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Syntheses and structure–activity relationships of novel 3′-difluoromethyl and 3′-trifluoromethyl-taxoids

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ABSTRACT

A series of novel 3′-difluoromethyl-taxoids and 3′-trifluoromethyl-taxoids with modifications at the C2 and C10 positions were synthesized and evaluated for their *in vitro* cytotoxicities against human breast carcinoma (MCF7-S, MCF7-R, LCC6-WT, LCC6-MDR), non-small cell lung carcinoma (H460) and colon adenocarcinoma (HT-29) cell lines. These second-generation fluoro-taxoids exhibited several times to more than 20 times better potency than paclitaxel against drug-sensitive cancer cell lines, MCF7-S, LCC6-WT, H460, and HT-29. These fluoro-taxoids also possess two orders of magnitude higher potency than paclitaxel against drug-resistant cancer cell lines, MCF7-R and LCC6-MDR. Structure–activity relationship study shows the importance of the C10 modification for increasing the activity against multidrug-resistant cancer cell lines. Effects of the C2-benzoate modifications on the potency in the 3′-difluoromethyl-taxoid series are very clear (i.e., $F < MeO < Cl < N_3$), while those in the 3′-trifluoromethyl-taxoid series are less obvious. Also, different trends in the sensitivity to the C2-substitution are observed between drug-sensitive cell lines and drug-resistant cancer cell lines that overexpress efflux pumps.

1. Introduction

The importance of fluorine in medicinal chemistry has been demonstrated by a large number of fluorinated compounds approved by the FDA for medical use [1,2]. It appears that fluorine has become the second "favorite heteroatom", after nitrogen in drug design [3]. Higher metabolic stability, often increased binding to target molecules, increased lipophilicity and membrane permeability, are some of the properties associated with the replacement of a C–H or C–O bond with a C–F bond in medicinally active compounds [4].

Paclitaxel (Taxol®) and its semi-synthetic analogue docetaxel are two of the most important chemotherapeutic drugs, currently used for the treatment of advanced ovarian cancer, metastatic breast cancer, melanoma, non-small cell lung cancer and Karposi's sarcoma [5,6]. More recently, these drugs have been used for the treatment of neck, prostate and cervical cancers [5,6]. Although paclitaxel and docetaxel possess potent antitumor activity, chemotherapy with these drugs encounters many undesirable side effects as well as multidrug-resistance (MDR) caused by overexpression of ABC efflux pumps, e.g., P-glycoprotein [5,7,8]. Therefore, it is important to develop new taxoid anticancer drugs as well as efficacious drug delivery systems with fewer side effects, superior pharmacological properties, and improved activity against various classes of tumors, especially against drug-resistant cancers.

Because of the aforementioned advantages of introducing fluorine into medicinally active molecules, we have been investigating the effects of strategic incorporation of fluorine(s) into paclitaxel and docetaxel molecules on the cytotoxicity and the blockage of known metabolic pathways through design, synthesis and structure–activity relationship (SAR) studies of novel "fluoro-taxoids" [9–12]. Along this line, we reported the synthesis and biological evaluation of a series of 3′-difluoromethyl- and 3′-trifluoromethyl-taxoids [11–14], which exhibited substantially better *in vitro* potency than paclitaxel and docetaxel against several human cancer cell lines, i.e., ovarian (A121), colon (HT-29), non-small cell lung (A549), breast (MCF-7, LCC6-WT) and drug-resistant breast (MCF7-R, LCC6-MDR) cancer cell lines. We describe here the synthesis and biological activity of a series of novel C2- and C10-modified 3′-difluoromethyl- and trifluoromethyl-taxoids ("second-generation fluoro-taxoids").

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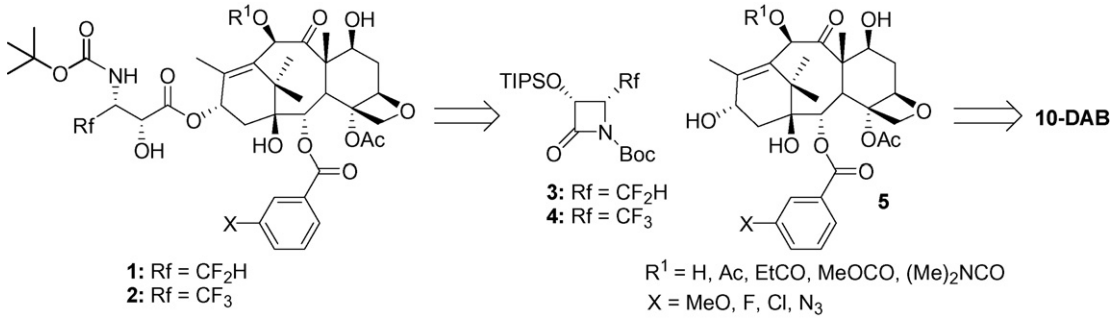


Scheme 1.

2. Results and discussion

2.1. Synthesis of second-generation 3′-difluoromethyl- and 3′-trifluoromethyl-taxoids

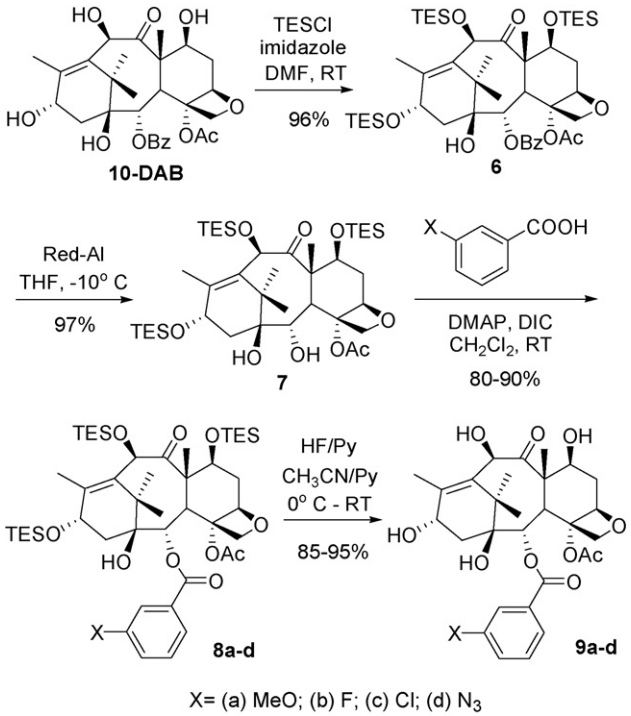
A series of novel second-generation 3′-difluoromethyl-taxoids **1** and 3′-trifluoromethyl-taxoids **2** were synthesized from 4-Rf-β-lactams **3**/**4** and modified baccatins **5** using the highly efficient Ojima-Holton coupling protocol based on the β-lactam synthon method (Scheme 1) [14–19].

The C2,10-modified baccatins **5** were synthesized starting from commercially available natural product, 10-deacetylbaccatin III (10-DAB), following the procedures previously reported by us with some modifications [20]. First, hydroxyl groups at the C7, C10, and C13 positions were protected with chlorotriethylsilane (TESCl) using imidazole as the base, yielding 7,10,13-triTES-10-deacetyl-baccatin (**6**) [21]. Next, the benzoyl group at the C2 position of **6** was reductively removed with Red-Al in THF at −10 °C to give 2-debenzoyl-7,10,13-triTES-DAB (**7**) in 97% yield [22]. Esterification of **7** with different *meta*-substituted benzoic acids (substituents: MeO, F, Cl and N_3) using DIC/DMAP afforded the corresponding 2-(3-substituted benzoyl)-triTES-DAB (**8a–d**) in good to excellent yields [20]. Then, the deprotection of the TES groups at the C7, C10 and C13 positions of **8a–d** with HF/pyridine gave the desired C2-modified baccatins **9a–d** in high yields (Scheme 2) [20].

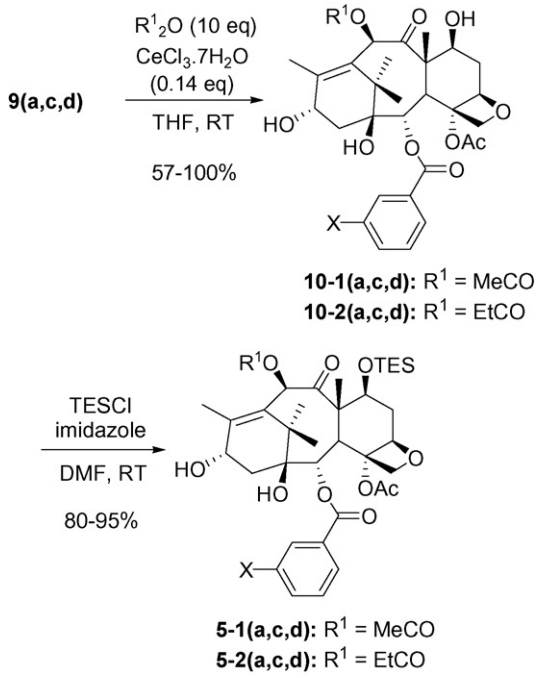
C2-Modified baccatins, **9a**, **9c** and **9d**, were reacted with acetic or propanoic anhydrides in the presence of cerium chloride [23], which gave the corresponding 10-acyl baccatins, **10-1(a,c,d)** and **10-2(a,c,d)**, exclusively in good to excellent yields. Protection the C7-hydroxyl group with TESCl/imidazole afforded the coupling-ready 7-TES-2,10-modified-baccatins, **5-1(a,c,d)** and **5-2(a,c,d)**, in high yields (Scheme 3).

Since the C10-acylation method mentioned above only worked when acid anhydrides were used, we needed to use another acylation method for employing acid chlorides and a silyl chloride. Thus, the C7-hydroxyl group of **9a–d** was protected with TESCl/imidazole first to afford baccatins **11a–d** in high yields. Acylation of the C10 hydroxyl group of **11a–d** with *N*,*N*-dimethylcarbamoyl chloride, methyl chloroformate and TES-Cl gave the coupling-ready 7-TES-2,10-modified-baccatins, **5-1b**, **5-2b**, **5-3(a–d)**, **5-4(a–d)** and **5-5(a–d)**, in high to excellent yields (Scheme 4).

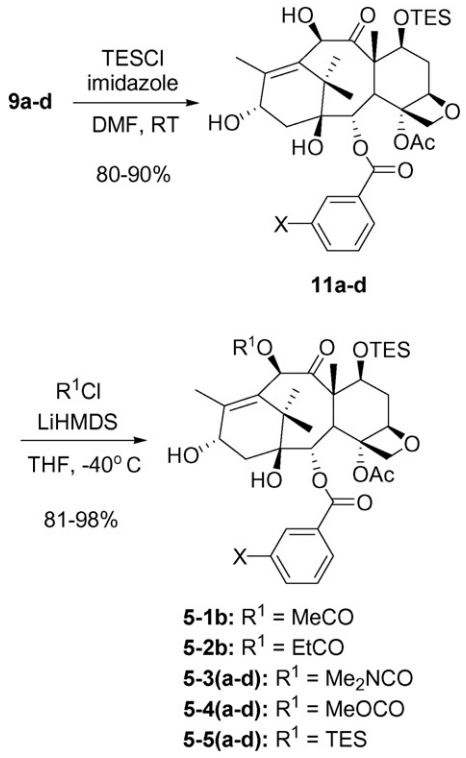
Next, (3*R*,4*R*)-1-*t*-Boc-3-TIPSO-4-difluoromethylazetidine (**3**) and (3*R*,4*R*)-1-*t*-Boc-3-TIPSO-4-trifluoromethylazetidine (**4**), the coupling partners of these 7-TES-2,10-modified-baccatins **5**, were



Scheme 2.



Scheme 3.



Scheme 4.

prepared using the methods previously reported by us [19], as shown in Schemes 5 and 6, respectively.

Novel fluoro-taxoids (**1a**–**p** and **2a**–**p**) were synthesized in good to excellent yields through the Ojima-Holton coupling of β-lactams, **3** and **4**, with 2,10-modified-baccatins **5** using LiHMDS as a base at −40 °C in THF, followed by deprotection of silyl groups by HF/pyridine (Scheme 7).

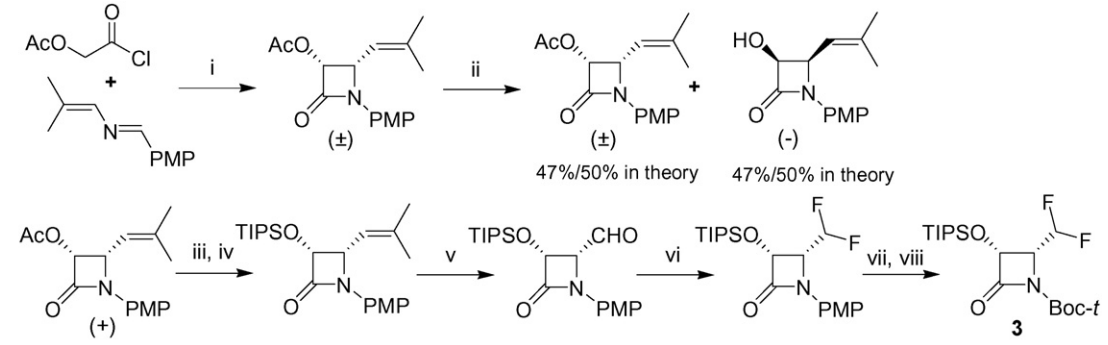
2.2. Biological activities of second-generation 3′-difluoromethyl- and 3′-trifluoromethyl-taxoids

The second-generation fluoro-taxoids **1a**–**p** and **2a**–**q** were evaluated for their *in vitro* cytotoxicity against several human cancer cell lines, i.e., breast carcinoma cell lines (MCF7-S and LCC6-WT) and their corresponding drug-resistant cell lines (MCF7-R and LCC6-MDR) as well as non-small cell lung carcinoma (H460) and colon adenocarcinoma (HT-29) cell lines. Results are summarized in Tables 1 and 2. The IC_{50} values were determined through 72 h exposure of the fluoro-taxoids to the cancer cells by means of the methods developed by Skehan et al. [24].

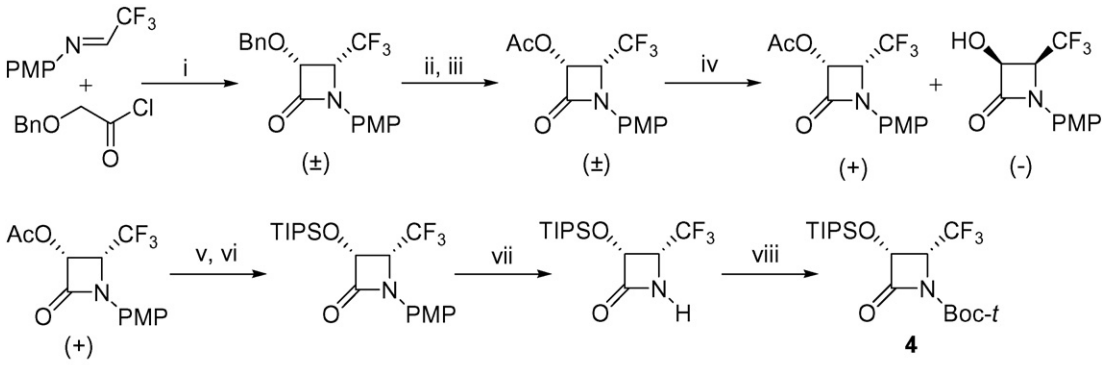
As Tables 1 and 2 show, 3′-difluoromethyl-taxoids **1** and 3′-trifluoromethyl-taxoids **2** possess substantially higher potency than those of paclitaxel and docetaxel with IC_{50} in the sub-nanomolar range against drug-sensitive cancer cell lines, i.e., MCF7-S, LCC6-WT, H460, and HT-29 (except for **1d** against LCC6-WT, **1p** against MCF7-S, and **2m**–**p** against LCC6-WT). Even more impressive are the cytotoxicity of fluoro-taxoids **1** and **2** against multidrug-resistant cancer cell lines, i.e., MCF7-R and LCC6-MDR. These second-generation fluoro-taxoids exhibit single-digit nanomolar IC_{50} values (except for **1d**, **1e** and **1g** against LCC6-MDR, **1h** for both cell lines, and **2q** against LCC6-MDR), which are two orders of magnitude more potent than paclitaxel in average. Thus, it is clear that these second-generation fluoro-taxoids possess the ability to effectively modulate multidrug-resistance caused by overexpression of P-glycoprotein and other efflux pumps. Fluoro-taxoids **1** and **2** exhibit, in general, comparable cytotoxicity against all cancer cell lines examined. However, the potency of 3′-difluoromethyl-taxoids **1** against MCF7-S and LCC6-WT is slightly higher and more uniform than that of 3′-trifluoromethyl-taxoids **2**, in average, with different substitution patterns. On the contrary, for multidrug-resistant cell lines, MCF7-R and LCC6-MDR, fluoro-taxoids **2** show more uniform activity than fluoro-taxoids **1**.

For fluoro-taxoids **1**, cytotoxicity against multidrug-resistant cell lines, MCF7-R and LCC6-MDR, depends on the nature of *meta* substituents of the C2-benzoate moiety, i.e., the potency increases in the order: F < MeO < Cl < N_3. In contrast, no clear trend is observed for fluoro-taxoids **2** against these multidrug-resistant cell lines. However, the introduction of 3-azidobenzoyl group to 3′-trifluoromethyl-taxoids (**2m**–**q**) clearly decreases the potency against LCC6-WT cell line. It should be noted that 10-acyl groups play an important role in increasing the potency against multi-drug-resistant cell lines (**2m**–**p** vs. **2q**), while the potency against drug-sensitive cell lines is independent of this substitution at the C10 position.

Among these second-generation fluoro-taxoids examined, fluoro-taxoid **1n** (R^1 = *n*-propanoyl; X = N_3) appears to be the most potent compound with the resistance factor (*R*/*S* ratio) of only 2.9–3.0 against two sets of drug-sensitive and drug-resistant human breast cancer cell lines. Further preclinical studies on these novel fluoro-taxoids are actively underway in these laboratories.



Scheme 5.

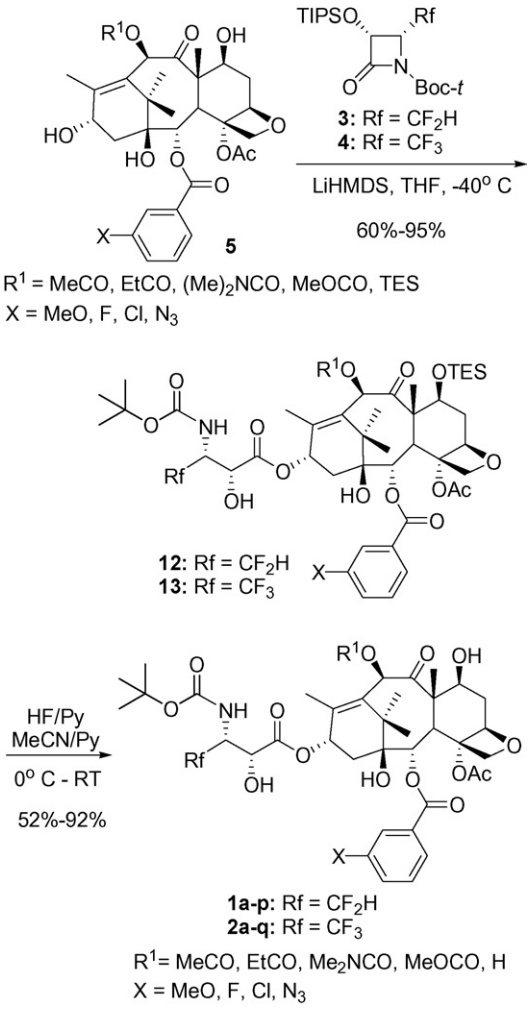


Scheme 6.

3. Experimental

3.1. General method

^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian 300, 400 or 500 MHz NMR spectrometer in $CDCl_3$. Tetramethylsilane was used as the internal standard for ^1H and ^{13}C NMR spectra, while $CFCl_3$ as the standard for ^{19}F NMR spectra. Melting points were measured on a Thomas Hoover Capillary melting point apparatus. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. TLC was performed on Merck DC-alufolien with Kieselgel 60F-254 and column chromatography was carried out on silica gel 60 (Merck; 230–400 mesh ASTM). Chiral HPLC analysis for the determination of enantiomeric purity was carried out with a Waters HPLC assembly consisting of a Waters M45 solvent delivery system, a Waters Model 680 gradient controller, and a Water M440 detector (at 254 nm) using a DAICEL-CHIRACEL OD chiral column (25 cm × 0.46 cm i.d.), employing hexan/2-propanol (99.5/0.5, v/v) as the solvent system with a flow rate of 1.0 mL/min. High resolution mass spectra were obtained at the Mass Spectrometry Laboratory, University of Illinois at Urbana-Champaign, Urbana, IL.



Scheme 7.

3.2. Materials

The chemicals were purchased from Aldrich Co. and Sigma and purified before use by standard methods. Tetrahydrofuran was freshly distilled under nitrogen from sodium metal and benzophenone. Dichloromethane was distilled immediately prior to use under nitrogen from calcium hydride. (3*R*,4*R*)-1-*tert*-Butoxycarbonyl-3-triisopropylsiloxy-4-difluoromethylazetidin-2-one (**3**) [19], (3*R*,4*R*)-1-*tert*-butoxycarbonyl-3-triisopropylsiloxy-4-trifluoromethylazetidin-2-one (**4**) [19], 2-debenzoyl-2-(3-chlorobenzoyl)-7-triethylsilyl-10-deacetyl-10-propanoylbaccatin III (**5-2c**) [19], and 2-debenzoyl-2-(3-azidobenzoyl)-7-triethylsilyl-10-deacetyl-10-propanoylbaccatin III (**5-2d**) [19], 2-debenzoyl-2-(3-chlorobenzoyl)-10-propanoyl-3′-dephenyl-3′-difluoromethyldocetaxel (**1j**) [19], 2-debenzoyl-2-(3-azidobenzoyl)-10-propanoyl-3′-dephenyl-3′-trifluoromethyldocetaxel (**2n**) [19] were prepared by the previously reported methods.

3.3. 2-Debenzoyl-2-(3-methoxybenzoyl)-10-acetyl-3′-dephenyl-3′-difluoromethyldocetaxel (1a)

A typical experimental procedure is described for the synthesis of **1a** as follows: 2-(3-methoxybenzoyl)-7-TES-10-propanoylbaccatin III (**5-1a**, 19 mg, 0.031 mmol) and (3*R*,4*R*)-difluoromethyl-β-lactam **3** (30 mg, 0.076 mmol) were dissolved in THF (1.0 mL). The mixture was cooled to −40 °C and LiHMDS (1*M* THF solution, 62 μL) was added. The reaction mixture was stirred for 2 h, and quenched with 1.0 mL of saturated aqueous NH_4Cl, the aqueous

Table 1
In vitro cytotoxicity (IC_{50}, nM)[a] of 3′-difluoromethyl-taxoids (**1a**–**p**)

Taxoid	R^1	X	MCF7-S[b] (breast)	MCF7-R[c] (breast)	*R*/*S*[d]	LCC6-WT[b] (breast)	LCC6-MDR[e] (breast)	*R*/*S*[d]	H460[f] (lung)	HT-29[g] (colon)
Paclitaxel			1.7	300	176	3.1	346	112	4.9	3.6
Docetaxel			1.0	215	215	–	–	–	–	1.0
1a	Ac	MeO	0.34	4.16	12	0.26	5.57	21	0.38	0.52
1b	Et–CO	MeO	1.14	4.05	3.5	0.69	4.92	7.1	0.40	0.59
1c	Me_2N–CO	MeO	0.45	4.51	10	0.69	7.06	10	0.40	0.43
1d	MeO–CO	MeO	0.81	6.59	8.1	1.03	10.2	9.9	0.30	0.44
1e	Ac	F	0.44	5.33	13	0.52	10.0	19	0.20	0.35
1f	Et–CO	F	0.53	7.24	14	0.88	4.63	3.5	0.41	0.86
1g	Me_2N–CO	F	0.52	8.13	16	0.69	10.6	15	0.20	0.35
1h	MeO–CO	F	0.59	11.38	19	0.86	12.6	15	0.30	0.43
1i	Ac	Cl	0.40	6.48	16	0.31	5.80	19	0.49	1.94
1j	Et–CO	Cl	0.44	5.20	12	0.52	4.71	9.1	0.30	0.43
1k	Me_2N–CO	Cl	0.31	2.96	9.5	0.21	3.87	18	0.36	0.58
1l	MeO–CO	Cl	0.26	2.08	8.0	0.13	1.82	14	0.25	0.29
1m	Ac	N_3	0.32	1.68	5.3	0.22	1.57	7.1	0.48	0.57
1n	Et–CO	N_3	0.32	0.96	3.0	0.39	1.15	2.9	0.27	0.37
1o	Me_2N–CO	N_3	0.37	1.44	3.9	0.29	1.69	5.8	0.52	0.40
1p	MeO–CO	N_3	1.69	2.56	1.5	0.26	2.06	7.9	0.23	0.36

[a] The concentration of compound inhibits 50% of the growth of a cancer cell line after 72 h drug exposure.
[b] Human breast carcinona.
[c] Multidrug-resistant human breast carcinoma.
[d] *R*/*S* = drug-resistance factor = IC_{50} (drug-resistant cell line)/IC_{50} (drug-sensitive cell line).
[e] Multidrug resistant human breast carcinoma.
[f] Human non-small cell lung carcinoma.
[g] Human caucasian colon adenocarcinoma.

layer was extracted with ethyl acetate, and the combined organic phases were washed with brine and dried over anhydrous $MgSO_4$. The crude product was purified on silica gel column (hexanes/EtOAc = 1/1) to give the desired coupling product, 2-debenzoyl-2-(3-methoxybenzoyl)-7-triethylsilyl-10-propanoyl-2′-triisopropylsilyl-3′-dephenyl-3′-difluoromethyldocetaxel (**12a**, 29.6 mg). To a solution of 7-TES-2′-TIPS-fluoro-taxoid **12a** (29.6 mg) in 2.0 mL of a 1:1 mixture of pyridine/CH_3CN was added 0.10 mL of HF-pyridine at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 26 h. The reaction was then quenched with 10 mL saturated aqueous $NaHCO_3$, extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous $CuSO_4$ and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate = 1/1) to afford 15.2 mg (44% yield for two steps) of desired fluoro-taxoid **1a** as a white solid: mp 181 °C; $[\alpha]_D^{20}$-79 (*c* = 0.76, $CHCl_3$): ^1H NMR ($CDCl_3$, 400 MHz): δ 1.14 (3H, s, H-17-CH_3), 1.25 (3H, s, H-16-CH_3), 1.29 (9H, s, Boc), 1.67 (3H, s, H-19-CH_3), 1.69 (1H, bs, OH), 1.89 (4H, m, H-18-CH_3, H-6b), 2.24 (4H, m,

Table 2
In vitro cytotoxicity (IC_{50} nM)[a] of 3′-trifluoromethyl-taxoids (**2a**–**q**)

Taxoid	R^1	X	MCF7-S[b] (breast)	MCF7-R[c] (breast)	*R*/*S*[d]	LCC6-WT[b] (breast)	LCC6-MDR[e] (breast)	*R*/*S*[d]	H460[f] (lung)	HT-29[g] (colon)
Paclitaxel			1.7	300	176	3.1	346	112	4.9	3.6
Docetaxel			1.0	215	215	–	–	–	–	1.0
2a	Ac	MeO	0.32	8.8	28	0.33	3.99	12	0.38	0.69
2b	Et–CO	MeO	0.19	2.16	11	0.45	4.24	9	0.41	0.54
2c	Me_2NCO	MeO	0.57	1.84	3.2	0.28	4.48	16	0.35	0.68
2d	MeOCO	MeO	0.17	2.88	17	0.27	3.99	15	0.38	0.53
2e	Ac	F	0.45	5.58	13	0.38	5.93	16	0.49	1.11
2f	Et–CO	F	0.68	3.78	5.6	0.82	4.27	5.2	0.59	1.15
2g	Me_2NCO	F	0.32	2.64	8.3	0.32	5.57	17	0.5	0.76
2h	MeOCO	F	0.31	4.88	16	0.39	5.81	15	0.61	0.85
2i	Ac	Cl	0.40	5.04	13	0.22	4.96	23	0.5	0.85
2j	Et–CO	Cl	0.34	3.28	9.6	0.39	2.54	6.5	0.63	1.11
2k	Me_2NCO	Cl	0.12	1.02	8.5	0.27	2.55	9.4	0.42	0.45
2l	MeOCO	Cl	0.65	4.72	7.3	0.29	5.08	18	0.43	0.68
2m	Ac	N_3	0.47	3.85	8.2	1.18	4.00	3.4	0.20	0.50
2n	Et–CO	N_3	0.38	1.61	4.2	1.09	2.56	2.3	0.20	0.40
2o	Me_2NCO	N_3	0.47	2.61	5.6	1.27	3.52	2.8	0.30	0.50
2p	MeOCO	N_3	0.47	2.92	6.2	1.09	4.00	3.7	0.20	0.40
2q	H	N_3	0.57	7.45	13	1.18	12.3	10	0.20	0.70

[a] The concentration of compound inhibits 50% of the growth of a cancer cell line after 72 h drug exposure.
[b] Human breast carcinona.
[c] Multidrug-resistant human breast carcinoma.
[d] *R*/*S* = drug-resistance factor = IC_{50} (drug-resistant cell line)/IC_{50} (drug-sensitive cell line).
[e] Multidrug resistant human breast carcinoma.
[f] Human non-small cell lung carcinoma.
[g] Human caucasian colon adenocarcinoma.

H-10-CH_3, H-14b), 2.35 (1 H, m, H-14a), 2.38 (3H, s, 4-OAc), 2.45 (1H, d, J = 3.6 Hz, OH) 2.55 (1H, ddd, J = 2.8, 5.6, 15.5 Hz, H-6a), 3.38 (1H, d, J = 4.0 Hz, OH-2′), 3.81 (1H, d, J = 6.8 Hz, H-3), 3.89 (3H, s, 2-m-MeO), 4.16 (1H, d, J = 8.4 Hz, H-20b), 4.35 (1H, d, J = 8.4 Hz, H-20a), 4.42 (2H, m, H-7, H-3′), 4.62 (1H, d, J = 2.4 Hz, H-2′), 4.95 (1H, bd, J = 7.6 Hz, H-5), 5.01 (1H, d, J = 10 Hz, NH), 5.66 (1H, d, J = 7.2 Hz, H-2), 5.85 (1H, ddd, J = 5.6, 56.0, 56.0 Hz, CF_2H), 6.24 (1H, t, J = 8.4 Hz, H-13), 6.29 (1H, s, H-10), 7.14 (1H, dd, J = 2.4, 8.4 Hz, arom.), 7.40 (1H, t, J = 8.0 Hz, arom.), 7.65 (1H, s, arom.), 7.71 (1H, d, J = 8.0 Hz, arom.); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.7, 15.0, 21.0, 22.1, 22.7, 26.9, 28.2, 35.7, 35.8, 43.5, 45.9, 55.0 (m), 55.6, 58.8, 68.7, 72.4, 73.2, 75.7, 76.7, 76.9, 79.3, 81.2 81.4, 84.7, 114.3 (m), 114.4, 120.9, 122.9, 129.9, 130.5, 133.5, 142.1, 155.2, 159.9, 167.3, 170.5, 171.5, 172.6, 203.9; ^{19}F NMR ($CDCl_3$, 282 MHz): δ −125.7 (ddd, J = 10.9, 54.7, 285.1 Hz), −128.2 (ddd, J = 9.3, 56.7, 285.1 Hz); HRMS (FAB$^+$, m/z): Calcd. for $C_{41}H_{53}F_2NO_{16}{\cdot}H^+$, 854.3405. Found: 854.3430.

3.4. 2-Dephenyl-2-(3-methoxybenzoyl)-10-propanoyl-3′-dephenyl-3′-difluoromethyldocetaxel (**1b**)

Yield 38% for two steps; mp 168 °C; $[\alpha]_D{}^{20}$-56 (c = 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (3H, s, H-17), 1.26 (6H, m, H-16, H-10 EtCO), 1.29 (9H, s, Boc), 1.58 (1H, bs, OH), 1.67 (3H, s, H-19), 1.69 (1H, bs, OH), 1.88 (4H, m, H-6b, H-18), 2.25 (2H, m, H-14), 2.39 (3H, s, 4OAc), 2.54 (3H, m, H-6a, H-10 EtCO), 3.36 (1H, d, J = 4.0 Hz, OH), 3.82 (1H, d, J = 6.8 Hz, H-3), 3.89 (3H, s, 2-m-MeO), 4.16 (1H, d, J = 8.4 Hz, H-20b), 4.36 (1H, d, J = 8.4 Hz, H-20a), 4.42 (2H, m, H-7, H-3′), 4.62 (1H, d, J = 3.6 Hz, H-2′), 4.96 (1H, d, J = 7.6 Hz, H-5), 5.01 (1H, d, J = 10.0 Hz, NH), 5.66 (1H, d, J = 6.8 Hz, H-2), 5.85 (1H, ddd, J = 6.0, 56, 56 Hz, CF_2H), 6.25 (1H, dd, J = 10, 10 Hz, H-13), 6.30 (1H, s, H-10), 7.14 (1H, d, J = 8.0 Hz, arom.), 7.40 (1H, t, J = 8.0 Hz, arom.), 7.65 (1H, s, arom.), 7.72 (1H, d, J = 8.0 Hz, arom.); ^{13}C (100 MHz, $CDCl_3$): δ 9.2, 9.8, 15.0, 22.2, 22.7, 26.9, 27.8, 28.2, 35.7, 35.8, 43.5, 45.9, 55.0 (m), 55.6, 58.8, 68.7, 72.4, 73.2, 75.3, 75.5, 76.9, 79.3, 81.3, 81.4, 84.7, 114.3 (t, J_{CF} = 230 Hz), 114.4, 120.9, 122.9, 129.9, 130.5, 133.8, 141.9, 154.5, 159.9, 167.3, 170.5, 172.3, 174.8, 203.9; ^{19}F (282 MHz, $CDCl_3$): δ −125.7 (ddd, J = 10.9, 56.6, 287.1 Hz), −128.2 (ddd, J = 9, 57, 286 Hz); HRMS (FAB$^+$, m/z): Calcd. for $C_{42}H_{55}F_2NO_{16}{\cdot}H^+$, 868.3562. Found: 868.3582.

3.5. 2-Dephenyl-2-(3-methoxybenzoyl)-10-dimethylcarbamoyl-3′-dephenyl-3′-difluoromethyldocetaxel (**1c**)

Yield 54% for two steps; mp 167 °C; $[\alpha]_D{}^{20}$-64 (c = 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (3H, s, H-17), 1.25 (3H, s, H-16), 1.29 (9H, s, Boc), 1.67 (3H, s, H-19), 1.71 (1H, bs, OH), 1.90 (1H, m, H-6b), 1.91 (3H, s, H-18), 2.25 (2H, m, H-14), 2.39 (3H, s, H-4OAc), 2.54 (1H, ddd, J = 4.8, 8.0, 14.8 Hz, H-6a), 2.96 (3H, s, 10-Me_2NCO), 3.05 (3H, s, 10-Me_2NCO), 3.18 (1H, bs, OH), 3.40 (1H, bs, 2′-OH), 3.81 (1H, d, J = 7 Hz, H-3), 3.90 (3H, s, 2-m-MeO), 4.17 (1H, d, J = 8.4 Hz, H-20b), 4.35 (1H, d, J = 8.4 Hz, H-20a), 4.48 (2H, m, 7H, 3′H), 4.63 (1H, J = 4 Hz 2′H), 4.97 (1H, d, J = 8 Hz, H-5), 5.03 (1H, d, J = 10.4 Hz, NH), 5.65 (1H, d, J = 7 Hz, H-2), 5.85 (1H, ddd, J = 5.6, 55.6, 55.6 Hz, CF_2H), 6.25 (2H, m, H-10, H-13), 7.14 (1H, dd, J = 2.8, 7.2 Hz, arom.), 7.40 (1H, dd, J = 8, 8 Hz, arom.), 7.65 (1H, m, arom.), 7.72 (1H, d, J = 8.0 Hz, arom.); ^{13}C (100 MHz, $CDCl_3$): δ 9.6, 15.1, 22.5, 22.7, 27.1, 28.2, 35.6, 35.7, 36.2, 36.9, 43.5, 45.8, 54.8 (m), 55.6, 58.8, 68.6, 72.7, 73.3, 75.4, 76.3, 76.7, 79.4, 81.2, 81.5, 84.9, 114.3 (m), 114.4, 120.9, 122.9, 129.9, 130.5, 133.9, 142.4, 155.2, 156.3, 159.9, 167.3, 170.4, 172.6, 205.8; ^{19}F (282 MHz, $CDCl_3$): δ −125.7 (ddd, J = 10.9, 54.7, 285.1 Hz), −128.3 (ddd, J = 10.9, 54.7, 285.1 Hz); HRMS (FAB$^+$, m/z): Calcd. for $C_{42}H_{56}F_2N_2O_{16}{\cdot}H^+$, 883.3671. Found: 883.3690.

3.6. 2-Dephenyl-2-(3-methoxybenzoyl)-10-methoxycarbonyl-3′-dephenyl-3′-difluoromethyldocetaxel (**1d**)

Yield 71% for two steps; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (3H, s, H-17), 1.27 (3H, s, H-16), 1.32 (9H, s, Boc), 1.72 (3H, s, H-19), 1.82–1.97 (1H, m, H-6b), 1.94 (3H, s, H-18), 2.22–2.68 (7H, m, H-4OAc, H-6a, H-14, 7-OH), 3.40 (1H, bd, J = 5 Hz, 2′-OH) 3.82 (1H, d, J = 7 Hz, H-3), 3.90 (3H, s, 2-m-MeO), 3.93 (3H, s, H-10 MeO), 4.20 (1H, d, J = 8.1 Hz, H-20b), 4.38–4.55 (3H, m, H-20a, H-7), 4.66 (2H, s, H-2′, H-3′), 4.96–5.06 (2H, m, H-5, NH-3′), 5.70 (1H, d, J = 7 Hz, H-2), 5.88 (1H, ddd, J = 6.3, 56.4, 56.4 Hz, H-3′ CF_2H), 6.14 (1H, s, H-10), 6.28 (1H, dd, J = 8.4, 8.4 Hz, H-13), 7.18 (1H, d, J = 7.2 Hz, arom.), 7.44 (1H, dd, J = 7.8, 7.8 Hz, arom.), 7.68 (1H, m, arom.), 7.75 (1H, d, J = 7.8 Hz, arom.); ^{13}C (75.5 MHz, $CDCl_3$): δ 9.8, 15.1, 22.2, 22.8, 27.0, 28.3, 35.7, 35.9, 43.5, 45.9, 54.9 (m), 55.6, 55.9, 58.9, 68.7, 72.0, 73.2, 75.3, 76.7, 77.5, 78.4, 79.3, 81.4, 84.7, 114.3 (m), 114.4, 120.9, 122.9, 129.9, 130.4, 133.1, 142.9, 155.1, 155.9, 159.8, 167.2, 170.4, 172.4, 203.9; ^{19}F (282 MHz, $CDCl_3$): δ −125.69 (ddd, 1F, J = 12.1, 55.8, 292.7 Hz), −128.2 (ddd, 1F, J = 9.02, 55.8, 283.4 Hz); HRMS (FAB$^+$, m/z): Calcd. for $C_{41}H_{53}F_2NO_{17}{\cdot}H^+$, 870.3354. Found: 868.3349.

3.7. 2-Debenzoyl-2-(3-fluorobenzoyl)-10-acetyl-3′-dephenyl-3′-difluoromethyldocetaxel (**1e**)

Yield 68% for two steps; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15 (3H, s, H-17-CH_3), 1.25 (3H, s, H-16-CH_3), 1.31 (9H, s, Boc), 1.67 (3H, s, H-19-CH_3), 1.85–1.91 (4H, m, H-18-CH_3, H-6b), 2.25 (3H, s, H-10-CH_3CO), 2.27–2.37 (2H, m, H-14), 2.41 (3H, s, H-4-OAc), 2.47 (1H, d, J = 4 Hz, OH), 2.52–2.60 (1H, m, H-6a), 3.39 (1H, d, J = 5.2 Hz, 2′-OH), 3.81 (1H, d, J = 7 Hz, H-3), 4.15 (1H, d, J = 8.4 Hz, H-20b), 4.31 (1H, d, J = 8.4 Hz, 20-Ha), 4.38–4.45 (2H, m, H-7, H-3′), 4.63 (1H, d, J = 4.4 Hz, H-2′), 4.95–4.98 (1H, m, H-5), 5.03 (1H, d, J = 9.6 Hz, NH), 5.64 (1H, d, J = 7 Hz, H-2), 5.87 (1H, ddd, J = 5.6, 56.4, 56.4 Hz, CF_2H), 6.24 (1H, dd, J = 8.8, 8.8 Hz, H-13), 6.29 (1H, s, H-10), 7.30 (1H, dd, J = 2, 8 Hz, arom.), 7.48–7.53 (1H, m, arom.), 7.81 (1H, d, J = 8.4 Hz, arom.), 7.92 (1H, d, J = 8 Hz, arom.); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.6, 14.9, 20.9, 22.0, 22.5, 26.8, 28.0, 35.4, 35.6, 43.3, 45.7, 54.6 (m), 58.6, 68.4, 72.2, 72.9, 75.5, 75.6, 76.3, 79.4, 81.3, 81.4, 84.4, 114.0 (m), 117.1 (d, J_{CF} = 24 Hz), 120.8 (d, J_{CF} = 21 Hz), 122.9, 125.9, 130.4 (d, J_{CF} = 7.5 Hz), 133.1, 141.9, 154.9, 162.3 (J_{CF} = 246 Hz), 165.9, 170.2, 171.1, 172.2, 203.3; NMR, ($CDCl_3$, 282 MHz): δ-111.8, −126.3 (ddd, 1F, J = 9.9, 67.2, 216.5 Hz), −128.2 (ddd, 1F, J = 6.8, 42.4, 216.5 Hz); HRMS (FAB$^+$, m/z): Calcd. for $C_{40}H_{50}F_3NO_{15}{\cdot}H^+$, 842.3205. Found: 842.3190.

3.8. 2-Debenzoyl-2-(3-fluorobenzoyl)-10-propanoyl-3′-dephenyl-3′-difluoromethyldocetaxel (**1f**)

Yield 60% for two steps; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, s, 17-CH_3), 1.21 (3H, s, 16-CH_3), 1.24 (9H, s, Boc), 1.29 (s, 3H, 10-CH_2CH_3), 1.60 (1H, bs, OH), 1.63 (3H, s, 19-CH_3), 1.87 (1H, m, 6-Hb), 1.89 (3H, s, 18-CH_3), 2.20–2.54 (8H, m, 10-CH_2CH_3, 6-Ha, 4-Ac, 14-Ha, 14-Hb), 3.40 (1H, bs, OH), 3.82 (1H, d, J = 7 Hz, 3-H), 4.15 (1H, d, J = 8 Hz, 20-Hb), 4.31 (1H, d, J = 8 Hz, 20-Ha), 4.43 (2H, m, 7-H, 3′-H), 4.63 (1H, d, J = 4 Hz, 2′-H), 4.96 (1H, d, J = 8 Hz, H-5), 5.00 (1H, d, J = 10 Hz, NH), 5.64 (1H, d, J = 7 Hz, 2-H), 5.82 (1H, ddd, J = 6, 55, 55 Hz, CF_2H), 6.24 (1H, m, 13-H), 6.30 (1H, s, 10-H), 7.32 (1H, m), 7.49 (1H, m), 7.60 (1H, m), 7.92 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.2 (CH_2CH_3), 9.7 (19-CH_3), 15.0 (18-CH_3), 22.1 (17-CH_3), 22.6 (4-Ac), 26.9 (16-CH_3), 27.7 (CH_2CH_3), 28.1 (Boc), 35.5 (14-CH_2), 35.8 (6-CH_2), 43.4 (15-C), 45.8 (3-CH), 54.4 (m, 3′-CH), 58.8 (8-C), 68.7 (2′-CH), 72.4 (13-CH), 73.1 (7-CH), 75.5 (2-CH), 75.6 (10-CH), 76.5 (20-CH_2), 76.9 (1-C), 79.3 (Boc), 81.3 (4-C), 84.7 (5-CH), 114.3 (q, J_{CF} = 242 Hz, CF_2H), 117.2 (d, J_{CF} = 28 Hz, arom.),

121.1(d, J_{CF} = 26 Hz, arom.), 126.2 (arom.), 130.7 (d, J_{CF} = 7 Hz arom.), 131.4 (arom.), 133.4 (11-C), 142.0 (12-C), 155.2 (Boc), 164.0 (d, J_{CF} = 246 Hz, CF arom.), 166.2 (2-benz), 170.5 (4-Ac), 172.6 (1′-C), 174.8 (10-prop), 203.8 (9-C); ^{19}F NMR (282 MHz, $CDCl_3$): δ −111.6 (m, 1 F, C_{Ar}–F), −126.2 (ddd, 1 F, J = 12, 55, 286 Hz),−127.0 (ddd, 1F, J = 9, 55, 286 Hz). HRMS (ES^+, m/z): Calcd. for $C_{41}H_{52}NO_{15}F_3{\cdot}H^+$, 856.3367. Found: 856.3374.

3.9. 2-Debenzoyl-2-(3-fluorobenzoyl)-10-dimethylcarbamoyl-3′-dephenyl-3′-difluoromethyldocetaxel (1g)

Yield 84% for two steps; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18 (3H, s, 17-CH_3), 1.27 (3H, s, 16-CH_3), 1.34 (9H, s, Boc), 1.70 (3H, s, 19-CH_3), 1.86–1.94 (1H, m, 6-Hb), 1.94 (3H, s, 18-CH_3), 2.25–2.38 (2H, m, 14-H), 2.44 (3H, s, 4-Ac), 2.52–2.62 (1H, m, 6-Ha), 2.99 (3H, s, NMe), 3.07 (3H, s, NMe), 3.25 (1H, bs), 3.35 (1H, bs, 2′-OH), 3.84 (1H, d, J = 7.2 Hz, 3-H), 4.18 (1H, d, J = 8.4 Hz, 20-Hb), 4.34 (1H, d, J = 8.4 Hz, 20-Ha), 4.44–4.45 (2H, m, 7-H, 3′-H), 4.67 (1H, bs, 2′-H), 5.01 (1H, d, J = 7.8 Hz, H-5), 5.07 (1H, d, J = 10 Hz, NH), 5.66 (1H, d, J = 7.2 Hz, 2-H), 5.90 (1H, ddd, J = 6.6, 55.8, 55.8 Hz, CH_2H), 6.25–6.31 (2H, m, 10-H, 13-H), 7.31–7.38 (1H, m, arom.), 7.49–7.56 (1H, m, arom.), 7.84 (1H, d, J = 8.7 Hz, arom.), 7.96 (1H, d, J = 8.1 Hz, arom.); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.3, 14.9, 22.3, 22.4, 26.9, 27.9, 35.4, 35.6, 36.3, 36.7, 43.2, 45.5, 54.5 (m), 58.5, 68.4, 72.0, 72.9, 76.0, 76.3, 77.2, 79.2, 81.3, 81.4, 84.7, 114.0 (q, J_{CF} = 242 Hz, CF_2H), 117.1 (d, J = 24 Hz), 120.8 (d, J = 21 Hz), 125.9, 130.4 (d, J = 10 Hz), 131.2, 133.4, 142.3, 155.0, 156.1, 163.0 (d, J = 219 Hz), 165.9, 170.3, 172.4, 205.5; HRMS (FAB^+, m/z): Calcd. for $C_{41}H_{53}F_3N_2O_{15}{\cdot}H^+$, 871.3471. Found: 871.3465.

3.10. 2-Debenzoyl-2-(3-fluorobenzoyl)-10-methoxycarbonyl-3′-dephenyl-3′-difluoromethyldocetaxel (1h)

Yield 79% for two steps; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15 (3H, s, Me), 1.25 (3H, s, Me), 1.30 (9H, s, Boc), 1.69 (3H, s, Me), 1.88–1.76 (1H, m), 1.92 (3H, s, Me), 2.21–2.36 (3H, m, H14), 2.40 (3H, s, Ac), 2.44 (1H, m, H6b), 2.57 (1H, ddd, J = 6.8, 9.6, 15.2 Hz, H6a), 3.39 (1H, bs, OH), 3.89 (1H, d, J = 7 Hz, H3), 3.87 (3H, s, OMe), 4.15 (1H, d, J = 8.4 Hz, H20b), 4.31 (1H, d, J = 8.4 Hz, H20a), 4.34–4.45 (2H, m, H7, H3′), 4.63 (1H, m, H2′), 4.96 (1H, d, J = 8 Hz, H-5), 5.10 (1H, d, J = 10 Hz, NH), 5.87 (1H, ddd, J = 6, 56, 56 Hz, CF2H), 6.12 (1H, s, H10), 6.24 (1H, dd, J = 10 Hz, H13), 7.32 (1H, ddd, J = 1.2, 8, 16.4 Hz,), 7.53–7.47 (1H, m), 7.81 (1H, d, J = 9.6 Hz), 7.92 (1H, d, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.8, 15.3, 22.2, 22.8, 26.9, 28.3, 35.6, 35.9, 43.4, 45.9, 54.7 (m), 55.9, 58.9, 68.7, 72.4, 73.1, 75.6, 76.6, 78.3, 79.4, 81.3, 81.6, 84.7, 114.3 (q, J_{CF} = 242 Hz, CF_2H), 117.3 (d, J_{CF} = 23 Hz), 121.0 (d, J_{CF} = 21 Hz), 126.2, 130.6 (d, J_{CF} = 7.6 Hz), 131.4 (d, J_{CF} = 5 Hz), 133.0, 142.9, 155.2, 155.8, 162.5 (d, J_{CF} = 246 Hz), 166.2, 170.5, 172.5, 203.8; ^{19}F NMR, ($CDCl_3$, 282 MHz): δ −111.6 (bs, 1F), −126.0 (ddd, 1F, J = 12.1, 55.1, 278.4 Hz), −128.0 (ddd, 1F, J = 9, 68.6, 283.7 Hz); HRMS (FAB^+, m/z): Calcd. for $C_{40}H_{50}F_3NO_{16}{\cdot}H^+$, 858.3154. Found; 858.3160.

3.11. 2-Debenzoyl-2-(3-chlorobenzoyl)-10-acetyl-3′-dephenyl-3′-difluoromethyldocetaxel (1i)

Yield 59% for two steps; mp 164–166 °C, $[\alpha]^{20}_D$ −57 ($CHCl_3$, c 0.96); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.16 (3H, s, 16-CH_3), 1.27 (3H, s, 17-CH_3), 1.33 (9H, s, Boc), 1.69 (3H, s, 19-CH_3), 1.91 (4H, m, 18-CH_3, H-6b), 2.27 (3H, s, 10-Ac), 2.30 (2H, m, H-14), 2.37 (s, 3H, 4-Ac), 2.60 (2H, m, 6-Ha, OH), 3.60 (1H, bs, OH), 3.83 (1H, d, J = 7 Hz, 3-H), 4.17 (1H, d, J = 8 Hz, H-20b), 4.33 (1H, d, J = 8 Hz, H-20a), 4.50 (2H, m, H-3′, H-7), 4.66 (1H, bs, H-2′), 4.99 (1H, bd, J = 7.8 Hz, H-5), 5.07 (1H, d, J = 10 Hz, NH), 5.65 (1H, d, J = 7 Hz, H-2), 5.90 (1H, dd, J = 57 Hz, CF_2H), 6.21 (1H, m, H-13), 6.30 (1H, s, H-10), 7.48 (1H, m, arom.), 7.60 (1H, m, arom.), 8.04 (1H, m, arom.), 8.10 (m, 1H, arom.);^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.5 (19-CH_3), 14.8 (18-CH_3), 20.8 (10-Ac), 21.8 (17-CH_3), 22.3 (4-Ac), 26.6 (16-CH_3), 27.9 (Boc), 35.3 (14-CH_2), 35.5 (6-CH_2), 43.1 (15-C), 45.6 (3-CH), 54.6 (m, 3′-CH), 58.5 (8-C), 68.5 (2′-CH), 72.2 (13-CH), 72.8 (7-CH), 75.3 (10-CH), 75.4 (2-CH), 76.3 (20-CH_2), 79.1 (1-C), 80.9 (Boc), 81.0 (4-C), 84.4 (5-CH), 114.0 (t, J_{CF} = 244 Hz, CF_2H), 128.3 (arom.), 130.1 (arom.), 130.4 (arom.), 130.8 (arom.), 133.0 (arom.), 133.7 (11-C), 134.8 (C^{IV} arom.), 141.9 (12-C), 155.0 (Boc), 165.8 (2-benz), 170.3 (10-Ac), 171.2 (4-Ac), 172.3 (1′-C), 203.5 (9-C); ^{19}F NMR ($CDCl_3$, 282 MHz): δ −126.5 (ddd, J = 13, 57, 287 Hz), −127.4 (ddd, J = 9, 57, 285 Hz); HRMS (ES^+, m/z): Calcd. for $C_{40}H_{50}ClF_2NO_{15}{\cdot}H^+$, 858.2910. Found: 858.2923.

3.12. 2-Debenzoyl-2-(3-chlorobenzoyl)-10-propanoyl-3′-dephenyl-3′-difluoromethyldocetaxel (1j)

Yield 75% for two steps; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.20–1.28 (9H, m, 16-CH_3, 17-CH_3, CH_3CH$_2$), 1.33 (9H, s, Boc), 1.60 (1H, bs, OH) 1.69 (3H, m, 19-CH_3), 1.91 (4H, m, 18-CH_3, H-6b), 2.30 (2H, m, H-14a, H-14b), 2.43 (3H, s, 4Ac), 2.56 (3H, m, CH_2CO, H-6a), 3.47 (1H, d, J = 5 Hz, OH-2′), 3.84 (1H, d, J = 7 Hz, H-3), 4.15 (1H, d, J = 8 Hz, H-20b), 4.32 (1H, d, J = 8 Hz, H-20a), 4.44 (2H, m, H-3′, H-7), 4.66 (1H, d, J = 5 Hz, H-2′), 4.98 (1H, m, H-5), 5.08 (d, 1H, J = 10 Hz, NH), 5.64 (1H, d, J = 7 Hz, H-2), 5.98 (1H, ddd, J = 6, 56, 56 Hz, CF_2H), 6.25 (1H, m, H-13), 6.33 (1H, s, H-10), 7.47 (1H, m, arom.), 7.62 (1H, m, arom.), 8.04 (1H, m, arom.), 8.18 (1H, m, arom.); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.3 (CH_2CH_3), 9.8 (19-CH_3), 15.1 (18-CH_3), 22.1 (17-CH_3), 22.6 (4-Ac), 26.9 (16-CH_3), 27.8 (CH_2CH_3), 28.2 (Boc), 35.6 (6-CH_2), 35.8 (14-CH_2), 43.4 (15-C), 45.9 (3-CH), 54.8 (m, 3′-CH), 58.7 (8-C), 68.9 (2′-CH), 72.5 (13-CH), 73.1 (7-CH), 75.5 (2-CH), 75.6 (10-CH), 76.5 (20-CH_2), 79.4 (1-C), 81.2 (Boc), 81.3 (4-C), 84.7 (5-CH), 114.3 (t, J_{CF} = 244 Hz, CF_2H), 128.5 (arom.), 130.4 (arom.), 130.6 (arom.), 131.1 (arom.), 133.4 (arom.), 134.0 (11-C), 135.1 (arom.), 142.1 (12-C), 155.3 (Boc), 166.0 (2-benz), 170.6 (4-Ac), 172.6 (1′-C), 174.9 (10-prop.), 203.8 (9-C); ^{19}F NMR ($CDCl_3$, 282 MHz): δ −126.0 (ddd, J = 12, 55, 283 Hz), −128.0 (ddd, J = 9, 55, 286 Hz); HRMS (ES^+, m/z): Calcd. for $C_{41}H_{52}ClF_2NO_{15}{\cdot}H^+$, 872.3066. Found: 872.3055.

3.13. 2-Debenzoyl-2-(3-chlorobenzoyl)-10-dimethylcarbamoyl-3′-dephenyl-3′-difluoromethyldocetaxel (1k)

Yield 56% for two steps; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, s, 17-CH_3), 1.24 (3H, s, 16-CH_3), 1.30 (9H, s, Boc), 1.66 (3H, s, 19-CH_3), 1.87 (1H, m, 6-Hb), 1.90 (3H, s, 18-CH_3), 2.28 (2H, m, H-14), 2.40 (3H, s, 4-Ac), 2.53 (1H, m, 6-Ha), 2.95 (3H, s, NMe), 3.03 (3H, s, NMe), 3.20 (1H, bs, OH), 3.50 (1H, d, J = 4 Hz, 2′-OH), 3.80 (1H, d, J = 7 Hz, H-3), 4.14 (1H, d, J = 8.4 Hz, H-20b), 4.28 (1H, d, J = 8.4 Hz, H-20a), 4.40 (2H, m, H-7, H-3′), 4.63 (1H, bs, 2′-H), 4.98 (1H, bd, J = 6 Hz, NH), 5.09 (1H, d, J = 10 Hz, H-5), 5.60 (1H, d, J = 7 Hz, 2-H), 5.85 (1H, ddd, J = 6, 56, 56 Hz, CF_2H), 6.23 (1H, m, 13-H), 6.24 (1H, s, 10-H), 7.45 (1H, m, arom.), 7.56 (1H, m, arom.), 7.99 (1H, m, arom.), 8.11 (1H, m, arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.69 (19-CH_3), 15.2 (18-CH_3), 22.6 (16-CH_3), 22.7 (4-Ac), 27.2 (17-CH_3), 28.4 (Boc), 35.7 (6-CH_2), 35.7 (NMe), 36.3 (NMe), 36.9 (14-CH_2), 43.3 (15-C), 45.8 (3-CH), 54.9 (m, 3′-CH), 58.7 (8-C), 68.7 (2′-CH), 72.7 (13-CH), 73.1 (7-CH), 75.8 (2-CH), 76.3 (10-CH), 76.5 (20-CH_2), 79.5 (1-C), 81.2 (4-C), 81.4 (Boc), 84.4 (5-CH), 114.2 (t, J_{CF} = 244 Hz, CF_2H,), 128.5 (arom.), 130.1 (arom.), 130.6 (arom.), 131.5 (arom.), 133.6 (arom.), 133.9 (11-C), 134.9 (arom.), 142.4 (12-C), 155.1 (Boc), 156.2 (10-carb), 166.0 (2-benz), 170.0 (4-Ac), 171.4 (1′-C), 205.5 (9-C); ^{19}F NMR, (282 MHz, $CDCl_3$) δ −126.0 (ddd, J = 12, 55, 286 Hz), −127.9 (ddd, J = 9, 58, 286 Hz); HRMS (ES^+, m/z): Calcd. for $C_{41}H_{53}N_2O_{15}F_2Cl{\cdot}H^+$,887.3181. Found: 887.3222.

*3.14. 2-Debenzoyl-2-(3-chlorobenzoyl)-10-methoxycarbonyl-3′-dephenyl-3′-difluoromethyldocetaxel (**1l**)*

Yield 86% for two steps; white solid; mp 143–145 °C; $[\alpha]_D^{20}$-38 ($CHCl_3$, c = 0.26); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, s, 17-CH_3), 1.24 (3H, s, 16-CH_3), 1.30 (9H, s, Boc), 1.68 (3H, s, 19-CH_3), 1.88 (1H, m, 6-Hb), 1.90 (3H, s, 18-CH_3), 2.60–2.10 (7H, m, 7-OH, 14-Ha, 14-Hb, 4-Ac, 6-Ha), 3.40 (1H, bd, J = 5 Hz, 2′-OH), 3.79 (1H, d, J = 7 Hz, 3-H), 3.87 (3H, s, OMe), 4.14 (1H, d, J = 8 Hz, 20-Hb), 4.30 (1H, d, J = 8 Hz, 20-Ha), 4.37 (2H, m, 7-H, H-3′), 4.62 (1H, d, J = 2.4 Hz, 2′-H), 4.97 (2H, m, 5-H, NH), 5.62 (1H, d, 2-H), 5.87 (1H, ddd, J = 5.6, 56, 56 Hz, CF_2H), 6.11 (1H, s, 10-H), 6.23 (1H, m, H-13), 7.45 (1H, m, arom.), 7.60 (1H, m, arom.), 8.00 (1H, m, arom.), 8.12 (1H, m, arom.); ^{13}C NMR (100 MHz, $CDCl_3$): (9.7 (19-CH_3), 15.1 (18-CH_3), 22.0 (17-CH_3), 22.6 (4-Ac), 26.8 (16-CH_3), 28.2 (Boc), 35.5 (6-CH_2), 35.8 (14-CH_2), 43.3 (15-C), 45.8 (3-CH), 54.0 (m, 3′-CH), 55.8 (OMe), 58.5 (8-C), 68.7 (2′-CH), 72.3 (13-CH), 73.0 (7-CH), 75.5 (2-CH), 76.5 (20-CH_2), 76.9 (10-CH), 78.4 (Boc), 79.4 (1-C), 81.2 (4-C), 84.6 (5-CH), 114.2 (t, J_{CF} = 244 Hz, CF_2H), 128.5 (arom.), 130.4 (arom.), 130.6 (arom.), 131.0 (arom.), 133.0 (arom.), 134.0 (11-C), 135.0 (arom.), 143.0 (12-C), 154.8 (10-carb), 155.9 (Boc), 166.0 (2-benz), 170.6 (4-Ac), 171.8 (1′-C), 203.9 (9-C); HRMS (ES$^+$, m/z): Calcd. for $C_{40}H_{50}NO_{16}F_2Cl{\cdot}H^+$,874.2864. Found: 874.2892.

*3.15. 2-Debenzoyl-2-(3-azidobenzoyl)-10-acetyl-3′-dephenyl-3′-difluoromethyldocetaxel (**1m**)*

Yield 53% for two steps; white solid; mp 173 °C; $[\alpha]_D^{20}$-46 (c = 0.81, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.14 (3H, s, H-17), 1.24 (3H, s, H-16), 1.29 (9H, s, Boc), 1.65 (1H, bs, OH), 1.67 (3H, s, H-19), 1.89 (4H, m, CH_3-18, H-6b), 2.25 (4H, m, H-10-CH_3, H-14b), 2.32 (1H, m, H-14a), 2.39 (3H, s, 4-OAc), 2.55 (3H, m, H-6a, $COCH_2$), 3.41 (1H, d, J = 4.8 Hz, OH-2′), 3.82 (1H, d, J = 7.2 Hz, H-3), 4.16 (1H, d, J = 8.0 Hz, H-20b), 4.32 (1H, d, J = 8.0 Hz, H-20a), 4.43 (2H, m, H-7, H-3′), 4.62 (1H, d, J = 2.4 Hz, H-2′), 4.96 (1H, bd, J = 9.6 Hz, H-5), 5.04 (1H, d, J = 10 Hz, NH′), 5.65 (1H, d, J = 8.0 Hz, H-2), 5.85 (1H, ddd, J = 5.6, 56.0, 56.0 Hz, CF_2H), 6.21 (1H, t, J = 7.6 Hz, H-13), 6.29 (1H, s, H-10), 7.22 (1H, d, J = 7.6 Hz, arom.), 7.48 (1H, t, J = 8.0 Hz, arom.), 7.83 (1H, s, arom.), 7.88 (1H, d, J = 8.0 Hz, arom.); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.8, 15.1, 21.0, 22.1, 22.6, 26.9, 28.2, 35.6, 35.8, 43.4, 45.9, 54.8 (m), 58.7, 68.9, 72.5, 73.1, 75.6, 75.7, 76.5, 79.4, 81.2, 81.3, 84.7, 114.3 (t, J_{CF} = 244 Hz) 120.1, 124.4, 126.7, 130.4, 130.6, 133.4, 140.8, 142.1, 155.3, 166.0, 170.6, 172.6, 174.9, 203 8; ^{19}F NMR, ($CDCl_3$, 282 MHz): δ −126.6 (ddd, J = 9, 42, 216 Hz), −128.1 (ddd, J = 6, 42, 216 Hz); HRMS (FAB$^+$, m/z): Calcd. for $C_{40}H_{50}F_2N_4O_{15}{\cdot}H^+$, 865.3314. Found: 865.3310.

*3.16. 2-Dephenyl-2(3-azidobenzoyl)-10-propanoyl-3′-difluoromethyldocetaxel (**1n**)*

Yield 79 % for two steps; mp 149 °C; $[\alpha]_D^{20}$-50 (c = 4.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (3H, s, CH_3-17), 1.26 (6H, m, CH_3-16, H-10 CH_3CH_2CO), 1.32 (9H, s, Boc), 1.69 (3H, s, H-19), 1.79 (1H, bs, OH), 1.91 (4H, m, H-6a, H-18), 2.32 (2H, m, H-14), 2.42 (3H, s, H-4OAc), 2.61 (3H, m, H-6b, H-10 CH_3CH_2CO), 3.52 (1H, d, J = 5.1 Hz, OH), 3.85 (1H, d, J = 7.2 Hz, H-3), 4.17 (1H, d, J = 8.4 Hz, H-20a), 4.35 (1H, d, J = 8.4 Hz, H-20b), 4.46 (2H, m, H-7, H-3′), 4.65 (1H, d, J = 4.2 Hz, H-2′), 4.99 (1H, d, J = 8.7 Hz, H-5), 5.13 (1H, d, J = 10.2 Hz, NH-3′), 5.67 (1H, d, J = 6.9, H-2), 5.88 (1H, ddd, J = 6.0, 56, 56 Hz, CF_2H), 6.24 (1H, t, J = 7.2, H-13), 6.33 (1H, s, H-10), 7.25 (1H, d, J = 7.8, arom.), 7.51 (1H, t, J = 7.8 Hz, arom.), 7.84 (1H, s, arom.), 7.90 (1H, d, J = 7.8, arom.); ^{13}C (100 MHz, $CDCl_3$): δ 8.9, 9.5, 14.8, 21.9, 22.5, 26.6, 27.5, 27.9, 35.3, 35.5, 43.2, 45.6, 54.5 (m), 58.5, 68.4, 72.1, 72.9, 75.3, 75.4, 76.3, 79.1, 80.4, 80.9, 84.5, 113.9 (t, J_{CF} = 244 Hz) 120.1, 124.4, 126.7, 130.2, 130.7, 133.2, 140.8, 141.8, 155.0, 166.2, 170.4, 171.2, 172.4, 203.6; ^{19}F (282 MHz, $CDCl_3$): δ −126.2 (ddd, J = 12, 55, 287 Hz), −127.9 (ddd, J = 9, 55, 287 Hz); HRMS (FAB$^+$, m/z): Calcd. for $C_{41}H_{52}F_2N_4O_{15}{\cdot}H^+$, 879.3470. Found: 879.3457.

*3.17. 2-Dephenyl-2(3-azidobenzoyl)-10-dimethylcarbamoyl-3′-difluoromethyldocetaxel (**1o**)*

Yield 37 % for two steps; mp 175 °C; $[\alpha]_D^{20}$-50 (c = 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (3H, s, 17-CH_3), 1.26 (3H, s, 16-CH_3), 1.32 (9 H, s, Boc), 1.67 (1H, bs, OH), 1.71 (3H, s, H-19), 1.95 (4H, m, 6-Hb, 18CH_3), 2.32 (2H, m, H-14), 2.41 (3H, s, 4-Ac), 2.58 (1H, m, 6-Ha), 3.00 (3H, s, Me_2NCO), 3.08 (3H, s, Me_2NCO), 3.25 (1H, bs, OH), 3.43 (1H, bs, OH), 3.84 (1H, d, J = 7 Hz, 3-H), 4.19 (1H, d, J = 8.4 Hz, 20-Hb), 4.36 (1H, d, J = 8.4 Hz, 20-Ha), 4.49 (2H, m, 7-H, 3′-H), 4.67 (1H, d, J = 4, 2′-H), 5.01 (1H, d, J = 8.4 Hz, 5-H), 5.08 (1H, d, J = 10 Hz, NH), 5.67 (1H, d, J = 7 Hz, 2-H), 5.88 (1H, ddd, J = 6.0, 56.4, 56.4, CF_2H), 6.25 (2H, m, 10-H, 13-H), 7.25 (1H, m, arom.), 7.51 (1H, m, arom.), 7.86 (1H, m, arom.), 7.92 (1H, d, J = 7.5 Hz, arom.); ^{13}C (100 MHz, $CDCl_3$): δ 9.4, 14.9, 22.3, 22.5, 26.8, 27.9, 35.3, 35.4, 36.0, 36.6, 43.2, 45.5, 54.5 (m), 58.5, 68.3, 72.4, 72.9, 75.6, 76.6, 77.2, 79.2, 80.9, 81.1, 84.7, 114.0 (t, J_{CF} = 244 Hz), 120.1, 124.4, 126.7, 130.2, 130.8, 133.4, 140.8, 142.3, 154.9, 156.1, 166.2, 170.4, 172.4, 205.5; ^{19}F (282 MHz, $CDCl_3$): δ −126.2 (ddd, J = 12, 55, 287 Hz), −127.9 (ddd, J = 9, 55, 296 Hz); HRMS (FAB$^+$, m/z): Calcd. for $C_{41}H_{53}F_2N_5O_{15}{\cdot}H^+$, 894.3579. Found: 894.3571.

*3.18. 2-Dephenyl-2(3-azidobenzoyl)-10-methoxycarbonyl-3′-difluoromethyldocetaxel (**1p**)*

Yield 70 % for two steps; mp 156–158 °C; $[\alpha]_D^{20}$-42 (c = 2.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (3H, s, CH_3-17), 1.26 (3H, s, CH_3-16), 1.31 (9H, s, Boc), 1.71 (3H, s, CH_3-19), 1.75 (2H, m), 1.87 (1H, m, H-6a), 1.94 (3H, s, CH_3-18), 2.32 (2H, m, H-14), 2.41 (3H, s, H-4OAc), 2.56 (1H, m, H-6b), 3.57 (1H, bs, OH), 3.84 (1H, d, J = 7 Hz, H-3), 4.17 (1H, d, J = 8.4 Hz, H-20b), 4.36 (1H, d, J = 8.4 Hz, H-6a), 4.43 (2H, m, H-7, H-3′), 4.65 (1H, m, H-2′), 5.03 (1H, d, J = 8.4 Hz, H-5), 5.16 (1H, d, J = 10 Hz, NH), 5.89 (ddd, J = 6.0, 56.4, 56.4 Hz, CF_2H), 6.14 (1H, s, H-10), 6.24 (1H, dd, J = 9, 9 Hz H-13), 7.24 (1H, d, J = 8.1 Hz, arom.), 7.51 (1H, dd, J = 8.1, 8.1 Hz, arom.), 7.86 (1H, s, arom.), 7.92 (1H, d, J = 7.5 Hz, arom.); ^{13}C (75 MHz, $CDCl_3$): δ 9.5, 14.9, 21.8, 22.5, 26.5, 27.9, 35.3, 35.5, 43.1, 45.5, 54.5 (m), 55.6, 58.5, 68.4, 71.9, 72.8, 75.4, 76.3, 78.1, 79.1, 80.8, 80.9, 84.4, 114.0 (t, J_{CF} = 244 Hz) 120.1, 124.4, 126.7, 130.2, 130.7, 132.7, 140.8, 142.8, 155.0, 155.7, 166.2, 170.5, 172.4, 203.8; ^{19}F (282 MHz, $CDCl_3$): δ −126.2 (ddd, J = 9, 55, 283 Hz), −128.0 (ddd, J = 9, 55, 287 Hz); HRMS (FAB$^+$, m/z): Calcd. for $C_{40}H_{50}F_2N_4O_{16}{\cdot}H^+$, 881.3263. Found: 881.3261.

*3.19. 2-Debenzoyl-2-(3-methoxybenzoyl)-10-acetyl-3′-dephenyl-3′-trifluoromethyldocetaxel (**2a**)*

Yield 36 % for two steps; white solid; mp 191 °C; $[\alpha]_D^{20}$-72 (c = 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.15 (3H, s, CH_3-17), 1.25 (3H, m, CH_3-16), 1.30 (9H, s, Boc), 1.67 (3H, s, CH_3-19), 1.70 (bs, 1 H, OH), 1.88 (4H, m, H-6b, CH_3-18), 2.25 (3H, s, 10-OAc), 2.32 (2H, m, H-14), 2.37 (3H, s, 4-OAc), 2.47 (1H, bs, OH), 2.56 (1H, m, H-6a), 3.38 (1H, bs, OH), 3.81 (1H, d, J = 7 Hz, H-3), 3.89 (3H, s, MeO), 4.17 (1H, d, J = 8.4 Hz, H-20b), 4.36 (1H, d, J = 8.4 Hz, H-20a), 4.42 (1H, m, H-7), 4.71 (1H, m, H-2′), 4.77 (1H, m, H-3′), 4.95 (1H, d, J = 8.4, H-5), 5.20 (1H, d, J = 10 Hz, NH′), 5.66 (1H, d, J = 7 Hz, H-2), 6.29 (2H, m, H-10, H-13), 7.15 (1H, d, J = 7.5 Hz), 7.41 (1H, d, J = 8 Hz), 7.65 (1H, s), 7.72 (1H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.6, 14.8, 20.8, 21.9, 22.3, 26.7, 27.9, 35.4, 35.5, 43.2, 45.6, 53.8 (m), 55.3, 58.6, 68.0, 72.1, 73.4, 74.9, 75.4, 76.5, 79.0, 81.2, 81.4, 84.4,

114.1, 120.7, 122.7, 125.0 (q, J_{CF} = 280 Hz), 129.7, 130.2, 133.4, 141.6, 154.6, 159.7, 167.1, 170.2, 171.2, 171.8, 203.5; ^{19}F NMR ($CDCl_3$, 282 MHz): δ −73.8 (d, J = 9.0 Hz); HRMS (FAB$^+$, m/z): Calcd. for $C_{41}H_{52}F_3NO_{16}{\cdot}H^+$, 872.3311. Found: 872.3321.

3.20. 2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3′-dephenyl-3′-trifluoromethyldocetaxel (2b)

Yield 43% for two steps; white solid; mp 156 °C; $[\alpha]_D^{20}$-57 (c = 0.54, $CHCl_3$): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.15 (3H, s, CH_3-16), 1.23 (6H, m, C-17, 10-CH_3CH_2CO), 1.30 (9H, s, Boc), 1.68 (3H, s, CH_3-19), 1.70 (1H, ds, OH), 1.88 (4H, m, H-6b, CH_3-18), 2.26 (2H, m, H-14), 2.37 (3H, s, 4-OAc), 2.54 (4H, m, H-6a, 10-CH_3CH_2CO, OH), 3.81 (1H, d, J = 7 Hz, H-3), 3.89 (3H, s, MeO), 4.17 (1H, d, J = 8.4 Hz, H-20b), 4.36 (1H, d, J = 8.4 Hz, H-20a), 4.42 (1H, dd, J = 4.0, 10.4 Hz, H-7), 4.70 (1H, bs, H-2′), 4.77 (1H, m, H-3′), 4.96 (1H, d, J = 8.0, H-5), 5.20 (1H, d, J = 10.8 Hz, NH′), 5.66 (1H, d, J = 7 Hz, H-2), 6.26 (1H, dd, J = 9, 9 Hz, H-13), 6.30 (1H, s, H-10), 7.15 (1H, d, J = 8.8 Hz), 7.40 (1H, dd, J = 8, 8 Hz), 7.84 (1H, s), 7.65 (1H, s), 7.72 (1H, d, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.3, 9.7, 15.1, 22.3, 22.6, 27.0, 27.9, 28.2, 35.7, 35.8, 43.5, 45.9, 53.8 (m), 55.9, 58.9, 68.4, 72.5, 73.7, 75.3, 75.6, 76.9, 79.3, 81.6, 81.7, 84.8, 114.4, 121.0, 123.0, 125.0 (q, J_{CF} = 280 Hz), 130.1, 130.5, 133.8, 141.8, 154.9, 159.8, 167.4, 170.5, 172.1, 174.9, 203.9; ^{19}F NMR ($CDCl_3$, 282 MHz): δ −73.8 (d, J = 7.3 Hz); HRMS (FAB$^+$, m/z): Calcd. for $C_{42}H_{54}F_3NO_{16}{\cdot}H^+$, 886.3467. Found: 886.3486.

3.21. 2-Debenzoyl-2-(3-methoxybenzoyl)-10-dimethylcarbamoyl-3′-dephenyl-3′-trifluoromethyldocetaxel (2c)

Yield 66 % for two steps; white solid; mp 164 °C; $[\alpha]_D^{20}$-58 (c = 3.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.15 (3H, s, CH_3-17,) 1.24 (3H, s, CH_3-16), 1.29 (9H, s, Boc), 1.67 (3H, s, CH_3-19), 1.78 (bs, 1 H, OH), 1.89 (4H, m, H-6b, CH_3-18), 2.24 (2H, m, H-14), 2.36 (3H, s, 4-OAc), 2.53 (1H, ddd, J = 2.8, 5.6, 15.2 Hz, H-6a), 2.96 (3H, s, N-CH_3), 3.04 (3H, s, N-CH_3), 3.21 (1H, bs, OH), 3.55 (1H, bs, OH), 3.80 (1H, d, J = 7 Hz, H-3), 3.89 (s, 3 H, MeO), 4.17 (1H, d, J = 8.4 Hz, H-20b), 4.35 (1H, d, J = 8.4 Hz, H-20a), 4.45 (1H, m, H-7), 4.70 (1H, s, H-2′), 4.77 (1H, m, H-3′), 4.96 (1H, d, J = 8 Hz, H-5), 5.28 (1H, d, J = 10.4 Hz, NH′), 5.65 (1H, d, J = 7 Hz, H-2), 6.27 (2H, m, H-10, H- 13), 7.13 (1H, dd, J = 2.8, 8.4 Hz, arom.), 7.39 (1H t, J = 8.0 Hz, arom.), 7.64 (1H, s, arom.), 7.71 (1H, d, J = 8.0 Hz, arom.); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.6, 15.1, 22.5, 22.7, 27.1, 28.1, 35.6, 35.8, 36.3, 36.9, 43.5, 45.8, 54.0 (m), 55.5, 58.8, 68.3, 72.6, 73.6, 75.4, 76.3, 76.7, 79.3, 81.2, 81.6, 84.9, 114.3, 120.9, 122.9, 125.0 (q, J_{CF} = 280 Hz), 129.9, 130.5, 133.9, 142.2, 154.8, 156.3, 159.9, 167.3, 170.3, 171.9, 205.7; ^{19}F NMR ($CDCl_3$, 282 MHz): δ −72.8 (d, J = 7.3 Hz); HRMS (FAB$^+$, m/z): Calcd. for $C_{42}H_{55}F_3N_2O_{16}{\cdot}H^+$, 901.3576. Found: 901.3586.

3.22. 2-Debenzoyl-2-(3-methoxybenzoyl)-10-methoxycarbonyl-3′-dephenyl-3′-trifluoromethyldocetaxel (2d)

Yield 90 % for two steps; white solid; mp 201 °C; $[\alpha]_D^{20}$-50 (c = 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15 (3H, s, CH_3-17,) 1.24 (3H, s, CH_3-16), 1.30 (9H, s, Boc), 1.69 (3H, s, CH_3-19), 1.72 (1H, bs, OH), 1.88 (1H, m, H-6b), 1.91 (s, 3H, CH_3-18), 2.26 (1H, m, H-14a), 2.35 (m, 1 H, H-14b), 2.39 (3H, s, 4-OAc), 2.45 (1H, bs, OH), 2.56 (3H, m, H-6a), 3.40 (1H, bs, OH), 3.79 (1H, d, J = 7.0 Hz, H-3), 3.87 (3H, s, 10-MeO), 3.89 (s, 3H, 2-m-MeO), 4.17 (1H, d, J = 8.5 Hz, H-20b), 4.36 (1H, d, J = 8.5 Hz, H-20a), 4.39 (1H, dd, J = 4.0, 11.0 Hz, H-7), 4.70 (1H, bs, H-2′), 4.77 (1H, m, H-3′), 4.95 (1H, d, J = 7.5 Hz, H-5), 5.21 (1H, d, J = 10.0 Hz, NH′), 5.66 (1H, d, J = 7 Hz, H-2), 6.11 (1H, s, H-10), 6.26 (1H, dd, J = 8, 8 Hz, H- 13), 7.24 (1H, dd, J = 2.5, 8.0 Hz, arom.), 7.38 (1H, dd, J = 7.5, 7.5 Hz, arom.), 7.65 (1H s, arom.), 7.72 (1H d, J = 8.0 Hz, arom.); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.7, 15.1, 22.1, 22.5, 26.9, 28.1, 35.6, 35.8, 43.4, 45.8, 54.2 (m), 55.5, 55.8, 58.8, 68.3, 72.3, 73.6, 76.7, 76.9, 78.4, 79.2, 81.5, 81.7, 84.6, 114.3, 120.9, 122.9, 125.0 (q, J_{CF} = 280 Hz), 129.9, 130.4, 133.3, 142.6, 154.9, 155.9, 159.9, 167.3, 170.4, 171.9, 203.9; ^{19}F NMR ($CDCl_3$, 282 MHz): δ −73.8 (d, J = 7.3 Hz); HRMS (FAB$^+$, m/z): Calcd. for $C_{41}H_{52}F_3NO_{17}{\cdot}H^+$, 888.3260. Found: 888.3242.

3.23. 2-Debenzoyl-2-(3-fluorobenzoyl)-10-acethyl-3′-dephenyl-3′-trifluoromethyldocetaxel (2e)

Yield 79% for two steps; white solid; mp 140–142 °C; $[\alpha]_D^{20}$-44 ($CHCl_3$, c = 0.26) ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, s, 17-CH_3), 1.24 (3H, s, 16-CH_3) 1.30 (9H, s, Boc), 1.60 (1H, bs, OH), 1.67 (3H, s, 19-CH_3), 1.80 (1H, m, H-6b), 1.88 (3H, s, 18-CH_3), 2.24 (3H, s, 10-Ac), 2.30 (2H, m, H-14a, H-14b), 2.38 (3H, s, 4-Ac), 2.42 (1H, bs, OH), 2.60 (1H, m, H-6a), 3.40 (1H, bs, OH), 3.80 (1H, d, J = 7 Hz, H-3), 4.15 (1H, d, J = 8 Hz, H-20b), 4.31 (1H, d, J = 8 Hz, H-20a), 4.40 (1H, dd, J = 7, 10 Hz H-7), 4.70 (1H, d, J = 1.2 Hz, H-2′), 4.80 (1H, m, H-3′), 4.95 (1H, d, J = 8 Hz, H-5), 5.20 (1H, d, J = 10 Hz, NH), 5.63 (1H, d, J = 7 Hz, H-2), 6.28 (2H, m, H-13, H-10), 7.32 (1H, m, arom.), 7.50 (1H, m, arom.), 7.80 (1H, m, arom.), 7.92 (1H, d, J = 8 Hz, arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.75 (19-CH_3), 15.0 (18-CH_3), 21.0 (10-Ac), 22.1 (17-CH_3), 22.5 (4-Ac), 26.9 (16-CH_3), 28.1 (Boc), 35.6 (14-CH_2), 35.7 (6-CH_2), 43.4 (15-C), 45.8 (3-CH), 54.0 (m, C3′), 58.8 (8-C), 68.3 (2′CH), 72.3, 73.4 (2-CH), 75.6 (10-CH), 76.6 (20-CH_2), 77.6 (7-CH), 79.3 (1-C), 81.4 (Boc), 81.6 (4-CH), 84.6 (5-CH), 117.4 (J_{CF} = 23 Hz, arom.), 121.1 (J_{CF} = 20 Hz, arom.), 124 (q, J_{CF} = 280 Hz CF_3), 126.2 (arom.), 130.7 (d, J_{CF} = 7 Hz, arom.), 131.0 (arom.), 133.5 (11-C), 141.9 (12-C), 154.8 (Boc), 163.1 (d, J_{CF} = 90 Hz, CF arom.), 166.1 (2-benz), 170.4 (10-Ac), 171.4 (4-Ac), 171.9 (1′-C), 203.6 (9-C); HRMS (ES$^+$, m/z): Calcd. for $C_{40}H_{49}NO_{15}F_4{\cdot}H^+$, 860.3117. Found: 860.3107. ^{19}F NMR, ($CDCl_3$, 282 MHz) δ −73.8 (d, J = 9 Hz), −111.61 (q, J = 6 Hz).

3.24. 2-Debenzoyl-2-(3-fluorobenzoyl)-10-propanoyl-3′-dephenyl-3′-trifluoromethyldocetaxel (2f)

Yield 85% for two steps; white solid, mp 128–130 °C; $[\alpha]_D^{20}$-28 ($CHCl_3$, c = 0.34); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, s, 16-CH_3), 1.23 (3H, t, CH_2CH_3), 1.24 (3H, s, 16-CH_3), 1.55 (9H, s, Boc), 1.67 (3H, s, 19-CH_3), 1.88 (4H, s, H-6b, 18-CH_3), 2.30 (2H, m, H-14a, H-14b), 2.38 (3H, s, 4-Ac), 2.60 (4H, m, OH, H-6a, CH_2CH_3), 3.32 (1H, d, J = 4 Hz, 2′-OH), 3.82 (1H, d, J = 7 Hz, H-3), 4.15 (1H, d, J = 8 Hz, H-20b), 4.31 (1H, d, J = 8 Hz, H-20), 4.40 (1H, m, H-7), 4.70 (1H, dd, J = 5, 1.2 Hz, H-2′), 7.80 (1H, m, arom.), 4.80 (1H, m, H-3′), 4.96 (1H, d, J = 8 Hz, H-5), 5.19 (1H, d, J = 10 Hz, NH), 5.63 (1H, d, J = 7 Hz, H-2), 6.21 (1H, m, H-13), 6.30 (1H, s, H-10), 7.32 (1H, m, arom.), 7.50 (1H, m, arom.), 7.92 (1H, m, arom.); ^{13}C NMR (100 MHz $CDCl_3$): δ 9.2 (CH_2CH_3), 9.7 (19-CH_3), 15.0 (18-CH_3), 22.1 (17-CH_3), 22.5 (4-Ac), 26.9 (16-CH_3), 27.8 (CH_2CH_3), 28.1 (Boc), 35.6 (14-CH_2), 35.7 (6-CH_2), 43.6 (15-C), 45.8 (3-CH), 54.1 (m, 3′-CH), 58.8 (8-C), 68.3 (2′-CH), 72.4 (7-CH), 73.5 (2-CH), 75.4 (10-CH), 75.6 (13-CH), 76.6 (20-CH_2), 79.4 (1-C), 81.4 (4-C), 81.6 (Boc), 84.6 (5-CH), 117.3 (d, J_{CF} = 16 Hz, arom.), 121.0 (d, J_{CF} = 21 Hz, arom.), 124.7 (q, J_{CF} = 280 Hz, CF_3), 126.2 (arom.), 130.7 (d, J_{CF} = 8 Hz, arom.), 131.4 (arom.), 133.6 (11-C), 141.8 (12-C), 154.8 (Boc), 163.0 (d, J_{CF} = 247 Hz, CF arom.), 166.4 (2-ben), 170.5 (4-Ac), 171.9 (1′-C), 174.8 (10-prop), 203.7 (9-C); HRMS (ES$^+$, m/z): Calcd. for $C_{41}H_{51}NO_{15}F_4H^+$, 874.3273. Found: 874.3316. ^{19}F NMR, ($CDCl_3$, 282 MHz) δ 73.8 (d, J = 6 Hz), −111.6 (q, J = 6 Hz).

3.25. 2-Debenzoyl-2-(3-fluorobenzoyl)-10-dimethylcarbomoyl-3′-dephenyl-3′-trifluoromethyldocetaxel (2g)

Yield 88 % for two steps; white solid; mp 175 °C; $[\alpha]_D^{20}$-59 (c = 4.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15 (3H, s, CH_3-17,)

1.25 (3H, s, CH_3-16), 1.30 (9H, s, Boc), 1.66 (3H, s, CH_3-19), 1.73 (1H, bs, OH), 1.88 (1H, m, H-6b), 1.90 (3H, s, CH_3-18), 2.20–2.37 (2H, m, H-14a,b), 2.38 (3H, s, 4-OAc), 2.53 (1H, m, H-6a), 2.96 (3H, s, $N(Me)_2$), 3.04 (3H, s, $N(Me)_2$), 3.20 (1H, s, OH), 3.51 (1H, bs, OH), 3.80 (1H, d, J = 7.2 Hz, H-3), 4.15 (1H, d, J = 8.4 Hz, H-20b), 4.29 (1H, d, J = 8.4 Hz, H-20a), 4.44 (1H, dd, J = 4.4, 10.8 Hz, H-7), 4.71 (1H, bs, H-2′), 4.78 (1H, m, H-3′), 4.97 (1H, d, J = 8.0 Hz, H-5), 5.27 (1H, d, J = 10.4 Hz, NH′), 5.62 (1H, d, J = 7.2 Hz, H-2), 6.26 (2H, m, H-13, H-10), 7.31 (1H, ddd, J = 1.6, 7.6, 7.6 Hz, arom.), 7.48 (1H, m, arom.), 7.80 (1H, d, J = 9.2 Hz, arom.), 7.92 (1H, d, J = 7.6 Hz, arom.); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.6, 15.1, 22.4, 22.5, 27.1, 28.1, 35.6, 35.7, 36.2, 36.9, 43.4, 45.8, 54.1 (m), 58.7, 68.3, 72.7, 73.5, 75.7, 76.3, 76.6, 79.4, 81.4, 81.5, 84.9, 117.3 (d, J_{CF} = 22.0 Hz), 121.0 (d, J_{CF} = 20.5 Hz), 124.0 (q, J_{CF} = 280 Hz), 126.2, 130.6 (d, J_{CF} = 7.6 Hz), 131.5 (d, J_{CF} = 7.6 Hz), 133.9, 142.3, 154.9, 156.3, 163.0 (d, J_{CF} = 246 Hz), 166.2, 170.4, 171.9, 205.6; ^{19}F NMR ($CDCl_3$, 282 MHz): δ –73.7 (d, J = 7.3 Hz); HRMS (FAB^+, m/z): Calcd. for $C_{41}H_{52}F_4N_2O_{15}{\cdot}H^+$, 889.3377. Found: 889.3383.

3.26. 2-Debenzoyl-2-(3-fluorobenzoyl)-10-methoxycarbonyl-3′-dephenyl-3′-trifluoromethyldocetaxel (2h)

Yield 74 % for two steps; white solid; mp 169 °C; $[\alpha]_D^{20}$-47 (c = 3.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.15 (3H, s, CH_3-17,) 1.24 (3H, s, CH_3-16), 1.30 (9H, s, Boc), 1.69 (3H, s, CH_3-19), 1.73 (1H, bs, OH), 1.83 (1H, m, H-6b), 1.91 (s, 3H, H-18), 2.25 (2H, m, H-14a,b), 2.38 (3H, s, 4-OAc), 2.57 (1H, m, H-6a), 3.40 (1H, bs, OH), 3.78 (1H, d, J = 7 Hz, H-3), 3.87 (3H, s, 10-MeO), 4.15 (1H, d, J = 8.4 Hz, H-20b), 4.30 (1H, d, J = 8.4 Hz, H-20a), 4.38 (1H, dd, J = 4.1, 11.0 Hz, H-7), 4.71 (1H, bs, H-2′), 4.77 (1H, m, H-3′), 4.95 (1H, d, J = 7.6 Hz, H-5), 5.28 (1H, d, J = 11.6 Hz, NH′), 5.63 (1H, d, J = 7 Hz, H-2), 6.11 (1H, s, H-10), 6.25 (1H, t, J = 8, 8 Hz, H- 13), 7.31 (1H, ddd, J = 2.4, 8, 8 Hz, arom.), 7.49 (1H, m, arom.), 7.79 (1H, d, J = 8.8 Hz, arom.), 7.91 (1H, d, J = 8.0 Hz, arom.); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.6, 15.1, 22.1, 22.5, 26.8, 28.1, 35.6, 35.8, 43.3, 45.9, 54.0 (m), 55.8, 58.8, 68.3, 72.3, 73.3, 75.6, 76.6, 78.3, 79.3, 81.3, 81.6, 84.6, 117.3 (d, J_{CF} = 22.8 Hz), 120.0 (d, J_{CF} = 21.3 Hz), 124.0 (q, J_{CF} = 280 Hz), 126.2, 130.7 (d, J_{CF} = 7.6 Hz), 131.5 (d, J_{CF} = 6.8 Hz), 133.17, 142.7, 154.9, 155.9, 163.0 (d, J_{CF} = 246 Hz), 166.2, 170.5, 171.9, 203.9; ^{19}F NMR, ($CDCl_3$, 282 MHz): δ –73.7 (d, J = 7.1 Hz); HRMS (FAB^+, m/z): Calcd. for $C_{40}H_{49}F_4NO_{16}{\cdot}H^+$, 876.3060. Found: 876.3068.

3.27. 2-Debenzoyl-2-(3-chlorobenzoyl)-10-acethyl-3′-dephenyl-3′-trifluoromethyldocetaxel (2i)

Yield 60% for two steps; mp 148–150 °C; $[\alpha]_D^{20}$-53.06 ($CHCl_3$, c = 0.49); ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, s, 17-CH_3), 1.30 (3H, s, 16-CH_3), 1.55 (9H, s, Boc), 1.84 (3H, s, 19-CH_3), 1.88 (1H, m, 6-Hb), 1.90 (1H, s, 18-CH_3), 2.28 (3H, s, 10-Ac), 2.30 (2H, m, 14-Ha, 14-Hb), 2.38 (3H, s, 4-Ac), 2.46 (1H, bs, OH), 2.60 (1H, m, H-6a), 3.37 (1H, bs, 2′-OH), 3.80 (1H, d, J = 7 Hz, H-3), 4.14 (1H, d, J = 8 Hz, H-20b), 4.29 (1H, d, J = 8 Hz, H-20a), 4.40 (1H, m, H-7), 4.70 (1H, bs, H-2′), 4.80 (1H, m, H-3′), 4.96 (1H, d, J = 8 Hz, H-5), 5.18 (1H, d, J = 10 Hz, NH), 5.60 (1H, d, J = 7 Hz, 2-H), 6.24 (1H, m, 13-H), 6.28 (1H, s, H-10), 7.45 (1H, m, arom.), 7.59 (1H, m, arom.), 8.00 (1H, d, J = 8 Hz, arom.), 8.13 (1H, s, arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.7 (19-CH_3), 15.0 (18-CH_3), 21.0 (10-Ac), 22.1 (17-CH_3), 22.4 (4-Ac), 26.9 (16-CH_3), 28.1 (Boc), 35.6 (6-CH_2), 35.8 (14-CH_2), 43.4 (15-C), 45.8 (3-CH), 55.8 (m, 3′-CH), 58.8 (8-C), 68.3 (2′CH), 72.2 (13-CH), 72.4 (7-CH), 73.5 (10-CH), 75.6 (2-CH), 76.5 (20-CH_2), 79.4 (1-C), 81.4 (Boc), 81.6 (4-C), 84.6 (5-CH), 124.0 (q, J_{CF} = 280 Hz, CF_3), 128.5 (arom.), 130.3 (arom.), 130.6 (arom.), 131.0 (arom.), 133.5 (arom.), 133.9 (11-C), 135.1 (C^{IV} arom.), 141.9 (12-C), 154.8 (Boc), 166.0 (2-benz), 170.4 (10-Ac), 171.4 (4-Ac), 171.9 (1′-C), 203.9 (9-C); HRMS (ES^+, m/z): Calcd. for $C_{40}H_{49}NO_{15}F_3Cl{\cdot}H^+$, 876.2821. Found: 876.2815. ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.8 (d, J = 9 Hz).

3.28. 2-Debenzoyl-2-(3-chlorobenzoyl)-10-propanoyl-3′-dephenyl-3′-trifluoromethyldocetaxel (2j)

Yield 72% for two steps; white solid, mp 154–157 °C; $[\alpha]_D^{20}$-58 ($CHCl_3$, c = 0.015); ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, s, 17-CH_3), 1.20 (6H, m, 16-CH_3, CH_3CH_2), 1.30 (9H, s, Boc), 1.67 (3H, s, 19-CH_3), 1.88 (4H, m, 18-CH_3, 6-Hb), 2.25 (2H, m, 14-Ha, 14-Hb), 2.38 (3H, s, 4-Ac), 2.55 (3H, m, CH_2CH_3, 6-Ha), 3.51 (1H, bs, 2′-OH), 3.81 (1H, d, J = 7 Hz, H-3), 4.15 (1H, d, J = 8 Hz, H-20b), 4.29 (1H, d, J = 8 Hz, H-20a), 4.40 (1H, m, H-7), 4.70 (1H, bs, H-2′), 4.77 (1H, m, H-3′), 4.96 (1H, d, J = 9 Hz, H-5), 5.26 (1H, d, J = 10 Hz, NH), 5.60 (1H, d, J = 7 Hz, H-2), 6.23 (1H, m, H-13), 6.30 (1H, s, H-10), 7.44 (1H, m, arom.), 7.58 (1H, m, arom.), 8.00 (1H, m, arom.), 8.11 (1H, m, arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.09 (CH_2CH_3), 9.62 (19-CH_3), 14.8 (18-CH_3), 21.9 (17-CH_3), 22.3 (4-Ac), 26.7 (16-CH_3), 27.6 (CH_2CH_3), 28.0 (Boc), 35.4 (6-CH_2), 35.6 (14-CH_2), 43.2 (15-C), 45.7 (3-CH), 54.0 (m, 3′-CH), 58.5 (8-C), 68.1 (2′-CH), 72.1 (13-CH), 73.2 (7-CH), 75.2 (10-CH), 75.4 (2-CH), 76.3 (20-CH_2), 79.1 (1-C), 81.1 (Boc), 81.3 (4-C), 84.4 (5-CH), 124.0 (q, J_{CF} = 280 Hz, CF_3), 128.1 (arom.), 129.9 (arom.), 130.3 (arom.), 130.7 (arom.), 133.2 (arom.), 133.6(11-C), 134.7 (arom.), 141.4 (12-C), 154.5 (Boc), 165.3 (2-benz), 170.0 (4-Ac), 171.5 (1′-C), 174.4 (10-prop.), 203.3 (9-C); HRMS (ES^+, m/z): Calcd. for $C_{41}H_{51}NO_{15}F_3Cl{\cdot}H^+$, 890.2978. Found: 890.2979. ^{19}F NMR ($CDCl_3$, 282 MHz) δ –73.8 (d, J = 9 Hz).

3.29. 2-Debenzoyl-2-(3-chlorobenzoyl)-10-dimethylcarbamoyl-3′-dephenyl-3′-trifluoromethyldocetaxel (2k)

Yield 58% for two steps; white solid; mp 175–177 °C; $[\alpha]_D^{20}$-62 ($CHCl_3$, c = 0.60); ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, s, 17-CH_3), 1.24 (3H, s, 16-CH_3), 1.30 (9H, s, Boc), 1.66 (3H, s, 19-CH_3), 1.87 (1H, m, H-6b), 1.90 (3H, s, 18-CH_3), 2.28 (2H, m, H-14a, H-14b), 2.38 (3H, s, 4-Ac), 2.50 (1H, m, H-6a), 2.96 (3H, s, NMe), 3.04 (3H, s, NMe), 3.20 (1H, bs, OH), 3.45 (1H, bs, 2′-OH), 3.80 (1H, d, J = 7 Hz, H-3), 4.14 (1H, d, J = 8 Hz, H-20b), 4.29 (1H, d, J = 8 Hz, 20-Ha), 4.42 (1H, dd, J = 7, 11 Hz, H-7), 4.70 (1H, bs, H-2′), 4.78 (1H, m, H-3′), 4.98 (1H, bd, J = 9 Hz, H-5), 5.20 (1H, d, J = 10.4 Hz, NH), 5.60 (1H, d, J = 7 Hz, H-2), 6.24 (2H, m, H-13, H-10), 7.45 (1H, m, arom.), 7.56 (1H, m, arom.), 7.99 (1H, m, arom.), 8.11 (1H, m, arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.56 (19-CH_3), 15.1 (18-CH_3), 22.4 (16-CH_3), 22.5 (4-Ac), 27.1 (17-CH_3), 28.1 (Boc), 35.6 (6-CH_2), 35.7 (NMe), 36.3 (NMe), 36.9 (14-CH_2), 43.3 (15-C), 45.8 (3-CH), 54.9 (m, 3′-CH), 58.7 (8-C), 68.7 (2′-CH), 72.7 (13-CH), 73.5 (7-CH), 75.8 (2-CH), 76.3 (10-CH), 76.5 (20-CH_2), 79.5 (1-C), 81.4 (4-C), 81.5 (Boc), 84.9 (5-CH), 124.2 (q, J_{CF} = 280 Hz, CF_3), 128.5 (arom.), 130.3 (arom.), 130.6 (arom.), 131.0 (arom.), 133.8 (arom.), 133.9 (11-C), 134.9 (arom.), 142.4 (12-C), 155.0 (Boc), 156.2 (10-carb), 166.0 (2-benz), 170.4 (4-Ac), 171.9 (1′-C), 205.6 (9-C); HRMS (ES^+, m/z): Calcd. For $C_{41}H_{52}N_2O_{15}F_3ClH^+$, 905.3087. Found: 905.3115. ^{19}F NMR, ($CDCl_3$, 282 MHz) δ –73.8 (d, J = 9.6 Hz).

3.30. 2-Debenzoyl-2-(3-chlorobenzoyl)-10-methoxycarbonyl-3′-dephenyl-3′-trifluoromethyldocetaxel (2l)

Yield 84% for two steps; white solid, mp 154–156 °C; $[\alpha]_D^{20}$-44 ($CHCl_3$, c = 0.18) ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, s, 17-CH_3), 1.24 (3H, s, 16-CH_3), 1.27 (9H, s, Boc), 1.68 (3H, s, 19-CH_3), 1.88 (1H, m, 6-Hb), 1.91 (3H, s, 18-CH_3), 2.28 (2H, m, 14-Ha, 14-Hb), 2.38 (3H, s, 4-Ac), 2.45 (1H, bs, OH), 2.56 (1H, m, 6-Ha), 3.40 (1H, bs, OH), 3.78 (1H, d, J = 7 Hz, 3-H), 3.87 (3H, s, OMe), 4.14 (1H, d, J = 7 Hz, 20-Hb), 4.29 (1H, d, J = 7 Hz, 20-Ha), 4.38 (1H, m, 7-H),

4.70 (1H, bs, 2′-H), 4.77 (1H, m, 3′-H), 4.96 (1H, d, J = 8 Hz, H-5), 5.20 (1H, d, J = 10 Hz, NH), 5.61 (1H, d, J = 7 Hz, H-2), 6.11 (1H, s, H-10), 6.24 (1H, m, H-13), 7.45 (1H, m, arom.), 7.58 (1H, d, J = 8 Hz, arom.), 8.00 (1H, d, J = 8 Hz, arom.), 8.12 (1H, s, arom.), ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.7 (19-CH_3), 15.1 (18-CH_3), 22.0 (17-CH_3), 22.4 (4-Ac), 26.8 (16-CH_3), 28.1 (Boc), 35.5 (6-CH_2), 35.8 (14-CH_2), 43.3 (15-C), 45.8 (3-CH), 54.0 (m, 3′-CH), 55.8 (OMe), 58.8 (8-C), 68.3 (2′-CH), 72.3 (13-CH), 73.4 (7-CH), 75.6 (2-CH), 76.5 (10-CH), 76.9 (20-CH_2), 79.4 (1-C), 81.3 (4-C), 81.6 (Boc), 84.6 (5-CH), 125.0 (q, J_{CF} = 280 Hz, CF_3), 128.5 (arom.), 130.1 (arom.), 130.6 (arom.), 131.0 (arom.), 133.1 (arom.), 133.9 (11-C), 135.1 (arom.), 142.7 (12-C), 154.8 (10-carb), 155.0 (Boc), 166.0 (2-benz), 170.4 (4-Ac), 171.9 (1′-C), 203.8 (9-C); ^{19}F NMR (282MHz, $CDCl_3$) δ −73.8 (d, J = 6 Hz); HRMS (ES^+, m/z): Calcd. for $C_{40}H_{49}NO_{16}F_3ClH^+$, 892.2770. Found: 892.2780.

3.31. 2-Debenzoyl-2-(3-azidobenzoyl)-10-acetyl-3′-dephenyl-3′-trifluoromethyldocetaxel (**2m**)

Yield 80% for two steps; white solid; mp 179 °C; $[\alpha]_D^{20}$-46 (c = 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.17 (3H, s, CH_3-16), 1.27 (3H, m, CH_3-17), 1.32 (9H, s, Boc), 1.69 (3H, s, CH_3-19), 1.91 (4H, m, H-6b, CH_3-18), 2.01 (1H, bs, OH), 2.27 (3H, s, 10-OAc),2.35 (1H, m, H-14), 2.39 (3H, s, 4-OAc), 2.58 (1H, ddd, J = 2.0, 6.5 Hz, H-6a), 3.43(1H, bs, OH), 3.84 (1H, d, J = 7.0 Hz, H-3), 4.18 (1H, d, J = 8.0 Hz, H-20b), 4.35 (1H, d, J = 8.0 Hz, H-20a), 4.44 (1H, dd, J = 4.0, 10.5 Hz, H-7), 4.72 (1H, s, H-5), 4.78 (1H, q, J = 8.5 Hz, H-3′), 4.98 (1H, d, J = 9.0 Hz, H-2′), 5.24 (1H, d, J = 10.5 Hz, NH′), 5.67 (1H, d, J = 7.0 Hz, H-2), 6.26 (1H, t, J = 9.0 Hz, H-13), 6.31 (1H, s, H-10), 7.24 (1H, d, J = 8.0 Hz), 7.50 (1H, t, J = 8.0 Hz), 7.85 (1H, s), 7.90 (1H, d, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.9, 15.1, 21.2, 22.2, 22.7, 27.0, 28.2, 35.7, 35.9, 43.5, 45.9, 53.3 (m), 58.4, 68.3, 72.3, 73.5, 75.7, 76.6, 77.5, 79.3, 81.4, 81.5, 84.7, 120.3, 124.6, 125.0 (q, J_{CF} = 280 Hz), 126.9, 130.4, 130.9, 133.5, 141.1, 141.8, 154.8, 166.3, 170.4, 171.3, 171.9, 203.5; ^{19}F NMR ($CDCl_3$, 282 MHz): δ −73.7 (d, J = 6.2 Hz); HRMS (FAB^+, m/z): Calcd. for $C_{40}H_{49}F_3N_4O_{15}{\cdot}H^+$, 883.3219. Found: 883.3226.

3.32. 2-Debenzoyl-2-(3-azidobenzoyl)-10-propanoyl-3′-dephenyl-3′-trifluoromethyldocetaxel (**2n**)

Yield 80 % for two steps; white solid; mp 170 °C; $[\alpha]_D^{20}$-47 (c = 3.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.16 (3H, s, CH_3-17), 1.25 (6H, m, CH_3-16, CH3), 1.32 (9H, s, Boc), 1.69 (3H, s, CH_3-19), 1.69 (1H, bs, OH), 1.90 (4H, m, H-6b, H-18), 2.32 (2H, m, H-14), 2.39 (3H, s, 4-OAc), 2.56 (4H, m, H-6a, $COCH_2$, OH), 3.55 (1H, bs, OH), 3.84 (1H, d, J = 7 Hz, H-3), 4.18 (1H, d, J = 8.4 Hz, H-20b), 4.34 (1H, d, J = 8.4 Hz, H-20a), 4.45 (1H, m, H-7), 4.72 (1H, bs, H-2′), 4.78 (1H, m, H-3′), 4.98 (1H, d, J = 8.1 Hz, H-5), 5.30 (1H, d, J = 10.2 Hz, NH′), 5.67 (1H, d, J = 7.2 Hz, H-2), 6.25 (1H, dd, J = 9, 9 Hz, H-13), 6.32 (1H, s, H-10), 7.24 (1H, d, J = 8.1 Hz), 7.50 (1H, dd, J = 7.8, 7.8 Hz), 7.84 (1H, s), 7.91 (1H, d, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.0, 9.5, 14.8, 21.9, 22.4, 26.6, 27.5, 27.8, 35.3, 35.5, 43.2, 45.6, 53.8 (m), 58.5, 68.1, 72.1, 73.3, 75.2, 75.4, 76.3, 79.0, 81.1, 81.2, 84.5, 120.0, 124.0, 124.5 (q, J_{CF} = 280 Hz), 126.7, 130.2, 130.7, 133.3, 140.9, 141.6, 154.6, 166.2, 170.3, 171.8, 174.6, 203.5; ^{19}F NMR, ($CDCl_3$, 282 MHz): δ −73.8 (d, J = 9.3 Hz); HRMS (FAB^+, m/z): Calcd. for $C_{41}H_{51}F_3N_4O_{15}{\cdot}H^+$, 897.3376. Found: 897.3406.

3.33. 2-Debenzoyl-2-(3-azidobenzoyl)-10-dimethylcarbamoyl-3′-dephenyl-3′-trifluoromethyldocetaxel (**2o**)

Yield 77 % for two steps; white solid; mp 188 °C; $[\alpha]_D^{20}$-51 (c = 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.17 (3H, s, CH_3-17,) 1.26 (3H, s, CH_3-16), 1.32 (9H, s, Boc), 1.69 (4H, s, CH_3-19, OH), 1.92 (4H, m, H-6b, CH_3-18), 2.29 (2H, m, H-14), 2.39 (3H, s, 4-OAc), 2.56 (1H, m, H-6a,), 2.98 (3H, s, N-CH_3), 3.06 (3H, s, N-CH_3), 3.22 (1H, bs, OH), 3.43 (1H, bs, OH), 3.84 (1H, d, J = 7.0 Hz, H-3), 4.18 (1H, d, J = 8.0 Hz, H-20b), 4.34 (1H, d, J = 8.0 Hz, H-20a), 4.48 (1H, m, H-7), 4.72 (1H, d, J = 3.5 Hz, H-2′), 4.79 (1H, m, H-3′), 4.99 (1H, d, J = 8 Hz, H-5), 5.24 (1H, d, J = 10.0 Hz, NH′), 5.66 (1H, d, J = 7.0 Hz, H-2), 6.27 (1H, m, H-10, H-13), 7.24 (1H, d, J = 8.5 Hz, arom.), 7.49 (1H, dd, J = 8.0, 8.0 Hz, arom.), 7.85 (1H, s, arom.), 7.91 (1H, d, J = 7.5 Hz, arom.); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.3, 14.9, 22.3, 22.4, 26.8, 27.9, 35.3, 35.4, 36.0 36.6, 43.2, 45.5, 53.6 (m), 58.5, 68.0, 72.3, 73.4, 75.5, 76.0, 76.3, 77.2, 79.2, 81.2, 84.7, 120.1, 124.4, 125.0 (q, J_{CF} = 280 Hz) 126.7, 130.2, 130.7, 133.6, 140.9, 142.0, 154.6, 156.0, 166.2, 170.2, 171.8, 205.4; ^{19}F NMR ($CDCl_3$, 282 MHz): δ −72.8 (d, J = 9.0 Hz); HRMS (FAB^+, m/z): Calcd. for $C_{41}H_{52}F_3N_5O_{15}{\cdot}Na^+$, 934.3304. Found: 934.3275.

3.34. 2-Debenzoyl-2-(3-azidobenzoyl)-10-methoxycarbonyl-3′-dephenyl-3′-trifluoromethyldocetaxel (**2p**)

Yield 53% for two steps; white solid; mp 173 °C; $[\alpha]_D^{20}$-42 (c = 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.17 (3H, s, CH_3-17,) 1.26 (3H, s, CH_3-16), 1.32 (9H, s, Boc), 1.63 (1H, bs, OH), 1.71 (3H, s, CH_3-19), 2.41 (4H, m, H-6b, CH_3-18), 2.32 (2H, m, H-14), 2.41 (3H, s, 4-OAc), 2.59 (1H, m, H-6a), 3.39 (1H, bs, OH), 3.82 (1H, d, J = 7.0 Hz, H-3), 3.89 (3H, s, 10-MeO), 4.19 (1H, d, J = 8.0 Hz, H-20b), 4.35 (1H, d, J = 8.0 Hz, H-20a), 4.42 (1H, m, H-7), 4.72 (1H, bs, H-2′), 4.78 (1H, m, H-3′), 4.98 (1H, d, J = 8 Hz, H-5), 5.22 (1H, d, J = 10 Hz, NH′), 5.69 (1H, d, J = 7.0 Hz, H-2), 6.13 (1H, s, H-10), 6.26 (1H, dd, J = 9, 9 Hz, H- 13), 7.24 (1H, d, J = 7.5 Hz, arom.), 7.50 (1H, dd, J = 8, 8 Hz, arom.), 7.85 (1H, s, arom.), 7.92 (1H, d, J = 8.0 Hz, arom.); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.5, 14.9, 21.8, 22.4, 26.6, 27.9, 29.7, 35.3, 35.5, 43.1, 45.5, 53.6 (m), 55.6, 58.5, 68.0, 71.9, 73.3, 75.4, 76.3, 78.1, 79.1, 81.1, 81.3, 84.4, 120.1, 124.0, 125.0 (q, J_{CF} = 280 Hz), 126.8, 130.2, 130.7, 132.9, 140.9, 142.6, 154.6, 155.7, 166.2, 170.3, 171.8, 203.7; HRMS (FAB^+, m/z): Calcd. for $C_{40}H_{49}F_3N_4O_{16}{\cdot}H^+$, 899.3168. Found: 899.3221.

3.35. 2-Dephenyl-2(3-azidobenzoyl)-3′-trifluoromethyldocetaxel (**2q**)

Yield 47 % for two steps; mp 184 °C; $[\alpha]_D^{20}$-27 (c = 0.60, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (3H, s, CH_3-17), 1.24 (3H, s, CH_3-16), 1.34 (9H, s, Boc), 1.64 (1H, bs, OH), 1.78 (3H, s, CH_3-19), 1.88 (1H, m, H-6a), 1.94 (3H, s, CH_3-18), 2.30 (2H, m, H-14), 2.41 (3H, s, H-4OAc), 2.63 (1H, m, H-6b), 3.44 (1H, bs, OH), 3.96 (1H, d, J = 7 Hz, H-3), 4.21 (1H, d, J = 8.4 Hz, H-20b), 4.28 (1H, dd, J = 4.5, 10.8 Hz, H-7) 4.37 (1H, d, J = 8.4 Hz, H-20a) 4.71 (1H, bs, H-10), 4.79 (1H, m, H-3′), 4.98 (1H, d, J = 7.8 Hz H-5), 5.25 (2H, m, H-2′, NH-3′), 5.70 (1H, d, J = 7 Hz, H-2), 6.26 (1H, dd, J = 9, 9 Hz, H-13), 7.23 (1H, d, J = 7.8 Hz, arom.), 7.49 (1H, dd, J = 8, 8 Hz, arom.), 7.86 (1H, s, arom.), 7.91 (1H, d, J = 7.8 Hz, arom.); ^{13}C (75.5 MHz, $CDCl_3$): δ 10.1, 14.6, 21.3, 22.7, 26.6, 28.2, 35.4, 35.8, 43.3, 46.7, 53.9 (m), 57.9, 68.4, 72.2, 73.7, 74.7, 75.5, 76.9, 79.1, 81.4, 81.6, 84.4, 120.3, 124.7, 125.0 (q, J_{CF} = 280 Hz), 127.0, 130.5, 131.0, 133.4, 140.8, 141.2, 154.9, 166.4, 170.7, 171.9, 204.4; ^{19}F NMR (282 MHz, $CDCl_3$): δ −73.85 (d, J = 6.2 Hz); HRMS (FAB^+, m/z): Calcd. for $C_{38}H_{47}F_3N_4O_{14}{\cdot}Na^+$, 863.2933. Found: 863.2960.

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