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Design and Synthesis of New Curcuminoid Compounds and their Derivatives as Antioxidant Agents

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Abstract

A series of new curcumin analogues and their derivatives were synthesized by reacting curcumin analogues with various substituted hydrazine compounds to afford new pyrazol derivatives. The preparation of ether and ester derivatives was also carried out. All synthesized compounds were characterized using FT-IR, ^{1}HNMR, ^{13}CNMR, and MS-ESI. The evaluations of these compounds have shown a good inhibition activity as antioxidant agents against the stable radical of diphenylpicrylhydrazyl (DPPH). Findings from this work demonstrated a high inhibition activity in compounds substituted with hydroxyl phenol groups in comparison with compounds with other groups.

Keywords:Curcumin; Curcuminoids; Pyrazol; Antioxidant; DPPH

1. Introdction

Curcuminoids are phenolic compounds that isolated from turmeric rhizome of curcuma longa L [1]. They consist of three isomers; curcumin, demethoxycurcumin and bisdemethoxycurcumin. Among the three isomers, curcumin is a major and most abundant isomer (77%) (Fig 1)[2].

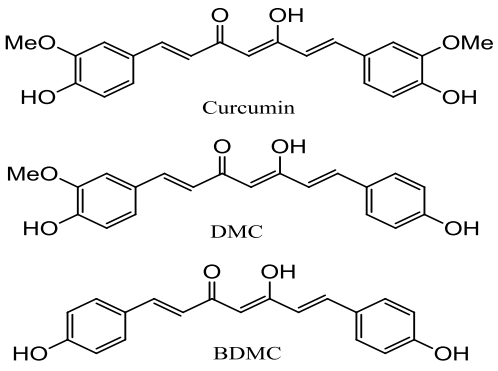

Fig. 1. Curcumin isomers of turmeric rhizome of curcuma longa L.

ot only in food systems, but also in the biological systems [3]. Curcuminoids play several health-beneficial roles by the transfer of hydrogenROS orRNS [4, 5]. Besides, they also possess biological activities such as anticancer [6, 7], anti-inflammatory [8], antimicrobial[9], antiviral[10], anti-diabetes[11], and anti-malarial activities[12]. Regardless of the many beneficial roles, the activities of curcuminoids are delimited due to the limited solubility in water and hydrolysis in an alkaline medium along with photochemical degradation [13]. These problems can be addressed by the modification of curcumin [14, 15]. For decades, the researchers have been trying to design and synthesize super curcumin from curcumin derivatives and their analogues [16, 17].

In the present work, curcuminoidspyrazoles derivatives, and curcumin analogues were synthesized and characterized by various spectroscopic techniques, and their antioxidant activity was evaluated against DPPH as a radical source. Due to the important role of bio-antioxidant compounds in the protection of human health [18], we have designed and synthesized new analogues from bio-antioxidants for the treatment of different human diseases.

2. Materials and Methods

All chemical material were obtained from commercial source. Melting points were measured by

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using electrothermal apparatus. FTIR spectra were recorded by Shimadzu FTIR-affinity spectrophotometer in the region 4000–400cm^{-1} in KBr pellet. The mass spectra were scanned by the ESI technique 5eV with waters ACQUITYQSM. ^{1}H and ^{13}CNMR spectra were scanned on a Bruker 400 MHz spectrometer with a field gradient to operating at 500 MHz for proton observation and 100 MHz for carbon observation. TMS as the internal standard was used as referenced to 0.0ppm. DMSO-d6 was used as solvent. Elemental analysis (CHNS) were measured by using elementarVario MICRO. UV-Visible were measured by spectrophotometer type PG-instrument T80^{+}.

2.1. General procedure for the synthesis of symmetric analogues compounds (1,2)[19]

Acetylacetone or chloroacetylacetone (0.0233 mol) and boric oxide (1.2 g, 0.017 mol) were stirred for 1 h. Then, vanillin (6.99 g, 0.046 mol) was dissolved in dry DMA (50 mL) and heated in a water bath at 80 ^{o}C.Trimethylborate (5g, 0.046 mol) was then added to the above mixture. The reaction mixture was stirred for 5 min followed by an addition of a solution of *n*-butylamine 0.737 g (0.01 mol) in DMAdropwise over a period of 1 h. The mixture was stirred for 3 h and set for overnight. 5% Acetic acid (70 mL) was then added at 80 °C and the resulting mixture was stirred for 1 h. Upon cooling the mixture, the solid product was precipitated and collected by filtration, washed by hot water twice, dried and then recrystallized from the appropriate solvent.

*2.1.1.(1E,6E)-4-Chloro-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (**1**)*

Orange crystals, recrystallized from ethanol, yield: 48%, m.p. 190–191 °C.^{1}HNMR (DMSO, δ ppm): 3.83 (6H, s, OCH_3), 6.64 (2H, d, *J* = 12 Hz, olefinic protons), 7.115 (2H, d, *J* = 6 Hz, Ar–H), 7.275 (2H, d, *J* = 6 Hz, Ar–H), 7.41 (2H, s, Ar–H), 7.805 (2H, d, *J* =18 Hz, olefinic protons), 9.95 (2H, s, OH).^{13}CNMR (DMSO, ppm) 56.0, 109.9, 114.8, 117.3, 123.6, 127.6, 142.4, 146.7, 148.3, 180.0. IR (υ, cm^{-1}): 3005, 2854, 1618, 1287, 1028, 821, 813. HRMS (ESI): (M + H) calculated: 403.0948, observed: 403.0943.

*2.1.2. (1E,6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione (**2**)*

Orange crystals, recrystallized from ethanol, yield: 62%, m.p. 180–182 °C. ^{1}HNMR (DMSO, δ ppm): 3.82 (6H, s, OCH_3), 6.83 (2H, d, *J* = 12 Hz, olefinic protons), 6.83 (2H, d, *J* = 6 Hz, Ar–H), 7.16 (2H, d, *J* = 6 Hz, Ar–H), 7.32 (2H, s, Ar–H), 7.65 (2H, d, *J* =18 Hz, olefinic protons), 9.69 (2H, s, OH). ^{13}CNMR (DMSO, ppm). IR (μ, cm^{-1}): 3217, 3005, 2854, 1622, 1600.1, 1562.

*2.2. General procedure for preparing pyrazol, and pyrazol derivatives (**3-7**)* [20]

To a solution of compounds **1** or **2** (0.63 mmol) in glacial acetic acid (20 mL), hydrazine monohydrate or hydrazine derivatives (0.65 mmol) was added. The mixture was heated under reflux under stirring for 20 h, cooled and further poured into an ice water (100 mL) to afford a white solid product. The mixture was then dried and recrystallized from the appropriate solvent.

*2.2.1. 4,4'-(4-Chloro-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxypheno (**3**)*

Beige powder, recrystallized from ethanol, yield: 50%, m.p. 186-188 °C.^{1}HNMR (DMSO, δ ppm): 3.83 (6H, s, OCH_3), 6.64 (2H, d, *J* = 12 Hz, olefinic protons), 7.115 (2H, d, *J* = 6 Hz, Ar–H), 7.275 (2H, d, *J* = 6 Hz, Ar–H), 7.41 (2H, s, Ar–H), 7.805 (2H, d, *J* =18 Hz, olefinic protons), 9.95 (2H, s, OH). ^{13}CNMR (DMSO, ppm): 149.1, 147.9, 146.5, 137.8, 132, 129, 127.2, 122.9, 121.4, 119, 116.2, 113.8, 111.5, 110.8, 57.1. IR (υ, cm^{-1}): 3392, 3005, 2952, 1658, 1593, 1514, 1463, 1452, 1429, 1340, 1274, 1207, 1112, 1031. Mass (ESI): (M + H) calculated: 633.62, observed: 633.3.

*2.2.2. 4,4'-((1E,1'E)-(4-Chloro-1-(2,4-dinitrophenyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol)(**4**)*

Brown powder, recrystallized from ethanol-chloroform, yield: 57%, m.p. 177-180 °C. ^{1}HNMR (DMSO, δ ppm): 3.83 (6H, s,OCH_3), 6.64 (2H, d, *J* = 12 Hz, olefinic protons), 7.115 (2H, d, J = 6, Ar–H), 7.275 (2H, d, *J* = 6 Hz, Ar–H), 7.41 (2H, s, Ar–H), 7.805 (2H, d, *J* =18 Hz, olefinic protons), 9.95 (2H, s, OH).^{13}CNMR (DMSO, ppm) 165.4, 158.5, 152.3, 142.6, 141.2, 136.4, 134.1, 131.1, 129.8, 128.5, 127.7, 124.4, 122.7, 120.2, 119.7, 114.3, 110.1, 574. IR (υ, cm^{-1}): 3495, 1618, 1589, 1514, 1429, 1274, 1215, 1065, 985. Mass (ESI): (M + H) calculated: 565.94, observed: 565.2.

*2.2.3. 4,4'-((4-Chloro-1-(4-nitrophenyl)-1H-pyrazole-3,5-diyl)bis (ethene-2,1-diyl))bis (2-methoxyphenol) (**5**)*

Beige powder, recrystallized from ethanol-chloroform, yield: 50%, m.p. 180-182 °C.^{1}HNMR (DMSO, δ ppm): 3.83 (6H, s,OCH_3), 6.64 (2H, d, *J* = 12 Hz, olefinic protons), 7.115 (2H, d, *J* = 6 Hz, Ar–H), 7.275 (2H, d, *J* = 6 Hz, Ar–H), 7.41 (2H, s, Ar–H), 7.805 (2H, d, *J* =18 Hz, olefinic protons), 9.95 (2H, s, OH). ^{13}CNMR (DMSO, ppm) 158.9, 148.4, 147.7, 144.7, 141, 136.1, 133, 129.1, 126.5, 124.7, 123, 120.3, 119.9, 116.2, 114.6, 112.6, 110.2, 56.2. IR (υ, cm^{-1}): 3437, 1639, 1561, 1516, 1424, 1218, 1060, 983, 817. Elemental analysis ($C_{27}H_{22}ClN_3O_6$): calculated: C, 62.37; H, 4.27; N, 8.08; found: C, 62.61; H, 4.19; N, 8.07%.

2.2.4. *4,4'-((1-(4-Ethoxythiazol-2-yl)-1H-pyrazole-3,5-di-yl)bis(ethene-2,1-diyl))bis(2-methoxy phenol)(**6**)*

Orange powder, recrystallized from ethanol-hexane, yield: 46%, m.p. 173-175 °C. ^{1}HNMR (DMSO, δ ppm): 3.83 (6H, s, OCH_3), 6.64 (2H, d, *J* = 12 Hz,olefinic protons), 7.115 (2H, d, *J* = 6 Hz, Ar–H), 7.275 (2H, d, *J* = 6 Hz, Ar–H), 7.41 (2H, s, Ar–H), 7.805 (2H, d, *J* =18 Hz, olefinic protons), 9.95 (2H, s, OH). ^{13}CNMR (DMSO, ppm) 165.4, 159.3, 157.5, 149.8, 148.4, 141.1, 131.7, 127, 123.6, 121.1, 118.3, 113.1, 111.7, 102, 101.2, 64.3, 56.1, 23.6. IR (υ, cm^{-1}): 3280, 3022, 2804, 1647, 1604, 1554, 1512, 1448, 1240, 1170, 966, 823. Elemental analysis ($C_{26}H_{25}N_3O_5S$); calculated: C, 63.53; H, 5.13; N, 8.55; S, 6.52; found: C, 63.36; H, 5.17; N, 8.65; S, 6.44%.

*2.2.5. 3,5-Bis((-4-hydroxy-3-methoxystyryl)-1H-pyrazole-1-carbothioamide (**7**)*

Orange powder, recrystallized from ethanol-hexane, yield: 48.5%, M.p: 100-102 °C.^{1}HNMR (DMSO, δ ppm): 3.83 (6H, s,OCH_3), 6.64 (2H, d, *J* = 12 Hz, olefinic protons), 7.115 (2H, d, *J* = 6 Hz, Ar–H), 7.275 (2H, d, *J* = 6 Hz, Ar–H), 7.41 (2H, s, Ar–H), 7.805 (2H, d, *J* =18 Hz, olefinic protons), 9.95 (2H, s, OH).^{13}CNMR (DMSO, ppm) 149.32, 147.65, 146.6, 129.4, 128.2, 127.3, 119.8, 115.4, 109.0, 55.4. Elemental analysis ($C_{22}H_{21}N_3O_4S$); calculated: C, 62.40; H, 5.00; N, 9.92; S, 7.57; found: C, 61.98; H, 5.06; N, 9.39; S, 7.39%.

*2.3.Procedure for the synthesis of ((1E,6E)-3,5-dioxohepta-1,6-diene-1,7-diyl)bis(2-methoxy-4,1-phenylene) bis(4-formylbenzoate) (**8**)*

In a round flask (100 mL) equipped with magnetic stirring, 4-formylbenzoic acid (0.9 g, 5.1 mmol), curcumin (1) (0.93 g, 24.45 mmol), DCC (5 mmol) and DMAP (0.4 mmol) were added with DCM (50 mL). The mixture was kept under vigorous stirring for 22 h. After the reaction was completed, the resulting mixture was filtered to remove DCU and the solvent was evaporated under reduced pressure. The crude product was recrystallized from ethanol. Yield: 75%, m.p. 230-232 °C. ^{1}HNMR (DMSO, δ ppm): 3.83 (6H, s, OCH_3), 6.64 (2H, d, *J* = 12 Hz, olefinic protons), 7.115 (2H, d, *J* = 6 Hz, Ar–H), 7.275 (2H, d, *J* = 6 Hz, Ar–H), 7.41 (2H, s, Ar–H), 7.805 (2H, d, *J* =18 Hz, olefinic protons), 9.95 (2H, s, OH).^{13}CNMR (DMSO, ppm) 193.4, 183.6, 163.9, 141.2, 140.2, 140.1, 134.6, 133.5, 131, 130.3, 125.3, 123.8, 112.7, 56.6. IR (υ, cm^{-1}): 3446, 3012, 2940, 1743, 1701, 1628, 1601, 1504, 1417, 1201, 1128, 1073, 975, 753. Mass (ESI): (M + H) calculated: 633.62, observed: 633.3.

2.4. Procedure for the synthesis of 2-chloro-1-(2,3,4-trihydroxyphenyl) ethan-1-one (THP)

To a 150 mL round flask with magnetic stirring, $AlCl_3$ (24 g) dissolved in DCM (80 mL) was added and stirred at 10-15 °C. After 20 min, 5 mL of chloroacerylchloride was added drop wise and the mixture was additionally stirred at room temperature for 4 h. After the resulting reaction was filtered, the solid product was thoroughly washed with diluted acetic acid, water, filtered and recrystallized from benzene. Yield 60%, m.p. 169-170 °C. White crystal,^{1}HNMR (DMSO, δ ppm): 5.07 (2H, s, CH_2-Cl), 6.44 (H, d, Ar-H), 7.30 (H, d, Ar-H), 8.77 (H, s, O–H), 10.28 (H, s, O–H), 11.63 (H, s, O–H).^{13}CNMR (DMSO, ppm) 195.2, 153.4, 152.2, 133, 123, 112, 109, 47.3. IR (υ, cm^{-1}): 3498, 3390, 3074, 2941, 1637, 1523, 1446, 1354, 1319, 1249, 1226, 1008, 896. Mass spectra (EI, 70 eV) calculate :202.59, observed: 202.1.

*2.5. Procedure for the synthesis of compounds (**9-11**)*

To a solution of curcuminoid (**1, 2** or **7**) (0.543 mmol) in ethanol (l50 mL), K_2CO_3 (0.15 g) was added. The reaction mixture was stirred for 15 min and THP (0.38 g, 1.08 mmol) was added to this mixture and heated under reflux with stirring for 16

h. The resulting mixture was further cooled to remove K_2CO_3 and poured to an ice water (100 mL) to furnish a solid product that was dried and recrystallized from a suitable solvent.

*2.5.1. (1E,6E)-1,7-Bis(3-methoxy-4-(2-oxo-2-(2,3,4-trihydroxy phenyl) ethoxy)phenyl)hepta-1,6-diene-3,5-dione (**9**)*

Orange powder, recrystallized from ether, yield: 55%, m.p. 176-178 °C. ^{1}HNMR (DMSO, δ ppm): 3.83 (6H, s, OCH_3), 6.64 (2H, d, *J* = 12 Hz, olefinic protons), 7.115 (2H, d, *J* = 6 Hz, Ar–H), 7.275 (2H, d, *J* = 6 Hz, Ar–H), 7.41 (2H, s, Ar–H), 7.805 (2H, d, *J* =18 Hz, olefinic protons), 9.95 (2H, s, OH). ^{13}CNMR (DMSO, ppm) 193.4, 183.6, 149.8, 148.4, 147.4, 143.1, 141.1, 135.7, 134.4, 133.9, 126.7, 123.9, 121.5, 166.1, 111.8, 101.3, 67.3, 59.9, 56.1. IR (υ, cm^{-1}): 3446, 3006, 2927, 1701, 1628, 1598, 1509, 1417, 1300, 1253, 1200, 1073, 997, 838. Masa (ESI): (M + H) calculated 701.65, observed 701.1.

*2.5.2. (1E,6E)-4-Chloro-1,7-bis(3-methoxy-4-(2-oxo-2-(2,3,4-tri hydroxyphenyl) ethoxy) phenyl) hepta-1,6-diene-3,5-dione(**10**)*

Orange powder, recrystallized from ether, yield: 52%, m.p. 184-186 °C. ^{1}HNMR (DMSO, δ ppm): 3.83 (6H, s, OCH_3), 6.64 (2H, d, *J* = 12 Hz, olefinic protons), 7.115 (2H, d, *J* = 6 Hz, Ar–H), 7.275 (2H, d, *J* = 6 Hz, Ar–H), 7.41 (2H, s, Ar–H), 7.805 (2H, d, *J* =18 Hz, olefinic protons), 9.95 (2H, s, OH). ^{13}CNMR (DMSO, ppm): 194.9, 184, 163.9, 156.3, 155, 153.6, 149.4, 136.8, 136.2, 132.2, 132, 130.9, 123.5, 120.4, 114.7, 112.4, 101.3, 75.6, 61.2, 55.0. IR (υ, cm^{-1}): 3134, 2987, 1685, 1628, 1602, 1514, 1462, 4102, 1336, 1293, 1182, 1037, 975, 808. MS-(ESI): (M + H) calculated: 736.09, observed: 736.3.

*2.5.3. 3,5-Bis((E)-3-methoxy-4-(2-oxo-2-(2,3,4-trihydroxyphenyl)ethoxy)styryl)-1H-pyrazole-1-carbothio amide(**11**)*

Orange powder, recrystallized from ethanol, yield: 57%, m.p. 201-203 °C.^{1}HNMR (DMSO, δ ppm): 3.83 (6H, s, OCH_3), 6.64 (2H, d, *J* = 12 Hz, olefinic protons), 7.115 (2H, d, *J* = 6 Hz, Ar–H), 7.275 (2H, d, *J* = 6 Hz, Ar–H), 7.41 (2H, s, Ar–H), 7.805 (2H, d, *J* =18 Hz, olefinic protons), 9.95 (2H, s, OH). ^{13}CNMR (DMSO, ppm): 190.6, 173.3, 153.9, 149.4, 148.3, 136.1, 134.4, 130.1, 129.5, 127.0, 126.4, 132.1, 120.5, 118.5, 116.0, 112.4, 109.9, 71.9, 56.0. MS-(ESI): (M + H) calculated: 756.75, observed: 756.4.

*2.6.Procedure for the synthesis ofdiethyl 2,2'-((((1E,1'E) -(4-chloro-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxy-4,1-phenylene))bis(oxy)) diacetate (**12**)*

In a round flask, ethanol (30 mL) was added to compound **1** (0.076 g, 0.182 mmol) and potassium carbonate (0.063 g, 0.456 mmol) followed by heating and stirring for 30 min. Chloroethylacetate (0.045g, 0.365 mmol) was then added to the above mixture and the mixture was heated under reflux under stirring for 16 h. The resulting mixture was cooled and filtrated to remove potassium carbonate and poured into an ice water. A pale yellow crystal was collected and recrystallized from ethanol, yield 40%, m.p. 210-212 °C.^{1}HNMR (DMSO, δ ppm): 3.83 (6H, s, OCH_3), 6.64 (2H, d, *J* = 12 Hz, olefinic protons), 7.115 (2H, d, *J* = 6 Hz, Ar–H), 7.275 (2H, d, *J* = 6 Hz, Ar–H), 7.41 (2H, s, Ar–H), 7.805 (2H, d, *J* =18 Hz, olefinic protons), 9.95 (2H, s, OH). ^{13}CNMR (DMSO, ppm): 169.1, 168.7, 158.1, 157.7, 150.2, 143.6, 131.7, 130.6, 130.2, 129.4, 128.6, 128.0, 119.2, 115.3, 115.2, 113.3, 99.5, 65.1, 61.5, 14.5. IR (υ, cm^{-1}): 3307, 3037, 1625, 1660, 1604, 1531, 1508, 1454, 1317, 1261, 1242, 1178, 1060, 974, 823. Elemental analysis ($C_{29}H_{31}ClN_2O_8$); calculated: C, 61.00; H, 5.47; N, 4.91; found: C, 61.41; H, 5.19; N, 4.57%.

*2.7.Procedure for the synthesis of bis(4-chloro-3,5-bis((E)-4-hydroxy-3-methoxystyryl) -1H-pyrazol-1-yl) methanone (**13**)*

Curcumin**1** (0.2 g, 0.5 mmol) was dissolved in of glacial acetic acid (40 mL) and followed by adding carbohydrazide (0.0224 g, 0.25 mmol). The mixture was heated under reflux for 12 h and then cooled and poured into an ice water. The orange powder product was collected by filtration, dried, and recrystallized from ethyl acetate: petroleum ether (1:1), yield: 48%, m.p. 278 °C < d. ^{1}HNMR (DMSO, δ ppm): 3.83 (6H, s, OCH_3), 6.64 (2H, d, *J* = 12 Hz, olefinic protons), 7.115 (2H, d, *J* = 6 Hz, Ar–H), 7.275 (2H, d, *J* = 6 Hz, Ar–H), 7.41 (2H, s, Ar–H), 7.805 (2H, d, *J* =18 Hz, olefinic protons), 9.95 (2H, s, OH). ^{13}CNMR (DMSO, ppm) 163.2, 162.5, 157.3, 140.8, 133.5, 133.1, 131.8, 129.5, 128.6, 126.0, 123.8, 121.6, 120.1, 118.2, 114.9, 110.5, 57.0. IR (υ, cm^{-1}): 3244, 3005, 2937, 1653, 1593, 1558, 1514, 1456,

1427, 1278, 1234, 1211, 1031, 960, 812 MS-(ESI): (M + H) calculated: 824.68, observed: 824.4.

*2.8.Procedure for the synthesis of acetylacetone derivatives (**14** and **15**)*

To a suspension solution of acetylacetone(6.8 g, 0.068 mmol) in of dry benzene (100 mL), NaH (3 g, 0.31 mmol) in dry benzene (50 mL) was added drop wise under stirring at room temperature. CS2 (5g, 0.068 mmol) was then added at 0 °C followed by an addition of DMF (100 mL). After stirring, the reaction mixture was cooled at 0 °C for 0.5 h. Alkyl halide (0.13 mmol) was added drop wise within 15 min. The resulting mixture was allowed to warm at room temperature, stirred overnight, and poured into an ice-water (75 mL).The organic phase was washed with water (5 × 80 mL), dried over anhydrous $NaSO_4$, filtered and concentrated in vacuum. The crude crystal product was recrystallized from ethanol.

*2.8.1. 3-(1,3-Dithian-2-ylidene) pentane-2,4-dione (**14**)*

Beige crystal yield: 62%, m.p. 99-100 °C. ^{1}HNMR (DMSO, δ ppm): 3.83 (6H, s, OCH_3), 6.64 (2H, d, *J* = 12 Hz, olefinic protons), 7.115 (2H, d, *J* = 6 Hz, Ar–H), 7.275 (2H, d, *J* = 6 Hz, Ar–H), 7.41 (2H, s, Ar–H), 7.805 (2H, d, *J* =18 Hz, olefinic protons), 9.95 (2H, s, OH). IR (υ, cm^{-1}): 2966, 1693, 1489, 1450, 1414, 1367, 1362, 1188, 970, 809. Elemental analysis ($C_9H_{12}O_2S_2$); calculated: C, 49.97; H, 5.59; S, 29.64; found: C, 50.36; H, 5.72; S, 29.95%.

*2.8.2. 3-(Bis(benzylthio)methylene) pentane-2,4-dione (**15**)*

White crystal, yield: 79%, m.p. 103-104 °C.^{1}HNMR (DMSO, δ ppm): 3.83 (6H, s, OCH_3), 6.64 (2H, d, *J* = 12 Hz, olefinic protons), 7.115 (2H, d, *J* = 6 Hz, Ar–H), 7.275 (2H, d, *J* = 6 Hz, Ar–H), 7.41 (2H, s, Ar–H), 7.805 (2H, d, *J* =18 Hz, olefinic protons), 9.95 (2H, s, OH).^{13}CNMR (DMSO, ppm) 183.2, 137.4, 129.4, 129.1, 128.0, 38.7, 30.7. IR (υ, cm^{-1}): 3030, 2985, 1681, 1600, 1544, 1494, 1454, 1415, 1350, 1247, 1230, 1188, 1068, 987, 873. Elemental analysis ($C_{20}H_{20}O_2S_2$); calculated: C, 67.38; H, 5.66; S, 17.99; found: C, 66.80; H, 5.61; S, 17.50%.

*2.9.Procedure for the synthesis of Curcumin analogues (**16** and **17**)*

In a 100 mL round flask, an appropriate aldehyde (0.005 mmol) was added to sodium ethoxide (0.45 g Na in 30 mL ethanol) at 0-5 °C. Then, acetyl acetone derivatives (**14** or **15**) (0.01 mmol) were added with stirring at 0-5 °C for 4 h. The product was collected by filtration and recrystallized from ethyl acetate-hexane (9:1).

*2.9.1. (1E,6E)-4-(1,3-Dithian-2-ylidene)-1,7-bis(4-methoxyphenyl) hepta-1,6-diene-3,5-dione (**16**)*

Orange powder, yield: 62%, m.p. 310 °C< d.^{1}HNMR (DMSO, δ ppm): 3.83 (6H, s, OCH_3), 6.64 (2H, d, *J* = 12 Hz, olefinic protons), 7.11 (2H, d, *J* = 6 Hz, Ar–H), 7.275 (2H, d, *J* = 6 Hz, Ar–H), 7.41 (2H, s, Ar–H), 7.805 (2H, d, *J* = 18 Hz, olefinic protons), 9.95 (2H, s, OH).^{13}CNMR (DMSO, ppm) 183.3, 162.7,157.9, 143.6, 131.2, 128.4, 127.9, 119.3, 115.4, 66.7, 31.2, 24.2. IR (υ, cm^{-1}): 3012, 2922, 1687, 1632, 1596, 1514, 1306, 1253, 1203, 983, 877. Mass (ESI): (M + H) calculated: 453.56, observed: 453.4.

*2.9.2. (1E,6E)-4-Bis(benzylthio)methylene)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene (**17**)*

Orange powder, yield: 64%, m.p. 146-147 °C. ^{1}HNMR (DMSO, δ ppm): 3.83 (3H, s, OCH_3), 6.64 (2H, d, *J* = 12 Hz, olefinic protons), 7.115 (2H, d, *J* = 6 Hz, Ar–H), 7.275 (2H, d, *J* = 6 Hz, Ar–H), 7.41 (2H, s, Ar–H), 7.805 (2H, d, *J* =18 Hz, olefinic protons), 9.95 (2H, s, OH). ^{13}CNMR (DMSO, ppm) 183.9, 150.1, 148.5, 146.8, 138.8, 131.8, 130.8, 130.3, 129.1, 126.8, 122.4, 113.6, 109.9, 109.0, 56.5. IR (υ, cm^{-1}): 3258, 3020, 1664, 1587, 1478, 1410, 1285, 1157, 1071, 925, 836.Mass (ESI): (M + H) calculated: 625.77, observed:625.4.

2.10.DPPH Radical Scavenging Assay

The antioxidant activity of the synthesized curcuminoids 1, 2, 9, 10, 11, 17, and 18, was determined by their ability to scavenge the stable α,α-diphenyl-β-picrylhydrazyl (DPPH) free radical according to Blois method [21]. The DPPH inhibition activity was measured spectrophotometrically by mixing 1 mL (200 μM) of methanolic solution of DPPH with 1 mL of different concentrations (50, 100, and 200 μM). The absorbance was recoreded at 517 nm. The decrease of absorbance with time (minutes) was measured by using UV-Visble spectrophotometer along with observing the change of DPPHcolor from violet to yellow or colorless. The percentage of inhibition was calculated by the following Equation (1) [22].

% inhibition percentage = Ac-As/As x 100…..Eq (1).

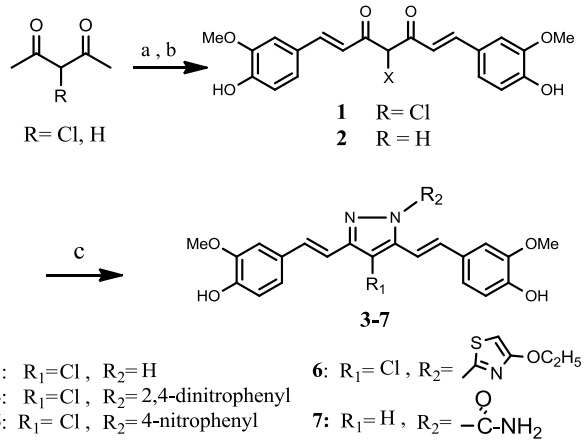
Where Ac = control absorbance, the absorbance of DPPH without sample

As = sample absorbance, the absorbance of DPPH with sample

3. Results and Discussion

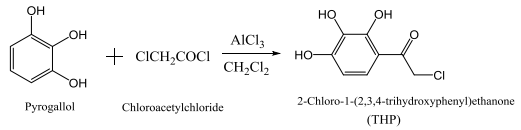
3.1. Chemistry

Compounds **1** and **2** were synthesized from vanillin by aldol condensation with 2,4-pentanedione or 5-chloro-2,4-pentanedione according to Pabon synthesis (Scheme 1).



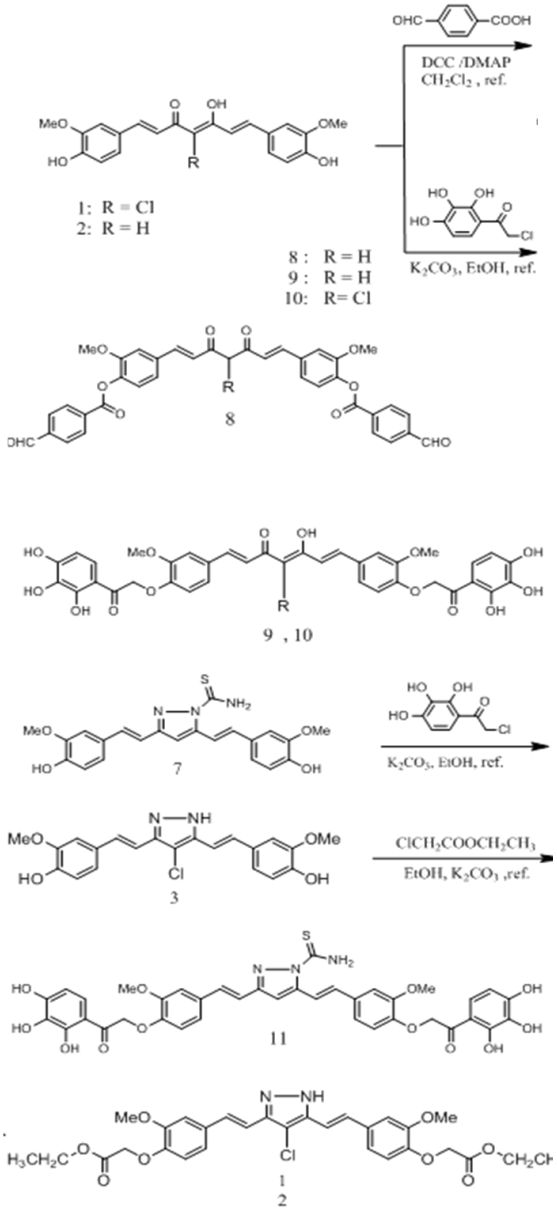
Scheme 1. Synthesis of curcuminoid and pyrazol compounds **1-7**.

The pyrazol derivatives **3-7** were prepared from curcuminoids with hydrazine or their derivatives in an acidic medium using glacial acetic acid as a solvent and catalyst. The curcumin ester **8** was prepared by reacting curcumin**1** with formyl benzoic acid in DCM as a solvent and DCC/DMAP as a catalyst. Likewise, the curcumin ether derivatives **9-12**were synthesized from curcuminoids and 2-chloro-1-(2,3,4-trihydroxyphenyl) ethan-1-one (THP) or chloroethyl acetate and potassium carbonate (Scheme 3). THP was prepared by friedel-crafts acylation reaction from pyragallol with chloroacetylchloride and $ALCl_3$ as catalysts according to Scheme 2.



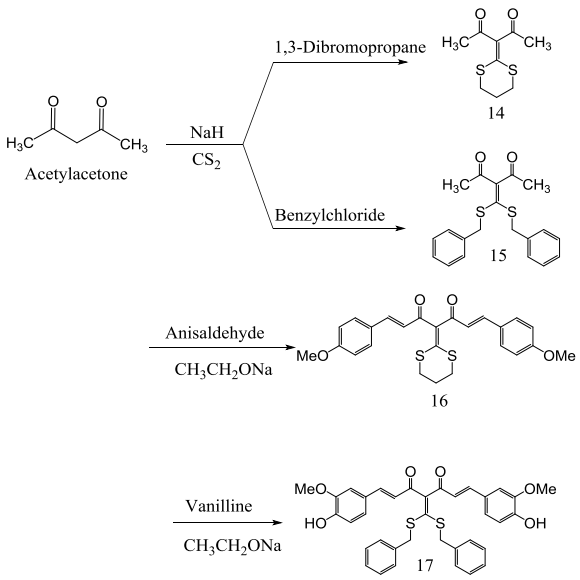
Scheme 2. Preparation of 2-chloro-1-(2,3,4-trihydroxyphenyl) ethan-1-one.

the curcumin ether derivatives 9-12, and curcuminpyrazol **13** were synthesized by the condensation of curcumin**1** and carbohydrazide in glacial acetic acid as a solvent using the catalyst in Schemes **3** . Curcumin analogues **16** and **17** were synthesized from acetylacetone derivatives **14** and **15** with an appropriate aldehyde.



Scheme 3. Synthesis of curcuminpyrazol compound **13**.

The acetylacetone derivatives **14** and **15** are usually prepared by a deprotonation of methylene ketone with a strong base such as NaH, followed by the addition of CS_2 and alkyl halide (Scheme 4).



Scheme 4. Preparation of acetylacetone derivatives and curcumin analogues **14-17**.

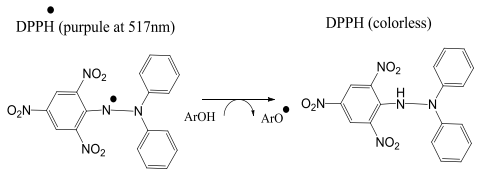
The proposed structure of the synthesized compounds was confirmed by using spectroscopic techniques such as, FT-IR, Mass spectra (ESI),^{1}H and ^{13}CNMR. The MS-ESI was used to determine the molecular weight of the prepared compounds in which the obtained molecular weight was in concordance with the theoretical values. The FT-IR spectra of the synthesized compounds showed bands for all the functional groups. The spectra of compounds **1** and **2** were characterized by bands corresponding to the stretching vibration of the carbonyl group which was shifted to lower frequencies (1618 and 1622) cm^{-1} as compared to the unconjugated ketone stretching frequencies of carbonyl group appearing at 1715 cm^{-1}. The shift was due to the participation of the group within the central intra-hydrogen bonded cheated ring. The (C-O) stretching vibration occurred as a strong band at (1287 and 1028) and (1278 and 1141) cm^{-1} for compounds **1** and **2**, respectively. The IR spectra of compounds **3-7** and **13** showed bands in the range (3392-3435) cm^{-1} that were attributed to the (OH) groups as well as the stretching vibration of (C=N) pyrazol ring at (1618-1658) cm^{-1} [23]. The spectra of curcuminoids derivatives **8-12** appeared as strong bands at (1625-1743) cm^{-1} were attributed to the carbonyl group. Acetylacetone derivatives and their curcumin analogues spectra showed stretching vibration bands for all groups which was in accordance with the proposed structure. The ^{1}HNMR spectra in all cases showed two signals at 2.5 and 3.29 ppm due to the solvent (DMSO-d_6). Previous studies have showed that the spectra of curcumin are characterized by three groups of signals; the methoxy group proton resonance appearing at 3.9 ppm, various peaks belonging to the olefinic and the phenyl protons appearing within the range 6.05- 7.83 ppm along with the signal at 9.93 ppm for phenolic OH. The Spectra of compounds **3-7** and **13** showed signals for OCH_3, olefinic, and aromatic protons. The HNMR spectra for the compounds **9 -10** showed three additional signals as compared to curcuma attributed to the phenolic OH within the range (8.77-8.96), (10.07-10.3) and (11.5-11.63) ppm. The spectrum of compound **12** showed no phenolic proton signal due to their resemblance to the ester group which resulted in three new signals for ester protons. Spectra of the compounds **14-17** showed no signal of vinylic proton due to the deprotonation of methylene ketone.

3.2. Antioxidant activity

The oxidation is essential for many living organisms to produce energy to feed the biological process [24]. However, the free radical's reactive oxygen species (ROS), which is produced continuously *in vivo* can destroy RNA and DNA by resulting in mutations, chromosomal damage and oxidizing unsaturated fatty acids. ROS also stimulates oxidative damage and contributes to atherosclerosis, coronary heart disease, neurological disorder as well as cancer and aging [25]. However, the antioxidant substances are able to protect the body from the damage caused by free radicals [26]. Several antioxidant scan be gathered under the topic of hydrogen atom transfer (HAT) or single electron transfer (SET).Their action can be clarified through the oxidative mechanism of phenolic antioxidants [27].

$$_{(n)}RO_2^{\bullet} + ArOH \longrightarrow {}_{(n)}ROOH + ArO^{\bullet} \quad (HAT)$$

The values of the scavenging activity of the synthesized compounds (**1, 2, 9, 10, 11, 16, 17**) at concentrations 25, 50, 75, 100,150 and 200 μM were measured by the decrease of DPPH absorbance at 517 nm with time and the change of the DPPHcolor from purple to yellow or colorless due to the transfer of hydrogen atom according to Scheme 5.



Scheme 5. The inhibition of free radicals by reacting DPPH with a phenolic compound.

The inhibition activity at a concentration of 200 µM was 86.764%, 90.098%, 94.215%, 95.764%, 96.862%, 85.381%, and 90.294%, for compounds **1, 2, 9, 10, 11, 16,** and **17**, respectively (Table 1 and Figs 2, 3, and 4).

Compounds **9, 10,** and **11** showed a very high DPPH inhibition activity (200 µM). Similar activity was also observed for the other concentrations. On the other hand, compounds **1** and **16** showed a lower activity of DPPH inhibition as a result of the hydroxyl phenolic group OH that gave the compound a high radical scavenging activity by donating a hydrogen atom to the DPPH radicals and inhibiting the radical activity by HAT [28]. The low activity of compound **16** was due to the structure of the compound lacking a hydroxyl group. Therefore, the radical scavenging activity of compounds **1, 2, 9, 10, 11, 16,** and **17** was in the order: **11**>**10**>**9**>**17**>**2**>**1** >**16**.

Table 1. *In vitro* antioxidant activities data of the synthesized compounds.

Compounds	Concentration					
	25 µM	50µM	100µM	150µM	200µM	
	Inhibition percentage of DPPH					IC_{50}µM
1	57.254	68.529	75.49	81.234	86.764	27.518 ± 0.189
2	62.215	70.49	78.921	84.984	90.098	25.647 ± 0.114
9	71.685	88.725	89.215	92.512	94.215	20.052 ± 0.044
10	80.045	89.028	92.352	93.108	95.764	19.228 ± 0.114
11	82.982	90.098	91.294	94.041	96.862	18.225 ± 0.026
16	64.579	71.666	78.431	83.941	85.381	24.826 ± 0.210
17	67.347	71.96	79.411	88.529	90.294	24.170 ± 0.068

The half maximal inhibitory concentration (IC_{50}) for the studied compounds was calculated by graphpad prism 8.02 (Figs. 5 and 6).The obtained range of IC_{50} inhibition was between [18.225 ± 0.026]- [27.518 ±0.189] µM. The results showed that the IC_{50} values were compatible with the inhibition activity of the studied compounds that had the largest number of hydroxyls of phenolic groups. It can be concluded that compounds with a hydroxyl of phenolic groups were the most efficient in scavenging free radicals and inhibiting the oxidising agent by hydrogen atom transfer (HAT) from the hydroxyl groups of the antioxidant compound to the radical sources.

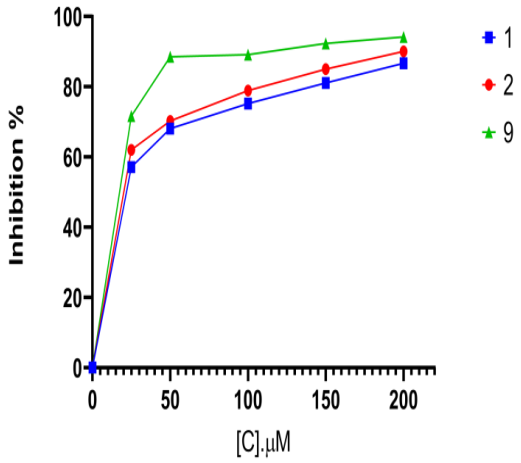


Fig. 2. The inhibition percentage activity with the concentration of compounds (**1, 2,** and **9**).

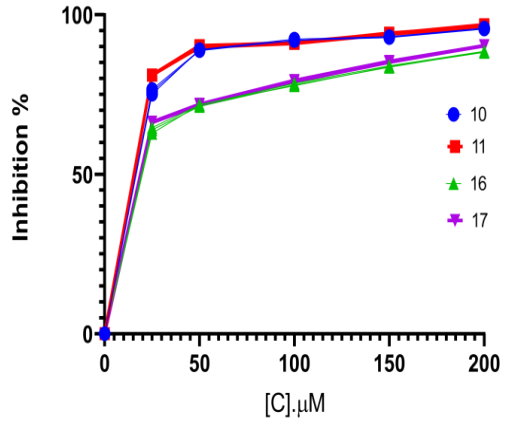


Fig. 3. The inhibition percentage activity with the concentration of compounds (**10, 11, 16,** and **17**).

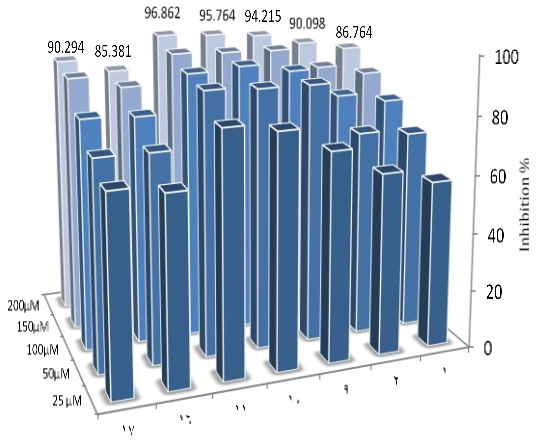


Fig. 4. DPPH free radical scavenging activity of compounds (**1, 2, 9, 10, 11, 16,** and **17**) at concentrations 25-200 µM showing the percentage of inhibition.

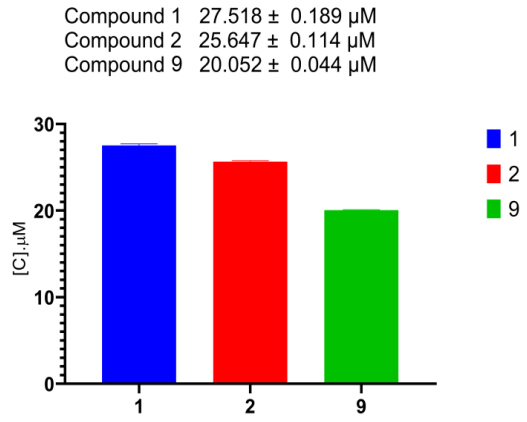


Fig. 5. The half maximal inhibitory concentration (IC50) for the studied compounds (**1, 2,** and **9**) calculated by graphpad prism 8.02 software.

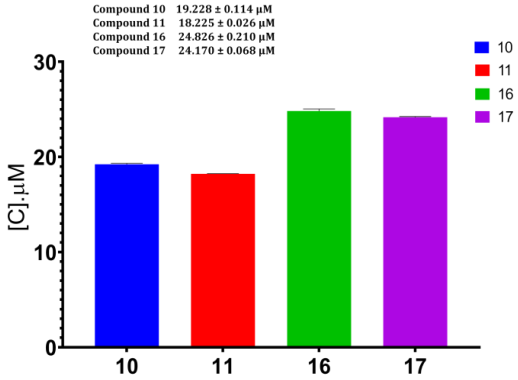


Fig. 6. The half maximal inhibitory concentration (IC_{50}) for the studied compounds (**10, 11, 16,** and **17**) calculated by graphpad prism 8.02 software.

4. Conclusion

In the present study, we have synthesized new curcuminouids and their derivatives as well as analogues. The newly compounds have study as antioxidant, the results shown the compounds which bearing a hydroxy phenolic groups have highest inhibition activity than other curcuminoids, therefore for future synthesis can modified curcumin by increased the hydroxyl groups to give more inhibition activity

Conflicts of interest

There are no conflicts to declare.

Funding

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تصميم و تحضير مركبات كركمين ومشتقاتها الجديدة ودراسة فعاليتها كمضادات للاكسدة

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تم تخليق سلسلة من نظائرالكركمين ومشتقاتها من تفاعل نظائرالكركمين مع عدد من مركبات الهيدرازين لتحضير مشتقات البيرازول الجديدة. بالاضافة الى مركبات الايثر للكركمينات والتي تحتوي على مجاميع هيدروكسي. شخصت جميع المركبات باستخدام FT-IR و^{1}HNMR و^{13}CNMR وMS-ESI. واظهر قسم من المركبات فعالية تثبيط جيدة كعوامل مضادة للأكسدة ضد الجذور المستقرة لـDPPH وقد أظهرت النتائج من هذه الدراسة نشاط تثبيط عالي للمركبات التي تحمل اكبر عدد من مجاميع الهيدروكسي الفينولية مقارنة بالمركبات المحضرة الأخرى.