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SHORT COMMUNICATIONS

6-Selenoguanine (2-amino-6-selenopurine). Synthesis and biological studies

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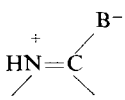
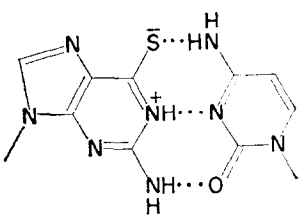
6-THIOGUANINE has been studied extensively as an inhibitor of the growth of transplantable neoplasms in animals and to some extent as an antileukemic agent in man. It exhibits antimitotic activity[1] and has been shown to be incorporated into deoxyribonucleic acid (DNA).[2] While the mechanism of action of this compound has not as yet been established, it seems possible that charge separation of the type:



which has been found to be greater in thiocarbamyl than in carbamyl compounds,[3, 4] might lead to unusually strong hydrogen-bonding with the amino group of cytosine facing thioguanine in the double helix of DNA:



Such intra-helical interaction would be expected to interfere with the replication of deoxyribonucleic acid.

Since replacement of sulfur by selenium leads to an even more marked polarization in this type of structure and because 6-seleno-purine had shown some antitumor activity in mice,[5, 6] in spite of its lack of stability, the synthesis of 6-selenoguanine was of interest.

2-Amino-6-selenopurine was prepared by the reaction of sodium hydroselenide with 2-amino-6-chloropurine (generously supplied by G. B. Elion and G. H. Hitchings of the Wellcome Research Laboratories) in a manner analogous to that used in the synthesis of 6-selenopurine.[4]

Stability studies with 6-selenoguanine in buffered solutions showed that this compound is more stable than is 6-selenopurine. Effective inhibition of the growth of *Lactobacillus casei* (ATCC 7469) occurred with selenoguanine with one-tenth the concentration required with thioguanine.

While the single-dose toxicity of selenoguanine in mice exceeded that of its sulfur analog, the opposite proved to be the case when the compounds were administered repeatedly.

The effects of selenoguanine and thioguanine on the growth *in vivo* of several experimental murine neoplasms: lymphomas L1210 (sublines A and B) and L5178Y, and Sarcoma 180, were determined, and it was found that the antitumor activities of these two compounds were comparable. However, the data obtained thus far indicate that selenoguanine possesses an appreciably higher therapeutic index than does thioguanine. The response of mice bearing either lymphoma L1210 (subline A), lymphoma L5178Y, or Sarcoma 180 to seven or eight daily intraperitoneal injections of selenoguanine or thioguanine revealed that, during the period of treatment, the therapeutic indices of the two compounds were the same; i.e., the maximally tolerated dose of selenoguanine was about four times that of thioguanine, and the dose of selenoguanine required to attain a given degree of antitumor activity was also four times that of thioguanine. However, when these mice were observed during the week

following the final injections of the two compounds, it was found that significantly fewer animals treated with selenoguanine succumbed to what appeared to be delayed drug toxicity than was the case with mice treated with thioguanine. In mice bearing lymphoma L1210 (subline B) (kindly provided by Dr. J. H. Burchenal of the Sloan-Kettering Institute), the higher therapeutic index of selenoguanine, compared with that of thioguanine, was seen even during the week of treatment: the maximally tolerated dose of selenoguanine was eight times that of thioguanine, while the dose of selenoguanine required to attain a given level of antitumor activity was only twice that of thioguanine.

TABLE 1. SINGLE- AND REPEATED-DOSE TOXICITY OF SELENOGUANINE AND THIOGUANINE IN HA/ICR SWISS MICE

Compound*	Intraperitoneal dose (mg/kg)	Dose schedule	Average† change in body weight (g)	Mortality (1st week)	Mortality (2nd week)
Selenoguanine	100	single injection	−2·0	3/4	—
Thioguanine	120	single injection	−2·0	0/4	1/4
Selenoguanine	16	daily × 7	−2·0	0/10	0/10
Thioguanine	4	daily × 7	−3·5	0/10	8/10

* The compounds were suspended in a 0·25% solution of carboxymethylcellulose; the volume injected was constant, 0·4 ml.

† Mice were individually weighed and numbered at the onset of the experiment. The average initial weight of these animals was 20 g. On the day following the last injection (8th day), each mouse was reweighed, and the average change in weight of each group of 10 was recorded. On the average, mice of this age, strain, and sex (female), receiving daily intraperitoneal injections of 0·4 ml of a 0·25% solution of carboxymethylcellulose, gain 1–2 g.

It was also found that the unresponsiveness of a 6-mercapto-purine-resistant tumor extended to selenoguanine as well as to thioguanine.

All findings considered, selenoguanine appears to offer considerable promise as an inhibitor of tumor growth, and additional studies of its properties are in progress. This work was supported in part by grants (CY-3937) and (CY-2817(C4)) from the United States Public Health Service.

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REFERENCES

1. J. J. BIESELE, *Ann. N.Y. Acad. Sci.* **71**, 1054 (1958).
2. G. A. LEPAGE, *Cancer Res.* **20**, 403 (1960).
3. H. G. MAUTNER and E. M. CLAYTON, *J. Amer. Chem. Soc.* **81**, 6270 (1959).
4. H. G. MAUTNER, *ibid.* **78**, 5292 (1956).
5. H. G. MAUTNER and J. J. JAFFE, *Cancer Res.* **18**, 294 (1958).
6. J. J. JAFFE and H. G. MAUTNER, *ibid.* **20**, 81 (1960).