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Design, semisynthesis and potent cytotoxic activity of novel 10-fluorocamptothecin derivatives

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ABSTRACT

Fluorination is a well-known strategy for improving the bioavailability of bioactive molecules in the lead optimization phase of drug discovery projects. In an attempt to improve the antitumor activity of camptothecins (CPTs), novel 10-fluoro-CPT derivatives were designed, synthesized and evaluated for cytotoxicity against five human cancer cell lines (A-549, MDA-MB-231, KB, KB-VIN and MCF-7). All of the derivatives showed more potent in vitro cytotoxic activity than the clinical CPT-derived drug irinotecan against the tumor cell lines tested, and most of them showed comparable or superior potency to topotecan. Remarkably, compounds **16b** (IC_{50}, 67.0 nM) and **19b** (IC_{50}, 99.2 nM) displayed the highest cytotoxicity against the multidrug-resistant (MDR) KB-VIN cell line and merit further development as preclinical drug candidates for treating cancer, including MDR phenotype. Our study suggested that incorporation of a fluorine atom into position 10 of CPT is an effective method for discovering new potent CPT derivatives.
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Fluorine, a highly active element, is widely used in drugs with high electronegativity and small size.[1,2] Fluorine incorporation often improves drug-like properties by blocking undesired metabolism at a specific site, increasing lipophilicity or binding affinity, or altering drug absorption, distribution, or excretion. The unique and complex physicochemical and biological properties provided by incorporation of fluorine atoms or fluorinated moieties into bioactive molecules have resulted in a wide application of fluorinated compounds for construction of new drugs.[3,4] As a result, more than 20% of the currently marketed drugs contain at least one fluorine atom. Particularly, an increasing number of fluorinated antitumor agents such as fluorouracil derivatives, enzalutamide, teriflunomide, ponatinib, sorefenib, gefitinib and vandetanib are becoming available for cancer treatment.[5] Therefore, derivatization of current pharmaceuticals to fluorinated analogues has become an increasingly attractive strategy to obtain more potent drugs for drug discovery.

Camptothecin (CPT, **1**), a naturally occurring quinoline alkaloid, exhibits significant antitumor activity against a broad spectrum of cancers via inhibition of DNA enzyme topoisomerase I (topo I).[6,7] Extensive structural modifications on the A-, B-, E-ring or acylation of the 20-hydroxy group of CPT led to the successful identification and development of the antitumor drugs irinotecan (**2**), topotecan (**3**) and belotecan (**4**), as well as several candidates such as lurtotecan (**5**), gimatecan (**6**), rubitecan (**7**), and prothecan (**8**), which are in various stages of preclinical development.[8–16] Significantly, newly emerging fluorinated derivatives, including exatecan (**9**) and BN-80915 (**10**), where a fluorine atom has been introduced on the A ring of CPT, have shown excellent antitumor activities both in vitro and in vivo and are currently undergoing clinical trials.[17,18] Recently, Zhang et al. reported the synthesis of **11** via a new strategy to improve the metabolic stability of CPT's lactone by replacing it with an α-fluoro ether as a lactone bioisostere.[19] The clinical successes and accumulated SAR studies have stimulated great interest in further exploration of CPT-derivatives with better antitumor activity Fig. 1.

In our continuous efforts to produce CPT-derived antitumor agents, we recently found that a series of novel 20-sulfonylamidine-CPT derivatives displayed potent antitumor activity with significantly different drug-resistance profiles from those of CPT. Among them, YQL-9a (**12**) showed excellent antitumor activities both in vitro and in vivo, indicating it to be a promising antitumor lead.[20,21] In addition, in prior SAR studies on CPT, addition of an

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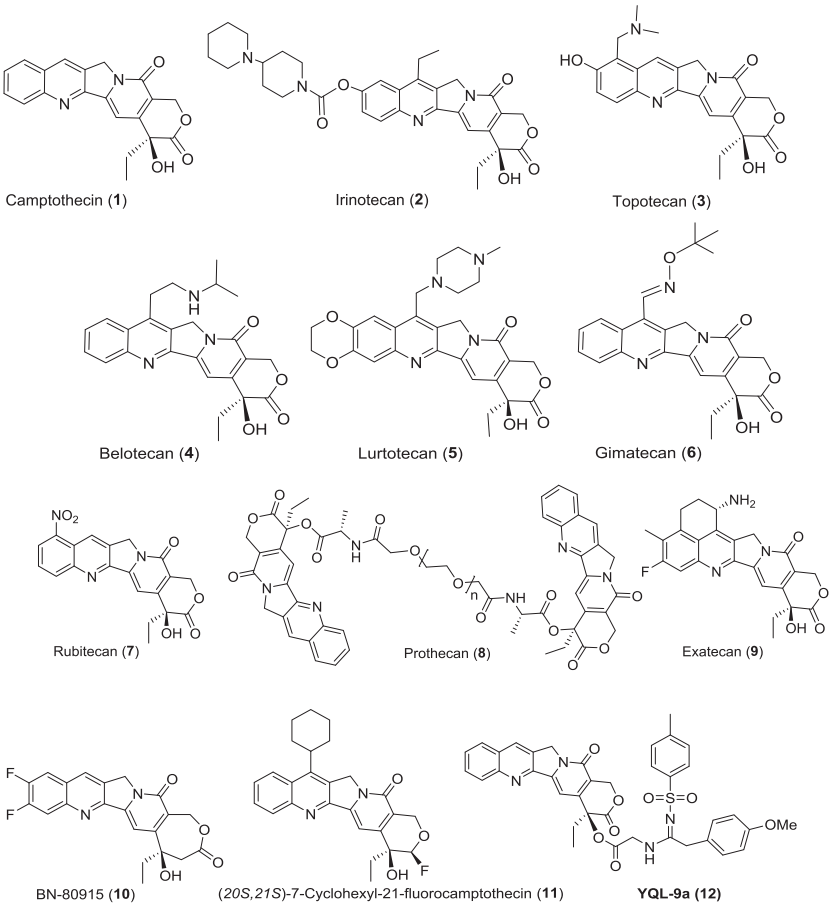

Fig. 1. Structures of CPT-derivatives.

electronegative substituent at C-10 has always resulted in improved cytotoxicity. Based on these facts, we postulated that the addition of fluorine at the C-10 positions of CPT and **12** would be an efficient way to increase the cytotoxicity of both compounds (Fig. 2). Also, as mentioned earlier, fluorination has the potential to improve the pharmacological profile of drugs. Therefore, herein, we report our synthesis of C-10 fluorinated CPT and **12** derivatives, as well as evaluation of their cytotoxic activity.

The synthetic routes to target compounds **16a-b** and **19a-b** are outlined in Scheme 1. Briefly, 10-(trifluoromethanesulfonyloxy)-camptothecins **14a** and **14b** were prepared from **13a** and **13b** by a classical synthetic method using *N*-phenylbis(trifluoromethanesulfonimide) and triethylamine in DMF. Next, both **14a** and **14b** were converted to 10-(tributylstannyl)camptothecins (**15a** and **15b**) in excellent yields by reaction with bis(tri-*n*-butyltin) in the presence of tetrakis(triphenylphosphine)palladium/lithium chloride.[22,23] Treatment of **15a** and **15b** with1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octanebis(hexafluorophosphate) (F-TEDA-PF6) and silver triflate (AgOTf) in dry acetone solution at 23 °C afforded the desired compounds **16a-b** in moderate yields.[24] Furthermore, the 20-hydroxy groups of **16a-b** were converted to *N*-Boc protected glycine esters (**17a-b**) using a combination of DIPC (*N,N'*-diisopropylcarbodiimide) and DMAP (4-dimethylaminopyridine). Deprotection of **17a** and **17b** with TFA/CH_2Cl_2 afforded the TFA salts (**18a-b**). Subsequently, the key intermediates (**18a-b**) were successfully reacted with 4-ethynylanisole and *p*-toluenesulfonyl azide in a Cu-catalyzed three-component reaction to produce the corresponding target compounds (**19a-b**) in good yields.[25]

The 10-fluorinated derivatives of CPT and **12** were evaluated for in vitro cytotoxic activity against five tumor cell lines, A-549 (lung carcinoma), MDA-MB-231 (triple-negative breast carcinoma), KB (originally isolated from epidermoid carcinoma of the nasopharynx), KB-VIN (MDR KB subline) and MCF-7 (breast adenocarcinoma) by using a sulforhodamine B colorimetric assay.[26,27] Irinotecan (**2**) and topotecan (**3**) were used as the positive controls. The screening results are shown in Table 1.

As shown in Table 1, all target compounds exhibited significant in vitro cytotoxic activity against the five tested tumor cell lines, with IC_{50} values ranging from 8.72 to 649 nM, and they exhibited more potent in vitro cytotoxic activity than **2**, while most of the new derivatives also showed comparable or superior potency to **3**. The data also revealed that the A-549 cell line was more sensitive than the other four cell lines to these compounds, which is consistent with the clinical behavior of other derivatives of CPT.[28] Remarkably, all of the compounds were more potent than **2** (IC_{50} >20,000 nM) against the MDR KB-VIN cell line, with **16b** (IC_{50} 67.0 nM) and **19b** (IC_{50} 99.2 nM) showing the greatest cytotoxicity against this cell line. They also showed increased cytotoxic potency against the triple-negative breast cancer (MDA-MB-231) cell line compared with **2** or **3**. This result implied that the introduction of a fluorine atom at C-10 position or a sulfonylamidine group at C-20 might combat the tumor MDR phenotype caused by P-glycoprotein overexpression. Compared with **16a** and **19a**, the corresponding 7-ethyl derivatives **16b** and **19b** exhibited greater in vitro cytotoxic activity against the five tested tumor cell lines. Thus, the introduction of a C-7 ethyl group contributed to improved cytotoxicity.

It is well known that therapeutic use of unmodified CPT is hindered by its poor solubility, high toxicity, and rapid inactivation through lactone ring hydrolysis in vivo. In addition, the carboxylate

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