Research Article

Synthesis and Evaluation of Some Novel Curcumin Derivatives as Anti-inflammatory Agents

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ABSTRACT

Starting with curcumin different pyrane, *N*-phenyl-1,3-thiazolidin and thiocurcumin derivatives were synthesized. 4-Oxo-3-phenyl-1,3-thiazolidin derivative was reacted with different organic reagents examply, benzaldehyde, triethylorthoformate and hydrazine hydrate to form new series of 5-benzylidine-4-oxo-3-phenyl-1,3-thiazolidin, 5-ethoxymethylene-4-oxo-3-phenyl-1,3-thiazolidin and [1,8] naphthyridine derivatives. Some of these derivatives were evaluated as anti- inflammatory agents. All compounds have been characterized by spectral analyses.

Keywords: curcumin, thiocurcumin, PTC, anti-inflammatory, [1,8] naphthyridine.

INTRODUCTION

According to the Literature Turmeric (Curcuma longa) has various medicinal properties for this reason it used as a coloring agent in food[1]. It includes many chemical components especially curcumin, which has been used topically on the skin for wounds, and for parasitic skin infections and acne. Curcumin has been used in blistering diseases such as pemphigus and herpes zoster. It is used via oral administration for the common cold, liver diseases, urinary tract diseases, and as a blood purifier. It has been used via inhalation[2,3] for chronic rhinitis and coryza. Curcuminoid fraction of *Curcuma longa* L. exhibited many interesting biological activities[4-12]. It has been identified as inhibitor of HIV-1 LTR directed gene expression and viral replication.

A previous study has shown that curcumin, a pharmacologically safe compound, is able to block HIV replication by inhibiting HIV-integrase and protease[13,14].

Due to the presence of the double bonds in curcumin molecule, it has definite conformational flexibility, this leads to its various properties. Its antioxidant activity decreases by blocking reaction of phenolic groups since these groups play critical role in enzymatic activity at receptor sites[15]. In the extension to our previous work[16] we interest to report in this study the synthesis of some new anti-inflammatory agents derived from curcumin.

MATERIALS AND METHODS

General

All melting points are uncorrected and were determined by Kofeler melting point apparatus. IR (cm^{-1}) spectra were recorded (KBr disc) on a Shimadzu DR-8001 spectrophotometer. ^{1}H-NMR (DMSO-d_6 or CDCl$_3$) spectra were recorded at 400 MHz on a Varian Mercury-300 BB at Sohag University, the chemical shift is expressed in δ value (ppm) using TMS as an internal reference. Mass spectra were performed on Micromass 7070 E`1 spectrometer using Direct Inlet and Shimadzu Qp-2010 Plus mass spectrometer using Electronic Ionization mode operating at 70 ev. Evaluation of Anti-inflammatory effect was carried out by Faculty of Medicine, Assuite University.

General Procedure

Synthesis of 4-phenyl-5-(4-hydroxy-3-methoxyphenyl propan-2-enoyl)-6-(4-hydroxy-3-methoxyphenyl ethylene)-2-imino-2*H*-pyran-3-carbonitrile (2)

To a solution of curcumin (**1**) (5.43g, 0.01 mol) in acetonitrile (20 ml) benzyaldhyde (0.16 ml, 0.01 mol), malonitrile (0. 66 g, 0.01 mol) and piperidine (0.09 ml, 0.01 mol) were added. The reaction mixture was stirred at room temperature for 2 hrs. The mixture was refluxed for additionally 3hrs. The separated product was filtered off on hot and crystallized from ethanol as yellow crystal; yield 78%; m.p. 255°C; IR (λ max, cm^{-1}): 3441(OH,NH), 3046(CH$_{arom}$), 2932(CH$_{aliph}$), 2197(CN), 1636(C=O), 1518(C=C), 1033(C-O); ^{1}H-NMR (CDCl$_3$), δ ppm: 8.62, 8.0 (s, 2H, 2OH, disappeared by D$_2$O), 7.65(d, 1H, =CH), 7.56(d, 1H, =CH), 7.44 -7.20(m, 6H, CH$_{arom}$), 6.90(d, 1H, =CH), 6.80(d, 1H, =CH), 6.72(d, 1H, CH-Ph), 3.90(d, 1H, CH-CN), 3.82, 3.71(s, 6H, 2OCH$_3$), 2.89(s, 1H, NH, disappeared by D$_2$O). Calc. for C$_{31}$H$_{27}$N$_2$O$_6$ (M. wt. 522.6).

Synthesis of Compounds 3 and 4

Method 1

A mixture of (4 g) anhydrous potassium carbonate, curcumin (**1**) (18.4 g, 0.05 mol) and catalytic amount of (TBAB) in DMF (30 ml), was treated with (7.0 ml, 0.05 mol) phenyl isothiocyanate with stirring for 1hr at R.T. Alkyl dihalid (dibromoethane and chloroacetyl chloride) (0.05 mol) was added to the mixture drop by drope with stirring for additional 4 hrs at R.T. The mixture was filtered off, the filtrate poured into ice cold water, the

separated solid was collected, and recrystallized from the proper solvent.

Method 2

To a stirred suspension of powdered potassium hydroxide (1.1g, 0.02 mol) in dry DMF (10 ml), curcumin (1) (3.68 g, 0.01 mol) was added at 10°C with continuous stirring for 1hrs, after that phenylisothiocyanate (1.4 ml, 0.01mol) was added to the mixture drop by drop. Finally, the proper dihalo compound (dibromoethane or chloro-acetylchloride) (0.01 mol) was added to the mixture with stirring at 20°C for additionally 2hrs. The mixture poured into crushed ice, the product filtrated off and recrystallized from appropriate solvent.

1,7-Bis-(4-hydroxy-3-methoxyphenyl)-4-(3-phenyl thiazolidin-2-ylidene)hepta-1,6-diene-3,5-dione (3)

Deep red powder from DMF; yield 54 %; m.p. 174°C; IR(λ max, cm^{-1}): 3406(OH), 3045(CH$_{arom}$), 2933 (CH$_{aliph}$), 1655(C=O), 1269(C-S), 1028(C-O); ^{1}H-NMR (DMSO-d$_6$), δ ppm: 9.23(s, 2H, 2OH), 7.56, 7.54(d, 1H, =CH), 7.39(d, 1H, =CH), 7.32-7.11(m, 6H, CH$_{arom}$), 6.95(d, 1H, =CH), 6.74(d, 1H, =CH), 3.82, 3.72(s, 6H, 2OCH$_3$), 2.89(s, 2H, CH$_2$-N), 2.73(s, 2H, CH$_2$-S). Calc. for C$_{30}$H$_{27}$NO$_6$S (M.wt. 529.603).

1,7-Bis-(4-hydroxy-3-methoxyphenyl)-4-(4-oxo-3-phenyl thiazolidin-2-ylidene)hepta-1,6-diene-3,5-dione (4)

Brownish red crystal from DMF; yield 65%; m.p. 130°C; IR (λ max, cm^{-1}): 3433(OH), 3050(CH$_{arom}$), 2931(CH$_{aliph}$), 1654(C=O), 1600(C=O), 1510(C=C), 1448(C-N), 1269(C-S), 1028 (C-O); ^{1}H-NMR (DMSO-d$_6$), δ ppm: 7.53(d, 1H, =CH), 7.44(d, 1H, =CH), 7.40-7.10(m, 6H, CH$_{arom}$), 6.88(d, 1H, =CH), 6.78(d, 1H, =CH), 6.73-6.72(m, 5H, CH$_{arom}$), 4.17(s, 2H, CH$_2$-C=O), 3.73(s, 3H, OCH$_3$), 3.68(s, 3H, OCH$_3$), 2.89(s, 1H, OH), 2.73(s, 1H, OH); M.S (m/z, I%): 544.1 (22.9)(M$^+$+1), 488.10(23.64), 387.10(40.36), 309.10(31.27), 175.10(32.36), 145.10(35.27), 125.10(37.45), 80.0(100), 64.0(88.73). Calc. for C$_{30}$H$_{25}$NO$_7$S (M. wt. 543.6).

Synthesis of 1,7-bis-(4-hydroxy-3-methoxyphenyl)-5-mercaptohepta-1,4,6-triene-3-thione (5)

A mixture of curcumin (1) (3.68 g, 0.01 mol) and phosphorous pentasulifide (11.1g, 0.05 mol) in dry pyridine (20 ml) was refluxed for 7 hrs. After cooling the mixture poured into ice-cold water (100 ml), the separated solid filtrated off and crystallized from methylene chloride as black crystal; yield 92%; m.p.> 300°C; IR(λ max, cm^{-1}): 3421(OH), 3046(CH$_{arom}$), 2926 (CH$_{aliph}$), 1603, 1503(C=C), 1116(C=S), 1024(C-O); ^{1}H-NMR (DMSO-d$_6$), δ ppm: 9.77(s, 2H, 2OH), 7.56-7.52(d, 1H, =CH), 7.32-7.31(d, 1H, =CH), 7.16-7.14(m, 6H, CH$_{arom}$), 6.83, 6.81(d, 1H, =CH), 6.77, 6.73(d, 1H, =CH), 6.06 (s, 1H, M-C=S), 3.83 (s, 6H, 2OCH$_3$), 1.00(s, 1H, SH); ^{13}C-NMR(DMSO-d$_6$), δ ppm: 183.67, 149.81, 148.46, 141.17, 126.80, 123.60, 121.56, 116.16, 111.79, 101.28, 56.16; M.S (m/z, I%): 400(6.4) (M$^+$), 248(10.3), 208(9.0), 105(100), 79(19.2), 70(16.7), 52(15.4). Calc. for C$_{21}$H$_{20}$O$_4$S$_2$ (M. wt. 400.5).

Synthesis of 4-(5-benzylidine-4-oxo-3-phenylthiazolidin-2-ylidene)-1,7-bis-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (6)

An equimolar mixture of compound 4 (5.4 g, 0.01 mol), benzaldehyde (1.0 ml, 0.01 mol) and triethylamine (1.4 ml, 0.01 mol) in dioxane (30 ml) was refluxed for 3 hrs. The separated solid was filtrated on hot and crystallized from dioxane as pale orange powder; yield 79%; m.p. 165°C; IR (λ max, cm^{-1}) at: 3321(OH), 3050(CH$_{arom}$), 2933(CH$_{aliph}$), 1629(O=C-N-ph), 1601(C=O), 1589(C=C); ^{1}H-NMR(CDCl$_3$), δ ppm: 10.00(s, 1H, =CH-Ar), 7.53(d, 1H, =CH), 7.49(d, 1H, =CH), 7.32-6.97(m, 16H, CH$_{arom}$), 6.86, 6.84(d, 1H, =CH), 6.42-6.38(d, 1H, =CH), 5.75(s, 1H, OH, disappeared by D$_2$O), 3.91(s, 1H, OH, disappeared by D$_2$O), 3.84, 3.79(s, 6H, 2OCH$_3$). Calc. for C$_{37}$H$_{29}$NO$_7$S(631.69).

Synthesis of 4-(5-ethoxymethylene-4-oxo-3-phenyl thiazolidin-2-ylidene)-1,7-bis-(4-hydroxy-3-methoxy phenyl)hepta-1,6-diene-3,5-dione (7)

A mixture of compound 4 (0.88 gm, 0.00147 mol) and triethylorthofomate (2 ml) was heated under reflux in acetic anhydride (15 ml) for 3 hrs. The mixture pured into ice cooled water (100 ml), the solid product was collected and crystallized from water as pale yellow crystal; yield 88%; m.p. 162°C; IR (λ max, cm^{-1}) at: 3342(OH), 3043(CH$_{arom}$), 2936(CH$_{aliph}$),1763(C=O), 1605(C=O), 1200(C-S), 1025(C-O); ^{1}H-NMR (CDCl$_3$), δ ppm: 7.54(d, 1H, =CH), 7.43(d, 1H, =CH), 7.90-7.03(m, 11H, CH$_{arom}$), 6.95(d, 1H, =CH), 6.92(d, 1H, =CH), 4.62(q, 2H, OCH$_2$), 4.01(s, 1H, =CH-O), 3.85, 3.75(s, 6H, 2OCH$_3$), 1.28(t, 3H, CH$_2$-CH$_3$); ^{13}C-NMR(CDCl$_3$), δ ppm: 169.17, 164.23, 151.57, 148.23, 136.25, 130.23, 139.40, 125.09, 123.31, 122.23, 119.88, 111.16, 55.96, 29.69, 20.65; M.S (m/z, I%): 600.20(7.53) (M$^+$+1), 599.09(8.85)(M$^+$), 511.20(5.95), 398.20(7.79), 351.20(5.87), 303.20(9.28), 193.15(45.71), 149.10(62.08), 104.10(61.65), 77.05(100), 65.05(18.30). Calc. for C$_{33}$H$_{29}$NO$_8$S (M.wt. 599.6).

Synthesis of 4-(5-aminomethylene-4-oxo-3-phenyl thiazolidin-2-ylidene)-1,7-bis-(4-hydroxy -3-methoxy phenyl)hepta-1,6-diene-3,5-dione (8)

To a solution of compound 7 (5.99 g, 0.01 mol) in acetone (20 ml), ammonia solution (3 ml) was added with stirring for 24 hrs at R.T. The mixture concentrated under reduced pressure, the precipitate was filtrated off, dried and crystallized from ethanol as black crystal; yield 49%; m.p. 295°C; IR (λ max cm^{-1}) at: 3409-3320(br, OH, NH$_2$), 3052(CH$_{arom}$), 2923(CH$_{aliph}$), 1650(C=O), 1630(C=O), 1268(C-S), 1033(C-O); ^{1}H-NMR(DMSO-d$_6$), δ ppm: 9.61, 9.51(s, 2H, 2OH, disappeared by D$_2$O), 7.66-7.61(d, 2H, 2 =CH), 7.58-6.92(m, 11H, CH$_{arom}$), 6.85-6.83(d, 2H, 2 =CH), 4.10(s, 1H, =CH), 3.74, 3.71(s, 6H, 2OCH$_3$), 1.29(br, 2H, NH$_2$, disappeared by D$_2$O); M.S. (m/z, I%): 567.2(5.49) (M$^+$-3), 492.2(20.53), 431.2(21.24), 374.2(18.14), 304.1(17.1), 211.1(39.14), 191.1(64.4), 174.5(79.24), 72.05(100). Calc. for C$_{31}$H$_{26}$N$_2$O$_7$S (M. wt. 570.6).

Synthesis of 1-amino-2,7-bis-(4-hydroxy-3-methoxy phenyl)-8-phenylhexahydro [1,8] naphthyridine -4,5-dione (9)

To a solution of compound **4** (2.17g, 0.004 mol) in dioxane (20 ml), hydrazine hydrate (0.55 ml, 0.025 mol) and few drops of triethylamine were added. The reaction mixture was refluxed for 3 hrs, concentrated under reduced pressure. The separated solid filtered off, dried and crystallized from ethanol as orange powder; yield 84%; m.p. 170°C; IR (λ max, cm^{-1}) at: 3412 and 3300(OH and NH$_2$), 3050(CH$_{arom}$), 2933(CH$_{aliph}$), 1645(C=O), 1034(C-O); ^{1}H-NMR (DMSO-d$_6$), δ ppm: 8.98, 8.82(s, 2H, 2OH, disappeared by D$_2$O), 7.37-6.76(m, 11H, CH$_{arom}$), 6.70, 6.64(t, 2H, 2CH-Ar), 5.29(s, br, 2H, NH$_2$, disappeared by D$_2$O), 4.17(d, 2H, CH$_2$), 3.81, 3.78(d, 2H, CH$_2$), 3.74, 3.64(s, 6H, 2OCH$_3$); ^{13}C-NMR(DMSO-d$_6$), δ ppm: 207.74, 178.56, 149.05, 148.05, 146.54, 129.34, 128.24, 124.74, 123.07 122.06, 120.89, 119.54, 116.36, 115.91, 115.66, 95.23, 73.94, 56.00, 31.23, 15.26. Calc. for C$_{28}$H$_{29}$N$_3$O$_6$ (M. wt. 503.6).

RESULTS AND DISCUSSION

Curcumin (**1**) was allowed to react with benzaldehyde and malononitrile in presence of piperidine in equimolar ratio with stirring in acetonitrile/ethanol for 2 hours followed by heating under reflux for additionally 3hrs forming phenyl propanenoylpyran derivative **2** (Scheme 1). The reaction is believed to proceed in three steps: firstly through the condensation reaction of malononitrile with benzaldehyde to form benzylidinemalononitrile, secondly, the active methylene group in curcumin molecule adding to the formed benzylidinemalononitrile via intrmolecular nucleophilic addition reaction, and thirdly, adding OH group of the enolizing curcumin form at the cyano group via intramolecular nucleophilic addition reaction (Scheme 2).

IR spectrum reveled new bands at 3441 and 2197 cm^{-1} corresponding to NH and CN groups in compound **2** and ^{1}H-NMR spectra showed new bands for two CH groups at 3.90 and 6.72 ppm corresponding to CH-CN and CH-Ph groups, respectively.

In a one pot-reaction using liquid-solid phase transfer catalysis (PTC) technique [DMF/ K$_2$CO$_3$/tetrabutylammonium bromide (TBAB)] and via the nucleophilic addition reaction of the active methylene group of curcumin (**1**) at phenyl isothiocyanate molecule, the formed intermediate was spontaneously cyclized with different halocompounds including dibromoethane, chloroacetyl chloride and/or ethylchloroacetate[17] to afford 1,7-bis-(4-hydroxy-3-methoxyphenyl)-4-(3-phenylthiazo-lidin-2-ylidene)hepta-1,6-diene-3,5-dione(**3**) and 1,7-bis-(4-hydroxy-3-methoxyphenyl)-4-(4-oxo-3-phenylthiazolidin-2-ylidene)hepta-1,6-diene-3,5-dione(**4**). These compounds were prepared by another experimental technique, through the reaction of compound **1** with phenyl isothiocyanate and halocompounds (dibromoethane, chloroacetylchloride

and/or ethylchloroacetate) in presence of potassium hydroxide in 1: 1: 1: 2 molar ratio at R.T.(Scheme 1). IR spectra of compounds **3** and **4** revealed the presence of characteristic signals at 3406-3433 and 1654 cm^{-1} for OH and C=O groups, respectively and M.S spectral analysis of compound **4** showed the molecular ion peak at m/z = 544 (M$^+$+1). The suggested structures were established by spectral analyses.

Curcumine (**1**) was reacted with phosphorus pentasulphide in refluxing pyridine to afford the corresponding thioanalogue **5** (Scheme 1).

The structure of thiocurcumin was confirmed by spectral analyses, since IR spectrum revealed the disappearance of the C=O groups and the appearance of C=S groups band at 1116 cm^{-1} and its M.S spectrum analysis showed molecular ion peak at m/z = 400 (M$^+$).

In refluxing dioxane,4-(5-benzylidine-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)-1,7-bis-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione) (**6**) was prepared by the condensation reaction of compound **4** with benzaldehyde and triethylamine in equimolar ratio (Scheme. 3). ^{1}H-NMR spectrum analysis for the condensate showed the presence of characteristic bands at δ = 10.00 ppm as singlet signal for = CH-Ph group and doublet signals at 7.53, 7.49, 6.86, 6.42 ppm for four = CH groups, the suggested structure was confirmed by spectral analyses.

Compound **4** was condensate also with triethylorthoformate in refluxing acetic anhydride via the elimination of two ethanol molecules to form 4-(5-ethoxynmethylene-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)-1,7-bis-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (**7**) which in turn was reacted with ammonia solution in stirred acetone forming 4-(5-aminomethylene-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)-1,7-bis-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (**8**) (scheme 3). IR spectral analysis of compound **7** reflected the presence of C=O groups at 1763, 1605 cm^{-1}, whereas the C=O groups of compound **8** appear at 1650, 1630 cm^{-1} in addition to broad bands at 3409-3320 cm^{-1} corresponding to OH and NH$_2$ groups.

Also ^{1}H-NMR spectrum for compound **7** pointed to the presence of new signals at δ = 4.62 ppm as quartet for OCH$_2$CH$_3$ group, 4.01 ppm as singlet signal for =CH-OEt group and as triplet signal at 1.28 ppm for CH$_2$CH$_3$ group. Mass spectrum analysis showed the molecular ion peak at m/z = 599 (M$^+$, 8.85) and 600 (M$^+$+1, 7.35%). Whereas ^{1}H-NMR spectrum of compound **8** pointed to the disappearance of the OCH$_2$CH$_3$ group and the presence of new signals at δ= 1.29, 4.10 ppm corresponding to NH$_2$ (disappeared by D$_2$O) and =CH-NH$_2$ groups respectively. Its mass spectrum showed the molecular ion peak at m/z = 567 (M$^+$-3, 5.49%).

The condensation reaction of compound **4** with hydrazine hydrate in 1: 2 molar ratio takes place in refluxing dioxane and catalytic amount of triethylamine to afford 1-amino-

2,7-bis-(4-hydroxy-3-methoxyphenyl)-8-phenylhexa hydro[1,8]naphthyridine-4,5-dione (9).

The reaction pathway tacks place *via* the nucleophilic attack of NH_2 group of the first hydrazine molecule at the C=C group and the NH_2 group of the second hydrazine molecule at the C=O group in 1,3-thiazole ring forming hydrazone and N-phenylhydrazeno derivative with the elimination of mercaptoacetohydrazied molecule, this intermediate was spontaneously underwent intermolecular addition reaction of the formed NH groups at the two ethylenic double bonds as in (Scheme 4).

IR spectrum of this compound pointed to the disappearance of C=O groups and the appearance of new broad signals at 3412, 3300 and 1645 cm^{-1} for OH, NH_2 and C=O groups, whereas its ^{1}H-NMR spectrum showed new characteristic signals at δ ppm = 5.29, 4.17 and 3.81 ppm for NH_2 and two CH_2 groups.

Moreover, ^{13}C-NMR analysis showed signals at 207.74, 178.56, 95.23, 73.94, 31.23, 15.26 ppm corresponding to two C=O, two CH-Ar and two CH_2 groups.

Anti-Inflammatory Evaluation

Chemical Reagents

Commercial Indomethacin was obtained from local pharmacy and carrageenan was obtained from sigma company USA

Experimental Design

Male rats weighing 200 - 250 gm from animal house of Assuit University. All animals were maintained with a balanced diet and water ad libitum.

The total 36 rats were divided into Group 1; Normal control rats and Group 2 induced inflammatory treatment for hind paw which injected with single dose of carrageenan that was dissolved in physiological saline solution (500 µl of 1% v/v)[18,19]. Edema inhibition paw thickness were measured just before the carrageenan injection, that is at 0 min and then at 30 min, 60 min, 120 min, 180 min, 240 min and 300 min after carrageenan injection. Increase in paw thickness was measured as the difference in paw thickness at 0 min and paw thickness at

respective min. The induced inflammatory in hind paw was subdivided after induction with carrageenan into 11 groups for the treatment of compounds 4-phenyl-5-(4-hydroxy-3-methoxyphenylpropan-2-enoyl)-6-(4-hydroxy-3-methoxyphenylethylene)-2-imino-2*H*-pyran-3-carbo nitrile**(2)**,1,7-Bis-(4-hydroxy-3-meth- oxyphenyl)-4-(4-oxo-3-phenylthiazolidin-2-ylidene)hepta-1,6-diene-3,5-dione **(4)**, 4-(5-benzylidine-4-oxo-3-phenylthiazolidin-2-ylidene)-1,7-bis-(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione **(6)**, 4-(5-aminomethylene-4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)-1,7-bis-(4-hydroxy-3-methoxy phenyl)hepta-1,6-diene-3,5-dione**(8)**,1-amino-2,7–bis-(4-hydroxy-3-methoxyphenyl)-8-phenylhexa hydro[1,8] naphthyridine-4,5-dione **(9)** derived from curcumin and indomethacin as a reference. The treatment was achieved at 30 min, 60 min, 120 min, 180 min, 240 min and 300 min after carrageenan induction for inflammation.

Statistical Analysis

The results were analyzed by one way analysis of variance (ANOVA) followed by Newman-Keuls Multiple Comparison Test as a post-Test.

These analyses were carried out using computer prism program for windows, version 3.0 (Graph pad software, Inc, San Diago CA. USA).

The significance difference between groups was accepted at $p < 0.05^{,}$, 0.001^*, and the data were expressed as mean ± Standard error (SE) after 5 hour as shown in Table (1, 2).

Table 1: Mean and Standard error after 5 hours

| No.	Mean	Std. Deviation	Std. Error
Control	0.31	.03335	.00577
Carrageenan	0.72	.02887	.01667
Comp 2	0.5333	0.02887	0.01667
Comp 4	0.4000	0.05000	0.02887
Comp 6	0.5167	0.02887	0.01667
Comp 8	0.4500	0.05000	0.02887
Comp 9	0.4833	0.05774	0.03333
Indomethacin	0.3833	0.02887	0.01667

Table 2: Comparison between reference treatment and effect of compounds after 5 hours

| (I) treatment using Ref.	(J) treatment using Comp.	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Indomethacin	Comp 2	-.15000-*	.02930	.000	-.2108-	-.0892-
	Comp 4	-.01667-	.02930	.575	-.0774-	.0441
	Comp 6	-.13333-*	.02930	.000	-.1941-	-.0726-
	Comp 8	-.06667-*	.02930	.033	-.1274-	-.0059-
	Comp 9	-.10000-*	.02930	.002	-.1608-	-.0392-

* The mean difference is significant at the 0.05 level.
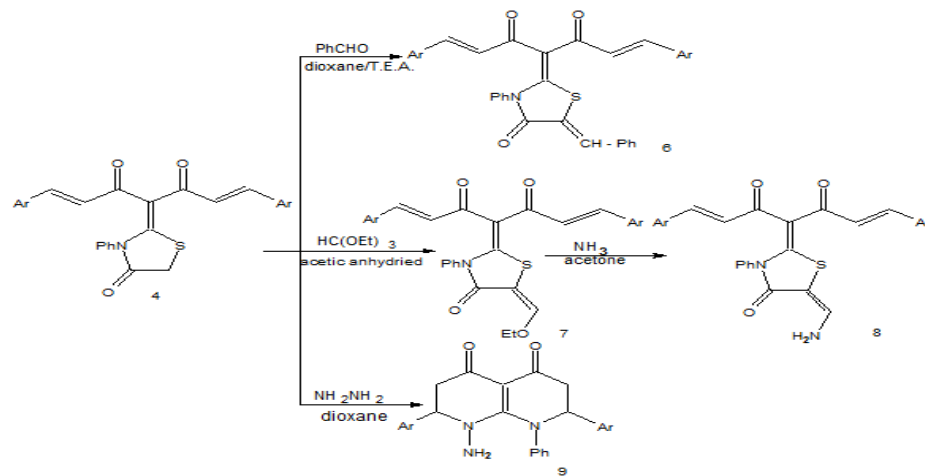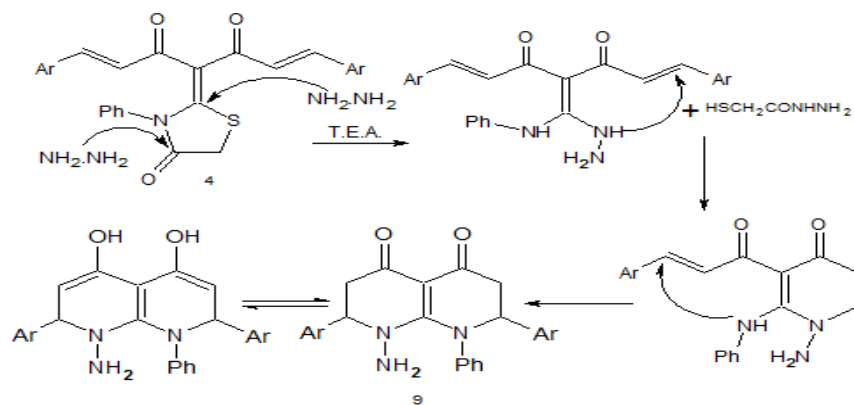
Scheme 1
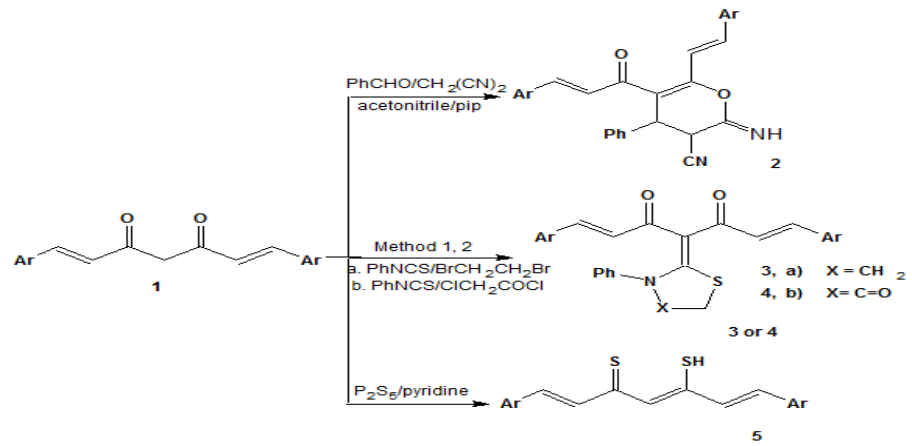
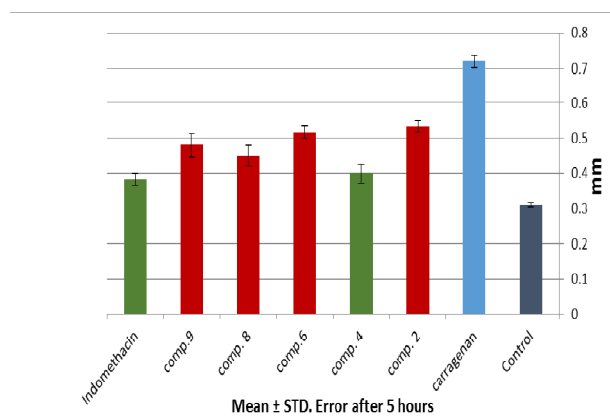**Scheme 2**
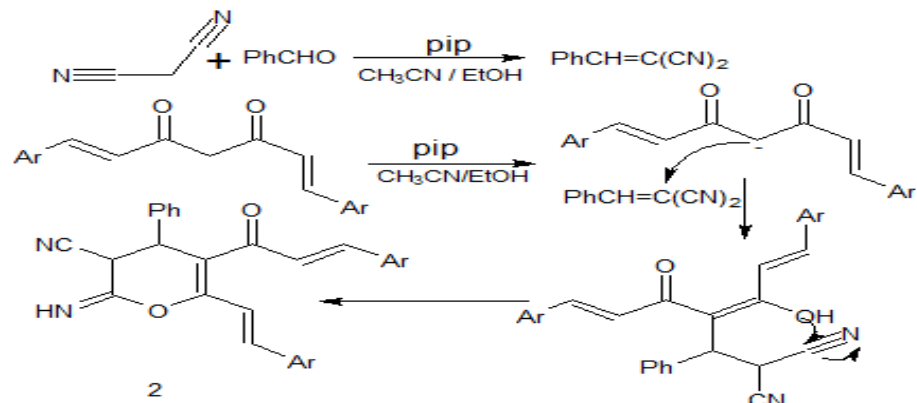
Scheme 3

Scheme 4

Figure 1: Plot of of Edema inhibition with time.

RESULTS

The rat that injected with carrageenan showed inflammation and swelling in the site of injection in hind paw and exhibited highly significant in swelling as compared to normal control indomethacin, on the other hand, after 5 hours from treatment with compounds of curcumin derivatives and indomethacin (as a reference treatment) showed improvement in the edema inhibition in hind paw; some of these curcumin derivatives as compound **4** showed highly improvement which have P value more than 0.05 that means these compounds show excellent effect on inflammation of rats hind paw according to control and indomethacin (as reference treatment) and exhibited non-significant in the swelling which means that this compound has the highest anti-inflammatory effect of the tested compounds.

The other compounds as **2, 6, 8** and **9** showed less improvement than the previous compound and exhibited significant in the swelling which have P value less than 0.05 that mean, these compounds show moderate effect on inflammation of rats hind paw according to control and indomethacin effect.

CONCLUSION

In summary, from the previous results we found that the tested compound **4** showed highly anti-inflammatory activity and this compound have values close to value of indomethacin. While the compounds **2, 6, 8** and **9** showed moderate anti-inflammatory activities compared with indomethacin as shown in (Figure 1).

REFERENCES

1. Peirce A. The American Pharmaceutical Association Practical Guide to Natural Medicines. New York, NY: The Stonesong Press, Inc., 1999.

2. Eigner D and Scholz D., Ferula asa-foetida and Curcuma longa in traditional medical treatment and diet in Nepal, Ferula. J Ethnopharmacol, 67, 1999, 1–6.

3. Majeed M, Badmaev V, Shivakumar U and Rajendran R., Curcuminoids Antioxidant Phytonutrients Piscataway, *NJ: Nutriscience Publishers*, Inc., 1995.

4. Okunade A.L., Elvin-Lewis M.P.F. and Lewis W.H., Natural antimycobacterial metabolites: current status, *Phytochemistry*; 65, 2004, 1017-1032.

5. Maheshwari R.K., Singh A.K., Gaddipatti J. and Srimal R.C., Multiple biological activities of curcumin: a short review *Life Sci.*, 78, 2006, 2081-2087.

6. Ruby A.J., Kuttan G., Babu K.D., Rajasekharan K.N. and Kuttan R., Anti-tumor and antioxidant activity of natural curcuminoids, *Cancer Lett.*, 94, 1995, 79-83.

7. Chan M.Y., Ho C.T. and Huang H.I., Effects of three dietary phytochemicals from tea, rosemary and turmeric on inflammation-induced nitrite production, Cancer *Lett.*, 96, 1995, 23-29.

8. Chan M.Y., Ho C.T., Huang H.I., Fenton M.R. and Fong D., *In vivo* inhibition of nitric oxide synthase gene expression by curcumin, a cancer preventive natural product with anti-inflammatory properties. *Biochem. Pharmacol.*, 55, 1998, 1955-1962.

9. Inano H., Onoda M., Inafuku N., Kubota M., Kamada Y., Osawa T., Kobayashi H. and WakabayashiK.,Potent preventive action of curcumin on radiation-induced initiation of mammary tumorigenesis in rats, Carcinogenesis; 21, 2000, 1835-1841.

10. Thapliyal R. and Maru G.B., Inhibition of cytochrome P-450 isozymes by curcumins *in vitro* and *in vivo*, *Food Chem. Toxicol.*, 39, 2001, 541-547.

11. Changtam C., Koning H.P., Ibrahim H., Sajid M.S., Gould M.K. and Suksamrarn A, Curcuminoid analogs with potent activity against *Trypanosoma and Leishmania* species, *Eur. J. Med. Chem.*, 45, 2010, 941-956.

12. Fatemeh Kazemi-L, Abbas R. and Nosratollah Z., Comparison of Inhibitory Effect of Curcumin Nanoparticles and Free Curcumin in Human Telomerase Reverse Transcriptase Gene Expression in Breast Cancer *Advanced Pharmaceutical Bulletin*, 3(1), 2013, 127-130.

13. Mazumder A., Raghavan K., Weinstein J., Kohn K. W. and Pommier Y., Inhibition of human immunodeficiency virus type-1 integrase by curcumin, *Biochem. Pharmacol.*, 49, 1995, 1165–1170.

14. Sui Z., Salto R., Li J., Craik C. and Ortiz de Montellano P.R., Inhibition of the HIV1 and the HIV2 Proteases by Curcumin and Curcumin Boron Complexes. *Bioorg. Med. Chem.*, 1, 1993, 415–422.

15. Ross C. B., Melinda R. V., Kazuo M., Hideo G., Yoshimi H., Aiko T. and Hidemitsu U.,On the Antioxidant Mechanism of Curcumin: Classical Methods Are Needed To Determine Antioxidant Mechanism and Activity, *Org. Lett.*, 2, 2000, 2841–2843.

16. Abd Allah O.A., El-Saghier A. M. and Kadry A. M.; Synthesis of Novel Curcumin Derivatives Having diverse Anti-inflammatory Activities (unpublished), 2015.

17. Abd Allah O.A., Synthesis of some New Fused and Polyfused (1,2,4)Triazolo(3,4-b) (1,3,4)Thiadiazepines, *Chemistry of Heterocyclic Compounds*; 8, 2005, 1256-1264.

18. Winter C. A., Risley E. A. and Nuss G. W., Carrageenan-induced edema in the hind paw of rat as an assay for anti-inflammatory activity, *Proceedings of the Society for Experimental Biology and Medicine*; 111, 1962, 544–547.

19. Takahiro K., Junichi T., Akihiro S., Yuichi N., Keiko Y., Mayuko M., Yuu I., Takaharu N., Takehito T. and Kiyonori Y., Protective Effects of Radon Inhalation on Carrageenan-Induced Inflammatory Paw Edema in Mice, *Inflammation,* 35, 2012, 1222.