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Research Article

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Synthesis and spectral characterization of curcumin and related curcuminoids

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Abstract In this research work various curcuminoids have been synthesized and characterized, as the first step curcumin was synthesized from Acetyl acetone and vanillin and then the corresponding curcumin derivatives weresynthesized by treating curcumin with epichlorhydrin and K_2CO_3 in DMF and then its amine derivative was synthesized by refluxing with methyl amine in presence of NaOH. Various curcuminoids were synthesized by treating acetyl acetone and various substituted aldehydes in the presence of boric anhydride and ethyl acetate at room temperature. Crude products then extracted with various suitable organic solvents and recrystallized from methanol. The synthesized products were checked for purity by TLC. All the products were characterized by H^1 NMR, MS, FT-IR spectroscopies.

Keywords Curcuminoids, Acetyl acetone, vanillin, epichlorhydrin, boric anhydride

1. Introduction

Curcumin is a secondary metabolite of the Asian spice *Curcuma longa*, which has been known for thousands of years in Ayurvedic system of medicine for the treatment of numerous ailments [1]. On the basis of the recent scientific information's the compound is a great promise as a potent modulator of activity of vital bio macromolecular targets involved in the mammalian physiology. The high chemical reactivity of the compound is due to its typical structure including extended conjugated double bond system prone to nucleophilic attack [2]. Many curcumin characters are unsuitable for use as drugs by themselves. They have poor solubility in water at acidic and physiological pH, and also hydrolyze rapidly in alkaline solutions.Curcuminoids, various linear diarylheptanoids, with different functional groups have been synthesized to increase solubility of curcumins and make them suitable for drug formulation.

2. Experimental Work

All chemicals were purchased from Sigma Aldrich Chemical Co. and Merck Chemical Co. (Germany). Meltingpoints of the compounds were determined by using an electrothermal digital melting point apparatus and were uncorrected. The infrared (IR) spectra of the compounds were recorded in the region of 4000-400 cm^{-1} using KBr on a FT-IR Perkin-Elmer spectrophotometer. Vibrational transition frequencies were reported in wave number (cm^{-1}). ^{1}H-NMR spectra were recorded on Bruker Spectroscope in ultra shield magnets 400 MHz instrument using TetramethylSilane (TMS) as an internal standard and MeOD as a solvent. The ESI^+VE MS spectra were recorded on a Bruker Daltonics LC-MS spectrometer.

3.1 Methods of preparation

3.1.1 Synthesis of curcumin

Ina 100 ml three necked round bottom flask, placed on magnetic stirrer, was charged with 1 ml of acetyl acetone, 0.068 gm of boric anhydride and 10 ml of ethyl acetate solution which was then stirred for a duration of 60 minutes.9.2 ml of tributyl borate and 3.04 gm of vanillin were added and stirring continued at room temperature. After almost 45 minutes, 1.1 gm of n-butyl amine dissolved in 10 ml of ethyl acetate solution was added drop wise from an addition funnel, at this point colour change was clearly visible. The reaction required at least 8hrs.The next step involved acid hydrolysis of the reaction mixture and for that 1.5 ml of conc. HCl was diluted using 8.5 ml of distilled water then added drop wise over a period of 30 minutes with constant stirring. The next step was placing the system on an oil bath and heating the contents up to 60 ^{o}C for 2.5 hrs with constant stirring. To monitor the progress of the reaction TLC analysis was done. To separate the product formed from the reaction mixture 30 ml ethyl acetate was added and transferred the whole reaction mixture into a separating funnel and water was added to remove the impurities. The organic layer was collected in a conical flask and added anhydrous sodium sulphate and the organic layer was filtered through a cotton plug, transferred to a round bottom flask and distilled in a rotavapor, finally a dark, reddish product was obtained. The crude product was recrystallized in methanol by refluxing for a period of 45 minutes, filtered and left overnight for crystallization. An orange yellow needle shaped crystals were obtained [3-4].

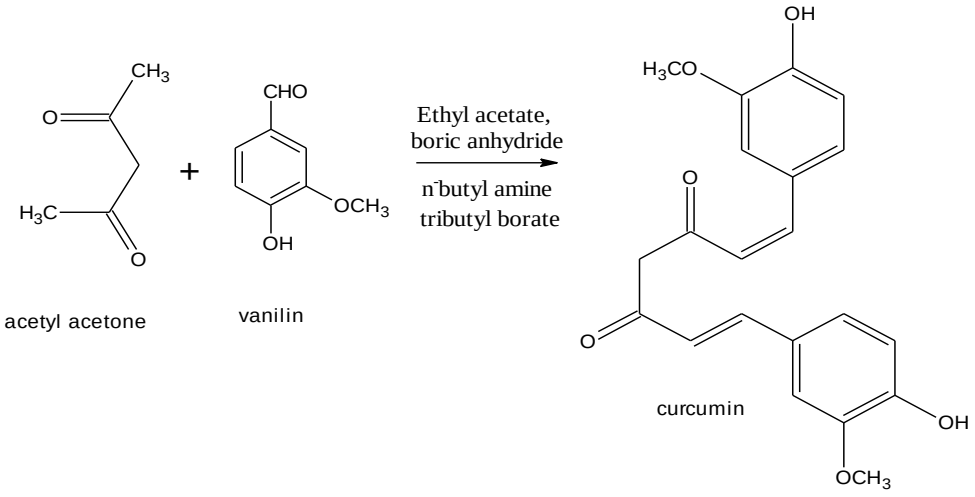
3.1.1a. Synthesis of epichlorohydrin derivative of curcumin

To a solution of curcumin in DMF, anhydrous K_2CO_3 was added and stirred for 10 min. After that epichlorohydrin dilutedwith DMF was added to the reaction mixture and heated to 60 ^{o}C for 6 hrs and monitor by TLC. The solvent was removed under reduced pressure. Residue was taken in water and extracted with ethyl acetate. Finally water wash was given to the organic layer and dried with anhydrous sodium sulphate. The solvent was evaporated to get the crude product which was then purified by column chromatography over silica gel (60-120 mesh) using $CHCl_3/CH_3OH$ as the eluent.

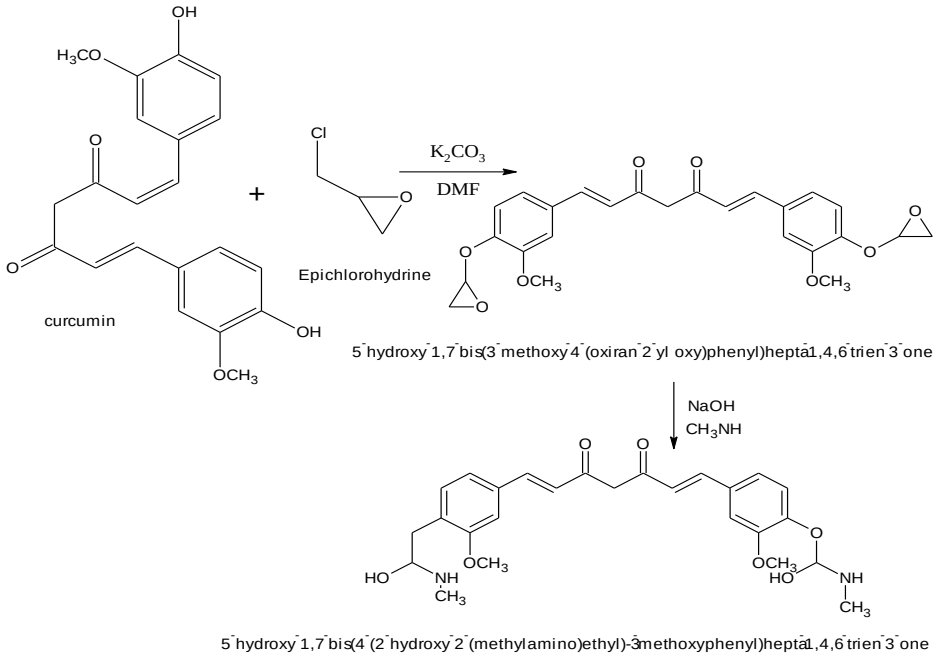
3.1.1b. Synthesis of amine derivative of epichlorhydrincurcuminoid

To a 100 ml RB flask fitted with calcium chloride guard tube Epichloro derivative of curcumin and methanol were added and refluxed. After 15 minutes NaOH and methyl amine were added and refluxed for 8-10 hrs. After the completion of the reaction methanol was distilled off under reduced pressure and residue was treated with ethyl acetate. The organic layer was separated and dried over anhydrous Na_2SO_4. The mixture was concentrated under reduced pressure to obtain the final product.

Scheme 1: Synthesis of curcumin

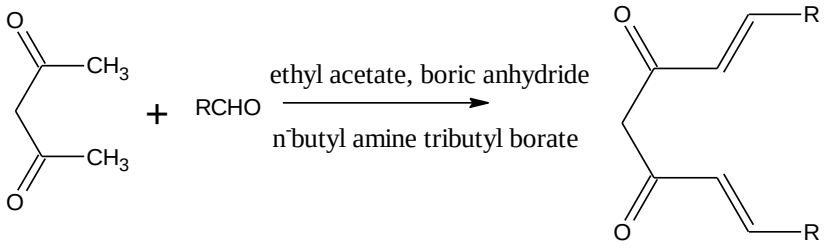


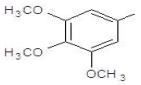
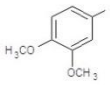
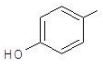
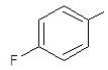
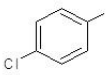
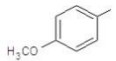
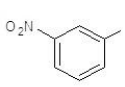
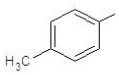
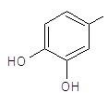
Scheme 2: Synthesis of amine and epichlorhydrin derivative of curcumin



3.1.2. General methods for the synthesis of various curcuminoids [5-6]

Scheme 3: General methods for the synthesis of various curcuminoids



Compound	R	Compound	R
3a		**3f**	
3b		**3g**	
3c		**3h**	
3d		**3i**	
3e		**3j**	

A 100 ml three necked RB flask, placed on magnetic stirrer, was charged with 1.0 ml of acetyl acetone, 0.068 gm of boric anhydride and 10 ml of ethyl acetate solution which was then stirred for a duration of 60 min. Then 9.2 ml of tributyl borate and benzaldehyde were added and stirring continued at room temperature. After 45 min 1.1 gm of n-butyl amine dissolved in 10 ml of ethyl acetate solution was added drop wise from an addition funnel, at this point colour change was clearly visible and the reaction time was 8 hours.

The next step involved the acid hydrolysis of the reaction mixture and for that 1.5 ml of con. HCl was diluted using 8.5 ml of distilled water the added drop wise over a period of 30 min with constant stirring. The next step was placing the system on an oil bath and heating the contents up to 60 ^{o}C for 2.5 hrs with constant stirring. To monitor the progress, the TLC analysis was done of the crude product. This involved taking little amount sample of compound in a test tube, dissolved in methanol and spotted against standard on pre coated TLC plate. To work up the mixture at first 30 ml of ethyl acetate was added and then transferred the whole mixture into aseparating funnel and then water was added to remove the impurities. The organic layer was collected in a conical flask and to this added anhydrous sodium sulphate and then the organic layer was filtered through a cotton plug, transferred to a round bottom flask and distilled to remove the solvent. Finally a dark reddish product was obtained, recrystallized from methanol by refluxing for 45 min and then filtered and left over night for crystallization. Orange yellow needle shaped crystals were obtained.

4. Results and Discussion

4.1. Spectral characters of Synthesized compounds

Curcumin ((1,7-bis(4-hydroxy-3-methoxy phenyl 1)- 1,6-heptadiene-3,5-dione (1)

H^1 NMR [300 MHz, $CDCl_3$]: δ 3.9560 (s, 6H, 2x3HCO-C_6H_4-), 5.8076 (s, 1H,=Cha-), 6.4568-6.5094 (d,2H$_{,2}$ x-CHb=CHc-), 6.9262-6.9536 (d, 2H, 2x-C_6H_4-) 7.0554-7.0603 (d, 2H,2x-C_6H_4-), 7.1146-7.1475(s, 2H, 2x-C_6H_4-), 7.5709-7.6234 (d, 2H, 2x-CHc=CHb-), EIMS: m/z 369.1$(M+1)^+$, 370.2 $(M+2)^+$, 177.0(base peak), IR: (KBr,cm^-1): 3504.3, 1628.5, 1375.8, 1314.5, 1205.7, 1117.8.

5-hydroxy-1,7-Bis[3-methoxy-4-(oxiran-2-yl-oxy)phenyl]-hepta-1,4,6-trien-3-one (2a)

H^1 NMR [300MHz,$CDCl_3$]: δ 5.7896 (s, 4H, 2x2HCO_2-C_6H_4-), 6.1023 (s, 1H, =CHa-), 6.4437-6.4961 (d, 2H,2x-CHb=CHc-), 6.8338-6.8603 (d, 2H, 2x-C_6H_4-), 7.0504 (s, 2H, 2x-C_6H_4-), 7.0779-7.0897 (d, 2H, 2x-C_6H_4-), 7.5672=-7.6196 (d, 2H, 2x-CHc=CHb-), 1.4407 (s,2H, 2x-CH_2), 1.2229 (s, 2H, 2x-CH_2), 1.114 (s,1H,2x-CH-).

5-hydroxy-7-Bis{4-[2-hydroxy-2-(methylamino)ethyl]-3-methoxyphenyl}- hepta-1,4,6-trien-3-one (2b)

H^1 NMR [300 MHz, $CDCl_3$] δ 5.7896 (s, 4H, 2x2HCO_2-C_6H_4-), 6.1023 (s, 1H, =CHa-), 6.4437-6.4961 (d, 2H, 2x-CHb=CHc-),6.8338-6.8603 (d, 2H, 2x-C_6H_4-), 7.0504 (S, 2H, 2x-C_6H_4), 7.0779-7.0897 (d, 2H ,2x-C_6H_4-), 7.5672-7.6196 (d, 2H, 2x-CHc=CHb-), 1.4407 (s, 2H, 2x,-CH_2), 1.2229 (s, 2H, 2x,-CH_2), 1.114 (s,1H,2x-CH-).

5-hydroxy-1,7-Bis(3,4,5-trimethoxy phenyl) hepta-1,4,6-trien-3-one (3a)

H^1 NMR [300 MHz, $CDCl_3$]: δ 5.7896 (s, 9H, 3x-$OCH_3C_6H_4$-), 6.1023 (s, 1H, =CHa-) 6.4437-6.4961 (d, 2H, 2x-CHb=CHc-), 6.8338-6.8603 (d, 2H, 2x-C_6H_4-), 7.0504 (s, 2H, 2x-C_6H_4-), 7.0779-7.0897 (d, 2H, 2x –C_6H_4-), 7.5672-7.6196 (d, 2H, 2x-CHc=CHb-) EIMS: m/z 457.1 (M+), 457.2 [$(M+1)^+$, Basepeak] IR (KBr, cm^{-1}): 3440.5, 1609.7, 1443.0, 1358.3, 1235.8, 1098.8.

5-hydroxy-1,7-Bis(4-chloro phenyl)-hepta-1,4,6-trien-3-one (3b)

H^1 NMR [300 MHz, $CDCl_3$]: δ 5.8176 (s, 1H, =CHa-), 6.5175-6.5694 (d, 2H, 2x–CHb=CHc-), 6.9724-7.0101 (m, 4H, 4x-C_6H_4-), 7.3486-7.3942 (m, 4H, 4x-C_6H_4-), 7.5479-7.5998 (d, 2H, 2x-CHc=CHb-). EIMS: m/z 308.0 (M+), 309.2 [$(M+1)^+$], 176.3 [Base peak] IR (KBr, cm^{-1}): 3213.0, 1702.1, 1441.3, 1340.5, 1269.2, 1139.1.

5-hydroxy1,7-Bis(4-hydroxyphenyl)-hepta-1,4,6-trien-3-one (3c)

H^1 NMR δ [300 MHz, $CDCl_3$]: δ 5.8474 (s, 1H, =CHa-), 6.5845-6.6374 (d, 2H, 2x-CHb=CHc-) 7.37987.4033 (d,4H,4x-C_6H_4-), 7.4986-7.5223 (d, 4H, 4x-C_6H_4-) 7.6093-7.6647 (d, 2H, 2x-CH=CHb-) EIMS: m/z 345.1(M)+, 336.3[$(M+2)^+$, base peak] IR (KBr cm^{-1}): 3420.9, 1636.8, 1403.5, 1090.4.

5-hydroxy1,7-Bis(3-nitro phenyl)-hepta-1,4,6-trien-3-one (3d)

H^1 NMR [300 MHz, $CDCl_3$]: δ 5.8420 (s, 1H, =CHa-), 6.5952-6.6501 (d, 2H, 2x-CHb=CHc-), 7.3637-7.3890 (m, 6H, 6x-C_6H_4-), 7.6271-7.6820 (d, 2H, 2x-CHc=CHb-), 7.9415-7.9746 (m, 2H, 2x-C_6H_4-) EIMS:m/z 366.1(M+), 367.2$(M+1)^+$, 368.1$(M+2)^+$, 190.5 (basepeak), IR (KBr cm^{-1}): 3412.9, 1627.8, 1509.4, 1284.5, 1141.5.

5-hydroxy1,7-Bis(4-methyl phenyl)- hepta-1,4,6-trien-3-one (3e)

H^1 NMR [300 MHz, $CDCl_3$]: δ 2.38 (s, 6H, 2xCH_3-C_6H_4-), 5.82 (s, 1H, =CHa=), 6.56-6.61 (d, 2H, 2x-CHb=CHc-), 7.19-7.21 (d, 4H, 4x-C_6H_4-), 7.44-7.47 (d, 4H, 4X-C_6H_4-), 7.61-7.66 (d, 2H, 2x-CHc=CHb-) EIMS: m/z 304.4(M+), 306.0 $(M+2)^+$, 289.0 (basepeak). IR (KBr cm^{-1}): 3414.0, 1623.5, 1322.9, 1139.4.

5-hydroxy1,7-Bis(3,4-dimethoxy phenyl)- hepta-1,4,6-trien-3-one (3f)

H^1 NMR [300 MHz, $CDCl_3$]: δ 3.9231 (s,12H, 4x CH_3-COC_6H_4-), 5.8445 (s, 1H, =CHa-), 6.4918-6.5444 (d, 2H, 2x-CHb=CHc-), 6.8908-6.9185 (d, 2H, 2x-C_6H_4-), 7.1043 (s, 2H, 2x-C_6H_4-), 7.1515-7.1791 (d, 2H, 2x-C_6H_4-),7.6040-7.6565 (D, 2H, 2x-CHc=CHb-), EIMS: m/z 397.1 [$(M+1)^+$, base peak], 398.1 $(M+2)^+$. IR (KBr cm^{-1}): 3600.2, 1725.4, 1442.9, 1263.4, 1135.9.

5-hydroxy1,7-Bis(4-flouro phenyl)-hepta-1,4,6-trien-3-one (3g)

H^1 NMR [300 MHz, $CDCl_3$]: δ 5.8710 (s, 1H, =CHa-), 6.6271-6.6690 (d, 2H, 2x-CHb=CHc), 7.0583-7.1770 (d, 4H, 4X-C_6H_4-), 7.3946-7.4471 (d, 4H, 4x-C_6H_4-), 7.7104-7.7523 (d, 2H, 2x-CHc=CHb-). EIMS: m/z 312.2 [M+,base peak], 313.2 $(M+1)^+$. IR (KBr cm^{-1}): 3417.5, 1659.5, 1356.5, 1159.0.

5-hydroxy 1,7-Bis(4-methoxy phenyl)- hepta-1,4,6-trien-3-one (3h)

H^1 NMR [300 MHz, $CDCl_3$]: δ 3.814 (s, 6H, 2XCH_3CO-C_6H_4-), 5.7830 (s, 1H, =CHa-), 6.4723-6.5249 (d, 2H, 2x-CHb=CHc-), 6.9022-6.9310 (d, 4H, 4x-C_6H_4-), 7.4952-7.5238 (d, 4H, 4x-C_6H_4-), 7.5943-7.6469 (d, 2H, 2x-CHc=CHb-). EIMS: m/z 335.1 [$(M-1)^+$, base peak], 336.3(M+). IR (KBr cm^{-1}): 3414.5, 1735.5, 135685, 1037.0.

5-hydroxy1,7-Diphenyl - hepta-1,4,6-trien-3-one (3i)

H^1 NMR [300 MHz, $CDCl_3$]: δ 5.8413 (s, 1H, =CHa-), 6.5941-6.6471 (d, 2H, 2x-CHb=CHc-), 7.3648-7.3886 (m, 6H, 6x-C_6H_4-), 7.5324-7.5640 (m, 4H, 4x-C_6H_4-), 7.6282-7.6811 (d, 2H, 2x-CHc=CHb-). EIMS: m/z 277.2 [$(M+1)^+$,base peak], 278.2$(M+2)^+$. IR (KBr cm^{-1}): 3407.8, 1728.1, 1376.2, 1044.7.

5-hydroxy1,7-Bis(3,4-dihydroxy phenyl)- hepta-1,4,6-trien-3-one (3j)

H^1 NMR [300 MHz, $CDCl_3$]: δ 5.8397(s,1H,-CHa-), 6.2737-6.3267(d,2H,2x-CHb-), 6.8590-6.8864 (d, 2H, 2x-C_6H_4-), 7.0032-7.0306 (d, 2H, 2x-C_6H_4-), 7.0710-7.1018 (S, 2H, 2x-C_6H_4-), 7.4068-7.4598 (d, 2H, 2x-CHc=CHb-). EIMS: m/z 340(M+),], 339.2$(M-1)^+$, 289.2 (base peak). IR (KBr cm^{-1}): 3234.5, 1651.6, 1445.0, 1388.7, 1298.0, 1192.2, 1117.9.

4.2. Physical Characters of Synthesized Compounds

Compound	% Yield	M. P. (°C)	Solvent
1	47	180-181	methanol
2a	56	199-201	DMSO
2b	37	205-207	chloroform
3a	43	193-195	methanol
3b	52	221-223	chloroform
3c	29	158-160	chloroform
3d	19	144-146	chloroform
3e	70	208-210	methanol
3f	55	130-131	chloroform
3g	27	151-153	chloroform
3h	37	166-167	methanol
3i	21	140-141	methanol
3j	40	304-306	chloroform

5. Summary and Conclusion

Extensive scientific research has proven that most of the activities, associated with turmeric, are due to curcumin. Curcumin has been shown to exhibit antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal, and anticancer activities and thus has a potential against various malignant diseases, diabetes, allergies, arthritis, Alzheimer's disease, and other chronic illnesses. These effects are mediated through the regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes. Curcumin exhibits activities similar to recently discovered tumor necrosis factor blockers (e.g., HUMIRA, REMICADE, and ENBREL), a vascular endothelial cell growth factor blocker (e.g., AVASTIN), human epidermal growth factor receptor blockers (e.g., ERBITUX, ERLOTINIB, and GEFTINIB), and a HER2 blocker (e.g., HERCEPTIN).[7] Based on these facts twelve new curcuminoids were synthesized and characterized for investigating the biological activity by retaining the basic pharmacophores in the natural curcumin. This work promises better leads that may result in the development of newer drug molecules.

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