Synthesis and Antitumor Activity of a Series of Sulfone Analogues of 1,4-Naphthoquinone[1]

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A series of novel substituted thiochromones and thiochroman-4-ones was synthesized. Compounds were designed as analogues of naphthoquinone and as potential "bioreductive alkylating agents" and were tested for antitumor activity. The lead compound, 3-(chloromethyl)thiochromone 1,1-dioxide (**4**), inhibited Ehrlich ascites tumor growth by 100% in CF_1 male mice at 10 (mg/kg)/day ip. Similarly, 18 of the 29 related compounds demonstrated good activity in this tumor screen. Few definitive structure–activity correlations were evident regarding the nature of the 3-substituent. However, the 2,3 double bond and a sulfone or sulfoxide were required for activity. Four of the compounds synthesized showed marginal but significant activity against P-388 lymphocytic leukemia.

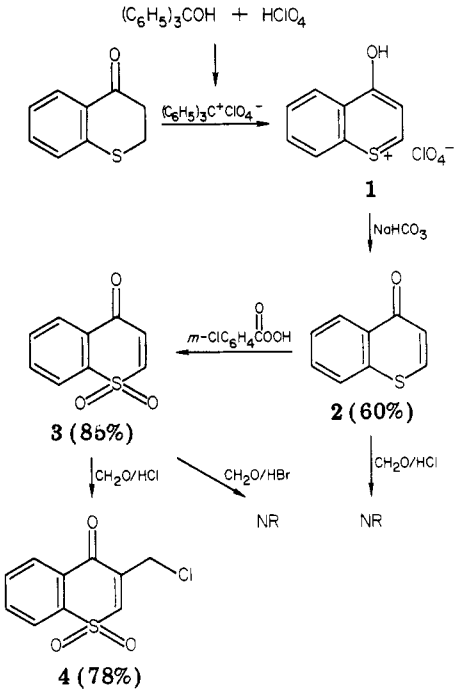
The antitumor activity of organic compounds containing the 1,4-naphthoquinone ring system has been investigated by various groups.[2-9] Lapachols,[5,6] aminoquinones,[10,11] and 2-(alkylmercapto)naphthoquinones[4] demonstrate activity vs. a variety of rodent tumors. Dichloroallyllawsone [NSC 126771, 2-(3,3-dichloroallyl)-3-hydroxy-1,4-naphthoquinone] is currently under clinical investigation by the National Cancer Institute[5,12] as an antineoplastic agent. Few synthetic compounds of this nature, the quinone function of which has been altered, have been reported in the literature.[10,12] For example, no sulfone analogues of naphthoquinones have been reported to possess antitumor activity.

The term "bioreductive alkylating agents" has been used to describe a series of substituted 1,4-naphthoquinones synthesized by Lin et al.[8,9] Members of this series of 2-(halomethyl)-, 2-(acetoxymethyl)-, and 2,3-bis(halomethyl)naphthoquinones were postulated to require bioactivation by reduction of the quinone and subsequent displacement of the leaving group to form the potential alkylating agents of the "*o*-naphthoquinonemethide"[13] type. Replacement of one of the naphthoquinone carbonyls with a sulfone group would alter the electronic character as well as the reduction potential of the molecule. For this reason, a series of novel 2-, 3- and 2,3-substituted thiochromones, thiochroman-4-ones, and their oxides were synthesized and tested for antitumor activity.

Chemistry. The chemistry of the thiochromone and thiochroman-4-one ring systems and their respective oxides is well known.[14-18] The lead compound, 3-(chloromethyl)thiochromone 1,1-dioxide (**4**), was synthesized as shown in Scheme I. Thiochromone (**2**) was synthesized by the method of Chauhan and Still using hydride abstraction from position 2 of thiochroman-4-one via triphenylmethyl perchlorate and subsequent neutralization of the sulfenium salt.[14] *m*-Chloroperbenzoic acid oxidation by the method of Bass and Evans[19] gave thiochromone 1,1-dioxide (**3**) in 85% yield. Prior use of hydrogen peroxide (30%) as the oxidizing agent had afforded only a 40% yield with a substantial amount of benzenesulfinic acid byproduct formed. Compound **3** was chloromethylated by treatment with formaldehyde (37%) and hydrogen chloride gas, affording **4** in 73% yield. Chloromethylation of **2**, as well as bromomethylation of **3** in an analogous manner, failed to give a product (Scheme I).

Compounds **5a–g**, the 3-[(alkyloxy)methyl]thiochromone 1,1-dioxides (Scheme II), were formed by displacement of the labile chlorine of **4** by the corresponding alcohol (for yields see Table I). The esters, **6a–c**, were synthesized by

Scheme I



(1) This paper has been presented in part (L. J. Loeffler); see "Abstracts of Papers", Second Chemical Congress of the North American Continent, Las Vegas, NV, Aug 24–29, 1980, American Chemical Society, Washington, D.C., 1980, Abstr MEDI 37.
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(6) M. da Consolacao, F. Linardi, M. M. de Oliveria, and M. R. P. Sampaio, *J. Med. Chem.*, 18, 1159 (1975).
(7) E. M. McKelvey, M. Lomedico, K. Lu, M. Chadwick, and T. L. Loo, *Clin. Pharmacol. Ther.*, 25, 586 (1979).
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(9) A. J. Lin, B. J. Lillis, and A. C. Sartorelli, *J. Med. Chem.*, 18, 917 (1975).
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(11) S. Okada, N. Mochizuki, and O. Tamemosa, *Chem. Pharm. Bull.*, 26, 1031 (1978).

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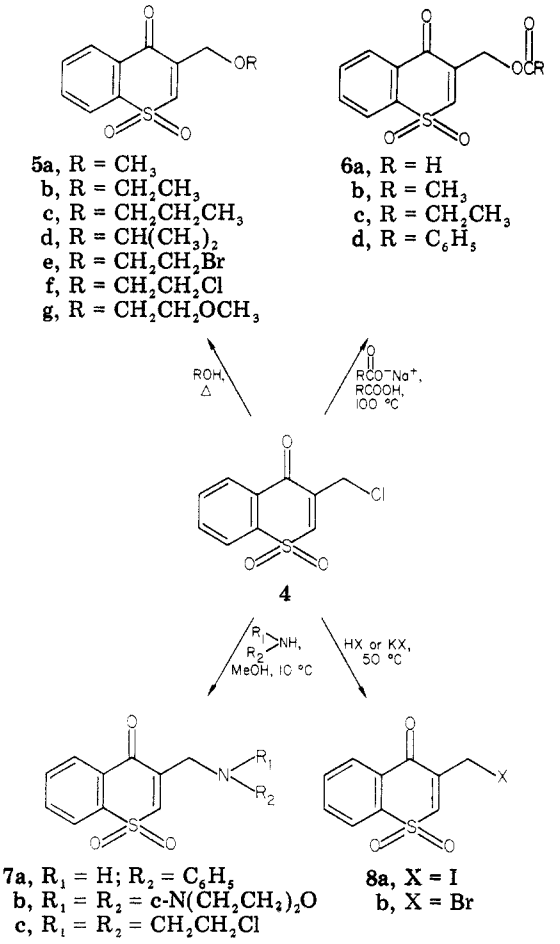
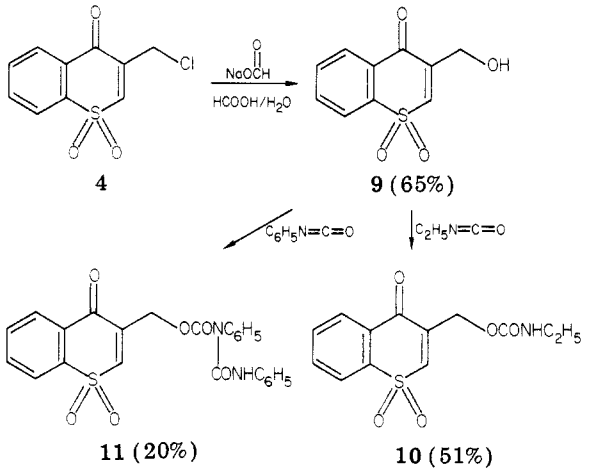
Scheme II

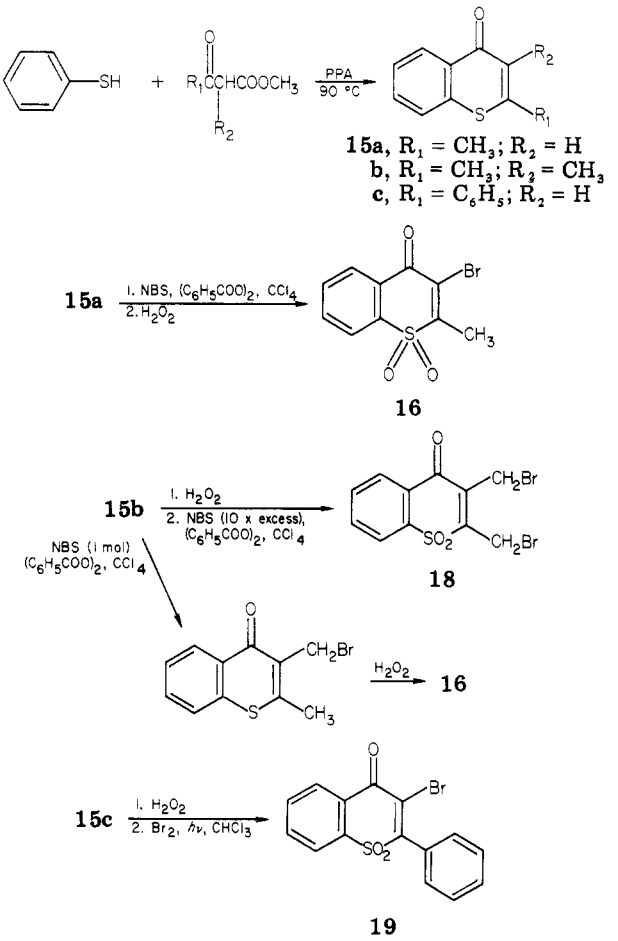


Scheme III



reaction of **4** with the sodium salt of the corresponding acid using that acid as the solvent. Formation of **6d**, however, utilized a solvent of acetic acid saturated with benzoic acid.

Scheme IV



Both primary and secondary amines will displace the labile chlorine of **4** more readily than alcohols, giving **7a–c**. Yet, compound **4** appeared to be refractory to reaction with sulfhydryl-containing molecules. Other 2-(halomethyl) derivatives were synthesized by reaction of **4** with HX or KX to give **8a** and **8b**.

The use of carbamoylating molecules as antitumor agents led to the synthesis of 3-*N*-carbamoyloxymethyl derivatives of thiochromone 1,1-dioxide as shown in Scheme III. The reaction of **4** with sodium formate and formic acid (50% in water) produced 3-(hydroxymethyl)thiochromone 1,1-dioxide (**9**). It is interesting to note that as the ratio of formic acid to water was increased the amount of 3-(formylmethyl)thiochromone 1,1-dioxide (**6a**) recovered was increased and the amount of **9** recovered was decreased. Compound **9** readily reacted with ethyl isocyanate (excess) under anhydrous conditions to form **10**. Under analogous reaction conditions using phenyl isocyanate (excess), 2 mol of the isocyanate reacted to produce **11**. The increased reactivity of the carbamyl nitrogen is due to a resonance-induced acidity increase and loss of the proton.

Synthesis of the 2,3-saturated derivative, 3-(chloromethyl)thiochroman-4-one 1,1-dioxide (**12b**), was accomplished to determine the effect of the double bond on the antitumor activity of this class of compounds. Oxidation of thiochroman-4-one with hydrogen peroxide and subsequent chloromethylation gave **12b**. The synthesis of the sulfoxide derivative, thiochromone 1-oxide (**13**), was accomplished by the method of Still et al.[16] 3-Bromothiochromone 1,1-dioxide (**14**) was formed by reaction of **3** with molecular bromine under UV irradiation. A byproduct of this reaction was a small amount of the product of addition

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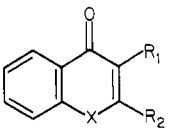
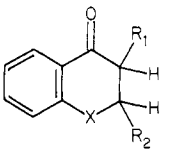
Table I. Properties of Thiochromone 1,1-Dioxide and Thiochroman-4-one 1,1-Dioxide Derivatives



no.	R_1	R_2	X	mp, °C	recrystn solvent[h]	% yield	formula	anal.
2[a]	H	H	S	78-79	C_6H_6-PE (1:4)	60	C_9H_6OS	
3[b]	H	H	SO_2	142-144	abs EtOH	78	$C_9H_6O_3S$	
4	CH_2Cl	H	SO_2	144-146	EtOAc	62	$C_{10}H_7ClO_3S$	C, H, Cl
5a	CH_2OCH_3	H	SO_2	125-127	MeOH	67	$C_{11}H_{10}O_4S$	C, H, S
5b	$CH_2OC_2H_5$	H	SO_2	101-102	abs EtOH	50	$C_{12}H_{14}O_4S$	C, H, S
5c	$CH_2OC_3H_7$	H	SO_2	81-82	*n*-PrOH	73	$C_{13}H_{14}O_4S$	C, H, S
5d	CH_2O-*i*-C_3H_7	H	SO_2	119-120	*i*-PrOH	68	$C_{13}H_{14}O_4S$	C, H, S
5e	$CH_2OCH_2CH_2Br$	H	SO_2	103-104	C_6H_6-PE (0.5:9.5)	45	$C_{12}H_{11}BrO_4S$	C, H, S
5f	$CH_2OCH_2CH_2Cl$	H	SO_2	113-114	EtOAc-PE (7:3)	70	$C_{12}H_{11}ClO_4S$	C, H, S
5g	$CH_2OCH_2CH_2OCH_3$	H	SO_2	87-89	EtOAc	34	$C_{13}H_{14}O_5S$	C, H, S
6a	CH_2OCOH	H	SO_2	75-77	EtOAc	26	$C_{11}H_8O_5S$	C, H, S
6b	CH_2OCOCH_3	H	SO_2	128-129	EtOAc	39	$C_{12}H_{10}O_5S$	C, H, S
6c	$CH_2OCOC_2H_5$	H	SO_2	125-126.5	EtOAc	36	$C_{13}H_{12}O_5S$	C, H, S
6d	$CH_2OCOC_6H_5$	H	SO_2	181-182	EtOAc	15	$C_{17}H_{12}O_5S$	C, H, S
7a	$CH_2NHC_6H_5$	H	SO_2	186-189	EtOAc	77	$C_{16}H_{13}NO_3S$	C, H, S
7b	CH_2-c-$N(CH_2CH_2)_2O$	H	SO_2	214-215	C_6H_6-PE (4:6)	51	$C_{14}H_{15}NO_4S$	C, H, S
7c	$CH_2N(CH_2CH_2Cl)_2$	H	SO_2	95-96	MeOH	24	$C_{14}H_{15}Cl_2NO_3S$	C, H, S
8a	CH_2I	H	SO_2	158-159	EtOAc	72	$C_{10}H_7IO_3S$	C, H, S
8b	CH_2Br	H	SO_2	123-125	EtOAc	70	$C_{10}H_7BrO_3S$	C, H, S
9	CH_2OH	H	SO_2	151-152	$CHCl_3$	65	$C_{10}H_8O_4S$	C, H, S
10	$CH_2OCONHC_2H_5$	H	SO_2	99-101	$CHCl_3$	51	$C_{13}H_{13}NO_5S$	C, H, S
11	$CH_2OCON(CONHC_6H_5)C_6H_5$	H	SO_2	175-177	acetone	20	$C_{24}H_{18}N_2O_5S$	C, H, N
13[c]	H	H	SO	127-128	EtOAc	60	$C_9H_6O_2S$	
14[d]	Br	H	SO_2	203-205	HOAc	73	$C_9H_5BrO_3S$	
15a[e]	H	CH_3	S	101-103	C_6H_6-PE (1:1)	40	$C_{10}H_8OS$	
15b[e]	CH_3	CH_3	S	110-112	abs EtOH	40	$C_{11}H_{10}OS$	
15c[e]	H	C_6H_5		119-122	C_6H_6-PE (1:1)	21	$C_{15}H_{10}OS$	
16	Br	CH_3	SO_2	217-218	EtOAc	60	$C_{10}H_7BrO_3S$	C, H, S
17	CH_2Br	CH_3	S	145-146	abs EtOH	74	$C_{11}H_9BrOS$	C, H, S
18	CH_2Br	CH_2Br	SO_2	193-195	EtOAc	10	$C_{11}H_8Br_2O_3S$	C, H, Br
19	Br	C_6H_5	SO_2	175-177	abs EtOH-EtOAc (3:1)	43	$C_{15}H_9BrO_3S$	C, H, S
20[f]	CH_2Cl	CH_2Cl	CO	142-143	abs EtOH	58	$C_{12}H_8Cl_2O_2$	



12a[g]	H	H	SO_2	130-130.5	$CHCl_3$	75	$C_9H_8O_3S$	
12b	CH_2Cl	H	SO_2	94-95	EtOAc	20	$C_{10}H_9ClO_3S$	C, H, S

[a] Reference 14. [b] Reference 18. [c] Reference 16. [d] Reference 28. [e] Reference 20. [f] Reference 8. [g] Reference 15. [h] PE = petroleum ether.

of bromine to the 2,3 double bond.

Polyphosphoric acid cyclizations afford a convenient method of synthesis of a 2-substituted or 2,3-disubstituted thiochromone ring system.[20] Compounds **15a–c** were synthesized as described in the patent literature (Scheme IV).[20] Free-radical bromination of **15a** with *N*-bromosuccinimide/benzoyl peroxide, followed by hydrogen peroxide oxidation, resulted in compound **16**. Both the 3-carbon of the thiochromone ring and the 3-methyl carbon of the substituted thiochromone ring are amenable to Ziegler free-radical bromination.[21] If a 10-fold excess of NBS was used, the 2-methyl group was brominated as in **18**. With both **15b** and **15c**, peroxide oxidation must precede bromination to obtain the desired product. A reverse of this process for **15b** resulted in a conversion to **16** (see Scheme IV). This appears to have occurred through loss of the 3-methyl group by oxidation and loss of formaldehyde, formation of bromine via peroxide oxidation, and ring bromination at the 3 position to give **16**. Compound **15c** required molecular bromine as the brominating agent.

The formation of **20**, 2,3-bis(chloromethyl)naphthoquinone, has been described by Lin et al.[8]

Antitumor Testing. Studies by Lin and Sartorelli[13] on halo- and acetoxymethyl quinones indicated the importance of the leaving group to the formation of the "quinonemethide". Thus, 2,3-bis(halomethyl) and 3-(halomethyl) derivatives, ethers, esters, aminomethylated derivatives, and (carbamoyloxy)methyl derivatives of thiochromone 1,1-dioxide were synthesized in an attempt to obtain a series of compounds of "graded" leaving group ability and to correlate this ability with antitumor activity.

Preliminary polarographic data indicate that sulfones such as **4** are reduced at half wave potentials (−0.59 V) nearly identical with those observed for the reduction of recently reported anthraquinones such as 2-(chloro-

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(21) A. J. S. Sorrie and R. H. Thomson, *J. Chem. Soc.*, 2238 (1955).

Table II. Effect of Thiochromone and Thiochroman-4-one Derivatives on P-388 Lymphocytic Leukemia[a] Growth

compd	dose,[b] (mg/kg)/day ip	av days survived[c]	T/C[d]
0.05% polysorbate 80		9.5	
4	6.25*	11.3	109
	12.50*	12.0	116
	25.00*	10.4	100
	10	12.4	130
	15	9.8	103
3	10	11.4	120
5a	10	12.0	126
5b	5	10.4	109
	10	12.2	128
	15	9.6	101
5d	10	11.6	122
6b	2.5	10.2	107
	4	11.3	118
	5	11.6	122
	10	6.6	69
8b	10	10.0	105
14	10	12.4	130
	15	9.4	99
16	15	10.2	107
17	10	11.4	120
18	10	10.3	108
19	10	11.4	120
20	10	12.2	128
12b	15	10.0	105
5-fluorouracil[e]	25	17.6	186

[a] 10^6 tumor cells were injected ip into six male BDF mice. The mice were dosed for 9 days. [b] An asterisk indicates these tests performed at the National Cancer Institute. The control value for the NIH data was 10.3 average days survived. [c] Treated mice. [d] T/C of greater than 125 is required for significant activity. No significant weight loss vs. control was observed for animals in this experiment. [e] Sigma Chemical Co.

methyl)anthraquinone (−0.52 V), which shows selective toxicity to hypoxic vs. normally oxygenated EMT6 mammary tumor cells in cell culture.[22]

The activity of this group of sulfones as a whole against P-388 lymphocytic leukemia growth was not promising (Table II). The lead compound **4**, the 3-(chloromethyl) derivative, initially demonstrated promising enough activity in our tests to stimulate synthesis of structural analogues. However, retesting both here and at the National Cancer Institute indicated only marginal activity at certain dose levels [T/C of 130 at 10 (mg/kg)/day] (see Table II).

Good activity was observed for a large percentage of the compounds against Ehrlich ascites tumor growth in CF_1 mice (Table III). However, no definitive structure–activity correlations between structural types are evident. As a rule, the esters, ethers, and halomethylated compounds showed high activity in this tumor system.

The bis(chloroethyl)aminomethyl derivative (**7c**) combines the thiochromone 1,1-dioxide nucleus with the classical alkylating moiety present in many anticancer agents. Similarly, the (*N*-ethylcarbamoyl)oxymethyl derivative (**10**) couples the nucleus with a carbamate moiety also present in known anticancer agents. Both of these compounds were active in the Ehrlich ascites tumor screen (99.9 and 99.3%, respectively) and warrant further testing. Interestingly, the N,N-disubstituted carbamate **11** demonstrated marginal activity (69% inhibition).

From this series of substituted thiochromones, thiochroman-4-ones, and their oxides, it is apparent that the halomethyl derivatives are more active than the bis(halomethyl) derivatives against Ehrlich ascites tumor growth. Furthermore, comparing the activity of compounds **4** and **12b** in this system, it is evident that the 2,3 double bond is required for activity. An unexpected high degree of anti-carcinoma activity was demonstrated by the unsubstituted thiochromone 1-oxide (**13**), which suggests a possible Michael addition as a mechanism of alkylation.

The thiochromone and thiochroman-4-one derivatives are stable crystalline compounds of high lipid solubility and low water solubility. Such characteristics could give the compounds some utility in the treatment of brain tumors.

Experimental Section

In Vivo Tumor Screens. All test compounds were homogenized in 0.05% polysorbate 80 (Tween 80) and administered in doses ranging from 2.5 to 30 (mg/kg)/day intraperitoneally (ip). The dosing of compounds was based on the optimum dose of compound **4** (10 mg/kg) in each tumor screen. Each structurally similar compound was administered at this dose in order that structure–activity relationships could be determined.

The P-388 lymphocytic leukemia screen was carried out on BDF_1 mice (~22 g, male). On day 0, 1×10^6 cells were injected ip. Test compounds were administered ip on days 1 through 9. T/C values were calculated according to NIH protocol 1:200.[23] 5-Fluorouracil was used as an internal standard. Six mice were used per test compound, and a T/C of greater than 125% was considered significant activity against P-388 tumor growth.

In the Ehrlich ascites tumor screen,[24] cells (2×10^6) were injected into CF_1 male mice (~25 g) on day 0 ($N = 6$). Test compounds were administered ip on days 1 through 8. On day 9, the mice were sacrificed and peritoneal ascites cell volume and packed cell volume (ascites-crit) were determined by the method of Piantadosi et al.[24] Results of this screen are reported as percent inhibition calculated by the following formula:

$$\% \text{ inhibn} = 100 - \left[\frac{(\text{vol of treated})(\text{ascrit of treated})}{(\text{vol of control})(\text{ascrit of control})} \right] \times 100$$

6-Mercaptopurine was used as an internal standard. Six to eight mice were used per test compound, and greater than 80% inhibition was considered significant.

Chemistry. All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Thin-layer chromatography was performed on precoated TLC plates (silica gel 60-F-254, EM Reagents) with fluorescent backing. The plates were visualized by ultraviolet light. Elemental analyses were done by Atlantic Microlab, Atlanta, GA, and agreed with theoretical values within ±0.4%.

Infrared spectra were obtained using a Perkin-Elmer Model 297 infrared spectrophotometer. Proton NMR spectra were taken on a JEOLCO JNM-FX60 using tetramethylsilane as an internal standard. All IR and NMR spectra were completely consistent with assigned structures. All starting materials were used as received from suppliers unless otherwise indicated.

Thiochromone 1,1-Dioxide (3). Compound **3** was synthesized by a modification of the method of Bass and Evans.[19] A solution of 37.6 g of *m*-chloroperbenzoic acid (85%, 0.185 mol) in 200 mL of methylene chloride was added dropwise to a solution of 15 g (0.0926 mol) of thiochromone[14] in 30 mL of CH_2Cl_2 at 0 °C. The resulting solution was stirred for 3 h at 10 °C and washed well with two 200-mL portions of saturated $NaHCO_3$ solution and then with one 200-mL portion of water. The CH_2Cl_2 solution was then dried over $MgSO_4$ and stripped in vacuo, and the resulting yellow powder was recrystallized in absolute EtOH to give 14 g (78%) of compound **3**, mp 142–144 °C (lit.[18] mp 142–144 °C); TLC (SilG,

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(24) C. Piantadosi, C. S. Kim, and J. L. Irvin, *J. Pharm. Sci.*, **58**, 921 (1969).

Table III. Effect of Thiochromone and Thiochroman-4-one Derivatives on Ehrlich Ascites Carcinoma[a] Growth

compd	dose, (mg/kg)/day ip	survival at day 9	ascrit[b]	ascites vol[c]	% inhibn[d]
0.05% polysorbate 80		34/40	33.6 ± 8.7	1.8 ± 1.02	
4	5	8/8	22.0	2.45	57.1
	10	8/8	0.0	0.0	100.0
	20	8/8	35.7	0.88	81.8
3	10	8/8	42.6	2.78	5.5
5a	10	8/8	0.1	0.1	99.9
5b	10	8/8	17.8	0.54	92.4
5c	10	6/6	0.19	0.12	99.9
5d	10	6/6	3.19	0.28	99.2
5e	10	8/8	0.0	0.05	100.0
5f	10	6/6	7.93	0.07	98.1
5g	10	6/6	8.2	0.07	98.2
6a	10	6/6	4.23	0.57	91.6
6b	10	8/8	2.0	0.33	99.5
6c	10	6/6	0.07	0.23	99.5
6d	10	8/8	33.7	2.7	0.0
7a	10	8/8	40.2	2.8	0.0
7b	10	8/8	43.3	1.25	0.0
7c	10	6/6	2.0	0.01	99.9
8a	10	6/6	9.57	0.15	98.0
8b	10	8/8	8.63	0.35	92.8
9	5	5/6	4.8	0.07	95.6
	10	3/8	0.7	0.4	99.3
10	10	6/6	1.33	0.38	99.3
11	10	6/6	38.0	0.58	69.3
13	10	6/6	27.8	0.27	89.6
14	10	8/8	38.3	0.99	69.9
16	10	8/8	34.3	2.82	22.8
17	10	8/8	42.7	2.1	25.8
18	10	8/8	37.2	0.76	53.9
	20	8/8	25.2	0.99	69.9
19	10	8/8	30.6	4.06	0.4
20	10	8/8	5.0	0.31	98.8
12b	10	8/8	43.5	1.84	36.3
6-mercaptopurine[e]	200	6/6	0.3	0.7	99.6

[a] 2×10^6 cells were injected ip into six male CF_1 mice on day 0. The drug was administered from day 1 to 8. On day 9 the mice were sacrificed and the experiment was evaluated. [b] Packed cell volume as a percent. [c] Per mouse. [d] Greater than 80% inhibition is required for significant activity. [e] Sigma Chemical Co.

95% EtOH) R_f 0.69; IR (KBr) 1660 (C=O), 1608 (C=C, conj), 1292 (S=O, antisym), 1167 (S=O, sym) cm^{-1}; NMR ($CDCl_3$) δ 6.72 (d, J = 10 Hz, 1, 3 H), 7.38 (d, J = 10 Hz, 1, 2 H), 7.66–8.30 (m, 4, 5–8 H).

3-(Chloromethyl)thiochromone 1,1-Dioxide (4). Chloromethylation was accomplished by a modification of the method of Lin, Lillis, and Sartorelli.[9] Thiochromone 1,1-dioxide (3; 10 g, 0.05 mol) was suspended in 250 mL of glacial acetic acid. Formaldehyde (37%; 250 mL, 3.1 mol excess) was added and HCl gas was passed through the mixture for 2 h. During this time, the temperature was kept below 50 °C with an ice bath. The solution was allowed to stir at room temperature overnight and poured into 1 L of ice–water, and the white precipitate was collected and dried in vacuo. Recrystallization from ethyl acetate gave 7.5 g (62%) of compound 4: mp 144–146 °C; TLC (SilG, $CHCl_3$) R_f 0.39; IR (KBr) 1665 (C=O), 1650 (C=C, conj), 1295 (S=O, antisym), 1158 (S=O, sym), 775 (C–Cl) cm^{-1}; NMR ($CDCl_3$) δ 4.56 (split s, 2, CH_2), 7.60 (t, 1, 2 H), 7.68–8.35 (m, 4, 5–8 H).

3-(Alkoxymethyl)thiochromone 1,1-Dioxides (5a–g). These compounds were formed by refluxing or heating (100 °C) 200 mg (0.82 mmol) of 3-(chloromethyl)thiochromone 1,1-dioxide (4) with the corresponding alcohol (15 mL) for 1 h. The remaining alcohol was evaporated in vacuo, and the resulting powder was recrystallized from an appropriate solvent. Recrystallization solvents, yields, and melting points are given in Table I.

Esters of 3-(Hydroxymethyl)thiochromone 1,1-Dioxide (6a–d). These compounds were prepared by refluxing a solution of 3-(chloromethyl)thiochromone 1,1-dioxide (4) with 1.1 equiv of the dry salt of the desired acid (sodium formate, acetate, propionate) for 2–3 h in 10–20 mL of the corresponding acid as solvent.[24] In the case of the benzoate (6d), glacial acetic acid saturated with benzoic acid was employed as a solvent. The products were isolated by dilution with water and filtration or by chloroform extraction. Recrystallization solvents, yields, and melting points are given in Table I.

3-(Anilinomethyl)thiochromone 1,1-Dioxide (7a). 3-(Chloromethyl)thiochromone 1,1-dioxide (4; 150 mg, 0.62 mmol) was dissolved in 10 mL of methanol and chilled in an ice bath. To this solution was added 0.5 g (5.4 mmol) of freshly distilled aniline. The solution was then stirred for 1 h at 10 °C and for 1 h at room temperature and the methanol was evaporated. The brown residue was recrystallized from ethyl acetate to give 130 mg (77%) of compound 21: mp 186–189 °C.

3-(Morpholinomethyl)thiochromone 1,1-Dioxide (7b). 3-(Chloromethyl)thiochromone 1,1-dioxide (4; 250 mg, 1.02 mmol) and 0.5 g (5.8 mmol) of morpholine were dissolved in 10 mL of ice-cold methanol. The solution was stirred for 2 h at 10 °C and then for 1 h at room temperature. The methanol was then evaporated and the brown resinous residue was recrystallized from benzene–petroleum ether (60–90 °C) (4:6) to give yellow crystals: mp 214–215 °C; yield 140 mg (51%).

3-[[Bis(2-chloroethyl)amino]methyl]thiochromone 1,1-Dioxide (7c). Compound 4 (200 mg, 0.82 mmol) was dissolved in a solution of 0.5 g of bis(2-chloroethyl)amine (3.5 mmol) in 10 mL of ice-cold methanol. After the mixture stirred for 1 h at 0 °C, the methanol was evaporated and the resinous material recrystallized in methanol to give 70 mg (24%) of compound 7c, mp 95–96 °C.

3-(Iodomethyl)thiochromone 1,1-Dioxide (8a). Potassium iodide (200 mg, 1.2 mmol) was dissolved in 20 mL of acetone. To this was added dropwise a solution of 250 mg (1.0 mmol) of 3-(chloromethyl)thiochromone 1,1-dioxide (4) in 5 mL of acetone at 35 °C. The resulting yellow solution was stirred for 1 h at 35 °C until no starting material was detected by TLC. After the solution cooled, the precipitated KCl was filtered and the resulting yellow filtrate was evaporated, leaving a yellow powder which was taken up in 100 mL of EtOAc and extracted with 2 portions of

water (100 mL). The ethyl acetate fraction was then dried over $MgSO_4$ and filtered, and the solvent was evaporated. Recrystallization from EtOAc gave 240 mg of yellow crystals (72%), mp 158–159 °C.

3-(Bromomethyl)thiochromone 1,1-Dioxide (8b). 3-(Chloromethyl)thiochromone 1,1-dioxide (**4**; 300 mg, 1.2 mmol) was dissolved in 5 mL of glacial acetic acid. The solution was warmed to 45 °C, 1 mL of a 30% solution of HBr in acetic acid (3.7 mmol) was added slowly, and the solution was stirred for 12 h at room temperature. The solution was then added to 80 mL of ice–water and the white precipitate was filtered. Two recrystallizations from EtOAc gave 200 mg of compound **8b** (70%), mp 123–125 °C.

3-(Hydroxymethy)thiochromone 1,1-Dioxide (9). Compound **9** was synthesized by heating 3-(chloromethyl)thiochromone 1,1-dioxide (**4**; 1 g, 4.0 mmol), 10 mL of 50% formic acid, and 300 mg of sodium formate (4.4 mmol) at 95 °C for 12 h. The resulting red solution was cooled and poured into 100 mL of ice–water. The precipitate was collected, dried in a vacuum desiccator, and recrystallized from chloroform to give 600 mg of yellow prisms [a minor product formed is 3-(formylmethyl)thiochromone 1,1-dioxide (**6a**)], mp 151–152 °C; yield 65%.

3-[[(*N*-Ethylcarbamoyl)oxy]methyl]thiochromone 1,1-Dioxide (10). Compound **10** was synthesized by the method of Lin, Shansky, and Sartorelli.[25] 3-(Hydroxymethyl)thiochromone 1,1-dioxide (**9**; 300 mg, 1.3 mmol) was refluxed for 5 h in 15 mL of dry ethyl isocyanate. The solvent was then carefully evaporated by a flow of dry air and the resulting white powder was recrystallized twice from chloroform to give 190 mg (41%) of colorless crystals, mp 99–101 °C.

3-[[[*N*-(*N*-Phenylcarbamoyl)-*N*-phenylcarbamoyl]oxy]methyl]thiochromone 1,1-Dioxide (11). Compound **11** was synthesized by a published method,[25] in which 300 mg (1.3 mmol) of 3-(hydroxymethyl)thiochromone 1,1-dioxide (**9**) was refluxed for 5 h in 15 mL of dry phenyl isocyanate. The solvent was then concentrated by the flow of dry air. The resulting precipitate was filtered and recrystallized twice from acetone to give 113 mg (20%) of yellow crystals: mp 175–177 °C; IR (Nujol) 1744 (carbamyl C=O), 1660 (C=O, conj), 1302 (S=O, antisym), 1200 (S=O, sym) cm^{-1}; NMR (acetone-d_6) δ 2.85 (s, 1, NH), 5.19 (s, 2, CH_2O), 6.80–8.20 (m, 15, aromatic and vinyl H).

Thiochroman-4-one 1,1-Dioxide (12a). Peroxide oxidation was accomplished by the method of Still and Thomas.[15] Thiochroman-4-one (10 g, 0.061 mol) was dissolved in 40 mL of glacial acetic acid. Hydrogen peroxide (30%; 40 mL, 0.35 mol) was added dropwise, and the solution was heated to 100 °C for 1 h. After the solution was cooled and diluted with 100 mL of ice–water, a precipitate formed. This was filtered, dried, and then recrystallized from chloroform to give 9 g (75%) of pure compound **12a**, mp 130–130.5 °C.

3-(Chloromethyl)thiochroman-4-one 1,1-Dioxide (12b). Thiochroman-4-one 1,1-dioxide (**12a**; 2 g, 0.01 mol) was dissolved in 40 mL of glacial acetic acid. To this solution was added 40 mL of 37% formaldehyde (0.05 mol), and HCl gas was then bubbled through the mixture for 2 h. The temperature of the solution was kept below 60 °C. The solution was then stirred overnight at room temperature. Ice-cold water (300 mL) was added to the solution, and the colorless precipitate was filtered, dried, and recrystallized from ethyl acetate to give compound **12b**: mp 94–95 °C; yield 500 mg (20%).

3-Bromothiochromone 1,1-Dioxide (14). Thiochromone 1,1-dioxide (**3**; 500 mg, 2.5 mmol) was dissolved in 10 mL of chloroform. The solution was then exposed to sunlight for 10 min, while 460 mg of bromine (2.8 mmol) was added slowly. After the solution was stirred for an additional 10 min in the sunlight, a white precipitate was collected by filtration. The product proved to be a combination of 2,3-dibromothiochroman-4-one 1,1-dioxide and 3-bromothiochromone 1,1-dioxide (**14**). Fractional recrystallization from glacial acetic acid gave 500 mg (73%) of compound **14**, mp 203–205 °C (lit.[27] 203–204 °C).

Thiochromones 15a–c. These thiochromones were formed by polyphosphoric acid cyclization as described in the patent literature.[20] To 90 mL of warm polyphosphoric acid was added an intimate mixture of thiophenol (15 g, 0.14 mol) and the appropriate β-keto ester (15 g). The mixture was then stirred and heated to 100 °C for 1 h. After the mixture cooled, the brown mass was poured into 1 L of ice–water with vigorous stirring. The resulting precipitate was filtered, washed with 10% sodium hydroxide and water, and recrystallized from the appropriate solvent. Recrystallization solvents, yields, and melting points are given in Table I.

3-Bromo-2-methylthiochromone 1,1-Dioxide (16). Ziegler bromination of compound **15a** was performed as described previously.[21] Recrystallization from absolute ethanol gave yellow crystals of 3-bromo-2-methylthiochromone: mp 146–148 °C; yield 20%; TLC [SilG, $CHCl_3$/MeOH (5:1)] R_f 0.82. Hydrogen peroxide oxidation of this product was accomplished as reported in the literature:[15] mp 217–218 °C; yield 60%.

3-(Bromomethyl)-2-methylthiochromone (17). Ziegler bromination was accomplished by a modification of the method of Sorrie and Thomson.[21] 2,3-Dimethylthiochromone (**15b**; 200 mg, 1 mmol), *N*-bromosuccinimide (400 mg, 2.2 mmol), and a trace of benzoyl peroxide were added to 20 mL of carbon tetrachloride. The suspension was refluxed for 20 h and then cooled. The excess NBS and succinimide were then filtered and the CCl_4 was evaporated. Yellow-brown needles were obtained upon recrystallization from absolute ethanol: mp 145–146 °C; yield 200 mg (74%).

2,3-Bis(bromomethyl)thiochromone 1,1-Dioxide (18). Compound **18** was synthesized by Ziegler bromination of the product of hydrogen peroxide treatment of **15b** using, in this case, a 5-fold excess of NBS.[21] Reflux time was 72 h, and the product was recrystallized repeatedly from ethyl acetate to give bright yellow crystals: mp 193–195 °C; yield 10%.

3-Bromo-2-phenylthiochromone 1,1-Dioxide (19). Hydrogen peroxide oxidation of compound **15c** was carried out as reported to give the oxidized product in 60% yield.[15] This compound (300 mg, 1.1 mmol) was dissolved in 10 mL of $CHCl_3$ and placed in a UV reactor (350-nm bulb) for 30 min. Bromine (250 mg, 1.5 mmol) was added and the solution was returned to the reactor for 3 h or until no more HBr had evolved. The solvent was then evaporated and the powder was recrystallized from ethanol/ethyl acetate (3:1) to give 150 mg (43%) of yellow crystals, mp 175–177 °C.

2,3-Bis(chloromethyl)-1,4-naphthoquinone (20). Compound **20** was synthesized by the method of Lin et al.[8] 1,4-Naphthoquinone (1 g, 6.7 mmol; sublimed at 100 °C), 6 mL of formaldehyde (37%, 0.7 mol), and 15 mL of glacial acetic acid were stirred together while dry HCl gas was bubbled through the mixture for 30 min. After the solution stirred at room temperature overnight, the brown crystals were filtered, washed with ice-cold 100% ethanol, and recrystallized from 100% ethanol: yield 990 mg (58%); mp 142–143 °C (lit.[8] 142–143 °C).

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