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Synthesis of 5-subsituted flavonols via the Algar-Flynn-Oyamada (AFO) reaction: The mechanistic implication

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ABSTRACT

Herein, we report a synthetic method with improved selectivity for 5-substituted flavonols via the Algar-Flynn-Oyamada reaction (AFO), by using of sodium carbonate/hydrogen peroxide A series of 5-substituted flavonols was obtained with moderate to high yields. The mechanism of the AFO reaction was elucidated. LCMS analysis and in situ ^{1}H NMR analysis indicated that the epoxide was involved in the transformation from chalcone to flavonol and/or aurone under alkaline base/peroxide conditions.

1. Introduction

Flavonols, also known as 3-hydroxyflavones, occur in a wide variety of natural plants. They attract considerable interest due to their biological effects, including antiviral, antitumor and antibiotic activities.[1] Most natural occurring flavonols with therapeutic significance contain substituents at the 5-position. For example, quercetin and kaempferol distinctly inhibit cancer cell lipogenesis in both prostate and breast cancer cells.[2] Icaritin inhibits malignant growth of hepatocellular carcinoma-initiating cells (HCICs) and may potentially be developed into an effective therapeutic agent for the treatment of hepatocellular carcinoma (HCC).[3]Unfortunately, these compounds are founded in low concentration in natural sources and are difficult to separate from structurally-similar analogs plant extracts. Construction of structurally diverse flavonols is attractive to synthetic chemists. Four main approaches exist for the synthesis of flavonols: The Auwers synthesis,[4] the Algar-Flynn-Oyamada reaction (AFO),[5] the Baker-Venkataraman synthesis[6] and flavone oxidation by 3,3-dimethyldioxirane (DMDO).[7] Due to the relative simplicity and convenience, the AFO reaction has been widely adapted for the synthesis of flavonols, which involves the oxidation of 2'- hydroxychalcone with hydrogen peroxide in alkaline alcohol solution. In terms of the synthesis of flavonols through the AFO reaction, 5-substituted flavonols are of lower yielding.[8] Gunduz et al. reported a one-pot synthesis of 3-hydroxyflavones.[5] However, this method does not lead to 5-substituted flavonols effectively. When 6-substituented 2-hydroxylacetophenone was subjected, aurone was obtained as the major product instead of flavonol.[9]

As to the mechanism of the AFO reaction, two hypothesis were proposed. The first one (Scheme 1a) proceeds through the conversion of 2-hydroxychalcone to the chalcone epoxide. Subsequent cyclization of epoxide may occur at either the α- or β-position, the aurone or the flavonol, respectively.[10] The other hypothesis for the formation of flavonol (Scheme 1b) starts with cyclization of chalcone anion, followed by electrophilic attack of hydrogen peroxide at *C-3* carbon atom of the anion, and the further formation of flavonol. Alternatively, a concert process may combine the two stages.[11,12]

To date, no experimental evidence had been reported that characterizes an epoxide intermediate or supports either mechanism. Blazejowski[13] conducted quantum-chemical analysis of the AFO reaction mechanism and concluded that the epoxide intermediate was likely rather than the synchronous mechanism. Due to

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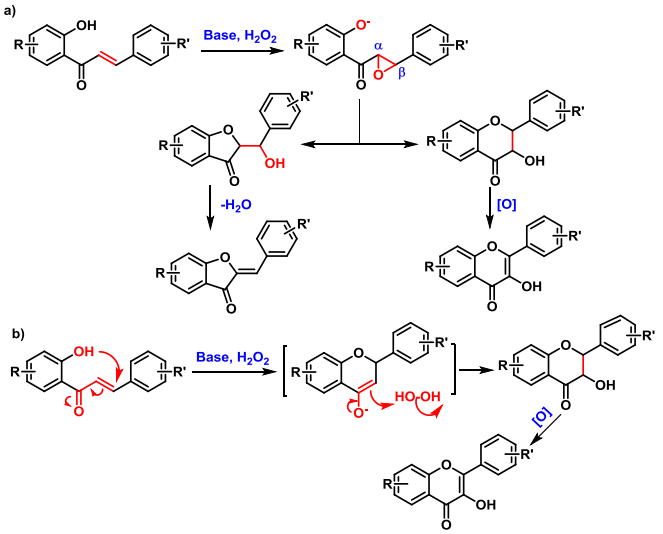


Scheme 1. Mechanisms proposed for the AFO reaction.

the extremely short anticipated life time of the 2′-hydroxyl chalcone epoxide intermediate, it would likely be very difficult to detect.

Recently, we have shown semi-synthetic approach to various 5-substotuted flavonol derivatives.[14] As part of our ongoing research programs directed to the development of efficient methods for flavonols synthesis, in particular the 5-substituted flavonols, we herein present a satisfactory solution to this target, by conducting the AFO transformation in a mild system of Na_2CO_3/H_2O_2 in methanol and water. Moreover, we gained the mechanism insights through LCMS study and in-situ ^1H NMR analysis.

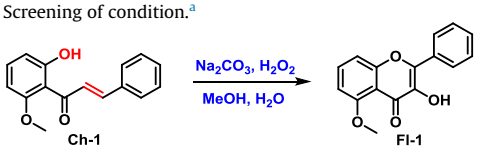
2. Result and discussion

We noticed during experiments that the AFO reaction of chalcone was very tunable to the conditions, especially to the strength of base. Therefore, we started our investigation by a fine-tuning of the conditions of this novel transformation using **Ch-1** as a model study (Table 1). A variety of organic and inorganic bases were screened in methanol/water mixed solvent in the presence of hydrogen peroxide at room temperature. Sodium carbonate was the best base with 33% yield (Entry 15).

Weak bases, such as sodium acetate and sodium bicarbonate, promoted O-Michael addition to generate flavanones rather than flavonols (Table 1, Entry 1 and 2). These were probably due to weak bases being unable to initiate the AFO reaction. On the other hand, strong bases, such as NaOEt, $N(Et)_3$, DBU and TBD (Table 1, Entry 5–8), produced 4-methoxybenzaldehyde and 2-hydroxy-6-methoxybenzoic acid as main products, which were possibly formed by over-oxidation of chalcone. Next, we carried out the reaction in different solvents. We found that the combination of methanol/water of 2:1 was the best among all other solvents tested.

To further optimize the favourable conditions for formation of flavonol, the equivalents of sodium carbonate and hydrogen peroxide were investigated. The combination of 5 equivalents of sodium carbonate and 2.5 equivalents of hydrogen peroxide were the best (Table 1, entry 15). We noticed that the lower equivalents of sodium carbonate and hydrogen peroxide converted chalcone into flavonone instead of flavonol, whereas an increasing amount of by-product 4-methoxybenzaldehyde and 2-hydroxy-6-methoxybenzoic acid were generated when high equivalences of Na_2CO_3/H_2O_2 were used. The reaction was also sensitive to

Table 1
Screening of condition.[a]



Entry	Base(5eq)	Solvent Ratio (MeOH/H_2O)	H_2O_2(eq)	Yield (%)[b]
1	NaOAc	2:1	5	n.d.
2	$NaHCO_3$	2:1	5	n.d.
3	K_2CO_3	2:1	5	22
4	NaOH	2:1	5	13
5	NaOEt	2:1	5	1
6	$N(Et)_3$	2:1	5	n.d.
7	DBU	2:1	5	17
8	TBD	2:1	5	20
9	Na_2CO_3	2:1	5	32
10	Na_2CO_3	1:1	5	28
11	Na_2CO_3	3:1	5	30
12	Na_2CO_3	4:1	5	22
13	Na_2CO_3	5:1	5	15
14	Na_2CO_3	7:1	5	4
15	**Na_2CO_3**	**2:1**	**2.5**	**33**
16	Na_2CO_3	2:1	7.5	14
17	Na_2CO_3	2:1	10	12
18	Na_2CO_3	2:1	12.5	8

[a] The reactions conducted using 1 eq. of **Ch-1**, 5 eq. of Na_2CO_3 and H_2O_2 in MeOH/H_2O at 0 °C for 30 min and then at 27 °C for 24 h.
[b] HPLC yields, n.d. = not detectable.

temperature. Flavanone was the main product at 0 °C. Performing the reaction at 5–10 °C produced a mixture of aurone and flavonol; increasing temperature from 10 °C to 27 °C increased the yields of flavonol. Temperature of 30 °C and above produced over oxidization affording 4-methoxybenzaldehyde and 2-hydroxy-6-methoxybenzoic acid by-products. Initially, the yield of flavonol of the model reaction was only 13% under the $NaOH/H_2O_2$ condition. In comparison, at the optimal condition, the yield increased to 32%.

With the optimized condition in hand, we next explored the substrate scope of this methodology. A series of 6'-substituted chalcones were synthesized through Claisen-Schmidt condensation of 2-hydroxylacetophenone and benzaldehyde. As shown in Table 2, 22 flavonols were successfully obtained with this method, included 14 5-substituented flavonols and 8 other flavonols for comparison.

To better understand the results in Table 2, it is necessary to clarify the mechanism first. Since 6-, 4-dimethoxyl chalcone (**Ch-2**) gave relatively high yield of flavonol **(Fl-2)**, we choose it as the model reaction for mechanism study (Scheme 2). We conducted the reaction with 2′–OH group protected chalcone under the same conditions to probe if the epoxide was present (Scheme S1). The corresponding epoxide was obtained quantitatively, suggesting that epoxide formation was feasible under the conditions.

Next, we conducted LCMS analysis for the model reaction (Fig. S1 summarises the LCMS monitoring of the reaction from 0 to 48 h). After 30 min of running the reaction, aurone and flavonone were detected based on comparison to known standards. Continuing the reaction to 2 h,a new peak 335 was observed, which could be assigned to the product arising from $-OOH^-$ attack of the epoxide intermediate (Scheme 2, **A**). At 24 h, the peak 335 disappeared. Further ion peaks at 169 and 137 were observed, which were assigned to 2-hydroxyl 5-methoxy-benzoic acid and benzaldehyde (Scheme 2, **B** and **C**), At longer reaction (48 h), $[M+1]^+$ at 165 was detected, which likely results from a retro-aldol reaction of

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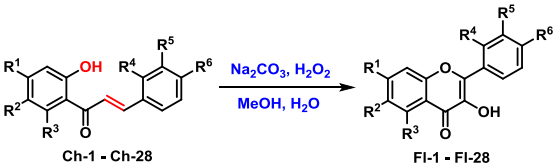
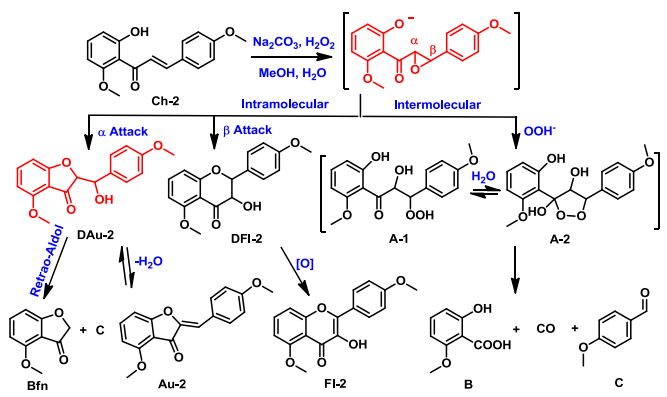
Table 2
Scope of the method.[a]



Products		Yield[b]
	Fl-1: $R_4 = R_5 = R_6 = H$	33%
	Fl-2: $R_4 = R_5 = H$, $R_6 = OCH_3$	74%
	Fl-3: $R_4 = OCH3$, $R_5 = R_6 = H$	40%
	Fl-4: $R_4 = R_5 = H$, $R_6 = CH_3$	45%
	Fl-5: $R_4 = R_5 = H$, $R_6 = F$	25%
	Fl-6: $R_4 = R_5 = H$, $R_6 = Cl$	27%
	Fl-7: $R_4 = H$, $R_5 = R_6 = CH_3$	50%
	Fl-8: $R_4 = H$, $R_5 = CH3$, $R_6 = H$	20%
	Fl-9: $R_4 = CH_3$, $R_5 = R_6 = H$	38%
	Fl-10: $R_4 = H$, $R_5 = R_6 = OCH_3$	47%
	Fl-11: $R_4 = R_5 = R_6 = OCH_3$	n.d.
	Fl-12: $R_4 = R_5 = H$, $R_6 = N(CH_3)_2$	40%
	Fl-13: $R_4 = R_5 = H$, $R_6 = NO_2$	n.d.
	Fl-14: $R_4 = R_5 = H$, $R_6 = OH$	40%
	Fl-15: $R_1 = OCH_3$, Ar = naphthalen-1-yl	n.d.
	Fl-16: $R_1 = OCH_3$, Ar = furan-2-yl	62%
	Fl-17: $R_1 = OCH_3$, Ar = thiophen-2-yl	68%
	Fl-18: $R_1 = F$, Ar = *p*-methoxyphenyl	76%
	Fl-19: $R_4 = OCH_3$, $R_5 = R_6 = H$	trace
	Fl-20: $R_4 = R_5 = H$, $R_6 = OCH_3$	trace
	Fl-21: $R_4 = R_5 = H$, $R_6 = F$	n.d.
	Fl-22: $R_2 = R_3 = R_4 = R_5 = R_6 = H$	84%
	Fl-23: $R_2 = R_3 = R_4 = R_5 = H$, $R_6 = Cl$	80%
	Fl-24: $R_2 = R_3 = R_4 = R_5 = H$, $R_6 = OCH_3$	64%
	Fl-25: $R_2 = R_3 = R_4 = R_5 = H$, $R_6 = N(CH_3)_2$	81%
	Fl-26: $R_2 = R_4 = R_5 = R_6 = H$,$R_3 = OCH_3$	61%
	Fl-27: $R_3 = R_4 = R_5 = R_6 = H$,$R_2 = Br$	71%
	Fl-28: $R_2 = R_4 = R_5 = H$,$R_3 = R_6 = OCH_3$	86%

[a] The reactions conducted in MeOH/H_2O (2:1) using 1 eq. of **Ch-2**, 5 eq. of Na_2CO_3 and 2.5 eq. of H_2O_2 at 0 °C for 30 min and then at 27 °C for 24 h.
[b] HPLC yields. n.d. = not detectable.

aurone (Scheme 2, **Bfn** and **C**). Increasing reaction times generated larger quantities of 2-hydroxyl 5-methoxy-benzoic acid and benzaldehyde, as determined by the These are the main by-products and surprisingly, 4-methoxybenzoic was not detected. These by-products can be explained from reaction of the chalcone epoxide, suggesting it is a key intermediate It is know that retro-aldol reaction of chalcone under basic hydrogen peroxide conditions



Scheme 2. Mechanism implication.

produces acetophenone and benzaldehyde.[15] Oxidation of flavonol generates 4-methoxybenzoic acid. The lack of 2-hydroxyl-4-methoxybenzophenone and 4-methoxybenzoic acid in the reaction system indicates neither retro-aldol of chalcone nor flavonol oxidation happened under the reaction conditions, although the latter is possible under a stronger oxidative condition.[16] Based on the LCMS analysis, we conclude that epoxide intermediate was involved in the AFO reaction (Scheme 2). Though directly detection of the epoxide was not feasible under acidic conditions, it is obvious that aurone, dihydroflavonol and the compound with a molecular ion peak at 335 appeared spontaneously at 2 h, which results from intramolecular attack of α- (aurone hydrate was fast converted into aurone under acidic condition) and β- carbon by 2′—OH, and competitive intermolecular attack of β-carbon by $-OOH^-$ of the epoxide, respectively. Once the $-OOH^-$-added intermediate was formed ($[M+1]^+ = 335$), it quickly decayed into **B** (169) and **C** (137). It should be mentioned that the yield of flavonol had reached the highest by 24 h. Further extending reaction time resulted in increased hyperoxidized by-product **B**, **C** and retro-aldol by-product **Bfn** from aurone.

To further probe the reaction mechanisms and obtain further information on the involvement of epoxide, we have conducted in situ ^1H NMR (Fig. 1).

Before addition of H_2O_2, chalcone (H_a, H_b) and flavonone (H_c, H_d and H_e) exist as an equilibrium in the presence of Na_2CO_3 in D_2O

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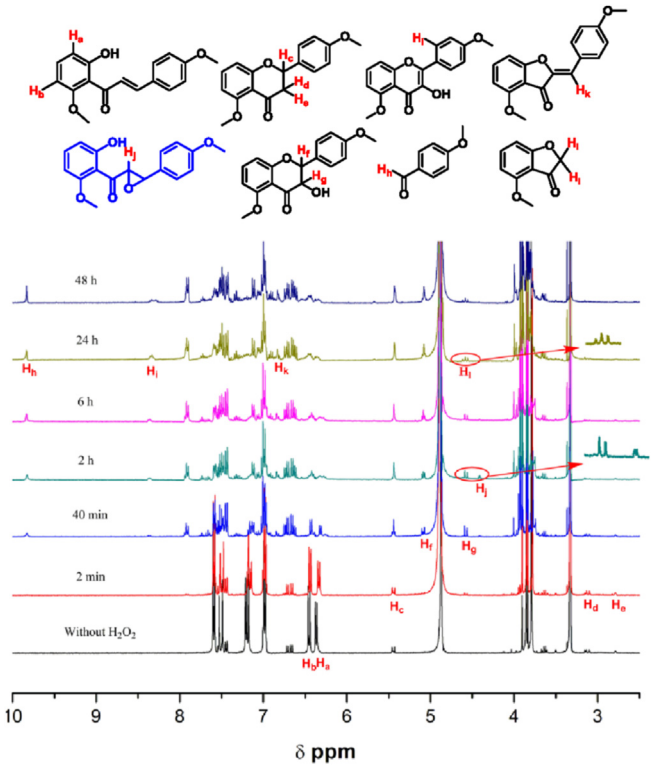

Fig. 1. In situ ^{1}H NMR study of the model reaction.

and CD_3OD. The in situ ^{1}H NMR spectroscopic analysis of the reaction of **Ch-2** suggests the spontaneous formation of aurone (**Au-2**, H_k) and dihydroxyflavonol (**DFl-2**, H_f, H_g) and H_j (speculated of chalcone epoxide) at 40 min, which was in accordance with the observation from LCMS. By comparison with the ^{1}H NMR of chalcone epoxide without 2'-hydroxyl (Fig. S3), H_j might be assigned to the α-H of the epoxide. Since the life time of the 2' -hydroxyl epoxide is very short under basic conditions,[17] and attempts to isolate it from the reaction were not successful. We also observed that dihydroxyflavonol (**DFl-2**, H_g) gradually converted into Flavonol (**Fl-2,** H_i) from 40 min to 24 h of the reaction. Fig. 1 shows that Bfn (H_l) appears and slightly increases at longer reaction time. Once the flavonol formed, it did not decrease, indicate that flavonol did not decompose or change into aurone under the reaction conditions. The concentration of benzaldehyde (**C**, H_h) appears to increase with the reaction time extending, probably resulted from the competitive intermolecular attack of $-OOH^-$ to the epoxide and the retro-aldol product of **DAu-2**, as demonstrated in Scheme 2.

Given the evidence the epoxide path for the mechanism, the inefficiency of the AFO reaction for the synthesis of 5-substituted flavonols. Despite of the intrinsic factors as literature suggested, it appears that the β-cyclization of the epoxide becomes disfavored due to the stereo-electronical effects of the 6'-substituent to the C=O group which would force the later out-of-plane with the aromatic ring it attached. Second that there is less delocalization from the 2′−O^- group onto the C=O, due to steric inhibition of resonance. As a result, not only the 2′−O− more nucleophilic but also the α-carbon to which it cyclizes is more electrophilic because of the increased electron-withdrawing capacity of the carbonyl group when it is out-of-plan.[18] Attempts to further optimize the reaction, should take into account the fact that the epoxide intermediate is easily decomposed under strong basic conditions. By using sodium carbonate instead of sodium hydroxide, the life time of the epoxide intermediate is relatively longer, and the 2′−OH is less ionizable in the lower pH environment, which should fever the intramolecular β-cyclization.

The stereo-electronic influences on the yields of flavanols could be rationalized based on the epoxide path. Electron-donating group ($-OCH_3$, $-CH_3$ and $-N(CH_3)_2$) at 4-position of B-ring seemed to be favourable for flavonol formation with the yields of 74%, 45% and 40%, respectively (Table 2, **Fl-2**, **Fl-4** and **Fl-12**). On the other hand, electron-withdrawing groups (F and Cl) at this position lowered the yields of flavonols (Table 2, **Fl-5** and **Fl-6**), and aurones were the major products. Thus, our results could be explained as the electron donating groups on B-ring favoring the 2′−*O*-attack to the *β*-position of the epoxide. Substituents at 3-position of chalcones, were unfavourable to the formation of flavonols (Table 2, **Fl-7**, **Fl-8** and **Fl-10**). Furan-2-yl and thiophene-2-yl, rather than phenyl group at *β*-C of chalcone, were well-tolerated to the reaction conditions, with yields of 62% and 68%, respectively (**Fl-16** and **Fl-17**), while naphthyl was unfavored (**Fl-15**), probably due to the steric influence of the bulk naphthyl group. Fluorine at 6'-position of chalcone was of similar effect as methoxyl group (**Fl-2** and **Fl-21**), indicated that the electronic feature of the substituents at 6'-position of chalcone had little influence to the selectivity of flavonols. On the other hand, the steric interaction of 6'-substituent with chalcone C=O group was of greater significance. Trace or no flavonols were detected in the cases of 4′, 6'- dimethoxyl substituted chalcones as substrates (**Fl-18**, **Fl-19** and **Fl-20**). These were due to the electron donating effects of double methoxyl groups on these chalcones, causing the 2′−OH less deprotonizable and uncompleted reactions.

3. Conclusions

A convenient method for the synthesis of 5-substituted flavonols from corresponding chalcones was established. The combination of sodium carbonate and hydrogen peroxide were favourable for the formation of flavonols other than aurones. Under this condition, a series of flavonols, including 14 5-substituented flavonols were successfully obtained. More importantly, mechanistic studies carried out by by LCMS and in situ 1H NMR analysis provided experimental evidences of the involvement of epoxide. Further study on factors governing the selectivity of flavonol is undergoing in our laboratory.

4. Experimental section

4.1. General experimental details

All commercially available chemicals and reagents were used without any further purification, unless otherwise indicated Melting Points were determined by an X-6 apparatus without correction. ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were recorded at 100 or 150 MHz. The spectra were recorded in $CDCl_3$, DMSO-d_6, CD_3OD or cetone-d_6 as the solvent. Multiplicities were indicated as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), etc. Coupling constants (J) were given in hertz. Chemical shifts (δ) were reported in parts per million relative to TMS as an internal standard. The peaks around δ 7.26 (^{1}H NMR) and 77.16 (^{13}C NMR) correspond to $CDCl_3$. The peaks around δ 2.50 (^{1}H NMR) and 39.52 (^{13}C NMR) correspond to DMSO-d_6. The peaks around δ 3.31 (^{1}H NMR) and 49.00 (^{13}C NMR) correspond to CD_3OD. The peaks around δ 2.05 (^{1}H NMR), 29.84 (^{13}C NMR) and 206.26 (^{13}C NMR) correspond to acetone-d_6. The ESI-HRMS was carried out on a Bruker Bio TOF IIIQ (quadrupole time of flight) mass spectrometer. Progress of the reactions was monitored by thin-layer chromatography (TLC). Silica gel (200−300 mesh size) was used for column chromatography.

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4.2. Synthesis of flavonols (**Fl-1** − **Fl-28**)

To a solution of chalcone (1 mmol) in MeOH (40 mL) was added Na_2CO_3 (5 mmol) and H_2O (20 mL), the reaction mixture was stirred at 0 °C for 30 min. Then 30% H_2O_2 (2.5 mmol) was drop wisely added in the mixture and stirred for 30 min, followed by slowly increasing the temperature to 27 °C. The stirring was continued for 24 h. The progress of the reaction was monitored using TLC (PE/EA = 3/1). After completion of the reaction, the mixture was acidified cautiously with 1 M HCl (aq) until pH = 5, then diluted with water. The product was extracted with EtOAc. The organic layer was washed with water (3 × 10 mL) and dried with anhydrous Na_2SO_4. After removing the solvent, the crude residue was purified by column chromatography with petroleum ether-ethyl acetate (3:1, v/v) to afford flavonol as pure product.

4.2.1. 3-Hydroxy-5-methoxy-2-phenyl-4H-chromen-4-one (**Fl-1**)

Yellow solid; yield: 33%; mp: 169–171 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, Acetone-d_6) δ 8.33–8.27 (m, 2H), 8.11 (s, 1H), 7.71 (t, J = 8.4 Hz, 1H), 7.59 (t, J = 7.5 Hz, 2H), 7.51 (t, J = 7.3 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 3.98 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d_6) δ 172.06, 159.72, 157.31, 141.57, 138.87, 134.17, 131.40, 129.62, 128.52, 127.27, 111.47, 110.04, 105.47, 55.69. HR-ESIMS: 291.0619; $[M+Na]^+$ (calc. for $C_{16}H_{12}NaO_4$, 291.0628).

4.2.2. 3-Hydroxy-5-methoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (**Fl-2**)

Yellow solid; yield: 74%; mp: 168–170 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.8 Hz, 2H), 7.59 (t, J = 8.3 Hz, 1H), 7.37 (s, 1H), 7.16 (d, J = 8.5 Hz, 1H), 7.06 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.1 Hz, 1H), 4.05 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.68, 160.86, 159.52, 157.17, 142.97, 137.86, 133.68, 129.19, 123.42, 114.06, 111.45, 110.30, 104.91, 56.46, 55.41. HR-ESIMS: 321.0720 $[M+Na]^+$ (calc. for $C_{17}H_{14}NaO_5$, 321.0733).

4.2.3. 3-Hydroxy-5-methoxy-2-(2-methoxyphenyl)-4H-chromen-4-one (**Fl-3**)

Yellow solid; yield: 40%; mp: 191–193 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 7.61–7.51 (m, 2H), 7.50–7.44 (m, 1H), 7.12–7.02 (m, 3H), 6.77 (d, J = 8.0 Hz, 2H), 4.02 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.77, 159.68, 158.00, 157.53, 143.26, 139.12, 133.59, 131.90, 130.98, 120.54, 119.57, 112.04, 111.98, 110.61, 104.79, 56.46, 55.93. HR-ESIMS: 321.0723; $[M+Na]^+$ (calc. for $C_{17}H_{14}NaO_5$, 321.0733).

4.2.4. 3-Hydroxy-5-methoxy-2-(4-methylphenyl)-4H-chromen-4-one (**Fl-4**)

Yellow solid; yield: 45%; mp: 165–167 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.3 Hz, 2H), 7.58 (t, J = 8.4 Hz, 1H), 7.37 (s, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.5 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 4.03 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.83, 159.59, 157.30, 142.92, 140.28, 138.37, 133.78, 129.32, 128.16, 127.41, 111.49, 110.35, 104.93, 56.45, 21.51. HR-ESIMS: 305.0773; $[M+Na]^+$ (calc. for $C_{17}H_{14}NaO_4$, 305.0784).

4.2.5. 2-(4-Fluorophenyl)-3-hydroxy-5-methoxy-4H-chromen-4-one (**Fl-5**)

Yellow solid; yield: 25%; mp: 199–201 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, J = 8.8, 5.4 Hz, 2H), 7.62 (t, J = 8.4 Hz, 1H), 7.41 (s, 1H), 7.24 (t, J = 8.7 Hz, 2H), 7.18 (d, J = 8.5 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 4.06 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.84, 164.30, 162.63, 159.66, 157.28, 141.74, 138.36, 134.03, 129.64, 127.17, 115.82, 115.74, 111.44, 110.26,105.10, 56.49. HR-ESIMS: 287.0714; $[M+H]^+$ (calc. for $C_{16}H_{12}FO_4$, 287.0714).

4.2.6. 2-(4-Chlorophenyl)-3-hydroxy-5-methoxy-4H-chromen-4-one (**Fl-6**)

Yellow solid; yield: 27%; mp: 195–197 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.7 Hz, 2H), 7.63 (t, J = 8.4 Hz, 1H), 7.52 (d, J = 8.7 Hz, 2H), 7.46 (s, 1H), 7.18 (d, J = 8.5 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 4.06 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.82, 159.68, 157.29, 141.44, 138.72, 135.90, 134.15, 129.49, 128.87, 128.72, 111.43, 110.27, 105.13, 56.49. HR-ESIMS: 325.0229; $[M+Na]^+$ (calc. for $C_{16}H_{11}ClNaO_4$, 325.0238).

4.2.7. 2-(3,4-Dimethylphenyl)-3-hydroxy-5-methoxy-4H-chromen-4-one (**Fl-7**)

Yellow solid; yield: 50%; mp: 189–191 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl^3$) δ 8.01 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 8.4 Hz, 1H), 7.36 (s, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 9.2 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 4.03 (s, 3H), 2.37 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.82, 159.59, 157.33, 143.11, 139.09, 138.37, 136.86, 133.72, 129.95, 128.47, 125.10, 111.51, 111.51, 110.39, 104.89, 56.45, 19.99, 19.85. HR-ESIMS: 319.0929; $[M+Na]^+$ (calc. for $C_{18}H_{16}NaO_4$, 319.0941).

4.2.8. 3-Hydroxy-5-methoxy-2-(3-methylphenyl)-4H-chromen-4-one (**Fl-8**)

White solid; yield: 20%; mp: 142–144 °C (CH_3OH–H_2O);^1H NMR (400 MHz, Acetone-d_6) δ 8.10 (d, J = 9.3 Hz, 2H), 7.71 (t, J = 8.4 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 3.98 (s, 3H), 2.46 (s, 3H).·^{13}C NMR (100 MHz, Acetone-d_6) δ 172.03, 159.71, 157.31, 141.76, 138.84, 138.05, 134.12, 131.35, 130.36, 128.43, 127.66, 124.58, 115.95, 111.45, 110.01, 105.44, 55.69. HR-ESIMS: 305.0772; $[M+Na]^+$ (calc. for $C_{17}H_{14}NaO_4$, 305.0784).

4.2.9. 3-Hydroxy-5-methoxy-2-(2-methylphenyl)-4H-chromen-4-one (**Fl-9**)

White solid; yield: 38%; mp: 125–127 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, J = 15.9, 7.5 Hz, 2H), 7.42 (dd, J = 10.5, 4.3 Hz, 1H), 7.40–7.32 (m, 2H), 7.13–7.07 (m, 1H), 6.83 (d, J = 7.5 Hz, 2H), 4.07 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.75, 159.73, 157.82, 145.07, 138.63, 137.66, 133.88, 130.85, 130.29, 129.84, 129.77, 125.74, 111.92, 110.44, 105.01, 56.52, 20.14. HR-ESIMS: 305.0769; $[M+Na]^+$ (calc. for $C_{17}H_{14}NaO_4$, 305.0784).

4.2.10. 2-(3,4-Dimethoxyphenyl)-3-hydroxy-5-methoxy-4H-chromen-4-one (**Fl-10**)

Yellow solid; yield: 47%; mp: 175–177 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92–7.80 (m, 2H), 7.60 (t, J = 8.4 Hz, 1H), 7.43 (s, 1H), 7.18 (d, J = 8.5 Hz, 1H), 7.04 (d, J = 9.1 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 4.06 (s, 3H), 4.01 (s, 3H), 3.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.69, 159.54, 157.16, 150.50, 148.83, 142.81, 137.99, 133.77, 123.62, 121.03, 110.92, 110.39, 104.96, 77.36, 77.04, 76.73, 56.48, 56.00. HR-ESIMS: 351.0827; $[M+Na]^+$ (calc. for $C_{18}H_{16}NaO_6$, 351.0839).

4.2.11. 2-(4-(Dimethylamino)phenyl)-3-hydroxy-5-methoxy-4H-chromen-4-one (**Fl-12**)

Yellow solid; yield: 40%; mp: 170–172 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 9.1 Hz, 2H), 7.55 (t, J = 8.4 Hz, 1H), 7.34 (s, 1H), 7.15 (d, J = 8.5 Hz, 1H), 6.80 (dd, J = 15.1, 8.7 Hz, 3H), 4.04 (s, 3H), 3.08 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.21, 159.40, 157.03, 151.19, 144.27, 137.21, 133.16, 128.87, 118.10, 111.56, 110.28, 104.75, 56.42, 40.12. HR-ESIMS: 334.1045; $[M+Na]^+$ (calc. for $C_{18}H_{17}NNaO_4$, 334.1050).

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4.2.12. 3-Hydroxy-5-methoxy-2-(4-hydroxyphenyl)-4H-chromen-4-one ***(Fl-14)***

A yellow needles; yield: 40%; mp: 240–242 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, DMSO) δ 10.08 (s, 1H), 8.95 (s, 1H), 8.07 (d, *J* = 8.9 Hz, 2H), 7.66 (t, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 6.99–6.89 (m, 3H), 3.90 (s, 3H), 3.38 (s, 14H). ^{13}C NMR (100 MHz, DMSO) δ 172.21, 159.49, 159.32, 156.82, 143.38, 138.35, 134.20, 129.57, 122.25, 115.93, 112.10, 110.39, 106.13, 56.65, 40.58, 40.37, 40.17, 39.96, 39.75, 39.54, 39.33. HR-ESIMS: 285.0757; $[M+H]^+$ (calc. for $C_{16}H_{13}O_5$, 285.0760).

4.2.13. 2-(Furan-2-yl)-3-hydroxy-5-methoxy-4H-chromen-4-one ***(Fl-16)***

Yellow solid; yield: 62%; mp: 200–202 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.60 (t, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 3.5 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.67 (dd, *J* = 3.5, 1.7 Hz, 1H), 4.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.01, 159.62, 156.98, 144.53, 144.26, 136.58, 133.93, 114.91, 112.60, 110.46, 105.26, 77.36, 77.04, 76.72, 56.51. HR-ESIMS: 281.0415 $[M+Na]^+$ (calc. for $C_{14}H_{10}NaO_5$, 281.0420).

4.2.14. 3-Hydroxy-5-methoxy-2-(thiophen-2-yl)-4H-chromen-4-one ***(Fl-17)***

Yellow solid; yield: 68%; mp: 204–206 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 3.8 Hz, 1H), 7.60 (dd, *J* = 10.2, 6.7 Hz, 2H), 7.25 (m, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 4.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.11, 159.60, 156.99, 140.30, 136.48, 133.87, 132.77, 129.36, 128.85, 128.06, 111.66, 110.29, 105.21, 56.50. HR-ESIMS: 297.0182 $[M+Na]^+$ (calc. for $C_{14}H_{10}NaO_4S$, 297.0192).

4.2.15. 5-Fluoro-3-hydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one ***(Fl-18)***

Yellow solid; yield: 76%; mp: 198–200 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 15.4, 3.4 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.58 (dd, *J* = 15.4, 1.9 Hz, 1H), 7.41 (td, *J* = 8.3, 6.4 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 1H), 6.66 (ddd, *J* = 12.1, 8.2, 1.0 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.33, 161.23, 159.46, 156.14,144.47, 137.87, 133.33, 129.45, 123.04, 114.36–113.84, 111.46, 110.72, 77.22, 77.00, 76.79, 55.42. HR-ESIMS: 309.0523; $[M+Na]^+$ (calc. for $C_{16}H_{11}FNaO_4$, 309.0534).

4.2.16. 3-Hydroxy -2-phenyl-4H-chromen-4-one ***(Fl-22)***

A brown needles; yield: 84%; mp: 168–170 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.5 Hz, 3H), 7.78–7.71 (m, 1H), 7.66–7.54 (m, 3H), 7.54–7.41 (m, 2H), 7.06 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.51, 155.43, 144.94, 138.49, 133.66, 131.08, 130.21, 128.62, 127.78, 125.48, 124.53, 120.66, 118.30, 77.38, 77.26, 77.06, 76.74. HR-ESIMS: 239.0713; $[M+H]^+$ (calc. for $C_{15}H_{11}O_3$, 239.0703).

4.2.17. 3-Hydroxy -2-(4-clorophenyl)-4H-chromen-4-one ***(Fl-23)***

Yellow solid; yield: 80%; mp: 171–185 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 8.32–8.16 (m, 3H), 7.72 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.56–7.47 (m, 2H), 7.48–7.39 (m, 1H), 7.07 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.43, 155.40, 143.77, 138.50, 136.23, 133.86, 129.56, 129.03, 128.93, 125.54, 124.69, 120.61, 118.27, 77.34, 77.22, 77.02, 76.70. HR-ESIMS: 271.0156 $[M-H]^-$ (calc. for $C_{15}H_8^{35}ClO_3$, 271.0157), 273.0122 $[M-H]^-$ (calc. for $C_{15}H_8^{37}ClO_3$, 273.0127).

4.2.18. 3-Hydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one ***(Fl-24)***

A colourless needles; yield: 64%; mp: 231–232 °C (CH_3O-H–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 9.5, 2.5 Hz, 3H), 7.72 (dd, *J* = 8.6, 7.1, 1.6 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.08 (dd, *J* = 9.5, 2.5 Hz, 2H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.14, 161.11, 155.30, 145.31, 137.64, 133.36, 129.53, 125.42, 124.43, 123.56, 120.73, 118.18, 114.11, 77.33, 77.01, 76.69, 55.42. HR-ESIMS: 267.0647 $[M-H]^-$ (calc. for $C_{16}H_{11}O_4$, 267.0652).

4.2.19. 3-Hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one ***(Fl-25)***

Yellow solid; yield: 81%; mp: 242–244 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 8.33–8.12 (m, 3H), 7.71–7.62 (m, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 6.85 (t, *J* = 25.6 Hz, 3H), 3.07 (s, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.53, 155.12, 151.37, 146.67, 136.96, 132.85, 129.22, 125.25, 124.18, 120.90, 118.20, 118.03, 111.53, 77.34, 77.03, 76.71, 40.09. HR-ESIMS: 282.1137; $[M+H]^+$ (calc. for $C_{17}H_{16}NO_3$, 282.1125).

4.2.20. 3-Hydroxy-7-methoxy-2-phenyl-4H-chromen-4-one ***(Fl-26)***

A yellow needles; yield: 61%; mp: 125–127 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 8.28–8.20 (m, 2H), 8.14 (d, *J* = 8.9 Hz, 1H), 7.49 (ddd, *J* = 11.2, 9.5, 6.1 Hz, 3H), 7.09–6.93 (m, 3H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.83, 164.30, 157.40, 144.17, 138.13, 131.22, 129.90, 128.58, 127.49, 126.78, 114.90, 114.60, 99.86, 77.34, 77.02, 76.70, 55.88. HR-ESIMS: 283.0969; $[M+H]^+$ (calc. for $C_{17}H_{15}O_4$, 283.0965).

4.2.21. 3-Hydroxy-6-bromo-2-phenyl-4H-chromen-4-one ***(Fl-27)***

Brown solid; yield: 71%; mp: 265 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 2.4 Hz, 13H), 8.28–8.19 (m, 28H), 7.77 (dd, *J* = 9.0, 2.4 Hz, 14H), 7.63–7.43 (m, 57H), 7.26 (s, 5H), 7.01 (s, 14H), 1.60 (s, 5H), 1.25 (s, 1H), 0.00 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.29, 154.13, 145.41, 138.62, 136.63, 130.70, 130.50, 128.69, 127.96, 127.81, 122.00, 120.25, 117.89, 77.35, 77.03, 76.72. HR-ESIMS: 338.9622; $[M+Na]^+$ (calc. for $C_{15}H_9BrNaO_3$, 338.9627).

4.2.22. 3-Hydroxy-7-methoxy-2-(4-methoxyphenyl)-4H-chromen-4-one ***(Fl-28)***

Brown solid; yield: 86%; mp: 192–193 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.6 Hz, 2H), 8.14 (d, *J* = 8.8 Hz, 1H), 7.16–6.96 (m, 6H), 3.95 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.58, 164.06, 160.83, 157.16, 144.62, 137.27, 129.21, 126.68, 123.69, 114.67, 114.03, 99.84, 55.85, 55.41. HR-ESIMS: 299.0914; $[M+H]^+$ (calc. for $C_{17}H_{15}O_5$, 299.0903).

4.3. The synthesis of aurones

The aurones were obtained using the general procedure for the synthesis of flavonols.

4.3.1. 4-Methoxy-2-(naphthalen-1-ylmethylene) benzofuran-3(2H)-one ***(Aurone-1)***

Yellow solid; yield: 89%; mp: 184–186 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 6.8 Hz, 1H), 8.33 (d, *J* = 8.4 Hz, 1H), 7.90 (dd, *J* = 7.8, 4.2 Hz, 2H), 7.65 (s, 1H), 7.58 (ddd, *J* = 19.7, 11.0, 5.8 Hz, 4H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 4.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.28, 167.20, 158.69, 147.80, 138.44, 133.74, 132.28, 130.28, 129.96, 128.91, 128.45, 127.00, 126.17, 125.58, 123.56, 111.04, 107.55, 105.26, 104.86, 56.33. HR-ESIMS: 325.0827; $[M+Na]^+$ (calc. for $C_{20}H_{14}NaO_3$, 325.0835).

4.3.2. 4-Methoxy-2-(2-methoxybenzylidene) benzofuran-3(2H)-one ***(Aurone-3)***

White solid; yield: 50%; mp: 199–201 °C (CH_3OH–H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.3 Hz, 1H), 7.58 (t, *J* = 8.2 Hz,

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1H), 7.43 (s, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 6.64 (d, J = 8.3 Hz, 1H), 4.03 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.40, 166.90, 158.70, 158.50, 146.96, 138.13, 131.81, 131.19, 121.44, 120.76, 111.09, 110.71, 106.17, 104.89, 56.27, 55.58. HR-ESIMS: 305.0780; $[M+Na]^+$ (calc. for $C_{17}H_{14}NaO_4$, 305.0784).

4.4. The synthesis of the standard samples

4.4.1. 2′-Hydroxy-4,6′-dimethoxychalcone (**Ch-2**)

The 2-Hydroxy-6-methoxyacetophenone (500 mg, 3.012 mmol) was dissolved in ethanol (30 mL), and sodium hydroxide (482 mg, 12.048 mmol) was added to the stirred solution at 35 °C. After stirring for 30 min, *p*-methoxybezaldehyde (428 μL, 3.150 mmol) was added to the solution. Overnight, the resulting mixture was acidified with dilute hydrochloric acid and water to pH = 7. Then the resulting precipitate was collected and on recrystallization from ethanol gave yellow needles (698 mg, 82%); mp: 116–117 °C (EtOH–H_2O); ^{1}H NMR (400 MHz, CD_3OD) δ 7.71–7.46 (m, 4H), 7.37 (t, J = 8.3 Hz, 1H), 7.08–6.94 (m, 2H), 6.58 (dd, J = 17.5, 8.3 Hz, 2H), 3.93 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 205.30, 195.15, 161.96, 161.76, 160.26, 143.76, 140.97, 134.26, 129.97, 127.67, 125.10, 114.13, 113.05, 109.56, 101.80, 55.07, 54.50. HR-ESIMS: 285.1121 $[M+H]^+$ (calc. for $C_{17}H_{17}O_4$, 285.1120).

4.4.2. 2,3-Dihydro-3-hydroxy-5-methoxy-2-(4-methoxyphenyl)-4H-1-benzopyran-4-one (**DFl-2**)

The 2′-hydroxy-4,6′-dimethoxychalcone (10 mg, 0.035 mmol) was suspended in H_2O (2 mL), then sodium hydroxide (38 mg, 0.670 mmol) and 30% H_2O_2 (18 μL, 0.178 mmol) were added at room temperature. After stirring for 2 h, the suspension was filtered. The residue was washed with H_2O and purified by column chromatography (PE/EA = 6/1). White solid (5 mg, 46%); mp: 144–146 °C (CH_3OH–H_2O); ^{1}H NMR (400 MHz, CD_3OD δ 7.54–7.45 (m, 3H), 7.00 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 8.4 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 5.08 (d, J = 11.9 Hz, 1H), 4.55 (d, J = 11.9 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 193.25, 162.90, 160.67, 160.25, 136.68, 129.12, 128.84, 113.38, 109.51, 103.93, 99.98, 82.99, 73.40, 55.08, 54.36. HR-ESIMS: 323.0890 $[M+Na]^+$ (calc. for $C_{17}H_{16}NaO_5$, 323.0891).

4.4.3. 2-3-Dihydro-5-methoxy-2-(4-methoxyphenyl)-4H-1-benzopyran-4-one (**Flavanone**)

The 2′-hydroxy-4,6′-dimethoxychalcone (50 mg, 0.176 mmol) was dissolved in methanol (3.2 mL) and H_2O (1.6 mL), then sodium carbonate (93 mg, 0.880 mmol) was added to the solution. After stirring at room temperature for 3 h, the mixture was diluted with water (20 mL) and extracted three times with diethyl ether (10 mL). The organic layers were combined and removed in vacuo then purified by column chromatography (PE/EA = 6/1). Pale yellow solid (20 mg, 35%); mp: 115–116 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.56–7.39 (m, 3H), 7.04–6.93 (m, 2H), 6.67 (dd, J = 11.9, 8.4 Hz, 2H), 5.44 (dd, J = 12.9, 2.9 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.13 (dd, J = 16.6, 12.9 Hz, 1H), 2.78 (dd, J = 16.6, 3.0 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 192.19, 163.51, 160.75, 160.02, 136.45, 130.92, 127.48, 113.61, 110.70, 109.81, 103.81, 78.62, 55.01, 54.37, 45.22. HR-ESIMS: 307.0941 $[M+Na]^+$ (calc. for $C_{17}H_{16}NaO_4$, 307.0934).

4.4.4. 4-Methoxy-2-(4-methoxybenzylidene)benzofuran-3(2H)-one (**Aurone-2**)

The 2′-hydroxy-4,6′-dimethoxychalcone (27 mg, 0.096 mmol) was dissolved in pyridine (10 mL), and mercuric acetate (46 mg, 0.143 mmol) was added to the solution, refluxing at 110 °C for 1.5 h. The resulting mixture cooled and was poured into ice water, then acidified with 30% hydrochloric acid to pH = 7. The resulting mixture was extracted three times with dichloromethane (15 mL x 3). The organic layers were combined and dried over Na_2SO_4. After evaporation, the residue was on recrystallization from ethanol gave yellow needles (23 mg, 85%); mp: 170 °C (EtOH–H_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.83 (m, 2H), 7.58 (ddd, J = 8.2, 4.9, 1.6 Hz, 1H), 7.08–6.95 (m, 2H), 6.89 (dd, J = 11.7, 10.4 Hz, 2H), 6.63 (d, J = 8.3 Hz, 1H), 4.03 (d, J = 1.4 Hz, 3H), 3.93–3.84 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.28, 166.83, 160.82, 158.49, 145.87, 138.02, 133.17, 125.22, 114.43, 112.23, 104.93, 104.77, 77.34, 77.02, 76.71, 56.26, 55.38. HR-ESIMS: 305.0784 $[M+Na]^+$ (calc. for $C_{17}H_{14}NaO_4$, 305.0789).

4.4.5. [3-(4-Methoxyphenyl)-2-oxiranyl](2-methoxyphenyl)-methanone (**Epoxide 1**)

The 4,2'- dimethoxychalcone (152 mg, 0.567 mmol) was dissolved in methanol (8 mL) and H_2O (4 mL), sodium carbonate (300 mg, 2.838 mmol) and 30% hydrogen peroxide (149 μL, 1.419 mmol) were added to the solution at room temperature. After stirring for 2 h, the mixture was diluted with water (15 mL). Then the resulting precipitate was collected and on recrystallization from diethyl ether gave white solid (149 mg, 93%); mp: 86–88 °C (Et_2O); 1H NMR (400 MHz, CDCl3) δ 7.82 (dd, J = 7.7, 1.7 Hz, 1H), 7.55–7.49 (m, 1H), 7.34–7.27 (m, 2H), 7.05 (t, J = 7.5 Hz, 1H), 6.97–6.88 (m, 3H), 4.31 (d, J = 1.9 Hz, 1H), 3.96 (d, J = 1.8 Hz, 1H), 3.83 (s, 3H), 3.63 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 191.13, 156.12, 155.63, 130.88, 126.73, 124.48, 123.26, 122.13, 117.08, 110.09, 107.64, 73.44, 73.12, 72.81, 60.50, 55.86, 51.70, 51.41. HR-ESIMS: 307.09477 $[M+Na]^+$ (calc. for $C_{17}H_{16}NaO_4$, 307.09408).

4.4.6. [3-(4-Methoxyphenyl)-2-oxiranyl](2,6-dimethoxyphenyl)-methanone (**Epoxide 2**)

The 4,2′,6'- trimethoxychalcone (168 mg, 0.567 mmol) was dissolved in methanol (20 mL) and H_2O (10 mL), then sodium carbonate (300 mg, 2.838 mmol) and 30% hydrogen peroxide (149 μL, 1.419 mmol) were added to the solution at room temperature. After stirring for 2 h, the mixture was diluted with water (25 mL). Then the resulting precipitate was collected and on recrystallization from diethyl ether gave white solid (160 mg, 90%); mp: 65–68 °C (Et_2O); ^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (t, J = 8.4 Hz, 1H), 7.27 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 6.72 (d, J = 8.4 Hz, 2H), 3.95–3.87 (m, 2H), 3.80 (d, J = 3.4 Hz, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ 198.75, 160.40, 158.28, 132.60, 127.64, 126.89, 116.03, 113.74, 103.97, 63.76, 59.27, 55.18, 54.37. HR-ESIMS: 337.1046 $[M+Na]^+$ (calc. for $C_{18}H_{18}NaO_5$, 337.1039).

4.4.7. 4-Methoxybenzofuran-3(2H)-one (**Bfn**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (t, J = 8.3 Hz, 1H), 6.68 (d, J = 8.3 Hz, 1H), 6.47 (d, J = 8.2 Hz, 1H), 4.60 (s, 2H), 3.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 175.4, 158.4, 139.6, 110.7, 105.6, 103.3, 74.9, 56.3.

4.4.8. 4-Methoxybenzaldehyde (**C**)

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H), 7.01 (d, J = 8.7 Hz, 2H), 7.84 (d, J = 8.8 Hz, 2H), 9.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.54, 114.26, 129.91, 131.94, 164.56, 190.7.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.06.064.

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