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

Aziz Behrami, Florent Dobroshi

Department of Food Technology, University of Mitrovica "Isa Boletini", Mitrovica, Kosova

Email address:
a.behrami_chem@live.com (A. Behrami)

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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, ^{1}H-NMR and ^{13}C-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 synthetized compounds has been characterized using advanced instrumental methods of analysis.

Keywords: Coumarine Derivatives, Antibacterial Activity, IR, ^{1}H-NM, ^{13}C-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 varius 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 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 [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, ^{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-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 4-(4-Methoxy-phenylamino)-2-oxo-2H-chromene-3-sulfonyl chloride (a)

For this synthesis is used as substrat 4g 4- hydroxy-chromen-2-one in a 100 ml flask mixed 2 g Anisidine, 8ml acetonitrile, 3ml$ClSO_3H$ and 1ml Et_3N. The mixture was refluxed at 90°C for ca. 4h. The obtained crystals white are filtered and rinsed with methanol and dried at room temperature. Recrystalization form absolute methanol gave a white product of 70% yield, melting point 310°C.

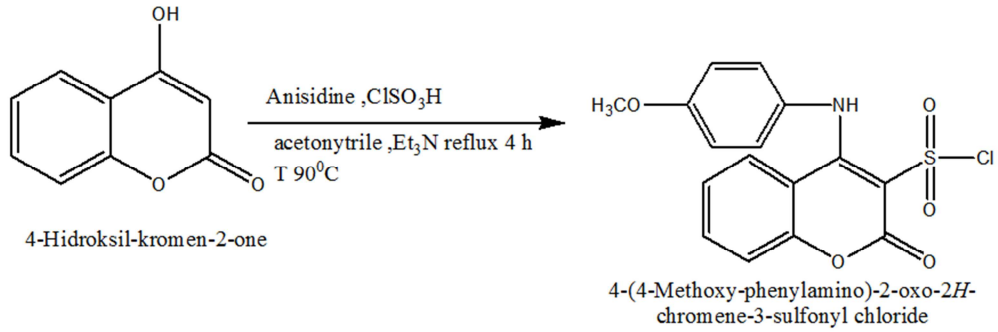

Figure 1. *Preparation of 4-(4-Methoxy-phenylamino)-2-oxo-2H-chromene-3-sulfonyl chloride (a).*

Preparation ofN-{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 –Chomen-2-one with 9ml C_2H_5OH, 4ml Aldehyd salicylic, 3g CH_3COONH_4, 1ml HCl. The mixture was refluxed at 100°C for ca. 7h. The obtained yellow crystals are filtered and dried at room temperatur. Recrystallization form C_2H_5OH gave yellow crystals product of 78 % yield, meltingpoint, 319°C.

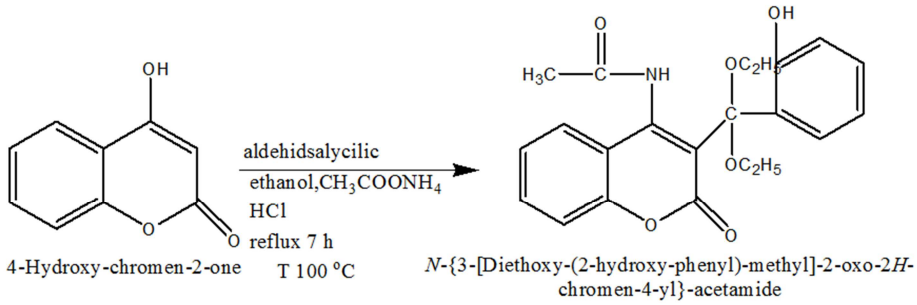

Figure 2. *Preparation of N-{3-[Diethoxy-(2-hydroxy-phenyl)-methyl]-2-oxo-2H-chromen-4-yl}-acetamide (b).*

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 2amino-6-nitro-benzotiazole, 8ml C_2H_5OH, 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 CH_3CN. The recrystallizacion gave a yellow product at 90% yield, melting. point; 248°C.

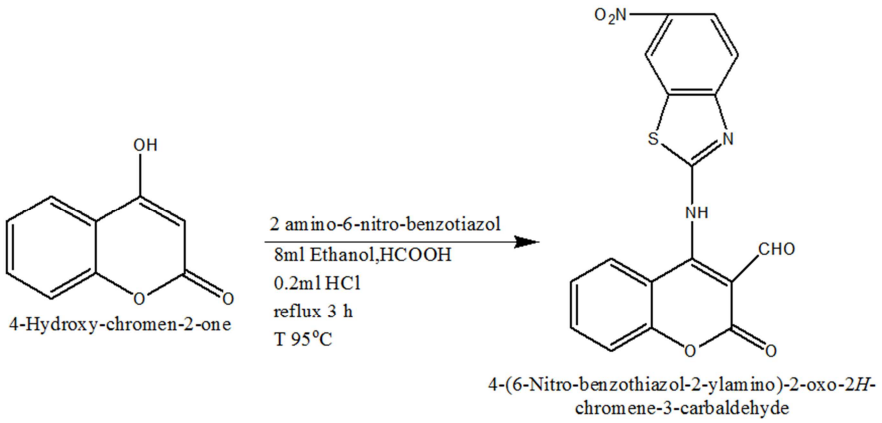

Figure 3. *Preparation of 4-(6-Nitro-benzothiazol-2-ylamino)-2-oxo-2H-chromene-3-carbaldehyde (c).*

Table 1. *Analytical data.*

Compd	Yeld %	m. p	M. F	Elemental analysis. Calculatet: Found (calc) %				
				C	H	N	O	Cl
a	70	310°C	$C_{16}H_{12}ClNO_5S$	52.54 51.65	3.31 3.30	3.33 3.50	21.87 21.80	9.69 9.50
b	78	319°C	$C_{22}H_{23}NO_6$	66.49 66.00	5.83 5,79	3.52 3.50	24.15 23.90	
c	90	248°C	$C_{17}H_9N_3O_5S$	55.58 55.40	2.47 2.30	11.44 11.30	21.78 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-Bayer 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 correspomding reagents (according scheme 1) under reflux reaction condictions product 1a is synthesized in 80 % yield.

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

The structure of 4,7 Dyhydroxy-chromen-2-one derivatives (a. b. c) were determined fromtheir IR, ^{1}H NMR, ^{13}C 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=0 stretch.)., 1600cm^{-1}(N-H); 1380cm^{-1}(SO_2Cl);720cm^{-1}(C-H aromatic)

^{1}H NMR (DMSO-d6) δppm;7.6-6.3 (6H aromatic);4.2 (H, NH); 3.73 (H, CH_3)

^{13} C 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, CH_3)

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)

^{1}H 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, CH_3)

^{13}C 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, CH_2),18.5 ppm (C, CH_3);15.4(C, CH_3);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-NO_2); 1256ppm(C-O stretch);720ppm(C-H aromatic);650 ppm (C-S)

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

^{13}CNMR (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 followin conclusion were drawn:The study provides the first evidence that compounds (a, b, c) obviously inhibit the growth of S. auerus, 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 synthesizen compounds were determined according to extensive NMR experiments and published data.

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