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Transition Metal Free Decarbonyl-Oxidation of 3-Arylbenzofuran-2(3*H*)-ones: Access to 2-Hydroxy Benzophenones

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Abstract

A transition metal-free decarbonyl-oxidation protocol for conversion of 3-Arylbenzofuran-2(3*H*)-ones to 2-hydroxybenzophenones under mild conditions has been developed. NMR studies confirmed the role of *in-situ* generated hydroperoxide in the conversion. The protocol was applied to a diverse range of substrates to access the target products in good to excellent yields. A structure-activity study for the 5-substituted-2-hydroxybenzophenones towards UV-protection abilities have been verified by mathematical calculations.

Keywords

2-Hydroxy benzophenone; decarbonyl-oxidation; transition metal-free; hydroperoxide; UV-protection

\Introduction

Benzophenone compounds are ubiquitous in nature, and show biological activities such as anti-inflammatory, antiviral, and anticancer effects [1]. Amongst these, 2-hydroxybenzophenones are regarded as one of the most important class of compounds owing to their varied bioactivities, including calcium channel blockers, anti-influenza drug, anti-HIV drug, and antispasmodic agents (**Fig. 1**) [2]. Along with that, oxybenzone, a 2-hydroxybenzophenone, has been widely used as a sun-protecting material in cosmetics [3]. Moreover, in general, 2-hydroxybenzophenones are regarded as an important ultraviolet absorber, as well as an important template in the synthesis [4].

Mechanistically, it has been well accepted that 2-hydroxybenzophenones show the UV absorbing as well as photo-antioxidant properties via an intramolecular hydrogen transfer [5]. The structure-activity relation between the substituents of 2-hydroxybenzophenones and their UV-absorption properties have been reported previously [6]. It was concluded that the ability to absorb UV and the corresponding abilities to prevent photo-degradation is improved substantially by a *p*-substituted 2-hydroxyl group than a *m*-substituted one. Moreover, either oxybenzone, containing a *m*-substituted-2-hydroxyl group and the most used UV-protector commercially, or its metabolites, has been associated with estrogenic activities [7]. A further structure-activity relationship study revealed that a 5-substitution decreases the estrogenic

activity. Similar results were obtained in another study where 2-Hydroxy-5-methyl-benzopheneone was found to be very weakly estrogenic [8]. Although a detailed SAR is still warranted, the initial reports prompted us to find a suitable, environment friendly synthetic method for 5-substituted 2-hydroxybenzopehneones, and to evaluate their UV-absorbing properties.

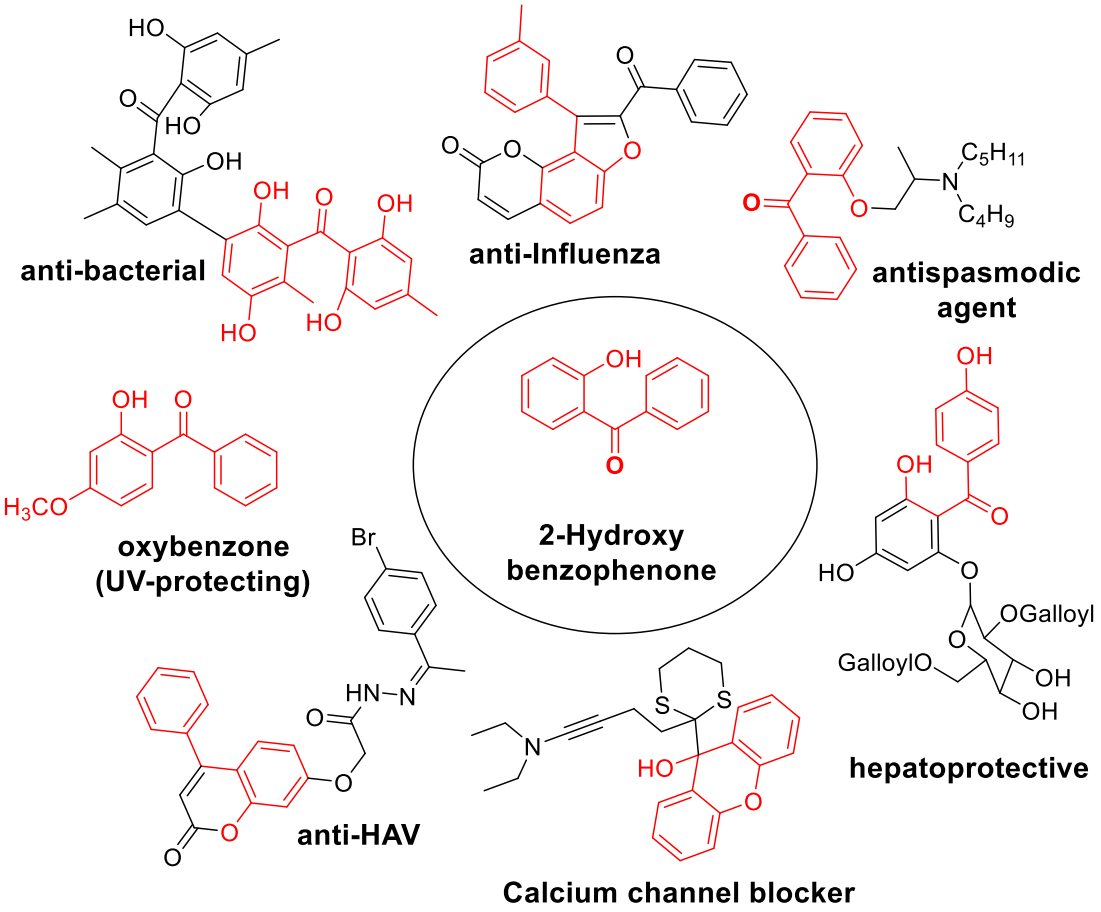


Figure 1: Some 2-hydroxybenzophenone derivatives with varied activities.

Various methods for the synthesis of benzophenones have been reported over the years (**Fig. 2**) [2]. Conventionally, benzophenones are synthesized by Friedel–Crafts acylation of benzoyl halides and aromatic compounds. However, the regioselectivity of Friedel–Crafts benzoylation at the desired position is difficult to control [9]. On the other hand, 2-hydroxybenzophenones are conventionally prepared via Fries rearrangement of phenyl ester [10]. Organocatalytic methods have also been reported for the

synthesis of 2-hydroxy benzophenones [11]. In addition, several metal mediated methods of synthesis have been reported. For example, Rh-catalyzed rearrangement of 2-Aryloxybenzaldehydes yielded 2-hydroxybenzophenone [12]. Pd-catalyzed ortho-hydroxylation of benzophenones gave moderate yield of the title compound, although Br-substituted substrates were found to be not compatible in this method [13]. Various metal (Rh, Cu Ir etc.) catalyzed oxidative coupling of salicylaldehyde with arylboronic acid also successfully produced 2-hydroxybenzophenones [14]. Recently, Ni-Catalyzed decarbonyl-oxidation of 3-Arylbenzofuran-2(3*H*)-ones has emerged as an innovative route to access 2-hydroxy benzophenones [2].

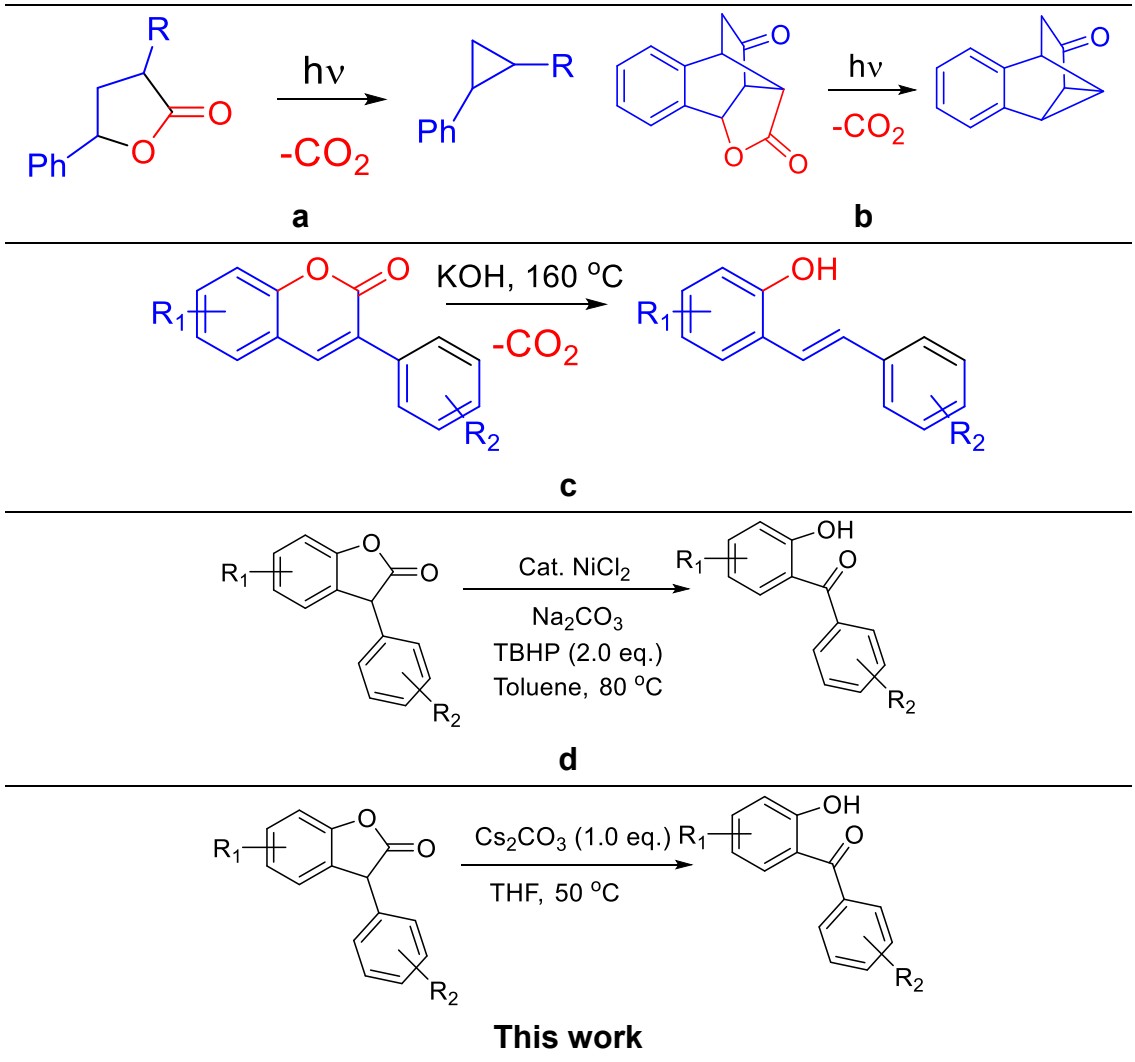
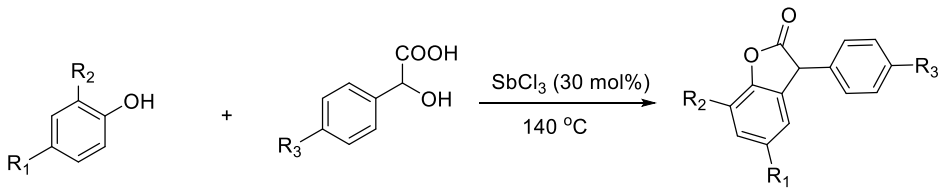


Figure 2: Decarbonyl-oxidation of lactones.

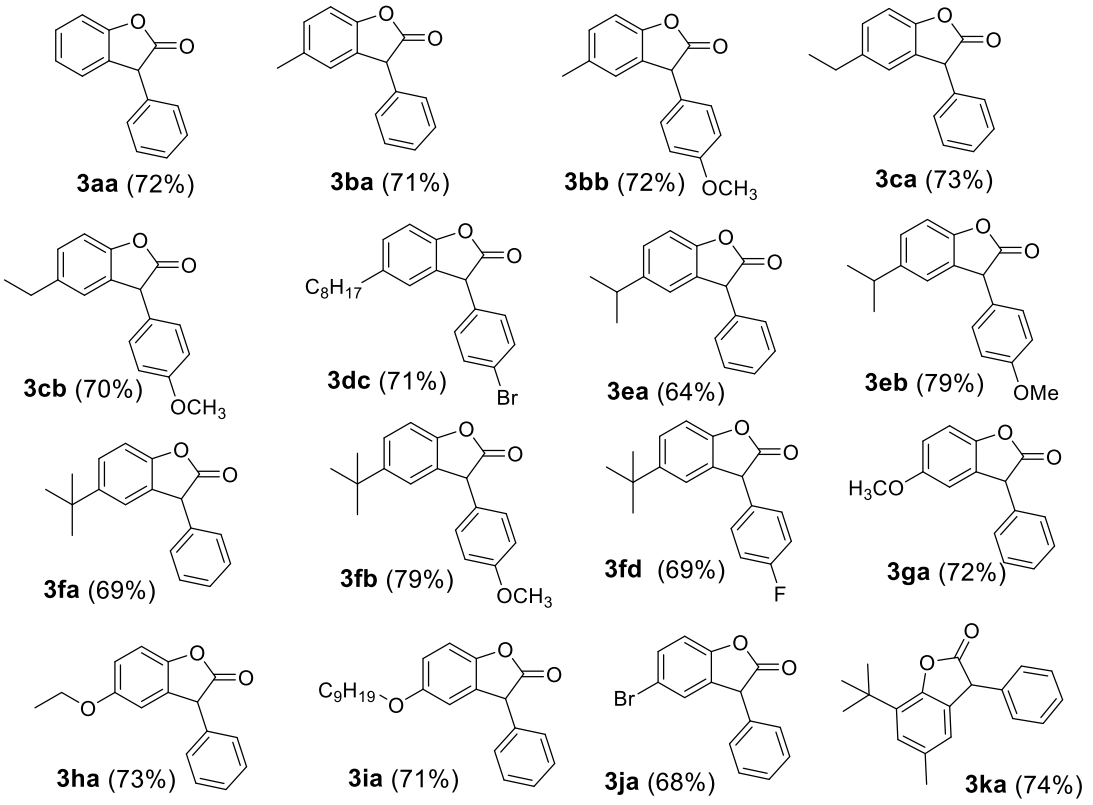
Use of transition metals poses environmental hazards, and this can only be circumvented using transition metal-free synthesis protocol. Decarbonylation of benzofuranone followed by oxidation is an environment friendly protocol, which produces only CO_2 as a non-toxic side product. Although decarboxylation of aldehydes, carboxylic acids and ketones are well known, albeit using metal catalysts, decarboxylation methods for lactones are limited. Both photochemical decarboxylation methods reported for α, γ-butyrolactone [15] and γ-butyrolactones [16] yielded the products in very poor to moderate yields (**Fig. 2a** and **2b**). Recently, a transition-metal free decarboxylation of *α*,*β*-unsaturated aromatic lactones was reported for the synthesis of *E*-ortho-hydroxystilbenes, albeit via a cascade hydolyzation-decarboxylation reaction at a very high temperature (**Fig. 2c**) [17]. However, a metal-free decarbonyl-oxidation method for benzofuranones is still unprecedented. The earlier report [2] on the Ni-catalyzed decarbonyl-oxidation protocol using a hydroperoxide (**Fig. 2d**) gave us an idea that use of an *in-situ* generated hydroperoxide may trigger the reaction, and may avoid the use of transition metal in the reaction. Many solvents, e.g. tetrahydrofuran (THF), dioxanes etc. are known for producing hydroperoxides in-situ on long standing. Also, it has been reported that the generation of the hydroperoxide may be accelerated by heating the solvent under open atmospheric conditions [18]. We envisaged that such autooxidation of THF [19] will produce THF-hydroperoxide, and this will facilitate the transformation of 3-Arylbenzofuran-2(3*H*)-ones to 2-hydroxybenzophenones via decarbonyl-oxidation quickly and without the need of a transition metal catalyst. Herein, a novel decarbonyl-oxidation method of 3-Arylbenzofuran-2(3*H*)-ones has been developed for the synthesis of 2-hydroxy benzophenones via a transition metal-free synthetic route



1a. R_1 = H; R_2 = H
1b. R_1 = CH_3; R_2 = H
1c. R_1 = C_2H_5; R_2 = H
1d. R_1 = C_8H_{17}; R_2 = H
1e. R_1 = $CH(CH_3)_2$; R_2 = H
1f. R_1 = $C(CH_3)_3$; R_2 = H
1g. R_1 = OCH_3; R_2 = H
1h. R1 = OC_2H_5; R_2 = H
1i. R_1 = OC_9H_{19}; R_2 = H
1j. R_1 = Br, ; R_2 = H
1k. R_1 = CH_3; R_2 = $C(CH_3)_3$

2a. R_3 = H
2b. R_3 = OCH_3
2c. R_3 = Br
2d. R_3 = F

3aa. R_1= H; R_2 = H; R_3 = H
3ba. R_1= CH_3; R_2 = H; R_3 = H
3bb. R_1= CH_3; R_2 = H; R_3 = OCH_3
3ca. R_1= C_2H_5; R_2 = H; R_3 = H
3cb. R_1= C_2H_5; R_2 = H; R_3 = OCH_3
3dc. R_1= C_8H_{17}; R_2 = H; R_3 = Br
3ea. R_1= $CH(CH_3)_2$; R_2 = H; R_3 = H
3eb. R_1= $CH(CH_3)_2$; R_2 = H; R_3 = OCH_3
3fa. R_1= $C(CH_3)_3$; R_2 = H; R_3 = H
3fb. R_1= $C(CH_3)_3$; R_2 = H; R_3 = OCH_3
3fd. R_1= $C(CH_3)_3$; R_2 = H; R_3 = F
3ga. R_1= OCH_3; R_2 = H; R_3 = H
3ha. R_1= OC_2H_5; R_2 = H; R_3 = H
3ia. R_1= OC_9H_{19}; R_2 = H; R_3 = H
3ja. R_1= Br; R_2 = H; R_3 = H
3ka. R_1= CH_3; R_2 = $C(CH_3)_3$; R_3 = H



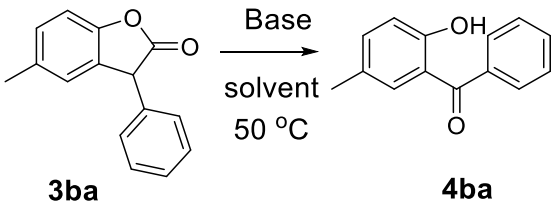
Scheme 1. Synthesis of 3-Arylbenzofuran-2(3*H*)-ones.

Initially, 3-Arylbenzofuran-2(3*H*)-ones (**3aa**-**3ma**) were prepared following a $SbCl_3$ catalyzed Friedel–Crafts alkylation of phenols (**1a**-**1m**) with benzylic alcohols (**2a**-**2d**), earlier reported by us (**Scheme 1**) [20-22]. All the synthesized 3-Arylbenzofuran-2(3*H*)-ones were characterized using ^{1}H NMR, ^{13}C NMR, FT-IR spectroscopy and elemental analysis.

Next, in a model experiment, initially, we carried out the decarbonyl-oxidation reaction of 5-Methyl-3-phenyl-benzofuran-2(3*H*)-one (**3ba**) using different bases in different solvents (Table 1) under open atmospheric conditions. In presence of Cs_2CO_3 (2.0 equiv.) in THF, the reaction gave 92% yield of the product **4ba** (Table 1, entry 1). When the amount of Cs_2CO_3 was decreased to 1 equiv., the yield of the reaction did not decrease appreciably (Table 1, entry 2). However, further decreasing the amount of Cs_2CO_3 decreased the reaction yield drastically (Table 1, entry 3). The yield of the product using K_2CO_3 in THF as a base was not high (46-54%) (Table 1, entry 4-6). Other bases like KO^{t}Bu or KOH or a mixture of both gave moderate to good yields (59-84%) (Table 1, entry 7-9). Use of BuLi as a base decreased the yield drastically (Table 1, entry 10). Other bases like NaOMe, Triethylamine, DBU, DMAP, sodium acetate or DABCO also produced the product in moderate to good yields (42-81%) when used in excess (Table 1, entry 11-16). Interestingly, the reaction did not proceed in presence of pyridine as a base (Table 1, entry 17). Finally, after getting the best yield of the product using Cs_2CO_3, we changed the solvent to dichloromethane, 1,4-dioxane and acetonitrile. Except in 1,4-dioxane (Table 1, entry 18-20), where hydroperoxide is known to get produced in-situ, the yields were very low. However, the reaction in 1,4-dioxane took a long time to complete. Hence, it was well established that only those solvents which can produce hydroperoxides in situ were suitable for the reaction. We chose Cs_2CO_3 as the base of choice, and performed the further reactions using 1.0 equiv. of Cs_2CO_3 in THF at 50 ^{o}C in open atmosphere. However, it must be noted that

the yields recorded in Table 1 are isolated yields. For the sake of eliminating errors in isolation, we have carried out every reaction in triplicate, and have considered the average yield as the isolated yield.

Table 1: Optimization of reaction conditions.



3ba **4ba**

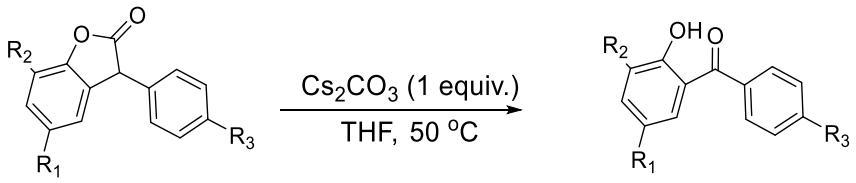
No.	Base (equiv.)	Solvent (2ml)	time (h)	Yield[b] (%)
1.	Cs_2CO_3 (2.0)	THF	4	92
2.	Cs_2CO_3 (1.0)	THF	4	91
3.	Cs_2CO_3 (0.5)	THF	4	61
4.	K_2CO_3 (2.0)	THF	6	54
5.	K_2CO_3 (1.0)	THF	6	51
6.	K_2CO_3 (0.5)	THF	6	46
7.	KO^tBu (2.0)	THF	6	84
8.	KOH (2.0)	THF	6	79
9.	KOH (1.0)[c]	THF	6	59
10.	BuLi (2.0)	THF	6	22
11.	NaOMe (2.0)	THF	6	81
12.	Et_3N (2.0)	THF	6	68
13.	DBU (2.0)	THF	9	79
14.	DMAP (2.0)	THF	9	46
15.	CH_3COONa (2.0)	THF	9	87
16.	DABCO (2.0)	THF	9	42
17.	Pyridine (2.0)	THF	NR[d]	-
18.	Cs_2CO_3 (1.0)	DCM	6	11
19.	Cs_2CO_3 (1.0)	1,4-dioxane	8	82
20.	Cs_2CO_3 (1.0)	CH_3CN	14	25

[a]The reactions were carried out in 0.5 mmol scale. [b]Isolated yields of the products. [c]0.5 equiv. KO^tBu was added. [d]NR = No Reaction.

Earlier, Qui et. al. reported [2] that transition metal catalyst was essential for this reaction to happen at a higher temperature, and the products were obtained in negligible yields without the catalyst. Our protocol established that the reaction proceeds without the need of a transition metal catalyst, as well as at a lower

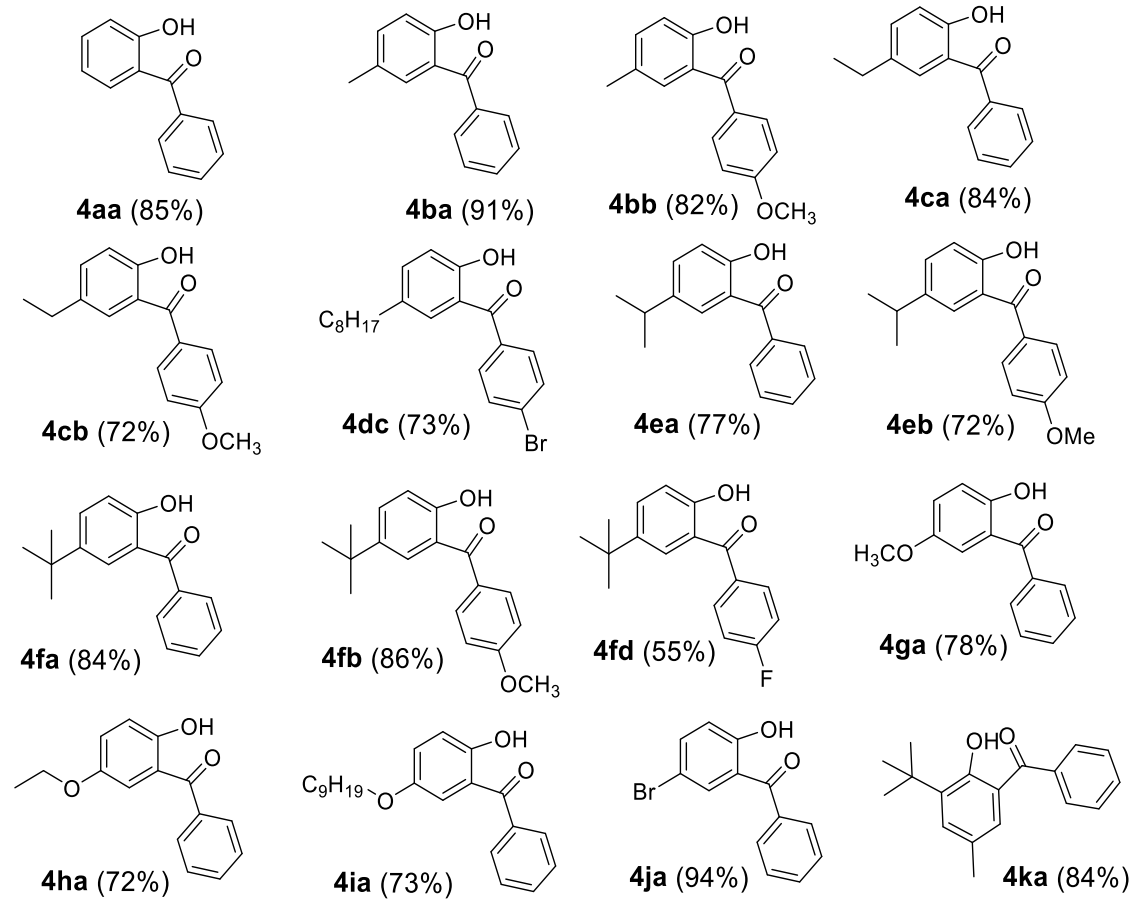
temperature. Additionally, the use of a hydroperoxide generating solvent made the protocol operationally simple.

To see the generality of the protocol, reaction with previously synthesized 3-Aryl benzofuran-2(3*H*)-ones (**3aa**-**3ka**) using 1.0 equiv. Cs_2CO_3 in THF under open atmospheric heating was explored. As revealed in **Scheme 2**, reaction of 3-Aryl benzofuran-2(3*H*)-ones with both electron-donating as well as electron-withdrawing substituents reacted smoothly to afford the corresponding benzophenones (**4aa-4ka**) in good to high yields. Substitutions at 5, 6 or 7 positions of benzofuranones did not hamper the reaction, although a substitution at 4 position of benzofuranone hindered the reaction, leading to very poor yield of the desired benzophenone product.



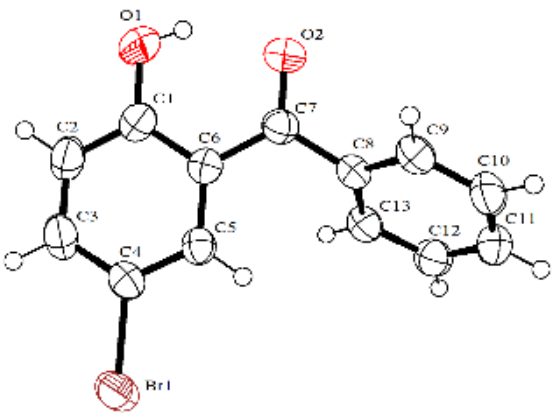
3aa. R_1= H; R_2 = H; R_3 = H
3ba. R_1= CH_3; R_2 = H; R_3 = H
3bb. R_1= CH_3; R_2 = H; R_3 = OCH_3
3ca. R_1= C_2H_5; R_2 = H; R_3 = H
3cb. R_1= C_2H_5; R_2 = H; R_3 = OCH_3
3dc. R_1= C_8H_{17}; R_2 = H; R_3 = Br
3ea. R_1= $CH(CH_3)_2$; R_2 = H; R_3 = H
3eb. R_1= $CH(CH_3)_2$; R_2 = H; R_3 = OCH_3
3fa. R_1= $C(CH_3)_3$; R_2 = H; R_3 = H
3fb. R_1= $C(CH_3)_3$; R_2 = H; R_3 = H
3fd. R_1= $C(CH_3)_3$; R_2 = H; R_3 = F
3ga. R_1= OCH_3; R_2 = H; R_3 = H
3ha. R_1= OC_2H_5; R_2 = H; R_3 = H
3ia. R_1= OC_9H_{19}; R_2 = H; R_3 = H
3ja. R_1= Br; R_2 = H; R_3 = H
3ka. R_1= CH_3; R_2 = $C(CH_3)_3$; R_3 = H

4aa. R_1= H; R_2 = H; R_3 = H
4ba. R_1= CH_3; R_2 = H; R_3 = H
4bb. R_1= CH_3; R_2 = H; R_3 = OCH_3
4ca. R_1= C_2H_5; R_2 = H; R_3 = H
4cb. R_1= C_2H_5; R_2 = H; R_3 = OCH_3
4dc. R_1= C_8H_{17}; R_2 = H; R_3 = Br
4ea. R_1= $CH(CH_3)_2$; R_2 = H; R_3 = H
4eb. R_1= $CH(CH_3)_2$; R_2 = H; R_3 = OCH_3
4fa. R_1= $C(CH_3)_3$; R_2 = H; R_3 = H
4fb. R_1= $C(CH_3)_3$; R_2 = H; R_3 = H
4fd. R_1= $C(CH_3)_3$; R_2 = H; R_3 = F
4ga. R_1= OCH_3; R_2 = H; R_3 = H
4ha. R_1= OC_2H_5; R_2 = H; R_3 = H
4ia. R_1= OC_9H_{19}; R_2 = H; R_3 = H
4ja. R_1= Br; R_2 = H; R_3 = H
4ka. R_1= CH_3; R_2 = $C(CH_3)_3$; R_3 = H

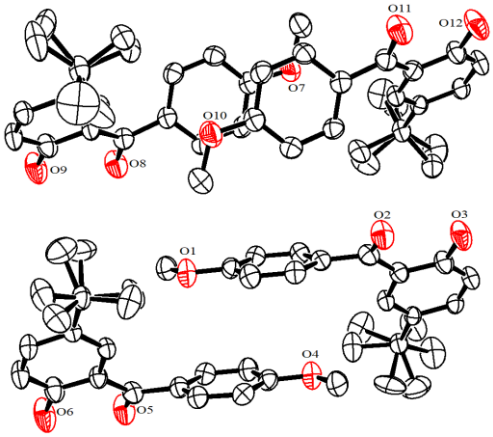


Scheme 2. Synthesis of 2-Hydroxybenzophenones.

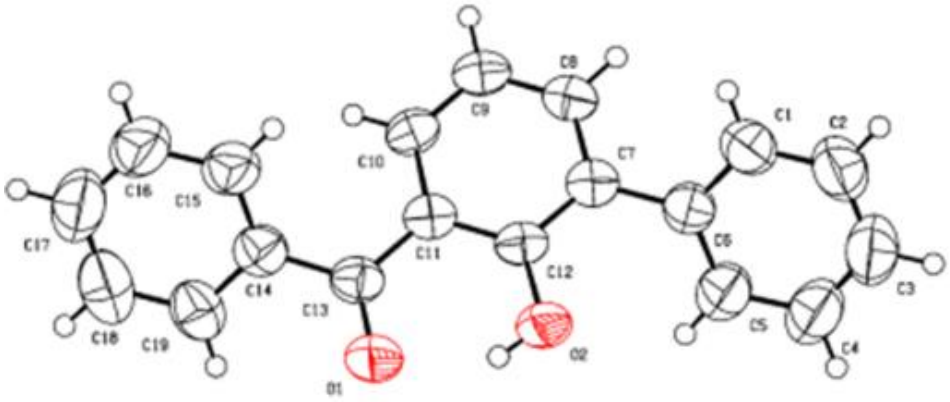
Further, to confirm the structure and the substitution pattern in the 2-hydroxybenzophenones, single crystal XRD data was collected for the representative compounds **4ja**, **4fb** and **4ma**. Whereas compound **4ja** and **4ma** showed an ideal single crystal behavior, compound **4fb** showed a dynamic disordered structure due to intramolecular vibrations in the unit cells, particularly because of the presence of the tert-butyl group, which can assume any rotation angle [23]. Never the less, all the structures corroborated with the expected structure, as shown in **Fig. 3**.



4ja
(CCDC 2348642)



4fb
(CCDC 2348641)

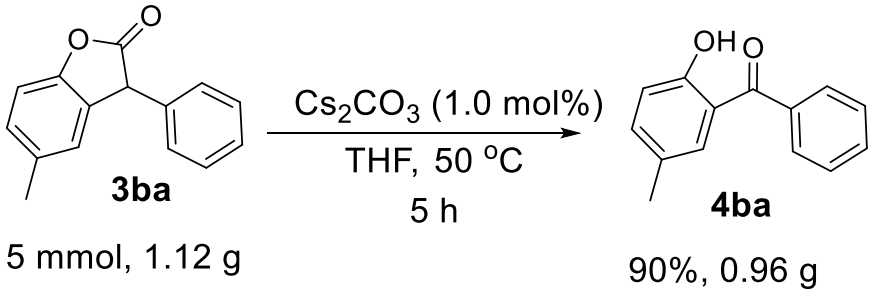


4ma
(CCDC 2348646)

Fig. 3. The ORTEP view of the compounds **4ja**, **4fb** and **4ma**.

To confirm the formation of hydroperoxide in THF via autooxidation, freshly distilled THF was heated under open atmosphere at 50 ^{o}C for 4 h, and was concentrated under vacuum to obtain the hydroperoxide residue. ^{1}H NMR of the residue, recorded in $CDCl_3$ (SI, **Fig. S1**) confirmed the presence of hydroperoxide. Resonances attributable to the O-CH-O were observed as a quartet centered at δ 5.40 ppm in the NMR spectrum. The -O-OH group in hydroperoxide gave rise to a singlet at 10.91 ppm. NMR spectrum was entirely consistent with the structure of tetrahydrofuran-2-hydroperoxide, and similar to the NMR reported earlier [24].

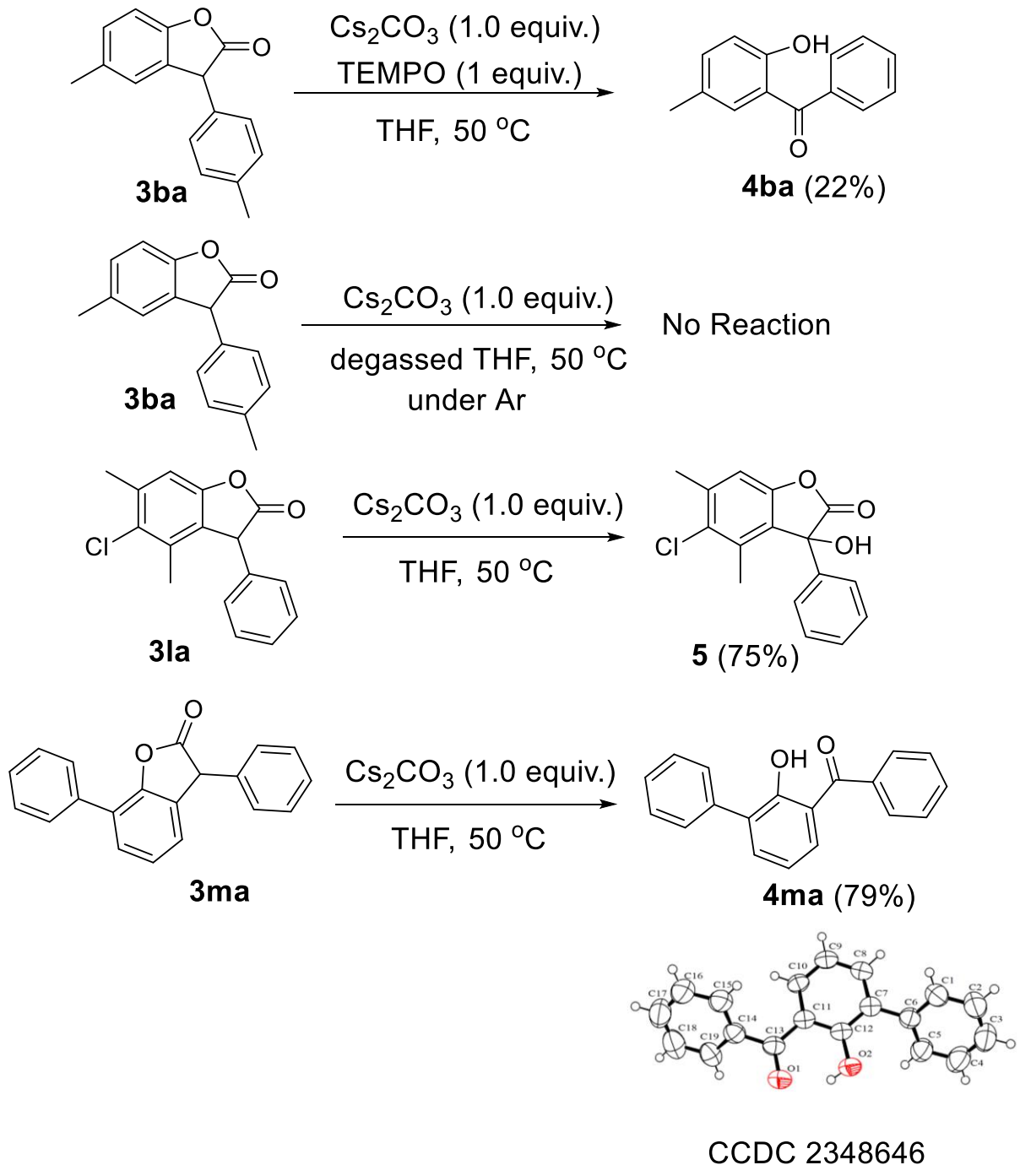
Further, the reaction of **3ba** was scaled up to show the synthetic utility of our protocol. The reactions involving hydroperoxides are known to be difficult to scale-up due to their violent reactions at elevated temperatures. Our protocol involves mild conditions, and to our expectations, a gram-scale conversion of **3ba** to **4ba** was smooth without appreciable loss in the reaction yield (**Scheme 3**). The reduced reaction time and a lower reaction temperature proved to be much advantageous compared to the reported Ni-catalysed decarbonyl-oxidation method of banzofuranones [2].



Scheme 3. Gram-scale experiment.

Next, to elucidate the mechanism of the decarbonyl-oxidation reaction of 3-aryl benzofuran-2(3*H*)-ones (**3aa**-**3ka**), control experiments were performed. Firstly, when it was observed that the reaction proceeds well only in solvents which can produce

hydroperoxides in-situ, it was quite clear that hydroperoxides have a role in the reaction mechanism. In order to confirm that the reaction proceeds through a radical mechanism, the decarbonyl-oxidation reaction of **3ba** was performed in presence of TEMPO, a known radical quencher [25]. To our expectations, the reaction did not proceed well in presence of TEMPO, giving a very poor yield of **4ba**, confirming the role of radical in the reaction (**Scheme 4**). In addition, since, it has been reported that the formation of hydroperoxides in THF is catalyzed by both dissolved oxygen and the atmospheric oxygen [26], we envisaged that a degassed THF solvent will not produce hydroperoxides, and hence the reaction will not proceed under such circumstances. To confirm, we degassed a freshly distilled THF solvent with Ar for 2 h, and then the reaction was performed under inert atmosphere. As expected, the reaction did not proceed in these conditions, confirming the role of hydroperoxide in the reaction. Additionally, as discussed earlier, we observed that the yields of 2-hydroxybenzophenone product using our protocol was very poor when a 4-substituted benzofuranone was treated even for 24 h under these conditions. To follow this, we prepared a 2-chloro-4,6-dimethyl-3-phenylbenzofuran-2(3*H*)-one (**3la**) and treated it under similar conditions. To our surprise, a 3-Phenyl-3-hydroxybenzofuran-2(3H)-one derivative **5** was obtained. This showed that the bulky THF hydroperoxide could not react with **3la** due to steric reasons. Similar poor yield for 6-substituted-2-hydroxybenzopehnones were previously reported in decarbonyl-oxidation reaction of benzofuranones [2]. To further confirm whether a bulky substitution at 7-position of the benzofuranone also hinders the formation of 2-hydroxybenzophenone, we prepared **3ma**. However, on heating **3ma** with Cs_2CO_3 in THF, the corresponding benzophenone **4ma** was obtained, which confirmed that a bulky 7-substitution does not hinder the reaction.



Scheme 4. Control experiments.

Further, to understand the origin of the product, we monitored the progress of the reaction of **3aa** using ^{1}H NMR spectroscopy. Aliquots from the reaction mixture was taken at different time intervals (**Fig. 3**), THF evaporated under vacuum, and was extracted with $CHCl_3$. ^{1}H NMR was recorded in $CDCl_3$.

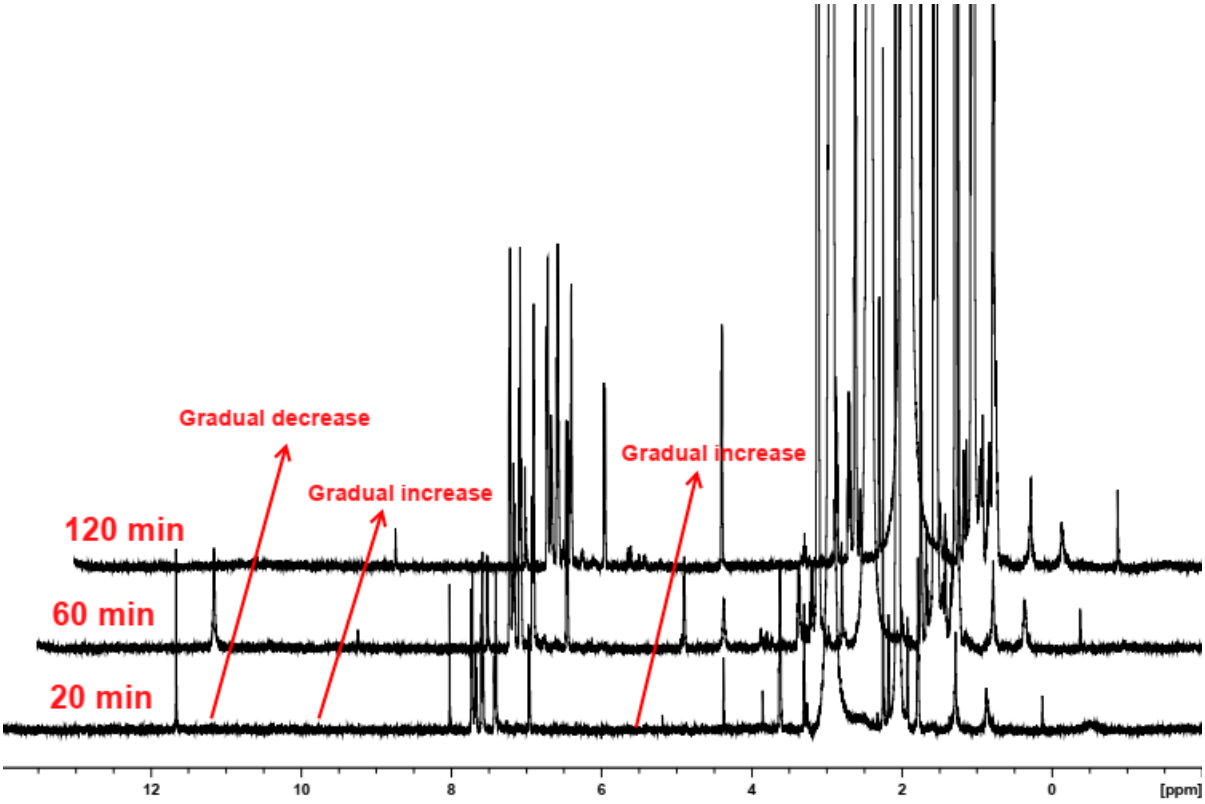


Fig. 3. Partial ^{1}H NMR spectra of the aliquots (taken at different time intervals) from the reaction mixture.

As could be seen from the plot, gradual increase in the peak at δ 5.3 ppm with concomitant decrease in the peak at δ 11.6 ppm indicated the gradual formation of THF-hydroperoxide, along with the concomitant insertion of the hydroperoxide to the substrate leading to the decrease in the -O-OH peak. An increase in the peak at δ 9.6 ppm indicated the formation of a phenolic moiety over time. Based on these observations, a plausible reaction mechanism is proposed (**Fig. 4**). Proton abstraction followed by enolization of benzofuranone **3** in the presence of a base produced intermediate **A**, which reacted with hydroperoxide to form **B** with the concomitant generation of the peroxy radical. Then, **B** reacted with peroxy radical to form intermediate **C**. Finally, **C** got hydrolysed with the release of one CO_2 and two 2-hydroxytetrahydrofuran molecules to give the target product **4**.

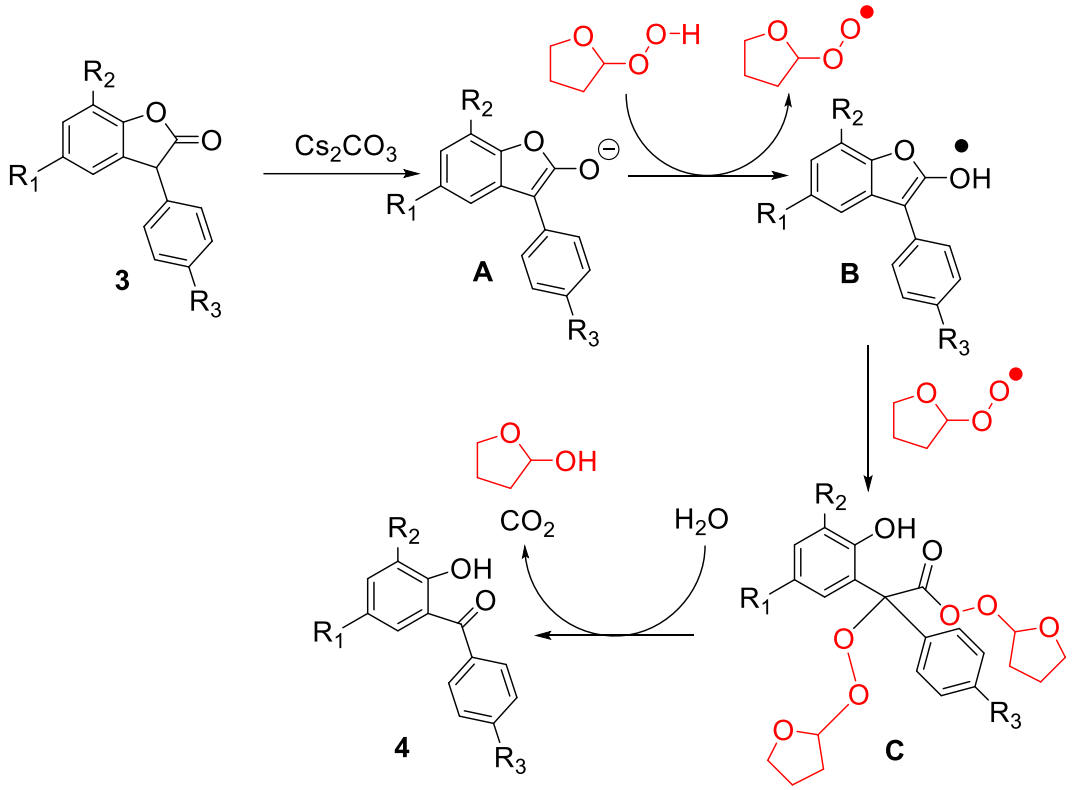


Fig. 4. Plausible mechanism for the transition metal-free decarbonyl-oxidation.

One of the commercially important 2-hydroxy benzophenone, oxybenzone, is widely used as an ingredient in sunscreen lotions, due to its ability to absorb UV light, both in UV-A and UV-B region [27-28]. However, oxybenzone, having a 4-methoxy substituent, has been reported to be associated with allergy reactions, Hirschsprung's disease and environment disrupting toxic substances [29]. This has led researchers to look for alternatives, particularly with the backbone of 2-hydroxy benzophenones [11]. As reported earlier, 4-substituted-2-hydroxy benzophenones showed a better photo-antioxidant ability, and can be an alternate to the commercially used UV-absorbers. Towards this, the UV absorption properties of the synthesized compounds were evaluated (**Fig. 5**).

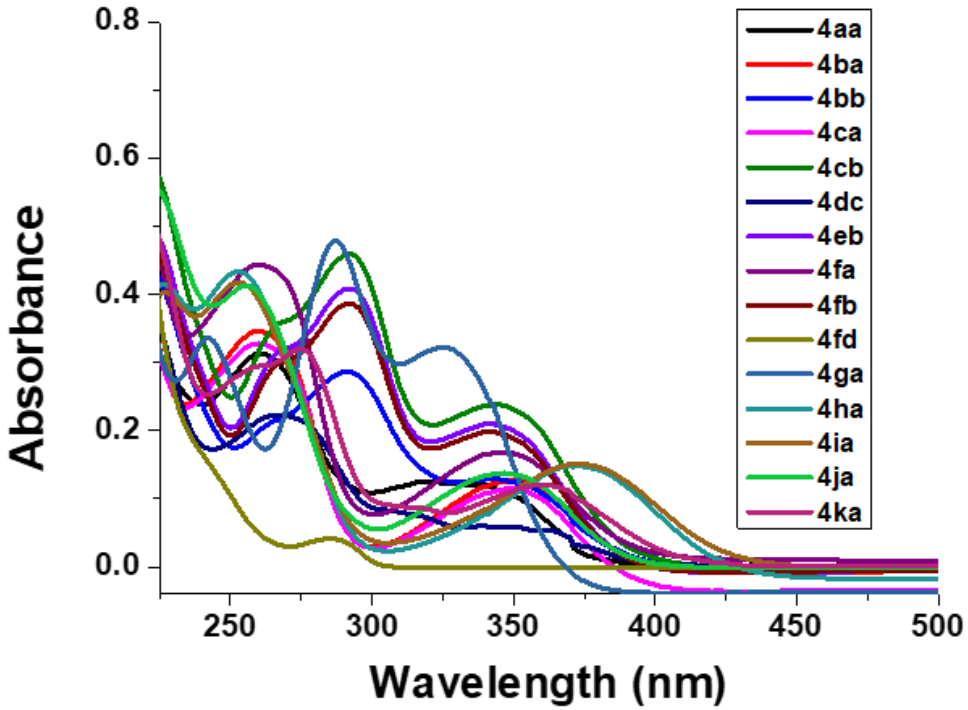


Fig. 5: UV-Vis absorption spectra of synthesized compounds (**4aa**-**4ma**) from 225-500 nm.

The abilities of the synthesized compounds for use as a protector from UV radiation were evaluated based on several parameters as tabulated in Table 2. Initially, the λ_{max} values for different absorption peaks were calculated. The critical wavelength (λ_c) were calculated using Diffey method [30]. λ_c values higher than 370 nm qualifies a substrate to be used for extensive UV protection [11]. Further, the in-vitro sun protection factor (SPF) were calculated for the compounds to determine their suitability as UV-protector. As could be seen from Table 2, an electron donating substituent on either of the benzene rings increases its UV protection abilities, via increasing the electron density. However, presence of a strong electron donating substituent e.g. $-OCH_3$ on the benzene ring attached to the carbonyl center has a more pronounced effect on the UV protection abilities (**4bb**, **4cb**, **4eb** and **4fb**), since it increases the electron density on the carbonyl center, and hence the hydrogen bonding between the carbonyl and the phenol residue is weakened. Similar phenomenon has been reported for 4′-substituted-

2-hydroxybenzophenones [6]. On the contrary, a strong electron withdrawing group viz. -F at the 4′-position (**4fd**) rendered the compound to be poor UV-protector. It was

No.	λ_{max} (nm)	ε (mol^{-1} $cm^{-1}L$)	λ_C (nm)	Broad spectrum	UVA/UVB	SPF
4aa	261 334	7856 3051	387	Y	0.91	10.45
4ba	259 350	8663 3168	374	Y	1.73	7.69
4bb	292 352	7188 3140	386	Y	0.76	9.59
4ca	260 350	8205 2858	384	Y	1.11	7.60
4cb	291 345	11495 6050	380	Y	0.64	10.55
4dc	269	5615	387	Y	0.88	7.76
4ea	264 352	8908 3463	388	Y	0.95	6.66
4eb	292 243	10190 5233	365	Y	1.17	10.79
4fa	261 347	11063 4180	373	Y	1.25	7.70
4fb	292 342	9650 4940	364	Y	0.42	11.02
4fd	286	1050	343	N	0.08	1.97
4ga	287 326	11968 8033	350	Y	0.38	8.95
4ha	253 372	10828 3790	390	Y	2.44	4.90
4ia	253 373	10450 3808	390	Y	1.47	3.78
4ja	256 347	10298 3433	374	Y	1.24	7.37
4ka	275	7998	386	Y	0.95	4.32

also observed that the presence of an alkoxy group at the 5-position of 2-hydroxy benzophenones (**4ga**, **4ha** and **4ia**) did not improve the UV-protection abilities to an appreciable extent, and the SPF values decreased with increasing alkyl chain length.

Table 2. Optical properties of the compounds (**4aa**-**4ma**).

Conclusion

In conclusion, we have developed a transition metal-free procedure to afford substituted 2-hydroxybenzophenones in a good to excellent yields. The method utilizes the hydroperoxide generated in-situ due to autooxidation of tetrahydrofuran. The mechanism of the transformation of benzofuranone to benzophenone has been proposed based on the control experiments. Further, the UV-protection abilities of the synthesized benzophenones have been evaluated mathematically. Although the mathematical procedure adopted herein in a very preliminary way to assess the UV-protection abilities of the synthesized compounds, the data obtained clearly emphasizes that 5′-substituted-2-hydroxybenzophenones, with an electron donating group at the 4′-position, are good candidates for further evaluation in-vitro and in-vivo, after validating possible sunscreen formulations which improves the effects in a synergistic way. We believe that this work will open up avenues towards evaluating 5′-substituted-2-hydroxybenzophenones as efficient UV-protectors.

Experimental

All chemicals were procured from Sigma Aldrich (AR grade) and used without any further purification. All solvents were purchased from Merck, and were distilled or dried,

whereever applicable, following standard procedures. The organic extracts were dried over anhydrous Na_2SO_4. FT-IR spectra were recorded as films with a BRUKER Tensor II spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded with a Varian 500 MHz NMR spectrometer, and were processed using Bruker TOPSPIN software. Melting points (mp) were measured in a Büchi B-540 apparatus. X-ray data were collected either on an Agilent Supernova system equipped with a microfocus Cu source (λ = 1.54184 Å) and a Titan CCD detector, or on a XtaLAB Synergy, Dualflex, HyPix four-circle diffractometer with a micro-focus sealed X-ray tube using mirror as monochromator and a HyPix detector. The elemental analyses were carried with an Elementar Vario micro cube.

*General Procedure for the Synthesis of 3-Arylbenzofuran-2(3H)-ones (**3aa**-**3ka**)*. 3-Arylbenzofuran-2(3*H*)-ones (3aa-3ka) were synthesized using a method previously reported by us [20]. A mixture of $SbCl_3$ (1.5 mmol), phenol/substituted phenol (1a-k) (5 mmol) and mandelic acid derivatives (**2a**-**d**) (6 mmol) were stirred and heated to 50 °C under nitrogen atmosphere until the mixture turned into a viscous oil. The viscous oil/paste was further heated to 140 °C till the reaction was complete (*cf.* TLC). The mixture was then brought to room temperature and a cold 10% aqueous $NaHCO_3$ solution was added. The reaction mixture was diluted with EtOAc and was filtered through a Celite bed. The filtrate was extracted with ethyl acetate (3 x 40 mL), the organic extract was washed with water and brine, and was dried with Na_2SO_4. The organic extract was concentrated under vacuum, and the residue was purified using silica-gel column chromatography. Compounds **3aa**, **3ba**, **3ea**, **3eb**, **3fa**, **3fb**, **3ga** and **3ja** were synthesized using the similar method as reported previously by us [20-22].

*3-(4-methoxyphenyl)-5-methylbenzofuran-2(3H)-one (**3bb**).* Reaction of **1b** with **2b** following the general procedure followed by purification by column chromatography (silica gel, 0-15% EtOAc-Hexane) yielded pure **3bb** as a colourless solid (Yield: 0.92

g, 72%). mp 137-138 °C; FT-IR (neat) v_{max} 2900, 1789, 1611, 1484, 1304, 1061 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.16-7.11 (m, 3H), 7.07-7.04 (m, 1H), 7.00 (s, 1H), 6.91-6.87 (m, 2H), 4.80 (s, 1H), 3.79 (s, 3H), 2.32 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 175.7, 159.4, 151.8, 134.1, 129.6, 129.3, 127.3, 127.2, 125.7, 114.5, 110.4, 55.3, 49.1, 21.0. Anal. Found: C, 75.30; H, 5.26. Calcd. for $C_{16}H_{14}O_3$: C, 75.58; H, 5.55 %.

*5-ethyl-3-phenylbenzofuran-2(3H)-one (**3ca**).* Reaction of **1c** with **2a** following the general procedure followed by purification by column chromatography (silica gel, 0-15% EtOAc-Hexane) yielded pure **3ca** as a colourless solid (Yield: 0.87 g, 73%). mp 66-67 °C; FT-IR (neat) v_{max} 2965, 1800, 1615, 1479, 1140 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.41-7.31 (m, 3H), 7.25-7.22 (m, 2H), 7.21-7.16 (m, 1H), 7.12-7.08 (m, 1H), 7.03 (s, 1H), 4.88 (s, 1H), 2.63 (q, *J* = 7.5 Hz, 2H), 1.20 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 175.4, 152.0, 140.7, 135.3, 129.1, 128.6, 128.3, 128.1, 127.0, 124.6, 110.5, 49.9, 28.5, 15.8. Anal. Found: C, 80.67; H, 5.53. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92 %.

*5-ethyl-3-(4-methoxyphenyl)benzofuran-2(3H)-one (**3cb**).* Reaction of **1c** with **2b** following the general procedure followed by purification by column chromatography (silica gel, 0-15% EtOAc-Hexane) yielded pure 3cb as a colourless solid (Yield: 0.94 g, 70%). mp 113-114 °C; FT-IR (neat) v_{max} 2969, 1808, 1510, 1247, 1067 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.19-7.12 (m, 3H), 7.09-7.06 (m, 1H), 7.01 (s, 1H), 6.91-6.87 (m, 2H), 4.80 (s, 1H), 3.79 (s, 3H), 2.62 (q, *J* = 7.5 Hz, 2H), 1.19 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 175.7, 159.5, 151.9, 140.7, 129.4, 128.5, 127.3, 127.2, 124.6, 114.5, 110.5, 55.3, 49.2, 28.5, 15.8. Anal. Found: C, 76.29; H, 5.64. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01 %.

*3-(4-bromophenyl)-5-octylbenzofuran-2(3H)-one (**3dc**)*. Reaction of **1d** with **2c** following the general procedure followed by purification by column chromatography

(silica gel, 0-15% EtOAc-Hexane) yielded pure **3dc** as a colourless viscous liquid (Yield: 1.42 g, 71%). FT-IR (neat) v_{max} 2957, 1807, 1485, 1189, 1060 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.49 (d, *J* = 8.5 Hz, 2H), 7.19-7.15 (m, 1H), 7.14-7.07 (m, 3H), 6.99 (s, 1H), 4.82 (s, 1H), 2.58 (t, *J* = 7.5 Hz, 2H), 1.29-1.21 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 174.8, 152.0, 139.6, 134.3, 132.2, 130.0, 129.4, 126.2, 125.0, 122.3, 110.6, 49.3, 35.5, 31.8, 31.6, 29.3, 29.2, 29.1, 22.6, 14.0. Anal. Found: C, 65.73; H, 6.47. Calcd. for $C_{22}H_{25}BrO_2$: C, 65.84; H, 6.28 %.

*5-(tert-butyl)-3-(4-fluorophenyl)benzofuran-2(3H)-one (**3fd**)*. Reaction of **1f** with **2d** following the general procedure followed by purification by column chromatography (silica gel, 0-15% EtOAc-Hexane) yielded pure **3fd** as a colourless viscous liquid (Yield: 0.98 mg, 69%). FT-IR (neat) v_{max} 2960, 1813, 1559, 1508, 1056 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.41 (d, *J* = 8.5 Hz, 1H), 7.25-7.19 (m, 3H), 7.14-7.04 (m, 3H), 4.86 (s, 1H), 1.31 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 175.2, 163.5, 161.5, 151.7, 131.1, 131.0, 130.0, 129.8, 126.3, 126.2, 122.1, 116.1, 115.9, 49.2, 34.7, 31.5. Anal. Found: C, 76.31; H, 5.65. Calcd. for $C_{18}H_{17}FO_2$: C, 76.04; H, 6.03 %.

*5-ethoxy-3-phenylbenzofuran-2(3H)-one (**3ha**).* Reaction of **1h** with **2a** following the general procedure followed by purification by column chromatography (silica gel, 0-15% EtOAc-Hexane) yielded pure **3ha** as a colourless solid **(**Yield: 0.93 g, 73%). mp: 60 -61 °C; FT-IR (neat) v_{max} 2982, 1797, 1486, 1144, 1038 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.38-7.31 (m, 3H), 7.24-7.21 (m, 2H), 7.07 (d, *J* = 9.0 Hz, 1H) 6.86 (dd, *J* = 2.5 and 3.0 Hz, 1H), 6.74 (d, *J* = 2.0 Hz, 1H), 4.86 (s, 1H), 3.98-3.93 (m, 2H), 1.38 (t, 6.5 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 175.4, 156.1, 147.7, 135.1, 129.1, 128.3, 128.2, 127.9, 115.2, 111.7, 111.3, 64.2, 50.4, 14.8. Anal. Found: C, 75.72; H, 5.21. Calcd. for $C_{16}H_{14}O_3$: C, 75.58; H, 5.55 %.

*5-(nonyloxy)-3-phenylbenzofuran-2(3H)-one (**3ia**)*. Reaction of **1i** with **2a** following the general procedure followed by purification by column chromatography (silica gel, 0-

15% EtOAc-Hexane) yielded pure **3ia** as a colourless viscous liquid (Yield: 1.25 g, 71%); FT-IR (neat) ν_{max} 2923, 1806, 1485, 1394, 1060 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.39-7.30 (m, 3H), 7.23 (d, *J* = 7.0 Hz, 2H), 7.09 (d, *J* = 9.0 Hz, 1H), 6.86 (dd, *J* = 2.5 and 2.5 Hz, 1H), 7.0 (d, *J* = 2.0 Hz, 1H), 4.85 (s, 1H), 3.87 (t, 6.5 Hz, 2H), 1.75-1.70 (m, 2H) 1.43-1.37 (m, 2H), 1.31-1.25 (m, 10H), 0.87 (t, 6.5 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 175.4, 156.4, 147.7, 135.2, 129.1, 128.3, 128.2, 127.8, 115.2, 111.7, 111.3, 68.8, 50.4, 31.8, 29.5, 29.3, 29.2, 26.0, 22.6, 14.1. Anal. Found: C, 78.62; H, 8.01. Calcd. for $C_{23}H_{28}O_3$: C, 78.38; H, 8.01 %.

*7-(tert-butyl)-5-methyl-3-phenylbenzofuran-2(3H)-one (**3ka**)*. Reaction of **1k** with **2a** following the general procedure followed by purification by column chromatography (silica gel, 0-15% EtOAc-Hexane) yielded pure **3ka** as a colourless solid (Yield: 1.04 g, 74%); mp: 160-161 ^{o}C; FT-IR (neat) ν_{max} 2959, 1781, 1453, 1267, 1072 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.40-7.30 (m, 3H), 7.27-7.22 (m, 2H), 7.11 (s, 1H), 6.86 (s, 1H), 4.83 (s, 1H), 2.33 (s, 3H), 1.45 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 175.5, 149.8, 135.6, 133.9, 133.7, 129.0, 128.3, 128.0, 127.4, 127.0, 123.1, 49.5, 34.1, 29.6, 21.2. Anal. Found: C, 81.69; H, 7.12. Calcd. for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19 %.

*5-chloro-4,6-dimethyl-3-phenylbenzofuran-2(3H)-one (**3la**)*. Reaction of 4-chloro-3,5-dimethylphenol (5 mmol) and mandelic acid (6 mmol) with 4-chloro-3,5-dimethylphenol (5 mmol) and mandelic acid (6 mmol) following the general procedure followed by purification by column chromatography (silica gel, 0-15% EtOAc-Hexane) yielded pure **3la** as a colourless solid (Yield: 0.98 g, 72%). mp: 138-139 °C; FT-IR (neat) ν_{max} 2964, 1794, 1452, 1393, 1027 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.39-7.34 (m, 3H), 7.18-7.16 (m, 2H), 6.97 (s, 1H), 4.82 (s, 1H), 2.45 (s, 3H), 2.04 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ = 174.8, 151.9, 137.9, 134.4, 133.9, 130.4, 129.3, 128.3, 128.1,

124.4, 110.6, 49.9, 21.5, 17.1. Anal. Found: C, 70.62; H, 4.45. Calcd. for $C_{19}H_{20}O_2$: C, 70.46; H, 4.80 %.

*General Procedure for the Synthesis of 2-Hydroxybenzophenones (**4aa**-**4ka**)*. 1 mmol Cs_2CO_3 was added to a solution of 3-Arylbenzofuran-2(3H)-ones (**3aa**-**3ka**) (1 mmol) in 2 ml of freshly distilled THF, and the mixture was heated at 50℃ with stirring under open atmosphere. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction (3-4 h, *cf*. TLC), the mixture was cooled to room temperature and THF present in the reaction mixture was evaporated. The residue was purified by preparative TLC (hexane/EtOAc) to obtain pure 2-hydroxybenzophenones.

*(2-hydroxyphenyl)(phenyl)methanone (**4aa**)* Reaction of **3aa** following the general procedure followed by purification by column chromatography (silica gel, 0-20% EtOAc-Hexane) yielded pure **4aa** as a colourless viscous liquid (Yield: 168 mg, 85%). FT-IR (neat) ν_{max} 3059, 2957, 1625, 1444, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 12.03 (s, 1H), 7.70-7.66 (m, 2H), 7.62-7.56 (m, 2H), 7.51 (t, *J* = 7.0 Hz, 3H), 7.07 (d, *J* = 8.5 Hz, 1H), 6.88 (t, *J* = 7.5, Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 201.6, 163.2, 137.9, 136.3, 133.6, 131.9, 129.1, 128.3, 119, 118.6, 118.4. Anal. Found: C, 78.44; H, 5.14. Calcd. for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09 %.

*(2-hydroxy-5-methylphenyl)(phenyl)methanone (**4ba**)* Reaction of **3ba** following the general procedure followed by purification by column chromatography (silica gel, 0-20% EtOAc-Hexane) yielded pure **4ba** as a colourless solid (Yield: 193 mg, 91%). mp: 81-82 °C; FT-IR (neat) ν_{max} 3200, 2918, 1625, 1445, 1225, 958 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.85 (s, 1H), 7.69-7.64 (m, 2H), 7.62-7.56 (m, 1H), 7.54-7.48 (m, 2H), 7.37-7.30 (m, 2H), 6.98 (d, *J* = 9.0 Hz, 1H), 2.25 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 201.6, 161.1, 138.0, 137.3, 131.2, 131.7, 129.1, 128.3, 127.7, 118.7, 118.1, 20.4. Anal. Found: C, 79.30; H, 5.47. Calcd. for $C_{14}H_{12}O_2$: C, 79.23; H, 5.70 %.

*3-(4-methoxyphenyl)-5-methylbenzofuran-2(3H)-one (**4bb**).* Reaction of **3bb** following the general procedure followed by purification by column chromatography (silica gel, 0-20% EtOAc-Hexane) yielded pure **4bb** as a colourless solid (Yield: 199 mg, 82%). mp: 109-110 °C; FT-IR (neat) v_{max} 2917, 1631, 1478, 1248, 1024 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.75 (s, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.39 (s, 1H), 7.29 (d, *J* = 8,5 Hz, 1H), 7.00-6.95 (m, 3H), 3.89 (s, 3H), 2.26 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 200.0, 162.8, 160.8, 136.7, 132.9, 131.7, 130.5, 127.6, 119.1, 118.0, 113.6, 55.4, 20.5. Anal. Found: C, 74.30; H, 5.65. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82 %.

*(5-ethyl-2-hydroxyphenyl)(phenyl)methanone (**4ca**).* Reaction of **3ca** following the general procedure followed by purification by column chromatography (silica gel, 0-20% EtOAc-Hexane) yielded pure **4ca** as a colourless viscous liquid (Yield: 190 mg, 84%). mp: 109-110 °C; FT-IR(neat) v_{max} 2964, 1630, 1481, 950 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.86 (s, 1H), 7.68 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.40-7.34 (m, 2H), 7.01 (d, *J* = 8.0 Hz, 1H), 2.55 (q, *J* = 7.5 Hz, 2H), 1.16 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 200.6, 161.3, 138.1, 136.2, 134.3, 132.1, 131.8, 129.1, 128.3, 118.8, 118.2, 27.9, 15.7. Anal. Found: C, 79.35; H, 6.25. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24%.

*(5-ethyl-2-hydroxyphenyl)(4-methoxyphenyl)methanone (**4cb**)*. Reaction of **3cb** following the general procedure followed by purification by column chromatography (silica gel, 0-20% EtOAc-Hexane) yielded pure **4cb** as a colourless viscous liquid (Yield: 184 mg, 72%); FT-IR (neat) v_{max} 2959, 1627, 1481, 1243, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.77 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.34 (dd, *J* = 2.0 and 6.5 Hz, 1H), 7.03-6.97 (m, 3H), 3.90 (s, 3H), 2.57 (q, *J* = 6.5 Hz, 2H), 1.18 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 200.0, 162.8, 160.9, 135.6, 134.1, 131.8, 131.7, 130.5, 119.1, 118.1, 113.6, 55.5, 27.9, 15.7. Anal. Found: C, 74.97; H, 6.31. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29 %.

*(4-bromophenyl)(2-hydroxy-5-octylphenyl)methanone (**4dc**).* Reaction of **3dc** following the general procedure followed by purification by column chromatography (silica gel, 0-20% EtOAc-Hexane) yielded pure **4dc** as a colourless viscous liquid (Yield: 284 mg, 73%); FT-IR (neat) v_{max} 2923, 1630, 1480, 1244, 1012 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.68 (s, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.34 (dd, *J* = 1.5 and 8.5 Hz, 1H), 7.29-7.27 (m, 1H), 7.26-7.25 (m, 1H), 2.49 (t, *J* = 7.5 Hz, 2H), 1.64-1.47 (m, 2H), 1.33-1.19 (m, 10H), 0.86 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 200.3, 161.3, 137.0, 136.8, 133.2, 132.3, 130.7, 126.7, 118.6, 118.3, 34.9, 31.8, 31.5, 29.3, 29.2, 29.0, 22.6, 14.0. Anal. Found: C, 64.66; H, 6.51. Calcd. for $C_{21}H_{25}BrO_2$: C, 64.79; H, 6.47 %.

*(2-hydroxy-5-isopropylphenyl)(phenyl)methanone (**4ea**)* Reaction of **3ea** following the general procedure followed by purification by column chromatography (silica gel, 0-20% EtOAc-Hexane) yielded pure **4ea** as a colourless viscous liquid (Yield: 185 mg, 77%); FT-IR (neat) v_{max} 3300, 2956, 1809, 1597, 1244, 1074 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.87 (s, 1H), 7.69 (d, *J* = 7.5 Hz, 2H), 7.60 (t, 7.5 Hz, 1H), 7.52 (t, 7.0 Hz, 2H), 7.44-7.38 (m, 2H), 7.02 (d, *J* = 8.0 Hz, 1H) 2.84-2.79 (m, 1H), 1.18 (d, *J* = 7.0 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 201.5, 161.3, 138.9, 138.0, 134.7, 131.8, 130.8, 129.2, 128.3, 118.7, 118.2, 33.2, 23.9. Anal. Found: C, 80.15; H, 6.56. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71 %.

*(2-hydroxy-5-isopropylphenyl)(4-methoxyphenyl)methanone (**4eb**).* Reaction of **3eb** following the general procedure followed by purification by column chromatography (silica gel, 0-20% EtOAc-Hexane) yielded pure **4eb** as a colourless viscous liquid (Yield: 195 mg, 72%). mp: 108-109 °C; FT-IR (neat) v_{max} 2959, 1627, 1337, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.78 (s, 1H), 7.21 (d, *J* = 9.0 Hz, 2H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.38-7.35 (m, 1H), 7.00-6.98 (m, 3H), 3.89 (s, 3H), 2.85-2.8(m, 1H), 1.19 (d, *J* = 6.5 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 199.9, 162.8, 160.9,

138.7, 134.2, 131.8, 130.5, 130.4, 118.9, 118.0, 113.6, 55.4, 33.2, 23.9. Anal. Found: C, 75.22; H, 6.45. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71 %.

*(5-(tert-butyl)-2-hydroxyphenyl)(phenyl)methanone (**4fa**).* Reaction of **3fa** following the general procedure followed by purification by column chromatography (silica gel, 0-20% EtOAc-Hexane) yielded pure **4fa** as a colourless viscous liquid (Yield: 214 mg, 84%); FT-IR (neat) v_{max} 3400, 2959, 1629, 1482, 968 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.86 (s, 1H), 7.69 (d, *J* = 7.5 Hz, 2H), 7.63-7.55 (m, 3H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 1H), 1.25 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 201.6, 160.9, 141.3, 138.1, 133.9, 131.9, 129.8, 129.2, 128.3, 118.4, 117.9, 34.0, 31.2. Anal. Found: C, 80.50; H, 7.10. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13 %.

*(5-(tert-butyl)-2-hydroxyphenyl)(4-methoxyphenyl)methanone (**4fb**)* Reaction of **3fb** following the general procedure followed by purification by column chromatography (silica gel, 0-20% EtOAc-Hexane) yielded pure **4fb** as a colourless solid (Yield: 245 mg, 86%). mp: 92-93 °C; FT-IR (neat) v_{max} 2919, 1626, 1565, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.76 (s, 1H), 7.73 (d, *J* = 9.0 Hz, 2H), 7.62 (d, *J* = 2 Hz, 1H), 7.56-7.53 (m, 1H), 7.01 (d, *J* = 8.5 Hz, 3H), 3.91 (s, 3H), 1.27 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 200.1, 162.9, 160.6, 141.1, 133.3, 131.8, 130.6, 129.6, 118.7, 117.8, 113.6, 55.5, 34.1, 31.3. Anal. Found: C, 75.87; H, 6.88. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09 %.

*(5-(tert-butyl)-2-hydroxyphenyl)(4-fluorophenyl)methanone (**4fd**).* Reaction of **3fd** following the general procedure followed by purification by column chromatography (silica gel, 0-20% EtOAc-Hexane) yielded pure **4fd** as a colourless solid (Yield: 150 mg, 55%). mp: 168-169 °C; FT-IR (neat) v_{max} 3402, 2918, 1784, 1319, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm):11.69 (s, 1H), 7.74-7.72 (m, 2H), 7.58-7.56 (m, 1H), 7.53 (d, *J* = 2.5 Hz 1H),7.21 (t, *J* = 9.0 Hz, 2H), 7.02 (d, *J* = 9.0 Hz 1H), 1.25 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 200.0, 166.0, 163.9, 160.9, 141.4, 133.9, 131.8,

131.7, 129.4, 118.3, 118.0, 115.6, 115.4, 34.1, 31.2. Anal. Found: C, 75.17; H, 6.52. Calcd. for $C_{17}H_{17}FO_2$: C, 74.98; H, 6.29 %.

*(2-hydroxy-5-methoxyphenyl)(phenyl)methanone (**4ga**).* Reaction of **3ga** following the general procedure followed by purification by column chromatography (silica gel, 0-20% EtOAc-Hexane) yielded pure **4ga** as a colourless solid (Yield: 178 mg, 78%). mp: 81-82 °C; FT-IR (neat) v_{max} 2917, 1633, 1483, 1039 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.59 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.60 (t, *J* = 8.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.14 (d, *J* = 8.5, Hz, 1H), 7.08-6.99 (m, 2H), 3.70 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 201.1, 157.5, 151.4, 137.9, 131.9, 129.1, 128.4, 124.0, 119.2, 118.7, 116.3, 55.9. Anal. Found: C, 73.54; H, 5.29. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30 %.

*(5-ethoxy-2-hydroxyphenyl)(phenyl)methanone (**4ha**).* Reaction of **3ha** following the general procedure followed by purification by column chromatography (silica gel, 0-20% EtOAc-Hexane) yielded pure **4ha** as a colourless viscous liquid (Yield: 174 mg, 72%). FT-IR (neat) v_{max} 2980, 1632, 1445, 1046 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.58 (s, 1H), 7.69 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 2H), 7.14 (dd, *J* = 9.0 Hz, 1H), 7.05 (d, *J* = 3.0, Hz, 1H), 7.00 (d, *J* = 9.0 Hz, 1H), 3.89, (q, *J* = 7.0 Hz, 2H), 1.35 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 201.2, 157.4, 150.7, 137.9, 131.9, 129.0, 128.3, 124.7, 119.1, 118.7, 117.3, 64.3, 14.7. Anal. Found: C, 74.51; H, 6.02. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82 %.

*(2-hydroxy-5-(nonyloxy)phenyl)(phenyl)methanone (**4ia**)*. Reaction of **3ia** following the general procedure followed by purification by column chromatography (silica gel, 0-20% EtOAc-Hexane) yielded pure **4ia** as a colourless viscous liquid (Yield: 249 mg, 73%). FT-IR (neat) v_{max} 2925, 1603, 1483, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.56 (s, 1H), 7.68 (d, *J* = 7.0 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 2H), 7.13 (dd, *J* = 3.0 and 9.0 Hz, 1H), 7.04 (d, *J* = 3.0 Hz, 1H), 7.99 (d, *J* = 4.0 Hz, 1H), 3.81, (t, *J* = 6.5 Hz, 2H), 1.72-1.66 (m, 2H), 1.41-1.35 (m, 2H), 1.32-1.24 (m,

10H), 0.86 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 201.2, 157.4, 150.9, 137.9, 131.9, 129.1, 128.3, 124.7, 119.1, 118.7, 117.3, 69.0, 31.8, 29.4, 29.3, 29.2, 29.1, 26.0, 22.6, 14.1. Anal. Found: C, 77.26; H, 8.07. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29 %.

*(5-bromo-2-hydroxyphenyl)(phenyl)methanone (**4ja**)*. Reaction of **3ja** following the general procedure followed by purification by column chromatography (silica gel, 0-20% EtOAc-Hexane) yielded pure **4ja** as a colourless solid (Yield: 233 mg, 94%); mp: 111 -112 °C; IR (neat) v_{max} 3300, 2917, 1620, 1466, 1080 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.93 (s, 1H), 7.72-7.65 (m, 3H), 7.64-7.51 (m, 4H), 6.99 (d, *J* = 8.5 Hz, 1H),; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 200.5, 162.1, 138.9, 137.2, 135.3, 132.4, 129.1, 128.6, 120.5, 120.4, 110.2. Anal. Found: C, 56.41; H, 3.64. Calcd. for $C_{13}H_9BrO_2$: C, 56.35; H, 3.27 %.

*(3-(tert-butyl)-2-hydroxy-5-methylphenyl)(phenyl)methanone (**4ka**).* Reaction of **3ka** following the general procedure followed by purification by column chromatography (silica gel, 0-20% EtOAc-Hexane) yielded pure **4ka** as a colourless viscous liquid (Yield: 225 mg, 84%). FT-IR (neat) v_{max} 3556, 2956, 1621, 1431, 986 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 12.7 (s, 1H), 7.64 (d, *J* = 7.5, Hz, 2H), 7.58 (t, *J* = 7.5, Hz, 1H), 7.50 (t, *J* = 8, Hz, 2H), 7.32 (d, *J* = 1.5, Hz, 1H), 7.20 (s, 1H), 2.23 (s, 3H), 1.45 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 202.4, 160.8, 138.7, 138.4, 134.8, 131.4, 131.2, 128.2, 126.4, 118.6, 34.8, 29.3, 20.8. Anal. Found: C, 80.42; H, 7.32. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51 %.

*(2-hydroxy-[1,1'-biphenyl]-3-yl)(phenyl)methanone (**4ma**)*. As described before, a mixture of $SbCl_3$ (0.5 mmol), [1,1'-biphenyl]-2-ol (1.5 mmol) and mandelic acid (2 mmol) were stirred and heated to 50 °C under nitrogen atmosphere until a viscous oil was obtained, which was further heated to 140 °C till the reaction was complete (*cf.* TLC). The reaction mixture was then cooled, quenched with a cold 10% aqueous $NaHCO_3$

solution, diluted with EtOAc and was filtered through a Celite bed. The filtrate was extracted with ethyl acetate (3 x 40 mL), the organic extract was washed with water and brine, and was dried with Na_2SO_4. The organic extract was concentrated under vacuum, and the residue was utilised for further reaction without purification.

A solution of the residue in 2 ml of freshly distilled THF was heated at 50℃ in presence of 1.0 mmol Cs_2CO_3 under open atmosphere. After completion of the reaction (*cf*. TLC), the mixture was cooled to room temperature and THF was evaporated under vacuum. The residue was purified by preparative TLC (hexane/EtOAc) to obtain pure **4ma** as a colourless solid (yield: 217 mg, 53% in two steps). mp: 102-103 °C; FT-IR (neat) ν_{max} 2921, 1608, 1446, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 12.56 (s, 1H), 7.74-7.69 (m, 2H), 7.66-7.57 (m, 5H), 7.53 (t, *J* = 8.5 Hz, 2H), 7.47 (t, *J* = 8.5 Hz, 2H), 7.38 (t, *J* = 6.5 Hz, 1H), 6.95 (t, *J* = 8.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 202.0, 160.5, 138.1, 137.2, 137.0, 133.0, 131.9, 131.2, 129.4, 129.2, 128.3, 128.2, 127.5, 119.3, 118.5. Anal. Found: C, 83.30; H, 5.23. Calcd. for $C_{19}H_{14}O_2$: C, 83.19 H, 5.14 %.

Synthesis of 5-chloro-3-hydroxy-4,6-dimethyl-3-phenylbenzofuran-2(3H)-one (**5**). As described before, a solution of **3na** (1.0 mmol) in 2 ml of freshly distilled THF was heated at 50℃ in presence of 1.0 mmol Cs_2CO_3 under open atmosphere. After completion of the reaction (*cf*. TLC), the mixture was cooled to room temperature and THF was evaporated under vacuum. The residue was purified by preparative TLC (hexane/EtOAc) to obtain pure **5** as a colourless solid (Yield: 216 mg, 75%). mp: 161-162 °C; FT-IR (neat) ν_{max} 3480, 2956, 1787, 1451, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.38-7.31 (m, 4H), 6.97 (s, 1H), 3.34 (s, 1H), 2.44 (s, 3H), 2.13 (s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 175.9, 151.4, 139.8, 137.5, 135.5, 131.3, 129.2, 128.9, 128.8, 126.1, 125.1, 111.0, 77.7, 21.6, 15.8. Anal. Found: C, 65.71; H, 4.25. Calcd. for $C_{16}H_{13}ClO_3$: C, 66.56 H, 4.54 %.

Single-Crystal XRD

The data were collected using a similar method as reported by us earlier [20-22], using a XtaLAB Synergy, Dualflex, HyPix four-circle diffractometer, a micro-focus sealed X-ray tube and a HyPix detector. The data were corrected using SCALE3 ABSPACK and the structure were solved using SHELXT. Disordered moieties were refined using bond lengths restraints and displacement parameter restraints. Crystallographic data (including structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC Nos. 2348642, 2348641 and 2348646).

UV-Absorption studies [11]

UV-Vis absorbance spectra of the 5-substituted-2-hydroxybenzopheneones (**4aa**-**4ka**) were recorded in triplicates at room temperature (298 K) in ethanol at a concentration of 40 µM, in the range of 225-500 nm at 1 nm interval. The obtained data were corrected using calibration methods with ethanol as a blank. The critical wavelength (λ_c) and UVA/UVB ratio were calculated using equation (1) and (2), respectively, as shown below.

$$\int_{290}^{\lambda c} A(\lambda)\, d\lambda = 0.9 \int_{290}^{400} A\,(\lambda)\, d\lambda \qquad \text{----------(1)}$$

$$\frac{UVA}{UVB} = \frac{\int_{320}^{400} A(\lambda)\, d\lambda \Big/ \int_{320}^{400} d\lambda}{\int_{290}^{320} A(\lambda)\, d\lambda \Big/ \int_{290}^{320} d\lambda} \qquad \text{----------(2)}$$

Determination of SPF (Sun Protection Factor) [11]

Ethanolic solution of the compounds (**4aa**-**4ka**) were prepared at a concentration of 200 µg/ml. The UV-Vis absorption spectra of samples were measured in the range of 290 to 450 nm, every 5 nm, using ethanol as a blank. The absorption data were

obtained in three replicates at each point, and the SPF value was calculated using the following equation (3).

$$SPF_{spectrometric}=CF\ X\ \sum_{290}^{320} EE\ (\lambda)\ X\ I(\lambda)\ X\ Abs\ (\lambda) \quad \text{--(3)}$$

Where, CF (correction factor) = 10; EE(λ) is the erythemal effect spectrum; I(λ) is the solar intensity spectrum; Abs(λ) is the experimental absorbance values at corresponding wavelength. The values of [EE (λ) x I (λ)] are constants as shown in Table 3 [31].

Table 3. Values of [EE (λ) x I (λ)] used in calculating SPF

Wavelength (λ) [nm]	**EE (λ) x I (λ)**
290	0.0150
295	0.0817
300	0.2874
305	0.3278
310	0.1874
315	0.0839
320	0.0180
Total	1.000

Supporting Information

Supporting Information File 1: PDF

File Name: SI.pdf

Author Contributions

Bhaskar B. Dhotare: Investigation, Methodology, Formal analysis. *Seema V. Kanojia*: Investigation, Formal analysis. *Chahna K. Sakhiya*: Investigation, Formal analysis. *Amey Wadawale*: Investigation, Formal analysis. *Dibakar Goswami*: Supervision. Writing - Original Draft. Writing- Reviewing and Editing.

Conflicts of interest

There are no conflicts of interest to declare.

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