Est. 1984

ORIENTAL JOURNAL OF CHEMISTRY
An International Open Free Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2014, Vol. 30, No. (4):
Pg. 1747-1752

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

AZIZ BEHRAMI

Faculty of Food Technology, University of Mitrovica, Kosovo.
*Corresponding author E-mail: a.behrami_chem@live.com

http://dx.doi.org/10.13005/ojc/300433

(Received: August 05, 2014; Accepted: September 26, 2014)

ABSTRACT

This work reports the synthesis of some new derivatives 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 concentractions 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.

Key words: 4-Chloro-chromen-2-one, Coumarine derivatives, Antibacterial activity, *Staphylococcus aureus*, *E.coli*, *Klebsiella*, Streptomycin.

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 (Govori *et al* 1996 ; Govori *et al* 2002 ; Stanovnik *et al* 1993).Coumarin is a chemical sompound (specifically , a benzo-α-pyrone) found in many plants (Lee *et al* 2002) 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), 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.

MATERIAL AND METHODS

Experimental Chemistry

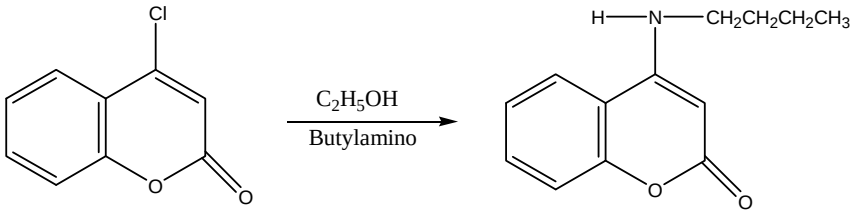
Compounds 4-Butylamino-chromen-2-one (1a) , 4-Butylamino-2-oxo-2H-chromene-3-sulfonyl chloride (2a) , 4-Butylamino-2-oxo-2H-chromene-3-sulfonic acid (2-hydroxy-phenyl)-amide (3a), 4-Butylamino-5-ethyl-2-oxo-7-(N'-phenyl-hydrazino)-2H-chromene-3-sulfonic acid (2-hydroxy-phenyl)-amide (4a),are synthesized.

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 determinated 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-d_6 as the solvent and TMS as the internal references standard (σ = 0,00 ppm).Chemical shifts are expressed in ´ 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.

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

For this synthesis is used as substrat 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 °C for ca. 90 min. The obtained crystals brown are filtred and rinsed with ethanol and dried at room temperature.Recrystallization form absolute ethanol gave a red product of 80% yield, melting point 117°C.(Sheme 1)



4-Chloro-chromen-2-one — **a**

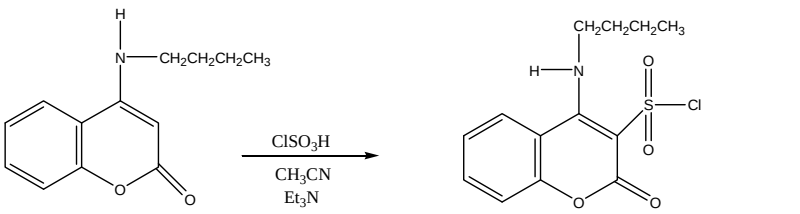
4-Butylamino-chromen-2-one — **1a**

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 °C for ca. 1.5 h . The obtained brown crystals are filtred and dried at room temperature . Recrystallization form C_2H_5OH gave brown crystals product of 70% yield,meltingpoint, 287 °C. (Scheme 2) .



4-Butylamino-chromen-2-one — **1a**

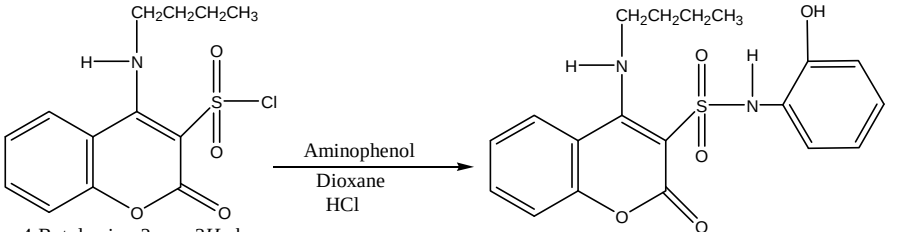
4-Butylamino-2-oxo-2*H*-chromene-3-sulfonyl chloride — **2a**

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 refkuxed at 92 °C 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 recrystallizacion from ethanol gave a yellow product at 70% yield, melting.point;180°C. (Scheme 3).



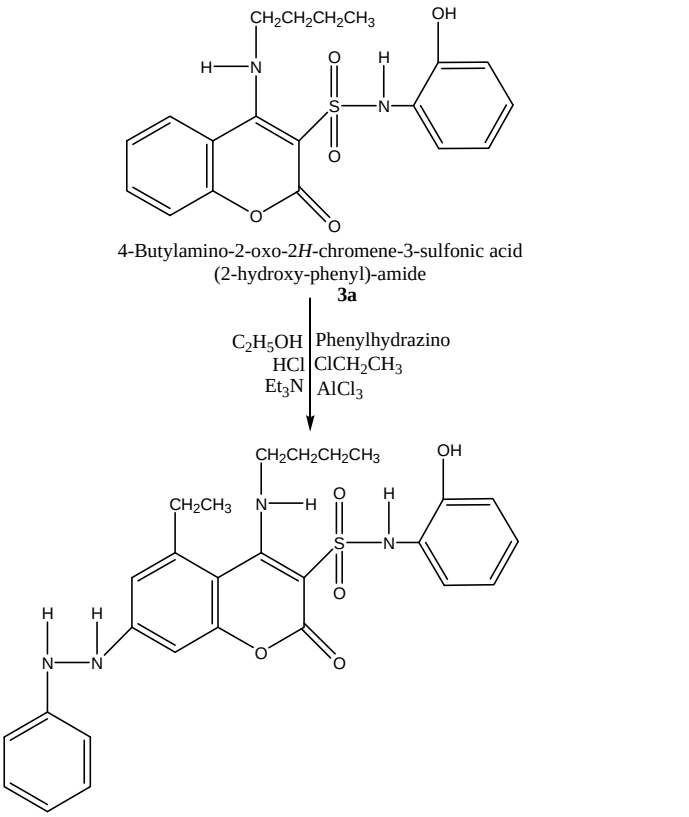
4-Butylamino-2-oxo-2*H*-chromene -3-sulfonyl chloride

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)



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

3a

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)

Table 1: Antibacterial activity- *Staphylococcus aureus* and the comparison with Streptomycine

Compound	Inhibition zone (mm)		
	2mg/ml	3mg /ml	5mg/ml
1a	10	13	15
2a	18	20	24
3a	19	21	25
4a	11	13	18
Streptomycine	20	20	20 10 µg

Table 2: Antibacterial activity *E.coli* and the comparison with Streptomycine

Compound	Inhibition zone (mm)		
	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 10µg

Table 3: Antibacterial activity *Klebsiella* and the comparison with Streptomycine

Compound	Inhibition zone (mm)		
	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 10µg

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 °C in water bath for ca. 2 h .The obtained red crystals are filtred and rinsed with CH_3CN and dried at room temperature.Recrystallization from ethanol gave a

Table 4

Compound	IR (cm^{-1})	^{1}H NMR ppm	^{13}C NMR ppm
1a	3370 (NH), 3010(C-H) ar, 2962(C-H)alifatic 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)
4[a]	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	6.96	6.45	14.73		
				72.00	7.11	6.15	14.32		
2a	70	287°C	$C_{13}H_{14}ClNO_4S$	49.45	4.47	4.44	20.27	11.23	10.15
				50.00	5.00	4.11	20.00	11.00	9.80
3a	70	180°C	$C_{19}H_{20}N_2O_5S$	58.75	5.19	7.21	20.59		8.20
				60.00	4.90	7.10	19.92		8.00
4a	60	204°C	$C_{27}H_{30}N_4O_5S$	62.05	5.79	10.72	15.31		6.14
				61.50	5.20	10.0	15.00		6.00

red product at 60 % yield , melting point 204 °C. (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)

CONCLUSION

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

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

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

ACKNOWLEDGEMENTS

The authors thank Prof.Branko Stanovnik,University of Ljubljana and its laboratory staff for ^{1}H NMR spectrum and elemental analyses.

REFERENCES

1. S.Govori,V.Kalaj,V.Rapic,L.Kalaj and S.Dakovic,*Heterocycel.Commun*., **2002**; *8*,129.
2. B.Stanovnik, H.Susachitzky and E.F.Scriven, Progress in Heterocyclic Chemistry, Pergamon Press ,Oxford , **1993**; *5*,pp.75-146.
3. S.H.Lee, D.-S.Shin, J.-S,Kim, K.-B. Oh and S.S.Kan*, Arch. Pharm. Res*, **2003**; 26.
4. K.B.Vyas, K.S.Nimavat, G.R.Jani and M.V. Hathi*, Orbital*, **2009**; *1*, 183.
5. A.Z.Abyshev, V.A.Gimdein, E.V. Semenov, E.M, E.MAgev, A.A. Abdulla - Zade and A.B.Gueseinov,*Pharm.Chem.J*., **2206**; *40*.607.
6. M.D.Aytemir , R.C.Hider , D.D.Erol , M.Ozalp and M.Ekizoglu .*Turk.J.chem*., **2003**; *27* : 445.
7. M.M.El.Saghier,M.B.Naili,B.Kh.Rammash, N.A.Saleh and K.M.Kreddan, Arkivoc, **2007**; 83.
8. Z.M.Nofal ,M.El-Zahar and S.Abd El Karim,*Molecules,* **2000**; *5*: 99.
9. Chaluvaraju KC and Ishwarbhat K.*Asian ,J Chem* **2008**; *20*, 4335.
10. Rajan Ra Kali , Jubie S,Grworamma B, and Suresh B,*Asian J Chem* **2008**: **20**: 5289.
11. Ali Mohammed Ashraf and Sharayar Mohammed . Boorg Med Chem. Lett **2009**; *17*: 3314.

12. Nofal ZM, El-Zahar M, Abd El-Karim S, Novel coumarin derivatives with expected biological activity, *Molecules*. **2000**; *5*: 99-113.

13. Vyas KB,Nimavat KS,Jani GR,Hathi MV, Synthesis and microbial activity of coumarin derivatives metal complex: An in vitro evaluation.Orbital, **2009**; *1*: 183-192.