Bioorganic & Medicinal Chemistry

Volume 11, Issue 8, April 2003, Pages 1809–1820

Substituted benzo[*j*]phenanthridines as mammalian topoisomerase-Targeting agents

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Abstract

Several benzo[*c*]phenanthridine and protoberberine alkaloids, such as nitidine and berberrubine, are known to induce DNA cleavage in the presence of either topoisomerase I or II. Structure–activity studies performed on various analogues related to benzo[*c*]phenanthridine and protoberberine alkaloids have provided insights into structural features that influence this topoisomerase-targeting activity. Modifications within the A-ring of benzo[*c*]phenanthridine and protoberberine alkaloids can significantly alter their ability to enhance the cleavable complex formation that occurs between DNA and topoisomerases. Select benzo[*j*]phenanthridines were synthesized as potential bioisosteres of

nitidine and its analogues. In the present study, 2,3-methylenedioxy-8,9-dimethoxybenzo[*l*]phenanthridine, 2,3-methylenedioxy-8,9-dimethoxy-5-methylbenzo[*l*]phenanthridine, 2,3,8,9-tetramethoxybenzo[*l*]phenanthridine and 5-methyl-2,3,8,9-tetramethoxybenzo[*l*]phenanthridine were synthesized. These benzo[*l*]phenanthridine derivatives were evaluated for their ability to enhance cleavable complex formation in the presence of topoisomerases and DNA as well as for their cytotoxicity against the human lymphoblastoma cell line, RPMI8402. 2,3-Methylenedioxy-8,9-dimethoxybenzo[*l*]phenanthridine (**4a**) and its 5-methyl derivative (**4b**) are active as topoisomerase I-targeting agents. In contrast to nitidine, the presence of the 5-methyl substituent in the case of **4b** is not associated with enhanced activity. Consistent with previous structure–activity studies on nitidine and protoberberine alkaloids, 2,3,8,9-teramethoxybenzo[*l*]phenanthridine, **5a**, and its 5-methyl derivative,**5b**, are inactive as topoisomerase I-targeting agents. These studies were extended to an evaluation of the relative pharmacological activities of 2,8,9-trimethoxybenzo[*l*]phenanthridine, 3,8,9-trimethoxybenzo[*l*]phenanthridine, and 2,3-methylenedioxy-8,9-methylenedioxybenzo[*l*]phenanthridine.