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Synthesis, structure characterization and biological activity of new coumarin derivatives

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Abstract

The 5-acetyl-4hydroxy-2methyl-8H-Pyrano (2,3e) benzoxazol-8One was synthesized by reaction of 3-acetyl-8-amino-6m7dihydroxy coumarin with acetic anhydride.
The structures of the prepared compounds 3a,3b,3c,4 and 5 were characterized by IR,^{1}H-NMR, mass spectroscopy and CHN analysis. The new products exhibited antibacterial and antifungal activities.

Keywords: coumarins, spectroscopic, biological activity

Introduction

Coumarin derivatives are important chemicals in the perfume, cosmetic, orgricultural industries[1]. Inflammatory diseases are becoming common in aginbiociety throughout the world .Recent studies indicate that the mediators and cellular effectors of inflammation are important constituents of the local environment of tumors [2]. The incorporation group as afused component into parent coumarin alters the property of parent coumarin and converts it into a more useful produce[3].

Coumarin is plant flavonoids widely distributed in nature. Natural cumarins are known to have antidiabetic activity[4]. Some of these coumarin derivatives have been found useful in photochemotherapy , antitumor[5] ,anti-HIV therapy[6,7], as CNS stimulants[8], antibacterial [9,10,11], anticoagulants [12,13,14], antifungal[15,16], antioxidant[17]agents and as dyes[18] . coumarins are an important class compounds because a large number of natural produce contains this heterocyclic nucleus.

They have a wide variety of biological activities i.e. Fluorescence sensors[19], brightening agents[20], anticoagulants[21], insecticides[22]etc. coumarins occupy an important place in the realm of natural products and synthetic organic chemistry [23,24] . Cuomarins comprise a group of natural compounds found in a variety of plant sources in the form of benzopyrene derivatives . Coumarins have important effects in plant biochemistry and physiology, as they act as antioxidants, enzyme inhibitors and precursors of toxic substances. In addition, these compounds are involved in the actions of plant growth hormones and growth regulators ,the control of respiration , photosynthesis , as well as defense against infection[25], coumarins have long been recognized to possess anti-inflammatory, antioxidant, antiallergic hepatoprotective, antithrombotic, antiviral and anticarcinogenic activites[26]. coumarins are important compounds found widely in nature[27] and have numerous applications in medicine (e. g . anticlotting) [28,29,30] and perfumery[31].

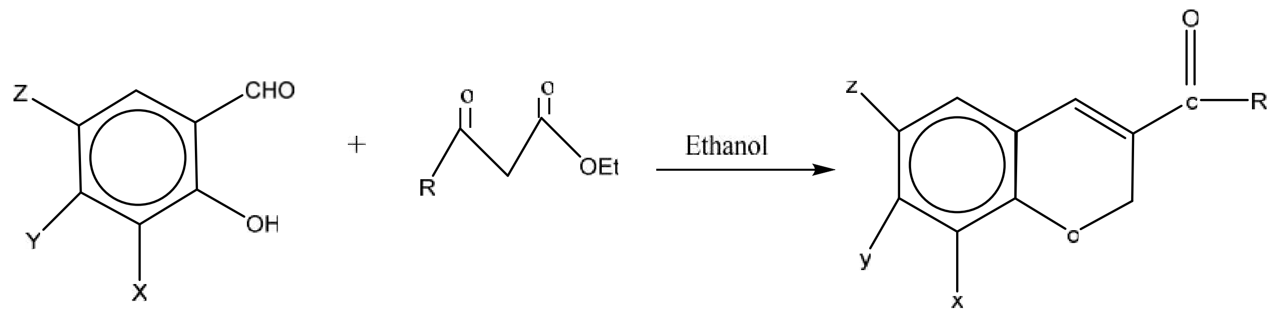
Experimental

Instrumentation

Melting points were measured on Gallenkamp electronic melting points apparatus , the IR spectra were recorded on a perkin Elmer 317 Grating IR spectrophotometer, using KBr. The ^{1}H-NMR spectra were recorded on a Varian MERCURY 300MHz spectrometer using TMS as internal stranded in deuterated dimethyl sulphoxide, the elemental analysis was performed on a perkin-Elmer 2400. The mass spectra were recorded on shimadzu GCMS-Q-P-1000EX mass spectrometer at 70ev.

Synthesis of 6-chloro – 3 ethoxycarbonyl 7,8 dimethoxy- coumarin(3a) :

A mixture of 5-bromo-2-hyroxy -3,4dimethoxy benzaldehyde (1a,2.17gm ,0.01mole) and diethylmalonate (2a,1.60gm,0.01 mole) in round bottom flask (205m) in Absolute ethanol(150m) and 2ml of piperidine was added. The mixture was heated to reflux for 2 hours and keep overnight .The solid products was separated by filtration. The solid was recrystallized from ethanol.



(1) (2) (3)

a:X=OMe;Y=OMe;Z=Br a:R=OEt
b:X=H;Y=CN;Z=Me b:R=Ph
c=X=No_2; Y=OH;Z=OH c:R= Me

Synthesis of 7 cyano-6methyl-3-phenonecoumarin (3b):

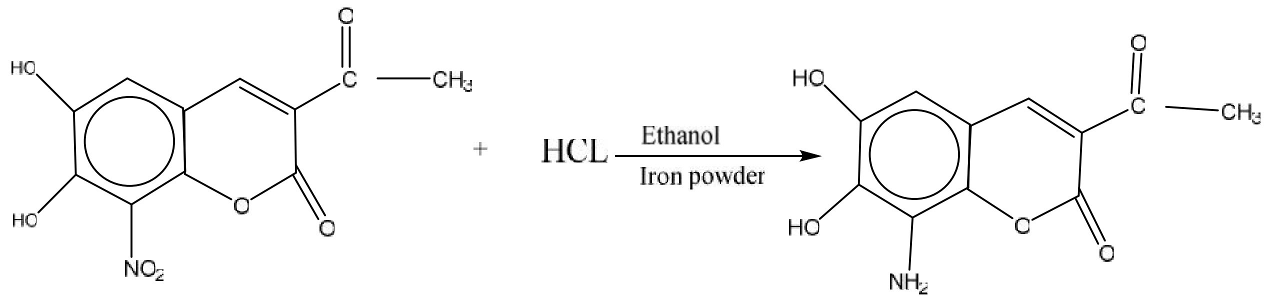
In a round bottom glass (pyrix) flask (500ml) dissolve (1b ,16.1gm ,0.1mole) of 4 cyano-2-hydroxy- 5-methyl benzaldehyde in 200ml ethanol then added (2b, 19.2gm, 0.1mole) of ethyl benzoyl acetate , stirr the mixture at room temperature for 1 hr. then few drop of piperidine about (2ml) . The mixture was heated to reflux for 2hrs and keep overnight .The solid was separated by filtration .the solid was recrystallized from ethanol.

Synthesis of 3-acetyl – 6,7 dihydroxy – 8 nitrocoumarin (3c):

Amexture of 2,4,5 - trihydroxy–3-nitrobenzaldhyde (1c,1.99gm ,0.01mole) and ethyl acetoacetate (2c,1.3gm,0.01 mole) in round bottom (pyrix) flask (205m) in Absolute ethanol (100m) and 2ml of piperidine was added .the mixture was heated to reflux for 2 hrs, the reaction mixture was cooled and the brown residue was separated by filtration. The solid was recrystallized from ethanol.

Synthesis of 3-acetyl – 8 amino- 6,7 dihydroxycoumarin (4):

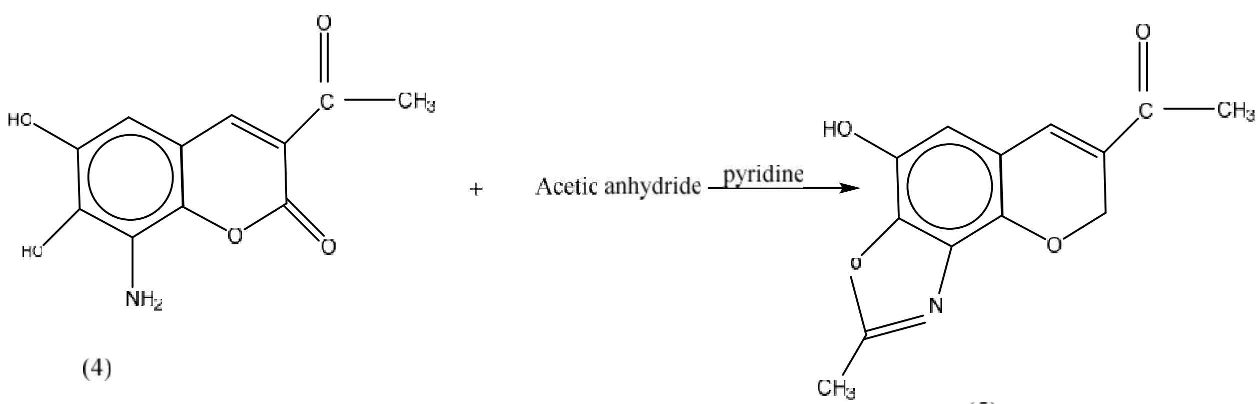
Dissolve (2.65gm, 10mmole) of 3-acetyl–8-nitro-6,7dihydroxy coumarin in 40 ethanol then added (30ml) of Conc hydrochloric acid. The reaction mixture was stirred at room temperature for 3 hrs in the presence of iron Powder (6gm) was added slowly to a stirred mixture. The mixture heated to reflux for 10hrs the solid produce that formed was collected by suction, washed with water, dried and recrystallized from ethanol.



(3C) (4)

Synthesis of 5-acetyl-4 hydroxy– 2methyl -8 H–pyrano (2,3e) benzoxazol – 8 one (5):

A mixture of of 3-acetyl – 8 amino- 6,7 dihydroxycoumarin (4) (0.23gm ,1 mmole) and acetic anhydride (0.102gm,1 m mole) in 20 ml pyridine .The mixture was heated to reflux for 16 hrs, cool, poured onto ice/HCL. The solid that was separated by filtration, dried and recrystallized from DMF.



(4) (5)

Results and Discussion

Infrared and NMR studies of 6 – chloro– 3 ethoxycarbonyl- 7,8 dimethoxycoumarin (3a).

The infrared spectrum of the (3a) table 2 exhibited a strong bands at 1688 and 1710 cm^{-1}corres ponding to ν (C=O) (lactone), ν(C=0) (ester), respectively.

^{1}H-NMRspectra of compound (3a) showed a singlet signals at 2.71 and 2.83 ppm due to ($2OCH_3$) protons . also ,the ^{1}H-NMRspectrum exhibit quartet signal at 4.11 ppm (q,2H,CH_2) and triplet signal at 1.31 ppm(t,3H,CH_3), 7.30-7.68 ppm (S,1H,Ar-H) and singlet signals at 6.52 ppm (S,1H,pyran ring) . The mass spectrum of (3a) the following peaks of m/z values followed by % relative abundances [M] 357(79.16), 327(51.22), 278(38.12), 254(85.27), 218(24.90), 176(40.03), 130(60.44), 102(25.14) 77(100).

Infrared and NMR studies of 7- Cyano – 6methyl-3- phenonecoumarin (3b)

The infrared spectrum of (3b) table (2) displayed absorption bands(v/cm^{-1}) at 1651 and 1702 corresponding to ν (C=O) (lactone) , ν(C=O) (ketone) , respectively.The^{1}H-NMRspectrum of the (3b) in deuterated DMSO-d_6 of table (2) showed a singlet signal at 2.56ppm due to (CH_3) , as well as multiplets in range 7.19-7.59 ppm due to phenyl protons .furthermore ,asinglet signal at 6.27ppm due to pyran ring proton.The mass spectrum of compound (3b) showed the molecular ion peak at m/z 289(93.16) the following peaks of values followed by % relative abundances (M+1) 290(77.35), 275(29.03), 250(34.14), 216(67.94), 171(74.55), 146(17.40), 127(69.13), 77(83.49), 65(100) .

Table 1: Physical characterization of coumarin derivatives.

Compound No.	MP.C° color	Solvent yield %	MF (M.wt)	Elemented analysis calcd/found		
				C%	H%	N%
3a	218-220 Brown	Ethanol 76	$C_{14}H_{13}O_6Br$ 357.0177	53.75 53.01	4.19 3.42	/ /
3b	207-209 Brown	Ethanol 84	$C_{18}H_{11}NO_3$ 289.2889	74.73 74.16	3.83 3.22	4.84 3.99
3C	252-254 Brown	Ethanol 69	$C_{11}H_7NO_7$ 265.1788	49.82 49.25	2.66 1.87	5.28 4.76
4	280-282 Brown	Ethanol 73	$C_{11}H_9NO_5$ 235.2848	56.15 55.39	3.58 3.16	5.95 5.62
5	>300 Brown	DMF 61	$C_{13}H_9NO_5$ 259.2168	60.23 59.76	3.49 2.85	5.40 4.71

Table 2: Spectroscopic data of coumarin derivatives.

Compound no.	IR(KBr) ν(cm^{-1})	^{1}H-NMR S(ppm)
3a	ν (C=O) 1710(ester) ν (C=O) 1688(lactone) ν (C=C)1608	2,71,2,83,(S,6H,2OCH$_3$) 4,11(q,2H,CH$_2$) 1.31(t,3H,CH$_3$) 7.30(S,1H,Ar-H) 6.52(S,H,pyran ring)
3b	ν (C=N) 2210 ν (C=O)1702 (ketone) ν (C=O)1651 (lactone) ν (C=C)1593	2.56(S,3H,CH$_3$) 7.19(m,2H,Ar-H) 6.27(S,1H,pyran ring)
3c	νOH 3403 ν (C=O) 1718 (ketone) ν (C=O)1670(lactone) ν (C=C)1619	12.71(S,1H,OH) 10.93(S,1H,OH) 7.70(S,1H,Ar-H) 6.88(S,1H,pyran ring) 3.02(S,3H,CH$_3$)
4	νOH 3461 νNH$_2$ 3380 3258 ν (C=O)1729(ketone) ν (C=O)1674 (lactone)	12.28,11.79(2S,2H,2OH) 2.73(S,2H,NH$_2$) 7.11(2H,coumarin protons)
5	νOH 3439 ν (C=O)1735(ketone) ν (C=O)1634 (lactone) ν (C=N)1610	11.20(S,1H,OH) 7.23(2H,coumarin protons) 2.65,2.40,(2S,6H,2CH$_3$)

Infrared and NMR studies of 3– acetyl – 6,7 dihydroxy-8- nitro coumarin (3c).

The infrared spectrum of the (3c) table 2 showed tow characteristic bands at 1670 and 1718 cm^{-1} due to ν (C=O) (lactone) , ν (C=O) (ketone) , respectively . furthermore , the IR spectrum displayed a broad band at 3430 cm^{-1} due to frequencies of the OH group .The ^{1}H-NMR spectrum(DMSO-d_6) of compound (3c) displayed from low to high field the following signals (δ/ppm):12.71 (S,1H,OH), 10.93(S,1H,OH) 7.70-7.96(S,3H,CH_3), 6.88(S,1H, pyran ring) and 3.02 (S,3H,CH_3).The mass spectrum of compound (3c) slowed the following peaks of m/z values followed by % relative abundances [M]265 (90.12), 251(33,28), 249(60.22), 233 (15.38), 220(74.56), 185(49.70), 178(56.83), 130(37.61), 118(78.44), 110(100), 94(55.13).

Infrared and NMR studies of 3 –acetyl –8 amino–6,7, dihydroxy coumarin (4).

The infrared spectrum of the (4) table 2 exhibited a absorption bands for OH ,NH and C=O at 3461,3380,3250,1674,and 1729 cm^{-1} respectively. The^{1}H-NMR spectra showed signals at 12.28,11.79ppm (2S,2X1H,2XOH), 2.73PPM (S,2H,NH_2). As well as singlet signal at 2.26ppm (S,3H,CH_3) and bands at 7.11-7.63 ppm (2H,coumarin protons).The mass spectrum of (4) slowed the following peaks of m/z values followed by % relative abundances: (M+1) 236(44.70), [m]235(86.15), 219(75.26), 203(94.20), 193(65.49), 176(30.12), 160(27.36), 113(71.18), 93(54.23), 77(28.24), 63(21.07), 52(100).

Infrared and NMR studies of 5 – acetyl –4-hydroxy –2– methyl– pyrano (2,3-e) – 8 - one (5).

The IR spectrum of the (5) table (2) exhibited a two bands at 1634 and 1735 cm^{-1} assigned to ν (C=O) (lactone)and ν (C=O)(ketone);respectively. furthermore the IR spectrum displayed band at 3439 cm^{-1} due to (OH) as well as the IR spectrum of compound(5) showed band at 1610 cm^{-1} due to (C=N) . The^{1}H-NMR spectrum of 5 table (2) in deuterated DMSO-d_6 showed singlet signals at 11.20(S,1H,OH) as well as bands at 7.23-7.49 ppm due to (2H , Coumarin protons) and singlet signals at2.40,2.65 ppm (2S,6H,2CH_3). The mass spectrum of compound (5) exhibited the molecular ion peak $[M]^{\cdot+}$ at m/z 259(67.13) , the following peaks of values followed by % relative abundances :245(31.98) ,231(64.20) ,228(74.19) ,214(53.29) ,171(24.67) ,157 (43.10) ,133(80.36) ,95(100) ,65(29.11) ,62(35.72).

Biological activity

measurement of antimicrobial activity using diffusion disc method : A filter paper sterilized disc (diameter 80mm) saturated with measured quantity of the sample is placed on plate containing solid bacterial medium (nutrient agar broth) or fungal medium (dox's medium) which has been heavily seeded with the spore suspension of the tested organisms . After incubation the clear zone of inhibitory surrounding the sample is taken as measure of inhibitory power of the sample.[32,33,34,35]

The experiments were performed using test bacterial organisms belonging to the gram positive and gram negative groups namely *Staphylococcus aureus* and *Escherichia coli* respectively, as well as *Aspergillus flavus* and *Candida albicans* as tested fungi . The compounds under investigation were dissolved in DMSO as an inactive solvent towards all microorganisms .The concentration of DMSO solutions were 0.2mg/ml. all the tested compunds showed antimicrobial activity and these activities were compared to standard amikacin, the results of antimicrobial studies are given in table 3.

Table 3: The inhibition zones (mm) of some coumarin derivatives against tested organisms

Sample / standard	Inhibition zone (mm/mg sample)			
	Escherichia coli (G-)	*Staphylococcus aureus* (G +)	*Aspergillus flavus* (fungus)	*Candida albicans* (fungus)
3a	21	32	28	23
3b	13	30	24	20
3c	18	39	25	28
4	20	36	29	22
5	15	35	20	22
Amikacin	19	37	27	25

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