Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 1797–1800

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

SYNTHESIS AND *IN VITRO* CYTOTOXICITY OF C(20)(*RS*)-CAMPTOTHECIN ANALOGUES MODIFIED AT BOTH B (OR A) AND E RING

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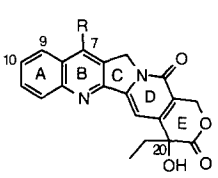
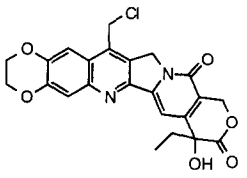
Received 3 March 1998; accepted 2 June 1998

Abstract : A series of C(7) and C(20)-substituted camptothecin derivatives (**12 - 14, 16 - 18**) are prepared. Their syntheses and *in vitro* cytotoxicities are reported.

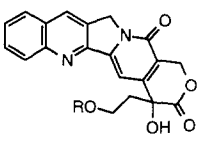
Camptothecin (C(20)(*S*)-**1**) is an alkaloid which was first isolated from chinese tree, *Camptotheca acuminata*[1]. C(20)(*S*)-**1** has been found to have a broad spectrum of antitumor activity[2], especially against human solid tumor. Mechanistic investigations have shown that the antitumor activity is associated with the inhibition of Topoisomerase I[3] (Topo I) which is essential for the transcription of supercoiled DNA. The above unusual mechanism led to develop semisynthetic analogues, Irinotecan[4] and Topotecan[5] as new commercial antitumor drugs with less toxicity than camptothecin itself. Also the development of total synthetic methods made it possible to investigate the intensive structure-activity relationship studies. Based on the accumulated SAR studies, the introduction of polar groups at C(7), C(9) and C(10) on C(20)(*S*)-**1** generally enhenced cytotoxicity. **2** is one of these compounds modified at A and B ring on C(20)(*S*)-**1** with polar groups[6]. Recently, we have develped a series of *C*(7)-substituted C(20)(*RS*)-camptothecin analogues[7] and C(20)(*RS*)-desethyl-20-substituted camptothecin analogues[8]. Among these derivatives, **3** and **4** showed significant antitumor activity compared with C(20)(*S*)-**1** in each series of derivatives.



1 R = H
4 R = -$(CH_2)_2$NH *i*-Pr



2



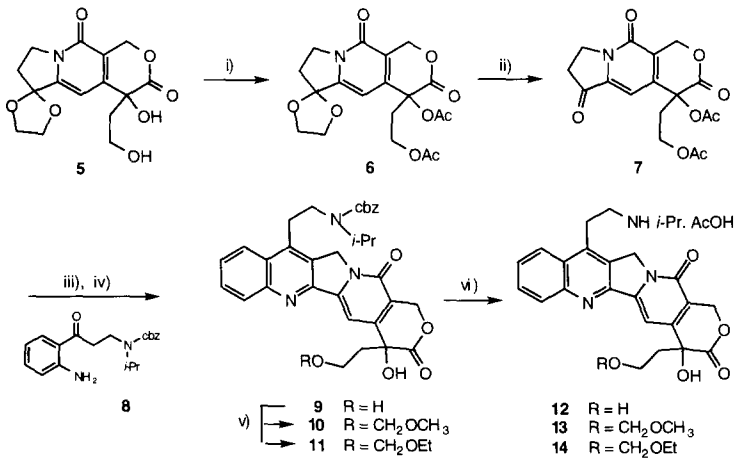
3 R = -CH_2OCH_3

Based on the our previous SAR studies, we expected the antitumor activity could be maximized by combinational modification of **2** and **3**, or **3** and **4**. In this paper, the syntheses and *in vitro* cytotoxicities of C(20)(*RS*)-camptothecin analogues modified at both B (or A) and E ring are reported.

0960-894X/98/$19.00
PII: S0960-894X(98)00317-5

The syntheses of the analogues modified at both B and E ring (**12** - **14**) were accomplished in 5 steps starting from diol **5** which could be easily prepared by previous procedure[7,8] (Scheme 1).

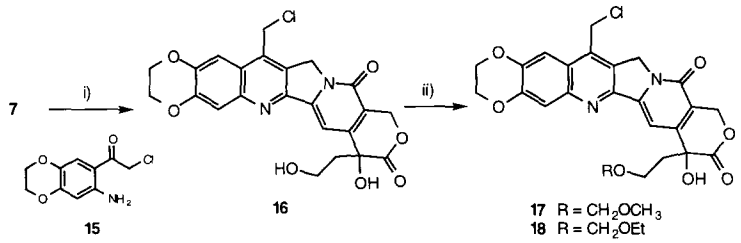
Scheme 1



Reagents : I) Ac_2O / CH_2Cl_2 / pyridine / cat. DMAP., rt, 15 h (94%), ii) 80% TFA, rt, 4 h (89%), iii) **8**/*cat.* *p*-TsOH/toluene, reflux, 5 h (65%)., iv) LiOH/MeOH/H_2O, rt, 6 h ; then 1 N HCl (pH = 3), rt, 1 h (21%), v) MOMCl (or chloromethyl ethyl ether)/CH_2Cl_2/*i*-pr_2NEt, 0°C to rt, 40 - 44 h (**10** (35%); **11** (52%)), vi) H_2, 10% Pd on C / AcOH, rt, 5 - 20 h (**12** (31%); **13** (28%); **14** (34%)).

The diacetylation of **5** with Ac_2O in pyridine gave **6,** which was converted to **7** by deketalization with 80% trifluoroacetic acid. The Friedlander condensation of **7** with **8**[7] followed by hydrolysis and relactonization provided **8**. The treatment of **8** with MOMCl or chloromethyl ethyl ether in basic condition gave **10** and **11** respectively. Finally, the catalytic hydrogenation of **9** - **11** in acetic acid solvent gave **12** - **14** respectively. The other series of analogues (**16** - **18**) were obtained from **7** (Scheme 2). The Friedlander condensation of **7** with amino ketone **15**[6] followed by hydrolysis and relactonization provided **16**. The ether formation was performed by the same method as Scheme 1 to get **17** and **18**.

Scheme 2



Reagents: i) **15**/*cat.* *p*-TsOH/toluene, reflux, 15 h; then LiOH/MeOH/H_2O, rt, 2 h ; then 1 N HCl (pH = 3), rt, 3 h (38%), ii) MOMCl (or chloromethyl ethyl ether)/CH_2Cl_2/*i*-pr_2NEt, 0°C to rt, 20 - 26 h (**17** (10%); **18** (9%)),

Table 1. *In vitro* Cytotoxicity[9] of Camptothecin Analogues against Human Tumor Cell Lines[10] (IC_{50}, μM).

Compd.	A172	DLD-1	CAOV-3	KATO-III	L1210
C(20)(*S*)-**1**	0.029	0.102	0.032	0.448	0.035
2	0.054	2.783	0.087	6.113	14.004
3	2.620	1.860	0.560	0.320	0.440
4	0.167	0.276	0.004	0.623	0.460
12	3.560	0.619	0.483	4.400	6.730
13	12.170	0.549	0.091	3.270	—[a]
14	5.460	2.100	0.024	4.210	14.110
16	0.391	0.055	0.010	0.135	0.898
17	0.029	0.108	0.003	1.460	0.307
18	—[a]	3.876	3.762	5.917	—[a]

[a]The test was not performed.

In vitro cytotoxic activities against five human tumor cell lines for the above camptothecin analogues[11] along with C(20)(*S*)-**1** are listed in Table 1. Generally, the both 7 and 20-substituted analogues (**12** - **14**) reduced the potency compared with **3** and **4**. This result was not consistent with our strategy to improve the cytotoxic activity by modification of both B and E ring in camptothecin. We suspect the both modification is not favorable in the binding process because of steric hindrance. On the other hand, A and E ring modified derivatives (**16** - **18**) which were fixed with relatively small chloromethyl group at *C*(7) showed comparable cytotoxicity with **2**, **3** and C(20)(*S*)-**1**. As shown in Table 1, **16** was 2 and 3 times more potent than C(20)(*S*)-**1** in DLD-1 and KATO-III cell lines, respectively. Especially **16** and **17** showed 3- and 10-fold cytotoxicity in CAOV-3 cell line compared with C(20)(*S*)-**1**, respectively. In conclusion, the combinational modification of **2** and **3** enhanced the cytotoxicities compared with each **2**, **3** except **18**. Especially the 10 times higher cytotoxicity of **17** compared with C(20)(*S*)-**1** in CAOV-3 cell line give us possible chance to develop specifically effective antitumor agent against ovarian cancer. Considering that these derivatives were racemate, optically active form of **16** and **17** would have even higher cytotoxicity. The study of chiral **16** and **17** is currently being investigated.

Acknowledgement : This research was supported by grants of the '96 Good Health R & D project from the Ministry of Health & Welfare, R. O. K. and the Research Center of New Drug Development of Seoul National University.

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10. *In vitro* antiproliferative activities of the analogues against five tumor cell lines (A172 human CNS cancer; DLD-1, human colon cancer; CAOV-3, human ovarian cancer; KATO-III, human gastric cancer; L1210, mouse leukemia) were measured by SRB assay[9] after 3 days of incubation and expressed as the doses required to inhibit the growth of 50 % of the cells cultivated (IC_{50}, μM).
11. All new compounds gave satisfactory spectroscopic data consistent with the proposed structures.