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2″-Substituted 5-phenylterbenzimidazoles as topoisomerase I poisons

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Abstract

5-Phenylterbenzimidazole (**1**) is active as a topoisomerase I poison (topo I) and is cytotoxic to human tumor cells. No cross-resistance was observed for **1** when it was evaluated against the camptothecin-resistant cell line, CPT-K5. Derivatives of **1** substituted at the 2″-position, however, did exhibit cross-resistance to this cell line. The basis for the resistance of this cell line towards CPT is that it possesses a mutant form of topo I. These results suggest that substituents at the 2″-position may be in proximity to the wild-type enzyme. Therefore, we hypothesized that terbenzimidazoles with 2″-substituents could be capable of interacting with the enzyme and thereby influence activity within this

class of topo I poisons. 5-Phenylterbenzimidazoles with a hydroxy, hydroxymethyl, mercapto, amino, *N*-benzoylaminomethyl, chloro, and trifluoromethyl group at the 2″-position were synthesized. In addition, several 2″-ethyl-5-phenylterbenzimidazoles were prepared containing either a methoxy, hydroxy, amino, or *N*-acetylamino group at the 2-position of the ethyl side-chain. These 2″-substituted 5-phenylterbenzimidazoles were evaluated as topo I poisons and for cytotoxic activity. The presence of a strong electron-withdrawing group at the 2″-position, such as a chloro or trifluoromethyl group, did enhance both topo I poisoning activity and cytotoxicity. Studies on the relative DNA binding affinity of **1** to its 2″-amino and 2″-trifluoromethyl derivatives did exhibit a correlation with their relative differences in biological activity