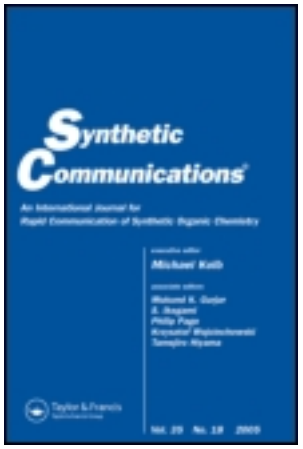

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One-Pot Synthesis of Salicylanilides by Direct Amide Bond Formation from Salicyclic Acid Under Microwave Irradiation

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ONE-POT SYNTHESIS OF SALICYLANILIDES BY DIRECT AMIDE BOND FORMATION FROM SALICYCLIC ACID UNDER MICROWAVE IRRADIATION

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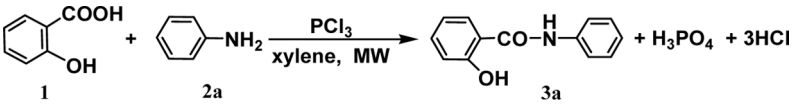
GRAPHICAL ABSTRACT



Abstract *A highly efficient protocol for the preparation of aromatic amides is described by the direct reactions between salicyclic acid and aromatic amines in the presence of phosphorous trichloride under microwave irradiation. The method has several advantages over the conventional methods, including operational simplicity, good yield, and reduced reaction time.*

Keywords Microwave irradiation; salicylanilide; synthesis

INTRODUCTION

Salicylanilide skeletons exist in many synthetic biologically active materials, and their derivatives are applied in various pharmaceutical and biochemical fields. Specifically functionalized salicylanilide and its derivatives may possess potential biological properties, including antifungal, antibacterial, antimycobacterial, and antitubercular activities and may act as potassium channel activators.[1] Thus, much attention has been paid to developing efficient methods for the synthesis of the structural unit of salicylanilides.

According to the literature, amides were typically synthesized by the aminolysis reaction of esters, nitrile, isocyanide, and other derivatives of carboxylic acid.[1d,2] Recently, effective oxidative amidations of aldehydes with amines to generate amides have been described in a few papers.[3] The smooth rearrangement of ketones with $TMSN_3$ in the presence of $FeCl_3$ to provide the corresponding amides has also been

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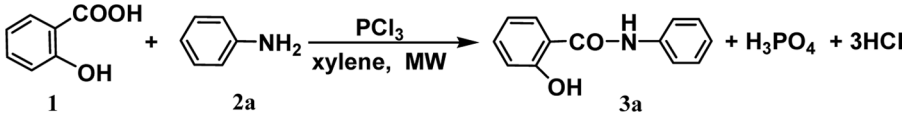
reported by J. S. Yadav and coworkers.[4] In addition, direct amidation of carboxylic acid is perhaps the most crucial and well-known transformation. However, in most cases, because of the poor reactivity of carboxylic acids, activation either separately prior to actual amidation or in situ using coupling reagents was required for a smooth reaction.[5] In this way, the application of the direct amidation of carboxylic acid is limited to some extent. Thus, we can see that these methods have several disadvantages, such as expensive reagents, long reaction time, complicated operation, and low to moderate yields.

With the development of MORE (microwave-induced organic reaction enhancement) chemistry, the direct amidation of carboxylic acid is modified successfully under microwave activation.[6] However, in these studies a limited number of aromatic amines were employed to afford the desired amides.[6a,f,g] With our growing interest in microwave (MW)–assisted organic chemistry, we performed reactions of various aromatic amines with salicylic acid as acyl donors in the presence of phosphorous trichloride under MW-assisted conditions. Herein, we present this efficient approach.

In a preliminary study, amide formation between aniline and salicyclic acid was used as the model reaction to screen the reaction conditions. The reaction temperature was set to 150 °C to favor shifting the equilibrium by removal of HCl. Meanwhile, for sake of comparison with conventional heating, almost the same conditions including molar ratio of the starting materials and solvent were applied. Neat compounds were mixed in a flask and irradiated under 500 W for 1 min to dissolve in xylene. Then phosphorous trichloride was added dropwise during the second period of microwave irradiation (Scheme 1).

After 10 min of irradiation, many materials were recovered under 100 W and 200 W. By-products were observed when the power was raised to 400 W or 500 W. The best result was gained under 300 W. Consequently, the reaction times were screened under the appropriate power. In Table 1, almost quantitative yield of salicylanilide was obtained under microwave irradiation with reduced reaction time (33 min), which is obviously better than with conventional heating using an oil bath (4 h, 85%). It revealed that the use of microwave activation can improve efficiency and reduce waste production. We studied the relationship between the amount of PCl_3 and the reaction efficiency subsequently. It can be seen from Table 2 that 40% molar ratio of PCl_3 afforded the best result.

Encouraged by these results, various aromatic amines were subjected to the reaction conditions, and representative examples are shown in Table 3. The reactions were monitored by thin-layer chromatography (TLC). Most of the aromatic amines, either bearing electron-withdrawing groups (such as halides and nitro group) or electron-donating groups (such as alkyl or alkoxyl groups), gave the expected salicylamide products with moderate to good yields under microwave conditions. All of



Scheme 1. Salicylanilide syntheses.

Table 1. Optimization of the reaction time of MW-assisted amide formation

Entry	Reaction time (min)	Yield[a] (%)
1	10	50
2	15	57
3	25	72
4	30	92
5	31	95
6	32	97
7	33	98
8	34	96
9[b]	240	85

[a]In isolated products. Conditions: 40 mol% PCl_3, in xylene, 300 W.
[b]By conventional heating (using an oil bath).

Table 2. Optimization of the amount of PCl_3 in the MW-assisted amide formation

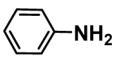
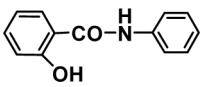
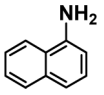
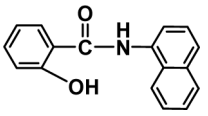
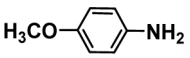
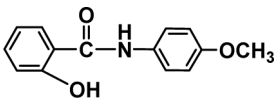
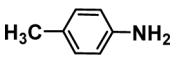
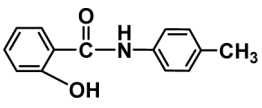
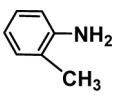
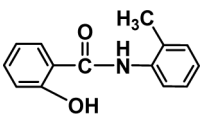
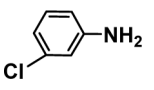
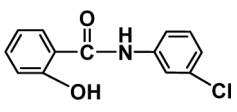
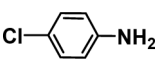
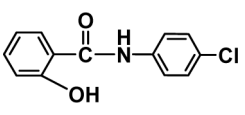
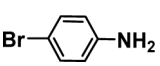
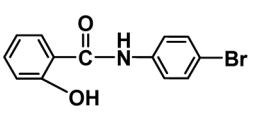
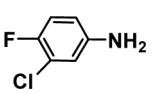
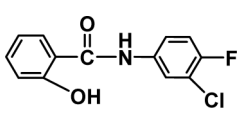
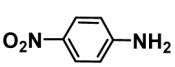
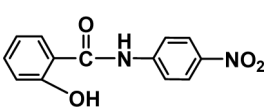
Entry	PCl_3 (molar ratio)	Yield[a] (%)
1	5	58
2	10	72
3	20	77
4	30	94
5	40	98

[a]In isolated products. Conditions: 33 min in xylene, 300 W.

the products were characterized by ^{1}H NMR, ^{13}C NMR, infrared (IR), and elemental analysis. The reaction times varied from 32 min to 55 min, which indicated the electronic effect of the substituents plays a critical role in this nucleophilic reaction. However, no desired products can be observed when N-methylaniline was reacted with salicyclic acid. This suggested that steric hinderance has significant effects on this reaction.

In this reaction, three possible products between phosphorous trichloride and salicylic acid were formulated in Fig. 1 (see also Scheme 2).[7] It is noticed that the molar ratio of PCl_3 to salicylic acid should be 1.09 to form the intermediates I and II. However, from our screening experiments for the amount of PCl_3, we know that the optimal amount of this reagent is about 30–40% of the molar ratio of the substrate, so we propose the following possible mechanism to explain the reaction. First, phosphorous trichloride reacts with salicylic acid in a 3:1 molar ratio to give salicylic chloride, which is proved by successfully recovering salicylic chloride quantitively after the reaction just between phosphorous trichloride and salicylic acid in a 3:1 molar ratio. Then protonation of the oxygen in the carbonyl group proceeds. In rate-determining step 3, the nitrogen atom of aniline acts as a nucleophile to attack the carbonyl group and give a tetrahedral intermediate IV. The tetrahedral intermediate eliminates the chloride to renew the carbonyl group rapidly. Finally, the deprotonation reaction is accomplished smoothly. In most cases, very important specific nonthermal microwave effects are evidenced, especially in the case of sluggish reactions.[8] The increase of polarity of the system will favor the progress

Table 3. Salicyl amide derivatives formed via MW-assisted synthesis[a]

Entry	Amine	Product	Reaction time (min)[b]	Yield (%)[c]
a			33	98
b			45	87
c			32	82
d			35	75
e			38	97
f			37	85
g			42	87
h			45	80
i			44	75
j			55 (240[d])	73 (44[d])

[a]In isolated products. Conditions: 40 mol% PCl_3, in xylene, 300 W.
[b]The time required for the disappearance of salicyclic acid on TLC.
[c]Isolated yields by recrystallization except entries a, e, and j.
[d]By conventional heating (using an oil bath).

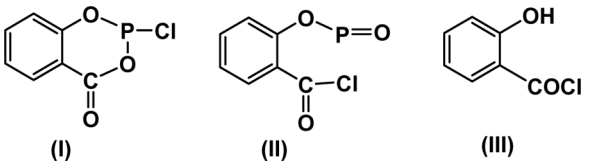
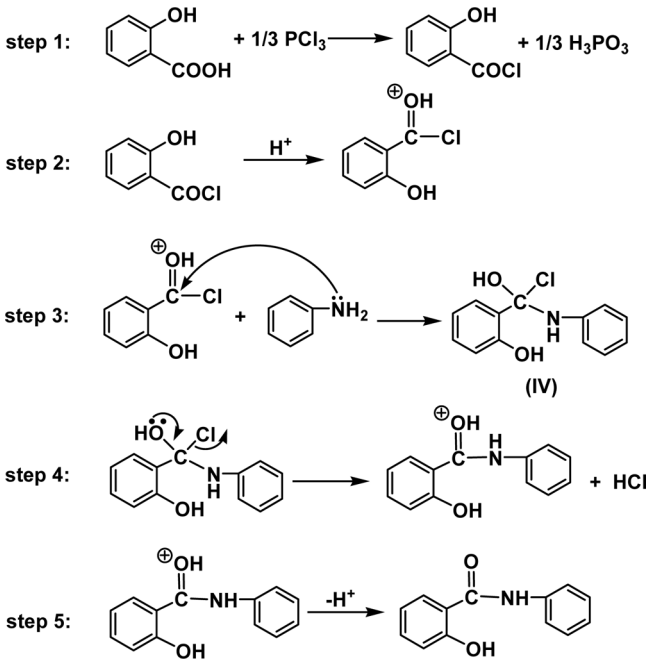


Figure 1. Hypothesis of the intermediate of the reaction of aniline and salicyl acid.



Scheme 2. Possible mechanism of the reaction of aniline and salicyl acid.

of the reaction concerned.[9] The processes of step 2 and step 4 increase the polarity of the system and favor the formation of polar amide. As the result, the reaction time is shortened distinctly.

In conclusion, a direct MW-mediated amidation between salicyclic acid and aromatic amines has been developed to afford desired salicyl amides, which was more efficient and wider in scope compared to traditional routes to these compounds. The important features of this method include short reaction time, convenient workup, and moderate to good yields.

EXPERIMENTAL

Reactants and Equipment

The commercial MW reactor was a multimode system (MAS-1, 100–1000 W, Shanghai Sineo Microwave Chemistry Science and Technology Co. Ltd., Shanghai,

China) with focused waves operating at 2.45 GHz. The temperature was controlled throughout the reaction and measured by an IR detector, which indicated the surface temperature. Mechanical stirring during the irradiation period provided good homogeneity (power and temperature).

The IR spectra were recorded on a Nicolet Magna-IR 550 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Unity Inova-400 spectrometer. Carbon, hydrogen, and nitrogen analyses were performed by direct combustion on a Carlo-Erba EA-1110 instrument, and the quoted data are the averages of at least two independent determinations.

General Procedure for the Synthesis of Amides

In a 100-mL flask, a solution of salicyclic acid (12.5 mmol) and aromatic amine (12.5 mmol) was mixed in 10 mL of xylene. The flask was positioned in the irradiation cavity, and the mixture was heated with stirring under MW irradiation with 500 W of input power for 1 min. The mixture was cooled to ambient temperature, and then an input power was set at 300 W for the appropriate reaction times. Meanwhile, PCl_3 (0.4 mL, 4.6 mmol) was added dropwise. After completion, the mixture was cooled to room temperature, and the crude product was precipitated, filtered, and purified by crystallization from EtOH, if necessary. The purity of the final product was measured (>99%) by high-performance liquid chromatography (HPLC) using $CH_3OH/H_2O/HOAc$ (75:25:0.05) as the moving phase on a Kromasil column.

Selected Data

Salicylanilide (3a). Solid; white powder; mp 137–138 °C. IR (KBr): 3294, 3032, 2669, 2561, 1612, 1550, 1496, 1450, 1373, 1334, 1234, 748, 709, 679 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.99$ (s, 1H, OH), 7.93 (s, 1H, NH), 7.58 (d, 2H, $J = 8.0$ Hz, ArH), 7.52 (d, 1H, $J = 8.0$ Hz, ArH), 7.48–7.39 (m, 3H, ArH), 7.21 (t, 1H, $J = 7.2$ Hz, ArH), 7.04 (d, 1H, $J = 8.0$ Hz, ArH), 6.93 (t, 1H, $J = 7.2$ Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.6$, 162.1, 136.8, 135.0, 129.5, 125.64, 125.57, 121.4, 119.2, 114.7. Anal. calcd. for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 72.99; H, 5.12; N, 6.66.

Salicylyl naphthylamine (3b). Solid; white powder; mp 186–187 °C. IR (KBr): 3217, 3040, 1643, 1612, 1550, 1497, 1450, 1404, 1350, 1303, 1226, 764, 733, 648, 602 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 12.02$ (s, 1H, OH), 8.26 (s, 1H, NH), 7.92 (t, 2H, $J = 6.4$ Hz, ArH), 7.84 (t, 2H, $J = 6.4$ Hz, ArH), 7.68 (d, 1H, $J = 8.0$ Hz, ArH), 7.57–7.47 (m, 4H, ArH), 7.06 (d, 1H, $J = 8.0$ Hz, ArH), 6.98 (t, 1H, $J = 7.2$ Hz, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 167.9$, 159.6, 135.0, 134.9, 134.3, 130.7, 129.6, 128.9, 127.5, 127.3, 126.9, 123.1, 122.9, 120.5, 118.5, 118.4. Anal. calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.33; H, 5.01; N, 5.42.

4′-Methoxysalicylanilide (3c). Solid; white powder; mp 158–160 °C. IR (KBr): 3311, 3172, 2956, 2840, 2701, 2555, 1628, 1567, 1512, 1458, 1358, 1250, 1026, 833, 749, 656, 525 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 12.10$ (s, 1H, OH), 10.48 (s, 1H, NH), 7.92 (d, 1H, $J = 8.0$ Hz, ArH), 7.51 (d, 1H, $J = 8.0$ Hz,

ArH), 7.44 (d, 2H, $J = 9.2$ Hz, ArH), 7.02 (t, 1H, $J = 8.4$ Hz, ArH), 6.96–6.90 (m, 3H, ArH), 3.83(s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 168.2$, 160.5, 157.5, 135.1, 132.4, 130.1, 124.3, 120.3, 118.7, 118.3, 115.3, 56.7. Anal. calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.83; H, 5.29; N, 5.78.

4′-Methylsalicylanilide (3d). Solid; white powder; mp 155–157 °C. IR (KBr): 3325, 3047, 2939, 2862, 2731, 2584, 1605, 1551, 1512, 1458, 1373, 1334, 1234, 903, 810, 748, 687, 509 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 12.08$ (s, 1H, OH), 7.89 (s, 1H, NH), 7.52 (d, 1H, $J = 8.0$ Hz, ArH), 7.46 (d, 3H, $J = 8.0$ Hz, ArH), 7.21 (d, 2H, $J = 8.0$ Hz, ArH), 7.04 (d, 1H, $J = 8.0$ Hz, ArH), 6.93 (t, 1H, $J = 7.6$ Hz, ArH), 2.37 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.1$, 135.5, 134.9, 134.1, 130.1, 130.0, 125.6, 125.5, 121.6, 119.2, 114.8, 21.2. Anal. calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.69; H, 5.98; N, 5.96.

2′-Methylsalicylanilide (3e). Solid; white powder; mp 144–145 °C. IR (KBr): 3305, 3086, 2935, 2731, 1628, 1581, 1551, 1504, 1458, 1381, 1334, 1234, 1034, 941, 825, 756, 679, 509 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 12.07$ (s, 1H, OH), 7.82 (s, 1H, NH), 7.74 (d, 1H, $J = 7.6$ Hz, ArH), 7.54 (d, 1H, $J = 8.0$ Hz, ArH), 7.47 (t, 1H, $J = 8.4$ Hz, ArH), 7.29 (t, 2H, $J = 7.2$ Hz, ArH), 7.20 (t, 1H, $J = 7.2$ Hz, ArH), 7.05 (d, 1H, $J = 8.0$ Hz, ArH), 6.95 (t, 1H, $J = 8.0$ Hz, ArH), 2.36 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 166.5$, 158.9, 136.9, 134.4, 131.1, 130.3, 127.1, 127.0, 126.0, 124.8, 120.0, 118.0, 114.9, 18.5. Anal. calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.85; H, 5.89; N, 5.93.

3′-Chrolosalicylanilide (3f). Solid; white powder; mp 171–173 °C. IR (KBr): 3280, 3010, 2894, 2825, 2670, 2555, 1621, 1567, 1482, 1459, 1366, 1335, 1235, 1204, 1096, 996, 880, 849, 780, 749, 718, 687, 533, 448 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 11.83$ (s, 1H, OH), 7.94 (s, 1H, NH), 7.73 (t, 1H, $J = 2.0$ Hz, ArH), 7.53–7.42 (m, 3H, ArH), 7.33 (t, 1H, $J = 8.0$ Hz, ArH), 7.17 (d, 1H, $J = 8.0$ Hz, ArH), 7.04 (d, 1H, $J = 8.0$ Hz, ArH), 6.94 (t, 1H, $J = 8.0$ Hz, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 167.8$, 159.3, 141.0, 134.9, 134.2, 131.6, 130.4, 124.9, 121.4, 120.4, 120.3, 119.0, 118.4. Anal. calcd. for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66. Found: C, 62.79; H, 4.28; N, 5.65.

4′-Chrolosalicylanilide (3g). Solid; white powder; mp 165–167 °C. IR (KBr): 3295, 3033, 2933, 2848, 2701, 2578, 1613, 1551, 1489, 1451, 1381, 1327, 1235, 1204, 1158, 1096, 903, 826, 756, 687, 664, 509, 432 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 11.89$ (s, 1H, OH), 7.94 (s, 1H, NH), 7.56–7.51 (m, 3H, ArH), 7.47 (t, 1H, $J = 8.4$ Hz, ArH), 7.37 (d, 2H, $J = 8.0$ Hz, ArH), 7.05 (d, 1H, $J = 8.0$ Hz, ArH), 6.94 (t, 1H, $J = 7.6$ Hz, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 167.5$, 159.1, 138.1, 134.6, 130.0, 129.5, 128.7, 123.3, 120.0, 118.6, 118.1. Anal. calcd. for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66. Found: C, 63.15; H, 4.19; N, 5.45.

4′-Bromosalicylanilide (3h). Solid; white powder; mp 173–174 °C. IR (KBr): 3294, 3056, 2924, 2855, 2677, 1605, 1551, 1481, 1450, 1373, 1327, 1234, 1204, 1157, 1072, 903, 818, 748, 709, 679, 610, 556 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 11.82$ (s, 1H, OH), 7.88 (s, 1H, NH), 7.51–7.43 (m, 6H, ArH), 7.02 (d, 1H, $J = 8.0$ Hz, ArH), 6.91 (t, 1H, $J = 7.6$ Hz, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 167.6$,

159.2, 138.6, 134.7, 132.5, 130.1, 123.8, 120.0, 118.7, 118.2, 116.8. Anal. calcd. for $C_{13}H_{10}BrNO_2$: C, 53.42; H, 3.42; N, 4.79. Found: C, 53.67; H, 3.47; N, 4.88.

4′-Fluoro-3′-chrolosalicylanilide (3i). Solid; white powder; mp 200–202 °C. IR (KBr): 3326, 3056, 2940, 2856, 2724, 2593, 1621, 1559, 1505, 1459, 1389, 1235, 1212, 1157, 880, 810, 741, 687, 648, 525 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 11.79$ (s, 1H, OH), 7.91 (s, 1H, NH), 7.80–7.77 (m, 1H, ArH), 7.51–7.48 (m, 2H, ArH), 7.42–7.39 (m, 1H, ArH), 7.18 (t, 1H, $J = 8.8$ Hz, ArH), 7.05 (d, 1H, $J = 8.0$ Hz, ArH), 6.94 (t, 1H, $J = 7.2$ Hz, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 167.2$, 158.7, 136.2, 134.4, 130.2, 129.8, 123.0, 122.0, 120.0, 119.8, 118.5, 117.9, 117.5. Anal. calcd. for $C_{13}H_9FClNO_2$: C, 58.77; H, 3.41; N, 5.27. Found: C, 58.89; H, 3.49; N, 5.08.

4′-Nitrosalicylanilide (3j). Solid; yellow powder; mp 228–229 °C. IR (KBr): 3256, 3056, 2940, 2856, 1644, 1620, 1558, 1512, 1458, 1334, 1258, 1234, 1118, 933, 856, 756, 718, 694, 509, 463, 440 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): $\delta = 11.4$ (s, 1H, OH), 10.8 (s, 1H, NH), 8.26 (d, 2H, $J = 8.8$ Hz, ArH), 8.00 (d, 2H, $J = 8.8$ Hz, ArH), 7.87 (d, 1H, $J = 8.0$ Hz, ArH), 7.45 (t, 1H, $J = 7.2$ Hz, ArH), 7.03–6.98 (m, 2H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 167.4$, 158.2, 145.7, 143.5, 134.7, 130.6, 125.9, 121.0, 120.2, 119.8, 118.0. Anal. calcd. for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.88; N, 10.85. Found: C, 60.19; H, 3.99; N, 10.80.

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