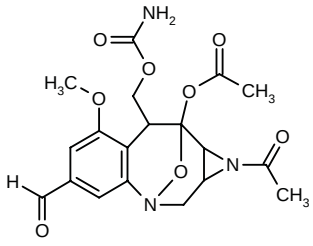
Drugs of the Future 1998, 23(5): 483-484
Copyright © 1998 PROUS SCIENCE
CCC: 0377-8282/98

FK-317

Antineoplastic Antibiotic

Acetic acid 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo[7.4.1.$0^{2,7}$.$0^{10,12}$]tetradeca-2,4,6-trien-9-yl ester

Acetic acid 1-acetyl-8-(carbamoyloxymethyl)-3,9-epoxy-5-formyl-7-methoxy-1a,2,3,8,9,9a-hexahydro-1*H*-azirino[2,3-*c*]-[1]benzazocin-9-yl ester



$C_{19}H_{21}N_3O_8$ Mol wt: 419.39

CAS: 102409-92-7

EN: 120835

Synthesis*

FR-900482 (I) was produced by culturing *Streptomyces sandaensis* No. 6897 (FERM P-7654) and recovered by conventional methods. The acetylation of (I) with acetic anhydride gave the triacetyl derivative (II), which was selectively deacetylated with $NaHCO_3$ in cool methanol yielding the diacetate (III). Finally, this compound was methylated by means of methyl iodide and K_2CO_3 in warm acetone (1). Scheme 1.

Introduction

FK-973 is an antineoplastic with the severe side effect of vascular leak syndrome. Therefore, in further studies, FK-317 was selected as an antitumor agent having a dihydrobenzoxazine structure with low toxicity (2, 3).

Pharmacological Actions

FK-317 was active against various murine and human tumors xenografted in nude mice (2-4). It was active against 24 of 34 (71%) tumors in nude mice as follows: 9/10 lung, 3/5 gastric, 2/6 colorectal, 1/3 pancreatic, 3/4 breast, 4/4 ovarian and 1/1 cervical carcinomas and 1/1 fibrosarcoma (3, 4). The reference compounds, mitomycin, doxorubicin and cisplatin, were active against human tumors implanted in nude mice in 18/34 (53%), 0/16 (0%) and 2/17 (12%), respectively. FK-317 was also active against various murine P388 leukemias resistant to mitomycin, CPT, vincristine, doxorubicin, 5-fluorouracil and cisplatin (5).

Mechanism of Action

FK-317 inhibited the synthesis of DNA, RNA and protein in L1210 leukemia cells *in vitro* and formed interstrand DNA-DNA and DNA-protein cross-links in cells, but not in cell free systems (3, 6). Deacetylated metabolites of FK-317 formed cross-links of DNA in cell free systems in the presence of a reducing agent such as $Na_2S_2O_4$ (6).

The cytotoxicity of FK-317 was AUC-dependent and especially active against lung carcinoma and leukemia. Lung carcinoma cells resistant to FK-317 showed highly decreased DT-diaphorase and elevated NADPH-P450 reductase. These resistant cells were also resistant to mitomycin (7).

Pharmacokinetics

FK-317 concentrations in tumor were lower than those in plasma and similar to those in bone marrow after intravenous injection. Active drug was eliminated from tissues within 6 h. Metabolites in tumors were alcohol form and in other tissues were carboxylic form. The sequence in decreasing order of activity in metabolites of FK-317 was aldehyde, alcohol and carboxylic forms (8).

Toxicity

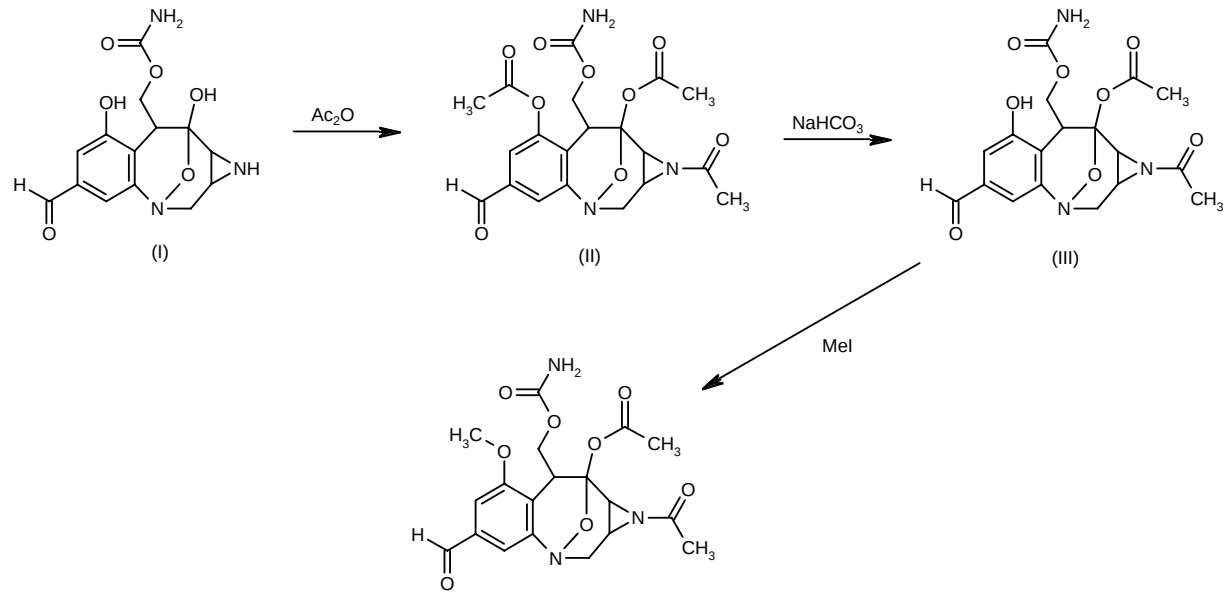
FK-317 reduced bone marrow CFU-C, CFU-S and CFU-M after intravenous administration. Recovery from the toxicity was more rapid after FK-317 than after mitomycin. Title compound also reduced peripheral leukocytes and platelets but not erythrocytes (8).

Clinical Studies

FK-317 is undergoing phase I clinical studies (9).

A. Hoshi, J. Castañer*. 3-4-10 Kameari, Katsushika-ku, Tokyo 125, Japan and Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of FK-317



Manufacturer

Fujisawa Pharmaceutical Co., Ltd. (JP).

References

1. Kohsaka, M., Terano, H., Komori, T. et al. (Fujisawa Pharm. Co., Ltd.). *New tetracyclo cpds., a process for their production and a pharmaceutical compsn. containing the same.* AU 8543728, EP 166389, ES 8703477, ES 8707961, ES 8707962, JP 86010590, JP 89199975, JP 95067623, US 4645765, US 4861774.

2. Matsumoto, S., Kawamura, I., Nishigaki, F., Tsujimoto, S., Naoe, Y., Inami, M., Manda, T., Shimomura, K. *Antitumor effects of FK317, a new antibiotic.* 55th Annu Meet Jpn Cancer Assoc (Oct 10-12, Yokohama) 1996, Abst 2308.

3. Naoe, Y., Matsumoto, S., Kawamura, I., Nishigaki, F., Tsujimoto, S., Inami, M., Manda, T., Shimomura, K. *A novel antitumor agent FK317: Antitumor activities in vivo and mechanism of action.* Proc Amer Assoc Cancer Res 1997, 38: Abst 1487.

4. Inami, M., Matsumoto, S., Naoe, Y., Manda, T. *Antitumor effects of FK317, a novel antitumor antibiotic, on human tumor xenografts.* 56th Annu Meet Jpn Cancer Assoc (Sept 25-27, Kyoto) 1997, Abst VAP-007.

5. Naoe, Y., Nishigaki, F., Matsumoto, S., Inami, M., Tsujimoto, S., Manda, T. *Antitumor effects of FK317, a new antitumor antibiotic, against various resistant tumors.* 56th Annu Meet Jpn Cancer Assoc (Sept 25-27, Kyoto) 1997, Abst VAP-008.

6. Naoe, Y., Manda, T., Shimomura, K. *Mechanism of cytotoxic activity induced by FK317, a novel antitumor antibiotic.* 55th Annu Meet Jpn Cancer Assoc (Oct 10-12, Yokohama) 1996, Abst 2309.

7. Nishigaki, F., Naoe, Y., Kawamura, I., Manda, T. *Cytotoxicity of a novel antitumor antibiotic FK317 and its characterization.* 56th Annu Meet Jpn Cancer Assoc (Sept 25-27, Kyoto) 1997, Abst VAP-005.

8. Tsujimoto, S., Matsumoto, S., Nishigaki, F., Kawamura, I., Naoe, Y., Inami, M., Manda, T. *Myelotoxicity of a novel antibiotic FK317 in mice.* 56th Annu Meet Jpn Cancer Assoc (Sept 25-27, Kyoto) 1997, Abst VAP-006.

9. *FK317 development status.* Fujisawa Pharmaceutical Co., Ltd. Company Communication April 24, 1997.