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Synthesis and Antibacterial Activity of Tetrahydrocurcuminoids

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The naturally occurring curcuminoids, curcumin (**1**), demethoxycurcumin (**2**) bisdemethoxycurcumin (**3**) were synthesised and converted into their tetrahydro derivatives (**4–6**) respectively. Compounds (**4–6**) showed enhanced antibacterial activity compared to naturally occurring curcuminoids.

INTRODUCTION

Turmeric was highly esteemed by the ancient Indo-European people for its golden-yellow dye resembling sunlight and has been used for centuries as a spice, food preservative and a colouring agent. Curcuminoids, phenolic diarylheptanoids (**1–3**), are chracteristic yellow colouring constituents of turmeric, the roots/ rhizomes of *Curcuma longa* L., *C. xanthorrhiza* Roxb, *C. zedoria* Christm and *C. aromatia* Salisb. Curcuminoids were reported to possess antioxidant[1,2], anti-inflammatory[3], antitumour, anticancer[4,5] and antiviral[6] properties. Discovery of antiviral properties in curcuminoids, particularly against HIV-1[6] is interesting and needs further study of their analogues. Further, although yellow coloured curcuminoids have been reported to be strong antioxidants, they cannot be used in food and the like which shall not be coloured. The tetrahydrocurcuminoids (**4, 5** and **6**) are colourless compounds and therefore find use in achromatic food and cosmetic applications. It may be of interest to note that tetrahydrocurcumin (**4**) showed better antioxidant activity than curcumin (**1**)[7]. Herein, we report the synthesis of tetrahydrocurcuminoids and the results of their antibacterial activity studies.

EXPERIMENTAL

Melting points were recorded in open capillaries and are not corrected. UV

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spectra were recorded on a Shimadzu UV–190 spectrophotometer. IR spectra were recorded on a Perkin-Elmer BX1 FT-IR spectrophotometer. ^{1}H NMR (90 MHz) spectra were recorded on Jeol JNM EX 90 FT NMR spectrometer. Acme silica gel G and silica gel (100–200 mesh) were used for analytical TLC and column chromatography, respectively.

Synthesis of curcuminoids: Compounds (**1–3**) were prepared according to the method reported in the literature[6, 8, 9].

1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione(curcumin, **1**): Crystallized from methanol, m.p. 178–180°C (Lit.[9] 182–183°C).

1-(4-Hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (demethoxycurcumin, **2**): Orange yellow powder, m.p. 169–171°C (Lit.[9] 172–173 °C).

1,7-Bis(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione(bisdemethoxy curcumin, **3**): Orange yellow powder, m.p. 220–222°C (Lit.[9] 223–224°C).

General procedure for the preparation of compounds 4–6.

To a solution of compound (1.5 mmol) in ethyl acetate (25 mL) was added palladium-charcoal (10%, 100 mg) and the reaction mixture was stirred under hydrogen atmosphere for 2 h. The catalyst was removed by filtration and the solvent was evaporated. The residue obtained was chromatographed over silica gel column using chloroform-methanol (96 : 4) as eluent.

1,7-Bis(4-hydroxy-3-methoxyphenyl)-heptane-3,5-dione) (4): Colourless powder, 69% yield, m.p. 94–96°C (Lit.[8] 95–96°C); UV (MeOH) λ_{max} (log ε) 205 (4.54); IR (Neat) ν_{max} 3440, 2930, 1722, 1699, 1611, 1515, 1271, 1033, 816 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.6–3.0 (8H, m), 3.83 (6H, s), 5.4 (1H, s), 6.64 (2H, d, J = 8 Hz), 6.66 (2H, s), 6.81 (2H, d, J = 8 Hz).

1-(4-Hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-heptan-3,5-dione (**5**): Colourless oil, 70% yield; UV (MeOH) λ_{max} (log ε) 223 (4.23), 280 (4.21); IR (Neat) ν_{max} 3398, 2936, 1721, 1697, 1613, 1515, 1269, 1033, 823 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.5–2.9 (8H, m), 3.81 (3H, s), 5.4 (1H, s), 6.6–7.0 (7H, m).

1,7-Bis(4-hydroxyphenyl)-heptan-3,5-dione (**6**): Colourless powder, 70% yield, m.p: 104–105° C; UV (MeOH) λ_{max} (log ε) 222 (4.18), 279 (4.15); IR (Neat) ν_{max} 3153, 1602, 1517, 1447, 1248, 1099, 826 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.52 (4H, t, J = 7.5 Hz), 2.84 (4H, t, J = 7.5 Hz), 5.36 (1H, s), 6.73 (4H, d, J = 8.3 Hz), 7.01 (4H, d, J = 8.3 Hz).

Antibacterial Activity Screening

Curcuminoids (**1–3**) and tetrahydrocurcuminoids (**4–6**) were screened for their antibacterial activity by the agar cup-plate diffusion method[10, 11], against the organisms *Escherichia coli, Pseudomonas aeruginosa* (gram –ve), *Bacillus subtilis, Bacillus pumilis* (gram +ve), at 50, 200, 500 μg concentrations. Interestingly, the tetrahydrocurcuminoid compounds are showing comparable or better antibacterial activity than the parent curcuminoids (Table-1).

TABLE-1
ANTIBACTERIAL ACTIVITIES OF THE COMPOUNDS **1–6**
[diameter of inhibition zone (in mm)]

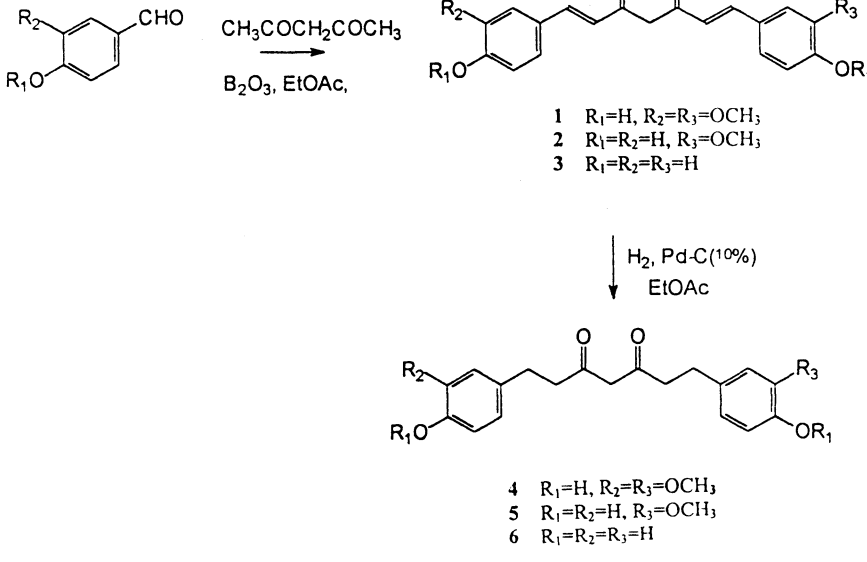
Comp.	*E. coli*			*P. aeruginosa*			*B. subtilis*			P. pumilis		
	50 μg	200 μg	500 μg	50 μg	200 μg	500 μg	50 μg	200 μg	500 μg	50 μg	200 μg	500 μg
1	—	—	—	—	—	—	—	—	—	—	—	—
2	—	—	—	8.5	9.5	10.0	9.5	10.0	10.0	8.5	9.0	9.5
3	—	—	—	11.0	12.0	12.0	—	9.0	10.0	—	8.0	8.0
4	—	—	10.0	—	9.5	10.0	9.5	10.0	11.0	—	8.5	9.0
5	—	9.5	10.0	8.5	9.5	10.5	10.0	11.0	11 .0	—	9.0	9.5
6	11.0	12.0	13.0	11.0	12.0	14.0	12.0	13.0	14.5	11.5	12.5	12.5

—No antibacterial activity, **1, 2, 3** natural curcuminoids **4, 5, 6** tetrahydrocurcuminoids

RESULTS AND DISCUSSION

Synthesis of naturally occurring curcuminoids and tetrahydrocurcuminoids

Curcumin (**1**), demethoxycurcumin (**2**), bisdemethoxycurcumin (**3**) were prepared from different substituted benzaldehydes and 2,4-pentanedione, boric oxide in ethyl acetate in the presence of tributyl borate and *n*-butylamine[8]. Creating a boron complex of 2,4-pentanedione protects the higher acidic methylene protons from Knoevenagel condensations, and the condensation can occur at the terminal methyl groups of the diketone[9] as shown in Scheme 1.



1 R_1=H, R_2=R_3=OCH_3
2 R_1=R_2=H, R_3=OCH_3
3 R_1=R_2=R_3=H

4 R_1=H, R_2=R_3=OCH_3
5 R_1=R_2=H, R_3=OCH_3
6 R_1=R_2=R_3=H

Curcumin (**1**) was hydrogenated in ethyl acetate over palladium-charcoal (10%) as catalyst to get tetrahydrocurcumin (**4**)[8], in 70% yield. The other curcuminoids (**2, 3**) were also hydrogenated to give corresponding tetrahydrocurcuminoids (**5,** 6) in good yield. All the compounds were characterised by their spectral data (UV, IR, ^{1}H NMR).

Conclusion

In conclusion, we have synthesised naturally occurring curcuminoids (**1–3**), and converted them into their tetrahydro derivatives (**4–6**). Compounds **4–6** have shown enchanced antibacterial activity.

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