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SYNTHESIS AND ANTIMICROBIAL PROPERTIES OF CAMPHORSULFONIC ACID DERIVED IMIDAZOLIUM SALTS

SYNTÉZA A ANTIMIKRÓBNE VLASTNOSTI IMIDAZÓLIOVÝCH SOLÍ ODVODENÝCH OD KYSELINY GÁFORSULFÓNOVEJ

Original research article

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Abstract A group of homochiral imidazolium salts bearing hydrophobic camphor derived moiety and ester or amide functional group were synthesized and characterized. The novel imidazolium bromides were tested as antimicrobial and antifungal agents and their minimal inhibitory concentration (MIC) was evaluated and compared to clinically used benzalkonium bromide (BAB) and carbethopendecinium bromide. The MIC values of amide derivatives **2a** and **2b** were slightly smaller than those for BAB, indicating their good activity. None of the prepared salts was more effective than carbethopendecinium bromide. The biocidal efficacy of amide derivatives was much higher compared to the ester analogues.

Slovak abstract Bola pripravená a charakterizovaná skupina homochirálnych imidazóliových solí obsahujúcich hydrofóbnu skupinu odvodenú od gáfru s esterovou a amidovou funkčnou skupinou. Na pripravených imidazóliových soliach bola testovaná ich antimikróbna a antifungálna aktivita. Stanovila sa ich minimálna inhibičná koncentrácia (MIC), ktorá bola porovnaná so štandardmi: benzalkónim bromidom (BAB) a karbetopendecínium bromidom. Hodnoty MIC pre amidové deriváty **2a** a **2b** boli nižšie ako pre BAB, čo indikuje ich dobrú inhibičnú aktivitu. Žiadna z pripravených solí nebola efektívnejšia ako karbetopendecínium bromid. Biocídna aktivita amidových derivátov bola oveľa vyššia v porovnaní s ich esterovými analógmi.

Keywords *imidazolium salts, antimicrobial activity, camphorsulfonic acid*

Kľúčové slová: *imidazóliové soli, antimikróbna aktivita, kyselina gáforsulfónová*

INTRODUCTION

The strong bactericidal activity of quaternary ammonium salts (QAS) with long alkyl chains have been known since 1915 (Jacobs & Heidelberger, 1915) and studied further on a broad range of microorganisms such as Gram positive (G+) and Gram negative (G–) bacteria and fungi (Lukáč *et al.*, 2010; Mikláš *et al.*, 2012, 2014), certain viruses (Wong *et al.*, 2002), herbicidal salts (Cojocaru *et al.*, 2013) and even anticancer agents (Kaushik *et al.*, 2012). Having the ability to intercalate into phospholipid membranes, they may affect the processes in biological systems, inducing cell autolysis leading to the leakage of intercellular materials into the environment and cell death (Devínsky *et al.*, 1987; Mlynarčík *et al.*, 1981). The widespread importance of surfactants in practical applications (Brak & Jacobsen, 2013; Cortesi *et al.*, 2012; Gilbert & Moore, 2005; Zhi *et al.*, 2012) and difficulties to recover or reuse them due to their water solubility causes their accumulation in environment, thus affecting aquatic ecosystem. Most QASs are not easily biodegraded; therefore, the aquatic microorganisms remain in contact with them for a longer period of time, which increases their toxicity. It was found (Kümmerer *et al.*, 1997) that LC50 of benzalkonium chloride to fish was between 0.5 and 5.0 mg l^{-1} and to daphnids even from 0.1 to 1.0 mg l^{-1}. In addition, the presence of QASs may decrease the biodegradation efficiency of linear alkylbenzene sulfonates.

The toxicity of QASs depends on both polar and hydrophobic parts of the molecule. Generally, the double-tail surfactants are less toxic than the single-tail counterparts (Pinnaduwage *et al.*, 1989). The length of the hydrophobic alkyl chain in QASs plays also an important role for toxicity. While for aliphatic single-tail cationic surfactants, the toxicity increases

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with the increasing alkyl chain length; (Rasia *et al.*, 2007) for double-tail cationic surfactant, the toxicity decreases as the alkyl chain length increases (Spelios & Savva, 2008). Concerning the polar part of the QAS`s molecule, the positive charge can be located on a quaternary ammonium group or delocalized in heterocyclic ring or in a guanidine group. Delocalization of the positive charge mostly helps to decrease the toxicity of such surfactants (Coleman *et al.*, 2012). In order to avoid systemic toxicity and environmental persistency of QAS antimicrobials, the "soft" drug approach developed by Bodor *et al.* (1980) was applied to this problem. The structural "soft" analogues, compared to their "hard" counterparts, have a specific easily degradable functional group built into their structures to provide their one-step detoxification. Various "soft" surfactants possessing a cleavable moiety, such as an ester and/or amide bond, have been synthesized and their antimicrobial activity and biodegradation was tested (Colomer *et al.*, 2012; Devínsky *et al.*, 1991; Fan *et al.*, 2013). The well-known antibacterial effect of essential oils containing bicyclic camphor or borneol (Ćavar *et al.*, 2012; Ruiz-Navajas *et al.*, 2012) resulted in the idea to design and synthesize potentially "soft" QASs bearing hydrophobic chiral camphor derived moieties, hoping that incorporation of two important antimicrobial active structures in one compound will improve their bioactivity. In this study, we have prepared a series of six new optically active quaternary imidazolium salts, which could be specified as potentially "soft" disinfectants due to the ester or amide bonds in the structure (Fig. 1). Their antimicrobial activity was tested against Gram-negative *Escherichia coli*, Gram-positive human pathogenic bacteria *Staphylococcus aureus* and human fungal pathogen *Candida albicans*.

2. EXPERIMENTAL

2.1 Materials and methods

All compounds used ((1*S*)-(+)-camphor-10-sulfonic acid (CSA), thionylchloride, triethylamine (TEA), diethyl ether, acetone, dichloromethane (DCM), ethyl acetate, petroleum ether (40–65°C), DMSO, bromoacetyl bromide, fatty alcohols and amines) are commercially available. DCM was pre-dried over $CaCl_2$ and then distilled from CaH_2 under a nitrogen atmosphere. Diethyl ether was pre-dried from KOH and then distilled from sodium. Acetone was distilled from potassium carbonate. Bromoacetic acid esters (Michniak *et al.*, 1996) and amides (Hoque *et al.*, 2012) were synthesized by modification of published procedures. ^1H and ^{13}C NMR spectra were measured on a Varian Gemini 300 spectrometer at 300 MHz and 75 MHz, respectively. Chemical shifts have been reported in ppm relative to an internal reference (TMS). IR spectra (in KBr pellets) were recorded on FTIR Impact 400D Nicolet instrument. Polarimetric measurements were obtained using a Jasco P-1010 polarimeter at 589 nm. Elemental analyses were carried out on a Carlo Erba 1108A instrument. All melting points reported were uncorrected and measured on Kofler hot stage.

2.2 Microbiology

The antimicrobial activity was tested against Gram-negative bacteria *Escherichia coli* CNCTC 377/79, Gram-positive bacteria *Staphylococcus aureus* ATCC 6538 and fungi *Candida albicans* CCM 8186. Solutions of the compounds studied were prepared in DMSO (5%, w/v). A suspension of the standard microorganism, prepared from 24-h cultures of bacteria in blood agar and from 24-h cultures in the Sabouraud agar for fungi had a concentration of 5x107 cfu ml^{-1} of bacteria and 5x105 cfu ml^{-1} of *Candida*. Concentration of microorganisms were determined spectrophotometrically at 540 nm and adjusted to absorbance A = 0.35. The microorganism suspension (5 µl) was added to solutions containing the compound under examination (100 µl) and to double-concentrated peptone broth medium (8%) for bacteria or Sabouraud medium (12%) for *Candida* (100 µl).The double-concentrated medium was used due to addition of the same volume of solution containing the compound tested, which resulted in the desired standard concentration of medium for experiments. The stock solution of tested compounds was serially diluted by half. The cultures were carried out using 96-well microliter plates. The microorganisms were incubated for 24 h at 37°C and then from each well, 5 µl of suspension were cultured on blood agar (bacteria) or on Sabouraud agar (fungi). After 24 h at 37°C, the lowest concentration of QAS, which prevented colony formation, was determined as minimal inhibitory concentration (MIC). Benzalkonium bromide (BAB, Ajatin®) and carbethopendecinium bromide (Septonex®) were used as the standards.

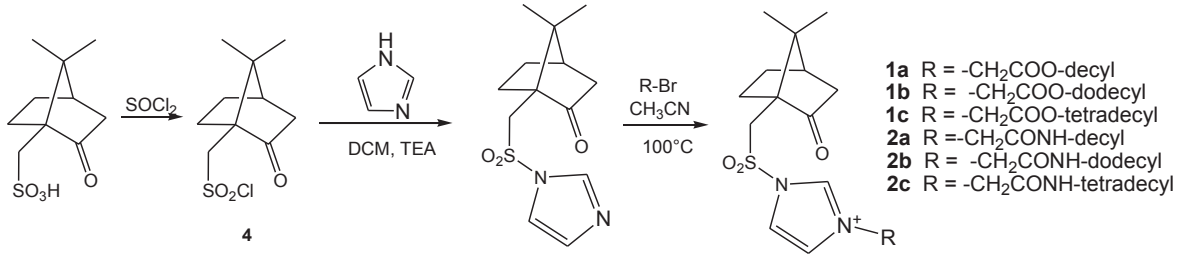

Figure 1. Preparation of camphorsulfonic acid derived imidazolium salts of the compounds in series 1 and 2.

2.3 Synthesis

Enantiopure camphor sulfonylchloride 4 was prepared according to the known procedure (Gayet *et al.*, 2004).

1-((1*H*-imidazol-1-ylsulfonyl)methyl)-7,7-dimethylbicyclo-[2.2.1]heptan-2-one (3)

To a solution of imidazole (7.1 g, 0.104 mol) and TEA (11.1 ml, 0.08 mol) in anhydrous DCM (50 ml) was added drop wise a solution of 4 (20.12 g, 0.08 mol) in anhydrous DCM (80 ml) at 0°C over 30 min. After the addition was complete, the reaction mixture was heated to reflux for 1.5 h. and then stirred overnight at ambient temperature. A precipitate was filtered off and filtrate was extracted with 20% (w/v) aqueous solution of Na_2CO_3 (2 x 50 ml) and brine (50 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to yield a yellowish solid. The crude product was recrystallized from acetone/petroleum ether (3:1, v/v) mixture to yield 19.1 g (84%) of white crystals.

General procedure for the synthesis of quaternary salts 1 and 2

The sulfonamide 3 (12 mmol) was mixed with 1.2 equivalents of the appropriate alkylating bromoderivative in CH_3CN (20 ml). Reaction mixture was stirred at ambient temperature for 2 h., then refluxed for 24 h. and allowed to cool. The reaction mixture was placed in the freezer for 2 days and the resulting crystals were filtered off, washed twice with 25 ml of anhydrous diethyl ether and the crude product was recrystallized repeatedly from anhydrous acetone. Characterisation and spectral data of the prepared salts are sumarized in Tables 1 and 2.

3. RESULTS AND DISCUSSION

Enantiopure QASs of the compounds in series 1 and 2 were synthesized as illustrated in Fig. 1. starting from (1*S*)-camphor-10-sulfonic acid. Although sulfonylchloride 4 is commercially available as a starting material, (1*S*)-camphor-10-sulfonic acid proved to be less expensive and can be easily converted to the sulfonylchloride 4 by the published procedure (Gayet *et al.*, 2004). Thus (1*S*)-camphor-10-sulfonic acid was reacted with thionylchloride providing compound 4 in 86% yield after crystallization from petroleum ether. The preparation of camphor sulfonamide 3 was carried out by dropwise addition of 4 in anhydrous DCM into the solution of imidazole in DCM in the presence of TEA as a base. Two series of imidazolium salts 1 and 2 were formed after quaternization of 3 by n-alkyl esters or *N*-alkyl amides of bromoacetic acid (alkyl = decyl, dodecyl, tetradecyl) in acetonitrile. All imidazolium salts were obtained as colorless crystals after several crystallizations from anhydrous acetone in yields ranging from 24 to 46%. They were identified and characterized thoroughly from spectral and analytical data.

The antimicrobial activities of imidazolium salts, were determined as a MIC, [μmol l^{-1}] against the Gram-positive human pathogenic bacteria *S. aureus*, Gram-negative bacteria *E. coli* and human fungal pathogen *C. albicans*, the values for which are given in Table 3. The MIC values were determined as lowest concentration of the imidazolium salt that completely prevented visible colony formation. All the compounds were dissolved in DMSO for biological evaluation. In order to prove that the solvent does not influence bacterial and fungal growth, a test with pure solvent was performed. This control test detected no inhibitory activity. Clinically used benzalkonium bromide (BAB, Ajatin®) and carbethopendecinium bromide (Septonex®) were used as standards.

According to the results, it can be observed that all of the synthesized imidazolium salts exhibit growth inhibition effect against all three types of microbes, with higher efficiency against *S. aureus* and *C. albicans* (Fig. 2). Gram-negative *E. coli* was found to be most resistant to the prepared salts, presumably due to the cell membrane composition. Gram-negative bacteria contain an outer membrane with an external com-

Table 1. Characterisation of camphorsulfonic acid derived imidazolium salts of the compounds in series 1 and 2

Compound	Formula / [α]D[21] (conc., solvent)	w_i(calc.)/% w_i(found)/%				Yield	M.p.
		C	H	N	S	%	°C
1a	$C_{25}H_{41}BrN_2O_5S$/ – 0.86 (0.1 g/100 ml, $CHCl_3$)	53.47 53.29	7.36 7.43	4.99 5.11	5.71 5.58	46	153–155
1b	$C_{27}H_{45}BrN_2O_5S$/ – 0.44 (0.1 g/100 ml, $CHCl_3$)	55.00 54.91	7.69 7.84	4.75 4.88	5.44 5.20	38	141–143
1c	$C_{29}H_{49}BrN_2O_5S$/ – 0.34 (0.1 g/100 ml, $CHCl_3$)	56.39 56.22	8.00 8.06	4.54 4.68	5.19 5.02	41	137–138
2a	$C_{25}H_{42}BrN_3O_4S$/ – 9.34 (0.1 g/100 ml, $CHCl_3$)	53.56 53.51	7.55 7.39	7.50 7.67	5.72 5.91	24	134–135
2b	$C_{27}H_{46}BrN_3O_4S$/ – 6.12 (0.1 g/100 ml, $CHCl_3$)	55.09 54.94	7.88 7.83	7.14 7.21	5.45 5.69	33	123–124
2c	$C_{29}H_{50}BrN_3O_4S$/ – 5.47 (0.1 g/100 ml, $CHCl_3$)	56.48 56.39	8.17 8.24	6.81 6.74	5.20 5.44	38	113–114
3	$C_{13}H_{18}N_2O_3S$/ – 15.5 (0.1 g/100 ml, $CHCl_3$)	55.30 55.12	6.43 6.51	9.92 9.78	11.36 11.49	84	173–175

Table 2. Spectroscopic data of camphorsulfonic acid derived imidazolium salts of the compounds in series 1 and 2

Compound	Spectral data
1a	IR, $\tilde{\nu}$/cm^{-1}: 3057, 2957, 2922, 2852, 1751,1563, 1467, 1234, 1183,1042, 969, 759, 601 1H NMR (DMSO-d_6, 300 MHz) δ 10.14 (s, 1H); 8.62 (s, 1H); 7.63 (s, 1H); 5.37 (s, 2H); 4.18 (t, 2H, J =7.2 Hz); 3.48 (d, 1H, J = 14.83 Hz); 2.88 (d, 1H, J = 14.83 Hz); 2.39–2.28 (m, 2H); 2.11–1.87 (m, 5H); 1.66 (t, 2H, J = 6.87Hz); 1.26 (s, 14H); 1.05 (s, 3H); 0.9–0.83 (m, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 217.1; 165.8; 139.3; 133.5; 123.2; 67.1; 58.4; 50.3; 48.1; 47.6; 43,0; 42.5; 31.8; 29.5; 29.4; 29.3; 29.2; 28.3; 27.0; 25.7; 24.5; 22.6; 19.8; 19.7; 14.1.
1b	IR, $\tilde{\nu}$/cm^{-1}: 3111, 2957, 2921, 2851, 1749, 1583, 1468, 1399, 1374, 1236, 1182, 1041, 968, 866, 763, 601 ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.13 (s, 1H); 8.61 (s, 1H); 7.63 (s, 1H); 5.36 (s, 2H); 4.18 (t, 2H, J =7,2 Hz); 3.48 (d, 1H, J = 14.84 Hz); 2.88 (d, 1H, J = 14.84 Hz); 2.39–2.28 (m, 2H); 2.11–1.87 (m, 5H); 1.66 (t, 2H, J = 6.87Hz); 1.26 (s, 18H); 1.05 (s, 3H); 0.9–0.83 (m, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 217.1; 165.9; 139.3; 133.5; 123.3; 67.1; 58.4; 50.3; 48.1; 47.6; 43,0; 42.6; 31.9; 29.7; 29.6; 29.5; 29.4; 29.3; 29.2; 28.3; 27.0; 25.7; 24.6; 22.7; 19.8; 19.7; 14.1.
1c	IR, $\tilde{\nu}$/cm^{-1}: 3111, 2956, 2920, 2851, 1748, 1584, 1468, 1396, 1374, 1234, 1182, 1042, 966, 788, 601 ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.13 (s, 1H); 8.61 (s, 1H); 7.63 (s, 1H); 5.36 (s, 2H); 4.18 (t, 2H, J =7,2 Hz); 3.48 (d, 1H, J = 14.84 Hz); 2.88 (d, 1H, J = 14.84 Hz); 2.39–2.28 (m, 2H); 2.11–1.87 (m, 5H); 1.66 (t, 2H, J = 6.87Hz); 1.26 (s, 22H); 1.05 (s, 3H); 0.9–0.83 (m, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 217.1; 166.0; 139.5; 133.8; 123.3; 67.1; 58.5; 50.3; 48.1; 47.7; 43.0; 42.6; 31.9; 29.7(2C); 29.6; 29.5; 29.4; 29.2; 28.4; 27.0; 25.7; 24.6; 22.7; 19.8; 19.7; 14.1.
2a	IR, $\tilde{\nu}$/cm^{-1}: 3447, 3241, 3081, 2957, 2922, 2851, 1743, 1662, 1560, 1476, 1257, 1171, 1041, 856, 775, 601 ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.44 (s, 1H); 8.91 (s, 1H); 8.23 (t, 1H, J = 5.63 Hz); 7.57 (s, 1H); 5.18 (s, 2H); 3.32 (d, 1H, J = 14.49 Hz); 3.20 (td, 2H, J1 = 6.44 Hz, J2 = 13.69 Hz); 2.88 (d, 1H, J = 14.49 Hz); 2.58–2.30 (m, 2H); 2.12–1.79 (m, 5H); 1.53 (t, 2H, J = 6.44Hz); 1.24 (s, 14H); 1.05 (s, 3H); 0,89-0,85 (m, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 217.3; 164.2; 137.5; 134.4; 122.9; 67.2; 58.5; 51.6; 48.3; 47.9; 43.0; 42.6; 40.1; 31.9; 29.6; 29.3; 29.1; 27.0; 24.7; 22.7; 19.8; 19.7; 14.1.
2b	IR, $\tilde{\nu}$/cm^{-1}: 3447, 3240, 3080, 2957, 2922, 2851, 1743, 1662, 1559, 1476, 1257, 1170, 1041, 856, 776, 601. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.44 (s, 1H); 8.92 (s, 1H); 8.23 (t, 1H, J = 5.63 Hz); 7.57 (s, 1H); 5.19 (s, 2H); 3.31 (d, 1H, J = 14.47 Hz); 3.20 (td, 2H, J1 = 6.44 Hz, J2 = 13.34 Hz); 2.88 (d, 1H, J = 14.47 Hz); 2.57–2.31 (m, 2H); 2.12–1.79 (m, 5H); 1.53 (t, 2H, J = 6.44Hz); 1.24 (s, 18H); 1.05 (s, 3H); 0.89–0.85 (m, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 217.3; 164.3; 137.5; 134.5; 123.0; 67.2; 58.5; 51.6; 48.3; 47.9; 43.0; 42.7; 40.1; 31.9; 29.6 (2C); 29.5; 29.3; 29.1; 27.0; 24.7; 22.7; 19.8; 19.7; 14.1.
2c	IR, $\tilde{\nu}$/cm^{-1}: 3447, 3241, 3080, 2957, 2922, 2851, 1743, 1662, 1559, 1476, 1257, 1170, 1041, 856, 776, 601. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.44 (s, 1H); 8.91 (s, 1H); 8.22 (t, 1H, J = 5.67 Hz); 7.57 (s, 1H); 5.18 (s, 2H); 3.32 (d, 1H, J = 14,49 Hz); 3.20 (td, 2H, J1 = 6.47 Hz, J2 = 13.62 Hz); 2.87 (d, 1H, J = 14.49 Hz); 2.57–2.31 (m, 2H); 2.12–1.79 (m, 5H); 1.53 (t, 2H, J = 6.44Hz); 1.24 (s, 22H); 1.05 (s, 3H); 0.89–0.85 (m, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 217.3; 164.3; 137.5; 134.5; 123.0; 67.2; 58.5; 51.6; 48.3; 47.9; 43.0; 42.7; 40.1; 31.9; 29.6 (2C); 29.5; 29.4 (2C), 29.3; 29.1; 27.0; 24.7; 22.7; 19.8; 19.7; 14.1.
3	^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.00 (s, 1H); 7.38 (s, 1H); 7.19 (s, 1H); 3.74 (d, 1H, J = 14.67 Hz); 3.19 (d, 1H, J = 14.67 Hz); 2.36-2.49 (m, 2H); 2.06-2.19 (m, 2H); 1.98 (d, 1H, J = 18.49 Hz); 1.73-1.82 (m, 1H); 1.50 (m, 1H); 1.14 (s, 3H); 0.89 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 217.2; 138.3; 132.9; 119.2; 58.4; 48.2; 47.6; 43.1; 42.6; 25.7; 24.6; 19.8; 19.7.

ponent that consists mainly of lipopolysaccharides, which acts as a barrier and prevents antimicrobial agents and biocides from entering the cell (Pérez *et al.*, 2009).

The importance of structure for the initiation of biodegradation was studied by Boethling *et al.* (1989). They found a decrease of biodegradability under aerobic conditions in the following order: ester, amide, anhydride, hydroxyl and carboxyl. Considering the structure of prepared salts, derivatives 1a-1c with an ester functional group were only slightly effective as antimicrobial agents compared to amide analogues 2a-2c,, probably due to the faster biodegradation of ester derivatives. QASs exhibit strong antimicrobial activities and they are widely used as a disinfectants and antiseptics. The main target site of QASs is the cytoplasmic membrane comprised of a phospholipid bilayer. QASs are able to intercalate into the phospholipid bilayer, which is accompanied by membrane disorganization and structural and functional changes in the cell membrane, inducing leakage of intracellular components (Gilbert and Moore, 2005; Tischer *et al.*, 2012; Wessels and Ingmer, 2013). In addition, QASs were found to inhibit ATP synthesis by neutralizing the proton motive force (PMF) (Denyer & Hugo, 1977). The PMF is initiated by a proton gradient across the cytoplasmic membrane and is involved in many respiratory and photosynthetic processes including ATP synthesis. QASs are surface active agents and therefore they denature proteins anchored in the cytoplasmic membrane or cause dissociation of an enzyme from its prosthetic group. This effect was observed at concentrations much higher than lethal ones, so the enzyme inhibition is not the primary or main lesion caused by cationic surfactants (Merianos 1991). It has been shown that some bisammonium salts also have intracellular targets and bind to DNA, which leads to the inhibition of DNA replication (Menzel *et al.*, 2011; Zinchenko *et al.*, 2004). On the other hand, for most of the QASs, no specific

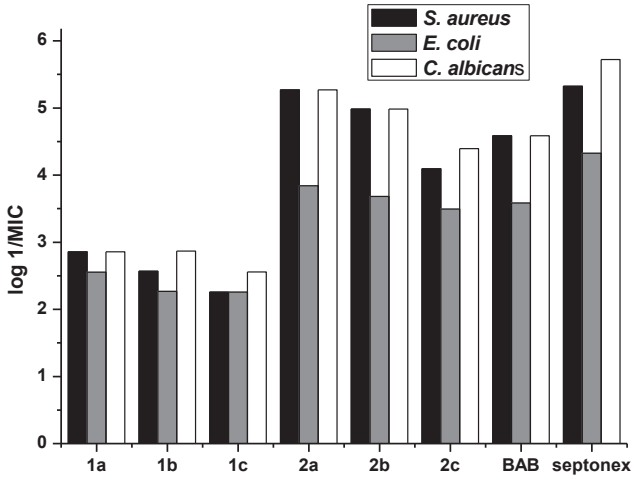

Figure 2. Antimicrobial activity Log 1/MIC of camphorsulfonic acid derived imidazolium salts in series 1 and 2.

target site has been recognized. However, it is not excluded that there can exist some target specificities, as shown by Menzel (2011) and Zhang (2013), because the antimicrobial activity of QASs fluctuates significantly against various types of microorganisms and explanation simply by the cationic charge and hydrophobic tail cannot be used. The antimicrobial activity of surfactants generally depends on the alkyl chain length, although this correlation is not linear. In the series of prepared imidazolium salts 1a-1c and 2a-2c, maximum antimicrobial activity was observed for compounds with 12 carbon atoms in alkyl chain 1a and 2a. Therefore, it can be inferred that increasing the number of carbon atoms in alkyl chain decreased the biological activity of the studied salts against all microorganisms tested.

It is noteworthy that among the salts examined in this study, the most active were 2a and 2b. Both compounds inhibited the growth of microorganisms at the concentrations lower than BAB. On the other hand, none of the prepared salts was more effective than carbethopendecinium bromide. However, the medical use of QAS in some fields is limited by their high toxicity and low biodegradability. The "soft" cationic amphiphilic compounds exhibit higher biodegradability and less toxicity that makes them more beneficial in medical applications despite slightly decreased biological activity.

CONCLUSIONS

In summary, we have designed and synthesized a new amphiphilic imidazolium salts that could be classified as potentially "soft" antimicrobials. Salts 2a-2c with amide functional group showed better antimicrobial and antifungal activity compared to their ester analogues 1a-1c. The maximum antimicrobial activity was observed for compounds with 12 carbon atoms in alkyl chain. Increasing the number of carbon atoms in alkyl chain decreased the biological activity of studied salts against all microorganisms tested. The best antimicrobial activity, shows 3-(2-decylamino-2-oxoethyl)-1-[(7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methylsulfonyl]imidazolium bromide 2a followed by 3-(2-dodecylamino-2-oxoethyl)-1-[(7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methylsulfonyl]imidazolium bromide 2b. Their activity was higher than clinically used BAB. Nevertheless, they were less effective than the other clinically used standard carbethopendecinium bromide.

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Table 3. MIC values (μmol l−1) of camphorsulfonic acid derived imidazolium salts of the compounds in series 1 and 2.

Compound	*S. aureus* ATCC 6538	*E. coli* CNCTC 377/79	*C. albicans* CCM 8186
1a	1391.1	2781.5	1391.1
1b	5406.9	2703.5	1351.1
1c	5560	5560	2780
2a	5.4	144.1	5.4
2b	10.4	208	10.4
2c	80.4	321.6	40.2
BAB	26	260	26
Septonex	4.7	47.3	1.9

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