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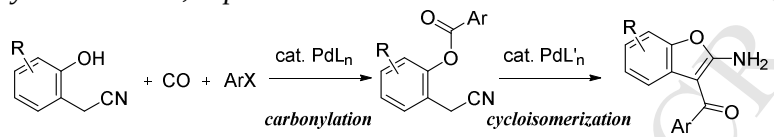

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Palladium-catalyzed three-component coupling reactions of 2-(cyanomethyl)phenol, aryl halides, and carbon monoxide

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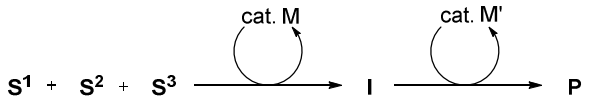
ABSTRACT

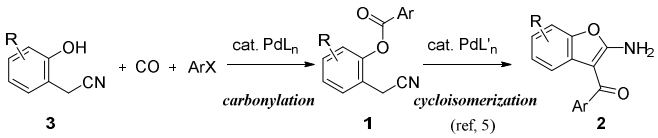
Three-component coupling reactions of 2-(cyanomethyl)phenol, aryl halides, and carbon monoxide (CO) in orthogonal–tandem catalysis were investigated. In the reactions, 2-(cyanomethyl)phenyl esters, which are produced through $Pd(PPh_3)_4$-catalyzed alkoxycarbonylation of aryl halides with 2-(cyanomethyl)phenol, undergo cycloisomerization in situ catalyzed by $Pd(PCy_3)_2$ as a co-catalyst to give 3-acyl-2-aminobenzofurans. Palladium species with homoleptic tertiary phosphines, such as $Pd(PPh_3)_4$ and $Pd(PCy_3)_2$, can catalyze the mechanistically distinct reactions in an orthogonal–tandem manner without interference. By switching the base used in this reaction, 3-acyl-2-(*N*-acylamino)benzofurans were obtained as major products instead of 3-acyl-2-aminobenzofurans. Given that 2-(cyanomethyl)phenols can be synthesized from commercially available salicylic acid derivatives in two steps, the present method thus provides facile access to synthetically useful 3-acyl-2-aminobenzofurans.

1. Introduction

Cascade and tandem reactions provide efficient access to structurally complex molecules from simple and readily available starting materials.[1] Almost all such reactions involve both inter- and intramolecular multibond-forming processes and they are usually straightforward to perform. Ideally, these approaches can minimize the amount of reagent, cost, byproduct formation, time, and complexity of separation processes required for a desired transformation. The development of step-economic processes through the use of tandem reactions involving different types of reactions promoted by more than two catalysts is a challenging subject.[2] In this context, we have developed a number of transition metal-catalyzed cascade reactions.[3,4] We have recently reported the one-pot synthesis of hetero α,α'-dimers of heterocycles involving the Sonogashira reaction of acyclic coupling partners and subsequent cycloisomerization reactions catalyzed by Pd and Cu species.[3] These examples represent a strategy that has been classified as orthogonal–tandem catalysis (Scheme 1).[2d] We have also developed palladium-catalyzed cycloisomerization reactions based on intramolecular oxypalladation to a C–N triple bond of 2-(cyanomethyl)phenyl esters **1** leading to 3-acyl-2-aminobenzofurans **2**[5] (the downstream reaction presented in Scheme 2).[6] In the course of our studies, we envisioned that the carbonylation reaction of aryl halides with 2-cyanomethylphenols **3** (the upstream reaction presented in Scheme 2) could be combined with such



Scheme 1. Orthogonal-tandem catalysis (M = M' or M ≠ M').



Scheme 2. Palladium-catalyzed cycloisomerization (the downstream reaction) and carbonylation (the upstream reaction).

cycloisomerization reactions for the short step synthesis of 3-acyl-2-aminobenzofurans **2**. Ideally, the mechanistically discrete reaction cascade could be catalyzed by a single catalyst; however, when more than two catalysts are required, it is essential for efficient operation that there is no interference between catalysts. Here, we wish to report an efficient and

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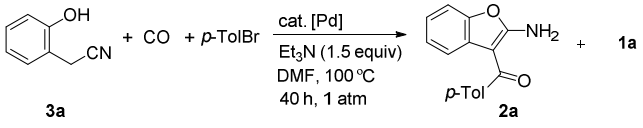
straightforward synthesis of 3-acyl-2-aminobenzofurans **2** by employing three-component coupling reactions of 2-(cyanomethyl)phenol derivatives **3**, aryl halides, and CO, catalyzed by two homoleptic tertiary phosphine-ligated palladium(0) species (Scheme 2). Because 3-acyl-2-aminobenzofurans have both an amino and a carbonyl group, they are useful building blocks for the synthesis of a range of benzofuran-fused heterocycles.

2. Results and discussion

Initially, the palladium-catalyzed, three-component coupling reaction of 2-(cyanomethyl)phenol **3a** and 4-bromotoluene (1.5 equiv) in the presence of Et_3N (1.5 equiv) in DMF at 100 °C under a CO atmosphere (1 atm) for 40 h was examined.[7] Although $Pd(PCy_3)_2$ was effective for the cycloisomerization of 2-(cyanomethyl)phenyl ester **1a** into 3-acyl-2-aminobenzofuran **2a**,[5] it was ineffective in the three-component coupling reaction even in the presence of $Zn(OAc)_2$ (10 mol%) as an additive (Scheme 3). The use of $Pd(PPh_3)_4$ (5 mol%) led to the selective formation of **1a** (94%) with none of **2a**.[8] However, when the reaction was carried out in the presence of both $Pd(PCy_3)_2$ and $Pd(PPh_3)_4$ (5 mol% each), **2a** was obtained in 28% yield along with **1a** (42% yield). Having found that two types of palladium catalysts are effective for the three-component synthesis of 3-acyl-2-aminobenzofuran, we then optimized the reaction conditions by using 4-bromotoluene with **3a** and CO. Gratifyingly, we found that the three-component coupling reaction led to the formation of **2a** in 52% yield in the presence of palladium catalysts, $Pd(PPh_3)_4$ (2 mol%) and $Pd(PCy_3)_2$ (8 mol%).[9]



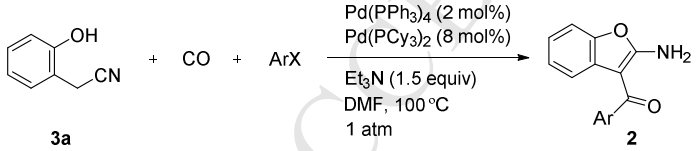
$Pd(PCy_3)_2$ (10 mol%), $Zn(OAc)_2$ (10 mol%)	0%	0%
$Pd(PPh_3)_4$ (5 mol%)	0%	94%
$Pd(PPh_3)_4$ (5 mol%), $Pd(PCy_3)_2$ (5 mol%)	28%	42%
$Pd(PPh_3)_4$ (2 mol%), $Pd(PCy_3)_2$ (8 mol%)	52%	12%

Scheme 3. Palladium-catalyzed three-component coupling.

Under the optimized reaction conditions [aryl bromide (1.5 equiv), $Pd(PPh_3)_4$ (2 mol %), $Pd(PCy_3)_2$ (8 mol %), and Et_3N (1.5 equiv) in DMF at 100 °C under 1 atm CO], the substrate scope of the reaction was examined by using a range of aryl halides. The results are summarized in Table 1. The reactions with aryl bromides having an electron-withdrawing group, such as a trifluoromethyl or a chloro group at the *para*-position, afforded the corresponding 3-acyl-2-aminobenzofurans **2b** and **2c** in 84 and 74% yields, respectively (entries 1 and 2). The presence of a substituent such as a chloro group at an *ortho*-position was also tolerated in the reaction (entry 3). The three-component cascade reaction was also applicable to aryl halides having either moderately electron-withdrawing or electron-donating substituents, although extended reaction times were required for these reactions to reach completion (entries 4–6). The reaction using 4-bromoanisole was sluggish, giving a small amount of 3-acyl-2-aminobenzofuran **2h**, whereas the reaction using 4-iodoanisole afforded **2h** in 42% yield (entries 7 and 8).[10]

The substrate scope of the reaction with respect to variation of 2-(cyanomethyl)phenols was also examined. As shown in Table 2, 2-(cyanomethyl)phenols **3** possessing a range of substituents participated in the cascade reactions to give the corresponding 3-acyl-2-aminobenzofuran derivatives **2i–l** in moderate to good yield (entries 1–4). It should be noted that a remote ester group of **2m** remained intact under the reaction conditions (entry 5). Silyloxy and methoxymethyloxy groups were compatible with the reaction conditions, affording **2n** and **2o** in 70 and 72% yields, respectively (entries 6 and 7).[11]

Table 1. Pd-catalyzed three-component coupling reactions using aryl halides, **3a**, and CO leading to 3-acyl-2-aminobenzofurans **2**[a]

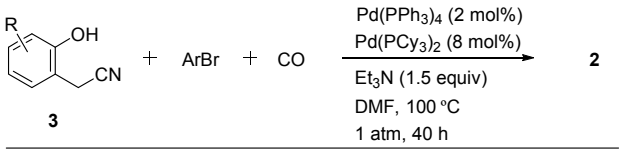


Entry	Ar	X	Time	Product	Yield[b]
1	4-$CF_3C_6H_4$	Br	20 h	**2b**	84%
2	4-ClC_6H_4	Br	30 h	**2c**	74%
3	2-ClC_6H_4	Br	30 h	**2d**	71%
4	4-FC_6H_4	Br	40 h	**2e**	60%
5	2-Naph	Br	40 h	**2f**	71%
6	Ph	Br	40 h	**2g**	57%
7	4-$MeOC_6H_4$	Br	40 h	**2h**	7%
8	4-$MeOC_6H_4$	I	40 h	**2h**	42%

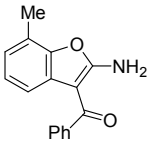
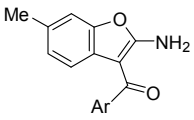
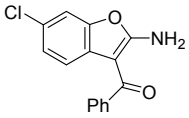
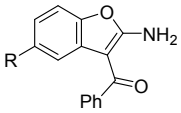
[a]Reaction conditions: **3a** (0.30 mmol), ArX (0.45 mmol), Et_3N (0.45 mmol), $Pd(PPh_3)_4$ (0.006 mmol), and $Pd(PCy_3)_2$ (0.024 mmol) in DMF (1.2 mL) under CO (1 atm).

[b]Isolated yield

Table 2. Pd-catalyzed three-component coupling reactions leading to 3-acyl-2-aminobenzofurans **2**[a]



3

Entry	Product (**2**)		Yield[b]
1		**2i**	55%
2		**2j** (Ar = 4-$CF_3C_6H_4$)	86%
3		**2k** (Ar = Ph)	71%
4		**2l**	66%
5		**2m** (R = OBz)	54%
6		**2n** (R = OTBDMS)	70%
7		**2o** (OMOM)	72%

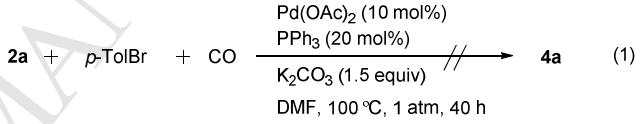
[a]Reaction conditions: **3** (0.30 mmol), ArBr (0.45 mmol), Et_3N (0.45 mmol), $Pd(PPh_3)_4$ (0.006 mmol), and $Pd(PCy_3)_2$ (0.024 mmol) in DMF (1.2 mL) under CO (1 atm).

[b]Isolated yields.

The most plausible catalytic cycle leading to 3-acyl-2-aminobenzofurans **2** is shown in Figure 1. The $Pd(PPh_3)_4$-catalyzed alkoxycarbonylation of an aryl halide, CO, and 2-cyanomethylphenol **3a** produces 2-(cyanomethyl)phenyl ester **1** (cycle A).[7] The latter then participates in a second catalytic cycle, and is converted into 3-acyl-2-aminobenzofuran **2** through cycloisomerization catalyzed by $Pd(PCy_3)_2$ (cycle B).[5] We propose that the mechanistically distinct cascade reactions can be catalyzed by two different types of catalyst with homoleptic tertiary phosphines.[12]

When the reaction was carried out by using K_2CO_3 or NaOEt as a base and $Pd(PPh_3)_4$ as a catalyst, 3-acyl-2-(*N*-acylamino)benzofuran **4a** was obtained in 9 and 4% yields, respectively, together with ester **1a**. The yield of **4a** increased to 73%, when $Pd(OAc)_2$, PPh_3 (Pd/P ratio 1:2), 4-bromotoluene (3 equiv), and K_2CO_3 were used, as shown in Table 3. Under these conditions, a variety of aryl halides afforded the corresponding 3-acyl-2-(*N*-acylamino)benzofurans **4b**–**g** in moderate to good yields (entries 2–7). In none of the cases was 3-acyl-2-aminobenzofuran **2** obtained. These results show that the reactions leading to **2** or **4** proceed through different pathways and that the course of the reaction is determined by the nature of the base used.

To gain insight into the reaction mechanism, we carried out the reaction of **2a** with 4-bromotoluene in the presence of a palladium catalyst and K_2CO_3 under CO. However, **4a** was not obtained even in the presence of an excess of 4-bromotoluene (eq 1). This result clearly shows that the conversion of **3a** into **4a** did not proceed via **2a**.



Based on these results, we propose a reaction mechanism leading to **4** as shown in Scheme 4. The reaction proceeds through acylation of **3a** followed by a 1,4-benzoyl shift to afford intermediate **X**. Direct attack of a phenolate anion of **X** to the nitrile moiety followed by a second acylation of the resulting iminyl anion **Y** gives cyclic intermediate **Z**, which leads to the formation of the 3-acyl-2-(*N*-acylamino)benzofuran **4** by prototropy.[13]

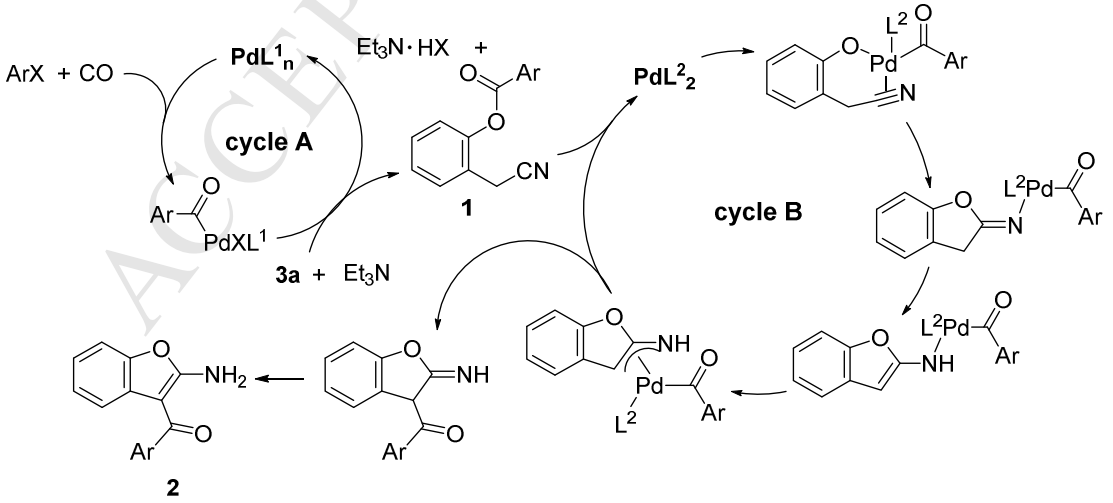
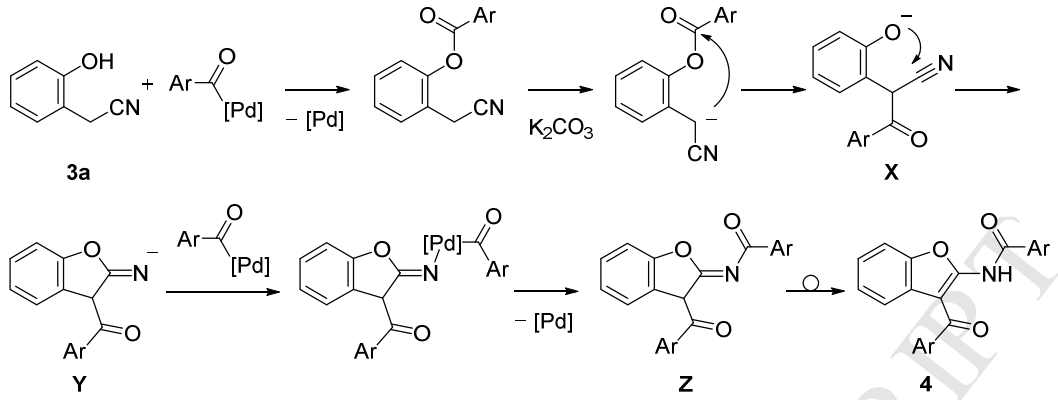
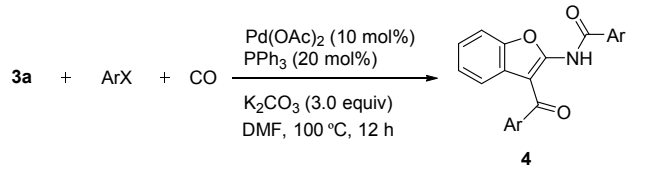


Figure 1. Plausible mechanism of palladium-catalyzed three component coupling reaction ($L^1 = PPh_3$, $L^2 = PCy_3$).



Scheme 4. Plausible mechanism for the formation of 3-acyl-2-(*N*-acylamino)benzofurans **4** in the presence of K_2CO_3.

Table 3. Pd-catalyzed three-component coupling reactions in the presence of K_2CO_3 leading to 3-acyl-2-(*N*-acylamino)-benzofurans **4**[a]

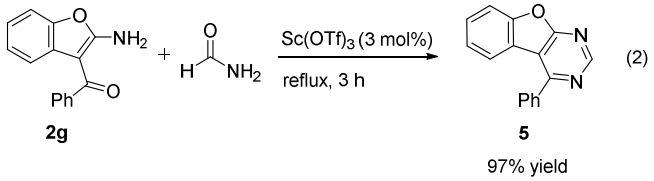


Entry	Ar	X	Product	Yield[b]
1	4-MeC_6H_4	Br	**4a**	73%
2	4-$CF_3C_6H_4$	Br	**4b**	91%
3	4-ClC_6H_4	Br	**4c**	63%
4	Ph	Br	**4d**	82%
5	2-Naph	Br	**4e**	88%
6	4-$MeOC_6H_4$	I	**4f**	41%
7	2-MeC_6H_4	I	**4g**	68%

[a]Reaction conditions: **3a** (0.30 mmol), ArX (0.90 mmol), K_2CO_3 (0.90 mmol), $Pd(OAc)_2$ (0.03 mmol), and PPh_3 (0.06 mmol) in DMF (1.2 mL) under CO (1 atm).

[b]Isolated yields.

Benzofurans obtained from the present palladium-catalyzed, three-component reactions possess both an amino and a carbonyl group; therefore, they can serve as key intermediates for the synthesis of benzofuran-fused, nitrogen-containing heterocycles.[14] For example, 3-acyl-2-aminobenzofuran **2g** was converted into the corresponding benzofuro[2,3-*d*]pyrimidine derivative **5** in 97% yield by simply heating with formamide in the presence of 3 mol% $Sc(OTf)_3$ (eq 2).



(2)

3. Conclusion

We have demonstrated a palladium-catalyzed, three-component cascade reaction of 2-(cyanomethyl)phenols, aryl halides, and CO, leading to 3-acyl-2-aminobenzofuran derivatives. A diverse array of functional groups is tolerated in the orthogonal–tandem catalysis. The present transformation is composed of two types of mechanistically discrete reactions catalyzed by independent palladium complexes: (i) $Pd(PPh_3)_4$-catalyzed alkoxycarbonylation of aryl halides with 2-(cyanomethyl)phenols, and (ii) $Pd(PCy_3)_2$-catalyzed cycloisomerization leading to 3-acyl-2-aminobenzofurans. In the synthesis of 3-acyl-2-aminobenzofuran and 3-acyl-2-(*N*-acylamino)benzofuran derivatives, 2-(cyanomethyl)phenol substrates serve as scaffolds for the carbonylative carbon–carbon and carbon–nitrogen bond-forming reactions. The present method using 2-(cyanomethyl)phenols, which can be easily prepared from commercially available salicylic acids, thus provides facile access to 3-acyl-2-aminobenzofuran derivatives.

4. Experimental section

4.1. General Information

Unless otherwise noted, chemicals obtained from commercial suppliers were used without further purification. CO gas (purity 99.97%) was purchased from Sumitomo Seika Co. Solvents were dried by the usual methods and distilled before use. Unless otherwise noted, reactions were carried out under nitrogen atmosphere. NMR spectra were measured for solutions in $CDCl_3$ or acetone-d_6 with tetramethylsilane as an internal standard (^1H and ^{13}C): the following abbreviations are used; br s: broad singlet, s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet. IR spectra were recorded with an FT-IR spectrometer. Melting points (mp) are uncorrected. Element analyses were performed at Microanalytical Center of Kyoto University. High-resolution mass spectra (HRMS) were measured with JEOL JMX-SX 102A spectrometer.

4.2. General procedure of palladium-catalyzed three-component coupling reactions leading to 3-acyl-2-aminobenzofurans.

A flame dried Schlenk flask was charged with $Pd(PCy_3)_2$ (16.1 mg, 0.024 mmol), $Pd(PPh_3)_4$ (6.9 mg, 0.006 mmol), 2-(cyanomethyl)phenols **3a** (0.30 mmol), aryl halides (0.45 mmol), Et_3N (0.063 mL, 0.45 mmol), and DMF (1.2 mL). The flask was then flushed with CO, and the system was closed. After the reaction mixture was stirred at 100 °C for the time specified in Scheme 3 and Tables 1 and 2, it was diluted with Et_2O and filtered through a short silica gel pad. The filtrate was washed with brine, and the aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layer was dried over $MgSO_4$, and then filtered. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt (v/v = 7/1-2/1) as eluents to afford the corresponding 3-acyl-2-aminobenzofurans **2**.

*4.2.1. 2-Amino-3-benzoyl-7-methylbenzo[b]furan (**2i**)*: A yellow solid; mp 153.8-154.7 °C. IR (KBr): 749, 772, 849, 920, 1062, 1170, 1281, 1340, 1477, 1645 (C=O), 3198, 3366 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ2.40 (s, 3H), 6.70 (d, *J* = 7.3 Hz, 1H), 6.84 (d, *J* = 6.8 Hz, 1H), 6.89 (t, *J* = 7.3 Hz, 1H), 7.11 (br s, 2H), 7.44-7.54 (m, 3H), 7.70 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ14.7, 94.7, 116.5, 120.1, 123.3, 123.6, 125.8, 127.4, 128.3, 130.8, 140.9, 147.9, 166.4, 190.9. Anal. calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21. Found: C, 76.38; H, 5.50.

*4.2.2. 2-Amino-6-methyl-3-(4'-trifluoromethylbenzoyl)benzo[b]-furan (**2j**)*: A yellow solid; mp 126.8-127.3 °C. IR (KBr): 782, 810, 859, 904, 980, 1018, 1067, 1109, 1125, 1173, 1250, 1323, 1475, 1589, 1656 (C=O), 3165, 3351 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ2.35 (s, 3H), 6.64 (d, *J* = 8.3 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 7.03 (s, 1H), 7.25 (br s, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ21.2, 94.2, 110.7, 118.2, 123.0, 123.8 (q, *J* = 271.9 Hz), 124.8, 125.4 (q, *J* = 3.3 Hz), 127.8, 132.4 (q, *J* = 32.2 Hz), 132.5, 144.1, 149.6, 166.9, 188.7. HRMS (FAB) calcd for $M+H^+$ of $C_{17}H_{12}F_3NO_2$ 320.0898, found 320.0891.

*4.2.3. 2-Amino3-benzoyl-6-chlorobenzo[b]furan (**2l**)*: A pale yellow solid; mp 121.3-122.5 °C. IR (KBr): 759, 799, 858, 920, 993, 1073, 1177, 1242, 1347, 1435, 1478, 1589, 1658 (C=O), 3110, 3325 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ6.84 (d, *J* = 2.0 Hz, 1H), 6.99 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.09 (br s, 2H), 7.13 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 7.3 Hz, 2H), 7.49-7.59 (m, 1H), 7.67 (d, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ94.0, 110.9, 118.8, 121.7, 127.3, 127.9, 128.5, 129.4, 131.3, 140.4, 147.5, 167.0, 190.7. Anal. calcd for $C_{15}H_{10}ClNO_2$: C, 66.31; H, 3.71. Found: C, 66.34; H, 3.53.

*4.2.4. 5-(2-Amino-3-benzoylbenzo[b]furyl) benzoate (**2m**)*: A yellow solid; mp 145.4-146.3 °C. IR (KBr): 757, 800, 873, 923, 1004, 1065 1165, 1266, 1450, 1479, 1593, 1656 (C=O), 1722 (C=O), 3096, 3329 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ6.72 (d, *J* = 2.0 Hz, 1H), 6.86 (dd, *J* = 2.0, 8.3 Hz, 1H), 7.17 (br s, 2H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.46-7.50 (m, 5H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.71 (d, *J* = 7.3 Hz, 2H), 8.14 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ94.4, 110.4, 112.3, 115.2, 127.4, 127.5, 128.4, 128.5, 129.5, 130.1, 131.1, 133.5, 140.5, 146.7, 147.3, 165.5, 167.3, 190.5. Anal. calcd for $C_{22}H_{15}NO_4$: C, 73.94; H, 4.23. Found: C, 73.77; H, 4.18.

*4.2.5. 2-Amino-3-benzoyl-5-(tert-butyldimethylsilyl)oxybenzo-[b]furan (**2n**)*: A yellow solid; mp 147.8-148.8 °C. IR (KBr): 752, 852, 920, 1073, 1156, 1232, 1364, 1438, 1479, 1590, 1655 (C=O), 3112, 3326 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ0.06 (s, 6H), 0.91 (s, 9H), 6.29 (d, *J* = 2.9 Hz, 1H), 6.52 (dd, *J* = 2.9, 8.6 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 7.19 (br s, 2H), 7.45-7.55 (m, 3H), 7.67 (d, *J* = 6.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ-4.64, 18.1, 25.6, 94.6, 110.0, 110.1, 113.9, 127.0, 127.1, 128.3, 130.6, 140.9, 144.2, 152.1, 167.2, 190.7. HRMS (FAB) calcd for $M+H^+$ of $C_{21}H_{25}NO_3Si$ 368.1682, found 368.1682.

*4.2.6. 2-Amino-3-benzoyl-4-(methoxymethyloxy)benzo[b]furan (**2o**)*: A yellow solid; mp 118.9-119.7 °C. IR (KBr): 756, 797, 920, 1023, 1079, 1152, 1175, 1246, 1342, 1480, 1593, 1651(C=O), 2942, 3111, 3325 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ3.40 (s, 3H), 4.98 (s, 2H), 6.55 (d, *J* = 2.5 Hz, 1H), 6.74 (dd, *J* = 2.5, 8.8 Hz, 1H), 7.06 (br s, 2H), 7.11 (d, *J* = 8.8 Hz, 1H), 7.49 (d, *J* = 6.8 Hz, 1H), 7.49-7.55 (m, 2H), 7.69 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ55.8, 94.7, 95.4, 107.6, 110.2, 110.7, 127.2, 127.4, 128.3, 130.9, 140.7, 144.8, 154.0, 167.1, 190.7. Anal. calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09. Found: C, 68.61; H, 5.11.

4.3. General Procedure of Palladium-Catalyzed Three-component Coupling Reactions Leading to 3-Acyl-2-(*N*-acylamino)benzofurans.

A flame dried Schlenk flask was charged with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), PPh_3 (15.7 mg, 0.06 mmol), 2-(cyanomethyl)phenol **3a** (39.9 mg, 0.30 mmol), aryl halides (0.9 mmol), K_2CO_3 (124 mg, 0.9 mmol), and DMF (1.2 mL). The flask was then flushed with CO, and the system was closed. After the reaction mixture was stirred at 100 °C for the time specified in Table 3, it was diluted with Et_2O and filtered through a short silica gel pad. The filtrate was washed with brine, and the aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layer was dried over $MgSO_4$, and then filtered. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt = 7/1-2/1 as eluents to afford the corresponding 3-acyl-2-(*N*-acylamino)benzofurans **4**.

*4.3.1. N-[3-(4'-Methylbenzoyl)-2-benzo[b]furyl]-4'-methylbenz-amide (**4a**)*: A yellow solid; mp 157.1-157.7 °C. IR (KBr): 745, 773, 828, 932, 1016, 1061, 1285, 1324, 1461, 1557, 1614 (C=O), 1712 (C=O), 2921, 3027 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 2.46 (s, 3H), 7.11-7.15 (m, 2H), 7.20-7.25 (m, 1H), 7.32 (d, *J* = 2.4 Hz, 2H), 7.33 (d, *J* = 2.4 Hz, 2H), 7.58 (d, *J* = 8.3 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 2H), 8.01 (d, *J* = 8.3 Hz, 2H), 12.2 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ21.5, 21.6, 100.0, 111.6, 120.2, 123.7, 123.8, 124.0, 124.2, 127.9, 128.2, 129.1, 129.6, 136.8, 142.8, 143.9, 150.7, 158.9, 163.1, 192.6. HRMS (FAB) calcd for $M+H^+$ of $C_{24}H_{19}NO_3$ 370.1443, found 370.1449.

*4.3.2. N-[3-(4'-Trifluoromethylbenzoyl)-2-benzo[b]furyl]-4'-trifluoromethylbenzamide (**4b**)*: A yellow solid; mp 176.2-176.9 °C. IR (KBr): 677, 751, 785, 855, 1014, 1068, 1124, 1170, 1287, 1326, 1462, 1558, 1617, 1718, 2361, 3077 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 4H), 7.91(d, *J* = 8.3 Hz, 2H), 8.21 (d, *J* = 7.8 Hz, 2H),

12.3 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.3, 111.9, 119.9, 123.1, 123.4 (q, J = 272.3 Hz), 123.6 (q, J = 272.3 Hz), 124.6, 124.8, 125.7 (q, J = 3.3 Hz), 126.2 (q, J = 3.3 Hz), 128.3, 128.4, 133.8 (q, J = 32.3 Hz), 134.8 (q, J = 32.3 Hz), 135.4, 142.4, 150.8, 159.0, 161.9, 191.6. HRMS (FAB) calcd for M+H$^+$ of $C_{24}H_{13}F_6NO_3$ 478.0878, found: 478.0884.

4.3.3. N-[3-(4'-Chlorobenzoyl)-2-benzo[b]furyl]-4'-chlorobenz

*amide (**4c**)*: A yellow solid; mp 181.2-181.9 °C. IR (KBr): 668, 742, 774, 845, 934, 1011, 1060, 1091, 1285, 1323, 1430, 1458, 1558, 1615, 1714, 2342, 2359. 3032 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, J = 7.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.27 (t, J = 7.6 Hz 1H), 7.52 (d, J = 8.3 Hz, 4H), 7.60 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 8.04 (d, J = 8.3 Hz, 2H), 12.2 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.1, 111.9, 120.1, 123.5, 124.3, 124.6, 128.9, 129.3, 129.4, 129.6, 130.7, 137.6, 138.6, 139.8, 150.8, 159.0, 162.1, 191.6. HRMS (FAB) calcd for M+H$^+$ of $C_{22}H_{13}Cl_2NO_3$ 410.0351, found 410.0344.

*4.3.4. N-(3-Benzoyl-2-benzo[b]furyl)benzamide (**4d**)*: A yellow solid; mp 162.4-163.0 °C. IR (KBr): 622, 698, 749, 860, 982, 1178, 1282, 1451, 1487, 1504, 1523, 1610, 1625, 1662, 2953, 3036, 3285 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (t, J = 7.8 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H), 7.26 (t, J = 8.8 Hz, 1H), 7.52-7.65 (m, 7H), 7.81 (d, J = 6.8 Hz, 2H), 8.13 (d, J = 7.3 Hz, 2H), 12.3 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.2, 111.8, 120.2, 123.9, 124.0, 124.4, 128.0, 128.1, 128.5, 129.1, 132.2, 132.4, 133.2, 139.5, 150.8, 159.0, 163.3, 193.0. HRMS (FAB) calcd for M+H$^+$ of $C_{22}H_{15}NO_3$ 342.1130, found 342.1131.

4.3.5. N-[3-(2'-Naphtoyl)-2-benzo[b]furyl]-2'-naphthalene-

*carboxamide (**4e**)*: A yellow solid; mp 184.0-184.5 °C. IR (KBr): 698, 749, 806, 932, 1060, 1125, 1198, 1224, 1286, 1318, 1435, 1457, 1473, 1558, 1607, 1704, 2258, 3027 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12-7.13 (m, 2H), 7.25-7.29 (m, 1H), 7.57-7.67 (m, 5H), 7.88-7.91 (dd, J = 1.5, 8.3 Hz, 1H), 7.93-7.97 (m, 3H), 8.00 (d, J = 8.8 Hz, 1H), 8.02 (d, J = 8.8 Hz, 1H), 8.07 (d, J = 7.8 Hz, 1H), 8.17 (dd, J = 1.5, 8.3 Hz, 1H), 8.38 (s, 1H), 8.67 (s, 1H), 12.5 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.4, 111.8, 120.3, 123.6, 123.9, 124.0, 124.4, 126.9, 127.0, 127.8, 127.9, 128.1, 128.5, 128.6, 129.0, 129.1, 129.2, 129.3, 129.4, 129.5, 129.6, 132.4, 132.5, 135.1, 135.4, 136.7, 150.8, 159.0, 163.3, 192.8. HRMS (FAB) calcd for M+H$^+$ of $C_{30}H_{19}NO_3$ 442.1443, found 442.1440.

4.3.6. N-[3-(4'-Methoxybenzoyl)-2-benzo[b]furyl]-4'-methoxy-

*benzamide (**4f**)*: A yellow solid; mp 202.9-203.7 °C. IR (KBr): 749, 780, 840, 933, 1032, 1063, 1174, 1192, 1246, 1286, 1328, 1430, 1463, 1558, 1576, 1615, 1698, 3040 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 3.93 (s, 3H), 7.03 (dd, J = 1.5, 8.8 Hz, 4H), 7.18 (d, J = 7.3 Hz, 1H), 7.24 (d, J =7.3 Hz, 1H), 7.26-7.27 (m, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 6.8 Hz, 2H), 8.09 (d, J = 8.8 Hz, 2H), 12.2 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4, 55.5, 100.0, 111.8, 113.7, 114.3, 120.3, 123.7, 124.1, 124.2, 124.8, 130.1, 130.6, 132.0, 150.8, 159.0, 162.8, 163.0, 163.6, 191.7. HRMS (FAB) calcd for M+H$^+$ of $C_{24}H_{19}NO_5$ 402.1341, found 402.1344.

4.3.7. N-[3-(2'-Methylbenzoyl)-2-benzo[b]furyl]-2'-methylbenz-

*amide (**4g**)*: A yellow solid; mp 169.7-170.3 °C. IR (KBr): 738, 763, 929, 1054, 1174, 1221, 1284, 1322, 1434, 1461, 1558, 1592, 1621, 1708, 3063 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 2.67 (s, 3H), 6.47 (d, J = 7.8 Hz, 1H) 7.06 (t, J = 8.3 Hz, 1H), 7.21 (t, J = 8.3 Hz, 1H), 7.30-7.37 (m, 5H), 7.42-7.47 (m, 2H), 7.58 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 11.8 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 20.7, 100.8, 111.6, 119.4, 123.7, 123.9, 124.6, 126.0, 126.3, 126.4, 127.7, 130.2, 130.9, 131.7, 132.0, 133.2, 134.7, 138.7, 140.1, 150.7, 158.3, 165.5, 194.7. HRMS (FAB) calcd for M+H$^+$ of $C_{24}H_{19}NO_3$ 370.1443, found 370.1444.

4.4. Synthesis of 4-Phenylbenzofuro[2,3-*d*]pyrimidine (5).

To a solution of 2-amino-3-benzoylbenzo[*b*]furan **2g** (94.9 mg, 0.40 mmol) in formamide (0.8 mL) was added $Sc(OTf)_3$ (5.9 mg, 0.012 mmol), and the resulting mixture was stirred at 140 °C for 3 h. The reaction mixture was washed with water and brine, and then dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica gel with hexane/AcOEt = 4/1 as eluents to afford 4-phenylbenzofuro[2,3-*d*]pyrimidine **5** as a white solid (95.5 mg, 0.39 mmol, 97% yield) as a white solid. mp 120.2-120.8 °C. IR (KBr): 750, 765, 816, 849, 930, 941, 1128, 1201, 1248, 1315, 1368, 1431, 1462, 1478, 1552, 1585, 3023, 3071 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (t, J = 7.3 Hz, 1H), 7.53 (t, J = 8.3 Hz, 1H), 7.60-7.68 (m, 4H), 7.91 (d, J = 7.8 Hz, 1H), 7.96-8.00 (m, 2H), 9.10 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.2, 112.3, 120.2, 122.8, 124.0, 128.7, 128.8, 129.2, 130.7, 137.1, 153.7, 155.4, 161.6, 168.9. Anal. calcd for $C_{16}H_{10}N_2O$: C, 78.03; H, 4.09. Found: C, 78.05; H, 4.37.

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8. Conditions for phenoxycarbonylation of *p*-TolBr have been optimized. For details, see: Supplementary material.
9. When $Pd(OAc)_2$ 10 mol%) as a precatalyst with PCy_3 and PPh_3 ($Pd:PCy_3:PPh_3$ = 1:1:1) was used instead of $Pd(PCy_3)_2$ and $Pd(PPh_3)_4$, the yield of **2a** deteriorated to 19% with **1a** (69%) as a major component.
10. In entry 7, almost all compounds **3a** and $4\text{-}MeOC_6H_4Br$ were recovered intact.
11. The present reaction is applicable to a scale-up experiment (up to 2 mmol) without defect on the chemical yield.
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Supplementary Material

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2015.xx.xxx.

Supplementary Material

Palladium-catalyzed Three-component Coupling Reactions of 2-(Cyanomethyl)phenol, Aryl Halides, and Carbon Monoxide

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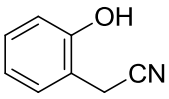
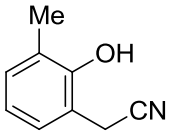
1. General Method. All reactions were carried out in dry solvent under an argon atmosphere. Unless otherwise noted, other chemicals obtained from commercial suppliers were used without further purification. CO gas (purity 99.97%) was purchased from Sumitomo Seika Co. Solvents were dried by the usual methods and distilled before use. Unless otherwise noted, reactions were carried out under nitrogen atmosphere. Proton chemical shifts are reported in ppm based on the solvent resonance resulting from incomplete deuteration ($CDCl_3$ at 7.26 ppm and acetone-d_6 at 2.05 ppm) as the internal standard. ^{13}C NMR was recorded with complete proton decoupling and the chemical shifts are reported relative to $CDCl_3$ at 77.00 ppm and acetone-d_6 at 29.8 ppm. The following abbreviations are used; br s: broad singlet, s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet. IR spectra were recorded with an FT-IR spectrometer. Melting points (mp) were measured on a Yanaco micromelting point apparatus and are uncorrected. Element analyses were performed at Microanalytical Center of Kyoto University. High-resolution mass spectra (HRMS) was measured with JEOL JMX-SX 102A spectrometer. The analytical data for **3m**, 3-acyl-2-aminobenzofurans **2a**-**2h**, and **2k** were reported previously by this group (Murai, M.; Miki, K.; Ohe, K. *Chem. Commun.* **2009**, 3466).

2. Preparation of 2-(Cyanomethyl)phenols 3

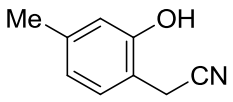


2-(Cyanomethyl)phenol (3a): To a solution of $LiAlH_4$ (2.1 g, 55 mmol) in THF (100 mL) was added salicylic acid (6.9 g, 50 mmol) at 0 °C, and stirred at 60 °C overnight. The reaction mixture was cooled to 0 °C, and then degassed water (2.0 mL), 15 wt% NaOH aqueous solution (2.0 mL), and water (6.0 mL) were successively added. After stirring at room temperature for 1 h, the mixture was filtered and washed with Et_2O (50 mL×3). The combined organic layer was washed with brine and dried over $MgSO_4$. The organic solvent was removed under reduced pressure to afford 2-hydroxymethyl phenol (4.5 g, 33.5 mmol, 67% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 2.26 (br s, 1H), 4.86 (s, 2H), 6.84 (t, J = 7.3 Hz, 1H), 6.88 (d, J = 6.8 Hz, 1H), 7.04 (d, J = 6.8 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H). A solution of 2-hydroxymethyl phenol (3.9 g, 30 mmol) in DMF (30 mL) was added to sodium cyanide (2.9 g, 60 mmol), and the resulting mixture was stirred at 100 °C for 12 h. After the resulting solution was cooled to room temperature, it was poured into 10% HCl aqueous solution (30 mL), and extracted with Et_2O (30 mL×3). The combined organic layer was dried over $MgSO_4$, and the organic solvent was removed under reduced pressure. The residue was filtered through a short silica

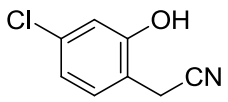
gel pad followed by recrystallization from hexane / $CHCl_3$ to furnish 2-(cyanomethyl)phenol **3a** (3.2 g, 24 mmol, 80% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72 (s, 2H), 5.05 (br s, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.95 (t, J = 7.9 Hz, 1H), 7.20 (t, J = 7.9 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H).



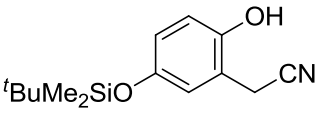
2-Cyanomethyl-6-methylphenol (3i): A yellow solid; mp 103.5-104.3 °C. IR (KBr / cm^{-1}): 762, 883, 958, 1097, 1160, 1193, 1216, 1333, 1411, 1472, 1595, 2255 (CN), 2926, 3422 (OH). ^{1}H NMR (400 MHz, acetone-d_6): δ 2.15 (s, 3H), 3.67 (s, 2H), 6.69 (t, J = 7.3 Hz, 1H), 6.98 (d, J = 7.3 Hz, 1H), 7.05 (d, J = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ 16.4, 18.8, 118.9, 119.0, 120.9, 125.3, 127.8, 131.4, 153.4. HRMS (FAB) calcd for M+H$^+$ of C_9H_9NO 148.0762, found 148.0758.



2-Cyanomethyl-5-methylphenol (3j): A yellow solid; mp 107.2-108.3 °C. IR (KBr / cm^{-1}): 734, 813, 858, 957, 1114, 1157, 1195, 1233, 1287, 1353, 1425, 1523, 1593, 1618, 2262 (CN), 2907, 2957, 3332 (OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 3.68 (s, 2H), 5.40 (br s, 1H), 6.60 (s, 1H), 6.75 (d, J = 7.8 Hz, 1H), 7.19 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 21.1, 113.8, 116.1, 118.2, 121.9, 129.4, 139.8, 153.0. HRMS (FAB) calcd for M+H$^+$ of C_9H_9NO 148.0762, found 148.0760.

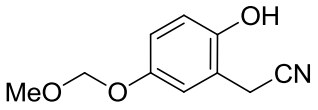


5-Chloro-2-(cyanomethyl)phenol (3l): An orange solid; mp 108.7-109.5 °C. IR (KBr / cm^{-1}): 724, 822, 870, 910, 1086, 1119, 1228, 1284, 1351, 1426, 1505, 1607, 2268 (CN), 2914, 2974, 3328 (OH). ^{1}H NMR (400 MHz, acetone-d_6): δ 3.76 (s, 2H), 6.90 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 7.31 (s, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ 18.4, 117.4, 118.4, 120.8, 124.7, 129.7, 129.9, 154.6. HRMS (FAB) calcd for M+H$^+$ of C_8H_6ClNO 168.0216, found 168.0210.



4-(*tert*-Butyldimethylsilyloxy)-2-(cyanomethyl)phenol (3n): A yellow solid; mp 69.7-70.4 °C. IR (KBr / cm^{-1}): 780, 813, 912, 985, 1093, 1151, 1206, 1270, 1362, 1438, 1511, 1614, 2277 (CN), 2856, 2892, 2927, 2957, 3325 (OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 6H), 0.97 (s, 9H), 3.67 (s, 2H), 5.73 (br s, 1H), 6.65-6.66 (m, 2H), 6.82 (s, 1H). ^{13}C NMR (100 MHz,

$CDCl_3$): δ -4.5, 18.1, 18.5, 25.6, 116.1, 117.5, 118.0, 120.4 (overlapped), 147.6, 149.3. HRMS (FAB) calcd for $M+H^+$ of $C_{14}H_{21}NO_2Si$ 264.1420, found 264.1428.



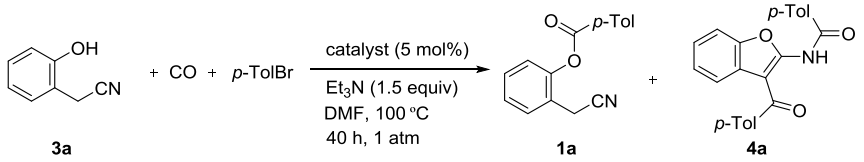
2-Cyanomethyl-4-(methoxymethoxy)phenol (3o): A yellow oil; IR (neat / cm^{-1}): 733, 810, 872, 1112, 1188, 1262, 1351, 1452, 1612, 2259 (CN), 2824, 2957, 3328 (OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.48 (s, 3H), 3.66 (s, 2H), 5.10 (br s, 1H), 6.69 (d, J = 8.8 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 7.00 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 55.8, 95.2, 116.0, 117.5, 117.6, 117.9, 118.0, 148.7, 150.7. HRMS (FAB) calcd for $M+H^+$ of $C_{10}H_{11}NO_3$ 194.0817, found 194.0812.

3. Phenoxycarbonylation of p-TolBr using 2-(Cyanomethyl)phenols 3

The reaction conditions for alkoxycarbonylation by using 4-bromotoluene with **3a** and CO were optimized; the results are summarized in Table S1.

When carbonylation of 4-bromotoluene with **3a** and CO was carried out by using 5 mol% $Pd(OAc)_2$ and 10 mol% PPh_3 as catalyst, **1a** was obtained in 91% yield (Table S1, entry 1). Although replacing PPh_3 by more sterically hindered P(o-Tol)$_3$ or basic P*t*Bu$_3$ was detrimental to the carbonylation reaction, the use of bidentate ligands such as dppf and DPEphos gave **1a** in 82 and 92% yields, respectively (entries 2–5). Among the catalysts screened, $Pd(PPh_3)_4$ showed the best catalytic activity for the alkoxycarbonylation; the use of this catalyst afforded **1a** in 94% yield (entry 6). The reaction was then examined with a range of bases and $Pd(PPh_3)_4$ as catalyst. Whereas *i*Pr$_2$EtN was comparably effective, affording **1a** in 94% yield, pyridine, K_2CO_3, and NaOEt were less effective, affording **1a** in moderate yields (entries 7–10). Interestingly, when inorganic bases such as K_2CO_3 or NaOEt were used, a small amount of 3-acyl-2-(*N*-acylamino)benzofuran **4a** was obtained together with **1a** (entries 9 and 10). However, the formation of 3-benzoyl-2-aminobenzofuran **2a** was not observed under any of the conditions listed in Table S1. These results show that the combination of $Pd(PPh_3)_4$ as a catalyst and Et_3N as a base is most effective for the alkoxycarbonylation, with **2a** remaining untouched under these conditions. The alkoxycarbonylation proceeded even when the loading of $Pd(PPh_3)_4$ was decreased to 2 mol% (entry 11).

Table S1. Pd-catalyzed alkoxycarbonylation of 4-bromotoluene with **3a** and CO[a]



3a **1a** **4a**

Entry	Catalyst	Base	Conversion[b]	Yield of **1a**[c]	Yield of **4a**[c]
1	$Pd(OAc)_2/PPh_3$ (1:2)	Et_3N	100%	91%	0%
2	$Pd(OAc)_2/P(o\text{-}Tol)_3$ (1:2)	Et_3N	68%	34%	0%
3	$Pd(OAc)_2/PtBu_3$ (1:2)	Et_3N	6%	0%	0%
4	$Pd(OAc)_2$/dppf (1:1)	Et_3N	100%	82%	0%
5	$Pd(OAc)_2$/DPEphos (1:1)	Et_3N	100%	92%	0%
6	$Pd(PPh_3)_4$	Et_3N	100%	94%	0%
7	$Pd(PPh_3)_4$	iPr_2EtN	100%	94%	0%
8	$Pd(PPh_3)_4$	pyridine	89%	63%	0%
9	$Pd(PPh_3)_4$	K_2CO_3	83%	68%	9%
10	$Pd(PPh_3)_4$	NaOEt	100%	79%	4%
11[d]	$Pd(PPh_3)_4$	Et_3N	100%	94%	0%

[a]Reaction conditions: **3a** (0.20 mmol), *p*-TolBr (0.30 mmol), base (0.30 mmol), catalyst (0.01 mmol) in DMF (0.8 mL) under CO (1 atm).

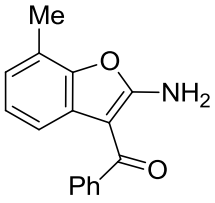
[b]Determined by ^1H NMR.

[c]Isolated yields.

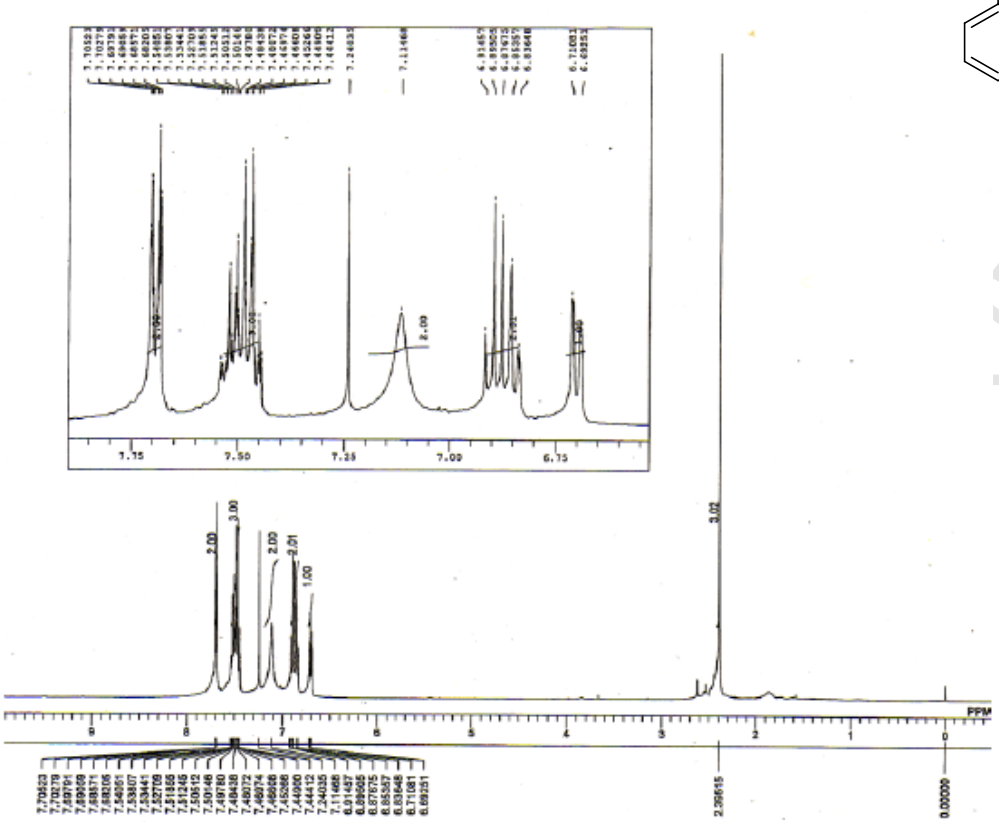
[d]$Pd(PPh_3)_4$ (0.004 mmol).

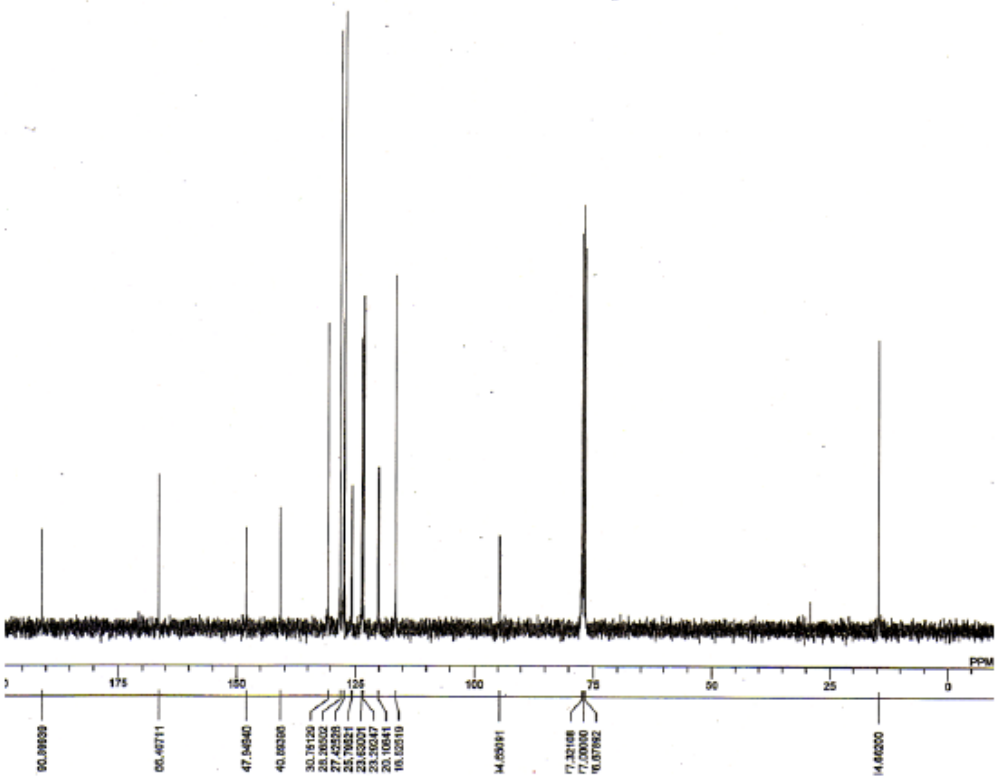
dppf = diphenylphosphinoferrocene. DPEphos = 2,2'-bis(diphenylphosphino)diphenyl ether.

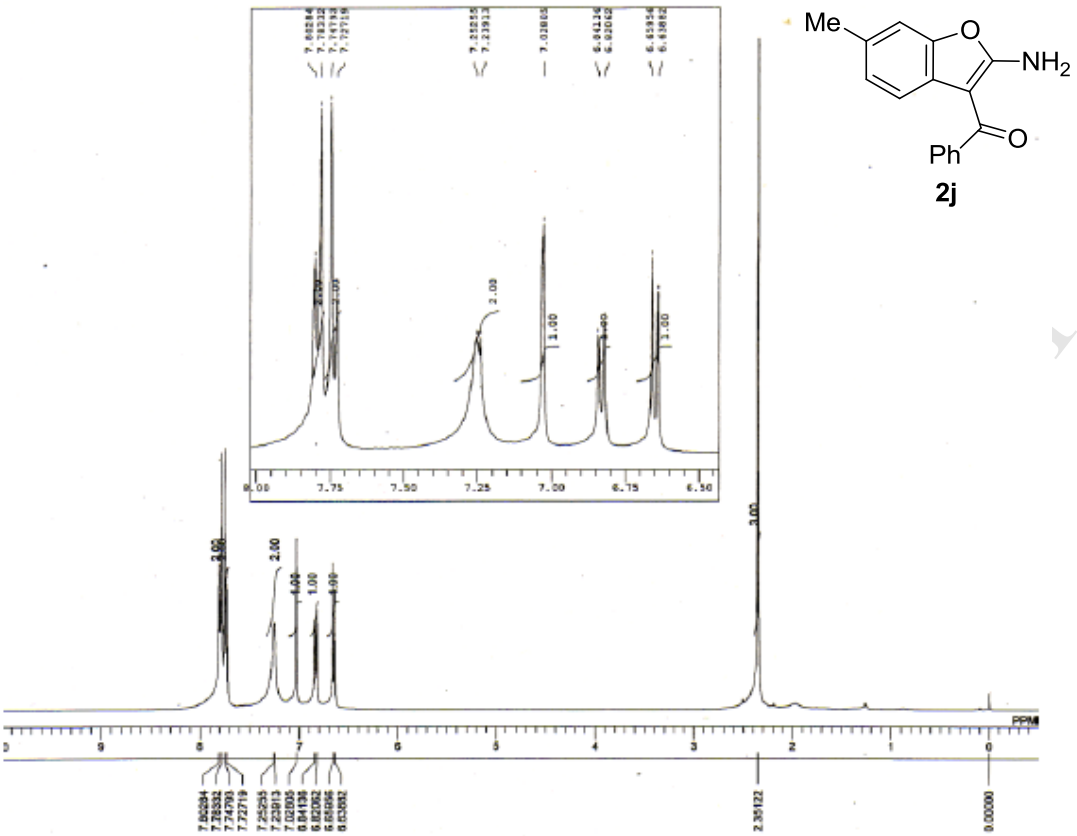
4. ^{1}H NMR and ^{13}C NMR Spectra of New Compounds



2i



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O
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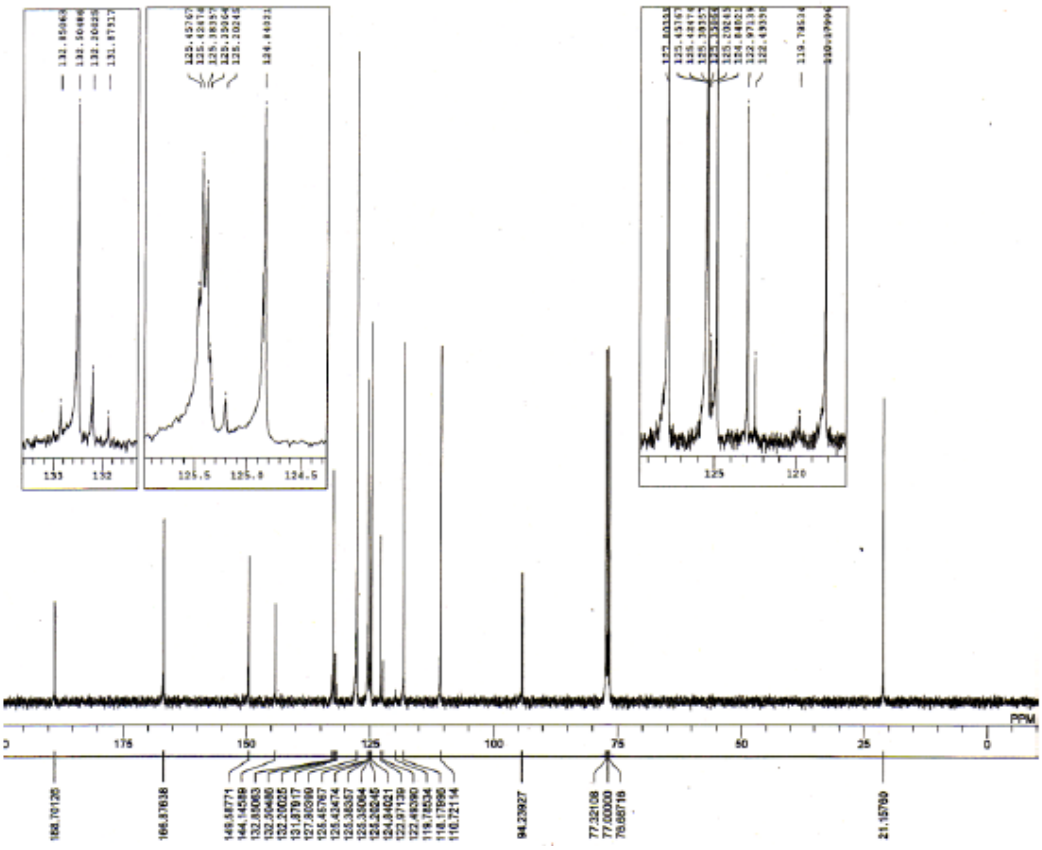

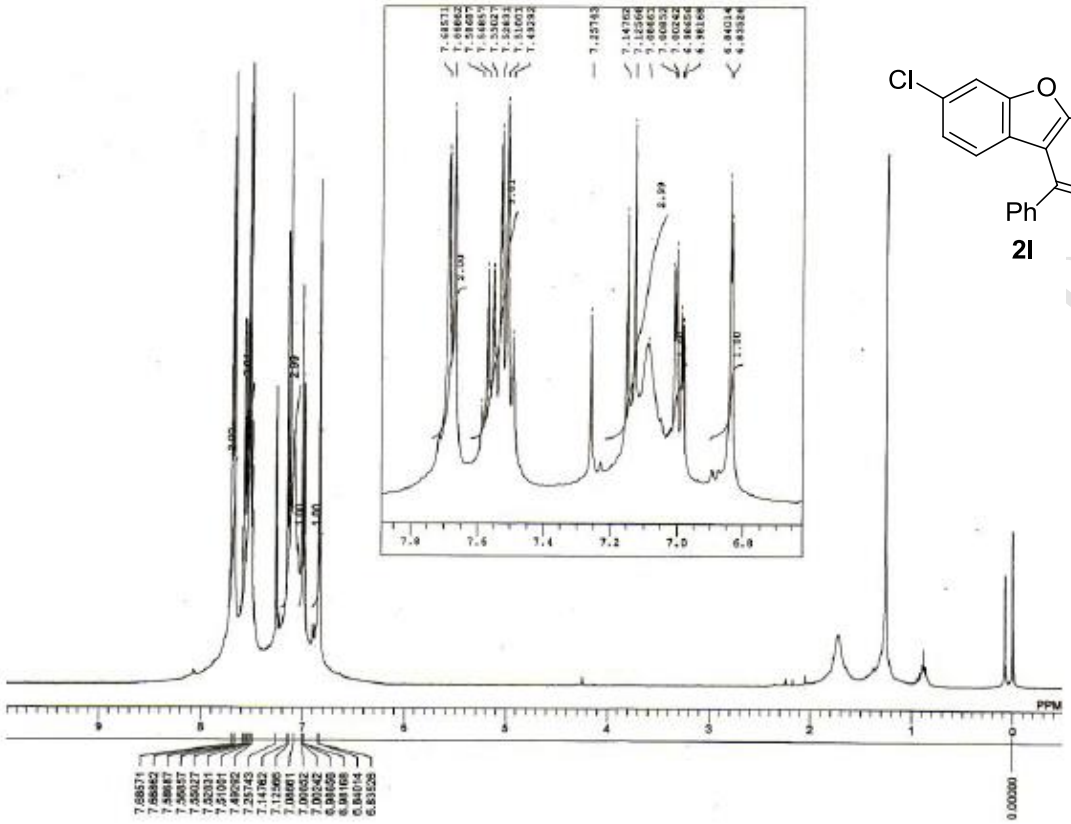

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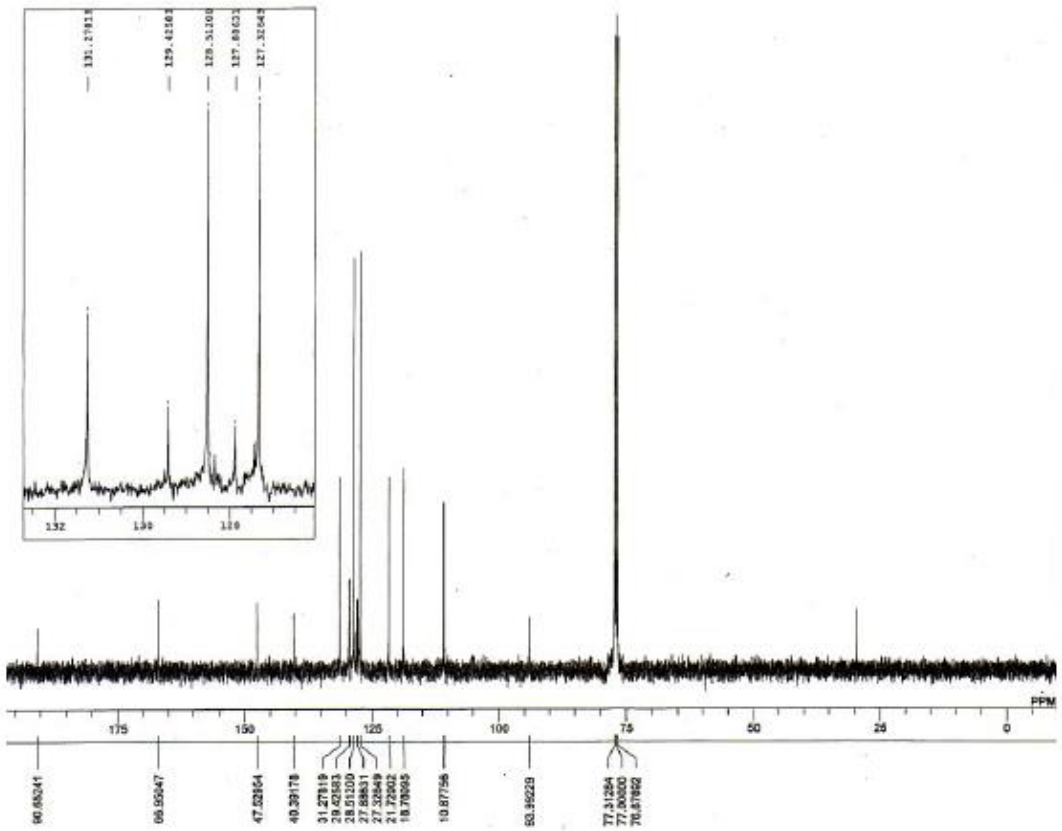

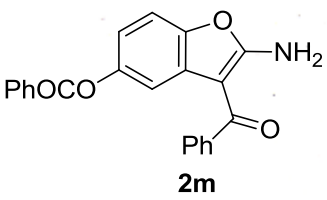

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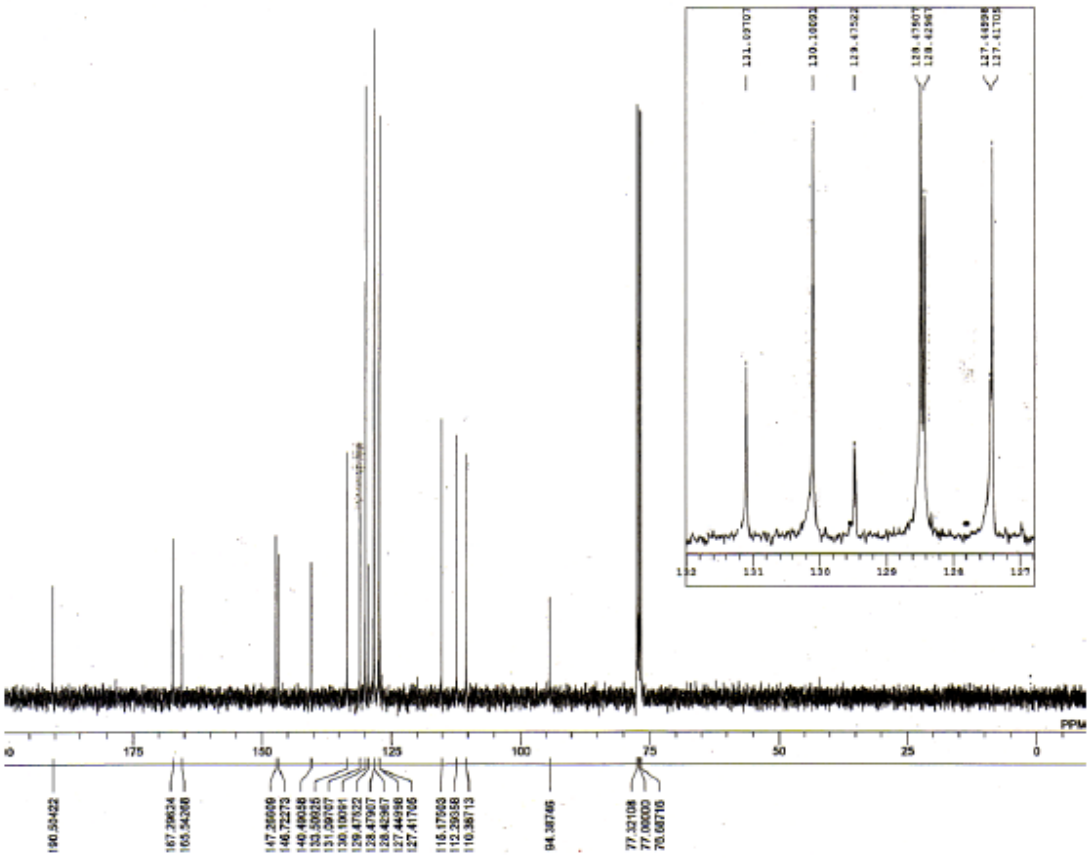

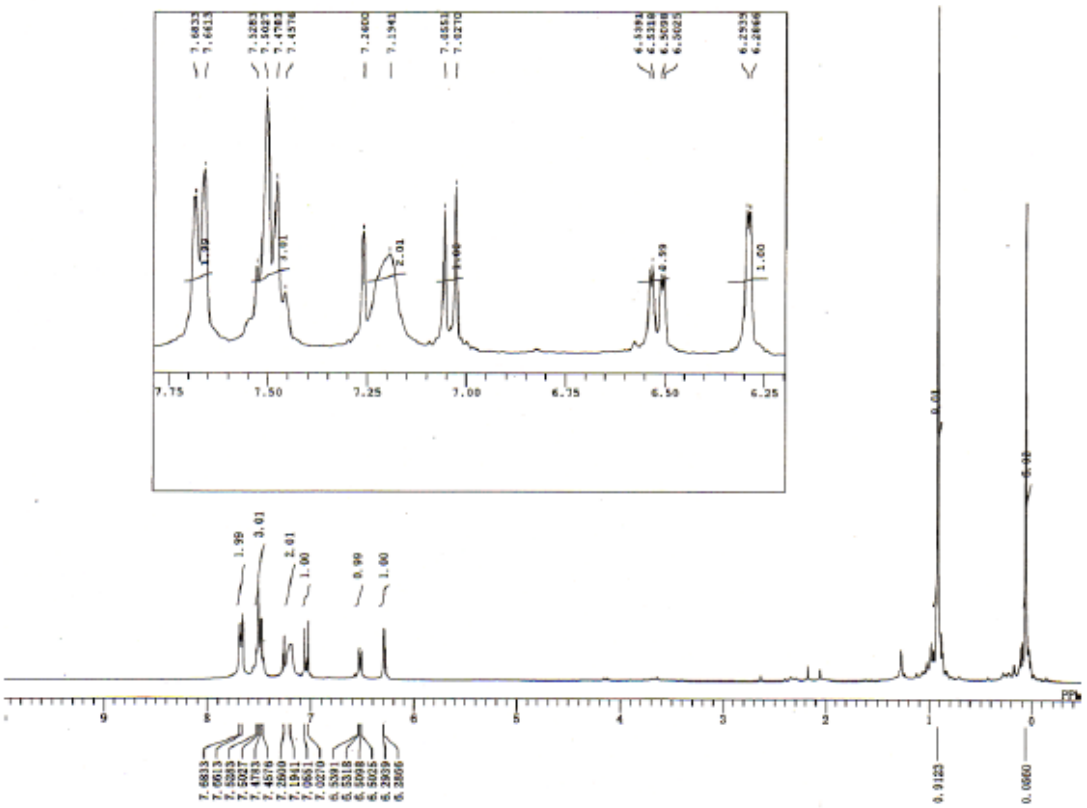

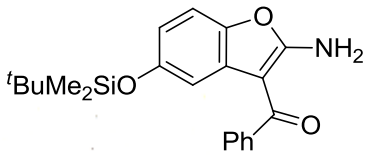

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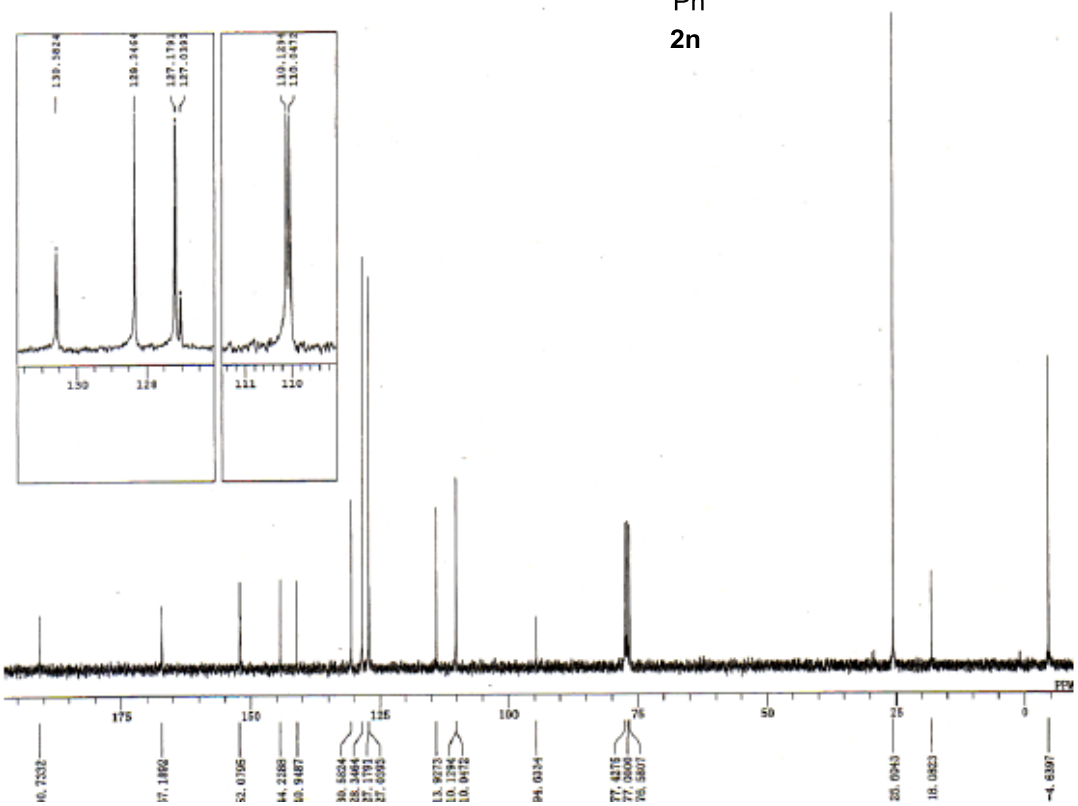

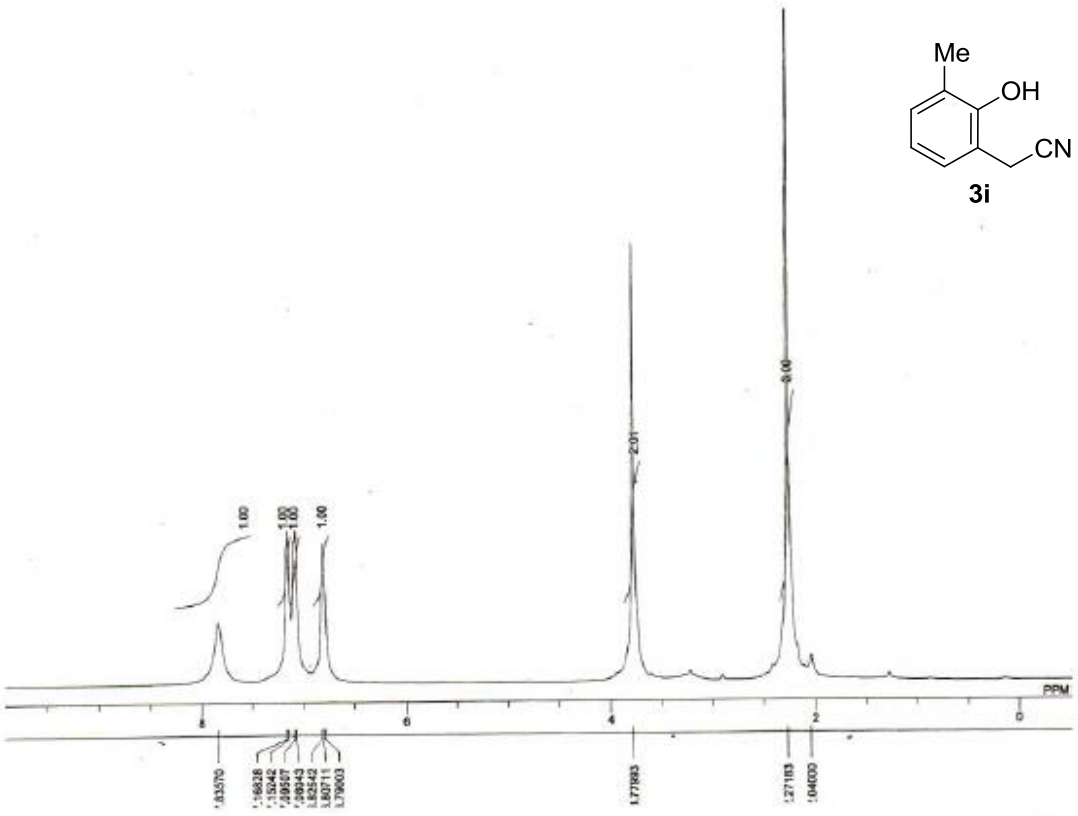
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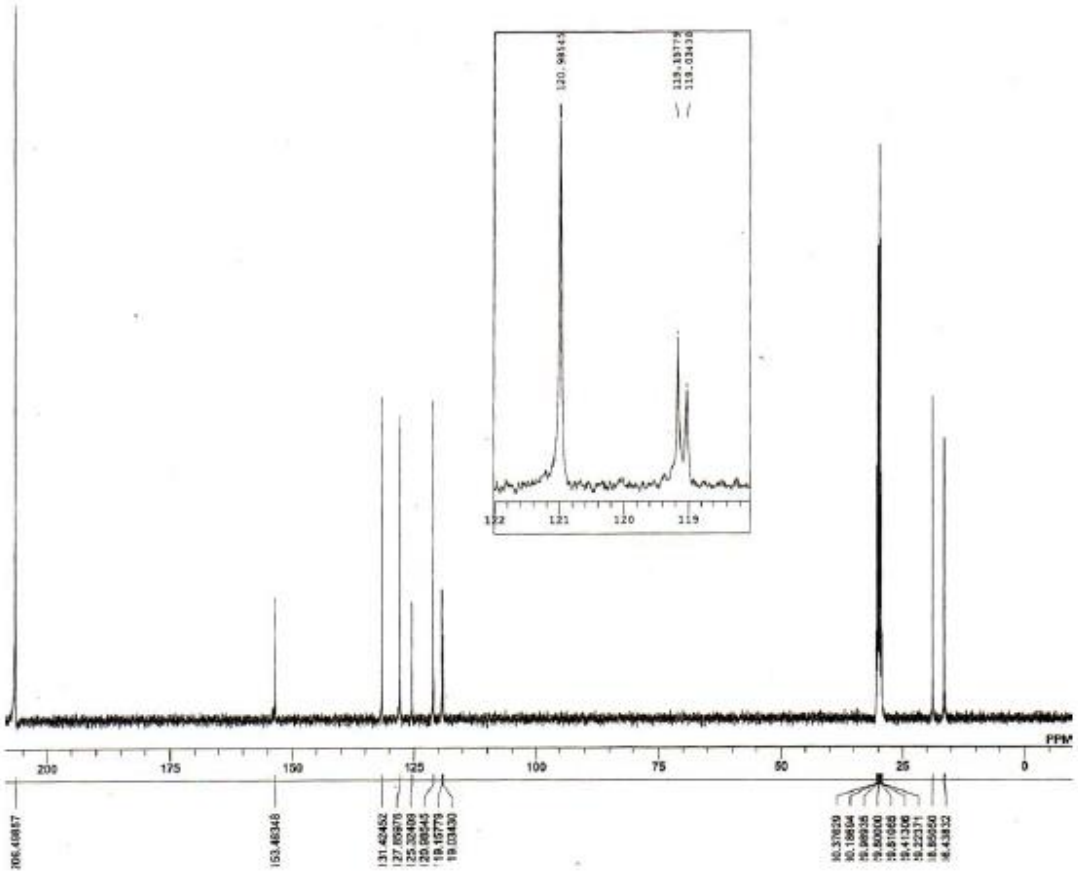
PPM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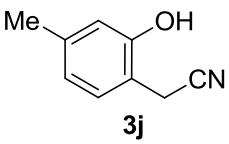

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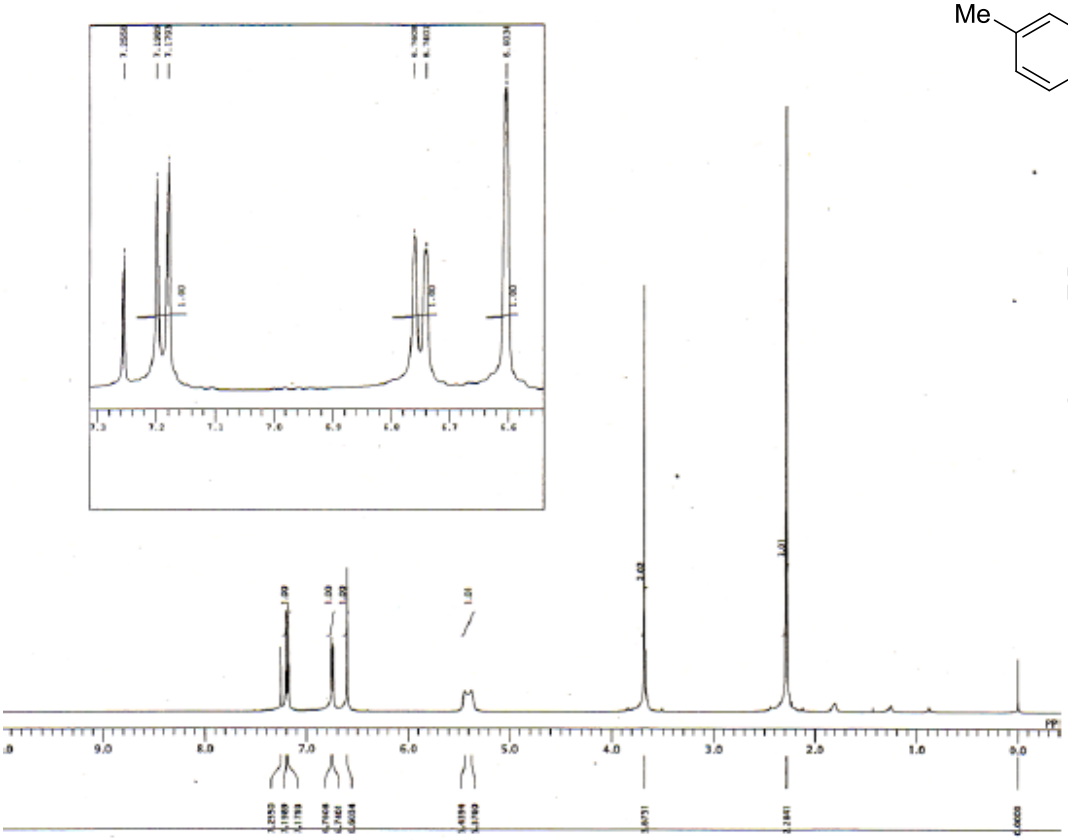

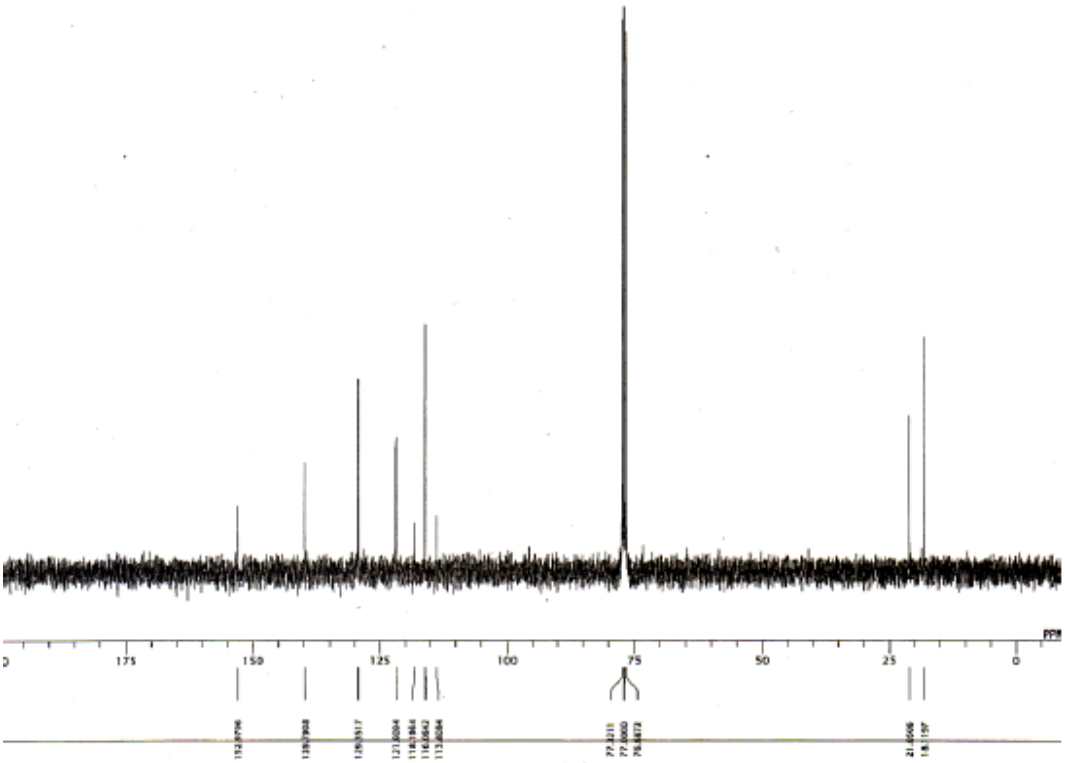

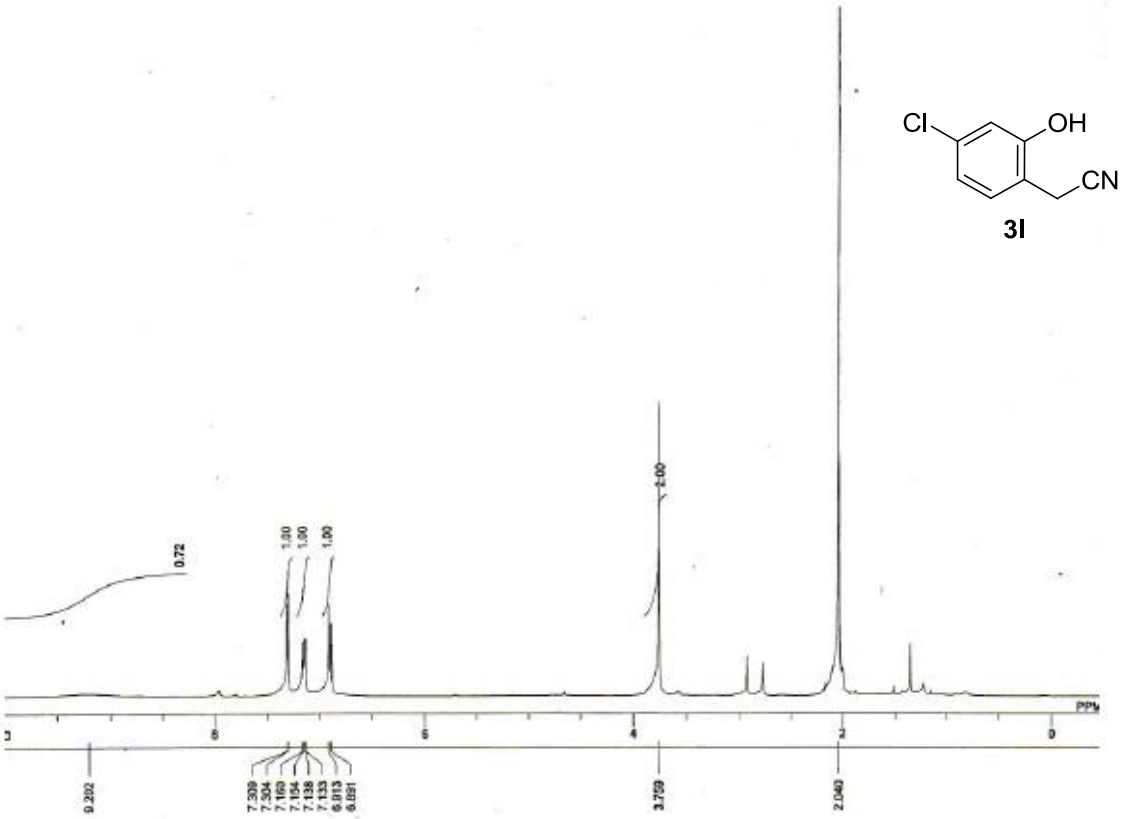
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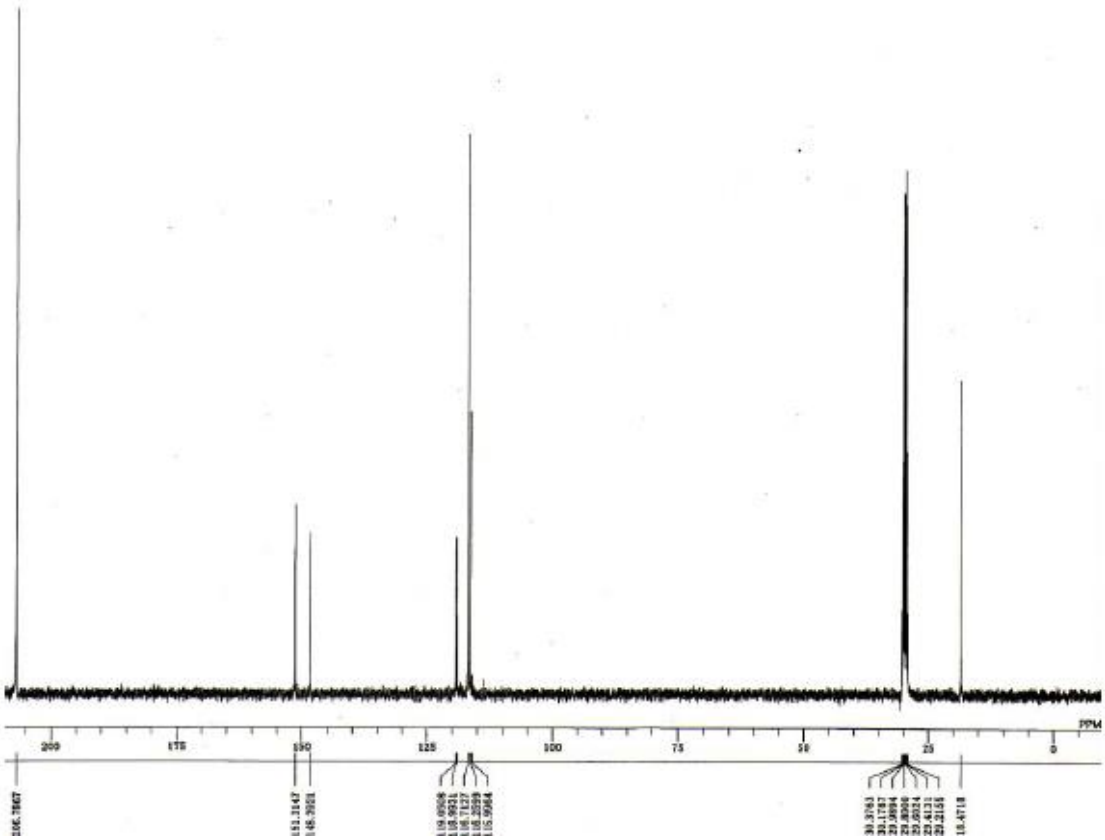
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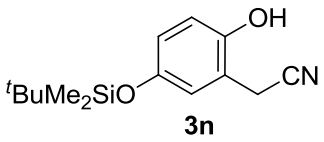

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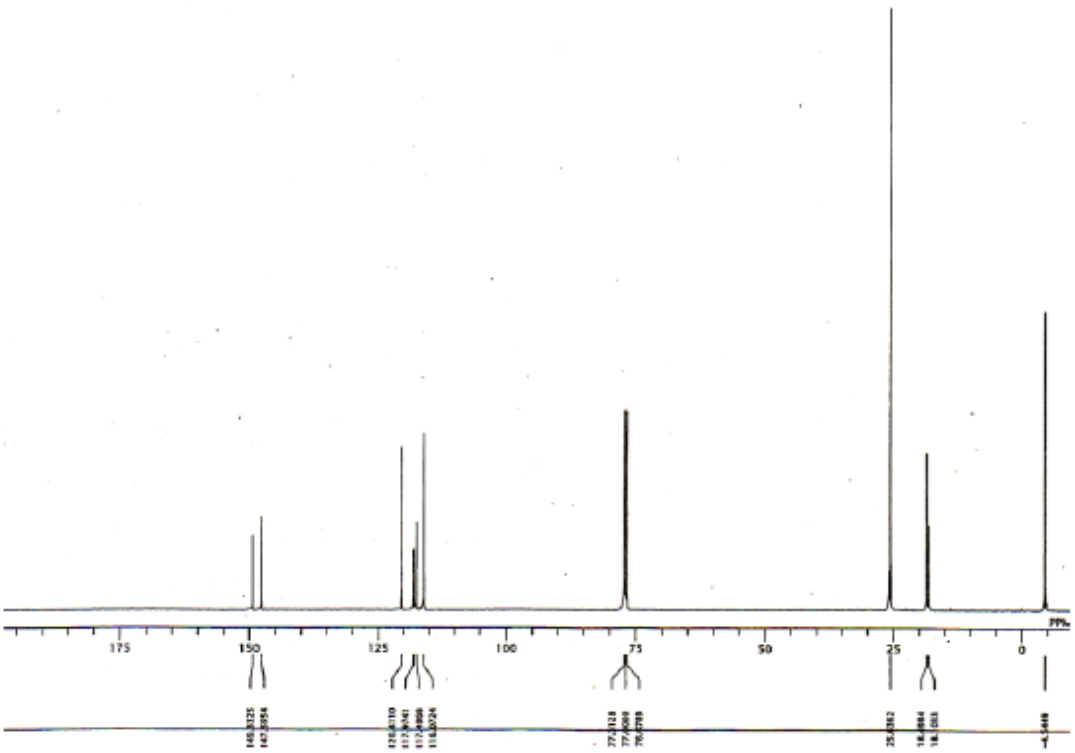

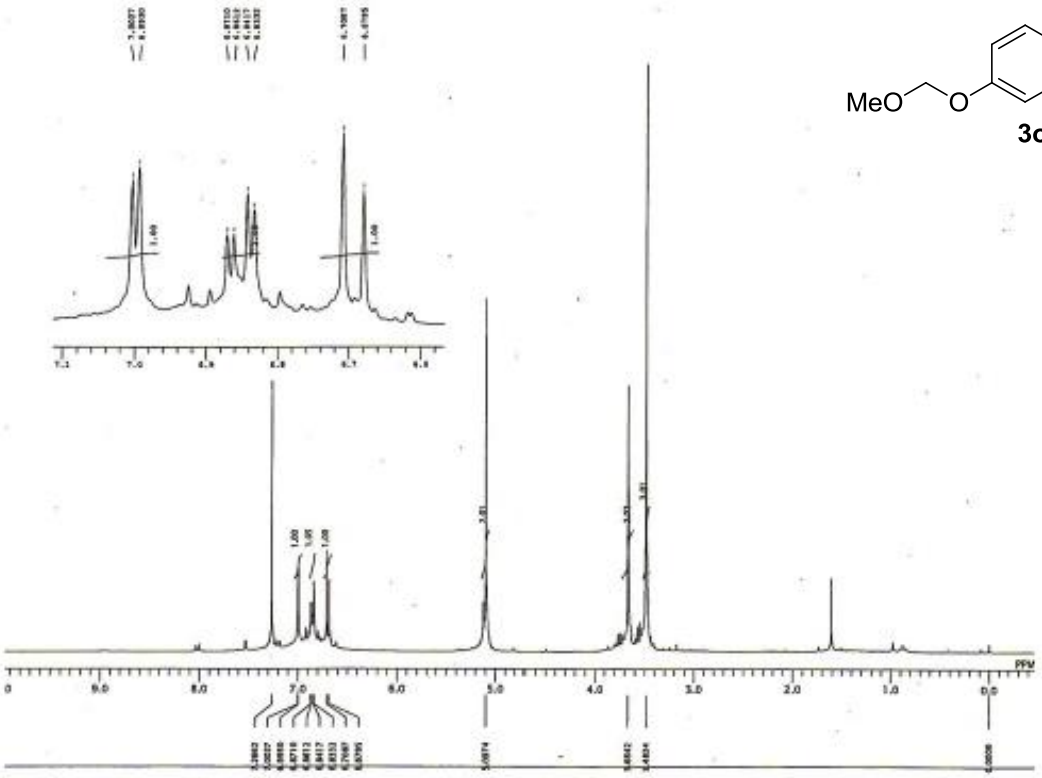

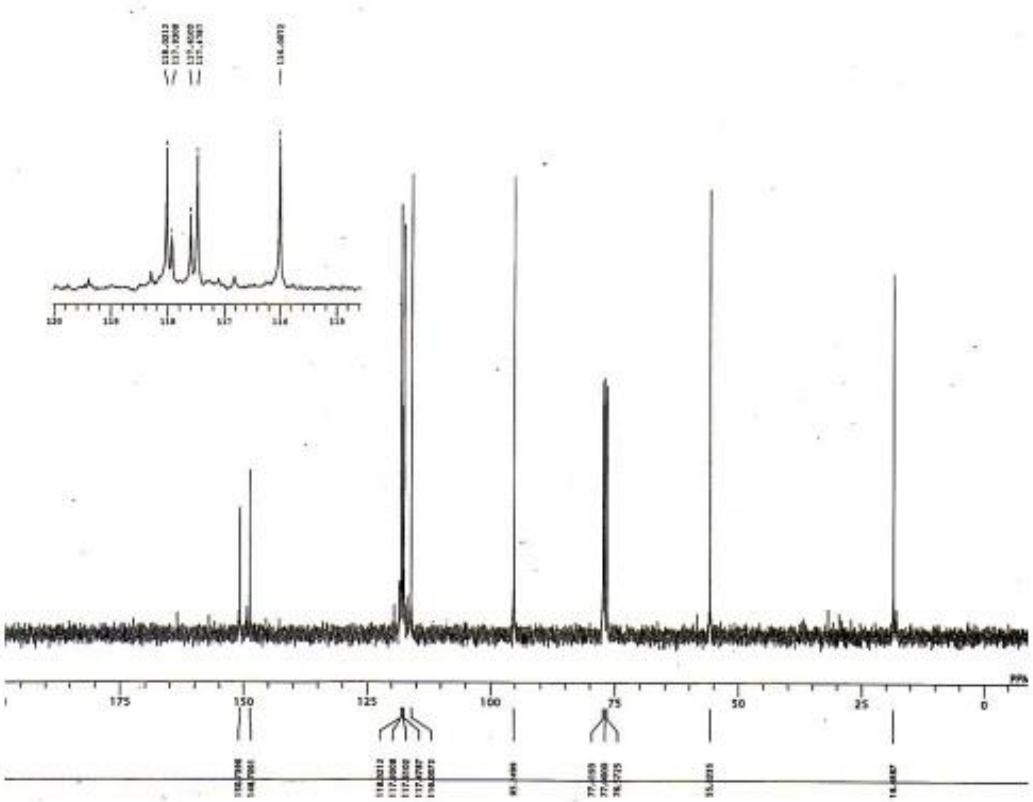

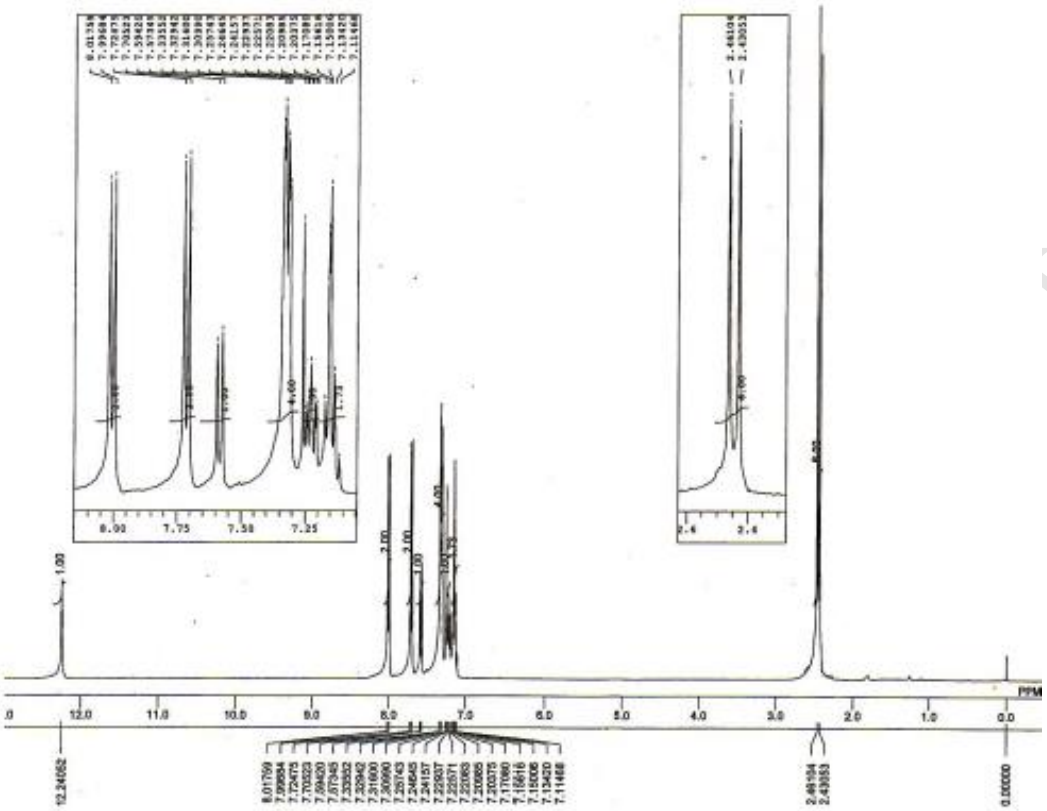

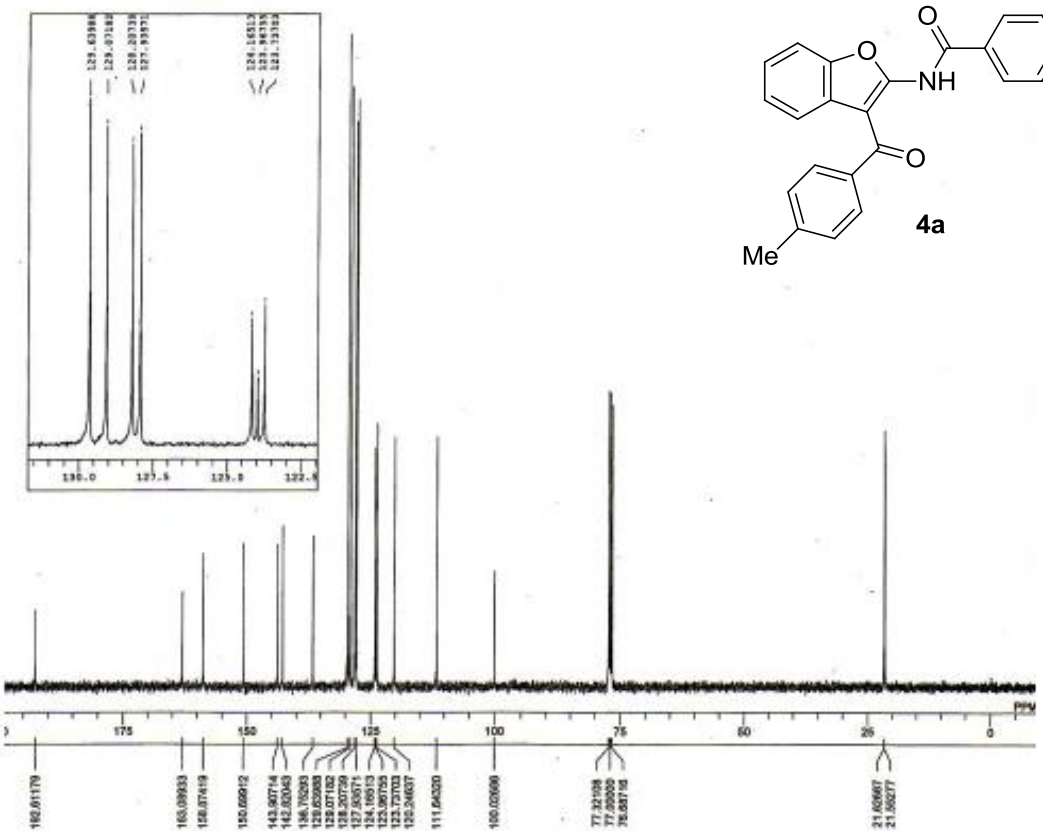

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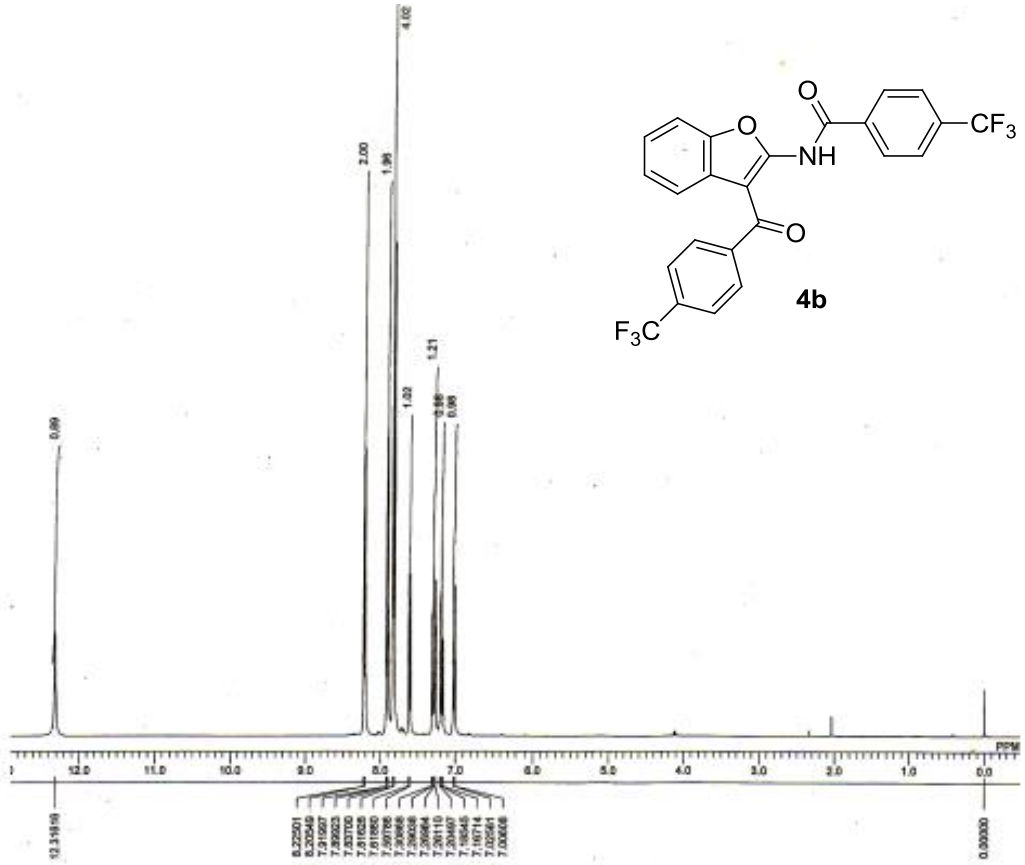
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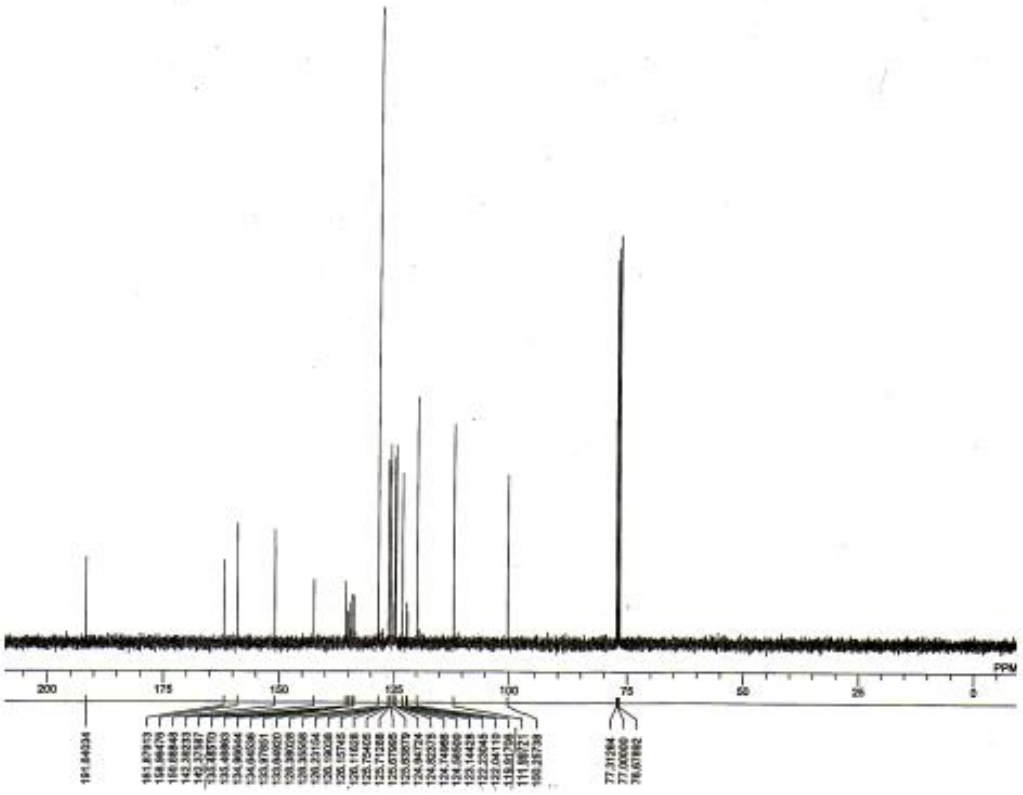
O
O
CF3
F3C
4b
PPM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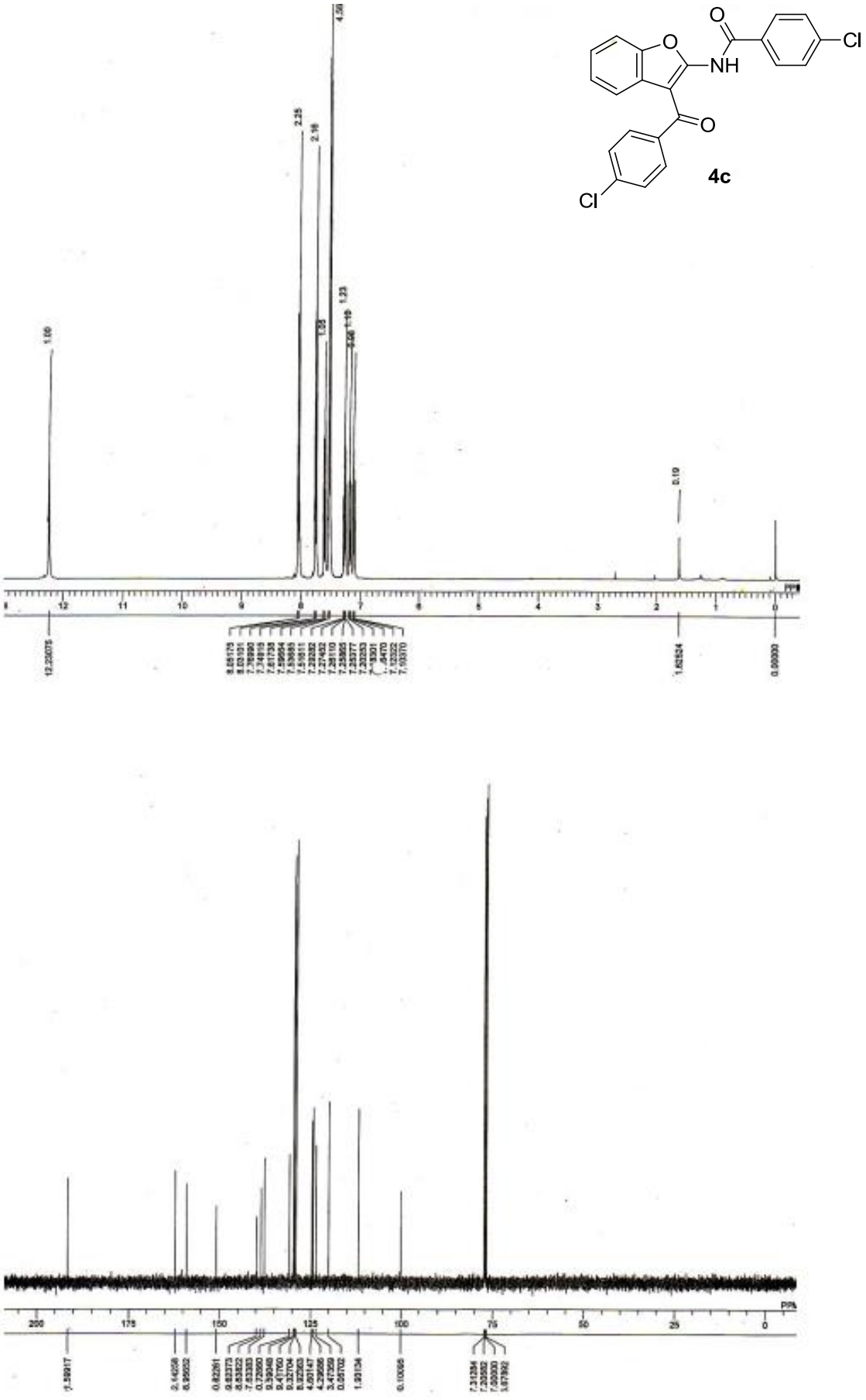
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O
Cl
O
Cl
4c
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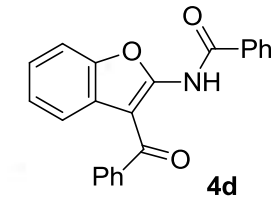

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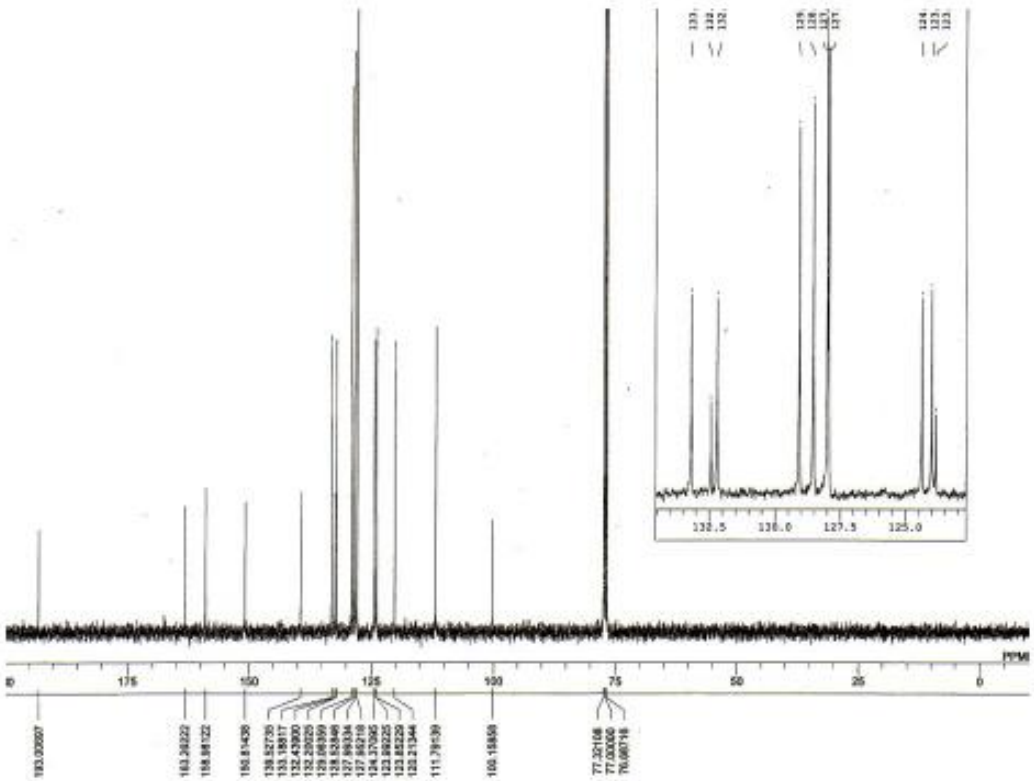

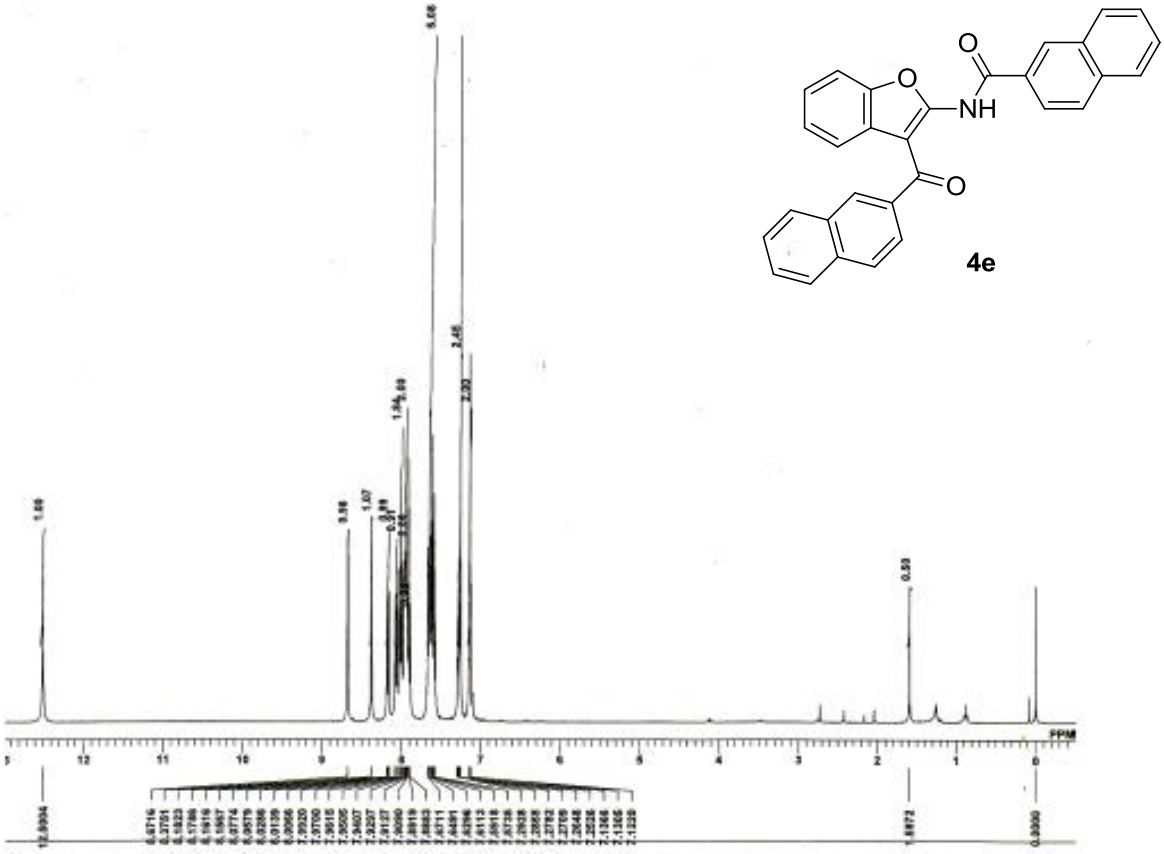
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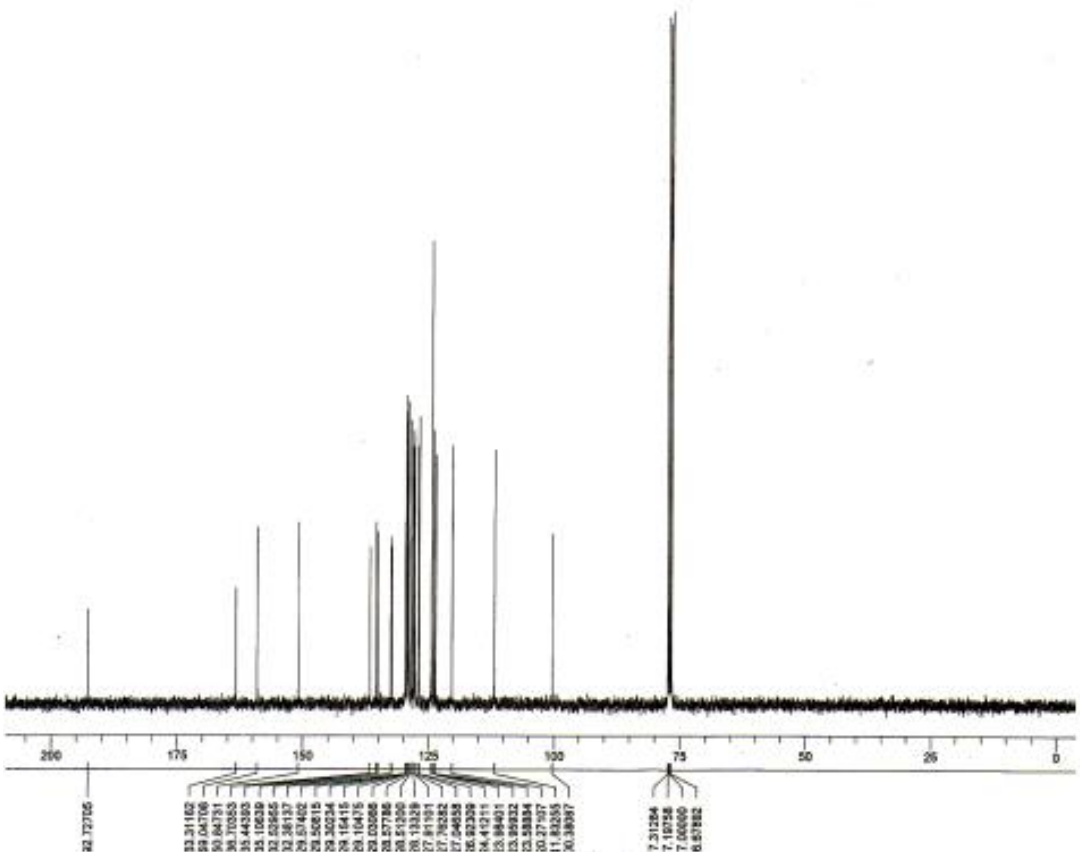
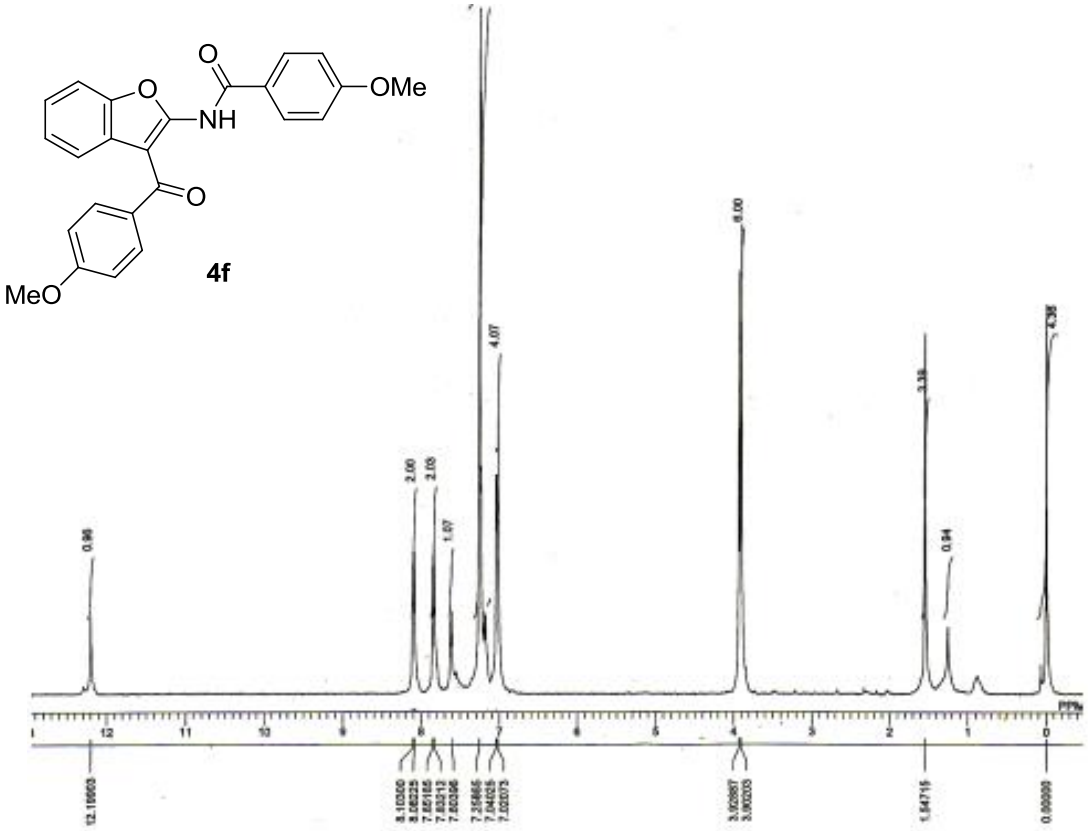
NH
O
4e
PPM

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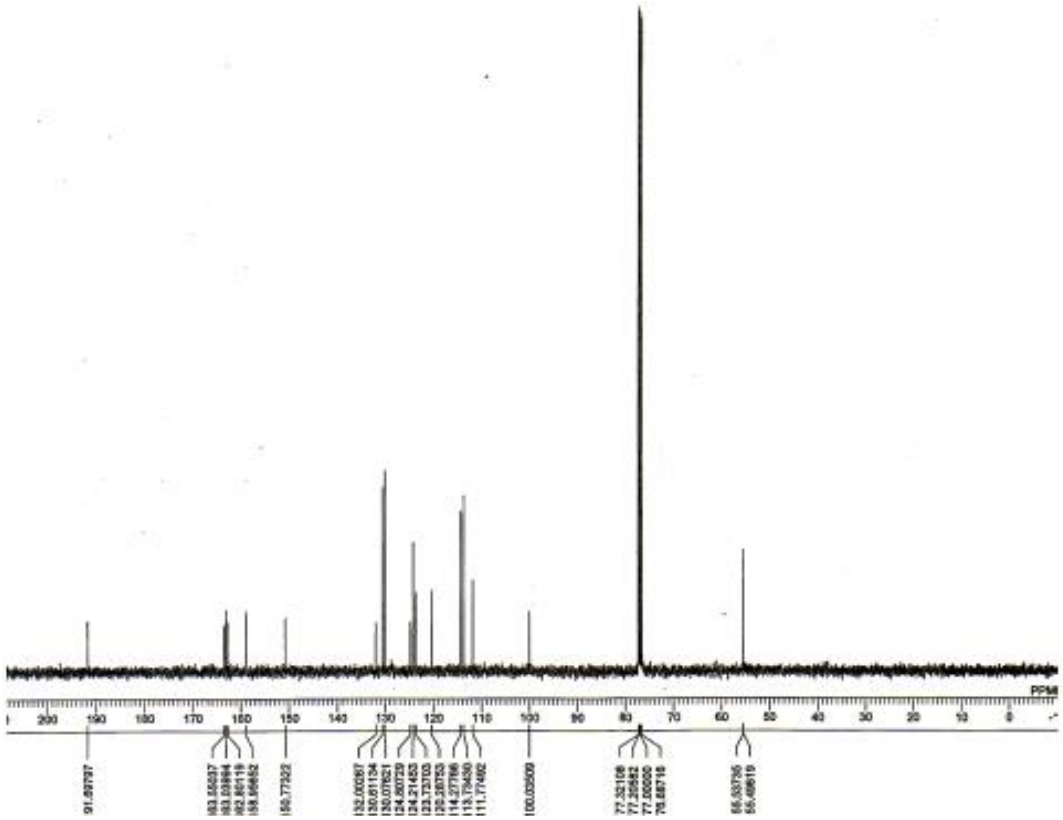
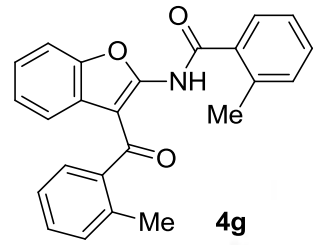
OMe
O
MeO
4f




O
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Me
O
Me

4g

PPM
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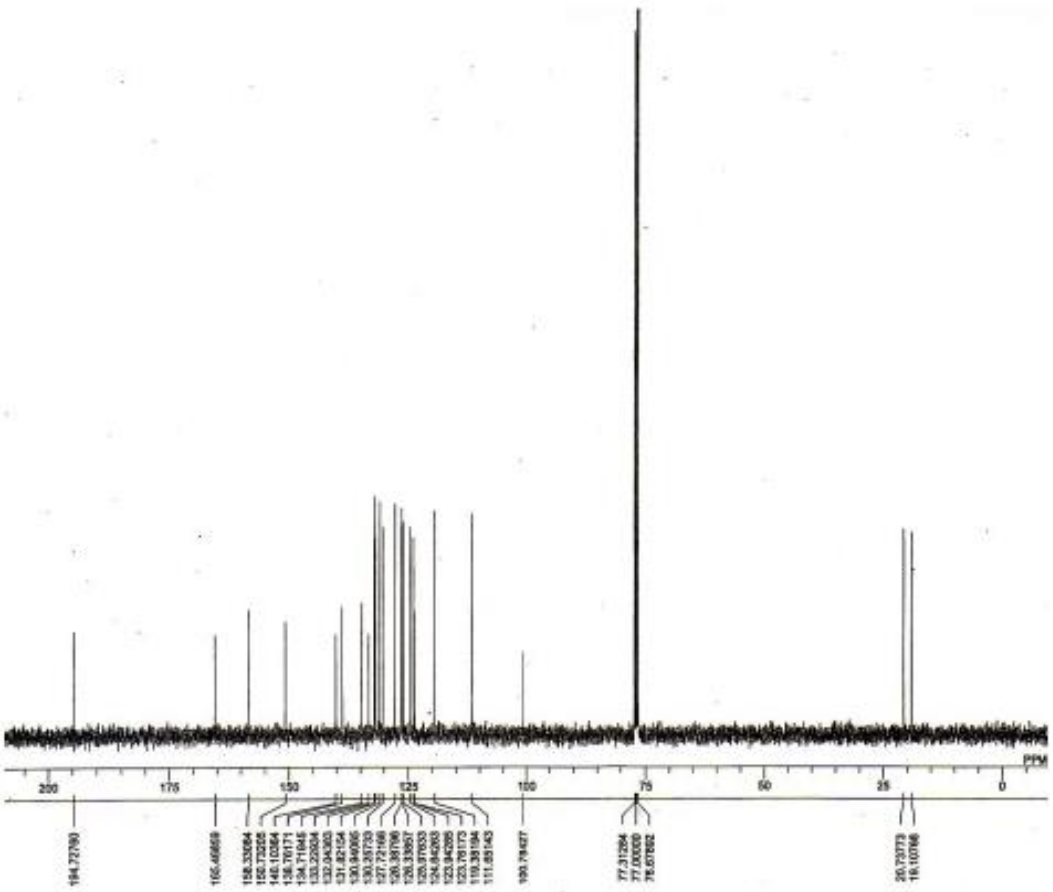
7.5
5.0
2.5
0.0


PPM
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150
125
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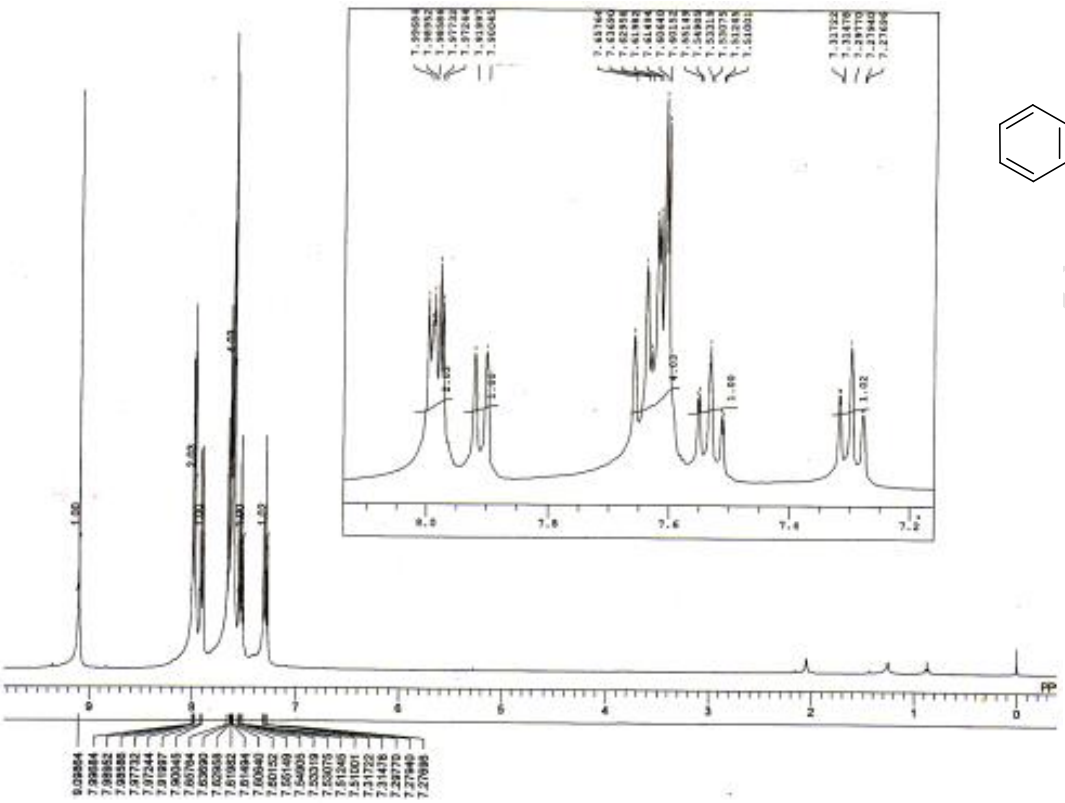
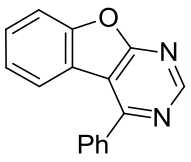
75
50
25
0





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