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Preliminary communication

First synthesis of novel spin-labeled derivatives of camptothecin as potential antineoplastic agents

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Abstract

In an effort to improve the stability of labile lactone ring and water solubility of camptothecin, five novel spin-labeled camptothecin derivatives were synthesized in quantitative yield by a simple modification of the carbodiimide method using the combination of scandium triflate ($Sc(OTf)_3$) and 4-dimethylaminopyridine (DMAP), and the *in vitro* pharmacokinetic determination of the lactones of representative compound **13a** showed that the biological life span of their lactone forms in human and mouse plasma significantly increased when compared with their mother compound camptothecin. Also, the *in vitro* cytotoxicity of compounds **13a–13e** against human bladder cancer T-24 showed either similar or better activity than that of the parent drug, camptothecin, and clinically available drug, irinotecan.

Keywords: Camptothecin; Antineoplastic properties; Spin-labeled

1. Introduction

Camptothecin (**1**) is a potent antineoplastic compound with selectively targeting topoisomerase I by trapping the catalytic intermediate of the TopI–DNA reaction, the cleavage complex [1–4]. Hydrophilization of the camptothecin molecules results in the identification and development of topotecan (**2**) and irinotecan (**3**) (Fig. 1), which have been clinically approved for treatment of ovarian and colon cancers, respectively [5–8]. However, the therapeutic use of unmodified CPT has been severely hindered by toxicity stemming in part from instability of the active lactone form due to preferential binding of the carboxylate to serum albumin and problems with delivery due to poor water solubility [9,10]. Ever since esterification of the 20-hydroxy group of camptothecin was demonstrated to prolong the biological life span of lactone in human and mouse plasma compared with their parent compounds. And meanwhile the overall toxicity of tested ester prodrugs against nude mice was much lower and their antitumor activity against human tumor xenografts in nude mice was maintained *via* enzymatical cleavage [11–14]. Simultaneous efforts to improve water solubility have resulted in development of water-soluble adducts, such as prothecan, afeletecan and camptothecin polyglutamate [15–17].

Furthermore, the nitroxyl free radicals have a wide range of activities in biology. Some studies have shown that the introduction of nitroxyl moiety can lead to a fast decomposition, higher alkylating, lower carbamoylating activity, better antimelanomic activity, lower general toxicity, and through cell membranes as a transport and while the nitroxyl free radicals possess low toxicity and are not mutagenic or carcinogenic by themselves [18–25]. In previous studies, a series of spin-labeled podophyllotoxin analogues, by modifying different positions, have been prepared by our group and these compounds showed significant antitumor activity with marked decrease in

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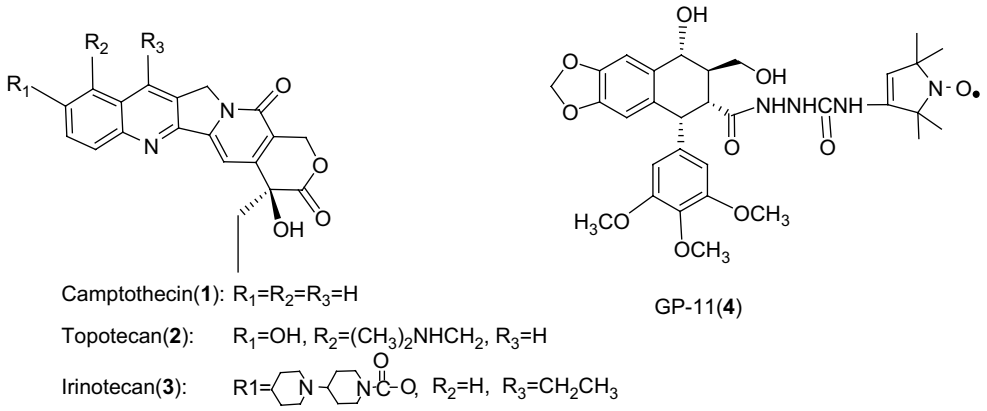

Fig. 1. Structure of camptothecin (**1**), topotecan (**2**), irinotecan (**3**) and GP-11 (**4**).

toxicity when compared with the parent compound [20,23,26–34]; in particular, GP-11 (**4**) was reported as low immunosuppressive antitumor agent, which increased the mitotic index and resulted in G_2/M phase, and to a lesser extent, S arrest. It has the possibility of becoming a promising new antitumor drug. Inspired by previous work as well as the fact that L-amino acids are actively transplanted into mammalian tissue have good water solubility, and are often used as carrier vehicles for some drugs, our approach to the above chemical stability/water solubility problems is to introduce the nitroxyl radical moiety into the molecule of camptothecin at its 20-hydroxyl via hydrophilic amino acid spacer that together provide (i) enhanced water solubility and (ii) improved stability of the lactone ring.

2. Chemistry

Camptothecin **1** was isolated from a Chinese medicinal plant *Camptotheca acuminata* and served as the starting material for the preparation of all the derivatives.

Compound **6** was prepared quite readily in quantitative yield by addition of bromine to the ketone **5**, which was further converted by 25% aqueous ammonia to the carboxamide **7** [35]; catalytic oxidation of **7** with hydrogen peroxide in the presence of sodium tungstate and catalytic amount of trylon-B yielded 1-oxyl-2,2,5,5-tetramethylpyrroline-3-carbamide **8**; alkaline hydrolysis of **8** led to amide cleavage to 1-oxyl-2,2,5,5-tetramethylpyrroline-3-carboxylic acid **9** [36,37], which on esterification with ethyl chloroformate in the presence of catalytic amount of triethylamine gave quantitative yields of its higher reactive mixed anhydride **10**; without isolation, the active anhydride **10** can be readily converted into the corresponding acid azide **11** [38,39] when dissolved in an aqueous acetone solution of sodium azide within a few minutes at 0 °C; without further purification, reaction of the free-radical acid azide **11** with the corresponding amino acids in the presence of magnesium oxide at room temperature afforded *N*-(1-oxyl-3-carbonyl-2,2,5,5-tetramethylpyrroline) amino acids **12a–12e**. Spectral data for **12a–12e** are identical to the data reported by Hankovszky [40] (Fig. 2).

Facile stereoselective esterification of the hindered tertiary alcohol 20(*S*)-camptothecin with *N*-(1-oxyl-3-carbonyl-2,2,5,5-tetramethylpyrroline) amino acids **12a–12e** has been achieved in quantitative yield by a simple modification of

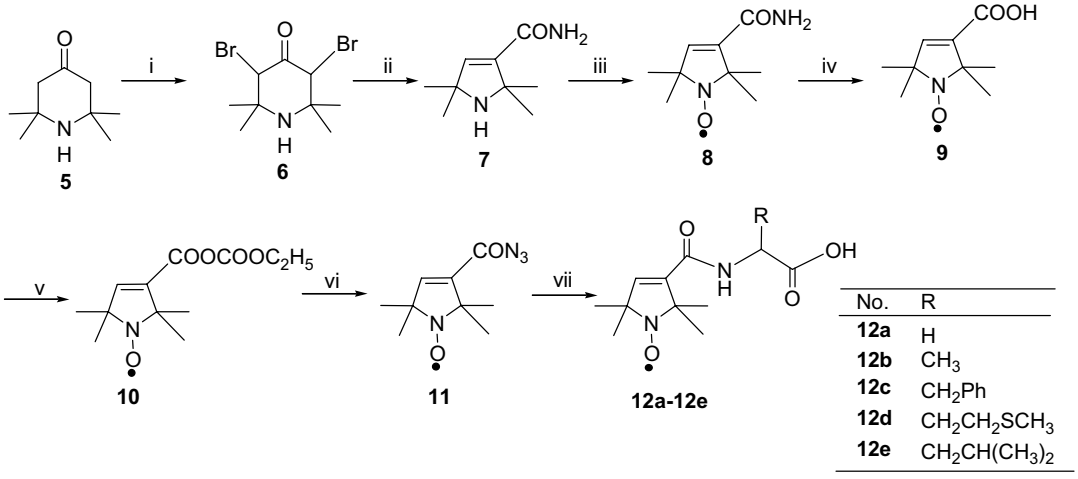

Fig. 2. *Reagents and conditions*: (i)–(iii) Na_2WO_4/H_2O_2/EDTA; (iv) 10% aqueous NaOH, reflux, stir; (v) ethyl chloroformate/NEt_3; (vi) NaN_3/water, stir; (vii) amino acids/MgO, stir, 24 h.

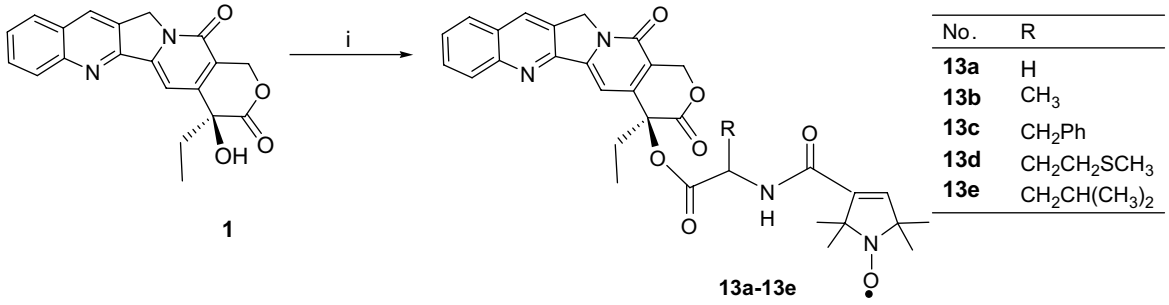

Fig. 3. *Reagents and conditions*: (i) DIPC/DMAP/$Sc(OTf)_3$, −10 °C, stir.

the carbodiimide method using the combination of scandium triflate ($Sc(OTf)_3$) and 4-dimethylaminopyridine (DMAP) to give the desired camptothecin esters **13a**–**13e** under an atmosphere of nitrogen at −20 °C (Fig. 3). Synthesized target compounds **13a**–**13e** were characterized by melting point, ESR, IR and HRMS spectral analyses.

The synthetic methodology for the preparation of *N*-(1-oxyl-3-carbonyl-2,2,5,5-tetramethylpyrroline) amino acids **12a**–**12e** is depicted in Fig. 2.

The synthetic methodology for the preparation of spin-labeled camptothecin derivatives **13a**–**13e** is depicted in Fig. 3.

3. Results and discussion

For the challenging acylation of the tertiary and unreactive 20-hydroxyl group, especially with bulky amino acid residues, we have developed an efficient route using a modified version of Greenwald's method [41] by the combination of scandium triflate ($Sc(OTf)_3$) and 4-dimethylaminopyridine (DMAP). The desired compounds have been obtained by facile acylation of the 20-hydroxyl group with *N*-(1-oxyl-3-carbonyl-2,2,5,5-tetramethylpyrroline) amino acids **12a**–**12e**.

The *in vitro* determination, based on literature method [42], of lactone levels in human and mouse plasma for camptothecin and compound **13a** is shown in Table 1. As shown in Table 1, the percent of the lactone of CPT in human plasma is 28.4% after 4 h, 14.6% after 8 h, and only 3.8% after 24 h. In other words, the active form of CPT is lost in a short time period after oral administration. This is opposite to what is observed in mice, in which the active lactone form lasts for relatively long time period. For example, the closed lactone form of CPT in mouse plasma is 40.5% after 4 h. The closed lactone form of **13a** in human plasma is much stable than its mother compound **1**. For example, 65.2% of **13a** is still detected as the closed lactone form even after 4 h. The results were further evident that the biological life span of lactone forms of their camptothecin esters in human and mouse plasma significantly increased when compared with their mother compound camptothecin. And the cleavage of **13a** in both mouse and human plasma was monitored by HPLC, which was clearly shown that compound **13a** was cleaved to afford mainly its parental compound of CPT in both mouse and human plasma. It was also the case in pH 7.4 phosphate buffer (data not shown).

Furthermore, the *in vitro* cytotoxicity of compounds **13a**–**13e** against human bladder cancer T-24 was tested based on MTT assay. The results are summarized in Table 2.

As illustrated in Table 2, compounds **13a**–**13e** showed more significant cytotoxicity against T-24 *in vitro* than its parental compound of CPT. Among them, compound **13a** exhibited most potent cytotoxicity against T-24 cell (inhibition rate is 34.5%), while the inhibition rate values of these analogues were either similar or better than those of the prototypical inhibitor irinotecan. Examination of the different amino acid linkages and the resulting activity in the inhibition of human bladder cancer T-24 *in vitro* reveal the following order of activity: L-glycine > L-phenyl alanine > L-alanine > L-methionine > L-leucine. These results indicated that the structures of L-amino acids have potential effects on the bioactivity of these compounds. Hence, a systemic, predictable correlation could be made between the nature of amino acids and anticancer activities. As can be seen, as a whole, the introduction of a stable nitroxyl radical into the molecule of camptothecin with L-amino acids led to potentiate their antitumor activity, which also indicated that the design and synthesis of these compounds should be beneficial for therapeutic values of camptothecin and they probably have synergistic action to tumor cell lines.

4. Conclusions

To improve the biological profile of the potent anticancer compound camptothecin, five novel spin-labeled derivatives of camptothecin have been synthesized by a modified version of Greenwald's method. The compounds selected for the *in vitro* determination of lactone levels showed that their biological

Table 1
Comparison of percent lactone of prodrug **13a** and camptothecin (CPT) in human and mouse plasma

	Time (h)					
	0	2	4	6	8	24
Human plasma						
% Lactone for **13a**	100.0	78.7	65.2	56.1	34.4	7.8
% Lactone for CPT	100.0	61.4	28.4	19.4	14.6	3.8
Mouse plasma						
% Lactone for **13a**	100.0	76.3	57.6	43.9	31.8	10.8
% Lactone for CPT	100.0	55.1	40.5	24.5	10.9	5.3

Table 2
In vitro cytotoxicity activity of compounds **13a–13e**

Compounds	Inhibition rate (%)
	T-24
13a	34.5
13b	25.9
13c	26.4
13d	25.5
13e	16.4
CPT	15.4
Irinotecan	23.8

life span in human and mouse plasma was much longer than that of the parent compound camptothecin. Meanwhile, all of these target compounds exhibited either similar or better cytotoxicity against T-24 *in vitro* than that of the prototypical inhibitor irinotecan. As can be seen, as a whole, the introduction of a stable nitroxyl radical into the molecule of camptothecin with L-amino acids led to enhanced stability of the lactone ring and improvement of their antitumor activity. Further biological evaluation is in progress to define their DNA topoisomerase I inhibition activity and to clarify whether spin-labeled camptothecin analogues might counteract the toxicity of this class antitumor drug.

5. Experimental

Melting points were taken on a Kofler melting point apparatus and are uncorrected; IR spectra were obtained on NIC-5DX spectrophotometer; mass spectral analysis was performed on a ZAB-HS and Bruker Daltonics APEXII49e instrument. Optical rotations were determined on Perkin–Elmer Model 341 spectropolarimeter. ESR spectra were obtained with a Bruker ER-200D-SRC X-band spectrometer. The starting camptothecin was isolated from a Chinese medicinal plant *C. acuminata* and was purified before being used. The *N*-(1-oxyl-3-carbonyl-2,2,5,5-tetramethylpyrroline) amino acids **12a–12e** used for the experiments were prepared by following a modified previous procedure [35–40].

5.1. General procedure for synthesis of target compounds (*13a–13e*)

A suspension of camptothecin (0.1 g, 0.288 mmol), scandium triflate (0.085 g, 0.173 mmol), *N*-(1-oxyl-3-carbonyl-2,2,5,5-tetramethylpyrroline) amino acids **12a–12e** (0.864 mmol) and 4-dimethylaminopyridine (0.11 g, 0.864 mmol) in anhydrous methylene chloride (10 mL) under an atmosphere of nitrogen was cooled to −20 °C in an ice-salt bath for 30 min, and DIPC (0.142 mL, 0.907 mmol) was added and the reaction mixture stirred at −10 °C for 30 min and allowed to warm to room temperature over 10 h. The reaction mixture was filtered and the filtrate was washed with 20 mL of 0.1 N HCl, 20 mL of 0.1 M $NaHCO_3$, and 20 mL of distilled water, and then dried over anhydrous $MgSO_4$. Evaporation of solvent left the crude product. The residue was chromatographically separated with chloroform–methanol as eluent. Synthesized target compounds **13a–13e** were characterized by melting point, ESR, IR and HRMS spectral analyses.

5.1.1. Camptothecin-20-O-[N-(1′-oxyl-3′-carbonyl-2′,2′,5′,5′-tetramethylpyrroline)]-glycinoate (*13a*)

Yellow powder, isolated yield: 50%; m.p. 168–170 °C; $[\alpha]_D^{20} = -91°$ ($c = 0.5$, DMF); IR (KBr, cm^{-1}): 3366 (NH), 1754 (NHCO), 3063, 1615, 1557 (ArH), 1662 (C=O), 1131, 1159, 1233 (C–O), 1356 (NO•); ESR: $g_0 = 2.0055$, $A_N = 14.62$ Gs (triplet peak in 1×10^{-4} M, DMF); HRMS: *m/z* calcd for $C_{31}H_{31}N_4O_7$: 572.2266 $[M+H]^+$, Found: 572.2260 $[M+H]^+$.

5.1.2. Camptothecin-20-O-[N-(1′-oxyl-3′-carbonyl-2′,2′,5′,5′-tetramethylpyrroline)]-alaninoate (*13b*)

Yellow powder, isolated yield: 46%; m.p. 166–168 °C; $[\alpha]_D^{20} = -87°$ ($c = 0.5$, DMF); IR (KBr, cm^{-1}): 3429 (NH), 1751 (NHCO), 3056, 1603, 1552 (ArH), 1662 (C=O), 1127, 1154, 1228 (C–O), 1358 (NO•); ESR: $g_0 = 2.0058$, $A_N = 14.62$ Gs (triplet peak in 1×10^{-4} M, DMF); HRMS: *m/z* calcd for $C_{32}H_{33}N_4O_7$: 586.2422 $[M+H]^+$, Found: 586.2416 $[M+H]^+$.

5.1.3. Camptothecin-20-O-[N-(1′-oxyl-3′-carbonyl-2′,2′,5′,5′-tetramethylpyrroline)]-phenylalaninoate (*13c*)

Yellow powder, isolated yield: 43%; m.p. 142–144 °C; $[\alpha]_D^{20} = -94°$ ($c = 0.5$, DMF); IR (KBr, cm^{-1}): 3434 (NH), 1750 (NHCO), 3060, 1617, 1561 (ArH), 1663 (C=O), 1130, 1159, 1231 (C–O), 1354 (NO•); ESR: $g_0 = 2.0055$, $A_N = 14.62$ Gs (triplet peak in 1×10^{-4} M, DMF); HRMS: *m/z* calcd for $C_{38}H_{37}N_4O_7$: 622.2735 $[M+H]^+$, Found: 622.2736 $[M+H]^+$.

5.1.4. Camptothecin-20-O-[N-(1′-oxyl-3′-carbonyl-2′,2′,5′,5′-tetramethylpyrroline)]-methioninoate (*13d*)

Yellow powder, isolated yield: 47%; m.p. 140–142 °C; $[\alpha]_D^{20} = -86°$ ($c = 0.5$, DMF); IR (KBr, cm^{-1}): 3481 (NH), 1749 (NHCO), 3060, 1616, 1560 (ArH), 1663 (C=O), 1131, 1157, 1230 (C–O), 1354 (NO•); ESR: $g_0 = 2.0055$, $A_N = 14.62$ Gs (triplet peak in 1×10^{-4} M, DMF); HRMS: *m/z* calcd for $C_{34}H_{37}N_4O_7S$: 646.2456 $[M+H]^+$, Found: 646.2454 $[M+H]^+$.

5.1.5. Camptothecin-20-O-[N-(1′-oxyl-3′-carbonyl-2′,2′,5′,5′-tetramethylpyrroline)]-leucinoate (*13e*)

Yellow powder, isolated yield: 25%; m.p. 145–147 °C; $[\alpha]_D^{20} = -82°$ ($c = 0.5$, DMF); IR (KBr, cm^{-1}): 33,679 (NH), 1749 (NHCO), 3061, 1617, 1559 (ArH), 1663 (C=O), 1127, 1155, 1233 (C–O), 1354 (NO•); ESR: $g_0 = 2.0055$, $A_N = 14.62$ Gs (triplet peak in 1×10^{-4} M, DMF); HRMS: *m/z* calcd for $C_{35}H_{39}N_4O_7$: 650.2711 $[M+Na]^+$, Found: 650.2714 $[M+Na]^+$.

5.2. In vitro determination of lactone levels in human and mouse plasma for **1** and **13a**

To 0.8 mL pre-incubated human and mouse plasma were added, respectively, the test compounds (0.2 mL, 100 μg/mL) in acetonitrile. The mixture was incubated at 37 °C and 100 μL aliquots were taken at 2, 4, 6, 8 and 24 h. To precipitate plasma protein, 400 μL acetonitrile (−20 °C) was added, vortexed for 20 s, and centrifuged at 10,000 rpm for 5 min. Supernatant was transferred to a glass vial and stored at −20 °C immediately until HPLC analysis. HPLC (HP1100) analysis: 20 μL of solution obtained above was injected onto a C-18 column (Zobax SB, 4.6 × 150 mm) and chromatographed with methanol/water/0.1% acetic acid as mobile phase. Compounds camptothecin and **13a** were detected (detector: DAB) at 254 nm. The percent of lactone was determined by the ratio of lactone levels measured at different time points to the lactone levels measured at starting point ($t = 0$ h).

5.3. Cytotoxicity assays

Cytotoxicity assays are performed on human bladder cancer (T-24) cell line. One thousand two hundred cells per well were plated in 96-well plates. After culturing for 24 h, compounds **13a**–**13e** were added onto triplicate wells with different concentration, and 0.1% DMSO for control. After 4 days of incubation, 10 mL MTT (3-[4,5-dimethyl thiazol-2-yl]-2,5-diphenyltetrazolium bromide) solution (5 mg/mL) was added to each well, and after shaking for 1 min, the plate was incubated further for 4 h. Formazan crystals were dissolved with 100 mL DMSO. The absorbance (OD) was quantitated with microplate spectrophotometer at 570 nm. Wells containing no drugs were used as blanks for the spectrophotometer. The survival of cells was expressed as percentage of untreated control wells. The prototypical inhibitors camptothecin and irinotecan were included as reference standards, the results of these assays were used to obtain the corresponding inhibition rates.

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