

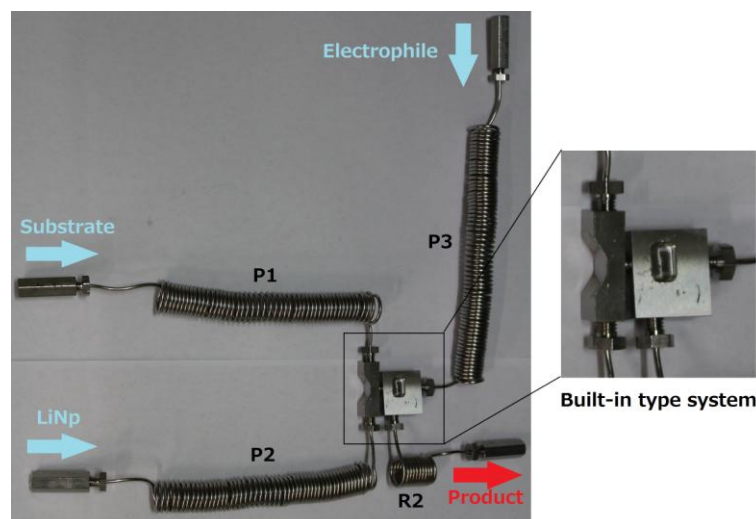
## Benzyllithiums Bearing Aldehyde Carbonyl Groups. A Flash Chemistry Approach

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### General Information

GC analysis was performed on a SHIMADZU GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column, CBP1; 0.22 mm x 25 m).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on Varian MERCURYplus-400 ( $^1\text{H}$  400 MHz and  $^{13}\text{C}$  100 MHz) spectrometer with  $\text{Me}_4\text{Si}$  or  $\text{CDCl}_3$  as a standard in  $\text{CDCl}_3$ . EI mass spectra were recorded on JMS-SX102A spectrometer. ESI mass spectra were recorded on a JEOL JMS-T100CS spectrometer. APCI mass spectra were recorded on EXACTIVE spectrometer. FT-IR spectra were recorded on SHIMADZU IRAffinity-1 spectrometer. Tetrahydrofuran and diethyl ether were purchased from Kanto Chemical Co., Inc. as a dry solvent and used without further purification. Benzyl chloride, benzyl bromide, lithium, naphthalene, methanol, methyl iodide, benzaldehyde, acetone, benzophenone, trimethylsilyl chloride, phenyl isocyanate, trimethylsilyl triflate, methyl triflate, 2-formylthiophene, toluene, bibenzyl, ethylbenzene, 2-methyl-1-phenylpropan-2-ol, benzyl trimethylsilane, 2-methylthiophene, 2-ethylthiophene, 1-(*p*-tolyl)propan-1-one, 4-methylbenzaldehyde, 1-(4-ethylphenyl)ethan-1-one, 2-thiophenemethanol, thionyl chloride, dichloromethane, zinc chloride, cyclohexyl magnesium chloride, 4-(chloromethyl)benzoyl chloride, *N*-bromosuccinimide, benzoyl peroxide, 4-ethylbenzaldehyde, carbon tetrachloride, phosphoryl trichloride, bis[ $\alpha,\alpha$ -bis(trifluoromethyl)benzenemethanolato]diphenylsulfur (martin sulfurane), sulfuric acid, and *N,N*-dimethylformamide were commercially available. Commercial available starting materials were purchased and used without further purification. 1-(4-(Chloromethyl)phenyl)propan-1-one,<sup>1</sup> 1-(4-(bromomethyl)phenyl)propan-1-one,<sup>2</sup> 1-(3-(chloromethyl)phenyl)propan-1-one,<sup>3</sup> (4-(chloromethyl)phenyl)(phenyl)methanone,<sup>4</sup> 1-(4-(chloromethyl)phenyl)ethan-1-one,<sup>5</sup> 4-(chloromethyl)benzaldehyde,<sup>6</sup> 3-(chloromethyl)benzaldehyde,<sup>7</sup> and 2-(chloromethyl)benzaldehyde<sup>8</sup> were synthesized according to the literature. All solutions used for flow reactions were prepared under the argon atmosphere using dry solvents.

Stainless steel (SUS304) T-shaped micromixers with inner diameter of 250, 500 and 800  $\mu\text{m}$  were manufactured by Sanko Seiki Co., Inc. The stainless steel (SUS316) integrated device (inner diameter of **M1**, **M2** and **R1**: 250  $\mu\text{m}$ , length of **R1**: 1.0 cm) was manufactured by YMC Co., Ltd. Stainless steel (SUS316) microtube reactors with inner diameter of 1000  $\mu\text{m}$  were purchased from GL Sciences. The micromixers and microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUN) (Figure S1). The flow microreactor system was dipped in a cooling bath to control the temperature. The solutions of reaction components, except that of lithium naphthalenide were introduced to the flow microreactor system using SHIMADZU LC-6AD plunger pumps. A solution of lithium naphthalenide was introduced to the flow microreactor system using Hurue Science *JP-H* micro feeder pumps equipped with syringes.



**Figure S1.** A picture of the flow microreactor system involving build-in type system

### Synthesis of 2-(Chloromethyl)thiophene

2-Thiophenemethanol (9.9 ml, 134 mmol) was added dropwise to  $\text{SOCl}_2$  (13.54 g, 114 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 ml) at room temperature over 30 min. Then, the solution was stirred at 30 °C for 30 min. Then, the bath was removed and the solution was stirred at an ambient temperature. After extraction with EtOAc, the organic layer was concentrated and distilled (55 °C, 8 Torr) to give 2-(chloromethyl)thiophene as a colorless liquid (12.2 g, 90%). The spectral data were identical to those of reported in the literature.<sup>9</sup>

### Synthesis of (4-(Chloromethyl)phenyl)(cyclohexyl)methanone

Zinc chloride (4.57 g, 33.5 mmol) was dissolved in THF (35 ml) and the solution was stirred at room temperature for 4 h. The solution was cooled to -10 °C and cyclohexyl magnesium chloride (16.4 ml, 32.8 mmol) (2.0 M in  $\text{Et}_2\text{O}$  solution) was added dropwise over 10 min. After being stirred for 30 min,  $\text{CuCN}\cdot 2\text{LiCl}$  solution was added. After being stirred for 30 min, 4-(chloromethyl)benzoyl chloride (5.01 g, 26.5 mmol) in THF (100 ml) was added. After being stirred for 2 h, the solution was quenched with  $\text{NH}_4\text{Cl}:\text{NH}_3$  (2:1) solution. The organic layer was separated and the remaining aqueous layer was extracted with  $\text{Et}_2\text{O}$  (200 ml $\times$ 3). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to give (4-(chloromethyl)phenyl)(cyclohexyl)methanone (4.54 g, 96%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.93 (dt,  $J$  = 8.4 Hz,  $J$  = 2.0 Hz, 2H), 7.48 (dt,  $J$  = 8.0 Hz,  $J$  = 2.0 Hz, 2H) 4.62 (s, 2H), 3.27-3.20 (m 1H), 1.90-1.25 (m 10H),  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  203.2, 150.3, 141.9, 136.1, 128.7, 45.6, 45.3, 29.3, 25.9, 25.8; HRMS (APCI) calcd. for  $\text{C}_{14}\text{H}_{18}\text{ClO}$  [ $\text{MH}^+$ ]: 237.1046, found: 237.1031; IR: 1672  $\text{cm}^{-1}$ .

### Synthesis of 4-(1-Bromoethyl)benzaldehyde

*N*-Bromosuccinimide (10.95 g, 0.062 mol) and benzoyl peroxide (0.080 g) were added to 4-ethylbenzaldehyde (6.7 g, 0.050 mol) in  $\text{CCl}_4$  (150 ml) and the mixture was refluxed. After stirred for 3 h, the solution was cooled to 5 °C, the precipitated succinimide was removed by filtration and the solid was washed with  $\text{CCl}_4$ . The filtrate and washings were combined and the solvent was evaporated. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to afford 4-(1-bromoethyl)benzaldehyde (6.2 g, 59%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.01 (s, 1H), 7.87 (dt,  $J$  = 8.4 Hz,  $J$  = 2.0 Hz, 2H), 7.60 (dt,  $J$  = 8.4 Hz,  $J$  = 2.0 Hz, 2H), 5.02 (q,  $J$  = 6.8 Hz, 1H), 2.07 (dd,  $J$  = 4.0 Hz,  $J$  = 2.0 Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  191.5, 149.5, 136.1, 130.1, 127.5, 47.6, 26.4; HRMS (APCI) calcd. for  $\text{C}_9\text{H}_{10}\text{BrO}$  [ $\text{MH}^+$ ]: 212.9915, found: 212.9907; IR: 1700  $\text{cm}^{-1}$ .

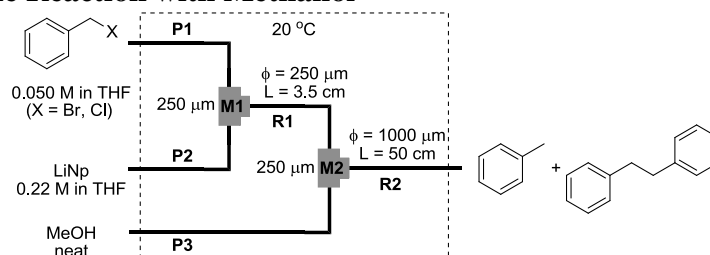
### Synthesis of 5-(Chloromethyl)thiophene-2-carbaldehyde

2-(Chloromethyl)thiophene (10.44 g, 79.1 mmol) in DMF (19.2 ml) was added to  $\text{POCl}_3$  (8.20 ml, 87.8 mmol) at room temperature and the solution was warmed to 80 °C. After being stirred for 3 h, the solution was cooled to room temperature and aq.  $\text{NaHCO}_3$  was added. The organic layer was separated and the remaining aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (200 ml $\times$ 3). The combined organic phase was washed by brine. The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 8/1) to afford 5-(chloromethyl)thiophene-2-carbaldehyde (3.30 g, 27%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.88 (s, 1H), 7.64 (d,  $J$  = 4.0 Hz, 1H), 7.18 (dt,  $J$  = 4.0 Hz,  $J$  = 0.8 Hz, 1H), 4.78 (d,  $J$  = 0.8 Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.8, 150.1, 144.2, 136.1, 128.2, 39.8; HRMS (EI) calcd. for  $\text{C}_6\text{H}_6\text{ClOS}$  [ $\text{MH}^+$ ]: 159.9750, found: 159.9748; IR: 1650  $\text{cm}^{-1}$ .

### Preparation of lithium naphthalenide (LiNp)

The preparation of lithium naphthalenide was carried out in a glovebox. Naphthalene (4.79 g, 37.4 mmol) was dissolved in anhydrous THF (169.5 ml) (0.22 M). Lithium (0.326 g, 47.1 mmol) was added and the mixture was stirred for 2 h until the solution became dark green, indicating that the reaction was completion.<sup>10</sup>

### Flow Microreactor System for the Lithiation of Benzyl Halides with Lithium Naphthalenide (LiNp) Followed by the Reaction with Methanol

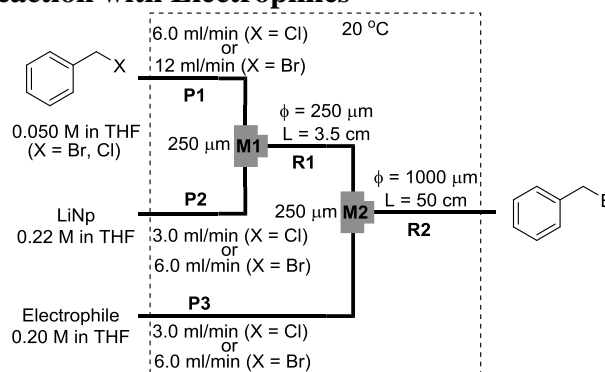


A flow microreactor system consisting of two T-shaped micromixers (**M1**, **M2**), two microtube reactors (**R1**, **R2**), and three pre-cooling units (**P1** (inner diameter  $\phi$  = 1000  $\mu$ m, length  $L$  = 300 cm), **P2** ( $\phi$  = 1000  $\mu$ m,  $L$  = 300 cm) and **P3** ( $\phi$  = 1000  $\mu$ m,  $L$  = 300 cm)) was used. The flow microreactor system was dipped in a cooling bath (20 °C). A solution of benzyl halides (0.05 M in THF) was introduced to **M1** using a plunger pump. A solution of lithium naphthalenide (LiNp) (0.22 M in THF) was introduced to **M1** using a micro feeder pump. The mixed solution was passed through **R1** ( $\phi$  = 250  $\mu$ m,  $L$  = 3.5 cm) and was introduced to **M2**. Methanol (neat) (flow rate: 3.0 mL/min) was introduced to **M2** ( $\phi$  = 250  $\mu$ m) using a plunger pump, and the resulting solution was passed through **R2** ( $\phi$  = 1000  $\mu$ m,  $L$  = 50 cm). After a steady state was reached, an aliquot of the product solution was collected and was treated with sat. aqueous  $\text{NH}_4\text{Cl}$ . Conversions of benzyl chloride ( $t_R$  10.4 min) and benzyl bromide ( $t_R$  12.2 min) (initial oven temperature, 160 °C (18 min); temperature increase rate, 18 °C/min (5 min); final temperature, 250 °C (10 min)), and yields of toluene ( $t_R$  4.2 min) and bibenzyl ( $t_R$  19.4 min) were determined by GC analysis (initial oven temperature, 160 °C (18 min); temperature increase rate, 18 °C/min (5 min); final temperature, 250 °C (10 min)) using an internal standard (tetradecane). The results are summarized in Table S-1.

**Table S-1.** Effect of the flow rate and the inner diameter of **M1** in the lithiation of benzyl halides using the flow microreactor system.

X	flow rate (mL/min)			inner diameter of <b>M1</b> ( $\mu$ m)	conversion (%)	yield (%)	
	benzyl halide	LiNp	total			toluene	bibenzyl
Cl	6.00	3.00	9.00	800	100	28	20
	6.00	3.00	9.00	500	100	70	13
	6.00	3.00	9.00	250	100	89	4
	3.00	1.50	4.50	250	100	81	4
	1.50	0.750	2.25	250	100	29	6
Br	6.00	3.00	9.00	800	100	15	29
	6.00	3.00	9.00	500	100	38	30
	6.00	3.00	9.00	250	100	77	10
	12.0	6.00	22.5	250	100	80	8
	3.00	1.50	4.50	250	100	49	24
	1.50	0.750	2.25	250	100	39	30

#### Flow Microreactor System for the Lithiation of Benzyl Halides with Lithium Naphthalenide (LiNp) Followed by the Reaction with Electrophiles



A flow microreactor system consisting of two T-shaped micromixers (**M1**, **M2**), two microtube reactors (**R1**, **R2**), and three pre-cooling units (**P1** (inner diameter  $\phi$  = 1000  $\mu$ m, length  $L$  = 300 cm), **P2** ( $\phi$  = 1000  $\mu$ m,  $L$  = 300 cm) and **P3** ( $\phi$  = 1000  $\mu$ m,  $L$  = 300 cm)) was used. The flow microreactor system was dipped in a cooling bath (20 °C). A solution of benzyl halides (0.05 M in THF) was introduced to **M1** using a plunger pump (6.0 mL/min (X = Cl) or 12 mL/min (X = Br)). A solution of lithium naphthalenide (LiNp) (0.22 M in THF) was introduced to **M1** using a micro feeder pump (3.0 mL/min (X = Cl) or 6.0 mL/min (X = Br)). The mixed solution was passed through **R1** ( $\phi$  = 250  $\mu$ m,  $L$  = 3.5 cm). The reaction mixture was mixed with a solution of electrophile (0.20 M in THF) in **M2** ( $\phi$  = 250  $\mu$ m) using a plunger pump (3.0 mL/min (X = Cl) or 6.0 mL/min (X = Br)), and the resulting solution was passed through **R2** ( $\phi$  = 1000  $\mu$ m,  $L$  = 50 cm). After a steady state was reached, an aliquot

of the product solution was collected and was treated with sat. aqueous  $\text{NH}_4\text{Cl}$  solution. Organic layer was analyzed by gas chromatography. The product was isolated by flash chromatography. The reaction of 2-(chloromethyl)thiophene was carried out under the same condition of benzyl bromide.

**Ethylbenzene.** Methyl iodide was used as an electrophile. Yields (82% ( $\text{X} = \text{Cl}$ ), 82% ( $\text{X} = \text{Br}$ )) were determined by GC analysis ( $t^{\text{R}}$  6.9 min) (initial oven temperature, 160 °C (18 min); temperature increase rate, 18 °C/min (5 min); final temperature, 250 °C (10 min)) using an internal standard (tetradecane). The spectral data were identical to those of commercially available authentic sample.

**1,2-Diphenylethan-1-ol.** Benzaldehyde was used as an electrophile. After extraction with EtOAc, the crude product was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to afford 1,2-diphenylethan-1-ol (80% ( $\text{X} = \text{Cl}$ ), 75% ( $\text{X} = \text{Br}$ )).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37-7.19 (m, 10H), 4.91 (dd,  $J = 8.4$  Hz,  $J = 4.8$  Hz, 1H), 3.08-2.96 (m, 2H), 1.93 (s, 1H); The spectral data were identical to those of reported in the literature.<sup>11</sup>

**2-Methyl-1-phenylpropan-2-ol.** Acetone was used as an electrophile. Yield (42% ( $\text{X} = \text{Cl}$ )) was determined by GC analysis ( $t^{\text{R}}$  13.5 min) (initial oven temperature, 160 °C (18 min); temperature increase rate, 18 °C/min (5 min); final temperature, 250 °C (10 min)) using an internal standard (tetradecane). The spectral data were identical to those of commercially available authentic sample.

**1,1,2-Triphenylethan-1-ol.** Benzophenone was used as an electrophile. After extraction with EtOAc, the crude product was purified by silica gel column chromatography (hexane/EtOAc = 20/1) to afford 1,1,2-triphenylethan-1-ol (93% ( $\text{X} = \text{Cl}$ ), 71% ( $\text{X} = \text{Br}$ )).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44-7.27 (m, 8H), 7.26-7.12 (m, 5H), 6.91-6.87 (m, 2H), 3.65 (s, 2H), 2.30 (s, 1H); The spectral data were identical to those of reported in the literature.<sup>12</sup>

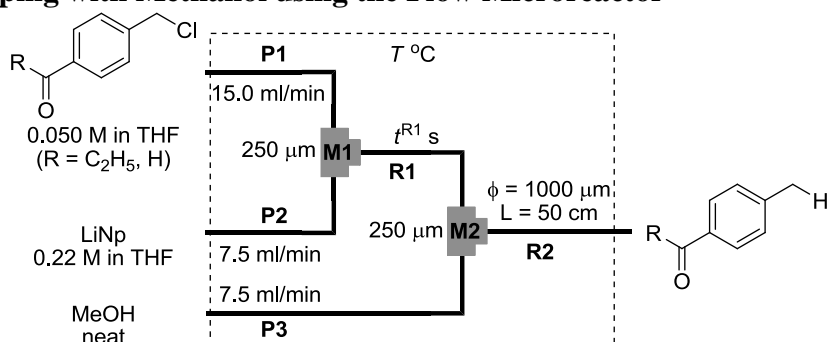
For gram-scale synthesis ( $\text{X} = \text{Cl}$ ), the product solution was collected for 15 min while being quenched with the sat. aq.  $\text{NH}_4\text{Cl}$  solution (50 mL). After AcOEt (100 mL) and brine (50 mL) was added, the organic layer was separated and the remaining aqueous layer was extracted with AcOEt (30 mL  $\times$  3). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated. The crude product was purified by column chromatography (hexane/AcOEt = 20:1) to obtain the title compound in 88% yield (1.09 g).

**Benzyltrimethylsilane.** Chlorotrimethylsilane was used as an electrophile. Yield (80% ( $\text{X} = \text{Cl}$ )) was determined by GC analysis ( $t^{\text{R}}$  12.4 min) (initial oven temperature, 160 °C (18 min); temperature increase rate, 18 °C/min (5 min); final temperature, 250 °C (10 min)) using an internal standard (tetradecane). The spectral data were identical to those of a commercially available authentic sample.

**2-Methylthiophene.** Methanol was used as an electrophile. Yield 97% was determined by GC analysis ( $t^{\text{R}}$  5.0 min) (initial oven temperature, 160 °C (18 min); temperature increase rate, 18 °C/min (5 min); final temperature, 250 °C (10 min)) using an internal standard (tetradecane). The spectral data were identical to those of commercially available authentic sample.

**2-Ethylthiophene.** Methyl iodide was used as an electrophile. Yield 72% was determined by GC analysis ( $t^{\text{R}}$  7.1 min) (initial oven temperature, 160 °C (18 min); temperature increase rate, 18 °C/min (5 min); final temperature, 250 °C (10 min)) using an internal standard (tetradecane). The spectral data were identical to those of commercially available authentic sample.

**Effects of the Temperature ( $T$ ) and the Residence Time ( $t^{\text{R1}}$ ) on the Yields of the Protonated Product for the Lithiation of *p*-Propanoylbenzyl and *p*-Formylbenzyl Chloride with LiNp Followed by Trapping with Methanol using the Flow Microreactor**



A flow microreactor system consisting of two T-shaped micromixers (**M1**, **M2**), two microtube reactors (**R1**, **R2**), and three pre-cooling units (**P1** (inner diameter  $\phi$  = 1000  $\mu\text{m}$ , length  $L$  = 300 cm), **P2** ( $\phi$  = 1000  $\mu\text{m}$ ,  $L$  = 300 cm) and **P3** ( $\phi$  = 1000  $\mu\text{m}$ ,  $L$  = 300 cm)) was used. The flow microreactor system was dipped in a cooling bath to control the temperature. A solution of *p*-propanoylbenzyl chloride or *p*-formylbenzyl chloride (0.05 M in THF) was introduced to **M1** using a plunger pump (15 mL/min). A solution of lithium naphthalenide (LiNp) (0.22 M in THF) was introduced to **M1** using a micro feeder pump (7.5 mL/min). The mixed solution was passed through **R1**. The reaction mixture was mixed with a solution of methanol (neat) in **M2** ( $\phi$  = 250  $\mu\text{m}$ ) using a plunger pump (7.5 mL/min), and the resulting solution was passed through **R2** ( $\phi$  = 1000  $\mu\text{m}$ ,  $L$  = 50 cm). After a steady state was reached, an aliquot of the product solution was collected and the solution was treated with sat. aqueous  $\text{NH}_4\text{Cl}$  solution. The reaction mixture was analyzed by GC. When the residence time in **R1** is 0.0013 s, the build-in type system in which two T-shaped micromixers (**M1** and **M2**) and a microtube reactor (**R1**) were combined was used. The results are summarized in Table S-2 and Table S-3.

**Table S-2.** Effects of the temperature ( $T$ ) and the residence Time in **R1** ( $t^{\text{R1}}$ ) on the yields of 1-(*p*-tolyl)propan-1-one for the lithiation of *p*-propanoylbenzyl chloride with LiNp followed by trapping with methanol using the flow microreactor

inner diameter of <b>R1</b> ( $\mu\text{m}$ )	length of <b>R1</b> (cm)	residence time in <b>R1</b> (s)	temperature ( $^{\circ}\text{C}$ )	conversion (%)	yield (%)
250	1.0	0.00131	0	100	66
500	3.5	0.0183		100	63
1000	6	0.126		100	63
1000	100	2.09		100	53
1000	1000	20.9		100	27
250	1.0	0.00131	-20	100	71
500	3.5	0.0183		100	66
1000	6	0.126		100	60
1000	100	2.09		100	62
1000	1000	20.9		100	35
250	1.0	0.00131	-40	100	75
500	3.5	0.0183		100	69
1000	6	0.126		100	62
1000	100	2.09		100	64
1000	1000	20.9		100	41
250	1.0	0.00131	-60	100	78
500	3.5	0.0183		100	67
1000	6	0.126		100	63
1000	100	2.09		100	64
1000	1000	20.9		100	41
250	1.0	0.00131	-78	100	80
500	3.5	0.0183		100	71
1000	6	0.126		100	67
1000	100	2.09		100	66
1000	1000	20.9		100	43

**Table S-3.** Effects of the temperature ( $T$ ) and the residence Time in **R1** ( $t^{\text{R1}}$ ) on the yields of the protonated product for the lithiation of *p*-formylbenzyl chloride with LiNp followed by trapping with methanol using the flow microreactor

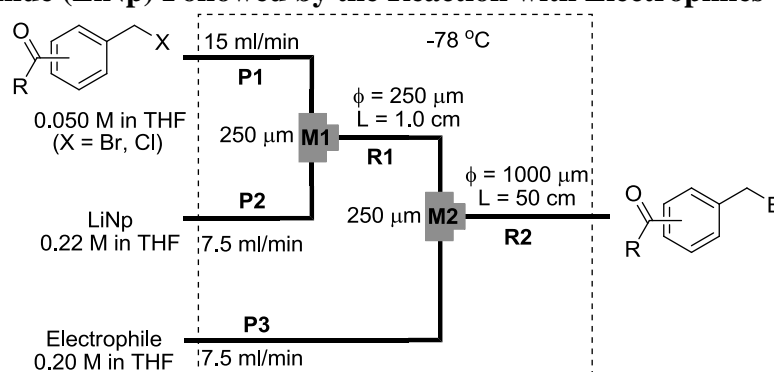
inner diameter of <b>R1</b> ( $\mu\text{m}$ )	length of <b>R1</b> (cm)	residence time in <b>R1</b> (s)	temperature ( $^{\circ}\text{C}$ )	conversion (%)	yield (%)
250	1.0	0.00131	0	100	52
500	3.5	0.0183		100	39
1000	6	0.126		100	31
1000	100	2.09		100	29
1000	1000	20.9		100	14

250	1.0	0.00131	-20	100	60
500	3.5	0.0183		100	45
1000	6	0.126		100	43
1000	100	2.09		100	34
1000	1000	20.9		100	17
250	1.0	0.00131	-40	100	62
500	3.5	0.0183		100	56
1000	6	0.126		100	46
1000	100	2.09		100	40
1000	1000	20.9		100	25
250	1.0	0.00131	-60	100	65
500	3.5	0.0183		100	57
1000	6	0.126		100	58
1000	100	2.09		100	42
1000	1000	20.9		100	38
250	1.0	0.00131	-78	100	68
500	3.5	0.0183		100	61
1000	6	0.126		100	60
1000	100	2.09		100	49
1000	1000	20.9		100	44

**1-(*p*-Tolyl)propan-1-one.** Yields were determined by GC analysis ( $t_R$  8.7 min) (initial oven temperature, 160 °C (18 min); temperature increase rate, 18 °C/min (5 min); final temperature, 250 °C (10 min)) using an internal standard (tetradecane). The spectral data were identical to those of commercially available authentic sample.

**4-Methylbenzaldehyde.** Yields were determined by GC analysis ( $t_R$  11.8 min) (initial oven temperature, 160 °C (18 min); temperature increase rate, 18 °C/min (5 min); final temperature, 250 °C (10 min)) using an internal standard (tetradecane). The spectral data were identical to those of commercially available authentic sample.

#### Flow Microreactor System for the Lithiation of Electrophilic-Functionalized Benzyl Halides with Lithium Naphthalenide (LiNp) Followed by the Reaction with Electrophiles



A flow microreactor system consisting of the build-in type system in which two T-shaped micromixers (**M1** and **M2**) and a microtube reactor (**R1**) were combined, a microreactor **R2**, and three pre-cooling units (**P1** (inner diameter  $\phi$  = 1000  $\mu$ m, length  $L$  = 300 cm), **P2** ( $\phi$  = 1000  $\mu$ m,  $L$  = 300 cm) and **P3** ( $\phi$  = 1000  $\mu$ m,  $L$  = 300 cm)) was used. The flow microreactor system was dipped in a cooling bath (-78 °C). A solution of electrophilic-functionalized benzyl halides (0.05 M in THF) was introduced to **M1** using a plunger pump (15 mL/min). A solution of lithium naphthalenide (LiNp) (0.22 M in THF) was introduced to **M1** using a micro feeder pump (7.5 mL/min). The mixed solution was passed through **R1** ( $\phi$  = 250  $\mu$ m,  $L$  = 1.0 cm) and was introduced to **M2**. A solution of electrophile (0.20 M in THF) was introduced to **M2** ( $\phi$  = 250  $\mu$ m) using a plunger pump (7.5 mL/min), and the resulting solution was passed through **R2** ( $\phi$  = 1000  $\mu$ m,  $L$  = 50 cm). After a steady state was reached, an aliquot of the product solution was collected and the solution was treated with sat. aqueous  $\text{NH}_4\text{Cl}$ .

solution. Organic layer was analyzed by gas chromatography. The product was isolated by flash chromatography and/or GPC.

***N*-Phenyl-2-(4-propionylphenyl)acetamide.** 1-(4-(Chloromethyl)phenyl)propan-1-one or 1-(4-(bromomethyl)phenyl)propan-1-one were used as a benzyl halide. Phenyl isocyanate was used as an electrophile. After extraction with EtOAc, the crude product was purified by GPC to afford *N*-phenyl-2-(4-propionylphenyl)acetamide in 78% yield (1-(4-(chloromethyl)phenyl)propan-1-one) or 60% yield (1-(4-(bromomethyl)phenyl)propan-1-one). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.44 (t, *J* = 8.4 Hz, 4H), 7.32-7.26 (m, 2H), 7.12-7.09 (m, 1H), 7.09-7.05 (m, 1H), 3.79 (s, 2H), 3.02 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 200.5, 168.4, 139.7, 137.5, 135.9, 129.6, 128.9, 128.6, 124.6, 119.9, 44.4, 31.8, 8.2; HRMS (ESI) calcd. for C<sub>17</sub>H<sub>18</sub>NO<sub>2</sub> [MH<sup>+</sup>]: 268.1338, found: 268.1331; IR: 3491, 1660, 1604 cm<sup>-1</sup>.

**1-(4-(2-Hydroxy-2-phenylethyl)phenyl)propan-1-one.** 1-(4-(Chloromethyl)phenyl)propan-1-one or 1-(4-(bromomethyl)phenyl)propan-1-one were used as a benzyl halide. Benzaldehyde was used as an electrophile. After extraction with EtOAc, the crude product was purified by GPC to afford 1-(4-(2-hydroxy-2-phenylethyl)phenyl)propan-1-one in 88% yield (1-(4-(chloromethyl)phenyl)propan-1-one) or 64% yield (1-(4-(bromomethyl)phenyl)propan-1-one). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.85 (dd, *J* = 8.4 Hz, *J* = 2.0 Hz, 2H), 7.35-7.23 (m, 7H), 4.91-4.87 (m, 1H), 3.10-3.02 (m, 2H), 2.98-2.92 (m, 2H), 2.32 (br s, 1H), 1.21-1.17 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 200.6, 143.6, 143.5, 135.1, 129.7, 128.4, 128.0, 127.7, 125.8, 75.0, 45.7, 31.6, 8.2; HRMS (APCI) calcd. for C<sub>17</sub>H<sub>19</sub>O<sub>2</sub> [MH<sup>+</sup>]: 255.1385, found: 255.1375; IR: 3492, 1658 cm<sup>-1</sup>.

**1-(3-((Trimethylsilyl)methyl)phenyl)propan-1-one.** 1-(3-(Chloromethyl)phenyl)propan-1-one was used as a benzyl halide. Trimethylsilyl triflate in Et<sub>2</sub>O was used as an electrophile. After extraction with EtOAc, the crude product was purified by GPC to afford 1-(3-((trimethylsilyl)methyl)phenyl)propan-1-one in 68% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.68-7.66 (m, 1H), 7.60 (t, *J* = 1.6 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 2.98 (q, *J* = 7.2 Hz, 2H), 2.14 (s, 2H), 1.22 (t, *J* = 7.6 Hz, 3H), -0.01 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 201.2, 141.1, 136.8, 132.5, 128.3, 127.3, 123.8, 31.8, 27.0, 8.3, -2.0; HRMS (APCI) calcd. for C<sub>13</sub>H<sub>21</sub>OSi [MH<sup>+</sup>]: 221.1362, found: 221.1348; IR: 1684 cm<sup>-1</sup>.

**1-(3-(2-Hydroxy-2-phenylethyl)phenyl)propan-1-one.** 1-(3-(Chloromethyl)phenyl)propan-1-one was used as a benzyl halide. Benzaldehyde was used as an electrophile. After extraction with EtOAc, the crude product was purified by GPC to afford 1-(3-(2-hydroxy-2-phenylethyl)phenyl)propan-1-one in 67% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.81 (m, 1H), 7.75 (s, 1H), 7.37-7.29 (m, 7H), 4.92 (t, *J* = 6.4 Hz, 1H), 3.78 (d, *J* = 6.8 Hz, 2H), 2.95 (q, *J* = 7.2 Hz, 2H), 1.95 (br s, 1H), 1.20 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 200.9, 143.6, 138.6, 137.0, 134.1, 129.0, 128.5, 128.5, 127.5, 126.2, 125.9, 75.2, 45.7, 31.8, 8.2; HRMS (ESI) calcd. for C<sub>17</sub>H<sub>18</sub>ClO<sub>2</sub> [MCl<sup>+</sup>]: 289.0095, found: 289.1002; IR: 2921, 1685 cm<sup>-1</sup>.

**(4-(2-Hydroxy-2-phenylethyl)phenyl)(phenyl)methanone.** (4-(Chloromethyl)phenyl)(phenyl)methanone was used as a benzyl halide. Benzaldehyde was used as an electrophile. After extraction with EtOAc, the crude product was purified by GPC to afford (4-(2-hydroxy-2-phenylethyl)phenyl)(phenyl)methanone in 89% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.79-7.76 (m, 2H), 7.73 (d, *J* = 6.0 Hz, 2H), 7.60-7.56 (m, 2H), 7.51-7.46 (m, 2H), 7.39-7.25 (m, 6H), 4.94 (dd, *J* = 7.2 Hz, *J* = 1.6 Hz, 1H), 3.11-3.09 (m, 2H), 2.08 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 196.4, 143.5, 143.2, 137.7, 135.8, 132.3, 130.3, 129.9, 129.4, 128.5, 128.2, 127.8, 125.9, 75.1, 45.8; HRMS (APCI) calcd. for C<sub>21</sub>H<sub>19</sub>O<sub>2</sub> [MH<sup>+</sup>]: 303.1385, found: 303.1378; IR: 3483, 1632 cm<sup>-1</sup>.

**2-(4-(Cyclohexanecarbonyl)phenyl)-*N*-phenylacetamide.** (4-(chloromethyl)phenyl)(cyclohexyl)methanone was used as a benzyl halide. Phenyl isocyanate was used as an electrophile. After extraction with EtOAc, the crude product was purified by GPC to afford 2-(4-(Cyclohexanecarbonyl)phenyl)-*N*-phenylacetamide in 77% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.94 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.46-7.44 (m, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.27-7.23 (m, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 3.70 (d, *J* = 2.8 Hz, 2H), 3.22 (m, 1H), 1.97-1.71 (m, 5H), 1.52-1.23 (m, 5H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 203.6, 168.5, 139.7, 137.6, 135.2, 129.6, 128.8, 128.8, 124.5, 120.0, 45.6, 44.3, 29.3, 25.8, 25.7; HRMS (ESI) calcd. for C<sub>21</sub>H<sub>24</sub>NO<sub>2</sub> [MH<sup>+</sup>]: 322.1807, found: 322.1800; IR: 1671, 1660 cm<sup>-1</sup>.

**Cyclohexyl(4-(2-hydroxy-2-phenylethyl)phenyl)methanone.** (4-(Chloromethyl)phenyl)(cyclohexyl)methanone was used as a benzyl halide. Benzaldehyde was used as an electrophile. After extraction with EtOAc, the crude product was purified by GPC to afford cyclohexyl(4-(2-hydroxy-2-phenylethyl)phenyl)methanone in 83% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.86-7.83 (m, 2H), 7.36-7.23 (m, 7H), 4.90 (dd, *J* = 7.6 Hz, *J* = 6.0 Hz, 1H), 3.22 (tt, *J* = 11.2, *J* = 3.2 Hz, 1H), 2.20 (s, 1H), 1.93-1.70 (m, 5H), 1.52-1.19 (m, 5H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 203.6, 143.6, 143.4, 134.6, 129.7, 128.4, 128.4, 127.7, 125.8, 75.0, 45.7, 45.5, 29.4, 25.9, 25.8; HRMS (ESI) calcd. for C<sub>21</sub>H<sub>25</sub>O<sub>2</sub> [MH<sup>+</sup>]: 309.1855, found: 309.1841; IR: 3489, 1654 cm<sup>-1</sup>.

**1-(4-(2-Hydroxy-2-phenylethyl)phenyl)ethan-1-one.** 1-(4-(Chloromethyl)phenyl)ethan-1-one was used as a benzyl halide. Benzaldehyde was used as an electrophile. After extraction with EtOAc, the crude product was purified by GPC to afford 1-(4-(2-hydroxy-2-phenylethyl)phenyl)ethan-1-one in 85% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.27-7.18 (m, 7H), 4.86 (dd, *J* = 7.2 Hz, *J* = 6.0 Hz, 1H), 3.02-3.00 (m, 2H), 2.50 (s, 3H), 1.84 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 197.9, 143.8, 143.5, 135.5, 129.8, 128.5, 128.4, 127.8, 125.8, 75.1, 45.8, 26.6; HRMS (APCI) calcd. for C<sub>16</sub>H<sub>17</sub>O<sub>2</sub> [MH<sup>+</sup>]: 241.1229, found: 241.1218; IR: 3513, 1659 cm<sup>-1</sup>.

**1-(4-Ethylphenyl)ethan-1-one.** 1-(4-(chloromethyl)phenyl)ethan-1-one was used as a benzyl halide. Methyl triflate in Et<sub>2</sub>O was used as an electrophile. Yield 41% was determined by GC analysis (*t*<sub>R</sub> 15.5 min) (initial oven temperature, 160 °C (18 min); temperature increase rate, 18 °C/min (5 min); final temperature, 250 °C (10 min)) using an internal standard (tetradecane) (41%). The spectral data were identical to those of commercially available authentic sample.

**4-(2-Hydroxy-2-phenylethyl)benzaldehyde.** 4-(Chloromethyl)benzaldehyde was used as a benzyl halide. Benzaldehyde was used as an electrophile. After extraction with EtOAc, the crude product was purified by GPC to afford 4-(2-hydroxy-2-phenylethyl)benzaldehyde in 55% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.90 (s, 1H), 7.73 (dt, *J* = 8.0 Hz, *J* = 1.6 Hz, 2H), 7.30-7.19 (m, 7H), 4.88 (dd, *J* = 7.6 Hz, *J* = 5.6 Hz, 1H), 3.09-3.00 (m, 2H), 1.86 (br s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 192.0, 145.5, 143.4, 134.9, 130.2, 129.8, 128.5, 127.9, 125.8, 75.1, 45.9; HRMS (NSI) calcd. for C<sub>15</sub>H<sub>15</sub>O<sub>2</sub> [MH<sup>+</sup>]: 227.1072, found: 227.1067; IR: 3443, 1679 cm<sup>-1</sup>.

**4-((Trimethylsilyl)methyl)benzaldehyde.** 4-(Chloromethyl)benzaldehyde was used as a benzyl halide. Trimethylsilyl triflate in Et<sub>2</sub>O was used as an electrophile. After extraction with EtOAc, the crude product was purified by GPC to afford 4-((trimethylsilyl)methyl)benzaldehyde in 58% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.92 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 2.20 (s, 2H), 0.06 (s, 9H); The spectral data were identical to those reported in the literature.<sup>13</sup>

**3-Phenylisochroman-1-ol.** 2-(Chloromethyl)benzaldehyde was used as a benzyl halide. Benzaldehyde was used as an electrophile. After extraction with EtOAc, the crude product was purified by silica gel column chromatography the crude product was purified by GPC to afford 3-phenylisochroman-1-ol in 59% yield (diastereomeric ratio = 87:13 (determined by <sup>1</sup>H NMR)). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.48-7.23 (m, 8H), 7.16-7.10 (m, 1H), 6.13 (d, *J* = 3.2 Hz) and 6.06 (d, *J* = 8.0 Hz) (total 1H, two diastereomers), 5.24 (dd, *J* = 11.6 Hz, *J* = 3.2 Hz) and 4.91 (dd, *J* = 11.2 Hz, *J* = 3.2 Hz) (total 1H, two diastereomers), 3.54 (br s) and 3.42 (br s) (total 1H, two diastereomers), 3.17-3.08 (m) and 3.07-2.98 (m) (total 1H, two diastereomers), 2.96-2.86 (m, 1H); The spectral data were identical to those reported in the literature.<sup>14</sup>

**4-(1-Hydroxy-1-phenylpropan-2-yl)benzaldehyde.** 4-(1-Bromoethyl)benzaldehyde was used as a benzyl halide. Benzaldehyde was used as an electrophile. After extraction with EtOAc, the crude product was purified by GPC to afford 4-(1-hydroxy-1-phenylpropan-2-yl)benzaldehyde in 76% yield (diastereomeric ratio = 60:40 (determined by <sup>1</sup>H NMR)). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.81 (s) and 9.75 (s) (total 1H, two diastereomers), 7.70 (d, *J* = 8.4 Hz) and 7.59 (d, *J* = 8.4 Hz) (total 2H, two diastereomers), 7.32-7.02 (m, 7H), 4.65 (d, *J* = 6.4 Hz) and 4.61 (d, *J* = 8.0 Hz) (total 1H, two diastereomers), 3.07-3.00 (m, 1H), 2.31 (s, 1H), 1.26 (d, *J* = 7.2 Hz) and 1.01 (d, *J* = 7.2 Hz) (total 3H, two diastereomers); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 192.1 and 192.1, 151.2 and 151.0, 142.4 and 142.3, 134.8 and 134.5, 129.7 and 129.5, 128.7 and 128.7, 128.2 and 128.0, 127.8 and 127.4, 126.6 and 126.2, 79.0 and 78.3, 47.9 and 47.5, 18.0 and 15.5; HRMS (APCI) calcd. for C<sub>16</sub>H<sub>17</sub>O<sub>2</sub> [MH<sup>+</sup>]: 241.1229, found: 241.1217; IR: 3500, 1698, 1681 cm<sup>-1</sup>.

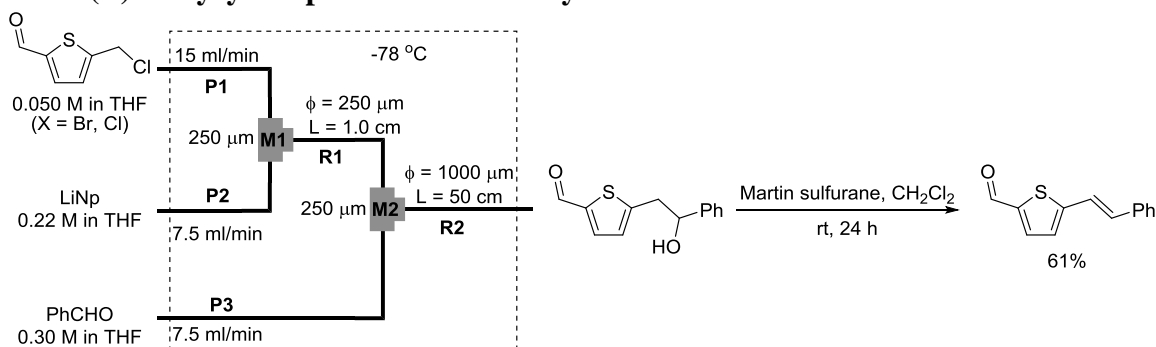
**5-(2-Hydroxy-2-phenylethyl)thiophene-2-carbaldehyde.** 5-(Chloromethyl)thiophene-2-carbaldehyde was used as a benzyl halide. Benzaldehyde was used as an electrophile. After extraction with EtOAc, the crude product was purified by GPC to afford 5-(2-hydroxy-2-phenylethyl)thiophene-2-



carbaldehyde in 77% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.80 (s, 1H), 7.59 (d,  $J$  = 3.6 Hz, 1H), 7.36-7.29 (m, 5H), 6.91 (d,  $J$  = 4.0 Hz, 1H), 4.95 (dd,  $J$  = 8.0 Hz,  $J$  = 5.2 Hz, 1H), 3.38-3.22 (m, 2H) 2.25 (br s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.8, 151.8, 142.8, 142.7, 136.7, 128.6, 128.1, 127.8, 125.8, 74.6, 40.5; HRMS (ESI) calcd. for  $\text{C}_{13}\text{H}_{13}\text{O}_2\text{S}^+[\text{MH}^+]$ : 233.0636 found: 233.0628; IR: 3407, 1651  $\text{cm}^{-1}$ .

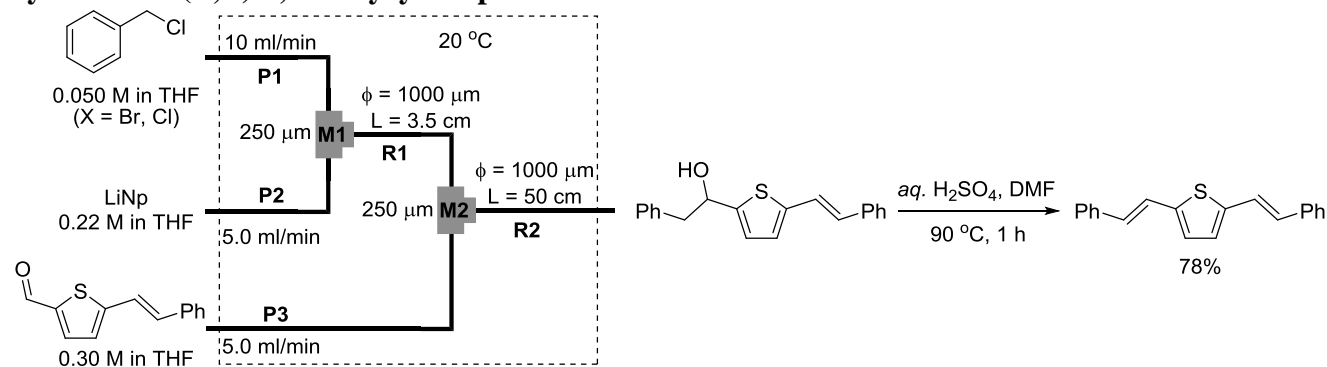
**5-(2-Hydroxy-2-(2-thiophenyl)ethyl)thiophene-2-carbaldehyde.** 5-(Chloromethyl)thiophene-2-carbaldehyde was used as a benzyl halide. 2-Thiophenecarboxaldehyde was used as an electrophile. After extraction with EtOAc, the crude product was purified by silica gel column chromatography (hexane/EtOAc = 2.5/1) to afford 5-(2-hydroxy-2-(2-thiophenyl)ethyl)thiophene-2-carbaldehyde. in 72% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.80 (s, 1H), 7.61 (d,  $J$  = 4.0 Hz, 1H), 7.28-7.26 (m, 1H), 6.99-6.95 (m, 3H), 5.23-5.19 (m, 1H), 3.43-3.27 (m 2H), 2.46 (d,  $J$  = 4.0 Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.9, 151.2, 146.5, 142.6, 136.8, 128.0, 126.7, 125.0, 124.3, 70.3, 40.6; HRMS (APCI) calcd. for  $\text{C}_{11}\text{H}_{11}\text{O}_2\text{S}_2^+[\text{MH}^+]$ : 239.0200 found: 239.0186; IR: 3401, 1647  $\text{cm}^{-1}$ .

### Synthesis of (*E*)-5-Styrylthiophene-2-carbaldehyde



A flow microreactor system consisting of the build-in type system in which two T-shaped micromixers (**M1** and **M2**) and a microtube reactor (**R1**) were combined, a microreactor **R2**, and three pre-cooling units (**P1** (inner diameter  $\phi$  = 1000  $\mu\text{m}$ , length  $L$  = 300 cm), **P2** ( $\phi$  = 1000  $\mu\text{m}$ ,  $L$  = 300 cm) and **P3** ( $\phi$  = 1000  $\mu\text{m}$ ,  $L$  = 300 cm)) was used. The flow microreactor system was dipped in a cooling bath ( $-78\text{ }^\circ\text{C}$ ). A solution of 5-(chloromethyl)thiophene-2-carbaldehyde (0.05 M in THF) was introduced to **M1** using a plunger pump (15 mL/min). A solution of lithium naphthalenide (LiNp) (0.22 M in THF) was introduced to **M1** using a micro feeder pump (7.5 mL/min). The mixed solution was passed through **R1** ( $\phi$  = 250  $\mu\text{m}$ ,  $L$  = 1.0 cm) and was introduced to **M2**. A solution of 2-thiophenecarboxaldehyde (0.30 M in THF) was introduced to **M2** ( $\phi$  = 250  $\mu\text{m}$ ) using a plunger pump (7.5 mL/min), and the resulting solution was passed through **R2** ( $\phi$  = 1000  $\mu\text{m}$ ,  $L$  = 50 cm). After a steady state was reached, an aliquot of the product solution was collected for 30 seconds and the solution was treated with sat. aqueous  $\text{NH}_4\text{Cl}$  solution. After extraction with EtOAc, the crude solution was used for the next reaction without further purification. In a 20mL vessel, bis[ $\alpha,\alpha$ -bis(trifluoromethyl)benzenemethanolato]diphenylsulfur (martin sulfurane) (300 mg, 675  $\mu\text{mol}$ , 1.8 equiv.) and  $\text{CH}_2\text{Cl}_2$  (4.0 ml) were added to a mixture of the crude product and the solution was stirred for 24 h at room temperature. After extraction with EtOAc, the crude product was purified by silica gel column chromatography (hexane/EtOAc = 15/1) to afford (*E*)-5-styrylthiophene-2-carbaldehyde in 61% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.86 (s, 1H), 7.66 (d,  $J$  = 4.0 Hz, 1H), 7.52-7.48 (m, 2H), 7.40-7.35 (m, 2H), 7.34-7.29 (m, 1H), 7.22 (d,  $J$  = 16.4 Hz, 1H), 7.15 (d,  $J$  = 4.0 Hz, 1H), 7.14 (d,  $J$  = 16.0 Hz, 1H); The spectral data were identical to those reported in the literature.<sup>15</sup>

## Synthesis of (*E,E*)-2,5-Distyrylthiophene.

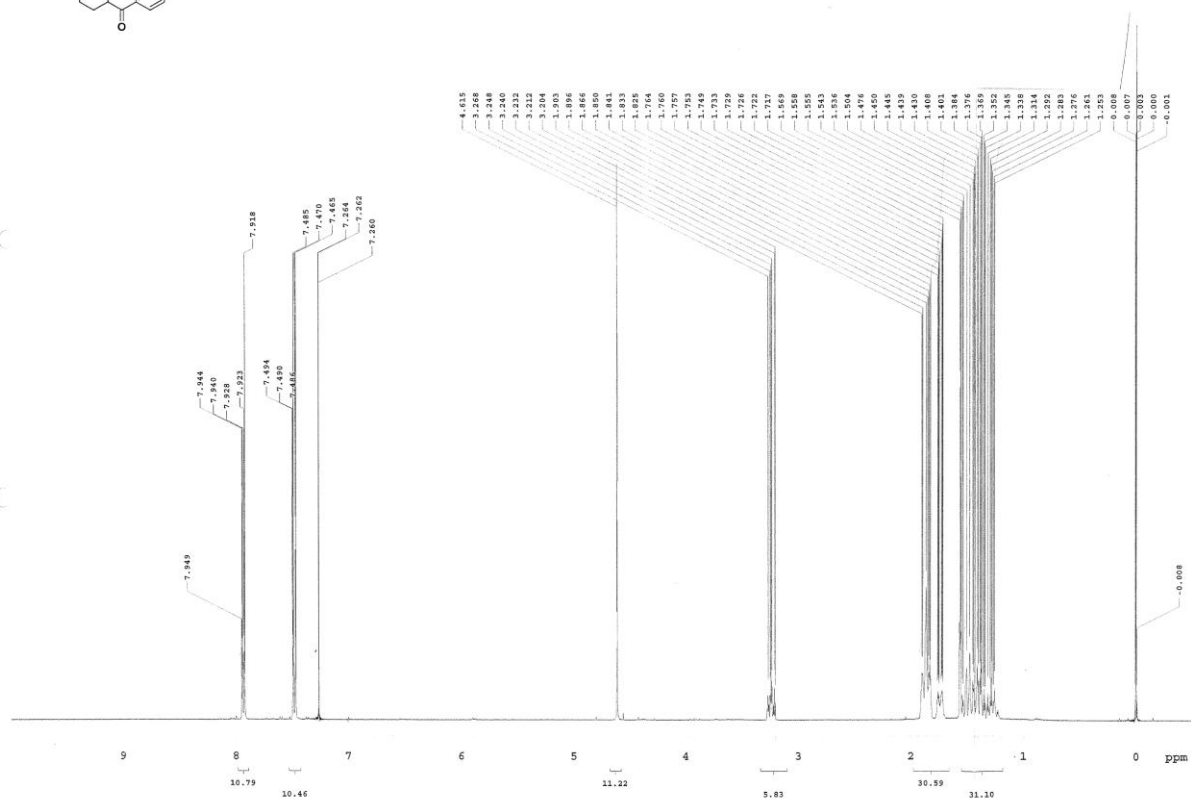
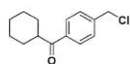


A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (inner diameter  $\phi = 1000\ \mu\text{m}$ , length  $L = 300\ \text{cm}$ ), **P2** ( $\phi = 1000\ \mu\text{m}$ ,  $L = 300\ \text{cm}$ ) and **P3** ( $\phi = 1000\ \mu\text{m}$ ,  $L = 300\ \text{cm}$ )) was used. The flow microreactor system was dipped in a cooling bath ( $20\ ^\circ\text{C}$ ). A solution of benzyl chloride (0.05 M in THF) was introduced to **M1** using a plunger pump (10 mL/min). A solution of lithium naphthalenide (LiNp) (0.22 M in THF) was introduced to **M1** using a micro feeder pump (5.0 mL/min). The mixed solution was passed through **R1** ( $\phi = 1000\ \mu\text{m}$ ,  $L = 3.5\ \text{cm}$ ) and was introduced to **M2**. A solution of (*E*)-5-styrylthiophene-2-carbaldehyde (0.30 M in THF) was introduced to **M2** ( $\phi = 250\ \mu\text{m}$ ) using a plunger pump (5.0 mL/min), and the resulting solution was passed through **R2** ( $\phi = 1000\ \mu\text{m}$ ,  $L = 50\ \text{cm}$ ). After a steady state was reached, an aliquot of the product solution was collected for 30 seconds and was treated with sat. aqueous  $\text{NH}_4\text{Cl}$  solution. After extraction with EtOAc, the solvent was removed by evaporation. The crude alcohol thus-obtained was used for the next reaction without further purification. In a 20 mL vessel, a mixture of the crude alcohol, DMF (1.77 mL),  $\text{H}_2\text{SO}_4$  (0.12 mL), and  $\text{H}_2\text{O}$  (0.11 mL) was heated at  $90\ ^\circ\text{C}$  for 1 h. After being cooled to room temperature, the mixture was neutralized with sat. aq.  $\text{NaHCO}_3$ . After extraction with EtOAc, the crude product was purified by silica gel column chromatography (hexane/EtOAc = 15/1) to afford (*E,E*)-2,5-distyrylthiophene in 78% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47 (d,  $J = 7.6\ \text{Hz}$ , 4H), 7.35 (t,  $J = 7.6\ \text{Hz}$ , 4H), 7.28-7.22 (m, Hz, 2H), 7.18 (d,  $J = 16.0\ \text{Hz}$ , 2H), 6.95 (s, 2H), 6.91 (d,  $J = 16.0\ \text{Hz}$ , 2H); The spectral data were identical to those reported in the literature.<sup>16</sup>

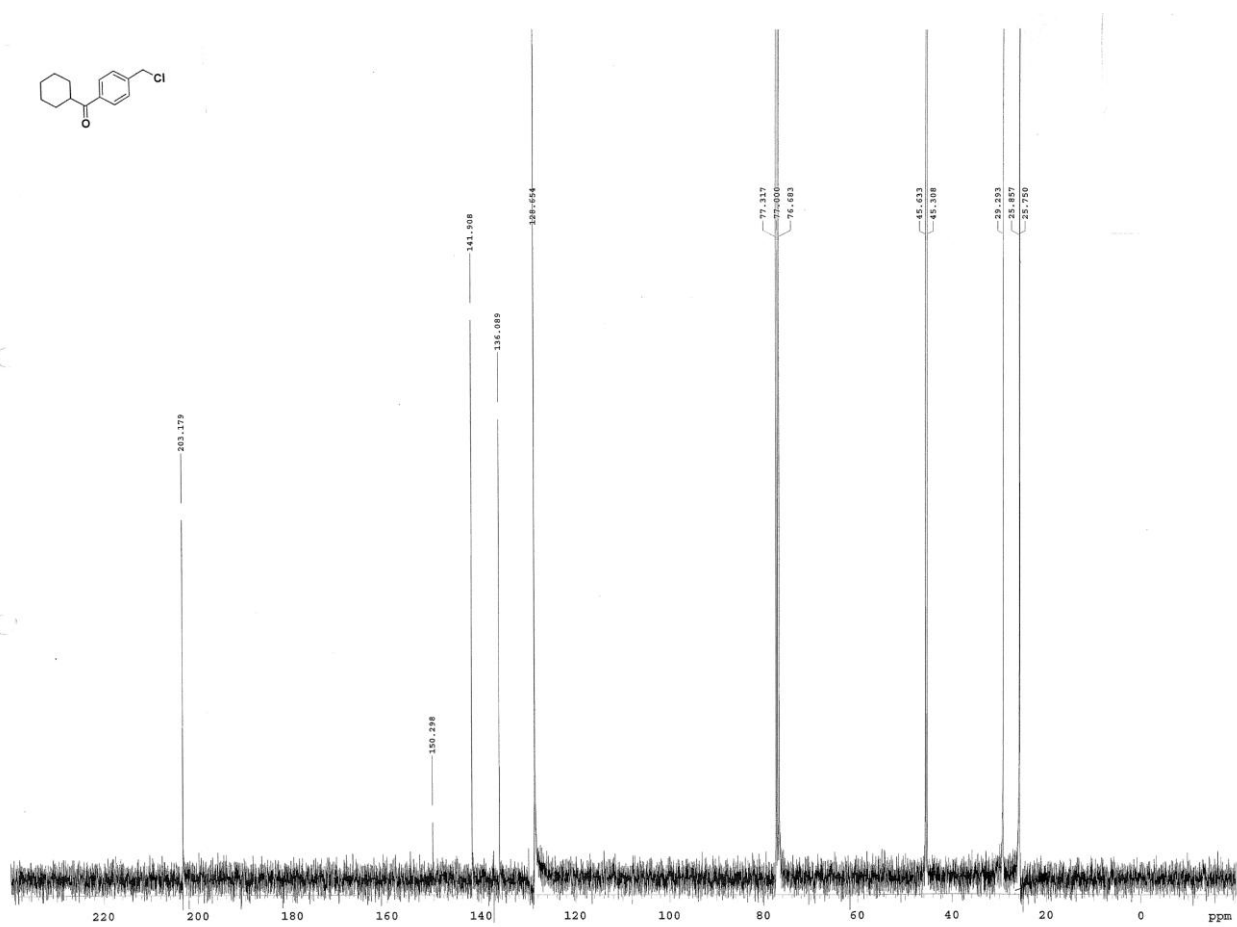
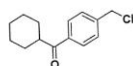
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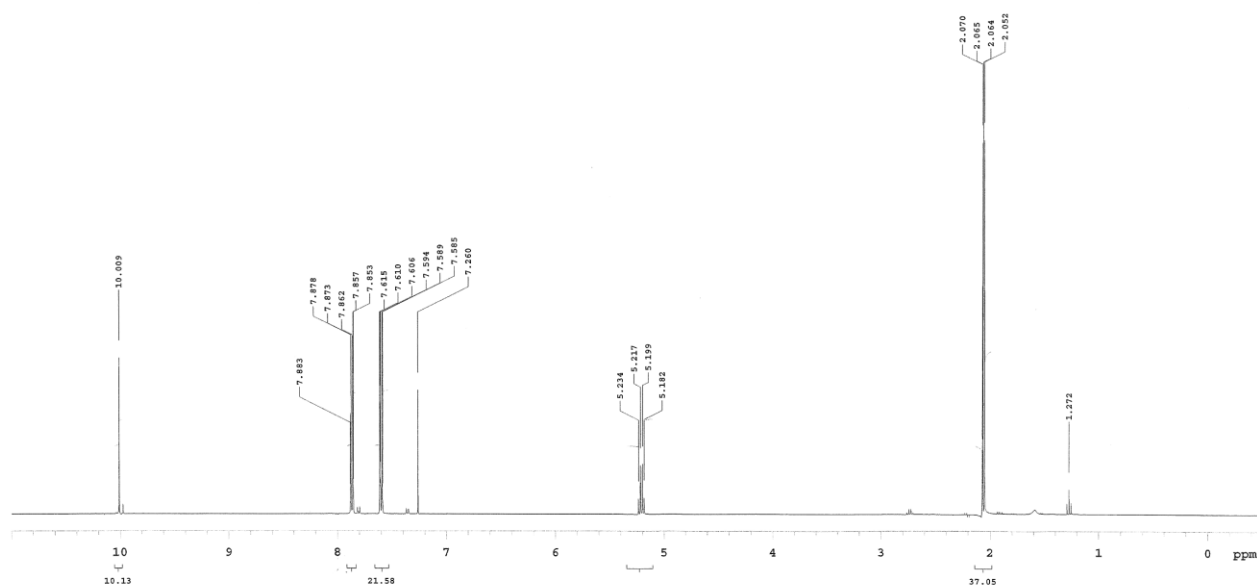
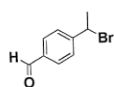
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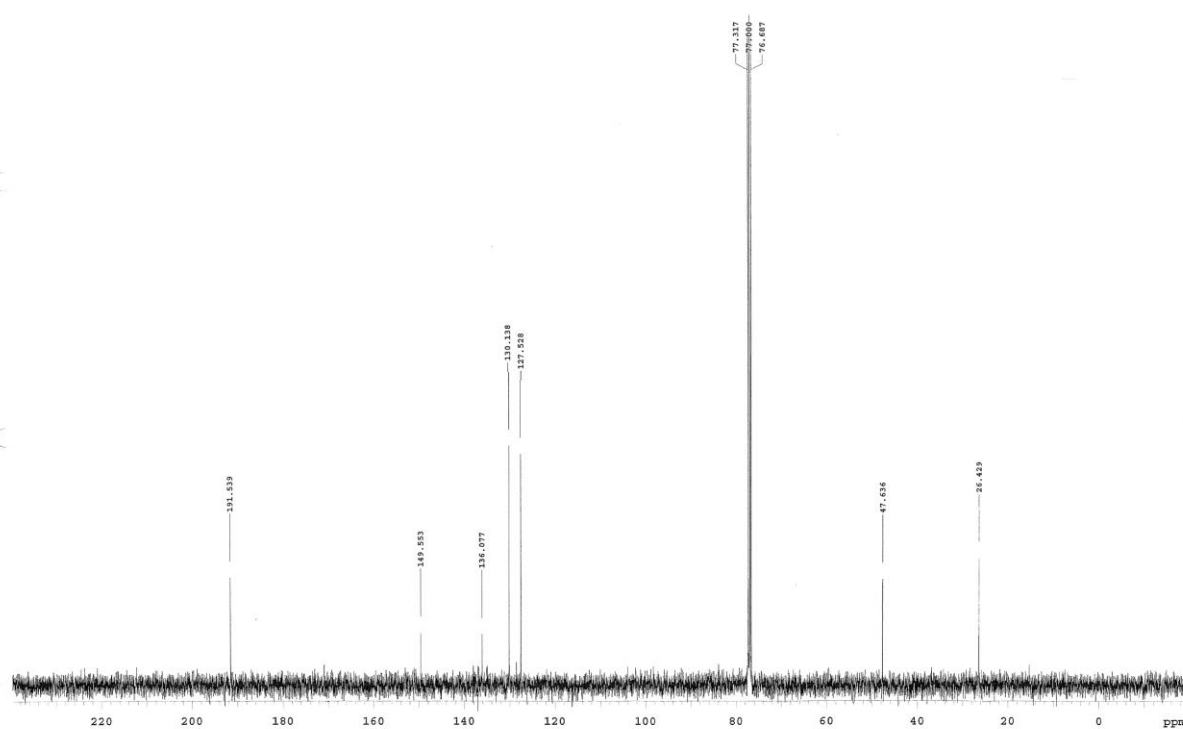
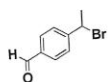
**<sup>1</sup>H NMR spectrum of (4-(chloromethyl)phenyl)(cyclohexyl)methanone**



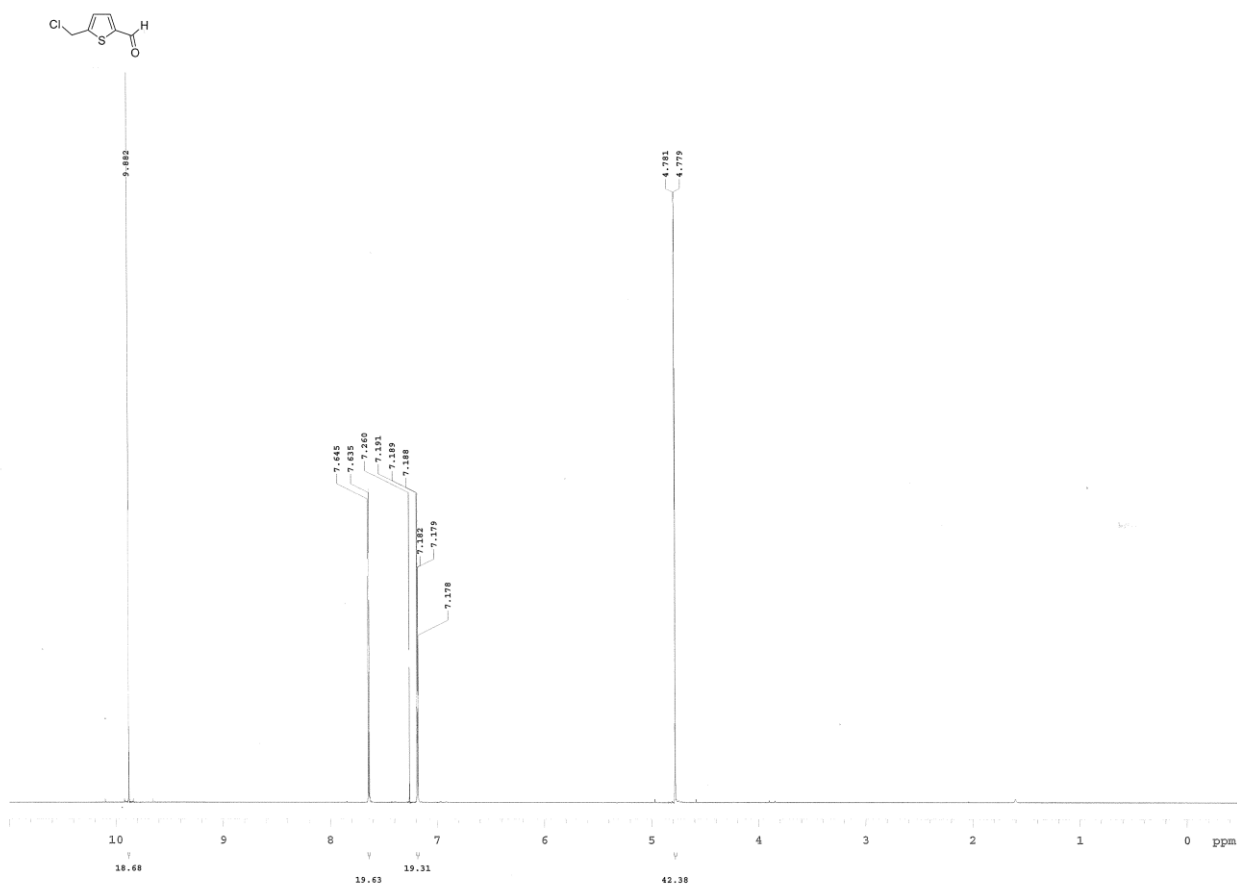
**<sup>13</sup>C NMR spectrum of (4-(chloromethyl)phenyl)(cyclohexyl)methanone**



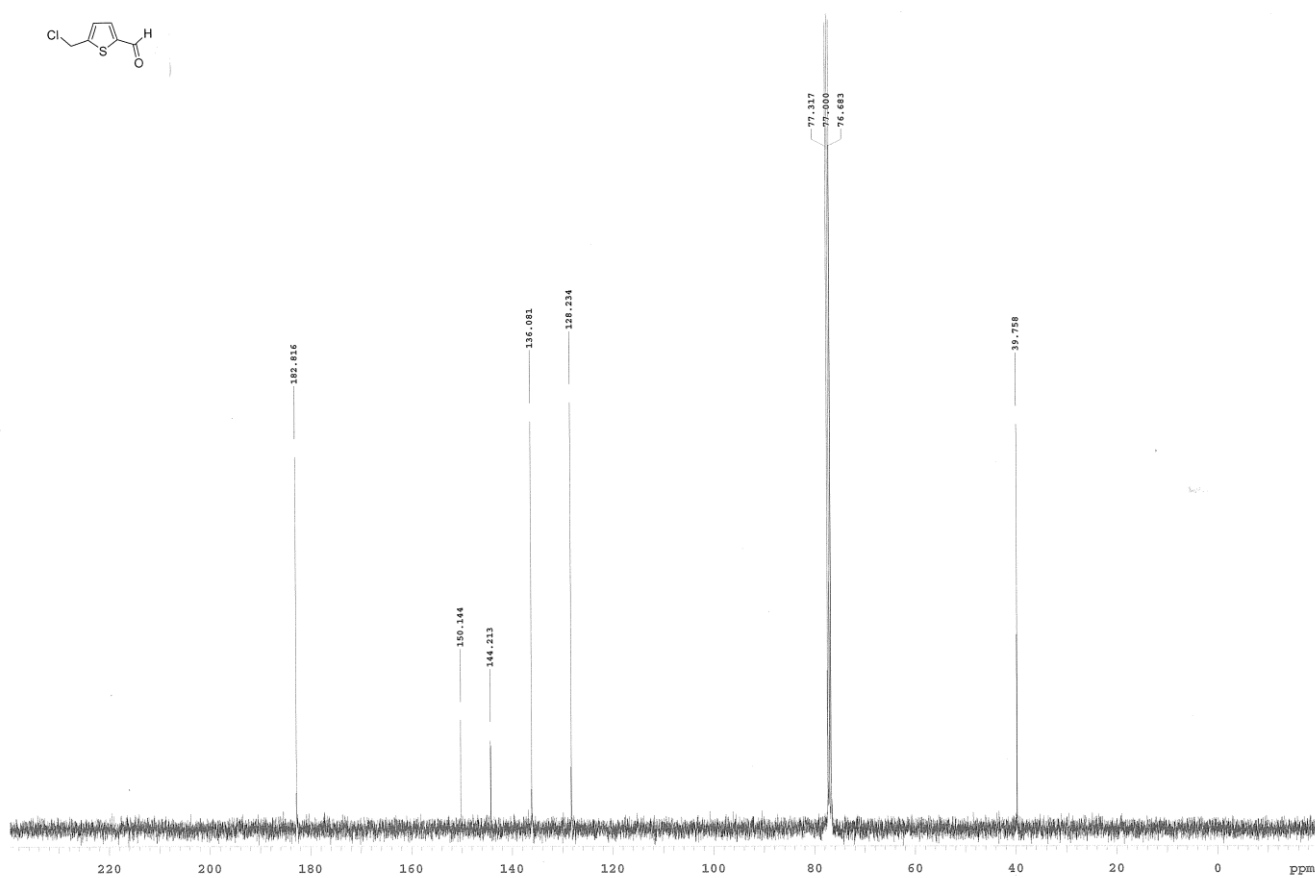
<sup>1</sup>H NMR spectrum of 4-(1-bromoethyl)benzaldehyde



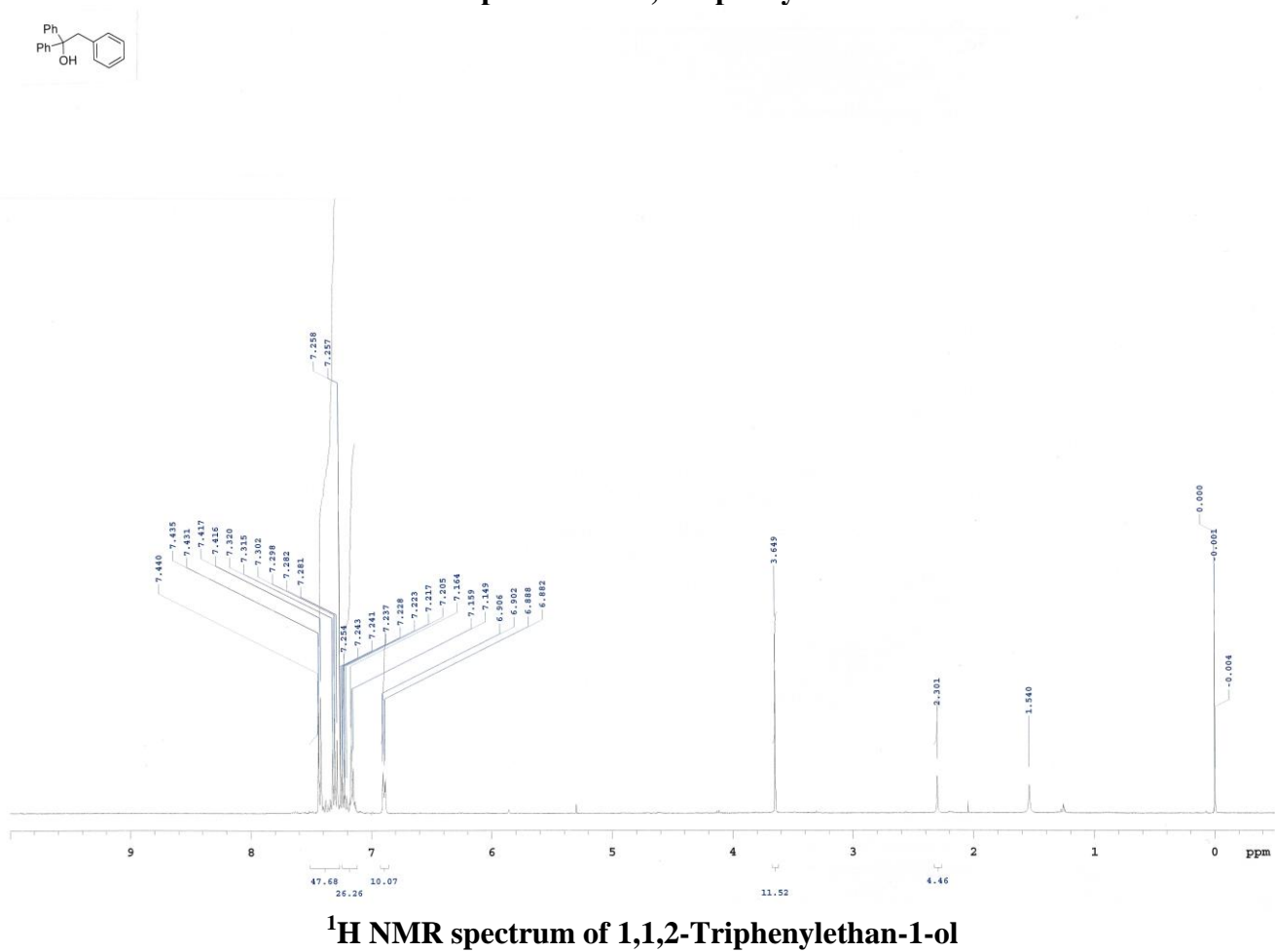
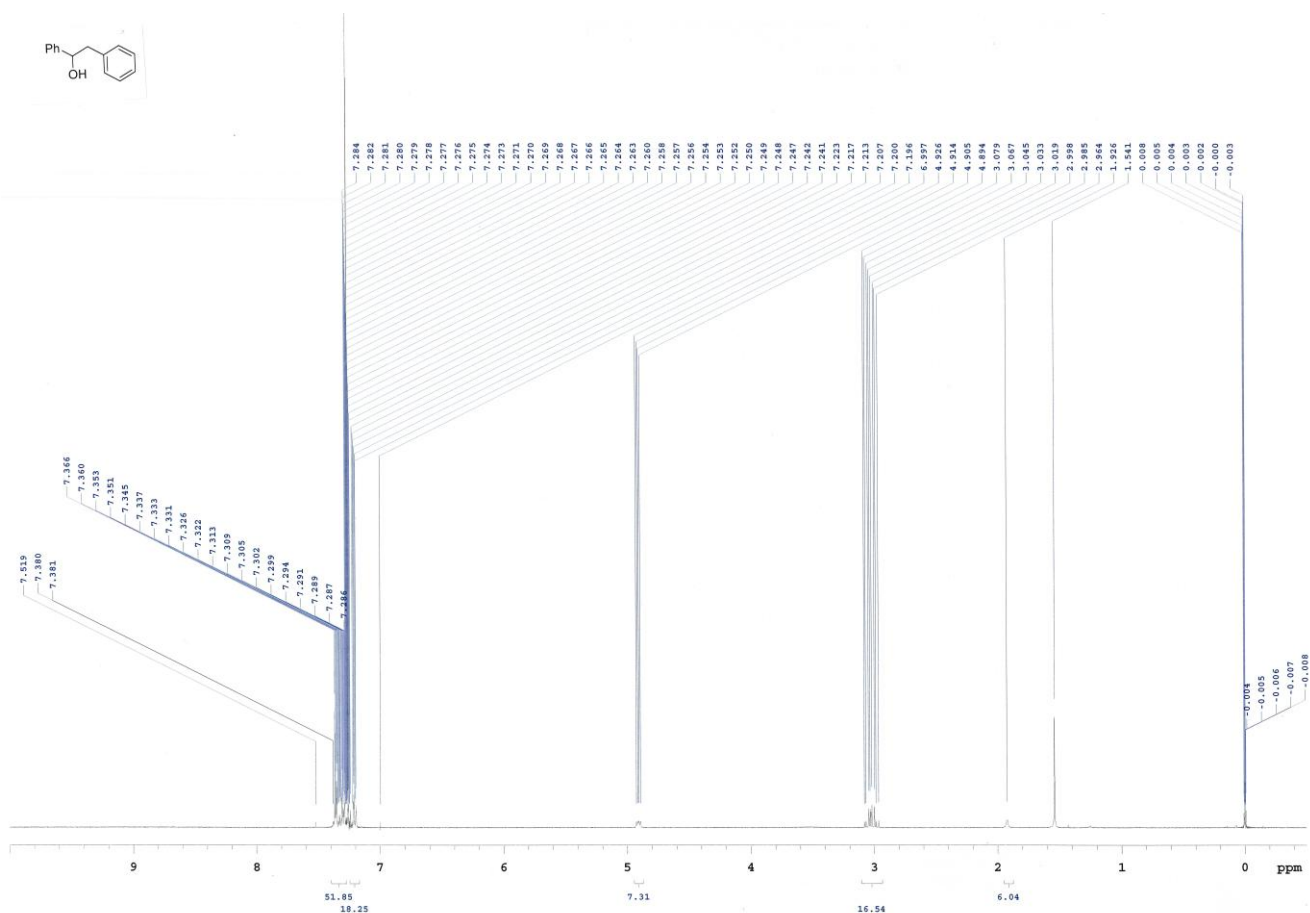
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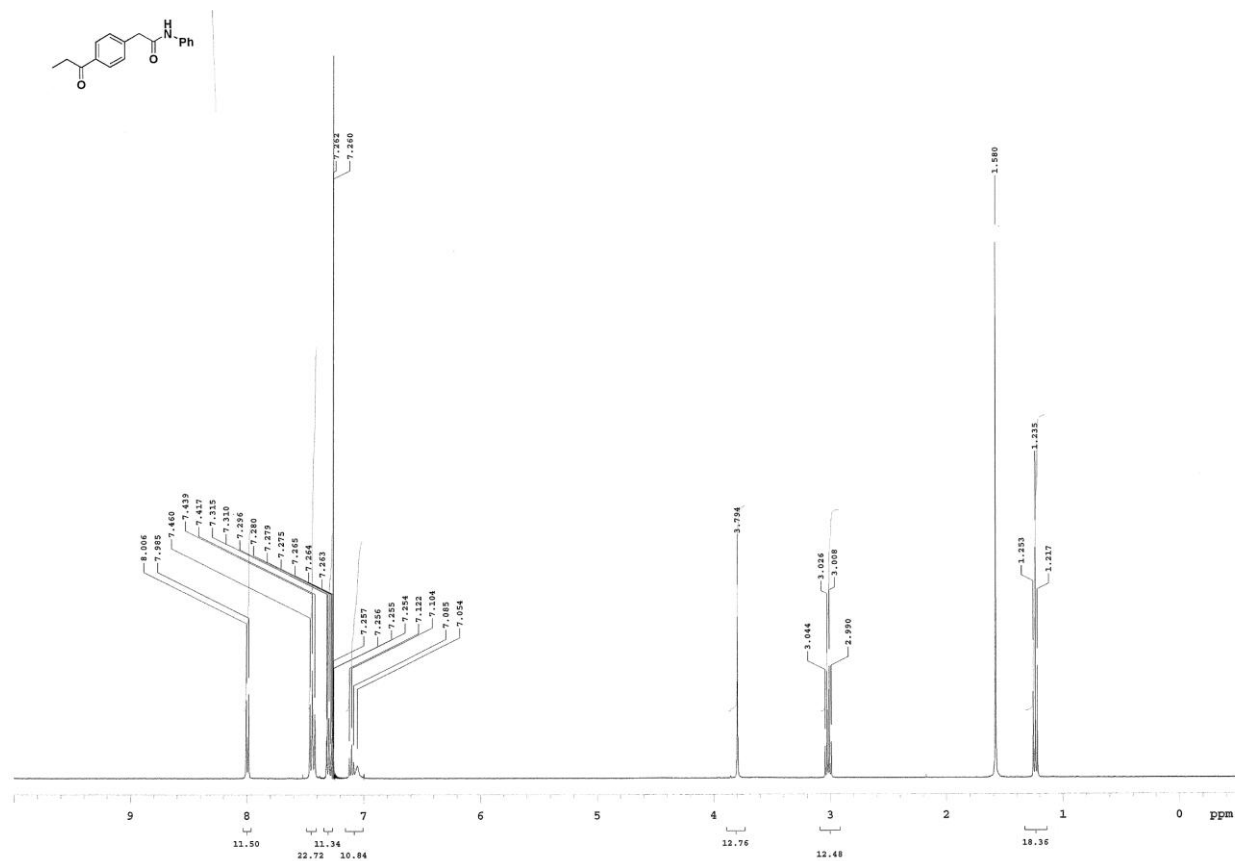


**<sup>1</sup>H NMR spectrum of 5-(chloromethyl)thiophene-2-carbaldehyde**

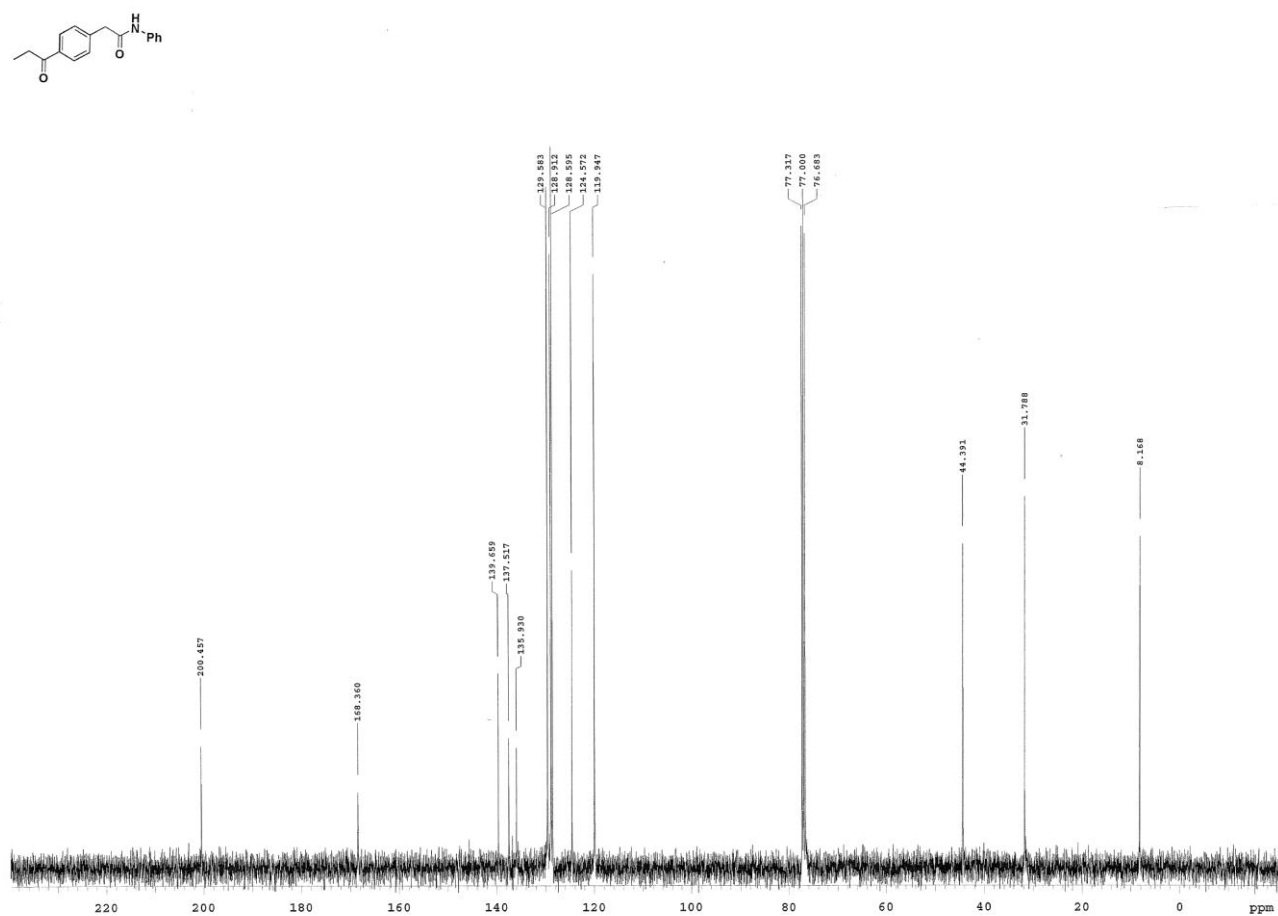


**<sup>13</sup>C NMR spectrum of 5-(chloromethyl)thiophene-2-carbaldehyde**



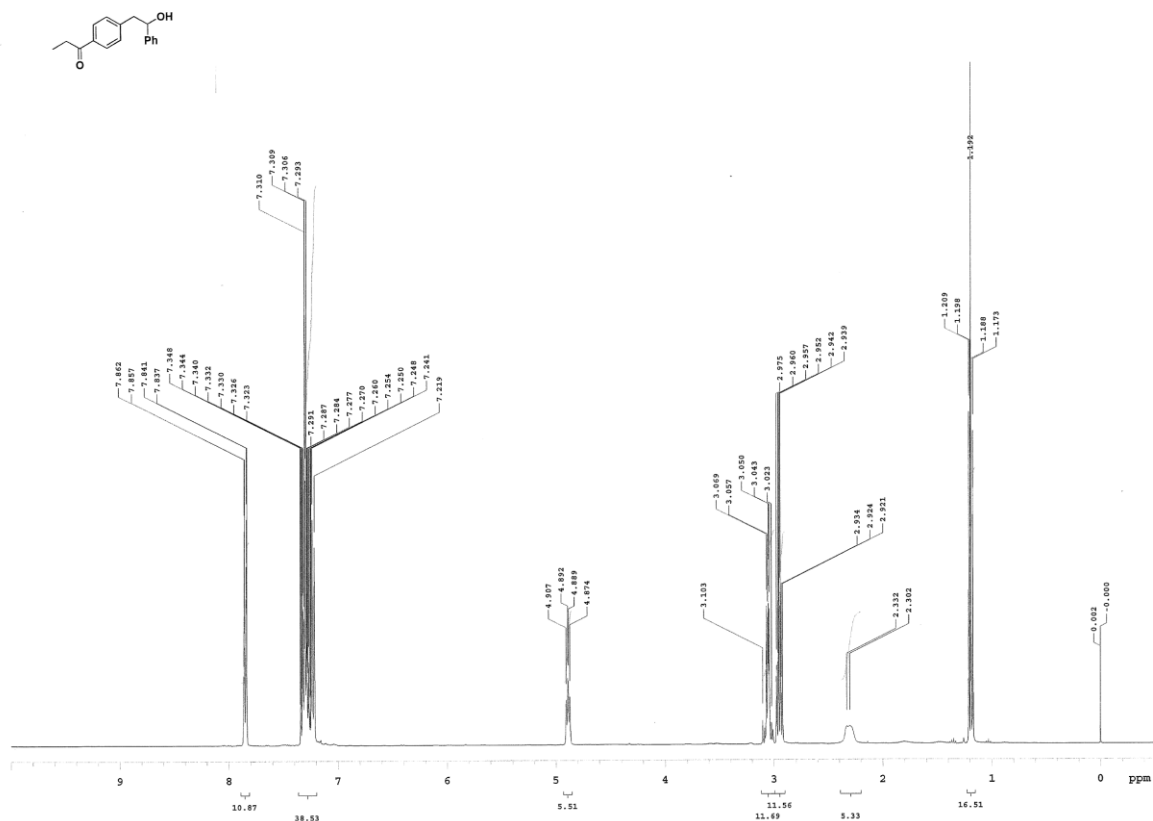


**<sup>1</sup>H NMR spectrum of *N*-phenyl-2-(4-propionylphenyl)acetamide**

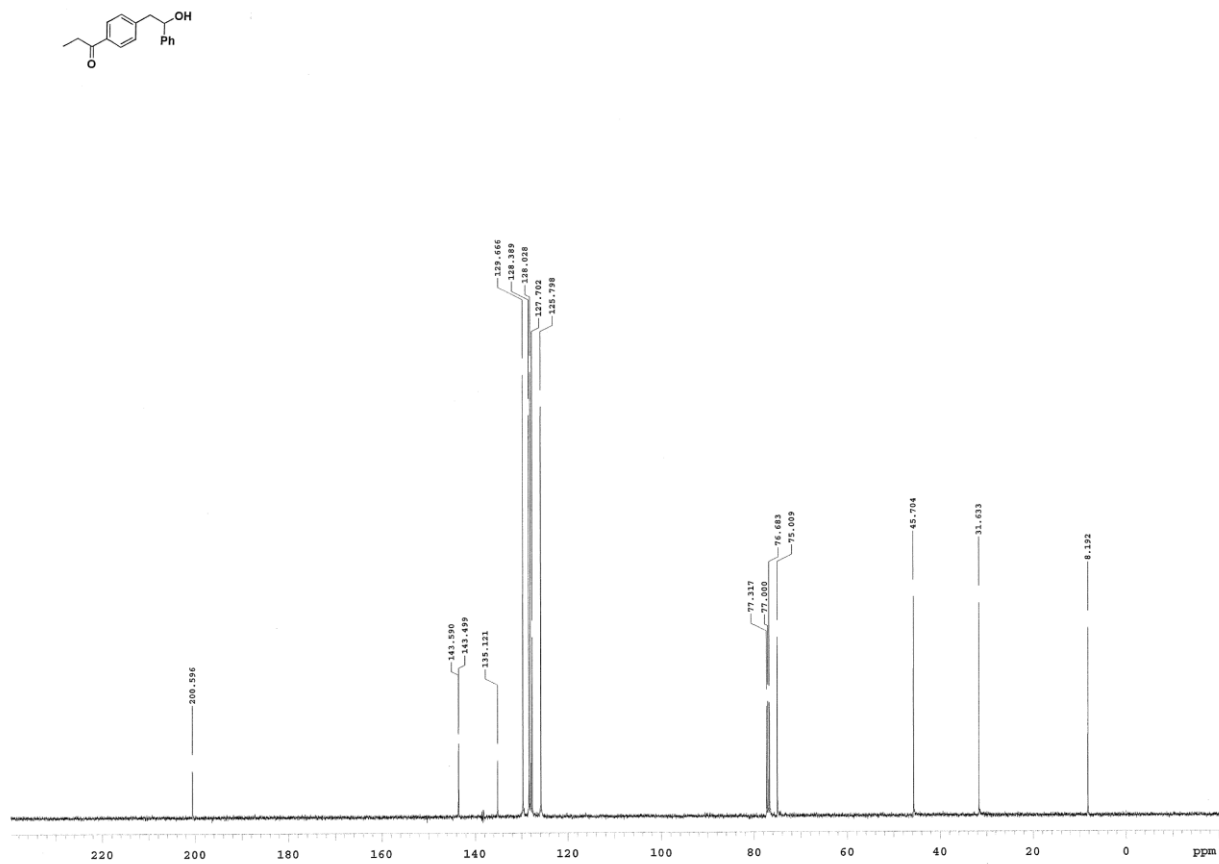


**<sup>13</sup>C NMR spectrum of *N*-phenyl-2-(4-propionylphenyl)acetamide**

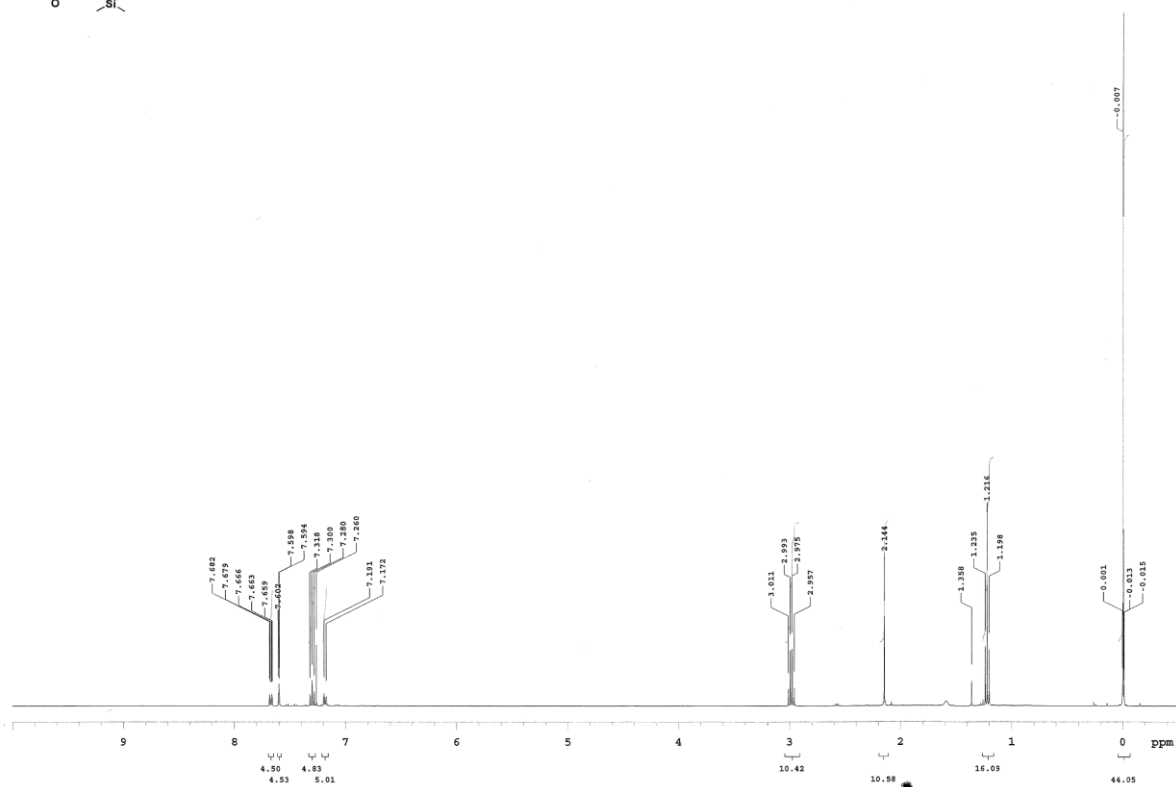
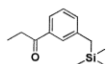




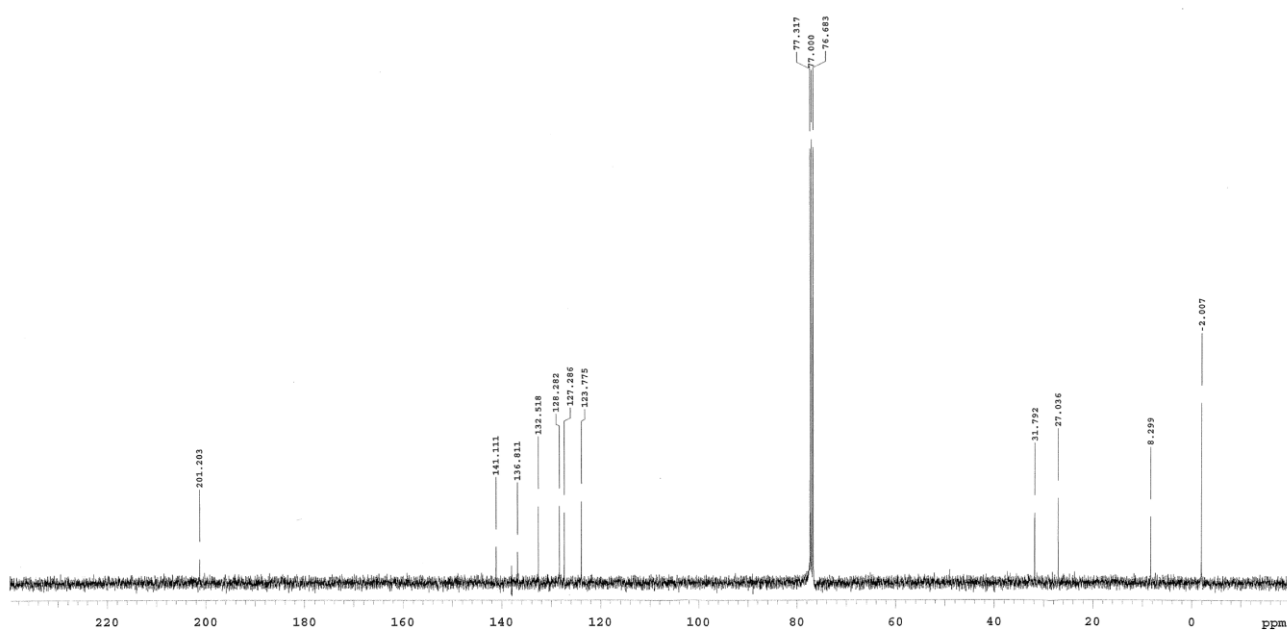
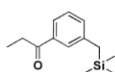
**<sup>1</sup>H NMR spectrum of 1-(4-(2-hydroxy-2-phenylethyl)phenyl)propan-1-one**



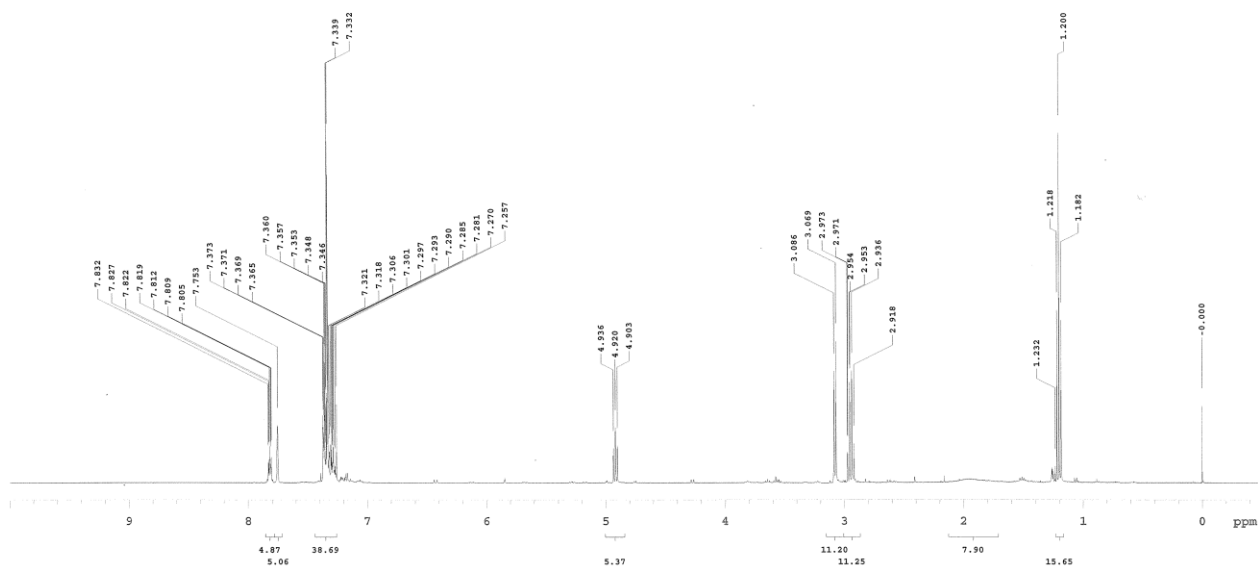
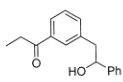
**<sup>13</sup>C NMR spectrum of 1-(4-(2-hydroxy-2-phenylethyl)phenyl)propan-1-one**



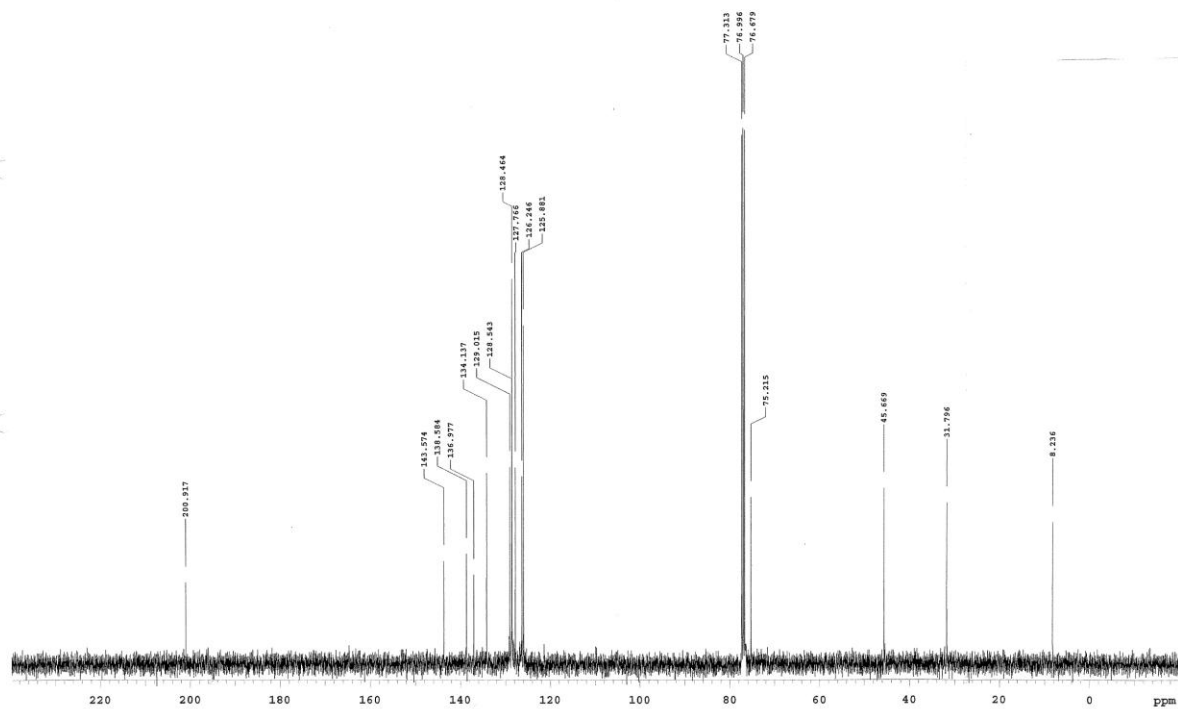
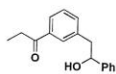
**<sup>1</sup>H NMR spectrum of 1-(3-((trimethylsilyl)methyl)phenyl)propan-1-one**



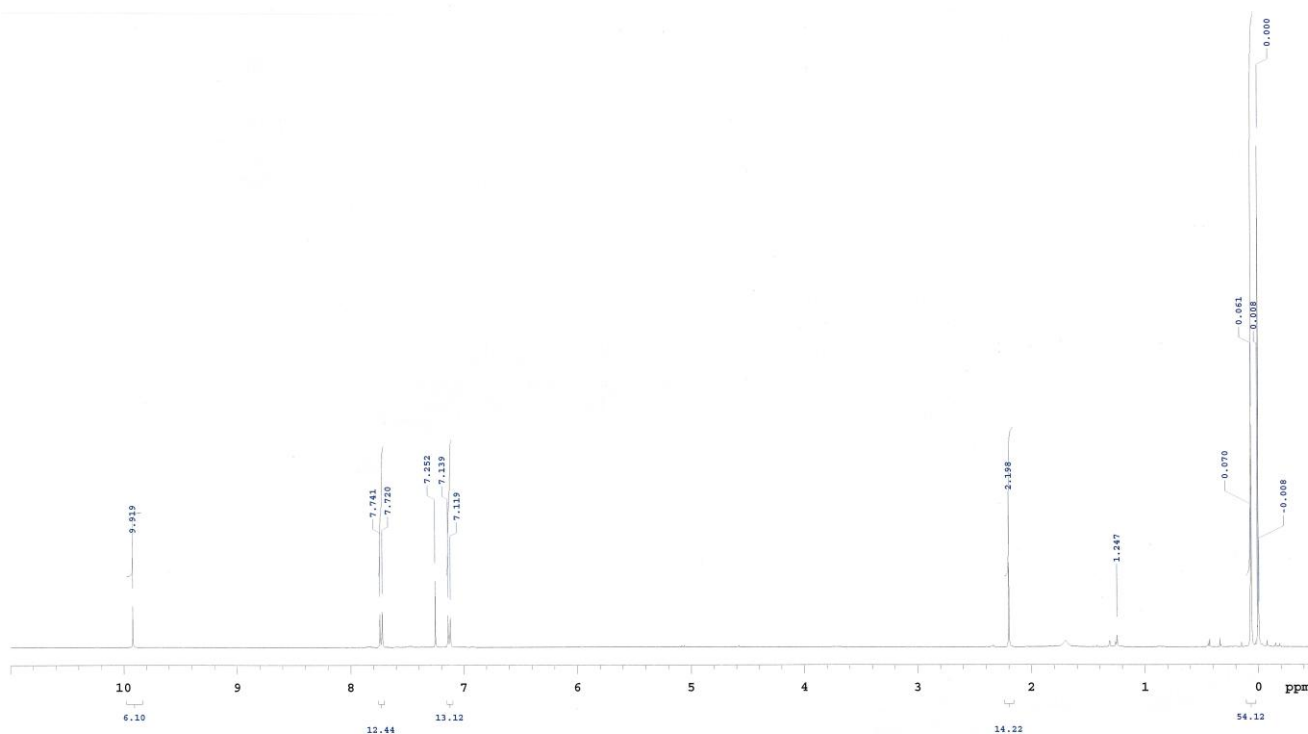
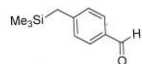
**<sup>13</sup>C NMR spectrum of 1-(3-((trimethylsilyl)methyl)phenyl)propan-1-one**



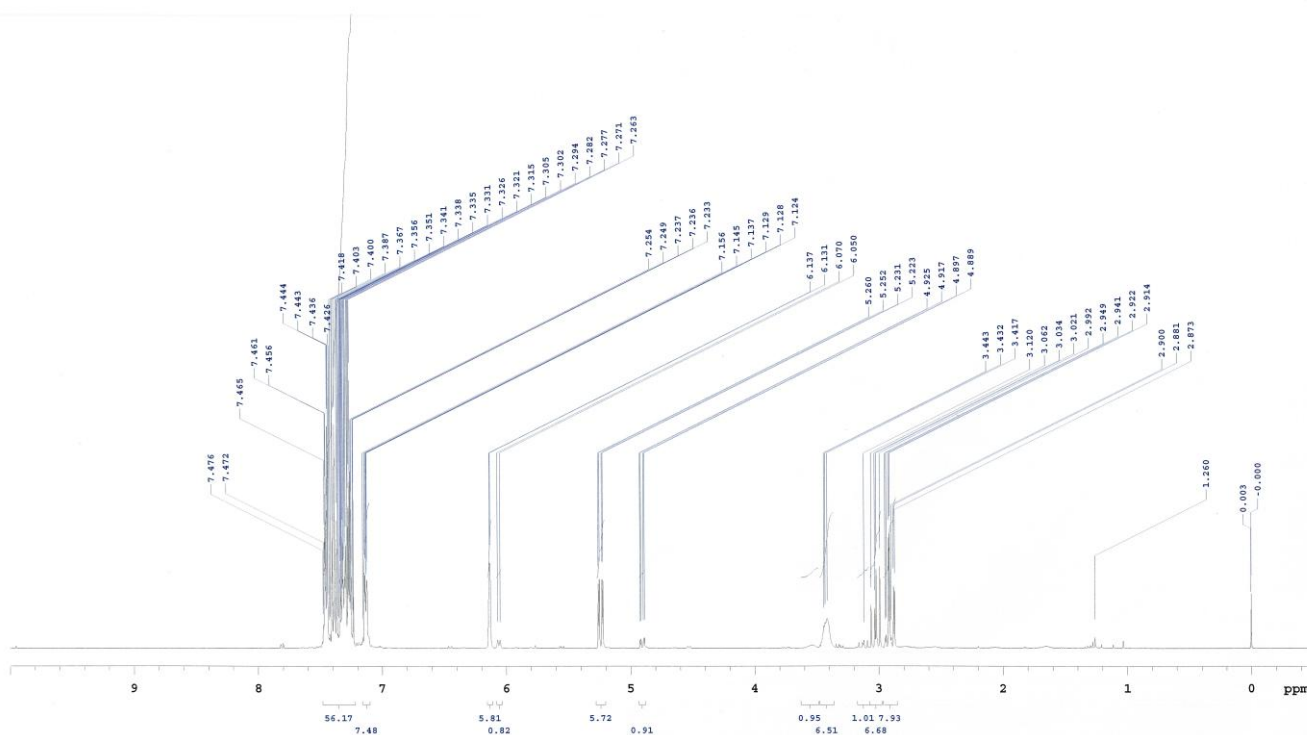
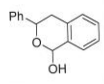
**<sup>1</sup>H NMR spectrum of 1-(3-(2-hydroxy-2-phenylethyl)phenyl)propan-1-one**



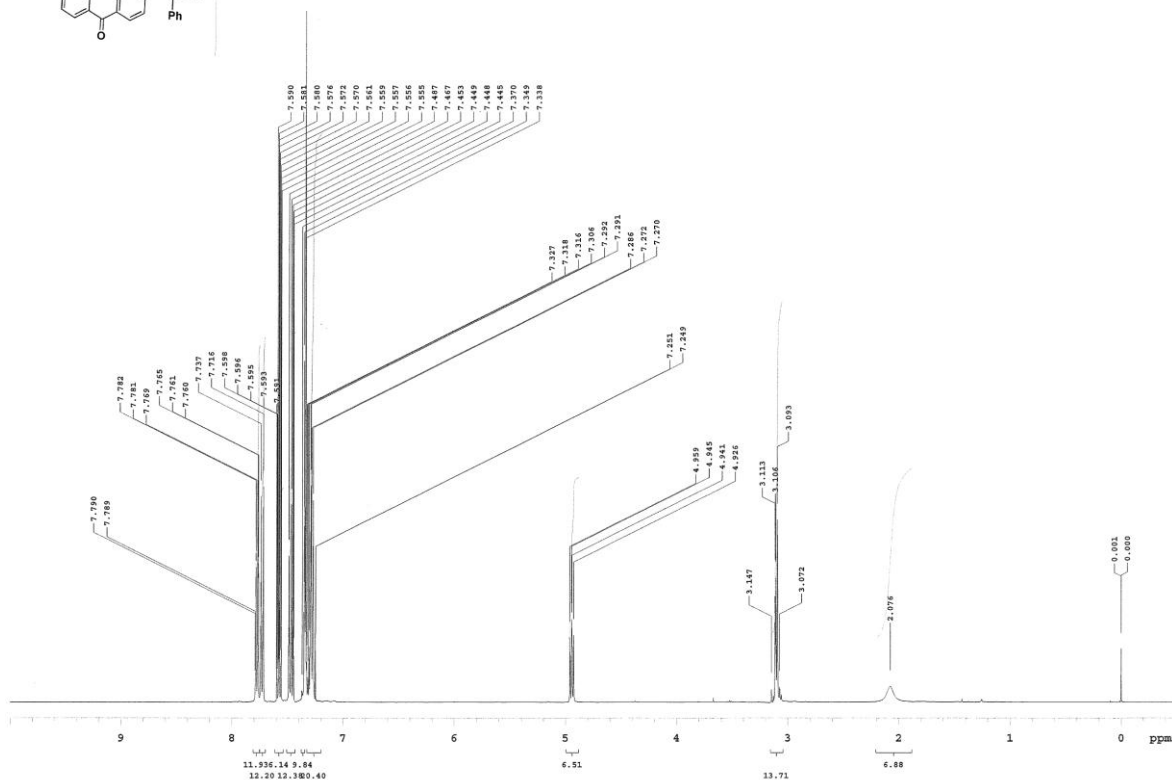
**<sup>13</sup>C NMR spectrum of 1-(3-(2-hydroxy-2-phenylethyl)phenyl)propan-1-one**



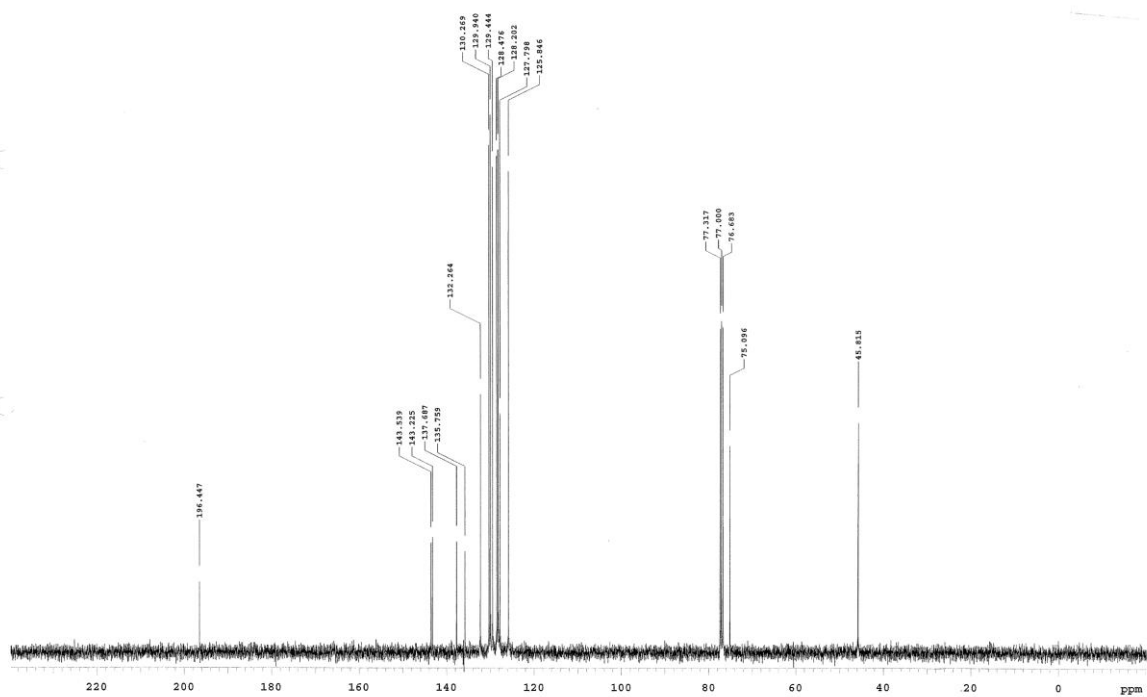
**<sup>1</sup>H NMR spectrum of 4-((Trimethylsilyl)methyl)benzaldehyde**



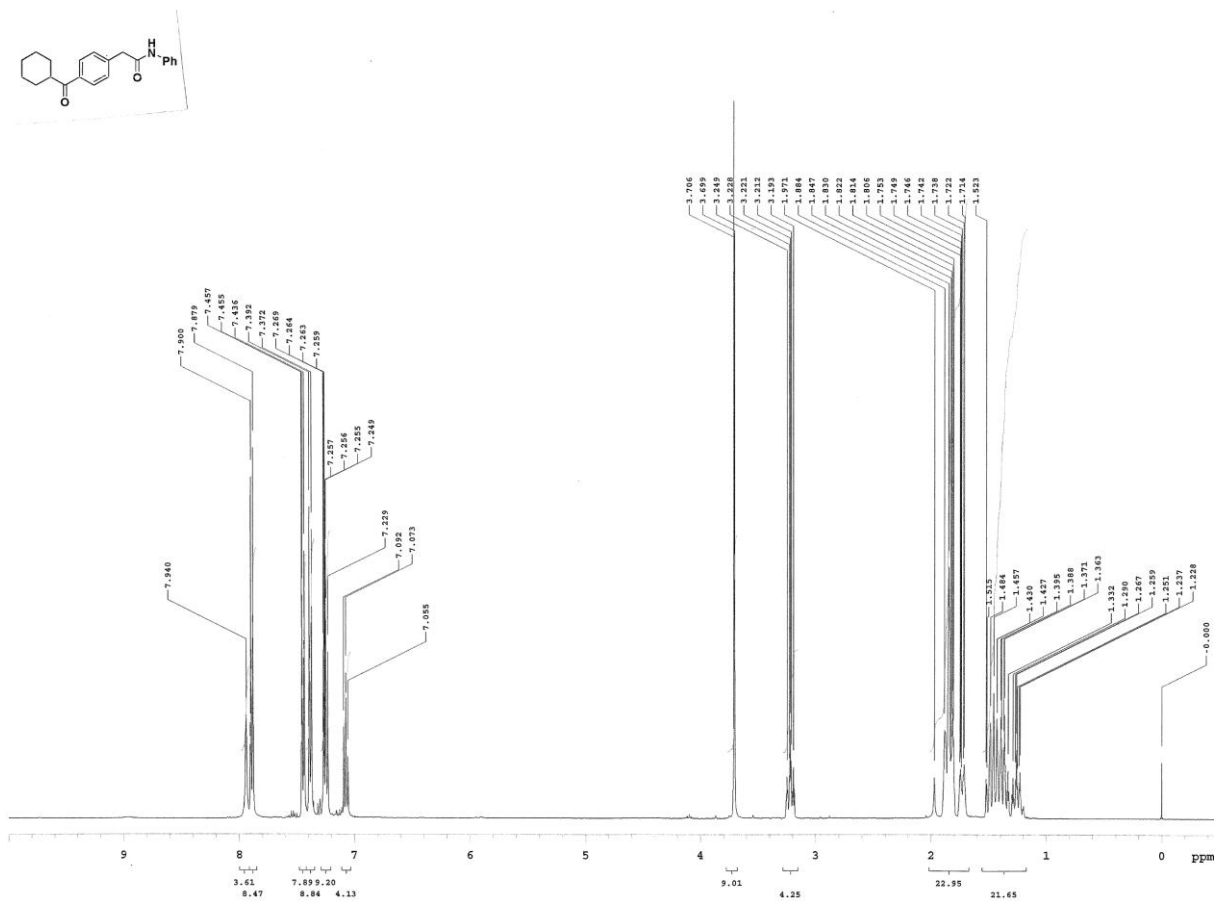
**<sup>1</sup>H NMR spectrum of 3-Phenylisochroman-1-ol**



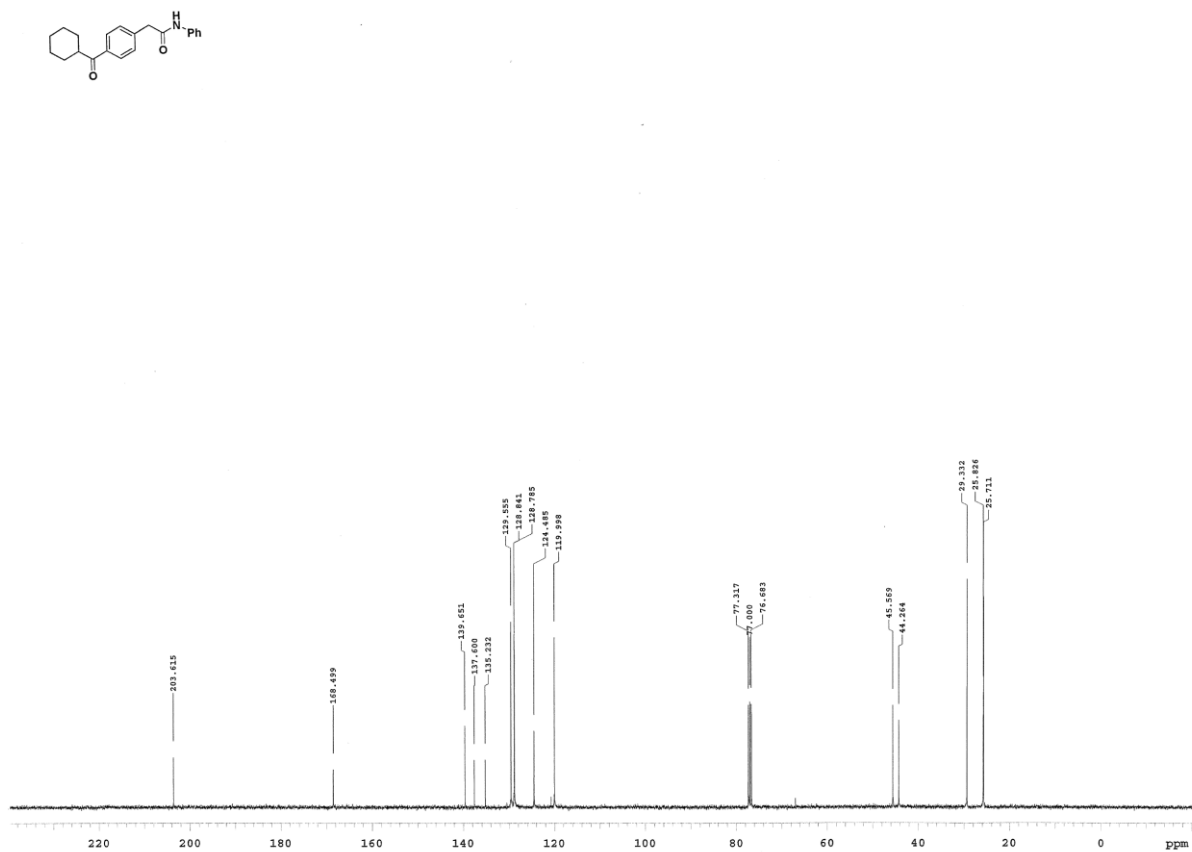
### <sup>1</sup>H NMR spectrum of (4-(2-hydroxy-2-phenylethyl)phenyl)(phenyl)methanone



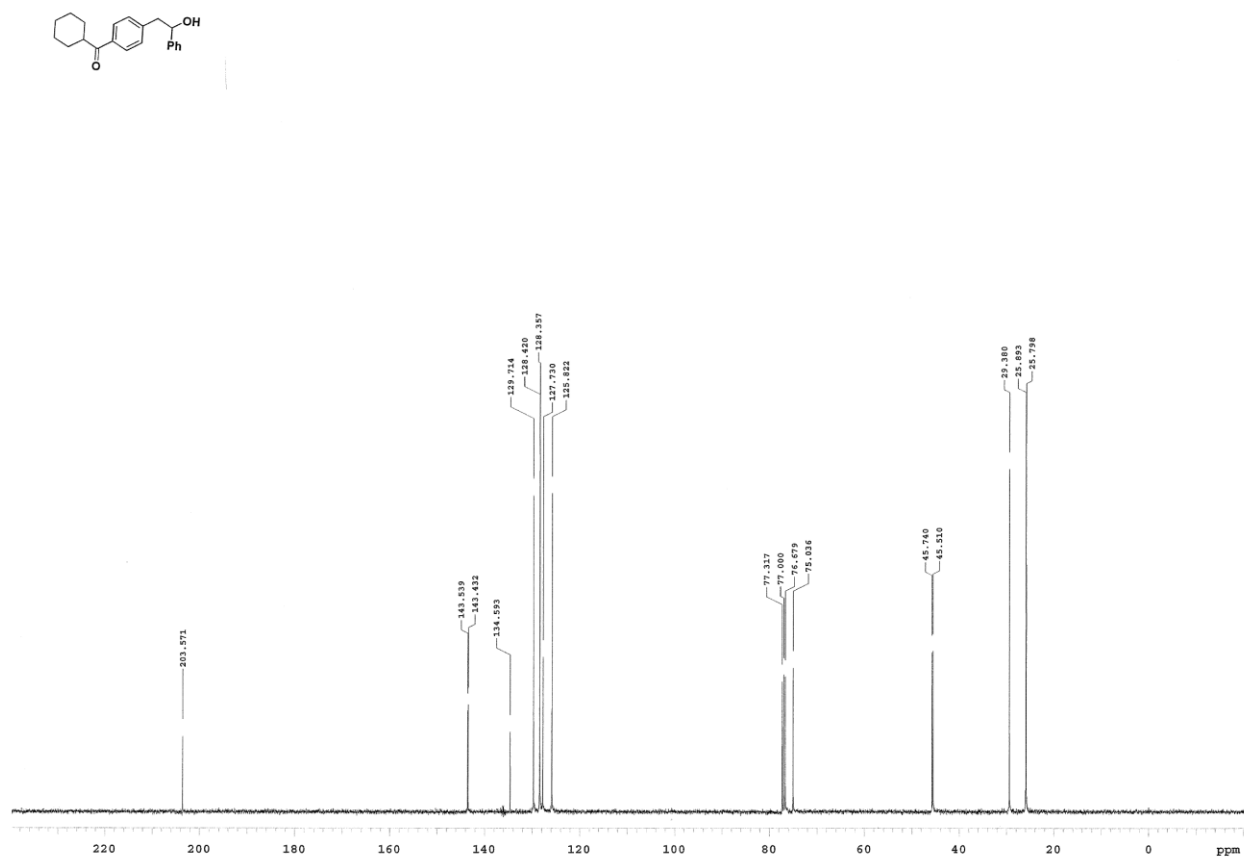
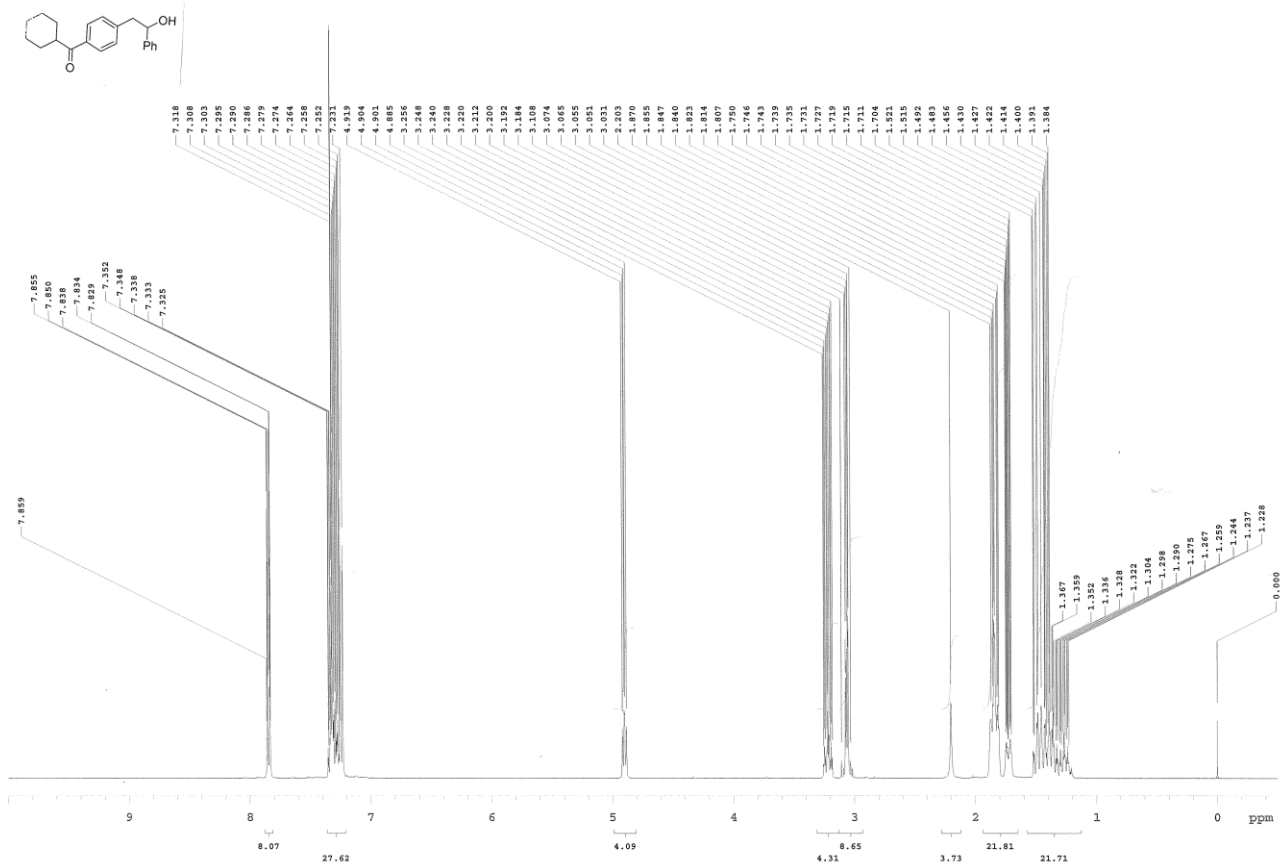
**<sup>13</sup>C NMR spectrum of (4-(2-hydroxy-2-phenylethyl)phenyl)(phenyl)methanone**

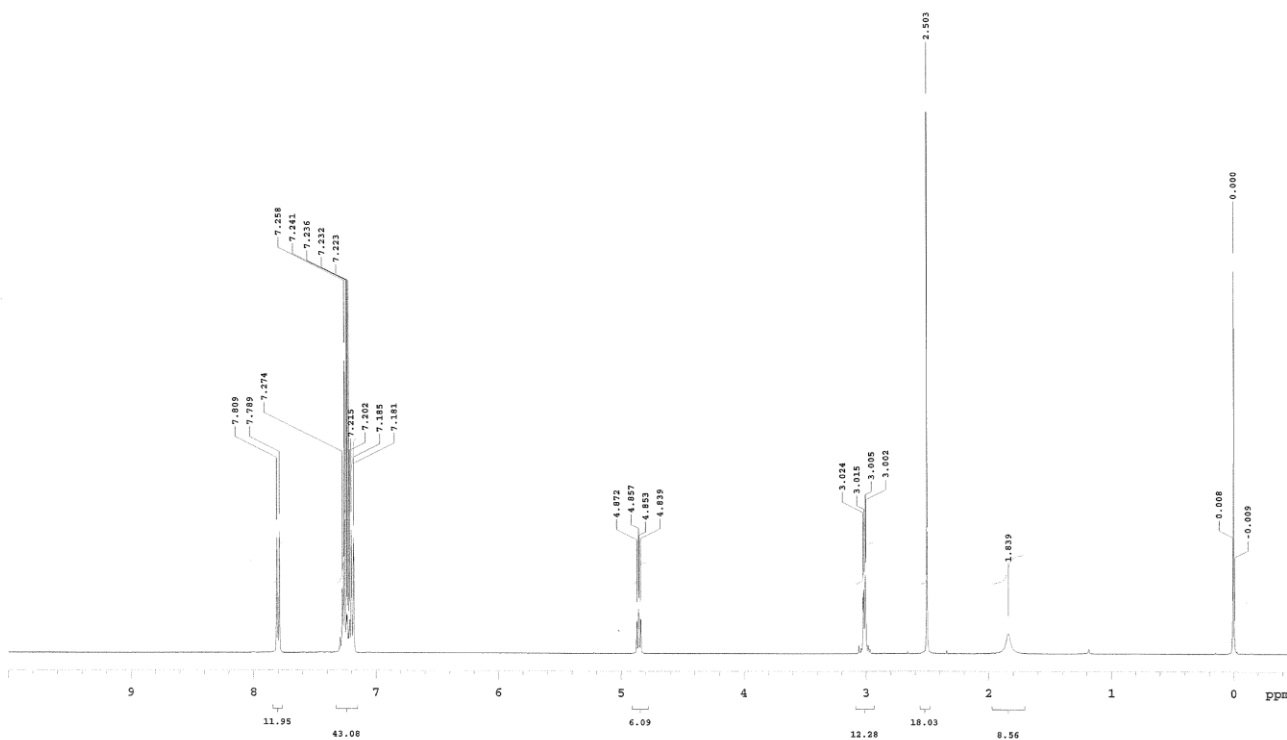
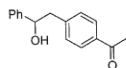


<sup>1</sup>H NMR spectrum of 2-(4-(cyclohexanecarbonyl)phenyl)-N-phenylacetamide

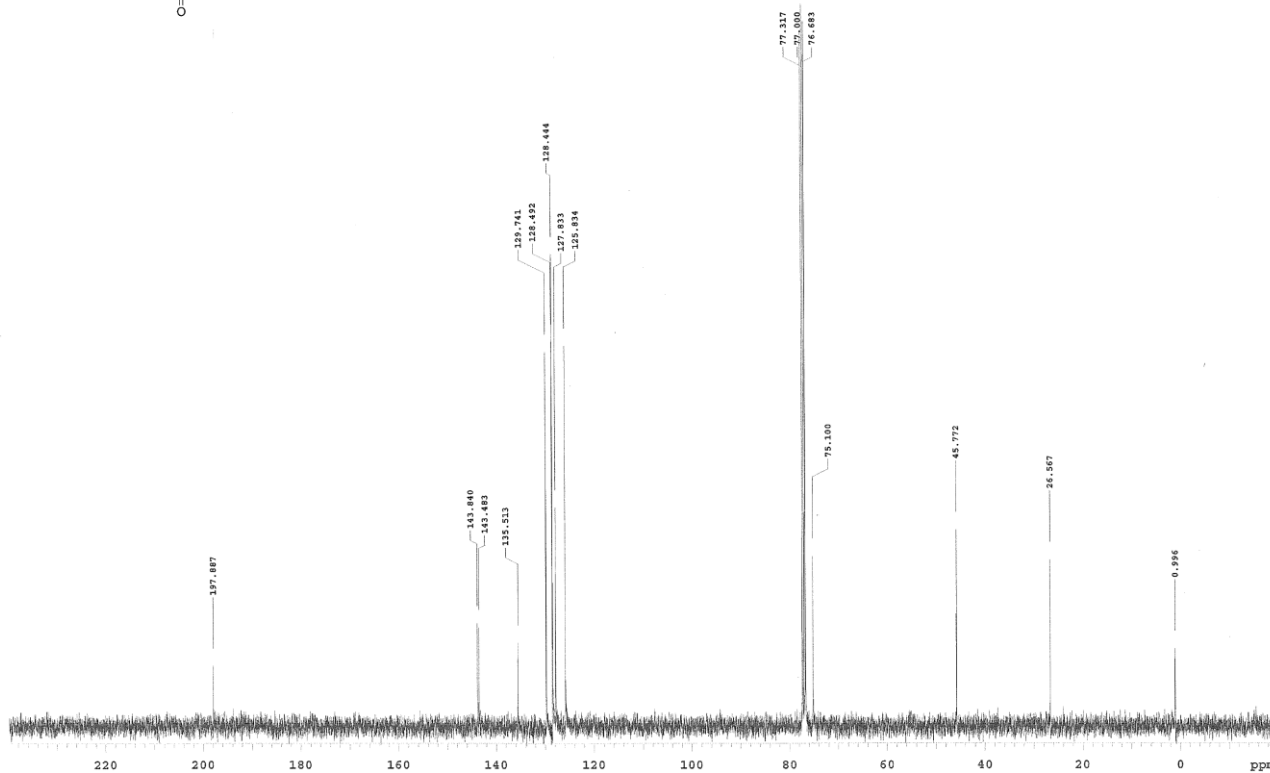
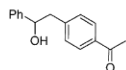


<sup>13</sup>C NMR spectrum of 2-(4-(cyclohexanecarbonyl)phenyl)-N-phenylacetamide



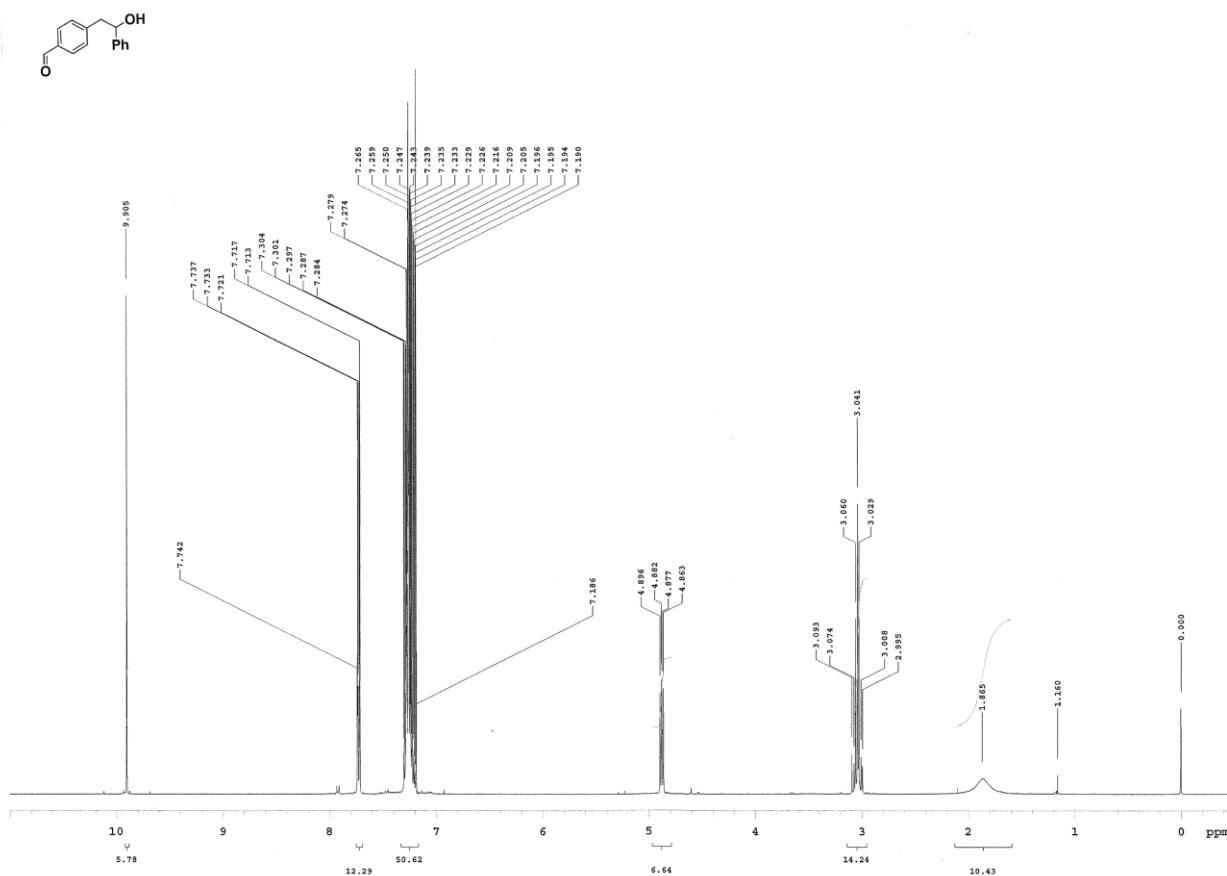


**<sup>1</sup>H NMR spectrum of 1-(4-(2-hydroxy-2-phenylethyl)phenyl)ethan-1-one**

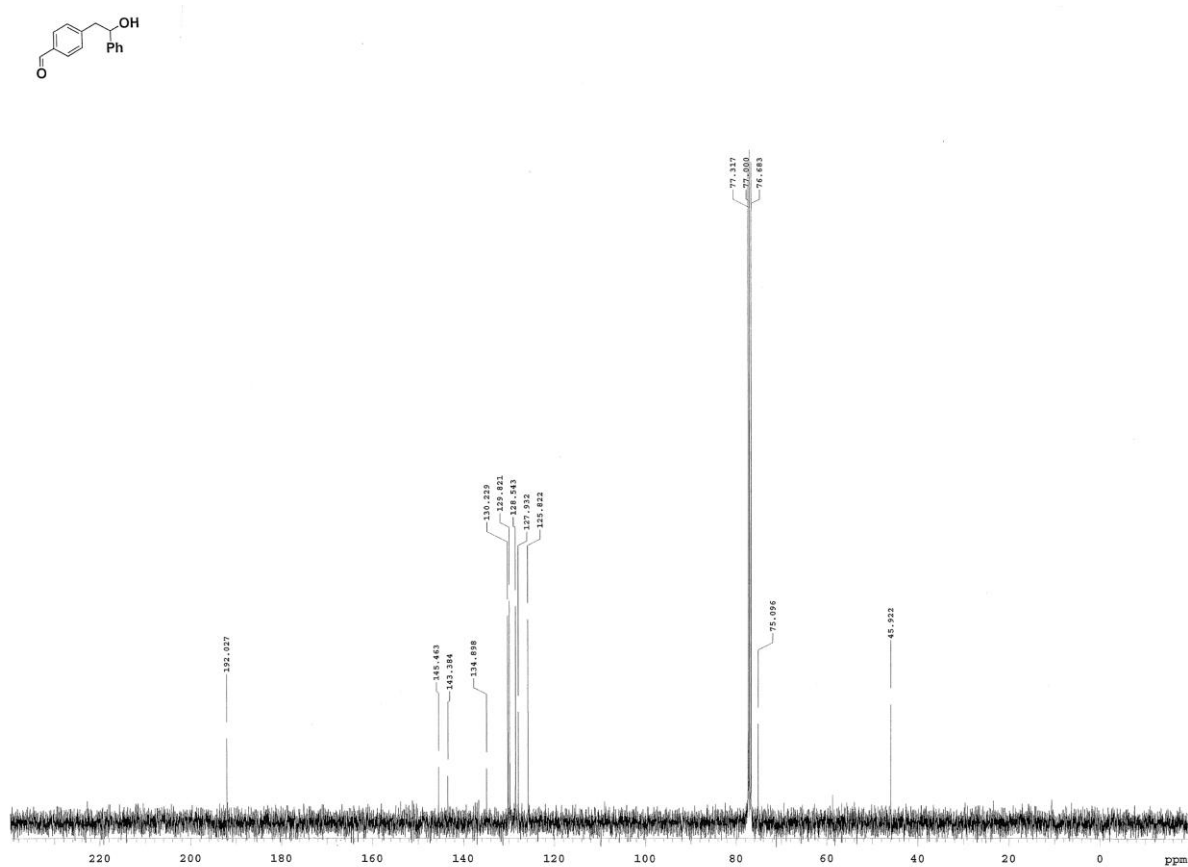


**<sup>13</sup>C NMR spectrum of 1-(4-(2-hydroxy-2-phenylethyl)phenyl)ethan-1-one**

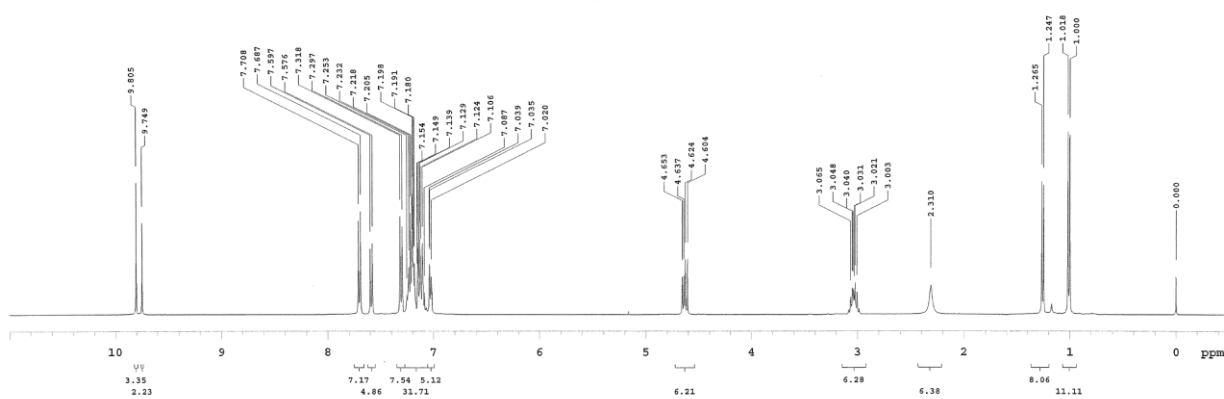
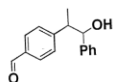




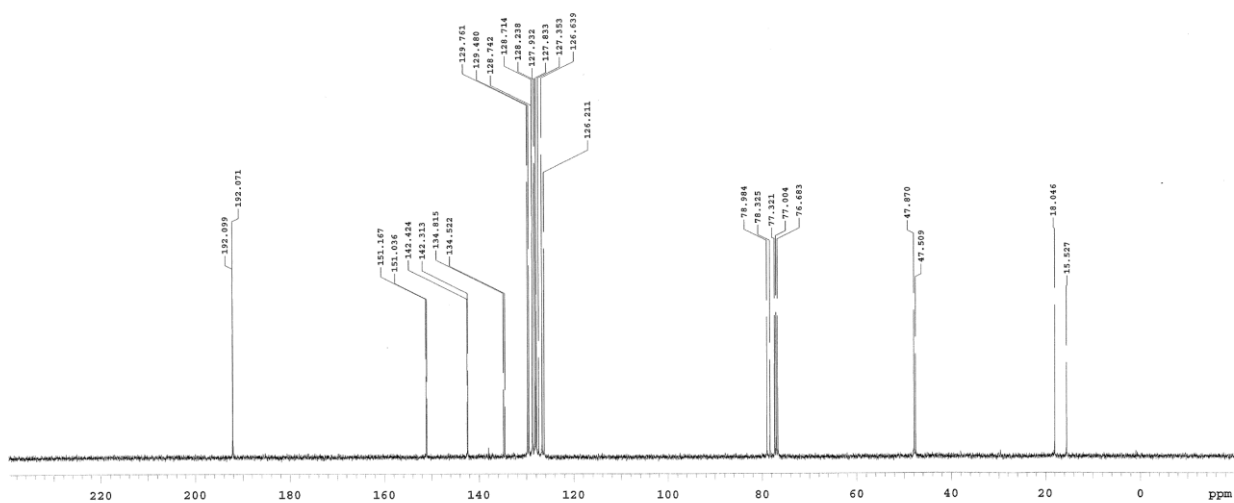
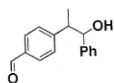
<sup>1</sup>H NMR spectrum of 4-(2-hydroxy-2-phenylethyl)benzaldehyde



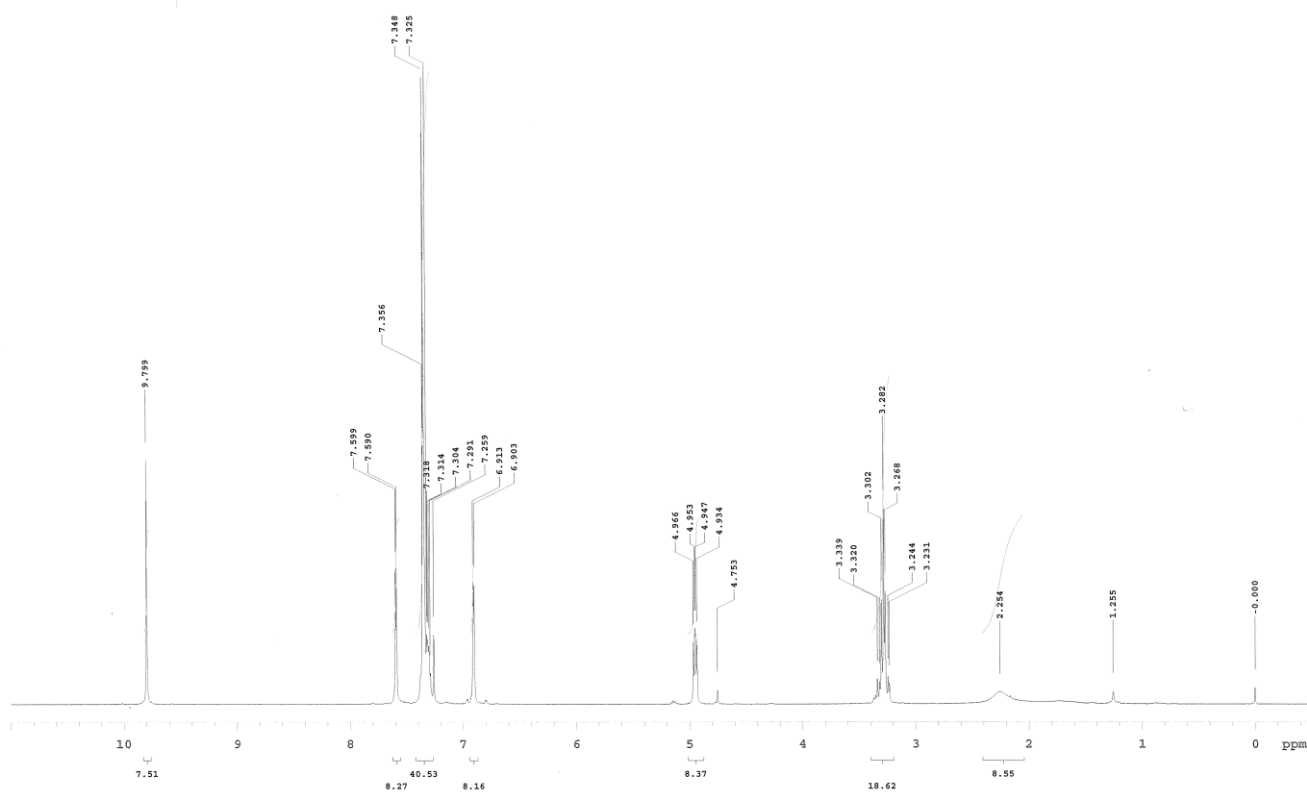
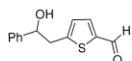
<sup>13</sup>C NMR spectrum of 4-(2-hydroxy-2-phenylethyl)benzaldehyde



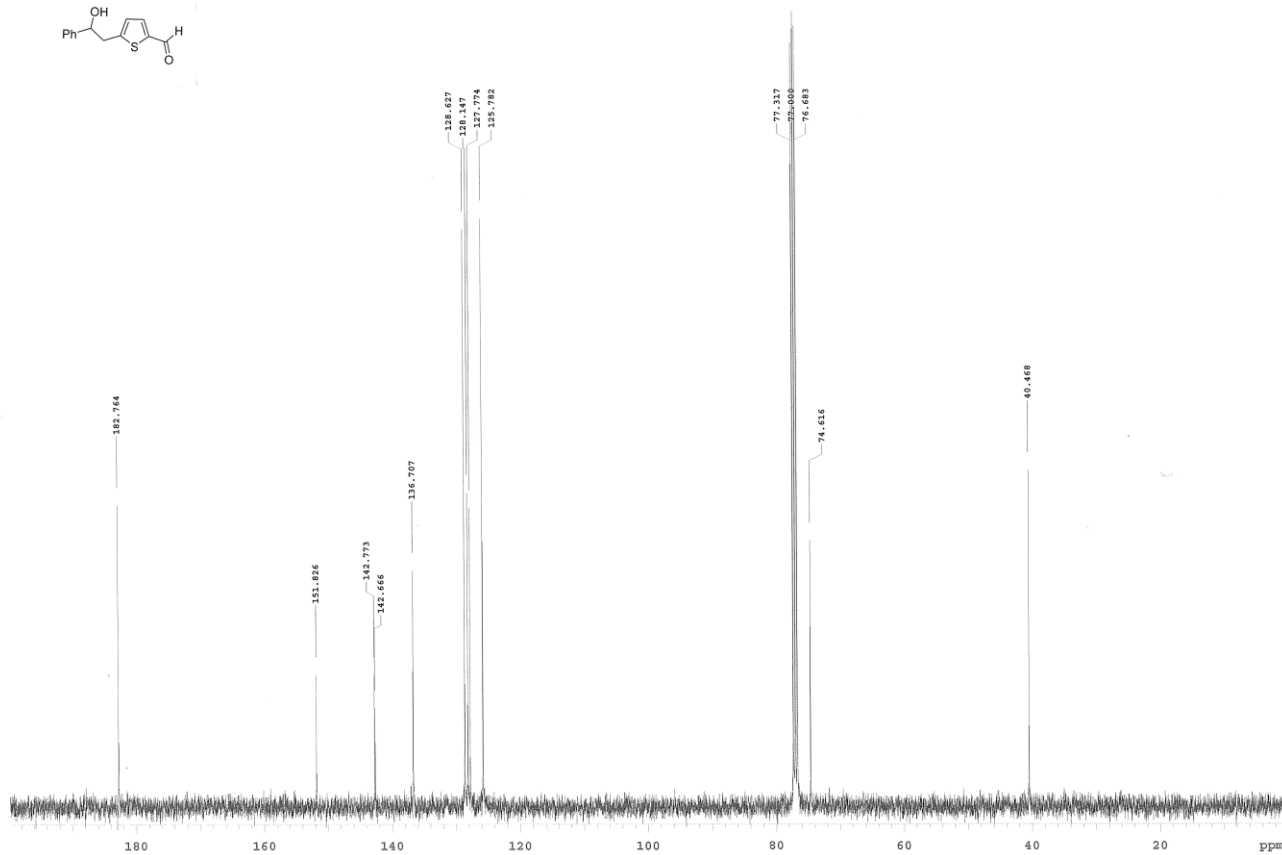
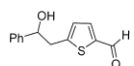
**<sup>1</sup>H NMR spectrum of 4-(1-hydroxy-1-phenylpropan-2-yl)benzaldehyde**



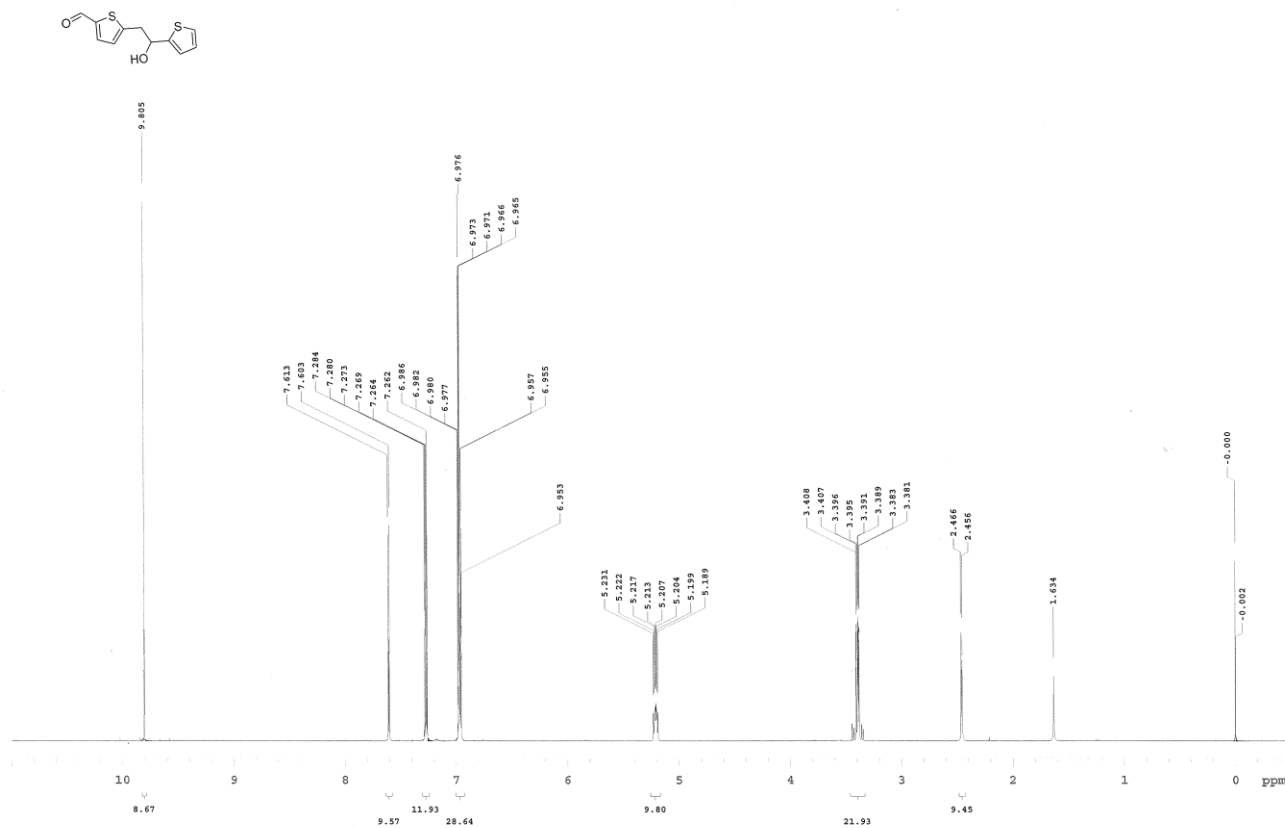
**<sup>13</sup>C NMR spectrum of 4-(1-hydroxy-1-phenylpropan-2-yl)benzaldehyde**



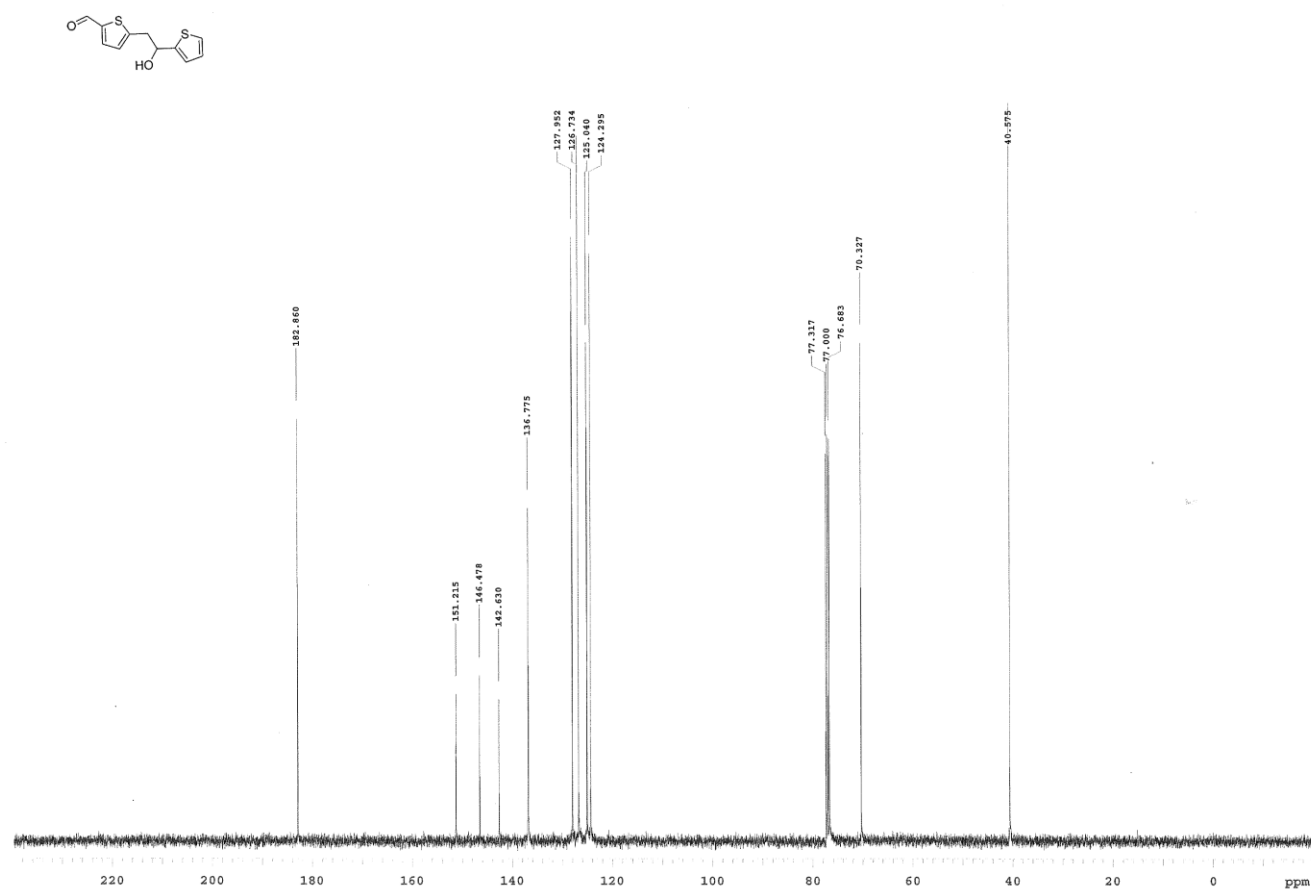
**<sup>1</sup>H NMR spectrum of 5-(2-hydroxy-2-phenylethyl)thiophene-2-carbaldehyde**



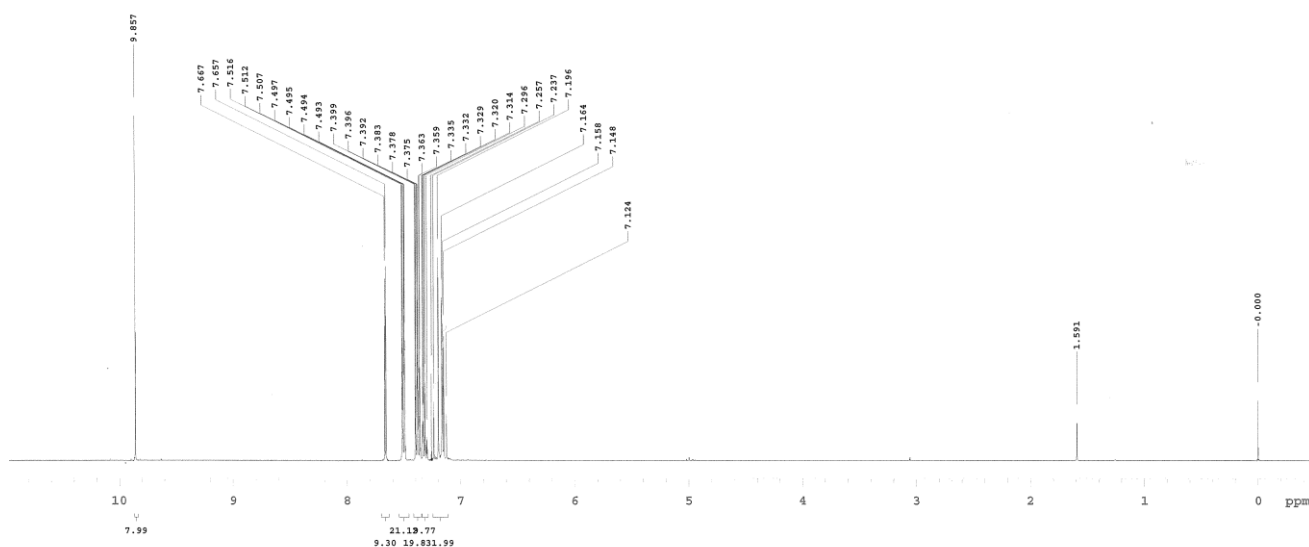
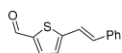
**<sup>13</sup>C NMR spectrum of 5-(2-hydroxy-2-phenylethyl)thiophene-2-carbaldehyde**



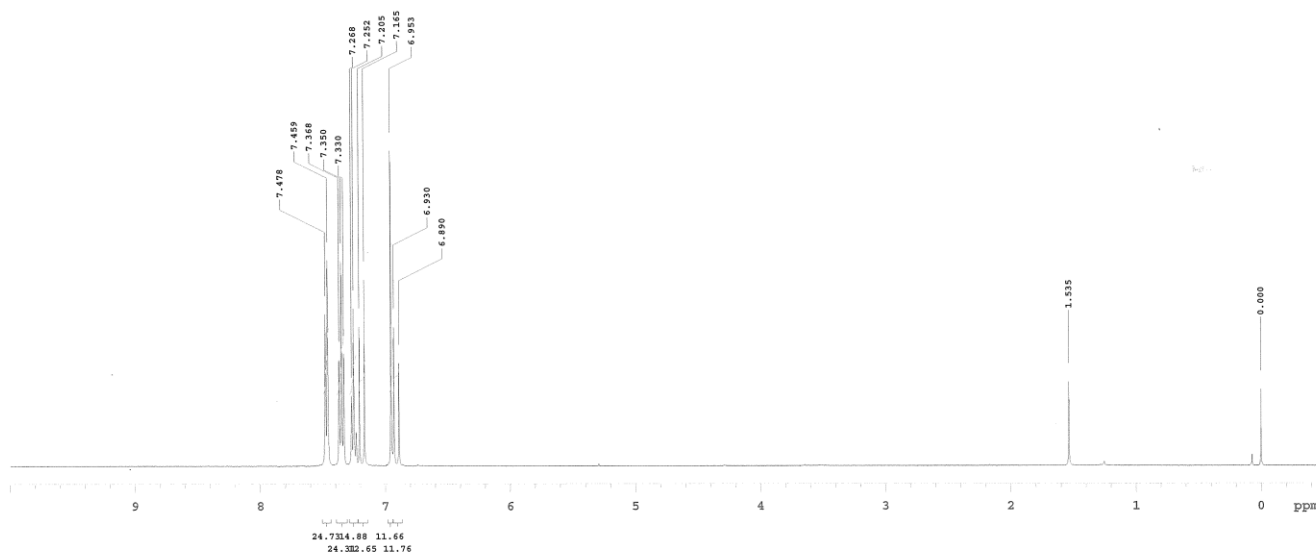
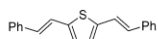
**<sup>1</sup>H NMR spectrum of 5-(2-hydroxy-2-(2-thiophenyl)ethyl)thiophene-2-carbaldehyde**



**<sup>13</sup>C NMR spectrum of 5-(2-hydroxy-2-(2-thiophenyl)ethyl)thiophene-2-carbaldehyde**



<sup>1</sup>H NMR spectrum of (E)-5-Styrylthiophene-2-carbaldehyde



<sup>1</sup>H NMR spectrum of (E,E)-2,5-Distyrylthiophene