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Research Article

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Antibacterial activity of coumarine derivatives synthesized from 7-chloro-4-hydroxy-chromen-2-one and comparison with standard drug

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ABSTRACT

In present paper , we report the organic syntheses of four compounds from 7-Chloro-4-hydroxy-chromen-2-one and describe the results of antibacterial activity of purified compounds as 4,7-Dichloro-chromen-2-one (1a), 7-chloro-4-(4-chloro-phenylamino)-chromen-2-one(2a),[4-(4-chloro-phenylamiono)-2-oxo-2H-chromen-7-ylamino]-acetic acid (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, ^{1}H-NMR, ^{13}C-NMR, Streptomycine.

INTRODUCTION

Starting from 7-Chloro-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 varius biological activities. Their fame has come mainly from their antithrombic, antiinflammatory, vasodilatory, and antiviral activities. Other several coumarin derivatives have antimicrobial properties (Sanghyun; et al 1996; Mohareb et al 2007; Nofal et al 2000), with reflux and condensation we have synthesize some new coumarin derivatives and to investigate their antibacterial activity against *Staphylococcus aureus*, *E.coli* and *Bacillus cereus*. The antibacterial activity of synthesized compounds is compared with antibacterial activity of Cefalexine and Streptomycine.

EXPERIMENTAL SECTION

Experimental Chemistry

Compounds 4,7-Dichloro-chromen-2-one **(1a),** 7-chloro-4-(4-chloro-phenylamino)-chromen-2-one **(2a)** , [4-(4-chloro-phenylamiono)-2-oxo-2H-chromen-7-ylamino]-acetic acid **(3a)** are synthesized.

Measurement

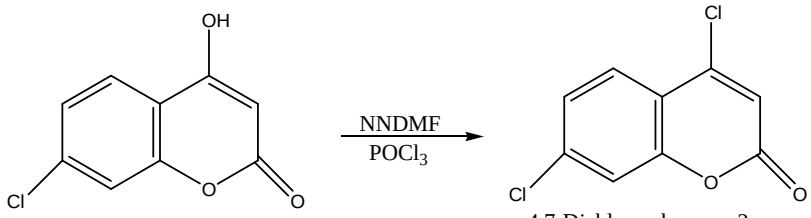
The identification of derivatives 7-Chloro-4-hydroxy-chromen-2-one **(1a,2a,3a)** , is made by using melting point , IR , 1H NMR , 13C NMR spectra and elemental analysis. Melting point was determined on a Electrothermal apparatus (Fisher Scientific 2555) in a open capillary tube and are uncorrected. Infrared spectra were recorded in cm-1 for KBr pellts 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. Element analysze 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 vapour for visualization.

Preparation of (1a) 4,7-Dichloro-chromen-2-one

For this synthesis is used as substrate 7-Chloro-4-hydroxy-chromen-2-one in a 100 ml flask mixed 3 g N.NDMF , and 2 ml $POCl_3$.

The mixture was refluxed at 50 ^{o}C for ca. 60 min. 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 220 ^{o}C.

(Scheme.1)



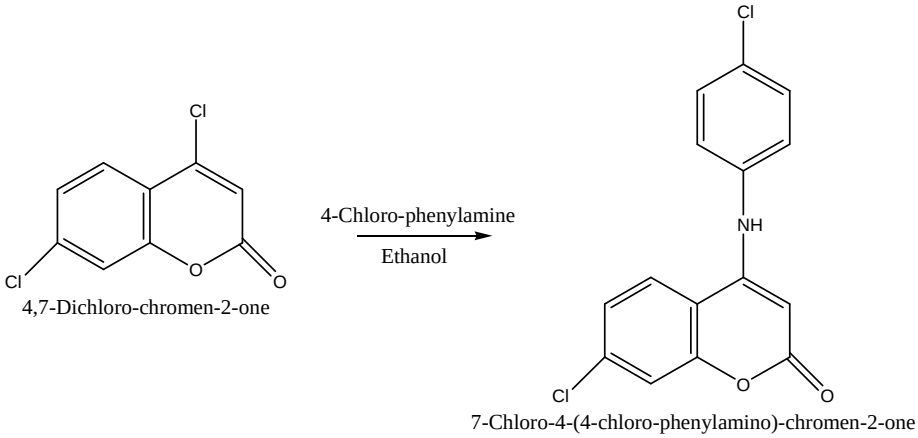
7-Chloro-4-hydroxy-chromen-2-one 4,7-Dichloro-chromen-2-one

Preparation of 7-chloro-4-(4-chloro-phenylamino)-chromen-2-one**(2a)**

In a 100 ml flask were mixed 3g 7-chloro-4-(4-chloro-phenylamino)-chromen-2-one with 8ml C_2H_5OH, 2g 4-chloro-phenylamine .The mixture was refluxed at 80 ^{o}C for ca. 12h.

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, 245 ^{o}C.

(Scheme 2) .



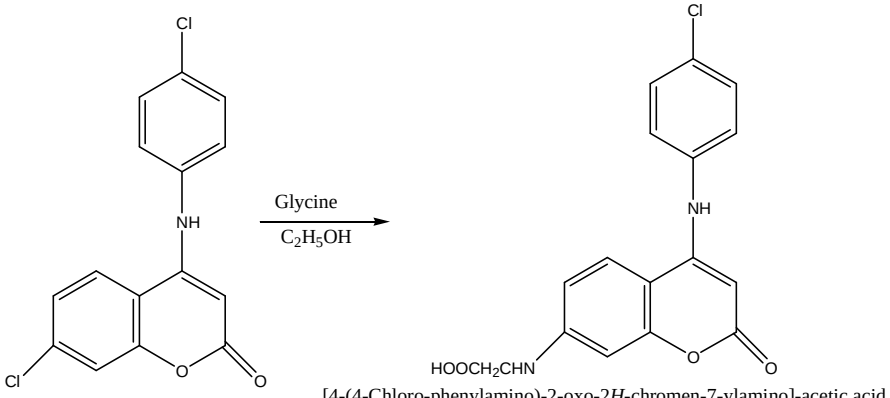
4,7-Dichloro-chromen-2-one 7-Chloro-4-(4-chloro-phenylamino)-chromen-2-one

Preparation of [4-(4-chloro-phenylamiono)-2-oxo-2H-chromen-7-ylamino]-acetic acid **(3a)**

In a 100 ml flask were mixed 2g of 7-chloro-4-(4-chloro-phenylamino)-chromen-2-one, 2g Glycine, with 6 ml C_2H_5OH and 0,2 ml Et_3N as catalyzer. The mixture was refluxed at 95 ^{o}C in water bath for ca. 22 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 yellow product at 70% yield, melting. point;180 ^oC.

(Scheme 3).



7-Chloro-4-(4-chloro-phenylamino)-chromen-2-one

[4-(4-Chloro-phenylamino)-2-oxo-2*H*-chromen-7-ylamino]-acetic acid

Table-1 Analytical data

Comp'd	m.p	M.F	Elemental analysis. Calculatet :Found (calc) %				
			C	H	N	O	Cl
1a	215 ^oC	$C_9H_4Cl_2O_2$	50.27 50.20	1.87 1.85		14.88 14,70	32.97 32.95
2a	306 ^oC	$C_{15}H_9Cl_2NO_2$	58.85 58.80	2.96 2.95	4.58 4.50	10.45 10.42	23.16 23.12
3a	345 ^oC	$C_{17}H_{13}ClN_2O_4$	59.23 59.20	3.80 3.80	8.13 8.11	18.56 18.53	10.28 10.25

Table 2 Antibacterial activity- *Staphylococcus aureus*

	Inhibition zone (mm)		
Compound	2mg/ml	3mg /ml	5mg/ml
1a	13	17	19
2a	14	18	21
3a	15	18	22
Cephalexine	9	9	0
Streptomycine	20	20	20

Table 3 Antibacterial activity – *E. coli*

	Inhibition zone (mm)		
Compound	2mg/ml	3mg /ml	5mg/ml
1a	10	15	19
2a	11	17	21
3a	12	18	22
Cephalexine	9	9	9
Streptomycine	20	20	20

Table 4 Antibacterial activity – *Bacillus cereus*

	Inhibition zone (mm)		
Compound	2mg/ml	3mg /ml	5mg/ml
1a	9	14	20
2a	10	15	21
3a	13	19	24
Cephalexine	9	9	9
Streptomycine	20	20	20

Antibacterial activity

The purified synthesized compounds (1a, 2a, 3a) was 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)

RESULTS AND DISCUSSION

By reacting equimolar amounts of 7-Chloro-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 4,7-Dichloro-chromen-2-one and corresponding reagents (according scheme 2) under reflux reaction conditions product 2a is synthesized in 70 % yield.

By reacting equimolar amounts of 7-chloro-4-(4-chloro-phenylamino)-chromen-2-one and corresponding reagents (according scheme 3) under reflux reaction conditions product 3a is synthesized in 70% yield.

The structure of 7-Chloro-4-hydroxy-chromen-2-one derivatives (1a, 2a, 3a) were determined from their IR, ^{1}H NMR, ^{13}C NMR spectra and their melting points as follows.

For (1a); IR bands (KBr, cm-1) 2720 cm^{-1} (C-H stretch.), 1720 cm^{-1} (C=O) , 1600 (C=C stretch.) , 750 cm^{-1} (C-H bend.) 600 cm^{-1} (C-Cl stretch.)

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

^{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)

For (2a) IR bands (KBr, cm -1) 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) , 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)

For (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 carbocylic),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 11.0ppm s(H,COOH), 7.4 ,6.5,6.4 (3H aromatic), 4.0 s(H,NH) , 3.53ppm t(2CH_2OH), 2.65ppm t(2H,CH_2N) , 1.48-1.52ppm t(4H,2CH_2), 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 (2C,2CH_2)

CONCLUSION

From the results the following conclusion were drawn: The study provides the first evidence that compounds (1a,2a,3a) obviously inhibit the growth of *S. aureus, 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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