

From the Research Laboratories
В изследователските лаборатории

NOVEL HETEROARYLAMINO-CHROMEN-2-ONES AND THEIR ANTIBACTERIAL ACTIVITY

¹Ramiz Hoti, ¹Naser Troni*, ¹Hamit Ismaili,
²Gjyle Mulliqi-Osmani, ¹Veprim Thaçi

¹University of Prishtina – Kosovo

²Institute of Public Health of Kosovo

Abstract. A series of heteroaryl-amino-chromen-2-ones 4(a-c) were synthesized by condensation reactions under catalytic conditions. 5-(3-Nitro-2-oxo-2H-chromen-4-ylamino)-3H-imidazole-4-carboxamide **4a**, 4-(7-Hydroxy-5-methyl-[1,8]-naphthyridin-2-ylamino)-3-nitrochromen-2-one **4b** and 4-(4-methylbenzothiazol-2-ylamino)-3-nitrochromen-2-ones **4(c-d)** were synthesized by condensation of 4-chloro-3-nitrochromen-2-one **2** with corresponding heteroarylamines **3(a-d)** under reflux reaction conditions. Alkali hydrolysis of compounds **4(a-d)** afforded the 2-hydroxy-*o*-nitroacetophenone **5**. The structures of the obtained compounds were established on the basis of FTIR and NMR spectrometric data and their elemental analysis. Compounds of series **4(a-c)** were screened for their antibacterial activity against *S. aureus*, *E. coli* and *Klebsiella* by Diffusion Disc Method. Compounds **4(a-c)** displayed considerable activity against these microorganisms and the impact of substitutions in antimicrobial activity was also explored.

Keywords: Chromen-2-one; imidazole; naphthyridine; benzothiazole; zones of inhibition

Introduction

Coumarins are important class of oxygen heterocycles and are well-known for their biological activity. Many of coumarin derivatives have been found in nature and isolated from various plants. Coumarinic derivatives play an important role in various life processes and they are found as an ingredient of the plant world. Some 4-Aryl-chromen-2-ones as the major structural type of neoflavonoids are reported to express anti-HIV activity (Olmedo et al., 2017). Many of such derivatives exhibited various biological activities (Kontogiorgis & Hadjipavlou-Litina, 2004). Novobiocin, coumaromycin and chartesium are potent antibiotics with coumarin moiety. Many of coumarins exhibited antibacterial (Rajasekaran et al., 2011; Kshwaha et al., 2014), anticoagulant (Manolov et al., 2006), antimicrobial (Mohamed et al., 2012), and antimalarial (Pingaew et al., 2014) activity. Some of coumarinic

analogues exhibited antioxidant (Vasquez-Rodriguez et al., 2013; Linet al., 2014), anti-tubercular (Keriet al., 2015) and anticonvulsant (Amin et al., 2008) activity as well. It was reported that a significant number of substituted coumarin derivatives showed, sedative (Mohammad et al., 2013), anti-HIV (Kostova et al., 2006) and hepatoprotective (Atmaca et al., 2011) activity. It is indicative that many of naturally and synthetic coumarins have found widespread usage in pharmacies (Küppers et al., 2016). The biological activity is conditioned by their structure, so the presence of different substituents on the coumarine ring indicates their impact on the type and potency of biological activity. Despite continuous efforts, the relationship between structure and biological activity of these derivatives, so far has not yet been sufficiently clarified. Extraordinary biological importance of derivatives on the basis of coumarine has generated a constant interest in their synthesis and research. In view of the considerable importance of these derivatives and in continuation of our previous studies (Hoti et al., 2014; 2016), the present work is aimed at the design and synthesis of new substituted 4-heteroaryl-amino-3-nitro-chromen-2-ones. Moreover, this study includes testing of target compounds for their antibacterial activity against *S. Aureus*, *E. Coli* and *Klebsiella*.

Material and methods

All the chemicals used in the synthesis were of analytical grade as commercial reagents of Aldrich company. The compounds are synthesized by refluxing using acetonitrile as an aprotic solvent. Reactions were monitored by TLC using MerckKieselgel-60 (F_{254}) as the stationary phase and a mixture of benzene, toluene, glacial acetic acid (v/v/v, 80:10:10) as the mobile phase and visualisation is made on a bromine bath. The synthesized products were purified by crystallization from methanol and ethanol. All melting points were determined on a paraffin oil bath with an open capillary tube. FTIR spectra were recorded in KBr discs on Shimadzu 8400xFTIR spectrometer with 4 cm^{-1} resolution. ^1H -NMR and ^{13}C -NMR spectra were recorded in DMSO on UNITYplus-300 "NMR 1" spectrometer and chemical shifts were reported in ppm downfield from TMS as an internal standard (δ 0.00). Microanalyses of the synthesized compounds were performed on a Perkin-Elmer 240 B CHN analyser. Screening of the antibacterial activity of these compounds was done on the basis of Standard Disc Method using standard discs ($d=5.0\text{mm}$, maximum capacity 10 μg). The experiments were carried out at three different concentrations and standard discs were previously impregnated with 2 mg/mL , 4 mg/mL and 6 mg/mL solutions of compounds in N,N-DMF.

4-Heteroaryl-amino-3-nitro-chromen-2-ones 4(a-d), general procedure

In a typical reaction, 4-Chloro-3-nitro-chromen-2-one **2** (2.25 g, 1.0 mmol) was dissolved in 15 mL of acetonitrile, then the mixture containing corresponding 1.0 mmol of heteroarylamine **3(a-d)** in 10 mL acetonitrile was added in small

portions. After that, three drops of triethylamine was added and the reaction mixture was stirred for 15 minutes at room temperature, then refluxed for 4 to 8 hours in a water bath. After cooling, the mixture was filtered off under vacuum and washed with 2×0.5 mL of acetonitrile. The crude product was dried and crystallized from methanol, giving corresponding 4-Heteroaryl-amino-3-nitro-chromen-2-ones 4(a-d).

5-(3-Nitro-2-oxo-2H-chromen-4-ylamino)-3H-imidazole-4-carboxamide 4a

Reflux: 4 hour, brown crystalline product, yield: 58.24%, m.p.: >270 °C. FT-IR(KBr, ν , cm^{-1}): 3344.24, 1656.32, 1606.76, 1557.92, 1551.27, 1427.49, 1367.37, 1335.15, 1276.74, 1123.64, 1065.28, 901.05, 761.43, 672.14. $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$, δ , ppm): δ 4.5 (s, 1H, N-H), δ 5.8 (s, 2H, NH_2), δ 7.2-7.7 (m, 4H, Ar-H), δ 8.2 (s, 1H, C-H imidazole), δ 10.5 (s, 1H, N-H imidazole). $^{13}\text{C-NMR}$ (300 MHz, $\text{DMSO-}d_6$, δ , ppm): 170.5 (CONH_2), 166.4 (C-NH_2), 163.2 (C=O), 152.1, 148.3, 135.6, 128.8, 128.1, 127.4, 125.5, 120.2, 108.4. Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{N}_5\text{O}_5$: C, 49.51, H, 2.88, N, 22.21, O, 25.39, Found: C, 49.48, H, 2.92, N, 22.12%.

4-(2-hydroxy-4-methyl-1,8-naphthyridyl-7-amino)-3-nitro-2H-[1]-benzopyran-2-one 4b

Reflux: 7 hour, green brown crystalline product, yield: 62.58%, m.p.: >270 °C. FT-IR(KBr, ν , cm^{-1}): 3368.36, 3344.32, 3139.74, 3059.47, 2957.22, 1664.16, 1624.46, 1547.35, 1524.93, 1425.38, 1370.72, 1248.86, 1151.44, 1064.24, 885.04, 842.68, 702.12, 685.63. $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$, δ , ppm): δ 2.5 (s, 3H, CH_3), δ 4.2 (s, 1H, NH), δ 5.3 (s, 1H, OH), δ 6.8-7.7 (m, 7H, Ar-H). $^{13}\text{C-NMR}$ (300 MHz, $\text{DMSO-}d_6$, δ , ppm): 165.1 (C-OH), 164.4 (C-NH), 162.0 (C=O), 161.5, 152.2, 149.4, 146.3, 139.5, 129.8, 127.2, 126.1, 125.6, 121.4, 121.2, 114.6, 109.2, 108.4, 20.5 (CH_3). Anal. Calcd. for $\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_4$: C, 65.05, H, 3.48, N, 16.09, O, 18.39, Found: C, 65.09, H, 3.49, N, 15.98%.

4-(2-Benzothiazolylamino)-3-nitro-2H-1-benzopyran-2-one, 4c

Reflux: 5 hour, yellow-orange crystalline product, yield: 62.58%, m.p.: >270 °C. FT-IR(KBr, ν , cm^{-1}): 3176.22, 3067.43, 1697.38, 1607.56, 1560.48, 1446.26, 1305.22, 1277.89, 1139.34, 1018.54, 849.78, 762.25. $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$, δ , ppm): δ 7.2-8.2 (m, 8H, Ar-H), δ 4.3 (s, 1H, NH). $^{13}\text{C-NMR}$ (300 MHz, $\text{DMSO-}d_6$, δ , ppm): 175.2 (C-NH), 166.1 (C-NH), 164.4 (C=O), 151.0, 145.5, 127.6, 127.5, 127.2, 126.8, 126.5, 126.3, 123.0, 122.8, 122.1, 120.4. Anal. Calcd. for $\text{C}_{16}\text{H}_9\text{N}_3\text{O}_4\text{S}$: C, 56.62, H, 2.67, N, 12.39, O, 18.88, S, 9.44, Found: C, 56.80, H, 2.70, N, 12.27, S, 9.71%.

4-(4-methoxy-2-benzothiazolylamino)-3-nitro-2H-1-benzopyran-2-one, 4d

Reflux: 4 hour, yellow crystalline product, yield: 87.24%, m.p.: 219-221 °C. FT-IR(KBr, v, cm⁻¹): 3177.85, 2940.38, 1709.64, 164603, 1596.16, 148.44, 1367.65, 1281.83, 1041.62, 764.26. ¹H-NMR (300 MHz, DMSO-*d*₆, δ, ppm): δ7.0-7.8 (m, 7H, Ar-H), δ4.2 (s, 1H, NH), δ3.6 (s, 3H, OCH₃). ¹³C-NMR(300 MHz, DMSO-*d*₆, δ, ppm): 171.5 (C-NH) 166.2 (C-NH), 163.7 (C=O), 158.4, 151.2, 136.0, 130.2, 128.1, 127.2, 126.9, 125.6, 123.5, 122.0, 116.1, 111.2, 109.5, 60.02 (OCH₃). Anal. Calcd. for C₁₇H₁₁N₃O₅S: C, 55.27, H, 3.00, N, 11.37, O, 21.67, S, 8.67, Found: C, 55.47, H, 3.02, N, 11.26, S, 8.72%.

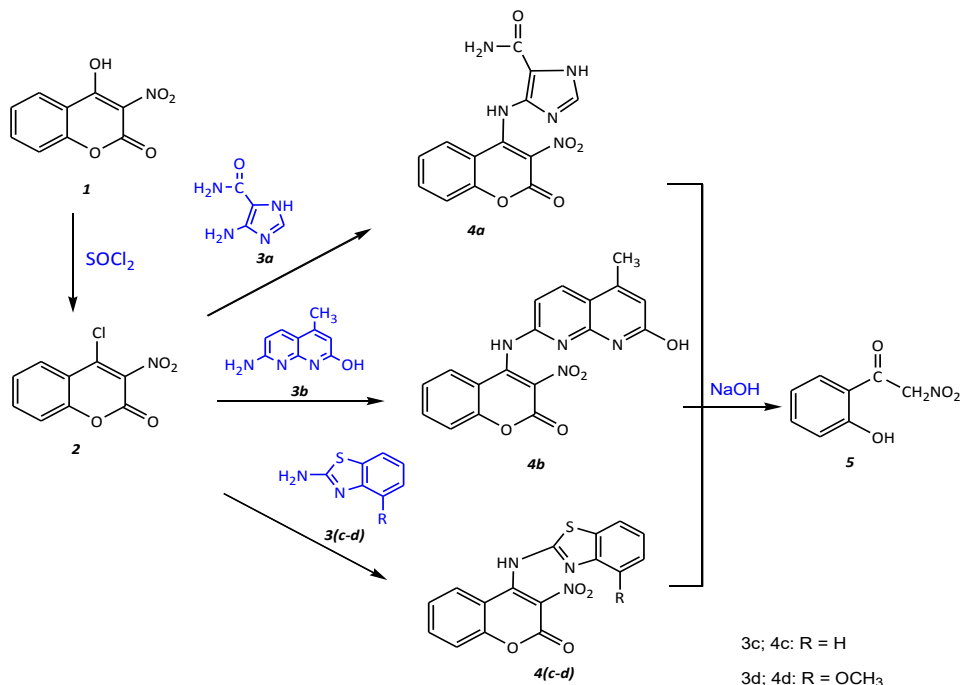
2-hydroxy-ω-nitroacetophenone 5

2 mmol of heteroaryl-amino-2H-1-chromen-2-one 4(a-c) was dissolved to a 10 mL of water solution of sodium hydroxide 5% and then heated for 1 hour at 95 °C. The reaction mixture was cooled and acidified with diluted hydrochloric acid and ice to pH=1. The crude product was filtered off and washed with 3 x 2 mL of distilled water. Crystallization from ethanol gave 0,3g (84%) of 2-hydroxy-ω-nitroacetophenone 5.

Mp=96-98 °C, **IR**: 3400.97, 3085.34, 2950.32, 1637.68, 1613.44, 1560.68, 1449.74, 1369.23, 754.41. **¹H-NMR**: δ12,92 (s, 1H), δ11,41 (s, 1H), δ7,87 (d, 1H), δ7,64 (d, 1H), δ7,18 (q, 2H), δ 6,28 (s, 2H). Anal. Calcd. For C₈H₇NO₄: C, 53.04, H, 3.89, N, 7.74, O, 35.32, Found: C, 52.94, H, 4.18, N, 7.71%.

Results and discussion

According to our previous investigation, by condensation reaction of 4-hydroxy-3-nitrobenzopyran-2-one **1** with phosphooxychloride in N,N-dimethyl-formamide, 4-chloro-3-nitro-2H-[1]-benzopyran-2 one **2** was synthesized in good yield. Corresponding heteroaryl-amino-chromen-2-ones **4(a-c)** were synthesized by condensation reactions of compound **2** with various heteroarylamines **3(a-d)**. Condensation of **2** with 4-aminoimidazole-5-carboxamide **3a** yielded 5-(3-nitro-2-oxo-2H-chromen-4-ylamino)-3H-imidazole-4-carboxamide **4a**. By condensation reaction of **2** with 7-amino-2-hydroxy-4-methyl-1,8-naphthyridine **3b**, corresponding 4-(2-hydroxy-4-methyl-1,8-naphthyridyl-7-amino)-3-nitro-2H-[1]-benzopyran-2-one **4b** was synthesized. On the other hand, reaction of compound **2** with 2-aminobenzithiazole **3c** and 4-methoxy-2-aminobenzothiazole **3d** afforded respective 4-(2-benzothiazolylamino)-3-nitro-chrome-2-one **4c** and 4-(4-methoxy-2-benzothiazolylamino)-3-nitro-chromen-2-one **4d**. By alkali hydrolysis of the products **4(a-d)** everyone gave 2-hydroxy-ω-nitroacetophenone **5**. Synthesis of heteroaryl-amino-chromen-2-ones and their hydrolysis are summarized in Scheme 1.



Scheme 1

Structural characterization of the synthesized products is based on spectrometric FTIR, ¹H-NMR and ¹³C-NMR data and on their elemental analysis as well. The IR spectrum of compound **4a** showed an absorption band at 3344.24 cm⁻¹ confirming the presence of -NH₂ group. Two peaks at 1656.32 and 1606.76 cm⁻¹ are assigned from corresponding lactone and amide carbonyl functions. The absorption signals at 1557.92 and 1551.27 cm⁻¹ appear due to aromatic ν(C=N) and ν(C=C) stretching vibrations. The typical modes for asymmetric and symmetric ν(NO₂) were appeared at 1427.49 and 1367.37 cm⁻¹ whereas a signal at 761.43 cm⁻¹ resulted from out of plane bending δ(CH) of aromatic system. On the other hand, the ¹H-NMR spectrum of **4a** corresponds to the absorption of respective protons. A multiplet at δ 7.2–7.7 ppm resulting from aromatic protons is displayed. Furthermore, characteristic signals at δ 5.8 ppm and δ 10.5 ppm correspond to amide and imidazole NH protons.

In the IR spectra of compound **4b** showed the absorption peaks at 3368.36 and 3344.32 cm⁻¹ which are responsible for ν(NH) and ν(OH) stretching vibrations, while the signals at 3059.47 and 2957.22 cm⁻¹ appear due to aromatic and methyl ν(CH) stretching vibrations. The characteristic peaks which may correspond to lactonic ν(CO), ν(C=N), and ν(C=C) respectively were appeared at 1664.16 cm⁻¹.

1624.46 and 1524.93 cm^{-1} . The absorption modes at 1425.38, 1370.72 and 842.68 cm^{-1} may be assigned from asymmetric and symmetric $\nu(\text{NO}_2)$ stretching and aromatic δCH out of plane vibrations. The ^1H -NMR spectra of **4b** show the multiplet signals of aromatic protons at 6.8-7.7 ppm. A proton singlet resulting from N-H at 4.2 ppm and another at 5.3 ppm from O-H appear as well. In the ^{13}C -NMR spectra of **4b** signals at 165.1, 164.4, and 162.0 ppm, correspond to C-OH, C-NH and C=O and a signal at 20.5 ppm resulting from CH_3 carbons is displayed as well.

The IR spectrum of compound **4c** show a broad signal at 3170 – 3200 cm^{-1} responsible for $\nu(\text{NH})$ stretching vibrations and two bands at about 3100–2900 cm^{-1} characteristic for $\nu(\text{CH})$ stretching vibration of aromatic ring. A sharp peak at 1697.38 cm^{-1} and peaks at 1607.56 and 1560.48 cm^{-1} responsible for stretching $\nu(\text{CO})$, $\nu(\text{C}=\text{N})$ and $\nu(\text{C}=\text{C})$ of aromatic system were appeared as well. The $\nu(\text{CO})$ mode was assigned to low frequencies, may be as a result of decreasing of the respective force constant and the bond order (Hoti et al., 1995). The peak at 1446.26 cm^{-1} corresponds to absorptions of $\nu(\text{NO}_2)$ stretching asymmetric, while the one at 1305.22 cm^{-1} resulted from $\nu(\text{NO}_2)$ stretching symmetric vibrations. The aromatic out of plane $\delta(\text{CH})$ bending mode at 762.25 cm^{-1} also was displayed. In the ^1H -NMR spectrum of **4c**, besides multiplets of aromatic protons at 7.2-8.2, a proton singlet resulting from N-H is appeared at 4.3 ppm. The ^{13}C -NMR spectrum of **4c** appeared signals at 175.2 and 166.1 ppm for C-NH and a signal at 164.4 for C=O is displayed as well.

The formation of **4d** is confirmed on the basis of ^1H -NMR spectrum where a 3 proton singlet at δ 3.6 ppm responsible for methoxy protons is appeared. The spectrum also displayed a proton singlet at δ 4.2 ppm assigned for NH and a multiplet for aromatic protons at δ 7.0-7.8 ppm. The ^{13}C -NMR spectrum of **4d** showed characteristic absorptions at 171.5 and 166.2 ppm for C-NH and a signal at 163.7 ppm due to C=O carbon.

In the IR spectrum of compound **5** the characteristic modes at 3080–3400 cm^{-1} (broad band) and 2950.32 cm^{-1} which are responsible for stretching $\nu(\text{OH})$, $\nu(\text{OH})$ (helat), aromatic $\nu(\text{CH})$ and methylene $\nu(\text{CH})$ absorptions were appeared. The characteristic peak resulted from lactonic carbonyl as a result of intramolecular hydrogen bond is moved down at 1637.68 cm^{-1} . The IR spectrum of the hydrolysis product **5** also showed bands at 1560.68 cm^{-1} for aromatic $\nu(\text{C}=\text{C})$, at 1449.74 cm^{-1} for asymmetric $\nu(\text{NO}_2)$, at 1369.23 cm^{-1} for symmetric $\nu(\text{NO}_2)$ and at 754.41 cm^{-1} for aromatic out of plane δCH bending vibrations. We may suppose that formation of product **5** followed by tautomerization of precursors resulting to imine formation, then imine hydrolysis and decarboxylation. In addition to that, the elemental analysis of the synthesized compounds indicated in favor of described structures.

Antibacterial activity of the products 4(a-c)

Following this study, synthesized compounds **4(a-c)** are investigated for their antibacterial activity. Our research is oriented to test the activity against bacteria *S.*

aureus, *E. coli* and *Klebsiella*, on the basis of Standard Disc Method (Bauer et al., 1966), by measuring the zones of inhibition. Standard discs have previously been impregnated with solutions of the compounds in N,N-DMF with concentrations of 2 mg mL⁻¹, 4 mg mL⁻¹ and 6 mg mL⁻¹. Results for diameter of zones of inhibition are expressed in mm and were summarized in Table 1 and Figs. 1-3.

Table 1. Zone of inhibition (mm) around the discs impregnated with various concentration of synthesized compound

	S. aureus			E. coli			Klebsiella		
	2 mg mL ⁻¹	4 mg mL ⁻¹	6 mg mL ⁻¹	2 mg mL ⁻¹	4 mg mL ⁻¹	6 mg mL ⁻¹	2 mg mL ⁻¹	4 mg mL ⁻¹	6 mg mL ⁻¹
4a	8.5	7.2	8.6	9.8	10.1	10.4	8.2	8.2	8.4
4b	7.6	7.4	7.8	8.8	9.5	8.9	9.1	9.2	9.2
4c	10.1	10.3	20.6	9.8	9.9	10.1	8.4	8.5	8.8
4d	12.6	10.4	20.4	9.1	9.1	9.3	9.8	10.2	10.2

Compounds of series **4** showed considerable antimicrobial activity against these microorganisms. Compounds **4d** and **4c** were most active against *S. aureus*. Emphatic activity against *E. coli* exhibited compound **4a**, whereas **4d** and **4b** were more active against *Klebsiella*. Antibacterial activity against *E. coli* and *Klebsiella* shown as bactericide activity is displayed in a large-scale. Furthermore, these compounds express both bacteriostatic and bactericide activity against *S. aureus*. Bacteriostatic activity is exhibited in large range (+2.5 mm), whereas bactericide activity shows smaller zone of inhibition. Heteroarylamine moiety shows significant impact on antimicrobial activity. Likewise, the impact substituents are distinctive.

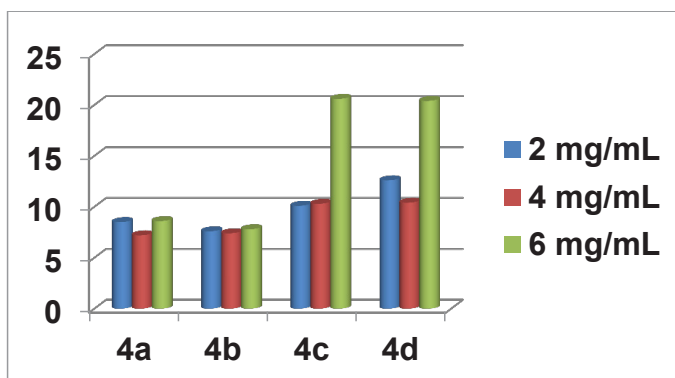


Fig. 1. Graphical presentation of zones of inhibition (mm) against *S. aureus*

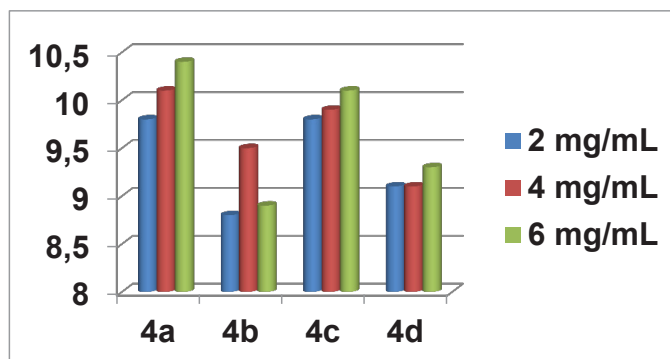


Fig. 2. Graphical presentation of zones of inhibition(mm) against *E. coli*

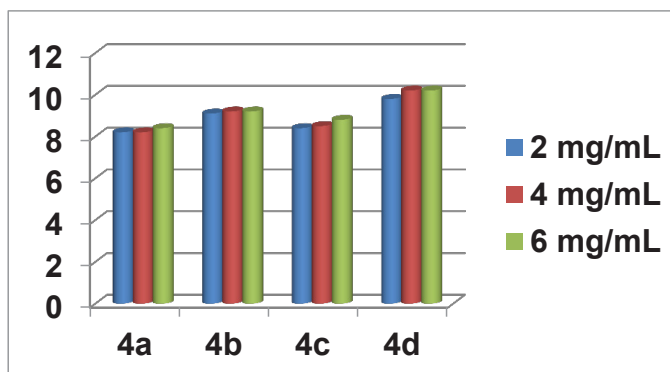


Fig. 3. Graphical presentation of zones of inhibition (mm) against *Klebsiella*

It has been assumed that antibacterial activity may result as a consequence of the involvement of these compounds in various enzymatic reactions. They may cause enzymatic inhibition cell wall construction of the microorganisms. However, the mechanism of enzymatic inhibition has not been fully studied yet. In general, by increasing the concentration of solvents, their antimicrobial activity increases.

Conclusion

Novel derivatives of heteroaryl-amino-chromen-2-ones **4(a-c)** are synthesized in the high and moderate yield. It has been concluded that compounds **4d** and **4c** show significant activity against *S. aureus*, compounds **4a** display more activity against *E. Coli*, whereas **4d** and **4b** were more active against *Klebsiella* bacteria. Antibacterial activity is shown to be proportional to the concentration of these compounds and the impact of structure and substituents in antibacterial activity was significant.

REFERENCES

- Amin, K.M., Abdel Rahman, D.E. & Al-Eryani, Y.A. (2008). Synthesis and preliminary evaluation of some substituted coumarins as anticonvulsant agents. *Biorg. & Med. Chem.*, 16, 5377 – 5388.
- Atmaca, M., Bilgin, H.M., Obay, B.D., Diken, H., Kelle, M. & Kale, E. (2011). The hepatoprotective effect of coumarin and coumarinderivates on carbon tetrachloride-induced hepatic injury by antioxidative activities in rats. *J. Physiol. Biochem.*, 67, 569 – 576.
- Bauer, A.W., Kirby, W.M., Sherris, J.C. & Turck, M. (1966). Antibiotic susceptibilitytesting by a standardized single disk method. *Amer. J. Clin. Pathol.*, 44, 493 – 496.
- Hoti, R., Vancik, H. & Mikalic, Z. (1995). About the nature of carbon-nitrogen triple bond in complexes of nitriles with strong Lewis acids. *Croatica Chimica Acta*, 68, 359 – 371.
- Hoti, R., Nura-Lama, A., Mulliqi-Osmani, G., Troni, N., Gashi, F., Ismaili, H. & Thaçi, V. (2014). Synthesis of 4-triazolylamino- and 4-benzothiazolylamino-3-nitro-2H-[1]-benzopyran-2-ones and their antimicrobial activity. *Orbital*, 6, 184 – 190.
- Hoti, R., Vehapi, I., Mulliqi-Osmani, G., Ismaili, H. & Thaçi, V. (2016). Synthesis of some new heteroaryl-amino-3-nitro-2H-[1]-benzopyran-2-ones and their antibacterial activity. *Amer. Sci. Res. J. Eng., Tech. & Sci.*, 22(1), 1 – 9.
- Keri, R.S., Sasidhar, B.S., Nagaraja, B.M. & Santos, M.A. (2015). Recent progress in the drug development of coumarin derivatives as potent antituberculosis agents. *Eur J. Med. Chem.*, 100, 257 – 269.
- Küppers, J., Schulz-Fincke, A.C., Palus, J., Giurg, M., Skarżewski, J. & Gütschow, M. (2016). Convergent synthesis of two fluorescent Ebselen-Coumarin heterodimers. *Pharmaceuticals*, 9(3), 43.
- Kontogiorgis, C.A. & Hadjipavlou-Litina, D.J. (2004). Synthesis and biological evaluation of novel coumarin derivatives with a 7-azomethine linkage. *Bioorg. & Med. Chem. Lett.*, 14, 611 – 614.
- Kostova, I. (2006). Coumarins as inhibitors of HIV reverse transcriptase. *Curr. HIV Res.*, 4, 347 – 363.
- Kushwaha, K., Kaushik, N., Lata & Jain, S.C. (2014). Design and synthesis of novel 2H-chromen-2-one derivatives bearing 1,2,3-triazole moiety as lead antimicrobials. *Biorg. & Med. Chem. Lett.*, 24, 1795 – 1801.
- Lin, C.-Z., Zhu, C.-C., Hu, M., Ai-Zhi, W., Bairu, Z.-D. & Kangsa, S.-Q. (2014). Structure-activity relationships of antioxidant activity *in vitro* about flavonoids isolated from *Pyrethrum tatsienense*. *J. Intercult. Ethnopharmacol.*, 3(3), 123 – 127.
- Manolov I., Maichle-Moessmer, C., Nicolova, I. & Danchev, N. (2006). Synthesis and anticoagulant activities of substituted 2,4-diketochromans,

- biscoumarins, and chromanocoumarins, *Arch. Pharm. Chem. LifeSci.* 339, 319 – 326.
- Mohamed, H.M., Abd El-Wahab, A.H., Ahmed, K.A., El-Agrody, A.M., Bedair, A.H., Eid, F.A. & Khafagy, M.M. (2012). Synthesis, reactions and antimicrobial activities of 8-ethoxycoumarin derivatives, *Molecules*, 17, 971 – 988.
- Mohammad, N., Sayed, M., Khan, H., Adhikari, A. & Khan, K.M. (2013). Muscle relaxant and sedative-hypnotic activities of extract of *violabetonifolia* in animal models supported by its isolated compound, 4-hydroxycoumarin. *J. Chem.*, 2013, art. no. 326263.
- Olmedo, D.A., López-Pérez, J.L., Del Olmo, E., Bedoya, L.M., Sancho, R., Alcamí, J., Munoz, E., Feliciano, A. S. & Gupta, M.P. (2017). Neoflavonoids as inhibitors of HIV-1 replication by targeting the tat and NF- κ B pathways. *Molecules*, 22, 321.
- Pingaew, R., Saekee, A., Mandi, P., Nantasenamat, C., Prachayasittikul, S., Ruchirawat, S. & Prachayasittikul, V. (2014). Synthesis, biological evaluation and molecular docking of novel chalcone-coumarin hybrids as anticancer and antimalarial agents. *Eur. J. Med. Chem.*, 85, 65 – 76.
- Rajasekaran, S., Rao, G.K., Sajay Pai, P.N. & Ranjan, A. (2011). Design, synthesis, antibacterial and in vitro antioxidant activity of substituted 2H-benzopyran-2-one derivatives. *Int. J. Chem Tech Res.*, 3, 555 – 559.
- Vazquez-Rodriguez, S., Guíñez, R.F., Matos, M.J., Olea-Azar, C., Maya, J.D., Uriarte, E., Sontana, L., Borges, F., (2013). Synthesis and trypanocidal properties of new coumarin-chalcone derivatives. *Med. Chem.*, 5, 160 – 172.

✉ **Dr. Naser Troni (corresponding author)**

Faculty of Nature Sciences

Department of Chemistry and Department of Biology

University of Prishtina

Mother Teresa Str.

10000 Prishtina, Kosovo

E-mail: naser_troni@yahoo.com

+