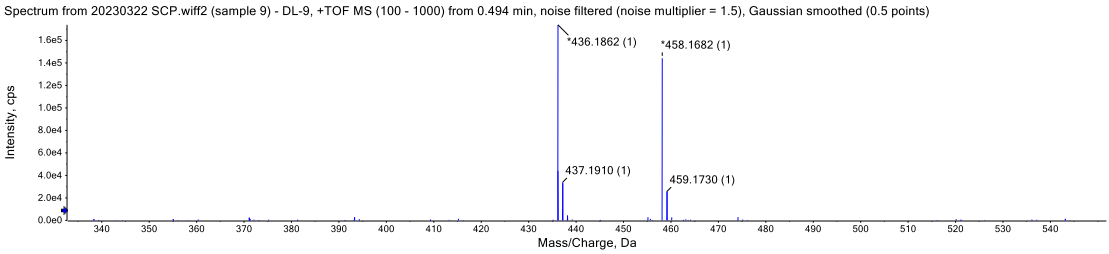
HRMS spectrum of compound 11a



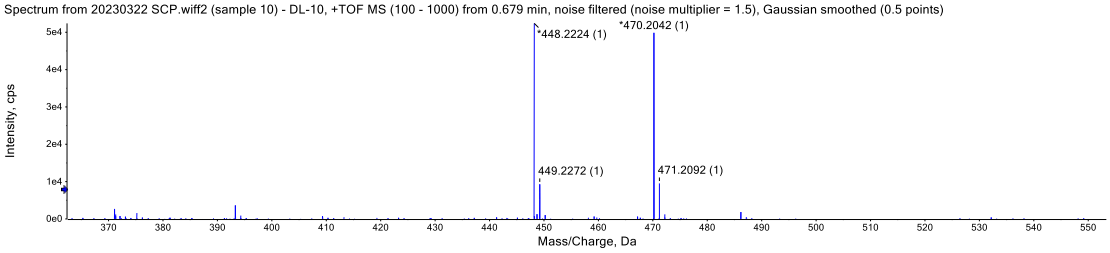
HRMS spectrum of compound 11b



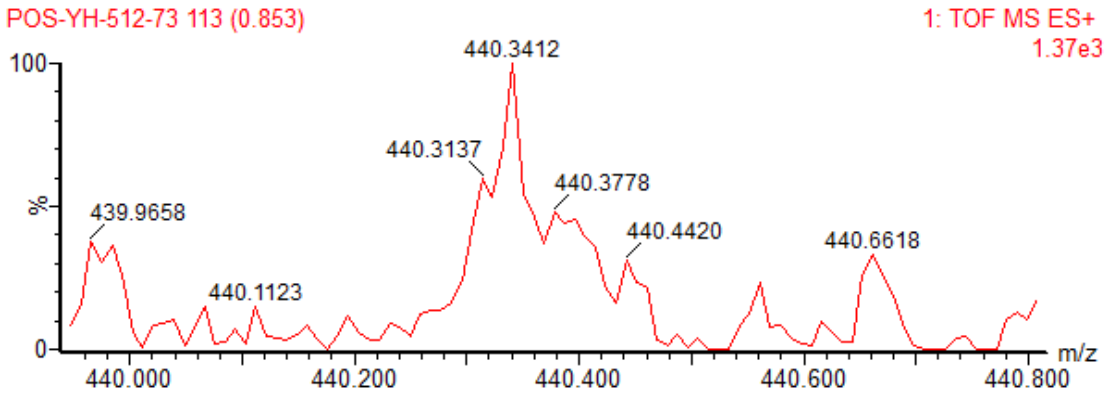
HRMS spectrum of compound 11c



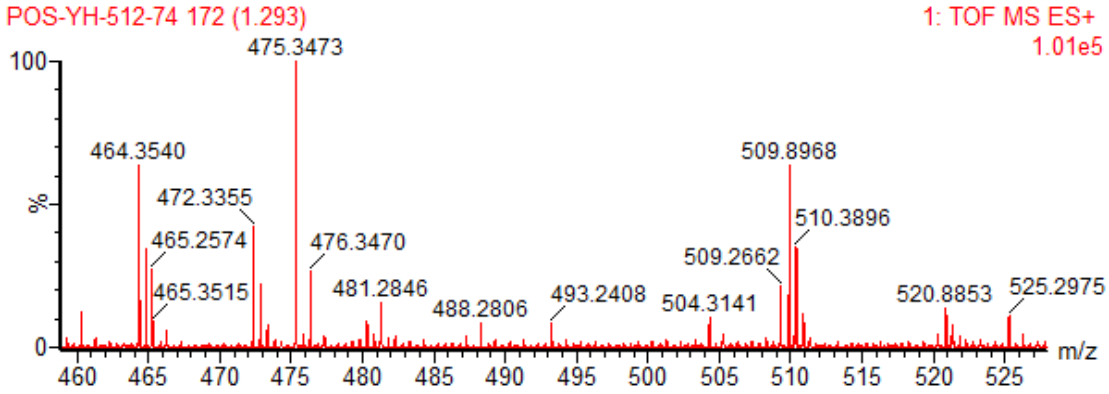
HRMS spectrum of compound 11d



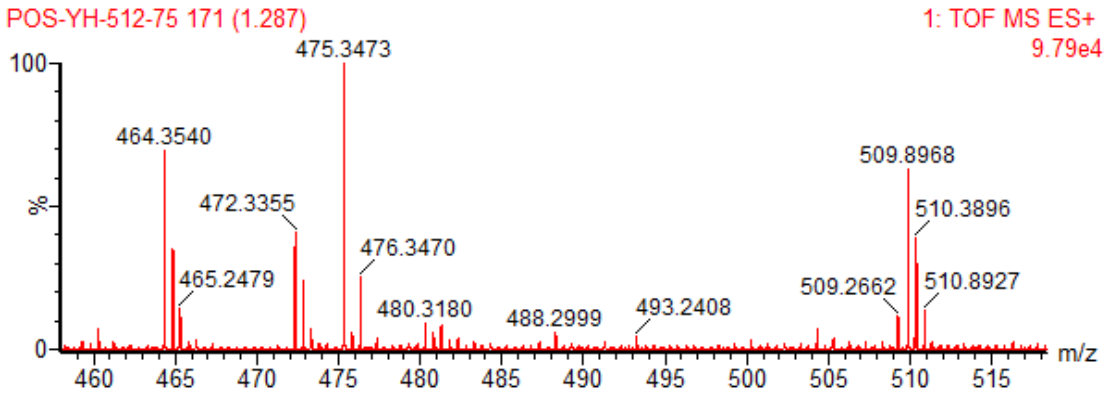
HRMS spectrum of compound 11e



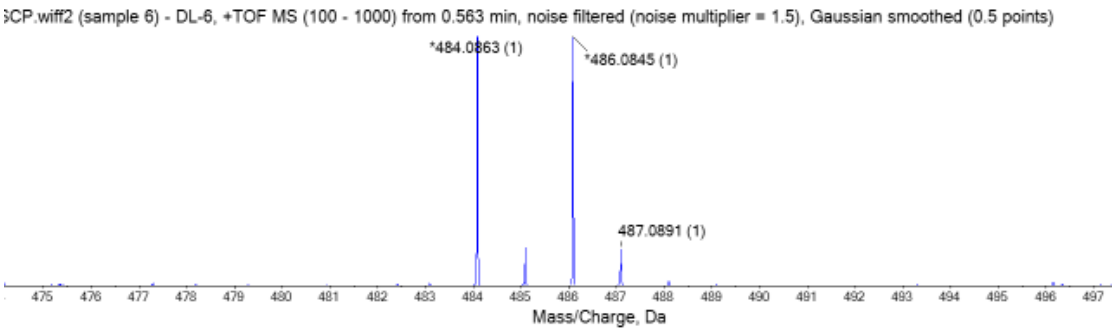
HRMS spectrum of compound 11f



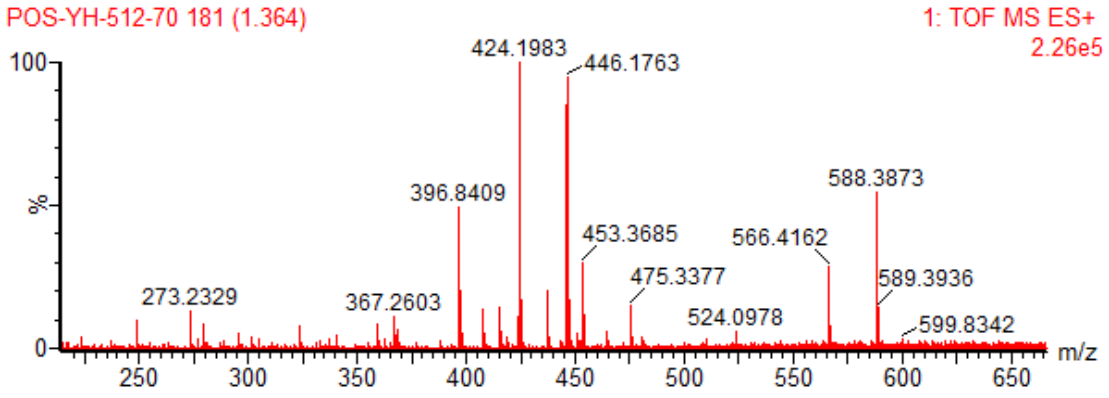
HRMS spectrum of compound 11h



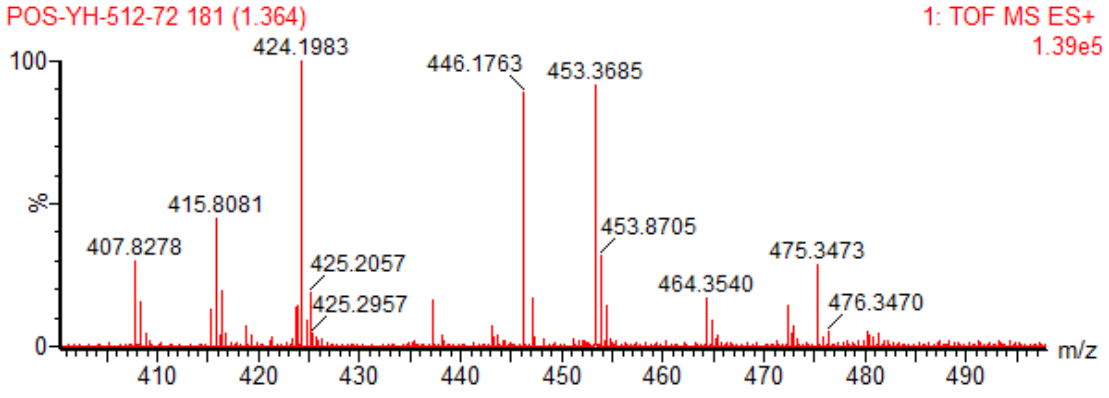
HRMS spectrum of compound 11i



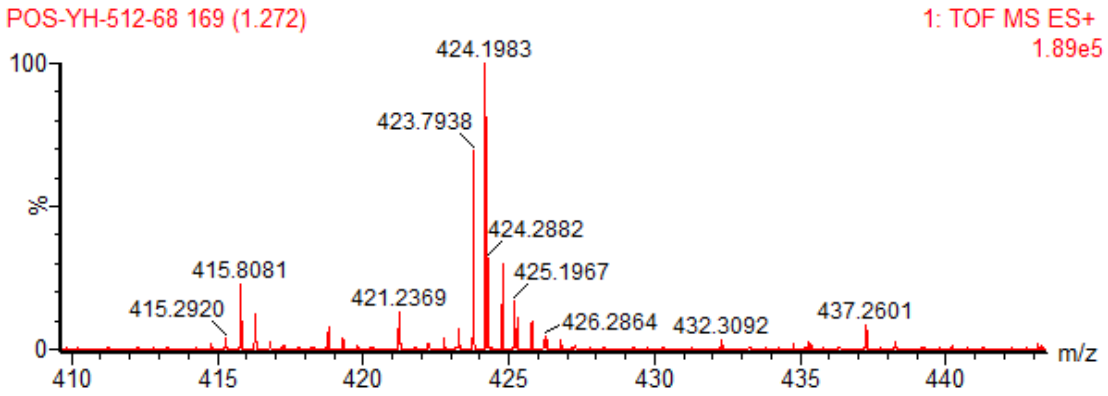
HRMS spectrum of compound 11j



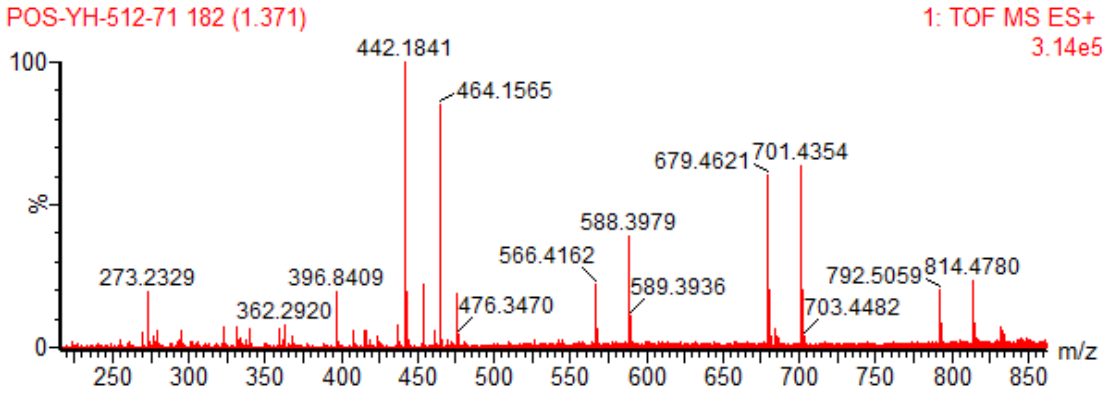
HRMS spectrum of compound 11k



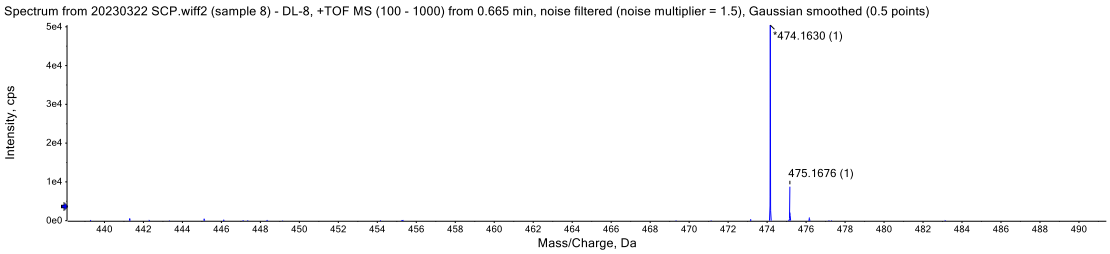
HRMS spectrum of compound 11l



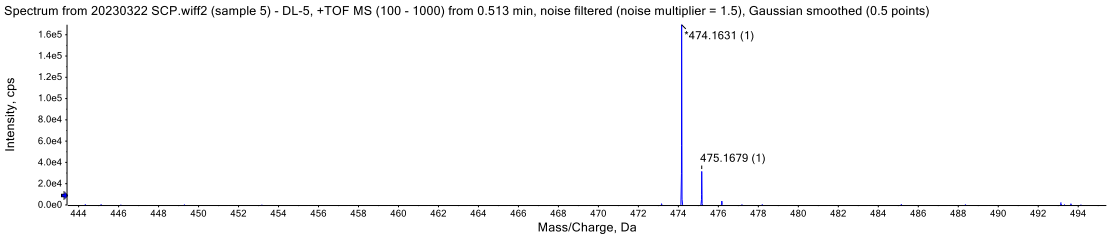
HRMS spectrum of compound 11m



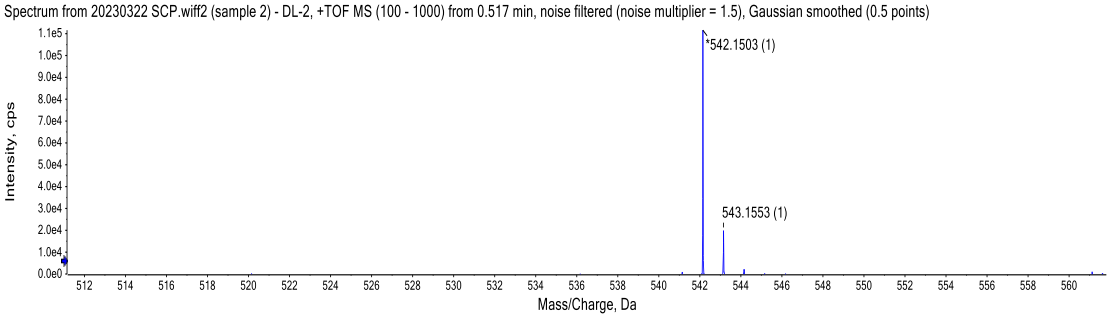
HRMS spectrum of compound 11n



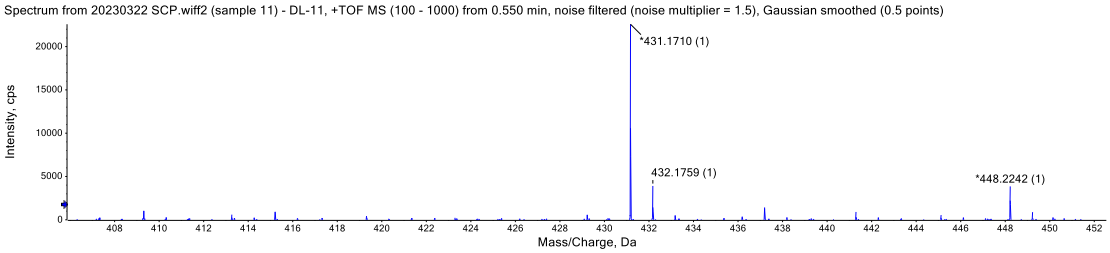
HRMS spectrum of compound 11o



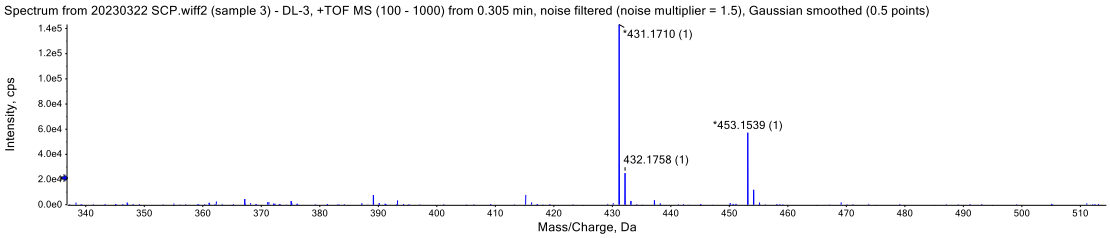
HRMS spectrum of compound 11p



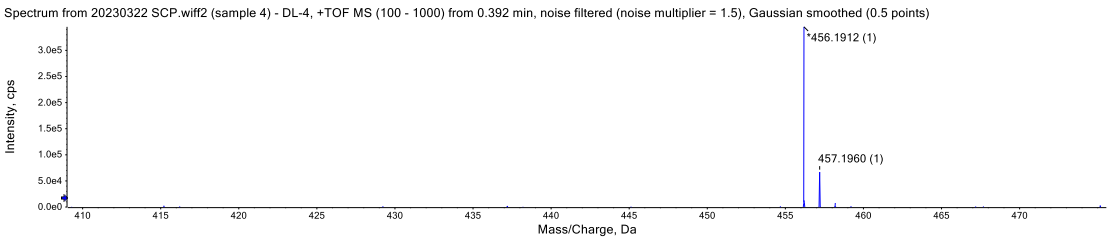
HRMS spectrum of compound 11q



HRMS spectrum of compound 11r



HRMS spectrum of compound 11s



HRMS spectrum of compound 11t