Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 1387–1390

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

THE NOVEL CYCLOPROPAPYRROLOINDOLE(CPI) BISALKYLATORS BEARING METHOXYCARBONYL AND TRIFLUOROMETHYL GROUPS

Yasumichi Fukuda*, Hirosuke Furuta, Yoshie Kusama, Hiroyuki Ebisu, Yasuo Oomori

Central Research Laboratories, Kyorin Pharmaceutical Co. Ltd., Mitarai, Nogi, Tochigi 329-0114, Japan

Shiro Terashima*

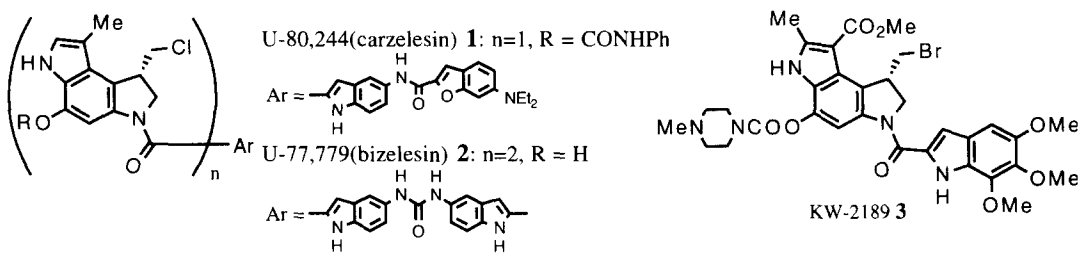
Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229-0012, Japan

Received 16 March 1998; accepted 21 April 1998

Abstract: The novel 3-methoxycarbonyl-2-trifluoromethylcyclopropapyrroloindole (MCTFCPI) bisalkylators were synthesized and their antitumor activity was evaluated. Among these derivatives, **7f** in which two MCTFCPI moieties are connected with a 5,5'-bis(2-carbonyl-1*H*-indole) group, was found to exhibit more prominent cytotoxicity and antitumor activity than U-77,779 (bizelesin) (**2**).

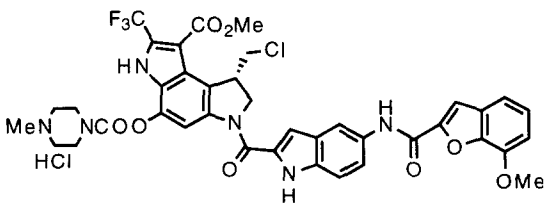
The cyclopropapyrroloindole(CPI) derivatives, U-80,244 (carzelesin) (**1**)[1] and KW-2189 (**3**)[2], are presently under clinical trials as the promising antitumor agents (**Figure 1**). Recently, we reported the synthesis

Figure 1



and antitumor activity of the novel 3-methoxycarbonyl-2-trifluoromethylCPI (MCTFCPI) derivatives and their prodrugs which show prominent cytotoxicity (*in vitro*) and antitumor activity (*in vivo*) against murine solid tumor.[3] Based on these studies, **AT-3510** (**4**) was explored to exhibit antitumor activity against human tumor xenografts more excellent than that for **1**, **3** and the clinically widely used anticancer agent, cisplatin.[4]

Figure 2



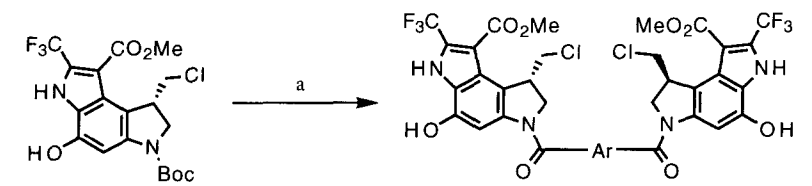
AT-3510 **4**

0960-894X/98/$19.00
PII: S0960-894X(98)00235-2

It is reported that U-77,779 (bizelesin) (**2**) in which two alkylating moieties are connected with a rigid linker, 1,3-bis(2-carbonyl-1*H*-indol-5-yl)urea group, behaves as a bisalkylator.[5a] It is also reported that, for the bisalkylators bearing flexible methylene linkers, their cytotoxicity highly depends upon the length of their methylene linkers.[5b] Although the studies on the length and type of rigid linkers have been of quite limited, it appeared that *in vivo* antitumor activity of **2** carrying rigid linker is more excellent than that of bisalkylators bearing flexible methylene linkers.[5b] Therefore, our synthetic attention on the novel bisalkylators was first focused on the length and type of rigid linker between the two MCTFCPI groups. Among them, **7f** was found to exhibit more promising *in vitro* and *in vivo* activity than **2**. The two MCTFCPI moieties of **7f** are connected with a 5,5'-bis(2-carbonyl-1*H*-indole) group, which has a carbon-carbon single bond between the two indole rings. Herein, we wish report on the synthesis and antitumor activity of the novel bisalkylators carrying two MCTFCPI rings.

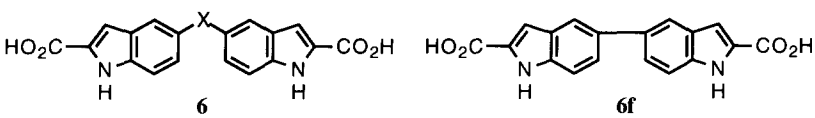
According to the procedure reported in the preceding paper,[4] we completed the synthesis of novel MCTFCPI bisalkylators **7a~f** by coupling two equivalents of the optically active phenol (*S*)-**5** with one equivalent of various dicarboxylic acids **6a~f** (**Scheme 1**).

Scheme 1



5 **7a~f**

a) i) 3MHCl-AcOEt ii) EDCI, HO_2C-Ar-CO_2H (**6a~f**),
7a; 86%, **7b**; 36%, **7c**; 33%, **7d**; 29%, **7e**; 48%, **7f**; 40%.

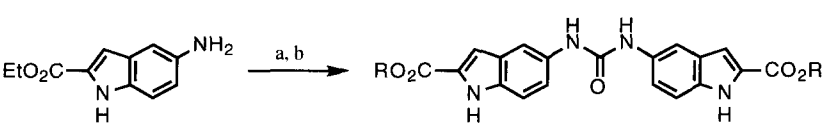


6 **6f**

a: X = NHCONH **d**: X = CH_2
b: X = C≡C **e**: X = O
c: X = CH_2CH_2

Among **6a~f**, bis(2-carboxyl-1*H*-indol-5-yl) derivatives **6c~f** were prepared according to the reported methods.[6] Synthesis of 1,3-bis(2-carboxyl-1*H*-indol-5-yl)urea (**6a**)[5] was achieved by acylation of ethyl 5-aminoindole-2-carboxylate (**8**) with 1,1'-carbonyldiimidazole (CDI) followed by alkaline hydrolysis of the formed diethyl ester **9** (**Scheme 2**). The synthesis of 1,2-bis(2-carboxyl-1*H*-indol-5-yl)ethyne (**6b**) was

Scheme 2

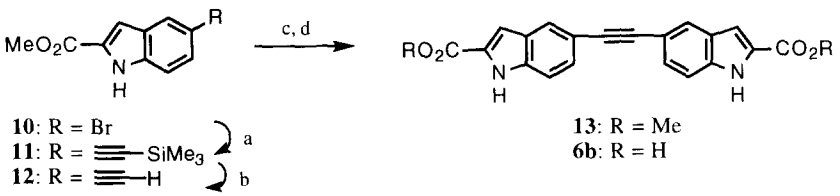


8 **9**: R = Et
6a: R = H

a) CDI, THF, rt, 58%. b) LiOH, 77%.

carried out starting from methyl 5-bromoindole-2-carboxylate (**10**) as shown in **Scheme 3**. Therein, a palladium-catalyzed coupling[7] was employed to insert an acetylenic bond between the two 5-positions in the indole rings.

Scheme 3



a) trimethylsilylacetylene, $Pd(PPh_3)_4$ (10mol%), CuI, Et_3N, MeCN, reflux, 75%. b) 0.2MNaOH, MeOH, rt, 76%. c) **10**, $Pd(PPh_3)_4$ (10mol%), CuI, Et_3N, MeCN, reflux, 48%. d) 20%KOH, EtOH, 80°C, 93%.

With the novel MCTFCPI bisalkylators **7a~f** in hand, we investigated cytotoxicity assay (*in vitro*) against HeLaS3 human uterine cervix carcinoma and antitumor activity assay (*in vivo*) against Colon 26 murine adenocarcinoma. As shown in **Table 1**, **7a** having a ureadiyl group as the linker similarly to **2** exhibited comparable cytotoxicity and antitumor activity to **2**.[8] Cytotoxicity and antitumor activity of **7f** were obviously

Table 1. Cytotoxicity Against HeLaS3 Human Uterine Cervix Carcinoma and Antitumor Activity Against Colon 26 Murine Adenocarcinoma

7	a	b	c	d	e	f	2
IC_{50} (ng/ml)[a)]	0.091	0.35	0.21	33	22	0.0049	0.060
TGI% (μg/kg)[b)]	94 (15.6)	82 (31.3)	87 (31.3)	80 (4000)	88 (4000)	84 (0.977)	90 (15.6)

a) Drug concentration required to inhibit the growth of HeLaS3 cells by 50%.
b) Colon 26 (10^6/mouse) cells were inoculated s.c. into male CDF1 mice on day 0. Drugs were administered i.v. on day 6. The percentage tumor growth inhibition as compared with the untreated group.

superior to those of **2**. In summary, it appeared evident that the length of a rigid linker gives a significant influence on cytotoxicity and antitumor activity rather than the type of a rigid linker. Further investigations on the MCTFCPI bisalkylators bearing novel rigid linkers are in progress and will be reported shortly.

Acknowledgments:

We are grateful to Dr. S. Suzue, Kyorin Pharmaceutical Co. Ltd., for many valuable suggestions and encouragement. We thank Dr. T. Ishizaki, Kyorin Pharmaceutical Co. Ltd., for proving us with a sample of dicarboxylic acid **6a**.

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