Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 2003–2004

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

THE NOVEL CYCLOPROPAPYRROLOINDOLE(CPI) BISALKYLATORS BEARING 3,3'-(1,4-PHENYLENE)DIACRYLOYL GROUP AS A LINKER

Yasumichi Fukuda*, Shigeki Seto, Hirosuke Furuta, Hiroyuki Ebisu, Yasuo Oomori

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

Shiro Terashima*

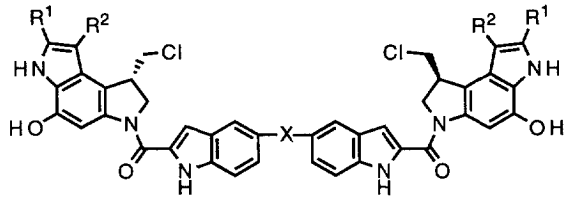
Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229-0012, Japan

Received 21 May 1998; accepted 23 June 1998

Abstract: The novel cyclopropapyrroloindole(CPI) bisalkylators were synthesized and their antitumor activity was evaluated. Among these derivatives, **AT-760 (5a)** in which the two 3-methoxycarbonyl-2-trifluoromethylCPI (MCTFCPI) moieties are connected with a 3,3'-(1,4-phenylene)diacryloyl group, was found to exhibit more prominent cytotoxicity and antitumor activity than U-77,779 (bizelesin) (**1**).

The cyclopropapyrroloindole(CPI) bisalkylator, U-77,779 (bizelesin) (**1**), showing promising antitumor activity has been reported, in which the two alkylating moieties are connected with a rigid linker, 1,3-bis(2-carbonyl-1*H*-indol-5-yl)urea group.[1] Recently, we reported the synthesis and antitumor activity of the novel 3-methoxycarbonyl-2-trifluoromethylCPI (MCTFCPI) bisalkylator **2**. In **2**, the two MCTFCPI groups are connected with a rigid linker, 5,5'-bis(2-carbonyl-1*H*-indole) group, and this bisalkylator **2** showed more excellent antitumor activity than **1** (**Figure 1**).[2]

Figure 1



1: R^1= H, R^2= Me, X= NHCONH [U-77,779(bizelesin)]

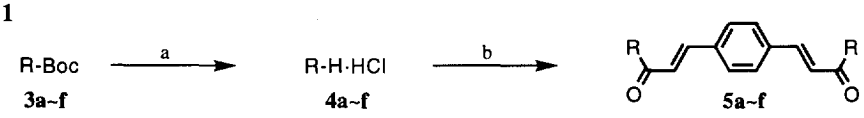
2: R^1= CF_3, R^2= CO_2Me, X= —

Based on these studies, it was uncovered that the length of rigid linker gives a significant influence on cytotoxicity and antitumor activity rather than the type of rigid linker.[2] Therefore, with an aim to explore the novel CPI bisalkylators showing even more excellent antitumor activity than **1**, we designed and synthesized the various CPI bisalkylators bearing 3,3'-(1,4-phenylene)diacryloyl group as a novel rigid linker whose length is shorter than that in **2**. Among them, **AT-760** (**5a**) was found to exhibit more excellent *in vitro* and *in vivo* activity than **1**. Herein, we wish report on the synthesis and antitumor activity of the various CPI bisalkylators carrying 3,3'-(1,4-phenylene)diacryloyl group as a linker.

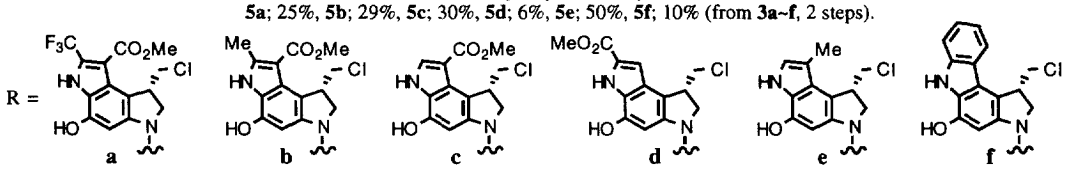
According to the procedure reported in the preceding paper,[2] we completed the synthesis of novel CPI bisalkylators **5a~f** by coupling two equivalents of the optically active phenols (*S*)-**4a~f** with one equivalent of 3,3'-(1,4-phenylene)diacrylic acid (**Scheme 1**). The phenols (*S*)-**4a~f** were derived from optically active N-protected indolines (*S*)-**3a~f**[3] by deprotection.

0960-894X/98/$ - see front matter
PII: S0960-894X(98)00346-1

Scheme 1



a) 3MHCl-AcOEt. b) 3,3'-(1,4-phenylene)diacrylic acid, EDCI, DMF,
5a; 25%, **5b**; 29%, **5c**; 30%, **5d**; 6%, **5e**; 50%, **5f**; 10% (from **3a~f**, 2 steps).



With the novel bisalkylators **5a~f** in hand, they were subjected to 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**, **AT-760 (5a)** having two MCTFCPI rings exhibited superior cytotoxicity and antitumor activity to **1**.[4] Furthermore, therapeutic index (MTD/TGI_{50}) of **5a** was obviously superior to those of **1** and **2**. Accordingly, it appeared evident that **5a** shows less toxicity than **1** and **2**, respectively. Further pharmacological investigations on **5a** are in progress.

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

	5a	5b	5c	5d	5e	5f	1	2
IC_{50} (ng/ml)[a)]	0.0027	0.00046	0.00035	0.023	0.0013	0.072	0.060	0.0049
TGI_{50} (μg/kg)[b)]	0.254	0.891	0.757	100	1.41	3.80	3.72	0.300
$MTD^{c)}/TGI_{50}$	30.7	8.8	10.3	–	5.5	8.2	8.4	3.3

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 7. The 50% tumor growth inhibition as compared with the untreated group.

c) Maximum dose within 10% body weight loss (μg/kg).

Acknowledgments:

We are grateful to Dr. S. Suzue, Kyorin Pharmaceutical Co. Ltd., for many valuable suggestions and encouragement.

References and Notes

1. Mitchell, M. A.; Kelly, R. C.; Wicnienski, N. A.; Hatzenbuhler, N. T.; Williams, M. G.; Petzold, G. L.; Slightom, J. L.; Siemieniak, D. R. *J. Am. Chem. Soc.*, **1991**, *113*, 8994.
2. Fukuda, Y.; Furuta, H.; Kusama, Y.; Ebisu, H.; Oomori, Y.; Terashima, S. *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 1387.
3. For the synthesis of **3a~f**, see, Fukuda, Y.; Furuta, H.; Shiga, F.; Oomori, Y.; Kusama, Y.; Ebisu, H.; Terashima, S. *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1683. (for **3a**), ref. 4. (for **3b,c** and **e**), Fukuda, Y.; Terashima, S. *Tetrahedron Lett.*, **1997**, *38*, 7207. (for **3d**), Fukuda, Y.; Furuta, H.; Kusama, Y.; Ebisu, H.; Oomori, Y.; Terashima, S. *Heterocycles*, in submitting. (for **3f**).
4. U-77,779 (bizelesin) (**1**) used as the standard compound was synthesized in our laboratories. Fukuda, Y.; Furuta, H.; Shiga, F.; Asahina, Y.; Terashima, S. *Heterocycles*, **1997**, *45*, 2303.