DUTOMYCIN, A NEW ANTHRACYCLINE ANTIBIOTIC FROM *Streptomyces*

Sir:

In the course of screening for new antitumor antibiotics, we found that *Streptomyces* sp. 1725[†] produces a new anthracycline antibiotic named dutomycin (**1**). In this communication, we report the production, isolation, physico-chemical and biological properties of **1**.

The producing microorganism was isolated from a soil sample collected at Yunnan, China, which was classified as a *Streptomyces* species. The inoculum was prepared on a rotatory shaker for 48 hours at 28°C in a medium consisting of glucose 5%, soybean meal 2%, soluble starch 2%, peptone 0.2%, $MgSO_4$ 0.05%, $(NH_4)_2SO_4$ 0.05%, NaCl 0.03% and $CaCO_3$ 0.6% in 500 ml Erlenmeyer flask. Further fermentation was run on a rotatory shaker for 168 hours at 28°C in a medium consisting of glucose 5%, soybean meal 2.5%, soluble starch 5%, peptone 0.3%, NaCl 0.03%, $CaCO_3$ 0.6% and seed 5% in 500 ml Erlenmeyer flask.

The harvested broth was centrifuged and the mycelial cake extracted with acetone. After concentration *in vacuo*, the residue was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water, and dried with anhydrous Na_2SO_4, then filtered. The filtrate was concentrated and chromatographed on a silica gel column with CH_2Cl_2-MeOH (50:1) as eluent. **1** was obtained as an orange powder. Its physico-chemical properties are summarized in Table 1.

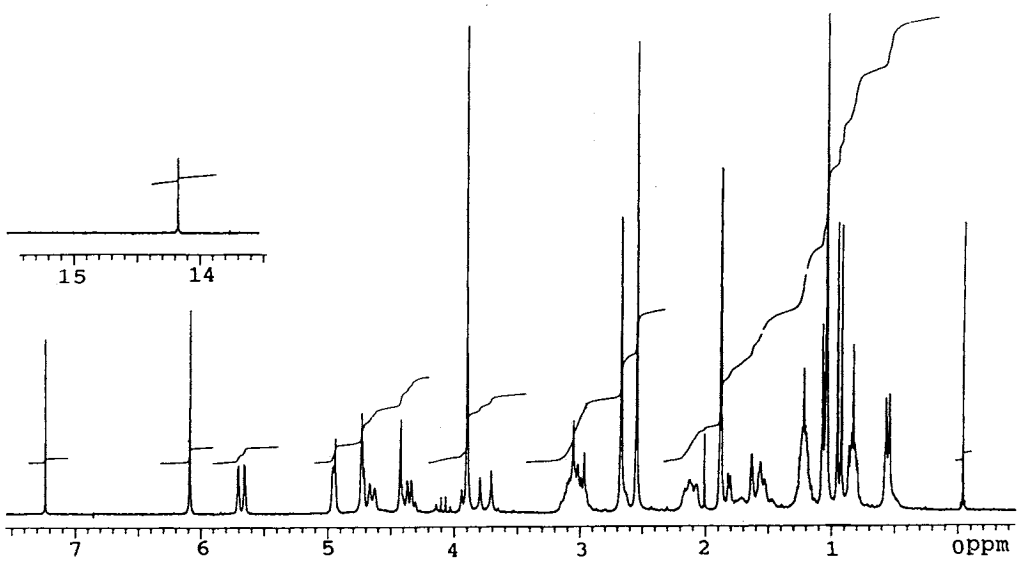
The UV and IR spectral data all suggested that **1** possesses quinone structure. Positive FD-MS gave the molecular weight as 855 $(M+H)^+$. Along with the result of elemental analysis, the molecular formula of **1** was determined by NMR spectral analysis and chemical degradation.

^1H NMR spectrum (Fig. 1) indicated the presences of four singlet signals of methyl group (2.70 ppm, 2.46 ppm, 1.10 ppm and 1.06 ppm), three doublet signals of methyl group at 0.58 ppm, 0.95 ppm and 1.90 ppm, one methoxy signal at 3.92 ppm. Two olefinic protons were also found at

Table 1. Physico-chemical properties of dutomycin (**1**).

Nature	Orange powdery crystal
$[\alpha]_D^{24}$	−85° (*c* 0.1, DMSO)
Molecular formula	$C_{44}H_{54}O_{17}$
MP	237~238°C
UV (nm)	
MeOH	201, 241, 279, 445
MeOH-NaOH	230, 266, 320, 541
IR (cm^{-1})	3400, 1690, 1640, 1605
Elemental analysis	
Found:	C 61.60, H 6.58, O 31.82
Calcd:	C 61.83, H 6.32, O 31.85
FD-MS (*m/z*)	855 $(M+H)^+$

Fig. 1. ^1H NMR spectrum of dutomycin (**1**) in $CDCl_3$ at 400 MHz.



[†] Taxonomic studies on this microorganism are in progress.

Fig. 2. Structures of dutomycin (1) and its derivatives.

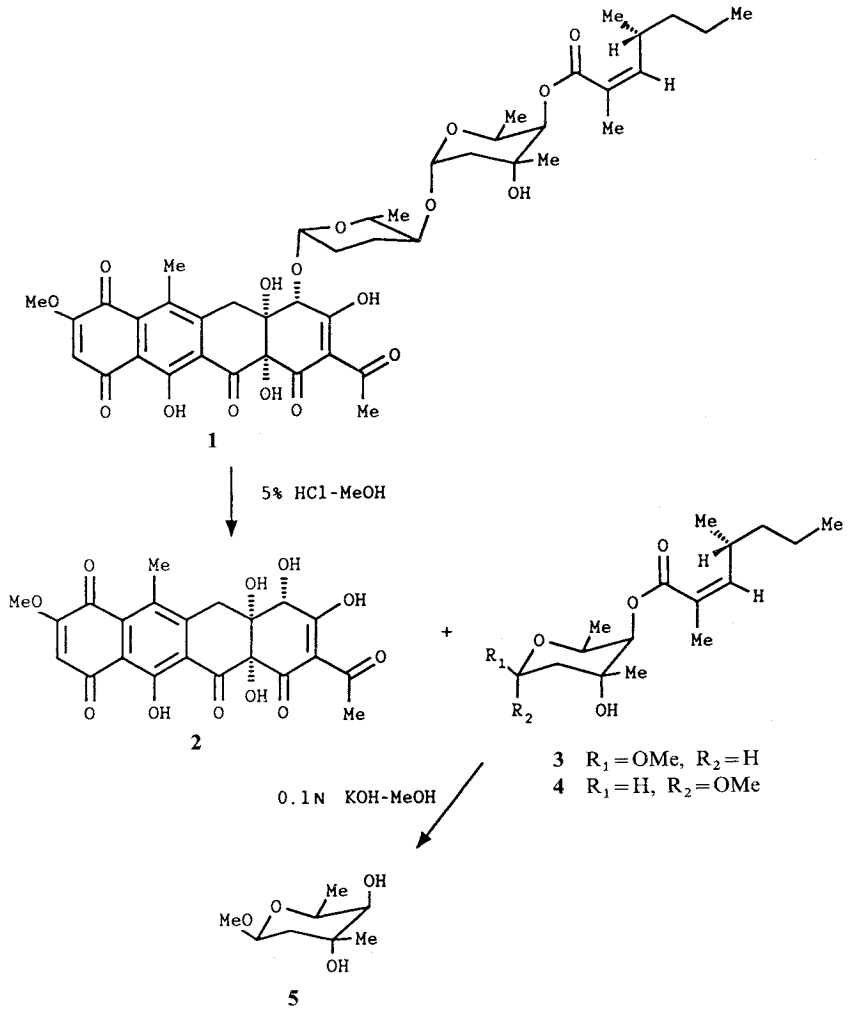
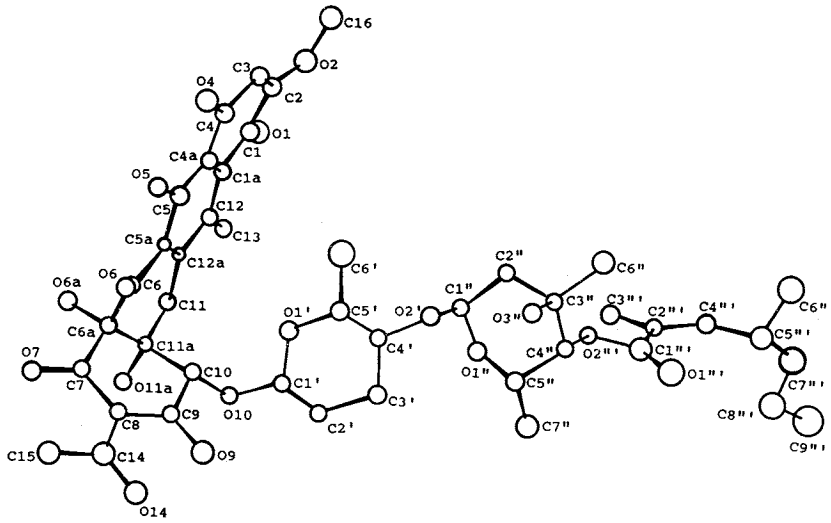


Table 2. ^{13}C NMR spectral data of dutomycin (1) (DMSO-d_6, 50 MHz).

Carbon	δ (ppm)	Carbon	δ (ppm)	Carbon	δ (ppm)
1a	132.690[a]	11	34.771	3″	68.634
1	181.310	12a	150.559	4″	74.272
2	161.073[b]	12	131.279[a]	5″	62.632
3	108.698	13	16.571	6″	20.903[d]
4	190.571	14	200.036	7″	20.548[d]
4a	113.616[c]	15	26.479	1‴	167.219
5	161.535[b]	16	56.893	2‴	124.989
5a	123.147	1′	102.002	3‴	16.571
6	192.407	2′	29.231	4‴	149.877
6a	80.870	3′	30.013	5‴	33.282
7	195.253	4′	73.954	6‴	25.560
8	110.503[c]	5′	73.278	7‴	39.569
9	190.062	6′	17.205	8‴	20.626
10	79.830	1″	100.119	9‴	14.178
11a	75.280	2″	36.736		

[a~d] Signals may be exchanged.

Fig. 3. Perspective view of dutomycin (**1**).



6.08 ppm as singlet and 5.68 ppm as dd. The assignment of ^{13}C NMR spectral data (Table 2) was acheived by the APT technique and comparison with known compounds.

Methanolysis of **1** with methanolic hydrochloric acid gave the aglycone (**2**) and a pair of anomeric isomers (**3** and **4**). **3** was further methanolized in alkaline methanol and L-axenose methyl glycoside (**5**) was obtained.

The results of X-ray analysis are consistent with above elucidation. **1** was crystallized from benzene-petroleum ether. Space group $P2_12_12_1$, $a=18.045(3)$, $b=18.963(3)$, $c=15.611(3)$ Å, $\alpha=\beta=\gamma=90°$, $Z=4$. The relative structure was solved by direct method (MULTAN-86). The final R value was 0.0703. A perspective drawing of **1** was given with the absolute configuration in Fig. 3 because the structure of **5** is known. Details of the structure determination of **1** will be reported later.

Dutomycin (**1**) showed strong *in vitro* cytotoxic activity against leukemia P388. 100% inhibition was acheived at a concentration of 1 μg/ml.

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LI-JIANG XUAN
SAO-HUA XU
HAI-LAN ZHANG
YA-MING XU*

Shanghai Institute of Materia Medica, Academia Sinica, 319 Yue-Yang Road, Shanghai, China

MING-QING CHEN

The Research Center of Analysis and Measurement, Fudan University, Shanghai, China

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