Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 16, pp. 1857-1860, 1995

0960-894X/95 $9.50+0.00

0960-894X(95)00304-5

2-SUBSTITUTED 2-AMINOETHANOL: MINIMUM ESSENTIAL STRUCTURE FOR IMMUNOSUPPRESSIVE ACTIVITY OF ISP-I (MYRIOCIN)

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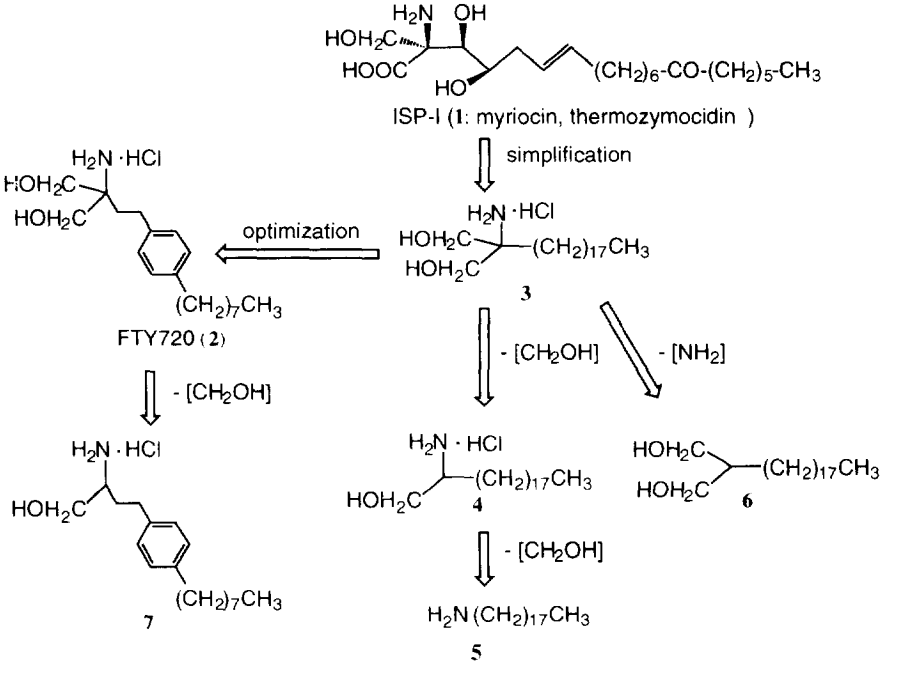
Abstruct: 2-Substituted 2-aminoethanol was shown to be the minimum essential structure for the immunosuppressive activity of ISP-I (myriocin, thermozymocidin) by simplification of 2-substituted 2-amino-1,3-propanediol, which was generated by modification of ISP-I. Among the series, 2-amino-4-(4-octylphenyl)butanol hydrochloride displayed comparably potent activity to 2-amino-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol hydrochloride, FTY720.

We isolated the immunosuppressant ISP-I[1] (**1**: myriocin[2], thermozymocidin[3]) from the culture broth of *Isaria sinclairii* (ATCC 24400). The structure-activity relationships of ISP-I derivatives[4] and mycestericins[5], which were isolated from an ISP-I-producing strain, *Mycelia sterilia* (ATCC 20349), showed that the 2-substituted 2-amino-1,3-propanediol[6] structure was the key basic structure for potent immunosuppressive activity. Furthermore, modification of the hydrophobic part indicated that the 2-(4-octylphenyl)ethyl group was optimum, affording the potent immunosuppressant, FTY720 (**2**)[7]. However, modification of the hydrophilic part had not been examined. In this paper, we report that further examination of the hydrophilic part in the 2-substituted 2-amino-1,3-propanediol led to the identificatin of 2-substituted 2-aminoethanol as the minimum basic structure for the biological activity.

Synthesis: Racemic compounds **4**[8] and **7**[9] were synthesized from 2-substituted diethyl 2-acetamidemalonates, octadecyl[6] and 2-(4-octylphenyl)ethyl[7] derivatives, respectively, by the following three-step sequence: (1) decarboxylation in refluxing 5 N hydrochloric acid, (2) esterification of the resulting amino acids with methanol and thionyl chloride, and (3) reduction of these corresponding methylesters with sodium borohydride in methanol. The diol **6**[10] was synthesized from diethyl malonate and octadecyl bromide in the usual manner[11].

Results and discussion: Compounds lacking the amino and the hydroxymethyl groups of 2-amino-2-octadecyl-1,3-propanediol hydrochloride (**3**), but having the same carbon skeleton as **1**, were synthesized (Scheme 1). The immunosuppressive activity (Table 1) was followed by measuring the IC_{50} value on the mouse allogeneic mixed lymphocyte reaction (MLR)[1b].



Scheme 1. Simplification of 2-substituted 2-amino-1,3-propanediol

Table 1. Effect of **1**-**7** on mouse allogeneic MLR

compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**
IC_{50} (nM)	8.0	6.1	12	140	>10000	>10000	11

The dehydroxymethyl derivative **4** of compound **3** retained weak activity, but stearyl amine **5** lacked the activity. The deamino derivative **6** of compound **3** was inactive. Consequently, among the simplified compounds, 2-amino-1-eicosanol hydrochloride (**4**) was the simplest compound having the biological activity.

These results imply that the 2-substituted 2-aminoethanol skeleton is the minimum key structure for the immunosuppressive activity of **1**. The amino alcohol, 2-amino-4-(4-octylphenyl)butanol hydrochloride (**7**), showed similar activity to those of **1** and **2** on the mouse allogeneic MLR. The 2-substituted 2-aminoethanol structure is simpler than the 2-substituted 2-amino-1,3-propanediol structure, and resembles the structure of sphingosine, the biosynthesis of which is inhibited by **1**[12]. However, **2** was no inhibitor of sphingosine biosynthesis according to our unpublished work. It is suggested that the immunosuppressive activities of **2** and **7** are caused by inhibition on the level of sphingosine acyltransferase.

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9. White powder: mp 93-95℃; IR (KBr): 3400, 2930, 2860, 1580, 1500, 1470, 1060, 820cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.85 (t, 3H, J = 6.8Hz), 1.24 (m, 10H), 1.53 (m, 2H), 1.81 (dt, 2H, J = 6.8, 15.8Hz), 2.51 (m, 2H), 2.63 (t, 2H, J = 8.4Hz), 3.02 (m, 1H), 3.51 (m, 1H), 3.62 (m, 1H), 5.34 (t, 1H, J = 4.9Hz), 7.11 (s, 4H), 8.08 (brs, 3H); HRMS (FAB, positive mode) *m/z*: calcd for $C_{18}H_{32}NO$ 278.2486, found 278.2481; *Anal.* calcd for $C_{18}H_{32}NOCl$ C, 68.87; H, 10.27; N, 4.46, found C, 68.76; H, 10.23; N, 4.48.
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(*Received in Japan* 26 *June* 1995; *accepted* 11 *July* 1995)