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ORIGINAL PAPER

Efficient synthesis of aurone Mannich bases and evaluation of their antineoplastic activity in PC-3 prostate cancer cells

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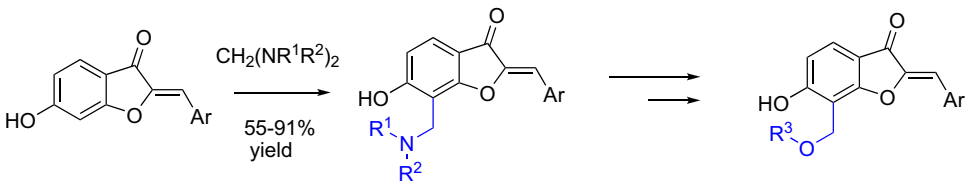
Abstract

An efficient method for regioselective synthesis of C-7 Mannich bases of 6-hydroxyaurones was accomplished by the *N,N*-dialkylaminomethylation using aminals prepared from dimethylamine, dipropylamine, bis(2-methoxyethyl)amine, *N*-methylbutylamine, *N*-methylbenzylamine, morpholine, piperidine, and 1-methylpiperazine. Further transformation of 7-(*N,N*-dialkylamino)methyl group in these aurones led to formation of C-7 acetoxymethyl and methoxymethyl derivatives of 6-hydroxyaurones, some of which showed promising inhibition of PC-3 prostate cancer cell proliferation in the high nanomolar to low micromolar range that exceeded that of cisplatin.

Graphical abstract Compound **12c** (R^3 = Ac, Ar = 3,4-OMePh) displays 75% inhibition of PC-3 prostate cancer cells proliferation at 300 nM concentration.



Keywords 6-hydroxyaurones · Mannich base · Aminomethylation · Prostate cancer

Introduction

2-Benzylidenebenzofuran-3(2*H*)-ones, commonly known as aurones, represent a subclass of flavonoids with pharmacological potential (Haudecoeur and Boumendjel 2012;

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Boumendjel 2003; Sim et al. 2011). Semisynthetic aurones display antitubercular (Horváti et al. 2012), anticancer (Schoepfer et al. 2002), antimalarial (Carrasco et al. 2014) activity, and aurones with tertiary amines, including Mannich bases, were reported as inhibitors of AChE (Sheng et al. 2009), PIM1 (Nakano et al. 2012), and p38 MAP kinase (Choi et al. 2012). Structure–activity relationships among the flavonoids, isoflavonoids, and semisynthetic aurones do not necessarily parallel one another (Lewin et al. 2012), but the high CDK1/Cyclin B inhibitory activity of flavonoid Mannich bases (Liu et al. 2007; Zhang et al. 2008) prompted us to consider auronoid Mannich bases for evaluation as antineoplastic agents. In contrast to flavonoids and isoflavonoids, reports on the synthesis and evaluation of auronoid Mannich bases were scarce. We ascribed this deficiency to poor yields encountered in the application of "classical Mannich reactions" to 6-hydroxyaurones **2** using aqueous paraformaldehyde and secondary amines in ethanol (Carrasco et al. 2014). Alternative methods for the synthesis of semisynthetic aurones introduced aminomethyl groups on alkoxy- or hydroxy-substituted benzofuran-3(2*H*)-one derivatives (Nakano et al. 2012; Gao et al. 2013) **1** prior to condensation with aryl or heteroaryl aldehydes to secure the semisynthetic aurones **2** (Ar = aryl or heteroaryl). Aminomethylation of benzofuran-3(2*H*)-one (**1**) generally proceed in poor yields because of competitive condensation at C-2 leading to 2,2-bis-(*N,N*-dialkylamino)methyl 6-hydroxybenzofuran-3(2*H*)-one derivatives (Bandgar et al. 2010; Lipeeva et al. 2013) (Fig. 1).

As a consequence, we explored a procedure for the direct aminomethylation of semisynthetic 6-hydroxyaurones **2** as a means of acquiring compounds for biological evaluation.

Results and discussion

The important criteria to consider in developing of a synthesis of *N,N*-dialkylaminomethyl derivatives of 6-hydroxyaurones included efficiency, simplicity, and regioselectivity. 6-Hydroxy-2-benzylidenebenzofuran-3(2*H*)-one **2** (Ar = C_6H_5) possessed two nucleophilic centers at C-5 and C-7, excluding possible centers in the benzylidene ring, for Mannich reactions. The efficient and selective aminomethylation of unsymmetrical phenols depended on

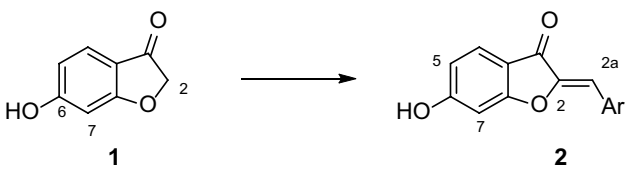


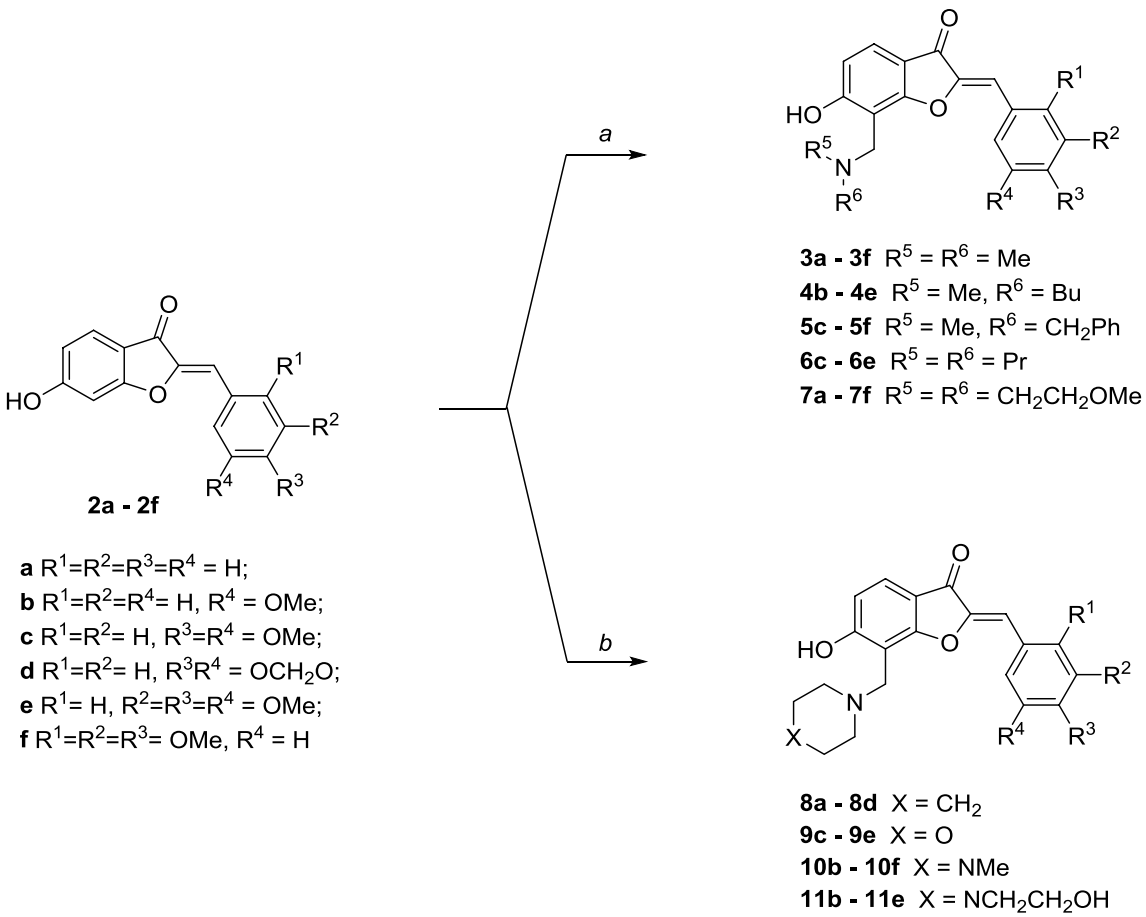
Fig. 1 6-Hydroxybenzofuran-3-(2*H*)-one **1** and 6-hydroxyaurones **2**

the structure of the substrate, the dialkylamine, solvent, the catalyst, the pH, and in particular, the aminomethylating agent. These agents include iminium salts or hemiaminals (Nguyen et al. 2011; Frasinyuk et al. 2015), imines (MacLeod et al. 2010; Cimarelli et al. 2011; Nguyen et al. 2012), and aminals (Mrug et al. 2013; Bondarenko et al. 2003) that effect the aminomethylation of a range of phenolic substrates.

For these reasons, we investigated the aminomethylation of 6-hydroxyaurones using various reagents and under conditions that included the following: [1] 40% aqueous formaldehyde and a secondary amine in refluxing ethanol; [2] 40% aqueous formaldehyde and a secondary amine hydrochloride in refluxing ethanol; and [3] 40% aqueous formaldehyde and a secondary amine under basic catalysis by 4-dimethylaminopyridine (DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or Et_3N in refluxing ethanol. We obtained the best yields using DMAP as a catalyst and using paraformaldehyde in place of aqueous formaldehyde. For example, the aminomethylation of aurone **2c** with 1-methylpiperazine gave 21% yield of the compound **10c** using aqueous formaldehyde without base, 32% yield using aqueous formaldehyde with DMAP, and 46% yield using paraformaldehyde with DMAP. The formation of 5,7-bisaminomethyl derivatives was observed in all cases under these reaction conditions. Carrying out the aminomethylation using *N*-hydroxymethylamines and *N,N*-bisaminomethanes (aminals) proved to be the most promising pathway for the synthesis of Mannich bases of aurones. For example, aminomethylation of aurone **2c** using 4,4'-methylenebis(1-methylpiperazine) increased the yield of **10c** to 80% of the desired product and simplified the purification of **10c** by minimizing the amount of the 5,7-bisaminomethyl derivatives.

Further studies revealed that the aminomethylation of most 6-hydroxyaurones **2** with aminals in isopropanol or, in case of aurone **2d,** in 1,4-dioxane gave the best yields. In these cases, we observed the regiospecific formation of 7-*N,N*-dialkylaminomethyl derivatives of these aurones. When using aminals prepared from dimethylamine, dipropylamine, bis(2-methoxyethyl)amine, *N*-methylbutylamine, *N*-methylbenzylamine, morpholine, piperidine, and 1-methylpiperazine, we did not observe formation of any 5,7-bisaminomethyl derivatives. The desired 7-(*N,N*-dialkylamino)methyl-6-hydroxyaurones **3–11** were isolated in 51-86% yield (Scheme 1). Formation of 7-(*N,N*-dialkylamino)methyl derivatives was confirmed by ^{1}H NMR in which the coupling constant (J = 8.4–8.5 Hz) between H-4 and H-5 excluded the regioisomeric 5-(*N,N*-dialkylamino) methyl-6-hydroxyaurones.

Heating 7-*(N,N*-dialkylamino)methyl-6-hydroxyaurones **3a**–**3d** with acetic anhydride in presence of potassium acetate afforded the corresponding diacetates **12a**–**12d** in excellent yield.



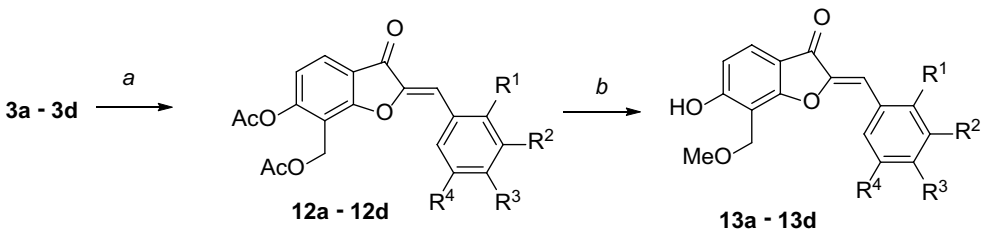
Scheme 1 Synthesis of Mannich bases of 6-hydroxyaurones **3–11**. Reagents and conditions: *a*) $CH_2(NR^5R^6)_2$, *i*-PrOH, 80 °C, 4-8 h; *b*) $CH_2(NC_4H_8X)_2$, *i*-PrOH, 80 °C, 4–6 h

(Scheme 2). Hydrolysis of **12** in methanol using hydrochloric acid led directly to the formation of 7-methoxymethyl derivatives **13a**–**13d**.

A screening program using inhibition of the proliferation of PC-3 prostate cancer cells revealed that several 6-hydroxyaurones **2**–**13** with C-7 *N,N*-dialkylaminomethyl, acetoxymethyl or methoxymethyl substituents exhibited antiproliferative activity in the low micromolar range (Table 1). In general, 7-(*N,N*-dialkylamino)methyl-6-hydroxyaurones possessed weak activity at these concentrations, but provided access to 7-acetoxymethylaurones that were the most potent. Thus, compounds **12c** and **12d** inhibited the growth of PC-3 cells at 1 μM concentration to the extent of 86.0 ± 2.2% and 87.1 ± 4.0, respectively. Additional testing of **12c** at a concentration of 300 nM showed good retention of this inhibition of cell proliferation (75.4 ± 15.6%).

Conclusions

Various aminals (i.e., bis(*N,N*-dialkylamino)methanes) derived from aliphatic and alicyclic amines afforded the regiospecific aminomethylation of 6-hydroxyaurones **2** (Scheme 1). The resulting Mannich bases in turn provided



Scheme 2 Conversion of *N,N*-dimethylaminomethyl derivatives **3a–3d** to acetoxymethyl- and methoxymethyl derivatives. Reagents and conditions: *a*, Ac_2O, KOAc*; b*, HCl, MeOH

Table 1 IC_{50} Values (μM) and percent inhibition of PC-3 cell proliferation by cisplatin (positive control) and selected aurones

Aurone	R^1	R^2	R^3	R^4	C-7	Inhibition at 10 μM (%)	IC_{50} (μM)
2a	H	H	H	H	H	7.1 ± 22.6	
2e	H	OMe	OMe	OMe	H	52.9 ± 31.7	
3a	H	H	H	H	CH_2NMe_2	9.3 ± 6.5	
3e	H	OMe	OMe	OMe	CH_2NMe_2	22.4 ± 8.3	
5c	H	OMe	OMe	H	$CH_2N(Me)CH_2Ph$	25.9 ± 12.9	
5d	H	OCH_2O		H	$CH_2N(Me)CH_2Ph$	8.8 ± 13.8	
5e	H	OMe	OMe	OMe	$CH_2N(Me)CH_2Ph$	63.0 ± 4.8	3.9 ± 0.28
6d	H	OCH_2O		H	CH_2NiPr_2	84.51 ± 0	8.8 ± 0.1
8a	H	H	H	H	1-piperidinylmethyl	6.5 ± 19.5	
8d	H	OCH_2O		H	1-piperidinylmethyl	11.7 ± 4.8	
9e	H	OMe	OMe	OMe	4-morpholinomethyl	31.4 ± 2.5	
10b	H	H	OMe	H	4-(1-methylpiperazinyl)-methyl	40.6 ± 5.6	
10c	H	OMe	OMe	H	4-(1-methylpiperazinyl)-methyl	45.8 ± 10.0	
11c	H	OMe	OMe	H	4-(1-(2-hydroxyethyl)piperazinyl)-methyl	47.9 ± 19.8	
12c	H	OMe	OMe	H	acetoxymethyl	99.5 ± 0.1	0.74 ± 0.03
12d	H	OCH_2O		H	acetoxymethyl	87.9 ± 2.3	3.7 ± 0.42
cisplatin							> 10

ready access to aurones **12** and **13** bearing either acetoxy or methoxy groups, respectively. Although the initial focus of this work required the identification of a viable synthetic route to the desired compounds, we were pleased to find that various aurones possessed in vitro activity in a PC-3 cell proliferation assay. Several analogs (i.e., **5e**, **6d**, **12c** and **12d**) possessed IC_{50} values against prostate cancer PC-3 cells that were larger than the IC_{50} of cisplatin (i.e., *cis*-diamminedichloridoplatinum(II)), a therapeutic antineoplastic agent in current use. In general, the aurones **3-11** possessing 3,4-dimethoxy or 3,4-methylenedioxy groups in the C-2 benzylidene subunit were more active in a PC-3 cell proliferation assay than those aurones with no alkoxy groups in the C-2 benzylidene subunit (i.e., **2e** > **2a**; and **3e** > **3a**). In general, the diacetoxy-substituted aurones **12** were more active in a PC-3 cell proliferation than the corresponding Mannich bases **3-11** (i.e., **12c** > **10–11c**, > **5c**; and **12d** > **8d** > **5d**). Exceptions to these generalizations were, however, noted (e.g., **6d**–**12d**), and future, additional SAR work will further define these distinctions.

Other factors, such as solubility and in vitro stability, presumably played a role in the results of these cell proliferation assays. The Mannich bases of aurones **3-11** were, as expected, slightly soluble in water, and aurone **6d** with a C-7 *N,N*-(diisopropylamino)methyl substituent and with promising inhibitor activity was soluble at pH 5-6 in phosphate, citrate and acetate buffers. The corresponding diacetoxy compound **12d** also showed promising activity but was insoluble in water. The methoxymethyl derivatives **13** were also insoluble in water, but were soluble, as expected, in slightly basic aqueous solution. Future studies will focus on: defining the stability of the most promising diacetoxy-substituted aurones **12** to esterases (*i.e.*, metabolism studies); determining if these aurones generate *ortho*-quinone methide intermediates; utilizing biotinylated intermediates to determine molecular target(s); evaluating toxicity issues; and performing xenograft studies to evaluate in vivo activity.

Experimental

Chemistry

Cisplatin was obtained from Sigma-Aldrich (St. Louis, MO 63146 USA). ^1H and ^{13}C NMR spectra were recorded on a Varian 500 spectrometer (at 500 MHz or at 125 MHz, respectively) or on a Varian 400 spectrometer (at 400 MHz or at 100 MHz, respectively) in deuterochloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-d_6). IR spectra were recorded on a Bruker Vertex 70 FT/IR spectrometer. Melting points were determined in open capillarity tubes with a Buchi B-535 apparatus and were uncorrected. Mass spectra were obtained with an Agilent 1100 spectrometer under chemical ionization conditions.

General procedure for the synthesis of 6-hydroxyaurones 2a–2f

To a stirred solution of 0.75 g (5 mmol) 6-hydroxybenzofuranone (**1**) in ethanol (5 mL) and *N,N*-dimethylformamide

(DMF) (5 mL) was added aldehyde (5 mmol) and 1.15 mL of 50% KOH. The mixture was stirred at room temperature for 4–6 h. The mixture was poured into 30 mL of hot water with vigorous stirring and neutralized with concentrated HCl at pH of 1–2. The precipitate was filtered, washed with water, dried and recrystallized from DMF-MeOH.

(2*Z*)-2-Benzylidene-6-hydroxy-1-benzofuran-3(2*H*)-one (2a)

Yellow solid (87% yield); mp: 259–260 °C; IR (KBr): ν_{max} 3072, 2960, 1674, 1644, 1580, 1455, 1376, 1285, 1109, 770 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.72 (1H, dd, ^3J = 8.4 Hz, ^4J = 1.7 Hz, H-5), 6.78 (1H, s, H-2a), 6.80 (1H, d, ^4J = 1.7 Hz, H-7), 7.38–7.53 (3H, m, H-3′, 4′, 5′), 7.63 (1H, d, ^3J = 8.4 Hz, H-4), 7.94 (2H, d, ^3J = 8.5 Hz, H-2′, 6′), 11.30 ppm (1H, br. s, OH-6); ^{13}C NMR (100 MHz, DMSO-d_6): δ 98.71, 110.41, 112.79, 113.18, 126.08, 129.04, 129.72, 131.12, 132.14, 147.45, 166.70, 168.05, 181.55 ppm; MS (CI): *m/z* 238.9 (MH^+, 100). Anal. calcd for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23. Found: C, 75.41; H, 4.05.

(2*Z*)-6-Hydroxy-2-(4-methoxybenzylidene)-1-benzofuran-3(2*H*)-one (2b)

Yellow solid (85% yield); mp: 268–270 °C; IR (KBr): ν_{max} 3081, 2899, 2598, 1675, 1566, 1455, 1285, 1256, 1108 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.81 (3H, s, OMe-4′), 6.71 (1H, dd, ^3J = 8.5 Hz, ^4J = 2.0 Hz, H-5), 6.77–6.81 (2H, m, H-2a, H-7), 7.05 (2H, d, ^3J = 8.4 Hz, H-3′, 5′), 7.61 (1H, d, ^3J = 8.5 Hz, H-4), 7.91 (2H, d, ^3J = 8.4 Hz, H-2′, 6′), 11.17 ppm (1H, s, OH-6); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.28, 98.46, 110.62, 112.81, 112.96, 114.48, 124.50, 125.65, 132.82, 146.05, 160.30, 166.11, 167.47, 181.08 ppm; MS (CI): *m/z* 269.1 (MH^+, 100). Anal. calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.45; H 4.38.

(2*Z*)-2-(3,4-Dimethoxybenzylidene)-6-hydroxy-1-benzofuran-3(2*H*)-one (2c)

Yellow solid (87% yield); mp: 224–226 °C; IR (KBr): ν_{max} 3122, 1679, 1582, 1509, 1259, 1235, 1125, 1092, 1015 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.82, 3.83 (each 3H, 2 s, OMe-3′,4′), 6.68 (1H, dd, ^3J = 8.5 Hz, ^4J = 1.8 Hz, H-5), 6.73 (1H, s, H-2a), 6.75 (1H, d, ^4J = 1.8 Hz, H-7), 7.07 (1H, d,^3J = 8.5 Hz, H-5′), 7.54-7.60 ppm (3H, m, H-4, 2′, 6′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.50, 55.55, 98.56, 111.07, 111.86, 112.83, 112.96, 114.13, 124.65, 124.98, 125.66, 146.11, 148.61, 150.25, 166.11, 167.45, 181.06 ppm; MS (CI): *m/z* 299.1 (MH^+, 100). Anal. calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.31; H 4.51.

(2*Z*)-2-(1,3-Benzodioxol-5-ylmethylene)-6-hydroxy-1-benzofuran-3(2*H*)-one (2d)

Yellow solid (91% yield); mp: 321–323 °C (decomp); IR (KBr): ν_{max} 3057, 2890, 1668, 1616, 1542, 1446, 1405, 1329, 1253, 1102, 1034 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.11 (2H, s, OCH_2O), 6.71 (1H, dd, ^3J = 8.5 Hz, ^4J = 1.8 Hz, H-5), 6.74 (1H, s, H-2a), 6.81 (1H, d, ^4J = 1.8 Hz, H-7), 7.04 (1H, d, ^3J = 8.1 Hz, H-7′), 7.47 (1H, dd, ^3J = 8.1 Hz, ^4J = 1.7 Hz, H-6′), 7.55 (1H, d, ^4J = 1.7 Hz, H-4′), 7.60 ppm (1H, d, ^3J = 8.5 Hz, H-4); ^{13}C NMR (100 MHz, DMSO-d_6): δ 98.58, 101.59, 108.80, 109.95, 110.64, 112.78, 112.93, 125.66, 126.12, 126.79, 146.15, 147.70, 148.50, 166.35, 167.52, 181.04 ppm; MS (CI): *m/z* 283.3 (MH^+, 100). Anal. calcd for $C_{16}H_{10}O_5$: C, 68.09; H, 3.57. Found: C, 67.95; H, 3.68.

(2*Z*)-6-Hydroxy-2-(3,4,5-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (2e)

Yellow solid (81% yield); mp: 254–256 °C; IR (KBr): ν_{max} 3271, 1678, 1637, 1582, 1454, 1315, 1242, 1129, 1108, 998 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.72 (3H, s, OMe-4′), 3.85 (6H, s, OMe-3′, 5′), 6.72 (1H, dd, ^3J = 8.4 Hz, ^2J = 2.0 Hz, H-5), 6.75 (1H, s, H-2a), 6.82 (1H, d, ^4J = 2.0 Hz, H-7), 7.30 (2H, s, H-2′, 6′), 7.61 (1H, d, ^3J = 8.4 Hz, H-4), 11.19 ppm (1H, br. s, OH-6); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.94, 60.12, 98.68, 108.73, 110.73, 112.74, 112.92, 125.73, 127.38, 139.03, 146.68, 152.83, 166.28, 167.61, 181.13 ppm; MS (CI): *m/z* 329.1 (MH^+, 100). Anal. calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found: C, 65.62; H; 5.04.

(2*Z*)-6-Hydroxy-2-(2,3,4-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (2f)

Yellow solid (78% yield); mp: 249–251 °C; IR (KBr): ν_{max} 3169, 2941, 1680, 1582, 1492, 1266, 1136, 1103, 1090, 976 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.78, 3.87, 3.88 (each 3H, s, OMe-2′, 3′, 4′), 6.71 (1H, dd, ^3J = 8.3 Hz, ^4J = 1.9 Hz, H-5), 6.77 (1H, d, ^4J = 1.9 Hz, H-7), 6.90 (1H, s, H-2a), 6.98 (1H, d, ^3J = 8.9 Hz, H-5′), 7.61 (1H, d, ^3J = 8.3 Hz, H-4), 7.93 (1H, d, ^3J = 8.9 Hz, H-6′), 11.15 ppm (1H, br. s, OH-6); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.96, 60.42, 61.61, 98.50, 104.01, 108.45, 112.86, 112.92, 118.25, 125.73, 126.25, 141.55, 146.79, 152.80, 154.95, 166.19, 167.48, 181.09 ppm; MS (CI): *m/z* 329.1 (MH^+, 100). Anal. calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found: C, 65.98; H, 5.12.

General procedure for the synthesis of Mannich bases 3–11

To a suspension of 2 mmol of **2a–f** in 10 mL of isopropyl alcohol or 1,4-dioxane (in case of compound **1d**) was added 2.2 mmol of aminal, and the mixture was refluxed for 4-6 h. The mixture was diluted with 10 mL of hexanes and cooled. The residue was filtered and recrystallized from an isopropanol-hexanes mixture.

(2*Z*)-2-Benzylidene-7-[(dimethylamino)methyl]-6-hydroxy-1-benzofuran-3(2*H*)-one (3a)

Yellow solid (77% yield); mp: 248–250 °C; IR (KBr): ν_{max} 3051, 2394, 1682, 1598, 1507, 1444, 1333, 1272, 1123, 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.51 (6H, s, NMe_2), 3.99 (2H, s, CH_2-7), 6.67 (1H, d, $^3J = 8.4$ Hz, H-5), 6.78 (1H, s, H-2a), 7.36–7.49 (3H, m, H-3′, 4′, 5′), 7.61 (1H, d, $^3J = 8.4$ Hz, H-4), 7.82 (2H, d, $^3J = 8.8$ Hz, H-2′, 6′), 10.69 ppm (1H, br. s, OH-7); ^{13}C NMR (125 MHz, $CDCl_3$): δ 44.55, 54.64, 104.19, 111.37, 113.16, 113.84, 125.53, 129.00, 129.55, 131.21, 132.72, 148.08, 165.86, 168.12, 182.78 ppm; MS (CI): *m/z* 296.2 (MH^+, 100). Anal. calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.04; H, 5.54; N, 4.61.

(2*Z*)-7-[(Dimethylamino)methyl]-6-hydroxy-2-(4-methoxybenzylidene)-1-benzofuran-3(2*H*)-one (3b)

Yellow solid (83% yield); mp: 171–173 °C; IR (KBr): ν_{max} 2960, 2836, 1692, 1600, 1509, 1252, 1126, 1036, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.49 (6H, s, NMe_2), 3.85 (3H, s, OMe-4′), 3.96 (2H, s, CH_2-7), 6.64 (1H, d, $^3J = 8.5$ Hz, H-5), 6.74 (1H, s, H-2a), 6.97 (2H, d, $^3J = 8.9$ Hz, H-3′, 5′), 7.58 (1H, d, $^3J = 8.5$ Hz, H-4), 7.77 (2H, d, $^3J = 8.9$ Hz, H-2′, 6′), 7.95 ppm (1H, br. s, OH-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.55, 54.72, 55.46, 104.21, 111.68, 113.43, 113.62, 114.56, 125.27, 125.35, 133.00, 146.97, 160.76, 165.48, 167.74, 182.73 ppm; MS (CI): *m/z* 326.2 (MH^+, 100). Anal. calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.90; H, 5.62; N, 4.55.

(2*Z*)-2-(3,4-Dimethoxybenzylidene)-7-[(dimethylamino)methyl]-6-hydroxy-1-benzofuran-3(2*H*)-one (3c)

Yellow solid (78% yield); mp: 91–93 °C; IR (KBr): ν_{max} 3451, 3387, 2834, 1672, 1588, 1514, 1455, 1336, 1266, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.45 (6H, s, NMe_2), 3.91 (2H, s, CH_2-7), 3.95, 3.98 (each 3H, 2 s, OMe-3′,4′), 6.65 (1H, d, $^3J = 8.3$ Hz, H-5), 6.77 (1H, s, H-2a), 6.96 (1H, d,$^3J = 8.4$ Hz, H-5′), 7.42 (1H, dd, $^3J = 8.3$ Hz, $^4J = 1.9$ Hz, H-6′), 7.50 (1H, d, $^4J = 1.9$ Hz, H-2′), 7.61 ppm (1H, d, $^3J = 8.4$ Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 44.74, 54.78, 55.85, 56.08, 104.22, 111.40, 111.95, 113.54, 113.63, 125.39, 125.43, 125.63, 147.10, 149.04, 150.54, 165.39, 167.46, 182.63 ppm; MS (CI): *m/z* 356.2 (MH^+, 100). Anal. calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.83; H, 6.17; N, 4.07.

(2*Z*)-2-(1,3-Benzodioxol-5-ylmethylene)-7-[(dimethylamino)methyl]-6-hydroxy-1-benzofuran-3(2*H*)-one (3d)

Yellow solid (84% yield); mp: 158–160 °C; IR (KBr): ν_{max} 2963, 2899, 1689, 1601, 1444, 1331, 1242, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.47 (6H, s, NMe_2), 3.94 (2H, s, CH_2-7), 6.05 (2H, s, OCH_2O), 6.64 (1H, d, $^3J = 8.5$ Hz, H-5), 6.72 (1H, s, H-2a), 6.89 (1H, d, $^3J = 8.1$ Hz, H-7′), 7.24–7.27 (1H, m, H-6′), 7.47 (1H, d, $^4J = 1.6$ Hz, H-4′), 7.60 ppm (1H, d, $^3J = 8.4$ Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 44.62, 54.98, 101.61, 104.50, 108.91, 110.31, 111.61, 113.37, 113.68, 125.17, 126.96, 127.12, 147.02, 148.20, 148.91, 165.37, 167.82, 182.64 ppm; MS (CI): *m/z* 340.0 (MH^+, 100). Anal. calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 66.98; H, 5.31; N, 4.42.

(2*Z*)-7-[(Dimethylamino)methyl]-6-hydroxy-2-(3,4,5-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (3e)

Yellow solid (76% yield); mp: 191–193 °C; IR (KBr): ν_{max} 3433, 2955, 1670, 1614, 1510, 1450, 1344, 1273, 1130, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (6H, s, NMe_2), 3.88 (2H, s, CH_2-7), 3.92 (3H, s, OMe-4′), 3.95 (6H, s, OMe-3′, 5′), 6.66 (1H, d, $^3J = 8.5$ Hz, H-5), 6.73 (1H, s, H-2a), 7.14 (2H, s, H-2′, 6′), 7.62 ppm (1H, d, $^3J = 8.5$ Hz, H-4); ^{13}C NMR (100 MHz, DMSO-d_6): δ 43.62, 52.26, 55.82, 60.14, 103.65, 108.15, 108.89, 109.11, 115.07, 124.78, 127.90, 138.43, 147.63, 152.80, 166.27, 171.55, 179.71 ppm; MS (CI): *m/z* 386.2 (MH^+, 100). Anal. calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.21; H, 6.15; N, 3.49.

(2*Z*)-7-[(Dimethylamino)methyl]-6-hydroxy-2-(2,3,4-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (3f)

Yellow solid (87% yield); mp: 152–154 °C; IR (KBr): ν_{max} 2940, 1678, 1599, 1496, 1453, 1278, 1122, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.47 (6H, s, NMe_2), 3.90, 3.95, 3.97 (each 3H, 3 s, OMe-2′, 3′, 4′), 3.93 (2H, s, CH_2-7), 6.65 (1H, d, $^3J = 8.4$ Hz, H-5), 6.84 (1H, d, $^3J = 8.9$ Hz, H-5′), 7.21 (1H, s, H-2a), 7.62 (1H, d, $^3J = 8.5$ Hz, H-4), 7.94 (1H, d, $^3J = 8.9$ Hz, H-6′), 8.24 ppm (1H, br. s, OH-7); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.37, 54.32, 56.07, 60.90, 61.84, 103.80, 105.74, 107.73, 113.47, 119.63, 125.36, 126.53, 142.21, 147.57, 153.86, 155.13, 165.38, 167.43, 182.51 ppm; MS (CI): *m/z* 386.2 (MH^+, 100). Anal. calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.17; H, 5.83; N, 3.90.

(2*Z*)-7-{[Butyl(methyl)amino]methyl}-6-hydroxy-2-(4-methoxybenzylidene)-1-benzofuran-3(2*H*)-one (4b)

Yellow solid (76% yield); mp: 112–114 °C; IR (KBr): ν_{max} 3421, 2958, 1664, 1606, 1510, 1460, 1257, 1130 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.88 (3H, t, $^3J = 7.3$ Hz, $CH_2CH_2CH_2C\underline{H}_3$), 1.24–1.38 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$), 1.52–1.69 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$), 2.43 (3H, s, NMe), 2.63–2.78 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$), 3.82 (3H, s, OMe-4′), 4.04 (2H, s, CH_2-7), 6.48 (1H, d, $^3J = 8.6$ Hz, H-5), 6.68 (1H, s, H-2a), 7.05 (2H, d, $^3J = 8.8$ Hz, H-3′, 5′), 7.45 (1H, d, $^3J = 8.6$ Hz, H-4), 7.90 ppm (2H, d, $^3J = 8.8$ Hz, H-2′, 6′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.71, 19.75, 27.87, 40.68, 51.17, 55.24, 55.73, 104.07, 109.03, 109.52, 114.41, 114.67, 124.33, 124.93, 132.53, 146.83, 159.91, 165.85, 171.15, 179.93 ppm; MS (CI): *m/z* 368.1 (MH^+, 100). Anal. calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.09; H, 6.63; N, 3.65.

(2*Z*)-7-{[Butyl(methyl)amino]methyl}-2-(3,4-dimethoxybenzylidene)-6-hydroxy-1-benzofuran-3(2*H*)-one (4c)

Yellow solid (73% yield); mp: 101–102 °C; IR (KBr): ν_{max} 2959, 1676, 1605, 1512, 1458, 1260, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, $^3J = 7.4$ Hz, $CH_2CH_2CH_2C\underline{H}_3$), 1.27– 1.46 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$), 1.48–1.70 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$), 2.41 (3H, s, NMe), 2.53– 2.65 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$), 3.92, 3.95 (each 3H, 2 s, OMe-3′,4′), 3.98 (2H, s, CH_2-7), 6.65 (1H, d, $^3J = 8.5$ Hz, H-5), 6.73 (1H, s, H-2a), 6.93 (1H, d,$^3J = 8.5$ Hz, H-5′), 7.38 (1H, dd, $^3J = 8.5$ Hz, $^4J = 2.0$ Hz, H-6′), 7.45 (1H, d, $^4J = 2.0$ Hz, H-2′), 7.58 ppm (1H, d, $^3J = 8.5$ Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.95, 20.41, 28.72, 41.37, 53.31, 55.83, 56.07, 57.09, 104.08, 111.39, 111.86, 113.47, 113.61, 113.67, 125.35, 125.40, 125.64, 147.12, 149.05, 150.52, 165.50, 167.62, 182.56 ppm; MS (CI): *m/z* 398.2 (MH^+, 100). Anal. calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.77; H, 7.03; N, 3.64.

(2*Z*)-7-{[Butyl(methyl)amino]methyl}-6-hydroxy-2-(3,4,5-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (4e)

Yellow solid (82% yield); mp: 147–149 °C; IR (KBr): ν_{max} 2959, 1677, 1603, 1511, 1459, 1334, 1274, 1117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (3H, t, $^3J = 7.4$ Hz, $CH_2CH_2CH_2C\underline{H}_3$), 1.31–1.43 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$), 1.56–1.68 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$), 2.43 (3H, s, NMe), 2.55– 2.77 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$), 3.91 (3H, s, OMe-4′), 3.93 (6H, s, OMe-3′, 5′), 3.99 (2H, s, CH_2-7), 6.58–6.78 (2H, m, H-2a, 5), 7.12 (2H, s, H-2′, 6′), 7.60 (1H, d, $^3J = 8.5$ Hz, H-4), 10.29 ppm (1H, br. s, OH-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.95, 20.40, 28.50, 41.34, 53.12, 56.18, 57.10, 61.13, 103.95, 108.64, 111.67, 113.34, 113.84, 125.61, 128.08, 139.75, 147.67, 153.37, 165.69, 167.71, 182.50 ppm; MS (CI): *m/z* 428.2 (MH^+, 100). Anal. calcd for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.18; H, 7.07; N, 3.08.

(2*Z*)-7-{[Benzyl(methyl)amino]methyl}-2-(3,4-dimethoxybenzylidene)-6-hydroxy-1-benzofuran-3(2*H*)-one (5c)

Yellow solid (71% yield); mp: 141–143 °C; IR (KBr): ν_{max} 2946, 2835, 1698, 1601, 1515, 1420, 1261, 1142, 1117, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.38 (3H, s, NMe), 3.73 (2H, s, $NC\underline{H}_2Ph$), 3.92, 3.96 (each 3H, 2 s, OMe-3′, 4′), 3.98 (2H, s, CH_2-7), 6.68 (1H, d, $^3J = 8.5$ Hz, H-5), 6.77 (1H, s, H-2a), 6.95 (1H, d,$^3J = 8.4$ Hz, H-5′), 7.28–7.43 (6H, m, H-6′, $NCH_2\underline{Ph}$), 7.49 (1H, d, $^4J = 1.9$ Hz, H-2′), 7.62 ppm (1H, d, $^3J = 8.4$ Hz, H-4); ^{13}C NMR (100 MHz, DMSO-d_6): δ 40.87, 50.48, 55.30, 55.54, 60.46, 106.10, 110.50, 111.60, 111.78, 113.41, 124.32, 124.88, 125.13, 127.29, 128.23, 129.06, 137.02, 146.41, 148.56, 150.07, 165.58, 167.56, 180.79 ppm; MS (CI): *m/z* 432.2 (MH^+, 100). Anal. calcd for $C_{26}H_{25}NO_5$: C, 72.37; H, 5.84; N, 3.25. Found: C, 72.16; H, 5.95; N, 3.42.

(2*Z*)-2-(1,3-Benzodioxol-5-ylmethylene)-7-{[benzyl(methyl)amino]methyl}-6-hydroxy-1-benzofuran-3(2*H*)-one (5d)

Yellow solid (69% yield; mp: 159–161 °C; IR (KBr): ν_{max} 2851, 1697, 1602, 1499, 1243, 1188, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.40 (3H, s, NMe), 3.77 (2H, s, $NC\underline{H}_2Ph$), 4.03 (2H, s, CH_2-7), 6.07 (2H, s, OCH_2O), 6.68 (1H, d, $^3J = 8.4$ Hz, H-5), 6.74 (1H, s, H-2a), 6.90 (1H, d, $^3J = 8.1$ Hz, H-7′), 7.22–7.43 (6H, m, H-6′, $NCH_2\underline{Ph}$), 7.48 (1H, d, $^4J = 1.7$ Hz, H-4′), 7.62 ppm (1H, d, $^3J = 8.4$ Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.38, 52.52, 61.31, 100.09, 101.64, 104.46, 108.94, 110.34, 111.76, 113.66, 125.35, 126.90, 127.16, 128.31, 128.93, 129.67, 135.39, 146.95, 148.23, 148.97, 165.49, 167.31, 182.62 ppm; MS (CI): *m/z* 416.2 (MH^+, 100). Anal. calcd for $C_{25}H_{21}NO_5$: C, 72.28; H, 5.10; N, 3.37. Found: C, 72.43; H, 5.36; N, 3.09.

(2*Z*)-7-{[Benzyl(methyl)amino]methyl}-6-hydroxy-2-(3,4,5-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (5e)

Yellow solid (68% yield); mp: 144–146 °C; IR (KBr): ν_{max} 2938, 2837, 1685, 1599, 1452, 1262, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.39 (3H, s, NMe), 3.73 (2H, s, $NC\underline{H}_2Ph$), 3.91 (6H, s, OMe-3′, 5′), 3.94 (3H, s, OMe-4′), 3.97 (2H, s, CH_2-7), 6.70 (1H, d, $^3J = 8.4$ Hz, H-5), 6.74 (1H, s, H-2a), 7.14 (2H, s, H-2′, 6′), 7.29–7.41 (5H, m, $NCH_2\underline{Ph}$), 7.64 ppm (1H, d, $^3J = 8.4$ Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$): 41.63, 52.22, 56.12, 61.13, 61.36, 104.45, 108.60, 111.75, 113.61, 113.70, 125.52, 128.06, 128.41, 128.95, 129.76, 134.88, 139.71, 147.62, 153.34, 165.50, 167.24,

182.59 ppm; MS (CI): *m/z* 462.0 (MH^+, 100). Anal. calcd for $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90; N, 3.03. Found: C, 70.50; H, 6.18; N, 3.31.

(2*Z*)-7-{[Benzyl(methyl)amino]methyl}-6-hydroxy-2-(2,3,4-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (5f)

Yellow solid (76% yield); mp: 139–141 °C; IR (KBr): ν_{max} 2940, 1692, 1601, 1460, 1256, 1133, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.40 (3H, s, NMe), 3.78 (2H, s, $NC\underline{H}_2Ph$), 3.89, 3.95, 3.96 (each 3H, 3 s, OMe-2′, 3′, 4′), 4.04 (2H, s, CH_2-7), 6.71 (1H, d, $^3J = 8.5$ Hz, H-5), 6.82 (1H, d, $^3J = 8.9$ Hz, H-5′), 7.21 (1H, s, H-2a), 7.29–7.44 (5H, m, $NCH_2\underline{Ph}$), 7.63 (1H, d, $^3J = 8.5$ Hz, H-4), 7.92 ppm (1H, d, $^3J = 8.9$ Hz, H-6′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.40, 52.43, 56.23, 61.04, 61.30, 61.98, 104.34, 105.93, 107.87, 113.51, 113.97, 119.82, 125.46, 126.71, 128.33, 128.95, 129.72, 135.33, 142.40, 147.70, 154.05, 155.29, 165.47, 167.01, 182.69 ppm; MS (CI): *m/z* 462.0 (MH^+, 100). Anal. calcd for $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90; N, 3.03. Found: C, 70.02; H, 5.65; N, 2.84.

(2*Z*)-2-(3,4-Dimethoxybenzylidene)-7-[(dipropylamino)methyl]-6-hydroxy-1-benzofuran-3(2*H*)-one (6c)

Yellow solid (73% yield); mp: 135–137 °C; IR (KBr): ν_{max} 2966, 1666, 1597, 1514, 1458, 1263, 1114, 1019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (6H, t, $^3J = 7.4$ Hz, $N(CH_2CH_2C\underline{H}_3)_2$), 1.53 –1.72 (4H, m, $N(CH_2C\underline{H}_2CH_3)_2$), 2.50–2.67 (4H, m, $N(C\underline{H}_2CH_2CH_3)_2$), 3.91, 3.94 (each 3H, 2 s, OMe-3′,4′), 4.01 (2H, s, CH_2-7), 6.61 (1H, d, $^3J = 8.5$ Hz, H-5), 6.71 (1H, s, H-2a), 6.91 (1H, d,$^3J = 8.2$ Hz, H-5′), 7.36 (1H, dd, $^3J = 8.2$ Hz, $^4J = 2.0$ Hz, H-6′), 7.45 (1H, d, $^4J = 2.0$ Hz, H-2′), 7.56 (1H, d, $^3J = 8.5$ Hz, H-4), 8.30 ppm (1H, br. s, OH-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.77, 19.27, 50.41, 55.71, 55.73, 56.02, 104.33, 111.32, 111.70, 113.26, 113.49, 113.71, 125.12, 125.37, 125.65, 147.14, 148.98, 150.44, 165.45, 167.94, 182.51 ppm; MS (CI): *m/z* 412.2 (MH^+, 100). Anal. calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 69.86; H, 7.35; N, 3.12.

(2*Z*)-2-(1,3-Benzodioxol-5-ylmethylene)-7-[(dipropylamino)methyl]-6-hydroxy-1-benzofuran-3(2*H*)-one (6d). Yellow solid (72% yield); mp: 117–119 °C; IR (KBr): ν_{max} 2963, 2875, 1690, 1596, 1486, 1442, 1254, 1188, 1110, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (6H, t, $^3J = 7.4$ Hz, $N(CH_2CH_2C\underline{H}_3)_2$), 1.59 –1.76 (4H, m, $N(CH_2C\underline{H}_2CH_3)_2$), 2.59–2.70 (4H, m, $N(C\underline{H}_2CH_2CH_3)_2$), 4.05 (2H, s, CH_2-7), 6.04 (2H, s, OCH_2O), 6.64 (1H, d, $^3J = 8.5$ Hz, H-5), 6.71 (1H, s, H-2a), 6.88 (1H, d, $^3J = 8.1$ Hz, H-7′), 7.21–7.27 (1H, m, H-6′), 7.45 (1H, d, $^4J = 1.7$ Hz, H-4′), 7.59 ppm (1H, d, $^3J = 8.4$ Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.86, 19.67, 50.76, 56.01, 101.63, 104.66, 108.97, 110.35, 111.47, 113.21, 113.90, 125.09, 127.11, 127.12, 147.18, 148.24, 148.89, 165.56, 168.34, 182.67 ppm; MS (CI): *m/z* 396.0 (MH^+, 100). Anal. calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.60; H, 6.20; N, 3.48.

(2*Z*)-7-[(Dipropylamino)methyl]-6-hydroxy-2-(3,4,5-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (6e)

Yellow solid (65% yield); mp: 172–174 °C; IR (KBr): ν_{max} 3472, 2962, 1686, 1603, 1460, 1269, 1134, 1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (6H, t, $^3J = 7.4$ Hz, $N(CH_2CH_2C\underline{H}_3)_2$), 1.57–1.65 (4H, m, $N(CH_2C\underline{H}_2CH_3)_2$), 2.57–2.60 (4H, m, $N(C\underline{H}_2CH_2CH_3)_2$), 3.91 (3H, s, OMe-4′), 3.94 (6H, s, OMe-3′, 5′), 4.00 (2H, s, CH_2-7), 6.63 (1H, d, $^3J = 8.5$ Hz, H-5), 6.72 (1H, s, H-2a), 7.14 (2H, s, H-2′,6′), 7.61 ppm (1H, d, $^3J = 8.5$ Hz, H-4); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.41, 18.21, 49.35, 54.41, 55.72, 60.11, 103.92, 108.31, 109.78, 110.21, 114.28, 124.45, 127.67, 138.61, 147.28, 152.76, 165.26, 170.30, 180.21 ppm; MS (CI): *m/z* 442.3 (MH^+, 100). Anal. calcd for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08; N, 3.17. Found: C, 68.15; H, 6.79; N, 2.99.

(2*Z*)-2-Benzylidene-7-{[bis(2-methoxyethyl)amino]methyl}-6-hydroxy-1-benzofuran-3(2*H*)-one (7a)

Yellow solid (69% yield); mp: 81–82 °C; IR (KBr): ν_{max} 2879, 1697, 1604, 128, 1187, 1128, 1105, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.96 (4H, t, $^3J = 5.3$ Hz, $N(C\underline{H}_2CH_2OMe)_2$), 3.35 (6H, s, $CH_2OC\underline{H}_3$), 3.59 (4H, t, $^3J = 5.3$ Hz, $N(CH_2C\underline{H}_2OMe)_2$), 4.19 (2H, s, CH_2-7), 6.68 (1H, d, $^3J = 8.4$ Hz, H-5), 6.79 (1H, s, H-2a), 7.33–7.51 (3H, m, H-3′, 4′, 5′), 7.61 (1H, d, $^3J = 8.4$ Hz, H-4), 7.85 ppm (2H, d, $^3J = 8.8$ Hz, H-2′, 6′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 50.15, 53.62, 58.93, 69.87, 105.39, 111.28, 113.35, 113.92, 125.25, 128.95, 129.51, 131.22, 132.76, 148.12, 165.94, 167.58, 182.94 ppm; MS (CI): *m/z* 384.0 (MH^+, 100). Anal. calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 69.15; H, 6.39; N, 3.71.

(2*Z*)-7-{[Bis(2-methoxyethyl)amino]methyl}-6-hydroxy-2-(4-methoxybenzylidene)-1-benzofuran-3(2*H*)-one (7b)

Yellow solid (83% yield); mp: 109–111 °C; IR (KBr): ν_{max} 3421, 2935, 1687, 1601, 1512, 1400, 1255, 1132, 1038 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.84 (4H, t, $^3J = 5.3$ Hz, $N(C\underline{H}_2CH_2OMe)_2$), 3.22 (6H, s, $CH_2OC\underline{H}_3$), 3.51 (4H, t, $^3J = 5.5$ Hz, $N(CH_2C\underline{H}_2OMe)_2$), 3.82 (3H, s, OMe-4′), 4.10 (2H, s, CH_2-7), 6.63 (1H, d, $^3J = 8.4$ Hz, H-5), 6.76 (1H, s, H-2a), 7.05 (2H, d, $^3J = 8.8$ Hz, H-3′, 5′), 7.52 (1H, d, $^3J = 8.4$ Hz, H-4), 7.91 ppm (2H, d, $^3J = 8.8$ Hz, H-2′, 6′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 48.68, 52.56, 55.30, 57.99, 69.13, 106.22, 110.44, 112.22, 113.18, 114.49, 124.14, 124.62, 132.83, 146.19, 160.26, 165.12, 166.96,

181.10 ppm; MS (CI): *m/z* 414.0 (MH^+, 100). Anal. calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.93; H, 6.73; N, 3.53.

(2*Z*)-7-{[Bis(2-methoxyethyl)amino]methyl}-2-(3,4-dimethoxybenzylidene)-6-hydroxy-1-benzofuran-3(2*H*)-one (7c)

Yellow solid (83% yield); mp: 80–82 °C; IR (KBr): ν_{max} 2835, 1687, 1593, 1519, 1322, 1261, 1123, 1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.95 (4H, t, $^3J = 5.2$ Hz, $N(C\underline{H}_2CH_2OMe)_2$), 3.32 (6H, s, $CH_2OC\underline{H}_3$), 3.59 (4H, t, $^3J = 5.2$ Hz, $N(CH_2C\underline{H}_2OMe)_2$), 3.93, 3.96 (each 3H, 2 s, OMe-3′,4′), 4.18 (2H, s, CH_2-7), 6.69 (1H, d, $^3J = 8.4$ Hz, H-5), 6.74 (1H, s, H-2a), 6.93 (1H, d,$^3J = 8.4$ Hz, H-5′), 7.40 (1H, dd, $^3J = 8.4$ Hz, $^4J = 2.0$ Hz, H-6′), 7.49 (1H, d, $^4J = 2.0$ Hz, H-2′), 7.59 ppm (1H, d, $^3J = 8.4$ Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 50.23, 53.67, 55.88, 56.07, 58.96, 69.80, 105.09, 111.35, 111.86, 113.60, 113.67, 113.81, 125.24, 125.47, 125.69, 147.12, 149.06, 150.53, 165.56, 167.08, 182.69 ppm; MS (CI): *m/z* 444.2 (MH^+, 100). Anal. calcd for $C_{24}H_{29}NO_7$: C, 65.00; H, 6.59; N, 3.16. Found: C, 64.81; H, 6.82; N, 3.00.

(2*Z*)-2-(1,3-Benzodioxol-5-ylmethylene)-7-{[bis(2-methoxyethyl)amino]methyl}-6-hydroxy-1-benzofuran-3(2*H*)-one (7d)

Yellow solid (77% yield); mp: 114–116 °C; IR (KBr): ν_{max} 3421. 1645, 1614, 1564, 1450, 1402, 1257, 1107, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.97 (4H, t, $^3J = 5.3$ Hz, $N(C\underline{H}_2CH_2OMe)_2$), 3.35 (6H, s, $CH_2OC\underline{H}_3$), 3.60 (4H, t, $^3J = 5.3$ Hz, $N(CH_2C\underline{H}_2OMe)_2$), 4.19 (2H, s, CH_2-7), 6.03 (2H, s, OCH_2O), 6.68 (1H, d, $^3J = 8.5$ Hz, H-5), 6.71 (1H, s, H-2a), 6.87 (1H, d, $^3J = 8.0$ Hz, H-7′), 7.25 (1H, dd, $^3J = 8.0$ Hz, $^4J = 1.8$ Hz, H-6′), 7.48 (1H, d, $^4J = 1.8$ Hz, H-4′), 7.59 ppm (1H, d, $^3J = 8.5$ Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 50.32, 53.61, 58.97, 70.03, 101.63, 105.54, 108.93, 110.36, 111.58, 113.56, 113.83, 125.07, 127.08, 127.15, 147.12, 148.26, 148.93, 165.60, 167.42, 182.81 ppm; MS (CI): *m/z* 428.1 (MH^+, 100). Anal. calcd for $C_{23}H_{25}NO_7$: C, 64.63; H, 5.90; N, 3.28. Found: C, 64.78; H, 5.67; N, 3.52.

(2*Z*)-7-{[Bis(2-methoxyethyl)amino]methyl}-6-hydroxy-2-(3,4,5-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (7e)

Yellow solid (88% yield); mp: 119–120 °C; IR (KBr): ν_{max} 2878, 1692, 1602, 1502, 1344, 1185, 1117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.91 (4H, t, $^3J = 5.2$ Hz, $N(C\underline{H}_2CH_2OMe)_2$), 3.33 (6H, s, $CH_2OC\underline{H}_3$), 3.58 (4H, t, $^3J = 5.2$ Hz, $N(CH_2C\underline{H}_2OMe)_2$), 3.92 (3H, s, OMe-4′), 3.95 (6H, s, OMe-3′, 5′), 4.14 (2H, s, CH_2-7), 6.67 (1H, d, $^3J = 8.5$ Hz, H-5), 6.72 (1H, s, H-2a), 7.15 (2H, s, H-2′, 6′), 7.61 ppm (1H, d, $^3J = 8.5$ Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 50.26, 53.64, 56.17, 58.95, 61.11, 69.69, 105.08, 108.61, 111.60, 113.46, 113.94, 125.37, 128.11, 139.68, 147.67, 153.34, 165.67, 167.25, 182.63 ppm; MS (CI): *m/z* 474.2 (MH^+, 100). Anal. calcd for $C_{25}H_{31}NO_8$: C, 63.41; H, 6.60; N, 2.96. Found: C, 63.30; H, 6.86; N, 3.11.

(2*Z*)-7-{[Bis(2-methoxyethyl)amino]methyl}-6-hydroxy-2-(2,3,4-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (7f)

Yellow solid (79% yield); mp: 105–107 °C; IR (KBr): ν_{max} 2943, 1691, 1605, 1594, 1303, 1130, 1091, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.93 (4H, t, $^3J = 5.2$ Hz, $N(C\underline{H}_2CH_2OMe)_2$), 3.35 (6H, s, $CH_2OC\underline{H}_3$), 3.59 (4H, t, $^3J = 5.2$ Hz, $N(CH_2C\underline{H}_2OMe)_2$), 3.90, 3.94, 3.97 (each 3H, 3 s, OMe-2′, 3′, 4′), 4.15 (2H, s, CH_2-7), 6.66 (1H, d, $^3J = 8.4$ Hz, H-5), 6.82 (1H, d, $^3J = 8.9$ Hz, H-5′), 7.20 (1H, s, H-2a), 7.61 (1H, d, $^3J = 8.4$ Hz, H-4), 7.96 ppm (1H, d, $^3J = 8.9$ Hz, H-6′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 50.24, 53.71, 56.15, 58.90, 60.97, 61.92, 70.01, 105.35, 105.58, 107.80, 113.59, 113.71, 119.84, 125.00, 126.67, 142.30, 147.74, 153.93, 155.15, 165.46, 167.08, 182.74 ppm; MS (CI): *m/z* 474.2 (MH^+, 100). Anal. calcd for $C_{25}H_{31}NO_8$: C, 63.41; H, 6.60; N, 2.96. Found: C, 63.70; H, 6.36; N, 2.75.

(2*Z*)-2-Benzylidene-6-hydroxy-7-(piperidin-1-ylmethyl)-1-benzofuran-3(2*H*)-one (8a)

Yellow solid (85% yield); mp: 187–189 °C; IR (KBr): ν_{max} 2950, 1678, 1608, 1502, 1451, 1371, 1279, 1179, 1117, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.36–3.46 (10H, m, piperidine moiety), 4.06 (2H, s, CH_2-7), 6.73 (1H, d, $^3J = 8.5$ Hz, H-5), 6.79 (1H, s, H-2a), 7.35–7.50 (3H, m, H-3′, 4′, 5′), 7.62 (1H, d, $^3J = 8.5$, H-4), 7.82 (2H, d, $^3J = 8.5$ Hz, H-2′, 6′), 10.08 ppm (1H, br. s, OH-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.40, 25.35, 53.43, 53.87, 103.34, 111.49, 113.26, 113.97, 125.74, 129.05, 129.63, 131.21, 132.69, 148.05, 166.21, 168.01, 182.76 ppm; MS (CI): *m/z* 336.1 (MH^+, 100). Anal. calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.03; H, 6.09; N, 4.34.

(2*Z*)-6-Hydroxy-2-(4-methoxybenzylidene)-7-(piperidin-1-ylmethyl)-1-benzofuran-3(2*H*)-one (8b)

Yellow solid (91% yield); mp: 125–126 °C; IR (KBr): ν_{max} 2935, 1692, 1598, 1509, 14477, 1256, 1187, 1124, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24–1.95, 2.21–3.37 (6H, 4H, 2 m, piperidine moiety), 3.80 (3H, s, OMe-4′), 3.92 (2H, s, CH_2-7), 6.57 (1H, d, $^3J = 8.5$ Hz, H-5), 6.69 (1H, s, H-2a), 6.92 (2H, d, $^3J = 8.5$ Hz, H-3′, 5′), 7.52 (1H, d, $^3J = 8.5$ Hz, H-4), 7.72 (2H, d, $^3J = 8.8$ Hz, H-2′, 6′), 11.51 ppm (1H, br. s, OH-6); ^{13}C NMR (100 MHz, $CDCl_3$):

δ 23.64, 25.66, 53.97, 54.16, 55.38, 103.94, 111.41, 113.27, 113.57, 114.48, 124.89, 125.32, 132.89, 146.95, 160.65, 165.52, 167.83, 182.60 ppm; MS (CI): *m/z* 366.0 (MH^+, 100). Anal. calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.39; H, 6.62; N, 3.59.

(2*Z*)-2-(3,4-Dimethoxybenzylidene)-6-hydroxy-7-(piperidin-1-ylmethyl)-1-benzofuran-3(2*H*)-one (8c)

Yellow solid (82% yield); mp: 180–182 °C; IR (KBr): ν_{max} 3446, 2937, 2677, 1676, 1616, 1512, 1458, 1269, 1144, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33– 3.46 (10H, m, piperidine moiety), 3.92 (2H, s, CH_2-7), 3.95, 3.98 (each 3H, 2 s, OMe-3′,4′), 6.63 (1H, d, $^3J = 8.4$ Hz, H-5), 6.76 (1H, s, H-2a), 6.95 (1H, d, $^3J = 8.4$ Hz, H-5′), 7.40 (1H, dd, $^3J = 8.4$ Hz, $^4J = 2.0$ Hz, H-6′), 7.51 (1H, d, $^4J = 2.0$ Hz, H-2′), 7.59 ppm (1H, d, $^3J = 8.4$ Hz, H-4); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.05, 24.85, 52.06, 53.05, 55.29, 55.54, 104.08, 110.17, 110.65, 111.80, 113.39, 114.05, 124.34, 124.92, 125.02, 146.54, 148.55, 149.99, 165.53, 169.26, 180.35 ppm; MS (CI): *m/z* 396.2 (MH^+, 100). Anal. calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.97; H, 6.51; N, 3.36.

(2*Z*)-2-(1,3-Benzodioxol-5-ylmethylene)-6-hydroxy-7-(piperidin-1-ylmethyl)-1-benzofuran-3(2*H*)-one (8d)

Yellow solid (74% yield); mp: 163–165 °C; IR (KBr): ν_{max} 3406, 2949, 1678, 1595, 1448, 1331, 1250, 1132, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.32– 3.56 (10H, m, piperidine moiety), 3.95 (2H, s, CH_2-7), 6.05 (2H, s, OCH_2O), 6.62 (1H, d, $^3J = 8.4$ Hz, H-5), 6.72 (1H, s, H-2a), 6.88 (1H, d, $^3J = 8.1$ Hz, H-7′), 7.14–7.33 (1H, m, H-6′), 7.46 (1H, d, $^4J = 1.7$ Hz, H-4′) 7.59 (1H, d, $^3J = 8.4$ Hz, H-4), 10.08 ppm (1H, br. s, OH-6); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.15, 25.00, 51.88, 53.08, 101.49, 104.46, 108.75, 109.21, 109.68, 109.74, 114.57, 124.19, 126.43, 126.57, 146.87, 147.69, 148.15, 165.91, 170.67, 180.02 ppm; MS (CI): *m/z* 380.0 (MH^+, 100). Anal. calcd for $C_{22}H_{21}NO_5$: C, 69.65; H, 5.58; N, 3.69. Found: C, 69.74; H, 5.47; N, 3.88.

(2*Z*)-2-(3,4-Dimethoxybenzylidene)-6-hydroxy-7-(morpholin-4-ylmethyl)-1-benzofuran-3(2*H*)-one (9c)

Yellow solid (67% yield); mp: 179–181 °C; IR (KBr): ν_{max} 2928, 2836, 1671, 1601,1435, 1264, 1133 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.55–2.88 (4H, m, N($C\underline{H}_2CH_2$)O), 3.74–3.86 (4H, m, N($CH_2C\underline{H}_2$)O), 3.93, 3.96 (each 3H, 2 s, OMe-3′,4′), 3.97 (2H, s, CH_2-7), 6.66 (1H, d, $^3J = 8.4$ Hz, H-5), 6.75 (1H, s, H-2a), 6.94 (1H, d,$^3J = 8.4$ Hz, H-5′), 7.39 (1H, dd, $^3J = 8.3$ Hz, $^4J = 1.9$ Hz, H-6′), 7.45 (1H, d, $^4J = 1.9$ Hz, H-2′), 7.60 ppm (1H, d, $^3J = 8.4$ Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 53.22, 53.76, 55.84, 56.07, 66.55, 103.40, 103.47, 111.41, 112.28, 113.52, 113.60, 114.02, 125.48, 125.52, 146.92, 149.06, 150.65, 165.58, 166.34, 182.56 ppm; MS (CI): *m/z* 398.0 (MH^+, 100). Anal. calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.21; H, 6.08; N, 3.30.

(2*Z*)-2-(1,3-Benzodioxol-5-ylmethylene)-6-hydroxy-7-(morpholin-4-ylmethyl)-1-benzofuran-3(2*H*)-one (9d)

Yellow solid (59% yield); mp: 189–191 °C; IR (KBr): ν_{max} 3419, 1668, 1599, 1502, 1442, 1254, 1119, 1038 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.52–2.61 (4H, m, N($C\underline{H}_2CH_2$)O), 3.57–3.65 (4H, m, N($CH_2C\underline{H}_2$)O), 3.78 (2H, s, CH_2-7), 6.10 (2H, s, OCH_2O), 6.65–6.77 (2H, m, H-2a, 5), 7.03 (1H, d, $^3J = 8.1$ Hz, H-7′), 7.45 (1H, dd, $^3J = 8.1$ Hz, $^4J = 1.7$ Hz, H-6′), 7.52 (1H, d, $^3J = 8.3$ Hz, H-4), 7.58 ppm (1H, d, $^4J = 1.6$ Hz, H-4′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 50.80, 52.93, 66.04, 101.60, 106.36, 108.79, 109.79, 110.64, 112.44, 112.74, 124.31, 126.25, 126.95, 146.18, 147.75, 148.51, 165.49, 165.86, 181.24 ppm; MS (CI): *m/z* 382.3 (MH^+, 100). Anal. calcd for $C_{21}H_{19}NO_6$: C, 66.14; H, 5.02; N, 3.67. Found: C, 65.96; H, 5.21; N, 3.90.

(2*Z*)-6-Hydroxy-7-(morpholin-4-ylmethyl)-2-(3,4,5-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (9e)

Yellow solid (74% yield); mp: 197–199 °C; IR (KBr): ν_{max} 2956, 2835, 1691, 1603, 1504, 1448, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.48–2.93 (4H, m, N($C\underline{H}_2CH_2$)O), 3.78–3.87 (4H, m, N($CH_2C\underline{H}_2$)O), 3.91 (3H, s, OMe-4′), 3.94 (6H, s, OMe-3′, 5′), 3.99 (2H, s, CH_2-7),6.63–6.78 (2H, m, H-2a, 5), 7.11 (2H, s, H-2′, 6′), 7.62 ppm (1H, d, $^3J = 8.4$ Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.23, 53.53, 56.20, 61.15, 66.38, 103.26, 108.68, 112.14, 113.76, 113.91, 125.85, 127.90, 139.90, 147.46, 153.39, 165.81, 166.43, 182.53 ppm; MS (CI): *m/z* 428.2 (MH^+, 100). Anal. calcd for $C_{23}H_{25}NO_7$: C, 64.63; H, 5.90; N, 3.28. Found: C, 64.37; H, 6.18; N, 3.50.

(2*Z*)-6-Hydroxy-2-(4-methoxybenzylidene)-7-[(4-methylpiperazin-1-yl)methyl]-1-benzofuran-3(2*H*)-one (10b)

Yellow solid (80% yield); mp: 156–158 °C; IR (KBr): ν_{max} 2801, 1692, 1601, 1509, 1257, 1183, 1129, 1032, 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.36 (3H, s, N′-CH_3), 2.39–3.15 (8H, m, piperazine moiety), 3.85 (3H, s, OMe-4′), 3.98 (2H, s, CH_2-7), 6.62 (1H, d, $^3J = 8.5$ Hz, H-5), 6.75 (1H, s, H-2a), 6.97 (2H, d, $^3J = 8.9$ Hz, H-3′, 5′), 7.58 (1H, d, $^3J = 8.5$ Hz, H-4), 7.77 (2H, d, $^3J = 8.8$ Hz,

H-2′, 6′), 10.25 ppm (1H, br. s, OH-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.64, 52.40, 53.39, 54.64, 55.37, 103.93, 111.74, 113.33, 113.75, 114.49, 125.03, 125.18, 132.94, 146.77, 160.72, 165.40, 166.68, 182.62 ppm; MS (CI): *m/z* 381.2 (MH^+, 100). Anal. calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.73; H, 6.55; N, 7.49.

(2*Z*)-2-(3,4-Dimethoxybenzylidene)-6-hydroxy-7-[(4-methylpiperazin-1-yl)methyl]-1-benzofuran-3(2*H*)-one (10c)

Yellow solid (86% yield); mp: 173–175 °C; IR (KBr): ν_{max} 3423, 2941, 2692, 1662, 1595, 1514, 1452, 1334, 1263, 1128 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09–3.47 (11H, m, piperazine moiety), 3.95 (3H, s) and 3.97 (5H, m, CH_2-7, OMe-3′,4′,), 6.65 (1H, d, ^3J = 8.4 Hz, H-5), 6.78 (1H, s, H-2a), 6.95 (1H, d, ^3J = 8.5 Hz, H-5′), 7.38 (1H, dd, ^3J = 8.5 Hz, ^4J = 1,7 Hz, H-6′), 7.55 (1H, d, ^4J = 1.7 Hz, H-2′), 7.62 ppm (1H, d, ^3J = 8.4 Hz, H-4); ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.53, 50.86, 52.23, 54.35, 55.34, 55.58, 105.74, 110.79, 111.83, 111.92, 113.24, 113.37, 124.35, 124.81, 125.32, 146.26, 148.58, 150.16, 165.57, 166.78, 180.95 ppm; MS (CI): *m/z* 411.1 (MH^+, 100). Anal. calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.53; H, 6.54; N, 6.65.

(2*Z*)-2-(1,3-Benzodioxol-5-ylmethylene)-6-hydroxy-7-[(4-methylpiperazin-1-yl)methyl]-1-benzofuran-3(2*H*)-one (10d)

Yellow solid (69% yield); mp: 190–912 °C; IR (KBr): ν_{max} 3410, 2937, 1689, 1603, 1500, 1446, 1342, 1257, 1188, 1036 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.17 (3H, s, N′-CH_3), 2.25–2.48 (4H, m) and 2.52–2.78 (4 H, m, piperazine ring), 3.84 (2H, s, CH_2-7), 6.11 (2H, s, OCH_2O), 6.65 (1H, d, ^3J = 8.5 Hz, H-5), 6.72 (1H, s, H-2a), 7.03 (1H, d, ^3J = 8.1 Hz, H-7′), 7.38–7.61 ppm (3H, m, H-4, 4′ 6′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.49, 50.77, 52.16, 54.36, 101.58, 105.96, 108.83, 109.81, 110.27, 111.67, 113.34, 124.25, 126.33, 126.84, 146.37, 147.74, 148.43, 165.75, 167.10, 180.90 ppm; MS (CI): *m/z* 395.1 (MH^+, 100). Anal. calcd for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.84; H, 5.83; N, 6.92.

(2*Z*)-6-Hydroxy-7-[(4-methylpiperazin-1-yl)methyl]-2-(3,4,5-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (10e)

Yellow solid (82% yield); mp: 201–203 °C; IR (KBr): ν_{max} 2936, 2810, 1692, 1603, 1422, 1262, 1124, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02–3.31 (11H, m, piperazine moiety), 3.91 (3H, s, OMe-4′), 3.93 (6H, s, OMe-3′, 5′), 3.94 (2H, s, CH_2-7), 6.66 (1H, d, ^3J = 8.5 Hz, H-5), 6.73 (1H, s, H-2a), 7.14 (2H, s, H-2′, 6′), 7.62 ppm (1H, d, ^3J = 8.5 Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 45.80, 52.95, 53.54, 54.67, 56.06, 61.10, 103.98, 108.54, 111.80, 113.59, 113.61, 125.33, 127.98, 139.69, 147.54, 153.30, 165.49, 166.87, 182.56 ppm; MS (CI): *m/z* 441.0 (MH^+, 100). Anal. calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.15; H, 6.30; N, 6.15.

(2*Z*)-6-Hydroxy-7-[(4-methylpiperazin-1-yl)methyl]-2-(2,3,4-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (10f)

Yellow solid (81% yield); mp: 188–190 °C; IR (KBr): ν_{max} 3425, 1635, 1608, 1556, 1456, 1402, 1279, 1093 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.17 (3H, s, N′-CH_3), 2.27–2.44 (4H, m) and 2.55–2.72 (4H, m, piperazine moiety), 3.78 (3H, s) and 3.88 (8H, s, OMe-2′, 3′, 4′, CH_2-7), 6.65 (1H, d, ^3J = 8.6 Hz, H-5), 6.88 (1H, s, H-2a), 7.01 (1H, d, ^3J = 8.9 Hz, H-5′), 7.52 (1H, d, ^3J = 8.6 Hz, H-4), 7.97 ppm (1H, d, ^3J = 8.9 Hz, H-6′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.43, 50.87, 51.99, 54.34, 56.01, 60.42, 61.62, 103.62, 105.67, 108.62, 111.90, 113.19, 118.36, 124.31, 126.16, 141.57, 146.90, 152.80, 154.88, 165.53, 166.80, 180.97 ppm; MS (CI): *m/z* 441.2 (MH^+, 100). Anal. calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.21; H, 6.67; N, 6.48.

(2*Z*)-6-Hydroxy-7-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}-2-(4-methoxybenzylidene)-1-benzofuran-3(2*H*)-one (11b)

Yellow solid (58% yield); mp: 179–181 °C; IR (KBr): ν_{max} 3410, 2958, 1668, 1605, 1510, 1443, 1254, 1132, 1028 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.40 (2H, t, ^3J = 6.1 Hz, N′C<u>H</u>$_2$$CH_2OH$), 2.52–2.69 (8H, m, CH_2-2″,3″, 5″,6″), 3.49 (2H, t, ^3J = 6.1 Hz, N′CH_2C<u>H</u>$_2$OH), 3.83 (3H, s, OMe-4′), 3.91 (2H, s, CH_2-7), 6.65 (1H, d, ^3J = 8.4 Hz, H-5), 6.75 (1H, s, H-2a), 7.07 (2H, d, ^3J = 8.7 Hz, H-3′, 5′), 7.51 (1H, d, ^3J = 8.4 Hz, H-4), 7.92 ppm (2H, d, ^3J = 8.7 Hz, H-2′, 6′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 50.97, 52.14, 52.84, 55.33, 58.44, 59.96, 105.57, 110.26, 111.82, 113.27, 114.55, 124.25, 124.70, 132.83, 146.27, 160.22, 165.59, 167.09, 180.96 ppm; MS (CI): *m/z* 411.0 (MH^+, 100). Anal. calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.51; H, 6.24; N, 6.66.

(2*Z*)-2-(3,4-Dimethoxybenzylidene)-6-hydroxy-7-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}-1-benzofuran-3(2*H*)-one (11c)

Yellow solid (63% yield); mp: 180–182 °C; IR (KBr): ν_{max} 2947, 1682, 1600, 1513, 1298, 1270, 1139, 1123, 1039 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08–3.36 (10H, m, N′C<u>H</u>$_2$$CH_2OH$ and piperazine ring), 3.65 (2H, t, ^3J = 5.4 Hz, N′CH_2C<u>H</u>$_2$OH), 3.95, 3.98 (each 3H, 2 s, OMe-3′,4′), 3.97 (2H, s, CH_2-7), 6.65 (1H, d, ^3J = 8.4 Hz, H-5), 6.78 (1H, s, H-2a), 6.95 (1H, d,^3J = 8.4 Hz, H-5′),

7.41 (1H, dd, $^3J = 8.4$ Hz, $^4J = 2.0$ Hz, H-6′), 7.50 (1H, d, $^4J = 2.0$ Hz, H-2′), 7.62 ppm (1H, d, $^3J = 8.4$ Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 52.68, 52.87, 53.56, 55.88, 56.10, 57.93, 59.33, 103.93, 111.43, 112.19, 113.52, 113.63, 113.92, 125.31, 125.54, 125.56, 147.02, 149.08, 150.64, 165.45, 166.66, 182.66 ppm; MS (CI): *m/z* 441.1 (MH^+, 100). Anal. calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.72; H, 6.70; N, 6.09.

(2*Z*)-2-(1,3-Benzodioxol-5-ylmethylene)-6-hydroxy-7-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}-1-benzofuran-3(2*H*)-one (11d)

Yellow solid (55% yield); mp: 162–164 °C; IR (KBr): ν_{max} 2944, 1690, 1608, 1499, 1451, 1291, 1262, 1115, 1042 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.47–2.91 (10H, m, N′C$\underline{H}_2$CH_2OH and piperazine ring), 3.64 (2H, t, $^3J = 5.3$ Hz, N′CH_2C$\underline{H}_2$OH), 3.96 (2H, s, CH_2-7), 6.01 (2H, s, OCH_2O), 6.60 (1H, d, $^3J = 8.3$ Hz, H-5), 6.68 (1H, s, H-2a), 6.84 (1H, d, $^3J = 8.0$ Hz, H-7′), 7.19–7.27 (1H, m, H-6′), 7.40 (1H, d, $^4J = 1.6$ Hz, H-4′), 7.56 ppm (1H, d, $^3J = 8.3$ Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.65, 52.69, 53.51, 57.90, 59.28, 101.64, 104.04, 108.93, 110.32, 111.93, 113.55, 113.75, 125.21, 126.83, 127.20, 146.88, 148.23, 149.02, 165.48, 166.87, 182.66 ppm; MS (CI): *m/z* 425.2 (MH^+, 100). Anal. calcd for $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 65.29; H, 5.93; N, 6.88.

(2*Z*)-6-Hydroxy-7-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}-2-(3,4,5-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one (11e)

Yellow solid (68% yield); mp: 187–189 °C; IR (KBr): ν_{max} 2939, 2820, 1688, 1602, 1451, 1309, 1262, 1133, 1120 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39–3.08 (10H, m, N′C$\underline{H}_2$CH_2OH and piperazine ring), 3.66 (2H, t, $^3J = 5.4$ Hz, N′CH_2C$\underline{H}_2$OH), 3.93 (3H, s, OMe-4′), 3.95 (8H, s, CH_2-7, OMe-3′, 5′), 6.67 (1H, d, $^3J = 8.5$ Hz, H-5), 6.74 (1H, s, H-2a), 7.15 (2H, s, H-2′, 6′), 7.63 ppm (1H, d, $^3J = 8.5$ Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.59, 53.06, 53.50, 56.12, 58.03, 59.29, 61.10, 103.93, 108.59, 108.67, 111.85, 113.62, 125.35, 127.97, 139.72, 147.53, 153.31, 165.50, 166.85, 182.57 ppm; MS (CI): *m/z* 471.2 (MH^+, 100). Anal. calcd for $C_{25}H_{30}N_2O_7$: C, 63.82; H, 6.43; N, 5.95. Found: C, 64.10; H, 6.71; N, 6.13.

General procedure for the synthesis of diacetates 12

A mixture of a Mannich base **3a–3d** (2 mmol) and 200 mg (2 mmol) of potassium acetate in 5 mL of acetic anhydride was refluxed for 5 min and cooled to room temperature. The mixture was diluted with water to afford a precipitate of **12a–12d**, that was recrystallized from acetonitrile–water.

[(2*Z*)-6-(Acetyloxy)-2-benzylidene-3-oxo-2,3-dihydro-1-benzofuran-7-yl]methyl acetate (12a)

Yellow solid (93% yield); mp: 145–147 °C; IR (KBr): ν_{max} 1770, 1738, 1706, 1605, 1434, 1255, 1188, 1129 cm^{-1};; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.09 (3H, s, CH_3COO-6), 2.39 (3H, s, C$\underline{H}_3$COOCH_2-7), 5.36 (2H, s, CH_2-7), 6.93 (1H, s, H-2a), 7.00 (1H, d, $^3J = 8.3$ Hz, H-5), 7.39–7.51 (3H, m, H-3′, 4′, 5′), 7.82 (1H, d, $^3J = 8.4$ Hz, H-4), 7.91 ppm (2H, d, $^3J = 8.3$ Hz, H-2′, 6′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.81, 20.94, 54.73, 114.02, 114.44, 118.87, 119.77, 125.70, 129.16, 130.34, 131.80, 132.15, 147.22, 156.25, 165.79, 168.60, 170.63, 183.39 ppm; MS (CI): *m/z* 353.0 (MH^+, 100). Anal. calcd for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found: C, 68.33; H, 4.45.

[(2*Z*)-6-(Acetyloxy)-2-(4-methoxybenzylidene)-3-oxo-2,3-dihydro-1-benzofuran-7-yl]methyl acetate (12b)

Yellow solid (81% yield); mp: 135–137 °C; IR (KBr): ν_{max} 2936, 2840, 1771, 1735, 1650, 1601, 1512, 1431, 1256, 1195, 1134 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (3H, s, CH_3COO-6), 2.39 (3H, s, C$\underline{H}_3$COOCH_2-7), 3.88 (3H, s, OMe-4′), 5.36 (2H, s, CH_2-7), 6.92 (1H, s, H-2a), 6.96–7.03 (3H, m, H-5, 3′, 5′), 7.82 (1H, d, $^3J = 8.3$ Hz, H-4), 7.88 ppm (2H, d, $^3J = 8.8$ Hz, H-2′, 6′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.77, 20.87, 54.61, 55.45, 114.10, 114.27, 114.67, 118.51, 119.97, 124.71, 125.49, 133.63, 146.07, 155.81, 161.35, 165.26, 168.60, 170.58, 183.02 ppm; MS (CI): *m/z* 383.2 (MH^+, 100). Anal. calcd for $C_{21}H_{18}O_7$: C, 65.97; H, 4.75. Found: C, 66.11; H, 5.03.

[(2*Z*)-6-(Acetyloxy)-2-(3,4-dimethoxybenzylidene)-3-oxo-2,3-dihydro-1-benzofuran-7-yl]methyl acetate (12c)

Yellow solid (91% yield); mp: 190–192 °C; IR (KBr): ν_{max} 2963, 2845, 1772, 1736, 1647, 1595, 1514, 1259, 1184, 1127, 1065, 1021 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (3H, s, CH_3COO-6), 2.38 (3H, s, C$\underline{H}_3$COOCH_2-7), 3.94, 3.96 (each 3H, 2 s, OMe-3′, 4′), 5.32 (2H, s, CH_2-7), 6.89 (1H, s, H-2a), 6.94 (1H, d, $^3J = 8.3$ Hz, H-5), 6.98 (1H, d,$^3J = 8.4$ Hz, H-5′), 7.35–7.47 (1H, m, H-6′), 7.62 (1H, d, $^4J = 2.0$ Hz, H-2′), 7.81 ppm (1H, d, $^3J = 8.3$ Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.81, 20.97, 54.68, 55.92, 56.10, 111.32, 113.56, 114.06, 114.68, 118.74, 120.00, 125.08, 125.70, 126.52, 146.22, 149.29, 151.26, 156.07, 165.25, 168.72, 170.59, 183.00 ppm; MS (CI): *m/z* 413.2 (MH^+, 100). Anal. calcd for $C_{22}H_{20}O_8$: C, 64.08; H, 4.89. Found: C, 63.92; H, 4.60.

[(2*Z*)-6-(Acetyloxy)-2-(1,3-benzodioxol-5-ylmethylene)-3-oxo-2,3-dihydro-1-benzofuran-7-yl] methyl acetate (12d)

Yellow solid (88% yield); mp: 170–172 °C; IR (KBr): ν_{max} 1765, 1737, 1704, 1649, 1611, 1257, 1200, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.09 (3H, s, CH_3COO-6), 2.39 (3H, s, $C\underline{H}_3COOCH_2$-7), 5.35 (2H, s, CH_2-7), 6.05 (2H, s, OCH_2O), 6.86 (1H, s, H-2a), 6.89 (1H, d, $^3J = 8.3$ Hz, H-5), 6.99 (1H, d, $^3J = 8.3$ Hz, H-7′), 7.29–7.35 (1H, m, H-6′), 7.58 (1H, d, $^4J = 1.6$ Hz, H-4′), 7.81 ppm (1H, d, $^3J = 8.3$ Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.87, 20.99, 54.71, 101.85, 109.03, 110.75, 114.34, 114.46, 118.74, 119.98, 125.61, 126.42, 128.12, 146.20, 148.51, 149.74, 155.95, 165.36, 168.74, 183.12 ppm; MS (CI): *m/z* 397.0 (MH^+, 100). Anal. calcd for $C_{21}H_{16}O_8$: C, 63.64; H, 4.07. Found: C, 63.87; H, 4.22.

General procedure for the synthesis of 7-methoxymethyl-6-hydroxyaurones 13a–13d

A mixture of diacetate **12a–12d** (2 mmol) and 0.1 mL of concentrated hydrochloric acid in 10 mL of methanol was refluxed for 16–24 h. The mixture was cooled and diluted with water, and the resulting precipitate was collected by filtration. The products were purified by chromatography using 1:20 methanol-dichloromethane.

(2*Z*)-2-Benzylidene-6-hydroxy-7-(methoxymethyl)-1-benzofuran-3(2*H*)-one (13a)

Yellow solid (43% yield); mp: 332–333 °C; IR (KBr): ν_{max} 2893, 1677, 1583, 1442, 1305, 1284, 1135, 1061 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.34 (3H, s, $C\underline{H}_3OCH_2$-7), 4.59 (2H, s, CH_2-7), 6.76–6.86 (2H, m, H-2a, 5), 7.41–7.55 (3H, m, H-3′, 4′, 5′), 7.61 (1H, d, $^3J = 8.5$ Hz, H-4), 7.95–8.01 (2H, d, $^3J = 8.8$ Hz, H-2′, 6′), 11.34 ppm (1H, br. s, OH-6); ^{13}C NMR (100 MHz, DMSO-d_6): δ 57.63, 61.60, 108.36, 110.43, 112.47, 112.61, 125.49, 129.02, 129.68, 131.08, 132.17, 147.37, 164.88, 166.86, 181.70 ppm; MS (CI): *m/z* 251.0 (MH^+-32, 100). Anal. calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.46; H, 5.19.

(2*Z*)-6-Hydroxy-2-(4-methoxybenzylidene)-7-(methoxymethyl)-1-benzofuran-3(2*H*)-one (13b)

Yellow solid (53% yield); mp: 185–187 cels; IR (KBr): ν_{max} 3097, 2926, 1674, 1600, 1446, 1287, 1263, 1137, 1064 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.33 (3H, s, $C\underline{H}_3OCH_2$-7), 3.83 (3H, s, OMe-4′), 4.59 (2H, s, CH_2-7), 6.76–6.84 (2H, m, H-2a, 5), 7.09 (2H, d, $^3J = 8.5$ Hz, H-3′, 5′), 7.59 (1H, d, $^3J = 8.4$ Hz, H-4), 7.94 (2H, d, $^3J = 8.5$ Hz, H-2′, 6′), 11.25 ppm (1H, br. s, OH-6); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.37, 57.62, 61.62, 108.27, 110.86, 112.44, 112.78, 114.67, 124.66, 125.28, 132.99, 146.16, 160.49, 164.54, 166.50, 181.49 ppm; MS (CI): *m/z* 313.2 (MH^+, 100). Anal. calcd for C18H16O5: C, 69.22; H, 5.16. Found: C, C, 69.48; H, 5.41.

(2*Z*)-2-(3,4-Dimethoxybenzylidene)-6-hydroxy-7-(methoxymethyl)-1-benzofuran-3(2*H*)-one (13c).

Yellow solid (69% yield); mp: 225–227 °C; IR (KBr): ν_{max} 2917, 1664, 1605, 1581, 1515, 1303, 1303, 1274, 1136 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 3.30 (3H, s, $C\underline{H}_3OCH_2$-7), 3.82, 3.86 (each 3H, 2 s, OMe-3′,4′), 4.57 (2H, s, CH_2-7), 6.77 (1H, s, H-2a), 6.80 (1H, d, $^3J = 8.4$ Hz, H-5), 7.07 (1H, d,$^3J = 8.4$ Hz, H-5′), 7.48 (1H, dd, $^3J = 8.3$ Hz, $^4J = 1.9$ Hz, H-6′), 7.58 (1H, d, $^3J = 8.4$ Hz, H-4), 7.69 (1H, d, $^4J = 1.9$ Hz, H-2′), 11.24 ppm (1H, br. s, OH-6); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.21, 55.56, 57.54, 61.72, 108.20, 111.28, 111.84, 112.42, 112.80, 113.32, 124.80, 125.25, 125.57, 146.15, 148.70, 150.37, 164.52, 166.42, 181.40 ppm; MS (CI): *m/z* 343.2 (MH^+, 100). Anal. calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.90; H, 5.48.

(2*Z*)-2-(1,3-Benzodioxol-5-ylmethylene)-6-hydroxy-7-(methoxymethyl)-1-benzofuran-3(2*H*)-one (13d)

Yellow solid (54% yield); mp: 310–311 °C; IR (KBr): ν_{max} 2900, 1671, 1603, 1442, 1295, 1258, 1147, 1033 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.32 (3H, s, $C\underline{H}_3OCH_2$-7), 4.56 (2H, s, CH_2-7), 6.11 (2H, s, OCH_2O), 6.76 (1H, s, H-2a), 6.79 (1H, d, $^3J = 8.5$ Hz, H-5), 7.04 (1H, d, $^3J = 8.1$ Hz, H-7′), 7.43–7.50 (1H, m, H-6′), 7.53–7.61 (2H, m, H-4, 4′), 11.26 ppm (1H, br. s, OH-6); ^{13}C NMR (100 MHz, DMSO-d_6): δ 57.66, 61.77, 101.68, 108.28, 108.93, 109.87, 110.92, 112.48, 112.71, 125.27, 126.29, 127.10, 146.22, 147.87, 148.69, 164.50, 166.49, 181.43 ppm; MS (CI): *m/z* 327.0 (MH^+, 100). Anal. calcd for $C_{18}H_{14}O_6$: C, 66.26; H, 4.32. Found: C, 66.03; H, 4.58.

Cell proliferation assay

Prostate cancer PC-3 cells (American Type Culture Collection, Manassas, VA 20110 USA) were cultured in DMEM/F-12 HAM Mixture (Sigma D8437) containing 10% Fetal Bovine Serum (Atlanta Biological S11150). Cells (3.5×10^4 cells per well) were split into 12-well plates. After 24 h, 10 mM of each compound were added to each well. DMSO was used as a control. Each experiment was done in triplicate. Cell viability and number were analyzed using the Vi-Cell XR Cell Viability Analyzer (Beckman Coulter). Compounds were tested in triplicate at concentrations of 100, 300 nM, 1, 3 and 10 μM, and IC_{50} values were

calculated using GraphPad Prism6 (GraphPad Software, La Jolla, CA, 92037, USA)

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