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Author	佐藤, 良博(Sato, Yoshihiro) 園田, よし子(Sonoda, Yoshiko) 森崎, 益雄(Morisaki, Masuo) 池川, 信夫(Ikekawa, Nobuo)
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Effects of Cholesterol Analogs on Cholesterol Biosynthesis from Lanosterol*

Yoshihiro SATO, Yoshiko SONODA, Masuo MORISAKI**,
and Nobuo IKEKAWA**

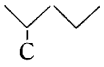
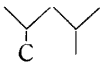
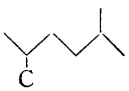
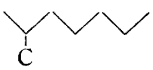
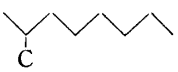
佐藤良博，園田よし子，森崎益雄,** 池川信夫**

Cholesterol biosynthesis was examined with rat hepatic subcellular 10000×g supernatant fraction incubated with [24-^{3}H]-lanosterol in the presence of twelve cholesterol analogs (**1**—**12**) including sitosterol. Cholesterol analogs (40 μM) with different sized of side chains exhibited very minor inhibitory effects (2—7%) compared with that of cholesterol (21%) on the synthesis of cholesterol from [24-^{3}H]-lanosterol (18 μM) as shown in Table I.

When compared to the previous results, it is evident that cholesterol analogs (**1**, **2**, and **5**) are less inhibitory than the corresponding lanosterol analogs. For example, 27-nor-24,25-dihydrolanosterol showed 81% inhibition but 27-norcholesterol (**5**) showed only 6% inhibition.

In summary, it may be concluded that the side chain structures and 14α-alkylated steroidal skeleton structure are critically important for inhibitory effect on cholesterol synthesis from lanosterol.

Table I. Cholesterol Biosynthesis during Incubation of S_{10} Fraction of Rat Liver Homogenate with [24-^{3}H]-Lanosterol in the Presence of Cholesterol Analogs

Compound		Lanosterol Fr. (%)	Cholesterol lFr. (%)	Inhibition (%)
None (control)		23.0	22.9	—
	(**1**)	22.1	21.5	6
	(**2**)	22.4	22.1	3
	(**3**)	22.4	21.7	5
	(**4**)	20.8	21.4	7
	(**5**)	24.8	21.5	6
	(**6**)	23.3	22.5	2

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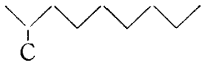
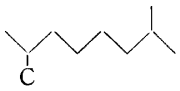
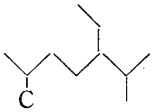
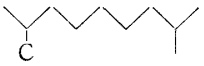
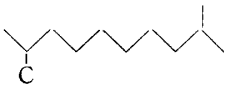
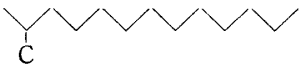
** 東京工業大学・理学部

Compound		Lanosterol Fr.(%)	Cholesterol Fr.(%)	Inhibition (%)
	(7)	19.2	22.5	2
	(8)	19.6	22.0	4
	(9)	19.3	21.6	6
	(10)	18.4	21.5	6
	(11)	18.8	21.5	6
	(12)	21.4	21.8	5
Cholesterol[a)]		35.2	18.2	21

[24-^{3}H]-Lanosterol (90600dpm; 0.43μCi/μmol) was incubated with rat liver S_{10} fraction (19.5—20.5mg protein/ml) at 37°C for 3 h. The incubation mixture contained, in a total volume of 5ml, 4ml of S_{10} fraction and cofactors. Inbcuation was started by the addition of the substrate and test compounds as an emulsion (0.1ml) with Tween 80 (3mg). Analytic methods for incubation products and the calculation of the percentage inhibition were described previously. Each incubation was carried out in triplicate and the standard deviation of each value listed was less than 5 percent.

a) This compound was tested as a reference; the result was somewhat different from that reported previously.