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Isoaurones: synthesis and stereochemical assignments of geometrical isomers☆

Somepalli Venkateswarlu, Gopala K. Panchagnula, Mothukuri Bala Guraiah and Gottumukkala V. Subbaraju*

Laila Research Centre, Unit 1, Phase III, Jawahar Autonagar, Vijayawada 520 007, Andhra Pradesh, India

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Abstract—A series of isoaurones have been synthesized for the first time from substituted acetophenones via benzo-2(3*H*)-furanone in three steps. Geometrical isomers of the isoaurones were separated. The differences in the proton and carbon NMR spectra of the *E*- and *Z*-isoaurones afford a useful method for distinguishing between the two isomers. Marginalin, a metabolite of *Dytiscus marginalis* has been synthesized and the spectral data of the synthetic *E*-isomer were in good agreement with those of the natural product. The antioxidant activity of isoaurones was determined by superoxide free radical (NBT) method and isoaurones **12** and **13** displayed excellent antioxidant activity.

1. Introduction

Aurones (**1**), 2-benzylidenebenzofuran-3(2*H*)-ones, and isoaurones (**2**), 3-benzylidenebenzofuran-2(3*H*)-ones, are naturally occurring yellow pigments of plants and are structurally related to flavonoids[1] (Fig. 1). In addition to the pigmentation role, they have been described as phytoalexins used by the plant as defense agents against various infections.[2] A few methods of syntheses were reported in the literature for aurones,[2–4] and *Z*-isomers are thermodynamically more stable and are the only products obtained using acidic or basic reagents. The stereochemistry of aurones was established by proton[5] and carbon[6] NMR spectroscopy and spectroscopies. Naturally occurring isoaurones are growing recently and a few compounds were reported, namely, marginalin,[7] isoaurostatin,[8] 4,6,4′-trihydroxyisoaurone,[9] and pterocarposide, the first isoaurone C-glucoside.[10] Synthetic studies on isoaurones are limited.[11] Even an attempted synthesis of marginalin[12] by Barbier did not give the natural product but gave an isomer of the natural marginalin. Isoaurostatin, a novel topoisomerase I inhibitor, was recently isolated from the culture filtrate of *Thermomonospora alba* strain No. 1520 and assigned *E*-configuration based on HMBC and NOE spectra.[8] We have synthesized both isomers of isoaurostatin,[13] but the spectral data did not match with those of the natural product and its structure was revised as daidzein, a well known isoflavone. Recently, isoaurones were found as potential anticancer agents,[14] but the authors did not assign the configuration. The stereochemistry of isoaurones has not been studied in detail except by converting *E*/*Z*-phenyl cinnamic acids into corresponding isoaurones.[15] In view of the importance of stereochemistry for the biological activity and lack of reports in the literature on the stereochemical assignments of isoaurones by NMR spectroscopy, in this paper we have presented the details of (a) isoaurones synthesis, isolation of stereoisomers, and spectroscopic methods to establish the stereochemistry at the double bond and (b) the synthesis of marginalin, a metabolite of *Dytiscus marginalis* (Coleoptera) and the establishment of its stereochemistry as *E*.

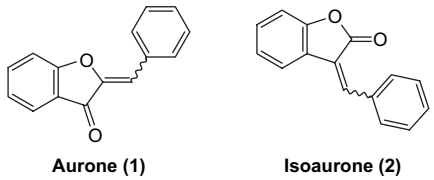

Figure 1. General structures of aurone and isoaurone.

2. Results and discussion

2.1. Synthesis

The general route for the synthesis of isoaurones involves the acid or base catalyzed condensation of substituted 2(3*H*)-benzofuranone with aromatic aldehydes. The desired substituted benzofuranones were synthesized as follows.

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* Corresponding author. Tel.: +91 866 2541303; fax: +91 866 2546216; e-mail: subbarajugottumukkala@hotmail.com

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Willgerodt–Kindler reaction of 2-hydroxy-5-methoxyacetophenone (**3a**) with sulfur and morpholine under phase transfer catalytic conditions[16] gave phenylacetic acid derivative **4a** in 64% yield. Lactonisation of **4a** in the presence of phosphorus oxychloride[17] yielded 5-methoxybenzo-2(3*H*)-furanone (**5a**) in 85% yield. Demethylation of **5a** using pyridine hydrochloride[18] furnished 5-hydroxybenzo-2(3*H*)-furanone (**5c**) in 66% yield (Scheme 1). The 5-methyl benzofuranone (**5b**) was prepared in a similar fashion. Condensation of **5a**, **b** or **c** with substituted benzaldehydes using KOH as a base gave isoaurones (**6–13**). In all examples, two isomers (*E* and *Z*) were formed, which could be separated by column chromatography, and are well characterized by their spectral data (IR, NMR, and Mass). But the ^{1}H NMR spectra of isoaurones **12** and **13** showed them to be a mixture of two isomers as also confirmed by HPLC. Attempts to separate these were not successful even by preparative HPLC. It is known that in aurones the *Z*-isomer is thermodynamically more stable but in isoaurones more of *E*-isomer is formed in our own studies as well in that of others.[19] Perhaps the interactions of carbonyl and the pendant aryl ring are minimum in the case of *E*-isomer.

The carbonyl absorptions in IR spectra of *E*- and *Z*-isoaurones are presented in Table 1. The data revealed that within the particular example, the difference is quite large to distinguish each other, but the data are not suitable for assigning the configuration.

The proton NMR data of *E*- and *Z*-isoaurones are presented in Table 2. As a rule in α,β-unsaturated carbonyl compounds, the anisotropic, diamagnetic deshielding of the carbonyl group causes the olefinic proton cis to the carbonyl to give an absorption at a lower field (ca. 1 ppm) than in the trans arrangement, so that the assignment of configuration can be made on the basis of the chemical shift of the olefinic proton.[20,21] The present study also reveals that the olefinic proton (H-10) in *E*-isomers gave a singlet as expected at lower field than the corresponding proton in *Z*-isomers. In all examples, the H-4 proton in *E*-isomer appeared at a lower field (ca. 0.04–0.34 ppm) than the corresponding proton in *Z*-isomer and the difference is useful to assign the configuration. Most importantly, in all *Z*-isomers, the protons (H-2′ and H-6′) of pendant aryl units appeared as a doublet at much lower field (ca. 0.49–0.77 ppm) than the corresponding protons in *E*-isomers and this chemical shift difference is large enough to assign the configuration.

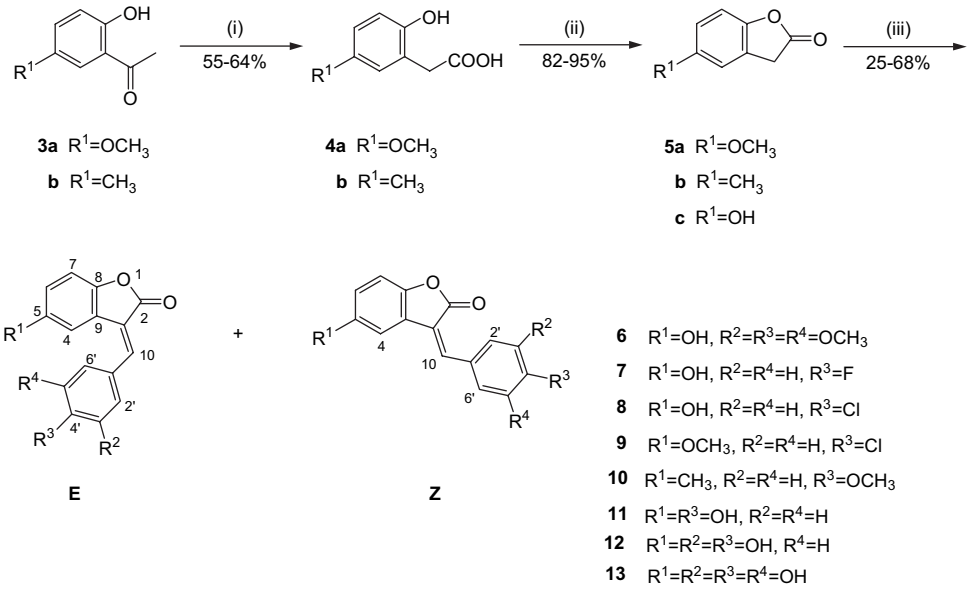
Table 1. IR data of *E*- and *Z*-isoaurones

Compd no.	C=O (λ_{max}, cm^{-1})	
	E	*Z*
6	1778	1721
7	1740	1762
8	1740	1760
9	1780	1756
10	1778	1754

Table 2. ^{1}H NMR data of *E*- and *Z*-isoaurones

Compd no.	*E*			*Z*		
	H-4	H-10	H-2′,6′	H-4	H-10	H-2′,6′
6	7.36	7.79	6.91	7.02	7.45	7.68
7	7.16	7.81	7.67	7.01	7.50	8.25
8	7.19	7.72	7.64	7.02	7.49	8.13
9	7.19	7.77	7.62	7.00	7.46	8.12
10	6.95	7.72	7.67	6.91	7.48	8.24

The carbon NMR data of *E*- and *Z*-isoaurones (Table 3) revealed that the chemical shift differences of olefinic carbon (C-10) are very little and are not useful to distinguish between the two isomers. In all *E*-isomers, the carbonyl absorption (~169 ppm) is at a lower field (ca. 3 ppm) than the corresponding carbonyl in *Z*-isomers (~166 ppm) and this difference could be used to assign the configuration at the double bond in isoaurones. The other carbons useful in



Scheme 1. Reagents and conditions: (i) S, morpholine, *p*-TSA, 20% NaOH, PTC, reflux, 16 h, 55–64%; (ii) $POCl_3$, DCE, rt, 15 h, 82–85%; (iii) substituted benzaldehyde, KOH, EtOH, rt, 10 h, 25–68%.

Table 3. ^{13}C NMR data of *E*- and *Z*-isoaurones

Compd no.	*E*		*Z*	
	C-2	C-2′,6′	C-2	C-2′,6′
6	169.3	106.5	166.5	109.6
7	169.4	131.5	166.5	134.3
8	169.2	130.7	166.4	133.2
9	169.0	130.6	166.2	133.2
10	169.7	131.6	166.7	134.4

this aspect are C-2′ and C-6′ carbons of the pendant aryl unit. In all examples, the C-2′ and C-6′ carbons of *Z*-isomers appeared at a lower field (ca. 2.3–3.1 ppm) than the corresponding carbons in *E*-isomers.

The stereochemistry of the double bond at C-3 and C-10 of isoaurones was confirmed further by the double irradiation experiments. Irradiation of H-4 (7.19, 1H, d, J=2.4 Hz) in compound **8*E*** showed positive NOE on H-2′,6′ (7.64, 2H, d, J=8.2 Hz). Similarly, irradiation of H-2′,6′ resulted in positive NOE on H-4. Based on the above, H-4 and the aryl ring are oriented spatially close to each other and confirm '*E*' stereochemistry for the double bond between C-3 and C-10.

Similarly, irradiation of H-4 (7.02, 1H, br s) in compound **8*Z*** showed positive NOE on H-10 (7.49, 1H, s). Further irradiation of the signal corresponding to H-2′,6′ (8.13, 2H, d, J=8.1 Hz) did not show any effect on H-4. Thus, H-4 and H-10 are spatially close and confirm '*Z*' stereochemistry for the double bond at C-3 and C-10.

Marginalin (**11**) was synthesized through base catalyzed condensation of 5-hydroxybenzo-2(3*H*)-furanone (**5c**) with 4-hydroxybenzaldehyde in 60% yield (Scheme 1). The ^{1}H NMR spectrum of **11** showed that it is a mixture of two isomers and was confirmed by HPLC (*E*/*Z*–70:30). The condensation reaction was tried with other reagents such as triethylamine, acetic anhydride, *p*-TSA, and neutral alumina. But in all cases, we isolated a mixture of *E*/*Z*-isomers. The *E*-isomer was obtained in 96% purity by repeated crystallizations, but we could isolate the *Z*-isomer in only 75% purity, however, the spectral data could be interpreted well. The configuration of both the isomers has been assigned based on the foregoing analogy, i.e. H-2′,6′ protons in *Z*-isomer appeared as doublet at δ 8.27, whereas the same protons in *E*-isomer appeared at δ 7.70. The ^{1}H NMR data of synthetic *E*-isomer **11** agree well with those of natural **11** and confirmed the natural product stereochemistry as *E* (see Table 4). Interestingly, the data on synthetic marginalin reported earlier[12] did not match either with *E*-isomer or *Z*-isomer and perhaps required further scrutiny.

2.2. Antioxidant activity

We have determined the antioxidant activity of isoaurones by nitro blue tetrazolium (NBT)[22,23] free radical scavenging method. The IC_{50} values of the active compounds are presented in Table 5. From the data, isoaurones **12** and **13** having catechol and pyrogallol moieties showed good activity and were several fold potent in comparison with the commercially available antioxidants like vitamin C and BHA.

Table 5. Antioxidant activity of isoaurones

Compd	NBT superoxide scavenging activity (IC_{50} in μM)
Marginalin (**11**)	59.0
12	40.2
13	24.7
Vitamin C	852
BHA	966

BHA: butylated hydroxyanisole. The lower the IC_{50} values, the higher is the antioxidant activity.

3. Conclusions

In summary, we have synthesized a series of isoaurones for the first time from substituted acetophenones via benzo-2(3*H*)-furanone in three steps and their geometrical isomers were separated. The configuration at the double bond could be assigned on the basis of proton and carbon NMR spectral data. The H-2′,6′ protons of pendant aryl unit in *Z*-isomers appeared as a doublet at much lower field (ca. 0.49–0.77 ppm) than the corresponding protons in *E*-isomers. Marginalin (**11**), isolated from *D. marginalis*, has been synthesized and its stereochemistry has been confirmed as *E*. The isoaurones **12** and **13** were potent antioxidants as confirmed by superoxide (NBT) free radical scavenging method.

4. Experimental

4.1. General

Melting points were recorded on a Mel-Temp melting point apparatus in open capillaries and are uncorrected. IR spectra were recorded on a Perkin–Elmer BX1 FTIR Spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Jeol JNM λ-300 spectrometer using TMS as internal reference and the values for chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) in hertz (Hz). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) was determined using DEPT-135, and are given in parentheses. Mass spectra were recorded on Agilent 1100 LC/MSD and elemental

Table 4. ^{1}H NMR data of marginalin (DMSO-d_6)

Position	Synthetic **11*E***	Synthetic **11*Z***	*Z*-Marginalin reported (Ref. 12)	Natural marginalin
4	7.31 (d, 2.4)	7.16 (d, 2.4)	6.56 (d, 3.0)	7.30 (d, 3.0)
6	6.79 (dd, 2.4, 8.6)	6.73 (dd, 2.4, 8.6)	5.80 (dd, 3.0, 8.0)	6.79 (dd, 3.0, 8.0)
7	7.09 (d, 8.6)	6.99 (d, 8.6)	6.16 (d, 8.0)	7.07 (d, 8.0)
10	7.72 (s)	7.86 (s)	6.72 (s)	7.72 (s)
2′,6′	7.70 (d, 8.6)	8.27 (d, 8.8)	7.13 (d, 8.0)	7.68 (d, 8.0)
3′,5′	6.96 (d, 8.6)	6.90 (d, 8.8)	5.90 (d, 8.0)	6.96 (d, 8.0)

analysis on a Vario El Elementar instrument. HPLC was recorded by a Shimadzu SCL-10A instrument under the following conditions: column, Phenomenex C18, 250 mm× 4.6 mm; flow rate, 1 mL/min; detection at 384 nm; mobile phase, 0.1% phosphoric acid/acetonitrile (65:35, v/v); retention time for **11*E***, 19.62 and for **11*Z***, 17.92 min. Acme silica gel G and silica gel (100–200 mesh) were used for analytical TLC and column chromatography, respectively. For antioxidant activity procedure see Ref. 23.

4.2. Phenylacetic acid derivative 4. General procedure

A mixture of **3** (50 mmol), sulfur (3.2 g, 100 mmol), morpholine (15 mL, 150 mmol), and *p*-toluenesulfonic acid (0.3 g, 1.75 mmol) was refluxed under constant stirring at 120–130 °C for 8 h. After completion of the reaction, the mixture was allowed to cool and 20% aq NaOH (70 mL) and tetrabutylammonium bromide (216 mg, 1.25 mmol) were added and hydrolysis was continued for further 8 h at 100 °C. The cooled reaction mixture was filtered and the filtrate was acidified with HCl to pH 2. The solution was extracted with EtOAc (3×150 mL) and the combined organic layer was washed with water (100 mL), brine (100 mL), and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over silica gel column using hexane–EtOAc mixtures as eluents to give **4**.

4.2.1. 2-(2-Hydroxy-5-methoxyphenyl)acetic acid (4a). Colorless powder (5.9 g, 64%), mp 128–130 °C (lit.[24] mp 131–133 °C); IR (neat): 3380, 1720, 1204, 1159, 1025, 819 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.67 (2H, s, Ar–CH_2–), 3.75 (3H, s, Ar–OCH_3), 6.70–6.76 (2H, m, Ar–H), 6.84 (1H, d, J=8.6 Hz, Ar–H); MS (ESI, negative scan): m/z 181 $(M-H)^-$.

4.2.2. 2-(2-Hydroxy-5-methylphenyl)acetic acid (4b). Colorless powder (4.5 g, 55%), mp 118–120 °C (lit.[25] mp 123.5 °C); IR (neat): 3458, 1699, 1622, 1290, 1219, 1157, 1109, 962 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.28 (3H, s, Ar–CH_3), 3.65 (2H, s, Ar–CH_2–), 6.71–6.73 (2H, m, Ar–H), 7.00 (1H, d, J=8.0 Hz, Ar–H); MS (ESI, negative scan): m/z 165 $(M-H)^-$.

4.3. 3-Hydrobenzo[*b*]furan-2-one derivative 5. General procedure

A mixture of **4** (3 g) and phosphorus oxychloride (15 mL) in dichloroethane (90 mL) was stirred at rt for 16 h. The reaction mixture was diluted with water (50 mL) and extracted with chloroform (3×30 mL) and the combined chloroform layer was washed with water (20 mL), sodium bicarbonate (20 mL), and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over silica gel column using hexane–EtOAc mixtures as eluents to give **5**.

4.3.1. 5-Methoxy-3-hydrobenzo[*b*]furan-2-one (5a). Light yellow powder (2.3 g, 85%), mp 98–100 °C (lit.[24] mp 95–98 °C); IR (neat): 2965, 1801, 1605, 1283, 1253, 1222, 1149, 1069, 1025, 921, 858, 814 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.72 (2H, s, H-3), 3.79 (3H, s, Ar–OCH_3), 6.81–6.85 (2H, m, Ar–H), 7.01 (1H, d, J=8.6 Hz, Ar–H); MS (ESI, positive scan): m/z 187 $(M+Na)^+$.

4.3.2. 5-Methyl-3-hydrobenzo[*b*]furan-2-one (5b). Colorless powder (2.2 g, 82%), mp 66–68 °C (lit.[26] mp 68.5–71.5 °C); IR (neat): 3399, 2920, 1809, 1606, 1156, 1083, 1027 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.38 (3H, s, Ar–CH_3), 3.69 (2H, s, H-3), 6.93–6.95 (2H, m, Ar–H), 7.15 (1H, d, J=7.9 Hz, Ar–H); MS (ESI, negative scan): m/z 147 $(M-H)^-$.

4.4. 5-Hydroxy-3-hydrobenzo[*b*]furan-2-one (5c)

A mixture of **5a** (1 g) and pyridine hydrochloride (10 g) was stirred in N_2 atmosphere at 180–190 °C for 3 h. The cooled reaction mixture was diluted with ice cold water (50 mL), acidified with dil HCl (10%, 20 mL), and extracted with EtOAc (3×50 mL). The combined EtOAc layer was washed with brine (25 mL) and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over silica gel column using chloroform–methanol mixtures as eluents to give **5c** as a light yellow powder (600 mg, 66%), mp 184–186 °C (lit.[27] mp 190 °C); IR (neat): 3322, 2923, 1761, 1602, 1242, 1149, 1074, 949, 890 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.84 (2H, s, H-3), 6.65 (1H, dd, J=8.6, 1.6 Hz, H-6), 6.75 (1H, d, J=1.6 Hz, H-4), 6.95 (2H, d, J=8.6 Hz, H-7), 9.28 (1H, s, Ar–OH); MS (ESI, negative scan): m/z 149 $(M-H)^-$.

4.5. 3-Benzylidenebenzofuran-2(3*H*)-ones (6–13). General procedure

To a solution of substituted 3-hydrobenzo[*b*]furan-2-one (1.5 mmol) in ethanol (15 mL) was added substituted benzaldehyde (3.0 mmol) and the pH was brought to 8 with few drops of ethanolic KOH solution. The mixture was stirred at rt for 1 h and again the pH was made 8 with few drops of KOH solution and the mixture was stirred at rt for 14 h. The reaction mixture was acidified with dilute aqueous HCl (10%, 20 mL) and extracted with EtOAc (3×50 mL). The combined EtOAc layer was washed with water (20 mL), brine (20 mL), and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over silica gel column using hexane–EtOAc mixtures as eluents to give isoaurones.

4.5.1. 3-[(3,4,5-Trimethoxyphenyl)methylene]-5-hydroxybenzo[*b*]furan-2-one (6*E*). Yellow powder (187 mg, 38%), mp 188–190 °C; IR (KBr): 3479, 1778, 1641, 1242, 1125, 1102, 999, 972 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.90 (6H, s, Ar–OCH_3), 3.95 (3H, s, Ar–OCH_3), 4.90 (1H, br s, Ar–OH), 6.81 (1H, dd, J=8.6, 2.5 Hz, H-6), 6.91 (2H, s, H-2′,6′), 7.02 (1H, d, J=8.6 Hz, H-7), 7.36 (1H, d, J=2.5 Hz, H-4), 7.79 (1H, s, H-10); ^{13}C NMR ($CDCl_3$): δ 169.3 (C-2), 153.5 (C-5), 152.9 (C-3′,5′), 147.3 (C-4′), 140.1 (C-10), 139.4 (C-8), 128.9 (C-1′), 121.9 (C-3), 121.8 (C-9), 117.6 (C-4), 111.2 (C-6), 109.2 (C-7), 106.5 (C-2′,6′), 60.6 (Ar–OCH_3), 55.9 (Ar–OCH_3); MS (ESI, positive scan): m/z 329 $(M+H)^+$. Analysis found: C, 65.79; H, 4.96%. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91%.

4.5.2. 3-[(3,4,5-Trimethoxyphenyl)methylene]-5-hydroxybenzo[*b*]furan-2-one (6*Z*). Yellow powder (74 mg, 15%), mp 189–191 °C; IR (KBr): 3340, 1721, 1607, 1258, 1125, 1082, 1004 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.96 (3H, s, Ar–OCH_3), 3.97 (6H, s, Ar–OCH_3), 4.79 (1H, br s, Ar–OH),

6.78 (1H, dd, J=8.6, 2.5 Hz, H-6), 6.98 (1H, d, J=8.6 Hz, H-7), 7.02 (1H, d, J=2.5 Hz, H-4), 7.45 (1H, s, H-10), 7.68 (2H, s, H-2′,6′); ^{13}C NMR ($CDCl_3$): δ 166.5 (C-2), 153.8 (C-5), 152.3 (C-3′,5′), 145.5 (C-4′), 140.5 (C-8), 139.9 (C-10), 128.5 (C-1′), 125.8 (C-3), 119.9 (C-9), 116.4 (C-4), 110.6 (C-6), 109.6 (C-2′,6′), 105.7 (C-7), 60.5 (Ar–OCH_3), 55.8 (Ar–OCH_3); MS (ESI, positive scan): m/z 329 $(M+H)^+$. Analysis found: C, 65.81; H, 4.95%. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91%.

4.5.3. 3-[(4-Fluorophenyl)methylene]-5-hydroxybenzo[*b*]furan-2-one (7*E*). Yellow powder (135 mg, 35%), mp 199–201 °C; IR (KBr): 3294, 1740, 1625, 1288, 1220, 1150, 1109, 1006 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.79 (1H, br s, Ar–OH), 6.83 (1H, dd, J=8.6, 2.5 Hz, H-6), 7.02 (1H, d, J=8.6 Hz, H-7), 7.16 (1H, d, J=2.5 Hz, H-4), 7.21 (2H, dd, J=8.6 Hz, H-3′,5′), 7.67 (2H, dd, J=8.6, 5.5 Hz, H-2′,6′), 7.81 (1H, s, H-10); ^{13}C NMR ($CDCl_3$+DMSO-d_6): δ 169.4 (C-2), 163.5 (d, $^1J_{CF}$=252 Hz, C-4′), 153.5 (C-5), 147.8 (C-8), 138.9 (C-10), 131.5 (d, $^3J_{CF}$=9 Hz, C-2′,6′), 130.2 (d, $^4J_{CF}$=3 Hz, C-1′), 123.1 (C-3), 121.9 (C-9), 118.1 (C-4), 116.0 (d, $^2J_{CF}$=22 Hz, C-3′,5′), 111.4 (C-6), 109.5 (C-7); MS (ESI, negative scan): m/z 255 $(M-H)^-$. Analysis found: C, 70.28; H, 3.57%. Calcd for $C_{15}H_9FO_3$: C, 70.31; H, 3.54%.

4.5.4. 3-[(4-Fluorophenyl)methylene]-5-hydroxybenzo[*b*]furan-2-one (7*Z*). Yellow powder (38 mg, 10%), mp 206–208 °C; IR (KBr): 3339, 1762, 1605, 1244, 1168, 1116, 1049, 990, 924 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.81 (1H, br s, Ar–OH), 6.80 (1H, dd, J=8.6, 2.5 Hz, H-6), 6.98 (1H, d, J=8.6 Hz, H-7), 7.01 (1H, d, J=2.5 Hz, H-4), 7.16 (2H, dd, J=8.6 Hz, H-3′,5′), 7.50 (1H, s, H-10), 8.25 (2H, dd, J=8.6, 5.5 Hz, H-2′,6′); ^{13}C NMR ($CDCl_3$+DMSO-d_6): δ 166.5 (C-2), 164.0 (d, $^1J_{CF}$=252 Hz, C-4′), 154.0 (C-5), 146.2 (C-8), 138.2 (C-10), 134.3 (d, $^3J_{CF}$=9 Hz, C-2′,6′), 129.6 (d, $^4J_{CF}$=3 Hz, C-1′), 125.6 (C-3), 121.2 (C-9), 117.1 (C-4), 115.5 (d, $^2J_{CF}$=22 Hz, C-3′,5′), 111.0 (C-6), 106.1 (C-7); MS (ESI, negative scan): m/z 255 $(M-H)^-$. Analysis found: C, 70.26; H, 3.58%. Calcd for $C_{15}H_9FO_3$: C, 70.31; H, 3.54%.

4.5.5. 3-[(4-Chlorophenyl)methylene]-5-hydroxybenzo[*b*]furan-2-one (8*E*). Yellow powder (180 mg, 44%), mp 216–218 °C; IR (neat): 3387, 2922, 1740, 1610, 1209, 1115, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 6.85 (1H, dd, J=8.7, 2.4 Hz, H-6), 6.95 (1H, d, J=8.7 Hz, H-7), 7.19 (1H, d, J=2.4 Hz, H-4), 7.48 (2H, d, J=8.2 Hz, H-3′,5′), 7.64 (2H, d, J=8.2 Hz, H-2′,6′), 7.72 (1H, s, H-10), 8.94 (1H, br s, Ar–OH); ^{13}C NMR ($CDCl_3$+DMSO-d_6): δ 169.2 (C-2), 153.7 (C-5), 147.7 (C-8), 138.4 (C-10), 135.9 (C-1′), 132.4 (C-4′), 130.7 (C-2′,6′), 129.1 (C-3′,5′), 123.6 (C-3), 121.6 (C-9), 118.3 (C-4), 111.5 (C-6), 109.5 (C-7); MS (ESI, negative scan): m/z 271 $(M-H)^-$, 273 $(M-H)^-$. Analysis found: C, 66.02; H, 3.35%. Calcd for $C_{15}H_9ClO_3$: C, 66.07; H, 3.33%.

4.5.6. 3-[(4-Chlorophenyl)methylene]-5-hydroxybenzo[*b*]furan-2-one (8*Z*). Yellow powder (100 mg, 25%), mp 200–202 °C; IR (neat): 3345, 1760, 1600, 1192, 1047, 918 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 6.83 (1H, d, J=8.4 Hz, H-6), 6.90 (1H, d, J=8.4 Hz, H-7), 7.02 (1H, br s, H-4), 7.41 (2H, d, J=8.1 Hz, H-3′,5′), 7.49 (1H, s, H-10), 8.13 (2H, d, J=8.1 Hz, H-2′,6′), 9.0 (1H, br s, Ar–OH); ^{13}C NMR ($CDCl_3$+DMSO-d_6): δ 166.4 (C-2), 154.1 (C-5), 146.3 (C-8), 138.1 (C-10), 136.8 (C-1′), 133.2 (C-2′,6′), 131.7 (C-4′), 128.6 (C-3′,5′), 125.5 (C-3), 122.1 (C-9), 117.4 (C-4), 111.1 (C-6), 106.3 (C-7); MS (ESI, negative scan): m/z 271 $(M-H)^-$, 273 $(M-H)^-$. Analysis found: C, 66.04; H, 3.36%. Calcd for $C_{15}H_9ClO_3$: C, 66.07; H, 3.33%.

4.5.7. 3-[(4-Chlorophenyl)methylene]-5-methoxybenzo[*b*]furan-2-one (9*E*). Yellow powder (150 mg, 35%), mp 156–158 °C; IR (KBr): 1780, 1619, 1236, 1209, 1110, 1086, 1033, 907 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.73 (3H, s, Ar–OCH_3), 6.90 (1H, dd, J=8.7, 2.2 Hz, H-6), 7.05 (1H, d, J=8.7 Hz, H-7), 7.19 (1H, d, J=2.2 Hz, H-4), 7.48 (2H, d, J=8.4 Hz, H-3′,5′), 7.62 (2H, d, J=8.4 Hz, H-2′,6′), 7.77 (1H, s, H-10); ^{13}C NMR ($CDCl_3$): δ 169.0 (C-2), 155.8 (C-5), 148.8 (C-8), 139.2 (C-10), 136.5 (C-1′), 132.3 (C-4′), 130.6 (C-2′,6′), 129.2 (C-3′,5′), 123.3 (C-3), 122.0 (C-9), 116.4 (C-4), 111.7 (C-6), 108.5 (C-7), 55.8 (Ar–OCH_3); MS (ESI, positive scan): m/z 287 $(M+H)^+$, 289 $(M+H)^+$. Analysis found: C, 67.01; H, 3.89%. Calcd for $C_{16}H_{11}ClO_3$: C, 67.03; H, 3.87%.

4.5.8. 3-[(4-Chlorophenyl)methylene]-5-methoxybenzo[*b*]furan-2-one (9*Z*). Yellow powder (40 mg, 9%), mp 168–170 °C; IR (KBr): 1756, 1611, 1281, 1215, 1053, 1034, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.84 (3H, s, Ar–OCH_3), 6.86 (1H, dd, J=8.7, 2.2 Hz, H-6), 6.99 (1H, d, J=8.7 Hz, H-7), 7.00 (1H, d, J=2.2 Hz, H-4), 7.41 (2H, d, J=8.1 Hz, H-3′,5′), 7.46 (1H, s, H-10), 8.12 (2H, d, J=8.1 Hz, H-2′,6′); ^{13}C NMR ($CDCl_3$): δ 166.2 (C-2), 156.4 (C-5), 147.3 (C-8), 138.4 (C-10), 137.3 (C-1′), 133.2 (C-2′,6′), 131.5 (C-4′), 128.8 (C-3′,5′), 125.6 (C-3), 121.8 (C-9), 116.1 (C-4), 111.4 (C-6), 104.5 (C-7), 55.9 (Ar–OCH_3); MS (ESI, positive scan): m/z 287 $(M+H)^+$, 289 $(M+H)^+$. Analysis found: C, 67.00; H, 3.90%. Calcd for $C_{16}H_{11}ClO_3$: C, 67.03; H, 3.87%.

4.5.9. 3-[(4-Methoxyphenyl)methylene]-5-methylbenzo[*b*]furan-2-one (10*E*). Yellow powder (120 mg, 30%), mp 102–104 °C; IR (neat): 1778, 1629, 1601, 1265, 1184, 1123, 1111, 1079, 1032, 968 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.39 (3H, s, Ar–CH_3), 3.89 (3H, s, Ar–OCH_3), 6.86 (1H, d, J=7.8 Hz, H-7), 6.95 (1H, s, H-4), 7.00 (2H, d, J=8.7 Hz, H-3′,5′), 7.67 (2H, d, J=8.7 Hz, H-2′,6′), 7.68 (1H, d, J=7.8 Hz, H-6), 7.72 (1H, s, H-10); ^{13}C NMR ($CDCl_3$): δ 169.7 (C-2), 161.4 (C-4′), 154.4 (C-8), 141.3 (C-1′), 139.6 (C-10), 131.6 (C-2′,6′), 126.7 (C-5), 124.2 (C-6), 122.1 (C-4), 120.0 (C-3), 119.5 (C-9), 114.2 (C-3′,5′), 111.6 (C-7), 55.4 (Ar–OCH_3), 21.9 (Ar–CH_3); MS (ESI, positive scan): m/z 267 $(M+H)^+$. Analysis found: C, 76.64; H, 5.36%. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30%.

4.5.10. 3-[(4-Methoxyphenyl)methylene]-5-methylbenzo[*b*]furan-2-one (10*Z*). Yellow powder (60 mg, 15%), mp 122–124 °C; IR (neat): 1754, 1621, 1264, 1219, 1178, 1043, 945 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.40 (3H, s, Ar–CH_3), 3.88 (3H, s, Ar–OCH_3), 6.91 (1H, s, H-4), 6.97 (2H, d, J=8.7 Hz, H-3′,5′), 6.98 (1H, dd, J=7.7, 2.1 Hz, H-6), 7.37 (1H, d, J=7.7 Hz, H-7), 7.48 (1H, s, H-10), 8.24 (2H, d, J=8.1 Hz, H-2′,6′); ^{13}C NMR ($CDCl_3$): δ 166.7 (C-2), 162.1 (C-4′), 152.8 (C-8), 139.8 (C-1′), 139.0 (C-10), 134.4 (C-2′,6′), 126.5 (C-5), 124.4 (C-6), 123.2 (C-3), 118.6

(C-4), 118.2 (C-9), 114.0 (C-3′,5′), 111.2 (C-7), 55.4 (Ar–OCH_3), 21.9 (Ar–CH_3); MS (ESI, positive scan): *m/z* 267 $(M+H)^+$. Analysis found: C, 76.65; H, 5.34%. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30%.

4.5.11. 5-Hydroxy-3-[(4-hydroxyphenyl)methylene]-benzo[*b*]furan-2-one (11*E*). Yellow powder (76 mg, 20%), mp 258–260 °C (lit.[7] mp 245–247 °C); IR (KBr): 3385, 3279, 1749, 1601, 1292, 1252, 1145, 1119 cm^{-1}; ^1H NMR (DMSO-d_6): see Table 4; ^{13}C NMR (DMSO-d_6): δ 169.6 (C-2), 159.8 (C-4′), 153.1 (C-5), 146.7 (C-8), 140.9 (C-10), 131.7 (C-2′,6′), 124.5 (C-1′), 122.1 (C-3), 119.1 (C-9), 116.6 (C-4), 115.6 (C-3′,5′), 110.6 (C-6), 108.9 (C-7); MS (ESI, negative scan): *m/z* 253 $(M-H)^-$.

4.5.12. 5-Hydroxy-3-[(4-hydroxyphenyl)methylene]-benzo[*b*]furan-2-one (11*Z*). Yellow powder (19 mg, 5%), mp 245–247 °C; IR (KBr): 3389, 3294, 1724, 1602, 1297, 1211, 1180, 1115, 1081 cm^{-1}; ^1H NMR (DMSO-d_6): see Table 4; MS (ESI, negative scan): *m/z* 253 $(M-H)^-$.

4.5.13. 5-Hydroxy-3-[(3,4-dihydroxyphenyl)methylene]-benzo[*b*]furan-2-one (12*E*/*Z*). Yellow powder (183 mg, 45%, HPLC: *E*/*Z* 79:19), mp 240–243 °C; IR (KBr): 3343, 3256, 1754, 1596, 1240, 1143, 1120, 1101, 1004 cm^{-1}; ^1H NMR (DMSO-d_6): δ peaks correspond to *E*-isomer, 6.78 (1H, dd, *J*=2.4, 8.4 Hz, H-6), 6.88 (1H, d, *J*=8.2 Hz, H-5′), 7.06 (1H, d, *J*=8.4 Hz, H-7), 7.17 (1H, d, *J*=8.2 Hz, H-6′), 7.23 (1H, d, *J*=1.8 Hz, H-2′), 7.37 (1H, d, *J*=2.4 Hz, H-4), 7.62 (1H, s, H-10); ^{13}C NMR ($CDCl_3$+DMSO-d_6): δ 169.7 (C-2), 153.1 (C-5), 148.1 (C-4′), 146.8 (C-8), 144.8 (C-3′), 141.4 (C-10), 125.2 (C-1′), 123.2 (C-2′), 122.2 (C-3), 119.0 (C-9), 116.6 (C-6′), 116.4 (C-5′), 115.5 (C-4), 110.6 (C-6), 109.3 (C-7); MS (ESI, negative scan): *m/z* 269 $(M-H)^-$. Analysis found: C, 66.64; H, 3.75%. Calcd for $C_{15}H_{10}O_5$: C, 66.67; H, 3.73%.

4.5.14. 5-Hydroxy-3-[(3,4,5-trihydroxyphenyl)methylene]-benzo[*b*]furan-2-one (13*E*/*Z*). Yellow powder (155 mg, 36%, HPLC: *E*/*Z* 80:20), mp 270–273 °C; IR (KBr): 3367, 1758, 1598, 1236, 1143, 1109, 1039, 990 cm^{-1}; ^1H NMR (DMSO-d_6): δ peaks correspond to *E*-isomer, 6.78 (2H, s, H-2′,6′), 6.79 (1H, dd, *J*=2.4, 8.6 Hz, H-6), 7.06 (1H, d, *J*=8.6 Hz, H-7), 7.40 (1H, d, *J*=2.4 Hz, H-4), 7.55 (1H, s, H-10), 9.12 (1H, br s, Ar–OH), 9.46 (2H, br s, 2×Ar–OH), 9.48 (1H, br s, Ar–OH); ^{13}C NMR (DMSO-d_6): δ 169.5 (C-2), 153.6 (C-8), 146.4 (C-5), 146.1 (C-3′,5′), 142.5 (C-10), 137.3 (C-4′), 123.7 (C-1′), 122.3 (C-3), 118.4 (C-9), 116.9 (C-4), 111.3 (C-6), 109.7 (C-2′,6′), 109.3 (C-7); MS (ESI, negative scan): *m/z* 285 $(M-H)^-$. Analysis found: C, 62.91; H, 3.55%. Calcd for $C_{15}H_{10}O_6$: C, 62.94; H, 3.52%.

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