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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Activity of ring-substituted 8-hydroxyquinoline-2-carboxanilides against intestinal sulfate-reducing bacteria *Desulfovibrio piger*

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Abstract *Desulfovibrio* genus is dominant among sulfate-reducing bacteria (SRB) in the large intestine of healthy people and animals. It is mostly isolated from patients with inflammatory bowel disease (IBD) and can be involved in the disease initiation. Primary in vitro screening of 8-hydroxyquinoline-2-carboxanilides was performed against *Desulfovibrio piger* Vib-7 representing SRB. The most effective compounds with MIC_{90}/MBC values in the range of 17–23 μM/20–23 μM, respectively, were substituted in C'$_{(3)}$ by CF_3, OCH_3, CH_3 and in C'$_{(4)}$ by CF_3. Their activity was twofold higher than that of ciprofloxacin. These compounds did not express any significant cytotoxic effect on THP-1 cells up to the tested concentration of 30 μM. The antibacterial efficacy of the most active C'$_{(3)}$-substituted compounds practically did not change with increasing compound lipophilicity, indicating that this position of substitution is favorable for significant antimicrobial effect, while the antibacterial activity of most of C'$_{(2)}$ and C'$_{(4)}$-substituted derivatives decreased linearly with increasing compound lipophilicity. In addition, the dependence of activity on electronic Hammett's σ parameter of the substituent R was quasi-parabolic for the most effective C'$_{(3)}$-substituted compounds.

Keywords 8-Hydroxyquinolines · Sulfate-reducing bacteria · Lipophilicity · Electronic parameter · Structure–activity relationships

Introduction

The species of *Desulfovibrio* genus are dominant among sulfate-reducing bacteria (SRB) and common inhabitants of the human and animal large intestine, capable of dissimilatory sulfate reduction (Gibson et al. 1991, 1993; Kushkevych 2015a, b; Kushkevych et al. 2015a, b; Wegmann et al. 2017). These microorganisms are the most isolated from patients with inflammatory bowel disease (IBD) and can be involved in the disease initiation caused by their main metabolite hydrogen sulfide, which is an inhibitor of butyrate oxidation in colonocytes. In addition, it is cytotoxic, mutagenic and cancerogenic to epithelial intestinal cells, which leads to the damage of the epithelial barrier function, resulting in inflammatory responses characteristic for IBD (Kushkevych et al. 2014; Pitcher and Cummings 1996; Zinkevich and Beech 2000). Therefore, the association between SRB and IBD, such as ulcerative colitis (UC), was hypothesized (Zinkevich and Beech 2000; Rowan et al. 2009; Loubinoux et al. 2002; Kushkevych 2014; Cummings et al. 2003). Over 1 million residents in the USA and 2.5 million in Europe are estimated to have IBD, with substantial costs for health care, whereas these estimates do not

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factor in the 'real' price of IBD, which can impede career aspirations, instil social stigma and impair quality of life in patients (Kaplan 2015). Unlike Crohn's disease, UC occurs only in the large bowel, where bacteria amount is greater than in the rest of the gut and also where the rate of passage of material is characterized by slow movement of digestive materials. Both acute and chronic forms of UC affect the colon and rectum and can be a highly uncomfortable condition (Cummings et al. 2003). UC usually has a relapsing/remitting pattern and current medical approaches focus on treating active disease to address symptoms, to improve the quality of life and thereafter to maintain remission. Diarrhea accompanied with blood, an urgent need to defecate and abdominal pain are the main symptoms of active disease or relapse. The reported incidence is 1.2 to 20.3 cases per 100,000 persons per year, and the prevalence is 7.6 to 245 cases per 100,000 per year (Feuerstein and Cheifetz 2014; Cesar da Silva et al. 2014).

The benefits of antibiotic therapy in UC are mediated by different mechanisms, such as decreasing the concentration of luminal bacteria, altering the composition of gut microflora, decreasing bacterial tissue invasion and decreasing bacterial translocation and systemic dissemination. Antibiotics have been prescribed for UC, however, they have been largely ineffective (Cummings et al. 2003; Garud and Peppercorn 2009). For example, the study of the in vitro activities of rifaximin and comparator agents against 536 anaerobic intestinal bacteria performed by Finegold et al. showed that the overall $MICs_{90}$ of rifaximin for 90% the tested strains were 338 µM, an activity equivalent to those of teicoplanin and vancomycin (Finegold et al. 2009). Nakao et al. (2009) tested the antimicrobial susceptibilities of 23 strains of *Desulfovibrio* spp. and found that they were susceptible to sulbactam-ampicillin, meropenem, clindamycin, and metronidazole with MIC_{90} corresponding to 17, 10, 0.45, and 1.46 µM, respectively. On the other hand, Lozniewski et al. (2001) tested the antimicrobial susceptibilities of 16 clinical isolates of *Desulfovibrio* spp. and found that these isolates were resistant to piperacillin-tazobactam, cefoxitin and cefotetan with MIC_{90} corresponding to 495, >600 and 111 µM, respectively. Therefore, it is necessary to study new antibacterial agents in order to improve the treatment and discover alternative therapeutics.

This paper follows our recently published articles dealing with the spectrum of biological activities of hydroxyquinoline-based compounds (Jampilek et al. 2005; Musiol et al. 2006, 2007, 2008, 2010; Mrozek-Wilczkiewicz et al. 2010; Gonec et al. 2012; Cieslik et al. 2012, 2015; Kos et al. 2015a; Jampilek et al. 2016). This study is focused on the investigation of the efficacy and searching for the structure–activity relationships within a series of 8-hydroxyquinoline-2-carboxanilides (Kos et al. 2015a) against *Desulfovibrio piger* Vib-7 representing SRB. *D. piger* is a Gram-negative strict anaerobe that is usually considered as a commensal bacterium in humans. More recently, it has attracted more interest as it was found to be the most prevalent species of SRB in feces of patients with IBDs (Kushkevych 2014; Barton and Hamilton 2010; Holt et al. 1994).

Material and methods

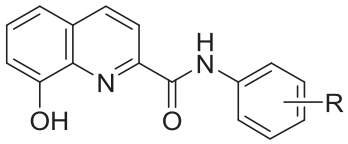
Synthesis

The discussed 8-hydroxyquinoline-2-carboxanilides **1–8c** (see Table 1) were synthesized previously (Kos et al. 2015a) by means of microwave-assisted synthesis. The compounds were fully characterized by melting point, infrared, nuclear magnetic resonance, and high-resolution mass spectrometry (Kos et al. 2015a).

In vitro antibacterial susceptibility testing

The synthesized compounds were evaluated for in vitro antibacterial activity against the intestinal SRB *Desulfovibrio piger* Vib-7 (Genbank: KT881309.1) that were isolated from the healthy human large intestine as described previously (Kushkevych 2013; Kushkevych et al. 2014). The strain has been kept in the collection of microorganisms at the Department of Molecular Biology and Pharmaceutical Biotechnology of the Faculty of Pharmacy at the University of Veterinary and Pharmaceutical Sciences Brno (Czech Republic). Ciprofloxacin (Sigma-Aldrich) was used as the standard. Prior to testing, the strain at exponential phase growth was passaged onto nutrition modified Kravtsov-Sorokin's (KS) agar medium (Kushkevych and Moroz 2012). Bacterial inocula were prepared by suspending a small portion of bacterial colony in sterile KS liquid medium (pH 7.5). Before bacterial passage in the medium, 10 mL/L of sterile Mohr's salt solution $[(NH_4)SO_4Fe(SO_4)_2{\cdot}6H_2O]$ (10%) for visual detecting colonies of the SRB was added. A culture sample (10 mL) was centrifuged at 15,000 rpm/20 min using a bench top centrifuge (Model CR 4-12, Jouan Inc., Winchester, VA, USA). Following removal of the supernatant, the pellet was washed in fresh liquid KS and re-suspended in fresh supplemented KS (10 mL). The turbidity was adjusted to match McFarland standard No. 1 (5×10^6 cfu) with KS using a densitometer (Densi-La-Meter, LIAP, Latvia). The final inoculum was made to a 1:20 dilution of the suspension with KS liquid medium. The antimicrobial susceptibility of SRB was investigated in a 96-well plate format. In these experiments, sterile KS (300 µL) was added to all outer-perimeter wells of the plates to minimize evaporation of the medium in the

Table 1 Experimentally determined values of lipophilicity log *k*, predicted electronic Hammett's σ parameters of substituents R, in vitro antibacterial activity against *Desulfovibrio piger* Vib-7 (MIC, IC_{50}, MBC) of the compounds in comparison with ciprofloxacin (*CPX*) standard



Compounds	R^1	log k^a	σ^b	MIC_{90} [μM]	IC_{50} [μM]	MBC [μM]
1	H	0.7600	0	23	12	25
2a	2-OCH_3	0.7935	−0.28	28	17	28
2b	3-OCH_3	0.8164	0.12	17	11	20
2c	4-OCH_3	0.7129	−0.27	557	380	557
3a	2-CH_3	0.6944	−0.17	44	15	48
3b	3-CH_3	0.9686	−0.07	23	10	23
3c	4-CH_3	0.9521	−0.17	75	40	80
4a	2-F	0.6806	0.06	90	50	95
4b	3-F	0.9420	0.34	45	20	50
4c	4-F	0.8598	0.06	60	28	60
5a	2-Cl	0.9566	0.22	120	95	123
5b	3-Cl	1.1718	0.37	50	20	55
5c	4-Cl	1.1543	0.23	480	330	486
6a	2-Br	1.0536	0.22	150	103	150
6b	3-Br	1.2357	0.39	33	18	35
6c	4-Br	1.2347	0.23	337	225	340
7a	2-CF_3	0.9147	0.51	48	35	50
7b	3-CF_3	1.3206	0.43	17	10	20
7c	4-CF_3	1.3653	0.51	20	10	22
8a	2-NO_2	1.1277	0.77	197	134	202
8b	3-NO_2	0.9845	0.71	237	218	240
8c	4-NO_2	1.0495	0.78	223	165	225
CPX	–	–	–	45	28	45

[a] Experimental procedure described in Kos et al. (2015a)

[b] Predicted using sw. ACD/Percepta ver. 2012

test wells during incubation. Sample wells were composed of 100 μL of test compound dilution and 100 μL of the bacterial stock being tested against. The compounds were dissolved in dimethyl sulfoxide (DMSO, Sigma), and the final concentration of DMSO in the KS liquid medium did not exceed 0.1% of the total solution composition. Dilutions of each compound were prepared in triplicate. The final concentrations of the evaluated compounds ranged from 100 to 0.05 μM. Plates were sealed with parafilm, introduced into an anaerobic box with oxygen uptake generators (GENbox anaer, France) for anaerobiosis. The determination of results was performed visually after 72 h of static incubation in the darkness at 37 °C under anaerobic conditions. In the process of bacterial growth, hydrogen sulfide was formed and interacted with Fe^{2+} from Mohr's salt. As a result, FeS was formed by the bacterial cells that caused black colored colonies that was interpreted as a presence of bacterial growth. The medium dilution micro-method modified according to NCCLS guidelines (CLSI 2012, 2014) in KS medium was used to determine the minimum inhibitory concentration (MIC_{90}), the inhibitory concentration (IC_{50}) and minimum bactericidal concentration (MBC). Drug-free controls, sterility controls and controls consisted of KS medium and DMSO alone were included. The MICs were defined as the lowest concentration of the compound at which no visible bacterial growth was observed. The IC_{50} values were defined as the compound concentration causing 50% inhibition of bacterial growth and the MBCs were defined as the lowest concentration of the compound at which an antimicrobial agent kills a bacteria (CLSI 2012, 2014). The results are summarized in Table 1.

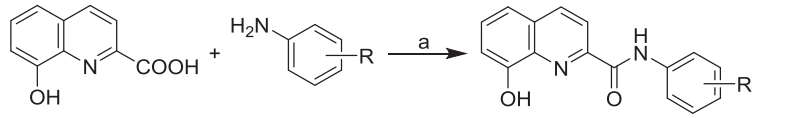
Results and discussion

In the previous studies it was confirmed that 2-substituted 8-hydroxyquinolines are promising antimicrobial agents (Jampilek et al. 2005; Musiol et al. 2006, 2010; Darby and Nathan 2010; Gonec et al. 2012; Cieslik et al. 2012; 2015; Kos et al. 2015a). Based on these observations, 8-hydroxyquinoline-2-carboxanilides prepared according to Scheme 1 and described recently (Kos et al. 2015a) were tested against *Desulfovibrio piger* Vib-7. The testing was performed according to Kushkevych et al. (2016).

The antibacterial potency of ring-substituted 8-hydroxyquinoline-2-carboxanilides was expressed as the MICs, IC_{50} values and MBCs, see Table 1. The activity of the most potent compounds **7b** (R = 3-CF_3; MIC = 17 μM, IC_{50} = 10 μM, MBC = 20 μM), **7c** (R = 4-CF_3; MIC = 20 μM, IC_{50} = 10 μM, MBC = 22 μM) and **2b** (R = 3-OCH_3; MIC = 17 μM, IC_{50} = 11 μM, MBC = 20 μM) was twofold higher that of the clinically used drug ciprofloxacin (MIC = MBC = 45 μM) that was used as the standard. Also other compounds such as **3b** (R = 3-CH_3; MBC = 23 μM), **1** (R = H; MBC = 25 μM), **2a** (R = 2-OCH_3; MBC = 28 μM), and **5b** (R = 3-Br; MBC = 35 μM) were effective in killing *D. piger* Vib-7. It is also important to note that no significant cytotoxic effect of these compounds on THP-1 cells up to tested concentration 30 μM was observed (Kos et al. 2015a).

The dependence of log(1/IC_{50}) on compound lipophilicity expressed by log *k* (Kos et al. 2015a) is shown in Fig. 1a. After exclusion of three derivatives: 4-OCH_3 (**2c**), which precipitated from testing solution due to limited

Scheme 1 Synthesis of ring-substituted 8-hydroxyquinoline-2-carboxanilides **1–8c**: Reagents and conditions: **a** PCl_3, chlorobenzene, microwave-assisted synthesis (Kos et al. 2015a)



R = H (**1**), OCH_3 (**2a-c**), CH_3 (**3a-c**), F (**4a-c**), Cl (**5a-c**), Br (**6a-c**), CF_3 (**7a-c**), NO_2 (**8a-c**)

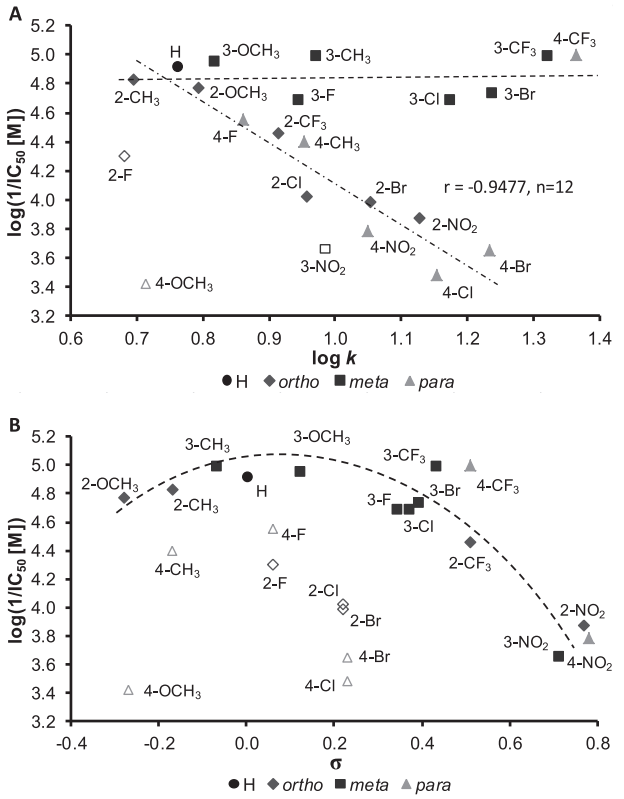


Fig. 1 Dependence of antibacterial activity against *Desulfovibrio piger* Vib-7 expressed as log(1/IC_{50}) [M] of tested compounds on lipophilicity expressed as log *k* (**a**) and on Hammett's σ constants of R substituent (**b**). (Compounds not included in individual SAR discussions are marked by empty symbol.)

aqueous solubility, and 2-F (**4a**) and 3-NO_2 (**8b**), showing lower activity than expected, the compounds can be divided into two groups. The antibacterial activity of nine derivatives with R = 2-CH_3 (**3a**), 2-OCH_3 (**2a**), 3-OCH_3 (**2a**), 3-F (**4b**), 3-CH_3 (**3b**), 3-Cl (**5b**), 3-Br (**6b**), 3-CF_3 (**7b**), and 4-CF_3 (**7c**) expressed by IC_{50} value was comparable with that of unsubstituted derivative **1** (R = H; IC_{50} = 12 μM) and varied in the range from 10 μM (3-CF_3 and 4-CF_3, 3-CH_3) to 20 μM (3-F and 3-Cl), while the antibacterial activity of other 12 tested (C'$_{(2)}$, C'$_{(4)}$-substituted derivatives and (**1**) compounds decreased linearly with increasing compound lipophilicity from log *k* = 0.6944 (2-CH_3, **3a**; IC_{50} = 15 μM) to log *k* = 1.2347 (4-Br, **6c**; IC_{50} = 225 μM) (r = −0.9477, n = 12). Thus, from seven C'$_{(3)}$-substituted compounds, six derivatives belonged to the set of the above-mentioned most active compounds, the antibacterial activity of which practically did not change with increasing compound lipophilicity, indicating that this position of substitution is favorable for significant antimicrobial effect.

The dependence of log(1/IC_{50}) on the Hammett's σ constants of the R substituent is shown in Fig. 1b. Except for derivatives with R = 4-OCH_3 (**2c**) and 4-CH_3 (**3c**) as well as derivatives with F, Cl, and Br substituents in positions C'$_{(2)}$ and C'$_{(4)}$, i.e., **4a**, **4c**, **5a**, **5c**, **6a**, and **6c**, for the remaining 14 compounds quasi-parabolic dependence of log(1/IC_{50}) on σ constants was estimated. However, it could be mentioned that within a narrow range of σ from 0.06 to 0.22/0.23, the activity of C'$_{(4)}$ halogen-substituted compounds decreased more sharply with increasing σ values than that of C'$_{(2)}$-substituted ones.

Similar trends as for the dependence of log(1/IC_{50}) on lipophilicity or on Hammett's σ constants can be found also for the dependences of the activity expressed as MIC or MBC values on both parameters; therefore, these dependences are not illustrated.

Summarizing, it can be concluded that generally for high antibacterial activity against *D. piger*, halogen substituent in the C'$_{(3)}$ position is favorable, whereby the highest antibacterial activity was exhibited by derivatives with R = 3-CF_3 and 4-CF_3, i.e., substituents that are known to promote electrostatic interactions with targets and improve the cellular membrane permeability of small molecules but also compounds with low lipophilicity (2-CH_3, 3-CH_3, 2-OCH_3, 3-OCH_3).

The estimated MIC values for *D. piger* (Table 1) are comparable with those estimated for the antimycobacterial activity of the tested compounds against *Mycobacterium tuberculosis* H37Ra ATCC 25177, *M. avium* complex CIT19/06 (clinical isolate) and *M. avium* subsp. *paratuberculosis* CIT03 (clinical isolate) (Kos et al. 2015a). It was found that with the exception of compounds with R = 4-OCH_3 (**2c**), 4-Cl (**5c**), 4-Br (**6c**), neither lipophilicity nor electronic properties of the R substituent nor the position of substitution exhibited any significant effect on the antitubercular activity against *M. tuberculosis*, and the 2-, 3- and 4-CF_3 (**7a–c**)-substituted derivatives belonged to the most active compounds with MIC = 24 μM. There were no any significant differences between antimycobacterial activities against *M. tuberculosis* and *M. avium* subsp. *paratuberculosis*. On the other hand, C'$_{(2)}$ and especially C'$_{(3)}$-

substituted derivatives expressed higher antimycobacterial activity against *M. avium* complex than C'$_{(4)}$-substituted ones, and antimycobacterial activity slightly increased with increasing lipophilicity (log *k* values) and electron-withdrawing effect of R substituents; the C'$_{(2)}$-substituted compounds with log $k > 0.8$ and Hammett's σ constants of R substituents > 0.1 and C'$_{(4)}$-substituted compounds with log $k < 0.8$ were found to be completely ineffective. However, the activity of compounds with potency against all three strains was achieved by the substitution of the C'$_{(3)}$ position of aniline. The significant bacterial/antimycobacterial activity of the studied compounds bearing an 8-hydroxyquinoline fragment and an amide moiety in their molecule is caused by the fact that these function groups are able to interact with a number of enzymes/receptors via hydrogen bonds and in this manner to affect the biological response (Pattabiraman and Bode 2011; Lavecchia and Di Giovanni 2013; Zumla et al. 2013). The significant contribution of the hydroxyl moiety in C$_{(8)}$ of quinoline to the antimycobacterial activity was reported by Gonec et al. (2012), who observed that its absence in quinoline-2-carboxanilides resulted in a decrease of antimycobacterial effect, while strengthening of antimycobacterial potency due to the presence of the hydroxyl moiety was observed with 1-hydroxynaphthalene-2-carboxanilides (Gonec et al. 2013) and 6-hydroxy-naphthalene-2-carboxanilides (Kos et al. 2015b) as compared to naphthalene-2-carboxanilides (Gonec et al. 2012).

Ring-substituted 8-hydroxyquinoline-2-carboxanilides were previously tested also as photosystem II (PS II) inhibitors (Jampilek et al 2016). The inhibition of photosynthetic electron transport (PET) in spinach chloroplasts by these compounds significantly depended on the position of substitution, and the inhibitory activity of C'$_{(3)}$-substituted compounds was by one or two orders higher than that of C'$_{(2)}$ and C'$_{(4)}$-substituted derivatives. For the most active compounds, the following IC_{50} values were observed: 2.7 µM (3-CH_3, **3b**), 2.3 µM (3-F, **4b**), 3.6 µM (3-Cl, **5b**), and 3.4 µM (3-Br, **6b**). However, it could be mentioned that the dependence of the PET-inhibiting activity on the lipophilicity of the compounds expressed by log *k* was quasi-parabolic for C'$_{(3)}$-substituted derivatives, while for C'$_{(2)}$ ones a slight increase and for C'$_{(4)}$ derivatives a sharp decrease of the activity were observed with increasing lipophilicity. Consequently, it could be assumed that for targeting the site of action in the photosynthetic apparatus suggested on the acceptor side of photosystem II between P680 and plastoquinone Q_B substitution in the C'$_{(3)}$ position is the most favorable.

Previously tested six 2-(phenylcarbamoyl)phenyl *N*-[(benzyloxy)carbonyl] alkanoates and three 2-hydroxy-*N*-[(2 *S*)-1-oxo-1-(phenylamino)alkan-2-yl]benzamides showed MIC values in the range from 0.22 to 0.35 µM against *D. piger* Vib-7 and in the range from 0.27 to 8.52 µM against *Desulfomicrobium* sp. Rod-9, while the MIC values of ciprofloxacin were 41.2 µM and 39.3 µM, respectively. Lipophilicity was recognized as a significant parameter affecting biological activities, and higher activity for both SRB was observed rather with electron-withdrawing R^2 substituent and less lipophilic (isopropyl or benzyl) R^3 substituent, and it was supposed that these derivatives interact with enzymatic systems of the bacteria affecting vital cell functions (Kushkevych 2015a, b; Kushkevych et al. 2015a, b; Kushkevych et al. 2016). This is in agreement with the presented results concerning the antibacterial activity of ring-substituted 8-hydroxyquinoline-2-carboxanilides against *D. piger* Vib-7. Thus, these results confirmed that the investigated compounds showed high efficiency not only against the aerobic microorganisms, but also against the anaerobic microorganism.

Conclusion

Primary in vitro screening of a prepared series of ring-substituted 8-hydroxyquinoline-2-carboxanilides was performed against *Desulfovibrio piger* Vib-7. The most effective compounds with MIC/MBC values in the range of 17–23 µM/20–23 µM, respectively, were as follows: 8-hydroxy-*N*-(3-trifluoromethylphenyl)- (**7b**), 8-hydroxy-*N*-(3-methoxyphenyl)- (**2b**) 8-hydroxy-*N*-(3-methylphenyl)- (**3b**), and 8-hydroxy-*N*-(4-trifluoromethylphenyl)quinoline-2-carboxamide (**7c**). Their activity was twofold higher than that of ciprofloxacin. The antibacterial efficacy of the most active C'$_{(3)}$-substituted compounds practically did not change with increasing compound lipophilicity, indicating that this position of substitution is favorable for significant antimicrobial effect, while the antibacterial activity of most of C'$_{(2)}$ and C'$_{(4)}$-substituted derivatives decreased linearly with increasing compound lipophilicity. In addition, the dependence of activity on electronic Hammett's σ parameter of the substituent R was quasi-parabolic for the most effective C'$_{(3)}$-substituted compounds. The most potent compounds did not express any significant cytotoxic effect on THP-1 cells up to the tested concentration of 30 µM.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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