Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(8):1041-1045

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

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

Islam Krasniqi[1], Aziz Behrami[2], Skender Demaku[3] and Ilir Shehu[3]

[1]Faculty of Education, Public University of Prishtina, Kosova
[2]Public University of Mitrovica, Kosova
[3]Department of Chemistry Faculty of Nature Sciences University of Prishtina, Kosova

---

ABSTRACT

In present paper, we report the organic syntheses of three compounds from 4-hydroxy-chromen-2-one and describe the results of antibacterial activity of purified compounds viz: 4-(2-Hydroxy –phenylamino)-chromen-2-one (1a), 2-Hydroxy-N-(2-hydroxy-phenyl)-N-(2-oxo-2H-chromen-4-yl)-benzamide (2a), N-[7-(3-Acetyl-thioureido)-2-oxo-2H-chromen-4-yl]-2-hydroxy-N-(2-hydroxy-phenyl)-benzamide (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 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, anti-inflammatory, 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

4-(2-Hydroxy –phenylamino)-chromen-2-one **(1a),** 2-Hydroxy-*N*-(2-hydroxy-phenyl)-*N*-(2-oxo-2H-chromen-4-yl)-benzamide **(2a)** , *N*-[7-(3-Acetyl-thioureido)-2-oxo-2*H*-chromen-4-yl]-2-hydroxy-*N*-(2-hydroxy-phenyl)-benzamide **(3a)** are synthesized.

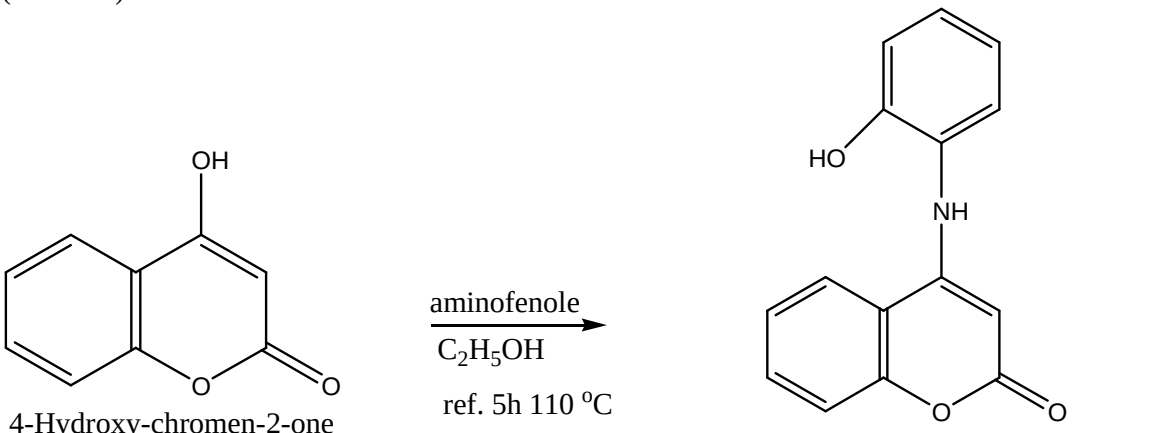
Measurement

The identification of derivatives 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

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-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 analyses 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 vapor for visualization.

Preparation of 4-(2-Hydroxy –phenylamino)-chromen-2-one **(1a)**
For this synthesis is used as substrate 4-hydroxy-chromen-2-one in a 100 ml flask mixed 3 g 4-hydroxy-chromen-2-one, 2 g aminophenol, 8ml C_2H_5OH
The mixture was refluxed at 110 ^{o}C for ca. 5h. 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 253 ^{o}C.

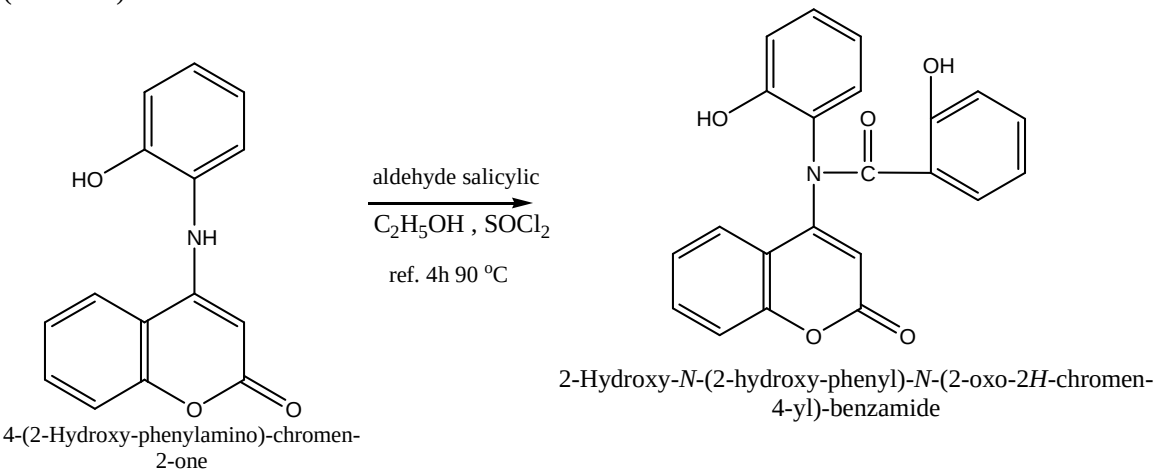
(Scheme.1)



Preparation of 2-Hydroxy-*N*-(2-hydroxy-phenyl)-*N*-(2-oxo-2H-chromen-4-yl)-benzamide **(2a)**
In a 100 ml flask were mixed 3g 4-(2-Hydroxy –phenylamino)-chromen-2-one with 8ml C_2H_5OH, 3g aldehyde salicylic , 2ml $SOCl_2$ .The mixture was refluxed at 90 ^{o}C for ca. 4h.

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, 373 ^{o}C.

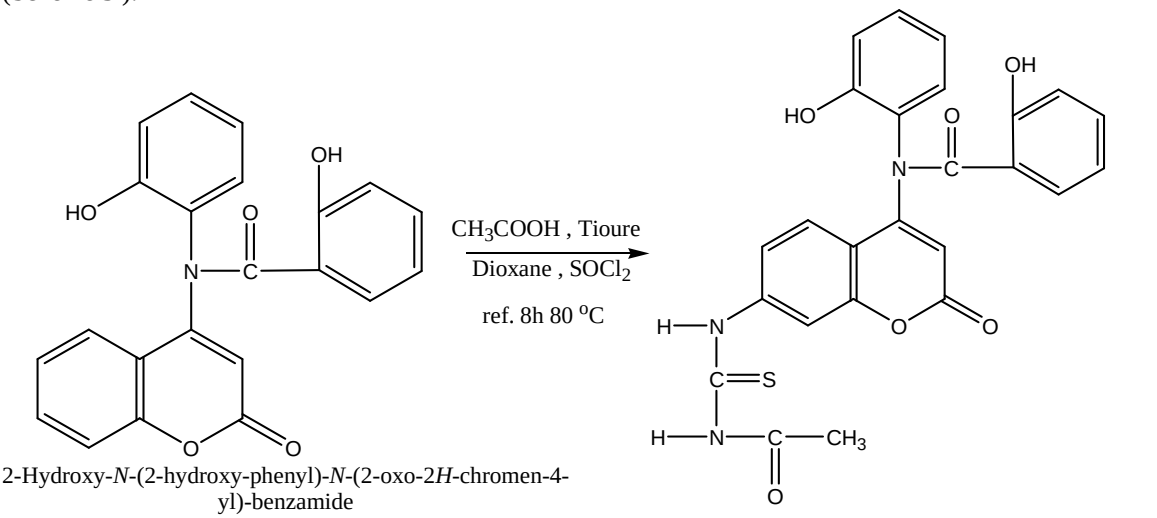
(Scheme 2).



Preparation of *N*-[7-(3-Acetyl-thioureido)-2-oxo-2*H*-chromen-4-yl]-2-hydroxy-*N*-(2-hydroxy-phenyl)-benzamide **(3a)**
In a 100 ml flask were mixed 2g of 2-Hydroxy-*N*-(2-hydroxy-phenyl)-*N*-(2-oxo-2H-chromen-4-yl)-benzamide, with 8 ml Dioxane, 1g tioure, 2ml $SOCl_2$ as katalyzer. The mixture was refluxed at 80 ^{o}C in water bath for ca. 8 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 red product at 70% yield, melting.point;180 ^oC.

(Scheme 3).



2-Hydroxy-*N*-(2-hydroxy-phenyl)-*N*-(2-oxo-2*H*-chromen-4-yl)-benzamide

N-[7-(3-Acetyl-thioureido)-2-oxo-2*H*-chromen-4-yl]-2-hydroxy-*N*-(2-hydroxy-phenyl)-benzamide

Table-1 Analytical data

Comp'd	m.p	M.F	Elemental analysis. Calculated :Found (calc) %				
			C	H	N	O	S
1a	253 ^oC	$C_{15}H_{11}NO_3$	71.14 71.00	4.38 4.30	5.53 5.50	18.95 18.90	
2a	373 ^oC	$C_{22}H_{15}NO_5$	70.77 70.71	4.05 4.00	3.75 3.70	21.43 21,40	
3a	489 ^oC	$C_{25}H_{19}N_3O_6$	61.34 61.29	3.91 3.90	3.75 3.70	19.81 19.75	6.55 6.50

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	12	16	18
2a	13	17	20
3a	14	17	21
Cephalexine	8	8	8
Streptomycine	20	20	20

Table 3 Antibacterial activity – E.Coli

Inhibition zone (mm)

Compound	2mg/ml	3mg /ml	5mg/ml
1a	8	13	17
2a	9	15	19
3a	10	19	18
Cephalexine	8	8	8
Streptomycine	20	20	20

Table 4 Antibacterial activity – Bacillus cereus

Inhibition zone (mm)

Compound	2mg/ml	3mg /ml	5mg/ml
1a	8	13	18
2a	9	14	19
3a	12	18	20
Cephalexine	9	9	9
Streptomycine	20	20	20

RESULTS AND DISCUSSION

By reacting equimolar amounts of 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-(2-Hydroxy–phenylamino)-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 2-Hydroxy-*N*-(2-hydroxy-phenyl)-*N*-(2-oxo-2H-chromen-4-yl)-benzamide and corresponding reagents (according scheme 3) under reflux reaction conditions product 3a is synthesized in 80% 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}) 3850-2400cm^{-1} (OH), NH; 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) δ ppm; 9.68 ppm s (H, CHO), 7.21-7.53 t (H, aromatic), 5.18 s (H, OH)

^{13}C NMR (DMSO) δ ppm; 166.9 ppm (C-Cl), 162 ppm (C, COO); 152 ppm (C, C-O); 133.4 (C, C-Cl); 121.7, 125.6, 128.0 (3C-aromatic)

For (2a) IR bands (KBr, cm^{-1}): 3400cm^{-1}(OH), 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) δ ppm: 6.37, 6.39, 7.41 t (3H aromatic), 5.0(H, OH), 4.0 d (H, NH), 4.0 ppm s(NH).

^{13}C NMR (DMSO) δ ppm: 181 ppm (C, C-NH), 162ppm (C, COO), 151 ppm (C, C-O), 105, 109, 116, 127 ppm (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 carboxylic), 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) δ ppm: 7.4, 6.5, 6.4 (3H aromatic), 5.0 (H, OH), 4.0 s (H, NH), 3.53 ppm t (2CH_2, OH), 2.65 ppm t(3H, CH_3N), 1.48-1.52 ppm t(3H, 2CH_3), 1.40-155 ppm t(4H, 2CH_2).

^{13}C NMR (DMSO) δ ppm: 176.0 ppm (C, COOH), 167 ppm (C, C-NH), 162.0 (C, C=O), 151.7 ppm(C, C-O), 127, 109, 105 ppm (3C aromatic), 51.6(C, C-N), 46.6 (C, C-N), 62.7(C, C-OH), 30.6, 27.8 ppm (C, CH_3).

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 *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 synthesized 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.KalajandS.Dakovic,*Heterocycel.Commun*. **2002**.,(8),129
[2],B.Stanovnik; H.Susachitzky and E.F.Scriven, Progress in Heterocyclic Chemistry, Pergamon Press ,Oxford, **1993**,(5).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],Vyas KB;Nimavat ;KS,Jani GR;Hathi MV, **2009**) Synthesisi of antimicrobial activity of coumarine derivatives metal complexes:An in vitro evalution. Orbital,(1),183-192.
[5], Abyshev AZ; Gimdein Va; Semenov EV ; Agaev EM, Abdulla-zade AA, Gueinov AB,**2006**
[6], A.Behrami;K.Vaso;I.Krasniqi, *J. Int .Environ .Appl.Sci*.**2010**, (5).247 .
[7],M.D.Aytemir ; R.C.Hider ; D.D.Erol ; M.Ozalp; and M.Ekizoglu .*Turk.J.chem.*, **2003**,445.
[8],M.M.El.Saghier;M.B.Naili;B.Kh.Rammash; N.A.Saleh and K.M.Kreddan, *Arkivoc*, **2007**,83.
[9], Z.M.Nofal ;M.El-Zahar; and S.Abd El Karim, *Molecules*, **2000**,(5).99 .
[10],Chaluvaraju KC and Ishwarbhat K.Asian , *J Chem* **2008**; (20), 4335.
[11],Rajan Ra Kali ;Jubie S,Grworamma B; and Suresh B,*Asian J Chem* **2008**:(20), 5289.
[12],Ali Mohammed Ashraf ; and Sharayar Mohammed . *Boorg Med Chem. Lett* **2009**;(17),3314.
[13],Pandeya SN;Lakshmi VS Aandey A. *Indian J Pharma Sci* **2003**;(65):213