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Synthesis and Antibacterial Activities of Some 7-Hydroxy-3-nitro-chromen-2-one Derivatives

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ABSTRACT

In present paper , we report the organic syntheses of four compounds from **7-Hydroxy-3-nitro-chromen-2-one** and describe the results of antibacterial activity of purified compounds. Compounds 7-Hydroxy-3-hydroxyamino-chromen-2-one **(1a)** , Benzoic acid 3-(benzoyl-hydroxy-amino)-2-oxo-2H-chromen-7-yl ester **(2a)**, Benzoic acid 3-(benzoyl-hydroxy-amino)-8-(2-chloro-ethyl)-4-(2,5-dioxo-pyrrolidin-1-yl)-2-oxo-2H-chromen-7-yl ester **(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 at concentrations of 1mg/ml, 3mg/ml and 5mg/ml , has been evaluated against two strains of bacterial culture; Staphylococcus aureus, and Klebsiella. The compounds show bacteriostatic and bactericidal activity.

Keywords: 7-Hydroxy-3-nitro-chromen-2-one, coumarine derivatives, antibacterial activity , Staphylococcus aureus, Klebsiella, streptomycin.

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INTRODUCTION

Starting from 7-Hydroxy-3-nitro-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 activities. Their fame has come mainly from their antithrombic, antiinflammatory, vasodilatory, and antiviral activities. Other several coumarin derivatives have antimicrobial properties, have urged us to synthesize some new coumarin derivatives and to investigate their antibacterial activity against staphylococcus aureus, E.coli and Klebsiella. The antibacterial activity of synthesized compounds is compared with antibacterial activity of Cefalexine [1-12].

MATERIALS AND METHODS

Experimental Chemistry

Compounds 7-Hydroxy-3-hydroxyamino-chromen-2-one **(1a)** , Benzoic acid 3-(benzoyl-hydroxy-amino)-2-oxo-2H-chromen-7-yl ester **(2a)**,Benzoic acid 3-(benzoyl-hydroxy-amino)-8-(2-chloro-ethyl)-4-(2,5-dioxo-pyrrolidin-1-yl)-2-oxo-2H-chromen-7-ylester **(3a)**, are synthesized. The identification of 2H-chromen-2-one derivatives (1a,2a,3a,) , is made by using melting point , infrared , ^{1}H NMR , ^{13}C NMR spectra and elemental analysis. Melting point was determinate on an Electro thermal apparatus (Fisher Scientific 2555) in an open capillary tube and is 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-d_6 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 analyze 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.

Synthesis of 7-Hydroxy-3-hydroxyamino-chromen-2- one (1a)

For this synthesis is used as substrat 7-Hydroxy-3-nitro-chromen-2-one in a 100 ml flask, mixed 3g of 7-Hydroxy-3-nitro-chromen-2-one with 10ml C_2H_5OH, 1g Zn, 3g NH_4Cl. The mixture was refluxed at 350 ^{o}C for ca. 140 min. The obtained crystals brown are filtered and rinsed with ethanol and dried at room temperature. Recrystallization form absolute ethanol gave a red product of 80% yield, melting point 140^{o}C.

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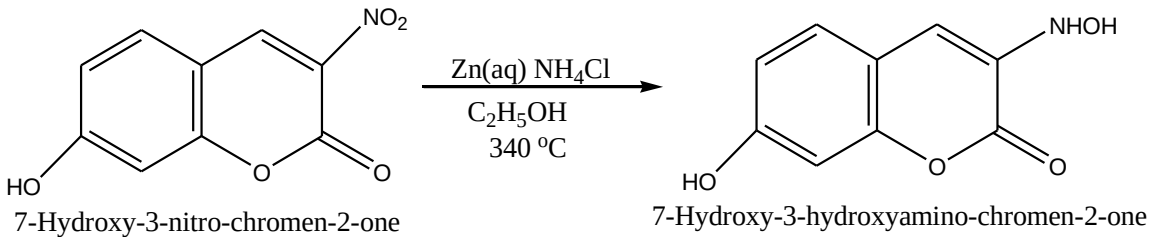


7-Hydroxy-3-nitro-chromen-2-one

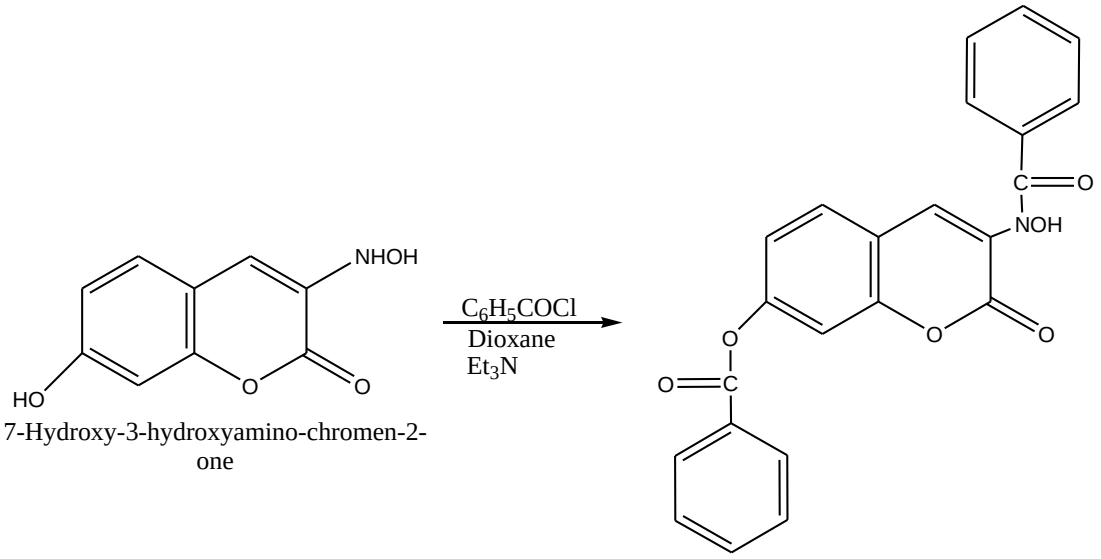
7-Hydroxy-3-hydroxyamino-chromen-2-one

Scheme 1 Synthesis of 7-Hydroxy-3-hydroxyamino-chromen-2- one (1a)

Synthesis of Benzoic acid 3-(benzoyl-hydroxy-amino)-2-oxo-2H-chromen-7-yl ester (2a)

In a 100 ml flask were mixed 2.5g of 7-Hydroxy-3-hydroxyamino-chromen-2- one , with 5ml C_2H_5OH , 2ml C_6H_5COCl , 0.3 ml Et_3N .

The mixture was refluxed at 80 ^oC for ca. 1.5 h. The obtained yellow crystals are filtered and dried at room temperature. Recrystallization form C_2H_5OH gave yellow crystals product of 70% yield, meltingpoint, 137 ^oC. (Scheme 2).



7-Hydroxy-3-hydroxyamino-chromen-2-one

Benzoic acid 3-(benzoyl-hydroxy-amino)-2-oxo-2*H*-chromen-7-yl ester

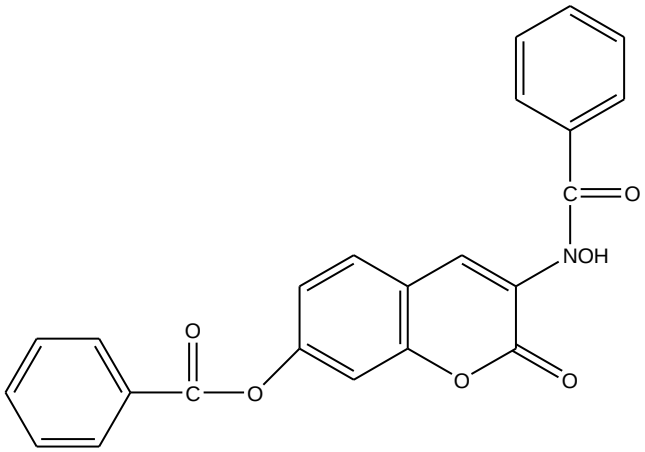
Scheme 2 - Benzoic acid 3-(benzoyl-hydroxy-amino)-2-oxo-2H-chromen-7-yl ester (2a)

Synthesis of Benzoic acid 3-(benzoyl-hydroxy-amino)-8-(2-chloro-ethyl)-4-(2, 5-dioxo-pyrrolidin-1-yl)-2-oxo-2H-chromen-7-yl ester (3a).

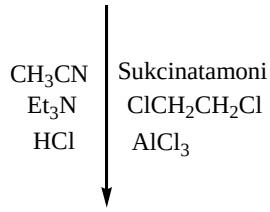
In a 100 ml flask were mixed 1.5g Benzoic acid 3-(benzoyl-hydroxy-amino)-2-oxo-2H-chromen-7-yl ester with 4 ml CH_3CN and 1g Sukcinatamon. The mixture was refluxed at 92 ^oC in

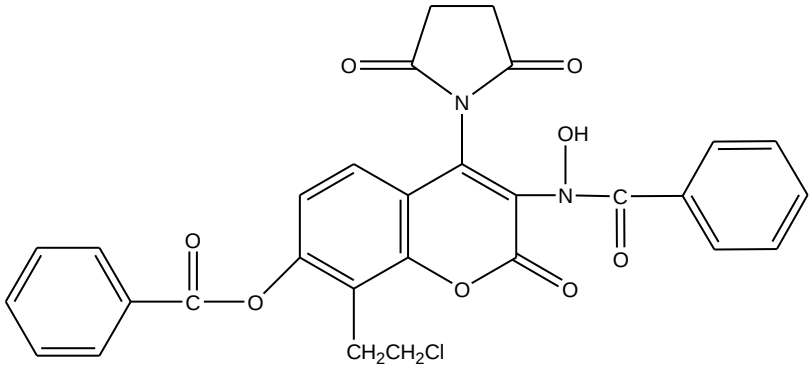
water bath for ca. 3 h .The flask was placed in an ice bath for 1h until yellow crystalline precipitate was formed.

After filtration the product was recrystallized from CH_3CN .The recrystallization gave a yellow product at 70% yield, meltingpoint; 180oC. (Scheme 3**)**.



Benzoic acid 3-(benzoyl-hydroxy-amino)-2-oxo-2*H*-chromen-7-yl ester





Benzoic acid 3-(benzoyl-hydroxy-amino)-8-(2-chloro-ethyl)-4-(2,5-dioxo-pyrrolidin-1-yl)-2-oxo-2*H*-chromen-7-yl ester

Scheme 3-Synthesis. Benzoic acid 3-(benzoyl-hydroxy-amino)-8-(2-chloro-ethyl)-4-(2, 5-dioxo-pyrrolidin-1-yl)-2-oxo-2H-chromen-7-yl ester (3a)

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RESULTS

Antibacterial activity

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

Table 1 Antibacterial activity- Staphylococcus aureus and the comparison with Cefalexine. Inhibition zone (mm)

Compound	2mg/ml	3mg /ml	5mg/ml
1a	10	13	15
2a	11	14	19
3a	8	10	18
Cefalexine	9	9	9 10 µg

Table 2 Antibacterial activity – Klebsiella and the comparison with Cefalexine. Inhibition zone (mm)

Compound	2mg/ml	3mg /ml	5mg/ml
1a	12	19	23
2a	11	14	21
3a	8	12	23
Cefalexine	11	11	11 10 µg

Table 3

Compound	IR (cm^{-1})	^{1}H NMR ppm	^{13}C NMR ppm
1a	3420 (OH ,3370 (NH), 3010(C-H) ar, 1720(C=O), 1570(C=C)ar, 1385(C-O),750(C-H)ar	**δ**. 2.0 d(,H,NH), 2.1 d(H,OH) 5.0t (H,OH), 6.54-6.69m(4H,ar)	**δ**. 162(C,COO),156(C-O) 152(C,CO),137.9(C=C-NHOH), 108-128(5C,ar)
2a	3417 (OH) , 3008(C-H)ar 2912(C-H),1740(C=O) , 1600(C=C) , 1285(C-O),720(C-H)ar	**δ**.2.0d(H-OH) .11-8.14m(14H,ar)	**δ .** 164(COO),162(COO), 157(NHCO),151(C-O) 124(C=C-NOH) 119-135.5(18C,ar)
3a	3419 (OH),3009(C-H)ar , 2850 (C-H)al, 1730(C-H),1275(C-O), 1250(C-O),740(C-H)ar 660(C-I)	**δ**. 2.0s(H-OH), 3.73t(CH_2CO) 2.83t(4H,2CH_2) 3.71s(2H,CH_2Cl) 7.16-8.14m(12H,ar)	**δ**.169(C,CON),157(C,CON) 150.6(C,C-O),127.8(C-N), 99.1(C=C-NOH),47(C,CH_2Cl),26.9(CH_2) 19(CH_2),118-133(18C,ar)

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Table-4 Analytical data

Compd	Yield (%)	m.p	M.F	Elemental analysis. Calculated (found) (%)				
				C	H	N	O	Cl
1a	80	140°C	$C_9H_{17}NO_4$	55.96 55.50	3.65 3.40	7.25 6.90	3.13 3.30	
2a	70	137°C	$C_{23}H_{15}NO_6$	66.33 66.90	3.70 3.50	3.49 3.30	23.92 24.00	
3a	70	180°C	$C_{29}H_{21}ClN_2O_8$	62.09 62.30	3.77 3.40	4.99 4.50	22.82 21.90	6.32 6.50

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 Staphylococcus auerus , and Klebsiella.

The compounds **(1a, 2a, 3a)** compared with the antibacterial activity of Cefalexine in S.aureus , and Klebsiella.

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

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