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Terreulactone A, a novel meroterpenoid with anti-acetylcholinesterase activity from *Aspergillus terreus*

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Abstract—A new sesquiterpene lactone type meroterpenoid, terreulactone A, was isolated from the solid-state fermentation of *Aspergillus terreus* and its structure was established by various spectral analysis. © 2002 Elsevier Science Ltd. All rights reserved.

Alzheimers disease is a neurodegenerative disorder that is the most common cause of dementia among the elderly. The neurophathological evidences have demonstrated that cholinergic functions declined in the basal forebrain and cortex in senile dementia of the Alzheimer type.[1,2] Accordingly, enhancement of cholinergic neurotransmission have been considered as one potential therapeutic approach against Alzheimers disease. One treatment strategy to enhance cholinergic functions is the use of acetylcholinesterase (AChE, EC 3.1.1.7) inhibitors to increase the amount of acetylcholine present in the synapses between cholinergic neurons.[3,4] In this respect, an inhibitor selective for acetylcholinesterase has attracted particular attention for treatment of the Alzheimer-type dementia.

In the course of our screening for selective acetylcholinesterase inhibitors from microbial metabolites,[5] we isolated a new meroterpenoid containing a uniquely fused lactone skeleton named terreulactone A (**1**)[6] from the solid-state fermentation (4.5 kg) of *Aspergillus terreus* Fb000501 (Fig. 1). An ethyl acetate extract of the solid culture of *A. terreus* Fb000501 was purified by SiO_2 and Sephadex LH-20 column chromatographies followed by an ODS column chromatography eluted with 55% CH_3CN to yield **1** (3.5 mg).

The molecular formula of **1** was determined to be $C_{28}H_{30}O_9$ on the basis of high resolution FAB-MS [$(M+H)^+$, 511.1991 m/z (+2.3 mmu error)] in combina-

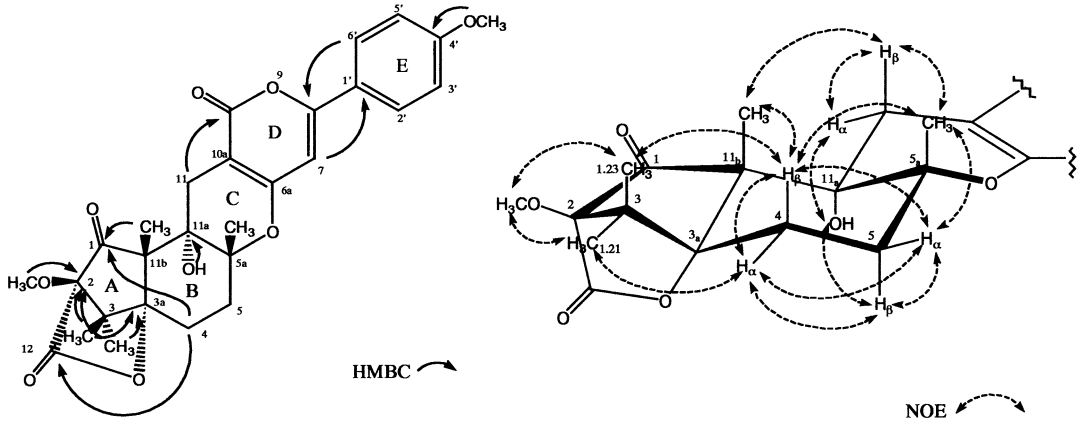

Figure 1. Key HMBC and NOE correlations of terreulactone A.

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Table 1. The ^{13}C (125 MHz) and ^{1}H (600 MHz) NMR spectral data of **1** in DMSO-d_6

C	DEPT	δ H(*J*, Hz)	HMBC	C	DEPT	δ H(*J*, Hz)	HMBC
1	208.4 s			8	157.1 s		
2	98.4 s			10	163.5 s		
2-OMe	54.8 q	3.73 (s)	C-2	10_a	97.3 s		
3	56.8 s			11	27.8 t	H_α 2.53 (d, 17.0)	C-6_a, C-10_a, C-11_a
3_α-Me	18.9 q	1.21 (s)	C-2, C-3, C-3_a, 3β-Me			H_β 2.97 (d, 17.0)	C-5_a, C-6_a, C-10, C-10_a, C-11_a
3_β-Me	21.3 q	1.23 (s)	C-2, C-3, C-3_a, 3α-Me	11_a	74.0 s		
3_a	92.2 s			11_a-OH		4.8 (s)	C-5_a, C-11, C-11_a, C-11_b
4	19.9 t	H_α 1.96 (d, 14.0)	C-3_a, C-5, C-12*	11_b	51.9 s		
		H_β 2.23 (ddd, 14.0, 13.6, 3.7)	C-1*, C-5_a, C-11_b,	11_b-Me	21.1 q	1.38 (s)	C-1, C-3_a, C-11_a, C-11_b
5	29.6 t	H_α 1.75 (d, 12.8)	C-3_a, C-5_a, 5_a-Me, C-11_a	12	166.9 s		
		H_β 2.45 (ddd, 13.6, 12.8, 3.7)	5_a-Me	1′	123.4 s		
5_a	80.8 s			2′,6′	126.8 d	7.81 (d, 8.9)	C-8, C-6′, C-4′
5_a-Me	24.5 q	1.42 (s)	C-5, C-5_a, C-11_a	3′,5′	123.4 d	7.03 (d, 8.9)	C-1′, C-5′, C-4′
6_a	162.8 q			4′	161.1 s		
7	96.7 d	6.73 (s)	C-6_a, C-9, C-1′, C-10_a	4′-OMe	55.4 q	3.81 (s)	C-4′

The assignments were aided by ^{1}H–^{1}H COSY, DEPT, NOESY, HMQC, and HMBC. *$CDCl_3$, optimized for 4.2 Hz.

tion with ^{1}H and ^{13}C NMR data. The IR data suggested the presence of a γ-lactone (1754 cm^{-1}) and a hydroxyl (3437 cm^{-1}) moiety. The ^{1}H and ^{13}C NMR data (Table 1) with DEPT, ^{1}H–^{1}H COSY, and HMQC data suggested the presence of a 1,4-disubstituted benzene ring, an olefinic methine, four isolated methyls, two methoxys, -CH_2-CH_2-, an isolated methylene, two carboxylic carbons, one carbonyl, five sp^2 quaternary carbons, six sp^3 quaternary carbons, and one exchangeable proton. These spectral data with HMBC data (Table 1) indicates the presence of the rings B, C, D, and E which are rare skeletons related to arisugacin.[7] The presence of the ring A fused with a γ-lactone was determined by HMBC spectral data. The long range coupling were observed from 11_b-Me (δ 1.38) to the carbonyl carbon (C-1, δ 208.4) and three sp^3 quaternary carbons [C-11a (δ 74.0), C-11_b (δ 51.9), and C-3_a (δ 92.2)] and from both 3_β-Me (δ 1.23) and 3_α-Me (δ 1.21) to three sp^3 quaternary carbons [C-2 (δ 98.4), C-3 (δ 56.8) and C-3a]. Together with the molecular formula and its unsaturation degree requiring the existence of two more rings, these HMBC data suggested the presence of a five-membered ring fused with a γ-lactone ring at C-2 and C-3_a. The chemical shift of C-2 and C-3_a indicated that the carbonyl carbon and oxygen atom of the γ-lactone should be connected to C-2 and C-3_a, respectively. In addition, the weak correlation of the γ-lactone carbonyl carbon (C-12) with 4-H_α was observed in the HMBC optimized for 4.2 Hz in $CDCl_3$ while 4-H_β was correlated to C-1. The relative stereochemistry of C-2 and C-3_a were determined to be all *R** by the NOEs effect between 4-H_β and 3_β-Me, and between 4-H_α and 3_α-Me. Also, the relative stereochemistry of C-5_a, C-11_a, and C-11_b were determined to be *R**, *S**, and *R**, respectively (Fig. 1).

Terreulactone A is a new meroterpenoid incorporating a uniquely fused lactone skeleton in its molecule. Since some derivatives of arisugacin B[7] were also detected in the same culture, terreulactone A seems to be biogenetically related to arisugacin isolated from *Penicillium* sp. So far a few meroterpenoid such as territrem,[8] pyripyropene,[9] and oxalicine,[10] were isolated from microbial metabolites. Terreulactone A is the first sesquiterpene lactone type meroterpenoid of microbial origin as far as I know. Terreulactone A inhibited acetylcholinesterase in a dose-dependent fashion with an IC_{50} (μM) value of 0.2 which showed higher activity than that (IC_{50} (μM): 0.42) of a methoxylated derivative of arisugacin B.

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6. Compound **1**: a white powder; mp 210–235°C; UV λ_{max} nm (ε) in MeOH: 214 (85,000), 253 (11,000), 331 (11,000); IR (KBr): 3437, 2924, 1800, 1754, 1704, 1572, 1513, 1259, 1178 cm^{-1}; $[\alpha]_D = +60°$ ($c = 0.1$, $CHCl_3$); HRFAB-MS: m/z 511.1991 $(M+H)^+$, $C_{28}H_{31}O_9$ requires 511.1968.
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