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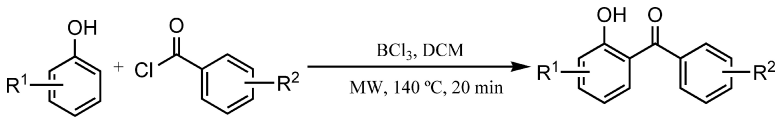

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Microwave-Assisted, Boron Trichloride Mediated Acylation of Phenols−Synthesis of (*o*-Hydroxyaryl)(Aryl)methanones and Xanthones

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A novel and efficient microwave-assisted, BCl_3 mediated coupling reaction to synthesize *o*-(hydroxyaryl)-(aryl)methanone structures from phenols and acyl chlorides is described. This reaction was further incorporated into a two-step synthesis of biologically interesting xanthones.

Introduction

The application of parallel synthesis to generate focused libraries based on privileged scaffolds from drugs and bioactive natural products as an efficient means of creating "drug-like" leads has gained considerable interest.[1] The drug-like properties of molecules from these focused libraries have been dramatically improved compared to those of traditional combinatorial libraries. By accelerating the synthesis of focused sublibraries around leads to quickly explore the structure−activity relationship (SAR), combinatorial chemistry has greatly impacted the drug-discovery process.[1−3] The shift from large libraries of simple, nondrug-like structures to more complex, drug-like structures demands a tremendous pool of optimized, fully characterized reactions for parallel synthesis to be useful.[2] In a continuation of our effort to establish validated reactions for in-house, drug-like focused library synthesis, we are expanding BCl_3 mediated coupling reactions[4] to acylation of phenols to synthesize (*o*-hydroxyaryl)(aryl)methanones. (*o*-Hydroxyaryl)(aryl)methanone is the basic scaffold of several bioactive compounds (Figure 1A).[5] This scaffold has been reported as a novel PKB inhibitor with a unique binding mode.[5b] This scaffold has also been discovered from our in-house virtual library design and virtual screening for various protein targets, including kinases. This justified the potential for new drugs coming from novel (*o*-hydroxyaryl)(aryl)methanone based compounds via exploring the diversity of (*o*-hydroxyaryl)(aryl)-methanones. The most useful reactions for the synthesis of these substances are the conventional Friedel−Crafts acylation and Fries type rearrangement of suitable aryl esters.[6] These procedures, however, suffer somewhat from a lack of selectivity. Both ortho- and para-acylation of phenols will occur to yield a mixture.[6,7] Another limitation for the application of these reactions in parallel synthesis is the limited functional group tolerance due to their harsh reaction conditions. Such limitations indicate that the regiocontrol of the acylation process of phenol derivatives is still an open problem and that further synthetic studies are appropriate. Couplings of thioesters or acyl chlorides with boronic acids are efficient routes to synthesize biaryl ketones.[8,9] However, the ortho selectivity to phenols has still been an issue waiting to be addressed. Preliminary works have been reported for ortho-acylation of phenols: these include BCl_3 mediated coupling reaction of phenols with acyl chlorides or nitriles, as well as bromomagnesium phenolates with acyl chlorides.[7,10,11] However, to our best knowledge, the reaction conditions for diverse functional groups have barely been explored to help us decide the scope of this reaction.[7,10,11] We are also concerned with general applicability of bromomagnesium phenolates in our parallel-synthesis platform. Therefore, we focused our attention on the scope and limitation of the BCl_3 mediated coupling reaction of phenols with acyl chlorides. In addition, the advantages of microwave-assisted synthesis have been widely recognized and have been designed as one efficient parallel-synthesis platform.[12] 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 the parallel synthesis of (*o*-hydroxyaryl)(aryl)methanone based libraries. Library-in-library has been a new way to increase library synthesis efficiency and diversity. Xanthones are bioactive natural products and have shown many biological activities (Figure 1B).[13] Syntheses of the xanthone scaffold typically involve the intermediacy of a benzophenone or a diaryl ether, plus harsh reaction conditions.[14] There is one recent publication of the one-pot synthesis of xanthones by tandem coupling−cyclization of arynes and salicylates.[14c] However, the application scope is limited to the availability of highly reactive arynes and their precursors. We speculate that xanthones can be synthesized from (*o*-hydroxyaryl)(aryl)methanone structures (Scheme 2). Here, we report our preliminary work on the synthesis of xanthones using our optimized BCl_3 coupling conditions.

Results and Discussion

Friedel−Crafts acylation and Fries type rearrangement of suitable aryl esters have been extensively applied to acylate

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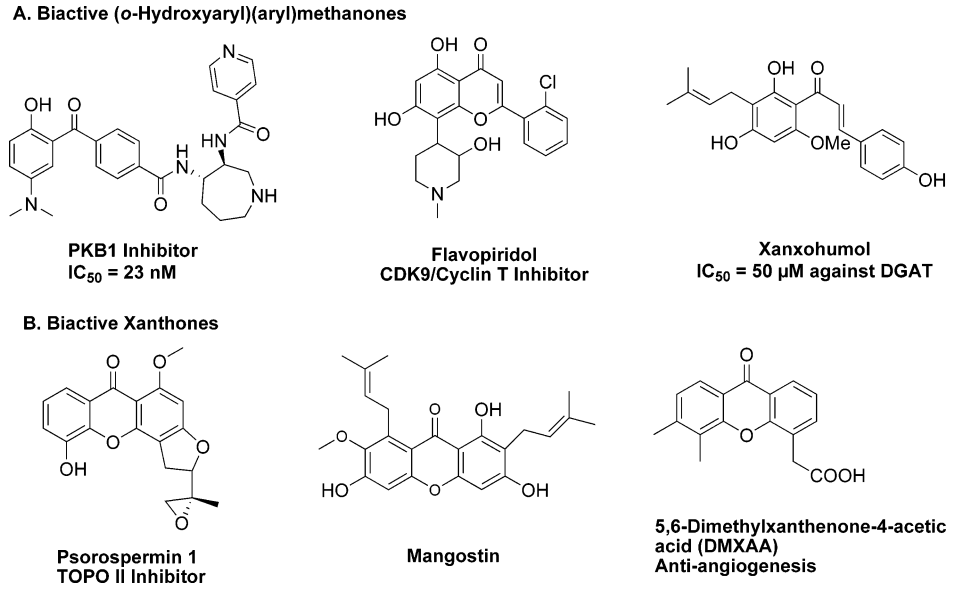
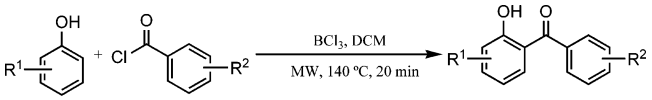


Figure 1. Structures of bioactive (*o*-hydroxyaryl)(aryl)methanones and xanthones.

Scheme 1. Synthesis of (*o*-Hydroxyaryl)(aryl)methanone Mediated by Microwave Irradiation and BCl_3 Catalysis



phenols.[6] Both reactions, however, suffer a lack of selectivity of ortho over para position. The conventional Houben−Hoesche reaction has been extensively used to acylate polyphenols, such as resorcinol, to give ortho-substitution.[7,15] However, this reaction is inert to monophenols without other electron-donating groups attached. Later, the Houben−Hoesche reaction was modified by using boron trichloride and $AlCl_3$ to produce exclusive ortho α-chloroacetyl phenol from phenol and α-chloroacetonitrile.[7] However, this modification suffers a lack of reactivity for substituted benzonitriles.[7] Boron trichloride has been demonstrated to be an efficient catalyst to produce salicylamides via coupling of phenols to isocyanates.[4,11] Boron trichloride has also been reported to be a catalyst for ortho-carbonylation of phenols to afford (*o*-hydroxyaryl)(aryl)methanones and diaryl ketones.[11] The conventional reactions were carried out in benzene under reflux for 10−24 h. Previous data only included 3-methoxyl substitution at a phenol moiety, and no other substitutions have been explored at both phenols and acyl chlorides. This has been a limitation for library design and synthesis for diverse structures. Many bioactive molecules bearing this scaffold have diverse substitution on both the phenols and acyl chlorides (Figure 1). Therefore, exploring reaction conditions for these kinds of structures and understanding the substituent effects are critical to design and synthesize libraries having diversity and drug-like features. BCl_3 mediated acyl coupling has been shown to occur only at 110 °C.[11] Microwave-assisted conditions have been well-known to facilitate these kinds of reactions.[4,12] Therefore, we applied BCl_3 mediated, microwave-assisted phenol-coupling conditions optimized in a previous report in our current work.[4] Here, we report our progress on the ortho-acylation of phenols with acyl chlorides and the effect of substitution patterns on coupling efficiency.

Synthesis of (*o*-hydroxyaryl)(aryl)methanones (Scheme 1) was carried out in a CEM microwave reactor. The results (Table 1) show the substitution on phenols has a drastic effect on the final yields. 3-Methoxyl substituted phenols consistently gave high yields regardless of the substitution on acyl chloride. Other substitution positions and groups on phenols have yielded no products or extremely low yield without synthetic usefulness. Our previous report of BCl_3 mediated coupling of phenols with isocyanates showed demethylation products as the major side products. However, the low yield here cannot be explained by demethylation because 3-OMe substituted phenols with methoxyl substitution on acyl chlorides consistently gave a decent high yield. Also, we have not detected major peaks of demethylation side products from liquid chromatography−mass spectrometry (LC−MS) analysis. The major side products identified in our study are starting materials and phenol esters. The phenoxydichloroborane intermediate is unstable, and therefore, coordination with electrophiles, such as acyl chlorides or isocyanates, is the key step to transform the unstable phenoxydichloroborane intermediate into a more stable complex via B−O or B−N bond formation.[16] The weaker B−O bond of the BCl_3 mediated complex of phenols and acyl chlorides compared to the B−N bond formed by isocyanates may explain the relatively sluggish reactivity and high phenol ester side products. Compared to the methoxyl group, methyl is a much weaker electron-donating group and 3-methyl phenols gave 20−30% desired products (Table 1, entries 12−15). Clearly, in our data, a strong electron-donating group at the meta-position of phenols is required to promote the ortho-carbonylation by substituted benzoyl moieties. Substituents on acyl chlorides play a relatively minor, but evident, role for the yields. Electron-withdrawing groups on acyl chlorides can increase electrophilicity and, therefore, gave better yields (Table 1, entries 22−24). Methoxyl substitution at acyl chlorides also has a major impact on final yields. The ortho- and para-substituted acyl chlorides gave much lower yields and meta-substitution had only a slightly lower yield compared to that with no substitution (Table 1, entries 19,

Scheme 2. Synthesis of Xanthones

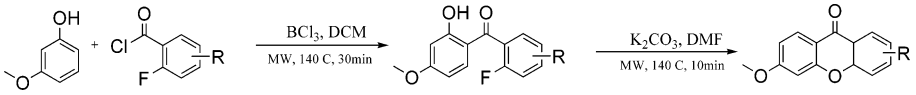
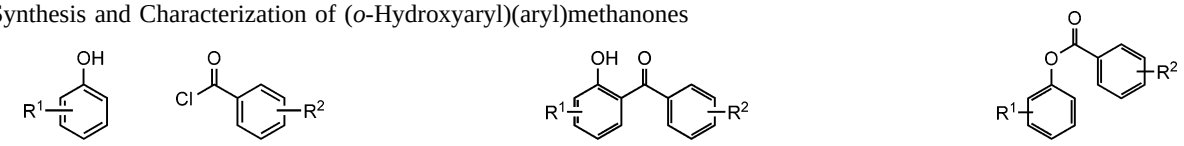


Table 1. Synthesis and Characterization of (*o*-Hydroxyaryl)(aryl)methanones



entry	R^1	R^2	conversion, HPLC %[a]	yield, isolated %	purity, %	HPLC[a], RT, min	yield, isolated %	HPLC[a], RT, min
1	H	H					15.5	7.03
2	H	2-F					28.3	8.26[b]
3	H	4-Me					9.1	7.68
4	H	4-MeO					32.9	6.89
5	3-Cl	2-F					21.3	9.05[b]
6	3-Br	H					12.0	8.25
7	3-Br	4-Me					17.3	9.03
8	3-Br	4-MeO					21.8	8.30
9	4-Br	H					1.3	8.20
10	4-Br	4-Me					15.2	8.93
11	4-Br	4-MeO					28.4	8.23
12	3-Me	H	26.3	16.1	98.9	7.50		
13	3-Me	2-F	27.1	15.7	98.3	7.54	33.2	8.87[b]
14	3-Me	4-Br	25.8	16.9	99.0	7.60	6.9	8.83
15	3-Me	4-MeO	31.4	22.1	100.0	7.68	18.1	7.68
16	4-Me	H					7.7	7.72
17	4-Me	4-Br					4.5	9.10
18	4-Me	4-MeO					28.5	7.68
19	3-MeO	H	85.4	76.5	100.0	6.88		
20	3-MeO	4-Br	72.0	63.5	98.4	8.27		
21	3-MeO	4-Me	90.2	81.8	99.5	7.78		
22	3-MeO	4-CF_3	93.5	82.8	100	8.09		
23	3-MeO	4-CO_2Me	84.3	74.7	99.0	6.72		
24	3-MeO	4-NO_2	95.5	84.2	94.0	6.59		
25	3-MeO	2-MeO	44.3	35.6	96.1	6.42		
26	3-MeO	3-MeO	84.5	73.8	98.3	6.90		
27	3-MeO	4-MeO	55.3	50	99.7	6.85		
28	3-MeO	2,4-$(MeO)_2$	32.7	49.6	84.7	6.42		
29	3-MeO	2,6-$(MeO)_2$	37.5	30.7	99.2	5.97		
30	3-MeO	3,4-$(MeO)_2$	57.3	50.8	88.4	5.81		
31	3-MeO	3,5-$(MeO)_2$	72.4	64.3	88.4	7.13		
32	3-MeO	3,4,5-$(MeO)_3$	55.5	48.4	69.7	6.15		
33	4-MeO	H					17.3	6.79
34	4-MeO	2-F					27.2	8.20[b]
35	4-MeO	4-Br					15.0	8.23
36	4-MeO	4-Me					14.9	7.61
37	3-CO_2Me_2	2-F					3.5	8.22[b]
38	3,4-Me_2	2-F					32.4	9.34[b]
39	3-Cl-4-Me	2-F					8.2	9.73[b]
40	3,4-Cl_2	2-F					24.0	9.63[b]

[a] 30−100% gradient MeCN in H_2O in 10 min. [b] 10−100% gradient MeCN in H_2O in 10 min.

25−32). On the basis of the results in Table 1, the scope of the BCl_3 mediated phenol coupling to acyl chlorides to give desired (*o*-hydroxyaryl)(aryl)methanones can only be applied to phenols with electron-donating groups at the meta-position. The substituents on acyl chlorides are not limited but prefer electron-withdrawing groups.

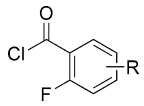
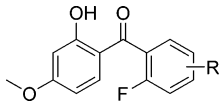
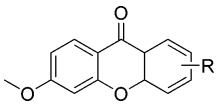
After establishing the scope for the synthesis of (*o*-hydroxyaryl)(aryl)methanones, we explored the synthesis of xanthones using (*o*-hydroxyaryl)(2-fluoro-aryl)methanone as intermediates (Scheme 2). Several 2-fluoro-substituted (*o*-hydroxyaryl)(aryl)methanones (Table 2) are synthesized using our optimized conditions. Under basic conditions and microwave irradiation, phenolates replace fluoride to cyclize and afford xanthones in high yields. This reaction sequence offered a new route to xanthones and will add diversity to xanthone-based drug discovery.

In summary, we have explored the scope and feasibility of microwave-assisted and BCl_3 mediated coupling of phenols with acyl chlorides to make (*o*-hydroxyaryl)(aryl)-methanones. The effect of diverse substitution groups, especially neutral and electron-withdrawing groups on the coupling reactions, has been analyzed. We further applied the optimized coupling reaction to make a small xanthone based library. These structures are currently being evaluated for their biological activity in our drug-discovery programs. Further development of the (*o*-hydroxyaryl)(aryl)methanone based and xanthone based libraries and their application 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

Table 2. Synthesis and Characterization of Xanthones

entry	R	conversion, HPLC %[a]	yield, isolated %	purity, %	HPLC[a], RT, min	conversion, HPLC %[a]	yield, isolated %	purity, %	HPLC[a], RT, min
41	H	70.8	64.9	99.1	8.30	100	98	99.1	7.58
42	4-Br	62.8	57.7	98.9	9.41	95.4	86.0	98.9	9.07
43	5-Cl	74.5	68.8	100.0	9.14	92.5	87.5	100.0	8.78
44	5-I	78.5	67.8	97.5	9.54	90.2	82.5	97.5	9.30
45	5-CF_3	73.8	64.1	99.1	9.07	85.5	78.9	99.1	9.07

[a] Gradient MeCN in H_2O, 10−100% in 10 min.

commercial suppliers and used without further purification. Reactions were carried out on a CEM Explorer microwave synthesizer. Purification of the reaction products was 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 ppm and coupling constants, *J*, are given in Hz. Mass spectra were obtained on a Thermo-Finnigan LCQ Advantage MAX spectrometer.

General Experimental Procedure for Microwave-Assisted Acylation of Phenol (1−40). To an oven dried 5 mL microwave reaction tube charged with a mixture of corresponding phenol (1.0 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 corresponding benzoyl chloride (1 mmol). The tube was capped and irradiated on a CEM Explorer microwave synthesizer at 140 °C for 20 min to afford a brown solution. After cooling to room temperature, 2 M HCl solution (2 mL) was introduced at 0 °C. The mixture was stirred at room temperature for 1 h 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 phase 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), and evaporated to dry. The mixture powder was packed into an ISCO sample tube and purified on an ISCO Optix 10 parallel purification system using 4 g silica gel column, eluted with linear gradient hexane/ethyl acetate (0−30% in 10 min). The product was collected, evaporated using a Thermo-Savant Explorer HT evaporator, and dried under high vacuum to give a white or slight yellow solid in most entries and a light yellow oil in a few cases. The products were characterized by ^{1}H NMR and LC-MS.

General Experimental Procedure for Microwave-Assisted Synthesis of Xanthenone (41−45). To an oven dried microwave reaction tube (10 mL) charged with corresponding phenol (1 mmol) and DCM (1 mL) was added at 0 °C a solution of BCl_3 in DCM (1 M, 1 mL). After stirring at 0 °C for 5 min, 2-fluorobenzoyl chloride (1 mmol) was introduced. The mixture was irradiated on a CEM Explorer microwave synthesizer at 140 °C for 20 min. After cooling to 0 °C, DCM (2 mL) and 2 N HCl solution (5 mL) were added under stirring. The mixture was allowed to stir overnight. The organic layer was separated, and the aqueous layer was extracted with DCM (2 × 5 mL). The combined organic phase was passed through an anhydrous Na_2SO_4 disk. Evaporation of solvent in a vacuum, the residue was dissolved in anhydrous DMF (3 mL), and anhydrous K_2CO_3 (150 mg) was then introduced. The mixture was irradiated on CEM Explorer microwave synthesizer at 140 °C for 10 min. Removal of solvent, the residue was dissolved in DCM (5 mL) and water (5 mL). The organic layer was separated, and the aqueous was extracted with DCM (2 × 5 mL). The combined organic phase was passed through an anhydrous Na_2SO_4 disk. The collection was evaporated with silica gel (1 g). The solid was transferred to an ISCO sample tube and purified on an ISCO Optix 10 parallel purification system with 4 g silica gel prepacked column, using a gradient of ethyl acetate in hexane (0−30%) in 10 min. The fractions were collected and solvent was removed on a Thermo-Savant Explorer HT-evaporator to give the product.

Phenyl Benzoate (1). ^{1}H NMR ($CDCl_3$): 8.22 (dd, J = 8.4, 1.2 Hz, 2H), 7.65 (m, 1H), 7.53 (t, J = 7.6 Hz, 2H), 7.45 (t, J = 8.0 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.23 (dd, J = 8.8, 2.4 Hz, 2H).

Phenyl 2-Fluorobenzoate (2). ^{1}H NMR ($CDCl_3$): 8.11 (dt, J = 7.6, 2.0 Hz, 1H), 7.60 (m, 1H), 7.44 (m, 2H), 7.30−7.19 (m, 5H).

Phenyl 4-Methylbenzoate (3). ^{1}H NMR ($CDCl_3$): 8.10 (d, J = 8.0 Hz, 2H), 7.43 (t, J = 8.0 Hz, 2H), 7.31 (dd, J = 8.4, 0.8 Hz, 2H), 7.27 (m, 1H), 7.21 (dd, J = 8.8, 0.8 Hz, 2H), 2.46 (s, 3H).

Phenyl 4-Methoxybenzoate (4). ^{1}H NMR ($CDCl_3$): 8.16 (d, J = 8.8 Hz, 2H), 7.42 (t, J = 8.0 Hz, 2H), 7.27 (m, 1H), 7.20 (d, J = 8.8, 2H), 6.99 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H).

3-Chlorophenyl 2-Fluorobenzoate (5). ^{1}H NMR ($CDCl_3$): 8.09 (dt, J = 7.6, 2.0 Hz, 1H), 7.61 (m, 1H), 7.34 (dt, J = 7.6, 0.8 Hz, 1H), 7.30−7.26 (m, 2H), 7.25−7.19 (m, 1H), 7.15 (ddd, J = 8.0, 2.4, 1.2 Hz, 1H).

3-Bromophenyl Benzoate (6). ^{1}H NMR ($CDCl_3$): 8.19 (dd, J = 8.4, 1.2 Hz, 2H), 7.65 (m, 1H), 7.52 (t, J = 8.0 Hz, 2H), 7.42 (m, 2H), 7.31 (t, J = 8.0 Hz, 1H), 7.18 (ddd, J = 8.4, 2.0, 0.8 Hz, 1H).

3-Bromophenyl 4-Methylbenzoate (7). ^{1}H NMR ($CDCl_3$): 8.07 (d, J = 8.0 Hz, 2H), 7.41 (m, 2H), 7.31 (m, 3H), 7.17 (ddd, J = 8.4, 2.0, 1.2 Hz, 1H), 2.46 (s, 3H).

3-Bromophenyl 4-Methoxybenzoate (8). ^{1}H NMR ($CDCl_3$): 8.13 (d, J = 8.8 Hz, 2H), 7.40 (m, 2H), 7.29 (t, J = 8.0 Hz, 1H), 7.17 (ddd, J = 8.4, 2.0, 1.2 Hz, 1H), 6.99 (d. J = 8.8 Hz, 2H), 3.90 (s, 3H).

4-Bromophenyl Benzoate (9). ^{1}H NMR ($CDCl_3$): 8.19 (d, J = 8.0 Hz, 2H), 7.65 (m, 1H), 7.53 (m, 4H), 7.12 (d, J = 8.8 Hz, 2H).

4-Bromophenyl 4-Methylbenzoate (10). ^{1}H NMR ($CDCl_3$): 8.07 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.31 (m, 2H), 7.11 (d, J = 8.8 Hz, 2H), 2.45 (s, 3H).

4-Bromophenyl 4-Methoxybenzoate (11). ^{1}H NMR ($CDCl_3$): 8.13 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 2.90 (s, 3H).

(2-Hydroxy-4-Methylphenyl)(phenyl)methanone (12). ^{1}H NMR ($CDCl_3$): 7.67−7.46 (m, 6H), 6.88 (s, 1H), 6.68 (d, J = 8.0 Hz, 1H), 2.38 (s, 3H).

***m*-Tolyl 2-Fluorobenzoate (13).** ^{1}H NMR ($CDCl_3$): 8.11 (dt, J = 7.6, 2.0 Hz, 1H), 7.60 (m, 1H), 7.34−7.19 (m, 3H), 7.11−7.03 (m, 3H), 2.40 (s, 3H).

***m*-Tolyl 4-Bromobenzoate (14).** ^{1}H NMR ($CDCl_3$): 8.05 (d, J = 8.8 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.0 Hz, 1H), 6.89 (s, 1H), 6.69 (m, 1H), 2.38 (s, 3H).

***m*-Tolyl 4-Methoxybenzoate (15).** ^{1}H NMR ($CDCl_3$): 8.15 (d, J = 8.8 Hz, 2H), 7.30 (t, J = 7.6 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 7.02−6.97 (m, 4H), 3.90 (s, 3H), 2.38 (s, 3H).

***p*-Tolyl Benzoate (16).** ^{1}H NMR ($CDCl_3$): 8.21 (d, J = 8.0 Hz, 2H), 7.63 (m, 1H), 7.51 (t, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 2.38 (s, 3H).

***p*-Tolyl 4-Bromobenzoate (17).** ^{1}H NMR ($CDCl_3$): 8.05 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 2.37 (s, 3H).

***p*-Tolyl 4-Methoxybenzoate (18).** ^{1}H NMR ($CDCl_3$): 8.15 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H), 2.37 (s, 3H).

(2-Hydroxy-4-methoxyphenyl)(phenyl)methanone (19). ^{1}H NMR ($CDCl_3$): 7.63 (m, 2H), 7.56 (m, 1H), 7.52−7.47 (m, 3H), 6.52 (d, J = 2.8 Hz, 1H), 6.41 (dd, J = 8.8, 2.8 Hz, 1H), 3.87 (s, 3H).

(2-Hydroxy-4-methoxyphenyl)(4′-bromophenyl)methanone (20). ^{1}H NMR ($CDCl_3$): 7.64 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 9.2 Hz, 1H), 6.52 (d, J = 2.4 Hz, 1H), 6.42 (dd, J = 8.8, 2.4 Hz, 1H), 3.87 (s, 3H).

(2-Hydroxy-4-methoxyphenyl)(4′-methylphenyl)methanone (21). ^{1}H NMR ($CDCl_3$): 7.55 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 6.52 (d, J = 2.4 Hz, 1H), 6.41 (dd, J = 8.8, 2.4 Hz, 1H), 3.86 (s, 3H), 2.44 (s, 3H).

(2-Hydroxy-4-methoxyphenyl)(4′-trifluoromethylphenyl)methanone (22). ^{1}H NMR ($CDCl_3$): 7.76 (m, 4H), 7.41 (d, J = 8.8 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 6.44 (dd, J = 8.8, 2.4 Hz, 1H), 3.89 (s, 3H). ESI-MS (m/z): $[M - H]^-$ = 295.5.

(2-Hydroxy-4-methoxyphenyl)(4′-methoxycarbonylphenyl)methanone (23). $[M - H]^-$ = 287.3.

(2-Hydroxy-4-methoxyphenyl)(4′-nitrophenyl)methanone (24). ^{1}H NMR ($CDCl_3$): 8.37 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.8 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 6.45 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 3.90 (s, 3H). ESI-MS (m/z): $[M - H]^-$ = 272.4.

(2-Hydroxy-4-methoxyphenyl)(2′-methoxyphenyl)methanone (25). ^{1}H NMR ($CDCl_3$): 7.47 (ddd, J = 8.0, 7.2, 2.4 Hz, 1H), 7.28 (dd, J = 7.6, 2.4 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 7.05 (dt, J = 7.6, 0.8 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 6.35 (dd, J = 8.8, 2.8 Hz, 1H), 3.86 (s, 3H), 3.801 (s, 3H). ESI-MS (m/z): $[M + H]^+$ = 259.2.

(2-Hydroxy-4-methoxyphenyl)(3′-methoxyphenyl)methanone (26). ^{1}H NMR ($CDCl_3$): 7.54 (d, J = 8.8 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.20 (dt, J = 7.2, 1.2 Hz, 1H), 7.17 (m, 1H), 7.11 (ddd, J = 8.4, 2.8, 1.2 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 6.42 (dd, J = 8.8, 2.4 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H). ESI-MS (m/z): $[M + H]^+$ = 259.2.

(2-Hydroxy-4-methoxyphenyl)(4′-methoxyphenyl)methanone (27). ^{1}H NMR ($CDCl_3$): 7.68 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.53 (d, J = 2.4 Hz, 1H), 6.43 (dd, J = 8.8, 2.4 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H). ESI-MS (m/z): $[M + H]^+$ = 259.3.

(2-Hydroxy-4-methoxyphenyl)(2′,4′-dimethoxyphenyl)-methanone (28). ^{1}H NMR ($CDCl_3$): 7.30 (d, J = 8.8 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 6.56 (dd, J = 8.0, 2.4 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 6.48 (d, J = 2.4 Hz, 1H), 6.36 (dd, J = 8.8, 2.4 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.78 (s, 3H). ESI-MS (m/z): $[M + H]^+$ = 289.2.

(2-Hydroxy-4-methoxyphenyl)(2′,6′-dimethoxyphenyl)-methanone (29). ^{1}H NMR ($CDCl_3$): 7.36 (t, J = 8.4 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 6.63 (d, J = 8.4 Hz, 2H), 6.48 (d, J = 2.4 Hz, 1H), 6.34 (dd, J = 8.8, 2.4 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 6H). ESI-MS (m/z): $[M + H]^+$ = 289.1.

(2-Hydroxy-4-methoxyphenyl)(3′,4′-dimethoxyphenyl)-methanone (30). ^{1}H NMR ($CDCl_3$): 7.60 (d, J = 8.8 Hz, 1H), 7.29 (dd, J = 8.0, 1.6 Hz, 1H), 7.27 (1H, overlapped by $CDCl_3$ signal), 6.95 (d, J = 8.0 Hz, 1H), 6.54 (d, J = 2.8 Hz, 1H), 6.44 (dd, J = 8.8, 2.8 Hz, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.88 (s, 3H). ESI-MS (m/z): $[M + H]^+$ = 289.2.

(2-Hydroxy-4-methoxyphenyl)(3′,5′-dimethoxyphenyl)-methanone (31). ^{1}H NMR ($CDCl_3$): 7.57 (d, J = 9.2 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 6.64 (t, J = 2.4 Hz, 1H), 6.52 (d, J = 2.8 Hz, 1H), 6.42 (dd, J = 9.2, 2.8 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 6H). ESI-MS (m/z): $[M + H]^+$ = 289.2.

(2-Hydroxy-4-methoxyphenyl)(3′,4′,5′-trimethoxyphenyl)methanone (32). ^{1}H NMR ($CDCl_3$): 7.59 (d, J = 8.8 Hz, 1H), 6.89 (s, 2H), 6.53 (d, J = 2.8 Hz, 1H), 6.44 (dd, J = 8.8, 2.8 Hz, 1H), 3.94 (s, 3H), 3.90 (s, 6H), 3.88 (s, 3H). ESI-MS (m/z): $[M + H]^+$ = 319.2.

4-Methoxyphenyl Benzoate (33). ^{1}H NMR ($CDCl_3$): 8.20 (d, J = 8.8 Hz, 2H), 7.63 (m, 1H), 7.51 (t, J = 8.0 Hz, 2H), 7.13 (d, J = 9.2 Hz, 2H), 6.94 (d, J = 9.2 Hz, 2H), 3.83 (s, 3H).

4-Methoxyphenyl 2-Fluorobenzoate (34). ^{1}H NMR ($CDCl_3$): 8.09 (dt, J = 7.6, 2.0 Hz, 1H), 7.60 (m, 1H), 7.29−7.18 (m, 2H), 7.15 (d, J = 9.2 Hz, 2H), 6.94 (d, J = 9.2 Hz, 2H), 3.82 (s, 3H).

4-Methoxyphenyl 4-Bromobenzoate (35). ^{1}H NMR ($CDCl_3$): 8.13 (d, J = 9.2 Hz, 2H), 7.53 (d, J = 9.2 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H). Mixture with 4-methoxyphenol (purity = 30−40%).

4-Methoxyphenyl 4-Methylbenzoate (36). ^{1}H NMR ($CDCl_3$): 8.08 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 9.2 Hz, 2H), 6.93 (d, J = 9.2 Hz, 2H), 3.82 (s, 3H), 2.45 (s, 3H).

3-Methoxycarbonylphenyl 2-Fluorobenzoate (37). ^{1}H NMR ($CDCl_3$): 8.11 (dt, J = 7.6, 2.0 Hz, 1H), 7.97 (dt, J = 8.0, 2.0 Hz, 1H), 7.91 (t, J = 2.0 Hz, 1H), 7.62 (m, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.44 (ddd, J = 8.0, 2.4, 1.2 Hz, 1H), 7.29 (dt, J = 7.6, 1.2 Hz, 1H), 7.23 (ddd, J = 10.8, 8.4, 0.8 Hz, 1H), 3.93 (s, 3H).

3,4-Dimethylphenyl 2-Fluorobenzoate (38). ^{1}H NMR ($CDCl_3$): 8.10 (dt, J = 7.6, 2.0 Hz, 1H), 7.59 (m, 1H), 7.27 (dt, J = 8.0, 1.2 Hz, 1H), 7.21 (ddd, J = 10.8, 8.4, 1.2 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 2.4 Hz, 1H), 6.97 (dd, J = 8.4, 2.4 Hz, 1H), 2.29 (s, 3H), 2.28 (s, 3H).

3-Chloro-4-methylphenyl 2-Fluorobenzoate (39). ^{1}H NMR ($CDCl_3$): 8.08 (dt, J = 7.6, 2.0 Hz, 1H), 7.59 (m, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.28 (m, 1H), 7.21 (ddd, J = 10.8, 8.4, 1.2 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 7.02 (dd, J = 8.4, 2.4 Hz, 1H), 2.40 (s, 3H).

3,4-Dichlorophenyl 2-Fluorobenzoate (40). ^{1}H NMR ($CDCl_3$): 8.08 (dt, J = 7.6, 2.0 Hz, 1H), 7.63 (m, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 2.8 Hz, 1H), 7.28 (m, 1H), 7.22 (ddd, J = 10.8, 8.4, 1.2 Hz, 1H), 7.13 (dd, J = 8.8, 2.4 Hz, 1H), 2.40 (s, 3H).

(2-Hydroxy-4-methoxyphenyl)(2′-fluorophenyl)methanone (41a). ^{1}H NMR ($CDCl_3$): 7.51 (m, 1H), 7.44 (m, 1H), 7.31−7.16 (m, 2H), 7.18 (m, 1H), 6.50 (d, J = 2.8 Hz, 1H), 6.40 (dd, J = 8.8, 2.8 Hz, 1H), 3.86 (s, 3H).

3-Methoxy-9*H*-xanthen-9-one (41b). ^{1}H NMR ($CDCl_3$): 8.33 (dd, J = 7.6, 1.6 Hz, 1H), 8.25 (d, J = 8.8 Hz, 1H), 7.69 (ddd, J = 8.4, 6.8, 1.6 Hz, 1H), 7.45 (dd, J = 8.8, 0.8 Hz, 1H), 7.37 (ddd, J = 8.4, 6.8, 1.2 Hz, 1H), 6.95 (dd, J = 8.8, 2.4 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 3.94 (s, 3H).

(2-Hydroxy-4-methoxyphenyl)(4′-bromo-2′-fluorophenyl)methanone (42a). ^{1}H NMR ($CDCl_3$): 7.45−7.14 (m, 4H), 6.50 (d, J = 2.4 Hz, 1H), 6.41 (dd, J = 8.8, 2.4 Hz, 1H), 3.86 (s, 3H).

3-Bromo-6-methoxy-9H-xanthen-9-one (42b). ^{1}H NMR ($CDCl_3$): 8.23 (d, J = 8.8 Hz, 1H), 8.18(d, J = 8.8 Hz, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.48 (dd, J = 8.4, 2.0 Hz, 1H), 6.96 (dd, J = 8.8, 2.4 Hz, 1H), 6.87 (d, J = 2.4 Hz, 1H), 3.94 (s, 3H).

(2-Hydroxy-4-methoxyphenyl)(5′-chloro-2′-fluorophenyl)methanone (43a). ^{1}H NMR ($CDCl_3$): 7.46 (m, 1H), 7.42 (m, 1H), 7.26 (dd, J = 8.8, 2.8 Hz, 2H), 7.14 (t, J = 8.8 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 6.42 (dd, J = 8.8, 2.4 Hz, 1H), 3.87 (s, 3H).

2-Chloro-6-methoxy-9H-xanthen-9-one (43b). ^{1}H NMR ($CDCl_3$): 8.28 (d, J = 2.4 Hz, 1H), 8.23(d, J = 8.8 Hz, 1H), 7.63 (dd, J = 8.8, 2.8 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 6.96 (dd, J = 8.8, 2.8 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 3.94 (s, 3H).

(2-Hydroxy-4-methoxyphenyl)(5′-iodo-2′-fluorophenyl)methanone (44a). ^{1}H NMR ($CDCl_3$): 7.80 (m, 1H), 7.74 (dd, J = 6.0, 2.0 Hz, 1H), 7.25 (dd, J = 8.8, 3.2 Hz, 1H), 6.96 (t, J = 9.0, 1H), 6.50 (d, J = 2.8 Hz, 1H), 6.42 (dd, J = 9.0, 2.8 Hz, 1H), 3.87 (s, 3H).

2-Iodo-6-methoxy-9H-xanthen-9-one (44b). ^{1}H NMR ($CDCl_3$): 8.62 (d, J = 2.0 Hz, 1H), 8.23(d, J = 8.8 Hz, 1H), 7.94 (dd, J = 8.8, 2.0 Hz, 1H), 7.24 (dd, J = 8.8 Hz, 1H), 6.96 (dd, J = 8.8, 2.0 Hz, 1H), 6.87 (d, J = 2.4 Hz, 1H), 3.94 (s, 3H).

(2-Hydroxy-4-methoxyphenyl)(5′-trifluoromethyl-2′-fluorophenyl)methanone (45a). ^{1}H NMR ($CDCl_3$): 7.79 (m, 1H), 7.74 (m, 1H), 7.32 (t, J = 8.8 Hz, 1H), 7.21 (dd, J = 9.2, 2.8 Hz, 1H), 6.51 (d, J = 2.8 Hz, 1H), 6.43 (dd, J = 9.2, 2.8 Hz, 1H), 3.87 (s, 3H).

6-Methoxy-2-(trifluoromethyl)-9H-xanthen-9-one (45b). ^{1}H NMR ($CDCl_3$): 8.62 (m, 1H), 8.26 (d, J = 8.8 Hz, 1H), 7.91 (m, 1H), 7.57 (d, J = 8.4, Hz, 1H), 6.99 (dd, J = 8.8, 2.4 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 3.94 (s, 3H).

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

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