



Original research article

Effect of selected 8-hydroxyquinoline-2-carboxanilides on viability and sulfate metabolism of *Desulfovibrio piger*Ivan Kushkevych^{a,*}, Monika Vítězová^a, Jiří Kos^b, Peter Kollár^c, Josef Jampílek^{b,**}^a Masaryk University, Faculty of Science, Department of Experimental Biology, Brno, Czech Republic^b Comenius University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Bratislava, Slovak Republic^c University of Veterinary and Pharmaceutical Sciences, Faculty of Pharmacy, Department of Human Pharmacology and Toxicology, Brno, Czech Republic

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ABSTRACT

An increased number of sulfate-reducing bacteria is often isolated from faeces of patients with gastrointestinal diseases, which can be the cause of the development of bowel inflammation. Frequent use of antibiotics causes the resistance of intestinal microorganisms and ineffective treatment of these diseases. The antimicrobial activity and biological properties of the selected ring-substituted 8-hydroxyquinoline-2-carboxanilides against *Desulfovibrio piger* Vib-7 were studied. The addition of these compounds in the cultivation medium inhibited the bacterial growth and the process of sulfate reduction dose-dependently. A significant cytotoxic activity under the influence of ring-substituted 8-hydroxyquinoline-2-carboxanilides was determined. The strongest cytotoxic effect of the derivatives was observed for compounds 8-hydroxy-*N*-(3-methoxyphenyl)quinoline-2-carboxamide and 8-hydroxy-*N*-(3-trifluoromethylphenyl)quinoline-2-carboxamide that caused a low survival of *D. piger* Vib-7 in concentration 17 μ M and high toxicity rates.

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Introduction

A high number of sulfate-reducing bacteria (SRB) and the intense process of dissimilatory sulfate reduction in the gut are thought to be significant risk factors of inflammatory bowel diseases in both humans and animals (Gibson et al., 1991, 1993; Kushkevych, 2016; Kushkevych et al., 2016). These bacteria are often found in patients with rheumatic diseases, ankylosing spondylitis, etc. (Barton and Hamilton, 2010). The species of *Desulfovibrio* genus can cause bloody diarrhea, weight loss, anorexia, epithelial hyperplasia, abscesses and inflammatory infiltrates in animals and humans (Loubinoux et al., 2000, 2002a,b). There is also an assumption that SRB can be responsible for some forms of cancer of the rectum through the formation of hydrogen sulfide that affects the metabolism of intestinal cells.

An increased number of SRB was found in faeces from people with ulcerative colitis in comparison with healthy individuals (Cummings et al., 2003). The injection of these bacteria in hamster intestine caused an infection clinically similar to human colitis (Cummings et al., 2003; Pitcher and Cummings, 1996). Using the model of laboratory rats, the etiological role of the cultures of SRB, *Desulfovibrio piger* Vib-7 and *Desulfomicrobium* sp. Rod-9, in the development of inflammatory processes in the intestine was examined. It was found that the introduction of pure cultures of SRB led to a high production of hydrogen sulfide and acetate in the intestine, and clinical manifestations similar to non-specific intestinal inflammation in humans appeared (Kushkevych, 2014).

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon that affects up to 12 per 100,000 people in Western countries, mostly between 15 and 30 years of age (Rowan et al., 2009). The treatment of mild to moderate UC includes, in the first instance, sulfasalazine and mainly 5-aminosalicylate containing drugs, the type and dosage of which depend on the location and severity of the disease. Other options of treatment include corticosteroids and immunosuppressants (for moderate to severe UC, with a high mortality) or probiotics (for improving the microbial balance) (Cummings et al., 2003; Kushkevych, 2016). Despite the bacterial nature of the disease, antibiotics have failed

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in the treatment of UC so far. However, new antibacterial compounds with high specific effect against SRB could yield better efficiency in the treatment of this disease.

Quinoline-based compounds have a wide range of promising biological properties (Cieslik et al., 2012; Jampilek, 2017; Jampilek et al., 2016; Kos et al., 2015; Mucaji et al., 2017; Musiol et al., 2006, 2007, 2008, 2010); therefore a special attention is paid to them at research and designing of new drugs (Cieslik et al., 2012; Jampilek et al., 2016; Kos et al., 2015; Musiol et al., 2006, 2007; Ranjith et al., 2017). This simple scaffold possesses unique physicochemical properties and provides a possibility of a great number of targeted modifications. Ring-substituted 8-hydroxyquinoline-2-carboxanilides were recently prepared (Kos et al., 2015) and published as compounds with noteworthy biological activities (Jampilek et al., 2016; Kos et al., 2015) based on the presence of an amide group and a hydroxy moiety in the quinoline scaffold (Gonec et al., 2012; Jampilek et al., 2016; Kos et al., 2015). Thus, in the context of the above-mentioned facts, the aim of this work was to evaluate viability of intestinal sulfate-reducing bacteria *Desulfovibrio piger* and parameters of their dissimilatory sulfate reduction (production of hydrogen sulfide and acetate as well as sulfate and lactate consumption) under effect of selected 8-hydroxyquinoline-2-carboxanilides (Kos et al., 2015).

Materials and methods

Tested compounds

The studied ring-substituted 8-hydroxyquinoline-2-carboxanilides were synthesized by means of microwave-assisted synthesis described recently. The compounds were isolated and fully characterized (melting point, elemental analysis, infrared as well as ^1H and ^{13}C NMR spectroscopy) (Kos et al., 2015). The compounds were kept in microtubes dissolved in dimethyl sulfoxide (DMSO) solution. The quantity of DMSO necessary to dissolve each compound was calculated previously to achieve the concentration of the component 30 mM. Afterwards it was diluted 4-fold in a proportion 1:3, and 5 different concentrations of the chemical compound – 5, 10, 15, 20, 25, 30 and 35 mM – were obtained. The maximum concentration of DMSO in the assays never exceeded 0.1%.

Bacterial culture and cultivation

The sulfate-reducing bacteria *D. piger* Vib-7 (GenBank: KT881309.1) 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 Experimental Biology, Faculty of Science at the Masaryk University (Brno, Czech Republic). The bacteria were grown for 36 h at 37 °C under anaerobic conditions in nutrition modified Postgate's liquid medium (Postgate, 1984). Before bacterial passage in the medium, 0.05 mM of sterile solution of $\text{Na}_2\text{S} \times 9\text{H}_2\text{O}$ (1%) was added. The sterile 10 ml solution of NaOH (0.9 mM) in the medium was used to provide the final pH 7.2. The medium was heated in boiling water for 30 min in order to obtain an oxygen-free medium and cooled to 30 °C. The tubes were brim-filled with medium and closed to provide anaerobic conditions.

Assay of bacterial cell concentration

The best concentration of *D. piger* Vib-7 was assessed to be 5×10^5 CFU/ml. Based on our previous work, the correlation between OD_{340} and the amount of cells in the solutions measured

in the biophotometer was determined as $y = 1.0 \times 10^9 \chi - 6.0 \times 10^6$, where y means the bacterial concentration and χ means the OD_{340} measured as was described in our previous paper (Kushkevych et al., 2015a).

Treatment of bacterial culture

The bacterial culture of the stationary phase of growth was centrifuged for 3 min at a rotation speed of 3500 rpm. Supernatant was removed and replaced by a fresh liquid medium, where the bacterial precipitate was diluted. The bacterial suspension was mixed, and OD_{340} was measured. Numbers and viabilities of the bacterial cells were determined by counting with a haemocytometer after staining with erythrosine B [0.1% erythrosine B (w/v) in phosphate-buffered saline (PBS), pH 7.2–7.4]. Unstained cells were considered to be viable.

The bacterial suspension (initial concentration 0.5 mg/ml) was poured in microtubes (350 μl) that contained samples + solvent control (DMSO) + sample control + blanks; each sample as well as the controls were prepared in triplicate, so that the average of the results did not had a great discrepancy from the results independently (except in 3 blanks). The sample controls contained only bacterial suspension and medium (free of tested compounds); and for the 3 blanks only medium. Calculations were made to assess how much bacterial solution should be in each, based on the OD. The determination of biomass and concentrations of sulfate, lactate, acetate and sulfide in the culture medium under the treatment of 5, 10, 15, 20, 25, 30 and 35 μM compounds after 36 h was carried out. During experiments, bacteria were grown at 37 °C under anaerobic conditions.

Analysis of viability of *D. piger* Vib-7 and cytotoxicity of compounds

The bacterial suspension (5×10^4 cells/well in 300 μl culture medium) was filled in 100-well plates in triplicate in the Postgate's liquid medium (without Mohr's salt), treated with 5, 10, 15, 20, 25, 30 and 35 μM compounds and incubated at +37 °C. The relative survival of *D. piger* Vib-7 cells and the cytotoxicity of the compounds were determined at the 36th hour of cultivation using a WST-1 assay kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's instructions. The relative survival rate was calculated by the following equation: $(A_{\text{Sample}} - A_{\text{Blank}}) / (A_{\text{Control}} - A_{\text{Blank}})$, and multiplied by 100 for the result in percentage. The relative toxicity rate was determined as described previously (Kos et al., 2015). All data were evaluated using GraphPad Prism 5.00 software (GraphPad Software, San Diego, CA, USA, <http://www.graphpad.com>).

Assay of sulfate, lactate, sulfide and acetate in cultivation medium

The sulfate ion concentration in the medium was determined by the turbidimetric method after it had been precipitated by barium chloride. To stabilize the suspension, glycerol was used (Kolmert et al., 2000). Lactate concentration was measured through the dehydrogenation reaction using Lactate Assay Kit (Sigma-Aldrich, Catalog Number MAK064). Sulfide concentration in the culture medium was assayed by the spectrophotometric method as was described (Cline, 1969). Accumulation of acetate ions in the process of bacterial growth in the medium was determined using Acetate Assay Kit (Colorimetric, Catalog Number KA3764).

Statistical analysis

The statistical calculations of the results were carried out using the software MS Office and Origin program. The research results were treated by methods of variation statistics using Student t -test.

Statistical significance was tested using the one-way analysis of variance with Dunnett's test and Tukey post-test for comparisons between the means, and differences between two conditions were retained for $P \leq 0.05$. Statistical significance was determined at levels of $P < 0.05$, $P < 0.01$, and $P < 0.001$ (Bailey, 1995).

Results

The structures of the selected and discussed ring-substituted 8-hydroxyquinoline-2-carboxanilides are shown in Table 1. A synthetic pathway and characterization were published by Kos et al. (2015).

The relative survival of *D. piger* Vib-7 cells and cytotoxicity of ring-substituted 8-hydroxyquinoline-2-carboxanilides were studied. In this series of experiments, compounds **1–7** exerted cytotoxicity against these bacteria already in low (5–35 μM) concentrations (Fig. 1).

Treatment with all tested compounds led to a significant dose-dependent activity with the strongest effect observed in compounds **3** ($R = 3\text{-OCH}_3$) and **6** ($R = 3\text{-CF}_3$). Since some of ring-substituted 8-hydroxyquinoline-2-carboxanilides (such as **3** or **6**) have a pronounced antimicrobial effect against *D. piger* Vib-7 (combination of low survival and high toxicity rates), they could be considered as promising agents against the growth of this type of bacteria.

The effect of different concentrations of ring-substituted 8-hydroxyquinoline-2-carboxanilides on the process of dissimilatory sulfate reduction in *D. piger* Vib-7 cells at the 36th h of cultivation was studied. As shown in Figs. 2 and 3, the addition of the compounds in the culture medium inhibits the process of dissimilation of sulfate directly proportional to the increase in concentrations (5–35 μM). Under these conditions, the utilization of sulfate and lactate was inhibited; hence the level of accumulation of hydrogen sulfide and acetate was reduced. These data are consistent with our research in previous series of the experiments. The percentage inhibition of sulfate reduction process correlates with the percentage of bacterial growth inhibition under the ring-substituted 8-hydroxyquinoline-2-carboxanilides treatment.

Based on the obtained results, the MIC and IC_{50} values of ring-substituted 8-hydroxyquinoline-2-carboxanilides against intestinal sulfate-reducing bacteria were established. As shown in Table 1, the MICs of all the compounds were $\leq 33 \mu\text{M}$. The

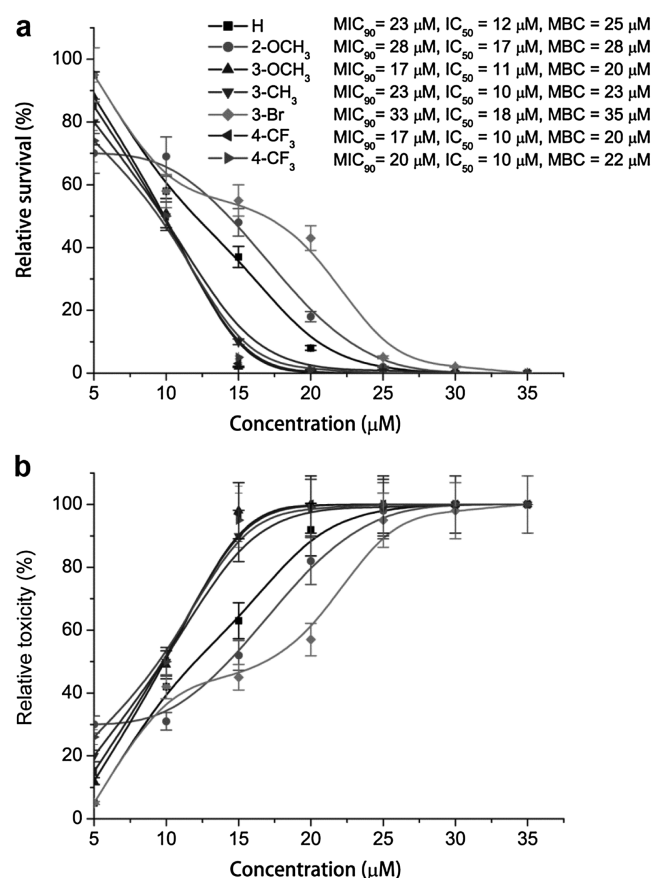


Fig. 1. Relative survival of *D. piger* Vib-7 cells (a) and toxicity (b) of ring-substituted 8-hydroxyquinoline-2-carboxanilides.

least potent compounds among the tested compounds for the bacterial strain were **2** ($R = 2\text{-OCH}_3$) and **5** ($R = 3\text{-Br}$), the MICs of which were 28 and 33 μM , respectively. The similar MICs were determined for compounds **1** ($R = \text{H}$) and **4** ($R = 3\text{-CH}_3$). It can be supposed that these compounds show the same cytotoxicity effect on sulfate-reducing bacteria *D. piger* Vib-7 cells. IC_{50} of compounds **4**, **6** and **7** was 10 μM . Compounds **2** and **5** had IC_{50} only 17 and 18 μM , which is consistent with the MICs of these compounds.

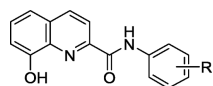
Discussion and conclusion

Sulfate-reducing bacteria of *Desulfovibrio* genus belong to the intestinal microbiota of humans and animals (Kushkevych, 2012, 2013). They are anaerobic microorganisms, dissimilating sulfate as an electron acceptor and organic compounds as an electron donor and carbon source in the process of “dissimilatory sulfate reduction” (also known as “dissimilatory anaerobic sulfate respiration”) (Kushkevych, 2016). Lactate is the most common substrate used by the species belonging to the intestinal sulfate-reducing bacteria. The species of *Desulfovibrio* oxidize lactate incompletely to acetate. Lactate oxidation to acetate occurs together with the concurrent reduction of sulfate to sulfide (Barton and Hamilton, 2010). The presence of lactate and sulfate in the human intestine contributes to the intensive bacteria growth and the accumulation of their final metabolic products, acetate and hydrogen sulfide, that are toxic, mutagenic and cancerogenic to epithelial intestinal cells (Pitcher and Cummings, 1996; Rowan et al., 2009). There is also an assumption that sulfate-reducing bacteria can cause some forms of cancer of the rectum through the

Table 1

Structures of ring-substituted 8-hydroxyquinoline-2-carboxanilides and *in vitro* antibacterial activity against *Desulfovibrio piger* Vib-7 (minimal inhibition concentration: MIC, half maximal inhibitory concentration: IC_{50} , minimal bactericidal concentration: MBC) of the compounds in comparison with ciprofloxacin (CPX).

Comp.	R	[μM]		
		MIC	IC_{50}	MBC
1	H	23	12	25
2	2-OCH ₃	28	17	28
3	3-OCH ₃	17	11	20
4	3-CH ₃	23	10	23
5	3-Br	33	18	35
6	3-CF ₃	17	10	20
7	4-CF ₃	20	10	22
CPX	–	45	28	45



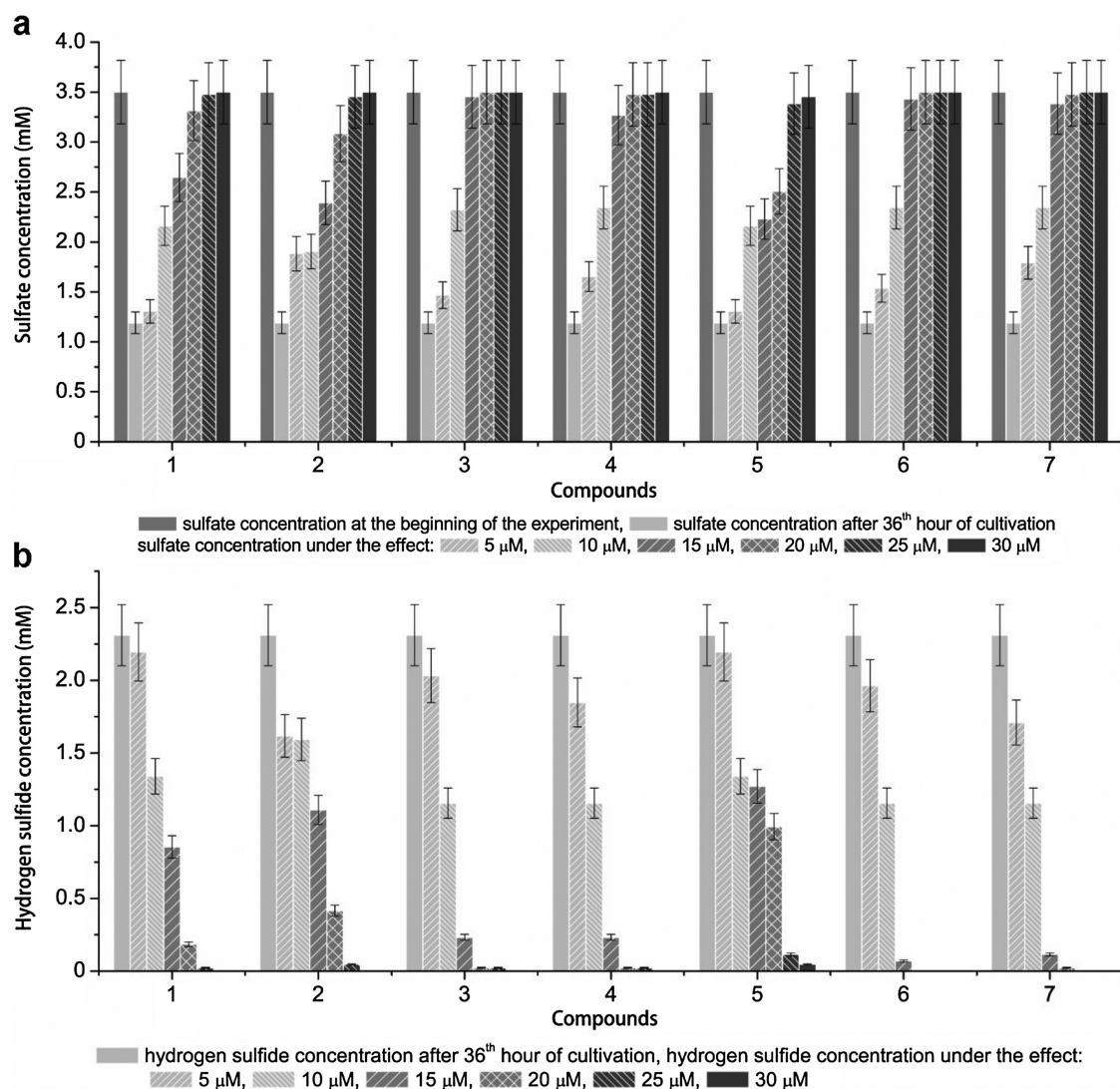


Fig. 2. Sulfate reduction of *D. piger* Vib-7 cells under the treatment of indicated doses of ring-substituted 8-hydroxyquinoline-2-carboxanilides: sulfate dissimilation (a), hydrogen sulfide production (b).

formation of hydrogen sulfide. In our previous studies, it was shown that bacteria *D. piger* Vib-7 consumed sulfate and accumulated hydrogen sulfide in concentration of 2.31 ± 0.21 mM (Kushkevych, 2013).

Based on all the obtained results in this study, it can be concluded that compounds **1–7** in concentrations 5–35 μ M inhibited the growth and, accordingly, the process of dissimilatory sulfate reduction. This antimicrobial activity was concentration-dependent, with the strongest effect in 30 μ M concentration. Similar effect was observed in our previous research for the activity of selected salicylamides against intestinal sulfate-reducing bacteria (Kushkevych et al., 2015a, 2016). Derivatives **1**, **2**, **4**, **5** and **7** showed cytotoxic affect at concentrations higher than 17 μ M. The highest level of inhibition of this process and high activity rates were observed at concentration 17 μ M of compounds **3** and **6** and thus are interesting for further studies. The cytotoxic effect of these compounds can be due to the inhibition of the enzymes of dissimilatory sulfate reduction (Kushkevych, 2015a,b; Kushkevych et al., 2015b), including sulfite reductase that is susceptible for various factors in intestinal sulfate-reducing bacteria *D. piger* Vib-7 (Kushkevych and Fafula, 2014). The tested

compounds can be considered good alternatives for the treatment of colitis or colorectal cancer although it should be taken in account that these compounds can be aggressive also to commensally bacteria and even to other parts of the human body. This should be a concern to be clarified in the near future with complementary assays.

Despite the fact that evaluated bacteria *Desulfovibrio* species are heterogeneous group of microorganisms which are widespread in anaerobic areas of soils, wetlands, marine and fresh water, they are available in microbiota of large intestine of humans and animals. It is known that intestinal *Desulfovibrio* species are different from other SRB by their biochemical and physiological properties (Barton and Hamilton, 2010; Brenner et al., 2005; Holt et al., 1994). So, the mechanisms of the effect of studied compounds on these bacteria can also differ. These compounds may influence the synthesis of the bacterial cell wall (peptidoglycan), ribosomes, enzymes or other phenotypic features such as inhibition the synthesis of desulfovibridin, cytochrome c3 and menaquinone MK-6. Effect of studied compounds may depend on their activity, structure and properties.

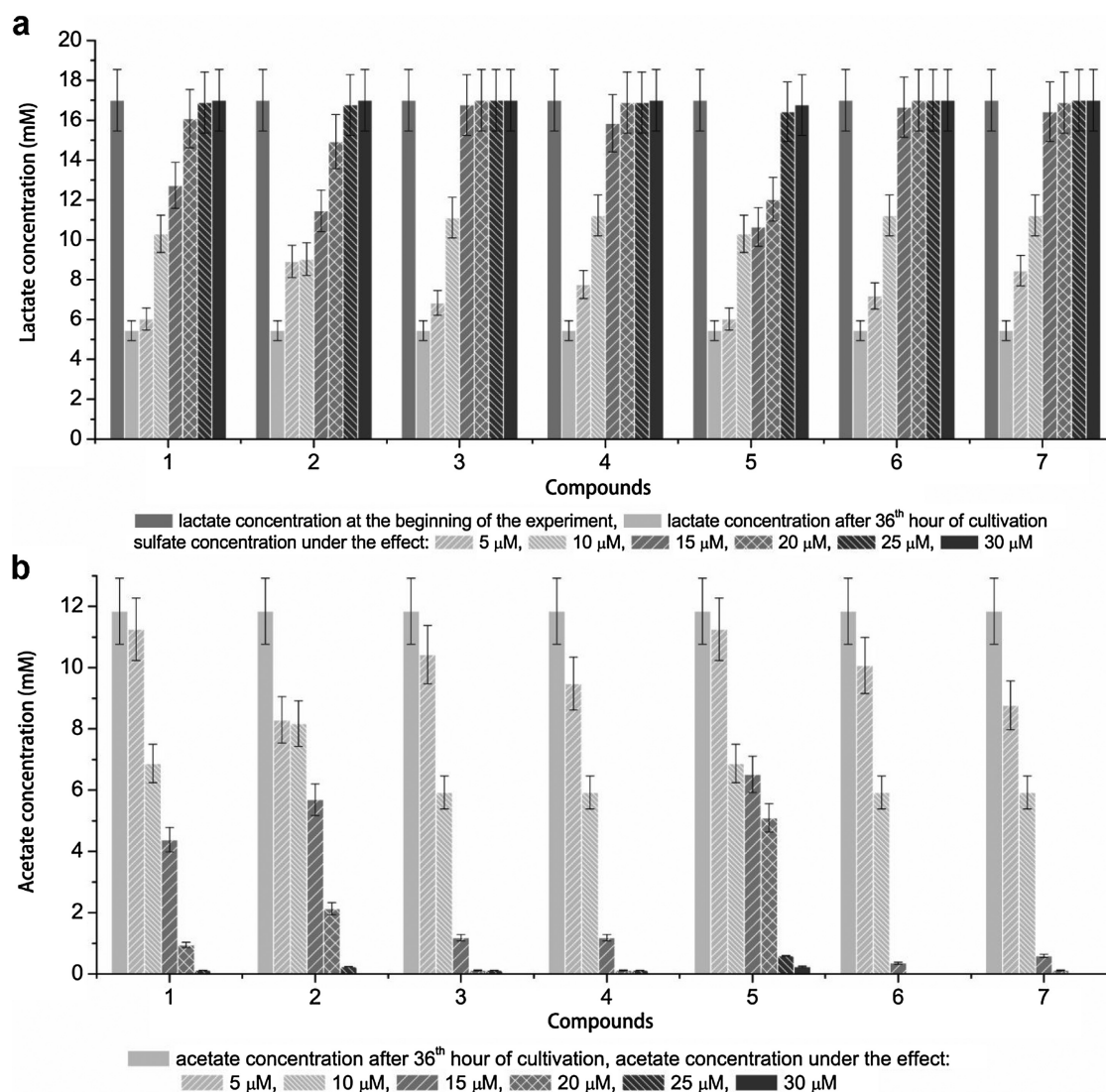


Fig. 3. The effect of ring-substituted 8-hydroxyquinoline-2-carboxanilides on lactate consumption (a) and acetate production (b) by *D. piger* Vib-7 cells.

The studied compounds are able to inhibit the number of sulfate-reducing bacteria and/or reduce the production of sulfide and acetate. This would help to clarify the factors influencing sulfide production in the human and animal colon.

Conflict of interests

The authors declare that they have no conflict of interests regarding the publication of this paper.

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