European Journal of Medicinal Chemistry 46 (2011) 5487–5497

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Design, synthesis and antibacterial activity of fluoroquinolones containing bulky arenesulfonyl fragment: 2D-QSAR and docking study

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ARTICLE INFO

Article history:
Received 15 July 2011
Received in revised form
5 September 2011
Accepted 7 September 2011
Available online 16 September 2011

Keywords:
Fluoroquinolones
Arenesulfonamido
Antibacterial
2D-QSAR
Molecular docking

ABSTRACT

Here in, we report the design, synthesis, and antibacterial activity of series of bulky arenesulfonamido derivatives using ciprofloxacin and norfloxacin as scaffolds. All the synthesized compounds were investigated *in vitro* for their antibacterial activities against two Gram-positive and two Gram-negative organisms using dilution broth method. Among the tested compounds examined, compounds **3**–**7** showed significance difference from the standard drug ciprofloxacin. 2D-QSAR study provides details on the fine relationship linking structure and activity and offers clues for structural modifications that can improve the activity. Docking study of the compound **3b** into the active site of the topoisomerase II DNA-gyrase enzymes revealed a similar binding mode to ciprofloxacin with additional classical and nonclassical hydrogen bonds.

1. Introduction

The fluoroquinolone antibacterial agents have been found to be one of the fastest growing groups of drugs in recent years [1–7]. They are compounds of intense interest because of their broad antibacterial spectrum against both Gram-positive and Gram-negative bacteria and their *in vivo* chemotherapeutic efficacy [8–10]. The fluoroquinolones are the only direct inhibitors of DNA synthesis by binding to the enzyme- DNA complex; they stabilize DNA strand breaks created by DNA gyrase and topoisomerase IV. Ternary complexes of drug, enzyme, and DNA block progress of the replication fork [7]. The inhibition of DNA gyrase and cell permeability of quinolones is greatly influenced by the nature of C-7 substituent on the standard structure of 4-quinolone-3-carboxylic acid [11,12]. During recent years a number of quinolones with substitution on piperazine ring at C-7 position of the basic structure of quinolones were synthesized and evaluated for antibacterial activities [13–16]. Most of these agents are substituted at the 7 position by a nitrogen heterocycle. Ciprofolxacin and norfloxacin [17–20] characterized by having a piperazine moiety at C-7, which represented a site of significant modification. Recently, benzenesulfonamidofluoroquinolones (BSFQs) are a new class of fluoroquinolones (Fig. 1A and B) reported previously by Manzo et al. [21,22]. Some of those BSFQs have exhibited high *in vitro* activity against *Staphylococcus aureus* ATCC 29213 [23,24] and also against other Gram-positive clinical strains [25]. The new compounds would exert their biological action through a quinolone-like mechanism of action [23]. It was also reported that BSFQs have displayed a more favorable kinetics of access to the bacterial cell in *S. aureus* ATCC 29213 [23]. Studies on *Staphylococcus pneumoniae* and *S. aureus* have identified the BSFQs as "dual targeting" agents [26,27]. It was reported that the new analogs with a sulfa moiety on piperazinyl group inhibit *Escherichia coli* DNA gyrase in similar way as ciprofolxacin [23]. According to the proposed mechanisms of action of fluoroquinolones, substituent at 7-position of quinolone ring would be involved in the interaction with the enzyme through electrostatic forces [12,19,28].

In this context, the present work describes the synthesis, the investigation of the antibacterial properties of new bulky arenesulfonylquinolones (Fig. 1C–G) and the achievement of a better antibacterial profile at lower concentrations. The strategy is intended to obtain potent broad spectrum antibacterial activity using traditional medicinal chemistry techniques motivated by the comparative modeling of quinolones (A–G) together with the

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doi:10.1016/j.ejmech.2011.09.011

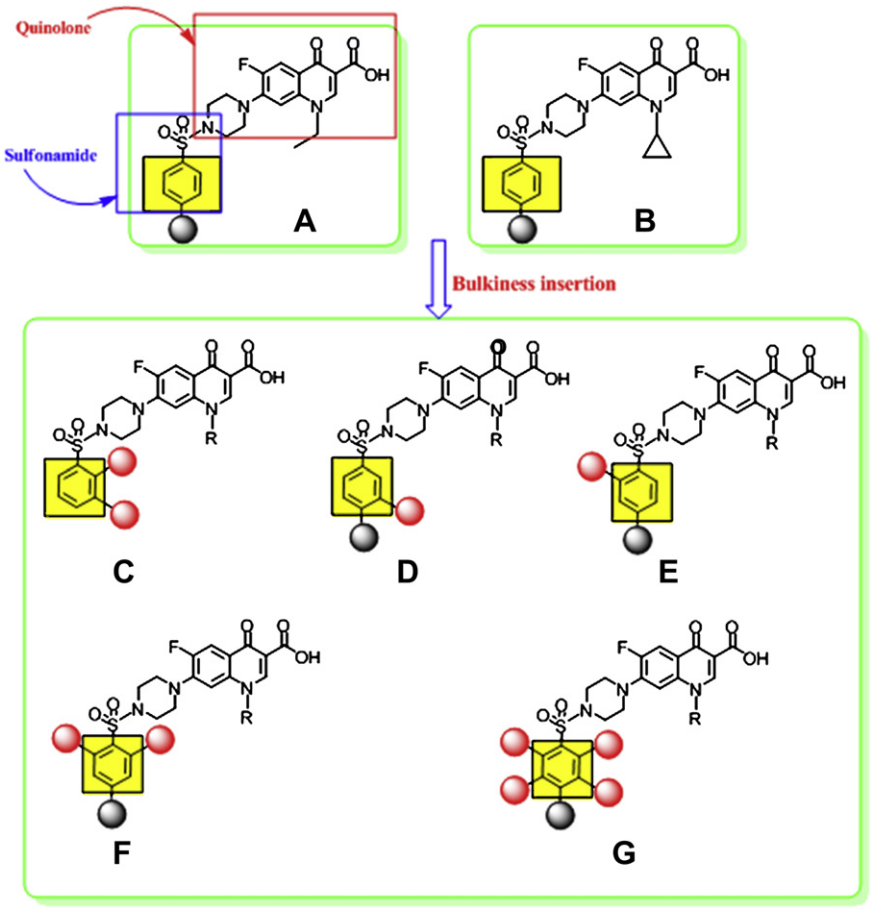

Fig. 1. Reported benzenesulfonamidonorfloxacin (A) and ciprofloxacin (B) and designed bulky arenesulfonyl derivatives (C–G).

available pharmacophore. Our strategy for synthesis such derivatives based on the modification of the structure of the known potent norfloxacin and ciprofloxacin. Moreover we describe a 2D-QSAR analysis for the complete series of arenesulfonylquinolones as well. Multiple linear regression analysis correlates biological activity values with various descriptors. Computer docking technique plays an important role in the drug design and discovery, as well as in the mechanistic study by placing a molecule into the binding site of the target macromolecule in a non-covalent fashion [29–33], and to predict the correct binding geometry for each ligand at the active site, which reveals the MOE score values and hydrogen bonds formed with the surrounding amino acids. MOE as flexible docking program enable us to predict favorable protein–ligand complex structures with reasonable accuracy and speed [34].

2. Results and discussion

2.1. Chemistry

2.1.1. Synthesis of compounds *1*–*11*

Scheme 1 outlines the synthetic pathway used to obtain compounds (**1**–**11**). Derivatives **1**–**7** were prepared by allowing norfloxacin (a) or ciprofloxacin (b) to react with the appropriate arenesulfonyl chloride in the presence of acetone and K_2CO_3 at room temperature for 24 h. On the other hand compounds **8**–**11** were obtained in relatively good yields by addition of the appropriate arenesulfonyl chloride to a stirred solution of norfloxacin (a) or ciprofloxacin (b) and K_2CO_3 in DMF at 50 °C for 12 h.

2.2. Biological activity

2.2.1. Antibacterial activities and structural–activity relationships

Compounds **1**–**11** in addition to the reference ciprofloxacin were tested for their *in vitro* antibacterial activity against two Gram-negative (*E. coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853) and two Gram-positive (*S. aureus* ATCC 29213 and *Bacillus subtilis* ATCC 10400) microorganisms. The minimal inhibitory concentrations (MIC in μg/mL and μmol/mL) or the lowest drug concentrations that prevent visible growth of bacteria (Table 1), were determined by a standard broth micro-dilution technique using the European Committee for Antimicrobial Susceptibility Testing (EUCAST) and Laboratory Standards method [35]. The results of MIC tests against Gram-positive and Gram-negative bacteria revealed that ciprofloxacin derivatives (R = cyclopropyl) were usually more active than norfloxacin derivatives (R = ethyl) especially against Gram-positive pathogens. From the obtained data (Table 1), the 3,4- and 2,4-disubstiuted benzenesulfonyl derivatives **3**–**4** and **6**–**7** exhibited potential activity against all the tested Gram-positive organism (MIC; 0.000463–0.000481 μmol/mL), which was more pronounced than that exhibited by the reference, ciprofloxacin (MIC; 0.000758 μmol/mL). The 1-naphthalenesulfonyl derivative **2b** (MIC; 0.000479 μmol/mL) revealed a better activity two times more active than ciprofloxacin (MIC; 0.000758 μmol/mL) against *B. subtilis* while the inhibition was moderate to weak with other tested strains. Similarly compounds **5b** (MIC; 0.000493 μmol/ml), **8a** (MIC; 0.000444 μmol/ml) and **8b** (MIC; 0.000435 μmol/ml), showed selective activity against *B. subtilis* two times more active than ciprofloxacin with lower activity against other strain. Other