

Synthesis, Biological and Pharmacological Activities of 2'-Hydroxy-4'5'-dimethyl Substituted Chalcones and Flavones

ANIL KUMAR PANDEY, SUHAS PEDNEKAR* and D.B PATIL†

*Organic Chemistry Research Laboratory,
Ramnarain Ruia College, Matunga, Mumbai-400 019, India
E-mail: pandeyanil20@yahoo.com*

2-Hydroxy-4,5-dimethyl acetophenones were allowed to react separately with the various substituted benzaldehydes in alkaline medium to yield the corresponding 2-hydroxy-4,5-dimethyl substituted chalcones, which are further leading in substituted flavones. The structures of these compounds were confirmed on the basis of their elemental analysis, chemical properties and spectral data. The compounds thus synthesized were screened for antimicrobial activity and pharmacological activity.

Key Words: Synthesis, Substituted chalcones, Biological activity, Pharmacological activity.

INTRODUCTION

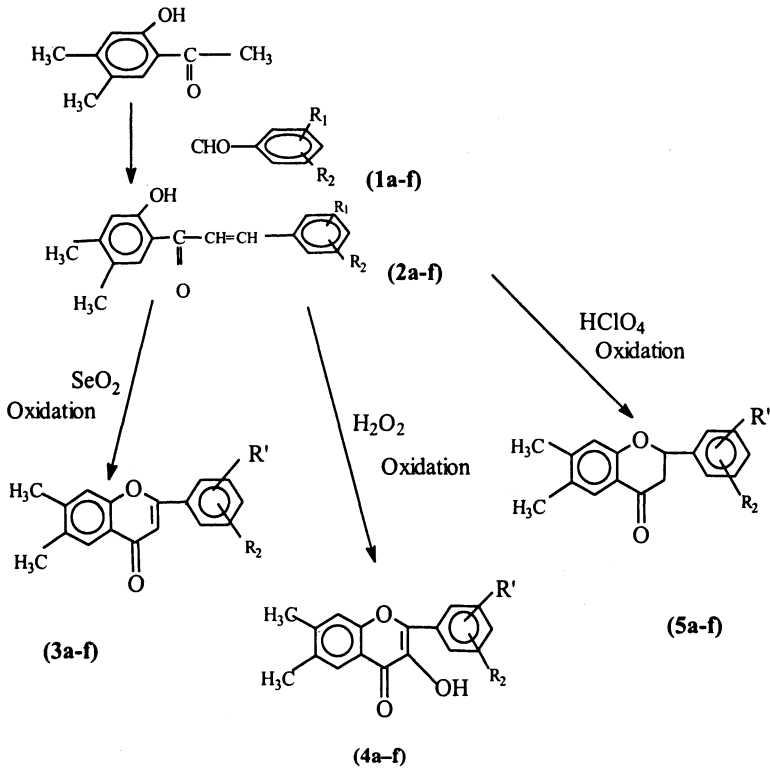
Chalcones have been studied extensively because of their wide range of biological activity. These compounds have been found to be effective as anaesthetic¹, antibacterial², antimalarial³, antitubercular⁴, anticancer⁵ and antifungal agents⁶. The diverse properties of chalcones have prompted us to synthesize them in order to study their biological and pharmacological activities. The present work deals with the study of biological and pharmacological activity of 2-hydroxy-4,5-dimethyl substituted chalcones and synthesize their flavones (Scheme-1).

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected.

2-Hydroxy-4',5'-dimethyl Substituted Chalcones (2a-f): 2-Hydroxy-4,5-dimethyl acetophenone (0.01 mol) was added to substituted benzaldehyde compounds (1a-f) (0.012 mol) were dissolved in ethyl alcohol (10 mL) and sodium hydroxide solution (2 mL) (10 N) was added gradually with constant stirring and the reaction mixture was allowed to stand for 10 h at room temperature. It was then poured on crushed ice and acidified with dilute hydrochloric acid. The solid obtained was filtered, washed with water, dried and crystallized from ethyl alcohol. UV-Vis: (207 & 310) λ_{\max} corresponding to $n-\pi^*$ transition. IR (KBr, cm^{-1}) (2a-f): 2917 $\nu(\text{—CH})$, 1643 $\nu(\text{C=O})$, 1571 $\nu(\text{Ph—C=C})$, 1497 $\nu(\text{Ph—C—C})$, 1360 $\nu(\text{—OH})$, 1186 $\nu(\text{C—O})$. ¹H NMR (CDCl_3): **Compds. 2a, (2c–2f):** δ 2.28 (s, 3H), 2.35 (s, 3H), 6.81 (s, =CH), 6.84 (s, 1H), 7.4 (m, 2H), 7.5 (m, 2H), 7.7 (s, 1H), (8.28s, =CH), 12.62 (s, 1H, OH—D₂O exchange). **Compd. 2b:** δ 2.28 (s, 3H), 2.35 (s, 3H), 6.81 (s, =CH), 6.84 (s, 1H), 7.4 (m, 2H), 7.5 (m, 2H), 8.28 (s, =CH), 12.62 (s, 1H, OH—D₂O exchange).

†Herbert Brown Pharmaceutical & Research Lab., Dombivali, Thane, India.



(a) $R_1 = 2\text{-Cl}$, $R_2 = \text{—H}$; (b) $R_1 = 2\text{-Cl}$, $R_2 = 3\text{-Cl}$; (c) $R_1 = 3\text{-Br}$, $R_2 = \text{—H}$; (d) $R_1 = 4\text{-Br}$, $R_2 = \text{—H}$; (e) $R_1 = 4\text{-F}$, $R_2 = \text{—H}$; (f) $R_1 = 4\text{-CN}$, $R_2 = \text{—H}$

The analytical and physical data of the compounds (2a-f) are given in Table-1.

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF COMPOUNDS (2a-f)

Compd. No.	m.f.	Yield (%)	m.p. (°C)	Analysis %, Found (Calcd.)		Mol. ion (m +)/e
				C	H	
2a	C ₁₇ H ₁₅ O ₂ Cl (287.7)	70	147–149	70.86 (70.97)	5.26 (5.24)	289
2b	C ₁₇ H ₁₄ O ₂ Cl ₂ (321.2)	60	180–182	63.59 (63.56)	4.35 (4.39)	323
2c	C ₁₇ H ₁₅ O ₂ Br (331.2)	60	125–127	61.61 (61.64)	4.59 (4.56)	333
2d	C ₁₇ H ₁₅ O ₂ Br (331.2)	65	182–183	61.64 (61.64)	4.56 (4.56)	332
2e	C ₁₇ H ₁₅ O ₂ F (270.3)	63	128–130	75.52 (73.53)	5.62 (5.59)	272
2f	C ₁₈ H ₁₅ NO ₂ (277.3)	70	196–198	78.02 (77.96)	5.51 (5.45)	278

6,7-Dimethyl substituted flavone (3a-f): Compound (2a-f) (0.003 mol), selenium dioxide (0.009 mol) and amyl alcohol (30 mL) were heated at 150–160°C for 20 h. The solution was concentrated to half volume and allowed to stand at room temperature. The separated solid was filtered, washed with petroleum ether, dried and crystallized from ethyl alcohol. IR (KBr, cm^{-1}) (3a-f): 3050–3000 ν (—CH), 1640–1620 ν (—C=O), 1600–1570 ν (Ph —C=C), 1380–1360 ν (—C—O). ^1H NMR (CDCl_3): **Compds. 3a, (3c-f):** δ 2.2 (s, 3H), 2.35 (s, 3H), 6.78 (s, 1H), 6.95 (s, 1H), 7.14 (s, 1H), 7.55–7.56 (m, 3H), 8.02–8.03 (m, 1H). **Compd. 3b:** δ 2.2 (s, 3H), 2.35 (s, 3H), 6.78 (s, 1H), 6.95 (s, 1H), 7.14 (s, 1H), 7.55–7.56 (m, 3H).

The analytical and physical data of the compounds 3a-f are given in Table-2.

TABLE-2
PHYSICAL AND ANALYTICAL DATA OF COMPOUNDS (3a-f)

Compd.	m.f.	Yield (%)	m.p. (°C)	Analysis % Found (Calcd.)		Mol. ion peak (m+) ^e
				C	H	
3a	C ₁₇ H ₁₃ O ₂ Cl (284.4)	60	145–147	71.6 (71.7)	4.65 (4.63)	286
3b	C ₁₇ H ₁₂ O ₂ Cl ₂ (319.18)	50	174–175	63.59 (63.97)	3.79 (3.78)	320
3c	C ₁₇ H ₁₃ O ₂ Br (328.38)	60	163–165	62.20 (62.18)	3.95 (3.99)	330
3d	C ₁₇ H ₁₃ O ₂ Br (328.38)	40	220–221	62.00 (62.18)	4.01 (3.99)	330
3e	C ₁₇ H ₁₃ O ₂ F (268.28)	40	185–187	76.30 (76.10)	4.83 (4.88)	269
3f	C ₁₈ H ₁₃ NO ₂ (275.3)	40	235–236	78.58 (78.53)	4.72 (4.75)	276

6,7-Dimethyl substituted flavonol (4a-f): Compound (2a-f) Ethyl alcohol (50 mL, 0.003 mol) and sodium hydroxide solution (5 mL, 1.25 N) and 10 mL solution of hydrogen peroxide (30%) was stirred continuously for 2 h at room temperature. It was then diluted with ice-cold water and acidified with dil. HCl. When solid separated, it was filtered, washed well with water, dried and crystallized from isopropyl alcohol. IR (KBr, cm^{-1}) (4a-f): 3500–3400 ν (—OH) 3050–3000 ν (—CH), 1640–1620 ν (—C=O), 1600–1550 ν (Ph —C=C), 1380–1300 ν (—C—O). **Compd. 4a, (4c-f):** ^1H NMR (CDCl_3) δ 2.2 (s, 3H), 2.35 (s, 3H), 6.78 (s, 1H), 6.95 (s, 1H), 7.14 (s, 1H), 7.55–7.56 (m, 3H), 8.02–8.03 (m, 1H). **Compd. 4b:** ^1H NMR (CDCl_3): δ 2.2 (s, 3H), 2.35 (s, 3H), 6.78 (s, 1H), 6.95 (s, 1H), 7.14 (s, 1H), 7.55–7.56 (m, 3H).

The analytical and physical data of the compound 4a-f are given in Table-3

TABLE-3
PHYSICAL AND ANALYTICAL DATA OF COMPOUND (4a-4f)

Compd.	m.f.	Yield	m.p.	Analysis %, Found (Calcd.)		Mol ion peak (m+)/e
				C	H	
4a	C ₁₇ H ₁₃ O ₃ Cl (300.7)	35%	160–162°C	67.78 (67.89)	4.40 (4.36)	301
4b	C ₁₇ H ₁₇ O ₃ Cl ₂ (335.18)	38%	187–189°C	60.95 (60.95)	3.59 (3.60)	336
4c	C ₁₇ H ₁₃ O ₃ Br (344.38)	30%	133–135°C	59.31 (59.29)	3.80 (3.81)	345
4d	C ₁₇ H ₁₃ O ₃ Br (331.2)	32%	210–211°C	59.31 (59.29)	3.80 (3.81)	332
4e	C ₁₇ H ₁₃ O ₃ F (284.3)	30%	135–137°C	71.75 (71.82)	4.59 (4.61)	285
4f	C ₁₈ H ₁₃ O ₃ N (291.3)	35%	201–202°C	74.32 (74.21)	4.51 (4.49)	292

6,7-Dimethyl substituted flavonone (5a–f): Compound (2a–f) Isopropyl alcohol (50 mL, 0.003 mol) and perchloric acid (5 mL) was refluxed for 30 h and diluted with 25 mL water, allowed to stand at room temperature. Filtered solid unconverted chalcone. Further diluted the filtrate and allowed to stand at room temperature. The solid separated was filtered, dried and crystallized from ethanol. IR (KBr, cm⁻¹) (5a–f): 3000–2950 v(—CH), 1650–1630 v(—C=O), 1600–1550 v(Ph —C=C), 1380–1300 v(—C—O). **Compd. 5a, (5c–f):** ¹H NMR (CDCl₃) δ 2.2 (s, 3H), 2.35 (s, 3H), 4.5 (s, 2H), 6.78 (s, 1H), 6.95 (s, 1H), 7.14 (s, 1H), 7.55–7.56 (m, 3H), 8.02–8.03 (m, 1H). **Compd. 5b,** ¹H NMR (CDCl₃) δ 2.2 (s, 3H), 2.35 (s, 3H), 4.5 (s, 2H), 6.78 (s, 1H), 6.95 (s, 1H), 7.14 (s, 1H), 7.55–7.56 (m, 3H).

The analytical and physical data of the compound 5a–f are given in Table-4.

TABLE-4
PHYSICAL AND ANALYTICAL DATA OF COMPOUNDS (5a–5f)

Compd.	m.f.	Yield	m.p.	Analysis %, Found (Calcd.)		Mol ion peak (m+)/e
				C	H	
5a	C ₁₇ H ₁₅ O ₂ Cl (286.7)	70%	147–149°C	71.02 (71.20)	5.16 (5.27)	289
5b	C ₁₇ H ₁₅ O ₂ Cl ₂ (321.2)	60%	180–182°C	63.61 (63.57)	4.42 (4.39)	323
5c	C ₁₇ H ₁₅ O ₂ Br (330.39)	60%	125–127°C	61.75 (61.80)	4.49 (4.57)	333
5d	C ₁₇ H ₁₅ O ₂ Br (330.39)	65%	182–183°C	61.86 (61.81)	4.68 (4.57)	332
5e	C ₁₇ H ₁₅ O ₂ F (270.30)	63%	128–130°C	75.34 (73.54)	5.68 (5.59)	272
5f	C ₁₈ H ₁₅ NO ₂ (277.3)	70%	196–198°C	78.01 (77.95)	5.50 (5.45)	278

The newly synthesized compounds (2a–f) were screened for their antibacterial activities by diffusion method in methanol solvent at 5 mg/mL dilution against *E. coli*, *S. aureus*, *A. niger* and *Candida albicans*. These compounds show no antimicrobial activity.

The compounds (2a–f) were given pharmacological tests to check the biological activity of chalcones in mice.

- 2a LD₅₀ > 800 mg/kg. Slight fall in blood pressure.
- 2b LD₅₀ > 800 mg/kg. Fall in blood pressure. Sedation at 800 mg/kg was observed at 1 h.
- 2c LD₅₀ > 800 mg/kg. No effect in blood pressure.
- 2d LD₅₀ > 800 mg/kg. Fall in blood pressure. Sedation at dose of 400–800 mg/kg was observed at 2 h.
- 2e LD₅₀ > 800 mg/kg. Mild sedation at dose of 400–800 mg/kg was observed at 2 h. Fall in blood pressure was observed.

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