BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Supporting Information

for

α,ß-Didehydrosuberoylanilide hydroxamic acid (DDSAHA) as precursor and possible analogue of the anticancer drug SAHA

Shital K. Chattopadhyay, Subhankar Ghosh, Sarita Sarkar and Kakali Bhadra

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Analytical data of all new compounds as well as copies of their ^{1}H and ^{13}C NMR spectra

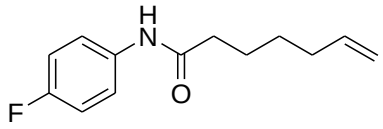
Contents

1. Experimental details

Infrared spectra were recorded with a Perkin–Elmer Infrared Spectrometer model No L120–000A. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker 400 MHz Ultrashield NMR spectrometer purchased through a DST-FIST grant. Mass spectra were recorded with a Water Xevo QTOF mass spectrometer purchased through DST-PURSE grant. Elemental analysis was performed with a Perkin–Elmer 2400 series II Instrument. All solvents obtained from commercial sources were dried with appropriate drying agents and were immediately distilled before use. Column chromatography was performed with silica gel (230–400) purchased from Spectrochem India Pvt. Ltd. Thin-layer chromatography was performed with pre-coated silica plates and were visualized under a UV lamp or with an iodine spray. Melting points were determined in open capillaries and are uncorrected.

The HeLa cell line was collected from the National Center for Cell Science, Pune, India, and used throughout the study. Cells were cultured in DMEM (Gibco BRL) supplemented with 10% FBS (Gibco BRL), and a 1% antibiotic mixture containing PSN (Gibco BRL) at 37 °C in a humidified incubator with 5% CO_2; cells were grown to 80–90% confluence, harvested with 0.025% trypsin (Gibco BRL) and 0.52 mm EDTA (Gibco BRL) in phosphate-buffered saline (PBS), plated at the desired cell concentration and allowed to re-equilibrate for 24 h before any treatment.

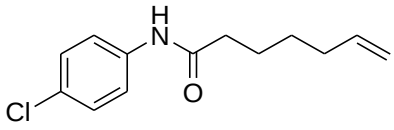
2. Characterization data for compounds 7b–g, 10b–g, 11b–g



N-(4-fluorophenyl)hept-6-enamide

***N*-(4-Fluorophenyl)hept-6-enamide (7b)**:

Eluent: hexane:ethyl acetate (85:15). Viscous liquid. Yield: 82%. IR (neat): 3265, 2858, 1660, 1618 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.82 (1H, brs), 7.48-7.43 (2H, m), 6.97 (2H, t, *J* = 8.4Hz), 5.88-5.73 (1H, m), 5.02-4.94 (2H, m), 2.33 (2H, t, *J* = 7.2Hz), 2.06 (2H, q, *J* = 6.8Hz), 1.71 (2H, quin, *J* = 7.6), 1.48-1.39 (2H, m).^{13}CNMR (100 MHz, $CDCl_3$) δ 171.7, 160.5(158.1), 138.3, 134.0, 121.9 (121.8), 115.6 (115.4), 114.8, 37.3, 33.4, 28.4, 25.1. Elemental analyses: calcd for $C_{13}H_{16}FNO$; C, 70.56; H, 7.29; N, 6.33; obsd, C, 70.45; H, 7.59; N, 6.42.

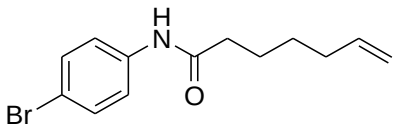


N-(4-chlorophenyl)hept-6-enamide

N-(4-Chlorophenyl)hept-6-enamide (7c):

Eluent: hexane:ethyl acetate (85:15). Yield: 93%. Colourless solid. M.p- 81-83°C. IR (KBr): 3296, 2935, 2852, 1656, 1592 cm^{-1}.^{1}HNMR (400 MHz, $CDCl_3$) δ 7.99 (1H, brs), 7.46 (2H, d, *J* = 8.8Hz), 7.23 (2H, d, *J* = 8.8Hz), 5.82-5.71 (1H, m), 5.01-4.93 (2H, m), 2.33 (2H, t, *J* = 2H, t, *J* =

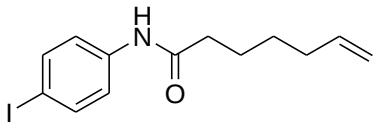
7.2Hz), 2.05 (2H, q, *J* = 7.2Hz), 1.70 (2H, quin, *J* = 7.2Hz), 1.46-1.39 (2H, m).^{13}CNMR (100 MHz, $CDCl_3$) δ 171.9, 138.2, 136.6, 129.2, 128.9, 121.4, 114.9, 37.4, 33.4, 28.4, 25.1.Elemental analyses: calcd for $C_{13}H_{16}ClNO$; C, 65.68; H, 6.78; N, 5.89; obsd, C, 65.90; H, 6.87; N, 5.68.



N-(4-bromophenyl)hept-6-enamide

***N*-(4-Bromophenyl)hept-6-enamide (7d)**:

Eluent: hexane:ethyl acetate (85:15).Yield: 94%. Colorless solid. M.p- 86°C.IR (KBr): 3296, 2933, 1655, 1590 cm^{-1}.^{1}HNMR (400 MHz, $CDCl_3$) δ 7.80 (1H, s), 7.42-7.37 (4H, m), 5.82-5.72 (1H, m), 5.02-4.94 (2H, m), 2.33 (2H, t, *J* = 7.2Hz), 2.06 (2H, q, *J* = 6.8Hz), 1.70 (2H, quin, *J* = 7.6Hz), 1.43 (2H, quin *J* = 8Hz).^{13}CNMR (100 MHz, $CDCl_3$) δ 171.7, 138.2, 137.1, 131.9, 121.6, 116.8, 114.9, 37.5, 33.4, 28.4, 25.0.Elemental analyses: calcd for $C_{13}H_{16}BrNO$; C, 55.33; H, 5.72; N, 4.96; obsd, C, 55.23; H, 5.95; N, 4.78.

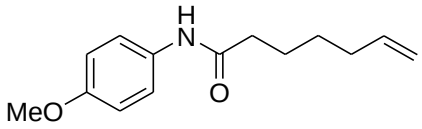


N-(4-iodophenyl)hept-6-enamide

***N*-(4-Iodophenyl)hept-6-enamide (7e)** :

Eluent: hexane:ethyl acetate (90:10).Yield: 91%. Colourless solid. M.p- 103-104°C. IR (KBr): 3295, 2931, 2850, 1655, 1523 cm^{-1}.^{1}HNMR (400 MHz, $CDCl_3$) δ 7.58 (2H, d, *J* = 8.8Hz), 7.30

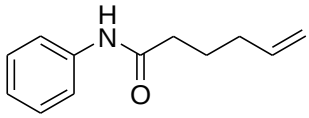
(2H, d, *J* = 8Hz), 5.83-5.73 (1H, m), 5.03-4.94 (2H, m), 2.34 (2H, t, *J* = 7.2Hz), 2.07 (2H, q, *J* = 6.8Hz), 1.71 (2H, quin, *J* = 7.2Hz), 1.48-1.41 (2H,m).^{13}CNMR (100 MHz, $CDCl_3$) δ 171.5, 138.3, 137.9, 137.7, 121.5, 114.9, 87.3, 37.5, 33.4, 28.4, 25.0. Elemental analyses: calcd for $C_{13}H_{16}INO$; C, 47.43; H, 4.90; N, 4.26; obsd, C, 47.19; H, 4.79; N, 4.48.



N-(4-methoxyphenyl)hept-6-enamide

***N*-(4-Methoxyphenyl)hept-6-enamide (7f)** :

Eluent: hexane:ethyl acetate (80:20).Yield: 97%. Colourless solid. M.p- 80 °C. IR (KBr): 3312, 2962, 2852, 1652, 1601 cm^{-1}.^{1}HNMR (400 MHz, $CDCl_3$) δ 7.95 (1H, brs), 7.40 (2H, d, *J* = 8.8Hz), 6.80 (2H, d, *J* = 8.8Hz), 5.81-5.74(1H, m), 5.01-4.93 (2H, m), 3.76 (3H, s), 2.03 (2H, t, *J* = 7.6Hz), 2.05 (2H, q, *J* = 7.2Hz), 1.69 (2H, quin, *J* = 7.6Hz), 1.42 (2H, quin, *J* = 7.6Hz). ^{13}CNMR (100 MHz, $CDCl_3$): δ 171.7, 156.3, 138.4, 131.2, 122.0, 114.7, 114.0, 55.4, 37.2, 33.5, 28.5, 25.2. Elemental analyses: calcd for $C_{14}H_{19}NO_2$; C, 72.07; H, 8.21; N, 6.00; obsd, C, 72.19; H, 8.38; N, 6.23.

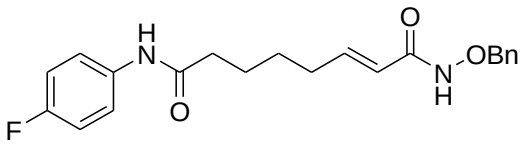


N-phenylhex-5-enamide

***N*-Phenylhex-5-enamide (7g)** :

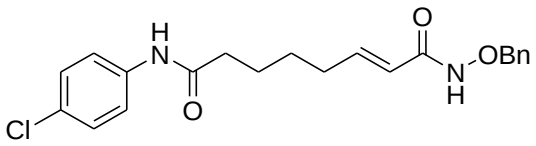
Eluent: hexane:ethyl acetate (85:15). Yield: 95%. Yellowish viscous liquid. IR (KBr): 3244, 2930, 1655, 1597 cm^{-1}.^{1}HNMR (400 MHz, $CDCl_3$) δ 8.60 (1H, brs), 7.43 (2H, d, *J* = 7.6Hz), 7.12 (2H, t, *J* = 8Hz), 6.94 (1H, t, *J* = 7.6Hz), 5.67-5.57 (1H, m), 4.90-4.83 (2H,m), 2.22 (2H, t, *J* = 7.6Hz), 1.95 (2H, q, *J* = 6,8Hz), 1.66(2H, quin, *J* = 7.6Hz). ^{13}CNMR (100 MHz, $CDCl_3$) δ 172.4, 138.3, 137.8, 128.8, 124.2, 120.5, 115.4, 36.7, 33.2, 24.9. Elemental analyses: calcd for $C_{12}H_{15}NO$; C, 76.16; H, 7.99; N, 7.40; obsd, C, 76.30; H, 8.22; N, 7.53.

Cross-metathesis products 10b–g



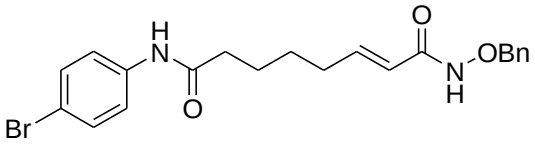
(*E*)-N^1-(Benzyloxy)-N^8-(4-fluorophenyl)oct-2-enediamide (10b) :

Eluent: $CHCl_3$:MeOH (98:2). Yield: 80%. Colourless solid. M.p- 165-166°C. IR (KBr): 3214, 3089, 2925, 2854, 1662, 1641 cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6): δ 11.17 (1H, brs), 9.99 (1H, s), 7.59-7.55 (2H, m,), 7.37-7.35 (5H, m), 7.11 (2H, t, *J*=8.8Hz), 6.71 (1H, dt, *J* = 15.2,7.6Hz), 5.72 (1H, d, *J* = 15.6Hz), 4.80 (2H, s), 2.28 (2H, t, *J* = 7.2), 2.15 (2H, q, *J* = 6.8Hz), 1.57 (2H, quin, *J* = 6.8Hz), 1.42 (2H, quin, *J* = 7.2Hz).^{13}C NMR (100 MHz, DMSO-d_6): δ 171.7, 163.4, 159.5, 157.1, 144.4, 136.3, 135.9, 129.2, 128.8, 121.4, 121.3 (121.2), 115.8 (115.5), 77.4, 36.4, 31.6, 27.7, 25.1. HRMS (TOF MS ES+): *m/z* [M + H] $^+$ calcd. for $C_{21}H_{24}FN_2O_3$ 371.1771; found 371.1758.



(*E*)-*N*^{1}-(Benzyloxy)-*N*^{8}-(4-chlorophenyl)oct-2-enediamide (10c) :

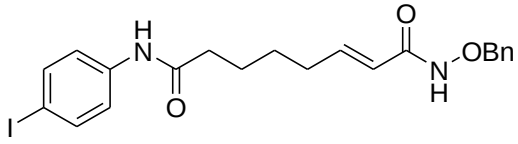
Eluent: $CHCl_3$:MeOH (97:3).Yield: 78%. Colorless solid. M.p- 182-184°C.IR (KBr): 3243, 3064, 2963, 2867, 1663, 1644 cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6): δ 11.13 (1H, brs), 11.05 (1H, s), 7.61 (2H, d, *J* = 8.8Hz), 7.39-7.32 (7H, m), 6.71 (1H, dt, *J* = 15.2,7.6Hz), 5.72 (1H, d, *J* = 15.2Hz), 4.81 (2H, s), 2.31 (2H, t, *J* = 7.2Hz), 2.17 (2H, q, *J* = 6.8Hz), 1.58 (2H, quin, *J* = 7.2Hz), 1.42 (2H, quin, *J* = 7.2Hz).^{13}C NMR (100 MHz, DMSO-d_6): δ 171.8, 163.3, 144.1, 138.7, 136.5, 129.2, 129.0, 128.8, 127.0, 121.4, 121.3, 121.0, 77.4, 36.6, 31.6, 27.8, 25.0. Elemental analyses: calcd for $C_{21}H_{23}ClN_2O_3$; C, 65.20; H, 5.99; N, 7.24; obsd, C, 65.39; H, 6.24; N, 7.41.



(*E*)-*N*^{1}-(Benzyloxy)-*N*^{8}-(4-bromophenyl)oct-2-enediamide (10d) :

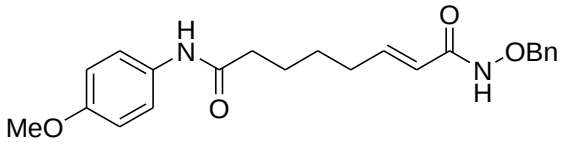
Eluent: $CHCl_3$:MeOH (98:2).Yield : 77%. Colourless solid. M.p- 170-172°C. IR (KBr): 3278, 3214, 2863, 1667, 1634 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.12 (1H, s), 10.04 (1H, s), 7.56 (2H, d, *J* = 8.8Hz), 7.46 (2H, d, *J* = 8.8Hz), 7.39-7.34 (5H, m), 6.71 (1H, dt, *J* = 15.6,8Hz), 5.72 (1H, d, *J* = 15.2Hz), 4.81 (2H, s), 2.31 (2H, t, *J* = 7.2Hz), 2.16 (2H, q, *J* = 6.8Hz), 1.58 (2H, quin, *J* = 7.6Hz), 1.41 (2H, quin, *J* = 7.6Hz).^{13}C NMR (100 MHz, DMSO-d_6): δ 171.8, 163.3, 144.1, 139.0, 136.4, 131.9, 129.2, 128.8, 128.7, 121.4, 115.0, 77.4, 36.6, 31.6, 27.8, 25.0.

Elemental analyses: calcd for $C_{21}H_{23}BrN_2O_3$; C, 58.48; H, 5.37; N, 6.49; obsd, C, 58.67; H, 5.51; N, 6.34



(*E*)-*N*^{1}-(Benzyloxy)-*N*^{8}-(4-iodophenyl)oct-2-enediamide (10e) :

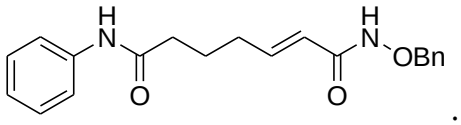
Eluent: $CHCl_3$:MeOH (98:2).Yield: 74%. Colourless solid. M.p- 198-200°C. IR (KBr): 3315, 2930, 2856, 1656, 1613 cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6): δ 11.17 (1H, brs), 10.04 (1H, s), 7.61 (2H, d, *J* = 8.8Hz), 7.42-7.33 (7H, m), 6.70 (1H, dt, *J* = 15.6,8Hz), 5.71 (1H, d, *J* = 15.2Hz), 4.79 (2H, s), 2.29 (2H, t, *J* = 7.2Hz), 2.15 (2H, q, *J* = 7.2Hz), 1.56 (2H, quin, *J* = 7.2Hz), 1.39 (2H, quin, *J* = 7.6Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.0, 163.9, 144.4, 139.4, 137.8, 136.3, 129.2, 128.8, 121.8, 121.2, 86.9, 77.4, 36.6, 31.5, 27.7, 25.0. Elemental analyses: calcd for $C_{21}H_{23}IN_2O_3$; C, 52.73; H, 4.85; N, 5.86; obsd, C, 52.87; H, 5.04; N, 5.74.



(*E*)-*N*^{1}-(Benzyloxy)-*N*^{8}-(4-methoxyphenyl)oct-2-enediamide (10f) :

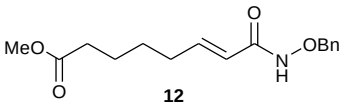
Eluent: $CHCl_3$:MeOH (97:3).Yield: 78%. Colorless solid.M.p-169-170°C. IR (KBr): 3269, 2972, 2872, 1659, 1618 cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6): δ 11.14 (1H, brs), 9.77 (1H, s), 7.48 (2H, d, *J* = 8.8Hz), 7.39-7.34 (5H, m), 6.86 (2H, d, *J* = 9.2Hz), 6,72 (1H, dt, *J* = 15.2,7.2Hz),

5.73 (1H, d, *J* = 15.2Hz), 4.81 (2H, s), 3.70 (3H, s), 2.27 (2H, t, *J* = 7.2Hz), 2.16 (2H, q, *J* = 8Hz), 1.58 (2H, quin, *J* = 7.6Hz), 1.41 (2H, quin, *J* = 7.6Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.2, 163.4, 155.5, 144.3, 136.4, 132.8, 129.2, 128.8, 121.3, 121.1, 114.2, 77.4, 55.6, 36.4, 31.6, 27.8, 25.2. Elemental analyses: calcd for $C_{22}H_{26}N_2O_4$; C, 69.09; H, 6.85; N, 7.32; obsd, C, 69.27; H, 6.74; N, 7.24.



(*E*)-*N*^{1}-(Benzyloxy)-*N*^{7}-phenylhept-2-enediamide (10g):

Eluent: $CHCl_3$:MeOH (98:2). Yield:75%. Colourless solid.M.p-152-153°C. IR (KBr): 3248, 3027, 2856, 1647, 1634 cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6): δ 11.33 (1H, s), 10.05 (1H, s), 7.61 (2H, d, *J* = 8Hz), 7.45-7.42 (5H, m), 7.37 (2H, t, *J* = 7.6Hz), 7.12 (1H, t, *J* = 7.2Hz), 6.81 (1H, dt, *J* = 15.6,8Hz), 5.82 (1H, d, *J* = 15.2Hz), 4.87 (2H, s), 2.39 (2H, t, *J* = 7.6Hz), 2.26 (2H, q, *J* = 6.8Hz), 1.78 (2H, quin, *J* = 7.2Hz).^{13}C NMR (100 MHz, DMSO-d_6): δ 171.9, 163.6, 144.3, 139.2, 136.1, 129.2, 129.2, 128.9, 123.9, 121.2, 119.8, 77.5, 36.0, 31.3, 24.1. Elemental analyses: calcd for $C_{20}H_{22}N_2O_3$; C, 70.99; H, 6.55; N, 8.28; obsd, C, 71.22; H, 6.42; N, 8.04.

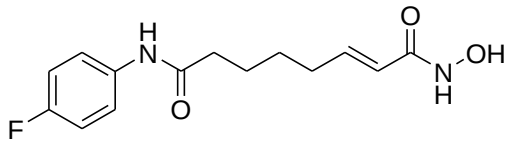


12

Cross metathesis of 12 with 8: Formation of (*E*)-methyl 8-(benzyloxyamino)-8-oxooct-6-enoate (12)

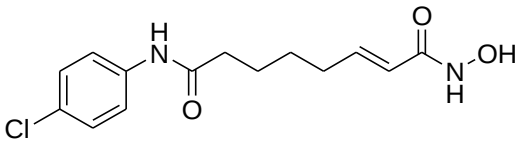
The reaction was conducted following the general procedure for CM. The product was obtained as a colourless viscous liquid after chromatography over silica gel using a mixture of hexane: ethyl acetate (60:40) as eluent. Yield: 81%. IR (neat): 3157, 2832, 2989, 1752, 1667, 1533 cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6): δ 11.10 (1H, s), 7.40-7.35 (5H, m), 6.69 (1H, dt, *J* = 14.4,6.4Hz), 5.72 (1H, d, *J* = 15.2Hz), 4.82 (2H, s), 3.58 (3H, s), 2.31 (2H, t, *J* = 7.6Hz), 2.l4 (2H, q, *J* = 7.2Hz), 1.54-1.49 (2H, m), 1.43-1.37 (2H, m).^{13}C NMR (100 MHz, DMSO-d_6): δ 173.7, 163.3, 143.9, 136.5, 129.2, 128.8, 128.7, 121.5, 77.4, 51.7, 33.5, 31.4, 27.5, 24.4. Elemental analyses: calcd for $C_{16}H_{21}NO_4$; C, 65.96; H, 7.27; N, 4.81; obsd, C, 66.22; H, 7.43; N, 4.69.

Didehydro SAHA derivatives 11b–g:



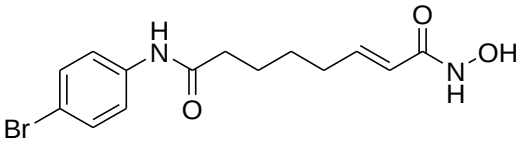
(*E*)-*N*^{8}-(4-Fluorophenyl)-*N*^{1}-hydroxyoct-2-enediamide (11b):

Eluent: $CHCl_3$:MeOH (95:5).Yield: 87%.Colourless solid. M.p- 150-151°C.IR (KBr): 3200, 3007, 2911, 1671, 1612 cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6): δ 10.59 (1H, s), 9.97 (1H, s), 8.92 (1H, brs), 7.60-7.57 (2H, m), 7.11 (2H, t, *J* = 8.8Hz), 6.63 (1H, dt, *J* = 15.6,6.4Hz), 5.74 (1H, d, *J* = 15.6Hz), 2.94 (2H, t, *J* = 7.2Hz), 2.15 (2H, q, *J* = 6.8Hz), 1.58 (2H, quin, *J* = 6.8Hz), 1.41 (2H, quin, *J* = 7.2Hz).^{13}C NMR (100 MHz, DMSO-d_6): δ 171.6, 163.3, 159.5 (157.1), 142.7, 136.0, 121.7, 121.3 (121.2), 115.8 (115.5), 36.5, 31.5, 27.9, 25.1. HRMS (TOF MS ES+): *m/z* $[M + Na]^+$ calcd. for $C_{14}H_{17}FN_2NaO_3$ 303.1121; found 303.1136.



(*E*)-*N*^{8}-(4-Chlorophenyl)-*N*^{1}-hydroxyoct-2-enediamide (11c)

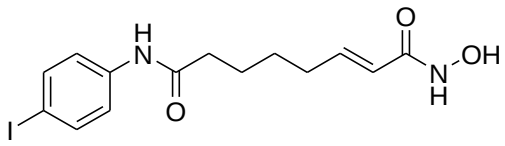
Eluent: $CHCl_3$:MeOH (95:5).Yield: 82%.Colourless solid. M.p- 154-155°C. IR (KBr): 3311, 3248, 2922, 1660, 1616 cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6): δ 10.69 (1H, brs), 10.08 (1H, s), 7.56 (2H, d, *J* = 8.4Hz), 7.30 (2H, d, *J* = 8.4Hz), 6.25 (1H, dt, *J* = 15.2,6.8Hz), 5.74 (1H, d, *J* = 15.6Hz), 2.29 (2H, t, *J* = 6.8Hz), 2.13 (2H, q, *J* = 8Hz), 1.55 (2H, quin, *J* = 8.8Hz), 1.39 (2H, quin, *J* = 6.8Hz).^{13}C NMR (100 MHz, DMSO-d_6): δ 172.2, 163.6, 143.2, 138.3, 129.0, 127.3, 121.4, 121.2, 36.5, 31.5, 27.7, 25.0. Elemental analyses: calcd for $C_{14}H_{17}ClN_2O_3$; C, 56.66; H, 5.77; N, 9.44; obsd, C, 56.90; H, 5.83; N, 9.23.



(*E*)-*N*^{8}-(4-Bromophenyl)-*N*^{1}-hydroxyoct-2-enediamide (11d)

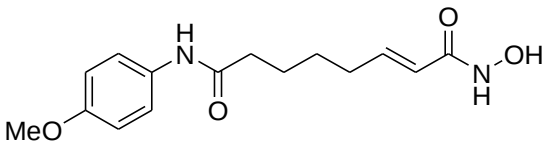
Eluent: $CHCl_3$:MeOH (93:7).Yield: 80%.Colourless solid. M.p- 158-159°C.IR (KBr): 3287, 2985, 1672, 1634 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.62 (1H, brs), 10.10(1H, s), 8.95 (1H, brs), 7.63 (2H, d, *J* = 8.4Hz), 7.53 (2H, d, *J* = 8.8Hz), 6.69 (1H, dt, *J* = 15.2,7.6Hz), 5.80 (1H, d, *J* = 15.6Hz), 2.38 (2H, t, *J* = 7.2Hz), 2.22 (2H, q, *J* = 6.4Hz), 1.65 (2H, quin, *J* = 6.8Hz),

1.52-1.45 (2H, m). ^{13}C NMR (100 MHz, dmso-d_6): δ 171.8, 163.1, 142.4, 139.1, 131.9, 121.8, 121.4, 114.9, 36.6, 31.5, 27.9, 25.0. HRMS (TOF MS ES+): *m/z* [M + Na] $^{+}$ calcd. for $C_{14}H_{17}FN_2NaO_3$ 363.0320, 365.0300; found 363.0349, 365.0334.



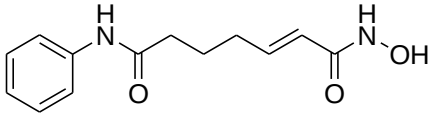
(*E*)-*N*^{1}-Hydroxy-*N*^{8}-(4-iodophenyl)oct-2-enediamide (11e)

Eluent: $CHCl_3$:MeOH (95:5).Yield: 88%. Colourless solid. M.p- 170-171 °C. IR (KBr): 3327, 3258, 2920, 1659, 1615 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.57 (1H, brs), 10.00 (1H, s), 8.89 (1H, brs), 7.61 (2H, d, *J* = 8.4Hz), 7.43 (2H, d, *J* = 8.4Hz), 6.63 (1H, dt, *J* = 15.6,6.4Hz), 5.74 (1H, d, *J* = 15.2Hz), 2.31 (2H, t, *J* = 7.2Hz), 2.14 (2H, q, *J* = 7.6Hz), 1.58 (2H, quin, *J* = 8Hz), 1.41 (2H, quin, *J* = 7.2Hz).^{13}C NMR (100 MHz, DMSO-d_6): δ 171.8, 163.2, 142.5, 139.5, 137.7, 121.8, 121.7, 86.8, 36.6, 31.5, 27.9, 25.0. Elemental analyses: calcd for $C_{14}H_{17}IN_2O_3$; C, 43.32; H, 4.41; N, 7.22; obsd, C, 43.54; H, 4.61; N,7.03.



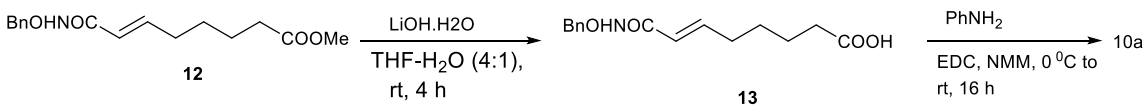
(*E*)-*N*^{1}-Hydroxy-*N*^{8}-(4-methoxyphenyl)oct-2-enediamide (11f)

Eluent: $CHCl_3$:MeOH (93:7).Yield: 84%. Colourless solid. M.p- 147-148°C. IR (KBr): 3315, 2930, 2856, 1656, 1613 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 10.68 (1H, brs), 9.85 (1H, s), 8.99 (1H, brs), 7.54 (2H, d, *J* = 8.8Hz), 6.93 (2H, d, *J* = 8.4Hz), 6.71 (1H, dt, *J* = 15.2,6.8Hz), 5.82 (1H, d, *J* = 15.6Hz), 3.78 (3H, s), 2.34 (2H, t, *J* = 6.8), 2.23-2.21 (2H, m), 1.65 (2H, quin, *J* = 7.6Hz), 1.48 (2H, quin, *J* = 7.2Hz).^{13}C NMR (100 MHz, DMSO-d_6): δ 171.2, 163.3, 155.5, 142.8, 132.8, 121.6, 121.2, 114.2, 55.6, 36.4, 31.5, 27.9, 25.2. Elemental analyses: calcd for $C_{15}H_{20}N_2O_4$; C, 61.63; H, 6.90; N, 9.58; obsd, C, 61.54; H, 7.01; N, 9.44.



(*E*)-N^1-Hydroxy-N^7-phenylhept-2-enediamide (11g)

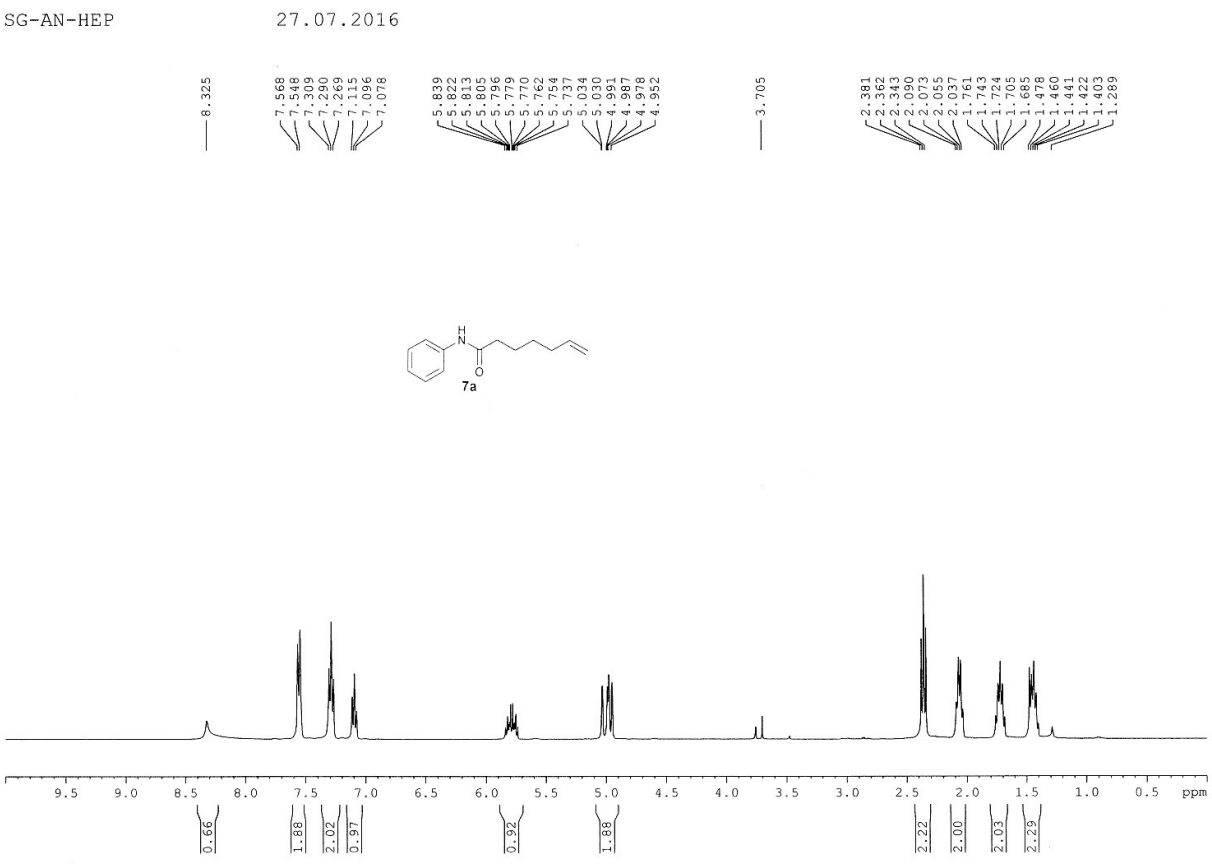
Eluent: $CHCl_3$:MeOH (93:7).Yield : 93%. Colourless solid. M.p- 159-160°C. IR (KBr): 3287, 3193, 2939, 2854, 1670, 1633 cm^{-1}.^1H NMR (400 MHz, DMSO-d_6): δ 10.83 (1H, brs), 10.01 (1H, s), 7.58 (2H, d, *J* = 8Hz), 7.33 (2H, t, *J* = 8Hz), 7.09 (1H, t, *J* = 7.2Hz), 6.71 (1H, dt, *J* = 15.6,8Hz), 5.81 (1H, d, *J* = 15.6Hz), 2.36 (2H, t, *J* = 7.6Hz), 2.21 (2H, q, *J* = 7.2Hz), 1.75 (2H, quin, *J* = 7.2Hz).^{13}C NMR (100 MHz, DMSO-d_6): δ 171.9, 163.6, 142.9, 139.2, 129.2, 123.9, 121.6, 119.8, 36.0, 31.2, 24.2. Elemental analyses: calcd for $C_{13}H_{16}N_2O_3$; C, 62.89; H, 6.50; N, 11.28; obsd, C, 63.06; H, 6.71; N, 11.14.



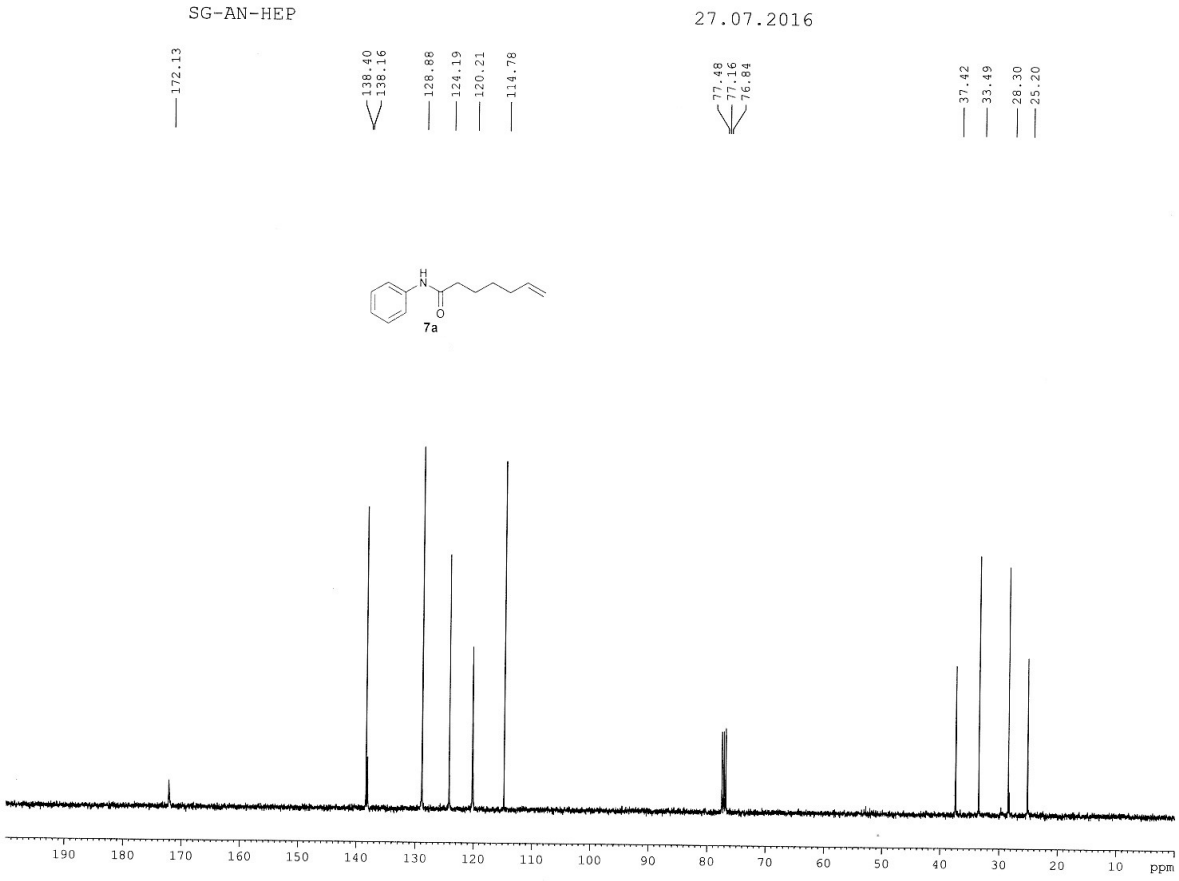
A mixture of the CM product **12** (100 mg, 0.34 mmol) and $LiOH \cdot H_2O$ (72 mg, 0.17 mmol) in THF/H_2O (5 ml, 4:1) was stirred at rt for 4 h. The reaction mixture was acidified to pH 2 using aq 2N HCl, and then extracted with EtOAc. The organic layer was washed with water (2 × 10 ml), brine (10 ml), and then dried over Na_2SO_4. It was filtered and the filtrate was concentrated under reduced pressure to leave a residue which was purified by column chromatography over silica gel using a mixture of $CHCl_3$:MeOH (98:2) as eluant to provide the product **13** as viscous colorless liquid. Yield: 84 mg (89%). IR (neat): 3419, 2947, 2859, 1647 cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (1H, s), 7.15-7.11 (5H, m), 6.49-6.44(1H, m), 5.48 (1H, d, *J* = 15.2Hz), 4.58 (2H, s), 1.98 (2H, t, *J* = 6.8Hz), 1.91 (2H, q, *J* = 6.8Hz), 1.27-1.22 (2H, m), 1.19-1.10 (2H, m).^{13}C NMR (100 MHz, DMSO-d_6): δ 173.7, 162.0, 142.8, 135.5, 128.1, 127.6, 127.5, 120.2, 76.2, 32.7, 30.4, 26.5, 23.3. Elemental analyses: calcd for $C_{15}H_{19}NO_4$; C, 64.97; H, 6.91; N, 5.05; obsd, C, 65.11; H, 7.05; N, 4.92.

Coupling of 14 with aniline: formation of 10a

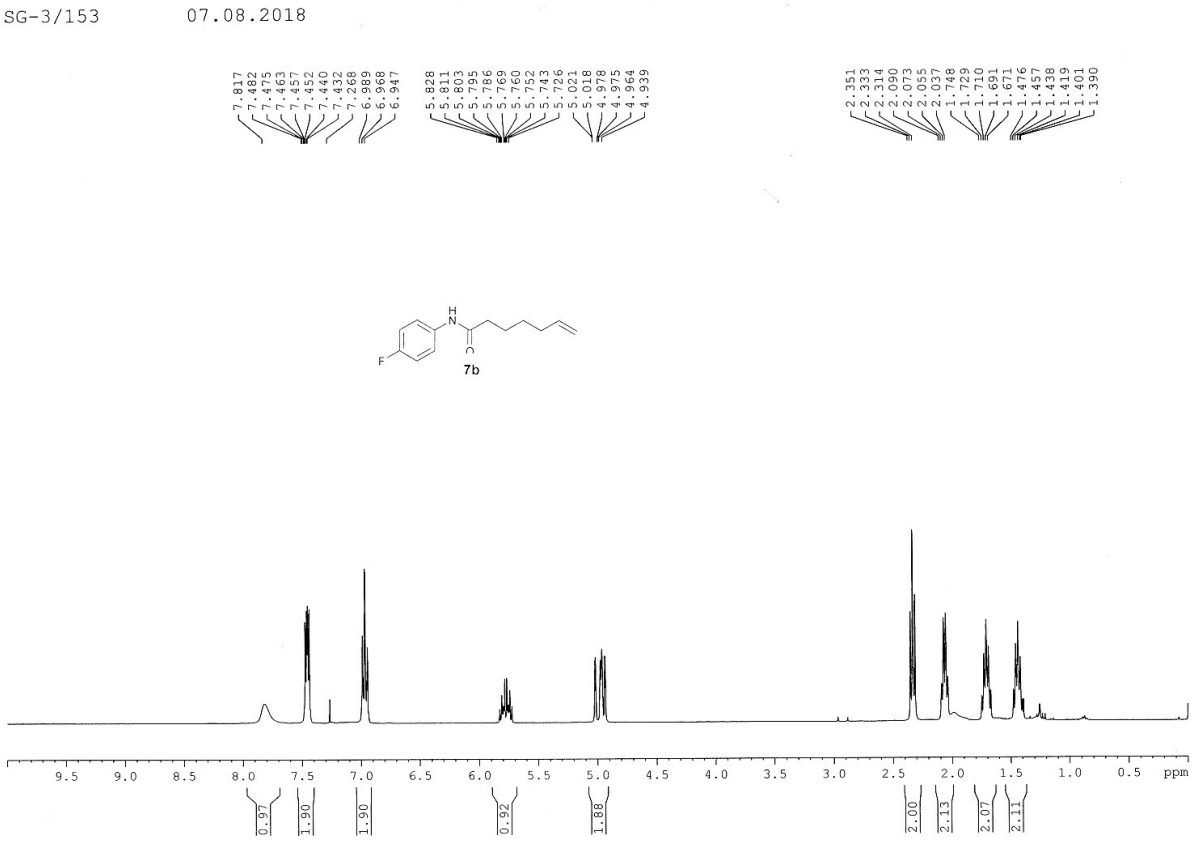
EDC.HCl (250 mg, 1.30 mmol) was added portion wise to a stirred solution of the acid **14** (178 mg, 0.65 mmol) in dry DCM (5 ml) at 0 °C during 15 minutes. Then a solution of aniline (50 mg, 0.54 mmol) and *N*-methylmorpholine (55 mg, 60 µl, 0.54 mmol) in dry DCM (3 ml) was added dropwise over 10 min to the solution of the acid at the same temperature. The reaction mixture was allowed to come to rt and stirred for 16 h. It was then diluted with DCM (20 ml) and the combined organic solution was washed successively with saturated aqueous solution of $NaHCO_3$ (2 × 15 ml), HCl (2 N, 2 × 10 ml), H_2O (1 × 20 ml), brine (1 × 20 ml), and then dried (Na_2SO_4). It was then filtered and the filtrate was concentrated to leave a residue which was purified by chromatography over silica gel using a mixture of $CHCl_3$:MeOH (98:2) as eluent to provide compound **10 a** as a colourless solid (147 mg, 78%).



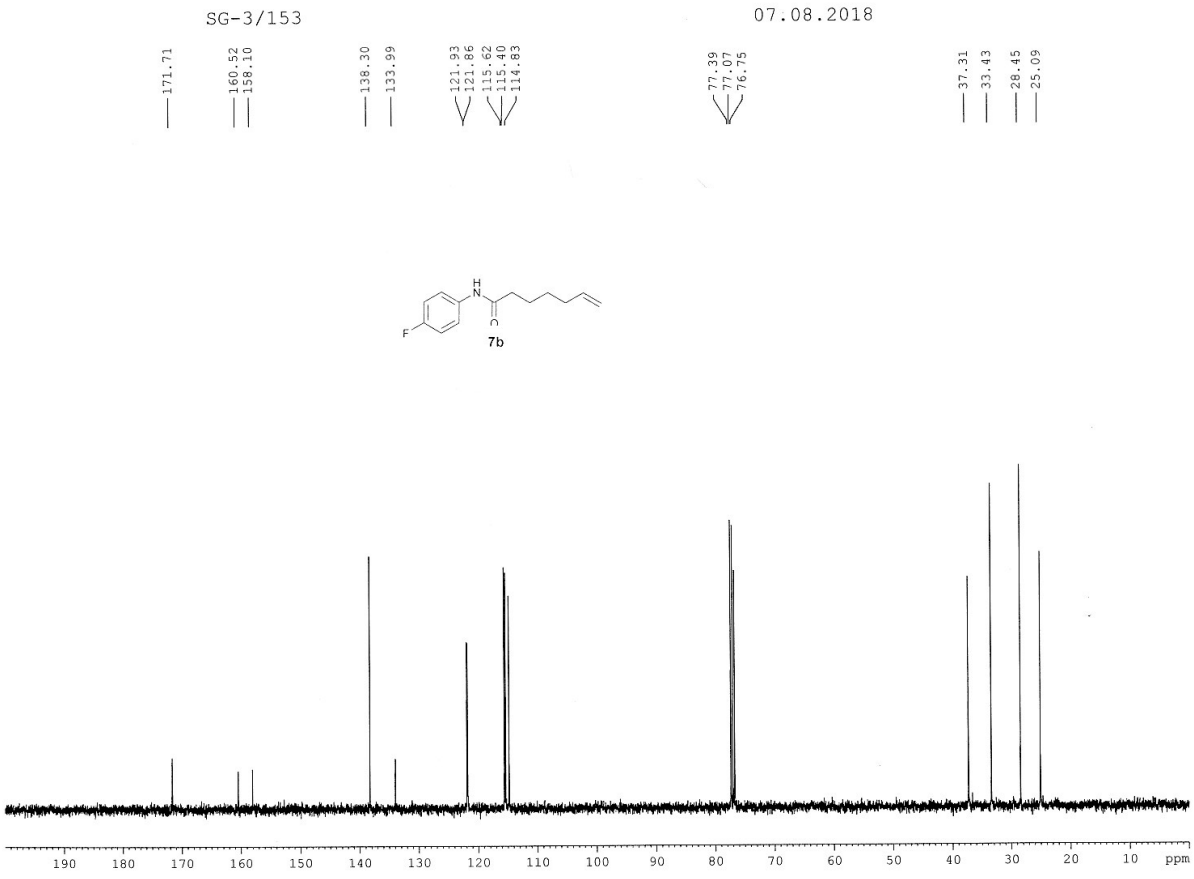
^{1}H NMR Spectrum of **7a** in $CDCl_3$



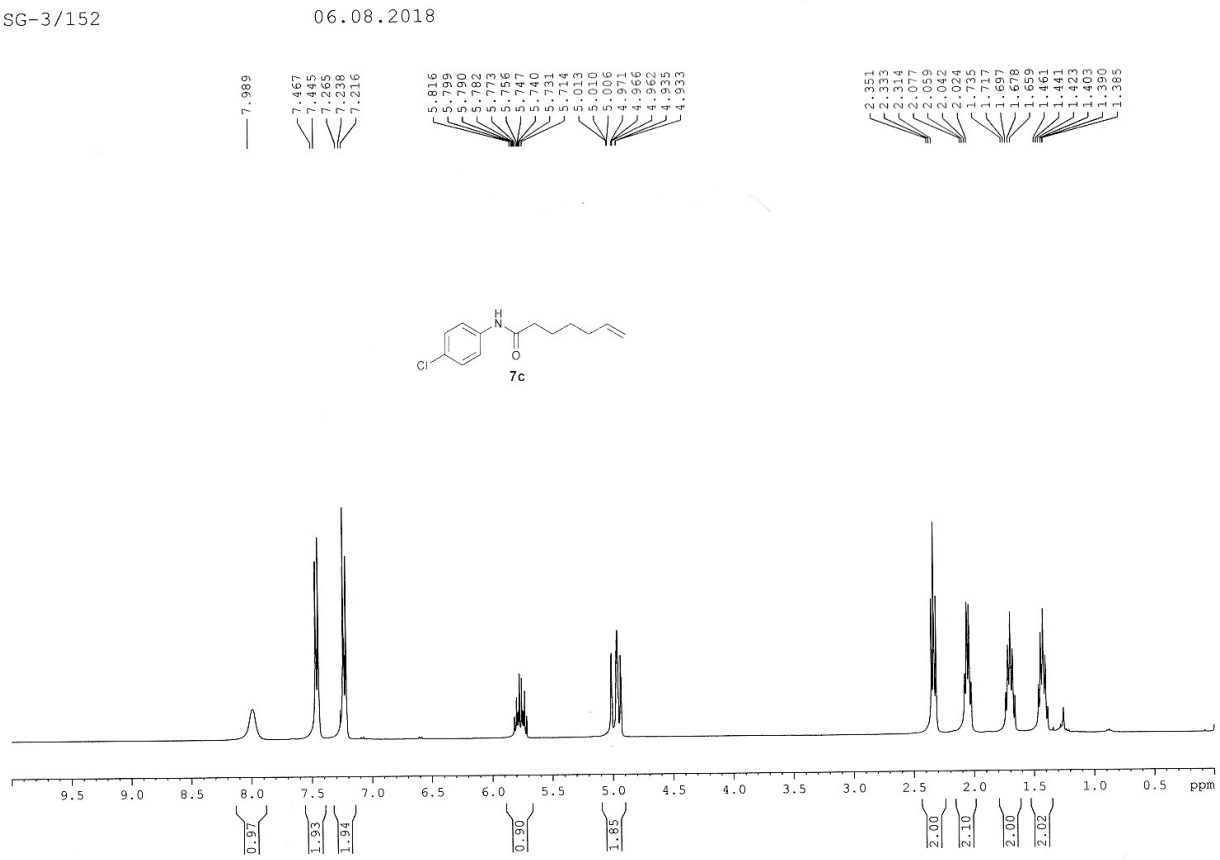
^{13}C NMR Spectrum of **7a** in $CDCl_3$



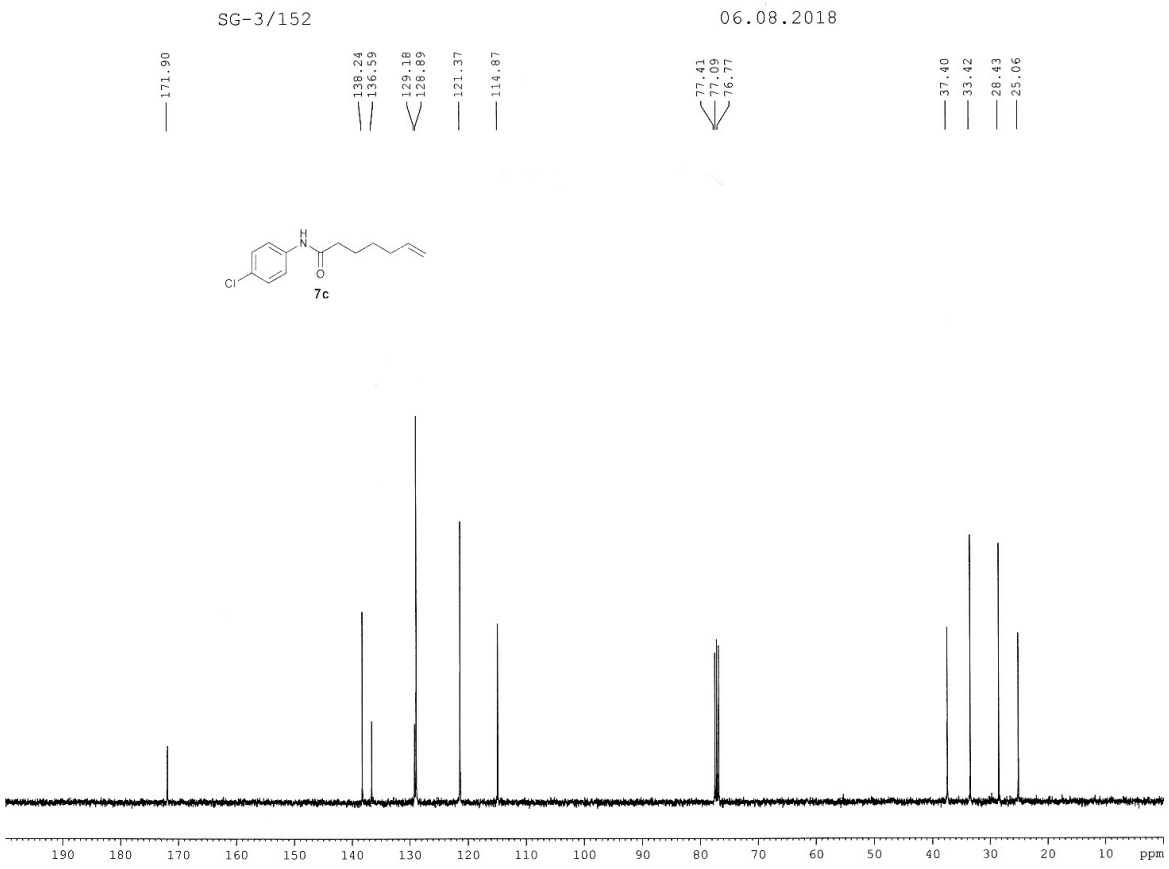
^{1}H NMR Spectrum of **7b** in $CDCl_3$



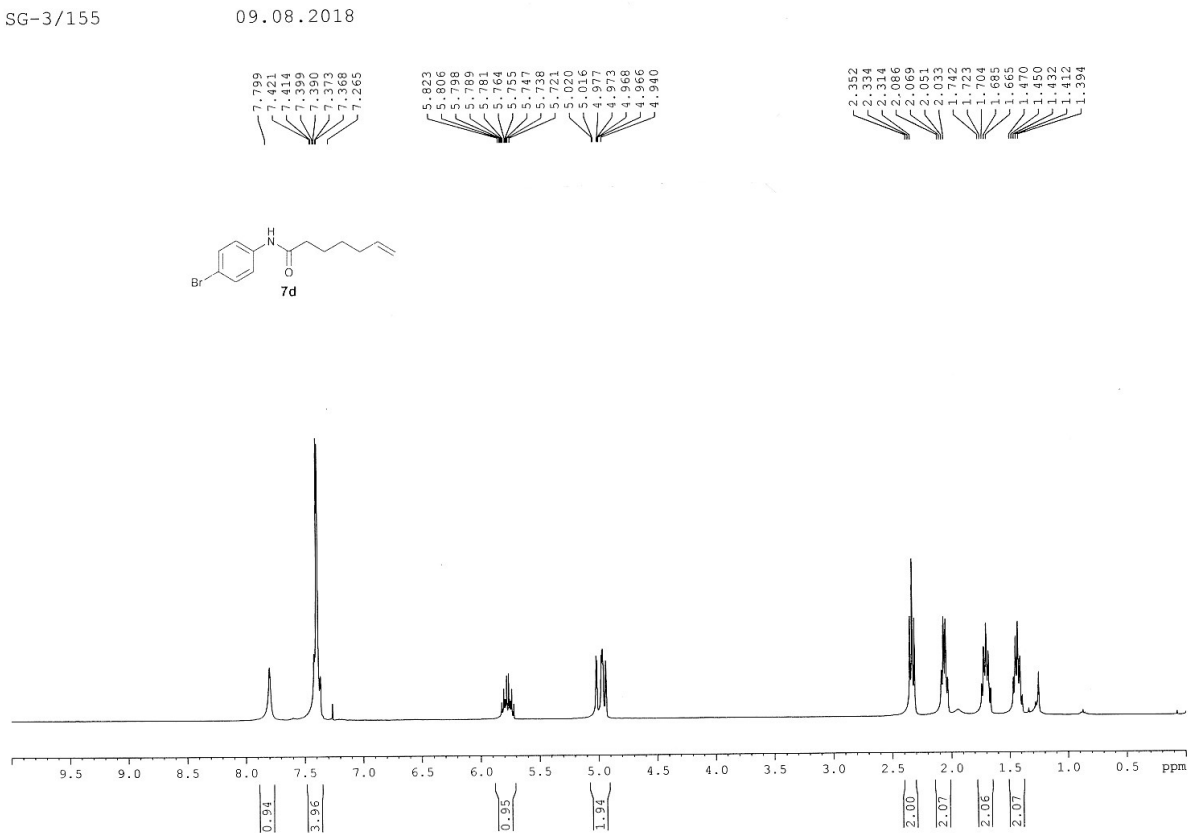
^{13}C NMR Spectrum of **7b** in $CDCl_3$



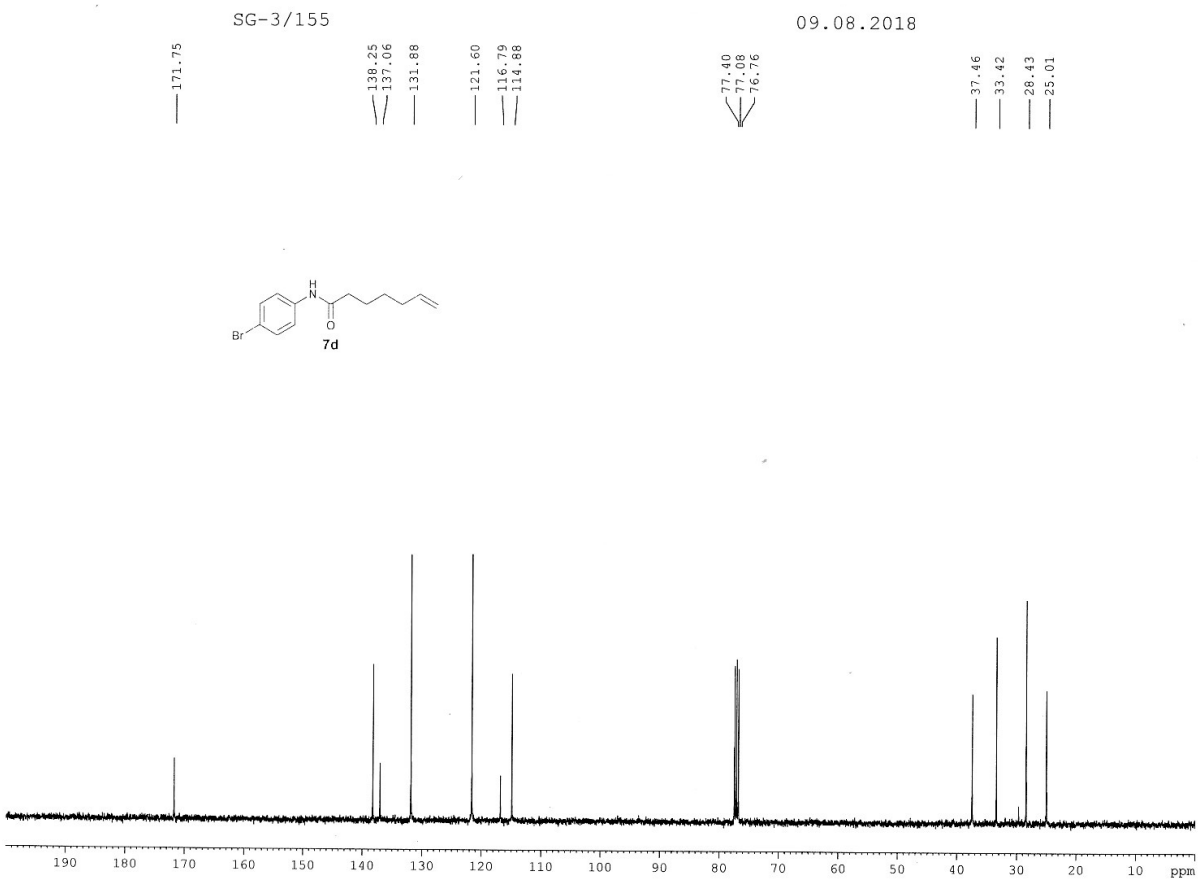
^{1}H NMR Spectrum of **7c** in $CDCl_3$



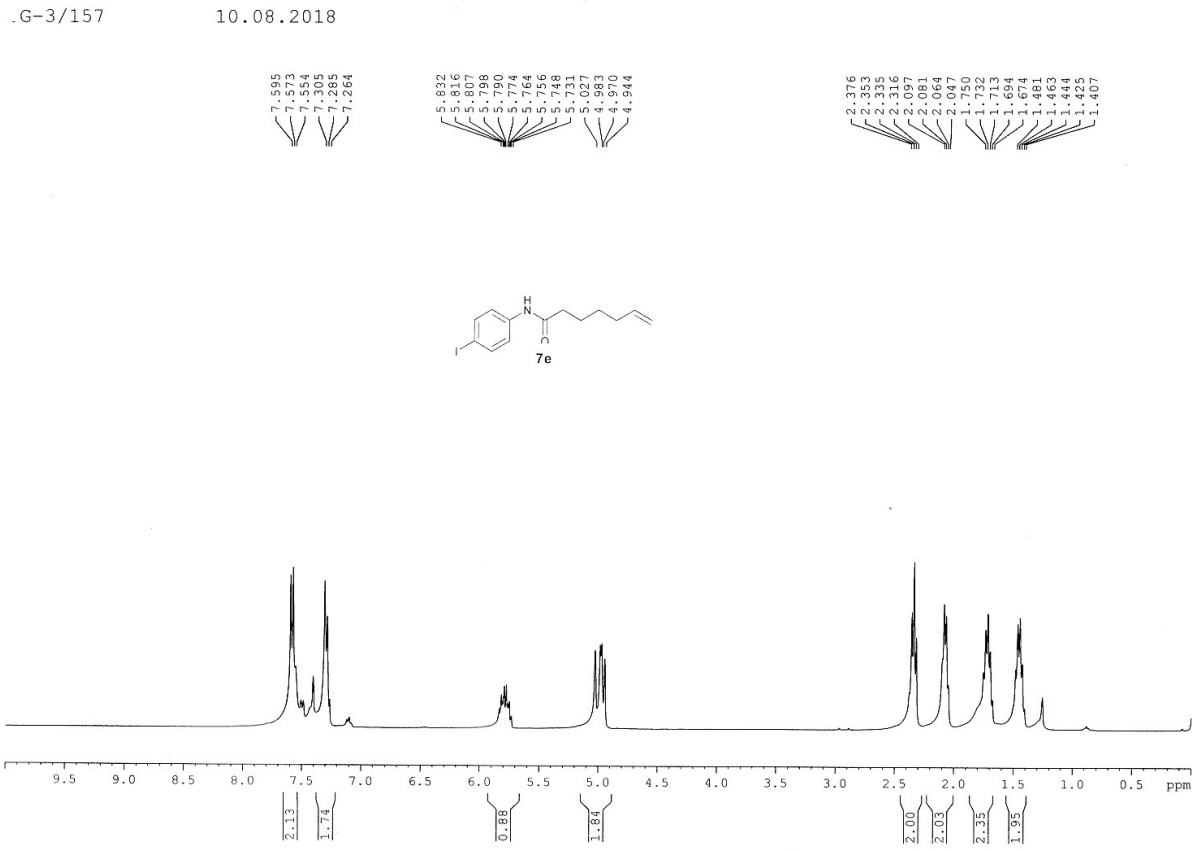
^{13}C NMR Spectrum of **7c** in $CDCl_3$



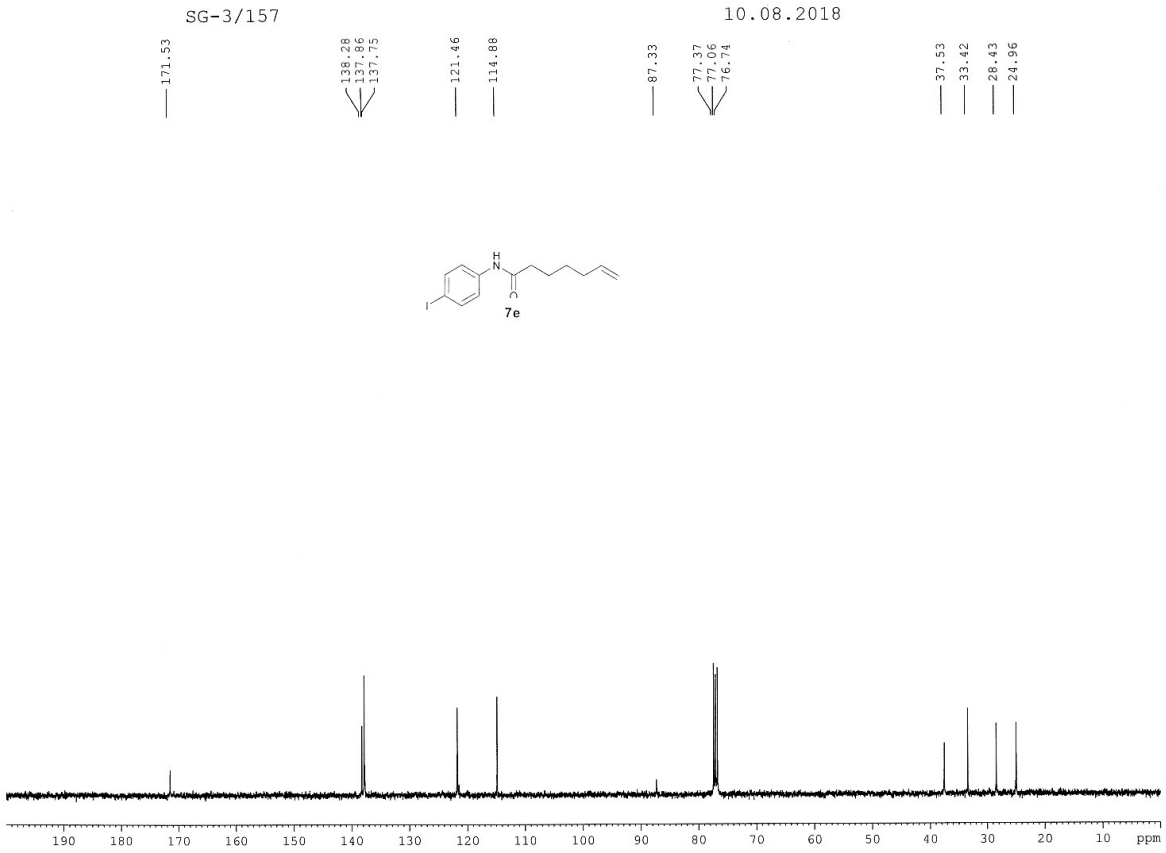
^{1}H NMR Spectrum of **7d** in $CDCl_3$



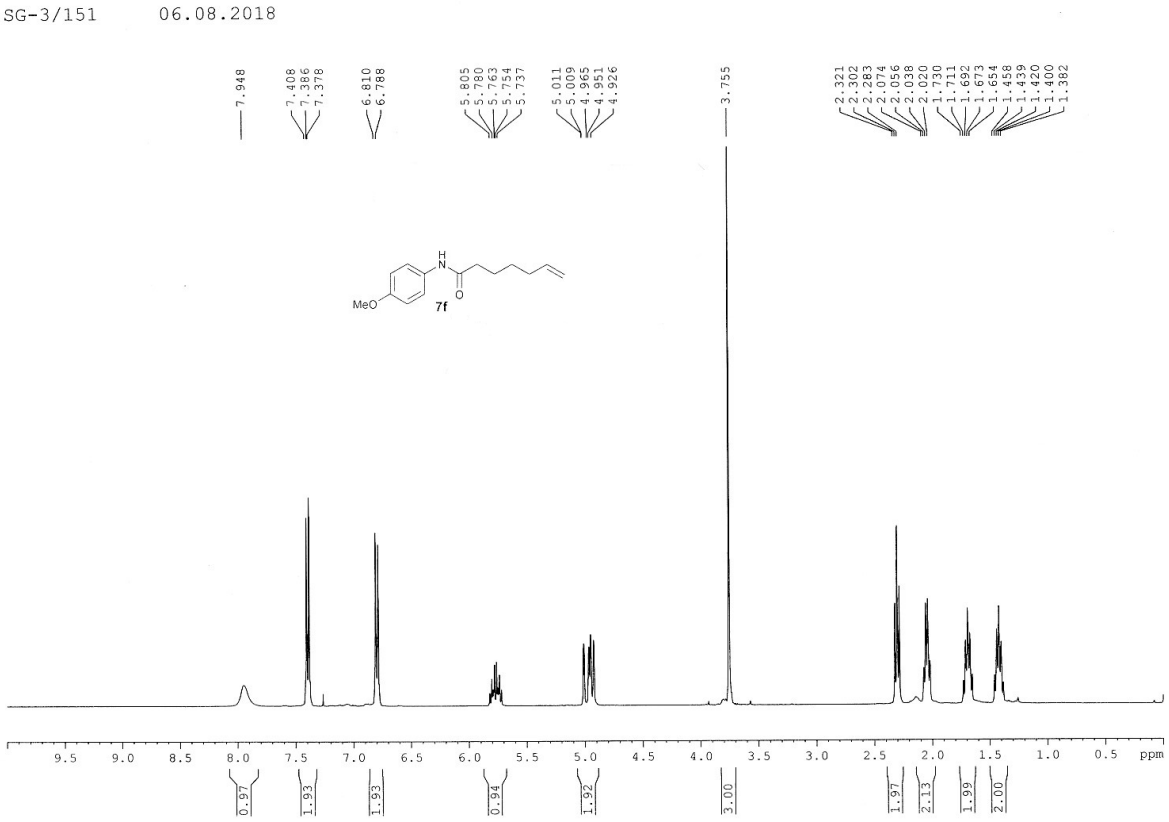
^{13}C NMR Spectrum of **7d** in $CDCl_3$



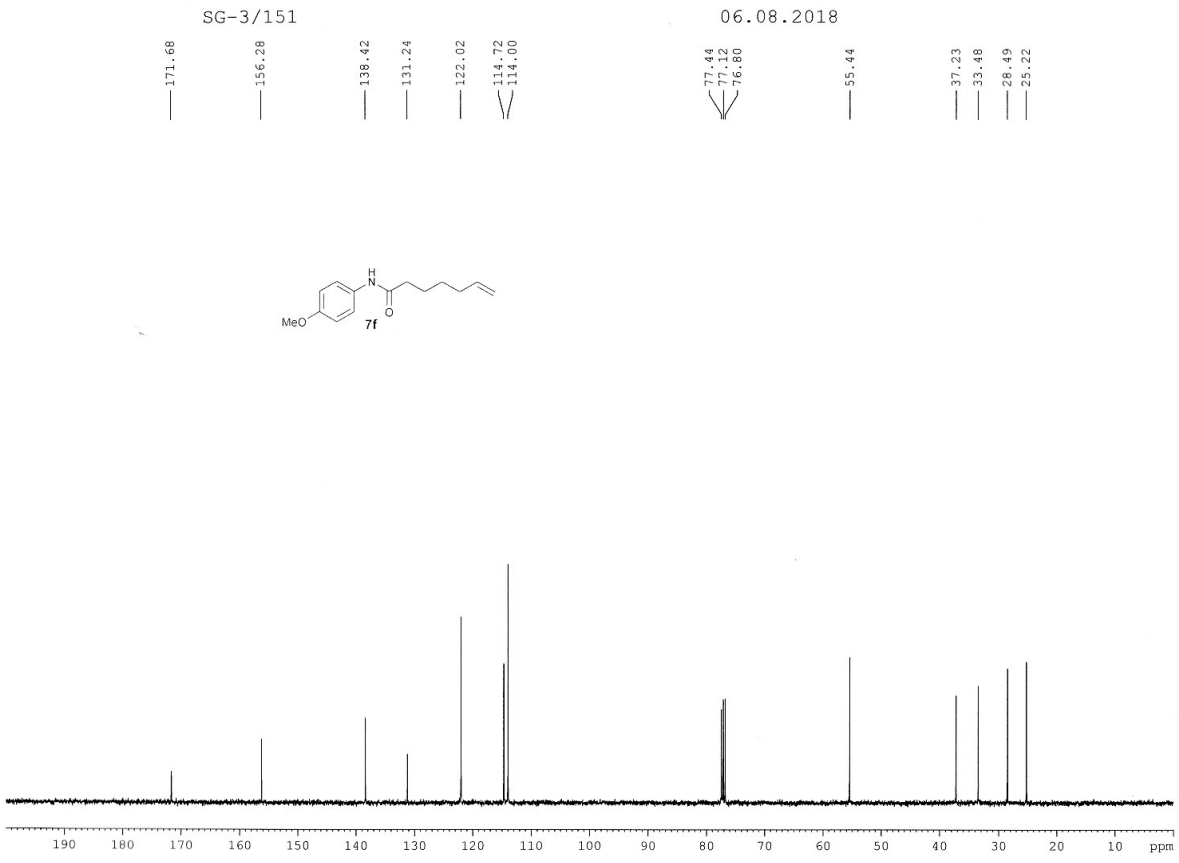
^{1}H NMR Spectrum of **7e** in $CDCl_3$



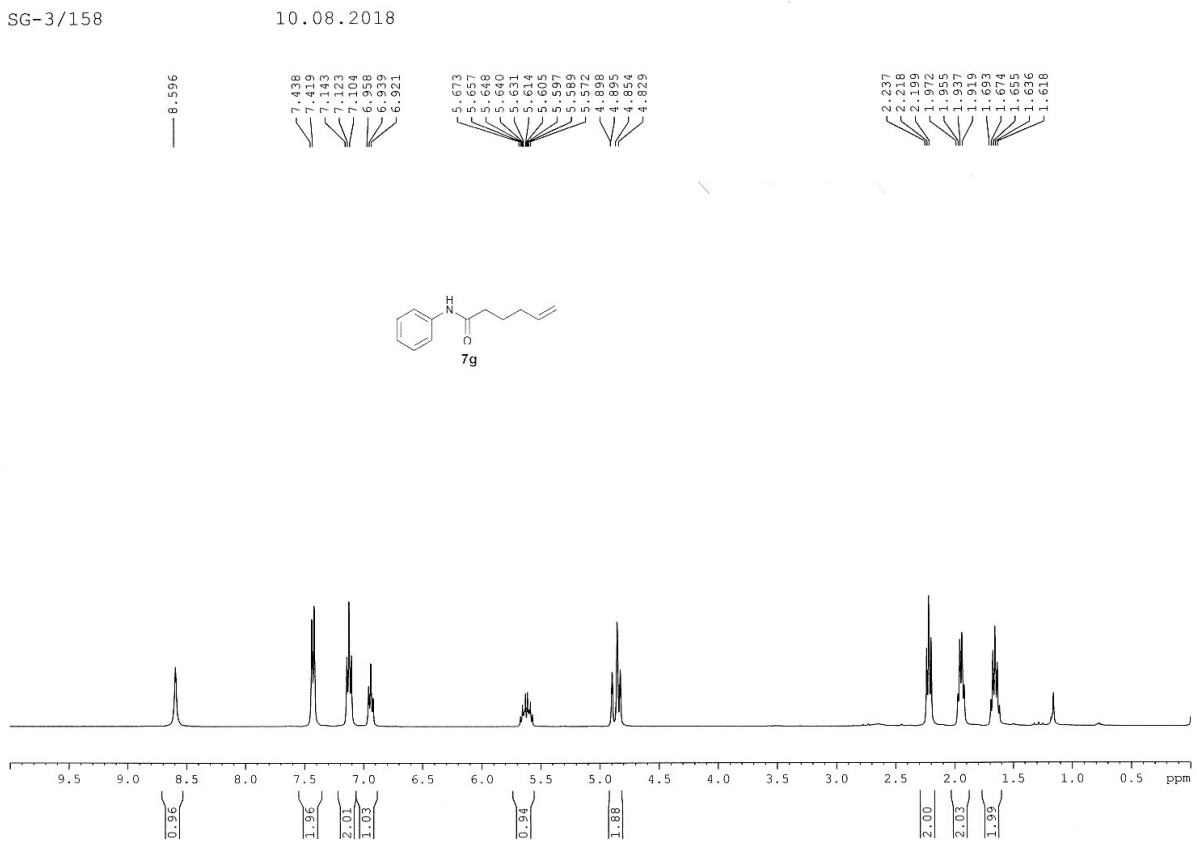
^{13}C NMR Spectrum of **7e** in $CDCl_3$



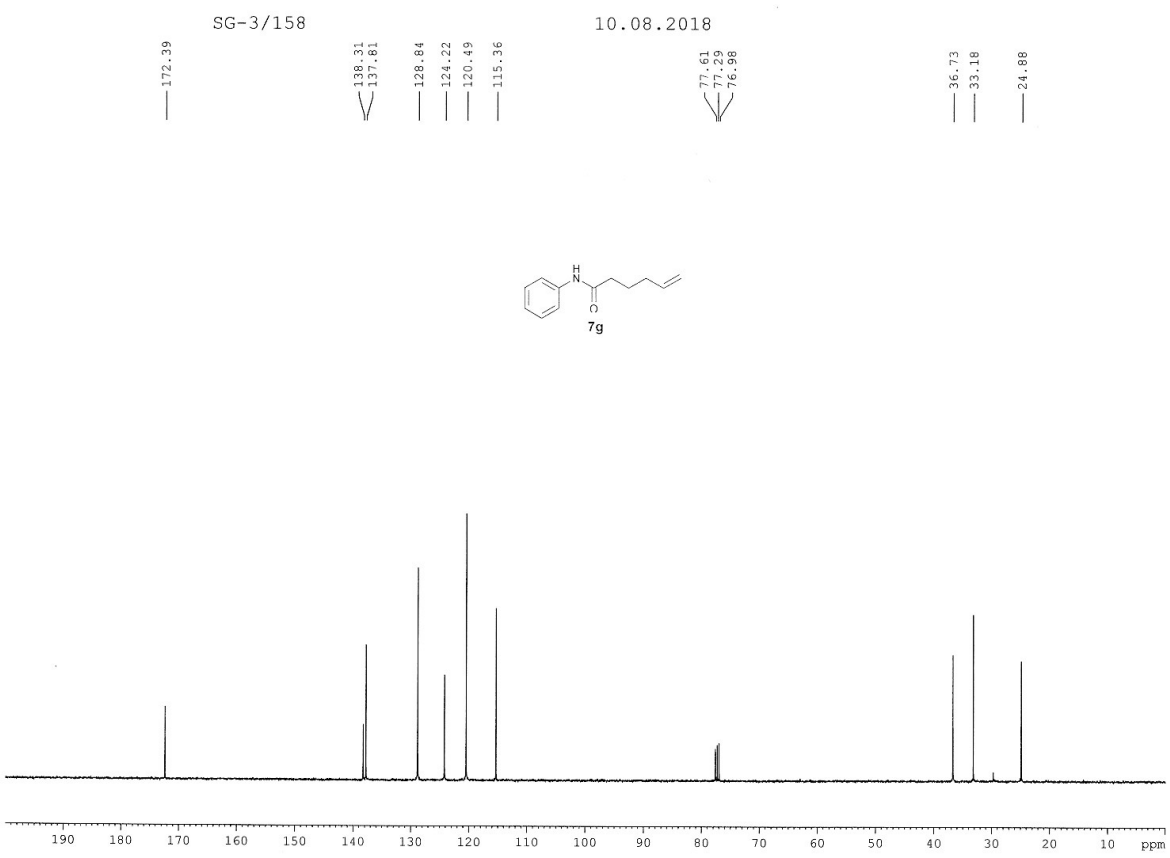
^{1}H NMR Spectrum of **7f** in $CDCl_3$



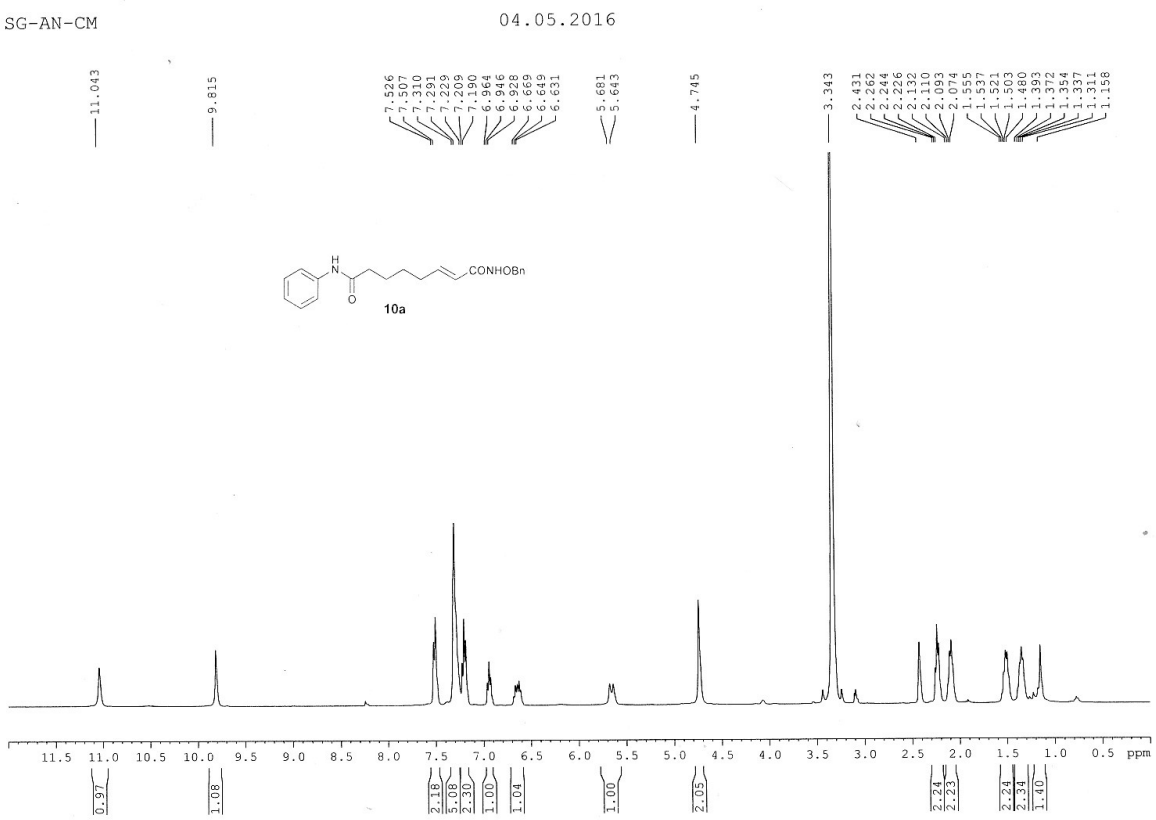
^{13}C NMR Spectrum of **7f** in $CDCl_3$



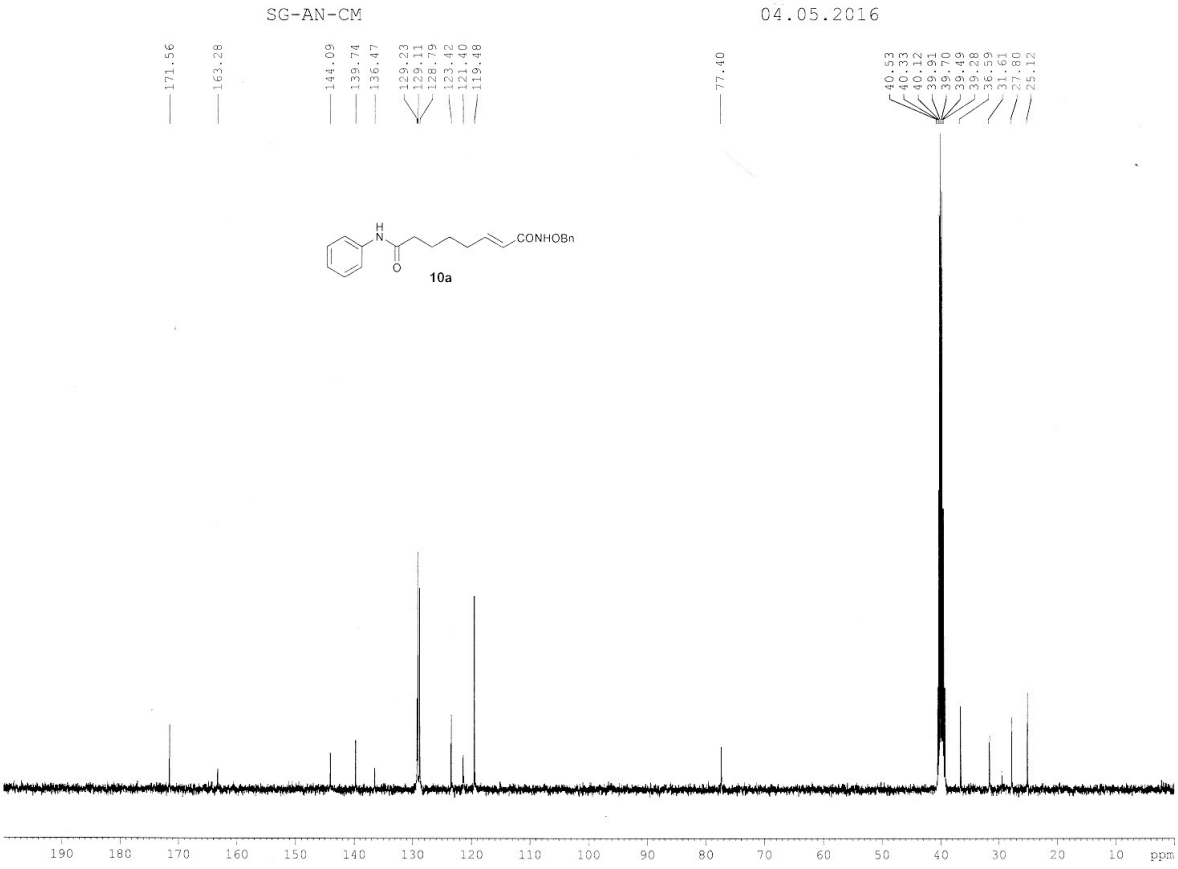
^{1}H NMR Spectrum of **7g** in $CDCl_3$



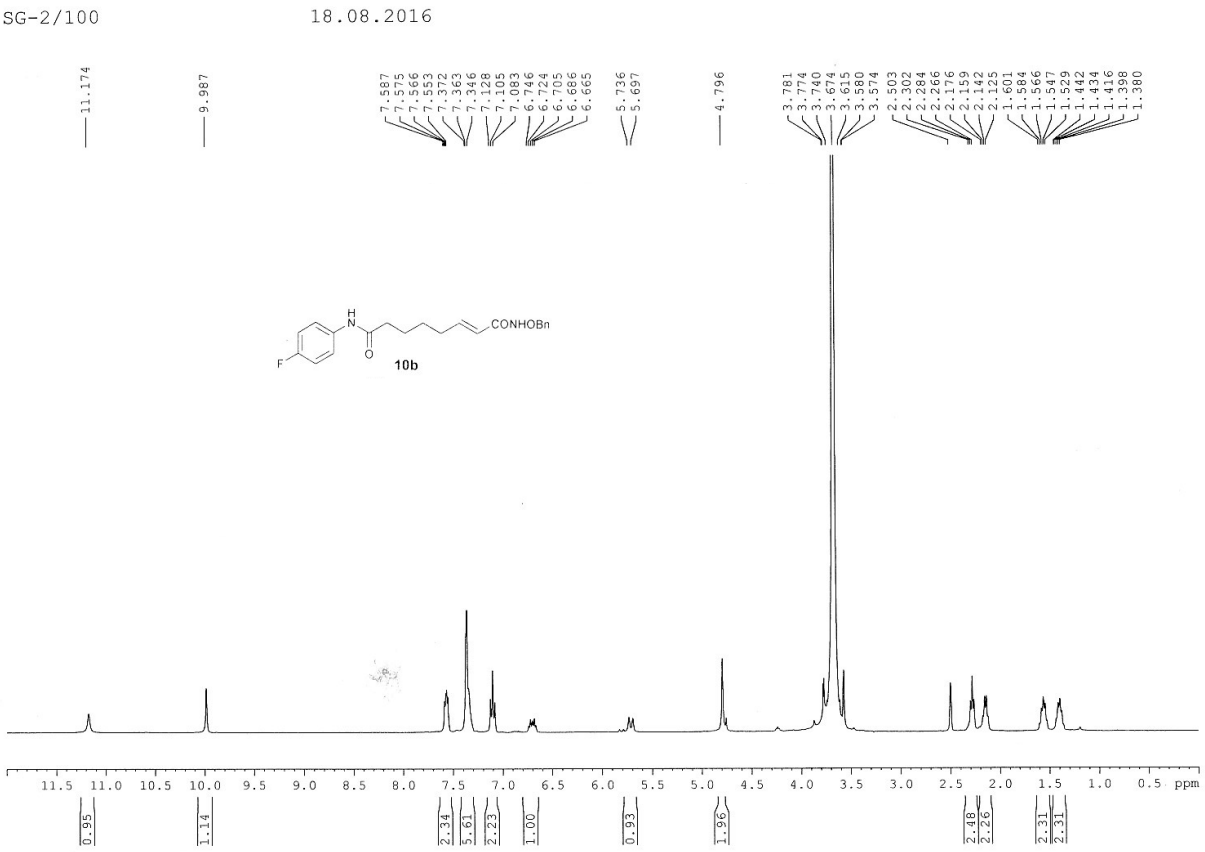
^{13}C NMR Spectrum of **7g** in $CDCl_3$



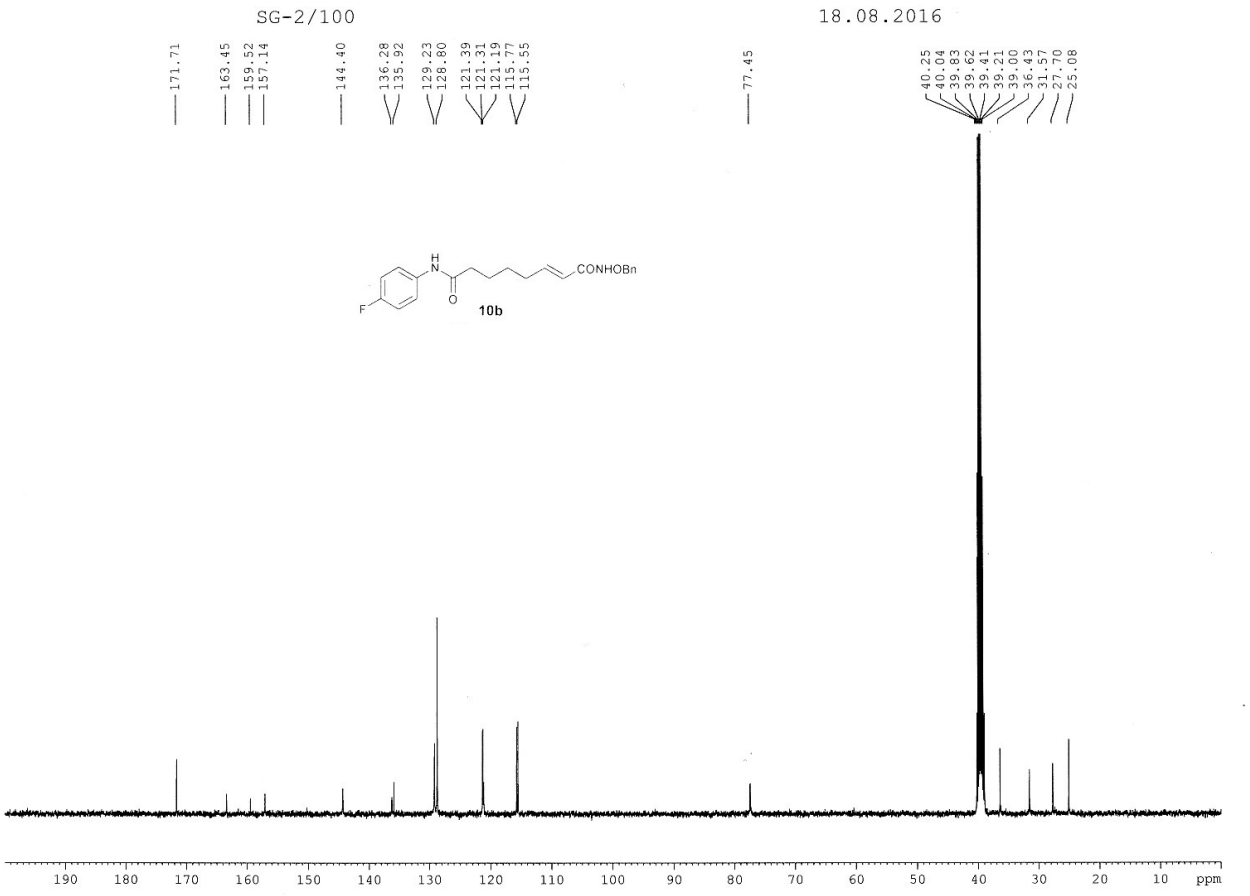
^{1}H NMR Spectrum of **10a** in DMSO-d_6



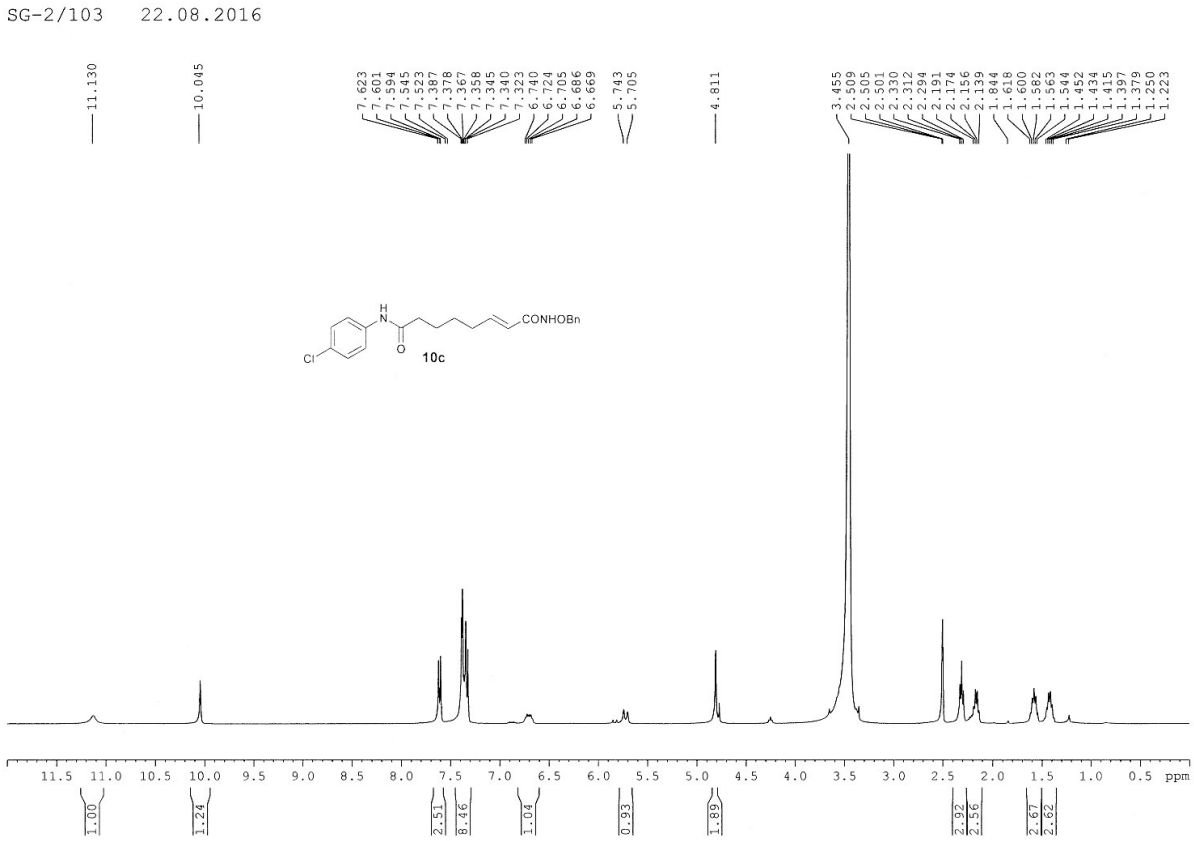
^{13}C NMR Spectrum of **10a** in DMSO-d_6



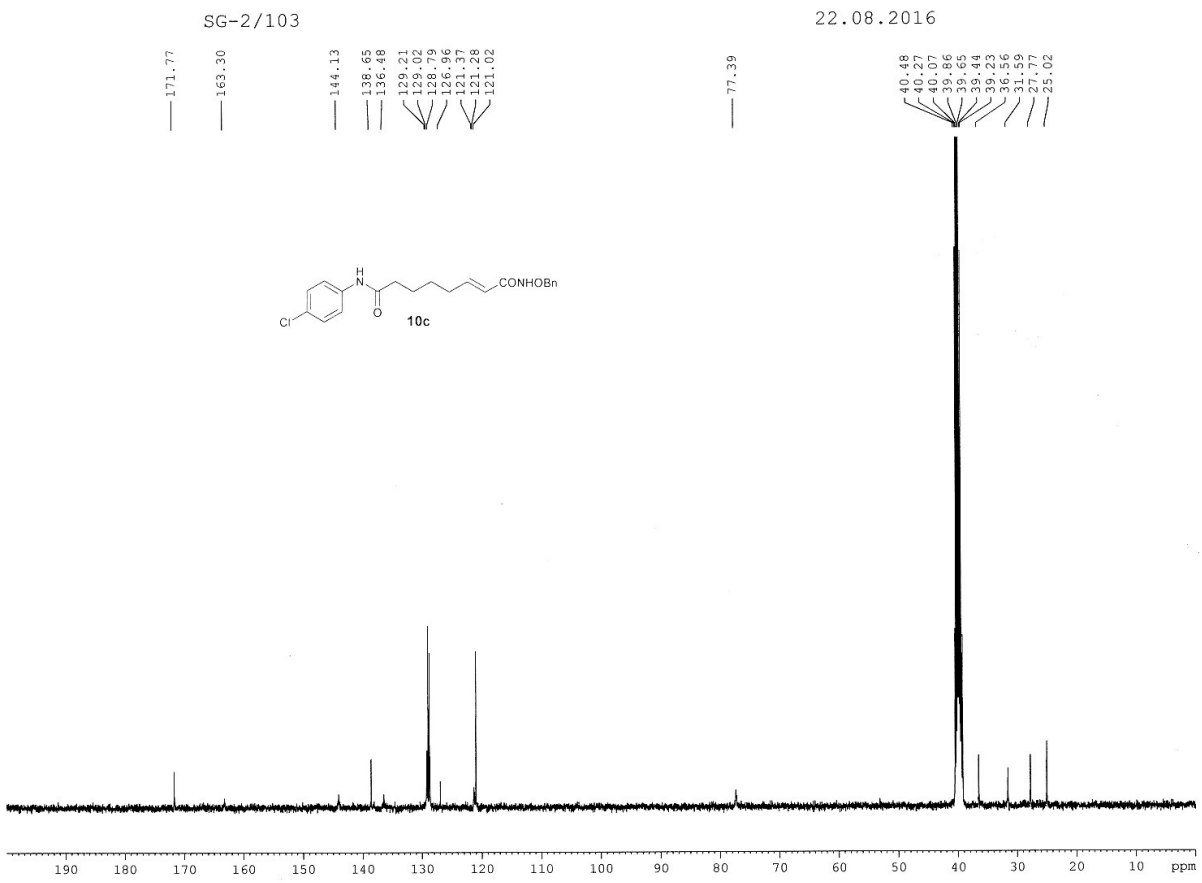
^{1}H NMR Spectrum of **10b** in DMSO-d_6



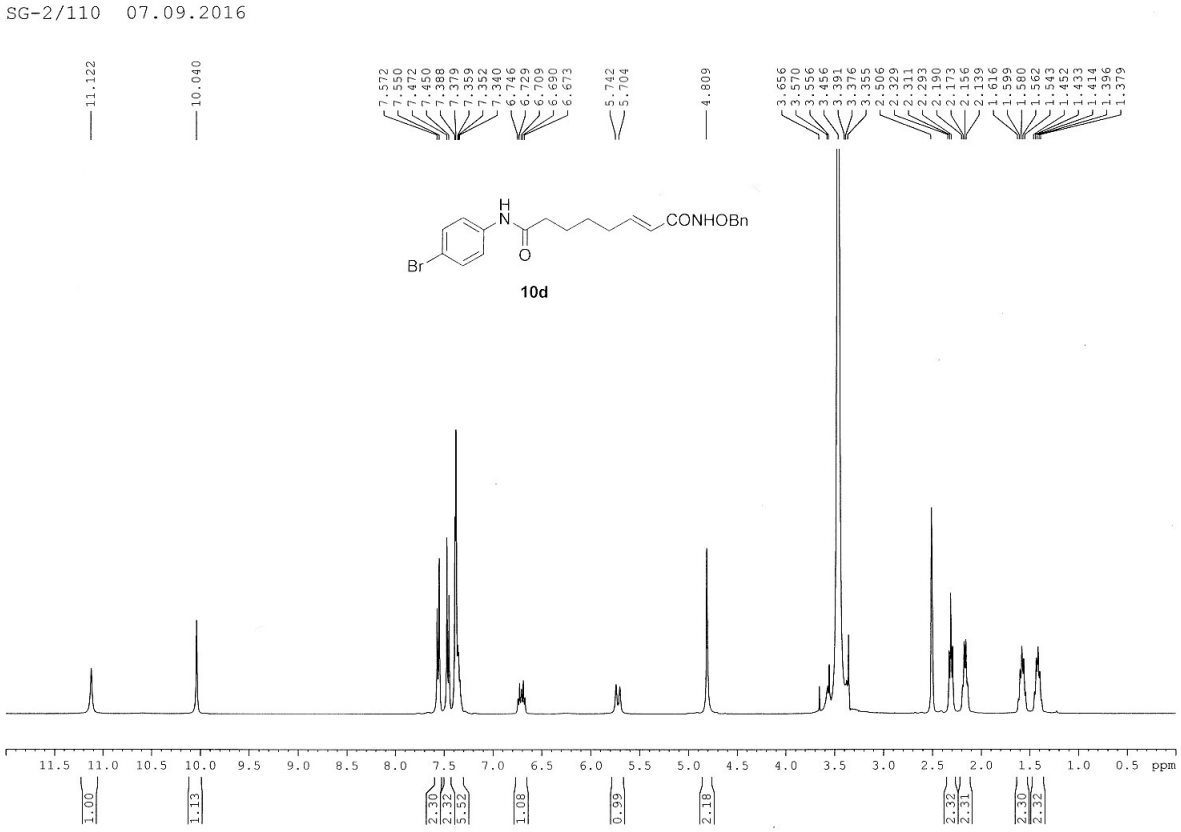
^{13}C NMR Spectrum of **10b** in DMSO-d_6



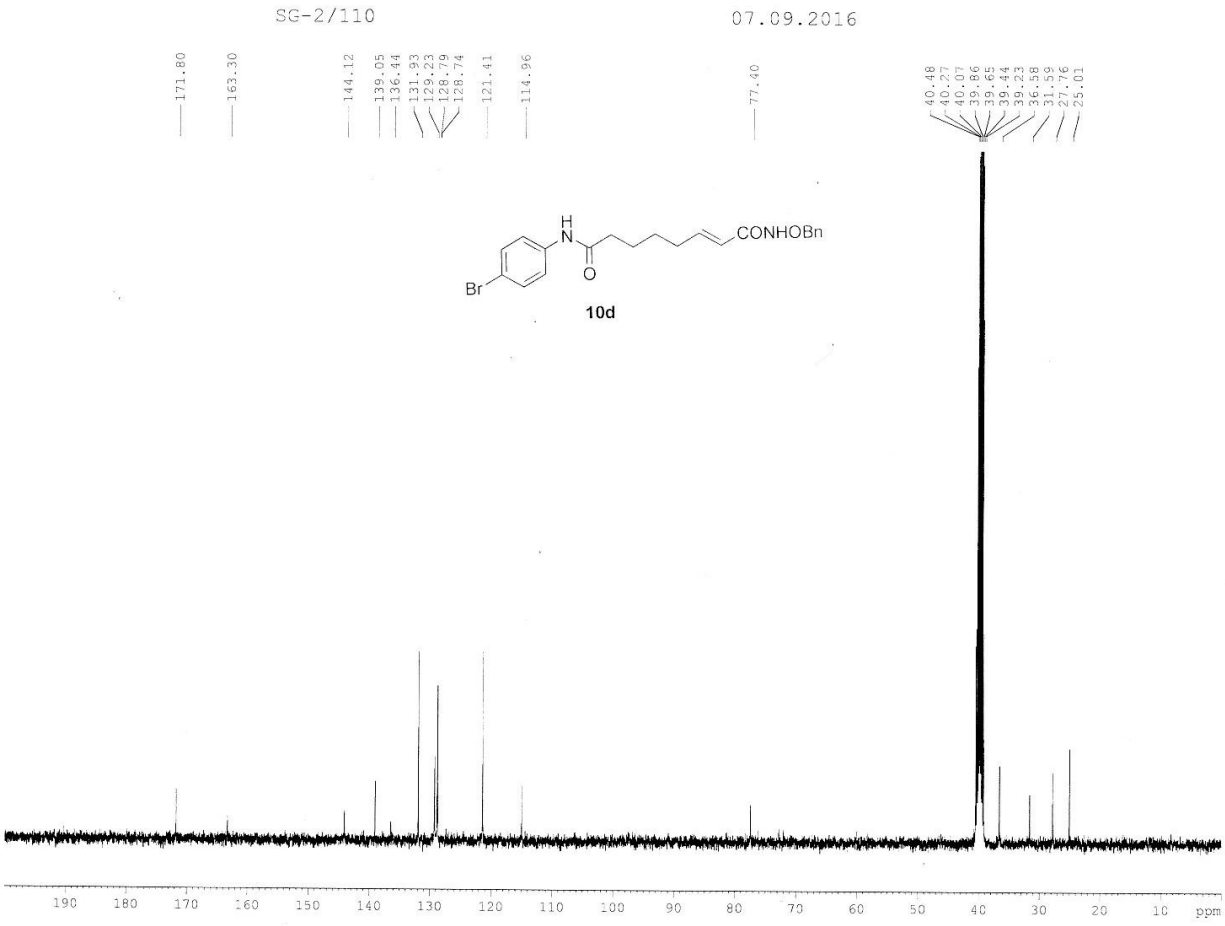
^{1}H NMR Spectrum of **10c** in DMSO-d_6



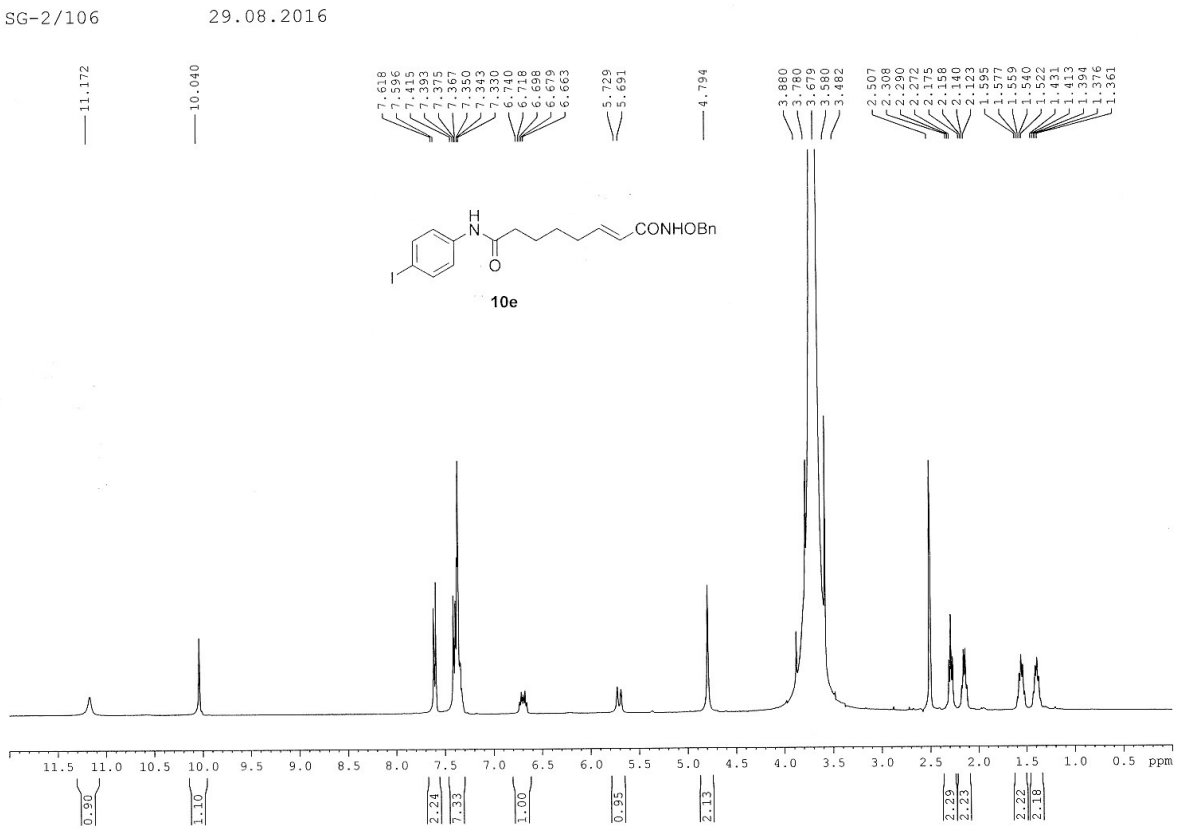
^{13}C NMR Spectrum of **10c** in DMSO-d_6



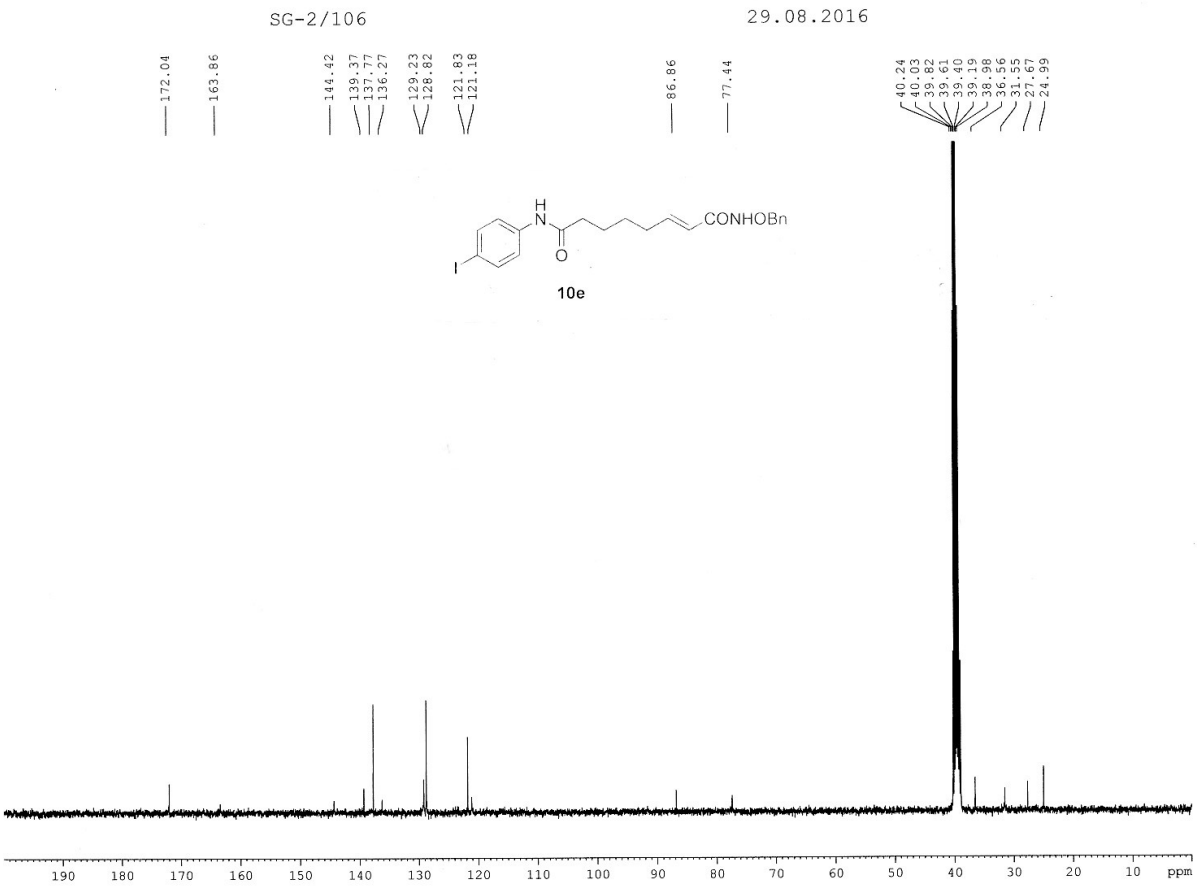
^{1}H NMR Spectrum of **10d** in DMSO-d_6



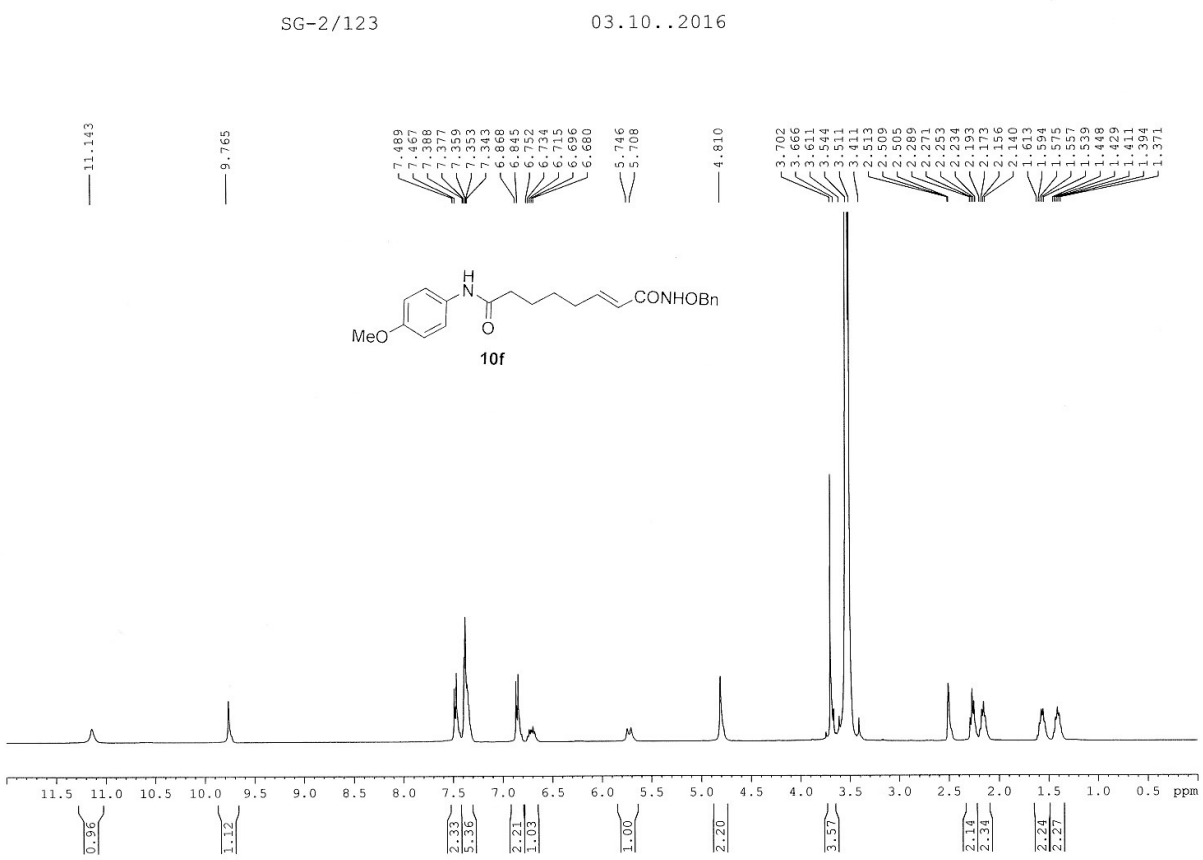
^{13}C NMR Spectrum of **10d** in DMSO-d_6



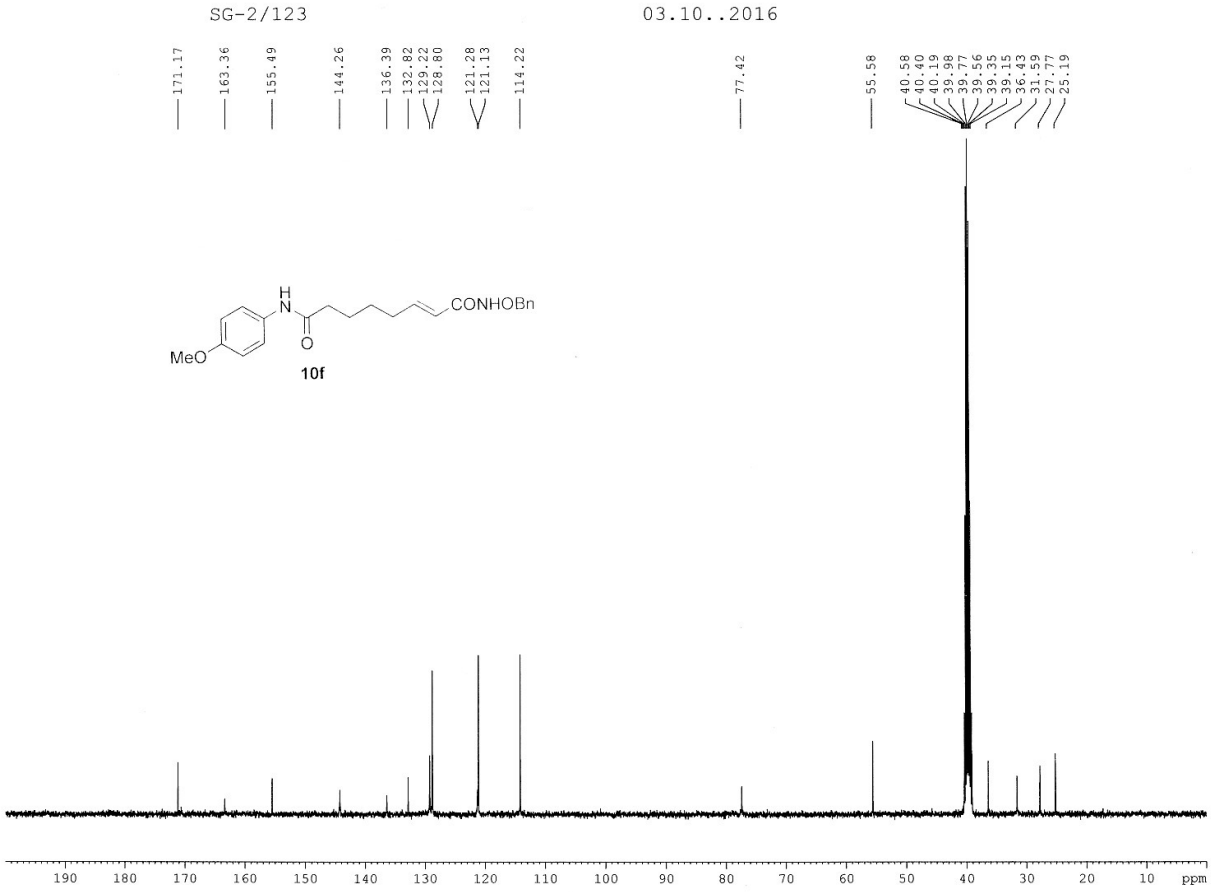
^{1}H NMR Spectrum of **10e** in DMSO-d_6



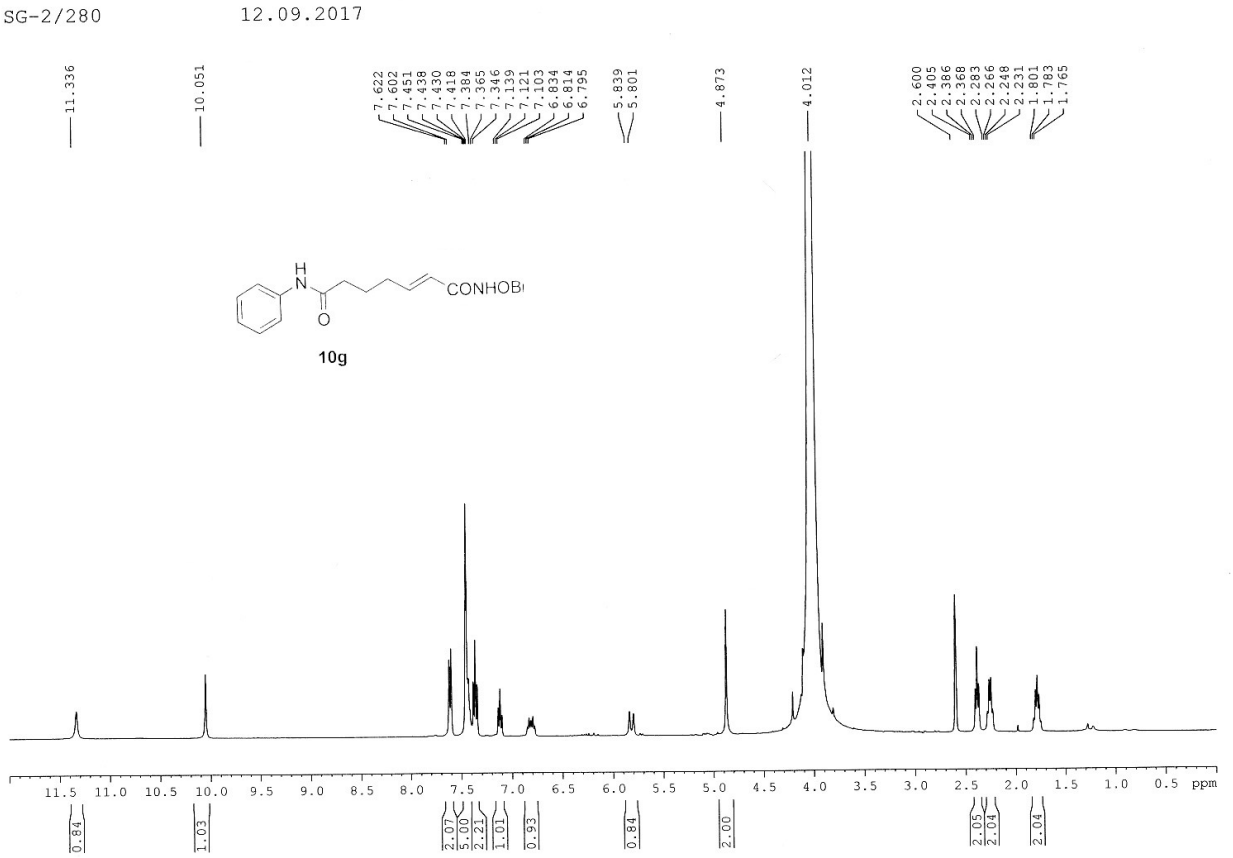
^{13}C NMR Spectrum of **10e** in DMSO-d_6



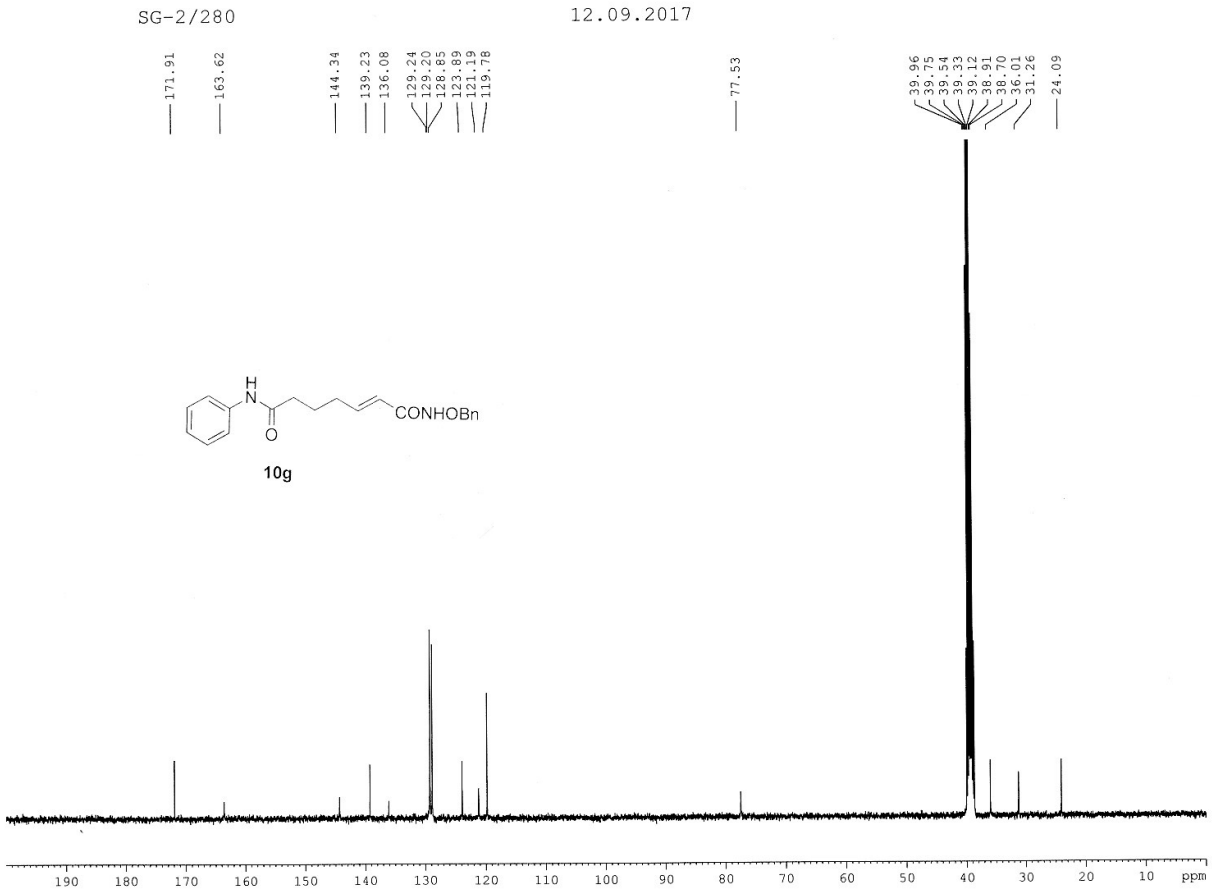
^{1}H NMR Spectrum of **10f** in DMSO-d_6



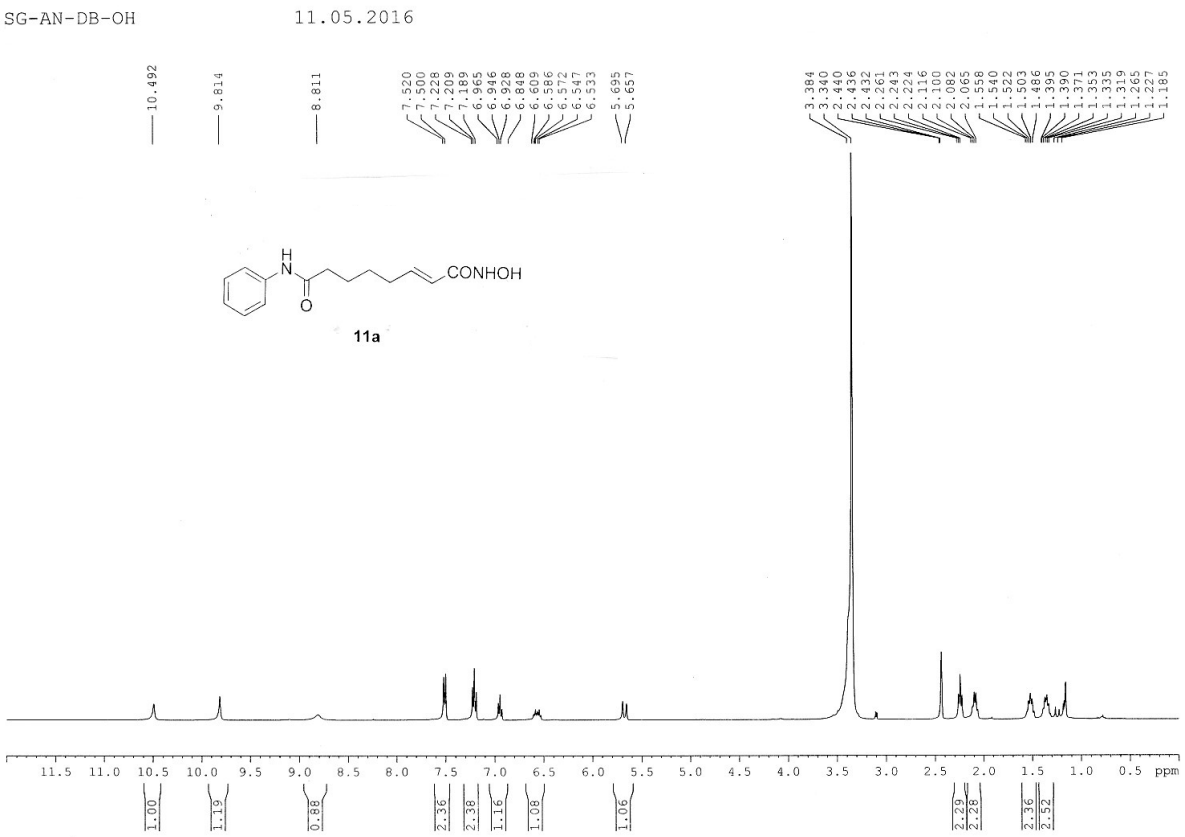
^{13}C NMR Spectrum of **10f** in DMSO-d_6



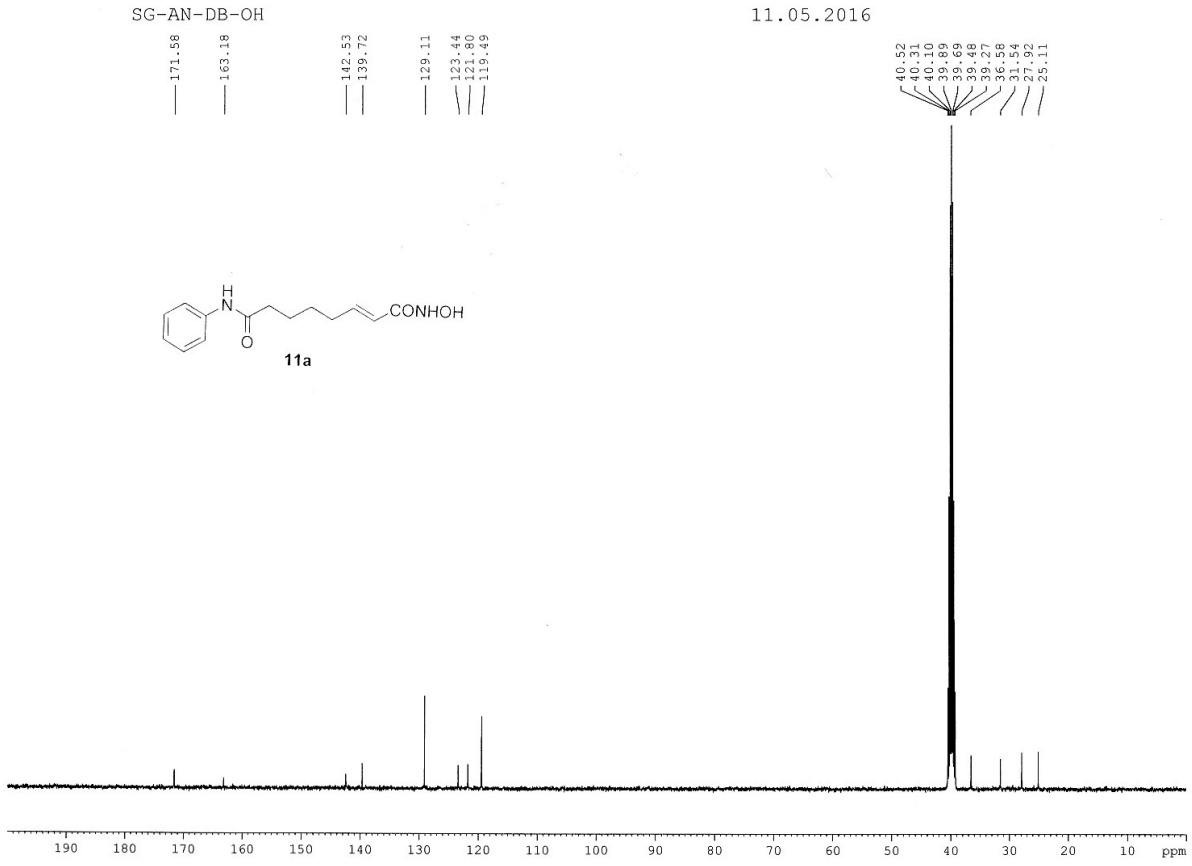
^{1}H NMR Spectrum of **10g** in DMSO-d_6



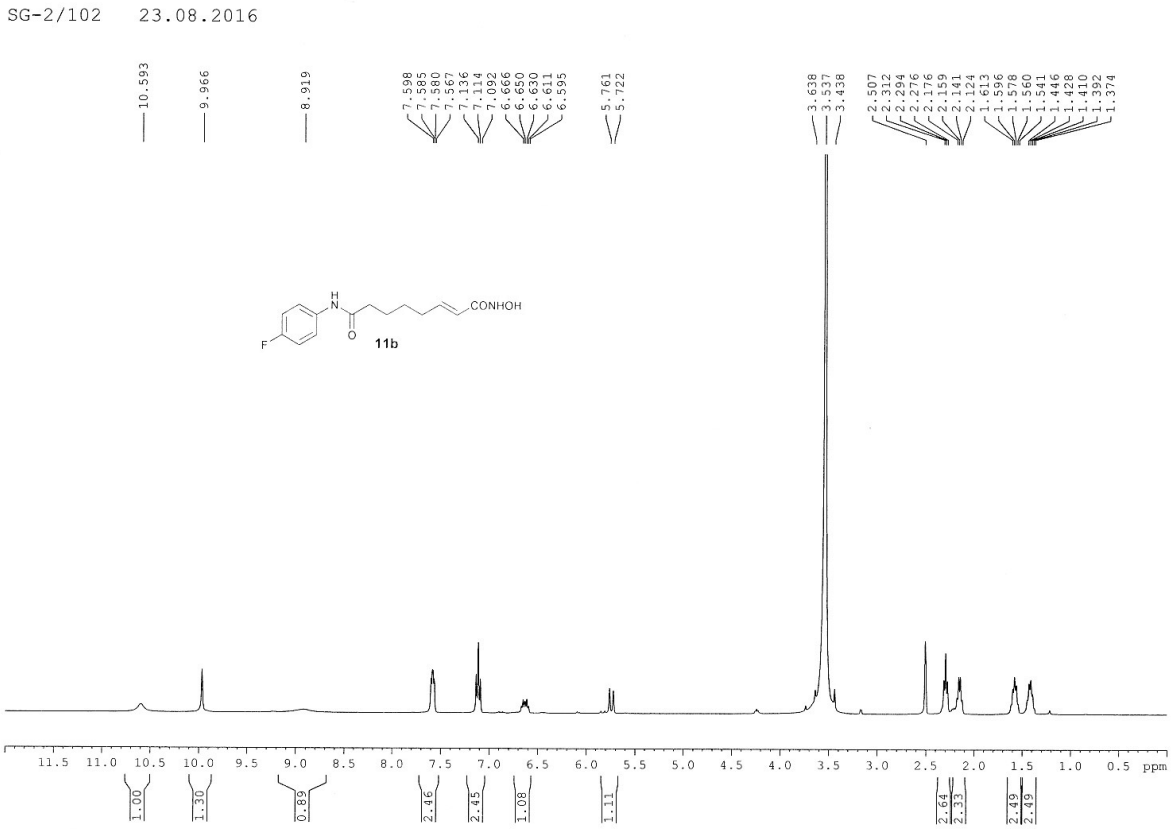
^{13}C NMR Spectrum of **10g** in DMSO-d_6



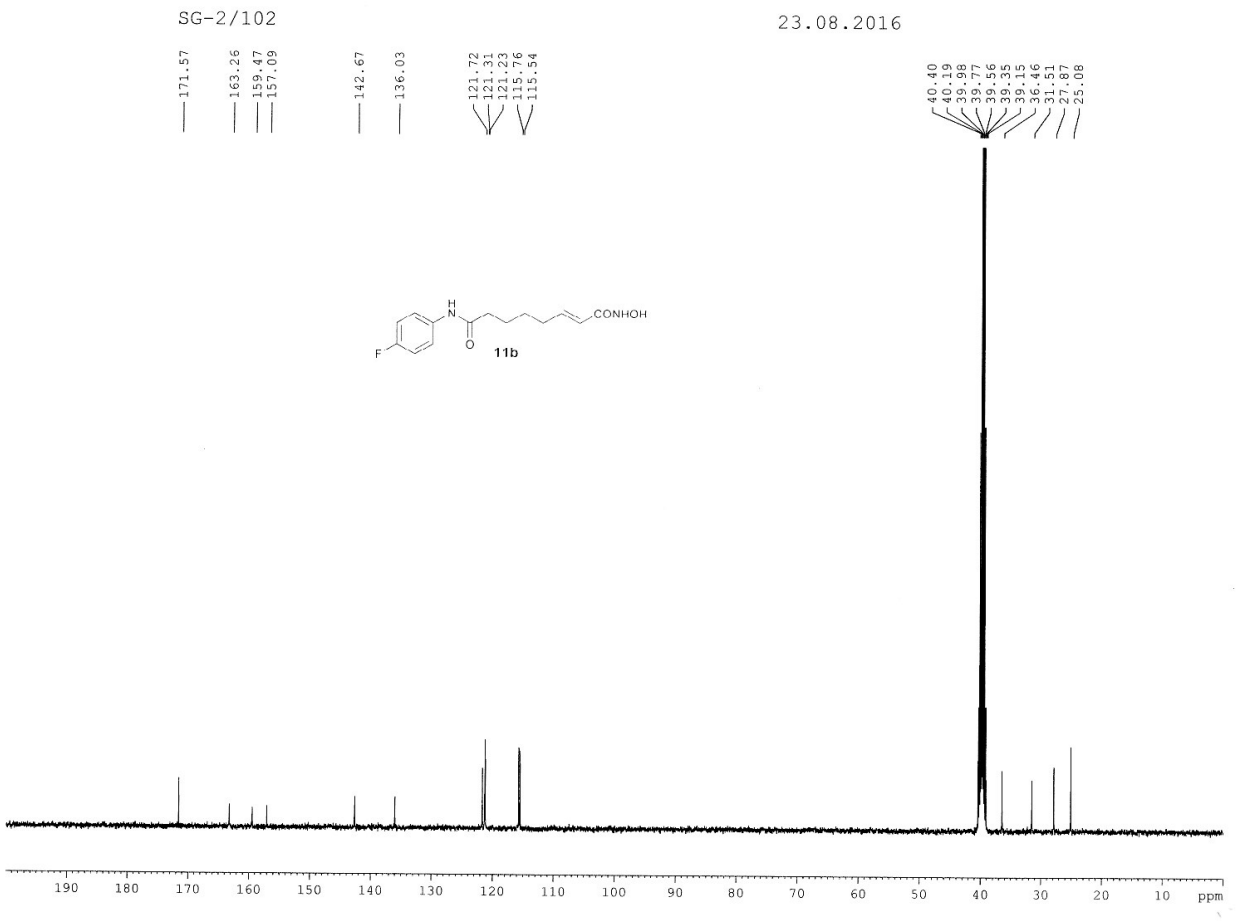
^{1}H NMR Spectrum of **11a** in DMSO-d_6



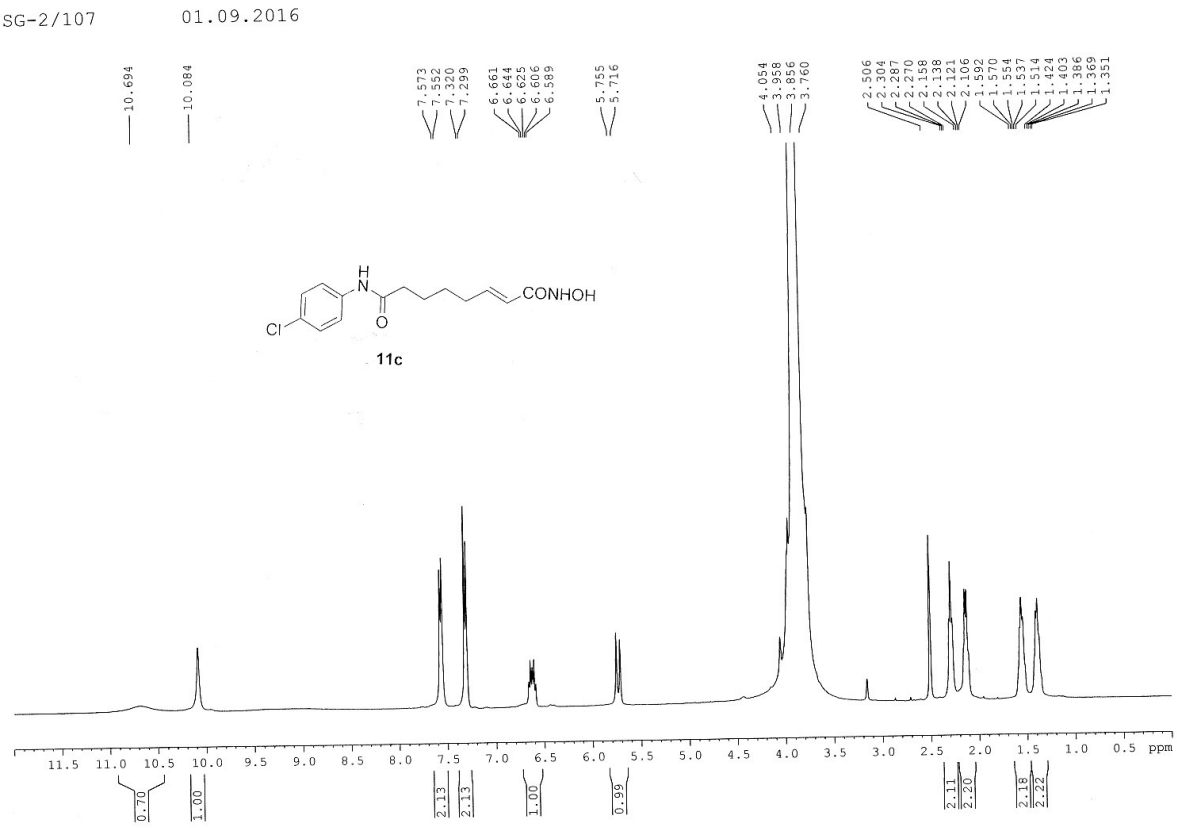
^{13}C NMR Spectrum of **11a** in DMSO-d_6



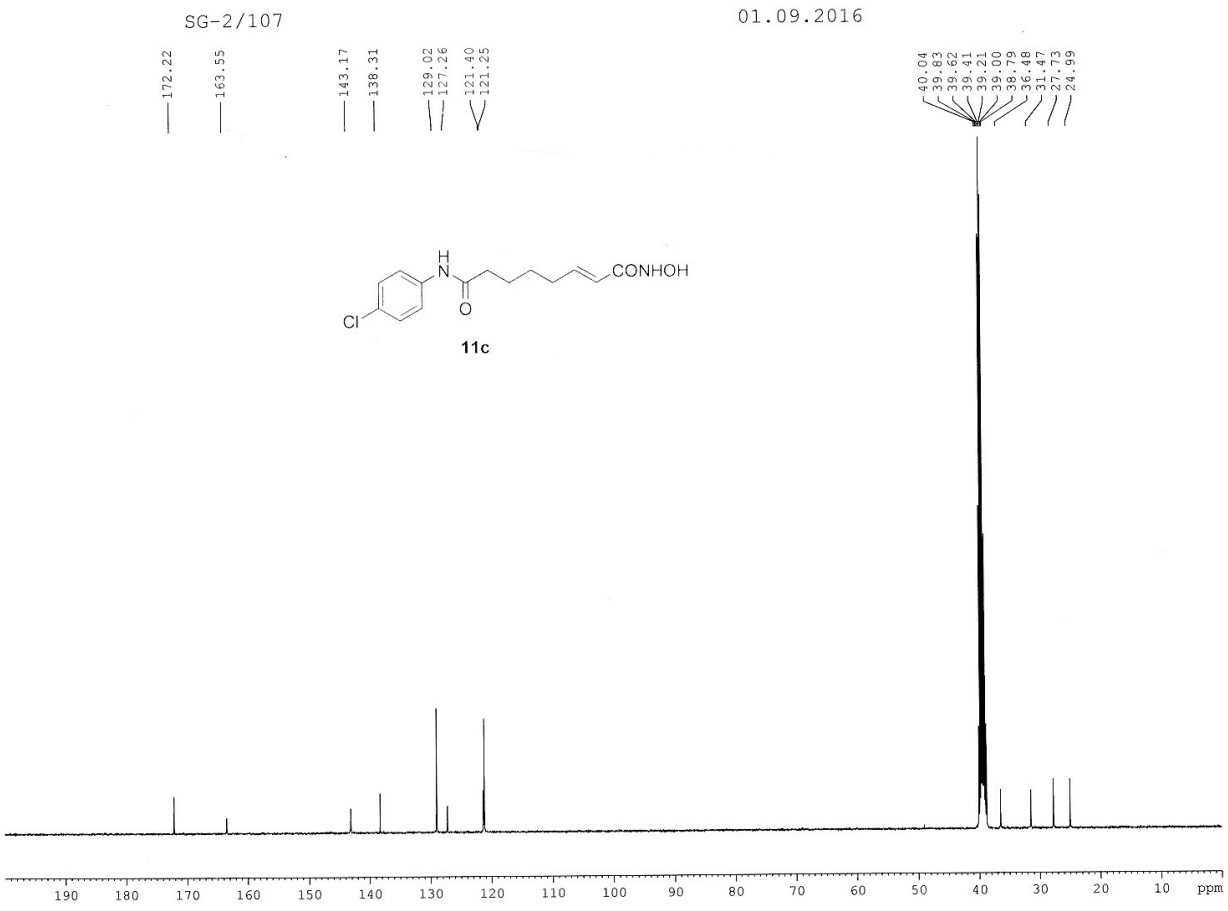
^{1}H NMR Spectrum of **11b** in DMSO-d_6



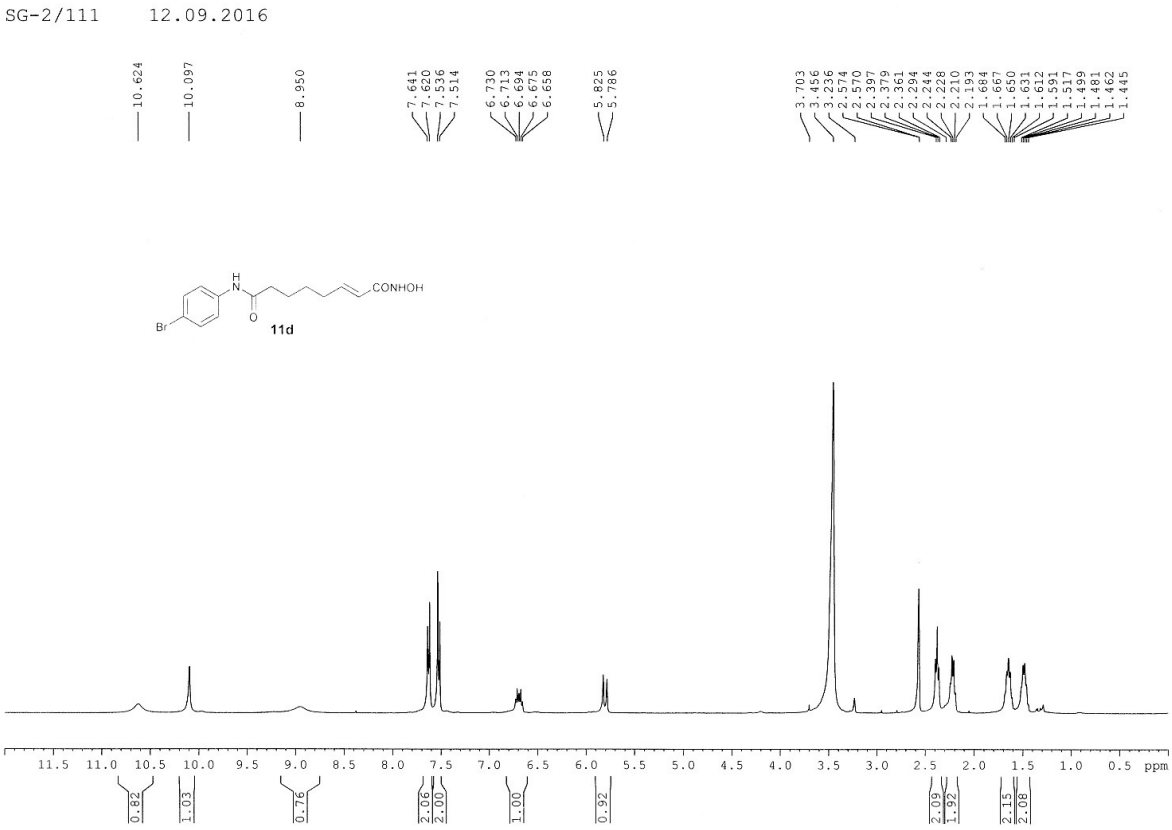
^{13}C NMR Spectrum of **11b** in DMSO-d_6



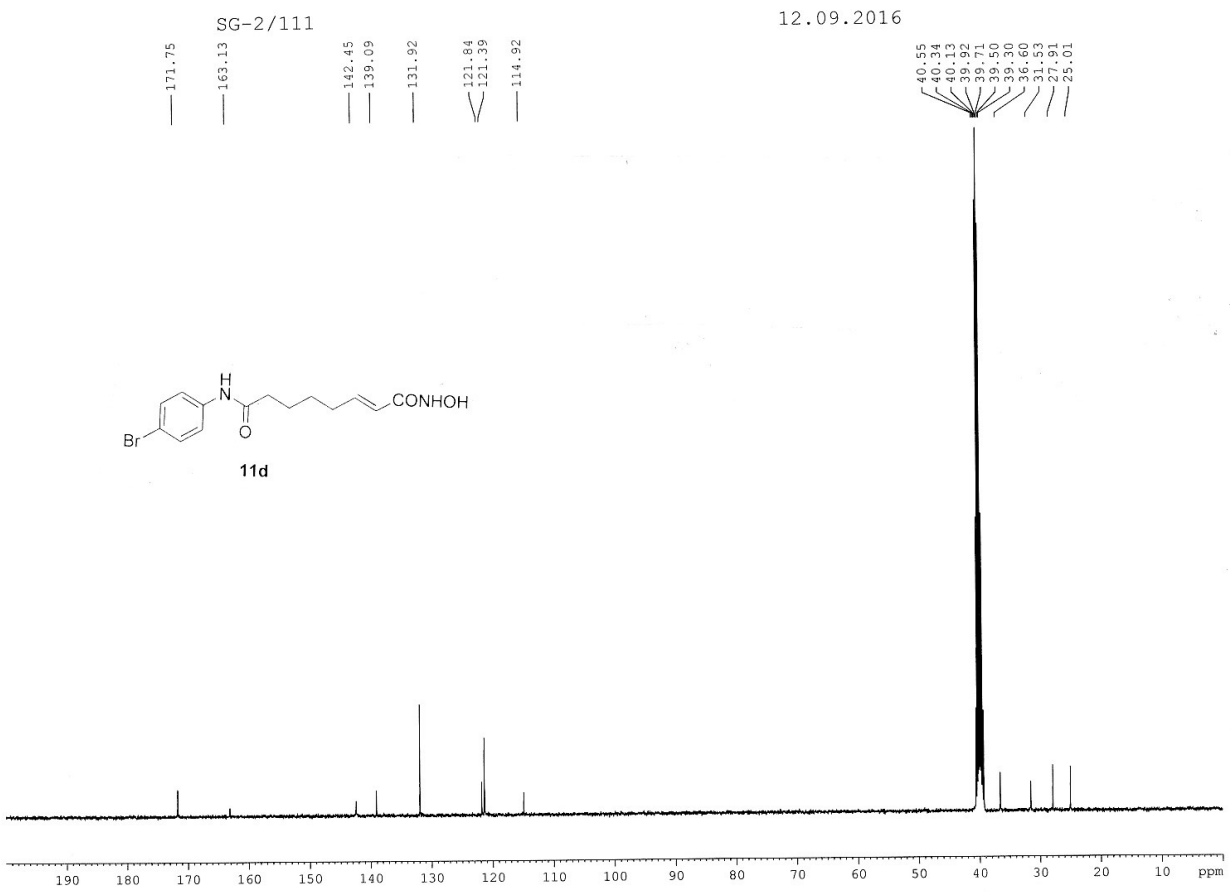
^{1}H NMR Spectrum of **11c** in DMSO-d_6



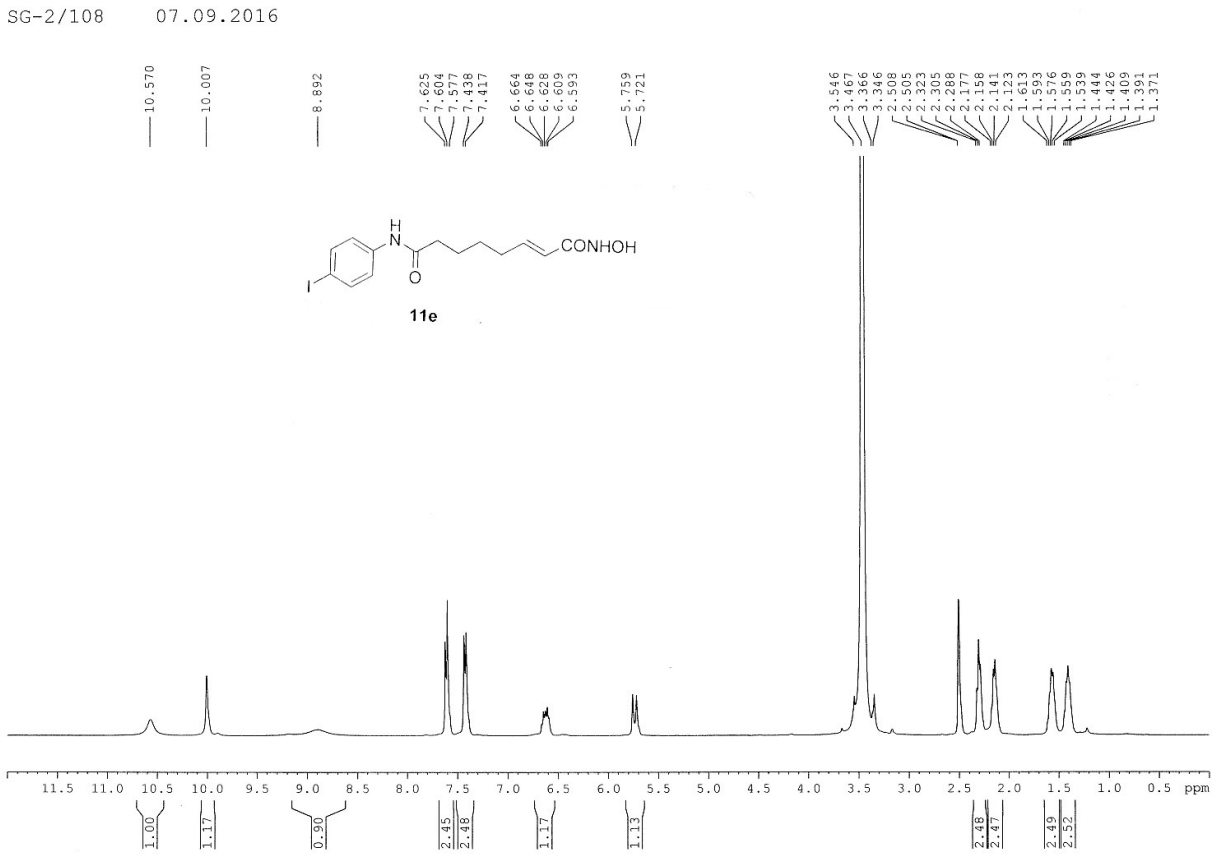
^{13}C NMR Spectrum of **11c** in DMSO-d_6



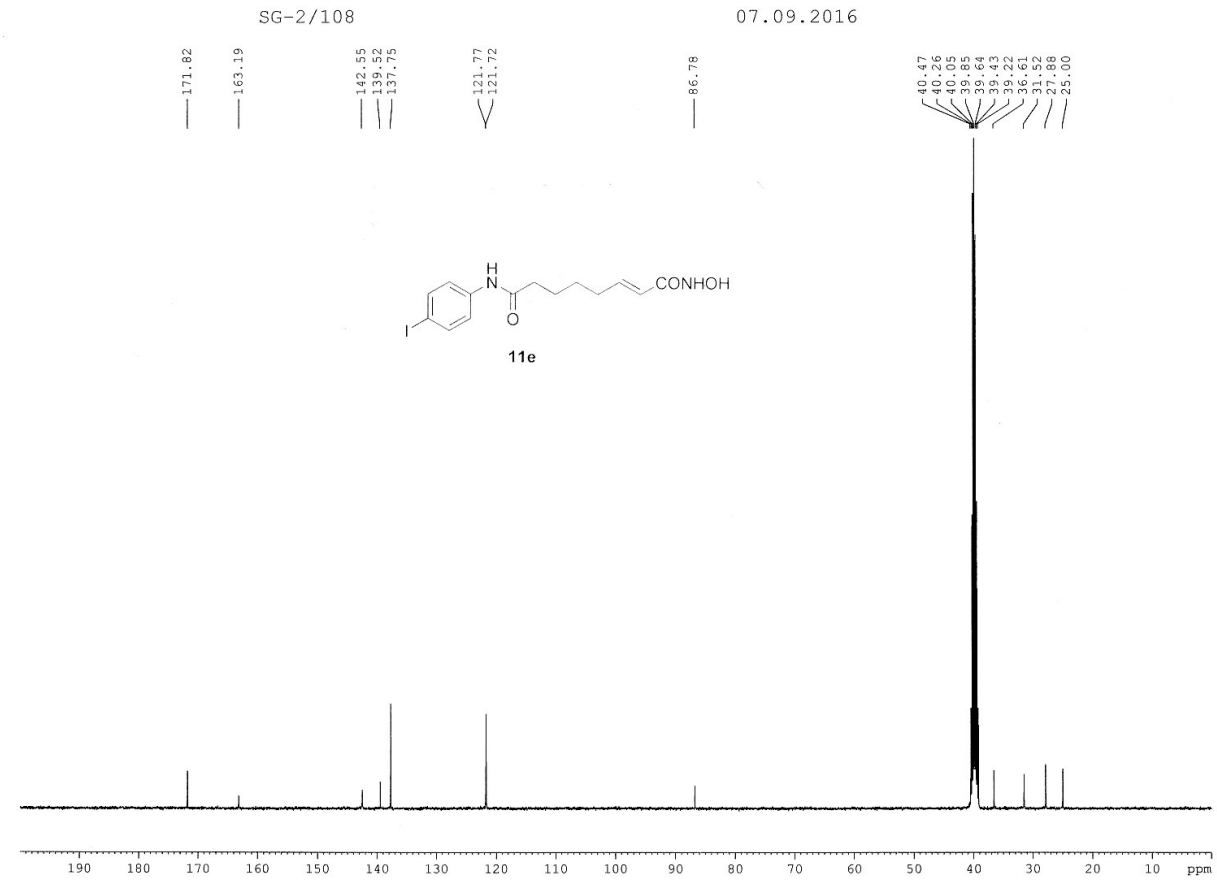
^{1}H NMR Spectrum of **11d** in DMSO-d_6



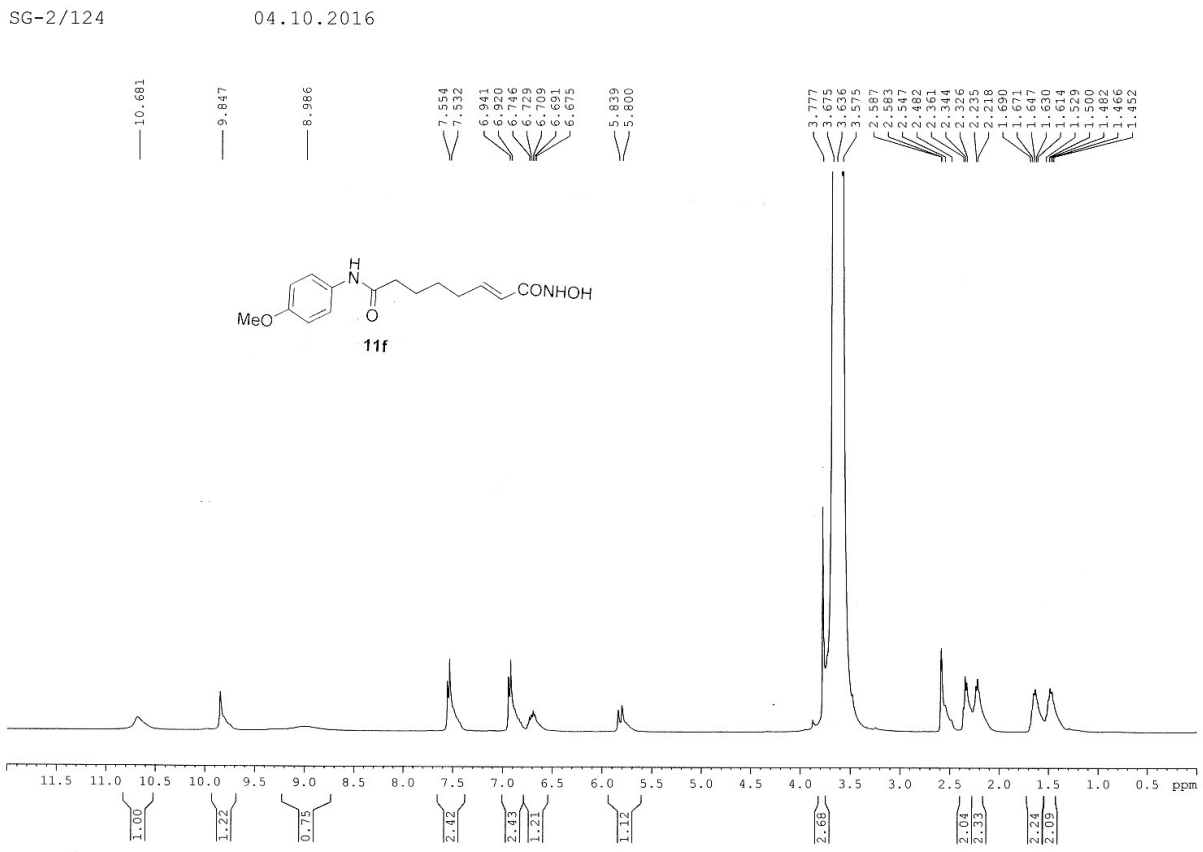
^{13}C NMR Spectrum of **11d** in DMSO-d_6



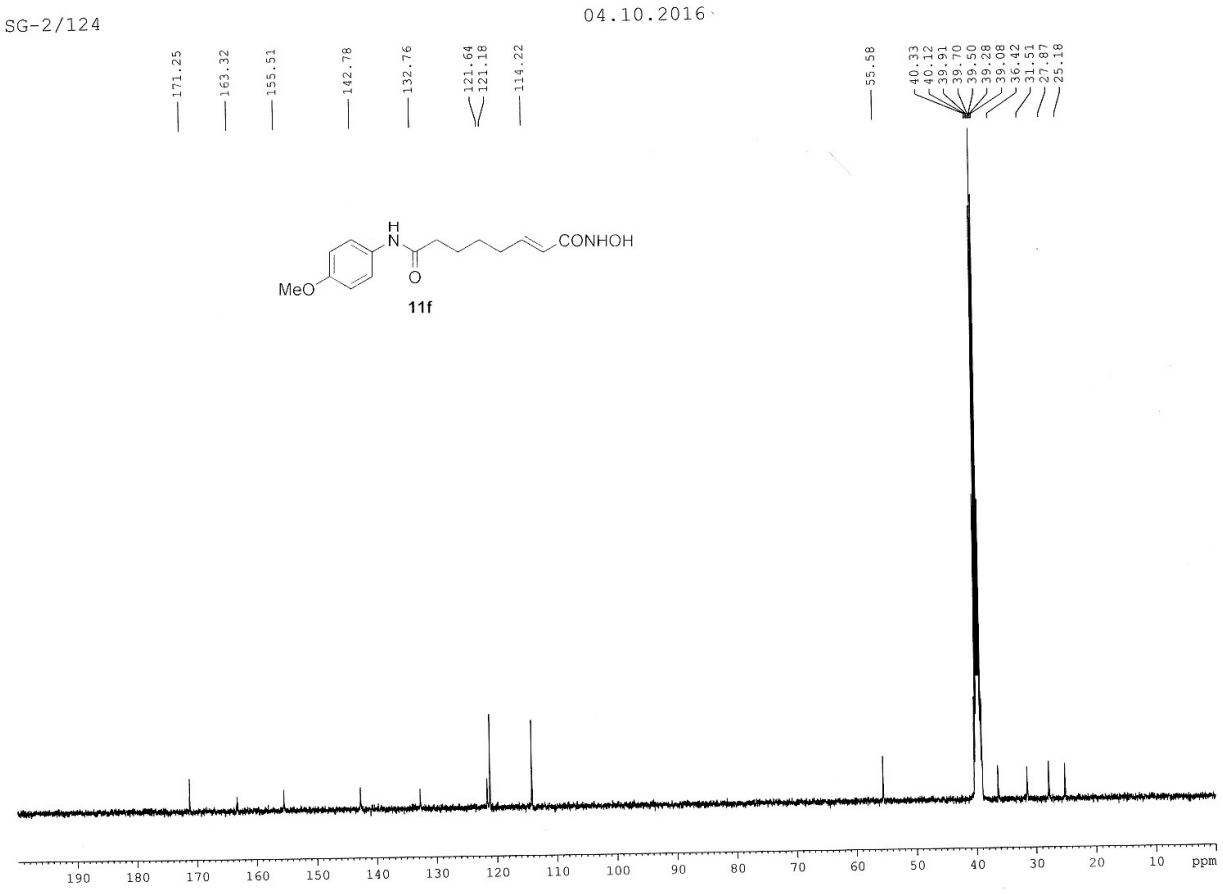
^{1}H NMR Spectrum of **11e** in DMSO-d_6



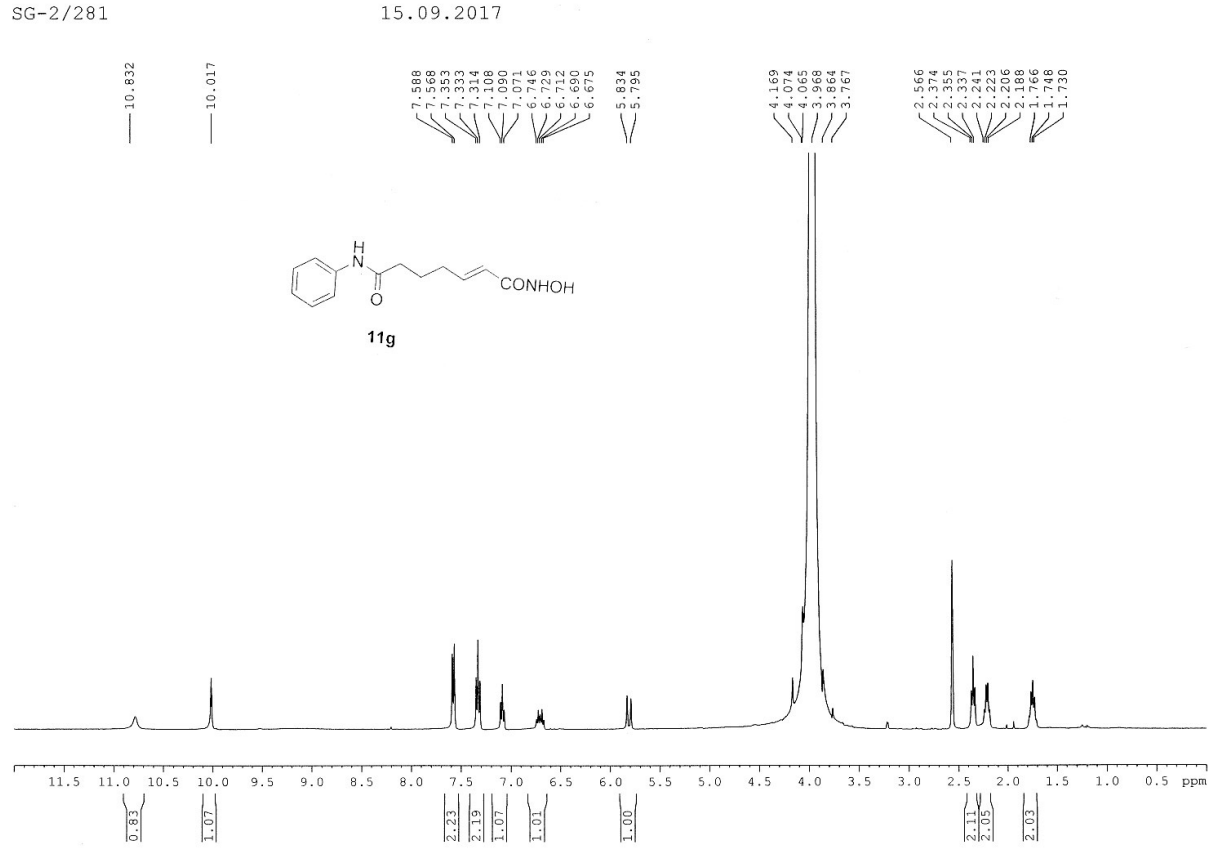
^{13}C NMR Spectrum of **11e** in DMSO-d_6



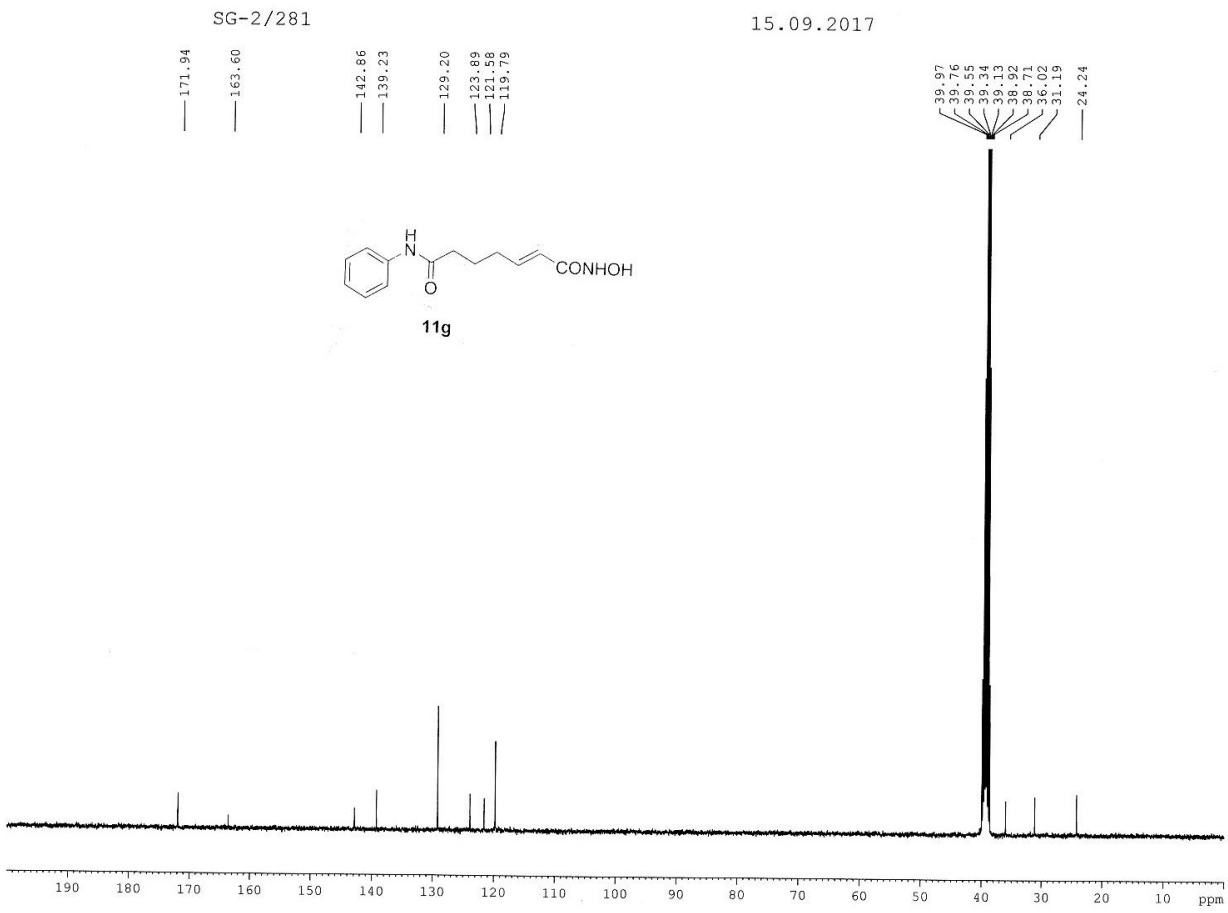
^{1}H NMR Spectrum of **11f** in DMSO-d_6



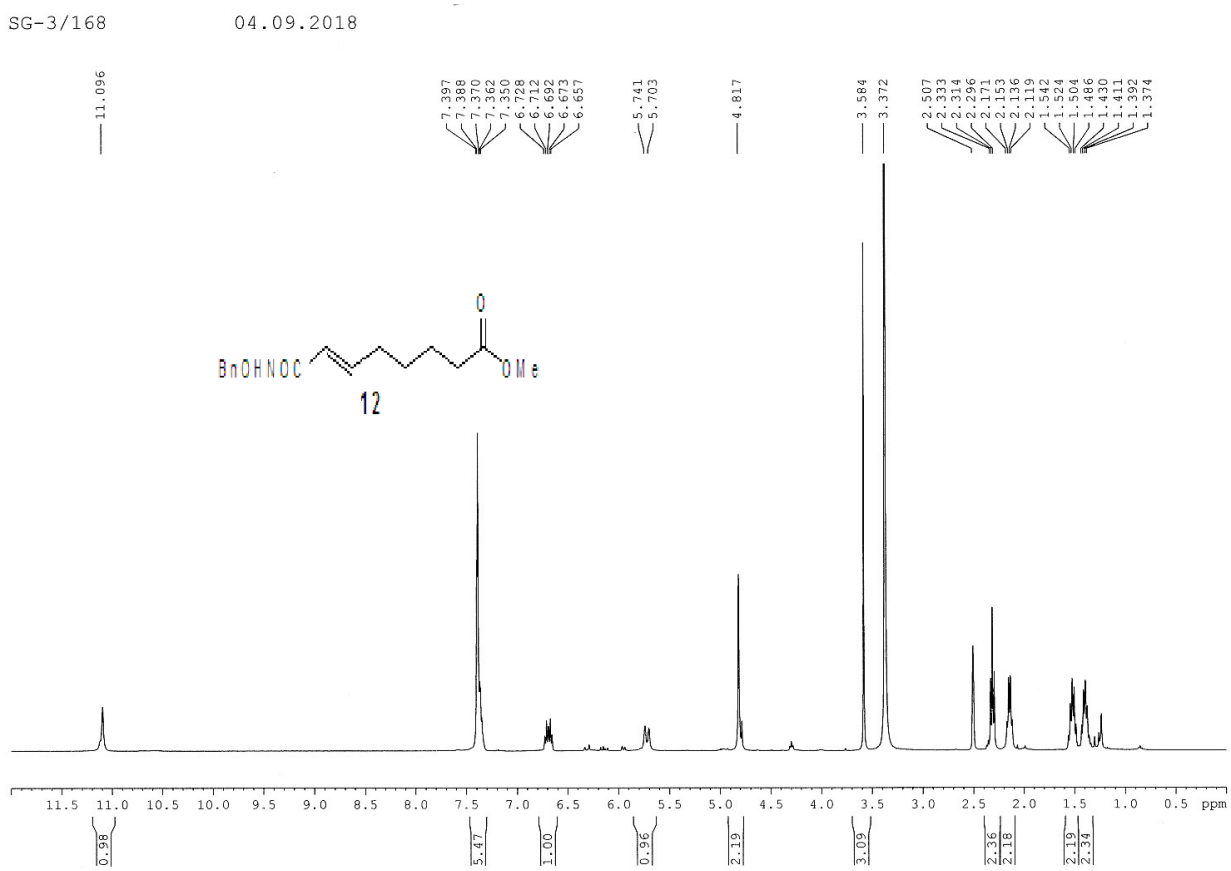
^{13}C NMR Spectrum of **11f** in DMSO-d_6



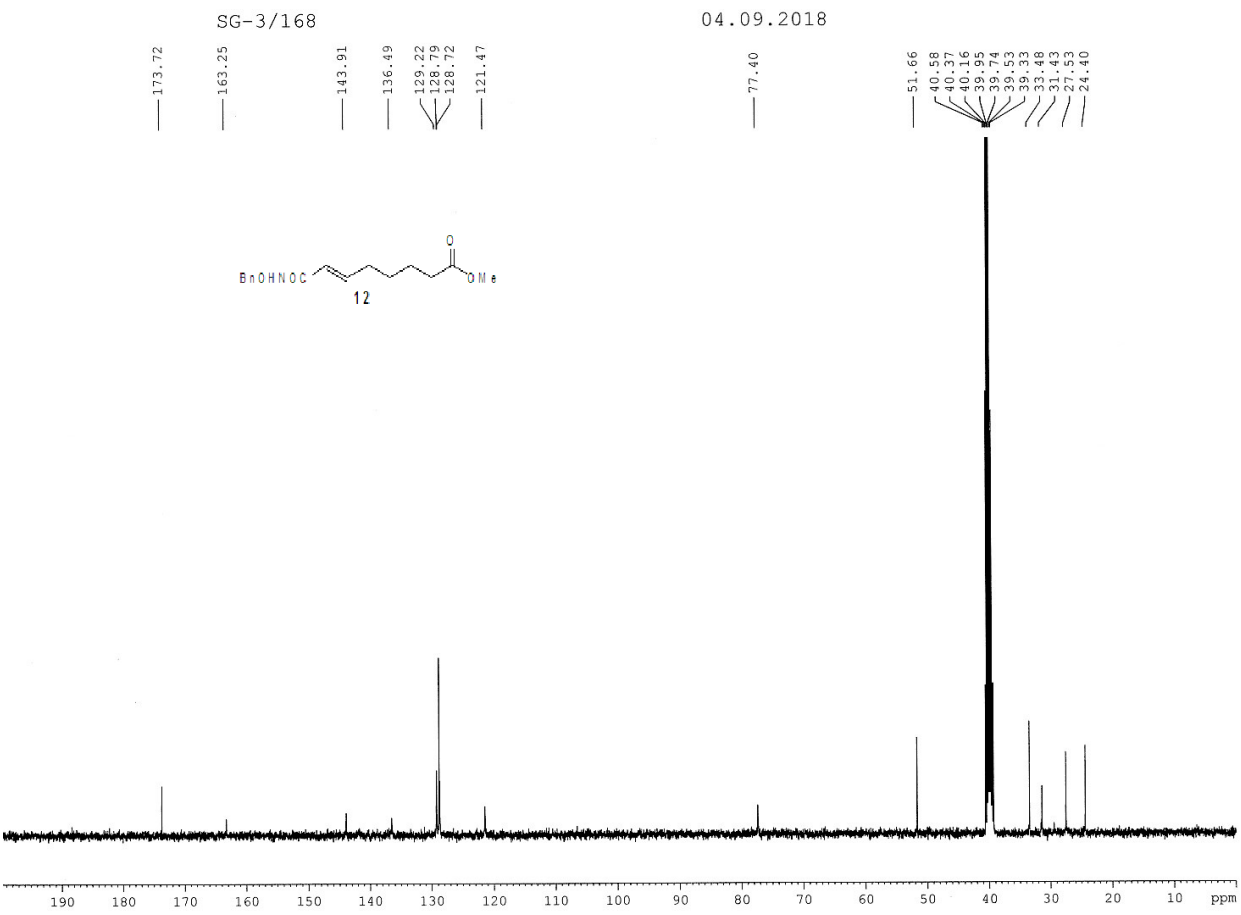
^{1}H NMR Spectrum of **11g** in DMSO-d_6



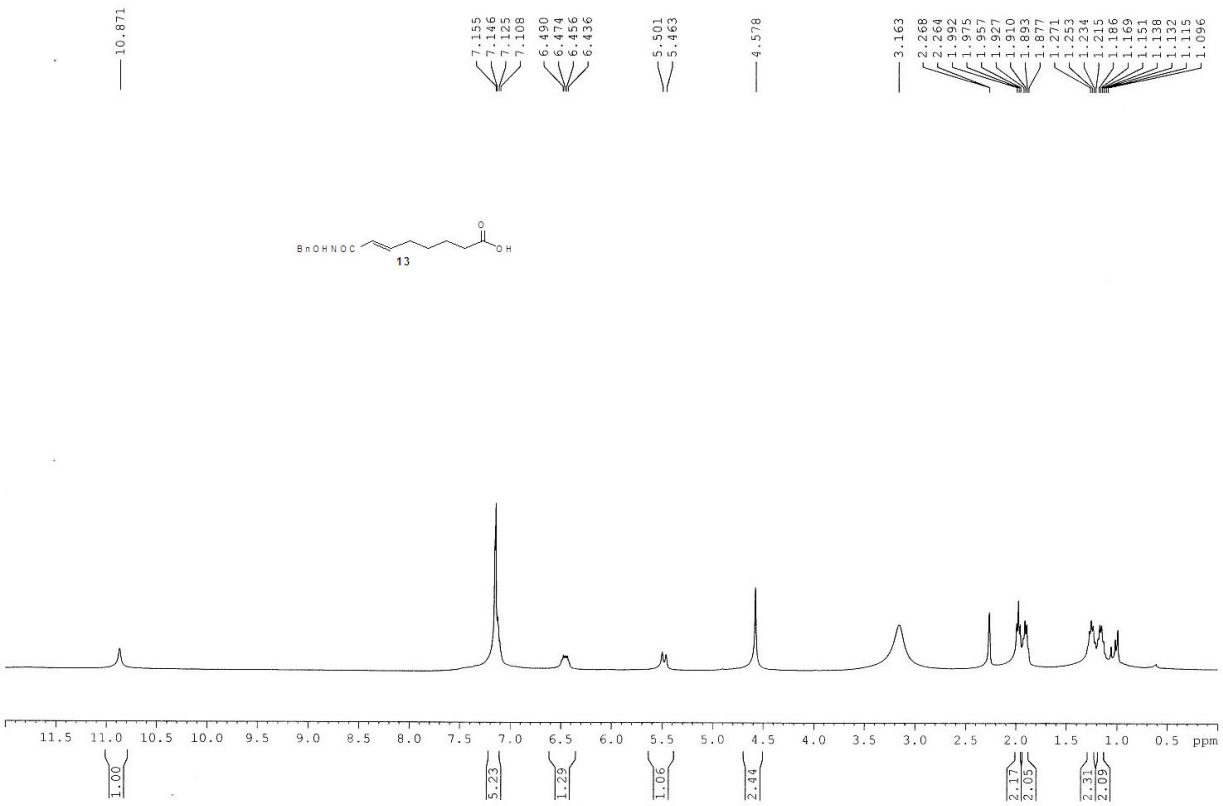
^{13}C NMR Spectrum of **11g** in DMSO-d_6



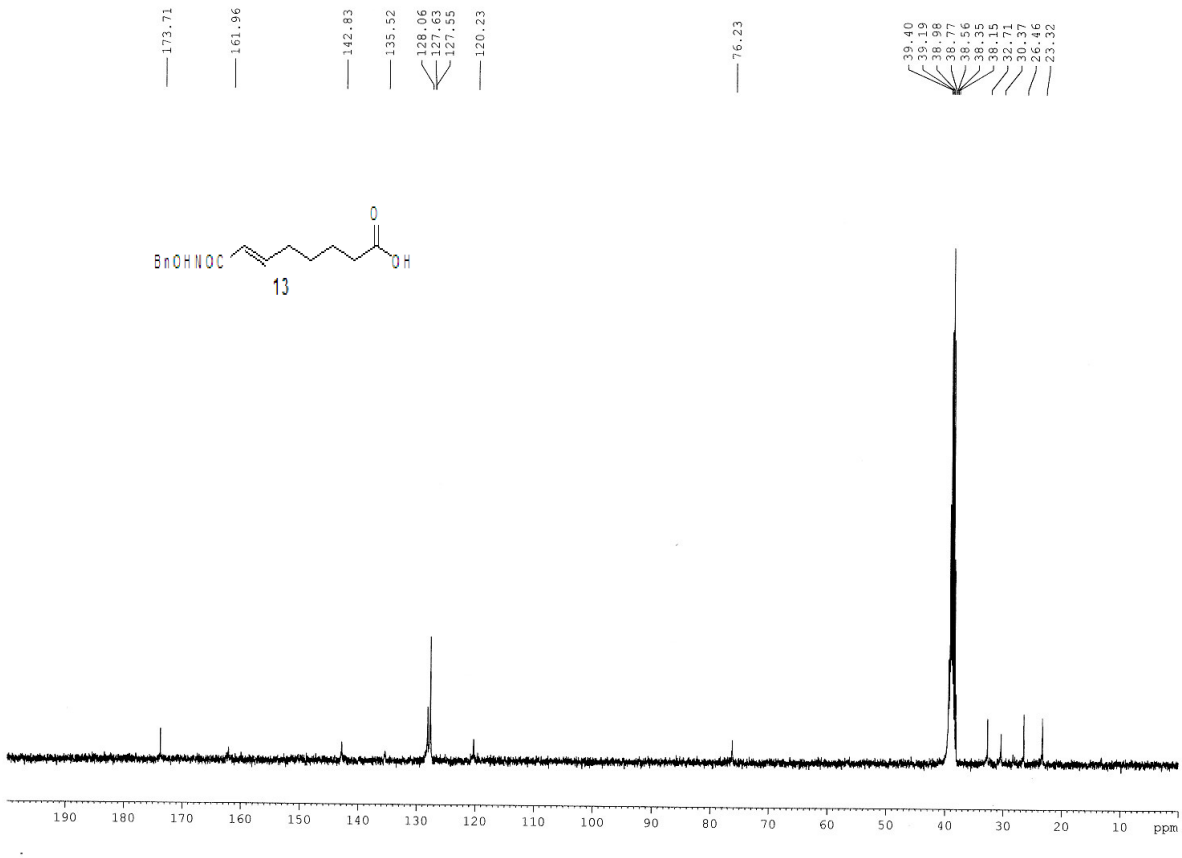
^{1}H NMR Spectrum of **12** in DMSO-d_6



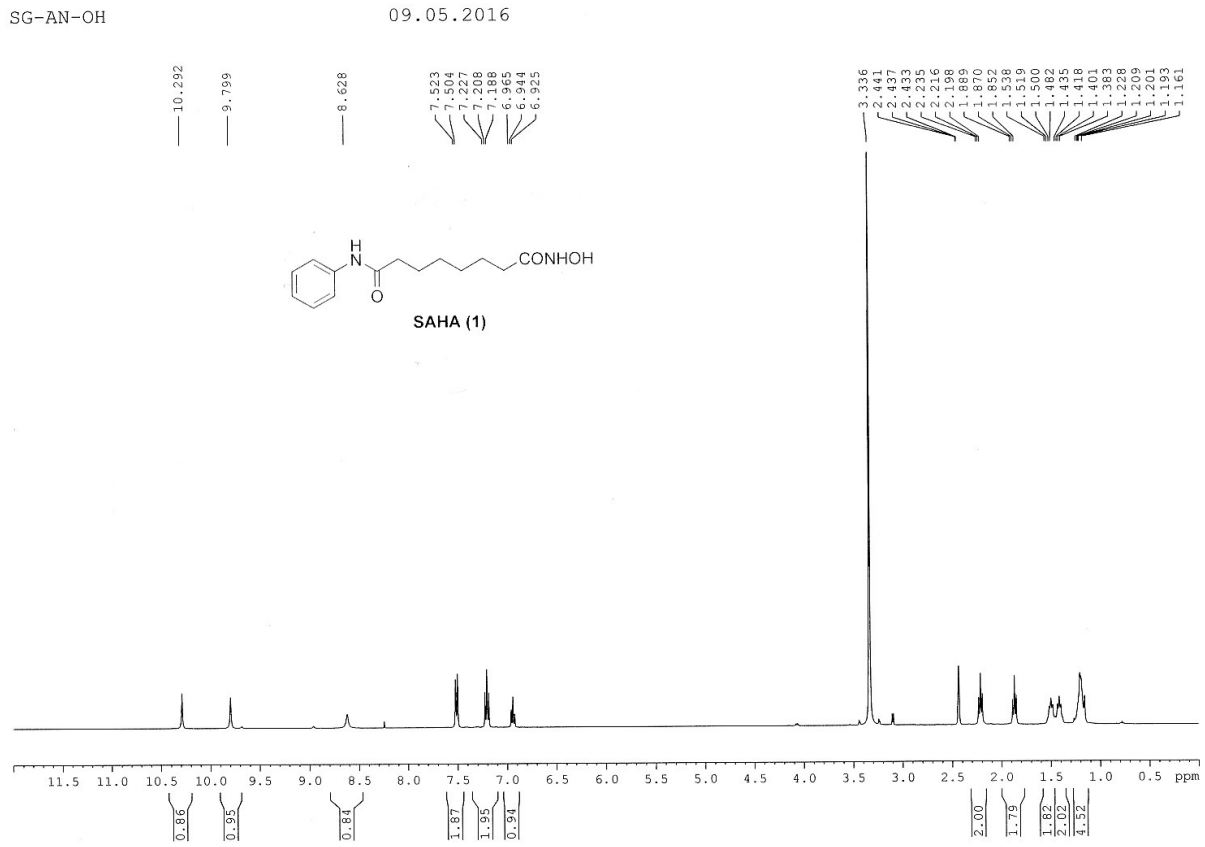
^{13}C NMR Spectrum of **12** in DMSO-d_6



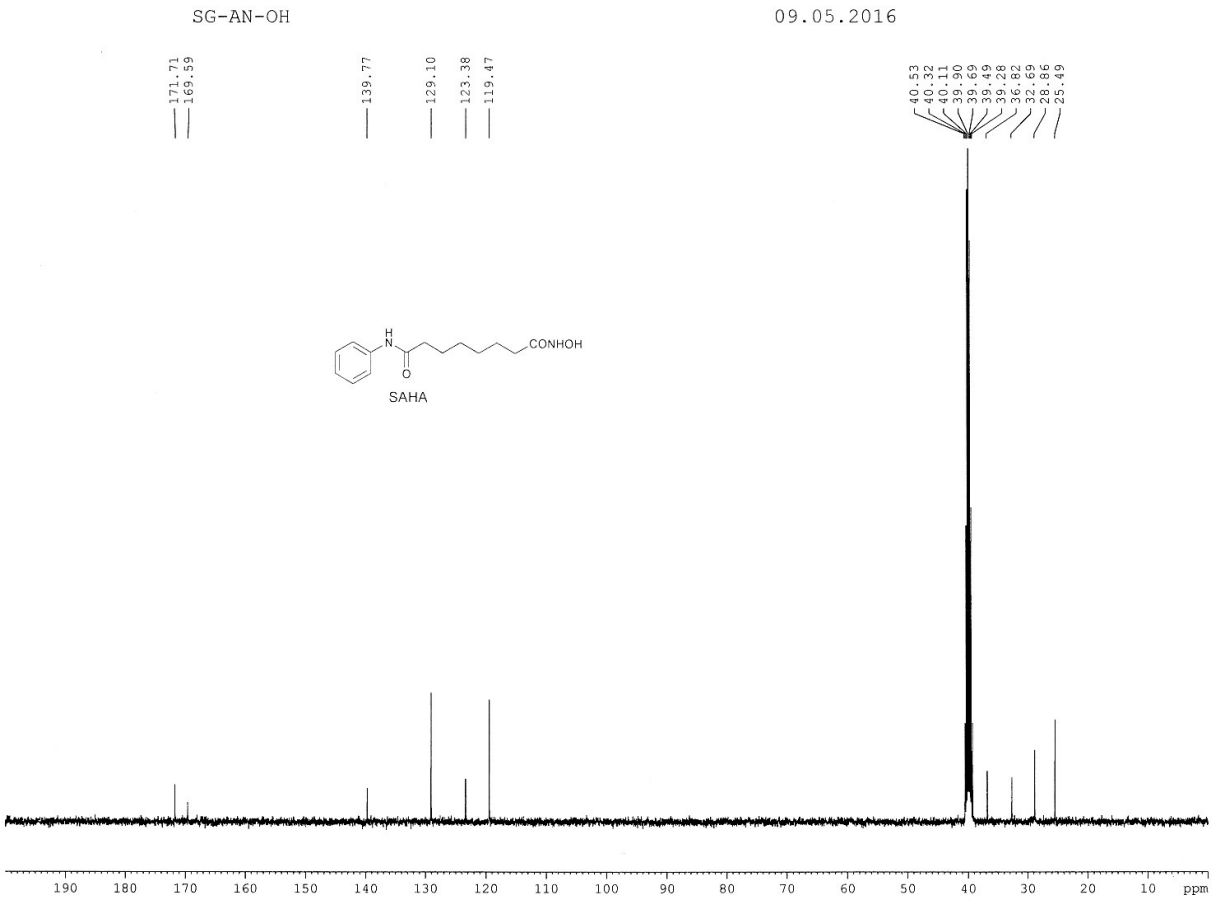
^{1}H NMR Spectrum of **13** in DMSO-d_6



^{13}C NMR Spectrum of **13** in DMSO-d_6



^{1}H NMR Spectrum of **1** in DMSO-d_6



^{13}C NMR Spectrum of **1** in DMSO-d_6