ELSEVIER

Bioorganic & Medicinal Chemistry

Volume 8, Issue 11, November 2000, Pages 2591–2600

Topoisomerase I inhibition and cytotoxicity of 5-Bromo- and 5-Phenylterbenzimidazoles

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Abstract

Topoisomerase I is an enzyme that is essential for maintaining the three-dimensional structure of DNA during the processes of transcription, translation and mitosis. With the introduction of new clinical agents that are effective in poisoning topoisomerase I, this enzyme has proved to be an attractive molecular target in the development of anticancer drugs. Several terbenzimidazoles have been identified as potent topoisomerase I poisons. Structure–activity data on various terbenzimidazoles have revealed that the presence of lipophilic substituents at the 5-position of various terbenzimidazoles correlates with enhanced cytotoxicity. While the effect of having substituents at both the 5- and 6-positions had not been evaluated, previous studies did indicate that the presence of a fused benzo-ring at the 5,6-position results in a significant decrease in topoisomerase I poisoning activity and cytotoxicity. In the present study we investigated whether

substituents at both the 5- and 6-positions of varied terbenzimidazoles would allow for retention of topo I poisoning activity. The 6-bromo, 6-methoxy, or 6-phenyl derivatives of both 5-bromo- and 5-phenylterbenzimidazole were synthesized and evaluated for topo I poisoning activity, as well as their cytotoxicity toward human lymphoblastoma cells. The data indicate that such derivatives do retain similar topo I poisoning activity and possess cytotoxicity equivalent to either 5-bromo- or 5-phenylterbenzimidazole. Significant enhancement in the topoisomerase I poisoning activity and cytotoxicity of 5-phenylterbenzimidazole is observed when the 2″-position is substituted with either a chloro or trifluoromethyl substituent. The influence of such substituents on the biological activity of 5,6-dibromoterbenzimidazole (**6a**) was also explored. In the case of either 2″-chloro-5,6-dibromoterbenzimidazole (**6b**) or 2″-trifluoromethyl-5,6-dibromoterbenzimidazole (**6c**), topoisomerase I poisoning was not enhanced relative to**6a**. While cytotoxicity toward RPMI 8402 was also not significantly affected, comparative studies performed against several solid human tumor cell lines did reveal a significant increase in cytotoxicity observed for **6c**as compared to **6a**.