Chinese Chemical Letters Vol. 13, No. 1, pp 17 – 18, 2002
http://www.imm.ac.cn/journal/ccl.html

Design and Synthesis of Muramyl Dipeptide Cyclic Analogue

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Abstract: A new conformationally restricted cyclic analogue of muramyl dipeptide was designed and manually synthesized by our "Meshed-Bag Gathered-Bunch" method with a combination of Fmoc, allyl and *N*-1-(4,4-dimethyl–2,6-dioxocyclo-hexylidene)ethyl chemical protection strategy.

Keywords: Muramyl dipeptide, "Meshed-Bag Gathered-Bunch" method, cyclic peptides, solid-phase synthesis.

Muramyl dipeptide (MDP) was identified in 1974 as the minimal immunologically active component of bacterial cell wall peptidoglycan[1]. However, its applications are limited due to its short duration of action and other undesired side effects[2]. As MDP is a conformationally flexible molecule, its multiple biological activities could be due to the interactions of its specific conformational structures with stereochemical receptors or their subtypes, although the exact receptors of MDP are still unknown. Thus, identification of bioactive conformation is essential for the rational design of peptidomimetics with properties radically superior to those of the natural peptidic lead. Consequently, the design and synthesis of cyclized analogues of MDP would be important for this purpose. To the best of our knowledge, no attempts have been made so far to impose a conformational restriction on muramyl dipeptide.

It has been proposed that *N*-Ac-CO, isoGln-CO, isoGln-N, and isoGln-δ-CO, might be the main features of the MDP pharmacophore, and D-iso-glutamine residue plays a critical role in its biological activities[3]. Based on this useful information, we have designed and synthesized a new cyclic analogue of MDP in which the iso-glutamine residue is conformationally restricted in a cycle by formation of a lactam ring between D-iso-Gln and near lysine residue through side chain coupled spacer (see **Figure 1**). Since the optimal ring size is difficult to predict, cyclic peptides of varying ring size or amino acid composition are preparing.

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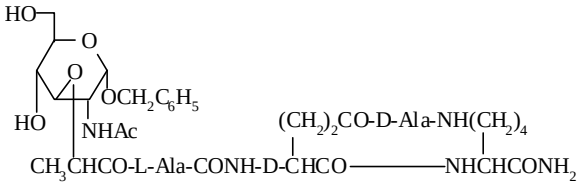
Figure 1 The cyclized muramyl dipeptide



Experimental

The cyclic peptide was manually synthesized by using our "Meshed-Bag Gathered-Bunch" method[4] with a combination of Fmoc, allyl and *N*-1-(4,4-dimethyl – 2,6-dioxocyclo-hexylidene)ethyl (Dde) protected methods. Rink amide resin was selected as solid phase support. The first building block of Fmoc-Lys(Dde)-OH was coupled onto the resin directly, followed by consecutive couplings of Fmoc-D-Glu(OAll)-OH, Fmoc-L-Ala-OH and protected muramic acid[5]. The Dde group was then removed by treatment with 2% hydrazine in DMF, and Fmoc-D-Ala-OH was subsequently coupled to the ω-amino group of lysine. The allyl side-chain protected group of D-Glu(OAll) residue was removed with $Pd(PPh_3)_4$ treatment at r.t. Cyclization was carried out *in situ* on resin by means of HBTU as coupling reagent, HOBt and NMM as additives after Fmoc removal. After cleavage from the resin using TFA as reagent and EDT, water, anisole and thioanisole as scavengers, performance of concentration by slow flow of nitrogen gas and ethyl ether precipitation steps gave a solid product. Purity and expected molecular weight of cyclic peptide were found as 86.5% and 764.1 (Cal. 763.8) by RP-HPLC and FAB-MS respectively.

References

1. F. Ellouz, A. Adam, R. Ciorbaru, *et al*., *Biochem. Biophys. Res. Commun.*, **1974**, *59*, 1317.
2. G. Baschang, *Tetrahedron*, **1989**, *45* (20), 6331.
3. P. Pristovsek, J. Kidric, D. Hadzi, *J Chem. Inf. Comput. Sci.*, **1997**, *37*, 971.
4. S. D. Zhang, G. Liu, S. Q. Xia, **2001**, submitted.
5. P. H. Gross, M. Rimpler, *Liebigs. Ann. Chem.*, **1986**, 37.

Received 14 May, 2001