Synthesis and antibacterial activity of 3-arylidene chromen-2, 4-dione derivatives

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Abstract: Derivatives of 3-arylidene chromen-2, 4-dione 1 were synthesized to be used as a starting material for synthesizing some new fused heterocyclic compounds containing coumarin moiety. When compounds 1 reacted with hydrazine derivatives, hydroxylamine hydrochloride, urea, thiourea, semicarbazide and thiosemicarbazide it gave the corresponding compounds 2-5. Compound 4a, b reacted with methyl iodide in DMF and K2CO3 at room temperature to afford the corresponding 6a, b. All these compounds were screened I*nVitro* for their antibacterial activity.

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1. Introduction

Coumarins are a class of the most important natural and synthetic compounds that possess a great variety of biological activities [1, 2], these compounds exhibit several types of pharmacological properties like antibacterial [3], antitumor [4] antioxidant [5, 6], anticancer [7], anti-HIV [8]. In addition, many of these compounds have been used as additives in food, perfumes, cosmetics, optical brighteners [9, 10], pharmaceuticals [11],, dispersed fluorescent and laser dyes [12].

4-Hydroxycoumarins (2H-1-benzopyran-2-ones) have aroused a great deal of interest due to their biological activity, such as anti-inflammatory, antibacterial, antiviral and anticancer. 4-Hydroxycoumarin and/or derivatives are interesting molecules which can be used as anticoagulants for the treatment of disorders in which there is excessive clotting, as thrombophlebitis [13]. Many of pharmacological investigations of these compounds are nontoxic. In addition, they can act as intermediates for different industrial applications such as pigments and/or dyes as well as liquid crystals.

2. Experimental

Melting points were determined by an electro thermal melting point apparatus and are uncorrected.The reaction times were determined using the thin-layer chromatography (TLC) technique which was performed with fluorescent silica gel plates HF245 (Merck) and plates were viewed under UV 245 and 265 light. Silica gel (230-400 mesh) was used for flash chromatography separations. Elemental analysis were carried out by Micro analytical Unit, (Faculty of Science, Cairo University), IR (KBr) spectra were recorded on a Pye-Unicam infrared spectrophotometer SP 2000 (Faculty of Science, Fayoum University), The mass spectra were run by a Shimadzu-GC-MS-GP 1000 EX using the direct inlet system and Nuclear magnetic resonance spectra were recorded on Varian Mercury 300MHz spectrometer using TMS as internal standard;chemical shifts are recorded in δ units (National Center Researcher)

2.1. Synthesis of 3- methylene chromen-2, 4-dione derivatives 1

A mixture of 4-hydroxycoumarin (16.2g, 0.01mol.), (0.01mol.) of aromatic aldehydes namely (pipronal) was refluxed in hot ethanol and few drops of piperidine for half an hour. The reaction mixture was poured into ice and hydrochloric acid, filtered off and crystallized from proper solvent.

1: crystallized from dioxane as pale yellow crystals in 88% yield, m.p.272 ºC.Analysis for C17H10O5 (M.wt. 294.26) Calculated % C 69.39, H 3.43, Found % C 69.12.H 3.20, IR (cm-1): 3067, 3008 due to νCH aromatic, 2898 due to νCH aliphatic,1706,1653 due to νCO of δ-lactone and ketone.

2.2. Synthesis of 4-oxo-3, 3a-dihydro-chromeno [4, 3-c] pyrazol derivatives 2 a, b

A mixture of compound 1 (2.94g, 0.01mol), excess of hydrazine hydrate (98%) or phenyl hydrazine (0.01mol.) was refluxed in hot ethanol and few drops of piperidine for 5-6 hrs. The reaction mixture was left to cool, the precipitated products was filtered off, washed with water, dried and crystallized from the proper solvent.

2a: crystallized from ethanol as yellow crystals in 70% yield, m.p.224ºC., Analysis for C17H12N2O4 (M.wt.308.29),Calculated %: C 66.23, H 3.92, N 9.09, Found %:C 66.30, H 3.71, N 9.17, IR (cm-1): 3189 due to νNH, 3043 due to νCH aromatic, 2920 due to νCH aliphatic, 1699 due to νCO of δ- lactone, MS (m/z%): 296 (.52%). 1H-NMR(δ, ppm, DMSOd6), 2a 2.9 (d,1H,CCHCHAr), 4.6(d,1H,CHAr), 5.85(s,2H,O-CH2-O), 6.50-7.62 (m,8H,2Ar-H,NH, pyrazol).

2b: crystallized from ethanol as red crystals in 86% yield,.m.p.183ºC, Analysis forC23H16N2O4 (M.wt.384.38), Calculated %: C 71.87, H 4.20, N 7.29, Found %: C 71.69, H 3.89, N 7.35, IR (cm-1): 3053 due to νCH aromatic, 1710 due toνCO of δ-lactone.

2.3. Synthesis of 3-benzo [1, 3] dioxol-5-yl-3, 3a-dihydro-chromeno [4, 3-c] isoxazol-4-one 3

A mixture of 1(2.94g, 0.01mol) and hydroxylamine hydrochloride (0.02mol.) was refluxed in hot ethanol and few drops of piperidine for 9hrs. The reaction mixture was left to cool, the precipitated products was filtered off, washed with water, dried and crystallized from methanol as brown crystals in 79% yield, m.p.235ºC. Analysis for C17H11NO5 (M.wt.309.27), Calculated %: C 66.02, H 3.58, N 4.53, Found % C 66.19, H 3.87, N 4.14, IR(cm-1): 3085, 3063 due to ν CHaromatic, 1698 due to νCOof δ-lactone.1H-NMR(δ,ppm,DMSO-d6): 2.7(d,1H,C-CH-CH-Ar), 5.00(d,1H,CH-Ar), 5.8(s,2H,CH2), 6.9-7.7(m,7H,2Ar-H).

2.4. Synthesis of 5-oxo-chromeno [4, 3-d] pyrimidine derivatives 4 a, b

A mixture of 1 (2.94g, 0.01mol.) and urea and /or thiourea (0.02mole) was heated under refluxed in boiling pyridine for 12hrs. The reaction mixture was cooled, poured into ice and hydrochloric acid, filtered off and crystallized from propel solvent.

4a: crystallized from methanol as brown crystals in 66% yield, m.p.238-240 ºC. Analysis for C18H12N2O5 (M.wt. 336),Calculated % C 64.29, H 3.60, N 8.33, Found % C 64.03, H 3.47, N 8.56, IR (cm-1): 3360, 3258 due to νNH, 3076 due to νCH aromatic, 2898 due to νCH aliphatic, 1727 and 1664 due to νCOof δ-lactone and amide.

4b: crystallized from ethanol as pale brown crystals in 68% yield, m.p.209 ºC. Analysis for C18H12N2O4S (M.wt.352.36), Calculated %:C 61.35, H 3.43, N 7.95 S 9.10, Found %: C 61.19, H 3.74, N 7.58, S 9.28, IR(cm-1): 3352, 3238 due to νNH, 3100 due to νCH aromatic, 2911 due to νCH aliphatic and at 1706 due to νCO of δ-lactone.

2.5. Synthesis of 7, 8, 9, 11-tetrahydro-8, 9, 11-triaza-cyclohepta[a]naphthalene-derivatives 5a, b

A mixture of 1 (2.94g, 0.01mol.) and (0.02mol) of semi carbazide or thiosemicarbazide was heated under reflux for 12hrs in boiling pyridine (15ml).The reaction mixture was poured into ice and hydrochloric acid. The solid product was filtered off and crystallized from proper solvent.

5a: crystallized from ethanol as pale brown crystals in 66% yield, m.p =235 ºC Analysis for C18H13N3O5 (M.wt.351.33),Calculated %: C 61.19, H 4.28, N 11.8 Found % C 61.39, H 4.01, N 12.00, IR(cm-1) 3319, 3255 due to νNH2, 3210 due to νNH, 3036 due to νCH aromatic, 2913 due to νCH aliphatic, 1710 and 1693 due to νCOof δ-lactone and amide.Ms (m/z%): 351(0.31%).

5b: crystallized from ethanol as brown crystals in 60% yield, m.p. =209ºC. Analysis for C18H13N3O4S (M.wt.364.38), Calculated %: C 58.85, H 3.57, N 11.44, S 8.73, Found %: C 58.66, H 3.64, N 11.32, S 8.50, IR (cm-1): 3309, 3260 due to νNH2, 3231 due to νNH, 3041 due to νCH aromatic, 2865 due to νCH aliphatic, 1702 due toνCO of δ-lactone.1H-NMR(δ,ppm,DMSO-d6): 2.00 (s,3H,NH,NH2), 3.45 (d,1H, CHCO),4.50 (d,1H,CH-Ar), 5.85 (s,2H,O-CH2-O), 6.55-7.09 (m,7H,2Ar-H).

2.6. Synthesis of 5-oxo-1, 3-dimethyl- chromeno [4, 3-d] pyrimidine derivatives 6a, b

To a solution of 4a, b (0.01mol) in DMF (30 ml), (0.02 mol) of methyl iodide and (2g) of anhydrous potassium carbonate was added. The reaction mixture was stirred overnight, and then poured into ice- hydrochloric acid. The precipitated solid was filtered off, washed well with water, dried and crystallization from the proper solvent 6a: crystallized from dioxane as white crystals in 60% yield, m.p.320ºC. Analysis for C20H16N2O5 (M.wt.364.35), Calculated %: C 65.93, H 4.43, N 7.69, Found %: C 65.97, H 4.42, N 7.66, IR(cm-1): 3053 due to νCH aromatic, 2890 due to νCH aliphatic, 1717 and 1661 due to νCO of δ- lactone and ketone. MS (m/z %): M+366(3.84%) and 364 (3.48%)

6b: crystallized from methanol as brown crystals in 56% yield, m.p.162ºC. Analysis for C20H16N2O4S (M.wt.380.42) Calculated %: C 63.14, H 4.24, N 7.36, S 8.43, Found %: C 62.80**,** H 4.38, N 7.03, S 8.29. IR(cm-1): 3089 due to νCH aromatic, 2921 due to νCH, aliphatic and 1705 νCO of δ- lactone.^{1}H-NMR (δ,ppm,DMSO-d6):

2.73(s,6H,2CH3),5.56(s,1H,CH-Ar),5.92 (s, 2H, O-CH2-O), 6.52-7.78 (m,7H,2Ar-H).

3. Antibacterial activity

4-Hydroxycoumarins are very interesting species of biologically active materials especially in medical fields. They act as anticoagulant drugs and there are some other drugs used such as Warfarin and Acenocoumarol.

The antibacterial activity of synthesized compounds was determined in vitro against a variety of bacteria. Compounds 2 a, b, and 3 showed strong activity against (Gram + ve) bacteria. While compound 2b showed the highest activity towards (Gram –ve) bacteria (Klebsiella Pneumoniae and E.coli), compound 3 exhibited only strong activity towards Klebsiella Pneumoniae, no activity against E.Coli and compound 2a exhibited moderate activity against E. coli and no activity towards Klebsiella Pneumoniae. Compound 4a is biologically inactive against Gram +ve and Gram –ve bacteria. The activity of compound 5b against Gram +veis higher than the activity of the rest of the prepared compounds. All compounds 4a, b and 5a, b exhibit no activity towards Gram–ve bacteria.

3.1. Antibacterial Assay

3.2. Culture media used

Muller-Hinton agar medium g/l	
Beef extract powder	3.0
Casein hydrolase	17.5
Starch	1.5
Agar	17.0

3.3. Preparation of agar

As described in ref. 14; "Muller-Hinton agar (38 g) was suspended in one liter of distilled water, heated to dissolve the medium completely then sterilized by autoclaving at 121 ºC for 15 min" [14].

3.4. Test Organisms

The Gram positive bacteria: Bacillus Subtilis and Streptococci.

The Gram negative bacteria: Klebsiella Pneumoniae and Escherichia Coli.

3.5. Antibacterial test

The antibacterial activities of each compound was examined in term of disc diffusion method [15] as described: "using sterile Whatman-No 5 filter paper discs (11 mm diameter). "Each compound (100 µg) was dissolved in N, N dimethyl formamid (DMF)". "Filter paper discs (11 mm) were loaded with certain amount of the tested material (50 µL) then left under hot air for dryness". "Test plate were prepared by pouring 10 ml Muller-Hinton agar medium seeded with the test organism". "The discs were deposited on the surface of agar plates along with control disc, which loaded only with used solvent". "The discs were incubated at 5 ºC for 1 hr in order to permit good diffusion". All the plates were then incubated for 24 hr at 37 ºC. The zones of inhibition were measured and tabulated.

Table 1. Antibacterial activity of compounds 2a, b, 3, 4a, b and5a, b.

Compound	Antibacterial activity			
	Gram +ve bacteria		Gram -ve bacteria	
	Bacillus Subtilis	*Streptococci*	*Klebsiella Pneumoniae*	*Escherichia Coli*
2a	++	>+++	-	+++
2b	>+++	-	>+++	>+++
3	>+++	-	>+++	-
4a	-	-	-	-
4b	+	++	-	-
5a	>+++	++	-	-
5b	>+++	>+++	-	-
Control	-	-	-	-

- = no activity + = weak activity
++, +++ = moderate activity >+++ = strong activity

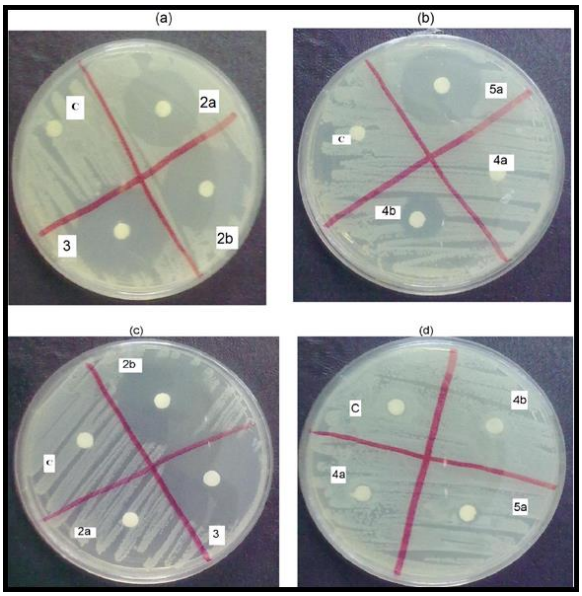
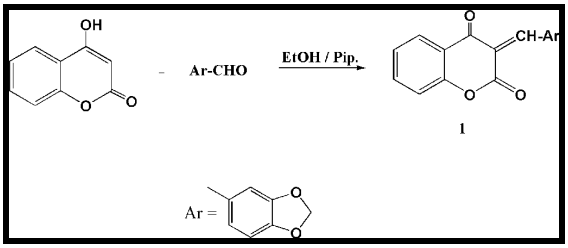


Figure1. Behavior of new coumarin derivatives against Gram (+) and Gram (-) bacteria.
(a)Antibacterial activity of compounds 2a, b and 3 against Bacillus Subtilis;
(b)Antibacterial activity of compounds 4a, b and 5a againstBacillus Subtilis;
(c)Antibacterial activity of compounds 2a, b and 3 against Klebsiella Pneumoniae;
(d)Antibacterial activity of compounds 4a, b and 5a against Klebsiella Pneumoniae.

4. Result and Discussion

In the present work, the starting compound 1 has been obtained via the condensation of 4-hydroxycoumarin with aldehyde (pipronal) [16].

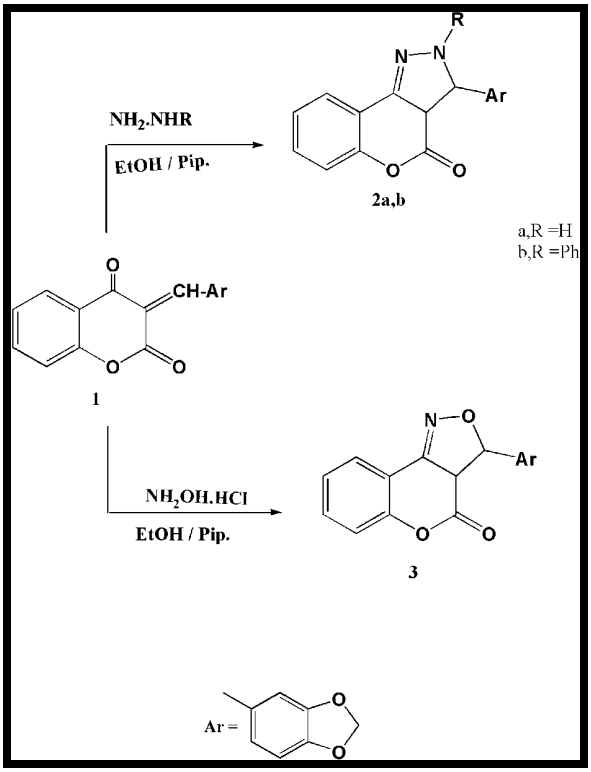


Scheme 1

This compound reacted with hydrazine hydrate and /or phenyl hydrazine under reflux in boiling ethanol and few drops of piperidine to give the corresponding chromeno [4,3-c]pyrazol-4-one derivatives 2a,b [14, 17]. The structures of compounds 2a, b were confirmed from their elemental analysis and spectral data. IR spectra of compound 2a showed strong at 3189 cm-1 due to νNH group but it absent in 2b. The two compounds showed absorption band 1710-1699 cm-1due to νCO of δ-lactone. The 1H-NMR (DMSO-d6) spectrum of compound 2a showed signal at δ 2.9 ppm (d,1H,CCHCHAr), 4.6 ppm (d,1H,CHAr), 5.85 ppm (s,2H,O-CH2-O), 6.50-7.62 ppm (m,8H,2Ar-H,NH pyrazol) and the mass spectrum of compound 2a revealed ion peak at m/e = 296(.52%) equivalent to molecular formula C17H12N2O4.

In the same manner [8], hydroxylamine hydrochloride reacted with 3-methylene chromene-2,4-dione derivative 1 under refluxing in ethanol and few drops of piperidine to afford the corresponding 3-benzo[1,3] dioxol-5-yl-3,3a-dihydro-chromeno-[4,3-c]isoxazol-4-one 3 in a good yield. The structure of isoxazoline derivative was confirmed from elemental analysis and spectral data. IR spectra showed strong absorption band at 1698 cm-1due to νCOof δ-lactone. The 1H-NMR (DMSO-d6) spectrum of compound 3 showed signal at δ 2.7 ppm (d,1H,C-CH-CH-Ar), 5.00 ppm (d,1H,CH-Ar), 5.8 ppm (s,2H,CH2), 6.9-7.7 ppm (m,7H,2Ar-H).

Condensation of urea and thiourea with α, β-unsaturated ketones has been previously reported [17, 18]. Here, compound 1 reacted with urea and thiourea by refluxing in boiling pyridine giving the corresponding chromeno [4, 3-d]-pyrimidine derivatives 4a, b. The structures of compounds 4a, b were confirmed from elemental analysis and spectral data. IR spectra showed strong absorption bands at 3360-3238 cm-1due to νNH, absorption bands at 1727-1706cm-1due to νCO of δ-lactone. Compound 4a showed absorption band at 1664 cm-1due to νCO of amide.

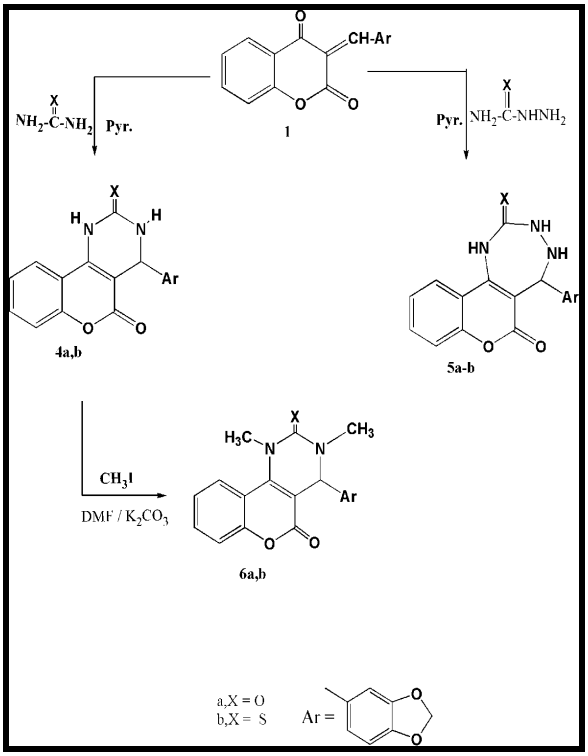


Scheme 2

The reaction of compound 1 with semicarbazide or thiosemicarbazide under reflux for 12hrs in boiling pyridine afforded seven-membered compounds 5a-c [11]. The structures of compounds 5a-b were confirmed from elemental analysis and spectral data.IR spectra showed strong broad bands at 3319-3255 cm -1due to νNH2, absorption bands at 3231-3210cm-1due to νNH, at 1710-1690cm-1due to νCOof δ-lactone compound 5a showed absorption band at 1693 cm-1due to νCO of ketone. The 1H-NMR (DMSO-d6) spectrum of compound 5b showed signal at δ 2.00ppm (s,3H,NH,NH2), 3.45ppm(d,1H,CHC=O), 4.50ppm (d,1H,CH-Ar), 5.85ppm (s,2H,O-CH2-O), 6.55-7.09ppm(m,7H,2Ar-H). The mass spectra of compound 5a, b revealed ion peak at m/e =353(0.31%) equivalent to molecular formula $C_{18}H_{15}N_3O_5$.

Compound 4a, b reacted with methyl iodide in DMF and K_2CO_3 at room temperature to afford dimethyl chromeno [4, 3-d]-pyrimidine derivatives 6a, b. The structures of compounds 6a, b were confirmed from elemental analysis and spectral data. IR spectra showed strong absorption band at 1717-1705cm-1 due to νCOof δ-lactone, compound 6a showed absorption band at 1661cm-1 due to νCO of amide.The 1H-NMR (DMSO-d6) spectrum of

compound 6b showed signal at δ2.73ppm (s,6H,2CH3), 5.56ppm (s,1H,CH-Ar),5.92ppm (s,2H,O-CH2-O),6.52-7.78ppm (m,7H,2Ar-H).The mass spectrum of 6a revealed ion peak at m/e = 366(3.84%), 364 (3.48%) equivalent to molecular formula **$C_{20}H_{16}N_2O_5$**.



Scheme 3

Conclusion

In this study, we prepared and characterized a series of new coumarin derivatives. All the newly synthesized compounds were tested for their antibacterial activities. Compounds 2a,b and 3 displayed maximum activity against both Gram positive and Gram negative bacteria and compounds 5a,b were more active towards Gram positive bacteria than compound 4b. All compounds 4a, b and 5a, b showed no activity towards Gram negative bacteria.

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