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Copper-free Sonogashira reaction using 7-chloro camptothecins

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Abstract—We studied copper-free Sonogashira reaction using 7-chloro camptothecins, and determined that *rac*-BINAP/Pd(OAc)$_2$ was an efficient catalyst for the coupling reaction. With this process, a number of 7-substituted camptothecins with a wide range of functional groups are potentially accessible. Besides, two drugs, SN-38 and BNP-1350, could be prepared by this method.

1. Introduction

Camptothecin (CPT **1**),[1] an alkaloid isolated from camptothecin acuminata by Wall and Wani in 1966, exhibits potent antitumor activity by inhibiting DNA topoisomerase I. However, the severe toxicity, the instability of the lactone and other defects[2] have promoted intensive efforts to study the structure–activity relationship (SAR) of CPT.

From SAR,[3] it appears that substituents in position 7 are very important to the activity of the CPT analogues. Recent studies have demonstrated that substitution in position 7 is no steric compromise.[4] A number of analogues with substituents in position 7 show enhanced biological profiles. One of them, SN-38 (**2**),[5] has been used in clinical practice to treat colon cancer. Others such as BNP-1350 (**3**),[6] silatecan (**4**),[7] ST-1481 (**5**),[8] lurtotecan (**6**)[9] are all in various stages of clinical development[10] (Fig. 1).

To date, the typical method to prepare 7-alkyl-substituted CPTs is the Minisci type reaction,[11] which proceeds via a carbon radical addition to electron-deficient heteroaromatics.[12] Although the Minisci type reaction has turned out to be fruitful, the radical reaction is potentially reactive to a broad range of functional groups.[13]

Thus, other processes are required to prepare 7-substituted CPTs. We envisioned that the Sonogashira coupling

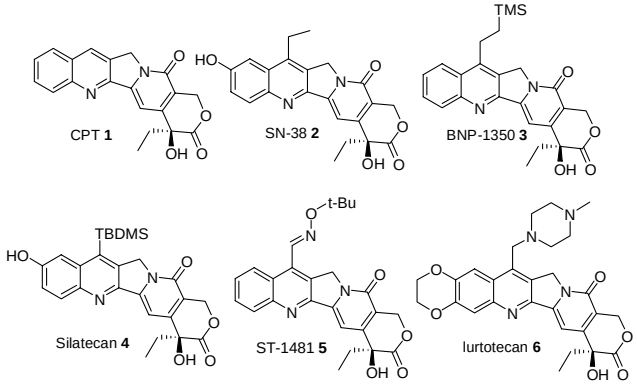

Figure 1.

reaction, which is carried out under mild reaction conditions and is compatible with a broad scope of functional groups,[14] could serve as a new approach to prepare 7-substituted CPT analogues. Although Hausheer and co-workers have reported coupling of 7-triflate camptothecins with a few alkynes under typical conditions,[15] the cocatalyst-free Sonogashira reaction using 7-chloride appears to be more appealing. In this paper, we report the development of a process to prepare 7-substituted CPT analogues by the copper-free Sonogashira coupling, and the application of our process to prepare SN-38 (**2**) and BNP-1350 (**3**).

2. Results and discussion

The synthesis of 7-chloride **8**, 7-bromide **9** and 7-iodide **10** CPT derivatives were accomplished as outlined in Scheme 1.

Keywords: Camptothecin; Topoisomerase I; Sonogashira coupling; Palladium; Catalysis.
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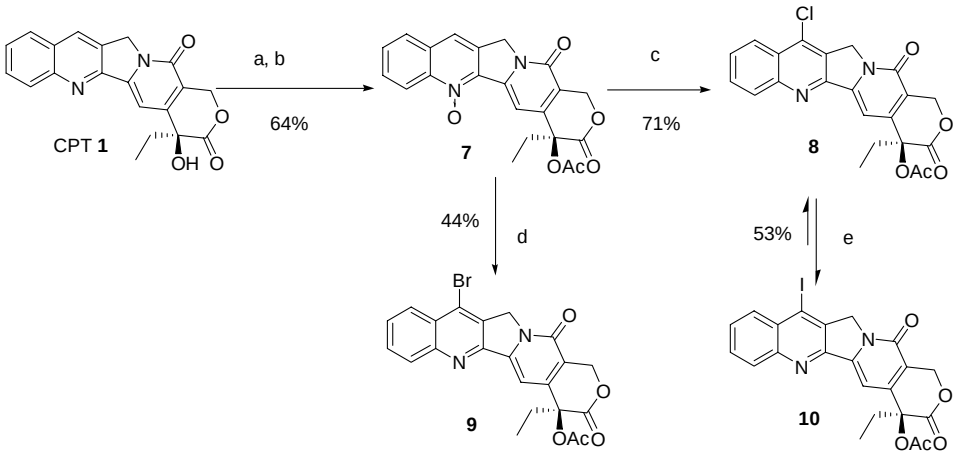
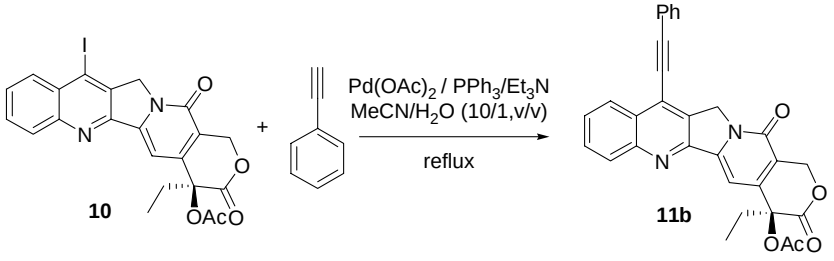


Scheme 1. Reagents and conditions: (a) Py/Ac_2O/DMAP; (b) 30% H_2O_2/AcOH; (c) DMF/$(COCl)_2$; (d) DMF/$POBr_3$; (e) NaI/AcCl/MeCN.



Scheme 2.

Thus, CPT (**1**) was acylated, and then oxidized in acetic acid with 30% hydrogen peroxide to give *N*-oxide **7**.[16] Then *N*-oxide **7** was treated with oxalyl chloride or phosphorus oxybromide in DMF to afford 7-chloride **8**[17] or 7-bromide **9** accordingly. The 7-iodide **10** was prepared by treating 7-chloride **8** with sodium iodide and acyl chloride in acetonitrile under reflux.[18] Unfortunately, an inseparable mixture of 7-iodide **10** and the starting material **8** was produced, because the chloride–iodide exchange is an equilibrium reaction. Longer reaction time did not change the results. The ^{1}H NMR indicated that the ratio of **10** to **8** was 4.8–1.

With these halides available, we attempted the Sonogashira reaction. Typical procedures for the Sonogashira reaction utilize catalytic amounts of palladium, a base and a copper salt as a cocatalyst.[19] Recent studies have shown that the copper cocatalyst induces homocoupling of terminal alkynes if the copper acetylide is exposed to oxidative agents or air.[20] In addition, we have previously reported that CPTs can be easily oxidized in air by catalytic amounts of copper (I) iodide.[21] Obviously, the copper-free Sonogashira reaction would be superior for our reaction. With respect to the organic halides, the following order of reactivity has been observed: aryl iodide > aryl bromide > aryl chloride.[22] As a result, we chose the inseparable mixture of iodide and chloride to test the coupling reaction with phenylacetylene under copper-free conditions. Thus, **11b** was synthesized smoothly using Sinou's protocol[23] (Scheme 2).

Although, 7-iodide **10** reacted with phenylacetylene smoothly, the inseparable 7-chloride **8** did not react with the alkyne under this condition, resulting in laborious separation after the reaction. Though 7-bromide **9** might be more reactive than 7-chloride **8**, the difficult availability of phosphorus oxybromide in large amounts and the low yield of **9** forced us to use the more easily available 7-chloride **8** to carry out the copper-free Sonogashira reaction.

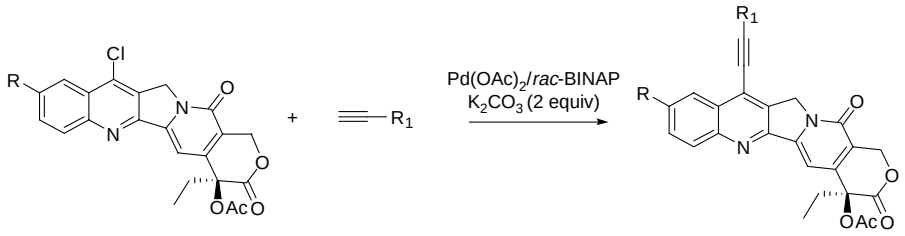
Although a significant volume of literature exists on copper-free Sonogashira reaction,[24] aryl chlorides are difficult to react under various conditions. Recently, a general protocol for employing aryl chlorides under copper-free conditions has been developed by Buchwald and co-workers.[25]

Table 1. Palladium-catalyzed Sonogashira coupling reaction of 7-chloride **8** with 1-heptyne[a]

Entry	Solvent	Base	Ligand	Yield (%)[b]
1[c]	Toluene	K_2CO_3	Tri-*o*-tolylphosphine	91
2[c]	Toluene	K_2CO_3	PPh_3	30
3	Toluene	K_2CO_3	DPPF	3
4	Toluene	K_2CO_3	DPPD	58
5	Toluene	K_2CO_3	DPPE	23
6	Toluene	K_2CO_3	*rac*-BINAP	95
7[d]	DMF	K_2CO_3	*rac*-BINAP	—
8	Toluene	$K_3PO_43H_2O$	*rac*-BINAP	82
9	Toluene	Cs_2CO_3	*rac*-BINAP	29
10	Toluene	DIEA	*rac*-BINAP	4
11[e]	Toluene	Tetramethyl guanidine	*rac*-BINAP	—

[a] Unless otherwise indicated, the reaction conditions were as following: 7-chloride **8** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), ligand (0.04 mmol), potassium carbonate (0.4 mmol), 1-heptyne (0.8 mmol), degassed toluene (17 mL) at 100 °C under Ar for 5 h.
[b] Isolated yields.
[c] 0.08 mmol ligand was used.
[d] Complete decomposition.
[e] Complicated products.

Table 2. The Sonogashira coupling catalyzed by $Pd(OAc)_2$/*rac*-BINAP[a]

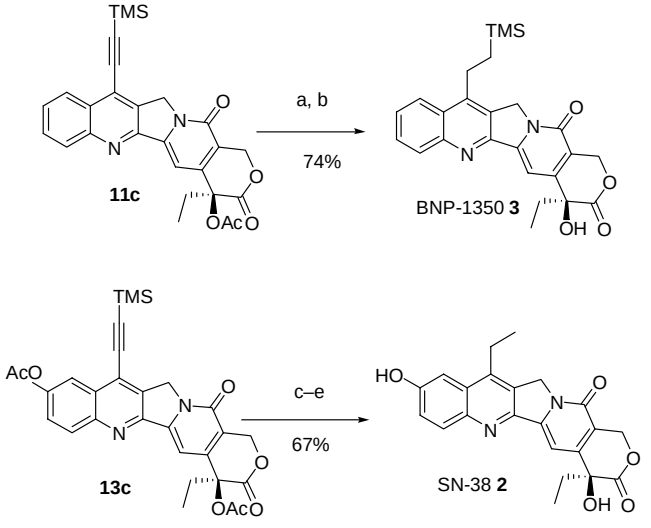


Entry	R	R_1	Time (h)	Product	Yield (%)[b]
1	H (8)	C_5H_{11}	5	11a	95
2	H (8)	Ph	9	11b	78
3[c]	H (8)	TMS	9	11c	68
4[d]	H (8)	2-Hydroxy-isopropyl	10	11d	75
5	OAc (12)	C_5H_{11}	5	13a	63
6	OAc (12)	Ph	9	13b	54
7[c]	OAc (12)	TMS	9	13c	60
8[d,e]	OAc (12)	2-Hydroxy-isopropyl	10	13d	—

[a] Unless otherwise indicated, the reaction conditions were as follows: 7-chloride (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), *rac*-BINAP (0.04 mmol), potassium carbonate (0.4 mmol), alkyne (0.8 mmol), degassed toluene (17 mL) at 100 °C under Ar for the indicated time.
[b] Isolated yields.
[c] $Pd(OAc)_2$ (0.04 mmol) and *rac*-BINAP (0.08 mmol) were used in a sealed tube.
[d] $Pd(OAc)_2$ (0.03 mmol) and *rac*-BINAP (0.06 mmol) were used.
[e] No reaction occurred.

However, the protocol has to use a ligand, which is not easily available. Thus, we had to establish the reaction condition for our reaction.

To screen for suitable reaction conditions, we chose to focus on the coupling of 7-chloride **8** with 1-heptyne as our test substrate. As shown in Table 1, among the six ligands tested, *rac*-BINAP was most effective in accomplishing the reaction. While tri-*o*-tolylphosphine was slightly less effective, it still provided a good yield. These data were in accordance with others' results that bulky, electron-rich phosphines could display unusually high reactivity in many coupling reactions. Among the five bases tested, anhydrous potassium carbonate was the best. In addition, DMF resulted in complete decomposition, while toluene furnished good yields.



Scheme 3. Reagents and conditions: (a) H_2/10% Pd/C; (b) $NaOCH_3$/CH_3OH; (c) KF/CH_3OH; (d) H_2/10% Pd/C; (e) $NaOCH_3$/CH_3OH.

Under these conditions, different camptothecin derivatives were coupled with a wide variety of terminal acetylenes (Table 2). Thus, 20-acetyl-7-chloro-camptothecin (**8**) reacted with an array of alkynes in moderate to good yields (entries 1–4). As illustrated in entries 5–7, the less reactive 10-acetoxyl-20-acetyl-7-chloro-camptothecin (**12**)[26] was also coupled with alkynes in moderate yields. Unfortunately, the $Pd(OAc)_2$/*rac*-BINAP catalytic system was ineffective for the coupling of **12** with 2-methyl-3-butyn-2-ol (entry 8).

After **11c** and **13c** were obtained, SN-38 (**2**) and BNP-1350 (**3**) were prepared as illustrated in Scheme 3. Compound **11c** was hydrogenated by 10% Pd/C, and then hydrolyzed with sodium methoxide in methanol to afford BNP-1350 (**3**) in 74% yield. Similarly, **13c** was treated with potassium fluoride in methanol, hydrogenated by 10% Pd/C, and then hydrolyzed with sodium methoxide in methanol to produce SN-38 (**2**) in 67% yield.

3. Conclusion

In summary, we have determined that *rac*-BINAP/$Pd(OAc)_2$ serves as an efficient catalyst for Sonogashira coupling to prepare 7-substituted CPT analogues. With this process, SN-38 (**2**) and BNP-1350 (**3**) have also been prepared. In addition, this study provides another example of the usefulness of bulky, electron-rich phosphines in palladium-catalyzed coupling reactions.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on either Gemini-300 or Bruker AM-400. Chemical shifts (δ ppm) were reported for signal center, and coupling constant J were

reported in units of Hz. High-resolution mass spectra were recorded on Varian MAT-711, MAT-95 or HT-5989 mass spectrometer. Column chromatograph was performed on 200–300 mesh silica gel. All reagents were used directly as obtained commercially, unless otherwise noted.

4.1.1. 20-Acetyl-7-(dec-1-ynyl)-camptothecin (11a). To a mixture of 7-chloride **8** (85 mg, 0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), *rac*-BINAP (0.04 mmol) and potassium carbonate (0.4 mmol), under an argon atmosphere, was added a solution of 1-heptyne (0.8 mmol) in degassed toluene (17 mL). The reaction mixture was heated at 100 °C for 5 h. Then the solvent was evaporated to give a residue, which was purified by flash column chromatography on silica gel (acetone/chloroform, 1:20) to give 92 mg of pure **11a** (95% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.93 (t, J=7.3 Hz, 6H), 1.38–1.57 (m, 4H), 1.71–1.82 (m, 2H), 2.21 (s, 3H), 2.10–2.30 (m, 2H), 2.66 (t, J=7.6 Hz, 2H), 5.26 (s, 2H), 5.40 (d, J=17.2 Hz, 1H), 5.68 (d, J=17.2 Hz, 1H), 7.18 (s, 1H), 7.68 (dd, J=8.0, 8.1 Hz, 1H), 7.81 (dd, J=7.9, 8.2 Hz, 1H), 8.17 (d, J=8.6 Hz, 1H), 8.32 (d, J=8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=7.5, 13.9, 19.9, 20.7, 22.1, 28.1, 31.2, 31.8, 50.3, 67.1, 73.9, 75.8, 96.1, 107.5, 120.3, 126.0, 126.6, 127.9, 128.1, 129.8, 130.5, 130.7, 145.8, 146.4, 148.8, 151.5, 157.3, 167.5, 169.8. MS (EI): m/z=484, 396 (base peak). HRMS (EI): m/z calcd for $C_{29}H_{28}N_2O_5$ [M^+]: 484.1998; found: 484.1993.

4.1.2. 20-Acetyl-7-(2-phenylethynly)-camptothecin (11b). To a mixture of 7-chloride **8** (85 mg, 0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), *rac*-BINAP (0.04 mmol) and potassium carbonate (0.4 mmol), under an argon atmosphere, was added a solution of phenylacetylene (0.8 mmol) in degassed toluene (17 mL). The reaction mixture was heated at 100 °C for 9 h. Then the solvent was evaporated to give a residue, which was purified by flash column chromatography (acetone/chloroform, 1:20) to give 76 mg of pure **11b** (78% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.98 (t, J=7.4 Hz, 3H), 2.12–2.30 (m, 2H), 2.25 (s, 3H), 5.38 (s, 2H), 5.39 (d, J=17.2 Hz, 1H), 5.68 (d, J=17.2 Hz, 1H), 7.22 (s, 1H), 7.46–7.51 (m, 3H), 7.71–7.76 (m, 3H), 7.86 (dd, J=6.9, 7.1 Hz, 1H), 8.22 (d, J=8.5 Hz, 1H), 8.43 (d, J=8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=7.4, 20.6, 31.6, 50.1, 66.8, 75.8, 81.6, 95.9, 104.4, 120.2, 121.0, 125.2, 125.6, 127.1, 128.2, 128.6, 129.7, 130.1, 130.6, 132.1, 145.8, 146.2, 148.5, 151.4, 157.0, 167.4, 169.7. MS (EI): m/z=490, 430 (base peak). HRMS (EI): m/z calcd for $C_{30}H_{22}N_2O_5$ [M^+]: 490.1529; found: 490.1527.

4.1.3. 20-Acetyl-7-(2-trimethylsilylethynly)-camptothecin (11c). To a mixture of 7-chloride **8** (85 mg, 0.2 mmol), $Pd(OAc)_2$ (0.04 mmol), *rac*-BINAP (0.08 mmol) and potassium carbonate (0.4 mmol), under an argon atmosphere, was added a solution of trimethylsilylacetylene (0.8 mmol) in degassed toluene (17 mL). The reaction mixture was heated at 100 °C for 9 h in sealed tube. Then the solvent was evaporated to give a residue, which was purified by flash column chromatography (acetone/chloroform, 1:20) to give 66 mg of pure **11c** (68% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.38 (s, 9H), 0.97 (t, J=7.7 Hz, 3H), 2.11–2.29 (m, 2H), 2.22 (s, 3H), 5.31 (s, 2H), 5.40 (d, J=17.1 Hz, 1H), 5.68 (d, J=17.1 Hz, 1H), 7.19 (s, 1H), 7.73 (dd, J=6.9, 7.8 Hz, 1H), 7.85 (dd, J=7.0, 6.9 Hz, 1H), 8.20 (d, J=8.6 Hz, 1H), 8.34 (d, J=8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=−0.2, 7.5, 20.7, 31.7, 50.2, 67.1, 75.8, 96.1, 96.6, 111.9, 120.5, 125.3, 125.9, 127.6, 128.5, 129.9, 130.8, 145.7, 146.2, 148.7, 151.6, 157.2, 167.5, 169.8. MS (EI): m/z=486, 149 (base peak). HRMS (EI): m/z calcd for $C_{27}H_{26}S_iN_2O_5$ [M^+]: 486.1611; found: 486.1618.

4.1.4. 20-Acetyl-7-(3,3-dimethly-3-hydroxyl-1-propylnyl)-camptothecin (11d). To a mixture of 7-chloride **8** (85 mg, 0.2 mmol), $Pd(OAc)_2$ (0.03 mmol), *rac*-BINAP (0.06 mmol) and potassium carbonate (0.4 mmol), under an argon atmosphere, was added a solution of 2-methyl-3-butyn-2-ol (0.8 mmol) in degassed toluene (17 mL). The reaction mixture was heated at 100 °C for 10 h. Then the solvent was evaporated to give a residue, which was purified by flash column chromatography (acetone/chloroform, 1:5) to give 71 mg of pure **11d** (75% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.97 (t, J=7.5 Hz, 3H), 1.78 (s, 6H), 2.10–2.31 (m, 2H), 2.22 (s, 3H), 5.29 (s, 2H), 5.39 (d, J=17.4 Hz, 1H), 5.67 (d, J=17.4 Hz, 1H), 7.19 (s, 1H), 7.71 (dd, J=7.8, 7.2 Hz, 1H), 7.84 (dd, J=8.7, 7.8 Hz, 1H), 8.20 (d, J=8.4 Hz, 1H), 8.29 (d, J=8.1 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=7.5, 20.5, 30.2, 31.2, 50.3, 64.1, 66.2, 73.7, 75.8, 95.2, 111.1, 119.2, 124.1, 125.4, 126.9, 128.6, 129.6, 130.9, 131.7, 145.5, 146.0, 147.8, 151.9, 156.5, 167.3, 169.6. MS (EI): m/z=472, 384 (base peak). HRMS (EI): m/z calcd for $C_{27}H_{24}N_2O_6$ [M^+]: 472.1634; found: 472.1674.

4.1.5. 10-Acetoxyl-20-acetyl-7-(dec-1-ynyl)-camptothecin (13a). To a mixture of 7-chloride **12** (97 mg, 0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), *rac*-BINAP (0.04 mmol) and potassium carbonate (0.4 mmol), under an argon atmosphere, was added a solution of 1-heptyne (0.8 mmol) in degassed toluene (17 mL). The reaction mixture was heated at 100 °C for 5 h. Then the solvent was evaporated to give a residue, which was purified by flash column chromatography (acetone/chloroform, 1:20) to give 68 mg of pure **13a** (63% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.92 (t, J=7.2 Hz, 6H), 1.36–1.54 (m, 4H), 1.67–1.77 (m, 2H), 2.09–2.27 (m, 2H), 2.18 (s, 3H), 2.36 (s, 3H), 2.62 (t, J=7.2 Hz, 2H), 5.22 (s, 2H), 5.35 (d, J=17.4 Hz, 1H), 5.63 (d, J=17.4 Hz, 1H), 7.13 (s, 1H), 7.53 (dd, J=9.0, 2.7 Hz, 1H), 7.98 (d, J=2.7 Hz, 1H), 8.13 (d, J=9.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=7.4, 13.8, 19.8, 20.5, 21.0, 22.0, 27.9, 31.0, 31.6, 50.2, 66.9, 73.5, 75.7, 95.9, 107.7, 116.9, 120.2, 125.9, 126.2, 128.4, 130.8, 131.1, 145.7, 146.2, 146.6, 149.9, 151.2, 157.1, 167.4, 169.1, 169.7. MS (EI): m/z=542, 482 (base peak). HRMS (EI): m/z calcd for $C_{31}H_{30}N_2O_7$ [M^+]: 542.2053; found: 542.2043.

4.1.6. 10-Acetoxyl-20-acetyl-7-(2-phenylethynly)-camptothecin (13b). To a mixture of 7-chloride **12** (97 mg, 0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), *rac*-BINAP (0.04 mmol) and potassium carbonate (0.4 mmol), under an argon atmosphere, was added a solution of phenylacetylene (0.8 mmol) in degassed toluene (17 mL). The reaction mixture was heated at 100 °C for 9 h. Then the solvent was evaporated to give a residue, which was purified by flash column chromatography (acetone/chloroform, 1:20) to give 59 mg of pure **13b** (54% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.98 (t, J=7.5 Hz, 3H), 2.11–2.33

(m, 2H), 2.22 (s, 3H), 2.41 (s, 3H), 5.36 (s, 2H), 5.40 (d, J=17.4 Hz, 1H), 5.68 (d, J=17.4 Hz, 1H), 7.17 (s, 1H), 7.43–7.49 (m, 3H), 7.60 (dd, J=9.0, 2.4 Hz, 1H), 7.69–7.72 (m, 2H), 8.13 (d, J=2.4 Hz, 1H), 8.21 (d, J=9.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=7.5, 20.6, 21.2, 31.7, 50.2, 66.9, 75.8, 81.4, 96.1, 104.9, 116.8, 120.5, 121.0, 125.3, 126.2, 128.0, 128.7, 130.2, 130.8, 131.3, 132.1, 145.8, 146.1, 146.7, 150.2, 151.5, 157.1, 167.4, 169.1, 169.8. MS (EI): m/z=548, 418 (base peak). HRMS (EI): m/z calcd for $C_{32}H_{24}N_2O_7$ [M^+]: 548.1584; found: 548.1597.

4.1.7. 10-Acetoxyl-20-acetyl-7-(2-trimethylsilylethynly)-camptothecin (13c). To a mixture of 7-chloride **12** (97 mg, 0.2 mmol), $Pd(OAc)_2$ (0.04 mmol), *rac*-BINAP (0.08 mmol) and potassium carbonate (0.4 mmol), under an argon atmosphere, was added a solution of trimethylsilylacetylene (0.8 mmol) in degassed toluene (17 mL). The reaction mixture was heated at 100 °C for 9 h in sealed tube. Then the solvent was evaporated to give a residue, which was purified by flash column chromatography (acetone/chloroform, 1:20) to give 65 mg of pure **13c** (60% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.38 (s, 9H), 0.97 (t, J=6.9 Hz, 3H), 2.10–2.31 (m, 2H), 2.20 (s, 3H), 2.42 (s, 3H), 5.30 (s, 2H), 5.40 (d, J=18 Hz, 1H), 5.68 (d, J=18 Hz, 1H), 7.17 (s, 1H), 7.60 (dd, J=9.3, 2.7 Hz, 1H), 8.05 (d, J=2.4 Hz, 1H), 8.20 (d, J=9.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=−0.3, 7.5, 20.7, 21.2, 31.7, 50.2, 67.0, 75.8, 96.1, 96.3, 112.4, 116.9, 120.6, 125.1, 126.2, 128.2, 131.3, 131.4, 145.8, 146.1, 146.7, 150.2, 151.6, 157.2, 167.4, 169.1, 169.8. MS (EI): m/z=544, 414 (base peak). HRMS (EI): m/z calcd for $C_{29}H_{28}SiN_2O_7$ [M^+]: 544.1666; found: 544.1670.

4.1.8. BNP-1350 (3). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.17 (s, 9H), 0.87–0.94 (m, 2H), 1.03 (t, J=7.2 Hz, 3H), 1.84–1.92 (m, 2H), 3.06–3.11 (m, 2H), 5.22 (s, 2H), 5.30 (d, J=16.8 Hz, 1H), 5.75 (d, J=16.8 Hz, 1H), 7.62–7.67 (m, 2H), 7.79 (dd, J=7.2, 7.8 Hz, 1H), 8.02 (d, J=8.4 Hz, 1H), 8.22 (d, J=8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=−1.8, 7.8, 17.7, 24.1, 31.5, 49.2, 66.3, 72.7, 98.0, 118.4, 123.2, 126.0, 126.6, 127.6, 129.9, 130.7, 147.0, 149.4, 150.1, 151.9, 157.6, 173.9. MS (EI): m/z=448, 448 (base peak). HRMS (EI): m/z calcd for $C_{25}H_{28}SiN_2O_4$ [M^+]: 448.1818; found: 448.1814.

4.1.9. SN-38 (2). ^{1}H NMR (300 MHz, DMSO-d_6): δ=0.85 (t, J=7.5 Hz, 3H), 1.28 (t, J=7.5 Hz, 3H), 1.80–1.88 (m, 2H), 3.06 (q, J=7.5 Hz, 2H), 5.25 (s, 2H), 5.39 (s, 2H), 7.23 (s, 1H), 7.38 (s, 1H), 7.40 (d, J=9.9 Hz, 1H), 8.01 (d, J=9.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=7.8, 13.4, 22.3, 30.2, 49.4, 65.3, 72.4, 95.9, 104.7, 118.1, 122.3, 127.9, 128.2, 131.6, 142.8, 143.6, 146.4, 148.8, 150.1, 156.5, 156.9, 172.6. MS (EI): m/z=392, 348 (base peak). HRMS (EI): m/z calcd for $C_{22}H_{20}N_2O_5$ [M^+]: 392.1372; found: 392.1383.

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26. 10-Acetoxyl-20-acetyl-7-chloro-camptothecin (**12**) was prepared in three steps from 10-hydroxyl-camptothecin in 50% yield by a process similarly with the preparation of 20-acetyl-7-chloro-camptothecin (**8**).