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MICROBIOLOGICAL ACTIVITY OF DERIVATIVES 4-CHLORO-7-HYDROXY-CHROMEN-2-ONE COMPARE WITH STANDARD DRUGS

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Abstract

Nucleophilic substitution and electrophilic of 4-Chloro-7-hydroxy-chromen-2-one are yielded compounds 4-(2,6-Dihydroxy –pyrimidin-4-ylamino)-2-oxo-2H-chromen -3-sulfonyl chloride (1a), {4-[Bis-(2-chloro-ethyl)-amino]-7-hydroxy-2-oxo-2H-chromen-3-yl}-phosphonic acid (2a), (3-Formyl-7-hydroxy-2-oxo-2H-chromen-4-yl)-dithiocarbamic acid(3a). Characterization synthetized chemical compounds was done by FTIR and NMR spectra and analysis of chemical composition of elements. Monitorization of antibacterial effect of synthesized compounds a,b,c was monitored at concentrations 2, 3, 5 mg/ml in three bacterial microorganism cultures: Staph. Aureus, E-coli and Bac. Cereus. The antibacterial activity of synthesized compound was compared to antibacterial activity of standard antibiotics cephalexine and streptomycin.

Keywords*: derivatives of 4-Chloro-7-hydroxy-chromen-2-one, antibacterial activity, S.Aureus, E.coli, Bacellus cereus, streptomycin.*

Introduction

Several coumarine derivative compounds was reported as a high antimicrobial, anticancer and anticoagulant activity. [1-4]. Several years ago some of coumarine anologe compounds of 3,4-disubstituted coumarins were define as antiomicrobial such as 2H-[1]-benzopiran-2-one [5,6].

For this reason coumarine derivatives was under intensive investigations especially for organic synthesis. Otherwise substitution of coumarine especially in position 3 and 4 was subject of research interests and this substitution of coumarine was rapid increases their biological activity [7]. Therefore, our research interest is starting from 4-Chloro-7-hydroxy-chromen-2-one to synthesize a several novel compound to improve their antibacteriological activity using as a comparative compounds standard commercial antibiotic.

Experimental Chemistry

4-(2,6-Dihydroxy-pyrimidin-4-ylamino)-2-oxo-2H-chromene-3-sulfonyl chloride **a**, {4-[Bis-(2-chloro-ethyl)-amino]-7-hydroxy-2-oxo-2H-chromen-3-yl}-phosphonic acid **b**, (3-Formyl-7-hydroxy-2-oxo-2H-chromen-4-yl)-dithiocarbamic acid **c**,are synthesized.

Materials and Methods

After lab synyhesis of compound in interests writed **(a, b, c),** was characterized using several parapeters such as melting point, FTIR-Spectroscopy, 1H NMR, 13C NMR spectra and finally analysis of elements in synthetized compounds. Used Equipment for melting point was,

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Fisher Scientific 2555, Electrothermal equipment. Fourier Transform Infrared spectra were analysed in region from 400-4000 cm^{-1} using KBr pellets on a FT-IR Shimadzu IRaffinity-1 resolution 4 cm-1 and 32 scan. ^1H NMR spectra were done by Bruker UNITY plus-500 'NMR 1' spectrometer dissolved in DMSO-d6 and TMS as the internal standard compounds ($\sigma = 0,00$ ppm). Mass spectra were taken on a LKB 9000 mass spectrometer. Analysis of elements was done by Perikin-Elmer 240 BCHN analyzer. Purity monitoration of the synthetized compounds was checked by TLC using Silicagel plate using mobile phase mixture of solvents benzene, toluene, glacial acetic acid (80:10:10).

Preparation of 4-(2,6-Dihydroxy-pyrimidin-4-ylamino)-2-oxo-2H-chromene-3-sulfonyl chloride (a)

For synthesized of first derivative is used 5g 4-Chloro-7-hydroxy-chromen-2-one as substrat dissolved in a 100 ml flask than mixed with 10 ml ethanol, and 2ml N.N DMF, where was catalysed with 1ml triethanolammine.

Synthesis was continue and for 7 hours heating under reflux at 120 ^oC. Precipitate material than was separated by filtration from the hot mixture, washed with ethanol, than drying in exicator and crystallized from N,N-Dimethyl formamide, synthetized orange crystals was in 80% yield and measured of melting point 286 ^oC.

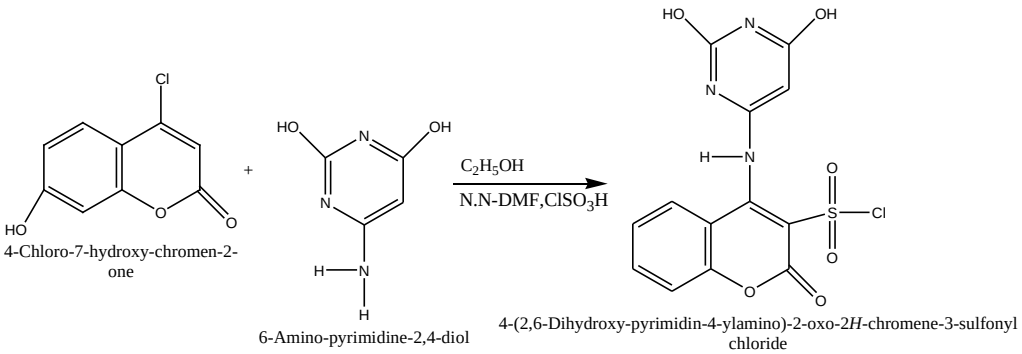


Fig. 1. 4-(2,6-Dihydroxy-pyrimidin-4-ylamino)-2-oxo-2H-chromene-3-sulfonyl chloride (a)

Preparation of {4-[Bis-(2-chloro-ethyl)-amino]-7-hydroxy-2-oxo-2H-chromen-3-yl}-phosphonic acid (b)

For synthesized of (b) are used 2g 4-Chloro-7-hydroxy –chromen-2-one: add 2g Bis-2(chloro-ethyl) amine in a 100 ml flask dissolved in 6ml ethanol and 3ml of phosphoric acid. Under reflux reaction was heated for 10 hours at 80 ^oC. Syntheetized yellow crystals are separated by filtration and dried at normal room temperature. It is necessary to do recrystallization using ethanol as a solvent which will obtain yellow crystals compounds with 65 % yield and meausered melting point, 230 ^oC.

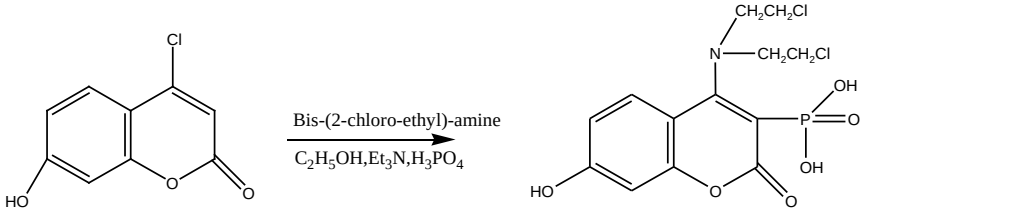
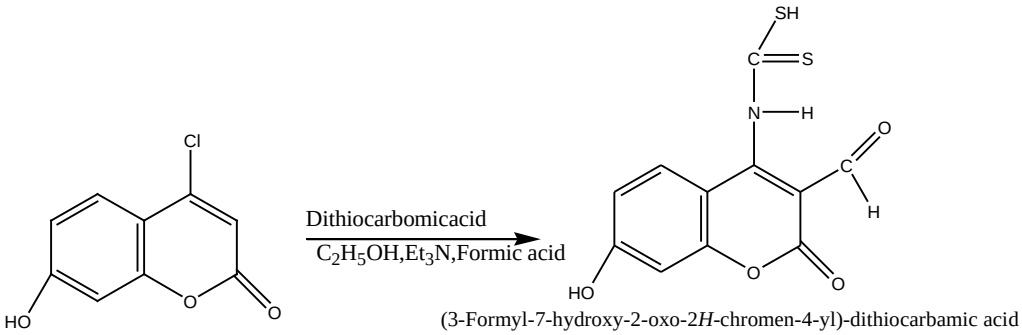


Fig. 2. {4-[Bis-(2-chloro-ethyl)-amino]-7-hydroxy-2-oxo-2H-chromen-3-yl}-phosphonic acid (b)

Preparation of (3-Formyl-7-hydroxy-2-oxo-2H-chromen-4-yl)-dithiocarbamic acid (c)

Added 2 g of 4-Chloro-7-hydroxy-chromen-2-one and dissolved in 100 ml flask were mixed with solvent 6ml ethanol and 1 ml triethanolammine as a catalysts, than add 4ml Dithiocarbomidacid, and 3ml formic acid. All mixture was heated for 22 hours under reflux at 100 ^{o}C in oil bath. After this flask was placed in an ice bath for 1h until obtaining white crystal. After product filtration it was recrystalized using CH_3CN as a solvent .

The recrystalization gave a white product at 90% yield, and meausered meltingpoint was 290 ^{o}C.



4-Chloro-7-hydroxy-chromen-2-one

(3-Formyl-7-hydroxy-2-oxo-2*H*-chromen-4-yl)-dithiocarbamic acid

Fig. 3. (3-Formyl-7-hydroxy-2-oxo-2H-chromen-4-yl)-dithiocarbamic acid (c)

Table 1. Characteristics and analytical data of the complexes

Comp	Yield %	m.p	M.F	C%	S%	Cl%	H%	N%	O%
a	80	286^{o}C	$C_{13}H_8ClN_3O_6S$	42.23	8.67	9.59	2.18	11.36	25.96
				42.18	8.60	9.50	2.15	11.38	25.98
b	65	230^{o}C	$C_{13}H_{14}Cl_2NO_6P$	40.86		18.59	3.69	3.67	25.12
				40.50		18.50	3.62	3.60	25.10
c	90	290^{o}C	$C_{11}H_7NO_4S_2$	46.97	22.80		2.51	4.98	22.75
				46.80	22.71		2.45	4.90	22.70

Antibacterial activity

All synthetized and characterized purified compounds (a,b,c) was tested for their antibacterial activity apply in three different bacterial culture: Staphylococcus aureus, E.Coli and B.cereus. Investigation was applied Kirby-Bayer method to test the antibacterial activity of compounds. [8].

Table 2. Antibacterial activity- Staphylococcus aureus

	Inhibition zone (mm)		
Compound	2mg/ml	3mg /ml	5mg/ml
a	8.5	11	15.5
b	9.2	15.5	17
c	7.5	10.8	13.5
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
a	7.8	10.2	12.7
b	8.8	13.2	14.4
c	10	11.6	14.8
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
a	10.9	14.3	22.7
b	9.1	14.7	21.6
c	8.7	10.8	12.9
Cephalexine	9	9	9 10 µg
Streptomycine	23	23	23 10 µg

Results and Discussion

All three synthesis of coumarine compounds was tested for their antibacterial activity in comparison with standard antiobiotics (cefalexine and streptomicine). In all three culture all three csynthetized compounds have higher activity in comparison with cefalexine and all three compounds are strongly competitive with streptomicine especially in bacillus cereus.

The structure of 4-Chloro-7-hydroxy-chromen-2-one derivatives (a,b,c)were determined fromtheir IR, ^{1}H NMR, ^{13}C NMR spectra and their melting points as follows.

For (1a); IR bands (KBr,cm-1) 3500stretch (OH); 3400 stretch (N-H), 3000stretch (CH-arom), 1742 stretch (C-O), 1580-1510 stretch (C=C aromatic.) 1410-1350 stretch (SO_2Cl);stretch (S-Cl).

^{1}H NMR (DMSO-d6) δppm, 4.9 ppm S(H-OH), 4.0 ppm h(NH) 5.0-5.5 ppm (2H,2OH); 7.20 ppm -7.63 (4H arom).

^{13} C NMR (DMSO) δppm; 121.3 -127.8 ppm m(5.C aromatic); 150.8 ppm (C,C-O); 162.0 ppm (C,C=O); 167 ppm (C,C-N); 164.4 (C,C-OH) 166 ppm (C,C-O); 89 ppm (C,C-SO_2)

For (2a) IR bands (KBr,cm -1) 3480 stretch (O-H stretch); 3418 stretch (N-H); 3000 stretch(C-H aromatic); 2870 stretch (C-H stretch); 1740 stretch (C=O);1600 stretch (C=C aromatic); 770 stretch (C-Cl).

^{1}H NMR (DMSO-d6) δ ppm 2.83 ppm d(4H,CH_2); 3.50 ppm d(4H,2CH_2Cl); 5.0 ppm s(H,OH); 2.0 ppm d(2H-2OH);6.5-7.5 ppm m(4H - aromatic).

^{13}C NMR (DMSO) δ ppm 53.3 ppm (C,CH_2); 45.1 ppm (C,CH_2Cl); 89.8 ppm (C,C-P); 181 ppm (C,C-N); 152.2 ppm (C,C-O); 162 ppm (C,C=O); 156.9ppm(C,C-OH) 113.4-128.0 ppm (3C aromatic).

For (3a) IR bands (KBr,cm -1) 3400 stretch (O-H, stretch.), 3380 stretch (N-H,stretch.), 2990 stretch (C-H aromatic),2870 stretch (C-H),1740 stretch(C=O); 1600 stretch (C=C aromatic),1240 stretch (C=S); 1050 stretch (C-O),1030 stretch (C-S),752 stretch(C-S) **^{1}H NMR (DMSO-d6) δ ppm** 1.8ppms (H,SH), 2.5 ppm (H,NH), 5.0 ppm s(H,OH), 6.67-7.46 ppm (3H aromatic);9.68 ppm (H-CHO).

^{13}CNMR (DMSO) δ ppm 108.5-128.4 ppm (4. C aromatic); 152.2 ppm (C,C-O);
156.9 ppm (C,C-OH); 181 ppm (C,C-NH); 190 ppm (C,CHO); 194.7 ppm (C,C=S.

Conclusion

Novelty coumarine derivatives compounds of 4-(2,6-Dihydroxy-pyrimidin-4-ylamino)-2-oxo-2H-chromene-3-sulfonyl chloride, 4-[Bis-(2-chloro-ethyl)-amino]-7-hydroxy-2-oxo-2H-chromen-3-yl}-phosphonic acid, 3-Formyl-7-hydroxy-2-oxo-2H-chromen-4-yl) dithiocarbamic acid were synthetized and characterized for their chemical properties and than evaluated for their anti-fungal and anti-bacterial activities for the first time.

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References

[1] I Kostova, *Synthetic and natural coumarine as cytotoxic agents* **Curr Med chem Anticancer Agents**, **5**, 2005, pp. 29-46.

[2] K. C. Fylaktakidou, D. J. Hadjipavlou – Litina, K. E. Litinas and D. N. Nicolaides, *Natural synthetic coumarine derivatives with anti-inflammatory/antioxidant activities* **Curr Pharm Des**, **10**, 2004, pp. 3813-3833.

[3] M. J. Matos, S. Vazques-Rodrigues, E. Uriatrte, L. Santana and D. Vina, *MAO inhibitory activity modulation :3-Phenylcoumarine versus 3-benzoylcoumarine,* **Bioorg Med Chem let**, **21**, 2011, pp. 4224-4227.

[4] T. Ojala, S. Remes, P. Haansuu, H. Vuorela and R. Hiltunen, *Antimicrobial activity of some coumarine containing herbal plants growing in Finland,* **J Ethenopharmacol**, **73**, 2000, pp. 299-305.

[5] Z. M. Nofal, M. I. El-Zahar and S. S. Abd El –Karim, *Novel Coumarine Derivatives with Exected Biological Activity,* **Molecules**, **5**, 2000, 99-113.

[6] M. D. Aytemir, R. C. Hider, D. D. Erol, M. Ozal. M. Ekizoglu and J. Turk, S*ynthesis of new antimicrobial of pyranones and pyridinones*, **Chem.**, **27**, 2003, p. 445.

[7] N. Batra, S. Batra, A. Prateek and B. N. Prakash, *Prevalenve of preventable medication – related hospitalizations in Australia : an opportunity to reduce harm*. **Int. J. Pharm. 24**, 2012, pp. 239-249.

[8] A. L. Barry, F. Garcia and L. D. Thrupp, *An improved single-disk metodh for testing the antibiotic susceptibility of rapidly-growing pathogens.* **Am**. **J. Clin. Pathol., 53(2)**, 1970, pp. 149-158.

[9] R. M. Mohareb, Z. Ho Jonatan and A.A Mohamed, *The Reaction of cyanoacetyl hydrazide with cyclopentanone: synthesis of coumarin, pyridine and thiazole derivatives,* **Egyptian Journal Of Chemistry**, **52(3),** 2007, pp. 349-360.

[10] M. M. Saghier, E. L. Naili, M. B Rammash, B. K Saleh N. A and Kreddan K. M. *Synthesis and antibacterial activity of some new fused chromenes* 2007 **Arkivoc 16:**83-91

[11] S H Lee, D. S. Shin, J. S. Kim, B. Oh and S. S. Kan, *Antibacterial compounds from the leaves ofAcanthopanax senticosus,* **Arch. Pharm. Res., 26,** 2003, pp. 40-42.

[12] K. B. Vyas, K. S. Nimavat, G. R. Jani and M. V. Hathi, **Orbital, 1**, 2009, p. 183.

[13] A. V. Abyshev, V. A. Gimdein, E. V. Semenov, E. M. Agev, A. A. Abdulla, A. Zade and F. Gueseinov, **Pharm. Chem. J., 40,** 2006, p. 607.

[14] M. M. El Saghier, M. B. Naili, M. Kh. Rammash, N. H. Saleh and K. M. Kreddan, *Synthesis and antibacterial activity of some new fused chromenes* **Arkivoc, xvi,** 2007**,** pp. 83-91.

[15] Z. Nofa, M. El-Zahar and M. Abd El Karim, **Molecules, 5,** 2000**,** p.99.

[16] K. C. Chaluvaraju, C. Ishwarbhat and K.Asian, **J. Chem., 20**, 2008, p. 4335.

[17] R. Ra Kali, S. Grworamma and B. Suresh, **Asian J. Chem., 20**, 2008, p. 5289.

[18] A. Mohammed Ashraf and S. H. Mohammed, *Synthesis, Characterization and Biological activity of new derivatives of Chromen-2-one* . **Boorg. Med. Chem. Lett., 17,** 2009, p. 3314.

[19] Z. M. Nofal, M. El-Zahar and S. Abd El-Karim, *Novel coumarin derivatives with expected biological activity,* **Molecules, 5**, 2000, pp. 99- 113.

[20] K. B. Vyas, K. S. Nimavat, G. R. Jani and M. V. Hathi, *Synthesis and microbial activity of coumarin derivatives metal complex: An in vitro evaluation*, **Orbital, 1**, 2009, pp. 183-192.

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