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Antibacterial Activity of Coumarine Derivatives Synthesized from 4-Chloro-chromen-2-one. The Comparison with Standard Drug

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ABSTRACT

In present paper, we report the organic syntheses of four compounds from 4-Chloro-chromen-2-one and describe the results of antibacterial activity of purified compounds. Compounds 4-Butylamino-chromen-2-one (1a) , 4-Butylamino-2-oxo-2H-chromene-3-sulfonyl chloride (2a) , 4-Butylamino-2-oxo-2H-chromene-3-sulfonic acid (2-hydroxy-phenyl)-amide (3a), 4-Butylamino-5-ethyl-2-oxo-7-(N'-phenyl-hydrazino)-2H-chromene-3-sulfonic acid (2-hydroxy-phenyl)-amide (4a) , 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 , have been evaluated against three strains of bacterial culture; Staphylococcus aureus, E.coli and Klebsiella. The compounds show bacteriostatic and bactericidal activity.

Keywords: 4-Chloro-chromen-2-one , coumarine derivatives , antibacterial activity , Staphylococcus aureus, E.coli , Klebsiella, streptomycin.

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INTRODUCTION

Starting from **4-Chloro-chromen-2-one (a);** derivatives (1a, 2a, 3a, 4a) 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, anti-inflammatory, vasodilator , 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 streptomycin [1-14].

MATERIALS AND METHODS

Experimental Chemistry

Compounds 4-Butylamino-chromen-2-one **(1a)** , 4-Butylamino-2-oxo-2H-chromene-3-sulfonyl chloride **(2a)** , 4-Butylamino-2-oxo-2H-chromene-3-sulfonic acid (2-hydroxy-phenyl)-amide **(3a)**, 4-Butylamino-5-ethyl-2-oxo-7-(N'-phenyl-hydrazino)-2H-chromene-3-sulfonic acid (2-hydroxy-phenyl)-amide **(4a),**are synthesized.

The identification of 2H-chromen-2-one derivatives (1a,2a,3a,4a) , is made by using melting point , infrared , ^{1}H NMR , ^{13}C NMR spectra and elemental analysis. Melting point was determinate on a Electro thermal apparatus (Fisher Scientific 2555) in a 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-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 4-Butylamino-chromen-2-one (1a)

For this synthesis is used as substrate 4-Chloro-chromen-2-one in a 100 ml flask mixed 3 g of 4-Chloro-chromen-2-one with 8ml C_2H_5OH , equivalent amount Butylamino. The mixture was refluxed at 250 ^{o}C for ca. 90 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 117^{o}C.

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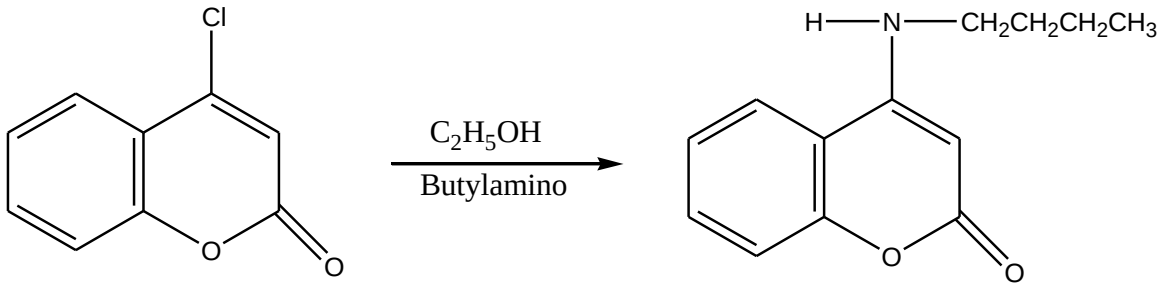


4-Chloro-chromen-2-one

a

4-Butylamino-chromen-2-one

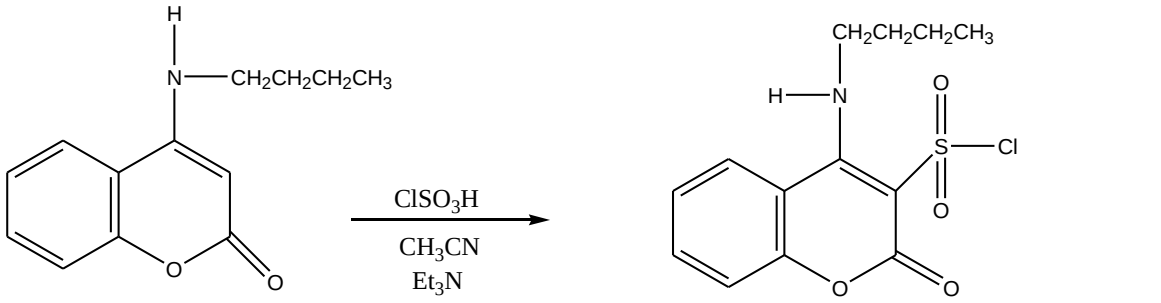
1a

Scheme 1 - Synthesis of Compounds 4-Butylamino-chromen-2-one **(1a)**

Synthesis of 4-Butylamino-2-oxo-2H-chromene-3-sulfonyl chloride **(2a)**

In a 100 ml flask were mixed 2.5g of 4-Butylamino-chromen-2-one, with 5ml CH_3CN , 1ml $ClSO_3H$, 0.3 ml Et_3N .

The mixture was refluxed at 80 ^oC for ca. 1.5 h . The obtained brown crystals are filtered and dried at room temperature . Recrystallization form C_2H_5OH gave brown crystals product of 70% yield, meltingpoint, 287 ^oC. (Scheme 2) .



4-Butylamino-chromen-2-one

1a

4-Butylamino-2-oxo-2*H*-chromene-3-sulfonyl chloride

2a

Scheme 2 - Synthesis of 4-Butylamino-2-oxo-2H-chromene-3-sulfonyl chloride (2a)

Synthesis of 4-Butylamino-2-oxo-2H-chromene-3-sulfonic acid (2-hydroxy-phenyl) -amide **(3a)**

In a 100 ml flask were mixed 1.5g 4- Butylamino – 2 – oxo - 2H- chromene - 3- sulfonyl chloride with 4 ml Dioxane and 1g aminophenol , 0.2 ml HCl , 0,2 ml Et_3N as katalyzer. The mixture was refluxed at 92 ^oC in water bath for ca. 2 h .The flask was placed in an ice bath for 1h until yellow crystalline precipitate was formed.

After filtration the product was recrystallized from ethanol .The recrystallization from ethanol gave a yellow product at 70% yield, melting point; 180^oC. (Scheme 3).

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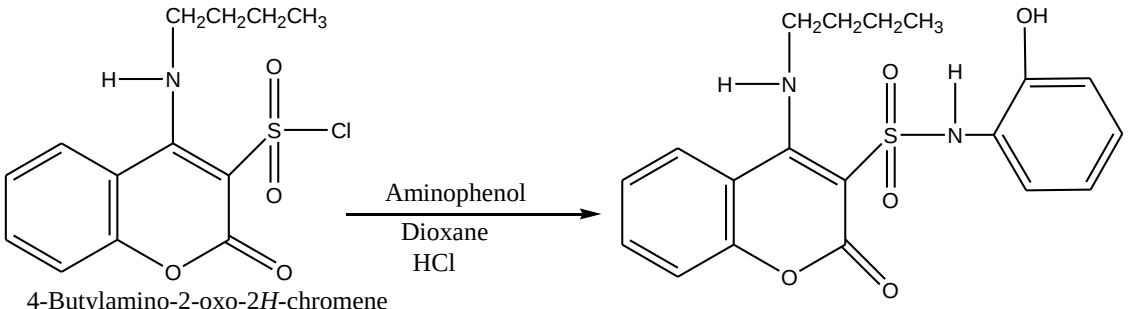

4-Butylamino-2-oxo-2*H*-chromene -3-sulfonyl chloride

2a

4-Butylamino-2-oxo-2*H*-chromene-3-sulfonic acid (2-hydroxy-phenyl)-amide

3a

Scheme 3 - Synthesis of 4-Butylamino-2-oxo-2H-chromene-3-sulfonic acid (2-hydroxy-phenyl) -amide (3a)

Synthesis of 4 – Butylamino – 5 – ethyl -2 – oxo -7 - (N' – phenyl – hydrazine)- 2H-chromene-3-sulfonic acid (2-hydroxy-phenyl)-amide **(4a)**

In a 100 ml flask were mixed 1g of 4-Butylamino-2-oxo-2H-chromene-3-sulfonic acid (2-hydroxy-phenyl) – amide **,** 0.8g phenylhidrazine with 4ml C_2H_5OH ,0.5ml $ClCH_2CH_3$, 0.2 ml Et_3N and 0.2 ml HCl. The mixture was refluxed at 95 ^oC in water bath for ca. 2 h .The obtained red crystals are filtered and rinsed with CH_3CN and dried at room temperature. Recrystallization from ethanol gave a red product at 60 % yield , melting point 204 ^oC. (Scheme 4)

Antibacterial activity

The purified synthesized compounds (1a,2a,3a,4a) was subjected to test in vitro its antibacterial activity against three bacterial cultures ; *Staphylococcus aureus, E.Coli* and Klebsiella. Antibacterial activity of compounds was investigated applying the Kirby-Bayer method [14] or disc method (d=5.5 mm max. capacity 10 µg)

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

Compound	2mg/ml	3mg /ml	5mg/ml
1a	10	13	15
2a	18	20	24
3a	19	21	25
4a	11	13	18
Streptomycin	20	20	20 10 µg

Table 2 Antibacterial activity – E.coli and the comparison with Streptomycin Inhibition zone (mm)

Compound	2mg/ml	3mg /ml	5mg/ml
1a	5	9	14
2a	10	15	21
3a	12	17	23
4a	11	15	20
Streptomycine	23	23	23 10 µg

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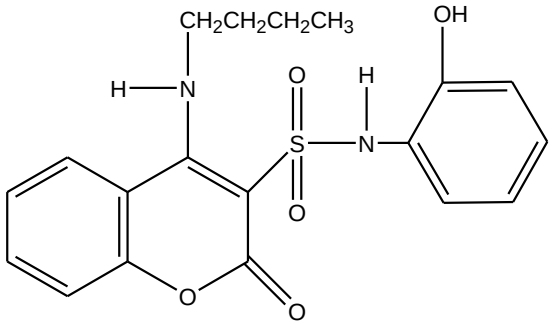
Table 3 Antibacterial activity – Klebsiella and the comparison with Streptomycin Inhibition zone (mm)

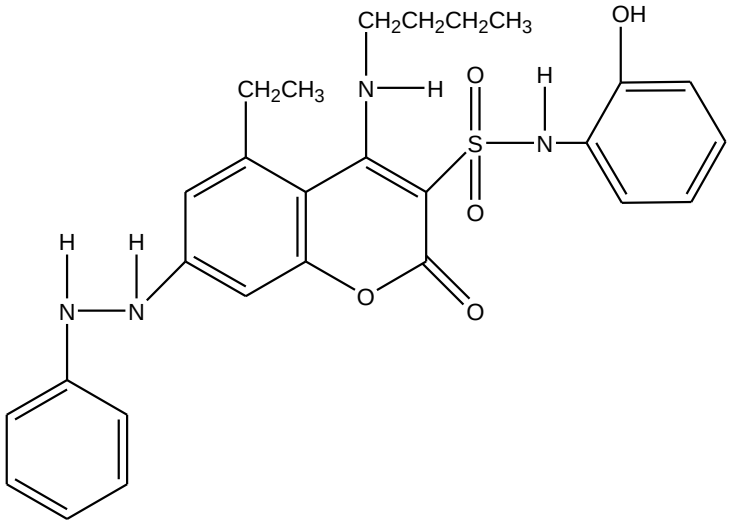
Compound	2mg/ml	3mg /ml	5mg/ml
1a	12	19	23
2a	13	18	25
3a	13	19	24
4a	10	17	21
Streptomycine	23	23	23 10 µg



4-Butylamino-2-oxo-2*H*-chromene-3-sulfonic acid (2-hydroxy-phenyl)-amide

3a

C_2H_5OH | Phenylhydrazino
HCl | $ClCH_2CH_3$
Et_3N | $AlCl_3$



4-Butylamino-5-ethyl-2-oxo-7-(*N*'-phenyl-hydrazino)-2*H*-chromene-3-sulfonic acid (2-hydroxy-phenyl)-amide

4a

Scheme 4- Synthesis of 4 – Butylamino – 5 – ethyl -2 – oxo -7 - (N' – phenyl – hydrazine)- 2H-chromene-3-sulfonic acid (2-hydroxy-phenyl)-amide (4a)

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Table 4

Compound	IR (cm^{-1})	^{1}H NMR ppm	^{13}C NMR ppm
1a	3370 (NH), 3010(C-H) ar, 2962(C-H)aliphatic 1720(C=O),1570(C=C)ar, 1385(C-O),750(C-H)ar	**δ**.0.96 s(3H,CH_3) 1.33 d(,4H,2CH_2) 1.55-2.0 d(,H,NH-CH_2) 2.65 s(,H,NH), 7.20-7.60m(,5H,ar)	**δ**. 166(C-NH),162(C,COO), 150(C-O),121-128(5C,ar) 88.9(C=C-H),46.3(C-NH) 34.8(C,CH_2),20.6(C,CH_2) 13.7(C,CH_3)
2a	3370(N-H),3008(C-H)ar 2960(CH)alifatic, 1740(C=O),1600(C=C) 1380(SO_2Cl),1285(C-O) 720(C-H)ar	**δ**.0.96 s(,3H,CH_3) 1.33-1.55,d(4H,2CH_2) 2.65 s(H,NHCH_2) 3.0 s(H,NH)ar 7.20-7.63m(4H,ar)	**δ**.167(C-NH),162(COO), 150.8(C-O),121-128(6C,ar) 89(C-SO_2),46.3(C-NH) 34.8(C,CH_2),20.6(C,CH_2) 13.7(C,CH_3)
3a	3400(OH),3300(NH), 3265(SO_2NH),3009 (C-H)ar, 2850 (C-H)al, 1730(C=O),1528(C=C) ar, 1280(N-H),1275(C-O), 1250(C-O),740(C-H)ar	**δ**. 0.96s(3H,CH_3) 1.33-1.55d(4H,2CH_2) 2.65s(H,NHCH_2) 3.0s(H,NH), 4.0s(H,NHSO_2) 5.0s(H,OH) 6.29-6.63m(8H,ar)	**δ**.167(C-NH),162(COO), 150(C-O),144(C-O), 134(C-NH),116-127(9C,ar) 46.2(C-NH)20.6(C,CH_2) 13.7(C,CH_3)
4a	3387(O-H),3330(N-H) 3270(SO_2NH),3010(C-H)ar 2900(C-H)al ,1728(C=O) 1600(C=C)ar,1280(N-H) 1270(C-O),750(C-H)ar	**δ.**0.96-1.24d(6H,2CH_3) 1.33-1.55d(4H,2CH_2) 2.0s(H,NH),2.65s(H,NH) 2.59s(H,CH_2),4.0t(H,NH) 5.0s(H,OH) 6.29-7.18m(11H,ar)	**δ**. 167(C-NH),162(COO), 151(C-O),144(C-O), 142(C-NH), 102-138(17C,ar),89(C-SO_2) 46.3(C-NH),22.5(C,CH_2) 13.7(C,CH_3),10.5(C,CH_3)

Table-5 Analytical data

Compd	Yield (%)	m.p	M.F	Elemental analysis. Calculated (found) (%)					
				C	H	N	O	Cl	S
1a	80	117°C	$C_{13}H_{15}NO_2$	71.87 72.00	6.96 7.11	6.45 6.15	14.73 14.32		
2a	70	287°C	$C_{13}H_{14}ClNO_4S$	49.45 50.00	4.47 5.00	4.44 4.11	20.27 20.00	11.23 11.00	10.15 9.80
3a	70	180°C	$C_{19}H_{20}N_2O_5S$	58.75 60.00	5.19 4.90	7.21 7.10	20.59 19.92		8.20 8.00
4a	60	204°C	$C_{27}H_{30}N_4O_5S$	62.05 61.50	5.79 5.20	10.72 10.0	15.31 15.00		6.14 6.00

CONCLUSION

From the results the following conclusion was drawn: The study provides the first evidence that compounds **(1a, 2a, 3a, 4a)** obviously inhibit the growth of *Staphylococcus auerus* , *E.coli* and *Klebsiella*.

The compounds **(1a, 2a, 3a, 4a)** compared with the antibacterial activity of *Streptomycin* in *S.aureus*, and *Klebsiella*.

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

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