curve was observed when 2,5-DHA was studied. In the absence of tyrosinase, no inhibitory effect upon the enzyme could be observed. When tested against the B-16 melanoma in vivo by daily intraperitoneal injection at doses ranging from 10 to 75 mg/kg, there was no significant prolongation of survival observed with either 3,4-DHA or 2,5-DHA. At higher doses, significant toxicity was observed.

DISCUSSION

Melanoma cells possess a unique enzymatic apparatus for the conversion of levodopa to the pigment melanin. It has been suggested that it may be possible to take advantage of the very high intracellular oxidative potential associated with the melanin pathway to design chemotherapeutic agents for melanoma [8–10].

Since the phenol L-glutamic acid γ-4-hydroxyanilide (MHA) was reported [3] to be inhibitory to the growth of B-16 melanoma, it seemed reasonable to prepare more readily oxidizable analogs in order to enhance activity. Our studies support the concept that cytotoxicity is, indeed, related to ease of oxidation, since each of the dihydroxy analogs of MHA is more toxic than the parent phenol when administered in vivo. The 2,5-dihydroxy derivative particularly is also more cytotoxic in vitro, suggesting that para positioning of hydroxy groups leads to an increased effect.

As reported earlier [3], the oxidation product of 3,4-DHA is a potent inhibitor of isolated DNA polymerase. Isomeric substitution of hydroxy groups in the 2,5-dihydroxy derivatives results in retention of the ability to inhibit DNA polymerase in the presence of tyrosinase. We have previously shown that 6-hydroxydopa, an analog of levodopa, differs significantly from the latter in the pattern of macromolecular synthesis inhibition [11]. A similar phenomenon is observed here, with the para derivative being less selective than the ortho.

Several mechanisms of cytotoxicity have been proposed for catechols, including inhibition of DNA polymerase by quinone metabolites and the intracellular generation of free radicals [11, 12]. It may be that, depending on which isomeric arrangement of hydroxy groups is present, one of these mechanisms is preferred.

At the present time, we do not have a definitive explanation for the marked host toxicity of 3,4-DHA and 2,5-DHA. One possibility that might be considered is cleavage of the γ-glutamyl amide bond, which would release 3,4-dihydroxyaniline and 2,5-dihydroxyaniline respectively. 3,4-Dihydroxyaniline is chemically a very unstable species, and data regarding its toxicity are unavailable in the literature. On the other hand, Torigoe [3] has reported the single-dose LD50 of 2,5-dihydroxyaniline in rats to be 30 mg/kg, and it seems very likely that the 3,4-dihydroxy compound would exhibit similar toxic properties. Perhaps, further chemical modification might result in increased stability of the amide bond and reduce systemic toxicity.

REFERENCES


Correction

In the October issue in the article “Ro 20-1724: An Agent that Significantly Improves Psoriatic Lesions in Double-Blind Clinical Trials” by Stawiski et al (73:261–263) Table II (which appeared on page 262) was misprinted. The correct version of the table appears here.

<table>
<thead>
<tr>
<th>Concentrations of Ro 20-1724</th>
<th>Number of test sites at each concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1%</td>
</tr>
<tr>
<td>Response</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Each of the nine patients tested in duplicate sites with the preparations above (see text). A possible dose response effect may be present at the 0.25% concentration. Response was graded as follows: no improvement = 0, minimal improvement = 1, and moderate or better improvement = 2.*