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# An Acetal Derivative of Illudin S with Improved Antitumor Activity

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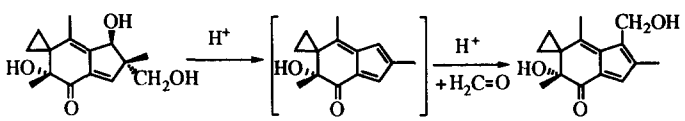
**Abstract:** Methylene acetal of an epimer of illudin S (**5**) was obtained by treating illudin S with a large excess of paraformaldehyde in 1N $H_2SO_4$ solution. X-ray crystallographic analysis showed that the configuration at the allylic carbon has been inverted. This acetal was found to be less toxic and showed a higher therapeutic index than illudin S. © 1997 Elsevier Science Ltd. All rights reserved.

The toxic sesquiterpene illudin S (**1**) is produced in cultures of the wood rotting fungus *Omphalotus illudens*.[1] This compound possesses antitumor activity but its selective toxicity toward tumor cells is poor. Investigations on modification of the structure to improve the therapeutic index have resulted in preparation of several analogs with superior antitumor properties.[2-4] Thus reaction of illudin S with formaldehyde in 1N $H_2SO_4$ solution gives the yellow analog HMAF (**3**) (Scheme 1).[4] This compound shows excellent efficacy against a variety of solid tumors implanted in mice and is presently undergoing clinical trials.[5]

**Scheme 1**

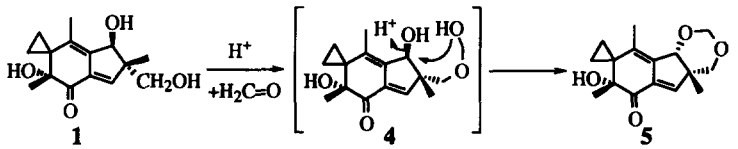



**1.** Illudin S **2** **3.** HMAF

In order to improve the yield and purity of HMAF, various conditions were studied and it was found that a large excess of paraformaldehyde in 1N $H_2SO_4$ solution gave the best results when illudin S was allowed to react for 2-4 days at room temperature. However, a white by-product was formed in 23% yield when the concentration of paraformaldehyde reached a level 200-300 times that of illudin S, and the yield of HMAF decreased. The structure of this by-product was analyzed: NMR ($^1H$ & $^{13}C$) data showed that an acetal was formed from formaldehyde and the 1, 3-diol moiety in illudin S. The MS showed a molecular ion m/z 276 and the HRMS revealed a formula of $C_{16}H_{20}O_4$.[6]

However, it seemed puzzling that this derivative was obtained because it would be expected to be highly strained and not easily formed, particularly in strong acidic aqueous medium. Finally an X-ray crystallographic analysis of the acetal derivative showed in fact that the structure is **5**, indicating inversion of the oxygen substituent in the five membered ring (Figure 1). A plausible intermediate is compound **4** whose protonated allylic hydroxyl group would be easily replaced (Scheme 2). Acetal derivative **5** was found to be somewhat less toxic than illudin S to lung adenocarcinoma (MV522) cells and human leukemia (HL60) cells but substantially less toxic to B-cell leukemia/lymphoma (8392) cells *in vitro* (Table 1).[7] It had an improved therapeutic index

**Scheme 2**




compared to the parent compound **1** when tested on MV522 cells implanted in nude mice. Its efficacy was comparable to that of mitomycin C, tested at the same time (Figure 2).

Table 1. $IC_{50}$ values (nM)*

| Compound | HL-60 | MV 522 | 8392 |
|---|---|---|---|
| Illudin S | 10 ± 1 | 19 ± 6 | 236 ± 20 |
| Acetal **5** | 25 ± 8 | 115 ± 30 | 9650 ± 200 |

* Cytotoxicity values were obtained by thymidine incorporation assay: See reference 7 for description of these methods.

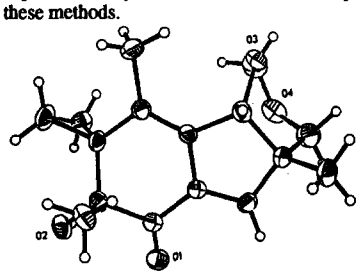



Figure 1. ORTEP view of X-ray molecular structure of acetal **5**.

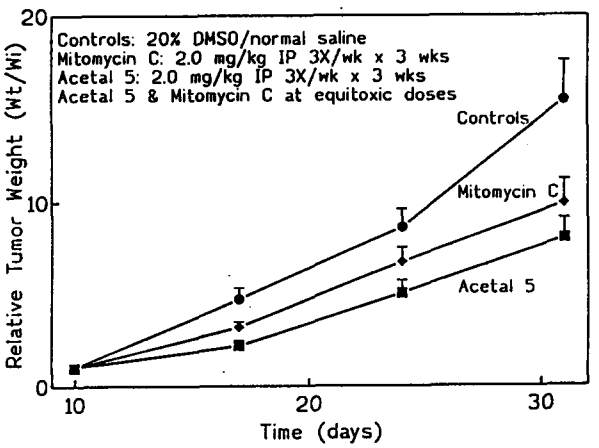



Figure 2. Efficacy of acetal **5**, compare to mitomycin C in the human lung MV522 multidrug resistant (gp 170 +) metastatic tumor model.

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6. Compound **5** is a white solid: mp 100.5-102.5 °C; IR (KBr) 3469, 2966, 2858, 1903, 1656, 1596 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.48 (m, 1H), 0.84 (m, 1H), 0.99 (m, 1H), 1.10 (s, 3H), 1.17 (m, 1H), 1.32 (s, 3H), 1.67 (s, 3H), 3.61 (s, 1H), 3.73 (d, J = 11.7 Hz, 1H), 3.96 (d, J = 11.7 Hz, 1H), 4.56 (s, 1H), 4.75 (d, J = 5.4 Hz, 1H), 4.91 (d, J = 5.4 Hz, 1H), 6.52 (s, 1H); $^{13}C$ NMR ($CDCl_3$) δ 199.7, 141.4, 136.3, 135.9, 134.7, 90.0, 80.3, 75.9, 70.8, 46.8, 32.3, 24.7, 22.5, 13.8, 8.9, 5.6; MS m/z 276 ($M^+$), 217, 201, 173; HRMS for $C_{16}H_{20}O_4$ calcd 276.1362, found 276.1364; UV λmax 305 nm (ε 3148).
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