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Original article

Design, synthesis and biological evaluation of novel fluorinated docetaxel analogues

Hong-Fu Lu [a], Xun Sun [a,*], Liang Xu [b], Li-Guang Lou [c], Guo-Qiang Lin [a,b]

[a] *Department of Chemistry of Natural Drugs, School of Pharmacy, Fudan University, 138 Yixueyuan Road, Shanghai 200032, China*
[b] *Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China*
[c] *Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, China*

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Abstract

A series of novel fluorinated docetaxel analogues have been synthesized and evaluated in vitro and in vivo. Incorporated one, two or three fluorine atom(s) either at both *meta* position on C-2 benzolate and 3′-*N*-*tert*-butyloxyl group or only at 3′-*N*-*tert*-butyloxyl group has resulted in potent analogues which have comparable or superior in vitro and in vivo cytotoxicity to docetaxel. Among them, compounds **14d** and **14e** have displayed more potent cytotoxicity than docetaxel both in human cancer cell line SK-OV-3 in vitro and in human non-small cell lung cancer A549 xenografts in vivo. Preliminary data show that compound **14a** has reduced acute animal toxicity in mice compared with docetaxel.
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Keywords: Docetaxel; Fluorinated docetaxel analogues; Cytotoxicity

1. Introduction

Paclitaxel (**1**), a complex natural diterpene first isolated from the bark of *Taxus brevifolia*, and its semi-synthetic derivative docetaxel (**2**) (Fig. 1) are currently considered to be the most important and exciting drugs used in cancer chemotherapy due to their unique mode of action involving stabilization of microtubules and inhabitation of tubulin depolymerization [1,2]. Although both of paclitaxel and docetaxel possess potent antitumor activity against various cancer cells, several major problems such as low aqueous solubility, multi-drug resistance (MDR), and low activity for oral administration have emerged after extensive clinical application for the treatment of ovarian, breast, and lung cancer in the recent decades [3]. To overcome these problems, developing new paclitaxel analogues as anticancer drugs with fewer side effects and improved activity against various classes of tumors are still necessary.

The fluorine substitution in drug design has been extensively exploited due to its unique and predictable physicochemical properties. It is well documented that fluorine could be effectively used as the bioisosterism of hydrogen in nearly any agents because of the complementarity between the carbon–hydrogen bond and the carbon–fluorine bond [4]. The replacement of hydrogen with fluorine does have consequence on molecular dipole and will produce new electrostatic interactions due to the strong electronegativity of fluorine. This property can be advantageous for the design of new bioactive molecules: (1) can alter both binding and functional property; and (2) more resistant to both chemical and metabolic degradation due to the high bond energy (C–F) [5]. Previous investigation revealed that both paclitaxel and docetaxel were metabolic liabilities for enzymes in the cytochrome P450 family. Major metabolites of these compounds arose from the positions of *para*-hydroxylation at the C-3′ phenyl ring and *meta*-hydroxylation at the C-2 benzoate moiety [6]. Thus, the blockage of these metabolic pathways of these molecules could increase their stability and possibly enhance the potency. The pioneering work reported by Ojima

* Corresponding author. Tel.: +86 21 54237127; fax: +86 21 54237607.
E-mail address: sunxunf@shmu.edu.cn (X. Sun).

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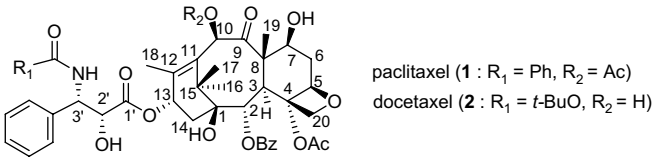


Fig. 1. Structures of paclitaxel (**1**) and docetaxel (**2**).

et al. [7] showed that the 3′-trifluoromethyl-10-acetyl analogues of docetaxel exhibit better cytotoxicity than paclitaxel and possesses more than one order of magnitude higher potency than paclitaxel and docetaxel against a drug resistant human breast cancer cell line. Further systematical studies by this group [8–10] demonstrated that incorporating fluorine at the metabolism site in the paclitaxel molecules did indeed block some of the metabolic pathways by enzymes of P450 (CYP) family and increased their stability. More interestingly, the 3′-*N*-*tert*-butyloxyl group on the side chain of docetaxel analogue, 2-(3-fluorobenzoyl)docetaxel, undergoes the unusual enzymatic hydroxylation by CYP 3A. However, no hydroxylation was observed for 2-(3-fluorobenzoyl)paclitaxel both at the phenyl ring of 2-(3-fluorobenzoyl) and at the 3′-phenyl ring. Possibly, this remarkable effect is the direct influence from the outlying fluorine moiety upon enzyme–substrate recognition and action [4]. These remarkable works lay a solid foundation that the fluorine replacement on the paclitaxel/docetaxel is a viable tool to enhance the potency, perhaps against multi-drug resistant (MDR) cancer cell lines. Herein, we described the syntheses of a series of docetaxel analogues incorporated fluorine(s) at 3′-*N*-*tert*-butyloxyl group (a potential metabolic position) and/or *meta* position on C-2 benzolate and their cytotoxic activity.

2. Results and discussion

2.1. Chemistry

The commercially available 10-deacetylbaccatin III (10-DAB, **3**) [11] was selected as the starting material for the synthesis of **14a–c**. Compound **3** reacted with TrocCl in pyridine to give 7,10-di-Troc-DAB **8A** in 91% yield (Scheme 1) [12]. In the presence of DCC and 4-dimethylaminopyridine (DMAP), **8A** coupled with enantiopure oxazolidine **9**, which was readily prepared according to a known literature procedure [13], to provide the corresponding product **10A**. Removal of 3′-*N*-Boc and acetonide protecting group of compound **10A** with 98% formic acid gave the amino alcohol compound **11A** [14,15]. Intermediates **13a–c** were prepared by acylation of amino group of compound **11A** with freshly prepared fluorine containing acyl chlorides, which could be generated by reaction of corresponding fluorinated *tert*-butyl alcohols [16,17] with phosgene in ether at low temperature. After removing the 7,10-Troc protecting groups on **13a–c** with zinc in acetic acid, new fluorinated docetaxel derivatives (**14a–c**) were synthesized in desirable yields (61–85%). To the best of our knowledge, the introduction of fluorine on the *tert*-butyl group of docetaxel has not been reported before [18].

For the syntheses of compounds **14d–f**, **7B** was chosen as the starting material. The synthesis of **7B** has been previously reported [19]. We adopted this synthetic route with a minor change to synthesize **7B** in four steps (Scheme 2). Compound **3** was selectively protected with TESCl in the presence of imidazole to afford **4** [20] which was converted to **5** [21] by debenzylation with Red-Al. Then compound **5** was transformed into **7** by coupling with 3-fluorobenzoic acid followed by the deprotection of TES groups. With **7B** in hand, fluorinated docetaxel analogues (**14d–f**) were obtained with 70–74% overall yields by following the same procedures described for the synthesis of **14a–c** (Scheme 1).

2.2. In vitro cytotoxic activity

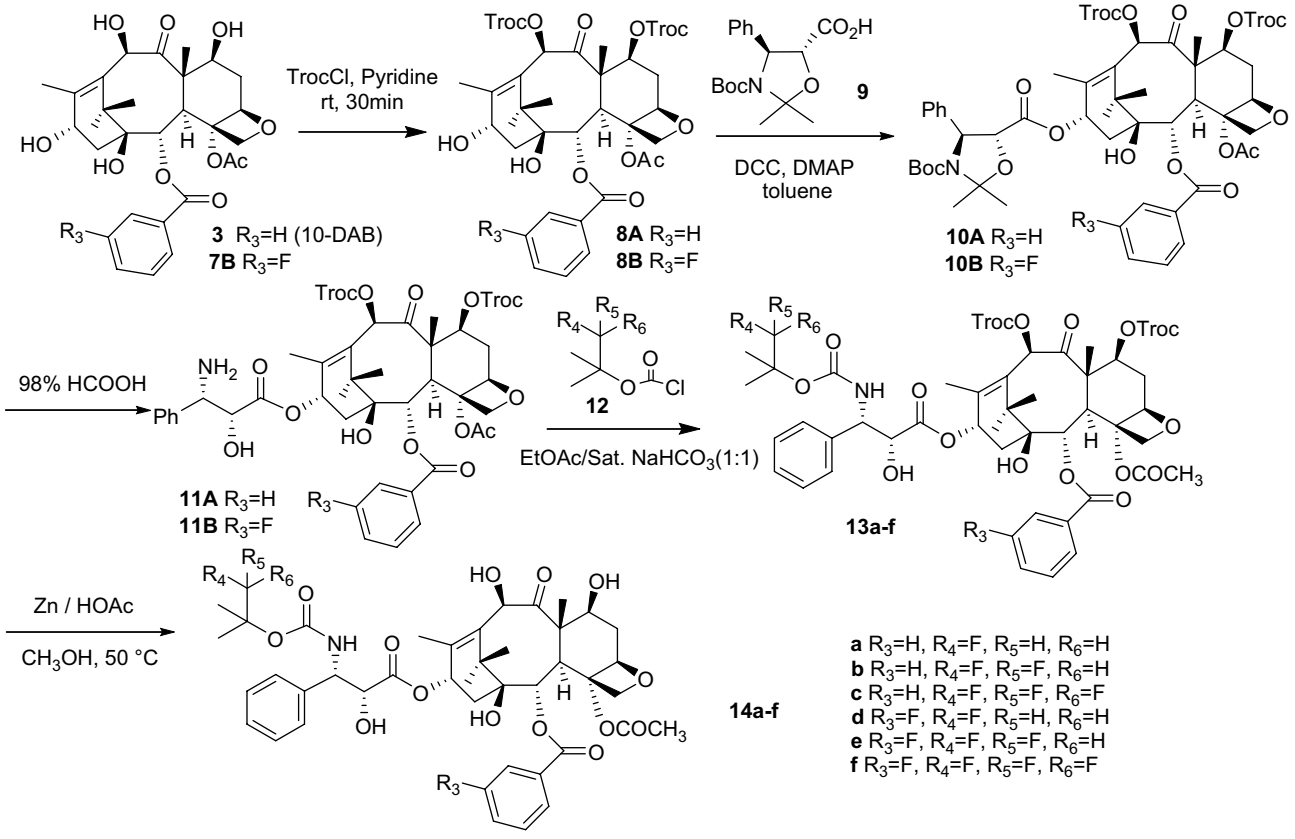
The cytotoxic activity of fluorinated docetaxel analogues (**14a–f**) was evaluated against human ovarian cell line SK-OV-3 and the results are listed in Table 1. As shown in Table 1, compound **14a**, which incorporated one fluorine atom at 3′-*N*-*tert*-butyloxyl group on the side chain of docetaxel, only exhibited similar activity as compared with its parent compound (docetaxel). However, compounds **14b–e**, which bear two or three fluorine atoms either at both *meta* position on C-2 benzolate and 3′-*N*-*tert*-butyloxyl group or only at 3′-*N*-*tert*-butyloxyl group, showed at least 76-fold enhancement in cytotoxicity relative to docetaxel. Interestingly, compound **14f**, a trifluoromethyl substituted analogue, showed 10-fold decrease of the cytotoxicity compared with docetaxel.

2.3. In vivo antitumor activity

Since five new fluorinated docetaxel analogues **14a–e** were relatively similar to or much more cytotoxic than docetaxel, they were selected for further in vivo evaluation against human non-small cell lung cancer A549 xenografts in nude mice. The results are shown in Table 2. It can be seen that the compounds **14a**, **14d** and **14e** showed greater inhibition rate of tumor growth than docetaxel in human non-small cell lung cancer A549-bearing nude mice following the intravenous administration.

2.4. Acute toxicity studies in mice

The acute toxicity investigation showed that there was a regular dose-dependent increase in mortality in both sexes of mice after i.p. administration and the death occurred after 7 days. In addition to death, the toxicities included hair-floppy, inactivity and loss of weight. The histological examination of the death mice indicated that the reason of death was closely related to obviously spleen shrink. The fluorinated docetaxel derivative **14a** was further selected for acute toxicity investigation and its LD_{50} value was calculated to be 118.8 mg/kg (95% confidence limits = 84.4–167.10 mg/kg), larger than the value of docetaxel (LD_{50} = 74.10 mg/kg by i.p.), indicating that **14a** was 1.6-fold less toxic than docetaxel.



Scheme 1. Synthesis of new fluorinated docetaxel derivatives (**14a–f**).

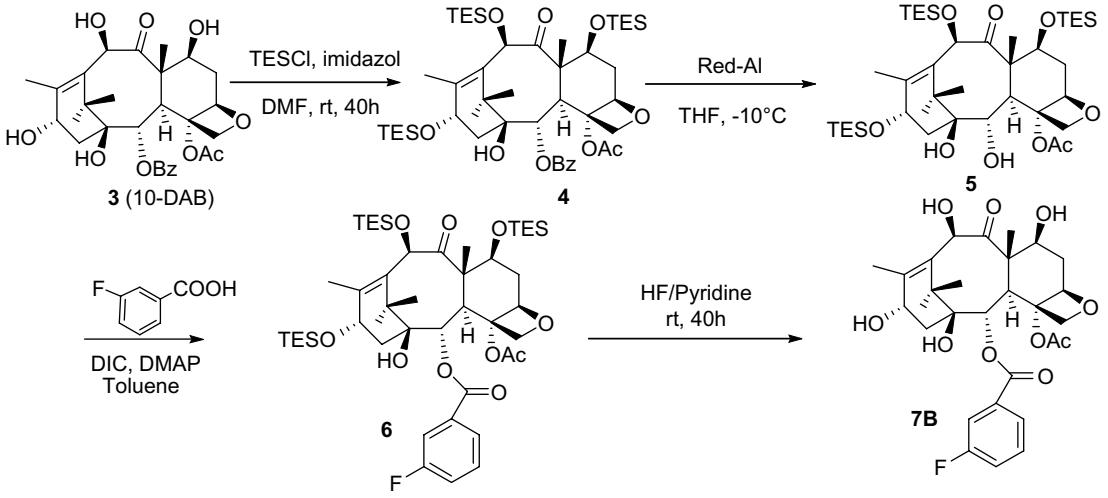
3. Conclusions

In conclusion, incorporated one, two or three fluorine atom(s) either at both *meta* position on C-2 benzolate and 3′-*N*-*tert*-butyloxyl group or only at 3′-*N*-*tert*-butyloxyl group resulted in a series of potent analogues which have comparable or superior in vitro and in vivo cytotoxicity to docetaxel and have reduced acute animal toxicity in mice. Further studies with these fluorinated docetaxel derivatives are currently underway to elucidate whether the blockage of the metabolic pathways plays a pivotal role for the enhancement of the cytotoxicity.

4. Experimental section

4.1. Materials and physical measurements

Reagents were purchased from Aldrich and TCI Chemical companies. All solvents are purified and dried in accordance with standard procedures, unless otherwise indicated. Ether,



Scheme 2. Synthesis of 2-debenzoyl-2-(*m*-fluorobenzoyl)-10-deacetylbaccatin III **7B**.

Table 1
In vitro cytotoxicity of fluorinated docetaxel analogues **14a–f** against human cancer cell line SK-OV-3

	Docetaxel	**14a**	**14b**	**14c**	**14d**	**14e**	**14f**
IC_{50} (μM)[a]	3.4×10^{-3}	3.8×10^{-3}	2.0×10^{-5}	1.0×10^{-5}	3.0×10^{-5}	5.0×10^{-5}	3.4×10^{-2}

[a] The concentration of compound which inhibits the proliferation of tumor cells by 50% (IC_{50}) after 72 h drug exposure.

tetrahydrofuran and toluene were dried over sodium/benzophenone; dichloromethane and pyridine were distilled from calcium hydride; and DMF was distilled from calcium hydride by reduced pressure. Oxygen-free and water-free operations were carried out under argon atmosphere in dried glassware unless otherwise noted. All reactions were monitored by TLC with precoated silica gel plates GF_{254}, 10–40 μm (Yantai, China). The purity of the samples was determined by column chromatography with the silica gel H 300–400 mesh (Yantai, China). Melting points (mp) were determined using an X-4 microscope melting point apparatus and were uncorrected. All ^{1}H NMR spectra were recorded on Varian Mercury 300 (300 MHz) or Bruker DRX-400 (400 MHz) spectrometer at room temperature and chemical shifts are reported in parts per million (δ) relative to TMS (0.00) as internal standard; expressed in peak shape, the number of hydrogen, and coupling constant in hertz. ^{13}C NMR spectra data were recorded on Bruker DRX-400 (100 MHz) or Bruker DPX-300 (75 MHz) spectrometer at room temperature and chemical shifts are reported in parts per million (δ) relative to *d*-substituted solvents (chloroform-*d* at 77.2 ppm, acetone-d_6 at 30.6 and 206.7 ppm) as internal standard. Mass spectra ware performed at the testing and analysis center of Shanghai Institute of Organic Chemistry: Low-resolution mass spectra (ESI) were performed on Shimadzu LCMS-2010EV and high-resolution mass spectra on IonSpec 4.7 Tesla FTMS (MALDI) or Bruker Daltonics, Inc. APEXIII7.0 TESLA FMS (ESI).

4.2. Chemistry

4.2.1. 7,10,13-Tris(triethylsilyl)-2-debenzoyl-2-(m-fluorobenzoyl)-10-deacetylbaccatin III (*6*)

Compound **5** (2 g, 2.55 mmol), DIC (4.83 g, 38.30 mmol), DMAP (30.50 mg, 0.25 mmol), and 3-fluorobenzoic acid (5.37 g, 38.30 mmol) were dissolved in toluene (20 mL). The resulting mixture was warmed to 60 °C and stirred overnight at this temperature. The reaction mixture was quenched with saturated $NaHCO_3$ (10 mL), and then extracted with EtOAc (20 mL × 2). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The obtained residue was purified by silica gel chromatography column (petroleum ether/ethyl acetate 20/1) to give **6** (1.80 g, 78%) as a white solid; mp 218–220 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.63 (m, 18H), 1.00 (m, 27H), 1.13 (s, 3H), 1.19 (s, 3H), 1.65 (s, 3H), 1.98 (s, 3H), 2.16 (m, 2H), 2.29 (s, 3H), 1.88 and 2.53 (2m, 2H), 3.86 (d, 1H, $J = 6.9$ Hz), 4.13 and 4.28 (2d, 2H, $J = 8.1$ Hz), 4.41 (dd, 1H, $J = 10.5$, 6.9 Hz), 4.92 (m, 1H), 4.96 (m, 1H), 5.19 (s, 1H), 5.59 (d, 1H, $J = 6.9$ Hz), 7.30 (m, 1H), 7.46 (m, 1H), 7.78 (m, 1H), 7.88 (m, 1H) [22].

4.2.2. 2-Debenzoyl-2-(m-fluorobenzoyl)-10-deacetylbaccatin III (*7B*)

To a solution of **6** (1.45 g, 1.60 mmol) in dried THF (40 mL) was added anhydrous pyridine (8.0 mL). The reaction mixture was cooled to 0 °C, and then HF–pyridine (8.0 mL) was added.

Table 2
In vivo antitumor activity of fluorinated docetaxel derivatives **14a–e** against human non-small cell lung cancer A549 xenograft in nude mice[a]

Groups	Dose (mg/kg)	No.of mice		Body wt change[d] (%)	T/C (%)
		d0[b]	dn[c]		
Control		12	12	0	
14a	12	6	6	−19.1	41.5[e]
14a	16	6	6	−22.0	37.9[e]
14b	12	6	6	0	91.5
14b	18	6	6	−7.7	83.5
14c	12	6	6	0	91.8
14c	18	6	6	−9.7	72.0
14d	12	5	5	−18.0	53.7[e]
14d	18	5	5	−31.3	30.2[e]
14e	12	5	5	−16.5	51.7[e]
14e	18	5	5	−26.7	24.4[e]
Docetaxel	12	6	6	−19.6	43.0[e]

[a] Nude mice were subcutaneously injected with A549 cells. When the tumor reached 80–150 mm^3 in volume, animals were i.v. administered **14a–e** or docetaxel.
[b] d0: at day before the first treatment.
[c] dn: the day when maximum effect was gained (at day 14 after the first treatment).
[d] Body weight was measured at the end of the experiment.
[e] $p < 0.01$ versus control.

The resulting mixture was allowed to warm to room temperature, and stirred for 40 h. The reaction mixture was diluted with EtOAc (200 mL), and the organic layer was washed with sodium bicarbonate, brine, dried over Na_2SO_4, and concentrated in vacuo. The obtained residue was purified by silica gel chromatography column (CH_2Cl_2/CH_3OH 40/1) to afford **7B** (800 mg, 89%) as a white solid; mp 227–229 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (s, 3H), 1.10 (s, 3H), 1.72 (s, 3H), 2.06 (s, 3H), 2.26 (s, 3H), 2.39 (m, 2H), 1.82 and 2.47 (2m, 2H), 3.60 (s, 1H), 4.04 (d, 1H, $J = 7.2$ Hz), 4.16 (s, 2H), 4.17 (d, 1H, $J = 6.0$ Hz), 4.24 (d, 1H, $J = 2.1$ Hz), 4.34 (m, 1H), 4.59 (d, 1H, $J = 4.5$ Hz), 4.91 (m, 1H), 4.98 (d, 1H, $J = 9.3$ Hz), 5.27 (d, 1H, $J = 1.8$ Hz), 5.63 (d, 1H, $J = 7.5$ Hz), 7.45 (m, 1H), 7.62 (m, 1H), 7.78 (d, 1H, $J = 8.1$ Hz), 7.94 (d, 1H, $J = 7.8$ Hz) [23].

4.2.3. 7,10-Di(2,2,2-trichloroethyloxycarbonyl)-2-debenzoyl-2-(m-fluorobenzoyl)-10-deacetylbaccatin III (**8B**)

To a solution of **7B** (1.03 g, 1.84 mmol) in anhydrous pyridine (20 mL) was added 2,2,2-trichloroethyl chloroformate (0.85 mL, 6.17 mmol) dropwise at 0 °C. Then the reaction mixture was warmed to room temperature and further stirred for 30 min. The reaction mixture was then quenched with water and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, and washed with diluted HCl and brine. Then the organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography column (petroleum ether/ethyl acetate 2/1) to give **8B** (1.58 g, 94% yield) as a white solid; mp 222–224 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (s, 3H), 1.15 (s, 3H), 1.85 (s, 3H), 2.17 (s, 3H), 2.30 (m, 2H), 2.31 (s, 3H), 2.05 and 2.65 (2m, 2H), 3.98 (d, 1H, $J = 6.6$ Hz), 4.14 and 4.33 (2d, 2H, $J = 8.4$ Hz), 4.61 and 4.92 (2d, 2H, $J = 12.0$ Hz), 4.78 (d, 2H, $J = 12.0$ Hz), 4.90 (m, 1H), 5.00 (d, 1H, $J = 7.8$ Hz), 5.59 (m, 1H), 5.62 (d, 1H, $J = 7.5$ Hz), 6.27 (s, 1H), 7.33 (m, 1H), 7.48 (m, 1H), 7.79 (m, 1H), 7.90 (d, 1H, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.6, 15.4, 20.1, 22.5, 26.6, 33.3, 38.4, 42.6, 47.4, 56.3, 67.8, 74.6, 76.2, 76.6, 77.1, 77.4, 78.7, 79.7, 80.4, 83.7, 94.2, 94.3, 116.9, 120.9, 125.9, 130.4, 130.8, 131.4, 146.6, 153.2, 153.3, 162.6 (d, $J_{C-F} = 246.4$ Hz), 165.7, 170.8, 201.1; ESIMS *m/z* 933.0 [$M + Na^+$]; HRMS (MALDI) *m/z* calcd for $C_{35}H_{37}O_{14}FCl_6Na^+$ [$M + Na^+$]: 933.0215, found: 933.01908.

4.2.4. 7,10-Di(2,2,2-trichloroethyloxycarbonyl)-2-debenzoyl-2-(m-fluorobenzoyl)-10-deacetylbaccatin III-13-O-[(4S,5R)-4-phenyl-3-(tert-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidine-5-carboxylate] (**10B**)

To a solution of anhydrous toluene (20 mL) were added **8B** (0.91 g, 1.00 mmol), **9** (0.96 g, 3.00 mmol), DCC (0.62 g, 3.00 mmol) and DMAP (12.2 mg, 0.10 mmol). The resulting mixture was stirred at 85 °C for 1 h. After the completion, the reaction mixture was washed with water (10 mL × 3), dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained residue was purified by silica gel flash chromatography column (petroleum ether/ethyl acetate 4/1) to afford **10B** (1.13 g, 93%) as a white solid; mp 221–223 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (s, 9H), 1.18 (s, 3H), 1.25 (s, 3H), 1.77 (s, 3H), 1.82 (s, 6H), 1.89 (s, 3H), 2.04 (s, 3H), 2.17 (m, 2H), 2.04 and 2.60 (2m, 2H), 3.89 (d, 1H, $J = 7.2$ Hz), 4.10 and 4.28 (2d, 2H, $J = 8.4$ Hz), 4.48 (d, 1H, $J = 6.9$ Hz), 4.60 and 4.91 (2d, 2H, $J = 12.0$ Hz), 4.78 (s, 2H), 4.91 (d, 1H, $J = 12.0$ Hz), 5.07 (br s, 1H), 5.57 (dd, 1H, $J = 10.8$, 6.9 Hz), 5.64 (d, 1H, $J = 7.2$ Hz), 6.24 (s, 1H), 6.28 (t, 1H, $J = 9.6$ Hz), 7.32–7.39 (m, 6H), 7.50 (m, 1H), 7.71 (d, 1H, $J = 8.1$ Hz), 7.85 (d, 1H, $J = 8.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.5, 14.5, 20.8, 21.2, 26.1, 26.4, 27.8 (three overlapping peaks), 29.5, 33.0, 35.2, 42.9, 44.8, 46.7, 55.9, 64.2, 70.9, 74.6, 75.9, 76.1, 77.0, 77.3, 78.8, 78.9, 80.2, 80.4, 80.8, 83.5, 94.0, 96.8, 116.6, 120.8, 125.8, 126.2 (two overlapping peaks), 127.8, 128.6 (two overlapping peaks), 130.2, 130.3, 131.1, 131.7, 142.6, 151.4, 153.0, 153.0, 162.4 (d, $J_{C-F} = 246.4$ Hz), 165.5, 169.7, 170.0, 200.4; ESIMS *m/z* 1236.2 [$M + Na^+$]; HRMS (MALDI) *m/z* calcd for $C_{52}H_{58}NO_{18}FCl_6Na^+$ [$M + Na^+$]: 1236.1625, found: 1236.16614.

4.2.5. N-De-tert-butoxycarbonyl-7,10-di(2,2,2-trichloroethyloxycarbonyl)-2-debenzoyl-2-(m-fluorobenzoyl)docetaxel (**11B**)

To a round-bottomed flask (10 mL) were added **10B** (800 mg, 0.66 mmol) and HCOOH (>98%, 20 mL). The reaction mixture was stirred at room temperature for 2 h. Then the resulting solution was neutralized by addition of saturated $NaHCO_3$. The water phase was extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated in vacuo. The obtained residue was purified by silica gel flash chromatography column (acetone/petroleum ether 1/3) to afford **11B** (700 mg, 99%) as a white solid; mp 155–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (s, 3H), 1.24 (s, 3H), 1.82 (s, 3H), 2.00 (s, 3H), 2.27 (s, 3H), 2.14 (m, 2H), 2.02 and 2.60 (2m, 2H), 3.85 (d, 1H, $J = 6.6$ Hz), 4.11 and 4.28 (2d, 2H, $J = 8.4$ Hz), 4.31 (m, 1H), 4.35 (br s, 1H), 4.60 and 4.91 (2d, 2H, $J = 11.7$ Hz), 4.77 (s, 2H), 4.90 (d, 1H, $J = 6.6$ Hz), 5.54 (dd, 1H, $J = 10.5$, 7.5 Hz), 5.64 (d, 1H, $J = 6.6$ Hz), 6.22 (t, 1H, $J = 8.7$ Hz), 6.22 (s, 1H), 7.36–7.43 (m, 6H), 7.51 (m, 1H), 7.71 (m, 1H), 7.86 (d, 1H, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.7, 14.6, 21.1, 21.2, 26.2, 26.8, 27.8, 33.1, 35.2, 43.0, 46.7, 55.9, 66.8, 70.6, 74.6, 76.0, 76.2, 77.3, 79.0, 80.2, 82.0, 83.6, 94.1, 98.8, 116.6, 121.0, 126.0, 126.8 (two overlapping peaks), 128.6, 129.1 (two overlapping peaks), 130.4, 131.2, 131.5, 137.9, 143.1, 153.1, 153.2, 162.5 (d, $J_{C-F} = 246.2$ Hz), 165.6, 170.2, 172.3, 200.6; ESIMS *m/z* 1096.1 [$M + Na^+$]; HRMS (MALDI) *m/z* calcd for $C_{44}H_{46}NO_{16}FCl_6Na^+$ [$M + Na^+$]: 1096.0810, found: 1096.08241.

4.2.6. General procedure for the preparation of **12**

To a dried round bottom flask were added ethyl fluoro-substituted acetate (0.1 mol), benzyl alcohol (0.3 mol) and boron trifluoride etherate (0.01 mol) under nitrogen atmosphere. The resulting mixture was stirred overnight at 75 °C. The reaction mixture was extracted with ethyl acetate (100 mL × 3) and the organic layer was washed with saturated $NaHCO_3$ solution, brine, dried over anhydrous $MgSO_4$, and

evacuated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate 20/1) to give the colorless liquid product benzyl fluoro-substituted acetate (60% yield). The obtained benzyl fluoro-substituted acetate in ether (20 mL) was added to a solution of methylmagnesium bromide (3 M, 36.7 mL). The mixture was stirred at 0–5 °C for 20 min and quenched with ice water and hydrochloric acid. The ethereal layer was separated, washed with diluted $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and distilled. The fractions with b.p. 96–98 °C were collected (21.7% yield). Then pyridine (11 mmol) in ether (8 mL) was added dropwise to a mixture of above obtained alcohol (10 mmol) and triphosgene (3.33 mmol) in ether (10 mL) at −30 °C. The mixture was stirred for 2 h at this temperature, slowly warmed to room temperature, and further stirred for 10 h. The resulting solution was used directly for the next step without further purification.

*4.2.7. General procedure for the preparation of **13a–f***

To a solution of **11A** (2.00 g, 1.89 mmol) or **11B** (2.03 g, 1.89 mmol) in EtOAc/H_2O (1/1, 120 mL) was dropwise added excessive **12** at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with ethyl acetate (20 mL × 3) and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The obtained residue was purified by silica gel flash chromatography column (petroleum ether/ethyl acetate 1/1) to afford **13a–f** as a white solid, which would be used directly for the next step.

*4.2.7.1. N-De-tert-butoxycarbonyl-N-[2-(1-fluoro-2-methyl)-propyloxycarbonyl]-7,10-di(2,2,2-trichloroethyloxycarbonyl)-docetaxel (**13a**).* Yield 27%; mp 176–179 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (s, 3H), 1.27 (s, 3H), 1.35 (s, 6H), 1.86 (s, 3H), 1.95 (s, 3H), 2.32 (m, 2H), 2.41 (s, 3H), 2.07 and 2.62 (2m, 2H), 3.91 (d, 1H, $J = 6.9$ Hz), 4.18 and 4.34 (2d, 2H, $J = 8.1$ Hz), 4.34 and 4.46 (m, 2H), 4.60 and 4.91 (2d, 2H, $J = 12.0$ Hz), 4.66 (m, 1H), 4.78 (s, 2H), 4.95 (d, 1H, $J = 11.4$ Hz), 5.28 (m, 1H), 5.55 (m, 1H), 5.57 (d, 1H, $J = 9.3$ Hz), 5.70 (d, 1H, $J = 6.9$ Hz), 6.24 (s, 1H), 6.24 (t, 1H, $J = 7.5$ Hz), 7.34–7.44 (m, 5H), 7.50 (t, 2H, $J = 7.5$ Hz), 7.63 (t, 1H, $J = 7.5$ Hz), 8.11 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.7, 14.6, 18.8, 21.0, 22.3, 22.3, 22.5, 26.3, 33.3, 35.4, 43.2, 46.9, 56.3, 69.6, 72.3, 73.5, 74.2, 76.4, 77.2, 77.4, 78.7, 79.1, 79.9 (d, $J_{C-F} = 18.8$ Hz), 80.9, 83.7, 86.8 (d, $J_{C-F} = 176.1$ Hz), 94.2 (two overlapping peaks), 126.7 (two overlapping peaks), 128.2, 128.7 (two overlapping peaks), 128.9 (two overlapping peaks), 129.1, 130.2 (two overlapping peaks), 132.1, 133.8, 138.0, 142.3, 153.2, 153.2, 154.8, 166.8, 170.4, 172.6, 200.7; ESIMS *m/z* 1196.1 [M + Na^+]; HRMS (MALDI) *m/z* calcd for $C_{49}H_{54}NO_{18}FCl_6Na^+$ [M + Na^+]: 1196.1373, found: 1196.13484.

*4.2.7.2. N-De-tert-butoxycarbonyl-N-[2-(1,1-difluoro-2-methyl)propyloxycarbonyl]-7,10-di(2,2,2-trichloroethyloxycarbonyl)docetaxel (**13b**).* Yield 76%; mp 166–169 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (s, 3H), 1.27 (s, 3H), 1.39 (s, 6H), 1.86 (s, 3H), 1.94 (s, 3H), 2.29 (m, 2H), 2.39 (s, 3H), 2.07 and 2.62 (2m, 2H), 3.41 (d, 1H, $J = 3.9$ Hz), 3.90 (d, 1H, $J = 6.6$ Hz), 4.18 and 4.34 (2d, 2H, $J = 8.4$ Hz), 4.60 and 4.91 (2d, 2H, $J = 11.7$ Hz), 4.66 (m, 1H), 4.78 (s, 2H), 4.95 (d, 1H, $J = 10.8$ Hz), 5.26 (d, 1H, $J = 8.1$ Hz), 5.54 (dd, 1H, $J = 10.5$, 7.2 Hz), 5.67 (d, 1H, $J = 2.7$ Hz), 5.70 (s, 1H), 6.00 (t, 1H, $J = 57.0$ Hz), 6.23 (s, 1H), 6.23 (m, 1H), 7.35–7.45 (m, 5H), 7.50 (t, 2H, $J = 7.5$ Hz), 7.63 (t, 1H, $J = 7.2$ Hz), 8.10 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.7, 14.6, 19.8 (two overlapping peaks), 20.9, 22.5, 26.3, 33.2, 35.3, 43.1, 46.9, 56.2, 56.4, 72.2, 73.3, 74.1, 76.3, 76.4, 77.1, 77.4, 78.6, 79.1, 79.8 (t, $J_{C-F} = 27.1$ Hz), 80.9, 83.6, 94.1 (two overlapping peaks), 114.8 (t, $J_{C-F} = 246.9$ Hz), 126.7 (two overlapping peaks), 128.3, 128.7 (two overlapping peaks), 128.9 (two overlapping peaks), 129.7, 130.1 (two overlapping peaks), 132.2, 133.8, 137.8, 142.2, 153.2, 153.2, 154.2, 166.8, 170.4, 172.4, 200.6; ESIMS *m/z* 1214.1 [M + Na^+]; HRMS (MALDI) *m/z* calcd for $C_{49}H_{53}NO_{18}F_2Cl_6Na^+$ [M + Na^+]: 1214.1230, found: 1214.12541.

*4.2.7.3. N-De-tert-butoxycarbonyl-N-[2-(1,1,1-trifluoro-2-methyl)propyloxycarbonyl]-7,10-di(2,2,2-trichloroethyloxycarbonyl)docetaxel (**13c**).* Yield 46%; mp 170–173 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (s, 3H), 1.27 (s, 3H), 1.54 (s, 3H), 1.58 (s, 3H), 1.85 (s, 3H), 1.93 (s, 3H), 2.29 (m, 2H), 2.37 (s, 3H), 2.06 and 2.58 (2m, 2H), 3.46 (br s, 1H), 3.90 (d, 1H, $J = 6.6$ Hz), 4.17 and 4.31 (2d, 2H, $J = 8.4$ Hz), 4.64 (m, 1H), 4.60 and 4.91 (2d, 2H, $J = 11.7$ Hz), 4.78 (s, 2H), 4.95 (d, 1H, $J = 10.2$ Hz), 5.25 (d, 1H, $J = 7.8$ Hz), 5.53 (dd, 1H, $J = 9.9$, 7.5 Hz), 5.69 (d, 1H, $J = 6.6$ Hz), 5.75 (d, 1H, $J = 9.3$ Hz), 6.20 (t, 1H, $J = 8.1$ Hz), 6.23 (s, 1H), 7.33–7.45 (m, 5H), 7.51 (t, 2H, $J = 7.5$ Hz), 7.64 (t, 1H, $J = 7.5$ Hz), 8.10 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.7, 14.6, 19.3, 19.6, 20.8, 22.4, 26.3, 33.2, 35.2, 43.1, 46.9, 56.2, 56.4, 60.4, 72.2, 73.3, 74.1, 76.3, 77.1, 77.4, 78.6, 78.6, 79.1, 80.9, 83.6, 94.1 (two overlapping peaks), 126.2, 126.8 (two overlapping peaks), 128.3, 128.7 (two overlapping peaks), 128.9 (two overlapping peaks), 129.7, 130.1 (two overlapping peaks), 132.2, 133.8, 137.7, 142.2, 153.1, 153.2, 153.5, 166.9, 170.3, 172.4, 200.6; ESIMS *m/z* 1232.1 [M + Na^+]; HRMS (MALDI) *m/z* calcd for $C_{49}H_{52}NO_{18}F_3Cl_6Na^+$ [M + Na^+]: 1232.1176, found: 1232.11599.

*4.2.7.4. N-De-tert-butoxycarbonyl-N-[2-(1-fluoro-2-methyl)-propyloxycarbonyl]-7,10-di(2,2,2-trichloroethyloxycarbonyl)-2-debenzoyl-2-(m-fluorobenzoyl)docetaxel (**13d**).* Yield 20%; mp 164–167 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (s, 3H), 1.20 (s, 3H), 1.28 (s, 6H), 1.86 (s, 3H), 1.94 (s, 3H), 2.25 (m, 2H), 2.37 (s, 3H), 2.06 and 2.63 (2m, 2H), 3.45 (d, 1H, $J = 5.1$ Hz), 3.90 (d, 1H, $J = 6.9$ Hz), 4.05 (dd, 2H, $J = 14.1$, 7.2 Hz), 4.20 and 4.31 (2d, 2H, $J = 8.4$ Hz), 4.61 and 4.92 (2d, 2H, $J = 12.0$ Hz), 4.65 (m, 1H), 4.78 (s, 2H), 4.95 (d, 1H, $J = 10.8$ Hz), 5.29 (br d, 1H, $J = 8.7$ Hz), 5.55 (m, 1H), 5.56 (m, 1H), 5.66 (d, 1H, $J = 6.9$ Hz), 6.23 (s,

1H), 6.23 (t, 1H, $J = 9.0$ Hz), 7.24–7.41 (m, 6H), 7.50 (m, 1H), 7.78 (d, 1H, $J = 8.7$ Hz), 7.91 (d, 1H, $J = 7.8$ Hz).

*4.2.7.5. N-De-tert-butoxycarbonyl-N-[2-(1,1-difluoro-2-methyl)propyloxycarbonyl]-7,10-di(2,2,2-trichloroethyloxycarbonyl)-2-debenzoyl-2-(m-fluorobenzoyl)docetaxel (**13e**).* Yield 75%; mp 144–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (s, 3H), 1.28 (s, 3H), 1.39 (s, 6H), 1.86 (s, 3H), 1.94 (s, 3H), 2.27 (m, 2H), 2.38 (s, 3H), 2.07 and 2.63 (2m, 2H), 3.32 (d, 1H, $J = 5.4$ Hz), 3.90 (d, 1H, $J = 6.9$ Hz), 4.17 and 4.33 (2d, 2H, $J = 8.4$ Hz), 4.60 and 4.91 (2d, 2H, $J = 11.7$ Hz), 4.66 (m, 1H), 4.78 (s, 2H), 4.96 (d, 1H, $J = 8.1$ Hz), 5.25 (d, 1H, $J = 11.1$ Hz), 5.54 (m, 1H), 5.61 (d, 1H, $J = 7.8$ Hz), 5.66 (d, 1H, $J = 6.9$ Hz), 6.01 (t, 1H, $J = 57.0$ Hz), 6.20 (m, 1H), 6.23 (s, 1H), 7.31–7.46 (m, 6H), 7.51 (m, 1H), 7.78 (m, 1H), 7.90 (d, 1H, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.7, 14.7, 19.8 (two overlapping peaks), 20.9, 22.4, 26.3, 33.3, 35.2, 43.1, 46.9, 56.2, 56.5, 68.2, 72.2, 73.4, 74.6, 76.2, 76.3, 77.2, 78.8, 79.1, 79.8 (t, $J_{C-F} = 27.1$ Hz), 80.9, 83.6, 94.2 (two overlapping peaks), 115.0 (t, $J_{C-F} = 244.5$ Hz), 116.9, 121.0, 126.0, 126.7 (two overlapping peaks), 128.8, 129.0 (two overlapping peaks), 130.5, 131.2, 132.1, 138.0, 142.3, 153.2, 153.2, 154.3, 163.7 (d, $J_{C-F} = 243.7$ Hz), 165.7, 170.4, 172.5, 200.5; ESIMS *m/z* 1232.1 [M + Na$^+$]; HRMS (MALDI) *m/z* calcd for $C_{49}H_{52}NO_{18}F_3Cl_6Na^+$ [M + Na$^+$]: 1232.1139, found: 1232.11599.

*4.2.7.6. N-De-tert-butoxycarbonyl-N-[2-(1,1,1-trifluoro-2-methyl)propyloxycarbonyl]-7,10-di(2,2,2-trichloroethyloxycarbonyl)-2-debenzoyl-2-(m-fluorobenzoyl)docetaxel (**13f**).* Yield 35%; mp 158–161 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (s, 3H), 1.27 (s, 3H), 1.56 (s, 3H), 1.58 (s, 3H), 1.86 (s, 3H), 1.93 (s, 3H), 2.27 (m, 2H), 2.36 (s, 3H), 2.07 and 2.63 (2m, 2H), 3.35 (d, 1H, $J = 5.1$ Hz), 3.90 (d, 1H, $J = 6.9$ Hz), 4.16 and 4.33 (2d, 2H, $J = 8.1$ Hz), 4.60 and 4.91 (2d, 2H, $J = 11.7$ Hz), 4.62 (m, 1H), 4.78 (s, 2H), 4.96 (d, 1H, $J = 11.7$ Hz), 5.24 (br d, 1H, $J = 9.6$ Hz), 5.53 (m, 1H), 5.66 (d, 1H, $J = 7.2$ Hz), 5.66 (m, 1H), 6.20 (t, 1H, $J = 10.5$ Hz), 6.23 (s, 1H), 7.33–7.46 (m, 6H), 7.51 (m, 1H), 7.78 (d, 1H, $J = 8.4$ Hz), 7.90 (d, 1H, $J = 7.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.6, 14.6, 19.4, 19.6, 20.8, 22.4, 26.3, 33.2, 35.1, 43.1, 46.9, 56.2, 56.5, 68.1, 72.1, 73.4, 74.5, 76.2, 76.3, 77.1, 77.4, 78.7, 79.1, 80.8, 83.6, 94.1 (two overlapping peaks), 109.7, 116.9, 121.0, 126.0, 126.8 (two overlapping peaks), 128.4, 129.0 (two overlapping peaks), 130.4, 131.2, 132.1, 138.0, 142.3, 153.2, 153.2, 154.3, 162.6 (d, $J_{C-F} = 246.2$ Hz), 165.7, 170.3, 172.4, 200.5; ESIMS *m/z* 1250.1 [M + Na$^+$]; HRMS (MALDI) *m/z* calcd for $C_{49}H_{51}NO_{18}F_4Cl_6Na^+$ [M + Na$^+$]: 1250.1056, found: 1250.10657.

*4.2.8. General procedure for the preparation of **14a–f***

To a solution of **13a–f** (0.53 mmol) in methanol (20 mL) were added glacial acetic acid (3 mL) and zinc powder (1.14 g, 17.54 mmol). The resulting mixture was stirred at 50 °C for 0.5 h. The reaction mixture was filtered to remove the zinc and solid formed. Removal of the solvent by distillation gave a white solid. The obtained solid was then dissolved in 60 ml ethyl acetate, which was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The obtained residue was purified by silica gel flash chromatography column (CH_2Cl_2/MeOH 40/1) to give **14a–f** as a white solid.

*4.2.8.1. N-De-tert-butoxycarbonyl-N-[2-(1-fluoro-2-methyl)-propyloxycarbonyl]docetaxel (**14a**).* Yield 81%; mp 164–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (s, 3H, 17-CH_3), 1.24 (s, 3H, 16-CH_3), 1.35 (s, 6H, –O–C(CH_3)$_2$–), 1.76 (s, 3H, 19-CH_3), 1.85 (s, 3H, 18-CH_3), 2.23 (m, 2H, 14-CH_2), 2.38 (s, 3H, OAc), 1.85 and 2.58 (2m, 2H, 6-CH_2), 3.38 (d, 1H, $J = 5.1$ Hz, 2′-OH), 3.92 (d, 1H, $J = 7.3$ Hz, 3-CH), 4.20 and 4.31 (2d, 2H, $J = 8.6$ Hz, 20-CH_2), 4.23 (m, 1H, 7-CH), 4.23–4.45 (m, 2H, F–CH_2–), 4.63 (br s, 1H, 2′-CH), 4.94 (d, 1H, $J = 7.7$ Hz, 5-CH), 5.20 (s, 1H, 10-CH), 5.27 (br d, 1H, $J = 8.9$ Hz, 3′-CH), 5.60 (d, 1H, $J = 9.5$ Hz, –CONH–), 5.68 (d, 1H, $J = 7.1$ Hz, 2-CH), 6.24 (t, 1H, $J = 8.6$ Hz, 13-CH), 7.38 (m, 5H, 3′-Ph), 7.49 (t, 2H, $J = 7.5$ Hz, *m*-OBz), 7.61 (t, 1H, $J = 7.4$ Hz, *p*-OBz), 8.11 (d, 2H, $J = 7.5$ Hz, *o*-OBz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.9 (C-19), 14.3 (C-18), 20.7 (C-17), 22.3 (OAc), 22.5 (two overlapping peaks, –O–C(CH_3)$_2$–), 26.4 (C-16), 35.7 (C-14), 36.8 (C-6), 43.1 (C-15), 46.5 (C-3), 56.2 (C-3′), 57.7 (C-8), 71.9 (C-7), 72.4 (C-13), 73.6 (C-2′), 74.5 (C-10), 74.9 (C-2), 76.6 (C-20), 78.8 (C-1), 79.8 (d, $J_{C-F} = 16.5$ Hz, –O–C(CH_3)$_2$), 81.1 (C-4), 84.2 (C-5), 86.9 (d, $J_{C-F} = 175.0$ Hz, F–CH_2–), 126.7 (two overlapping peaks, *o*-Ph), 128.0 (*p*-Ph), 128.7 (two overlapping peaks, *m*-OBz), 128.8 (two overlapping peaks, *m*-Ph), 129.3 (C-1, OBz), 130.2 (two overlapping peaks, *o*-OBz), 133.7 (*p*-OBz), 136.0 (C-11), 138.2 (C-12), 138.4 (C-1, Ph), 154.9 (–NHCO–), 166.9 (C=O in OBz), 170.3 (OAc), 172.6 (C-1′), 211.2 (C-9); ESIMS *m/z* 848.4 [M + Na$^+$]; HRMS (ESI) *m/z* calcd for $C_{43}H_{53}FNO_{14}^+$ [M + H$^+$]: 826.3423, found: 826.3450.

*4.2.8.2. N-De-tert-butoxycarbonyl-N-[2-(1,1-difluoro-2-methyl)propyloxycarbonyl]docetaxel (**14b**).* Yield 61%; mp 166–168 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (s, 3H, 17-CH_3), 1.23 (s, 3H, 16-CH_3), 1.36 (s, 6H, –O–C(CH_3)$_2$–), 1.73 (s, 3H, 19-CH_3), 1.83 (s, 3H, 18-CH_3), 2.22 (m, 2H, 14-CH_2), 2.36 (s, 3H, OAc), 1.83 and 2.55 (2m, 2H, 6-CH_2), 3.39 (m, 1H, 2′-OH), 3.88 (d, 1H, $J = 6.9$ Hz, 3-CH), 4.18 and 4.31 (2d, 2H, $J = 8.1$ Hz, 20-CH_2), 4.24 (m, 1H, 7-CH), 4.65 (br s, 1H, 2′-CH), 4.94 (d, 1H, $J = 9.0$ Hz, 5-CH), 5.25 (s, H, 10-CH), 5.25 (m, 1H, 3′-CH), 5.65 (d, 1H, $J = 7.2$ Hz, 2-CH), 5.88 (d, 1H, $J = 7.5$ Hz, –CONH–), 5.97 (t, 1H, $J = 57.0$ Hz, F_2–CH–), 6.22 (t, 1H, $J = 8.1$ Hz, 13-CH), 7.33–7.40 (m, 5H, 3′-Ph), 7.49 (t, 2H, $J = 7.5$ Hz, *m*-OBz), 7.62 (t, 1H, $J = 7.5$ Hz, *p*-OBz), 8.10 (d, 2H, $J = 7.5$ Hz, *o*-OBz); ^{13}C NMR (CD_3COCD_3, 75 MHz): δ 10.3 (C-19), 14.3 (C-18), 20.0 (C-17), 21.3 (OAc), 23.0 (two overlapping peaks, –O–C(CH_3)$_2$–), 27.0 (C-16), 36.7 (C-14), 37.4 (C-6), 44.0 (C-15), 47.4 (C-3), 58.3 (C-3′), 58.5 (C-8), 72.0 (C-7), 72.2 (C-13), 74.9 (C-2′), 75.0 (C-10), 75.9 (C-2), 76.8 (C-20), 78.5 (C-1), 79.2 (d, $J_{C-F} = 27.1$ Hz, –O–C(CH_3)$_2$), 81.7

(C-4), 85.0 (C-5), 116.3 (t, $J_{C-F} = 244.1$ Hz, F_2–CH–), 128.0 (two overlapping peaks, *o*-Ph), 128.4 (*p*-Ph), 129.2 (two overlapping peaks, *m*-OBz), 129.4 (two overlapping peaks, *m*-Ph), 130.7 (two overlapping peaks, *o*-OBz), 131.2 (C-1, OBz), 134.1 (*p*-OBz), 137.5 (C-11), 138.4 (C-12), 140.1 (C-1, Ph), 155.2 (–NHCO–), 166.6 (C=O in OBz), 171.0 (OAc), 173.5 (C-1′), 211.3 (C-9); ESIMS *m/z* 866.4 [M + Na^+]; HRMS (ESI) *m/z* calcd for $C_{43}H_{51}F_2NO_{14}Na^+$ [M + Na^+]: 866.31653, found: 866.31698.

*4.2.8.3. N-De-tert-butoxycarbonyl-N-[2-(1,1,1-trifluoro-2-methyl)propyloxycarbonyl]docetaxel (**14c**).* Yield 85%; mp 178–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (s, 3H, 17-CH_3), 1.25 (s, 3H, 16-CH_3), 1.53 (s, 3H, 1 CH_3 of –O–$C(CH_3)_2$–), 1.57 (s, 3H, 1CH_3 of –O–$C(CH_3)_2$–), 1.75 (s, 3H, 19-CH_3), 1.82 (s, 3H, 18-CH_3), 2.23 (m, 2H, 14-CH_2), 2.36 (s, 3H, OAc), 1.82 and 2.59 (2m, 2H, 6-CH_2), 3.45 (br s, 1H, 2′-OH), 3.90 (d, 1H, $J = 6.3$ Hz, 3-CH), 4.18 and 4.32 (2d, 2H, $J = 8.1$ Hz, 20-CH_2), 4.24 (m, 1H, 7-CH), 4.24 (br s, 1H, 10-OH), 4.62 (br s, 1H, 2′-CH), 4.94 (d, 1H, $J = 8.1$ Hz, 5-CH), 5.21 (s, 1H, 10-CH), 5.26 (br s, 1H, 3′-CH), 5.67 (d, 1H, $J = 6.9$ Hz, 2-CH), 5.78 (d, 1H, $J = 9.0$ Hz, –CONH–), 6.21 (t, 1H, $J = 8.7$ Hz, 13-CH), 7.34–7.45 (m, 5H, 3′-Ph), 7.50 (t, 2H, $J = 7.5$ Hz, *m*-OBz), 7.63 (t, 1H, $J = 7.5$ Hz, *p*-OBz), 8.10 (d, 2H, $J = 7.5$ Hz, *m*-OBz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.8 (C-19), 14.3 (C-18), 19.3 (–O–$C(CH_3)_2$–), 19.6 (–O–$C(CH_3)_2$–), 20.5 (C-17), 22.5 (OAc), 26.5 (C-16), 35.6 (C-14), 36.9 (C-6), 43.1 (C-15), 46.5 (C-3), 56.4 (C-3′), 57.5 (C-8), 71.9 (C-7), 72.4 (C-13), 73.5 (C-2′), 74.5 (C-10), 74.8 (C-2), 76.6 (C-20), 77.2 (–O–$C(CH_3)_2$), 78.8 (C-1), 81.2 (C-4), 84.2 (C-5), 126.0 (F_3–C–), 126.7 (two overlapping peaks, *o*-Ph), 128.3 (*p*-Ph), 128.7 (two overlapping peaks, *m*-OBz), 128.9 (two overlapping peaks, *m*-Ph), 129.2 (C-1, OBz), 130.1 (two overlapping peaks, *o*-OBz), 133.7 (*p*-OBz), 136.1 (C-11), 137.8 (C-12), 138.2 (C-1, Ph), 153.4 (–NHCO–), 167.0 (C=O in OBz), 170.3 (OAc), 172.3 (C-1′), 211.2 (C-9); ESIMS *m/z* 884.4 [M + Na^+]; HRMS (MALDI) *m/z* calcd for $C_{43}H_{50}NO_{14}F_3Na^+$ [M + Na^+]: 884.3085, found: 884.30756.

*4.2.8.4. N-De-tert-butoxycarbonyl-N-[2-(1-fluoro-2-methyl)-propyloxycarbonyl]-2-debenzoyl-2-(m-fluorobenzoyl)docetaxel (**14d**).* Yield 70%; mp 152–155 °C; ^{1}H NMR (400 MHz, CD_3COCD_3): δ 1.13 (s, 3H, 17-CH_3), 1.19 (s, 3H, 16-CH_3), 1.36 (s, 6H, –O–$C(CH_3)_2$–), 1.71 (s, 3H, 19-CH_3), 1.89 (s, 3H, 18-CH_3), 2.21 (m, 2H, 14-CH_2), 2.38 (s, 3H, OAc), 1.83 and 2.45 (2m, 2H, 6-CH_2), 3.91 (1H, d, $J = 7.3$ Hz, 3-CH), 4.16 (s, 2H, 20-CH_2), 4.27 (m, 1H, 7-CH), 4.35–4.48 (m, 2H, F–CH_2–), 4.62 (m, 1H, 2′-CH), 4.97 (d, 1H, $J = 9.7$ Hz, 5-CH), 5.18 (br s, 1H, 3′-CH), 5.24 (s, 1H, 10-CH), 5.59 (s, 1H, –CONH–), 5.65 (d, 1H, $J = 7.2$ Hz, 2-CH), 6.16 (t, 1H, $J = 9.0$ Hz, 13-CH), 7.26 (t, 1H, $J = 7.3$ Hz, *p*-Ph), 7.39 (t, 2H, $J = 7.5$ Hz, *o*-Ph), 7.46 (m, 2H, *m*-Ph), 7.46 (m, 1H, 5-CH in OBz), 7.63 (m, 1H, 4-CH in OBz), 7.77 (d, 1H, $J = 9.5$ Hz, 2-CH in OBz), 7.93 (d, 1H, $J = 7.7$ Hz, 6-CH in OBz); ^{13}C NMR (CD_3COCD_3, 100 MHz): δ 10.7 (C-19), 14.7 (C-18), 19.5 (C-17), 21.7 (OAc), 22.9 (–O–$C(CH_3)_2$–), 23.3 (–O–$C(CH_3)_2$–), 27.4 (C-16), 37.1 (C-14), 37.8 (C-6), 44.4 (C-15), 47.7 (C-3), 58.5 (C-3′), 58.9 (C-8), 72.3 (C-7), 72.6 (C-13), 75.4 (C-2′), 75.5 (C-10), 76.9 (C-2), 77.2 (C-20), 78.9 (C-1), 80.8 (d, $J_{C-F} = 16.5$ Hz, –O–$C(CH_3)_2$), 82.1 (C-4), 85.4 (C-5), 88.2 (d, $J_{C-F} = 173.7$ Hz, F–CH_2–), 117.6 (C-2, OBz), 121.4 (C-4, OBz), 127.2 (C-6, OBz), 128.4 (two overlapping peaks, *o*-Ph), 128.8 (*p*-Ph), 129.6 (two overlapping peaks, *m*-Ph), 131.9 (C-5, OBz), 133.9 (C-1, OBz), 137.8 (C-11), 138.9 (C-12), 140.7 (C-1, Ph), 156.3 (–NHCO–), 163.7 (d, $J_{C-F} = 243.9$ Hz, C-3, OBz), 165.9 (C=O in OBz), 171.4 (OAc), 174.0 (C-1′), 211.6 (C-9); ESIMS *m/z* 848.4 [M + H^+], 866.3 [M + Na^+]; HRMS (MALDI) *m/z* calcd for $C_{43}H_{51}NO_{14}F_2Na^+$ [M + Na^+]: 866.3184, found: 866.31699.

*4.2.8.5. N-De-tert-butoxycarbonyl-N-[2-(1,1-difluoro-2-methyl)propyloxycarbonyl]-2-debenzoyl-2-(m-fluorobenzoyl)docetaxel (**14e**).* Yield 73%; mp 156–158 °C; ^{1}H NMR (400 MHz, CD_3COCD_3): δ 1.13 (s, 3H, 17-CH_3), 1.19 (s, 3H, 16-CH_3), 1.35 (s, 6H, –O–$C(CH_3)_2$–), 1.71 (s, 3H, 19-CH_3), 1.89 (s, 3H, 18-CH_3), 2.21 (m, 2H, 14-CH_2), 2.37 (s, 3H, OAc), 1.83 and 2.46 (2m, 2H, 6-CH_2), 3.29 (s, 1H, 2′-OH), 3.91 (d, 1H, $J = 7.1$ Hz, 3-CH), 4.16 (s, 2H, 20-CH_2), 4.27 (m, 1H, 7-CH), 4.63 (d, 1H, $J = 4.2$ Hz, 2′-CH), 4.97 (d, 1H, $J = 8.5$ Hz, 5-CH), 5.18 (m, 1H, 3′-CH), 5.24 (s, 1H, 10-CH), 5.64 (d, 1H, $J = 7.2$ Hz, 2-CH), 6.13 (t, 1H, $J = 57.0$ Hz, F_2–CH–), 6.15 (t, 1H, $J = 8.9$ Hz, 13-CH), 7.27 (t, 1H, $J = 7.3$ Hz, *p*-Ph), 7.39 (t, 2H, $J = 7.6$ Hz, *o*-Ph), 7.46 (m, 2H, *m*-Ph), 7.46 (m, 1H, 5-CH in OBz), 7.63 (m, 1H, 4-CH in OBz), 7.76 (d, 1H, $J = 9.3$ Hz, 2-CH in OBz), 7.93 (d, 1H, $J = 7.7$ Hz, 6-CH in OBz); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 10.7 (C-19), 14.7 (C-18), 20.4 (C-17), 20.5 (OAc), 21.7 (–O–$C(CH_3)_2$–), 23.3 (–O–$C(CH_3)_2$–), 27.3 (C-16), 37.1 (C-14), 37.8 (C-6), 44.4 (C-15), 47.7 (C-3), 58.7 (C-3′), 58.9 (C-8), 72.3 (C-7), 72.6 (C-13), 75.3 (C-2′), 75.4 (C-10), 76.9 (C-2), 77.1 (C-20), 78.9 (C-1), 79.9 (t, $J_{C-F} = 22.9$ Hz, –O–$C(CH_3)_2$), 82.1 (C-4), 85.4 (C-5), 116.7 (t, $J_{C-F} = 244.5$ Hz, F_2–CH–), 117.6 (C-2, OBz), 121.4 (C-4, OBz), 127.2 (C-6, OBz), 128.4 (two overlapping peaks, *o*-Ph), 128.9 (*p*-Ph), 129.6 (two overlapping peaks, *m*-Ph), 131.9 (C-5, OBz), 133.9 (C-1, OBz), 137.5 (C-11), 138.9 (C-12), 140.4 (C-1, Ph), 155.8 (–NHCO–), 163.7 (d, $J_{C-F} = 243.7$ Hz, C-3, OBz), 165.9 (C=O in OBz), 171.4 (OAc), 173.9 (C-1′), 211.6 (C-9); ESIMS *m/z* 884.3 [M + Na^+]; HRMS (MALDI) *m/z* calcd for $C_{43}H_{50}NO_{14}F_3Na^+$ [M + Na^+]: 884.3092, found: 884.30756.

*4.2.8.6. N-De-tert-butoxycarbonyl-N-[2-(1,1,1-trifluoro-2-methyl)propyloxycarbonyl]-2-debenzoyl-2-(m-fluorobenzoyl)-docetaxel (**14f**).* Yield 74%; mp 161–164 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (s, 3H, 17-CH_3), 1.23 (s, 3H, 16-CH_3), 1.54 (s, 3H, 1CH_3 of –O–$C(CH_3)_2$–), 1.57 (s, 3H, 1CH_3 of –O–$C(CH_3)_2$–), 1.75 (s, 3H, 19-CH_3), 1.82 (s, 3H, 18-CH_3), 2.21 (m, 2H, 14-CH_2), 2.34 (s, 3H, OAc), 1.82 and 2.59 (2m, 2H, 6-CH_2), 3.42 (br s, 1H, 2′-OH), 3.90 (d,

1H, $J = 6.9$ Hz, 3-CH), 4.16 and 4.31 (2d, 2H, $J = 8.7$ Hz, 20-CH_2), 4.23 (m, 1H, 7-CH), 4.23 (br s, 1H, 10-OH), 4.61 (br s, 1H, 2′-CH), 4.95 (d, 1H, $J = 8.1$ Hz, 5-CH), 5.21 (s, 1H, 10-CH), 5.23 (m, 1H, 3′-CH), 5.64 (d, 1H, $J = 7.2$ Hz, 2-CH), 5.75 (d, 1H, $J = 9.3$ Hz, −CONH−), 6.20 (t, 1H, $J = 8.5$ Hz, 13-CH), 7.31−7.46 (m, 5H, 3′-Ph), 7.46 (m, 1H, 5-CH in OBz), 7.50 (m, 1H, 4-CH in OBz), 7.78 (d, 1H, $J = 9.0$ Hz, 2-CH in OBz), 7.90 (d, 1H, $J = 7.8$ Hz, 6-CH in OBz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.8 (C-19), 14.3 (C-18), 19.3 (−O−$C(CH_3)_2$−), 19.5 (C-17), 20.4 (−O−$C(CH_3)_2$−), 22.4 (OAc), 26.4 (C-16), 35.6 (C-14), 37.0 (C-6), 43.0 (C-15), 46.5 (C-3), 56.4 (C-3′), 57.6 (C-8), 72.0 (C-7), 72.3 (C-13), 73.5 (C-2′), 74.5 (C-10), 75.2 (C-2), 76.5 (C-20), 78.9 (C-1), 80.0 (q, −O−$C(CH_3)_2$), 81.1 (C-4), 84.1 (C-5), 116.9 (C-2, OBz), 120.8 (C-4, OBz), 124.8 (q, $J_{C-F} = 280.4$ Hz, F_3−C−), 125.9 (C-6, OBz), 126.8 (two overlapping peaks, *o*-Ph), 128.3 (*p*-Ph), 128.9 (two overlapping peaks, *m*-Ph), 130.4 (C-5, OBz), 131.4 (C-1, OBz), 136.0 (C-11), 137.8 (C-12), 138.2 (C-1, Ph), 153.4 (−NHCO−), 162.6 (d, $J_{C-F} = 246.1$ Hz, C-3, OBz), 165.8 (C═O in OBz), 170.2 (OAc), 172.3 (C-1′), 211.1 (C-9); ESIMS *m/z* 902.3 [$M + Na^+$]; HRMS (MALDI) *m/z* calcd for $C_{43}H_{49}NO_{14}F_4Na^+$ [$M + Na^+$]: 902.3000, found: 902.29814.

4.3. In vitro cytotoxicity

Potential cytotoxicity was evaluated against human ovarian cell line SK-OV-3. The compounds were pre-dissolved in DMSO and diluted with cell culture medium to at least five required concentrations. The content of DMSO in the final concentrations did not exceed 0.1%. At this content, DMSO was found to be nontoxic to the cells tested. All cells were cultured in RPMI 1640 supplemented with 10% fetal bovine serum, at 37 °C in a humidified atmosphere of 5% CO_2. The cells were seeded at a density of $0.4–1.0 \times 10^4$ cells per well in 96-well microplates. After 24 h, the cells were treated with 10 times diluted concentration test compound. The cells were exposed to drugs for 72 h. Cell growth was assayed using sulforhodamine B (SRB). The optical density (OD) was read at 520 nm. All cytotoxicity tests were performed 3 times in quadruplicate. The IC_{50} values were calculated from curves constructed by plotting cell survival (%) versus compound concentration (in nM).

4.4. Antitumor activity

A549 human NSCLC cells were injected subcutaneous onto BALB/cA-nude mice (18 ± 3 g body weight, 6 animals per group). After 2−3 passages, A549 human NSCLC tumors were grafted subcutaneously onto the right oxter of the nude mice. The volume of tumor masses was measured with calipers. When the tumor was palpable (about 100−300 mm^3), the nude mice were divided randomly into non-treated group, positive control (docetaxel) group and treated group. The dosage used in this study is shown in Table 2. The treatment started at day. All the drugs were administered intravenously. The tumor volumes and mice body weights were measured 2−3 times each week. Data were expressed as T/C (%), where the T/C value has been calculated as follows: (mean tumor volume of the treated group/mean tumor volume of the control group) × 100.

4.5. Acute toxicity study in mice

Healthy Kunming mice of both sexes, weighing 18−22 g, were divided into 7 groups of 10 animals matched for weight and size. The fluorinated docetaxel derivative (**14a**) was i.p. administered at the dose of 92.0, 115.0, 143.0, 179.0, 224.0, 280.0, 350.0 mg/kg body weight. Behavior and changes in the weight of mice were monitored and the death was recorded within 14 days. The LD_{50} values were calculated using Bliss method.

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