Electronic Supplementary Information

Design, multicomponent synthesis and anticancer activity of a focused histone deacetylase (HDAC) inhibitor library with peptoid-based cap groups

Viktoria Krieger,[†] Alexandra Hamacher,[†] Christoph G. W. Gertzen,[†] Johanna Senger,[‡] Martijn R. H. Zwinderman,[§] Martin Marek,[#] Christophe Romier,[#] Frank J. Dekker,[§] Thomas Kurz,[†] Manfred Jung,[‡] Holger Gohlke,[†] Matthias U. Kassack,[†] and Finn K. Hansen[†,Δ]*

[†]Institut für Pharmazeutische und Medizinische Chemie, Heinrich-Heine-Universität Düsseldorf, Universitätsstr. 1, 40225 Düsseldorf, Germany.

[‡]Institut für Pharmazeutische Wissenschaften, Albert-Ludwigs-Universität Freiburg, Albertstraße 25, 79104 Freiburg i.Br., Germany.

[§]Department of Chemical and Pharmaceutical Biology, Groningen Research Institute of Pharmacy, University of Groningen, The Netherlands.

[§]Département de Biologie Structurale Intégrative, Institut de Génétique et Biologie Moléculaire et Cellulaire (IGBMC), Université de Strasbourg (UDS), CNRS, INSERM, 1 Rue Laurent Fries, 67404 Illkirch Cedex, France.

[Δ]Pharmaceutical/Medicinal Chemistry, Institute of Pharmacy, Leipzig University, Brüderstraße 34, 04103 Leipzig, Germany.

Table of Contents

1. Supplemental Figures and Tables 3
2. Chemistry 5
   Synthetic procedure for the synthesis of **7** 9
   General procedure for the synthesis of **8a-f** 13
3. Spectral data 17
   Copies of ^{1}H NMR and ^{13}C NMR spectra 17
4. References 59

1. Supplemental Figures and Tables

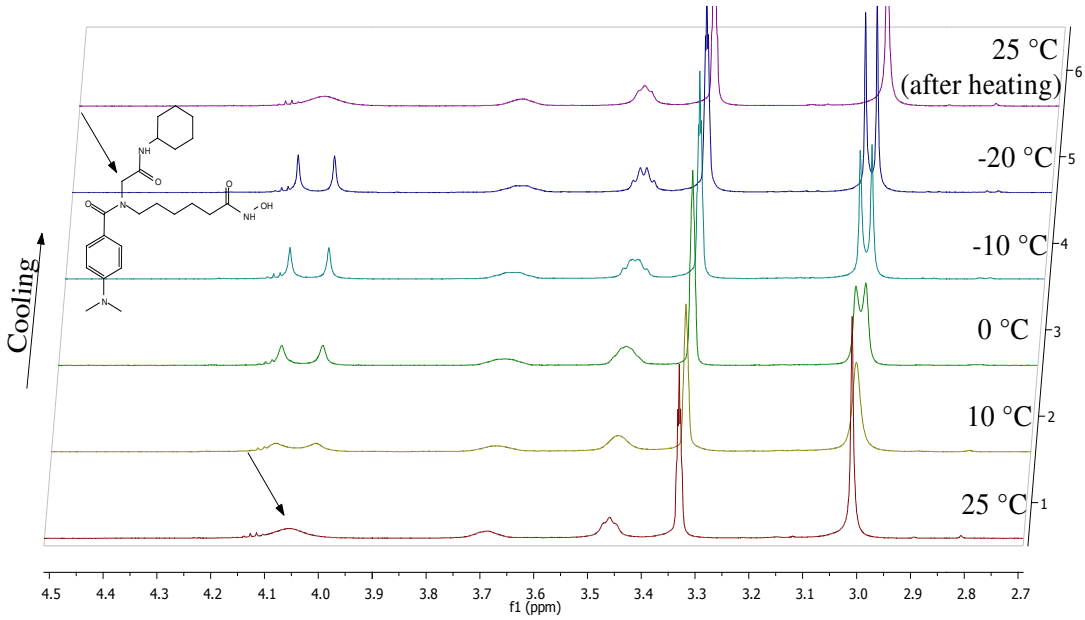


Figure S1. VT NMR spectra of compound **4c** in MeOH-d_4.

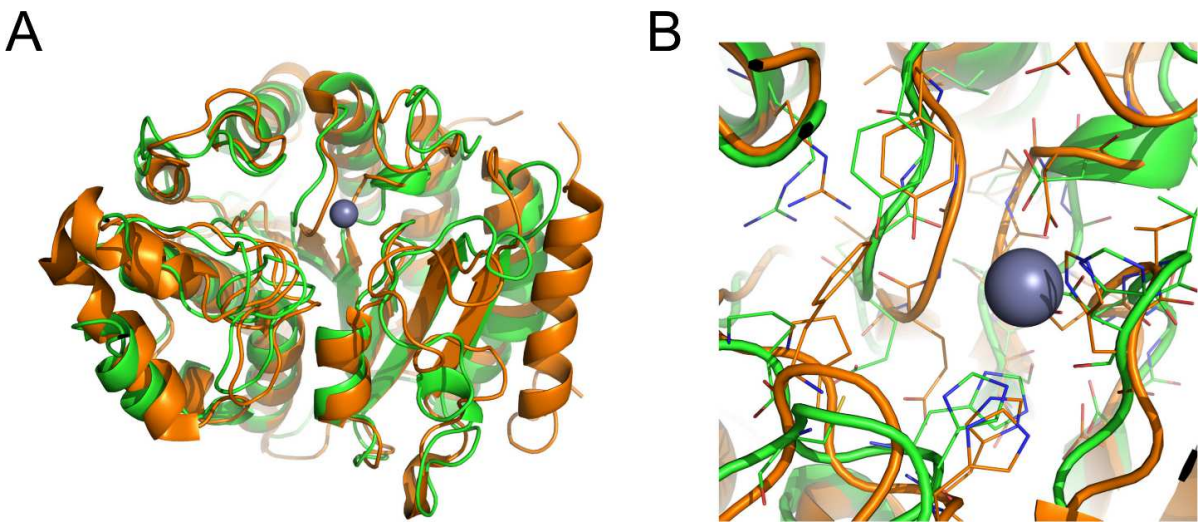
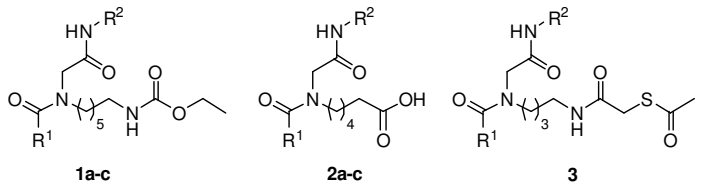


Figure S2. Comparison of the HDAC6 X-ray crystal structure[1] and the homology model used in this study. **A** Structural alignment of the HDAC6 X-ray crystal structure (orange) and homology model (green) with the zinc atom (sphere) in the binding pocket. **B** Detailed view of the binding pocket with residues within 8 Å of the zinc atom shown in lines representation.

Table S1. HDAC inhibition and cytotoxicity of the compounds **1a-c**, **2a-c**, and **3**.[a]



compd	R^1	R^2	HDACi IC_{50} [µM]		MTT IC_{50} [µM]	
			A2780	A2780 CisR	A2780	A2780 CisR
1a	Ph	c-Hex	n.e.	n.e.	366	336
1b	1-Naphthyl	c-Hex	n.e.	134	112	105
1c	4-Me_2N-Ph	*t*Bu	n.e.	n.e.	149	221
2a	Ph	c-Hex	n.e.	n.e.	n.e.	n.e.
2b	1-Naphthyl	c-Hex	n.e.	n.e.	n.e.	n.e.
2c	Ph	*t*Bu	n.e.	n.e.	n.e.	n.e.
3	Ph	c-Hex	80.4	100	212	116
vorinostat	---	---	0.96	0.97	2.42[b]	3.12[b]
cisplatin	---	---	---	---	2.25	17.2

[a]Values are the mean of three experiments. The standard deviations are < 10% of the mean.

n.e. = no effect up to 100 µM. [b]Data from ref. 2.

2. Chemistry

Ethyl (6-(*N*-(2-(cyclohexylamino)-2-oxoethyl)-1-naphthamido)hexyl)carbamate (1b). White solid; 53% yield; mp. 77 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 8.19 – 7.36 (m, 8H), 7.07*/6.92 (t, J = 5.3 Hz, 1H), 4.45 – 2.76 (m, 9H), 1.81 – 0.90 (m, 21H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 169.98, 169.96, 166.85, 166.74, 156.26, 156.14, 129.21, 128.96, 128.57, 128.54, 128.26, 128.11, 126.79, 126.44, 126.32, 125.40, 125.23, 125.15, 124.67, 123.58, 123.42, 59.37, 59.33, 50.91, 49.11, 47.70, 47.45, 46.77, 45.71, 40.09, 40.06, 32.53, 32.11, 29.45, 29.06, 27.54, 26.69, 26.29, 26.09, 25.55, 25.42, 25.23, 25.10, 24.55, 24.37, 14.70, 14.68. Anal. Calcd. for $C_{26}H_{28}N_2O_8S$: C 59.08; H 5.34; N 5.30. Found: C 58.95; H 5.41; N 5.20.

Ethyl (6-(*N*-(2-(*tert*-butylamino)-2-oxoethyl)-4-(dimethylamino)benzamido)hexyl)carbamate (1c). Colourless oil; 41% yield; t_R = 12.03 min, purity = 97.3%; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.31 – 7.30 (m, 2H), 6.64 – 6.63 (m, 2H), 4.86 – 4.74 (m, 1H), 4.07 – 4.04 (m, 2H), 3.94 (s, 2H), 3.40 – 3.38 (m, 2H), 3.08 – 3.06 (m, 2H), 2.97 (s, 6H), 1.61 – 1.56 (m, 2H), 1.40 – 1.38 (m, 2H), 1.32 (s, 9H), 1.20 – 1.18 (m, 5H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.34, 169.29, 156.79, 151.72, 129.01, 122.20, 111.35, 60.76, 52.96, 51.23, 40.89, 4.33, 29.91, 28.84, 28.29, 26.36, 26.30, 14.80. HRMS (ESI) $[M+H]^+$: 449.3123, Calcd. for $C_{24}H_{41}N_4O_4$: 449.3122.

Methyl 6-(*N*-(2-(cyclohexylamino)-2-oxoethyl)benzamido)hexanoate (6a). White solid; 59% yield; mp. 67 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 7.80 – 7.76 (m, 1H), 7.44 – 7.34 (m, 5H), 4.00*/3.73 (s, 2H), 3.59*/3.55 (s, 3H), 3.52 – 3.51 (m, 1H), 3.35 – 3.13 (m, 2H), 2.32/2.19* (t, J = 7.3 Hz, 2H), 1.76 – 1.02 (m, 16H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 173.33, 173.16, 170.93, 170.83, 167.02, 166.85, 136.81, 136.63, 129.13, 128.33, 128.19, 126.47, 126.34, 51.39, 51.17, 49.45, 47.59, 47.24, 45.69, 33.18, 32.98, 32.44, 32.23, 27.27, 26.16, 25.84, 25.32, 25.20, 25.14, 24.54, 24.45, 24.23, 23.83. Anal. Calcd. for $C_{22}H_{32}N_2O_4$: C 68.01; H 8.30; N 7.21. Found: C 67.76; H 8.28; N 7.10.

Methyl 6-(*N*-(2-(cyclohexylamino)-2-oxoethyl)-1-naphthamido)hexanoate (6b). White solid; 71% yield; mp. 105 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 8.19 – 7.36 (m, 8H), 4.45 – 2.95 (m, 8H), 2.37*/2.07 (t, J = 7.4 Hz, 2H), 1.81 – 0.91 (m, 16H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 173.35, 173.06, 170.01, 169.96, 166.85, 166.74, 134.79, 134.53, 132.97,

132.79, 129.19, 128.96, 128.58, 128.55, 128.25, 128.11, 126.79, 126.44, 126.33, 125.38, 125.21, 125.14, 124.71, 123.57, 123.42, 51.20, 51.10, 50.87, 48.99, 47.71, 47.45, 46.76, 45.55, 33.23, 32.81, 32.52, 32.14, 27.21, 26.37, 26.00, 25.23, 25.12, 25.10, 24.55, 24.37, 24.25, 23.68. Anal. Calcd. for $C_{26}H_{34}N_2O_4$: C 71.21; H 7.81; N 6.39. Found: C 71.50; H 8.05; N 6.34.

Methyl 6-(*N*-(2-(*tert*-butylamino)-2-oxoethyl)benzamido)hexanoate (6c). White solid; 79% yield; mp. 57 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 7.53*/7.48 (s, 1H), 7.44 – 7.33 (m, 5H), 3.97*/3.70 (s, 2H), 3.59/3.55* (s, 3H), 3.35 – 3.11 (m, 2H), 2.32/2.19* (t, *J* = 7.3 Hz, 2H), 1.56 – 1.03 (m, 15H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 173.32, 173.15, 170.96, 170.80, 167.44, 167.13, 136.90, 136.68, 129.10, 128.34, 128.16, 126.48, 126.33, 51.65, 51.17, 50.22, 50.16, 49.33, 47.40, 45.70, 33.19, 32.97, 28.55, 28.33, 27.26, 26.23, 25.84, 25.33, 24.23, 23.83. Anal. Calcd. for $C_{20}H_{30}N_2O_4$: C 66.27; H 8.34; N 7.73. Found: C 66.24; H 8.33; N 7.66.

Methyl 6-(*N*-(2-(cyclohexylamino)-2-oxoethyl)-4-(dimethylamino)benzamido)hexanoate (6d). White solid; 72% yield; mp. 93 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 7.80 (d, *J* = 6.7 Hz, 1H), 7.27 – 7.24 (m, 2H), 6.69 – 6.66 (m, 2H), 3.94 – 3.82 (m, 2H), 3.57 – 3.54 (m, 4H), 3.30 – 3.25 (m, 2H), 2.93 (s, 6H), 2.27 (t, *J* = 6.8 Hz, 2H), 1.74 – 1.09 (m, 16H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 173.27, 171.23, 167.38, 150.92, 128.39, 123.08, 110.95, 51.16, 47.53, 33.13, 32.33, 25.74, 25.18, 24.50, 24.12. Anal. Calcd. for $C_{24}H_{37}N_3O_4$: C 66.79; H 8.64; N 9.74. Found: C 66.57; H 8.75; N 9.60.

Methyl 6-(*N*-(2-(cyclohexylamino)-2-oxoethyl)-3,5-dimethylbenzamido)hexanoate (6e). White solid; 89% yield; mp. 80 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 7.78*/7.74 (d, *J* = 7.7 Hz, 1H), 7.06 – 6.91 (m, 3H), 3.97*/3.72 (s, 2H), 3.59 – 3.52 (m, 4H), 3.35 – 3.12 (m, 2H), 2.32/2.19* (t, *J* = 7.4 Hz, 2H), 2.29*/2.25 (s, 6H), 1.75 – 1.04 (m, 16H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 173.32, 173.15, 171.01, 167.14, 166.88, 137.46, 137.30, 136.79, 136.61, 130.38, 123.99, 123.91, 51.32, 51.16, 49.30, 47.59, 47.08, 45.69, 33.1732.97, 32.43, 32.29, 27.22, 26.11, 25.83, 25.26, 25.20, 25.15, 24.53, 24.46, 24.24, 23.79, 20.76. Anal. Calcd. for $C_{24}H_{36}N_2O_4$: C 69.20; H 8.71; N 6.73. Found: C 69.12; H 8.48; N 6.67.

Methyl 6-(*N*-(2-(*tert*-butylamino)-2-oxoethyl)-4-(dimethylamino)benzamido)hexanoate (6f). White solid; 68% yield; mp. 94 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 7.51 (s, 1H),

7.26 – 7.24 (m, 2H), 6.68 – 6.67 (m, 2H), 3.84 (bs, 2H), 3.58 (s, 3H), 3.28 – 3.25 (m, 2H), 2.93 (s, 6H), 2.35 – 2.21 (m, 2H), 1.52 – 1.26 (m, 15H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 173.27, 171.22, 167.80, 150.91, 128.39, 123.20, 110.94, 51.16, 50.18, 39.78, 33.13, 28.45, 25.73, 24.12. Anal. Calcd. for $C_{22}H_{35}N_3O_4$: C 65.16; H 8.70; N 10.36. Found: C 65.04; H 8.41; N 10.35.

Methyl 6-(*N*-(2-(butylamino)-2-oxoethyl)-4-(dimethylamino)benzamido)hexanoate (6g). White solid; 61% yield; mp. 79 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 7.96 – 7.83 (m, 1H), 7.27 – 7.25 (m, 2H), 6.68 – 6.67 (m, 2H), 3.88 (bs, 2H), 3.57 (s, 3H), 3.29 – 3.26 (m, 2H), 3.08 (dd, J = 12.7, 6.8 Hz, 2H), 2.93 (s, 6H), 2.35 – 2.21 (m, 2H), 1.54 – 1.20 (m, 10H), 0.87 (t, J = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 173.26, 171.25, 168.24, 150.93, 128.41, 123.00, 110.91, 51.15, 39.75, 38.16, 33.13, 31.18, 25.70, 24.10, 19.50, 13.64. Anal. Calcd. for $C_{22}H_{35}N_3O_4$: C 65.16; H 8.70; N 10.36. Found: C 65.04; H 8.79; N 10.24.

Methyl 6-(4-(dimethylamino)-*N*-(2-oxo-2-(*p*-tolylamino)ethyl)benzamido)hexanoate (6h). Yellow oil; 50% yield; t_R = 13.44 min, purity = 97.5%; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 9.90 (s, 1H), 7.47 – 7.46 (m, 2H), 7.28 – 7.26 (m, 2H), 7.12 – 7.10 (m, 2H), 6.70 – 6.69 (m, 2H), 4.11 (bs, 2H), 3.57 (s, 3H), 3.36 – 3.33 (m, 2H), 2.93 (bs, 6H), 2.28 – 2.25 (m, 5H), 1.59 – 1.08 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 173.26, 171.39, 167.19, 150.98, 129.11, 128.35, 122.90, 119.09, 111.01, 51.16, 33.14, 25.68, 24.08, 20.42. HRMS (ESI) $[M+H]^+$: 440.2545, Calcd. for $C_{25}H_{34}N_3O_4$: 440.2544.

Methyl 6-(3,5-dimethyl-*N*-(2-oxo-2-(*p*-tolylamino)ethyl)benzamido)hexanoate (6i). Yellow oil; 56% yield; t_R = 18.45 min, purity = 98.3%; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.09 (s, 1H), 7.41 – 7.00 (m, 7H), 4.23 (s, 2H), 3.62 (s, 3H), 3.44 – 3.31 (m, 2H), 2.32 – 2.30 (m, 9H), 2.23 – 2.12 (m, 2H), 1.63 – 1.15 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.88, 173.84, 167.67, 138.45, 135.52, 135.15, 133.88, 131.79, 129.53, 124.44, 119.99, 52.21, 51.57, 51.34, 33.78, 28.23, 25.96, 24.35, 21.32, 20.96. HRMS (ESI) $[M+H]^+$: 425.2432, Calcd. for $C_{25}H_{33}N_2O_4$: 425.2435.

Methyl 6-(*N*-(2-(benzylamino)-2-oxoethyl)-4-(dimethylamino)benzamido)hexanoate (6j). White solid; 73% yield; mp. 82 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 8.51 – 8.31 (m, 1H), 7.34 – 6.65 (m, 9H), 4.31 (d, J = 5.8 Hz, 2H), 3.97 (bs, 2H), 3.58 (s, 3H), 3.32 – 3.30 (m, 2H),

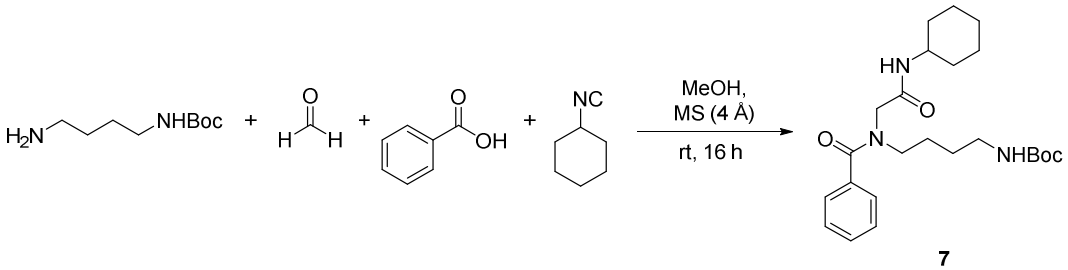
2.93 (s, 6H), 2.36 – 2.21 (m, 2H), 1.56 – 1.17 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 173.32, 171.38, 168.65, 150.96, 139.38, 128.43, 128.28, 127.28, 126.83, 122.95, 110.94, 51.20, 42.14, 33.17, 27.49, 25.75, 24.14. Anal. Calcd. for $C_{25}H_{33}N_3O_4$: C 68.31; H 7.57; N 9.56. Found: C 68.06; H 7.28; N 9.58.

Methyl 6-(*N*-(2-(benzylamino)-2-oxoethyl)-3,5-dimethylbenzamido)hexanoate (6k). White solid; 89% yield; mp. 86 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 8.45 – 8.39 (m, 1H), 7.33 – 6.92 (m, 8H), 4.33*/4.27 (d, J = 5.6 Hz, 2H), 4.06*/3.84 (s, 1H), 3.59/3.56* (s, 3H), 3.37 – 3.16 (m, 2H), 2.33 – 2.18 (m, 8H), 1.57 – 1.05 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 173.34, 173.17, 171.11, 171.09, 168.19, 168.17, 139.44, 139.20, 137.44, 137.41, 136.70, 136.47, 130.45, 128.27, 128.24, 127.24, 127.15, 126.86, 126.73, 124.01, 123.98, 51.36, 49.54, 51.17, 51.15, 47.55, 45.64, 42.15, 42.06, 33.19, 32.97, 27.31, 26.09, 25.83, 25.25, 24.24, 23.79, 20.76. Anal. Calcd. for $C_{25}H_{32}N_2O_4$: C 70.73; H 7.60; N 6.60. Found: C 70.84; H 7.51; N 6.90.

6-(*N*-(2-(Cyclohexylamino)-2-oxoethyl)-1-naphthamido)hexanoic acid (2b). White solid; quantitative yield; mp. 101 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.95 (s, 1H), 8.19 – 7.36 (m, 8H), 4.46 – 2.94 (m, 5H), 2.27*/1.99 (t, J = 7.4 Hz, 2H), 1.81 – 0.82 (m, 16H).^{13}C NMR (126 MHz, DMSO-d_6) δ = 174.34, 174.09, 170.01, 169.96, 166.83, 166.69, 134.75, 134.51, 132.93, 132.76, 129.17, 128.95, 128.51, 128.16, 128.05, 126.72, 126.37, 126.24, 125.30, 125.14, 125.06, 124.67, 123.56, 123.38, 50.90, 49.01, 47.68, 47.44, 46.79, 45.53, 33.59, 33.22, 32.44, 32.04, 27.28, 26.38, 26.07, 25.26, 25.18, 25.05, 24.46, 24.28, 23.77. Anal. Calcd. for $C_{25}H_{32}N_2O_4$: C 70.73; H 7.60; N 6.60. Found: C 70.50; H 7.80; N 6.59.

6-(*N*-(2-(*tert*-Butylamino)-2-oxoethyl)benzamido)hexanoic acid (2c). White solid; quantitative yield; mp. 135 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.97 (s, 1H), 7.53 – 7.33 (m, 5H), 3.97*/3.70 (s, 2H), 3.33 – 3.11 (m, 2H), 2.22/2.10* (t, J = 7.3 Hz, 2H), 1.55 – 1.04 (m, 15H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 174.46, 174.29, 170.96, 170.81, 167.44, 167.14, 136.92, 136.71, 129.13, 129.10, 128.35, 128.17, 126.49, 126.33, 51.65, 50.23, 50.18, 49.39, 47.39, 45.73, 33.57, 33.41, 28.56, 28.34, 27.36, 26.31, 25.95, 25.46, 24.31, 23.93. Anal. Calcd. for $C_{19}H_{28}N_2O_4$: C 65.49; H 8.10; N 8.04. Found: C 65.27; H 7.84; N 8.02.

Synthetic procedure for the synthesis of 7



A mixture of *tert*-butyl (4-aminobutyl)carbamate (681 mg, 3.62 mmol, 1.2 equiv), paraformaldehyde (109 mg, 3.62 mmol, 1.2 equiv), and 300 mg of crushed molecular sieves (MS) 4 Å was stirred in dry methanol (3 mL, 0.5 M) at room temperature for 30 min. Subsequently, benzoic acid (369 mg, 3.02 mmol, 1.0 equiv) and after further 10 min cyclohexyl isocyanide (376 µL, 3.02 mmol, 1.0 equiv) were added. The reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (prepacked silica cartridge, hexane-ethyl acetate, gradient: 100:00 → 50:50 in 30 min) to yield the desired product **7**.

***tert*-Butyl (4-(*N*-(2-(cyclohexylamino)-2-oxoethyl)benzamido)butyl)carbamate (7).** Colourless oil; 57% yield; t_R = 16.17 min, 91.0% purity; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.74 – 7.73 (m, 1H), 7.44 – 7.36 (m, 5H), 6.76/6.68* (s, 1H), 4.00*/3.74 (s, 2H), 3.57 – 3.52 (m, 1H), 3.36 – 3.19 (m, 2H), 2.94 – 2.77 (m, 2H), 1.75 – 1.09 (m, 23H).^{13}C NMR (126 MHz, DMSO-d_6) δ 170.82, 166.91, 155.52, 129.01, 128.14, 128.08, 126.32, 77.26, 54.70, 51.38, 47.51, 45.60, 32.12, 28.16, 27.83, 25.07, 24.35, 23.94. HRMS (ESI) $[M+H]^+$: 432.2858, Calcd. for $C_{24}H_{38}N_3O_4$: 432.2857.

***N*-(2-(Cyclohexylamino)-2-oxoethyl)-*N*-(6-(hydroxyamino)-6-oxohexyl)-1-naphthamide (4b).** White/yellowish solid; 55% yield; mp. 82 °C; t_R = 13.06 min, purity = 95.3%; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 10.39*/10.24 (s, 1H), 8.69*/8.61 (s, 1H), 8.20 – 7.36 (m, 8H), 4.47 – 2.94 (m, 5H), 2.02 – 0.88 (m, 18 H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 170.00, 169.99, 169.07, 168.82, 166.85, 166.75, 134.82, 134.54, 132.97, 132.77, 129.19, 128.96, 128.59, 128.56, 128.25, 128.12, 126.86, 126.83, 126.47, 126.33, 125.38, 125.29, 125.15, 124.72, 123.57, 123.44, 50.88, 49.07, 47.72, 47.46, 46.68, 45.63, 32.53, 32.26, 32.15, 32.01, 27.41, 26.48, 26.19, 25.43, 25.23, 25.10, 24.98, 24.56, 24.38. HRMS (ESI) $[M+H]^+$: 440.2548, Calcd. for $C_{25}H_{34}N_3O_4$: 440.2544.

***N*-(2-(Cyclohexylamino)-2-oxoethyl)-4-(dimethylamino)-*N*-(6-(hydroxyamino)-6-oxo-ethyl)benzamide (4c).** White solid; 42% yield; mp. 105 °C; t_R = 9.73 min, purity = 98.4%; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 10.32 (s, 1H), 8.65 (bs, 1H), 7.80 (bs, 1H), 7.26 – 7.24 (m, 2H), 6.68 – 6.67 (m, 2H), 3.86 (bs, 2H), 3.56 – 3.55 (m, 1H), 3.28 – 3.25 (m, 2H), 2.93 (s, 6H), 1.97 – 1.87 (m, 2H), 1.73 – 1.13 (m, 16H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 171.22, 168.99, 167.39, 150.93, 128.40, 123.10, 110.96, 47.54, 32.34, 32.19, 25.99, 25.19, 24.89, 24.51. HRMS (ESI) $[M+H]^+$: 433.2813, Calcd. for $C_{23}H_{37}N_4O_4$: 433.2809.

***N*-(2-(Cyclohexylamino)-2-oxoethyl)-*N*-(6-(hydroxyamino)-6-oxohexyl)-3,5-dimethyl-benzamide (4d).** White solid; 33% yield; mp. 140 °C; t_R = 13.10 min, purity = 100%; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 10.34/10.28* (s, 1H), 8.66/8.63* (s, 1H), 7.78*/7.74 (d, J = 7.7 Hz, 1H), 7.06 – 6.91 (m, 3H), 3.97*/3.72 (s, 2H), 3.58 – 3.52 (m, 1H), 3.34 – 3.12 (m, 2H), 2.29*/2.25 (s, 6H), 1.96/1.85* (t, J = 7.2 Hz, 2H), 1.75 – 1.00 (m, 16H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 171.48, 169.53, 169.37, 167.63, 167.37, 137.97, 137.80, 137.27, 137.09, 130.88, 124.47, 124.39, 51.81, 49.91, 48.07, 47.51, 46.31, 32.91, 32.77, 32.71, 32.58, 27.90, 26.73, 26.53, 26.00, 25.68, 25.62, 25.47, 25.11, 25.02, 24.94, 21.26. HRMS (ESI) $[M+H]^+$: 418.2696, Calcd. for $C_{23}H_{36}N_3O_4$: 418.2700.

***N*-(2-(*tert*-Butylamino)-2-oxoethyl)-*N*-(6-(hydroxyamino)-6-oxohexyl)benzamide (4e).** White solid; 45% yield; mp. 80 °C; t_R = 10.74 min, purity = 95.3%; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 10.34/10.29* (s, 1H), 8.66 – 8.64 (m, 1H), 7.53*/7.48 (s, 1H), 7.44 – 7.33 (m, 5H), 3.97*/3.70 (s, 2H), 3.33 – 3.10 (m, 2H), 1.96/1.85* (t, J = 7.3 Hz, 2H), 1.55 – 0.99 (m, 15H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 170.95, 170.81, 169.06, 168.86, 167.45, 167.13, 136.91, 136.68, 129.13, 129.10, 128.37, 128.16, 126.49, 126.33, 51.65, 50.23, 50.17, 49.43, 47.34, 45.80, 32.24, 32.06, 28.56, 28.34, 27.42, 26.38, 26.05, 25.55, 24.99, 24.61. HRMS (ESI) $[M+H]^+$: 364.2230, Calcd. for $C_{19}H_{30}N_3O_4$: 364.2231.

4-(Dimethylamino)-*N*-(6-(hydroxyamino)-6-oxohexyl)-*N*-(2-oxo-2-(*p*-tolylamino)ethyl)-benzamide (4f). Beige solid; 46% yield; mp. 78 °C; t_R = 8.33 min, purity = 100%; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 10.32 (s, 1H), 8.65 (s, 1H), 7.51 (s, 1H), 7.26 – 7.24 (m, 2H), 6.68 – 6.67 (m, 2H), 3.83 (bs, 2H), 3.27 – 3.25 (m, 2H), 2.93 (s, 6H), 1.99 – 1.86 (m, 2H), 1.50 – 1.15 (m, 15H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 171.22, 169.01, 167.81, 150.92, 128.41,

123.18, 110.96, 51.96, 50.19, 45.91, 40.06, 32.20, 28.48, 25.96, 24.91. HRMS (ESI) $[M+H]^+$: 407.2651, Calcd. for $C_{21}H_{35}N_4O_4$: 407.2653.

***N*-(2-(Butylamino)-2-oxoethyl)-4-(dimethylamino)-*N*-(6-(hydroxyamino)-6-oxohexyl)-benzamide (4g).** White solid; 32% yield; mp. 73 °C; t_R = 8.48 min, purity = 98.7%; ^{1}H NMR (500 MHz, DMSO-d_6) δ = 10.29 (s, 1H), 8.61 (s, 1H), 7.85 (bs, 1H), 7.27 – 7.25 (m, 2H), 6.68 – 6.67 (m, 2H), 3.88 (bs, 2H), 3.29 – 3.26 (m, 2H), 3.08 (dd, J = 12.7, 6.6 Hz, 2H), 2.93 (s, 6H), 1.97 – 1.87 (m, 2H), 1.52 – 1.11 (m, 10H), 0.87 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 171.18, 168.91, 168.15, 150.87, 128.30, 123.01, 110.87, 38.09, 32.10, 31.08, 26.45, 25.84, 24.76, 19.39, 13.51. HRMS (ESI) $[M+H]^+$: 407.2652, Calcd. for $C_{21}H_{34}N_4O_4$: 407.2653.

4-(Dimethylamino)-*N*-(6-(hydroxyamino)-6-oxohexyl)-*N*-(2-oxo-2-(*p*-tolylamino)ethyl)-benzamide (4h). Orange solid; 39% yield; mp. 85 °C; t_R = 10.02 min, purity = 98.6%; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 10.32 (s, 1H), 9.90 (s, 1H), 8.65 (s, 1H), 7.47 – 6.70 (m, 8H), 4.11 (bs, 2H), 3.35 – 3.32 (m, 2H), 2.93 (s, 6H), 2.25 (s, 3H), 1.97 – 1.89 (m, 2H), 1.59 – 1.16 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 171.41, 169.00, 167.22, 151.00, 129.13, 128.38, 119.11, 111.03, 32.25, 27.49, 26.00, 24.89, 20.44. HRMS (ESI) $[M+H]^+$: 441.2502, Calcd. for $C_{24}H_{33}N_4O_4$: 441.2496.

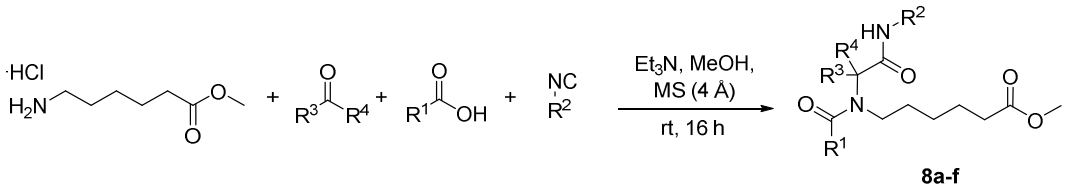
***N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-*N*-(6-(hydroxyamino)-6-oxohexyl)benzamide (4i).** Orange solid; 28% yield; mp. 86 °C; t_R = 13.84 min, purity = 100.0%; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 10.34*/10.29 (s, 1H), 9.97/9.78* (s, 1H), 8.66 – 8.63 (m, 1H), 7.50 – 6.94 (m, 7H), 4.18/3.97* (s, 2H), 3.40 – 3.21 (m, 2H), 2.31 – 2.22 (m, 9H), 1.96 – 1.87 (m, 2H), 1.53 – 1.05 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 171.20, 171.16, 169.06, 168.91, 167.04, 166.72, 137.56, 137.46, 136.73, 136.52, 136.45, 136.02, 132.43, 132.00, 130.53, 130.46, 129.14, 123.95, 119.30, 118.98, 51.99, 49.74, 47.94, 45.89, 32.25, 32.12, 27.60, 26.41, 26.03, 25.53, 25.00, 24.63, 20.78, 20.43. HRMS (ESI) $[M+H]^+$: 426.2385, Calcd. for $C_{24}H_{32}N_3O_4$: 426.2387.

***N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-*N*-(6-(hydroxyamino)-6-oxohexyl)benzamide (4j).** White solid; 32% yield; mp. 76 °C; t_R = 9.15 min, purity = 98.9%; ^{1}H NMR (500 MHz, DMSO-d_6) δ = 10.30 (s, 1H), 8.62 (s, 1H), 8.41 (bs, 1H), 7.34 – 6.65 (m, 9H), 4.31 (d, J = 5.8 Hz, 2H), 3.97 (bs, 2H), 3.32 – 3.29 (m, 2H), 2.93 (s, 6H), 1.93 – 1.91 (m, 2H), 1.56 – 1.15 (m,

6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 171.24, 168.92, 168.50, 150.87, 139.27, 128.30, 128.15, 127.16, 126.68, 122.96, 110.87, 42.06, 32.11, 26.72, 25.85, 24.76. HRMS (ESI) $[M+H]^+$: 441.2499, Calcd. for $C_{24}H_{33}N_4O_4$: 441.2496.

***N*-(6-(Hydroxyamino)-6-oxohexyl)-3,5-dimethyl-*N*-(2-oxo-2-(*p*-tolylamino)ethyl)benz-amide (4k).** White solid; 38% yield; mp. 143 °C; t_R = 12.78 min, purity = 99.6%; ^{1}H NMR (500 MHz, DMSO-d_6) δ = 10.32/10.26* (s, 1H), 8.63/8.60* (s, 1H), 8.42 – 8.35 (m, 1H), 7.31 – 6.92 (m, 8H), 4.33*/4.27 (d, J = 4.8 Hz, 2H), 4.06*/3.84 (s, 2H), 3.37 – 3.18 (m, 2H), 2.30*/2.22 (s, 6H), 2.01 – 1.81 (m, 2H), 1.54 – 1.03 (m, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 171.01, 168.94, 168.83, 168.09, 139.33, 139.12, 137.32, 136.66, 136.45, 130.34, 128.15, 127.11, 126.71, 123.91, 51.34, 49.57, 47.45, 45.68, 42.08, 32.14, 32.04, 27.43, 26.16, 25.97, 25.45, 24.87, 24.53, 20.67. HRMS (ESI) $[M+H]^+$: 426.2389, Calcd. for $C_{24}H_{32}N_3O_4$: 426.2387.

General procedure for the synthesis of 8a-f



A mixture of methyl 6-aminohexanoate hydrochloride (153 mg, 0.84 mmol, 1.2 equiv), the respective aldehyde or ketone (1.2 equiv), triethylamine (116 µL, 0.84 mmol, 1.2 equiv) and 150 mg of crushed molecular sieves (MS) 4 Å was stirred in dry methanol (2 mL, 0.5 M) at room temperature for 30 min. Subsequently, the appropriate carboxylic acid (1.0 mmol, 1.0 equiv) and after further 10 min the isocyanide (1.0 mmol, 1.0 equiv) were added. The reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was filtered and the solvent was removed under reduced pressure. The crude products were purified by flash column chromatography (prepacked silica cartridge, hexane-ethyl acetate, gradient: 100:00 → 50:50 in 30 min). The products were crystallized from ethyl acetate-hexane to yield the desired products **8a-f**.

Methyl 6-(*N*-(1-(cyclohexylamino)-2-methyl-1-oxopropan-2-yl)benzamido)hexanoate (8a). Yellowish oil; 65% yield; t_R = 16.32 min, purity = 95.6%; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.39 – 7.32 (m, 5H), 6.02 (d, *J* = 7.7 Hz, 1H), 3.79 – 3.74 (m, 1H), 3.63 (s, 3H), 3.32 – 3.29 (m, 2H), 2.16 (t, *J* = 7.4 Hz, 2H), 1.93 – 1.01 (m, 22H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 174.03, 173.82, 173.03, 138.04, 129.40, 128.62, 126.41, 62.42, 51.57, 48.39, 46.82, 33.84, 33.20, 31.24, 26.34, 25.87, 25.05, 24.95, 24.29. HRMS (ESI) $[M+H]^+$: 546.1901, Calcd. for $C_{26}H_{32}N_3O_8S$: 546.1905.

Methyl 6-(*N*-(1-(cyclohexylamino)-2-methyl-1-oxopropan-2-yl)-4-(dimethylamino)benzamido)hexanoate (8b). Yellow oil; 66% yield; t_R = 12.25 min, purity = 95.2%; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.26 – 7.25 (m, 2H), 6.61 – 6.60 (m, 2H), 3.72 – 3.66 (m, 1H), 3.58 (s, 3H), 3.41 – 3.38 (m, 2H), 2.95 (s, 6H) 2.14 (t, *J* = 7.5 Hz, 2H), 1.87 – 1.02 (m, 22H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 174.57, 174.23, 173.83, 151.40, 128.68, 124.58, 111.28, 62.27, 51.45, 48.02, 47.56, 40.21, 33.77, 32.91, 30.79, 26.27, 25.69, 25.17, 24.74, 24.30. HRMS (ESI) $[M+H]^+$: 460.3169, Calcd. for $C_{26}H_{42}N_3O_4$: 460.3170.

Methyl 6-(*N*-(1-(*tert*-butylamino)-2-methyl-1-oxopropan-2-yl)benzamido)hexanoate (8c). Yellow oil; 56% yield; t_R = 15.67 min, purity = 96.1%; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.31

– 7.24 (m, 5H), 5.92 (s, 1H), 3.55 (s, 3H), 3.24 – 3.21 (m, 2H), 2.08 (t, J = 7.4 Hz, 2H), 1.51 – 0.93 (m, 21H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.86, 173.61, 172.61, 137.71, 129.20, 128.44, 126.02, 62.54, 51.38, 50.69, 46.45, 33.56, 31.04, 28.54, 26.05, 24.66, 23.98. HRMS (ESI) $[M+H]^+$: 359.2595, Calcd. for $C_{22}H_{35}N_2O_4$: 391.2591.

Methyl 6-(*N*-(1-(cyclohexylcarbamoyl)cyclohexyl)benzamido)hexanoate (8d). White solid; 75% yield; mp. 89 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 7.53 (d, J = 8.1 Hz, 1H), 7.45 – 7.36 (m, 5H), 3.56 – 3.52 (m, 4H), 3.26 – 3.23 (m, 2H), 2.19 – 0.90 (m, 28H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 173.06, 172.38, 138.38, 129.08, 128.35, 126.25, 63.88, 51.14, 47.17, 46.47, 32.90, 32.38, 32.34, 29.82, 25.56, 25.30, 25.14, 24.62, 23.60, 22.13. Anal. Calcd. for $C_{27}H_{40}N_2O_4$: C 71.02, H 8.83, N 6.13 Found: C 71.15; H 9.12; N 5.99.

Methyl 6-(*N*-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)benzamido)hexanoate (8e). White solid; 57% yield; mp. 84 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 8.06*/7.81 (bs, 1H), 7.45 – 7.19 (m, 10H), 6.06*/5.27 (bs, 1H), 3.64 – 3.63 (m, 1H), 3.54 (bs, 3H), 3.41 – 3.13 (m, 2H), 2.11 – 1.94 (m, 2H), 1.74 – 0.66 (m, 16H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 173.07, 171.43, 171.04, 168.09, 167.95, 137.08, 136.59, 129.16, 128.94, 128.50, 127.98, 126.14, 65.10, 60.79, 51.09, 47.67, 46.58, 44.73, 32.86, 32.10, 28.80, 27.05, 25.90, 25.44, 24.54, 24.46, 23.83, 23.37, 17.42. Anal. Calcd. for $C_{28}H_{36}N_2O_4$: C 72.39; H 7.81; N 6.03. Found: C 72.39; H 7.79; N 6.08.

Methyl 6-(*N*-(2-(cyclohexylamino)-2-oxo-1-(*p*-tolyl)ethyl)benzamido)hexanoate (8f). White solid; 59% yield; mp. 86 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 7.98*/7.75 (bs, 1H), 7.44 – 7.06 (m, 9H), 5.99*/5.22 (bs, 1H), 3.63 – 3.61 (m, 1H), 3.54 (bs, 3H), 3.41 – 3.11 (m, 2H), 2.30 (bs, 3H), 2.10 – 0.66 (m, 18H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 173.12, 171.39, 168.14, 137.34, 137.15, 133.48, 129.15, 129.04, 128.77, 128.49, 126.13, 51.11, 47.63, 32.80, 32.11, 25.15, 24.54, 24.46, 20.65. Anal. Calcd. for $C_{29}H_{38}N_2O_4$: C 72.77; H 8.00; N 5.85. Found: C 72.74; H 8.11; N 5.80.

***N*-(1-(Cyclohexylamino)-2-methyl-1-oxopropan-2-yl)-4-(dimethylamino)-*N*-(6-(hydroxy-amino)-6-oxohexyl)benzamide (5b).** Brownish solid; 66% yield; mp. 87 °C; t_R = 9.41 min, purity = 95.8%; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 10.28 (s, 1H), 8.63 (s, 1H), 7.28 – 7.26 (m, 2H), 7.02 (d, J = 8.3 Hz, 1H), 6.70 – 6.68 (m, 2H), 3.46 – 3.41 (m, 1H), 3.37 – 3.33 (m,

2H), 2.93 (s, 6H), 1.83 (t, J = 7.3 Hz, 2H), 1.64 – 0.92 (m, 22H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 173.14, 171.87, 168.84, 150.55, 127.85, 125.31, 111.04, 61.00, 47.56, 46.33, 39.85, 32.43, 32.04, 30.63, 25.81, 25.34, 24.81, 24.57, 24.30. HRMS (ESI) $[M+H]^+$: 461.3121, Calcd. for $C_{25}H_{41}N_4O_4$: 461.3122.

***N*-(1-(*tert*-Butylamino)-2-methyl-1-oxopropan-2-yl)-*N*-(6-(hydroxyamino)-6-oxohexyl)-benzamide (5c).** White solid; 48% yield; mp. 107 °C; t_R = 10.93 min, purity = 95.5%; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 10.27 (s, 1H), 8.63 (s, 1H), 7.44 – 7.34 (m, 5H), 6.65 (s, 1H), 3.28 – 3.22 (m, 2H), 1.80 (t, J = 7.2 Hz, 2H), 1.42 – 0.87 (m, 21H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 173.01, 170.86, 168.75, 138.24, 128.70, 128.21, 125.80, 61.55, 49.74, 46.08, 31.92, 30.44, 28.44, 25.71, 24.26, 24.02. HRMS (ESI) $[M+H]^+$: 392.2543, Calcd. for $C_{21}H_{34}N_3O_4$: 392.2544.

***N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-*N*-(6-(hydroxyamino)-6-oxohexyl)benzamide (5d).** Slight orange solid; 27% yield; mp. 98 °C; t_R = 14.93 min, purity = 95.7%; ^{1}H NMR (500 MHz, DMSO-d_6) δ = 10.23 (s, 1H), 8.58 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.44 – 7.36 (m, 5H), 3.58 – 3.52 (m, 1H), 3.25 – 3.22 (m, 2H), 2.18 – 0.86 (m, 28H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.50, 172.36, 168.67, 138.30, 129.04, 128.27, 126.21, 63.93, 47.10, 46.60, 32.24, 31.92, 29.89, 25.79, 25.22, 25.04, 24.45, 24.32, 22.03. HRMS (ESI) $[M+H]^+$: 458.3013, Calcd. for $C_{26}H_{40}N_3O_4$: 458.3013.

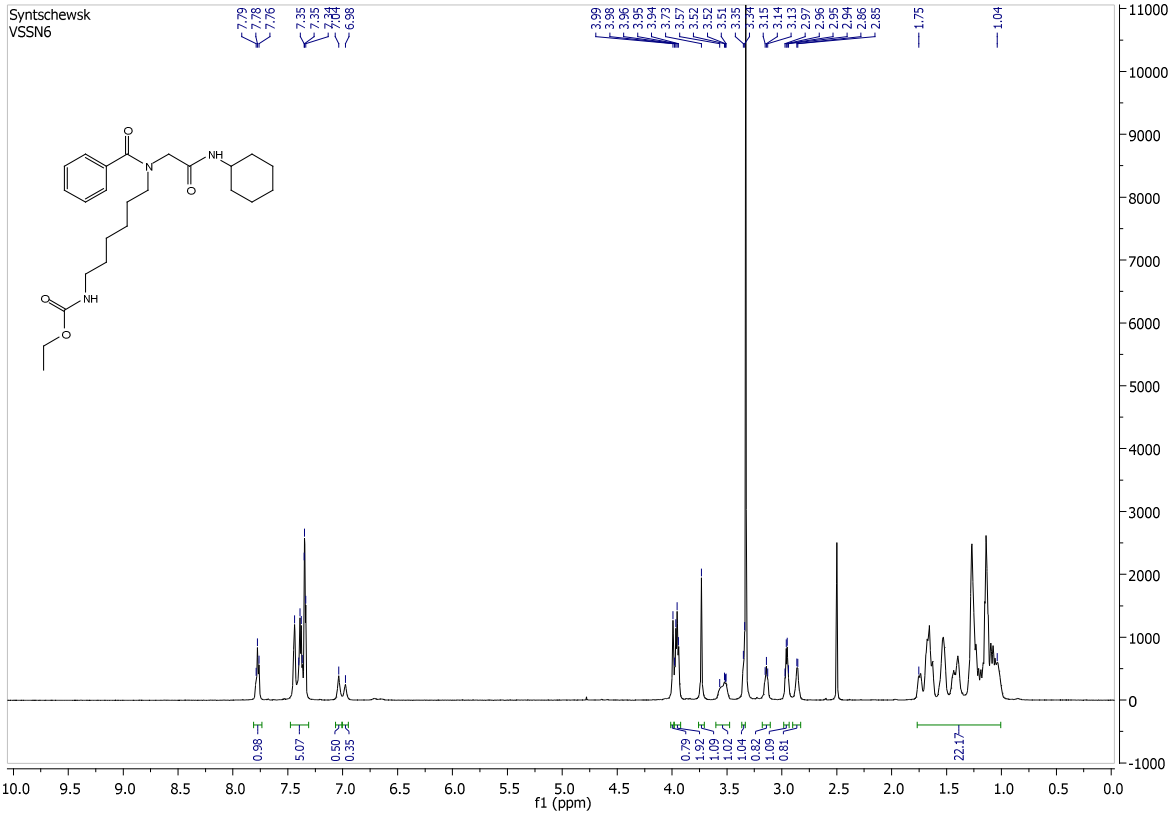
***N*-(2-(Cyclohexylamino)-2-oxo-1-phenylethyl)-*N*-(6-(hydroxyamino)-6-oxohexyl)benz-amide (5e).** White solid; 33% yield; mp. 87 °C; t_R = 14.06 min, purity = 99.3%; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 10.28 – 10.15 (m, 1H), 8.61 (s, 1H), 8.05*/7.81 (bs, 1H), 7.45 – 7.19 (m, 9H), 6.04*/5.27 (bs, 1H), 3.64 – 3.63 (m, 1H), 3.23 – 3.02 (m, 2H), 1.75 – 0.56 (m, 18H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 171.21, 171.00, 168.93, 168.16, 167.97, 137.10, 136.59, 129.22, 128.88, 128.55, 128.04, 126.16, 65.05, 60.86, 47.70, 46.97, 46.83, 44.89, 32.12, 25.17, 24.55, 24.48. HRMS (ESI) $[M+H]^+$: 466.2698, Calcd. for $C_{27}H_{36}N_3O_4$: 466.2700.

***N*-(2-(Cyclohexylamino)-2-oxo-1-(*p*-tolyl)ethyl)-*N*-(6-(hydroxyamino)-6-oxohexyl)benz-amide (5f).** White solid; 47% yield; mp. 80 °C; t_R = 14.10 min, purity = 96.4%; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 10.26 – 10.24 (m, 1H), 8.62 – 8.61 (m, 1H), 7.94/7.75* (s, 1H), 7.44 – 7.06 (m, 9H), 5.99/5.22* (s, 1H), 3.63 – 3.61 (m, 1H), 3.21 – 3.05 (m, 2H), 2.30 (s,

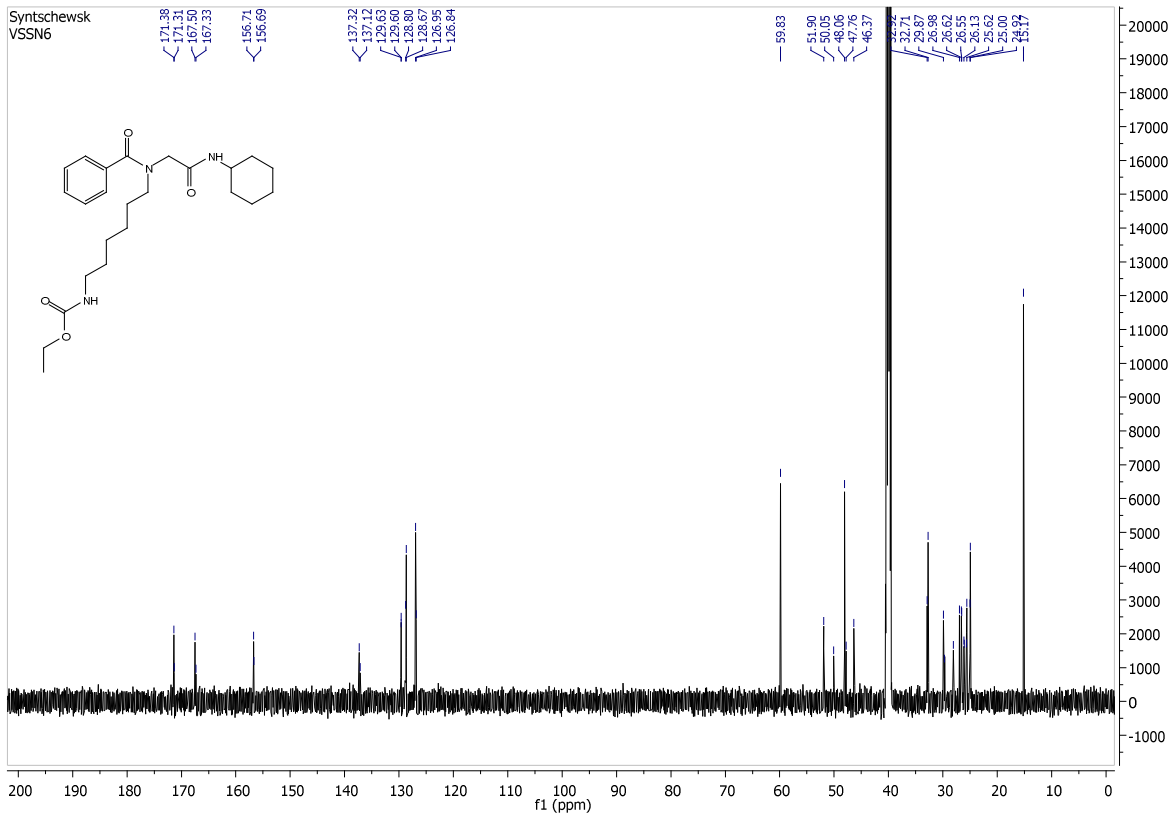
3H), 1.76 – 0.67 (m, 18H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 168.95, 168.87, 168.47, 137.31, 137.14, 133.48, 129.17, 129.07, 128.92, 128.51, 128.36, 126.15, 47.67, 32.20, 32.11, 26.01, 25.15, 24.54, 24.47, 20.68. HRMS (ESI) $[M+H]^+$: 480.2856, Calcd. for $C_{28}H_{37}N_3O_4$: 480.2857.

3. Spectral data

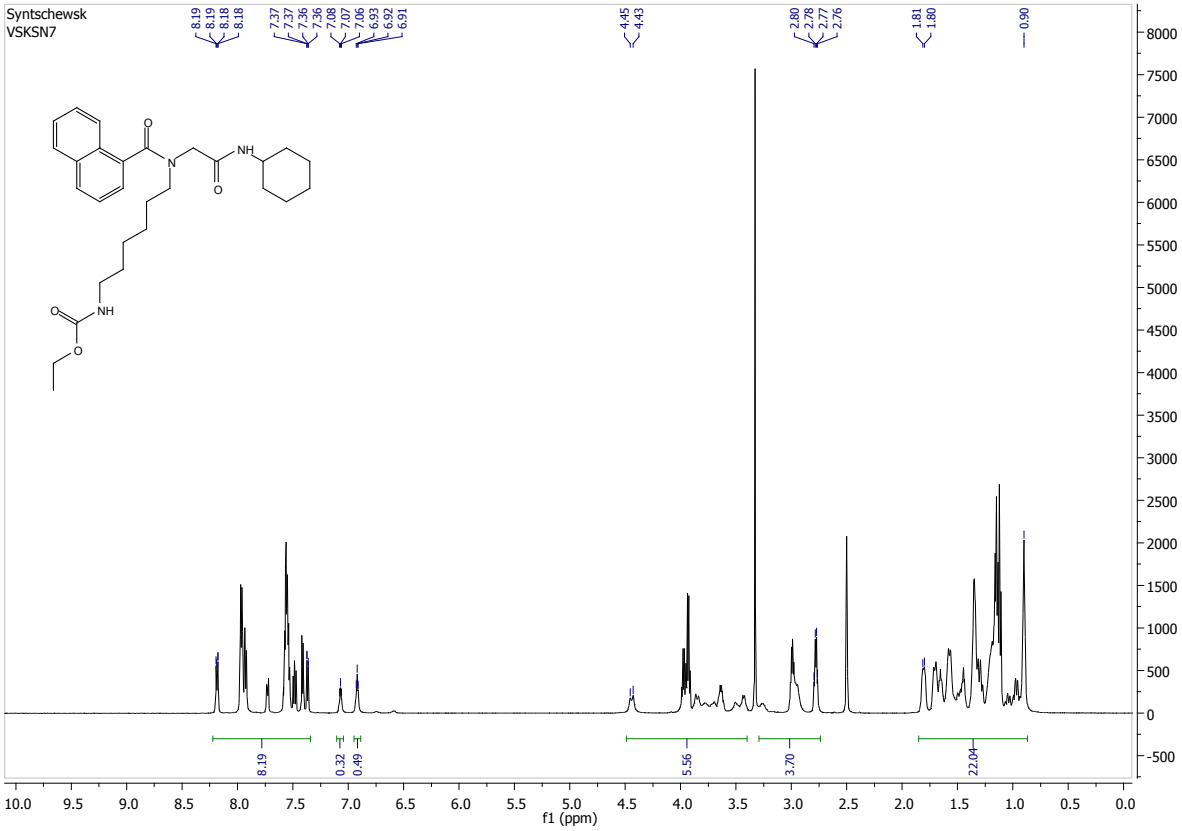
Copies of ^{1}H NMR and ^{13}C NMR spectra



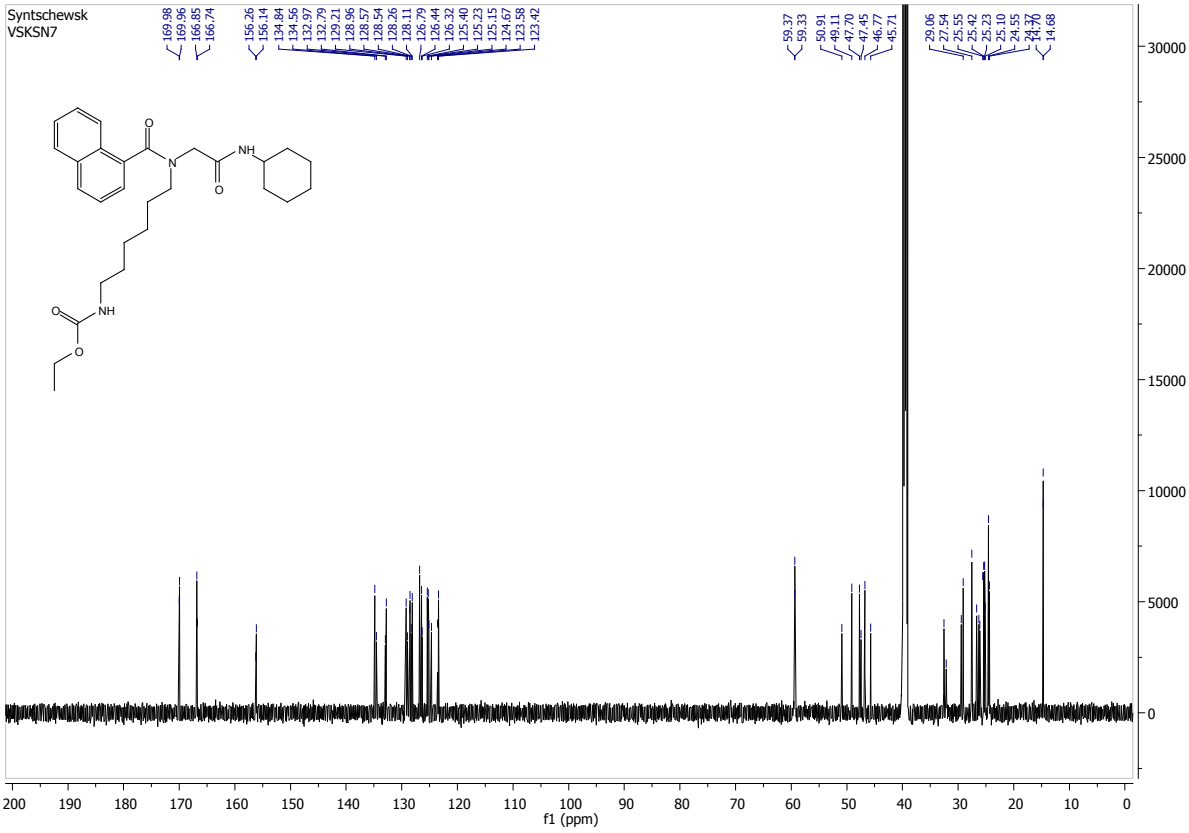
^{1}H NMR (600 MHz, DMSO-d_6) of compound **1a**.



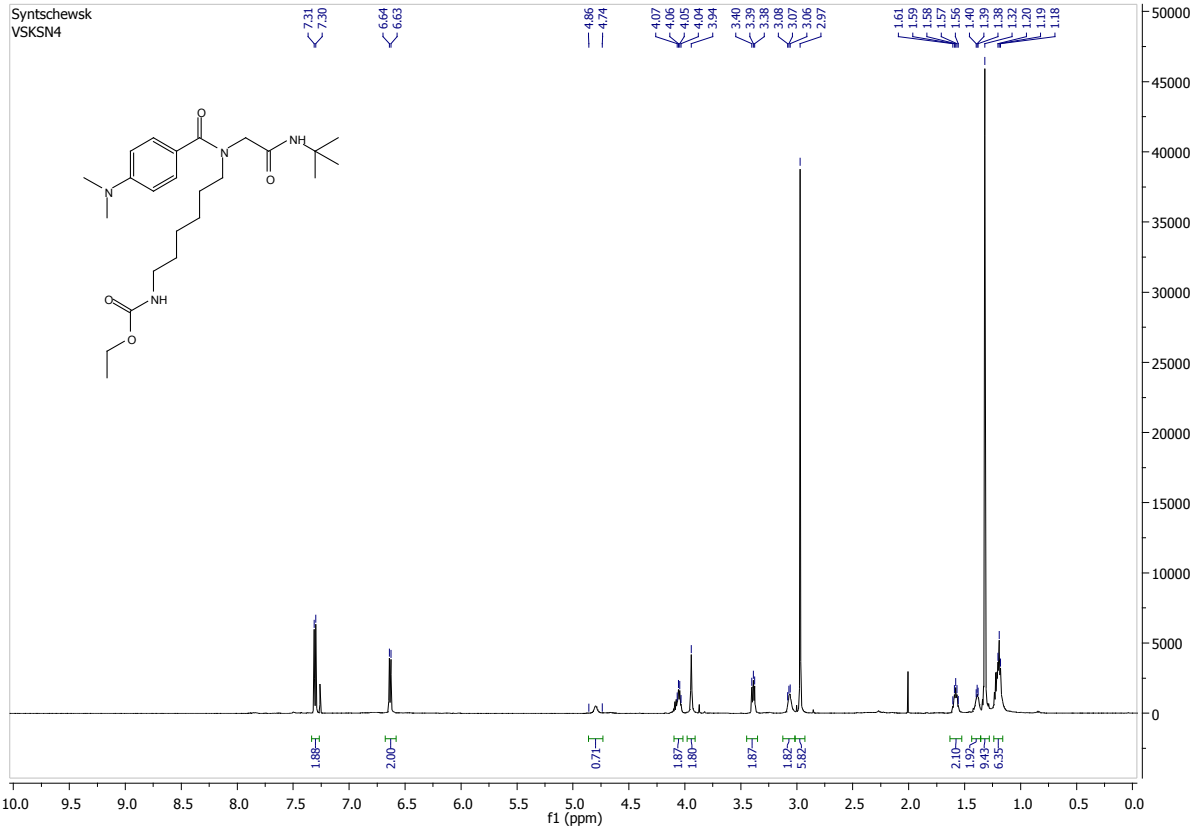
^{13}C NMR (151 MHz, DMSO-d_6) of compound **1a**.



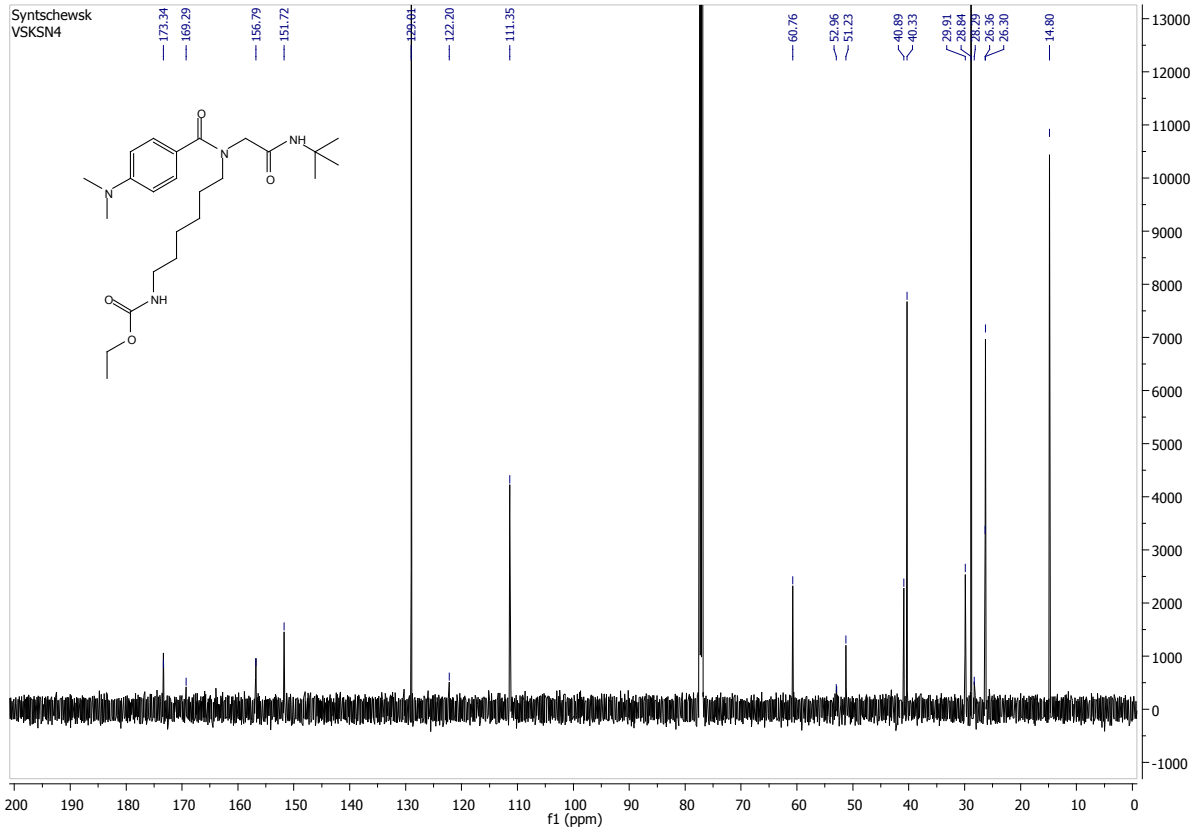
^{1}H NMR (600 MHz, DMSO-d_6) of compound **1b**.



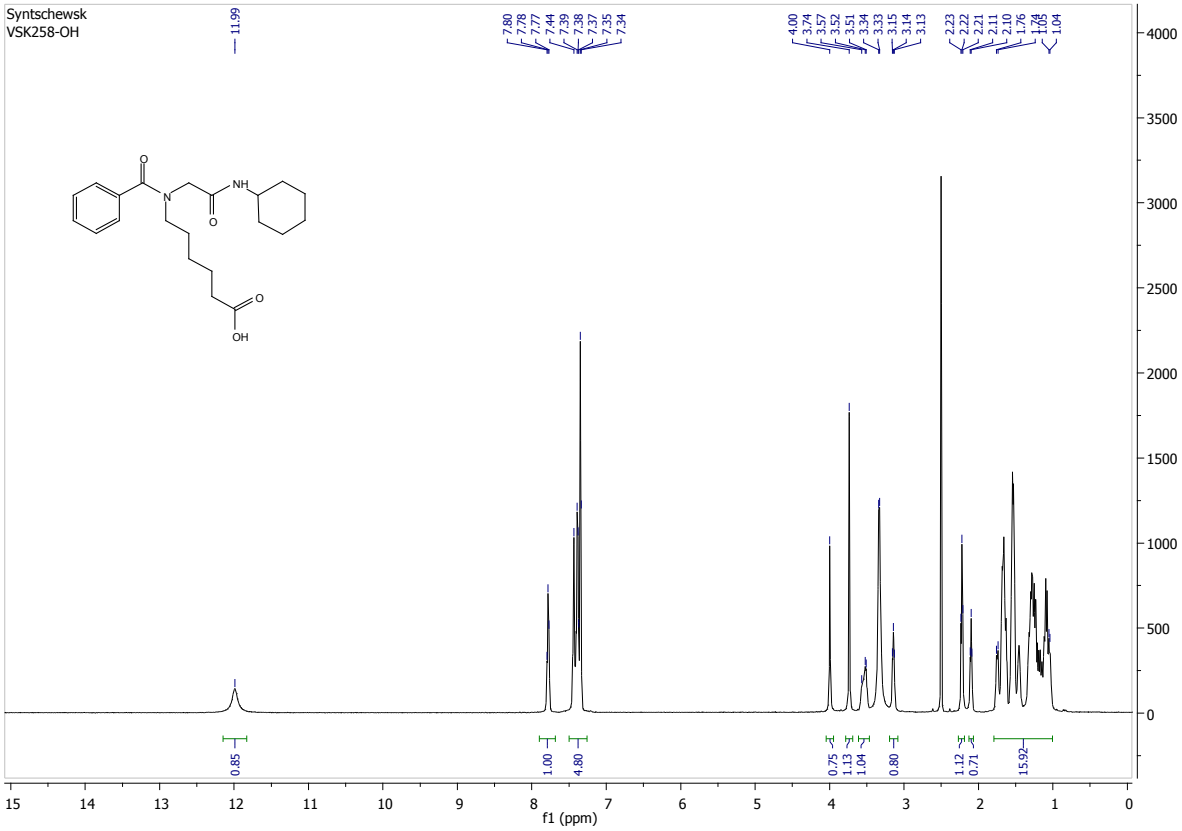
^{13}C NMR (151 MHz, DMSO-d_6) of compound **1b**.



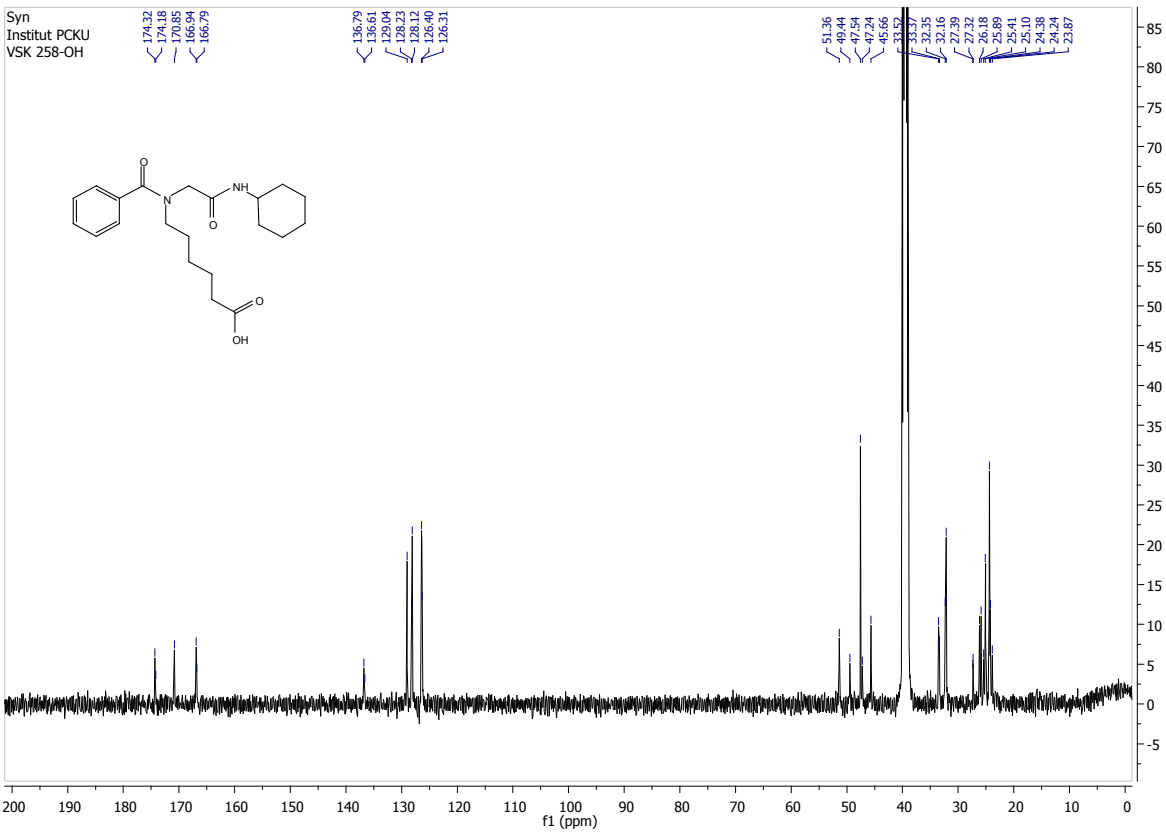
^{1}H NMR (600 MHz, $CDCl_3$) of compound **1c**.



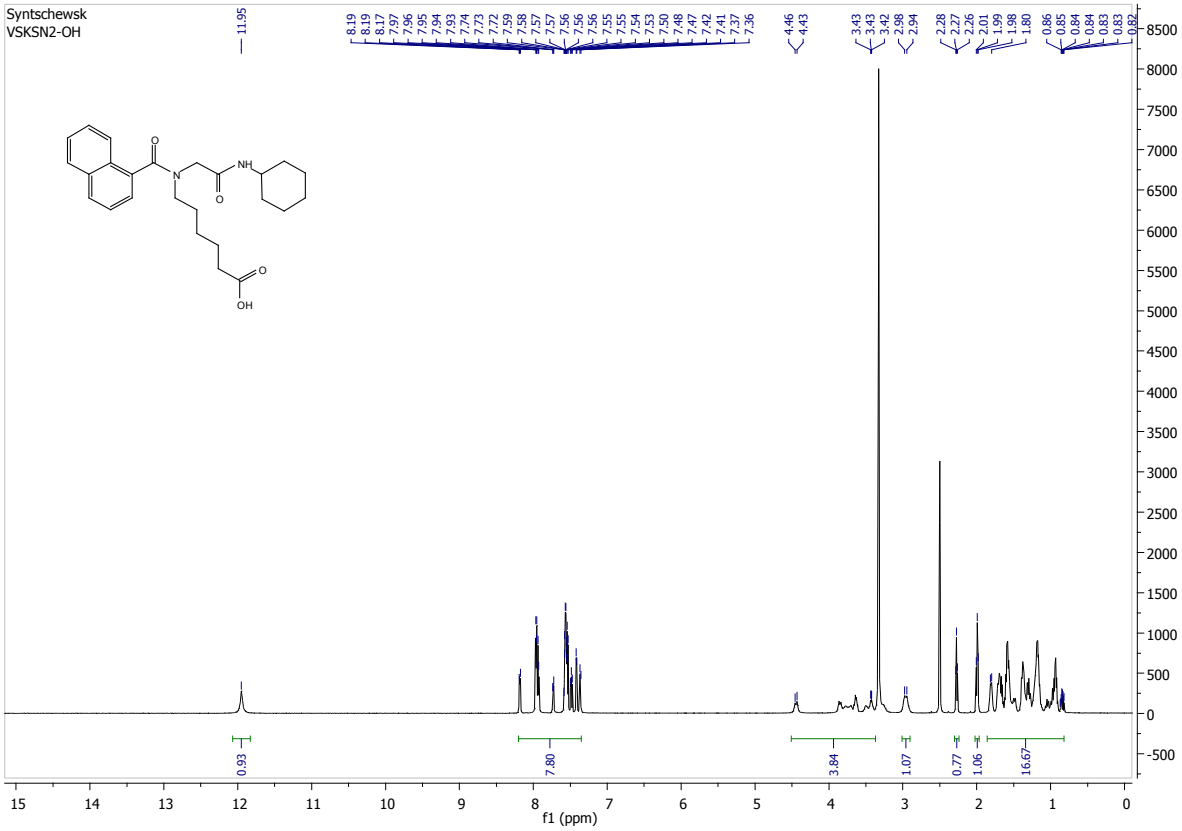
^{13}C NMR (151 MHz, $CDCl_3$) of compound **1c**.



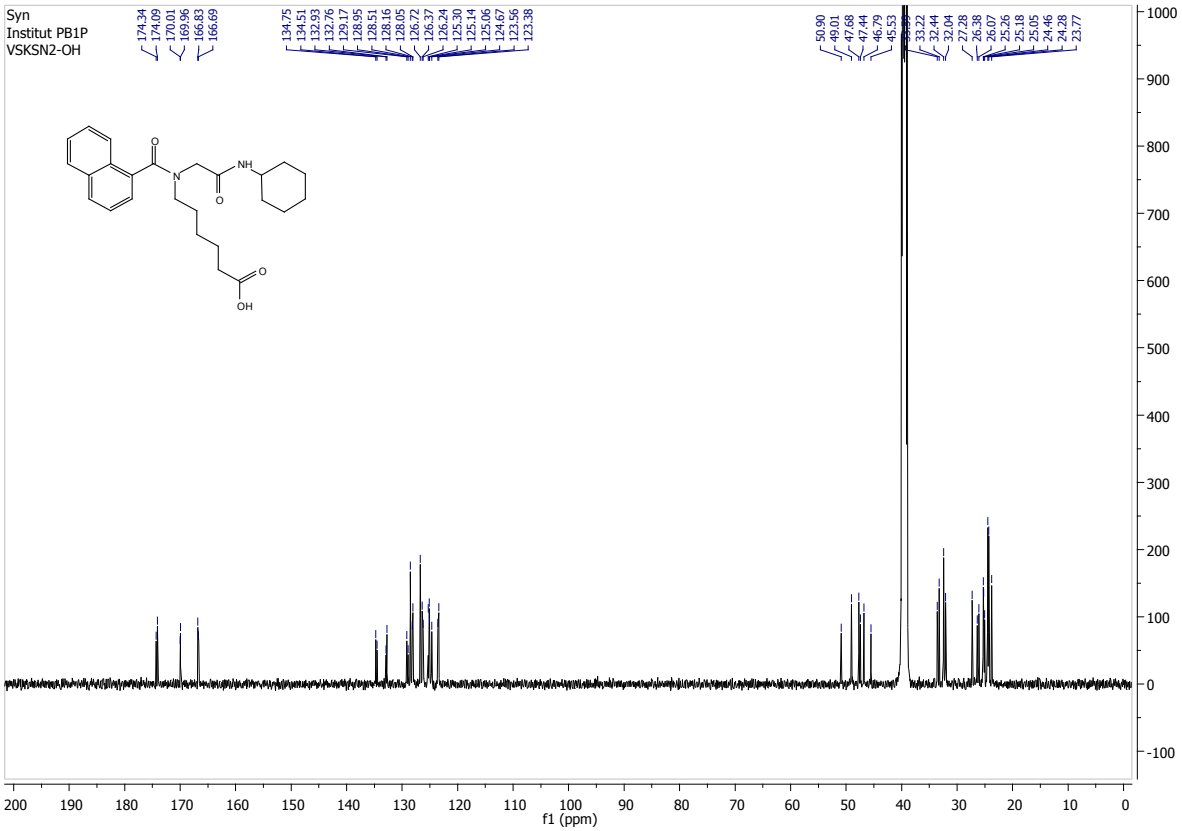
^{1}H NMR (600 MHz, DMSO-d_6) of compound **2a**.



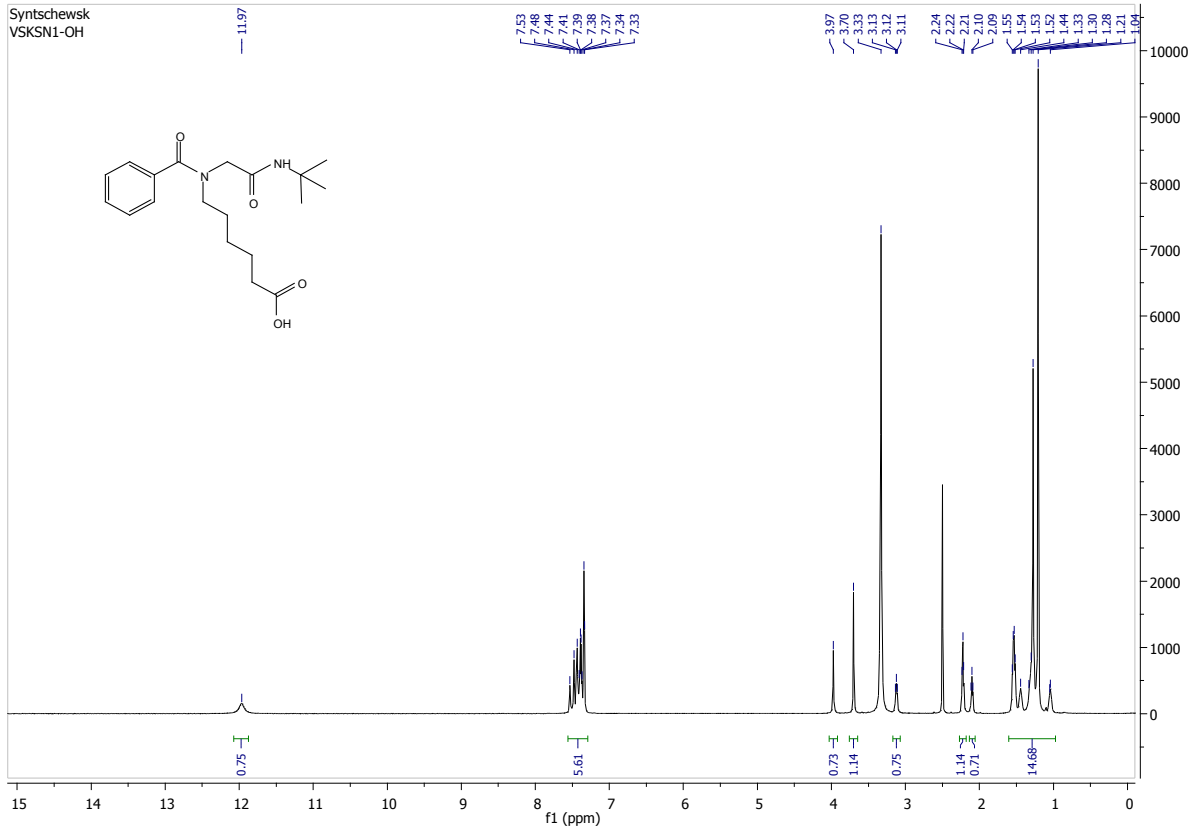
^{13}C NMR (126 MHz, DMSO-d_6) of compound **2a**.



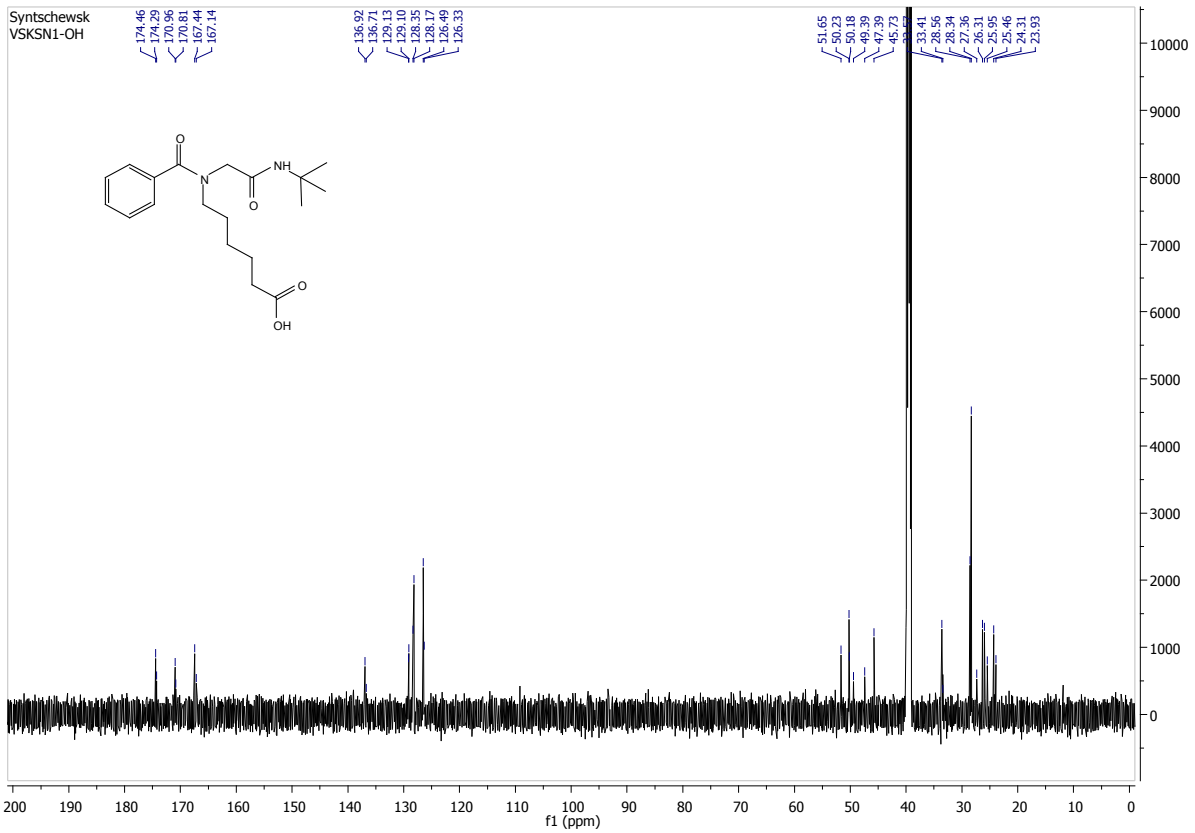
^{1}H NMR (600 MHz, DMSO-d_6) of compound **2b**.



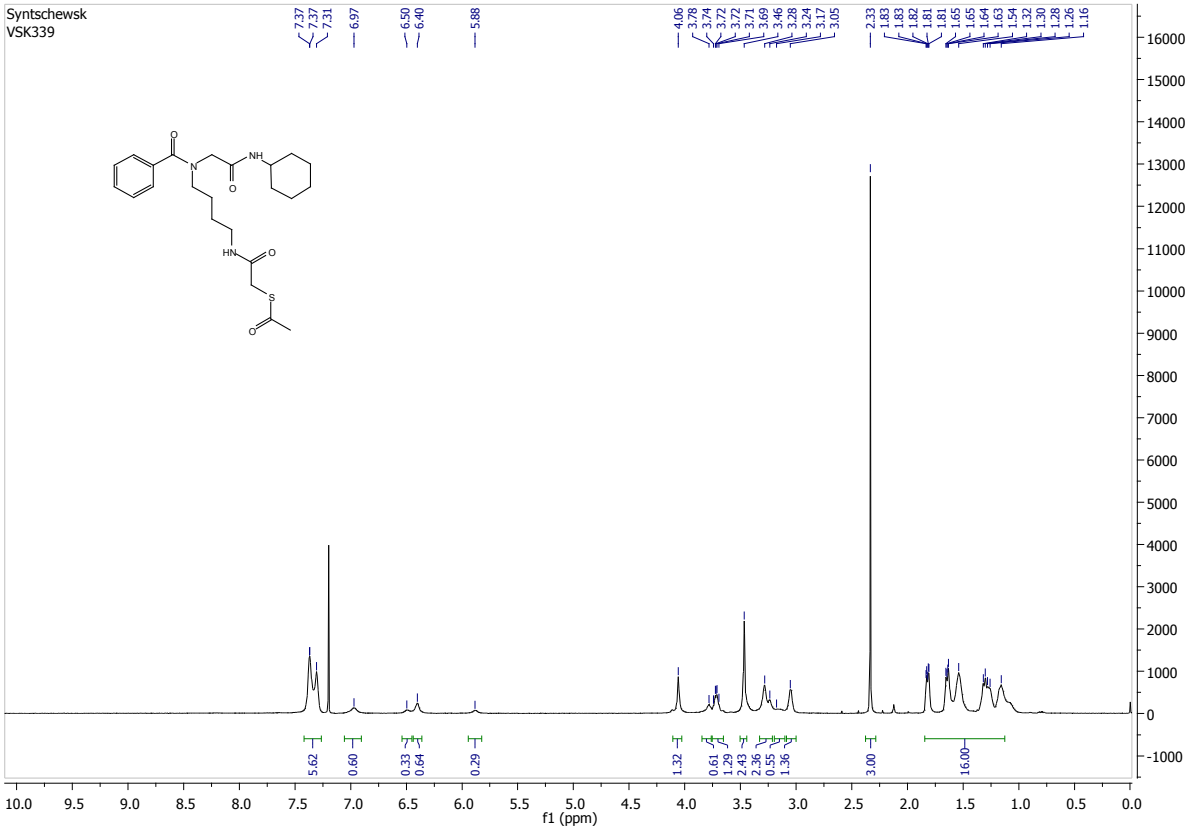
^{13}C NMR (126 MHz, DMSO-d_6) of compound **2b**.



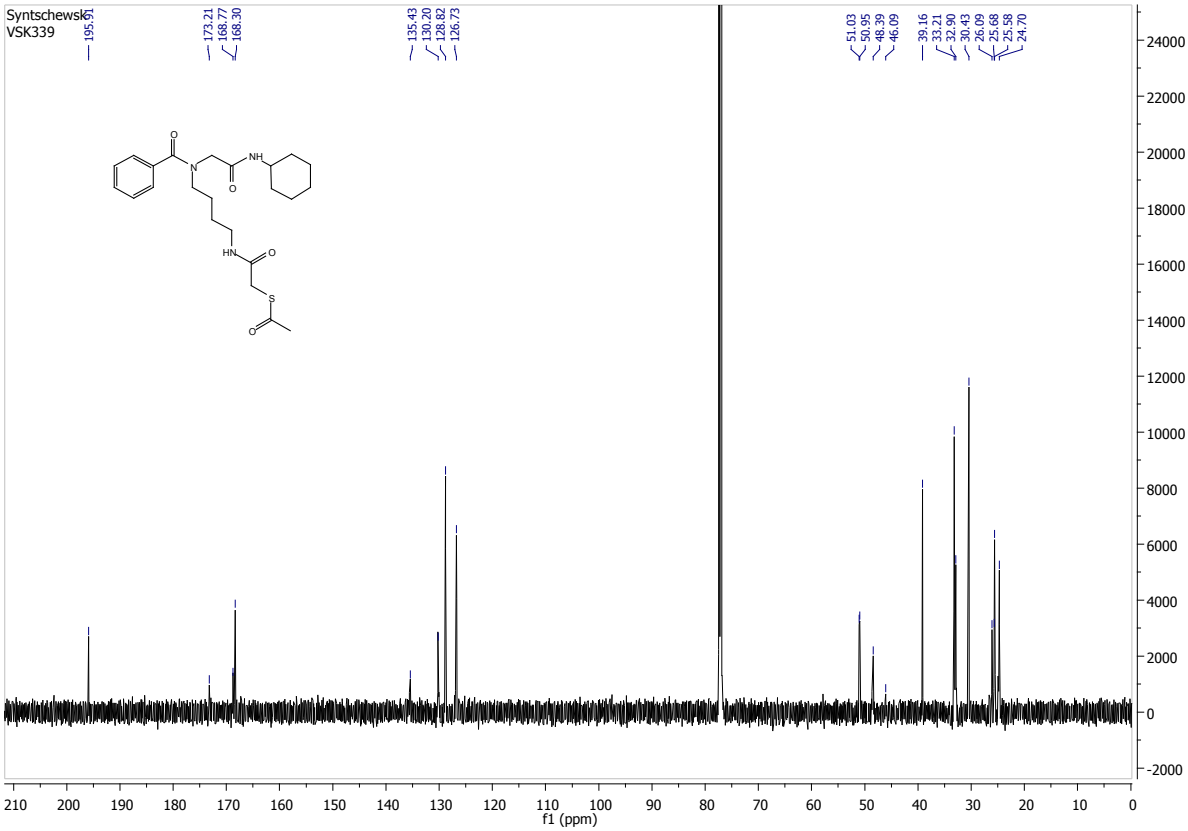
^{1}H NMR (600 MHz, DMSO-d_6) of compound **2c**.



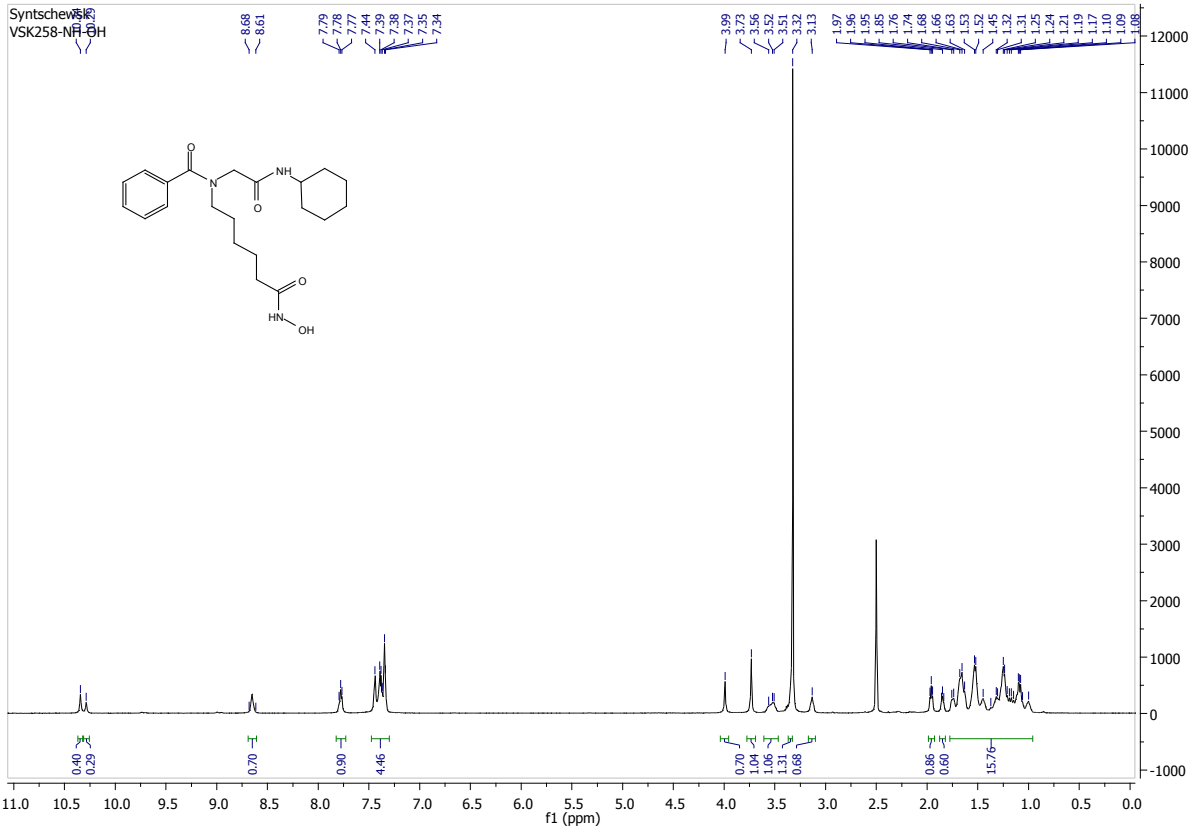
^{13}C NMR (151 MHz, DMSO-d_6) of compound **2c**.



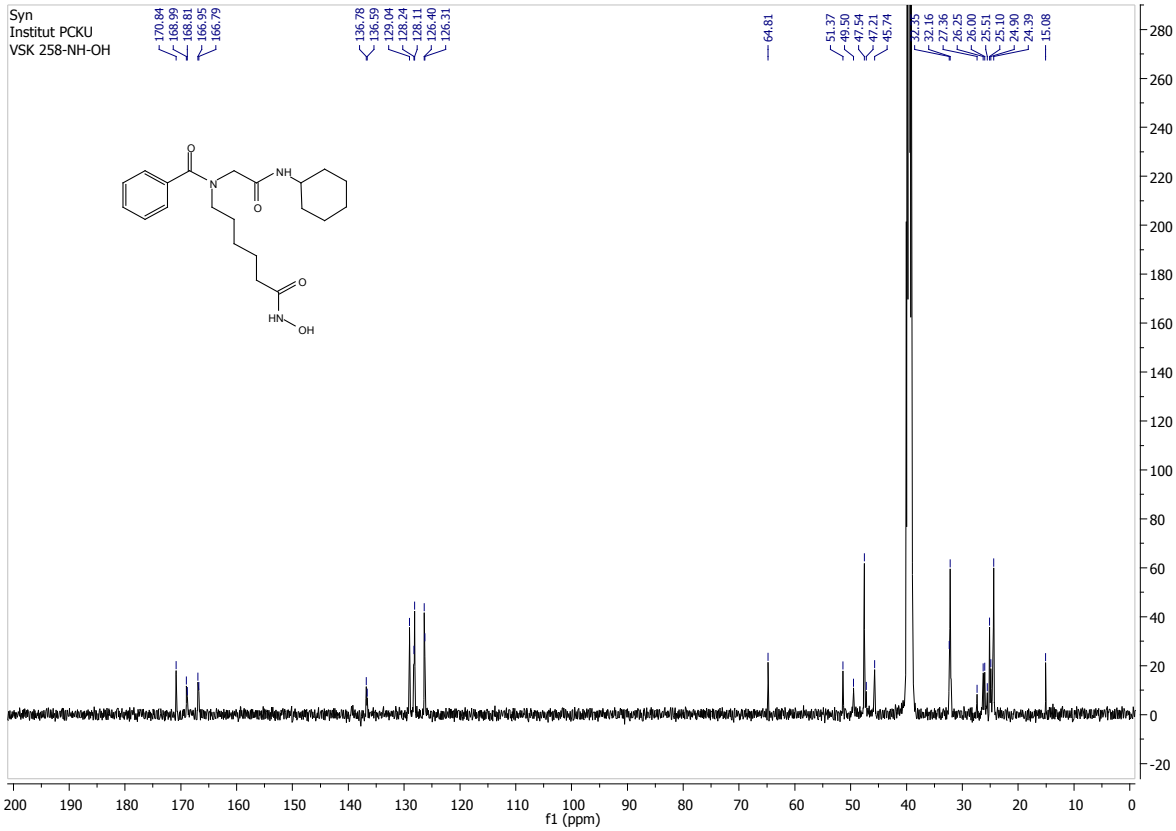
^{1}H NMR (600 MHz, $CDCl_3$) of compound **3**.



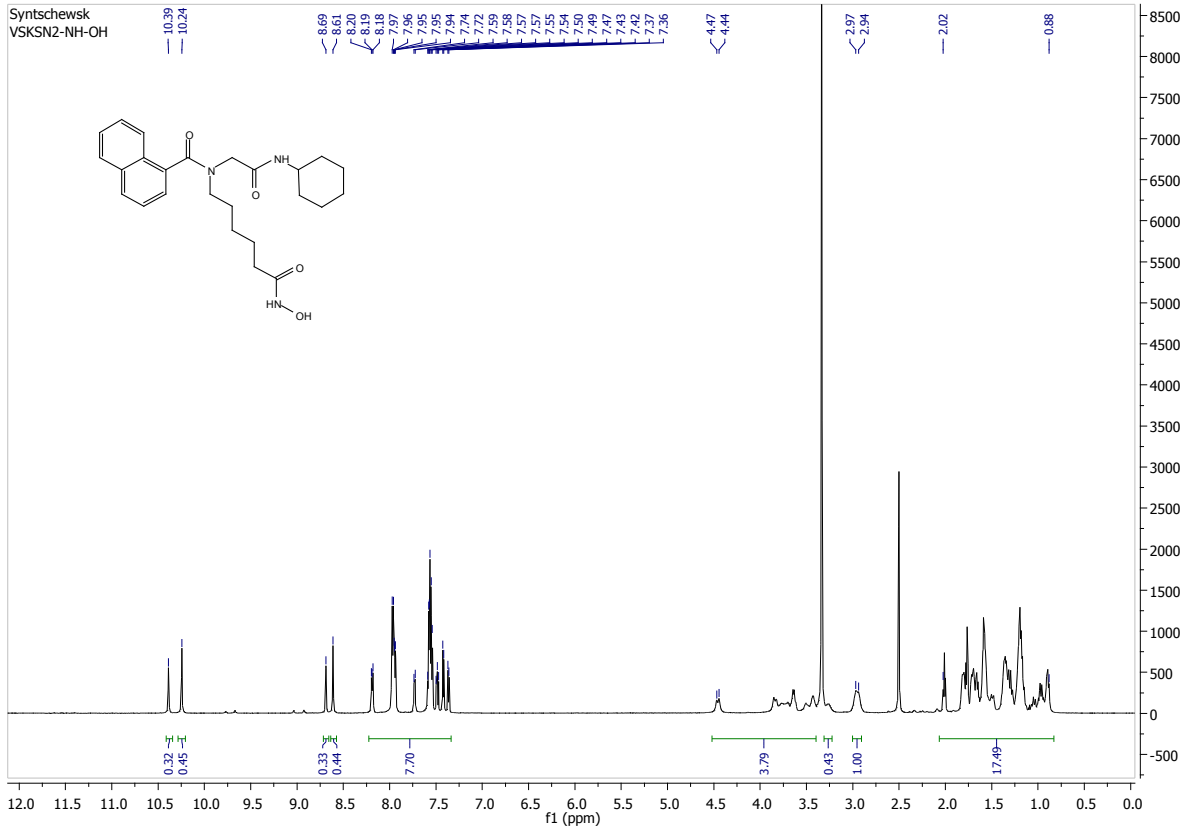
^{13}C NMR (151 MHz, $CDCl_3$) of compound **3**.



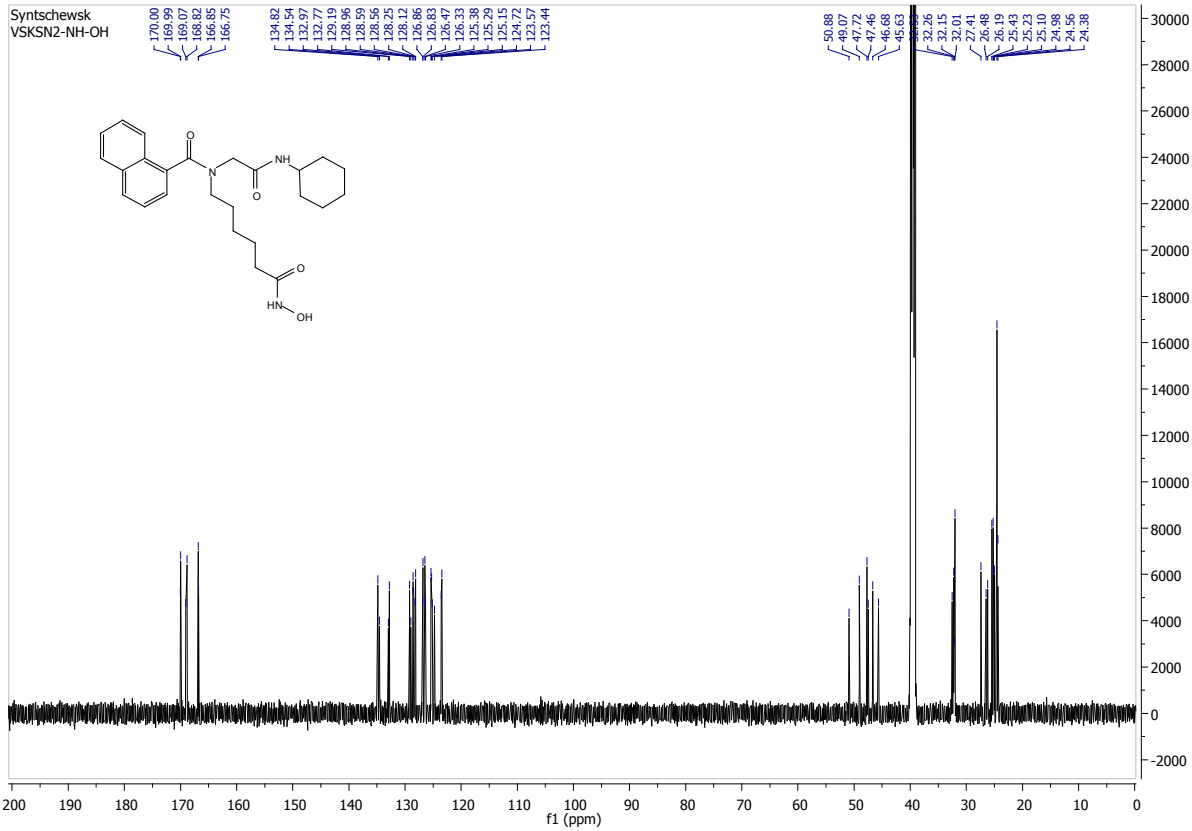
^{1}H NMR (600 MHz,DMSO-d_6) of compound **4a**.



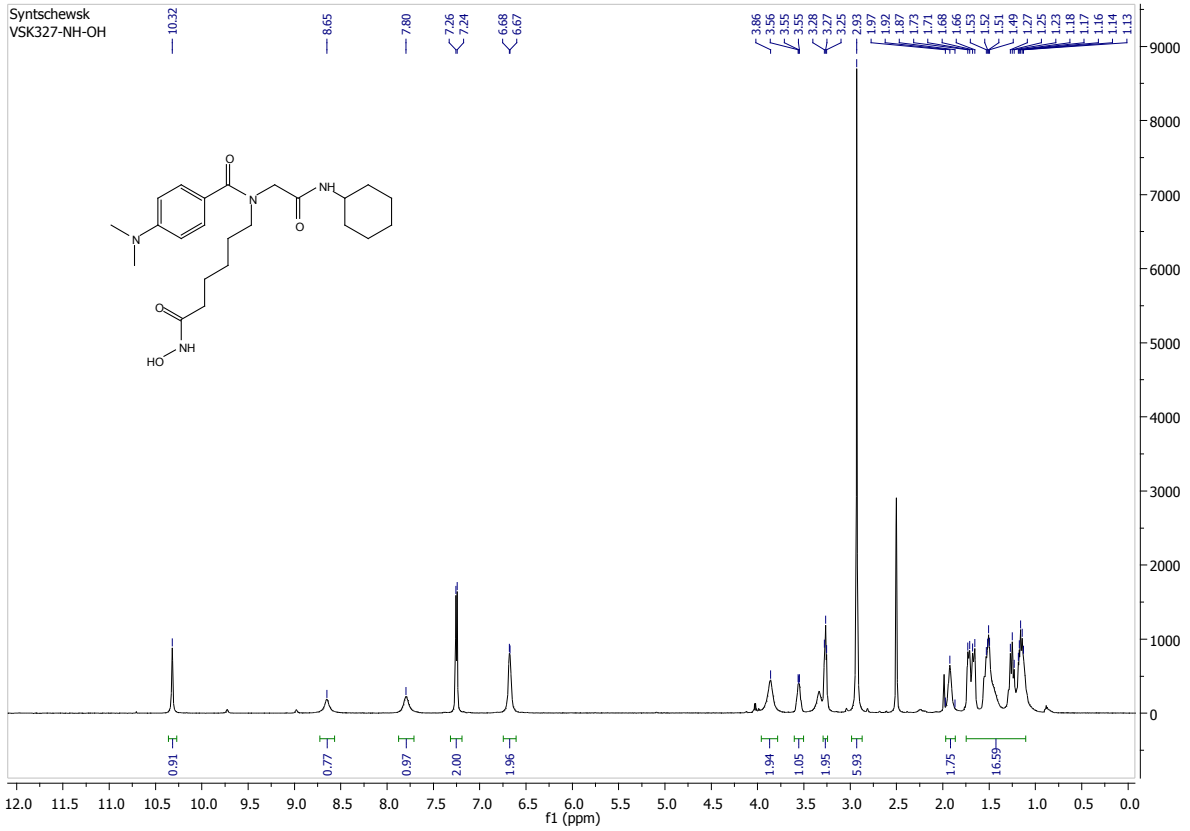
^{13}C NMR (126 MHz, DMSO-d_6) of compound **4a**.



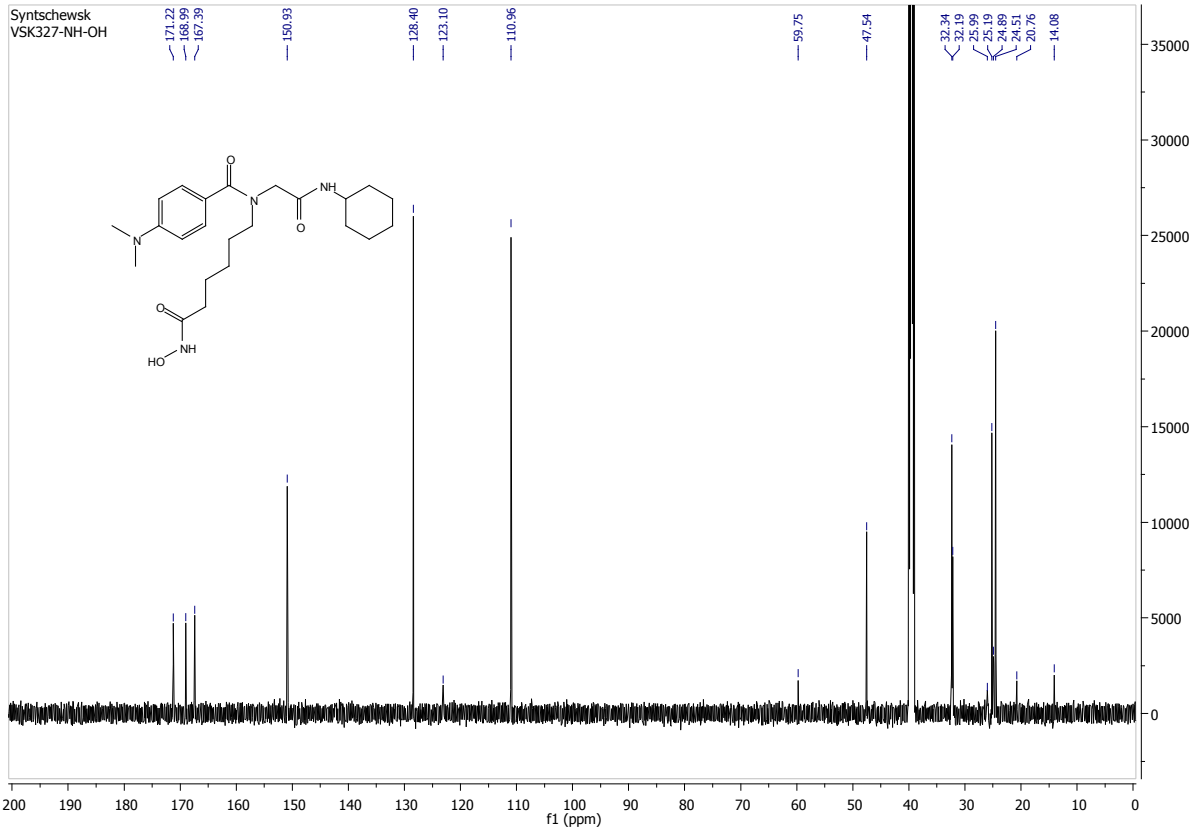
^{1}H NMR (600 MHz, DMSO-d_6) of compound **4b**.



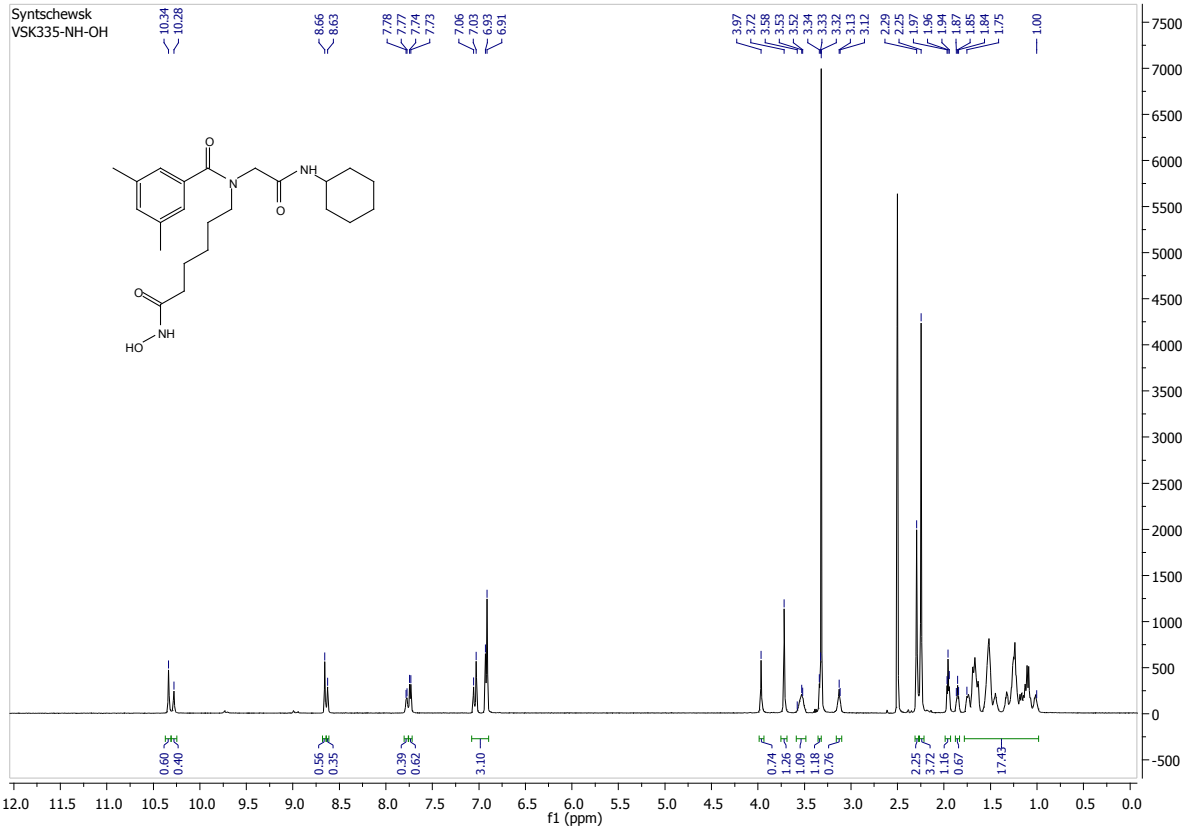
^{13}C NMR (151 MHz, DMSO-d_6) of compound **4b**.



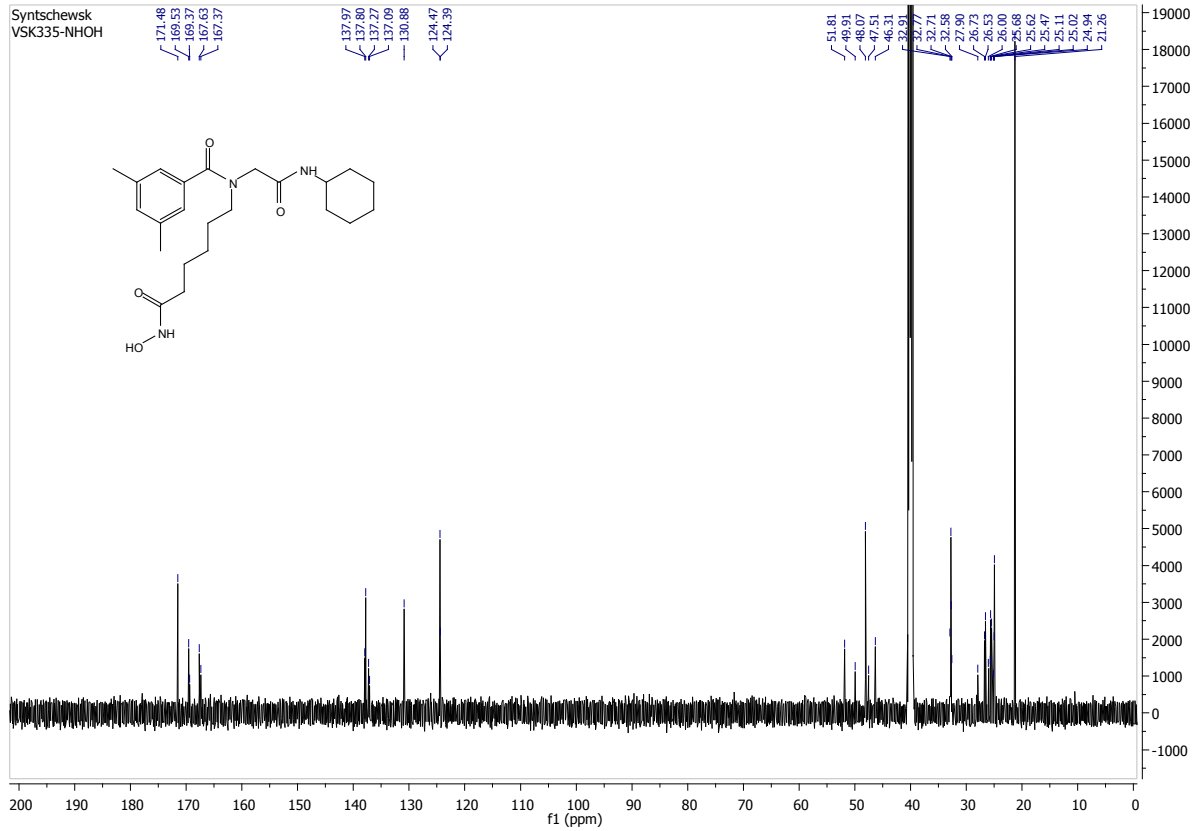
^{1}H NMR (600 MHz, DMSO-d_6) of compound **4c**.



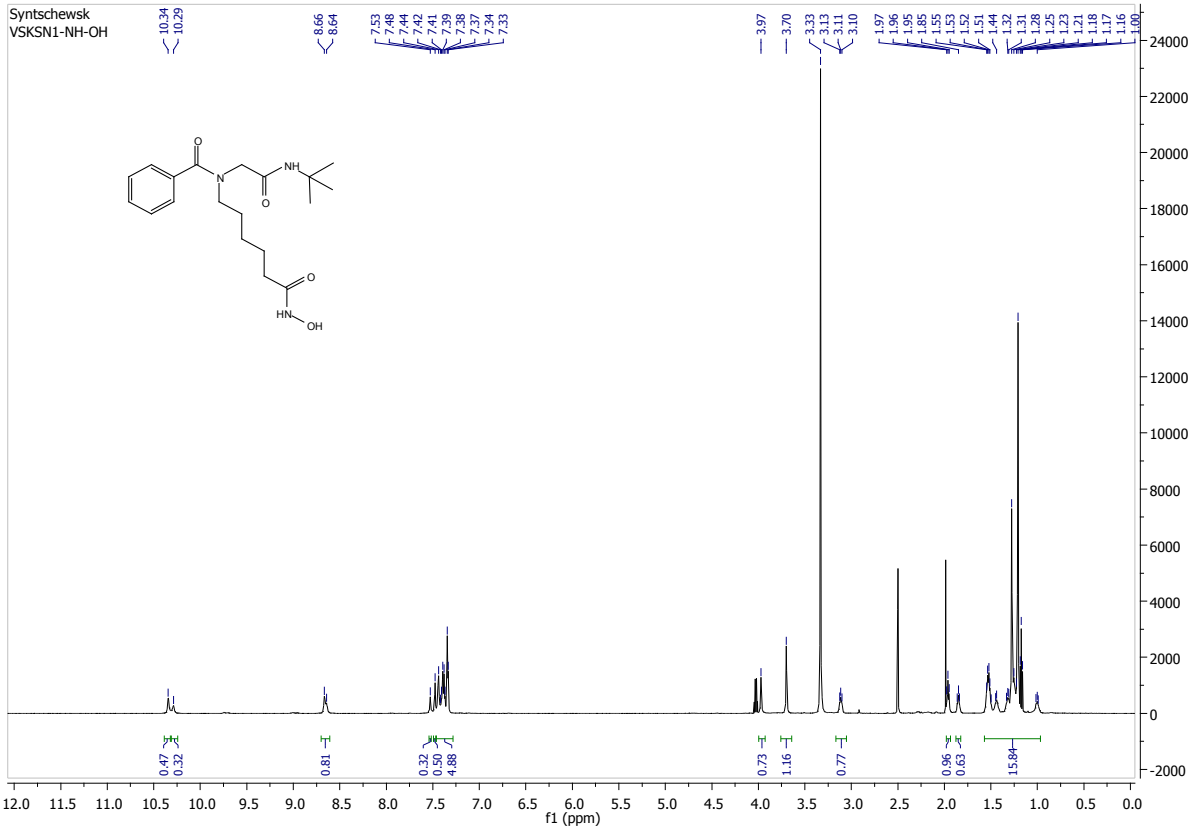
^{13}C NMR (151 MHz, DMSO-d_6) of compound **4c**.



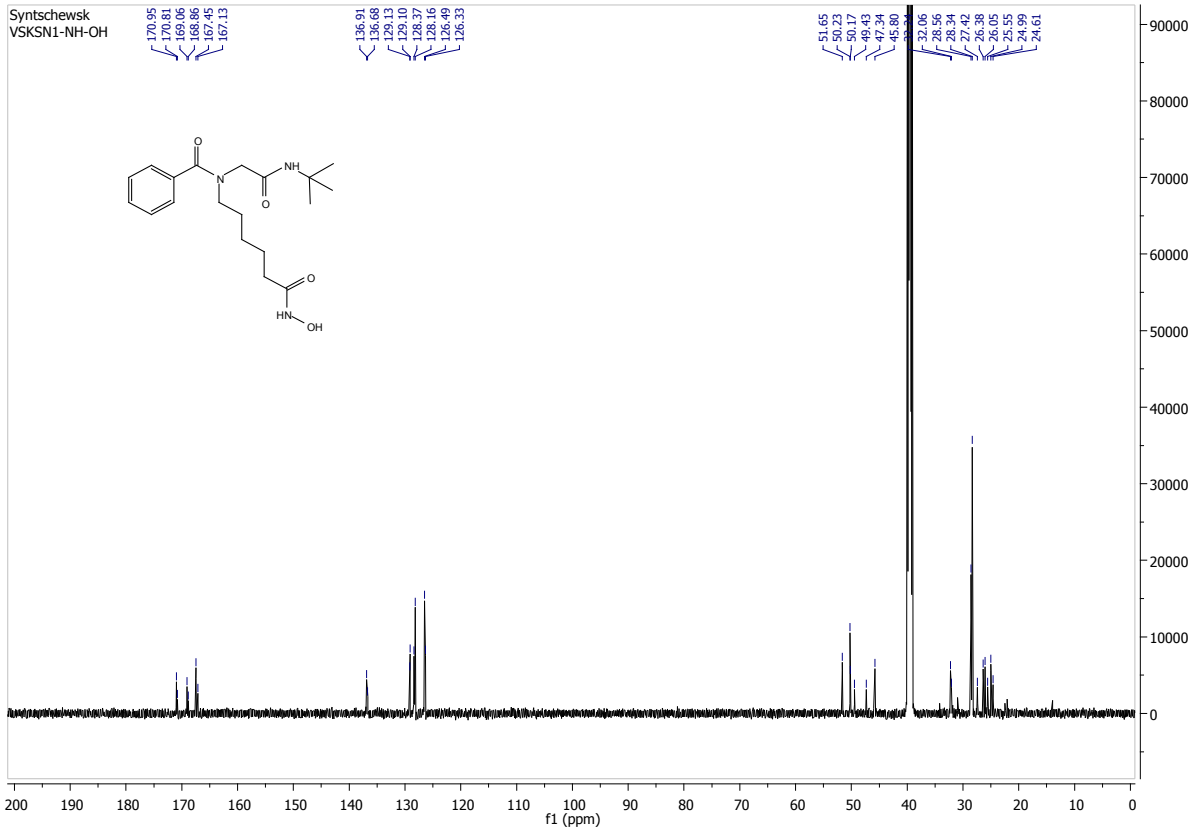
^{1}H NMR (600 MHz, DMSO-d_6) of compound **4d**.



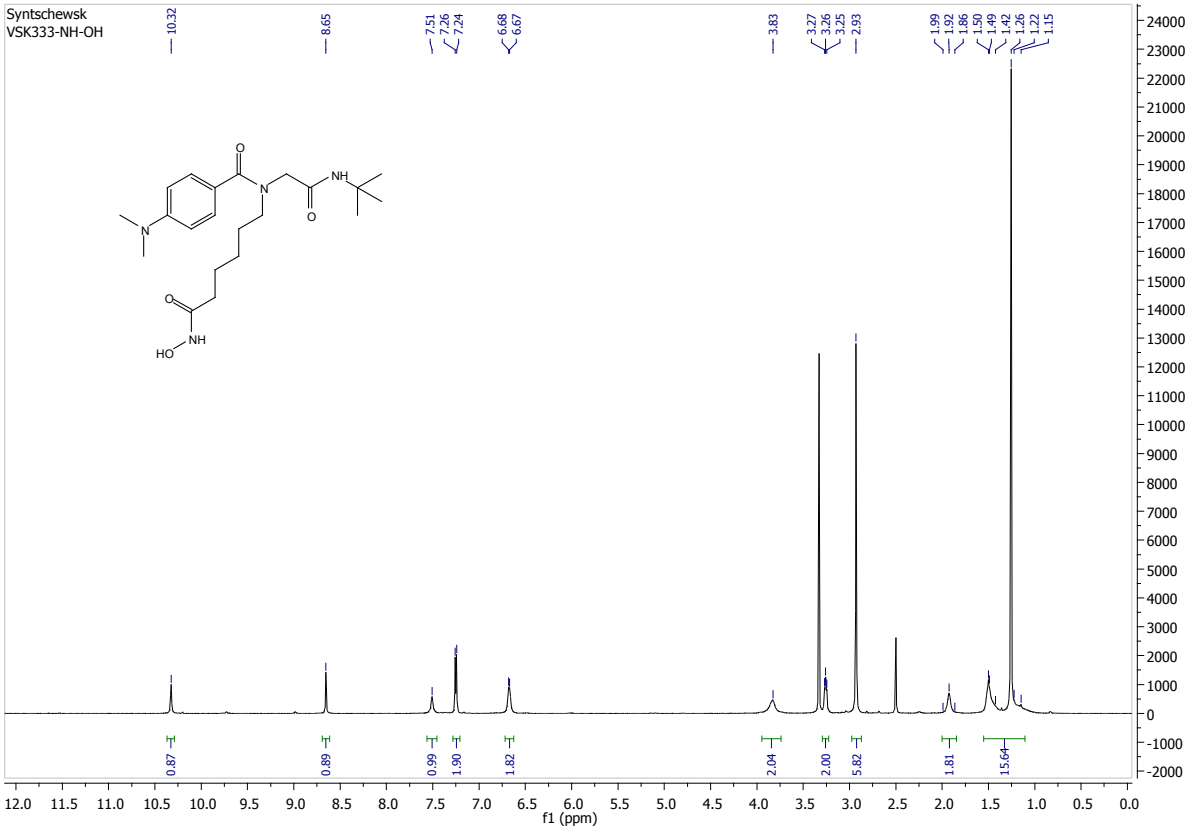
^{13}C NMR (151 MHz, DMSO-d_6) of compound **4d**.



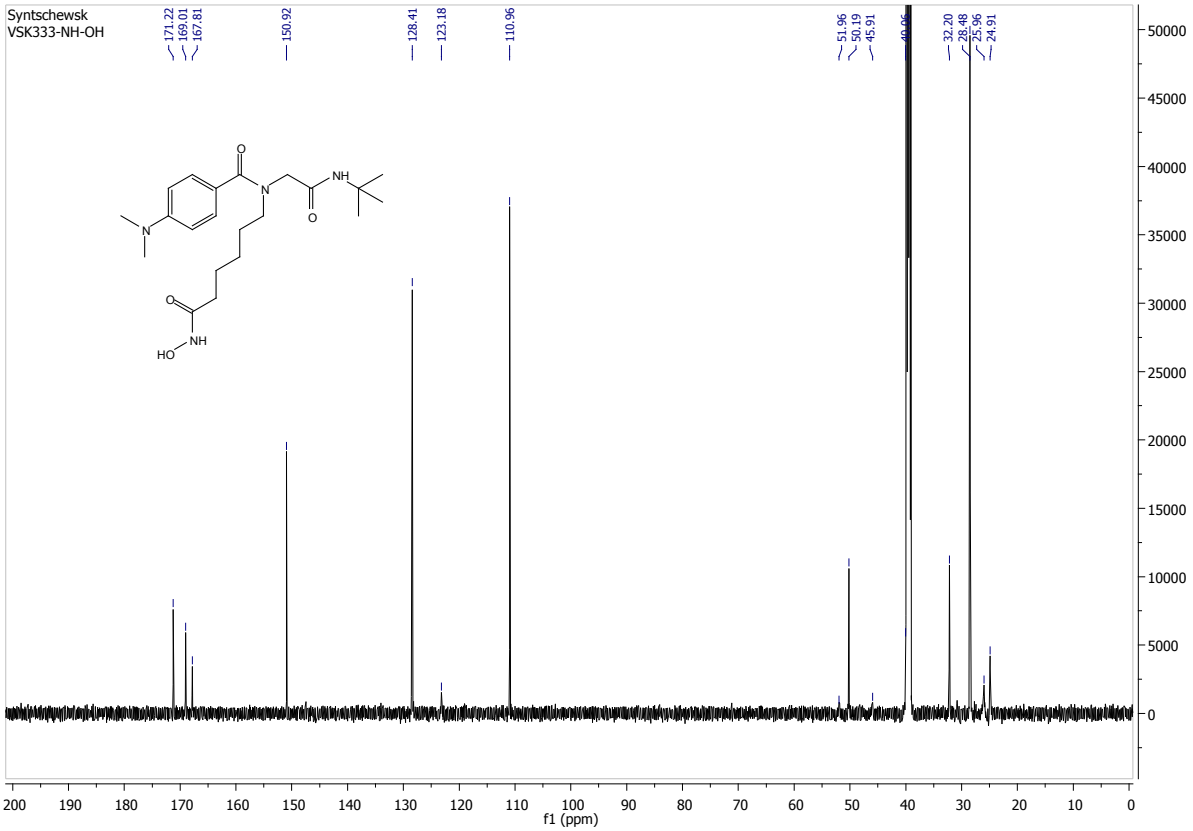
^{1}H NMR (600 MHz, DMSO-d_6) of compound **4e**.



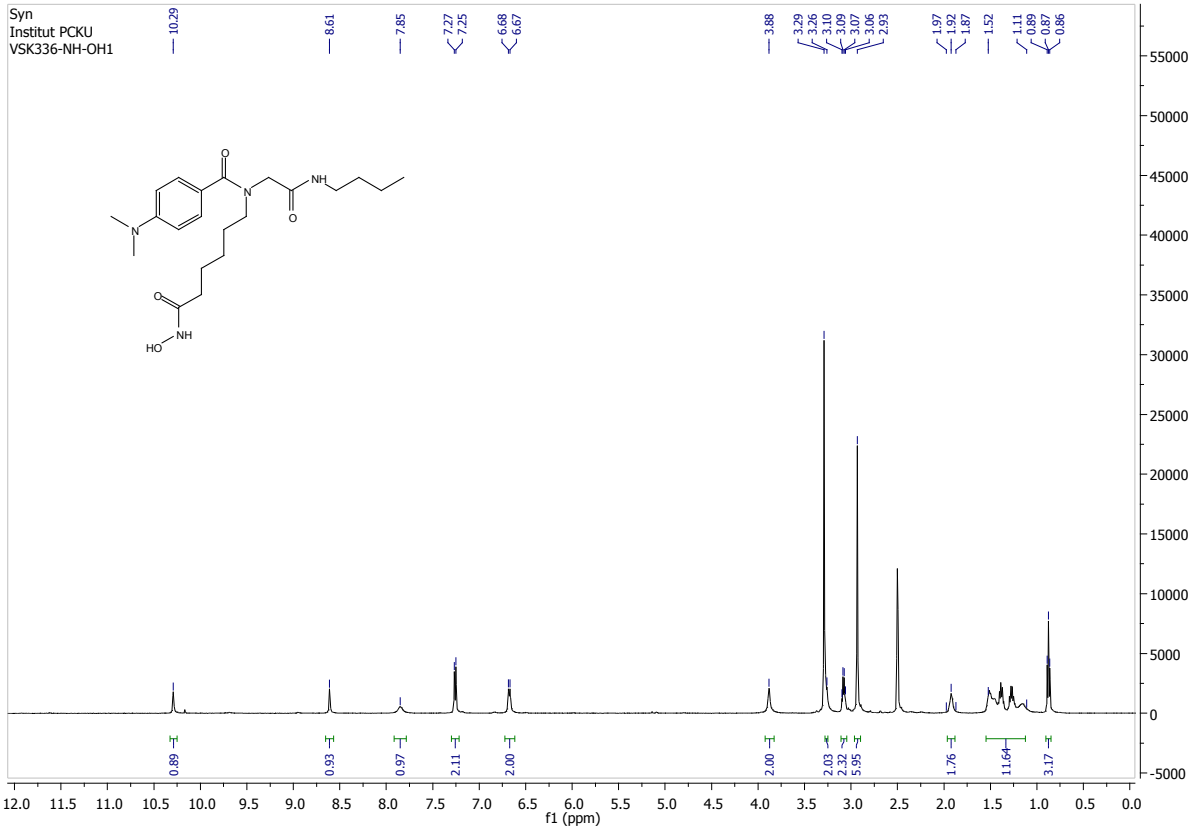
^{13}C NMR (151 MHz, DMSO-d_6) of compound **4e**.



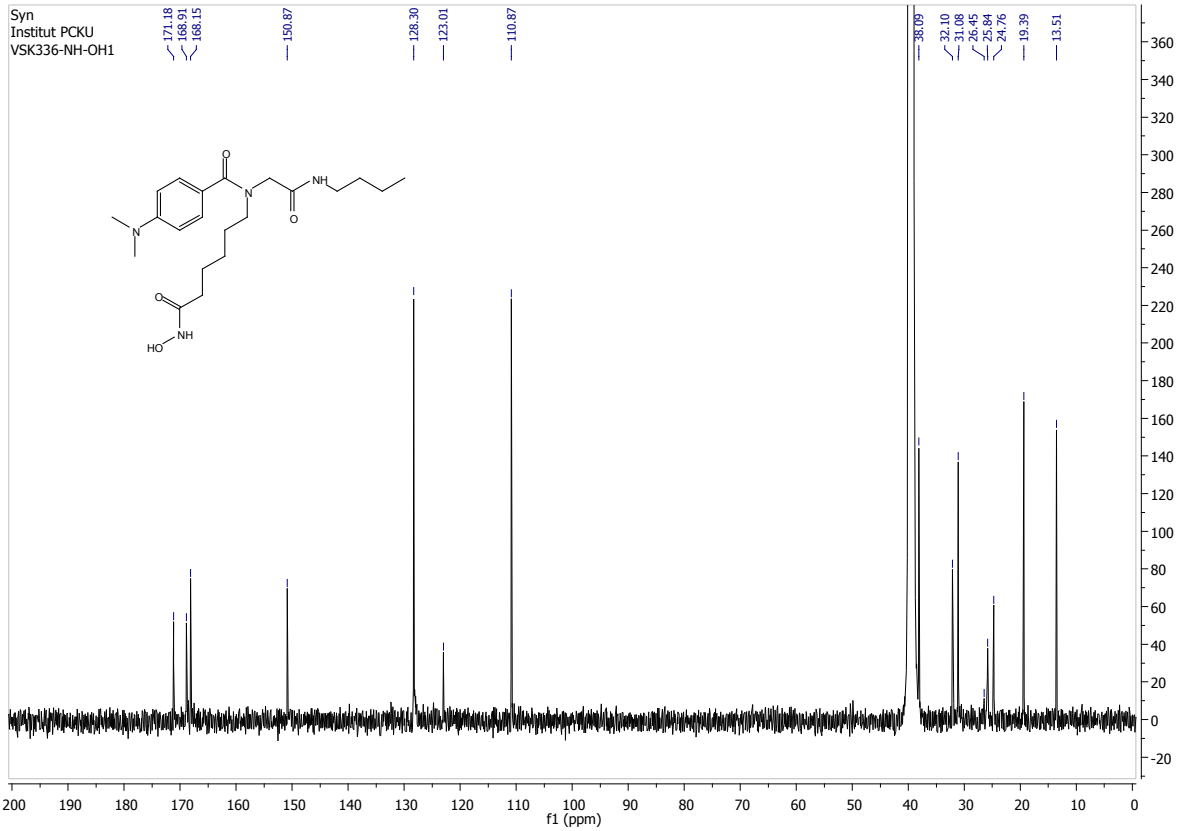
^{1}H NMR (600 MHz, DMSO-d_6) of compound **4f**.



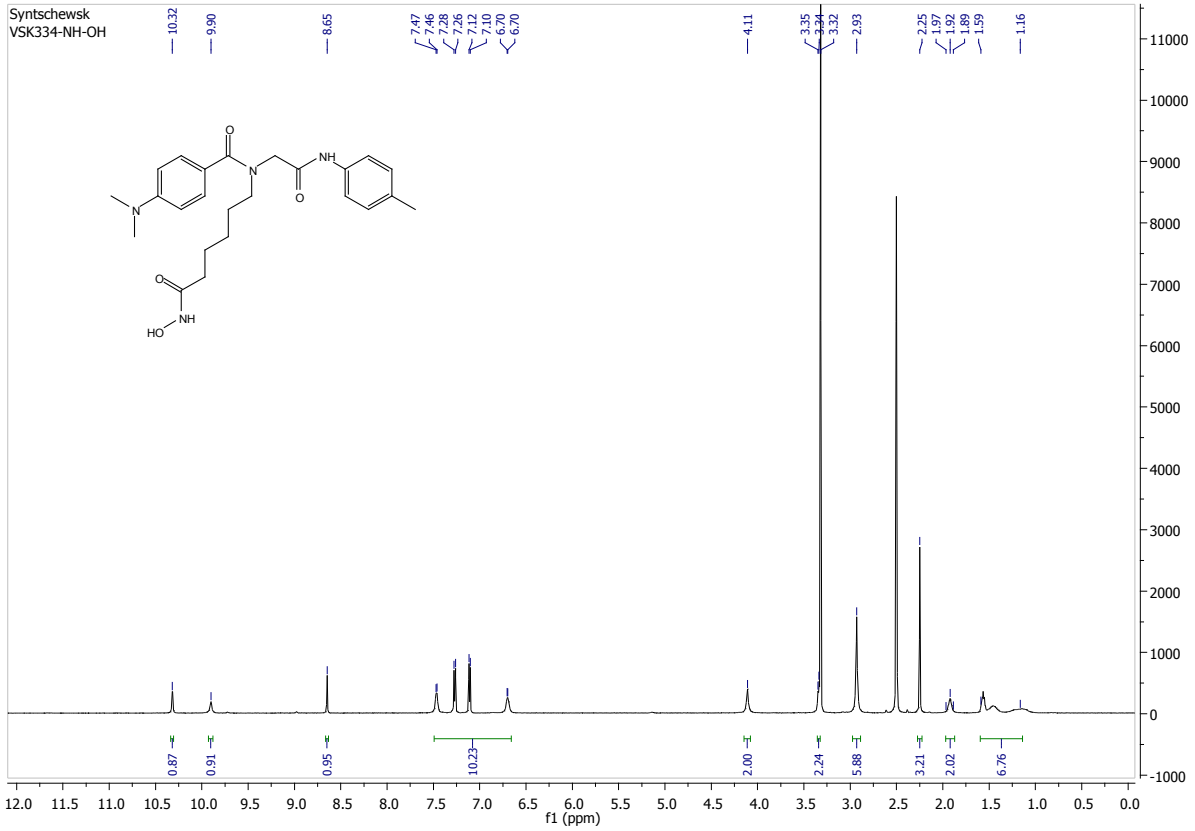
^{13}C NMR (151 MHz, DMSO-d_6) of compound **4f**.



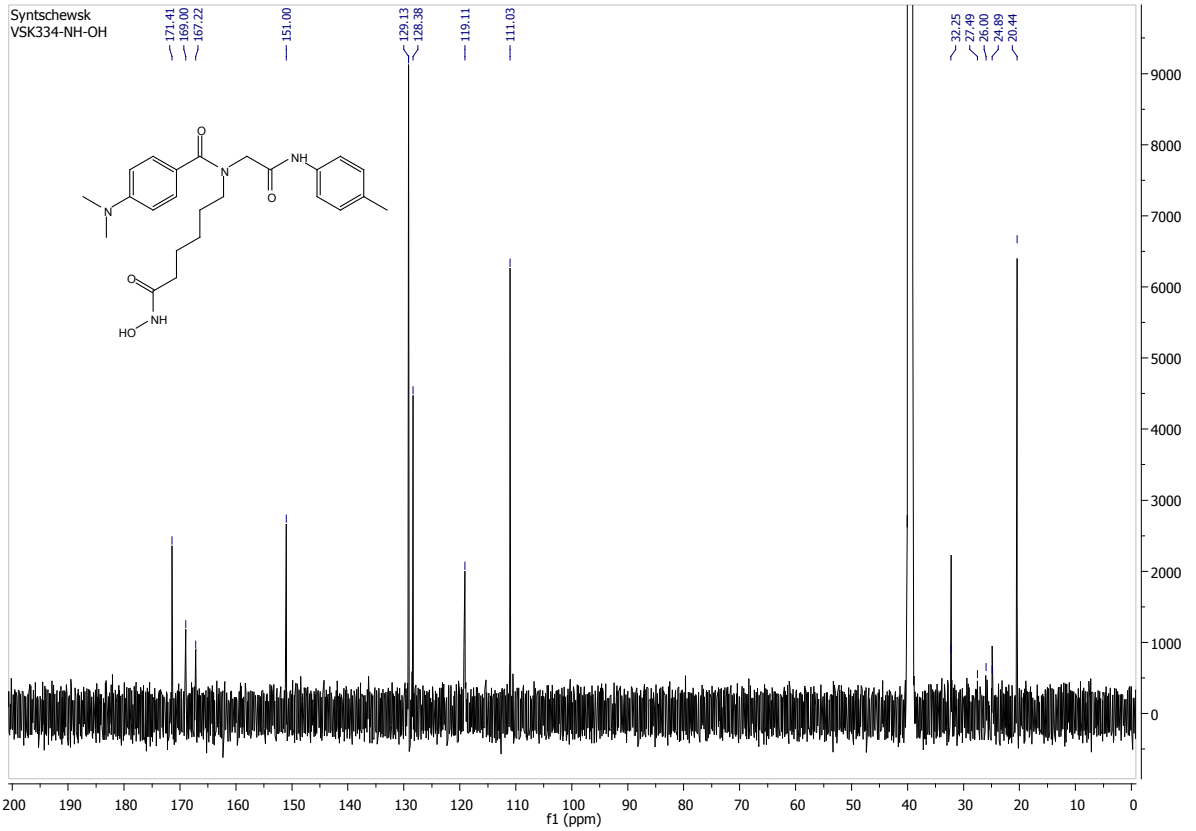
^{1}H NMR (500 MHz, DMSO-d_6) of compound **4g**.



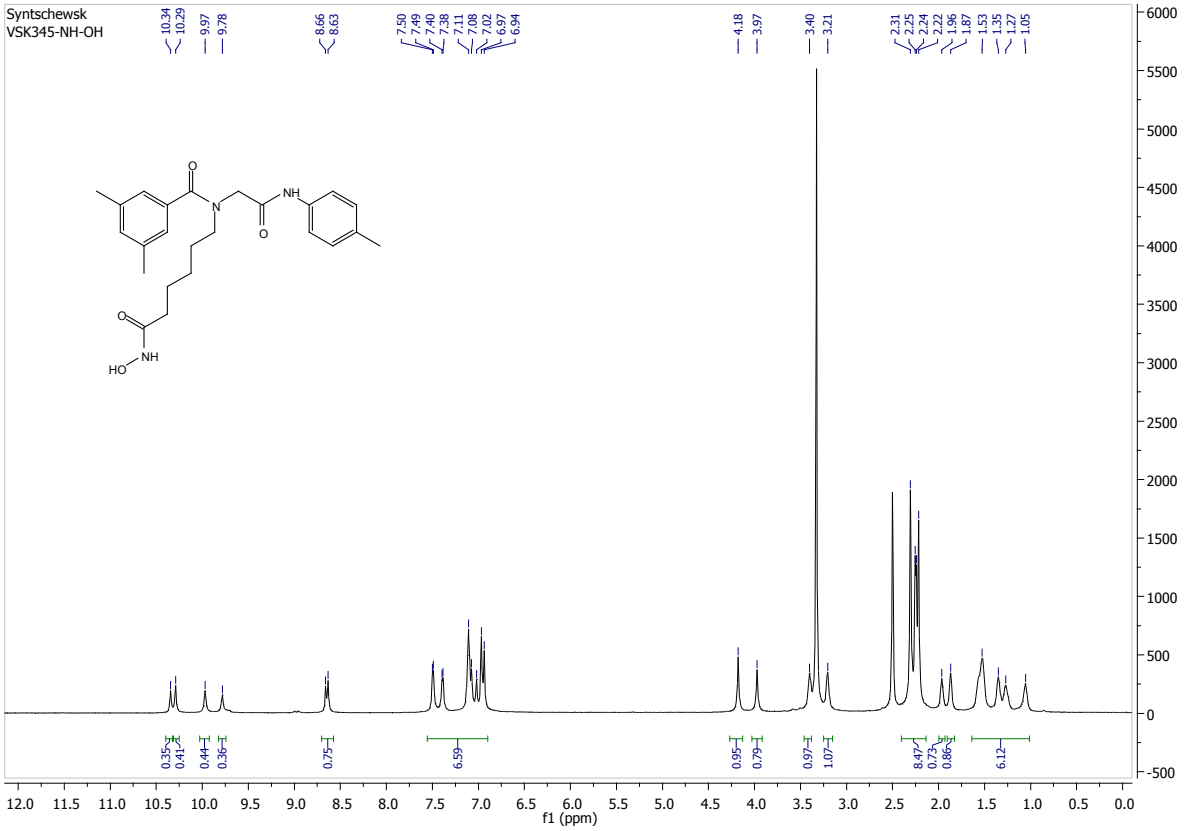
^{13}C NMR (126 MHz, DMSO-d_6) of compound **4g**.



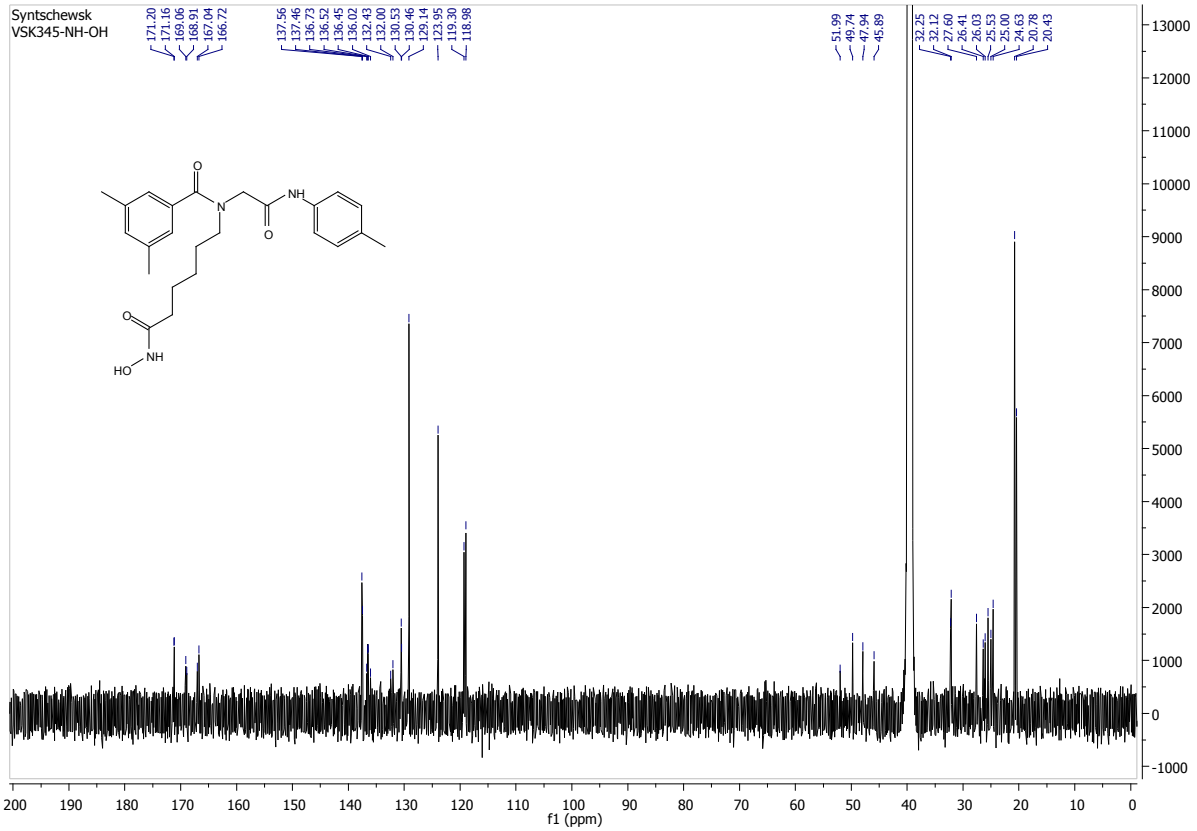
^{1}H NMR (600 MHz, DMSO-d_6) of compound **4h**.



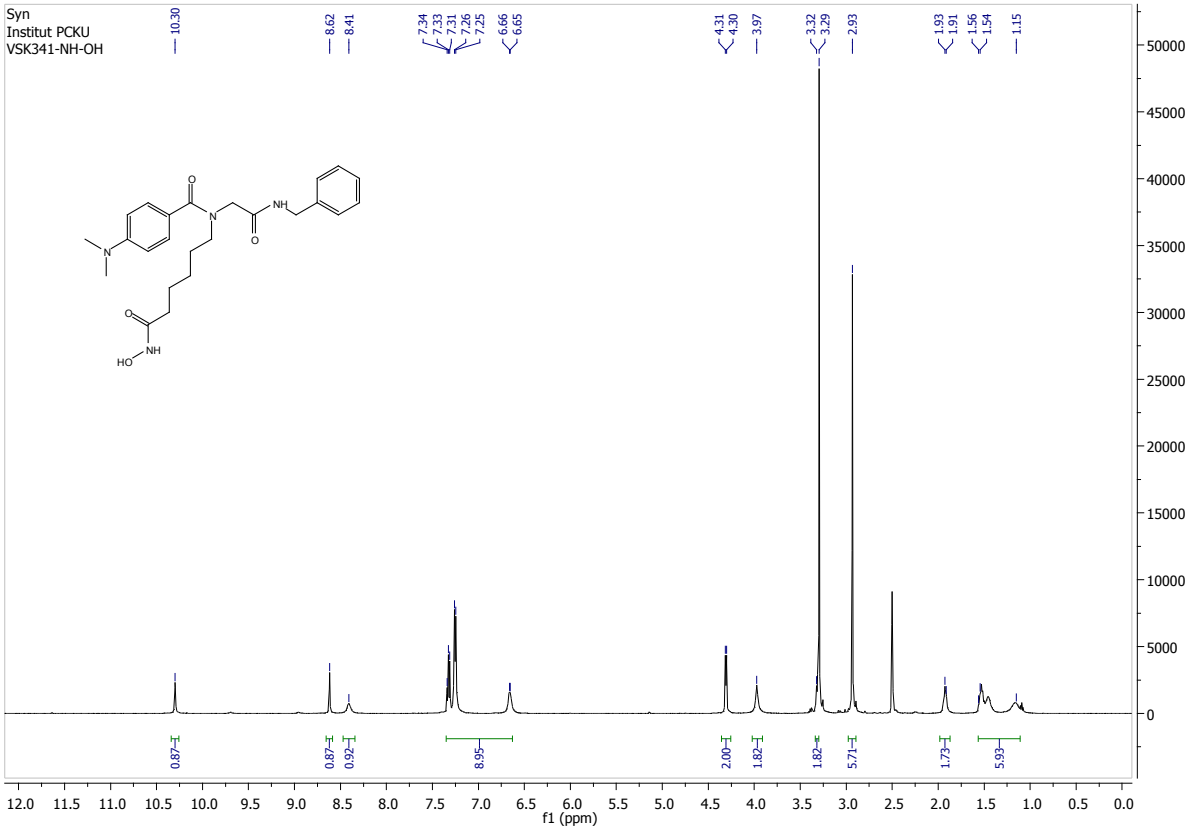
^{13}C NMR (151 MHz, DMSO-d_6) of compound **4h**.



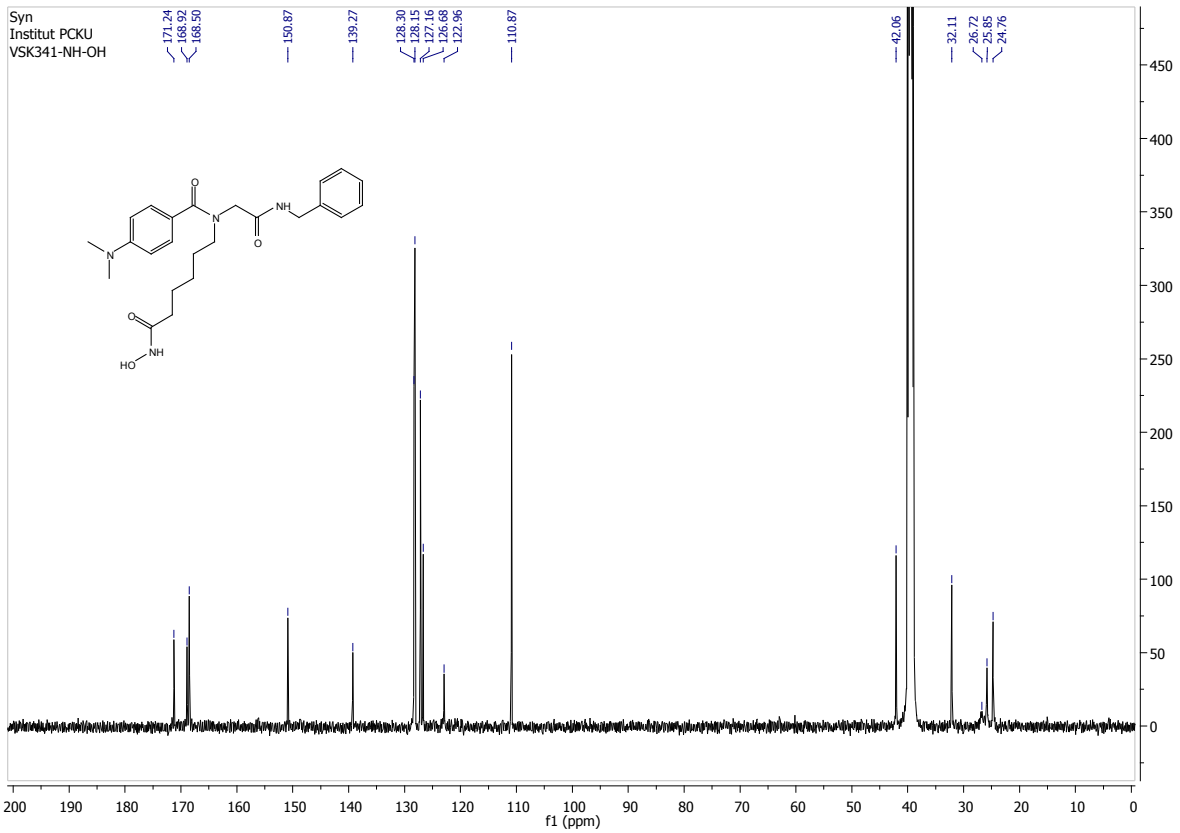
^{1}H NMR (600 MHz, DMSO-d_6) of compound **4i**.



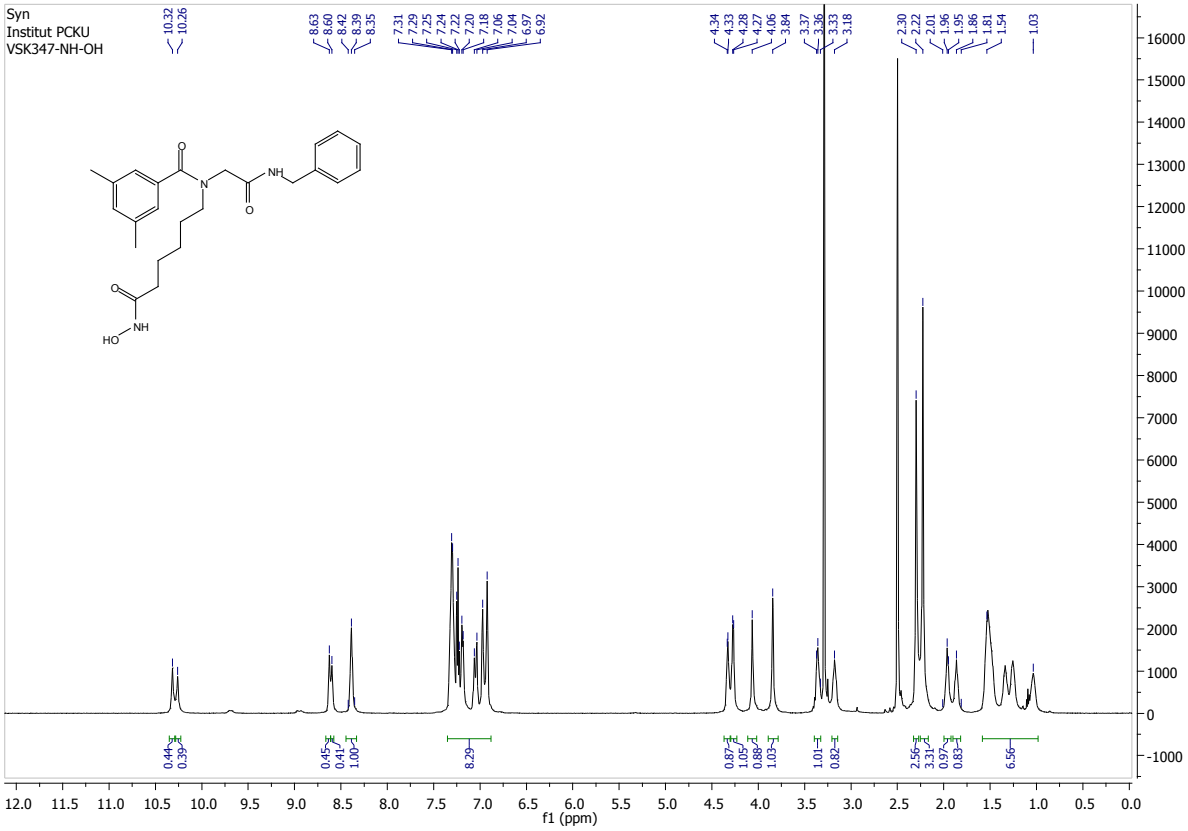
^{13}C NMR (151 MHz, DMSO-d_6) of compound **4i**.



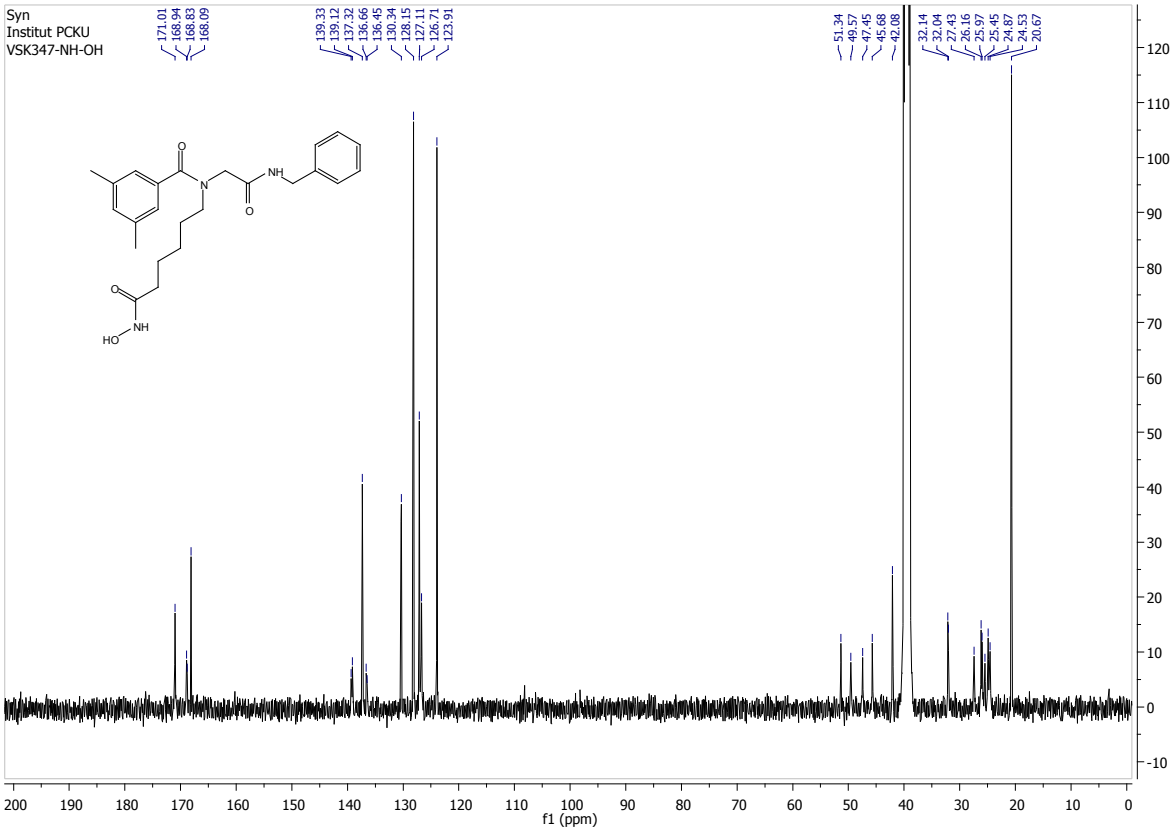
^{1}H NMR (500 MHz, DMSO-d_6) of compound **4j**.



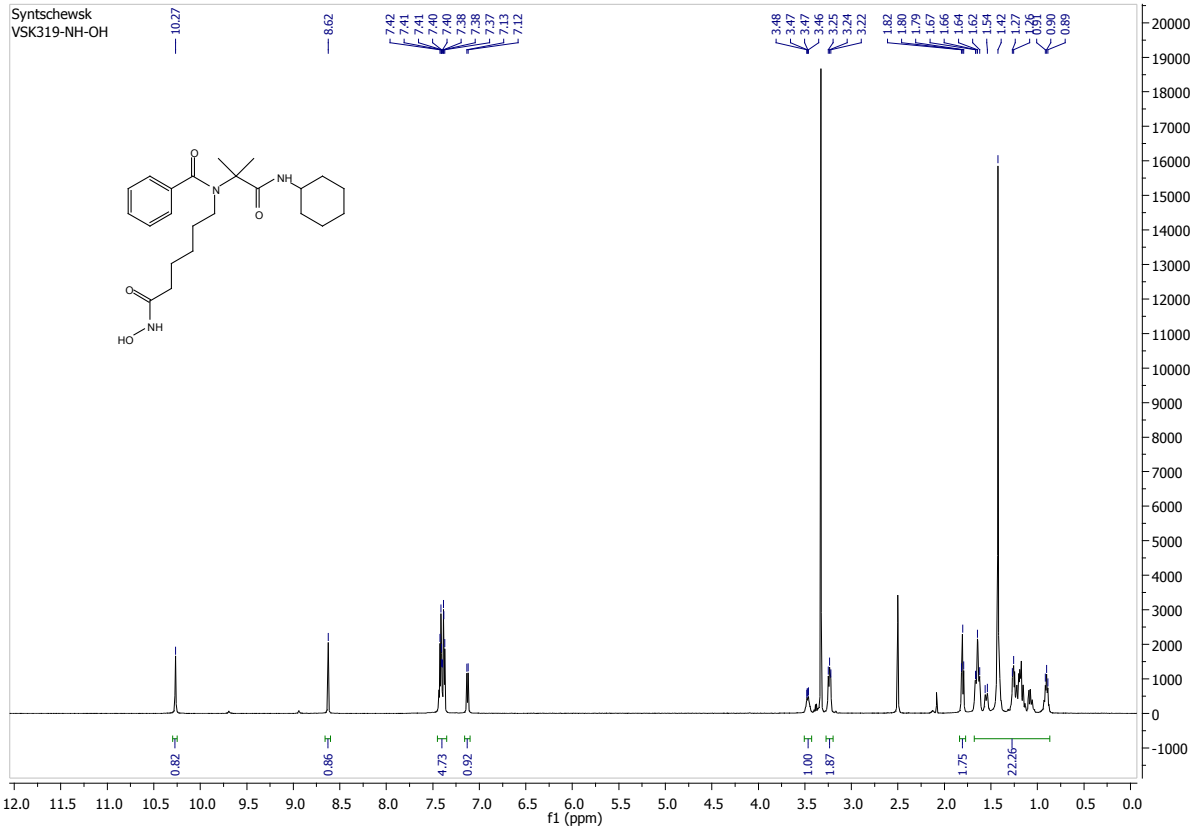
^{13}C NMR (126 MHz, DMSO-d_6) of compound **4j**.



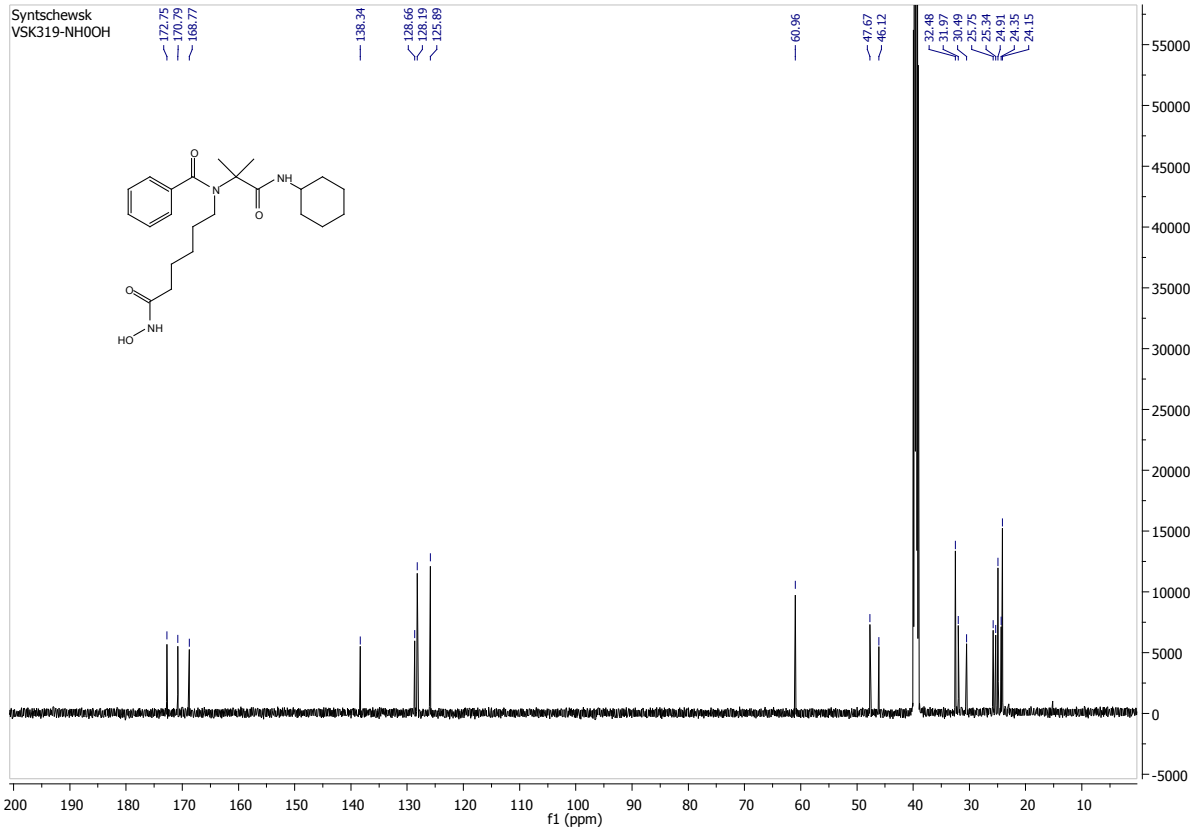
^{1}H NMR (500 MHz, DMSO-d_6) of compound **4k**.



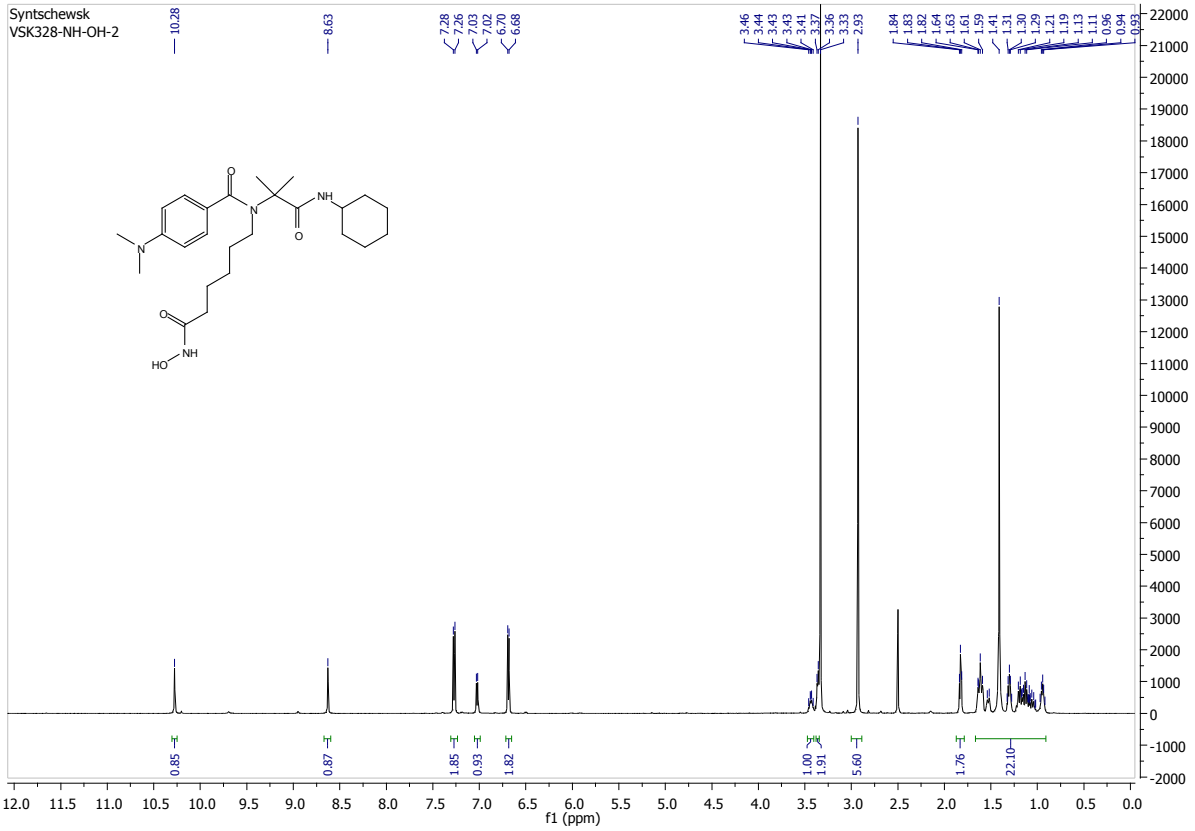
^{13}C NMR (126 MHz, DMSO-d_6) of compound **4k**.



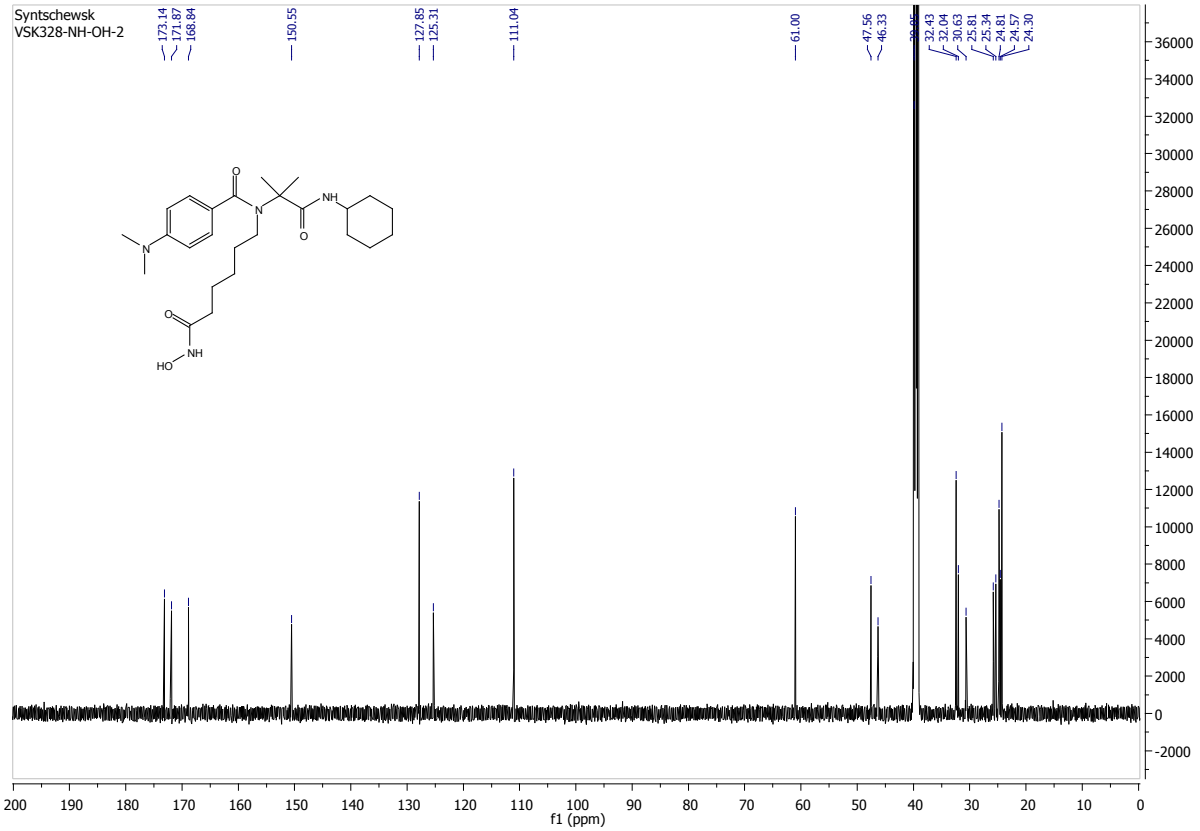
^{1}H NMR (600 MHz, DMSO-d_6) of compound **5a**.



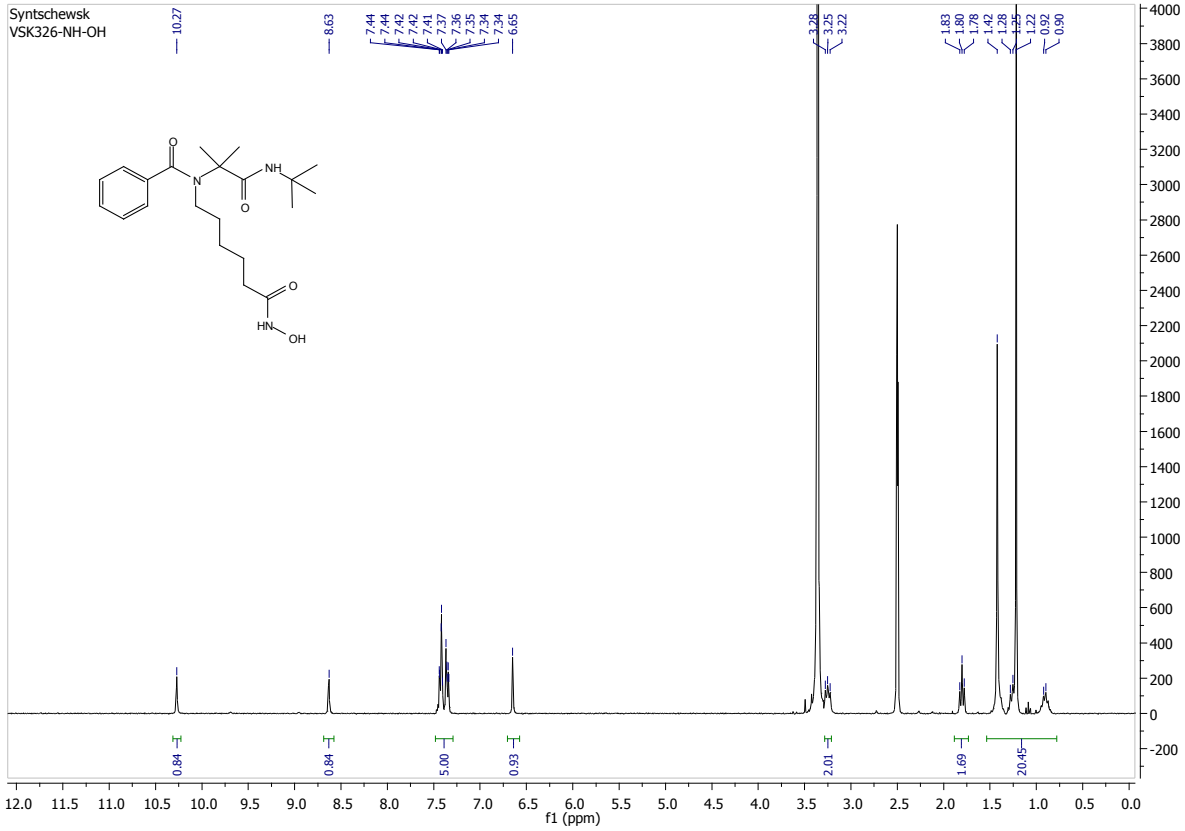
^{13}C NMR (151 MHz, DMSO-d_6) of compound **5a**.



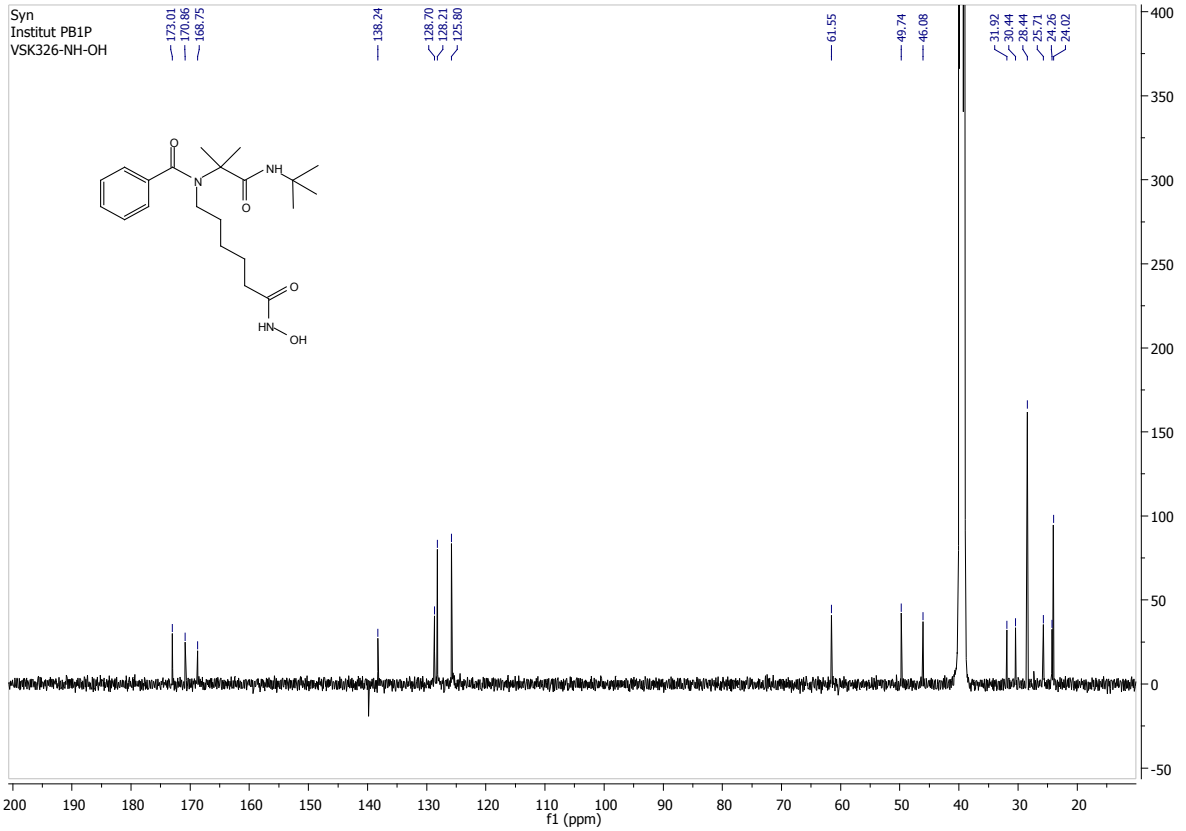
^{1}H NMR (600 MHz, DMSO-d_6) of compound **5b**.



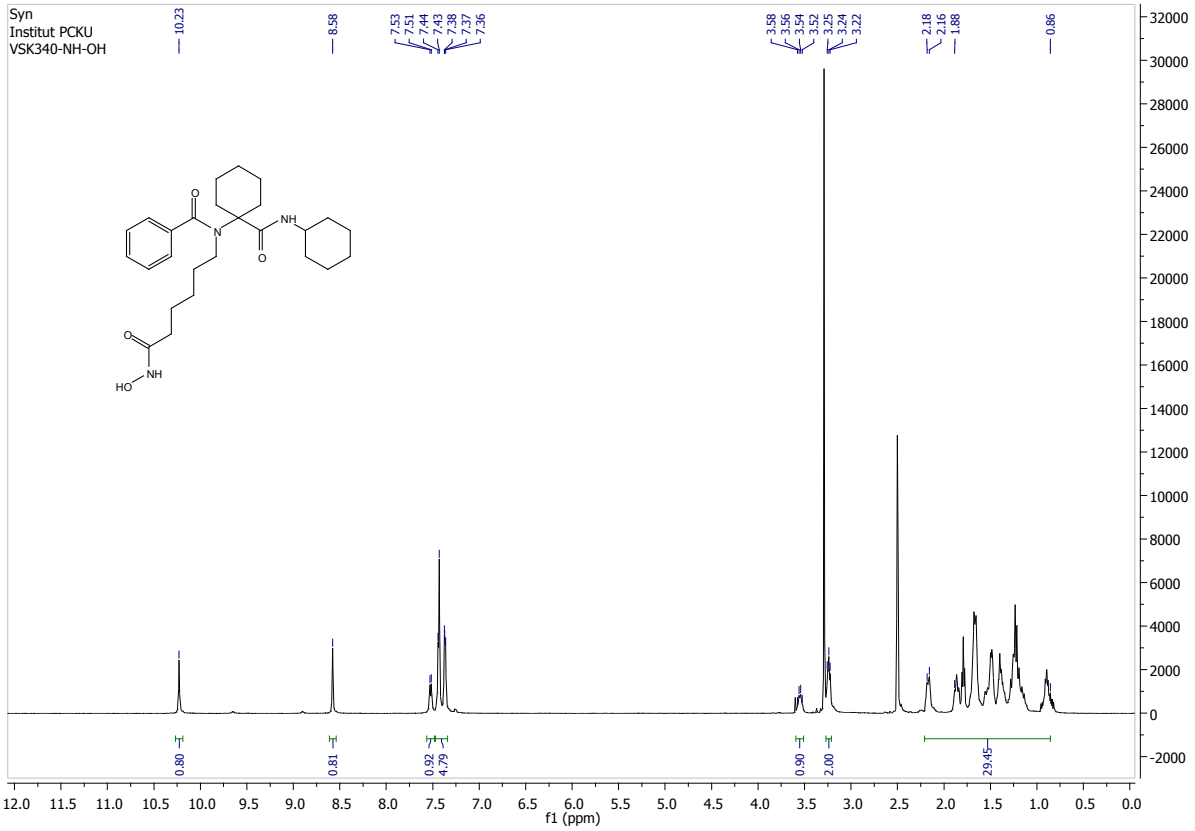
^{13}C NMR (151 MHz, DMSO-d_6) of compound **5b**.



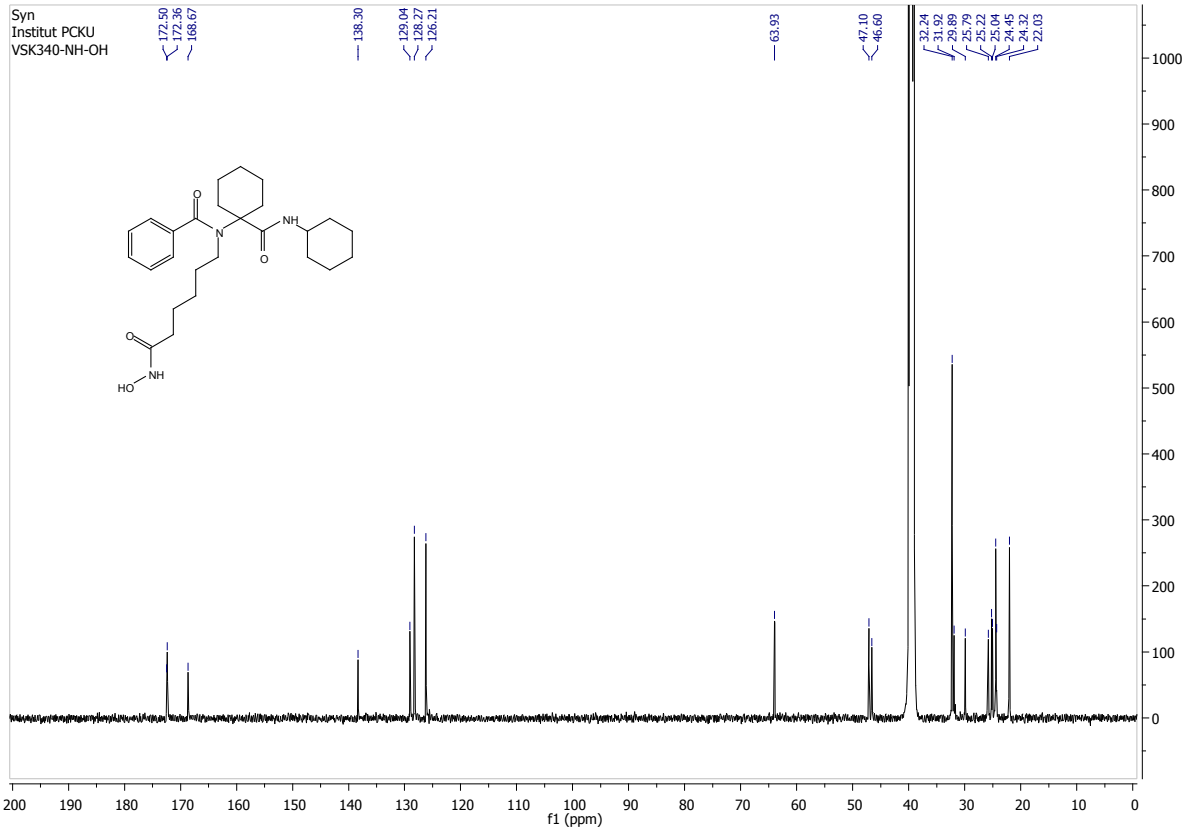
^{1}H NMR (300 MHz, DMSO-d_6) of compound **5c**.



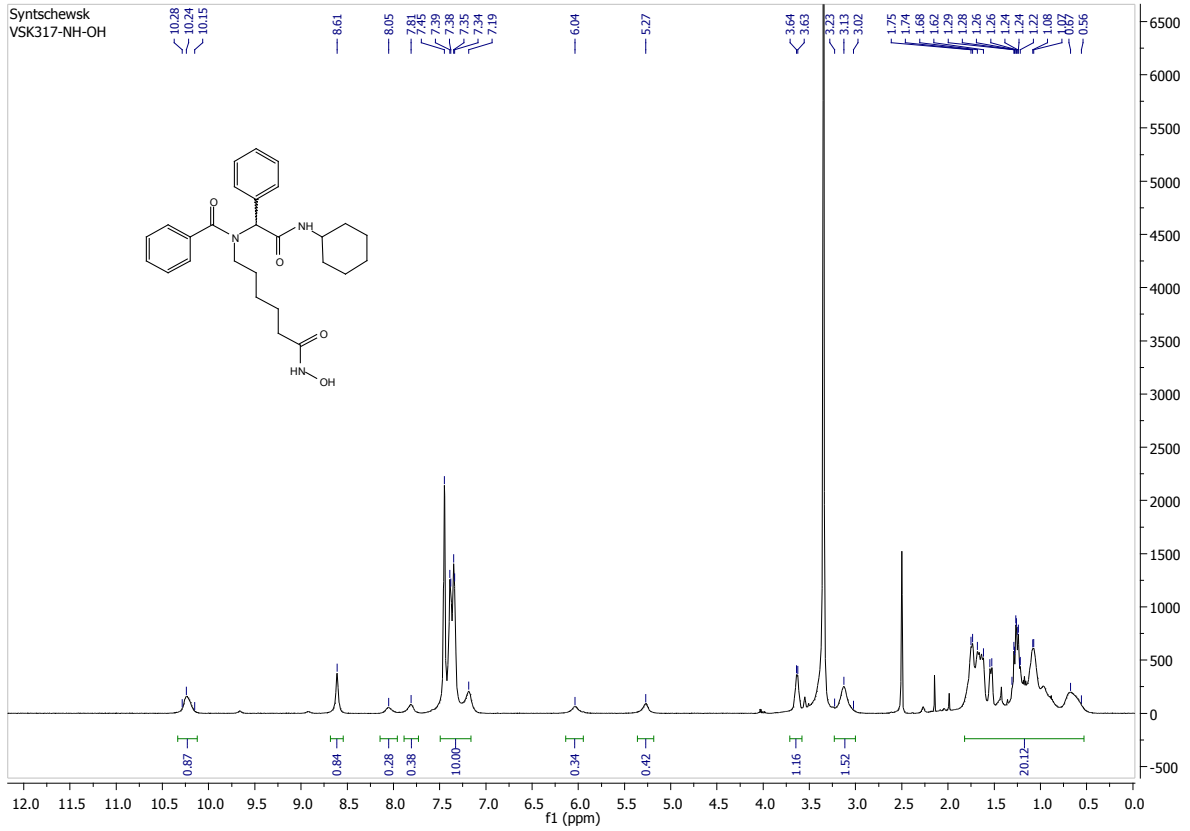
^{13}C NMR (126 MHz, DMSO-d_6) of compound **5c**.



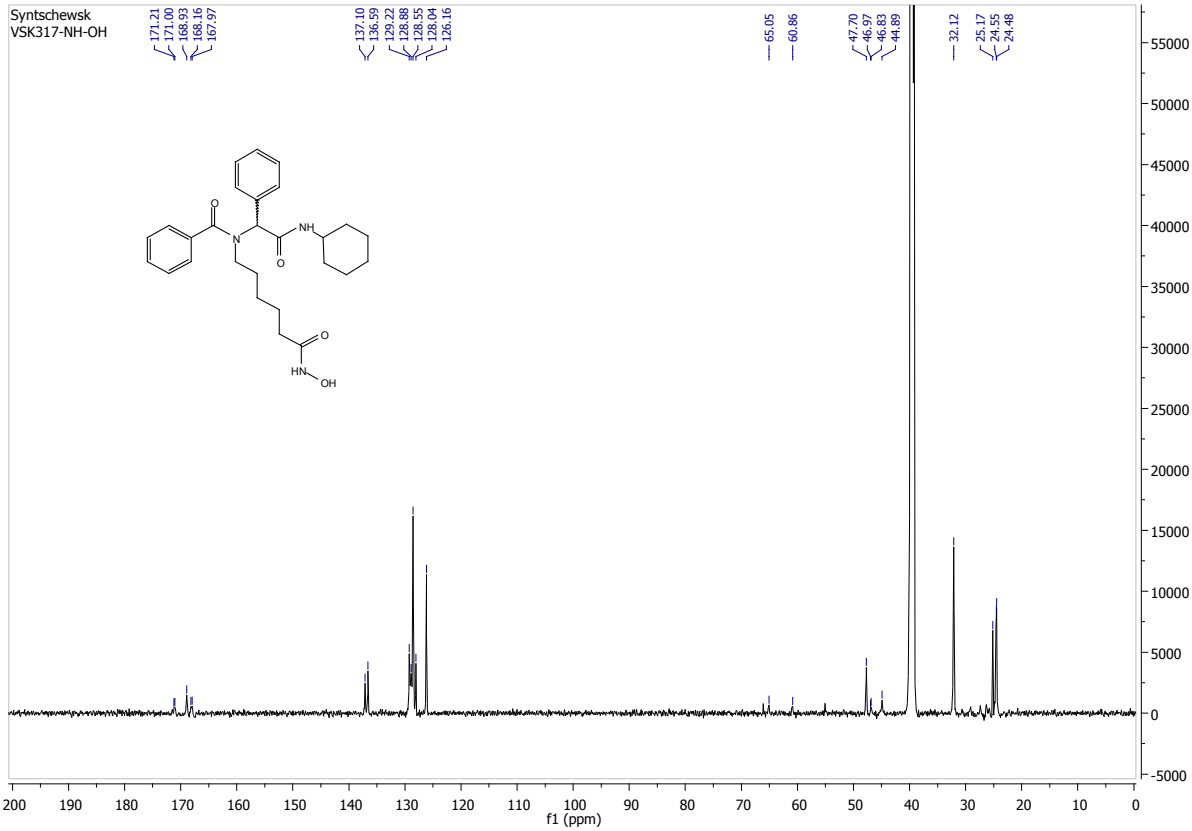
^{1}H NMR (500 MHz, DMSO-d_6) of compound **5d**.



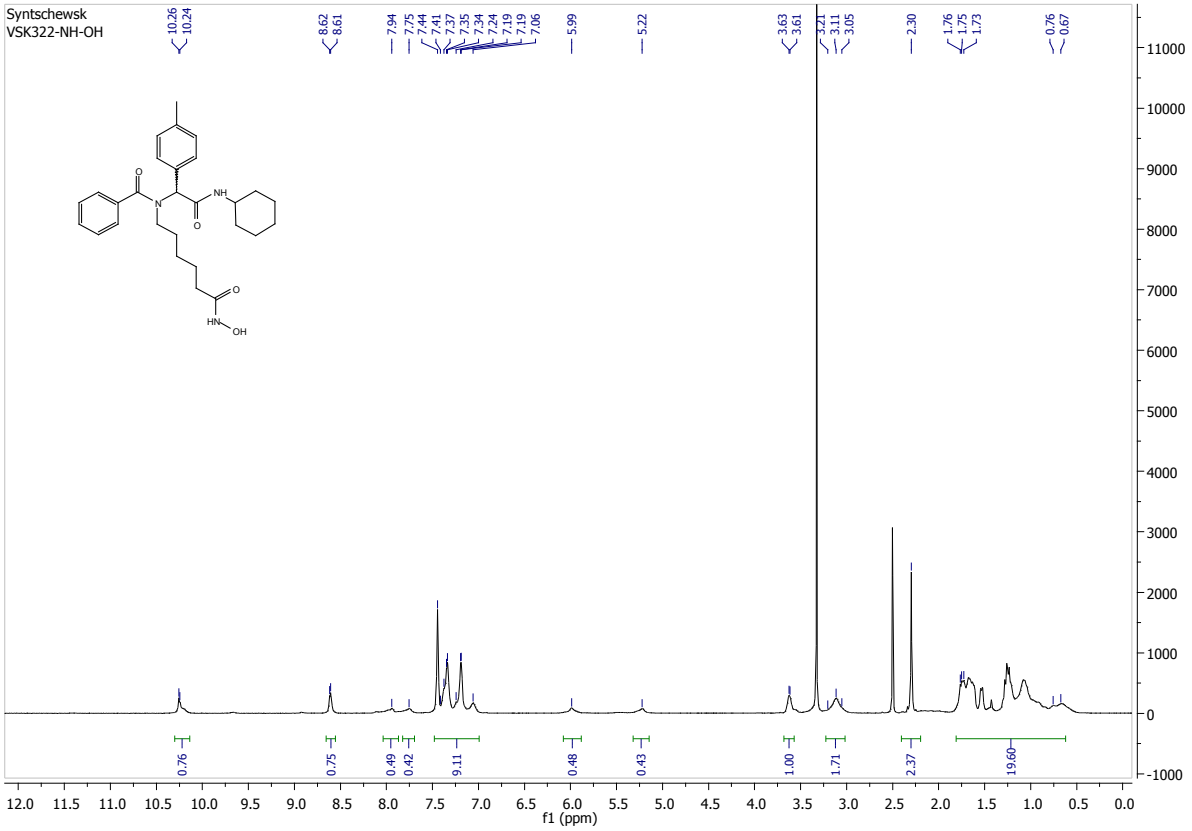
^{13}C NMR (126 MHz, DMSO-d_6) of compound **5d**.



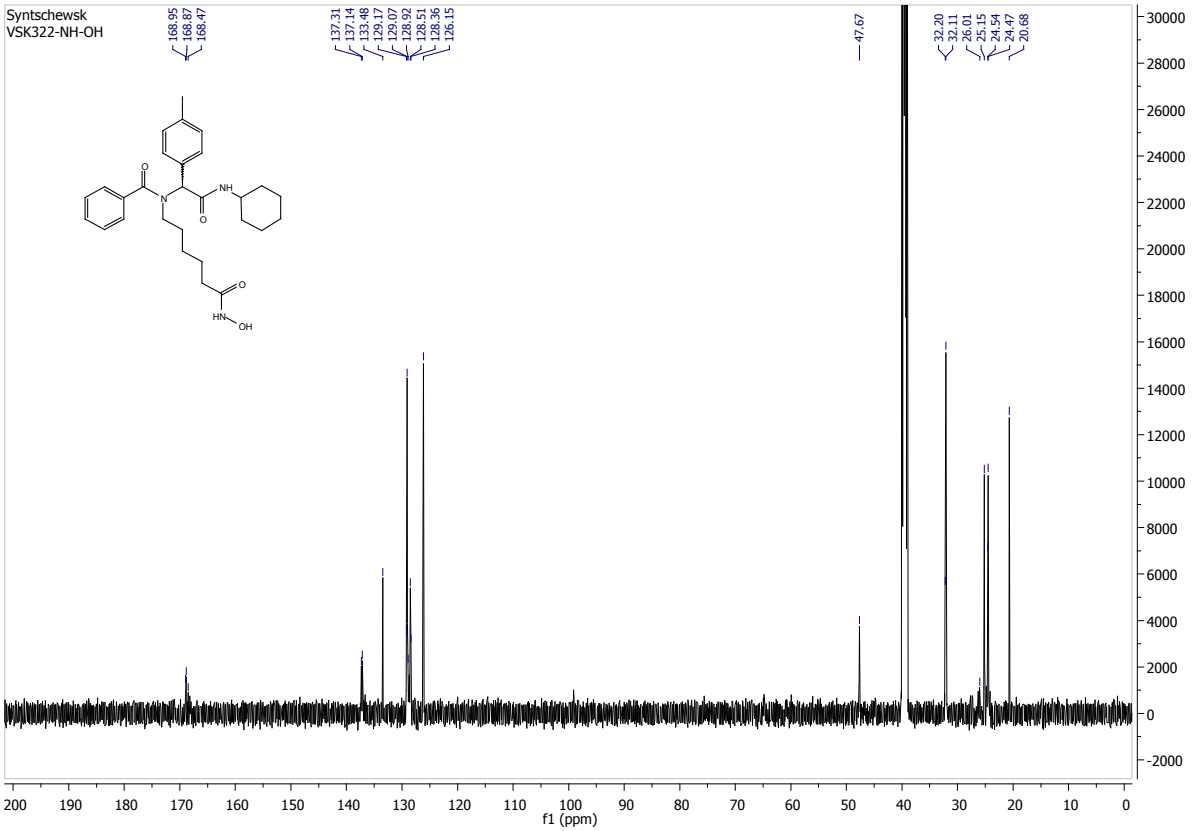
^{1}H NMR (600 MHz, DMSO-d_6) of compound **5e**.



^{13}C NMR (151 MHz, DMSO-d_6) of compound **5e**.

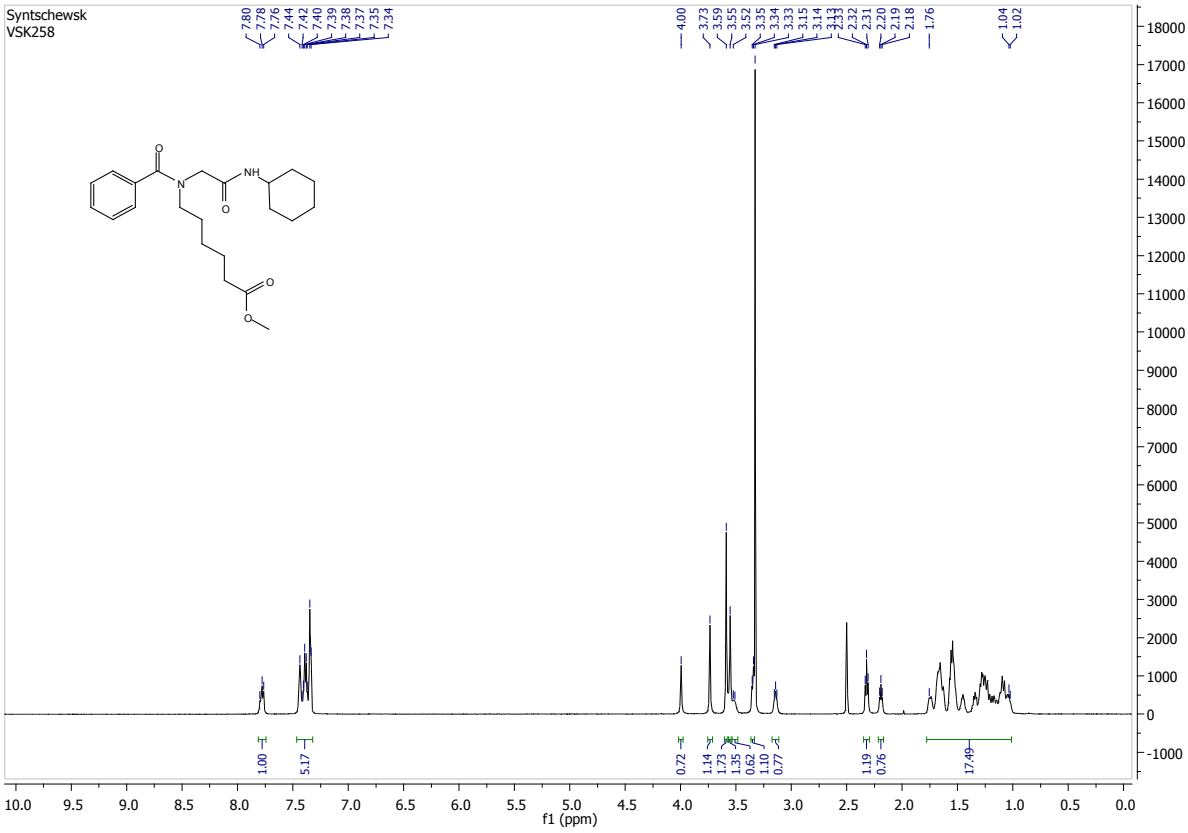


^{1}H NMR (600 MHz, DMSO-d_6) of compound **5f**.

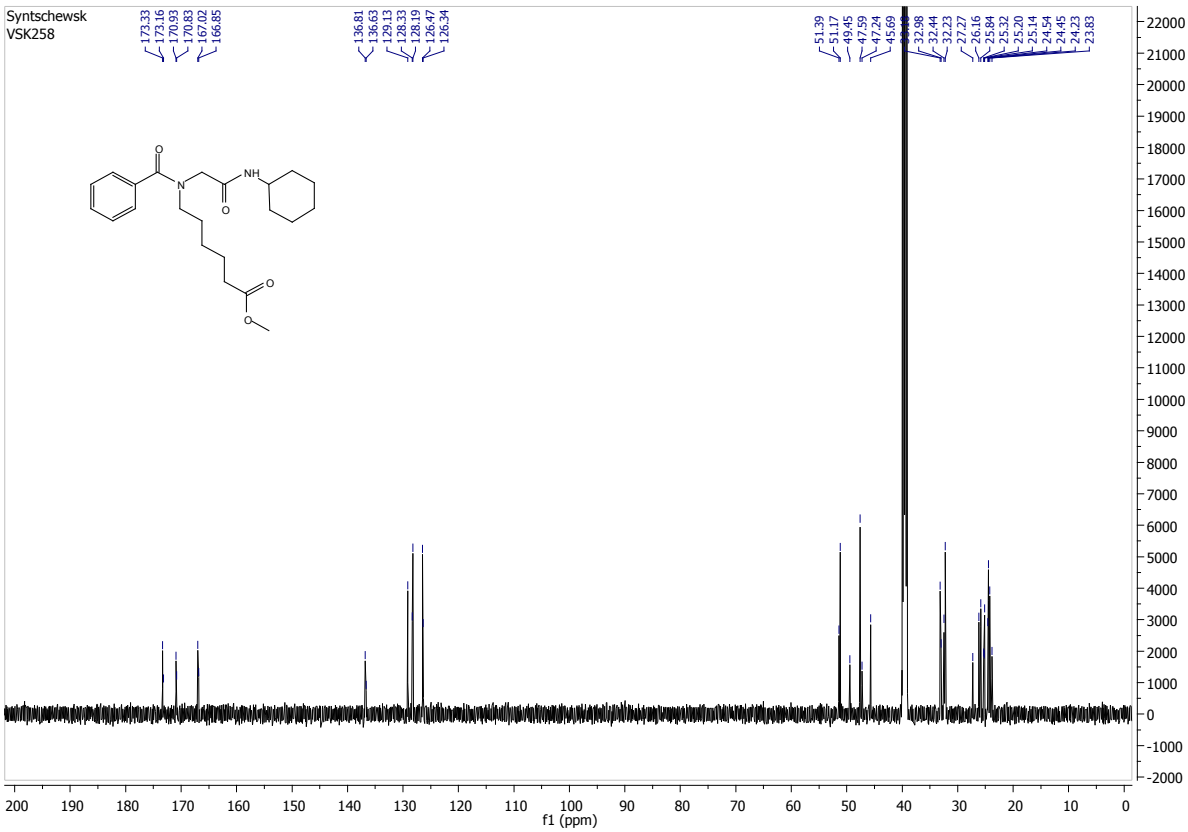


^{13}C NMR (151 MHz, DMSO-d_6) of compound **5f**.

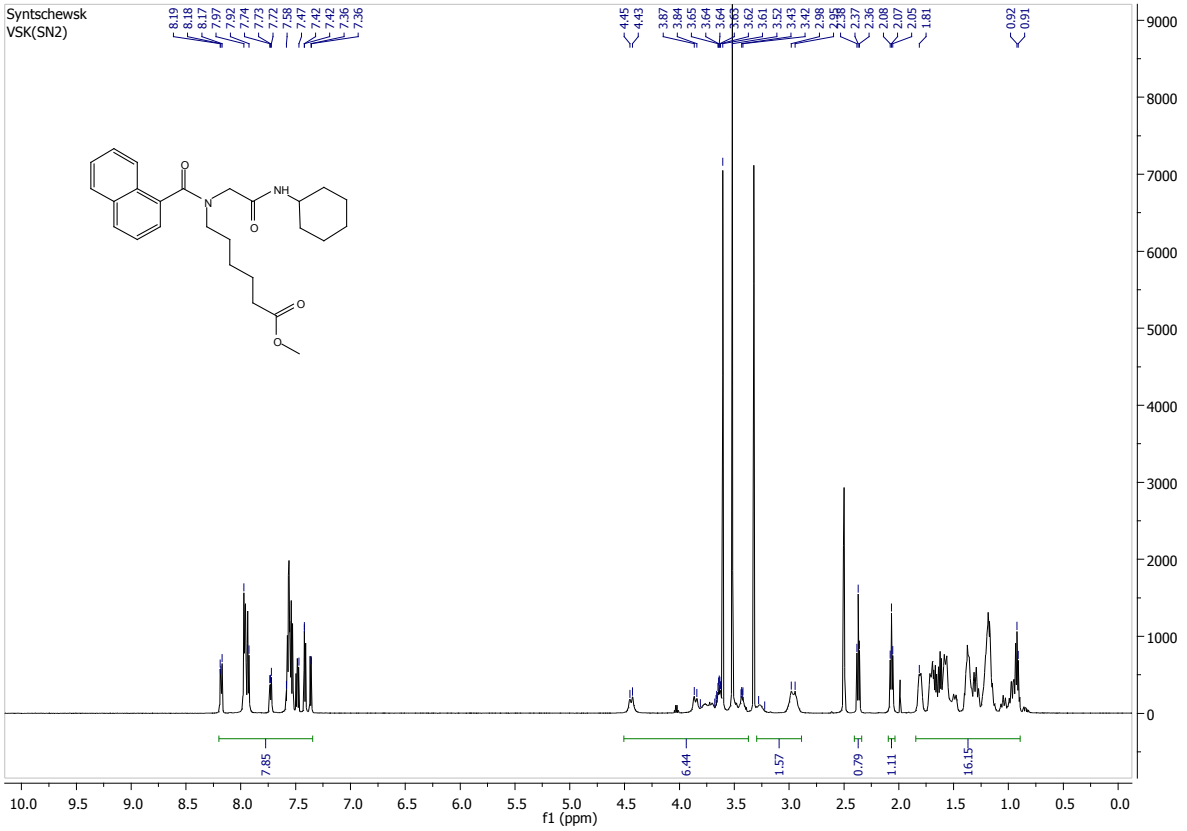
^{1}H and ^{13}C NMR spectra of intermediates



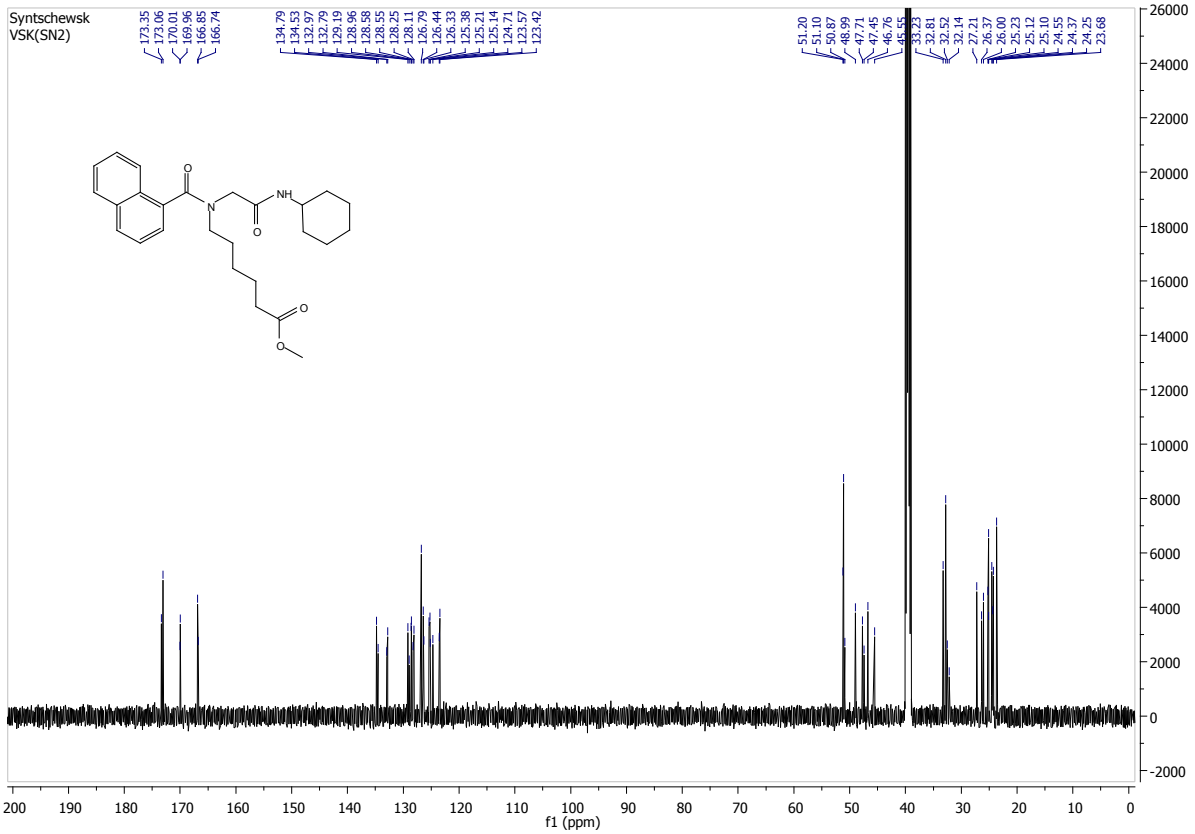
^{1}H NMR (600 MHz, DMSO-d_6) of compound **6a**.



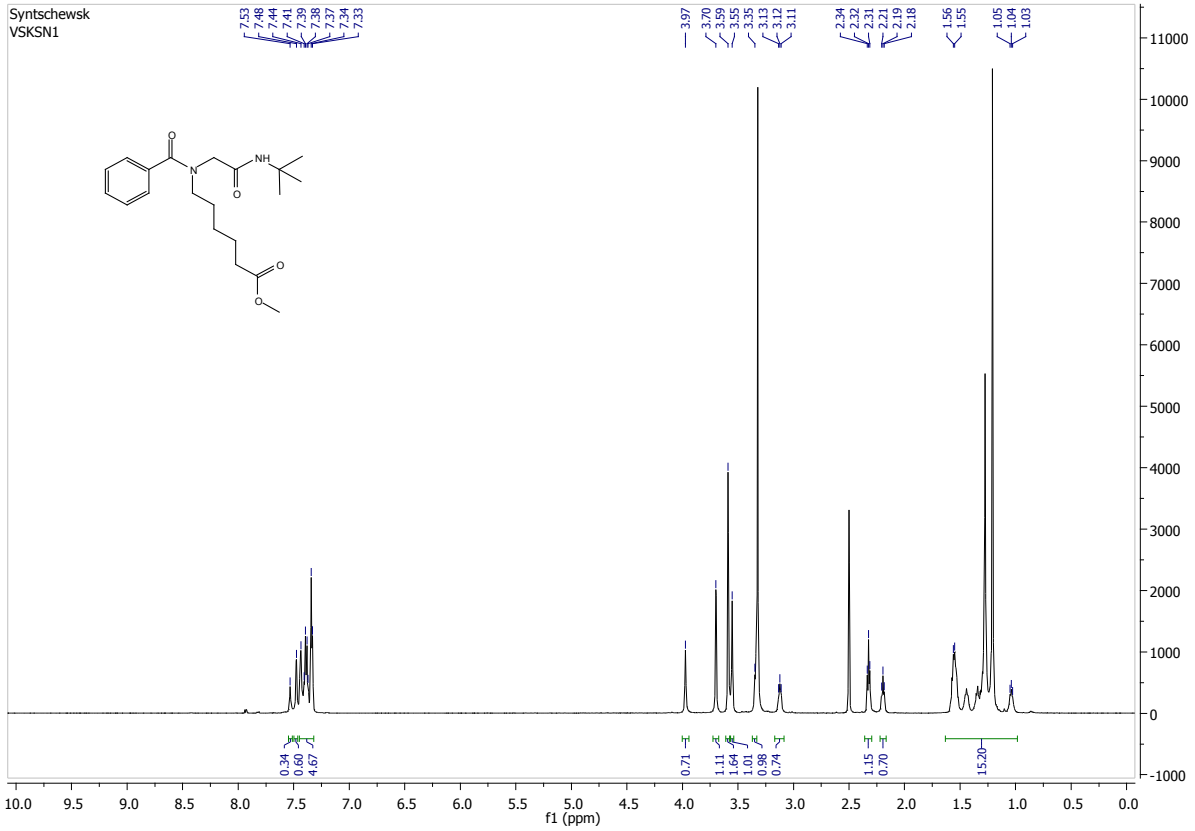
^{13}C NMR (151 MHz, DMSO-d_6) of compound **6a**.



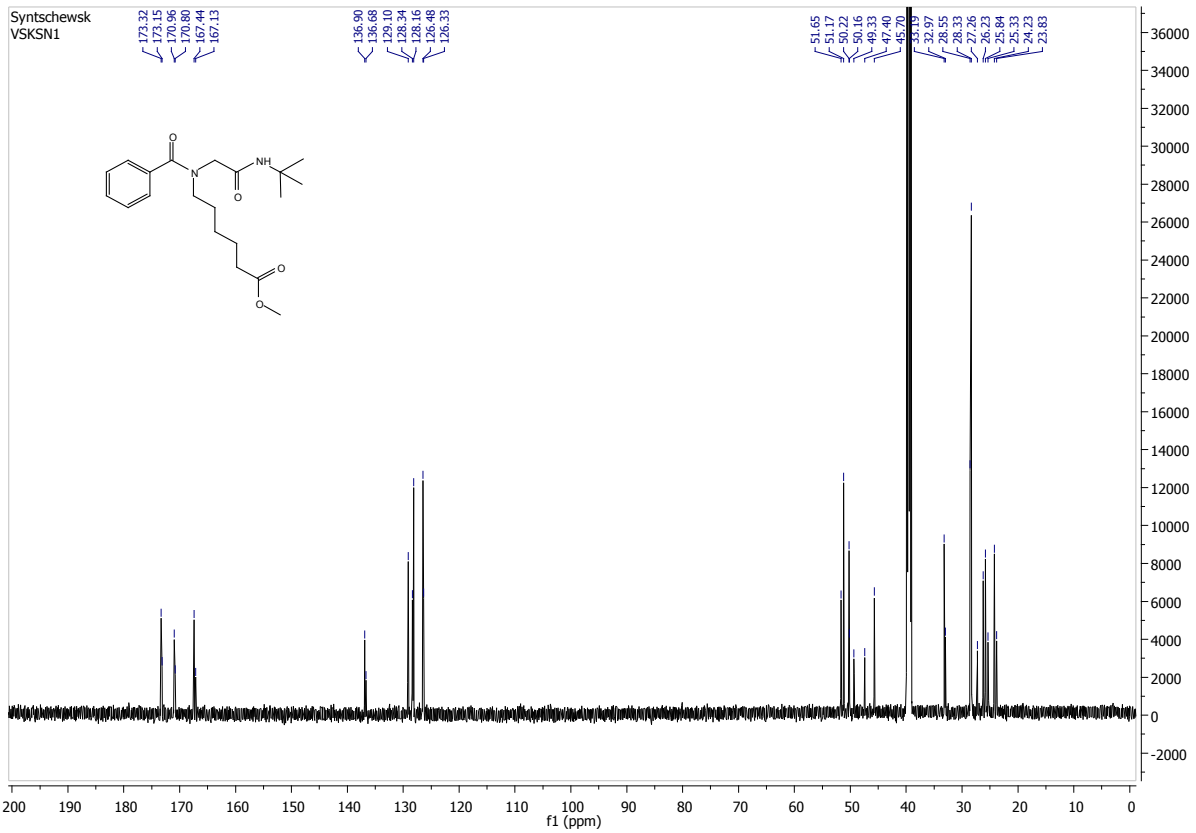
^{1}H NMR (600 MHz, DMSO-d_6) of compound **6b**.



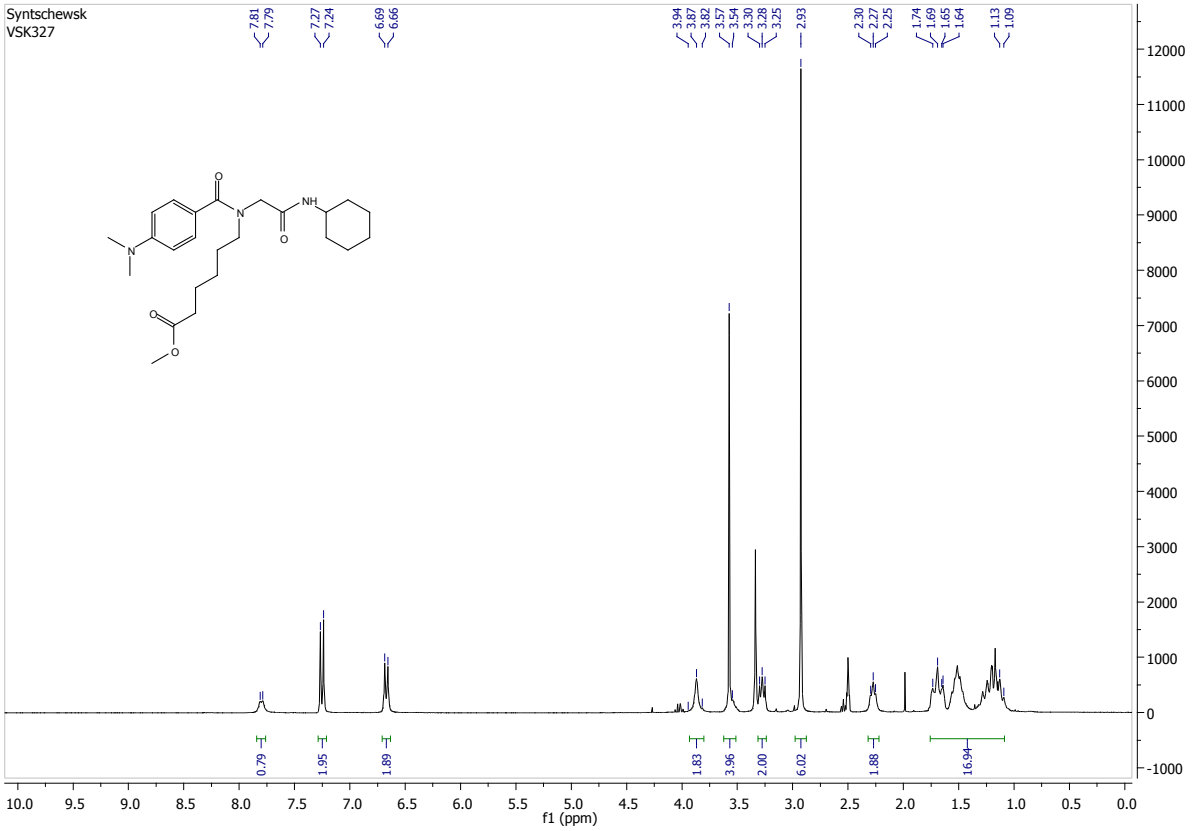
^{13}C NMR (151 MHz, DMSO-d_6) of compound **6b**.



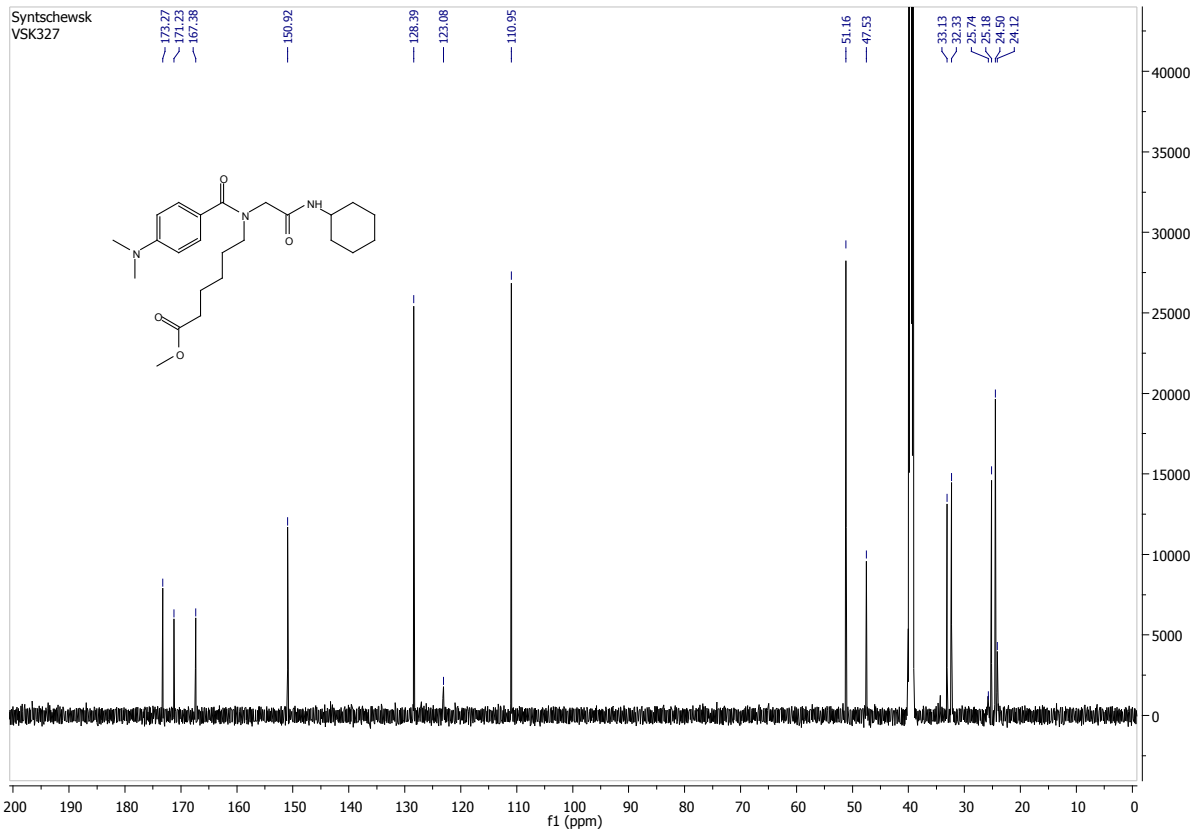
^{1}H NMR (600 MHz, DMSO-d_6) of compound **6c**.



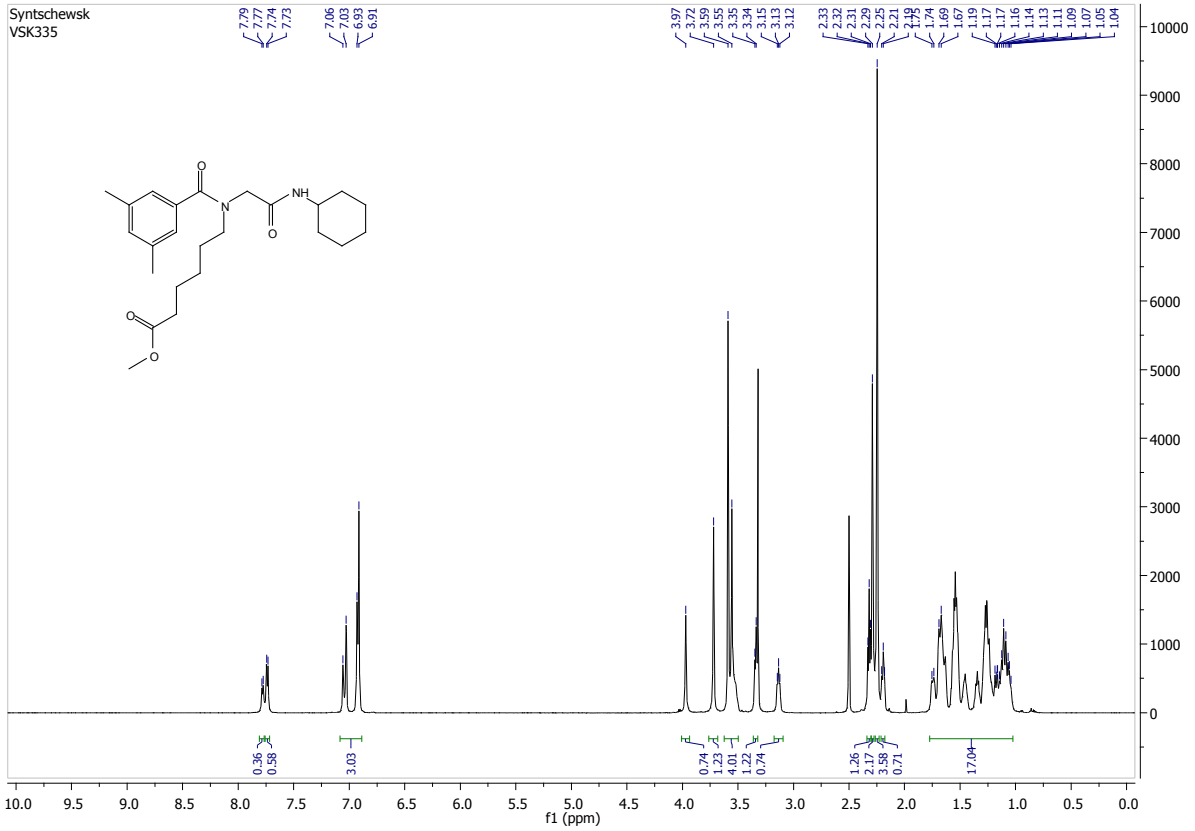
^{13}C NMR (151 MHz, DMSO-d_6) of compound **6c**.



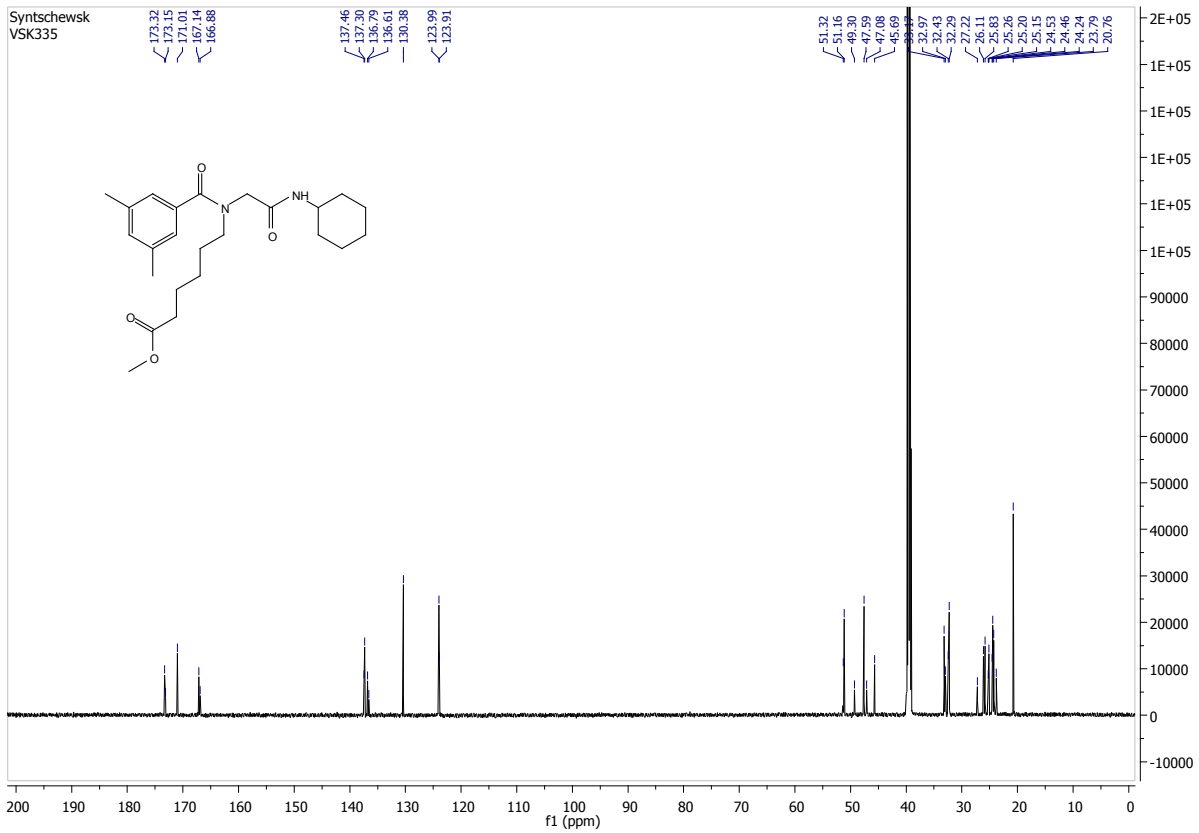
^{1}H NMR (600 MHz, DMSO-d_6) of compound **6d**.



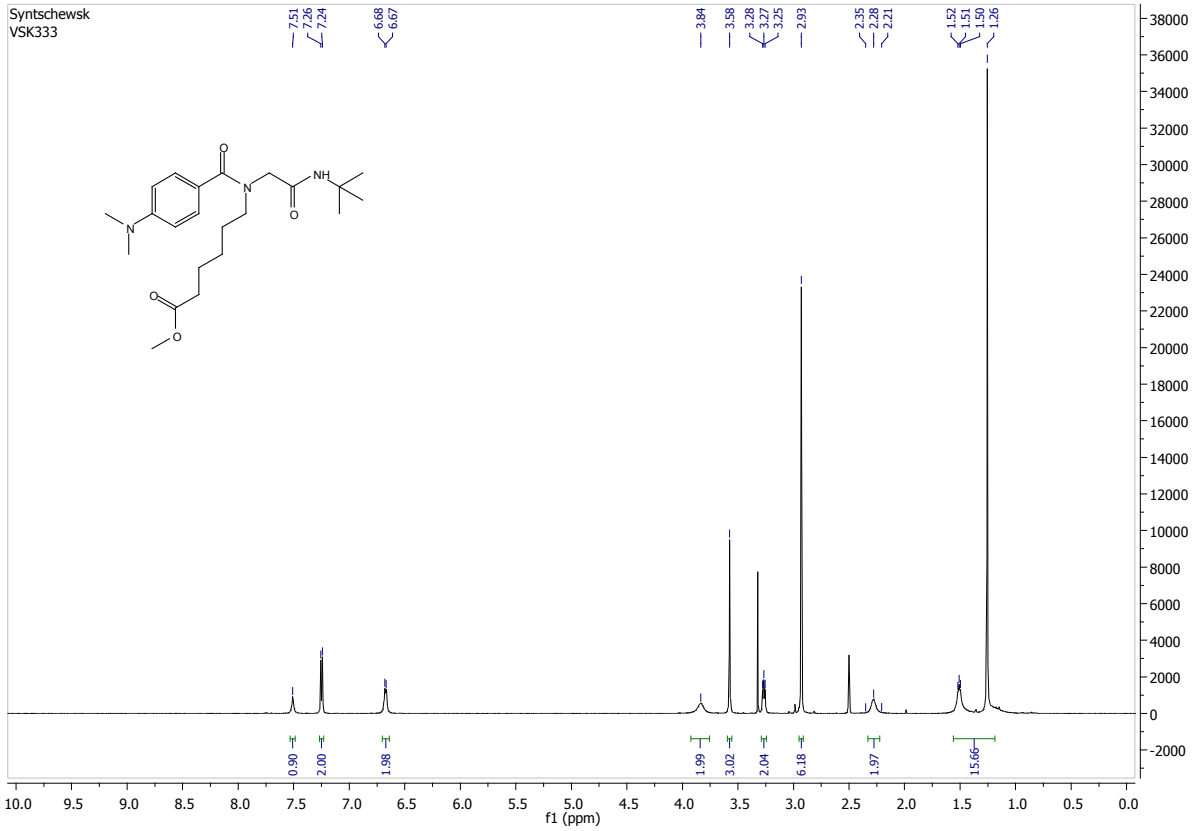
^{13}C NMR (151 MHz, DMSO-d_6) of compound **6d**.



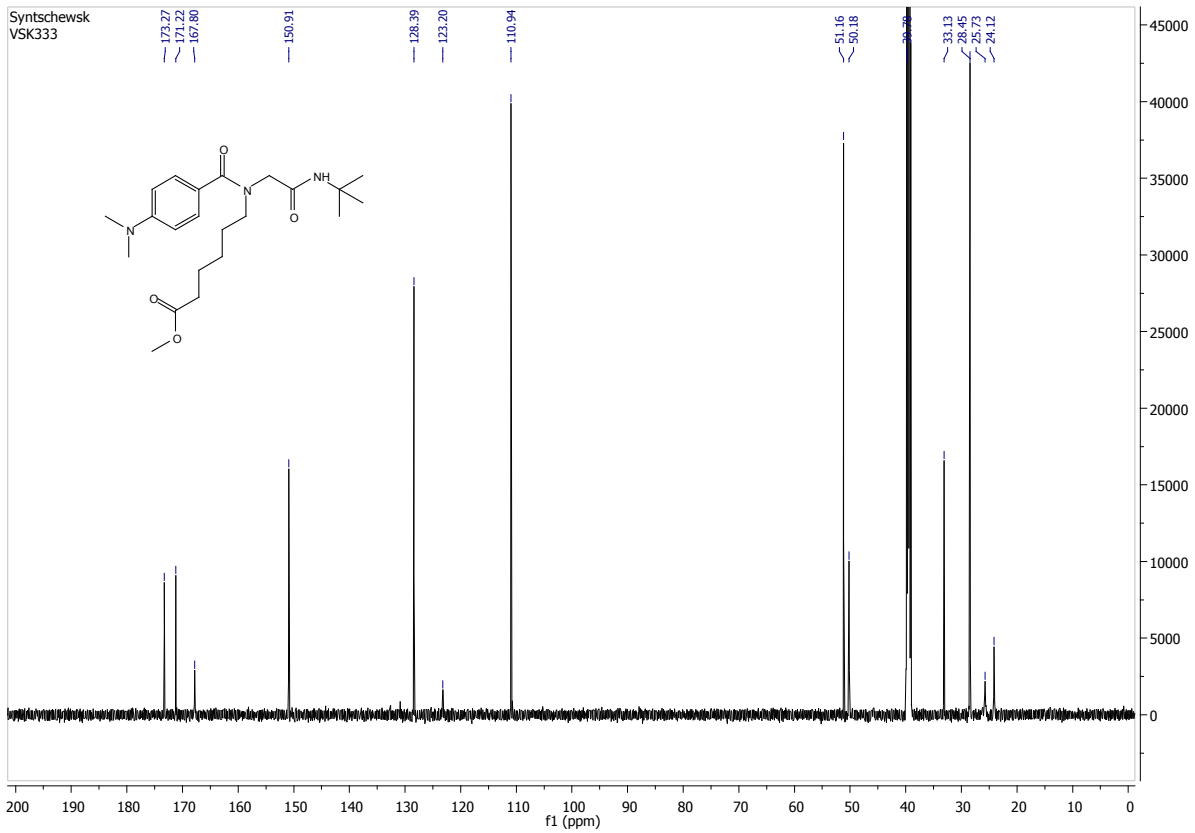
^{1}H NMR (600 MHz, DMSO-d_6) of compound **6e**.



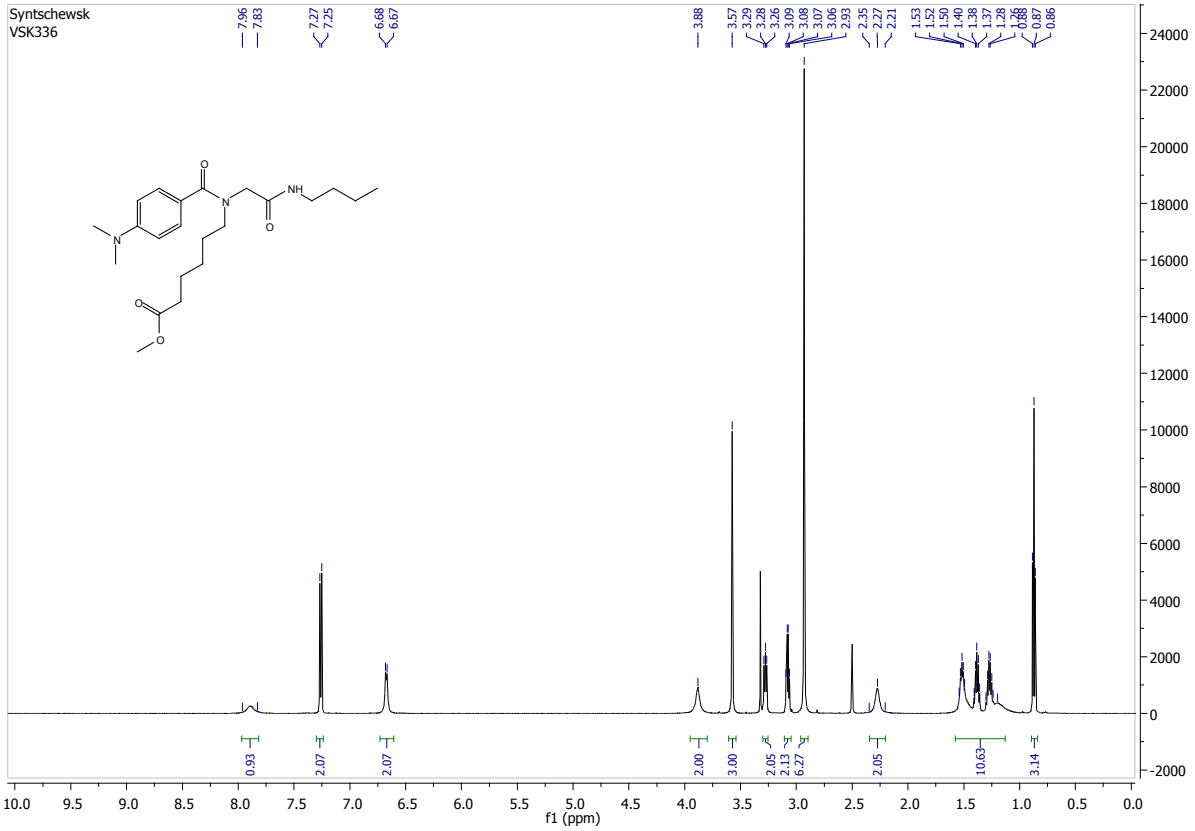
^{13}C NMR (151 MHz, DMSO-d_6) of compound **6e**.



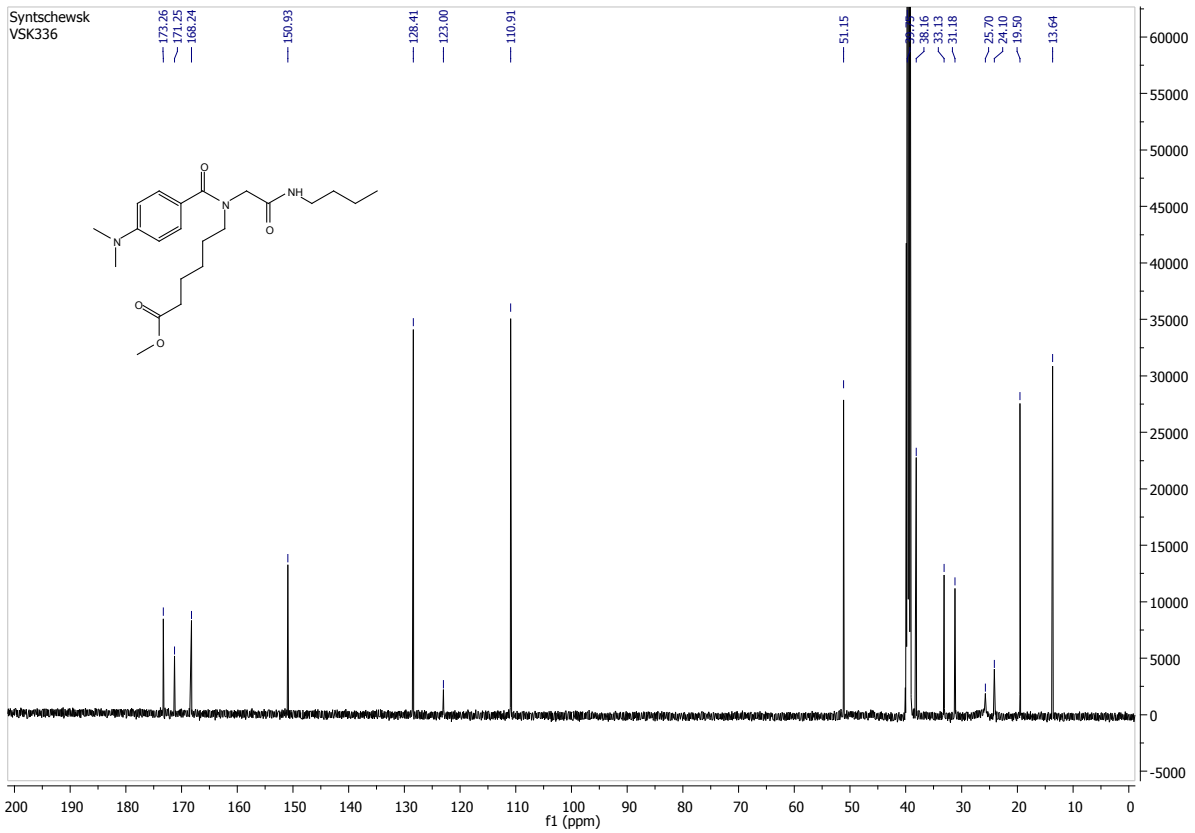
^{1}H NMR (600 MHz, DMSO-d_6) of compound **6f**.



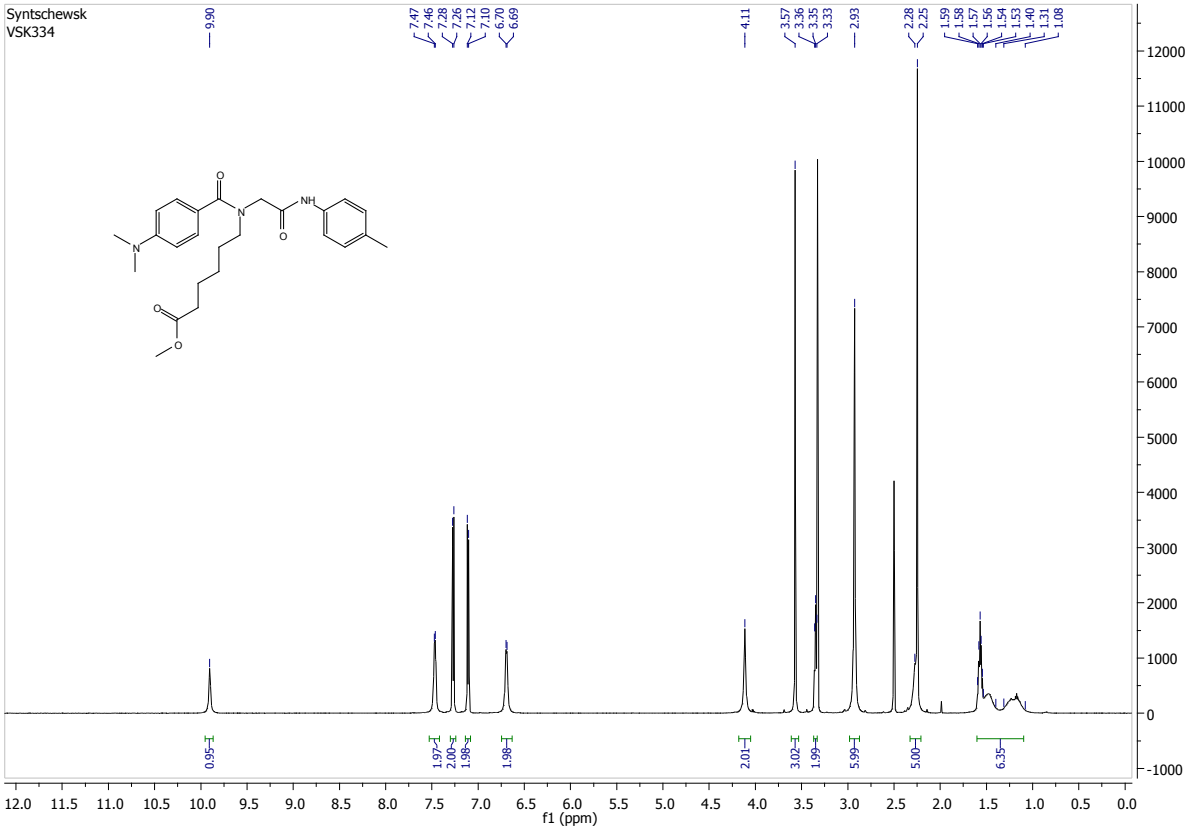
^{13}C NMR (151 MHz, DMSO-d_6) of compound **6f**.



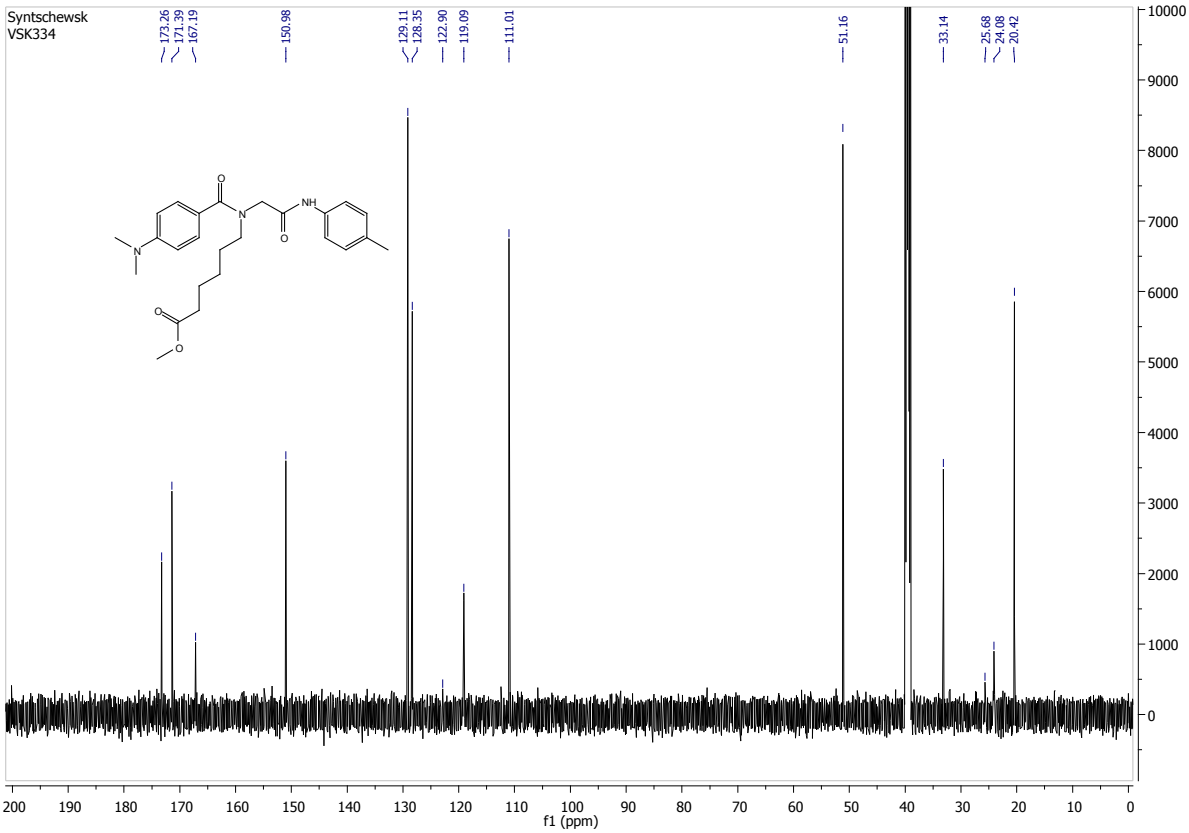
^{1}H NMR (600 MHz, DMSO-d_6) of compound **6g**.



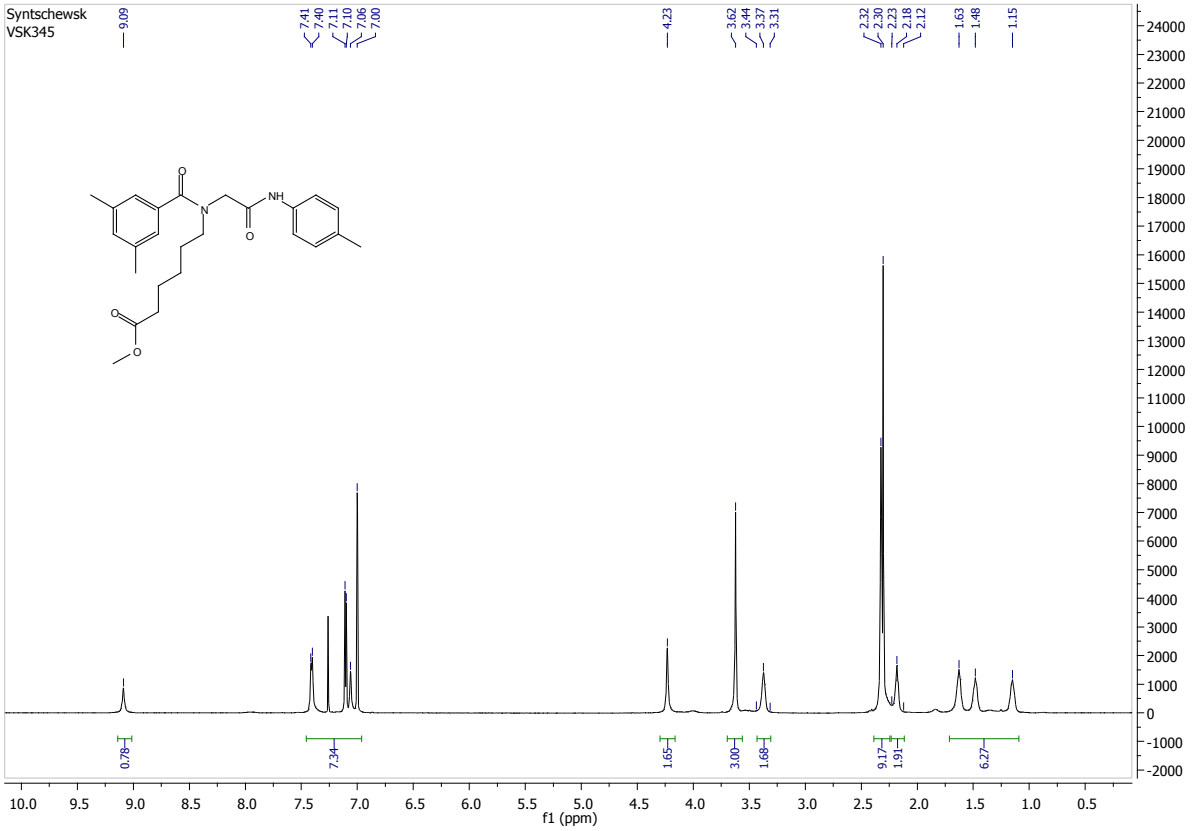
^{13}C NMR (151 MHz, DMSO-d_6) of compound **6g**.



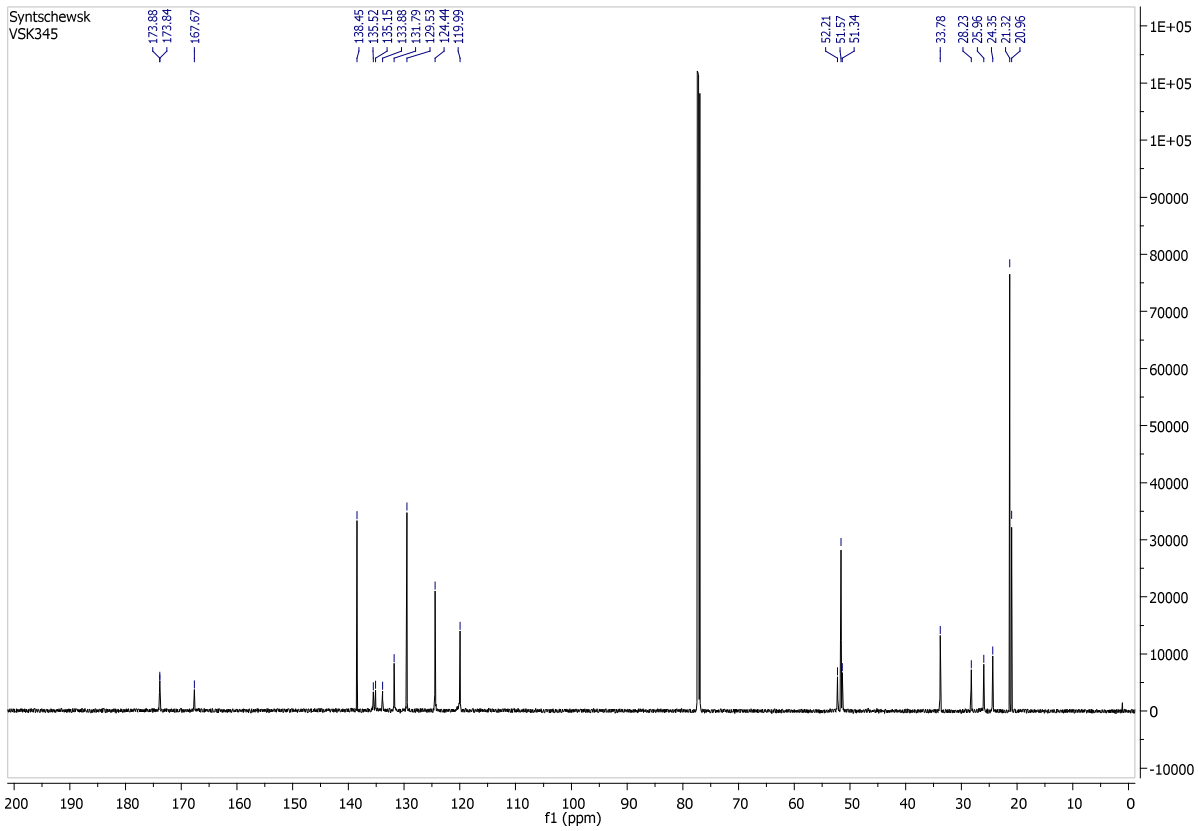
^{1}H NMR (600 MHz, DMSO-d_6) of compound **6h**.



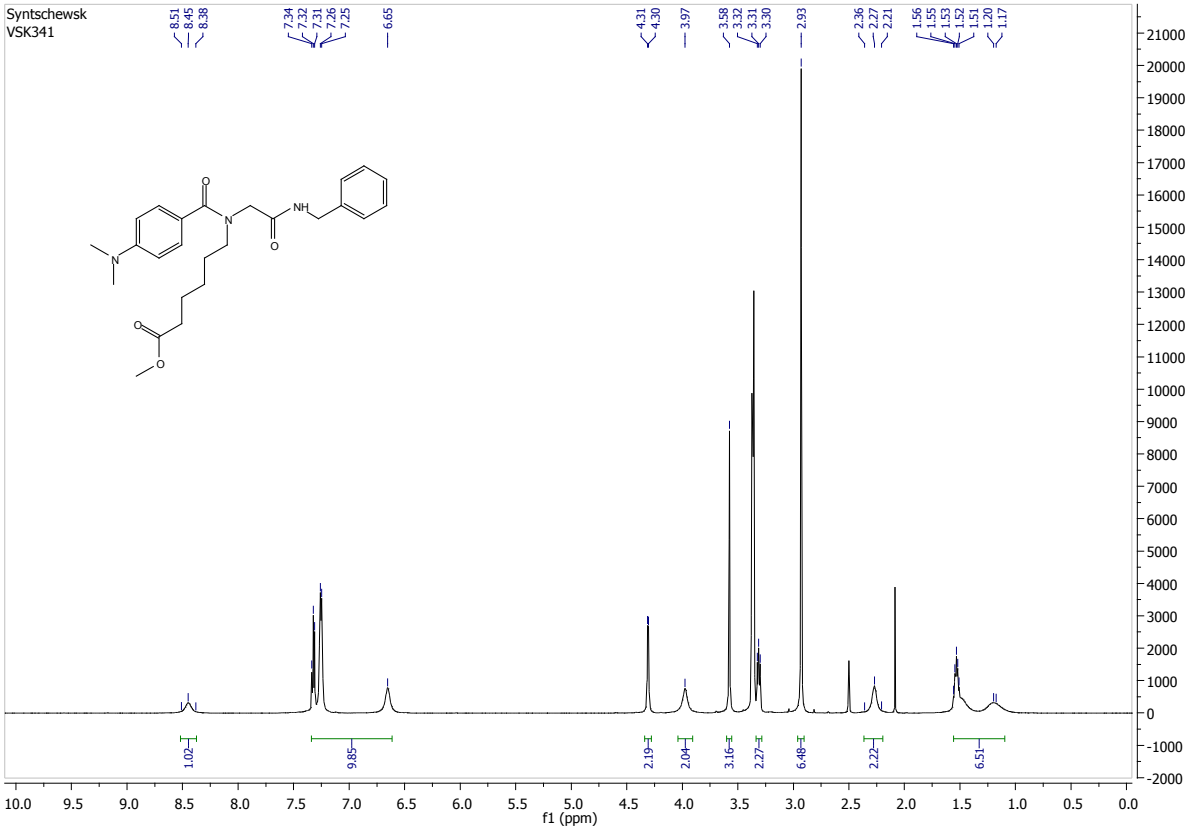
^{13}C NMR (151 MHz, DMSO-d_6) of compound **6h**.



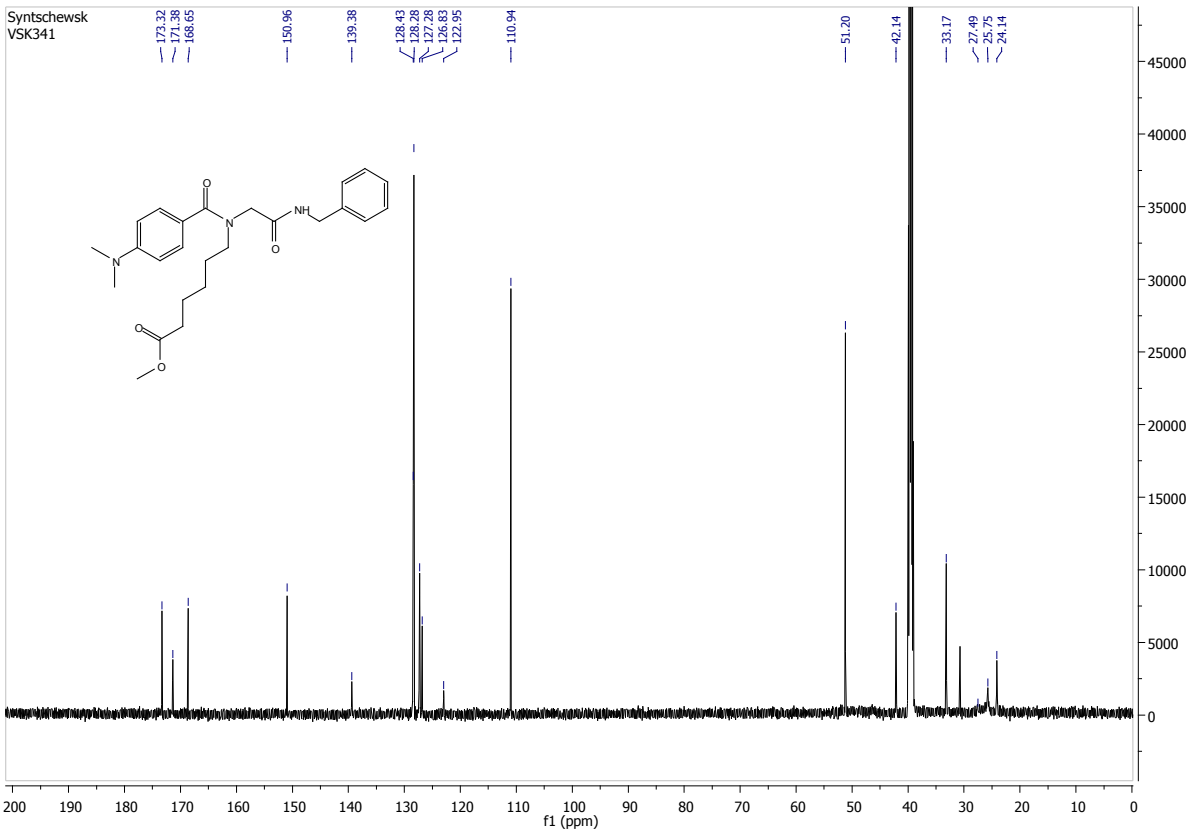
^{1}H NMR (600 MHz, $CDCl_3$) of compound **6i**.



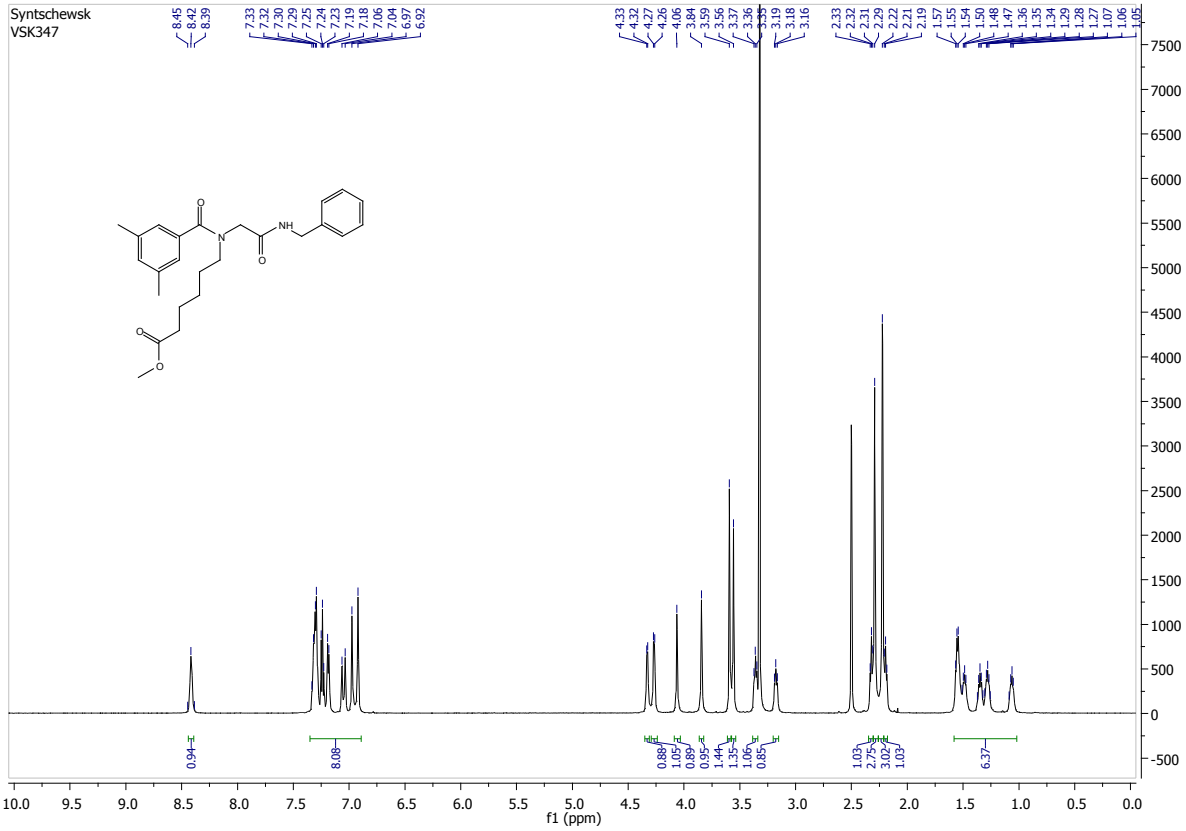
^{13}C NMR (151 MHz, $CDCl_3$) of compound **6i**.



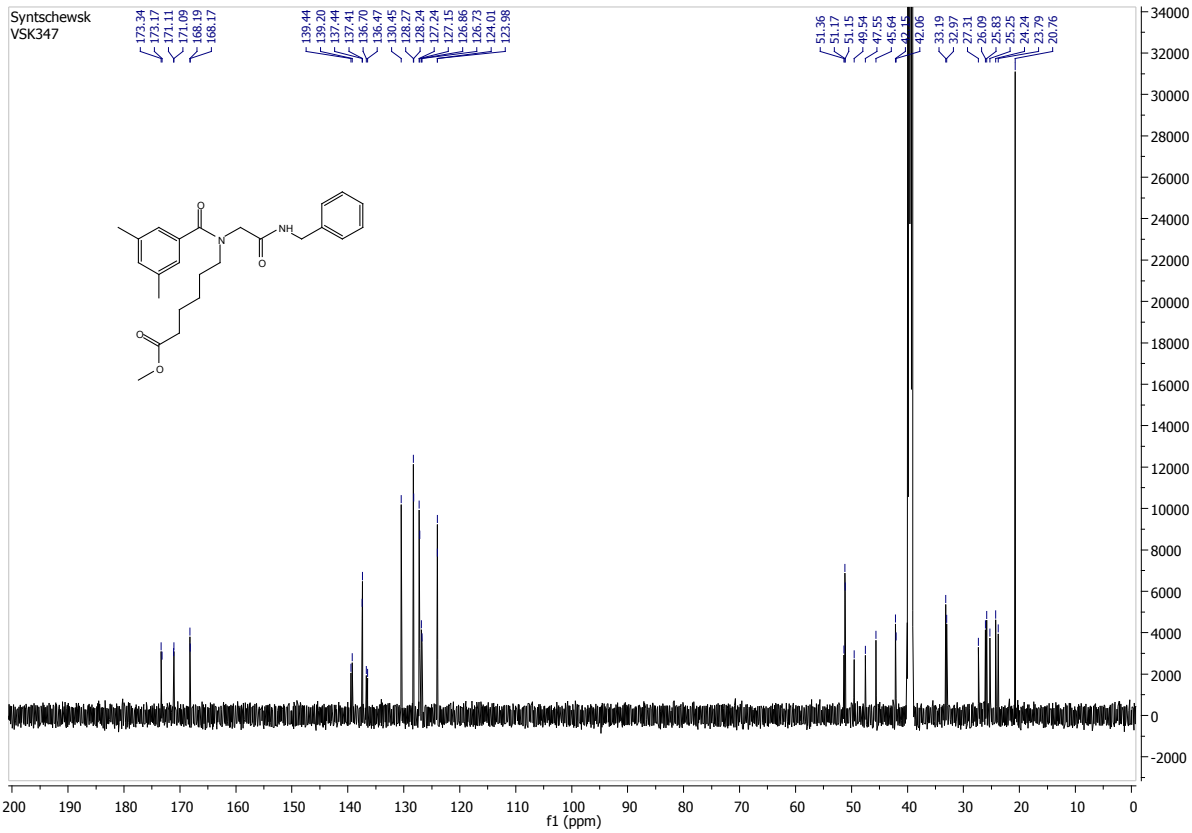
^{1}H NMR (600 MHz, DMSO-d_6) of compound **6j**.



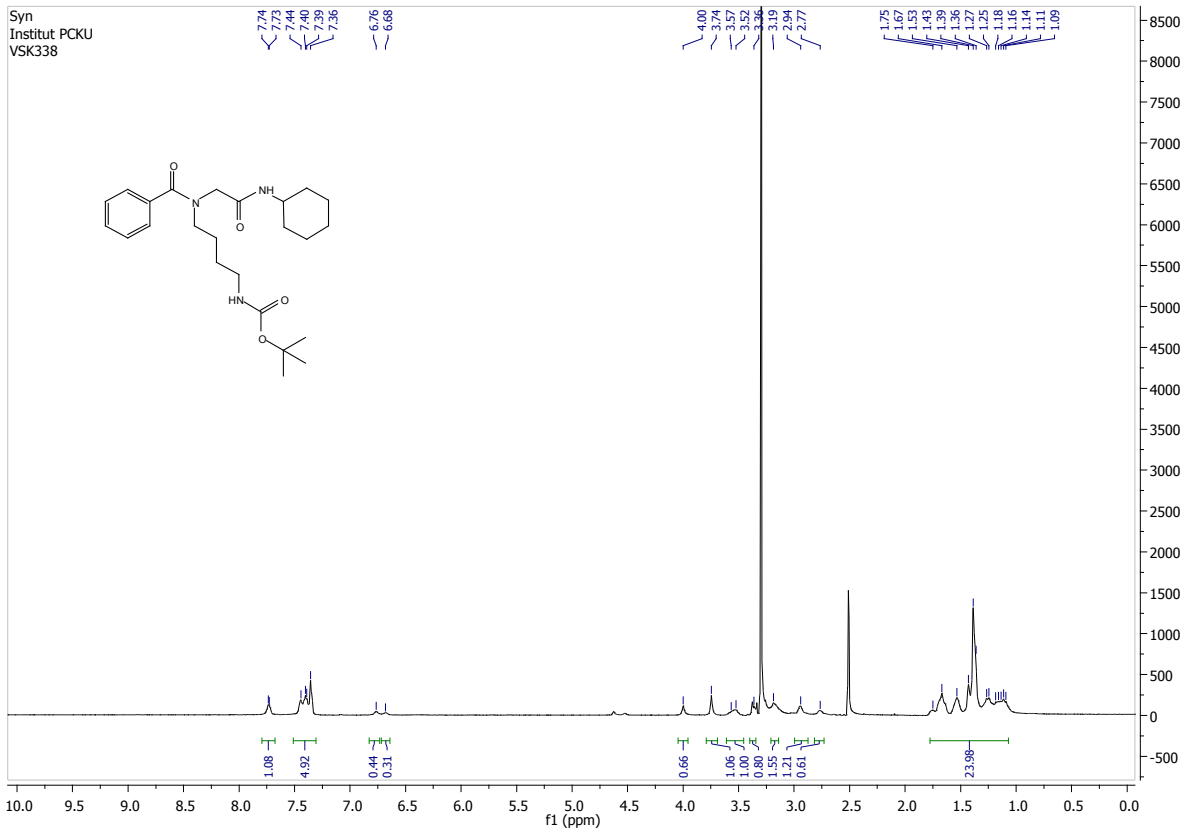
^{13}C NMR (151 MHz, DMSO-d_6) of compound **6j**.



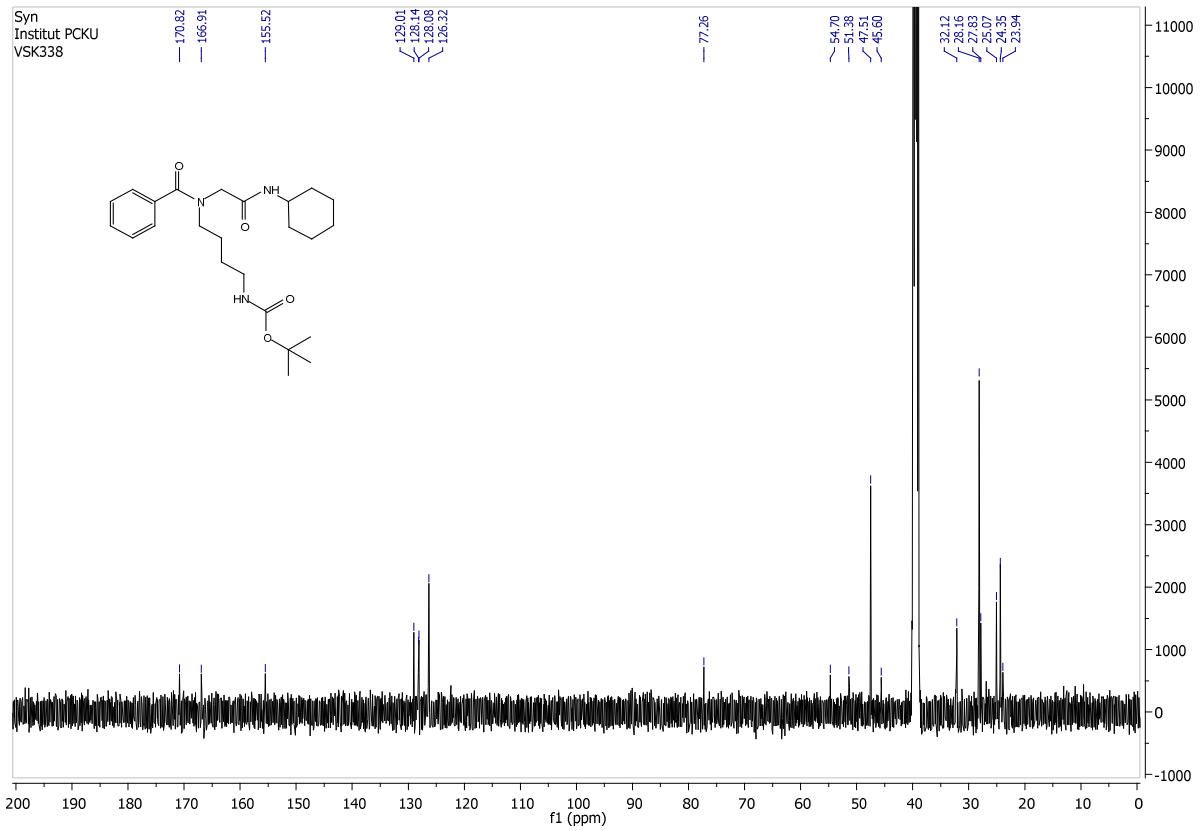
^{1}H NMR (600 MHz, DMSO-d_6) of compound **6k**.



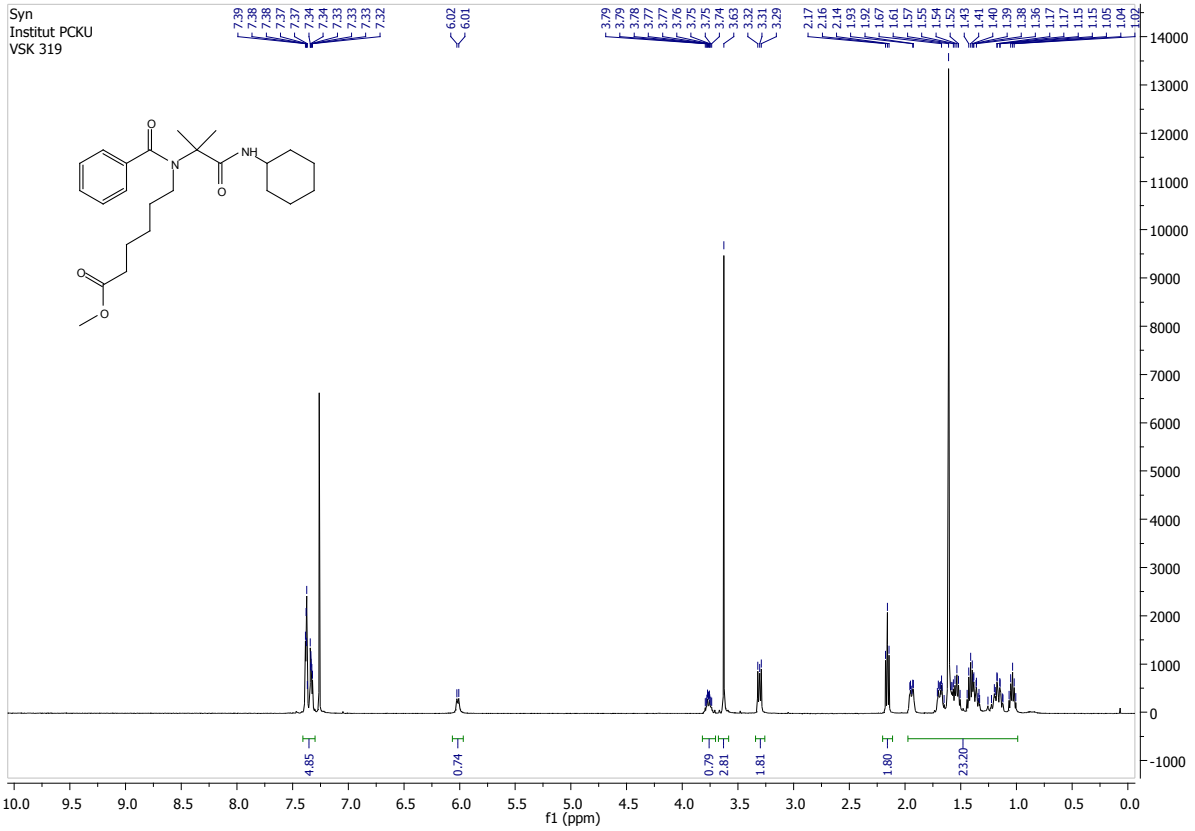
^{13}C NMR (151 MHz, DMSO-d_6) of compound **6k**.



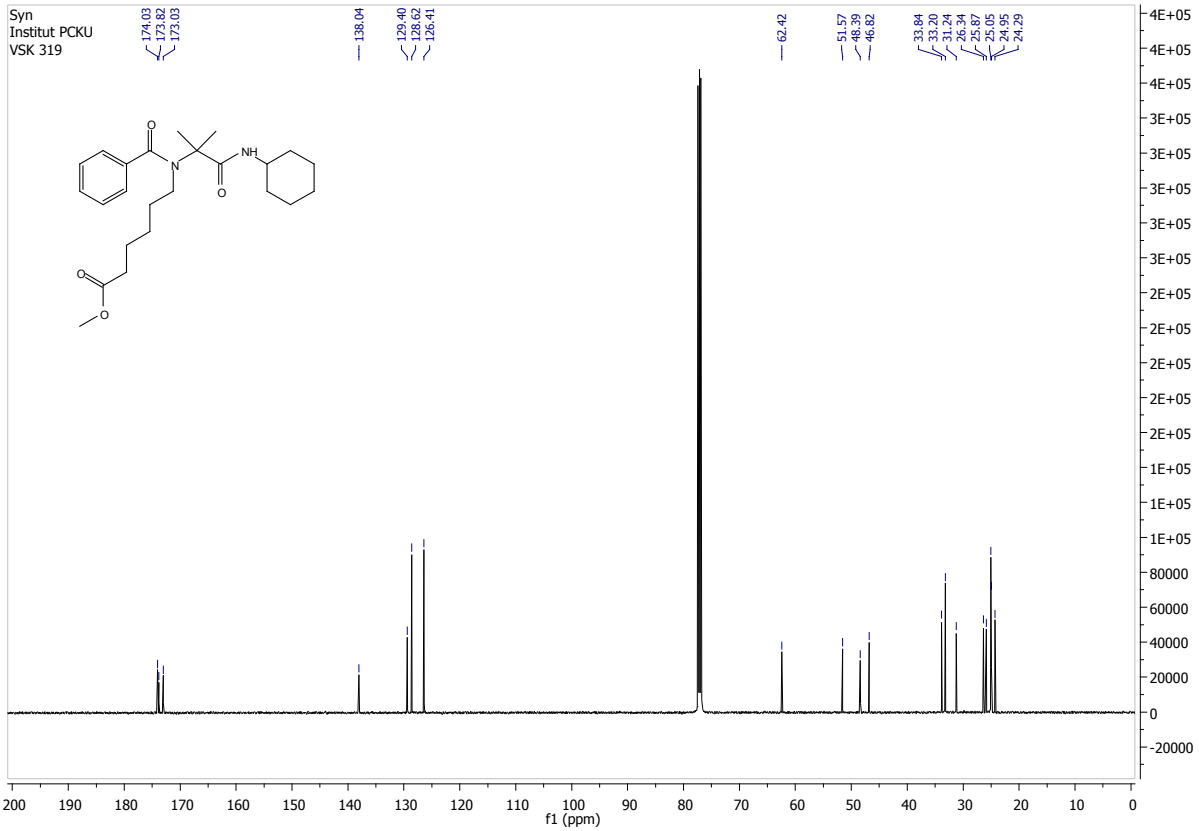
^{1}H NMR (500 MHz, DMSO-d_6) of compound **7**.



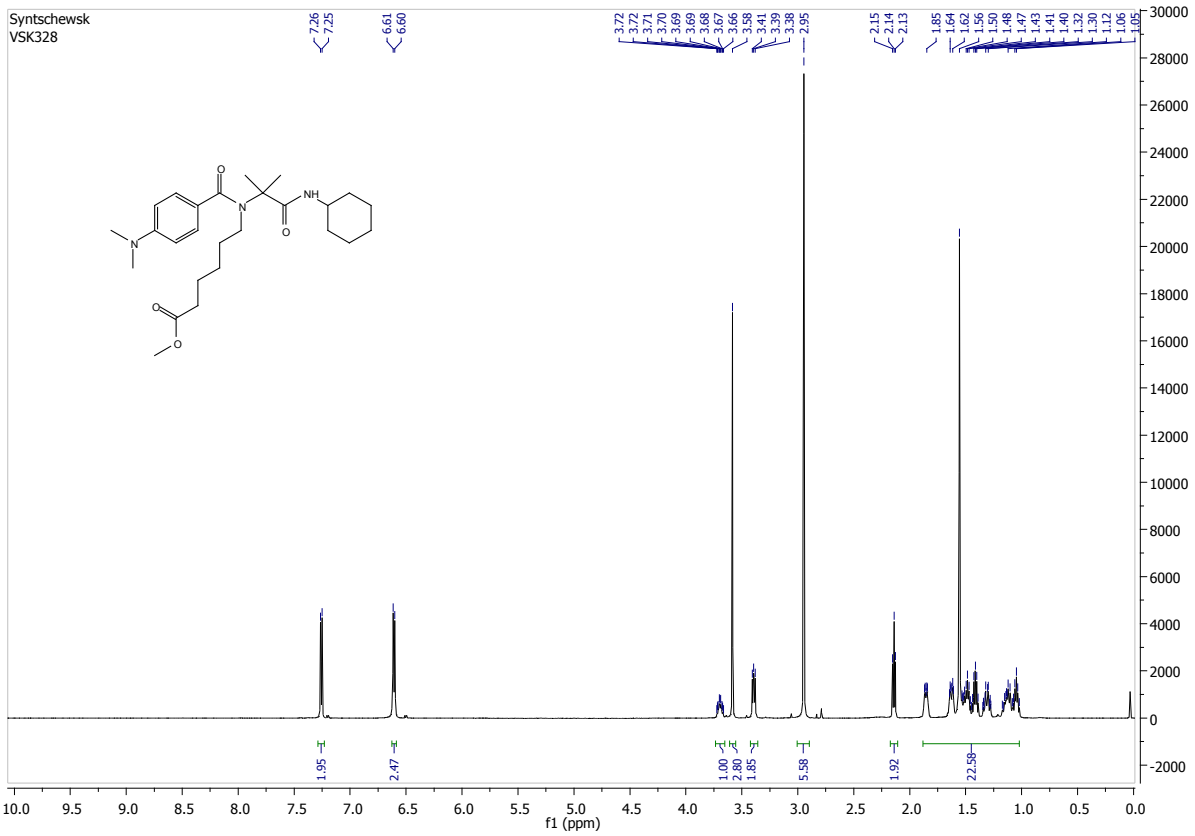
^{13}C NMR (126 MHz, DMSO-d_6) of compound **7**.



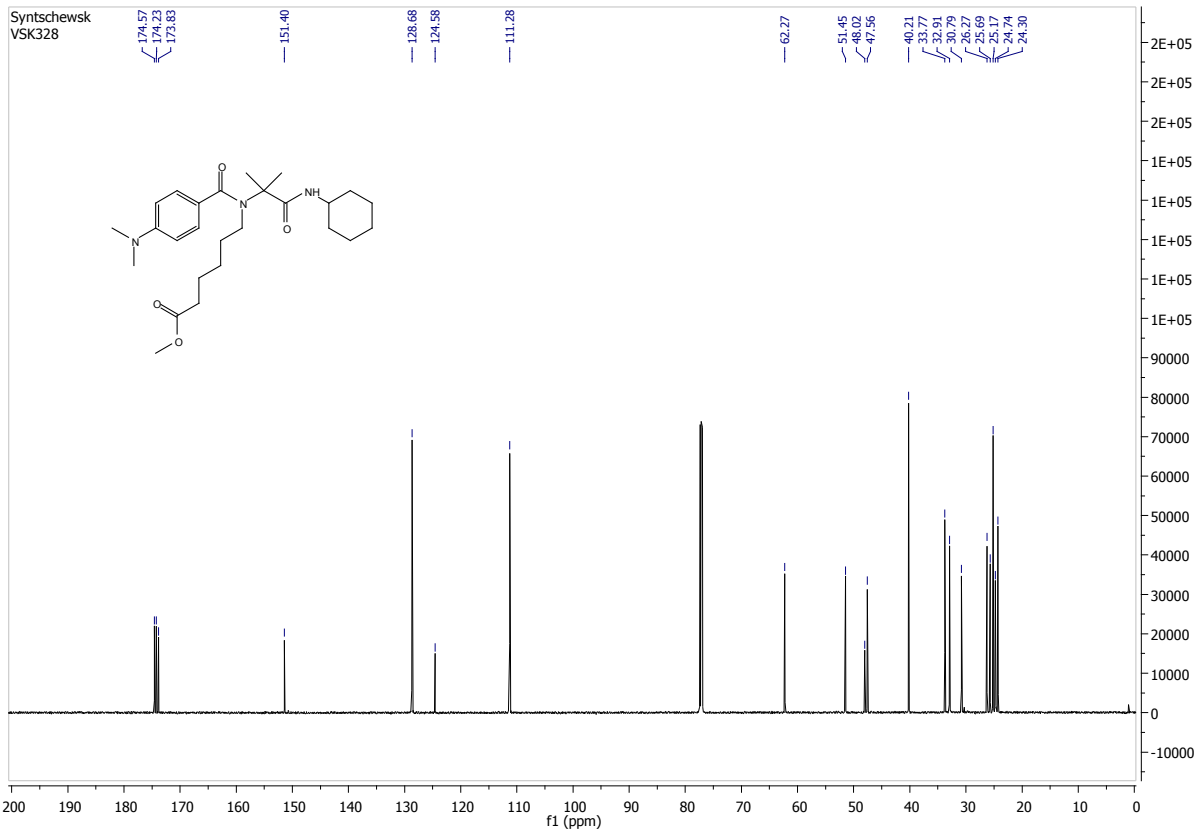
^{1}H NMR (600 MHz, $CDCl_3$) of compound **8a**.



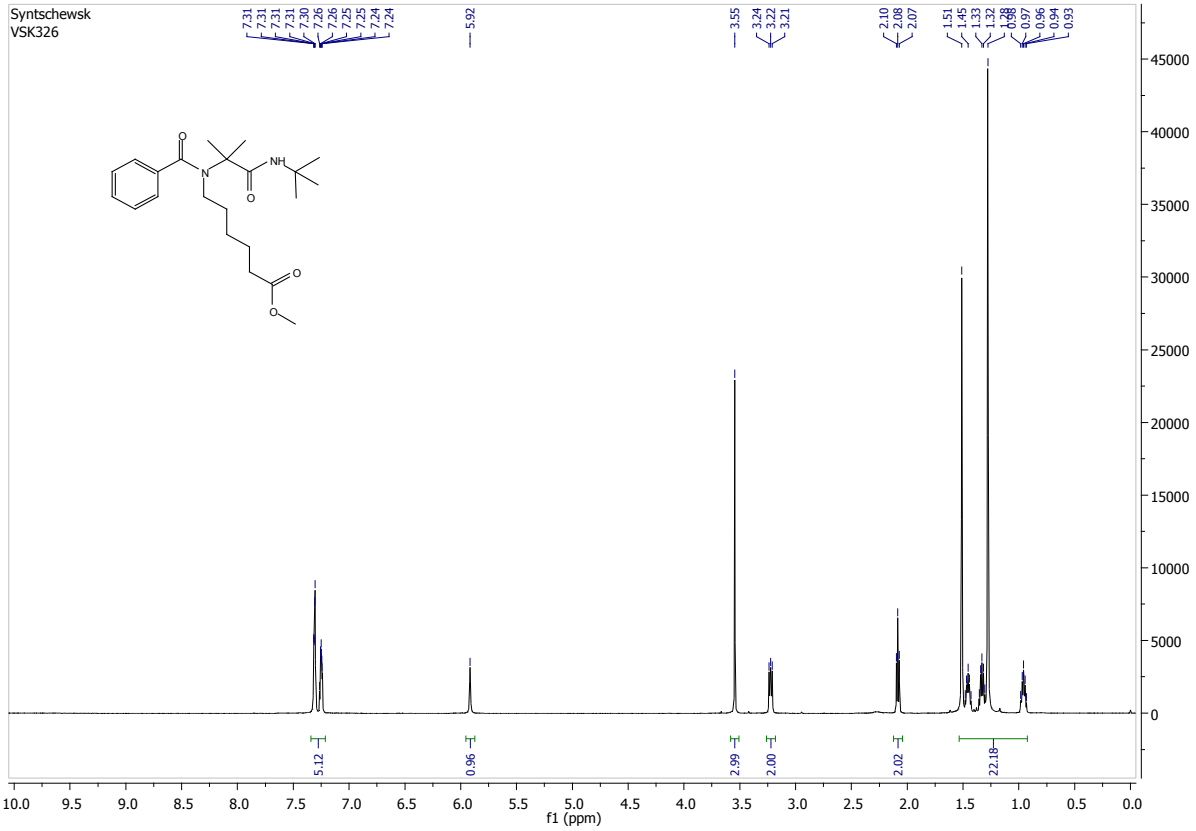
^{13}C NMR (151 MHz, $CDCl_3$) of compound **8a**.



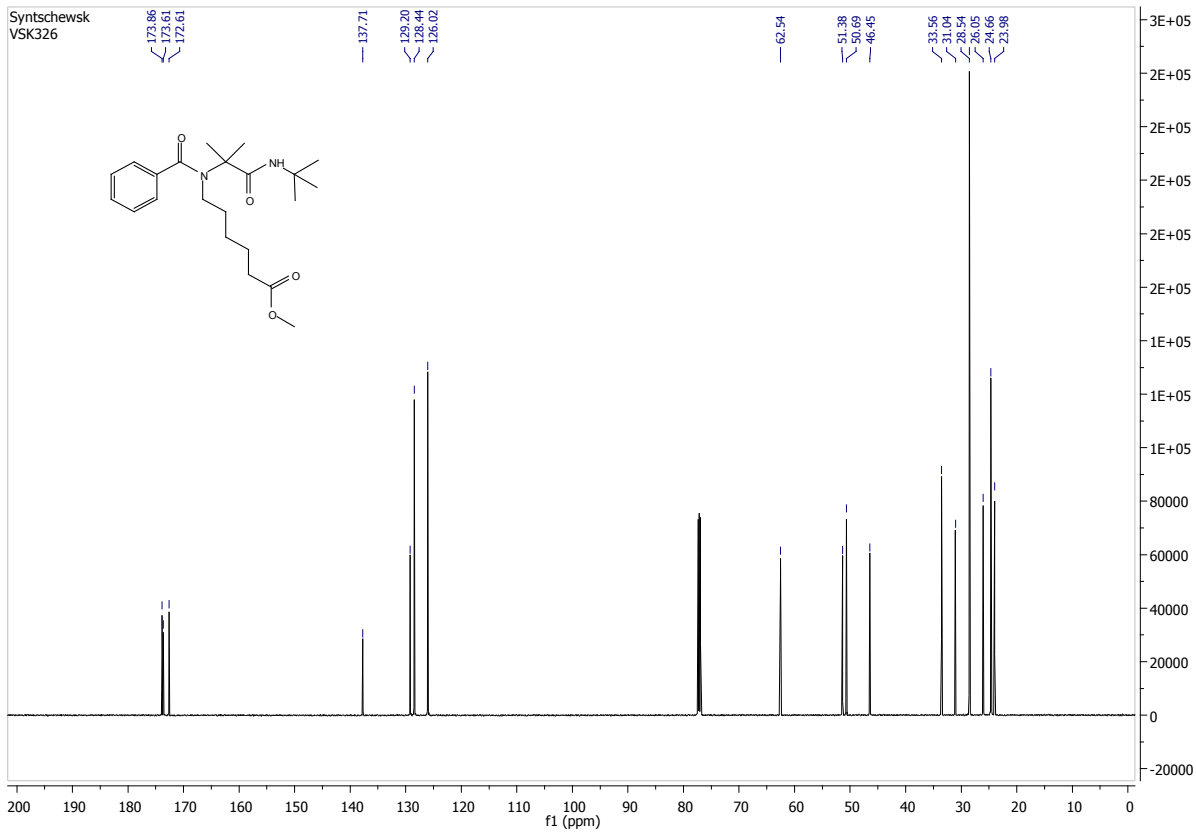
^{1}H NMR (600 MHz, $CDCl_3$) of compound **8b**.



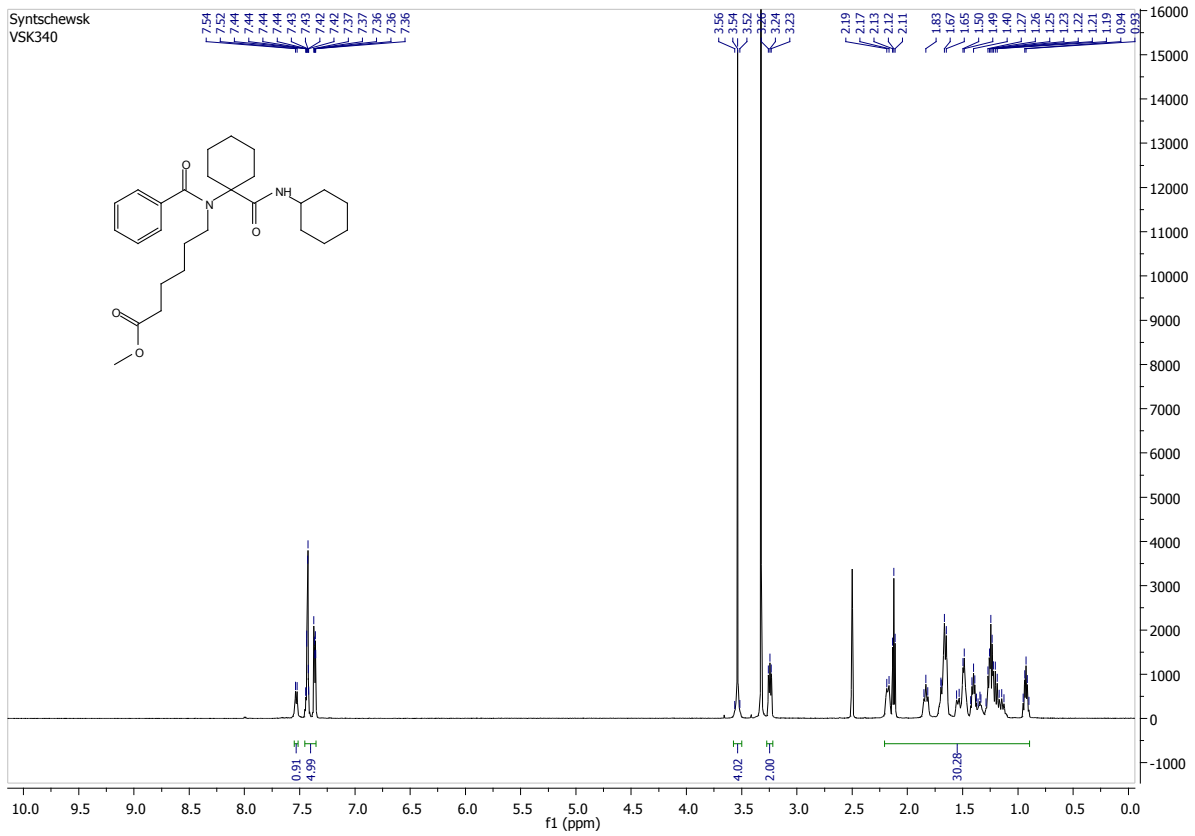
^{13}C NMR (151 MHz, $CDCl_3$) of compound **8b**.



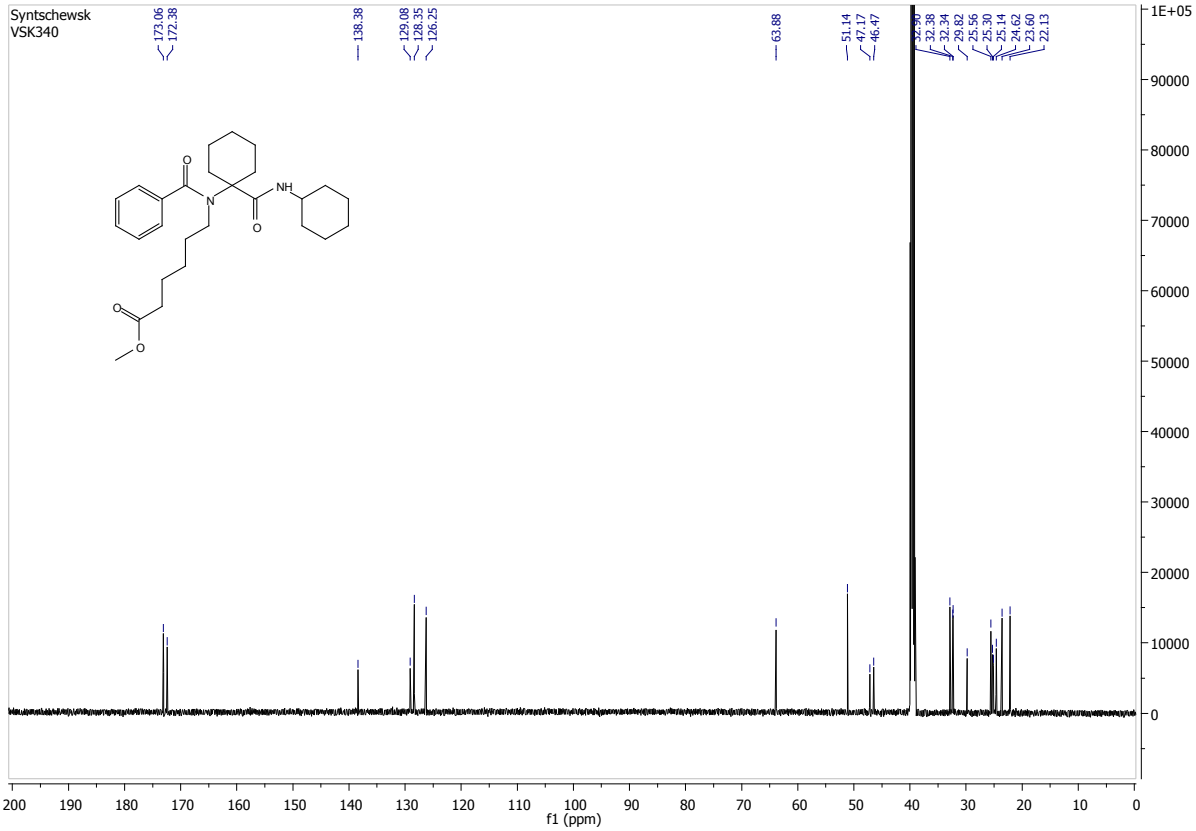
^{1}H NMR (600 MHz, $CDCl_3$) of compound **8c**.



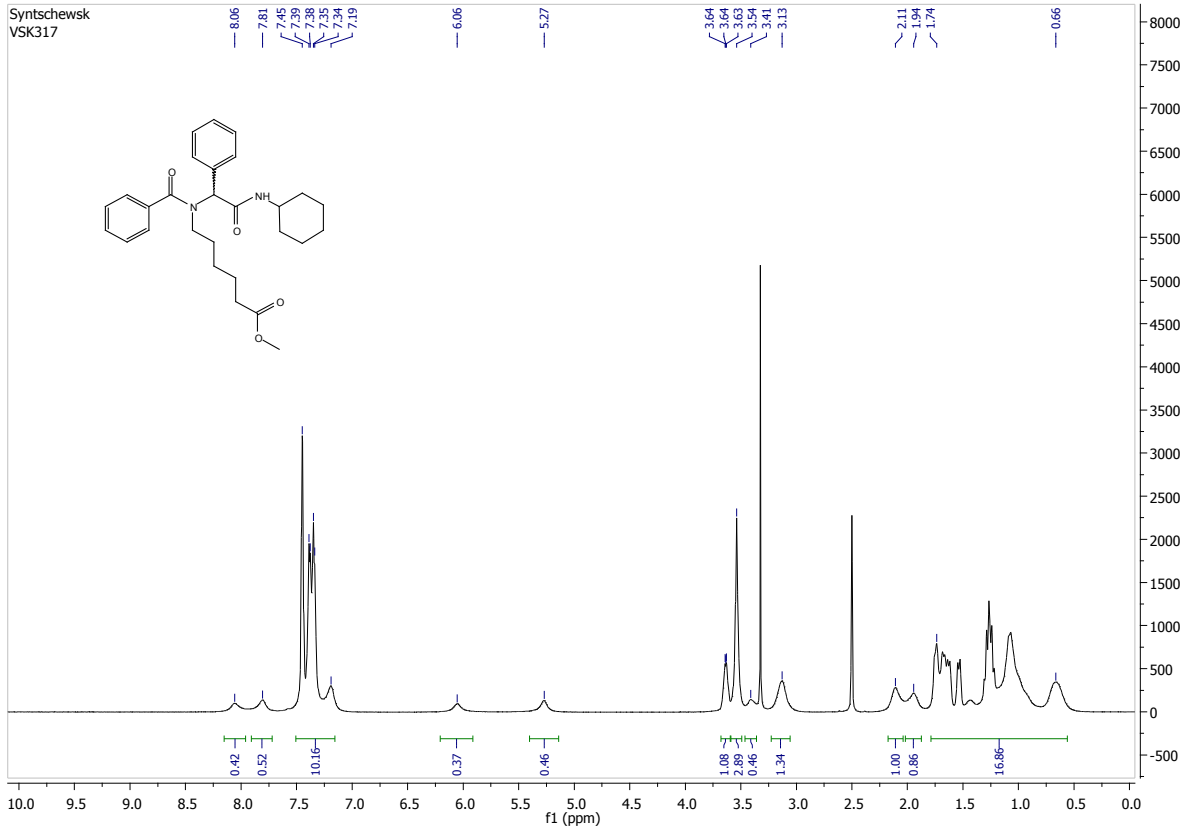
^{13}C NMR (151 MHz, $CDCl_3$) of compound **8c**.



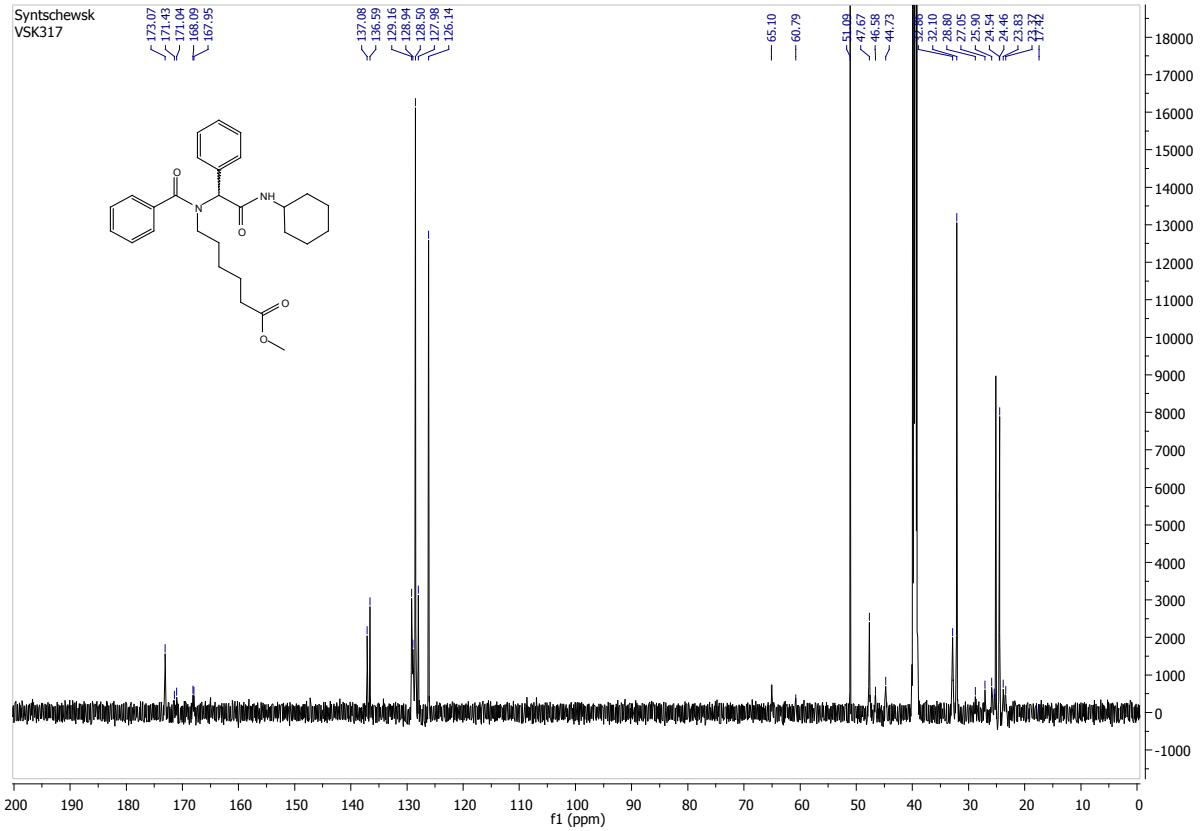
^{1}H NMR (600 MHz, DMSO-d_6) of compound **8d**.



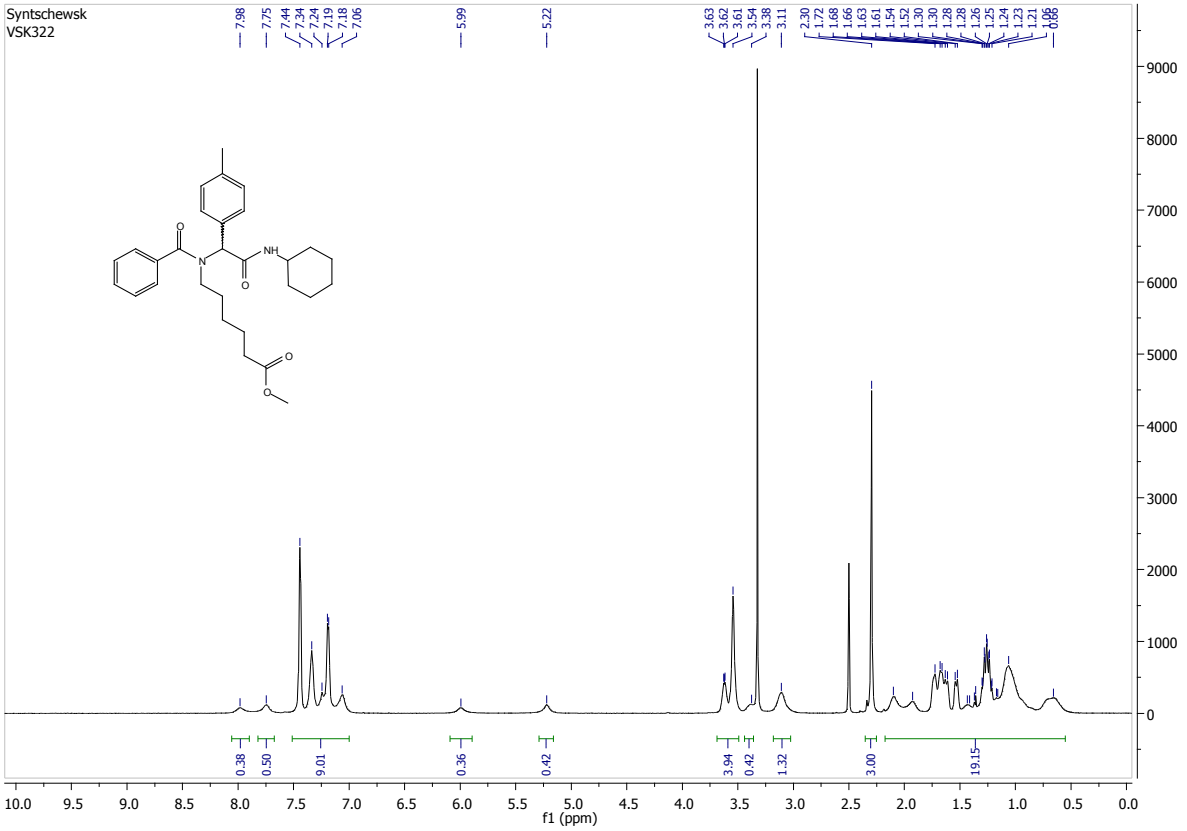
^{13}C NMR (151 MHz, DMSO-d_6) of compound **8d**.



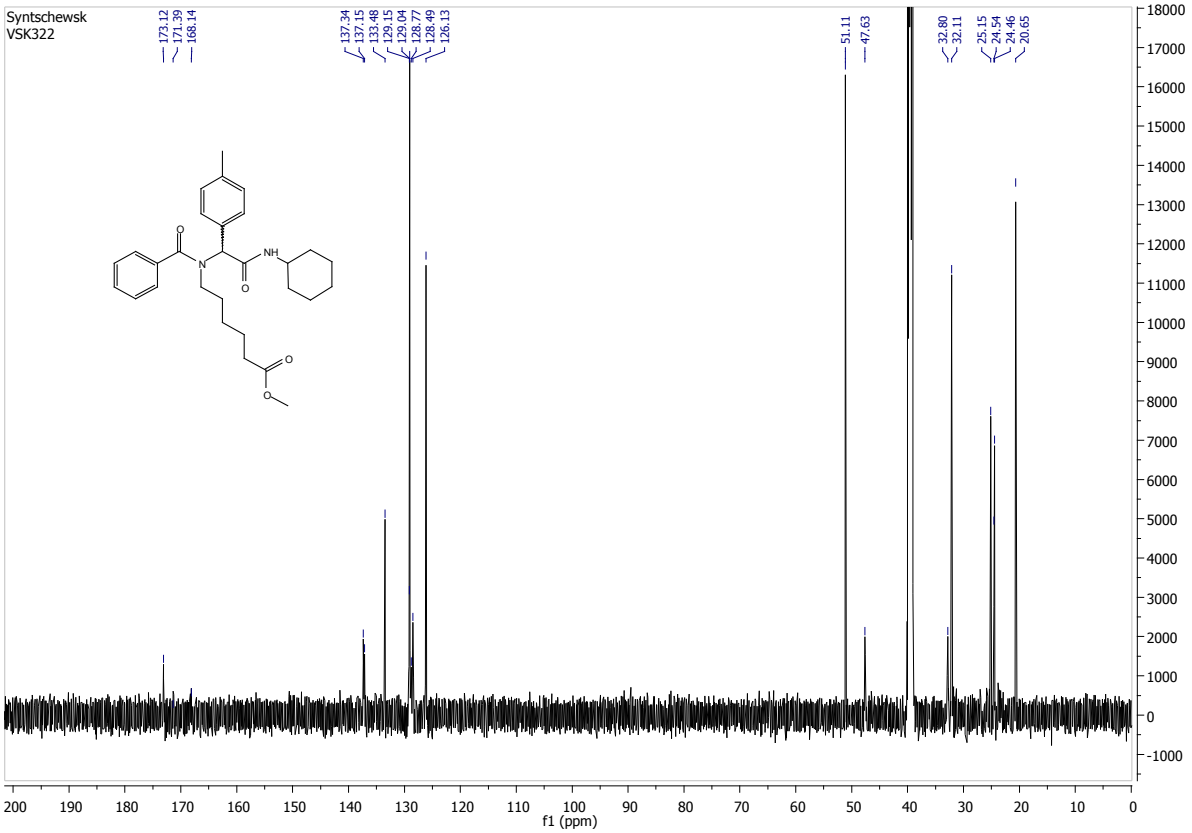
^{1}H NMR (600 MHz, DMSO-d_6) of compound **8e**.



^{13}C NMR (151 MHz, DMSO-d_6) of compound **8e**.



^{1}H NMR (600 MHz, DMSO-d_6) of compound **8f**.



^{13}C NMR (151 MHz, DMSO-d_6) of compound **8f**.

4. References

1. Hai, Y.; Christianson, D. W. Histone deacetylase 6 structure and molecular basis of catalysis and inhibition. *Nat. Chem. Biol*. **2016**, *12*, 741–747.
2. Marek, L.; Hamacher, A.; Hansen, F. K.; Kuna, K.; Gohlke, H.; Kassack, M. U.; Kurz, T. Histone deacetylase (HDAC) inhibitors with a novel connecting unit linker region reveal a selectivity profile for HDAC4 and HDAC5 with improved activity against chemoresistant cancer cells. *J. Med. Chem.* **2013**, *56*, 427–436.