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Characterization, Biological activity and synthesis of new derivatives of Chromen-2-one

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Abstract

We report the organic syntheses of new derivatives from Chromen-2-one and their antibacterial activity. Compounds 3-Hydroxy-4-(2-oxo-2H-chromen-4-ylamino) - benzenesulfonyl chloride **(1a)**, 4-[3-(acetyl-phenyl-sulfamoyl)-2-oxo-2H-chromen-4-ylamino]-3-hydroxy-benzenesulfonyl chloride **2a**

4-[3-(Acetyl-phenyl-sulfamoyl)-4-(4-chlorosulfonyl-2-hydroxy-phenylamino-2-oxo-2H-chromen-7-ylamino]-isophthalic acid **3a.**

All Structures have been synthesized and characterized using melting points, IR spectra, ^{1}H-NMR, ^{13}C-NMR spectra, and elemental analyses. The purified synthesized compounds (**1a,2a,3a)**, at concentrations 2,3,5 mg/ml was tested for their antibacterial activity against three bacterial cultures; Staphylococcus aureus, Escherchia coli and Bacillus cereus. The antibacterial activity of synthesized compounds are compared with antibacterial activity of standard antibiotics cephalexine and streptomycine.

The compounds **(1a,2a,3a)** shows different bacteriostatic and bacteriocidal activity.

Keywords: Chromen-2-one derivatives streptomycine

1.Introduction

Starting from Chromen-2-one (a); are synthesized some new derivatives 1a,2a,3a (Schemes 1,2,3). Coumarine derivatives are large group of heterocyclic with oxygen as heteroatom.Coumarine 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.

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 coumarine 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.

Material and Methods

2.Experimental Chemistry

Compounds 4-[Acetyl-(2-oxo-2H-chromen-4-yl)-amino]-benzenesulfonyl chloride **1a**,

4-[Acetyl-(2-oxo-3-phenylsulfamoyl-2H-chromen-4-yl)-amino]-benzenesulfonyl chloride **2a**,2-{4-[Acetyl-(4-chlorosulfonyl-phenyl)-amino]-2-oxo-3-phenylsulfamoyl-2H-chromen-7-ylamino}-benzoic acid **3a.**, are synthesized.

2.1. Measurement

The identification of Chromen-2-one derivatives **(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 a open capillary tube and wa not corrected. 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 3-Hydroxy-4-(2-oxo-2H-chromen-4-ylamino)-benzenesulfonyl

chloride **(1a)**

For this synthesis is used 5g Chromen-2-one as substrate, 5g Amino-phenol, and 0.5ml HCl, 5ml HSO_3Cl,10ml CH_3CN, 1 ml Et_3N as catalyze.

The mixture was refluxed at 65 ^{o}C for ca. 1h.

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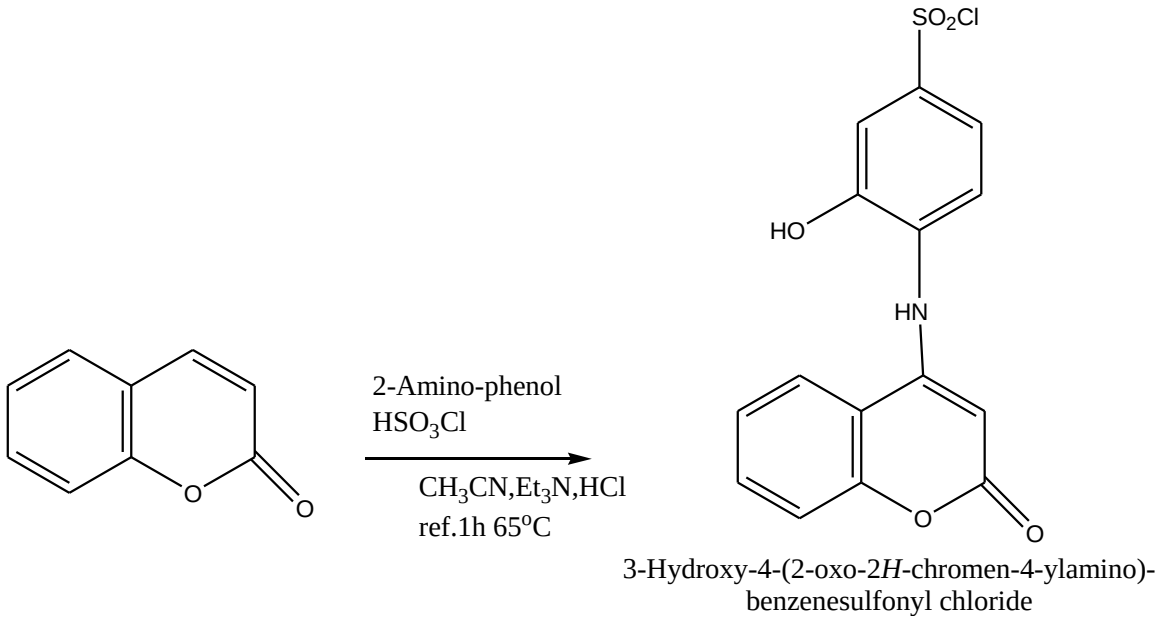
The obtained crystals are filtred and rinsed with CH_3CN and dried at room temperature. Recrystallization form absolute CH_3CN gave a yellow product of (80% yield, melting point 298 ^{o} C.



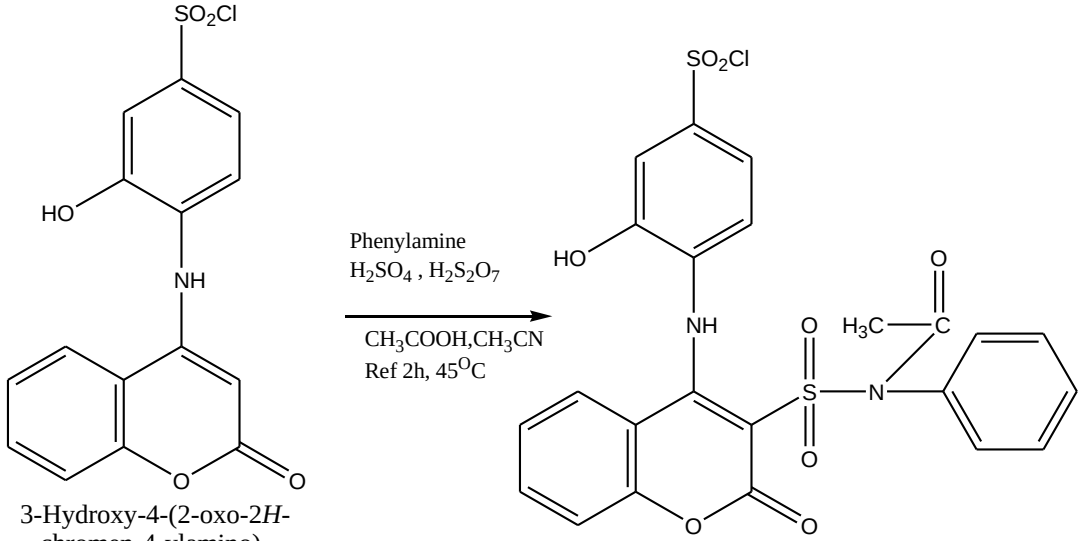
3-Hydroxy-4-(2-oxo-2*H*-chromen-4-ylamino)-benzenesulfonyl chloride

Figure 1. 3-Hydroxy-4-(2-oxo-2H-chromen-4-ylamino)-benzenesulfonyl chloride**(1a)**

Preparation of 4-[3-(acetyl-phenyl-sulfamoyl)-2-oxo-2H-chromen-4-ylamino]-3-hydroxy-benzenesulfonyl chloride **(2a)**

In a 100 ml flask were mixed 3g 3-Hydroxy-4-(2-oxo-2H-chromen-4-ylamino)-benzenesulfonyl chloride with 6 ml phenylamine, 3ml H_2SO4, 2ml $H_2S_2O_7$, 10 ml CH_3CN and 1ml Et_3N,3ml CH_3COOH the mixture was refluxed at 45 ^{o}C for ca. 2h.

The obtained crystals are filtred and dried at room temperature. Recrystallization form CH_3CN gave yellow crystals product of 75 % yield, meltingpoint, 315 ^{o}C.



3-Hydroxy-4-(2-oxo-2*H*-chromen-4-ylamino)-benzenesulfonyl chloride

4-[3-(Acetyl-phenyl-sulfamoyl)-2-oxo-2*H*-chromen-4-ylamino]-3-hydroxy-benzenesulfonyl chloride

Figure 2. 4-[3-(acetyl-phenyl-sulfamoyl)-2-oxo-2H-chromen-4-ylamino]-3-hydroxy-benzenesulfonyl chloride

Preparation of 4-[3-(Acetyl-phenyl-sulfamoyl)-4-(4-chlorosulfonyl-2-hydroxy-phenylamino-2-oxo-2H-chromen-7-ylamino]-isophthalic acid **(3a)**

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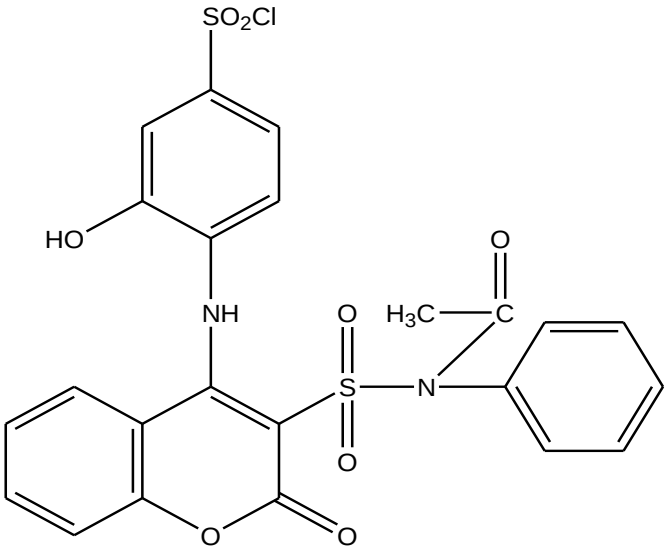
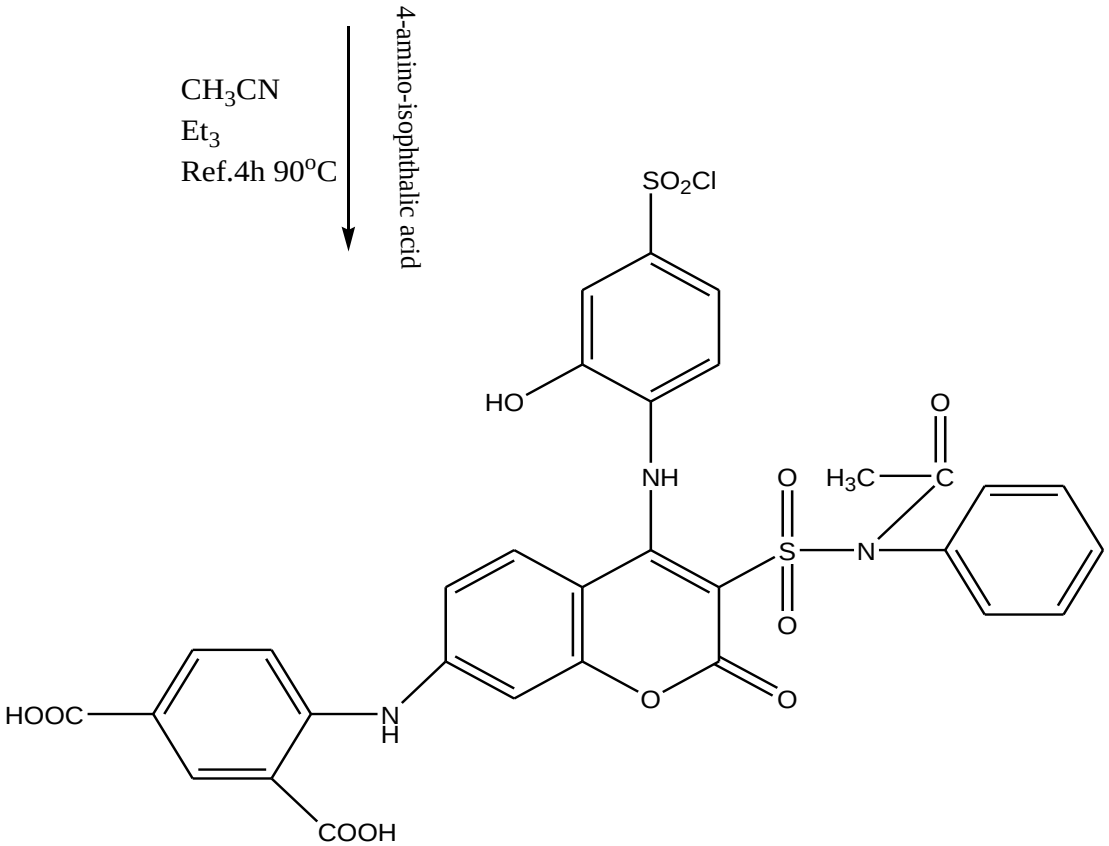
In a 100 ml flask were mixed 2.5g, 4-[3-(Acetyl-phenyl-sulfamoyl)-2-oxo-2H-chromen-4-ylamino]-3-hydroxy-benzenesulfonyl chloride with 10ml Acetonitrile, 3g 2-amino benzoic acid, 0.5ml Et_3N as katalyzer.The mixture was refkuxed at 45 ^oC in water bath for ca.2h. After filtration the product was recrystallized from C_2H_5OH the recrystallizacion gave a red product at 70% yield, melting point; 322 ^oC.



4-[3-(Acetyl-phenyl-sulfamoyl)-2-oxo-2*H*-chromen-4-ylamino]-3-hydroxy-benzenesulfonyl chloride



4-[3-(Acetyl-phenyl-sulfamoyl)-4-(4-chlorosulfonyl-2-hydroxy-phenylamino)-2-oxo-2*H*-chromen-7-ylamino]-isophthalic acid

Figure 3: 4-[3-(Acetyl-phenyl-sulfamoyl)-4-(4-chlorosulfonyl-2-hydroxy-phenylamino-2-oxo-2H-chromen-7-ylamino]-isophthalic acid (3a)

Table-1: characteristics and analytical data of the complexes

Comp	Yeld %	m.p	M.F	C	S	Cl	H	N	O
1a	80	298 °C	$C_{17}H_{12}ClNO_5S$	54.05 53.92	8.49 8.45	9.38 9.30	3.20 3.10	3.71 3.68	21.17 21.14
2a	75	315 °C	$C_{23}H_{17}ClN_2O_7S$	51.82 51	12.01 11.94	6.65 6.60	3.21 3.18	5.26 5.21	21.01 20.90
3a	70	322 °C	$C_{28}H_{20}ClN_3O_9S_2$	52.38 52.0	9.99 9.94	5.52 5.49	3.14 3.12	6.54 6.52	22.43 22.39

2.2. 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)

Table 2 Antibacterial activity- Staphylococcus aureus

Inhibition zone (mm)

Compound	2mg/ml	3mg /ml	5mg/ml	
1a	11	16	19	
2a	11	17	18	
3a	10	17	17	
Cefalexine	9	9	9	10 µg
Streptomycine	20	20	20	10 µg

Table 3 Antibacterial activity – E.Coli

Inhibition zone (mm)

Compound	2mg/ml	3mg /ml	5mg/ml	
1a	10	11	17	
2a	11	12	18	
3a	11	13	19	
Cephalexine	9	9	9	10 µg
Streptomycine	23	23	23	10 µg

Table 4 Antibacterial activity – Bacillus cereus

Inhibition zone (mm)

Compound	2mg/ml	3mg /ml	5mg/ml	
1a	11	15	21	
2a	10	15	22	
3a	12	18	24	
Cephalexine	9	9	9	10 µg
Streptomycine	23	23	23	10 µg

3.RESULTS AND DISCUSSION

By reacting equimolar amounts of Chromen-2-one and correspomding reagents (according scheme 1) under reflux reaction condictions product **1a** is synthesized in 80 % yield.

By reacting equimolar amounts of 3-Hydroxy-4-(2-oxo-2H-chromen-4-ylamino)-benzenesulfonyl chloride **1a** and corresponding reagents (according scheme 2) under reflux reaction condictions product4-[3-(acetyl-phenyl-sulfamoyl)-2-oxo-2H-chromen-4-ylamino]-3-hydroxy-benzenesulfonyl chloride **2a** is synthesized in 75 % yield.

By reacting equimolar amounts of **2a**, and corresponding reagents (according scheme 3) under reflux reaction condictions 4-[3-(Acetyl-phenyl-sulfamoyl)-4-(4-chlorosulfonyl-2-hydroxy-phenylamino-2-oxo-2H-chromen-7-ylamino]-isophthalic acid **3a** is synthesized in 70% yield.

The structure of Chromen-2-one derivative (1a,2a,3a) were determined fromtheir IR, ^{1}H NMR, ^{13}C NMR spectar and their melting points as follows.

3.1. For (1a); IR bands (KBr,cm^{-1}) 3146cm^{-1} (C-H stretch. aromatic) ; 3070 cm^{-1} (C-H stretch. aromatic) ; 2938cm^{-1} (C-H stretch. alifatic) ;1680 cm^{-1} (C=O); 1600 cm^{-1} (C=O α -pyron) ; 1315 cm^{-1} (C-O stretch.) ; 1240cm^{-1} (SO_2Cl) ; 758cm^{-1} (C-C aromatic)

^{1}H NMR (DMSO-d_6) δppm, 7.92ppm; 7.22ppm; 7.45ppm; 7.87ppm; 7.63ppm ;5.88ppm; m(9H.aromatic); 2.02ppm s(H,CH_3)

^{13} C NMR (DMSO) δppm , 162.0ppm (C=O,α pyron) ; 162.8ppm (C-N);

150.8ppm; (C-O); 147.6ppm (C-N); 139.7ppm (C-S); 128.1ppm; 127ppm; 125.2ppm 121.6ppm (10C aromatic); 15.8ppm(CCH_3)

3.2. For (2a) IR bands (KBr,cm^{-1}) 3140cm^{-1} (C-H aromatic); 2936 cm^{-1} (C-H alifatic) ;1680cm^{-1} (C=O stretch.) ; 1600cm^{-1} (C=Oα pyron) ; 1380 cm^{-1} (CONH); 1230 cm^{-1} (SO_2Cl); 1210 cm^{-1} (SO_2-NH); 1150 cm^{-1} (CONH); 750cm^{-1} (C-C aromatic)

^{1}H NMR (DMSO-d_6) δppm 7.82ppm; 7.63ppm; 7.45ppm; 7,27ppm 7.20ppm; 7.01ppm; 6.62ppm; 6.46ppm; m(13.H aromatic) ; 4.0ppm s(H,NH) ; 2.09ppm s(H,CH_3).

^{13}C NMR (DMSO) δppm 162.42ppm (C-N);160.0 (C, C=O); 150.8ppm (C-O); 147.7ppm (C-N); 139.7ppm (C-S);128.1ppm ; 127.0ppm ; 125.2ppm ; 129.3ppm ; 118.5ppm (14C. aromatic) ; 15.8ppm (C,CH_3)

3.3. For (3a) IR bands (KBr,cm^{-1}) 3300cm-^{1}(O-H, stretch.) ; 3065cm^{-1}(C-H,stretch. aromatic); 1680cm^{-1} (C=O) ; 1720cm^{-1}(C=O,stretch.);1680cm^{-1}(C=O);1320cm^{-1}(SO_2Cl);1280cm^{-1} (NH) ; 740cm^{-1}(C-C aromatic).

^{1}H NMR (DMSO-d_6) δppm 11.2ppm s(H, COOH) ; 7.92ppm ; 7.88ppm ; 7.87ppm ; 7.35ppm ; 7.01ppm ; 6.83ppm ; 6.46ppm ; 6.42ppm ; 6.40ppm ; (16.H aromatic) 4.0ppm ; s(H,NH); 2.02ppm s(H,CH_3).

^{13}CNMR (DMSO) δppm 172ppm (C,COOH); 162.8ppm (C,C=O); 160.2ppm (C,C=Oα pyron) ; 162ppm (C-N) ;151.7ppm (C-O) ; 142.8ppm (C-N);139.7ppm (C-S); 134.6ppm ; 129.3ppm ; 127ppm ; 118.5ppm ; 117.8ppm ; 115.1ppm ; 114.6ppm (17C.aromatic);15.8ppm (C,CH_3).

4.CONCLUSION

From the results the followin conclusion 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 Streptomycine 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 synthesizen compounds were determined according to extensive NMR experiments and published data.

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