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SYNTHESIS AND ANTITUMOR ACTIVITY OF CAMPTOTHECIN DERIVATIVES BEARING FIVE-MEMBERED HETEROCYCLE CONTAINING 10-SUBSTITUENTS

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Abstract: A series of new camptothecin derivatives bearing five-membered ring heterocycle containing substituents in the 10-position were synthesized and evaluated for *in vitro* cytotoxic activity. Camptothecin derivatives bearing a pyrrole or a thiophene ring were significantly more potent than camptothecin, however those bearing furan were less potent than camptothecin.

Since camptothecin (**I**) was discovered as an antitumor alkaloid by Wall *et al.* in 1966,[1] efforts have been made to develop more effective anticancer analogues. The synthesis of numerous substituted and ring-modified camptothecin derivatives have contributed to the understanding of the structure-activity relationships.[2,3]

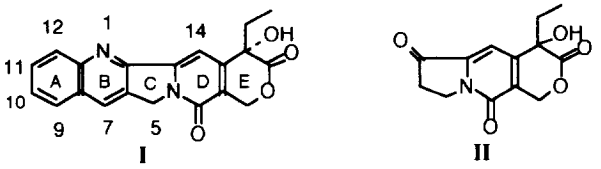
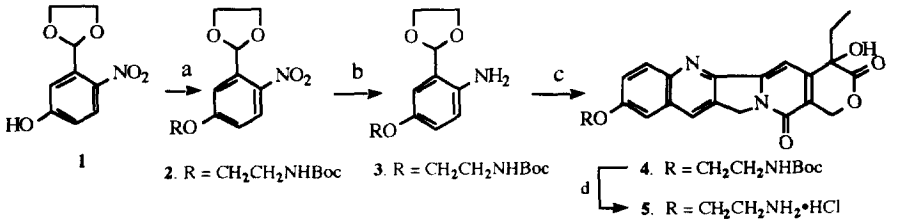


Figure I Structure of camptothecin (**I**) and the tricyclic ketone (**II**)

Thus previous studies have shown that the α-hydroxyl lactone moiety and aromatic ring ABCD nucleus of camptothecin and its analogues are essential for antitumor activity, and substitution at positions 7, 9, and 10 generally increase anti-topoisomerase I and antitumor activities. The camptothecin derivatives CPT-11 and Topocan, which were substituted by water soluble moieties at the 9 and 10 positions of ring A, are currently in clinical trials.[4] Recently we reported that incorporation of appropriate five membered heterocyclic substituents into a pharmacophore often confers improved biological properties.[5,6] As an extension of this approach, we describe herein the synthesis and *in vitro* evaluation of nine new 10-substituted camptothecins.

The synthesis of the camptothecin derivative with an amino moiety in position 10 (**5**) is shown in Scheme I. The overall strategy is that of Friedlander condensation of known tricyclic ketone (**II**) with aminoacetal (**3**) to give the camptothecin pentacyclic structure (**4**).[7] Aminoacetal (**3**) was prepared from **1** in two steps.

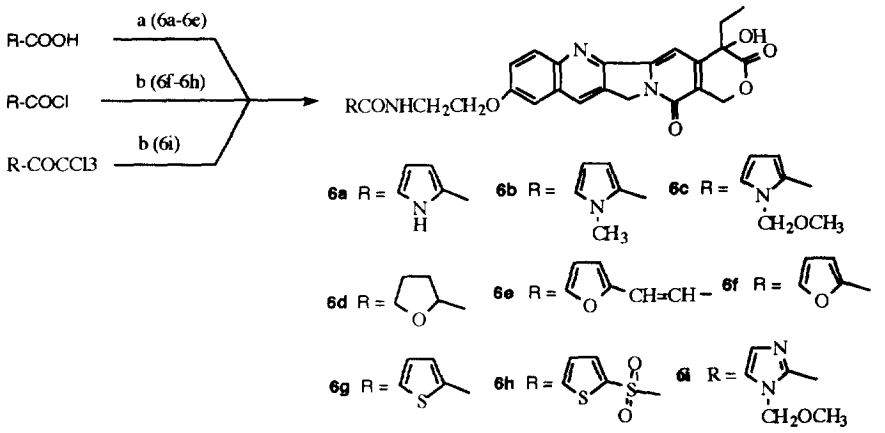
Scheme I



Reaction conditions: (a) RBr, K_2CO_3, CH_3CN (85%); (b) H_2, Raney Ni, EtOH (91%); (c) **II**, TsOH, Toluene (61%); (d) Dry HCl, MeOH (98%).

Thus **1** was condensed with *N*-2-bromoethyl-t-butylcarbamate in the presence of potassium carbonate in DMF, followed by reduction of the nitro group in the presence of Raney Ni under hydrogen at atmospheric pressure give **3**. Compound **4** was deprotected to amine (**5**)[8] in dry HCl/MeOH solution.

Scheme II



Reaction conditions: (a) DCC, HOBt, **5**, DMF (71-78%); (b) Et_3N, **5**, DMF (82-85%).

Synthesis of the final camptothecin five-membered ring-substituted derivatives (**6**) was accomplished by coupling of the camptothecin amino derivative (**5**) with acid in the presence of the coupling agent DCC/HOBt, acid chloride and the trichloroacetyl derivative (Scheme II).

Compounds (**6a-i**) were evaluated by *in vitro* cytotoxicity assays using camptothecin as a standard (see Table I).[9] Most of the camptothecin five-membered ring derivatives were significantly more potent against the following human tumor cell lines: KB, HCT116, L1210 and L1210/Adr. Compounds **6a**, **6b**, **6g** and **6h** were approximately 16 to 20 times more potent than camptothecin against KB, 150 to 600 times more potent than camptothecin against HCT-116, 50 to 117 times than camptothecin against L1210, 30 to 450 times more potent than camptothecin against 1210/Adr. Most of the compounds were less potent than camptothecin against MCF-7. In general, the new camptothecin derivatives bearing either a pyrrole ring or a thiophene ring containing substituent were more potent than camptothecin, however those bearing a furan ring were less potent than camptothecin and compound **6h** was the most potent compound of this series. Extensions of this approach and an examination of the effects of chirality of the pharmacophore and implications of topoisomerase I inhibition are now in progress.

Table I Cytotoxicity in Vitro

Compound	In vitro cytotoxicity TD_{50}(ug/ml) KB	HCT-116	MCF-7	L1210	L1210/Adr
6a	4.0×10^{-4}	1.0×10^{-5}	2.6×10^{-1}	1.0×10^{-4}	1.0×10^{-3}
6b	5.0×10^{-4}	1.0×10^{-5}	1.4×10^{-1}	2.0×10^{-4}	9.5×10^{-4}
6c	5.0×10^{-3}	7.0×10^{-4}	1.2×10^{-1}	1.0×10^{-3}	1.5×10^{-2}
6d	6.9×10^{-2}	5.5×10^{-2}	9.0×10^{-1}	5.0×10^{-2}	3.2×10^{-1}
6e	8.3×10^{-2}	6.5×10^{-2}	1.0	5.0×10^{-2}	1.4×10^{-1}
6f	5.0×10^{-3}	1.0×10^{-3}	8.2×10^{-1}	4.0×10^{-3}	1.5×10^{-2}
6g	5.0×10^{-4}	4.0×10^{-5}	6.8×10^{-2}	1.0×10^{-4}	1.5×10^{-3}
6h	5.0×10^{-4}	1.0×10^{-5}	1.0×10^{-1}	8.5×10^{-5}	1.0×10^{-4}
6i	7.0×10^{-3}	3.0×10^{-3}	7.5×10^{-1}	2.0×10^{-3}	1.0×10^{-2}
camptothecin	8.0×10^{-3}	6.0×10^{-3}	1.0×10^{-2}	1.0×10^{-2}	4.5×10^{-2}
adriamycin	1.5×10^{-2}	3.0×10^{-2}	1.5×10^{-1}	6.0×10^{-3}	4.0×10^{-1}

The TD_{50} values (toxic dose 50%) are calculated to the indicate the concentration of sample which inhibits the growth of the cells to 50% of the control.

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8 Spectroscopic data for **5**: mp 250°C (decompose); ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 8.60 (s, 1H), 8.19 (bs, 3H), 8.10(d, J = 8 Hz, 1H), 7.57 (m, 2H), 7.19 (s, 1H), 6.80-6.40 (bs, 1H, OH), 5.42 (s, 2H), 5.28 (s, 2H), 4.36 (t, J = 6 Hz, 2H), 3.34 (m, 2H), 1.89 (m, 2H), 0.85 (t, J = 7 Hz, 3H); EIHRMS : Calcd. for $C_{22}H_{21}N_3O_5$ 407.1481. Found 407.1472 (M^+, 42%).
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