Bioorganic & Medicinal Chemistry Letters 21 (2011) 133–136

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Peptide deformylase inhibitors with non-peptide scaffold: Synthesis and structure–activity relationships

Seung Kyu Lee [a,c], Kwang Hyun Choi [a], Sang Jae Lee [a], Jong Sun Lee [a], Ji Yun Park [a], B. Moon Kim [b], Bong Jin Lee [a,c,*]

[a] Promeditech Ltd, College of Pharmacy, Seoul National University, Seoul 151-742, Republic of Korea
[b] Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-747, Republic of Korea
[c] Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, 599 Gwanak-Ro, Gwanak-Gu, Seoul 151-742, Republic of Korea

ARTICLE INFO

Article history:
Received 22 June 2010
Revised 27 October 2010
Accepted 10 November 2010
Available online 16 November 2010

Keywords:
PDF
SAR
Antibacterial
Non-peptide

ABSTRACT

Peptide deformylase (PDF), which removes the formyl group at the N-terminal methionine residue of nascent protein, has been recognized as a potent target for antibacterial therapy. We report herein the synthesis and structure–activity relationship studies of non-peptide PDF inhibitors.

Increasing antibacterial resistance poses a severe threat to human health.[1] As consequences, there is a growing need to identify new antibiotics that do not share the targets of existing antibacterial drugs. Many novel and potentially useful targets are discovered by analysis of microbial genomes, but only a few targets succeed to yield active antibiotics.[2,3] One of novel and potentially useful targets that have recently received a particular attention is peptide deformylase (PDF).[4] The difference in protein synthesis between bacteria and mammalian cells stems from transformylation and deformylation of initiating methionine. Protein synthesis in bacteria is initiated with *N*-formylmethionine which is generated by transformylation of methionine. PDF removes the formyl group at the N-terminal methionine residue of nascent protein.[5] The fact that the peptide deformylase is essentially required for producing mature protein in bacteria provides a rational basis to choose it as a potential antibacterial target.

In a previous study, we have reported that PDF inhibitor **1**[6] and its analogs have potent antibacterial activity against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* which are known to cause respiratory tract-associated infection (Fig. 1). But PDF inhibitor **1** and analogs have lower antibacterial activity against *Staphylococcus aureus*. During the course of our PDF inhibitor program, we found that replacement of the *N*-alkyl side chain and the hydroxamic acid moiety of compound **1** with chiral alkyl chain and reverse hydroxamic acid, respectively, significantly increases antibacterial activity against *S. aureus*. Here, we describe the synthesis of non-peptide PDF inhibitors **2** and corresponding SAR around the P_3' positions.

The synthesis of PDF inhibitors used in this study is outlined in Schemes 1–3.[7] Coupling of *N*-Boc amino acid **3** with Meldrum's acid in the presence of DCC and DMAP gave acyl Meldrum's acid and subsequent treatment with benzyl alcohol provided β-keto ester **4**.[8] In this step tetramic acid, which was produced from undesired cyclization reaction, was easily removed by silica-gel column chromatography. Compound **5** was prepared from alkylation with butyl group at the α-position of the β-keto ester **4**. Removal of benzyl group by hydrogenolysis in the presence of 10% Pd/C afforded a β-keto acid, which was treated with formaldehyde and piperidine to give compound **6**. Since the β-keto acid was easily decarboxylated at room temperature, storing the β-keto acid is not recommended. Conjugate addition of benzylhydroxylamine formed diastereomeric adducts (72:28, *RS*:*SS* diastereomeric ratio). The desired (*R*)-diastereomer **7** was isolated from purification through silica-gel column chromatography. Treatment of compound **7** with formic acid and acetic anhydride provided compound **8**. Final compound **9** was obtained from removal of the benzyl group through hydrogenolysis.

For the synthesis of PDF inhibitors with amide moiety at P_3' position, compound **8b** was treated with trifluoroacetic acid to afford compound **10**. Amine **10** was coupled with corresponding carboxylic acid to provide compound **11**. Removal of *O*-benzyl group with hydrogenolysis gave final compound **12**.

* Corresponding author. Tel.: +82 2 880 7869; fax: +82 2 872 3632.
E-mail address: lbj@nmr.snu.ac.kr (B.J. Lee).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.11.056

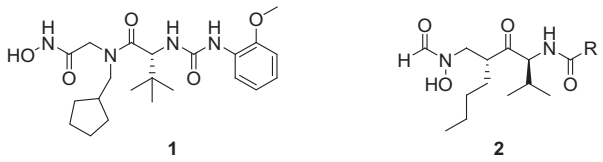
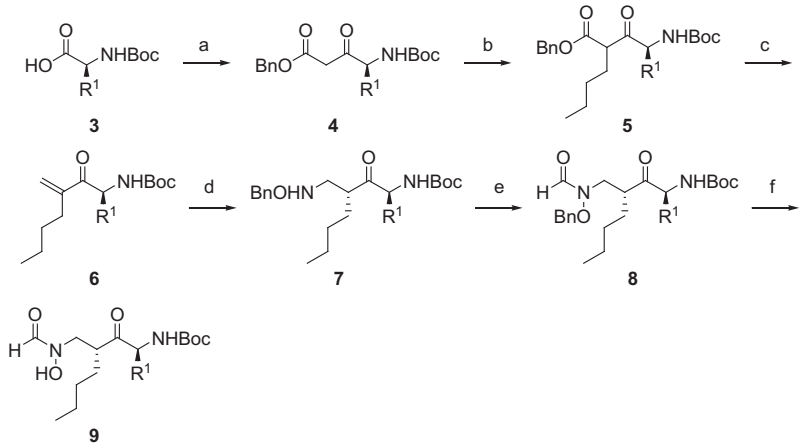


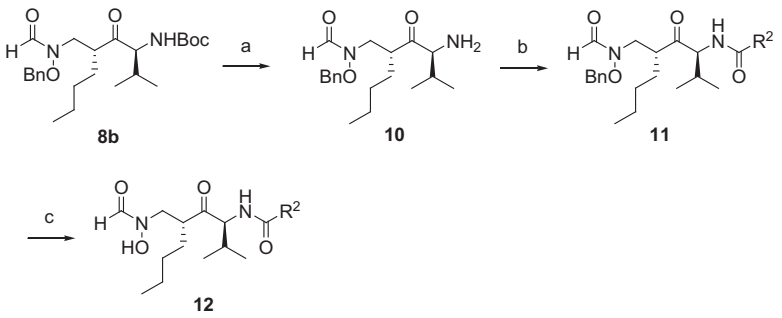
Figure 1. Structures of PDF inhibitor **1** and non-peptide PDF inhibitor **2**.

Compound **10** was treated with carbonyl diimidazole[9] and the resulting imidazolide **13** was coupled with the corresponding amine in toluene to give compound **14**. The final urea **15** was obtained by deprotection of benzyl group using hydrogenolysis.

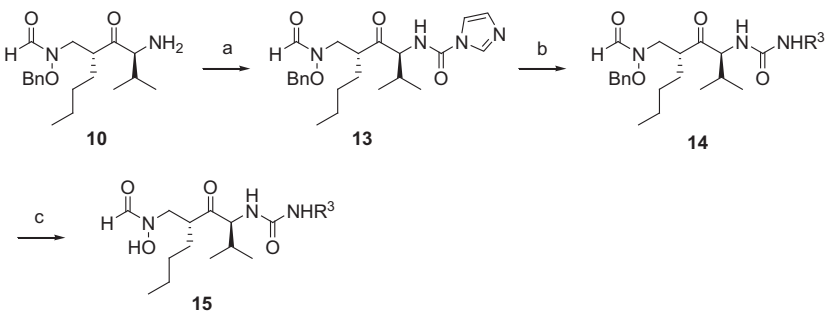
Compounds were tested using a *P. aeruginosa* Ni-PDF enzyme assay[10] and primary in vitro antibacterial activity was tested against *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. aureus*. The size of the amino acid side chain at P_2' position appears to have significant effect on the enzyme inhibition activity, and antibacterial activity against *S. aureus*. From the assay data summarized in Table 1, preferred side chain for P_2' site appears to be an isopropyl group because valine derivative (**9b**) revealed potent inhibition against enzyme and bacterial strains. The loss in activity of *t*-leucine derivative (**9c**) against *S. aureus* shows that P_2' binding pocket is not suitable for binding with side chain bigger than isopropyl group.



Scheme 1. Reagents and conditions: (a) Meldrum's acid, DCC, DMAP, rt, then toluene, BnOH, 80 °C, 30–50%; (b) K_2CO_3, NaI, *n*-BuBr, acetone, reflux, 18 h, 50–60%; (c) 10% Pd/C, H_2, EtOH, then CH_2O, piperidine, 80 °C to rt, 55–65%; (d) $BnONH_2$, 40 °C, 12 h, 55–60%; (e) HCO_2H, Ac_2O, EtOAc, rt, 1 h, 90–95%; (f) 10% Pd/C, H_2, MeOH, rt, 2 h, 40–50%.



Scheme 2. Reagents and conditions: (a) TFA, dichloromethane, rt, 6 h, 98%; (b) R^2CO_2H, HOBt, EDC, *N*,*N*-diisopropylamine, dichloromethane, rt, 12 h, 35–50%; (c) 10% Pd/C, H_2, MeOH, rt, 2 h, 40–50%.



Scheme 3. Reagents and conditions: (a) carbonyl diimidazole, *N*,*N*-diisopropylethylamine, dichloromethane, rt, 4 h, 88%; (b) R^3NH_2, toluene, reflux, 18 h, 35–50%; (c) 10% Pd/C, H_2, MeOH, rt, 2 h, 40–50%.