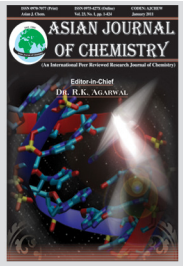
Asian Journal of Chemistry; Vol. 23, No. 9 (2011), 3996-3998

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in



Synthesis and Antibacterial Activities of Some 2*H*-Chromen-2-one Derivatives

KOZETA VASO[1,*], AZIZ BEHRAMI[2], SEVDIJE GOVORI[2] and IDRIZ VEHAPI[2]

[1]Department of Chemistry, Faculty of Natural Sciences, University of Tirana, Tirana, Albania
[2]Department of Chemistry, University of Pristine, Pristine, Kosovo

*Corresponding author: E-mail: kozeta_v@yahoo.it

(*Received*: 3 November 2010; *Accepted*: 14 May 2011) AJC-9952

This work reports the syntheses of some new 2*H*-chromen-2-one derivatives and their antibacterial activity. 4-(Naphthalen-1-ylamino)-2-oxo-2*H*-chromen-3-carbaldehyde (**a1**), N-(3-formyl-2-oxo-2*H*-chromen-4-yl)-N-naphthalen-1-yl-benzamide (**a2**), N-(7-butylamino-3-formyl-2-oxo-2*H*-chromen-4-yl)-N-naphtalen-1-yl-benzamide (**a3**) have been synthesized and characterized by IR spectra, ^{1}H NMR spectra and elemental analyses. The purified synthesized compound **a3** at concentrations 2, 3 and 5 mg/mL was subjected to test the antibacterial activity against three bacterial cultures; *Staphylococcus aureus*, *Escherichia coli* and *Bacillus cereus*. The antibacterial activity of synthesized compounds were compared with antibacterial activity of the standard antibiotics cephalexine and streptomycine. The compound shows different bacteriostatic and bactericidal activity.

Key Words: 2*H*-Chromen-2-one derivatives, Antibacterial activity, *Staphylococcus aureus*, *Escherichia coli*, *Bacillus cereus*, Cephalexine, Streptomycin, Cefaleksin.

INTRODUCTION

Using 4-hydroxy-2-oxo-chromen-3-carbaldehyde (**a**) as starting material, some new 2*H*-chromen-2-one (coumarin, 2*H*-1-benzopyran-2-one) derivatives **a1**, **a2** and **a3** are synthesized (**Scheme-I**). 2*H*-Chromen-2-one derivatives which are known as coumarin (specifically, a benzo-α-pyrone) derivatives are a large group of heterocyclic with oxygen as heteroatom[1-3]. Coumarin and its derivatives have various biological activities[4,5]. Most of them show antibacterial, bactericidal and bacteriostatic properties[6-8].

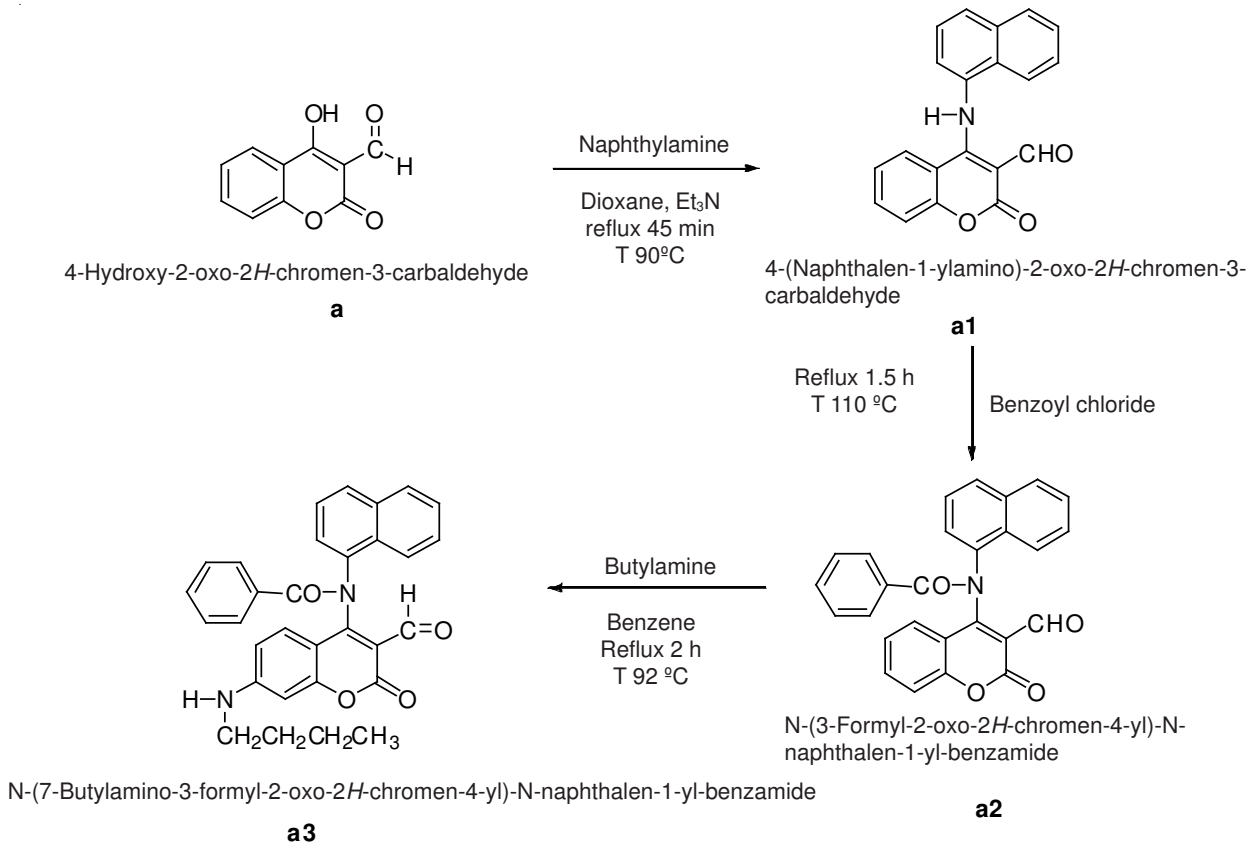
Biological activity of coumarin derivatives is linked with their structure. The different substituent in the structure of benzo-α-pyrone or benzene of coumarine has different effect in biological activity[9].

Literature shows that the biological activity of coumarin derivatives is closely linked with their influence in enzymatic processes or has an analogy of their structure with the active enzymatic centers. But, it's very important to stress that a general correlation between the structure of coumarin derivatives and their microbiological activity it's not yet found, although many efforts made by different researches[10].

These wide ranges of biological properties[11-13] have stimulated us to synthesize some new coumarin derivatives, to find optimal method, optimal conditions of the synthesis and mechanisms of reactions and to investigate their antibacterial activity against three bacterial cultures *Staphylococcus aureus*, *Escherichia coli* and *Bacillus cereus*. The antibacterial activity of synthesized compounds were compared with antibacterial activity of streptomycin and cephalexine as standard antibiotics.

EXPERIMENTAL

Compounds 4-(naphthalen-1-ylamino)-2-oxo-2*H*-chromen-3-carbaldehyde (**a1**), N-(3-formyl-2-oxo-2*H*-chromen-4-yl)-N-naphthalen-1-yl-benzamide (**a2**) and N-(7-butylamino-3-formyl-2-oxo-2*H*-chromen-4-yl)-N-naphthalen-1-yl-benzamide (**a3**) are synthesized. The identification of 2*H*-chromen-2-one derivative (**a3**) is made by using melting point, infrared, ^{1}H NMR spectra and elemental analysis. Melting point was determinated on an 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}. ^{1}H NMR spectra were recorded on a Bruker UNITY plus-500 'NMR 1' spectrometer using DMSO-d_6 as the solvent and TMS as the internal reference standard (σ = 0,00 ppm). Chemical shifts are expressed in δ ppm. Mass spectra were taken on a LKB 9000 mass spectrometer. Elemental analyze was preformed on a Perkin-Elmer 240 BCHN analyzer. The purity of the compounds (synthesized) was routinely checked by TLC using Merck Kieselgel-60 (F-254) and benzen:toluen:glacial acetic



Scheme-I: Synthesis of 2*H*-chromen-2-one derivatives **a1**, **a2** and **a3**

acid (80:10:10) as mobile phase. The spots were exposed in iodine vapour for visualization.

Synthesis of 4-(naphthalen-1-ylamino)-2-oxo-2*H*-chromen-3-carbaldehyde (a1): For this synthesis, 4-hydroxy-2-oxo-chromen-3-carbaldehyde is used as substrate. In a 100 mL flask mixed 3 g of 4-hydroxy-2-oxo-chromen-3-carbaldehyde (**a**) with 1.5 g α-naphthylamine diluted in 10 mL dioxane and 0.3 mL triethylamine as catalyzer. The mixture was refluxed at 90 ºC for *ca.* 45 min. The obtained crystals yellow and orange are filtered and rinsed with dioxane and dried at room temperature. Recrystallization from absolute ethanol gave a yellow product of **a1** compound at 80 % yield (**Scheme-I**).

Synthesis of N-(3-formyl-2-oxo-2*H*-chromen-4-yl)-N-naphthalen-1-yl-benzamide (a2): In a 100 mL flask were mixed 2.5 g of 4-(naphthalen-1-ylamino)-2-oxo-2*H*-chromen-3-carbaldehyde (**a1**) with 3 mL benzoyl chloride. The mixture was refluxed at 110 ºC for *ca.* 1.5 h. The obtained yellow crystals are filtered and dried at room temperature. Recrystallization from benzene gave a yellow product of **a2** compound at 72 % yield (**Scheme-I**).

Synthesis of N-(7-butylamino-3-formyl-2-oxo-2*H*-chromen-4-yl)-N-naphthalen-1-yl-benzamide (a3): In a 100 mL flask were mixed 2 g OF N-(3-formyl-2-oxo-2*H*-chromen-4-yl)-N-naphthalen-1-yl-benzamide (**a2**) with 10 mL benzene and 1 mL butylamine. The mixture was refluxed at 92 ºC in water bath for *ca.* 2 h. The flask was placed in AN ice bath for 1 h until a yellow crystalline precipitate was formed. After filtration the product was recrystallized from benzene. The recrystallization from benzene gave a yellow product of **a3** compound at 72 % yield, melting point 150 ºC (**Scheme-I**).

Antibacterial activity: The purified synthesized compound **a3** was subjected to test *in vitro* its antibacterial activity against three bacterial cultures; *Staphylococcus aureus*, *Escherichia coli* and *Bacillus cereus*. Antibacterial activity of compound was investigated applying the Kirby-Bayer method[14] or disc method (d = 5.5 mm, max. capacity 10 μg).

RESULTS AND DISCUSSION

By reacting equimolar amounts of 4-hydroxy-2-oxo-chromen-3-carbaldehyde (**a**) and corresponding reagents acoording to **Scheme-I**, under reflux reaction conditions product (**a3**), is synthesized in 65 % yield. The structure of N-(7-butylamino-3-formyl-2-oxo-2*H*-chromen-4-yl)-N-naphthalen-1-yl-benzamide (**a3**) was determined from its IR, ^{1}H NMR spectra, melting point and elemental analyze as follows:

IR bands (KBr, ν_{max}, cm^{-1}): 3300, 3010-2820 (N-H vibration, C-H aromatic, C-H aliphatic), 1720-1650 (C=O, α-pironi), 1570-1400 (C=C aromatic vibration), 750 (C-C aromatic). ^{1}H NMR (DMSO-d_6) δ ppm: 9.06 s(1H; CHO); 8.12-7.37 m(16 H aromatic), 3.90-3.22 d(NH); 2.73-2.27 d(6H, CH_2); 0.94-0.88 s(6H CH_3); 1.23 (H, $NHCH_2$).m.f. $C_{31}H_{28}N_2O_4$, m.p. 150 ºC. Elemental analysis: calcd. (found) (%): C 73 (72); H 4.80 (4.30); N 4.90 (4.40).

Antibacterial activity against *Staphylococcus aureus*, *Escherichia coli* and *Bacillus cereus*: The purified synthesized compound **a3** was screened for its antibacterial activity

TABLE-1
ANTIBACTERIAL ACTIVITY OF COMPOUND **a3**

Compd.	*Staphylococcus aureus*			*Escherichia coli*			*Bacillus cereus*		
	2 mg/mL	3 mg/mL	5 mg/mL	2 mg/mL	3 mg/mL	5 mg/mL	2 mg/mL	3 mg/mL	5 mg/mL
	Inhibition zone (mm)			Inhibition zone (mm)			Inhibition zone (mm)		
a3	6	10	13	6	7	10	12	14	16
Cephalexine	7	7	7	11	11	11	9	9	9
Streptomycine	20	20	20	7	7	7	23	23	23

against three bacterial cultures; *Staphylococcus aureus*, *Escherichia coli* and *Bacillus cereus*. Antibacterial activity of compound was investigated applying the Kirby-Bayer method[14] or disc method (d = 5.5 mm, max. capacity 10 µg). The disc was wetted with N,N-DMF solutions of the synthesized compound in concentrations 2, 3 and 5 mg/mL and then are placed in petridish (d = 15 cm). The bacterial cultures *Staphylococcus aureus*, *Escherichia coli* and *Bacillus cereus* were poured and spread in petridish in blood Agar. The discs were incubated at 35 ºC for 48 h. The control was also maintained with DMF, streptomycine and cephalexine in similar manner. The diameters of the inhibition zones of the bacterial growth were measured in mm and the results are given in Table-1.

In *Staphylococcus aureus* antibacterial activity of **a3** compound is weaker than of streptomycine and antibacterial activity of **a3** compound is stronger than of cephalexine. In *Staphylococcus aureus* **a3** compound compared with the antibacterial activity of cephalexine.

In *Escherichia coli* antibacterial activity of **a3** compound is stronger than of streptomycine and antibacterial activity of **a3** compound is almost the same as cephalexine in concentration 5 mg/mL. In *Escherichia coli* **a3** compound compared with the antibacterial activity of streptomycine.

In *Bacillus cereus* antibacterial activity of **a3** compound is weaker than of streptomycine and antibacterial activity of **a3** compound is stronger than of cephalexine. In *Bacillus cereus* **a3** compound compared with the antibacterial activity of cephalexine.

Conclusion

From the results the following conclusions were drawn:

(1) This study provides the first evidence that compound **a3** obviously inhibit the growth of *Staphylococcus aureus*, *Escherichia coli* and *Bacillus cereus*.

(2) According to extensive NMR experiments and published data, the chemical structures of synthesized compound was determined.

(3) Comparing the inhibition zones of the compound **a3** it is observed a significant antibacterial effect against *Staphylococcus aureus*, *Escherichia coli* and *Bacillus cereus*.

(4) Comparing the inhibition zones of the compound **a3** it is observed that the increasing of concentration causes high antibacterial activity against these microorganisms.

(5) Antibacterial activity of **a3** compound is stronger than of cephalexine in *Staphylococcus aureus* and *Bacillus cereus*. The **a3** compound compared with the antibacterial activity of cephalexine in *Staphylococcus aureus* and *Bacillus cereus* is bactericide.

(6) Antibacterial activity of **a3** compound is stronger than of streptomycine in *Escherichia coli*. The **a3** compound compared with the antibacterial activity of streptomycine in *Escherichia coli* is bactericid.

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. Rapic, O. Leci, M. Cacic and I. Tabakovic, *J. Heterocycl. Chem.*, **33**, 351 (1996).
2. S. Govori, V. Kalaj, V. Rapic, L. Kalaj and S. Dakovic, *Heterocycl. Commun.*, **8**, 129 (2002).
3. B. Stanovnik, H. Susachitzky and E.F. Scriven, Progress in Heterocyclic Chemistry, Pergamon Press, Oxford, Vol. 5, pp. 75-146 (1993).
4. S.H. Lee, D.-S. Shin, J.S. Kim, K.-B. Oh and S.S. Kan, *Arch. Pharm. Res.*, **26**, (2003).
5. K.B. Vyas, K.S. Nimavat, G.R. Jani and M.V. Hathi, *Orbital*, **1**, 183 (2009).
6. A.Z. Abyshev, V.A. Gimdein, E.V. Semenov, E.M. Agaev, A.A. Abdulla-Zade and A.B. Guseinov, *Pharm. Chem. J.*, **40**, 607 (2006).
7. A. Behrami, K. Vaso and I. Krasniqi, *J. Int. Environ. Appl. Sci.*, **5**, 247 (2010).
8. R. Hoti, O. Leci, V. Kalaj, M. Bicaj, S. Govori and V. Kolshi, *Acta Chim. Kosovica*, **12**, 91 (2003),
9. M.D. Aytemir, R.C. Hider, D.D. Erol, M. Ozalp and M. Ekizoglu, *Turk. J. Chem.*, **27**, 445 (2003).
10. M.M. El-Saghier, M.B. Naili, B. Kh. Rammash, N.A. Saleh and K.M. Kreddan, *Arkivoc*, 83 (2007).
11. J.R. Hoult and M. Paya, *Gen. Pharmacol.*, **27**, 713 (1996).
12. R.M. Mohareb, J.Z. Ho and A.A. Mohamed, *Phosophus Sulfur Silicon Rel. Elem.*, **182**, 1661 (2007).
13. Z.M. Nofal, M. El-Zahar and S. Abd El-Karim, *Molecules*, **5**, 99 (2000).
14. A.L. Barry, Procedure and Theoretical Consideration for Testing Antimicrobial Agents in Agar Media, William Wilkins Baltimore, edn. 5 (1991).