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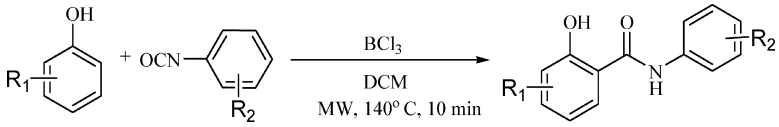

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Microwave-Assisted Synthesis of Salicylamide via BCl_3 Mediated Coupling

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A novel and efficient microwave-assisted, BCl_3-mediated coupling reaction to synthesize salicylamide structures from phenols and isocyanates is described.

Introduction

The application of parallel synthesis to generate focused combinatorial libraries as an efficient means of creating "druglike" leads has gained considerable interest. By accelerating the synthesis of focused sublibraries around the leads to quickly explore the structure−activity relationship (SAR), combinatorial chemistry has greatly impacted the drug discovery process.[1−3] Owing to the intimate incorporation of parallel synthesis technologies into all phases of the drug discovery process, the focus of combinatorial chemistry has shifted from large libraries of simpler and nondruglike structures to more complex and druglike structures. This trend demands large pool of reactions to be fully investigated and optimized to fit into parallel synthesis.[3] In addition, scaffolds originated from natural products and known drugs have been the recent focus of druglike combinatorial library design and synthesis.[4]

Salicylamide is the basic scaffold of several known drugs and bioactive compounds (Figure 1).[5] Drugs having a salicylamide scaffold or its derivative scaffold benzoxazinedione, are orally available. This justifies the potential for new drugs coming from novel salicylamide-based compounds via further exploration of the diversity of salicylamides. The current method to make salicylamides is based on the amide coupling reaction of substituted salicylic acids and anilines;[5b−e,6] however, substituted salicylic acids have a limited commercial pool, and using the Kolbe−Schmitt reaction to get access to them suffers from the harsh reaction conditions and lack of some functional group tolerance.[7] Therefore, new synthetic routes are needed to increase the structural diversity of salicylamide-based libraries. In our drug discovery programs, we are facing the challenge of the synthesis of some salicylamide-based structures for a SAR study. Some of the structures, however, cannot be made from commercially available substituted salicylic acids. This has forced us to explore new methods to synthesize these structures. During the literature search, we were attracted by one BCl_3-mediated coupling reaction of phenols with isocyanates.[8] Boron trichloride specifically induces ortho selectivity via formation of a cyclic intermediate between phenols and isocyanates. The wide availability of phenols made this method very attractive for testing as a parallel synthesis method. However, to the best of our knowledge, the reaction conditions for diverse functional groups have barely been explored to help us to decide the scope of this reaction.[8] Therefore, further investigation of the scope and limitation of this reaction and elaboration and optimization of the reaction conditions are essential to apply this reaction to parallel synthesis schemes. In addition, the advantages of microwave-assisted synthesis have been widely recognized and have been designed as one efficient parallel synthesis platform.[9] Successful application of microwave-assisted conditions can tremendously reduce library production time and also may significantly improve the yields, which can greatly simplify the parallel purification load. Therefore, elaboration of microwave conditions for this reaction will be valuable for parallel synthesis of salicylamide-based libraries.

Results and Discussion

Boron trichloride was an efficient catalyst for ortho-carbonylation of phenols to afford good to excellent yields of salicylamide and diaryl ketone.[8a] The conventional reactions were carried out in dichloromethane, benzene, or toluene under reflux for 4−16 h. Previous data and our preliminary results (Table 1) indicate the strong preference of the electron-donating groups in the phenol for Lewis acid-mediated ortho-nucleophilic adduction. If both phenols and isocyanates have electron-withdrawing groups (Table 1, entry 7), the reaction gives a messy mixture without the desired product. This has been a limitation for library design and synthesis for electron-poor substrates. As we can see, many known drugs bearing this scaffold have electron-withdrawing or neutral groups on the phenol ring (Figure 1). Therefore, exploring reaction conditions for these kinds of structures and understanding the substituent effects are critically important to synthesize libraries having diversity and druglike features.

BCl_3-mediated coupling has been shown to give a higher yield when the temperature is relatively high.[8] Our preliminary data (Table 1) also show that a longer reaction time is required to complete the conversion. Microwave irradiation has the feature of directly transfering energy to the reactants,

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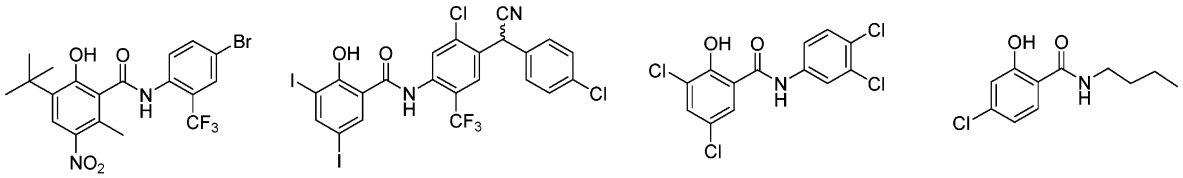
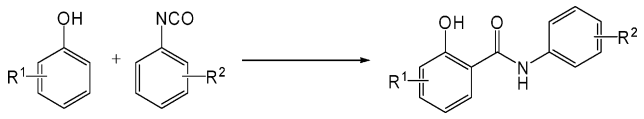


Figure 1. Structures of salicylamides.

Table 1. Conventional Synthesis of Salicylamides with Various Phenols and Isocyanates



					conversion (%, HPLC)[a]			MS found (*m*/*z*)	
entry	R_1	R_2	reaction solvent	reaction time (h)	starting material[c]	product + byproduct[b]	R.T. (min)	$[M + H]^+$	$[M - H]^-$
1	3-MeO	4-Me	DCM	5	20	67 + 10[b]	5.59, 5.86[b]	244.1, 230.1[b]	242.1, 228.1[b]
2	3-MeO	4-MeO	DCM	5	22	64 + 12[b]	6.36, 5.86[b]	258.1, 244.2[b]	256.1, 242.1[b]
3	3-MeO	4-NO_2	DCM	5	36	53 + 7[b]	5.63, 5.10[b]	274.1, 272.0[b]	260.1, 258.1[b]
4	3-MeO	4-NO_2	DCM	10	24	56 + 11[b]	6.04, 5.69[b]	289.1, 287.1[b]	275.1, 273.0[b]
5	3-MeO	4-NO_2	DCM	16	8	61 + 15[b]	6.04, 5.69[b]	289.1, 287.1[b]	275.1, 273.0[b]
6	3-MeO	4-NO_2	toluene	16	5	63 + 10[b]	6.04, 5.69[b]	289.1, 287.1[b]	275.1, 273.0[b]
7	3-CO_2Me	4-NO_2	toluene	16	8	0[d]			

[a] Gradient MeCN in H_2O 30−100%, 10 min. [b] Demethylation compound. [c] Corresponding phenols. [d] Messy mixture.

Table 2. Assessment of Microwave-assisted Coupling Conditions[a]

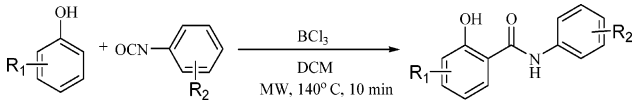
temp (°C)[b]	time (min)	conversion (%)[c]	temp (°C)[b]	time (min)	conversion (%)[c]
80	5	34.8	120	10	83.4
80	10	44.0	120	20	87.7
80	20	53.7	140	5	96.7
100	5	60.2	140	10	95.7
100	10	70.6	140	20	92.8
100	20	78.9	160	5	94.8
120	5	79.5	160	10	94.3

[a] Reaction conditions: phenol, 1 equiv; isocyanate, 1 equiv; BCl_3, 1 equiv. [b] Temperature. [c] HPLC.

not through the solvent, as conventional heating does, and thus can dramatically shorten the reaction time and improve the yields of many reactions, especially the reactions that demand a high temperature and long heating time.[9] In addition, microwave irradiation has been widely applied in combinatorial library synthesis, drug discovery, and general organic synthesis.[9]

We have considered the reaction of phenol and *p*-tolyl isocyanate as a model reaction for condition optimization of microwave-mediated ortho-carbonylation. In Table 2 are reported the results of different times and temperatures of microwave irradiation on the model reaction. The reaction is remarkably dependent on the irradiation temperature. For 10 min of reaction, the transformation of the product has been increased from around 35% to above 97% when the temperature is raised from 80 to 140 °C. It demonstrates clearly that higher temperature facilitates the conversion.

Scheme 1. Synthesis of Salicylamides Mediated by Microwave Irradiation and BCl_3 Catalysis



When the temperature was higher than 140 °C, some decomposition might have occurred and gave no further improvement for the reaction. Compared to temperature, the reaction time played a minor role in the microwave irradiation. The conversion was increased ∼10% per 5 min at lower temperature (80−100 °C). Slight decomposition might happen for extended time when the temperature is higher than 140 °C. The best conversion was given at 140 °C and 5−10 min of irradiation. This indicated the transition from the boron complex to the final product is an energy-dependent and fast process. On the basis of these results, we selected 140 °C for 10 min as the microwave conditions for our further studies.

After optimization of the microwave reaction conditions for the model reaction, we turned our attention to the effects of substituent groups on both phenols and isocyanates (Scheme 1). The corresponding phenol was charged in a 10-mL microwave reaction tube and mixed with anhydrous dichloromethane. Boron trichloride (1 equiv) was added dropwise at 0 °C, followed by addition of the corresponding isocyanate (1 equiv). The tube was capped and irradiated on the microwave synthesizer at 140 °C for 10 min to afford a brown solution. A small volume of the solution was taken out, and the solvent was removed. The crude product was analyzed by HPLC/MS to identify the conversion rate of each reaction (Table 3). The reaction demonstrated high C- vs O-acylation selectivity and ortho vs para regioselectivity. No

Table 3. Microwave-Assisted Synthesis of Salicylamides with Various Phenols and Isocyanates

			conversion	yield	HPLC for product[a]		MS Found (*m*/*z*)		TLC (R_f)	
entry	R_1	R_2	HPLC %[a]	isolated %	R.T. (min)	purity (%)	$[M + H]^+$	$[M - H]^-$	D/M (98:2)[c]	H/E (6:1)[d]
1	H	4-Me	90	77.1	2.65	95.3	228.2	226.2	0.75	0.35
2	H	4-MeO	81.7	72.8	2.09	100	244.2	242.2	0.48	0.20
3	H	4-NO_2	84.5	18.6	2.28	100		257.2	0.46	0.10
4	2-allyl	4-Me	80.5	62.2	4.77	100	268.2	266.3	0.92	0.51
5	2-allyl	4-MeO	86.9	63.6	3.82	100	284.2	282.2	0.77	0.40
6	2-allyl	4-NO_2	75	72.1	4.41	73.4		287.2	0.74	0.23
7	3-MeO	4-Me	83.6, 16.4[d]	68.9	2.82	100	258.2	256.3	0.68	0.31
8	3-MeO	4-MeO	88.6, 8.4[d]	67.8	2.20	100	274.2	272.2	0.47	0.16
9	3-MeO	4-NO_2	85.8, 9.9[d]	48.6	2.50	60.5	289.2	287.2	0.42	0.06
10	4-Cl	4-Me	47.7	43.6	3.58	90.7	262.2	260.2	0.72	0.44
11	4-Cl	4-MeO	42.9	41.5	2.84	95	278.2	276.2	0.52	0.29
12	4-Cl	4-NO_2	52	17.1	3.01	95		291.2	0.43	0.10
13	4-CO_2Me	4-Me	27.1	18.9	3.03	100		284.3	0.51	0.29
14	4-CO_2Me	4-MeO	32.8	8.3	5.46[g]	98.9	302.3	300.2	0.30	0.12
15	4-CO_2Me	4-NO_2	9.6					315.2	0.20	0.0
16[e]	4-CO_2Me	4-MeO	60.2, 2.8[d]	20.9			302.3	300.2	0.30	0.12

[a] Gradient MeCN in H_2O 30−100%, 10 min. [b] Dichloromethane/methanol. [c] Hexane/ethyl acetate. [d] Demethylation product. [e] MW, 140 °C, 30 min.

O-acylation or para-position acylation products were detected and isolated in any of the entries.

The conversion rate of the reactions was strongly affected by the nature of the substituents on both reagents. Thus, electron-withdrawing groups on both phenol (entries 13−15) and isocyanate (entries 3, 6, 9, and 15) sides had strong negative influence on coupling transformation and gave low yields. No product was isolated while both sides had strong electron-withdawing substituents (entry 15). In an additional reaction of the entry 14, the conversion yield was increased from 33 to 60% when the reaction was prolonged from 10 to 30 min (see entry 16). When phenols had neutral or slight electron-withdrawing groups, the yields were drastically affected by the substituents on isocyanate moieties (entries 1−3 and 10−12). However, strong electron-donating groups on phenols gave consistently high yields (entries 4−9).

Microwave-assisted conditions produced ~10% demethylation as a byproduct when the reaction time was 10 min, as shown on LC/MS spectra (entries 7−9). The creation of this side product is consistent with the known behavior of a BCl_3-mediated coupling reaction run for extended periods of time. In consideration of the reaction rate acceleration induced by the 3-methoxy group on the phenol, we propose that the reaction finished in a significantly shorter time than the 10-min duration of our reaction protocol (10 min). The relatively long irradiation time leads to more demethylation byproduct. However, demethylation side product was barely detectable for entries carrying a methoxy group on the electron withdrawing groups, such as an isocyanate (2, 5, 14), and it was only 2.8% for entry 16. Accordingly, demethylation product was not increased for entry 8, which possessed methoxy groups on both reagents, in comparison with the methoxy group substituted only on phenol (entries 7 and 9). Further, the results demonstrate that the demethylation reaction occurred more easily and faster for the methoxy group on a phenol moiety than on an aniline moiety. These selective demethylation results can be explained by the Lewis acid nature of BCl_3.[10a] To cleave the ether bond, boron and ether oxygen need to form a complex, and electron-withdrawing groups will inhibit the formation of the complex.[10b]

In summary, we have demonstrated the utility of microwave-assisted, BCl_3-mediated coupling of phenols with isocyanates to make a salicylamide-based exploratory library. The effect of diverse substitution groups, especially neutral and electron-withdrawing groups on the coupling reactions, has been analyzed. These structures are currently evaluated for their biological activity in our drug discovery programs. Further development of the salicylamide-based libraries and their utility in drug discovery programs will be reported in due course.

Experimental Section

All reactions were performed in oven-dried glassware unless otherwise noted. Reagents were purchased from commercial suppliers and used without further purification. Reactions were carried out on a CEM Explorer Microwave Synthesizer. Purifications of the reaction products were performed on an Isco Optix 10 parallel purification system. Solvents in collected fraction tubes were evaporated by a Thermo-Savant Explorer HT evaporator. NMR spectra were recorded on a Varian Mercury 400 (^{1}H NMR at 400 MHz) spectrometer in DMSO-d_6 or $CDCl_3$ using residual solvent peaks as internal standard (2.49 (DMSO-d_6) or 7.27 ($CDCl_3$) ppm. Chemical shifts are given in parts per million and coupling constants, *J*, are given in Hz. Mass spectra were obtained on a Thermo-Finnigan LCQ Advantage MAX spectrometer.

General Experimental Procedure for the Synthesis of Salicylamides. To a solution of phenol (1 mmol) in anhydrous dichloromethane (1 mL) was added a solution of 1 M boron trichloride in dichloromethane (1 mL, 1 mmol) at 0 °C. The mixture was stirred at room temperature for 5 min, and a corresponding phenyl isocyanate (1 mmol) was added. The resulting mixture was refluxed for various times as specified in Table 1. The conversion was monitored by analyzing the reaction mixture by LC/MS. After the reaction was completed, the solution was cooled to 0 °C, and 1 N HCl (5 mL) and diethyl ether (10 mL) were introduced. The

mixture was stirred at room temperature for a few hours. The precipitated solid was filtered out, washed with water and diethyl ether, and dried under vacuum to give pure product (analyzed by HPLC/MS). The filtrate was extracted by diethyl ether (3 × 5 mL), and the combined organic phase was washed with saturated brine, dried over Na_2SO_4, and evaporated to give additional product.

General Experimental Procedure for Microwave-Assisted Synthesis of Salicylamides (1−15). To an oven-dried 10-mL microwave reaction tube charged with a mixture of corresponding phenols (1 mmol) and anhydrous dichloromethane (1 mL) was added a solution of 1 M boron trichloride in dichloromethane (1 mmol, 1 mL), followed by addition of the corresponding isocyanate (1 mmol) at 0 °C. The tube was capped and irradiated on the microwave synthesizer at 140 °C for 10 min to afford a brown solution. After cooling to room temperature, 1 M HCl solution (5 mL) was introduced at 0 °C. The mixture was stirred at room temperature for a few hours to give a clear two-phase solution. The organic layer was separated, and the aqueous solution was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was filtered through a short column packed with Celite and anhydrous sodium sulfate. The filtrate was concentrated to 2 mL, mixed with silica gel (1 g), evaporated to dryness, packed into an ISCO sample tube, and purified on an ISCO CombiFlash Optix10 using a 4-g ISCO RediSep prepacked silica gel column eluting with linear gradient methanol in dichloromethane. The product was collected, and the solvents were evaporated using the Thermo-Savant Explorer HT Evaporator and dried under high vacuum to give the solid product. The product was characterized by ^{1}H NMR and LC/MS.

2-Hydroxy-*N*-*p*-tolylbenzamide (1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (br, 1H), 10.34 (s, 1H), 7.95 (dd, J = 8.0, 1.6 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.44−7.40 (m, 1H), 7.17 (d, J = 8.0 Hz, 2H), 6.97−6.93 (m, 2H), 2.48 (s, 3H). ESI-MS $[M - H]^-$ = 226.3.

2-Hydroxy-*N*-(4-methoxyphenyl)benzamide (2). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (br, 1H), 10.29 (s, 1H), 7.96 (dd, J = 8.0, 1,2 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.44−7.40 (m, 1H), 6.96−6.92 (m, 4H), 3.74 (s, 3H). ESI-MS $[M - H]^-$ = 242.2.

2-Hydroxy-*N*-(4-nitrophenyl)benzamide (3). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (br, 1H), 8.26 (d, J = 9.2 Hz, 2H), 7.99 (d, J = 9.2 Hz, 2H), 7.85 (dd, J = 8.0, 2.0 Hz, 1H), 7.45−7.41 (m, 1H), 7.01−6.94 (m, 2H). ESI-MS $[M - H]^-$ = 257.2.

3-Allyl-2-hydroxy-*N*-*p*-tolylbenzamide (4). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 7.94 (dd, J = 7.6, 1.2 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.33 (dd, J = 7.6, 1.2 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 6.90 (t, J = 7.6 Hz, 1H), 5.96 (m, 1H), 5.08−5.01 (m, 2H), 3.36 (d, J = 6.8 Hz, 2H, partially overlapped by H_2O peak), 2.29 (s, 3H). ESI-MS $[M - H]^-$ = 266.3.

3-Allyl-2-hydroxy-*N*-(4-methoxyphenyl)benzamide (5). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 7.93 (dd, J = 8.0, 1.2 Hz, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.32 (dd, J = 8.0, 1.2 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 6.90 (t, J = 8.0 Hz, 1H), 6.02−5.92 (m, 1H), 5.08−5.01 (m, 2H), 3.75 (s, 3H), 3.35 (d, 2H, partially overlapped by H_2O peak). ESI-MS $[M - H]^-$ = 282.2.

3-Allyl-2-hydroxy-*N*-(4-nitrophenyl)benzamide (6). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (s, 1H), 10.86 (s, 1H), 8.28 (d, J = 9.2 Hz, 2H), 8.01 (d, J = 9.2 Hz, 2H), 7.95−7.92 (m, 1H), 7.38 (dd, J = 8.0, 1.6 Hz, 1H), 6.96 (t, J = 8.0 Hz, 1H), 6.03−5.93 (m, 1H), 5.09−5.02 (m, 1H), 3.37 (d, J = 7.2 Hz, 2H). ESI-MS $[M - H]^-$ = 297.2.

2-Hydroxy-4-methoxy-*N*-*p*-tolylbenzamide (7). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 6.54 (dd, J = 8.8, 2.4 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 3.78 (s, 3H), 2.28 (s, 3H). ESI-MS $[M - H]^-$ = 256.3.

2-Hydroxy-4-methoxy-*N*-(4-methoxyphenyl)benzamide (8). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (br, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 9.2 Hz, 2H), 6.93 (d, J = 9.2 Hz, 2H), 6.53 (dd, J = 8.8, 2.8 Hz, 1H), 6.46 (d, J = 2.8 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H). ESI-MS $[M - H]^-$ =272.2.

2-Hydroxy-4-methoxy-*N*-(4-nitrophenyl)benzamide (9). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (br, 1H), 10.67 (s, 1H), 8.26 (d, J = 9.2 Hz, 2H), 7.98 (d, J = 9.2 Hz, 2H), 7.95 (d, J = 8.8 Hz, 1H), 6.58 (dd, J = 8.8, 2.4 Hz, 1H), 6.52 (d, J = 2.4 Hz, 1H), 3.80 (s, 3H). ESI-MS $[M - H]^-$ = 287.2, 273.2.

5-Chloro-2-hydrox-*N*-*p*-tolylbenzamide (10). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (br, 1H), 10.35 (s, 1H), 7.97 (d, J = 2.4 Hz, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.45 (dd, J = 8.8, 2.4 Hz, 1H), 7.17 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 1H), 2.78 (s, 3H). ESI-MS $[M - H]^-$ = 260.2.

5-Chloro-2-hydrox-*N*-(4-methoxyphenyl)benzamide (11). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (br, 1H), 10.33 (s, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.58 (d, J = 9.2 HZ, 2H), 7.45 (dd, J = 8.8, 2.4 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 9.2 Hz, 2H), 3.74 (s, 3H). ESI-MS $[M - H]^-$ = 276.2.

5-Chloro-2-hydroxy-*N*-(4-nitrophenyl)benzamide (12). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 8.27 (d, J = 9.2 HZ, 2H), 7.98 (d, J = 9.2 Hz, 2H), 7.81 (d, J = 2.4 Hz, 1H), 7.46 (dd, J = 8.8, 2.4 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H). ESI-MS $[M - H]^-$ = 291.2.

Methyl 4-Hydroxy-3-(*p*-tolylcarbamoyl)benzoate (13). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (br, 1H), 8.55 (d, J = 2.0 Hz, 1H), 7.98 (dd, J = 8.4, 2.0 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 1H). ESI-MS $[M - H]^-$ = 284.3.

Methyl 4-Hydroxy-3-((4-methoxyphenyl)carbamoyl)-benzoate (14). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 2.0 Hz, 1H), 8.10 (dd, J = 8.6, 2.0 Hz, 1H), 8.04 (br, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 3.94 (s, 3H), 3.84 (s, 3H). ESI-MS $[M + H]^+$ = 302.3; $[M - H]^-$ = 300.2.

Supporting Information Available. Experimental procedures and analytical data for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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