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Synthesis and Antibacterial Activity of New Quinoline Derivatives Started from Coumarin Compounds

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An efficient synthetic method for the preparation of quinoline derivatives started from coumarin compounds was described. Fused coumarin derivative 1 reacted with amm acetate to afford 3-methylene-quinoline-2, 4-dione 2. In the same way active methylene compounds as ethyl acetoacetate, ethyl cyanoacetate, acetyl acetone and malonitrile reacted with compound 1 and gave the corresponding quinolines derivatives 3-6. All the newly compounds were characterized by elemental analysis, IR and mass spectra.

Key words: Coumarin, Active methylene, Ammonium acetate, Quinoline, Antibacterial activity.

Quinolines represent one of the most active classes of compounds which are naturally occurring[1,2]. Recently, quinoline nucleus has attracted a great attention among chemists and biologists to synthesiz it due to its wide spectrum of biological activities such as antituberculosis[3], antimalarial[4,5], anti-inflammatory[6], anticancer[7], antibiotic[8].

In addition, coumarins have a wide application in medicine and industry because their compounds possess several types of pharmacological properties as anticoagulant[10-11], antiarthirtis[12], antiinflammatory[13], antipyretic [14] and antiviral [15]. Also many of these compounds have been used in food, perfumes, cosmetics, optical brighteners[16].

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In this study, we aimed to prepare a novel series of quinolines using coumarin moiety as starting compound.

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 HF_{245} (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 recrded 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 ´ units(National Center Researcher).

Synthesis of 3-benzo[1,3]dioxol-5-ylmethylene -1H-quinoline-2,4-dione 2

A mixture of compound **1** (2.94g , 0.01mol)was heated under reflux with ammonium acetate for 15hrs .The reaction mixture was poured into ice, the solid product was filtered off and washed with water several times . The solid product crystallized from ethanol as black crystal in 50% yield , m.p. 316º C.Analysis for $C_{17}H_{11}NO_4$ (M.wt.293.27).Calculated % :C 69.62 , H 3.78 , N 4.78 , Found %:C : 69.66 , H 3.77 , N 4.80 , IR(cm^{-1}): 3316 ν_{NH}, 3045 due to ν_{CH} aromatic and broad band at 1664 ν_{CO} due to amide and ketone.

Synthesis of 3-substituted-4-aryl-1H,3H,4H-trihydropyrido[2,3-c]-6-hydro-quinoline-2,5-dione derivatives 3, 4

A mixture of **1** (2.94g, 0.01mol) and ethyl acetoacetate and/or ethyl cyanoacetate (0.01mole) was refluxed in ammonium acetate for 15hrs. The reaction mixture was cooled and poured into water. The solid product was filtered , washed with water several times and crystallized from propel solvent.

3

Crystallized from dioxane as brown crystals in 66% yield ,m.p.330 ºC. Analysis for $C_{21}H_{16}N_2O_5$ (M.wt. 376.36). Calculated %: C 67.02 , H 4.28 , N 7.4, Found % : C 66.98, H 4.30 , N 7.48 , IR(cm^{-1}) : 3373 , 3240ν_{NH} ,3030 due to ν_{CH} aromatic, 2886 due to ν_{CH} aliphatic, 1680 due to ν_{CO} of amide and acetyl group .

4

Crystallized from methanol as dark brown in 58% yield ,m.p.298 ºC.Analysisfor $C_{20}H_{14}N_2O_6$ (M.wt. 378.33). Calculated % : C 63.49, H 3.73 , N 7.40, Found % : C 63.88 , H 3.30 , N 7.68 , IR(cm^{-1}) : 3452 due to ν_{OH}, 3327, 3189 due to ν_{NH} ,3079 due to ν_{CH} aromatic, 2946 due to ν_{CH} aliphatic, broad band at 1686 and 1650 due to ν_{CO} of amide and carboxylic group .

Synthesis of 3-acetyl-2-methyl-1H, 3H, 4H-trihydropyrido[2,3-c]-6-hydro-quinoline -5-one-derivative 5

A mixture of **1** (2.94g, 0.01mol.) and acetylacetone (0.01mole) was refluxed in ammonium acetate for 15hrs. The reaction mixture was cooled and poured into water. The solid product was filtered, washed with water several times and crystallized from dioxane as brown crystals in 66% yield, m.p. 320. Analysis for $C_{22}H_{20}N_2O_4$ (M.wt.376.41).Calculated % : C 70.20 , H 5.36, N 7.4, Found %: C 69.85, H 5.11 , N 7.00 , IR(cm^{-1}) :3342, 3263 due to ν_{NH} ,3015due to ν_{CH} aromatic, 2926 due to ν_{CH} aliphatic, 1677 due to ν_{CO} of amide and acetyl group.

Synthesis of 2-amino-5-oxo-3-carbonitrile quinoline derivative 6 and 2-amino-5-oxo- -3-carboxylic acid amide quinoline derivative 7

A mixture of **1** (2.94g, 0.01mol.) and malonitrile (0.01mole) was refluxed in ammonium acetate for 15hrs. The reaction mixture was cooled and poured into water. The solid product was filtered , washed with water several times and crystallized from ethanol as brown crystals. IR(cm^{-1}) : 3362 , 3363 due to ν_{NH2} , 3289 due to $\nu_{NH,}$ 3050 due to ν_{CH} aromatic, 2844 due to ν_{CH} aliphatic , 2210due to ν_{CN} , 1656 due to ν_{CO} of amide.

RESULTS AND DISCUSSION

Our target in this study is to obtain quinoline ring from the nucleus of coumarin.[17] When compound **1** fused with ammonium acetate for long time , it afforded derivative of 3-methylene-quinoline-2,4-dione **2**, the coumarin ring converted into quinoline via hetero ring opening of the nucleus of coumarin followed by recyclization[17] as shown in scheme 1.

The reaction possibly takes place via the following mechanism

The structure of this compound 2 was confirmed from elemental analysis and spectral data. IR spectrum of 2 showed strong absorption band at 3316 cm^{-1} due to ν_{NH}, absorption band at 3045 cm^{-1} due to ν_{CH} aromatic, 1664 cm^{-1} due to ν_{CO} of amide and ketone.

Similarly, the reaction of 1 with active methylene such as ethyl acetoacetate, ethyl cyanoacetate, acetylacetone and malonitrile fusion in ammonium acetate afforded the corresponding quinoline derivatives 3-7 as shown in scheme 2.

The structures of compounds 3-7 were confirmed from elemental analysis and spectral data. IR spectrum showed strong absorption bands at 3373-3231 cm^{-1}due to ν_{NH}, absorption band at 3080-3021 cm^{-1} due to ν_{CH} aromatic, at 2888-2886 cm^{-1} due to ν_{CH} aliphatic, broad band at 1686-1650 cm^{-1} due to ν_{CO} of amide.

Antibacterial Assay

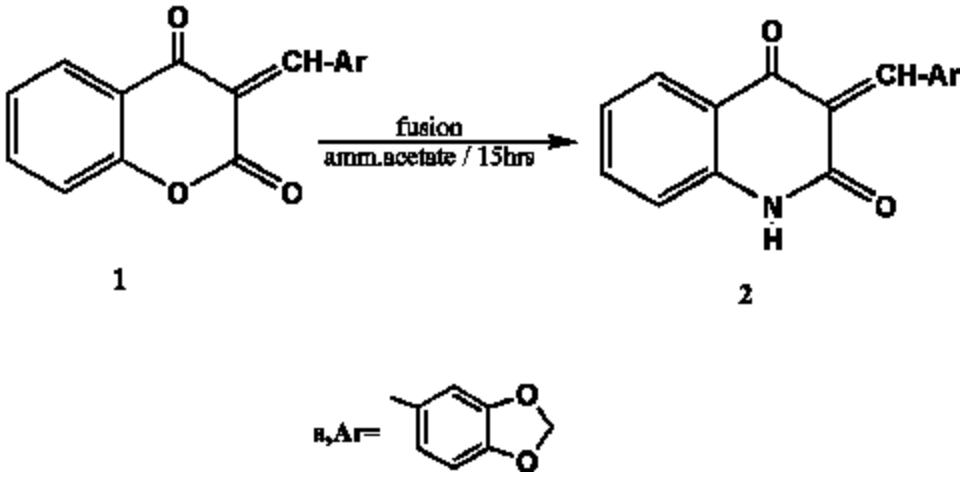
Some of the newly quinolines derivatives were tested for their antibacterial activity against different types of bacteria: Gram-positive bacteria (*Streptococci*) and Gram-negative bacteria (*Escherichia coli*). Compounds 4 showed good activity against *Streptococci*, while compounds 3, 5 exhibited no activity. Compound 3 demonstrated good activity against *E.coli* as shown in Fig. 1, but compounds 4,5 showed no activity.

Culture media used

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

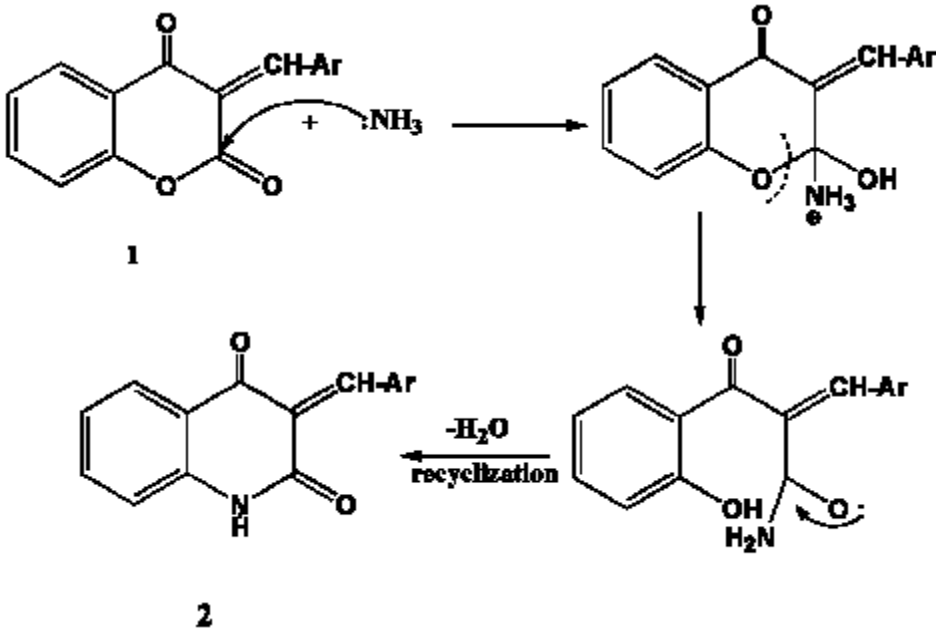
Preparation of agar

Muller-Hinton agar (38 g) was suspended



Scheme 1.

The reaction possibly takes place via the following mechanism:

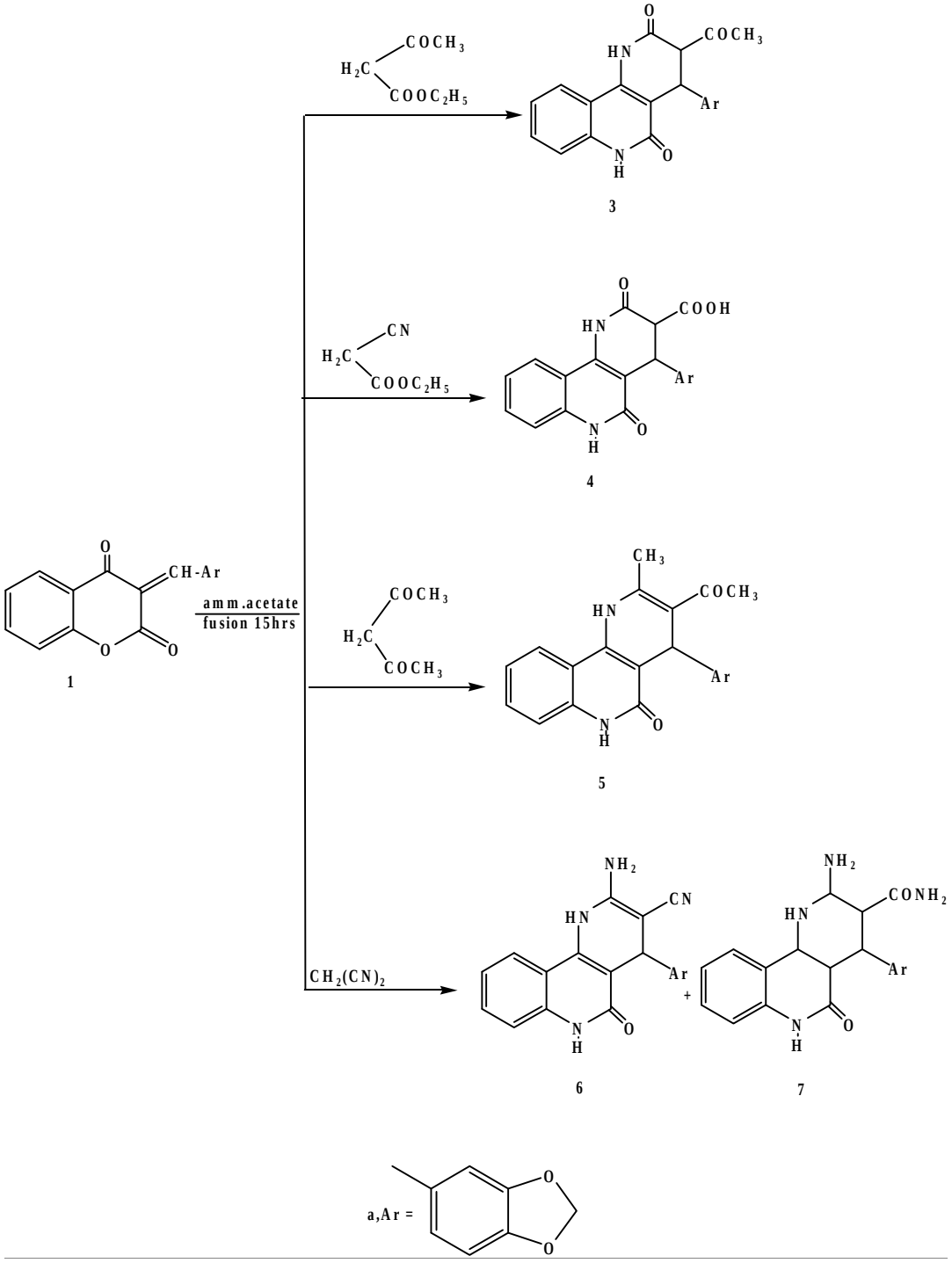


Reaction mechanism of coumarin with amm.acetate in fusion condition

in one liter of distilled water, heated to dissolve the medium completely then sterilized by autoclaving at 121 ºC for 15 min.

Test Organisms

The Gram positive bacteria: *Bacillus subtilis* and *Streptococci.*



Scheme 2

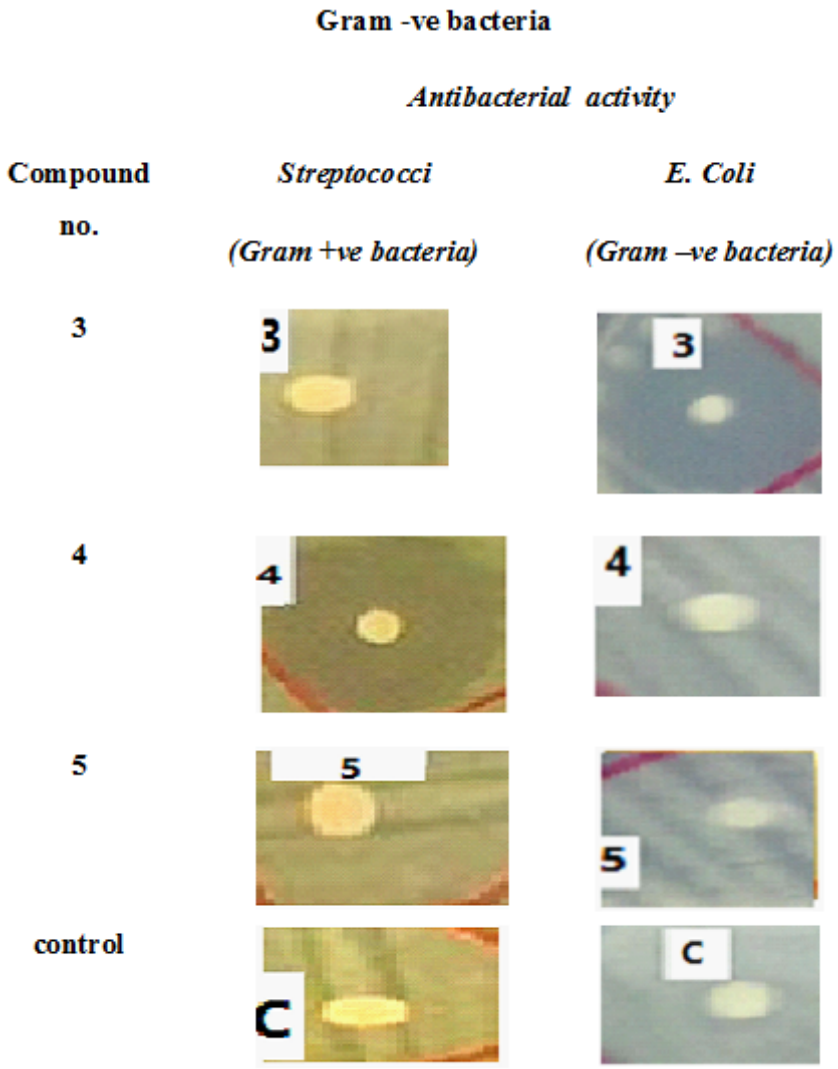


Fig. 1. antibacterial activity of compounds 3,4,5 against Gram +ve and Gram –ve bacteria

· The Gram negative bacteria: *Klebsiella pneumoniae* and *Escherichia coli*.

Antibacterial test

The antibacterial activities of tested compounds were evaluated by the disc diffusion method[18,19] using sterile Whatman-No5 filter paper discs (11 mm diameter). Tested compounds were dissolved in N,N-dimethylformamide (DMF) . Filter paper discs (11 mm) were loaded with certain amount of the tested material (50µL) then left with care under hot air to complete dryness. Test plates 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 h, to permit good diffusion. All the plates were then incubated for 24 h at 37 ºC. The zones of inhibition were measured .

CONCLUSION

Quinoline ring could be obtained from coumarin moiety under special condition.3-methylene coumarin derivative **1** fused with ammonium acetate and gave compound **2**. In addition, it fused with active methylene compounds as (ethyl acetoacetate, ethyl cyanoacetate, acetyl acetone and malonitrile) in

ammonium acetate for long time to give quinolines derivatives **3-7.** Some of the newly compounds showed good activity against Gram +ve and Gram –ve bacteria.

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