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Synthesis of new series of 3-hydroxy/acetoxy-2-phenyl-4*H*-chromen-4-ones and their biological importance

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Abstract. 3-Hydroxy-2-aryl/heteroaryl-4*H*-chromones **4**(**a**–**n**) were synthesized from appropriate chalcones **3**(**a**–**n**) and acetylated to afford the corresponding acetoxy derivatives **5**(**a**–**n**). All compounds were evaluated for antimicrobial activity against *Staphylococus aureus*, *Bacillus subtillis*, *Escherichia coli* and *Pseudomonas aeruginosa* as well as fungi e.g., *Candida albicans* and *Aspergius niger*. Inhibition caused by hydroxy flavones was relatively low, whereas that of their acetoxy ester analogues was substantially high. Structure of 6-chloro-2-(furan-2-yl)-4-oxo-4*H*-chromen-3-yl acetate (**5j**) was also supported by means of single crystal X-ray diffraction.

Keywords. Chalcones; flavones; acetoxy ester; microwave irradiation; antimicrobial; X-ray crystal structure.

1. Introduction

Chromones constitute a major class of naturally occurring compounds and interest in their chemistry continues unabated because of their usefulness as biologically active agents.[1] Some of the biological activities attributed to chromone derivatives include cytotoxic (anticancer),[2–4] neuroprotective,[5] HIV-inhibitory,[6] antimicrobial,[7,8] antifungal[9] and antioxidant activities.[10] Chromone derivatives are present in large amounts in the human diet,[11] due to their abundance in plants and their low mammalian toxicity. Synthesis of chromone derivatives is a research field of great interest and has a long history.[12] Flavonoids (2-phenyl chromone derivatives) are phenolic compounds widely distributed in the plant kingdom. They are known to exhibit antioxidant,[13] anti-inflammatory, antimicrobial, antihypertensive, antiplatelet, gastroprotective, antitumour,[14–16] antiallergic, etc. activities. Flavonoids and iso-flavonoids, which are natural components of plants with antifungal properties, have been investigated. Consideration has been given to increase the understanding of the mode of action of these natural fungicides and of improving their effectiveness through substitutions. There is evidence that their action is linked with lipophilicity suggesting that it may be possible to increase fungitoxicity by replacing a hydroxyl group on a flavone molecule with an acetoxy group. The substituted acetic acid esters were more active in reducing mycelium growth of *Cladosporium herbarum* and *Penicillium glabrum* ' than were the hydroxylated flavones.[17–19] This prompted us to synthesize new 3-hydroxy flavones and their acetyl derivatives.

Flavonols were synthesized through a series of reactions on the corresponding o-hydroxy acetophenones. Aldol condensation of acetophenones with benzaldehydes formed chalcones, which upon Algar–Flynn–Oyamada (AFO) oxidation[20] gave flavonols. Abundant literature on this topic prompted us to modify the benzopyrone ring to explore the biological activities associated with this nucleus.[21–25] In the present work, 3-hydroxy/acetoxy chromones have been synthesized and explored for antimicrobial activities.

2. Experimental

2.1 *Materials, methods and instruments*

All the chemicals and solvents were obtained from Merck (LR grade) and used without further purification. Melting points were taken in an open capillary tube and are uncorrected. Microwave-assisted syntheses of 3-acetoxyflavones were carried out using laboratory

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microwave reactor, bench mate model CEM-908010. FT-IR spectra were recorded (KBr disk) on a Shimadzu 8101A FT-IR Spectrophotometer. ^{1}H and ^{13}C-Nuclear Magnetic Resonance (NMR) were obtained from Bruker Avance II 400 MHz Spectrophotometer using tetramethylsilane as an internal standard in $CDCl_3$. Mass spectra were recorded on water Micromass Q-T of Micro Spectrometer equipped with an Electron Spin Impact (ESI) source. All the elemental analyses were done using Perkin Elmer 2400 CHN Analyser. Reactions were monitored on pre-coated Thin Layer Chromatography (TLC) plates (Silica gel 60 F254, Merck), using iodine vapour as visualizing agent.

2.2 *General method for the synthesis of compounds* ***4(a–n)***

The mixture of 1-(2-hydroxyphenyl)-3-arylprop-2-en-1-one **3**(**a**–**n**) (0.01 mol), ethanol (50 mL), NaOH (10%, 56 mL) and H_2O_2 (30%, 13 mL) was stirred vigorously for 30 min and kept for 4 h at ice cold condition. It was poured on to cold 80 mL of 5.0 N HCl. The solid was filtered, washed with water, dried and crystallized from alcohol to afford compound with good yield (62–69%).

2.2a *3-Hydroxy-2-phenyl-4H-chromen-4-one* (***4a***): Yield 66%; mp 170°C (lit.[26,27] mp 170°C); FT-IR (KBr): 3222 (Ar–OH), due to presence of phenolic –OH group, 3033, 3075 (aromatic str.), 1611 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H, OH), 7.26–8.27 (m, 9H, Ar–H) ppm; MS-EI, m/z = $[M]^+$ = 238. Anal. Calcd. for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23%. Found: C, 75.71; H, 4.13%.

2.2b *3-Hydroxy-2-p-tolyl-4H-chromen-4-one* (***4b***): Yield 69%; mp 206°C (lit.[28] mp 195–197°C); FT-IR (KBr): 3218 (Ar–OH), 1615 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 7.02 (s, 1H, OH), 7.26–8.27 (m, 8H, Ar–H) ppm; MS-EI, m/z = $[M]^+$ = 252. Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79%. Found: C, 76.11; H, 4.85%.

2.2c *3-Hydroxy-2-(3,4-dimethoxyphenyl)-4H-chromen-4-one* (***4c***): Yield 68%; mp 210°C (lit.[26] mp 200–202°C); FT-IR (KBr): 3212 (Ar–OH), 1622 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.02 (s, 1H, OH), 7.00–8.25 (m, 7H, Ar–H) ppm; MS-EI, m/z = $[M]^+$ = 298. Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73%. Found: C, 68.53; H, 4.67%.

2.2d *3-Hydroxy-2-(3,4-dimethoxyphenyl)-6-chloro-4H-chromen-4-one* (***4d***): Yield 67%; mp 262°C; FT-IR (KBr): 3226 (Ar–OH), 1618 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.02 (s, 1H, OH), 7.00–8.25 (m, 6H, Ar–H) ppm; MS-EI, m/z = $[M]^+$ = 332. Anal. Calcd. for $C_{17}H_{13}ClO_5$: C, 61.36; H, 3.94%. Found: C, 61.42; H, 3.99%.

2.2e *3-Hydroxy-2-(4-chlorophenyl)-4H-chromen-4-one* (***4e***): Yield 65%; mp 192°C (lit.[29] mp 202–204°C); FT-IR (KBr): 3202 (Ar–OH), 1619 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H, OH), 7.26–8.27 (m, 8H, Ar–H) ppm; MS-EI, m/z = $[M]^+$ = 272. Anal. Calcd. for $C_{15}H_9ClO_3$: C, 66.07; H, 3.33%. Found: C, 66.14; H, 3.29%.

2.2f *3-Hydroxy-6-chloro-2-(4-chlorophenyl)-4H-chromen-4-one* (***4f***): Yield 66%; mp 232°C; FT-IR (KBr): 3212 (Ar–OH), 1608 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H, OH), 7.26–8.27 (m, 7H, Ar–H) ppm; MS-EI, m/z = $[M]^+$ = 306. Anal. Calcd. for $C_{15}H_8Cl_2O_3$: C, 58.66; H, 2.63%. Found: C, 58.72; H, 2.69%.

2.2g *3-Hydroxy-6-chloro-2-phenyl-4H-chromen-4-one* (***4g***): Yield 68%; mp 169°C; FT-IR (KBr): 3227 (Ar–OH), 1616 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H, OH), 7.26–8.27 (m, 8H, Ar–H) ppm; MS-EI, m/z = $[M]^+$ = 272. Anal. Calcd. for $C_{15}H_9ClO_3$: C, 66.07; H, 3.33%. Found: C, 66.19; H, 3.45%.

2.2h *3-Hydroxy-6-chloro-2-(4-(dimethylamino)phenyl)-4H-chromen-4-one* (***4h***): Yield 66%; mp 242°C; FT-IR (KBr): 3215 (Ar–OH), 1632 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.06 (s, 6H, $N(CH_3)_2$), 6.89 (s, 1H, OH), 6.87–8.24 (m, 7H, Ar–H) ppm; MS-EI, m/z = $[M]^+$ = 315. Anal. Calcd. for $C_{17}H_{14}ClNO_3$: C, 64.67; H, 4.47; N, 4.44%. Found: C, 64.71; H, 4.39; N, 4.48%.

2.2i *3-Hydroxy-2-(furan-2-yl)-4H-chromen-4-one* (***4i***): Yield 64%; mp 151°C (lit.[28] mp 171–172°C); FT-IR (KBr): 3218 (Ar–OH), 1617 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.22 (s, 1H, OH), 5.11–8.16 (m, 7H, Ar–H) ppm; MS-EI, m/z = $[M]^+$ = 228. Anal. Calcd. for $C_{13}H_8O_4$: C, 68.42; H, 3.53%. Found: C, 68.47; H, 3.59%.

2.2j *3-Hydroxy-6-chloro-2-(furan-2-yl)-4H-chromen-4-one* (***4j***): Yield 64%; mp 212°C; FT-IR (KBr): 3229 (Ar–OH), 1615 (C=O pyrone ring) cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$): δ 11.22 (s, 1H, OH), 5.11–8.16 (m, 6H, Ar–H) ppm; MS-EI, $m/z = [M]^+ = 262$. Anal. Calcd. for $C_{13}H_7ClO_4$: C, 59.45; H, 2.69%. Found: C, 59.55; H, 2.63%.

2.2k *3-Hydroxy-2-(4-fluorophenyl)-4H-chromen-4-one (**4k**)*: Yield 63%; mp 162°C (lit.[29] mp 151–152°C); FT-IR (KBr): 3220 (Ar–OH), 1614 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H, OH), 7.26–8.27 (m, 8H, Ar–H) ppm; MS-EI, $m/z = [M]^+ = 256$. Anal. Calcd. for $C_{15}H_9FO_3$: C, 70.31; H, 3.54%. Found: C, 70.44; H, 3.51%.

2.2l *3-Hydroxy-6-chloro-2-(4-fluorophenyl)-4H-chromen-4-one (**4l**)*: Yield 65%; mp 215°C; FT-IR (KBr): 3221 (Ar–OH), 1613 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H, OH), 7.26–8.27 (m, 7H, Ar–H) ppm; MS-EI, $m/z = [M]^+ = 290$. Anal. Calcd. for $C_{15}H_8ClFO_3$: C, 61.98; H, 2.77%. Found: C, 61.92; H, 2.83%.

2.2m *3-Hydroxy-6-chloro-2-(4-methoxyphenyl)-4H-chromen-4-one (**4m**)*: Yield 68%; mp 219°C; FT-IR (KBr): 3225 (Ar–OH), 1617 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 3H, (OCH_3)), 7.02 (s, 1H, OH), 7.00–8.25 (m, 7H, Ar–H) ppm; MS-EI, $m/z = [M]^+ = 302$. Anal. Calcd. for $C_{16}H_{11}ClO_4$: C, 63.48; H, 3.66%. Found: C, 63.40; H, 3.74%.

2.2n *3-Hydroxy-2-(4-(dimethylamino)phenyl)-4H-chromen-4-one (**4n**)*: Yield 62%; mp 196°C (lit.[30] mp 191°C); FT-IR (KBr): 3227 (Ar–OH), 1621 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.06 (s, 6H, $N(CH_3)_2$), 6.89 (s, 1H, OH), 6.87–8.24 (m, 8H, Ar–H) ppm; MS-EI, $m/z = [M]^+ = 281$. Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98%. Found: C, 72.70; H, 5.25; N, 5.03%.

2.3 *General method for the synthesis of compounds **5(a–n)***

The mixture of 3-hydroxyflavones **4**(**a**–**n**) (0.004 mol) and acetyl chloride (0.006 mol) was successively added to a 10 ml crimp-sealed, thick-walled glass tube and then exposed to microwave irradiation (intermittently at 1 min intervals; 90 W, 100°C for 3 min). The completion of reaction was monitored by TLC (n-hexane:ethyl acetate (7:3)) and $FeCl_3$. The solid obtained was filtered, washed thoroughly with water, dried and crystallized from alcohol to afford compound with good yield 84–91%.

2.3a *4-Oxo-2-phenyl-4H-chromen-3-yl acetate (**5a**)*: Yield 89%; mp 109°C; FT-IR (KBr): 3003, 3038, 3065 ($CO–CH_3$), 1763 (C=O) 1651 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H, $CO–CH_3$), 7.26–7.88 (m, 9H, Ar–H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.6 (CH_3), 168 (C=O), 172 (C=O pyrone ring), 117, 123, 126, 128, 128, 130, 133 ppm etc. for aromatic carbons; MS-ESI, $m/z = [M+Na]^+ = 303$. Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32%. Found: C, 72.71; H, 4.39%.

2.3b *4-Oxo-2-p-tolyl-4H-chromen-3-yl acetate (**5b**)*: Yield 86%; mp 136°C; FT-IR (KBr): 3012, 3028, 3055 ($CO–CH_3$), 1763 (C=O) 1651 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 3H, $CO–CH_3$), 2.35 (s, 3H, CH_3), 6.92–7.64 (m, 8H, Ar–H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.6 (CH_3), 24.2 (CH_3), 168 (C=O), 172 (C=O pyrone ring), 117, 123, 124, 126, 127, 129, 133 ppm etc. for aromatic carbons; MS-ESI, $m/z = [M+Na]^+ = 317$. Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.46; H, 4.79%. Found: C, 73.41; H, 4.72%.

2.3c *2-(3,4-Dimethoxyphenyl)-4-oxo-4H-chromen-3-yl acetate (**5c**)*: Yield 91%; mp 112°C; FT-IR (KBr): 3009, 3042, 3068 ($CO–CH_3$), 1763 (C=O) 1651 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H, $CO–CH_3$), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.98–8.27 (m, 7H, Ar–H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.65 (CH_3), 56.05, 56.06 $(OCH_3)_2$, 168 (C=O), 172 (C=O pyrone ring), 110, 111, 118, 122, 123, 125, 126, 133, 148 ppm etc. for aromatic carbons; MS-ESI, $m/z = [M+Na]^+ = 363$. Anal. Calcd. for $C_{19}H_{16}O_6$: C, 67.05; H, 4.74%. Found: C, 67.19; H, 4.69%.

2.3d *6-Chloro-2-(3,4-dimethoxyphenyl)-4-oxo-4H-chromen-3-yl acetate (**5d**)*: Yield 90%; mp 198°C; FT-IR (KBr): 3006, 3034, 3061 ($CO–CH_3$), 1763 (C=O) 1651 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H, $CO–CH_3$), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3) 6.98–8.27 (m, 6H, Ar–H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.65 (CH_3), 56.05, 56.06 $(OCH_3)_2$, 168 (C=O), 172 (C=O pyrone ring), 110, 111, 118, 122, 123, 125, 126, 133 ppm etc. for aromatic carbons; MS-ESI, $m/z = [M+Na]^+ = 397$. Anal. Calcd. for $C_{19}H_{15}ClO_6$: C, 60.89; H, 4.03%. Found: C, 60.83; H, 4.09%.

2.3e *2-(4-Chlorophenyl)-4-oxo-4H-chromen-3-yl acetate (**5e**)*: Yield 87%; mp 144°C; FT-IR (KBr): 3001, 3029, 3058 ($CO–CH_3$), 1763 (C=O) 1651 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ

2.35 (s, 3H, CO–CH_3), 7.26–7.88 (m, 8H, Ar–H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.6 (CH_3), 168 (C=O), 172 (C=O pyrone ring), 117, 123, 126, 128, 130, 133 ppm etc. for aromatic carbons; MS-ESI, $m/z = [M+Na]^+ = 337$. Anal. Calcd. for $C_{17}H_{11}ClO_4$: C, 64.88; H, 3.52%. Found: C, 64.91; H, 3.59%.

2.3f *6-Chloro-2-(4-chlorophenyl)-4-oxo-4H-chromen-3-yl acetate (**5f**)*: Yield 88%; mp 215°C; FT-IR (KBr): 3005, 3032, 3064 (CO–CH_3), 1763 (C=O) 1651 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H, CO–CH_3), 7.26–7.88 (m, 7H, Ar–H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.6 (CH_3), 168 (C=O), 172 (C=O pyrone ring), 117, 123, 126, 128, 128, 130, 133 ppm etc. for aromatic carbons; MS-ESI, $m/z = [M+Na]^+ = 372$. Anal. Calcd. for $C_{17}H_{10}Cl_2O_4$: C, 58.48; H, 2.89%. Found: C, 58.54; H, 2.93%.

2.3g *6-Chloro-4-oxo-2-phenyl-4H-chromen-3-yl acetate (**5g**)*: Yield 87%; mp 148°C; FT-IR (KBr): 3011, 3042, 3069 (CO–CH_3), 1763 (C=O) 1651 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H, CO–CH_3), 7.26–7.88 (m, 8H, Ar–H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.6 (CH_3), 168 (C=O), 172 (C=O pyrone ring), 117, 123, 126, 128, 130, 133 ppm etc. for aromatic carbons; MS-ESI, $m/z = [M+Na]^+ = 337$. Anal. Calcd. for $C_{17}H_{11}ClO_4$: C, 64.88; H, 3.52%. Found: C, 64.79; H, 3.59%.

2.3h *6-Chloro-2-(4-(dimethylamino)phenyl)-4-oxo-4H-chromen-3-yl acetate (**5h**)*: Yield 91%; mp 212°C; FT-IR (KBr): 3008, 3028, 3070 (CO–CH_3), 1763 (C=O) 1651 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3H, CO–CH_3), 3.06 (s, 6H, N(CH_3)$_2$)), 6.75–8.24 (m, 7H, Ar–H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.72 (CH_3), 40.17 (N(CH_3)$_2$), 168.09 (C=O), 172 (C=O pyrone ring), 111, 117, 123, 124, 125, 129, 132 ppm etc. for aromatic carbons; MS-ESI, $m/z = [M+Na]^+ = 380$. Anal. Calcd. for $C_{19}H_{16}ClNO_4$: C, 63.78; H, 4.51; N, 3.91%. Found: C, 63.83; H, 4.49; N, 3.85%.

2.3i *2-(Furan-2-yl)-4-oxo-4H-chromen-3-yl acetate (**5i**)*: Yield 85%; mp 146°C; FT-IR (KBr): 3007, 3035, 3068 (CO–CH_3), 1763 (C=O) 1651 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.30 (s, 3H, CO–CH_3), 6.69–8.18 (m, 7H, Ar–H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.54 (CH_3), 167.80 (C=O), 170.68 (C=O pyrone ring), 112, 116, 119, 124, 125, 131, 134, 143 ppm etc. for aromatic carbons; MS-ESI, $m/z = [M+Na]^+ = 293$. Anal. Calcd. for $C_{15}H_{10}O_5$: C, 66.67; H, 3.73%. Found: C, 66.61; H, 3.79%.

2.3j *6-Chloro-2-(furan-2-yl)-4-oxo-4H-chromen-3-yl acetate (**5j**)*: Yield 84%; mp 150°C; FT-IR (KBr): 3004, 3036, 3059 (CO–CH_3), 1763 (C=O) 1651 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.30 (s, 3H, CO–CH_3), 6.69–8.18 (m, 6H, Ar–H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.54 (CH_3), 167.80 (C=O), 170.68 (C=O pyrone ring), 112, 116, 119, 124, 125, 131, 134, 143 ppm etc. for aromatic carbons; MS-ESI, $m/z = [M+Na]^+ = 327$. Anal. Calcd. for $C_{15}H_9ClO_5$: C, 59.13; H, 2.98%. Found: C, 59.23; H, 3.09%.

2.3k *2-(4-Fluorophenyl)-4-oxo-4H-chromen-3-yl acetate (**5k**)*: Yield 86%; mp 140°C; FT-IR (KBr): 3001, 3032, 3057 (CO–CH_3), 1763 (C=O) 1651 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.37 (s, 3H, CO–CH_3), 7.20–8.21 (m, 8H, Ar–H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.54 (CH_3), 168 (C=O), 171 (C=O pyrone ring), 115, 116, 119, 124, 125, 130, 131, 133, 134 ppm etc. for aromatic carbons; MS-ESI, $m/z = [M+Na]^+ = 321$. Anal. Calcd. for $C_{17}H_{11}FO_4$: C, 68.46; H, 3.72%. Found: C, 68.53; H, 3.59%.

2.3l *6-Chloro-2-(4-fluorophenyl)-4-oxo-4H-chromen-3-yl acetate (**5l**)*: Yield 87%; mp 202°C; FT-IR (KBr): 3014, 3043, 3071 (CO–CH_3), 1763 (C=O) 1651 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.37 (s, 3H, CO–CH_3), 7.20–8.21 (m, 7H, Ar–H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.54 (CH_3), 168 (C=O), 171 (C=O pyrone ring), 115, 116, 119, 124, 125, 130, 131, 133, 134 ppm etc. for aromatic carbons; MS-ESI, $m/z = [M+Na]^+ = 355$. Anal. Calcd. for $C_{17}H_{10}ClFO_4$: C, 61.37; H, 3.03%. Found: C, 61.42; H, 3.09%.

2.3m *6-Chloro-2-(4-methoxyphenyl)-4-oxo-4H-chromen-3-yl acetate (**5m**)*: Yield 88%; mp 198°C; FT-IR (KBr): 3009, 3033, 3067 (CO–CH_3), 1763 (C=O) 1651 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H, CO–CH_3), 3.73 (s, 3H, OCH_3) 6.86–7.65 (m, 7H, Ar–H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.65 (CH_3), 56.05 (OCH_3), 168 (C=O), 172 (C=O pyrone ring), 110, 111, 118, 122, 123, 125, 126 ppm etc. for aromatic carbons; MS-ESI, $m/z = [M+Na]^+ = 367$. Anal. Calcd. for $C_{18}H_{13}ClO_5$: C, 62.71; H, 3.80%. Found: C, 62.81; H, 3.79%.

2.3n *2-(4-(Dimethylamino)phenyl)-4-oxo-4H-chromen-3-yl acetate (**5n**)*: Yield 87%; mp 186°C (lit.[30] mp 151°C); FT-IR (KBr): 3006, 3041, 3069 (CO–CH_3), 1763 (C=O) 1651 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H, CO–CH_3), 3.06 (s, 6H, N(CH_3)$_2$)), 6.75–8.24 (m, 8H, Ar–H) ppm;

Table 1. Biological activity of 3-hydroxy-2-aryl/heteroaryl-4*H*-chromones **4**(**a**–**n**).

	Zone of inhibition[a] (mm) (Activity index)[std]					
	Antibacterial activity					
	Gram-positive		Gram-negative		Antifungal activity	
Compound	*S. aureus*	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
4a	14(0.42)* (0.45)#	13(0.45)* (0.50)#	15(0.44)* (0.52)#	12(0.54)* (0.57)#	13(0.62)* (0.56)#	12(0.48)* (0.50)#
4b	13(0.39)* (0.42)#	12(0.41)* (0.46)#	12(0.35)* (0.41)#	11(0.50)* (0.52)#	14(0.67)* (0.61)#	12(0.48)* (0.50)#
4c	11(0.33)* (0.35)#	11(0.38)* (0.42)#	12(0.35)* (0.41)#	11(0.50)* (0.52)#	12(0.57)* (0.52)#	11(0.44)* (0.46)#
4d	18(0.54)* (0.58)#	19(0.65)* (0.73)#	20(0.59)* (0.69)#	18(0.82)* (0.86)#	18(0.86)* (0.78)#	16(0.64)* (0.67)#
4e	15(0.45)* (0.48)#	16(0.55)* (0.61)#	16(0.47)* (0.55)#	15(0.68)* (0.71)#	14(0.67)* (0.61)#	15(0.6)* (0.62)#
4f	16(0.48)* (0.52)#	18(0.62)* (0.69)#	18(0.53)* (0.62)#	17(0.77)* (0.81)#	15(0.71)* (0.65)#	17(0.68)* (0.71)#
4g	15(0.45)* (0.48)#	16(0.55)* (0.61)#	16(0.47)* (0.55)#	14(0.64)* (0.67)#	14(0.67)* (0.61)#	15(0.6)* (0.62)#
4h	17(0.51)* (0.55)#	16(0.55)* (0.61)#	15(0.44)* (0.52)#	12(0.54)* (0.57)#	13(0.62)* (0.56)#	–(–)* –(–)#
4i	19(0.57)* (0.61)#	21(0.72)* (0.81)#	21(0.62)* (0.72)#	20(0.91)* (0.95)#	18(0.86)* (0.78)#	17(0.68)* (0.71)#
4j	21(0.64)* (0.68)#	20(0.69)* (0.77)#	19(0.59)* (0.65)#	20(0.91)* (0.95)#	18(0.86)* (0.78)#	21(0.84)* (0.87)#
4k	16(0.48)* (0.52)#	15(0.52)* (0.58)#	17(0.5)* (0.59)#	17(0.77)* (0.81)#	16(0.76)* (0.69)#	18(0.72)* (0.75)#
4l	15(0.45)* (0.48)#	16(0.55)* (0.62)#	16(0.47)* (0.55)#	14(0.64)* (0.67)#	15(0.71)* (0.65)#	17(0.68)* (0.71)#
4m	17(0.51)* (0.55)#	18(0.62)* (0.69)#	18(0.53)* (0.62)#	15(0.68)* (0.71)#	16(0.76)* (0.69)#	19(0.76)* (0.79)#
4n	16(0.48)* (0.52)#	15(0.52)* (0.58)#	17(0.5)* (0.59)#	11(0.5)* (0.52)#	14(0.67)* (0.61)#	–(–)* –(–)#
Std 1	33	29	34	22	21	25
Std 2	31	26	29	21	23	24

Table 2. Biological activity of 3-acetoxy-2-aryl/heteroaryl-4*H*-chromones **5**(**a**–**n**).

	Zone of inhibition (mm)[a] (Activity index)[std]					
	Antibacterial activity					
	Gram-positive		Gram-negative		Antifungal activity	
Compound	*S. aureus*	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
5a	16(0.49)* (0.51)#	15(0.52)* (0.58)#	16(0.47)* (0.55)#	14(0.64)* (0.67)#	15(0.71)* (0.65)#	14(0.56)* (0.58)#
5b	15(0.45)* (0.48)#	14(0.48)* (0.54)#	14(0.41)* (0.48)#	13(0.59)* (0.62)#	15(0.71)* (0.65)#	13(0.52)* (0.54)#
5c	13(0.39)* (0.42)#	12(0.41)* (0.46)#	13(0.38)* (0.44)#	12(0.54)* (0.57)#	14(0.67)* (0.61)#	13(0.52)* (0.54)#
5d	23(0.70)* (0.74)#	24(0.83)* (0.92)#	22(0.65)* (0.76)#	20(0.91)* (0.95)#	18(0.85)* (0.78)#	19(0.76)* (0.79)#
5e	20(0.61)* (0.64)#	19(0.65)* (0.73)#	21(0.62)* (0.72)#	22(1.00)* (1.05)#	17(0.81)* (0.74)#	18(0.72)* (0.75)#
5f	21(0.64)* (0.68)#	22(0.76)* (0.85)#	23(0.68)* (0.79)#	21(0.95)* (1.00)#	20(0.95)* (0.87)#	22(0.88)* (0.92)#
5g	19(0.57)* (0.61)#	18(0.62)* (0.69)#	20(0.59)* (0.69)#	18(0.82)* (0.85)#	17(0.81)* (0.74)#	19(0.76)* (0.79)#
5h	22(0.67)* (0.71)#	21(0.72)* (0.81)#	21(0.62)* (0.72)#	15(0.68)* (0.71)#	19(0.90)* (0.83)#	14(0.56)* (0.58)#
5i	24(0.73)* (0.77)#	25(0.86)* (0.96)#	25(0.73)* (0.86)#	26(1.18)* (1.24)#	24(1.14)* (1.04)#	25(1.00)* (1.04)#
5j	26(0.79)* (0.84)#	27(0.93)* (1.03)#	27(0.79)* (0.93)#	27(1.23)* (1.28)#	25(1.19)* (1.09)#	25(1.00)* (1.04)#
5k	20(0.61)* (0.64)#	21(0.72)* (0.81)#	21(0.62)* (0.72)#	19(0.86)* (0.90)#	18(0.86)* (0.78)#	19(0.76)* (0.79)#
5l	18(0.54)* (0.58)#	18(0.62)* (0.69)#	22(0.65)* (0.76)#	21(0.95)* (1.00)#	19(0.90)* (0.83)#	18(0.72)* (0.75)#
5m	18(0.54)* (0.58)#	20(0.69)* (0.77)#	21(0.62)* (0.72)#	21(0.95)* (1.00)#	20(0.95)* (0.87)#	22(0.88)* (0.92)#
5n	17(0.51)* (0.55)#	16(0.55)* (0.61)#	18(0.53)* (0.62)#	14(0.64)* (0.67)#	19(0.90)* (0.83)#	13(0.52)* (0.54)#
Std 1	33	29	34	22	21	25
Std 2	31	26	29	21	23	24

[a] = Average zone of inhibition in mm,
(Activity index) = Inhibition zone of the sample/Inhibition zone of standard,
* = Activity index against std. 1
# = Activity index against std. 2
For antibacterial activity: Std. 1 = Ciprofloxacin and Std. 2 = Sulphacetamide; for antifungal activity: Std. 1 = Gentamycin and Std. 2 = Clotrimazole

^{13}C NMR (400 MHz, $CDCl_3$): δ 20.72 (CH_3), 40.17 ($N(CH_3)_2$), 168.09 (C=O), 156 (C=C pyrone ring), 172 (C=O pyrone ring), 111, 117, 123, 124, 125, 129, 132 ppm etc. for aromatic carbons; MS-ESI, m/z = $[M+Na]^+$ = 346. Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33%. Found: C, 70.64; H, 5.39; N, 4.37%.

2.4 *Crystal structure determination*

Single-crystal X-ray diffraction data for the compound (**5j**) was collected on an Oxford Xcalibur Eos (Mova) CCD Detector Diffractometer with a graphite monochromated KαMo radiation (λ = 0.71073 Å), absorption correction was done with multiscan (*CrysAlis RED*; Oxford Diffraction, 2009) having T_{min} = 0.9147, T_{max} = 0.9420, structure was refined with least square full matrix (direct method). Molecular diagram was generated using ORTEP.

2.5 *Antimicrobial activity*

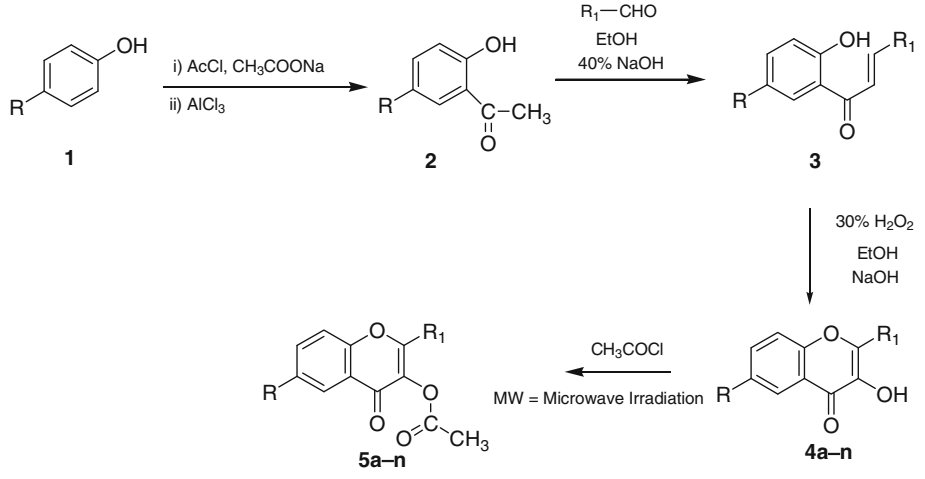
2.5a *Antibacterial activity*: Synthesized compounds were screened for their antibacterial activities against pathogenic bacteria such as *E. coli*, *S. aureus*, *B. subtilis* and *P. aeruginosa* by using the cup plate diffusion method. The test compounds were dissolved in dimethyl sulphoxide at a concentration of 100 µg/mL using Ciprofloxacin and Sulphacetamide as standard drugs. All the inoculated plates were incubated at 37°C and the results were evaluated after 24 h of incubation (tables 1 and 2).

2.5b *Antifungal activity*: Synthesized compounds were also screened for their antifungal activity against *A. niger* and *C. albicans* using the cup plate diffusion method. The test compounds were dissolved in dimethyl sulphoxide at a concentration of 100 µg/mL. The zone of inhibition was observed after 7 days at 25°C and it was compared with Gentamycin and Clotrimazole as standard drugs (tables 1 and 2).

3. Results and discussion

3.1 *Synthesis*

Acetylation (esterification) of phenols followed by Fries migration yielded 2-hydroxy acetophenones, reaction of 2-hydroxy acetophenones with different aromatic aldehydes produced 1-(2-hydroxyphenyl)-3-arylprop-2-en-1-one (chalcones) **3**(**a**–**n**), which on cyclization in alkaline H_2O_2 yielded 3-hydroxy-2-aryl/heteroaryl-4*H*-chromones (flavones)[31] **4**(**a**–**n**) (scheme 1). IR spectrum of **4a** shows a broad peak at 3222 (Ar–OH), due to presence of phenolic –OH group, 3033, 3075 (aromatic str.), 1611 (C=O pyrone ring). ^{1}H NMR δ 7.02 (s, 1H, OH), 7.26–8.27 (m, 9H, Ar–H). 3-Hydroxy-2-aryl/heteroaryl-4*H*-chromones on acetylation under microwave irradiation afforded 3-acetoxy-2-aryl/heteroaryl-4*H*-chromones[32] **5**(**a**–**n**) in excellent yield (scheme 1). The compound structure was confirmed by the IR spectrum (absence of phenolic –OH group at 3222 cm^{-1} and presence of 3003, 3038, 3065 (CO–CH_3), 1763 (C=O) 1651 (C=O pyrone ring) cm^{-1}) and



R = i) H, ii) Cl

R_1 = i) C_6H_5 ii) 4-$CH_3C_6H_4$ iii) 3,4-$(OCH_3)C_6H_3$ iv) 4-Cl C_6H_4
v) 4-$N(CH_3)_2C_6H_4$ vi) C_4H_3O vii) 4-F C_6H_5 viii) 4-$OCH_3C_6H_4$

Scheme 1. Synthesis of 3-acetoxy-2-aryl/heteroaryl-4*H*-chromones.

Table 3. Crystallographic details of 6-chloro-2-(furan-2-yl)-4-oxo-4*H*-chromen-3-yl acetate **5j**.

Data	6-Chloro-2-(furan-2-yl)-4-oxo-4*H*-chromen-3-yl acetate
Formula	$C_{15}H_9ClO_5$
Formula weight	304.62
Colour	Colourless
Crystal morphology	Block
Temperature/K	295(1)
Radiation	Mo Kα
Wavelength/Å	0.71073
Crystal system	Monoclinic
Space group	$P2_1/n$
a (Å)	5.0656(3)
b (Å)	14.4661(10)
c (Å)	18.4123(14)
β (°)	93.376(7)
Volume (Å^3)	1346.89(5)
Z	4
Density (g/ml)	1.50
μ (1/mm)	0.302
F (000)	623.9
θ (min, max)	2.6, 26.0
No. of unique Refln	2644
No. of parameters	191
R_obs, wR_2_obs	0.046, 0.108
$\Delta\rho_{min}$, $\Delta\rho_{max}$ (eÅ^{-3})	−0.269, 0.237
GooF	0.898

the ^{1}H–NMR spectra (absence of δ 7.02 (s, 1H, OH) and presence of δ 2.35 (s, 3H, CO–CH_3). A new method for synthesis of compounds **5**(**a**–**n**) has been proposed. All compounds **5**(**a**–**n**) gave satisfactory IR, NMR, mass spectra and elemental analysis data correlation with the assigned structure.

3.2 *Crystal structure analysis*

Summary of the crystallographic data and ORTEP structure for the 6-chloro-2-(furan-2-yl)-4-oxo-4*H*-chromen-3-yl acetate (**5j**) are shown in table 3 and figure 1.

3.3 *Antimicrobial evaluation*

Compounds (**4** and **5** (**a**–**n**)) were screened for their antibacterial and antifungal activities against some selected bacteria and fungi, respectively. Investigation of antimicrobial data (tables 1 and 2) revealed that the compounds **4i**, **4j**, **5i** and **5j** have shown more activity in the series, whereas the compounds **4** (**d**, **e**, **f**, **g**, **k**, **l**, **m**) and **5** (**d**, **e**, **f**, **g**, **h**, **k**, **l**, **m**) showed moderate activity and rest of the compounds showed less activity. All the strains were compared with standard drugs.

Our investigations have shown that the compounds have a structure activity relationship (SAR) because activity of compounds varied with substitution. On the basis of SAR, it can be concluded that the activity of compounds depends on the presence of electron-withdrawing group on the aromatic ring which increases the antimicrobial activities of the tested compounds compared to compounds having electron-donating group. Sequence of the activity is furan > halogen > methoxy > methyl > *N*,*N*-dimethylamine. Acetoxy flavones were more active than the corresponding hydroxyl flavones; it might be due to functionalized two-ketone system having combined pharmacophore sites in these compounds which play an important role in antimicrobial activity. This functionalized system may be responsible for the enhancement of hydrophobic character and liposolubility of the molecules.

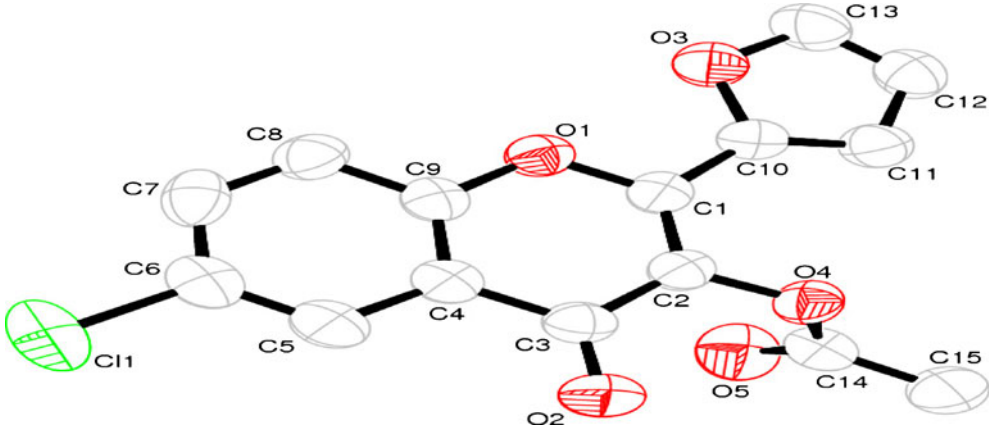


Figure 1. ORTEP diagram of 6-chloro-2-(furan-2-yl)-4-oxo-4*H*-chromen-3-yl acetate **5j** drawn at 50% ellipsoidal probability. Hydrogen atoms are omitted for clarity.

4. Conclusion

3-Hydroxy-2-aryl/heteroaryl-4*H*-chromones and their acetoxy derivatives were synthesized with good yield as well as purity. 3-Acetoxy flavones were more active in reducing microbial growth than the corresponding hydroxy compounds. The present study demonstrates that the antimicrobial potential of certain flavonoids increases significantly by a simple chemical modification.

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