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"On water" synthesis of aurones: first synthesis of 4,5,3',4',5'-pentamethoxy-6-hydroxyaurone from *Smilax riparia*

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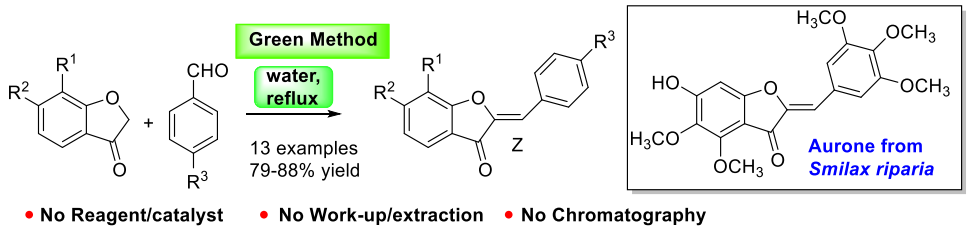
Abstract

A simple and green method for the synthesis of aurones by condensation of benzofuranone with aromatic aldehyde in neat water has been developed. The main advantages of this protocol include good yields, absence of catalyst, reagent, organic solvent, work-up and chromatographic purification. 4,5,3',4',5'-Pentamethoxy-6-hydroxyaurone, isolated from *Smilax riparia* was synthesized for the first time from 3-benzyloxy-4,5-dimethoxybenzaldehyde in five steps.



Keywords: Aurone, on water, green chemistry, 4,5,3',4',5'-pentamethoxy-6-hydroxyaurone, *Smilax riparia*

Introduction

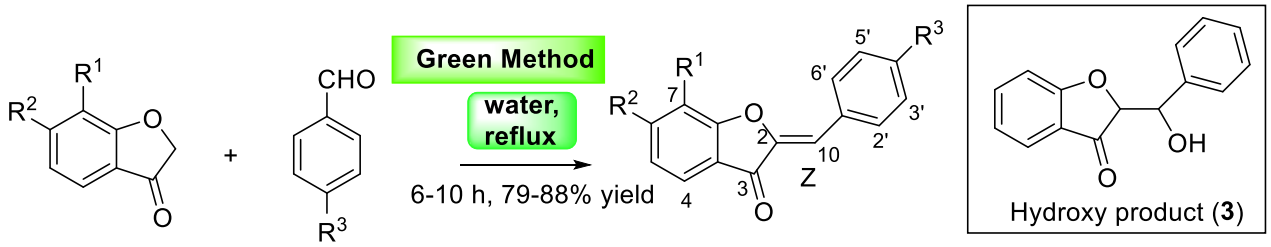
Aurones [2-benzylidenebenzofuran-3(2*H*)-ones] are yellow pigments of plants mainly occurs from yellow flowers and fruits. Plants use aurones as phytoalexins against various infections.[1] Aurones possess a wide spectrum of pharmacological activities[2] such as anti-tumor/anti-cancer,[3-6] anti-diabetic,[7] anti-inflammatory,[8] anti-oxidant,[9] anti-bacterial,[10] anti-Alzheimer's,[11] insect antifeedant,[12] and tyrosinase.[13] Various approaches have been reported for the synthesis of aurones: (i) oxidative cyclization of 2'-hydroxychalcones using $Hg(OAc)_2$[14,15] or Thallium(III) nitrate;[16] (ii) cyclization of 2'-acetoxychalcones using tetrabutylammonium tribromide;[17] (iii) ring closing reaction of 2-(1-hydroxy-3-arylprop-2-ynyl)phenols catalyzed by $AuCl_2$;[18] (iv) recently via dihaloacrylic acids[19] and Cu-catalyzed cyclization of (2-halogenphenyl)(3-phenyloxiran-2-yl)methanones;[20] (v) the more convenient and practical use involves the condensation of benzofuran-3(2*H*)-ones with aryl aldehydes using various acidic or basic catalysts[21] under different conditions, such as KOH or $NaOH/CH_3OH$,[10] HCl/CH_3COOH,[22] Al_2O_3/CH_2Cl_2,[23] $KF\text{-}Al_2O_3/CH_2Cl_2/MW$,[24] $EDDA/CH_3CN$/Ultrasound,[25] acetic anhydride[26] and using deep eutectic solvent.[27] These methods suffers a severe limitation in the synthesis of hydroxy substituted aurones. Furthermore, the acidic and basic conditions are not compatible with acid and base sensitive functionalities.

Nowadays, major chemical processes employ large amounts of hazardous and toxic solvents, reagents. The challenges in organic synthesis are to develop convenient processes, reaction media, conditions and utility of materials based on the green chemistry principles. The 'green chemistry' concept is focused on the design of products and processes that minimize the use and generation of hazardous substances.

Most of the methods reported early for synthesis of aurones use the organic solvents and reagents. Due to our interest on aurones and isoaurones,[9,14,28] here we report a simple, green and environment friendly method for the synthesis of aurones from readily available benzofuranones and benzaldehydes.

Results and Discussion

Water plays an essential role in life processes. However, its use as a solvent has been limited in organic synthesis. Despite the fact that it is the cheapest, safest and non-toxic solvent in the world, its presence is generally avoided through the dehydrative drying of substances and solvents. Therefore, the use of water as a reaction medium for organic reactions is one of the latest challenges for modern organic chemists.[29,30] Condensation of benzofuranone with benzaldehyde in water is investigated as shown in scheme 1.



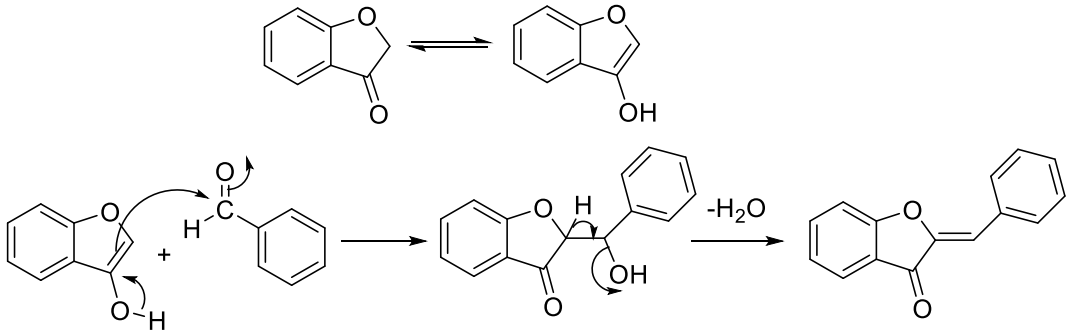
1a: $R^1=R^2=H$
1b: $R^1=H$, $R^2=OMe$

2a: $R^3=H$; **2b**: $R^3=Cl$
2c: $R^3=OMe$; **2d**: $R^3=OH$
2e: $R^3=NO_2$; **2f**: $R^3=NMe_2$

4a: $R^1=R^2=R^3=H$; **4b**: $R^1=R^2=H$, $R^3=Cl$
4c: $R^1=R^2=H$, $R^3=OMe$; **4d**: $R^1=R^2=H$, $R^3=OH$
4e: $R^1=R^2=H$, $R^3=NO_2$; **4f**: $R^1=R^2=H$, $R^3=NMe_2$
4g: $R^1=R^3=H$, $R^2=OMe$; **4h**: $R^1=H$, $R^2=OMe$,$R^3=Cl$
4i: $R^1=H$, $R^2=R^3=OMe$,; **4j**: $R^1=H$, $R^2=OMe$,$R^3=OH$
4k: $R^1=H$,$R^2=OMe$,$R^3=NO_2$

Scheme 1. Green method for the synthesis of aurones.

Initially, the reaction of benzofuranone (**1a**) with benzaldehyde (**2a**) at various temperatures was investigated and the results were presented in table 1. The reaction of **1a** with **2a** at rt for 24 h gave exclusively β-hydroxy product (**3**)[31] with low yield and the reaction not completed even after 96 h (entry 1 and 2). It was interesting to observe that the exclusive formation of β-hydroxy product (**3**) without detectable amount of aurone (**4a**) at rt. At higher temperatures, the reaction gave a mixture of β-hydroxy product (**3**) and aurone (**4a**), which were separated by column chromatography (entry 3–5). Surprisingly at reflux temperature, the reaction proceeded cleanly and exclusively gave aurone (**4a**) in good yield. At reflux condition, absence of β-hydroxy product indicates that the dehydration reaction is fast under these conditions. Few initial experiments revealed that 1.1 eq of benzaldehyde is required for completion of the reaction (entry 6–8). Thus, reaction of benzofuranone (**1a**) with benzaldehyde (**2a**) in water at reflux temperature for 8 h gave aurone (**4a**) in 86% yield, after simple filtration of the aqueous reaction mixture (entry 7). The structure of the product has been deduced from its spectroscopic data and finally confirmed by comparing with that described in the literature.[23] The proposed mechanism for the reaction based on the isolated hydroxy product (**3**) was shown in scheme 2. First, enol form of the benzofuranone is reacted with benzaldehyde to give β-hydroxy product and this converts into the desired aurone by simple dehydration at reflux temperature.



Scheme 2. Proposed mechanism for synthesis of aurones.

Table 1. Optimization[a] of aurone **4a**

Entry	Benzaldehyde (eq)	Temp (°C)	Time (h)	Yield (%)[b]	
				3	Aurone (**4a**)
1	1.0	rt	24	8[c]	0
2	1.0	rt	96	21[c]	0
3	1.0	45–50	48	63	10
4	1.0	60–65	16	52	29
5	1.0	80–85	12	37	45
6	1.0	reflux	9	0	77
7	1.1	reflux	8	0	86
8	1.2	reflux	8	0	85

[a] Reaction conditions: Benzofuran-3(2*H*)-one **1a** (2.0 mmol, 1.0 equiv), benzaldehyde **2a** (1.0–1.2 equiv) and water (5 mL). [b] Isolated yield. [c] Reaction not completed and absence of aurone by TLC.

After having the optimized condition in hand, the scope and generality of this green method has been established and generated substituted aurones **4a-k** were summarized in table 2. A wide variety of substituents on the benzofuranone and benzaldehyde were tolerated including methoxy, hydroxy, nitro and halogen. The

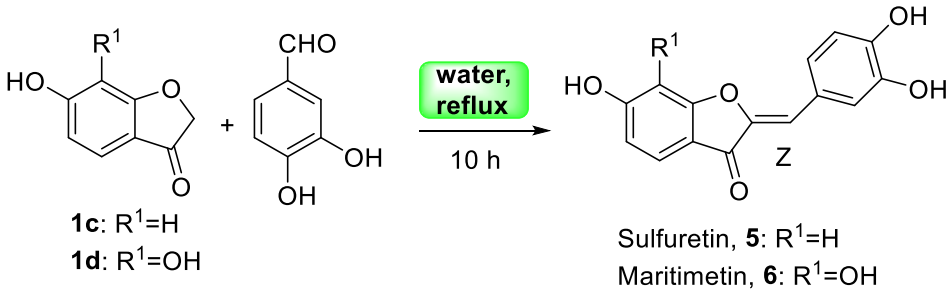
reaction worked well with electron-donating and electron-withdrawing groups either on benzofuranone or benzaldehyde.

Table 2. Green method for the synthesis of aurones[a]

Entry	Furanone	Aldehyde	Aurone	Time (h)	Yield[b] (%)
1	**1a**	**2a**	**4a**	8	86
2	**1a**	**2b**	**4b**	6	88
3	**1a**	**2c**	**4c**	9	84
4	**1a**	**2d**	**4d**	6	86
5	**1a**	**2e**	**4e**	8	82
6	**1a**	**2f**	**4f**	7	79
7	**1b**	**2a**	**4g**	10	83
8	**1b**	**2b**	**4h**	8	82
9	**1b**	**2c**	**4i**	10	84
10	**1b**	**2d**	**4j**	10	84
11	**1b**	**2e**	**4k**	10	83

[a] All the reactions were performed with benzofuranone (2.0 mmol), benzaldehyde (2.2 mmol) and water (5 mL).
[b] Isolated yield.

Sulfuretin (**5**), maritimetin (**6**) are two important natural aurones isolated from various sources[9,32-34] and having potent biological activities. Structurally sulfuretin and maritimetin have three and four hydroxy groups respectively. One of the synthetic route for preparation of this hydroxy substituted aurones uses the basic catalyst, but after completion of the reaction, it need to be acidified to get the desired products.[6] In another method acetic anhydride is used as condensation agent, but in this method the hydroxy groups will be acylated, and to get the desired product an additional hydrolysis step is needed.[9] However, the present green method does not require either hydrolysis or protection/deprotection of hydroxy groups. Thus, the condensation of benzofuranones **1c** and **1d** with 3,4-dihydroxybenzaldehyde in water at reflux temperature for 10 h gave sulfuretin (**5**), maritimetin (**6**) in 81% and 80% yields respectively (scheme 3).



1c: R^1=H
1d: R^1=OH

Sulfuretin, **5**: R^1=H
Maritimetin, **6**: R^1=OH

Scheme 3. Application of green method for the synthesis of sulfuretin (**5**) and maritimetin (**6**)

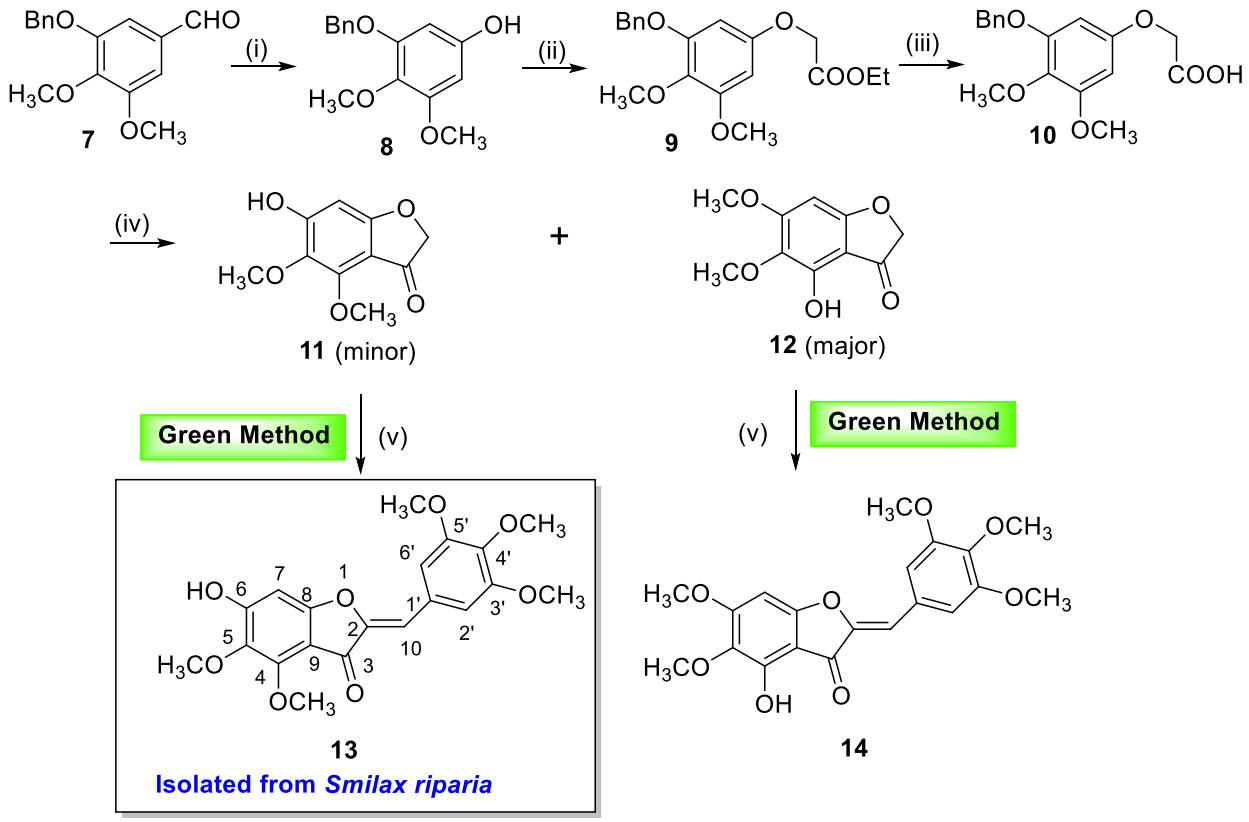
All the compounds (**3**, **4a–k**, **5** & **6**) were well characterized by their spectral (NMR and MS) data. It is evident from the spectral data that a single geometric isomer (Z) was obtained in all the cases, as the Z-isomer is known to be thermodynamically more stable than E-isomer. The geometry of the double bond has been established

based on chemical shift (δ) value of the vinylic proton as well as carbon observed in the corresponding ^{1}H and ^{13}C NMR spectra.[14,35]

Thus the present method does not require any use of organic solvent or acid or base or catalyst. In fact aurones were isolated in a practically pure form by simple Buchner filtration of the final aqueous reaction mixture, require neither work-up/extraction nor silica column purification. Using water as the reaction medium made the isolation of aurones from reaction mixture much easier than any organic solvents.

4,5,3',4',5'-Pentamethoxy-6-hydroxyaurone (**13**) was isolated from *Smilax riparia* and its structure was deduced from spectroscopic data.[36] The present green method for aurones was extended to the first synthesis of **13** by condensation of corresponding benzofuranone (**11**) with 3,4,5-trimethoxybenzaldehyde. The desired benzofuranone (**11**) was prepared, in turn, from **7** as depicted in scheme 4.

Oxidation of 3-benzyloxy-4,5-dimethoxybenzaldehyde (**7**)[37] using performic acid gave **8** in good yield. Treatment of **8** with ethyl bromoacetate in presence of K_2CO_3 gave **9**, which on hydrolysis afforded **10**. Debenzylation of **10** with H_2/Pd-C followed by cyclization using $BF_3.OEt_2$ afforded two isomeric benzofuranones **11** & **12**, which were well separated by column chromatography. Next, condensation of **11** with 3,4,5-trimethoxybenzaldehyde using the present green method gave aurone **13** in 79% yield. Similarly, condensation of **12** with 3,4,5-trimethoxybenzaldehyde gave aurone **14** in 81% yield. Structures of the two isomeric aurones were confirmed based on spectroscopic data including 2D NMR techniques. The NMR data of synthetic **13** were exactly identical with those of natural **13** and is presented in Table-3.



Scheme 4. *Reagents & Conditions*: (i) Performic acid, $CHCl_3$, 4h; TEA, MeOH, rt, 1 h (ii) $BrCH_2COOEt$, K_2CO_3, PEG-400, 80 °C, 2 h (iii) NaOH, methanol, rt, 2 h (iv) 10% Pd-C, H_2, methanol, rt, 1 h, $BF_3.OEt_2$, 60–70 °C, 3 h (v) 3,4,5-trimethoxybenzaldehyde, water, reflux, 10 h.

Table 3. ^{1}H and ^{13}C NMR data of synthetic **13** and natural **13**

Position	Synthetic **13**[a]		Natural **13**[b]	
	δ_H (ppm)	δ_C (ppm)	δ_H (ppm)	δ_C (ppm)
2		147.1		147.1
3		180.6		180.6
4		150.8		150.6
5		134.5		134.4
6		157.7		157.6
7	6.54 s	93.4	6.55 s	93.4
8		163.5		163.5
9		106.9		106.9
10	6.68 s	111.4	6.68 s	111.4
1'		127.9		127.9
2',6'	7.12 s	108.7	7.12 s	108.6
3',5'		153.4		153.3
4'		139.9		139.4
4-OCH_3	4.29 s	62.6	4.29 s	62.6
5-OCH_3	3.93 s	61.8	3.94 s	61.9
3',5'-OCH_3	3.93 s	56.2	3.93 s	56.2
4'-OCH_3	3.91 s	61.0	3.91 s	61.0

[a] ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) in $CDCl_3$. [b] ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) in $CDCl_3$ are taken from ref. 28.

Conclusions

We have developed a simple, convenient and green method for the synthesis of aurones from benzofuranones and aromatic aldehydes in good yields. Water as a solvent and absence of reagent/catalyst/chromatography make this protocol clean, inexpensive and valuable from an environmental point of view. Moreover, the method is also suitable for hydroxy substituted aurones without protection and deprotection of hydroxy groups. So far, this is the most efficient and green protocol for the synthesis of aurones. In terms of both economical and environmental considerations, we believe that the method holds a potential value in laboratory and industry in near future. 4,5,3',4',5'-Pentamethoxy-6-hydroxyaurone, isolated from *Smilax riparia* was synthesized for the first time from 3-benzyloxy-4,5-dimethoxybenzaldehyde in five steps. The spectral data of synthetic aurone is in good agreement with those of natural product.

Experimental Section

General. Reagents and solvents were analytical grade and were used without further purification. Melting points were recorded on a Mel-Temp melting point apparatus, in open capillaries and are uncorrected. IR spectra were recorded on a Bruker (Alpha) FTIR Spectrophotometer. ^{1}H NMR (400 MHz), ^{13}C NMR-DEPT (100 MHz) spectra were recorded on a Bruker AMX 400 MHz NMR spectrometer. The chemical shifts (δ ppm) and coupling

constants (Hz) are reported in the standard fashion. In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) was determined by DEPT-135 spectra. Mass spectra were recorded on Agilent 1100 LC/MSD. HRMS were recorded on Micromass Q-TOF spectrometer using electro-spray ionization mode.

2-(Hydroxy(phenyl)methyl)benzofuran-3(2*H*)-one (3). A mixture of **1a** (268 mg, 2.0 mmol), **2a** (212 mg, 2.0 mmol) and water (5 mL) was stirred at rt for 96 h. The reaction mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layer was washed with brine (5 mL) and dried over Na_2SO_4. The solution was filtered and evaporated the solvent under reduced pressure. The residue was chromatographed over silica gel column using hexane:EtOAc (90:10) as eluents to give **3** as a pale yellow color solid (100 mg, 21%), mp 88–90 °C (lit.[31] oil). IR (Neat, $\nu_{max,}$ cm^{-1}) 3466, 3032, 2898, 1696, 1596, 1454, 1387, 1247, 1061, 1007, 758. ^1H NMR ($CDCl_3$): δ 7.66 (1H, d, *J* 7.6 Hz), 7.61 (1H, t, *J* 7.6 Hz), 7.50 (2H, d, *J* 7.6 Hz), 7.40 (2H, t, *J* 7.2 Hz), 7.35 (1H, d, *J* 7.2 Hz), 7.15 (1H, d, *J* 8.4 Hz), 7.08 (1H, t, *J* 7.4 Hz), 5.34 (1H, d, *J* 2.8 Hz), 4.77 (1H, d, *J* 2.4 Hz), 2.50 (1H, d, *J* 6.0 Hz, exchangeable with D_2O). ^{13}C NMR ($CDCl_3$): δ 199.9, 173.5, 139.5, 138.1, 128.6, 128.4, 126.6, 124.3, 122.2, 121.7, 113.5, 87.3, 73.3. LC-MS (positive ion mode): *m/z* 263 $(M+Na)^+$. HRMS-(EI) (*m/z*): $(M+Na)^+$ calcd for $C_{15}H_{12}O_3Na$ 263.0684, found 263.0690.

General procedure for aurones 4a-k, 5,6. A mixture of benzofuran-3(2*H*)-one (2.0 mmol), benzaldehyde (2.2 mmol) and water (5 mL) was stirred at reflux temperature for 6–10 h. Completion of the reaction was checked on TLC. Then the mixture was allowed to rt and stirred for 1 h. The precipitated solids were filtered, washed with water (2 × 5 mL) and dried to give the product.

(Z)-2-Benzylidenebenzofuran-3(2*H*)-one (4a). Pale yellow color solid (380 mg, 86%), mp 102–104 °C (lit.[23] mp 110–111 °C). ^1H NMR ($CDCl_3$): δ 7.93 (2H, d, *J* 6.8 Hz), 7.82 (1H, d, *J* 7.6 Hz), 7.66 (1H, t, *J* 8.2 Hz), 7.38–7.48 (3H, m), 7.34 (1H, d, *J* 8.0 Hz), 7.22 (1H, t, *J* 7.4 Hz), 6.90 (1H, s); ^{13}C NMR ($CDCl_3$): δ 184.7, 166.2, 146.9, 136.8, 132.4, 131.5, 129.9, 128.9, 124.7, 123.5, 121.7, 113.0, 112.9; LC-MS (positive ion mode): *m/z* 223 $(M+H)^+$.

(Z)-2-(4-Chlorobenzylidene)benzofuran-3(2*H*)-one (4b). Pale yellow color solid (450 mg, 88%), mp 160–166 °C (lit.[14] mp 156–158 °C). ^1H NMR ($CDCl_3$): δ 7.86 (2H, d, *J* 8.4 Hz), 7.82 (1H, dd, *J* 7.6, 0.8 Hz), 7.68 (1H, td, *J* 7.6, 1.2 Hz), 7.43 (2H, d, *J* 8.4 Hz), 7.34 (1H, d, *J* 8.0 Hz), 7.22–7.25 (1H, m), 6.84 (1H, s); ^{13}C NMR ($CDCl_3$): δ 184.6, 166.2, 147.1, 137.0, 135.9, 132.6, 130.9, 129.2, 124.8, 123.7, 121.6, 113.0, 111.5; LC-MS (positive ion mode): *m/z* 257, 259 $(M+H)^+$.

(Z)-2-(4-Methoxybenzylidene)benzofuran-3(2*H*)-one (4c). Yellow color solid (425 mg, 84%), mp 138–140 °C (lit.[23] mp 138–139 °C). ^1H NMR ($CDCl_3$): δ 7.89 (2H, d, *J* 8.8 Hz), 7.80 (1H, dd, *J* 7.6, 0.4 Hz), 7.64 (1H, td, *J* 7.6, 1.2 Hz), 7.32 (1H, d, *J* 8.4 Hz), 7.21 (1H, t, *J* 7.4 Hz), 6.98 (2H, d, *J* 8.8 Hz), 6.89 (1H, s), 3.87 (3H, s); ^{13}C NMR ($CDCl_3$): δ 184.5, 165.9, 161.2, 146.0, 136.5, 133.5, 125.2, 124.6, 123.3, 122.0, 114.6, 113.4, 112.9, 55.4; LC-MS (positive ion mode): *m/z* 253 $(M+H)^+$.

(Z)-2-(4-Hydroxybenzylidene)benzofuran-3(2*H*)-one (4d). Yellow color solid (410 mg, 86%), mp 258–260 °C (lit.[14] mp 261–263 °C). ^1H NMR (DMSO-d_6): δ 10.23 (1H, s), 7.89 (2H, d, *J* 8.8 Hz), 7.77–7.81 (2H, m), 7.56 (1H, d, *J* 8.4 Hz), 7.32 (1H, t, *J* 7.4 Hz), 6.92 (2H, d, *J* 7.6 Hz), 6.91 (1H, s); ^{13}C NMR (DMSO-d_6): δ 183.1, 165.0, 159.7, 144.7, 137.1, 133.7, 124.0, 123.7, 122.9, 121.3, 116.2, 113.4, 113.1; LC-MS (negative ion mode): *m/z* 237 $(M-H)^-$.

(Z)-2-(4-Nitrobenzylidene)benzofuran-3(2*H*)-one (4e). Yellow color solid (438 mg, 82%), mp 212–214 °C (lit.[23] mp 211–212 °C). ^1H NMR (DMSO-d_6): δ 8.34 (2H, d, *J* 8.8 Hz), 8.24 (2H, d, *J* 8.8 Hz), 7.83–7.88 (2H, m), 7.59 (1H, d, *J* 8.4 Hz), 7.37 (1H, t, *J* 7.4 Hz), 7.08 (1H, s); ^{13}C NMR (DMSO-d_6): δ 183.7, 165.7, 147.8, 147.3, 138.6, 138.2, 132.0, 124.6, 124.4, 123.9, 120.5, 113.3, 109.1; LC-MS (negative ion mode): *m/z* 266 $(M-H)^-$.

(Z)-2-(4-(Dimethylamino)benzylidene)benzofuran-3(2*H*)-one (4f). Orange red color solid (420 mg, 79%), mp 174–176 °C (lit.[14] mp 174–176 °C). ^1H NMR ($CDCl_3$): δ 7.85 (2H, d, *J* 8.8 Hz), 7.80 (1H, dd, *J* 7.6, 0.4 Hz), 7.60 (1H, td, *J* 7.8, 1.6 Hz), 7.31 (1H, d, *J* 8.0 Hz), 7.18 (1H, t, *J* 7.4 Hz), 6.92 (1H, s), 6.74 (2H, d, *J* 8.8 Hz), 3.06 (6H, s); ^{13}C

NMR ($CDCl_3$): δ 183.9, 165.3, 151.4, 145.1, 135.7, 133.6, 124.3, 122.9, 122.5, 120.2, 115.2, 112.7, 112.0, 40.0; LC-MS (positive ion mode): *m/z* 266 $(M+H)^+$.

(Z)-2-Benzylidene-6-methoxybenzofuran-3(2*H*)-one (4g). Pale yellow color solid (420 mg, 83%), mp 138–140 °C (lit.[15] mp 147–148 °C). ^1H NMR ($CDCl_3$): δ 7.89 (2H, d, *J* 7.2 Hz), 7.71 (1H, d, *J* 8.4 Hz), 7.45 (2H, t, *J* 7.2 Hz), 7.36–7.40 (1H, m), 6.82 (1H, s), 6.77–6.78 (1H, m), 6.75 (1H, d, *J* 2.0 Hz), 3.93 (3H, s); ^{13}C NMR ($CDCl_3$): δ 183.0, 168.6, 167.5, 147.9, 132.5, 131.3, 129.6, 128.8, 125.8, 114.9, 112.1, 111.8, 96.7, 56.0; LC-MS (positive ion mode): *m/z* 253 $(M+H)^+$.

(Z)-2-(4-Chlorobenzylidene)-6-methoxybenzofuran-3(2*H*)-one (4h). Pale yellow color solid (470 mg, 82%), mp 168–172 °C (lit.[38] mp 174–175 °C). ^1H NMR ($CDCl_3$): δ 7.82 (2H, d, *J* 8.4 Hz), 7.71 (1H, d, *J* 8.8 Hz), 7.41 (2H, d, *J* 8.8 Hz), 6.75–6.78 (3H, m), 3.94 (3H, s); ^{13}C NMR ($CDCl_3$): δ 182.8, 168.6, 167.6, 148.1, 135.6, 132.4, 131.0, 129.2, 126.0, 114.8, 112.3, 110.4, 96.8, 56.1; LC-MS (positive ion mode): *m/z* 287, 289 $(M+H)^+$.

(Z)-2-(4-Methoxybenzylidene)-6-methoxybenzofuran-3(2*H*)-one (4i). Pale yellow color solid (470 mg, 83%), mp 130–132 °C (lit.[40] mp 132–134 °C). ^1H NMR ($CDCl_3$): δ 7.85 (2H, d, *J* 8.8 Hz), 7.69 (1H, d, *J* 8.4 Hz), 6.96 (2H, d, *J* 8.4 Hz), 6.80 (1H, s), 6.73–6.76 (2H, m), 3.92 (3H, s), 3.86 (3H, s); ^{13}C NMR ($CDCl_3$): δ 182.8, 168.2, 167.2, 160.9, 146.8, 133.1, 125.7, 125.2, 115.2, 114.4, 112.1, 111.9, 96.6, 56.0, 55.3; LC-MS (positive ion mode): *m/z* 283 $(M+H)^+$.

(Z)-2-(4-Hydroxybenzylidene)-6-methoxybenzofuran-3(2*H*)-one (4j). Pale yellow color solid (450 mg, 84%), mp 212–214 °C (lit.[39] mp 215–217 °C). ^1H NMR (DMSO-d_6): δ 10.17 (1H, s), 7.86 (2H, d, *J* 8.4 Hz), 7.68 (1H, d, *J* 8.4 Hz), 7.14 (1H, d, *J* 1.6 Hz), 6.90 (2H, d, *J* 8.4 Hz), 6.85 (1H, dd, *J* 8.6, 1.8 Hz), 6.80 (1H, s), 3.93 (3H, s); ^{13}C NMR (DMSO-d_6): δ 181.4, 167.5, 167.0, 159.4, 145.6, 133.3, 125.2, 123.0, 116.1, 114.3, 112.4, 111.9, 97.0, 56.3; LC-MS (negative ion mode): *m/z* 267 $(M-H)^-$.

(Z)-2-(4-Nitrobenzylidene)-6-methoxybenzofuran-3(2*H*)-one (4k). Pale yellow color solid (500 mg, 84%), mp 252–254 °C (lit.[39] mp 255–258 °C). ^1H NMR ($CDCl_3$): δ 8.29 (2H, d, *J* 8.8 Hz), 8.03 (2H, d, *J* 8.8 Hz), 7.73 (1H, d, *J* 8.8 Hz), 6.79–6.82 (3H, m), 3.96 (3H, s); ^{13}C NMR ($CDCl_3$): δ 182.6, 168.9, 168.1, 149.5, 147.6, 139.0, 131.6, 126.3, 124.0, 114.4, 112.7, 108.3, 97.0, 56.2; LC-MS (positive ion mode): *m/z* 298 $(M+H)^+$. **(Z)-2-(3,4-Dihydroxybenzylidene)-6-hydroxybenzofuran-3(2*H*)-one (5)**: Yellow color solid (440 mg, 81%), mp 315–317 °C (lit.[34] mp 315 °C). ^1H NMR (DMSO-d_6): δ 11.12 (1H, br s, exchangeable with D_2O), 9.68 (1H, br s, exchangeable with D_2O), 9.27 (1H, br s, exchangeable with D_2O), 7.61 (1H, d, *J* 8.4 Hz), 7.46 (1H, d, *J* 1.6 Hz), 7.26 (1H, dd, *J* 8.4, 2.0 Hz), 6.85 (1H, d, *J* 8.0 Hz), 6.76 (1H, d, *J* 2.0 Hz), 6.71 (1H, dd, *J* 8.4, 1.6 Hz), 6.65 (1H, s); ^{13}C NMR (DMSO-d_6): δ 181.1, 167.4, 166.1, 148.0, 145.7, 145.5, 125.7, 124.5, 123.4, 118.0, 116.0, 113.2, 112.8, 111.8, 98.3; LC-MS (negative ion mode): *m/z* 269 $(M-H)^-$.

(Z)-2-(3,4-Dihydroxybenzylidene)-6,7-dihydroxybenzofuran-3(2*H*)-one (6): Yellow color solid (460 mg, 80%), mp 294–298 °C (lit.[9] mp 286–288 °C). ^1H NMR (DMSO-d_6): δ 10.66 (1H, br s), 9.67 (1H, br s), 9.50 (1H, br s), 9.22 (1H, br s), 7.44 (1H, br s), 7.39 (1H, d, *J*=8.0 Hz), 7.13 (1H, d, *J*=8.0 Hz), 6.86 (1H, d, *J*=8.0 Hz), 6.74 (1H, d, *J*=8.0 Hz), 6.63 (1H, s); ^{13}C NMR (DMSO-d_6): δ 182.0, 155.0, 154.2, 147.9, 145.9, 145.4, 130.1, 124.5, 123.5, 118.4, 116.0, 115.2, 114.6, 112.6, 111.7; LC-MS (negative ion mode): *m/z* 285 $(M-H)^-$.

3-Benzyloxy-4,5-dimethoxyphenol (8). To an ice cold solution of **7** (4.4 g) in chloroform (44 mL) was added performic acid (44 mL) slowly for 30 min. The reaction mixture was allowed to rt and stirred for 4 h. Chloroform layer was separated and aqueous layer was extracted with chloroform (2 × 100 mL). The combined chloroform layer was washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. The solution was filtered and evaporated the solvent. The residue was dissolved in methanol (80 mL) and triethylamine (4 mL) was added at rt. The reaction mixture was stirred for 1 h and poured into ice cold water (100 mL). The solution was acidified with dil HCl and extracted with EtOAc (3 × 100 mL). The combined EtOAc layer was washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. The solution was filtered and evaporated the solvent. The residue was chromatographed over silica gel column using chloroform-methanol (98:02) as eluents to give **8** as pale yellow color oil (3.3 g, 78%).IR (Neat, $\nu_{max,}$ cm^{-1}): 3465, 2937, 2833, 1597, 1503, 1467, 1383, 1224, 871. ^1H NMR ($CDCl_3$): δ 7.41–7.43 (2H, m), 7.34–7.38 (2H, m), 7.28–7.32 (1H, m), 6.09 (2H, s), 5.08 (2H, s), 4.71 (1H, s), 3.81 (6H, s).

^{13}C NMR ($CDCl_3$): δ 154.1, 153.0, 152.1, 137.1, 133.0, 128.6, 127.9, 127.2, 95.3, 93.8, 71.2, 61.1, 56.1. LC-MS (positive ion mode): *m/z* 261 $(M+H)^+$. HRMS-(EI) (*m/z*): $(M+H)^+$ calcd for $C_{15}H_{17}O_4$ 261.1127, found 261.1130.

Ethyl 2-(3-(benzyloxy)-4,5-dimethoxyphenoxy)acetate (9). A mixture of **8** (2.2 g, 8.46 mmol), K_2CO_3 (2.33 g, 16.92 mmol), ethyl bromoacetate (1.46 mL, 12.69 mmol) and PEG-400 (20 mL) was stirred at 80°C for 2 h. The reaction mixture was allowed to rt and poured into ice cold water (100 mL). The solution was extracted with EtOAc (3 × 100 mL). The combined EtOAc layer was washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. The solution was filtered and evaporated the solvent. The residue was chromatographed over silica gel column using chloroform-methanol (98:02) as eluents to give **9** as colorless oil (2.5 g, 85%). IR (Neat, ν_{max}, cm^{-1}): 2936, 1754, 1595, 1501, 1454, 1215, 1006, 812, 740. ^{1}H NMR ($CDCl_3$): δ 7.41–7.43 (2H, m), 7.35–7.39 (2H, m), 7.28–7.32 (1H, m), 6.20 (1H, d, *J* 2.8 Hz), 6.18 (1H, d, *J* 2.8 Hz), 5.10 (2H, s), 4.52 (2H, s), 4.25 (2H, q, *J* 7.2 Hz), 3.83 (3H, s), 3.81 (3H, s), 1.29 (3H, t, *J* 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 168.8, 154.3, 154.0, 152.9, 137.1, 134.2, 128.5, 127.9, 127.3, 95.0, 93.9, 71.4, 66.0, 61.3, 61.0, 56.2, 14.2. LC-MS (positive ion mode): *m/z* 347 $(M+H)^+$. HRMS-(EI) (*m/z*): $(M+H)^+$ calcd for $C_{19}H_{23}O_6$ 347.1495, found 347.1490.

2-(3-(Benzyloxy)-4,5-dimethoxyphenoxy)acetic acid (10). To an ice cold solution of **9** (2.25 g, 6.5 mmol) in methanol (20 mL) was added successively NaOH (520 mg, 13.0 mmol), water (2.0 mL) and PEG-400 (catalytic). The mixture was stirred at rt for 2 h and after completion of the reaction, it was poured into ice cold water (100 mL). The solution was acidified with dil HCl and stirred for 30 min. The precipitated solid was filtered and washed with ice cold water (10 mL) and dried to give **10** as an off-white color solid (2.0 g, 97%), mp 96–100 °C. IR (Neat, ν_{max}, cm^{-1}): 3513, 3031, 2933, 2850, 1731, 1597, 1504, 1454, 1385, 1299, 1227, 1088, 827, 759. ^{1}H NMR ($CDCl_3$): δ 7.41–7.43 (2H, m), 7.34–7.39 (2H, m), 7.28–7.32 (1H, m), 6.18–6.21 (2H, m), 5.10 (2H, s), 4.58 (2H, s), 3.83 (3H, s), 3.82 (3H, s). ^{13}C NMR (DMSO-d_6): δ 170.4, 154.3, 153.4, 152.3, 137.1, 132.5, 128.4, 127.8, 127.5, 94.3, 93.2, 70.1, 65.5, 60.1, 55.9. LC–MS (negative ion mode): *m/z* 317 $(M-H)^-$. HRMS-(EI) (*m/z*): $(M+Na)^+$ calcd for $C_{17}H_{18}O_6Na$ 341.1001, found 341.1002.

Cyclization: To a solution of **10** (3.9 g) in methanol (80 mL) was added 10% Pd-C (100 mg) and hydrogenated using hydrogen balloon at rt for 1 h. The mixture was filtered through hyflow gel and washed the bed with methanol (10 mL). The filtrate was evaporated to dryness to give the debenzylated product, which was used without further purification. To the residue, $BF_3.OEt_2$ (30 mL) was added and stirred at 60–70°C for 4 h. The mixture was allowed to rt and poured into ice cold water. The solution was basified with aq 10% NaOAc (20 mL) and extracted with chloroform (3 × 100 mL). The combined chloroform layer was washed with water, brine and dried over Na_2SO_4. The solution was filtered and evaporated the solvent. The residue was chromatographed over silica gel column using chloroform as eluents to give **11**. Further elution of the column with chloroform-methanol (98:02) as eluents gave **12**.

6-Hydroxy-4,5-dimethoxybenzofuran-3(2*H*)-one (11). White color solid (180 mg, 7%), mp 160–164 °C. IR (Neat, ν_{max}, cm^{-1}): 3466, 3061, 2936, 1696, 1594, 1403, 1390, 1247, 1092, 832, 693. ^{1}H NMR ($CDCl_3$): δ 6.68 (1H, s), 6.37 (1H, s), 4.57 (2H, s), 4.18 (3H, s), 3.90 (3H, s). ^{13}C NMR ($CDCl_3$): δ 195.4, 171.8, 158.8, 149.8, 133.6, 106.7, 93.6, 75.3, 62.3, 61.8. LC–MS (negative ion mode): *m/z* 209 $(M-H)^-$. HRMS-(EI) (*m/z*): $(M+Na)^+$ calcd for $C_{10}H_{10}O_5Na$ 233.0426, found 233.0430.

4-Hydroxy-5,6-dimethoxybenzofuran-3(2*H*)-one (12). White color solid (1.6 g, 62%), mp 156–158 °C. IR (Neat, ν_{max}, cm^{-1}): 3466, 3063, 2931, 2850, 1690, 1599, 1454, 1384, 1253, 1061, 835, 689. ^{1}H NMR ($CDCl_3$): δ 7.37 (1H, s, exchangeable with D_2O), 6.19 (1H, s), 4.61 (2H, s), 3.93 (3H, s), 3.83 (3H, s). ^{13}C NMR ($CDCl_3$): δ 198.0, 170.4, 162.9, 147.6, 130.7, 103.7, 88.2, 75.4, 61.2, 56.5. LC–MS (negative ion mode): *m/z* 209 $(M-H)^-$. HRMS-(EI) (*m/z*): $(M+Na)^+$ calcd for $C_{10}H_{10}O_5Na$ 233.0426, found 233.0431.

(*Z*)-6-Hydroxy-4,5-dimethoxy-2-(3,4,5-trimethoxybenzylidene)benzofuran-3(2*H*)-one (13). Using the above general aurone procedure, **13** was obtained as a yellow color solid (613 mg, 79%), mp 196–198 °C. IR (Neat, ν_{max}, cm^{-1}): 3466, 3061, 2926, 2850, 1696, 1590, 1455, 1423, 1385, 1249, 1090, 832. For ^{1}H & ^{13}C NMR see Table 3.

LC–MS (ESI, negative ion mode): *m/z* 387 $(M–H)^-$. HRMS-(EI) (*m/z*): $(M+H)^+$ calcd for $C_{20}H_{21}O_8$ 389.1236, found 389.1239.

(*Z*)-4-Hydroxy-5,6-dimethoxy-2-(3,4,5-trimethoxybenzylidene)benzofuran-3(2*H*)-one (14). Using the above general aurone procedure, **14** was obtained as a yellow color solid (628 mg, 81%), mp 164–166 °C. IR (Neat, $\nu_{max,}$ cm^{-1}): 3466, 2937, 2837, 1692, 1596, 1454, 1387, 1245, 1076, 836. ^1H NMR ($CDCl_3$): δ 7.42 (1H, s, exchangeable with D_2O), 7.13 (2H, s), 6.71 (1H, s), 6.37 (1H, s), 4.00 (3H, s), 3.94 (6H, s), 3.92 (3H, s), 3.88 (3H, s). ^{13}C NMR ($CDCl_3$): δ 183.3, 162.2, 161.9, 153.4, 148.4, 147.1, 140.2, 131.9, 127.6, 112.1, 109.1, 104.1, 88.4, 61.2, 61.0, 56.7, 56.3. LC–MS (negative ion mode): *m/z* 387 $(M–H)^-$. HRMS-(EI) (*m/z*): $(M+H)^+$ calcd for $C_{20}H_{21}O_8$ 389.1236, found 389.1231.

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