STRUCTURE-ACTIVITY RELATIONSHIP OF LIPOPEPTIDE FROM OUTER MEMBRANE OF ESCHERICHIA COLI AND SYNTHESIS OF HIGHLY IMMUNOPOTENTING LIPOPEPTIDE DERIVATIVES WITH AN ACHIRAL LIPO-PART

Muneaki KURIMURA and Kazuo ACHIWA*
School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Shizuoka 422, Japan

For outstanding the structure-activity relationship of lipopeptide derivatives, high biologically active lipopeptide derivatives with an achiral lipo-part were newly synthesized

KEYWORDS lipoprotein; lipopeptide derivative having an achiral lipo-part; mitogenic activity

It has been known that a lipopeptide from the outer membrane of Escherichia coli is an active mitogen and polyclonal activator for B lymphocytes. In the preceding paper, we reported a new synthesis of chiral lipopeptides, their derivatives(I) with higher activity than the native lipopeptide and the structure-activity relationship between number of amino acids and biological activity. Now we focused our attention on the lipo-part; to investigate the influence of the length and number of the aliphatic chain and its mitogenic activity, and also to find high biologically active lipopeptide derivatives with an achiral lipo-part, we have synthesized lipopeptide derivatives with one aliphatic chain linked to the propane skeleton 1, 2, 3, 4, 5, 6, 7, 8, linked to the ethanol 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 2-cysteinylglycerol type 20 shown in Fig.2.

Fig. 1. Structure of Lipopeptide Derivative with High Activity

Fig. 2. Structure of Lipopeptide Derivatives

© 1993 Pharmaceutical Society of Japan
\[ R^1\text{-OH} \]
\[ \text{a)} \]
\[ R^1\text{-O-}(\text{CH}_2)_{n}\text{-OTHP} \]
\[ \text{b, c, d)} \]
\[ R^1\text{-O-}(\text{CH}_2)_{n}\text{-1} \]
\[ \text{e, g)} \]
\[ \text{Troc} \]
\[ R^1\text{-O-}(\text{CH}_2)_{n}\text{-Cys-OBu}^i \]
\[ \text{f, g)} \]
\[ \text{Troc} \]
\[ R^1\text{-O-}(\text{CH}_2)_{n}\text{-Cys-Ser(Bu')-Ser(Bu')-Asn-OBu}^i \]
\[ \text{h)} \]
\[ R^1 = \text{C}_{12}H_{25}, \text{ C}_{22}H_{45} \]
\[ 1, 2, 3, 4 \]
\[ n = 2, 3 \]

**Chart 1.** Synthesis of Ether Type Lipopeptide Derivatives

\[ \text{HO-}(\text{CH}_2)_3\text{I} \]
\[ \text{i)} \]
\[ \text{Troc} \]
\[ \text{HO-}(\text{CH}_2)_2\text{-Cys-OBu}^i \]
\[ \text{j)} \]
\[ \text{Troc} \]
\[ R^2\text{-O-}(\text{CH}_2)_2\text{-Cys-OBu}^i \]
\[ \text{k, l)} \]
\[ \text{Troc} \]
\[ R^2\text{-O-}(\text{CH}_2)_2\text{-Cys-Ser(Bu')-Ser(Bu')-Asn-OBu}^i \]
\[ \text{n, o)} \]
\[ 5, 6, 7 \]
\[ R^3 = \text{Cys-Ser(Bu')-Ser(Bu')-Asn-OBu}^i \]
\[ \text{p)} \]

**Chart 2.** Synthesis of Ester Type Lipopeptide Derivatives

\[ \text{COOEt} \quad \text{CH}_2 \quad \text{4 steps} \quad \text{COOEt} \]
\[ \text{diethyl malonate} \]

\[ \text{a, b, c, d)} \]
\[ \text{HO-CH}_2\text{I} \]
\[ \text{d)} \]
\[ \text{HO-CH}_2\text{Cys-OBu}^i \]

\[ \text{e, f)} \]
\[ \text{RO-CH}_2\text{-Cys-OH} \]
\[ \text{g)} \]
\[ \text{RO-CH}_2\text{Cys-Ser(Bu')-Ser(Bu')-Asn-OBu}^i \]
\[ \text{h)} \]
\[ \text{R} = \text{CO(CH}_2)_2\text{CH}_3 \]

**Chart 3**

\[ \text{a)} \]
\[ \text{Et}_3\text{N, CH}_2\text{Cl}_2, \text{TsCl, 60% b)} \]
\[ \text{MeOH, 1N HCl, 85% c)} \]
\[ \text{Nal, acetone, 40% d)} \]
\[ \text{Troc-Cys-OBu}^i, \text{i-Pr}_2\text{NEt, DMF, 86% e)} \]
\[ \text{CH}_2\text{(CH}_2)_2\text{OCOCl, i-Pr}_2\text{NEt, CH}_2\text{Cl}_2 \]
\[ \text{DMAP, 87% f)} \]
\[ \text{TFA, 64% g)} \]
\[ \text{BOP reagent, Et}_3\text{N, H-Ser(Bu')-Ser(Bu')-Asn-OBu}^i, \text{CH}_2\text{Cl}_2, \text{56% h)} \]
\[ \text{TFA, 53% i)} \]
\[ \text{Zn, AcOH, 85% j)} \]
\[ \text{TFA, 80%} \]
The mitogenic activity of all compounds 1–12 were measured and compared with the natural lipopeptide derivative\(^{22}\) (I). The activities of 1–9 were greatly reduced, and compound 10,11 did not show activity as high as that of compound (I), while compound 12 had the same degree of activity as compound (I). These results indicate that the lipopeptide derivatives with one aliphatic chain cannot show a high activity and that glyceryl part is necessary for lipopeptide derivatives to show a higher activity.

REFERENCES AND NOTES

9) mp 164–166°C, [\(\alpha\)]\(_D\)\(^{22}\) -5.4°(c 0.36, CHCl\(_3\)), FABMS(m/z) 810(M+H)+.
10) mp 163–165°C, [\(\alpha\)]\(_D\)\(^{22}\) -8.4°(c 0.21, CHCl\(_3\)), FABMS(m/z) 952(M+H)+.
11) mp 167–169°C, [\(\alpha\)]\(_D\)\(^{22}\) -15.3°(c 0.19, MeOH), FABMS(m/z) 796(M+H)+.
12) mp 168–170°C, [\(\alpha\)]\(_D\)\(^{22}\) -3.5°(c 0.22, CHCl\(_3\); MeOH=1:1), FABMS(m/z) 936(M+H)+.
13) mp 161–164°C, [\(\alpha\)]\(_D\)\(^{22}\) -3.8°(c 0.40, CHCl\(_3\)), FABMS(m/z) 824(M+H)+.
14) mp 169–171°C, [\(\alpha\)]\(_D\)\(^{22}\) -4.2°(c 0.33, CHCl\(_3\)), FABMS(m/z) 880(M+H)+.
15) mp 170–173°C, [\(\alpha\)]\(_D\)\(^{22}\) -4.3°(c 0.32, CHCl\(_3\)), FABMS(m/z) 964(M+H)+.
16) mp 204–206°C, FABMS(m/z) 945(M+H)+.
17) mp 205–207°C, FABMS(m/z) 931(M+H)+.
18) mp 170–172°C, [\(\alpha\)]\(_D\)\(^{22}\) +10.4°(c 0.20, DMF), FABMS(m/z) 1149(M+H)+.
19) mp 238–240°C(dec), [\(\alpha\)]\(_D\)\(^{22}\) +7.0°(c 1.44, CHCl\(_3\)), FABMS(m/z) 975(M+H)+.
20) mp 192–194°C, [\(\alpha\)]\(_D\)\(^{22}\) -10.0°(c 0.32, CHCl\(_3\)), FABMS(m/z) 1135(M+H)+.
22) The detailed paper will be published elsewhere.

(Received November 27, 1992)