IJPSR (2017), Vol. 8, Issue 1 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 15 July, 2016; received in revised form, 12 September, 2016; accepted, 04 November, 2016; published 01 January, 2017

BIOLOGICAL ACTIVITY EVALUATION OF NOVEL *N*-HETEROCYCLIC CARBENE PRECURSORS

Senem Akkoç [*1], Yetkin Gök [2], Hülya Erdoğan [2] and Sevil Albayrak [3]

Department of Chemistry [1], Department of Biology [3], Faculty of Sciences, Erciyes University, 38039, Kayseri, Turkey.
Department of Chemistry [2], Faculty of Arts and Sciences, Inönü University, 44280 Malatya, Turkey.

Keywords:

N-heterocyclic carbene, Benzimidazolium salts, Antimicrobial activity

Correspondence to Author:
Senem Akkoç

Department of Chemistry, Faculty of Sciences, Erciyes University, 38039, Kayseri, Turkey.

E-mail: senemakkoc44@gmail.com

ABSTRACT: Five novel benzimidazolium salts were synthesized as *N*-heterocyclic carbene (NHC) precursors (**1a-e**). They were characterized by different techniques. The antimicrobial activities of these compounds were tested. The compounds showed moderate activity against three Gram (+) and seven Gram (-) bacteria in comparison to tetracycline, which was used as the standard antibiotic, whereas all the compounds (**1a-e**) showed no activity against the test yeast *C. albicans.*

INTRODUCTION: In the past few decades, infections caused by multi-drug resistant bacteria have increased at frightening levels all over the world. Microbial infections are a growing problem in contemporary medicine and the use of antibiotics is common worldwide. In particular, infections caused by the Gram-positive bacterium *Staphylococcus aureus* and species of the genus *Enterococcus* have become a major worldwide health problem due to their ability to develop resistance to multiple antibiotics. To overcome these emerging resistance problems, there is an urgent need to discover novel chemotherapeutic agents, which have a broad spectrum of activity and, if possible, with new modes of action [1-4].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.8(1).262-67

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8 (1).262-67

The benzimidazole nucleus is a constituent of many bioactive N- containing heterocyclic compounds [5, 6]. Specifically, this nucleus is a constituent of Vitamin-B12 [5]. Benzimidazole and its derivatives have been reported to show various pharmacological activities, such as antiarrhythmic, antifungal, antiviral, antihelmintic and inotropic activities and are used as a treatment for intestinal cystitis [7, 8].

Additionally, it was reported to possess antitumor, antihistamine, antiulcer, antibacterial, antiproliferative activities and cytotoxicity [7-12] as well as anti-inflammatory, analgesic, antioxidant, antiallergic, antikinase, anticancer and anti-HIV activities [10-12]. Its application in the treatment of diverse diseases like diabetes, epilepsy and for antifertility have also been reported [10, 11]. The biological activities showed by compounds containing benzimidazole moiety have prompted chemists to synthesis more and more benzimidazole libraries and screen them for potential activities [6].

Encouraged by these observations, and as a continuation of our earlier work on biologically important heterocycles [13], we report herein the synthesis of a novel series of 1-((2,3-dihydrobenzo [*b*][1,4]dioxin-2-yl) methyl) - 3-alkyl benzimidazo lium salts (**1a-e**) and the *in vitro* screening results of their antimicrobial activities.

Experimental:

General considerations: Using Schlenk techniques, the necessary reactions for the synthesis of benzimidazolium salts (**1a-e)** were carried out under argon. All reagents and chemicals were commercially purchased from various firms. For all the new benzimidazolium salts, 1D NMR methods such as ^{1}H NMR and ^{13}C NMR were taken in DMSO-d_6 and $CDCl_3$. The ^{1}H and ^{13}C NMR spectra were recorded by using a Bruker AC300P FT spectrometer operating at 300.13 MHz (^{1}H NMR) and 75.47 MHz (^{13}C NMR). Taking into account TMS, chemical shifts (δ) were given in ppm. Coupling constants (*J*) were generated in hertz (Hz). ^{1}H NMR peaks are labeled as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), hextet (h) and multiplet (m) signals. The FT-IR spectra of the synthesized benzimidazolium salts were recorded in the 450–4000 cm^{-1} region with a Shimadzu FT-IR 8400 spectrophotometer and wave numbers are given in cm^{-1}. Melting points (m.p.) were determined in glass capillary tubes by using an Electrothermal-9200 melting point appliance. Elemental analyses were performed by means of a TruSpec MICRO elemental analysis device.

General preparation of 1-((2,3-dihydro benzo [b][1,4]dioxin-2-yl)methyl)-3-alkyl benzimidazol ium salts, 1a-e: Firstly, the benzimidazole nucleus was synthesized from o-phenylenediamine (20 g), formic acid (11 ml) and water (2 ml). Then, alkyl halides (1 mmol) and potassium hydroxide were added to a solution of benzimidazole (1 mmol) in ethyl alcohol (10 ml). The resulting mixture was refluxed for 12 h. In the third step, 1-bromomethyl-1,4-benzodioxane was added to N-alkyl benzimidazole for the synthesis of different benzimidazolium salts (1a-e) and was stirred at 80 ºC for 24 h. The obtained compounds were washed with diethylether (3x15 ml) and dried under vacuum. The product was crystallized from ethyl alcohol-diethyl ether (2-1) mixture at room temperature.

1-((2,3-dihydrobenzo[b][1,4]dioxin-2-yl)methyl)-3-methylbenzimidazolium bromide, 1a: Yield: 87 %; m.p.: 309-310 ºC; FT-IR$_{\nu(CN)}$: 1492.8 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ; 4.29 (s, 3 H, C*H*$_3$); 4.32 and 4.92 [m, 2 H, NC*H*$_2$CH(CH$_2$)O]; 4.98 [m, 1 H, NCH$_2$C*H*(CH$_2$)O]; 5.45 and 5.57 [m, 2 H, NCH$_2$CH(C*H*$_2$)O]; 6.79-6.88 (m, 4 H, Ar-*H*$_{Benzod}$ioxane); 7.46-7.74 (m, 4 H, Ar-*H*$_{\text{Benzimidazole}}$); 11.21 (s, 1 H, 2-C*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$),δ; 32.5 (*C*H$_3$); 47.5, 64.7 and 72.3 [N*C*H$_2$*C*H(*C*H$_2$)O]; 112.5, 113.9, 117.5, 122.0, 122.1, 125.1, 127.4, 127.5, 131.6, 132.2, 141.4 and 142.8 (Ar-*C*); 143.4 (2-*C*H). Anal. Calcd. for $C_{17}H_{17}N_2O_2Br$ (361.23 g/mol): C 56.52, H 4.74, N 7.75. Found: C 56.43, H 4.85, N 7.70 %.

1-((2,3-dihydrobenzo[b][1,4]dioxin-2-yl)methyl)-3-ethylbenzimidazolium bromide, 1b: Yield: 79 %; FT-IR$_{\nu(CN)}$: 1448.7 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6), δ; 1.54 (t, 3 H, *J*: 6.9 Hz, CH$_2$C*H*$_3$); 4.52 (q, 2 H, *J*: 6.9 Hz, C*H*$_2$CH$_3$); 4.53 and 4.82 [m, 2 H, NC*H*$_2$CH(CH$_2$)O]; 4.97 (m, 1 H, NCH$_2$C*H*(CH$_2$)O); 4.12 and 4.81 [m, 2 H, NCH$_2$CH(C*H*$_2$)O]; 6.83-6.86 (m, 4 H, Ar-*H*$_{\text{Benzodioxane}}$); 7.45-7.92 (m, 4 H, Ar-*H*$_{\text{Benzimidazole}}$); 10.10 (s, 1 H, 2-C*H*). ^{13}C NMR (75.47 MHz, DMSO), δ; 14.5 and 42.7 (*C*H$_2$*C*H$_3$); 47.2, 64.9 and 71.2 [N*C*H$_2$*C*H(*C*H$_2$)O]; 114.0, 114.3, 117.6, 117.7, 122.3, 127.2, 127.3, 131.2, 132.0, 142.1 and 142.5 (Ar-*C*); 143.0 (2-*C*H). Anal. Calcd. for $C_{18}H_{19}N_2O_2Br$ (375.26 g/mol): C 57.61, H 5.10, N 7.47. Found: C 57.53, H 5.18, N 7.43 %.

1-((2,3-dihydrobenzo[b][1,4]dioxin-2-yl)methyl)-3-butylbenzimidazolium bromide, 1c: Yield: 89 %; m.p.: 287-288 ºC; FT-IR$_{\nu(CN)}$: 1485.1 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ; 1.01 (t, 3 H, *J*: 6.9 Hz, CH$_2$CH$_2$CH$_2$C*H*$_3$); 1.49 (h, 2 H, *J*: 6.9 Hz, CH$_2$CH$_2$C*H*$_2$CH$_3$); 2.02 (p, 2 H, *J*: 6.9 Hz, CH$_2$C*H*$_2$CH$_2$CH$_3$); 4.88 (t, 2 H, *J*: 6.9 Hz, C*H*$_2$CH$_2$CH$_2$CH$_3$); 4.31 and 4.32 [m, 2 H, NC*H*$_2$CH(CH$_2$)O] 4.93 [m, 1 H, NCH$_2$C*H*(CH$_2$)O]; 4.58 and 5.45 [m, 2H, NCH$_2$CH(C*H*$_2$)O]; 6.66-6.85 (m, 4 H, Ar-*H*$_{\text{Benzodioxane}}$); 7.56-7.73 (m, 4 H, Ar-*H*$_{\text{Benzimidazole}}$); 11.35 (s, 1 H, 2-C*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$), δ; 13.5, 19.9, 31.1 and 47.6 (*C*H$_2$*C*H$_2$*C*H$_2$*C*H$_3$); 47.7, 64.8 and 72.4 [N*C*H$_2$*C*H(*C*H$_2$)O]; 112.7, 114.2, 117.4, 117.6, 122.0, 122.1, 127.2, 130.8, 132.4 and 141.4 (Ar-*C*); 142.8 (2-*C*H). Anal. Calcd. for $C_{20}H_{23}N_2O_2Br$

(403.31 g/mol): C 59.56, H 5.75, N 6.95. Found: C 59.71, H 5.83, N 6.89 %.

1-((2,3-dihydrobenzo[b][1,4]dioxin-2-yl)methyl)-(2-methoxyethyl)benzimidazolium bromide, 1d: Yield: 81 %; m.p.: 167-168 ^{o}C; FT-IR$_{\nu(CN)}$: 1486.3 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ; 3.36 (s, 3 H, $CH_2CH_2OCH_3$); 3.95 (t, 2 H, *J*: 4.5 Hz, $CH_2CH_2OCH_3$); 4.81 (t, 2 H, *J*: 4.5 Hz, $CH_2CH_2OCH_3$); 4.29 and 4.58 [m, 2 H, $NCH_2CH(CH_2)O$]; 4.90 (m, 1 H, OCH_2CHO); 4.88 and 5.38 [m, 2 H, $NCH_2CH(CH_2)O$]; 6.67-6.84 (m, 4 H, Ar-$H_{Benzodioxane}$); 7.44-8.02 (m, 4 H, Ar-$H_{Benzimidazole}$); 10.86 (s, 1 H, 2-C*H*). Anal. Calcd. for $C_{19}H_{21}N_2O_3Br$ (405.29 g/mol): C 56.31, H 5.22, N 6.91. Found: C 56.25, H 5.33, N 6.96 %.

1-((2,3-dihydrobenzo[b][1,4]dioxin-2-yl)methyl)-3-(2-ethoxyethyl)benzimidazolium bromide, 1e: Yield: 86 %; m.p.: 139-140 ^{o}C; FT-IR$_{\nu(CN)}$: 1496.7 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ; 1.14 (t, 3 H, *J*: 7.2 Hz, $CH_2CH_2OCH_2CH_3$); 3.84 (q, 2 H, *J*: 7.2 Hz, $CH_2CH_2OCH_2CH_3$); 3.90 (t, 2 H, *J*: 4.8 Hz, $CH_2CH_2OCH_2CH_3$); 4.72 (t, 2 H, *J*: 4.8 Hz, $CH_2CH_2OCH_2CH_3$); 4.34 and 4.58 [m, 2 H, $NCH_2CH(CH_2)O$]; 4.98 (m, 1 H, OCH_2CHO); 4.68 and 5.45 [m, 2 H, $NCH_2CH(CH_2)O$]; 6.75-6.98 (m, 4 H, Ar-$H_{Benzodioxane}$); 7.32-7.69 (m, 4 H, Ar-$H_{Benzimidazole}$); 10.95 (s, 1 H, 2-C*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$), δ; 15.0, 47.6, 48.3 and 48.3 ($CH_2CH_2OCH_2CH_3$); 64.8, 66.1 and 72.1 [$OCH_2CH(CH_2)O$]; 113.2, 113.8, 117.5, 117.6, 122.0, 122.1, 127.0, 127.1, 131.6, 132.1, 141.1 and 142.8 (Ar-*C*); 143.1 (2-*C*H). Anal. Calcd. for $C_{20}H_{23}N_2O_3Br$ (419.31 g/mol): C 57.29, H 5.53, N 6.68. Found: C 57.38, H 5.48, N 6.72 %.

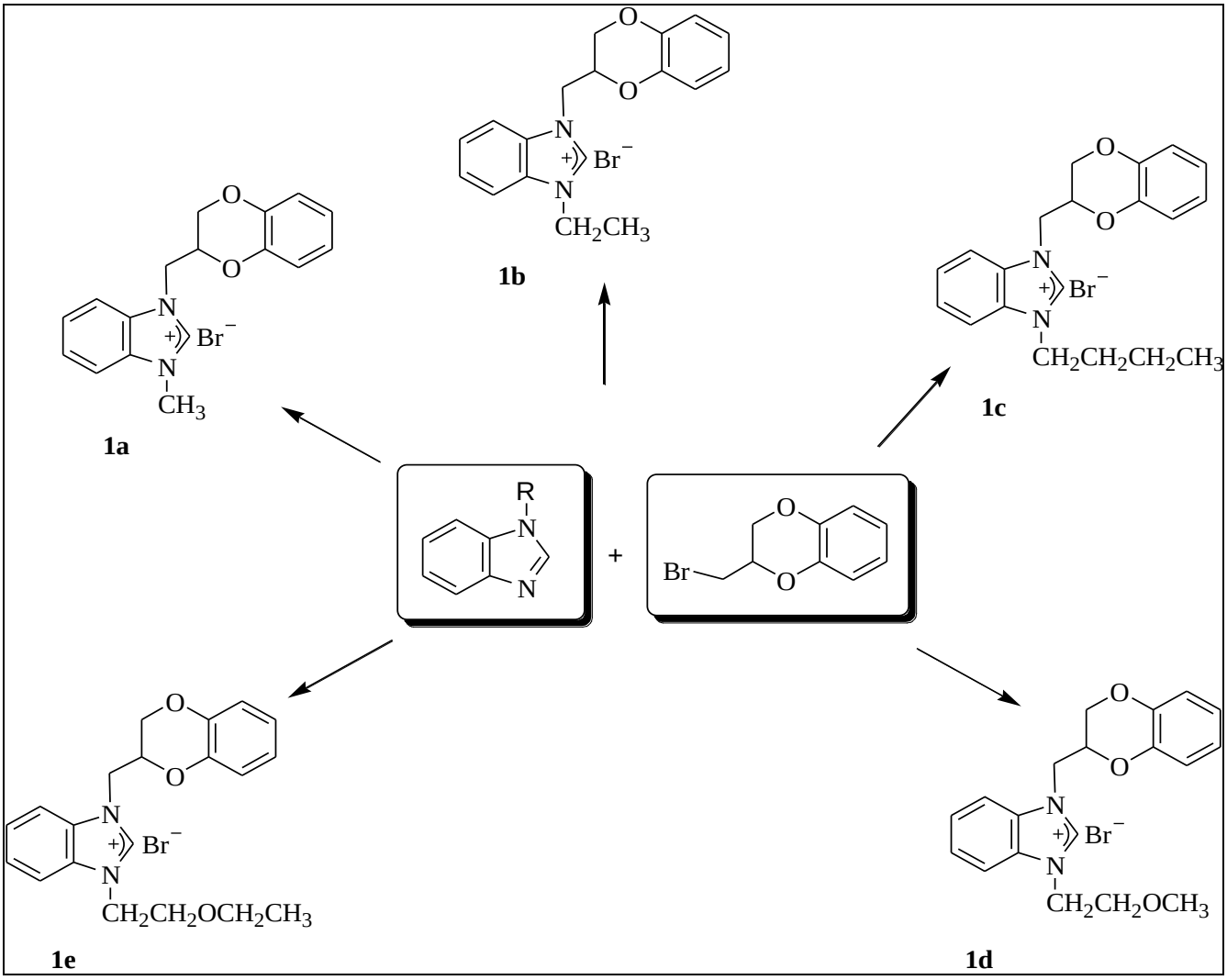
Evaluation of antimicrobial activity: Eleven microorganisms, consisting of ten bacteria and one yeast, were used as test organisms: *Aeromonas hydrophila* (ATCC 7965), *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (FMC 5), *Proteus mirabilis* (BC 3624), *Pseudomonas aeruginosa* (ATCC 27853), *Salmonella typhimurium* (NRRLE 4463), *Yersinia enterocolitica* (ATCC 1501), *Bacillus cereus* (FMC 19), *Listeria monocytogenes* (1/2B), *Staphylococcus aureus* (ATCC 29213) and *Candida albicans* (ATCC 1223).

The antimicrobial activities of the five compounds **1a-e** were studied *in vitro* using the agar-well diffusion method [14]. The stock solutions (10 mg ml^{-1}) of the test compounds were prepared by dissolving them in dimethyl sulfoxide (DMSO). All samples were sterilized through a 0.2 µm membrane filter. *C. albicans* and *Y. enterocolitica* were grown in malt extract and nutrient broths at 25^{o}C for 18 h, respectively. The other microorganisms were grown in nutrient broth at 35^{o}C for 18 h and suspensions were adjusted to 0.5 McFarland standard turbidity. Then 250 µl of each microorganism was added into a flask containing 25 ml sterile mueller hinton agar or malt extract agar at 45 ^{o}C and poured into Petri dishes (9 cm diameter). The agars were then allowed to solidify at 4 ^{o}C for 1 h. Holes were made in the agar using sterile cork borers (Ø = 6 mm). Solutions of the compounds (50 µl) were applied to the holes using a pipettor and DMSO was used as a control. *Y. enterocolitica* and *C. albicans* were incubated at 25^{o}C for 14-24 h in the inverted position. The other microorganisms were incubated at 35 ^{o}C for 18-24 h. At the end of the period, the inhibition zones which formed on the medium were measured in millimeters (mm). Tetracycline (10 mg ml^{-1}) (Sigma T3258-56) standard antibiotic was used as positive control.

RESULTS AND DISCUSSION:

Synthesis of new benzimidazolium salts: Five novel benzimidazolium salts as NHC precursors were synthesized by quaternization of *N*-alkylbenzimidazole with 2-bromomethyl-1,4-benzodioxane in dimethylformamide (Scheme 1). These synthesized salts **1a-e** were characterized by means of FT-IR, 1D NMR methods such as ^{1}H and ^{13}C NMR and elemental analysis. In the ^{1}H NMR spectra, the resonances of important protons NCHN from benzimidazole moiety prove the structures of the synthesized novel benzimidazolium salts as NHC precursors. Characteristic peaks (NC*H*N) were observed as sharp singlets at 11.21, 10.10, 11.35, 10.86 and 10.95 ppm for **1a-e**, respectively. ^{13}C NMR chemical shifts corresponded to the suggested structures of benzimidazolium salts; the imino carbons are typical singlets in the ^{1}H-decoupled mode at 143.4, 143.0, 142.8 and 143.1 ppm for **1a-c** and **1e,** respectively.

The FT-IR data clearly indicate the presence of –C=N- with a ν(C=N) at 1492.8, 1448.7, 1485.1, 1486.3 and 1496.7 cm^{-1} for benzimidazolium salts **1a-e**, respectively.



SCHEME 1: SYNTHESIS OF NOVEL BENZIMIDAZOLIUM SALTS (1a-e).

Evaluation of the antimicrobial activity: Five novel synthesized compounds (**1a-e**) were assayed *in vitro* for their antimicrobial activity against seven Gram (-) bacteria (*A. hydrophila, E. coli, K. pneumoniae, P. mirabilis, P. aeruginosa, S. typhimurium* and *Y. enterocolitica*), three Gram (+) bacteria (*B. cereus, L. monocytogenes* and *S. aureus*) and one yeast (*C. albicans*). The results of antibacterial activity are shown in **Table 1**. Compounds **1a-e** exerted moderate activity against the tested bacterial species. Among the tested compounds only **1c**, containing the *n*-butyl substituent, and **1a**, containing the methyl group, were effective against *E. coli*. Also only **1b**, containing the ethyl group, and **1c** had an inhibitory effect on *S. typhimurium* among the tested compounds. It could be said that **1c** had a wide spectrum of antibacterial activity as it was able to inhibit all test bacterial organisms comparable to other tested compounds. This result suggests that *n* butyl group substituted benzimidazole ring showed higher antibacterial activity in comparison to the other substituted analogues. On the other hand **1a**, which only had a slight effect against *E. coli* (7.0 mm), had the least activity among the tested compounds. Compounds **1a-e** showed no inhibitory effect on *C. albicans* at 10 mg ml^{-1} concentration (not shown in the **Table 1**). For evaluating antimicrobial activity tetracycline was used as the standard drug for comparison. As can be seen from **Table 1**, it is evident that all of the tested compounds showed slight activity in comparison to tetracycline.

TABLE 1: ANTIMICROBIAL ACTIVITIES OF COMPOUNDS 1A-E AND REFERENCE DRUG AGAINST THE TESTED MICROORGANISMS.

Organisms	Compounds					Tetracycline (10 mg ml^{-1})
	1a	1b	1c	1d	1e	
Gram (-)						
A. hydrophila	-	8.0	9.0	8.0	8.0	22.0
E. coli	7.0	-	8.0	-	-	21.0
K. pneumoniae	-	10.0	9.0	9.0	10.0	23.0
P. mirabilis	-	7.0	8.0	8.0	7.0	24.0
P. aeruginosa	-	8.0	9.0	8.0	8.0	21.0
S. typhimurium	-	8.0	6.5	-	-	16.0
Y. enterocolitica	-	9.0	7.0	7.0	-	27.0
Gram (+)						
B. cereus	-	8.0	8.0	8.0	8.0	26.0
L. monocytogenes	-	7.0	9.0	8.0	7.0	21.0
S. aureus	-	8.0	9.0	8.0	7.0	23.0

*: Inhibition zones include diameter of hole (6 mm). Sample amount 50 µl.
-: Not active

CONCLUSION: Five novel benzimidazolium salts (**1a**-**e**) were synthesized and their structures were completely verified by means of elemental analysis, FT-IR, 1D NMR: ^{1}H NMR, ^{13}C NMR. The biological activities of these salts were examined and were found to show moderate activity. The **1c** salt displayed the best activity against *A. hydrophila*, *P. aeruginosa*, *E. coli*, *S. aureus* and *L. monocytogenes* as Gram +/- microorganisms. The **1b** salt showed significant activity compared to the other salts (**1a**, **1c-e**) against *S. typhimurium* and *Y. enterocolitica*. Finally, it could be concluded that compounds **1b-e** exerted moderate antibacterial activity while **1a**, which contained the methyl group, showed slight activity against the tested bacterial species.

ACKNOWLEDGMENTS: This work was financially supported by Inönü University Research Fund (I.U.B.A.P. 2012/2).

REFERENCES:

1. T.H. Al-Tel, R.A. Al-Qawasmeh, Post Groebke–Blackburn multicomponent protocol: Synthesis of new polyfunctional imidazo[1,2-a]pyridine and imidazo[1,2-a]pyrimidine derivatives as potential antimicrobial agents, European Journal of Medicinal Chemistry, 2010; 45 5848-5855.
2. Y. He, B. Wu, J. Yang, D. Robinson, L. Risen, R. Ranken, L. Blyn, S. Sheng, E.E. Swayze, 2-Piperidin-4-yl-benzimidazoles with broad spectrum antibacterial activities, Bioorganic & Medicinal Chemistry Letters, 2003; 13 3253-3256.
3. Y. He, J. Yang, B. Wu, L. Risen, E.E. Swayze, Synthesis and biological evaluations of novel benzimidazoles as potential antibacterial agents, Bioorganic & Medicinal Chemistry Letters, 2014; 14 1217-1220.
4. Y. Kotaiah, K. Nagaraju, N. Harikrishna, C. Venkata Rao, L. Yamini, M. Vijjulatha, Synthesis, docking and evaluation of antioxidant and antimicrobial activities of novel 1,2,4-triazolo[3,4-b][1,3,4]thiadiazol-6-yl) seleno pheno[2,3-d]pyrimidines, European Journal of Medicinal Chemistry, 2014; 75 195-202.
5. B.V.S. Kumar, S.D. Vaidya, R.V. Kumar, S.B. Bhirud, R.B. Mane, Synthesis and anti-bacterial activity of some novel 2-(6-fluorochroman-2-yl) - 1 - alkyl/acyl/ aroyl- 1H-benzimidazoles, European Journal of Medicinal Chemistry, 2006; 41 599-604.
6. R. Vinodkumar, S.D. Vaidya, B.V. Siva Kumar, U.N. Bhise, S.B. Bhirud, U.C. Mashelkar, Synthesis, anti-bacterial, anti-asthmatic and anti-diabetic activities of novel N-substituted-2-(4-phenylethynyl-phenyl) - 1H-benzimidazoles and N-substituted 2[4-(4,4-dimethyl-thiochroman-6-yl-ethynyl)-phenyl)-1H-benzimidazoles, European Journal of Medicinal Chemistry, 2008; 43 986-995.
7. S. Sharma, S. Gangal, A. Rauf, Convenient one-pot synthesis of novel 2-substituted benzimidazoles, tetrahydrobenzimidazoles and imidazoles and evaluation of their in vitro antibacterial and antifungal activities, European Journal of Medicinal Chemistry, 2009; 44 1751-1757.
8. Y. Gök, S. Akkoç, H. Erdoğan, S. Albayrak, In vitro antimicrobial studies of new benzimidazolium salts and silver N-heterocyclic carbene complexes, Journal of Enzyme Inhibition and Medicinal Chemistry, 2016; 1-6.
9. Y. Gök, S. Akkoç, Ö.Ö. Çelikal, İ. Özdemir, S. Günal, In vitro antimicrobial studies of naphthalen-1-ylmethyl substituted silver N-heterocyclic carbene complexes, Arabian Journal of Chemistry.
10. P.K. Ranjith, P. Rajeesh, K.R. Haridas, N.K. Susanta, T.N. Guru Row, R. Rishikesan, N. Suchetha Kumari, Design and synthesis of positional isomers of 5 and 6-bromo-1-[(phenyl)sulfonyl]-2-[(4-nitrophenoxy)methyl] - 1 H - benzimidazoles as possible antimicrobial and antitubercular agents, Bioorganic & Medicinal Chemistry Letters, 2013; 23 5228-5234.
11. R.V. Shingalapur, K.M. Hosamani, R.S. Keri, Synthesis and evaluation of in vitro anti-microbial and anti-tubercular activity of 2-styryl benzimidazoles, European Journal of Medicinal Chemistry, 2009; 44 4244-4248.
12. S. Akkoç, İ. Özer İlhan, Y. Gök, P.J. Upadhyay, V. Kayser, In vitro cytotoxic activities of new silver and PEPPSI palladium N-heterocyclic carbene complexes derived from benzimidazolium salts, Inorganica Chimica Acta, 2016; 449 75-81.

13. Y. Gök, S. Akkoç, S. Albayrak, M. Akkurt, M.N. Tahir, N-Phenyl-substituted carbene precursors and their silver complexes: synthesis, characterization and antimicrobial activities, Applied Organometallic Chemistry, 2014; 28 244-251.

14. R. Aggarwal, G. Sumran, N. Garg, A. Agarwal, A regioselective synthesis of some new pyrazol-1′-ylpyrazolo[1,5-a]pyrimidines in aqueous medium and their evaluation as antimicrobial agents, European Journal of Medicinal Chemistry, 2011; 46 3038-3046.

How to cite this article:
Akkoç S, Gök Y, Erdoğan H and Albayrak S: Biological activity evaluation of novel n-heterocyclic carbene precursors. Int J Pharm Sci Res 2017; 8(1): 262-67.doi: 10.13040/IJPSR.0975-8232.8(1).262-67.