Communications to the Editor

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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**).

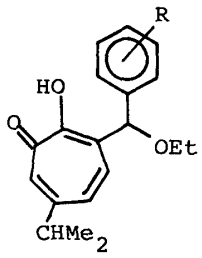
KEYWORDS ——— 8-hydroxyquinoline; tropolone; KB cell; leukemia P388; antitumor activity

We[1] previously synthesized 3-(α-ethoxycarbonyl)-6-isopropyltropolones (**1**) and α,α-bis(2-hydroxy-6-isopropyltropon-3-yl)toluenes (**2**) by treating hinokitiol[2] 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 equaly 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 study[3] 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.

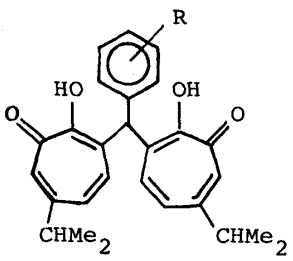
From these considerations, we have prepared 7-[α-(2-hydroxy-6-isopropyltropon-3-yl)-4-methoxybenzyl]-8-hydroxyquinoline (**3**)[3] or α,α-bis(8-hydroxyquinolin-7-yl)-4-methoxytoluene (**4**), in which one or two tropolone rings in **2a** is replaced by 8-hydroxyquinoline, a strong chelating agent. Compound **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.[4] 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-



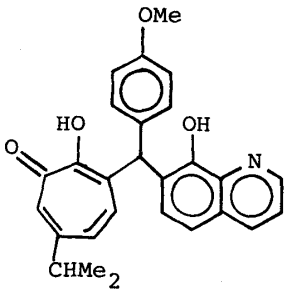
1

a: R = *p*-OMe

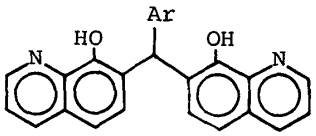


2

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 grater 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 thiosemicarbazones[5] with potent antitumor activity were reported to inhibit ribonucleoside diphosphate reductase,[6] 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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