STRUCTURE ACTIVITY RELATIONSHIPS OF SYNTHETIC ANTIBIOTIC ANALOGUES OF CHRYSCANDIN

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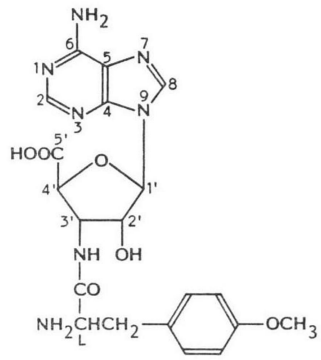
Anti-yeast activity with a series of chryscandin derivatives showed that the *O*-methyl-L-tyrosyl moiety is not always required for activity at the target site. On the other hand, the adenyl-3′-aminoribofuranuronic acid moiety seems to be essential for biological activity. Therefore, the various acyl derivatives on the amino group of the sugar part of the nucleoside were synthesized. 1-(6-Amino-9*H*-purin-9-yl)-3-(*S*-benzyl-L-cysteinylamino)-1,3-dideoxy-β-D-ribofuranuronic acid (**16**) showed the highest efficacy among them against *Candida albicans*. It exhibited sixteen-fold enhanced activity *in vitro* compared with that of native chryscandin. The *in vivo* activity of **16** against experimental infection of *C. albicans* showed the almost same as that of 5-fluorocytosine and a superior to that of ketoconazole.

Chryscandin is a peptidyl nucleoside antibiotic (Fig. 1), isolated from a strain of fungi *Chrysosporium pannorum*[1], and inhibited the growth of *Candida albicans*. The chemical structure and total synthesis of the antibiotic have been elucidated[2,3,4]. Concerning the chemical structure, chryscandin resembles puromycin[5], the biological properties, however, differ from those of puromycin[6,7]. That is, the former possesses an activity against *Candida* and has a low toxicity, whereas the latter shows an activity against only bacteria and shows a fairly high toxicity. Therefore, numerous puromycin analogues have been synthesized by a large number of investigators in order to lower its toxicity and to enhance biological activities such as antibacterial[8], anti-trypanosoma[9~12] and antitumor activities[13~18]. Whereas, as an extension of our studies to synthesize a new chryscandin analogue which shows high inhibitory effect on *Candida*, we tried to make more modifications of chryscandin by introducing a variety of substituents at 5′ position of chryscandin and/or by replacing an R group in the 3′-aminoacyl side chain of chryscandin.

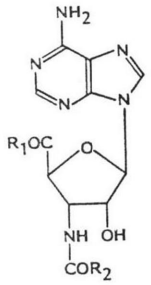
Fig. 1. Structure of chryscandin.



Chemistry

Chryscandin is composed of three parts, a base (adenine), a sugar (aminoribofuranuronic acid) and an amino acid (*O*-methyl-L-tyrosine). First of all, therefore, it is considered important to grasp their effects on the anti-yeast activity: (1) With regard to the adenine base, when either the adenine was exchanged for a uracil (**92** and **93**) or the primary amino group located on adenine was substituted by

Table 1. The 3′ and/or 5′ substituted chryscandin derivatives.



Compound	R_1	R_2	Method	Deprotection method	MP (°C, dec)
1 (Chryscandin)	OH	*p*-CH_3O-C_6H_4-CH_2-$^{L}CHNH_2$	1	A, B	215~230
2	OH	$C_6H_5CH_2$-$^{L}CHNH_2$	1	A, B	194~196
3	OH	C_6H_5-$^{DL}CH(NH_2)$-CH_2-	1	A, B	206~207
4	OH	C_6H_5-$^{DL,\ erythro}CH(OCH_3)$-$CHNH_2$	1	A, C	185~190
5	OH	CH_3-$^{L}CHNH_2$	1	A, B	150~155
6	OH	$NH_2(CH_2)_2$-	1	A, B	202~205
7	OH	$C_6H_5CH_2$-$^{D}CHNH_2$	1	A, B	203~205
8	OH	C_6H_5-$^{DL}CHNH_2$	1	A, C	197~205
9	OH	*p*-F-C_6H_4-CH_2-$^{DL}CHNH_2$	1	A, C	120~130
10	OH	$NH_2(CH_2)_4$-$^{L}CHNH_2$	1	A, B	165~172
11	OH	*p*-CH_3O-C_6H_4-CH_2-$^{L}CHNHCOCH_2NH_2$	1	A, C	194~197
12	OH	$C_6H_5CH_2$-$^{L}CHNHCHO$	1	A	169~181
13	OH	C_6H_5-$^{D}CHOH$	5	A	ND
14	OH	$C_6H_5SCH_2$-$^{DL}CHNH_2$	3	C	161~166
15	OH	$C_6H_5SSCH_2$-$^{L}CHNH_2$	3	C	189~195
16	OH	$C_6H_5CH_2SCH_2$-$^{L}CHNH_2$	2	C, E	178~180

Table 1. (Continued)

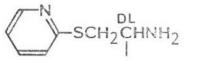
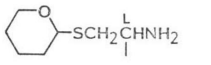
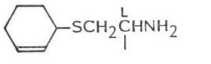
Compound	R_1	R_2	Method	Deprotection method	MP (°C, dec)
17	OH	$CH_2=CHCH_2SCH_2\overset{L}{C}HNH_2$	2	D, E	185~195
18	OH	$CH\equiv CCH_2SCH_2\overset{L}{C}HNH_2$	2	D, E	195~205
19	OH	$C_6H_5CH=CHCH_2SCH_2\overset{L}{C}HNH_2$	2	D, E	170~178
20	OH	$CH_3CONHCH_2SCH_2\overset{L}{C}HNH_2$	2	D, E	180~190
21	OH	p-CH_3-C_6H_4-$CH_2SCH_2\overset{L}{C}HNH_2$	2	D, E	185~193
22	OH	p-Cl-C_6H_4-$CH_2SCH_2\overset{L}{C}HNH_2$	2	D, E	193~197
23	OH	o-Cl-C_6H_4-$CH_2SCH_2\overset{L}{C}HNH_2$	2	D, E	180~182
24	OH	$NH_2CH_2CH_2SCH_2\overset{L}{C}HNH_2$	2	D, E	ND
25	OH		2	D, E	194~198
26	OH		2	D, E	187~192
27	OH		2	D, E	160~165
28	OH		2	D, E	161~169
29	OH		2	D, E	202~204
30	OH		2	D, E	173~176
31	OH	p-CH_3O-C_6H_4-$CH_2SCH_2\overset{L}{C}HNH_2$	2	D, E	190~195
32	OH	$C_2H_5SCH_2CH_2\overset{DL}{C}HNH_2$	2	C, E	182~184
33	OH		2	C, E	180~190
34	OH	$(CH_3)_2CHSCH_2CH_2\overset{L}{C}HNH_2$	2	C, E	175~178
35	OH	$(C_6H_5)_3CSCH_2\overset{L}{C}HNH_2$	2	C, E	175~182
36	OH	$CH_2=CHCH_2SCH_2CH_2\overset{L}{C}HNH_2$	2	C, E	114~121

Table 1. (Continued)

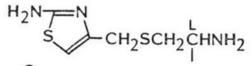
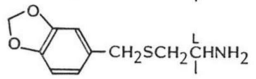
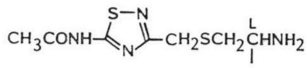
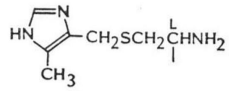
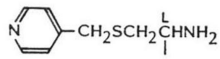
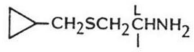
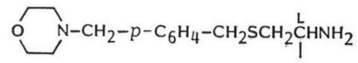
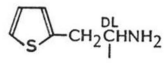
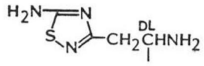
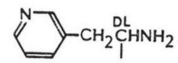
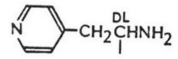
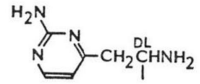
Compound	R_1	R_2	Method	Deprotection method	MP (°C, dec)
37	OH	$CH_3SCH_2CH_2CH_2\overset{DL}{C}HNH_2$	2	C, E	152~163
38	OH		2	C, E	108~114
39	OH		2	D, E	165~170
40	OH	p-$(CH_3)_2N$-C_6H_4-$CH_2SCH_2\overset{L}{C}HNH_2$	2	D, E	131~136
41	OH	p-HO-C_6H_4-$CH_2SCH_2\overset{L}{C}HNH_2$	2	D, E	140~150
42	OH	$HOOCCH_2SCH_2\overset{L}{C}HNH_2$	2	D, E	90~100
43	OH	$C_6H_5\overset{DL}{C}HSCH_2\overset{L}{C}HNH_2$ (CH$_3$)	2	C, E	151~158
44	OH	$CH_3SCH_2CH_2\overset{L}{C}HNH_2$ (O)	2	C, E	109~122
45	OH		2	C, E	202~207
46	OH		2	C, E	202~209
47	OH		2	C, E	181~187
48	OH		3	C	92~101
49	OH		3	C	106~114
50	OH		2	C, E	170~180
51	OH		2	C, E	221~228
52	OH		2	C, E	207~210
53	OH		2	C, E	214~221
54	OH		2	C, E	108~114

Table 1. (Continued)

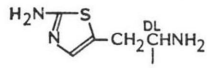
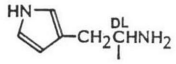
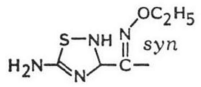
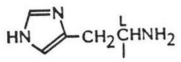
Compound	R_1	R_2	Method	Deprotection method	MP (°C, dec)
55	OH		2	C, E	106~112
56	OH		2	C, E	140~150
57	OH	H_2N, HN, $CNH(CH_2)_3{}^{L}CHNH_2$	2	C, E	215~219
58	OH	$C_6H_5CH_2{}^{D}CHNH_2$	1	A, B	203~204
59	OH	*o*-Cl–C_6H_4–$CH_2{}^{DL}CHNH_2$	2	D, E	160~170
60	OH	*p*-Cl–C_6H_4–$CH_2{}^{DL}CHNH_2$	2	D, E	170~178
61	OH	*m*-Cl–C_6H_4–$CH_2{}^{DL}CHNH_2$	2	D, E	165~170
62	OH	*p*-NO_2–C_6H_4–$CH_2{}^{DL}CHNH_2$	2	D, E	195~205
63	OH	*p*-CH_3O–C_6H_4–$CH_2{}^{L}CH$– $NHCO{}^{L}CH(CH_2)_3NHC(NH_2)=NH$ NH_2	2	C, E	194~200
64	OH	*p*-CH_3O–C_6H_4–$CH_2{}^{L}CH$– $NHCO{}^{D}CHCH_2C_6H_5$ NH_2	2	C, E	175~182
65	OH	*p*-CH_3O–C_6H_4–$CH_2{}^{L}CH$– $NHCO{}^{L}CHCH_2$–C_6H_4–*p*-OCH_3 NH_2	2	C, E	175~177
66	OH	*p*-$HOOCCH_2O$–C_6H_4–$CH_2{}^{L}CHNH_2$	3	C, E	209~212
67	OH	*p*-$NH_2(CH_2)_3O$–C_6H_4–$CH_2{}^{L}CHNH_2$	3	C, E	150~160
68	$NHNH_2$	*p*-CH_3O–C_6H_4–$CH_2{}^{L}CHNHCONHNH_2$	7		152~158
69	$NHNH_2$	*p*-CH_3O–C_6H_4–$CH_2{}^{L}CHNH_2$	7		131~140
70	$NHBu^n$	*p*-CH_3O–C_6H_4–$CH_2{}^{L}CHNHCONHBu^n$	7		111~115
71	$NHCH_2$-COOH	*p*-CH_3O–C_6H_4–$CH_2{}^{L}CHNH_2$	6	A, B	194~196
72	OH	$C_6H_5CH_2$–	4	A	159~165

Table 1. (Continued)

Compound	R_1	R_2	Method	Deprotection method	MP (°C, dec)
73	OH	$C_6H_5CH_2CH_2-$	4	A	191~197
74	OH	C_6H_5-	4	A	237~239
75	OH	$C_6H_5CH=CH-$	4	A	179~185
76	OH		4	A	86~94
77	OH	$CH_3SCH_2\overset{L}{C}HNH_2$ |	3	C, E	187~192
78	OH	$CH_3SCH_2\overset{D}{C}HNH_2$ |	3	C, E	182~186
79	OH	$CH_3SCH_2CH_2\overset{L}{C}HNH_2$ |	3	C, E	191~196
80	OH		3	E	117~124
81	OH		3	D	175~180
82	OH	$CH_3\overset{O}{\overset{\uparrow}{S}}CH_2\overset{L}{C}HNH_2$ |	3	C, E	125~142
83	OH	$CH_3\overset{O}{\overset{\uparrow}{S}}CH_2\overset{L}{C}HNH_2$ | $\underset{O}{\downarrow}$	3	C	156~162
84	OH	$ClCH=\underset{Cl}{C}CH_2SCH_2\overset{L}{C}HNH_2$ | |	3	C	189~190

an *N*-methyl amino, *N*,*N*-dimethyl amino, hydroxyl and methoxy, respectively, no activity was found in any case (**94~97**). Therefore, adenine nucleus seemed to be an essential moiety. (2) Amidation of the carboxyl group (**68~71** and **85~91**) or etherification of the hydroxyl group (**98** and **99**) on the aminoribofuranuronic acid resulted in little activity against *Candida*. These facts show that these particular functional groups play an important role in its biological activity. (3) Subsequently, it was observed that the anti-yeast property was completely destroyed by removing the aminoacyl side chain of chryscandin with alkaline solution. However, its biological activity was regenerated by introducing another acyl group, which resulted in more potent activity than native chryscandin in some cases (**16~19**, **21~23**, **25**, **26**, **29**, **31**, **39~41**, **47** and **77**). It is suggested that the *O*-methyl-L-tyrosyl moiety is not required for activity at the target site, but it probably effects penetration. Thus, our efforts were mainly directed at elucidating the effects of the acyl group of adenyl-3′-acyl aminoribofuranuronic acid (Tables 1~3).

The starting material, 3-amino-1-(6-benzoylamino-9*H*-purin-9-yl)-1,3-dideoxy-β-D-ribofuranuronic acid (**I**) (Fig. 2), of the series was prepared as previously reported[3,4] from D-xylose and N^6-benzoyladenine in nine steps. Condensation of **I** with an active ester of the *N*-protected amino acid, in the

Table 2. The 3′ and 5′ substituted *S*-benzyl-L-cysteine derivatives.

Compound	R_1 (5′)	R_2 (3′)	Method	Deprotection method	MP (°C, dec)
85	$-NH\overset{DL}{C}HPO(OH)_2$ (CH$_3$)	$C_6H_5CH_2SCH_2\overset{L}{C}HNH_2$	8	C	113~118
86	$-NHCH_2COOH$	$C_6H_5CH_2SCH_2\overset{L}{C}HNH_2$	6	A, B	164~169
87	$-NHCH_2CH_2PO(OC_2H_5)_2$	$C_6H_5CH_2SCH_2\overset{L}{C}HNH_2$	8	C	155~168
88	$-NHCH_2CH_2PO(OH)_2$	$C_6H_5CH_2SCH_2\overset{L}{C}HNH_2$	8	C	98~106
89	$-NHOH$	$C_6H_5CH_2SCH_2\overset{L}{C}HNH_2$	8	C	223~231
90	$-NHCH_2CH_2SO_3H$	$C_6H_5CH_2SCH_2\overset{L}{C}HNH_2$	8	C	110~115
91	$-NH(CH_2)_3\overset{L}{C}HCOOH$ (NH_2)	$C_6H_5CH_2SCH_2\overset{L}{C}HNH_2$	6	A, B	160~170

Table 3. Miscellaneous derivatives of chryscandin.

Compound	2′	3′	Base
92	OH	p-CH_3O-C_6H_4-$CH_2\overset{L}{C}HNH_2$	Uracil
93	OH	$C_6H_5CH_2\overset{L}{C}HNH_2$	Uracil
94	OH	p-CH_3O-C_6H_4-$CH_2\overset{L}{C}HNH_2$	Adenine-6-N(CH_3)(CH_3)
95	OH	p-CH_3O-C_6H_4-$CH_2\overset{L}{C}HNH_2$	Adenine-6-OH
96	OH	p-CH_3O-C_6H_4-$CH_2\overset{L}{C}HNH_2$	Adenine-6-$NHCH_3$
97	OH	p-CH_3O-C_6H_4-$CH_2\overset{L}{C}HNH_2$	Adenine-6-OCH_3
98	OCH_3	$CH_3SCH_2\overset{L}{C}HNH_2$	Adenine-6-NH_2
99	OCH_3	p-CH_3O-C_6H_4-$CH_2\overset{L}{C}HNH_2$	Adenine-6-NH_2

presence of triethylamine, produced **1**~**12** and **58** (Method 1). In order to protect the amino group benzyloxycarbonyl (Z) or *tert*-butoxycarbonyl (*t*-Boc) and, for activation of carboxylic acid, *N*-hydroxysuccinimide (HOSu) were used in the conventional manner. These protective groups were removed by the usual methods as shown in the Experimental section and Fig. 4. *N*,*N*′-Dicyclohexylcarbodiimide (DCC) was applied to the condensation of methyl (or ethyl)-1-(6-amino-9*H*-purin-9-yl)-

Fig. 2. Synthesis of adenyl-3′-aminoacylribofuranuronic acids and its esters.

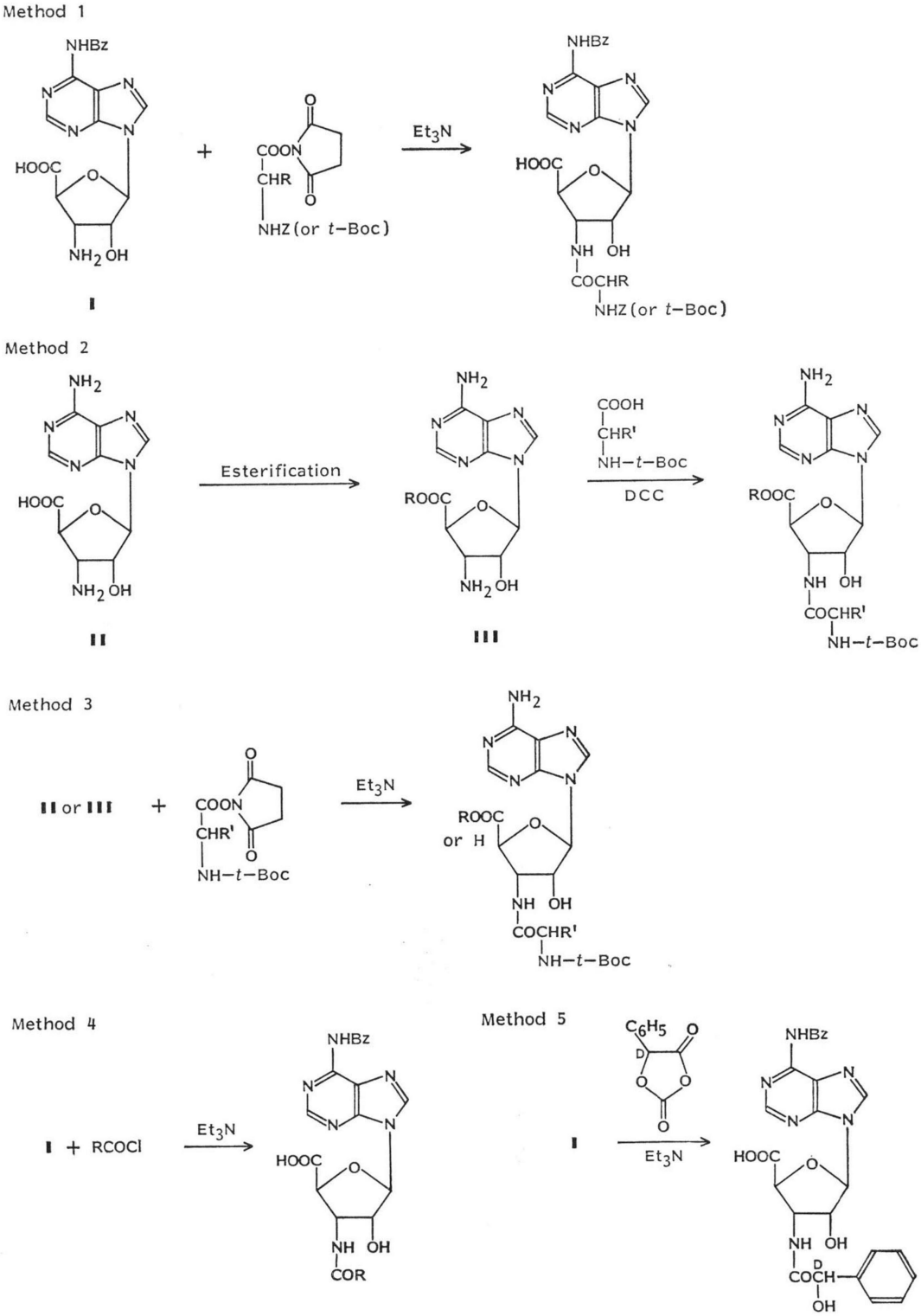
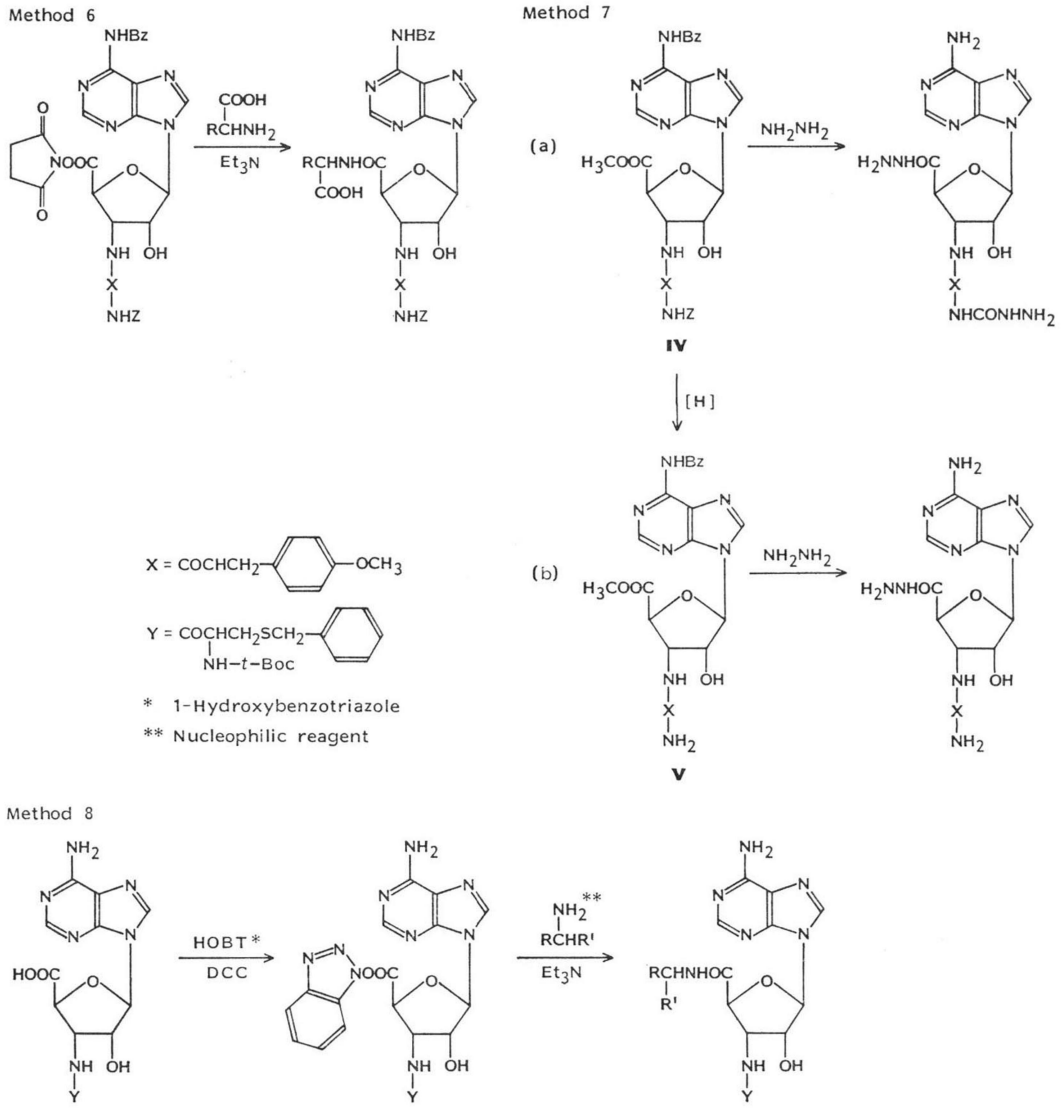


Fig. 3. Synthesis of 5′-substituted chryscandin and 5′-substituted *S*-benzylcysteine.



1,3-dideoxy-β-D-ribofuranuronate (**III**) with an *N*-*t*-Boc protected amino acid (**16**～**47**, **50**～**57** and **59**～**65**) (Method 2). Afterwards, it was found that **II** (free) or **III** (ester) was directly condensed with an active ester of *N*-*t*-Boc amino acid, in a good yield (**14**, **15**, **48**, **49**, **66**, **67** and **77**～**84**) (Method 3). Acylation of **I** with acyl chloride was carried out with **72**～**76** (Method 4). Compound **13** possessing a hydroxyl group was prepared by reacting **I** with 2,4-dioxo-5-phenyl-1,3-dioxolane, prepared from D-mandelic acid and phosgene, according to a similar manner to that of Method 1 (Method 5). Both reactions of an amino acid with an active ester of chryscandin in the presence of triethylamine and hydrazine with methylester of chryscandin led to a 5′-substituted chryscandin, respectively (**71**, **86** and **91**, and **68**～**70**) (Methods 6 and 7, respectively). For a 5′-substituted *S*-benzylcysteine, derivative of **16**, its active ester was also used with some nucleophilic reagents (**85** and **87**～**90**) (Method 8) (Fig. 3). The structure of the resulting acylamino derivatives was confirmed by IR and ^{1}H NMR as

Table 4. IR and ^{1}H NMR data of 3′ and/or 5′ substituted chryscandin.

Compound	IR (Nujol) (cm^{-1})	^{1}H NMR (δ)
1 (Chryscandin)[1~4]		
2	3300, 3175, 1640, 1600, 1400, 1325, 1300, 1245, 1210, 1170, 1075	(DCl+D_2O) 3.24 (2H, m), 6.21 (1H, d, J=2 Hz), 7.34 (5H, s), 8.41 (1H, s), 8.58 (1H, s)
3	3700~3000, 1640, 1600, 1415, 1330, 1300, 1240, 1210, 1075	(DCl+D_2O) 3.19 (2H, m), 6.25 (1H, m), 7.45 (5H, s), 8.42 (1H, s), 8.59 (1H, s)
4	3300, 3170, 1640, 1600, 1090, 1070	(DMSO-d_6+D_2O) 3.13 (3H, s), 3.5 (1H, m), 3.9~4.1 (1H, m), 4.1~4.7 (3H, m), 6.1 (1H, m), 7.27 (5H, s), 8.12 (1H, s), 8.89 (1H, br s)
5	3400~3100, 1650, 1600, 1580, 1560	(DCl+D_2O) 1.63 (3H, d, J=7 Hz), 4.36 (1H, q, J=7 Hz), 4.7~5.4 (3H, m), 6.49 (1H, d, J=2 Hz), 8.63 (1H, s), 9.22 (1H, s)
6	3400~3150, 1660, 1640, 1605, 1580, 1550	(DCl+D_2O) 2.62 (2H, t, J=7 Hz), 3.33 (2H, t, J=7 Hz), 6.34 (1H, d, J=2 Hz), 8.47 (1H, s), 8.67 (1H, s)
7	3325, 3175, 1640, 1600, 1330, 1245, 1210, 1175, 1110, 1075	(DCl+D_2O) 3.25 (2H, d), 6.25 (1H, m), 7.32 (5H, s), 8.46 (1H, s), 8.61 (1H, s)
8	3300, 3200, 1635, 1595, 1070	(DMSO-d_6+D_2O) 4.1~4.7 (3H, m), 4.8 (1H, m), 6.1 (1H, m), 7.1~7.6 (5H, m), 8.10 (1H, s), 8.77 and 8.82 (1H, s)
9	3300, 3200, 1640, 1600, 1510, 1300, 1220, 1075	(DMSO-d_6+D_2O) 2.7~3.1 (2H, m), 3.6~4.1 (1H, m), 4.1~4.3 (1H, m), 4.3~4.6 (2H, m), 6.1 (1H, m), 6.8~7.5 (4H, m), 8.13 (1H, s), 9.10 (1H, s)
10	3300, 3150, 3050, 1640, 1600	(DMSO-d_6+D_2O) 1.1~1.9 (6H, m), 2.5~2.9 (2H, m), 3.3~3.9 (1H, m), 4.1~4.7 (3H, m), 6.0 (1H, m), 8.17 (1H, s), 9.10 (1H, s)
11	3300, 3180, 1650, 1605, 1510, 1300, 1245, 1210, 1180, 1110, 1080	(DMSO-d_6+D_2O) 2.69~2.99 (2H, m), 3.41 (2H, m), 3.70 (3H, s), 4.16~4.72 (4H, m), 6.09 (1H, m), 6.72~6.88 (2H, m), 7.02~7.24 (2H, m), 8.16 (1H, s), 9.14 (1H, m)
12	3350, 3250, 1685, 1650, 1500, 1220, 1090	(DMSO-d_6+D_2O) 2.92~3.24 (2H, m), 3.84~4.95 (4H, m), 6.05 (1H, m), 7.19 (5H, s), 7.84 (1H, m), 8.14 (1H, m), 8.36 (1H, m)
13	3700~3000, 1690, 1650, 1600, 1525, 1410, 1300, 1210, 1080~1060	(DMSO-d_6) 4.37~4.77 (4H, m), 5.00 (1H, m), 6.09 (1H, d, J=1.5 Hz), 6.23~6.53 (1H, m), 7.32 (7H, m), 8.12 (1H, s), 8.40 (1H, s)
14	3300, 3200, 1640, 1600, 1400, 1330, 1300, 1250, 1210	(DMSO-d_6+D_2O) 3.0~3.5 (2H, m), 3.5~4.0 (1H, m), 4.1~4.8 (3H, m), 6.10 (1H, m), 7.1~7.6 (5H, m), 8.20 (1H, s)
15	3320, 3160, 3050, 1680, 1635, 1596, 1327, 1300, 1245, 1210	(DMSO-d_6+D_2O) 2.97 (2H, m), 4.26~4.93 (4H, m), 6.08 (1H, m), 7.39 (5H, m), 8.13 (1H, s), 8.77 (1H, m)
16	3450, 3330, 3200, 3050, 2700, 2250, 1690, 1660, 1640, 1600	(DCl+D_2O) 3.05 (2H, d, J=6 Hz), 3.90 (2H, s), 4.7~5.5 (4H, m), 6.40 (1H, d, J=2 Hz), 7.46 (5H, s), 8.55 (1H, s), 8.75 (1H, s)
17	3350, 3200, 2750, 2320, 1690, 1660, 1640, 1600, 1575	(DCl+D_2O) 3.12 (2H, d, J=6 Hz), 3.43 (2H, d, J=7 Hz), 4.38 (1H, t, J=7 Hz), 4.8~6.2 (6H, m), 6.42 (1H, d, J=2 Hz), 8.53 (1H, s), 8.70 (1H, s)
18	3350, 3170, 2700, 2350, 1690, 1660, 1640, 1600, 1570	(DCl+D_2O) 2.80 (1H, t, J=3 Hz), 3.2~3.6 (3H, m), 4.47 (1H, t, J=6 Hz), 4.6~5.5 (3H, m), 6.38 (1H, d, J=2 Hz), 8.50 (1H, s), 8.65 (1H, s)
19	3350~3000, 1690, 1640, 1600, 1580, 1540, 1400, 1250	(DMSO-d_6) 2.7~3.0 (2H, m), 3.26~3.6 (2H, m), 3.6~4.0 (1H, m), 4.2~4.4 (2H, m), 4.4~4.7 (2H, m), 5.9~6.7 (2H, m), 6.07 (1H, m), 7.0~7.5 (5H, m), 8.07 (1H, m), 8.83 (1H, s)

Table 4. (Continued)

Compound	IR (Nujol) (cm^{-1})	^1H NMR (δ)
20	3300, 3160, 2700, 2300, 1690, 1660, 1600, 1570	(DMSO-d_6) 1.83 (3H, s), 2.90 (2H, m), 3.7~4.8 (6H, m), 6.03 (1H, m), 8.05 (1H, s), 8.73 (1H, s)
21	3320, 3200, 3100, 2700, 2250, 1685, 1640, 1600, 1570	(DMSO-d_6+D_2O) 2.28 (3H, s), 2.80 (2H, m), 3.77 (2H, s), 4.0~4.8 (4H, m), 6.12 (1H, m), 7.16 (4H, s), 8.16 (1H, s), 8.82 (1H, s)
22	3320, 3200, 2700, 2300, 1690, 1655, 1640, 1600, 1570	(DMSO-d_6+D_2O) 2.75 (2H, m), 3.75 (2H, s), 4.0~4.8 (4H, m), 6.05 (1H, m), 7.27 (4H, s), 8.05 (1H, s), 8.68 (1H, s)
23	3450, 3300, 3200, 2700, 2250, 1690, 1650, 1600, 1575	(DMSO-d_6+D_2O) 2.88 (2H, m), 3.85 (2H, s), 4.1~4.8 (4H, m), 6.10 (1H, d, J=2 Hz), 7.0~7.6 (4H, m), 8.10 (1H, s), 8.75 (1H, s)
24	3300, 3200, 1640, 1590, 1330, 1300, 1250	(DMSO-d_6+D_2O) 2.6~3.3 (6H, m), 3.6~4.1 (1H, m), 4.1~4.6 (3H, m), 6.01 (1H, s), 8.17 (1H, s), 9.12 (1H, s)
25	3300, 3150, 3100, 1660, 1610, 1580, 1420, 1320, 1270, 1240	(DMSO-d_6+D_2O) 2.8~3.2 (2H, m), 3.7~4.0 (1H, m), 4.08 (2H, s), 4.3~4.8 (3H, m), 6.10 (1H, m), 6.8~7.1 (2H, m), 7.3~7.5 (1H, m), 8.18 (1H, s), 8.87 (1H, s)
26	3300, 3150, 3100, 1700, 1660, 1610, 1580, 1330, 1310, 1280, 1240	(DMSO-d_6+D_2O) 2.6~3.0 (2H, m), 3.6~4.1 (1H, m), 4.83 (2H, s), 4.2~4.7 (3H, m), 6.10 (1H, m), 6.3 (2H, m), 7.5 (1H, m), 8.10 (1H, s), 8.75 (1H, s)
27	3300, 3200, 1690~1550, 1410, 1330, 1250, 1210	(DMSO-d_6+D_2O) 3.1~3.7 (2H, m), 3.7~4.2 (1H, m), 4.2~4.5 (1H, m), 4.5~4.7 (2H, m), 6.10 (1H, m), 7.6~7.9 (3H, m), 8.13 (1H, s), 8.4~8.5 (1H, m), 8.8~8.9 (1H, m)
28	3320, 3180, 1640, 1595, 1300, 1245, 1205	(DMSO-d_6+D_2O) 2.92 (2H, m), 3.92 (2H, s), 4.32~4.78 (4H, m), 6.13 (1H, d, J=1 Hz), 7.11~7.53 (2H, m), 7.67 (2H, m), 8.16 (1H, s), 8.49 (1H, m), 8.87 (1H, s)
29	3320, 3170, 3050, 1680, 1650, 1595, 1570, 1420, 1324, 1307, 1205	(DMSO-d_6+D_2O) 2.85 (2H, m), 3.83 (2H, s), 4.27~4.72 (4H, m), 6.15 (1H, d, J=1.5 Hz), 7.32 (1H, m), 7.78 (1H, m), 8.16 (1H, s), 8.50 (2H, m), 8.81 (1H, s)
30	3300, 3200, 1640, 1600, 1330, 1300, 1250, 1210	(DMSO-d_6+D_2O) 1.2~2.0 (6H, m), 2.7~3.2 (2H, m), 3.5~4.0 (1H, m), 4.2~4.7 (3H, m), 4.8~5.0 (1H, m), 6.10 (1H, m), 8.12 (1H, s), 8.87 (1H, s)
31	3320, 3200, 3150, 2700, 2300, 1690, 1680, 1660, 1640, 1610, 1580	(DMSO-d_6+D_2O) 2.90 (2H, m), 3.76 (3H, s), 3.83 (2H, s), 4.0~4.9 (4H, m), 6.17 (1H, d, J=2 Hz), 6.90 (2H, d, J=8 Hz), 7.30 (2H, d, J=8 Hz), 8.20 (1H, s), 8.55 (1H, s)
32	3300, 3200, 1640, 1600, 1330, 1300, 1250	(DMSO-d_6+D_2O) 1.17 (3H, t, J=7 Hz), 1.7~2.3 (2H, m), 2.3~3.0 (4H, m), 3.6~4.0 (1H, m), 4.2~4.4 (1H, m), 4.4~4.7 (2H, m), 6.0~6.2 (1H, m), 8.16 (1H, s), 8.32 and 8.36 (1H, s)
33	3300, 3200, 1700, 1660, 1600, 1570, 1420	(DMSO-d_6+D_2O) 1.5~2.2 (6H, m), 2.7~3.1 (2H, m), 3.4~4.0 (4H, m), 4.2~4.6 (1H, m), 4.6~4.9 (2H, m), 5.7~5.9 (2H, m), 6.2 (1H, m), 8.22 (1H, s), 8.83 (1H, s)
34	3300, 3200, 1640, 1590, 1330, 1300, 1250	(DMSO-d_6+D_2O) 1.18 (6H, d, J=7 Hz), 1.7~2.3 (2H, m), 2.4~2.8 (2H, m), 2.8~3.1 (1H, m), 3.4~3.9 (1H, m), 4.1~4.4 (1H, m), 4.4~4.7 (2H, m), 6.10 (1H, m), 8.17 (1H, s), 9.02 (1H, m)
35	3300, 3200, 1640, 1600, 1330, 1240, 1210	(DMSO-d_6+D_2O) 2.3~2.7 (2H, m), 3.3~3.7 (1H, m), 4.2~4.5 (1H, m), 4.5~4.8 (2H, m), 6.2 (1H, m), 7.0~7.6 (15H, m), 8.20 (1H, s), 8.77 (1H, s)

Table 4. (Continued)

Compound	IR (Nujol) (cm^{-1})	^1H NMR (δ)
36	3320, 3170, 1615, 1595, 1330, 1300, 1245, 1210	(DMSO-d_6+D_2O) 1.95 (2H, m), 3.13 (2H, d, J=7 Hz), 4.3~4.7 (4H, m), 4.9~5.3 (2H, m), 5.4~6.0 (1H, m), 6.12 (1H, m), 8.15 (1H, s), 9.05 (1H, s)
37	3320, 3180, 1635, 1600, 1300, 1245, 1205	(DMSO-d_6+D_2O) 1.75 (4H, m), 1.95 (3H, s), 2.40 (2H, m), 4.2~4.7 (4H, m), 6.08 (1H, m), 8.11 (1H, s), 8.98 (1H, s)
38	3300, 3150, 1630, 1595, 1515, 1330, 1300, 1240, 1210	(DMSO-d_6+D_2O) 2.7~3.1 (2H, m), 3.58 (2H, m), 4.2~4.6 (4H, m), 6.03 (1H, d, J=2 Hz), 6.33 (1H, s), 8.12 (1H, s), 9.24 (1H, s)
39	3570, 3430, 3300, 3200, 1685, 1660, 1605, 1580	(DMSO-d_6+D_2O) 3.00 (2H, m), 3.80 (2H, s), 4.20~5.10 (4H, m), 6.03 (2H, s), 6.22 (1H, d, J=2 Hz), 6.80~7.10 (3H, m), 8.17 (1H, s), 9.03 (1H, s)
40	3600, 3500, 3340, 3200, 1690, 1680, 1660, 1615, 1590	(DCl+D_2O) 3.03 (2H, d, J=6 Hz), 3.28 (6H, s), 3.93 (2H, s), 4.15~5.20 (4H, m), 6.33 (1H, d, J=2 Hz), 7.60 (4H, s), 8.45 (1H, s), 8.63 (1H, s)
41	3350, 3150, 3100, 1730, 1675, 1595	(DMSO-d_6+D_2O) 3.00 (2H, m), 3.87 (2H, s), 4.20~5.15 (4H, m), 6.27 (1H, m), 6.85 (2H, d, J=8 Hz), 7.30 (2H, d, J=8 Hz), 8.30 (1H, s), 9.08 (1H, s)
42	3300, 3180, 1690, 1660, 1640, 1600, 1570	(D_2O) 3.20 (2H, m), 3.40 (2H, s), 4.05~5.20 (4H, m), 6.17 (1H, m), 8.10 (1H, s), 8.62 (1H, s)
43	3300, 3180, 1635, 1600, 1330, 1300, 1245, 1210	(DMSO-d_6+D_2O) 1.41 (3H, d, J=7 Hz), 2.67 (2H, m), 4.06 (1H, q, J=7 Hz), 4.2~4.7 (4H, m), 6.07 (1H, m), 7.15 (5H, m), 8.08 (1H, s), 8.71 (1H, s)
44	3330, 3150, 1640, 1595, 1300, 1243, 1207	(DMSO-d_6+D_2O) 2.00 (2H, m), 2.83 (2H, m), 4.15~4.55 (4H, m), 6.06 (1H, s), 8.13 (1H, s), 9.11 (1H, s)
45	3320, 3150, 1640, 1600, 1545, 1410, 1330, 1285, 1210	(DMSO-d_6+D_2O) 2.26 (3H, s), 3.03 (2H, m), 3.86 (2H, s), 4.37 (4H, m), 6.03 (1H, d, J=1 Hz), 8.07 (1H, s), 8.97 (1H, s)
46	3320, 3160, 1640, 1600, 1330, 1300, 1245, 1210	(DMSO-d_6+D_2O) 2.11 (3H, s), 2.82 (2H, m), 3.69 (2H, s), 4.46 (4H, m), 6.05 (1H, m), 7.50 (1H, s), 8.10 (1H, s), 8.96 (1H, s)
47	3320, 3160, 1640, 1600, 1330, 1300, 1250, 1210	(DMSO-d_6+D_2O) 2.73 (2H, m), 3.80 (2H, s), 4.2~4.7 (4H, m), 6.13 (1H, d, J=2 Hz), 7.34 (2H, m), 8.16 (1H, s), 8.38 (2H, m), 9.09 (1H, s)
48	3320, 3180, 1640, 1600, 1410, 1330, 1300, 1245, 1210	(DMSO-d_6+D_2O) 0.1~0.7 (4H, m), 0.7~1.2 (1H, m), 2.43 (2H, m), 2.88 (2H, d, J=6 Hz), 3.4~3.9 (1H, m), 4.2~4.6 (3H, m), 6.13 (1H, d, J=2 Hz), 8.19 (1H, s), 9.18 (1H, s)
49	3320, 3160, 1640, 1600, 1330, 1300, 1240, 1210	(DMSO-d_6+D_2O) 2.31 (4H, m), 2.72 (2H, m), 3.41 (2H, s), 3.56 (4H, m), 3.74 (2H, s), 4.2~4.7 (4H, m), 6.10 (1H, m), 7.21 (4H, s), 8.11 (1H, s), 9.07 (1H, s)
50	3650~2000, 1690, 1660, 1600, 1570	(DCl+D_2O) 3.54 (2H, d, J=7 Hz), 4.10~5.33 (4H, m), 6.33 (1H, br s), 7.08 (2H, m), 7.43 (1H, m), 8.48 (1H, s), 8.63 (1H, s)
51	3300, 3150, 1630, 1600, 1415, 1330, 1298, 1243, 1208	(DMSO-d_6+D_2O) 3.09 (2H, d, J=7 Hz), 4.30~4.93 (4H, m), 6.19 (1H, m), 8.23 (1H, s), 8.82 (1H, s)
52	3320, 3180, 1640, 1597, 1330, 1300, 1246, 1210	(DMSO-d_6+D_2O) 3.13 (2H, m), 4.20~4.67 (4H, m), 6.13 (1H, m), 7.20~7.50 (1H, m), 7.62~7.88 (1H, m), 8.21 (1H, s), 8.48 (2H, m), 9.11 (1H, m)
53	3300, 3175, 1645, 1600, 1516, 1330, 1300, 1248, 1212	(DMSO-d_6+D_2O) 3.03 (2H, m), 4.61 (4H, m), 6.14 (1H, m), 7.32 (2H, m), 8.21 (1H, s), 8.48 (2H, m), 9.62 (1H, m)

Table 4. (Continued)

Compound	IR (Nujol) (cm^{-1})	^1H NMR (δ)
54	3330, 3200, 1630, 1590, 1333, 1301, 1246, 1211	(DMSO-d_6) 3.05 (2H, m), 4.17~4.54 (4H, m), 6.12 (1H, d, J=2 Hz), 6.48 (2H, s), 6.51 (1H, d, J=5 Hz), 7.22 (2H, s), 8.10 (1H, d, J=5 Hz), 8.16 (1H, s), 9.23 (1H, s)
55	3320, 3280, 1640, 1600, 1517, 1330, 1310, 1250, 1210	(DMSO-d_6) 2.81 (2H, m), 4.15~4.50 (4H, m), 6.03 (1H, d, J=2 Hz), 6.63 (2H, m), 6.65 (1H, s), 7.17 (2H, m), 8.11 (1H, s), 8.20 (1H, m), 9.20 (1H, s)
56	3650~2000, 1690, 1660, 1640, 1600, 1580	(DMSO-d_6+D_2O) 3.03 (2H, m), 4.2~5.0 (4H, m), 5.83 (2H, m), 6.03 (1H, m), 6.50 (1H, br s), 8.20 (1H, s), 8.90 (1H, s)
57	3300, 3170, 1685~1580, 1410, 1330, 1300, 1246, 1205, 1170, 1072, 1053, 955, 823, 796, 720	(DMSO-d_6+D_2O) 1.71 (4H, m), 3.18 (2H, m), 3.67~4.57 (4H, m), 6.09 (1H, m), 8.19 (2H, m)
58	3325, 3175, 1640, 1600, 1330, 1300, 1245, 1210, 1175, 1110, 1075	(DCl+D_2O) 3.25 (2H, m), 6.25 (1H, m), 7.32 (5H, s), 8.46 (1H, s), 8.61 (1H, s)
59	3650~2300, 1690, 1660, 1640, 1600	(DCl+D_2O) 3.29 (2H, d, J=7 Hz), 4.3~5.3 (4H, m), 6.3 (1H, m), 7.4 (4H, m), 8.52 (1H, s), 8.67 (1H, s)
60	3600~2100, 1660, 1640, 1600	(DCl+D_2O) 3.27 (2H, d, J=8 Hz), 4.3~5.2 (4H, m), 6.23 (1H, d, J=2 Hz), 7.2~7.5 (4H, m), 8.45 (1H, s), 8.63 (1H, s)
61	3650, 2000, 1690, 1660, 1640, 1600, 1575	(DCl+D_2O) 3.25 (2H, d, J=7 Hz), 4.2~5.2 (4H, m), 6.28 (1H, d, J=1 Hz), 7.2~7.5 (4H, m), 8.50 (1H, s), 8.63 (1H, s)
62	3650~2250, 1690, 1660, 1640, 1600, 1575	(DCl+D_2O) 3.45 (2H, d, J=7 Hz), 4.3~5.2 (4H, m), 6.20 (1H, d, J=2 Hz), 7.58 (2H, d, J=8 Hz), 8.28 (2H, d, J=8 Hz), 8.50 (1H, s), 8.63 (1H, s)
63	3330, 3180, 1640, 1600, 1515, 1330, 1300, 1244, 1176, 1075, 1028	(DMSO-d_6+D_2O) 1.58 (4H, m), 3.01 (5H, m), 4.00~4.55 (4H, m), 6.03 (1H, m), 6.79 (2H, d, J=8 Hz), 7.16 (2H, d, J=8 Hz), 8.17 (1H, s), 8.97 (1H, s)
64	3250, 3150, 1650, 1600, 1510, 1250, 1080, 700	(DMSO-d_6+D_2O) 2.5~3.2 (4H, m), 3.67 (3H, s), 4.1~4.8 (5H, m), 6.1 (1H, m), 6.80 (2H, d, J=8 Hz), 7.17 (5H, s), 7.18 (2H, d, J=8 Hz), 8.18 (1H, s), 9.03 (1H, s)
65	3400~3100, 1640, 1610, 1510, 1300, 1250, 1180, 1080, 1030	(DMSO-d_6+D_2O) 2.7~3.1 (4H, m), 3.72 (6H, s), 4.0~4.8 (5H, m), 6.2 (1H, m), 6.82 (4H, d, J=8 Hz), 7.12 (2H, d, J=8 Hz), 7.20 (2H, d, J=8 Hz), 8.20 (1H, s), 9.10 (1H, s)
66	3400~3000, 1700~1560, 1510, 1400, 1220, 1060, 730	(DMSO-d_6+D_2O) 2.7~3.2 (2H, m), 3.8~4.2 (1H, m), 4.1~4.7 (5H, m), 6.1 (1H, m), 6.82 (2H, d, J=8 Hz), 7.23 (2H, d, J=8 Hz), 8.20 (1H, s), 8.83 (1H, s)
67	3600~2250, 1680~1540, 1510	(DMSO-d_6+D_2O) 2.0 (2H, m), 2.8~3.1 (4H, m), 3.7 (1H, m), 3.9~4.7 (6H, m), 6.05 (1H, m), 6.80 (2H, d, J=8 Hz), 7.30 (2H, d, J=8 Hz), 8.15 (1H, s), 9.03 (1H, s)
68	3300, 3200, 1640, 1610, 1560, 1510, 1330, 1300, 1245, 1180	(DMSO-d_6) 2.79 (3H, m), 3.78 (3H, s), 4.20~4.45 (2H, m), 4.52 (2H, m), 6.12 (1H, m), 6.61 (2H, m), 6.87~6.96 (2H, m), 7.08~7.28 (2H, m), 7.38 (2H, m), 8.32 (1H, s), 8.73 (1H, m)
69	3280, 1655, 1605, 1510, 1330, 1295, 1245, 1210, 1170, 1100, 1080, 1025	(DMSO-d_6) 2.80~3.06 (2H, m), 4.40 (2H, m), 4.60 (2H, m), 6.10 (1H, m), 6.84 (2H, d, J=9 Hz), 7.17 (2H, d, J=9 Hz), 7.32 (1H, m), 8.20 (1H, s), 8.68 (1H, s)

Table 4. (Continued)

Compound	IR (Nujol) (cm^{-1})	^1H NMR (δ)
70	3300, 3200, 3100, 1640, 1560, 1505, 1335, 1300, 1245, 1175, 1105, 1075, 1035	(DMSO-d_6) 0.85 (6H, m), 1.28 (8H, m), 2.68~2.92 (2H, m), 3.05 (4H, m), 3.68 (3H, s), 4.18~4.55 (4H, m), 5.98 (1H, m), 6.32~6.65 (1H, m), 6.75 (2H, d, J=8 Hz), 7.05 (2H, d, J=8 Hz), 7.25 (1H, s), 7.69 (1H, m), 8.11 (1H, s), 8.24 (1H, m), 8.53 (1H, m)
71	3700~3000, 1660, 1640, 1600, 1515, 1330, 1305, 1245	(DMSO-d_6) 2.80~2.92 (2H, m), 3.59 (2H, s), 3.67 (3H, s), 4.13~4.82 (4H, m), 6.08 (1H, m), 6.83 (2H, d, J=8 Hz), 7.17 (2H, d, J=8 Hz), 7.20 (2H, m), 7.90 (1H, m), 8.13 (1H, s), 8.63 (1H, s)
72	3350~3150, 1690, 1650, 1600, 1210, 1080	(DMSO-d_6+D_2O) 3.55 (2H, s), 4.2~4.9 (2H, m), 6.1 (1H, m), 7.23 (5H, s), 8.13 (1H, s), 8.42 (1H, s)
73	3400, 3300, 1690, 1650, 1610, 1545, 1535, 1415, 1240, 1220, 1090	(DMSO-d_6) 2.74 (4H, m), 4.33~5.00 (3H, m), 6.15 (1H, d, J=2 Hz), 7.24 (5H, s), 7.31 (2H, s), 8.18 (1H, s), 8.29 (1H, s), 8.46 (1H, s)
74	3420, 3310, 3210, 3140, 3075, 1715, 1690, 1650, 1610, 1570, 1525, 1290, 1240, 1193, 1170, 1100, 1080	(DCl+D_2O) 5.15 (3H, m), 6.66 (1H, s), 7.44~7.96 (5H, m), 8.76 (1H, s), 9.72 (1H, s)
75	3300, 1690, 1650, 1610, 1210, 1080	(DMSO-d_6+D_2O) 4.2~4.9 (3H, m), 6.1 (1H, m), 6.82 (1H, d, J=16 Hz), 7.1~7.6 (5H, m), 7.47 (1H, d, J=16 Hz), 8.17 (1H, s), 8.55 (1H, s)
76	3300, 3150, 1670, 1620, 1530, 1060, 1035	(DMSO-d_6+D_2O) 1.20 (3H, t, J=7 Hz), 4.17 (2H, q, J=7 Hz), 4.3~4.9 (3H, m), 6.2 (1H, m), 8.17 (1H, s), 8.47 (1H, s)
77	3400~3000, 1640, 1600, 1330, 1250, 1210	(DMSO-d_6+D_2O) 2.07 (3H, s), 2.6~3.0 (2H, m), 3.6~4.1 (1H, m), 4.2~4.5 (1H, m), 4.5~4.7 (2H, m), 6.10 (1H, m), 8.15 (1H, s), 8.90 (1H, s)
78	Same as that of **77**	Same as that of **77**
79	3320, 3170, 1635, 1595, 1327, 1300, 1244, 1210	(DMSO-d_6+D_2O) 2.13 (3H, s), 2.22 (2H, m), 4.13 (1H, m), 6.15 (1H, d, J=2 Hz), 8.23 (1H, s), 8.81 (1H, s)
80	3300, 3200, 1643, 1600, 1335, 1300, 1250, 1212	(DMSO-d_6) 3.01 (2H, d, J=6 Hz), 3.91~4.58 (6H, m), 6.11 (2H, m), 7.27 (2H, s), 8.25 (1H, s), 8.34 (1H, m), 9.38 (1H, s)
81	3700~2250, 1710~1650	(D_2O) 3.5 (2H, m), 4.35~5.4 (4H, m), 6.26 (1H, br s), 7.56 (1H, m), 8.37 (1H, s), 8.70 (1H, s), 8.76 (1H, m)
82	3330, 3180, 1640, 1600, 1410, 1330, 1300, 1228, 1210	(DMSO-d_6+D_2O) 2.62 (3H, s), 3.08 (2H, m), 4.23~4.70 (4H, m), 6.10 (1H, m), 8.17 (1H, s), 8.90 (1H, s)
83	3350, 1690, 1635, 1290, 1220	(DMSO-d_6+D_2O) 3.10 (3H, s), 3.43 (2H, m), 4.30~4.77 (4H, m), 6.10 (1H, m), 8.11 (1H, s), 8.19 (1H, s)
84	3320, 3180, 1640, 1600, 1400, 1330, 1300, 1225, 1210	(DMSO-d_6+D_2O) 2.85 (2H, m), 3.70 (2H, m), 4.2~4.7 (4H, m), 6.09 (1H, d, J=1.5 Hz), 6.71 (0.6H, s), 6.93 (0.4H, s), 8.14 (1H, s), 8.89 (1H, s)
85	3320, 3180, 1640, 1595, 1490, 1210	(DMSO-d_6+D_2O) 1.05~1.40 (3H, m), 2.85 (2H, m), 3.82 (2H, s), 4.4~4.8 (5H, m), 6.11 (1H, m), 7.26 (5H, s), 8.19 (1H, s), 8.73 (1H, s)
86	3400~3100, 1640, 1600, 1300, 1250	(DMSO-d_6+D_2O) 2.7~3.1 (2H, m), 3.69~3.9 (1H, m), 3.82 (2H, s), 4.4~4.9 (3H, m), 6.18 (1H, m), 7.2~7.5 (5H, m), 8.22 (1H, s), 8.57 (1H, s)
87	3340, 3180, 1640, 1600, 1300, 1250, 1200	(DMSO-d_6+D_2O) 1.21 (6H, t, J=7 Hz), 1.4~2.3 (2H, m), 2.65 (2H, m), 3.2~4.2 (9H, m), 4.3~4.7 (3H, m), 6.12 (1H, m), 7.32 (5H, m), 8.27 (1H, s), 8.4~8.7 (1H, m)

Table 4. (Continued)

Compound	IR (Nujol) (cm^{-1})	^1H NMR (δ)
88	3330, 3190, 1645, 1600, 1330, 1300	(DMSO-d_6+D_2O) 1.3~2.0 (2H, m), 2.80 (2H, m), 3.2~3.9 (5H, m), 4.52 (3H, m), 6.10 (1H, m), 7.27 (5H, s), 8.15 (1H, s), 8.80 (1H, s)
89	3310, 3170, 1640, 1595, 1290, 1245, 1200	(DMSO-d_6+D_2O) 2.76 (2H, m), 3.77 (2H, s), 4.3~4.8 (4H, m), 6.11 (1H, m), 7.28 (5H, s), 8.16 (1H, s), 8.61 (1H, m)
90	3400~3200, 1640, 1600, 1210	(DMSO-d_6+D_2O) 2.8~3.1 (2H, m), 3.1~3.7 (2H, m), 3.8~4.3 (1H, m), 3.88 (2H, s), 4.3~4.6 (2H, m), 4.6~4.9 (1H, m), 6.2~6.3 (1H, m), 7.2~7.5 (5H, m), 8.20 (1H, s), 8.62 (1H, m)
91	3200, 1640, 1600, 1330, 1300, 1250, 1210	(DMSO-d_6+D_2O) 1.4~2.0 (4H, m), 2.6~2.7 (2H, m), 2.9~3.5 (3H, m), 3.5~4.0 (1H, m), 4.3~4.7 (3H, m), 6.10 (1H, m), 7.2~7.4 (5H, m), 8.17 (1H, s), 8.58 (1H, s)

shown in Table 4.

Microbiology

The minimum inhibitory concentrations (MIC) of the synthesized compounds against *C. albicans*, *Staphylococcus aureus* 209P and *Escherichia coli* NIHJ are shown in Table 5.

In this series, L-α-aminoacyl derivatives were prepared since **7**, **58** and **78** including D-aminoacyl or **3** and **6** containing β- and γ-aminoacyl resulted in a greatly diminished activity against *Candida*.

In general, the compounds having β-aryl-α-L-aminoacyl groups conferred superior activity against *Candida* to those having aliphatic α-L-aminoacyl (**5** and **10**) and α-aryl-α-L-aminoacyl groups (**4** and **8**). Furthermore, a series of α-L-aminoacyl analogs possessing *S*-alkyl cysteinyl moiety was prepared systematically on account of the high anti-candida activity of its members.

Taking these facts into consideration, a total of 99 compounds were prepared according to methods 1~8 (Tables 1~3 and Chemistry). Among them, some aminoalkanoyl derivatives having a cysteinyl exhibited two- to sixteen-fold enhanced anti-yeast activity compared with that of native chryscandin (**16~19**, **21~23**, **25**, **26**, **29**, **31**, **39~41**, **47** and **77**). Especially, **16** indicated the highest efficacy against *C. albicans*. Data of the ED_{50} values on the protective effect against experimental infections in mice are shown in Table 6. The efficacy of **16** was almost the same as that of 5-fluorocytosine and a superior to that of ketoconazole.

Experimental

Melting points were measured on a Yanagimoto microscope hot-stage apparatus and were not corrected. IR spectra were recorded on Jasco IRA-2 or Jasco A-102 spectrophotometer. ^1H NMR spectra were recorded using Jeol PMX-60 or Jeol PS-100 spectrophotometer.

General Procedures for Removal of Protection Groups

Deprotection was carried out as follows.

Debenzoylation: A suspension of a benzoylamino derivative (0.1 mmol) in a mixture of MeOH (5 ml) and butylamine (2.3 ml) was boiled under reflux for 1 hour. The mixture was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel and eluted with a mixture of $CHCl_3$ - MeOH (7: 3) (Method A).

Table 5. MIC values of chryscandin derivatives.

Compound	MIC (μg/ml)			Compound	MIC (μg/ml)		
	Ca[a]	Ec[b]	Sa[c]		Ca[a]	Ec[b]	Sa[c]
1	1.6	>100	25	**46**	3.1	>100	>100
2	3.1	>100	>100	**47**	0.8	>100	>100
3	>100	>100	>100	**48**	3.1	>100	>100
4	>100	>100	>100	**49**	25	>100	>100
5	100	>100	>100	**50**	1.6	>100	>100
6	>100	>100	>100	**51**	50	>100	>100
7	>100	>100	>100	**52**	25	>100	>100
8	>100	>100	>100	**53**	12.5	>100	>100
9	25	>100	>100	**54**	12.5	>100	>100
10	>100	>100	>100	**55**	6.2	>100	>100
11	>100	>100	>100	**56**	100	>100	>100
12	>100	>100	>100	**57**	12.5	>100	>100
13	>100	>100	>100	**58**	>100	>100	>100
14	3.1	>100	>100	**59**	12.5	>100	>100
15	25	>100	>100	**60**	6.2	50	>100
16	0.1	>100	>100	**61**	3.1	>100	>100
17	0.2	>100	>100	**62**	50	>100	>100
18	0.2	>100	>100	**63**	100	>100	12.5
19	0.2	>100	>100	**64**	>100	>100	>100
20	>100	>100	>100	**65**	>100	>100	>100
21	0.2	>100	>100	**66**	>100	>100	>100
22	0.2	>100	>100	**67**	>100	>100	>100
23	0.8	>100	>100	**68**	>100	>100	>100
24	25	>100	>100	**69**	6.2	>100	>100
25	0.8	>100	>100	**70**	>100	>100	>100
26	0.8	>100	>100	**71**	6.2	>100	>100
27	12.5	>100	>100	**72**	>100	>100	>100
28	1.6	6.2	>100	**73**	>100	>100	>100
29	0.8	100	>100	**74**	>100	>100	>100
30	>100	>100	>100	**75**	>100	>100	>100
31	0.4	>100	>100	**76**	>100	>100	>100
32	6.2	>100	>100	**77**	0.2	50	>100
33	12.5	>100	>100	**78**	>100	>100	>100
34	25	>100	>100	**79**	1.6	>100	50
35	>100	>100	>100	**80**	>100	>100	>100
36	12.5	>100	>100	**81**	12.5	>100	>100
37	25	>100	>100	**82**	>100	>100	>100
38	1.6	>100	>100	**83**	>100	>100	>100
39	0.2	>100	>100	**84**	50	>100	>100
40	0.8	>100	>100	**85**	1.6	>100	>100
41	0.2	>100	>100	**86**	100	>100	>100
42	>100	>100	>100	**87**	3.1	>100	>100
43	50	>100	>100	**88**	25	>100	>100
44	>100	>100	>100	**89**	6.2	>100	>100
45	25	>100	>100	**90~99**	>100	>100	>100

[a] *Candida albicans*. [b] *Escherichia coli* NIHJ. [c] *Staphylococcus aureus* 209P.

Debenzyloxycarbonylation: A suspension of a derivative of *N*-benzyloxycarbonyl methyl ester (0.1 mmol) in H_2O (80 ml) was adjusted to pH 3 with 1 N HCl. The resulting mixture was hydrogenated under medium pressure (3.0~3.5 atm) over palladium black (12 mg) for 3 hours. The catalyst was removed by filtration and the filtrate was adjusted to pH 7 with 1 N NaOH. The result-

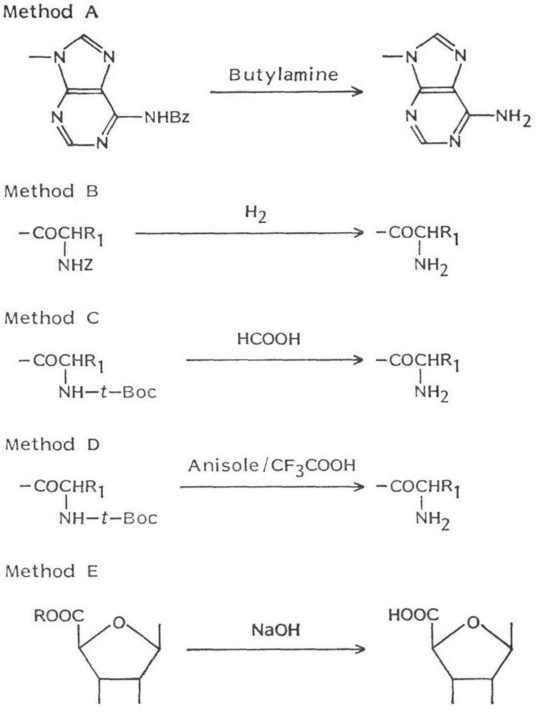
Table 6. Protective effect of derivatives of chryscandin.

Compounds	MIC* (μg/ml)	ED_{50}** (mg/kg)
1 (Chryscandin)	1.6	15
16	0.1	10
17	0.2	15
77	0.2	20
5-Fluorocytosine	3.2	15
Ketoconazole	0.2	50

* Against *C. albicans* FP-633. Agar dilution method. Medium in malt extract.

** Route: sc.

Fig. 4. Procedures of removal of protection groups.



ing mixture was concentrated under reduced pressure to a volume of 12 ml. The concentrate was applied to a column of non-ionic adsorption resin HP-20 (Mitsubishi Kasei, 20 ml) and the column was washed with H_2O (40 ml) and then eluted with a mixture of MeOH - H_2O (3:7, 40 ml) (Method B).

De-*tert*-butoxycarbonylation: A mixture of a *tert*-butoxycarbonylamino derivative (0.1 mmol) and formic acid (1 ml) was stirred for 2 hours at room temp and evaporated to dryness. The residue was dissolved in H_2O (7.5 ml) and adjusted to pH 7 with aq $NaHCO_3$. The solution was subjected to column chromatography on the Diaion HP-20 (30 ml). After the column was washed with H_2O, the elution was carried out with 30% aq MeOH (Method C). A mixture of a *tert*-butoxycarbonylamino derivative (0.1 mmol) and anisole (0.1 ml) was stirred in an ice-bath, and TFA (1 ml) was added. After stirring for 1 hour in an ice-bath, Et_2O was added to the mixture. The resulting precipitates were collected by filtration (Method D).

Deesterification: To the precipitates, 1 N NaOH (1 ml) was continuously added, and stirred for 30 minutes in an ice-bath. The reaction mixture was neutralized with 1 N HCl, and subjected to the Diaion HP-20 column (Method E) (Fig. 4).

Synthesis of **1**. Method 1

To a stirred solution of *N*-benzoyloxycarbonyl-*O*-methyl-L-tyrosine (181 mg) and *N*-hydroxysuccinimide (HOSu) (64 mg) in dioxane (10 ml) was added *N,N'*-dicyclohexylcarbodiimide (DDC) (114 mg) under cooling in an ice-bath. The mixture was stirred overnight at room temp. The suspension was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in THF (5 ml) and the solution was added to a solution of 3-amino-1-(6-benzoylamino-9*H*-purin-9-yl)-1,3-dideoxy-β-D-ribofuranuronic acid (150 mg) and triethylamine (0.08 ml) in H_2O (5 ml). The mixture was stirred for a day at room temp. THF was evaporated *in vacuo* and the residual aq solution was adjusted to pH 2 with 1 N HCl and extracted with EtOAc (30 ml $\times$ 3). The extracts were combined, washed with satd NaCl, dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was subjected to column chromatography on silica gel and eluted with a mixture of $CHCl_3$ - MeOH (8:2). The fractions containing the object compound were combined and evaporated *in vacuo* to give 1-(6-benzoylamino-9*H*-purin-9-yl)-3-((*N*-benzoyloxycarbonyl-*O*-methyl-L-tyrosyl)amino)-1,3-dideoxy-β-D-ribofuranuronic acid (150 mg) as syrup. Deprotection by Methods A and B yielded 1-(6-amino-9*H*-purin-9-yl)-1,3-dideoxy-3-((*O*-methyl-L-tyrosyl)amino)-β-D-ribofuranuronic acid dihydrochloride monohydrate (**1**, chryscandin, 40 mg), mp 215~230°C (dec). In a similar way, **2**~**12** and **58** were

prepared, mp, spectral data and antimicrobial activities of these compounds are shown in Tables 1 and 4.

Synthesis of **16**. Method 2

A mixture of ethyl-1-(6-amino-9*H*-purin-9-yl)-1,3-dideoxy-3-amino-β-D-ribofuranuronate (308 mg), *N-tert*-butoxycarbonyl-*S*-benzyl-L-cysteine (311 mg) and DCC (206 mg) in THF (15 ml) and H_2O (5 ml) was stirred overnight. The precipitates were removed by filtration. The filtrate was diluted with H_2O (50 ml), extracted with EtOAc, washed with H_2O and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was subjected to column chromatography on silica gel. The elution was carried out with a mixed solvent $CHCl_3$ - MeOH (97: 3). The eluate was evaporated to dryness to give ethyl-1-(6-amino-9*H*-purin-9-yl)-1,3-dideoxy-3-((*N-tert*-butoxycarbonyl-*S*-benzyl-L-cysteinyl)-amino)-β-D-ribofuranuronate (507 mg), mp 103~110°C; IR (Nujol) 3300, 3170, 2700, 2300, 1740, 1690, 1675, 1660, 1640, 1600 and 1580 cm^{-1}; ^1H NMR (DMSO-d_6+D_2O) δ 1.15 (3H, t, J=7 Hz), 1.45 (9H, s), 2.80 (2H, m), 3.83 (2H, s), 3.9~5.0 (6H, m), 6.20 (1H, m), 7.38 (5H, s), 8.24 (1H, s) and 8.50 (1H, s). Deprotection by Methods C and E yielded 1-(6-amino-9*H*-purin-9-yl)-1,3-dideoxy-3-(*S*-benzyl-L-cysteinylamino)-β-D-ribofuranuronic acid (**16**, 153 mg), mp 178~180°C (dec); IR and ^1H NMR are shown in Table 4. In a similar way, **17**~**47**, **50**~**57** and **59**~**65** were prepared (Table 2).

Synthesis of **14**. Method 3

To a mixture of 1-(6-amino-9*H*-purin-9-yl)-1,3-dideoxy-3-amino-β-D-ribofuranuronic acid monohydrate (149 mg) and triethylamine (0.21 ml) in H_2O (5 ml) was added a solution of the *N*-hydroxysuccinimide ester of *N-tert*-butoxycarbonyl-*S*-phenyl-DL-cysteine in THF (5 ml) under stirring overnight at room temp. The reaction mixture was washed with Et_2O and the remaining aq solution was adjusted to pH 2 with 1 N HCl. The resulting precipitates were filtered off, washed with H_2O and dried in a desiccator to yield 1-(6-amino-9*H*-purin-9-yl)-1,3-dideoxy-3-((*N-tert*-butoxycarbonyl-*S*-phenyl-DL-cysteinyl)amino)-β-D-ribofuranuronic acid (180 mg), mp 85~95°C (dec); IR (Nujol) 3400~3150, 1690, 1500, 1250 and 1160 cm^{-1}; ^1H NMR (DMSO-d_6+D_2O) δ 1.37 (9H, s), 3.0~3.6 (2H, m), 3.8~4.6 (2H, m), 4.6~4.9 (2H, m), 6.20 (1H, m), 7.33 (5H, s), 8.23 (1H, s) and 8.48 (1H, s). Deprotection by Method C yielded 1-(6-amino-9*H*-purin-9-yl)-1,3-dideoxy-3-((*S*-phenyl-DL-cysteinyl)amino)-β-D-ribofuranuronic acid (**14**, 42 mg), mp 161~166°C (dec); IR and ^1H NMR are shown in Table 4. According to a similar manner **15**, **48**, **49**, **66**, **67** and **77**~**84** were synthesized (Table 1).

Synthesis of **72**. Method 4

To a mixture of 1-(6-benzoylamino-9*H*-purin-9-yl)-1,3-dideoxy-3-amino-β-D-ribofuranuronic acid (384 mg) and triethylamine (0.35 ml) in H_2O (10 ml) was dropped a solution of phenylacetyl chloride (0.171 g) in THF (10 ml) under cooling in an ice-bath and stirring, which was continued for 30 minutes at the same temp. The mixture was evaporated *in vacuo* and the remaining aq solution was washed with Et_2O and acidified with 6 N HCl. The mixture was extracted with a mixture (80 ml) of EtOH - $CHCl_3$ (1: 1) and the extract was dried over $MgSO_4$, evaporated and triturated with Et_2O to give 1-(6-benzoylamino-9*H*-purin-9-yl)-3-(phenylacetylamino)-1,3-dideoxy-β-D-ribofuranuronic acid (370 mg), mp 135~140°C (dec); IR (Nujol) 3300, 1710, 1645, 1600, 1580, 1450, 1240, 1220, 1080 and 1060 cm^{-1}; ^1H NMR (DMSO-d_6+D_2O) δ 3.62 (2H, s), 4.5~4.6 (1H, m), 4.7~4.9 (2H, m), 6.3 (1H, m), 7.37 (5H, s), 7.5~7.8 (3H, m), 7.9~8.2 (2H, m), 8.87 (1H, s) and 8.97 (1H, s). Deprotection by Method A yielded 1-(6-amino-9*H*-purin-9-yl)-3-(phenylacetylamino)-1,3-dideoxy-β-D-ribofuranuronic acid (**72**, 106 mg), mp 159~165°C (dec); IR and ^1H NMR are shown in Table 4. According to a similar manner **73**~**76** were prepared (Table 1).

Synthesis of **13**. Method 5

1-(6-Benzoylamino-9*H*-purin-9-yl)-3-D-mandelylamino-1,3-dideoxy-β-D-ribofuranuronic acid (300 mg) was prepared by reacting 1-(6-benzoylamino-9*H*-purin-9-yl)-1,3-dideoxy-3-amino-β-D-ribofuranuronic acid (300 mg) with 2,4-dioxo-5-phenyl-1,3-dioxolane (253 mg), prepared from D-mandelic acid and phosgene, according to a similar procedure to that of Method 1, mp 223~227°C (dec); IR (Nujol) 3440, 3310, 3200, 1705, 1645, 1605, 1590, 1520, 1400, 1360, 1330, 1295, 1280, 1240, 1220, 1205, 1180, 1140, 1100, 1090, 1080 and 1065 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.43~4.65 (1H, m), 4.56 (1H, m), 4.78 (2H, m), 5.01 (1H, m), 6.25 (1H, d, J=2 Hz), 6.25~6.72 (1H, m), 7.19~7.44 (5H, m), 7.44~

7.65 (3H, m), 7.90~8.22 (3H, m), 8.71 (1H, s) and 8.76 (1H, s).

The deprotection of the compound was carried out according to Method A. IR and ^{1}H NMR are shown in Table 4.

Synthesis of **71**. Method 6

To a stirred suspension of 1-(6-benzoylamino-9*H*-purin-9-yl)-3-((*N*-benzyloxycarbonyl-*O*-methyl-L-tyrosyl)amino)-1,3-dideoxy-β-D-ribofuranuronic acid (250 mg) and HOSu (41.3 mg) in THF (5 ml) was added DCC (75 mg) at room temp. The mixture was stirred overnight at same temp. The urea was filtered off and the filtrate evaporated to a syrup *in vacuo*. The syrup was dissolved in THF (5 ml) and to the solution was added a solution of glycine (33 mg), triethylamine (0.085 ml) and H_2O (0.5 ml) under stirring at room temp. The mixture was stirred for 22 hours at the same temp. THF was evaporated *in vacuo* and the resulting aq solution was extracted by a mixture of $CHCl_3$ - EtOH (1 : 1) (50 ml×3). The extracts were combined, washed with H_2O, dried over $MgSO_4$, evaporated to a colorless syrup and triturated with Et_2O to give *N*-(1-(6-benzoylamino-9*H*-purin-9-yl)-3-((*N*-benzoyloxycarbonyl-*O*-methyl-L-tyrosyl)amino)-1,3-dideoxy-β-D-ribofuranuroylglycine (268 mg), mp 122~130°C (dec); IR (Nujol) 3320, 1680, 1610, 1580, 1510, 1295 and 1240 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.98~3.19 (2H, m), 3.79 (3H, s), 3.88 (2H, m), 4.27~4.91 (4H, m), 4.97 (2H, s), 6.35 (1H, m), 6.85 (2H, d, J=9 Hz), 7.32 (7H, m), 7.52~7.71 (3H, m), 8.00~8.20 (2H, m), 8.87 (1H, s) and 9.11 (1H, d, J=10 Hz). The deprotection of the above compound was carried out according to Methods A and B to give **71** as a colorless powder (yield, 41.4%), mp 194~196°C (dec). IR and ^{1}H NMR were shown in Table 4. In a similar way **86** and **91** were prepared (Table 2).

Synthesis of **68** and **69**. Method 7

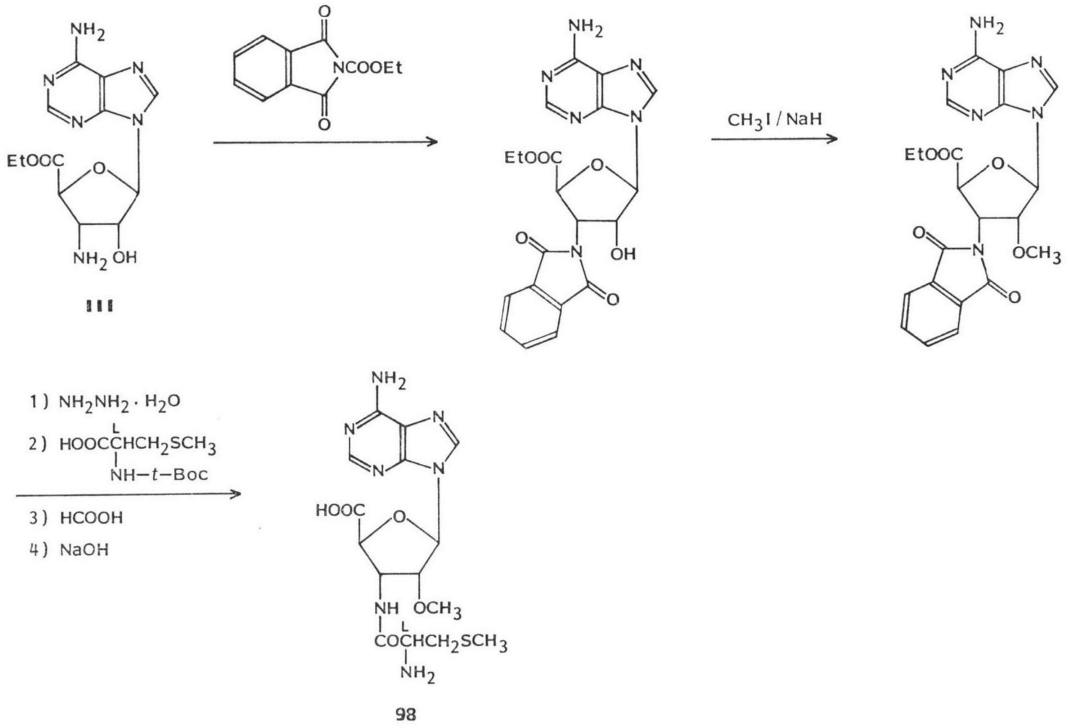
(a) A mixture of methyl 1-(6-benzoylamino-9*H*-purin-9-yl)-1,3-dideoxy-3-((*N*-benzoyloxycarbonyl-*O*-methyl-L-tyrosyl)amino)-β-D-ribofuranuronate (**IV**, 300 mg) and 100% hydrazine hydrate (4 ml) in MeOH (10 ml) was refluxed for 5 hours and evaporated to dryness. The residue was solidified by adding a small amount of MeOH and triturated with Et_2O to give 1-(6-amino-9*H*-purin-9-yl)-1,3-dideoxy-3-((*N*-carbazoyl-*O*-methyl-L-tyrosyl)amino)-β-D-ribofuranuranohydrazide (**68**, 190 mg), mp 152~158°C (dec). IR and ^{1}H NMR were shown in Table 4.

(b) Methyl 1-(6-benzoylamino-9*H*-purin-9-yl)-1,3-dideoxy-3-((*O*-methyl-L-tyrosyl)amino)-β-D-ribofuranuronate (**V**, 238 mg) was prepared as amorphous powder by hydrogenation of **IV** (604 mg) according to a similar manner of Method B. IR (Nujol) 1750, 1675, 1615, 1584, 1515, 1300, 1250, 1180, 1100, 1070 and 1035 cm^{-1}; ^{1}H NMR (DMSO-d_6+D_2O) δ 3.72 (2H, m), 4.26~4.46 (2H, m), 4.65 (2H, m), 6.18 (2H, m), 6.65~7.21 (4H, m), 7.42~7.59 (3H, m), 7.85~8.16 (2H, m) and 8.66 (2H, s). **69** (165 mg) was prepared by reaction of **V** with 100% hydrazine hydrate (4 ml) according to a similar manner to that of **68**, mp 131~140°C (dec). IR and ^{1}H NMR were shown in Table 4 (Fig. 3). **70** (208 mg) was prepared from **68** (355 mg) by refluxing in butylamine (5 ml) and MeOH (5 ml) for 9 hours, mp 111~115°C (dec). IR and ^{1}H NMR were also shown in Table 4.

Synthesis of **85**. Method 8

To a mixture of 1-(6-amino-9*H*-purin-9-yl)-1,3-dideoxy-3-((*N*-*tert*-butoxycarbonyl-*S*-benzyl-L-cysteinyl)amino)-β-D-ribofuranuronic acid (400 mg) and 1-DL-aminoethyl diphenylphosphite hydrobromide (250 mg) in 83% aq THF (18 ml) were successively added triethylamine (0.097 ml), HOBT (106 mg) and DCC (200 mg) at room temp. The mixture was stirred for 2 days at the same temp. After filtration the solution was evaporated to dryness. The residue was dissolved in EtOAc. The solution was washed with aq $NaHCO_3$ and subsequently with aq NaCl, dried over $MgSO_4$, and evaporated to dryness. The residue was stirred with Et_2O, and dried *in vacuo* to yield DL-1-(1-(6-amino-9*H*-purin-9-yl)-1,3-dideoxy-3-((*N*-*tert*-butoxycarbonyl-*S*-benzyl-L-cysteinyl)amino)-β-D-ribofuranuronylamino ethyl diphenylphosphite (435 mg), mp 84~97°C (dec); IR (Nujol) 3320, 1675~1625, 1590, 1490, 1245 and 1210 cm^{-1}; ^{1}H NMR (DMSO-d_6+D_2O) δ 1.1~1.8 (3H, m), 1.42 (9H, s), 2.75 (2H, m), 3.76 (2H, s), 4.2~5.0 (5H, m), 6.16 (1H, m), 7.48 (15H, m), 8.21 (1H, s) and 8.39 (1H, s) (Fig. 3). Deprotection was carried out according to Method C to give **85** (127 mg), mp 113~118°C (dec). In a similar way, **87~90** were prepared, mp, IR and ^{1}H NMR were shown in Table 4.

Fig. 5. Preparation of **98**.



III

98

Synthesis of **92**~**97**

The preparation methods of **92**~**97** were similar to that of chryscandin (Table 3).

Synthesis of **98**

Ethyl ester of **II** (2.80 g), *N*-carboethoxyphthalimide (2.39 g) and $NaHCO_3$ (764 mg) in 50% aq THF (56 ml) were stirred at room temp for 4 hours. The resulting precipitates were filtered off, washed with 50% aq THF and dried *in vacuo* to yield as a colorless powder (2.51 g), ethyl 1-(6-amino-9*H*-purin-9-yl)-1,3-dideoxy-3-phthalimido-β-D-ribofuranuronate, mp 248~251°C (dec); IR (Nujol) 3250, 3100, 1755, 1720, 1685, 1610, 1335 and 1210 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.17 (3H, t, J=7 Hz), 4.18 (2H, q, J=7 Hz), 5.00~5.40 (3H, m), 6.09 (1H, d, J=5 Hz), 6.33 (1H, d, J=6 Hz), 7.28 (2H, br s), 7.92 (5H, s), 8.12 (1H, s) and 8.45 (1H, s). To this compound (1.9 g) in DMF (15 ml) was added NaH (229 mg) under stirring and cooling in an ice-bath for 30 minutes. Furthermore, to the mixture was added MeI (0.81 ml) and stirring continued for 40 minutes. The reaction mixture was poured into 0.1 N HCl (100 ml), adjusted to pH 2 with 2 N NaOH and then extracted with EtOAc (100 ml×2). The extracts were combined, washed with H_2O and satd NaCl, dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was subjected to column chromatography on silica gel and eluted with a mixture of $CHCl_3$ - EtOAc (3: 10). The fractions containing the object compound were combined and evaporated *in vacuo* to give as a colorless powder (158 mg), ethyl 1-(6-amino-9*H*-purin-9-yl)-1,3-dideoxy-2-*O*-methyl-3-phthalimido-β-D-ribofuranuronate, mp 158~160°C (dec); IR (Nujol) 3300, 3150, 1740, 1660 and 1600 cm^{-1}; ^1H NMR (DMSO-d_6+D_2O) δ 1.12 (2H, t, J=7 Hz), 3.12 (3H, s), 4.20 (2H, q, J=7 Hz), 4.70~5.10 (1H, m), 5.20~5.70 (2H, m), 6.53 (1H, d, J=7 Hz), 7.97 (4H, s), 8.23 (1H, s) and 8.52 (1H, s).

This methyl ether (116 mg) was dissolved in THF (0.5 ml), added 1 M ethanolic hydrazine hydrate (0.257 ml) and stirred for 5 minutes at room temp. The solution was evaporated to dryness *in vacuo*. To the residue were added *N*-*tert*-butoxycarbonyl-*S*-methyl-L-cysteine (60.0 mg), DCC (79.0 mg), H_2O (1.0 ml) and THF (5.0 ml), stirred for 8 hours at room temp. After filtration the solution was ex-

tracted with Et_2O (10 ml×2), combined, washed with H_2O and subsequently satd NaCl, dried over $MgSO_4$, evaporated to dryness and triturated with Et_2O to give 115 mg of ethyl 1-(6-amino-9*H*-purin-9-yl)-3-((*N*-*tert*-butoxycarbonyl-*S*-methyl-L-cysteinyl)amino)-β-D-ribofuranuronate as a colorless powder, mp 141~145°C (dec); IR (Nujol) 3300, 3200, 1740, 1680~1600, 1570 and 1530 cm^{-1}; ^1H NMR (DMSO-d_6+D_2O) δ 1.22 (3H, t, J=7 Hz), 1.38 (9H, s), 2.07 (3H, s), 2.60~2.90 (2H, m), 3.44 (3H, s), 3.90~4.50 (2H, m), 4.22 (2H, q, J=7 Hz), 4.50~4.80 (2H, m), 6.30~6.50 (1H, m), 8.20 (1H, s) and 8.50 (1H, s). Deprotection was carried out according to Methods C and E to give **98** (47% yield) as a colorless powder, mp 148~152°C (dec); IR (Nujol) 3300, 1740, 1720 and 1630 cm^{-1}; ^1H NMR (DMSO-d_6+D_2O) δ 2.18 (3H, s), 2.80~3.20 (2H, m), 4.70~5.00 (1H, m), 6.30~6.50 (1H, m), 8.31 (1H, s) and 9.18 (1H, s) (Fig. 5). In a similar procedure, **99** was prepared.

Protective Efficacy in Experimental Infection in Mice

The *in vivo* activity of **1** (chryscandin), **16**, **17**, **77**, 5-fluorocytosine and ketoconazole against experimental infections of *C. albicans* FP-633 in mice was examined. One hour after intravenous injection of 3.0×10^6 cells/ml of *C. albicans* FP-633 to each *dd*Y-strain of mice aged 5 weeks averaging 20 g in weight. The drug solutions were administered subcutaneously. A group of 7 mice was used for each dosage level with animals being observed for seven days to determine the median effective dose (ED_{50}). The efficacy is shown in Table 6.

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