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GERI-BP001, A New Inhibitor Of Acyl-CoA: Cholesterol Acyltransferase Produced By *Aspergillus fumigatus* F37

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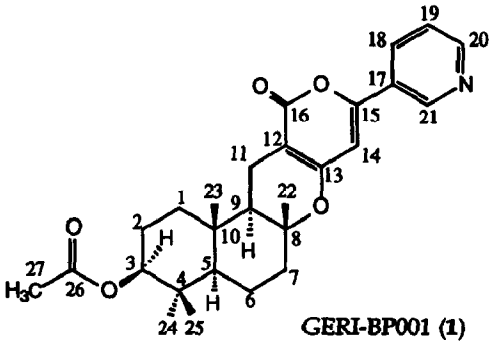
Abstract: GERI-BP001, a new inhibitor (IC_{50} 50μM) of acyl-CoA: cholesterol acyltransferase (ACAT), was isolated from a culture broth of *Aspergillus fumigatus* F37 and the structure elucidated on the basis of spectroscopic data.

Acyl-CoA: cholesterol acyltransferase (ACAT, EC 2.3.1.26) is a key enzyme responsible for cholesterol ester formation in atherogenesis and cholesterol absorption from the intestines[1]. ACAT inhibitors are expected to be effective for treatment of atherosclerosis and hypercholesterolemia. Although a wide variety of synthetic inhibitors of ACAT are now under clinical or preclinical evaluation[2], there are only a few ACAT inhibitors from microbial origin, for examples, purpactins[3], AS-183[4] and pyripyropenes[5]. In the course of our screening program for ACAT inhibitors of microbial source, GERI-BP001 (1) was isolated from the fermentation broth of a fungal strain, *Aspergillus fumigatus* F37. The mycelial cake from fermentation broth (1*L*) of *Aspergillus fumigatus* F37 was extracted with acetone and the extract was partitioned between ethyl acetate and water. The ethyl acetate soluble fraction (370mg) was chromatographed on silica gel (SiO_2) and eluted with 50-100 % ethyl acetate in hexane followed by reverse-phase HPLC (Phenomenex Ultracarb 10 ODS 30, Methanol/H_2O, 90:10) to yield **1** (3.1mg).



GERI-BP001 (1)

1[6] was optically active and its molecular fomular was determined as $C_{27}H_{33}NO_5$ by HREIMS (M^+: 451.2347, calcd: 451.2358). IR absorptions at 1246 and 1716 cm^{-1} suggested the presence of ester groups. Intensive NMR work, summarized Table 1 (COSY, C-H COSY, NOESY and HMBC experiments), brought to the determination of structure with three parts; sesquiterpene, α-pyrone and pyridine. The relative stereochemistry of **1** was deduced by analysis of its NOESY spectrum. On the basis of a series of HMBC experiments (mixing times 0.056 to 0.100 s), the positions of seven sp^3 carbons (^{13}C δ 36.70, 37.69, 80.79, 100.22, 127.58, 155.58, 162.76) were confirmed. Thus the structure of GERI-BP001 was determined.

IC_{50} value of **1** against ACAT in an enzyme assay system using rat liver microsomes[7] was 50 μM. Acute toxic effect was not observed when **1** was subcutaneously injected to ICR mouse at 500 mg/kg.

Table 1. NMR Data for 1

C#	δ ^{13}C [a]	δ ^{1}H (mult, *J*, Hz) [b]	COSY [c]	NOESY [c]	HMBC [d]
1	37.09	$^{\alpha}$1.15 (dt, 3.4, 12.7)	1β, 2	5α, 9α	
		$^{\beta}$1.77 (dt, 3.4, 13.2)	1α, 2	6β, 7β	
2	23.41	$^{\alpha,\beta}$1.59~1.74 (m)	1α, 1β, 3		
3	80.07	4.48 (dd, 4.7, 11.7)	1β, 2	1α, 5, 24	
4	36.70				9, 23
5	55.00	1.06 (dd, 2.0, 12.1)	6α, 6β	7α, 9, 24	
6	19.21	$^{\alpha}$1.77 (dt, 3.4, 13.2)	5, 6β, 7α, 7β	5, 7α, 24	
		$^{\beta}$1.42 (dd, 2.2, 12.2)	5, 6α, 7α, 7β	7β, 22, 23, 25	
7	40.16	$^{\alpha}$1.65 (m)	6α, 6β, 7β	5, 9	
		$^{\beta}$2.11 (ddd, 3.1, 3.1, 12.6)	6α, 6β, 7α	6β, 22	
8	80.79				7α, 9, 11α, 22
9	51.36	1.48 (dd, 4.8, 12.9)	11α, 11β	1α, 5, 11α	
10	37.69				2, 25
11	17.25	$^{\alpha}$2.48 (dd, 4.7, 17.1)	9, 11β	9	
		$^{\beta}$2.21 (dd, 12.9, 17.1)	9, 11α	22, 23	
12	100.22				11α, 11β, 14
13	162.76				11α, 11β, 14
14	99.34	6.39 (s)		21	
15	155.58				14
16	163.95				11α
17	127.58				14
18	132.71	8.07 (d, 8.1)	19	14, 19	
19	123.56	7.35 (dd, 4.8, 8.0)	18, 20	18, 20	
20	151.01	8.62 (s)		19	
21	146.59	8.96 (s)		14	
22	20.64	1.23 (s)		6β, 7β, 11β, 23	
23	15.10	0.91 (s)		6β, 11β, 22, 25	
24	28.02	0.87 (s)		5, 6α	
25	16.55	0.58 (s)		6β, 23	
26	170.81				27
27	21.19	2.03 (s)			

[a] ($CDCl_3$, 125.75 MHz). [b] ($CDCl_3$, 500.13 MHz). [c] Correlations to proton No. [d] C to H correlations.

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6. 1: white powder; $[\alpha]^{18}$ +146.2° (c 0.5 in $CHCl_3$); mp 141-142°C (decompose); UV (MeOH) λ_{max} 232 nm (ε 19200), 322 nm (ε 11100); IR (film) ν_{max} 2947, 1716, 1643, 1577, 1400, 1246 cm^{-1}; HREIMS *m/z* 451.2347 (451.2358 calcd for $C_{27}H_{33}NO_5$): 451 (100%), 376 (9%), 255 (26%), 202 (78%), 148 (17%), 106 (24%), 69 (15%).
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