Antimicrobial action of arylsulfonamides bearing (aza)norbornane and related motifs: evaluation of new promising anti-MRSA agents

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Abstract
Arylsulfonamides bearing (aza)norbornane and related motifs were evaluated for: (1) antimicrobial activity toward five key ESKAPE pathogenic bacteria, one Gram-positive bacteria methicillin-resistant Staphylococcus aureus (MRSA, ATCC 43300), four Gram-negative bacteria, Escherichia coli (ATCC 25922), Klebsiella pneumonia (ATCC 700603), Acinetobacter baumannii (ATCC 19606), and Pseudomonas aeruginosa (ATCC 27853), and (2) antifungal activity towards two pathogenic fungal strains - Candida albicans (ATCC 90028) and Cryptococcus neoformans var. Grubii (H99; ATCC 208821). Four compounds with 4-nitrobenzenesulfonamide motif (VP-4556, VP-4604, VP-4605, and VP-4509) demonstrated high toxicity towards methicillin-resistant Staphylococcus aureus (ATCC 43300) with the MIC value of 14.7–49.3 µM. These compounds also possessed high antibacterial activity towards gram-negative bacteria P. aeruginosa (ATCC9027) with the MIC value of 460–555 µM. According to the results of toxicity studies of the compounds to HEK-293, HaCaT, Balb/c 3T3, red blood cells and normal mitogen-activated lymphocytes, three compounds - VP-4556, VP-4604 and VP-4509 - bearing azanorbornene, octahydro-3,5-methanocyclopenta[b]pyrrole and bio-isosteric piperidine motifs were selected for further studies as biocompatible agents with promising antimicrobial activity.

Graphical Abstract

Keywords Arylsulfonamides · Azanorbornane · Norbornane · Antimicrobial activity · Antifungal activity · ESKAPE pathogenic bacteria

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Introduction

In recent years, infectious diseases have become a major challenge to the global health system as killing millions of people worldwide. In addition, they affect socio-economic stability, contributing not only to the growth of the disease’s cases, but also leading to psychological disorders, reduction of the economy and living standard [1–3]. A wide variety of pathogens and the constant emergence of new multidrug-resistant pathogenic strains complicate the treatment and prevention of infectious diseases. At least 30 new infections have insidiously emerged and spread to threaten the health of billions of people around the world, especially in low-income countries. Unfortunately, for many of them, there are no successful pharmaceuticals or vaccines [4]. To address the above problems, there is an urgent need to develop new antimicrobial drugs.

Cage compounds are characterized by three-dimensional structures which have defined rigid geometry and due to their unique properties were in a focus in drug discovery research, especially as lipophilic scaffolds for the neuroactive drugs [5–8]. Up to date, the literature survey showed a significant interest in the medicinal chemistry of the polycyclic derivatives with (aza)norbornane cores and their unsaturated analogues (Fig. 1). These fragments were detected in many compounds with specific affinity for the opioid sigma (σ) receptors [9–14], non-steroidal anti-inflammatory drugs [15], potential anti-tuberculosis agents [16], adenosine A1 receptor antagonists [17]. Also, a number of compounds with these moieties are known as potential nitric oxide synthase inhibitors [18, 19], exhibited anti-plasmodial activity at nanomolar concentrations [20, 21] and have outstanding antiviral properties [22].

Recently, we found that the thieno[2,3-d]pyrimidin-4(3H)-one bearing norbornane motif possessed a high toxicity towards human leukemia HL-60, cervix carcinoma KB3-1, and colon carcinoma HCT116 cells [23]. The most common neurodegenerative disorders, such as Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, schizophrenia, and stroke, as well as drug abuse, have been modulated with the polycyclic cage derivatives [5, 24–26].

A significant progress in the use of cage compounds in the drug discovery was caused by the development of lead-oriented synthesis concept [27, 28]. Thus, cage compounds were proposed as bio-isosteres for arenes, to reduce the number of the aromatic rings in lead-like molecules [29]. Moreover, these compounds have been identified as valuable conformationally constrained analogues of various biologically active molecules, like piperidine or pyrrolidine alkaloids and proline [30].

In this regard, synthesis and chemistry of the polycyclic cage-like heterocycles bearing (aza)norbornane and related motifs have attracted considerable attention both of our group and many others [31–42]. As an example, 2-azabi-cyclo[2.2.1]heptane (azanorbornane) derivatives have also been applied as convenient precursors in the stereoselective synthesis of monocyclic systems useful in the medicinal chemistry [30].

In summary, cage-like molecules are attractive for the drugs discovery in terms of modern medical chemistry and new concepts, and, therefore, we set out to design and synthesize such derivatives that would be of interest as the antimicrobial agents.

Results and discussion

Chemistry

A fragment-oriented approach was chosen for the design of (aza)norbornane compounds for screening for antimicrobial activity. In particular, it is proposed to combine (aza)norbornane with sulfonamide motif, which is a well-known pharmacophore for the discovery of antimicrobial agents [43–45]. Thus, based on previous works of our group a number of cage sulfonamides (VP-4509, VP-4556,
VP-4563, VP-4580, VP-4583, VP-4584, VP-4585, VP-4589, VP-4604, and VP-4605 were designed and synthesized as summarized in Scheme 1. At first, sulfonamides VP-4556 [46], VP-4580 [47], VP-4583 [48], VP-4584 [48], VP-4585 [48] and VP-4589 [49], were synthesized by sulfonylation of the appropriate cage-like amines 1 with Et3N in DCM or aq. NaOH in Et2O (Scheme 1, A). In addition, derivatives of non-cage-like morpholine and piperidine (compounds VP-4604 [50, 51] and VP-4605 [50] respectively) were obtained for comparison and control. The target azanorbornane acid VP-4563 was synthesized based on hetero-Diels-Alder cycloaddition followed by hydrolysis of the ester 2 (Scheme 1, B) [52, 53]. Azabrendane VP-4509 [33], was synthesized via epoxidation followed by intramolecular heterocyclization of amides 3 (Scheme 1, C).

Chemical absorption, distribution, metabolism, excretion, and toxicity (ADMET), play key roles in drug discovery and development. A high-quality drug candidate should not only have sufficient efficacy against the therapeutic target, but also show appropriate ADMET properties at a therapeutic dose. We performed in silico evaluation all the tested compounds using SwissADME tool [54]. Considering druglikeness, we can conclude that all compounds match parameters for Lipinski, Ghose, Veber, Egan and Muegge rules. Lipophilicity in terms of Log P octanol/water for our set of compounds is in the range 0.64-2.60. All compounds are soluble or moderately soluble in water, have high gastrointestinal absorption and no alerts for PAINS filter. For more detailed information, see ESI.
Thus, we proposed methods for obtaining compounds that are convenient, variable and allow rapid optimization of the structure, which is especially valuable in drug discovery.

Biology

Antimicrobial screening

The primary screening of arylsulfonamides bearing (aza) norbornane and related motifs against 5 key ESKAPE pathogens and 2 fungi was performed by the Community for the Antimicrobial Drug Discovery (CO-ADD), funded by the Wellcome Trust (UK) and The University of Queensland Australia [55, 56]. All synthesized compounds were evaluated at 32 µg/mL dose (approx. 100 µM) for (1) antimicrobial activity towards five pathogenic bacteria, methicillin-resistant *Staphylococcus aureus* (ATCC 43300) as Gram-positive bacteria and *Escherichia coli* (ATCC 25922), *Klebsiella pneumonia* (ATCC 700603), *Acinetobacter baumannii* (ATCC 19606), and *Pseudomonas aeruginosa* (ATCC 27853) as Gram-negative bacteria, and (2) antifungal activity towards two pathogenic fungal strains *Candida albicans* (ATCC 90028) and *Cryptococcus neoformans* var. *Grubii* (H99; ATCC 208821). The results of two parallel trials are presented in ESI (Table S1).

It is important to underline the relationships between the structure and activity of the tested compounds. In all cases, the compounds with the 4-methyl/bromo-benzenesulfonamide moiety showed low activity. However, several compounds maintenance and electron acceptor nitro group showed excellent activity towards the bacterium *Staphylococcus aureus* (ATCC 43300). Noteworthy, only nitro derivatives with a para-position of the nitro group possessed high activity.

Bacterial pathogens have rapidly developed resistance to antimicrobial agents. The antimicrobial resistance systems involve the involvement of bacterial molecular and cellular-based machinery [57–60]. These resulted in an urgent need to develop novel effective antibiotics. To confirm the antibacterial potential, we have examined the toxicity of these drugs towards methicillin-resistant *Staphylococcus aureus*. Thus, a number of compounds (VP-4556, VP-4604, VP-4605, and VP-4509) were discovered that totally inhibited the growth of methicillin-resistant *Staphylococcus aureus* with growth inhibition GI > 95% (see Table S1 in ESI). All five highly active compounds contained a 4-nitrobenzenesulfonamide motif, indicating its beneficial role for inducing antimicrobial effect. Among them, there are two cage compounds VP-4556 and VP-4604 and two containing morpholine VP-4604 and piperidine VP-4604 substruents, respectively. This strain of bacteria spread mostly in hospitals and has resistance to multiple antibiotics. Therefore, obtaining substances with antibacterial activity to this strain will reduce the number of nosocomial infections, which provides a lot of death and side effects [61]. Thus, compounds with 4-nitrobenzenesulfonamide motif possessed high growth inhibition activity towards drug-resistant *S. aureus* and could be promising antimicrobial agents.

The minimal inhibitory concentration (MIC; µM) measurements were performed for compounds with significant microbial growth inhibition (VP-4556, VP-4604, VP-4605 and VP-4509) towards *Staphylococcus aureus* (ATCC 43300), using ceftriaxone, as a reference drug. At the same time, for the active compounds, primary cytotoxicity towards human embryonic kidney cell line and hemolysis of human red blood cells human cells was determined. Haemolysis assay is the most commonly used for initial toxicity investigation of different agents. Human erythrocytes are the most frequently used for the preliminary in vitro study of the haemolytic activity of antimicrobial and other drugs [62]. Compounds VP-4556, VP-4604, VP-4605, and VP-4509 have the best antibacterial activity, comparable to ceftriaxone. Cytotoxic concentration (CC50) of the compound VP-4605 is approximately 5 times higher (71.4 ± 4.4 µM) for HEK-293 cells than that of MIC (14.7 ± 1.3 µM) towards methicillin-resistant *S. aureus*. Another tested compounds VP-4556, VP-4604, and VP-4509 were also tolerated and non-toxic for human cells, as the cytotoxic and hemolytic dose was higher than the therapeutic dose (Table 1). The MIC of ceftriaxone was 57.7 µM for methicillin-resistant *S. aureus*. Negi at al. (2016) reported that the MIC of oxacillin was more 318 µM for 2 methicillin-resistant *S. aureus* strains [63]. It was reported that neomycin was more effective against MRSA with MIC of 203.4 µM, kanamycin with MIC of 258–516 µM, vancomycin with MIC of 0.35–0.7 µM, ciprofloxacin with MIC of 11.5 µM, ampicillin with MIC of 22.3 µM [64].

Taking into account the primary screening results, next we checked the antibacterial effect of most active compounds towards not-resistant *S. aureus* ATCC25923 and another strain of the Gram-negative bacteria *P. aeruginosa* (ATCC9027) using the MTT assay. This method is based on the changes of a colour reaction due to the metabolism of the MTT reagent in bacteria. The substances under study were solved in DMSO, thus, we used DMSO as a substance for comparison in equal doses like the doses of the studied compound.

The most active compounds were tested towards *Staphylococcus aureus* ATCC25923. Figure 2 presents the effect of compounds VP-4556, VP-4604, VP-4605, and VP-4509 towards *S. aureus*. Compound VP-4556 was most active towards *S. aureus* (Fig. 2) in a low concentration.
Primary screening data showed low activity of the compounds towards Gram-negative bacteria *Escherichia coli* (ATCC 25922), *Klebsiella pneumonia* (ATCC 700603), *Acinetobacter baumannii* (ATCC 19606), and *Pseudomonas aeruginosa* (ATCC 27853). In addition, we tested the most active compounds towards another strain of the Gram-negative bacteria *Pseudomonas aeruginosa* (ATCC9027) (Fig. 3). It was found, that compounds VP-4556, VP-4604, VP-4605, and VP-4509 possessed high antibacterial activity towards gram-negative bacteria *P. aeruginosa* (ATCC9027). The MIC of VP-4509 was 460 µM, 527 µM – for VP-4605, and 555 µM – for VP-4556, VP-4604.

In conclusion, the results obtained by screening methicillin-resistant *Staphylococcus aureus* (MRSA) strain and other microorganisms differ from the results obtained at using the MTT method. These results allow us to argue that 4-nitrobenzenesulfonamide derivatives have a specific effect on bacteria, rather than a general toxic effect. We can suggest that the synthesized 4-nitrobenzenesulfonamides cause the destruction of bacterial walls by interacting with structural elements of the bacterial wall, as well as specifically affect them or some internal mechanisms of bacteria functioning. In future, we are going to identify which of the biomolecules could interact with the studied 4-nitrobenzenesulfonamide.

### Table 1

| Compound     | MIC (µM) for methicillin-resistant *S. aureus* | CC<sub>50</sub> (µM) for HEK-293 | CC<sub>50</sub> (µM) for RBC |
|--------------|---------------------------------------------|----------------------------------|-----------------------------|
| VP-4556      | 28.6 ± 2.0                                  | >114.3                           | >114.3                      |
| VP-4604      | 22.2 ± 10.3<sup>a</sup>                    | >118.4                           | >118.4                      |
| VP-4605      | 14.7 ± 1.3                                  | 71.4 ± 4.4<sup>a</sup>          | >117.5                      |
| VP-4509      | 49.3 ± 4.7                                  | >98.7                            | >98.7                       |
| Ceftriaxone  | >57.7 ± 4.5                                 | not tested                       | not tested                  |

<sup>a</sup>Results of two independent trials

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**Fig. 2** Antibacterial effect of studied compounds towards *Staphylococcus aureus* ATCC25923. C – control data, * – P ≤ 0.05, compare to control(C), # – P ≤ 0.05, compare to solvent for each concentration (DMSO)

**Fig. 3** Antibacterial effect of studied compounds in *Pseudomonas aeruginosa* ATCC9027. C – control data, * – P ≤ 0.05, compare to control(C), # – P ≤ 0.05, compare to solvent for each concentration (DMSO)
Cytotoxicity

The antimicrobial agents needs to demonstrate low or no toxicity towards mammalian cells [65, 66]. Cytotoxicity of the five most active compounds (VP-4509, VP-4556, VP-4604, VP-4605) was further evaluated towards human keratinocytes of HaCaT cell line, Balb/c 3T3 line (murine fibroblasts) and lymphocytes of healthy human donor. Studied compounds had low cytotoxic action towards normal cells of HaCaT line (human keratinocytes) and Balb/c 3T3 line (murine fibroblasts) (Fig. 4). Compounds did not reached the CC50 value for Balb/c 3T3 cells up to 2500 µM. The inhibition of growth of Balb/c 3T3 cells equalled in the range of 11.1–45.6% at the action of studied derivatives at this dose. CC50 value of compound VP-4556 for HaCaT cells was 1792 µM. The CC50 value of compounds VP-4509 and VP-4605 for HaCaT cells was approximately 2500 µM. Compound VP-4604 inhibited the growth of HaCaT cells by 44.1% at 2500 µM. DMSO demonstrated low toxicity for HaCaT and Balb/c 3T3 cells. It inhibited the growth of HaCaT cells by 41.9% at 2500 µM.

Doxorubicin was used as a standard positive control drug, and it demonstrated high cytotoxicity towards HaCaT and Balb/c 3T3 cells. Doxorubicin showed higher cytotoxic effect than studied compounds towards HaCaT and Balb/c 3T3 cells with the CC50 value of 0.8 µM and 0.9 µM, respectively.

Studied derivatives demonstrated low toxicity towards mitogen-activated lymphocytes isolated from healthy adult human peripheral blood. The CC50 value of studied derivatives VP-4509, VP-4556, VP-4604, VP-4605 towards mitogen-activated lymphocytes was approximately 2500 µM for mitogen-activated human blood lymphocytes (Fig. 5).

Fig. 4 Cytotoxicity of studied derivatives towards human keratinocytes of HaCaT line, Balb/c 3T3 murine fibroblasts. After a total experimental time (72 h), cell vitality was evaluated by the MTT assay.

Fig. 5 Cytotoxicity of studied derivatives towards mitogen-activated lymphocytes isolated from healthy adult human peripheral blood. After a total experimental time (48 h), cell vitality was evaluated by the MTT assay.

In order to establish a therapeutic potential of derivatives VP-4509, VP-4556, VP-4604, VP-4605, we have calculated the values of the selectivity index (SI) of the tested derivatives towards methicillin-resistant *S. aureus* compared to normal mammalian cells of HEK-293, HaCaT and Balb/c 3T3 lines, and lymphocytes isolated from healthy adult human peripheral blood. The higher values of SI indicate greater specificity, and the compounds displaying the SI above 10.0 are considered to be selective [67]. The median SI above 10.0 was found for studied compounds VP-4509, VP-4556, VP-4604, VP-4605 towards methicillin-resistant *S. aureus* (Table 2). Thus, studied derivatives demonstrated high selectivity towards methicillin-resistant *S. aureus*.

Conclusion

Summarizing the results of the antibacterial activity and toxicity, we found that the 4-nitrobenzenesulfonamides
bearing azanorbornene, octahydro-3,5-methanocyclopenta [b]pyrrole and bio-isosteric piperidine motifs VP-4556, VP-4604 and VP-4509 respectively, have a stronger anti-microbial effect on methicillin-resistant *S. aureus* compared to normal mammalian cells of HEK-293, HaCaT and Balb/c 3T3 lines, and lymphocytes isolated from healthy adult human peripheral blood.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare no competing interests.

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