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Screening of Potential Cancer-Inhibiting Agents

Maxwell Gordon, Jean B. Siri

Jane G. Campbell and Melvin Calvin

June 22, 1950

Berkeley, California

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ABSTRACT
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Screening of Potential Cancer-Inhibiting Agents[1]

Maxwell Gordon[2,3], Jean B. Siri,

Jane G. Campbell and Melvin Calvin

Radiation Laboratory, Department of Chemistry and Division of Medical Physics,

University of California, Berkeley

ABSTRACT

June 22, 1950

One [3',2'-h]-thiazolinopurine and ten purines and pyrimidines, which were prepared as thiazolinopurine intermediates, were screened for possible cancer-inhibiting action. C57 black mice bearing myeloid leukemias (C1498) were utilized.

The possible cancer-inhibiting action of six of the above compounds was also tested on C57 mice bearing adenocarcinomas (Eo771).

None of the compounds prepared in this program to date exhibited any cancer-inhibiting action.

For publication in "Science"

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1 The work described in this paper was sponsored by the Atomic Energy Commission.

2 Atomic Energy Commission Postdoctorate Research Fellow in the Physical Sciences of the National Research Council 1949-1950.

3 Present address: Organic Chemistry Department, Imperial College of Science and Technology, London S.W. 7, England.

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Screening of Potential Cancer-Inhibiting Agents[1]

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Feldes (1), in 1940, stated that modified essential metabolites should be sufficiently closely related to the essential metabolites on which they are based as to fit the same enzyme, but sufficiently different to be devoid of essential metabolic activity.

Since various investigators (2) had reported that the concentration of nucleic acids in tumor-bearing animals is greater than in normal animals, it was apparent that adenine and guanine inhibitors might be found which would retard tumor growth, without adversely affecting the whole animal. Hitchings (3) and Burchenal (4) have demonstrated the adenine inhibition of 2,6-diaminopurine, and Hitchings (5) and Kidder (6) showed the anti-metabolite action of 8-azaguanine.

In this laboratory we have been working on the synthesis of some thiazolinopurines related to 2,6-diaminopurine[4] and to other purines to be reported later. None of the compounds prepared in this program to date

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[2] Atomic Energy Commission Postdoctorate Research Fellow in the Physical Sciences of the National Research Council 1949-1950.

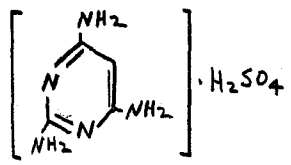
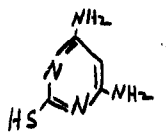
[3] Present address: Organic Chemistry Department, Imperial College of Science and Technology, London S.W.7, England.

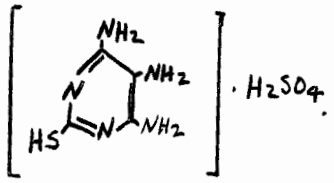
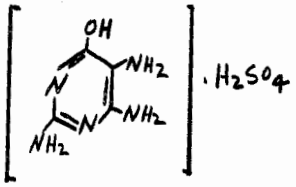
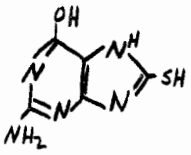
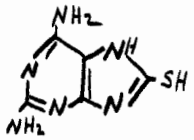
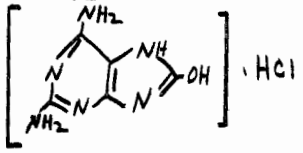
[4] The syntheses of these compounds are being reported elsewhere.

showed any cancer-inhibiting action, but they are being reported in an effort to avoid duplication by other investigators. Some of the pyrimidines reported were used as intermediates in other syntheses, but are included here since their anti-leukemic possibilities had not previously been explored.

The customary screening procedure was carried out using C57 black mice into which had been implanted either the undifferentiated adenocarcinoma No 771 or the myeloid leukemia C1498. Dosage of the compounds to be screened was arbitrarily set at 40% of the MLD/50 dose, except in cases where the animals reacted unfavorably to this amount.

Table I. Survival of Mice Bearing Myeloid Leukemia C1498.

Ref. No.	Formula and Name	MLD/50 mg./20g. mouse	Dose mg./20g. mouse	No. of I.P. Injections weekly	Mean Survival Time (Days)	Mean Survival Time of Controls
1.	2,4,6-Triamino-pyrimidine sulfate 	>40	4.0	3	10.8	10.3
2.	4,6-Diamino-2-mercaptopyrimidine 	> 40	4.0	3	10.3	10.3

3.	4,5,6-Triamino-2-mercaptopyrimidine Sulfate 	40	4.0	3	8.0	10.3
4.	2,4,5-Triamino-6-hydroxypyrimidine Sulfate 	2.5	1.0	3	10.2	10.3
5.	2-Amino-6-hydroxy-8-mercaptopurine 	0.5	0.2	3	10.5	9.5
6.	2,6-Diamino-8-mercaptopurine 	1.0	0.6	3	5.0	9.5
7.	2,6-Diamino-8-hydroxypurine·HCl 	5.0	0.4	3	4.0	7.5

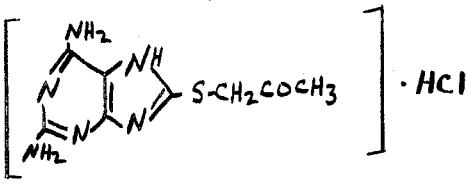
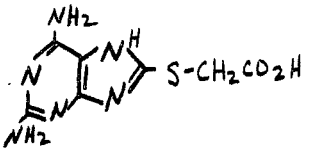
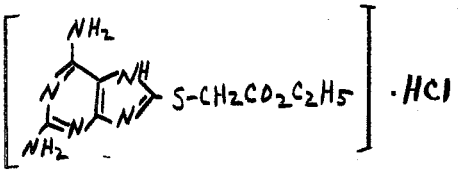
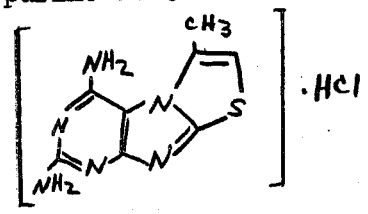
8.	2,6-Diamino-8-acetonylmercapto-purine·HCl 	50	20	14	6.0	11.0
9.	2,6-Diamino-8-carboxymethyl-mercaptopurine 	0.05	0.02	3	9.0	9.5
10.	2,6-Diamino-8-carbethoxymethyl-mercaptopurine·HCl 	0.5	0.2	3	5.0	9.5
11.	2,6-Diamino-4'-methyl [3',2'-h]-thiazolino-purine·HCl. 	2.5	1.0	3	9.8	10.3

Table II. Survival Time of Mice Bearing Mammary Tumors (Eo771).

5.	2-amino-6-hydroxy-8-mercaptopurine	0.5	0.2	3	8.0	22.5
6.	2,6-Diamino-8-mercaptopurine	1.0	0.6	3	10.5	22.5
7.	2,6-Diamino-8-hydroxypurine·HCl	5.0	0.4	3	23.0	22.5
8.	2,6-Diamino-8-acetonylmercaptopurine·HCl	50	20	14	12.5	21.0
9.	2,6-Diamino-8-carboxymethylmercaptopurine	0.05	0.02	3	19.5	22.5
10.	2,6-Diamino-8-carbethoxymethylmercaptopurine·HCl	0.5	0.2	3	15.0	22.5

Recently Skipper (7), working with Ak 4 mouse leukemia, reported that substitution of the 8-position of 2,6-diaminopurine eliminates its anti-leukemic activity. These results are confirmed by our data. Studies are now in progress with purine derivatives, similar to those in Table I (6-11), in the adenine, guanine, and isoguanine series.

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1. Feldes, Lancet, 1, 955 (1940).

2. Stowell, "Symposia of the Society of Experimental Biology. I. Nucleic Acids" 190 (1947). A review

3. Hitchings, et.al., J.Biol.Chem., 174, 765 (1948).

4. Burchenal, et.al., Cancer, 2, 119 (1949).

5. Hitchings, et.al., Federation Proceedings, 7, 160 (1948).

6. Kidder, et.al., Science, 109, 511 (1949).

7. Skipper, et.al., Cancer Research, 10, 166 (1950).