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CONVERGENT APPROACH TO WATER SOLUBLE CAMPTOTHECIN DERIVATIVES

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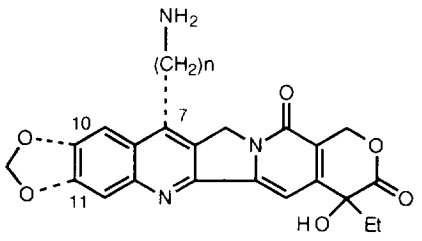
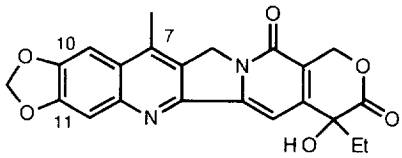
Abstract: New water soluble camptothecin derivatives with excellent antitumor activity have been designed and synthesized. The synthetic approach includes an efficient route to 7-aminoethyl and 7-aminomethyl camptothecins using either N-Boc protected aminopropion(or aceto)aldehyde or N-methylacetamide as alkylating agents.

Camptothecin[1] is derived from a variety of common tree of the camptotheca spp, which was discarded as a clinical drug for cancer chemotherapy in 1970s because it caused an untreatable haemorrhagic cystitis, despite its good cytotoxicity. Recent demonstration that DNA topoisomerase I has been identified as a principal target of 20(S)-camptothecin has aroused great interest in research and development of its analogs as antitumor drugs[2]. Since camptothecin itself has a disadvantage of poor aqueous solubility which also precludes its development as a drug, considerable interest has been directed on the design and synthesis of water soluble analogs of camptothecin[3].

Our own endeavor has focused on design and synthesis of novel water soluble camptothecin analogs. Specifically, we were interested in the synthesis of hexacyclic compound like **A**. The rational design of compound **A** was based on our finding that 7-methyl-10,11-methylenedioxy-20(RS)-camptothecin (compound **B**) has potent antitumor activity[4]. Therefore, we hoped that introduction of an aminoalkyl group into camptothecin at 7-position would improve water solubility of camptothecin, and additional methylenedioxy group attached by linkage of camptothecin between 10- and 11-position would contribute to enhancement of activity.



A

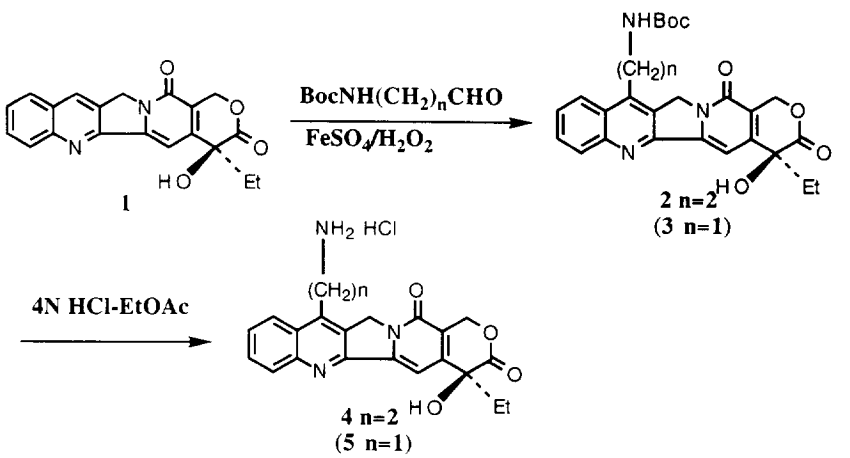


B

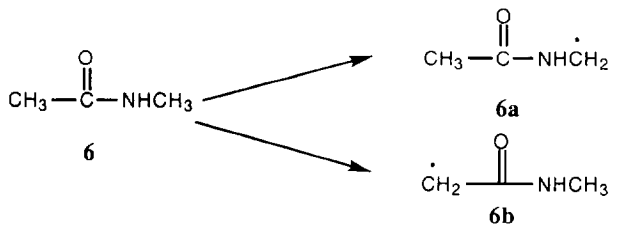
The fundamental step involved in the synthesis of designed molecule is the incorporation of an appropriate aminoalkyl group into camptothecin at 7-position. We perceived an opportunity to employ radical reaction[6] to directly alkylate camptothecin at 7-position. Thus, radical reaction of camptothecin **1** with

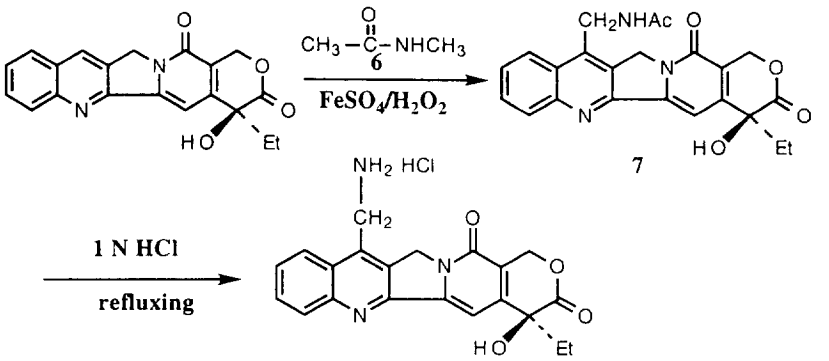
3-N-t-butoxycarbonylaminopropionaldehyde in the presence of $FeSO_4$ and H_2O_2 provided

7-N-butoxycarbonylaminoethyl camptothecin **2** in 41% yield. This reaction did not proceed in completion in spite of varying the reaction condition. Facile cleavage of Boc-moiety afforded 7-aminoethylcamptothecin **4** in quantitative yield. Although corresponding 7-N-butoxycarbonylaminomethyl camptothecin **3** would be obtained using a similar radical reaction between camptothecin and 2-N-t-butoxycarbonylaminoacetoaldehyde, failure to isolate the product **3** efficiently renders this reaction less practical for preparing 7-aminomethylcamptothecin **5**.



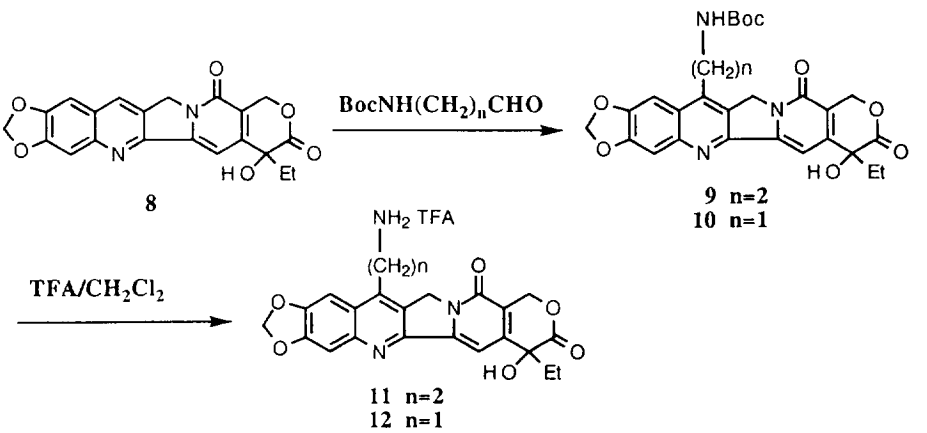
An alternative solution was therefore sought. It is envisioned that under a redox system, N-methylacetamide can lead to two types of radicals (type **6a** and type **6b**). Because a carbonyl group is adjacent to carbon radical **6b**, this radical is less reactive than carbon radical **6a**. Therefore, only radical **6a** could undergo nucleophilic attack on camptothecin at 7-position to provide 7-N-acetylaminomethyl camptothecin **7**.





As expected, addition of H_2O_2 to a mixture of camptothecin, N-methylacetamide and $FeSO_4$, did afford desired product **7** in 83% yield[7]. Deprotection was effected by refluxing a 1N HCl solution of compound **7** to provide amine product **5**. In comparison with use of aldehyde, the choice of N-methylacetamide as alkylating agent represents a new convenient approach for introducing aminomethyl moiety.

Subjection of compound **8**[8] to 3-N-tert-butoxycarbonylaminopropionaldehyde in the presence of Iron(II) sulfate heptahydrate and hydrogen peroxide furnished compound **9** in 38% yield, which was conveniently converted to its corresponding amine **11**. Similarly, compound **12** with methyleneamino function at 7-position was synthesized by radical reaction of compound **8** with 2-N-t-butoxycarbonylaminoacetoaldehyde followed by deprotection with TFA.



These new water soluble compounds[10] were found to show good antitumor activity. **Table 1** outlines a selected preliminary *in vivo* result. The activity of compound **11** is comparable to that of topotecan. Whether or not these synthetic agents are superior to topotecan and other water soluble compounds in toxicity remains to be investigated in future studies.

Table 1. Inhibitory Effects of Topotecan and Compound **11** on the Growth of Murine Tumors Transplanted Subcutaneously into Mice

Compound	Dose	Route	Tumor weight (T/C%)	
	mg/kg/day x 5		Colon 26	P388/CPT(1)
Topotecan	2	iv	60	59
	4	iv	51	46
11	2	iv	55	65
	4	iv	49	36

Colon carcinoma 26 (Colon 26) and leukemia P388 were maintained in our laboratories as described elsewhere[9]. A subline of P388 resistant of camptothecin (P388/CPT) was obtained by treating P388-bearing mice with camptothecin in serial transplantation of the tumor. Colon 26($5x10^5$ cells and P388/CPT ($1x10^6$ cells) were transplanted subcutaneously into Crj: BALB/c and Crj: BDF_1 female mice, respectively, on Day 0. Drugs were injected intravenously into the mice daily for 5 days starting on Day 7 (Colon 26) or on Day 1(P388/CPT). Tumors were weighed on Day 14 (Colon 26) and Day 10 (P388/CPT) and the mean tumors weight of treated group (T, n=5) was expressed as the percentage of that of control group (C, n=10).

Acknowledgement:

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4.The *in vivo* antitumor activity of compound **B** against Colon 26 and P388 was more potent than that of camptothecin (Xie, Z.F.; et al. unpublished data).

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7. The yield was based on the recovery of starting material.

8. Compound **8** was prepared using a similar approach to that reported by Wani, M.C.; Ronman, P.E.; Lindley, J.T.; Wall, M.E. *J. Med. Chem.* **1980**, *23*, 554.

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10. All new compounds gave analytical and spectroscopic results consistent with the assigned structure. Both aminoethyl and aminomethyl camptothecin derivatives synthesized in this research were water soluble.

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