

Answer 1:

Bibliographic Information

Medicinal chemistry of probimane and MST-16: comparison of anticancer effects between bisdioxopiperazines. Lu, Da-Yong; Huang, Min; Xu, Cheng-Hui; Zhu, Hong; Xu, Bin; Ding, Jian. School of Life Sciences, Shanghai University, Shanghai, Peop. Rep. China. *Medicinal Chemistry* (2006), 2(4), 369-375. Publisher: Bentham Science Publishers Ltd., CODEN: MCEHAJ ISSN: 1573-4064. Journal written in English. CAN 145:262672 AN 2006:672037 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Bisdioxopiperazines, including ICRF-154 and razoxane (ICRF-159, Raz), are a family of anticancer agents developed in the UK, specifically targeting neoplastic metastases. Two other bisdioxopiperazine derivs., probimane (Pro) and MST-16, were synthesized at the Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China. To det. the similarities and differences between these agents in medical chem., we evaluated the antitumor and anti-metastatic effects of Pro and MST-16 in vitro and in vivo against a no. of human tumor cell lines and one of murine origin (Lewis lung carcinoma, LLC), and one human tumor xenograft (LAX-83) in nude mice. Our results show that Pro was cytotoxic to human tumor cell lines in vitro (IC50 < 50 μ M for 48 h), approx. 3 to 20-fold more than MST-16. Pro and MST-16 manifested more prolonged cytotoxicity than some other first-line anticancer drugs including 5-fluorouracil, vincristine and doxorubicin, and maintain their cytotoxic effects for 4 days in vitro. In animal expts., Pro and Raz were active against primary tumor growth (35-50 %) and significantly inhibited pulmonary metastasis of LLC (inhibition > 90 %) at dosage below LD5. Both Raz and Pro were effective in administration schedules of 1, 5 and 9 days. Both Raz (25-32 %) and Pro (55-60 %) caused statistically significant inhibition of the growth of LAX 83 (a human lung adenocarcinoma xenograft) in nude mice. In this model, Pro was more effective against LAX83 than Raz at equitoxic dosages. These findings suggest that Pro is active against more categories of tumors both in vivo and in vitrom, which in some circumstances may make it superior to the currently-used anticancer bisdioxopiperazines, including razoxane and MST-16.

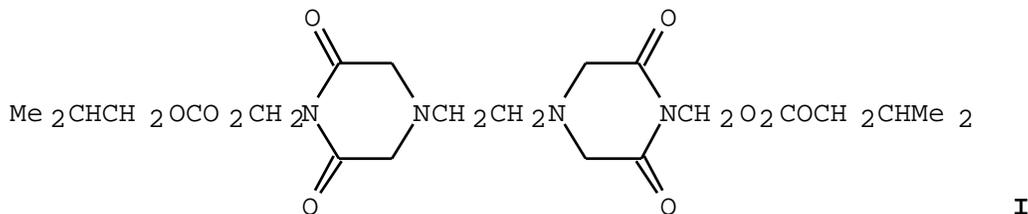
Answer 2:

Bibliographic Information

Antitumor activities and schedule dependence of orally administered MST 16, a novel derivative of bis(2,6-dioxopiperazine). Narita, Toshiharu; Koide, Yuji; Yaguchi, Shinichi; Kimura, Shoji; Izumisawa, Yasuhiro; Takase, Muneaki; Inaba, Makoto; Tsukagoshi, Shigeru. Res. Lab., Zenyaku Kogyo Co., Ltd., Tokyo, Japan. *Cancer Chemotherapy and Pharmacology* (1991), 28(4), 235-40. CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 115:247629 AN 1991:647629 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The authors studied bioavailability, treatment schedule dependence, and therapeutic efficacy of orally administered MST 16 (I) against murine tumors and human tumor xenografts. The rate of its intestinal absorption was .apprx.50%, and it was immediately metabolized to its parent compd., ICRF-154. Therapeutic efficacy of MST 16 was heavily dependent on the treatment schedule: 9 daily oral administrations and treatment every 4 h on day 1 only were much more effective against s.c.-implanted L1210 leukemia than a single dose or five daily administrations giving the same total dose. Orally administered MST 16 showed potent life-prolonging effects (1196%, 219% and 148%) in mice inoculated i.p. with P388, L1210 leukemia, and C-26 colon adenocarcinoma, resp., but had no effect on B16 melanoma inoculated in the same way. MST 16 inhibited more than 80% growth of Lewis lung carcinoma, B16 melanoma, and C-38 colon adenocarcinoma implanted s.c., but had only a minor effect on M5076 fibrosarcoma. Lung metastasis of Lewis lung carcinoma was also effectively suppressed. Furthermore, MST 16 inhibited growth of human colon, lung and breast cancers implanted s.c. in nude mice. The authors also made a kinetic anal. of the in vitro cell-killing effect by ICRF-154, the active form of MST 16 in vivo. It demonstrated a cell cycle phase-specific and time-dependent action, providing a reasonable explanation for the schedule-dependent therapeutic effect of MST 16.



Answer 3:

Bibliographic Information

Phase II study: treatment of non-Hodgkin's lymphoma with an oral antitumor derivative of bis(2,6-dioxopiperazine). Ohno R; Yamada K; Hirano M; Shirakawa S; Tanaka M; Oguri T; Kodera Y; Mitomo Y; Ikeda Y; Yokomaku S; + Department of Medicine, Nagoya University School of Medicine, Branch Hospital, Japan Journal of the National Cancer Institute (1992), 84(6), 435-8. Journal code: 7503089. ISSN:0027-8874. (CLINICAL TRIAL); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1538420 AN 92167304 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Although razoxane (ICRF-159), a derivative of bis(2,6-dioxopiperazine), has shown significant antitumor activity in several murine tumors, inadequate bioavailability has limited its clinical efficacy. Sobuzoxane (MST-16), another derivative of bis(2,6-dioxopiperazine), has shown activity against a broad spectrum of murine tumors and human tumor xenografts in nude mice and a lack of cross-resistance to vincristine, doxorubicin, cyclophosphamide, fluorouracil, etoposide, and mitomycin C. These findings suggest that MST-16 has a mode of cytotoxic activity different from that of other antitumor agents. **PURPOSE:** The present late phase II study was conducted to evaluate the clinical efficacy and toxicity of MST-16 in non-Hodgkin's lymphoma (NHL). **METHODS:** As part of a multi-institutional cooperative study, we conducted a study of MST-16 in 27 patients with NHL who were assessable for drug efficacy and toxicity. MST-16, a bis(2,6-dioxopiperazine) analogue and an inhibitor of topoisomerase II, was administered orally at a dose of 1600 mg/m² a day for 5-7 days at intervals of 2-3 weeks. **RESULTS:** Response consisted of one complete remission and seven partial remissions in 27 assessable patients. Response was achieved at a median of 13 days (range, 9-62 days) after initiation of therapy and lasted a median of 46 days (range, 29-155 days). Major toxic effects were leukopenia in 70% of the patients, thrombocytopenia in 44%, and gastrointestinal disorders in 37%. **CONCLUSIONS:** MST-16 was shown to be effective in NHL and deserves further clinical trial, since the drug shows little cross-resistance to available antitumor drugs. **IMPLICATIONS:** Phase II clinical studies of MST-16 in treatment of breast cancer, gastric cancer, and adult T-cell leukemia and lymphoma are also being conducted in Japan. Future trials of combination chemotherapy using MST-16 with other antitumor drugs are warranted in view of the additive effects observed in studies of MOLT-3 cells and studies of L1210 leukemia in mice.