ANTITUMOR ACTIVITY OF 15-ACETOXYSCIRPEN-3,4-DIOL

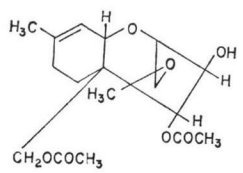
Sir:

Anguidine (4,15-diacetoxyscirpen-3-ol, **1**), a member of a class of naturally-occurring 12,13-epoxytricothecenes[1] produced by strains of *Fusarium equiseti*[2], has been shown to have activity *in vivo* against the transplantable mouse tumor P-388 lymphatic leukemia (W. T. BRADNER, unpublished results). Phase I clinical trials of anguidine in the United States have been completed[3,4] and phase II trials have started. We wish to report the improvement of the antileukemic activity by a chemically prepared derivative of anguidine, 15-acetoxyscirpen-3,4-diol (**2**).

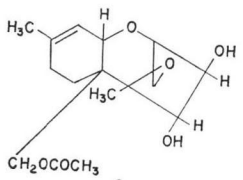
The 15-acetoxyscirpenol was prepared by mild base hydrolysis of anguidine by the procedure of SIGG *et al.*[5] The *in vivo* mouse tumor inhibition test was conducted according to the protocols established by the National Cancer Institute.[6] The tissue culture tests were performed following published procedures.[7]

The results of three experiments recording the effect of anguidine and 15-acetoxyscirpenol on P-388 leukemia in mice are given in Table 1. The 15-acetoxyscirpenol shows activity at an eight-fold smaller dose than anguidine, and, moreover, produces a marked increase in the median survival time (T/C > 200), indicative of greater antitumor effectiveness over a range of three doses, not evident with anguidine. In addition, the maximum tolerated dose for anguidine is 1.6 ~ 3.2 mg/kg/day and for 15-acetoxyscirpenol 0.8 mg/kg/day, suggesting at least a two- to four-fold difference in toxicity. This represents at least a two-fold improvement in the therapeutic ratio.

In Table 2, where the results of a cytotoxicity measurement employing HeLa and L929 cell cultures are given, it can be seen that the activity of 15-acetoxyscirpenol is about the same or perhaps slightly less than that of anguidine.



1



2

Table 1. Effect of 15-acetoxyscirpenol on P-388 lymphatic leukemia

Compound	Dose mg/kg/day	Tumor inhibition MST %T/C		
		Exp 1	Exp 2	Exp 3
NSC-141537 anguidine	3.2	211	200	83
	1.6	178	189	178
	0.8	194	178	167
	0.4	144	144	161
	0.2	139	144	144
	0.1	128	144	128
	0.05	111	122	122
	0.025	100	111	100
NSC-267030 15-acetoxy-scirpenol	25.6	Tox		
	12.8	Tox		
	6.4	Tox		
	3.2	78	Tox	
	1.6	83	89	
	0.8	206	228	233
	0.4	222	222	211
	0.2	211	206	206
	0.1		178	178
	0.05		156	156
	0.025		144	139
	0.0125			128
	0.00625			111

Treatment: Once daily for nine injections.
Evaluation: MST = median survival time.
% T/C = MST treated/MST control × 100.
Criterion: T/C ≧ 125 considered significant antitumor effect.
Toxicity: < 4/6 survivors, Day 5.

Table 2. Cytotoxicity measurement of anguidine and 15-acetoxyscirpenol

Compound	Cell cultures TD_{50}* in μg/ml	
	HeLa	L929
Anguidine	0.0024	0.0041
15-Acetoxyscirpenol	0.0053	0.0097

*TD_{50} Concentration required to cause a 50% reduction in net protein production.

The antitumor activity of a number of other analogues of anguidine prepared either by microbiological or chemical transformations will be the subject of a further communication.

Acknowledgement

Thanks are extended to A. SCHLEIN for the tissue culture cytotoxicity tests.

This work was performed in part under Public Health Service Contract N01-CM43759 from the National Cancer Institute.

C. A. CLARIDGE*
W. T. BRADNER*
HENRY SCHMITZ†

*Antitumor Biology Department
†Antitumor Chemistry Department
Research Division
Bristol Laboratories
Syracuse, New York 13201
U.S.A.

(Received February 18, 1978)

References

1) BAMBURG, J. R. & F. M. STRONG: 12,13-Epoxytrichothecenes. *In*: S. KADIS, A. CIEGLER & S. J. AJL (*eds.*) Microbial Toxins. Vol. VII, pp. 207~292, New York, Academic Press, 1971
2) BRIAN, P. W.; A. W. DAWKINS, J. F. GROVE, H. G. HEMMING, D. LOWE & G. L. F. NORRIS: Phytotoxic compounds produced by *Fusarium equiseti*. J. Exp. Botany 12: 1~12, 1961
3) MURPHY, W. K.; R. B. LIVINGSTON, J. A. GOTTLIEB, M. A. BURGESS & R. W. RAWSON: Phase I evaluation of anguidine. Proc. Amer. Assoc. Cancer Res. 17: 90, 1976
4) HAAS, C.; W. GOODWIN, C. LENTE, R. STEPHENS & B. HOOGSTRATEN: Phase I study of anguidine (diacetoxyscirpenol NSC #141537). Proc. Amer. Assoc. Cancer Res. 18: 296, 1977
5) SIGG, H. P.; R. MAULI, E. FLURY & D. HAUSER: Die Konstitution von Diacetoxyscirpenol. Helv. Chim. Acta 48: 962~988, 1965
6) GERAN, R. I.; N. N. GREENBERG, M. M. MACDONALD, A. M. SCHUMACHER & B. J. ABBOTT: Protocols for screening chemical agents and natural products against animal tumors and other biological systems. Cancer Chemoth. Rep. 3: 1~103, 1972
7) BRADNER, W. T.; B. HEINEMANN & A. GOUREVITCH: Hedamycin, a new antitumor antibiotic. II. Biological properties. Antimicr. Agents & Chemoth.-1966: 613~618, 1967