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Synthesis and Microbiological Activity of Some Newly Condensed Derivatives of 2-Oxo-2*H*-chromen-2-one

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By the action of 2-amino-5-ethylthio-1,3,4-thidiazole, 3-amino-5-methyl isoxazole and 2-amino benzimidazole on 4-hydroxy-2-oxo-2*H*-chromene-3-sulfonyl chloride, corresponding 4-hydroxy-2-oxo-2*H*-chromene-3-sulfonic acid (5-ethyl-[1,3,4]thiadiazol-2-yl)-amide, 4-hydroxy-2-oxo-2*H*-chromene-3-sulfonic acid (5-methyl-isoxazol-3-yl)-amide and 4-hydroxy-2-oxo-2*H*-chromene-3-sulfonic acid (1*H*-benzimidazol-2-yl)-amide were formed and they have been isolated in satisfying yields. Based on the biological activity of chromene-2-ones and heterocyclic compounds condensed in position 3 and 4, we also studied microbiological activity of these new compounds (**4-6**), against *Staphylococcus aureus* ATCC 25923, *Streptococcus pneumoniae, Aeromonas salmonicida, Bacillus spp* and some of them exhibited significant activity.

Key Words: 2-Oxo-2*H*-chromen-2-one, Heterocyclic amines, Synthesis, Microbiological activity.

INTRODUCTION

4-Hydroxychromene-2-one differs for its chemical reactivity from all other chromene-2-ones, as it contains the enolized β-ketoesteric system. The molecule of 4-hydroxy-chromene-2-one contains two cycles: the benzene and the α-pyrone one, which has the -OH group attached at the 4th position. This α-pyrone nucleus, reacts faster than benzene one, with either electrophilic or nucleophilic reagents.

In continuation of our work[1-3] on the chemistry of 3,4-disubstituted-2-oxo-2*H*-chromene and the derived coumarines annelated in the 3,4-position, we decided to prepare some new 2-oxo-2*H*-chromene derivatives with a variety of nucleophiles, where we produced a number of novel condensed coumarines.

Chromene-2-one derivatives have been reported for anti-coagulant[4-6], antibacterial[7,8], anti inflamatory[9], antimicrobial[10], anti HIV[11-14], antioxidant[15], anticancer[16] and antiproliferative and antiviral[17] activities. It was found that when one biodynamic heterocyclic system was coupled with another heterocyclic system, enhanced biological activities were produced. These newly synthesized compounds (**4-6**), have similar structure with lots of chromene-2-one compounds that are well known for their physiological activities[18-20].

These wide ranges of biological properties, stimulated us to synthesize some new coumarin derivatives, to find optimal conditions of the organic synthesis and mechanisms of reactions and to investigate their microbiological activity against four *Staphylococcus aureus* ATCC, *Streptococcus pneumoniae, Aeromonas salmonicida* and *Bacillus spp*. The antibacterial activity of synthesized compound was compared with anti-bacterial activity of novobiocin as standard antibiotic.

EXPERIMENTAL

Melting points of synthesized compounds (**4-6**) were determined with a Buechi apparatus and are uncorrected. IR spectra (KBr in cm^{-1}) were recorded on Perkin Elmer Spectrum BXFTIR spectrophotometer, ^1H NMR were recorded on Bruker Avance DPX 300 spectrophotometer at 300 MHz for ^1H, using DMSO-d_6 and $CDCl_3$ as solvent, with TMS as the internal standard (chemical shifts in δ ppm). The purity of the compounds was monitored by TLC using precoated HF254 (60) silica gel plates.

Synthesis: 4-Hydroxychromene-2-one (**1**, 8 g) was added in 25 mL of dioxane and than carefully 6.6 mL of mono-chlorosulfonic acid was added. After short mixing solution was left for short period at a room temperature and then voluminous precipitate was formed. Precipitate (**2**) was filtered on a glass funnel and washed first with dioxane (20 mL) then with ethyl acetate (20 mL) and then with ether (20 mL). After washing we obtained a white powder (93 % yield). 5 g of precipitate **2**, (3-sulfo-4-hydroxycoumarinic acid), were added in 20 mL of thionyl chloride. The mixture was refluxed for 2 h, than solution was evaporated completely. We added a small amount of ethyl acetate to the residue, filtered and than washed with

ether. White crystals of 4-hydroxy-2-oxo-2*H*-chromene-3-sulfonyl chloride (**3**, yield 85 %) were recrystallize with small amount of benzene.

1 g, (0.0038 mol) of 4-hydroxy-2-oxo-2*H*-chromene-3-sulfonyl chloride (**3**) was dissolved in 20 mL of dry benzene and an appropriate equivalent portion of heterocyclic amino derivatives was added, in presence of triethylamine (2 mL), as catalyst and the mixture was refluxed for 2-8 h. After cooling, the precipitate was filtered off, washed with hot benzene and dried.

4-Hydroxy-2-oxo-2*H*-chromene-3-sulfonic acid (5-ethylsulfanyl-[1,3,4]thiadiazol-2-yl)-amide (4): A mixture of 4-hydroxy-2-oxo-2*H*-chromene-3-sulfonyl chloride (1 g, 0.0036 mol), 20 mL of dry benzene, 0,62 g (0.0038 mol) of 2-amino-5-ethylthio-1,3,4-thiadiazole and a portion of thriethylamine were refluxed for 2 h. The solution was filtered, washed off with benzene then crystallized from ethanol. The obtained product was white colour.

Yield 35.62 % m.p. 135 ºC, IR (KBr, ν_{max}, cm^{-1}) : 3800-3153 (OH, NH); 2920 (C-H al); 1703 (C=O, α-pir); 1621 (C=N); 1562-1356 (C=Car); 1207-1161 (SO_2); 751(C-Car); 648(C-S-C); ^{1}H RBM (DMSO-d_6) (ppm): 14.1 s (1H, OH); 7.88-5.75 m (4H, arom); 4.2 s (1H, NH); 3.14-2.49 s (3H, CH_3). $C_{13}H_{11}N_3O_5S_3$: C 40.51, H 2.87, N 10.90, Exp: C 39.50, H 2.90, N 10.40 M^+teo: 385.43; M^+exp: 385.43. M($C_{13}H_{11}N_3O_5S_3$) : 385 (7.2), 368 (21.5), 242 (88.7), 162 (93), 120 (100), 74 (46).

4-Hydroxy-2-oxo-2*H*-chromen3-3- sulfonic acid (5-methyl-isoxazole-3-yl)-amide (5): A mixture of 4-hydroxy-2-oxo-2*H*-chromene-3-sulfonyl chloride (1 g, 0.0036 mol), 20 mL of dry benzene, 0.37 g (0.0038 mol) 3-amino-5-methyl isoxazole and a portion of thriethylamine were refluxed for 4 h. The solution was filtered, washed off with benzene then crystallized from ethanol. The obtained product was white colour.

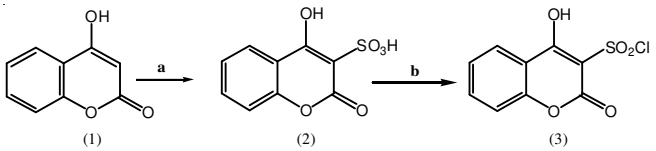
Yield 61.3 % m.p. 165.8 ºC, IR (KBr, ν_{max}, cm^{-1}): 3851-3158 (OH, NH); 3025 (C-Har); 2929 (C-H al); 1715 (C=O, α-pir); 1620 (C=N); 1556-1352 (C=Car); 1222-1164 (SO_2); 758 (C-Car); ^{1}H RBM (DMSO-d_6) (ppm): 14.09 s (1H, OH); 7.89-6.07 m (5H, arom); 3.14 s (1H, NH); 2.51-2.20 s (3H, CH_3). $C_{13}H_{10}N_2O_6S$: C 48.44, H 3.13, N 8.69, Exp: C 47.04, H 3.07, N 8.15.

4-Hydroxy-2-oxo-2*H*-chromene-3-sulfonic acid (1*H*-benzoimidazol-2-yl)-amide (6): A mixture of 4-hydroxy-2-oxo-2*H*-chromene-3-sulfonyl chloride (1 g, 0.0036 mol), 20 mL of dry benzene, 0.51 g (0.0038 mol) 2-amino benzimidazole and a portion of thriethylamine were refluxed for 8 h. The solution was filtered, washed off with benzene then crystallized from methanol. The obtained product was white colour.

Yield (97.05 %) m.p. 250.9 ºC, IR (KBr, ν_{max}, cm^{-1}): 3820-3300 (OH, NH); 1707-1671 (C=O, α-pir); 1608 (C=N); 1553-1430 (C=Car); 1261-1143 (SO_2); 749 (C-Car); ^{1}H RBM (DMSO-d_6) (ppm): 14.02 s (1H, OH); 12.37 s (1H, N-H); 8.36-7.21 m (8H, arom); 3.57 s (1H, NH). $C_{16}H_{11}N_3O_5S$: C 53.77, H 3.10, N 11.76, exp.: C 52.90, H 3.20, N11.02.

RESULTS AND DISCUSSION

4-Hydroxy-2-oxo-2*H*-chromene-3-sulfonyl chloride (**3**) was prepared by the series of reactions of 4-hydroxy-chromene-2-one with $ClSO_3H$ and $SOCl_2$. New compounds (**4-6**) (Fig. 1) were obtained in reaction of (**3**) with amino derivatives of heterocyclic compounds in presence of triethylamine (**Scheme-I**).



Scheme-I: Synthesis of 4-hydroxy-2-oxo-2*H*-chromene-3-sulfonyl chloride (**3**) Reagents: (a) $ClSO_3H$, (b) $SOCl_2$

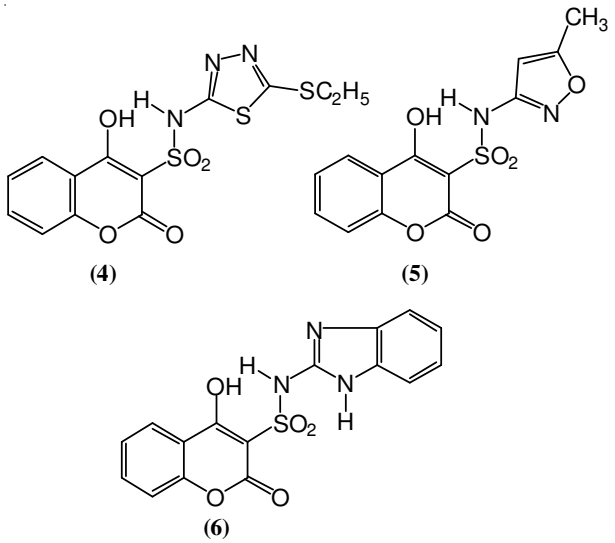


Fig. 1. Structure of synthesized compounds (**4-6**)

The structures of the compounds (**4-6**) were determined from spectral analysis IR, ^{1}H NMR, mass spectroscopy and elementary analysis. In IR spectra of (**4-6**) analyzed compounds we can see characteristic bands in region 1703-1715 cm^{-1} corresponding to C=O stretching, 1608-1621 cm^{-1} there is another band from C=N stretching, 1553-1352 cm^{-1} there is characteristic band for aromatic double bond C=C and SO_2 vibration are visible in 1207-1143 cm^{-1}.

In ^{1}H NMR spectra of gained compounds there are signals in expected positions, signals as multiplets that come from aromatic protons, are in 8.50-5.75 ppm.

Among the compounds tested for antibacterial activity, compounds showed highest zone of inhibition against *S. aureus* in higher concentrations and in lower concentration, the inhibition zone was higher against *Aeromonas salmonicida* and *Bacillus spp*.

Biological activity: The antimicrobial activity of synthesized compounds (**4-6**) was determined by cup plate, Kirby-Bauer method (Table-1). Antimicrobial activity was carried out against 24 h old cultures of *Staphylococcus aureus* β-lactamase positive ATCC 25923, collection of WRC (water regional company) from regional hospital, *Staphylococcus aureus* collection of WRC outside the regional hospital, *Streptococcus pneumoniae, Aeromonas salmonicida* collection of WRC, *Bacillus spp*, collection of WRC. The compounds were tested at three concentrations, 0.1, 0.3 and 0.5 mg/mL in dimethylformamide against all organisms. Novobiocin was used as standard drug for antibacterial activity.

TABLE-1
MICROBIOLOGICAL ACTIVITY OF NEWLY SYNTHESIZED COMPOUND

Comp.	Conc. (mg/mL)	*Staph. aureus ATCC (mm)*	*Staph. aureus hospital (mm)*	*Staph. aureus outside of hospital (mm)*	*Strept. pneum. (mm)*	*Aeromonas. salmon. salmonicida (mm)*	*Bacillus Spp. (mm)*	*Novobiocin (mm)*
	0.1	5	3	2	3	4	3	
4	0.3	7	2	0	3	4	3	29
	0.5	8	0	6	0	11	5	
	0.1	5	2	5	5	9	4	30
5	0.3	7	3	5	5	11	0	
	0.5	3	4	13	6	7	0	
	0.1	6	4	5	0	7	0	
6	0.3	6	2	7	8	9	0	25
	0.5	7	4	13	8	0	2	

The compounds showed strong to moderate activity in reducing the microbial growth. The inhibitory effects of compounds were affected by their substitution patterns. Compounds **5** and **6** showed the most effective antibacterial activity against *Staphylococcus aureus* in concentration 0.5 mg/mL (Fig. 3).

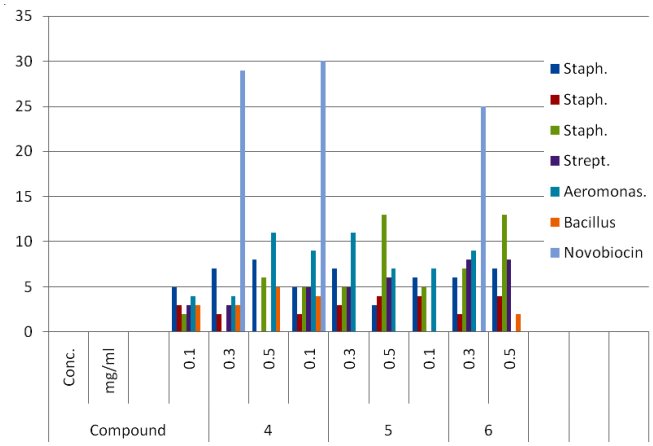


Fig. 3. Graphs of microbiological activity results for compounds **4-6**

Conclusion

The present study was aimed at synthesize some novel chromene-2-one derivatives. The compounds were screened for antibacterial activities and were found to possess considerable activity.

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