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THE SYNTHESIS AND ANTITUMOR ACTIVITIES OF TROPOLONE AND
8-HYDROXYQUINOLINE DERIVATIVES

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The bis-derivatives (4-6) of 8-hydroxyquinoline, which, like tropolones, readily form a chelate, were synthesized and found to be actively antitumorous in tests of survival using P388 mice. 4 was almost as potent as bistropolone (2a).

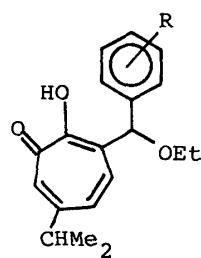
KEYWORDS ——— 8-hydroxyquinoline; tropolone; KB cell; leukemia P388; antitumor activity

We³¹ previously synthesized 3-(α -ethoxycarbonyl)-6-isopropyltropolones (1) and α,α -bis(2-hydroxy-6-isopropyltropon-3-yl)toluenes (2) by treating hinokitiol²¹ with *o*-, *m*-, and *p*-substituted benzaldehyde diethyl acetals and tested their antitumor activities. Although both types of tropolone derivatives (1 and 2) were almost equally potent inhibiting the growth of KB cells (*in vitro* system), generally, the bistropolones (2) were much more potent than the monotropolones (1) in survival tests with P388 mice (*in vivo* system).

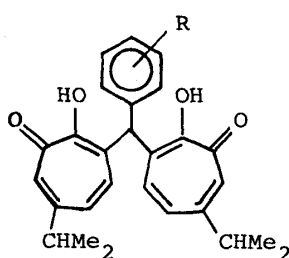
A subsequent study³¹ of the structure-activity relationship of monotropolones (1) and bistropolones (2) demonstrated that two pairs of an acidic hydroxyl and a proton-accepting group situated in neighboring positions in a molecule are necessary to produce potent activity in the *in vivo* system. Tropolones are known to be potent chelators of various metal ions. Consequently, we considered that the ability of the two carbonyl-hydroxyl pairs to form a chelate in 2 is closely related to its strong antitumor activity.

From these considerations, we have prepared 7-[α -(2-hydroxy-6-isopropyltropon-3-yl)-4-methoxybenzyl]-8-hydroxyquinoline (3)³¹ or α,α -bis(8-hydroxyquinolin-7-yl)-4-methoxytoluene (4), in which one or two tropolone rings in 2a is replaced by 8-hydroxyquinoline, a strong chelating agent. Compound 4 was synthesized by treating *p*-anisaldehyde diethyl acetal with 8-hydroxyquinoline in the presence of a catalytic amount of potassium *tert*-butoxide in refluxing cymene. Compounds 3 and 4 were relatively potent at low doses even in the *in vivo* system.⁴¹ Similarly, the thiophene and furan analogues (5 and 6) were synthesized and found to be more active at low doses than monotropolone (1a).

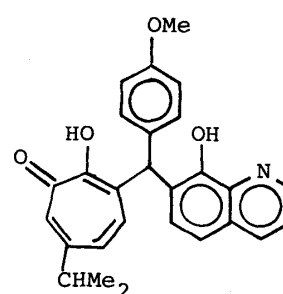
Various types of antitumor agents are applied clinically. The effects of most of these are a consequence of their ability to interact reversibly or irreversibly with DNA by intercalation, alkylation, oxidative cleavage, etc. Bis-



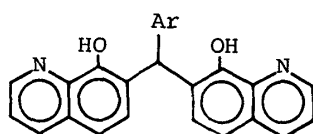
1

a: R = *p*-OMe

2

a: R = *p*-OMe

3



4: Ar = 4-anisyl

5: Ar = 2-thiophenyl

6: Ar = 2-furyl

Table I. Antitumor Activities of Tropolone and 8-Hydroxyquinoline Derivatives

Compd. No.	Inhibition of KB ^{a)} Cell growth IC ₅₀ (μg/ml)	Antitumor Act. in P388 mice, i.p.	
		Doses (mg/Kg) ^{b)}	T/C (%) ^{c)}
1a	0.5	100	140
		200	128
		400	140
2a	0.5	0.6	127
		2.5	134
		5	173
3	N. T. ^{d)}	3.1	144
		6.3	151
		12.5	141
4	< 0.3	3.1	111
		6.3	128
		12.5	164
5	< 0.3	2.5	108
		10	125
		20	136
6	< 0.3	10	113
		20	120
		40	138

a) See Ref. 1c. b) The dose listed was given once a day for 1 and 5 days. c) T/C: medium survival time of the treated animals/that of untreated controls x 100. A compound is considered to demonstrate antitumor activity if the test gives T/C values equal to or greater than 120%. d) N. T.: not tested.

tropolones (2) and bis-8-hydroxyquinolines (4-6) were thought to lack such ability because of their structures. On the other hand, α -N-heterocyclic carboxaldehyde thiosemicarbazones⁵¹ with potent antitumor activity were reported to inhibit ribonucleoside diphosphate reductase,⁵¹ which catalyzes the conversion of ribonucleotides to deoxyribonucleotides on the DNA biosynthetic pathways and requires iron ions for the activity.

Present results led us to conclude that antitumor-active tropolones and bis-8-hydroxyquinolines chelate the iron necessary for the enzyme thus inhibiting enzyme activity. A study of the antitumor mechanism is in progress and the results will be reported in the near future.

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