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Original scientific paper

Anticancer and antimicrobial properties of imidazolium based ionic liquids with salicylate anion

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Abstract: Ionic liquids (ILs) are well known for their physicochemical properties that recommend them for many purposes. However, many ILs are not environmentally friendly. Bearing these facts in mind, a series of imidazolium- and salicylate-based ILs with low general toxicity were designed and their pharmacological potential studied. Herein, their antiproliferative effect against human cancer cell lines and antimicrobial activity on selected Gram-positive and Gram-negative bacteria and *Candida* strains are presented. ILs with 1-butyl--3-methylimidazolium or imidazolium cation (IL **1** and compound **5**), with the lowest dipole moments and highest lipophilicity, exerted highest cytotoxicity against colon and/or lung cancer cells, manifesting high selectivity to the normal cells. The most non-polar IL with the 1-butyl-3-methylimidazolium cation expressed the strongest anticancer potential, but it was also toxic against normal cells, although its cytotoxicity was less than the cytotoxic effect of commercially used chemotherapeutic agents. The same compounds, IL **1** and compound **5**, expressed modest effect on the bacterial strain that causes serious lung diseases and pulmonary infections (*Staphylococcus aureus*) or which are included in colon cancer formation (*Escherichia coli* and *Enterococcus faecalis*). Salicylate itself was toxic against lung cancer cell line A549 and affected some *Candida* strains.

Keywords: ionic liquids; imidazolium; salicylate; cytotoxicity, antibacterial activity, antifungal activity.

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INTRODUCTION

Ionic liquids (ILs) express wide range of physicochemical features that could find many different applications, including biomedicine. Therefore, it is not surprising that they have drawn the attention of biomedical researchers as convenient catalytic media for drug synthesis, as well as potential components of drug formulations. Several notable reviews have emphasized the advantages of using ionic liquids in medicinal chemistry.[1–3] Improvement of water-solubility and thus bioavailability, by conversion of active pharmaceutical ingredients (API) to ionic liquid represents a common way for improving drug formulations. The physical, chemical and biological properties of these compounds, such as lipophilicity or toxicity, are also connected to their bioavailability. Furthermore, there are many well-known examples where combined biologically active cations and anions result in salts that exhibit therapeutic effects of both of its components.[4] Moreover, it should be emphasized and taken into account that many ILs have not been declared as environmentally friendly chemicals, and hence, their toxicity has to be tested before medical use and, *vice versa*, thanks to their toxicity, a plethora of distinct new opportunities for their application, especially in the area of medicine, are being created.

There are not many studies presenting the cytotoxic potential of salicylate-based ILs against human or animal cell lines or against microorganisms, while imidazolium-based ILs are more studied.[5–7] The particular mechanism of biological activity of ILs may vary among the different organisms, but water seems to be of great importance for most mechanisms in the living systems. Water-solubility and interactions with water are crucial factors determining biological, pharmacological, and also environmental activity of ILs. Biological activity of ILs was shown to depend on their hydrophilicity and hydration state/hydration number.[8–11] Starting from the assumption ‘more polar–less toxic’, lower cytotoxicity of ILs with polar groups was presumed, which was thus tested. Accordingly, the aim of this study was to assess the anticancer potential of imidazolium-based ionic liquids with salicylate anion in human cancer cell lines using the MTT cell viability assay, as well as antimicrobial potential of these compounds against several bacterial and *Candida* strains by the standard double diluted antimicrobial procedure.

EXPERIMENTAL

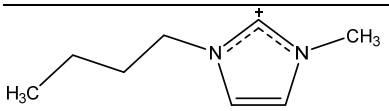
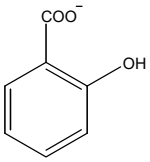
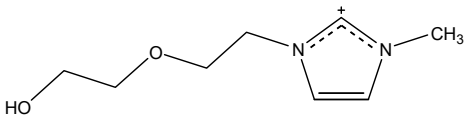
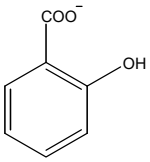
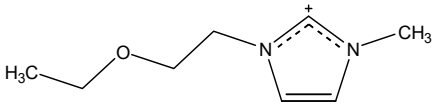
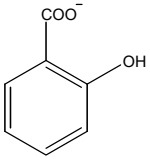
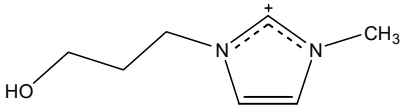
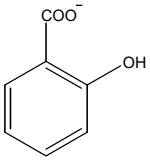
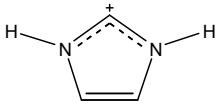
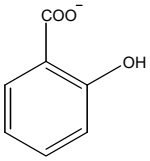
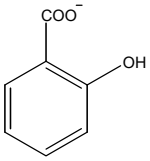
The tested imidazolium based ILs with salicylate anion

Imidazolium-based ionic liquids **1–4** and salt **5** with salicylate anion were prepared according to a previously published procedure.[12] Their structures and names are presented in the Table I. Since ILs are water-soluble compounds, stock solutions of each were prepared by dissolution in distilled water, as well as diluted solutions for the tests.

In order to obtain values of dipole moments for tested compounds, DFT calculations were performed using the Maestro program, as a part of the Schrödinger Suite 2015-2 pack-

age. All structures were geometrically optimized first, using a conformational search and later DFT calculations were performed using the functional B3LYP-d3 with the basis set 6-31+G(d,p). Dipole moments were calculated from the obtained results, using the method developed by Rashin *et al.*[13]

TABLE I. Structures and names of the tested ILs **1**–**4**, salt **5** and the reference sodium salicylate (**6**)

Structure of the cation	Structure of anion	Name of compound/Code
		1-Butyl-3-methylimidazolium salicylate (**1**)
		[2-(4-Hydroxyethoxy)ethyl]-3-methylimidazolium salicylate (**2**)
		(2-Ethoxyethyl)-3-methyl-imidazolium salicylate (**3**)
		1-(3-Hydroxypropyl)-3-methylimidazolium salicylate (**4**)
		Imidazolium salicylate (**5**)
Na^+		Sodium salicylate (**6**)

Determination of antiproliferative activity

Antiproliferative activity of the imidazolium based ILs with salicylate anion was tested against six human cancer cell lines: two types of human breast adenocarcinoma, *i.e.*, the estrogen receptor positive (ER+) MCF-7 (American Type Culture Collection – ATCC HTB-22)

and the triple negative MDA-MB-231 (ATCC HTB-26), prostate cancer PC-3 (ATCC CRL-1435), cervix adenocarcinoma HeLa (ATCC CCL-2), colon cancer HT-29 (ATCC HTB-38) and lung cancer A549 (ATCC CCL-185) cell lines, as well as normal fetal lung fibroblast cell line MRC-5 (ATCC CCL-171). The cells were grown in Dulbecco's modified Eagle's medium (DMEM) with 4.5 % glucose, supplemented with 10 % fetal calf serum (Sigma) and the antibiotics 100 IU mL^{-1} penicillin and 100 μg mL^{-1} streptomycin (Sigma). The cells were cultured in flasks (Costar, 25 cm^2) at 37 °C in high humidity with 5 % CO_2. Only viable cells were used in the assays, and cell viability was determined by the trypan blue dye exclusion test.

Antiproliferative activity of the imidazolium salicylate-based ILs was evaluated by the tetrazolium colorimetric MTT assay,[14] as previously described.[15] To measure the number of viable cells in microwell plates, the cells were exposed to the test compounds for 72 h at five concentrations ranging from 0.01 to 100 μM (0.01, 0.1, 1, 10 and 100 μM). The reference compounds used in this assay were cisplatin (Cis) and doxorubicin (Dox), as nonselective anticancer agents[16,17] and sodium salicylate to test salicylate toxicity, respectively. The IC_{50} value, defined as the dose of a compound that inhibits the cell growth by 50 % relative to the control (untreated) cells, was determined for each tested compound by median effect analysis.[18]

Antimicrobial activity and data analysis

Six bacterial strains including three Gram-positive (G^+) bacteria, *i.e*., *Staphylococcus aureus* h (human), *Bacillus subtilis* ATCC 6633 and *Enterococcus faecalis* ATCC 19433, and three Gram-negative (G^-) bacteria, i.e., *Proteus mirabilis* h, *Escherichia coli* ATCC 11229 and *Pseudomonas aeruginosa* ATCC 15692, and four yeast strains, two of which (*Candida albicans* L. (laboratory strain) and *C. albicans* ATCC 10231) were obtained from the culture collection of microorganisms from the Department of Biology and Ecology, University of Novi Sad, Serbia, while two human yeast isolates (*C. albicans* III h and *Candida* IV h) were obtained from the Faculty of Medicine, Clinical Centre of Vojvodina, Serbia. All human isolates of the microorganisms were obtained from the Faculty of Medicine, Department of Obstetrics and Gynecology, University of Novi Sad, Serbia, under a protocol that was approved by the Institutional Ethical Board of the same Institution. The antibacterial activity of ILs was evaluated as the minimum inhibitory concentration (*MIC*) values and the minimum bactericidal/fungicidal concentration (*MBC*/*MFC*) values, by the double-microdilution method according to the CLSI procedure.[19,20]

Statistical analysis

Data were subjected to nonparametric analysis (principal component analysis – PCA, and hierarchical cluster analysis – HCA) using software Statistica 13.3 (Statsoft, Tulsa, OK, USA) based on the obtained *MIC* and *MBC*/*MFC* values on the tested microbial strains.

RESULTS AND DISCUSSION

It was postulated and proved that ionic liquids with polar ether, hydroxyl or nitrile functional groups within the side chains exhibit lower cytotoxicity compared to their structural analogues with non-polar alkyl side chains.[21–23] These functional groups were thought to impede cellular uptake by membrane diffusion and reduce lipophilicity-based interactions with the cell membrane.[23,24] Otherwise, the study of the cytotoxicity of imidazolium-based ionic liquids showed that the chain length of alkyl substitution at the N-3 position of imidazole ring plays a crucial role towards their anti-cancer activity.[25,26]

In a previous report, the synthesis and general toxicity of ionic liquids **1**–**5** were presented. Among them was 1-butyl-3-methylimidazolium salicylate (**1**), a salicilyte analogue of the well-known $BMIM^+$ cation-based ionic liquid, which expresses very good physicochemical properties and, accordingly, has a wide range of applications.[27–29] Compared to compound **1** that possesses a non-polar *n*-butyl substituent at N-1, ILs with more polar substituents (compounds **2**–**5**) showed lower general toxicity (Table II).[12]

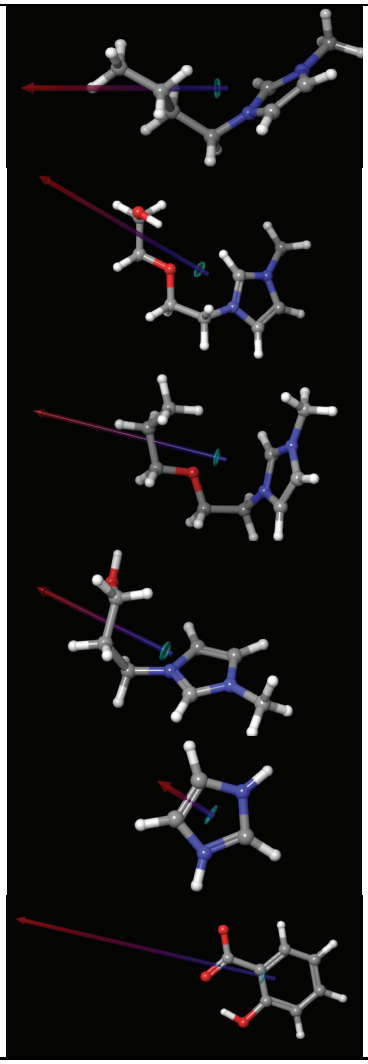
TABLE II. Antiproliferative effect, estimated by MTT test and presented as IC_{50} values (μM), of the tested imidazolium-based ILs and salt **1**–**5** and reference compounds: sodium salicylate, doxorubicin and cisplatin after 72 h treatment; N/A – IC_{50} value was not available due to very low effect

Compd.	Cell line						
	MCF-7	MDA-MB-231	PC-3	HeLa	HT-29	A549	MRC-5[12]
1	>100	>100	>100	75.46	14.89	>100	27.54
2	>100	>100	>100	>100	9.26	>100	>100
3	>100	>100	>100	>100	>100	57.31	>100
4	>100	>100	>100	>100	>100	>100	N/A
5	>100	>100	>100	>100	39.94	23.03	>100
6	>100	>100	>100	>100	>100	44.39	>100
Dox	0.29	0.09	89.90	1.68	0.10	7.52	0.11
Cis	1.60	2.64	4.56	2.10	4.10	3.20	0.24

In this study, the effect of imidazolium based ILs with salicylate anion **1**–**4** and salts **5** and **6** was tested against human cancer cell lines, as well as against selected bacteria or fungal strains. The most sensitive cell line was colon cancer cell line HT-29. The most cytotoxic against these cells was ionic liquid **2**, with IC_{50} value of 9.26 μM. The substituent on the N-1 position of this compound is quite polar, containing both ether and hydroxyl functions. Salicylate **5**, with non-substituted imidazolium moiety as cation, showed modest cytotoxicity against HT-29 cells, with an IC_{50} value of 39.94 μM, while the other salicylate-based compounds did not decrease the number of HT-29 cells significantly, *i.e.*, their effects were very weak, even at the highest tested concentrations (Table II). A similar effect as **2** was expressed by compound **1** (IC_{50} = 14.89 μM), with the most non-polar group (*n*-butyl), although compound **1** showed general toxicity, *i.e.*, it was also toxic against normal human lung fibroblasts (MRC-5 cell line, IC_{50} = 27.54 μM). Besides the colon carcinoma cell line, the lung adenocarcinoma cell line A549 was sensitive to the tested salicylate ILs as well, although in a more modest manner. Against this cell line, a modest effect was expressed by compounds **3** and **5** (IC_{50} of 57.31 and 23.03 μM, respectively), carrying an ether group (**3**), or with no substituents on imidazole ring (**4**). The reference sodium salicylate also expressed moderate antiproliferative effect against these cells (IC_{50} = 44.39 μM).

Structure–activity relationship study could be based on the polarity of the tested ionic liquid compounds, studied *via* dipole moment vectors (Table III). The ILs with larger dipole moments (**2**–**4**) induced lower effects on the cancer cells, and *vice versa*, ILs with smaller dipole moments expressed stronger effects against the cancer cell lines.

TABLE III. Dipole moments of the cations and anion of the tested imidazolium-salicylate-based compounds **1**–**5**

Compd.	Function on N-1 of cation/anion	Visualization of dipole moment	Dipole moment, D*
1	*n*-Butyl		5.40
2	2-(2-Hydroxy-ethoxy)ethyl		8.14
3	2-Ethoxyethyl		8.62
4	3-Hydroxypropyl		7.14
5	H		3.92
6	No imidazolium cation, sodium salicylate		6.68

* 1 D = 3.33564×10^{-30} C m

The widely used anticancer agents cisplatin (Cis) and doxorubicin (Dox) were used as reference compounds in this study. They are not selective. On the contrary, they were similarly effective in the lowering of number of both normal and cancer cells (Table II), which is in accordance to the results of other studies.[16,17]

The most non-polar IL from the group of tested ILs, the *n*-butyl derivative **1** was the only IL that decreased the number of normal cells, which is in agreement with other results on reducing toxicity with increasing polarity.[21–23] Selectivity indexes for tested ILs **1**–**5** could not be calculated and thus the selectivity of ILs quantified, except for compound **1**, because the IC_{50} values for compounds **2**–**5** are too high (though the IC_{50} values in Table II are presented simply as values higher than 100 μM), *i.e.*, the cytotoxicity of these compounds, even in the highest tested concentration, is very low.

On the other hand, salicylic acid (which is also metabolically obtained from acetylsalicylic acid/aspirin) has long been recognized in *in vitro* tests as an anticancer agent,[30] which induces apoptosis by activating caspases. Still, it also could be used in pre-administration, and thus increase the chemosensitivity of some cancer cells, because it suppresses NF–κB activation, and is included in pro-apoptotic signal modulation therapy.[31] Considering the fact that ionic liquids contain salicylate anion, the overall effect of the ionic liquids could be attributed partly to the effect of the salicylate anion itself, although in the present study, the reference compound sodium salicylate (**6**) expressed a modest antiproliferative effect only against the A549 lung adenocarcinoma cell line (Table II).

In the antimicrobial testing (Table S-I of the Supplementary material to this paper), the most resistant strains (*R**) towards common antibiotics streptomycin, kanamycin and ampicillin were *P. aeruginosa* ATCC 15692 and *P. mirabilis* h. Two ATCC strains *B. subtilis* and *E. coli* and one human isolate, *S. aureus* h, were sensitive towards all antibiotics at the lowest concentrations applied (0.01 mg mL^{-1}). On the contrary, the tested ionic liquids expressed weak antimicrobial potential towards all treated bacterial strains, except compounds **1** and **5** that were the most effective, exerting modest antimicrobial activity against *S. aureus* (both compounds) and *P. aeruginosa* (**5**). Since *P. aeruginosa*, a Gram-negative opportunistic pathogen, was resistant towards almost all tested antibiotics, this result gains in importance, especially bearing in mind that this bacterial species often causes acute pneumonia with a high mortality rate, especially in the compromised host.[32] Compound **5** was also effective in decreasing the number of lung carcinoma cells A549.

Furthermore, both compounds **1** and **5** affected *S. aureus*, for which connection with lung diseases is also postulated, since it causes serious pulmonary infections in adults with concomitant illnesses that are typically nosocomial or in patients with cystic fibrosis.[33] Human isolates, such as the strain *S. aureus* h, are

well known to be more resistant to common antibiotics due to general phenomena of antibiotic resistance that is accelerated by the misuse or overuse of antibiotics, as well as poor infection prevention and control.[34] Hence, the modest effect obtained for both compounds **1** and **5** on tested human strains could implicate these ILs as new pharmacons with antimicrobial potential.

E. coli is a common minor component of the colonic microbiota,[35] while some bacterial strains, such are the tested *E. coli* and *E. faecalis*, present pathogens that are responsible for the initiative process of colon cancer and promotion of tumorigenesis *via* genotoxic effect.[36] Although in the present study tested ILs exerted quite low antibacterial effect against these two strains compared to the antibiotics, it should be kept in mind that these compounds, namely **1** and **5**, affected colon adenocarcinoma cells HT-29, which make them worthy of attention in further drug development.

All tested ionic liquids or salts (**1**–**5**), possessing both imidazolium-based cation and salicylate anion, were effective against *Candida* strains. Still, compounds **4** and **5** expressed the strongest effects against *Candida* strains (Table S-I). Salicylate salt with non-substituted imidazolium cation (**5**) was the most active in the testing of anticancer and antibacterial potential. The role of water in living organisms was recognized long time ago, but the roles of water in sustaining life are not understood well yet, even though many researchers are working in this research area.[37] Still, in the protic surroundings of living cells, protons from the N atoms of the imidazolium ring of ionic liquid **5** looks likely to play an important role in the biological activity of this compound.

According to the antimicrobial activity of the salicylate anion (compound **6**) tested in this study, its antibacterial effect was low, while its antifungal property was more expressed, *i.e.*, it was effective towards eukaryotic cells of all four *Candida* strains, including both human isolates (III h, IV h) of gynecological origin. Salicylic acid (salicylate) is already known for some time as good antifungal agent, useful in treatment of *Candida* strains, especially against *Candida* biofilm formation.[38–40] It was reported previously that salicylic acid suppresses growth of *C. albicans via* the selective suppression of (3*R*)-hydroxy oxylipins, selectively located in *Candida* hyphae and other filamentous structures. Moreover, *C. albicans* stimulates prostaglandin E2 (PGE2) production in HeLa cells.[40] All tested ILs contain salicylate anion and hence, it could be assumed that expressed anti-candida properties are derived therefrom, as well as connection to the effect of salicylate-based ionic liquid **1** against HeLa cells.

According to hierarchical cluster analysis (HCA) presented in Fig. 1a, it could be seen that all investigated ionic liquids are grouped into two clusters and one outlier due to the different alkyl chain length on the imidazolium ring in position N-1. The first cluster is formed from the ionic liquids with an alkyl chain with four carbon atoms: ILs **1**–**3**. Compounds **5** and **6** without any alkyl chain form

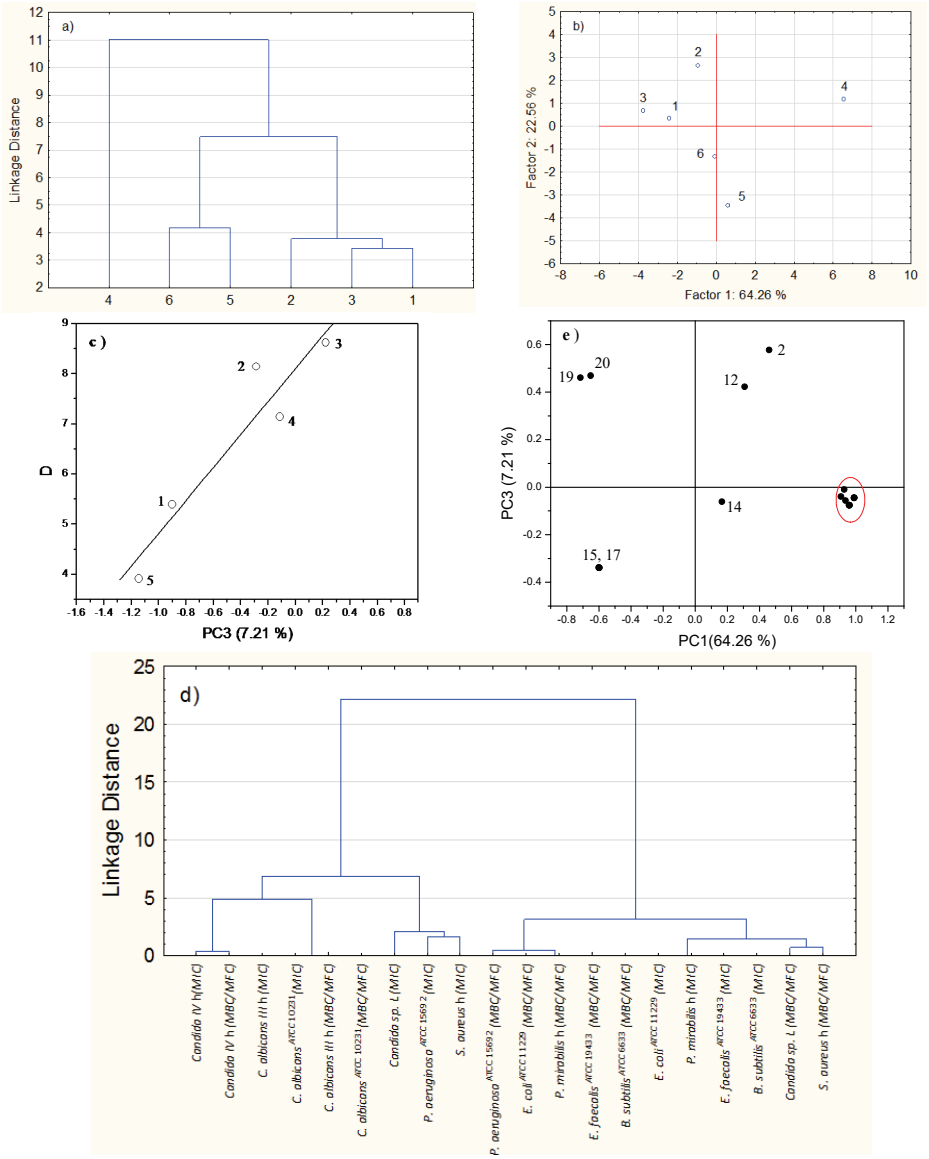


Fig. 1. HCA and PCA: a – Dendrogram of the examined compounds according to their antimicrobial activity; b – score plot as a PCA result of PC1 variation with PC2 for the investigated compounds; c – dependence of PC3 on the dipole moments (D) of the studied imidazolium based compounds **1**–**5**. Correlation coefficient $R = 0.946$; d – dendrogram of the examined bacterial and yeast strains; e – score plot as a PCA result of PC1 variation with PC2 for the investigated bacterial and yeast strains: 20 – *Candida* IV h *MIC*; 19 – *C. albicans* IV h MBC/MFC; 17 – *C. albicans* III h MBC/MFC; 15 – *C. albicans* ATCC10231 MBC/MFC; 14 – *C. albicans* sp. L. MIC; 12 – *P. aeruginosa* ATCC15692 MIC; 2 – *S. aureus* h MIC; circled – all other.

the second cluster, and IL **4** with a propyl-derived substituent is an outlier. Thus, it could be concluded that the antimicrobial activity of studied ionic liquids mainly depends on the alkyl chain length in the cation structure.

In the present case, three principal components described 94 % of the total variance in the data (PC1 64.26 %, PC2 22.56 % and PC3 7.21 %). The results of the principal component analysis (PCA) are in a good agreement with those obtained using HCA and the same trend is observed in Fig. 1b, where the first two PCs separate the studied ionic liquids according to the alkyl chain length in position N-1 of the imidazolium ion.

The obtained PC3 represented by 7.21 % could be related to the polarity of investigated ILs. Namely, variation of PC3 with the calculated dipole moments of the ILs is linear, as shown in Fig. 1c. The obtained linear dependence means that PC3 carries important information on the influence of the dipole moment on the antimicrobial activity of the investigated ILs.

The same analyses (HCA and PCA) were performed using *MIC* and *MBC*/ /*MFC* values obtained for all investigated bacterial and yeast strains. The dendrogram obtained using HCA presented in Fig. 1d shows two main clusters, dominantly separating *Candida* strains into one cluster and bacterial strains into the second one. In the second cluster, two subclusters could be observed, where the bacterial strains are divided according to their *MIC* and *MBC*/*MFC* values. Furthermore, the results obtained by PCA (Fig. 1e) indicate the same trend since the PC1 separates *Candida* strains from the studied bacterial strains. In addition, PC2 separates the procaryotic-cell bacteria *P. aeruginosa* ATCC 15692 and *S. aureus* h from all others, as indicated in Fig. 1e. Among the eucaryotic *Candida* strains, it could be seen that *Candida* sp. L. is slightly distant, which is based on its highest sensitivity.

CONCLUSION

Ionic liquids, being water soluble, are usable for many purposes, including as pharmaceuticals. The studied imidazolium-based ILs possess different substituents at the N-1 position, containing an alkyl chain with different polarity, and the salicylate anion. IL **2**, with alkyl chain containing both ether and hydroxyl functions, expressed the best anticancer potential against colon cancer cells. Compound **5** with non-substituted imidazolium cation has a large dipole moment as well, and it showed modest anticancer potential against both lung and colon cancer cells. These compounds were selective towards cancer cell lines only. The IL with the most non-polar cation, IL **1**, expressed the highest cytotoxicity, but with no selectivity. Further experiments towards ILs for pharmacological purposes are in progress.

SUPPLEMENTARY MATERIAL

Additional data are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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И З В О Д

АНТИКАНЦЕРСКЕ И АНТИМИКРОБНЕ ОСОБИНЕ ЈОНСКИХ ТЕЧНОСТИ НА БАЗИ ИМИДАЗОЛА СА САЛИЦИЛАТНИМ АНЈОНОМ

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Јонске течности (ЈТ) су добро познате по својим физичко–хемијским својствима која их препоручују за употребу у многе сврхе. Ипак, многе ЈТ нису еколошки прихватљиве. Имајући у виду ове чињенице, дизајнирали смо низ имидазолијумских ЈТ са салицилатним анјоном ниске опште токсичности и проучавали њихов фармаколошки потенцијал. У раду је приказан њихов антипролиферативни ефекат на ћелијске линије хуманих канцера и антимикробна активност на одабраним Грам-позитивним и Грам-негативним бактеријским и *Candida* сојевима. ЈТ са 1-бутил-3-метилимидазолијумовим или имидазолијумовим катјоном (ЈТ **1** и једињење **5**), са најнижим диполним моментима и највишом липофилношћу, показале су највећу цитотоксичност на ћелије канцера колона и/или плућа, испољавајући високу селективност према нормалним ћелијама. Најнеполарнија ЈТ, са 1-бутил-3-метилимидазолијумовим катјоном, показала је најјачи антиканцерски потенцијал, али је такође била токсична и на нормалне ћелије, мада је њена цитотоксичност била мања од цитотоксичног ефекта комерцијално коришћених хемотерапеутских средстава. Иста једињења (ЈТ **1** и једињење **5**) испољила су и мањи ефекат на бакт * us*), као и на сојеве укључене у настанак канцера колона (*E. coli* и *E. faecalis*). Сам салицилатни еријске сојеве који узрокују озбиљне плућне болести и плућне инфекције (*S. aure* анјон је био токсичан за ћелијску линију рака плућа A549, а деловао је и на неке *Candida* сојеве.

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