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From the Research Laboratories
В изследователските лаборатории

SYNTHESIS OF NEW 3-[(CHROMEN-3-YL)-ETHYLIDENEAMINO]-PHENYL]-THIAZOLIDIN-4-ONES AND THEIR ANTIBACTERIAL ACTIVITY

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Abstract. A series of novel substituted thiazolidyn-4-ones were synthesized by cyclization of various Schiff bases of chromen-3-one with thioacetic acid. 3-(1-4-Amino-phenylamino)-ethyl-4-hydroxybenzopyran-2-one **3** is synthesized in high yield by condensation reaction of 4-hydroxy-3-acetylcoumarin **2** and 1,4-benzenediamine. The catalytic condensation of product **3** with benzaldehyde and their analogues (salicylaldehyde and 3-nitrobenzaldehyde) yielded corresponding 3-[1-(4-benzylidene-amino)-phenylamino]-ethyl-4-hydroxybenzopyran-2-ones **4(a-c)**. The cyclization reaction of compounds **4(a-c)** with thioacetic acid yielded corresponding substituted thiazolidin-4-ones **5(a-c)**. The structures of the synthesised compounds were established by FT-IR and NMR spectrometric data and their elemental analysis. Compounds of series **4(a-c)** and **5(a-c)** were screened for their antibacterial activity against *S. aureus*, *E. coli* and *Klebsiella* by Diffusion Disc Method. Antibacterial activity of the compounds **4(a-c)** and **5(a-c)** against *S. aureus*, *E. coli* and *Klebsiella* was examined by measuring the zones of inhibition around the disks impregnated with the corresponding solutions in N,N-DMF concentration 2 mg/mL , 4 mg/mL and 6 mg/mL. Compounds of series **4** exhibited significant antibacterial activity, whereas compounds of series **5** displayed moderate activity against these microorganisms. The impact of substitutions in antimicrobial activity was also explored.

*Keywords:*t hiazolidin-4-one; benzopyran-2-on; condensiation; cyclization; zones of inhibition

Introduction

Benzopyran-2-one derivatives are important class of heterocyclic compounds that have been found as ingredient of the plant world. Many such compounds are well known for their biological activities (Mohamed et al., 2012; Rajasekaran et al., 2011) sush as antimicrobial (Desai et al., 2013; Reihman et al., 2013; Mayeka-

r&Mulwad, 2008), antifungal (De Araújo et al., 2013) and antimalarial (Sashidhara et al., 2012). Novobiocin, chartesium and coumaromycin are potent antibiotics with benzopyrone moiety. Many of coumarins exhibited antioxidant (Tyagi et al., 2005; Osman et al., 2012; Vazquez-Rodriguez et al., 2013), and antitumor activity (Nawrot-Modranka et al., 2006). It was reported that a significant number of substituted benzopyran-2-ones showed anticoagulant, anti-HIV (Rao et al., 2002; Yu et al., 2003), sedative, analgesic and hepatoprotective activity (Ahmed et al., 2003; Okamota et al., 2007; Atmaca et al., 2011). It is indicative that many of naturally and synthetic coumarins have found widespread usage in pharmacies (Rajasekaran et al., 2011). On the other hand, thiazolidynone derivatives also have great importance and demonstrate a wide range of pharmacological activities, including those anti-convulsant (Siddiqui et al., 2007), antibacterial (Mayekar & Mulwad, 2008) and anti-fungal (Mazzei et al., 2008) activity. The biological activity is conditioned by their structure and the presence of different substituents on the benzopyrone 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 biologically importance of compounds with thiazolidine-4-one moiety has generated a constant interest for their synthesis and research. In view of the considerable importance of these derivatives and in continuation of our previous studies (Hoti et al., 2014; 2017a; 2017b), the present work is aimed at the design and synthesis of new Schiff bases and related thiazolidyne-4-ones with benzopyran-2-one moiety which could serve as pharmaceutical products. Moreover, the study includes testing of target compounds for their antibacterial activity against *S. Aureus*, *E. Coli* and *Klebsiella*.

Material and methods

Synthesis reactions were conducted by refluxing under catalytic conditions. All the chemicals used in the synthesis were of analytical grade as commercial reagents of Aldrich company. Reactions were monitored by TLC using Merck Kieselgel-60 (F-254) as the stationary phase and a mixture of benzene, toluene, glacial acetic acid (v/v/v, 75:10:15) as the mobile phase. The synthesized products were purified by crystallization from methanol and ethanol. Melting points were determined in paraffin oil bath with open capillary tube. FT-IR spectra were recorded in KBr discs on Shimadzu 8400xFTIR spectrometer with 4 $cm^{1\ resolution}$. ^{1}H-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 (δ0.00).

Screening of the antibacterial activity of the synthesized compounds was done on the basis of Standard Disc Method using standard discs (*d=5.0 mm*, maximum capacity 10 pg). 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.

3-[1-4-Amino-phenylimino)-ethyl]-4-hydroxy-benzopyran-2-one, 3

4-Hydroxy-3-acetyl-benzopyran-2-one (6.1g, 0.05 mol) was dissolved in 30 mL of methanol, then the mixture containing benzene-1,4-diamine (6.5 g, 0.06 mmol) in 10 mL of methanol was added in small portions and then 2-3 drops of triethylamine were added into the mixture. The reaction mixture was stirred for 15 minutes at room temperature, then refluxed for about 6 hours. After cooling, the mixture was concentrated in the rotary evaporator and the crystalline product was filtered off under vacuum and washed with 2 × 1 mL of methanol. The crystalline product was dried and crystallized from methanol, giving 3-[1-4-Amino-phenylimino)-ethyl]-4-hydroxybenzopyran-2-one, yield = 35.83%. mp = 214-215 °C. **FT-IR** (KBr disc, cm^{-1}): 3415.08 3288.59, 2205.54, 1711.36, 1675.78, 1058.96, 754.50. 3423.67, 3400-3300, 3055.16, 2930.6, 2847.26, 1696.25, 1610.25, 1645.05, 1196.14, 750.71.

3-(1-(4-benzylidene-amino)-phenylamino]-ethyl-4-hydroxybenzopyran-2-ones, 4(a-c)

Compound **3** (0.6 g (0.002 mol) was dissolved in 20 mL of absolute ethanol and then 0.003 mol of corresponding aromatic aldehyde (benzaldehyde, salicylaldehyde or 3-nitrobenzaldehyde) dissolved in 15 mL of absolute ethanol was added in small portions to this mixture. Then two drops of piperidine as a catalyst were added and the mixture was stirred for 15 min at room temperature and then refluxed for 8 to 9 hours. After cooling, the mixture is concentrated and the residue was filtered off under reduced pressure, then washed with 2 × 1 mL of ethanol and dried in the air. Crystallization of the products **4(a-c)** was conducted using ethanol or methanol.

4a; Mp=161-162 °C, yield=12.82 %, **FT-IR** (KBr disc, cm^{-1}): 3400-3300, 3059.28, 2919.9, 1662.45, 1610.25, 1610.9, 1533.19, 1196.14, 757.67. **^{1}H-NMR**; (δ, ppm)8.4 (s, 1H, N=C-H), 7.5-7.6 (m, 3H, Ar), 7.2-7.4 (m, 8H, Ar), 5.1 (1H, OH), 0.9 (s, 3H, CH_3). **^{13}C-NMR**; (δ, ppm) 173.2 (C-OH), 164.1, 163.4 (C=N), 161.7(C=O), 152,3, 151.2, 147,2, 131,3, 130.4, 129.3, 128.2, 127,4, 126,9, 126.6, 125.9 , 125.2, 123.2, 121.0 (C-ar), 82.2, 9,6 (CH_3).

4b; Mp=166-167 °C, yield=98.46 %, **FT-IR** (KBr disc, cm^{-1}): 3450-3300, 3055.6, 2931.1, 1690.29, 1655.49, 1510.25, 1192.66, 750.71. **^{1}H-NMR**; (δ, ppm) 8.3 (s, 1H, N=C-H), 7.2-7.5 (m, 7H, Ar), 6.8-7.0 (m, 3H, Ar), 5.0, 5.1, (2H, OH), 0.9 (s, 3H, CH_3).**^{13}C-NMR**;(δ, ppm) 173.1 (C-OH), 164.3, 163.7 (C=N), 161.9 (C=O), 157.2 (C-OH ar), 151.4, 150.5, 148.8, 147,2, 132.3, 131,5, 130.4, 128.5, 128.3, 127,3, 126,7, 125.6 , 123.4, 121.4, 115.9, (C-ar), 82.2, 15,1 (CH_3).

4c; Mp=208-210 °C, yield=58.29 %, **FT-IR** (KBr disc, cm^{-1}): 3430-3300, 3076.44, 2923.65, 1620.69, 1618.25, 1519.77, 1352.74, 1196.14, 740.27. **^{1}H-NMR**; (δ, ppm) 8.4 (s, 1H, N=C-H), 8.0-8.3 (m, 3H, Ar), 7.2-7.5 (m, 7H, Ar), 5.2, (1H,

OH), 0.9 (s, 3H, CH_3).**^{13}C-NMR**; (δ, ppm) 173.4 (C-OH), 164.1, 163.2 (C=N), 162.2 (C=O), 151.9, 150.8, 150.5, 148.1, 147,2, 135.4, 131,9, 129.2, 128.0, 127.2, 126,4, 125.7 , 124.4, 123.2, 121.6, 115.9, (C-ar), 82.9, 15,8 (CH_3).

(2H-Benzopyron -4-ylamino)-2-phenyl-thiazolidyne-4-ones 5(a-c)

The corresponding product **4(a-c)** (0.1 mmol) was dissolved in 10 mL of benzene and then 0.12 g (0.25 mmol) of thioacetic acid was added. The reaction mixture was stirred for 10 min at room temperature and then refluxed for 12-14 hours. After cooling the product was concentrated and the remaining solid was dissolved in 5 mL of ethanol, then heated to the boiling point and the excess of acetic acid was neutralized by adding 0.06 mmol sodium bicarbonate (controlled with litmus paper until the solution takes a blue color). The mixture was cooled in an ice bath and filtered off under vacuum, then washed with 2×1 mL of ether and dried in air. The products were crystallized using methanol.

5a; Mp=239-240 °C, yield=54.20 %, **FT-IR** (KBr disc, cm^{-1}): 3450-3350, 3076.44, 2930.65, 1662.45, 1519.77, 1515.2, 1352.74, 1196.14, 740.27. **^{1}H-NMR**; (δ, ppm) 7.4-7.6 (m, 3H, Ar), 7.1-7.3 (m, 7H, Ar), 5.8 (s, 1H, N-C-H), 3.5 (q, 3H, CH_3) 1,6 (d, 3H, CH_3) 0.9 (s, 3H, CH_3). **^{13}C-NMR**; (δ, ppm) 174.5 (C-OH), 172.3, 164.1, 161.7(C=O), 150.6, 150.1, 145,6, 138.2, 138.6, 129.0, 128.5, 126,7, 126,1, 125.5, 123.8, 122.4, 121.7, 121.4, (C-ar), 82.4, 56.2 (C-N), 45.6, 18.8 (CH_3), 9.5 (CH_3).

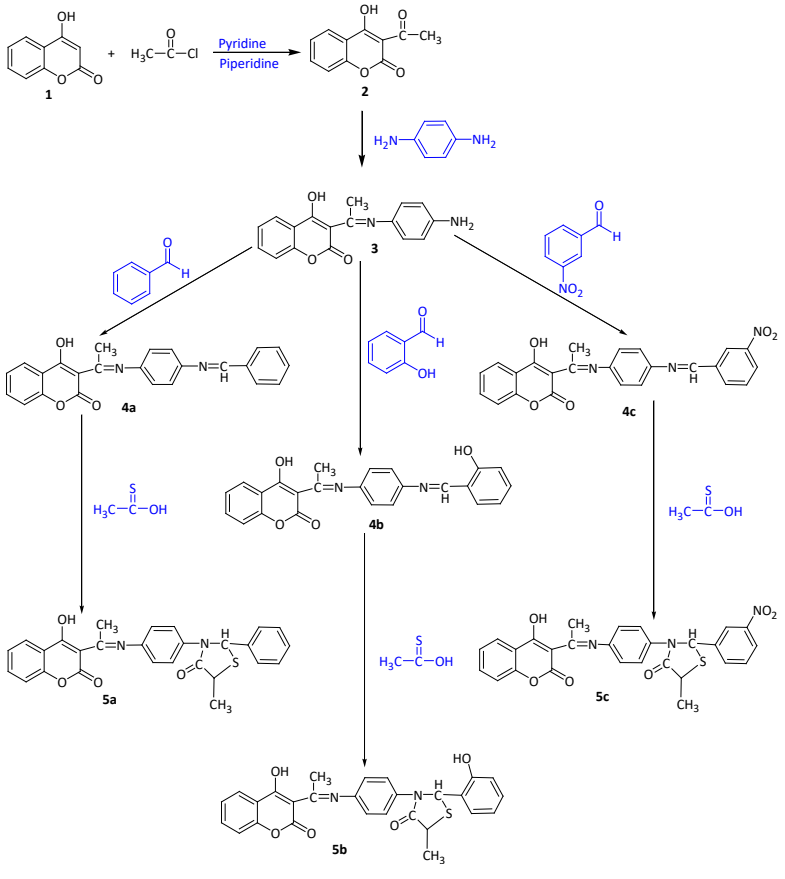
5b; Mp=227-229 °C, yield=40.26 %, **FT-IR** (KBr disc, cm^{-1}): 3500-3350, 3050, 2926.87, 1695, 1617.21, 1561.53, 1116.1, 621.95. **^{1}H-NMR**; (δ, ppm)7.2-7.6 (m, 2H, Ar), 6.7-7.1(m, 8H, Ar), 5.9 (s, 1H, N-C-H), 3.7 (q, 3H, CH_3) 1,5 (d, 3H, CH_3) 0.9 (s, 3H, CH_3). **^{13}C-NMR**; (δ, ppm) 173.4 (C-OH), 171.9, 165.3, 162.5 (C=O), 157.0, 151.1, 150.5, 144,8, 139.9, 139.3, 138.5, 127.9, 126,7, 126,1, 125.5, 123.8, 123.2, 122.4, 121.7, 121.4, (C-ar), 82.4, 46.3 (C-N), 45.2, 17.3(CH_3), 9.9 (CH_3).

5c; Mp=194-195 °C, yield=33.21 %, **FT-IR** (KBr disc, cm^{-1}): 3450-3350, 3076.44, 2930.65, 1662.45, 1660.0, 1605.5, 1519, 1349.26, 1025.62 765.5.

Results and discussion

By condensation reaction of 4-hydroxy-3-acetylcoumarin **2** with ethane-1,2-diamine, 3-(1-4-amino-phenylamino)-ethyl-4-hydroxybenzopyran-2-one **3** was synthesized in good yield. Corresponding Schiff bases are synthesized by condensation reaction of compound **3** with benzaldehyde, salicylaldehyde and/or 3-nitrobenzaldehyde. Novel 3-(1-(4-benzylidene-amino)-phenylamino]-ethyl-4-hydroxybenzopiran-2-ones, **4(ac)** as condensation products are synthesized in good yield. In the last step, by cyclization of compounds **4(a-c)** with thioacetic acid, corresponding thiazolidinones **5(a-c)** are synthesized. Synthesis of Schiff bases and related azetidine-2-ones are summarized in Scheme 1.

Structural characterization of the synthesized products is based on spectrometric data. The IR spectrum of compound **3** showed an absorption signal absorption at 3423.67 cm^{-1} confirming the presence of -NH_2 group. The absorption signal at 3400-3300 cm^{-1} appears due to ν(OH) stretching vibrations while the absorption at 3055.16 cm^{-1} due to aromatic ν(CH) stretching vibrations. The absorption signals at 2930.6 cm^{-1} and 2847.26 cm^{-1} are responsible for asymmetric and symmetric ν(CH) stretching vibrations of methyl group. A sharp peak appeared at 1696.25 cm^{-1} is responsible for ν(C=O) stretching vibrations, whereas the absorption peak at 1610.25 cm^{-1} results from aromatic ν(C=C) stretching vibrations. The presence of the C=N double bond of the aromatic system was indicated from their stretching absorption at 1645.05 cm^{-1}. On the other hand, the peak at 1196.14 cm^{-1} results due to lactonic ν(C-O-C) stretching vibrations, while the sharp peak at 750.71 cm^{-1} correspond to characteristic aromatic δ(C-H) oop bending vibrations.



Scheme 1. Synthesis of some Schiff bases and related azetidine-2-ones

The IR spectrum of compound **4a** showed a signal at 3400-3300 cm^{-1} responsible for ν(OH) stretching vibrations, a peak at 3059.28 cm^{-1} for aromatic ν(CH) stretching, while the absorption peak at 2919.9 cm^{-1} due to methyl ν(CH) asymmetric stretching vibrations. The sharp peak at 1662.45 cm^{-1} correspond to ν(C=O) stretching vibrations, whereas the peak at 1610.25 cm^{-1} resulted from aromatic ν(C=C) stretching vibrations. A signal at 1196.14 cm^{-1} is characteristic for lactonic (C-O-C) stretching vibrations and the sharp peak at 757.67 cm^{-1} results from aromatic δ(C-H) bending oop vibrations. In the ^{1}H-NMR spectrum, besides multiplets of aromatic protons, a proton singlet resulting from N=C-H is appeared at 8.4 ppm. In the ^{13}C-NMR spectrum two signals at 161.1 and 163.8 ppm for C=N carbons are appeared.

For compound **4b**, the IR spectrum showed an absorption signal at 3450-3300 cm^{-1} which is responsible for ν(OH) stretching vibrations, while a signal at 3055.6 cm^{-1} corresponds to aromatic ν(CH) stretching vibrations. The peak at 2931.1 cm^{-1} results from methyl ν(CH) stretching vibrations. At 1690.3 cm^{-1} appears the absorption signal which responds to ν(C=O) stretching vibrations, the peak at 1192.6 cm^{-1} correspond due to lactonic (C-O-C) stretching vibrations, whereas the sharp peak at 750.7 cm^{-1} is characteristic for aromatic bending δ(C-H) oop vibrations. On the other hand, the ^{1}H-NMR spectrum correspond to the absorption of respective protons. At 8.3 ppm a proton singlet resulting from N=C-H is displayed. Also in the ^{13}C-NMR spectrum signals at 164.3 and 163.7 ppm that corresponds to the C=N carbon are displayed.

The IR spectra of compound **4c** show a broad absorption peak at 3400-3300 cm^{-1} which is responsible for ν(OH) stretching vibrations, while the signals at 3076.44 and 2923.65 cm^{-1} appear due to aromatic and methyl ν(CH) stretching vibrations. The peak at 1620.69 cm^{-1} is responsible for absorbing the ν(C=O) stretching vibrations while signals at 1618.25 and 1519.77 cm^{-1} result from aromatic ν(C=N) and ν(C=C) stretching vibrations. The sharp peak at 1515.2 cm^{-1} results from $\nu(NO_2)$ asymmetric stretching vibrations, while absorption signal at 1352.74 cm^{-1} reflects $\nu(NO_2)$ symmetric stretching vibrations. A signal at 1196.14 cm^{-1} is characteristic for lactonic (C-O-C) stretching vibrations, while the sharp peak at 740.27 cm^{-1} appears from aromatic δ(C-H) bending oop vibrations. The ^{1}H-NMR spectra show the multiplet signals of aromatic protons at 8.1-8.3 ppm and 7.7-7.4 ppm. A proton singlet resulting from N=C-H at 8.4 ppm appears as well. In the ^{13}C-NMR spectra two signals at 164.1 and 163.2 ppm, that correspond to C=N and a signal at 173.4 ppm resulting from C-OH are apeared.

In the IR spectra of the compound **5a** a broad absorption signal appears at 3450-3350 cm^{-1} which is responsible for ν(OH) stretching vibrations whereas the absorption peak at 3076.44 cm^{-1} results from aromatic ν(CH) vibrations. A medium band at 2930.65 cm^{-1} resulted from aliphatic ν(CH) stretching vibrations, whereas a sharp peak at 1662.45 cm^{-1} correspond to ν(C=O) stretching vibrations. The absorp-

tion signals at 1618.25 and 1519.77cm^{-1} result from aromatic ν(C=N) and ν(C=C) stretching vibrations. The absorption peak at 1196.14 cm^{-1}results from lactonic ν(C-O-C) stretching vibrations, whereas at 740.27 cm^{-1} due to aromatic δ(CH) oop vibrations. The ^{1}H-NMR spectra, a proton singlet at 5.8 ppm results from N-C-H, while a doublet at 1.6 ppm and a singlet 0.9 ppm appear due to methyl protons. The ^{13}C-NMR spectra exhibits a signal at 56.2 ppm results due to C-N carbon, while signals at 18.8 and 9.5 ppm appear due to methyl carbons.

Table 1. Physical properties of compounds 4(a-c) and 5(a-c) and their elemental analysis

Nr	Molecular formulas	Molecular Mass	Elemental analysis (%), calc / found	mp/ oC	Yield (%)
4a	C24H18N2O3	382.40	(C-75.376; H-4.744; N-7.327; O-12.552) (C-75.380; H-4.742; N-7.330)	161-162	12.82
4b	C24H18N2O4	398.40	(C-72.349; H-4.553; N-7.033; O-16.064) (C-72.352; H-4.549; N-7.065)	166-167	98.46
4c	C24H17N3O5	427.41	(C-67.439; H-4.001; N-9.834; O-18.717) (C-67.443; H-3.997; N-9.831)	208-210	58.29
5a	C27H22N2O4S	470.54	(C-68.914; H-4.714; N-5.955; O-13.601; S-6.816) (C-68.917; H-4.710; N-5.960; S-6.811)	239-240	54.20
5b	C27H22N2O5S	486.54	(C-66.648; H-4.559; N-5.759; O-16.443; S-6.591) (C-66.65; H-4.554; N-5.761; S- 6.586)	227-229	40.26
5c	C27H21N3O6S	515.54	(C-62.899; H-4.106; N-8.153; O-18.621; S-6.221) (C-62.914; H-4.102; N-8.147; S-6.218)	194-195	33.21

In the IR spectra of compound **5b,** a broad absorption signal appears at 3500-3350 cm^{-1} which is responsible for ν(OH) stretching vibrations and the signal at 3050 cm^{-1} for aromatic ν(CH) stretching vibrations. The peak at 2926.87 cm^{-1} results from methyl ν(CH) stretching vibrations, while the peak at 1695 cm^{-1} correspond to ν(C=O) stretching vibrations. The characteristic peaks at 1617.21 and 1561,53 cm^{-1} result from ν(C=N) and ν(C=C) stretching vibrations of aromatic moiety. A signal at 1116.1 cm^{-1} results from lactonic ν(C-O-C) vibrations, while the sharp peak at 621.95 cm^{-1} is characteristic for δ(C-S) bending vibrations. In the ^{1}H-NMR spectra are shown a singlet at 5.9 ppm, a quartet at 3.7 ppm and a doublet at 1.5 ppm due to thiazole proton N-C-H, CH and CH_3 protons. The ^{13}C-NMR spectrum also show corresponding signals for thiazole carbons.

IR spectrum of compound **5c** exhibit the absorption signal at 3450-3350 cm^{-1} responsible for ν(OH) stretching vibrations and a signal at 3076.44 cm^{-1} which resulted from aromatic ν(CH) stretching vibrations. The peak at 2930.65 cm^{-1} results from the absorptions of methyl stretching vibrations, while the signal at 1662.45 cm^{-1} reflects the ν(C=O) stretching vibrations. The peak at 1660.0 cm^{-1} results from

ν(C=N) stretching mode, while aromatic ν(C=C) stretching vibrations show a signal at 1605.5 cm^{-1}. A signal at 1025.62 cm^{-1} is characteristic for lactonic (C-O-C) stretching vibrations, whereas the sharp peak at 765.5 cm^{-1} is characteristic for aromatic δ(C-H) oop bending vibrations.

Antibacterial activity of the compounds 4(a-c) and 5(a-c)

Following this study, compounds 4 (a-c) and 5(a-c) are screened 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 (Bayer et al., 1966), by measuring the zones of inhibition. The 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 are expressed in mm and were summarized in Figs. 1 – 3.

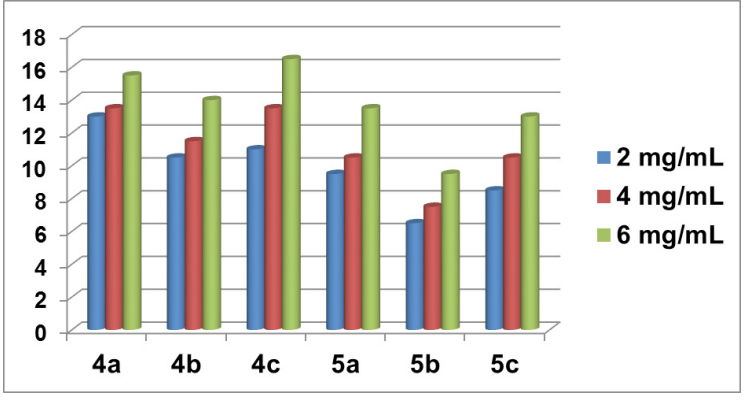


Figure 1. Graphical presentation of zones of inhibition (mm) against *S. aureus*

Compounds of series **4** showed significant antimicrobial activity against these microorganisms, while those of series **5** exhibited moderate activity. Compounds **4a** and **4c** were most active against *S. aureus*, compounds **4c** and **5c** showed the most activity against *E. Coli* whereas **4b** was more active against *Klebsiella*.

Antibacterial activity against *E. Coli* and *Klebsiella* shown as bactericide activity is displayed in a moderate range. Furthermore, these compounds express both bacteriostatic and bactericide activity against *S. Aureus*. Bacteriostatic activity is exhibited in large range (+2.0 mm), whereas bactericide activity showed smaller zones of inhibition. Thiazolidin-4-one moiety showed small impact on antimicrobial activity. Likewise, the impact of polar groups was distinctive. It is particularly noted the impact of the nitro group, which affected the increasing of antibacterial activity. The impact of the hydroxy group of **5b**, which has affected the increase of antibacterial activity, has been particularly noted. Moreover, nitro group of **4b** has shown significant impact on the range of inhibition of *E. coli*.

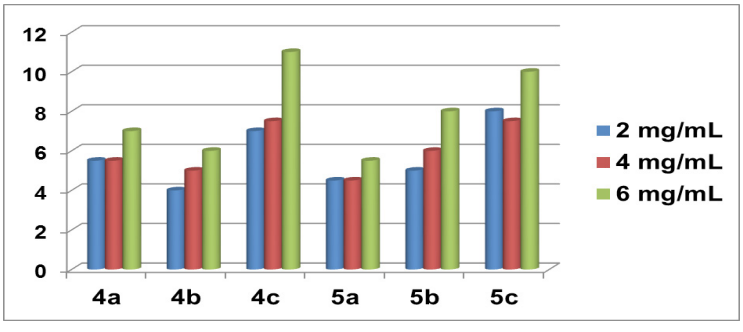


Figure 2. Graphical presentation of zones of inhibition (mm) against *E. coli*

It has been assumed that antibacterial activity may result as a consequence of the involvement of these compounds in 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.

Conclusions

Novel derivatives of 3(1-(4-benzylidene-amino)-phenylamino]-ethyl-4-hydroxybenzopyran-2-one **4(a-c)** and respective thiazolidin-4-ones **5(a-c)** are synthesized in the moderate and high yield. It has been concluded that compounds **4a** and **4c** show significant activity against *S. aureus,* compounds **4c** and **5c** display more activity against *E. Coli*, whereas **4b** was more active against *Klebsiella* bacteria. The impact of polar groups in antibacterial activity was significant. Antibacterial activity is shown to be proportional to the concentration of these compounds.

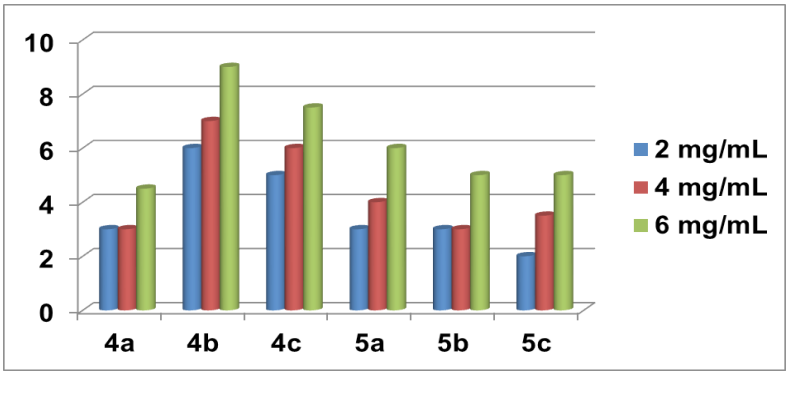


Figure 3. Graphical presentation of zones of inhibition (mm)) against *Klebsiella*

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