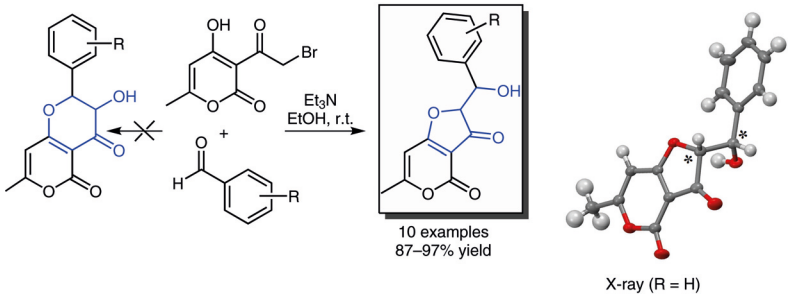
Synlett Y. Abdi et al. Letter

A One-Pot Diastereoselective Synthesis of 2-[Aryl(hydroxy)-methyl]-6-methyl-2*H*-furo[3,2-*c*]pyran-3,4-diones: Crystallographic Evidence for the Furanone Ring Closure

Yamina Abdi[a,b]
Baya Boutemeur-Kheddis[*a]
Maamar Hamdi[a]
Oualid Talhi[c,d]
Filipe A. Almeida Paz[e]
Gilbert Kirsch[f]
Artur M. S. Silva[*c]

[a] Laboratoire de Chimie Organique Appliquée (Groupe Hétérocycles), Faculté de Chimie, Université des Sciences et de la Technologie Houari Boumediène BP 32, El-Alia Bab-Ezzouar, 16111, Alger, Algeria
kheddis.2012@gmail.com
[b] Ecole Préparatoire Sciences et Techniques (EPST), BP 474, Place des Martyres, 16000, Alger, Algeria
[c] QOPNA, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal
artur.silva@ua.pt
[d] Centre de Recherche Scientifique et Technique en Analyses Physico-Chimiques CRAPC, BP 384, Bou-Ismail, 42004, Tipaza, Algeria
[e] CICECO Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal
[f] Laboratoire Structure et Réactivité des Systèmes Moléculaires Complexes, UMR 7565, Université de Lorraine, Avenue du Général Delestraint, 57070 Metz, France



Received: 14.03.3015
Accepted after revision: 21.04.2015
Published online: 21.05.2015
DOI: 10.1055/s-0034-1380214; Art ID: st-2015-d0185-l

Abstract Novel furopyran-3,4-dione-fused heterocycles have been obtained by a one-pot reaction of α-brominated dehydroacetic acid and benzaldehydes under organobase conditions. The prepared 2-[aryl(hydroxy)methyl]-6-methyl-2*H*-furo[3,2-*c*]pyran-3,4-diones were fully characterized by 2D NMR spectroscopy and supported by single-crystal X-ray analysis to unequivocally prove the furan-3-one five-membered ring-closure mechanism instead of the dihydroflavanon-3-ol six-membered cyclization which has recently been proposed in the literature.

Keywords furan-3-ones, pyran-2-ones, dehydroacetic acid, synthesis, organobase, 2D NMRspectroscopy, single-crystal X-ray diffraction

Furan-3-ones and pyran-2-ones are important oxygen heterocycles which are mostly present in the structure of a variety of biologically active natural compounds.[1,2] Such substances sharing five- or six-membered ring systems have deserved considerable attention in organic chemistry due to their structural simplicity and low-molecular weight advantages, being readily accessible by several synthetic routes.[3,4] The furan-3-one ring system is found in aurones [2-benzylidenebenzofuran-3(2*H*)-ones, Figure 1] which are abundant colored natural flavonoids with outstanding therapeutic potential.[5a] Furan-3-one-containing molecules continue to attract interest, and we have recently reported some valuable anticancer and photosensitive templates, namely the [benzopyran-(2 or 4)-one/benzofuran-3-one][5b] and [benzofuran-3-one/hydantoin][5c,d] conjugate dyads.

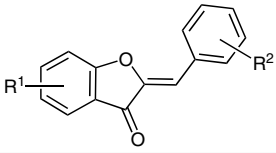


Figure 1 Aurone general structure

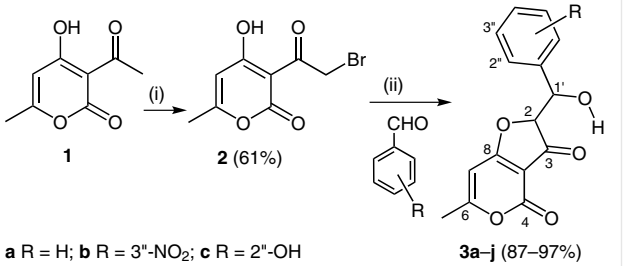
Pyran-2-ones, six-membered lactones, constitute a large family of biologically active natural products mainly encountered in animals, insects, plants, and microbial systems.[2] Simple chemical modification of the substitution pattern in the pyran-2-one ring has often led to diverse biological properties, for instance, 4-hydroxypyran-2-ones constitute an important class of anti-HIV agents and also exhibit antifungal, phytotoxic, antimicrobial, cytotoxic, and neurotoxic activities.[6]

Aiming at the preparation of aurone mimics, we recently reported the covalent combination of furan-3-one and pyran-2-one into a fused dyad. The route relies on the treatment of 3-(bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one with aliphatic primary amines in ethanol, leading to the formation of a single product 6-methyl-2*H*-furo[3,2-*c*]pyran-3,4-dione. Under acidic conditions, this compound undergoes classical Knoevenagel condensation of the furan-3-one ring (through its active methylene group) with benzaldehydes to yield 2-arylidene-6-methyl-2*H*-furo[3,2-*c*]pyran-3,4-diones.[7a,b] The synthesis of these aurone-type compounds has also been initiated by heating dehydroacetic acid (DHA = 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one) in the presence of several aliphatic and aromatic

amines.[7g] DHA and its brominated derivatives have shown a wide synthetic potential, being readily converted into interesting heterocyclic systems (e.g., pyrazoles, 1,2-benzothiazepines, benzodiazepines, and pyrimidines) through their condensation with a variety of bisnucleophiles.[8]

Following our interest in the use of DHA (**1**) as a synthetic precursor of pyran-2-ones, we focused our efforts on its selective α-monobromination to afford 3-(bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (**2**, acetyl methylene group: δ_H = 4.71 ppm, δ_C = 35.2 ppm) in good yield (up to 61%), by refluxing **1** with one equivalent of bromine in glacial acetic acid (Scheme 1).[9] α-Haloketones are general and versatile synthons used for the preparation of various heterocyclic compounds due to their high reactivity and selective chemical transformations.[7] Finally, in the context of this communication, the development of practical and efficient methodologies for the synthesis of substituted furo[3,2-*c*]pyran-4-ones is still gaining interest.

Herein we report the diastereoselective synthesis of 2-[aryl(hydroxy)methyl]-6-methyl-2*H*-furo[3,2-c]pyran-3,4-diones **3** by the condensation of α-brominated DHA **2** with various benzaldehydes in ethanol at ambient temperature using an equimolar amount of triethylamine (Scheme 1). This procedure leads to furo[3,2-*c*]pyran-3,4-diones **3** in high yields (87–97%), in short reaction time (15 min).[10] Stereochemically, two adjacent asymmetric carbons have been created in a fused furopyran-3,4-dione heterocyclic scaffold **3** with the potential to generate a pair of diastereomers.

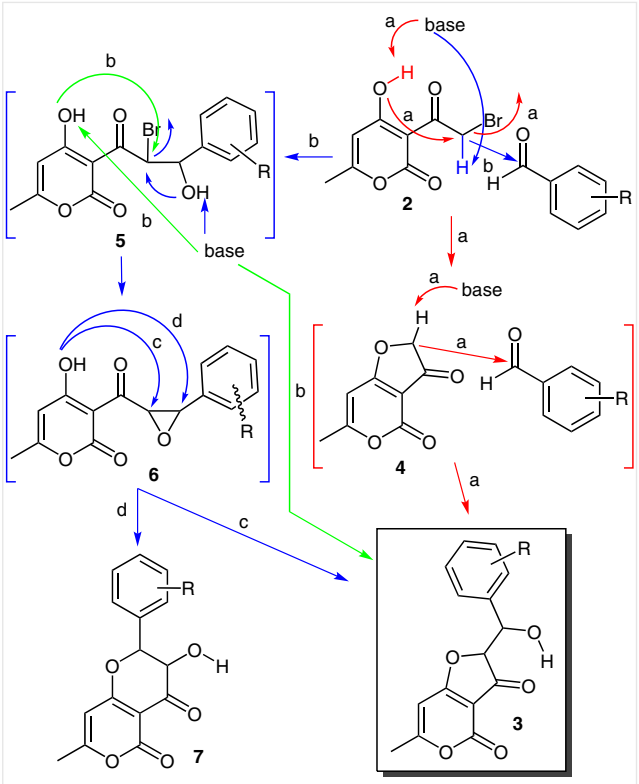


a R = H; **b** R = 3"-NO_2; **c** R = 2"-OH
d R = 3"-OH; **e** R = 4"-Cl; **f** R = 2"-Me
g R = 4"-OMe; **h** R = 3"-Br; **i** R = 4"-Br
j R = 4"-F

Scheme 1 Synthesis of 2-[aryl(hydroxy)methyl)-6-methyl-2*H*-furo[3,2-*c*]pyran-3,4-diones **3a–j**. Reagents and conditions: (i) Br_2, glacial acetic acid, reflux 60 °C; (ii) Et_3N (1 equiv), EtOH, r.t.

A detailed analysis of proton acidity of the α-bromo-DHA **2** in basic medium (such as Et_3N) suggests two possible deprotonation sites leading to quiet different intermediates that could be involved in the reaction with the benzaldehyde (Scheme 2). A plausible reaction mechanism for the synthesis of compounds **3** can be drawn via initial deprotonation at the 4-hydroxyl group which may drive the α-bromo-DHA **2** to a furan-3-one ring closure via nucleophilic attack on the bromomethyl group, affording **4** as previously noted.[7a,b] Compound **4** can undergo in situ condensation with the benzaldehyde under organobase conditions to afford 2-[aryl(hydroxy)methyl]-6-methyl-2*H*-furo[3,2-*c*]pyran-3,4-diones **3** (Scheme 2, pathway a). An alternative deprotonation can occur at the active methylene of the α-bromo-DHA **2** creating a carbanion that directly condenses with the benzaldehyde leading to the intermediates **5**. Assuming a subsequent deprotonation of the 4-OH in the intermediates **5**, the furan-3-one cyclization can occur by nucleophilic attack on the bromomethyl group, thus affording **3** (Scheme 2, pathway b). Recent reports have shown that the condensation between similar α-halocarbonyl compounds **2** and carbonyl compounds (such as benzaldehydes) in basic medium is a useful synthetic route to access α,β-epoxycarbonyl derivatives.[11] In this way, the formation of the epoxides **6** is expected through deprotonation of β-OH in **5** and subsequent nucleophilic substitution of the α-bromo substituent. Such epoxide derivatives **6** are known to be versatile synthetic intermediates that can be converted into a wide range of multifunctional heterocyclic scaffolds. Thus, the presence of a free 4-hydroxyl group on the pyran-2-one makes α,β-epoxycarbonyl **6** capable of undergoing intramolecular heterocyclization to give, either the five-membered furan-3-one ring **3** via nucleophilic attack on the α-carbon (Scheme 2, pathway c), or six-membered dihydroflavanon-3-ols **7** through ring closure at the β-carbon (Scheme 2, pathway d). Recent literature data disclose that dihydroflavanon-3-ols are preferably formed following condensation reaction of α-halocarbonyl compounds with benzaldehydes under basic conditions.[12] The Wheeler reaction, usually employed for the synthesis of aurones, has also been adapted to access dihydroflavanon-3-ols via opening of 2′-hydroxychalcone α,β-epoxides at the β-carbon.[12a] Several authors have provided evidence that dihydroflavonols are selectively obtained from 2′-hydroxychalcone α,β-epoxides using different catalysts rather than 2-[aryl(hydroxy)methyl] benzofuran-3-ones, but this conclusion was only supported by ^{1}H NMR and ^{13}C NMR data.[12b,c] The differentiation between a dihydroflavanon-3-ol **7** and a 2-[aryl(hydroxy)methyl]benzofuran-3-one **3** using ^{1}H NMR and ^{13}C NMR assignments is not trivial because other studies suggest that both α- or β-cyclizations of α,β-epoxycarbonyl substrates may take place in the presence of a free hydroxyl group (such as in 2′-hydroxychalcone α,β-epoxides). Moreover, this is strongly dependent on the nature of the catalyst.[12d]

To overcome the potential for structural ambiguity between such five- and six-membered heterocycles, we studied the structure of products **3** in detail based on their 2D NMR spectra (HSQC, HMBC, and NOESY). In the ^{1}H NMR spectra H-2 and H-1′ appear at δ_H = 5.07–5.38 ppm as doublets (J = 0.5–1.6 Hz) and doublets of doublets; these assignments being confirmed by their HSQC correlations with two different carbons at δ_C = ca. 70 and ca. 90 ppm, respectively. The doublet assigned to 1′-OH (δ_H = 5.76–6.68 ppm, J = 3.7–6.4 Hz) does not show any HSQC connectivity. Be-



Scheme 2 Possible mechanistic pathways for the formation of furopyran-3,4-diones **3** and/or dihydroflavanon-3-ols **7**

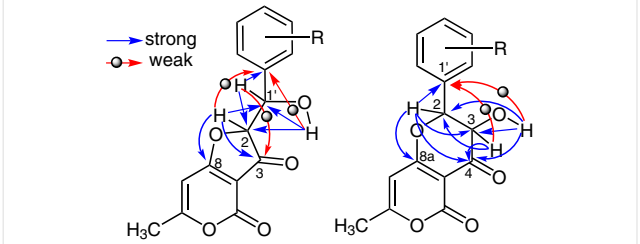


Figure 2 Comparison between the experimental HMBC correlations observed in the synthesized furopyrandiones **3** and the predicted HMBC connectivities which would be present in the proposed dihydroflavanon-3-ols **7**

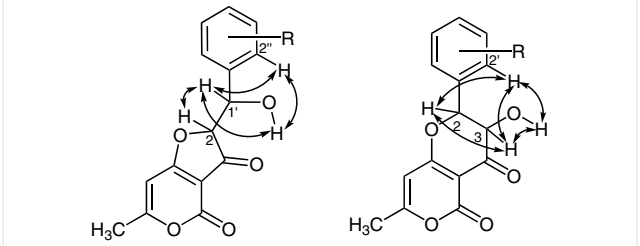


Figure 3 Comparison between the experimental NOE effects observed in the synthesized furopyrandiones **3** and the predicted NOE cross-couplings that could be present in the proposed dihydroflavanon-3-ols **7**

sides the exact determination of the C2–C1′ bond, the key ^{13}C NMR resonances of **3a–j** present characteristic signals assigned by HMBC experiments (Figure 2 and Figures S16, S17 in Supporting Information for compound **3g**), namely C-1″ (δ_C = 127.4–143.7 ppm), C-8 (δ_C = 188.2–188.4 ppm), and C-3 (δ_C = 192.2–193.3 ppm), respectively. We also observed weak HMBC connectivities between the 1′-OH and C-1″, making us less confident of such structural interpretation because the expected HMBC correlations of the dihydroflavanon-3-ols **7** are similar to those observed in furopyrandiones **3** (Figure 2). For this reason, the 2D NMR study of compounds **3** was extended to NOESY experiments that were helpful in suggesting the stereochemical arrangement of the whole scaffold **3**. Notable NOE enhancements were observed between H-2 and H-1′; H-1′ and 1′-OH; 1′-OH and H-2″ and of H-1′ with H-2″,6″ (Figure 3 and Figure S18 in Supporting Information for compound **3g**). Likewise, the expected NOE effects in the dihydroflavanon-3-ols **7** have led us to the same conclusions as summarized in Figure 3. The 2D NMR spectral determination is important and extremely useful in most of the cases, particularly for complicated structural elucidation procedures. However, a rare similarity was found between the isomeric compounds furopyrandiones **3** and dihydroflavanon-3-ols **7**, ultimately leading to inconclusive results.

Single-crystal X-ray diffraction was performed in order to describe the 3D structure of the furopyran-3,4-diones **3** unambiguously. Good-quality crystals of compound **3a** were isolated from a 5:2 mixture of hexane–ethanol by a slow evaporation at 6 °C. X-ray diffraction studies revealed structure **3a**, which is in a complete agreement with the 2D NMR studies (Figure 4). Two asymmetric carbon atoms (C8 and C9 crystallographic numbering, Figure 4) are clearly observed in the crystal structure. Because **3a** crystallizes in centrosymmetric $P\bar{1}$ triclinic space groups, the unit cell contains the mirror image of the organic molecule depicted in Figure 3, leading to a solid-state racemic mixture of two possible enantiomers [(2*R*,1′*S*) and (2*S*,1′*R*)]. In this context, we can conclude that this protocol represents a diastereoselective synthetic approach towards furopyran-3,4-diones **3**.

In conclusion, we have described a simple and efficient diastereoselective route towards 2-[aryl(hydroxy)methyl]-6-methyl-2*H*-furo[3,2-*c*]pyran-3,4-diones via condensation of α-bromo-DHA with a variety of benzaldehydes using organobase catalysis. This reaction could follow different mechanistic pathways where the most likely one is the formation of an α,β-epoxycarbonyl intermediate that undergoes preferential α-cyclization to afford a fused furo[3,2-*c*]pyran-3,4-dione. 2D NMR spectroscopic studies were used for tentative differentiation between the furan-3-one and the largely reported dihydroflavanon-3-ol ring closure. However, due to the high structural similarity between

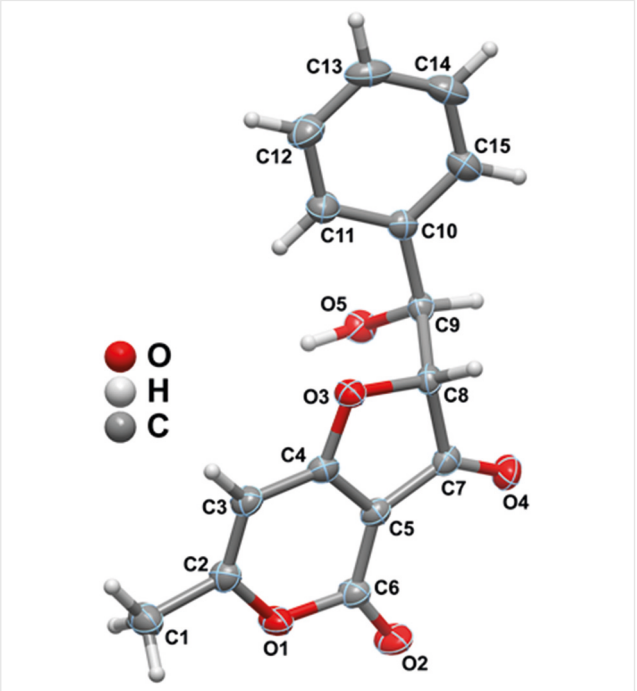


Figure 4 Schematic representation of the molecular unit present in the asymmetric unit of compound **3a**. Atoms C8 and C9 correspond to stereocenters. Nonhydrogen atoms are represented as thermal ellipsoids drawn at the 50% probability level and hydrogen atoms as small spheres with arbitrary radii. The half-occupied water molecule present in the asymmetric unit of **3a** and the second position for the hydrogen atom bound to O5 have been omitted for clarity.

these scaffolds, results were not wholly conclusive. However, single-crystal X-ray diffraction study was decisive in the elucidation of the diastereoselective synthetic pathway toward 2-[aryl(hydroxy)methyl]-6-methyl-2*H*-furo[3,2-c]pyran-3,4-diones. We believe that this result may lead to the revision of many previously reported β-hydroxyfuran-3-one and 3-hydroxypyran-4-one structures synthesized from α,β-epoxycarbonyls, for which only 2D NMR spectroscopic analysis was used.

Acknowledgment

Thanks are due to the University of Aveiro, Fundação para a Ciência e a Tecnologia (FCT, Portugal), EU, QREN, FEDER, COMPETE, for funding the Organic Chemistry Research Unit (project PEst-C/QUI/UI0062/2013), and the Portuguese National NMR Network (RNRMN). We would like to thank the General Directorate for Scientific Research and Technological Development-DGRSDT of Algeria for the financial support. O. Talhi also thanks the project New Strategies Applied to Neuropathological Disorders (CENTRO-07-ST24-FEDER-002034), co-funded by QREN, 'Mais Centro-Programa Operacional Regional do Centro' and EU, FEDER for his postdoctoral position. We further wish to thank CICECO Aveiro Institute of Materials (Ref. FCT UID /CTM /50011/2013), financed by national funds through the FCT/MEC, and when applicable co-financed by FEDER under the PT2020 Partnership Agreement, for funding the purchase of the single-crystal X-ray diffractometer.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380214.

References and Notes

(1) (a) Lin, C. F.; Chen, Y. J.; Huang, Y. L.; Chiou, W. F.; Chiu, J. H.; Chen, C. C. *J. Asian Nat. Prod. Res.* **2012**, *14*, 704. (b) Fan, R.; Ban, S.; Feng, X.; Zhao, C.; Li, Q. *Chem. Res. Chin. Univ.* **2012**, *28*, 438.

(2) (a) Miyakado, M.; Inoue, S.; Tanabe, Y.; Watanabe, K.; Ohno, N.; Yoshioka, H.; Mabry, T. *J. Chem. Lett.* **1982**, 1539. (b) Akizawa, T.; Yasuhara, T.; Azuma, H.; Nakajima, T. *Biomed. Res.* **1985**, *6*, 437. (c) Azuma, S.; Sekizaki, S.; Akizawa, T.; Yasuhara, T.; Nakajima, T. *J. Pharm. Pharmacol.* **1986**, *38*, 388. (d) Cutler, H. G.; Jacyno, J. M. *Agric. Biol. Chem.* **1991**, *55*, 2629. (e) Rasoanaivo, P.; Galeffi, G.; Multari, G.; Nicoletti, M.; Capolongo, L. *Gazz. Chim. Ital.* **1993**, *123*, 539. (f) Steyn, P. S.; Van Heerden, F. R. *Nat. Prod. Rep.* **1998**, *15*, 397.

(3) (a) Yiyi, W.; Qixu, C.; Weike, S. *J. Org. Chem.* **2014**, *79*, 4218. (b) Masahiro, Y.; Tomomi, N.; Kouki, K.; Kozo, S. *J. Org. Chem.* **2013**, *78*, 1687. (c) Rueping, M.; Parra, A.; Uria, U.; Besselievre, F.; Merino, E. *Org. Lett.* **2010**, *12*, 5680. (d) Ye, Y.; Wang, L.; Fan, R. *J. Org. Chem.* **2010**, *75*, 1760.

(4) (a) Yokoe, H.; Mitsuhashi, C.; Matsuoka, Y.; Yoshimura, T.; Yoshida, M.; Shishido, K. *J. Am. Chem. Soc.* **2011**, *133*, 8854. (b) Takikawa, H.; Hirooka, M.; Sasaki, M. *Tetrahedron Lett.* **2003**, *44*, 5235. (c) Takikawa, H.; Imamura, Y.; Sasaki, M. *Tetrahedron* **2006**, *62*, 39. (d) Hagiwara, H.; Sato, K.; Nishino, D.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, *1*, 2946.

(5) (a) Zwergel, C.; Gaascht, F.; Valente, S.; Diederich, M.; Bagrel, D.; Kirsch, G. *Nat. Prod. Commun.* **2012**, *7*, 389. (b) Zwergel, C.; Valente, S.; Salvato, A.; Xu, Z.; Talhi, O.; Mai, A.; Silva, A. M. S.; Altuccice, L.; Kirsch, G. *Med. Chem. Commun.* **2013**, *4*, 1571. (c) Talhi, O.; Fernandes, J. A.; Pinto, D. C. G. A.; Paz, F. A. A.; Silva, A. M. S. *Tetrahedron* **2013**, *69*, 5413. (d) Talhi, O.; Lopes, G. R.; Santos, S. M.; Pinto, D. C. G. A.; Silva, A. M. S. *J. Phys. Org. Chem.* **2014**, *27*, 756.

(6) (a) Singh, K.; Sharma, P. K. *Int. J. Pharm. Pharm. Sci.* **2014**, *6*, 345. (b) Aggarwal, R.; Rani, C.; Kumar, R.; Garg, G.; Sharma, J. *ARKIVOC* **2014**, *(ii)*, 120. (c) Fadda, A. A.; Amine, M. S.; Arief, M. M. H.; Farahat, E. K. *Pharmacol.* **2014**, *5*, 1. (d) Kashar, T. I.; El-Sehli, A. H. *J. Chem. Pharm. Res.* **2013**, *5*, 474.

(7) (a) Hikem-Oukacha, D.; Rachedi, Y.; Hamdi, M.; Silva, A. M. S. *J. Heterocycl. Chem.* **2010**, *48*, 31. (b) Hikem-Oukacha, D.; Hamdi, M.; Silva, A. M. S.; Rachedi, Y. *J. Heterocycl. Chem.* **2011**, *48*, 63. (c) Aychiluhim, T. B.; Penta, S.; Rao, V. R. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2014**, *53*, 1242. (d) Penta, S.; Rao, V. R. *Russian J. Gen. Chem.* **2012**, *82*, 1464. (e) Penta, S.; Gadidasu, K. K.; Basavoju, S.; Rao, V. R. *Tetrahedron Lett.* **2013**, *54*, 5663. (f) Penta, S.; Rao, V. R. *J. Sulfur Chem.* **2011**, *32*, 327. (g) Stephen, J. F.; Marcus, E. *J. Org. Chem.* **1969**, *34*, 2527.

(8) (a) Purushothaman, K. K.; Sarada, A.; Connolly, J. D. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1984**, *23*, 611. (b) El Abbassi, M.; Essassi, E. M.; Fifani, J. *Tetrahedron Lett.* **1987**, *28*, 1389. (c) Rachedi, Y.; Hamdi, M.; Speziale, V. *Synth. Commun.* **1989**, *19*, 3427. (d) Kherfi, H. N.; Hamdi, M.; Speziale, V. *J. Heterocycl. Chem.* **1990**, *27*, 1401. (e) Nedjar-Kolli, B.; Hamdi, M.;

Pecher, J. *Synth. Commun.* **1990**, *20*, 1579. (f) Rachedi, Y.; Hamdi, M.; Sakellariou, R.; Speziale, V. *Synth. Commun.* **1991**, *21*, 1189. (g) Hernández-Galán, R.; Salvá, J.; Massanet, G. M.; Collado, I. G. *Tetrahedron* **1993**, *49*, 1701. (h) Bendaas, A.; Hamdi, M.; Sellier, N. *J. Heterocycl. Chem.* **1999**, *36*, 1291. (i) Boutemeur-Kheddis, B.; Hamdi, M.; Sellier, N.; Silva, A. M. S. *J. Heterocycl. Chem.* **2001**, *38*, 227. (j) Makhloufi-Chebli, M.; Hamdi, M.; Silva, A. M. S.; Duval, O.; Helesbeux, J. J. *J. Heterocycl. Chem.* **2009**, *46*, 18.

(9) **Synthesis of 3-Bromoacetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (2)**

A solution of bromine (0.27 mL, 5 mmol) in AcOH (10 mL) was added portionwise to a solution of DHA (**1**, 0.84 g, 5 mmol) in AcOH (20 mL). After heating to reflux for 2 h, the reaction mixture was poured into H_2O (100 mL) and ice (50 g). The solid obtained was filtered off and recrystallized from a 1:1 mixture of hexane–$CHCl_3$ to afford compound **2**.

Analytical Data for Compd 2

$C_8H_7BrO_4$ (yellow crystals, MW = 247.04 g/mol, 0.75 g, 61%; mp 118–119 °C [111–114 °C][7]). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, 6-CH_3), 4.71 (s, 2 H, CH_2Br), 6.03 (s, 1 H, H-5), 15.51 (s, 1 H, OH) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 20.8 (6-*C*H_3), 35.2 (CH_2Br), 99.4 (C-3), 101.3 (C-5), 160.6 (C-6), 170.1 (C-2), 180.9 (C-4), 197.2 (C-3) ppm. ESI$^+$-MS: *m/z* = 271 (^{81}Br, 18) [M + Na]$^+$, 269 (^{79}Br, 20) [M + Na]$^+$, 249 (^{81}Br, 90) [M + H]$^+$, 247 (^{79}Br, 95) [M + H]$^+$, 167 (100) [M – Br]$^+$. Anal. Calcd (%) for $C_8H_7BrO_4$: C, 38.89; H, 2.86. Found: C, 39.10; H, 2.80.

(10) **Synthesis of 2-[Aryl(hydroxy)methyl]-6-methyl-2*H*-furo[3,2-*c*]pyran-3,4-diones 3a–j**

A suspension of the appropriate benzaldehyde (1 mmol), 3-(bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (**2**, 0.25 g, 1 mmol), and Et_3N (0.2 mL, 1.5 mmol) was stirred in EtOH (3 mL) at ambient temperature for 15 min. The powder formed was collected by filtration, washed with H_2O and then allowed to dry. The crude compounds thus obtained were recrystallized from EtOH to give pure compounds **3a**–**j**.

Representative Analytical Data

2-[Hydroxy(phenyl)methyl]-6-methyl-2*H*-furo[3,2-*c*]pyran-3,4-dione (3a)

$C_{15}H_{12}O_5$ (violet solid, MW = 272.26 g/mol, 0.25 g, 92%; mp 160 °C). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.34 (s, 3 H, 6-CH_3), 5.16 (dd, *J* = 1.5, 3.7 Hz, 1 H, H-1′), 5.20 (d, *J* = 1.5 Hz, 1 H, H-2), 5.99 (d, *J* = 3.7 Hz, 1 H, 1′-OH), 6.69 (s, 1 H, H-7), 7.20–7.41 (m, 5 H, H-2″3 ″,4″,5″,6″) ppm. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 20.7 (6-CH_3), 70.9 (C-1′), 91.4 (C-2), 96.8 (C-7), 99.7 (C-9), 126.2 (C-2″,6″), 127.4 (C-4″), 128.0 (C-3″,5″), 140.9 (C-1″), 155.4 (C-4), 174.1 (C-6), 188.3 (C-8), 192.8 (C-3) ppm. ESI$^+$-HRMS: *m/z* calcd for [$C_{15}H_{12}O_5$ + Na]$^+$: 295.0582; found: 295.0588.

Crystal Data for Compound 3a

$(C_{15}H_{12}O_5)_2{\cdot}H_2O$, *M* = 562.51, triclinic, space group $P\bar{1}$, *Z* = 1, *a* = 7.1249(5) Å, *b* = 8.0504(6) Å, *c* = 12.2442(10) Å, *α* = 107.237(4)°, *β* = 96.608(5)°, *γ* = 102.845(4)°, *V* = 641.51(9) Å^3, *μ*(Mo-Kα) = 0.112 mm^{-1}, D_c = 1.456 g cm^{-3}, red block, crystal size of 0.20 × 0.12 × 0.10 mm^3. Of a total of 4402 reflections collected, 2331 were independent (R_{int} = 0.0292). Final *R*1 = 0.0391 [*I* > 2*σ*(*I*)] and *wR*2 = 0.0966 (all data). Data completeness to *θ* = 25.24°, 98.8%; CCDC 1050452.

2-[Hydroxy(3-nitrophenyl)methyl]-6-methyl-2*H*-furo[3,2-*c*]pyran-3,4-dione (3b)

$C_{15}H_{11}NO_7$ (pale violet solid, MW = 317.25 g/mol, 0.29 g, 91%; mp 208 °C). ^{1}H NMR (**???** MHz, DMSO-d_6): δ = 2.35 (s, 3 H, 6-CH_3), 5.35–5.36 (m, 2 H, H-1′, H-2), 6.37 (d, *J* = 6.4 Hz, 1 H, 1′-OH), 6.70 (s, 1 H, H-7), 7.69 (dd, *J* = 7.8, 7.9 *Hz*, 1 H, H-5″), 7.98 (d, *J* = 7.8 Hz, 1 H, H-6″) 8.19 (dd, *J* = 1.7, 7.9 Hz, 1 H, H-4″), 8.36 (d, *J* = 1.7 Hz, 1 H, H-2″) ppm. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 20.7 (6-CH_3), 69.8 (C-1′), 90.7 (C-2), 96.7 (C-7), 99.7 (C-9), 121.1 (C-2″), 122.5 (C-4″), 129.7 (C-5″), 133.1 (C-6″), 143.4 (C-1″), 147.7 (C-3″), 155.4 (C-4), 174.3 (C-6), 188.2 (C-8), 192.2 (C-3) ppm. ESI$^+$-HRMS: *m/z* calcd for [$C_{15}H_{11}NO_7$ + Na]$^+$: 340.0433; found: 340.0439.

2-[Hydroxy(2-hydroxyphenyl)methyl]-6-methyl-2*H*-furo[3,2-*c*]pyran-3,4-dione (3c)

$C_{15}H_{12}O_6$ (grey solid, MW = 288.25 g/mol, 0.27 g, 94%; mp 185 °C). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.34 (s, 3 H, 6-CH_3), 5.11 (d, *J* = 1.5 Hz, 1 H, H-2), 5.38 (dd, *J* = 1.5, 4.8 Hz, 1 H, H-1′), 5.76 (d, *J* = 4.8 Hz, 1 H, 1′-OH), 6.66 (s, 1 H, H-7), 6.81–6.88 (m, 2 H, H-3″, H-5″), 7.09–7.17 (m, 1 H, H-4″), 7.40 (dd, *J* = 7.7, 1.1 Hz, 1 H, H-6″), 9.81 (s, 1 H, 2″-OH) ppm. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 20.7 (6-CH_3), 66.2 (C-1′), 89.8 (C-2), 96.8 (C-7), 99.8 (C-9), 114.6 (C-3″), 118.8 (C-5″), 126.9 (C-6″), 127.4 (C-1″), 128.2 (C-4″), 153.2 (C-2″), 155.5 (C-4), 173.9 (C-6), 188.4 (C-8), 193.3 (C-3) ppm. ESI$^+$-HRMS: *m/z* calcd for [$C_{15}H_{12}O_6$ + Na]$^+$: 311.0532; found: 311.0541.

2-[Hydroxy(3-hydroxyphenyl)methyl]-6-methyl-2*H*-furo[3,2-*c*]pyran-3,4-dione (3d)

$C_{15}H_{12}O_6$ (pale violet solid, MW = 288.25 g/mol, 0.26 g, 90%; mp 205–206 °C). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.35 (s, 3 H, 6-CH_3), 5.07 (dd, *J* = 1.3, 5.4 Hz, 1 H, H-1′), 5.15 (d, *J* = 1.3 Hz, 1 H, H-2), 5.91 (d, *J* = 5.4 Hz, 1 H, 1′-OH), 6.68 (s, 1 H, H-7), 6.70–6.71 (m, 1 H, H-4″), 6.87–6.90 (m, 2 H, H-2″, H-6″), 7.13–7.19 (m, 1 H, H-5″), 9.41 (s, 1 H, 3″-OH) ppm. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 20.7 (6-CH_3), 70.8 (C-1′), 91.5 (C-2), 96.7 (C-7), 99.7 (C-9), 113.3 (C-2″), 114.3 (C-4″), 116.7 (C-6″), 129.1 (C-5″), 142.5 (C-1″), 155.4 (C-3″), 157.2 (C-4), 174.1 (C-6), 188.3 (C-8), 192.9 (C-3) ppm. ESI$^+$-HRMS: *m/z* calcd for [$C_{15}H_{12}O_6$ + Na]$^+$: 311.0532; found: 311.0535.

2-[Hydroxy(4-chlorophenyl)methyl]-6-methyl-2*H*-furo[3,2-*c*]pyran-3,4-dione (3e)

$C_{15}H_{11}ClO_5$ (pale yellow solid, MW = 306.69 g/mol, 0.28 g, 91%; mp 268 °C). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.34 (s, 3 H, 6-CH_3), 5.17–5.20 (m, 2 H, H-1′, H-2), 6.10 (d, *J* = 5.5 Hz, 1 H, 1′-OH), 6.67 (s, 1 H, H-7), 7.44 and 7.52 (2 d, *J* = 8.5 Hz, 2 × 2 H, H-2″,3″, H-5″,6″) ppm. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 20.7 (6-CH_3), 70.2 (C-1′), 91.1 (C-2), 96.7 (C-7), 99.8 (C-9), 128.1 and 128.2 (C-2″,3″ and C-5″,6″), 132.1 (C-4″), 140.0 (C-1″), 155.4 (C-4), 174.2 (C-6), 188.3 (C-8), 192.6 (C-3) ppm. ESI$^+$-HRMS: *m/z* calcd for [$C_{15}H_{11}ClO_5$ + Na]$^+$: 329.0193; found: 329.0192.

2-[Hydroxy(*o*-tolyl)methyl]-6-methyl-2*H*-furo[3,2-*c*]pyran-3,4-dione (3f)

$C_{16}H_{14}O_5$ (red violet solid, MW = 286.27 g/mol, 0.25 g, 87%; mp 207 °C). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.35 and 2.36 (2 s, 6 H, 2″-CH_3, 6-CH_3), 5.12 (d, *J* = 1.0 Hz, 1 H, H-2), 5.33 (dd, *J* = 1.0, 5.3 Hz, 1 H, H-1′), 5.87 (d, *J* = 5.3 Hz, 1 H, 1′-OH), 6.72 (s, 1 H, H-7), 7.16–7.30 (m, 3 H, H-3″, H-4″, H-5″), 77.56 (dd, *J* = 7.5, 5.3 Hz, 1 H, H-6″) ppm. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 18.5 (2″-CH_3), 20.6 (6-CH_3), 67.8 (C-1′), 89.7 (C-2), 96.6 (C-7), 99.6 (C-9), 125.5 (C-5″), 126.9 (C-6″), 127.2 (C-3″), 130.0 (C-4″), 133.7 (C-2″), 138.6 (C-1″), 155.3 (C-4), 174.1 (C-6), 188.3 (C-8), 192.9 (C-3) ppm. ESI$^+$-HRMS: *m/z* calcd for [$C_{16}H_{14}O_5$ + Na]$^+$: 309.0793; found: 309.0777.

2-[Hydroxy(4-methoxyphenyl)methyl]-6-methyl-2*H*-furo[3,2-*c*]pyran-3,4-dione (3g)

$C_{16}H_{14}O_6$ (pale brown solid, MW = 302.27 g/mol, 0.27 g, 89%; mp 195 °C). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.35 (s, 3 H, 6-*CH*$_3$), 3.76 (s, 3 H, 4″-OCH_3), 5.11 (dd, *J* = 1.5, 5.2 Hz, 1 H, H-1′), 5.13 (d, *J* = 1.5 Hz, 1 H, H-2), 5.89 (d, *J* = 5.2 Hz, 1 H, 1′-OH), 6.89

(s, 1 H, H-7), 6.94 (d, *J* = 8.7 Hz, 2 H, H-3″,5″), 7.39 (d, *J* = 8.7 Hz, 2 H, H-2″,6″) ppm. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 20.7 (6-CH_3), 55.1 (4″-OCH_3), 70.6 (C-1′), 91.6 (C-2), 96.8 (C-7), 99.8 (C-9), 113.4 (C-3″,5″), 127.5 (C-2″,6″), 132.9 (C-1″), 155.4 (C-4), 158.6 (C-4″), 174.0 (C-6), 188.2 (C-8), 192.8 (C-3) ppm. ESI$^+$-HRMS: *m/z* calcd for $[C_{16}H_{14}O_6 + Na]^+$: 325.0688; found: 325.0721.

(11) (a) Erian, A. W.; Sherif, S. M.; Gaber, H. M. *Molecules* **2003**, *8*, 793. (b) Shibata, I.; Yamasaki, H.; Baba, A.; Matsuda, H. *Synlett* **1990**, 490.

(12) (a) Marais, J. P. J.; Ferreira, D.; Slade, D. *Phytochemistry* **2005**, *66*, 2145. (b) Rajesh, U. C.; Manohar, S.; Rawat, D. S. *Adv. Synth. Catal.* **2013**, *355*, 3170. (c) Van Rensburg, H.; Van Heerden, P. S.; Bezuidenhoudt, B. C. B.; Ferreira, D. *Tetrahedron* **1997**, *53*, 14141. (d) Patonay, T.; Lévai, A.; Nemes, C.; Timar, T.; Toth, G.; Adam, W. *J. Org. Chem.* **1996**, *61*, 5375. (e) Samir, B. *J. Heterocycl. Chem.* **2014**, *51*, 127.