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A SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL STUDIES OF COUMARINE DERIVATIVES SYNTHESIZED FROM 4-HYDROXY-CHROMEN-2-ONE AND COMPARISON WITH STANDARD DRUG

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ABSTRACT

In present paper, we report the organic syntheses of three compounds from 4-hydroxy-chromen-2-one and describe the results of antibacterial activity of purified compounds.4-hydroxy-3-(3-Hydroxy-benzoyl)-chromen-2-one **(1a).** 3-(3-Hydroxy-benzoyl)-4-(2-hydroxy-phenylamino)-chromen-2-one **(2a),***N*-[3-(3-Hydroxy-benzoyl)-2-oxo-7-thioureido-2H-chromen-4-yl]-N-(2-hydroxy-phenyl)-acetamide **(3a),** have been synthesized and characterized using melting points , IR spectra , ^{1}H-NMR and ^{13}C-NMR spectra. The antibacterial activity of synthesized compounds and streptomycin and cefalexine at concentrations of 2mg/ml, 3mg/ml and 5mg/ml, have been evaluated against three strains of bacterial culture; *Staphylococcus aureus, E.coli and Bacillus cereus*. The compounds show bacteriostatic and bactericidal activity.

Keywords: Coumarine derivatives, antibacterial activity, IR, ^{1H}-NM, ^{13C}-NMR, Streptomycin.

INTRODUCTION

Starting from 4-hydroxy-chromen-2-one (a); derivatives **(1a, 2a, 3a)** are synthesized. Coumarin derivatives are large group of heterocyclic with oxygen as heteroatom. Coumarin is a chemical compound (specifically, a benzo-α-pyrone) found in many plants notably in high concentration in the tonka bean (Dipteryx odorata), vanilla grass (Anthoxanthum odoratum), woodruff (Galium odoratum), mullein (Verbascum spp), and sweet grass (Hierochloe odorata).Coumarine and their derivatives have shown various biological[1,2] activities. Their fame has come mainly from their antithrombic[3], antiinflammatory[3], vasodilatory, and antiviral activities. With reflux and condensation we have synthesize some new coumarin derivatives and to investigate their antibacterial[13] activity against *Staphylococcus aureus, E.coli* and *Bacillus cereus*. The antibacterial activity of synthesized compounds is compared with antibacterial[13] activity of Cefalexine and Streptomycin.[4-14]

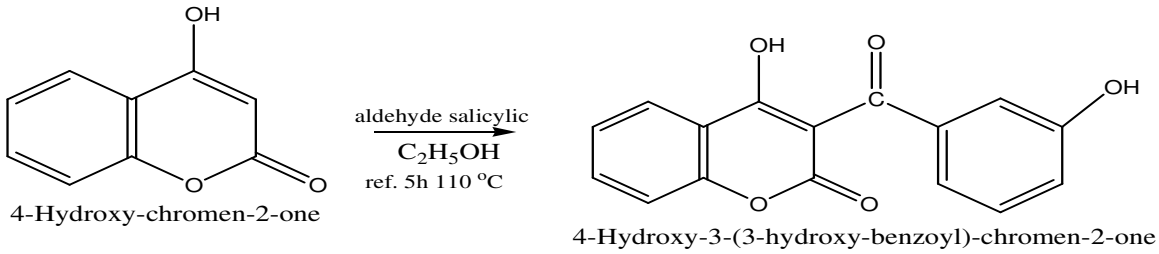
EXPERIMENTAL

4-hydroxy-3-(3-Hydroxy-benzoyl)-chromen-2-one **(1a),** 3-(3-Hydroxy-benzoyl)-4-(2-hydroxy-phenylamino)-chromen-2-one **(2a)** , N-[3-(3-Hydroxy-benzoyl)-2-oxo-7-thioureido-2H-chromen-4-yl]-N-(2-hydroxy-phenyl)-acetamide **(3a)** were synthesized. The identification of derivatives 4-hydroxy-chromen-2-one **(1a, 2a, 3a)** , is made by using melting point, IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis. Melting point was determinated on an electrothermal apparatus (Fisher Scientific 2555) in an open capillary tube and are uncorrected. Infrared spectra were recorded in cm-1 for KBr pellets on a FT-IR Shimadzu 8400S spectrophotometer with resolution 4 cm^{-1} . ^{1}H NMR spectra were recorded on a Bruker UNITY plus-500 'NMR 1' spectrometer using DMSO-d6 as the solvent and TMS as the internal references standard (σ = 0, 00 ppm).Chemical shifts are expressed in δ ppm. Mass spectra were taken on a LKB 9000 mass spectrometer. Elemental analysis was performed on a Perikin-Elmer 240 BCHN analyzer. The purity of the compounds (synthesized) was routinely checked by TLC using Merck

Kieselgel-60 (F-254) and benzene, toluene, glacial acetic acid (80:10:10) as mobile phase. The spots were exposed in iodine vapor for visualization.

Preparation of 4-hydroxy-3-(3-Hydroxy-benzoyl)-chromen-2-one (1a)

For this synthesis is used as substrate 4-hydroxy-chromen-2-one in a 100 ml flask mixed 3g 4-hydroxy-chromen-2-one, 2 g aldehyde salicylic, 8ml C_2H_5OH. The mixture was refluxed at 110 ^oC for ca. 5h. The obtained crystals yellow are filtered and rinsed with ethanol and dried at room temperature. Recrystallization form absolute ethanol gave a yellow product of 80% yield, melting point 253 ^oC.



4-Hydroxy-chromen-2-one

4-Hydroxy-3-(3-hydroxy-benzoyl)-chromen-2-one

Scheme-1

Preparation of 3-(3-Hydroxy-benzoyl)-4-(2-hydroxy-phenylamino)-chromen-2-one (2a)

In a 100 ml flask were mixed 3g 3-(3-Hydroxy –benzoyl)-chromen-2-one with 10ml C_2H_5OH, 3g amino phenol .The mixture was refluxed at 100 ^oC for ca. 4h . The obtained red crystals are filtered and dried at room temperature. Recrystallization form C_2H_5OH gave red crystals product of 70 % yield, melting point, 373 ^oC.

Preparation of *N*-[3-(3-Hydroxy-benzoyl)-2-oxo-*7*-thioureido-2H-chromen-4-yl]-N-(2-hydroxy-phenyl)-acetamide (3a)

In a 100 ml flask were mixed 2g of 3-(3-Hydroxy-benzoyl)-4-(2-hydroxy-phenylamino)-chromen-2-one ,with 8 ml C_2H_5OH , 1g tioure , 2ml $SOCl_2$ as catalyzer. The mixture was refluxed at 80 ^oC in water bath for ca. 6 h .The flask was placed in an ice bath for 1h until yellow crystalline precipitate was formed. After filtration the product was recrystallized from CH_3CN . The recrystallization gave a red product at 70% yield, melting point; 180 ^oC.

RESULTS AND DISCUSSION

By reacting equimolar amounts of 4-hydroxy-chromen-2-one and corresponding reagents (according Scheme-1) under reflux reaction conditions product 1a is synthesized in 80 % yield.

By reacting equimolar amounts of 4-hydroxy-3-(3-Hydroxy-benzoyl)-chromen-2-one and corresponding reagents (Scheme-2) under reflux reaction conditions product 2a is synthesized in 70 % yield.

By reacting equimolar amounts of 3-(3-Hydroxy-benzoyl)-4-(2-hydroxy-phenylamino)-chromen-2-one and corresponding reagents (Scheme-3) under reflux reaction conditions product 3a is synthesized in 80% yield.

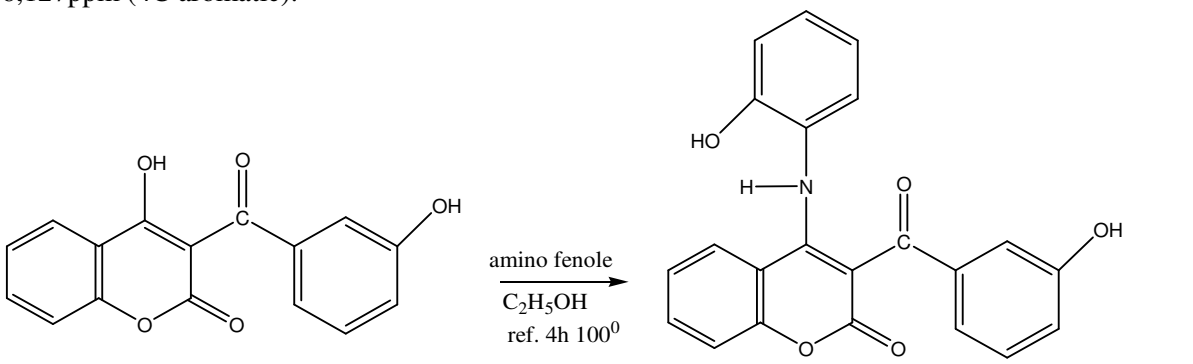
The structure of 4-hydroxy-chromen-2-one derivatives **(1a, 2a and 3a)** were determined from their IR, ^1H NMR, ^{13}C NMR spectra and their melting points as follows-

1a: IR bands (KBr, cm^{-1}) 3850-2400cm^{-1} (OH), (C-H stretch.), 1720 cm^{-1} (C=O), 1600 (C=C stretch.), 750 cm^{-1} (C-H bend.) 600 cm^{-1} (C-Cl stretch.)

^1H NMR (DMSO-d6) δppm; 9.68 ppm s (H, CHO), 7.21-7.53 t (H, aromatic), 5.18 s (H, OH)

^{13} C NMR (DMSO) δppm ; 166.9ppm (C-Cl), 162ppm (C,COO) ; 152ppm (C,C-O) ; 133.4 (C,C-Cl); 121.7, 125.6 , 128.0 (3C-aromatic)

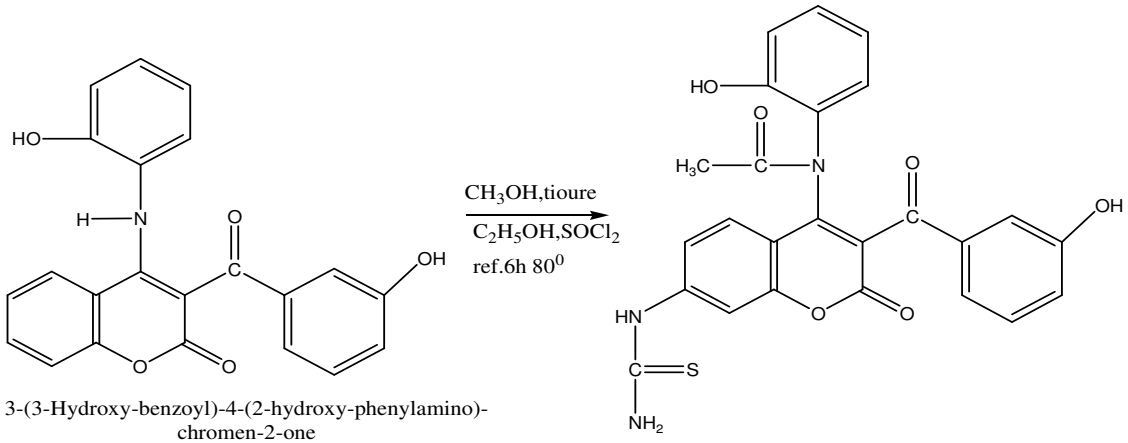
2a: IR bands (KBr,cm^{-1}) 3400cm^{-1}(OH) 3200 cm^{-1} (N-H stretch.) , 3000 cm^{-1} (C-H stretch.), 3200 cm^{1} (N-H stretch.), 2730cm^{1} (C-H stretch.) , 1725cm^{1} (C=O stretch.),1600cm^{1}(C=C stretch.) , 1050cm^{1}(C-O stretch), 750cm^{1}(C-H bend.)
^{1}H NMR (DMSO-d6) δppm 6.37, 6.39, 7.41 t (3H aromatic) 5.0(H, OH), 4.0 d (H, NH), 4.0ppm s (NH)
^{13}C NMR (DMSO) δppm 181ppm (C, C-NH), 162ppm (C, COO), 151ppm (C, C-O), 105,109, 116,127ppm (4C aromatic).



4-Hydroxy-3-(3-hydroxy-benzoyl)-chromen-2-one

3-(3-Hydroxy-benzoyl)-4-(2-hydroxy-phenylamino)-chromen-2-one

Scheme-2



3-(3-Hydroxy-benzoyl)-4-(2-hydroxy-phenylamino)-chromen-2-one

N-[3-(3-Hydroxy-benzoyl)-2-oxo-7-thioureido-2*H*-chromen-4-yl]-*N*-(2-hydroxy-phenyl)-acetamide

Scheme-3

Table-1 Analytical data

Compd.	m.p	M.F	% Elemental analysis Found (Calculated)				
			C	H	N	O	S
1a	253 ºC	$C_{15}H_{11}NO_3$	71.14 (71.00)	4.38 (4.30)	5.53 (5.50)	18.95 (18.90)	
2a	373 ºC	$C_{22}H_{15}NO_5$	70.77 (70.71)	4.05 (4.00)	3.75 (3.70)	21.43 (21.40)	
3a	489 ºC	$C_{25}H_{19}N_3O_6$	61.34 (61.29)	3.91 (3.90)	3.75 (3.70)	19.81 (19.75)	6.55 (6.50)

3a: IR bands (KBr,cm^{-1}) 3280 cm^{-1} (O-H stretch.),3180cm^{-1}(NH stretch.), 3000cm^{-1}(C-H stretch.),2400cm^{-1}(O-H carbocyclic),1760cm^{-1}(C=O stretch.),1600cm^{-1}(C=C stretch),1710cm^{-1}(C=O),1020cm^{-1}(C-O),750cm^{-1}(C-H bend.)
^{1}H NMR (DMSO-d6) δppm 7.4 ,6.5,6.4 (3H aromatic), 5.0 (H.OH) , 4.0 s(H,NH) , 3.53ppm t(2CH_2OH), 2.65ppm t(3H,CH_3N) , 1.48-1.52ppm t(3H,2CH_3), 1.40-155 ppm t(4H,2CH_2)
^{13}CNMR (DMSO) δppm 176.0ppm (C,COOH), 167.ppm (C,C-NH), 162.0 (C,C=O), 151.7ppm(C,C-O), 127,109,105ppm (3C aromatic), 51.6(C,C-N), 46.6(C,C-N) , 62.7(C,C-OH), 30.6,27.8ppm (C,CH_3)

Table-2: Zone of inhibition (mm) of Antibacterial activity in *Staphylococcus aureus*
Inhibition zone (mm)

Compound	2mg/ml	3mg /ml	5mg/ml
1a	12	16	18
2a	13	17	20
3a	14	17	21
Cephalexin	8	8	8
Streptomycin	20	20	20

Table-3: Zone of inhibition (mm) of Antibacterial activity in *E.Coli*
Inhibition zone (mm)

Compound	2mg/ml	3mg /ml	5mg/ml
1a	8	13	17
2a	9	15	19
3a	10	19	18
Cephalexin	8	8	8
Streptomycine	20	20	20

Table-4: Zone of inhibition (mm) of Antibacterial activity in *Bacillus cereus*
Inhibition zone (mm)

Compound	2mg/ml	3mg /ml	5mg/ml
1a	8	13	18
2a	9	14	19
3a	12	18	20
Cephalexin	9	9	9
Streptomycine	20	20	20

Antibacterial activity
The purified synthesized compounds **(1a, 2a, 3a)** were subjected to test in vitro its antibacterial activity against three bacterial cultures; Staphylococcus aureus, E.Coli and B.cereus. Antibacterial activity of compounds was investigated applying the Kirby-Bayer method or disc method (d=5.5 mm max. capacity 10 μg).

CONCLUSION

From the results the following conclusions were drawn:

- The study provides the first evidence that compounds **(1a, 2a, 3a)** obviously inhibit the growth of *S.auerus , E.coli* and *B.cereus.*
- The compounds **(1a, 2a, 3a)** compared with the antibacterial activity of Streptomycin in *S.aureus, E.coli* and *B.cereus.*
- This study provided the first evidence that these compounds **1a, 2a, 3a** showed a significant antibacterial effect against *S.aureus, E.coli* and *B.Cereus*.

- The chemical structures of synthesized compounds were determined according to extensive NMR experiments and published data.

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