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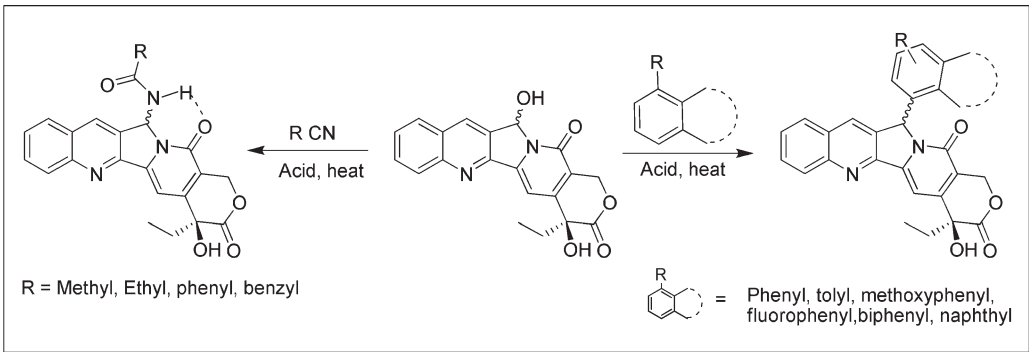

A variety of 5-aryl-(20*S*)-camptothecin derivatives were synthesized by the reaction of 5-hydroxy-(20*S*)-camptothecin with aromatic hydrocarbons under Friedel-Craft reaction conditions in moderate to good yield as diastereomeric pairs. The methodology was then extended for the synthesis of 5-amido-(20*S*)-camptothecin derivatives by reacting 5-hydroxy-(20*S*)-camptothecin with alkyl and aryl nitriles under Ritter type reaction conditions. The reaction is presumed to proceed through an iminium ion intermediate under Friedel Craft and Ritter type reaction condition, which is further trapped by nucleophile present in the reaction medium.

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INTRODUCTION

(20*S*)-Camptothecin **1** is an alkaloid with novel pentacyclic structural frame work, isolated from leaves and barks of Camptotheca accuminata (Nyssacease) and *Nothapodytes foetida* [1]. Camptothecin displayed significant activity in mice leukemia L1210 and Walker 256 sarcoma in rats (Fig. 1) [2]. Camptothecin exerts its biological effects by stabilizing the covalent binary complex formed between DNA and topoisomerase 1 inhibitor during DNA relaxation time and lead to cell death [3]. Antitumor drugs such as irinotecan **3** (formerly called as CPT-11 and now called campstar) [4], and topotecan **4** (now called hycamtin) [5] were developed from camptothecin and currently used for the treatment of ovarian and small lung cancer, and for colorectal cancer. At present, a number of camptothecin-based drugs are in different stages of clinical development [6].

RESULTS AND DISCUSSIONS

Several reports are known in the literature for the synthesis of (20*S*)-camptothecin analogues by utilizing the masked aldehyde functionality **5** (Scheme 1) embedded in 5-hydroxy-(20*S*)-camptothecin **2** under basic reaction conditions [7]. However, literature reports on the reactivity of 5-hydroxy-(20*S*)-camptothecin **2** under Lewis or protic acid conditions are very rare [8]. 5-Hydroxy-(20*S*)-camptothecin **2** can form an iminium ion **6** under Lewis or protic acid conditions, which on further reaction with nucleophiles will yield 5-substituted (20*S*)-camptothecin analogues. To the best of our knowledge, 5-aryl or 5-amido-(20*S*)-camptothecin analogues are not reported in the literature. In the course of a synthetic project, we need a general method to prepare 5-aryl and 5-amido-(20*S*)-camptothecin analogues and found that 5-hydroxy-(20*S*)-camptothcin is one of the potential synthon for synthesis of these target molecules. Herein, we report a full account of our studies toward the successful synthesis of these novel camptothecin analogues.

The 5-hydroxy-(20*S*)-camptothecin required for our study was prepared according to the reported literature procedure [9]. 5-Aryl and 5-amido-(20*S*)-camptothecin analogues described herein were synthesized by a one pot reaction of 5-hydroxy-(20*S*)-camptothecin **2** with various aromatic hydrocarbons, aryl, and alkyl nitriles in

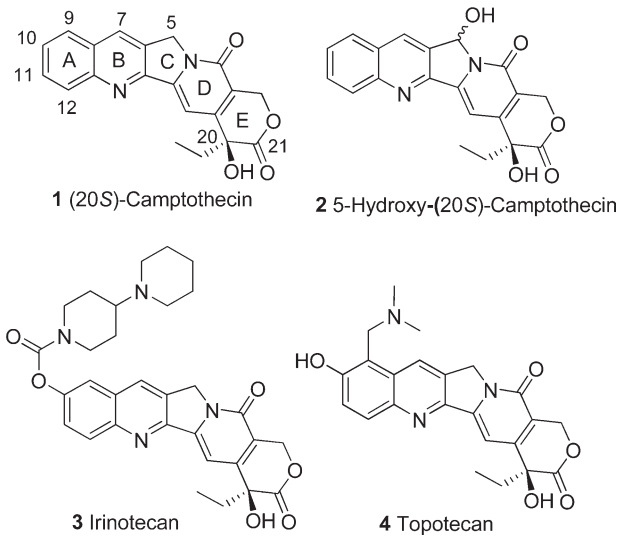


Figure 1. Structure of camptothecin and camptothecin based anticancer drugs.

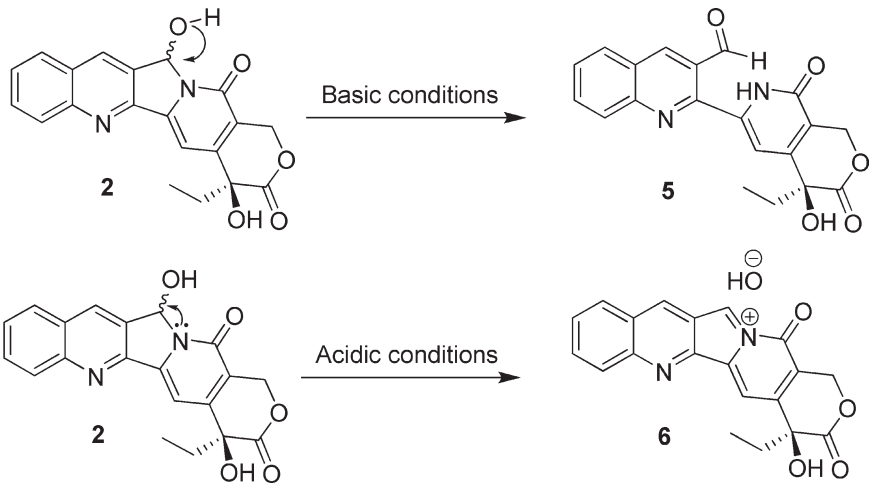
presence of protic acids at moderate temperature in good to average yields. Synthesis of 5-aryl and 5-amido-(20*S*)-camptothecin derived from 5-hydroxy-(20*S*)-camptothecin is outlined in Scheme 2. To a suspension of 5-hydroxy-(20*S*)-camptothecin **2** in toluene (**7**), sulphuric acid was added at room temperature and the reaction mixture was refluxed in toluene at 110–115°C for 4–5 h. After complete disappearance of the starting material **2** (by TLC), reaction mixture was cooled to room temperature, diluted with ethyl acetate and washed with 5% aq. sodium bicarbonate solution and water. Organic layer was then separated, concentrated under reduced pressure, and the product was isolated by chromatographic purification in 66% of yield (Scheme 2) as light yellow solid. HPLC analysis of the product indicated the presence of four isomers in the ratio 22.13%, 45.38%, 7.81%, and 23.09%, respectively along with two unidentified impurities of around 1.3%. Products were then separated by preparative TLC as diastereomeric pairs. Structure of the products was then confirmed by NMR, Mass spectrum analysis, and by other analytical methods as 5-(4-methylphenyl)-(20*S*)-camptothecin (**8**) as major and 5-(2-methylphenyl)-(20*S*)-camptothecin (**9**) as minor isomer [10].

To prove the assigned structure, NOESY, HMBC, and COSY NMR experiments were conducted. These studies further confirmed 5-para isomer **8** as the major regioisomer formed in the reaction. Our attempt to generate a single crystal of the major diastereomer from product mixture with various solvents were not successful, however a single crystal in the form of twin crystal was able to generate from chloroform and XRD of the twin crystal was studied further. ORTEP diagram of the twin crystal confirms (5*R*), (20*S*) configuration at asymmetric centers of the products **8** and **9** [11]. Thus, diastereoselectivity of the reaction is partly influenced by remote chiral C-(20*S*) carbon atom in which bulky ethyl group is trans to the incoming nucleophile (Fig. 2).

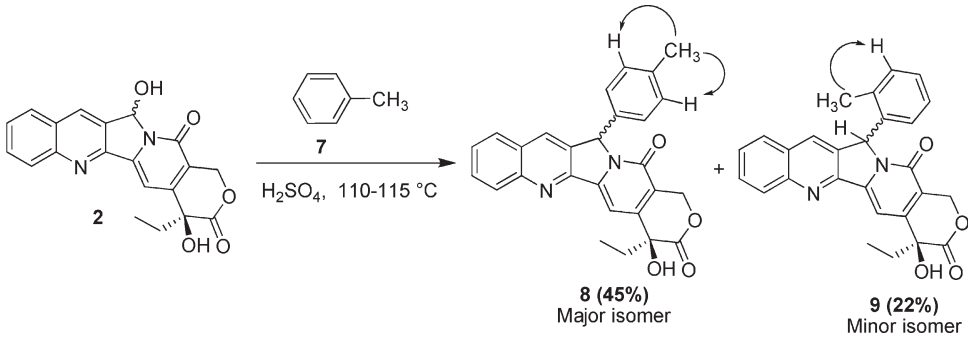
A typical mechanism of the reaction involves protonation of C5-hydroxyl group by protic acid and subsequent elimination of water molecule leads to the formation of iminium ion **11**. Iminium ion **11** is then trapped by the nucleophile present (in this case toluene) in the reaction medium resulted in the formation of **12**, which on further proton loss leads to products **8** and **9**. Depending on the nature of substitution pattern on aromatic hydrocarbon, reaction will result regioisomeric mixture of 5-aryl-(20*S*)-camptothecins as diastereomeric pairs (Scheme 3).

Encouraged by these findings, reactivity of 5-hydroxy-(20*S*)-camptothecin toward other aromatic hydrocarbons were then studied in detail under protic acid conditions. 5-Hydroxy-(20*S*)-camptothecin (**2**) thus

Scheme 1



Scheme 2



was reacted with aromatic hydrocarbons such as benzene (**13**), fluorobenzene (**14**), anisole (**15**), biphenyl (**16**), and naphthalene (**21**), respectively in presence of various protic acids, and the products 5-aryl-(20*S*)-camptothecins (**17–20b**) were isolated in moderate to good yields. The reaction of 5-hydroxy-(20*S*)-camptothecin (**2**) with benzene, fluorobenzene, anisole, and biphenyl were performed under neat reaction conditions in presence of sulphuric acid. As expected, the reaction of fluorobenzene, anisole and biphenyl with **2** resulted in regioisomeric mixture of ortho and para products as a diastereomeric pairs, where as benzene resulted (5*R*,*S*)-phenyl-(20*S*)-camptothecin **17** in 1.2:1 diastereomeric ratio in 86% of yield. In the case of reaction of **2** with fluorobenzene (**14**), anisole (**15**), and biphenyl (**16**), major product isolated were the para regioisomer. The formation of para regioisomer as major product in these reactions can be attributed solely to the less steric crowding during nucleophilic attack on the so-formed iminium ion by the substituted aromatic hydrocarbons. Thus the reaction of **2** with fluorobenzene (**14**) resulted 5-(4-fluorophenyl)-(20*S*)-camptothecin (**18a**) and 5-(2-fluorophenyl)-(20*S*)-camptothecin (**18b**) in overall 37.9% of yield, where as anisole (**15**) and biphenyl (**16**) resulted the products, **19a, b** and **20a**, **b** in overall 43.3% and 45.7% yields, respectively (Scheme 4). Structure of the products was then confirmed by NMR, mass spectral data, and by other analytical and spectroscopic methods.

Reaction of 5-hydroxy-(20*S*) camptothecin **2** with naphthalene **21** was then studied in detail. The reaction was conducted in 1, 2-dichloroethane in presence of trifluoroacetic acid at 60–70°C (Scheme 5). Marked improvement in diastereoselectivity was observed in this reaction, as naphthalene resulted product, (5*R*,*S*)-naphthyl-(20*S*)-camptothecin (**22**) in 5:1 ratio, however product was isolated in low yield (40%). The low yield of product formation **22** is solely due to increased steric repulsion between the planar bulky molecules, naphthalene, and camptothecin.

In principle, any functionality capable of producing a carbonium ion under acidic conditions will able to participate in Ritter type reaction [12]. Thus we have attempted the reaction of **2** with acetonitrile in a view to synthesis hither to unreported 5-amido substituted camptothecins under Ritter reaction conditions (Scheme 6). Thus to a suspension of 5-hydroxy-(20*S*)-camptothecin **2** in acetonitrile (**23**), trifluoroacetic acid was added, and the reaction mixture was refluxed for 6–8 h. After usual aqueous work up and column chromatographic purification, product 5-acetamido-(20*S*)-camptothecin (**24**) was isolated in low yield (25%) as yellow crystalline solid without any diastereoselectivity. The LCMS analysis of the crude reaction mixture also indicated the formation of 5-diacetamido-(20*S*)-camptothecin (**25**) in 5–7%. However our attempt to isolate the product **25** in pure form was not successful.

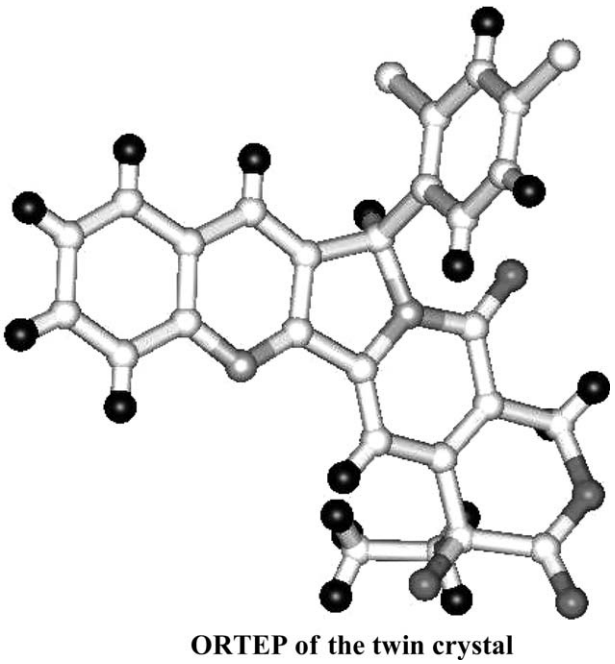
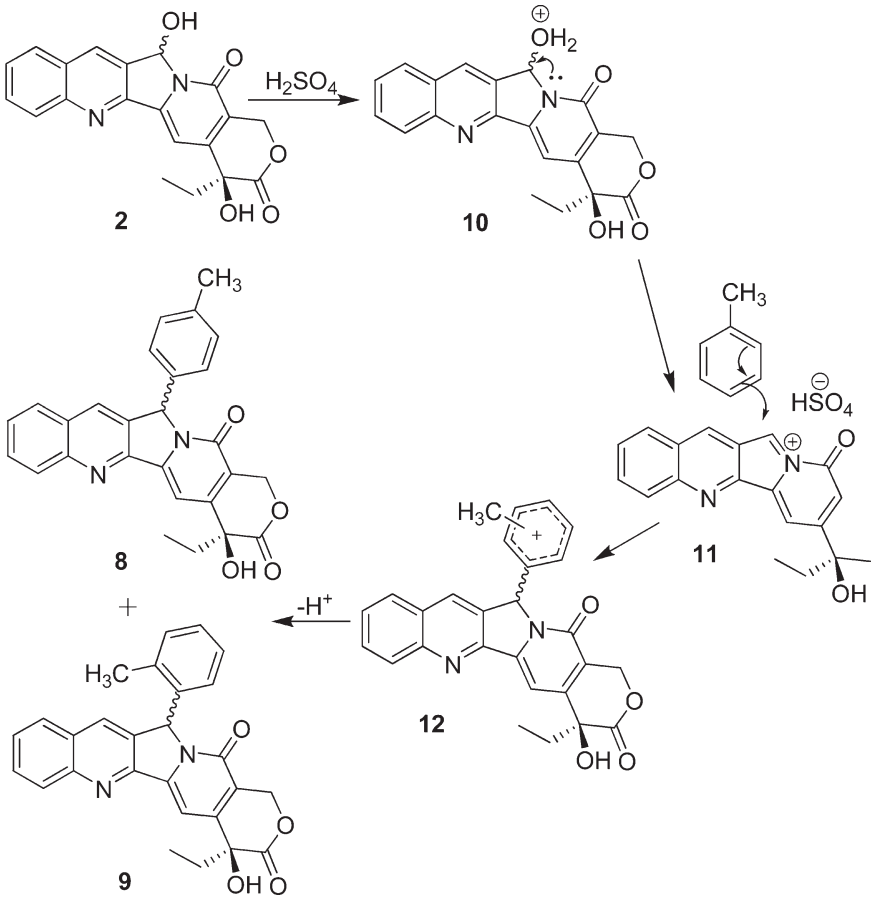


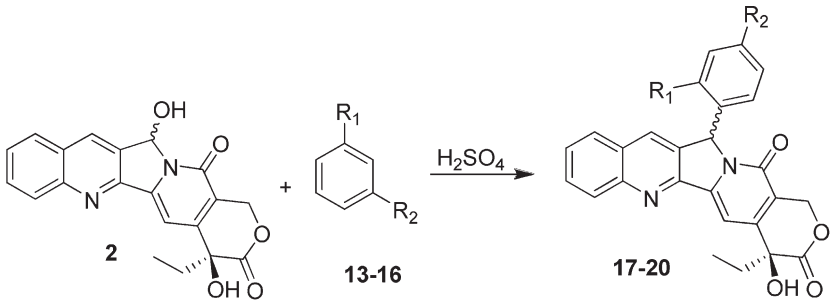
Figure 2. The ORTEP presentation of 5-para toluyl (**8**) and 5-ortho toluylcamptothecins (**9**).

Scheme 3



The Ritter type reaction was then extended to alkyl nitriles like propionitrile (**26**), and phenylacetonitrile (**27**), also with benzonitrile (**28**) under identical reaction conditions (Scheme 7). The product 5-propionamido-(20*S*)-camptothecin (**29**), phenylacetamidocamptothecin (**30**), and benzamidocamptothecin (**31**), were isolated in 40%, 31%, and 37% of yields, respectively, as yellow crystalline solid. In the case of reaction of propionitrile with **2**, diamido compound **32** was isolated in 9% of yield and was fully characterized. Formation of diamide

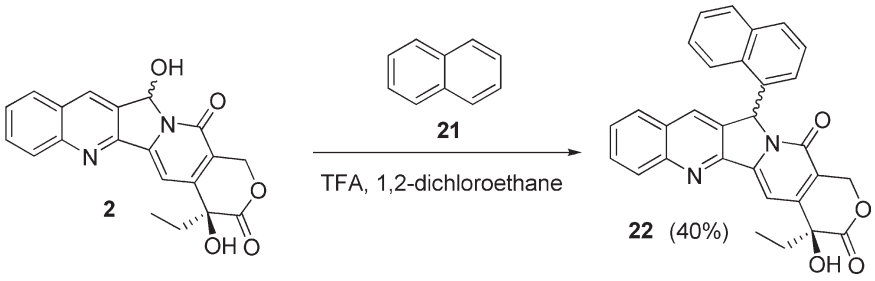
Scheme 4



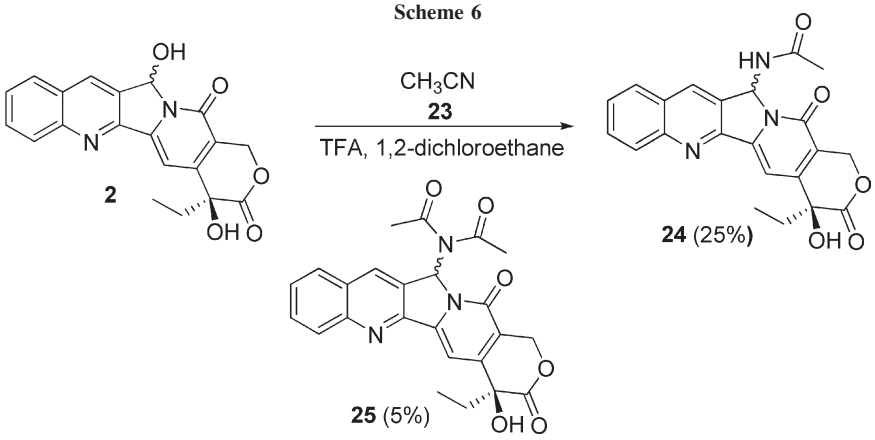
13, R_1=R_2=H
14, R_1=F, R_2=H
15, R_1=OCH_3,R_2=H
16, R_1=C_6H_5, R_2=H

17, R_1=H, R_2 =H (86%)
18a, R_1=H, R_2=F (major) (25.6%)
18b, R_1=F, R_2=H (minor) (12.3%)
19a, R_1=H, R_2=OCH_3 (major) (31.68%)
19b, R_1=OCH_3, R_2=H (minor) (11.70%)
20a, R_1=H, R_2=C_6H_5 (major) (40.7%)
20b, R=C_6H_5, R_2=H (minor) (5%)

Scheme 5



Scheme 6



25 as well as **32** under Ritter reaction conditions probably due to less bulky nature of acetonitrile and propionitrile, and further the reaction of these nitrile with soformed monoamides **24** and **25** [13]. All the amidocamptothecin were isolated as diastereomeric pairs without any diastereoselectivity.

We have evaluated compounds **8**, **9, 17, 18a**, **b,** and **19a**, **b** for *in vitro* anticancer activity in three human cancer cell lines HT-29 (colon), NCI-H460 (lung), and LoVo (colon) following the NCI standard protocol for screening anticancer molecules [14]. The compounds were tested at 100, 10, 1.0, 0.1, and 0.01 μM concentrations (Table 1). The average concentration that causes 50% growth inhibition (GI_{50} value) of cells with these compounds was found to be 32, 45, 52, and 13 μM, respectively. Compound **19a**, **b** exhibited significant anticancer properties. This study thus indicates that these analogues could serve as potential scaffolds for the development of novel anticancer agents.

CONCLUSION

In conclusion, we have demonstrated that 5-hydroxy-(20*S*)-camptothecin **2** can utilize as a potential source for the generation of iminium ion at C-5 position of camptothecin. The iminium ion thus formed can be trapped with different nucleophiles present in the reaction medium. The diastereoselectivity of these nucleophilic substitution reactions are partly controlled by the remote C-(20*S*) carbon atom bearing the ethyl group. No diastereoselectivity was observed during the reaction of aromatic and alkyl nitriles with **2** under Ritter type reaction conditions. As a result of these studies, a new

Scheme 7

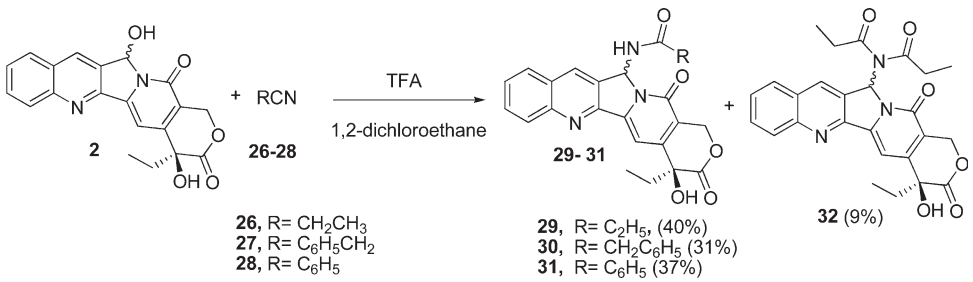


Table 1

Results of anticancer activity stadies of several compounds.

Cell line	% Growth					Growth inhibition in μM	
Compound no: **8**, **9**							
	100 μM	10 μM	1 μM	0.1 μM	0.01 μM	G150	TG1
HT29	34	85	78	90	97	49	100
H460	3	62	81	91	101	16	100
LoVo	13	89	90	100	113	33	100
Average						32	100
Compound no: **17**							
	100 μM	10 μM	1 μM	0.1 μM	0.01 mM	G150	TG1
HT29	49	94	104	103	103	94	100
H460	20	54	91	97	98	13	100
LoVo	11	81	99	100	101	28	100
Average						45	100
Compound no: **18a**, **b**							
	100 μM	10 μM	1 μM	0.1 μM	0.01 μM	G150	TG1
HT29	51	98	101	101	92	100	100
H460	23	73	89	97	94	29	100
LoVo	14	76	90	89	92	26	100
Average						52	100
Compound no: **19a**, **b**							
	100 μM	10 μM	1 μM	0.1 μM	0.01 μM	G150	TG1
HT29	22	73	97	102	104	28	100
H460	11	34	77	91	94	4	100
LoVo	4	40	79	97	99	5	100
Average						13	100

GI_{50} is the concentration of test drug where $100 \times (T - T0)/(C - T0) = 50$, where the optical density of the test cell after a 48-h period of exposure to test drug is T, the optical density at time zero is $T0$, and the control optical density is C. The TGI is the concentration of test drug where $100 \times (T - T0)/(C - T0) = 0$. Thus, the TGI signifies a cytostatic effect.

series of hither to unreported novel classes of 5-aryl and 5-amido substituted (20*S*)-camptothecin analogues were synthesized. The biological properties of few of these compounds were tested against HT-29 (colon), NCI-H460 (lung), and LoVo (colon) cell line panels and found that some of these compounds can be potential scaffold for the development of novel anticancer agents.

EXPERIMENTAL

Experimental section. Solvents and reagents are obtained from commercial sources and are not purified unless specified. ^{1}H-NMR data was recorded on Varian Gemini 400 MHz FT NMR spectrometer and ^{13}C was recorded on Varian Gemini 100 MHz FT NMR spectrometer. Infrared spectra (IR) were recorded on Perkin-Elmer 1650 FT-IR spectrometer. Mass spectra were recorded on HP-5989A quadrapole mass spectrometer. Melting points were taken in open capillaries and are uncorrected. The HPLC analysis was performed on Water HPLC system with Millennium software.

Synthesis of 5-(4-methylphenyl)-(20*S*)-camptothecin (8) and 5-(2-methylphenyl)-(20*S*)-camptothecin (9). To a well stirred suspension of 5-hydroxy-(20*S*)-camptothecin (**2**) (2.0 g, 5.49 mmol) in toluene (20 mL, 10 volume) was added, conc. sulfuric acid (1.6 g, 16.44 mmol) at room temperature. The reaction mixture was slowly refluxed for 3–4 h (monitored by TLC). The reaction mixture was then cooled to room temperature, diluted with 5% aq. sodium bicarbonate solution (100 mL) and extracted with ethyl acetate (3 × 75 mL). The organic layer was then separated and washed with water (2 × 100 mL) and dried over sodium sulphate. The solvent was then removed under vacuum to obtain the crude product which was further purified by column chromatography to yield 1.6 g of product in 66% of yield, as pale yellow solid; mp 238–240°C; HPLC purity: 21.13, 42.38, 7.81, and 23.09%; IR (KBr) cm^{-1}: 3422, 1750, 1659, 1617, 1405, 1156, 1041, 824; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 8Hz, 1H), 7.86 (t, J = 7.6 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.4 (dd, J = 4, 3.2 Hz, 1H), 7.3 (d, J = 7.2 Hz, 0.5 H), 7.12 (t, J = 6.8 Hz, 1.5H), 6.98 (dd, J = 9.6, 5.6 Hz, 1H), 6.74 (s, 1H), 6.51 (dd, J = 4.0, 4.4 Hz, 1H), 5.35 (tddd, 2H), 2.8 (s, 1H), 2.23 (s, 3H), 1.85 (m, 2H), 0.90 (t, 3H); ^{13}C-NMR (100 MHz, DMSO): δ 172.4, 156.4, 151.4, 150.1, 148.2, 145.3, 137.3, 136.5, 135.7, 134.7, 134.5, 131.6, 130.6, 129.3, 128.9, 128.1, 127.6, 126.7, 124.6, 120.4, 96.7, 72.3, 65.2, 61.3, 30.3, 20.6, 7.8; M^+ (*m*/*e*): 439 (97%), 395 (12%), 243 (8%), 215 (5%), 137(10%); Anal calcd for $C_{27}H_{22}N_2O_4$: C, 73.94; H, 5.06; N, 6.39; Found: C, 73.94; H, 4.83; N, 6.38, O, 14.59.

Synthesis of 5-phenyl-(20*S*)-camptothecin (17). The synthesis of **17** was achieved by adopting the same procedure of **8**, instead of toluene (**7**); benzene (**13**) was used as the solvent. The reaction was done with 1 g (2.74 mmol) of 5-hydroxy-(20*S*)-camptothecin **2**. The reaction yielded the product **17** (1.0 g, 86%) as a mixture of diastereomers in 54.65:44.51 ratios in HPLC. pale yellow solid, mp 255–256°C. IR (KBr) cm^{-1}:

3462, 1749, 1657, 1609, 1155, 824, 616; ^{1}H-NMR (400 MHz, DMSO) δ 8.4 (s, 1H), 8.2 (d, *J*= 8.4 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.86 (t, *J* = 7.6 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 3.6Hz, 1H), 7.38–7.22 (m, 5H), 6.83 (d, *J* = 11.6 Hz, 1H), 6.53 (d, *J* = 10.8 Hz, 1H), 5.34 (dtd, *J* = 6.4, 6.6, 4.8 Hz, 2H), 1.85 (m, 2H), 0.87 (t, 3H); ^{13}C-NMR (100 MHz, DMSO) δ 172.3, 157.1, 156.4, 151.1, 150.2, 148.2, 145.1, 137.5, 134.5, 131.6, 130.5, 128.9, 128.7, 128.5, 128.1, 127.8, 127.6, 126.6, 120.4, 96.8, 79.5, 78.8, 72.3, 65.1, 30.3, 7.8; M^+ (*m*/*e*): 425 (97%), 381 (43%), 95 (2%); Anal calcd for $C_{26}H_{20}N_2O_4$: C, 73.56; H, 4.75; N, 6.60; Found: C, 73.56; H, 4.75; N, 6.60; O, 15.07.

Synthesis of 5-(fluorophenyl)-(20*S*)-camptothecin (18a, b). The product 18a and 18b were synthesized as per the procedure adopted for compound (8), using fluorobenzene (14) as the solvent instead of toluene (7). The reaction was done with 1.0 g (2.74 mmol) of 5-hydroxy-(20*S*)-camptothecin 2 and yielded 18a, b (0.45 g, 37.9%) as pale yellow solid, mp 245–248°C; HPLC Purity: 38.35, 17.3, and 41.5%; IR (KBr) cm^{-1}: 3235, 2927, 1749, 1656, 1608, 1590, 1406, 1229, 1196, 1157, 1039, 824, 767; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.4 (s, 1H), 8.17 (t, *J* = 8.8 Hz, 1H), 8.08 (t, *J* = 7.2 Hz, 1H), 7.87 (t, 1H), 7.68 (t, *J* = 7.6 Hz ,1H), 7.4 (d, *J* = 3.2 Hz, 1H), 7.38 (t, *J* = 4, 0.5H), 7.31 (dd, *J* = 3.6, 3.2, 2.0 Hz, 1H), 7.21 (s, 0.5H), 7.15 (ddd, *J* = 3.6, 3.6, 3.6 Hz, 1H), 6.97 (dd, *J* = 7.68 Hz, 1H), 6.84 (S, 1H), 6.53 (td, *J* = 4, 3.2 Hz, 1H), 5.35 (q, 2H), 1.87 (m, 2H), 0.90 (t, 3H); ^{13}C-NMR (100 MHz, DMSO) δ 172.2, 159.2, 156.4, 151.2, 150.1, 148.2, 145.1, 143.4, 134.5, 133.5, 132.7, 131.8, 131.3, 130.7, 129.0, 128.6, 128.1, 127.7, 124.8, 120.5, 115.8, 74.3, 72.3, 65.1, 30.2, 7.7; M^+ (*m*/*e*): 443 (97%), 399 (60%), 154 (18%); Anal calcd for $C_{26}H_{19}N_2O_4F$: C, 70.72, H, 4.11, N, 6.16; Found: C, 70.41; H, 4.16, N, 6.17, F, 4.28.

Synthesis of 5-(4-methoxy phenyl)-(20*S*)-camptothecin and 5-(2-methoxy phenyl)-(20*S*)-camptothecin (19a, b). The product **19a** and **19b** was synthesized as per the procedure adopted for compound **8**, using anisole (**15**) as the solvent instead of toluene (**7**). The reaction was done with 1.0 g (2.74 mmol) of 5-hydroxy-(20*S*)-camptothecin **2** and yielded **19a** and **19b** (0.46 g, 43.37%) as pale yellow solid; mp 166–168°C; HPLC Purity: 22.35, 48.07, 24.76, and 1.25%; IR (KBr) cm^{-1}: 3392, 2935, 1751, 1660, 1608, 1511, 1461, 1406, 1247, 1157, 1046, 757; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.17 (t, *J* = 7.2 Hz, 1H), 8.07 (d, *J* = 8.4, 1H), 7.86 (q, *J* = 8.0Hz, 1H), 7.65 (q, *J* = 6.8 Hz, 1H), 7.4 (d, *J* = 3.6 Hz, 1H), 7.28 (m, 0.5 H), 7.14 (dd, *J* = 2.4, 2.0, 2.8 Hz, 1H), 6.91 (m, 0.5 H), 6.87 (dd, *J* = 2.4, 2.0, 2.4 Hz, 1H), 6.77 (s, 1H), 6.5 (dd, *J* = 4.0, 3.2 Hz, 1H), 5.36 (q, 2H), 3.74 (s, 3H), 1.88 (m, 3H), 0.89 (t, 3H); ^{13}C-NMR (100 MHz, DMSO): δ 172.5, 158.9, 156.4, 151.2, 150.1, 148.2, 145.6, 145.0, 134.9, 131.6, 130.5, 129.4, 128.9, 128.3, 128.2, 128.1, 127.6, 125.0, 120.7, 114.1, 112.1, 96.6, 72.3, 65.2, 55.7, 30.3, 7.7; M^+ (*m*/*e*): 455 (97%), 411 (8%); Anal calcd for $C_{27}H_{22}N_2O_5$: C, 71.34; H, 4.88; N, 6.11; Found: C, 71.34; H, 4.88; N, 6.16; O, 17.60.

Synthesis of 5-(4-biphenyl)-(20*S*)-camptothecin and 5-(2-biphenyl)-(20*S*)-camptothecin (20a, b). 5-Hydroxy-(20*S*)-camptothecin **2** (1.0 g, 2.74 mmol), biphenyl (**16**) (0.466 g, 3.02 mmol) and trifluoroacetic acid (1.23 g, 8.22 mmol) were taken in round bottomed flask under nitrogen atmosphere at room temperature. Reaction mixture was heated to 65–75°C and maintained for 10–14 h. Reaction mixture was cooled to room temperature, diluted with 5% aq. sodium bicarbonate solution (100 mL) and extracted with dichloromethane (3 × 75 mL). The organic layer was separated and washed with water (2 × 100 mL), solvent removed under reduced pressure to obtain the crude product. It was then purified by column chromatography furnished **20a** (0.56 g, 40.7%); Major isomer: Melting range 189–190°C; IR (KBr) cm^{-1}: 3395, 3057, 2969, 1747, 1662, 1617, 1559, 1404, 1221, 1155, 1045, 824, 757, 704; ^{1}H-NMR (400 MHz, DMSO) δ 8.2 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 7.9 (dd, *J* = 7.2, 6.4 Hz, 1H), 7.85 (t, *J* = 8.0 Hz, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 3H), 7.16 (t, *J* = 8.0 Hz, 1H), 6.85 (s, 1H), 6.75 (s, 1H), 6.56 (t, *J* = 4.0 Hz, 1H), 6.53 (s, 1H), 5.31 (d, *J* = 7.6 Hz, 1H), 1.86 (m, 2H), 1.24 (s, 1H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, DMSO): δ 172.2, 156.3, 151.1, 150.0, 148.0, 145.3, 141.7, 135.2, 134.8, 130.9, 130.5, 130.2, 129.8, 128.8, 128.4, 128.2, 128.0, 127.7, 127.6, 127.4, 124.7, 120.3, 96.7, 72.2, 65.2, 32.1, 30.3, 7.7. M^+ (*m*/*e*): 501.2. Anal calcd for $C_{32}H_{24}N_2O_4$: C, 76.78; H, 4.83; N, 5.60; O, 12.79. Found: C, 76.77; H, 4.84; N, 5.59; O, 12.78.

Minor isomer (**20b**): Yield 5%; Melting range 192–194°C; IR (KBr) cm^{-1}: 3418, 3056, 2969, 1746, 1662, 1618, 1559, 1404, 1222, 1155, 1046, 824, 758, 702; ^{1}H-NMR (400 MHz, DMSO) δ 8.45 (s, 0.5H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.08 (t, *J* = 7.6, 7.2 Hz, 1H), 7.93 (t, *J* = 6.8, 6.4 Hz, 1H), 7.87 (q, *J* = 8.8 Hz, 1H), 7.68 (t, *J* = 7.2 Hz, 1H), 7.6 (q, *J* = 8.0 Hz, 2H), 7.44 (m, 2H), 7.36 (m, 3H), 7.16 (d, *J* = 6.8 Hz, 1H), 6.8 (s, 0.5H), 6.75 (s, 1H), 6.55 (d, *J* = 8.8 Hz, 1H), 5.34 (m, 2H), 1.89 (m, 2H), 1.24 (s, 1H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, DMSO): δ 172.2, 156.4, 151.2, 150.1, 148.2, 145.1, 139.8, 139.5, 135.0, 134.5, 131.7, 130.6, 129.8, 128.8, 128.5, 127.3, 126.5, 120.4, 96.7, 72.2, 65.1, 30.3, 7.9. M^+ (*m*/*e*): 501.2. Anal calcd for $C_{32}H_{24}N_2O_4$: C, 76.78; H, 4.83; N, 5.60; O, 12.79. Found: C, 76.71; H, 4.80; N, 5.56; O, 12.74.

Synthesis of 5-(1-naphthyl)-(20*S*)-camptothecin (22). To a suspension of 5-hydroxy-(20*S*)-camptothecin **2** (2.5 g, 6.86 mmol) in 1, 2-dichloroethane (25 mL) at room temperature was added naphthalene (**21**) (8.79 g, 68.6 mmol) and stirred for 10 min. To this suspension, trifluoroacetic acid (8.65 g) was added. The reaction mixture was heated to 65–75°C and maintained for 12–16 h (monitored by TLC). It was then cooled to room temperature, diluted with 5% aq. sodium bicarbonate solution (100 mL), and extracted with dichloromethane (3 × 75 mL). The organic layer was separated and washed with water (2 × 100 mL), and the solvent removed under reduced pressure to obtain crude product. Purification by column chromatography furnished **22** (1.3 g, 40%) as a yellow solid. mp 197–198°C; HPLC Purity: 58.18 and 34.81%; IR (KBr) cm^{-1}: 3433, 1794, 1759, 1673, 1623, 1143, 825, 789, and 772; ^{1}H-NMR (400 MHz, DMSO) δ 8.82 (s, 1H), 8.26 (d, *J* = 7.2 Hz, 1H), 8.2 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.92 (m, 2H), 7.82 (q, 2H), 7.71 (t, *J* = 7.4 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.51 (dd, *J* = 3.2, 3.6 Hz, 2H), 7.32 (m, 1H), 6.76 (dd, *J* = 7.2 Hz, 1H), 5.45 (m, 2H), 2.36 (m, 2H), 1.02 (t, 3H); ^{13}C-NMR (100 MHz, DMSO): δ 165.3, 155.8, 150.7, 148.1, 146.7, 143.5, 135.1, 133.7, 133.2, 132.9, 130.7, 128.8, 128.6, 128.2, 128.2, 127.7, 126.9, 126.2, 125.6, 123.5, 121.7, 120.5, 120.5, 94.3, 80.5, 72.3, 66.4, 61.0, 29.8, 7.8; M^+ (*m*/*e*): 474.5 (25%), 473.4 (50%) 443 (12%), 346.9 (8%); Anal calcd for $C_{30}H_{22}N_2O_4$: C,

75.94; H, 4.67; N, 5.90; O, 13.49, Found: C, 75.92; H, 4.60; N, 5.86; O, 13.41.

Synthesis of 5-acetamido-(20*S*)-camptothecin (24). 5-Hydroxy-(20*S*)-camptothecin **2** (2.5 g, 6.86 mmol) was suspended in acetonitrile (**23**) (25.0 g) and stirred for 10 min. To the reaction mixture was added, trifluoroacetic acid (8.65 g, 41.2 mmol) at room temperature. Reaction mixture was heated to 65–75°C and maintained for 12–16 h. Reaction mixture was cooled to room temperature, diluted with 5% aq. sodium bicarbonate solution (100 mL) and extracted with dichloromethane (2 × 75 mL). The organic layer was separated and washed with water (2 × 100 mL), solvent was removed under reduced pressure to obtain the crude product. It was then purified by column chromatography resulted **24** as yellow solid in 25% (0.69 g) of yield, mp: 269–270°C; HPLC Purity: 54.8 and 43.1%; IR (KBr) cm^{-1}: 3376, 1744, 1667, 1618, 1158, 760; ^{1}H-NMR (400 MHz, DMSO) δ 9.1 (dd, J = 8.0, 8.0 Hz, 1H), 8.54 (d, J = 5.6 Hz, 1H), 8.15 (t, J = 8.2 Hz, 2H), 7.87 (t, J = 7.8 Hz, 1H), 7.70 (t, J = 7.2 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.14 (dd, J = 8.4, 6.8 Hz, 1H), 6.51 (d, J = 4.4 Hz, 1H), 5.4 (m, 2H), 1.84 (m, 5H), 0.89 (m, 3H); ^{13}C-NMR (100 MHz, DMSO): δ 172.2, 169.1, 156.6, 151.7, 150.1, 148.3, 144.6, 131.9, 131.1, 130.6, 128.9, 128.7, 128.2, 127.6, 120.9, 96.4, 72.2, 66.3, 65.2, 30.2, 22.5, 7.7; M^+ (*m*/*e*): 406.3 (97%), 347.3 (30%), 303 (10%); Anal calcd for $C_{22}H_{19}N_3O_5$: C, 65.18; H, 4.72; N, 10.37; O, 19.73. Found: C, 65.10; H, 4.79; N, 10.35; O, 19.69.

Synthesis of 5-propionamido-(20*S*)-camptothecin (29). 5-Hydroxy-(20*S*)-camptothecin **2** (2.0 g, 5.49 mmol) was suspended in propionitrile (**26**) (7.45 g, 68.6 mmol) and stirred for 10 min. To the reaction mixture was added trifluoroacetic acid (2.5 g) in at room temperature. Reaction mixture was heated to 65–75°C and maintained for 8–12 h. Reaction mixture was cooled to room temperature, diluted with 5% aq. sodium bicarbonate solution (100 mL) and extracted with dichloromethane (3 × 75 mL). The combined organic layer was washed with water (2 × 100 mL) and separated. Organic layer was concentrated under reduced pressure to obtain the crude product which was further purified by column chromatography and obtained **29** in 40% (0.92 g) of yield, mp: 208–209°C; IR (KBr) cm^{-1}: 3314, 3061, 2975, 1746, 1663, 1614, 1562, 1406, 1227, 1155, 1044, 791, 769; ^{1}H-NMR (400 MHz, DMSO) δ 9.04 (dd, J = 8.0, 8.4 Hz, 1H), 8.64 (dd, J = 3.2, 6.8 Hz, 1H), 8.17 (dd, J = 8.4, 8.2 Hz, 2H), 7.88 (t, J = 6.8 Hz, 1H), 7.77 (t, J = 5.6 Hz, 1H), 7.26 (dd, J = *4*.0, 4.4 Hz, 1H), 7.18 (dd, J = 8,7.6 Hz, 1H), 6.54 (dd, J = 4.0, 2.0 Hz, 1H), 5.4 (m, 2H), 2.13 (m, 2H), 1.88 (m, 2H), 0.99 (m, 3H), 0.89 (m, 3H); ^{13}C-NMR (100 MHz, DMSO): δ 172.7, 172.3, 156.8, 151.5, 150.1, 148.5, 144.6, 143.7, 133.1, 132.3, 131.9, 131.8, 131.1, 130.9, 130.6, 128.9, 128.7, 128.2, 127.5, 120.8, 120.5, 96.3, 73.0, 72.3, 69.7, 66.3, 65.2, 30.2, 28.2, 9.3, 7.7; M^+ (*m*/*e*): 419 (100%); Anal calcd for $C_{23}H_{21}N_3O_5$: C, 65.86; H, 5.05; N, 10.02; O, 19.07, Found: C, 65.80; H, 5.01; N, 10.08; O, 19.01.

5-(*N*,*N*-Dipropionamide-(20*S*)-camptothecin (32). ^{1}H-NMR (400 MHz, DMSO): δ 8.97 (d, 1H, J =8.4,8.0), 8.53 (s, 2H), 8.15 (m, 2H), 7.86 (t. 2H, J =8,7.2), 7.7 (t, 1H, J =6.8,8.4), 7.2 (m, 1H), 6.96 (s, 1H), 5.4 (d, 2H, J =13.6), 2.51 (s, 4H), 2.12 (m, 2H), 1.09 (m, 6H), 0.94 (t, 3H, J =3.2,4.4); M^+ (*m*/*e*): 476.2 (100%), 403 (10%).

Synthesis of 5-phenylacetamido-(20*S*)-camptothecin (30). 5-Hydroxy-(20*S*)-camptothecin **2** (2.0 g, 5.49 mmol) was suspended in phenyl acetonitrile (**27**) (0.75 g, 6.0 mmol) and stirred for 10 min. Trifluoroacetic acid (2.5 g) was added into the reaction mass at room temperature. Reaction mixture was heated to 65–75°C and maintained for 8–12 h. Reaction mixture was cooled to room temperature, diluted with 5% aq. sodium bicarbonate solution (100 mL) and extracted with dichloromethane (3 × 75 mL). The organic layer was washed with water (2 × 100 mL), separated and solvent was removed under reduced pressure to obtain the crude product which was further purified by column chromatography and resulted **30** in 31% (0.82 g) of yield, mp: 155–156°C; IR (KBr) cm^{-1}: 3302, 3060, 2973, 1747, 1662, 1614, 1567, 1403, 1227, 1157, 1046, 758; ^{1}H-NMR (400 MHz, DMSO) δ 9.43 (d, J = 7.2 Hz, 1H), 8.68 (d, J = 2.8 Hz, 1H), 8.47 (s, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8 Hz, 1H), 7.9 (q, J = 8 Hz, 1H), 7.7 (dd, J = 8.4, 8.6 Hz, 1H), 7.33–7.18 (m, 3H), 7.13 (d, J = 7.2 Hz, 1H), 6.97 (dd, J = *8*.0, 8.4 Hz, 1H), 6.33 (s, 1H), 5.4 (d, J = 8.0 Hz, 2H), 3.46 (m, 2H), 1.86 (m, 2H), 0.88 (m, 3H); ^{13}C-NMR (100 MHz, DMSO): δ 172.3, 170.1, 167.1, 157.1, 156.1, 151.8, 151.2, 150.4, 150.0, 150.1, 148.7, 144.7, 143.5, 136.5, 135.5, 132.8, 132.3, 131.8, 130.9, 129.3, 129.1, 129.0, 128.8, 128.1, 127.7, 126.4, 121.4, 120.9, 96.4, 82.7, 72.2, 66.6, 65.3, 40.2, 30.2, 7.8; M^+ (*m*/*e*): 481.5 (100%); Anal calcd for $C_{27}H_{21}N_3O_5$: C, 69.37; H, 4.53; N, 8.99; O, 17.11. Found: C, 69.40, H, 4.51; N, 8.90; O, 17.09.

Synthesis of 5-benzamido-(20*S*)-camptothecin (31). 5-Hydroxy-(20*S*)-camptothecin **2** (2.0 g, 5.49 mmol) was suspended in benzonitrile (**28**) (1.7 g, 16.4 mmol) and stirred for 10 min. Trifluoroacetic acid (2.5 g) was added into the reaction mixture at room temperature. The contents were heated to 65–75°C and maintained for 8–12 h. Reaction mixture was cooled to room temperature, diluted with 5% aq. sodium bicarbonate solution (100 mL) and extracted with dichloromethane (3 × 75 mL). The organic layer was washed with water (2 × 100 mL) separated and solvent was removed under reduced pressure to obtain the crude product which was further purified by column chromatography and resulted **31** in 37% (0.95 g) of yield, mp: 204–205°C; IR (KBr) cm^{-1}: 3366, 3302, 3058, 2972, 1751, 1658, 1614, 1578, 1529, 1520, 1403, 1367, 1226, 1155, 1055, 790, 743, 683; ^{1}H-NMR (400 MHz, DMSO) δ 9.68 (d, J = 8.0 Hz 1H), 8.77 (d, J = 6.8 Hz, 1H), 8.62 (d, J = 8.0 Hz, 1H), 8.2 (d, J = 8.8 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.9 (s, 1H), 7.88 (dd, J = 8.4, 8.6 Hz, 2H), 7.69 (m, 1H), 7.6–7.4 (m, 4H), 7.38 (s, 1H), 7.34 (d, J = 9.4 Hz, 1H), 5.37 (t, J = 9.2 Hz, 2H), 1.88 (m, 2H), 0.88 (m, 3H); ^{13}C-NMR (100 MHz, DMSO): δ 172.1, 167.7, 165.5, 156.6, 150.0, 144.8, 134.1, 133.0, 131.8, 131.0, 130.6, 128.9, 128.6, 128.2, 128.0, 127.3, 120.8, 96.3, 72.2, 66.6, 30.2, 7.8; M^+ (*m*/*e*): 419 (100%); Anal calcd for $C_{28}H_{21}N_3O_5$: C, 69.84; H, 4.81; N, 8.73; O, 16.61, Found: C, 69.80; H, 4.80; N, 8.71; O, 16.60.

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