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One-pot Synthesis and Antimicrobial Evolution of Some New Substituted 9-Hydroxy-4-methyl-8-phenylpyrano[2,3-*f*]chromene-2,10-diones

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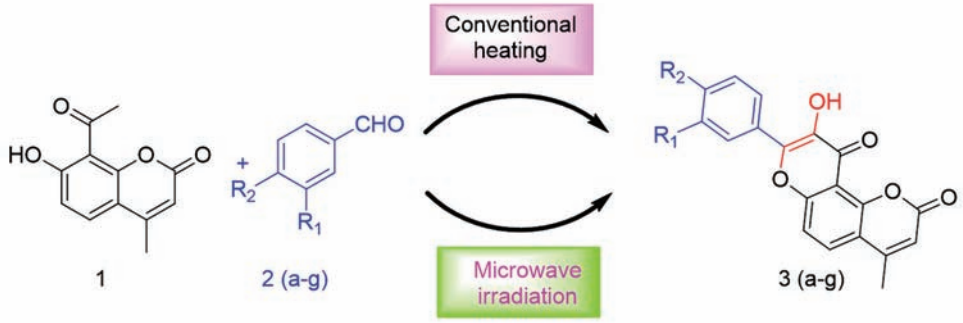
ABSTRACT A simple, inexpensive, and efficient microwave-assisted one-pot synthesis of substituted 9-hydroxy-4-methyl-8-phenylpyrano[2,3-*f*]chromene-2,10-diones **(3a-3g)** was achieved by Algar-Flynn-Oyamada reaction. All the synthesized compounds were characterized by infrared, ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, MS, and elemental analyses and screened for antibacterial and antifungal activity. Among the compounds tested, methoxy-substituted derivatives showed the best antimicrobial profile.



KEYWORDS Algar-Flynn-Oyamada reaction, Pyranochromenones, Microwave-assisted synthesis, One-pot condensation, Hydrogen peroxide.

INTRODUCTION

Chromone word is derived from the Greek word *chroma*, meaning "color," which indicates that many chromone derivatives exhibit a wide variation of colors.[1] Coumarin derivatives have been shown to possess a remarkably broad spectrum of biological activities, including antibacterial,[2] antifungal,[3-5] anticoagulant,[6] anti-inflammatory,[7] antitumor,[8,9] and anti-HIV.[10] In addition, these compounds are used as additives in food and cosmetics,[11] dispersed fluorescent brightening agents and as dyes for tuning lasers.[12] Chromenes and fused chromenes are biologically important compounds due to their antibacterial,[13] antifungal,[14] and antitumor[15] activity. 3-Hydroxyflavones **[Figure 1]**, a unique class of flavonoids, are composed of fused phenyl and pyranyl rings (A and C-rings) and a phenyl moiety (B-ring) attached to the ring C. The most studied flavonols are kaempferol and quercetin **[Figure 1]** which have been found to exhibit various biological activities, including anticancer activity.[16]

3-Hydroxyflavones are a class of natural benzopyran dyes that have well-known activities including hepatoprotective activity antibacterial activity anti-inflammatory activity[17] cytotoxic,[18-20] neuroprotective,[21] HIV inhibitory,[22] antimicrobial,[23,24] antifungal,[25] and antioxidant activities.[26] Moreover, it has been indicated that a daily intake of flavonoids from fruits and vegetables reduces the danger of coronary heart disease.[27] Hybrid compounds containing both coumarin and chromene moieties, called

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pyranochromenones, may exhibit good biological activity due to combined effect. Patil *et al*.[28] have reported such pyranochromenone derivatives as soulattrolide, inophyllum G-1, and cordatolide A [**Figure 2**]

Microwave irradiation is known to afford enhanced reaction rate and improved product yield in chemical synthesis and is quite successful in the formation of a variety of carbon-heteroatom bonds. In recent years, microwaves have been extensively used for carrying out chemical reactions and have become a useful non-conventional energy source for performing organic synthesis.[29,30]

The Algar, Flynn and Oyamada[31,32] reported more than a century ago, the synthesis of 3-hydroxyflavones, by a very simple one-pot condensation reaction of 2-hydroxyacetophenone and benzaldehyde in ethanol. In view of biological importance of 3-hydroxychromone skeleton and coumarin, we have taken up microwave-assisted synthesis of substituted 9-hydroxy-4-methyl-8-phenylpyrano[2,3-*f*]chromene-2,10-diones (**3a-3g**) by modified AFO reaction and evaluation of their antimicrobial activity.

RESULTS AND DISCUSSION

The synthesis of (**3a-3g)** was carried out using both conventional and microwave methods [**Scheme 1**]. 8-Acetyl-7-hydroxy-4-methyl-2*H*-chromen-2-one (**1)** was initially reacted with benzaldehyde (**2a)** to give the corresponding chalcone. This intermediate was used without further purification for the oxidative cyclization (Algar-Flynn-Oyamada reaction**)**, at room temperature using hydrogen peroxide (30% H_2O_2) in alkaline medium at room temperature to give the corresponding flavonol analog **3a**. As the model case, synthesis of derivatives **3a** was carried out in both conventional and microwave irradiation method. In microwave irradiation **3a** was achieved with 80% yield in 9 min, while in the conventional method, the **3a** was obtained with 65% yield in 4 h of stirring at RT. We found that microwave irradiation provides much more conversion of starting compounds and higher yields (yields 79–84%, reaction time 9–12 min) than the conventional method (yields 60–68%, reaction time 4–6 h). The comparisons of reaction time and yields of the synthesized compounds **3a-3g** in both the methods are represented in **Table 1.**

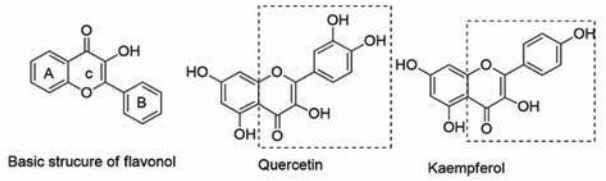


Figure 1: Structures of biologically active 3-Hydroxy flavonols

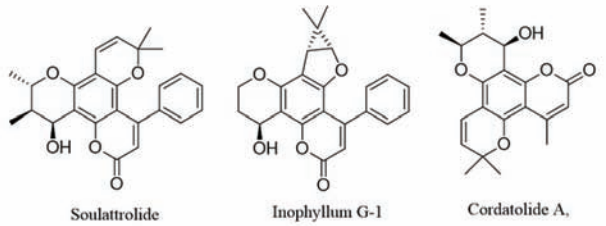


Figure 2: Structures of biologically active pyranochromenone derivatives

The compound **3a** was characterized by detailed spectral analysis, including Fourier-transform infrared (FT-IR), ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, and mass spectrum. In the IR spectrum (KBr) of **3a**, the characteristic carbonyl absorption of flavonol was observed at 1606 cm^{-1} (>C=O) and hydroxy group absorption at 3300 cm^{-1}. The ^{1}H NMR spectrum of compound **3a** exhibited a singlet at δ 6.85 corresponding to -OH proton, the protons of aromatic ring appeared as multiplet in the range of 7.11–7.56. In ^{13}C NMR spectrum of compound **3a**, the carbonyl carbon appeared at δ 177.9. ESI-MS mass spectrum of **3a** *m/z:* 321 $[M+H]^+$ appeared as a base peak.

ANTIMICROBIAL EVALUATION

Newly synthesized compounds **3a-3g** were screened for their antibacterial and antifungal activities against some selected bacteria and fungi, respectively. All the strains were compared with standard drugs. Investigation of antimicrobial data [**Table 2**] revealed that the compounds **3c** (dimethoxy)**, 3b** (methoxy), and **3d** (methyl) showed better activity in the series, but not more than ciprofloxacin. The compounds **3a, 3e, 3f,** and **3g** showed moderate activity and the rest of the compounds showed less activity. Further, among halogen-substituted compounds, the activity increased from fluoro **3e** to chloro **3f** and then to bromo **3g**.

EXPERIMENTAL SECTION

All used materials were commercial products and purchased mostly from Sigma-Aldrich and used without further purification. The melting points were determined in open capillaries and are uncorrected. The purity of the newly synthesized compounds was checked by thin-layer chromatography (TLC) on silica gel 60 F254 (Merck). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 spectrometer using tetramethylsilane as an internal standard. The IR spectra were recorded in KBr on a Shimadzu FT-IR 8400S spectrometer. The mass spectra were obtained on a Shimadzu GCMS-QP 1000 instrument. Microwave-assisted reactions were carried out in a Milestone multi-SYNTH microwave system.

General procedure for synthesis of substituted 9-hydroxy-4-methyl-8-phenyl pyrano[2,3-*f*] chromene-2,10-diones (3a-3g)

Conventional method (Method A)

To a well-stirred solution of 8-acetyl-7-hydroxy-4-methyl-2*H*-chromen-2-one (**1**, 1 mmol) and substituted benzaldehyde (**2a-2g,** 1 mmol) in ethanol (20 mL), KOH (6 mmol in 6 mL of ethanol) was added at room temperature. The reaction mixture was stirred, after consumption of the majority of reactants (as indicated by TLC), 30% H_2O_2 (3 mL) was added dropwise to the reaction mixture and continued

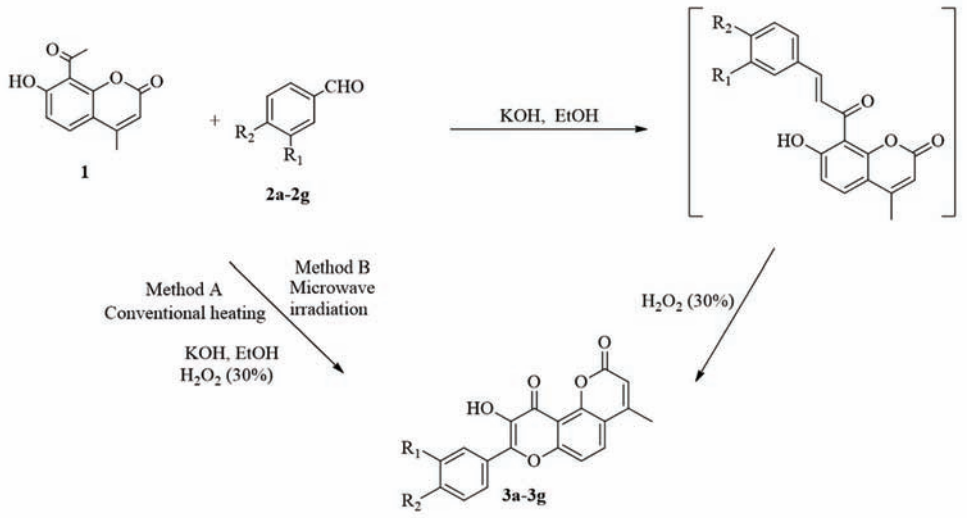
Table 1: Comparison of the time and yield of synthesized of compounds 3a-3g under both methods

Compound	M.P. (°C)	Conventional		Microwave irradiation	
		Time (h)	Yield (%)	Time (min)	Yield (%)
3a	182–184	4	65	9	80
3b	175–177	6	60	10	79
3c	184–186	5	68	10	84
3d	172–174	6	67	12	82
3e	151–153	4	66	9	80
3f	145–147	4	67	9	83
3g	170–172	5	66	10	81

Table 2: Antimicrobial activity of compounds 3a-3g

Compound	Zone of inhibition (mm)							
	S. aureus		*E. coli C.*		*C. albicans*		*A. niger*	
	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg
3a	25	25	20	19	16	15	17	15
3b	25	23	22	24	18	17	21	18
3c	26	24	23	24	19	18	19	22
3d	24	22	23	23	17	18	20	18
3e	22	20	17	16	15	13	14	15
3f	22	22	18	17	13	15	17	15
3g	24	23	20	18	14	16	16	18
Ciprofloxacin	33		29					
Gentamycin					21		25	

E. coli: Escherichia coli, S. aureus: Staphylococcus aureus, A. niger: Aspergillus niger, C. albicans: Candida albicans



	a	b	c	d	e	f	g
R_1	H	OCH_3	OCH_3	CH_3	F	Cl	Br
R_2	H	H	OCH_3	H	H	H	H

Scheme 1: Synthesis of substituted 9-hydroxy-4-methyl-8-phenyl pyrano[2,3-*f*]chromene-2,10-diones (3a-3g)

the stirring. After completion of the reaction, the resulting light yellow reaction mixture was poured on crushed ice and neutralized with dil. HCl. The light yellow solid thus obtained was filtered, washed with water, and dried. The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate (7:3v/v) as eluent to

give the desired product, substituted 9-hydroxy-4-methyl-8-phenylpyrano[2,3-*f*]chromene-2,10-diones **(3a-3g).**

Microwave irradiation method (Method B)

A mixture of 8-acetyl-7-hydroxy-4-methyl-2*H*-chromen-2-one (**1**, 1 mmol) and substituted benzaldehyde (**2a-2g,** 1 mmol) in the presence of KOH 6 mmoles, in ethanol (5 mL) was taken in a quartz tube and inserted into the Teflon vial with screw-capped and subjected to microwave irradiation at 180W, with an interval of 30 s. After consumption of the majority of reactants (as indicated by TLC), 30% H_2O_2 (3 mL) was added dropwise to the reaction mixture and continued the irradiation, after completion of reaction, the resulting light yellow reaction mixture was poured on crushed ice and neutralized with dil. HCl. The light yellow solid thus obtained was filtered, washed with water and dried. The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate (7:3v/v) as eluent to give the desired product substituted 9-hydroxy-4-methyl-8-phenyl pyrano[2,3-*f*]chromene-2,10-diones **(3a-3g).**

9-hydroxy-4-methyl-8-phenylpyrano[2,3-*f*]chromene-2,10-dione (3a)

IR (*v*, cm^{-1}, KBr): 1606 (C=O), 1748 (lactone), 3300 (-OH); ^{1}H NMR (400 MHz, $CDCl_3$, δ) ppm: *J*= Hz: 2.39 (d, 3H, -CH_3, *J* = 1.00), 6.25 (d, 1H, H_3, *J* = 1.00), 6.84–6.86 (m, 2H, H_6, OH), 7.11–7.16 (m, 2H, Ar-H), 7.23–7.27 (m, 2H, Ar-H), 7.44–7.46 (m, 1H, Ar-H), 7.55 (d, 1H, H_5, *J* = 8.78); ^{13}C NMR (100 MHz,$CDCl_3$, δ)ppm: 18.8, 114.1, 117.8, 118.8, 119.8, 120.6, 122.1, 122.8, 123.2, 123.8, 126.5, 126.9, 140.5, 141.6, 157.9, 164.3, 177.9;MS *(m/z):*321 $[M+H]^+$(100%).Analysis calculated for $C_{19}H_{12}O_5$: C, 71.25; H, 3.78; O, 24.98 Found: C, 71.27; H, 3.80; O, 25.00.

9-hydroxy-8-(4-methoxyphenyl)-4-methylpyrano[2,3-*f*]chromene-2,10-dione (3b)

IR (*v*, cm^{-1}, KBr): 1604 (C=O), 1728 (lactone), 3161 (-OH); ^{1}H NMR (400 MHz, $CDCl_3$, δ) ppm: *J*= Hz: 2.44 (d, 3H, -CH_3, *J* = 1.00), 3.88 (s, 3H, -OCH_3), 6.19 (d, 1H, H_3, *J* = 1.00), 6.95 (d, 1H, H_6, *J* = 9.03), 6.99 (s, 1H, OH), 7.05 (d, 2H,Ar- H, *J* = 8.78), 7.66-7.68 (m, 3H, Ar-H, H_5);^{13}C NMR (100 MHz,$CDCl_3$, δ)ppm:19.3, 55.4, 110.9, 114.3, 115.3, 119.4, 124.6, 127.2, 127.5, 129.5, 130.0, 130.8, 136.6, 136.9, 139.4, 160.1, 167.4, 183.4;MS *(m/z):*351 $[M+H]^+$(100%). Analysis calculated for $C_{20}H_{14}O_6$: C 68.57; H, 4.03; O, 27.40. Found: C, 68.59; H, 4.05; O, 27.42.

8-(3, 4-dimethoxyphenyl)-9-hydroxy-4-methylpyrano[2,3-*f*]chromene-2,10-dione (3c)

IR (*v*, cm^{-1}, KBr): 1606 (C=O), 1732 (lactone), 3310 (-OH); ^{1}H NMR (400 MHz, $CDCl_3$, δ) ppm: *J* = Hz: 2.44 (d, 3H, -CH_3, *J* = 1.00), 3.88 (s, 3H, -OCH_3), 3.89 (s, 3H, -OCH_3), 6.21 (d, 1H, H_3, *J* = 1.00), 6.82 (s, 1H, Ar-H), 6.91 (d, 1H, H_6, *J* = 9.03), 7.11 (s, 1H, OH), 7.04–7.08 (m, 2H, H_5, Ar- H);^{13}C NMR (100 MHz,$CDCl_3$, δ) ppm: 19.8, 55.8, 56.0, 108.8, 111.9, 114.1, 115.4, 119.6, 120.7, 122.0, 122.6, 123.6, 124.2, 125.6, 126.3, 129.5, 140.4, 146.5, 167.0, 168.1, 182.0; MS *(m/z):* 381 $[M+H]^+$(100%). Analysis calculated for. $C_{21}H_{16}O_7$: C, 66.31; H, 4.24; O, 29.45; Found: C, 66.33; H, 4.25; O, 29.47.

9-hydroxy-4-methyl-8-(*p*-tolyl)pyrano[2,3-*f*]chromene-2,10-dione (3d)

IR (*v*, cm^{-1}, KBr): 1616 (C=O), 1732 (lactone), 3320 (-OH); ^{1}H NMR (400 MHz, $CDCl_3$, δ) ppm: *J* = Hz: 2.24 (s, 3H, -CH_3), 2.44 (d, 3H, -CH_3, *J* = 1.00), 6.24 (d, 1H, H_3, *J* = 1.00), 6.88 (d, 1H, H_6, *J* = 8.78), 6.91 (d, 2H, Ar-H, *J* = 9.03), 7.11 (s, 1H, OH), 7.04 (d, 2H, Ar- H, *J* = 9.03), 7.16 (d, 1H, H_6, *J* = 8.78); ^{13}C NMR (100 MHz,$CDCl_3$, δ) ppm: 18.6, 19.8, 110.9, 114.3, 115.7, 119.5, 120.7, 122.0, 122.8, 123.6, 124.3, 125.7, 126.5, 129.7, 140.4, 146.5, 167.0, 167.8, 182.3; MS *(m/z):* 334 $[M+H]^+$(100%). Analysis calculated for $C_{20}H_{14}O_5$: C, 71.85; H, 4.22; O, 23.93; Found: C, 71.87; H, 4.24; O, 23.95.

8-(4-fluorophenyl)-9-hydroxy-4-methylpyrano[2,3-*f*]chromene-2,10-dione (3e)

IR (*v*, cm^{-1}, KBr): 1618 (C=O), 1725 (lactone), 3213 (-OH); ^{1}H NMR (400 MHz, $CDCl_3$, δ) ppm: *J*= Hz:2.41 (s, 3H, CH_3), 6.48 (s, 1H, H_3), 7.0 (s, 1H, OH) 7.3–8.1 (m, 6H, Ar-H, H_5, H_6); ^{13}C NMR (100 MHz,$CDCl_3$, δ) ppm: 19.2, 108.1, 113.2, 114.1, 114.7, 116.4, 128.6, 128.8, 130.2, 134.1, 151.3, 152.5, 157.3, 158.3, 159.5, 168.3, 175.5; MS *(m/z):* 339 $[M+H]^+$(100%). Analysis calculated for$C_{19}H_{11}FO_5$: C, 67.46; H, 3.28; O, 23.65; Found: C, 67.48; H, 3.29; O, 23.67.

8-(4-chlorophenyl)-9-hydroxy-4-methylpyrano[2,3-*f*]chromene-2,10-dione (3f)

IR (*v*, cm^{-1}, KBr): 1606 (C=O), 1745 (lactone), 3325 (-OH); ^{1}H NMR (400 MHz, $CDCl_3$, δ) ppm: *J*= Hz:2.41 (s, 3H, CH_3), 6.51 (s, 1H, H_3), 6.68 (s, 1H, OH), 7.5–8.1 (m, 6H, Ar-H, H_5, H_6); ^{13}C NMR (100 MHz,$CDCl_3$, δ)ppm: 18.6, 113.8, 114.2, 114.4, 115.2, 116.3, 112.3, 124.3, 127.8, 130.5, 130.6, 131.4, 131.8, 132.7, 153, 158.5, 159.3, 160.4, 174.9; MS *(m/z):* 355 $[M+H]^+$(100%). Analysis calculated for $C_{19}H_{11}ClO_5$.: C, 64.35; H, 3.15; O, 22.57; Found: C, 64.33; H, 3.13; O, 22.55.

8-(4-bromophenyl)-9-hydroxy-4-methylpyrano[2,3-*f*]chromene-2,10-dione (3g)

IR (*v*, cm^{-1}, KBr): 1606 (C=O); 1747 (lactone), 3305 (-OH); ^{1}H NMR (400 MHz, $CDCl_3$, δ) ppm: *J*= Hz:2.42 (s, 3H, CH_3), 6.49 (s, 1H, H_3), 7.03 (s, 1H, OH), 7.08–8.1 (m, 6H, Ar-H, H_5, H_6); ^{13}C NMR (100 MHz,$CDCl_3$, δ)ppm: 18.6, 55.5, 56.9, 107.2, 113.5, 114.4, 114.5, 115.2, 116.0, 122.2, 126.1, 128.1, 130.0, 131.5, 133.2, 153, 158.2, 160.7, 162.1, 174.98; MS *(m/z)*: 399 $[M+H]^+$(100%). Analysis calculated for $C_{19}H_{11}BrO_5$:C, 62.12; H, 3.17; N, 5.17; O, 14.78; Found: C, 62.14; H, 3.19; N, 5.19; O, 14.80.

Antimicrobial activity

Antibacterial activity

Synthesized compounds were screened for their antibacterial activities against pathogenic bacteria such as *Escherichia coli* and *Staphylococcus aureus* using the cup

plate diffusion method. The test compounds were dissolved in dimethyl sulfoxide at a concentration of 50 µg/mL, and 100 µg/mL using ciprofloxacin as standard drugs. All the inoculated plates were incubated at 37°C and the results were evaluated after 24 h of incubation **[Table 2].**

Antifungal activity

Synthesized compounds were also screened for their antifungal activity against *Aspergillus niger* and *Candida albicans* using the cup plate diffusion method. The test compounds were dissolved in dimethyl sulfoxide at a concentration of 50 µg/mL and 100 µg/mL. The zone of inhibition was observed after 7 days at 25°C and it was compared with gentamycin as standard drugs **[Table 2].**

CONCLUSION

We have successfully described the one-pot synthesis of new substituted 9-hydroxy-4-methyl-8-phenylpyrano[2,3-*f*] chromene-2,10-diones **(3a-3g)** under conventional and microwave irradiation methods. The microwave irradiation method was proved to be high yielding with a higher rate of acceleration and eco-friendly. The compounds **3c** (dimethoxy)**, 3b** (methoxy) and **3d** (methyl) were found to show better activity compared with other compounds, against standard drugs, Ciprofloxacin and Gentamycin.

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