SPECIALIA

Topochemical Approach to the Structure-Activity Relation. Retroenantio-Gly^{5,10}-Gramicidin S

Earlier[1] we showed that biologically active peptides and depsipeptides may have the molecule, as a whole, so modified as to give analogs sufficiently close to the original compounds in both steric, i.e. topological, and electronic aspects. Thus, the topochemical analog of the depsipeptide antibiotic enniatin B exhibited, as could be expected, a high biological activity which proved in all respects to be equal to the natural antibiotic[1].

However, the case of enniatin B, with its high molecular symmetry, is very specific. Now we are able to show that such an approach is applicable to a number of other types of biologically active compounds. To show that similar stereochemical relations can also obtain in non-symmetric cyclopeptides, let us consider the transformations of the hypothetical cyclopeptide I (Figure 1). Compound II is its enantiomer, while compound III≡IV is the retro-form of the latter with reverse direction of acylation (cyclodiastereomer according to PRELOG[2]). It is readily seen that cyclopeptide I is topologically quite analogous to IV since both compounds differ only in the atomic arrangement of the amide groupings (CO-NH and NH-CO). One might therefore expect such topochemically similar cyclopeptides to often show similar biological properties.

In realization of this expectation, we have synthesized retroenantio-Gly^{5,10}-gramicidin S (Figure 2)[3]. In confirmation of our predictions, the resultant compound displayed an antimicrobial activity commensurate with that[4] of Gly^{5,10}-gramicidin S[5].

This result, as well as our previous data[1], clearly shows that the topochemical approach has considerable potentialities in structure-activity studies, presenting a new aspect to the mode of action of biologically active peptides and rationalizing the synthetic search for their analogs. Since, under certain conditions, the topochemical approach can be extended to linear peptides, it also allows the problem of the functional centres of enzyme systems to be attacked from a new angle.

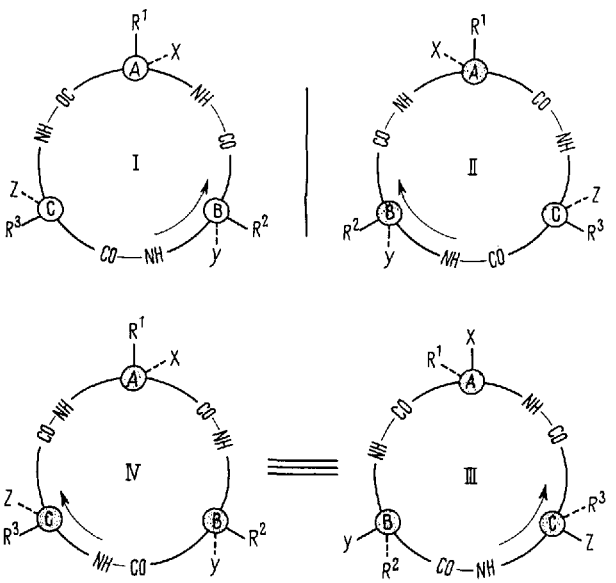

Fig. 1

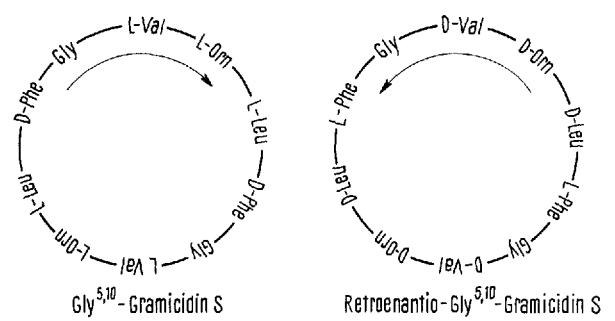

Fig. 2

Выводы. Исходя из топохимических предпосылок, предложен новый принцип модификации биологически активных циклопептидов. Показано, что ретроэнантио-Gly^{5,10}-грамицидин С обладает активностью, сравнимой с активностью Gly^{5,10}-грамицидина С.

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[1] M. M. SHEMYAKIN, YU. A. OVCHINNIKOV, V. T. IVANOV and A. V. EVSTRATOV, Nature *213*, 412 (1967).

[2] V. PRELOG, H. GERLACH, Helv. chim. acta *47*, 2288 (1964).

[3] The synthesis of retroenantio-Gly^{5,10}-gramicidin S was carried out by doubling of the glycine C-terminated linear pentapeptide ONP-ester obtained by building up the peptide chain stepwise from the N-terminus. The δ-amino group of ornithin was protected by a phtaloyl grouping.

[4] H. AOYAGI, T. KATO, M. OHNO, M. KONDO, M. WAKI, S. MAKISUMI and N. IZUMIYA, Bull. Chem. Soc. Japan *38*, 2139 (1965).

[5] It is noteworthy that the retro-form of Gly^{5,10}-gramicidin S, synthesized analogously to the retroenantio-isomer, also displays a high antimicrobial activity. This is apparently due to the fact that on superimposing the L-Orn residues of the retro-Gly^{5,10}-gramicidin S on those of Gly^{5,10}-gramicidin S, the 2 compounds differ only in mutual exchange of the residues Gly ⇄ D-Phe and L-Leu ⇆ L-Val.