

Antibacterial Effects and Synthesized New Derivatives of 4-Hydroxy-Chromen-2-One

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To cite this article:

Aziz Behrami, Florent Dobroschi. Antibacterial Effects and Synthesized New Derivatives of 4-Hydroxy-Chromen-2-One. *American Journal of Heterocyclic Chemistry*. Vol. 5, No. 1, 2019, pp. 7-10. doi: 10.11648/j.ajhc.20190501.13

Received: January 28, 2019; Accepted: March 21, 2019; Published: April 15, 2019

Abstract: In present paper, we report the organic syntheses of three compounds exactly 4-hydroxy-chromen-2-one and describe the results of antibacterial activity of purified compounds. Compounds 4-(4-Methoxy-phenylamino)-2-oxo-2H-chromene-3-sulfonyl chloride (a), N-{3-[Diethoxy-(2-hydroxy-phenyl)-methyl]-2-oxo-2H-chromen-4-yl}-acetamide (b), 4-(6-Nitro-benzothiazol-2-ylamino)-2-oxo-2H-chromene-3-carbaldehyde (c), have been synthesized and characterized using melting points, IR spectra, ¹H-NMR and ¹³C-NMR spectra. Our research goal is synthesis novel organic compounds which prove high level of antibacterial activity. 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 in high level and also synthesized compounds has been characterized using advanced instrumental methods of analysis.

Keywords: Coumarine Derivatives, Antibacterial Activity, IR, ¹H-NM, ¹³C-NMR, Streptomycine

1. Introduction

Starting from 4-hydroxy-chromen-2-one; derivatives (a, b, c) 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 [12-15] with reflux and condensation we have synthesized 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 [1-11].

2. Materials and Methods

2.1. Experimental Chemistry

4-(4-Methoxy-phenylamino)-2-oxo-2H-chromene-3-sulfonyl chloride (a), N-{3-[Diethoxy-(2-hydroxy-phenyl)-methyl]-2-oxo-2H-chromen-4-yl}-acetamide (b), 4-(6-Nitro-benzothiazol-2-ylamino)-2-oxo-2H-chromene-3-carbaldehyde (c).

2.2. Measurement

The identification of Benzene – 1,3,5-triol derivatives (a, b, c), 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 an 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. ¹H NMR spectra were recorded on a Bruker UNITY plus-500 'NMR 1' spectrometer using DMSO-d₆ as the solvent and TMS as the internal reference standard ($\sigma = 0,00$ 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.

Preparation of 4-(4-Methoxy-phenylamino)-2-oxo-2H-chromene-3-sulfonyl chloride (a)

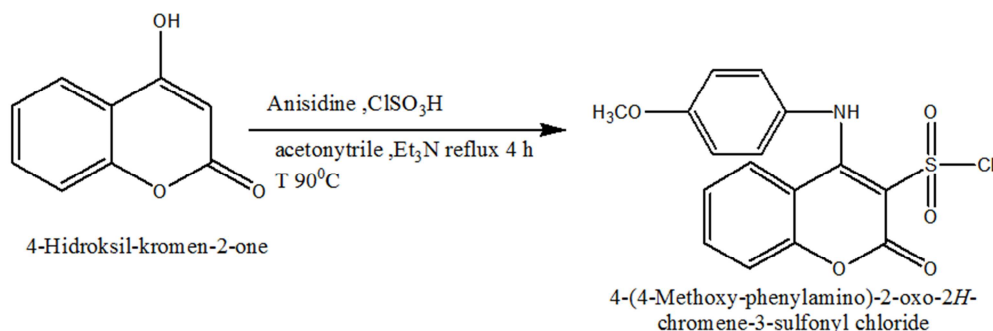


Figure 1. Preparation of 4-(4-Methoxy-phenylamino)-2-oxo-2H-chromene-3-sulfonyl chloride (a).

Preparation of N-{3-[Diethoxy-(2-hydroxy-phenyl)-methyl]-2-oxo-2H-chromen-4-yl}-acetamide (b)

In a 100 ml flask were mixed 3.5 g 4-hydroxy-Chromen-2-one with 9ml C₂H₅OH, 4ml Aldehyd salicylic, 3g

CH₃COONH₄, 1ml HCl. The mixture was refluxed at 100°C for ca. 7h. The obtained yellow crystals are filtered and dried at room temperature. Recrystallization from C₂H₅OH gave yellow crystals product of 78 % yield, meltingpoint, 319°C.

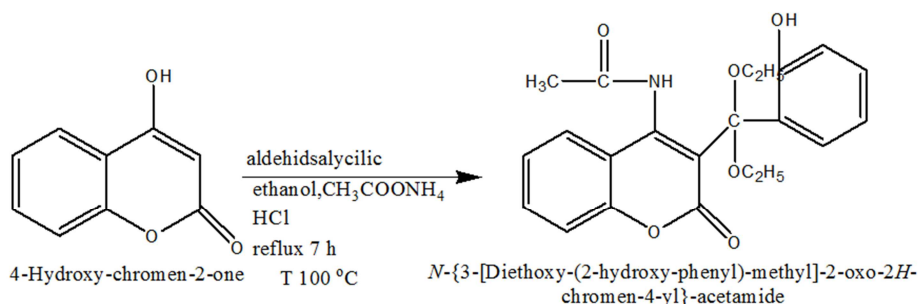


Figure 2. Preparation of N-{3-[Diethoxy-(2-hydroxy-phenyl)-methyl]-2-oxo-2H-chromen-4-yl}-acetamide (b).

Preparation of 4-(6-Nitro-benzothiazol-2-ylamino)-2-oxo-2H-chromene-3-carbaldehyde (c)

In a 100 ml flask were mixed 2.5g of 4-Hydroxy-chromen-2-one, 2g 2-amino-6-nitro-benzothiazole, 8ml C₂H₅OH, with 4 ml HCOOH. The mixture was refluxed at 95°C 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 CH₃CN. The recrystallization gave a yellow product at 90% yield, melting. point; 248°C.

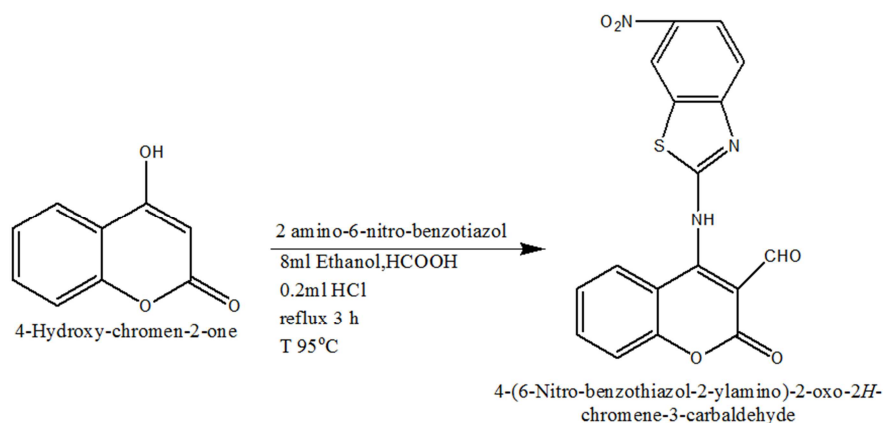


Figure 3. Preparation of 4-(6-Nitro-benzothiazol-2-ylamino)-2-oxo-2H-chromene-3-carbaldehyde (c).

Table 1. Analytical data.

Compd	Yield %	m. p	M. F	Elemental analysis. Calculated: Found (calc) %				
				C	H	N	O	Cl
a	70	310°C	C ₁₆ H ₁₂ ClNO ₅ S	52.54	3.31	3.33	21.87	9.69
				51.65	3.30	3.50	21.80	9.50
b	78	319°C	C ₂₂ H ₂₃ NO ₆	66.49	5.83	3.52	24.15	
				66.00	5.79	3.50	23.90	
c	90	248°C	C ₁₇ H ₉ N ₃ O ₅ S	55.58	2.47	11.44	21.78	
				55.40	2.30	11.30	21.70	

2.3. Antibacterial Activity

The purified synthesized compounds (a, b, c) 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-Bauer method or disc method (d=5.5 mm max. capacity 10 µg)

Table 2. Antibacterial activity- *Staphylococcus aureus*.

Compound	Inhibition zone (mm)		
	2 mg/ml	3 mg/ml	5 mg/ml
a	7	8,5	10,2
b	7,7	8	11,3
c	8,2	9	12,7
Cephalexine	9	9	9 - 10 µg
Streptomycine	20	20	20 - 10 µg

Table 3. Antibacterial activity – *E. coli*.

Compound	Inhibition zone (mm)		
	2mg/ml	3mg/ml	5mg/ml
a	10.4	13.7	18.8
b	11	18.8	21.5
c	10	19	21.0
Cephalexine	9	9	9 - 10 µg
Streptomycine	23	23	23 - 10 µg

Table 4. Antibacterial activity – *Bacillus cereus*.

Compound	Inhibition zone (mm)		
	2mg/ml	3mg/ml	5mg/ml
a	9.2	14.4	20.8
b	10.6	15.2	22.7
c	11	18.5	21.9
Cephalexine	9	9	9 - 10 µg
Streptomycine	23	23	23 - 10 µg

4. Results and Discussion

By reacting equimolar amounts of 3-oxo-butiric acid ethyl ester and corresponding reagents (according scheme 1) under reflux reaction conditions product 1a is synthesized in 80 % yield.

By reacting equimolar amounts of 4,7 Dyhydroxy 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 4,7 Dychloro-chromen-2-one and corresponding reagents (according scheme 3) under reflux reaction conditions product 3a is synthesized in 70% yield.

The structure of 4,7 Dyhydroxy-chromen-2-one derivatives (a, b, c) were determined from their IR, ¹H NMR, ¹³C NMR spectar and their melting points as follows.

For (a); IR bands (KBr, cm⁻¹) 3428cm⁻¹ (N-H stretch.), 3000 cm⁻¹ (C-H aromatic), 2800cm⁻¹ (C-H stretch.), 1740 cm⁻¹ (C=O stretch.), 1600cm⁻¹(N-H); 1380cm⁻¹(SO₂Cl);720cm⁻¹(C-H aromatic)

¹H NMR (DMSO-d₆) δppm;7.6-6.3 (6H aromatic);4.2 (H, NH); 3.73 (H, CH₃)

¹³C NMR (DMSO) δppm; 162 (C, C=O); 163.0 ppm (C-NH); 150.8 (C-O); 152ppm(C-O);114-128.1ppm (6C aromatic);139.6ppm(C-N);56.0ppm(C, CH₃)

For (b) IR bands (KBr, cm⁻¹) 3400 cm⁻¹ (OH stretch.); 3140 cm⁻¹ (C-H aromatic.); 2936cm⁻¹ (C-H alifatic.); 1680 cm⁻¹ (C-O stretch.); 1740cm⁻¹(alfa pironi); 1380cm⁻¹(CONH);1220cm⁻¹(C-O); 1150 cm⁻¹(CO-N);748cm⁻¹(C-C aromatic)

¹H NMR (DMSO-d₆) δppm 8.0 ppm(H, N-CO) 6.72-7.63 (8H aromatic);5.0(H, OH);3.41(4H,2CH);2.2 (3H, CH₃)

¹³C NMR (DMSO) δppm 167.3 ppm (C-CONH); 162 ppm (C, C=O); 156.4ppm (C-OH);150.8 ppm (C-O); 144.8(C-NH),54,6(C, CH₂),18.5 ppm (C, CH₃);15.4(C, CH₃);121.3-129.0(8C aromatic)

For (c) IR bands (KBr, cm⁻¹) 3380 cm⁻¹ (N-H stretch.);2990cm⁻¹(C-H aromatic.); 2840cm⁻¹(C-H aldehyde); 1740cm⁻¹(C=O); 1620cm⁻¹(N-H),1547cm⁻¹(C=N);1523(Ar-NO₂); 1256ppm(C-O stretch);720ppm(C-H aromatic);650 ppm (C-S)

¹H NMR (DMSO-d₆) δppm 9.68ppm (H, CHO), 7.20-9.05 (7H aromatic);4.1(H, NH)

¹³CNMR (DMSO) δppm 190.0ppm (C, CHO), 162ppm (C, C=O); 181.1ppm (C, C-N); 174.5ppm (C-C=N) 150.8ppm (C, C-O); 121.3-126.6(10 C aromatic)

5. Conclusion

From the results the following conclusion were drawn:The study provides the first evidence that compounds (a, b, c) obviously inhibit the growth of *S. aureus*, *E. coli* and *B. cereus*.

The compounds (a, b, c) compared with the antibacterial activity of Streptomycine in *S. aureus*, *E. coli* and *B. cereus*.

This study provided the first evidence that these

compounds a, b, c 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 ¹H NMR spectrum and elemental analyses.

References

- [1] Govori. S, Kalaj. V, Rapic. V, Kalaj. L, and Dakovic. S, *Heterocycl. Commun.*, 2002; 8,(129).
- [2] Stanovnik. B, Susachitzky. H, and. Scriven. E. F, *Progress in Heterocyclic Chemistry*, Pergamon Press, Oxford, 1993; 5,(75-146).
- [3] Lee. S. H, Shin, D. S, Kim. J. S, K.-B. Oh and Kan. S. S, *Arch. Pharm. Res*, 2003; (26).
- [4] Vyas. K. B, Nimavat. K. S, Jani. G. R, and Hathi. M. V, *Orbital*, 2009; 1, (183).
- [5] Abyshev. A. V, Gimdein. V. A, Semenov. E. V, E. M. Agev. E. M, Abdulla. A. A, Zade and Guseinov, *Pharm. Chem. J.*, 2006; 40.(607).
- [6] Aytimir. M. D, Hider. R. C, Erol. D. D, Ozalp. M and Ekizoglu. M, *Turk. J. chem.*, 2003; 27: (445).
- [7] El. Saghier. M. M, Naili. M. B, Rammash. M. Kh, Saleh. N. H and Kreddan. K. M, *Arkivoc*, 2007;(83).
- [8] Nofa. Z. M, El-Zahar. M and Abd El Karim. M, *Molecules*, 2000; 5: (99).
- [9] Chaluvvaraju. K C and Ishwarbhat, K. Asian, *J Chem* 2008; 20, (4335).
- [10] Ra Kali. R, S, Grworamma. J, and Suresh. B, *Asian J Chem* 2008; 20: (5289).
- [11] Mohammed Ashraf. A and Mohammed. SH. 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). Design, synthesis of novel azo derivatives of benzimidazole as potent antibacterial and anti tubercular agents
- [14] A. A. Abou-Hussein, Wolfgang Linert, Synthesis, spectroscopic studies and inhibitory activity against bacteria and fungi of acyclic and macrocyclic transition metal complexes containing a triamine coumarine Schiff base ligand *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, Volume 141, 15 April 2015, Pages 223-23.
- [15] Danijela Lj Stojković, Verica V. Jevtić, Nenad Vuković, Milena Vukić, Srećko R. Trifunović, Synthesis, characterization, antimicrobial and antitumor reactivity of new palladium(II) complexes with methionine and tryptophane coumarine derivatives. *Journal of Molecular Structure*, Volume 1157, 5 April 2018, Pages 425-433.