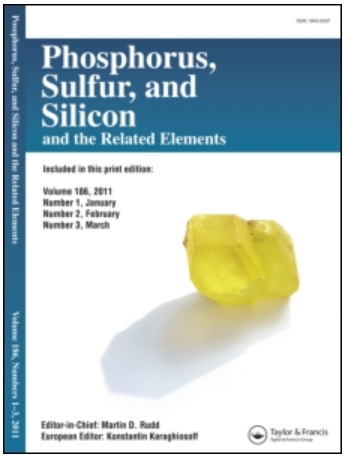

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MARGINAL ANTILEUKEMIC ACTIVITY IN A RANDOM POPULATION OF ELECTRON-DEPLETED THIOCARBONYL COMPOUNDS

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MARGINAL ANTILEUKEMIC ACTIVITY IN A RANDOM POPULATION OF ELECTRON-DEPLETED THIOCARBONYL COMPOUNDS

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Out of sixteen thiocarbonyl and related compounds tested four exhibited reproducible antileukemic activity. The tentative concept of a bioacylating agent is proposed.

Following a suggestion by the US National Cancer Institute we submitted twelve electron-depleted thiocarbonyl compounds and four closely related miscellaneous compounds to NCI routine chemotherapeutic screening. The compounds were available from previous synthetic and mechanistic studies of *C*-sulfonylthioformamides[1] and trithiocarbonate *S,S*-dioxides.[2,3] Properties which might be relevant to the chemotherapeutic potential of our compounds are their activity as thioacylating agents[1,2,4] as well as their ready participation in redox reactions.[1–3] Tables I–III contain the structural data of the sixteen compounds tested.

TABLE I

C-Sulfonylthioformamides R^1–SO_2–CS–NR^2R^3

Compound	NSC No.	R_1	R_2	R_3	Ref.
1	277527	methyl	methyl	methyl	1
2	277524	methyl	phenyl	methyl	1
3	277526	1-adamantyl	phenyl	methyl	1
4	277522	phenyl	methyl	methyl	1
5	277525	*p*-tolyl	methyl	dimethylamino	1
6	277530	*p*-chlorophenyl	methyl	methyl	1
7	277521	*p*-nitrophenyl	methyl	methyl	1

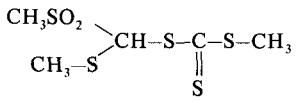
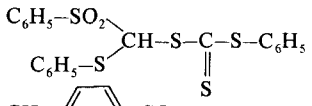
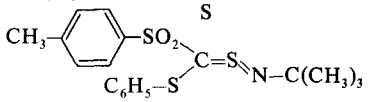
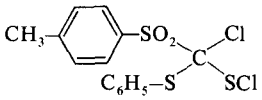
TABLE II

Trithiocarbonate *S,S*-Dioxides R^1–SO_2–CS–S–R^2

Compound	NSC No.	R^1	R^2	Ref.
8	277529	methyl	phenyl	2
9	277667	1-adamantyl	methyl	2
10	277531	*p*-tolyl	ethyl	2
11	277532	*p*-tolyl	phenyl	2
12	277523	*p*-chlorophenyl	isopropyl	2

TABLE III

Miscellaneous Compounds

Compound	NSC No.	Structure	Ref.
13	277533		2
14	277534		[a]
15	289799		3
16	289798		3

[a] N. H. Nilsson and A. Senning, unpublished work, mp 85–86°C.

EXPERIMENTAL

The biological screening was carried out by the National Cancer Institute, Bethesda, MD 20014, USA. Details of the experimental procedure are given in the "Instruction 14" available from the NCI. The test system was a murine P 338 lymphocytic leukemia, the compounds were administered by intraperitoneal injection, and the test parameter was "percent T/C", the survival time of the test animals expressed as a percentage of the survival time of the leukemic control animals. Thus, T/C values above 100% indicate activity.

RESULTS AND DISCUSSION

Of the sixteen compounds tested eight (compounds **1, 2, 6, 8, 13, 14, 15,** and **16**) were inactive.

Four compounds did show activity at some stage of the test which, however, could not be confirmed in repeated and/or extended tests. The compounds in question are **7, 9, 11,** and **12.** The highest erratic activities seen in **9** were T/C 144% (dose 9 × 50.0

TABLE IV

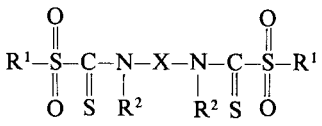
Antileukemic Compounds

Compound	Dose (mg/kg)	Toxicity day survivors	Survival (days) test/control	T/C (%)
3	9 × 50.0	6/6	14.7/10.4	141
	9 × 25.0	6/6	13.4/10.4	128
	9 × 12.5	6/6	13.3/10.4	127
	9 × 50.0	6/6	13.3/10.7	124
	9 × 25.0	6/6	13.8/10.7	128
	9 × 12.5	6/6	12.7/10.7	118
4	9 × 50.0	4/6	13.0/10.5	123
	9 × 50.0	3/6	9.8/11.2	87
	9 × 25.0	6/6	13.8/11.2	123
	9 × 12.5	6/6	13.8/11.2	123
5	9 × 50.0	6/6	13.3/10.5	126
	9 × 50.0	6/6	14.0/11.1	126
	9 × 25.0	6/6	13.0/11.1	117
	9 × 12.5	6/6	12.8/11.1	115
10	9 × 50.0	4/6	13.0/10.5	123
	9 × 50.0	6/6	12.1/10.5	115
	9 × 25.0	5/6	11.1/10.5	105
	9 × 12.5	6/6	12.7/10.5	120

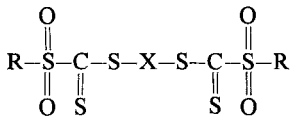
mg/kg), 131% (dose 9 × 25.0 mg/kg), and 153% (dose 9 × 12.5 mg/kg).

The remaining compounds **3**, **4**, **5**, and **10** reached the NCI status "presumptive activity confirmed by first screener" the (simplified) data being presented in Table IV.

Considering the limited number of compounds and the marginal character of the activities displayed it is obviously premature to enter into structure/activity discussions. However, we do feel encouraged to extend our synthetic program to obtain additional compounds for biological testing. Specifically, we intend to synthesize difunctional structures such as **17** and **18**



17



18

which might behave as "bioacylating agents" with *in vivo* properties paralleling those of the well-known bioalkylating agents.[5] The basic rationale of a bioacylating agent would be the assumption that it could acylate in a *reversible* fashion the cell sites which are *irreversibly* alkylated by bioalkylating agents. Hopefully, the ensuing deacylation might be sufficiently slow for lethal damage of rapidly proliferating malignant cells and fast enough to allow the recovery of more slowly proliferating non-malignant cells.

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