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Short Communication

Synthesis and biological activities of fluorinated 10-hydroxycamptothecin and SN38

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ABSTRACT

It is an important strategy for fluorine substitution in drug design because of its small size and high electronegativity. Fluorinated 10-hydroxycamptothecin and SN 38 were prepared and screened for antiproliferative activities. Among them, fluorinated compound **MF-6** showed higher antiproliferative activities against A549, HCT116 and MDA-MB-435 cancer cells than unfluorinated compound. The result of Topoisomerase I activity also confirmed that the C-21 carbonyl group of camptothecin structure is unnecessary to antitumor activity.

1. Introduction

Fluorinated molecules were the most important organohalogen drugs among the marked pharmaceuticals because of their special properties. There are more than 20% of drugs containing at least one fluorine atom in all the clinical drugs [1–3]. Very important anticancer drugs, such as cytotoxic drugs fluorouracil derivatives and protein kinase inhibitors sorefenib, gefitinib and vandetanib, are fluorinated drugs [4,5]. In addition, fluorine substitution has been a successful strategy in drug design from natural bioactive products. Taxoid, as the famous anticancer drug, had been investigated with strategic fluorine incorporation for elevation of cytotoxicity and metabolic stability [6]. Another well-known anticancer natural product camptothecin had also been designed by fluorine substitution for increased activity. Lavergne et al. achieved the fluorinated camptothecin analogue diflomotecan with excellent antitumor activities both *in vitro* and *in vivo* by introducing two fluorine atom to the A aromatic ring of homocamptothecin [7]. Exatecan, another successful fluorinated camptothecin derivative with fluorine at position 10 on ring A, is currently in Phase III [8].

It is well known that the E-ring of camptothecin with an integrity α-hydroxylactone is essential to antitumor activity of camptothecin. Although 20-fluorocamptothecin with lower lactone stability is less active in cytotoxicity and Topoisomerase I assays [9], 21-fluorocamptothecins with excellent antitumor activities were fortunately obtained which were substituted with fluorine on position 21 instead of carbonyl group of camptothecin E-ring [10]. Our previous results indicated that compound **MF-1** exhibited higher activity against all three cancer cell lines than its diastereoisomer **MF-2**. Herein, we report the synthesis and biological activities of two fluorinated camptothecin drugs 10-hydoxycamptothecin and SN 38 which is the active metabolite of Irinotecan (Fig. 1).

2. Results and discussion

The synthesis of fluorinated camptothecin derivatives is outlined in Scheme 1. Compounds **MF-3** and **MF-4** as 10-hydroxycamptothecin derivatives was synthesized in three and four steps respectively. In order to avoid the side fluorinated impurities during fluorination by DAST, hydroxyl group on A ring of natural 10-hydroxycamptothecin was protected with benzyl group. Thus, compound **MF-3** was obtained based on our previous fluorination method [10]. Compound **MF-3** reduced the benzyl group to afford compound **MF-4** in 90% yield. Compounds **MF-5** and **MF-6** was easily achieved by the same route from active metabolite of Irinotecan with good yield.

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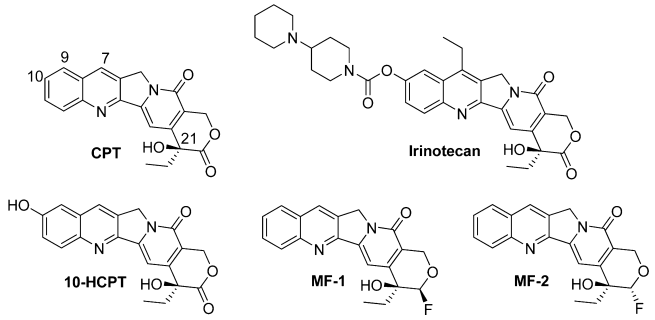


Fig. 1. The structures of camptothecin drugs and fluorinated camptothecin isomers.

Table 1
In vitro antiproliferative activities of fluorinated camptothecin derivatives (inhibition rate at 100 μg/mL).

Compounds	A549	MDA-MB-435	HCT116
MF-3	26.83 ± 3.38	55.36 ± 1.90	83.76 ± 2.76
MF-4	29.23 ± 3.42	77.19 ± 1.09	88.28 ± 0.60
MF-5	56.24 ± 2.19	85.22 ± 1.99	79.33 ± 0.77
MF-6	83.64 ± 3.53	98.13 ± 1.87	81.72 ± 1.83
10-HCPT	88.23 ± 3.03	75.06 ± 1.93	75.82 ± 1.43
SN 38	83.41 ± 1.92	75.23 ± 1.04	80.34 ± 4.01

Reagents and conditions of reactions: (a) K_2CO_3, dried DMF, benzyl bromide, 50 °C; (b) KBH_4, CH_3OH, rt; (c) DAST, CH_2Cl_2, −95 °C–0 °C; (d) Pt/C, H_2, CH_3OH, rt.

The *in vitro* antiproliferative activity of fluorinated camptothecin derivatives were evaluated in three cancer cells A549, MDA-MB-435 and HCT116 by MTT assay. The results are summarized in Table 1 and all the target compounds indicated potent antiproliferative activities. As expected, compounds **MF-4** and **MF-6** showed higher activity against three cancer cells than that of their corresponding compounds with benzyl group at the concentration of 100 μg/mL. In addition, most of fluorinated compounds were more selective to breast cancer cells MDA-MB-435 and colon cancer cells HCT116 than non-small-cell lung cells A549 which was not consistent to our previous work [10]. For example, compound **MF-4** possessed high activities against MDA-MB-435 and HCT116 cells with 77.19% and 88.28% proliferative inhibition while the inhibition of A549 cells was 29.23%. More importantly, compound **MF-6** demonstrated exclusively the most potent activity in all three cancer cell lines than both fluorinated camptothecin derivatives and clinical drug 10-HCPT and SN 38. As demonstrated in Fig. 2, the same trend was observed for the

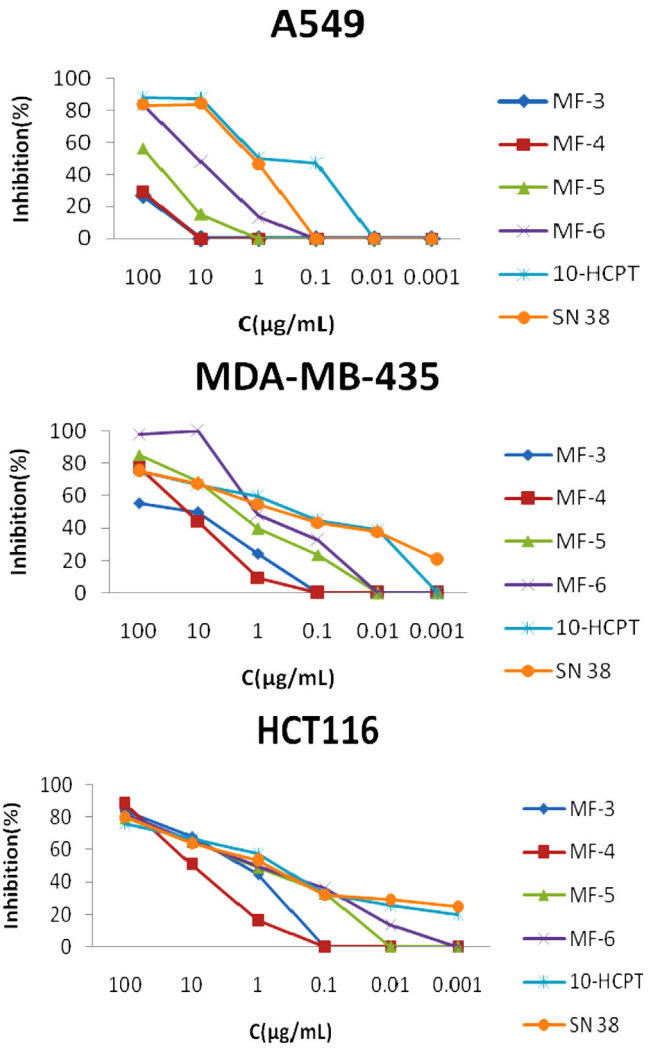
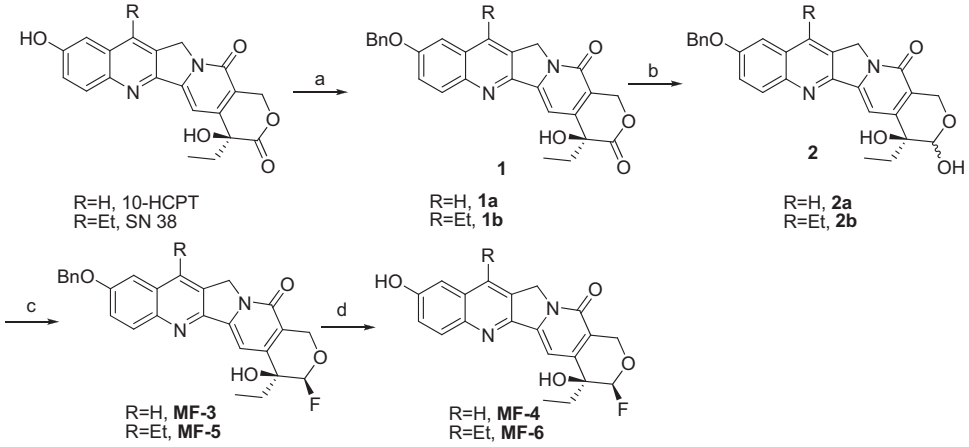


Fig. 2. Antiproliferative activities of fluorinated camptothecin derivatives at the concentration of 100–0.001 μg/mL.

comparison of **MF-6** and10-HCPT and SN 38 for the antiproliferative activity at every concentration.

Encouraged by this result, Topo I-mediated DNA cleavage assays of the most potent fluorinated camptothecin derivative **MF-6** and fluorinated camptothecin isomers **MF-1** and **MF-2** were investigated. As expected, compound **MF-6** was found to be active



Scheme 1. Synthesis of fluorinated 10-hydroxycamptothecin derivatives.

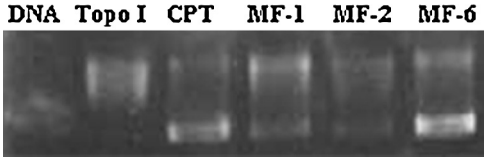


Fig. 3. Effect of the selected compounds on Topo I-mediated DNA relaxation in single concentration with 100 μM. Lane 1, supercoiled plasmid DNA; Lane 2, DNA + Topo I; Lane 3, DNA + Topo I + CPT; Lane 4–6, DNA + Topo I + fluorinated camptothecin derivatives (**MF-1**, **MF-2** and **MF-6**, respectively).

against Topo I-mediated relaxation of supercoiled DNA at a high concentration of 100 μM which was similar to natural camptothecin (Fig. 3). As is evident, this result confirmed that the *S*-isomer of fluorinated camptothecin derivative indicated higher activity than that of *R*-isomer which was presented by our previous study [10].

3. Conclusion

In this report, we have demonstrated that it is a successful strategy for fluorine substitution on position 21 of camptothecin clinical drugs. Fluorinated 10-hydroxycamptothecin and SN 38 were prepared by a same synthetic route. As the potent topoisomerase I inhibitor, **MF-6** showed higher antiproliferative activities against A549, MDA-MB-435 and HCT116 cancer cells than 10-HCPT and SN38. Moreover, this result also confirmed that the C-21 carbonyl group of camptothecin structure is unnecessary to antitumor activity.

4. Experimental

Chemistry. General Methods. All starting materials were commercially available and analytical pure. Melting points were measured on an uncorrected X-5 digital melting point apparatus (Gongyi City Yuhua Instrument Co., Ltd.; China). ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker Avance 300 spectrometer, a Bruker Avance 500 spectrometer or a Bruker Avance 600 spectrometer (Bruker Company, Germany), using TMS as an internal standard and $CDCl_3$ or DMSO-d_6 as solvents. Chemical shifts (δ values) and coupling constants (J values) are given in ppm and Hz, respectively. The mass spectra were recorded on an Esquire 3000 LC–MS mass spectrometer. TLC analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical, China). Flash column chromatography was carried out on silica gel 300–400 mesh using a Biotage instrument. Anhydrous solvent and reagents were all analytical pure and dried through routine protocols.

4.1. General procedure for synthesis of diol-CPTs

To a suspension of 10-hydroxycamptothecin (10.0 mmol) and K_2CO_3 (15.0 mmol) in dried DMF (50 mL), benzyl bromide (15.0 mmol) was added dropwise at 0 °C. The reaction was stirred for another 4 h at 50 °C. After being cooled, the reaction mixture was diluted with ice-water and extracted with dichloromethane. After the removal of solvent, the residue was purified by flash chromatography on silica gel (CH_2Cl_2/CH_3OH= 100:2) to afford **1a** as a yellow solid.

To a suspension of **1a** (0.5 mmol) in methanol (30 mL) was slowly added KBH_4 (10.0 mmol). The reaction was stirred for another 4 h at room temperature. After the removal of solvent, water (50 mL) was added to the residue. The resulting solution was acidulated with acetic acid. The precipitate was collected and washed with water to give white solid **2a**.

4.1.1. 10-Benzyloxy-(20S, 21S)-diolcamptothecin(*2a*)

Light Yellow solid, Yield 89%, m.p. 238–240 °C, $[\alpha]_D^{25}$ = +856.6(*c* 0.030, DMF). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 0.90 (t, 3H, J = 7.5 Hz, C$\underline{H}_3$CH$_2$), 1.71 (q, 2H, J = 7.2 Hz, CH$_3$C$\underline{H}_2$), 4.48–4.62 (q, 2H, J = 17.1 Hz, OCH$_2$), 4.90 (s, 1H, CH), 4.99 (d, 1H, J = 5.4 Hz, OH), 5.21 (s, 2H, NCH$_2$), 5.29 (s, 2H, CH$_2$O), 6.71 (d, 1H, J = 5.4 Hz, OH), 7.27 (s, 1H, C$_{14}$-H), 7.36 (d, 1H, J = 2.7 Hz, C$_{11}$-H), 7.42–7.44 (m, 2H), 7.54–7.62 (m, 4H), 8.07 (d, 1H, J = 9.0 Hz, C$_{12}$-H), 8.50 (s, 1H, C$_7$-H); MS (ESI): 457 (M+H). Anal. calcd for $C_{29}H_{28}ClN_3O_4$: C, 71.04; H, 5.30; N, 6.14; found C, 71.13; H, 5.29; N,6.15.

4.1.2. 7-Ethyl-10-benzyloxy-(20S, 21S)-diolcamptothecin (*2b*)

Light Yellow solid, Yield 91%, m.p. 273–275 °C, $[\alpha]_D^{25}$ = +1537.0(*c* 0.020, DMF). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 0.90 (t, 3H, J = 7.5 Hz, C$\underline{H}_3$CH$_2$), 1.24 (t, 3H, J = 7.8 Hz, C$\underline{H}_3$CH$_2$), 1.71 (q, 2H, J = 7.2 Hz, CH$_3$C$\underline{H}_2$), 3.14 (q, 2H, J = 7.2 Hz, CH$_3$C$\underline{H}_2$), 4.48–4.63 (q, 2H, J = 17.1 Hz, OCH$_2$), 4.90 (s, 1H, CH), 4.99 (d, 1H, J = 5.4 Hz, OH), 5.22 (s, 2H, NCH$_2$), 5.36 (s, 2H, CH$_2$O), 6.71 (d, 1H, J = 5.4 Hz, OH), 7.28 (s, 1H, C$_{14}$-H), 7.36 (d, 1H, J = 2.7 Hz, C$_{11}$-H), 7.42–7.43 (m, 2H), 7.55–7.57 (m, 4H), 8.06 (d, 1H, J = 9.0 Hz, C$_{12}$-H); MS (ESI): 485 (M+H). Anal. calcd for $C_{29}H_{28}ClN_3O_4$: C, 71.47; H, 5.57; N, 5.95; found C, 71.34; H, 5.56; N,5.96.

4.2. General procedure for synthesis of fluorinated camptothecins

A solution of **2a** (1.4 mmol) in dichloromethane (30 mL) under nitrogen at – 95 °C was added DAST (1.6 mmol) as soon as possible. After 10 min, the reaction was stirred for another 2 h at 0 °C. Then, the reaction was quenched with $NaHCO_3$ saturated solution then extracted with dichloromethane. After the removal of solvent, the residue was purified by flash chromatography on silica gel (CH_2Cl_2/CH_3OH= 100:1) to afford targeted compound as a yellow solid **MF-3**.

To a solution of **MF-3** (1.1 mmol) in ethanol (15 mL), Pt/C (5%, 10 mg) was added as catalyst and hydrogenation followed at 3 bar for 12 h at room temperature. The resulting suspension was filtered and concentrated under reduced pressure to afford **MF-4**.

4.2.1. 10-Benzyloxy-(20S, 21S)-fluorcamptothecin (*MF-3*)

Yellow solid, Yield 35%, m.p. 185–187 °C, $[\alpha]_D^{20}$ = +670.5(*c* 0.056, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.90 (t, 3H, J = 7.5 Hz, C$\underline{H}_3$CH$_2$), 1.70 (q, 2H, J = 7.2 Hz, CH$_3$C$\underline{H}_2$), 4.70–4.78 (q, 2H, J = 17.1 Hz, OCH$_2$), 4.90 (s, 1H, CH), 5.24 (d, 1H, J = 4.6 Hz, NCH$_2$), 5.29 (s, 2H, OCH$_2$), 5.69 (d, 1H, J = 54.2 Hz, CH-F), 5.86 (s, 1H, OH), 7.33 (s, 1H, C$_{14}$-H), 7.37 (d, 1H, J = 2.7 Hz, C$_{11}$-H), 7.42–7.43 (m, 2H), 7.54–7.63 (m, 4H), 8.08 (d, 1H, J = 9.2 Hz, C$_{12}$-H), 8.52 (s, 1H, C$_7$-H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 7.64, 32.21, 50.33, 60.84, 70.09, 70.23, 97.46, 107.02, 108.04, 108.82, 120.53, 123.52, 128.37, 128.47, 128.93, 129.61, 129.89, 130.38, 130.90, 136.94, 144.31, 144.46, 148.54, 151.01, 157.33; ^{19}F NMR (470 MHz, DMSO-d_6) δ: −140.87; MS (ESI): 459 (M+H). Anal. calcd for $C_{29}H_{28}ClN_3O_4$: C, 70.73; H, 5.06; N, 6.11; found C, 70.85; H, 5.05; N,6.10.

4.2.2. 10-Hydroxy-(20S, 21S)-fluorcamptothecin (*MF-4*)

Brown solid, Yield 90%, m.p. >260 °C, $[\alpha]_D^{20}$ = +224(*c* 0.09, DMF). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.91 (t, 3H, J = 7.4 Hz, C$\underline{H}_3$CH$_2$), 1.71 (q, 2H, J = 7.1 Hz, CH$_3$C$\underline{H}_2$), 4.72 (s, 2H, OCH$_2$), 5.20 (s, 2H, NCH$_2$), 5.62 (d, 1H, J = 54.0 Hz, CH-F), 5.85 (s, 1H, OH), 7.26 (d, 1H, J = 2.7 Hz, C$_9$-H), 7.29 (s, 1H, C$_{14}$-H), 7.38–7.42 (dd, 1H, J = 2.7 Hz, J = 6.6 Hz, C$_{11}$-H), 8.01 (d, 1H, J = 9.0 Hz, C$_{12}$-H), 8.42 (s, 1H, C$_7$-H), 10.29 (s, 1H, OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 7.61, 32.20, 50.22, 60.83, 70.29, 97.21, 108.73, 109.26, 120.25, 123.31, 129.61, 129.98, 130.93, 143.65, 144.48, 148.56, 150.15, 156.94, 157.36, 162.71; ^{19}F NMR (470 MHz, DMSO-d_6) δ: −140.85; MS

(ESI): 367 (M−H). Anal. calcd for $C_{29}H_{28}ClN_3O_4$: C, 65.21; H, 4.65; N, 7.60; found C, 65.13; H, 4.66; N,7.61.

*4.2.3. 7-Ethyl-10-benzyloxy-(20S, 21S)-fluorcamptothecin (**MF-5**)*

Yellow solid, Yield 32%, m.p. 211–213 °C, $[\alpha]_D^{20}$ = +159.5(*c* 0.15, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.89 (t, 3H, *J* = 7.5 Hz, $C\underline{H}_3CH_2$), 1.01 (t, 3H, *J* = 7.7 Hz, $C\underline{H}_3CH_2$), 1.24 (t, 3H, *J* = 7.7 Hz, $C\underline{H}_3CH_2$), 1.70 (q, 2H, $CH_3C\underline{H}_2$), 1.72–2.35 (dm, 2H, $CH_3C\underline{H}_2$), 3.16 (q, 2H, *J* = 7.2 Hz, $CH_3C\underline{H}_2$), 4.72–4.78 (m, 4H, OCH_2), 5.26–5.28 (q, 4H, NCH_2), 5.37 (s, 4H, CH_2O), 5.61–5.73 (dd, 2H, CH), 5.85 (s, 1H, OH), 5.87 (s, 1H, OH), 7.25 (s, 1H, C_{14}-H), 7.30 (s, 1H, C_{14}-H), 7.35–7.37 (m, 3H), 7.41–7.44 (m, 4H), 7.55–7.59 (m, 8H), 8.07–8.09 (d s, 1H, C_{12}-H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 7.64, 8.01, 13.81, 22.63, 28.38, 32.21, 49.56, 60.67, 67.08, 70.22, 97.40, 104.28, 107.04, 108.26, 108.84, 120.39, 121.82, 122.89, 128.07, 128.27, 128.40, 128.95, 131.74, 137.11, 144.19, 144.85, 145.25, 147.08, 148.55, 150.30; ^{19}F NMR (470 MHz, DMSO-d_6) δ: −142.49, −140.80; HRMS (EI) *m*/*z*: 486.1952. Anal.calcd for $C_{29}H_{28}ClN_3O_4$: C, 71.17; H, 5.33; N, 5.93; found C, 71.25; H, 5.32; N,5.92.

*4.2.4. 7-Ethyl-10-hydroxy-(20S, 21S)-fluorcamptothecin (**MF-6**)*

Yellow solid, Yield 95%, m.p. >260 °C, $[\alpha]_D^{20}$ = +422.4(*c* 0.083, DMF). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.90 (t, 3H, *J* = 7.4 Hz, $C\underline{H}_3CH_2$), 1.01 (t, 3H, *J* = 7.5 Hz, $C\underline{H}_3CH_2$), 1.71 (q, 2H, *J* = 7.3 Hz, $CH_3C\underline{H}_2$), 3.09 (q, 2H, *J* = 7.6 Hz, $CH_3C\underline{H}_2$), 4.72–4.78 (q, 2H, *J* = 8.3 Hz, OCH_2), 5.22–5.29 (q, 2H, *J* = 18.2 Hz, NCH_2), 5.62 (d, 1H, *J* = 54.0 Hz, CH-F), 5.87 (s, 1H, OH), 7.26 (d, 1H, *J* = 2.7 Hz, C_9-H), 7.29 (s, 1H, C_{14}-H), 7.38–7.42 (dd, 1H, *J* = 2.7 Hz, *J* = 6.6 Hz, C_{11}-H), 8.02 (d, 1H, *J* = 8.9 Hz, C_{12}-H), 10.28 (s, 1H, OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 7.63, 13.76, 22.70, 28.38, 32.21, 49.53, 60.85, 70.30, 97.16, 105.25, 107.06, 108.29, 108.86, 110.07, 120.13, 121.58, 122.70, 128.04, 128.53, 131.84, 143.13, 144.06, 145.03, 145.43, 147.11, 148.57, 149.53, 149.61; ^{19}F NMR (470 MHz, DMSO-d_6) δ: −142.46, −140.76; MS (ESI): 395 (M−H). Anal. calcd for $C_{29}H_{28}ClN_3O_4$: C, 65.96; H, 5.01; N, 7.33; found C, 65.87; H, 5.02; N,7.35.

In vitro cytotoxicity assay. Cells were plated in 96-well microtiter plates at a density of 5×10^3/well and incubated in a humidified atmosphere with 5% CO_2 at 37 °C for 24 h. Test compounds were added onto triplicate wells with different concentrations and 0.1% DMSO for control. After they had been incubated for 72 h, 20 μL of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) solution (5 mg/mL) was added to each well and the plate was incubated for an additional 4 h. The formazan was dissolved in 100 μL of DMSO. The absorbance (OD) was read on a Wellscan MK-2 microplate reader (Lab systems) at 570 nm. The concentration causing 50% inhibition of cell growth (IC_{50}) was determined by the Logit method. All the experiments were performed three times.

Topo I inhibitory activity assay. DNA relaxation assays were employed according to the procedure described in previous studies [10]. The reaction mixture contained 35 mM Tris–HCl (pH 8.0), 72 mM KCl, 5 mM $MgCl_2$, 5 mM dithiothreitol, 5 mM spermidine, 0.1% bovine serum albumin (BSA), pBR322 plasmid DNA (0.25 μg), the indicated drug concentrations (1% DMSO), and 1 unit of Topo I (TaKaRa Biotechnology Co., Ltd., Dalian) in a final volume of 20 μL. Reaction mixtures were incubated for 15 min at 37 °C and stopped by addition of 2 μL of 10× loading buffer (0.9% sodium dodecyl sulfate (SDS), 0.05% bromophenol blue, and 50% glycerol). Electrophoresis was carried out in a 0.8% agarose gel in TAE (Tris-acetate-EDTA) at 8 V/cm for 1 h. Gels were stained with ethidium bromide (0.5 μg/mL) for 60 min. The DNA band was visualized over UV light and photographed with Gel Doc Ez imager (Bio-Rad Laboratories Ltd.)

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