The Carcinostatic Activity of Benzylidene Analogs of Puromycin

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A variety of biological activities has been reported for the antibiotic, puromycin. These include in vitro inhibition of certain microorganisms (4, 10), in vivo inhibition of Trypanosoma equiperdum and Trypanosoma cruzi (5, 8), Toxoplasma gondii (11), Endamoeba histolytica (12), and oxyurids and tapeworms (7). Troy et al. (13) found that the antibiotic would inhibit the growth of a mouse mammary adenocarcinoma. The carcinostatic activity was found to be contained in the aminonucleoside portion of the molecule (9). Waller et al. (14) have characterized the compound (Chart 1). A series of 21 amino acid analogs of puromycin, prepared by Baker and co-workers (2) have been tested for their carcinostatic activity by Bennett et al. (3), and certain structure-activity relations for this series have been pointed out.

This report is concerned with the carcinostatic activity of a series of benzylidene derivatives of the aminonucleoside against two mouse mammary adenocarcinomas. These compounds, with the exception of 4007L, are water-insoluble and were tested as depot intramuscular preparations.

MATERIALS AND METHODS

Two experimental tumors were used in these experiments, a transplantable mammary adenocarcinoma in C3H mice and the 755 mammary adenocarcinoma in C57BL6 mice. It has been found that either tumor can be used to assay any of the puromycin analogs thus far prepared. Healthy animals weighing 18-20 gm. were implanted subcutaneously by trocar in the axillary region. Tumor fragments of 0.5 c.mm. were used. After the implants had become established and had grown to palpable size (1-3 weeks after implantation), the animals were uniformly grouped according to tumor size, sex, and weight. Six to ten mice were used per group, unless otherwise indicated in the tables. A saline-treated control group was included in each test. The compounds tested were suspended in 1 per cent starch and injected intramuscularly once daily for 7 days at the levels indicated in Table 1.

On the 8th day the mice were weighed and sacrificed, the tumors were excised, weighed, and examined grossly and microscopically.

Several prolonged tests were made with two of the compounds to determine whether the extended therapy would prolong life or cause complete regression of the tumor. The treatment schedule is given in Table 2. The compounds were administered until 100 per cent mortality occurred in the saline-treated control group. At this time all treatment was stopped, and the animals were maintained for observations at intervals until death.

RESULTS AND DISCUSSION

The carcinostatic activity of fifteen benzylidene derivatives is shown in Table 1. Eleven of these
produced tumor inhibitions of 74 per cent or more, while the remainder produced a 50 per cent or greater inhibition. The differences in activity observed in this series of compounds are not great enough to make any general statements concerning the relation of the structure of the benzylidene substituent to carcinostatic activity. This is in marked contrast to previously reported differences in the activity of various amino acid analogs (3).

The experiments show the marked carcinostatic activity of a new series of analogs of puromycin. An appreciable incidence of complete tumor regression was obtained, although not without some toxicity to the host and some recurrences after cessation of treatment. The entire series of compounds appear to be readily available to the animal, although it is not known whether these derivatives are active per se or are hydrolyzed to the aminonucleoside.

At the present time little is known about the mechanism of action of this class of compounds. Bortle and Oleson (4) found that the inhibition of T. pyriformis by puromycin could be reversed by guanylic acid. Hewitt and co-workers (7) could reverse the trypanocidal activity in vivo with several
purine derivatives. Agosin and von Brand (1), using T. equiperdum in vitro, showed that puromycin inhibited the over-all carbohydrate metabolism of the organism while the aminonucleoside primarily inhibited oxygen consumption and pyruvate production. These effects could be reversed by adenine.

We have not been successful in completely reversing the carcinostatic activity with any of several nucleic acid derivatives. However, it would appear that these compounds act primarily on some phase of nucleic acid metabolism.

**SUMMARY**

Fifteen benzylidene analogs of puromycin were shown to be carcinostatic for mammary adenocarcinomas of C3H and C57 mice.

In several prolonged tests, an appreciable incidence of tumor regression was observed.
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REFERENCES

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