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SYNTHESIS AND ANTIMICROBIAL PROPERTIES OF BINAPHTHYL DERIVED QUATERNARY AMMONIUM BROMIDES

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(*S*)-*N*-(2-(4,5-dihydro-3*H*-dinaphtho[2,1-c:1',2'-e]azepin-1-yl)ethyl)-*N*,*N*-dimethyl-*N*-dodecyl ammonium bromide **(*S*)-1a** and (*S*)-*N*-(2-(4,5-dihydro-3*H*-dinaphtho[2,1-c:1',2'-e]azepin-1-yl)ethyl)-*N*,*N*-dimethyl-*N*-tetradecylammonium bromide **(*S*)-1b** have been synthesized as optically active quaternary ammonium salts starting from 1,1´-binaphthyl-2,2´-diol. Their antimicrobial activity expressed as minimal inhibition concentration (MIC) was tested against Gram-positive human pathogenic bacteria *S. Aureus*, Gram-negative bacteria *E. coli* and human fungal pathogen *C. Albicans*.

Keywords: *quaternary ammonium bromides – antimicrobial activity – binaphthyl*

INTRODUCTION

Quaternary ammonium salts (QUATs) have been prepared for the first time in 1890 by Menschutkin (Menschutkin, 1890) by reaction of a tertiary amine with alkyl halides. Practical applications of quaternary ammonium salts were found in textile finishes (excellent fabric softeners), antielectrostatic agents and wood preservatives (Gilbert & Moore, 2005, Kim & Sun, 2002), catalysts (Kano et al., 2004) and, starting with 1998, also as ionic liquids (Welton, 1999). Since it was found that cationic lipids, known as cytofectins, are efficient for delivering functional genes (Brigham et al., 1989), the use of cationic amphiphiles for mediating DNA transfection has increased. Development of resistance in microorganisms towards disinfectants or antibiotics (Heinzel, 1988) brings a necessity to supply presently applied antimicrobial agents by new ones, and thus search for new and effective molecules goes on (Semenov et al, 2011, LaDow et al., 2011, Cole et al., 2011, Colomer et al., 2011, Chanawanno et al., 2010). The strong

bactericidal activity of QUATs with long alkyl chains have been known from 1915 (Jacobs & Heidelberger, 1915a, 1915b) and studied further on a broad range of microorganisms such as bacteria (both G+ and G-) (Merianos, 1991), fungi (Lukáč et al., 2010, Struga et al., 2008, Pernak & Chwala 2003) and certain viruses (Wong et al., 2002). The QUATs, with at least one long alkyl chain belong to amphiphilic compounds. These salts possess properties such as reduction of surface tension and also the attraction for negatively charged bacteria surface. With 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, Lukáč et al., 2010). Although, the mode of action of cationic surfactants on bacteria`s membrane cannot be reduced to surface activity only, the disruption of membrane plays a crucial role in the cell death process. The antimicrobial effect of QUATs is parabolically related to their surfactant properties and therefore to the length of the alkyl chains. The antimicrobial activity for G+ bacteria is optimal when the maximum of the carbon chain length is C12 – C14 while for G- bacteria activity is increased with the chain length of C14 – C16 (Zhao & Sun, 2008, Gilbert & Al-Taae, 1985). Molecules with n-alkyl chain length below C4 and above C18 are antimicrobial ineffective. Several researchers have focused on n-alkyl chain – activity relationship. The antimicrobial activity in fact is affected not only by alkyl chain but also by other hydrophobic groups in the molecule. The study of this effect on antimicrobial properties could help in development of new active QUATs.

We have prepared new optically active quaternary ammonium derivatives **1** (Fig. 1) bearing hydrophobic 1,1`-binaphthyl moiety, which were tested against *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans*.

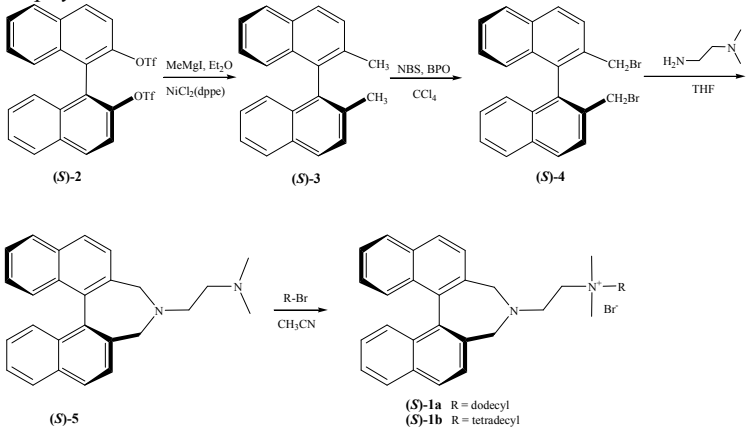

Figure 1. Synthesis of quaternary ammonium bromides 1

EXPERIMENTAL DETAILS

Racemic and enantiomerically pure 1,1´-binaphthyl-2,2´-diyl-bis(trifluoromethanesulfonates) were prepared *via* multistep synthesis according to the literature procedures (Pummerer et al., 1929, Cai et al., 2004a, Cai et al., 2004b) starting from 2-naphthol. TLC was performed on Merck silica plates 60 F_{254} and observed by UV visualization. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian Gemini 300 spectrophotometer at 300 MHz and 75 MHz, respectively. Polarimetric measurements were performed on Jasco P-1010 polarimeter at 589 nm. Elemental analyses were recorded on Carlo Erba 1108A instrument. Melting points were measured on a Kofler hot stage and are uncorrected.

Synthesis of (*S*)-2,2`-dimethyl-1,1`-binaphthyl (*S*)-3 (Mecca et al., 2001)

To a solution of ditriflate **(*S*)-2** (3.36 g, 6 mmol) and $NiCl_2$(dppe) (462 mg, 0.87 mmol) in anhydrous Et_2O (40 mL) under nitrogen, was slowly added a solution of MeMgI (24 mmol) in Et_2O. During the addition, the mixture spontaneously warmed and the solvent started to boil vigorously. The reaction was refluxed 12 h and then cooled with a water-ice bath. Cold reaction mixture was quenched by slow addition of 5 % aqueous HCl (20 mL), extracted with chloroform (3 x 50 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (SiO_2; petroleum ether) affording **(*S*)-3** as a colourless glass (2.26 g, 88 %). M.p. 70 – 72°C. e.e. 99 %; $[\alpha]_D^{21}$= +36.9 (*c* 1.0; $CHCl_3$) ^{1}H NMR (300 MHz,$CDCl_3$) δ: 2.01 (s, 6H), 7.04 (d, 2H, *J*=8.4 Hz), 7.21 (m, 2H),7.42 (t, 2H, *J*=7.4 Hz), 7.49 (d, 2H, *J*=8.4 Hz), 7.92 (m,4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.0, 122.8, 124.6, 125.0, 126.4, 126.9, 127.7, 131.1, 131.7, 133.2, 134.1.

Synthesis of (*S*)-2,2`-bis(bromomethyl)-1,1`-binaphthyl (*S*)-4 (Lu et al., 2001)

A solution of dimethyl derivative **(*S*)-3** (1 g, 3.54 mmol), NBS (1.26 g, 7.08 mmol) and BPO (13 mg) in tetrachloromethane (20 mL) was heated to reflux for 10 h and then cooled to room temperature. The precipitate formed was filtered off and the filtrate was washed with water (30 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (SiO_2; petroleum ether/benzene 5:1) affording **(*S*)-4** as a white solid (1.0 g , 64 %) Mp 183.0 – 185.0°C, (ref. (Mecca et al., 2001) mp 183.0 – 183.7°C). $[\alpha]_D^{21}$= −163.2 (benzene, c = 1.0) (ref (Mecca et al., 2001) $[\alpha]_D^{20}$= −160.0 (benzene, c = 1.0) for **(*S*)-4** in 99 % e.e.). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4,25(s, 4H, CH_2); 7,08(d, J = 8 Hz, 2H, Ar-H); 7,27(ddd, J = 1,0, 8,7 Hz, 2H, Ar-H); 7,49(ddd, J = 2,0, 8,7 Hz, 2H, Ar-H); 7,75(d, J = 9 Hz, 2H, Ar-H); 7,92(d, J = 8 Hz, 2H, Ar-H); 8,02(d, J = 9 Hz, 2H, AR-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ:33.8, 123.4, 123.6, 125.0, 125.4, 127.6, 128.7, 131.2, 132.9, 134.2, 134.3.

Synthesis of binaphthyldiamine (*S*)-5 (Rosini et al., 1996)

A bromoderivative **(*S*)-4** (0.35 g 0.8 mmol), *N*,*N*-dimethylethane-1,2-diamine (0.51 ml, 4.7 mmol) and dry THF (10 ml) were introduced into a three-necked round bottomed flask, equipped with a mechanical stirrer and a reflux condenser, under a nitrogen atmosphere. This solution was refluxed for 48 h. After completion of reaction, the solvent was removed by evaporation under reduced pressure and the crude product was partitioned between aqueous 3 M NaOH and chloroform. The organic extracts were concen-

trated and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was washed thoroughly with pentane and dried, yielding **(*S*)-5** (0.98 g, 56 %) as a white solid: mp 123.0 – 125.0°C; $[\alpha]_D^{21}$ = +311 (ethanol, c = 1.1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.29(s, 6H, CH_3); 2.54(t, 3H, CH_2); 2.74(t, 1H, CH_2); 2.33(dd, 2H, CH_2); 3.70(dd, 2H, CH_2); 7.29(d, 2H, Ar-H); 7.43(ddd, 2H, Ar-H); 7.46(ddd, 2H, Ar-H); 7.58(d, 2H, Ar-H); 7.93(d, 2H, Ar-H); 7.96(d, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 46.1, 53.2, 54.7, 58.1, 125.3, 125.7, 127.4, 127.8, 128.3, 131.2, 133.1, 133.5.

Synthesis of (*S*)-*N*-(2-(4,5-dihydro-3*H*-dinaphtho[2,1-c:1',2'-e]azepin-1-yl)ethyl)-*N*,*N*-dimethyl-*N*-dodecylammonium bromide (*S*)-1a.

A solution of diamine **(*S*)-5** (0.40 g, 1.09 mmol) and 1-bromododecane (0.30 g, 1.2 mmol) in acetonitrile (12 ml) was refluxed 10 h and cooled to room temperature. The solvent was removed by evaporation under reduced pressure and the residual was purified by flash chromatography (SiO_2; $CHCl_3$: MeOH 10/1) affording **(*S*)-1a** as a white solid (0,34 g, 46%). Mp 169.0 – 170.0°C $[\alpha]_D^{22}$ = +116 ($CDCl_3$, c = 0.1).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87(t, 3H, CH_3); 1.21(m, 18H, CH_2); 1.88(m, 2H, CH_2); 2.80(t, 1H,N-CH_2); 3.15(t, 1H, N-CH_2); 3.21(dd, 2H, CH_2); 3.51 (s, 6H, CH_3); 3.65(t, 2H, CH_2); 3.79 (dd, 2H, CH_2); 4.01 (t, 2H, CH_2); 7.24(d, 2H, Ar-H); 7.40(ddd, 2H, Ar-H); 7.45(ddd, 2H, Ar-H); 7.59(d, 2H, Ar-H); 7.90(d, 2H, Ar-H); 7.93(d, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.7, 22.9, 26.3, 29.2, 29.3, 29.4, 29.5, 29.6, 31.9, 49.6, 51.6, 51.7, 55.2, 60.6, 64.9, 125.7, 125.9, 127.4, 127.5, 128.3, 128.7, 131.3,132.3, 133.2, 135.0. Elemental Anal. Calcd. for $C_{38}H_{51}BrN_2$: C 74.12, H 8.35, Br 12.98, N 4.55. Found C 74.05, H 8.39, Br 12.91, N 4.65.

The (*S*)-*N*-(2-(4,5-dihydro-3*H*-dinaphtho[2,1-c:1',2'-e]azepin-1-yl)ethyl)-*N*,*N*-dimethyl-*N*-tetradecylammonium bromide **(*S*)-1b** was prepared by the same procedure as dodecyl analogue affording a white solid (0,79 g, 83 %). M.p. 173.0 – 175.0°C, $[\alpha]_D^{22}$ = +120 ($CDCl_3$, c = 0.1),^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87(t, 3H, CH_3); 1.24(m, 20H, CH_2); 1.76(m, 2H, CH_2); 2.83(t, 1H,N-CH_2); 3.15(t, 1H, N-CH_2); 3.23(dd, 2H, CH_2); 3.51 (s, 6H, CH_3); 3.66(t, 2H, CH_2); 3.76 (dd, 2H, CH_2); 4.01 (t, 2H, CH_2); 7.29(d, 2H, Ar-H); 7.42(ddd, 2H, Ar-H); 7.45(ddd, 2H, Ar-H); 7.59(d, 2H, Ar-H); 7.92(d, 2H, Ar-H); 7.95(d, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.7, 22.9, 26.3, 29.2, 29.35, 29.4, 29.46, 29.57, 29.62, 29.63, 29.66, 31.9, 49.5, 51.6, 51.7, 55.2, 60.6, 64.9, 125.6, 125.9, 127.4, 127.5, 128.3, 128.7, 131.3,132.4, 133.2, 135.0. Elemental Anal. Calcd. for $C_{40}H_{55}BrN_2$: C 74.63, H 8.61, Br 12.41, N 4.35. Found C 74.55, H 8.65, Br 12.37, N 4.43.

Antimicrobial activity

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. The solutions of studied compounds were prepared in DMSO (5%). 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 $5x10^7$ cfu ml^{-1} of bacteria and $5x10^5$ cfu ml^{-1} of *Candida*. Concentration of microorganisms was determined spectrophotometrically at 540 nm and adjusted to absorbance A = 0.35. The microorganism suspension was added to solutions containing the tested compounds and to double concentrated peptone broth medium

(8%) for bacteria or Sabouraud medium (12%) for *Candida*. The stock solution of tested compounds was serially diluted by half. The cultures were done in 96-well microtiter plates. The microorganism were incubated for 24 h at 37°C and then from each well 5 μL of suspension was cultured on blood agar (bacteria) or on Sabouraud agar (fungi). After 24 h at 37°C the lowest concentration of QUATs, which prevented colony formation was determined as minimal inhibitory concentration (MIC).

RESULTS AND DISCUSSION

QUATs bearing 1,1`-binaphthyl moiety were synthesized according to the procedure shown in the Fig. 1. The starting compound, (*S*)-1,1'-binaphthyl-2,2'-diyl-bis(trifluoromethanesulfonate) **(*S*)-2** used here was prepared from 2-naphthol *via* multi-step synthesis and resolution already published (Pummerer et al., 1929, Cai et al., 2004a, Cai et al., 2004b). In the first step we synthesized 2,2`-dimethyl-1,1`-binaphthyl **(*S*)-3** by cross-coupling reaction of ditriflate **(*S*)-2** with Grignard reagent (methylmagnesium iodide) catalyzed by nickel(II) complex (Mecca et al., 2001). The advantage of this method is, except of high reactivity of Grignard reagent leading to high yield, also stereo selectivity. In the next step the bromine was introduced to sp^3 carbon by radical substitution (Lu et al., 2001). The bis bromomethyl **(*S*)-4**, isolated from monobromomethyl by product after column chromatography, undergoes reaction with *N,N*-dimethylethane-1,2-diamine to give binaphthyldiamine **(*S*)-5** (Rosini et al., 1996). The binaphthyldiamine **(*S*)-5** was quaternised with 1-bromododecane and 1-bromotetradecane to produce optically active quaternary ammonium salts **(*S*)-1a** and **(*S*)-1b,** respectively.

The antimicrobial activities of the binaphthyl QUATs **(*S*)-1a** and **(*S*)-1b**, summarized in table 1, were determined as a minimal inhibitory concentration (MIC, [μmol/l]) against the Gram-positive human pathogenic bacteria *S. Aureus*, Gram-negative bacteria *E. coli* and human fungal pathogen *C. albicans.* All the studies were carried out in DMSO. 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 inhibiting activity. Clinically used benzalkonium bromide (BAB, Ajatin®) was used as a standard.

Both of the tested QUATs showed antimicrobial activities lower compared to standard (Fig. 2). This could be due to their poor solubility in water and bulky rigid binaphthyl moiety which disable them to interact better with bacterial membrane, leading to less efficient killing of bacteria. The quaternary salt **(*S*)-1b** with longer alkyl chain (C14) is slightly more active against all tested microorganisms than shorter analogue **(*S*)-1a**. The Gram-negative bacteria *E. coli* was found to be the most resistant against tested compounds. The same trend can be seen in the case of standard BAB. MIC values of prepared salts are higher compared to BAB approximately 2.5 times for **(*S*)-1a** and 3 times for **(*S*)-1b**. Gram-positive human pathogenic bacteria *S. aureus* and human fungal pathogen *C. albicans* have showed smaller resistance to tested ammonium salts **(*S*)-1a** and **(*S*)-1b**. Salts **(*S*)-1a** and **(*S*)-1b** were less potent 6 times and 15 times, respectively, as compared with BAB.

Table 1. Antimicrobial activity of prepared compounds and standard

Compounds / **Microorganisms**	**BAB** MIC [μmol/l]	**1a** MIC [μmol/l]	**1b** MIC [μmol/l]
S. aureus	26	162.3	390.1
E. coli	260	649.2	780.2
C. albicans	26	324.6	390.1

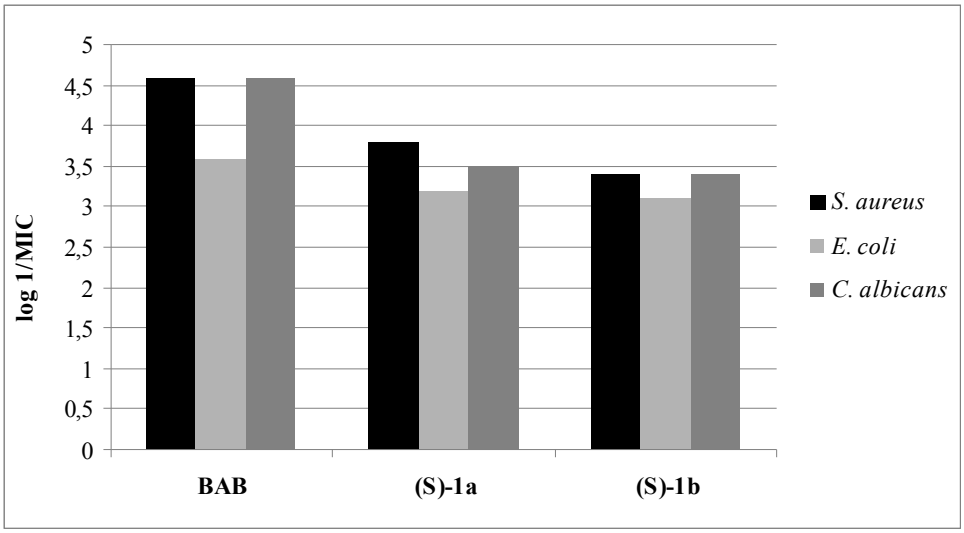

Figure 2. Comparison of antimicrobial activity of prepared compounds with BAB

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SYNTÉZA A ANTIMIKRÓBNE VLASTNOSTI BINAFTYLOVÝCH KVARTÉRNYCH AMÓNIUM BROMIDOV

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Vychádzajúc z 1,1´-binaftyl-2,2´-diolu boli pripravené (*S*)-*N*-(2-(4,5-dihydro-3*H*-dinafto[2,1-c:1',2'-e]azepín-1-yl)etyl)-*N*,*N*-dimetyl-*N*-dodecyl amónium bromid **(*S*)-1a** a (*S*)-*N*-(2-(4,5-dihydro-3*H*-dinafto[2,1-c:1',2'-e]azepín-1-yl)etyl)-*N*,*N*-dimetyl-*N*-tetradecylamónium bromid **(*S*)-1b.** ako opticky aktívne amóniové soli. Bola testovaná ich antimikróbna aktivita, vyjadrená ako minimálna inhibičná koncentrácia (MIC), na Gram-pozitívnu patogénnu baktériu *Escherichia coli*, Gram-negatívnu baktériu *Staphylococcus aureus* a kvasinku *Candida albicans*.

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