Conference paper

Ana R. Jesus, Ana P. Marques and Amélia P. Rauter*

An easy approach to dihydrochalcones *via* chalcone *in situ* hydrogenation

DOI 10.1515/pac-2016-0303

Abstract: Dihydrochalcones are polyphenols that exhibit a diversity of bioactivities, namely anti-inflammatory, antimicrobial and antiviral. We have explored the synthetic access to such molecular entities, and describe now an easy and scalable approach based on reduction of the olefinic double bond of chalcone precursors via *in situ* hydrogenation with the system Et_3SiH-Pd/C in very high yield. The intermediate chalcones were synthesized also by a simple and efficient microwave-assisted Claisen–Schmidt condensation of aromatic aldehydes with acetophenones, conveniently protected with ethoxymethyl ether, if required. Chalcones were obtained as single reaction product in high yield in 2–3 h, while under conventional conditions at room temperature the reaction was carried out with completion only after 24 h. In addition, microwave irradiation has proven very efficient for deprotection of ethoxymethyl ether with iron chloride in only 10 min and very high yield.

Keywords: aldol reactions; aromatic compounds; biomolecular chemistry; chalcone; chemical synthesis; dihydrochalcone; ESOC-19; hydrogenation.

Dedicated to: The memory of Hans Weidmann, the Ph.D. supervisor of Amélia P. Rauter.

Introduction

Dihydrochalcones are open chain flavonoids, named systematically as propanone derivatives, structurally related to 1,3-diphenylpropenones (chalcones), biosynthesized in plants and exhibiting a wide spectrum of biological activities [1, 2], namely anti-inflammatory [3, 4], anti-infective [5–7], antioxidant [6, 8], and anti-carcinogenic [9, 10]. Chalcones are key intermediates for the synthesis of a number of biologically relevant compounds, such as coumarinyl heterocycles with antioxidant actitivity [11], chalcone phthalimidoesters with anti-inflammatory and antimicrobial activities [12] or 5,7-disubstituted-1,2,4-triazolo[1,5-a]pyrimidines, which are privileged structures with *in vitro* cytotoxicity higher than the anticancer drug doxorubicin [13]. A diversity of biological activities has also been reported for dihydrochalcones, namely anti-inflammatory [14], antimicrobial [15], antioxidant [16], and antiviral [17], among others. Therefore, synthetic methodologies

Article note: A collection of invited papers based on presentations at the 19th European Symposium on Organic Chemistry (ESOC-19), Lisbon, Portugal, 12–16 July 2015.

***Corresponding author: Amélia P. Rauter,** Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Carbohydrate Chemistry Group, Edifício C8, 5° piso, 1749-016, Lisboa, Portugal, e-mail: aprauter@fc.ul.pt
Ana R. Jesus: Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Carbohydrate Chemistry Group, Edifício C8, 5° piso, 1749-016, Lisboa, Portugal. http://orcid.org/0000-0002-0840-6289
Ana P. Marques: Laboratório de FTICR e Espectrometria de Massa Estrutural, Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal. http://orcid.org/0000-0002-7393-8556

for an easy access to chalcone and dihydrochalcone structures, whose chemical and biological properties change according to the substitution pattern of their aromatic rings, remains a challenge for the organic chemistry community.

The presence of the double bond conjugated with the carbonyl group in chalcones predicts the isomeric (*Z*)- and (*E*)-chalcones, of which the (*E*)-isomer is the one found in nature. When synthetic procedures are applied to access chalcones, the (*E*)-isomer is also the major product formed [18], although stereoselective synthesis of (Z)-chalcones is also possible, as reported by Yoshizawa and Shioiri [19]. Starting from 1,3-diarylpropyn-2-yl silyl ethers, chalcones with (Z)/(*E*) ratios ranging from 70:30 to 97:3 were prepared in good yields under mild conditions.

Synthesis of chalcones can be achieved by Claisen–Schmidt condensation of an aldehyde and a ketone in basic conditions in yields ranging from 40 % to 80 % [20, 21], while in acidic conditions yields from 70 % to 80 % have been reported [22, 23]. Also Suzuki coupling [24, 25], Heck reactions [26, 27], ruthenium-catalyzed cross aldol condensation [28] or alternatively using silica-supported reagents [29] have been described for the preparation of chalcones.

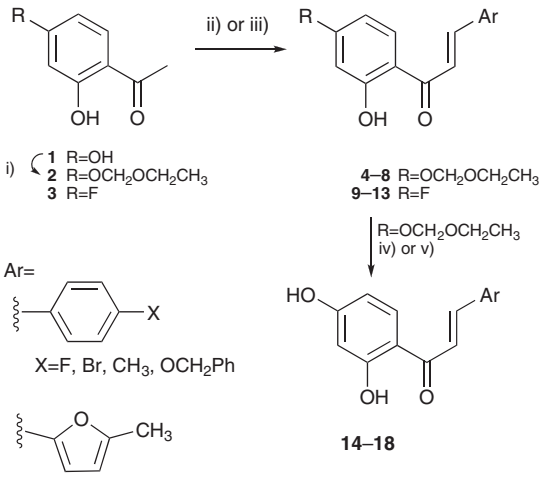
Regarding the synthesis of dihydrochalcones, there are only few reports in the literature. Beyond the acylation and alkylation of arenes with alk-2-enoyl chloride [30], also the treatment of chalcones with the systems Zn/AcOH [31] or with $Zn/NH_4Cl/C_2H_5OH/H_2O$ under ultrasound radiation [32] should be cited. Functionalization as glycosides by chemical [33] or enzymatic [34] procedures has proven relevant to afford molecular entities with a broad range of biological properties, namely antidiabetic [35] and anti-inflammatory activities [36]. Hence, new approaches for dihydrochalcone synthesis are mandatory, in particular for substrates protected with functionalities unstable under acid conditions. Also the preparation of fluorinated dihydrochalcones has been encouraged as well as that of fluorochalcones, some of them previously described as highly active against human melanoma cell line A375 [37]. Some related structures have also proven efficient for the treatment of arthritis in rats [38], while others are known as anti-inflammatory agents [39].

In this paper we present a simple, efficient and scalable methodology for the synthesis of substituted dihydrochalcones, namely 2′,4′-dihydroxy- and 4′-fluoro-2′-hydroxydihydrochalcones, by *in situ* catalytic hydrogenation of the intermediate chalcone double bond conjugated with a carbonyl group, that is not reduced under these reaction conditions. Chalcone precursors were synthesized by Claisen–Schmidt condensation under microwave irradiation or by the conventional procedure for comparison of reaction time, yield and side product formation.

Results and discussion

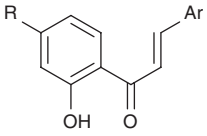
Chalcone synthesis started with acetophenone derivatives **1** and **3**. Compound **1** was selectively protected with the ethoxymethyl group, easily introduced, stable under the reaction conditions used, and rapidly and efficiently removed. This monoprotected derivative **2** was easily accessed and in very good yield (93.8 % isolated yield) (Scheme 1). Aldol condensation of **2** and **3** was carried out in ethanol with *p*-substituted aromatic aldehydes bearing a halogen, methyl or benzyloxy groups as well as with 5-methylfuran-2-carbaldehyde, in order to confirm the usefulness of this methodology. The reaction was carried out under conventional conditions, at room temperature for 24 h affording chalcones in high yield (Table 1, Scheme 1). Alternatively, microwave irradiation under reaction temperature of 40 °C afforded slightly higher yields and a considerable decrease of reaction time from 24 h to 2–3 h. The major advantage of the applied microwave-assisted reaction conditions, when compared to those previously reported using home-conventional microwave ovens or solvent-free reactions [40, 41], is that no side products were formed. The expected stereoselectivity for the (*E*)-isomer, the single chalcone detected, has been confirmed by NMR through the coupling constant of the olefinic protons ($J = 14–15$ Hz), while for (*Z*)-chalcone coupling constants of ca. $J = 11–12$ Hz would be expected.

The present reaction conditions seem to be the best choice for chalcones' synthesis, affording cleaner reactions and generating products in high yield and in much lower reaction time than under conventional conditions (Table 1).



Scheme 1: Synthesis of 2′,4′-dihydroxy- and 4′-fluoro-2′-hydroxychalcones. Reagents and conditions: i) 1. DIPEA, CH_2Cl_2, 0 °C, 15 min; 2. $ClCH_2OCH_2CH_3$, 0 °C, then r.t.; ii) EtOH, aq. NaOH 50 % (w/v), r.t, 24 h; iii) EtOH, aq. NaOH 50 % (w/v), 40 °C, 2–3 h, 250 W; iv) $FeCl_3{\cdot}6H_2O$, MeOH, reflux, 2–3 h; v) $FeCl_3{\cdot}6H_2O$, MeOH, reflux, 10 or 7 min, 250 W.

Table 1: Claisen–Schmidt condensation of acetophenones with aromatic aldehydes under conventional conditions and microwave irradiation (MW), carried out in ethanol.

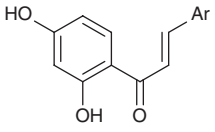
Compound Nr.		ArCHO	Yield (%)	
	R		Conv. rt	MW
4	$OCH_2OCH_2CH_3$	4-methylbenzaldehyde	89.2	92.8
5	$OCH_2OCH_2CH_3$	4-fluorobenzaldehyde	91.2	86.3
6	$OCH_2OCH_2CH_3$	4-bromobenzaldehyde	85.0	86.0
7	$OCH_2OCH_2CH_3$	4-benzyloxybenzaldehyde	92.3	93.8
8	$OCH_2OCH_2CH_3$	5-methylfuran-2-carbaldehyde	68.9	74.6
9	F	4-methylbenzaldehyde	83.0	95.1
10	F	4-fluorobenzaldehyde	72.6	87.5
11	F	4-bromobenzaldehyde	87.3	93.4
12	F	4-benzyloxybenzaldehyde	89.9	90.5
13	F	5-methylfuran-2-carbaldehyde	84.6	89.9

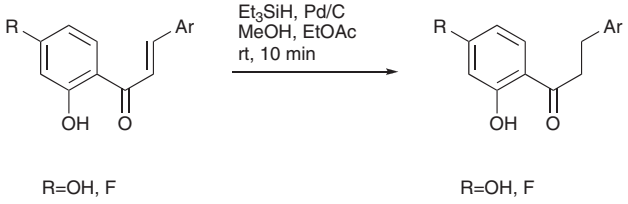
Removal of the ethoxymethyl group was first tried under the described classical conditions, with 2.5 N HCl in methanol [42], but flavanones were formed either as major or as single reaction products. Alternatively, treatment with $FeCl_3{\cdot}6H_2O$ in methanol (Scheme 1), afforded only the dihydroxychalcones in high yield within 2–3 h. When the reaction was carried out under microwave irradiation, reaction time was considerably reduced to 7–10 min with a low increase of reaction yield (Table 2).

In situ generation of molecular hydrogen [43] by addition of triethylsilane to palladium-charcoal catalyst is here applied for the first time to afford dihydrochalcones by chalcone hydrogenation (Scheme 2), resulting in rapid and efficient reduction of chalcone olefinic bond. The reaction was carried out at room temperature for 10 min and the yields were, in general, almost quantitative (98.2–99.7 %) (Table 3). Reaction completion was also easily detected by discoloration of the yellow-reddish chalcone solution.

All reactions afforded the dihydrochalcone product, but the 4-bromophenyl group was reduced to the phenyl group as shown in compounds **21** and **26**. This result could be expected since reductive dehalogenation

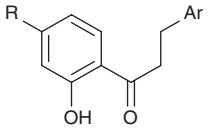
Table 2: Deprotection of chalcones by reaction with $FeCl_3 \cdot 6H_2O$.

Compound Nr.		Yield (%)	
	Ar	Conventional procedure	MW irradiation
14	4-methylphenyl	96.8	97.2
15	4-fluorophenyl	84.6	94.5
16	4-bromophenyl	93.7	98.1
17	4-benzyloxyphenyl	96.7	97.8
18	5-methylfuranyl	90.9	97.6



Scheme 2: Synthesis of 2′,4′-dihydroxy- and 4′-fluoro-2′-hydroxydihydrochalcones.

Table 3: Synthesis of dihydrochalcones by *in situ* generation of molecular hydrogen.

Compound Nr.	Ar		Yield (%)
		R	
19	4-methylphenyl	OH	99.1
20	4-fluorophenyl	OH	99.7
21	phenyl	OH	98.7
22	4-benzyloxyphenyl	OH	99.0
23	5-methylfuranyl	OH	98.2
24	4-methylphenyl	F	99.0
25	4-fluorophenyl	F	99.3
26	phenyl	F	99.4
27	4-benzyloxyphenyl	F	98.2
28	5-methylfuranyl	F	58.4
29[a]	5-methyltetrahydrofuranyl[a]	F	40.8

[a]Compound **29** is a secondary product bearing a tetrahydrofuranyl group resulting from double bond hydrogenation of the furanyl moiety.

of aryl halides by triethylsilane catalyzed by palladium chloride under microwave irradiation has been previously reported [44].

Although Kursanov et al. [45] have reported the reduction of substituted furans to tetrahydrofuran derivatives in the presence of triethylsilane, only the fluorochalcone **13** afforded a dihydrochalcone bearing a tetrahydrofuranyl group as a secondary product, as confirmed by NMR. The signals corresponding to furanyl double bonds of compound **28** were easily identified as doublets with small coupling constants (~1.5–2.0 Hz) while those corresponding to the H-2, H-3, H-4 and H-5 protons of compound **29** appear at considerably lower

chemical shifts and coupling constants, resulting from furanyl double bond reduction. HMRS also confirmed the molecular mass of this compound.

Conclusion

In this work an efficient and simple synthetic method to afford dihydrochalcones has been developed using for the first time the *in situ* production of molecular hydrogen by Et_3SiH/Pd-C system to selectively reduce the olefinic bond of chalcones. Chalcone starting materials were synthesized in high yield via conventional or microwave-assisted methodologies, the latter reducing significantly the reaction time, without formation of side products. In addition, it should be highlighted the usefulness the Lewis acid $FeCl_3$ in promoting chalcone deprotection without flavanone formation. This short synthetic pathway is easily carried out, and has proven scalable and very efficient to afford dihydrochalcones in high overall yield.

Experimental section

General information

Reagents were obtained from Sigma–Aldrich, TCI or Acros with a purity >99 %. All the solvents used in flash chromatography were purchased from VWR or LaborSpirit and used without further purification. The solvents used in the reactions were purchased from Sigma–Aldrich with HPLC quality. Qualitative thin layer chromatography (TLC) was performed on pre-coated 0.50-m silica gel 60 plates with a UV indicator; compounds were detected by UV light (254 nm) and spraying with a 5 % ethanolic solution of $FeCl_3 \cdot 6H_2O$ followed by heating for phenol containing molecules. Column chromatography was carried out on silica gel (40–60 μm). Microwave assisted synthesis was performed with a CEM Discover and Explorer SP at 250 W. NMR spectra were obtained on a Bruker 400 (399.96 MHz for ^1H and 100.57 MHz for ^{13}C) spectrometer. ^1H NMR chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane, with the residual solvent peak used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), and multiplet (m). Protons and carbons in ring A are assigned as H′, C′, in ring B as H″, C″, while those belonging to the propanone or propenone moiety are assigned as C, H in order to facilitate the description of the corresponding chemical shifts. Melting points were obtained on a Stuart SMP 30 apparatus. HRMS spectra were acquired in an FTICR mass spectrometer equipped with a dual ESI/MALDI ion source and a 7T actively shielded magnet.

Experimental synthetic procedures and compounds' characterization

1-[4-(Ethoxymethoxy)-2-hydroxyphenyl]ethan-1-one (2)

To a solution of 2′,4′-dihydroxyacetophenone (**1**) (65.7 mmol) in dichloromethane (55.0 mL) was added *N*,*N*-diisopropylethylamine (DIPEA) (2.2 equiv.) at 0 °C and the solution was stirred for 15 min. Ethoxymethyl chloride (2.2 equiv.) was added and the reaction mixture was kept for 15 min at 0 °C and then temperature allowed to increase to room temperature. The reaction was monitored by TLC and after 2 h the mixture was poured into water and extracted with dichloromethane. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The product was purified by column chromatography (60:1 hexane/ethyl acetate) and obtained as an oil in 93.8 % yield. R_f (6:1 hexane/ethyl acetate) = 0.60; ^1H RMN ($CDCl_3$), δ (*ppm*) 12.63 (s, 1H, OH-2′); 7.62 (d, 1H, $J_{5',6'} = 8.87$ Hz, H-6′); 6.59 (d, 1H, $J_{3,5} = 1.66$ Hz, H-3′); 6.55 (dd, 1H, H-5′); 5.25 (s, 2H, O$\underline{CH_2}$O); 3.72 (q, 2H, $J_{CH2,CH3'} = 7.11$ Hz, $C\underline{H_2}$-Et); 2.56 (s, 3H, H-2); 1.22 (t, 3H, CH_3-Et); ^{13}C RMN ($CDCl_3$), δ (*ppm*) 202.7 (C-1); 164.8 (C-2′); 163.8 (C-4′); 132.4 (C-6′); 114.6 (C-1′); 108.2 (C-5′); 103.7 (C-3′); 92.7 (O$\underline{C}H_2$C); 64.8 ($\underline{C}H_2$-Et); 26.3 (C-2); 15.1 ($\underline{C}H_3$-Et); HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{11}H_{15}O_4$ 211.09649; found 211.09656.

General procedure for the synthesis of 4′-(ethoxymethoxy)-2′-hydroxychalcones (conventional reaction conditions)

To a solution of 1-[4-(ethoxymethoxy)-2-hydroxyphenyl]ethan-1-one (**2**) (200 mg, 0.703 mmol) and the aryl aldehyde (2.0 equiv.) in 1,4-dioxane (4.1 mL) was added, at room temperature, sodium hydroxide aqueous solution 50 % (w/v) (4.1 mL). The reaction was stirred for 24 h at room temperature. The solution was neutralized using 10 % HCl aqueous solution. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated in vacuum. Chalcones were purified by column chromatography (30:1 hexane/ethyl acetate).

General microwave assisted procedure for the synthesis of 4′-(ethoxymethoxy)-2′-hydroxychalcones

To solution of 1-[4-(ethoxymethoxy)-2-hydroxyphenyl]ethan-1-one (**2**) (200 mg, 0.703 mmol) and the aryl aldehyde (2.0 equiv.) in 1,4-dioxane (4.1 mL) was added, at room temperature, sodium hydroxide aqueous solution 50 % (w/v) (4.1 mL). The reaction proceeded in a microwave oven at 250 W and 40 °C for 3 h. The solution was neutralized using 10 % HCl aqueous solution. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The chalcones derivatives were purified by column chromatography (30:1 hexane/ethyl acetate).

(*E*)-1-[4-(Ethoxymethoxy)-2-hydroxyphenyl]-3-(4-methylphenyl)prop-2-en-1-one (4)

Yield 89.2 %; MW 92.8 %; orange solid; m.p. = 91.7–92.1 °C; R_f (8:1 hexane/ethyl acetate) = 0.24; ^{1}H RMN ($CDCl_3$) δ (*ppm*)13.34 (s, 1H, OH-2′); 7.88 (d, 1H, $J_{2,3}$ = 15.04 Hz, H-3); 7.84 (d, 1H, $J_{5',6'}$ = 8.11, H-6′); 7.55 (d, 2H, $J_{2'',3''} = J_{5'',6''}$ = 7.73 Hz, H-2″, H-6″); 7.54 (d, 1H, H-2); 7.23 (d, 2H, H-3″, H-5″); 6.65 (d, 1H, $J_{3',5'}$ = 1.52 Hz, H-3′); 6.59 (dd, 1H, H-5′); 5.27 (s, 2H, O$\underline{C}H_2$O); 3.73 (q, 2H, $J_{CH2,CH3}$ = 7.03 Hz, $\underline{C}H_2$-Et); 2.40 (s, 3H, $\underline{C}H_3$-4″); 1.23 (t, 3H, CH_3-Et); ^{13}C RMN ($CDCl_3$) δ (*ppm*) 192.1 (C-1); 166.2 (C-2′); 163.8 (C-4′); 144.7 (C-3); 141.3 (C-4″); 132.0 (C-1″); 131.3 (C-6′); 129.8 (C-3″, C-5″); 128.6 (C-2″, C-6″); 119.3 (C-2); 114.9 (C-1′); 108.2 (C-5′); 103.9 (C-3′); 92.8 (O$\underline{C}H_2$O); 64.8 ($\underline{C}H_2$-Et); 21.6 ($\underline{C}H_3$-4″); 15.1 (CH_3-Et); HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{19}H_{20}NaO_4$ 335.12538; found 335.12582.

(*E*)-1-[4-(Ethoxymethoxy)-2-hydroxyphenyl]-3-(4-fluorophenyl)prop-2-en-1-one (5)

Yield 91.2 %; MW 86.3 %; orange solid; m.p. = 96.3–96.8 °C; R_f (8:1 hexane/ethyl acetate) = 0.44; ^{1}H RMN ($CDCl_3$) δ (*ppm*) 13.27 (s, 1H, OH-2′); 7.88 (d, 1H, $J_{2,3}$ = 15.43 Hz, H-3); 7.86 (d, 1H, $J_{5',6'}$ = 8.82 Hz, H-6′); 7.67 (dd, 2H, $J_{2'',F} = J_{6'',F}$ = 5.40 Hz, $J_{2'',3''} = J_{6'',5''}$ = 8.72 Hz, H-2″, H-6″); 7.53 (d, 1H, H-2); 7.15 (t, 2H, $J_{3'',F} = J_{5'',F} = J_{2'',3''} = J_{6'',5''}$ = 8.72 Hz, H-3″, H-5″); 6.68 (d, 1H, $J_{3',5'}$ = 2.32 Hz, H-3′); 6.62 (dd, 1H, H-5′); 5.30 (s, 2H, O$\underline{C}H_2$O); 3.76 ($J_{CH2,CH3}$ = 7.13 Hz, CH_2, Et); 1.28 (t, 3H, CH_3, Et); ^{13}C RMN ($CDCl_3$) δ (*ppm*) 191.8 (C-1); 166.3 (C-2′); 163.9 (C-4′); 163.9 (d, $J_{C,F}$ = 252.5 Hz, C-4″); 143.2 (C-3); 131.0 (d, $J_{C,F}$ = 3.4 Hz, C-1″); 131.3 (C-6′); 130.5 (d, $J_{C,F}$ = 8.4 Hz, C-2″, C-6″); 120.0 (C-2); 116.2 (d, $J_{C,F}$ = 21.7 Hz, C-3″, C-5″); 114.8 (C-1′); 108.3 (C-5′); 103.9 (C-3′); 92.8 (O$\underline{C}H_2$O); 64.9 ($\underline{C}H_2$, Et); 15.1 ($\underline{C}H_3$, Et); HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{18}H_{17}FNaO_4$ 339.10031; found 339.10069

(*E*)-3-(4-Bromophenyl)-1-[4-(ethoxymethoxy)-2-hydroxyphenyl]prop-2-en-1-one (6)

Yield 85.0 %; MW 86.0 %; orange solid; m.p. = 78.7–79.2 °C; R_f (8:1 hexane/ethyl acetate) = 0.36; ^{1}H RMN (acetone-d^6) δ (*ppm*) 13.35 (s, 1H, OH-2′); 8.23 (d, 1H, $J_{5',6'}$ = 8.57 Hz, H-6′); 8.03 (d, 1H, $J_{2,3}$ = 15.21 Hz, H-2); 7.86 (d, 2H, H-3); 7.84 (dd, 2H, $J_{2'',3''} = J_{6'',5''}$ = 8.97 Hz, H-2″, H-6″); 7.66 (d, 2H, H-3″, H-5″); 6.64 (dd, 1H, $J_{3',5'}$ = 2.39 Hz, H-5′); 6.61 (d, 1H, H-3′); 5.36 (s, 2H, O$\underline{C}H_2$O); 3.74 (q, 2H, $J_{CH2,CH3}$ = 7.07 Hz, CH_2, Et); 1.20 (t, 3H, CH_3, Et); ^{13}C RMN (acetone-d^6) δ (*ppm*) 192.1 (C-1); 166.3 (C-2′); 164.2 (C-4′); 142.9 (C-3); 134.2 (C-1″); 132.2 (C-6′); 132.1 (C-2″, C-6″);

130.6 (C-3″, C-5″); 124.3 (C-4″); 121.6 (C-2); 114.6 (C-1′); 108.3 (C-5′); 103.3 (C-3′); 92.8 (O<u>C</u>H$_2$O); 64.4 (<u>C</u>H$_2$, Et); 14.6 (<u>C</u>H$_3$, Et); HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{18}H_{17}BrNaO_4$ 399.02024; found 399.02084

(*E*)-3-[4-(Benzyloxy)phenyl]-1-[4-(ethoxymethoxy)-2-hydroxyphenyl]prop-2-en-1-one (7)

Yield 92.3 %; MW 93.8 %; orange solid; m.p. = 101.5–102.0 °C; R_f (8:1 hexane/ethyl acetate) = 0.56; ^{1}H RMN ($CDCl_3$) δ (*ppm*) 13.40 (s, 1H, OH-2′); 7.86 (d, 1H, $J_{2,3}$ = 14.14 Hz, H-3); 7.83 (d, 1H, $J_{6',5'}$ = 8.45 Hz, H-6′); 7.61 (d, 2H, $J_{2'',3''} = J_{2'',3''}$ = 8.45 Hz, H-2″, H-6″); 7.48–7.32 (m, 6H, H-2, Ar<u>H</u>); 7.02 (d, 2H, H-3″, H-5″); 6.65 (d, 1H, $J_{3',5'}$ = 2.26 Hz, H-3′); 6.58 (dd, 1H, H-5′); 5.27 (s, 2H,O<u>C</u>H$_2$O); 5.12 (s, 2H, -O<u>C</u>H$_2$Ph);3.73 (q, 2H, $J_{CH2,CH3}$ = 7.20 Hz, CH$_2$, Et); 1.23 (t, 3H, CH$_3$, Et); ^{13}C RMN ($CDCl_3$) δ (*ppm*) 192.0 (C-1); 166.1 (C-2′); 163.7 (C-4′); 160.9 (C-4″); 144.3 (C-3); 136.4 (<u>C</u$_q$, Ph); 131.2 (C-6′); 130.4 (C-2″, C-6″); 128.7, 128.2, 127.5 (<u>C</u>H, Ph); 127.7 (C-1″); 117.9 (C-2); 115.3 (C-3″, C-5″); 114.9 (C-1′); 108.2 (C-5′); 103.9 (C-3′); 92.8 (O<u>C</u>H$_2$O); 70.1 (-O<u>C</u>H$_2$Ph); 64.8 (<u>C</u>H$_2$, Et); 15.1 (<u>C</u>H$_3$, Et); HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{25}H_{24}NaO_5$ 427.15159; 427.15250.

(*E*)-1-[4-(Ethoxymethoxy)-2-hydroxyphenyl]-3-(5-methylfuran-2-yl)prop-2-en-1-one (8)

Yield 68.9 %; MW 74.6 %; reddish solid; m.p. = 127.4–127.7 °C; R_f (8:1 hexane/ethyl acetate) = 0.52; ^{1}H RMN (acetone-d^6) δ (*ppm*) 13.52 (s, 1H, OH-2′); 8.06 (d, 1H, $J_{5',6'}$ = 8.95, H-6′); 7.66 (d, 1H, $J_{2,3}$ = 15.14 Hz, H-2); 7.53 (d, 1H, H-3); 6.94 (d, 1H, $J_{3'',4''}$ = 3.60 Hz, H-3″); 6.65 (d, 1H, $J_{3',5'}$ = 2.20 Hz, H-5′); 6.59 (dd, 1H, H-3′); 6.31 (d, 1H, H-4″); 5.36 (s, 2H, O<u>C</u>H$_2$O); 3.75 (q, 2H, $J_{CH2,CH3}$ = 7.10 Hz, CH$_2$, Et); 2.42 (s, 3H, C<u>H</u$_3$-5″); 1.20 (t, 3H,C<u>H</u$_3$, Et); ^{13}C RMN (acetone-d^6) δ (*ppm*) 191.7 (C-1); 166.1 (C-2′); 163.9 (C-4′); 156.7 (C-5″); 150.4 (C-2″); 131.7 (C-6′); 130.6 (C-2); 119.0 (C-3″); 115.8 (C-3); 114.6 (C-1′); 109.7 (C-4″); 108.3 (C-5′); 103.3 (C-3′); 92.7 (O<u>C</u>H$_2$O); 64.4 (<u>C</u>H$_2$, Et); 14.5 (<u>C</u>H$_3$, Et); 13.0 (<u>C</u>H$_3$-4″); HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{17}H_{18}NaO_5$ 325.10464; 325.10494.

General procedure for the synthesis of 4′-fluoro-2′-hydroxychalcones (conventional reaction conditions)

To solution of 1-(4-fluoro-2-hydroxyphenyl)ethan-1-one (**3**) (200 mg, 1.30 mmol) and the aryl aldehyde (2.0 equiv.) in ethanol (2.5 mL), sodium hydroxide aqueous solution 50 % (w/v) (2.5 mL) was added at room temperature. The reaction mixture was stirred for 24 h at room temperature. The solution was neutralized with 10 % HCl aqueous solution. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated in vacuum. Chalcones were purified by column chromatography (40:1 hexane/ethyl acetate).

General microwave assisted procedure for the synthesis of 4′-fluoro-2′- hydroxychalcones

To solution of 1-(4-fluoro-2-hydroxyphenyl)ethan-1-one (**4**) (200 mg, 1.300 mmol) and the aryl aldehyde (2.0 equiv.) in ethanol (2.5 mL) sodium hydroxide aqueous solution 50 % (w/v) (2.5 mL) was added at room temperature. The reaction proceeded in a microwave oven at 250 W and 40 °C for 2 h. The solution was neutralized with 10 % HCl aqueous solution. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated in vacuum. Chalcones were purified by column chromatography (30:1 hexane/ethyl acetate).

(*E*)-1-(4-fluoro-2-hydroxyphenyl)-3-(4-methylphenyl)prop-2-en-1-one (9)

Yield 83.0 %; MW 95.1 %; redish solid; m.p. = 87.9–88.3 °C; R_f (10:1 hexane/ethyl acetate) = 0.54; ^{1}H RMN (acetone-d^6) δ 13.43 (s, 1H, OH-2′); 8.42 (dd, 1H, $J_{6',F}$ = 6.50, $J_{5',6'}$ = 8.83, H-6′); 8.02 (d, 1H, $J_{2,3}$ = 15.38 Hz, H-2); 7.95

(d, 1H, H-3); 7.81 (d, 2H, $J_{2'',3''} = J_{5'',6''} = 8.73$ Hz, H-2″, H-6″); 7.32 (d, 2H, H-3″, H-5″); 6.82–6.74 (m, 2H, H-3′, H-5′); 2.40 (s, 1H, C<u>H</u>$_3$-4″); ^{13}C RMN (acetone-d^6) 193.0 (C-1); 167.0 (d, $J_{C,F} = 249.9$ Hz, C-4′); 167.1 (C-2′); 146.6 (C-3); 142.6 (C-4″); 134.2 (d, $J_{C,F} = 11.7$ Hz, C-6′); 132.9 (C-1″); 130.6 (C-3″, C-5″); 130.1 (C-2″, C-6″); 120.2 (C-2); 118.2 (C-1′); 107.7 (d, $J_{C,F} = 23.7$ Hz, C-5′); 105.2 (d, $J_{C,F} = 23.9$ Hz, C-3′); 21.5 (<u>C</u>H$_3$-4″); HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{16}H_{14}FO_2$ 257.09723; found 257.09759.

(*E*)-1-(4-Fluoro-2-hydroxyphenyl)-3-(4-fluorophenyl)prop-2-en-1-one (10)

Yield 72.6 %; MW 87.5 %; orange solid; m.p. = 90.9–91.4 °C; R_f (10:1 hexane/ethyl acetate) = 0.63; ^{1}H RMN (acetone-d^6) δ (*ppm*) 13.33 (s, 1H, OH-2′); 8.42 (dd, 1H, $J_{6',F} = 6.82$, $J_{5',6'} = 8.93$, H-6′); 8.04–7.93 (m, 4H, H-2, H-3, H-2″, H-6″); 7.27 (t, 2H, $J_{2'',3''} = J_{5'',6''} = J_{F,3''} = J_{F,5''} = 8.66$ Hz, H-3″, H-5″); 6.80–6.74 (m, 2H, H-3′, H-5′); ^{13}C RMN (acetone-d^6) δ (*ppm*) 192.9 (C-1); 166.2 (d, $J_{C,F} = 254.3$ Hz, C-4′); 166.2 (d, $J_{C,F} = 7.8$ Hz, C-2′); 167.2 (d, $J_{C,F} = 254.1$ Hz, C-4″); 144.3 (C-3); 133.4 (d, $J_{C,F} = 12.4$ Hz, C-6′); 131.4 (d, $J_{C,F} = 8.4$ Hz, C-1″, C-2″, C-6″); 120.4 (C-2); 117.2 (C-1′); 115.9 (d, $J_{C,F} = 21.8$ Hz, C-3″, C-5″); 106.9 (d, $J_{C,F} = 21.8$ Hz, C-5′); 104.3 (d, $J_{C,F} = 24.4$ Hz, C-3′); HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{15}H_{11}F_2O_2$ 261.07216; 261.07361.

(*E*)-3-(4-Bromophenyl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-one (11)

Yield 87.3 %; MW 93.1 %; yellow solid; m.p. = 89.4–89.9 °C; R_f (10:1 hexane/ethyl acetate) = 0.59; ^{1}H RMN (acetone-d^6) δ (*ppm*) 13.29 (s, 1H, OH-2′); 8.43 (dd, 1H, $J_{6',F} = 7.04$, $J_{5',6'} = 8.71$, H-6′); 8.11 (d, 1H, $J_{2,3} = 15.68$ Hz, H-2); 7.93 (d, 1H, H-3); 7.88 (d, 2H, $J_{2'',3''} = J_{5'',6''} = 8.28$ Hz, H-2″, H-6″); 7.69 (d, 2H, H-3″, H-5″); 6.83–6.75 (m, 2H, H-3′, H-5′); ^{13}C RMN (acetone-d^6) δ (*ppm*) 193.9 (C-1); 169.6 (d, $J_{C,F} = 250.9$ Hz, C-4′); 167.1 (d, $J = 13.9$ Hz, C-2′); 144.9 (C-3); 125.6 (C-4″); 134.4 (d, $J_{C,F} = 11.9$ Hz, C-6′); 134.8 (C-1″); 133.0 (C-3″, C-5″); 131.7 (C-2″, C-6″); 122.2 (C-2); 118.1 (C-1′); 107.8 (d, $J_{C,F} = 23.6$ Hz, C-5′); 105.2 (d, $J_{C,F} = 23.5$ Hz, C-3′); HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{15}H_{11}BrFO_2$ 320.99210; found 320.99422.

(*E*)-3-[4-(Benzyloxy)phenyl]-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-one (12)

Yield 89.9 %; MW 90.5 %; reddish solid; m.p. = 95.4–95.7.0 °C; R_f (10:1 hexane/ethyl acetate) = 0.60; ^{1}H RMN (acetone-d^6) δ (*ppm*) 13.50 (s, 1H, OH-2′); 8.40 (dd, 1H, $J_{6',F} = 6.60$, $J_{5',6'} = 8.97$, H-6′); 7.96 (d, 1H, $J_{2,3} = 15.32$ Hz, H-2); 7.90 (d, 1H, H-3); 7.88 (d, 2H, $J_{2'',3''} = J_{5'',6''} = 8.66$ Hz, H-2″, H-6″); 7.53–7.35 (m, 5H, C<u>H</u>, Ph); 7.15 (t, 2H, H-3″, H-5″); 6.81–6.72 (m, 2H, H-3′, H-5′); 5.24 (s, 2H, C<u>H</u>$_2$Ph); ^{13}C RMN (Acetone-d^6) δ (*ppm*) 192.9 (C-1); 168.5 (d, $J_{C,F} = 251.9$ Hz, C-4′); 165.6 (C-2′); 161.5 (C-4″); 145.6 (C-3); 136.9 (<u>C</u>$_q$, Ph); 133.2 (d, $J_{C,F} = 11.6$ Hz, C-6′); 131.1 (C-2″, C-6″); 128.5 (<u>C</u>H, Ph); 127.9 (<u>C</u>H, Ph); 127.6 (<u>C</u>H, Ph); 127.5 (C-1″); 117.9 (C-2); 117.3 (C-1′); 115.4 (C-3″, C-5″); 106.7 (d, $J_{C,F} = 22.4$ Hz, C-5′); 104.2 (d, $J_{C,F} = 23.8$ Hz, C-3′); 69.8 (<u>C</u>H$_2$Ph); HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{15}H_{11}BrFO_2$ 320.99210; found 320.99422.

(*E*)-1-(4-Fluoro-2-hydroxyphenyl)-3-(5-methylfuran-2-yl)prop-2-en-1-one (13)

Yield 84.6 %; MW 89.9 %; reddish oil; R_f (10:1 hexane/ethyl acetate) = 0.63; ^{1}H RMN (acetone-d^6) δ (*ppm*) 13.33 (s, 1H, OH-2′); 8.10 (dd, 1H, $J_{6',F} = 7.12$, $J_{5',6'} = 8.57$, H-6′); 7.56 (d, 1H, $J_{2,3} = 14.84$ Hz, H-2); 7.42 (d, 1H, H-3); 6.87 (d, 1H, $J_{3'',4''} = 2.70$ Hz, H-3″); 6.59 (dd, $J_{3',5'} = 1.89$ Hz, $J_{3',F} = 10.75$ Hz, H-3′); 6.68–6.63 (m, 1H, H-5′); 6.19 (d, 1H, H-4″); 2.28 (s, 3H, C<u>H</u>$_3$-5″); ^{13}C RMN (acetone-d^6) δ (*ppm*) 192.4 (C-1); 167.5 (d, $J_{C,F} = 260.1$ Hz, C-4′); 166.0 (C-2′); 157.2 (C-5″); 150.3 (C-2″); 132.9 (d, $J_{C,F} = 11.9$ Hz, C-6′); 131.5 (C-2); 119.9 (C-3″); 117.2 (C-1′); 115.3 (C-3); 109.9 (C-4″); 106.8 (d, $J = 22.9$ Hz, C-5′); 104.3 (d, $J = 23.4$ Hz, C-3′); 13.1 (<u>C</u>H$_3$-4′); HRMS-ESI (*m*/*z*): [M + H]$^+$ calcd for $C_{14}H_{12}FO_3$ 247.07650; found 247.07688.

General procedure for the synthesis of 2′,4′-dihydroxychalcones (conventional reaction conditions)

The protected chalcones (**4–8**) (0.5 mmol) were dissolved in methanol (6.4 mL) and $FeCl_3 \cdot 6H_2O$ (2.5 equiv.) was added. After 2 h–3 h under reflux, the reaction mixture was concentrated and purified by column chromatography (3:1 hexane/ ethyl acetate) to give the 2′,4′-dihydroxychalcones.

General microwave-assisted procedure for the synthesis of 2′,4′-dihydroxychalcones

The protected chalcones (**4–8**) (0.5 mmol) were dissolved in methanol (6.4 mL) and $FeCl_3 \cdot 6H_2O$ (2.5 equiv.) was added. The reaction proceeded in the microwave oven at 250 W and 65 °C for 7 min. The residues were concentrated and purified by column chromatography (3:1 hexane/ethyl acetate) to afford the 2′,4′-dihydroxychalcones.

(*E*)-1-(2,4-Dihydroxyphenyl)-3-(4-methylphenyl)prop-2-en-1-one (14)

Yield 96.8 %; MW 97.2 %; yellow solid; m.p. = 132.1–133.4 °C; R_f (3:1 hexane/ethyl acetate) = 0.12; ^{1}H RMN (acetone-d^6) δ (*ppm*) 13.55 (s, 1H, OH-2′); 9.56 (s, 1H, OH-4′); 8.18 (d, 1H, $J_{5',6'}$ = 7.19, H-6′); 7.93 (d, 1H, $J_{2,3}$ = 15.53 Hz, H-2); 7.86 (d, 1H, H-3); 7.77 (d, 2H, $J_{2'',3''} = J_{5'',6''}$ = 7.86 Hz, H-2″, H-6″); 7.31 (d, 2H, H-3″, H-5″); 6.50 (dd, 1H, $J_{3',5'}$ = 1.97 Hz, H-5′); 6.39 (dd, 1H, H-3′); 2.40 (s, 1H, C$\underline{H}_3$-4″); ^{13}C RMN (acetone-d^6) δ (*ppm*) 191.9 (C-1); 166.8 (C-2′); 164.9 (C-4′); 144.0 (C-3); 141.1 (C-4″); 132.6 (C-6′); 132.3 (C-1″); 119.7 (C-2); 129.6 (C-3″, C-5″);128.9 (C-2″, C-6″); 113.6 (C-1′); 107.9 (C-5′); 102.8 (C-3′); 20.6 (C$\underline{H}_3$-4″); HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{16}H_{14}NaO_3$ 277.08352; found 277.08370.

(*E*)-1-(2,4-Dihydroxyphenyl)-3-(4-fluorophenyl)prop-2-en-1-one (15)

Yield 84.6 %; MW 94.5 %; yellow solid; m.p. = 129.1–129.8 °C; R_f (3:1 hexane/ethyl acetate) = 0.30; ^{1}H RMN (acetone-d^6) δ (*ppm*) 13.49 (s, 1H, OH-2′); 9.52 (s, 1H, OH-4′); 8.17 (d, 1H, $J_{5',6'}$ = 8.93, H-6′); 7.98–7.93 (m, 3H, H-2, H-2″, H-6″); 7.87 (d, 1H, $J_{2,3}$ = 15.53 Hz, H-3); 7.26 (t, 2H, $J_{2'',3''} = J_{5'',6''} = J_{5'',F} = J_{3'',F}$ = 8.84 Hz, H-3″, H-5″); 6.50 (dd, 1H, $J_{3',5'}$ = 1.44 Hz, H-5′); 6.40 (dd, 1H, H-3′); ^{13}C RMN (acetone-d^6) δ (*ppm*) 191.8 (C-1); 166.8 (C-2′); 165.0 (C-4′); 164.0 (d, $J_{C,F}$ = 248.7 Hz, C-4″); 142.6 (C-3); 132.7 (C-6′); 131.6 (d, $J_{C,F}$ = 2.9 Hz, C-1″); 131.1 (d, $J_{C,F}$ = 8.8 Hz, C-2″, C-6″); 120.7 (C-2); 115.9 (d, $J_{C,F}$ = 22.1 Hz, C-3″, C-5″); 113.6 (C-1′); 108.0 (C-5′); 102.9 (C-3′); HRMS-ESI (*m*/*z*): [M + H]$^+$ calcd for $C_{15}H_{12}FO_3$ 259.07650; found 259.07678.

(*E*)-3-(4-Bromophenyl)-1-(2,4-dihydroxyphenyl)prop-2-en-1-one (16)

Yield 93.7 %; MW 98.1 %; yellow solid; m.p. = 134.6–135.0 °C; R_f (3:1 hexane/ethyl acetate) = 0.45; ^{1}H RMN (acetone-d^6) δ (*ppm*) 13.42 (s, 1H, OH-2′); 9.64 (s, 1H, OH-4′); 8.17 (d, 1H, $J_{5',6'}$ = 8.86, H-6′); 8.02 (d, 1H, $J_{2,3}$ = 15.28 Hz, H-2); 7.86–7.83 (m, 3H, H-3, H-2″, H-6″); 7.67 (d, 2H, $J_{2'',3''} = J_{5'',6''}$ = 8.39 Hz, H-3″, H-5″); 6.50 (dd, 1H, $J_{3',5'}$ = 1.92 Hz, H-5′); 6.40 (d, 1H, H-3′); ^{13}C RMN (acetone-d^6) δ (*ppm*) 191.7 (C-1); 166.8 (C-2′); 165.1 (C-4′); 142.4 (C-3); 134.3 (C-1″); 132.7 (C-6′); 132.1 (C-3″, C-5″); 130.5 (C-2″, C-6″); 124.2 (C-4″); 121.7 (C-2); 113.6 (C-1′); 108.1 (C-5′); 102.9 (C-3′); HRMS-ESI (*m*/*z*): [M + H]$^+$ calcd for $C_{15}H_{12}BrO_3$ 318.99643; found 318.99680.

(*E*)-3-[4-(Benzyloxy)phenyl]-1-(2,4-dihydroxyphenyl)prop-2-en-1-one (17)

Yield 96.7 %; MW 97.8 %; yellow solid; m.p. = 127.5–128.1 °C; R_f (3:1 hexane/ethyl acetate) = 0.21; ^{1}H RMN (acetone-d^6) δ (*ppm*) 13.62 (s, 1H, OH-2′); 9.68 (s, 1H, OH-4′); 8.15 (d, 1H, $J_{5',6'}$ = 8.88, H-6′); 7.89–7.80 (m, 4H, H-2,

H-3, H-2″, H-6″); 7.52–7.36 (m, 5H, ArH, Ph); 7.12 (d, 2H, $J_{2'',3''} = J_{5'',6''} = 8.71$ Hz, H-3″, H-5″); 6.49 (dd, 1H, $J_{3',5'} = 2.19$ Hz, H-5′); 6.40 (d, 1H, H-3′); 5.22 (s, 2H, CH_2Ph); ^{13}C RMN (acetone-d^6) δ (*ppm*) 191.9 (C-1); 166.7 (C-2′); 164.8 (C-4′); 161.1 (C-4″); 143.9 (C-3); 137.0 (C_q, Ph); 132.5 (C-6′); 130.7 (C-2″, C-6″); 128.8 (CH, Ph); 128.2 (CH, Ph); 127.9 (CH, Ph); 127.8 (C-1″); 118.4 (C-2); 115.3 (C-3″, C-5″); 113.6 (C-1′); 107.8 (C-5′); 102.9 (C-3′); 69.7 (CH_2Ph); HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{18}NaO_4$ 369.10973; found 369.10992.

(*E*)-1-(2,4-Dihydroxyphenyl)-3-(5-methylfuran-2-yl)prop-2-en-1-one (18)

Yield 90.9 %; MW 97.6 %; yellow solid; m.p. = 125.6–125.9 °C; R_f (3:1 hexane/ethyl acetate) = 0.35; ^{1}H RMN (acetone-d^6) δ (*ppm*) 13.43 (s, 1H, OH-2′); 9.41 (s, 1H, OH-4′); 7.85 (d, 1H, $J_{5',6'} = 8.65$, H-6′); 7.48 (d, 1H, $J_{2,3} = 14.92$ Hz, H-2); 7.37 (d, 1H, H-3); 6.78 (d, $J_{3'',4''} = 2.84$ Hz, H-3″); 6.36 (dd, 1H, $J_{3',5'} = 1.98$ Hz, H-5′); 6.23 (d, 1H, H-3′); 6.16 (d, 1H, H-4″); 2.27 (s, 3H, CH_3-5″); ^{13}C RMN (acetone-d^6) δ (*ppm*) 191.3 (C-1); 166.6 (C-2′); 164.8 (C-4′); 156.4 (C-5″); 150.4 (C-2″); 132.2 (C-6′); 130.2 (C-2); 118.7 (C-3″); 115.9 (C-3); 113.5 (C-1′); 109.6 (C-4″); 108.0 (C-5′); 102.9 (C-3′); 13.0 (CH_3-5″); HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{13}O_4$ 245.08084; found 245.08115.

General procedure for the synthesis of dihydrochalcones

To a solution of chalcone (2.0 mmol) in ethyl acetate (5 mL), methanol was added (2–3 mL). Pd/C (10 % mmol) was added to this solution in N_2 atmosphere. Triethylsilane (Et_3SiH) (5–10 equiv.) was slowly added until hydrogen is being formed *in situ*. After complete addition of Et_3SiH, the reaction mixture was kept at room temperature for 10–30 min until reaction mixture color change (orange/yellow to clear). TLC confirmed reaction completion. Catalyst was filtered off through celite. Solvent was removed in vacuo and the residue extraction with acetonitrile/hexane removed most of the Et_3SiH from the mixture. The final product was purified by column chromatography (10:1 or 7:1 hexane/ethyl acetate).

1-(2,4-Dihydroxyphenyl)-3-(4-methylphenyl)propan-1-one (19)

Yield 99.1 %; white solid; m.p. = 190.0–190.7 °C; R_f (3:1 hexane/ethyl acetate) = 0.25; ^{1}H NMR (acetone-d^6), δ (*ppm*) 12.80 (s, 2H, OH-2′); 9.62 (s, 1H, OH-4′); 7.84 (d, 1H, $J_{5',6'} = 8.78$ Hz, H-6′); 7.19 (d, 2H, $J_{2'',3''} = J_{5'',6''} = 7.90$ Hz, H-2″, H-6″); 7.10 (d, 2H, H-3″, H-5″); 6.43 (dd, 1H, $J_{3',5'} = 2.34$ Hz, H-5′); 6.33 (d, 1H, H-3′); 3.30 (t, 1H, $J_{2,3} = 7.41$ Hz, H-2); 2.99 (t, 1H, H-3); 2.89 (s, 3H, CH_3-4″); ^{13}C NMR (acetone-d^6), δ (*ppm*) 204.8 (C-1); 165.3 (C-2′, C-4′); 138.2 (C-4″); 135.7 (C-1″); 128.9 (C-2″, C-6″); 128.3 (C-3″, C-5″); 132.7 (C-6′); 112.9 (C-1′); 107.9 (C-5′); 102.7 (C-3′); 39.2 (C-2); 29.5 (C-3); 20.1 (CH_3-4″); HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{16}NaO_3$ 279.09917; found 279.09922.

1-(2,4-Dihydroxyphenyl)-3-(4-fluorophenyl)propan-1-one (20)

Yield 99.7 %; white solid; m.p. = 187.6–187.9 °C; R_f (3:1 hexane/ethyl acetate) = 0.29; ^{1}H NMR (acetone-d^6), δ (*ppm*) 12.61 (s, 2H, OH-2′); 9.52 (s, 1H, OH-4′); 7.68 (d, 1H, $J_{5',6'} = 8.78$ Hz, H-6′); 7.20 (dd, 2H, $J_{2'',3''} = J_{5'',6''} = 7.99$ Hz, $J_{6'',F} = 6.03$ Hz, H-2″, H-6″); 6.90 (t, 2H, H-3″, H-5″); 6.28 (dd, 1H, $J_{3',5'} = 2.48$ Hz, H-5′); 6.19 (d, 1H, H-3′); 3.18 (t, 1H, $J_{2,3} = 7.37$ Hz, H-2); 2.88 (t, 1H, H-3); ^{13}C NMR (acetone-d^6), δ (*ppm*) 203.7 (C-1); 165.3 (C-2′); 164.7 (C-4′); 161.4 (d, $J_{C,F} = 243.7$ Hz, C-4″); 137.3 (d, $J_{C,F} = 3.3$ Hz, C-1″); 132.7 (C-6′); 130.2 (d, $J_{C,F} = 8.1$ Hz, C-2″, C-6″); 114.8 (d, $J_{C,F} = 21.0$ Hz, C-3″, C-5″); 112.9 (C-1′); 107.9 (C-5′); 102.7 (C-3′); 39.0 (C-2); 29.1 (C-3); HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{14}FO_3$ 261.09215; found 261.09245.

1-(2,4-Dihydroxyphenyl)-3-phenylpropan-1-one (21)

Yield 98.7 %; white solid; m.p. = 190.9–191.4 °C; R_f (3:1 hexane/ethyl acetate) = 0.50; ^{1}H NMR (acetone-d^6), δ (*ppm*) 12.80 (s, 2H, OH-2′); 9.47 (s, 1H, OH-4′); 7.87 (d, 1H, $J_{5',6'}$ = 9.90 Hz, H-6′); 7.33–7.28 (m, 4H, H-2″, H-3″, H-5″, H-6″); 7.20 (t, 1H, $J_{4'',5''} = J_{5'',6''}$ = 7.56 Hz, H-4″); 6.44 (dd, 1H, $J_{3',5'}$ = 2.42 Hz, H-5′); 6.34 (d, 1H, H-3′); 3.34 (t, 1H, $J_{2,3}$ = 7.23 Hz, H-2); 3.03 (t, 1H, H-3); ^{13}C NMR (acetone-d^6), δ (*ppm*) 203.9 (C-1); 165.4 (C-2′); 164.6 (C-4′); 141.3 (C-1″); 132.7 (C-6′); 128.4 (C-2″, C-6″); 128.3 (C-3″, C-5″); 125.0 (C-4″); 112.9 (C-1′); 107.9 (C-5′); 102.7 (C-3′); 39.0 (C-2); 30.0 (C-3); HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{15}H_{14}NaO_3$ 265.08532; found 265.08366.

1-(2,4-Dihydroxyphenyl)-3-(4-hydroxyphenyl)propan-1-one (22)

Yield 99.0 %; white solid; m.p. = 205.9–206.4 °C; R_f (3:1 hexane/ethyl acetate) = 0.25; ^{1}H RMN (acetone-d^6) δ (*ppm*) 12.84 (s, 1H, OH-2′); 8.64 (brs, 1H, OH-4′); 7.81 (d, 1H, $J_{5',6'}$ = 9.13, H-6′); 7.12 (d, 2H, $J_{2'',3''} = J_{5'',6''}$ = 8.91 Hz, H-2″, H-6″); 6.78 (d, 2H, H-3″, H-5″); 6.44 (dd, 1H, $J_{3',5'}$ = 2.40 Hz H-5′); 6.35 (d, 1H, H-3′); 3.24 (t, 2H, $J_{2,3}$ = 7.86 Hz, H-2); 2.93 (t, 2H, H-3); ^{13}C RMN (acetone-d^6) δ (*ppm*) 204.2 (C-1); 165.4 (C-2′); 164.6 (C-4′); 155.6 (C-4″); 132.7 (C-6′); 131.9 (C-1″); 129.4 (C-2″, C-6″); 115.2 (C-3″, C-5″); 113.0 (C-1′); 107.9 (C-5′); 102.7 (C-3′); 39.5 (C-2); 29.4 (C-3); HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{15}H_{14}NaO_4$ 281.07843; found 281.07850.

1-(2,4-Dihydroxyphenyl)-3-(5-methylfuran-2-yl)propan-1-one (23)

Yield 98.2 %; white solid; m.p. = 198.3–198.5 °C; R_f (3:1 hexane/ethyl acetate) = 0.40; ^{1}H RMN (acetone-d^6) δ (*ppm*) 12.73 (s, 1H, OH-2′); 9.57 (s, 1H, OH-4′); 7.84 (d, 1H, $J_{5',6'}$ = 8.84, H-6′); 5.97 (d, 1H, $J_{3'',4''}$ = 2.25 Hz, H-3″); 5.86 (d, 1H, H-4″); 6.46 (dd, 1H, $J_{3',5'}$ = 1.86 Hz H-5′); 6.35 (d, 1H, H-3′); 3.31 (t, 2H, $J_{2,3}$ = 7.56 Hz, H-2); 2.98 (t, 2H, H-3); 2.21 (s, 3H, C$\underline{H}_3$-5″); ^{13}C RMN (acetone-d^6) δ (*ppm*) 203.9 (C-1); 165.3 (C-2′); 164.7 (C-4′); 152.8 (C-2″); 150.2 (C-5″); 132.7 (C-6′); 112.9 (C-1′); 107.9 (C-3″); 106.0 (C-4″); 105.9 (C-5′); 102.7 (C-3′); 35.7 (C-2); 22.4 (C-3); 12.6 (C$\underline{H}_3$-5″); HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{14}H_{14}NaO_4$ 269.07843; found 269.07860.

1-(4-Fluoro-2-hydroxyphenyl)-3-(4-methylphenyl)propan-1-one (24)

Yield 99.0 %; white solid; m.p. = 210.9–211.4 °C; R_f (3:1 hexane/ethyl acetate) = 0.53; ^{1}H RMN (acetone-d^6) δ (*ppm*) 12.72 (s, 1H, OH-2′); 8.04 (dd, 1H, $J_{6',F}$ = 6.85, $J_{5',6'}$ = 8.62, H-6′); 7.19 (d, 2H, $J_{2'',3''} = J_{5'',6''}$ = 7.75 Hz, H-2″, H-6″); 7.10 (d, 2H, H-3″, H-5″); 6.74–6.67 (m, 2H, H-3′, H-5′); 3.37 (t, 2H, $J_{2,3}$ = 7.55 Hz, H-2); 3.00 (t, 2H, H-3); 2.29 (s, 3H, C$\underline{H}_3$-4″); ^{13}C RMN (acetone-d^6) δ (*ppm*) 205.2 (C-1); 167.1 (d, $J_{C,F}$ = 220.3 Hz, C-4′); 164.8 (d, $J_{C,F}$ = 17.5 Hz, C-2′); 137.9 (C-1″); 135.3 (C-4″); 133.6 (d, $J_{C,F}$ = 11.5 Hz, C-6′); 129.0 (C-3″, C-5″); 128.3 (C-2″, C-6″); 116.7 (C-1′); 106.9 (d, $J_{C,F}$ = 22.6 Hz, C-5′); 104.2 (d, $J_{C,F}$ = 23.7 Hz, C-3′); 39.8 (C-2); 29.2 (C-3); 20.2 (C$\underline{H}_3$-4″); HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{16}H_{15}FNaO_2$ 281.09483; found 281.09501.

1-(4-Fluoro-2-hydroxyphenyl)-3-(4-fluorophenyl)propan-1-one (25)

Yield 99.3 %; white solid; m.p. = 212.7–213.3 °C; R_f (3:1 hexane/ethyl acetate) = 0.62; ^{1}H RMN (acetone-d^6) δ (*ppm*) 12.51 (s, 1H, OH-2′); 7.95 (dd, 1H, $J_{6',F}$ = 6.87, $J_{5',6'}$ = 8.70, H-6′); 7.21 (dd, 2H, $J_{2'',3''} = J_{5'',6''}$ = 8.20 Hz, $J_{2'',F} = J_{6'',F}$ = 5.93 Hz, H-2″, H-6″); 6.91 (t, 2H, $J_{3'',F} = J_{5'',F}$ = 8.68 Hz, H-3″, H-5″); 6.61–6.53 (m, 2H, H-3′, H-5′); 3.31 (t, 2H, $J_{2,3}$ = 7.83 Hz, H-2); 2.91 (t, 2H, H-3); ^{13}C RMN (acetone-d^6) δ (*ppm*) 205.1 (C-1); 167.1 (d, $J_{C,F}$ = 251.4 Hz, C-4′); 164.8 (d, $J_{C,F}$ = 14.4 Hz, C-2′); 137.0 (d, $J_{C,F}$ = 3.2 Hz, C-1″); 161.4 (d, $J_{C,F}$ = 246.4 Hz, C-4″); 133.5 (d, $J_{C,F}$ = 11.5 Hz, C-6′); 114.9

(d, $J_{C,F}$ = 2.3 Hz, C-3″, C-5″); 130.2 (d, $J_{C,F}$ = 7.9 Hz, C-2″, C-6″); 116.7 (d, $J_{C,F}$ = 2.3 Hz, C-1′); 106.8 (d, $J_{C,F}$ = 22.4 Hz, C-5′); 104.2 (d, $J_{C,F}$ = 22.5 Hz, C-3′); 39.7 (C-2); 28.6 (C-3); HRMS-ESI (*m*/*z*): [M + H]$^+$ calcd for $C_{15}H_{13}F_2O_2$ 263.08781; found 263.08951.

1-(4-Fluoro-2-hydroxyphenyl)-3-(4-phenyl)propan-1-one (26)

Yield 99.4 %; syrup; R_f (3:1 hexane/ethyl acetate) = 0.62; ^{1}H RMN (acetone-d^6) δ (*ppm*) 12.71 (s, 1H, OH-2′); 8.11 (dd, 1H, $J_{6',F}$ = 6.78, $J_{5',6'}$ = 9.31, H-6′); 7.34–7.28 (m 4H, H-2″, H-3″, H-5″, H-6″); 7.21 (t, 1H, $J_{3'',4''} = J_{4'',5''}$ = 7.02, H-4″); 6.77–6.69 (m, 2H, H-3′, H-5′); 3.46 (t, 2H, $J_{2,3}$ = 7.94 Hz, H-2); 3.06 (t, 2H, H-3); ^{13}C RMN (acetone-d^6) δ (*ppm*) 205.1 (C-1); 167.1 (d, $J_{C,F}$ = 259.2 Hz, C-4′); 164.8 (d, $J_{C,F}$ = 12.6 Hz, C-2′); 141.0 (C-1″); 133.3 (d, $J_{C,F}$ = 13.3 Hz, C-6′); 128.5 (C-3″, C-5″); 128.4 (C-2″, C-6″); 126.1 (C-4″); 116.7 (C-1′); 106.9 (d, $J_{C,F}$ = 23.6 Hz, C-5′); 104.3 (d, $J_{C,F}$ = 24.6 Hz, C-3′); 39.8 (C-2); 29.2 (C-3); 20.2 (C$\underline{H}_3$-4″); HRMS-ESI (*m*/*z*): [M + H]$^+$ calcd for $C_{15}H_{14}FO_2$ 245.09723; found 245.09863.

1-(4-Fluoro-2-hydroxyphenyl)-3-(4-hydroxyphenyl)propan-1-one (27)

Yield 98.2 %; white solid; m.p. = 209.6–209.9 °C; R_f (3:1 hexane/ethyl acetate) = 0.65; ^{1}H RMN (acetone-d^6) δ ^{1}H RMN ($CDCl_3$) δ (*ppm*) 12.73 (s, 1H, OH-2′); 8.16 (s, 1H, OH-4″); 8.10 (dd, 1H, $J_{6',F}$ = 6.64, $J_{5',6'}$ = 8.74, H-6′); 7.13 (d, 2H, $J_{2'',3''} = J_{5'',6''}$ = 7.93 Hz, H-2″, H-6″); 6.77 (d, 2H, H-3″, H-5″); 6.76–6.68 (m, 2H, H-3′, H-5′); 3.38 (t, 2H, $J_{2,3}$ = 7.49 Hz, H-2); 2.96 (t, 2H, H-3)^{13}C RMN (acetone-d^6) δ (*ppm*) 205.2 (C-1); 167.1 (d, $J_{C,F}$ = 256.3 Hz, C-4′); 164.8 (d, $J_{C,F}$ = 17.5 Hz, C-2′); 137.9 (C-1″); 135.3 (C-4″); 133.6 (d, $J_{C,F}$ = 11.5 Hz, C-6′); 129.0 (C-3″, C-5″); 128.3 (C-2″, C-6″); 116.7 (C-1′); 106.9 (d, $J_{C,F}$ = 22.6 Hz, C-5′); 104.2 (d, $J_{C,F}$ = 23.7 Hz, C-3′); 39.8 (C-2); 29.2 (C-3); 20.2 (C$\underline{H}_3$-4″); HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{15}H_{13}FNaO_3$ 283.07409; found 283.07579.

1-(4-Fluoro-2-hydroxyphenyl)-3-(5-methylfuran-2-yl)propan-1-one (28)

Yield 58.4 %; syrup; R_f (3:1 hexane/ethyl acetate) = 0.80; ^{1}H RMN (acetone-d^6) δ (*ppm*) 12.63 (s, 1H, OH-2′); 8.10 (dd, 1H, $J_{6',F}$ = 6.31, $J_{5',6'}$ = 8.32, H-6′); 6.78–6.69 (m, 2H, H-3′, H-5′); 5.99 (s, 1H, H-3″); 5.89 (s, 1H, H-4″); 3.44 (t, 2H, $J_{2,3}$ = 7.24 Hz, H-2); 3.01 (t, 2H, H-3); 2.22 (s, 3H, C$\underline{H}_3$-5″); ^{13}C RMN (acetone-d^6) δ (*ppm*) 204.7 (C-1); 167.1 (d, $J_{C,F}$ = 252.2 Hz, C-4′); 164.8 (d, $J_{C,F}$ = 13.6 Hz, C-2′); 152.6 (C-5″); 150.2 (C-2″); 133.4 (d, $J_{C,F}$ = 11.4 Hz, C-6′); 116.7 (C-1′); 106.9 (d, $J_{C,F}$ = 22.6 Hz, C-5′); 106.0 (C-4″); 105.9 (C-3″); 104.2 (d, $J_{C,F}$ = 23.8 Hz, C-3′); 36.4 (C-2); 22.1 (C-3); 12.5 (C$\underline{H}_3$-5″); HRMS-ESI (*m*/*z*): [M + H]$^+$ calcd for $C_{14}H_{14}FO_3$ 249.09215; found 249.09372.

1-(4-Fluoro-2-hydroxyphenyl)-3-(5-methyltetrahydrofuran-2-yl)propan-1-one (29)

Yield 40.8 %; syrup; R_f (3:1 hexane/ethyl acetate) = 0.69; ^{1}H RMN (acetone-d^6) δ (*ppm*) 12.74 (s, 1H, OH-2′); 8.10 (dd, 1H, $J_{6',F}$ = 6.69, $J_{5',6'}$ = 8.94, H-6′); 6.78–6.68 (m, 2H, H-3′, H-5′); 3.93–3.85 (m, 2H, H-2″, H-5″); 3.21–3.16 (m, 2H, H-2); 2.08–1.83 (m, 4H, H-3, H-3a″, H-4a″); 1.63–1.56 (m, 1H, H-3b″); 1.48–1.42 (m, 1H, H-4b″); 1.17 (d, 3H, $J_{4'',5''}$ = 5.86 Hz, C$\underline{H}_3$-5″); ^{13}C RMN (acetone-d^6) δ (*ppm*) 206.2 (C-1); 167.0 (d, $J_{C,F}$ = 253.6 Hz, C-4′); 164.8 (d, $J_{C,F}$ = 14.7 Hz, C-2′); 133.4 (d, $J_{C,F}$ = 11.6 Hz, C-6′); 116.7 (C-1′); 106.8 (d, $J_{C,F}$ = 22.2 Hz, C-5′); 104.1 (d, $J_{C,F}$ = 23.5 Hz, C-3′); 77.9 (C-2″); 75.0 (C-5″); 34.8 (C-2); 32.7 (C-4″); 30.9 (C-3″); 30.5 (C-3); 26.6 (C$\underline{H}_3$-5″); HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{14}H_{17}FNaO_3$ 275.10539; found 275.10557.

Acknowledgments: The authors are grateful to the European Union for the support of project FP7-PEOPLE-2013-IAPP, under Grant Agreement Nr. 612347 and to the Fundação para a Ciência e a Tecnologia for the support of the Ph.D. grant of Ana Rita Jesus (SFRH/BD/78236/2011), of the project PEST UID/MULTI/00612/2013 and also for the funding of the equipment used for HRMS data (project REDE/1501/REM/2005).

References

[1] D. Batovska, I. Todorova. *Cur. Clin. Pharm*. **5**, 1 (2010).
[2] P. Singh, A. Anand, V. Kumar. *Eur. J. Med. Chem*. **85**, 758 (2014).
[3] A. Gómez-Rivera, H. Aguilar-Mariscal, N. Romero-Ceronio, L. F. Roa-de la Fuente, C. E. Lobato-García. *Bioorg. Med. Chem. Lett.* **23**, 5519 (2013).
[4] Y. H. Kim, J. Kim, H. Park, H. H. P. Kim. *Biol. Pharm. Bull. **30***, 1450 (2007).
[5] D. K. Mahapatra, S. K. Bharti, S. Asati. *Eur. J. Med. Chem*.**101**, 496 (2015).
[6] T. Doan, D. Tran. *Pharmac. Pharm.* **2**, 282 (2011).
[7] S. Nielsen, M. Larsen, T. Boesen, K. Schønning, H. Kromann. *J. Med. Chem*. **48**, 2667 (2005).
[8] Y. Nakamura, S. Watanabe, N. Miyake, H. Kohno, T. Osawa. *J. Agric. Food Chem.* **51**, 3309 (2003).
[9] M. L. Go, X. Wu, X. L. Liu. *Curr. Med. Chem.* **12**, 481 (2005).
[10] S. Syam, S. I. Abdelwahab, M. A. Al-Mamary, A. Mohan. *Molecules* **17**, 6179 (2012).
[11] B. S. Jayashree, S. Arora, K. N. Venugopala. *Asian J. Chem.* **20**, 1 (2008).
[12] K. V. Gaikwad, S. V. Gaikwad, S. B. Jadhav, S. D. Rathod. *Indian J. Chem.* **49B**, 131 (2010).
[13] X. He, S. E. Kassab, G. Heinzl, F. Xue. *Tetrahedron Lett.* **56**, 1034 (2015).
[14] J. Somsrisa, P. Meepowpan, S. Krachodnok, H. Thaisuchat, S. Punyanitya, N. Nantasaen, W. Pompimon. *Molecules* **18**, 6898 (2013).
[15] M. Awouafack, S. Kouam, H. Hussain, D. Ngamga, P. Tane, B. Schulz, I. R. Green, K. Krohn. *Planta Med.* **74**, 50 (2008).
[16] A. Bentes, R. Borges, W. Monteiro, L. Macedo, C. Alves. *Molecules* **16**, 1749 (2011).
[17] M. M. D. Mohammed, A.-H.A. Hamdy, N. M. El-Fiky, W. S. A. Mettwally, A. A. El-Beih, N. Kobayashi. *Nat. Prod. Res.* **28**, 377 (2014).
[18] M. L. Climent, H. Garcia, J. Primo.*Catal. Lett.***4**, 85 (1990).
[19] K. Yoshizawa, T. Shioiri. *Tetrahedron Lett.* **47**, 4943 (2006).
[20] M. R. Ahmad, V. G. Sastry, N. Bano. *J. Pharm. Res.* **4**, 2354 (2011).
[21] X. Fang, B. Yang, Z. Cheng, P. Zhang, M. Yang. *Res. Chem. Intermed.* **40**, 1715 (2014).
[22] T. Narender, K. P. Reddy. *Tetrahedron Lett.* **48**, 3177 (2007).
[23] T. Narender, K. Venkateswarlu, B. V. Nayak, S. Sarkar. *Tetrahedron Lett.* **52**, 5794 (2011).
[24] S. Eddarir, N. Cotelle, Y. Bakkoura, C. Roland. *Tetrahedron Lett.* **44**, 5359 (2003).
[25] L. C. C. Vieira, M. W. Paixão, A. G. Corrêa. *Tetrahedron Lett*. **53**, 2715 (2012).
[26] X. Wu, H. Neumann, A. Spannenberg, T. Schulz, H. Jiao, M. Beller. *J. Am. Chem. Soc.* **132**, 14596 (2010).
[27] T. Guo, Q. Jiang, L. Yu, Z. Yu. *Chinese J. Catal.* **36**, 78 (2015).
[28] K. Tabatabaeian, M. Mamaghani, N. O. Mahmoodi, E. Keshavarz. *Arkivoc* **2**, 68 (2009).
[29] A. Hasaninejad, A. Zare, L. Balooty, H. Mehregan, M. Shekouhy. *Syn. Comm*. **1**, 488 (2010).
[30] Y. Zhou, X. Li, S. Hou, J. Xu. *J. Mol.Cat. A Chem.* **365**, 203 (2012).
[31] L. Zhang, W. Zhang, X. Wang, K. Bao, G. Lu, J. Lin. *Lett. Org. Chem*. **5**, 370 (2008).
[32] J.-P. Li, Y. X. Zhang, Y. Ji. *J. Chinese Chem. Soc*. **55**, 390 (2008).
[33] J. Jr. Dudash, X. Zhang, R. E. Zeck, S. G. Johnson, G. G. Cox, B. R. Conway, P. J. Rybczynski, K. T. Demarest. *Bioorg. Med. Chem. Lett.* **14**, 5121 (2004).
[34] Y. Suzuki, K. Uchida. in *Methods in Biotechnology: Carbohydrate Biotechnology Protocols*, C. Bucke (Ed.), vol. 10, pp. 297–312, Humana Press, Totowa, New Jersey (1999).
[35] Z. Han, M. C. Achilonu, P. S. Kendrekar, E. Joubert, D. Ferreira, S. L. Bonnet, J. H. van der Westhuizen. *J. Nat. Prod.* **77**, 583 (2014).
[36] E. Katengua-Thamahane, J. L. Marnewick, O. R. Ajuwon, N. N. Chegou, G. Szücs, P. Ferdinandy, T. Csont, C. Csonka, J. van Rooyen. *J. Inflamm*. **11**, 41 (2014).
[37] K. Henmi, Y. Hiwatashi, E. Hikita, N. Toyama, T. Hirano. *Biol. Pharm. Bull*. **32**, 1109 (2009).
[38] J. Rojas, M. Paya, L. Devesa, J. N. Dominguez, M. Ferrándiz. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **368**, 225 (2003).
[39] A. H. More, C. S. Ramaa. *Indian J. Chem.* **49B**, 364 (2010).
[40] D. Kakati, J. C. Sarma. *Chem. Central J.* **5**, 8 (2011).
[41] D. R. Palleros. *J. Chem. Edu*. **81**, 1345 (2004).
[42] L. Xia, M. Narasimhulu, X. Li, J.-J. Shim, Y. R. Lee. *Bull. Korean Chem. Soc.* **31**, 664 (2010).
[43] P. K. Mandal, J. S. McMurray. *J. Org. Chem.* **72**, 6599 (2007).
[44] D. Villemin, B. Nechab. *J. Chem. Res*. (*S*). **9**, 432 (2000).
[45] G. I. Bolestova, Z. N. Parnes, D. N. Kursanov. *J. Org. Chem*. USSR (Engl. Transl.) **15**, 1129 (1979).