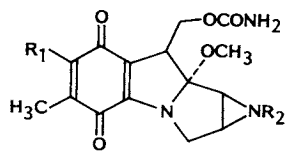
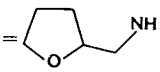
CYCLIC ACETAL DERIVATIVES OF MITOMYCIN C

Sir:

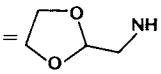
Since the discovery of mitomycins, there have been numerous mitomycin analogues prepared[1] and some of them are currently being developed toward clinical trials. A survey of earlier analogues suggested mitosanes having a 1,3-dioxacyclopent-2-ylmethylamino group at the C-7 position might be of interest. For example, compound **2** gave much greater increases in life span than mitomycin C against both P388 leukemia and B16 melanoma[2]. Compound **3** was reported to have activity comparable to mitomycin C against P388 and L1210 leukemias[3]. It intrigued us then to see what effect two heteroatoms in a cyclic acetal form would have on antitumor activity. In this communication we report the synthesis of such derivatives and their rather remarkable antitumor activity.

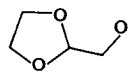


1 $R_1=NH_2$ $R_2=H$

2 $R_1=$  $R_2=H$

3 $R_1=(CH_3O)_2CHCH_2NH$ $R_2=H$

9 $R_1=$  $R_2=CH_3$

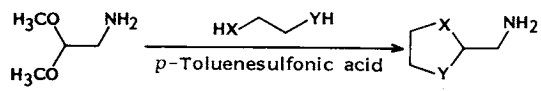
10 $R_1=$  $R_2=H$

The desired derivatives were synthesized by either one of the following two methods: One is to substitute the methoxy group of mitomycin A (**4**) with an appropriate amine[4]. The other is to use bis-(*N*,*N*-dimethylamidino) derivative (**5**) of mitomycin C. This compound is prepared directly from mitomycin C and it can be substituted at C-7 position with a primary amine[5]. The prerequisite primary amines were prepared in good yield from aminoacetaldehyde dimethyl acetal by an acid catalyzed exchange with ethylene glycol, 1,2-ethanedithiol, or 2-mercaptoethanol (Fig. 1).

Thus, a reaction of **5** with 3 equiv of *N*-(1,3-dioxacyclopent-2-ylmethyl)amine in methanol at room temperature for 18 hours gave compound **6** in 44% yield. Reactions with mitomycin A with *N*-(1,3-dithiacyclopent-2-ylmethyl)amine or *N*-(1-oxa-3-thiacyclopent-2-ylmethyl)amine in methanol gave compounds **7** and **8** in 80 and 74% yield, respectively. The porfiromycin acetal derivative (**9**) was prepared in 81% yield by methylation of the aziridine nitrogen with methyl iodide[6,7].

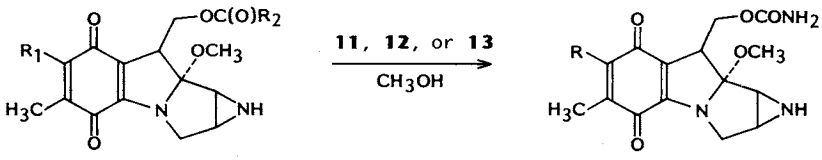
The antitumor activity of these derivatives against P388 leukemia is shown in Table 1. As can be seen, these derivatives possess antileukemic activity superior or at least equal to mitomycin C on the daily treatment schedule. Table 2 shows their activity

Fig. 1. Synthesis of cyclic acetal amines.

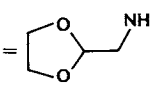


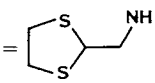
11 X=Y=O
12 X=Y=S
13 X=O Y=S

Fig. 2. Synthesis of cyclic acetal derivertives of mitomycin C.



4 $R_1=CH_3O$ $R_2=NH_2$
5 $R_1=(CH_3)_2NCH=N$ $R_2=(CH_3)_2NCH=N$

6 R= 

7 R= 

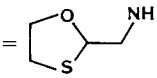
8 R= 

Table 1. Antitumor activity of cyclic acetal derivatives of mitomycin C against P388 leukemia[a].

Compound	Dose, ip[b] (mg/kg)		Max % T/C[c] (cures/total)	
	Schedule A	Schedule B	Schedule A	Schedule B
Mitomycin C (**1**)	3.2	1.6	311	189
6	12.8	3.2	>378 (3/6)	>378 (3/6)
7	12.8	3.2	>378 (1/6)	183
8	12.8	3.2	>378	328

[a] P388 leukemia, 10^6 cells, were implanted ip on day 0 into CDF_1, mice. Control mice had a median survival time of 9.0 days; none survived.
[b] Optimum doses (those associated with the highest % T/C) administered on Schedule A, day 1 only post-implant, or Schedule B, daily for 5 days.
[c] Maximum (Max) % T/C was based upon the median survival times of treated (T) and control (C) mice, including any mice alive at the termination of the experiment. "Cures" were tumor-free mice as of day 34 post-implant, the day the experiment was terminated.

Table 2. Antitumor activity of cyclic acetal derivatives of mitomycin C against B16 melanoma[a].

Compound	Dose, ip[b] (mg/kg/injection)	Max % T/C (cures/total)[c]	Survivors (on day 63)
Mitomycin C (**1**)	3	>315 (5/10)	5
6	4	>315 (9/10)	9
7	8	>315 (10/10)	10
8	6	>315 (9/10)	9

[a] B16 melanoma, 0.5 ml of a 10% tumor brei, was inoculated ip on day 0 into BDF_1 mice.
[b] Optimum dose (causing highest % T/C) administered on days 1, 5 and 9.
[c] Maximum (Max) % T/C was based upon the median survival times of treated (T) and control (C) mice, including any mice alive at the termination of the experiment. "Cures" were tumor-free mice on day 63 post-implant, the day the experiment was terminated.

against ip inoculated B16 melanoma. It indicates that these derivatives are exceptionally active against ip implanted B16 melanoma as reflected by the presence of numerous cured mice. It is of interest that in studies performed parallel to ours but involving the corresponding mitomycin A analogues (**10**) having a cyclic acetal structure, these compounds were also found to be quite active against P388 leukemia[1]. It was further reported that compounds **6**, **7** and **9** were preferentially toxic *in vitro* to hypoxic EMT6 cells[8]. Thus, these derivatives appear to be uniquely active compounds among the mitomycin C analogues.

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(Received September 4, 1989)

References

1) SAMI, S. M.; W. A. REMERS & W. T. BRADNER: Preparation and antitumor activity of additional mitomycin A analogues. J. Med. Chem. 32: 703~708, 1989 and references therein
2) IYENGAR, B. S.; H.-J. LIN, L. CHENG & W. A. REMERS: Development of new mitomycin C and porfiromycin analogues. J. Med. Chem. 24: 975~981, 1981
3) IYENGER, B. S.; S. M. SAMI, W. A. REMERS, W. T. BRADNER & J. E. SCHURIG: Mitomycin C and porfiromycin analogues with substituted ethylamines at position 7. J. Med. Chem. 26: 16~20, 1983
4) KINOSHITA, S.; K. UZU, K. NAKANO, M. SHIMIZU, T. TAKAHASHI & M. MATSUI: Mitomycin derivatives. 1. Preparation of mitosane and mitosene compounds and their biological activities. J. Med. Chem. 14:

103～109, 1971

5) VYAS, D. M.; Y. CHIANG, D. BENIGNI & T. W. DOYLE: Novel mitomycin C amidines: Synthesis and their reactions with amines. J. Org. Chem. 52: 5601～5605, 1987

6) WEBB, J. S.; D. B. COSULICH, J. H. MOWAT, J. B. PATRICK, R. W. BROSCHARD, W. E. MEYER, R. P. WILLIAMS, C. F. WOLF, W. FULMOR, C. PIDACKS & J. E. LANCASTER: The structures of mitomycins A, B and C and porfiromycin — Part I. J. Am. Chem. Soc. 84: 3185～3187, 1962

7) WEBB, J. S.; D. B. COSULICH, J. H. MOWAT, J. B. PATRICK, R. W. BROSCHARD, W. E. MEYER, R. P. WILLIAMS, C. F. WOLF, W. FULMOR, C. PIDACKS & J. E. LANCASTER: The structures of mitomycins A, B, and C and porfiromycin — Part II. J. Am. Chem. Soc. 84: 3187～3188, 1962

8) KEYES, S. R.; R. LOOMIS, D. M. VYAS, T. KANEKO, T. W. DOYLE, H. WONG, S. ROCKWELL & A. C. SARTORELLI: Cytotoxicity of mitomycin analogues BMY43324, BMY42549 and BMY42355 to hypoxic EMT6 tumor cells *in vivo* and *in vitro*. Proc. Am. Assoc. Cancer Res. 30: 544, 1989