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2,3-Dimethoxybenzo[*j*]phenanthridines: topoisomerase I-targeting anticancer agents

- Dajie Li[a],
- Baoping Zhao[a],
- Sai-Peng Sim[b],
- Tsai-Kun Li[b],
- Angela Liu[b],
- Leroy F Liu[b, c],
- Edmond J LaVoie[a, c],
- [a] Department of Pharmaceutical Chemistry, Rutgers, The State University of New Jersey, 160 Frelinghuysen Road, Piscataway, NJ 08854-8020, USA
- [b] Department of Pharmacology, The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway, NJ 08854, USA
- [c] The Cancer Institute of New Jersey, New Brunswick, NJ 08901, USA

Abstract

Appropriately substituted benzo[*j*]phenanthridines structurally related to nitidine, a benzo[*c*]phenanthridine alkaloid with antitumor activity, are active as topoisomerase I-targeting agents. Studies on benzo[*j*]phenanthridines have indicated analogues that possess a 2,3-methylenedioxy moiety and at least one and preferably two methoxyl groups at the 8- and 9-positions, such as 8,9-dimethoxy-2,3-methylenedioxybenzo[*j*]phenanthridine, **2**, are active as topoisomerase I-targeting agents. Tetramethoxylated benzo[*j*]phenanthridines, wherein the 2,3-methylenedioxy moiety is replaced with methoxyl groups at the 2- and 3-position, are inactive as a topoisomerase I-targeting agent. These results initially suggested that the 2,3-methylenedioxy moiety was critical to the

retention of potent activity. Further studies revealed that 2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine, **7a**, is more potent than **2**as a topoisomerase I-targeting agent. The observation that 2,3-dimethoxylated benzo[*i*]phenanthridines can actually exhibit enhanced activity prompted the present study in which several 8-substituted 2,3-dimethoxybenzo[*i*]phenanthridines were prepared and their pharmacological activities evaluated. The influence of NH_2, CN, CH_2OH, OBn, OCH_3, OH, and $NHCOCH_3$ substituents at the 8-position on the relative activity of these 2,3-dimethoxybenzo[*i*]phenanthridines was examined. Relative to these derivatives, **7a** was the most potent topoisomerase I-targeting agent, possessing similar cytotoxicity to that of nitidine in the human lymphoblast tumor cell line, RPMI8402.