European Journal of Medicinal Chemistry 126 (2017) 7–14

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Short communication

Design, synthesis and antimicrobial evaluation of novel benzoxazole derivatives

Wei Zhang [a, b], Jingbao Liu [a], Jocelyn M. Macho [b], Xizhen Jiang [a], Dongsheng Xie [a], Faqin Jiang [a], Wenlu Liu [a, *], Lei Fu [a, **]

[a] School of Pharmacy, Shanghai Jiao Tong University, 800 Dongchuan Rd., Shanghai 200240, China
[b] Department of Chemistry, University of Florida, Gainesville, FL, 32611-7200, USA

ARTICLE INFO

Article history:
Received 30 July 2016
Received in revised form
3 October 2016
Accepted 5 October 2016
Available online 6 October 2016

Keywords:
Antibacterial activity
Minimum inhibitory concentration
Benzoxazole
Propanoic acid

ABSTRACT

The synthesis of (*S*)-2-(4-*tert*-butylphenoxy)-3-(benzoxazol-5-yl) propanoic acid derivatives (**2a-k**) were described and their *in vitro* antibacterial activities were determined against Gram-negative and -positive bacteria. These compounds were found to exert a broad spectrum of activity against the screened bacteria, but poor MIC values were found for *Candida albicans* fungi. Compound **2b** bearing a hydrophobic aromatic tie was the most active derivative against all bacteria studied with MIC values ranging from 0.098 to 0.78 μg/mL. The activity of **2b** against *B. subtilis* was 2-fold higher than Penicillin, and 8- to 510-fold higher than other control antibiotics.

1. Introduction

Benzoxazole derivatives were widely reported as a class of biologically active compounds with anti-bacterial and anti-tumor activities [1–5]. In the early 1980s, Hisano et al. reported the first synthetic compounds with benzoxazole skeletons that displayed potential antimicrobial activities [6]. Over the past twenty years, a large library of benzoxazole derivatives has been developed, some of which have exerted good minimum inhibitory concentration (MIC) values [7–15]. In addition, some benzoxazole-containing natural products were also proven to have antimicrobial abilities, for example calcimycin, routeennocin and cezomycin separated from *Streptomyces chartreusis* [16–18], and pseudopteroxazole from *Pseudopterogorgia elisabethae* [19].

Previously, we reported the synthesis and antibacterial study of a series of (*S*)-2-(substituted-hydroxyl)-3-(benzoxazol-5-yl)propanoic acid derivatives (Fig. 1) [20]. This family of compounds was designed by an integration of four fragments: an aromatic tie, a linker, a benzoxazole skeleton and a polar acidic head. In our previous report, we investigated the effect of the chiral side chain on anti-bacterial activity; our preliminary structure-activity study revealed that the hydrophobic substitutes, 4-*tert*-butyl (**1a**), 4-phenyl (**1b**) and 4-benzyloxyl (**1c**) on the phenoxyl side chain displayed best activities against all Gram-negative and Gram-positive bacteria studied with MIC values between 1.56 and 6.25 μg/mL.

As we continue efforts in search for more active benzoxazole-containing compounds while gaining a better understanding of the mechanism of action, herein, we focused on further structural modification of the aromatic tie of **1a**, and examined their antibacterial activities (Fig. 2). Our previous study suggested that the hydrophobicity of agents may alter the functional biology activities significantly [20–23]. Specifically, in this study the modification of the aromatic tie (R group), with either hydrophobic or hydrophilic groups, resulted in a new family of (*S*)-2-(*tert*-butylphenoxy)-3-(benzoxazol-5-yl)propanoic acid derivatives.

2. Chemistry

Similar to our previously reported procedures [20], the synthesis of compounds **2a-k** was achieved in thirteen steps as shown in Scheme 1. Intermediate **5** was easily obtained from 3-(4-hydroxyphenyl) propanoic acid **3** by nitration and esterification. The hydroxyl-protected **6** was produced by using CH_3OCH_2Cl. After hydrolysis of **6**, the resulting acid **7** was coupled with (*R*)-4-isopropyloxazolidin-2-one to give Evans amide **8**. Davis

* Corresponding author.
** Corresponding author.
E-mail addresses: sdwenlu@sjtu.edu.cn (W. Liu), leifu@sjtu.edu.cn (L. Fu).

http://dx.doi.org/10.1016/j.ejmech.2016.10.010
0223-5234/

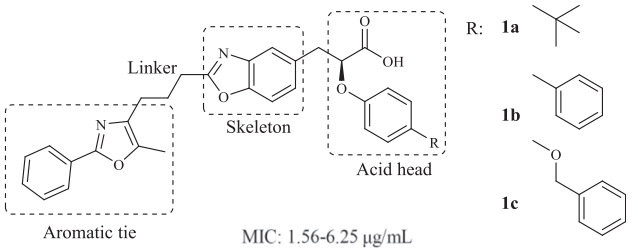

Fig. 1. (*S*)-2-(substituted-hydroxyl)-3-(benzoxazol-5-ly)propanoic acid derivatives **1a-c**.

asymmetric oxidation conditions converted **8** to a chiral hydroxyl compound **9**. The chiral accessory (*R*)-4-isopropyloxazolidin-2-one was removed by using magnesium methoxide to produce methyl (*R*)-α-hydroxyl-propanoic acid **10**. (*S*)-**11** was obtained by treating **10** with 4-*tert*-butylphenol under Mitsunobu conditions [24]. Treatment of **11** with HCl/MeOH yielded **12**, quantitatively. The benzoxazole skeleton **13** was obtained from **12** by sequential treatment with Pd/C and acetimidate [25]. **14** was produced from **13** by using $P(EtO)_3$. Compound **15** was obtained from **14** by treating with respective acetones and aldehydes via Horner-Wadsworth-Emmons olefination and platinum dioxide hydrogenation conditions successively. The final propanoic acids **2a**-**k** were produced by treatment of **15a**-**k** with LiOH.

3. Antimicrobial activity evaluations

According to the National Committee for Clinical Laboratory Standards, we adopted a 96-well microtiter broth dilution method to determinate MIC values [26,27]. Activities of the newly synthesized compounds were determined against fungus *Candida albicans ATCC 10231*, Gram-negative bacteria *Escherichia coli ATCC 11303* and Gram-positive bacteria *Staphylococcus aureus ATCC 10832*, Methicillin-resistant *Staphylococcus aureus ATCC 700699*, *Bacillus subtilis ATCC 33712*. The MIC value is defined as the lowest antibiotic concentration that resulted in visible growth after incubation at 37 °C for 24 h. Compound **1a**, Ceftazidime, Cefotaxime, Cefradine, Sodium Penicillin, Miconazole nitrate, and Ketoconazole were used as reference or control drugs. The antimicrobial activity data of the compounds and the control drugs are given as MIC (μg/mL) values in Table 1.

4. Results and discussion

Table 1 summarized the results of the minimum inhibitory concentration (MIC) assays of eleven compounds synthesized. Compared to the lead compound **1a**, general improvement of antibacterial activity was observed, while none for fungus.

When the aromatic tail of **1a** was substituted with phenyl (**2a**), 4-*iso*propyl-phenyl (**2b**) and 4-fluorophenyl (**2c**), the antibacterial activities were increased by 8–32 fold. 4-*Iso*propyl phenyl (**2b**) especially exerted the best activities against all Gram-positive and -negative bacteria with MIC value between 0.098 and 0.78 μg/mL. The activity of **2b** against *B. subtilis* was 2-fold higher than sodium penicillin, and 8- to 510-fold higher than other antibiotics. Compound **2h**, a short linker homologue of **1a**, showed 2- to 4-fold higher activities than **1a** on some bacteria (*E. coli* and *MRSA*).

From the MIC values of compounds **2a**-**2d** and **2h**, we found that the hydrophobicity of tail fragments impacted the anti-bacterial activities dramatically. The law of anti-bacterial activity was in full accordance with the order of calculated logP value (clogP): **2b** (clogP 7.98) > **2c** (6.90) > **2h** (6.79) > **2a** (6.74) > **2d** (6.36), and corresponded with our previous study, namely hydrophobicity-activity relationship which indicates that hydrophobicity can increase the antibacterial activities [20]. Evidently, the hydrophilic aromatic tie 3,4,5-trimethoxyphenyl (**2d**) produced a negative effect on the inhibition of bacterial proliferation, with MIC values only at 100–200 μg/mL. Furthermore, the polar heterocyclic ties (e.g. imidazo [1,2-a]pyridine-2-yl (**2e**) and oxazol-5-yl (**2f**)) were also proved to decrease the antibacterial activity dramatically.

Benzofuran-2-yl (**2g**) (clogP 6.27) displayed a unique broad-spectrum activity against all screened bacteria without following the hydrophobicity-activity relationship. We reason that benzofuran moiety might possess special characteristics against bacteria as it was reported in our previous studies [28,29].

When the tail fragment of compound **1a** was converted to long-chain heptyl (**2j**), similar anti-bacterial activities were retained and the *iso*-propyl substituted derivative (**2i**) exhibited 1-fold increasing activity. However, when the alkyl tail contained an oxygen atom, tetrahydropyran-4-yl (**2k**), weak inhibitory effects were observed. These results were also fully consistent with the contribution of hydrophobicity on the structure-activity relationship (SAR): **2j** (clog P 7.22) > **2i** (6.30) > **2k** (4.96).

5. Conclusions

Based on the structure of the lead compound (**1a**), a novel series of (*S*)-2-(4-*tert*-butylphenoxy)-3-(benzoxazl-5-yl)propanoic acid derivatives **2** were designed and synthesized by structural modification with different lipophilic and hydrophilic fragments, which were introduced into the tail fragment of the leading. The newly designed compounds displayed a broad spectrum of *in vitro* activities against Gram-positive bacteria such as *S. aureus*, *MRSA*, *B. subtilis*, and Gram-negative bacteria *E. coli* as well.

Furthermore, we have demonstrated that hydrophobic tails, like phenyl (**2a**), 4-*iso*propyl-phenyl (**2b**) and 4-fluorophenyl (**2c**), *iso*-propyl (**2i**), heptyl (**2j**) showed the best prominent antibacterial activities in all screened assays, and were even better than the leading compound (**1a**) and positive control antibiotics examined in this study.

The introduction of the hydrophobic groups on the tail fragment

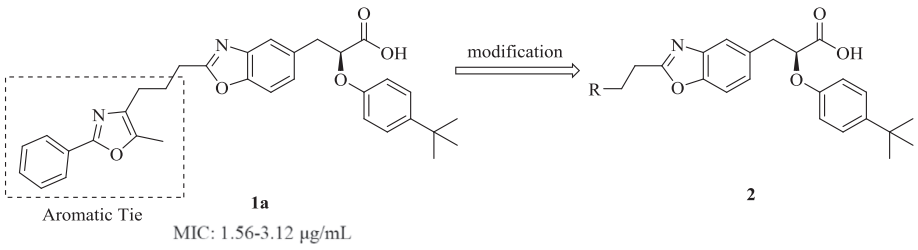

Fig. 2. Structural modification of compound **1a**.