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CETP INHIBITORY ACTIVITY OF CERAMIDES , ISOLATED FROM THE GORGONIAN *ACABARIA UNDULATA*

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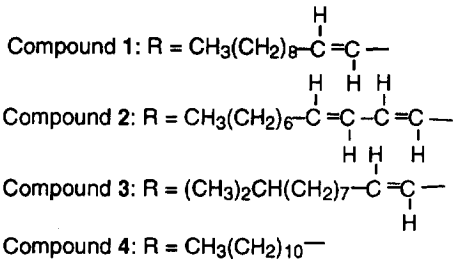
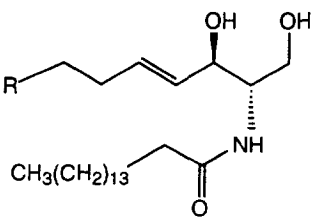
Absract: Four ceramides, isolated from the gorgonian *Acabaria Undulata*, and sphingosine analogs exhibited significant cholesteryl ester transfer protein (CETP)-inhibitory activity. The ceramides **1**, **2**, **3**, **4** and N,N-dimethylsphingosine inhibited human CETP with IC_{50} values of 46.8, 57.3, 86.3, 65.6 and 6.3 μM, respectively.

The plasma cholesteryl Ester Transfer Protein (CETP) is a lipid transfer protein, which mediates the transfer of cholesterol ester and triglyceride between high-density lipoprotein(HDL) and other low-density lipoproteins (VLDL, LDL).[1] Evidences from transgenic mouse and genetic deficiency human indicate that elevation in CETP activity strongly relates to the development of atherosclerotic cardiovascular diseases.[2,3]

In the course of our screening program for CETP inhibitor from natural sources, we measured the inhibitory activities of ceramides, isolated from the extract of the bright red gorgonian *Acabaria undulata* Kukenthal[4], against CETP our screening method.[5] To survey the inhibitory activities of sphingosines, sphingosine, dimethylsphingosine, galactosyl sphingosine, dihydrosphingosine and sphingosyl-phosphorylcholine were also tested under the same condition as did for ceramides.[6]





The inhibitory activities of the compounds and U-106305,[7] which was one of well known CETP inhibitors, were summarized in Table 1.

Table 1. Inhibitory activity of CETP by Sphingosine derivatives

Compounds	IC_{50} (μM)	Compounds	IC_{50} (μM)
Compound **1**	46.8	D-Sphingosine	11.5
Compound **2**	57.3	1-β-D-Galactosyl sphingosine	19.7
Compound **3**	86.3	DL-*erythro*-dihydrosphingosine	12.9
Compound **4**	65.6	Sphingosylphosphorylcholine	156.9
U-106305	25.0	N,N-Dimethylsphingosine	6.3

The inhibition of CETP by these compounds ranged from an IC_{50} of 156.9 to 6.3 μM. Dimethyl sphingosine showed the strogest inhibitory activity in comparision with other analogs.

Ceramides were extensively studied as a secondary messenger for kinases and transcription factors.[8] Although the cerimides only mildly inhibit CETP, the results are of interest in connection with the biological activities of the compounds.

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