

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, Rtx-200; 0.25 mm x 30 m). ^1H and ^{13}C NMR spectra were recorded on Varian MERCURYplus-400 (^1H 400 MHz, ^{13}C 100 MHz) spectrometer with Me_4Si as an internal standard in CDCl_3 . ESI and APCI mass spectra were recorded on executive spectrometer. Gel permeation chromatography (GPC) was carried out on Japan Analytical Industry LC-9201. THF and Et_2O were purchased from Wako as a dry solvent and used without further purification. Hexane was purchased from Wako, distilled before use, and stored over molecular sieves 4A. *n*-Butyllithium, phenyllithium, methanol, acetic acid, methyl 4-formylbenzoate, 4-nitrobenzaldehyde, 4-cyanobenzaldehyde, 4-isocyanatobenzonitrile, methyl 4-isocyanatobenzoate, methyl 3-formyl-4-nitrobenzoate, 4-bromobenzonitrile, 1-iodo-4-nitrobenzene, ethyl 4-iodobenzoate, and mesityl bromide were commercially available. 5-Cyanopentanal and ethyl 4-formylcyclohexanecarboxylate were purchased from a commercial supplier. 6-oxo-6-phenylhexanal¹, methyl 6-oxohexanoate², 3-benzoylbenzaldehyde³, 4-benzoylbenzaldehyde⁴, cyclohexyl(4-iodophenyl)methanone⁵, 1-(4-iodophenyl)-1-pentanone⁵ were synthesized according to the literature.

A Stainless steel (SUS304) T-shaped micromixer with the inner diameter of 250, 500, and 800 μm and a stainless steel (SUS304) V-shaped micromixer with inner diameter of 250 μm were manufactured by Sanko Seiki Co., Inc (Figure S1). Stainless steel (SUS316) microtube reactors with inner diameter of 250 and 1000 μm were purchased from GL Sciences. The micromixers and microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUN). The flow microreactor system was dipped in a cooling bath to control the temperature. Solutions were introduced to the flow microreactor system using syringe pumps, Harvard PHD 2000, Harvard PHD 4400 or Harvard PHD Ultra, equipped with gastight syringes purchased from SGE (Harvard PHD 2000 or Harvard PHD Ultra) or stainless steel syringes (Harvard PHD 4400).

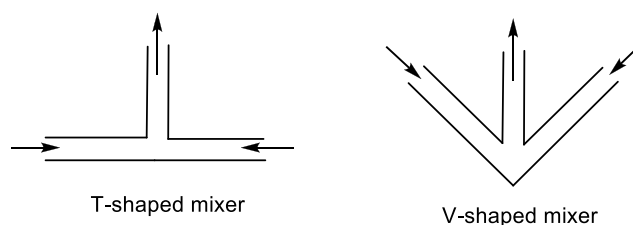
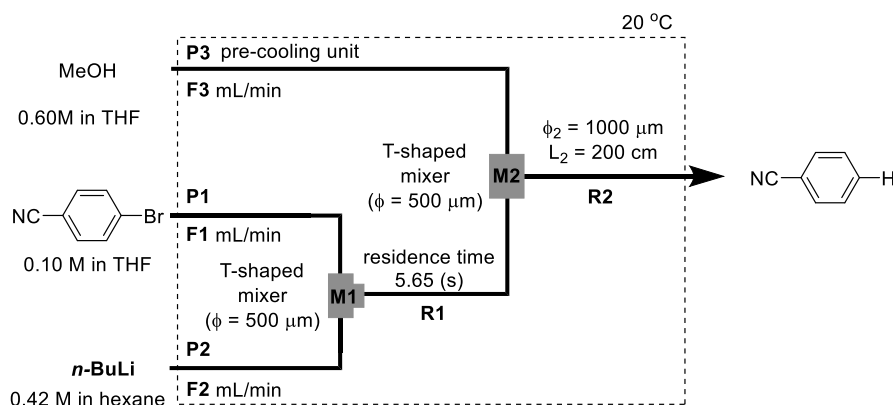


Figure S1. Schematic diagrams of the T-shaped micromixer and the V-shaped micromixer.

General Procedure for Bromine-lithium Exchange of 4-Cyanobromobenzene with *n*-BuLi followed by Reaction with Methanol



A flow microreactor system consisting of two T-shaped micromixers ($\phi = 500 \mu\text{m}$) (**M1**, **M2**), a microtube reactor (**R1**, **R2**), and three pre-cooling units (**P1** (inner diameter $\phi = 1000 \mu\text{m}$, length $L = 100 \text{ cm}$), **P2** ($\phi = 1000 \mu\text{m}$, $L = 50 \text{ cm}$) and **P3** ($\phi = 1000 \mu\text{m}$, $L = 50 \text{ cm}$)) was used. When the total flow rate was 20 mL/min, three pre-cooling units (**P1** ($\phi = 1000 \mu\text{m}$, length $L = 200 \text{ cm}$), **P2** ($\phi = 1000 \mu\text{m}$, $L = 100 \text{ cm}$) and **P3** ($\phi = 1000 \mu\text{m}$, $L = 100 \text{ cm}$)) was used. The flow microreactor system was dipped in a cooling bath of 20 $^{\circ}\text{C}$. A solution of 4-bromobenzonitrile (**1**) (0.10 M in THF) (flow rate $F1 \text{ mL/min}$) and a solution of *n*-BuLi (0.42 M in hexane) (flow rate $F2 \text{ mL/min}$) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** ($\phi = 1000 \mu\text{m}$, $L_1 \text{ cm}$) and was mixed with a solution of MeOH (1.0 M in THF) (flow rate $F3 \text{ mL/min}$) in **M2**. The resulting solution was passed through **R2** ($\phi = 1000 \mu\text{m}$, $L = 200 \text{ cm}$). After a steady state was reached, an aliquot of the product solution was collected in a flask containing brine for 30 s. The conversion of 4-bromobenzonitrile

(1) and the yields of benzonitrile were determined by GC analysis using an internal standard (tetradecane) (Table S1). In the case of slower flow rate condition (F1 = 2.0 ml/min, F2 = 0.50 ml/min, F3 = 0.50 ml/min), the formation of 1-phenylpentan-1-one was observed by GC-Mass analysis (Figure S2).

Table S1. Bromine-lithium exchange of 4-cyanobromobenzene with *n*-BuLi followed by reaction with methanol

F1 (mL/min)	F2 (mL/min)	F3 (mL/min)	conversion (%)	yield (%)
2.0	0.50	0.50	100	36
4.0	1.0	1.0	100	61
8.0	2.0	2.0	100	75
16	4.0	4.0	100	85

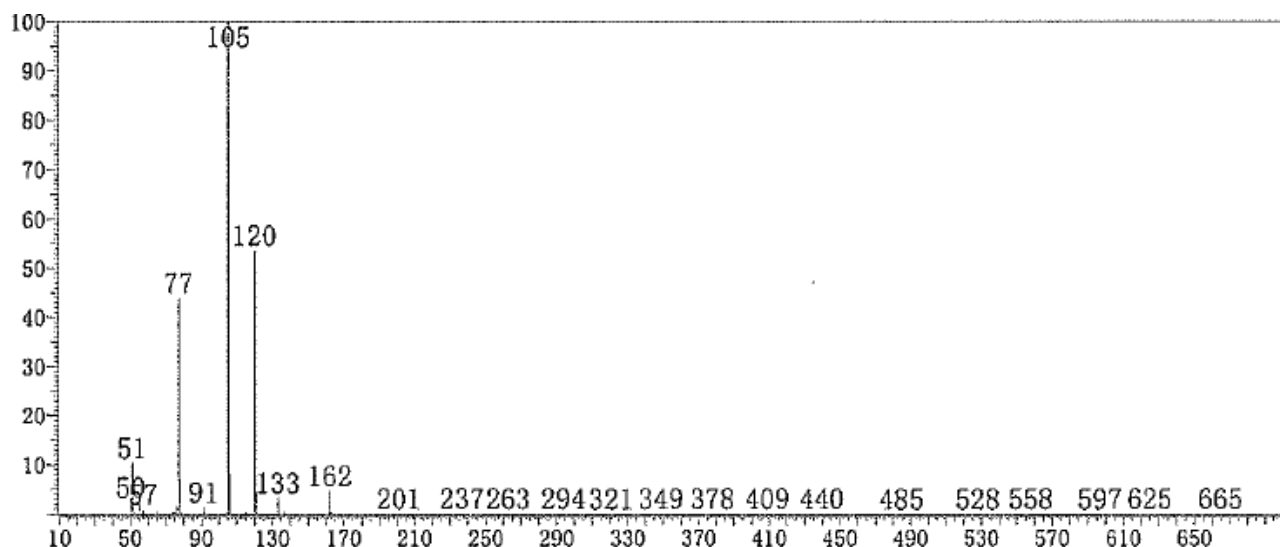
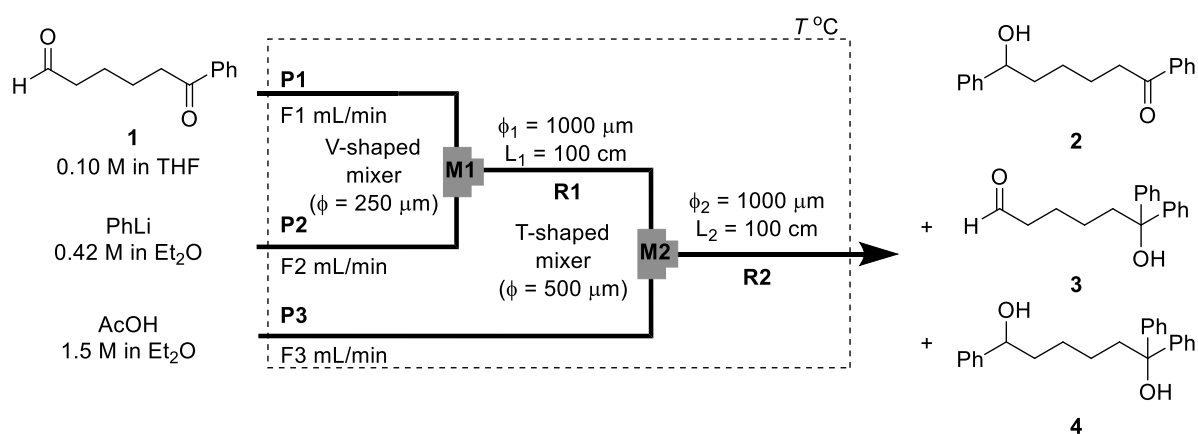


Figure S2. GC-MS analysis of the reaction of 4-bromobenzonitrile with *n*-BuLi

General Procedure for Reactions of Phenyllithium with 6-Oxo-6-phenylhexanal in a Flow Microreactor System



A flow microreactor system consisting of V-shaped micromixer ($\phi = 250 \mu\text{m}$) (**M1**), T-shaped micromixer ($\phi = 500 \mu\text{m}$) (**M2**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (inner diameter $\phi = 1000 \mu\text{m}$, length $L = 200 \text{ cm}$), **P2** ($\phi = 1000 \mu\text{m}$, $L = 100 \text{ cm}$) and **P3** ($\phi = 1000 \mu\text{m}$, $L = 50 \text{ cm}$)) was used. A solution of 6-oxo-6-phenylhexanal (0.10 M in THF) (flow rate: F1 mL/min) and a solution of PhLi (0.42 M in Et₂O/cyclohexane (74/26 v/v)) (flow rate: F2 mL/min) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** (residence time t^{R1} (s)) and was mixed with a solution of AcOH (1.5 M in Et₂O) (flow rate: F3 mL/min) in **M2**. The resulting solution was passed through **R2** ($\phi = 1000 \mu\text{m}$, $L = 100 \text{ cm}$). After a steady state was reached, an aliquot of the product solution was collected to the sat. NaHCO₃ aqueous solution for 30 s (when the total flow rate in **M1** was 2.5 mL/min, an aliquot of the product solution was collected for 1 min,

when total flow rate in **M1** was 30 mL/min, an aliquot of the product solution was collected for 20 s) to neutralize the solution. The flow microreactor system was dipped in a cooling bath of -40 °C. The reaction mixture was analyzed by GC using an internal standard. The results are summarized in Table S2.

Table S2. Reactions of phenyllithium with 6-oxo-6-phenylhexanal

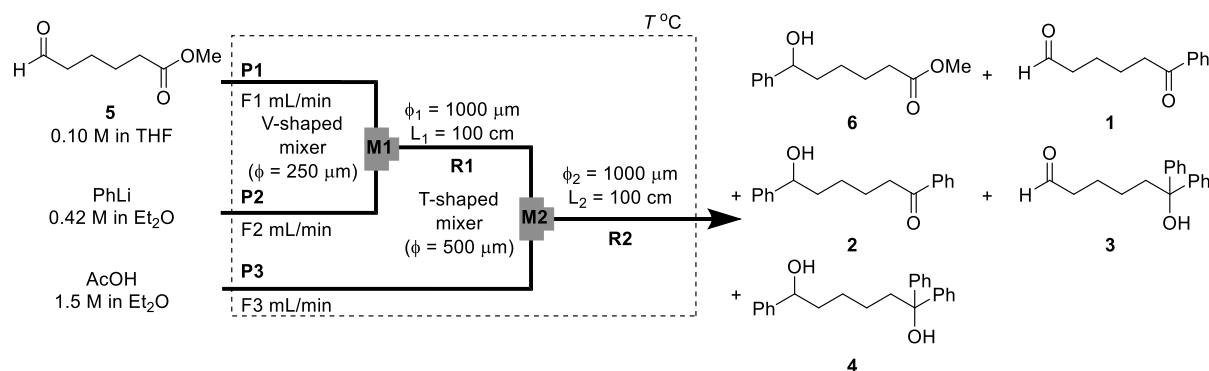
temperature (°C)	F1 (mL/min)	F2 (mL/min)	F3 (mL/min)	conversion (%)	yield (%)		
					2	3	4
-40	2.0	0.50	0.50	66	10	20	29
-40	8.0	2.0	2.0	65	36	12	19
-40	24	6.0	6.0	77	48	10	18
-70	2.0	0.50	0.50	67	11	23	26
-70	8.0	2.0	2.0	72	27	18	22
-70	24	6.0	6.0	73	44	12	17

6-Oxo-1,6-diphenylhexan-1-ol (2). Obtained by 48% yield (GC yield using an internal standard (hexadecane)) from 6-oxo-6-phenylhexanal and PhLi. GC *t*_R 20.0 min (initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec). After extraction, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 10/1 to 1/1) and purified by GPC to obtain a pure compound as a white solid. : GC *t*_R 20.0 min (initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 30 cm/sec); ¹H NMR (400 MHz, CDCl₃) δ 1.34-1.60 (m, 2H), 1.72-1.94 (m, 5H), 2.97 (t, *J* = 7.4 Hz, 2H), 4.66-4.74 (m, 1H), 7.25-7.39 (m, 5H), 7.42-7.50 (m, 2H), 7.52-7.60 (m, 1H), 7.92-7.98 ppm (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 24.0, 25.5, 38.4, 38.8, 74.3, 125.8, 127.5, 128.0, 128.4, 128.5, 132.9, 136.9, 144.7, 150.3, 200.3 ppm; HRMS (EI) *m/z* calcd for C₁₈H₂₀O₂⁺ [M]⁺: 268.1458, found: 268.1458.

6-Hydroxy-6,6-diphenylhexanal (3). Obtained in 10% yield (GC yield using an internal standard (dodecane)). GC *t*_R 18.2 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 30 cm/sec). After extraction, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 10/1 to 3/1) and purified by GPC to obtain a pure compound as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 1.28-1.36 (m, 2H), 1.64-1.68 (m, 2H), 2.09 (s, 1H), 2.26-2.34 (m, 2H), 2.38-2.44 (m, 2H), 7.20-7.42 (m, 10H), 9.72 ppm (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 22.3, 23.4, 41.6, 43.8, 78.0, 125.9, 126.8, 128.1, 146.9, 202.6 ppm; HRMS (EI) *m/z* calcd for C₁₈H₂₀O₂⁺ [M]⁺: 268.1458, found: 268.1452.

1,1,6-Triphenylhexane-1,6-diol (4). Obtained in 18% yield (GC yield using an internal standard (dodecane)) GC *t*_R 22.9 min (initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 30 cm/sec). After extraction, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 10/1 to 1/1) and purified by GPC to obtain a pure compound as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 1.28-1.40 (m, 2H), 1.60-1.72 (m, 2H), 2.09 (s, 1H), 2.27-2.36 (m, 2H), 2.39-2.44 (m, 2H), 7.20-7.42 (m, 10H), 9.72 ppm (t, *J* = 1.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 22.3, 23.4, 41.6, 43.8, 78.0, 125.9, 126.8, 128.1, 146.9, 202.6 ppm; HRMS (ESI) *m/z* calcd for C₂₄H₂₆O₂Na⁺ [M+Na]⁺: 369.1831, found: 369.1817.

General Procedure for Reactions of Phenyllithium with Methyl 6-oxohexanoate in a Flow Microreactor System



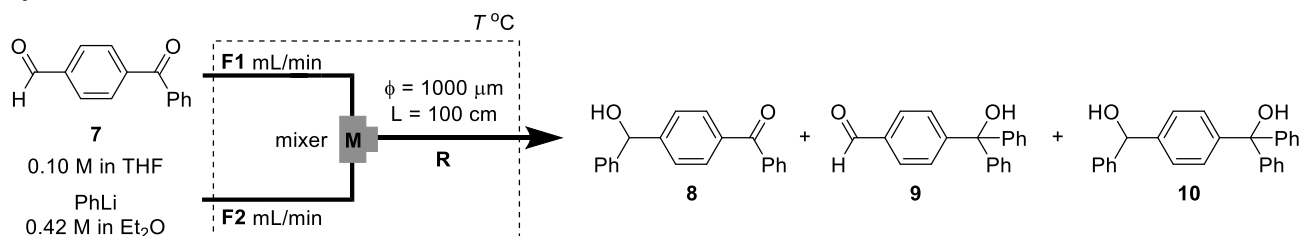
A flow microreactor system consisting of V-shaped micromixer ($\phi = 250\ \mu\text{m}$) (**M1**), T-shaped micromixer ($\phi = 500\ \mu\text{m}$) (**M2**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (inner diameter $\phi = 1000\ \mu\text{m}$, length $L = 200\ \text{cm}$), **P2** ($\phi = 1000\ \mu\text{m}$, $L = 100\ \text{cm}$) and **P3** ($\phi = 1000\ \mu\text{m}$, $L = 50\ \text{cm}$)) was used. A solution of methyl 6-oxohexanoate (0.10 M in THF) (flow rate: F1 mL/min) and a solution of PhLi (0.42 M in Et₂O/cyclohexane (74/26 v/v)) (flow rate: F2 mL/min) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** (residence time t^{R1} (s)) and was mixed with a solution of AcOH (1.5 M in Et₂O) (flow rate: F3 mL/min) in **M2**. The resulting solution was passed through **R2** ($\phi = 1000\ \mu\text{m}$, $L = 100\ \text{cm}$). After a steady state was reached, an aliquot of the product solution was collected to the sat. NaHCO₃ aqueous solution for 30 s (when the total flow rate in **M1** was 2.5 mL/min, an aliquot of the product solution was collected for 1 min, when total flow rate in **M1** was 30 mL/min, an aliquot of the product solution was collected for 20 s) to neutralize the solution. The flow microreactor system was dipped in a cooling bath of $-40\ ^\circ\text{C}$. The reaction mixture was analyzed by GC using an internal standard. The results are summarized in Table S3.

Table S3. Reactions of phenyllithium with 6-oxohexanoate

temperature ($^\circ\text{C}$)	F1 (mL/min)	F2 (mL/min)	F3 (mL/min)	conversion (%)	yield (%)				
					6	1	2	3	4
-40	2.0	0.50	0.50	59	22	0	19	9	0
-40	8.0	2.0	2.0	82	69	0	4	2	5
-40	24	6.0	6.0	81	72	0	3	1	5
-70	2.0	0.50	0.50	62	22	0	15	11	2
-70	8.0	2.0	2.0	72	52	3	6	3	5
-70	24	6.0	6.0	74	60	2	4	2	5

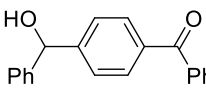
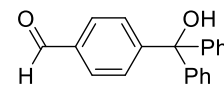
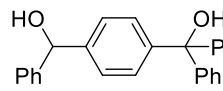
Methyl 6-hydroxy-6-phenylhexanoate (6). Obtained in 72% yield (GC yield using an internal standard (dodecane)) from methyl 6-oxohexanoate and PhLi. The spectral data were identical to those reported in the literature⁶. (GC *t*_R 13.9 min; initial oven temperature, $100\ ^\circ\text{C}$ for 2 min; rate of temperature increase, $10\ ^\circ\text{C}/\text{min}$; He linear velocity, 30 cm/sec).

Typical Procedure for the Reaction of 4-Benzoylbenzaldehyde with Phenyllithium in a Flow Microreactor System



A flow microreactor system consisting of a V-shaped 45° micromixer ($\phi = 250\ \mu\text{m}$) or T-shaped micromixer ($\phi = 500, 800\ \mu\text{m}$) (**M**), a microtube reactor (**R**), and two tube pre-cooling units (**P1** (inner diameter $\phi = 1000\ \mu\text{m}$, length $L = 200\ \text{cm}$) and **P2** ($\phi = 1000\ \mu\text{m}$, $L = 100\ \text{cm}$)) was used. A solution of 4-benzoylbenzaldehyde (0.10 M in THF) (flow rate: F1 mL/min) and a solution of PhLi (0.42 M in Et₂O/cyclohexane (74/26 v/v)) (flow rate: F2 mL/min) were introduced to **M** by syringe pumps. The resulting solution was passed through **R** ($\phi = 1000\ \mu\text{m}$, $L = 100\ \text{cm}$). After a steady state was reached, an aliquot of the product solution was collected to the sat. NH₄Cl aqueous solution for 30 s to quench the reaction. (when total flow rate in **M** was under 1.875 mL/min, an aliquot of the product solution was collected for 1 min, when total flow rate in **M** was over 20 mL/min, an aliquot of the product solution was collected for 20 s). The flow microreactor system was dipped in a cooling bath of $T\ ^\circ\text{C}$. The reaction mixture was analyzed by GC. The results are summarized in Table S4.

Table S4. Reactions of 4-benzoylbenzaldehyde with phenyllithium in a flow microreactor system

inner diameter in M (μm)	<i>T</i> ($^{\circ}\text{C}$)	F1 (mL/min)	F2 (mL/min)	conversion of 7 (%)	yield (%)		
					 8	 9	 10
800 (90 $^{\circ}$)	-40	12	3.0	65	23	3	40
500 (90 $^{\circ}$)	-40	12	3.0	71	34	3	32
250 (45 $^{\circ}$)	-40	12	3.0	83	66	2	15
250 (45 $^{\circ}$)	-78	12	3.0	78	60	4	17
250 (45 $^{\circ}$)	-20	12	3.0	79	57	2	18
250 (45 $^{\circ}$)	0	12	3.0	81	61	2	21
250 (45 $^{\circ}$)	20	12	3.0	81	57	2	22
250 (45 $^{\circ}$)	-40	0.50	0.125	61	7	5	40
250 (45 $^{\circ}$)	-40	1.0	0.25	56	8	5	41
250 (45 $^{\circ}$)	-40	2.0	0.50	60	15	5	38
250 (45 $^{\circ}$)	-40	4.0	1.0	74	42	5	29
250 (45 $^{\circ}$)	-40	8.0	2.0	82	60	3	20
250 (45 $^{\circ}$)	-40	16	4.0	84	69	2	15
250 (45 $^{\circ}$)	-40	20	5.0	78	70	2	8
250 (45 $^{\circ}$)	-40	24	6.0	81	73	1	8

4-Benzoylbenzhydrol (8). Obtained in 73% yield (GC yield) on the condition of using V-shaped 45 $^{\circ}$ micromixer, F1 = 24 mL/min, F2 = 6.0 mL/min, *T* = -40 $^{\circ}\text{C}$. The spectral data were identical to those reported in the literature.⁷ (GC *t*_R 21.1 min; initial oven temperature, 100 $^{\circ}\text{C}$ for 2 min; rate of temperature increase, 10 $^{\circ}\text{C}/\text{min}$; He linear velocity, 30 cm/sec)

4-(Hydroxydiphenylmethyl)benzaldehyde (9). Obtained 1% yield (GC yield) on the condition of using V-shaped 45 $^{\circ}$ micromixer, F1 = 24 mL/min, F2 = 6.0 mL/min, *T* = -40 $^{\circ}\text{C}$. The spectral data were identical to those reported in the literature (GC *t*_R 19.2 min; initial oven temperature, 100 $^{\circ}\text{C}$ for 2 min; rate of temperature increase, 10 $^{\circ}\text{C}/\text{min}$; He linear velocity, 30 cm/sec).⁸

4-(Hydroxydiphenylmethyl)benzhydrol (10). Obtained 8% yield (GC yield) on the condition of using V-shaped 45 $^{\circ}$ micromixer, F1 = 24 mL/min, F2 = 6.0 mL/min, *T* = -40 $^{\circ}\text{C}$. This product was synthesized by alternate method to make a calibration curve. A solution of methyl terephthalaldehyde (0.3283 g, 2.00 mmol) in THF (20 mL) was stirred in a flask (100 mL round bottom glass flask with a magnetic stirrer) at -78 $^{\circ}\text{C}$. A solution of PhLi (1.07 M in Et₂O/cyclohexane (30/70 v/v), 6.17 mL, 6.60 mmol) was added and a cooling bath was removed. After stirring for 15 min, sat. NH₄Cl aqueous solution (15 mL) was added. The organic layer was separated and the remaining aqueous layer was extracted with Et₂O (50 mL \times 3). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 3/1) to give 4-(hydroxydiphenylmethyl)benzhydrol (0.6262 g, 86%): GC *t*_R 23.1 min (initial oven temperature, 100 $^{\circ}\text{C}$ for 2 min; rate of temperature increase, 10 $^{\circ}\text{C}/\text{min}$; He linear velocity, 30 cm/sec); ¹H NMR (400 MHz, CDCl₃) δ 2.20 (d, *J* = 3.6 Hz, 1H), 2.75 (s, 1H), 5.84 (d, *J* = 3.2 Hz, 1H), 7.22-7.41 ppm (m, 19H); ¹³C NMR (100 MHz, CDCl₃) δ 76.0, 81.8, 126.1, 126.5, 127.2, 127.6, 127.8, 127.9, 128.1, 128.5, 142.6, 143.6, 146.1, 146.7 ppm; HRMS (ESI) *m/z* calcd for C₂₆H₂₂O₂Na⁺ [M+Na]⁺: 389.1512, found: 389.1503.

General Procedure for the Reaction of 4-Benzoylbenzaldehyde with Phenyllithium in a Batch Macro Reactor.

Method A. A cooled solution of PhLi in Et₂O/cyclohexane (74/26 v/v) (0.42 M, 3.0 mL (1.05 eq), *T* $^{\circ}\text{C}$) was

added dropwise for 1.0 min using a glass syringe to a solution of 4-benzoylbenzaldehyde (**7**) in THF (0.10 M, 12 mL) in a 50 mL round bottom glass flask with a magnetic stirrer at T °C. After being stirred for 10 min at T °C, sat. aq. NH_4Cl solution (2.0 mL) was added, and the cooling bath was removed. The conversion of 4-benzoylbenzaldehyde (**7**) and the yields of (4-(hydroxy(phenyl)methyl)phenyl)(phenyl)methanone (**8**), 4-(hydroxydiphenylmethyl)benzaldehyde (**9**), and 4-(hydroxydiphenylmethyl)benzhydrol (**10**) were determined by GC analysis using an internal standard (pentadecane). The results are summarized in Table S5.

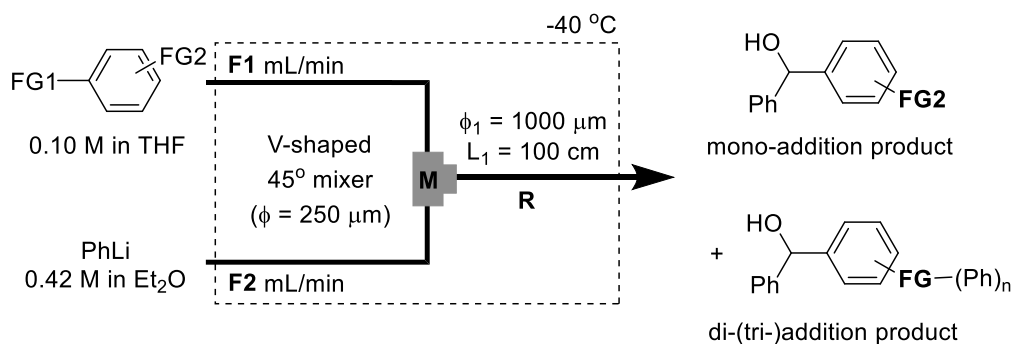
Method B. A cooled solution of 4-benzoylbenzaldehyde (**7**) in THF (0.10 M, 12 mL, T °C) was added dropwise for 1.0 min using a glass syringe to a solution of PhLi in Et_2O /cyclohexane (74/26 v/v) (0.42 M, 3.0 mL (1.05 eq)) in a 50 mL round bottom glass flask with a magnetic stirrer at T °C. After being stirred for 10 min at T °C, sat. aq. NH_4Cl solution (2.0 mL) was added, and the cooling bath was removed. The conversion of 4-benzoylbenzaldehyde (**7**) and the yields of (4-(hydroxy(phenyl)methyl)phenyl)(phenyl)methanone (**8**), 4-(hydroxydiphenylmethyl)benzaldehyde (**9**), and 4-(hydroxydiphenylmethyl)benzhydrol (**10**) were determined by GC analysis using an internal standard (pentadecane). The results are summarized in Table S5.

Method C. A cooled solution of PhLi in Et_2O /cyclohexane (74/26 v/v) (0.42 M, 3.0 mL (1.05 eq), -78 °C) and a cooled solution of 4-benzoylbenzaldehyde (**7**) in THF (0.10 M, 12 mL, -78 °C) were added for 1.0 min to a 50 mL flask equipped with a stirring bar at -78 °C simultaneously. After the resulting solution was stirred for 10 min at -78 °C, sat. aq. NH_4Cl solution (2.0 mL) was added, and the cooling bath was removed. The conversion of 4-benzoylbenzaldehyde (**7**) and the yields of (4-(hydroxy(phenyl)methyl)phenyl)(phenyl)methanone (**8**), 4-(hydroxydiphenylmethyl)benzaldehyde (**9**), and 4-(hydroxydiphenylmethyl)benzhydrol (**10**) were determined by GC analysis using an internal standard (pentadecane). The results are summarized in Table S5.

Table S5. Reactions of 4-benzoylbenzaldehyde (**7**) and phenyllithium using a conventional macro batch reactor.

T (°C)	method of addition	conversion of 7 (%)	yield (%)		
			8	9	10
-78	addition of PhLi to 7 (method A)	65	28	7	25
-40	addition of PhLi to 7 (method A)	64	23	7	26
-20	addition of PhLi to 7 (method A)	64	20	7	30
0	addition of PhLi to 7 (method A)	64	12	6	30
20	addition of PhLi to 7 (method A)	61	12	5	33
-78	addition of 7 to PhLi (method B)	33	6	2	26
-40	addition of 7 to PhLi (method B)	37	5	1	27
-20	addition of 7 to PhLi (method B)	46	4	1	35
0	addition of 7 to PhLi (method B)	51	2	1	37
20	addition of 7 to PhLi (method B)	55	1	1	40
-78	simultaneous addition of 7 and PhLi (method C)	51	16	9	26

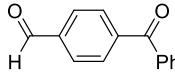
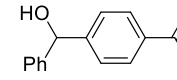
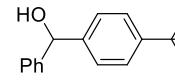
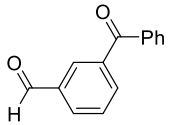
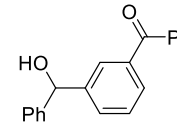
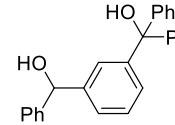
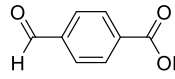
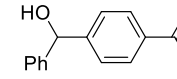
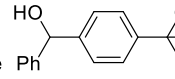
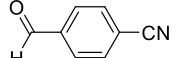
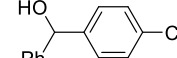
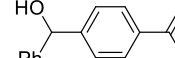
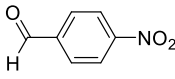
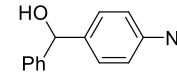
General Procedure of the Reaction of Aromatic Compounds Having two Different Electrophilic Groups with PhLi using the Flow Microreactors



A flow microreactor system consisting of a V-shaped micromixer ($\phi = 250 \mu\text{m}$) (**M**), a microtube reactor (**R**) and two pre-cooling units (**P1** (inner diameter $\phi = 1000 \mu\text{m}$, length $L = 200 \text{ cm}$) and **P2** ($\phi = 1000 \mu\text{m}$, $L = 100 \text{ cm}$)) was used. The flow microreactor system was dipped in a cooling bath of -40 °C. A solution of a difunctional

electrophile (0.10 M in THF) (flow rate: F1 mL/min) and a solution of PhLi (0.42 M in Et₂O/cyclohexane (74/26 v/v)) (flow rate: F2 mL/min) were introduced to **M** by syringe pumps. The resulting solution was passed through **R** (ϕ = 1000 μ m, L = 100 cm). After a steady state was reached, an aliquot of the product solution was collected in a flask containing the sat. aq. NH₄Cl solution for 30 s. The reaction mixture was analyzed by GC using an internal standard (pentadecane). The results are summarized in Table S6. For comparison, the reactions in the batch reactor were performed using method **A** (-78 °C).

Table S6. General procedure of the reaction of aromatic compounds having two different electrophilic groups with PhLi using the flow microreactors

substrate	F1 (mL/min)	F2 (mL/min)	conversion (%)	yield (%)	
				mono-addition product	di-(tri-)addition product
				 28	 25
macrobatch (-78 °C)	-	-	65		
microreactor	2.0	0.5	60	15	38
microreactor	8.0	2.0	82	60	20
microreactor	24	6.0	81	73	8
				 29	 26
macrobatch (-78 °C)	-	-	62	29	26
microreactor	2.0	0.5	57	13	35
microreactor	8.0	2.0	72	55	14
microreactor	24	6.0	78	71	7
				 56	 5
macrobatch (-78 °C)	-	-	65	56	5
microreactor	2.0	0.5	68	56	8
microreactor	8.0	2.0	85	83	1
microreactor	24	6.0	85	84	0
				 65	 0
macrobatch (-78 °C)	-	-	65	65	0
microreactor	2.0	0.5	69	54	13
microreactor	8.0	2.0	88	88	0
microreactor	24	6.0	89	89	0
				 36	(PhOH)
macrobatch (-78 °C)	-	-	49	36	24
microreactor	2.0	0.5	52	29	21
microreactor	8.0	2.0	72	72	4
microreactor	24	6.0	76	76	3

The Reaction of 3-Benzoylbenzaldehyde with Phenyllithium.

3-Benzoylbenzhydrol. 71% yield (flow microreactor) and 29% yield (batch) (GC yield using an internal standard (pentadecane)). GC *t*_R 20.6 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 30 cm/sec. The spectral data were identical to those reported in the literature.⁹

3-(Hydroxydiphenylmethyl)benzhydrol. 7% yield (flow microreactor) and 26% yield (batch) (GC yield using an internal standard (pentadecane)). GC *t*_R 22.1 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 30 cm/sec. ¹H NMR (400 MHz, CDCl₃) δ 2.29 (s, 1H), 2.89 (s, 1H), 5.72 (s, 1H), 7.06-7.12 (m, 1H), 7.20-7.31 (m, 17H) 7.41 ppm (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 76.2, 82.0, 125.3, 126.1, 126.4, 127.2, 127.3, 127.5, 127.8, 127.9 128.0, 128.4, 143.5, 143.7, 146.7, 147.0 ppm; HRMS (ESI) *m/z* calcd for C₂₆H₂₂O₂Na⁺ [M+Na]⁺: 389.1512, found: 389.1508.

The Reaction of 4-(Methoxycarbonyl)benzaldehyde and Phenyllithium.

4-(Methoxycarbonyl)benzhydrol. 84% yield (flow microreactor) and 56% yield (batch) (GC yield using an internal standard (pentadecane)). GC *t*_R 16.2 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 30 cm/sec. The spectral data were identical to those reported in the literature.¹⁰

4-(Hydroxy(phenyl)methyl)phenyl(phenyl)methanone. 5% yield (batch) (GC yield using an internal standard (pentadecane)). GC *t*_R 21.1 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 30 cm/sec. The spectral data were identical to those reported in the literature.⁷

The Reaction of 4-Nitrobenzaldehyde and Phenyllithium.

4-Nitrobenzhydrol. 76% yield (flow microreactor) and 36% yield (batch) (GC yield using an internal standard (pentadecane)). GC *t*_R 17.3 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 30 cm/sec. The spectral data were identical to those reported in the literature.¹¹

The Reaction of 4-Cyanobenzaldehyde and Phenyllithium.

4-Cyanobenzhydrol. 89% yield (flow microreactor) and 65% yield (batch) (GC yield using an internal standard (pentadecane)). GC *t*_R 16.2 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 30 cm/sec. The spectral data were identical to those reported in the literature.¹²

The Reaction of 4-Isocyanatobenzonitrile and Phenyllithium.

N-(4-Cyanophenyl)benzamide. 82% yield (flow microreactor) and 5% yield (batch) (GC yield using an internal standard (pentadecane)). GC *t*_R 18.0 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec. The spectral data were identical to those reported in the literature.¹³

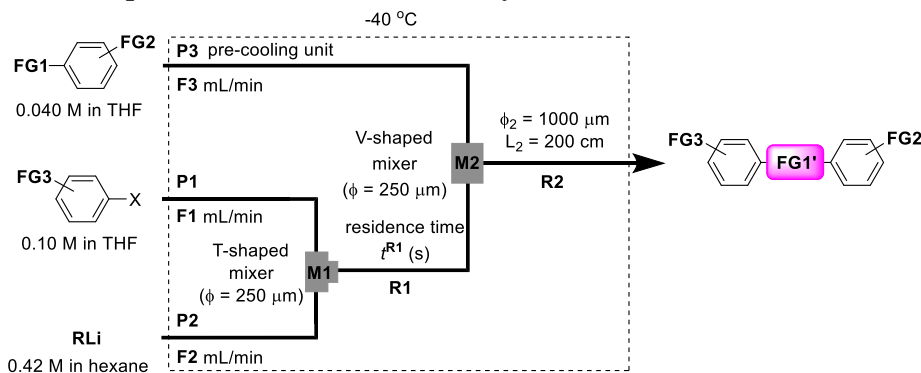
N-(4-Benzoylphenyl)benzamide. 1% yield (batch) (GC yield using an internal standard (pentadecane)). GC *t*_R 22.3 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec. The spectral data were identical to those reported in the literature.¹⁴

The Reaction of Methyl 4-Isocyanatobenzoate and Phenyllithium.

Methyl 4-benzamidobenzoate. 91% yield (flow microreactor) and 18% yield (batch) (GC yield using an internal standard (pentadecane)) (GC *t*_R 17.9 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec). The spectral data were identical to those reported in the literature.¹⁵

N-[4-(Hydroxydiphenylmethyl)phenyl]benzamide. 1% yield (flow microreactor) and 4% yield (batch) (GC yield using an internal standard (pentadecane)). GC *t*_R 24.1 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec. The product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 5/2) followed by GPC to give N-[4-(hydroxydiphenylmethyl)phenyl]benzamide. ¹H NMR (400 MHz, CDCl₃) δ 2.80 (s, 1H), 7.26-7.36 (m, 12H), 7.47-7.62 (m, 5H), 7.78-7.83 (br, 1H), 7.85-7.91 ppm (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 81.8, 119.6, 127.0, 127.3, 127.9, 128.0, 128.7, 128.8, 131.9, 134.9, 136.9, 143.1, 146.7, 165.7 ppm; HRMS (ESI) *m/z* calcd for C₂₆H₂₂NO₅⁺ [M+H]⁺: 380.1645, found: 380.1640.

Typical Procedure for the Generation of Functionalized Aryllithiums Followed by the Selective Reaction with Difunctional Electrophiles in a Flow Microreactor System.



A flow microreactor system consisting of a T-shaped micromixer ($\phi = 250 \mu\text{m}$) (**M1**), a V-shaped micromixer ($\phi = 250 \mu\text{m}$) (**M2**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (inner diameter $\phi = 1000 \mu\text{m}$, length $L = 100 \text{ cm}$), **P2** ($\phi = 1000 \mu\text{m}$, $L = 50 \text{ cm}$), and **P3** ($\phi = 1000 \mu\text{m}$, $L = 200 \text{ cm}$)) was used. A solution of a halobenzene (0.10 M in THF) (flow rate: $F1 \text{ mL/min}$) and a solution of a lithiating agent (0.42 M in hexane) (flow rate: $F2 \text{ mL/min}$) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** (residence time $t^{R1} \text{ (s)}$), and was mixed with a solution of a difunctional electrophile (0.040 M in THF) (flow rate: $F3 \text{ mL/min}$) in **M2**. The resulting solution was passed through **R2** ($\phi = 1000 \mu\text{m}$, $L = 200 \text{ cm}$). After a steady state was reached, an aliquot of the product solution was collected in a flask containing the sat. aq. NH_4Cl solution for 30 s. The flow microreactor system was dipped in a cooling bath of -40°C . The reaction mixture was analyzed by GC using an internal standard (pentadecane). In some cases the GC peak of a desired product overlapped with a peak of some unidentified byproduct. In such cases the product was isolated by silica-gel flash chromatography, and the isolated yields were indicated. The conditions of lithiation are summarized in Table S7.

Table S7. The conditions of lithiation

halobenzene	lithiating agent	polyfunctional electrophile	residence time in R1	flow rate (mL/min)		
				F1	F2	F3
4-bromobenzonitrile	<i>n</i> -BuLi	4-benzoylbenzaldehyde	0.20	6.8	1.7	14
1-iodo-4-nitrobenzene	PhLi	4-benzoylbenzaldehyde	0.21	6.4	1.6	15
ethyl 4-iodobenzoate	PhLi	4-benzoylbenzaldehyde	0.013	6.4	1.6	15
4-bromobenzonitrile	<i>n</i> -BuLi	methyl 4-formylbenzoate	0.20	6.8	1.7	14
1-iodo-4-nitrobenzene	PhLi	methyl 4-formylbenzoate	0.20	6.8	1.7	14
ethyl 4-iodobenzoate	PhLi	methyl 4-formylbenzoate	0.013	6.4	1.6	15
4-bromobenzonitrile	<i>n</i> -BuLi	4-nitrobenzaldehyde	0.20	6.8	1.7	14
ethyl 4-iodobenzoate	PhLi	4-nitrobenzaldehyde	0.012	6.8	1.7	14
ethyl 4-iodobenzoate	PhLi	4-cyanobenzaldehyde	0.012	6.8	1.7	14
4-bromobenzonitrile	<i>n</i> -BuLi	methyl 3-formyl-4-nitrobenzoate	0.20	6.8	1.7	14
4-bromobenzonitrile	<i>n</i> -BuLi	methyl 4-isocyanatobenzoate	0.20	6.8	1.7	14
1-iodo-4-nitrobenzene	PhLi	methyl 4-isocyanatobenzoate	0.20	6.8	1.7	14
ethyl 4-iodobenzoate	PhLi	methyl 4-isocyanatobenzoate	0.012	6.8	1.7	14
4-bromobenzonitrile	<i>n</i> -BuLi	4-isocyanatobenzonitrile	0.20	6.8	1.7	14
1-iodo-4-nitrobenzene	PhLi	4-isocyanatobenzonitrile	0.20	6.8	1.7	14
ethyl 4-iodobenzoate	PhLi	4-isocyanatobenzonitrile	0.012	6.8	1.7	14
4-bromobenzonitrile	<i>n</i> -BuLi	5-cyanopentanal	3.14	6.0	1.5	15
4-bromobenzonitrile	<i>n</i> -BuLi	ethyl 4-formylcyclohexanecarboxylate	3.14	6.0	1.5	15

4-Benzoyl-4'-cyanobenzhydrol. Obtained in 78% yield (GC yield using an internal standard (pentadecane)) from 4-bromobenzonitrile, *n*-BuLi, and 4-benzoylbenzaldehyde. GC t^R 22.7 min; initial oven temperature, 100°C for 2 min; rate of temperature increase, 10°C/min ; He linear velocity, 60 cm/sec. After extraction, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 5/2 to 2/1) to obtain a pure compound, which was characterized by NMR and MS. ^1H NMR (400 MHz, CDCl_3) δ 2.59 (d, $J = 3.6 \text{ Hz}$, 1H), 5.96 (d, $J = 3.2 \text{ Hz}$, 1H), 7.44-7.68 (m, 10H), 7.74-7.81 ppm (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 75.5, 111.9, 118.9,

126.6, 127.3, 128.6, 130.2, 130.8, 132.7, 132.9, 133.8, 137.6, 147.2, 148.4, 196.4 ppm; HRMS (ESI) m/z calcd for $C_{21}H_{14}NO_2^-$ [M-H] $^-$: 312.1030, found: 312.1034.

4-Benzoyl-4'-nitrobenzhydrol. Obtained in 79% yield (isolated yield) from 1-iodo-4-nitrobenzene, PhLi, and 4-benzoylbenzaldehyde. After extraction, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 5/2) to obtain a pure compound, which was characterized by NMR and MS. 1H NMR (400 MHz, $CDCl_3$) δ 2.58 (d, J = 3.2 Hz, 1H), 6.01 (d, J = 3.2 Hz, 1H), 7.44-7.51 (m, 4H), 7.57-7.63 (m, 3H), 7.75-7.82 (m, 4H), 8.19-8.24 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.3, 124.1, 126.7, 127.4, 128.6, 130.3, 130.9, 132.9, 137.5, 137.6, 147.2, 147.6, 150.4, 196.5 ppm; HRMS (ESI) m/z calcd for $C_{20}H_{14}NO_4^-$ [M-H] $^-$: 332.0928, found: 332.0933.

4-Benzoyl-4'-(ethoxycarbonyl)benzhydrol. Obtained in 67% (GC yield using an internal standard (pentadecane)) from ethyl 4-iodobenzoate, PhLi, and 4-benzoylbenzaldehyde. GC t_R 22.6 min (initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec. After extraction, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 5/2) to obtain a pure compound, which was characterized by NMR and MS. 1H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.2 Hz, 3H), 2.60 (d, J = 3.6 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 5.96 (d, J = 3.6 Hz 1H), 7.42-7.53 (m, 6H), 7.55-7.61 (m, 1H), 7.74-7.80 (m, 4H), 8.00-8.05 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, some of the ^{13}C NMR signals were the same places) δ 14.3, 61.0, 75.5, 126.3, 126.4, 128.3, 129.9, 130.0, 130.4, 132.5, 137.0, 137.4, 147.6, 147.9, 166.3, 196.3 ppm; HRMS (ESI) m/z calcd for $C_{23}H_{19}O_4^-$ [M-H] $^-$: 359.1289, found: 359.1299.

4-Cyano-4'-(methoxycarbonyl)benzhydrol. Obtained in 86% yield (GC yield using an internal standard (pentadecane)) from 4-bromobenzonitrile, *n*-BuLi, and methyl 4-formylbenzoate. GC t_R 18.4 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec. The spectral data were identical to those reported in the literature.¹⁶

4-(Methoxycarbonyl)-4'-nitrobenzhydrol. Obtained in 90% yield (GC yield using an internal standard (pentadecane)) from 1-iodo-4-nitrobenzene, PhLi, and methyl 4-formylbenzoate. GC t_R 19.3 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec. After extraction, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 5/2) to obtain a pure compound, which was characterized by NMR and MS. 1H NMR (400 MHz, $CDCl_3$) δ 2.56 (d, J = 3.6 Hz, 1H), 3.91 (s, 3H), 5.98 (d, J = 3.2 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H), 8.20 ppm (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, some of the ^{13}C NMR signals were the same places) δ 52.2, 75.1, 123.8, 126.5, 127.1, 130.0, 130.2, 147.4, 150.0, 166.6 ppm; HRMS (ESI) m/z calcd for $C_{15}H_{12}NO_5^-$ [M-H] $^-$: 286.0721, found: 286.0714.

4-(Ethoxycarbonyl)-4'-(methoxycarbonyl)benzhydrol. Obtained in 78% yield (GC yield using an internal standard (pentadecane)) from ethyl 4-iodobenzoate, PhLi, and methyl 4-formylbenzoate. GC t_R 18.6 min (initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec. After extraction, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 3/1) to obtain a pure compound, which was characterized by NMR and MS. 1H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.0 Hz, 3H), 2.65 (d, J = 3.6 Hz, 1H), 3.90 (s, 3H), 4.35 (q, J = 7.2 Hz, 2H), 5.92 (d, J = 3.6 Hz, 1H), 7.42-7.46 (m, 4H), 7.97-8.02 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 52.1, 61.0, 75.4, 126.3, 126.4, 129.4, 129.7, 129.8, 129.9, 148.0, 148.1, 166.3, 166.8 ppm; HRMS (ESI) m/z calcd for $C_{18}H_{17}O_5^-$ [M-H] $^-$: 313.1081, found: 313.1078.

4-Cyano-4'-nitrobenzhydrol. Obtained in 86% yield (GC yield using an internal standard (pentadecane)) from 4-bromobenzonitrile, *n*-BuLi, and 4-nitrobenzaldehyde. GC t_R 20.1 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec. After extraction, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 3/1 to 5/2) to obtain a pure compound, which was characterized by NMR and MS. 1H NMR (400 MHz, $CDCl_3$) δ 2.55 (d, J = 3.6 Hz, 1H), 5.98 (d, J = 3.2 Hz, 1H), 7.49-7.60 (m, 4H), 7.60-7.68 (m, 2H), 8.19-8.23 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, some ^{13}C NMR signals overlapped) δ 74.7, 112.0, 118.4, 124.0, 127.1, 127.2, 132.6, 147.5, 149.5 ppm; HRMS (APCI) m/z calcd for $C_{14}H_9N_2O_3$ [M-H] $^-$: 253.0619, found: 253.0614.

4-(Ethoxycarbonyl)-4'-nitrobenzhydrol. Obtained in 69% yield (GC yield using an internal standard (pentadecane)) from ethyl 4-iodobenzoate, PhLi, and 4-nitrobenzaldehyde. GC t_R 19.6 min; initial oven

temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec. After extraction, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 3/1 to 5/2) to obtain a pure compound, which was characterized by NMR and MS. ¹H NMR (400 MHz, CDCl₃) δ 1.38 (t, *J* = 7.2 Hz, 3H), 2.52 (d, *J* = 3.2 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 5.98 (d, *J* = 3.2 Hz, 1H), 7.43-7.47 (m, 2H), 7.55-7.59 (m, 2H), 8.02-8.06 (m, 2H), 8.18-8.22 ppm (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 14.2, 61.1, 75.0, 123.8, 126.4, 127.1, 130.1, 130.2, 147.3, 147.4, 150.1, 166.2 ppm; HRMS (APCI) *m/z* calcd for C₁₆H₁₅NO₅Cl[M+Cl]⁺: 336.0633, found: 336.0644.

4-Cyano-4'-(ethoxycarbonyl)benzhydrol. Obtained in 74% yield (GC yield using an internal standard (pentadecane)) from ethyl 4-iodobenzoate, PhLi, and 4-cyanobenzaldehyde. GC *t*_R 18.8 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec. After extraction, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 3/1 to 5/2) to obtain a pure compound, which was characterized by NMR and MS. ¹H NMR (400 MHz, CDCl₃) δ 1.38 (t, *J* = 7.2 Hz, 3H), 2.51 (d, *J* = 3.6 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 5.92 (d, *J* = 3.6 Hz, 1H), 7.40-7.44 (m, 2H), 7.48-7.52 (m, 2H), 7.60-7.65 (m, 2H), 8.00-8.04 ppm (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 14.2, 61.1, 75.1, 111.4, 118.6, 126.4, 127.0, 130.0, 130.1, 132.4, 147.5, 148.3, 166.2 ppm; HRMS (APCI) *m/z* calcd. for C₁₇H₁₅NO₃Cl[M+Cl]⁺: 316.0735, found: 316.0743.

5-Methoxycarbonyl-2-nitro-4'-cyanobenzhydrol. Obtained in 75% yield (GC yield using an internal standard (pentadecane)) from 4-bromobenzonitrile, *n*-BuLi, and methyl 3-formyl-4-nitrobenzoate. GC *t*_R 20.3 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec. After extraction, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 3/1 to 5/2) to obtain a pure compound, which was characterized by NMR and MS. ¹H NMR (400 MHz, CDCl₃) δ 2.95 (d, *J* = 4.8 Hz, 1H), 3.97 (s, 3H), 6.47 (d, *J* = 4.8 Hz, 1H), 7.47-7.52 (m, 2H), 7.63-7.68 (m, 2H), 8.00 (d, *J* = 8.4 Hz, 1H), 8.15 (dd, *J* = 1.6, 8.4 Hz, 1H), 8.38 ppm (d, *J* = 1.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 52.9, 70.3, 111.7, 118.4, 124.8, 127.6, 130.0, 130.6, 132.4, 134.5, 137.7, 146.3, 150.3, 164.9 ppm; HRMS (ESI) *m/z* calcd for C₁₆H₁₂N₂O₅Cl [M+Cl]⁺: 347.0429, found: 347.0445.

4-Cyano-*N*-[4-(methoxycarbonyl)phenyl]benzamide. Obtained in 79% yield (GC yield using an internal standard (pentadecane)) from 4-bromobenzonitrile, *n*-BuLi, and methyl 4-isocyanatobenzoate. GC *t*_R 21.5 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec. After extraction with ether, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 5/2 to 2/1) followed by washing with dichloromethane to obtain a pure compound, which was characterized by NMR and MS. ¹H NMR (400 MHz, DMSO) δ 3.84 (s, 3H), 7.91-8.13 (m, 8H), 10.72-10.84 ppm (br, 1H); ¹³C NMR (100 MHz, DMSO) δ 51.9, 114.0, 118.2, 119.7, 124.7, 128.6, 130.1, 132.5, 138.5, 143.1, 164.6, 165.7 ppm; HRMS (ESI) *m/z* calcd for C₁₆H₁₁N₂O₃⁻ [M-H]⁻: 279.0775, found: 279.0767.

***N*-[4-(Methoxycarbonyl)phenyl]-4-nitrobenzamide.** Obtained in 90% yield (GC yield using an internal standard (pentadecane)) from 1-iodo-4-nitrobenzene, PhLi, and methyl 4-isocyanatobenzoate. GC *t*_R 22.1 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec. The spectral data were identical to those reported in the literature.¹⁷

4-(Ethoxycarbonyl)-*N*-[4-(methoxycarbonyl)phenyl]benzamide. Obtained in 72% yield (GC yield using an internal standard (pentadecane)) from ethyl 4-iodobenzoate, PhLi, and methyl 4-isocyanatobenzoate. GC *t*_R 21.7 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec. After extraction with ether, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 3/1) followed by washing with dichloromethane to obtain a pure compound, which was characterized by NMR and MS. ¹H NMR (400 MHz, CDCl₃) δ 1.43 (t, *J* = 7.2 Hz, 3H), 3.92 (s, 3H), 4.42 (q, *J* = 7.1 Hz, 2H), 7.74-7.79 (m, 2H), 7.91-8.05 (m, 3H), 8.06-8.09 (m, 2H), 8.14-8.19 ppm (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 14.3, 52.1, 61.5, 119.3, 126.2, 127.1, 130.0, 130.9, 133.7, 138.3, 141.8, 165.0, 165.6, 166.5 ppm; HRMS (ESI) *m/z* calcd for C₁₈H₁₆NO₅⁻ [M-H]⁻: 326.1034, found: 326.1026.

4-Cyano-*N*-(4-cyanophenyl)benzamide. Obtained in 74% yield (GC yield using an internal standard (pentadecane)) from 4-bromobenzonitrile, *n*-BuLi, and 4-isocyanatobenzonitrile. GC *t*_R 22.0 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec. The spectral data were identical to those reported in the literature.¹⁸

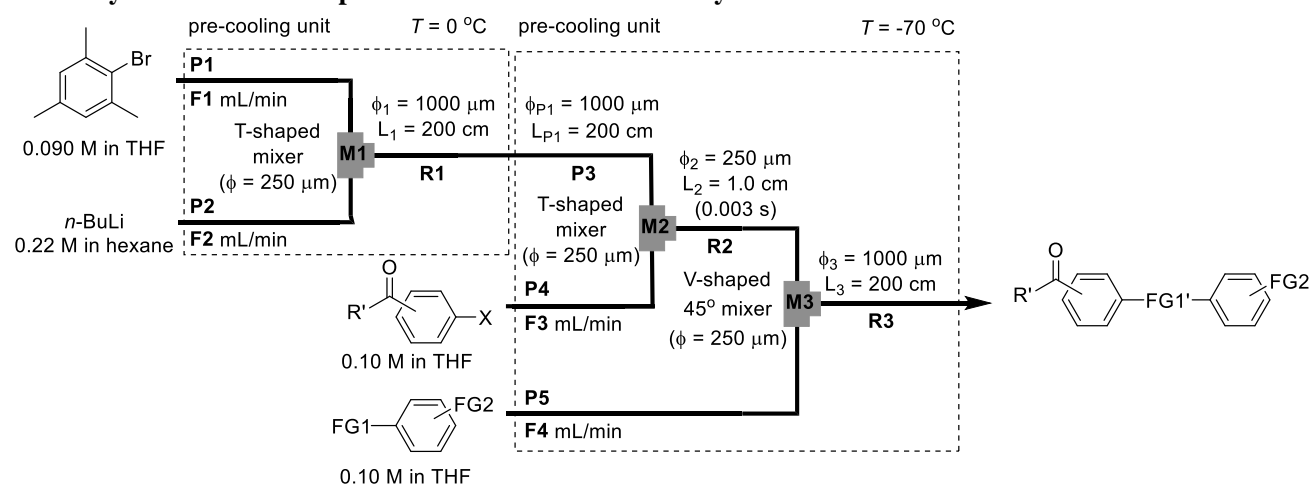
***N*-(4-Cyanophenyl)-4-nitrobenzamide.** Obtained in 74% yield (GC yield using an internal standard (pentadecane)) from 1-iodo-4-nitrobenzene, PhLi, and 4-isocyanatobenzonitrile. GC *t*_R 22.7 min; initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec. After extraction with ethyl acetate, the crude product was washed with dichloromethane and then with ethanol to obtain a pure compound, which was characterized by NMR and MS. ¹H NMR (400 MHz, DMSO) δ 7.83-7.88 (m, 2H), 7.97-8.01 (m, 2H), 8.17-8.21 (m, 2H), 8.36-8.40 (m, 2H), 10.80-11.10 ppm (br, 1H); ¹³C NMR (100 MHz, DMSO) δ 105.8, 118.9, 120.3, 123.6, 129.4, 133.2, 139.9, 142.9, 149.3, 164.5 ppm; HRMS (ESI) *m/z* calcd for C₁₄H₈N₃O₃⁻ [M-H]⁻: 266.0571, found: 266.0563.

***N*-(4-Cyanophenyl)-4-(ethoxycarbonyl)benzamide.** Obtained in 71% yield (GC yield using an internal standard (pentadecane)) from ethyl 4-iodobenzoate, PhLi, and 4-isocyanatobenzonitrile. GC *t*_R 21.9 min (initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec. After extraction with ethyl acetate, the crude product was washed with dichloromethane and then with ethanol to obtain a pure compound, which was characterized by NMR and MS. ¹H NMR (400 MHz, DMSO) δ 1.35 (t, *J* = 7.0 Hz, 3H), 4.36 (q, *J* = 7.1 Hz, 2H), 7.82-7.86 (m, 2H), 7.97-8.13 (m, 6H), 10.72-10.92 ppm (br, 1H); ¹³C NMR (100 MHz, DMSO) δ 14.1, 61.1, 105.6, 118.9, 120.3, 128.2, 129.1, 132.6, 133.1, 138.3, 143.1, 165.0, 165.3 ppm; HRMS (ESI) *m/z* calcd for C₁₇H₁₃N₂O₃⁻ [M-H]⁻: 293.0932, found: 293.0925.

4-(5-Cyano-1-hydroxypentyl)benzonitrile. Obtained in 64% yield (isolated yield) from 4-bromobenzonitrile, *n*-BuLi, and 5-cyanopentanal. GC *t*_R 29.5 min and 29.9 min (initial oven temperature, 50 °C for 5 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec.) After extraction with EtOAc, the organic layer was dried over MgSO₄. The crude compound was purified by silica gel chromatography (hexane/EtOAc = 3/1) to obtain a pure compound, which was characterized by NMR and MS. ¹H NMR (400 MHz, CDCl₃) δ 1.44-1.82 (m, 6H), 2.14-2.18 (br, 1H), 2.35 (t, *J* = 6.8 Hz, 2H), 4.77 (quint, *J* = 3.9 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 10.72-10.92 ppm (br, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 17.1, 24.7, 25.2, 38.2, 73.3, 111.3, 118.7, 119.5, 126.4, 132.4, 149.8 ppm; HRMS (APCI) *m/z* calcd for C₁₃H₁₄N₂OCl⁻ [M+Cl]⁻: 249.0800, found: 249.0799.

Ethyl 4-((4-cyanophenyl)(hydroxy)methyl)cyclohexanecarboxylate. Obtained in 60% yield (isolated yield) from 4-bromobenzonitrile, *n*-BuLi, and ethyl 4-formylcyclohexanecarboxylate. GC *t*_R 30.0 min and 30.9 (initial oven temperature, 50 °C for 5 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec.) After extraction with EtOAc, the organic layer was dried over MgSO₄. The crude product was purified by silica gel chromatography (hexane/EtOAc = 2/1) to obtain a mixture of two diastereomers, which was characterized by NMR and MS. ¹H NMR (400 MHz, CDCl₃) δ 1.02-1.15 (m, 2H), 1.21-1.26 (m, 3H), 1.33-1.44 (m, 2H), 1.49-1.53 (m, 1H), 1.58-1.69 (m, 1H), 1.92-2.05 (m, 4H), 2.14-2.23 (m, 1H), 4.48-4.52 (m, 1H), 7.41-7.43 (m, 2H), 7.62-7.65 ppm (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 14.2, 27.0, 28.43 and 28.45, 43.1, 44.2, 60.2, 78.0, 111.30, 118.8, 127.2, 132.1, 148.6, 175.7 ppm; HRMS (APCI) *m/z* calcd for C₁₇H₂₁NO₃Cl⁻ [M+Cl]⁻: 322.1215, found: 322.1215.

General Procedure for the Generation of Acyl-substituted Aryllithiums Followed by the Selective Reaction with Polyfunctional Electrophiles in a Flow Microreactor System



An integrated flow microreactor system consisting of two T-shaped micromixers ($\phi = 250\text{ }\mu\text{m}$) (M1 and M2),

a V-shaped 45° micromixer ($\phi = 250 \mu\text{m}$) (**M3**), three microtube reactors (**R1**, **R2**, and **R3**), and five tube pre-cooling units (**P1** (inner diameter $\phi = 1000 \mu\text{m}$, length $L = 200 \text{ cm}$), **P2** ($\phi = 1000 \mu\text{m}$, $L = 50 \text{ cm}$), **P3** ($\phi = 1000 \mu\text{m}$, $L = 200 \text{ cm}$), **P4** ($\phi = 1000 \mu\text{m}$, $L = 100 \text{ cm}$), and **P5** ($\phi = 1000 \mu\text{m}$, $L = 100 \text{ cm}$)) were used. A solution of mesityl bromide (0.090 M in THF) (flow rate: F1 mL/min) and a solution of *n*-BuLi (0.22 M in hexane) (flow rate: F2 mL/min) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** and **P3** ($\phi = 1000 \mu\text{m}$, $L = 410 \text{ cm}$ (200 cm at 0 °C, 10 cm at ambient temperature and 200 cm at -70 °C)) and was mixed with a solution of cyclohexyl(4-iodophenyl)methanone (0.10 M in THF) (flow rate: F3 mL/min) in **M2**. The resulting solution was passed through **R2** ($\phi = 250 \mu\text{m}$, $L = 1.0 \text{ cm}$) and was mixed with a solution of 4-benzoylbenzophenone (0.10 M in THF) (flow rate: F4 mL/min) in **M3**. The resulting solution was passed through **R3** ($\phi = 1000 \mu\text{m}$, $L = 200 \text{ cm}$). After a steady state was reached, an aliquot of the product solution was collected to the sat. NH_4Cl aqueous solution (2 mL) for 30 s to quench the reaction. The reaction mixture was analyzed by GC.

4-Benzoyl-4'-(cyclohexylcarbonyl)benzhydrol. Obtained in 65% yield (GC yield) from cyclohexyl(4-iodophenyl)methanone and 4-benzoylbenzaldehyde on the condition of F1 = 5.0 mL/min, F2 = 1.8 mL/min, F3 = 3.0 mL/min, F4 = 4.2 mL/min. After extraction, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 6/1 to 2/1): GC *R* 25.3 min (initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 70 cm/sec); ^1H NMR (400 MHz, CDCl_3) δ 1.22-1.54 (m, 5H), 1.69-1.92 (m, 5H), 2.41 (d, $J = 3.6 \text{ Hz}$, 1H), 3.23 (tt, $J = 3.0, 11.2 \text{ Hz}$, 1H), 5.97 (d, $J = 3.2 \text{ Hz}$, 1H), 7.45-7.53 (m, 6H), 7.56-7.62 (m, 1H), 7.76-7.81 (m, 4H), 7.92-7.96 ppm (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.7, 25.8, 29.3, 45.5, 75.2, 126.2, 126.6, 128.2, 128.5, 129.9, 130.3, 132.5, 135.4, 136.6, 137.2, 147.9, 148.1, 196.4, 203.7 ppm; HRMS (ESI) m/z calcd for $\text{C}_{27}\text{H}_{25}\text{O}_3$ [M-H]: 397.1809, found: 397.1803.

4-Benzoyl-4'-pentanoylbenzhydrol. Obtained in 30% yield (GC yield) from 1-(4-iodophenyl)-1-pentanone and 4-benzoylbenzaldehyde on the condition of F1 = 5.0 mL/min, F2 = 1.8 mL/min, F3 = 3.0 mL/min, F4 = 6.0 mL/min. After extraction, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 5/2) and purified by GPC: GC *R* 24.0 min (initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec); ^1H NMR (400 MHz, CDCl_3) δ 0.95 (t, $J = 7.4 \text{ Hz}$, 3H), 1.40 (sext., $J = 7.4 \text{ Hz}$, 2H), 1.71 (quint., $J = 7.6 \text{ Hz}$, 2H), 2.46 (d, $J = 3.6 \text{ Hz}$, 1H), 2.95 (t, $J = 7.4 \text{ Hz}$, 2H), 5.97 (d, $J = 3.6 \text{ Hz}$, 1H), 7.45-7.53 (m, 6H), 7.56-7.62 (m, 1H), 7.76-7.81 (m, 4H), 7.94-7.98 ppm (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2, 22.7, 26.7, 38.6, 75.8, 126.6, 126.8, 128.6, 128.8, 130.3, 130.7, 132.8, 136.8, 137.3, 137.7, 147.8, 148.2, 196.5, 200.4 ppm; HRMS (ESI) m/z calcd for $\text{C}_{25}\text{H}_{23}\text{O}_3$ [M-H]: 371.1653, found: 371.1651.

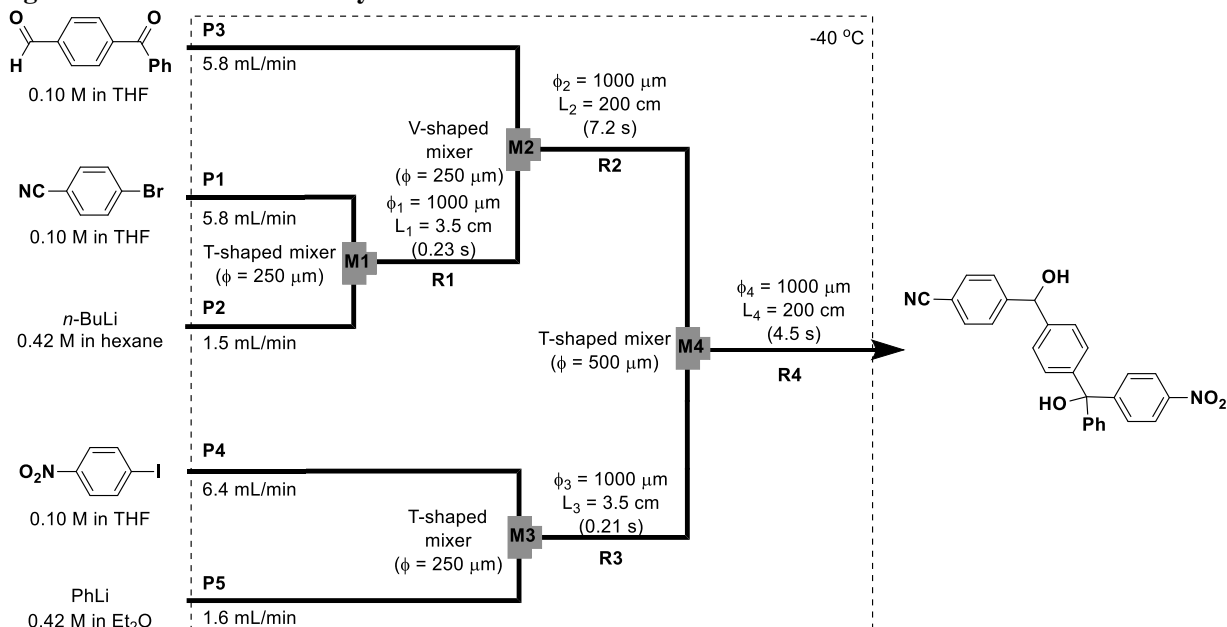
***N*-[4-(Methoxycarbonyl)phenyl]-4-(cyclohexylcarbonyl)benzamide.** Obtained in 73% yield (GC yield) from cyclohexyl(4-iodophenyl)methanone and methyl 4-isocyanatobenzoate on the condition of F1 = 5.0 mL/min, F2 = 1.8 mL/min, F3 = 3.0 mL/min, F4 = 4.2 mL/min. After extraction, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 3/1 to 5/2): GC *R* 25.1 min (initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec); ^1H NMR (400 MHz, CDCl_3) δ 1.21-1.61 (m, 5H), 1.72-1.95 (m, 5H), 3.27 (tt, $J = 3.3, 11.2 \text{ Hz}$, 1H), 3.93 (s, 3H), 7.74-7.79 (m, 2H), 7.94-8.11 ppm (m, 7H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.0, 25.5, 28.9, 44.6, 51.9, 119.6, 124.5, 128.1, 128.2, 130.1, 138.1, 138.2, 143.4, 165.3, 165.8, 203.0 ppm; HRMS (ESI) m/z calcd. for $\text{C}_{22}\text{H}_{22}\text{NO}_4$ [M-H]: 364.1554, found: 364.1554.

***N*-[4-(Methoxycarbonyl)phenyl]-4-pentanoylbenzamide.** Obtained in 51% yield (GC yield) from 1-(4-iodophenyl)-1-pentanone and methyl 4-isocyanatobenzoate on the condition of F1 = 10 mL/min, F2 = 3.6 mL/min, F3 = 6.0 mL/min, F4 = 6.0 mL/min. After extraction, the crude product was washed with chloroform: GC *R* 23.2 min (initial oven temperature, 100 °C for 2 min; rate of temperature increase, 10 °C/min; He linear velocity, 60 cm/sec); ^1H NMR (400 MHz, CDCl_3) δ 0.97 (t, $J = 7.4 \text{ Hz}$, 3H), 1.43 (sext. $J = 7.4 \text{ Hz}$, 2H), 1.74 (quint, $J = 7.5 \text{ Hz}$, 2H), 3.01 (t, $J = 7.4 \text{ Hz}$, 2H), 3.92 (s, 3H), 7.74-7.78 (m, 2H), 7.94-7.98 (m, 2H), 7.99-8.03 (s, 1H), 8.05-8.10 ppm (m, 4H); ^{13}C NMR (100 MHz, DMSO) δ 13.8, 21.7, 25.8, 37.9, 51.9, 119.4, 124.5, 127.9, 128.1, 130.1, 138.1, 139.0, 143.3, 165.2, 165.8, 199.9 ppm; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_4$ [M-H]: 338.1398, found: 338.1397.

***N*-(4-cyanophenyl)-4-(cyclohexylcarbonyl)benzamide.** Obtained in 52% yield (isolated yield) from cyclohexyl(4-iodophenyl)methanone and 4-isocyanatobenzonitrile on the condition of F1 = 5.0 mL/min, F2 = 1.8 mL/min, F3 = 3.0 mL/min, F4 = 4.2 mL/min. After extraction, the crude product was purified by silica-gel flash

chromatography (chloroform only): ^1H NMR (400 MHz, CDCl_3) δ 1.21-1.56 (m, 5H), 1.72-1.94 (m, 5H), 3.27 (tt, $J = 3.2, 11.2$ Hz, 1H), 7.67-7.72 (m, 2H), 7.81-7.85 (m, 2H), 7.93-7.98 (m, 2H), 8.02-8.09 ppm (m, 3H); ^{13}C NMR (100 MHz, DMSO) δ 25.0, 25.5, 28.9, 44.6, 105.6, 119.0, 120.2, 128.2, 128.3, 133.1, 137.9, 138.3, 143.2, 165.5, 202.9 ppm; HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{19}\text{N}_2\text{O}_2$ $[\text{M}-\text{H}]^-$: 331.1452, found: 331.1450.

Synthesis of 4-(Hydroxy(4-(hydroxy(4-nitrophenyl)(phenyl)methyl)phenyl)methyl)benzonitrile in an Integrated Flow Microreactor System.

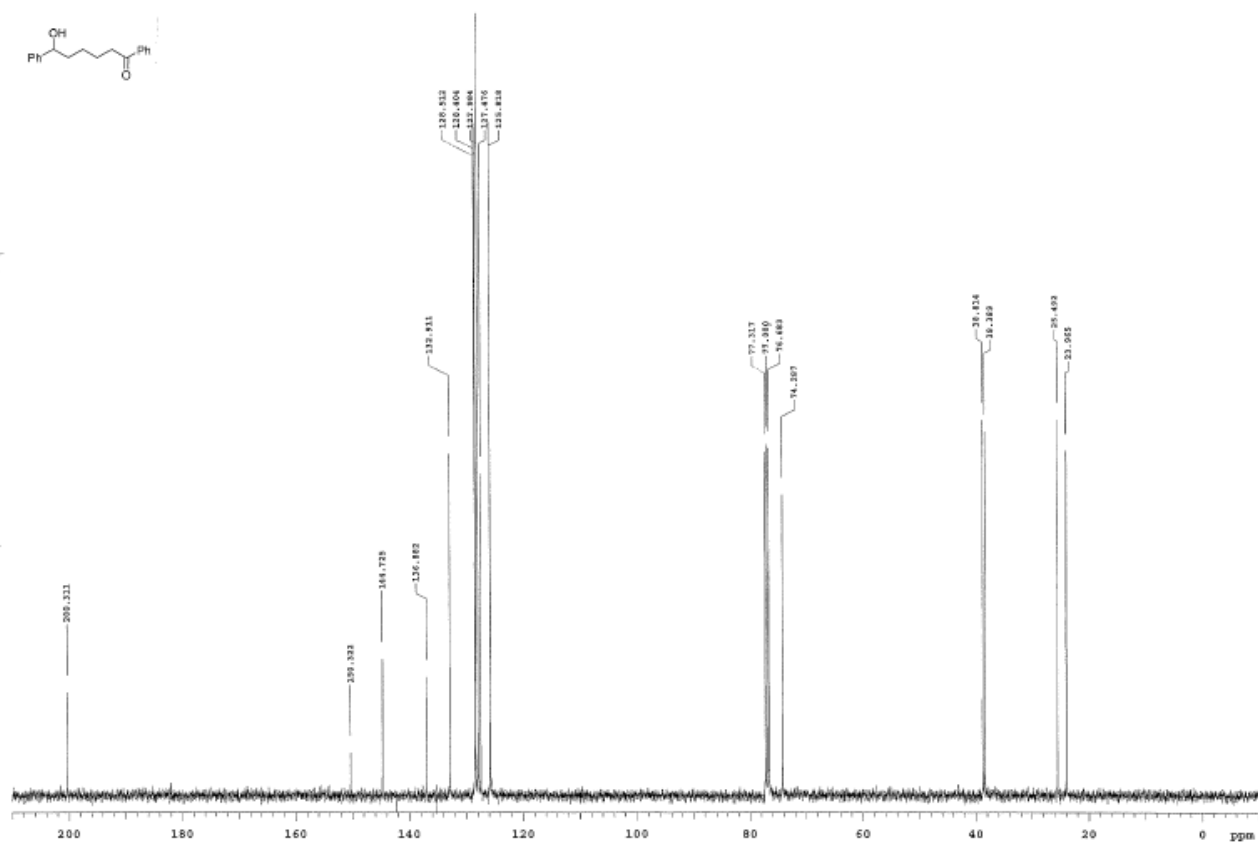
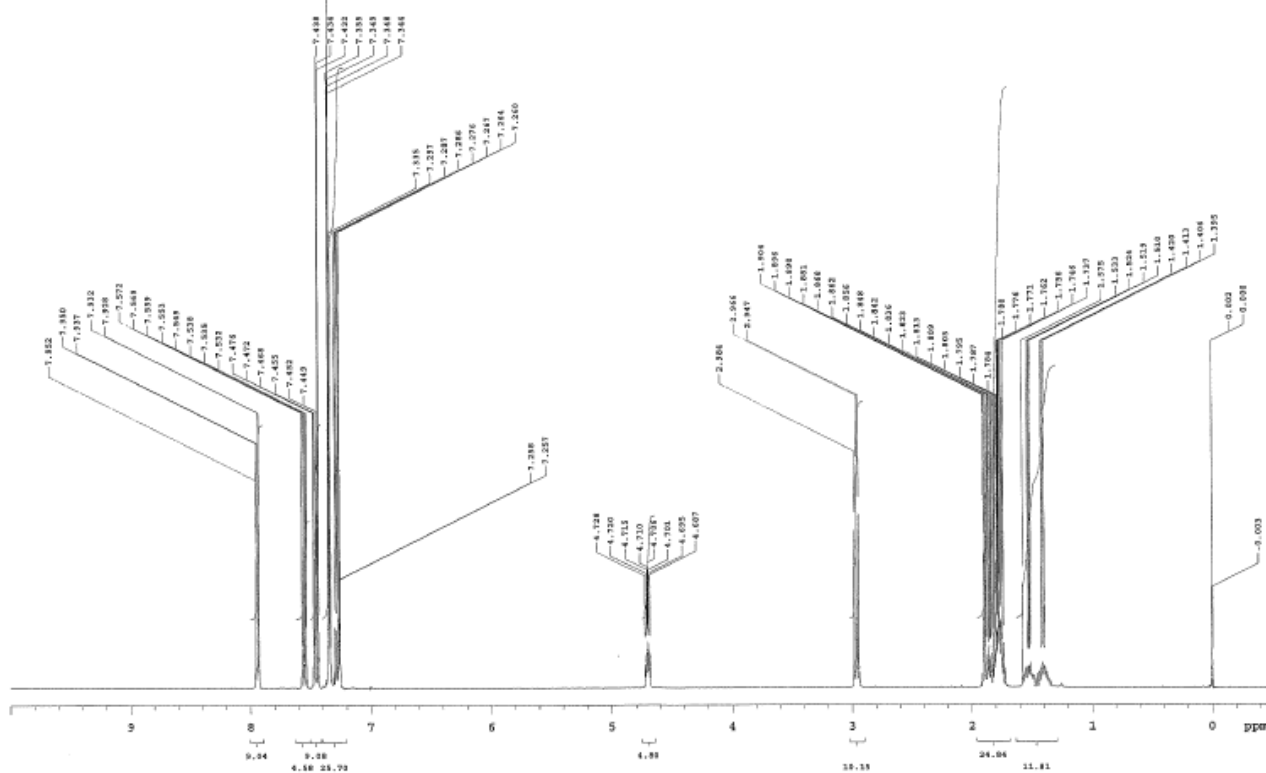


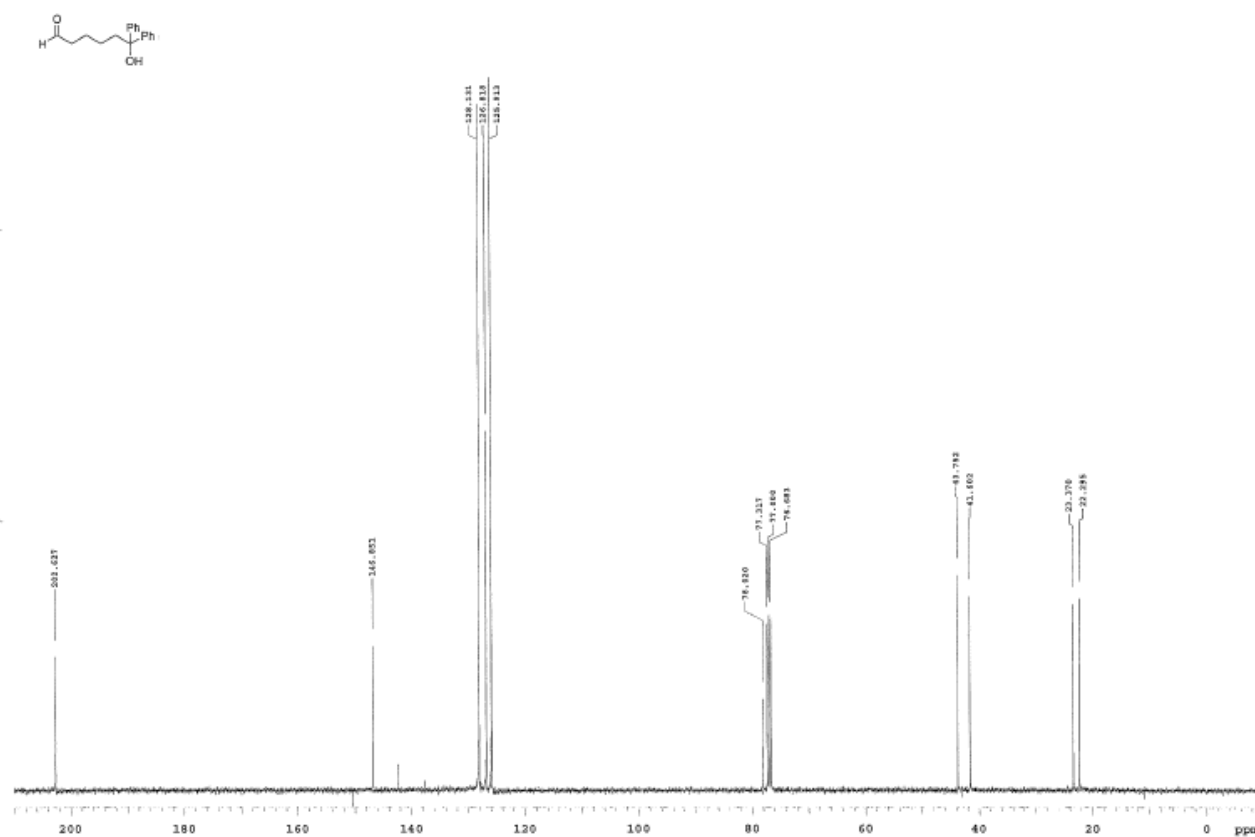
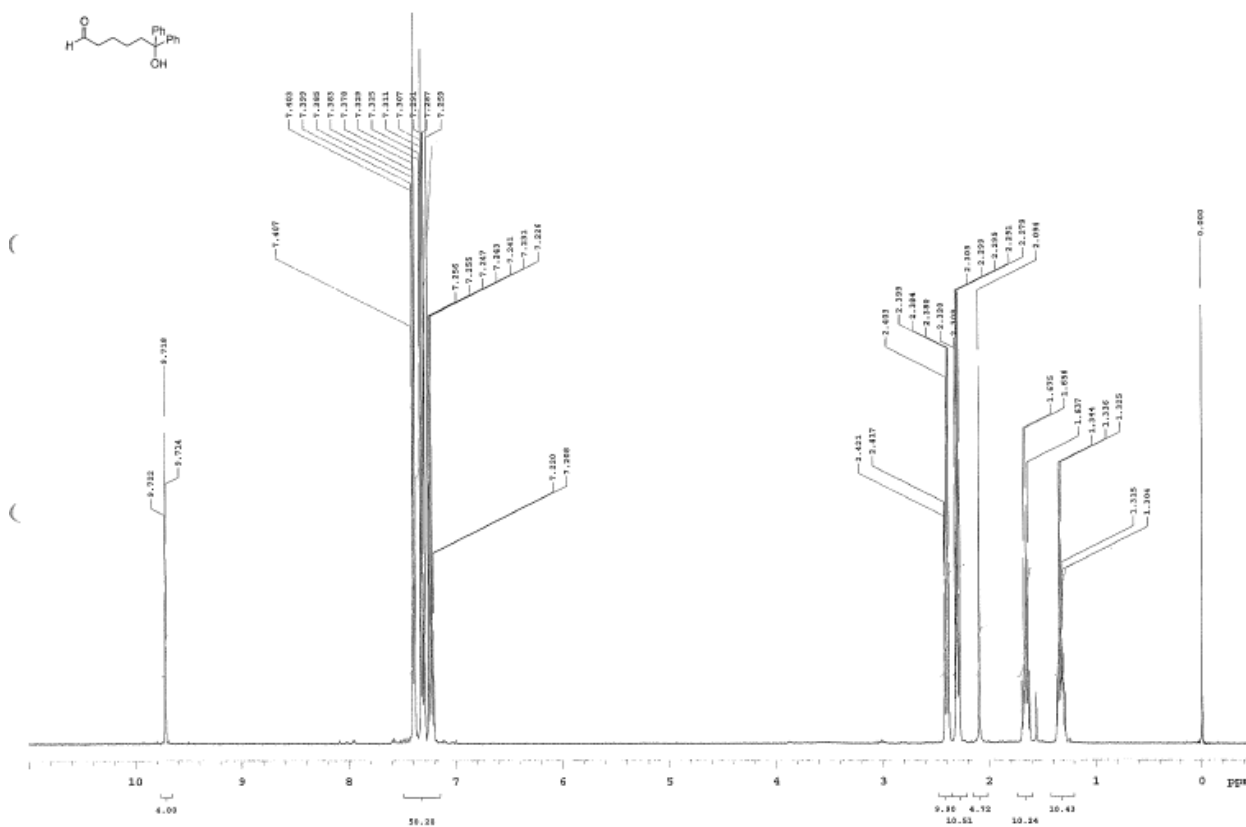
A flow microreactor system consisting of two T-shaped micromixers ($\phi = 250\ \mu\text{m}$) (**M1** and **M3**), a V-shaped micromixer ($\phi = 250\ \mu\text{m}$) (**M2**), a T-shaped micromixer ($\phi = 500\ \mu\text{m}$) (**M4**), four microtube reactors (**R1**, **R2**, **R3** and **R4**) and five pre-cooling units (**P1** (inner diameter $\phi = 1000\ \mu\text{m}$, length $L = 100\ \text{cm}$), **P2** ($\phi = 1000\ \mu\text{m}$, $L = 50\ \text{cm}$), **P3** ($\phi = 1000\ \mu\text{m}$, $L = 100\ \text{cm}$), **P4** ($\phi = 1000\ \mu\text{m}$, $L = 100\ \text{cm}$), **P5** ($\phi = 1000\ \mu\text{m}$, $L = 50\ \text{cm}$)) was used. A solution of 4-bromobenzonitrile (0.10 M in THF) (flow rate: 5.8 mL/min) and a solution of *n*-BuLi (0.42 M in hexane) (flow rate: 1.5 mL/min) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** and was mixed with a solution of 4-benzoylbenzaldehyde (0.10 M in THF) (flow rate: 5.8 mL/min) in **M2** and passed through **R2**. On the other hand, a solution of 1-iodo-4-nitrobenzene (0.10 M in THF) (flow rate: 6.4 mL/min) and a solution of PhLi (0.42 M in $\text{Et}_2\text{O}/\text{cyclohexane}$ (74/26 v/v)) (flow rate: 1.6 mL/min) were introduced to **M3** by syringe pumps and was passed through **R3**. Then, two resulting solutions were mixed with **M4** and passed through **R4**. After a steady state was reached, an aliquot of the product solution was collected to the sat. aq. NH_4Cl solution (2 mL) for 3 min to quench the reaction. After extraction with ether, the crude product was purified by silica-gel flash chromatography (hexane/ethyl acetate = 4/1 to 3/2) to obtain the title compound in 61% yield (467.3 mg, 3 min). Although a single set of signals was obtained in ^1H and ^{13}C NMR, it does not necessarily mean that a single diastereomer was obtained. ^1H NMR (400 MHz, CDCl_3) δ 2.34 (d, $J = 3.2$ Hz, 1H), 2.81 (s, 1H), 5.89 (d, $J = 3.2$ Hz, 1H), 7.19-7.40 (m, 9H), 7.52 (d, $J = 8.0$ Hz, 4H), 7.63 (d, $J = 8.0$ Hz, 2H), 8.16 (d, $J = 8.0$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 75.1, 81.5, 111.2, 118.7, 123.1, 126.5, 126.9, 127.7, 128.0, 128.2, 128.4, 128.6, 132.3, 142.3, 145.3, 145.6, 146.9, 148.5, 153.5 ppm; HRMS (APCI) m/z calcd for $\text{C}_{27}\text{H}_{20}\text{N}_2\text{O}_4\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 459.1321, found: 459.1309.

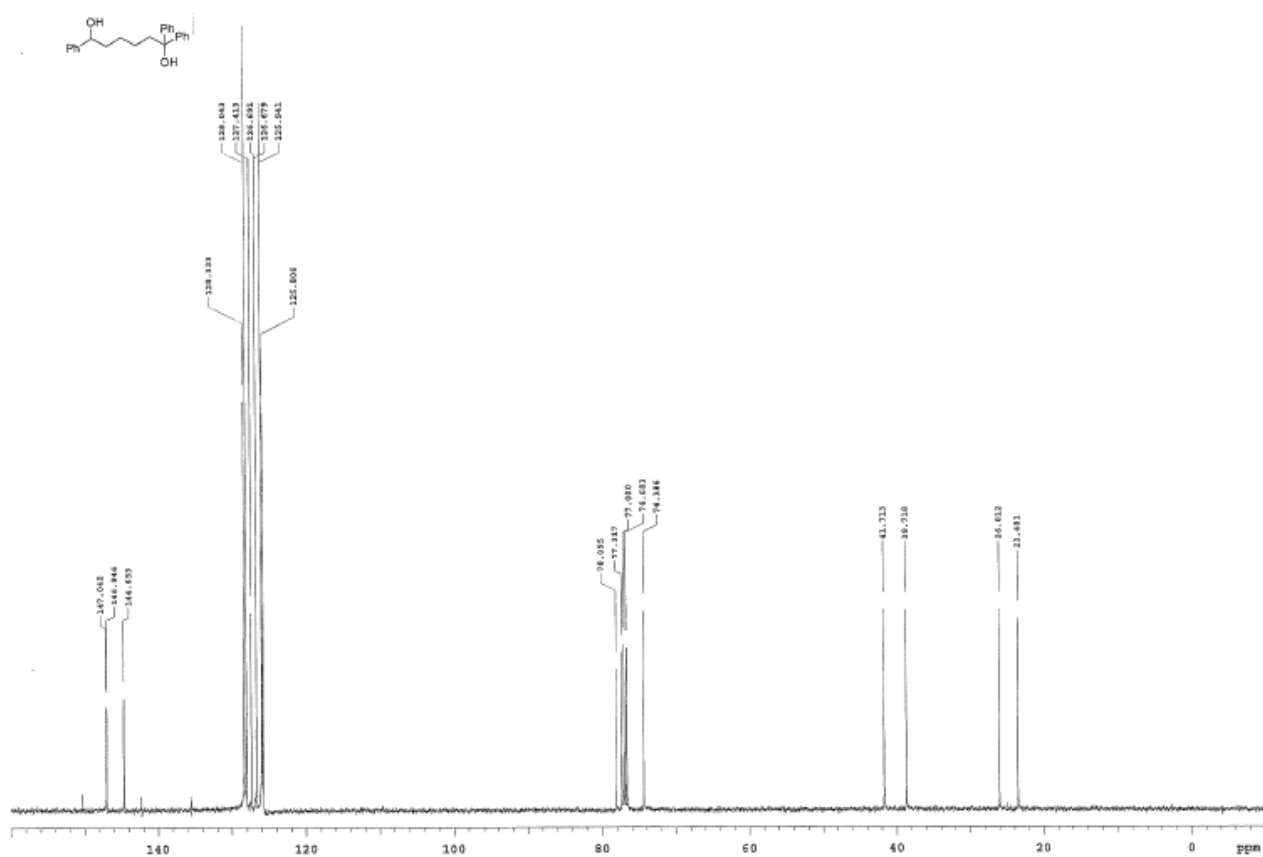
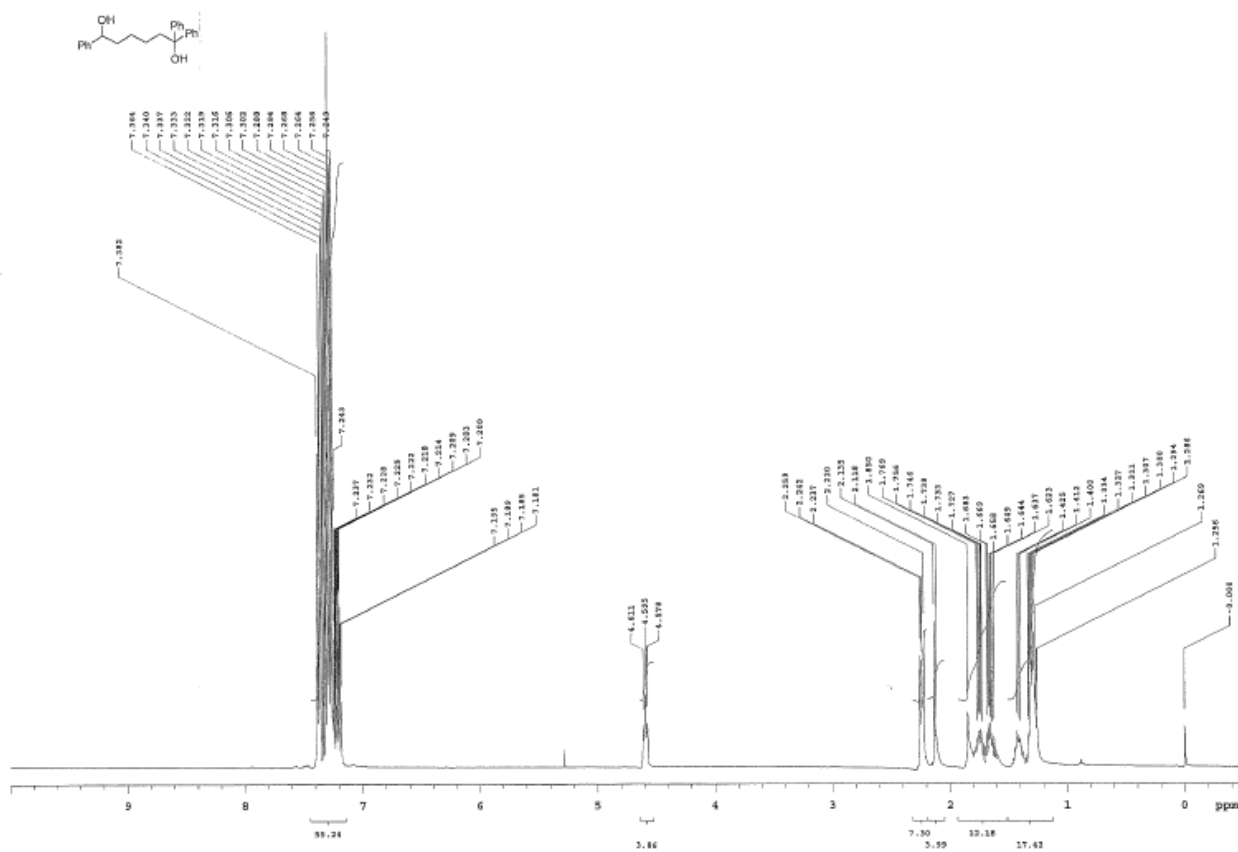
References

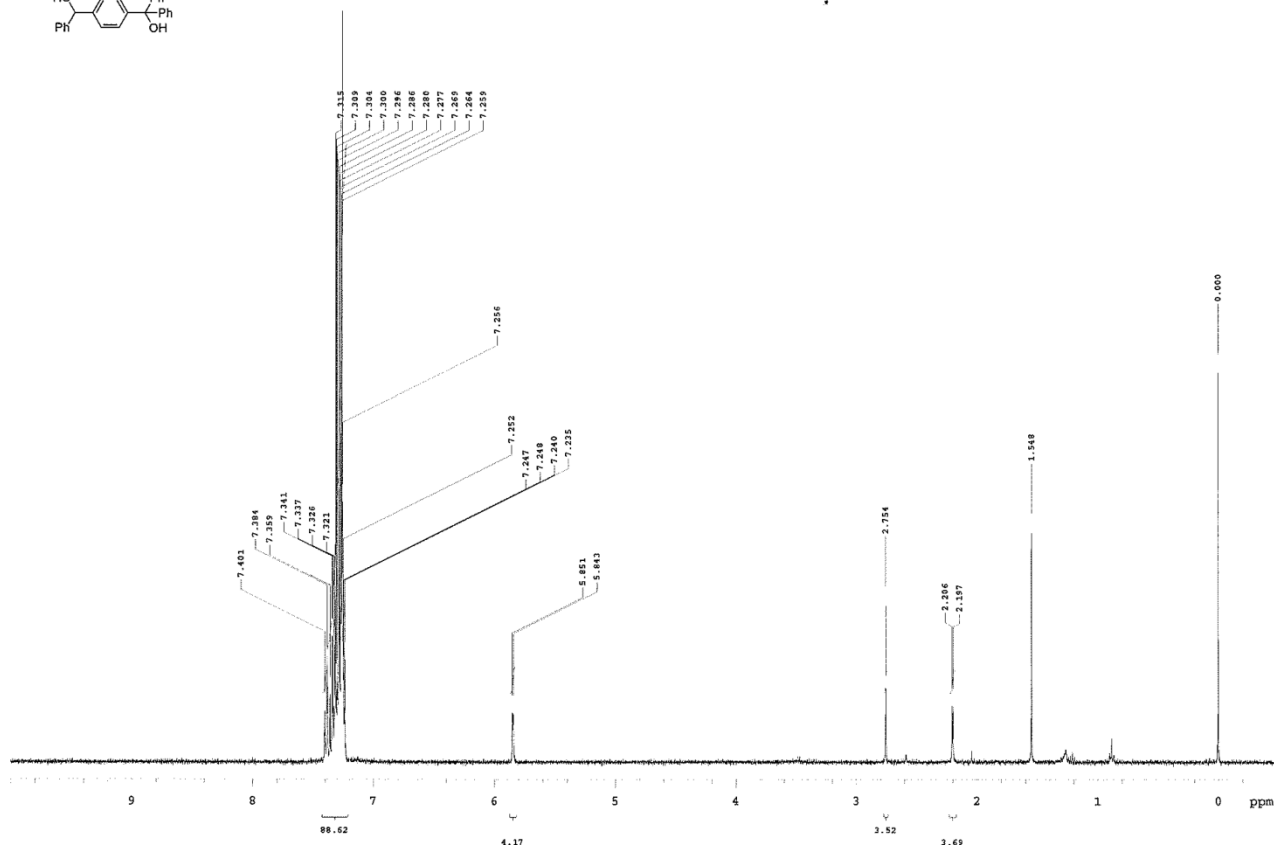
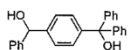
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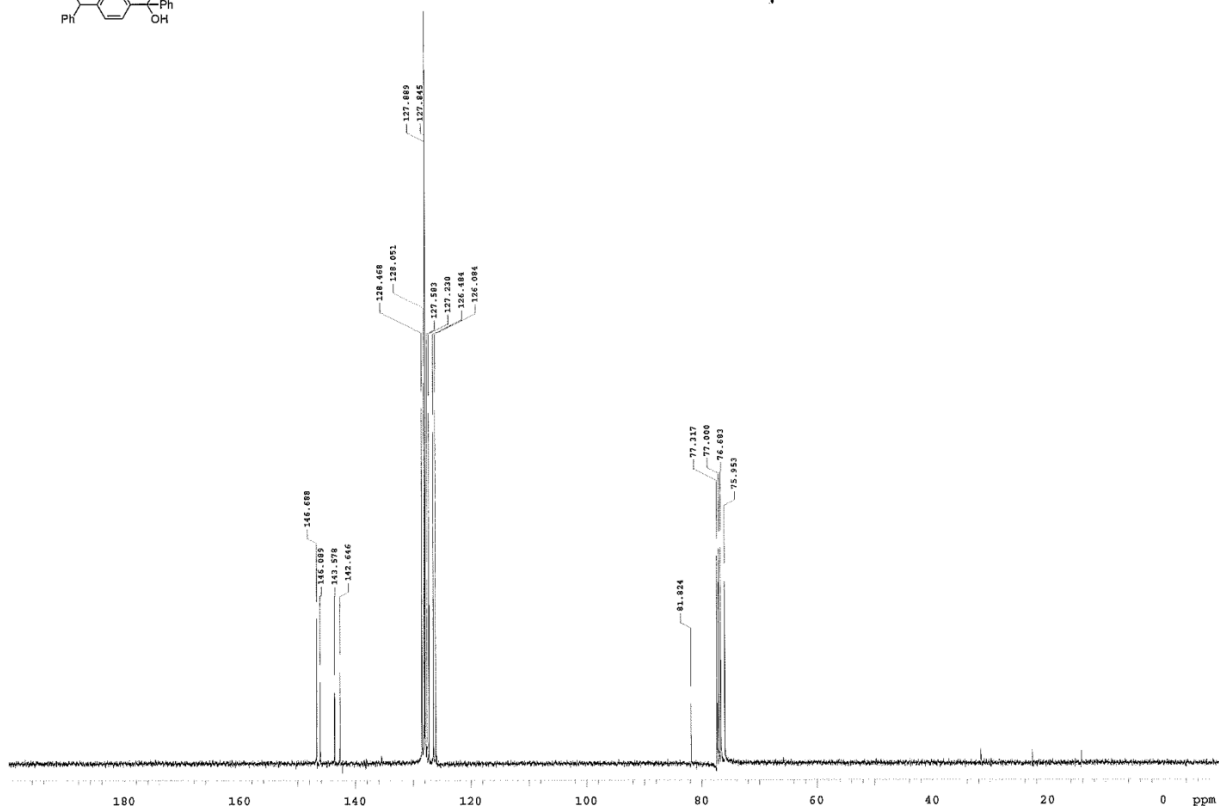
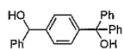




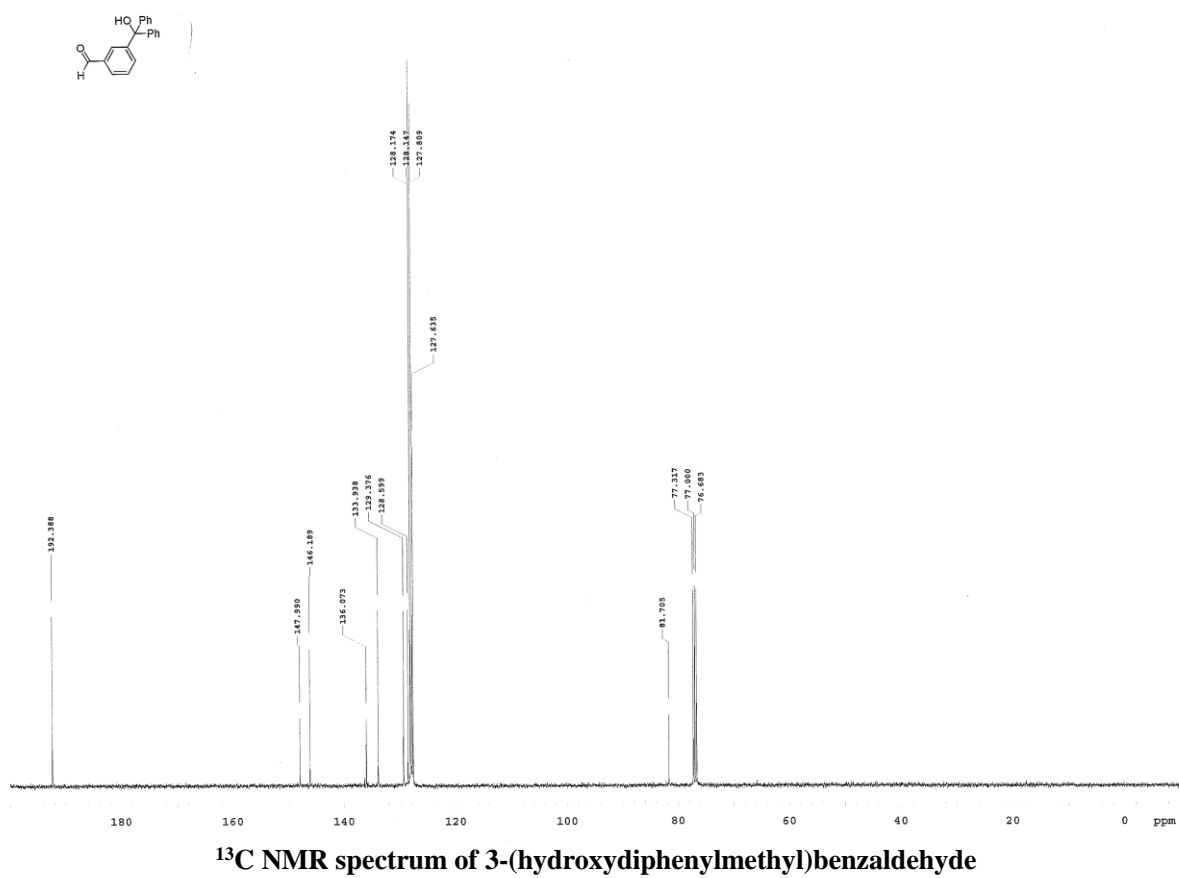
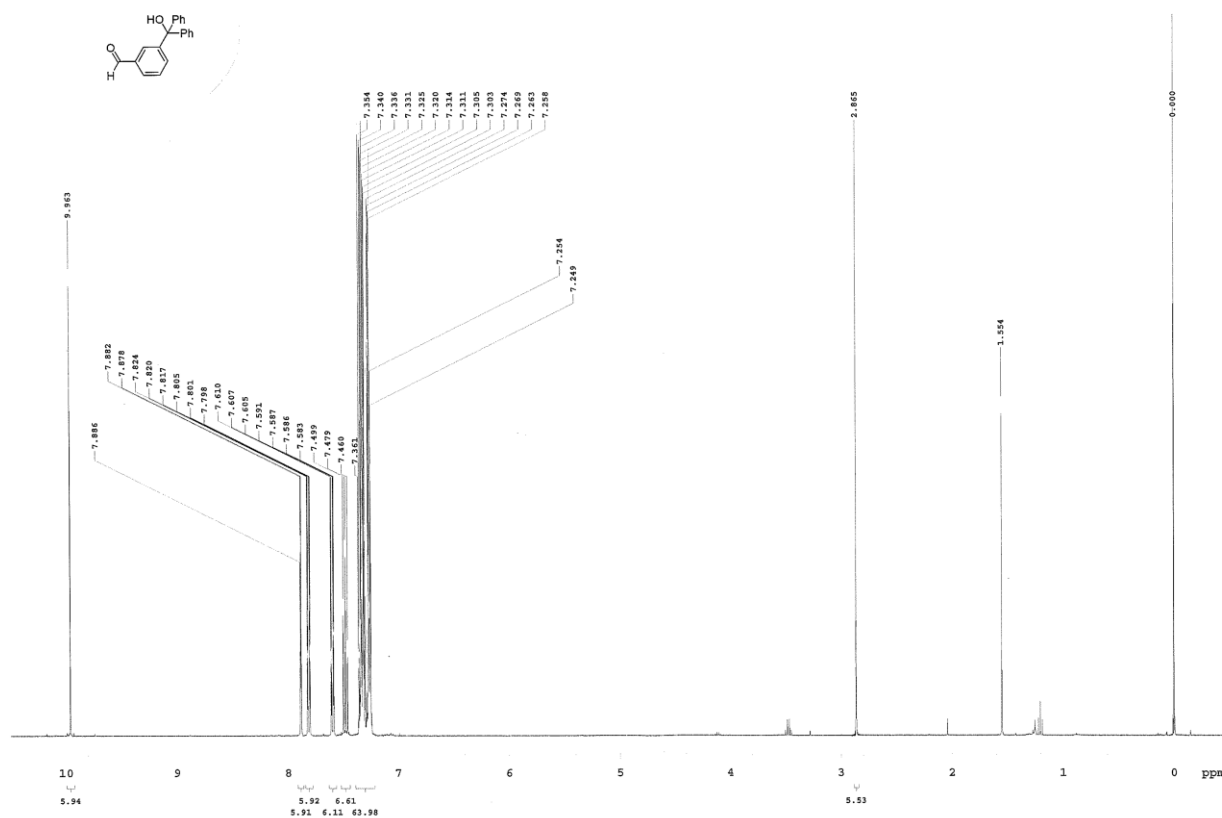


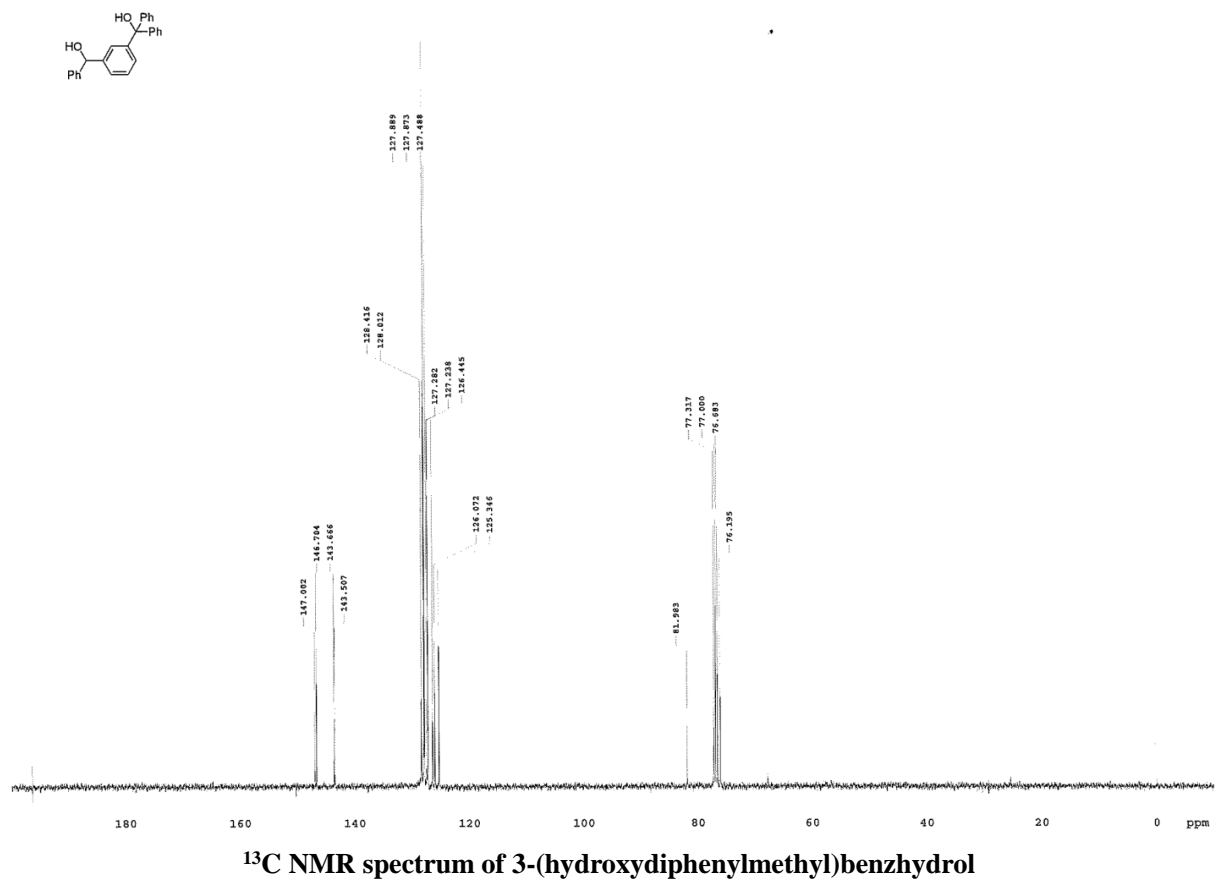
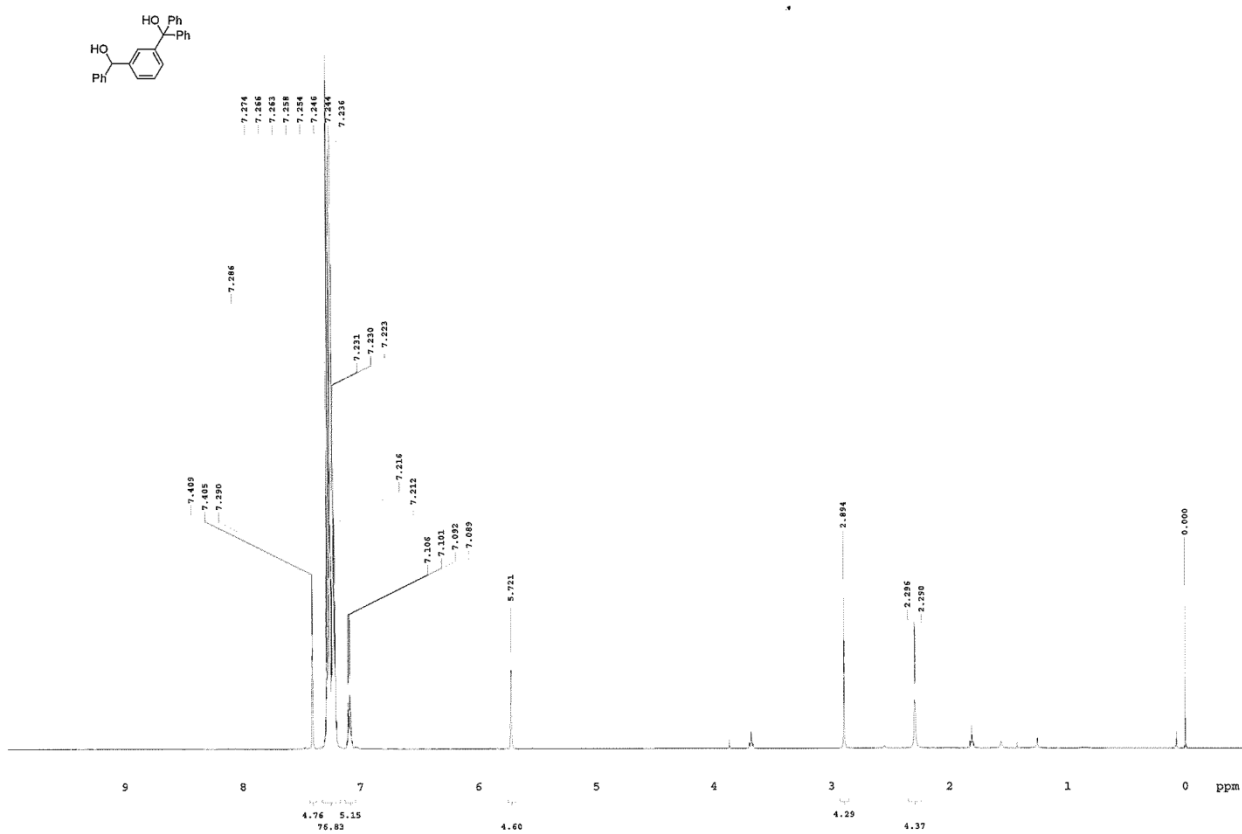


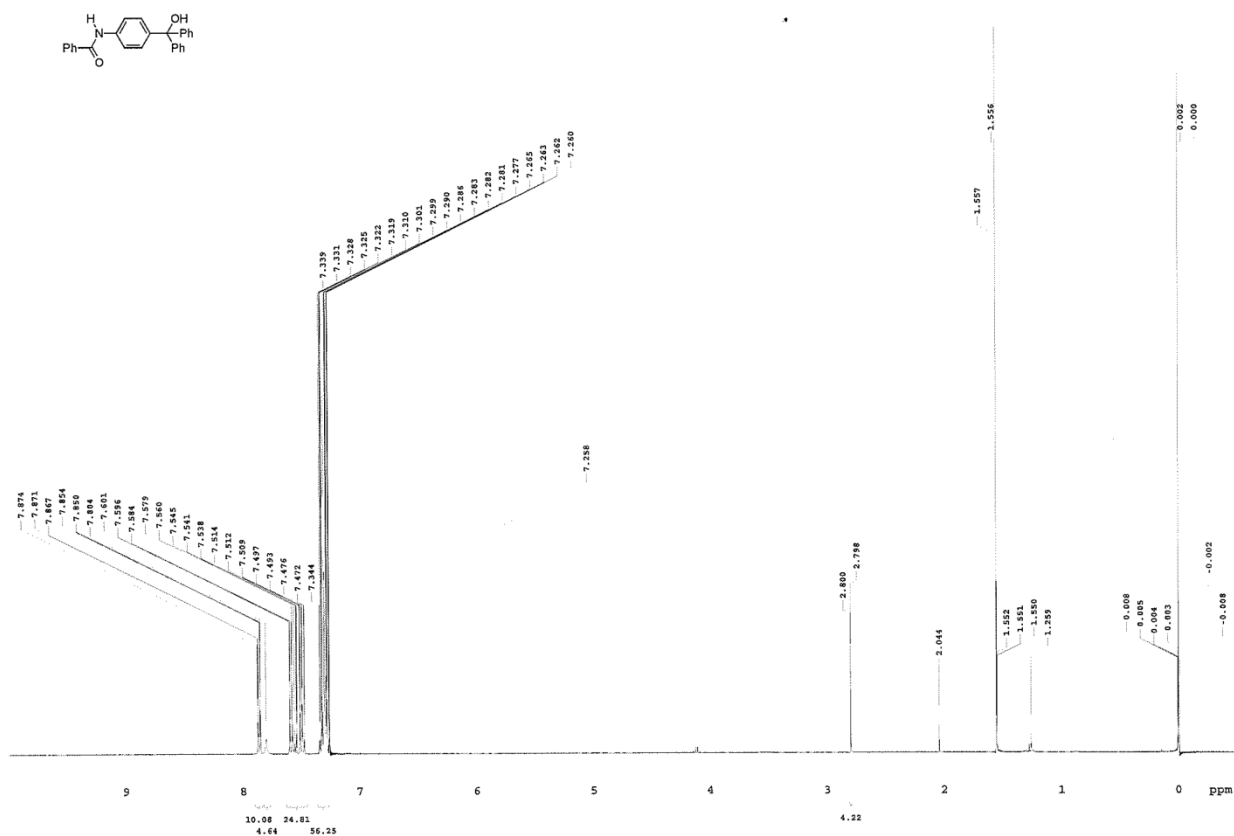
¹H NMR spectrum of (4-(hydroxy(phenyl)methyl)phenyl)diphenylmethanol

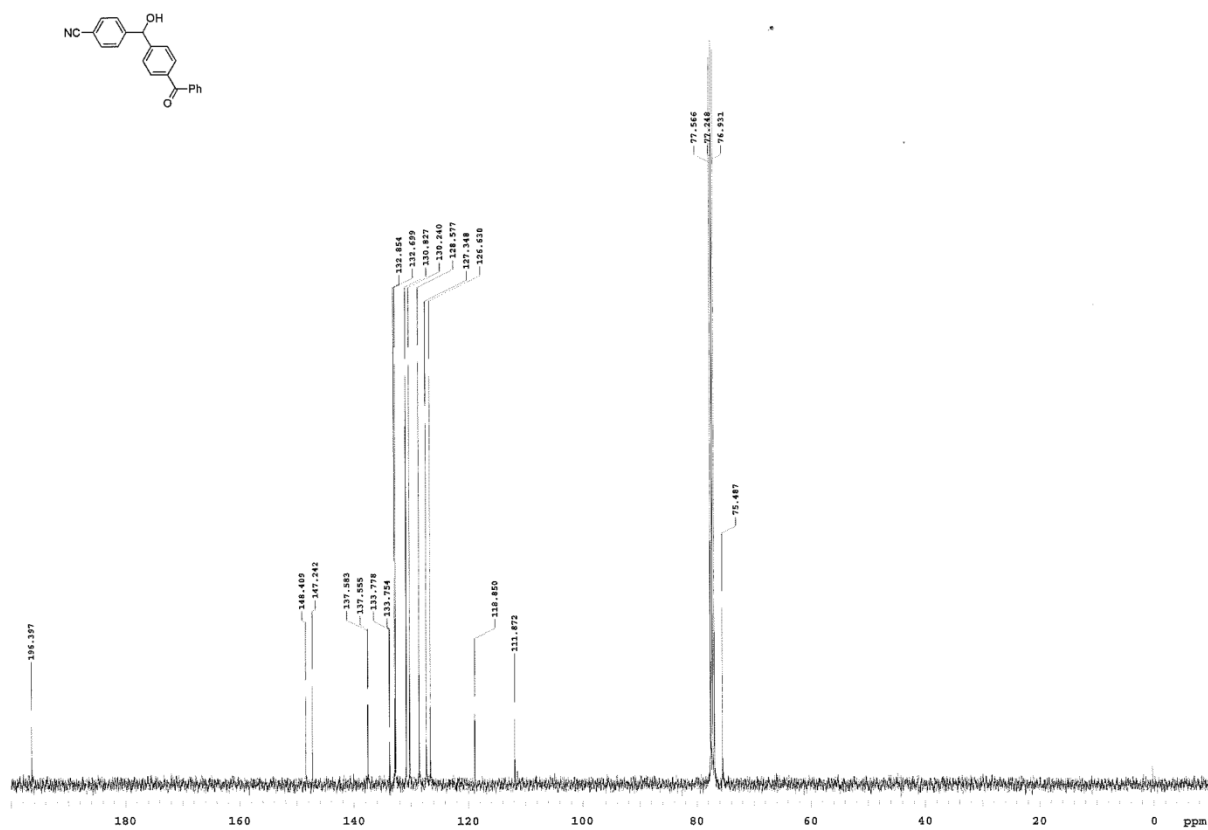
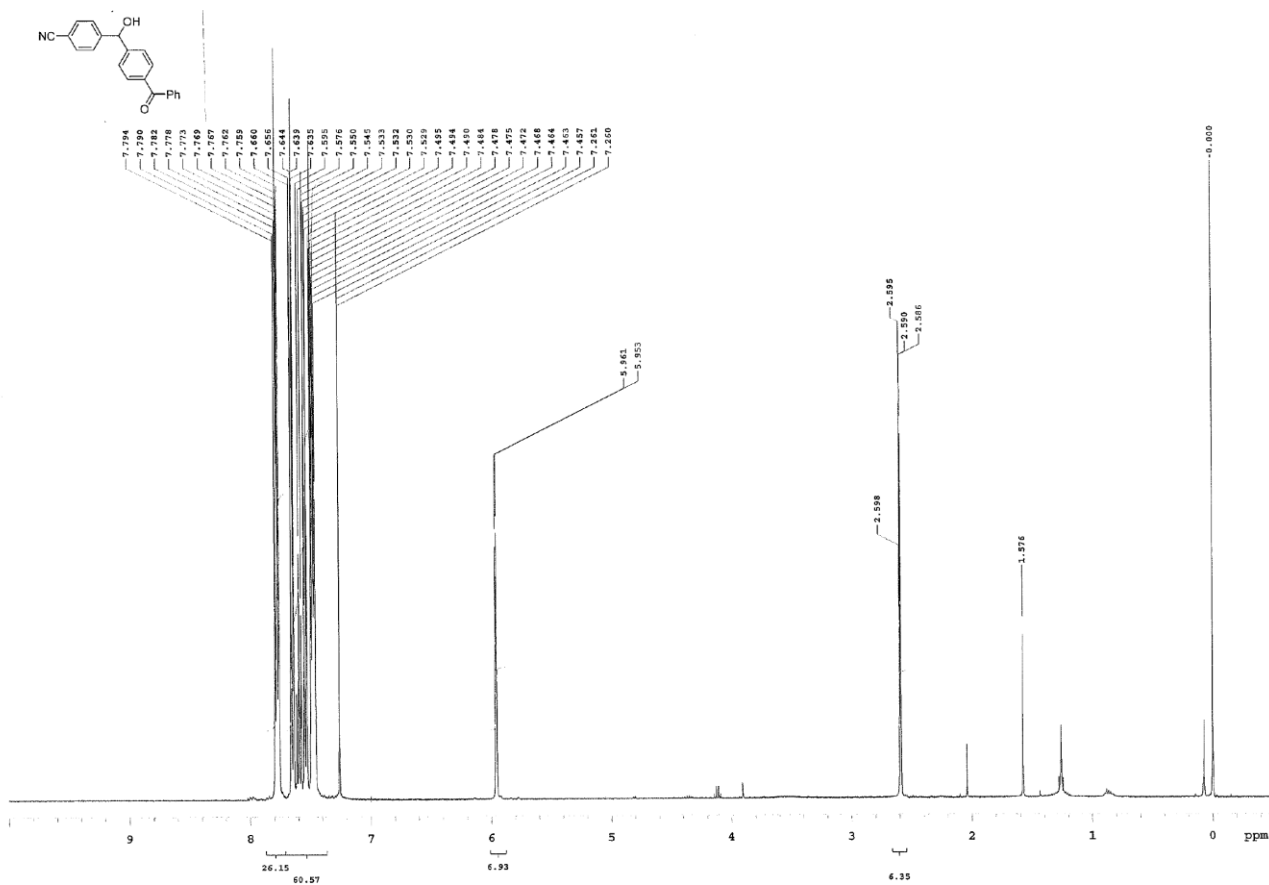


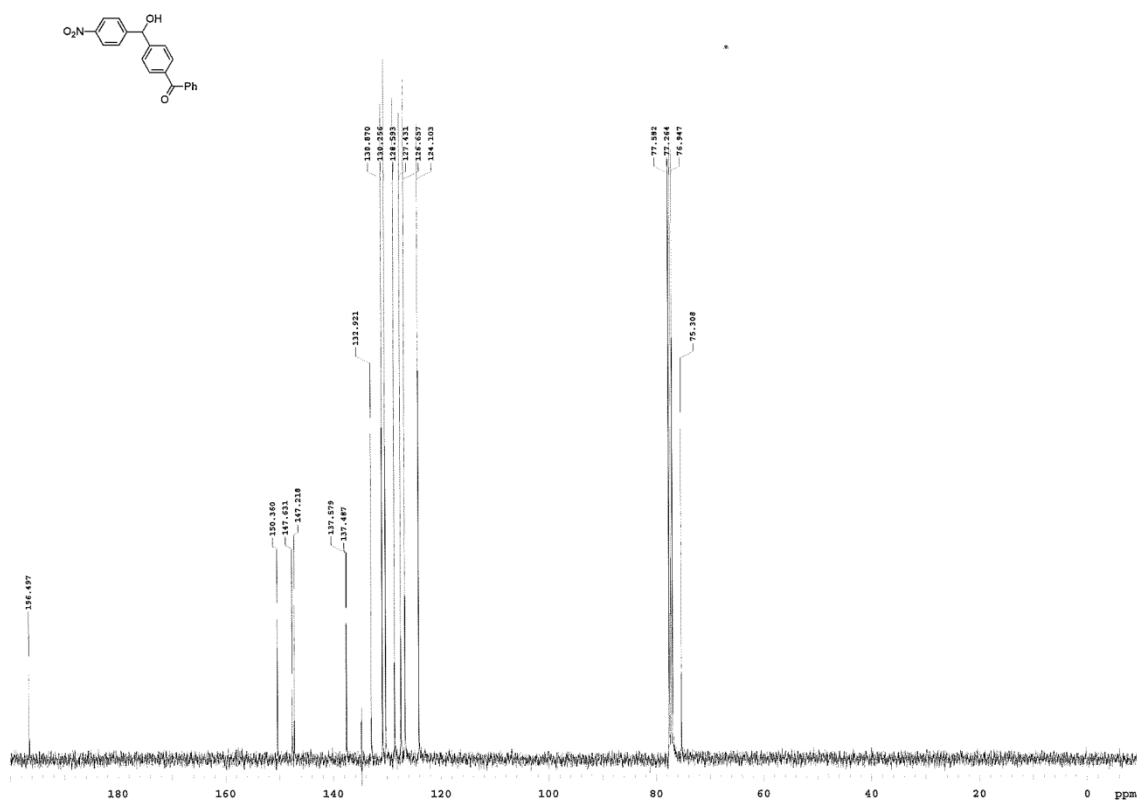
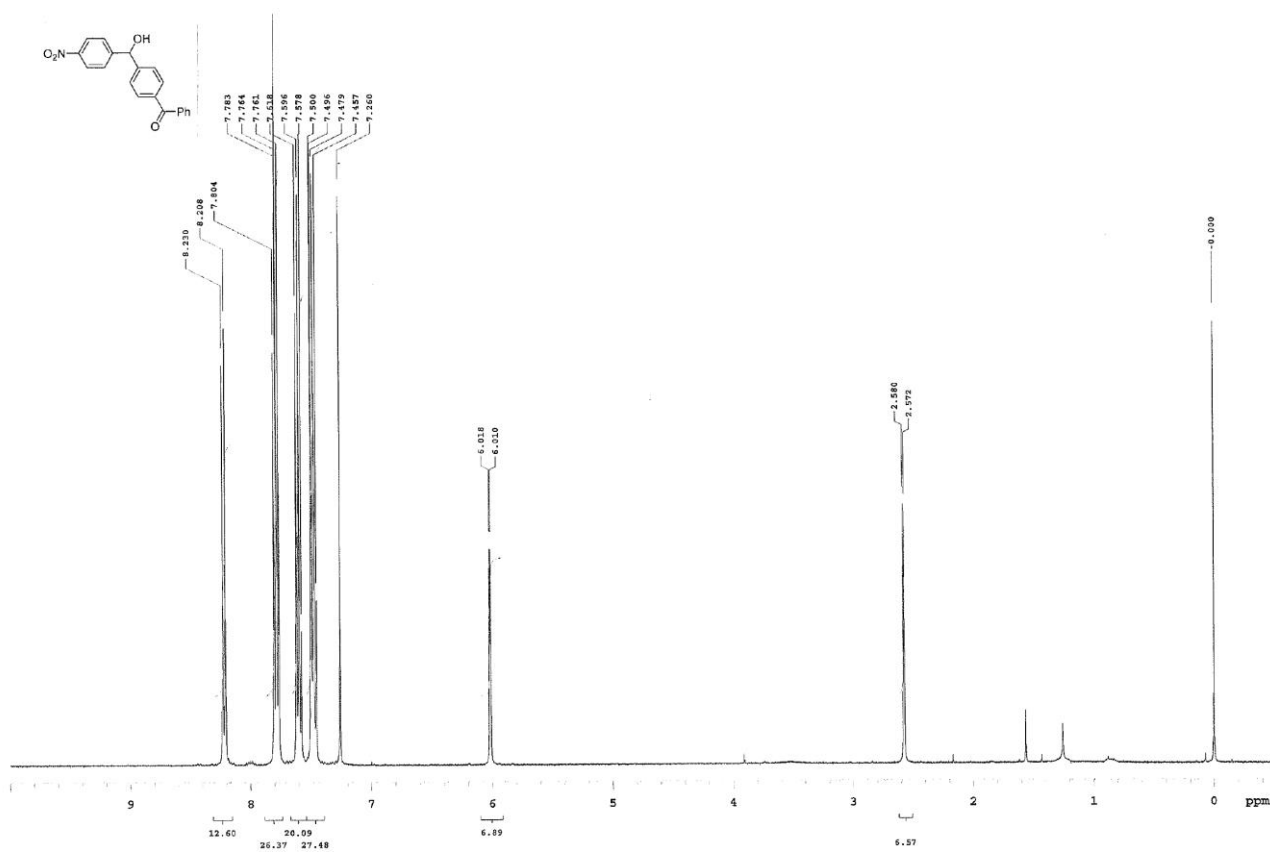
¹³C NMR spectrum of (4-(hydroxy(phenyl)methyl)phenyl)diphenylmethanol

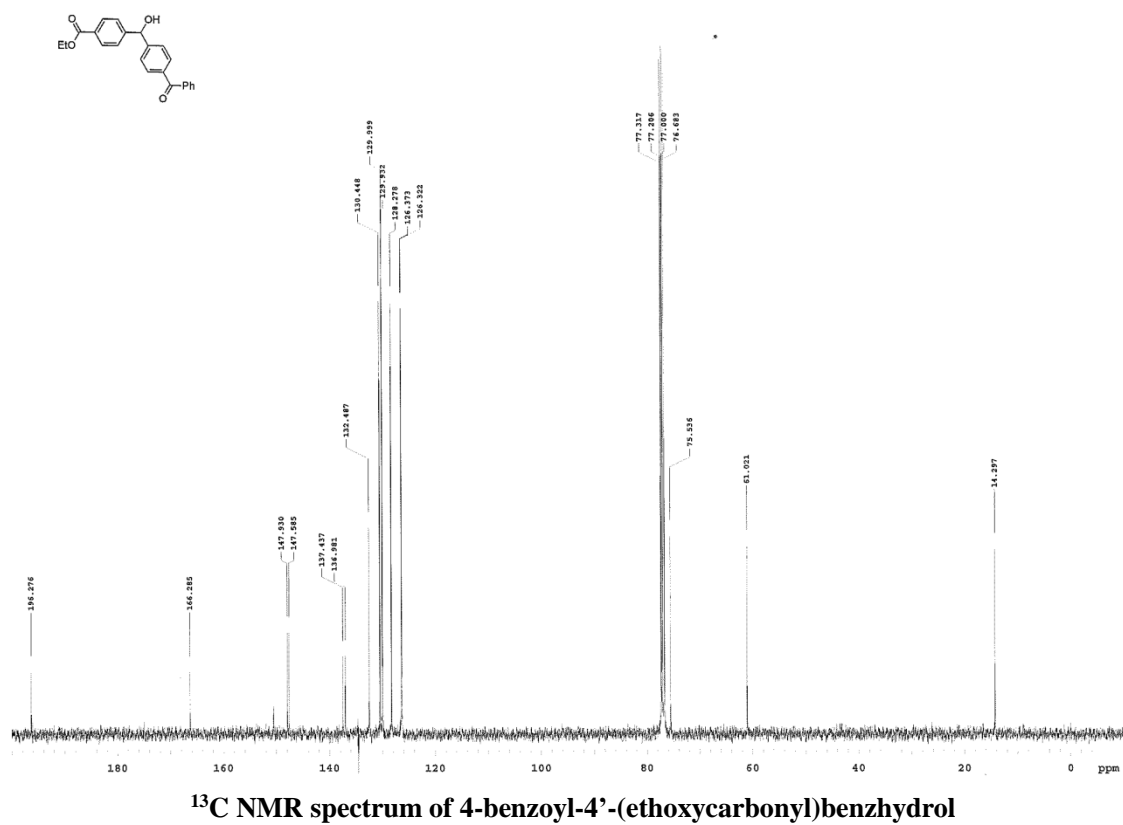
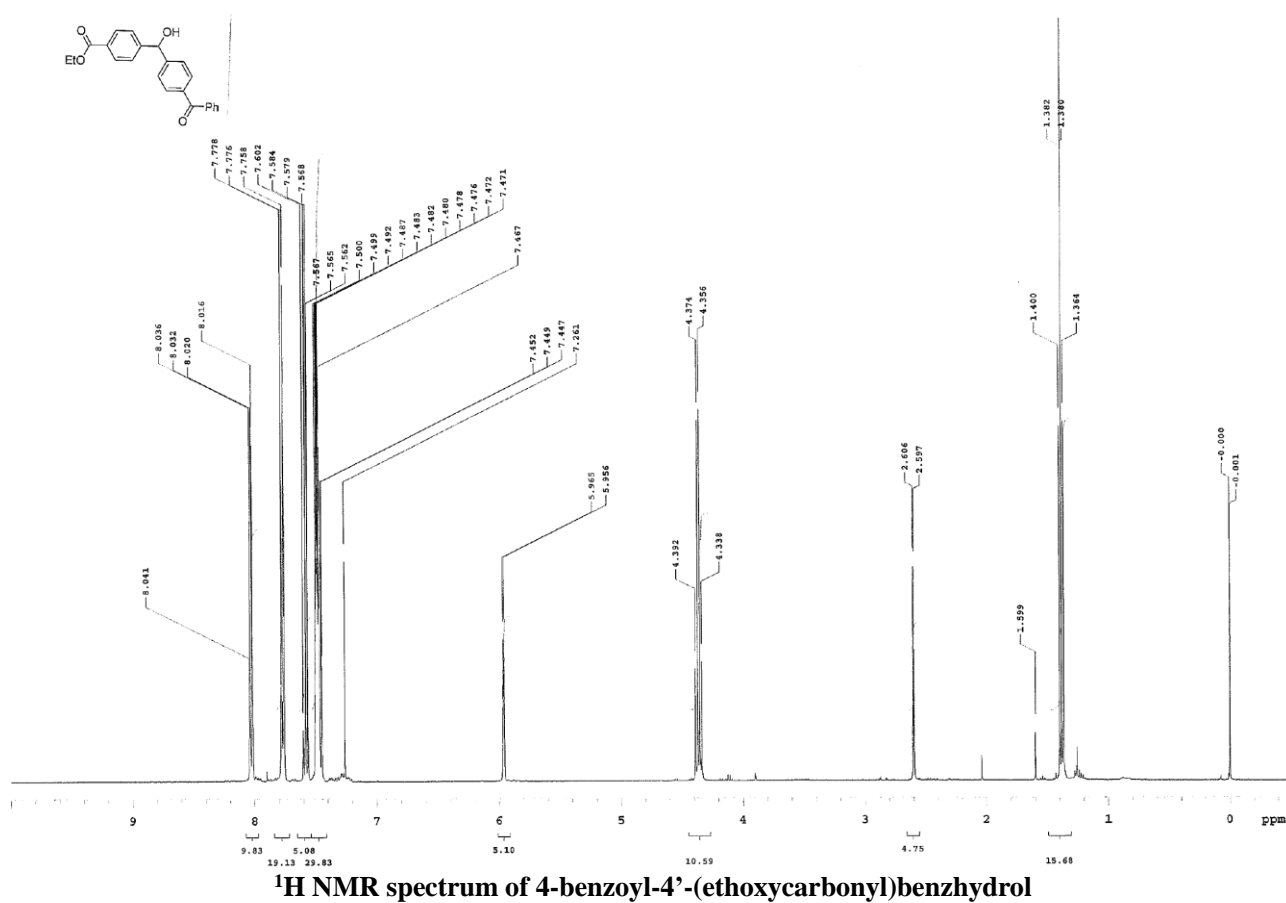


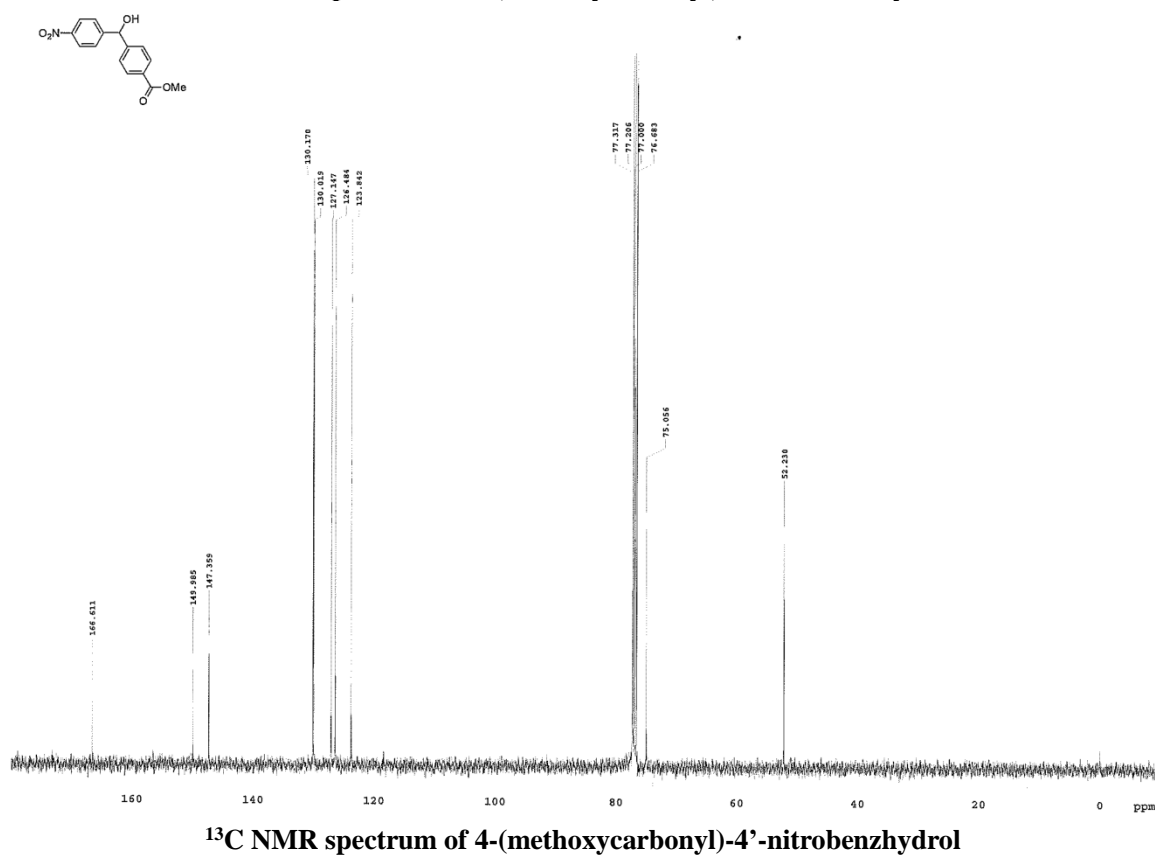
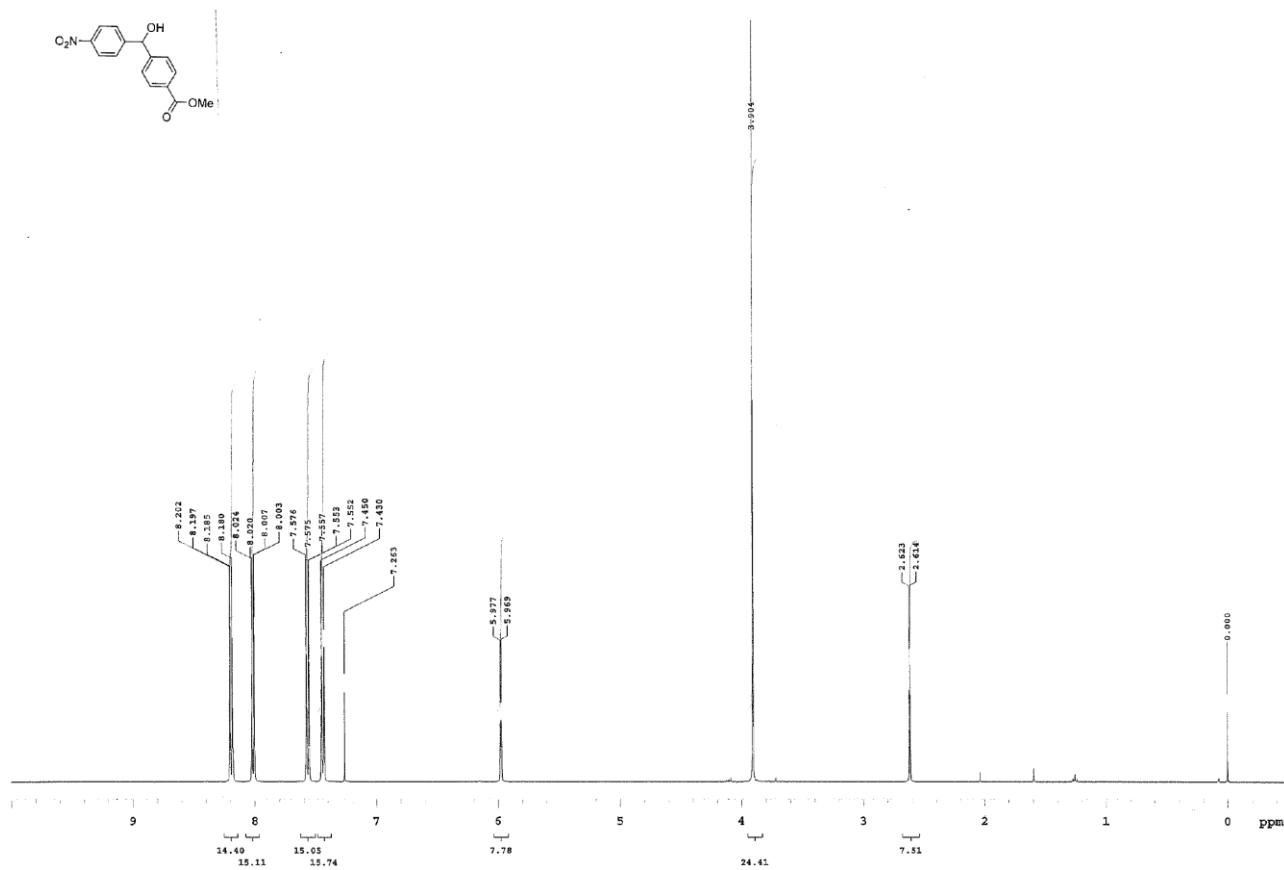


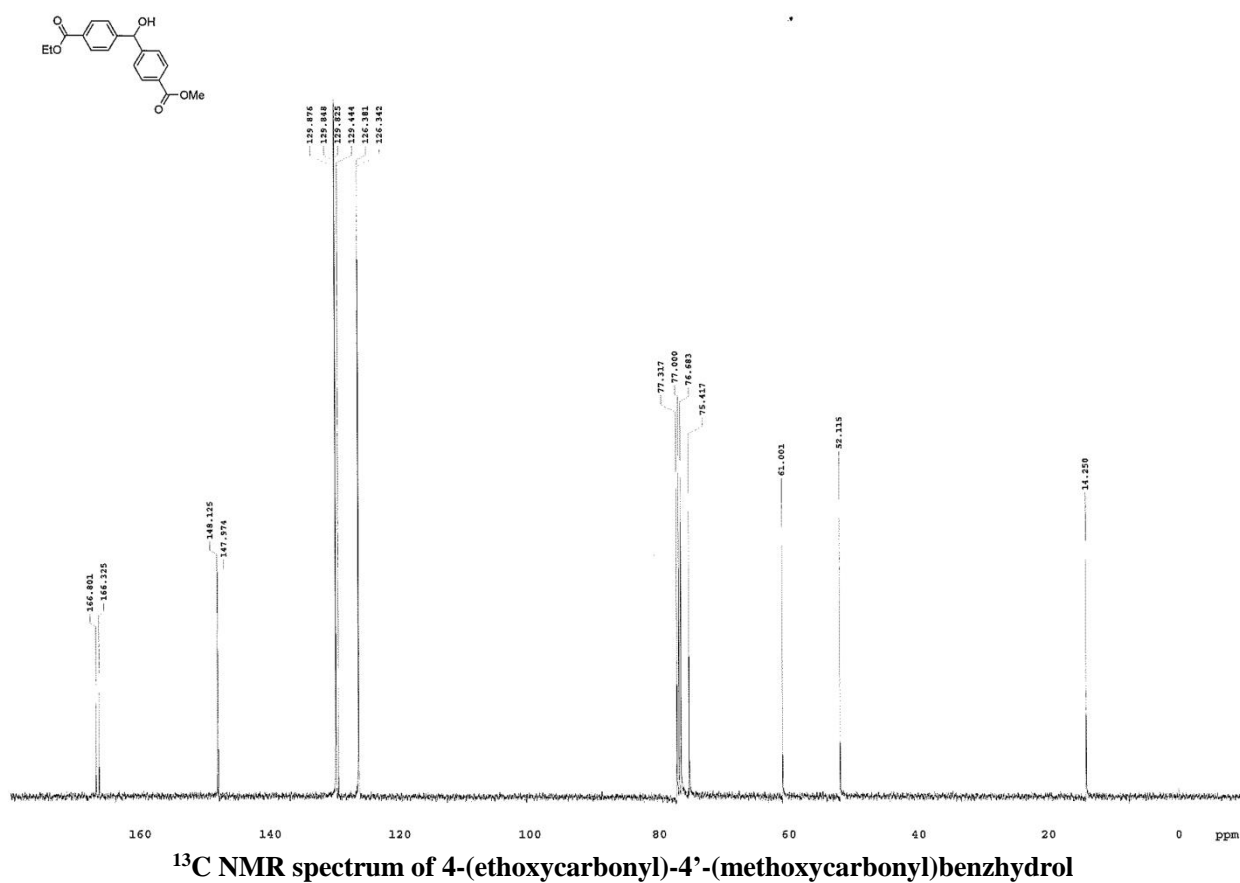
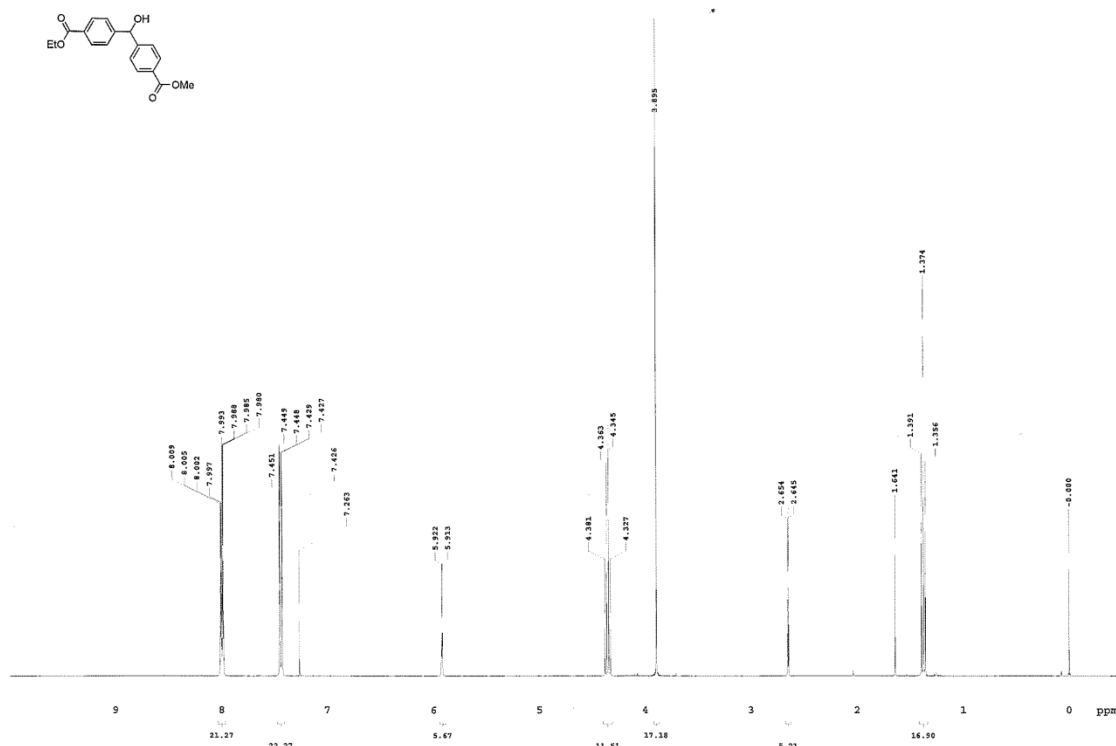


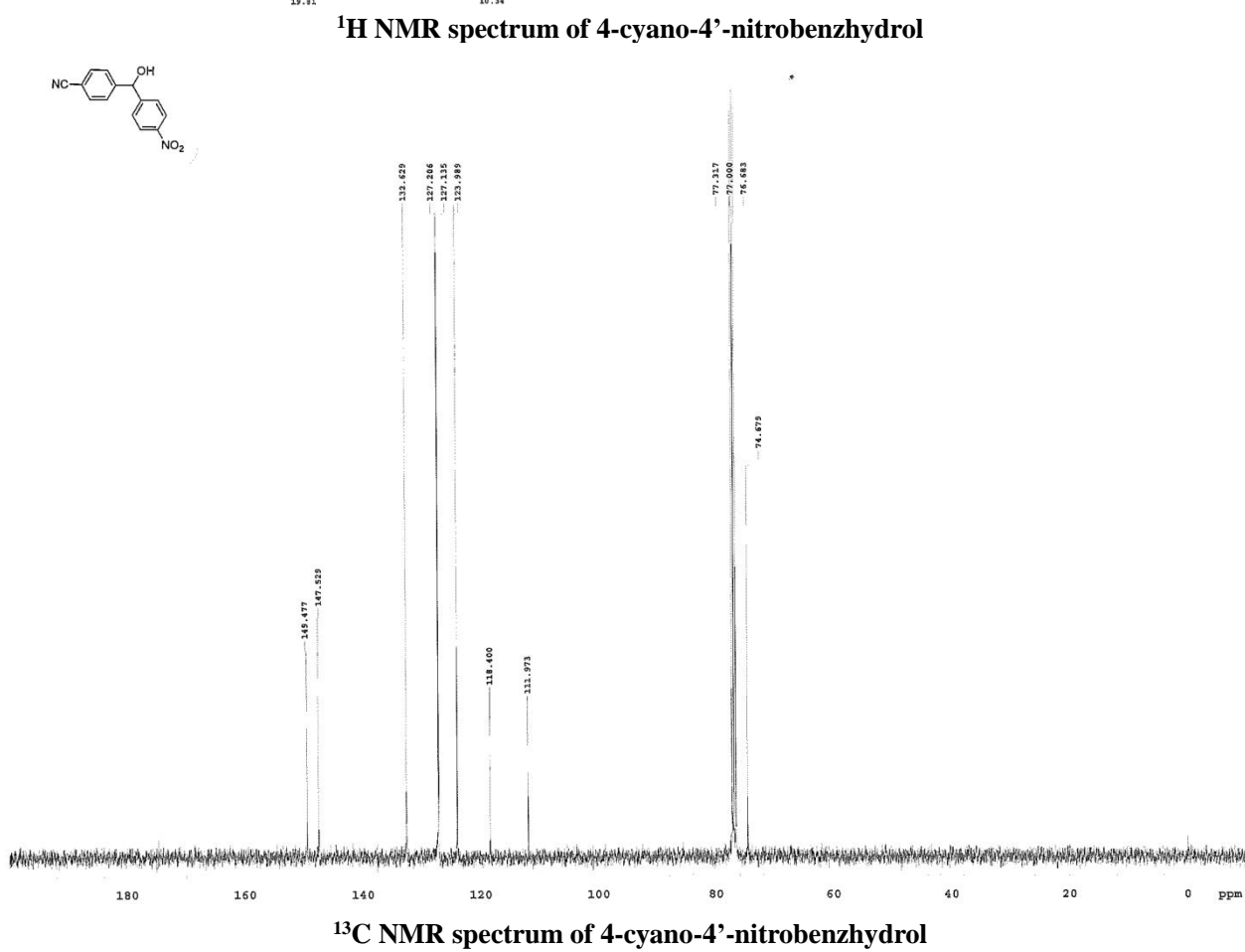
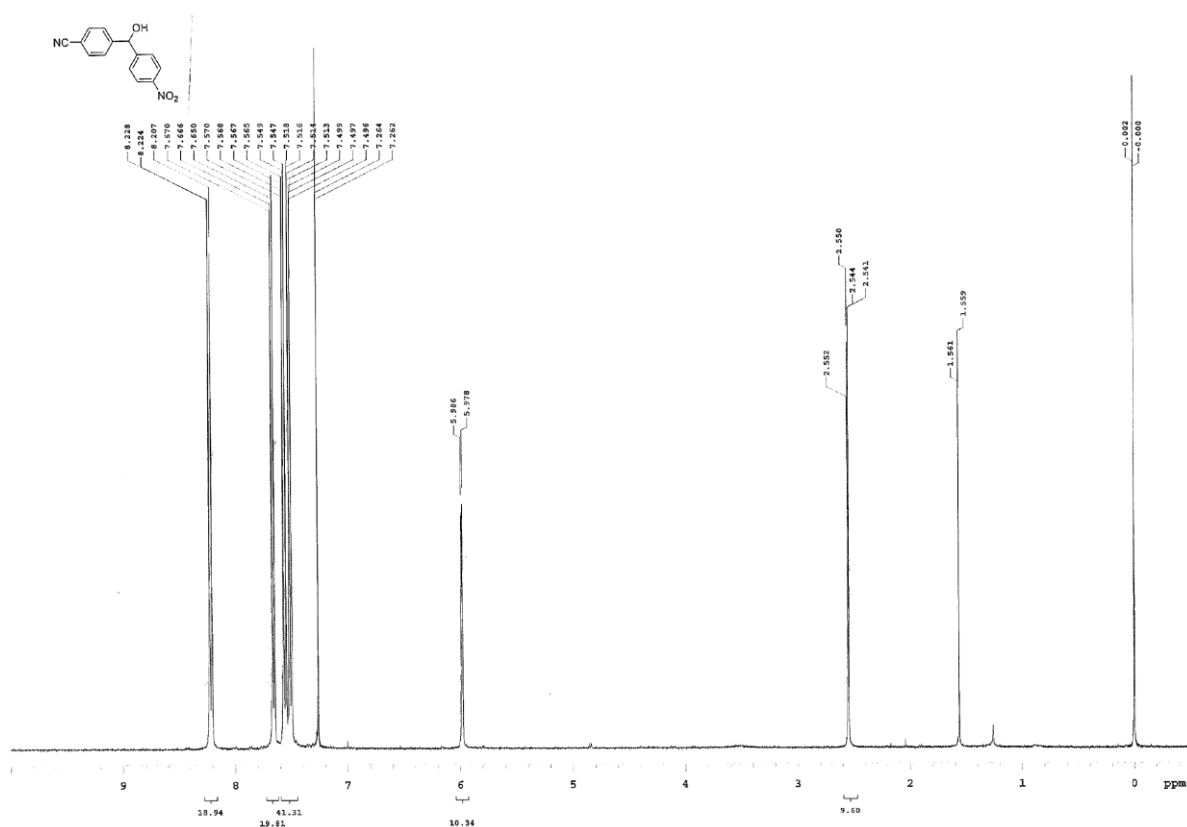


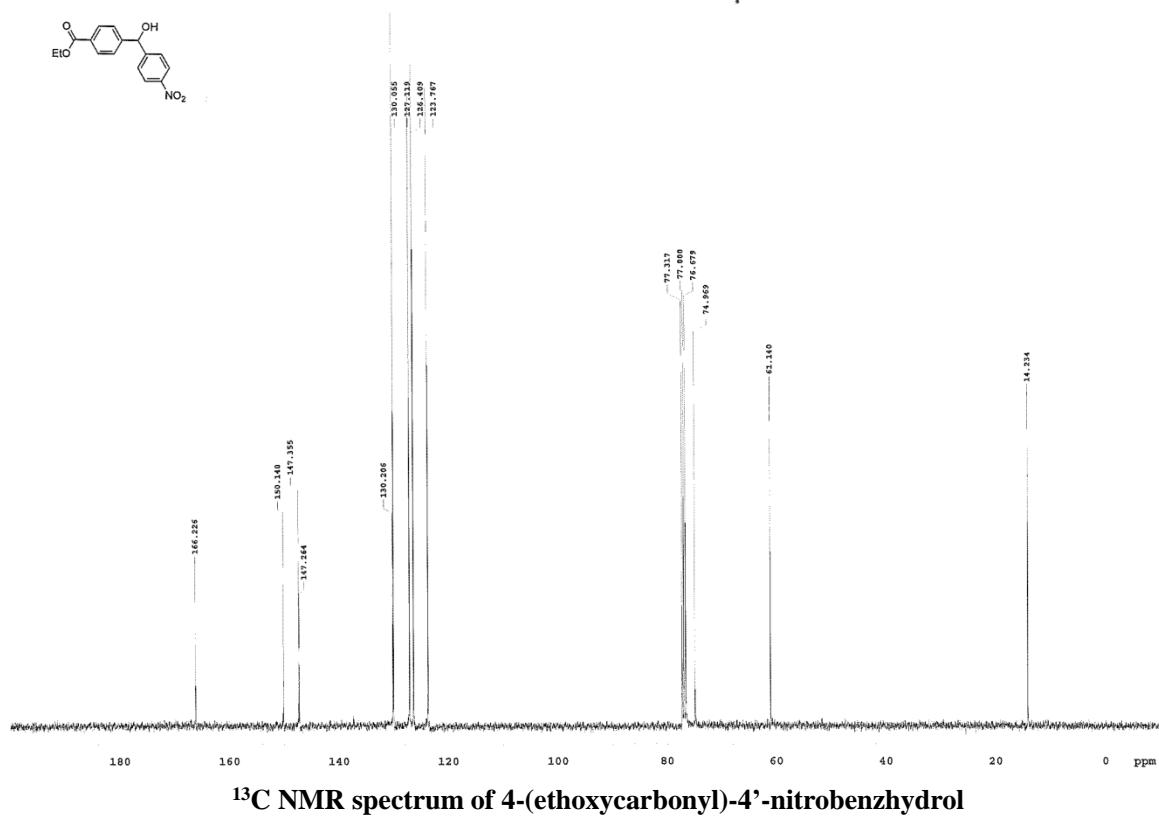
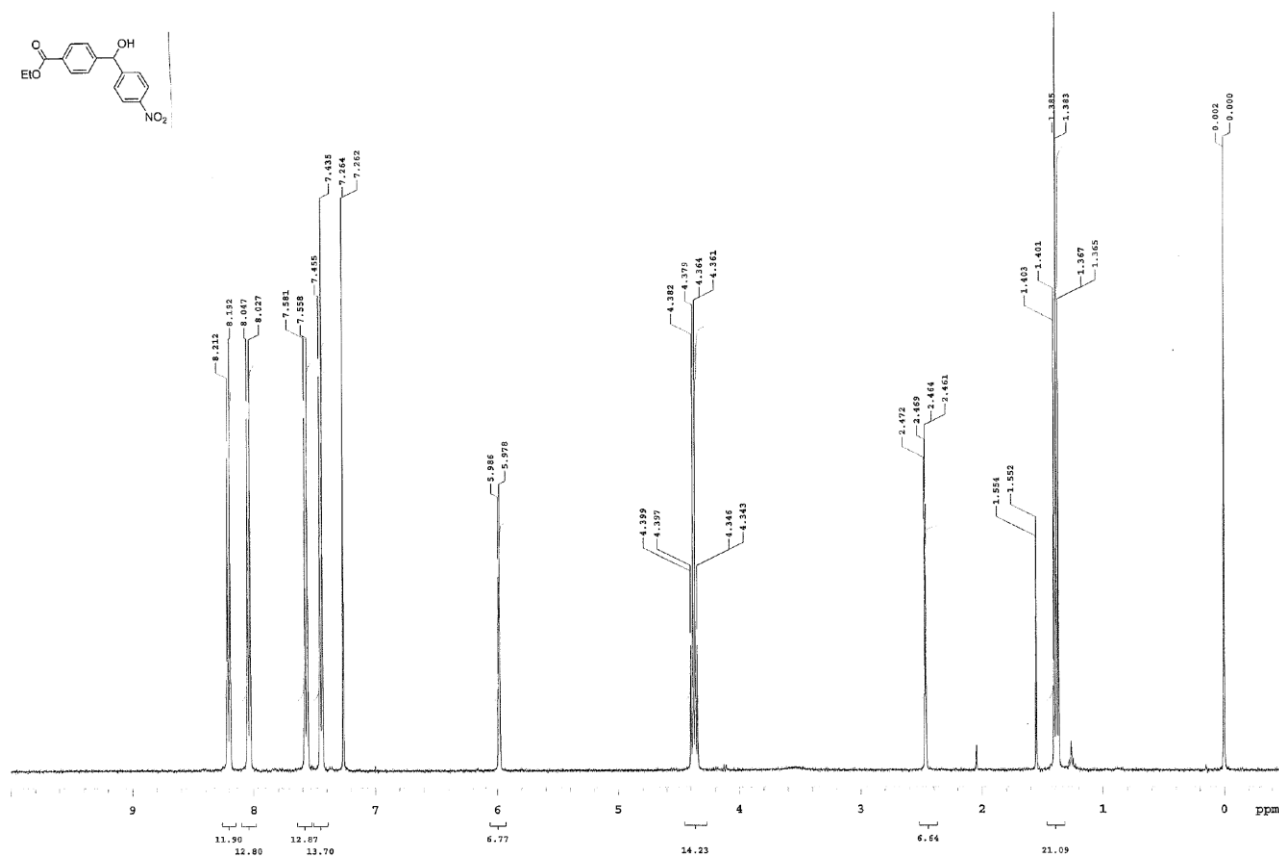


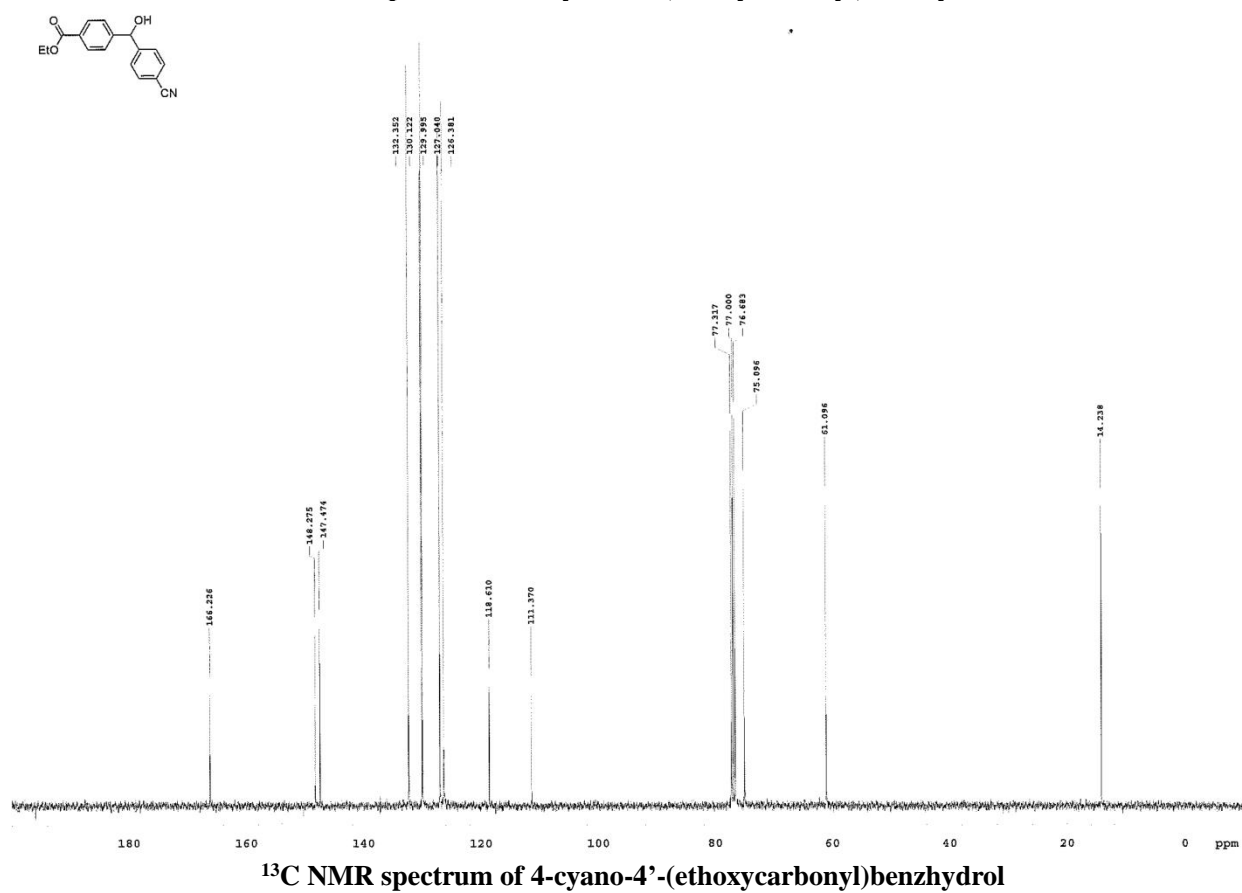
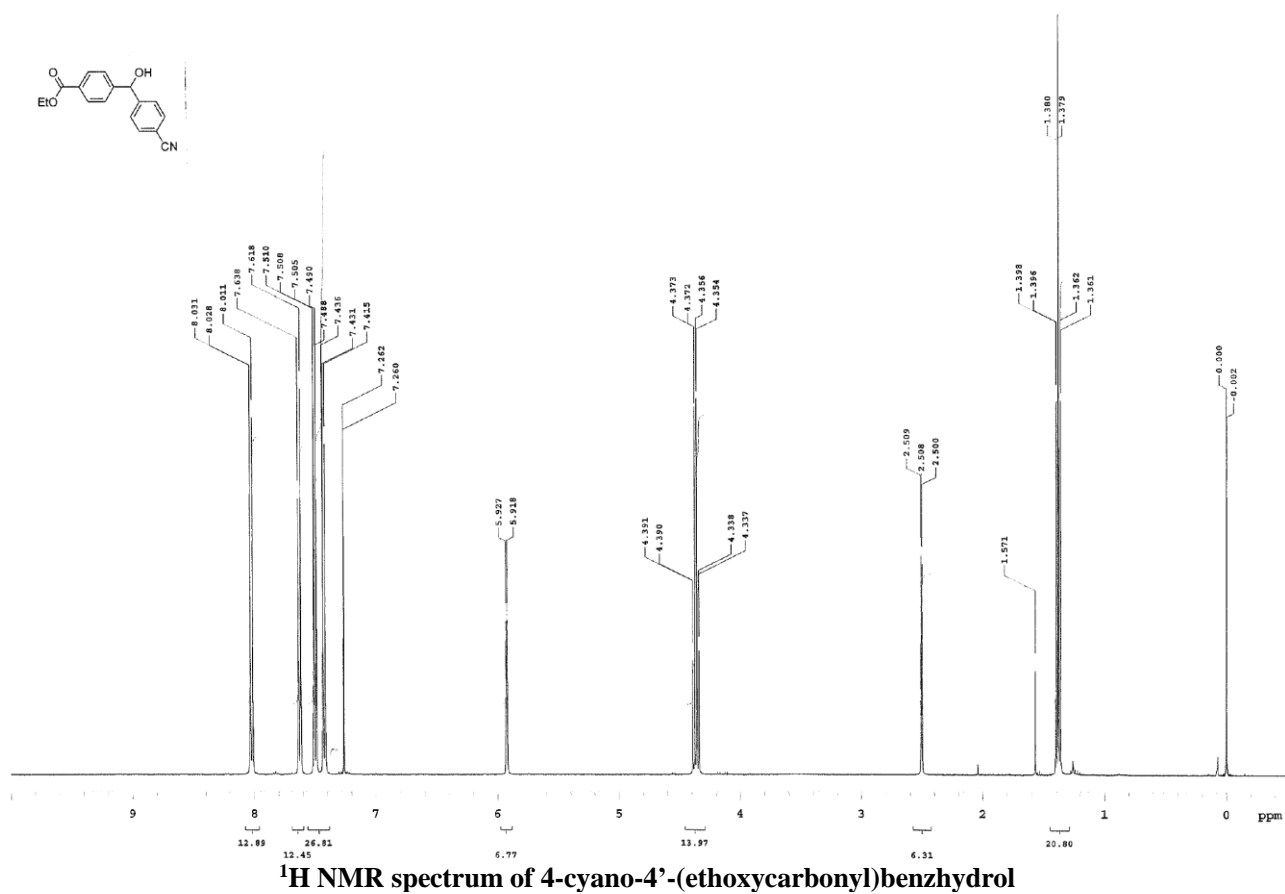


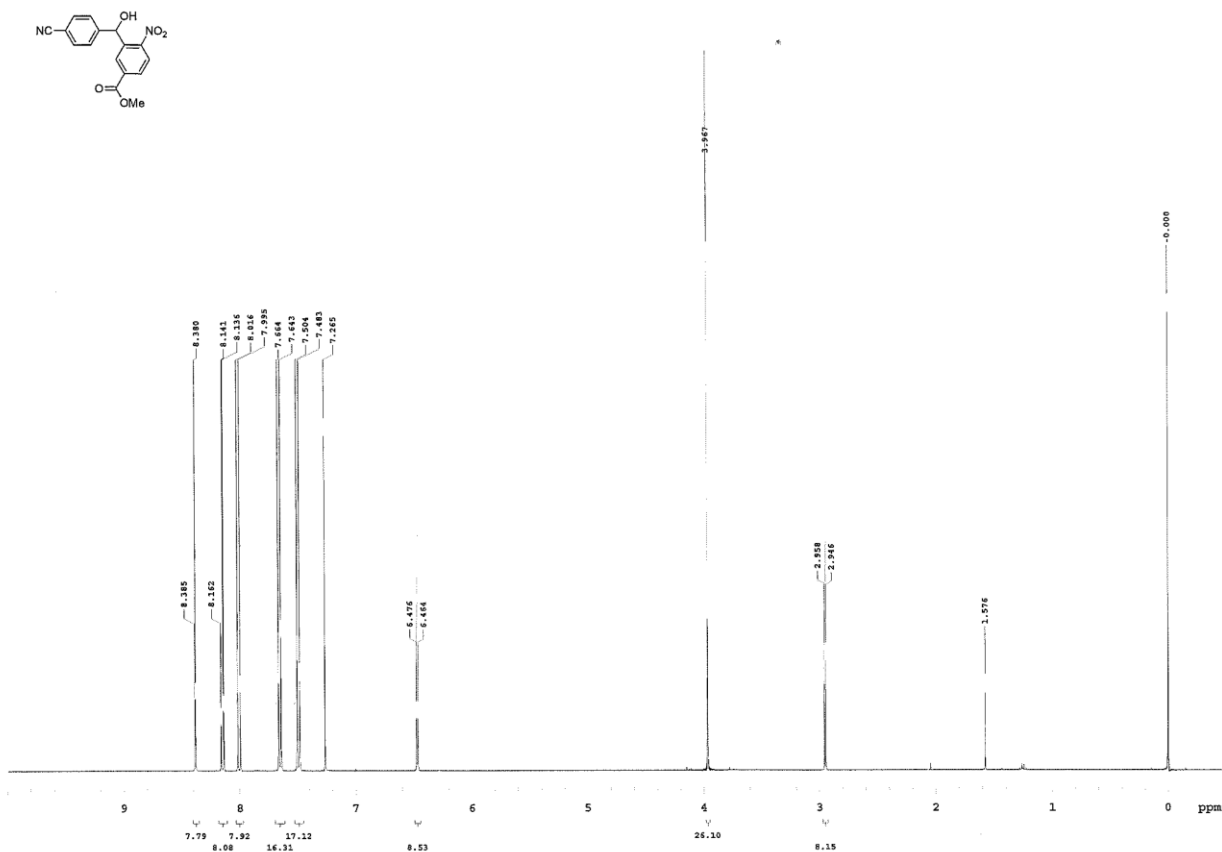




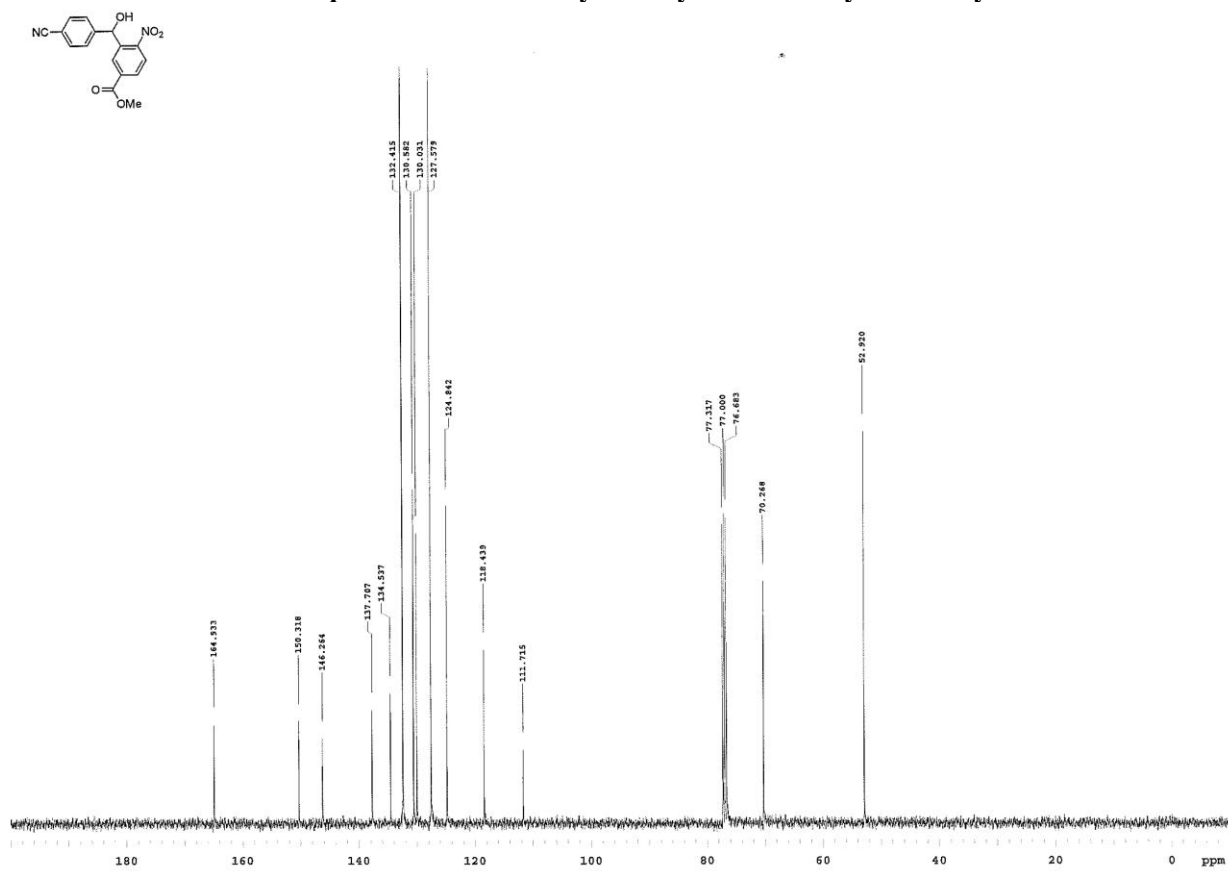




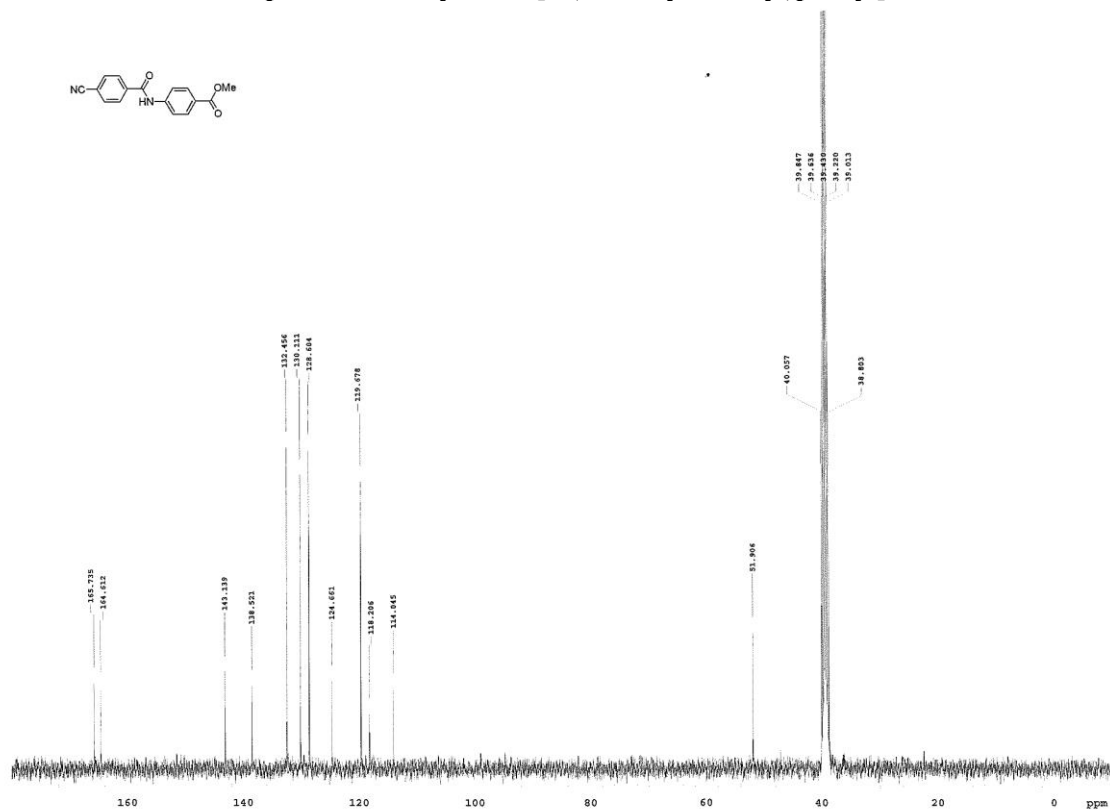
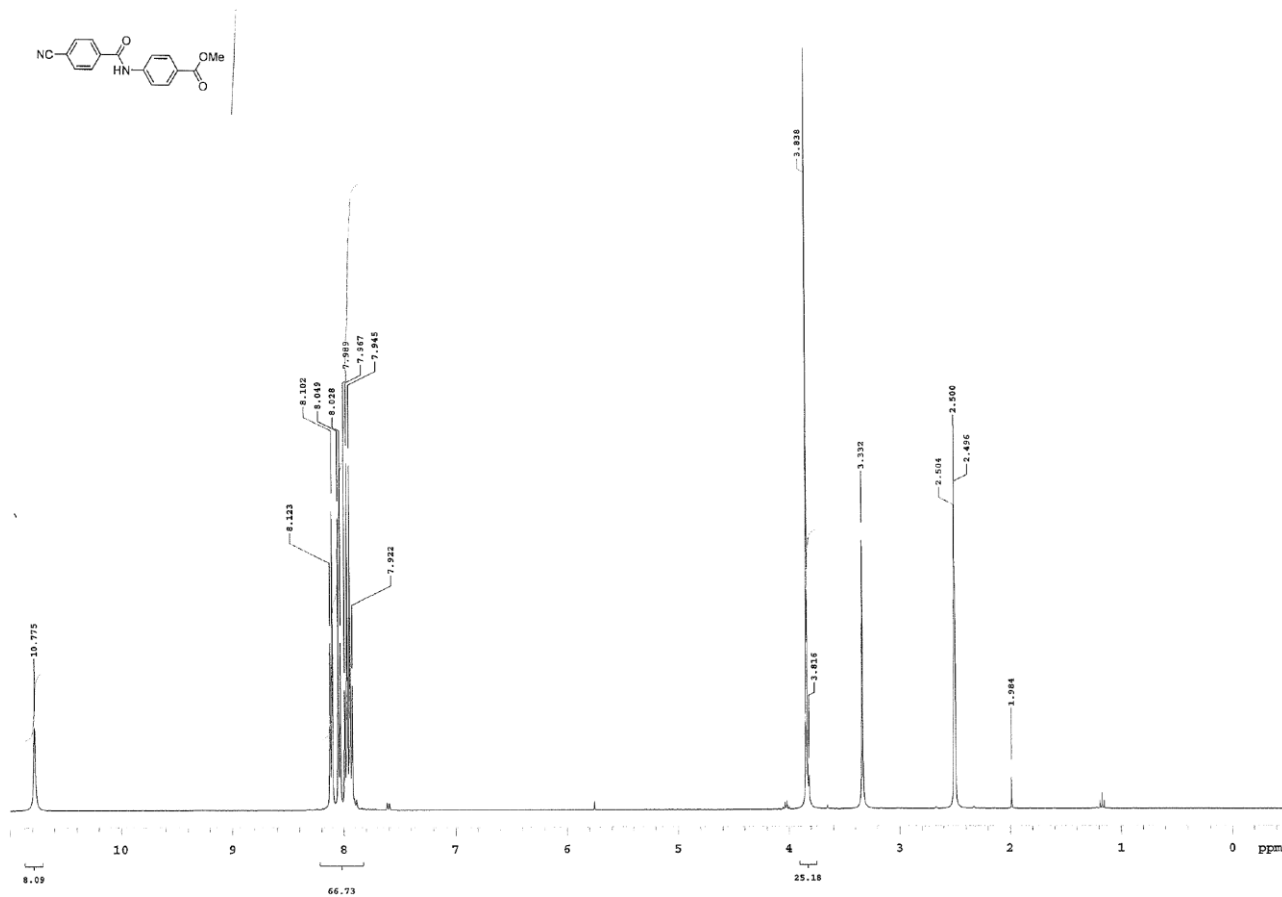


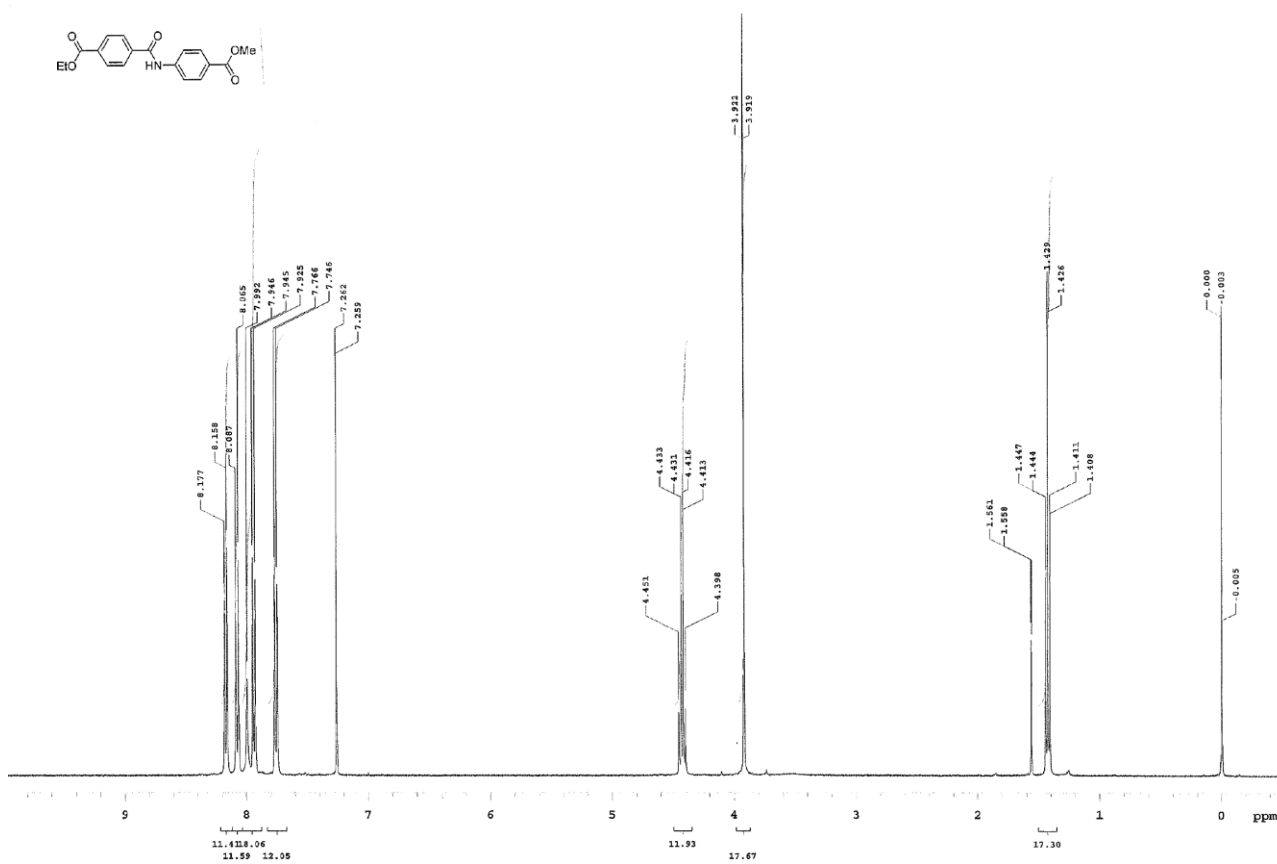
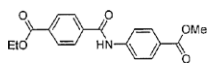


¹H NMR spectrum of 5-methoxycarbonyl-2-nitro-4'-cyanobenzhydrol

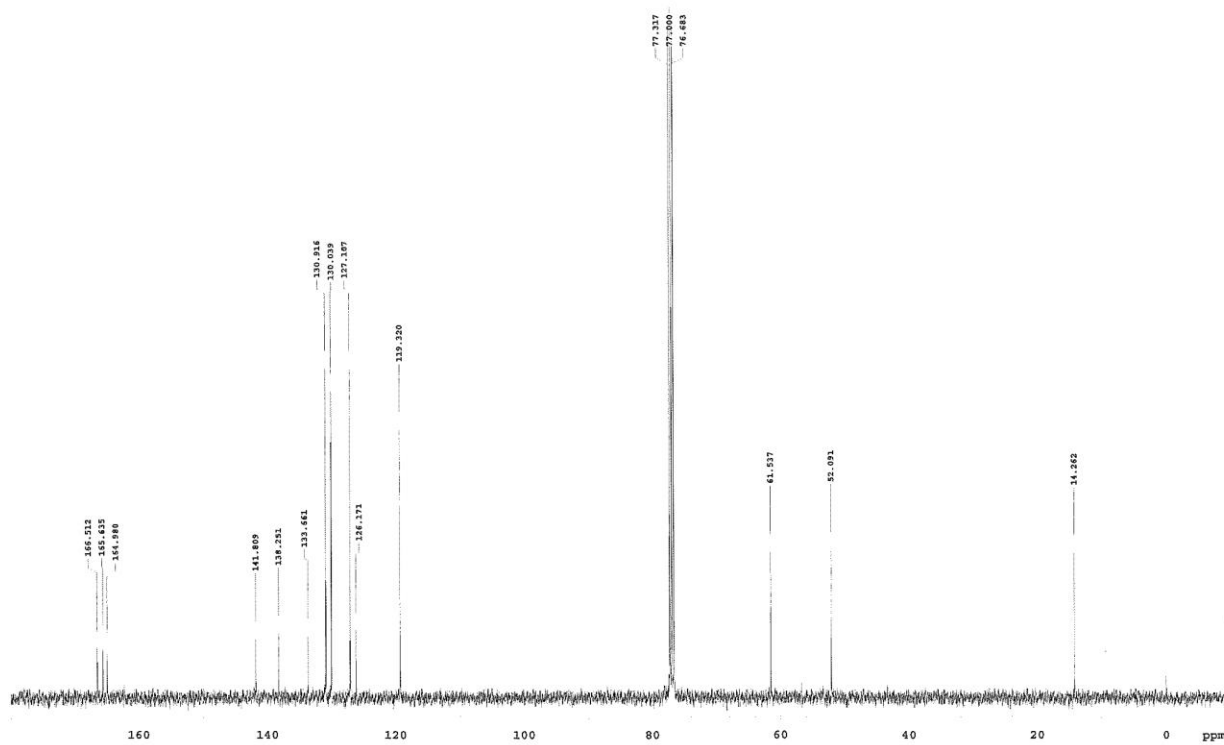
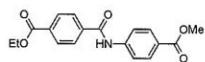


¹³C NMR spectrum of 5-methoxycarbonyl-2-nitro-4'-cyanobenzhydrol

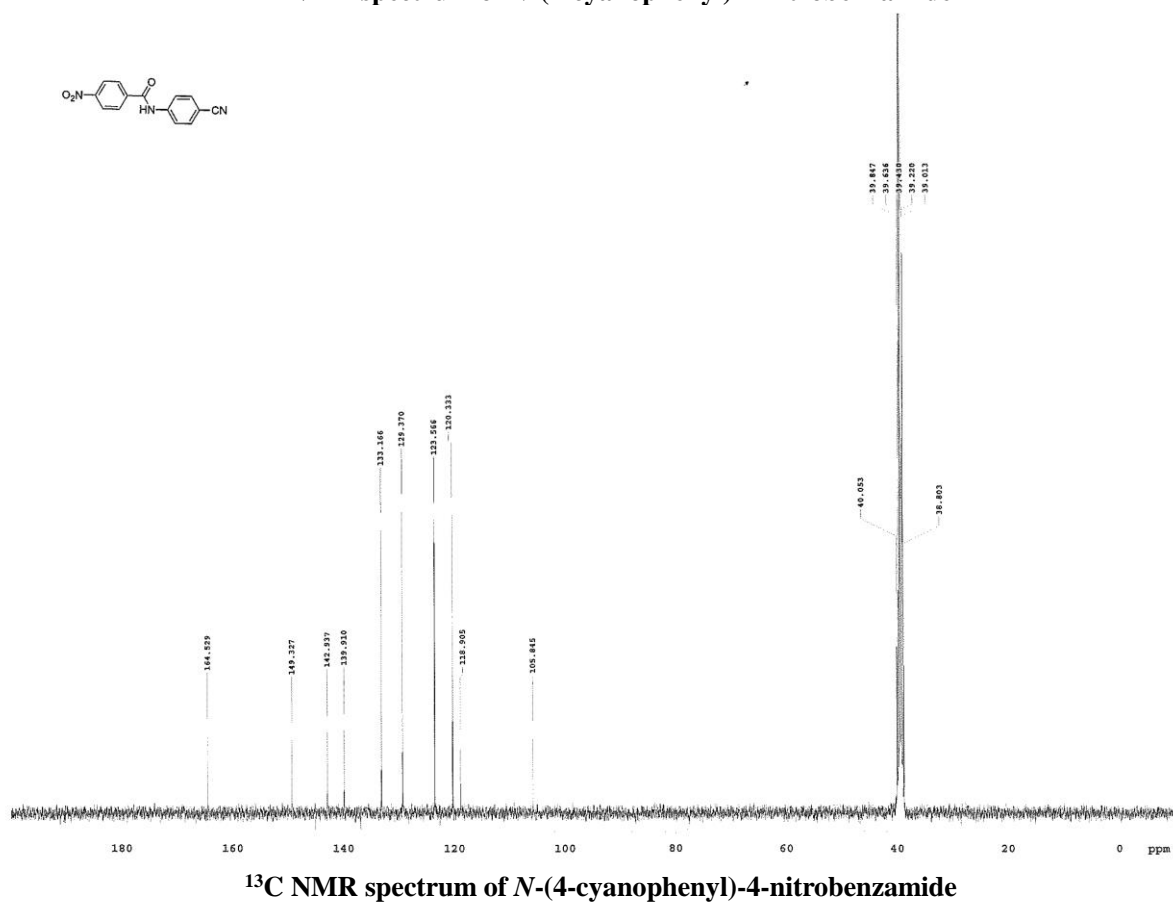
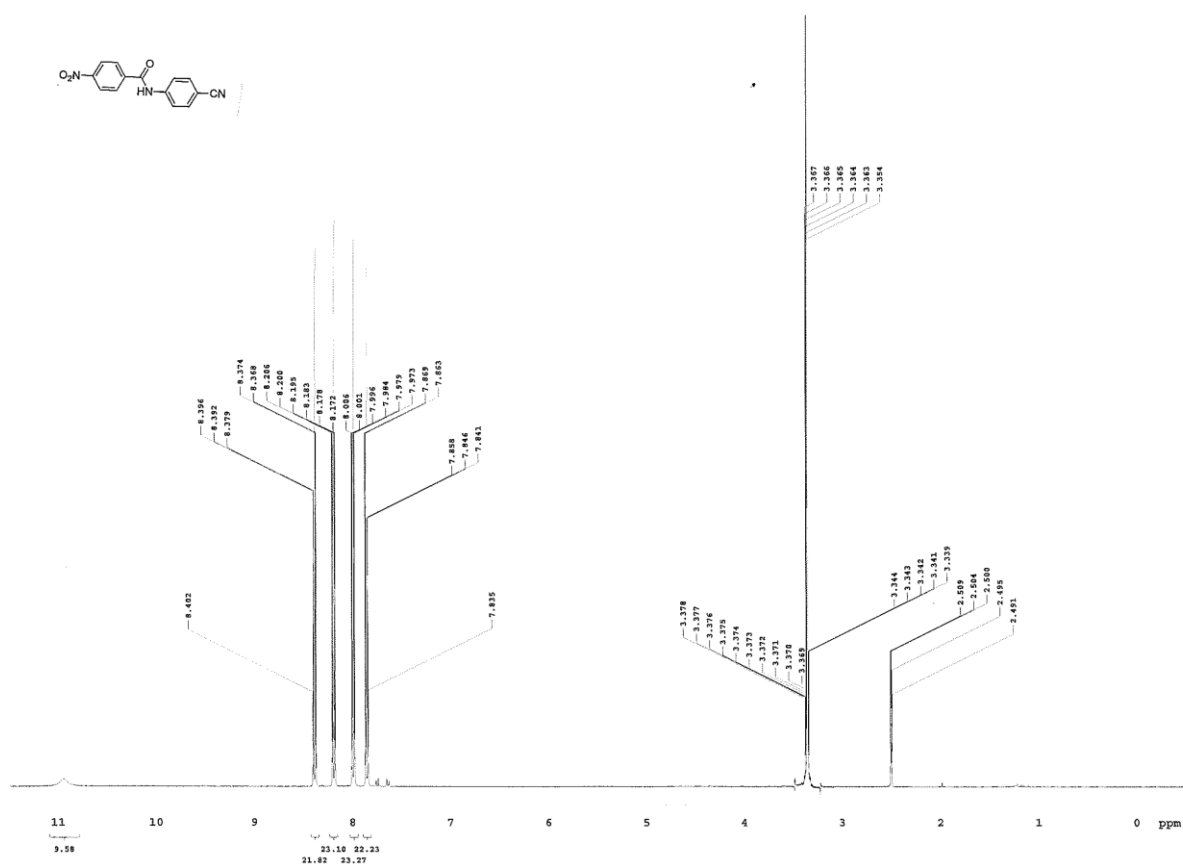


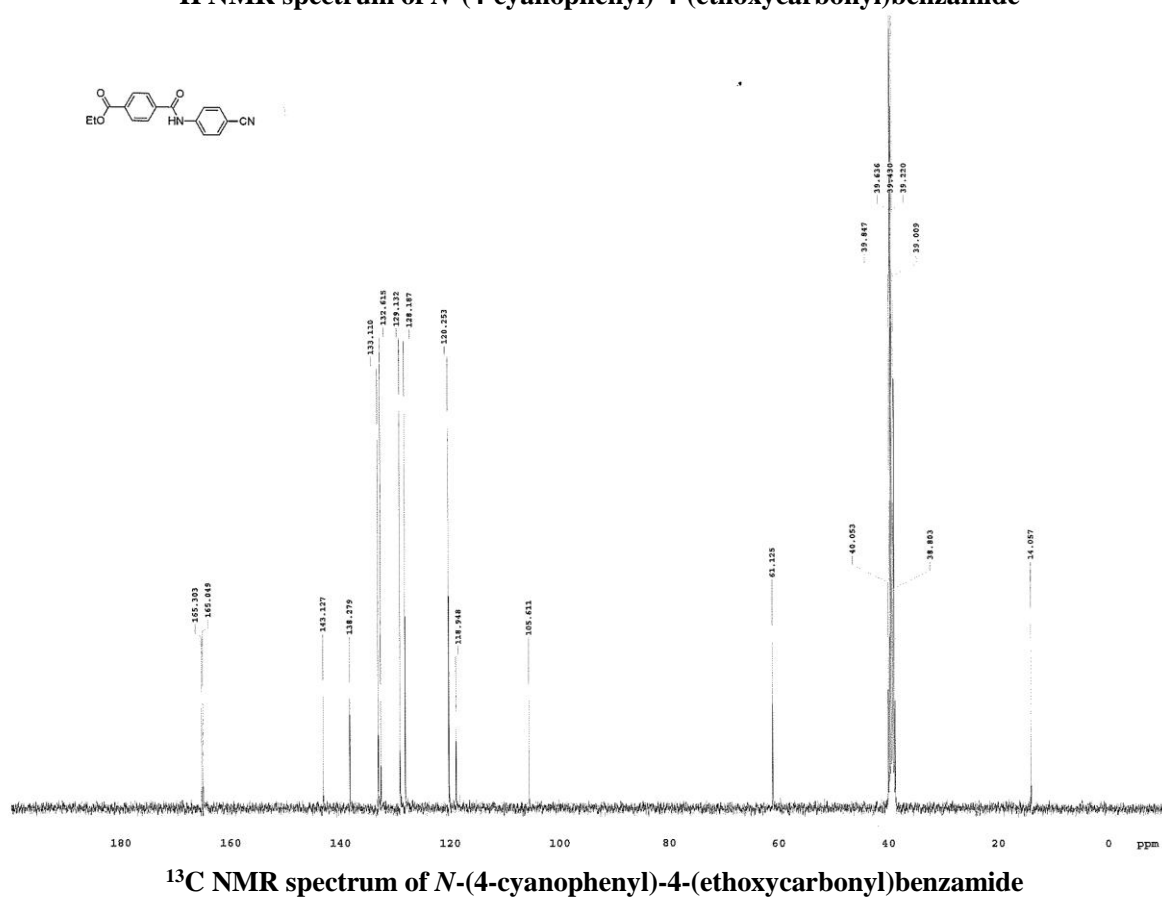
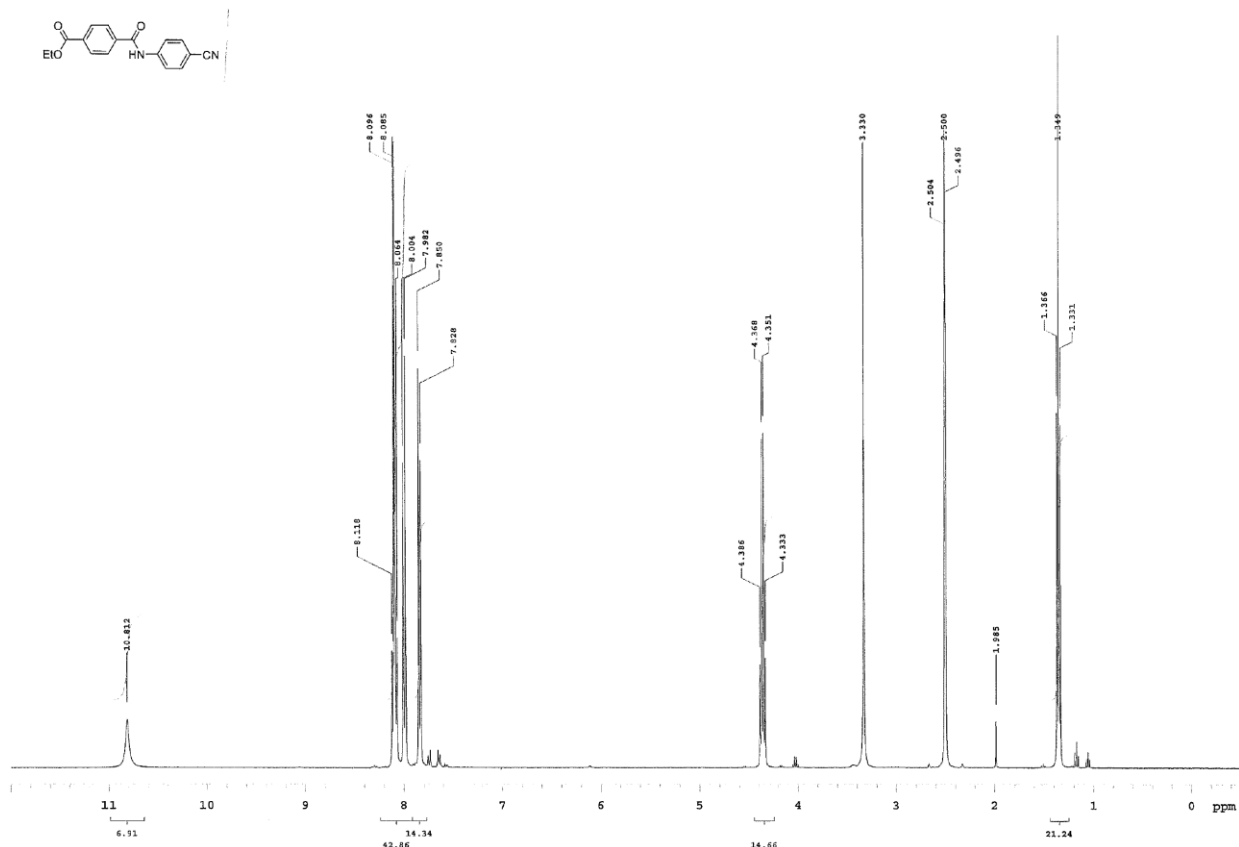


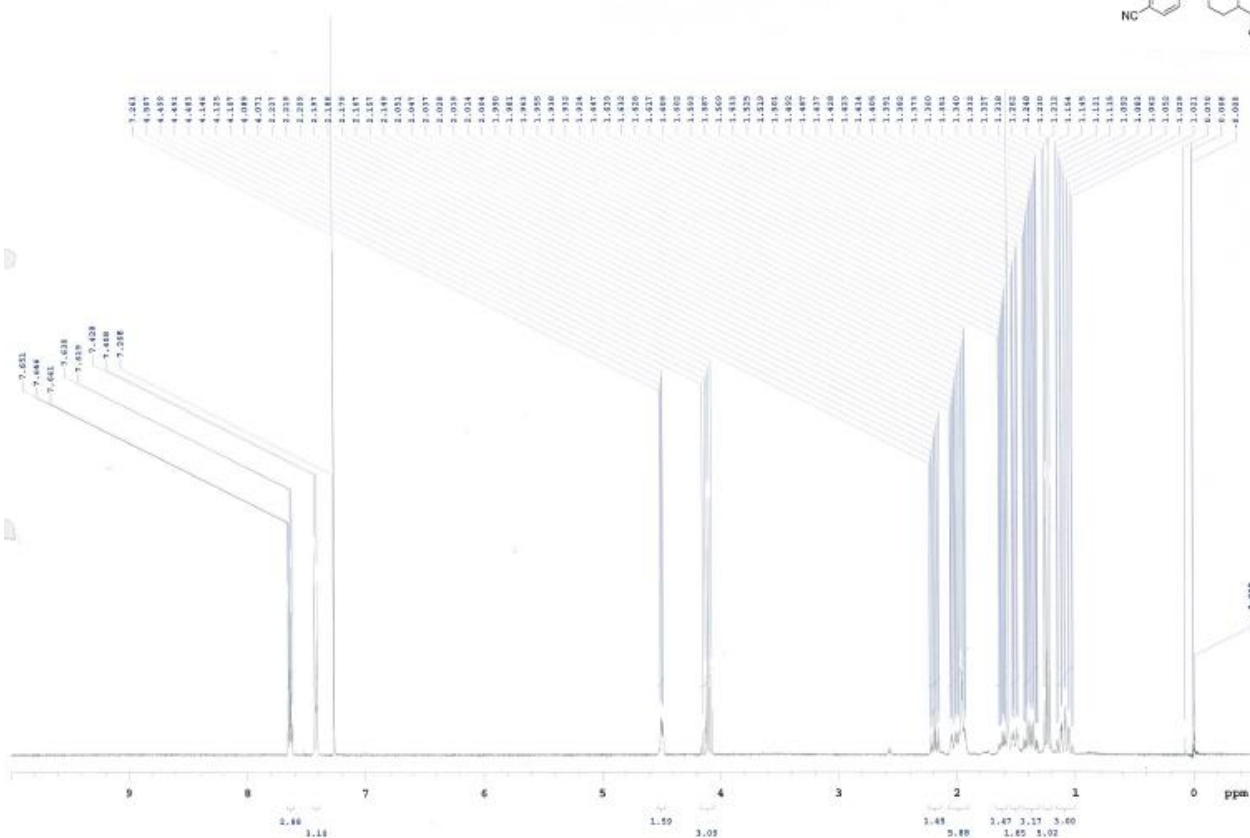
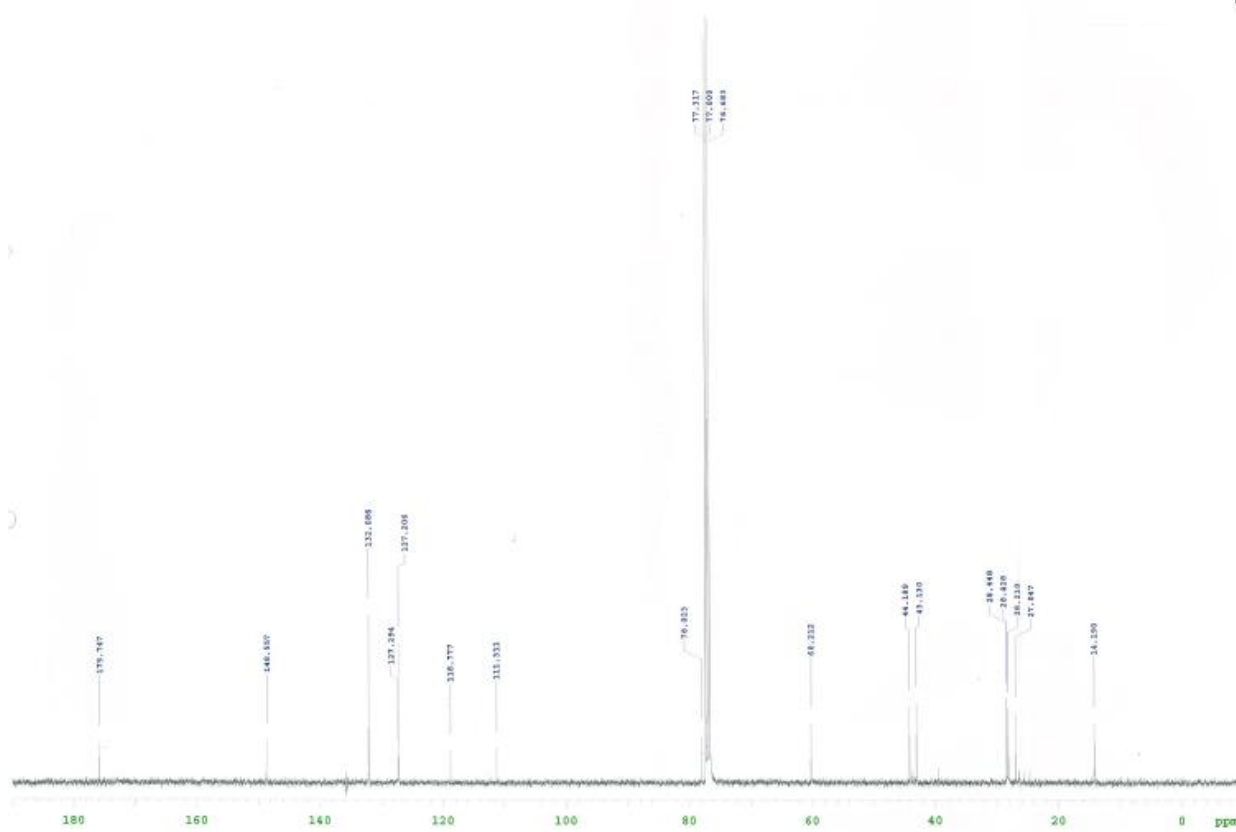
¹H NMR spectrum of 4-(ethoxycarbonyl)-N-[4-(methoxycarbonyl)phenyl]benzamide

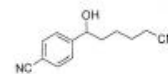


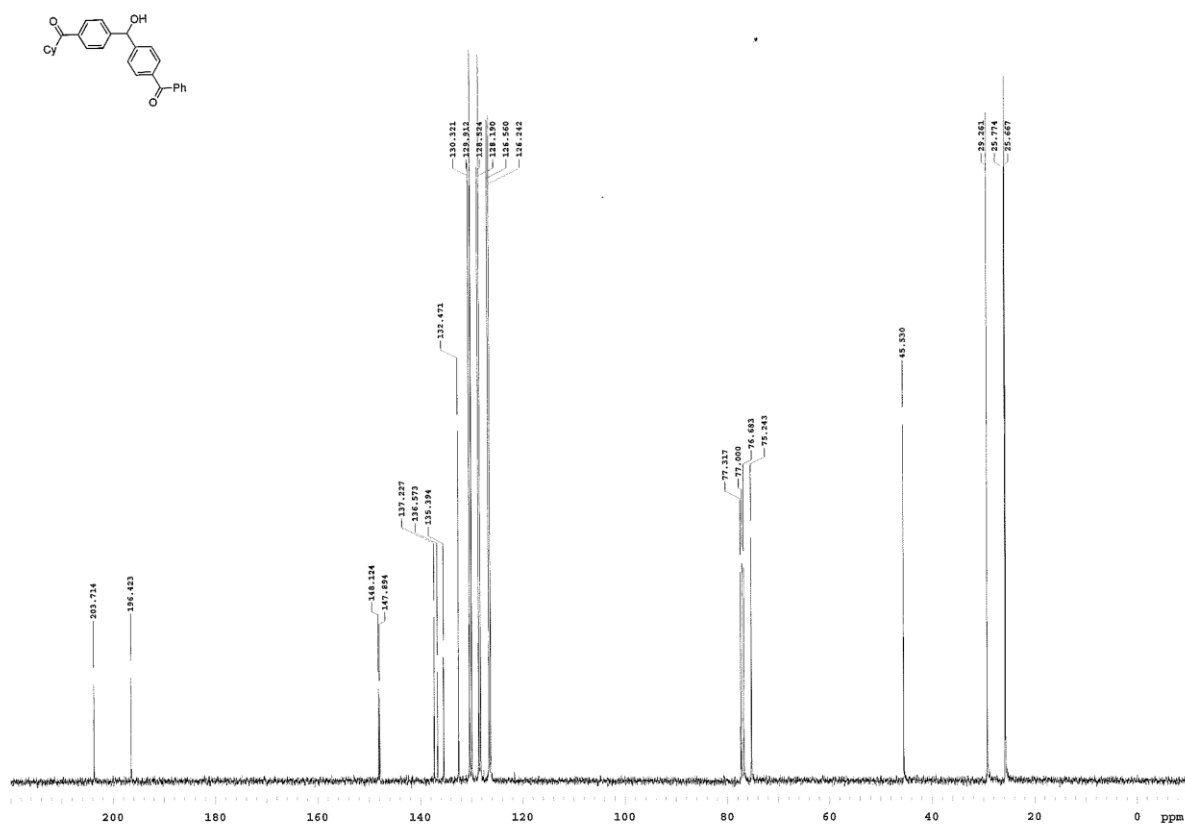
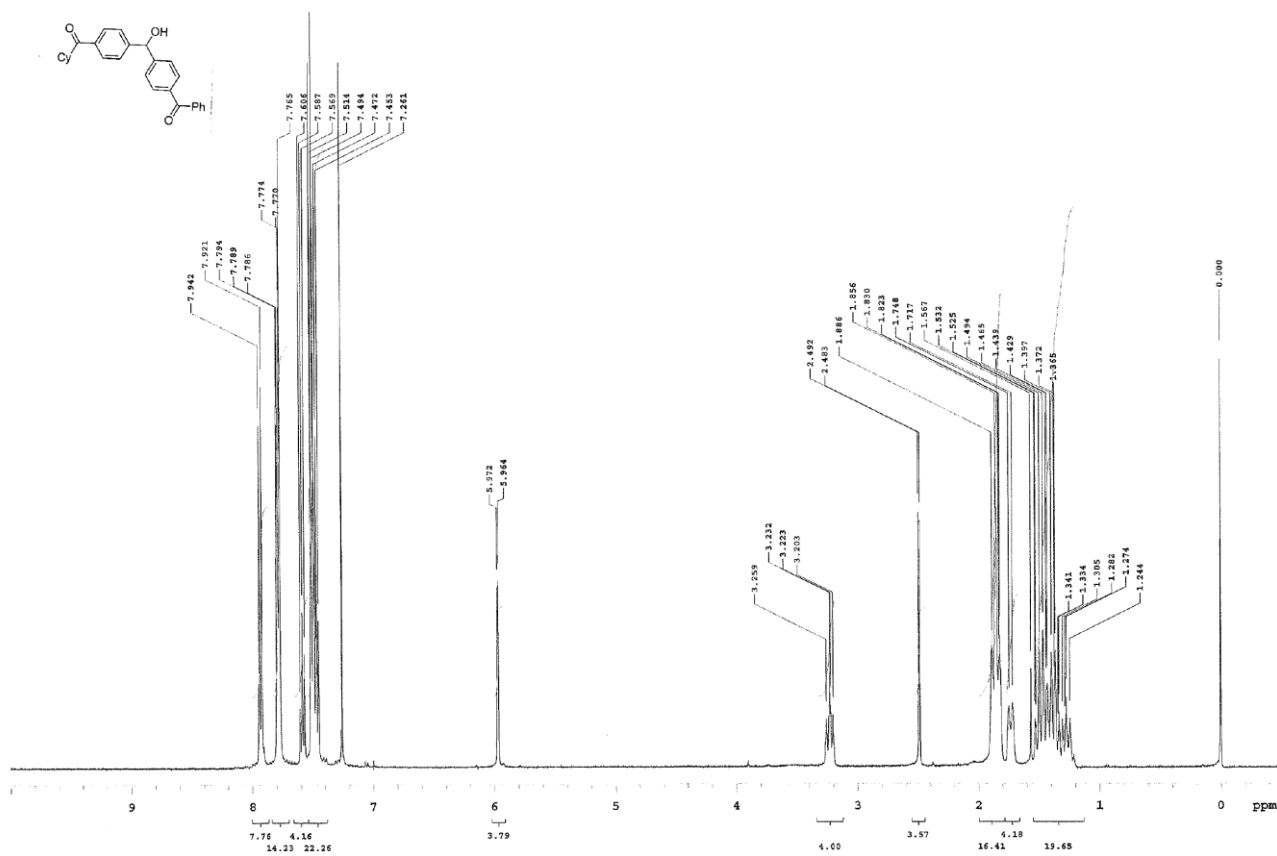
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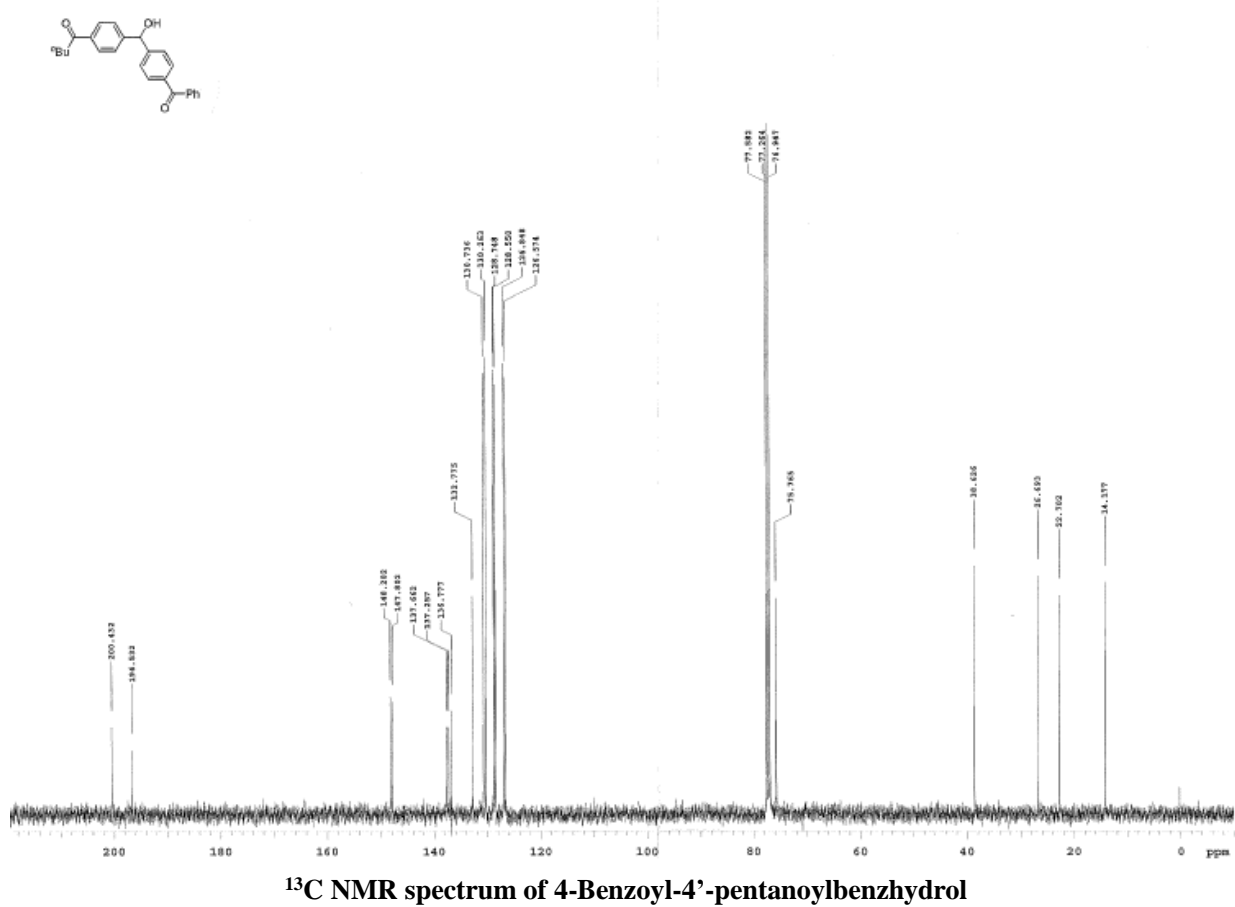
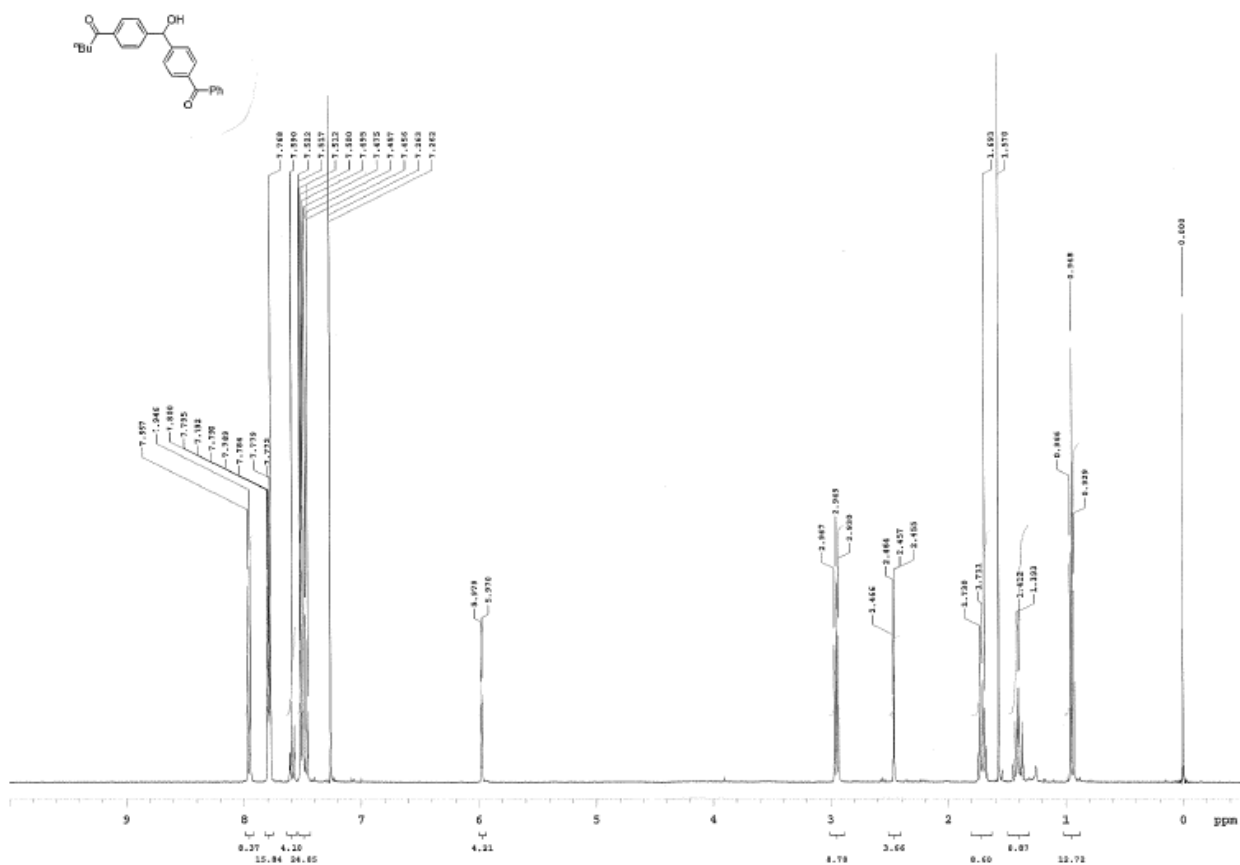


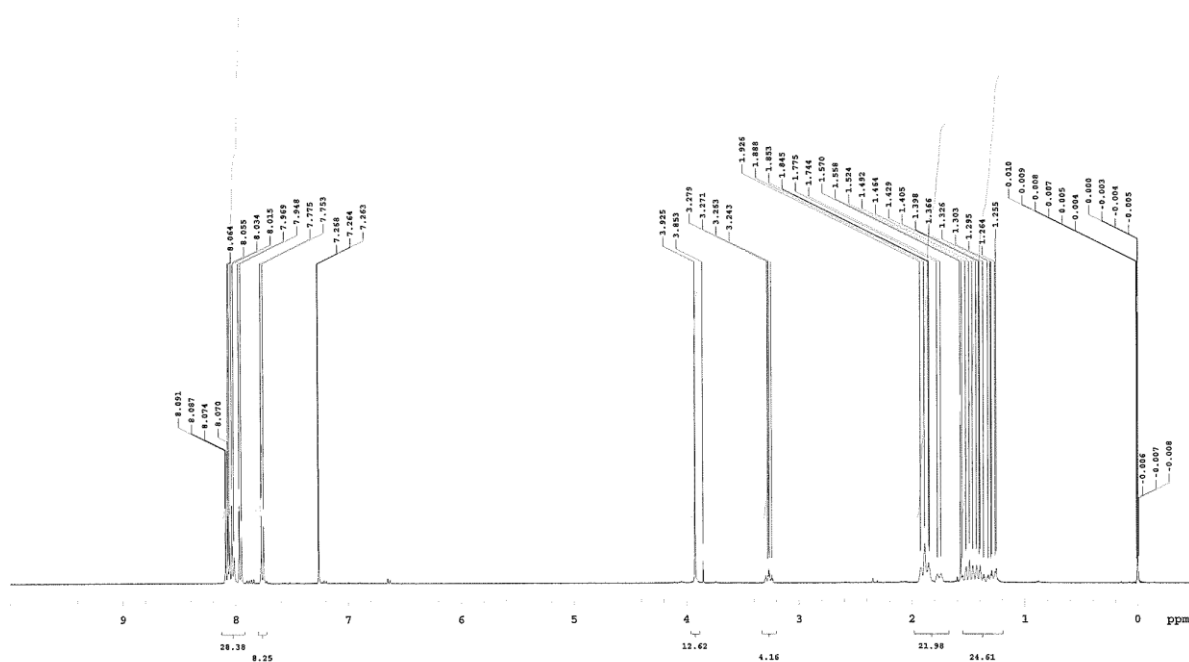
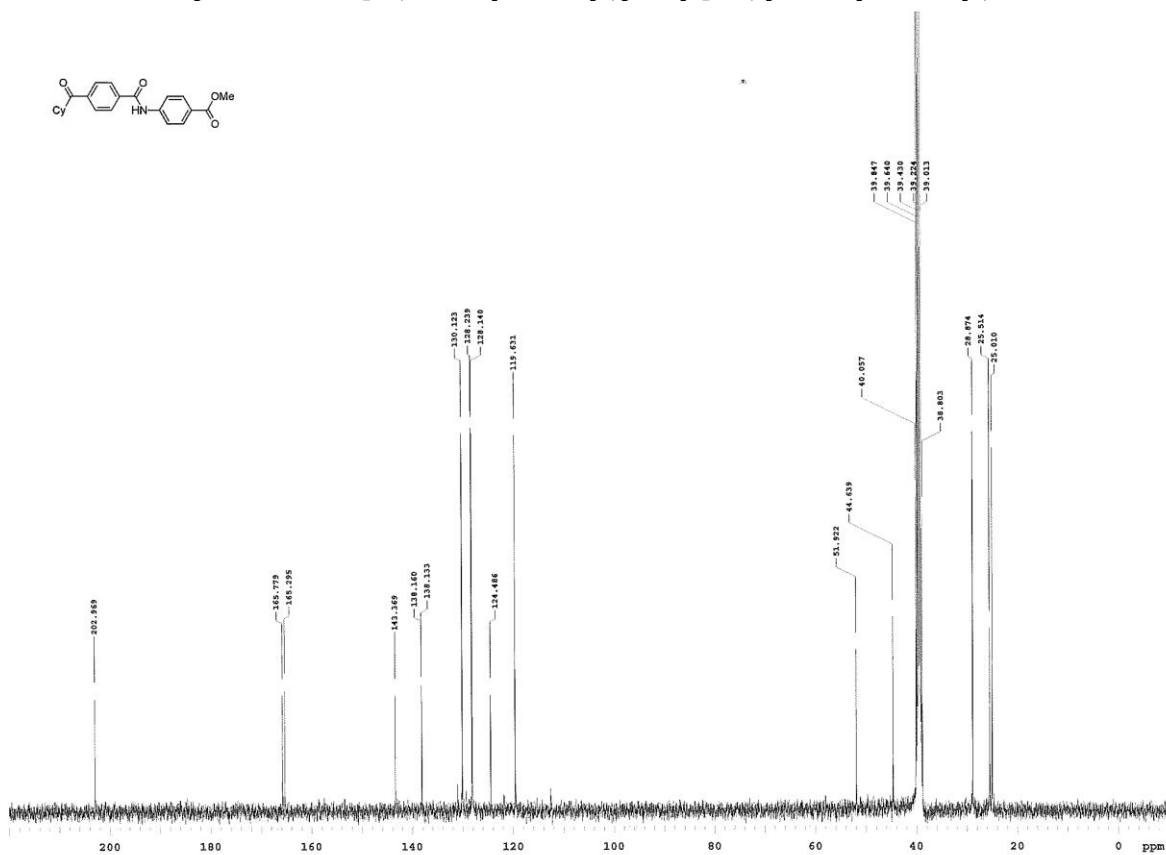


CCOC(=O)C1CCCCC1C(O)C2=CC=C(C#N)C=C2

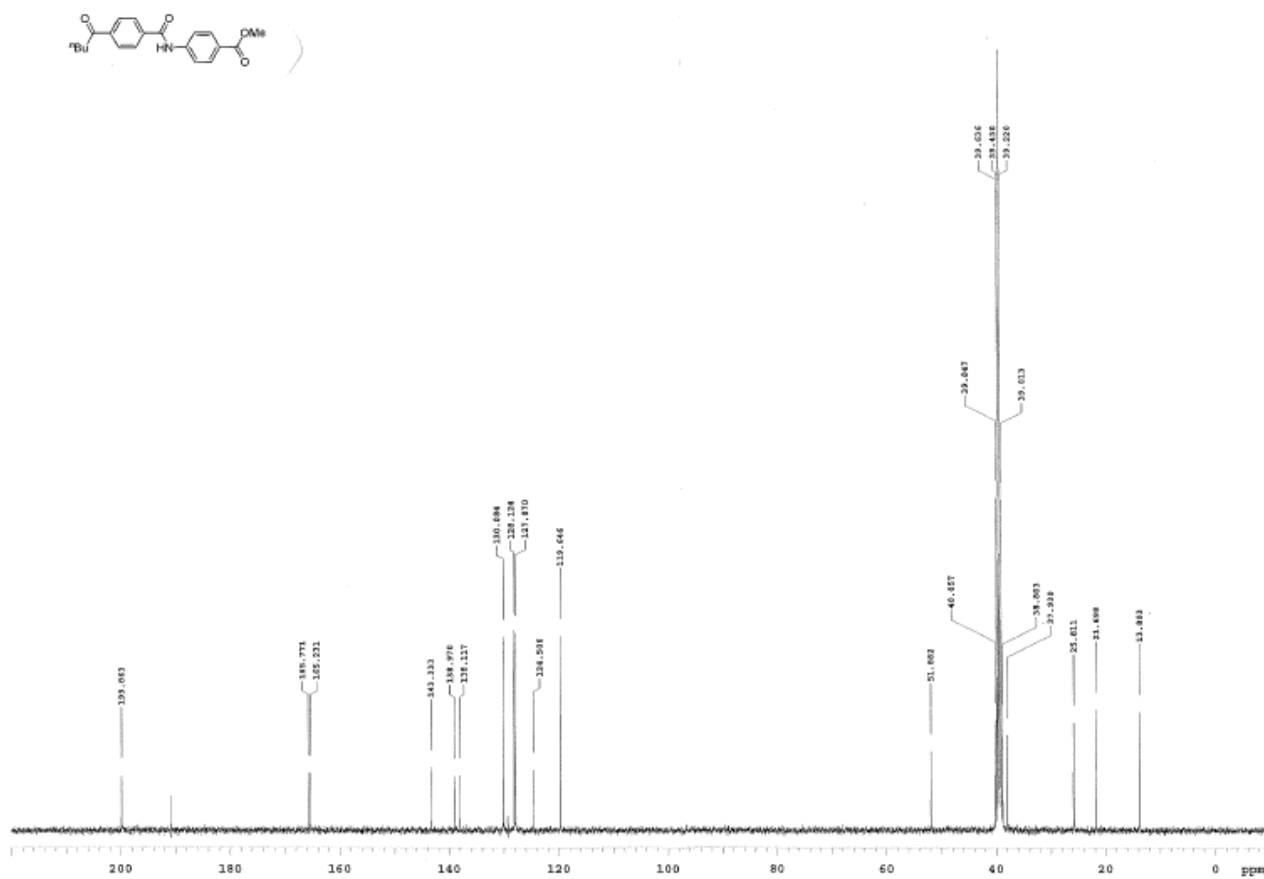
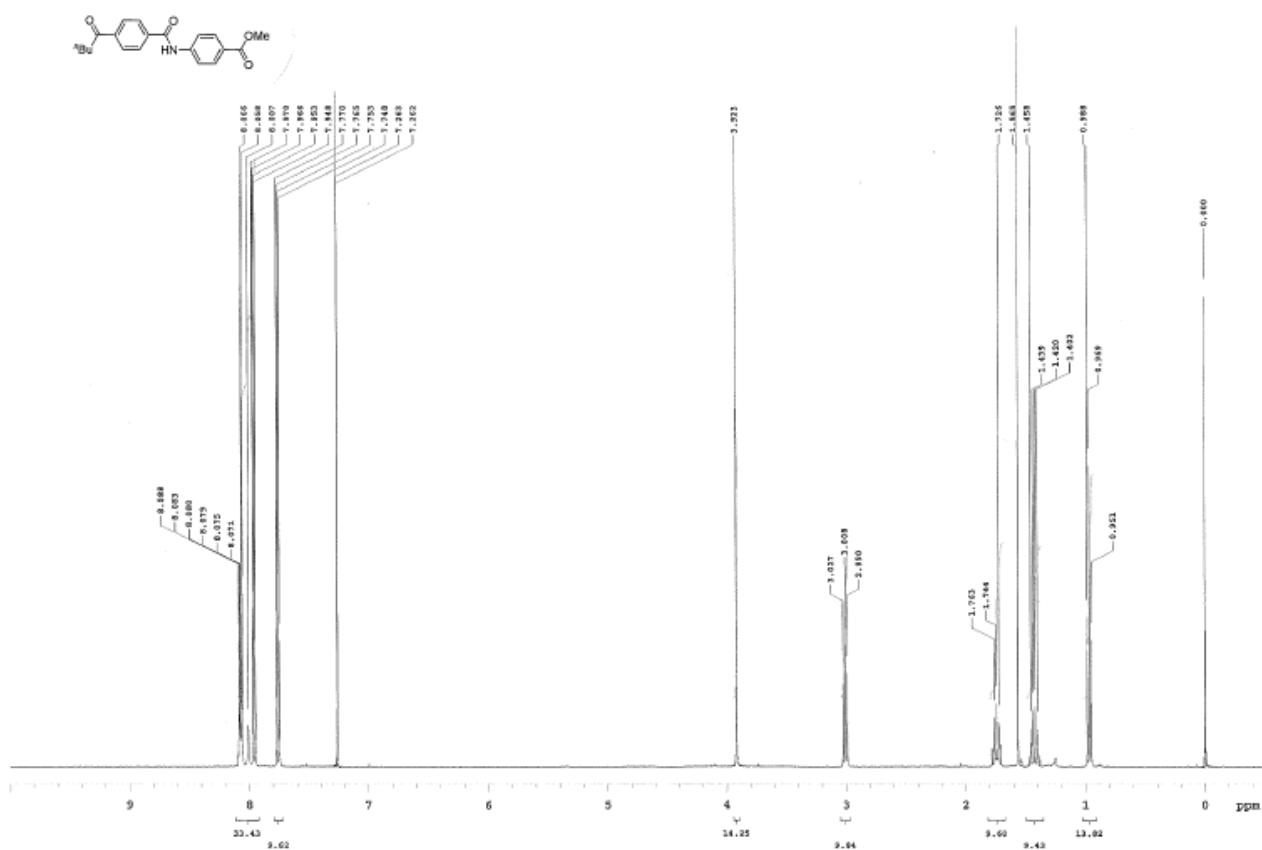
NC#Cc1ccc(cc1)C(O)CCCCCN

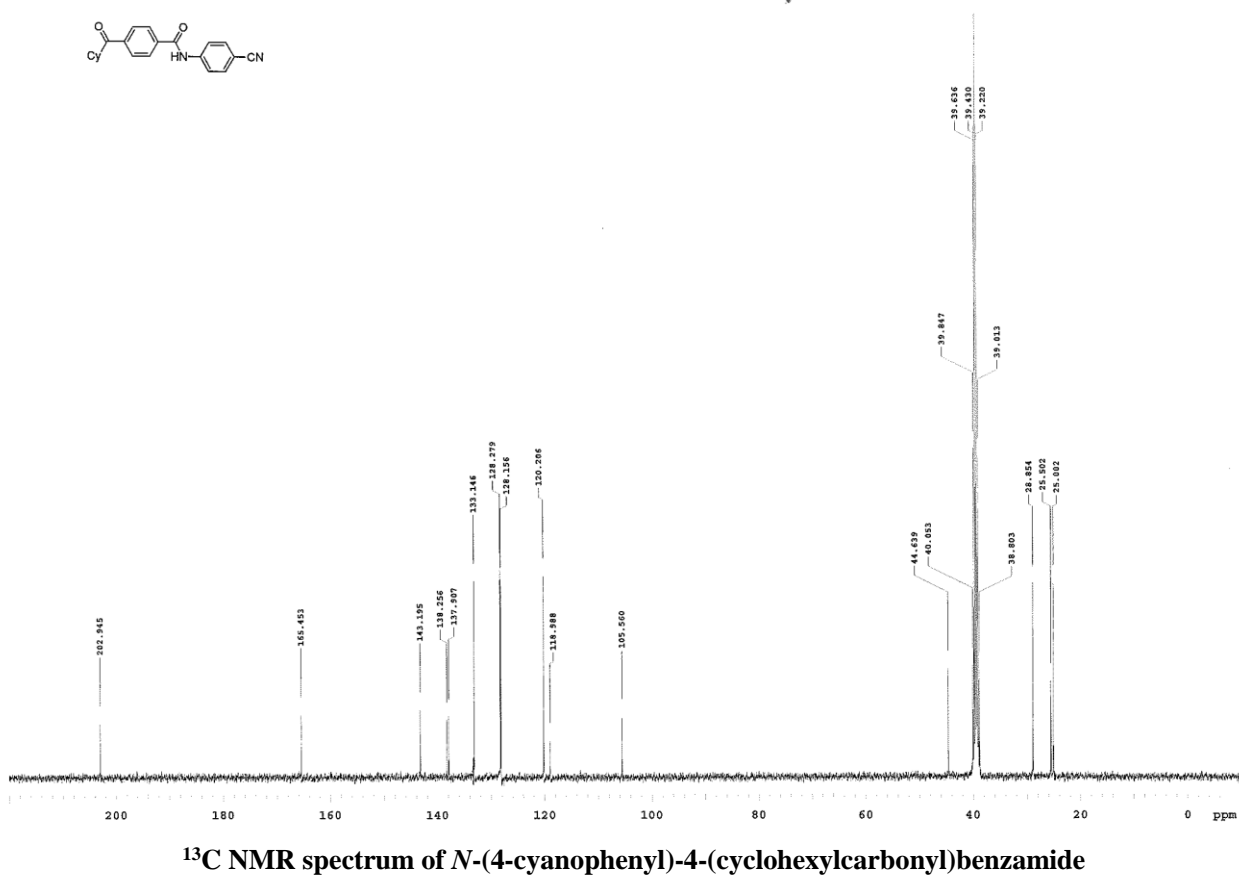
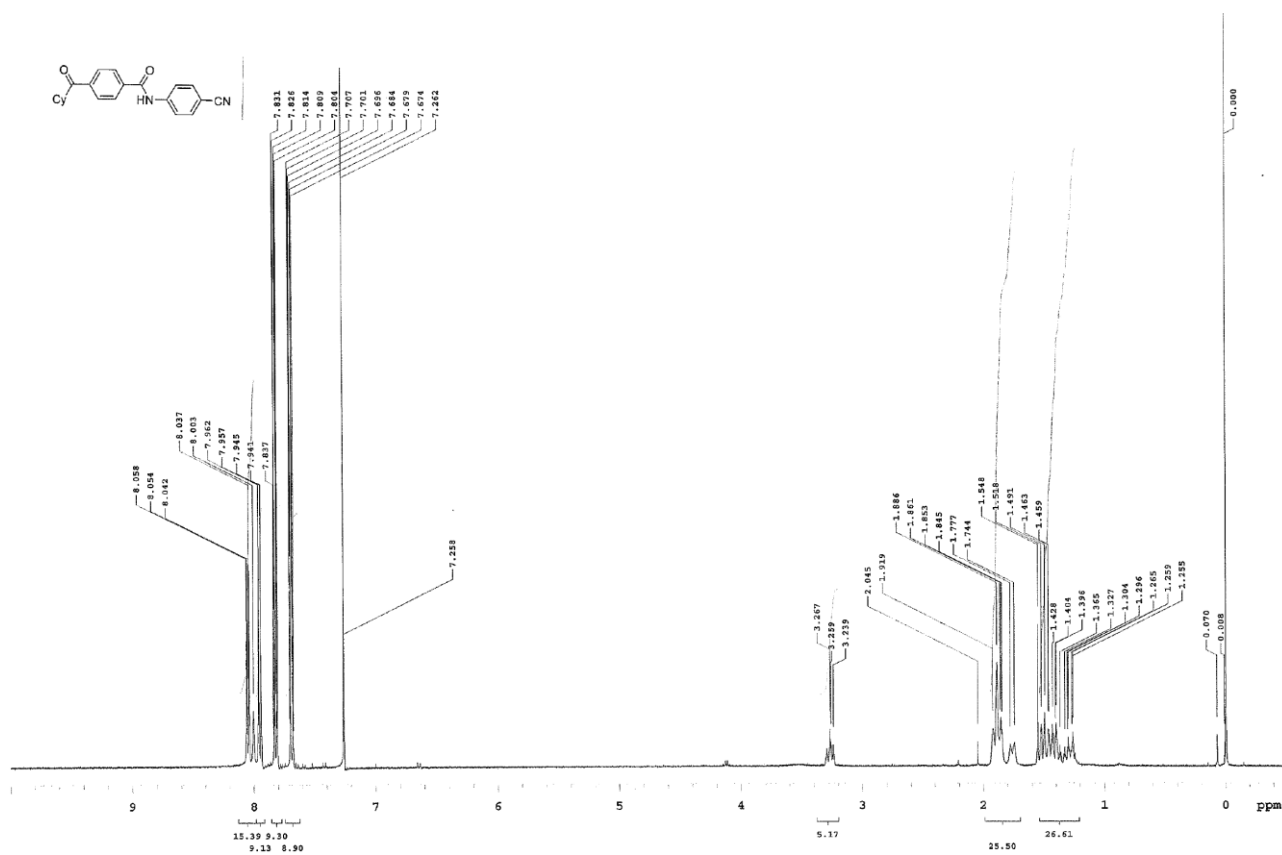


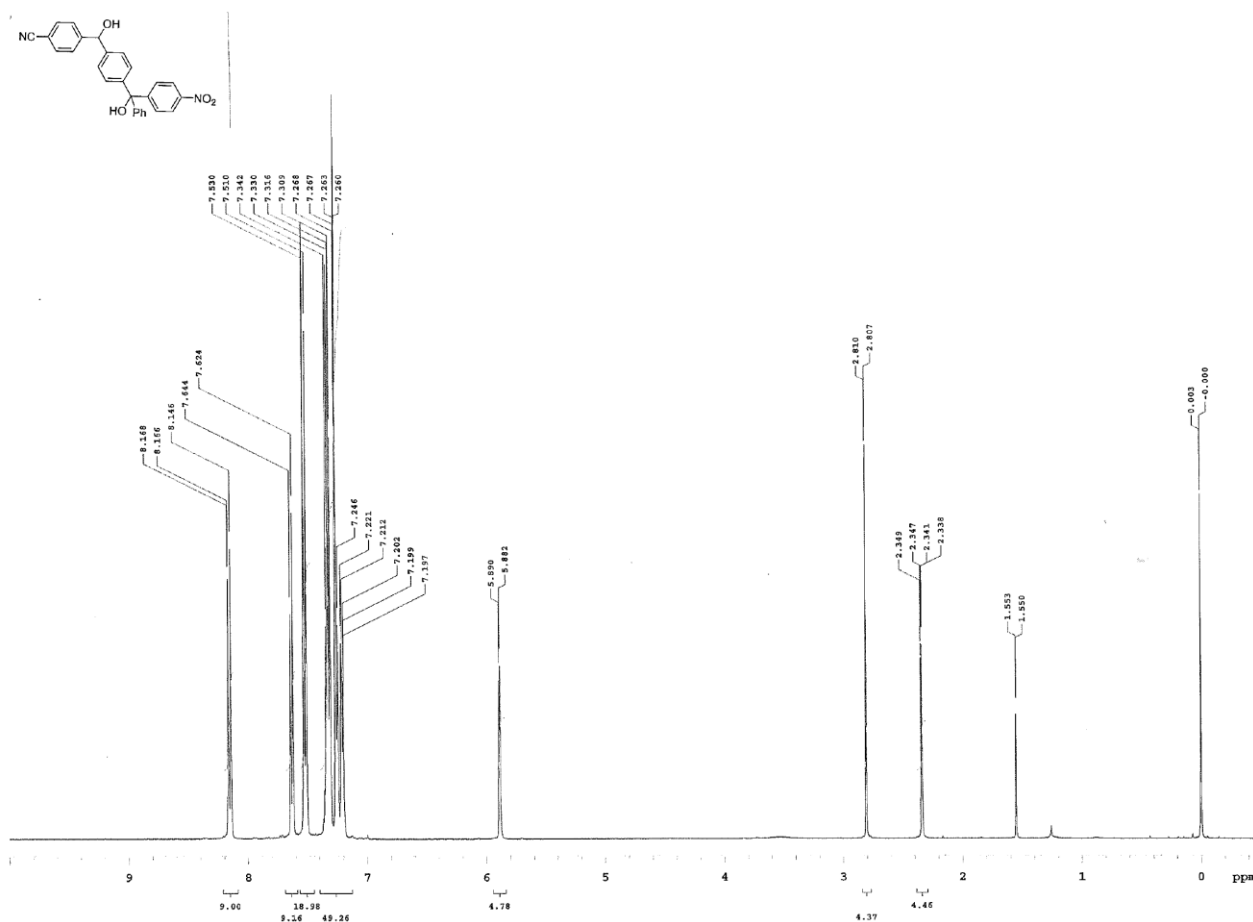


COC(=O)c1ccc(NC(=O)c2ccc(C(=O)C#N)cc2)cc1

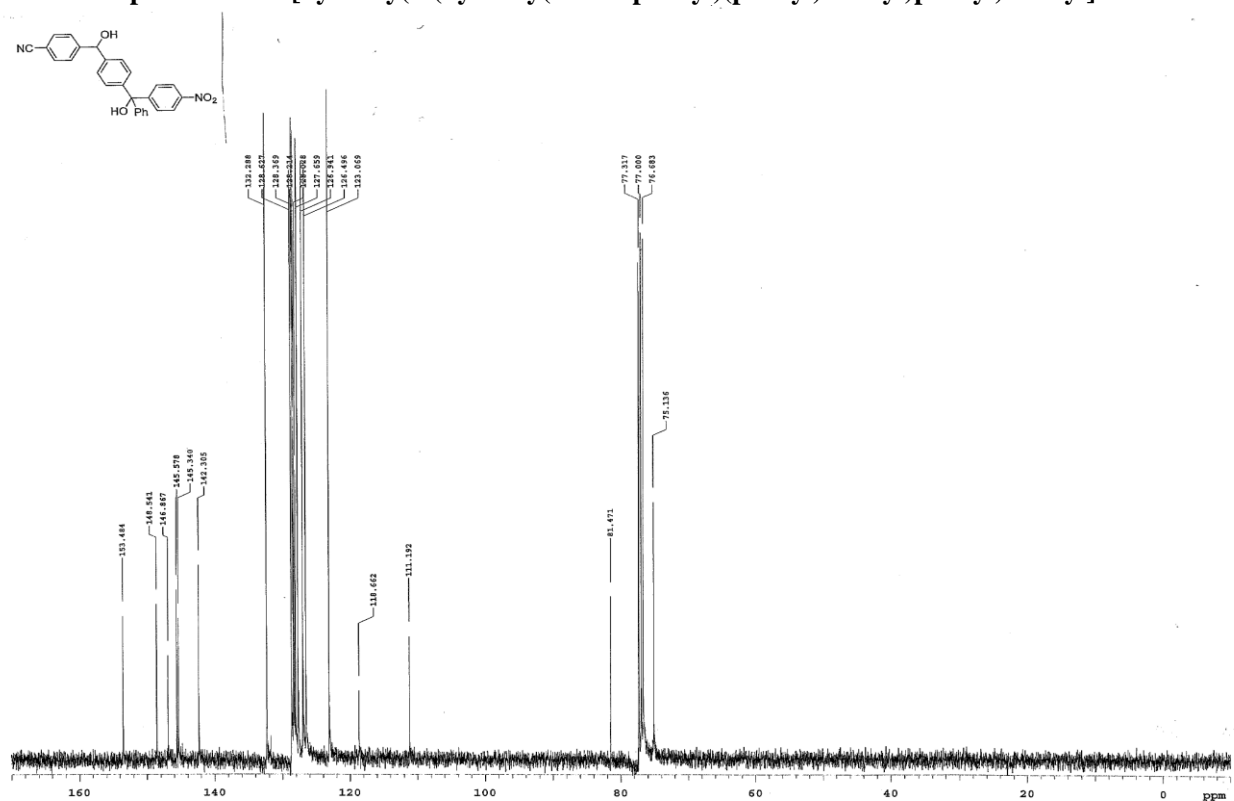
¹³C NMR spectrum of *N*-[4-(methoxycarbonyl)phenyl]-4-(cyclohexylcarbonyl)benzamide







¹H NMR spectrum of 4-[hydroxy(4-(hydroxy(4-nitrophenyl)(phenyl)methyl)phenyl)methyl]benzonitrile



¹³C NMR spectrum of 4-[hydroxy(4-(hydroxy(4-nitrophenyl)(phenyl)methyl)phenyl)methyl]benzonitrile

