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Synthesis and cytotoxicity of water soluble quaternary salt derivatives of camptothecin ☆

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Abstract—In an effort to improve the water solubility of camptothecin, 16 water soluble 10-substituted quaternary ammonium salt derivatives of camptothecin were prepared. Their antitumor activity was evaluated on cancer cells in vitro. All of these salts possess lower cytotoxicities than CPT in comparison. The camptothecin salts **16**, **20** showed similar cytotoxic activity to topotecan. Especially the salts 21 showed similar cytotoxic activity to CPT in vitro.

Camptothecin (CPT, **1**) was isolated by Wall and coworkers from *Camptotheca acuminata*.[1] The promising results for testing as an antitumor agent in animal models led to the evaluation of camptothecin in the clinic.[2,3] The clinical application of camptothecin as an anticancer agent was limited due to its nonmechanism-related toxicity and an extremely poor solubility profile.[4] In an attempt to circumvent the solubility problem, some researchers have evaluated the soluble sodium salt of hydroxyl acid form (**2**) in the clinic.[5] Severe and unpredictable toxicity led to suspension of the clinical trials. The discovery that the primary cellular target for CPT is DNA topoisomerase I has created renewed interest in the compound and led to the successful identification and development of the antitumor agents topotecan (**3**) and irinotecan (**4**).[6,7] At least 10 additional CPT analogues are in various stages of clinical trials.

A number of approaches are being used to improve the antitumor efficiency of the CPT family. This includes the development of prodrugs (conjugates and polymer-bound camptothecins), new formulations (liposomes or microparticulate carriers), and the synthesis of lipophilic camptothecins.[8] The identification of new water-soluble CPT analogues also continues to be of great interest. We explored a series of compounds, which placed the several water-solubilizing groups in the 10-position of camptothecin as aromatic quaternary ammonium salts. These salts showed good water solubility and different cytotoxicities in vitro (Fig. 1).

In our experiments, 10-hydroxy-camptothecin (**5**) was initially converted into 10-bromine-ethyoxyl-camptothecin (**6**) in good yields according to Kim et al.,[9] and then **6** was dissolved in pyridines or a solution of pyridines in DMSO. The resulting mixture was then stirred at 50 °C until the reaction was complete. After $CHCL_3$ was added, the precipitate of corresponding pyridines salts (**8**–**15**) were obtained (Scheme 1). The compound **7** and corresponding salt derivatives of camptothecin (**16**–**23**) were also prepared in the similar conditions (Scheme 1). The yields of **7** and its related quaternary salt derivatives (**16**–**23**) ranging from 80.7% to 95.6% are higher than the yields of **6** and its corresponding quaternary salt derivatives (**8**–**15**) ranging from 68.0% to 92.3%. The ^1H NMR spectra of these novel camptothecin salts showed the right characteristic protons for their different pyridines.[10] We found the compounds **9**, **17**, **10**, **18**, **23** have the specificity in their mass spectrum. In the mass spectrogram of the compound **9**, the m/z is 512 (M^+) when the compound **9** was analyzed in water, but the m/z is 512 (M^+), 544 $(M+CH_3OH)^+$ when the compound **9** was analyzed in CH_3OH. The show of the compound **17**, **23** in their mass spectrograms is similar to the compound **9**. Furthermore, in the mass spectrogram of the compound **10**, the m/z is 498 (M^+) (little), 516 $(M+H_2O)^+$ when the compound **10** was analyzed in

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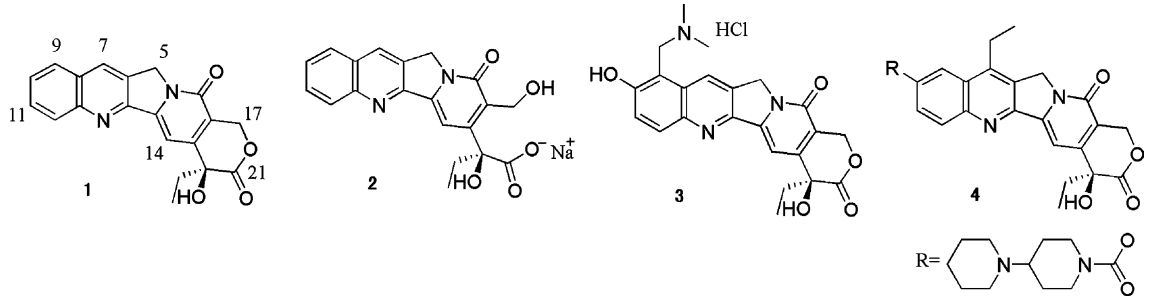
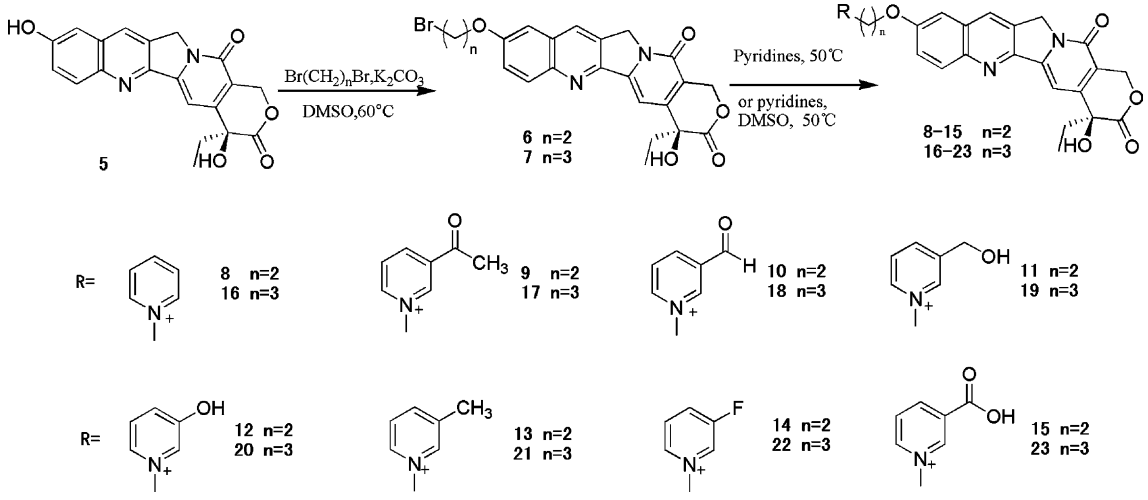


Figure 1. Structures of camptothecin (**1**), its carboxylate form (**2**), topotecan (**3**), irinotecan (**4**).



Scheme 1.

water, but the m/z is 530 $(M+CH_3OH)^+$ when the compound **10** was analyzed in CH_3OH. The show of the compound **18** in its mass spectrogram is similar to the compound **10**. So, the carbonyl of these compounds are active in the environment of MS(ESI). All of the camptothecin quaternary salt derivatives are soluble in water.

Cytotoxicity of these camptothecin quaternary salt derivatives in Table 1 were evaluated on three different human cancer cell lines (KB, HCT-8 and BEl7402) using MTT assay. Topotecan and CPT were used as reference compounds. Most of the compounds (**16**–**23**) showed more active in vitro than their related compounds (**8**–**15**), so the length of the alkane chain between camptothecin and pyridines effects the activity of the compounds. The camptothecin salts **16**, **20** showed similar cytotoxic activity to topotecan. Especially the salts **21** showed similar cytotoxic activity to CPT in vitro. All the derivatives except **21** showed lower cytotoxic in vitro than CPT. This result is consistent with the SAR of CPT, that is likely large substituted groups at C-10 reduces the cytotoxicity of CPT, moreover, the good solubility may also help to reduce the cytotoxicity.

Table 1. Cytotoxocity of quaternary salt derivatives of camptothecin

Compds	In vitro cytotoxicity (IC_{50}, μg/mL)		
	KB	HCT-8	Bel7402
CPT	<0.005	<0.005	2.724
Topotecan	0.023	0.035	0.40
8	0.337	0.458	3.532
9	3.214	3.012	5
10	0.344	0.354	3.731
11	3.288	3.739	5
12	0.320	0.428	0.47
13	0.63	1.427	0.47
14	0.334	0.382	5
15	0.318	0.277	5
16	0.032	0.035	0.44
17	3.138	3.151	5
18	0.275	0.170	0.46
19	0.318	0.342	2.878
20	0.04	0.039	3.924
21	<0.005	<0.005	0.048
22	3.401	2.023	5
23	0.324	0.33	0.44

KB, human epidermoid carcinoma of the nasopharynx, HCT-8, human colon cancer, Bel7402, human liver cancer.

In summary, we developed a simple and efficient route to synthesis of 10-substituted camptothecin quaternary salt derivatives. Preliminary biological studies showed that 10-substituted water soluble camptothecin quaternary salts possessed lower cytotoxicities in vitro than CPT, and the salts **16**, **20**, **21** possessed higher cytotoxicities than topotecan. Further investigation is progressing in the pharmacology.

Acknowledgements

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10. Compounds data: **6**. Yield 68.0%, mp 235–237 °C, ^{1}H NMR (300 Hz, DMSO-d_6) δ 0.87 (3H, t, $J = 7.2$ Hz, H-18), 1.85 (2H, q, $J = 7.2$ Hz, H-19), 3.91 (2H, t, $J = 5.4$ Hz, –CH_2Br), 4.51 (2H, t, $J = 5.4$ Hz, –OCH_2–), 5.25 (2H, s, H-5), 5.41 (2H, s, H-17), 6.51 (1H, s, OH-20), 7.27 (1H, s, H-14), 7.54 (1H, d, $J = 9.3$ Hz, H-11), 7.55 (1H, s, H-9), 8.08 (1H, d, $J = 9.3$ Hz, H-12), 8.52 (1H, s, H-7); MS(ESI) m/z 472 (MH^+); **7**. Yield 85.7%, mp 224–226 °C, ^{1}H NMR (500 Hz, DMSO-d_6) δ 0.88 (3H, s, H-18), 1.86 (2H, s, H-19), 2.36 (2H, s, CH_2), 3.74 (2H, s, CH_2), 4.26 (2H, s, CH_2), 5.25 (2H, s, H-5), 5.41 (2H, s, H-17), 6.53 (1H, s, 20-OH), 7.27 (1H, s, H-14), 7.50 (1H, d, $J = 10$ Hz, H-11), 7.55 (1H, s, H-9), 8.05 (1H, d, $J = 10$ Hz, H-12), 8.53 (1H, s, H-7); MS(ESI) m/z 485 (M^+); **8**. Yield 92.3%, mp 208–210 °C, ^{1}H NMR (300 Hz, DMSO-d_6) δ 0.85 (3H, t, $J = 6.9$ Hz, H-18), 1.83 (2H, m, $J = 6.9$ Hz, H-19), 4.71 (2H, s, CH_2), 5.15 (2H, s, CH_2), 5.21 (2H, s, H-5), 5.38 (2H, s, H-17), 6.49 (1H, s, 20-OH), 7.23 (1H, s, H-14), 7.46 (1H, d, $J = 9.3$ Hz, H-11), 7.53 (1H, s, H-9), 8.03 (1H, d, $J = 9.3$ Hz, H-12), 8.21 (2H, t, $J = 6.9$ Hz), 8.51 (1H, s, H-7), 8.65 (1H, t, $J = 6.9$ Hz), 9.20 (2H, d, $J = 6.9$ Hz); MS(ESI) m/z 470 (M^+); **9**. Yield 85.7%, mp 210–212 °C, ^{1}H NMR (300 Hz, DMSO-d_6) δ 0.86 (3H, t, $J = 6.9$ Hz, H-18), 1.85 (2H, m, $J = 6.9$ Hz, H-19), 2.75 (3H, s, CH_3), 4.74 (2H, s, CH_2), 5.26 (2H, s, CH_2), 5.26 (2H, s, H-5), 5.40 (2H, s, H-17), 6.51 (1H, s, 20-OH), 7.25 (1H, s, H-14), 7.48 (1H, d, $J = 9.3$ Hz, H-11), 7.55 (1H, s, H-9), 8.05 (1H, d, $J = 9.3$ Hz, H-12), 8.36 (1H, t), 8.55 (1H, s, H-7), 9.05 (1H, d), 9.40 (1H, d), 9.74 (1H, s); MS(ESI) m/z 512 (M^+), 544 ($M+CH_3OH)^+$; **10**. Yield 95.7%, mp > 300 °C, ^{1}H NMR (400 Hz, DMSO-d_6) δ 0.87 (3H, t, $J = 8$ Hz, H-18), 1.85 (2H, m, $J = 8$ Hz, H-19), 4.74 (2H, s, CH_2), 5.26 (2H, s, CH_2), 5.26 (2H, s, H-5), 5.41 (2H, s, H-17), 6.49 (1H, s, 20-OH), 7.27 (1H, s, H-14), 7.50 (1H, d, $J = 12$ Hz, H-11), 7.56 (1H, s, H-9), 8.07 (1H, d, $J = 12$ Hz, H-12), 8.41 (1H, t), 8.56 (1H, s, H-7), 9.07 (1H, d), 9.41 (1H, d), 9.74 (1H, s), 10.20 (1H, s, CHO); MS(ESI) m/z 498 (M^+), 516 $(M+H_2O)^+$, 530 $(M+CH_3OH)^+$; **11**. Yield 91.5%, mp 203–205 °C, ^{1}H NMR (500 Hz, DMSO-d_6) δ 0.87 (3H, t, $J = 5.0$ Hz, H-18), 1.85 (2H, m, $J = 5.0$ Hz, H-19), 4.71 (2H, t, $J = 4.5$ Hz, CH_2), 4.77 (2H, d, $J = 5.5$ Hz, CH_2), 5.16 (2H, t, $J = 4.5$ Hz, CH_2), 5.26 (2H, s, H-5), 5.41 (2H, s, H-17), 5.91 (1H, t, –OH), 6.49 (1H, s, 20-OH), 7.27 (1H, s, H-14), 7.46 (1H, dd, $J_1 = 2.5$ Hz, $J_2 = 6.5$ Hz, H-11), 7.56 (1H, d, $J = 2.5$ Hz, H-9), 8.07 (1H, d, $J = 6.5$ Hz, H-12), 8.18 (1H, t, $J = 6$ Hz), 8.55 (1H, s, H-7), 8.56 (1H, d, $J = 6$ Hz), 9.10 (1H, d, $J = 6$ Hz), 9.15 (1H, s); MS(ESI) m/z 500 (M^+); **12**. Yield 80.4%, mp 208–210 °C, ^{1}H NMR (500 Hz, DMSO-d_6) δ 0.86 (3H, t, $J = 5.0$ Hz, H-18), 1.85 (2H, m, $J = 5.0$ Hz, H-19), 4.64 (2H, s, CH_2), 4.94 (2H, s, CH_2), 5.20 (2H, s, H-5), 5.40 (2H, s, H-17), 6.51 (1H, br, 20-OH), 7.24 (1H, s, H-14), 7.34 (1H, d, $J = 8.0$ Hz, H-11), 7.48 (1H, s, H-9), 7.62 (1H, d, $J = 8.0$ Hz, H-12), 7.75 (1H, t, $J_1 = 5$ Hz, $J_2 = 9$ Hz), 7.98 (1H, d, $J = 9$ Hz), 8.25 (1H, d, $J = 5$ Hz), 8.30 (1H, s), 8.47 (1H, s, H-7); MS(ESI) m/z 486 (M^+); **13**. Yield 90.4%, mp 208–210 °C, ^{1}H NMR (500 Hz, DMSO-d_6) δ 0.87 (3H, t, $J = 7.5$ Hz, H-18), 1.86 (2H, m, $J = 7.5$ Hz, H-19), 2.53 (3H, s, –CH_3), 4.72 (2H, t, CH_2), 5.10 (2H, t, CH_2), 5.25 (2H, s, H-5), 5.40 (2H, s, H-17), 6.49 (1H, s, 20-OH), 7.26 (1H, s, H-14), 7.47 (1H, dd, $J_1 = 2.5$ Hz, $J_2 = 9.5$ Hz, H-11), 7.55 (1H, d, $J = 2.5$ Hz, H-9), 8.06 (1H, d, $J = 9.5$ Hz, H-12), 8.11 (1H, t, $J_1 = 6.5$ Hz, $J_2 = 7.5$ Hz), 8.51 (1H, d, $J = 7.5$ Hz), 8.54 (1H, s, H-7), 9.05 (1H, d, $J = 6.5$ Hz), 9.13 (1H, s); MS(ESI) m/z 484 (M^+); **14**. Yield 80.9%, mp > 300 °C, ^{1}H NMR (500 Hz, DMSO-d_6) δ 0.87 (3H, s, H-18), 1.85 (2H, t, H-19), 4.74 (2H, s, CH_2), 5.21 (2H, s, CH_2), 5.23 (2H, s, H-5), 5.40 (2H, s, H-17), 6.49 (1H, s, 20-OH), 7.25 (1H, s, H-14), 7.49 (1H, d, $J = 8.0$ Hz, H-11), 7.56 (1H, s, H-9), 8.05 (1H, d, $J = 8.0$ Hz, H-12), 8.34 (1H, s), 8.55 (1H, s, H-7), 8.74 (1H, s), 9.21 (1H, s), 9.69 (1H, s); MS(ESI) m/z 488 (M^+); **15**. Yield 70.5%, mp 215–217 °C, ^{1}H NMR (500 Hz, DMSO-d_6) δ 0.86 (3H, t, $J = 7.5$ Hz, H-18), 1.85 (2H, m, $J = 7.5$ Hz, H-19), 4.73 (2H, s, CH_2), 5.24 (2H, s, CH_2), 5.25 (2H, s, H-5), 5.41 (2H, s, H-17), 6.49 (1H, s, 20-OH), 7.26 (1H, s, H-14), 7.46 (1H, dd, $J_1 = 2.5$ Hz, $J_2 = 9.5$ Hz, H-11), 7.54 (1H, d, $J = 2.5$ Hz, H-9), 8.07 (1H, d, $J = 9.5$ Hz, H-12), 8.28 (1H, t, $J = 7$ Hz), 8.54 (1H, s, H-7), 8.97 (1H, d, $J = 7.5$ Hz), 9.3 (1H, d, $J = 6.0$ Hz), 9.63 (1H, s); MS(ESI) m/z 514 (M^+); **16**. Yield 95.6%, mp 203–205 °C, ^{1}H NMR (500 Hz, DMSO-d_6) δ 0.88 (3H, t, $J = 7.5$ Hz, H-18), 1.86 (2H, m, $J = 7.5$ Hz, H-19), 2.55 (2H, t, $J = 6.0$ Hz, CH_2), 4.29 (2H, t, $J = 6.0$ Hz, CH_2), 4.87 (2H, t, $J = 6.0$ Hz, CH_2), 5.27 (2H, s, H-5), 5.42 (2H, s, H-17), 6.50 (1H, s, 20-OH), 7.25 (1H, dd, $J_1 = 2.5$ Hz, $J_2 = 9.5$ Hz, H-11), 7.28 (1H, s, H-14), 7.47 (1H, d, $J = 2.5$ Hz, H-9), 8.05 (1H, d, $J = 9.5$ Hz, H-12), 8.18 (2H, t, $J = 5.0$ Hz), 8.53 (1H, s, H-7), 8.64 (1H, t, $J = 5.0$ Hz), 9.18 (2H, d, $J = 5.0$ Hz); MS(ESI) m/z 484 (M^+); **17**. Yield 90.4%, mp 192.2–194.3 °C, ^{1}H NMR (300 Hz, DMSO-d_6) δ 0.85 (3H, t, $J = 6.9$ Hz, H-18), 1.83 (2H, m, $J = 6.9$ Hz, H-19), 2.55 (2H, t, $J = 6.3$ Hz, CH_2), 2.67 (3H, s, CH_3), 4.30 (2H, t, $J = 6.3$ Hz, CH_2), 4.95 (2H, t, $J = 6.3$ Hz, CH_2), 5.24 (2H, s, H-5), 5.39 (2H, s, H-17), 6.50 (1H, s, 20-OH), 7.20 (1H, d, $J = 9.0$ Hz, H-11), 7.24 (1H, s, H-14), 7.46 (1H, s, H-9), 8.01 (1H, d, $J = 9.6$ Hz, H-12), 8.30 (1H, t, $J_1 = 6.0$ Hz, $J_2 = 9.0$ Hz), 8.51 (1H, s, H-7), 9.02 (1H, d, $J = 9.0$ Hz), 9.34 (1H, d, 6.0 Hz), 9.68 (1H, s); MS(ESI) m/z 526 (M^+), 558$(M+CH_3OH)^+$; **18**. Yield 88.8%, mp > 300 °C, ^{1}H NMR (300 Hz, DMSO-d_6) δ 0.84 (3H, t, $J = 6.9$ Hz,

H-18), 1.85 (2H, m, $J = 6.9$ Hz, H-19), 2.55 (2H, t, CH_2), 4.29 (2H, t, CH_2), 4.93 (2H, t, CH_2), 5.24 (2H, s, H-5), 5.39 (2H, s, H-17), 6.50 (1H, s, 20-OH), 7.19 (1H, d, $J = 9$ Hz, H-11), 7.24 (1H, s, H-14), 7.45 (1H, s, H-9), 8.02 (1H, d, $J = 9$ Hz, H-12), 8.34 (1H, t), 8.50 (1H, s, H-7), 9.03 (1H, d), 9.36 (1H, d), 9.71 (1H, s), 10.13 (1H, s, –CHO); MS(ESI) m/z 512 (M^+), 530 ($M+H_2O)^+$, 544 ($M+CH_3OH)^+$; **19**. Yield 95.3%, mp 192.6–193.6 °C, ^{1}H NMR (400 Hz, DMSO-d_6) δ 0.87 (3H, t, $J = 7.2$ Hz, H-18), 1.85 (2H, m, $J = 7.2$ Hz, H-19), 2.55 (2H, t, CH_2), 4.29 (2H, t, CH_2), 4.71 (2H, d, CH_2), 4.88 (2H, t, CH_2), 5.25 (2H, s, H-5), 5.41 (2H, s, H-17), 5.87 (1H, t, -OH), 6.50 (1H, s, 20-OH), 7.24 (1H, d, $J_1 = 2.4$ Hz, $J_2 = 9.2$ Hz, H-11), 7.27 (1H, s, H-14), 7.47 (1H, d, $J = 2.4$ Hz, H-9), 8.03 (1H, d, $J = 9.2$ Hz, H-12), 8.13 (1H, t), 8.52 (1H, s, H-7), 8.54 (1H, d), 9.07 (1H, d), 9.13 (1H, s); MS(ESI) m/z 514 (M^+); **20**. Yield 80.4%, mp 293.2–295.1 °C, ^{1}H NMR (300 Hz, DMSO-d_6) δ 0.86 (3H, t, $J = 6.9$ Hz, H-18), 1.85 (2H, m, $J = 6.9$ Hz, H-19), 2.70, 2.86 (2H, CH_2), 4.24 (2H, t, CH_2), 4.75 (2H, t, CH_2), 5.24 (2H, s, H-5), 5.39 (2H, s, H-17), 6.49 (1H, br, 20-OH), 7.25 (1H, s, H-14), 7.29 (1H, d, H-11), 7.46 (1H, s, H-9), 7.92 (2H, s), 8.03 (1H, d, $J = 9$ Hz, H-12), 8.50 (1H, s, H-7), 8.59 (1H, s), 8.64 (1H, s); MS(ESI) m/z 500 (M^+); **21**. Yield 91.6%, mp 203–205 °C, ^{1}H NMR (300 Hz, DMSO-d_6) δ 0.85 (3H, t, $J = 7.5$ Hz, H-18), 1.86 (2H, m, $J = 7.5$ Hz, H-19), 2.47 (3H, s, –CH_3), 2.53 (2H, CH_2), 4.26 (2H, t, CH_2), 4.78 (2H, t, CH_2), 5.24 (2H, s, H-5), 5.39 (2H, s, H-17), 6.50 (1H, s, 20-OH), 7.20 (1H, d, H-11), 7.25 (1H, s, H-14), 7.45 (1H, s, H-9), 8.04 (1H, d, H-12), 8.06 (1H, t, $J_1 = 6$ Hz, $J_2 = 9$ Hz), 8.43 (1H, d, $J = 9$ Hz), 8.50 (1H, s, H-7), 8.96 (1H, d, $J = 6$ Hz), 9.07 (1H, s); MS(ESI) m/z 498 (M^+); **22**. Yield 84.4%, mp 210.9–211.2 °C, ^{1}H NMR (300 Hz, DMSO-d_6) δ 0.85 (3H, t, $J = 7.5$ Hz, H-18), 1.83 (2H, m, $J = 7.5$ Hz, H-19), 2.54 (2H, t, $J_1 = 4.8$ Hz, $J_2 = 6.3$ Hz, CH_2), 4.28 (2H, t, $J = 4.8$ Hz, CH_2), 4.86 (2H, t, $J = 6.3$ Hz, CH_2), 5.24 (2H, s, H-5), 5.39 (2H, s, H-17), 6.50 (1H, s, 20-OH), 7.25 (1H, s, H-14), 7.27 (1H, d, H-11), 7.46 (1H, d, H-9), 8.05 (1H, d, H-12), 8.24 (1H, q), 8.51 (1H, s, H-7), 8.69 (1H, t), 9.11 (1H, d), 9.57 (1H, s); MS(ESI) m/z 502 (M^+); **23**. Yield 80.7%, mp 216.6–218.4 °C, ^{1}H NMR (500 Hz, DMSO-d_6) δ 0.86 (3H, t, $J = 7.5$ Hz, H-18), 1.85 (2H, m, $J = 7.5$ Hz, H-19), 2.55 (2H, t, $J = 5.0$ Hz, CH_2), 4.32 (2H, t, $J = 5.0$ Hz, CH_2), 4.95 (2H, t, $J = 5.0$ Hz, CH_2), 5.26 (2H, s, H-5), 5.41 (2H, s, H-17), 6.50 (1H, s, 20-OH), 7.22 (1H, d, $J = 10$ Hz, H-11), 7.27 (1H, s, H-14), 7.46 (1H, s, H-9), 8.03 (1H, d, $J = 10$ Hz, H-12), 8.22 (1H, s), 8.52 (1H, s, H-7), 8.94 (1H, d, $J = 8$ Hz), 9.27 (1H, s), 9.60 (1H, s); MS(ESI) m/z 528 (M^+), 550 ($M+CH_3OH)^+$.